

Supporting information

- 1 Spectral data
- 2 NCI-60 cell line screening
- 3 Docking studies
- 4 ADMET analysis

1 Spectral data

1.1 3a

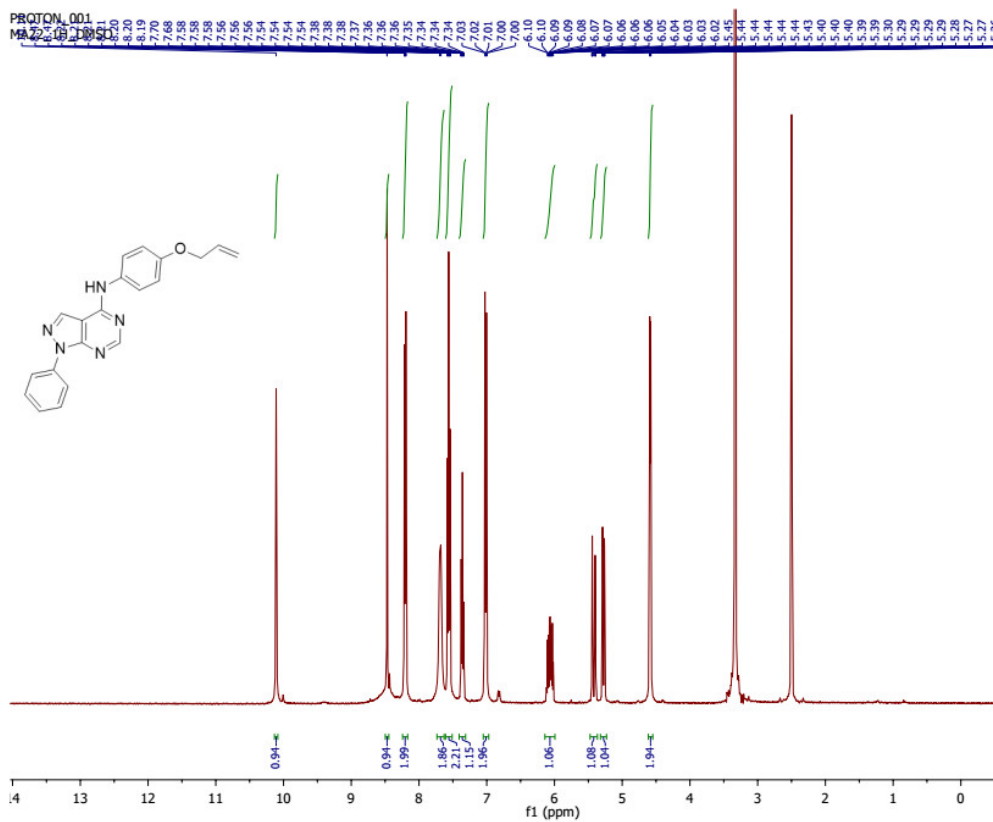


Figure S1. ¹H NMR of 3a.

1.2 3b

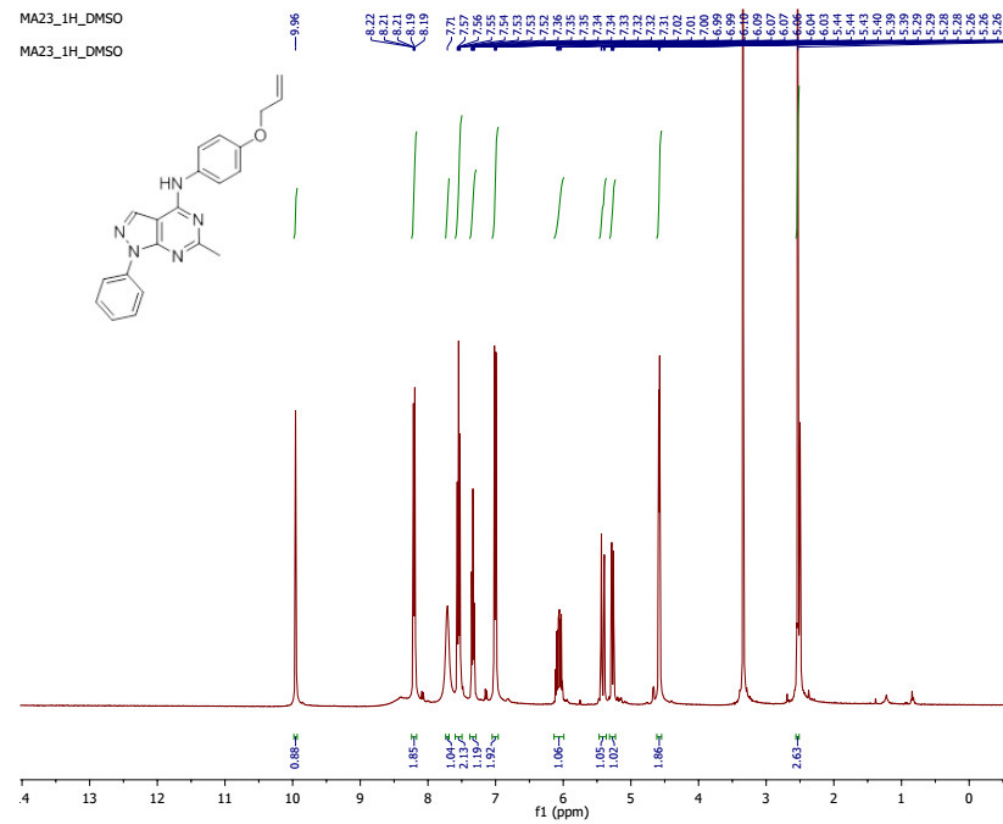


Figure S2. ¹H NMR of 3b.

1.3 3c

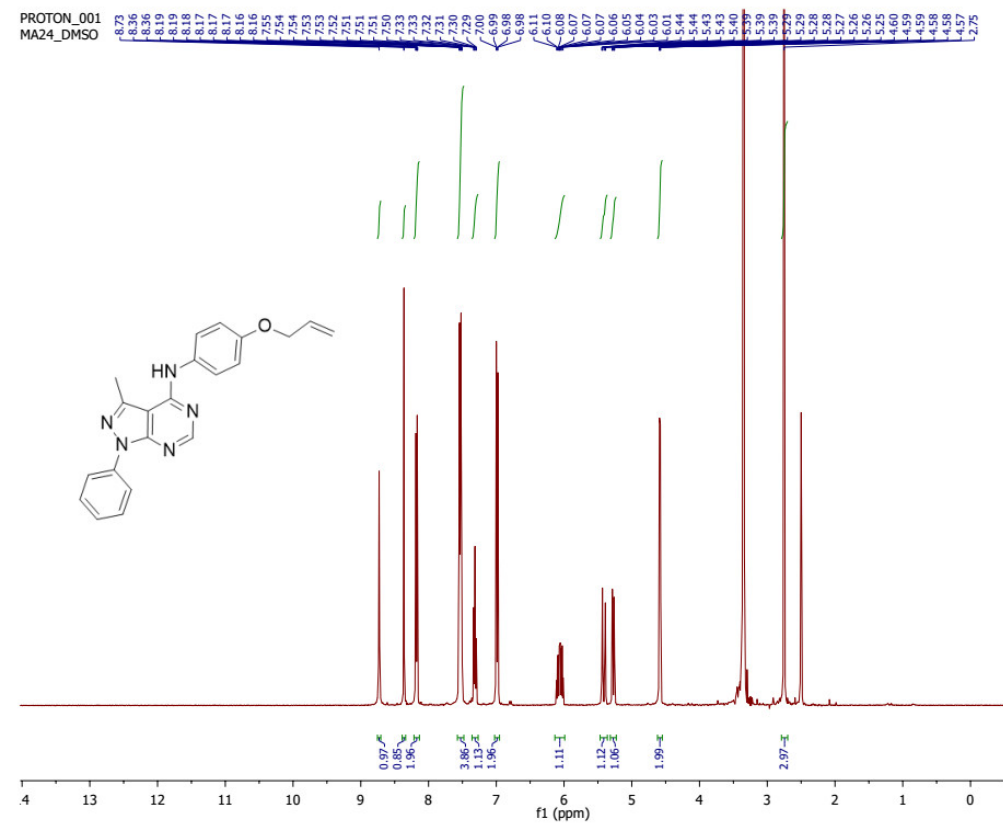


Figure S3. ¹H NMR of 3c.

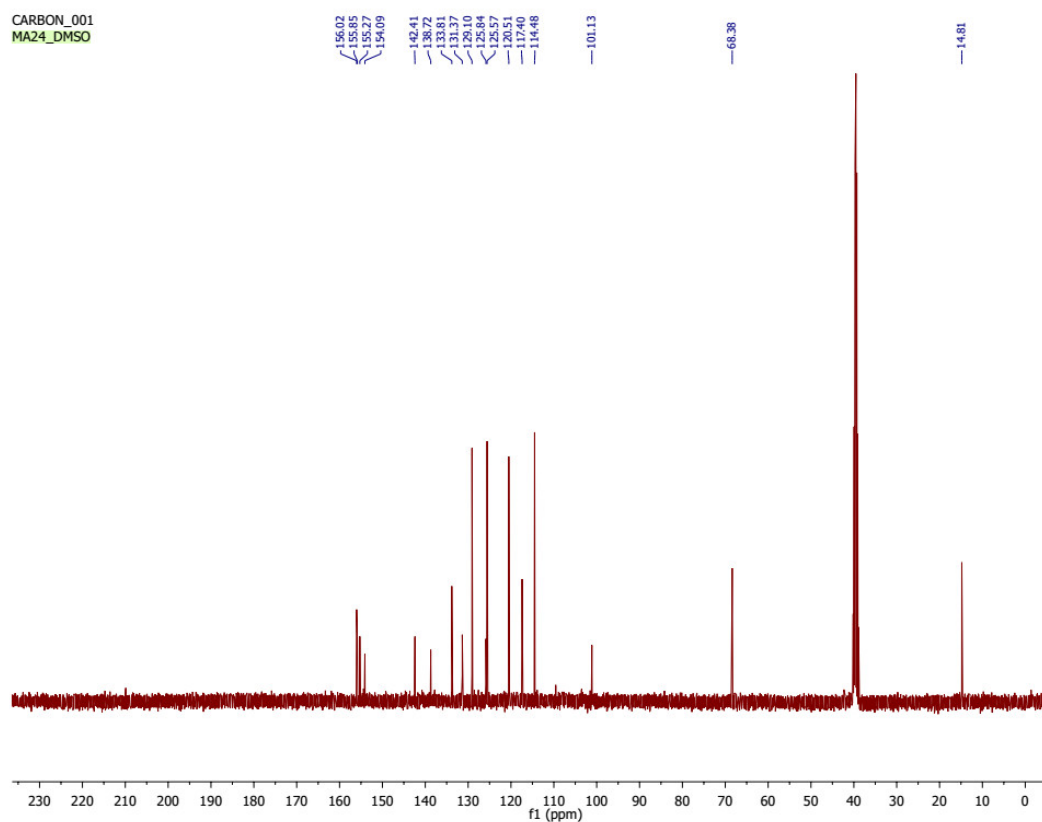


Figure S4. ^{13}C NMR of 3c.

1.4 3d

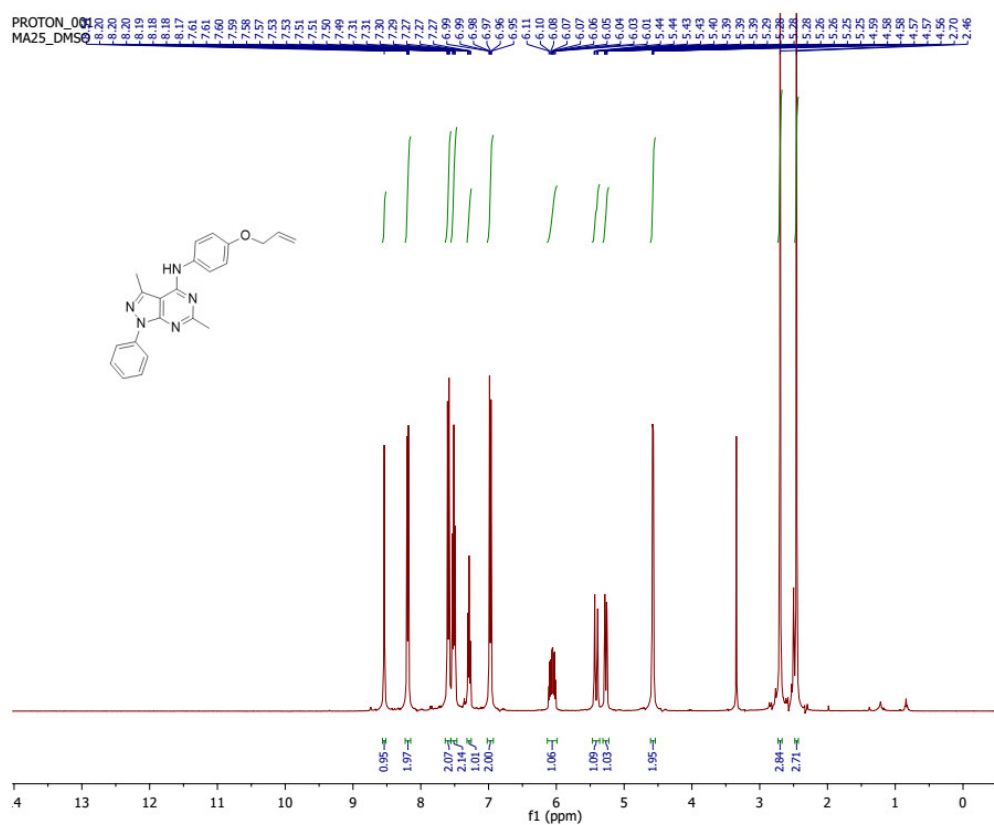


Figure S5. ^1H NMR of 3d.

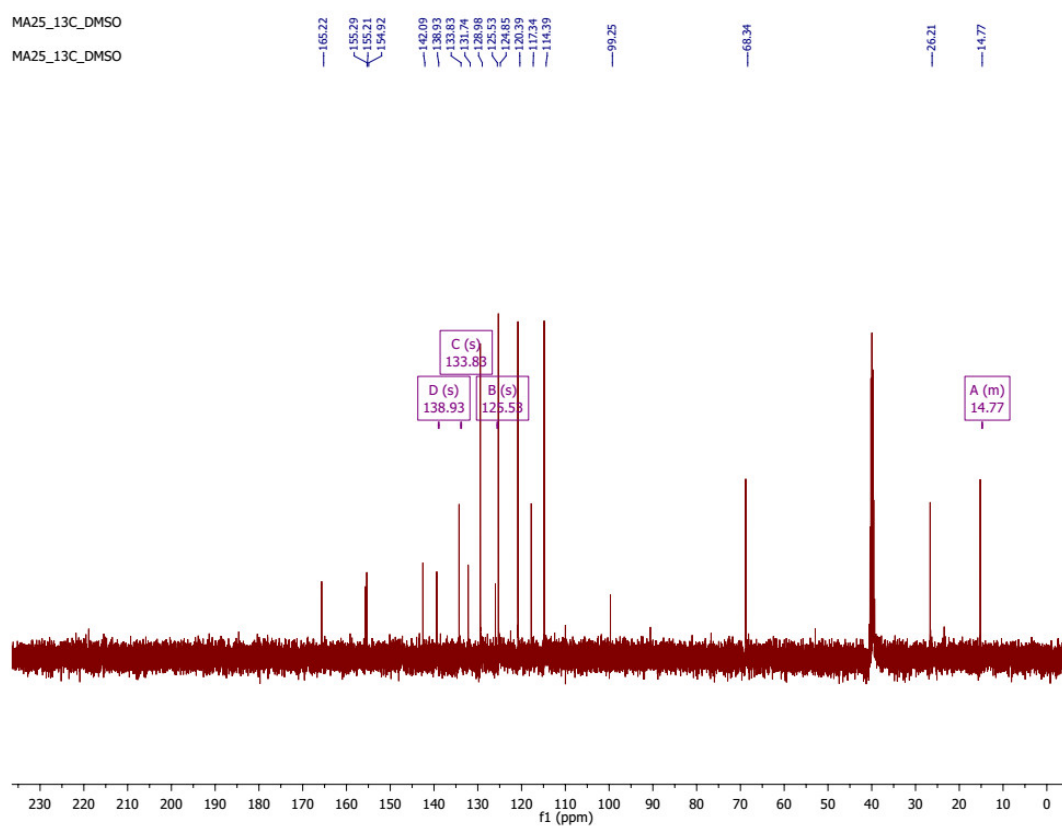


Figure S6. ^{13}C NMR of 3d.

1.5 5a

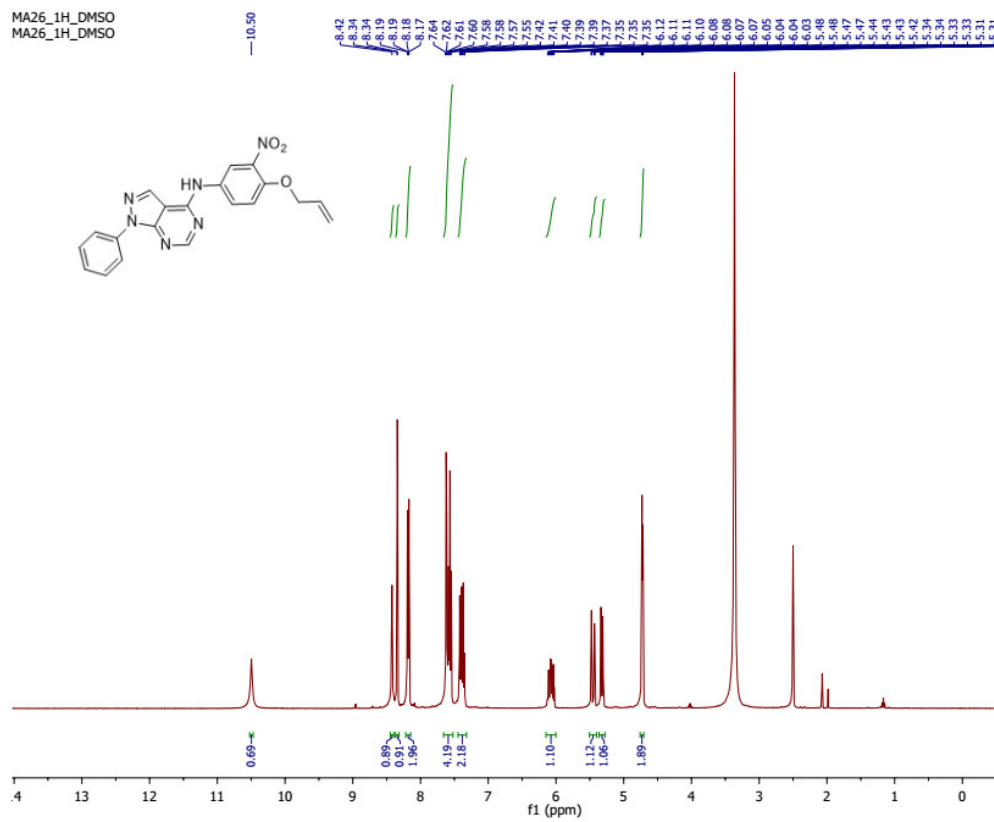


Figure S7. ^1H NMR of 5a.

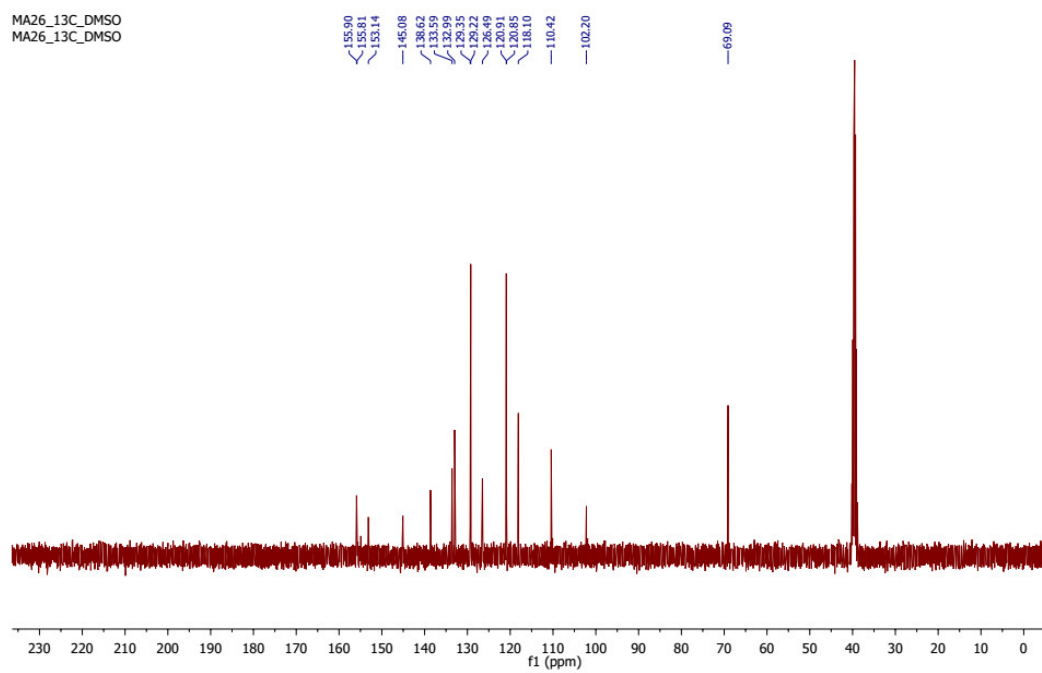


Figure S8. ^{13}C NMR of 5a.

1.6 5b

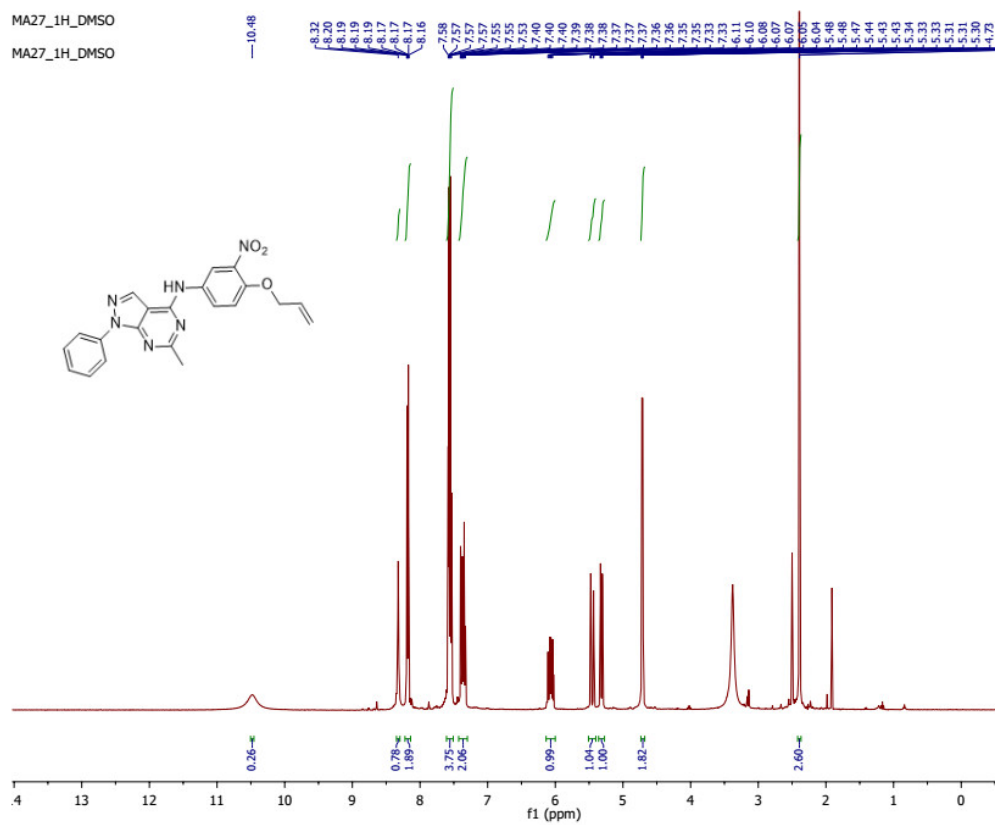


Figure S9. ^1H NMR of 5b.

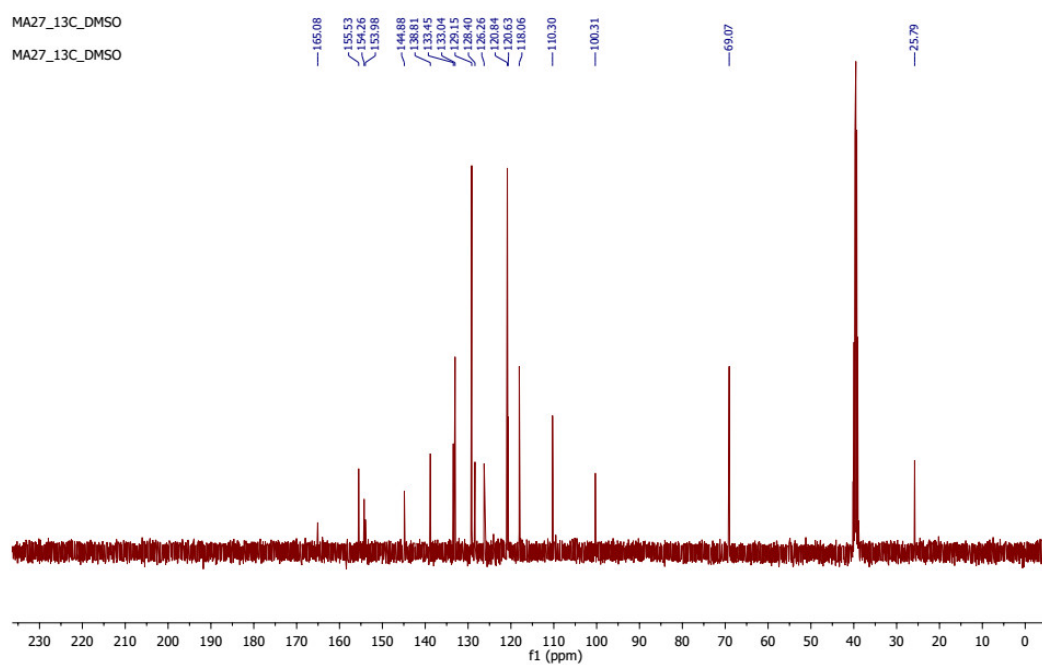


Figure S10. ^{13}C NMR of **5b**.

1.7 5c

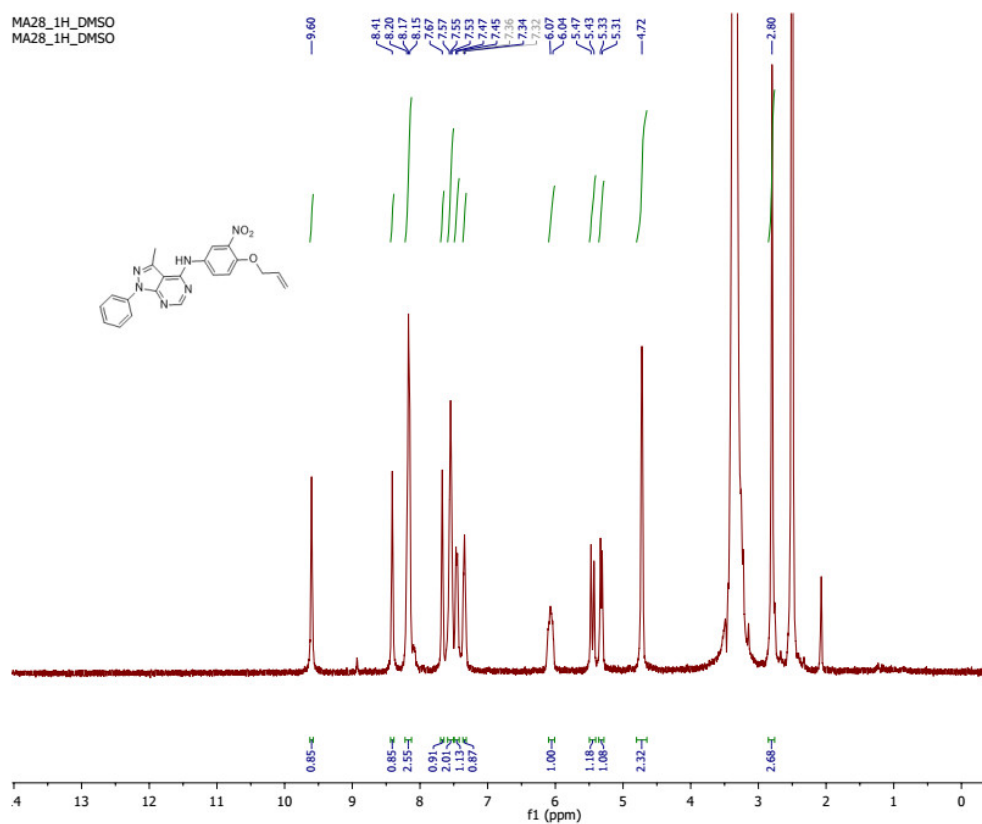


Figure S11. ^1H NMR of **5c**.

1.8 5d

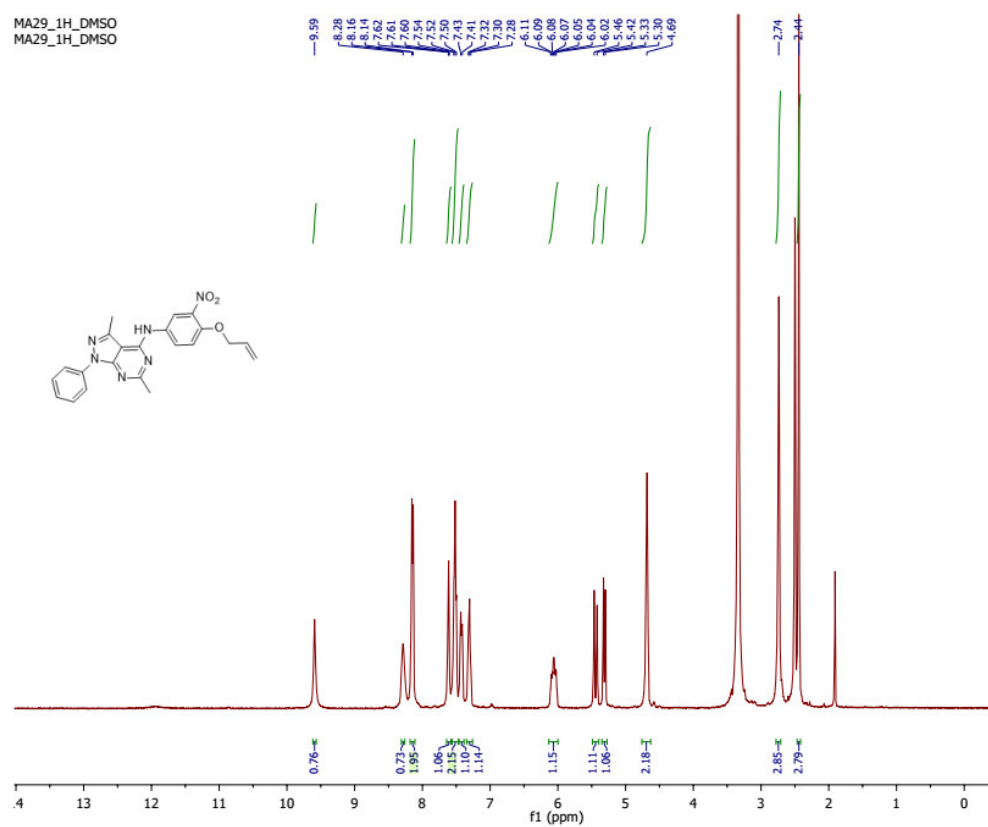


Figure S12. ¹³C NMR of 5d.

1.9 6a

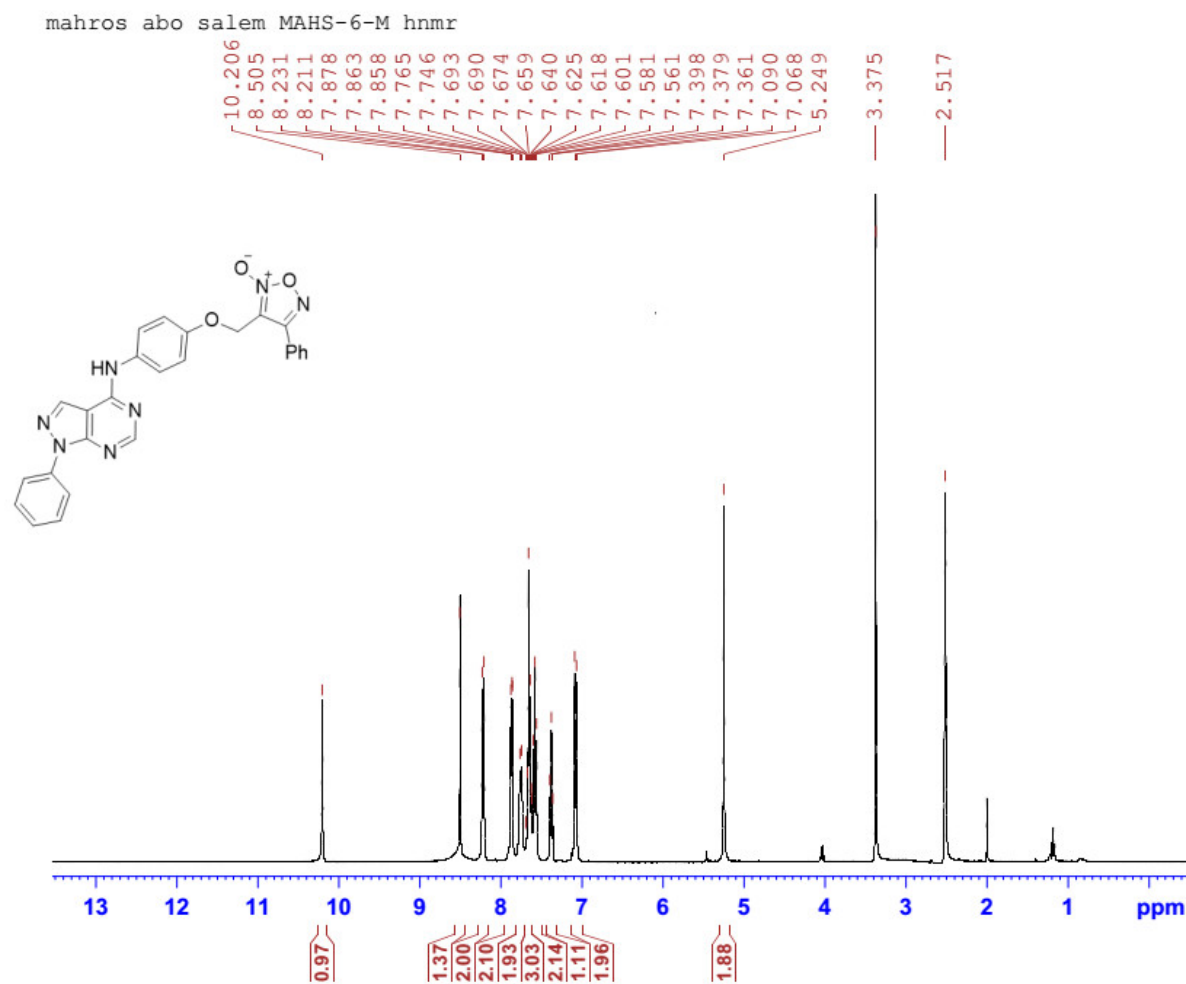


Figure S13. ¹H NMR of 6a.

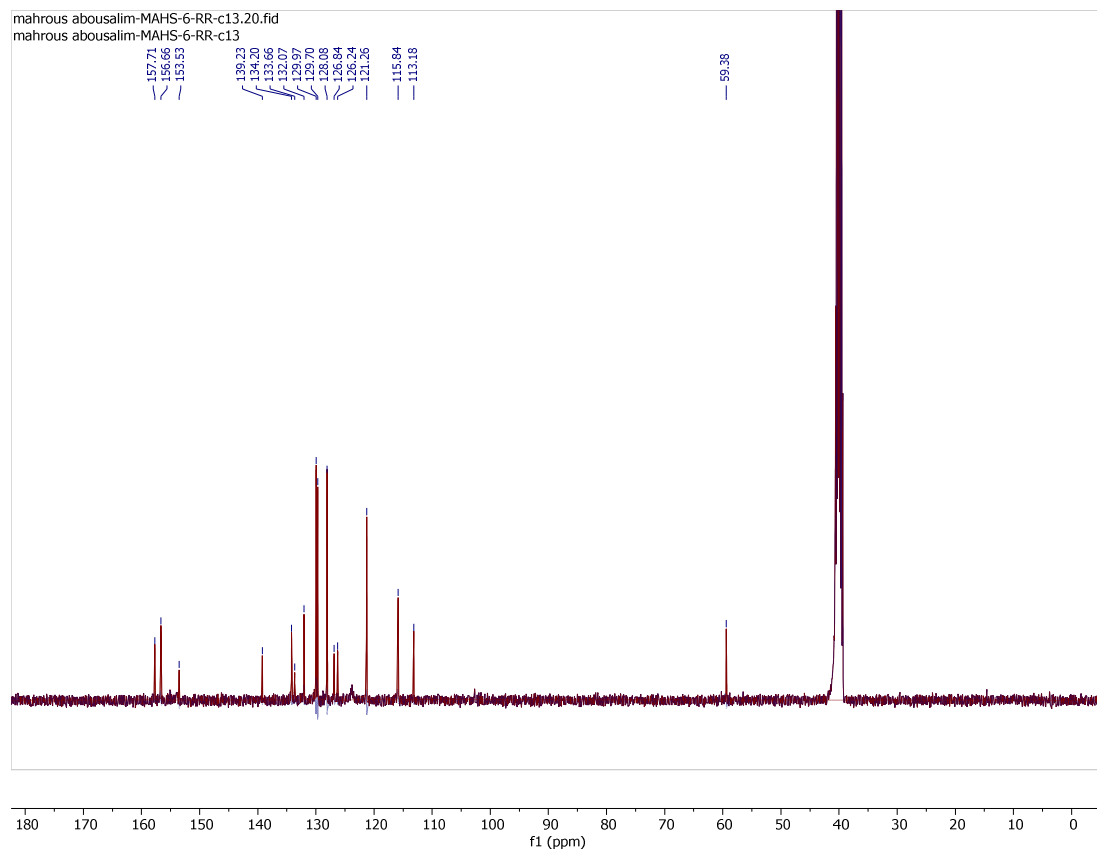


Figure S14. ¹³C NMR of 6a.

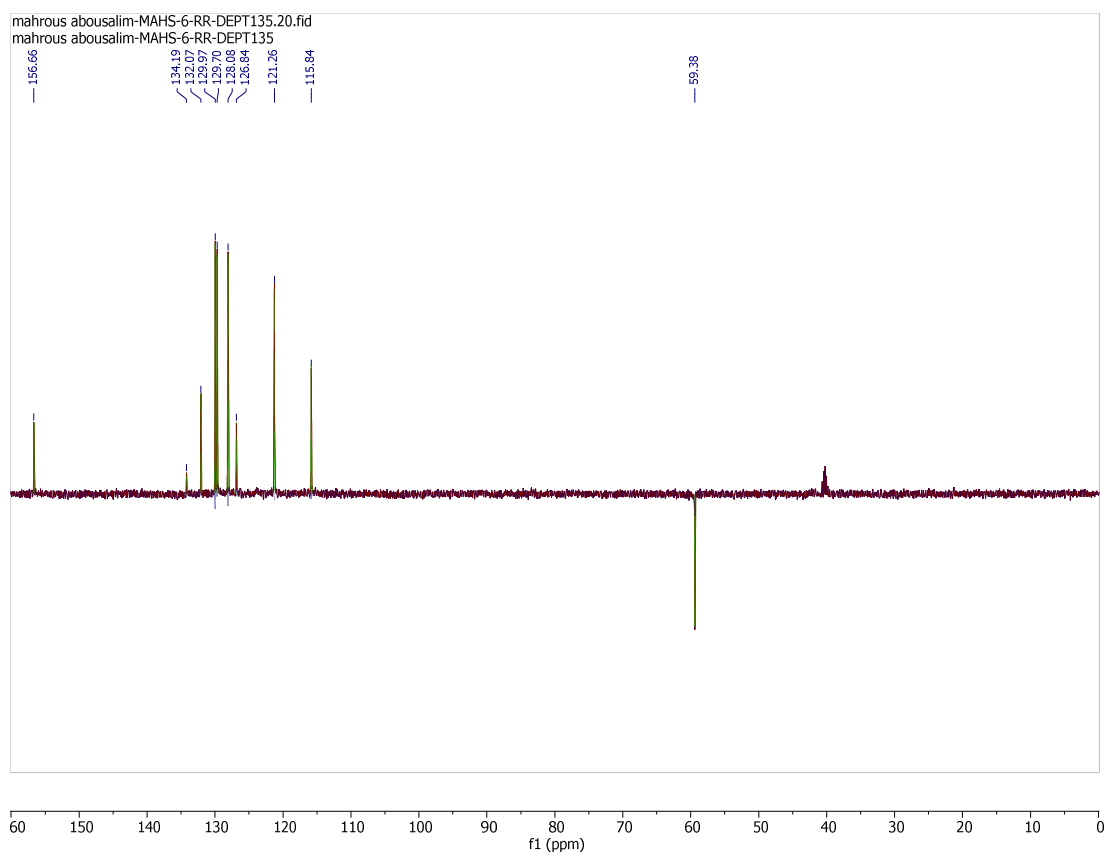


Figure S15. DEPT135 ^{13}C NMR of **6a**.

1.10 6b

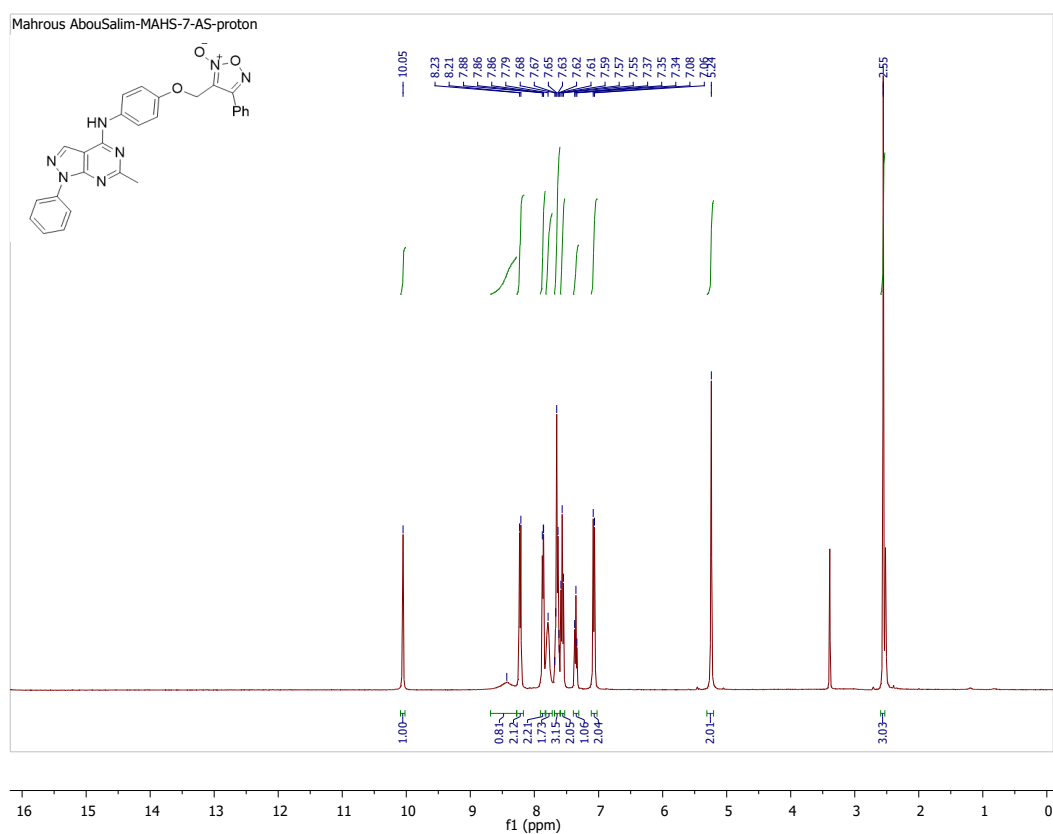


Figure S16. ^1H NMR of **6b**.

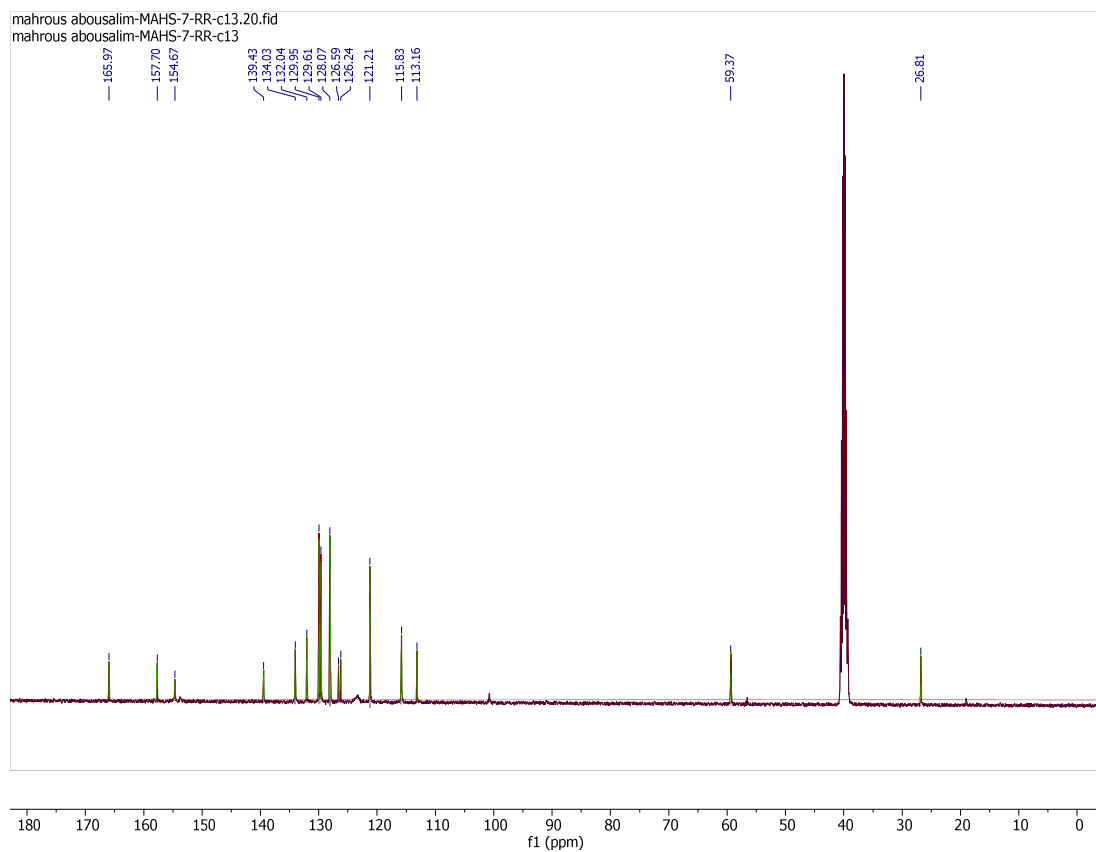


Figure S17. ^{13}C NMR of **6b**.

1.11 6c

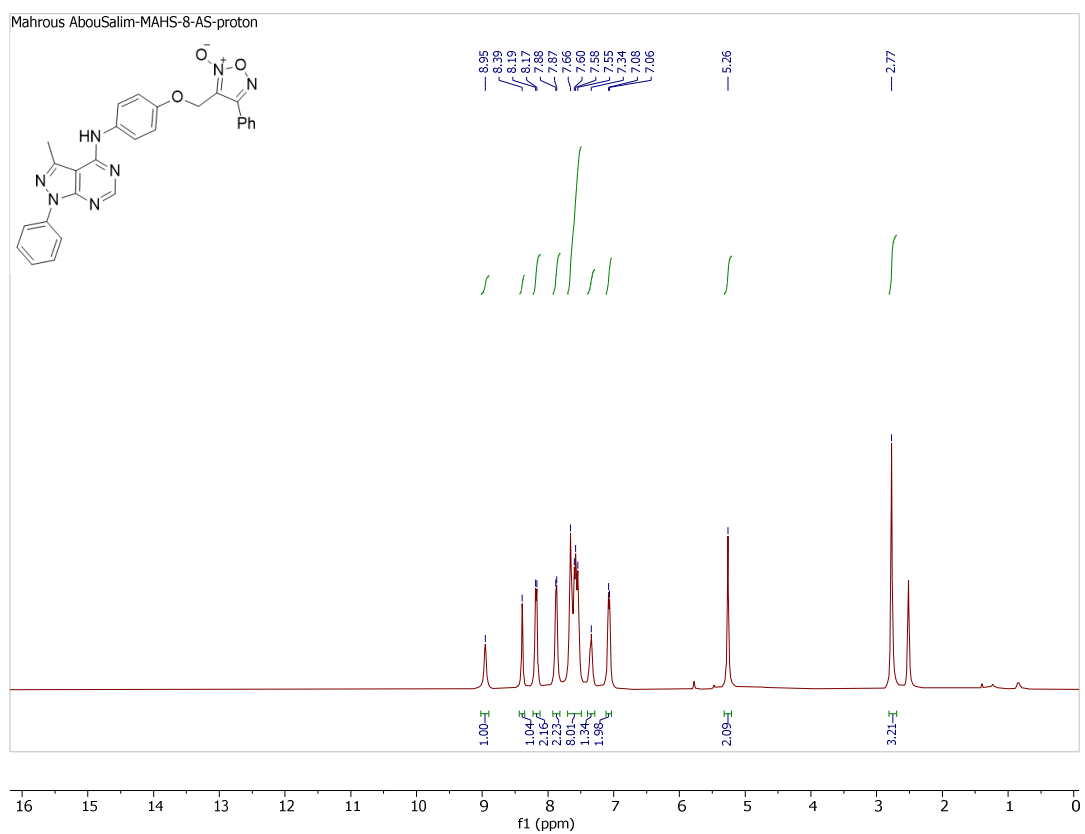


Figure S18. ^1H NMR of **6c**.

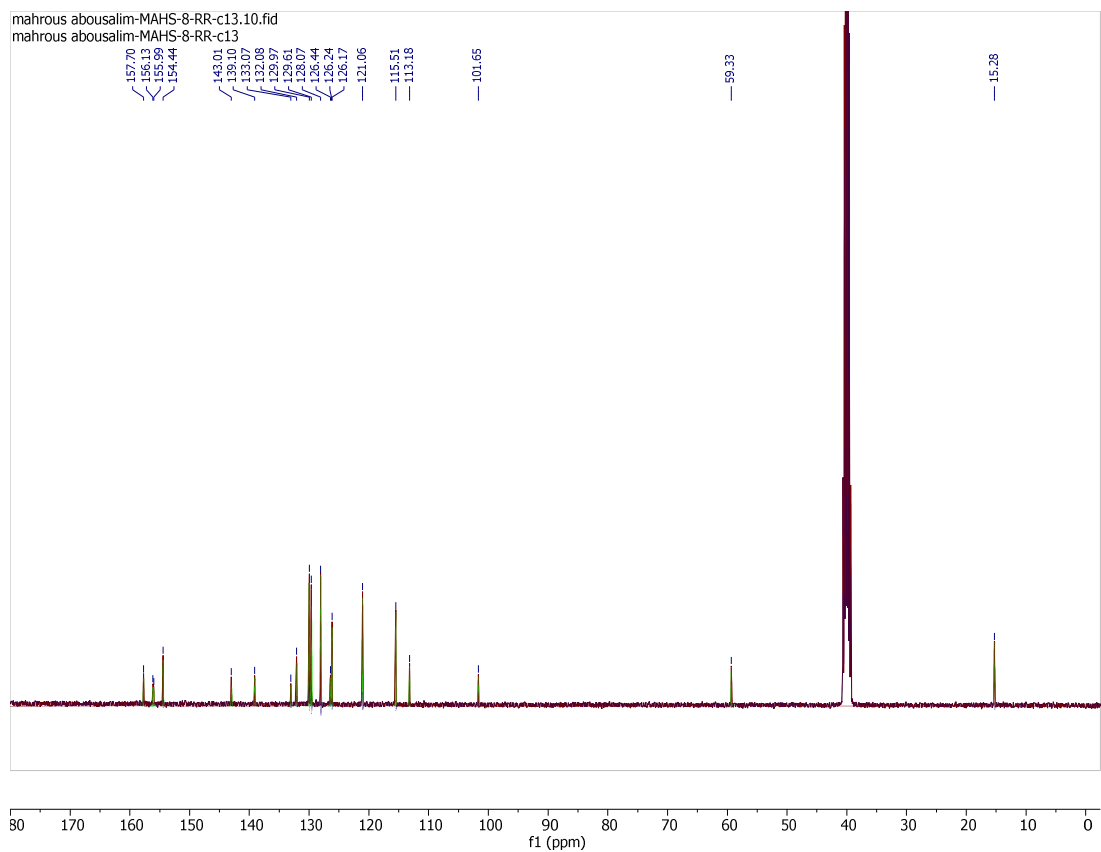


Figure S19. ^{13}C NMR of **6c**.

1.12 6d

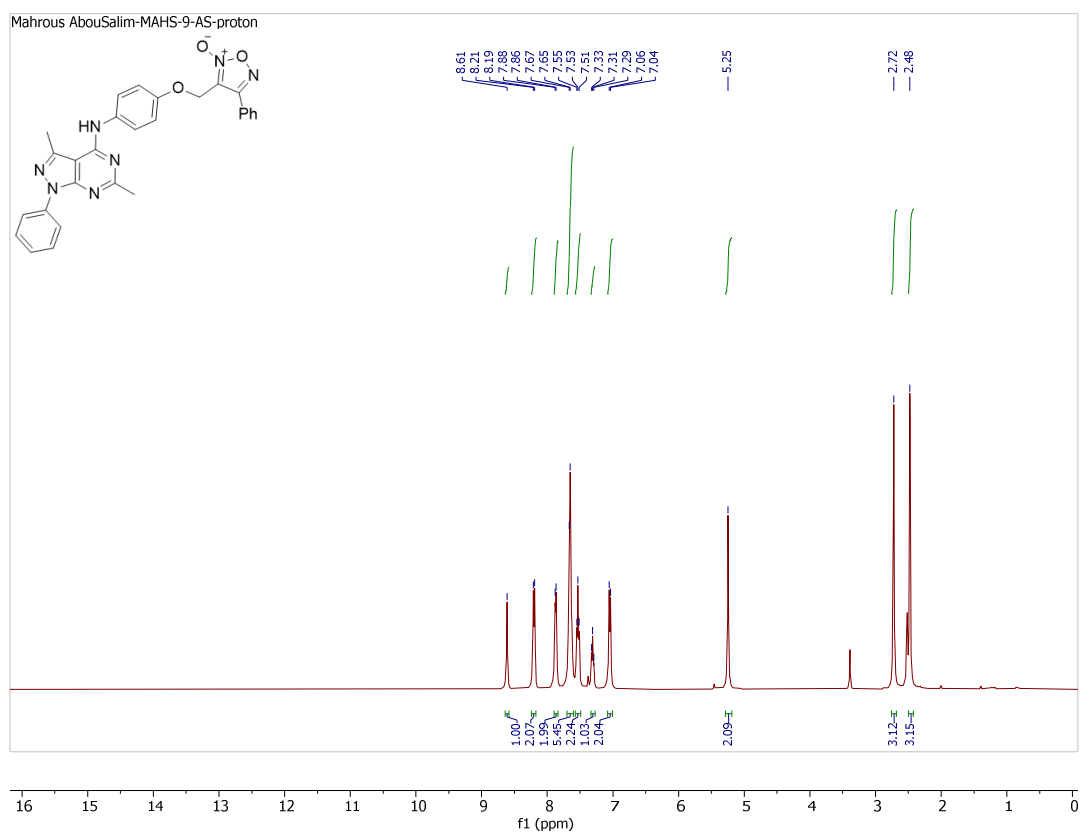


Figure S20. ^1H NMR of **6d**.

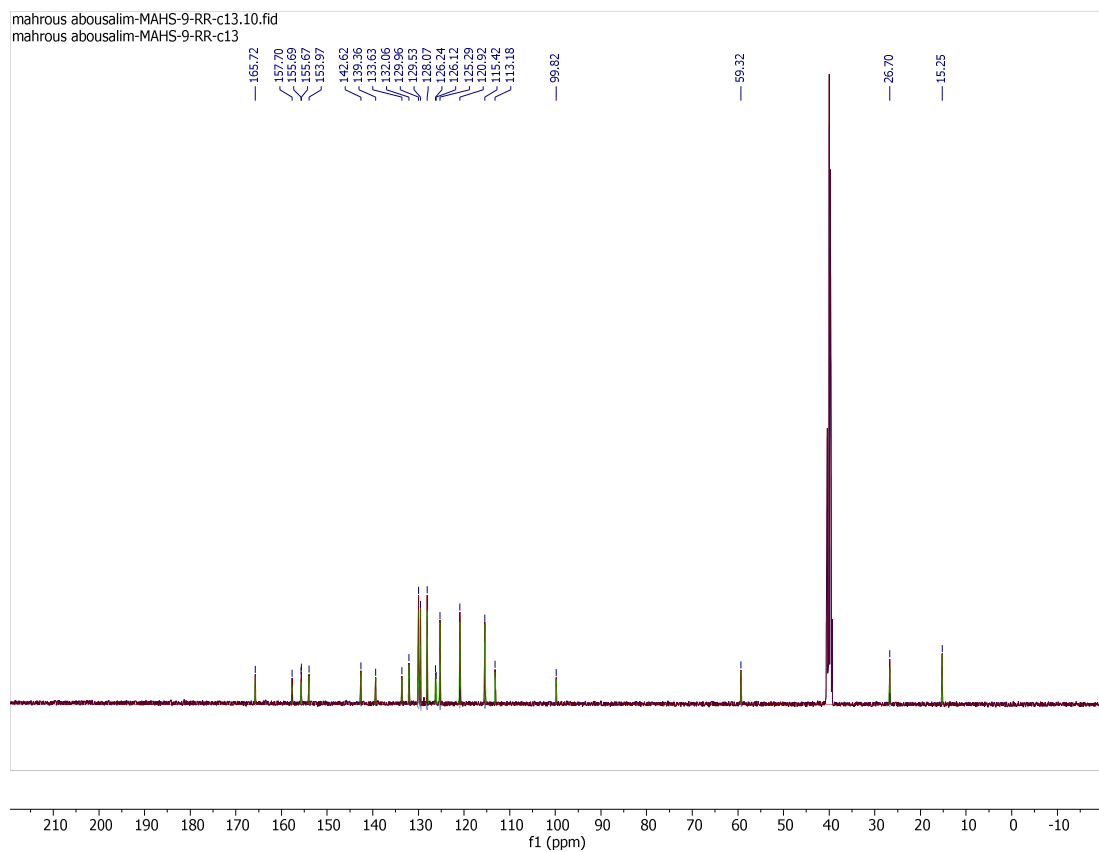


Figure S21. ^{13}C NMR of **6d**.

1.13 6e

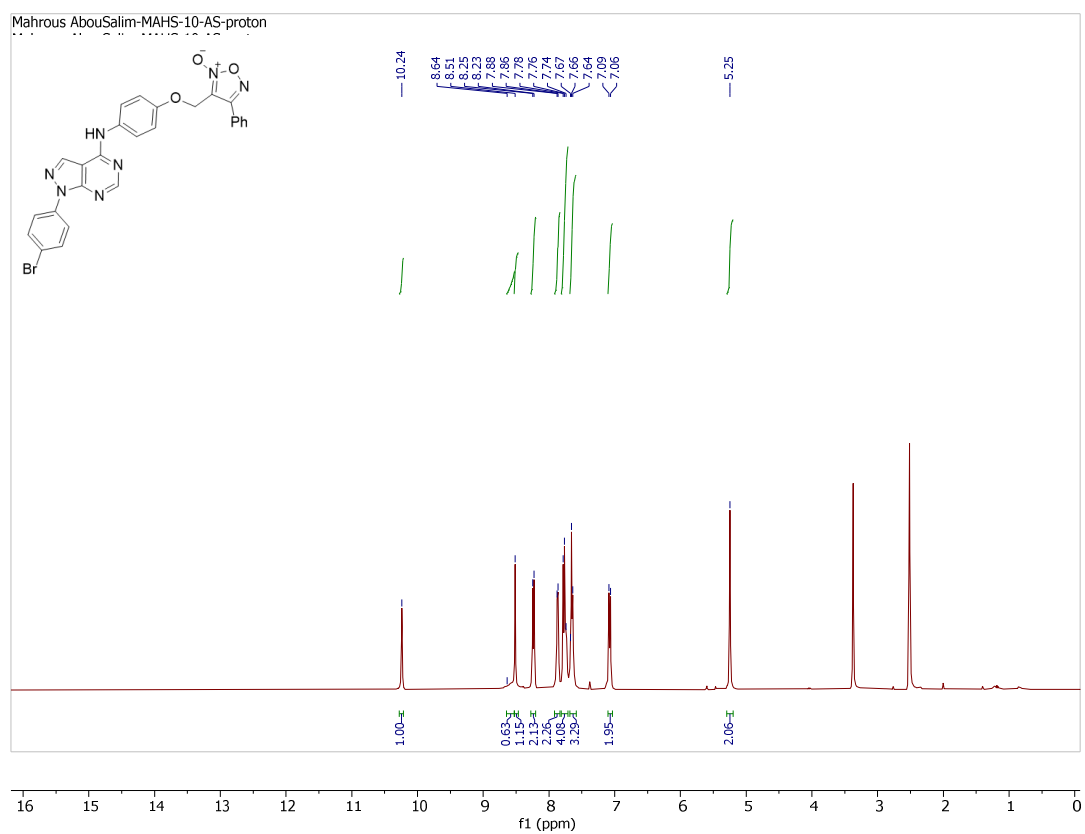


Figure S22. ^1H NMR of **6e**.

1.14 6f

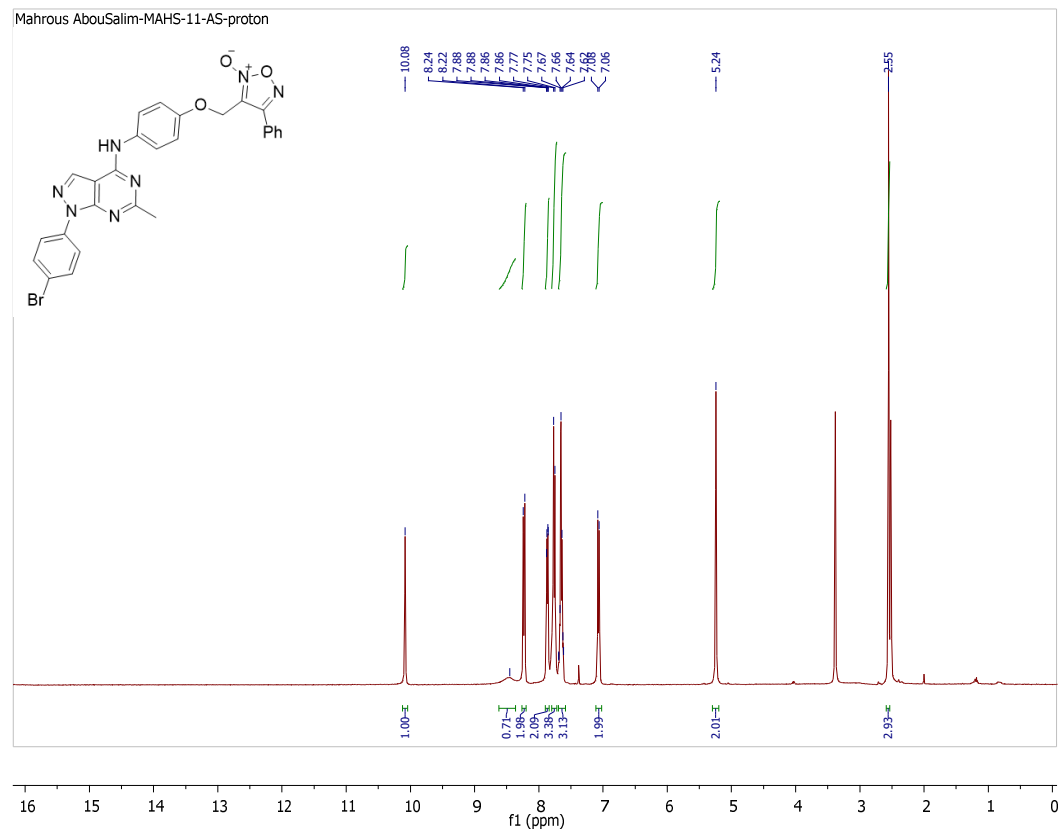


Figure S23. ¹H NMR of 6f.

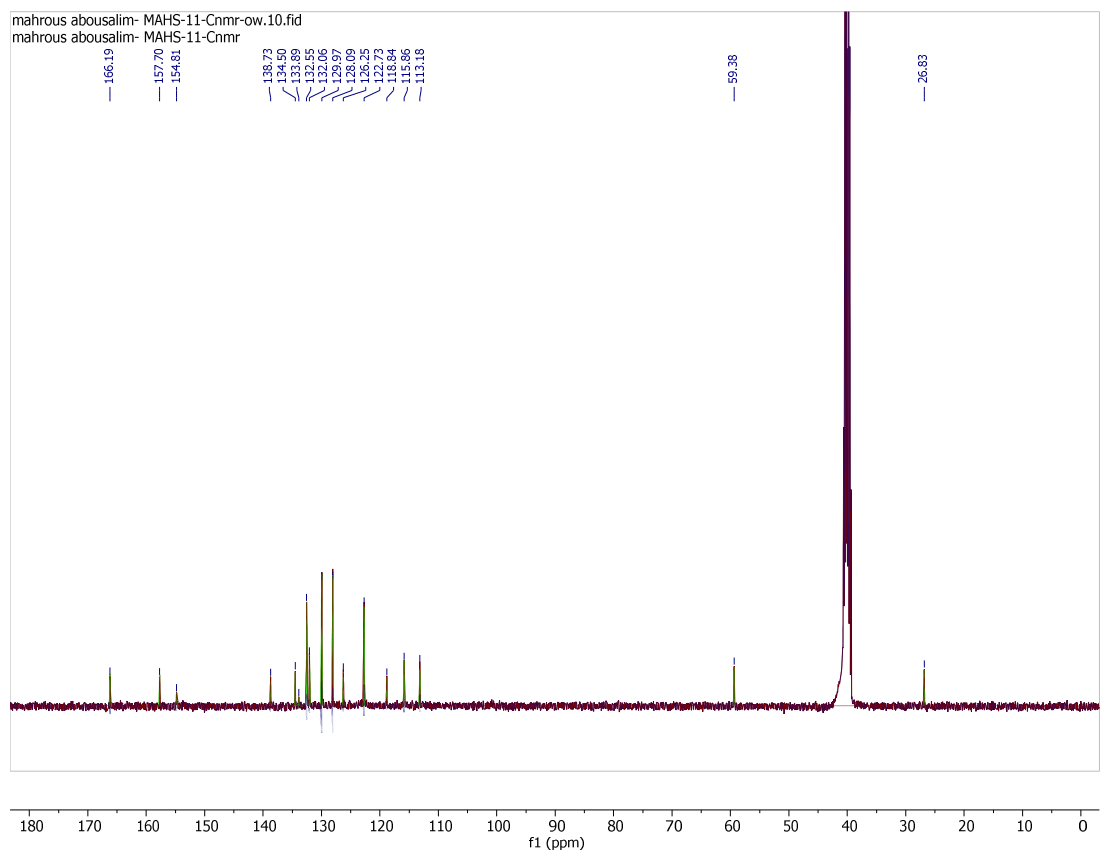


Figure S24. ¹³C NMR of 6f.

1.15 6g

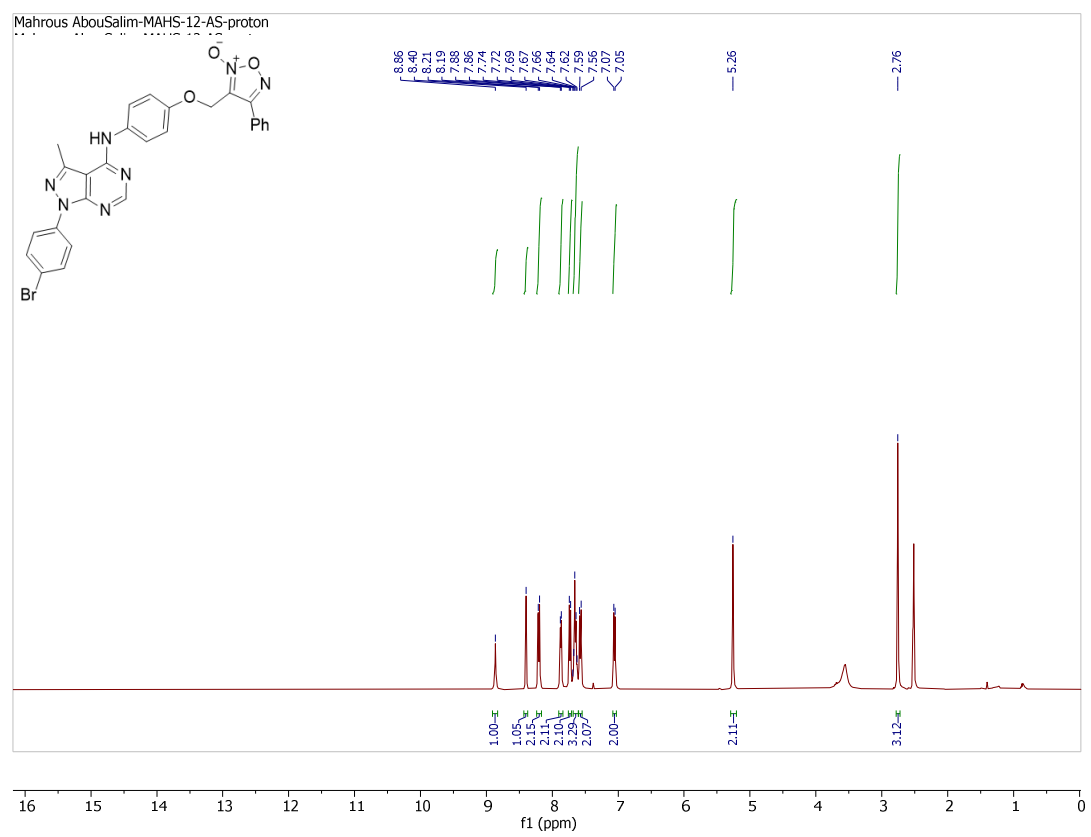


Figure S25. ¹H NMR of 6g.

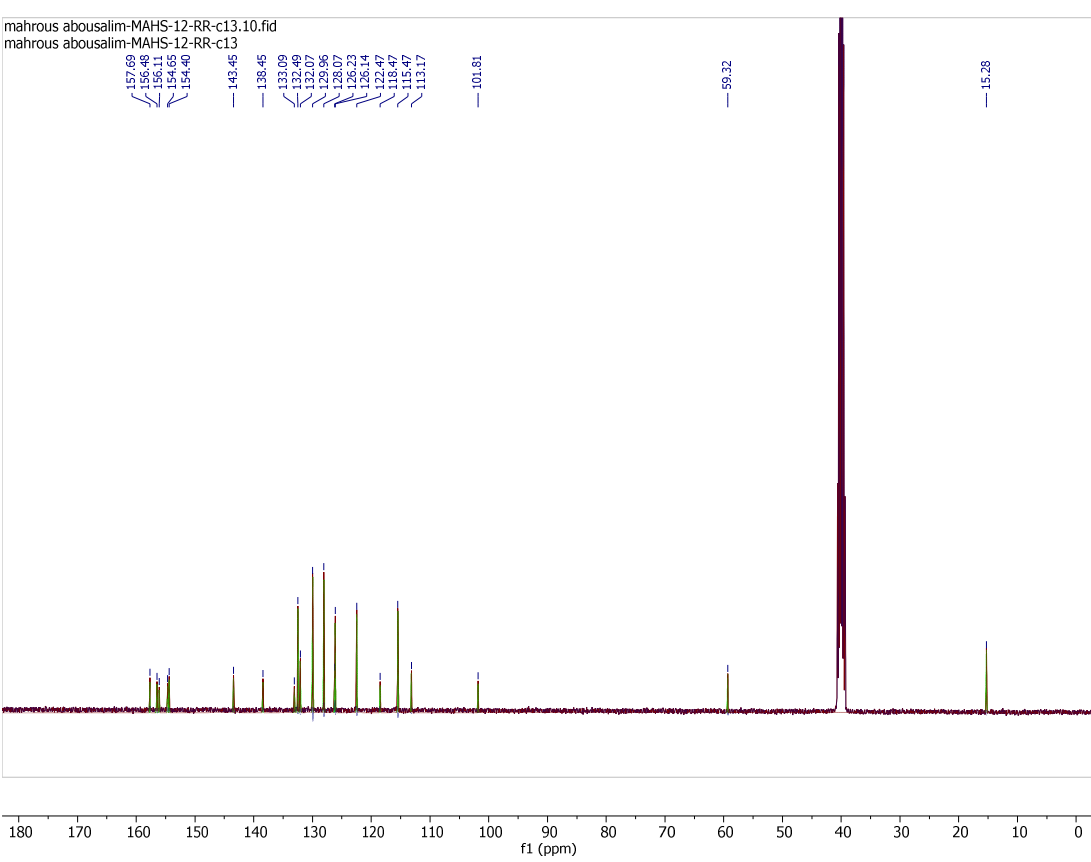


Figure 26. ¹³C NMR of 6g.

1.16 6h

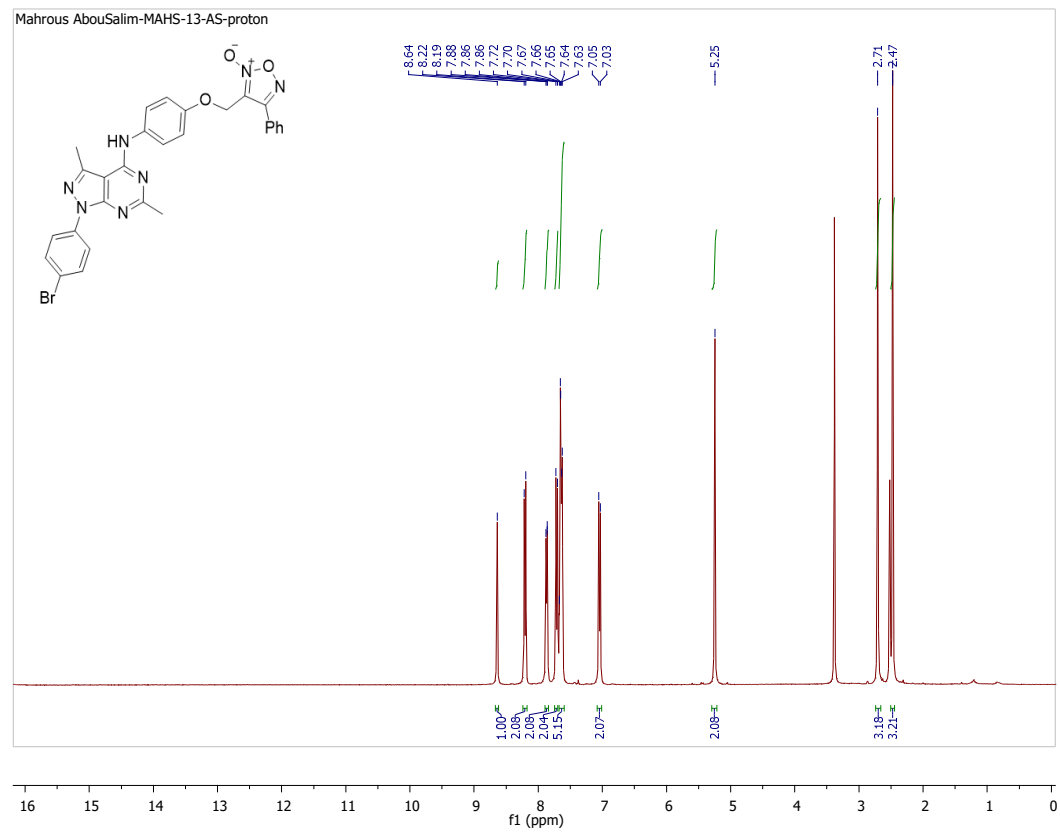


Figure S27. ¹H NMR of 6h.

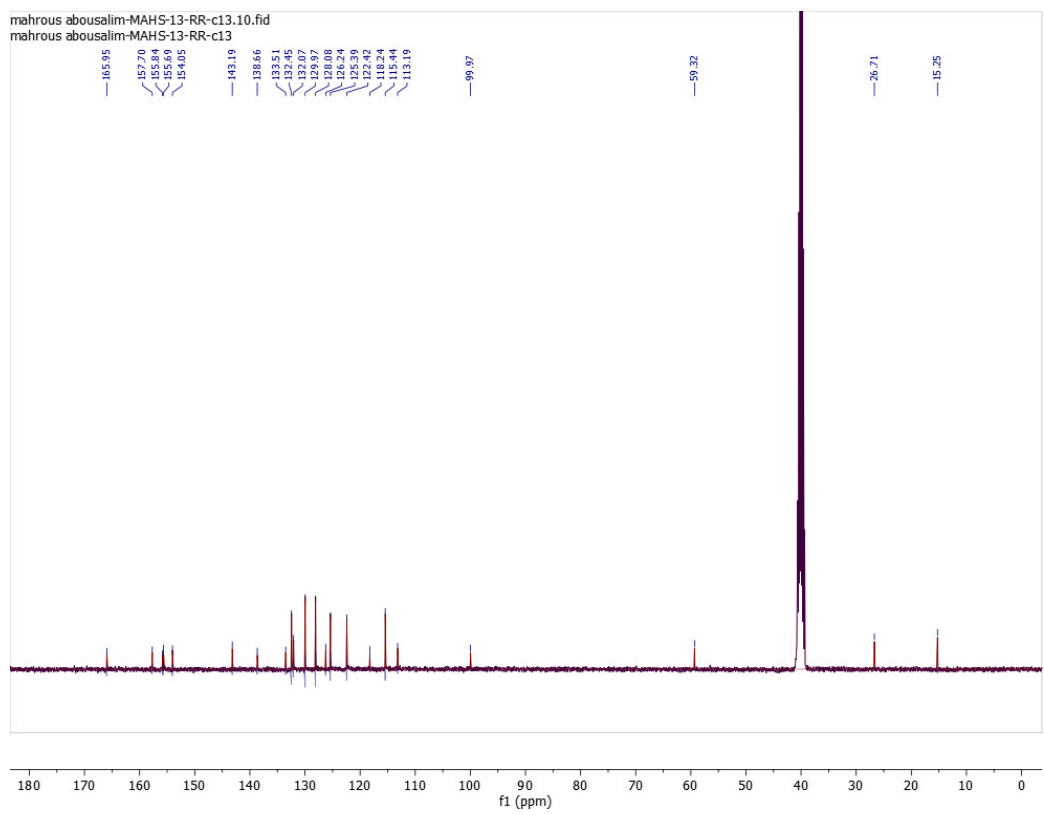


Figure S28. ¹³C NMR of 6h.

1.17 8b

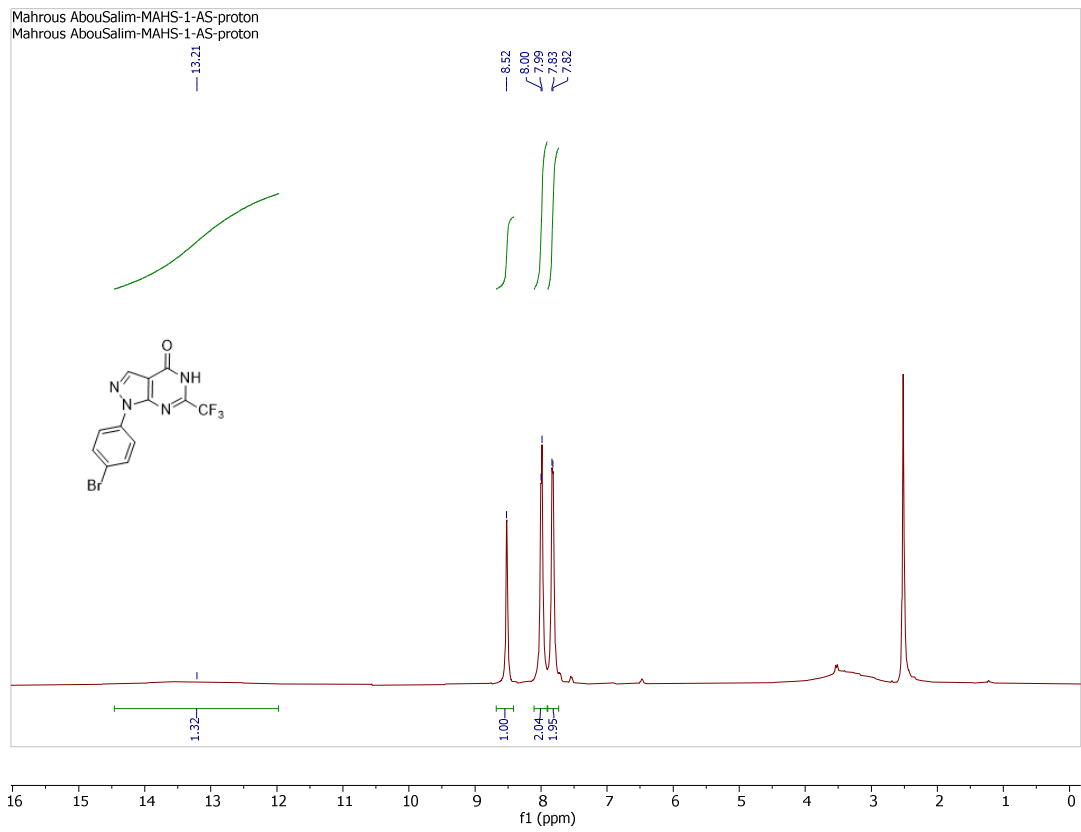


Figure S29. ¹H NMR of 8b.

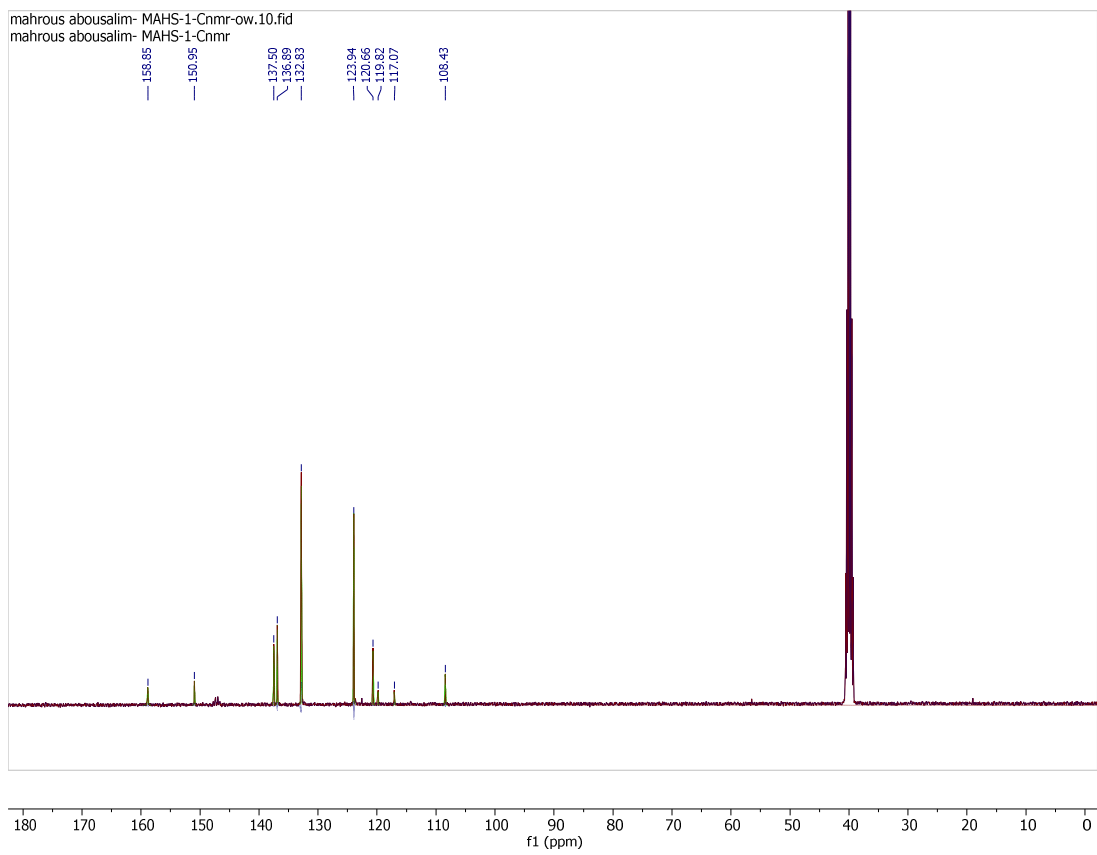


Figure S30. ¹³C NMR of 8b.

1.18 8c

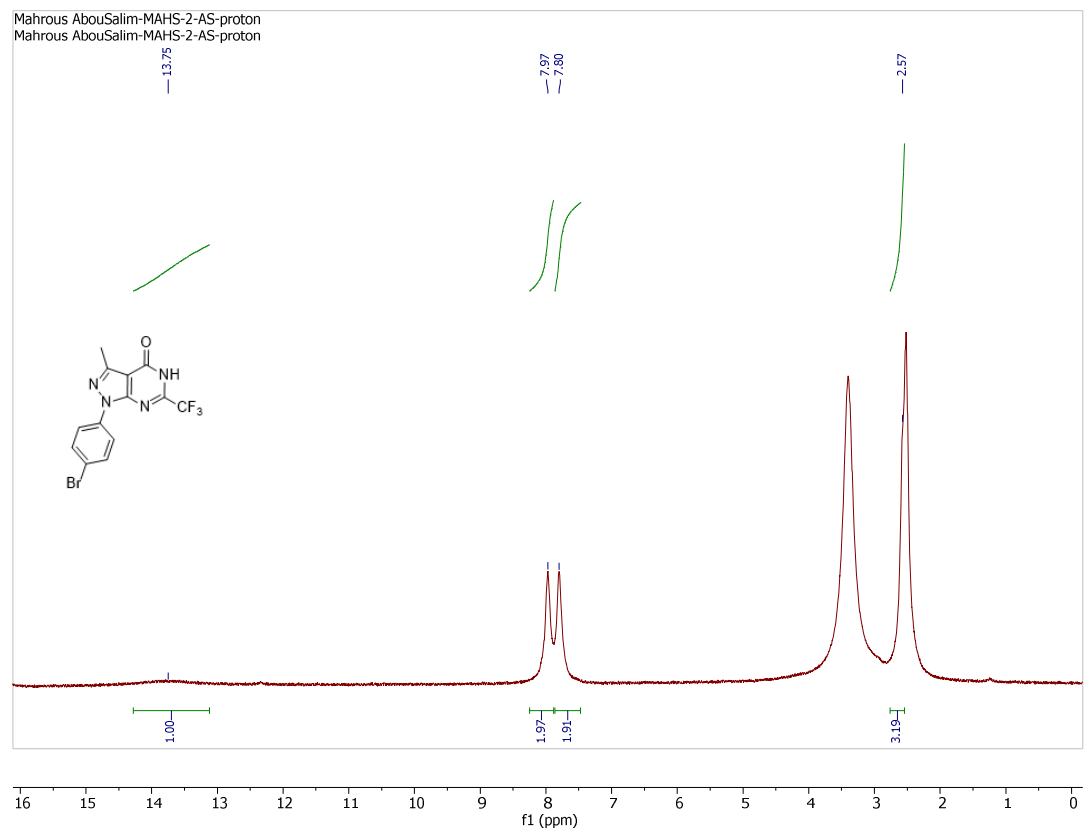


Figure S31. ¹H NMR of 8c.

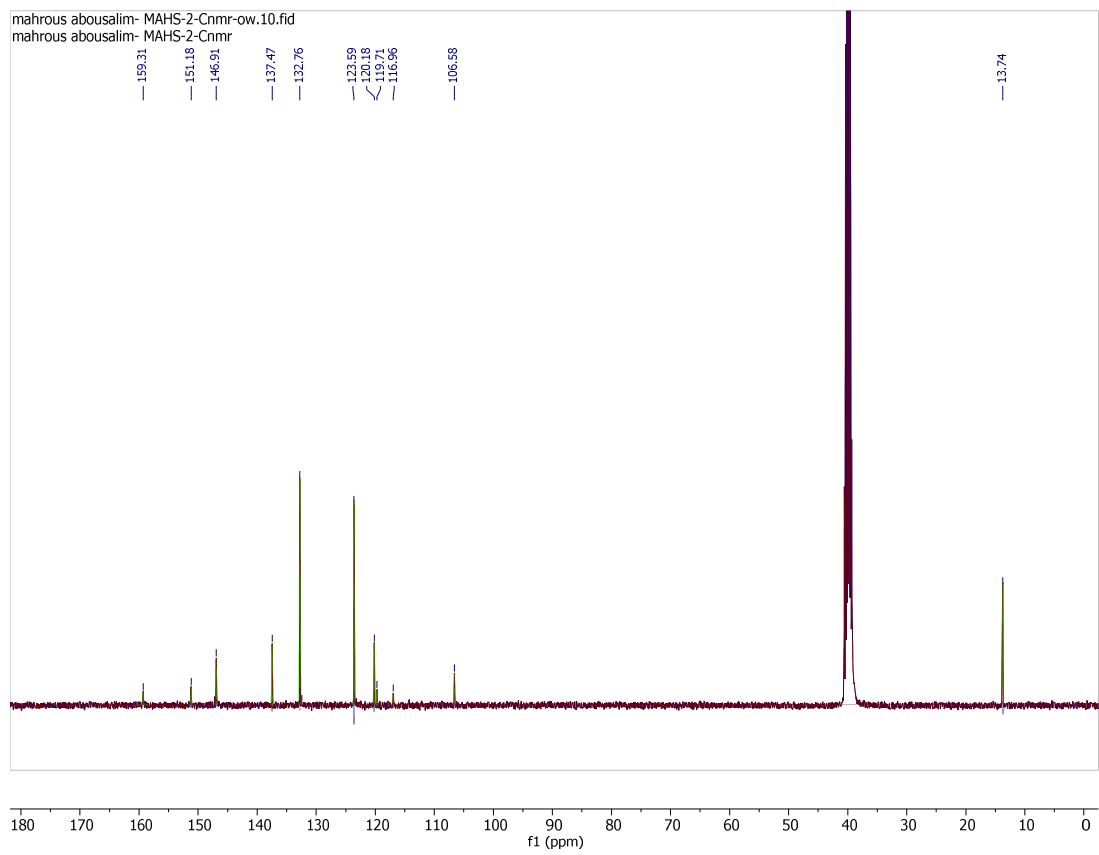


Figure S32. ¹³C NMR of 8c.

1.19 9a

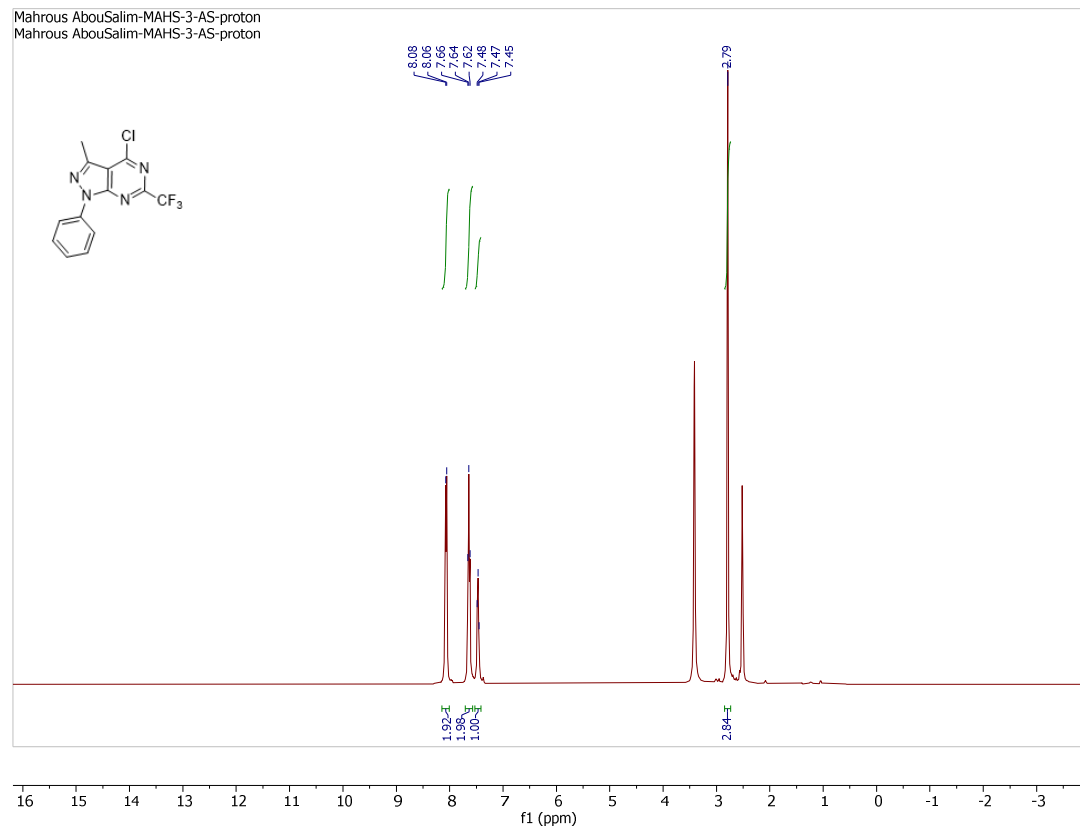


Figure S33. ¹H NMR of 9a.

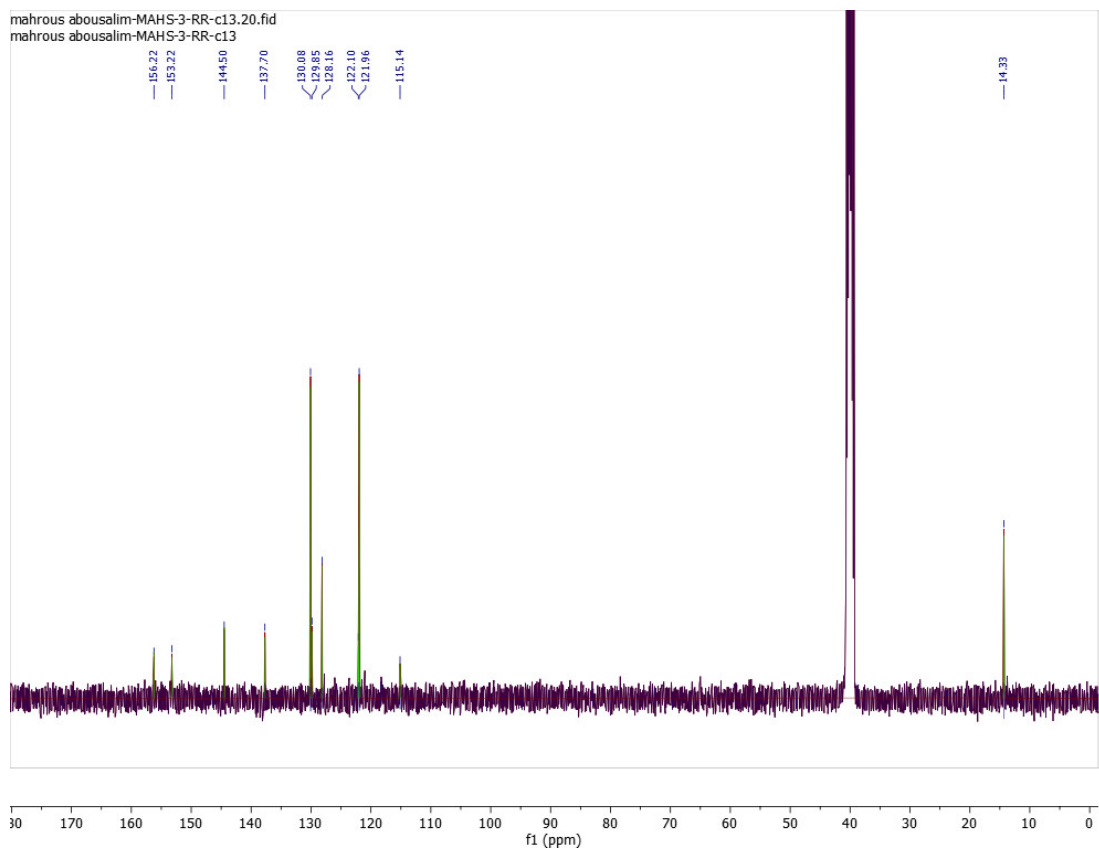
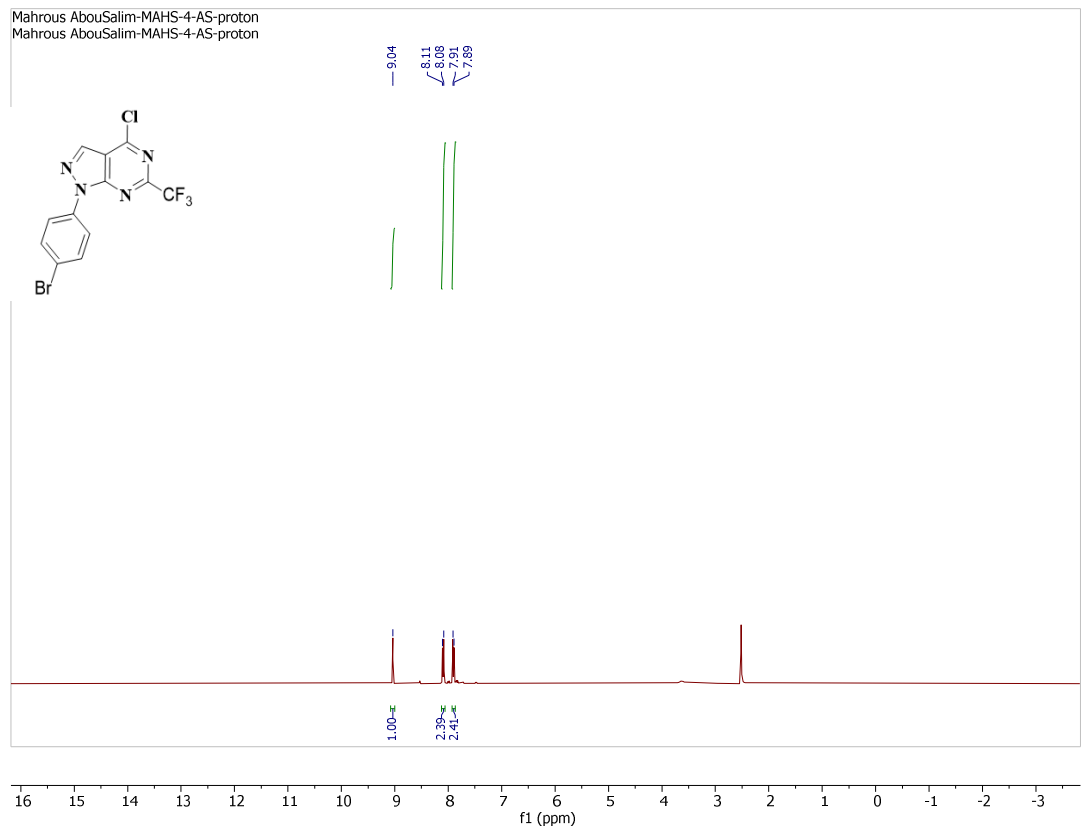
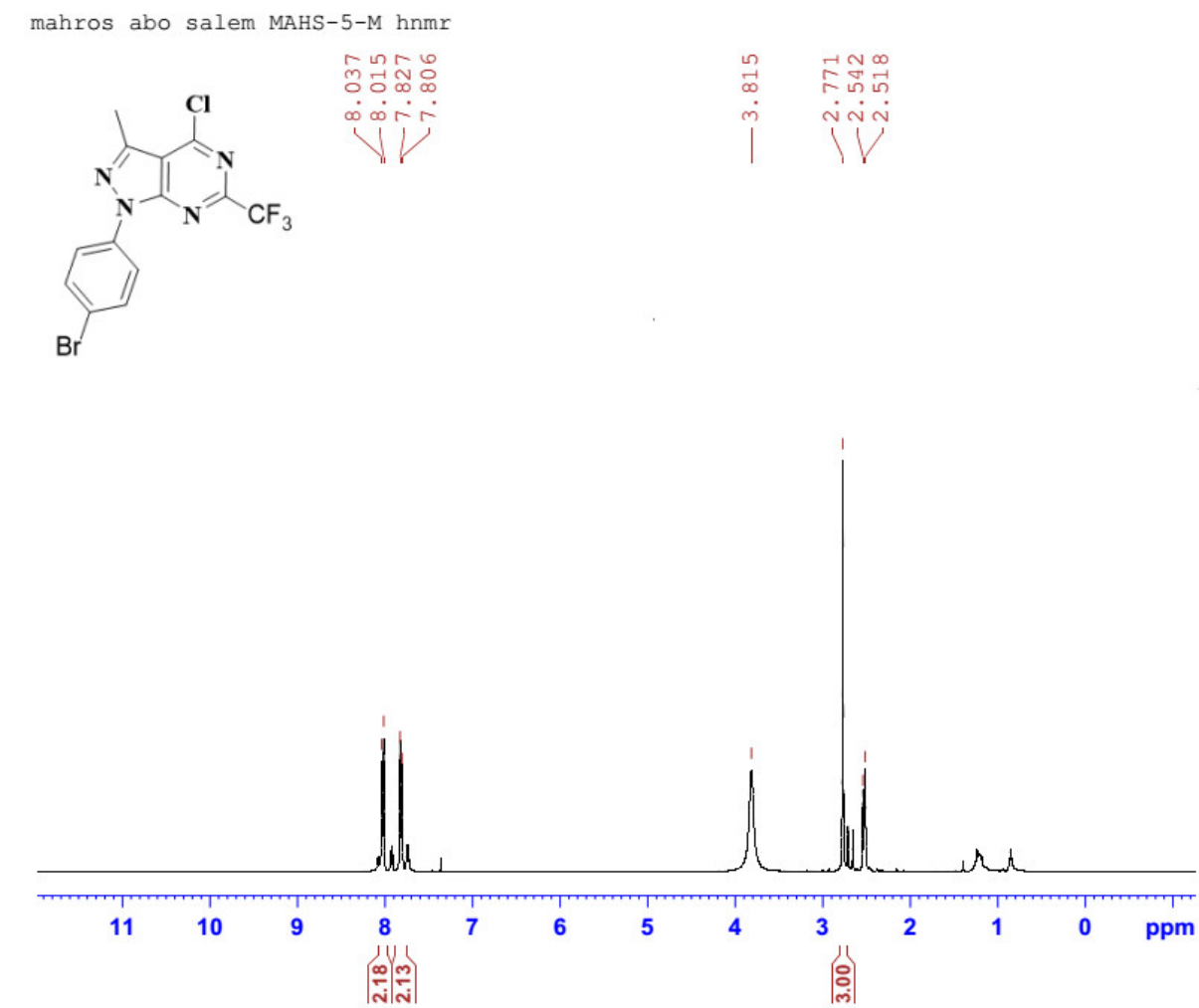


Figure S34. ¹³C NMR of 9a.

1.20 9b



1.21 9c



1.22 11

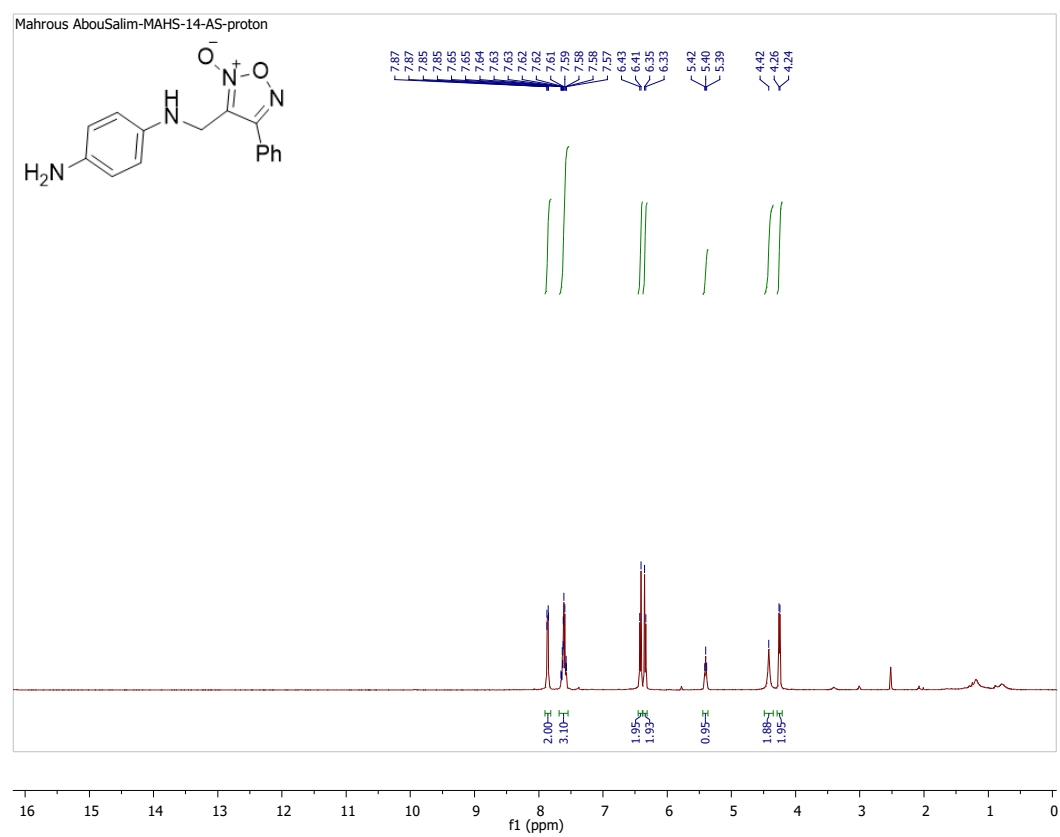


Figure S37. ¹H NMR of 11.

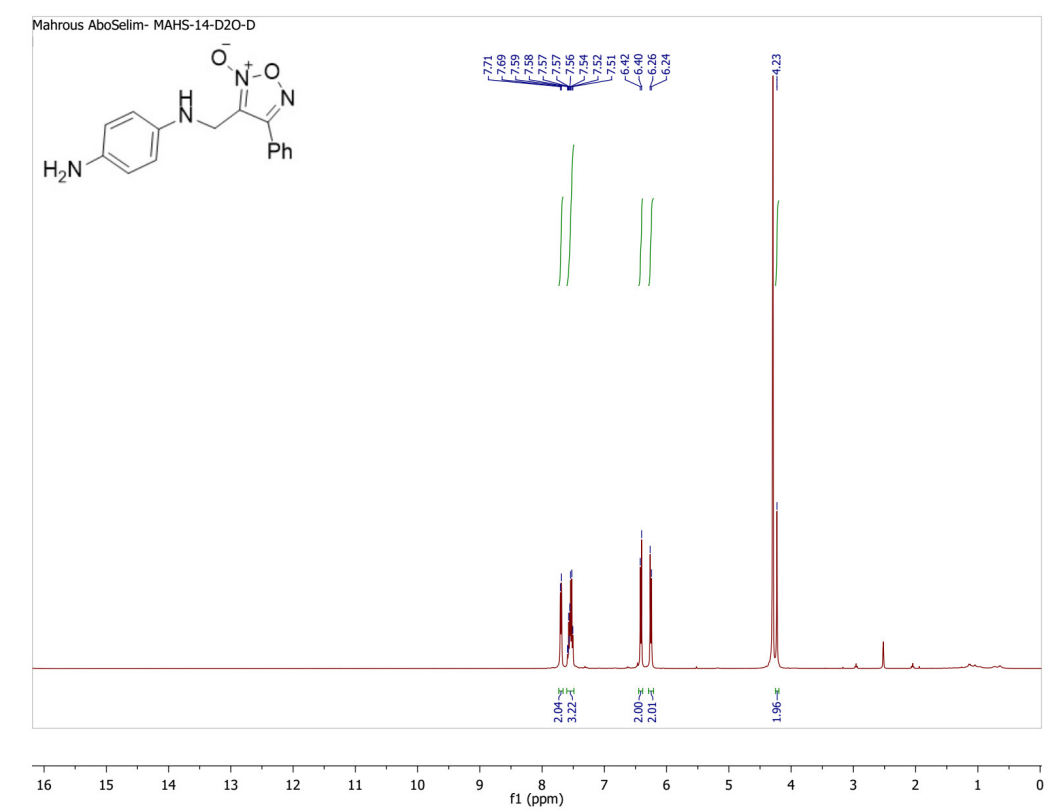


Figure S38. ¹H NMR (D₂O) of 11.

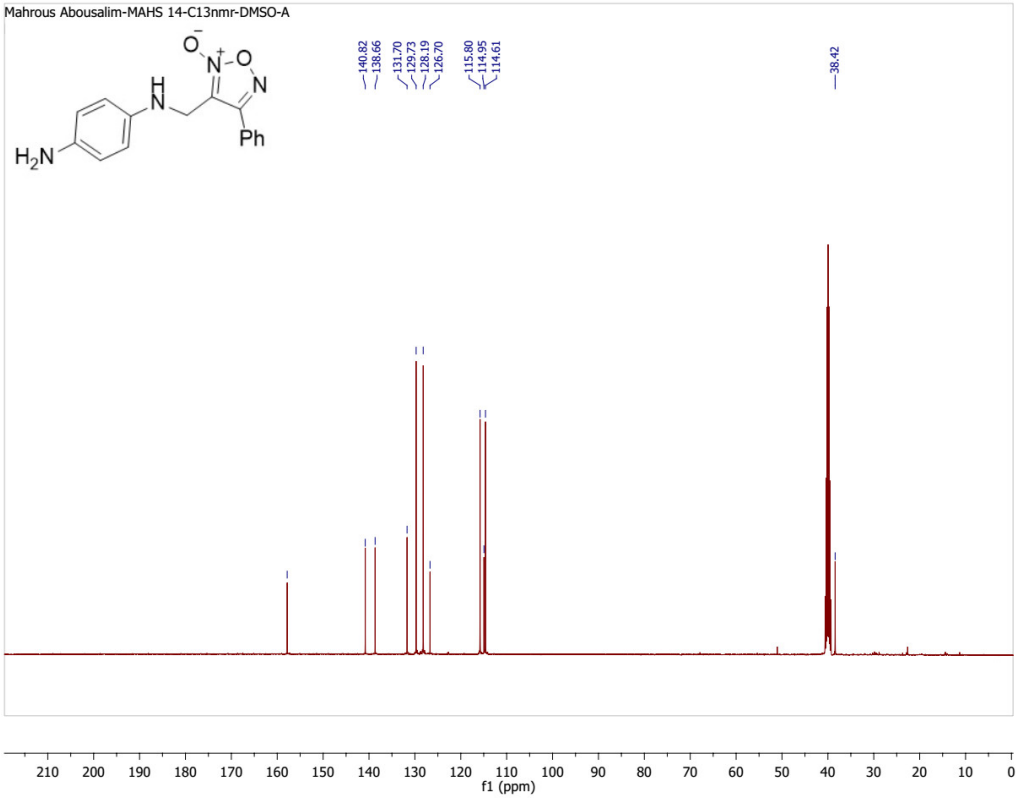


Figure S39. ¹³C NMR of 11.

1.23 12a

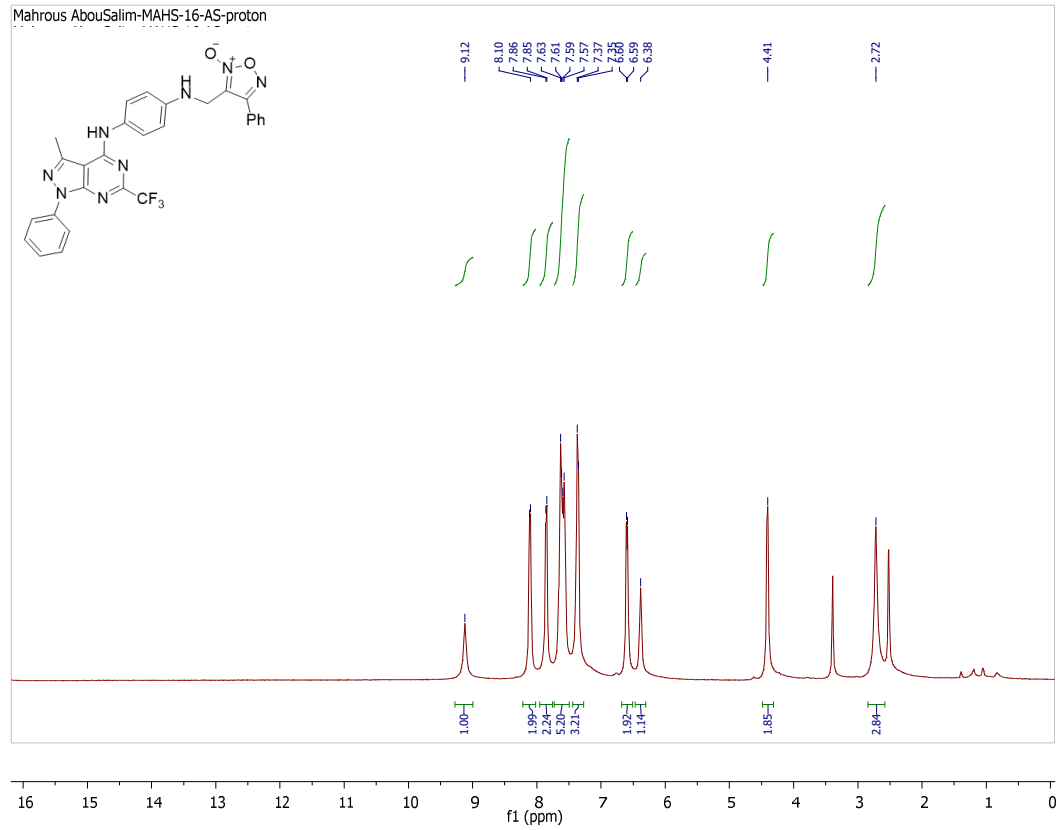


Figure S40. ¹H NMR of 12a.

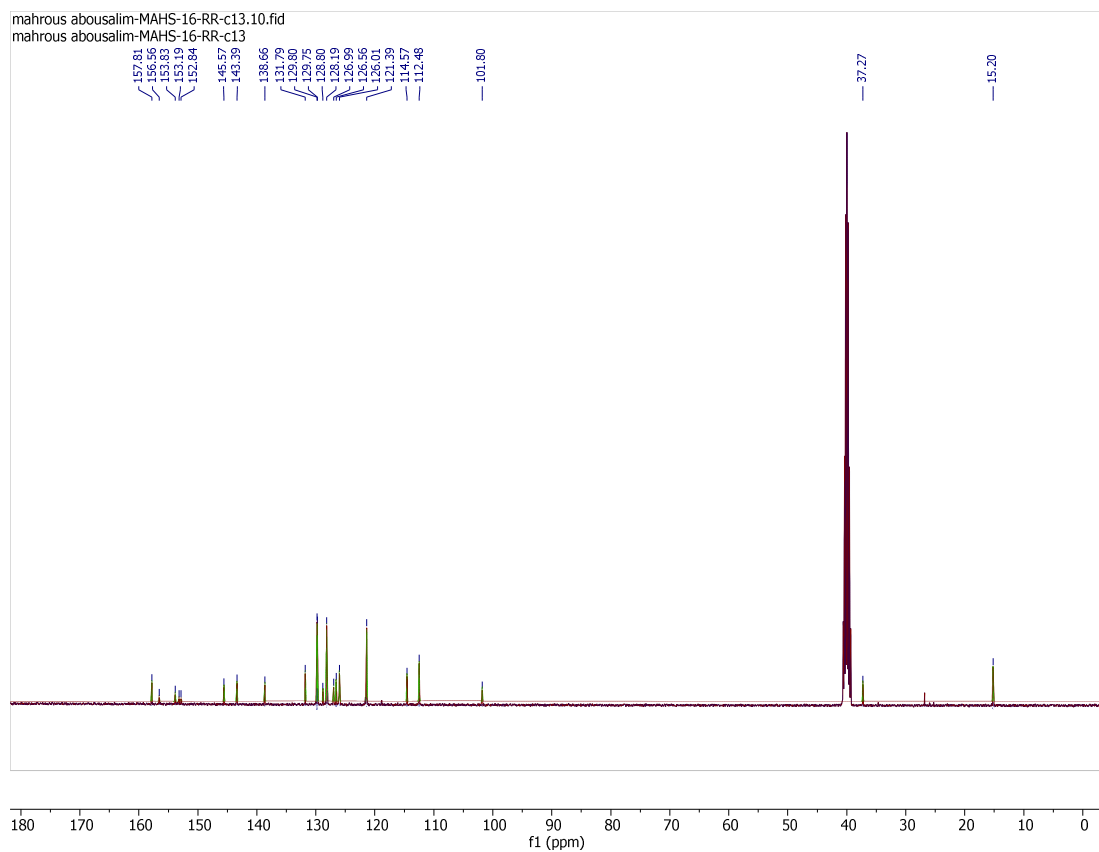


Figure S41. ^{13}C NMR of **12a**.

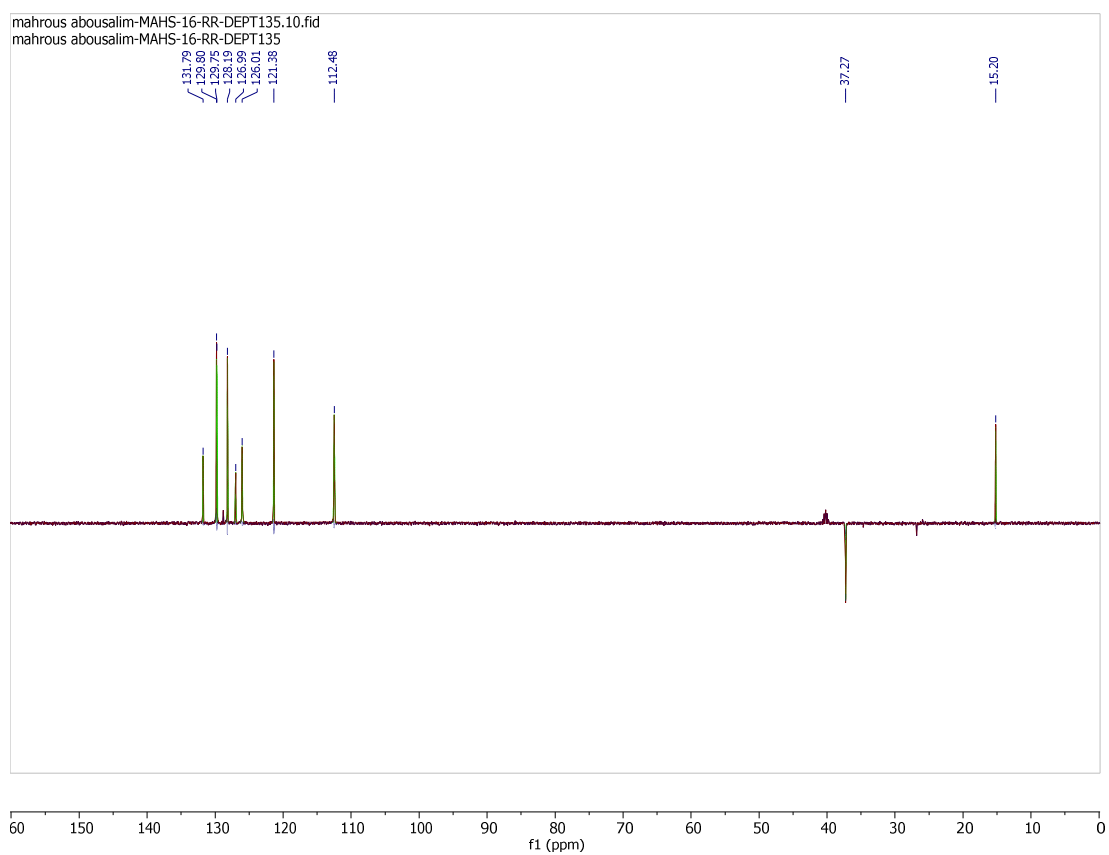


Figure S42. DEPT135 ^{13}C NMR of **12a**.

1.24 12b

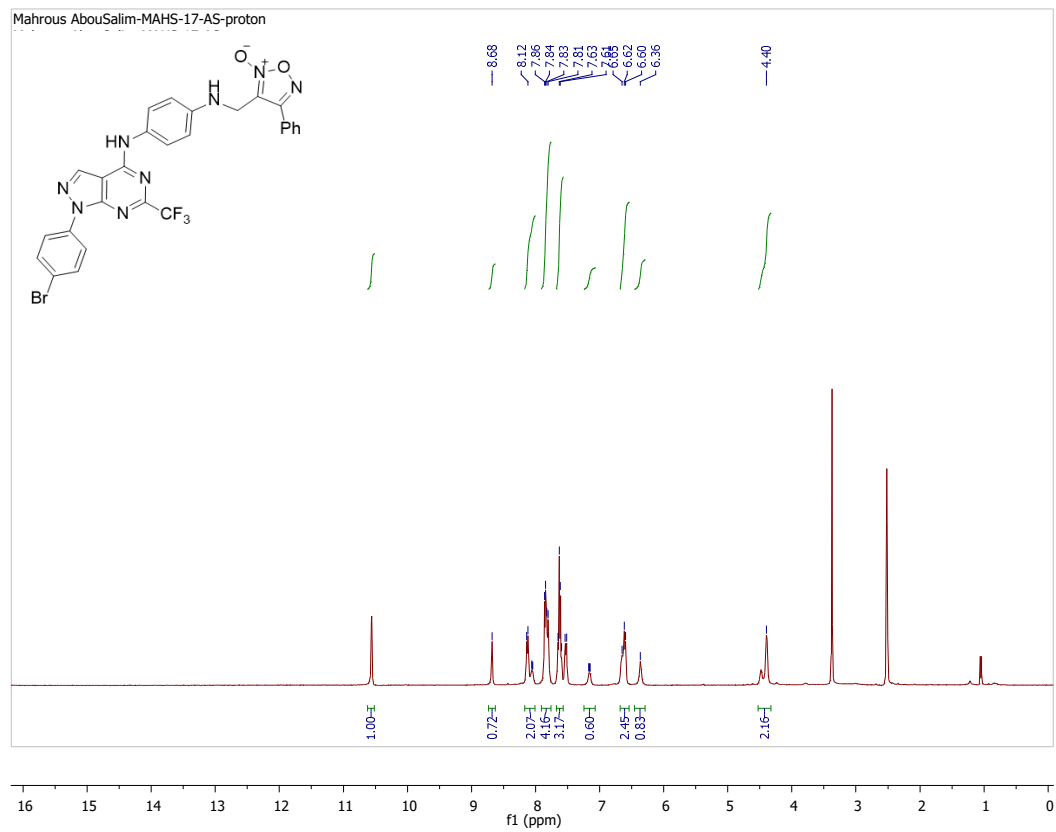


Figure S43. ¹H NMR of 12b.

1.25 12c

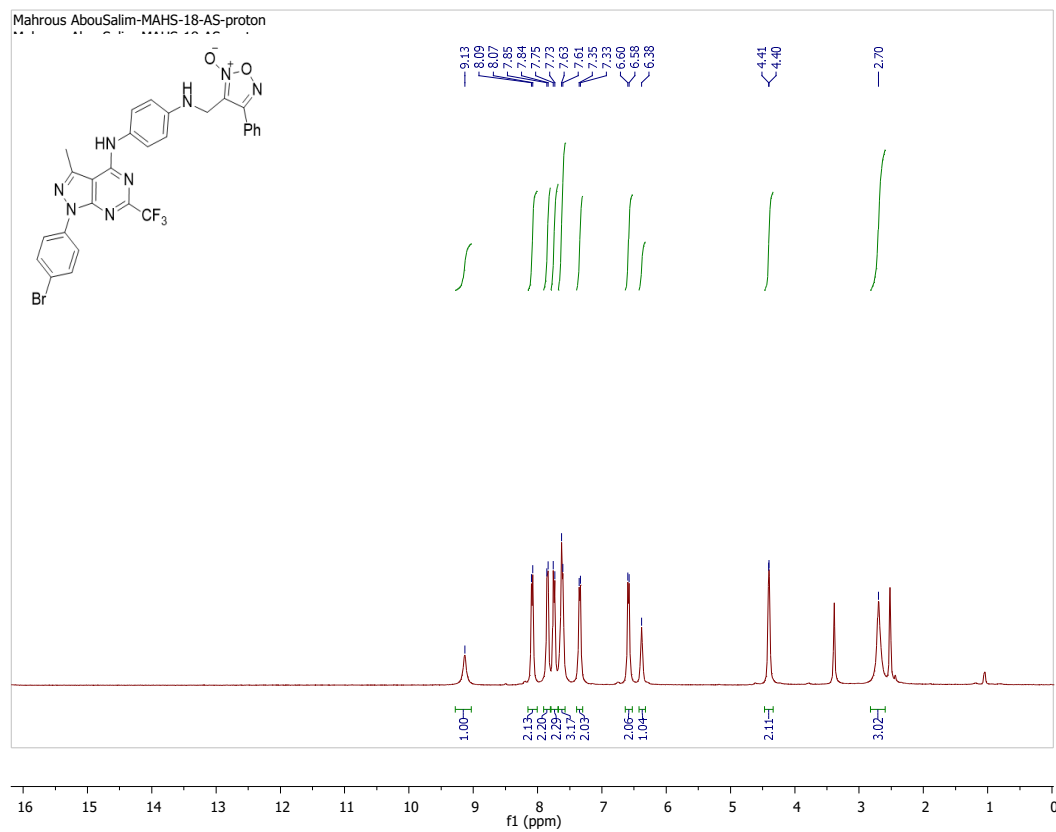


Figure S44. ¹H NMR of 12c.

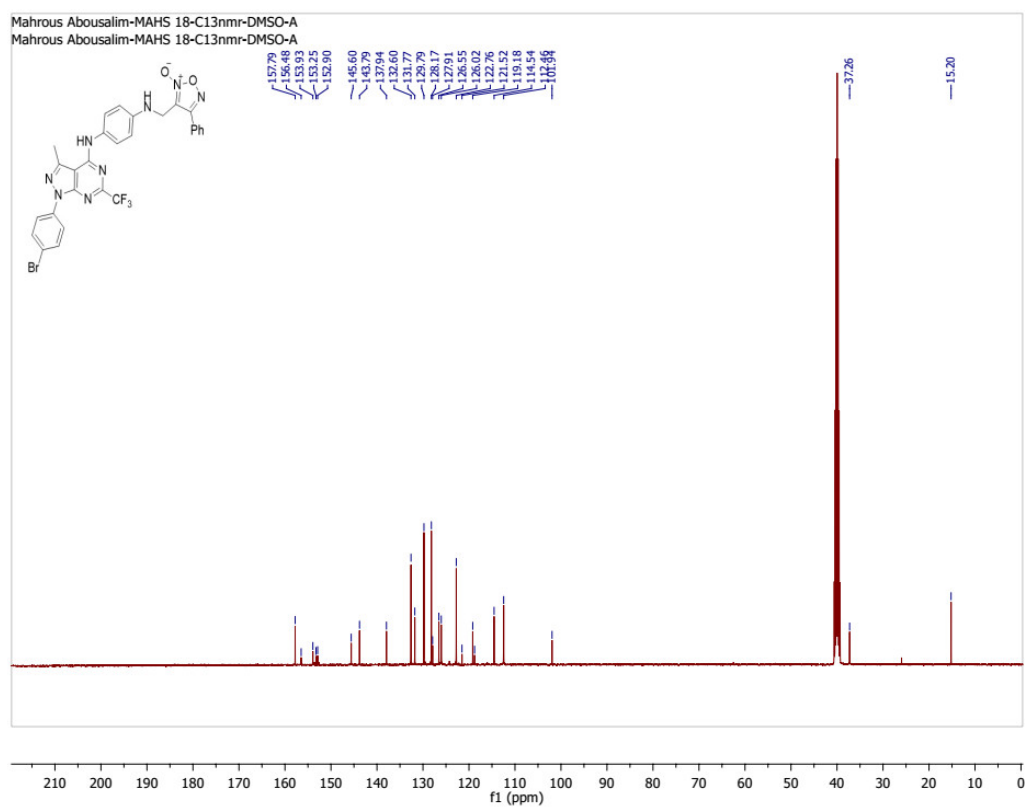
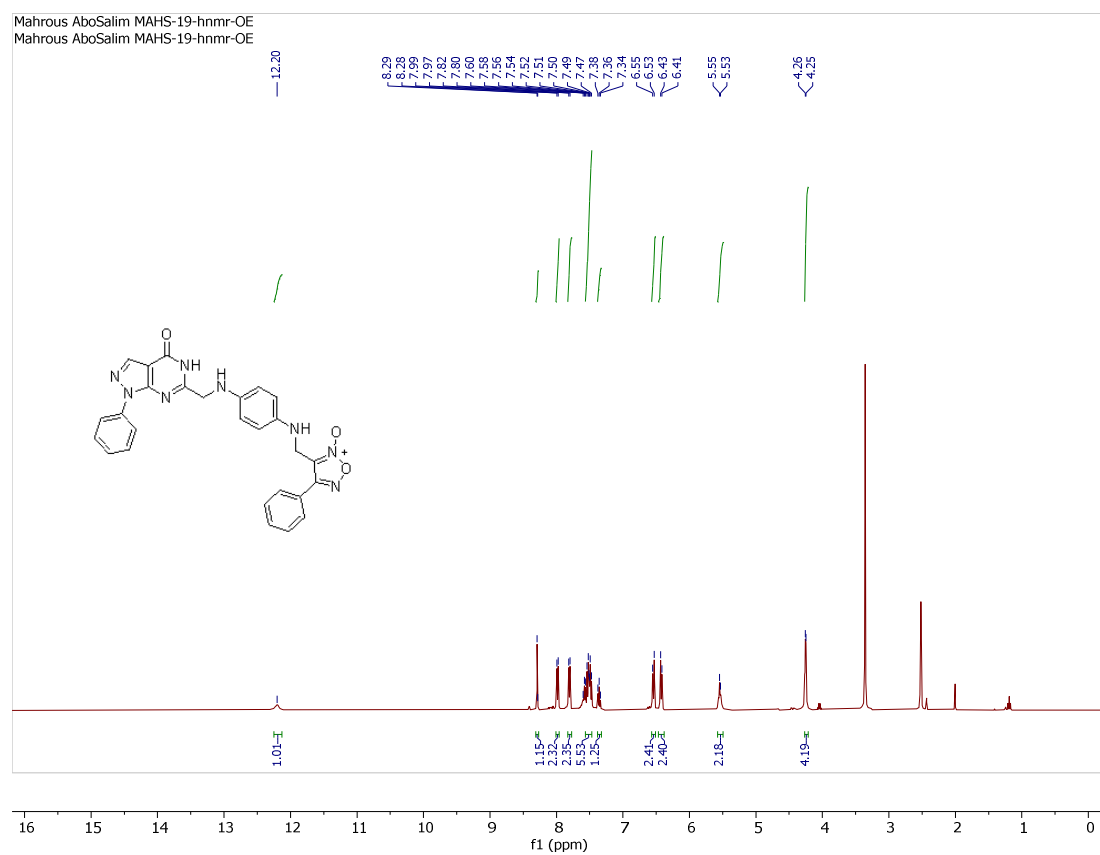


Figure S45. ^{13}C NMR of **12c**.

1.26 14a



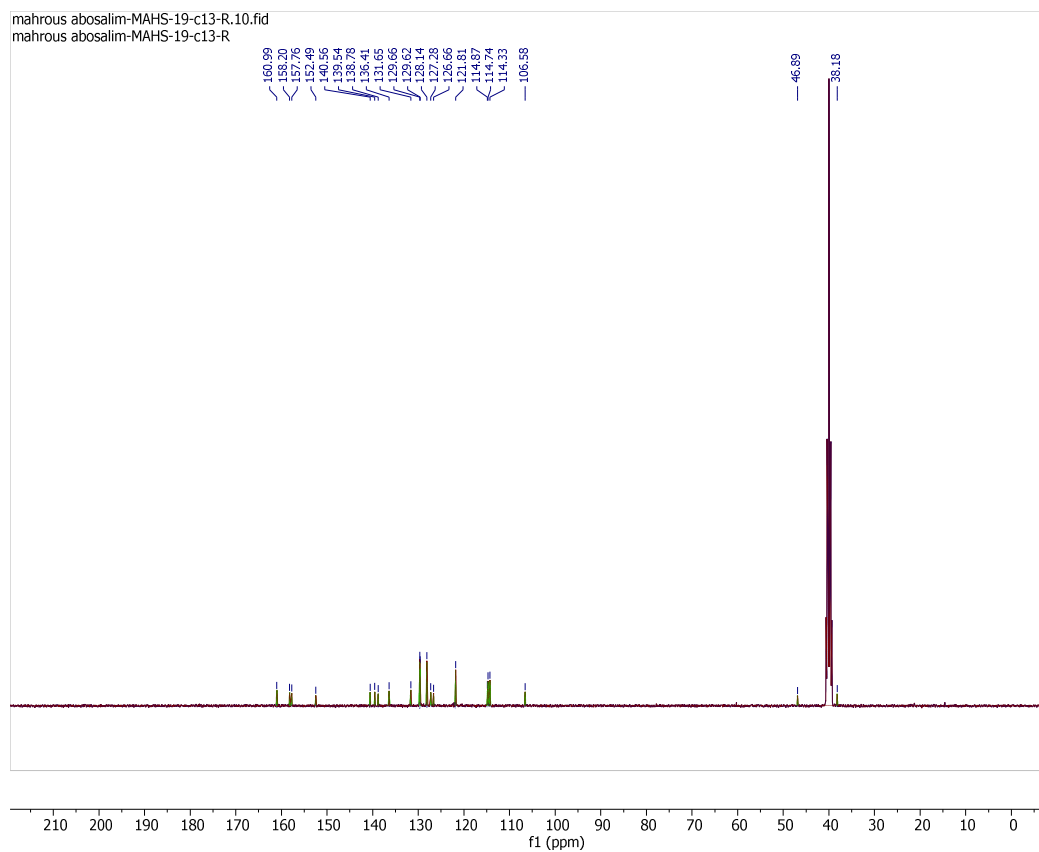


Figure S47. ^{13}C NMR of **14a**.

1.27 14b

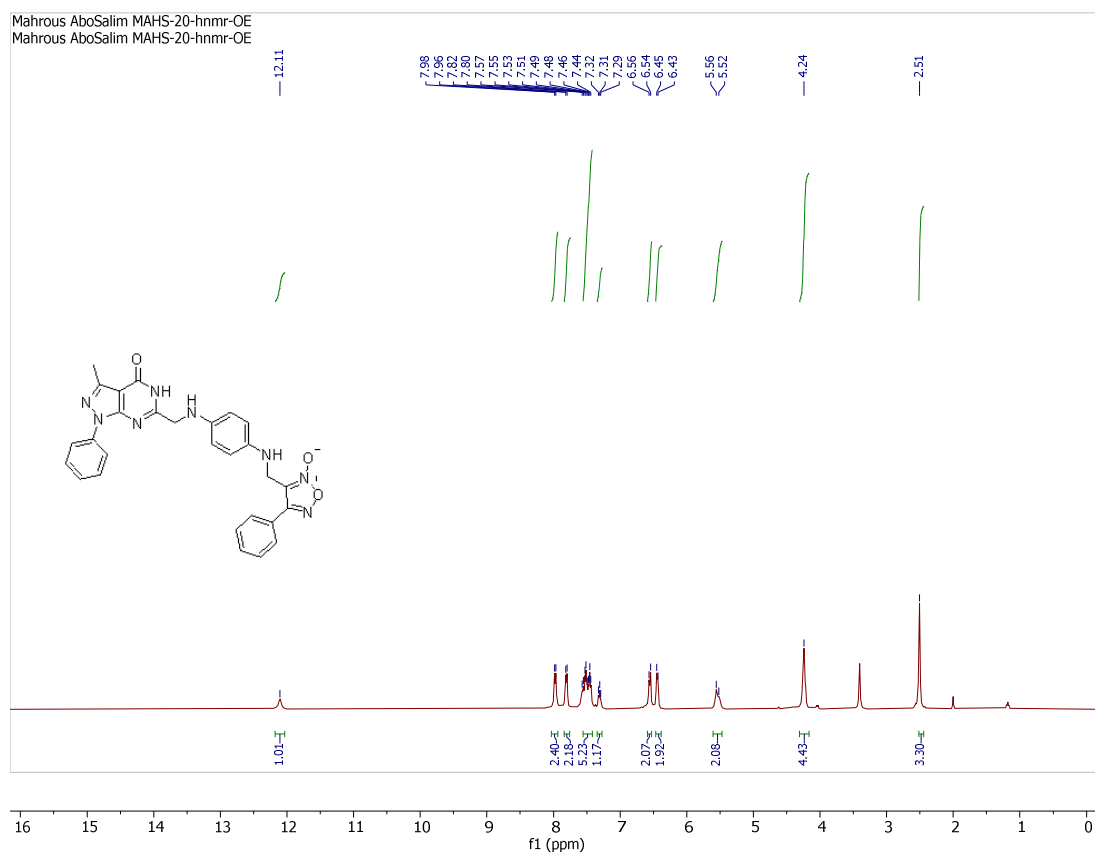


Figure S48. ^1H NMR of **14b**.

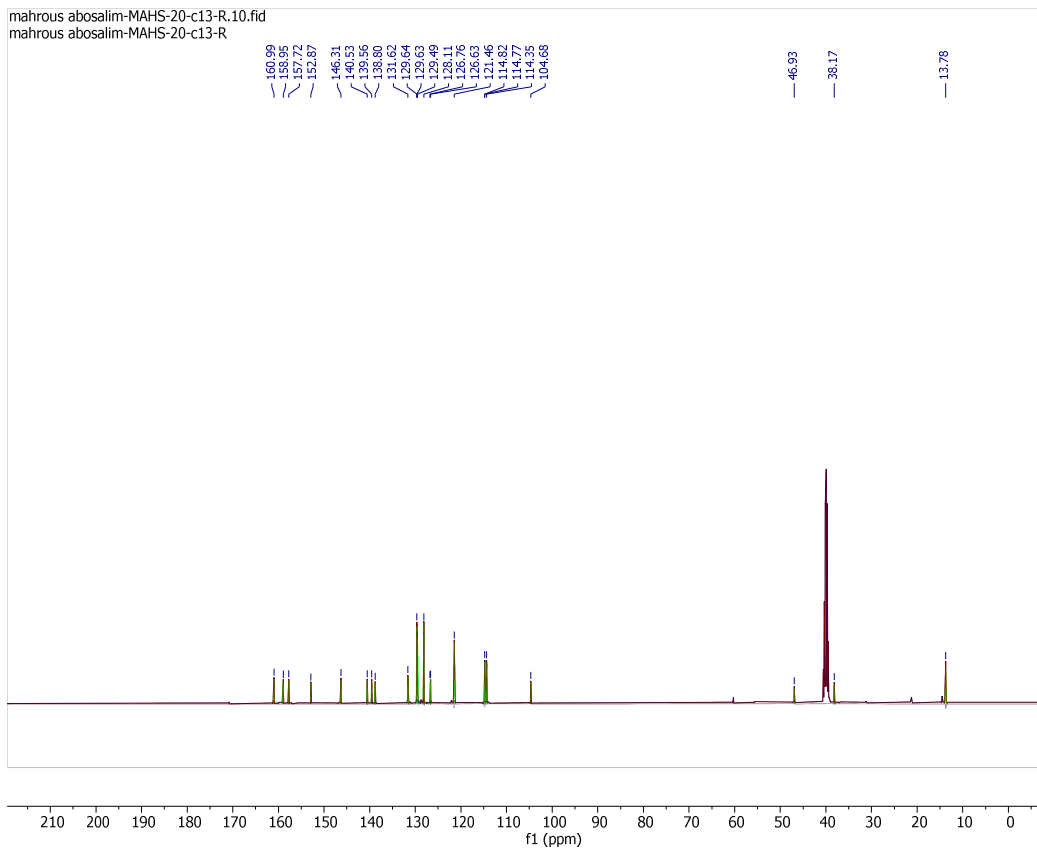


Figure S49. ¹³C NMR of 14b.

1.28 14c

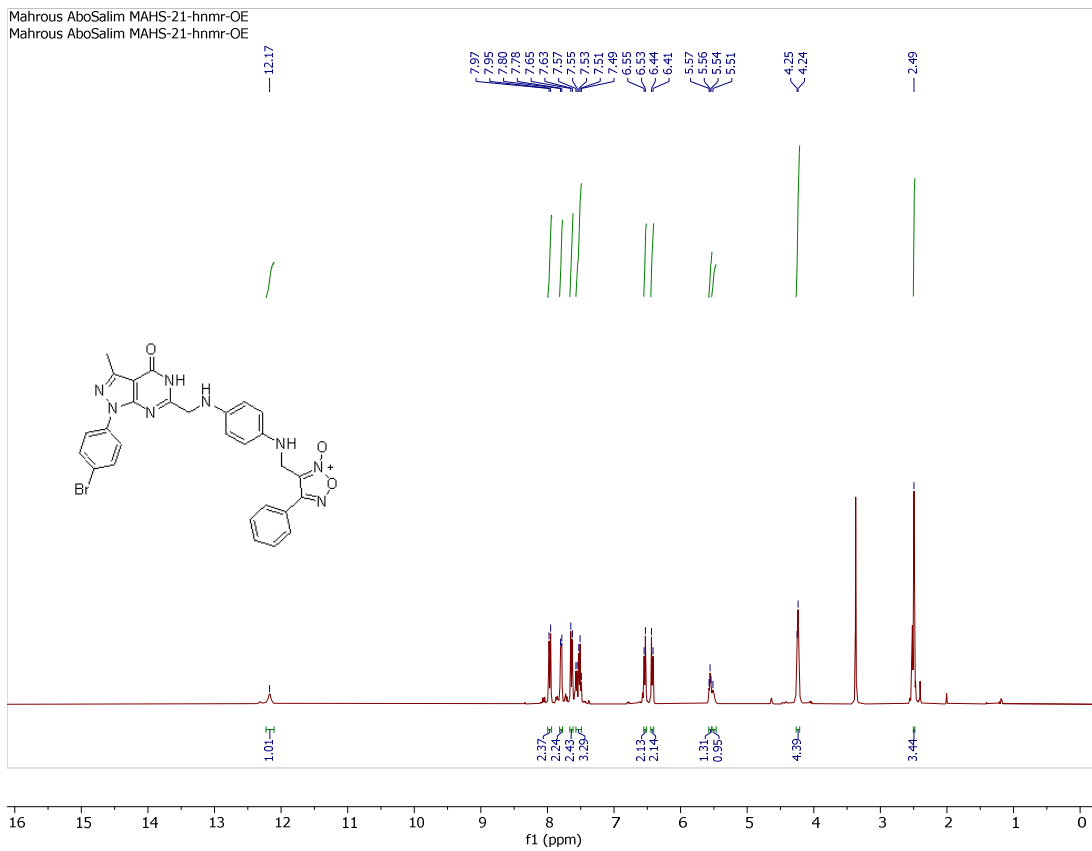


Figure S50. ¹H NMR of 14c.

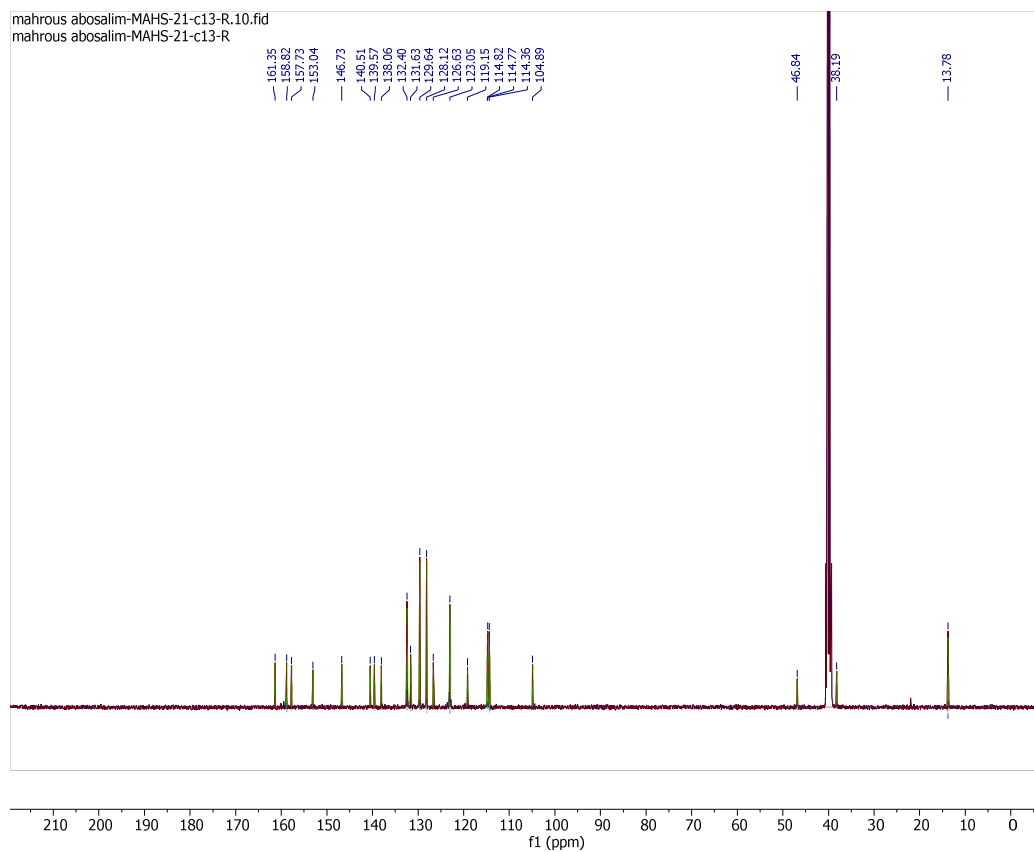


Figure S51. ^{13}C NMR of **14c**.

1.29 15a

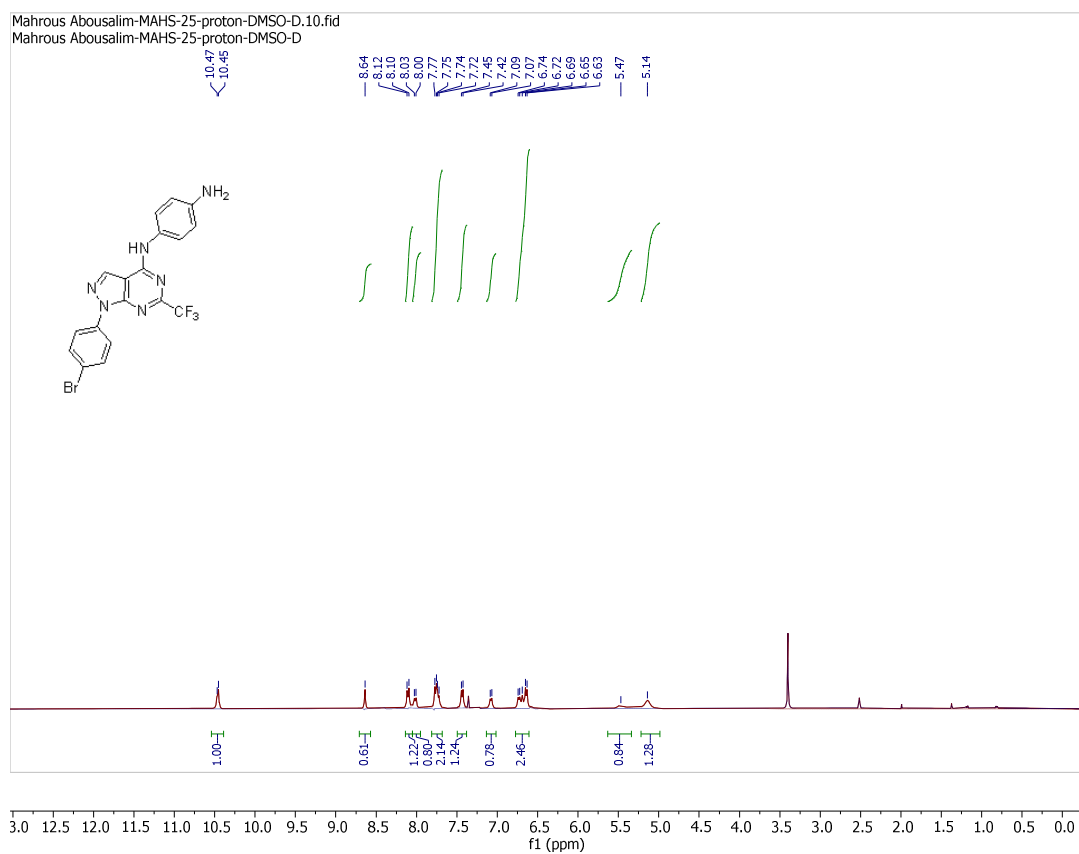


Figure S52. ^1H NMR of **15a**.

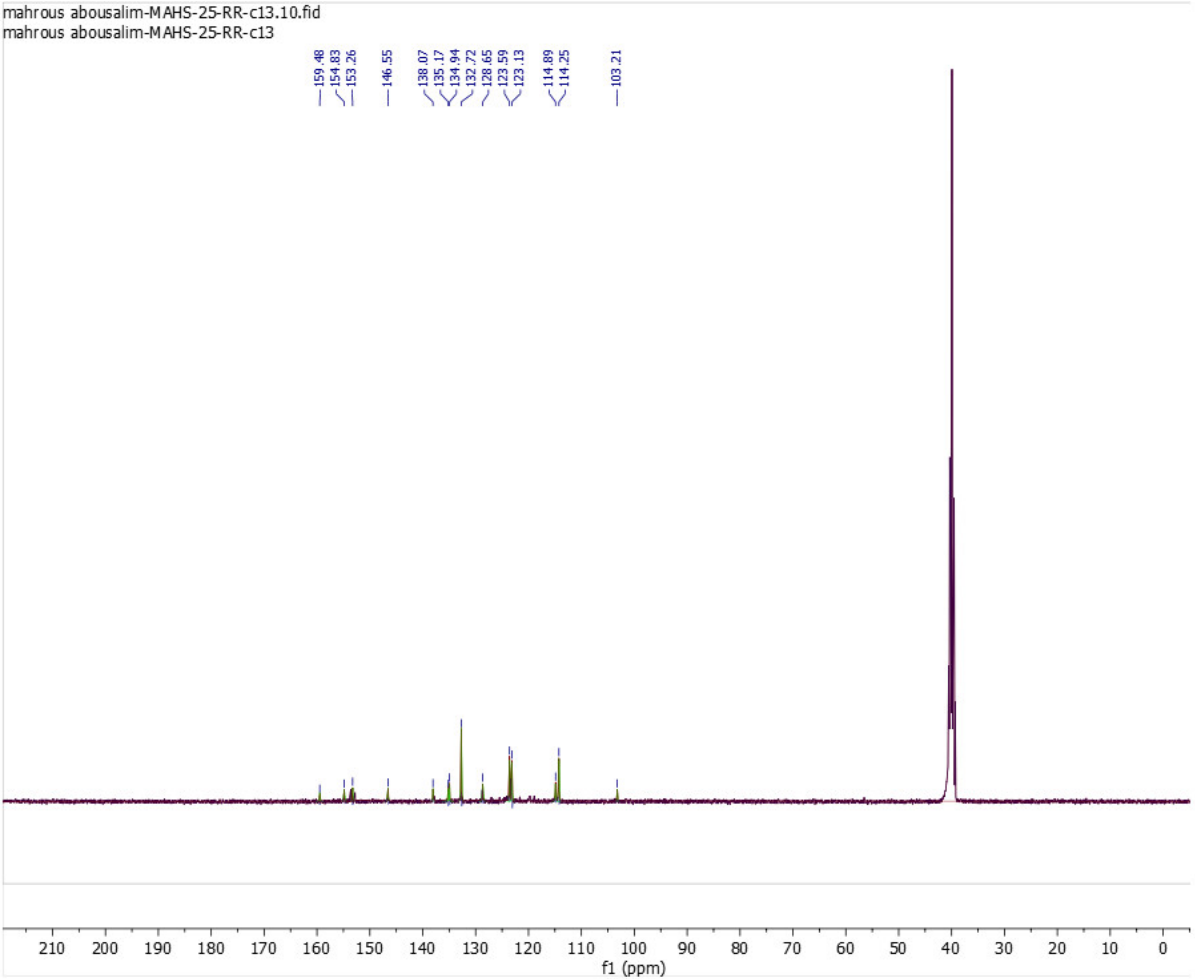


Figure S53. ^{13}C NMR of **15a**.

1.30 **15b**

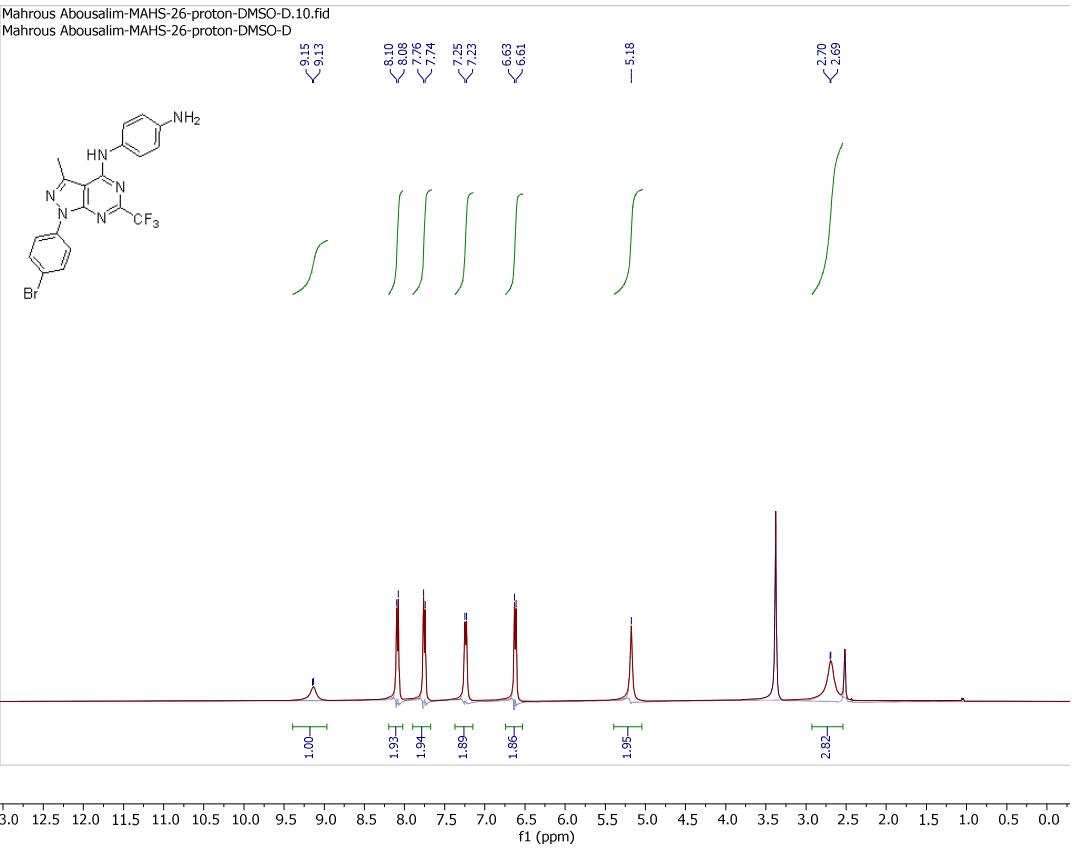


Figure S54. ^1H NMR of **15b**.

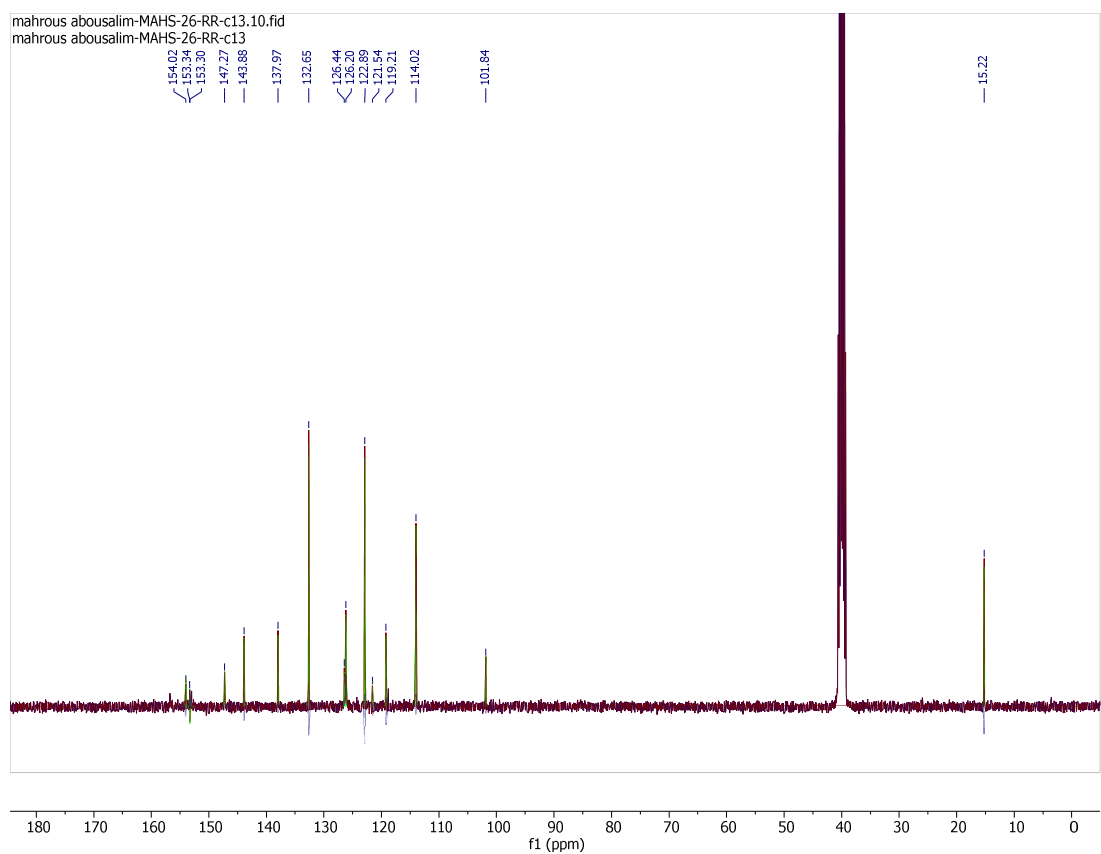
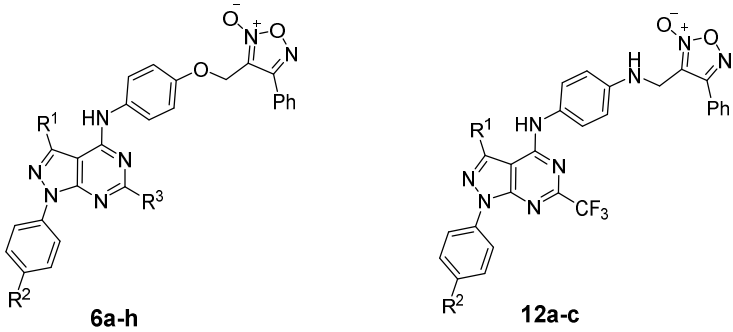


Figure S55. ^{13}C NMR of **15b**.

2 NCI-60 cell line screening

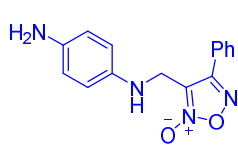
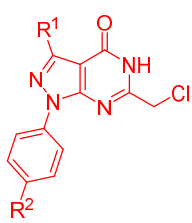
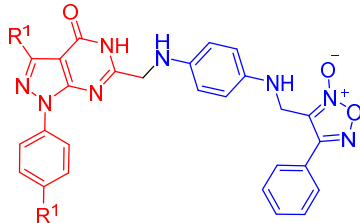
Table S1. NCI-60 cell line growth percentage screening results for target compounds 6a–h and 12a–c.



| Panel name | Cell name | 6a | 6b | 6c | 6d | 6e | 6f | 6g | 6h | 12a | 12b | 12c |
|----------------------------|-----------|--------|--------|--------|--------|--------|--------|--------|--------|-------|-------|-------|
| Leukemia | CCRF-CEM | 91.04 | 102.25 | 97.37 | 112.57 | 107.88 | 104.28 | 98.11 | 103.16 | 59.23 | 48.49 | 60.4 |
| | HL-60(TB) | 94.67 | 122.25 | 118.81 | 111.45 | 96.09 | 100.13 | 115.37 | 70.79 | 77.18 | 79.82 | 83.19 |
| | K-562 | 88 | 111.46 | 90.21 | 99.35 | 98.54 | 91.14 | 103.09 | 83.62 | 39.8 | 22.77 | 51.35 |
| | MOLT-4 | 87.43 | 117.37 | 92.87 | 110.12 | 103.05 | 91.55 | 97.69 | 87.63 | 56.39 | 46.97 | 60.31 |
| | RPMI-8226 | 104.16 | 114.03 | 93.99 | 106.01 | 111.23 | 115.2 | 108.22 | 90.59 | 83.41 | 73.8 | 91.13 |
| | SR | 85.21 | 89.14 | 73.92 | 102.41 | 97.95 | 87.08 | 120.7 | 72 | 58.67 | 43.47 | 55.48 |
| Non-Small Cell Lung Cancer | A549/ATCC | 96 | 100.55 | 99.3 | 103.09 | 93.53 | 94.86 | 97.27 | 96.4 | 76.64 | 64.44 | 82.38 |
| | EKVX | 98.92 | 93.09 | 90.37 | 101.7 | 96.35 | 91.4 | 83.47 | 92.26 | 73.16 | 65.4 | 71.11 |
| | HOP-62 | 107.4 | 102.98 | 105.46 | 106.91 | 104.86 | 110.13 | 94.01 | 103.88 | 93.1 | 77.94 | 68.33 |
| | HOP-92 | 114.93 | 91.42 | 91.18 | 103.5 | 108.9 | 111.33 | 86.53 | 94.56 | 90.13 | 68.36 | 82.26 |
| | NCI-H226 | 111.11 | 94.74 | 97.32 | 101.32 | 104.26 | 107.9 | 89.92 | 108.63 | 85.58 | 76.99 | 74.96 |
| | NCI-H23 | 104.58 | 101.56 | 98.12 | 102.1 | 100.58 | 95.84 | 94.95 | 96.57 | 96.74 | 72.37 | 91.64 |
| | NCI-H322M | 108.65 | 99.46 | 90.96 | 99.86 | 97.89 | 90.8 | 94.49 | 94.39 | 77.61 | 74.07 | 85.06 |
| | NCI-H460 | 73.59 | 110.9 | 109.35 | 111.7 | 110.94 | 103.18 | 100.15 | 100.25 | 52.95 | 35.58 | 46.57 |
| | NCI-H522 | 99.18 | 96.28 | 84.78 | 104.58 | 96.1 | 92.48 | 92.02 | 84.04 | 91.36 | 72.57 | 83.51 |
| Colon Cancer | COLO 205 | 104.07 | 114.17 | 116.19 | 106.94 | 104.65 | 118.82 | 116.74 | 94.42 | 73.59 | 74.58 | 73.25 |
| | HCC-2998 | 106.2 | 108.15 | 105.91 | 107.21 | 106.26 | 104.05 | 104.45 | 105.94 | 85.58 | 75.1 | 96.07 |
| | HCT-116 | 92.96 | 99.24 | 81.85 | 103.76 | 92.74 | 97.47 | 90.71 | 71.46 | 41.11 | 46.67 | 31.88 |
| | HCT-15 | 54.21 | 96.4 | 91.51 | 103.97 | 94.88 | 98.14 | 97.15 | 78.98 | 41.95 | 38.07 | 34.6 |
| | HT29 | 96.01 | 105.66 | 93.24 | 119.1 | 94.52 | 97.26 | 101.19 | 90.03 | 61.53 | 43.9 | 70.41 |
| | KM12 | 102.78 | 101.83 | 99.82 | 103.66 | 103.18 | 101.14 | 98.6 | 97.69 | 56.73 | 41.24 | 74.26 |
| | SW-620 | 105.91 | 120.29 | 106.71 | 118.65 | 114.8 | 108.63 | 106.99 | 101.06 | 85.99 | 84.76 | 79.72 |
| CNS Cancer | SF-268 | 103.42 | 102.96 | 96.49 | 105.79 | 100.82 | 99.92 | 104.45 | 94.7 | 68.61 | 64.95 | 73.2 |
| | SF-295 | 98.39 | 97.09 | 99.05 | 107.96 | 100.94 | 102.15 | 87.58 | 105.37 | 76.59 | 54.52 | 57.45 |
| | SF-539 | 95.73 | 101.85 | 96.18 | 99.82 | 98.37 | 94.25 | 90.41 | 96.08 | 78.06 | 68.29 | 59.37 |
| | SNB-19 | 104.92 | 99.29 | 100.81 | 99.6 | 103.12 | 91.49 | 99.19 | 94.47 | 88 | 78.94 | 84.13 |
| | U251 | 107.44 | 103.53 | 97.24 | 105.73 | 101.51 | 99 | 102.06 | 96.36 | 69.93 | 73.17 | 54.13 |
| Melanoma | LOX IMVI | 94.26 | 97.58 | 100.63 | 96.64 | 110.64 | 104.53 | 94.96 | 98.91 | 57.95 | 27.94 | 48.54 |
| | MALME-3M | 90.01 | 99.35 | 98.19 | 101.49 | 95.27 | 105.63 | 91.61 | 96.03 | 91.04 | 93.53 | 77.7 |

| Panel name | Cell name | 6a | 6b | 6c | 6d | 6e | 6f | 6g | 6h | 12a | 12b | 12c |
|-----------------|-----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | M14 | 103.71 | 102.97 | 90.27 | 96.17 | 101.79 | 94.24 | 94 | 89.47 | 68.7 | 68.18 | 71.9 |
| | MDA-MB-435 | 114.31 | 99.7 | 93.4 | 104.96 | 94.48 | 94.48 | 101.38 | 96.74 | 78.65 | 72.77 | 86.57 |
| | SK-MEL-2 | 104.56 | 109.32 | 102.54 | 120.98 | 99.16 | 113.67 | 101.23 | 96.89 | 105.94 | 99.8 | 103.84 |
| | SK-MEL-28 | 104.38 | 100.93 | 101.78 | 101.92 | 99.32 | 103.33 | 99.45 | 101.07 | 92.4 | 89.22 | 89.51 |
| | SK-MEL-5 | 101.72 | 102.79 | 90.37 | 97.99 | 95.87 | 99.66 | 96.52 | 91.48 | 70.32 | 86 | 61.69 |
| | UACC-257 | 98.86 | 101.17 | 104.84 | 109.22 | 103.6 | 101.48 | 97.09 | 99.8 | 102.82 | 102.46 | 95.7 |
| | UACC-62 | 102.94 | 88.41 | 81.38 | 89.61 | 89.07 | 84.79 | 80.3 | 80.24 | 64.87 | 64.92 | 62.51 |
| Ovarian Cancer | IGROV1 | 95.05 | 101.42 | 97.12 | 106.25 | 105.56 | 101.06 | 88.15 | 99.02 | 77.88 | 60.07 | 59.62 |
| | OVCAR-3 | 95.93 | 108.51 | 105.27 | 113.83 | 116.58 | 113.86 | 111.9 | 104.26 | 105.05 | 91.97 | 91.56 |
| | OVCAR-4 | 130.15 | 101.92 | 90.57 | 102.62 | 100.33 | 99.53 | 95.72 | 96.99 | 70.76 | 78.52 | 81.28 |
| | OVCAR-5 | 110.22 | 105.87 | 103.77 | 100.77 | 98.76 | 99.29 | 99.26 | 102.49 | 93.72 | 77.15 | 89.54 |
| | OVCAR-8 | 105.02 | 105.16 | 101.28 | 107.45 | 104.85 | 106.4 | 93.92 | 102.21 | 89.7 | 72.77 | 75.76 |
| | NCI/ADR-RES | 102.17 | 103.18 | 91.74 | 102.3 | 106.51 | 105.74 | 93.83 | 101.88 | 83 | 66.38 | 88.75 |
| | SK-OV-3 | 101.8 | 109.92 | 104.32 | 109.35 | 104.43 | 113.29 | 96.19 | 108.54 | 96.87 | 88.84 | 82.71 |
| Renal Cancer | 786-0 | 115.3 | 95.78 | 106.76 | 107.35 | 96.13 | 82.25 | 121.94 | 106.67 | 92.39 | 67.15 | 88.11 |
| | A498 | 103 | 101.84 | 86.35 | 111.89 | 93.98 | 87.19 | 106.36 | 109.59 | 94.43 | 97.4 | 116.68 |
| | ACHN | 104.77 | 104.8 | 97.31 | 95.53 | 103.23 | 101.44 | 88.01 | 98.67 | 77.73 | 56.91 | 68.07 |
| | CAKI-1 | 99.36 | 87.57 | 85.97 | 101.17 | 82.14 | 81.89 | 84.89 | 83.77 | 53.03 | 31.1 | 55.05 |
| | RXF 393 | 98.39 | 110.52 | 112.21 | 118.64 | 118.82 | 121.41 | 131.01 | 135.54 | 86.8 | 51.18 | 89.2 |
| | SN12C | 97.31 | 100.82 | 87.9 | 98.39 | 96.43 | 94.79 | 91.26 | 96.43 | 77.71 | 57.98 | 76.16 |
| | TK-10 | 103.11 | 94.81 | 110.09 | 125.68 | 106.77 | 97.66 | 122.57 | 114.06 | 94.39 | 86.83 | 109.09 |
| | UO-31 | 94.17 | 95.03 | 77.03 | 88.52 | 84.68 | 82.73 | 81.52 | 74.04 | 57.52 | 43.42 | 50.26 |
| Prostate Cancer | PC-3 | 98.13 | 103.14 | 83.52 | 99.01 | 96.95 | 102.74 | 90.94 | 67.39 | 45.65 | 48.22 | 46.96 |
| | DU-145 | 107.32 | 104.51 | 105.81 | 111.53 | 107.32 | 103.93 | 109.58 | 102.44 | 82.25 | 70.76 | 84.78 |
| Breast Cancer | MCF7 | 96.12 | 92.38 | 83.01 | 95.41 | 87.88 | 85.3 | 89.04 | 87.38 | 58.52 | 38.79 | 68.23 |
| | MDA-MB-231/ATCC | 97.55 | 106 | 95.65 | 101.12 | 107.57 | 106.3 | 84.9 | 99.97 | 84.4 | 69.7 | 65.9 |
| | HS 578T | 98.73 | 109.67 | 97.53 | 101.62 | 109.81 | 93.64 | 93.41 | 94.75 | 77.88 | 77.61 | 83.15 |
| | BT-549 | 95.38 | 94.95 | 101.3 | 102.15 | 95.83 | 94.5 | 104.23 | 91.1 | 103.19 | 97.5 | 97.42 |
| | T-47D | 96 | 105.6 | 71.97 | 104.36 | 99.88 | 97.15 | 98.47 | 81.39 | 80.45 | 68.83 | 85.62 |
| | MDA-MB-468 | 106.81 | 94.26 | 97.08 | 107.05 | 105.66 | 111.1 | 97.42 | 116.06 | 75.83 | 71.95 | 84.2 |
| Mean | | 100.06 | 102.34 | 96.2 | 104.91 | 101.07 | 99.74 | 98.42 | 95.43 | 76.8 | 66.83 | 74.78 |
| Delta | | 45.85 | 14.77 | 24.23 | 16.39 | 18.93 | 17.85 | 18.12 | 28.04 | 37 | 44.06 | 42.9 |
| Range | | 75.94 | 34.68 | 46.84 | 37.16 | 36.68 | 39.52 | 50.71 | 68.15 | 66.14 | 79.69 | 84.8 |

Table S2. NCI-60 cell line growth percentage screening results for compounds **11**, **13a–c**, and **14a–c**.

| | | | | | | | | |
|-----------------------------------------------------------------------------------|-----------|-----------------------------------------------------------------------------------|--------------|------------------------------------------------------------------------------------|------------|------------|------------|------------|
|  | |  | |  | | | | |
| | | 11 | 13a-c | 13b | 13c | 14a | 14b | 14c |
| Leukemia | CCRF-CEM | 83.37 | 101.21 | ND | 83.65 | 57.91 | 78.76 | 105.22 |
| | HL-60(TB) | 95.51 | 108.73 | 33.07 | ND | 63.09 | 93.68 | 103.2 |
| | K-562 | 99.1 | 87.53 | 19.16 | 75.57 | 49.77 | 75.8 | 110.66 |
| | MOLT-4 | 91.79 | 103.59 | 79.63 | ND | 44.02 | 61.55 | 87.17 |
| | RPMI-8226 | 97.48 | 82.53 | ND | -53.91 | 61.94 | 78.99 | 111.75 |
| | SR | 103.87 | 87.13 | 39.76 | ND | 45.67 | 73.05 | 95.15 |
| Non-Small Cell Lung Cancer | A549/ATCC | 95.09 | 98.55 | 97.67 | 96.91 | 63.76 | 74.31 | 97.39 |
| | EKVX | 108.98 | 99.95 | 99.24 | 99.52 | 51.31 | 83.05 | 98.93 |
| | HOP-62 | 135.92 | 125.45 | 98.34 | 98.54 | 104.53 | 109.59 | 116.09 |
| | HOP-92 | 116.12 | 100.94 | 117.39 | 100.66 | 85.39 | 93.19 | 107.67 |
| | NCI-H226 | 114.2 | 110.08 | 111.37 | 101.58 | 77.15 | 100.85 | 108.98 |
| | NCI-H23 | 104.56 | 101.47 | 98.81 | 102.56 | 63.38 | 86.6 | 103.09 |
| | NCI-H322M | 102.53 | 101.08 | 102.74 | 104.14 | 80.21 | 88.99 | 104.06 |
| | NCI-H460 | 101.49 | 101.49 | 102.13 | 108.94 | 64.19 | 89.95 | 106.97 |
| | NCI-H522 | 93.47 | 102.7 | 89.79 | 85.46 | 60.75 | 80.86 | 90.77 |
| Colon Cancer | COLO 205 | 120.75 | 113.67 | 110.35 | 102.99 | 101.27 | 116.22 | 114.51 |
| | HCC-2998 | 117.73 | 105.37 | 107.9 | 105.26 | 84.43 | 110.82 | 112.32 |
| | HCT-116 | 98.42 | 94.89 | 24.88 | 98.34 | 49.64 | 78.98 | 93.76 |
| | HCT-15 | 104 | 99.88 | 90.57 | 103.06 | 71.19 | 80.57 | 97.31 |
| | HT29 | 110.92 | 114.56 | 105.88 | 103.6 | 92.01 | 107.47 | 110.02 |
| | KM12 | 103.2 | 100.52 | 53.31 | 83.63 | 73.35 | 94.46 | 105.52 |
| | SW-620 | 114.98 | 101.71 | 85.06 | 109.62 | 92.79 | 109.92 | 111.22 |
| CNS Cancer | SF-268 | 101.06 | 99.94 | 106.41 | 99.42 | 73.46 | 84.94 | 95.24 |
| | SF-295 | 117.43 | 109.84 | 109.05 | 100.36 | 71.76 | 102.54 | 115.3 |
| | SF-539 | 103.88 | 97.09 | 36.89 | 76.97 | 92.62 | 99.39 | 101.75 |
| | SNB-19 | 109.54 | 96.35 | 89.43 | 97.13 | 94.01 | 100.52 | 101.91 |
| | U251 | 101.65 | 93.65 | 93.92 | 99.72 | 76.08 | 94.56 | 99.13 |
| el an o m | LOX IMVI | 107.14 | 102.65 | 100.54 | 98.49 | 85.52 | 97.63 | 101.98 |

| Panel name | Cell name | 11 | 13a | 13b | 13c | 14a | 14b | 14c |
|-----------------|-----------------|--------|--------|--------|--------|--------|--------|--------|
| | MALME-3M | 100 | -38.51 | 2.09 | -9.8 | 63.61 | 74.09 | 92.51 |
| | M14 | 102.33 | 110.15 | 102.62 | 105.69 | 80 | 105.91 | 106.53 |
| | MDA-MB-435 | 90.2 | 95.67 | 98.99 | 101.41 | 70.69 | 91.56 | 101.36 |
| | SK-MEL-2 | 104.62 | 103.78 | 97.9 | 103.15 | 77.81 | 100.37 | 106.96 |
| | SK-MEL-28 | 100.57 | -89.82 | 104.62 | 99.87 | 77.17 | 99.23 | 102.96 |
| | SK-MEL-5 | 111.85 | 106.69 | 109.98 | 102.63 | 85.29 | 108.26 | 103.56 |
| | UACC-257 | 99.18 | 98.96 | 98.75 | 101.87 | 39.03 | 90.08 | 101.25 |
| | UACC-62 | 95.53 | 96.17 | 97.9 | 100.63 | 60.63 | 98.47 | 105.22 |
| Ovarian Cancer | IGROV1 | 88.73 | 96.21 | 96.16 | 95.09 | 52.51 | 64.36 | 85.58 |
| | OVCAR-3 | 111.29 | 95.9 | 97.39 | 97.37 | 73.46 | 87.63 | 93.9 |
| | OVCAR-4 | 117.84 | 100.13 | 90.89 | 115.85 | 94.45 | 101.91 | 127.06 |
| | OVCAR-5 | 115.66 | 110.66 | 109.54 | 115.89 | 64.29 | 95.44 | 110.28 |
| | OVCAR-8 | 131.45 | 114.21 | 112.48 | 102.24 | 108.67 | 117.17 | 111.71 |
| | NCI/ADR-RES | 104.44 | 103.77 | 102.43 | 101.76 | 79.36 | 92.4 | 101.27 |
| | SK-OV-3 | 105.07 | 106.32 | 104.73 | 104.49 | 60.57 | 85.44 | 106.58 |
| Renal Cancer | 786-0 | 140.04 | 121.81 | 122.34 | 105.65 | 101.89 | 125.21 | 119.28 |
| | A498 | 108.09 | 77.86 | 4.55 | -88.76 | 85.95 | 97.94 | 104.38 |
| | ACHN | 104.06 | 96.68 | 90.25 | 94.79 | 70.42 | 88.76 | 96.91 |
| | CAKI-1 | 108.4 | 97.61 | 99.62 | 96.32 | 55.06 | 67.06 | 90.2 |
| | RXF 393 | 134.38 | 94.11 | 99.19 | 119.04 | 98.44 | 107.68 | 116.98 |
| | SN12C | 108.69 | 99.78 | 95.71 | 100.14 | 78.95 | 89.43 | 98.75 |
| | TK-10 | 155.84 | 154.35 | 63.25 | 111.26 | 102.29 | 136.8 | 132.5 |
| | UO-31 | 98.87 | -20.87 | -86.33 | -90.14 | 55.94 | 72.36 | 83.36 |
| Prostate Cancer | PC-3 | 95.12 | 104.61 | 102.15 | 96.35 | 63.34 | 77.68 | 96.61 |
| | DU-145 | 111.76 | 98.62 | 83.61 | 110.05 | 74.63 | 90.74 | 106.83 |
| Breast Cancer | MCF7 | 85.52 | 79.53 | 16.43 | 82.32 | 50.05 | 77 | 88.1 |
| | MDA-MB-231/ATCC | 103.56 | 101.02 | 88.41 | 94.07 | 72.55 | 82.67 | 96.45 |
| | HS 578T | 108.57 | 110.78 | 120.34 | 107.81 | 85.78 | 103.67 | 107.75 |
| | BT-549 | 103.01 | 94.08 | 100.47 | 100.62 | 62.13 | 95.93 | 98.09 |
| | T-47D | 100.8 | 95.24 | 65.98 | 91.53 | 42.5 | 75.49 | 103.34 |
| | MDA-MB-468 | 85.34 | 96.59 | 26.64 | 94.03 | 33.2 | 66.94 | 94.39 |
| Mean | | 106.53 | 94.15 | 82.85 | 88.31 | 72.07 | 91.78 | 103.35 |
| Delta | | 23.16 | 183.97 | 169.18 | 178.45 | 38.87 | 30.23 | 19.99 |
| Range | | 72.47 | 244.17 | 208.67 | 209.18 | 75.47 | 75.25 | 49.14 |

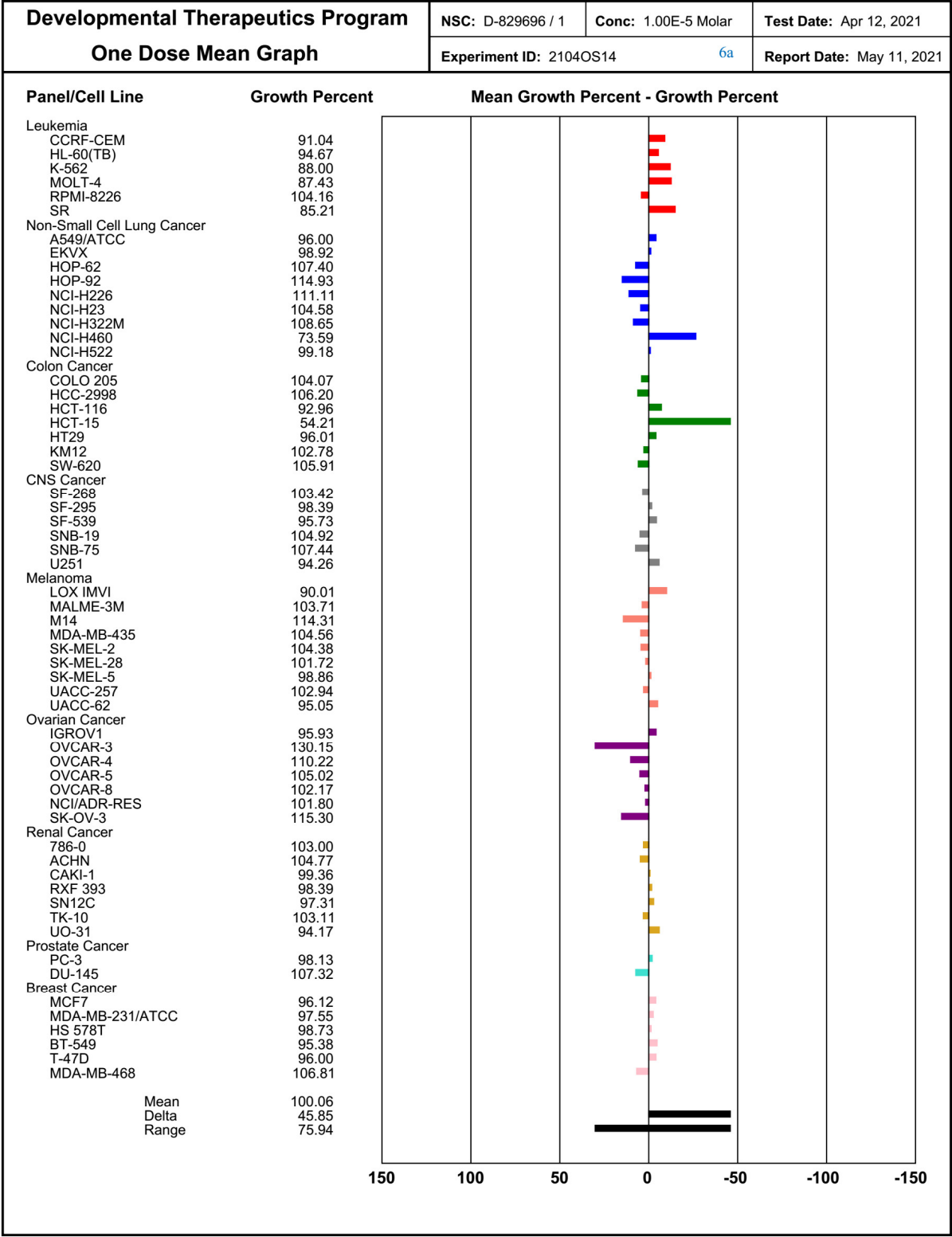


Figure S56. One dose mean graph of 6a.

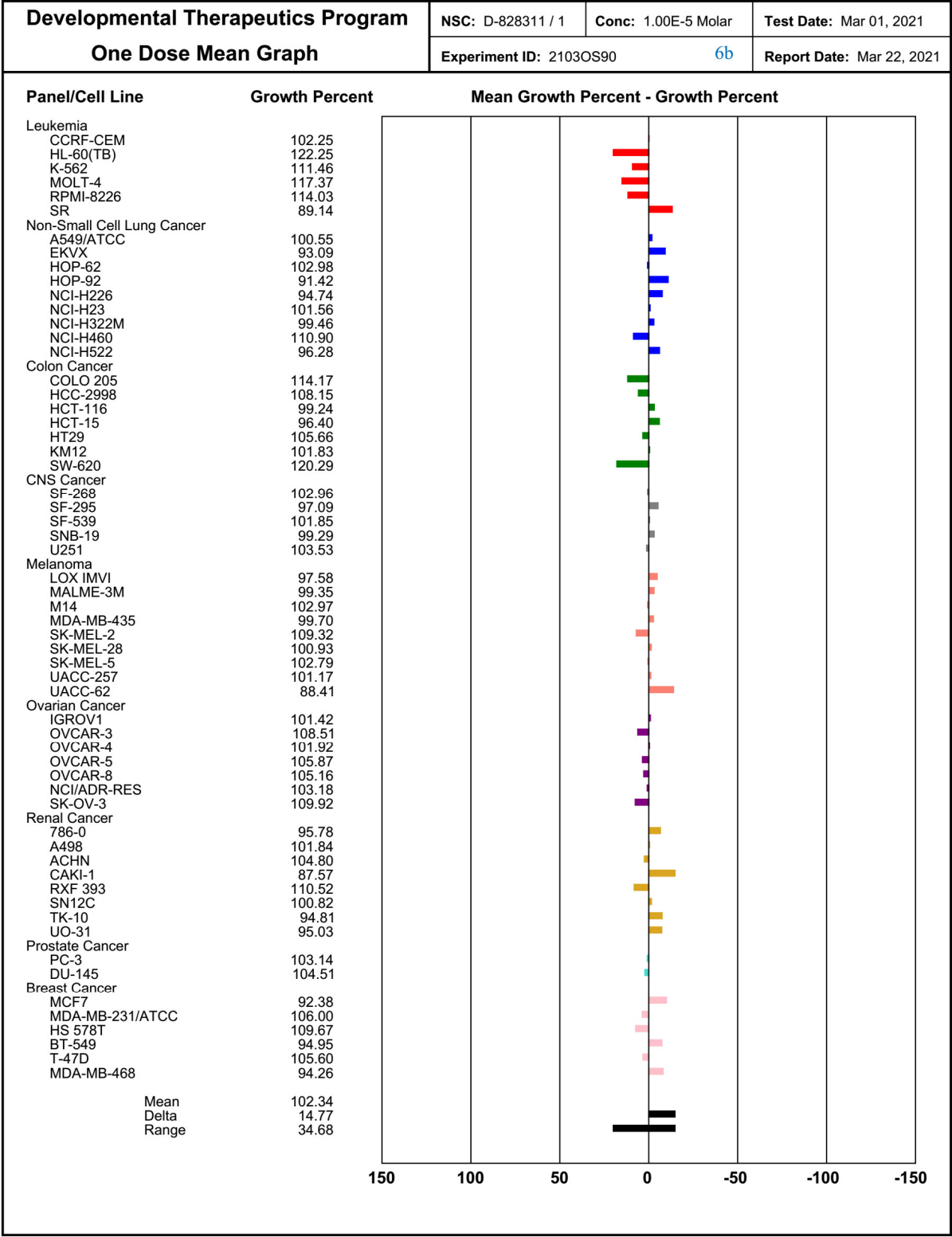


Figure S57. One dose mean graph of 6b.

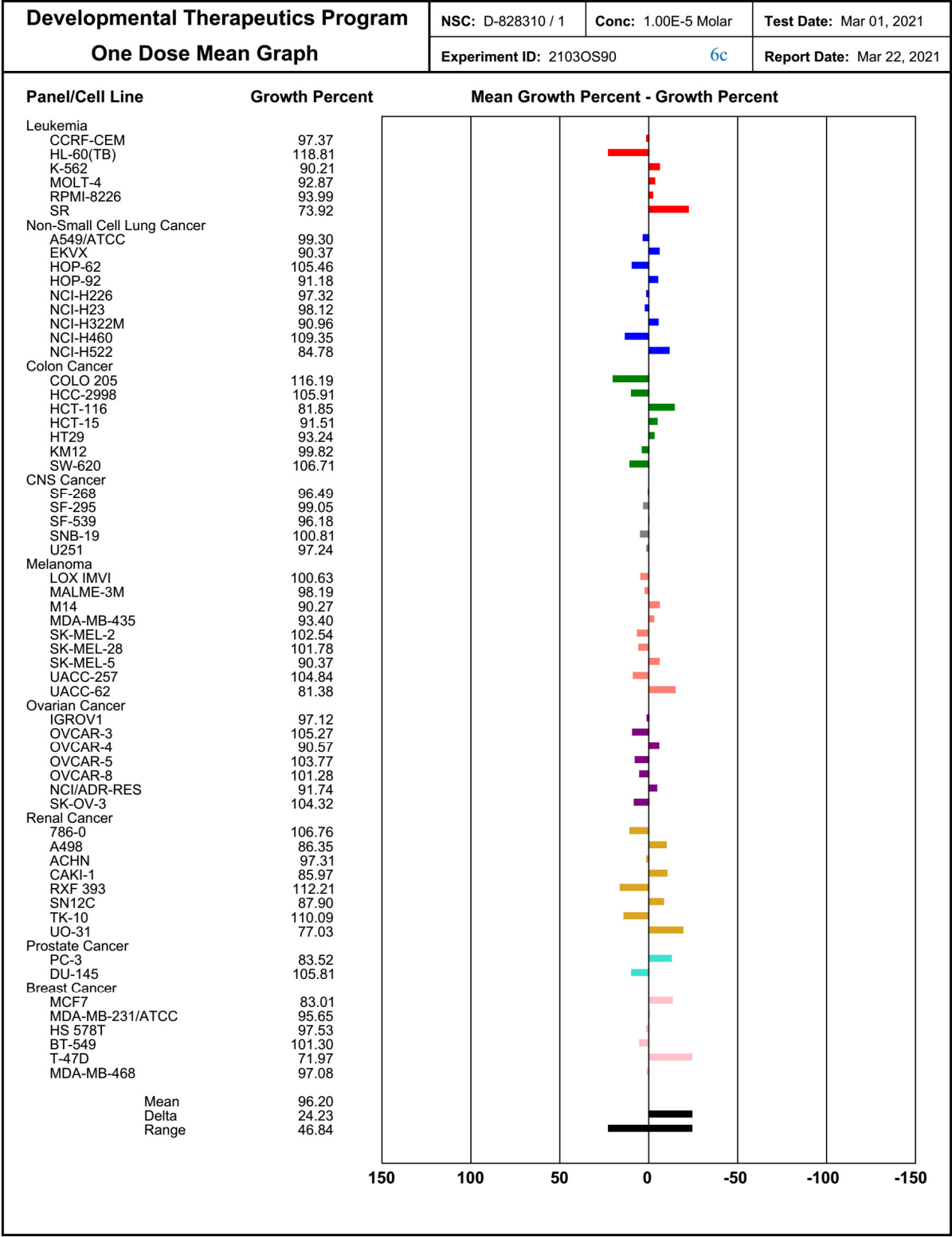


Figure S58. One dose mean graph of 6c.

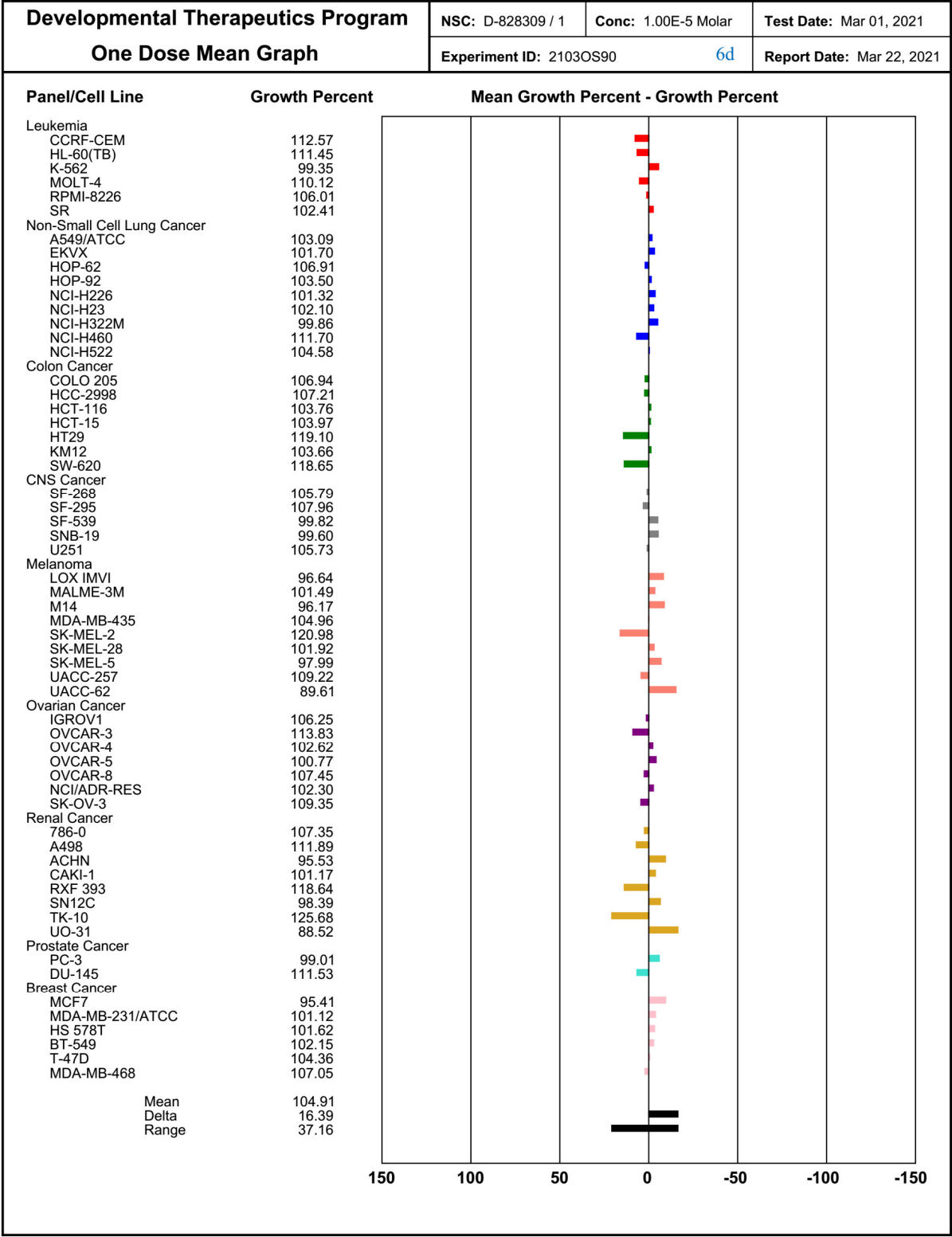


Figure S59. One dose mean graph of 6d.

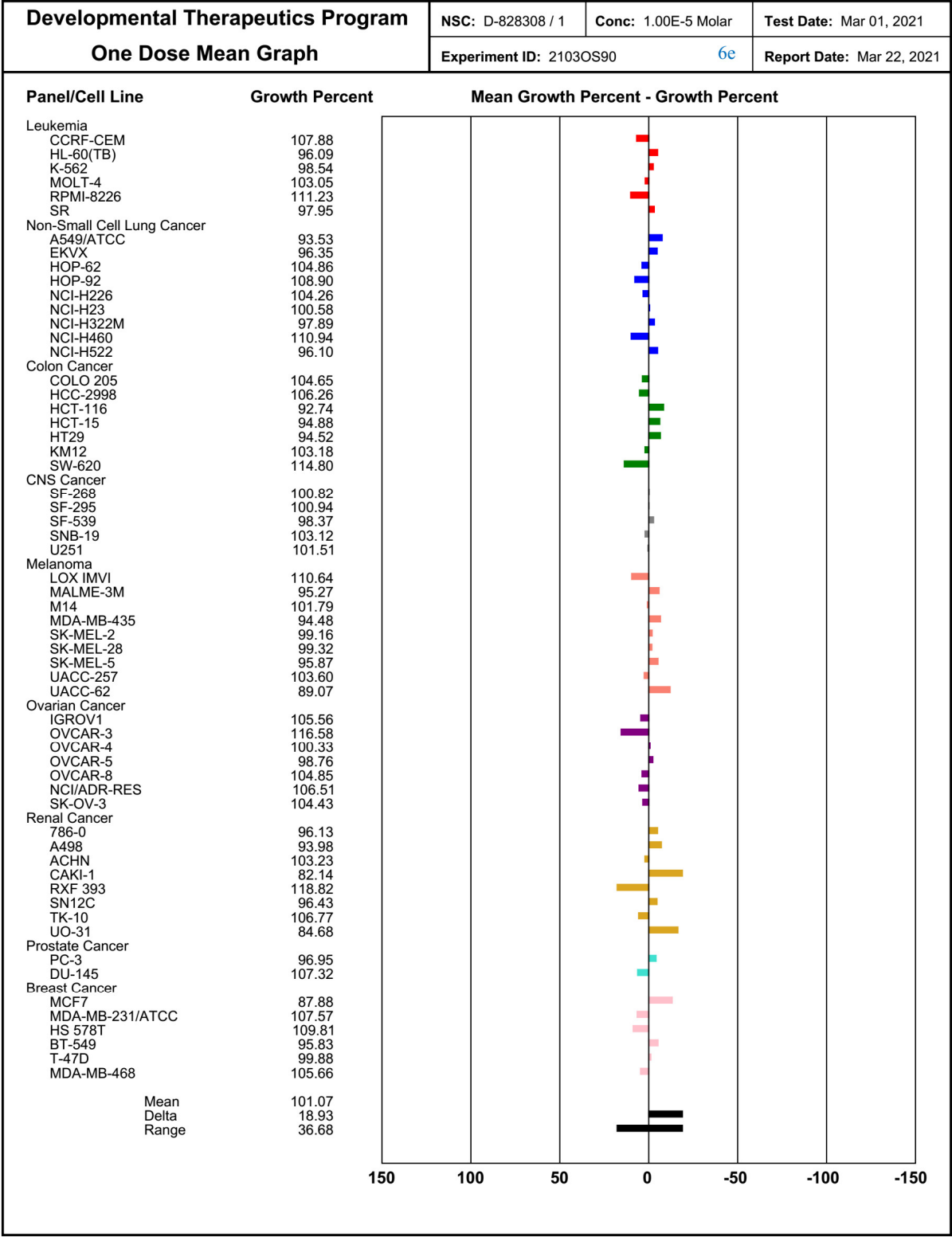


Figure S60. One dose mean graph of 6e.

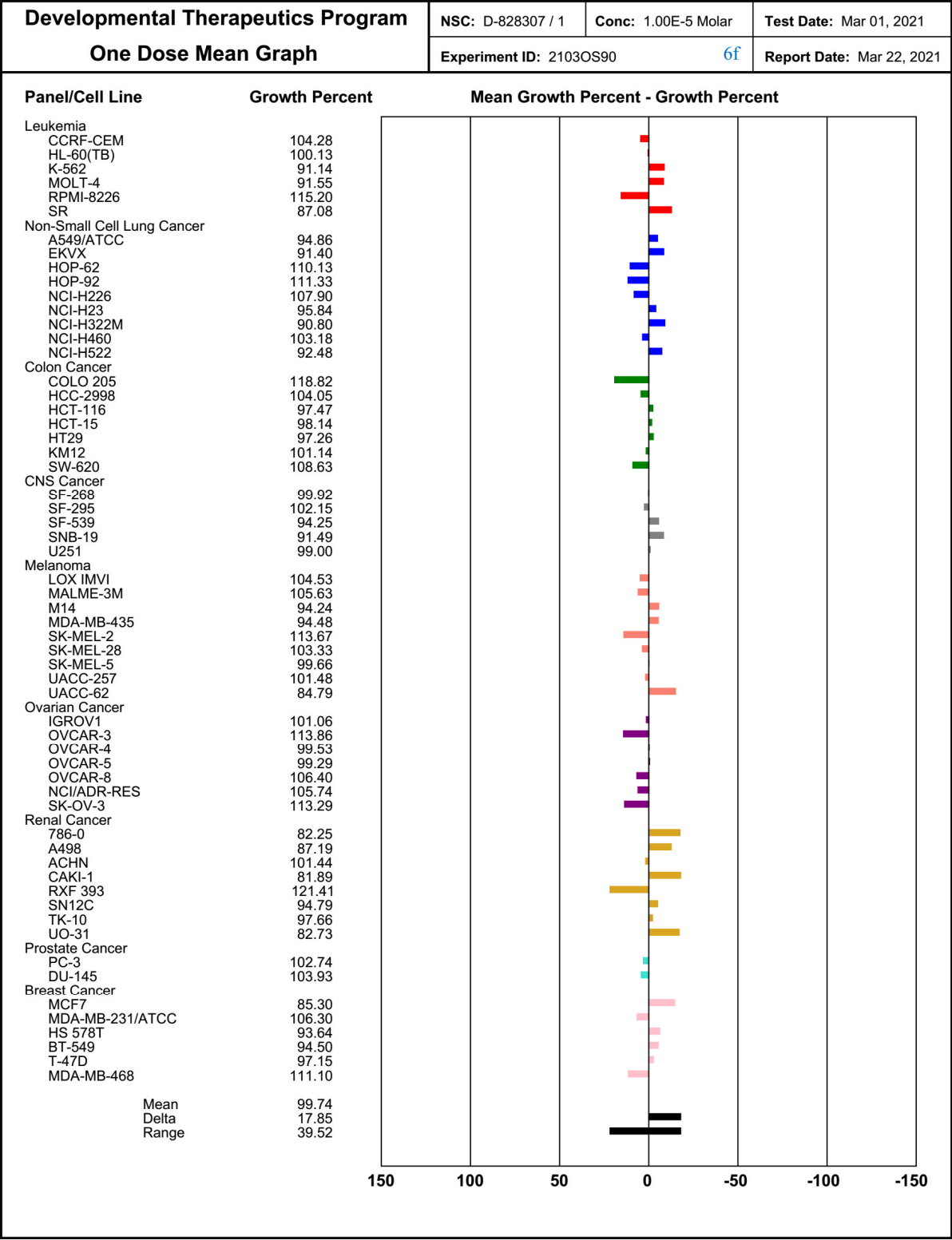


Figure S61. One dose mean graph of 6f.

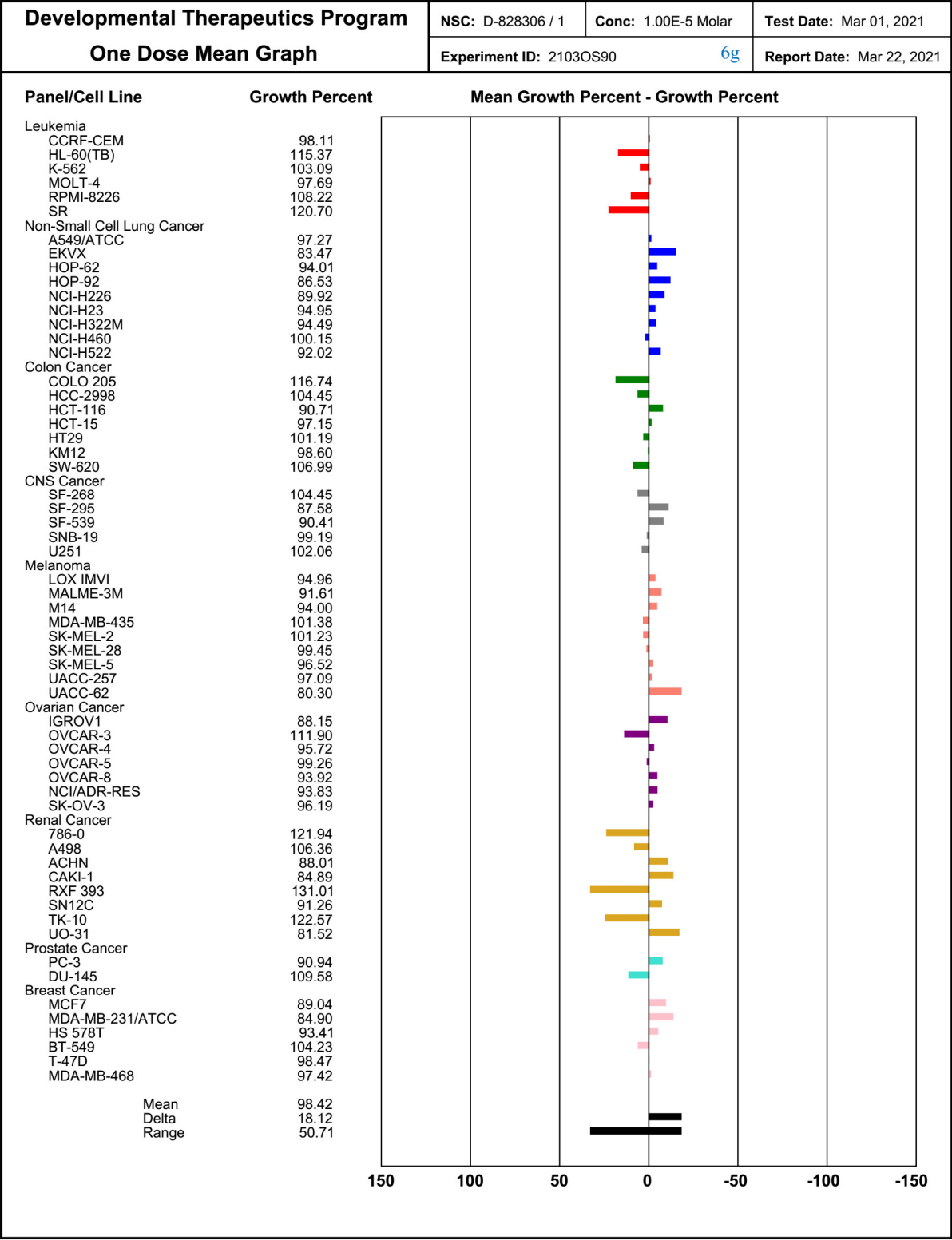


Figure S62. One dose mean graph of 6g.

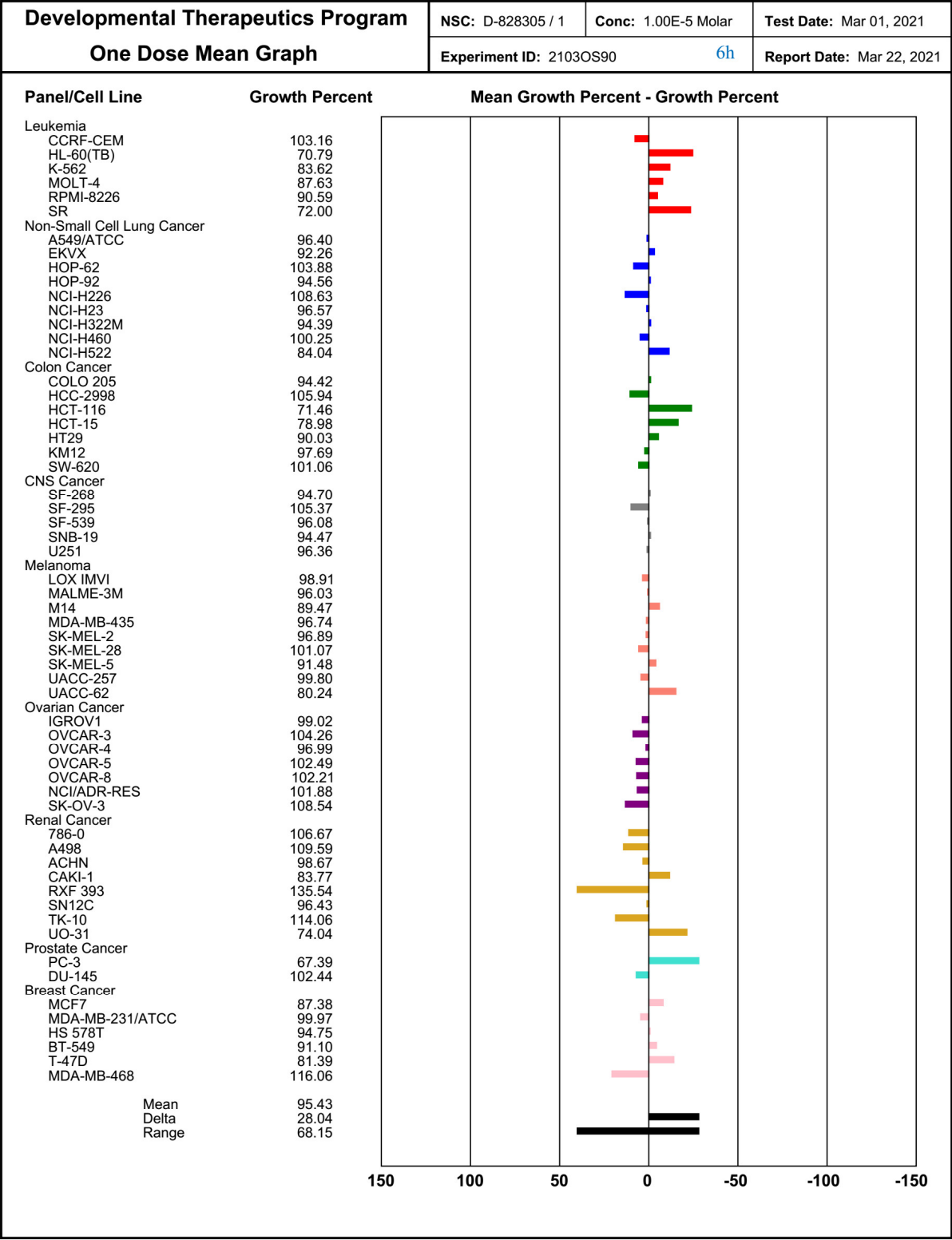


Figure S63. One dose mean graph of 6h.

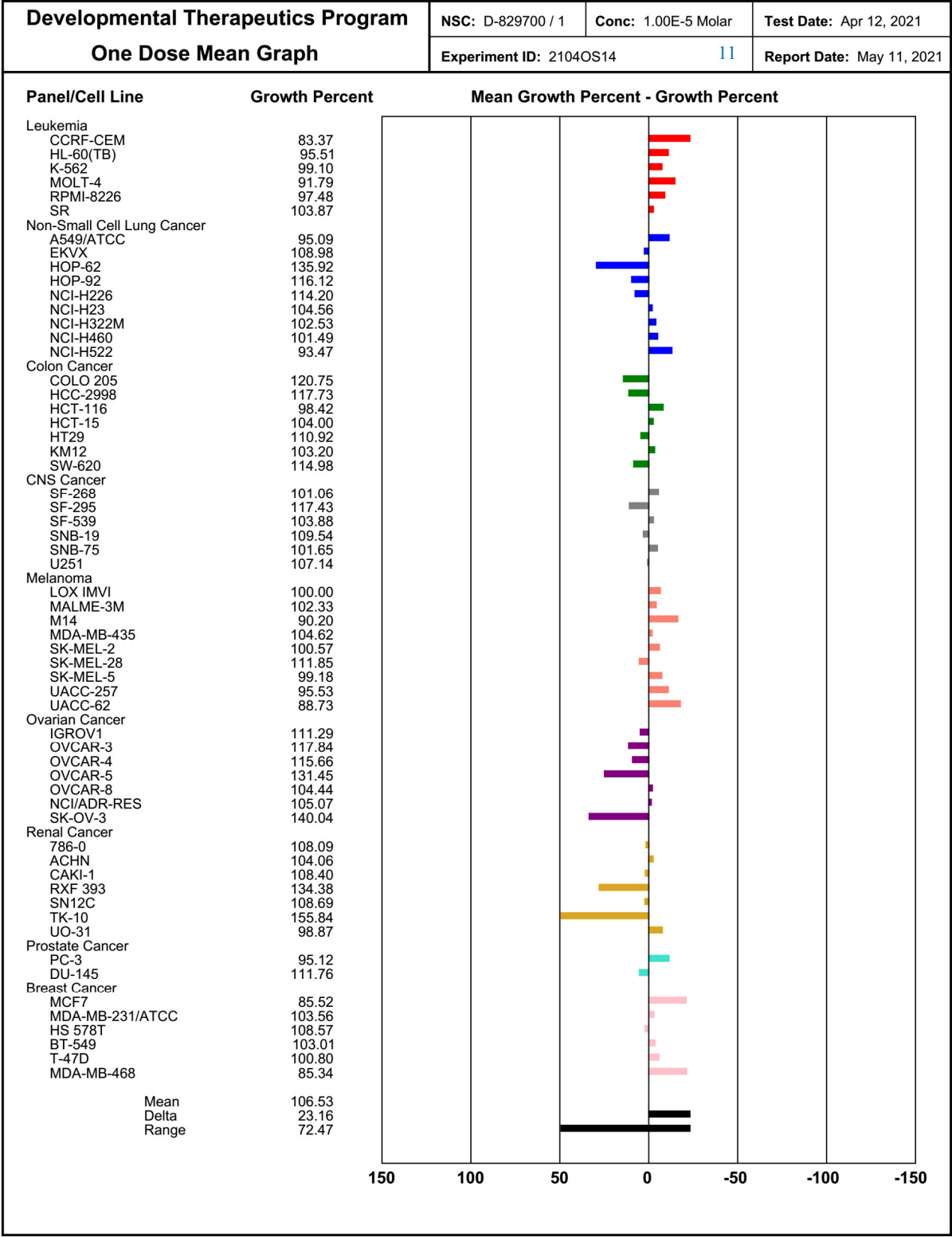


Figure S64. One dose mean graph of 11.

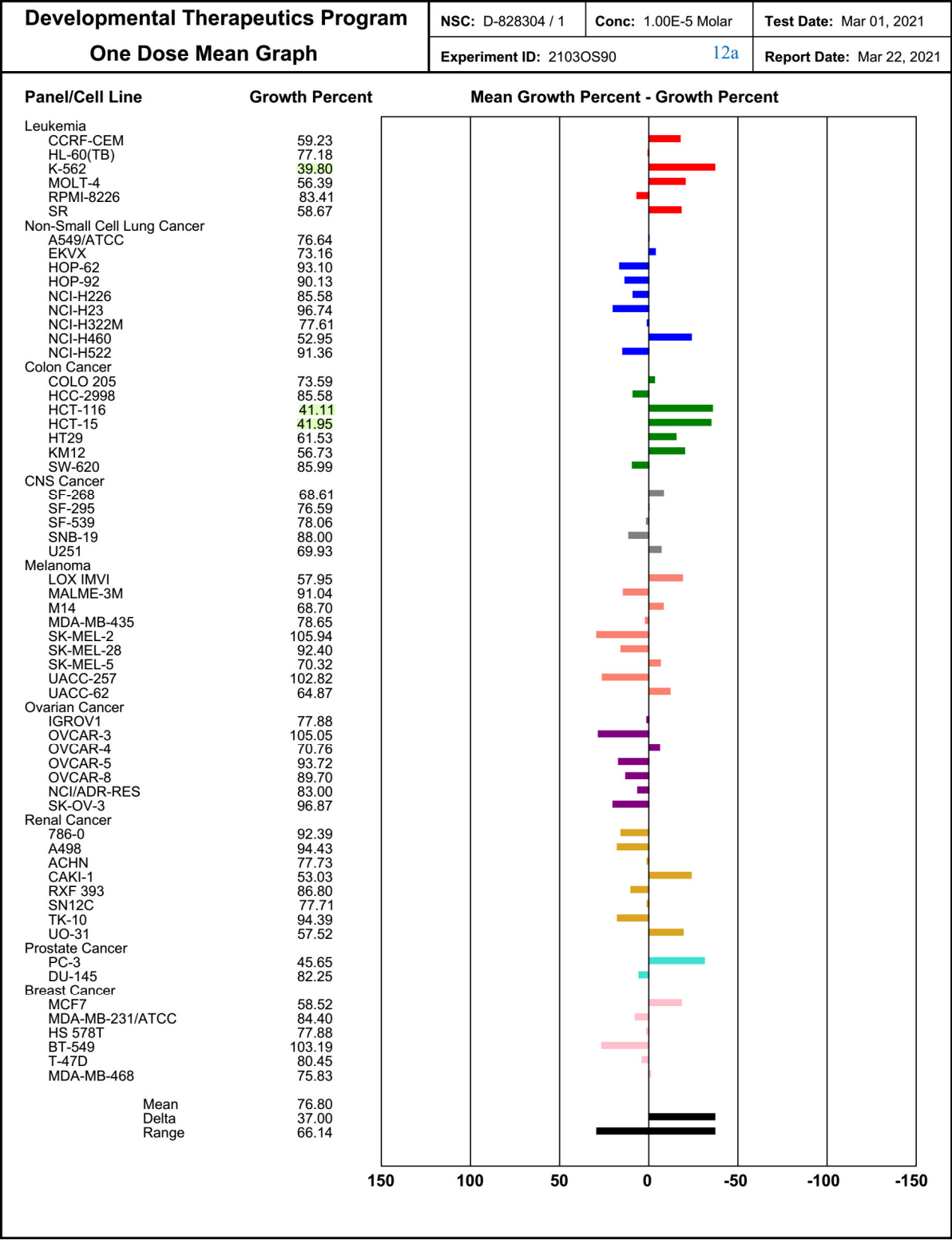


Figure S65. One dose mean graph of 12a.

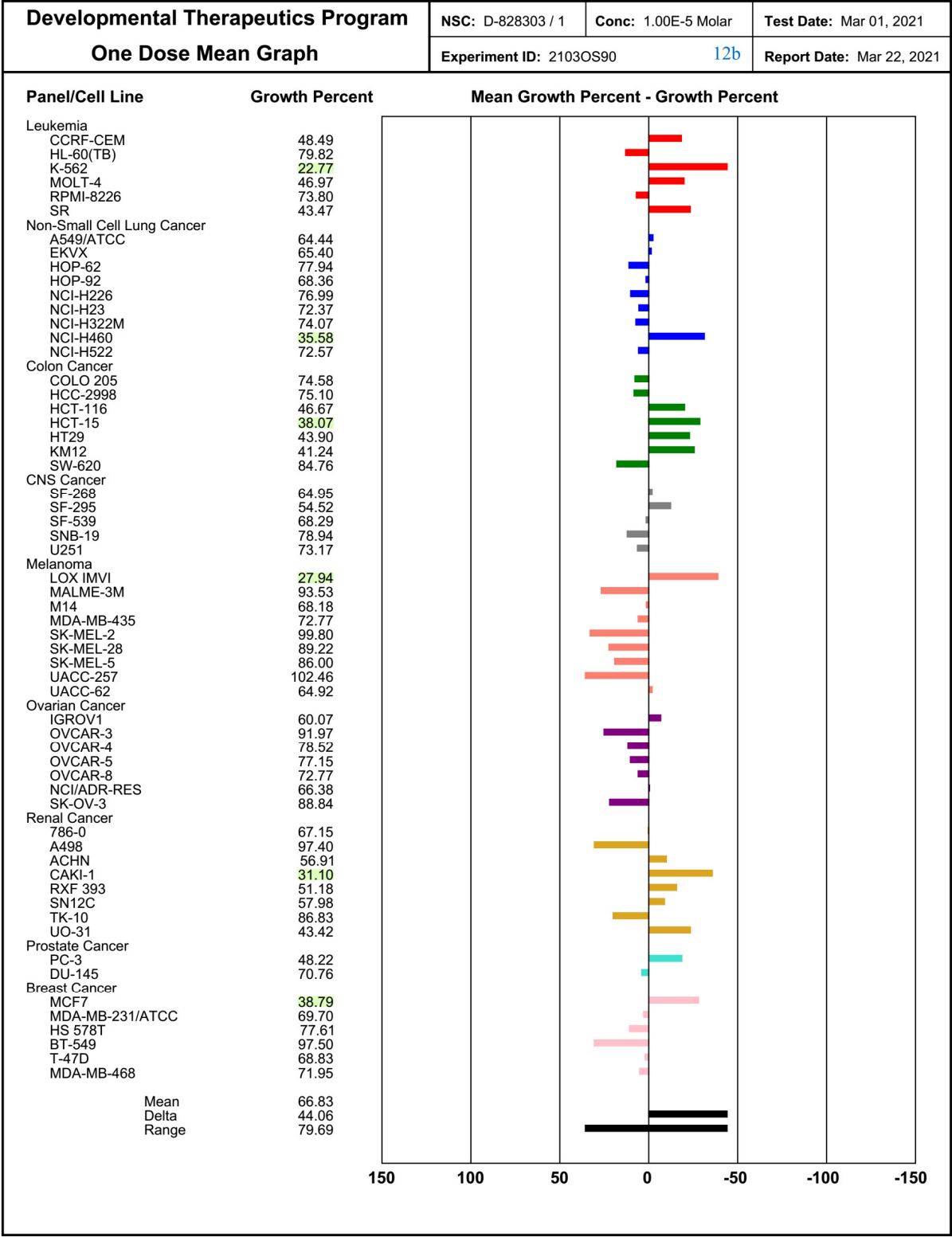


Figure S66. One dose mean graph of 12b.

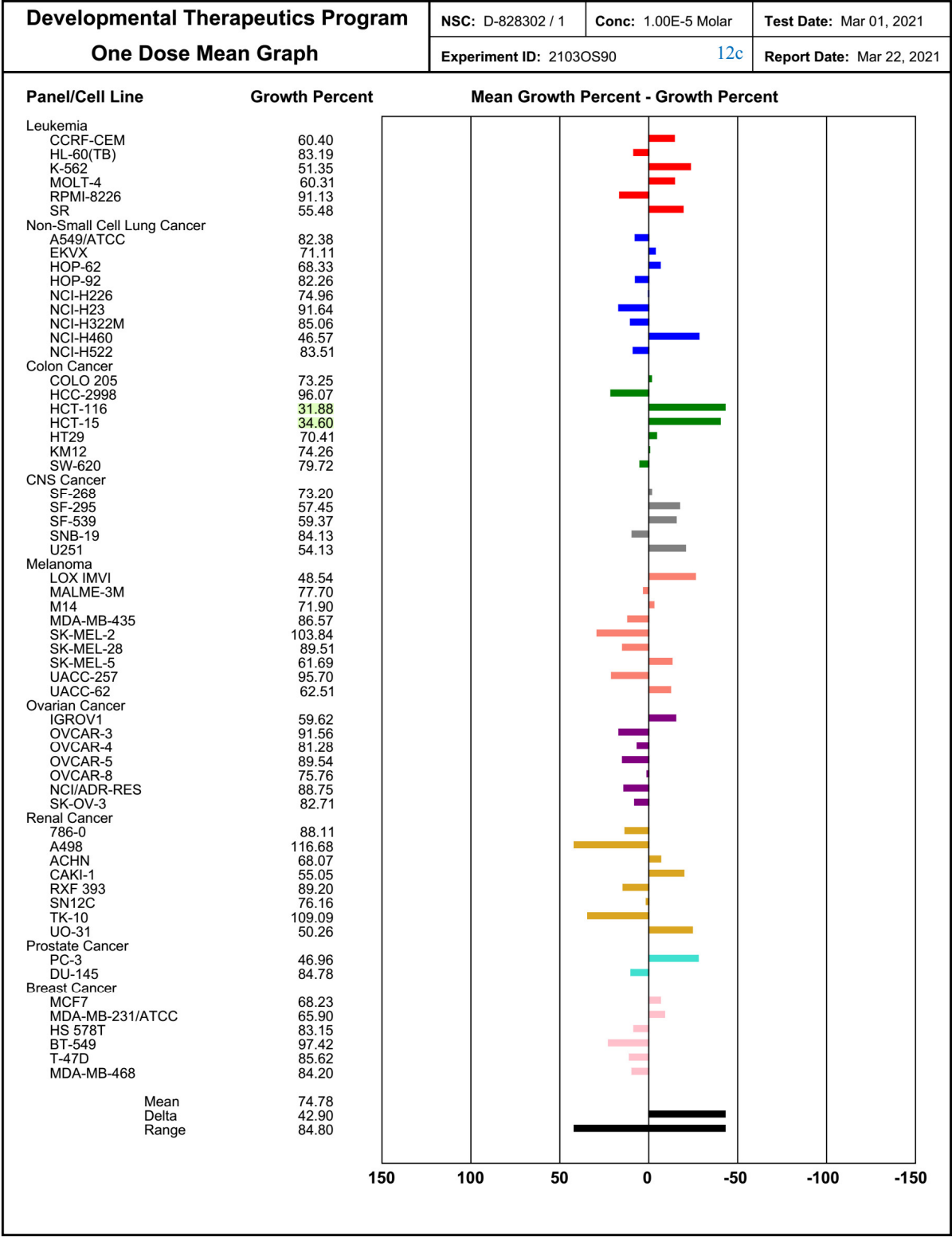


Figure S67. One dose mean graph of 12c.

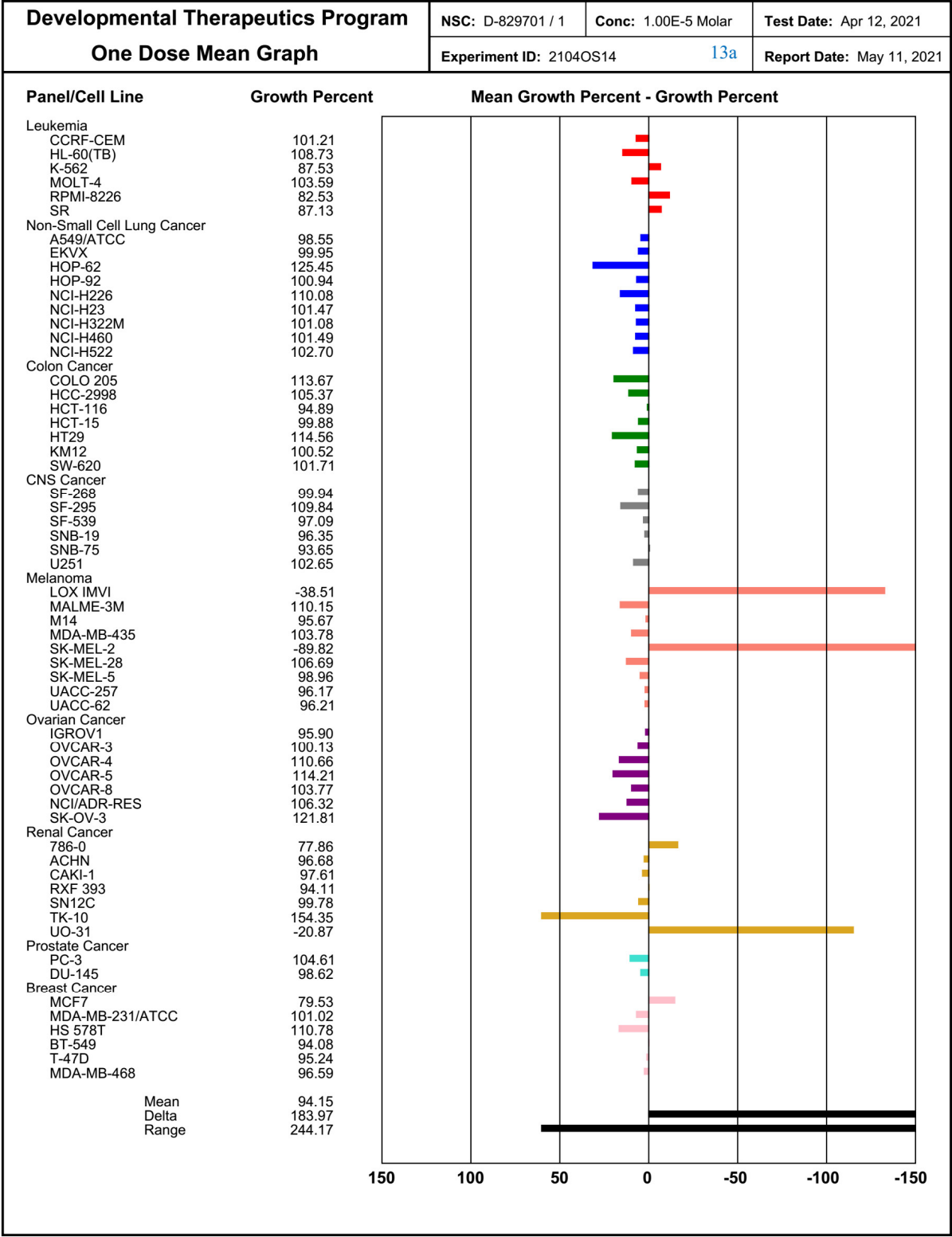


Figure S68. One dose mean graph of 13a.

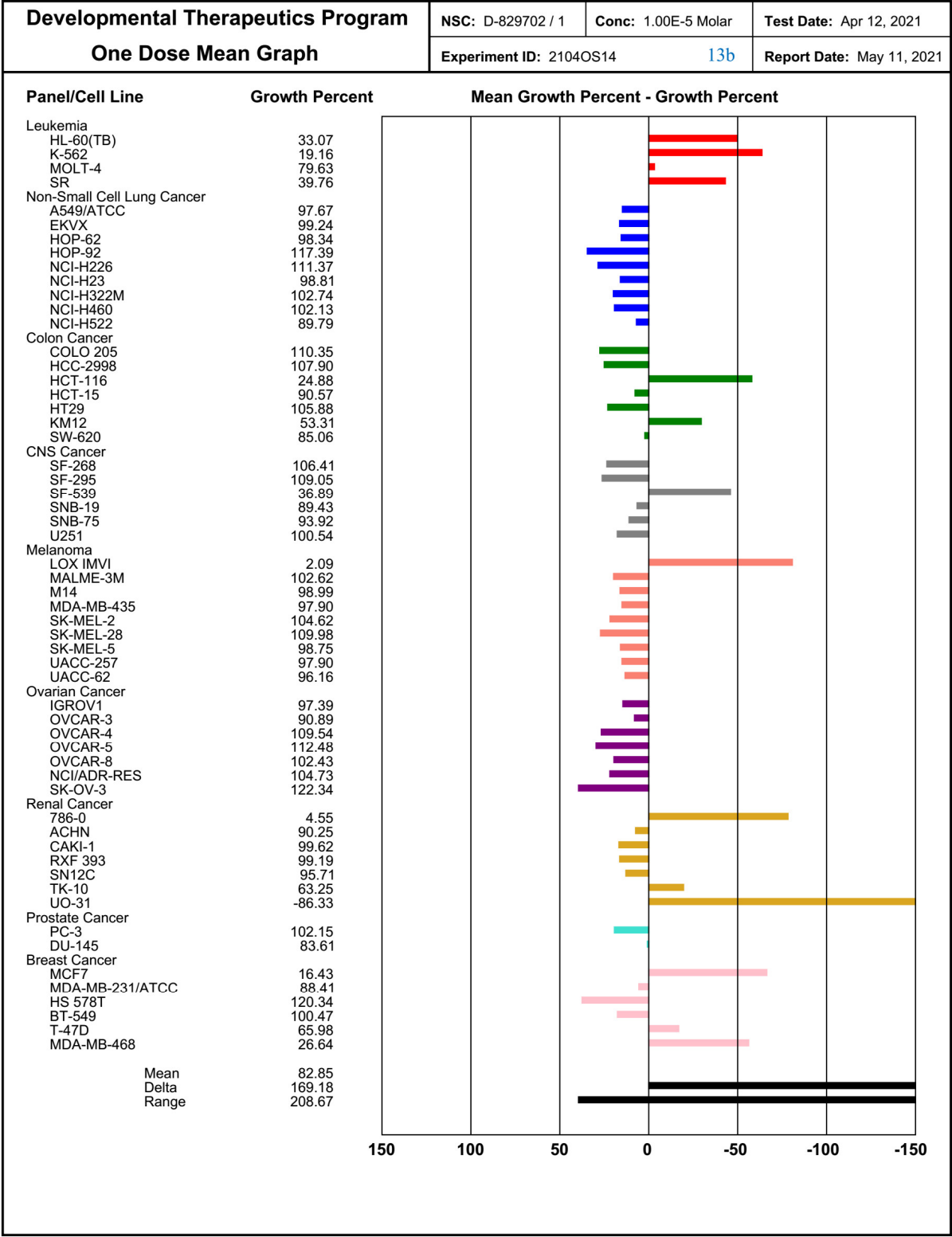


Figure S69. One dose mean graph of 13b.

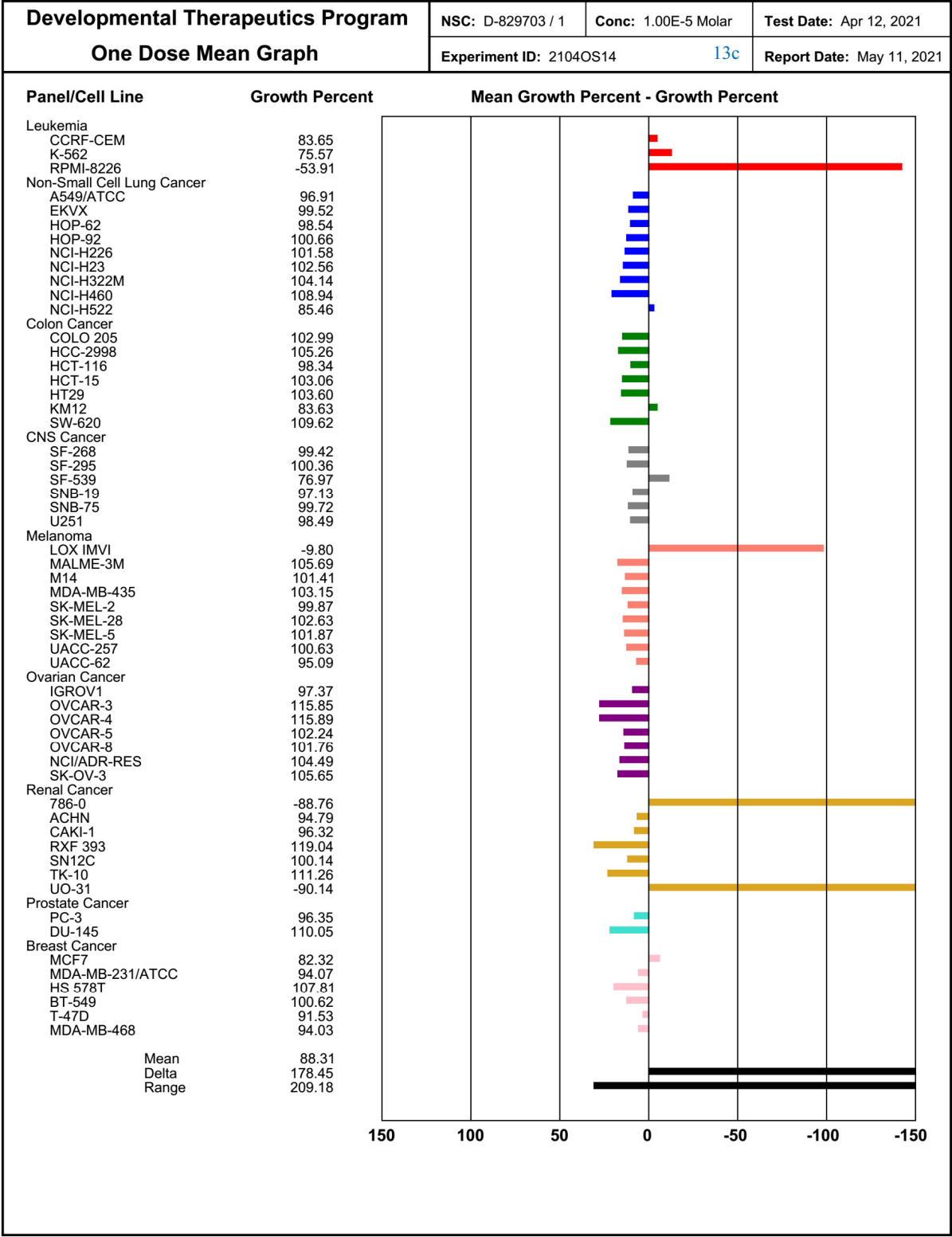


Figure S70. One dose mean graph of 13c.

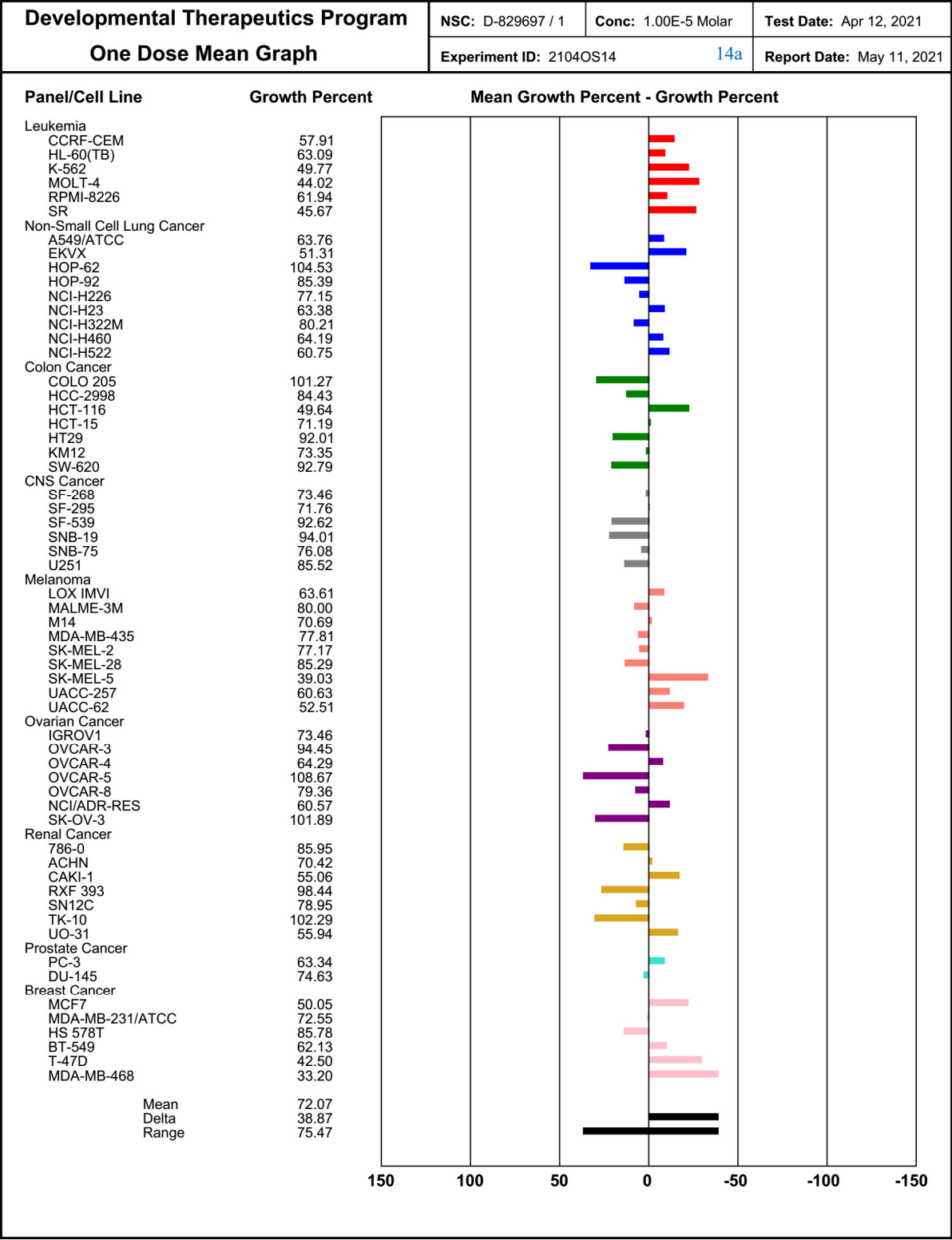


Figure S71. One dose mean graph of 14a.

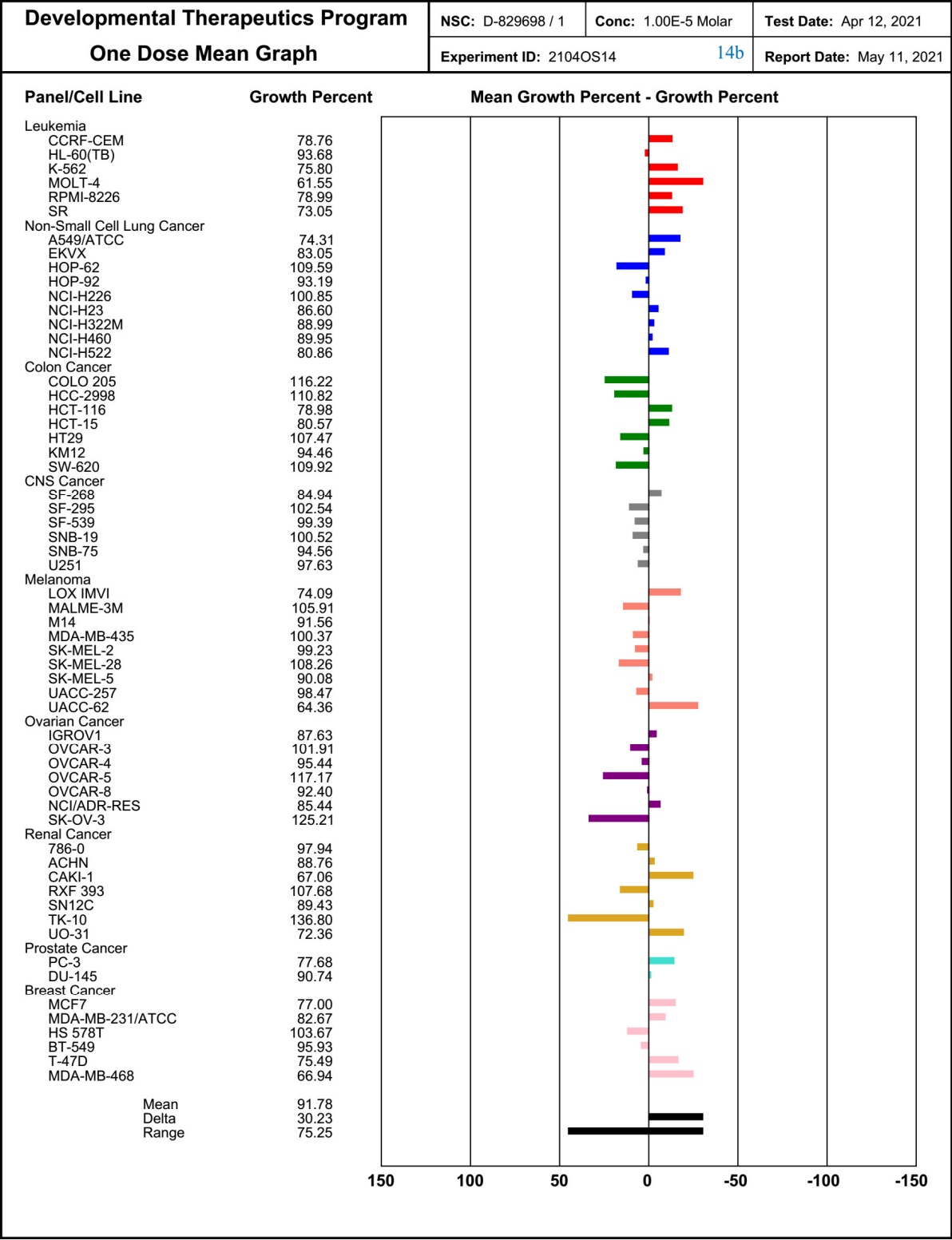


Figure S72. One dose mean graph of 14b.

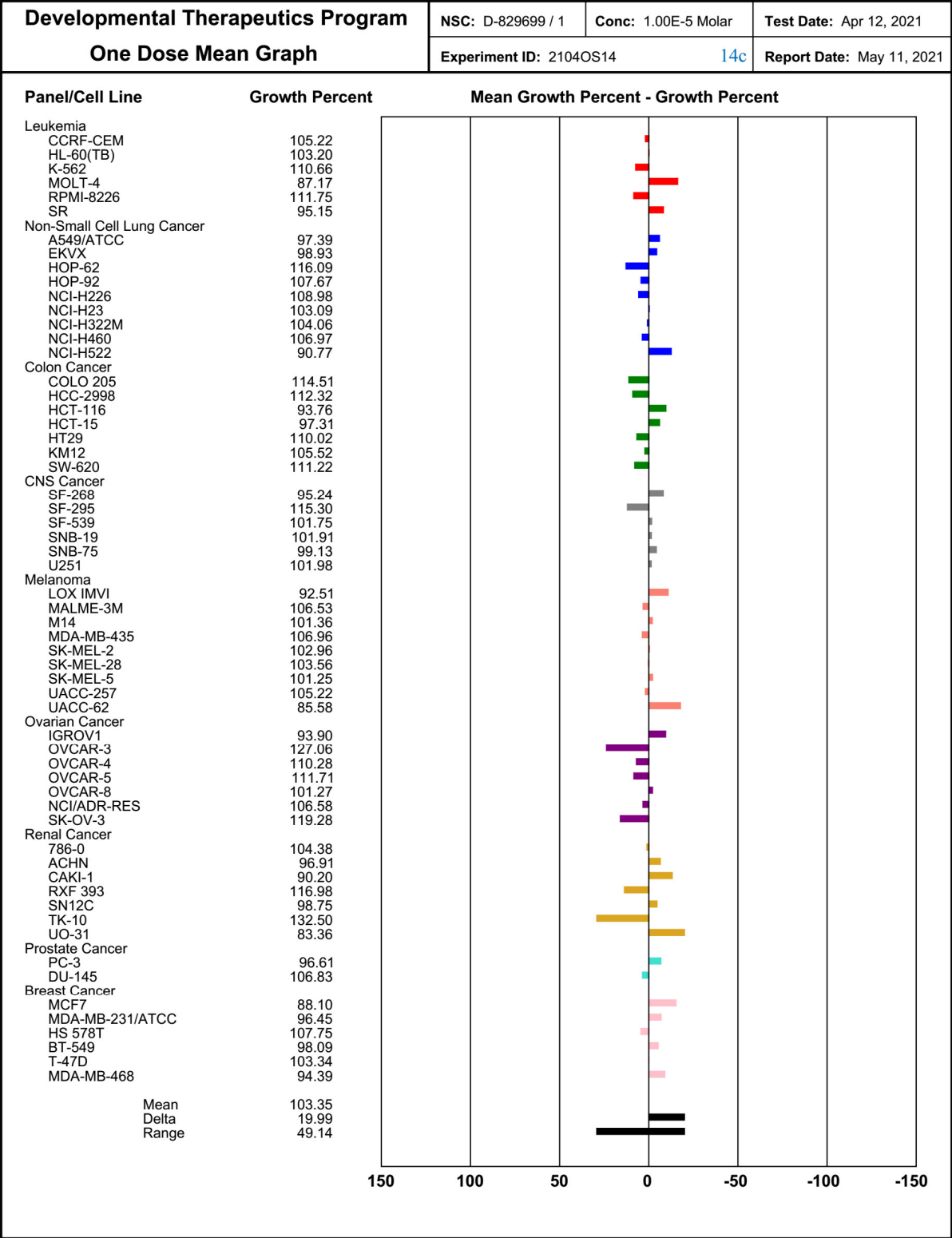


Figure S73. One dose mean graph of 14c.

3 Docking studies

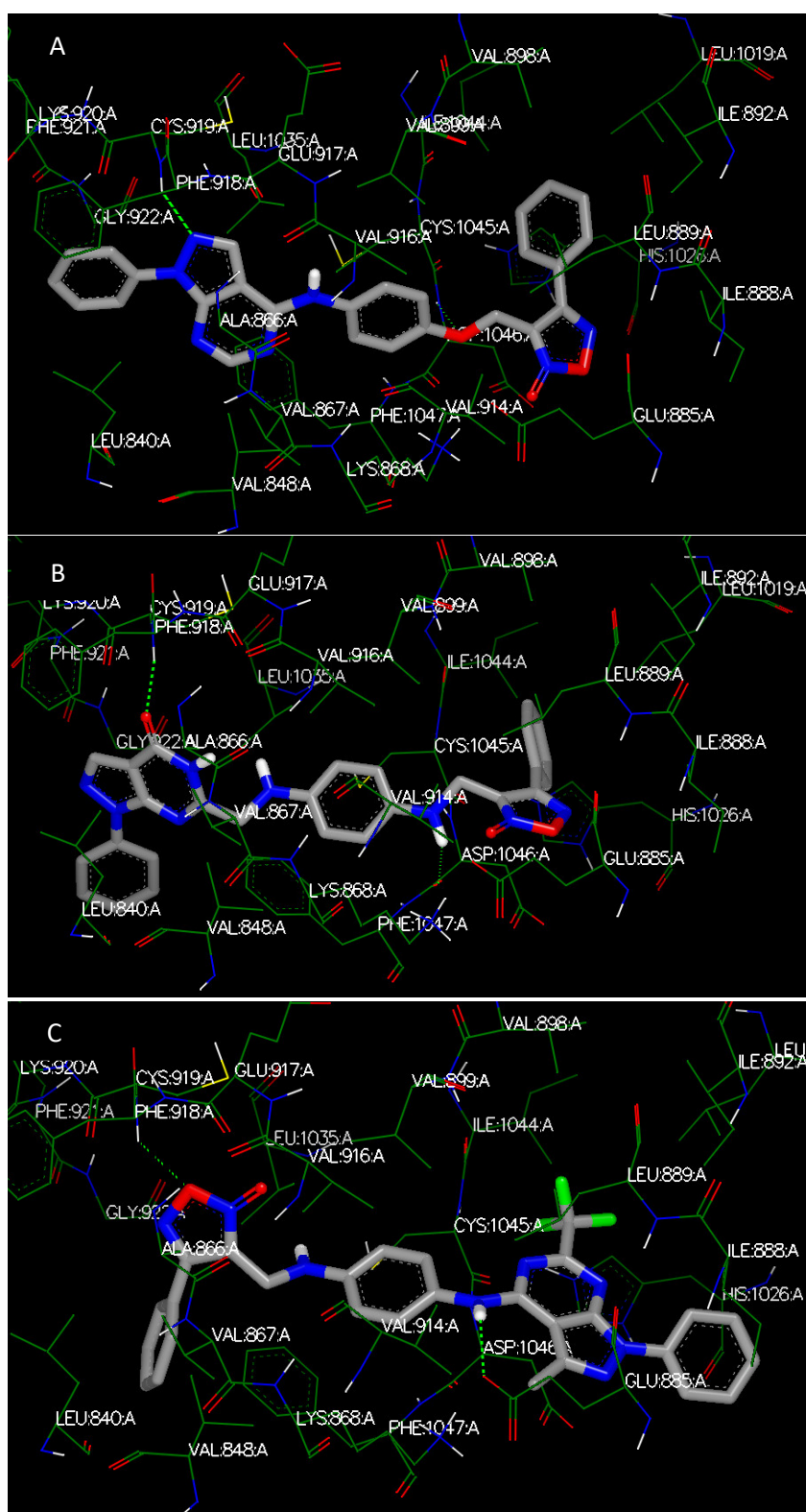
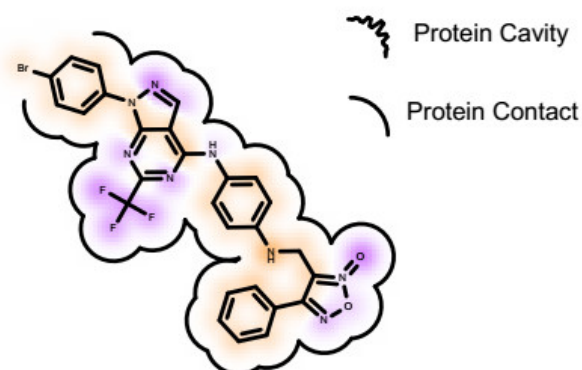


Figure S74. Docking poses of some target compounds inside VEGFR-2 active site: A) Compound 6a; B) Compound 14a; C) Compound 12a.

Residue Fingerprint

| | |
|----------------|----------------|
| ALA866A | ARG1027A |
| ASN923A | ASP1046A |
| CYS1024A | CYS1045A |
| CYS919A | GLU885A |
| GLU917A | GLY841A |
| GLY922A | HIS1026A |
| ILE1025A | ILE1044A |
| ILE888A | ILE892A |
| LEU1019A | LEU1035A |
| LEU840A | LEU889A |
| LYS868A | LYS920A |
| PHE1047A | PHE918A |
| PHE921A | VAL848A |
| VAL898A | VAL899A |
| VAL916A | |

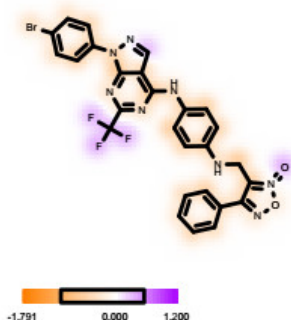
Total Score -11.37



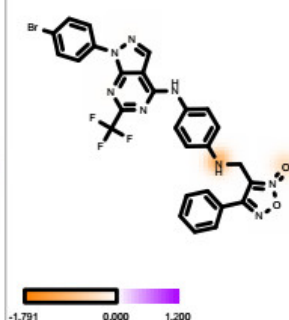
| | |
|-----------------|----------------|
| Acceptor | Donor |
| Metal | Contact |



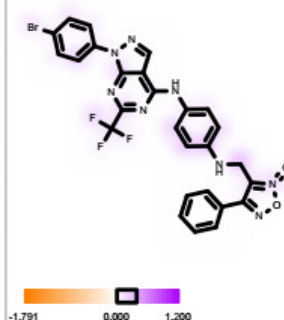
Shape -20.60



Hydrogen Bond -2.62



Protein Desolvation 4.42



Ligand Desolvation 7.42

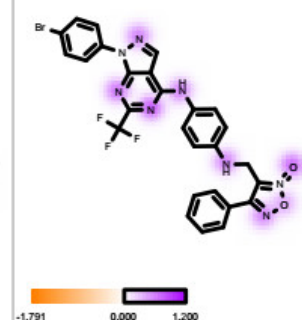


Figure S75. FRED docking report of **12b** in VEGFR-2, showing fitness in the binding pocket and residues in contact.

4 ADMET analysis

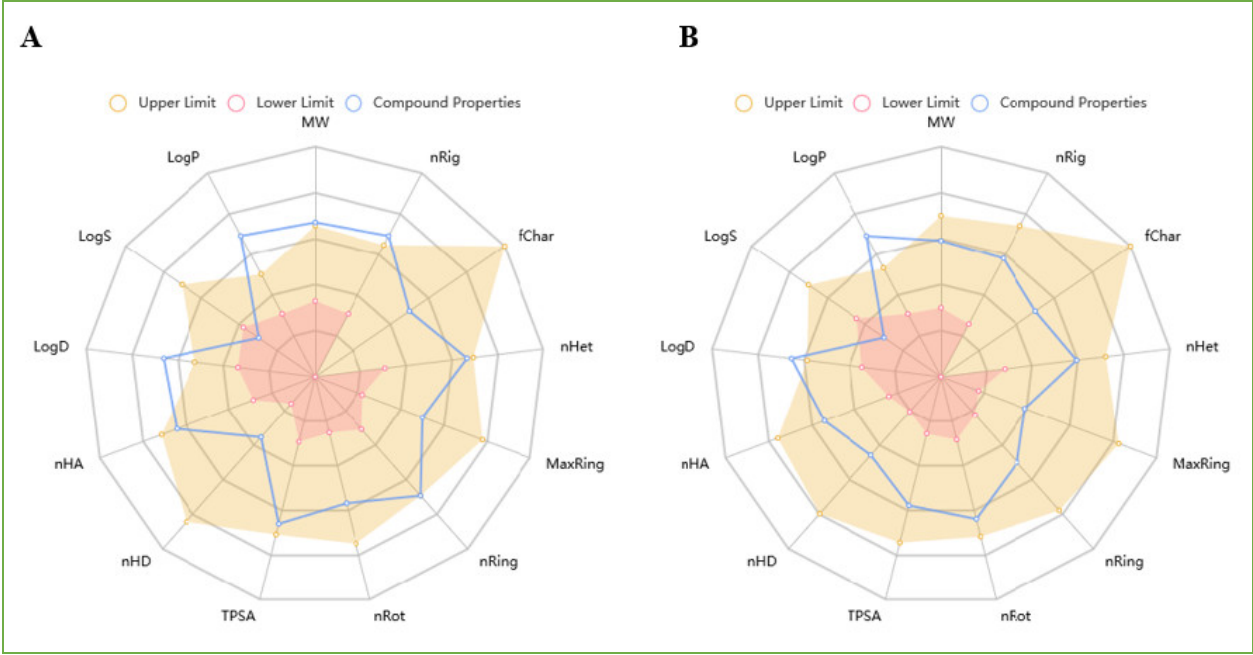


Figure S76. Radar graph of physicochemical properties of A) compound **12b** and B) **sorafenib**, obtained from ADMETlab 2.0.

Table S3. ADMET properties of compound **12b**, predicted using the web-based ADMETlab 2.0 tool.

| | Property | Value | Meaning and Preference |
|---------------------|---------------------------------------------|----------------------|----------------------------------------|
| Medicinal Chemistry | Pfizer Rule | Accepted | log P = 5.918 and TPSA = 123.86 |
| | SAscore (Synthetic accessibility score) | 3.406 | Easy to be synthesized. |
| | NPscore (Natural product-likeness score) | -1.455 | Within the range (-5 to 5). |
| | QED (Drug-likeness based on desirability) | 0.231 | Too complex (<0.34) |
| Absorption | Caco-2 Permeability | -4.977 | Optimal (> -5.15 Log unit) |
| | MDCK Permeability | 1.5×10 ⁻⁵ | Optimal (2–20 × 10 ⁻⁶ cm/s) |
| | Pgp inhibitor | 0.596 | Inhibitor |
| | Pgp substrate | 0.001 | Non-substrate |
| | HIA (Human Intestinal Absorption) | 0.009 | HIA < 30% |
| | F20% (20% Bioavailability) | 0.001 | bioavailability = 20% |
| Distribution | F30% (30% Bioavailability) | 0.0 | bioavailability = 30% |
| | PPB (Plasma Protein Binding) | 99.67% | Optimal: <90%. |
| | VD (Volume Distribution) | 1.945 | Optimal (0.04–20 L/kg) |
| | BBB (Blood–Brain Barrier) Penetration | 0.672 | Medium |

| | Property | Value | Meaning and Preference |
|------------|--------------------------------------------------------------------------------|----------|---------------------------------------------|
| Excretion | CL (Clearance) | 3.038 | low (<5 mL/min/kg) |
| | T _{1/2} (half-life) | 0.227 | short (<3h) |
| Toxicity | hERG Blockers | 0.801 | Active |
| | H-HT (Human Hepatotoxicity) | 0.955 | Positive |
| | DILI (Drug-Induced Liver Injury) | 0.99 | High risk |
| | AMES Toxicity | 0.637 | Medium |
| | Rat Oral Acute Toxicity | 0.951 | High |
| | FDAMDD (Maximum Recommended Daily Dose) | 0.914 | Positive |
| | Skin Sensitization | 0.084 | Non-sensitizer |
| | Carcinogenicity | 0.685 | Medium |
| | Eye Corrosion | 0.003 | Non-corrosive |
| | Eye Irritation | 0.008 | non-irritant |
| | Acute Toxicity Rule (during oral administration) | 0 Alerts | No Alerts |
| | Bioconcentration Factors | 1.383 | Unit: -log ₁₀ [(mg/L)/(1000*MW)] |
| Metabolism | IGC ₅₀ (Tetrahymena pyriformis 50% growth inhibition concentration) | 5.086 | Unit: -log[(mg/L)/(1000*MW)] |
| | CYP1A2 inhibitor | Positive | |
| | CYP1A2 substrate | Negative | |
| | CYP2C19 inhibitor | Positive | |
| | CYP2C19 substrate | Negative | |
| | CYP2C9 inhibitor | Positive | |
| | CYP2C9 substrate | Negative | |
| | CYP2D6 inhibitor | Negative | |
| | CYP2D6 substrate | Negative | |
| | CYP3A4 inhibitor | Negative | |
| | CYP3A4 substrate | Negative | |