

SUPPLEMENTARY INFORMATION

Characterization of compounds (3a-c)

3,5-Bis(4-hydroxy-3-methylstyryl)-N-(2-methoxyphenyl)-1H-pyrazole-1-carboxamide (3a) Yield 82%; Brown solid (EtOH), mp 150-152 °C; yield 78%; IR (KBr) ν_{\max} : 3427 (OH), 3299 (NH), 1650 (C=O), 1544 (C=N), 1355 (O-CH₃) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 3.69 (3H, s, OCH₃), 3.83 (6H, s, OCH₃), 4.62 (2H, s, CH₂), 6.61 (1H, s, CH=C), 6.73 (2H, d, *J* = 12.4 Hz, CH and CH), 6.75 (2H, d, *J* = 12.4 Hz, CH and CH), 6.80-7.13 (10H, m, ArH), 9.14 (1H, s, ArOH), 9.56 (1H, s, ArOH), 10.56 (1H, s, CONH); ¹³C NMR (100 MHz, DMSO-*d*₆): δ ppm 162.91, 156.81, 151.32, 147.21, 144.93, 133.22, 133.41, 128.81, 128.03, 123.60, 120.09, 122.68, 116.82, 114.07, 107.73, 56.24; EIMS *m/z* = 514.1 [M+1]⁺.

3,5-Bis(4-hydroxy-3-methoxystyryl)-1H-pyrazole-1-yl-(phenoxy)ethanone (3b) Yield, 80%; Light brown solid, mp 140-142 °C; IR (KBr) ν_{\max} : 3431 (OH), 1600 (C=O), 1548 (C=N), 1514 (C=C), 1280 (C-O) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 3.83 (6H, s, OCH₃), 4.60 (2H, s, CH₂), 6.61 (1H, s, CH=C), 6.75 (2H, d, *J* = 14.2 Hz, CH and CH), 6.77 (2H, d, *J* = 14.4 Hz, CH and CH), 6.83-7.56 (11H, m, ArH), 9.14 (1H, s, ArOH), 9.64 (1H, s, ArOH); ¹³C NMR (100 MHz, DMSO-*d*₆): δ ppm 160.71, 151.32, 147.46, 144.89, 137.31, 133.41, 129.83, 128.81, 123.6, 121.18, 120.19, 116.80, 114.31, 112.101, 107.72, 72.09, 56.41; EIMS *m/z* = 499.51 [M+1]⁺.

3,5-Bis(4-hydroxy-3-methoxystyryl)-1H-pyrazole-1-yl-(2,4-dichlorophenoxy)ethanone (3c) Yield 78%; Light yellow solid, mp 102-104 °C; yield 74%; IR (KBr) ν_{\max} : 3427 (OH), 1610 (C=O), 1585 (C=N), 1548 (C=C), 1276 (C-O), 680 (C-Cl) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 3.82 (6H, s, OCH₃), 4.80 (2H, s, CH₂), 6.61 (1H, s, CH=C), 6.75 (2H, d, *J* = 14.4 Hz, CH and CH), 6.77 (2H, d, *J* = 14.4 Hz, CH and CH), 6.91-7.59 (9H, m, ArH), 9.15 (1H, s, ArOH), 9.91 (1H, s, ArOH); ¹³C NMR (100 MHz, DMSO-*d*₆): δ ppm 162.71, 152.81, 151.32, 147.21, 144.89, 133.41, 133.01, 128.81, 128.03, 124.60, 120.18, 117.13, 116.81, 112.01, 107.71, 72.24, 56.25; EIMS *m/z* = 567.41 [M]⁺, 569.4 [M+2]⁺.

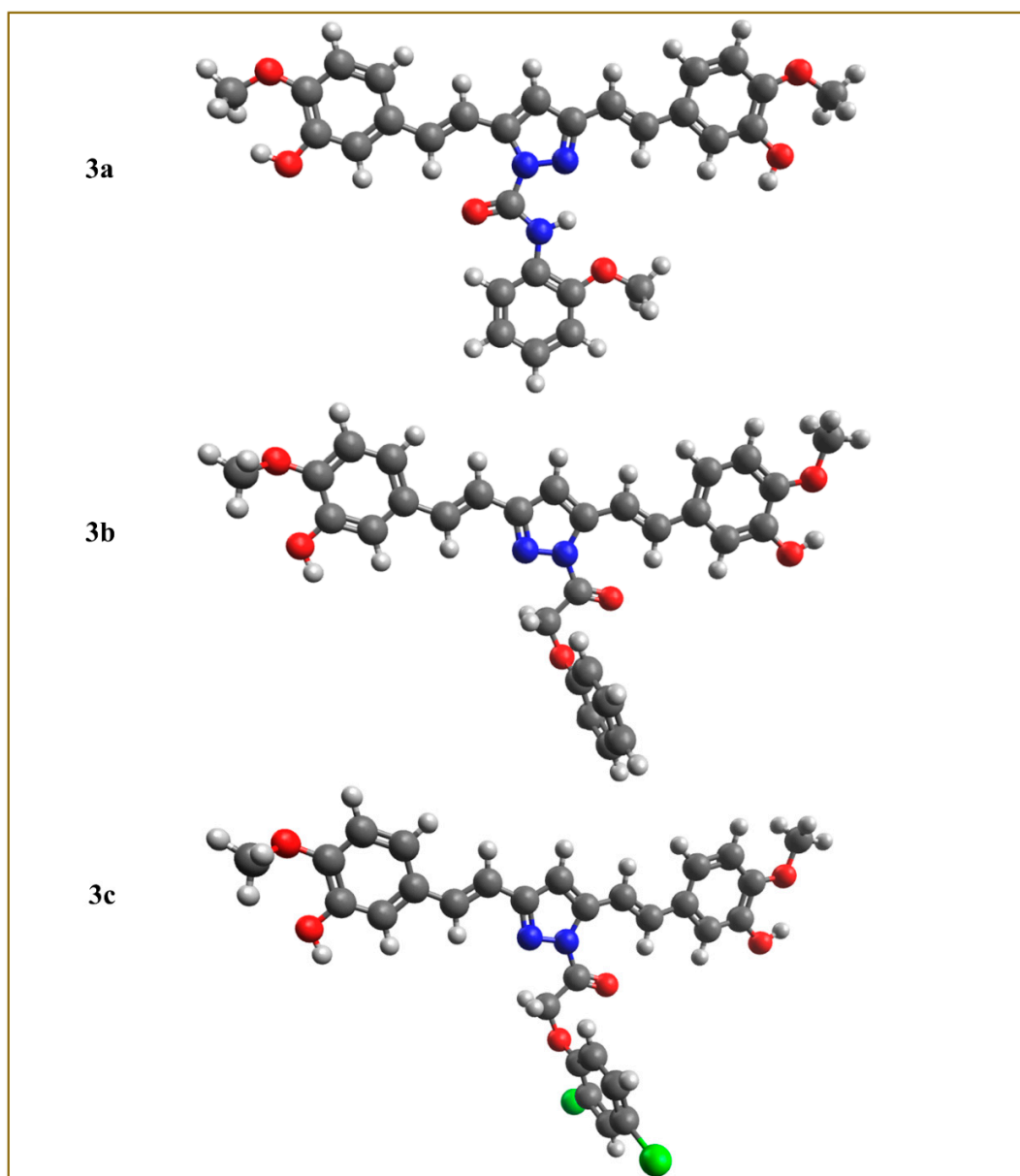


Figure S1. The DFT-optimized conformations of the compounds **3a–c**.

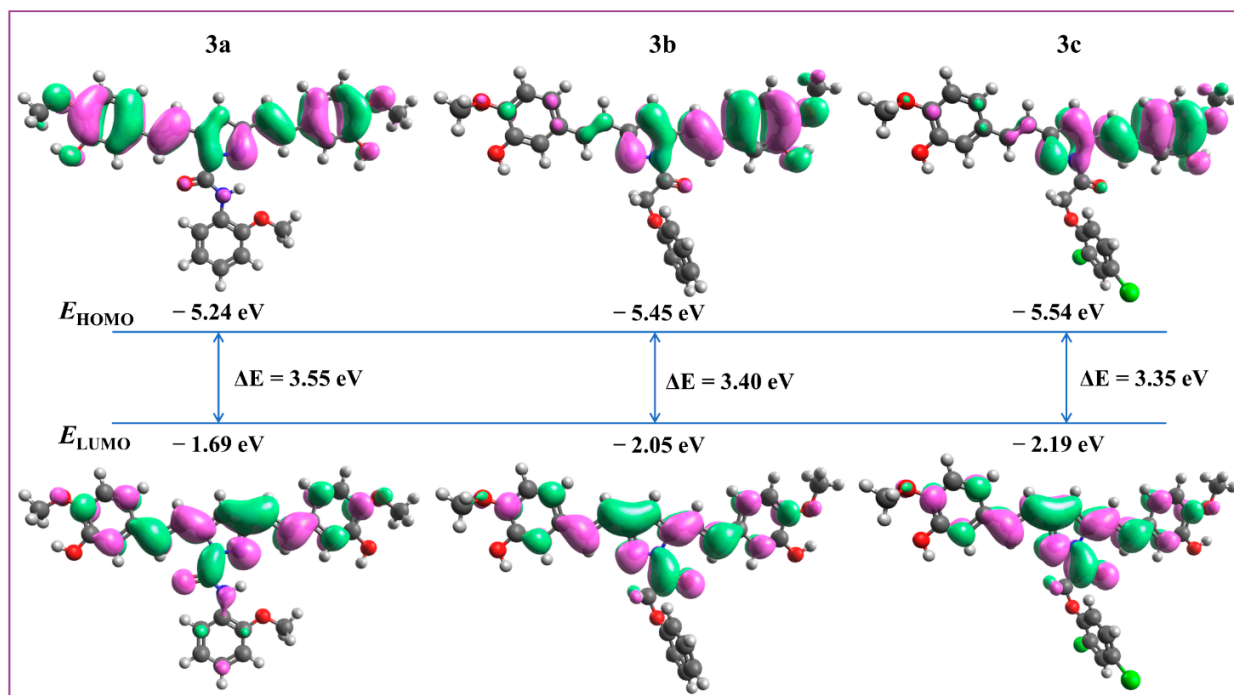


Figure S2. Visualization of HOMO/LUMO of compounds 3a-c.

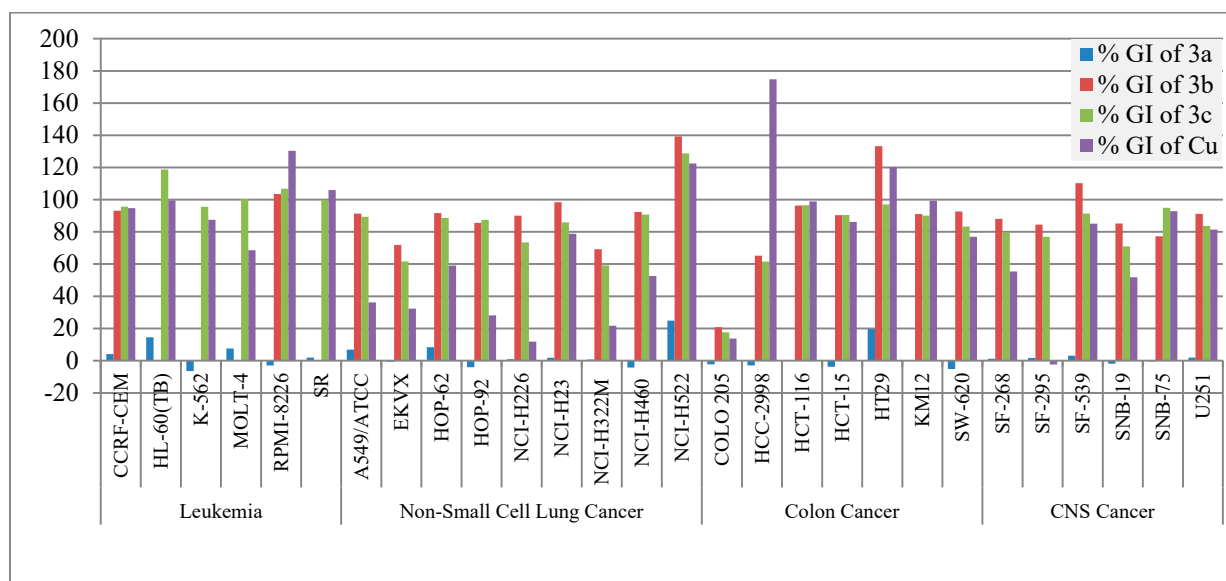


Figure S3. The comparative %GIs of curcumin analogues (3a-c) and curcumin (Cu) against leukemia, non-small lung cancer, colon and CNS cancer panels at 10 μM .

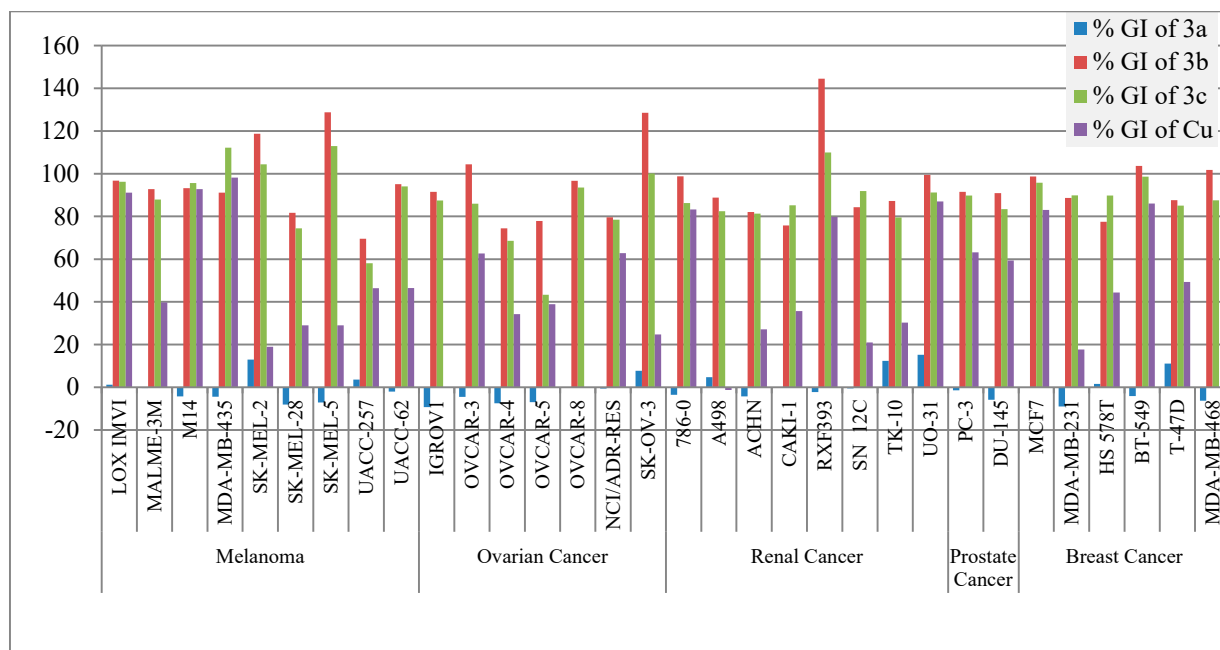


Figure S4. The comparative %GIs of curcumin analogues (**3a-c**) and curcumin (**Cu**) against melanoma, ovarian, renal, prostate and breast cancer panels at 10 μ M.

Table S1: 59 NCI cancer cell lines based antiproliferative activity of curcumin analogues **3a-c** in single dose (10 μ M) and 5-dose assay (0.001-100 μ M) of curcumin analogues **3b-c**.

| Panel | Cell line | One dose assay (10 μ M) | | | Five dose assay | | | |
|----------------------------|-----------|-----------------------------|--------|--------|-----------------|------------------|-------|------------------|
| | | 3a | 3b | 3c | 3b | | 3c | |
| | | GP | GP | GP | TGI | LC ₅₀ | TGI | LC ₅₀ |
| Leukemia | CCRF-CEM | 95.87 | 6.79 | 4.35 | 1.34 | >100 | >100 | >100 |
| | HL-60(TB) | 85.39 | - | -18.70 | 0.901 | >100 | 1.31 | >100 |
| | K-562 | 106.41 | - | 4.41 | 1.08 | >100 | >100 | >100 |
| | MOLT-4 | 92.36 | - | -0.33 | 3.26 | >100 | 3.46 | >100 |
| | RPMI-8226 | 102.92 | -3.54 | -6.80 | 2.36 | >100 | 7.62 | >100 |
| | SR | 98.12 | - | 0.01 | 2.46 | >100 | - | >100 |
| Non-Small Cell Lung Cancer | A549/ATCC | 93.11 | 8.68 | 10.58 | 11.1 | 47.2 | 10.3 | 54.2 |
| | EKVX | 100.71 | 28.12 | 38.35 | 10.3 | 32.4 | 9.72 | 36.2 |
| | HOP-62 | 91.63 | 8.39 | 11.28 | 4.95 | 33.3 | 3.16 | 26.7 |
| | HOP-92 | 104.08 | 14.37 | 12.55 | 20.4 | >100 | 7.94 | 36.5 |
| | NCI-H226 | 99.06 | 9.96 | 26.52 | 9.94 | >100 | 10.2 | >100 |
| | NCI-H23 | 98.21 | 1.60 | 14.08 | 6.64 | >100 | 5.00 | >100 |
| | NCI-H322M | 99.22 | 30.84 | 40.82 | 10.3 | 46.2 | 11.3 | 56.0 |
| | NCI-H460 | 104.28 | 7.60 | 9.28 | 10.2 | 49.2 | 14.2 | >100 |
| | NCI-H522 | 73.19 | -39.28 | -28.71 | 0.97 | 10.8 | 0.837 | 24.9 |

| | | | | | | | | |
|-----------------------|-------------|--------|--------|--------|-------|------|------|------|
| <i>Colon Cancer</i> | COLO 205 | 102.26 | 79.25 | 82.37 | 3.95 | 7.94 | 4.01 | 8.12 |
| | HCC-2998 | 102.95 | 34.76 | 38.48 | 10.2 | 32.0 | 12.4 | 37.5 |
| | HCT-116 | - | 3.68 | 3.48 | 10 | >100 | 6.21 | 53.1 |
| | HCT-15 | 103.77 | 9.64 | 9.52 | 7.96 | 35.1 | 3.61 | 53.8 |
| | HT29 | 80.40 | -33.23 | 2.93 | 6.35 | 44.7 | 7.03 | >100 |
| | KM12 | 99.93 | 8.96 | 9.93 | 6.81 | 51.7 | 26.2 | >100 |
| | SW-620 | 105.14 | 7.35 | 16.73 | 9.02 | 82.3 | >100 | >100 |
| <i>CNS Cancer</i> | SF-268 | 98.73 | 11.95 | 20.22 | 5.65 | 29.4 | 9.84 | >100 |
| | SF-295 | 98.22 | 15.50 | 23.11 | 7.70 | 38.5 | 8.87 | 41.6 |
| | SF-539 | 96.92 | -10.32 | 8.64 | 2.47 | 32.5 | 2.85 | 25.4 |
| | SNB-19 | 101.82 | 14.75 | 28.98 | 9.59 | 61.7 | 11.7 | 43.5 |
| | SNB-75 | 100.46 | 22.74 | 5.12 | 5.30 | 40.2 | 7.81 | >100 |
| | U251 | 98.12 | 8.81 | 16.31 | 5.96 | 28.0 | 6.15 | 30.8 |
| <i>Melanoma</i> | LOX IMVI | 98.77 | 3.23 | 3.79 | 3.29 | >100 | 3.29 | 57.1 |
| | MALME-3M | 100.37 | 7.21 | 12.09 | 3.71 | 33.8 | 5.03 | 35.1 |
| | M14 | 104.24 | 6.75 | 4.34 | 2.68 | 28.6 | 4.83 | 35.9 |
| | MDA-MB-435 | 104.44 | 8.84 | -12.15 | 0.492 | 46.9 | 14.7 | >100 |
| | SK-MEL-2 | 87.05 | -18.73 | -4.36 | 3.56 | 23.0 | 1.54 | 34.9 |
| | SK-MEL-28 | 108.09 | 18.37 | 26.56 | 10.4 | >100 | 7.32 | 41.4 |
| | SK-MEL-5 | 107.15 | -28.80 | -12.95 | 3.52 | 16.8 | 3.03 | 15.3 |
| | UACC-257 | 96.54 | 30.45 | 41.91 | 7.34 | 27.3 | 7.13 | 26.8 |
| | UACC-62 | 102.07 | 4.88 | 5.87 | 1.27 | 8.65 | 12.0 | >100 |
| <i>Ovarian Cancer</i> | IGROV1 | 109.32 | 8.43 | 12.54 | 8.00 | >100 | 10.3 | >100 |
| | OVCAR-3 | 104.55 | -4.46 | 13.99 | 2.77 | >100 | - | >100 |
| | OVCAR-4 | 107.52 | 25.60 | 31.42 | 12.3 | >100 | >100 | >100 |
| | OVCAR-5 | 106.96 | 22.11 | 56.73 | 6.81 | >100 | 8.32 | >100 |
| | OVCAR-8 | 100.06 | 3.26 | 6.52 | 8.57 | 35.2 | 6.09 | >100 |
| | NCI/ADR-RES | 100.60 | 20.44 | 21.50 | 11.7 | >100 | 21.1 | >100 |
| | SK-OV-3 | 92.27 | -28.58 | -0.16 | 3.45 | 7.75 | 3.43 | 9.35 |
| <i>Renal Cancer</i> | 786-0 | 103.54 | 1.27 | 13.69 | 3.58 | 13.6 | 2.52 | 8.35 |
| | A498 | 95.30 | 11.17 | 17.56 | 6.49 | 21.8 | 12.0 | 35.8 |
| | ACHN | 104.23 | 17.96 | 18.70 | 11.1 | >100 | 9.13 | 44.1 |
| | CAKI-1 | - | 24.20 | 14.79 | 12.4 | >100 | >100 | >100 |
| | RXF 393 | 102.31 | -44.52 | -9.98 | 2.52 | 6.34 | 3.33 | 8.77 |
| | SN 12C | 100.45 | 15.71 | 8.09 | 7.66 | >100 | 65.8 | >100 |
| | TK-10 | 87.62 | 12.73 | 20.52 | 10.9 | 33.0 | 8.06 | 29.2 |
| | UO-31 | 84.77 | 0.48 | 8.72 | 4.12 | 26.7 | 2.30 | 11.4 |
| <i>Prostate</i> | PC-3 | 101.38 | 8.49 | 10.23 | >100 | >100 | 8.02 | >100 |

| | | | | | | | | |
|--|------------|--------|-------|-------|------|------|------|------|
| <i>Cancer</i> | DU-145 | 105.84 | 9.09 | 16.54 | 8.06 | 29.4 | 9.94 | 32.2 |
| <i>Breast Cancer</i> | MCF7 | - | 1.30 | 4.21 | 2.83 | 4.48 | 2.33 | 94.8 |
| | MDA-MB-231 | 109.02 | 11.33 | 10.15 | 15.3 | >100 | 23.4 | >100 |
| | HS 578T | 98.44 | 22.50 | 10.22 | 6.84 | >100 | >100 | >100 |
| | BT-549 | 104.15 | -3.68 | 1.41 | 4.03 | >100 | 3.34 | 19.2 |
| | T-47D | 88.93 | 12.43 | 14.98 | 6.95 | 50.9 | 3.99 | >100 |
| | MDA-MB-468 | 106.31 | -1.76 | 12.50 | 7.39 | 38.5 | 5.34 | 25.3 |
| Mean | | 99.22 | 7.59 | 12.72 | | | | |
| (-) Indicates activity not tested; ^a The average sensitivity of all cell lines toward the test agent in μM ; ^b The average sensitivity of all cell lines of a particular subpanel toward the test agent in μM ; Bold font showed the good growth percent (GP) ($\leq 32\%$) in one dose assay; LC ₅₀ and TGI stand for 50% lethal concentration, and total growth inhibition respectively. | | | | | | | | |

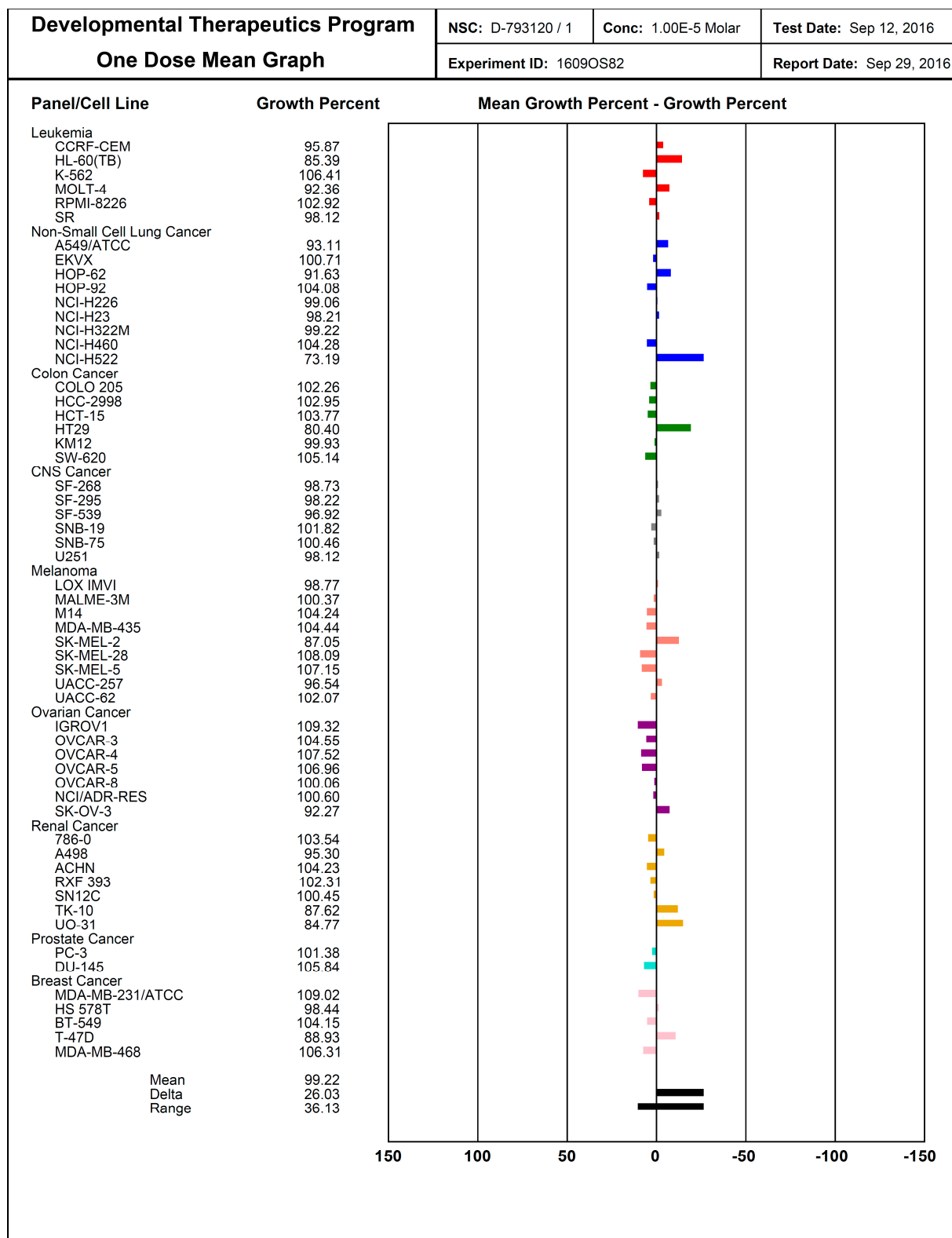
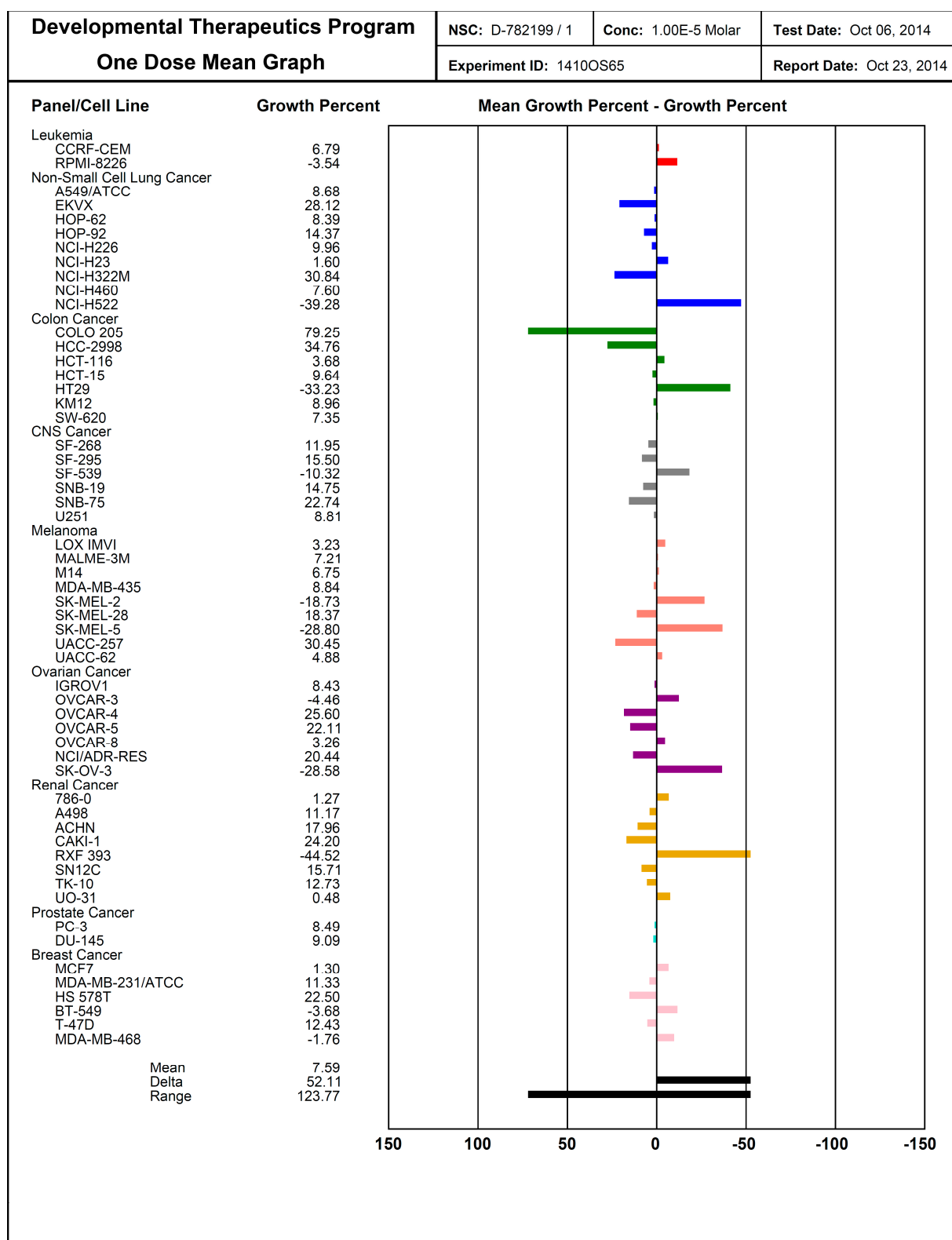


Figure S5. The anticancer data of compound **3a** at 10 μ M.



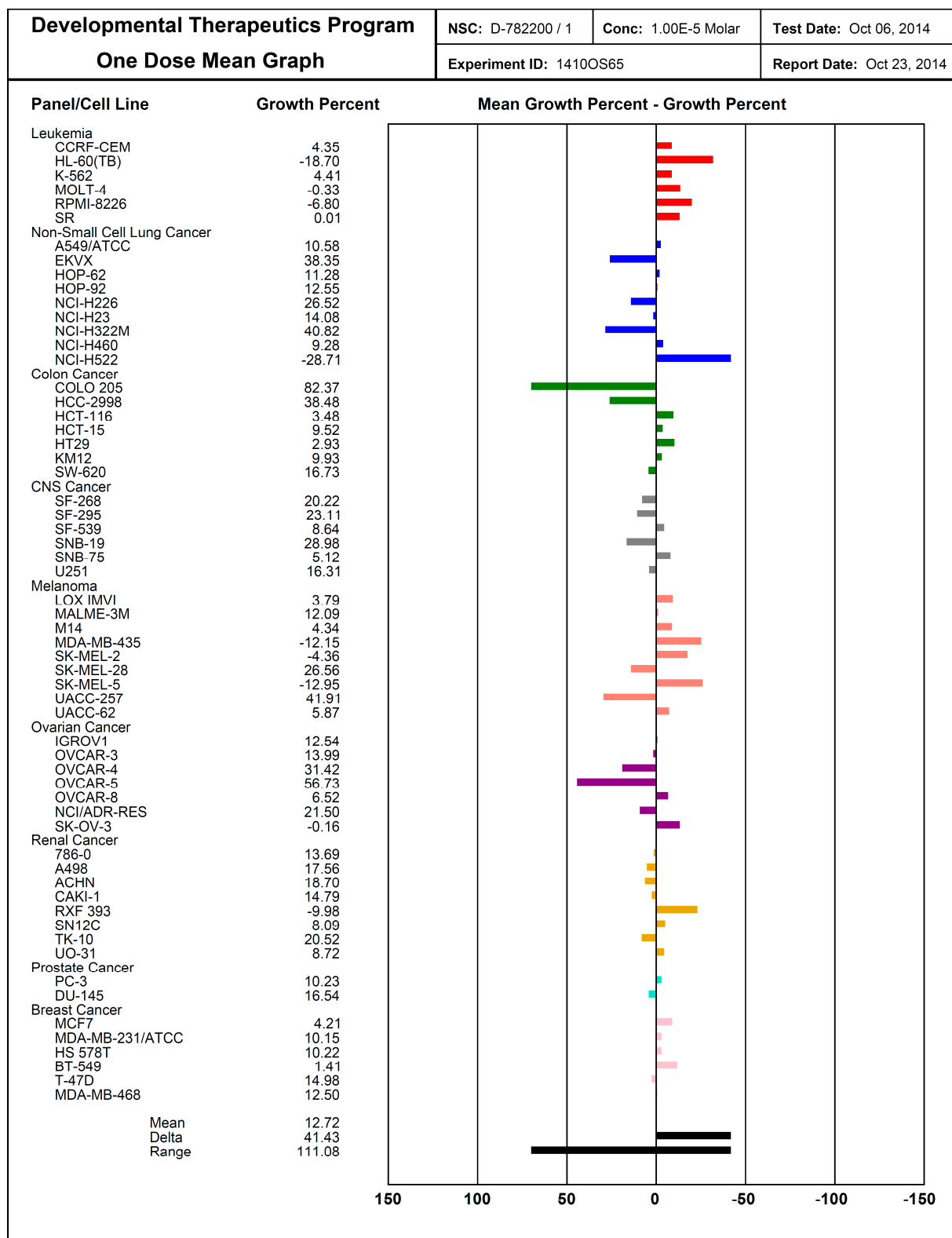


Figure S7. The anticancer data of compound **3c** at 10 μ M.

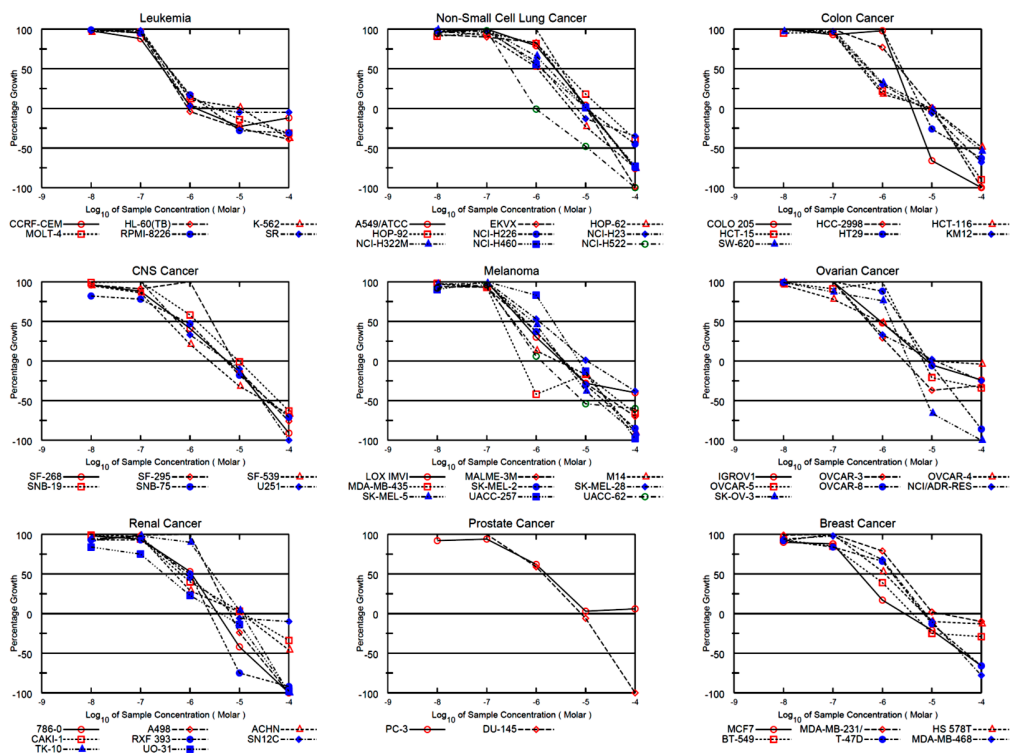


Figure S8. 60 NCI cancer cell lines based antiproliferative activity of curcumin analogue 3b.

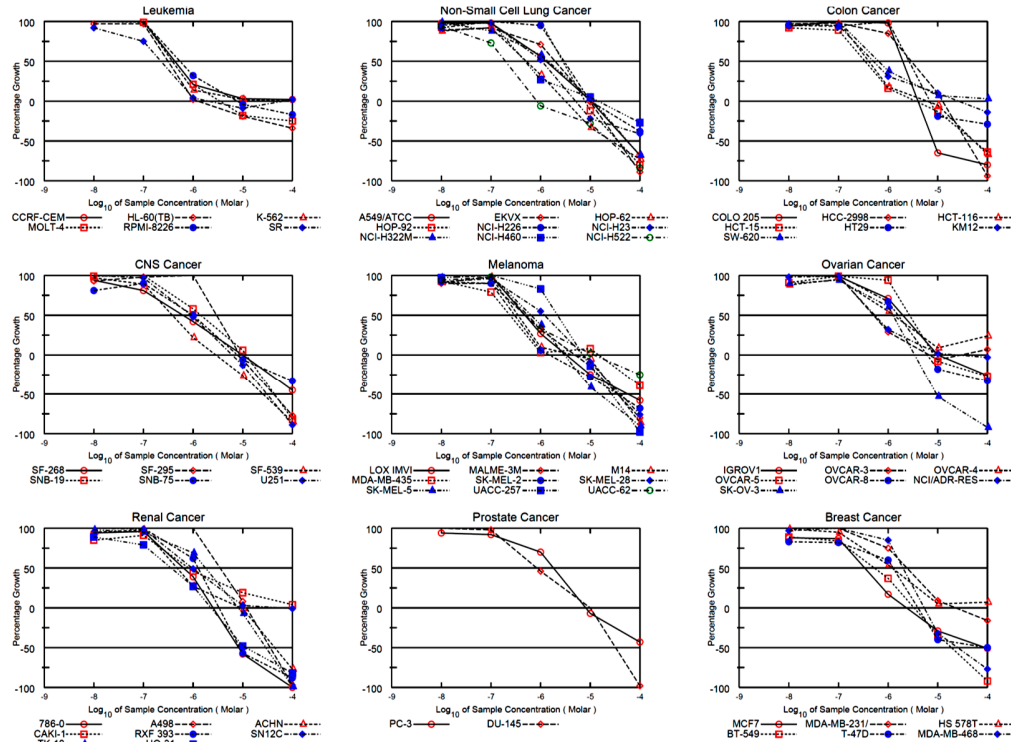


Figure S9. 60 NCI cancer cell lines based antiproliferative activity of curcumin analogue 3c.