

Supporting Information

Benzimidazolyl-pyrazolo[3,4-*b*]pyridinones - selective inhibitors of MOLT-4 leukemia cell growth and sea urchin embryo spiculogenesis: Target quest.

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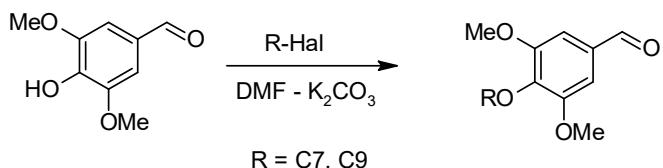
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Content

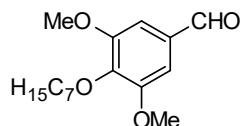
	Pages
Synthesis of 2j, 2t, 2u, 3-Oxobutanenitrile, 20, and 21.....	S3–S4
Analytical Data for Compounds 11–18.....	S4–S23
Table S1. Compound 11j Activity Against a Panel of Kinases.....	S24–S25
Table S2. Effects of MMP Inhibitors on Sea Urchin Embryos.....	S25
Table S3. Phenotypic Responses of Sea Urchin Embryos to BIPP 11 and Different Standard Inhibitors Related to Regulation of Spicule Development.....	S26–S27
Table S4. Leukemia Cell Lines.....	S28
Figures S1–S21. NCI60 screen graphs.....	S29–S49
Figure S22. RF-QSAR results for compound 11j. List of top-10 targets.....	S50
Figure S23. Steps of PMC differentiation.....	S51
Figure S24. Mean graph for murrayafoline A.....	S52
References.....	S53

*General Alkylation Procedure of 4-Hydroxy-3,5-dimethoxybenzaldehyde (**2j**).*



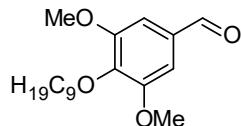
A mixture of 4-hydroxy-3,5-dimethoxybenzaldehyde (**2j**) (182 mg, 1 mmol), C₇H₁₅I or C₉H₁₉Br (1 mmol), and potassium carbonate (137 mg, 1 mmol) in DMF (3 mL) was stirred at 75–80 °C for 3 h (TLC control) until the disappearance of starting compounds. The mixture was diluted with water (15 mL) and extracted with CH₂Cl₂ (3 × 5 mL). The extract was dried by filtration through cotton wool and evaporated *in vacuo*. The products **2t** and **2u** were used in further transformations without additional purification.

*4-(Heptyloxy)-3,5-dimethoxybenzaldehyde (**2t**).*



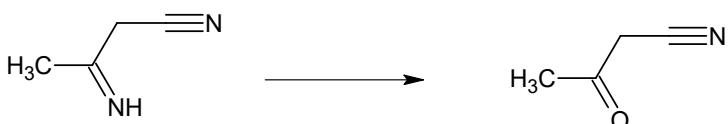
¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.88 (br.s, 3H, CH₃), 1.21–1.48 (m, 8H, CH₂), 1.64 (2H, m, 2H, CH₂), 3.86 (6H, s, OCH₃-3,5), 3.97 (2H, t, *J* = 6.3 Hz, OCH₂), 7.26 (s, H-2,6), 9.89 (s, 1H, CHO).

*3,5-Dimethoxy-4-(nonyloxy)benzaldehyde (**2u**).*



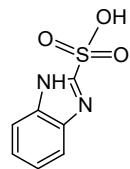
¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.87 (m, 3H, CH₃), 1.27 (br.s, 10H, CH₂), 1.41 (m, 2H, CH₂), 1.64 (m, 2H, CH₂), 3.86 (s, 6H, OCH₃-3,5), 3.97 (t, *J* = 6.3 Hz, 2H, OCH₂), 7.26 (s, 2H, H-2,6), 9.89 (s, 1H, CHO).

Synthesis of 3-Oxobutanenitrile.



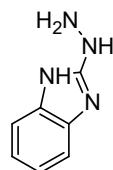
The solution of 3-iminobutanenitrile (30 g, 0.365 M) in 6 N HCl (90 mL) was heated for 3 h at 80 °C, cooled to room temperature and extracted with CH₂Cl₂ (6 × 60 mL). The extract was dried with MgSO₄, evaporated under reduced pressure, and reddish residue oil was distilled *in vacuo* to afford 15 g (48%) of 3-oxobutanenitrile as unstable colorless liquid (bp 1 mmHg/56–58 °C). ¹H NMR (DMSO-*d*₆, 500 MHz) δ 4.03 (s, 2H), 2.16 (s, 3H). It was used immediately in the next reaction step without further purification.

*Synthesis of 1*H*-Benzimidazole-2-sulfonic Acid (**20**).*



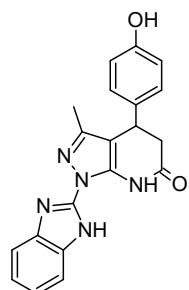
1,3-Dihydro-2*H*-benzimidazole-2-thione (**19**) (68 g, 0.46 M) was added by small portions to a warm solution of percarbonate (160 g, 1.02 M) in water (1.2 L) during 30–45 min, until the temperature of the mixture rose up to 85 °C. The reaction mixture was boiled for ~12 h to stop gas evolution (control with Tishchenko vessel) and stored overnight. At the same time, the presence of initial thione was observed (TLC control, EtOAc/EtOH = 9:1). Next day the new portion of percarbonate (72 g, 0.46 M) was added and boiled for 1 h. Then charcoal (20 g) was added and heated with stirring at 70 °C for 30 min. The reaction mixture was filtered from charcoal, acidified with hydrochloric acid to pH 1.0, cooled to 10 °C, and left for 2 h. The precipitate was filtered off, washed with water (2 × 60 mL), dried in air, and washed with ether to afford target sulfonic acid **20**, 58.8 g (66%), mp 326–329 °C [lit.¹ mp 325–330 °C (H₂O)].

*Synthesis of 2-Hydrazinyl-1*H*-benzimidazole (**21**).*



A solution of 1*H*-benzimidazole-2-sulfonic acid (**20**) (35 g, 0.177 M) in 75% hydrazine (150 mL) was heated for 4 h at 120 °C in a glass autoclave (champagne bottle) and cooled to room temperature. The precipitated crystals were filtered off, washed with water, and dried in air to afford **21**, 21.8 g (84%), mp 218–219 °C (lit.² mp 221–222 °C).

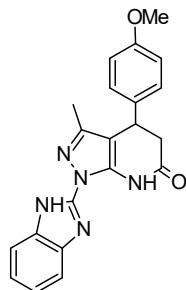
*I-(1*H*-Benzimidazol-2-yl)-4-(4-hydroxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one (**11a**).*



White crystals, yield 55%; mp 228–229 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ 1.95 (s, 3H, CH₃), 2.70 (dd, *J* = 5.4 Hz, *J* = 16.4 Hz, 1H, CH₂), 3.08 (dd, *J* = 7.6 Hz, *J* = 16.4 Hz, 1H, CH₂), 4.21 (dd, *J* = 5.4 Hz, *J* = 7.6 Hz, 1H, CH), 6.72 (d, *J* = 8.4 Hz, 2H, H-3",5"), 7.04 (d, *J* = 8.4 Hz, 2H, H-2",6"), 7.20 (m, 2H, H-

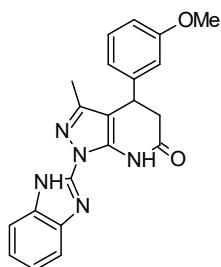
5',6'), 7.43 (m, 1H, H-4'), 7.63 (m, 1H, H-7'), 9.31 (s, 1H, OH-4''), 9.93 (s, 1H, CONH), 13.12 (s, 1H, NH); EIMS m/z 360 [M+1]⁺ (13), 359 [M]⁺ (61), 331 (31), 316 (18), 266 (20), 252 (45), 226 (100), 225 (65), 224 (79), 211 (44), 180 (23), 168 (31), 158 (50), 144 (34), 134 (38), 133 (83), 132 (45), 131 (37), 119 (47), 118 (93), 105 (51), 91 (49), 90 (66), 77 (48); anal. C 66.78; H 4.74; N 19.60; calcd for C₂₀H₁₇N₅O₂, C 66.84; H 4.77; N 19.49.

*1-(1*H*-Benzimidazol-2-yl)-4-(4-methoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one (11b).*



White crystals, yield 76%; mp 220–221 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ 1.95 (s, 3H, CH₃), 2.71 (dd, *J* = 5.4 Hz, *J* = 16.4 Hz, 1H, CH₂), 3.10 (dd, *J* = 7.6 Hz, *J* = 16.4 Hz, 1H, CH₂), 3.73 (s, 3H, OCH₃-4''), 4.27 (dd, *J* = 5.4 Hz, *J* = 7.6 Hz, 1H, CH), 6.91 (d, *J* = 8.6 Hz, 2H, H-3'',5''), 7.17 (d, *J* = 8.6 Hz, 2H, H-2'',6''), 7.21 (m, 2H, H-5',6'), 7.44 (m, 1H, H-4'), 7.64 (m, 1H, H-7'), 9.95 (s, 1H, CONH), 13.12 (s, 1H, NH); EIMS m/z 374 [M+1]⁺ (14), 373 [M]⁺ (57), 345 (33), 266 (21), 252 (45), 226 (56), 225 (100), 224 (81), 211 (35), 187 (41), 168 (28), 158 (31), 148 (57), 133 (67), 121 (95), 118 (62), 105 (31), 90 (42), 77 (33); anal. C 67.47; H 5.09; N 18.84; calcd for C₂₁H₁₉N₅O₂, C 67.55; H 5.13; N 18.75.

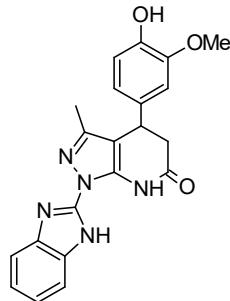
*1-(1*H*-Benzimidazol-2-yl)-4-(3-methoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one (11c).*



White crystals, yield 69%; mp 211–212 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ 1.97 (s, 3H, CH₃), 2.76 (dd, *J* = 5.3 Hz, *J* = 16.4 Hz, 1H, CH₂), 3.13 (dd, *J* = 7.7 Hz, *J* = 16.4 Hz, 1H, CH₂), 3.73 (s, 3H, OCH₃-3''), 4.30 (dd, *J* = 5.3 Hz, *J* = 7.7 Hz, 1H, CH), 6.83 (m, 3H, H-2'',4'',6''), 7.21 (m, 2H, H-5',6'), 7.24 (m, 1H, H-5''), 7.43 (m, 1H, H-4'), 7.64 (m, 1H, H-7'), 9.97 (s, 1H, CONH), 13.15 (s, 1H, NH); EIMS m/z 374

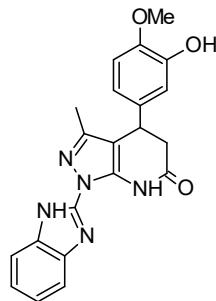
$[M+1]^+$ (24), 373 $[M]^+$ (100), 345 (17), 331 (16), 266 (40), 252 (86), 226 (18), 225 (63), 224 (67), 211 (27), 187 (13), 168 (24), 158 (23), 133 (73), 118 (53), 105 (28), 90 (38), 77 (30); anal. C 67.44; H 5.10; N 18.81; calcd for $C_{21}H_{19}N_5O_2$, C 67.55; H 5.13; N 18.75.

I-(1H-Benzimidazol-2-yl)-4-(4-hydroxy-3-methoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (11d).



White crystals, yield 58%; mp 240–241 °C; 1H NMR (DMSO- d_6 , 500 MHz) δ 1.95 (s, 3H, CH_3), 2.77 (dd, $J = 6.0$ Hz, $J = 16.3$ Hz, 1H, CH_2), 3.05 (dd, $J = 7.5$ Hz, $J = 16.3$ Hz, 1H, CH_2), 3.74 (s, 3H, OCH_3 -3''), 4.21 (dd, $J = 6.0$ Hz, $J = 7.5$ Hz, 1H, CH), 6.60 (dd, $J = 1.8$ Hz, $J = 8.1$ Hz, 1H, H-6''), 6.71 (d, $J = 8.1$ Hz, 1H, H-5''), 6.86 (d, $J = 1.8$ Hz, 1H, H-2''), 7.21 (m, 2H, H-5',6'), 7.43 (m, 1H, H-4'), 7.64 (m, 1H, H-7'), 8.89 (s, 1H, OH-4''), 9.93 (s, 1H, CONH), 13.13 (s, 1H, NH); EIMS m/z 390 $[M+1]^+$ (13), 389 $[M]^+$ (53), 361 (16), 266 (14), 252 (20), 226 (100), 225 (23), 224 (29), 211 (15), 195 (15), 168 (17), 164 (23), 158 (20), 144 (18), 137 (26), 133 (38), 118 (51), 105 (30), 90 (39), 77 (28); anal. C 64.82; H 4.96; N 17.94; calcd for $C_{21}H_{19}N_5O_3$, C 64.77; H 4.92; N 17.98.

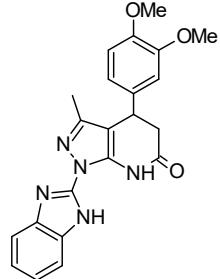
I-(1H-Benzimidazol-2-yl)-4-(3-hydroxy-4-methoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (11e).



White crystals, yield 63%; mp 232–233 °C; 1H NMR (DMSO- d_6 , 500 MHz) δ 2.00 (s, 3H, CH_3), 2.66 (dd, $J = 4.8$ Hz, $J = 16.4$ Hz, 1H, CH_2), 3.11 (dd, $J = 7.7$ Hz, $J = 16.4$ Hz, 1H, CH_2), 3.73 (s, 3H, OCH_3 -4''), 4.18 (dd, $J = 4.8$ Hz, $J = 7.7$ Hz, 1H, CH), 6.63 (m, 2H, H-2'',6''), 6.86 (d, $J = 8.1$ Hz, 1H, H-5''), 7.21 (m, 2H, H-5',6'), 7.43 (m, 1H, H-4'), 7.65 (m, 1H, H-7'), 8.95 (s, 1H, OH-4''), 9.94 (s, 1H, CONH), 13.15 (s,

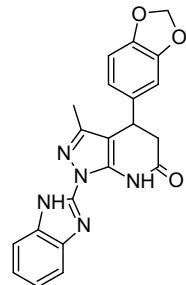
1H, NH); EIMS m/z 390 [M+1]⁺ (15), 389 [M]⁺ (63), 361 (23), 266 (22), 252 (41), 226 (100), 225 (28), 224 (27), 211 (15), 195 (23), 168 (15), 164 (19), 158 (18), 144 (16), 137 (37), 133 (32), 118 (33), 105 (18), 90 (22), 77 (14); anal. C 64.87; H 4.95; N 17.91; calcd for C₂₁H₁₉N₅O₃, C 64.77; H 4.92; N 17.98.

I-(1H-Benzimidazol-2-yl)-4-(3,4-dimethoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (11f).



White crystals, yield 82%; mp 206–207 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ 1.96 (s, 3H, CH₃), 2.79 (dd, *J* = 6.0 Hz, *J* = 16.3 Hz, 1H, CH₂), 3.07 (dd, *J* = 7.5 Hz, *J* = 16.3 Hz, 1H, CH₂), 3.72 (s, 3H, OCH₃-3''), 3.73 (s, 3H, OCH₃-4''), 4.27 (dd, *J* = 6.0 Hz, *J* = 7.5 Hz, 1H, CH), 6.71 (dd, *J* = 2.0 Hz, *J* = 8.3 Hz, 1H, H-6''), 6.89 (d, *J* = 8.3 Hz, 1H, H-5''), 6.91 (d, *J* = 2.0 Hz, 1H, H-2''), 7.21 (m, 2H, H-5',6'), 7.44 (m, 1H, H-4'), 7.64 (m, 1H, H-7'), 9.95 (s, 1H, CONH), 13.14 (s, 1H, NH); EIMS m/z 404 [M+1]⁺ (3), 403 [M]⁺ (13), 266 (16), 252 (24), 226 (23), 225 (33), 224 (26), 202 (26), 178 (100), 168 (13), 160 (9), 159 (10), 158 (16), 151 (64), 144 (11), 133 (23), 118 (31), 105 (16), 90 (22), 77 (16); anal. C 65.56; H 5.27; N 17.32; calcd for C₂₂H₂₁N₅O₃, C 65.50; H 5.25; N 17.36.

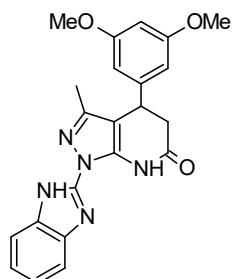
I-(1H-Benzimidazol-2-yl)-4-(1,3-benzodioxol-5-yl)-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (11g).



White crystals, yield 78%; mp 227–228 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ 1.97 (s, 3H, CH₃), 2.72 (dd, *J* = 5.4 Hz, *J* = 16.4 Hz, 1H, CH₂), 3.09 (dd, *J* = 7.6 Hz, *J* = 16.4 Hz, 1H, CH₂), 4.26 (dd, *J* = 5.4 Hz, *J* = 7.6 Hz, 1H, CH), 5.99 (s, 2H, OCH₂O), 6.70 (d, *J* = 8.0 Hz, 1H, H-5''), 6.86 (m, 2H, H-2'',6''), 7.21 (m, 2H, H-5',6'), 7.43 (m, 1H, H-4'), 7.64 (m, 1H, H-7'), 9.95 (s, 1H, CONH), 13.14 (s, 1H, NH); EIMS m/z 388 [M+1]⁺ (25), 387 [M]⁺ (100), 359 (32), 266 (14), 252 (31), 226 (27), 225 (49), 224 (38), 211 (15), 162

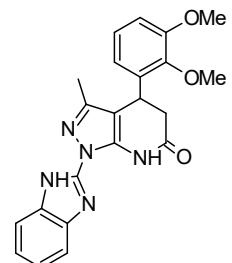
(21), 135 (21), 133 (16), 118 (19), 90 (15), 77 (9); anal. C 65.04; H 4.40; N 18.14; calcd for $C_{21}H_{17}N_5O_3$, C 65.11; H 4.42; N 18.08.

*1-(1*H*-Benzimidazol-2-yl)-4-(3,5-dimethoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one (**11h**).*



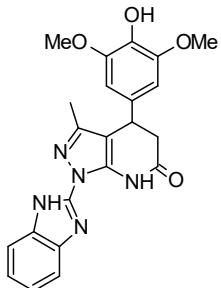
White crystals, yield 72%; mp 234–236 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 2.01 (s, 3H, CH₃), 2.82 (dd, *J* = 5.3 Hz, *J* = 16.1 Hz, 1H, CH₂), 3.11 (dd, *J* = 6.4 Hz, *J* = 16.1 Hz, 1H, CH₂), 3.74 (s, 6H, OCH₃-3",5"), 4.26 (dd, *J* = 5.3 Hz, *J* = 6.4 Hz, 1H, CH), 6.43 (s, 3H, H-2",4",6"), 7.23 (m, 2H, H-5',6'), 7.45 (m, 1H, H-4'), 7.66 (m, 1H, H-7'), 9.99 (s, 1H, CONH), 13.17 (s, 1H, NH); EIMS *m/z* 404 [M+1]⁺ (4), 403 [M]⁺ (17), 266 (26), 252 (32), 225 (16), 224 (24), 211 (16), 170 (16), 168 (36), 158 (39), 144 (37), 133 (99), 119 (54), 118 (100), 117 (98), 105 (99), 91 (99), 90 (99), 77 (91); anal. C 65.58; H 5.28; N 17.28; calcd for $C_{22}H_{21}N_5O_3$, C 65.50; H 5.25; N 17.36.

*1-(1*H*-Benzimidazol-2-yl)-4-(2,3-dimethoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one (**11i**).*



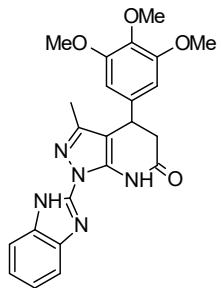
White crystals, yield 59%; mp 236–237 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 1.95 (s, 3H, CH₃), 2.59 (dd, *J* = 4.0 Hz, *J* = 16.7 Hz, 1H, CH₂), 3.17 (dd, *J* = 8.7 Hz, *J* = 16.7 Hz, 1H, CH₂), 3.69 (s, 3H, OCH₃-3"), 3.81 (s, 3H, OCH₃-2"), 4.51 (dd, *J* = 4.0 Hz, *J* = 8.7 Hz, 1H, CH), 6.72 (d, *J* = 7.2 Hz, 1H, H-6"), 6.99 (m, 2H, H-4",5"), 7.21 (m, 2H, H-5',6'), 7.43 (m, 1H, H-4'), 7.65 (m, 1H, H-7'), 9.97 (s, 1H, CONH), 13.14 (s, 1H, NH); EIMS *m/z* 404 [M+1]⁺ (17), 403 [M]⁺ (66), 388 (11), 372 (46), 361 (23), 345 (32), 344 (30), 343 (24), 266 (68), 253 (17), 252 (100), 226 (41), 225 (58), 224 (45), 211 (26), 194 (60), 168 (24), 160 (20), 159 (26), 158 (33), 144 (20), 134 (26), 133 (65), 132 (25), 119 (20), 118 (52), 105 (30), 90 (31), 77 (27); anal. C 65.60; H 5.29; N 17.29; calcd for $C_{22}H_{21}N_5O_3$, C 65.50; H 5.25; N 17.36.

*I-(1H-Benzimidazol-2-yl)-4-(4-hydroxy-3,5-dimethoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*b*]pyridin-6-one (**11j**).*



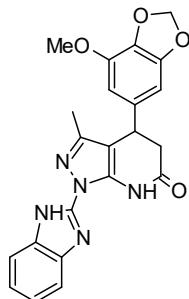
White crystals, yield 80%; mp 257–259 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 1.95 (s, 3H, CH₃), 2.83 (dd, *J* = 6.7 Hz, *J* = 16.3 Hz, 1H, CH₂), 3.02 (dd, *J* = 7.4 Hz, *J* = 16.3 Hz, 1H, CH₂), 3.72 (s, 6H, OCH₃-3",5"), 4.21 (dd, *J* = 6.7 Hz, *J* = 7.4 Hz, 1H, CH), 6.53 (s, 2H, H-2",6"), 7.21 (m, 2H, H-5',6'), 7.43 (m, 1H, H-4'), 7.64 (m, 1H, H-7'), 8.28 (s, 1H, OH-4"), 9.94 (s, 1H, CONH), 13.13 (s, 1H, NH); EIMS *m/z* 420 [M+1]⁺ (11), 419 [M]⁺ (46), 266 (21), 252 (30), 226 (100), 224 (17), 210 (15), 194 (28), 167 (18), 133 (17), 118 (32), 90 (24), 77 (14); anal. C 63.11; H 5.09; N 16.64; calcd for C₂₂H₂₁N₅O₄, C 63.00; H 5.05; N 16.70.

*I-(1H-Benzimidazol-2-yl)-3-methyl-4-(3,4,5-trimethoxyphenyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*b*]pyridin-6-one (**11k**).*



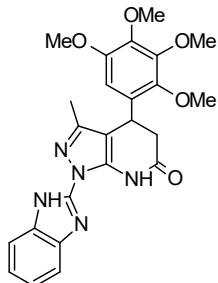
White crystals, yield 77%; mp 254–257 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 1.97 (s, 3H, CH₃), 2.84 (dd, *J* = 6.5 Hz, *J* = 16.4 Hz, 1H, CH₂), 3.06 (dd, *J* = 7.5 Hz, *J* = 16.4 Hz, 1H, CH₂), 3.65 (s, 3H, OCH₃-4"), 3.74 (s, 6H, OCH₃-3",5"), 4.27 (dd, *J* = 6.5 Hz, *J* = 7.5 Hz, 1H, CH), 6.58 (s, 2H, H-2",6"), 7.20 (m, 2H, H-5',6'), 7.43 (m, 1H, H-4'), 7.64 (m, 1H, H-7'), 9.96 (s, 1H, CONH), 13.12 (s, 1H, NH); EIMS *m/z* 434 [M+1]⁺ (1), 433 [M]⁺ (4), 266 (20), 252 (30), 226 (12), 225 (15), 224 (13), 217 (24), 208 (100), 181 (73), 168 (19), 158 (22), 144 (20), 133 (33), 132 (22), 131 (15), 119 (18), 118 (49), 105 (30), 91 (26), 90 (42), 77 (27); anal. C 63.78; H 5.38; N 16.21; calcd for C₂₃H₂₃N₅O₄, C 63.73; H 5.35; N 16.16.

*I-(1H-Benzimidazol-2-yl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*b*]pyridin-6-one (**11l**).*



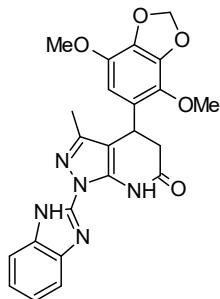
White crystals, yield 82%; mp 262–263 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 1.98 (s, 3H, CH₃), 2.76 (dd, *J* = 5.9 Hz, *J* = 16.3 Hz, 1H, CH₂), 3.07 (dd, *J* = 7.6 Hz, *J* = 16.3 Hz, 1H, CH₂), 3.81 (s, 3H, OCH₃-5''), 4.25 (dd, *J* = 5.9 Hz, *J* = 7.6 Hz, 1H, CH), 5.97 (s, 2H, OCH₂O), 6.48 (s, 1H, H-4''), 6.58 (s, 1H, H-6''), 7.21 (m, 2H, H-5',6'), 7.44 (m, 1H, H-4'), 7.64 (m, 1H, H-7'), 9.95 (s, 1H, CONH), 13.13 (s, 1H, NH); EIMS *m/z* 418 [M+1]⁺ (26), 417 [M]⁺ (100), 389 (33), 266 (17), 252 (26), 225 (17), 224 (23), 192 (31), 165 (27), 158 (18), 133 (20), 118 (50), 105 (23), 91 (16), 90 (25), 77 (13); anal. C 63.40; H 4.62; N 16.66; calcd for C₂₂H₁₉N₅O₄, C 63.30; H 4.59; N 16.78.

I-(1H-Benzimidazol-2-yl)-3-methyl-4-(2,3,4,5-tetramethoxyphenyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (11m).



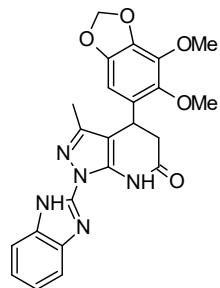
White crystals, yield 66%; mp 217–218 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 1.95 (s, 3H, CH₃), 2.71 (dd, *J* = 5.5 Hz, *J* = 16.7 Hz, 1H, CH₂), 3.08 (dd, *J* = 8.4 Hz, *J* = 16.7 Hz, 1H, CH₂), 3.66 (s, 3H, OCH₃-2''), 3.69 (s, 3H, OCH₃-3''), 3.75 (s, 3H, OCH₃-4''), 3.83 (s, 3H, OCH₃-5''), 4.47 (dd, *J* = 5.5 Hz, *J* = 8.4 Hz, 1H, CH), 6.60 (s, 1H, H-6''), 7.21 (m, 2H, H-5',6'), 7.43 (m, 1H, H-4'), 7.65 (m, 1H, H-7'), 9.97 (s, 1H, CONH), 13.11 (s, 1H, NH); EIMS *m/z* 464 [M+1]⁺ (18), 463 [M]⁺ (71), 432 (15), 266 (14), 252 (19), 238 (34), 224 (23), 223 (22), 211 (37), 168 (23), 158 (35), 143 (34), 133 (45), 132 (37), 131 (30), 119 (33), 118 (100), 105 (56), 91 (44), 90 (63), 77 (42); anal. C 62.31; H 5.47; N 15.01; calcd for C₂₄H₂₅N₅O₅, C 62.19; H 5.44; N 15.11.

I-(1H-Benzimidazol-2-yl)-4-(4,7-dimethoxy-1,3-benzodioxol-5-yl)-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (11n).



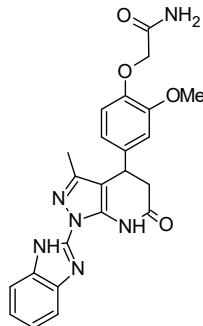
White crystals, yield 81%; mp 282–284 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 1.99 (s, 3H, CH₃), 2.62 (dd, *J* = 4.2 Hz, *J* = 16.8 Hz, 1H, CH₂), 3.12 (dd, *J* = 8.7 Hz, *J* = 16.8 Hz, 1H, CH₂), 3.73 (s, 3H, OCH₃-4''), 3.74 (s, 3H, OCH₃-7''), 4.41 (dd, *J* = 4.2 Hz, *J* = 8.7 Hz, 1H, CH), 6.00 (s, 1H, OCH₂O), 6.01 (s, 1H, OCH₂O), 6.45 (s, 1H, H-6''), 7.21 (m, 2H, H-5',6'), 7.43 (m, 1H, H-4'), 7.65 (m, 1H, H-7'), 9.93 (s, 1H, CONH), 13.10 (s, 1H, NH); EIMS *m/z* 447 [M]⁺ (71), 416 (10), 266 (22), 252 (31), 222 (98), 211 (24), 195 (63), 168 (31), 158 (36), 144 (29), 143 (20), 133 (43), 119 (25), 118 (100), 105 (54), 91 (44), 90 (67), 78 (30), 77 (39); anal. C 61.88; H 4.78; N 15.52; calcd for C₂₃H₂₁N₅O₅, C 61.74; H 4.73; N 15.65.

1-(1H-Benzimidazol-2-yl)-4-(6,7-dimethoxy-1,3-benzodioxol-5-yl)-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (11o).



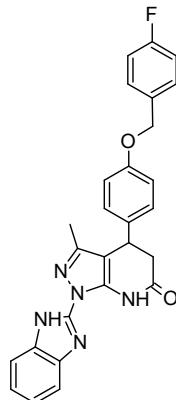
White crystals, yield 69%; mp 268–270 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 1.98 (s, 3H, CH₃), 2.59 (dd, *J* = 4.6 Hz, *J* = 16.5 Hz, 1H, CH₂), 3.10 (dd, *J* = 8.4 Hz, *J* = 16.5 Hz, 1H, CH₂), 3.67 (s, 3H, OCH₃-6''), 3.95 (s, 3H, OCH₃-7''), 4.45 (dd, *J* = 4.6 Hz, *J* = 8.4 Hz, 1H, CH), 5.96 (s, 2H, OCH₂O), 6.40 (s, 1H, H-4''), 7.21 (m, 2H, H-5',6'), 7.43 (m, 1H, H-4'), 7.64 (m, 1H, H-7'), 9.93 (s, 1H, CONH), 13.11 (s, 1H, NH); EIMS *m/z* 448 [M+1]⁺ (27), 447 [M]⁺ (100), 432 (15), 416 (30), 389 (10), 388 (15), 387 (13), 266 (11), 252 (11), 222 (18), 195 (11), 118 (11); anal. C 61.85; H 4.77; N 15.56; calcd for C₂₃H₂₁N₅O₅, C 61.74; H 4.73; N 15.65.

2-{4-[1-(1H-Benzimidazol-2-yl)-3-methyl-6-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-b]pyridin-4-yl]-2-methoxyphenoxy}acetamide (11p).



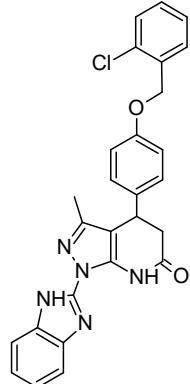
Purchased from Chemical Block Ltd. White crystals, mp 265–266 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 1.96 (s, 3H, CH₃), 2.80 (dd, *J* = 5.8 Hz, *J* = 16.3 Hz, 1H, CH₂), 3.08 (dd, *J* = 7.5 Hz, *J* = 16.3 Hz, 1H, CH₂), 3.77 (s, 3H, OCH₃-2'), 4.28 (dd, *J* = 5.8 Hz, *J* = 7.5 Hz, 1H, CH), 4.39 (s, 2H, OCH₂), 6.71 (d, *J* = 8.0 Hz, 1H, H-5'), 6.86 (d, *J* = 8.0 Hz, 1H, H-6'), 6.96 (s, 1H, H-3'), 7.20 (m, 2H, H-5'',6''), 7.30 (br.s, 1H, NH₂), 7.38 (br.s, 1H, NH₂), 7.43 (m, 1H, H-4''), 7.65 (m, 1H, H-7''), 9.95 (s, 1H, CONH), 13.14 (s, 1H, NH); EIMS *m/z* 446 [M]⁺ (4), 388 (10), 266 (24), 252 (100), 226 (220), 225 (35), 224 (27), 221 (22), 211 (22), 194 (29), 168 (20), 158 (20), 134 (15), 133 (35), 132 (17), 118 (35), 105 (18), 90 (20), 77 (10); anal. C 61.80; H 4.94; N 18.97; calcd for C₂₃H₂₂N₆O₄, C 61.88; H 4.97; N 18.82.

I-(1H-Benzimidazol-2-yl)-4-{4-[(4-fluorobenzyl)oxy]phenyl}-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (11q).



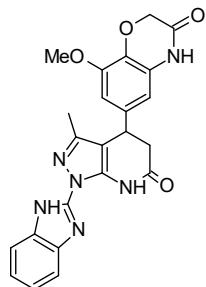
White crystals, yield 73%; mp 213–214 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 1.95 (s, 3H, CH₃), 2.71 (dd, *J* = 5.3 Hz, *J* = 16.3 Hz, 1H, CH₂), 3.11 (dd, *J* = 7.3 Hz, *J* = 16.3 Hz, 1H, CH₂), 4.28 (dd, *J* = 5.3 Hz, *J* = 7.3 Hz, 1H, CH), 5.05 (s, 2H, OCH₂), 6.97 (d, *J* = 8.7 Hz, 2H, H-3'',5''), 7.18 (d, *J* = 8.7 Hz, 2H, H-2'',6''), 7.21 (m, 4H, H-5',6',2'',6''), 7.43 (m, 1H, H-4'), 7.49 (m, 2H, H-3'',5''), 7.64 (m, 1H, H-7'), 9.95 (s, 1H, CONH), 13.15 (s, 1H, NH); EIMS *m/z* 467 [M]⁺ (2), 109 (100); anal. C 69.51; H 4.78; N 14.90; calcd for C₂₇H₂₂FN₅O₂, C 69.37; H 4.74; N 14.98.

*I-(1H-Benzimidazol-2-yl)-4-{4-[(2-chlorobenzyl)oxy]phenyl}-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*b*]pyridin-6-one (**11r**).*



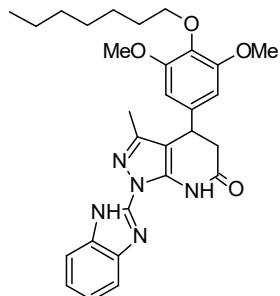
White crystals, yield 81%; mp 229–230 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 1.96 (s, 3H, CH₃), 2.72 (dd, *J* = 5.2 Hz, *J* = 16.4 Hz, 1H, CH₂), 3.12 (dd, *J* = 7.6 Hz, *J* = 16.4 Hz, 1H, CH₂), 4.29 (dd, *J* = 5.2 Hz, *J* = 7.6 Hz, 1H, CH), 5.13 (s, 2H, OCH₂), 6.99 (d, *J* = 8.7 Hz, 2H, H-3",5"), 7.19 (d, *J* = 8.7 Hz, 2H, H-2",6"), 7.22 (m, 2H, H-5',6'), 7.38 (m, 2H, H_{Ar}), 7.43 (m, 1H, H-4'), 7.50 (m, 1H, H_{Ar}), 7.59 (m, 1H, H_{Ar}), 7.64 (m, 1H, H-7'), 9.96 (s, 1H, CONH), 13.15 (s, 1H, NH); EIMS *m/z* 485 [M+2]⁺ (1), 483 [M]⁺ (3), 358 (17), 127 (31), 125 (100), 118 (7), 90 (11); anal. C 67.19; H 4.65; N 14.35; calcd for C₂₇H₂₂ClN₅O₂, C 67.01; H 4.58; N 14.47.

*6-[I-(1H-Benzimidazol-2-yl)-3-methyl-6-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-*b*]pyridin-4-yl]-8-methoxy-2H-1,4-benzoxazin-3(4H)-one (**11s**).*



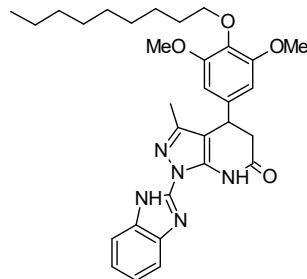
White crystals, yield 62%; mp 289–290 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 2.03 (s, 3H, CH₃), 2.72 (dd, *J* = 4.6 Hz, *J* = 16.4 Hz, 1H, CH₂), 3.14 (dd, *J* = 7.7 Hz, *J* = 16.4 Hz, 1H, CH₂), 3.77 (s, 3H, OCH₃-8), 4.25 (dd, *J* = 4.6 Hz, *J* = 7.7 Hz, 1H, CH), 4.50 (s, 2H, OCH₂), 6.35 (s, 1H, H-5), 6.67 (s, 1H, H-7), 7.22 (m, 2H, H-5",6"), 7.44 (m, 1H, H-4"), 7.65 (m, 1H, H-7"), 9.96 (s, 1H, CONH), 10.49 (s, 1H, CONH), 13.17 (s, 1H, NH); EIMS *m/z* 445 [M+1]⁺ (29), 444 [M]⁺ (100), 416 (25), 266 (23), 252 (75), 226 (37), 225 (29), 224 (37), 192 (18), 168 (21), 158 (22), 133 (36), 118 (54), 105 (25), 91 (22), 90 (32), 77 (17); anal. C 62.07; H 4.52; N 19.01; calcd for C₂₃H₂₀N₆O₄, C 62.16; H 4.54; N 18.91.

*I-(1H-Benzimidazol-2-yl)-4-[4-(heptyloxy)-3,5-dimethoxyphenyl]-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*b*]pyridin-6-one (**11t**).*



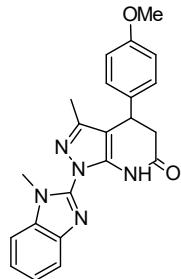
White crystals, yield 54%; mp 164–166 °C; ^1H NMR (DMSO-*d*₆, 300 MHz) δ 0.85 (t, *J* = 7.2 Hz, 3H, CH₃), 1.20–1.45 (m, 8H, CH₂), 1.59 (m, 2H, CH₂), 1.98 (s, 3H, CH₃), 2.86 (dd, *J* = 6.9 Hz, *J* = 16.0 Hz, 1H, CH₂), 3.05 (dd, *J* = 7.5 Hz, *J* = 16.0 Hz, 1H, CH₂), 3.70 (s, 6H, OCH₃-3",5"), 3.79 (m, 2H, OCH₂), 4.27 (dd, *J* = 6.9 Hz, *J* = 7.5 Hz, 1H, CH), 6.58 (s, 2H, H-2",6"), 7.22 (m, 2H, H-5',6'), 7.44 (m, 1H, H-4'), 7.65 (m, 1H, H-7'), 9.98 (s, 1H, CONH), 13.12 (s, 1H, NH); EIMS *m/z* 518 [M+1]⁺ (34), 517 [M]⁺ (100), 420 (16), 419 (55), 418 (24), 391 (42), 266 (7), 226 (9); anal. C 67.43; H 6.86; N 13.40; calcd for C₂₉H₃₅N₅O₄, C 67.29; H 6.82; N 13.53.

*I-(1H-Benzimidazol-2-yl)-4-[3,5-dimethoxy-4-(nonyloxy)phenyl]-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*b*]pyridin-6-one (**11u**).*



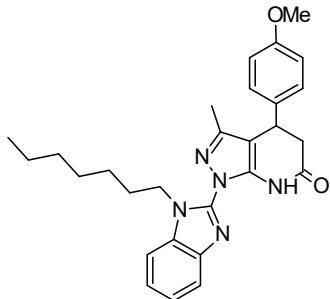
White crystals, yield 49%; mp 152 °C; ^1H NMR (DMSO-*d*₆, 300 MHz) δ 0.85 (t, *J* = 7.2 Hz, 3H, CH₃), 1.20–1.50 (m, 12H, 6CH₂), 1.60 (m, 2H, CH₂), 1.99 (s, 3H, CH₃), 2.86 (dd, *J* = 6.9 Hz, *J* = 16.0 Hz, 1H, CH₂), 3.06 (dd, *J* = 7.5 Hz, *J* = 16.0 Hz, 1H, CH₂), 3.70 (s, 6H, OCH₃-3",5"), 3.80 (m, 2H, OCH₂), 4.29 (dd, *J* = 6.9 Hz, *J* = 7.5 Hz, 1H, CH), 6.60 (s, 2H, H-2",6"), 7.21 (m, 2H, H-5',6'), 7.4–7.6 (br.s, 1H, H-4'), 7.6–7.75 (br.s, 1H, H-7'), 10.0 (br.s, 1H, CONH), 13.1 (br.s, 1H, NH). EIMS *m/z* 546 [M+1]⁺ (5), 545 [M]⁺ (13), 419 (20), 418 (10), 391 (18), 266 (14), 252 (16), 226 (45), 194 (15), 167 (13), 133 (14), 132 (10), 118 (19), 71 (32), 69 (20), 57 (78), 55 (63), 43 (99), 41 (100); anal. C 68.33; H 7.24; N 12.78; calcd for C₃₁H₃₉N₅O₄, C 68.23; H 7.20; N 12.83.

*4-(4-Methoxyphenyl)-3-methyl-1-(1-methyl-1*H*-benzimidazol-2-yl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one (11bx).*



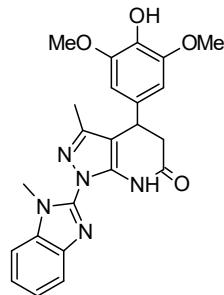
White crystals, yield 74%; mp 194–196 °C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.97 (s, 3H, CH₃), 2.70 (dd, *J* = 6.6 Hz, *J* = 16.1 Hz, 1H, CH₂), 3.06 (dd, *J* = 7.2 Hz, *J* = 16.1 Hz, 1H, CH₂), 3.75 (s, 3H, OCH₃-4''), 4.00 (s, 3H, NCH₃), 4.28 (dd, *J* = 6.6 Hz, *J* = 7.2 Hz, 1H, CH), 6.94 (d, *J* = 8.4 Hz, 2H, H-3'',5''), 7.19 (d, *J* = 8.4 Hz, 2H, H-2'',6''), 7.35 (m, 2H, H-5',6'), 7.69 (m, 2H, H-4',7'), 10.31 (s, 1H, CONH); EIMS *m/z* 388 [M+1]⁺ (15), 387 [M]⁺ (100), 266 (18), 252 (8), 240 (6), 225 (17), 212 (27), 187 (27), 168 (18), 158 (21), 148 (9), 133 (27), 121 (7), 118 (9), 105 (12), 77 (8); anal. C 68.13; H 5.42; N 18.17; calcd for C₂₂H₂₁N₅O₂, C 68.20; H 5.46; N 18.08.

*1-(1-Heptyl-1*H*-benzimidazol-2-yl)-4-(4-methoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one (11by).*



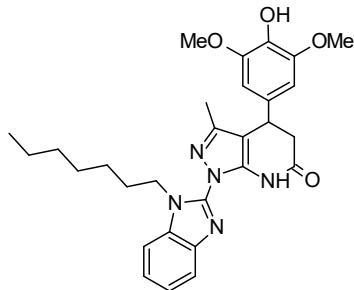
Oil, yield 42%; ¹H NMR (DMSO-*d*₆, 500 MHz) δ 0.81 (t, *J* = 7.2 Hz, 3H, CH₃), 1.24 (m, 8H, CH₂), 1.73 (m, 2H, CH₂), 1.93 (s, 3H, CH₃-3), 2.67 (dd, *J* = 5.8 Hz, *J* = 16.1 Hz, 1H, CH₂), 3.06 (dd, *J* = 8.1 Hz, *J* = 16.1 Hz, 1H, CH₂), 3.73 (s, 3H, OCH₃-4''), 4.27 (dd, *J* = 5.8 Hz, *J* = 8.1 Hz, 1H, CH), 4.50 (m, 2H, NCH₂), 6.90 (d, *J* = 8.5 Hz, 2H, H-3'',5''), 7.14 (d, *J* = 8.5 Hz, 2H, H-2'',6''), 7.30 (m, 2H, H-5',6'), 7.64 (m, 1H, H-4'), 7.70 (m, 1H, H-7'), 10.37 (s, 1H, NH); EIMS *m/z* 472 [M+1]⁺ (23), 471 [M]⁺ (74), 373 (25), 345 (22), 225 (10), 216 (16), 215 (100), 172 (16), 171 (16), 159 (16), 158 (21), 133 (31), 118 (25), 77 (19); anal. C 71.40; H 7.09; N 14.78; calcd for C₂₈H₃₃N₅O₂, C 71.31; H 7.05; N 14.85.

*4-(4-Hydroxy-3,5-dimethoxyphenyl)-3-methyl-1-(1-methyl-1*H*-benzimidazol-2-yl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one (11jx).*



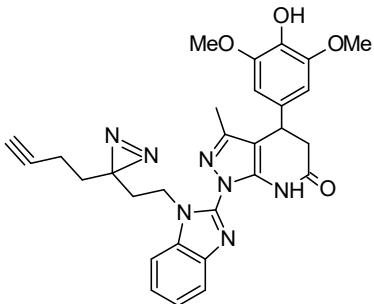
White crystals, yield 66%; mp 193–196 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 1.93 (s, 3H, CH₃), 2.81 (dd, *J* = 6.6 Hz, *J* = 16.1 Hz, 1H, CH₂), 2.97 (dd, *J* = 7.2 Hz, *J* = 16.1 Hz, 1H, CH₂), 3.72 (s, 6H, OCH₃-3",5"), 3.98 (s, 3H, NCH₃), 4.21 (dd, *J* = 6.6 Hz, *J* = 7.2 Hz, 1H, CH), 6.52 (s, 2H, H-2",6"), 7.31 (m, 2H, H-5',6'), 7.63 (m, 1H, H-4'), 7.69 (m, 1H, H-7'), 8.29 (s, 1H, OH-4"), 10.26 (s, 1H, NH); EIMS *m/z* 434 [M+1]⁺ (27), 433 [M]⁺ (100), 405 (15), 280 (15), 267 (16), 266 (64), 240 (41), 225 (21), 173 (10), 158 (10), 146 (16), 132 (13), 131 (19), 118 (6), 77 (7); anal. C 63.79; H 5.38; N 16.06; calcd for C₂₃H₂₃N₅O₄, C 63.73; H 5.35; N 16.16.

1-(1-Heptyl-1H-benzimidazol-2-yl)-4-(4-hydroxy-3,5-dimethoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (1Ijy).



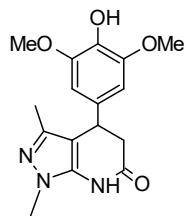
Oil, yield 47%; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 0.81 (t, *J* = 7.2 Hz, 3H, CH₃), 1.22 (m, 8H, CH₂), 1.73 (m, 2H, CH₂), 1.95 (s, 3H, CH₃-3), 2.79 (dd, *J* = 6.9 Hz, *J* = 16.0 Hz, 1H, CH₂), 2.98 (dd, *J* = 7.5 Hz, *J* = 16.0 Hz, 1H, CH₂), 3.72 (s, 6H, OCH₃-3",5"), 4.20 (dd, *J* = 6.9 Hz, *J* = 7.5 Hz, 1H, CH), 4.51 (m, 2H, NCH₂), 6.50 (s, 2H, H-2",6"), 7.31 (m, 2H, H-5',6'), 7.64 (m, 1H, H-4'), 7.70 (m, 1H, H-7'), 8.28 (s, 1H, OH-4"), 10.34 (s, 1H, NH); EIMS *m/z* 518 [M+1]⁺ (20), 517 [M]⁺ (70), 419 (29), 391 (14), 350 (12), 266 (10), 216 (16), 215 (100), 133 (8), 118 (8); anal. C 67.42; H 6.87; N 13.41; calcd for C₂₉H₃₅N₅O₄, C 67.29; H 6.82; N 13.53.

1-{1-[2-(3-But-3-yn-1-yl-3H-diaziren-3-yl)ethyl]-1H-benzimidazol-2-yl}-4-(4-hydroxy-3,5-dimethoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (1Ijz).



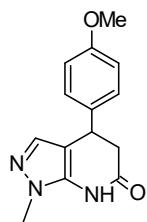
Oil, yield 50%; HRMS C₂₉H₂₉N₇O₄, for [M+H] calcd 540.2354; found 540.2351; for [M+Na] calcd 562.2173; found 562.2168.

4-(4-Hydroxy-3,5-dimethoxyphenyl)-1,3-dimethyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (12j).



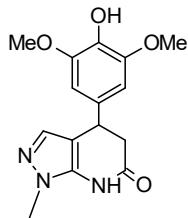
White crystals, yield 51%; mp 223–224 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ 1.75 (s, 3H, CH₃), 2.62 (dd, *J* = 6.4 Hz, *J* = 15.9 Hz, 1H, CH₂), 2.78 (dd, *J* = 7.0 Hz, *J* = 15.9 Hz, 1H, CH₂), 3.59 (s, 3H, NCH₃), 3.69 (s, 6H, OCH₃-3',5'), 4.01 (dd, *J* = 6.4 Hz, *J* = 7.0 Hz, 1H, CH), 6.42 (s, 2H, H-2',6'), 8.20 (s, 1H, OH-4'), 10.65 (s, 1H, NH); EIMS *m/z* 318 [M+1]⁺ (13), 317 [M]⁺ (67), 302 (11), 286 (14), 274 (25), 165 (10), 164 (100), 146 (10), 135 (12), 112 (21), 111 (25), 105 (11), 93 (20), 77 (34); anal. C 60.63; H 6.07; N 13.17; calcd for C₁₆H₁₉N₃O₄, C 60.56; H 6.03; N 13.24.

4-(4-Methoxyphenyl)-1-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (13b).



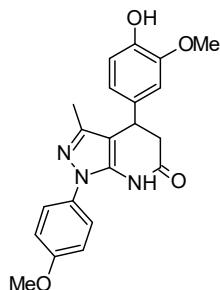
White crystals, yield 47%; mp 187–189 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ 2.57 (dd, *J* = 7.3 Hz, *J* = 15.8 Hz, 1H, CH₂), 2.77 (dd, *J* = 6.7 Hz, *J* = 15.8 Hz, 1H, CH₂), 3.67 (s, 3H, NCH₃), 3.72 (s, 3H, OCH₃-4'), 4.13 (dd, *J* = 6.7 Hz, *J* = 7.3 Hz, 1H, CH), 6.87 (d, *J* = 8.6 Hz, 2H, H-3',5'), 6.96 (s, 1H, H-C=N), 7.11 (d, *J* = 8.6 Hz, 2H, H-2',6'), 10.73 (s, 1H, NH); EIMS *m/z* 258 [M+1]⁺ (15), 257 [M]⁺ (100), 256 (43), 242 (7), 229 (10), 226 (33), 214 (76), 150 (26), 77 (9); anal. C 64.43; H 5.92; N 16.27; calcd for C₁₄H₁₅N₃O₂, C 65.36; H 5.88; N 16.33.

*4-(4-Hydroxy-3,5-dimethoxyphenyl)-1-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*b*]pyridin-6-one (13j).*



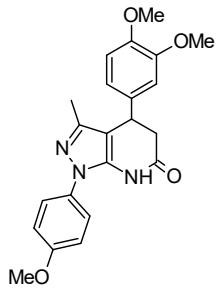
White crystals, yield 55%; mp 215–216 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 2.62 (dd, *J* = 8.6 Hz, *J* = 15.7 Hz, 1H, CH₂), 2.71 (dd, *J* = 6.5 Hz, *J* = 15.7 Hz, 1H, CH₂), 3.67 (s, 3H, NCH₃), 3.70 (s, 6H, OCH₃-3',5'), 4.07 (dd, *J* = 6.5 Hz, *J* = 8.6 Hz, 1H, CH), 6.48 (s, 2H, H-2',6'), 6.99 (s, 1H, H-C=N), 8.17 (s, 1H, OH-4'), 10.71 (s, 1H, NH); EIMS *m/z* 304 [M+1]⁺ (13), 303 [M]⁺ (76), 302 (14), 288 (9), 286 (8), 272 (52), 260 (27), 230 (12), 228 (10), 150 (57), 132 (12), 121 (16), 105 (15), 98 (30), 77 (35), 44 (65), 43 (100); anal. C 59.48; H 5.68; N 13.80; calcd for C₁₅H₁₇N₃O₄, C 59.40; H 5.65; N 13.85.

*4-(4-Hydroxy-3-methoxyphenyl)-1-(4-methoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*b*]pyridin-6-one (14d).*



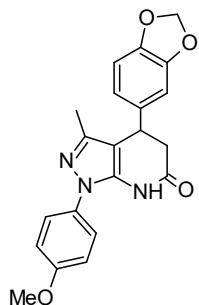
White crystals, yield 62%; mp 201–203 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 1.87 (s, 3H, CH₃), 2.64 (dd, *J* = 5.0 Hz, *J* = 15.7 Hz, 1H, CH₂), 2.91 (dd, *J* = 7.0 Hz, *J* = 15.7 Hz, 1H, CH₂), 3.73 (s, 3H, OCH₃-3''), 3.79 (s, 3H, OCH₃-4'), 4.10 (dd, *J* = 5.0 Hz, *J* = 7.0 Hz, 1H, CH), 6.52 (d, *J* = 7.8 Hz, 1H, H-5''), 6.69 (d, *J* = 7.8 Hz, 1H, H-6''), 6.81 (s, 1H, H-2''), 7.02 (d, *J* = 8.5 Hz, 2H, H-3',5'), 7.40 (d, *J* = 8.5 Hz, 2H, H-2',6'), 8.84 (s, 1H, OH-4''), 10.38 (s, 1H, NH); EIMS *m/z* 380 [M+1]⁺ (23), 379 [M]⁺ (100), 364 (10), 336 (21), 256 (60), 230 (40), 148 (24), 133 (12), 131 (12), 122 (22), 121 (17), 108 (22), 107 (22), 92 (46), 90 (13), 77 (75); anal. C 66.56; H 5.62; N 10.96; calcd for C₂₁H₂₁N₃O₄, C 66.48; H 5.58; N 11.07.

*4-(3,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*b*]pyridin-6-one (14f).*



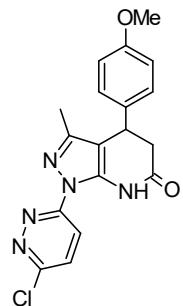
White crystals, yield 69%; mp 176–177 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 1.88 (s, 3H, CH₃), 2.66 (dd, *J* = 4.7 Hz, *J* = 15.7 Hz, 1H, CH₂), 2.93 (dd, *J* = 6.8 Hz, *J* = 15.7 Hz, 1H, CH₂), 3.71 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃-4'), 4.14 (dd, *J* = 4.7 Hz, *J* = 6.8 Hz, 1H, CH), 6.64 (m, 1H, H-5''), 6.87 (m, 2H, H-2'',6''), 7.02 (d, *J* = 8.4 Hz, 2H, H-3',5'), 7.41 (d, *J* = 8.4 Hz, 2H, H-2',6'), 10.38 (s, 1H, NH); EIMS *m/z* 394 [M+1]⁺ (26), 393 [M]⁺ (100), 362 (12), 350 (18), 256 (41), 244 (21), 148 (22), 133 (13), 122 (25), 121 (20), 108 (21), 107 (22), 105 (11), 92 (33), 77 (52); anal. C 67.21; H 5.92; N 10.60; calcd for C₂₂H₂₃N₃O₄, C 67.16; H 5.89; N 10.68.

4-(1,3-Benzodioxol-5-yl)-1-(4-methoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (14g).



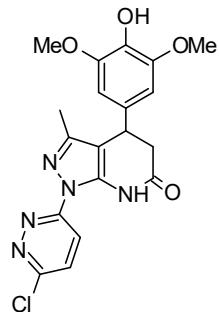
White crystals, yield 73%; mp 147–149 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 1.88 (s, 3H, CH₃), 2.59 (dd, *J* = 4.0 Hz, *J* = 15.5 Hz, 1H, CH₂), 2.95 (dd, *J* = 7.0 Hz, *J* = 15.5 Hz, 1H, CH₂), 3.79 (s, 3H, OCH₃-4'), 4.13 (dd, *J* = 4.0 Hz, *J* = 7.0 Hz, 1H, CH), 5.98 (s, 2H, OCH₂O), 6.63 (d, *J* = 7.7 Hz, 1H, H-7''), 6.76 (s, 1H, H-4''), 6.84 (d, *J* = 7.7 Hz, 1H, H-6''), 7.02 (d, *J* = 8.4 Hz, 2H, H-3',5'), 7.41 (d, *J* = 8.4 Hz, 2H, H-2',6'), 10.40 (s, 1H, NH); EIMS *m/z* 378 [M+1]⁺ (21), 377 [M]⁺ (100), 334 (20), 256 (38), 228 (18), 108 (5), 77 (12); anal. C 66.97; H 5.11; N 11.01; calcd for C₂₁H₁₉N₃O₄, C 66.83; H 5.07; N 11.13.

1-(6-Chloropyridazin-3-yl)-4-(4-methoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (15b).



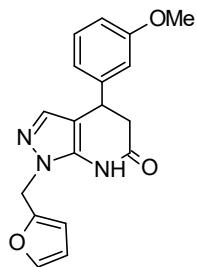
White crystals, yield 47%; mp 136–137 °C; ^1H NMR (DMSO- d_6 , 500 MHz) δ 1.92 (s, 3H, CH₃), 2.69 (dd, J = 4.9 Hz, J = 16.2 Hz, 1H, CH₂), 3.07 (dd, J = 7.6 Hz, J = 16.2 Hz, 1H, CH₂), 3.73 (s, 3H, OCH₃-4''), 4.25 (dd, J = 4.9 Hz, J = 7.6 Hz, 1H, CH), 6.89 (d, J = 8.4 Hz, 2H, H-3'',5''), 7.15 (d, J = 8.4 Hz, 2H, H-2'',6''), 8.07 (d, J = 9.3 Hz, 1H, H_{Het}), 8.15 (d, J = 9.3 Hz, 1H, H_{Het}), 10.01 (s, 1H, NH); EIMS m/z 371 [M+2]⁺ (17), 369 [M]⁺ (51), 262 (10), 222 (10), 148 (100), 121 (11), 77 (9); anal. C 58.33 H 4.31; N 19.09; calcd for C₁₈H₁₆ClN₅O₂, C 58.46; H 4.36; N 18.94.

I-(6-Chloropyridazin-3-yl)-4-(4-hydroxy-3,5-dimethoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (15j).



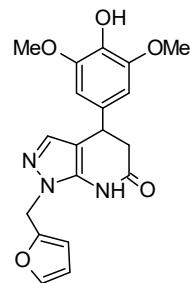
White crystals, yield 56%; mp 209–210 °C; ^1H NMR (DMSO- d_6 , 500 MHz) δ 1.91 (s, 3H, CH₃), 2.80 (dd, J = 6.5 Hz, J = 16.2 Hz, 1H, CH₂), 2.99 (dd, J = 7.4 Hz, J = 16.2 Hz, 1H, CH₂), 3.71 (s, 6H, OCH₃-3'',5''), 4.19 (dd, J = 6.5 Hz, J = 7.4 Hz, 1H, CH), 6.51 (s, 2H, H-2'',6''), 8.05 (d, J = 9.3 Hz, 1H, H_{Het}), 8.15 (d, J = 9.3 Hz, 1H, H_{Het}), 8.26 (s, 1H, OH-4''), 9.98 (s, 1H, NH); EIMS m/z 417 [M+2]⁺ (2), 415 [M]⁺ (6), 262 (25), 224 (21), 222 (70), 194 (48), 167 (32), 156 (15), 154 (15), 130 (18), 116 (16), 115 (26), 113 (26), 79 (100), 77 (56); anal. C 54.96; H 4.39; N 16.76; calcd for C₁₉H₁₈ClN₅O₄, C 54.88; H 4.36; N 16.84.

I-(2-Furylmethyl)-4-(3-methoxyphenyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-b]pyridin-6-one (16c).



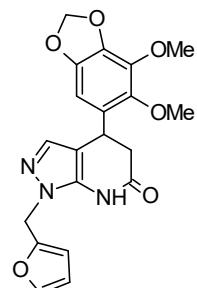
White crystals, yield 43%; mp 110–111 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ 2.61 (dd, *J* = 6.9 Hz, *J* = 16.0 Hz, 1H, CH₂), 2.85 (dd, *J* = 7.0 Hz, *J* = 16.0 Hz, 1H, CH₂), 3.71 (s, 3H, OCH₃-3''), 4.18 (dd, *J* = 6.9 Hz, *J* = 7.0 Hz, 1H, CH), 5.25 (d, *J* = 16.0 Hz, 1H, NCH₂), 5.29 (d, *J* = 16.0 Hz, 1H, NCH₂), 6.36 (m, 1H, H-3'), 6.41 (m, 1H, H-4'), 6.78 (m, 3H, H-2'',4'',6''), 7.05 (s, 1H, H-5'), 7.22 (m, 1H, H-5''), 7.61 (s, 1H, H-C≡N), 10.91 (s, 1H, NH); EIMS *m/z* 324 [M+1]⁺ (3), 323 [M]⁺ (13), 81 (100), 53 (37); anal. C 66.92; H 5.33; N 12.95; calcd for C₁₈H₁₇N₃O₃, C 66.86; H 5.30; N 13.00.

I-(2-Furylmethyl)-4-(4-hydroxy-3,5-dimethoxyphenyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*b*]pyridin-6-one (**16j**).



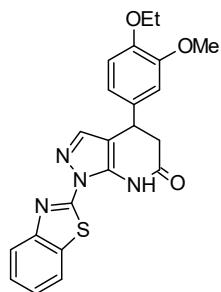
White crystals, yield 51%; mp 158–160 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ 2.64 (dd, *J* = 8.0 Hz, *J* = 15.9 Hz, 1H, CH₂), 2.76 (dd, *J* = 6.7 Hz, *J* = 15.9 Hz, 1H, CH₂), 3.69 (s, 6H, OCH₃-3'',5''), 4.09 (dd, *J* = 6.7 Hz, *J* = 8.0 Hz, 1H, CH), 5.27 (s, 2H, NCH₂), 6.36 (m, 1H, H-3'), 6.40 (m, 1H, H-4'), 6.45 (s, 2H, H-2'',6''), 7.05 (s, 1H, H-5'), 7.60 (s, 1H, H-C≡N), 8.19 (s, 1H, OH-4''), 10.88 (s, 1H, NH); EIMS *m/z* 369 [M]⁺ (1), 81 (100), 53 (55); anal. C 61.85; H 5.21; N 11.32; calcd for C₁₉H₁₉N₃O₅, C 61.78; H 5.18; N 11.38.

4-(6,7-Dimethoxy-1,3-benzodioxol-5-yl)-1-(2-furylmethyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*b*]pyridin-6-one (**16o**).



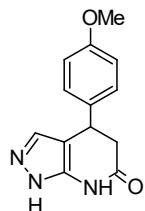
White crystals, yield 63%; mp 182–183 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 2.49 (dd, *J* = 6.7 Hz, *J* = 16.1 Hz, 1H, CH₂), 2.78 (dd, *J* = 7.3 Hz, *J* = 16.1 Hz, 1H, CH₂), 3.68 (s, 3H, OCH₃-2'), 3.93 (s, 3H, OCH₃-3'), 4.35 (dd, *J* = 6.7 Hz, *J* = 7.3 Hz, 1H, CH), 5.24 (d, *J* = 15.9 Hz, 1H, NCH₂), 5.29 (d, *J* = 15.9 Hz, 1H, NCH₂), 5.93 (d, *J* = 0.9 Hz, 1H, OCH₂O), 5.94 (d, *J* = 0.9 Hz, 1H, OCH₂O), 6.21 (s, 1H, H-6'), 6.37 (m, 1H, H-3"), 6.41 (m, 1H, H-4"), 6.99 (s, 1H, H-5"), 7.60 (s, 1H, H-C=N), 10.89 (s, 1H, NH); EIMS *m/z* 398 [M+1]⁺ (4), 397 [M]⁺ (20), 316 (9), 81 (100); anal. C 60.58; H .84; N 10.48; calcd for C₂₀H₁₉N₃O₆, C 60.45; H 4.84; N 10.57.

*I-(1,3-Benzothiazol-2-yl)-4-(4-ethoxy-3-methoxyphenyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*b*]pyridin-6-one (17v).*



White crystals, yield 82%; mp 168–169 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 1.30 (t, *J* = 7.1 Hz, 3H, CH₃), 2.85 (m, 1H, CH₂), 2.96 (m, 1H, CH₂), 3.74 (s, 3H, OCH₃-3"), 3.97 (m, 2H, OCH₂-4"), 4.29 (m, 1H, CH), 6.74 (m, 1H, H-5"), 6.88 (m, 1H, H-6"), 6.93 (s, 1H, H-2"), 7.42 (m, 2H, H-5',6'), 7.53 (s, 1H, H-C=N), 8.01 (m, 1H, H-4'), 8.09 (m, 1H, H-7'), 10.02 (s, 1H, NH); EIMS *m/z* 421 [M+1]⁺ (20), 420 [M]⁺ (75), 389 (12), 375 (13), 269 (13), 229 (11), 192 (100), 164 (18), 163 (15), 151 (17), 150 (30), 149 (28), 136 (27), 135 (48), 134 (46), 109 (22), 108 (33), 105 (15), 91 (13), 90 (17), 77 (20); anal. C 62.91; H 4.82; N 13.23; calcd for C₂₂H₂₀N₄O₃S, C 62.84; H 4.79; N 13.32.

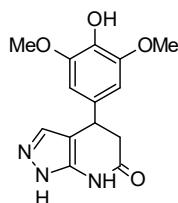
*4-(4-Methoxyphenyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*b*]pyridin-6-one (18b).*



White crystals, yield 65%; mp 248–250 °C; ^1H NMR (DMSO-*d*₆, 500 MHz) δ 2.55 (dd, *J* = 7.8 Hz, *J* = 15.7 Hz, 1H, CH₂), 2.69 (dd, *J* = 6.5 Hz, *J* = 15.7 Hz, 1H, CH₂), 3.71 (s, 3H, OCH₃-4'), 4.15 (dd, *J* = 6.5 Hz, *J* = 7.8 Hz, 1H, CH), 6.87 (d, *J* = 8.6 Hz, 2H, H-3',5), 7.13 (d, *J* = 8.6 Hz, 2H, H-2',6'), 7.25 (s, 1H,

H–C=N), 10.37 (s, 1H, CONH), 12.07 (s, 1H, NH); EIMS m/z 244 [M+1]⁺ (16), 243 [M]⁺ (100), 242 (30), 214 (14), 212 (37), 200 (31), 136 (15), 134 (13), 77 (9); anal. C 64.28; H 5.42; N 17.20; calcd for C₁₃H₁₃N₃O₂, C 64.19; H 5.39; N 17.27.

*4-(4-Hydroxy-3,5-dimethoxyphenyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*b*]pyridin-6-one (18j).*



White crystals, yield 53%; mp 230–234 °C; ¹H NMR (DMSO-*d*₆, 500 MHz) δ 2.63 (m, 2H, CH₂-5), 3.70 (s, 6H, OCH₃-3',5'), 4.09 (dd, *J* = 6.3 Hz, *J* = 7.6 Hz, 1H, CH), 6.50 (s, 2H, H-2',6'), 7.27 (s, 1H, H–C=N), 8.19 (s, 1H, OH-4'), 10.35 (s, 1H, CONH), 12.06 (s, 1H, NH); EIMS m/z 290 [M+1]⁺ (15), 289 [M]⁺ (100), 290 (15), 289 (100), 274 (5), 258 (24), 136 (13), 77 (8); anal. C 58.18; H 5.28; N 14.41; calcd for C₁₄H₁₅N₃O₄, C 58.13; H 5.23; N 14.53.

Table S1. Compound 11j Activity Against a Panel of Kinases

official full name	abbreviation	description	expression ^a	IC ₅₀ , μM
Receptor-type tyrosine-protein kinases				
Aurora kinase A	AURKA	Associates with mitotic spindle, regulates chromosome segregation.	NA	>10
Fibroblast growth factor receptor 2	FGFR2	Receptor for fibroblast growth factor.	NA	>10
Fibroblast growth factor receptor 4	FGFR4	Receptor for fibroblast growth factor.	NA	>10
Fms like tyrosine kinase 3	FLT3	Expressed on the surface of hematopoietic cells; involved in apoptosis, proliferation, and differentiation of hematopoietic cells in bone marrow.	NA	>10
Zeta chain of T cell receptor associated protein kinase 70	ZAP70	Cytoplasmic kinase, role in T-cell signaling.	2.70914	>10
Non-receptor tyrosine-protein kinases				
Abelson murine leukemia viral oncogene homolog 1	ABL1	Involved in regulation of actin polymerization and transcription.	NA	>10
Activin A receptor, type I	ACVR1	Mediates the TGF-β signaling.	-0.982145	>10
Bruton's tyrosine kinase	BTK	Role in B-lymphocyte development, differentiation, and signaling.	NA	>10
Janus kinase 2	JAK2	Involved in the JAK/STAT signaling pathway, especially important for hematopoiesis.	NA	>10
Lck/Yes novel tyrosine kinase, Src family tyrosine kinase	Lyn	Involved in diverse cellular signaling pathways.	-0.974616	>10
Serine/threonine-protein kinases				
Death-associated protein kinase 1	DAPK1	Apoptosis inducing activity.	NA	>10
Glycogen synthase kinase 3β	GSK3B	Negative regulator of glucose homeostasis, Wnt signaling, transcription factors and microtubules.	NA	>10
Interleukin-1 receptor-associated kinase 1	IRAK1	Involved in Toll-like receptor and interleukin-1 receptor signaling pathways.	-0.850127	>10
Interleukin-1 receptor-associated kinase 4	IRAK4		NA	>10
Mitogen-activated protein kinase kinase kinase 7	MAP3K7	Mediates TGF-β and BMP signaling.	NA	>10
Mitogen-activated protein kinase kinase kinase 4	MAP4K4	Activates MAPK8/JNK, mediates the TNF-α signaling.	NA	>10
Protein kinase Cα	PRKCA	Involved in diverse cellular signaling pathways.	NA	>10

Protein kinase C δ	PRKCQ	Expressed at high level in T-lymphocytes; involved in diverse cellular signaling pathways.	1.0326	>10
Serine/threonine-protein kinase 4	STK4	Cytoplasmic kinase, acts upstream of MAPK cascade.	NA	>10
Serine/threonine-protein kinase17A	STK17A	Apoptosis inducing activity.	NA	>10
Serine/threonine-protein kinase17B	STK17B	Apoptosis inducing activity.	NA	>10

^aStandardized value for MOLT-4, relative to other cell lines from the HPA Cell Line Gene Expression Profiles dataset.

(https://amp.pharm.mssm.edu/Harmonizome/gene_set/molt4/HPA%2BCell%2BLine%2BGene%2BExpression%2BProfiles)

Table S2. Effects of MMP Inhibitors on Sea Urchin Embryos

inhibitor	target	effective (threshold) concentration, μM		
		hatching inhibition	spicule alteration	spicule missing
GM6001	MMP-1,2,3,7,8,9,12,14,26	0.02	0.2	1
Marimastat	MMP-1,2,7,9,14	0.05	0.2	4
CTS-1027	MMP-2,13	1	4 (minor)	>4
T-5224	MMP-3,13	>4	>4	>4

Table S3. Phenotypic Responses of Sea Urchin Embryos to BIPP 11 and Different Standard Inhibitors Related to Regulation of Spicule Development^a

inhibitor	target	cleavage	hatching	PMC ^b ingression	spicules		other effects
					altered	missed	
BIPP 11	Unknown	-/+	+/-	-	+	+	NA ^c
AS703026	MEK1/2	-	-	+	+	+	Exogastrulation with archenteron differentiation
AZD8330		-	-	+	+	+	NA ^c
Binimetinib		-	-	+	+	+	Exogastrulation with archenteron differentiation
Cobimetinib		-	-	+	+	+	Exogastrulation with archenteron differentiation
GDC-0623		-	-	+	+	+	Exogastrulation with archenteron differentiation
PD184352		-	-	+	+	+	Exogastrulation with archenteron differentiation
PD318088		-	-	+	+	+	NA ^c
Refametinib		-	-	+	+	+	Exogastrulation with archenteron differentiation
RO4987655		-	-	+	+	+	Exogastrulation with archenteron differentiation
Selumetinib		-	-	+	+	+	NA ^c
TAK-733		-	-	+	+	+	Exogastrulation with archenteron differentiation
Trametinib		-	-	+	+	+	Exogastrulation with archenteron differentiation
FR 180204	ERK1/2	-	-	+	+	+	NA ^c
GDC-0994		-	-	+	+	+	NA ^c
SCH772984		-	-	+	+	+	NA ^c
Ulixertinib		+	-	+	+	+	NA ^c
VX-11e		-	-	+	+	+	Exogastrulation with archenteron differentiation
AZ628	RAF	-	-	+	+	+	Exogastrulation with archenteron differentiation
Dabrafenib		-	-	+	+	+	Embryo cilia immobilization
GDC-0879		-	-	+	+	+	Exogastrulation with archenteron differentiation
SB590885		-	+	-	+	+	NA ^c
TAK-632		-	-	-	+	+	NA ^c
PD173074	FGFR1/ VEGFR2	-	-	-	+	-	NA ^c
EW-7197	TGFβ/ALK5	-	-	-	+	+	Radialization, bell-shaped embryos
GW788388		-	-	-	+	-	Radialization, bell-shaped embryos
RepSox		-	-	-	+	-	Radialization, bell-shaped embryos
SB431542		-	-	-	+	-	Radialization, bell-shaped embryos
LY3200882	TGFβR type I	-	-	-	+	-	Radialization, bell-shaped embryos
ITD-1	TGFβR type II	-	-	-	-	-	NA ^c

LY3039478	Notch	-	-	-	+	-	Exogastrulation without gut differentiation; inhibition of secondary mesenchyme cells, coelomic pouches, and pigment cells formation
LY-411575	Notch/ γ -secretase	-	-	-	+	-	Exogastrulation without gut differentiation; inhibition of secondary mesenchyme cells, coelomic pouches, and pigment cells formation
Semagacestat		-	-	-	+	-	Inhibition of secondary mesenchyme cells, coelomic pouches, and pigment cells formation
Murrayafoline A	Wnt/ β -catenin degradation	+	-	-	NA ^c	NA ^c	Low microtubule destabilizing activity, toxicity
IWR-1-endo	Wnt/ β -catenin	-	-	-	+	-	NA ^c
XAV-939	Wnt/ β -catenin/ Tankyrase1/2	-	-	-	+	-	NA ^c
IWP-2	Wnt processing and secretion	-	-	-	+	-	NA ^c
LGK-974	Wnt/PORCN	+	-	-	+	-	NA ^c
Wnt-C59		+	-	-	+	-	NA ^c
NCB-0846	Wnt/TNIK	+	+	-	+	NA ^c	Toxicity, embryo mortality
BML-284	Wnt activator	+	-	-	+	NA ^c	Microtubule destabilizing activity

^a Inhibitors were added to zygotes at 8–18 min postfertilization. Embryo development was monitored up to four-arm mid-pluteus stage.

Maximum tested concentration was 4 μ M. '+' - effect was observed; '−' - no effect. ^b PMC: primary mesenchyme cells. ^c NA: not available.

Table S4. Leukemia Cell Lines

cell line	origin	source	cell culture medium
SUP-T11	T-ALL ^a	DSMZ ACC 605	90% RPMI 1640 + 10% h.i. FBS
LOUCY	T-ALL ^a	ATCC® CRL-2629™	90% RPMI 1640 + 10% h.i. FBS
Jeko-1	B-cell lymphoma	DSMZ ACC 553	80% RPMI 1640 + 20% h.i. FBS
Mino	B-cell lymphoma	ATCC® CRL-3000™	85% RPMI 1640 + 15% h.i. FBS
MOLT-16	T-ALL ^a	DSMZ ACC 29	80–90% RPMI 1640 + 10–20% h.i. FBS
HL-60	Promyelocytic leukemia	ATCC® CCL-240™	80% RPMI 1640 + 20% h.i. FBS
Jurkat	T-ALL ^a	DSMZ ACC 282	90% RPMI 1640 + 10% h.i. FBS
MOLT-4	T-ALL ^a	ATCC® CRL-1582™	90% RPMI 1640 + 10% h.i. FBS
HPB-ALL	T-ALL ^a	DSMZ ACC 483	80–90% RPMI 1640 + 10–20% h.i. FBS
RPMI-8402	T-ALL ^a	DSMZ ACC 290	90% RPMI 1640 + 10% h.i. FBS
Rec-1	B-cell lymphoma	ATCC® CRL-3004™	90% RPMI 1640 + 10% h.i. FBS

^aT-ALL: T-cell acute lymphoblastic leukemia

All Cell Lines

11b

Molt-4

Percentage Growth

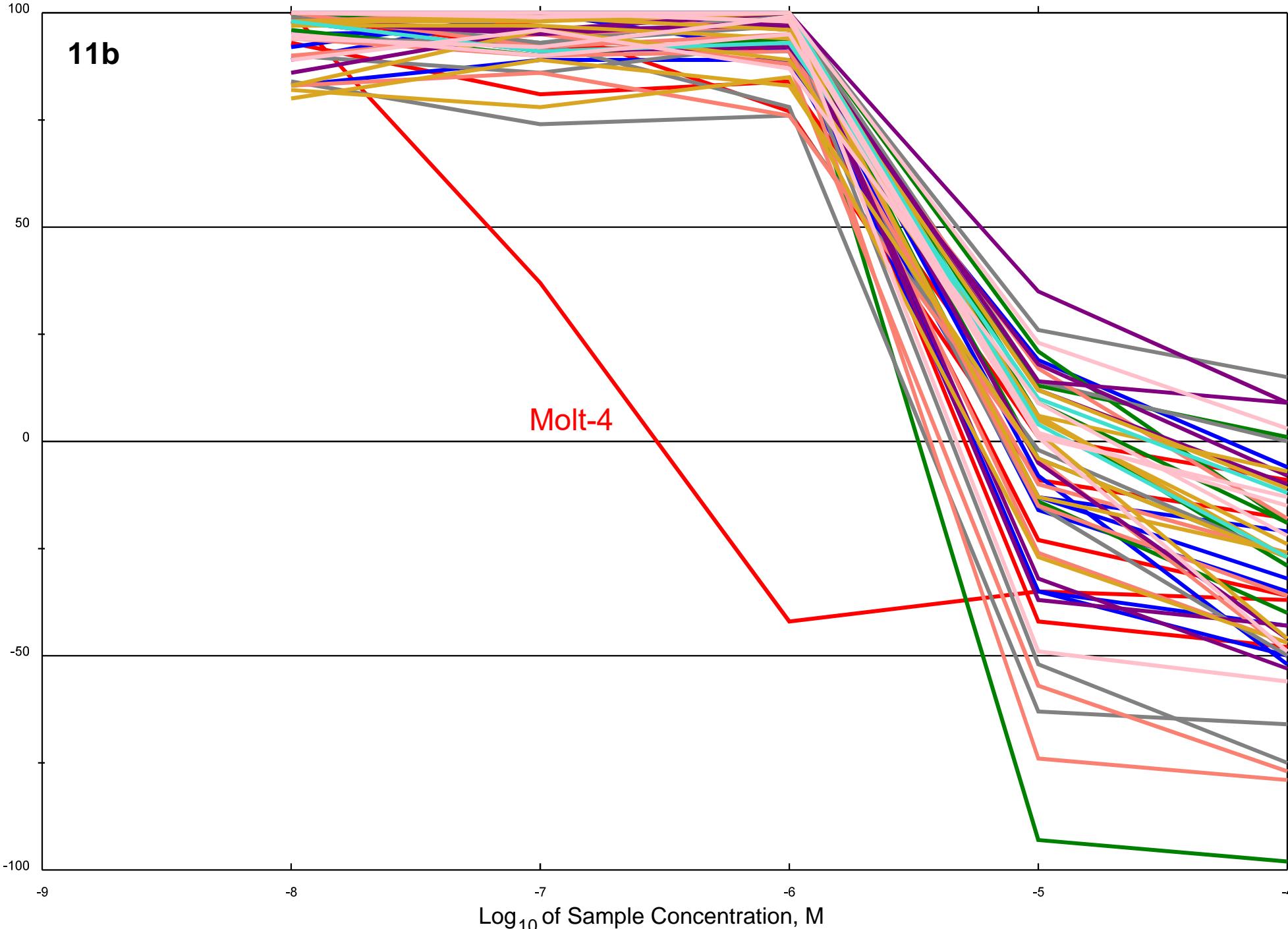


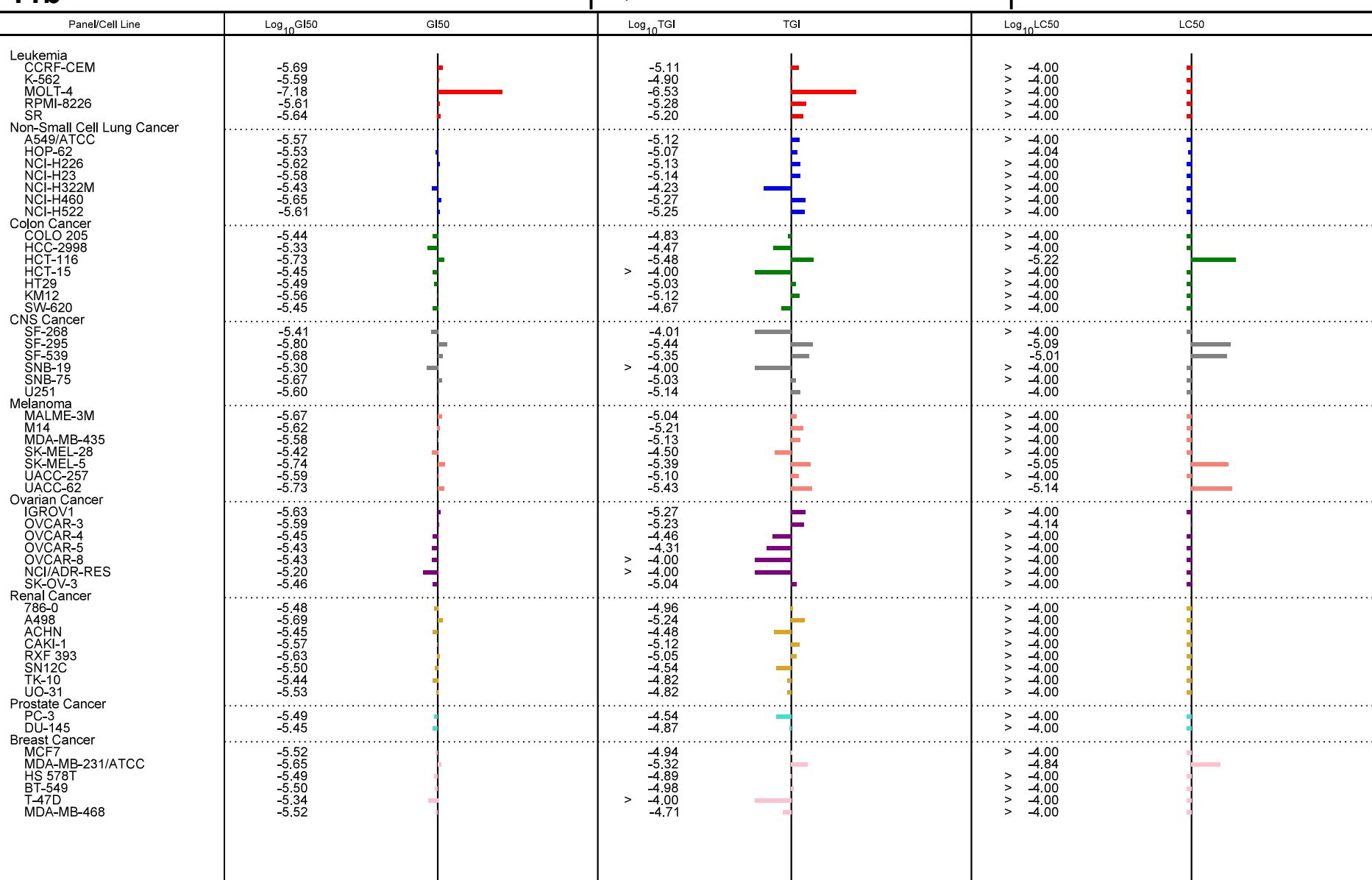
Figure S1. Dose-response curves for compound 11b.

11b

Mean Graphs

Report Date :November 27, 2013

Test Date :March 18, 2013

**Figure S2. Mean graphs for compound 11b.**_MID
Delta
Range-5.57
1.61
1.98

+3 +2 +1 0 -1 -2 -3

-4.91
1.62
2.53

+3 +2 +1 0 -1 -2 -3

-4.12
1.1
1.22

+3 +2 +1 0 -1 -2 -3

All Cell Lines

11f

Molt-4

Percentage Growth

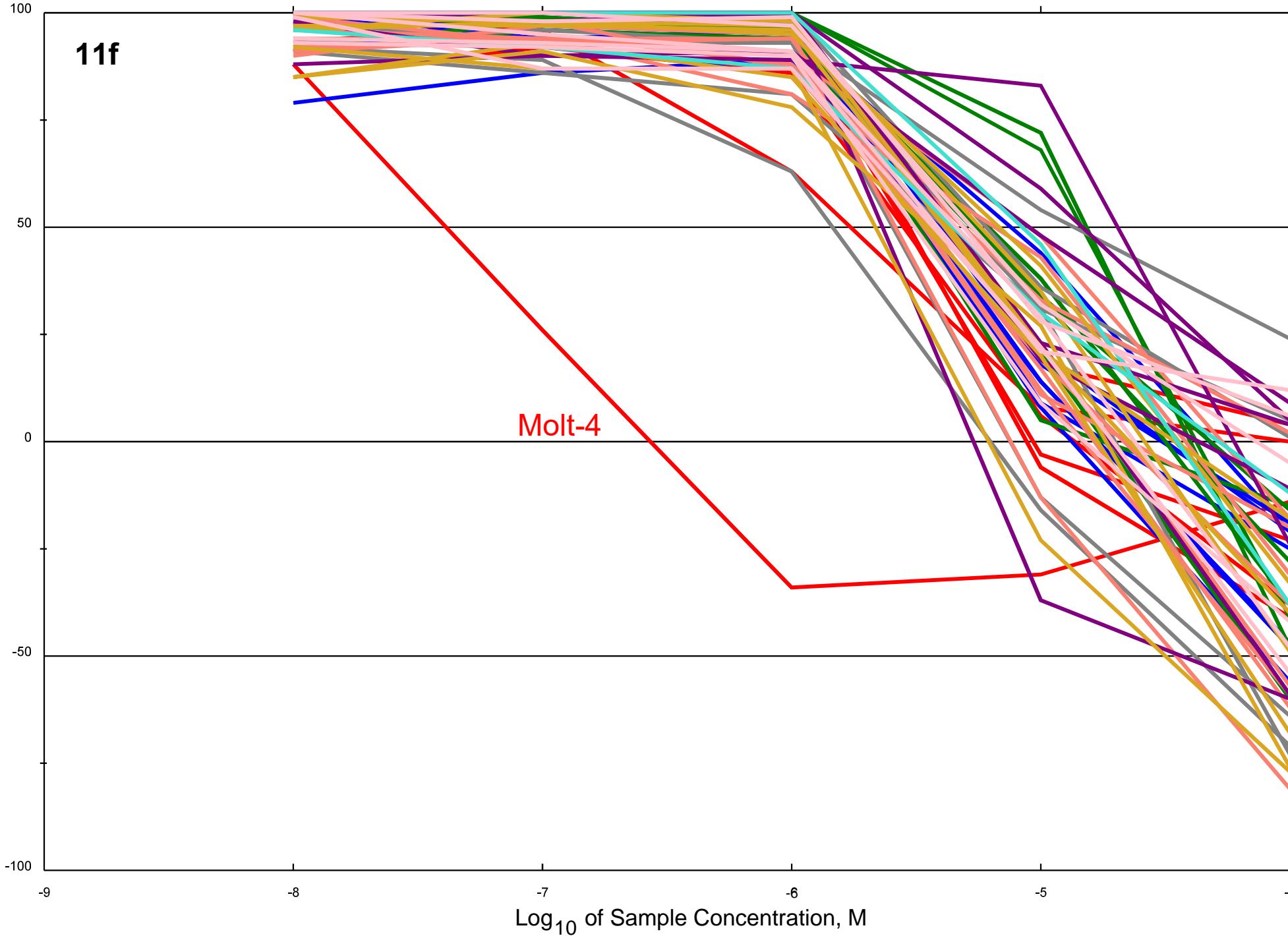


Figure S3. Dose-response curves for compound 11f.

11f

Mean Graphs

Report Date :June 28, 2017

Test Date :March 25, 2013

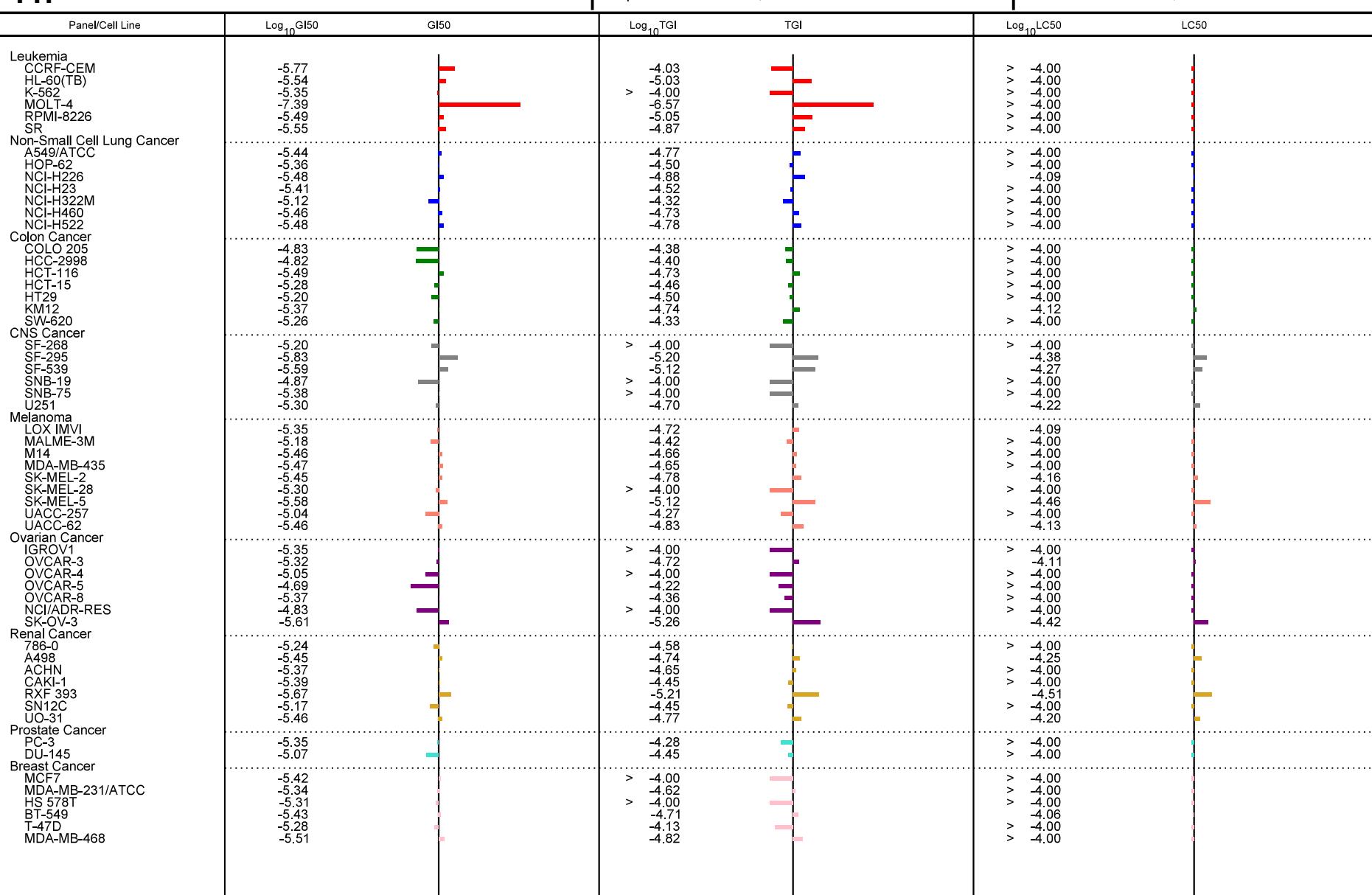


Figure S4. Mean graphs for compound 11f.

MID
Delta
Range-5.37
2.02
2.7

+3 +2 +1 0 -1 -2 -3

-4.57
2
2.57

+3 +2 +1 0 -1 -2 -3

-4.06
0.45
0.51

+3 +2 +1 0 -1 -2 -3

All Cell Lines

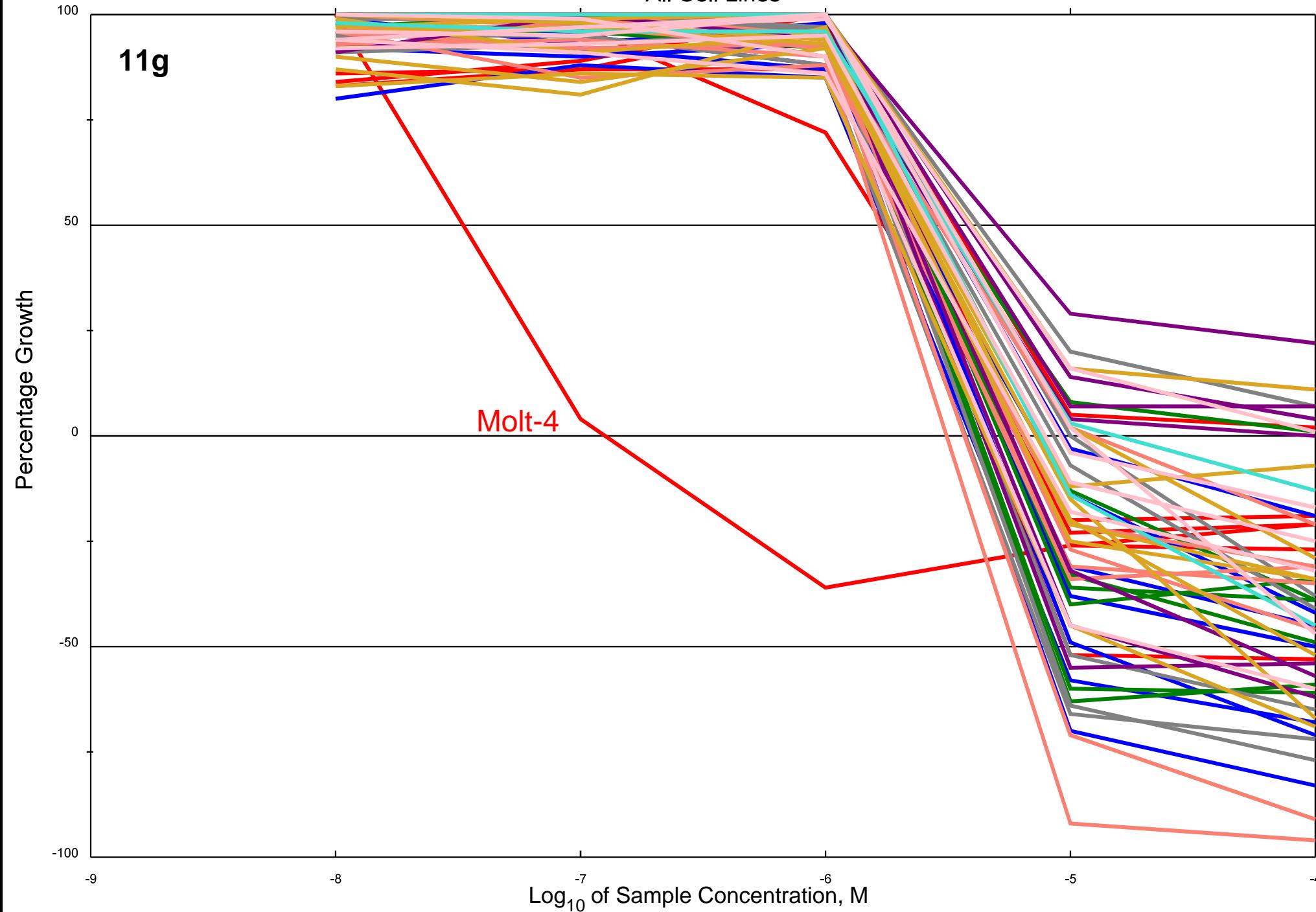


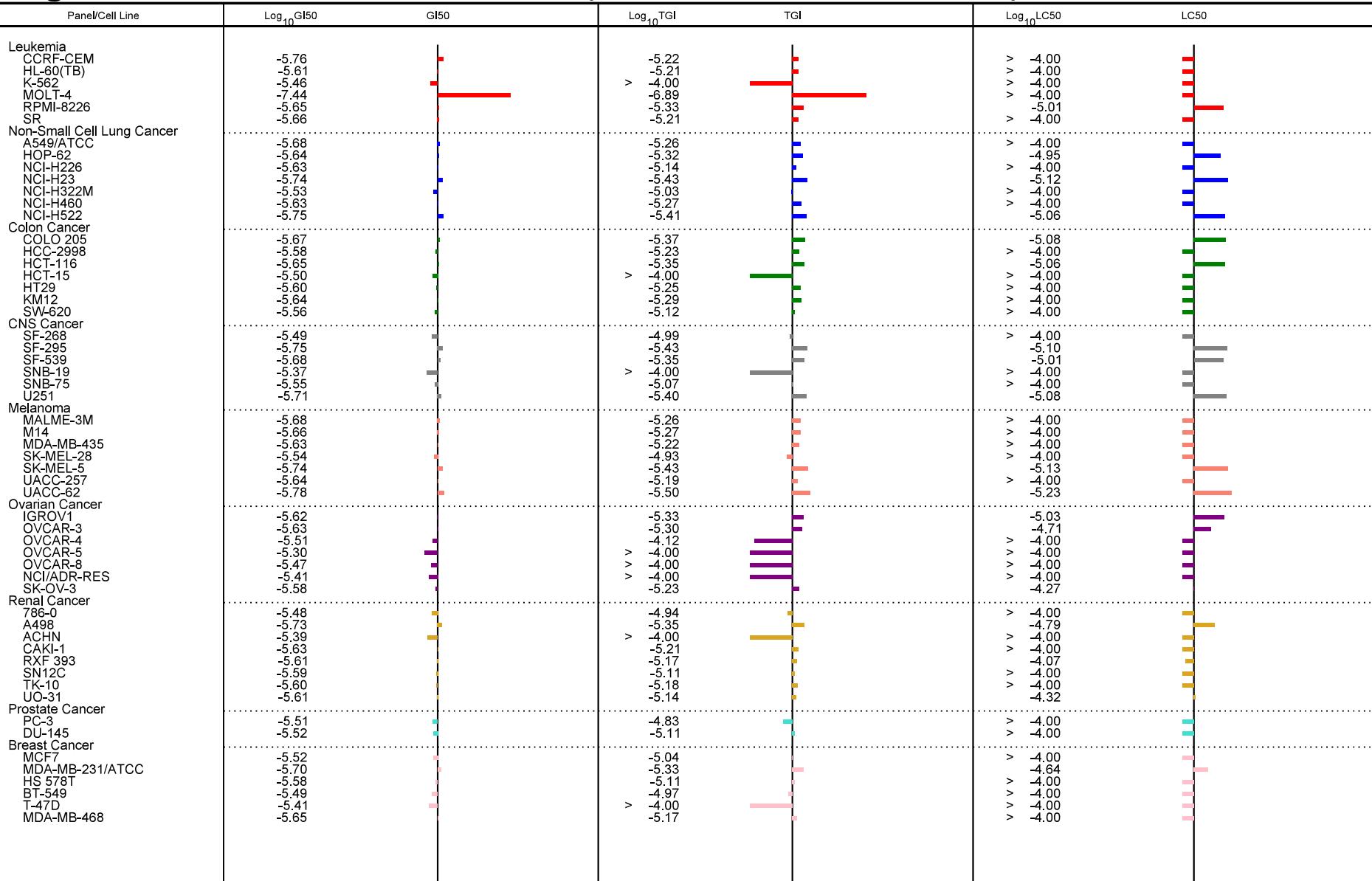
Figure S5. Dose-response curves for compound 11g.

11g

Mean Graphs

Report Date :June 27, 2017

Test Date :March 18, 2013

**Figure S6. Mean graphs for compound 11g.**

MID
Delta
Range

-5.63
1.81
2.14

+3 +2 +1 0 -1 -2 -3

-5.05
1.84
2.89

+3 +2 +1 0 -1 -2 -3

-4.28
0.95
1.23

+3 +2 +1 0 -1 -2 -3

All Cell Lines

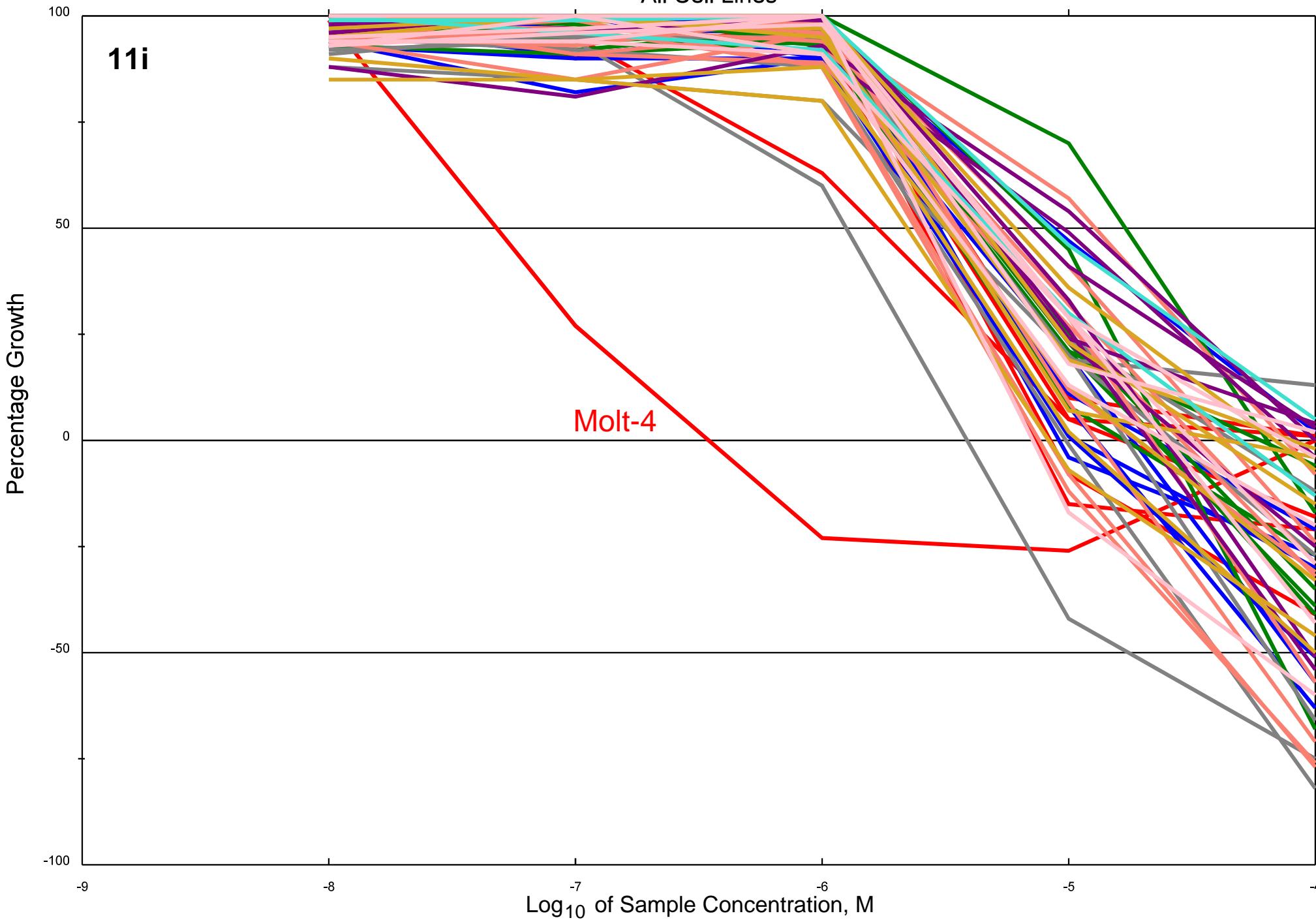


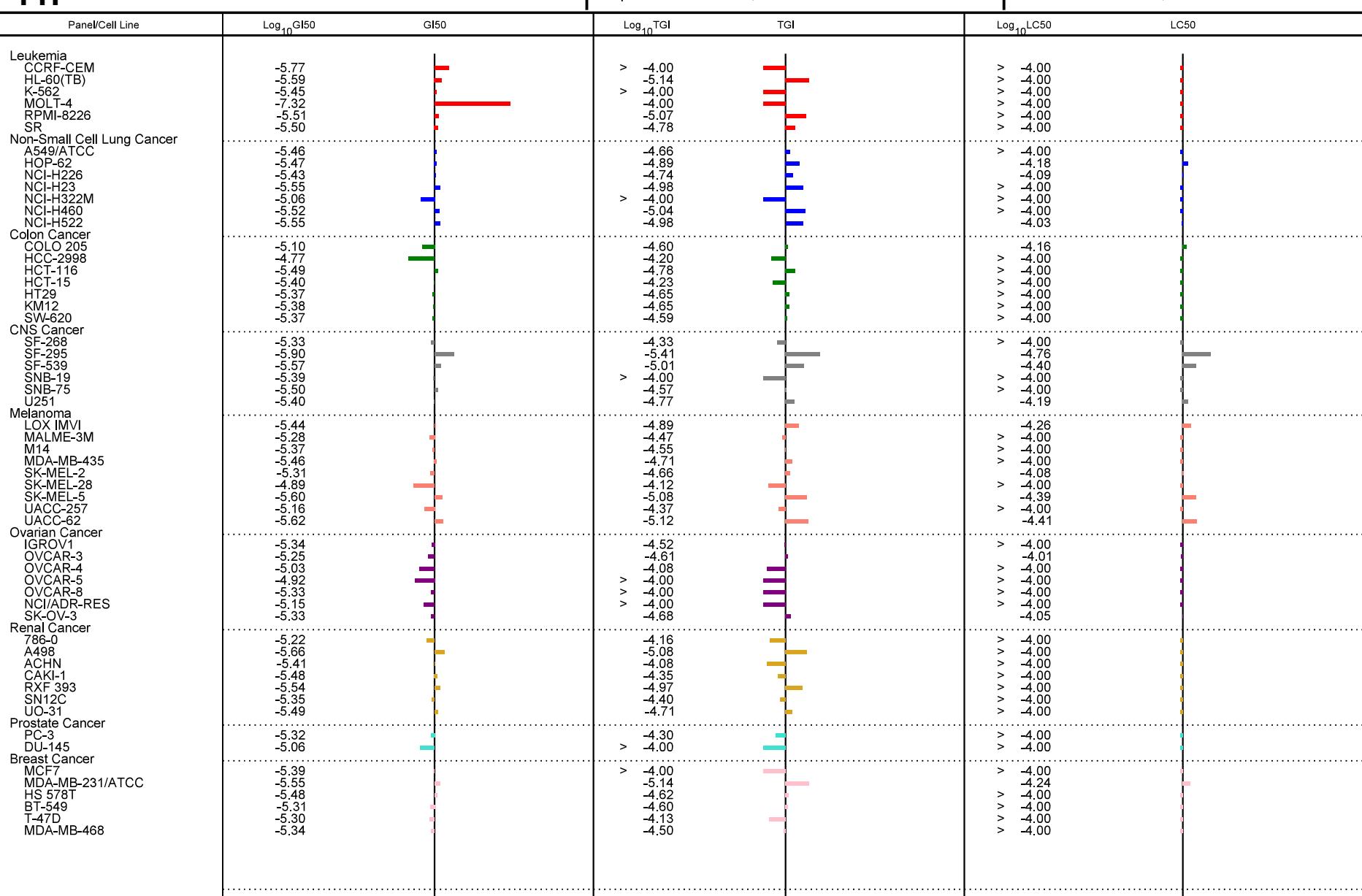
Figure S7. Dose-response curves for compound 11i.

11i

Mean Graphs

Report Date :June 27, 2017

Test Date :March 25, 2013

**Figure S8. Mean graphs for compound 11i.**MID
Delta
Range-5.41
1.91
2.55

+3 +2 +1 0 -1 -2 -3

-4.54
0.87
1.41

+3 +2 +1 0 -1 -2 -3

-4.06
0.7
0.76

+3 +2 +1 0 -1 -2 -3

All Cell Lines

11j

Molt-4

Percentage Growth

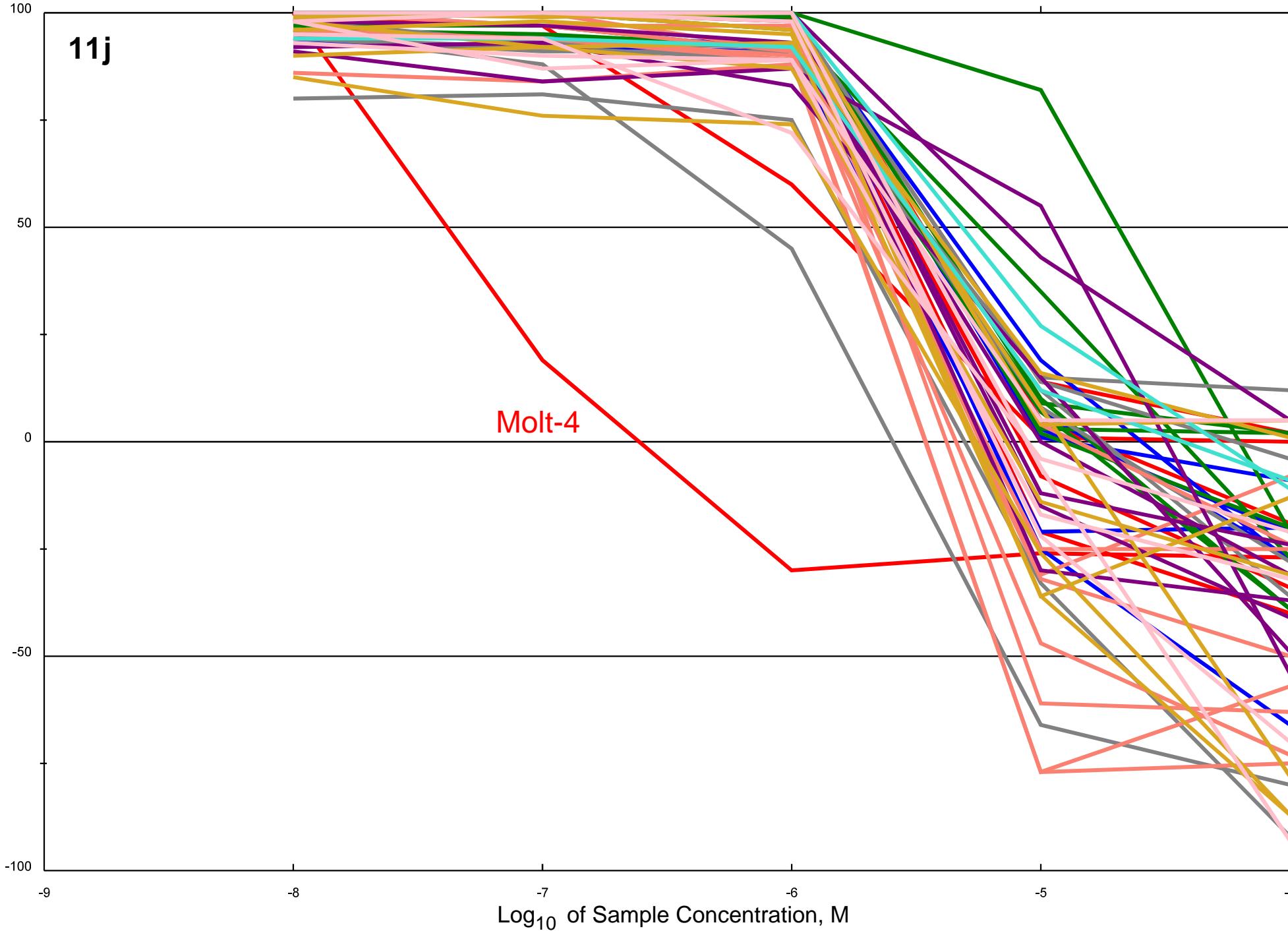


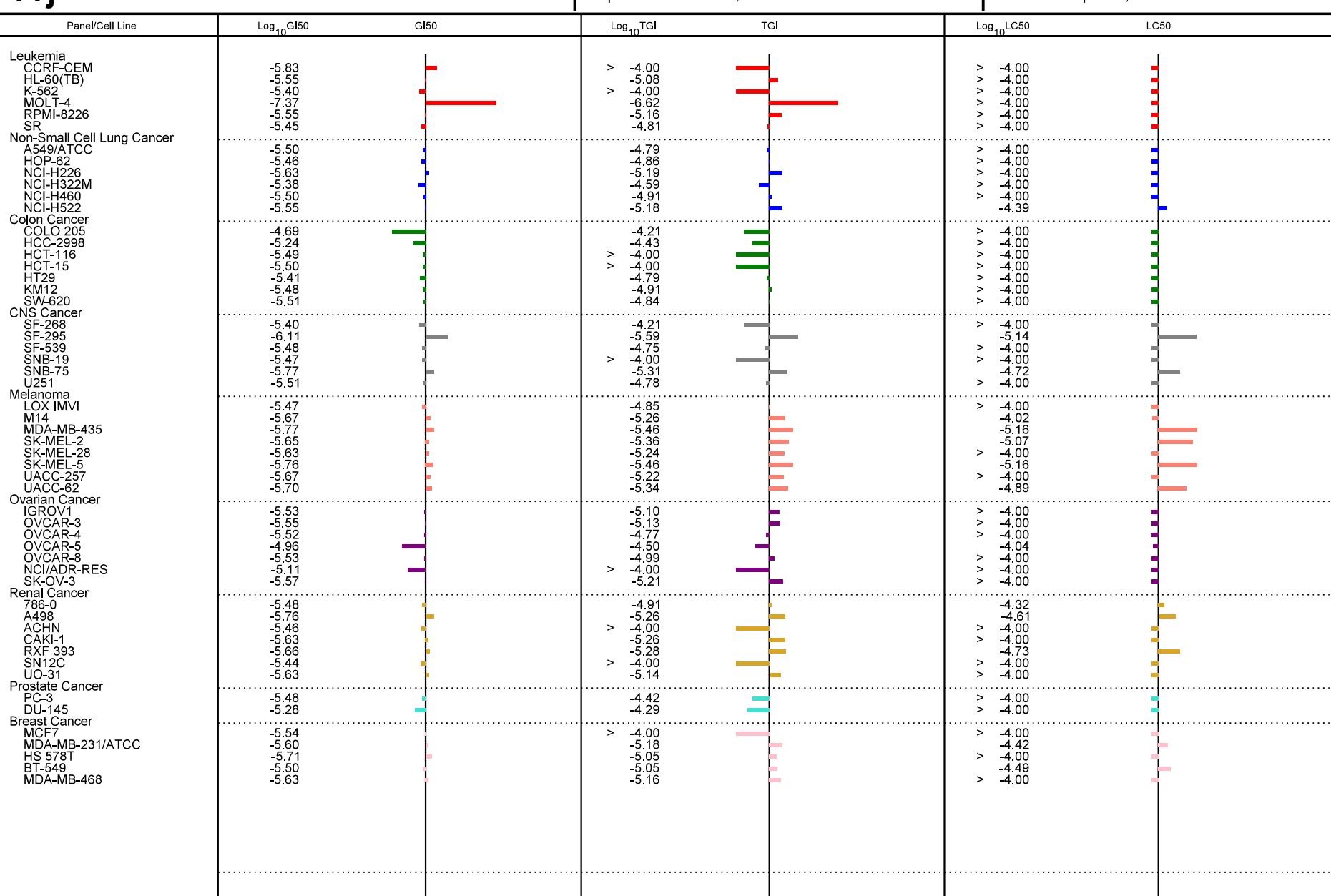
Figure S9. Dose-response curves for compound 11j.

11j

Mean Graphs

Report Date :June 27, 2017

Test Date :April 08, 2013

**Figure S10. Mean graphs for compound 11j.**

MID
Delta
Range

-5.56
1.81
2.68

+3 +2 +1 0 -1 -2 -3

-4.85
1.77
2.62

+3 +2 +1 0 -1 -2 -3

-4.17
0.99
1.16

+3 +2 +1 0 -1 -2 -3

11b One Dose Mean Graph

Experiment ID: 1211OS83

Report Date: Jan 17, 2018

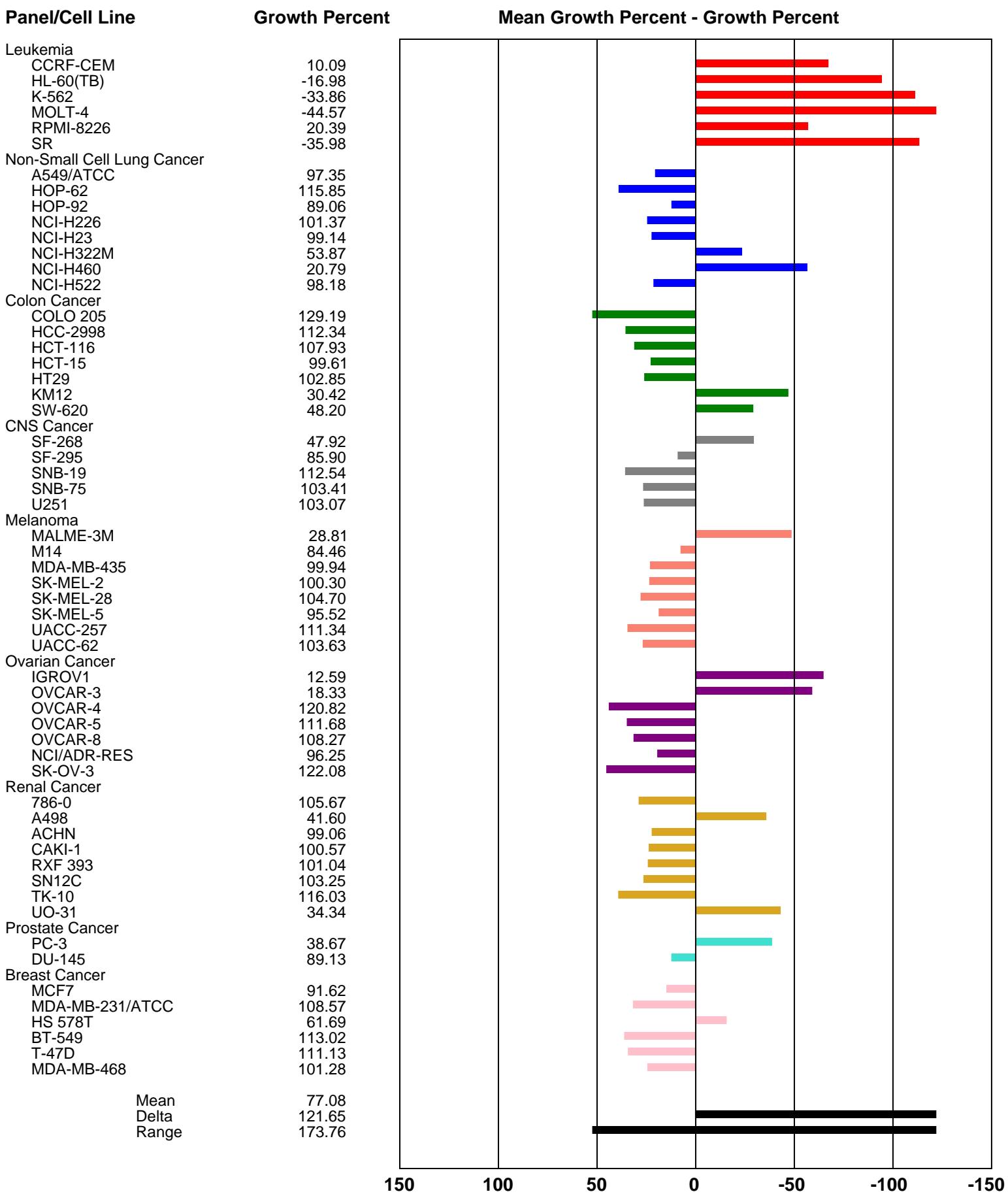


Figure S11. One-dose mean graph for compound 11b.

11f One Dose Mean Graph

Experiment ID: 1212OS84

Report Date: Jan 17, 2018

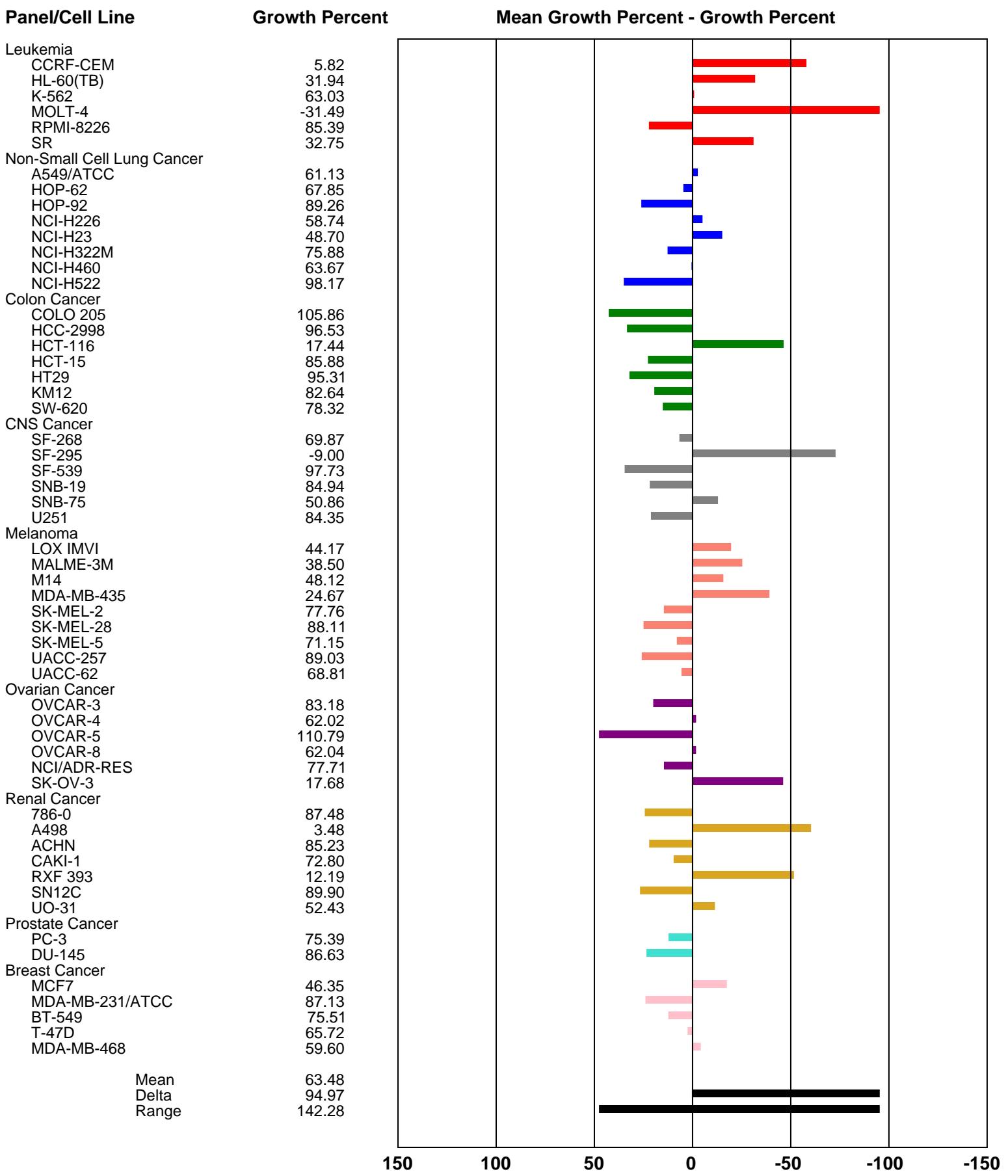


Figure S12. One-dose mean graph for compound 11f.

11g One Dose Mean Graph

Experiment ID: 1211OS83

Report Date: Jan 17, 2018

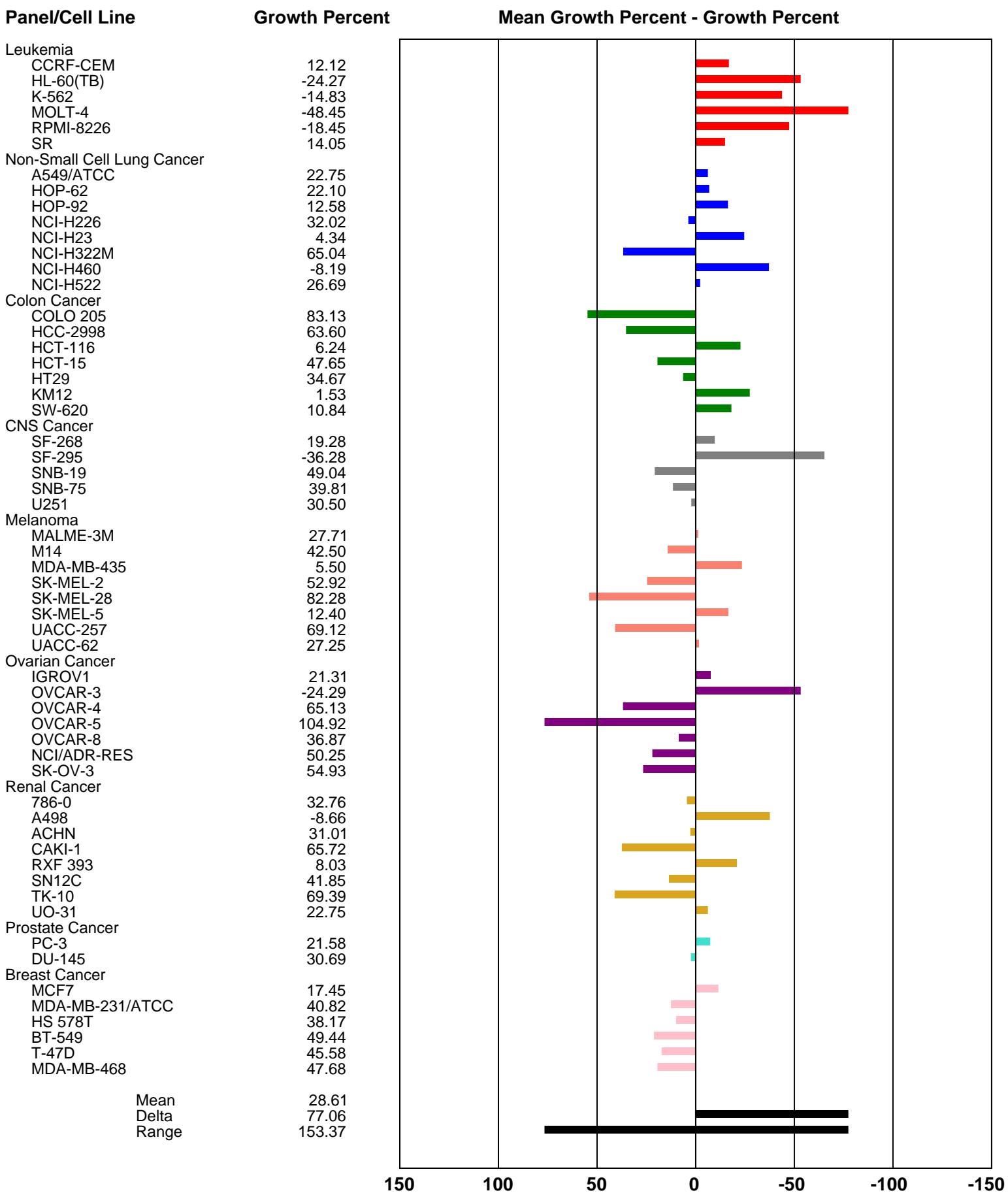


Figure S13. One-dose mean graph for compound 11g.

11i One Dose Mean Graph

Experiment ID: 1212OS84

Report Date: Jan 17, 2018

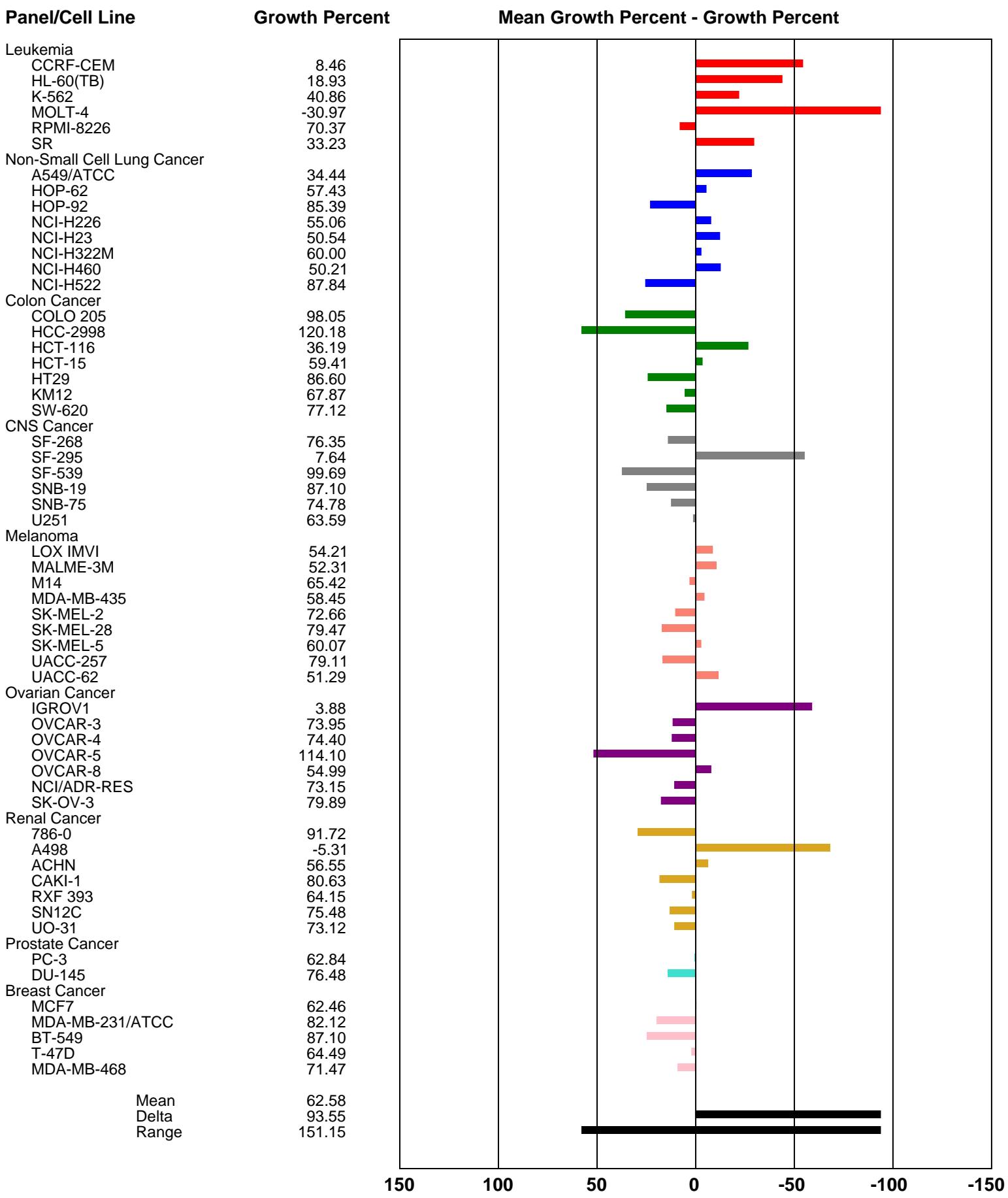


Figure S14. One-dose mean graph for compound 11i.

11j One Dose Mean Graph

Experiment ID: 1301OS10

Report Date: Jan 17, 2018

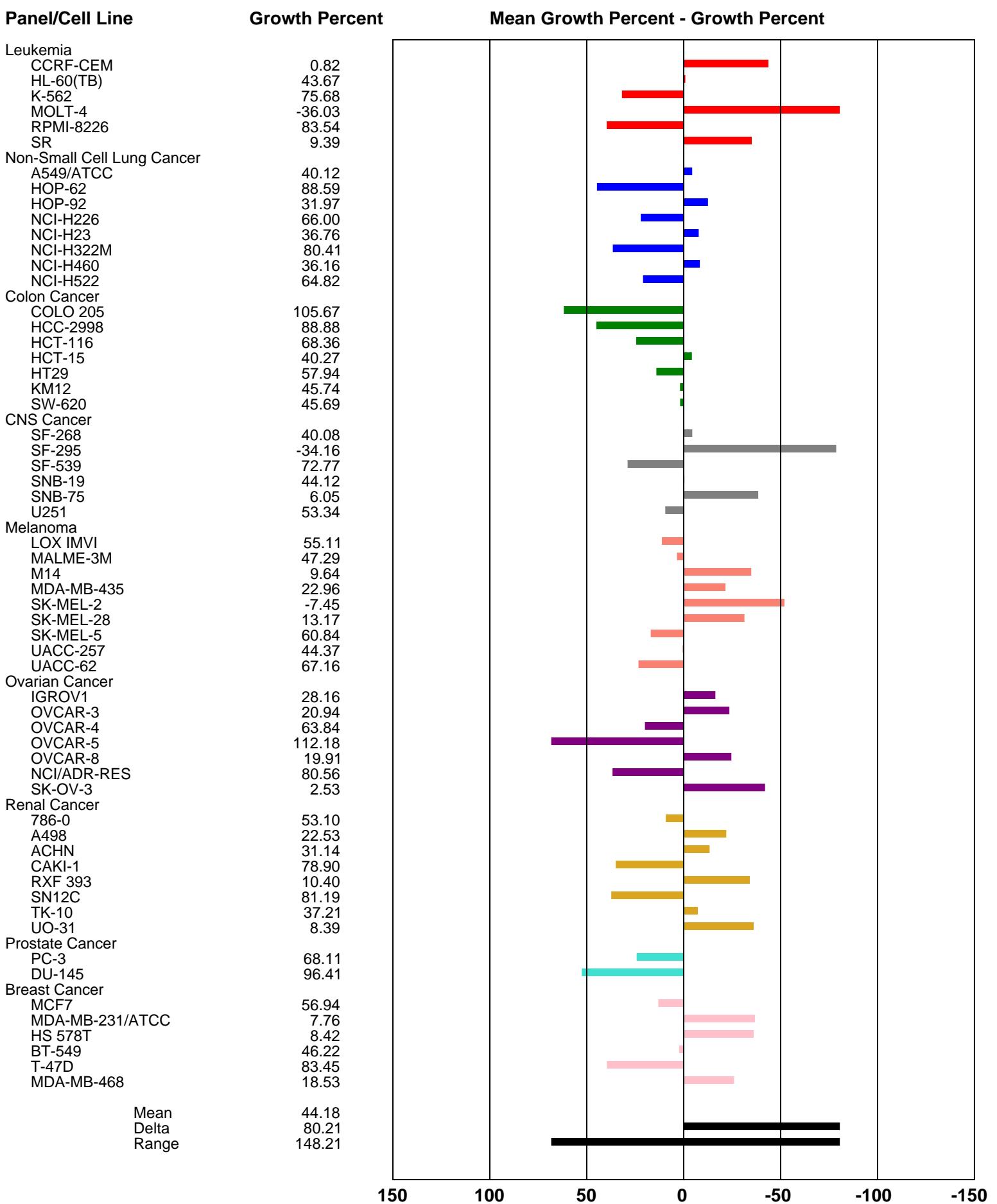


Figure S15. One-dose mean graph for compound 11j.

11k One Dose Mean Graph

Experiment ID: 1211OS83

Report Date: Jun 27, 2017

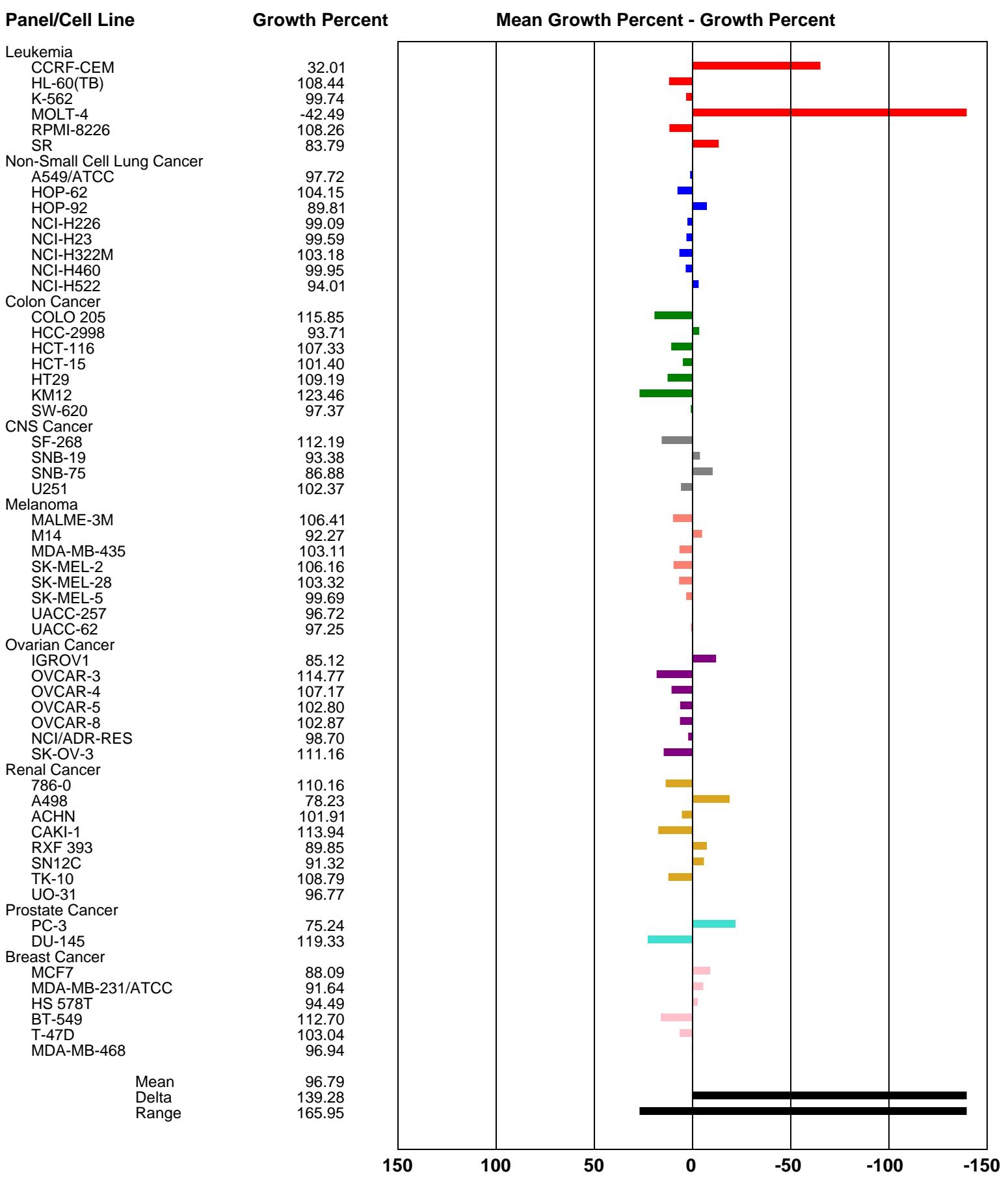


Figure S16. One-dose mean graph for compound 11k.

11a One Dose Mean Graph

Experiment ID: 1507OS19

Report Date: Jun 27, 2017

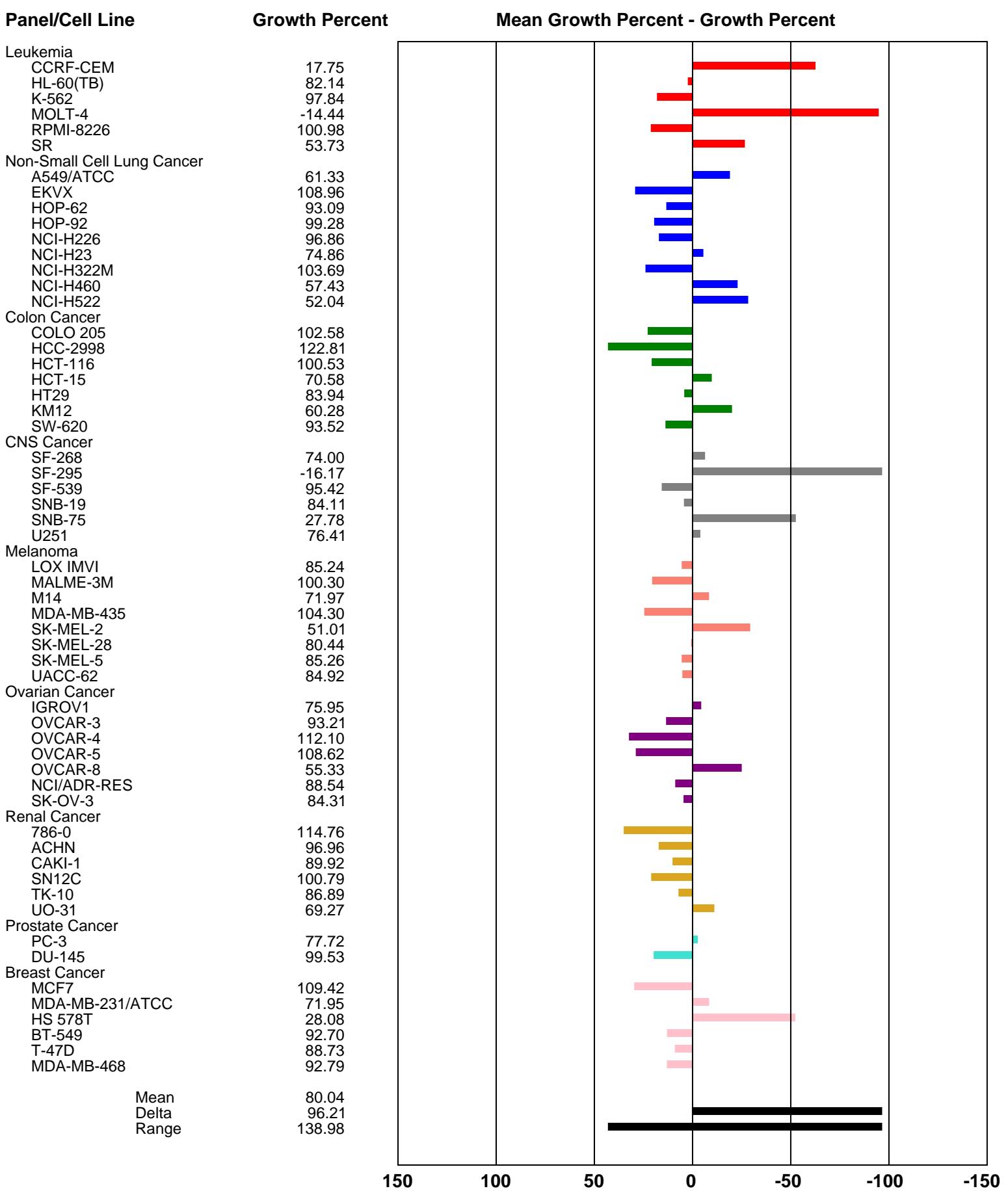


Figure S17. One-dose mean graph for compound 11a.

11q One Dose Mean Graph

Experiment ID: 1507OS19

Report Date: Jun 27, 2017

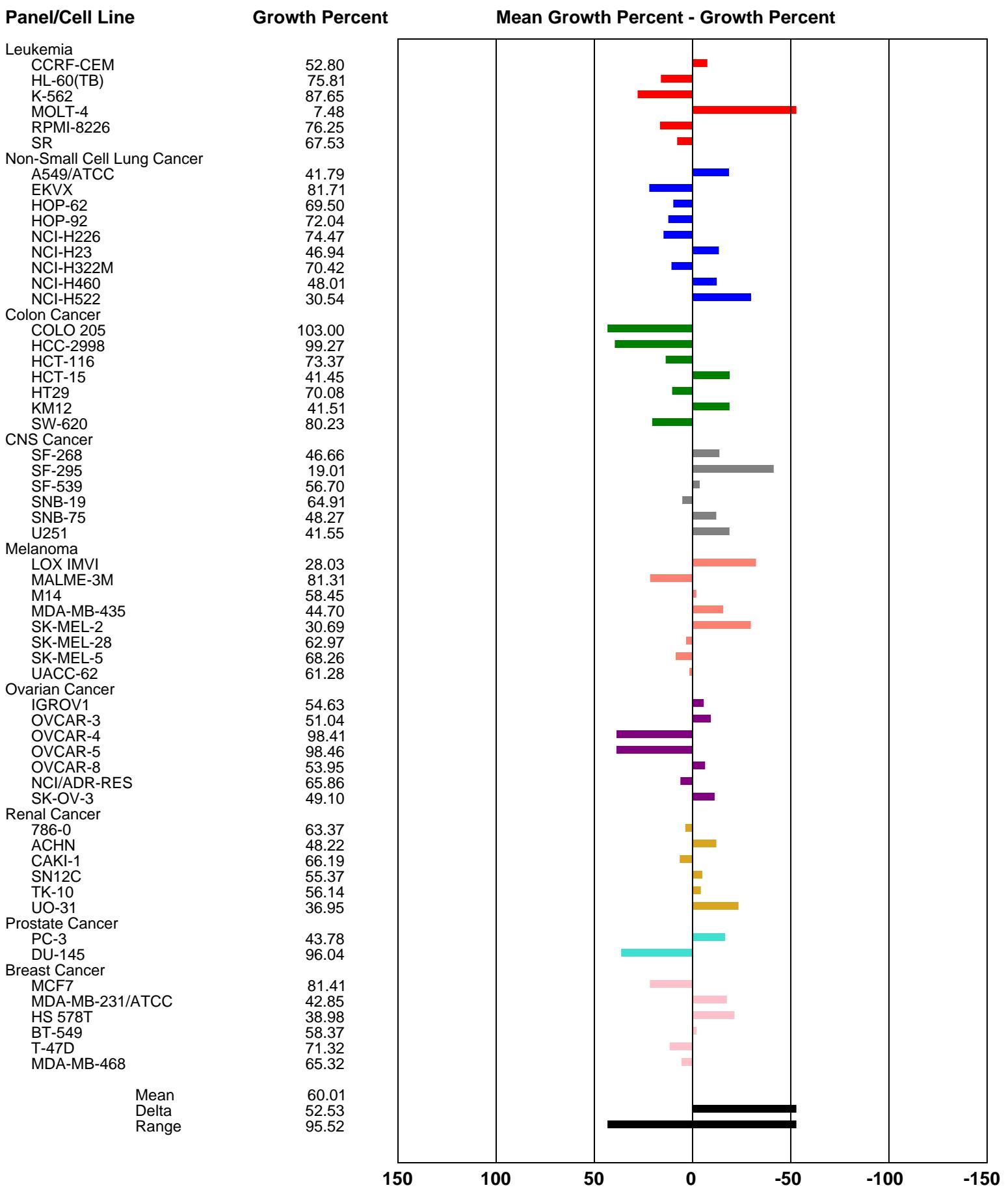


Figure S18. One-dose mean graph for compound 11q.

11r One Dose Mean Graph

Experiment ID: 1507OS19

Report Date: Jun 27, 2017

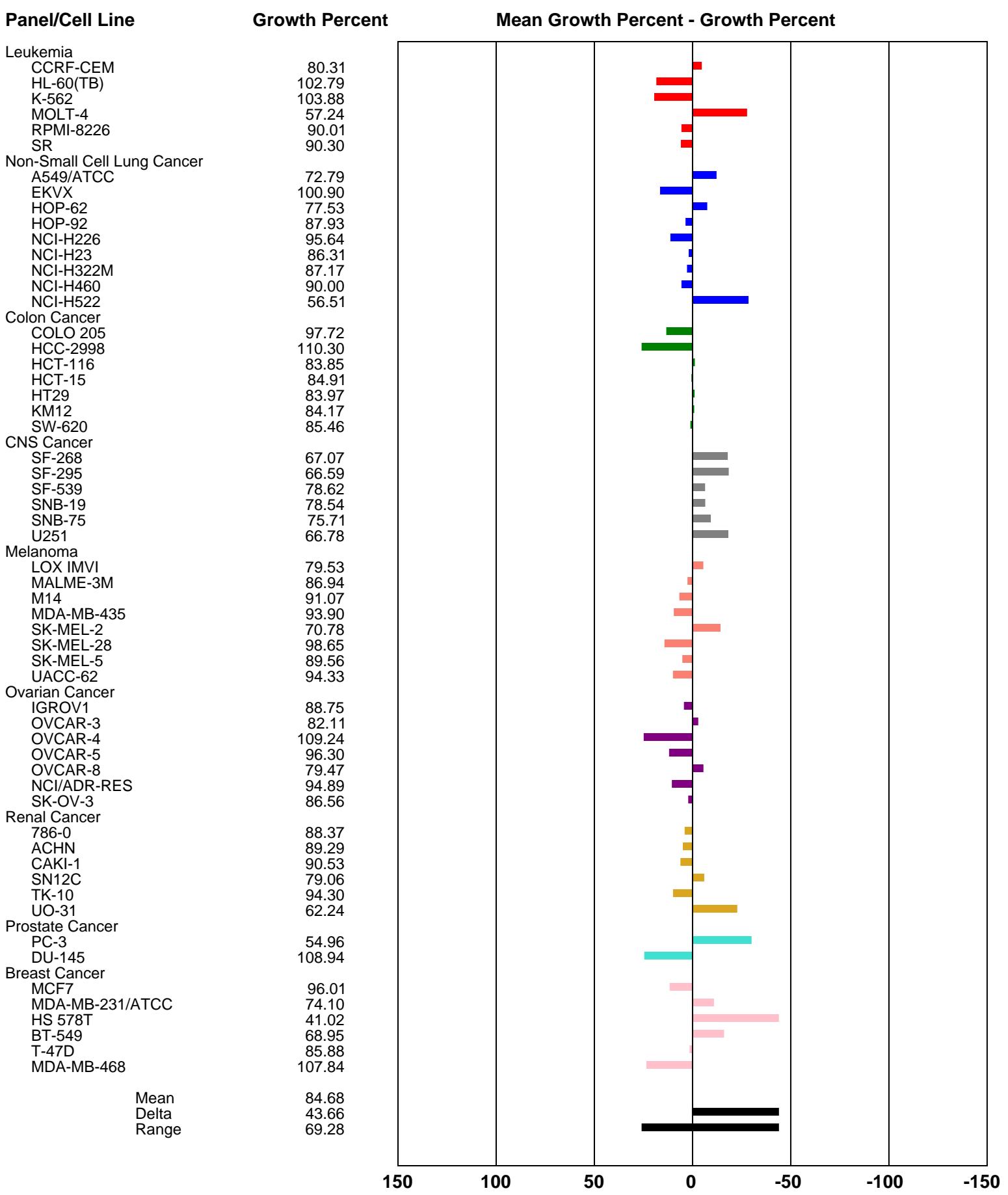


Figure S19. One-dose mean graph for compound 11r.

All Cell Lines

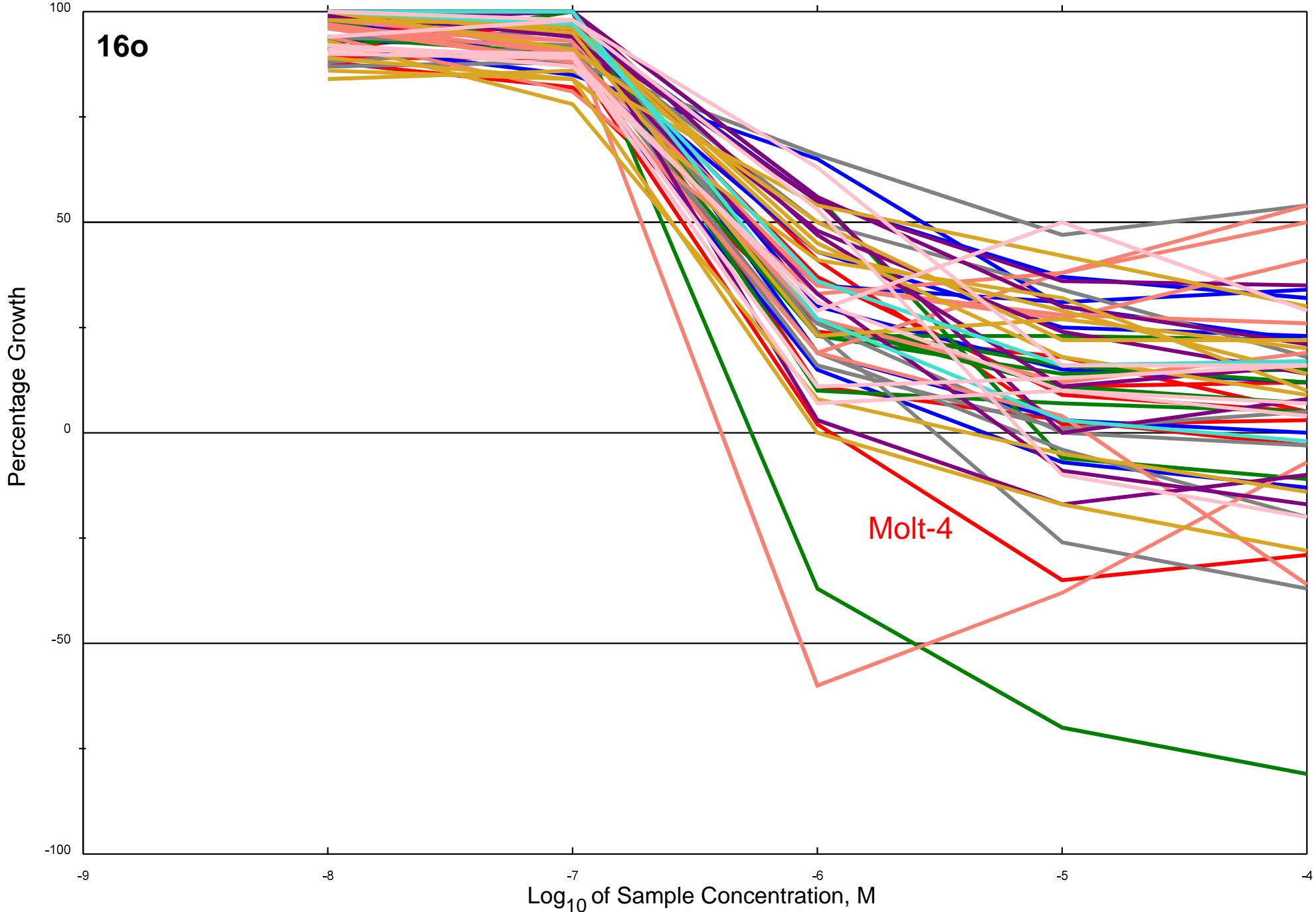


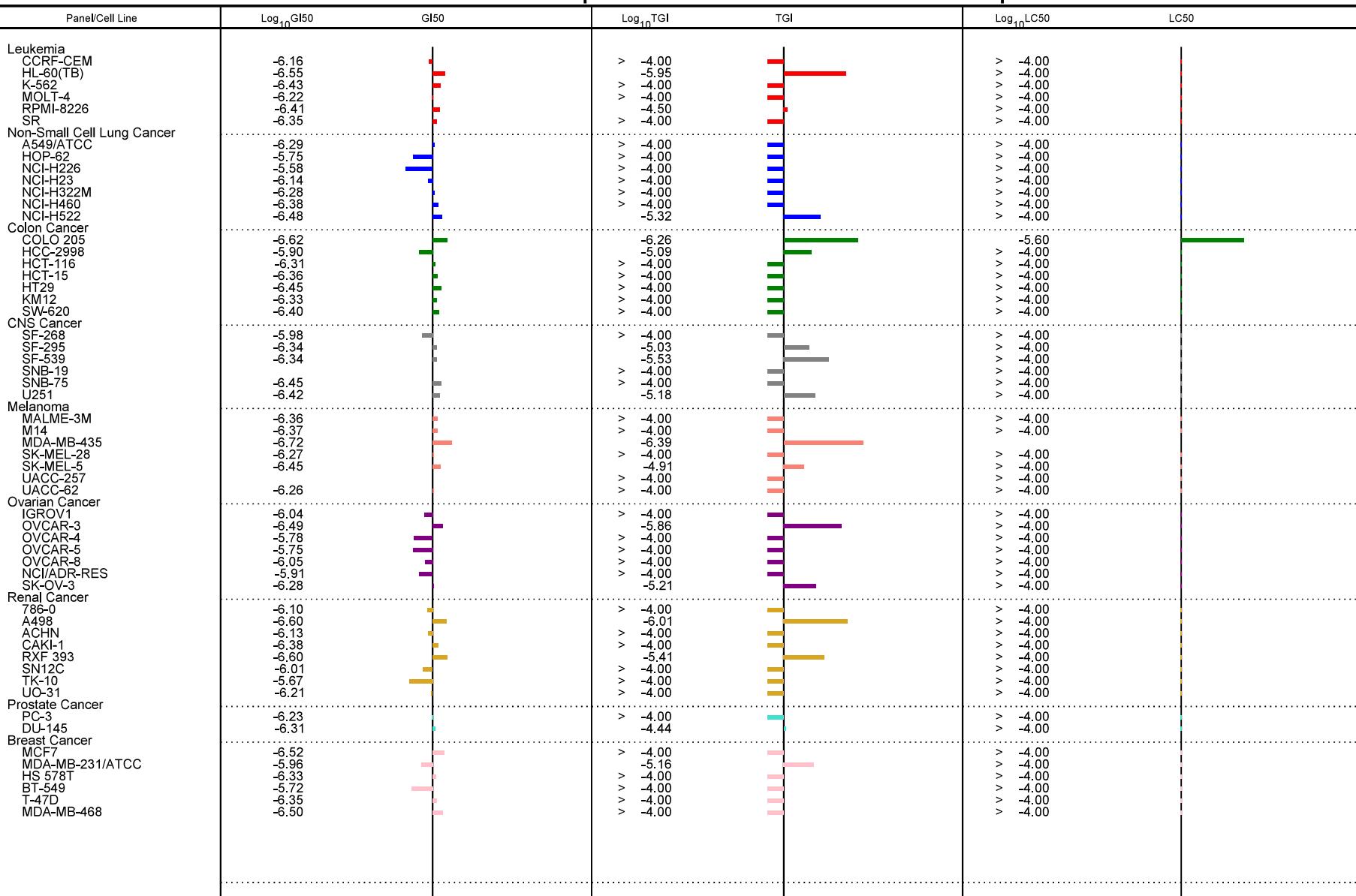
Figure S20. Dose-response curves for compound 16o.

16o

Mean Graphs

Report Date :July 01, 2017

Test Date :March 18, 2013

**Figure S21. Mean graphs for compound 16o.**MID
Delta
Range-6.25
0.47
1.14

+3 +2 +1 0 -1 -2 -3

-4.4
1.99
2.39

+3 +2 +1 0 -1 -2 -3

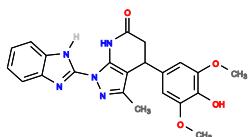
-4.03
1.57
1.6

+3 +2 +1 0 -1 -2 -3

Your job id: 1554874260_634614005

Your Query:

```
COc1cc(C2CC(=O)Nc3c2c(C)nn3-c2nc3cccc3[nH]2)cc(OC)c1O
COC1=CC(=CC(OC)=C1O)C1CC(=O)NC2=C1C(C)=NN2c1nc2cccc2n1
```

11j**Target filter**

All targets(1288)

Proportion among top-k

Enzymes(751)

- Membrane receptor (220)
- Ion channel (65)
- Epigenetic regulator (73)
- Transcription factor (41)
- Transporter (45)
- Other cytosolic protein (17)
- Secreted protein (15)
- Adhesion (7)
- Auxiliary transport protein (4)
- Surface antigen (4)
- Other nuclear protein (3)
- Other membrane protein (2)
- Structural protein (2)
- Unclassified protein (65)

1/10(10%)

1/10(10%)

1/10(10%)

- Kinase (328)
- Protease (111)
- Cytochrome P450 (18)
- Oxidoreductase (18)
- Phosphodiesterase (18)
- Phosphatase (19)
- Lyase (13)
- Hydrolase (10)
- Transferase (6)
- Isomerase (4)
- Aminoacyltransferase (1)
- Ligase (1)
- Other enzyme (214)

top-k= **Rerun**Assay file: [download](#)

Top	Name	ChEMBL	UniProt	PDB	Probability	Class	Sequence	Domains	Similar ligands
1	Fibroblast growth factor receptor 1	CHEMBL3650	P11362	50	0.28	Kinase	822	4(1)	0
2	Alpha-ketoglutarate-dependent dioxygenase alkB homolog 3	CHEMBL3112376	Q96Q83	1	0.28	Other enzyme	286	1(0)	0
3	Bile acid receptor FXR	CHEMBL2047	Q96RI1	66	0.14	Transcription factor	486	2(1)	0
4	Platelet-derived growth factor receptor beta	CHEMBL1913	P09619	8	0.14	Kinase	1106	4(1)	0
5	Mitogen-activated protein kinase kinase kinase kinase 2	CHEMBL5330	Q12851	0	0.14	Kinase	820	2(1)	0
6	Cell division protein kinase 8	CHEMBL5719	P49336	25	0.10	Kinase	464	1(1)	0
7	Glycogen synthase kinase-3 beta	CHEMBL262	P49841	72	0.10	Kinase	420	1(1)	0
8	Protein kinase C theta	CHEMBL3920	Q04759	8	0.10	Kinase	706	4(1)	0
9	Norepinephrine transporter	CHEMBL222	P23975	0	0.10	Transporter	617	1(1)	0
10	Kappa opioid receptor	CHEMBL237	P41145	3	0.10	Membrane receptor	380	1(1)	0

Figure S22. RF-QSAR results for compound 11j. List of top-10 targets.

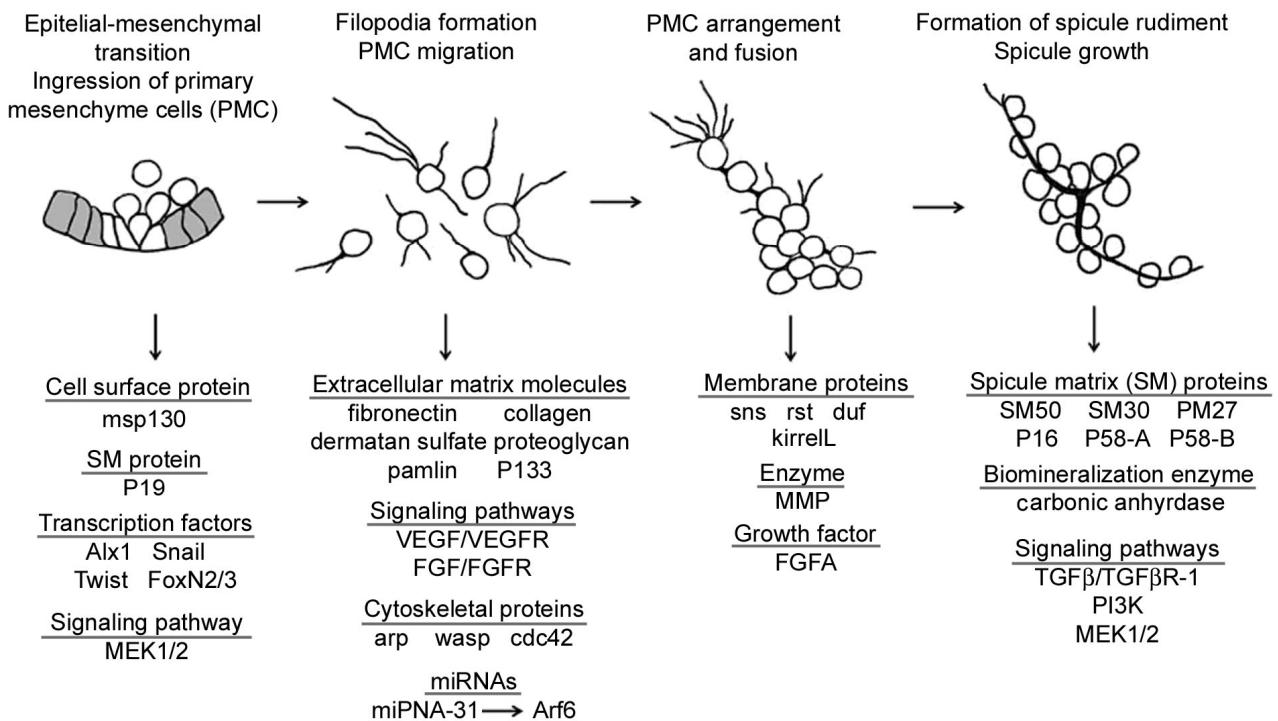


Figure S23. Steps of PMC differentiation: ingression inside the blastocoel through the epithelial-mesenchymal transition, migration by filopodia, arrangement into two ventro-lateral clusters, fusion forming a syncytium, and spicule construction by deposition of Ca-Mg-carbonate and proteinaceous organic matrix into the syncytial cable. A list of molecules and transcription factors involved in each step of PMC differentiation is shown. Adapted from European Journal of Cell Biology, Vol 95, Zito, F.; Lampiasi, N.; Kireev, I.; Russo, R., United We Stand: Adhesion and Molecular Mechanisms Driving Cell Fusion Across Species, 552–562, Copyright (2016), with permission from Elsevier.³ Additional data from.⁴⁻¹⁶

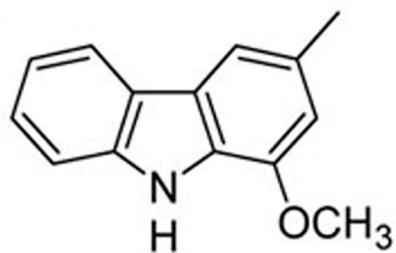
NCI Cancer Screen Data

GI_{50} Mean Graph

Murrayafoline A

NSC# 654284

GI_{50} MOLT-4: 0.0025 μ M



Average GI_{50} over all cell lines: 9.39 μ M

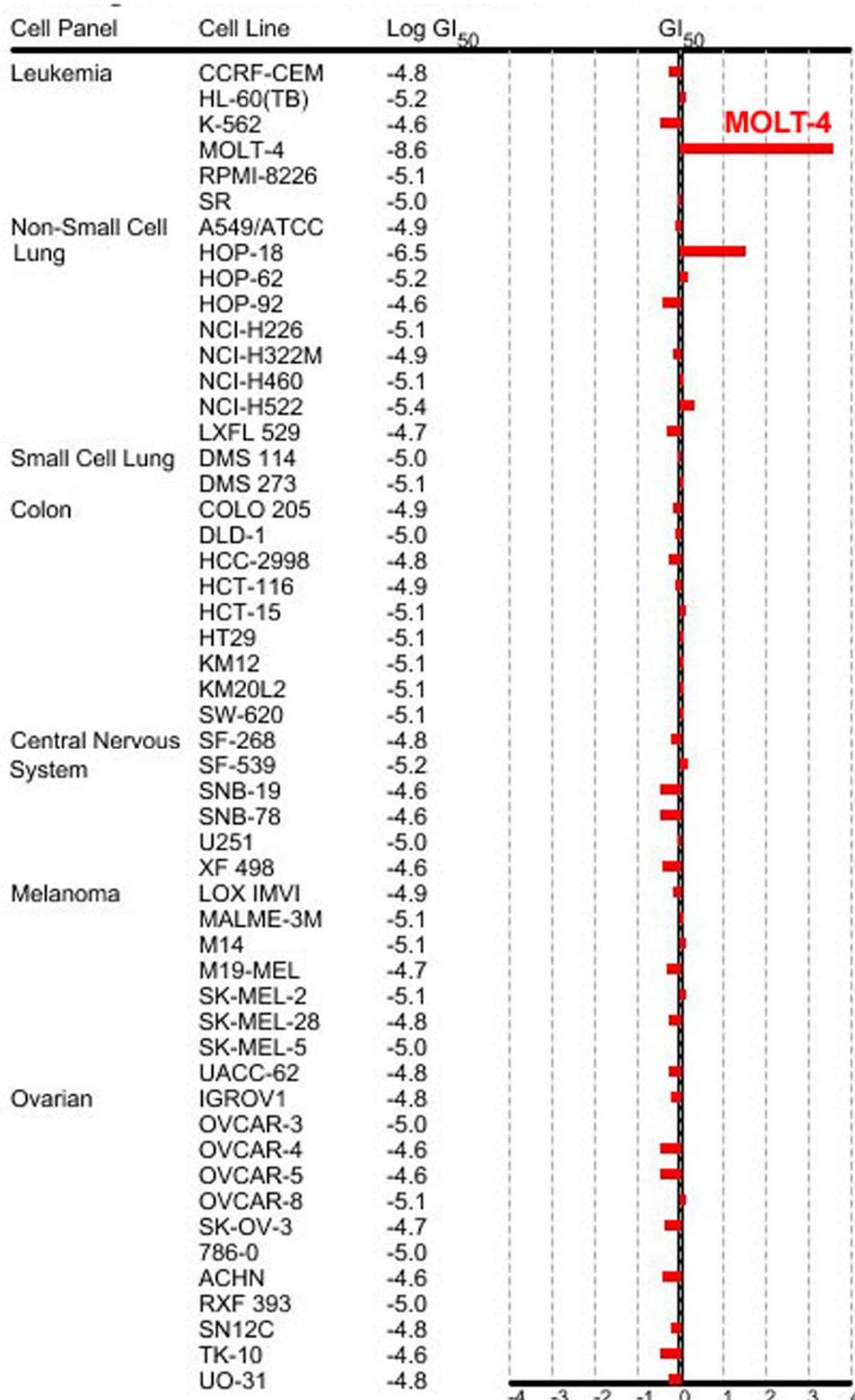


Figure S24. Mean graph for murrayafoline A.

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