

Scaffold Repurposing of In-House Small Molecule Candidates Leads to Discovery of First-In-Class CDK-1/HER-2 Dual Inhibitors: *In vitro* and *In Silico* Screening

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S.1. Chemistry

S.1.1. General

All solvents and reagents were obtained from commercial suppliers and used without further purification. Microwave-assisted synthetic procedure was applied in a Biotage Initiator+ apparatus operating in single mode; the microwave cavity producing controlled irradiation at 2.45 GHz (Biotage AB, Uppsala, Sweden). The reactions were carried out in sealed vessels by employing magnetic stirring with maintaining the desired temperature for the programmed time period. TLC was performed using glass sheets pre-coated with silica gel 60 F₂₅₄ purchased by Merk. The NMR spectra were obtained on Bruker Avance 400. Column chromatography was carried out on Merck Silica Gel 60 (230–400 mesh). High-resolution spectra were performed on Waters ACQUITY UPLC BEH C18 1.7 μ -Q-TOF SYNAPT G2-Si High Definition Mass Spectrometry.

Table S1. SMILES codes for the final target compounds **15a–l**.

Compound	SMILES code
15a	<chem>C[N]1C=CC2=CC(=CC=C12)NC(=O)C3=CC=CN=C3</chem>
15b	<chem>C[N]1C=CC2=CC(=CC=C12)NC(=O)C3=NC=CN=C3</chem>
15c	<chem>C[N]1C=CC2=CC(=CC=C12)NC(=O)C3=CC=NN=C3</chem>
15d	<chem>FC1=CC=C(C[N]2C=CC3=CC(=CC=C23)NC(=O)C4=CC=CN=C4)C=C1</chem>
15e	<chem>FC1=CC=C(C[N]2C=CC3=CC(=CC=C23)NC(=O)C4=NC=CN=C4)C=C1</chem>
15f	<chem>FC1=CC=C(C[N]2C=CC3=CC(=CC=C23)NC(=O)C4=CC=NN=C4)C=C1</chem>
15g	<chem>O=C(NC1=CC=C2[N](CC3=NC=CC=C3)C=CC2=C1)C4=CC=CN=C4</chem>
15h	<chem>O=C(NC1=CC=C2[N](CC3=NC=CC=C3)C=CC2=C1)C4=NC=CN=C4</chem>
15i	<chem>O=C(NC1=CC=C2[N](CC3=NC=CC=C3)C=CC2=C1)C4=CC=NN=C4</chem>
15j	<chem>FC1=CC(=CC=C1)C(=O)[N]2C=CC3=CC(=CC=C23)NC(=O)C4=CC=CN=C4</chem>
15k	<chem>FC1=CC(=CC=C1)C(=O)[N]2C=CC3=CC(=CC=C23)NC(=O)C4=NC=CN=C4</chem>
15l	<chem>FC1=CC(=CC=C1)C(=O)[N]2C=CC3=CC(=CC=C23)NC(=O)C4=CC=NN=C4</chem>

S.1.2. Synthesis of 1-methyl-5-nitro-1*H*-indole (**13a**)

K₂CO₃ (55.3 mg, 0.24 mmol) was added to a solution of 5-nitroindole (**12**, 162.2 mg, 1.0 mmol) in DMF (5 mL). Dimethyl carbonate (0.17 mL, 2.0 mmol) was added and the reaction mixture was refluxed for 3 h, then cooled to 4–5 °C, followed by adding ice-cold water to the mixture. Precipitated solid was filtered and washed with water. Yellow solid, yield: 83%, mp: 164.7–165.9 °C, ¹H NMR (400 MHz, CDCl₃) δ 3.85 (s, 3H), 6.66 (d, *J* = 2.8 Hz, 1H), 7.21 (d, *J* = 2.9 Hz, 1H), 7.33 (d, *J* = 9.0 Hz, 1H), 8.11 (d, *J* = 9.0 Hz, 1H), 8.57 (s, 1H).

S.1.3. General procedure for synthesis of compounds **13b–d**

NaH (60% in oil, 48.0 mg, 1.2 mmol) was added to a solution of 5-nitroindole (**12**, 162.2 mg, 1.0 mmol) dissolved in DMF (11 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. The appropriate aryl halide (1.0 mmol) was added to the mixture. The mixture was then stirred at 100 °C for 24 h, cooled to room

temperature, and partitioned between EA and water using aqueous NaHCO₃. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Finally, the residue was purified by column chromatography (SiO₂, EA/*n*-Hex) to get the target intermediate.

S.1.3.1. 1-(4-Fluorobenzyl)-5-nitro-1*H*-indole (13b)

Yellow solid, yield: 91%, mp: 126.4–127.0 °C, ¹H NMR (400 MHz, CDCl₃) δ 5.34 (s, 2H), 6.74 (s, 1H), 7.03 (d, *J* = 8.1 Hz, 2H), 7.08 (s, 2H), 7.28 (d, *J* = 10.6 Hz, 2H), 8.08 (d, *J* = 8.6 Hz, 1H), 8.60 (s, 1H).

S.1.3.2. 5-Nitro-1-(pyridin-2-ylmethyl)-1*H*-indole (13c)

Yellow solid, yield: 24%, ¹H NMR (400 MHz, CDCl₃) δ 5.49 (s, 2H), 6.76–6.80 (m, 2H), 7.20–7.23 (m, 1H), 7.33 (d, *J* = 9.0 Hz, 1H), 7.37 (d, *J* = 3.2 Hz, 1H), 7.59 (td, *J* = 1.6 Hz, 7.7 Hz, 1H), 8.08 (dd, *J* = 2.1 Hz, 9.1 Hz, 1H), 8.61 (d, *J* = 1.9 Hz, 2H).

S.1.3.3. (3-Fluorophenyl)(5-nitro-1*H*-indol-1-yl)methanone (13d)

Yellowish white solid, yield: 67%, mp: 151.0–152.0 °C, ¹H NMR (400 MHz, CDCl₃) δ 6.79 (d, *J* = 3.7 Hz, 1H), 7.35–7.40 (m, 1H), 7.47–7.50 (m, 2H), 7.54–7.60 (m, 2H), 8.25 (dd, *J* = 2.2 Hz, 9.1 Hz, 1H), 8.47–8.51 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 109.24, 116.52, 116.53 (*J*_{C-F} = 24.1 Hz), 117.20, 119.86 (*J*_{C-F} = 21.1 Hz), 120.27, 125.06 (*J*_{C-F} = 3.0 Hz), 130.06, 130.69 (*J*_{C-F} = 5.0 Hz), 130.79, 135.29 (*J*_{C-F} = 8.1 Hz), 138.97, 144.55, 162.51 (*J*_{C-F} = 249.5 Hz), 167.08.

S.1.4. General procedure for synthesis of compounds 14a–d

Each of compounds **13a–d** (1.0 mmol) was dissolved in EtOH/H₂O (5/2), followed by adding NH₄Cl (267.5 mg, 5.0 mmol) and iron powder (558.5 mg, 10.0 mmol). The reaction mixture was refluxed for 1 h and filtered on celite then washed with EtOH. The residue was extracted using EA, water and aqueous NaHCO₃. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, EA/*n*-Hex) to get the target intermediate.

S.1.4.1. 1-Methyl-1*H*-indol-5-amine (14a)

Brown solid, yield: 78%, mp: 103.0–103.9 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.68 (s, 3H), 4.48 (s, 2H), 6.12 (d, *J* = 2.7 Hz, 1H), 6.56 (dd, *J* = 2.0 Hz, 8.6 Hz, 1H), 6.70 (d, *J* = 1.8 Hz, 1H), 7.09–7.12 (m, 2H).

S.1.4.2. 1-(4-Fluorobenzyl)-1H-indol-5-amine (14b)

Brown solid, yield: 80%, mp: 76.2–77.4 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.49 (s, 2H), 5.27 (s, 2H), 6.18 (d, *J* = 2.8 Hz, 1H), 6.49 (dd, *J* = 1.8 Hz, 8.6 Hz, 1H), 6.69 (d, *J* = 1.6 Hz, 1H), 7.12 (t, *J* = 9.0 Hz, 3H), 7.20 (t, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 3.0 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 48.80, 99.98, 104.01, 110.64, 112.32, 115.65 (*J*_{C-F} = 21.1 Hz), 128.94, 129.41 (*J*_{C-F} = 8.0 Hz), 129.80, 130.07, 135.35 (*J*_{C-F} = 3.0 Hz), 142.00, 161.79 (*J*_{C-F} = 243.5 Hz).

S.1.4.3. 1-(Pyridin-2-ylmethyl)-1H-indol-5-amine (14c)

Light orange solid, yield: 72%, mp: 94.1–95.3 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.51 (s, 2H), 5.38 (s, 2H), 6.22 (s, 1H), 6.49 (d, *J* = 8.2 Hz, 1H), 6.71 (s, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 7.26–7.30 (m, 2H), 7.69 (t, *J* = 6.8 Hz, 1H), 8.54 (d, *J* = 3.5 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 51.69, 100.09, 104.01, 110.57, 112.34, 121.39, 122.91, 129.30, 129.76, 130.26, 137.45, 142.05, 149.55, 158.41.

S.1.4.4. (5-Amino-1H-indol-1-yl)(3-fluorophenyl)methanone (14d)

Orange solid, yield: 91%, mp: 91.7–92.9 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ 5.06 (s, 2H), 6.54 (d, *J* = 3.7 Hz, 1H), 6.68 (dd, *J* = 2.1 Hz, 8.7 Hz, 1H), 6.77 (d, *J* = 2.0 Hz, 1H), 7.19 (d, *J* = 3.7 Hz, 1H), 7.49–7.66 (m, 4H), 8.01 (d, *J* = 8.7 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 104.60, 109.35, 113.38, 116.07 (*J*_{C-F} = 23.1 Hz), 116.81, 118.88 (*J*_{C-F} = 21.1 Hz), 125.23 (*J*_{C-F} = 3.0 Hz), 128.06, 128.23, 131.36 (*J*_{C-F} = 8.1 Hz), 132.34, 137.14 (*J*_{C-F} = 7.0 Hz), 146.25, 162.17 (*J*_{C-F} = 245.5 Hz).

S.1.5. General procedure for synthesis of compounds 15a-l

To a MW vial, were successively added compounds **14a–d** (0.1 mmol), HATU (41.8 mg, 0.11 mmol), DIPEA (0.05 mL, 0.27 mmol), the appropriate heteroaryl carboxylic acid derivative (0.11 mmol) and DMF (12 mL) at room temperature. The MW vial was sealed and heated under MW conditions for 45 min at 116 °C. The reaction mixture was extracted using EA, water and brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, EA/*n*-Hex) to get the desired target compound.

S.1.5.1. N-(1-Methyl-1H-indol-5-yl)nicotinamide (15a)

White solid, yield: 22%, mp: 164.2–164.9 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.80 (s, 3H), 6.43 (d, *J* = 2.9 Hz, 1H), 7.34 (d, *J* = 3.0 Hz, 1H), 7.42–7.49 (m, 2H), 7.56–7.60 (m, 1H), 8.03 (d, *J* = 1.2 Hz, 1H), 8.32–8.34 (m, 1H),

8.77 (dd, $J = 1.4$ Hz, 4.8 Hz, 1H), 9.15 (d, $J = 1.7$ Hz, 1H), 10.33 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 33.01, 100.84, 109.91, 112.89, 116.37, 123.92, 128.21, 130.74, 131.27, 131.41, 134.16, 135.77, 149.07, 152.27, 164.03.

S.1.5.2. *N*-(1-Methyl-1*H*-indol-5-yl)pyrazine-2-carboxamide (15b)

Brown solid, yield: 63%, mp: 172.5–174.0 °C, ^1H NMR (400 MHz, DMSO- d_6) δ 3.80 (s, 3H), 6.44 (s, 1H), 7.34 (s, 1H), 7.44 (d, $J = 7.8$ Hz, 1H), 7.61 (d, $J = 7.1$ Hz, 1H), 8.15 (s, 1H), 8.83 (s, 1H), 8.94 (s, 1H), 9.32 (s, 1H), 10.57 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 33.01, 100.90, 110.00, 112.72, 116.22, 128.19, 130.67, 130.83, 134.26, 143.66, 144.34, 145.94, 147.90, 161.59.

S.1.5.3. *N*-(1-Methyl-1*H*-indol-5-yl)pyridazine-4-carboxamide (15c)

Yellowish green solid, yield: 28%, mp: 181.1–182.0 °C, ^1H NMR (400 MHz, DMSO- d_6) δ 3.81 (s, 3H), 6.45 (d, $J = 3.0$ Hz, 1H), 7.36 (d, $J = 3.0$ Hz, 1H), 7.47 (s, 2H), 8.04 (s, 1H), 8.15 (dd, $J = 2.3$ Hz, 5.3 Hz, 1H), 9.50 (dd, $J = 1.0$ Hz, 5.3 Hz, 1H), 9.69 (t, $J = 1.0$ Hz, 1H), 10.61 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 33.03, 100.94, 110.08, 112.94, 116.15, 124.91, 128.20, 130.77, 130.94, 133.03, 134.35, 149.49, 152.53, 162.25.

S.1.5.4. *N*-(1-(4-Fluorobenzyl)-1*H*-indol-5-yl)nicotinamide (15d)

White solid, yield: 53%, mp: 200.0–200.4 °C, ^1H NMR (400 MHz, DMSO- d_6) δ 5.42 (s, 2H), 6.50 (d, $J = 3.0$ Hz, 1H), 7.15 (t, $J = 8.9$ Hz, 2H), 7.25–7.28 (m, 2H), 7.44 (dd, $J = 8.8$ Hz, 17.8 Hz, 2H), 7.53 (d, $J = 3.0$ Hz, 1H), 7.56–7.59 (m, 1H), 8.04 (s, 1H), 8.31 (d, $J = 8.0$ Hz, 1H), 8.76 (d, $J = 3.5$ Hz, 1H), 9.13 (d, $J = 1.4$ Hz, 1H), 10.34 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 48.87, 101.72, 110.42, 113.08, 115.77 ($J_{\text{C-F}} = 22.1$ Hz), 116.61, 123.93, 128.58, 129.51 ($J_{\text{C-F}} = 9.1$ Hz), 130.20, 131.37, 131.49, 133.39, 134.98 ($J_{\text{C-F}} = 3.0$ Hz), 135.78, 161.88 ($J_{\text{C-F}} = 242.5$ Hz), 164.06.

S.1.5.5. *N*-(1-(4-Fluorobenzyl)-1*H*-indol-5-yl)pyrazine-2-carboxamide (15e)

Light yellow solid, yield: 73%, mp: 161.5–162.0 °C, HPLC purity: 6.02 min, 100%, ^1H NMR (400 MHz, DMSO- d_6) δ 5.42 (s, 2H), 6.51 (d, $J = 3.0$ Hz, 1H), 7.15 (t, $J = 8.9$ Hz, 2H), 7.26–7.30 (m, 2H), 7.46 (d, $J = 8.8$ Hz, 1H), 7.53–7.56 (m, 2H), 8.16 (d, $J = 1.5$ Hz, 1H), 8.82 (t, $J = 1.5$ Hz, 1H), 8.93 (d, $J = 2.4$ Hz, 1H), 9.32 (d, $J = 1.2$ Hz, 1H), 10.58 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 48.88, 101.76, 110.48, 113.00, 115.78 ($J_{\text{C-F}} = 21.1$ Hz), 116.53, 128.55, 129.55 ($J_{\text{C-F}} = 9.1$ Hz), 130.27, 130.87, 133.48, 134.95 ($J_{\text{C-F}} = 4.0$ Hz), 143.65, 144.35, 145.86, 147.92, 161.60, 161.88 ($J_{\text{C-F}} = 243.5$ Hz). HRMS (ESI) m/z calcd. for $\text{C}_{20}\text{H}_{15}\text{FN}_4\text{O}$ $[\text{M}+\text{H}]^+$: 347.1308. Found: 347.1306.

S.1.5.6. *N*-(1-(4-Fluorobenzyl)-1*H*-indol-5-yl)pyridazine-4-carboxamide (15f)

Yellowish green solid, yield: 46%, mp: 212.6–213.1 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ 5.42 (s, 2H), 6.52 (d, *J* = 2.6 Hz, 1H), 7.15 (t, *J* = 8.8 Hz, 2H), 7.26 (t, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.54 (d, *J* = 2.8 Hz, 1H), 8.04 (s, 1H), 8.13 (d, *J* = 2.9 Hz, 1H), 9.48 (d, *J* = 4.7 Hz, 1H), 9.67 (s, 1H), 10.59 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 48.89, 101.82, 110.57, 113.13, 115.80 (*J*_{C-F} = 21.1 Hz), 116.40, 124.92, 128.58, 129.53 (*J*_{C-F} = 8.1 Hz), 130.39, 130.99, 132.98, 133.59, 134.93 (*J*_{C-F} = 3.0 Hz), 149.47, 152.54, 161.89 (*J*_{C-F} = 243.5 Hz), 162.29.

S.1.5.7. *N*-(1-(Pyridin-2-ylmethyl)-1*H*-indol-5-yl)nicotinamide (15g)

Light brown solid, yield: 38%, mp: 142.9–144.3 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ 5.52 (s, 2H), 6.52 (d, *J* = 2.9 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 4.9 Hz, 1H), 7.41 (s, 2H), 7.52 (d, *J* = 2.9 Hz, 1H), 7.56–7.59 (m, 1H), 7.70–7.74 (m, 1H), 8.05 (s, 1H), 8.31 (d, *J* = 7.8 Hz, 1H), 8.55 (d, *J* = 4.2 Hz, 1H), 8.76 (d, *J* = 3.5 Hz, 1H), 9.13 (s, 1H), 10.32 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 51.71, 101.76, 110.41, 113.10, 116.65, 121.51, 123.08, 123.93, 128.55, 130.59, 131.37, 131.52, 133.64, 135.79, 137.58, 149.07, 149.70, 152.31, 157.96, 164.08.

S.1.5.8. *N*-(1-(Pyridin-2-ylmethyl)-1*H*-indol-5-yl)pyrazine-2-carboxamide (15h)

Light yellow solid, yield: 39%, mp: 152.0–152.9 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ 5.51 (s, 2H), 6.52 (d, *J* = 3.0 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 7.26–7.29 (m, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.51–7.53 (m, 2H), 7.71 (td, *J* = 1.6 Hz, 7.6 Hz, 1H), 8.15 (d, *J* = 1.5 Hz, 1H), 8.54 (d, *J* = 4.6 Hz, 1H), 8.81 (d, *J* = 1.5 Hz, 1H), 8.92 (d, *J* = 2.4 Hz, 1H), 9.31 (s, 1H), 10.57 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 51.70, 101.80, 110.47, 113.00, 116.56, 121.55, 123.09, 128.52, 130.67, 130.89, 133.74, 137.59, 143.66, 144.36, 145.87, 147.93, 149.71, 157.93, 161.62.

S.1.5.9. *N*-(1-(pyridin-2-ylmethyl)-1*H*-indol-5-yl)pyridazine-4-carboxamide (15i)

Yellow solid, yield: 85%, mp: 141.8–143.0 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ 5.52 (s, 2H), 6.54 (d, *J* = 2.7 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 5.3 Hz, 1H), 7.39–7.45 (m, 2H), 7.53 (d, *J* = 2.9 Hz, 1H), 7.71 (t, *J* = 6.9 Hz, 1H), 8.06 (s, 1H), 8.13–8.14 (m, 1H), 8.55 (d, *J* = 4.4 Hz, 1H), 9.49 (d, *J* = 5.1 Hz, 1H), 9.67 (s, 1H), 10.61 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 51.70, 101.85, 110.57, 113.13, 116.44, 121.53, 123.10, 124.93, 128.55, 130.77, 131.01, 132.98, 133.84, 137.59, 149.48, 149.72, 152.55, 157.89, 162.29.

S.1.5.10. *N*-(1-(3-Fluorobenzoyl)-1*H*-indol-5-yl)nicotinamide (15j)

White solid, yield: 57%, mp: 212.9–214.2 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.82 (d, *J* = 3.6 Hz, 1H), 7.43 (d, *J* = 3.6 Hz, 1H), 7.56–7.73 (m, 6H), 8.23 (d, *J* = 1.5 Hz, 1H), 8.30 (d, *J* = 8.9 Hz, 1H), 8.35 (d, *J* = 7.9 Hz, 1H),

8.78–8.79 (m, 1H), 9.16 (d, $J = 1.5$ Hz, 1H), 10.58 (s, 1H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 109.57, 113.07, 116.36 ($J_{\text{C-F}} = 24.1$ Hz), 116.38, 118.63, 119.34 ($J_{\text{C-F}} = 21.1$ Hz), 123.99, 125.51, 129.29, 131.12, 131.37, 131.49 ($J_{\text{C-F}} = 8.1$ Hz), 132.46, 135.64, 135.92, 136.63 ($J_{\text{C-F}} = 7.0$ Hz), 149.15, 152.55, 162.20 ($J_{\text{C-F}} = 245.5$ Hz), 164.47, 167.15.

S.1.5.11. *N*-(1-(3-Fluorobenzoyl)-1*H*-indol-5-yl)pyrazine-2-carboxamide (15k)

White solid, yield: 94%, mp: 221.3–222.2 °C, HPLC purity: 6.00 min, 100%, ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 6.81 (d, $J = 2.8$ Hz, 1H), 7.43 (d, $J = 3.0$ Hz, 1H), 7.56 (t, $J = 8.4$ Hz, 1H), 7.61–7.67 (m, 3H), 7.86 (d, $J = 8.9$ Hz, 1H), 8.28 (d, $J = 8.8$ Hz, 1H), 8.32 (s, 1H), 8.85 (s, 1H), 8.96 (s, 1H), 9.34 (s, 1H), 10.85 (s, 1H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 109.54, 113.16, 116.32, 116.37 ($J_{\text{C-F}} = 23.1$ Hz), 118.77, 119.36 ($J_{\text{C-F}} = 20.1$ Hz), 125.55, 129.33, 131.33, 131.49 ($J_{\text{C-F}} = 8.1$ Hz), 132.61, 134.97, 136.59 ($J_{\text{C-F}} = 8.1$ Hz), 143.72, 144.49, 145.65, 148.13, 162.11, 162.20 ($J_{\text{C-F}} = 245.5$ Hz), 167.13. HRMS (ESI) m/z calcd. for $\text{C}_{20}\text{H}_{13}\text{FN}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 361.1101. Found: 361.1095.

S.1.5.12. *N*-(1-(3-Fluorobenzoyl)-1*H*-indol-5-yl)pyridazine-4-carboxamide (15l)

Yellowish white solid, yield: 75%, mp: 196.7–196.9 °C, ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 6.84 (d, $J = 3.6$ Hz, 1H), 7.44 (d, $J = 3.6$ Hz, 1H), 7.54–7.71 (m, 5H), 8.16–8.18 (m, 1H), 8.23 (s, 1H), 8.33 (d, $J = 8.9$ Hz, 1H), 9.52 (d, $J = 4.9$ Hz, 1H), 9.70 (s, 1H), 10.85 (s, 1H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 109.54, 113.17, 116.26, 116.51, 118.57, 119.37 ($J_{\text{C-F}} = 20.1$ Hz), 125.01, 125.55 ($J_{\text{C-F}} = 3.0$ Hz), 129.45, 131.40, 131.45, 131.53, 132.75 ($J_{\text{C-F}} = 5.0$ Hz), 135.08, 136.57 ($J_{\text{C-F}} = 7.04$ Hz), 149.46, 152.58, 162.20 ($J_{\text{C-F}} = 245.5$ Hz), 162.75, 167.18.

S.2. Biological evaluation

S.2.1. *In vitro* cytotoxicity data

Table S2. Mean growth % of tested compounds **15a–l** over NCI human cancer cell lines.

Compound	Leukemia	NSCL*	Colon	CNS**	Melanoma	Ovarian	Renal	Prostate	Breast
15a	99.4	99.0	99.5	97.1	96.2	99.9	93.1	96.7	98.4
15b	94.9	98.6	99.5	97.7	95.8	99.8	91.1	99.3	97.3
15c	100.0	90.1	100.0	90.8	99.1	95.0	76.9	98.0	94.9
15d	78.1	85.3	90.9	84.0	90.3	89.2	59.4	83.6	79.3
15e	88.1	88.2	96.6	86.6	91.3	91.8	64.0	91.8	88.6
15f	83.4	71.8	92.9	81.1	89.7	88.7	58.1	79.5	87.5
15g	98.6	91.3	100.0	91.7	99.2	94.8	72.3	95.1	98.0
15h	97.3	88.9	99.1	89.3	98.4	93.2	67.1	97.8	97.0
15i	98.8	88.9	98.9	88.4	98.1	91.9	69.3	90.3	91.7
15j	86.3	91.8	98.1	93.0	98.3	94.4	67.8	90.2	97.6
15k	98.4	93.4	100.0	89.6	98.9	96.6	79.3	95.0	96.7
15l	94.3	91.5	99.1	91.3	98.6	95.9	76.2	99.2	98.8

* NSCL, non-small cell lung

** CNS, central nervous system

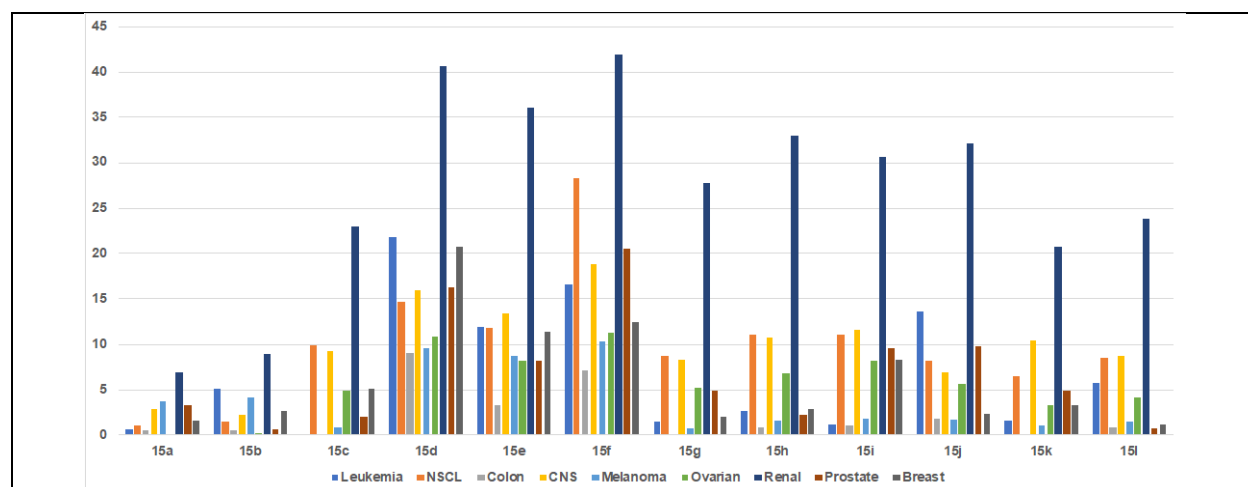


Figure S1. Graphical representation of *in vitro* cytotoxic evaluation of compounds **15a–l** over NCI human cancer cell lines. **Y-axis**, mean % inhibition; **X-axis**, target compounds. The graph shows that the renal cancer cell lines (deep blue) is more sensitive to the tested compounds compared to other NCI cancer cell lines.

S.2.2. NCI reports

Compound	NCI code	Compound	NCI code
15a	D-828867	15g	D-827532
15b	D-828866	15h	D-827531
15c	D-827533	15i	D-827530
15d	D-827526	15j	D-827529
15e	D-827525	15k	D-827528
15f	D-827524	15l	D-827527

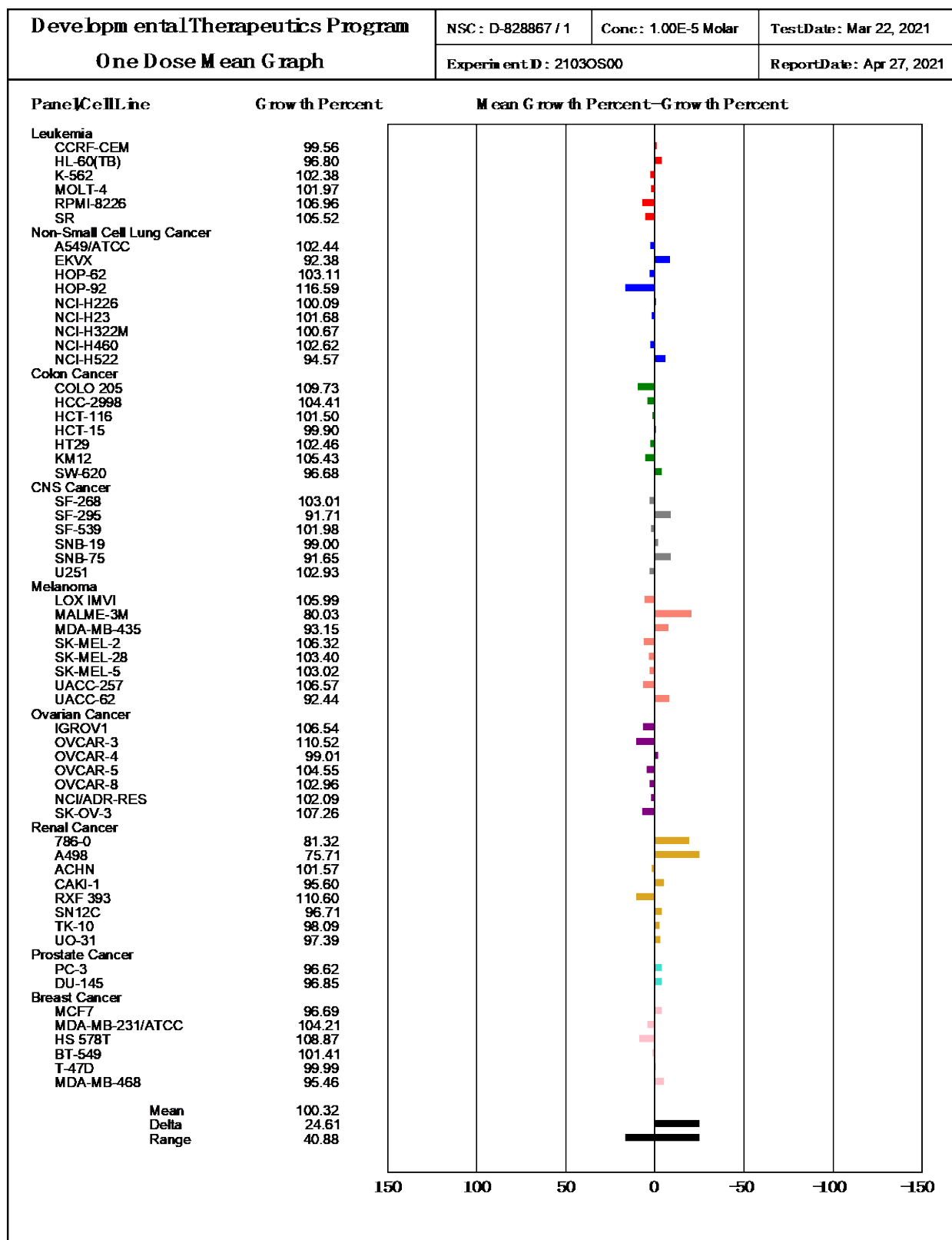


Figure S2. One dose mean growth % of compound 15a over NCI human cancer cell lines.

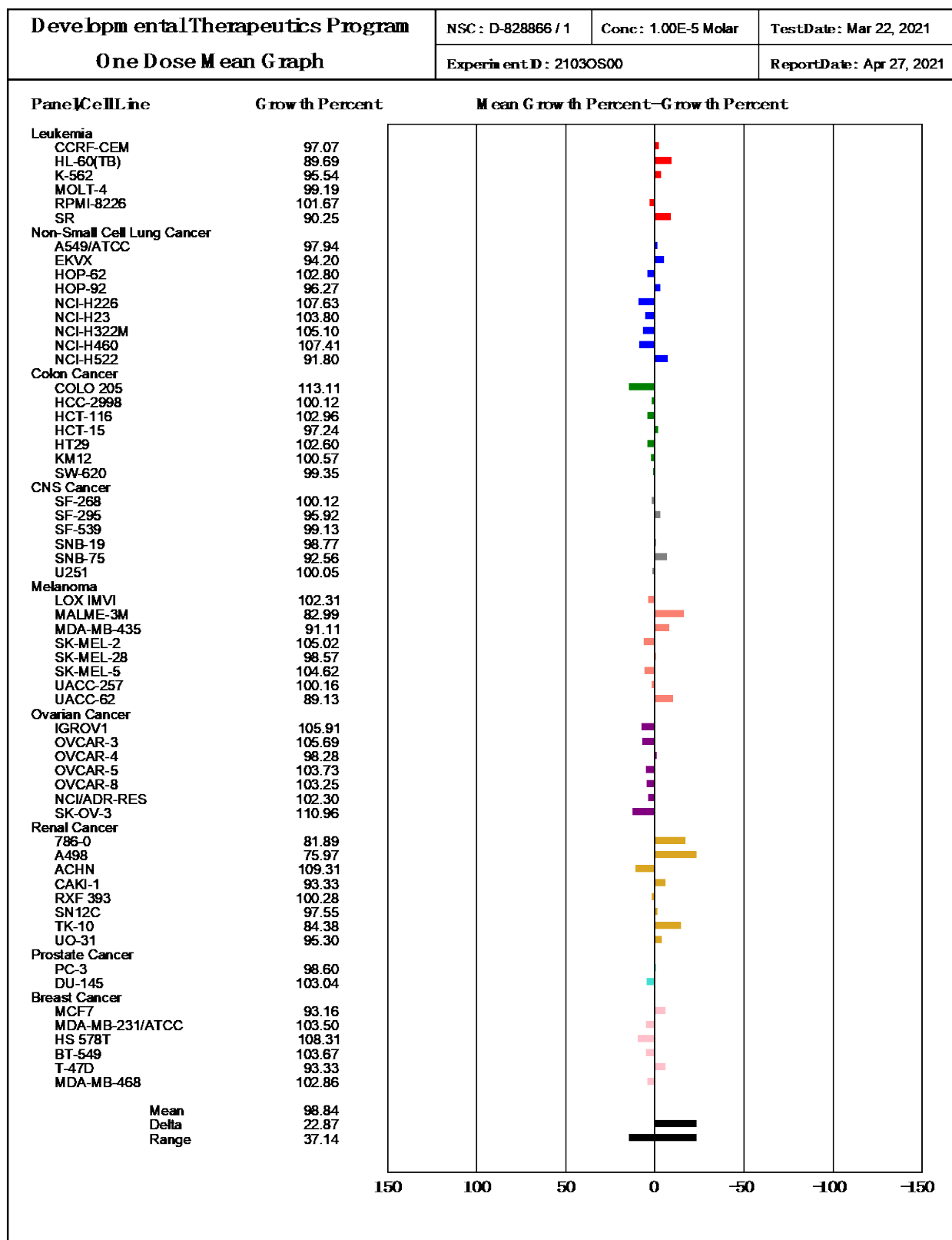


Figure S3. One dose mean growth % of compound **15b** over NCI human cancer cell lines.

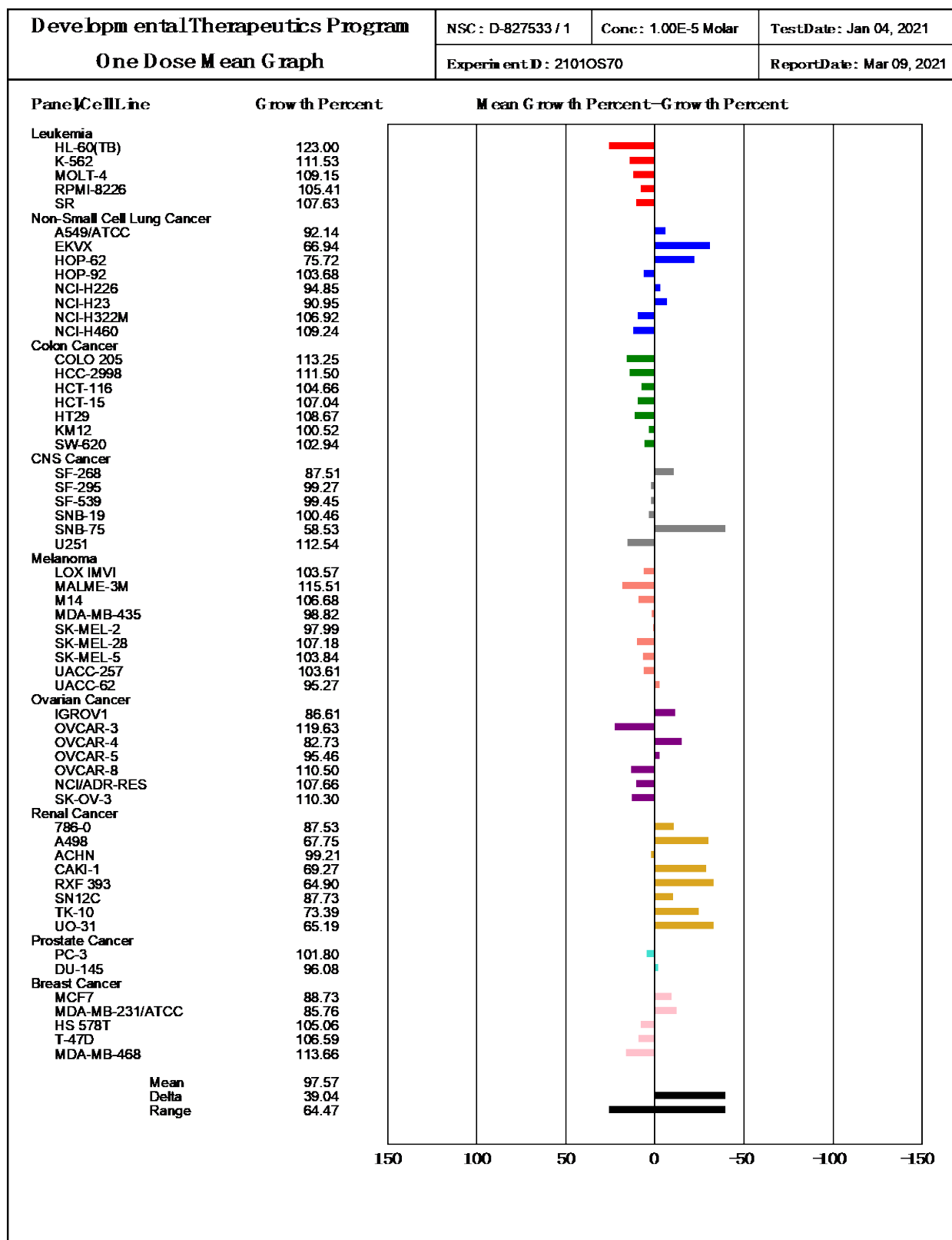


Figure S4. One dose mean growth % of compound 15c over NCI human cancer cell lines.

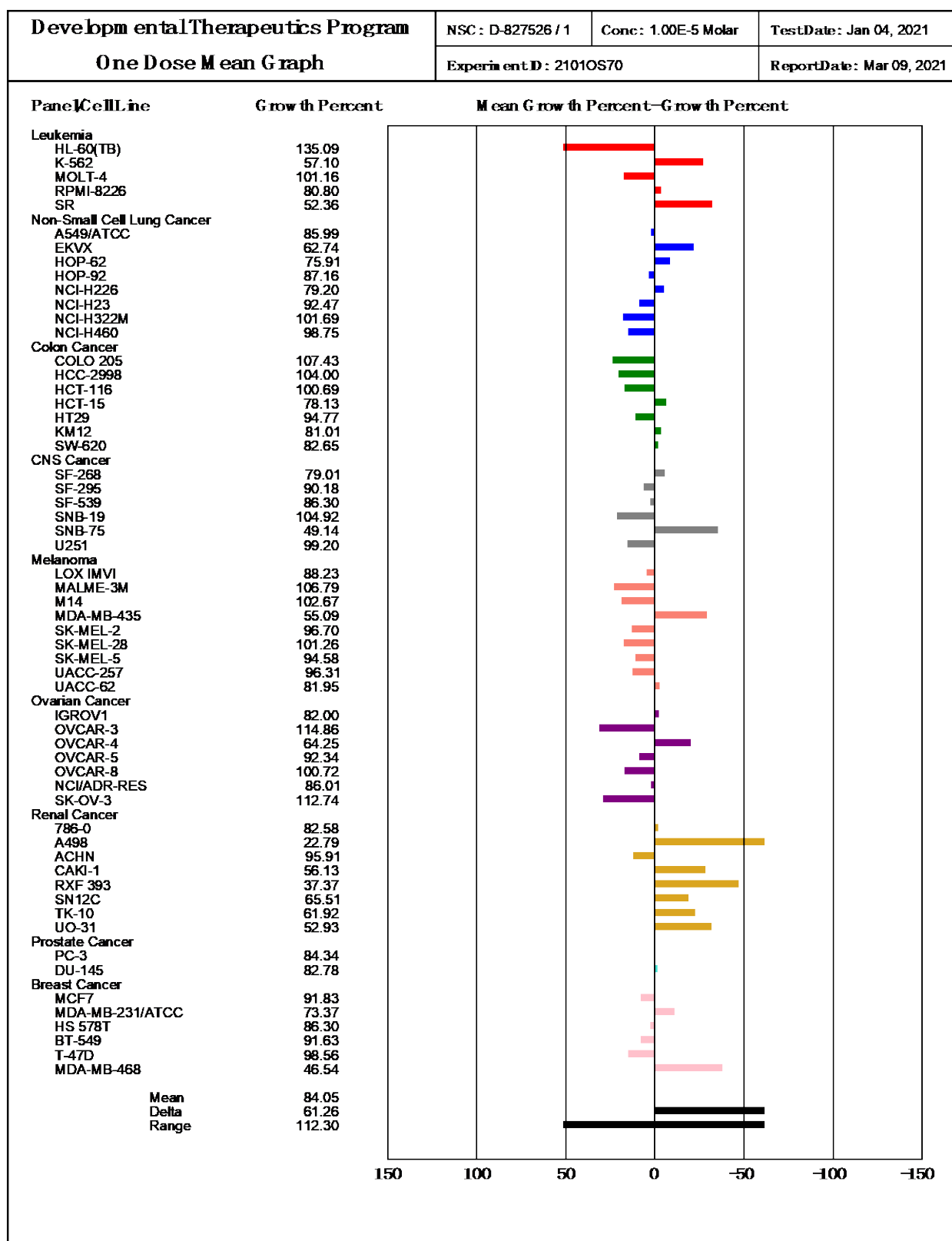


Figure S5. One dose mean growth % of compound 15d over NCI human cancer cell lines.

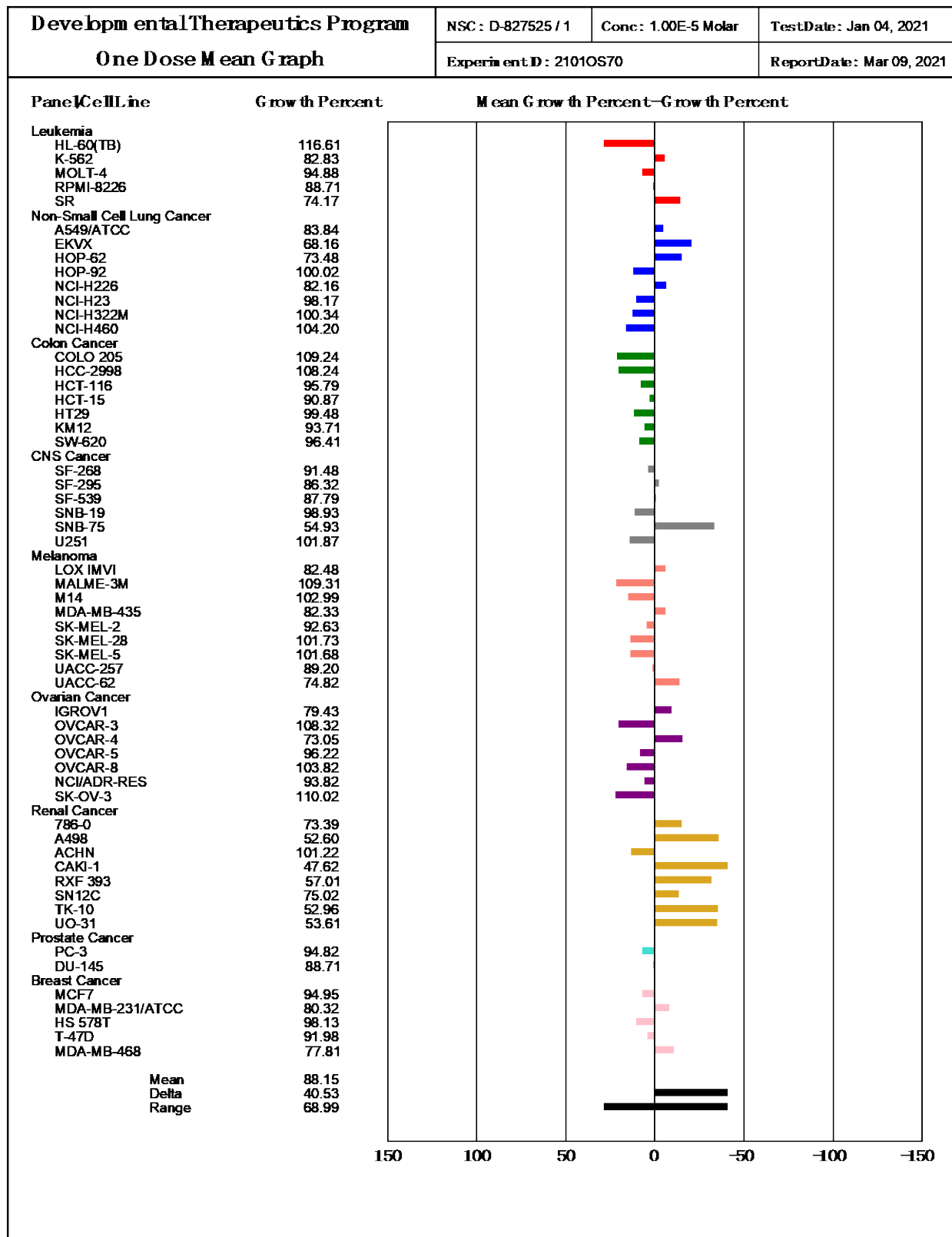


Figure S6. One dose mean growth % of compound 15e over NCI human cancer cell lines.

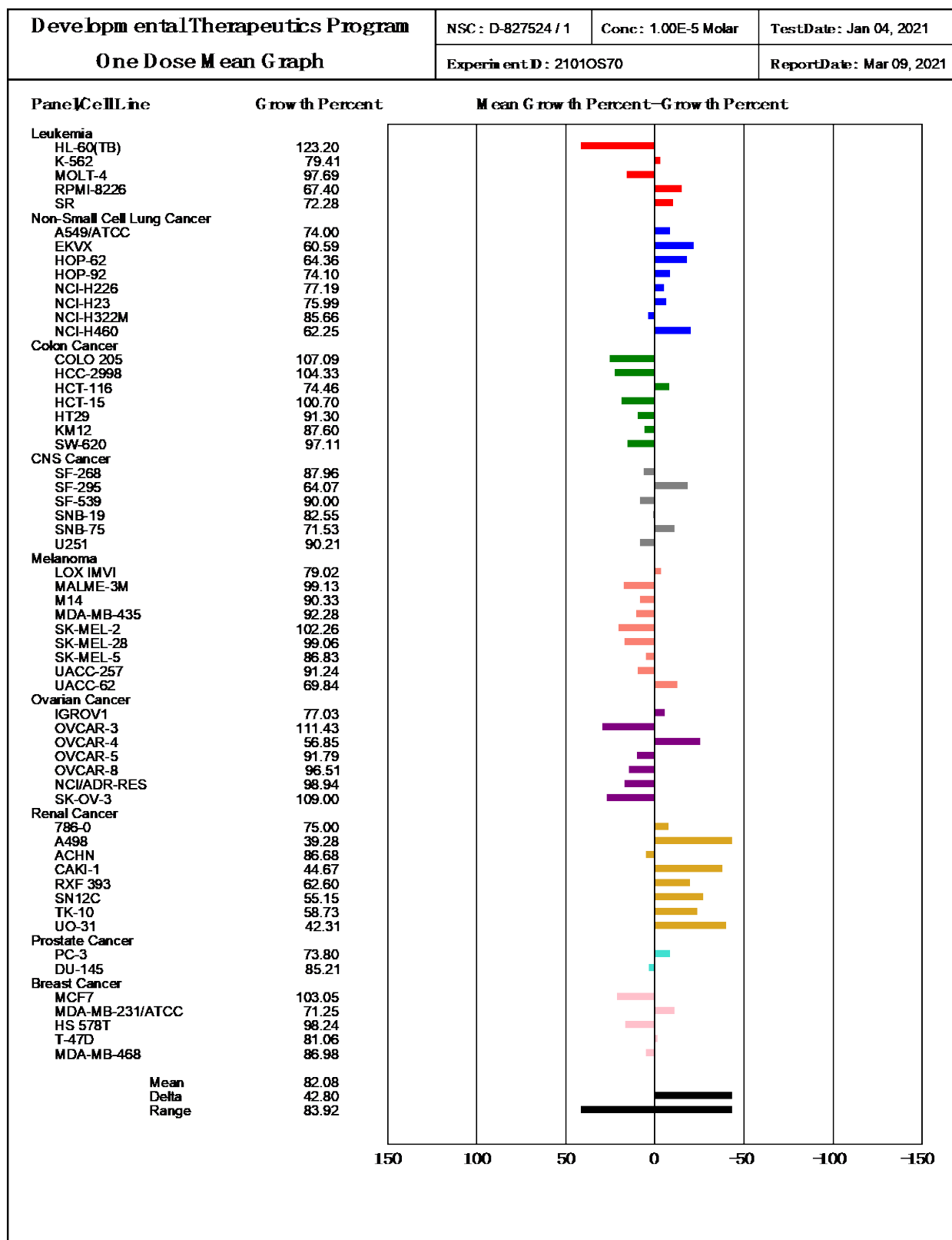
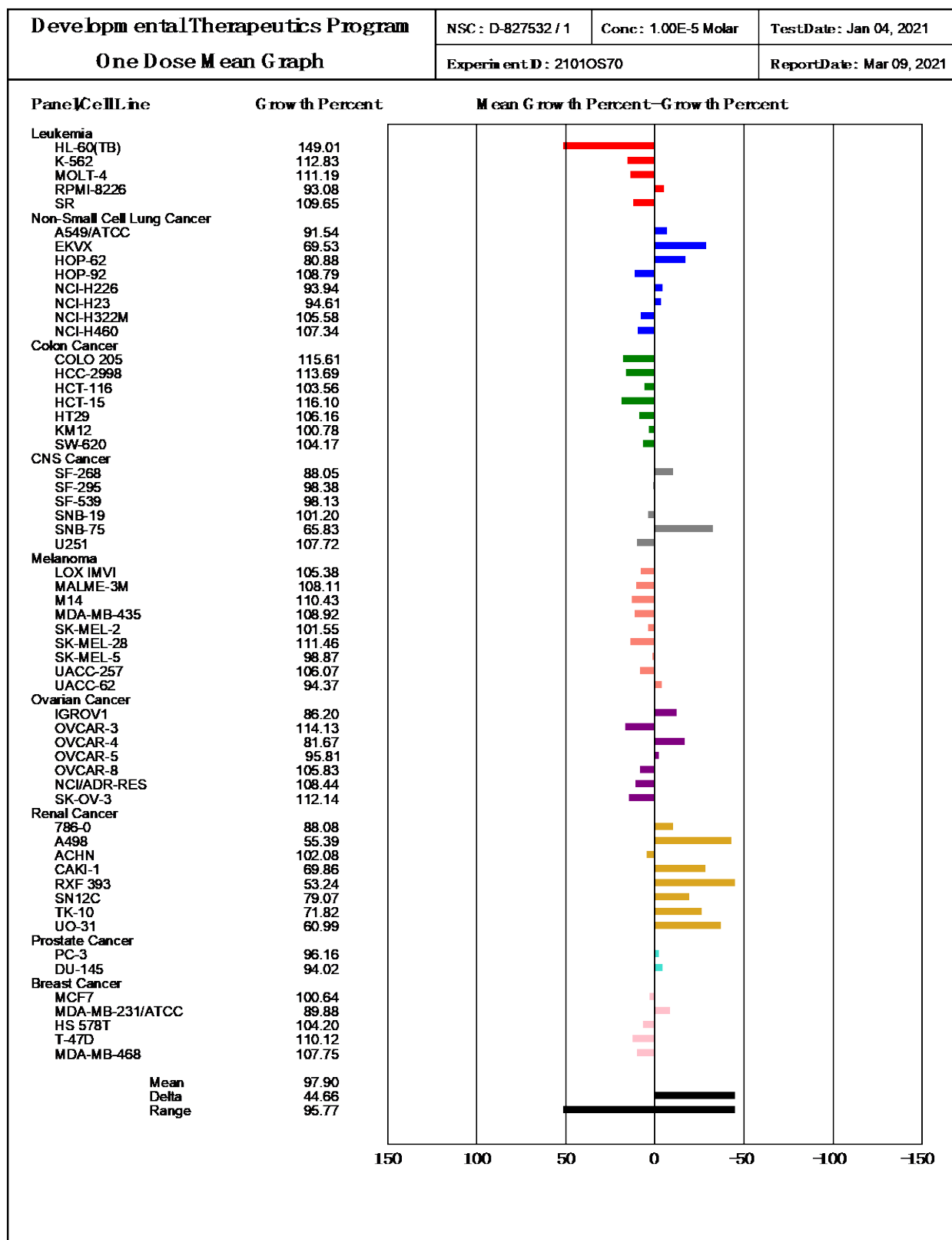


Figure S7. One dose mean growth % of compound 15f over NCI human cancer cell lines.



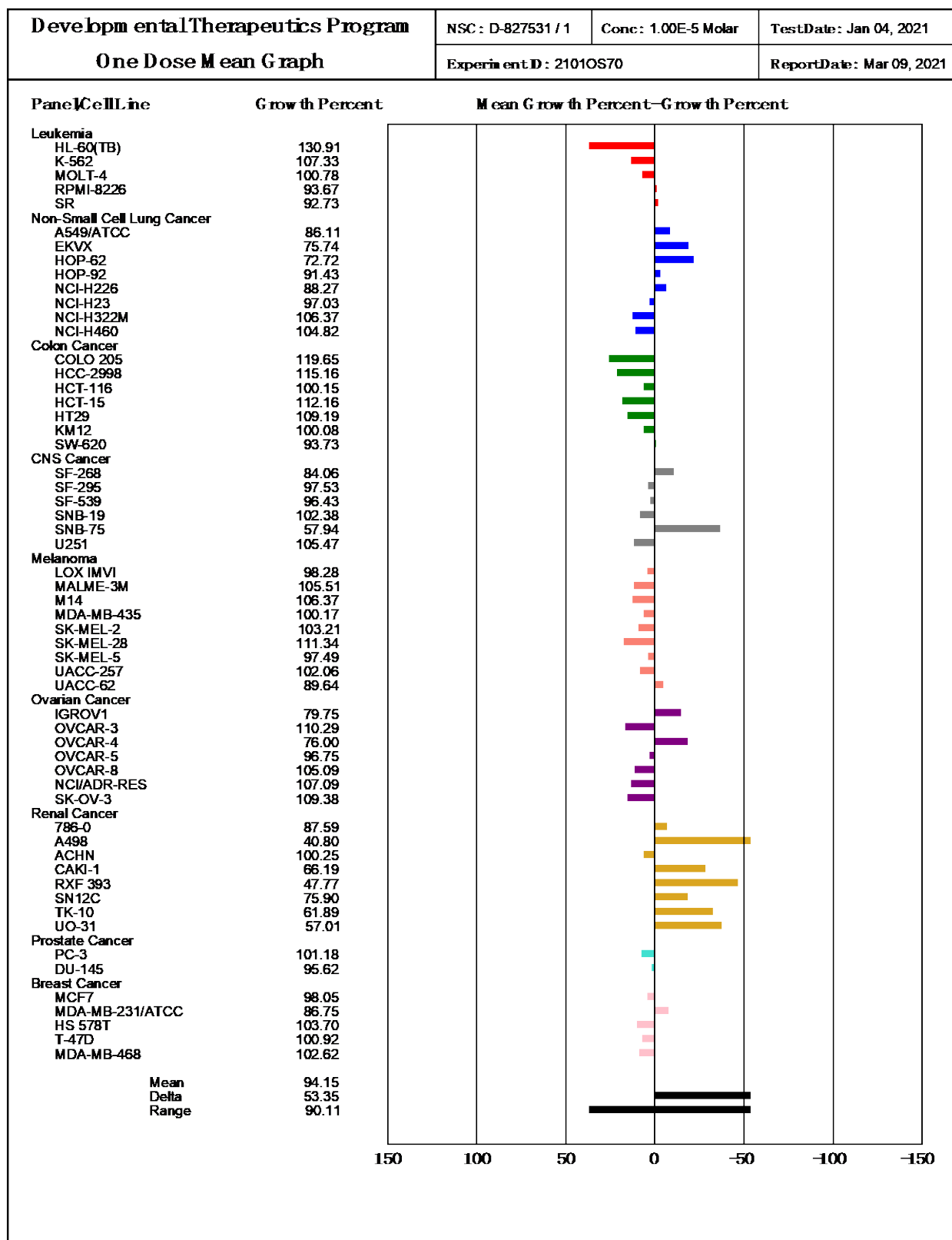


Figure S9. One dose mean growth % of compound **15h** over NCI human cancer cell lines.

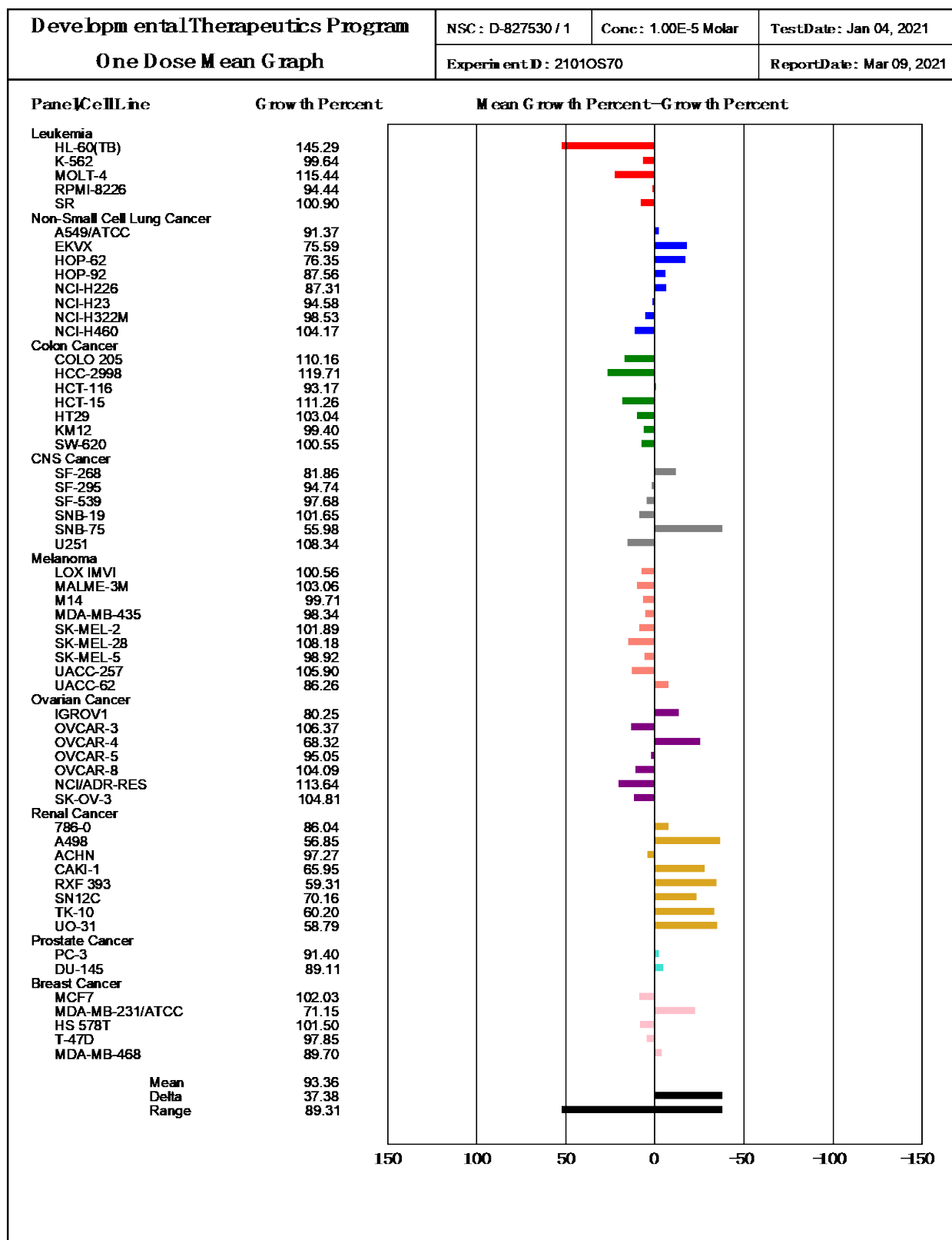


Figure S10. One dose mean growth % of compound 15i over NCI human cancer cell lines.

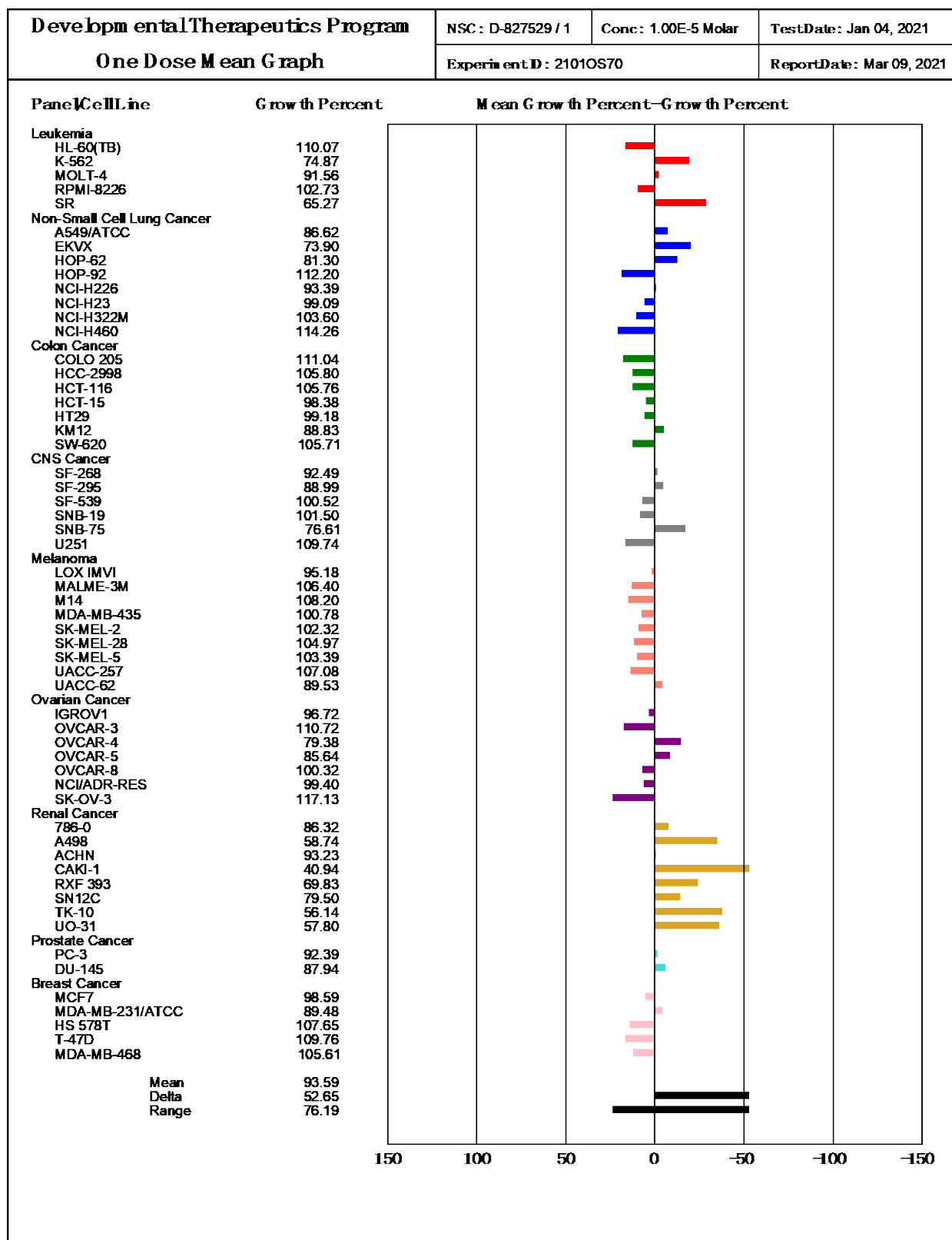


Figure S11. One dose mean growth % of compound 15j over NCI human cancer cell lines.

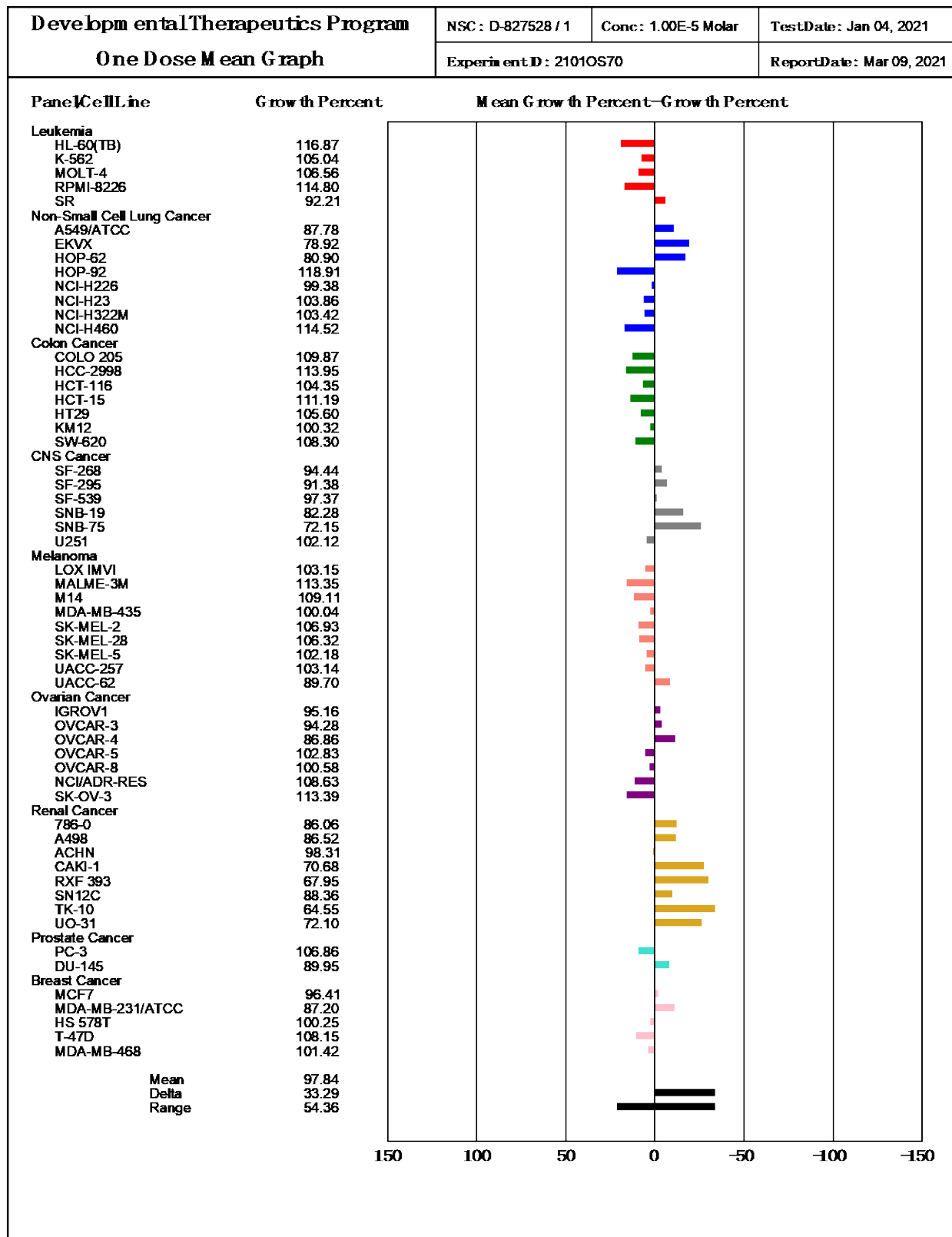


Figure S12. One dose mean growth % of compound 15k over NCI human cancer cell lines.

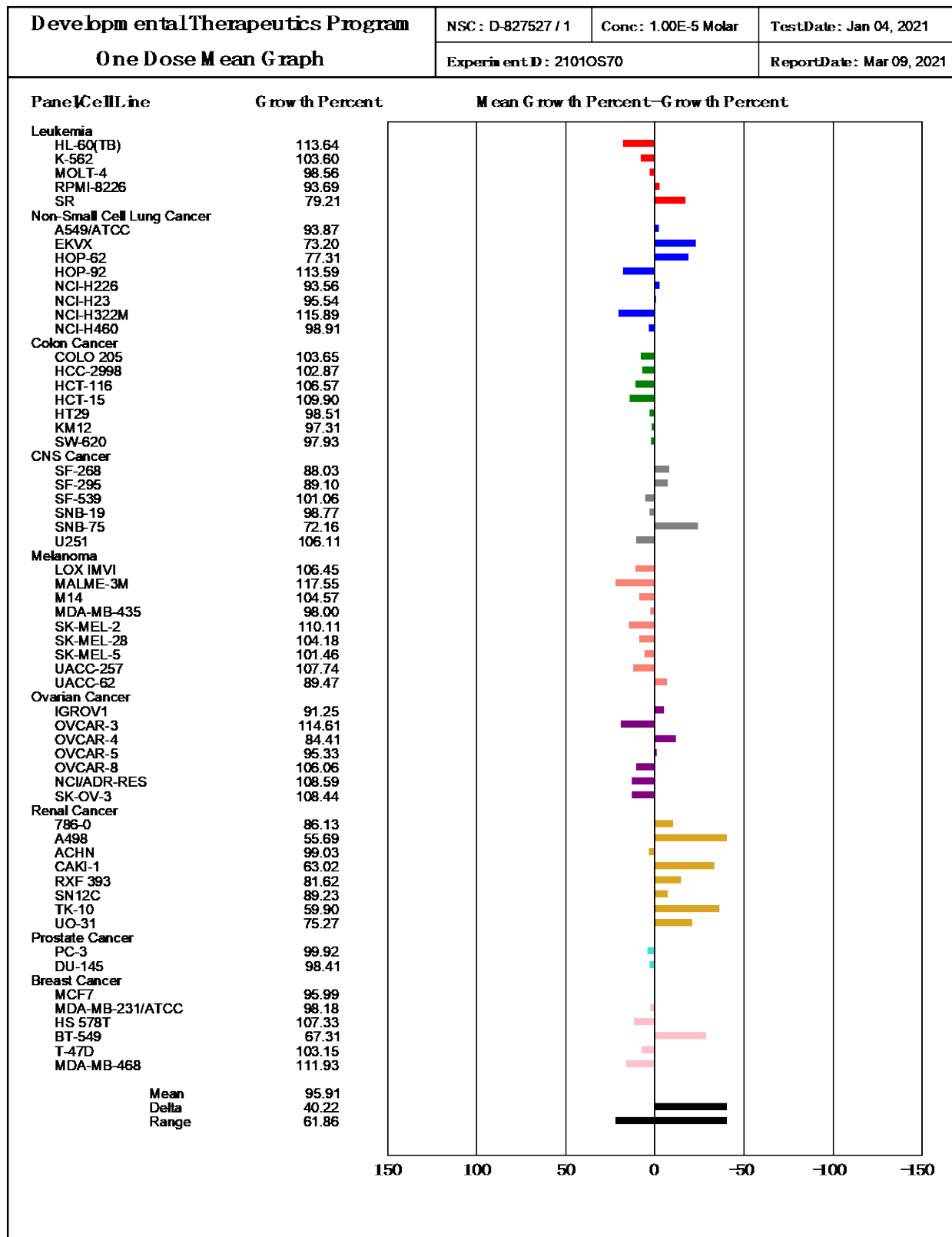


Figure S13. One dose mean growth % of compound 151 over NCI human cancer cell lines.