Electronic Supplementary Material (ESI) for New Journal of Chemistry.

A revised synthesis of 6-alkoxy-2-aminopurines with late-stage convergence allowing for increased molecular complexity

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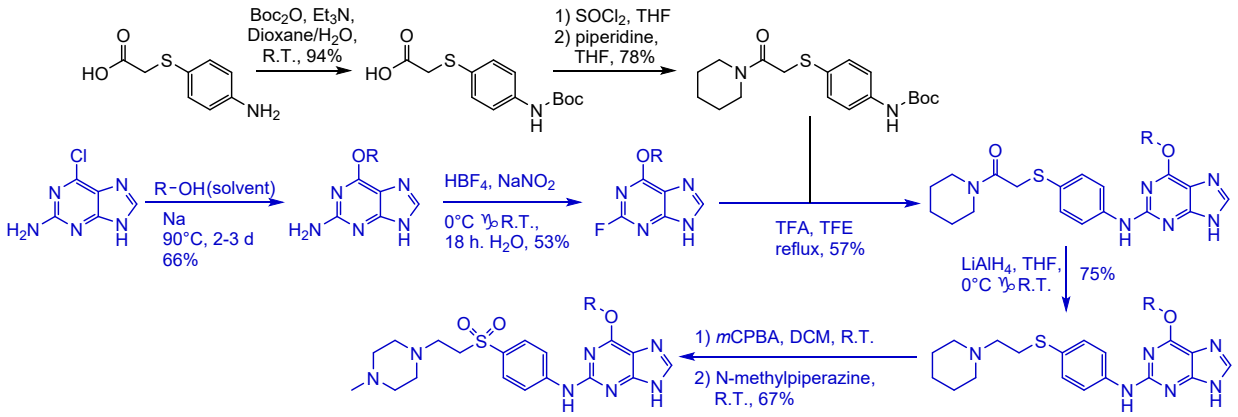
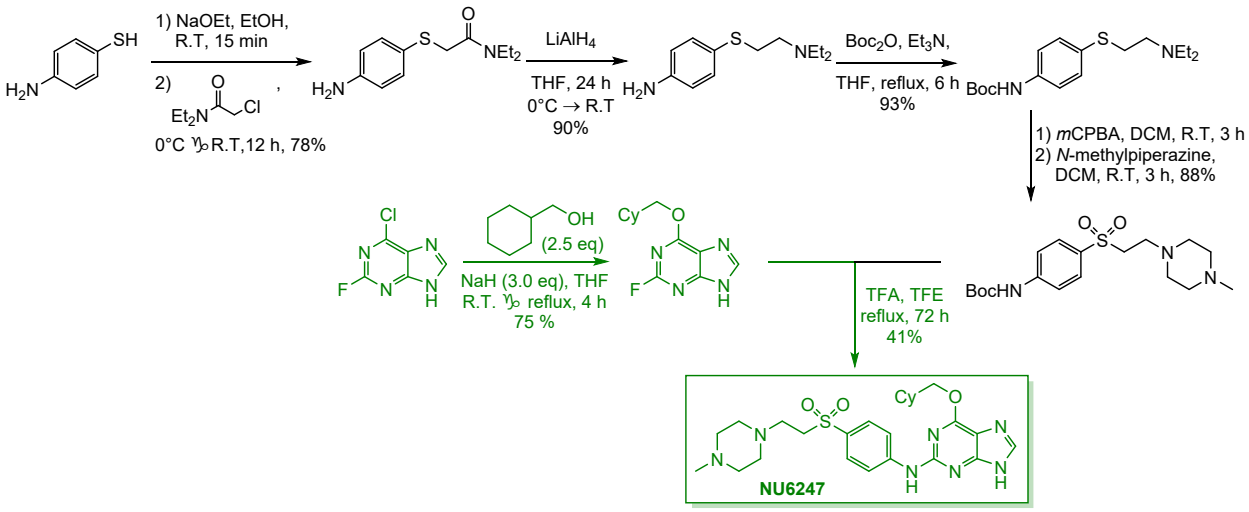
Supporting Information

Comparison of existing and refocused syntheses

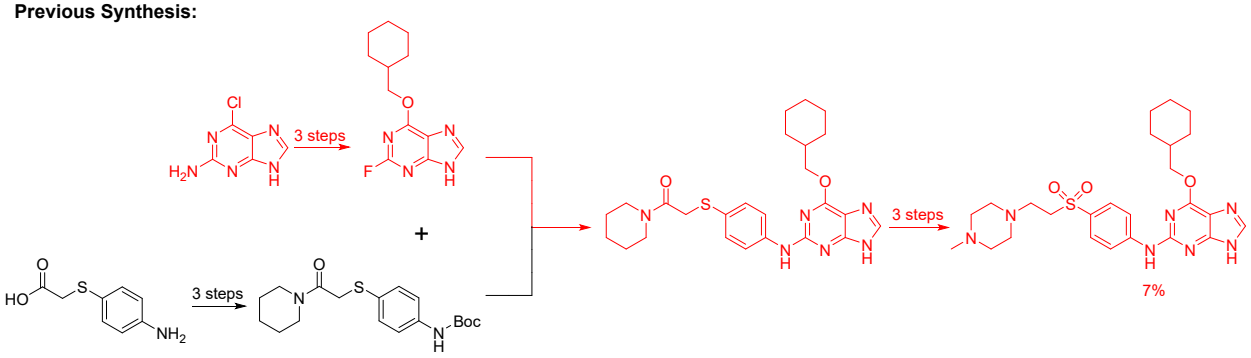


Scheme S1 Previous synthesis of NU6247.[1] The synthetic steps featuring the O-6 moiety are highlighted in blue. R = Cyclohexylmethyl.

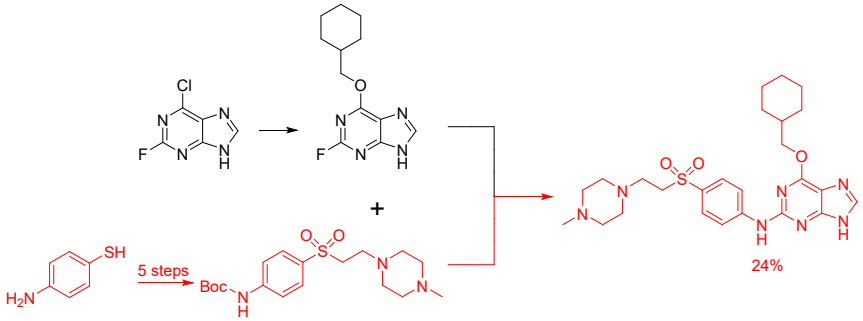


Scheme S2 Refocused synthesis of NU6247 (this work). The synthetic steps featuring the O-6 moiety are highlighted in green.

Previous Synthesis:



This work:



Scheme S2 Comparison of previous and newly developed synthesis of NU6247 with the yield limiting linear sequences shown in red, which were used to calculate the overall yield.

Synthesis of 3-aminobenzyl alcohol

3-nitrobenzyl alcohol (16)

To a solution of 3-nitrobenzaldehyde (1 g, 6.63 mmol, 1.0 eq) in absolute EtOH (15 mL) was added a suspension of $NaBH_4$ (0.165 g, 4.87 mmol, 0.66 eq) in absolute EtOH (7 mL) dropwise. The reaction was stirred at room temperature for 1 h and then quenched with 10% NaOH solution (3 mL). Water (5 mL) was added and EtOH was removed under reduced pressure. The product was extracted using EtOAc (5 × 10 mL). The combined organic layers were washed with 5% $NaHCO_3$ (15 mL) followed by water (10 mL) and then dried over $MgSO_4$. EtOAc was removed *in vacuo* to yield a yellow oil (0.93 g, 92%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ_{ppm} 8.17 (apparent s, 1H), 8.08-8.05 (apparent dd, *J* = 8.1 Hz, 1.8 Hz, 1H), 7.66-7.63 (apparent dd, *J* = 8.1 Hz, 1.8 Hz, 1H), 7.51-7.45 (apparent t, J = 8.1 Hz, 1H), 4.76 (s, 2H), 2.88 (br s, 1H). This reaction was performed twice for this project, providing the same yield both times Characterization data is consistent with previously reported values.[2]

3-aminobenzyl alcohol (17)

To a solution of 3-nitrobenzyl alcohol **(**1.5 g, 9.79 mmol, 1.0 eq) in MeOH (50 mL) under a N_2 atmosphere was added 10% Pd/C (0.15 g, 10 wt %). The reaction mixture was exposed to hydrogen gas using a hydrogen balloon, while displacing nitrogen gas through a bubbler. The bubbler was removed, and the reaction was stirred at room temperature for 24 h, replacing the balloon as needed. The mixture was filtered through celite,

concentrated *in vacuo*, and purified by flash column chromatography (5% MeOH/EtOAc, R_f = 0.51) to yield a yellow crystalline solid (0.77 g, 64%). **^{1}H NMR** (300 MHz, DMSO-d_6) δ_{ppm} 6.96-6.91 (apparent t, *J* = 7.5 Hz, 1H), 6.55-6.54 (apparent dd, *J* = 2.5 Hz, 1.6 Hz, 1H), 6.45-6.40 (apparent ddd, *J* = 7.5 Hz, 2.5 Hz, 1.6 Hz, 2H), 4.99-4.95 (t, *J* = 5.7 Hz, 1H), 4.96 (br s, 1H), 4.35-4.33 (d, *J* = 5.7 Hz, 1H). This reaction was performed once for this project. Characterization data is consistent with previously reported values.[3]

NMR Spectra

Figure S1. ^{1}H NMR (300 MHz, DMSO-d_6) of Compound 4a

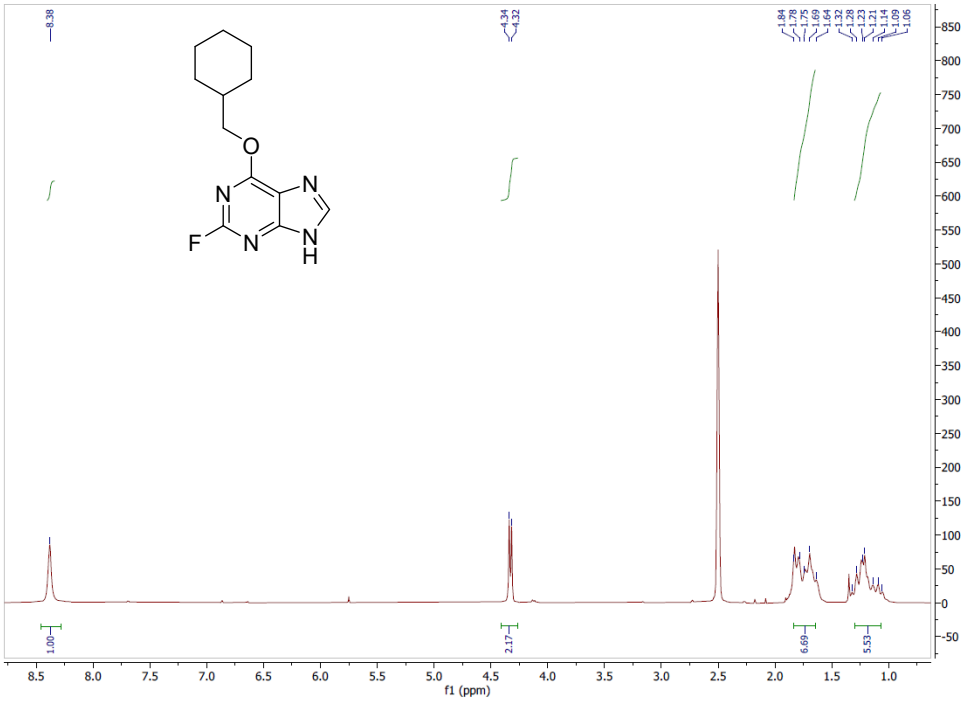


Figure S2. ^{13}C NMR (125 MHz, DMSO-d_6) of Compound 4a

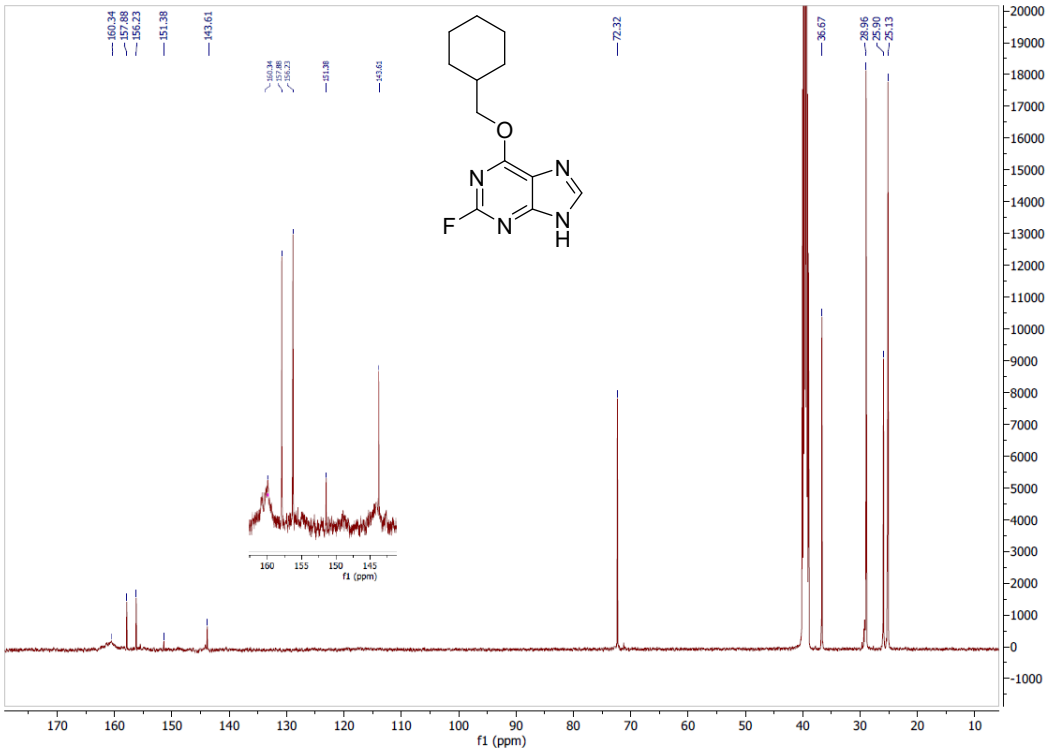


Figure S3. ^{19}F NMR (470 MHz, DMSO-d_6) of Compound 4a

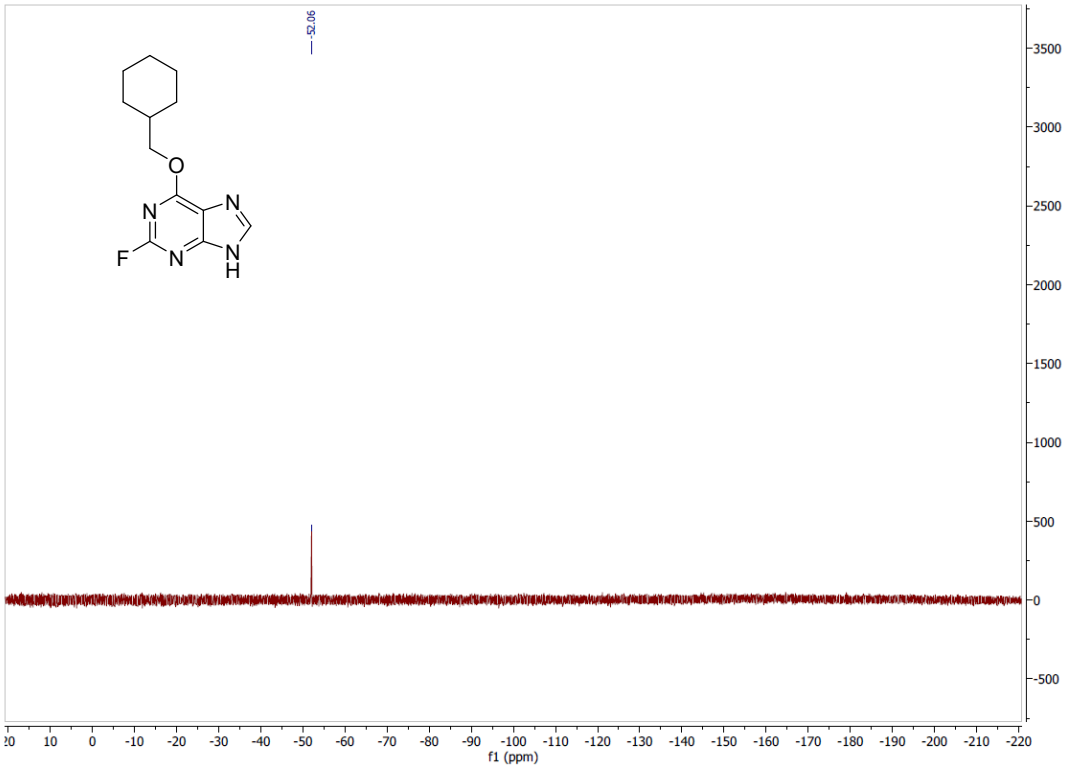


Figure S4. ^{1}H NMR (300 MHz, DMSO-d_6) of Compound 4b.

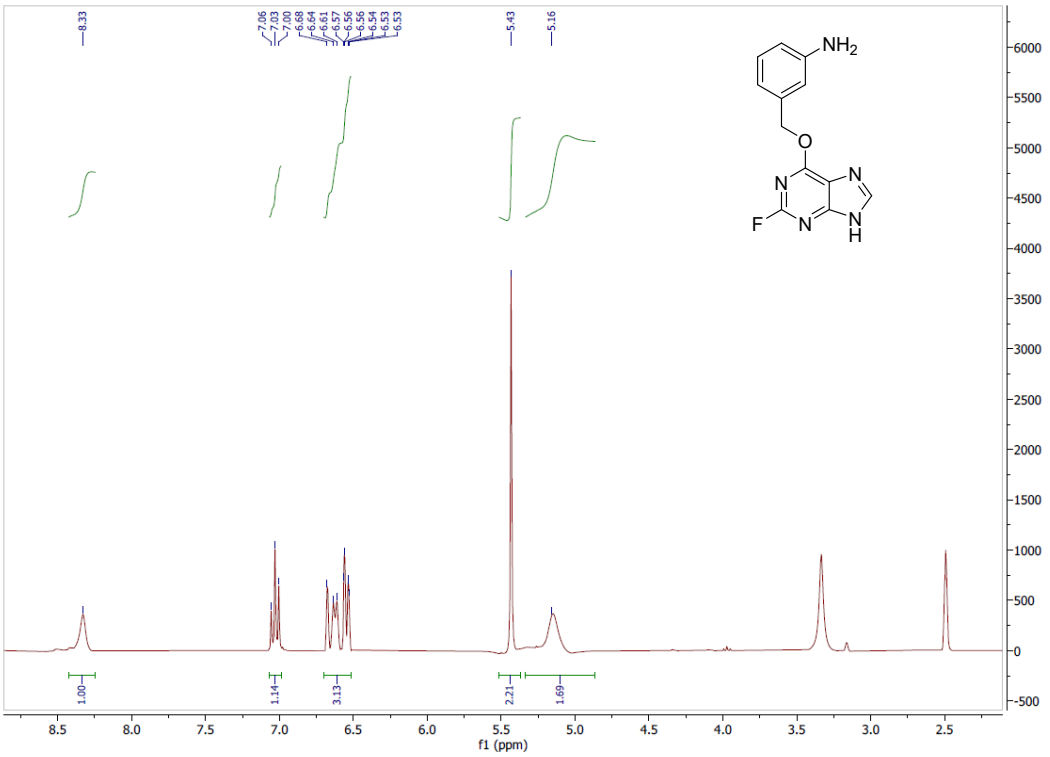


Figure S5. ^{13}C NMR (125 MHz, DMSO-d_6) of Compound 4b.

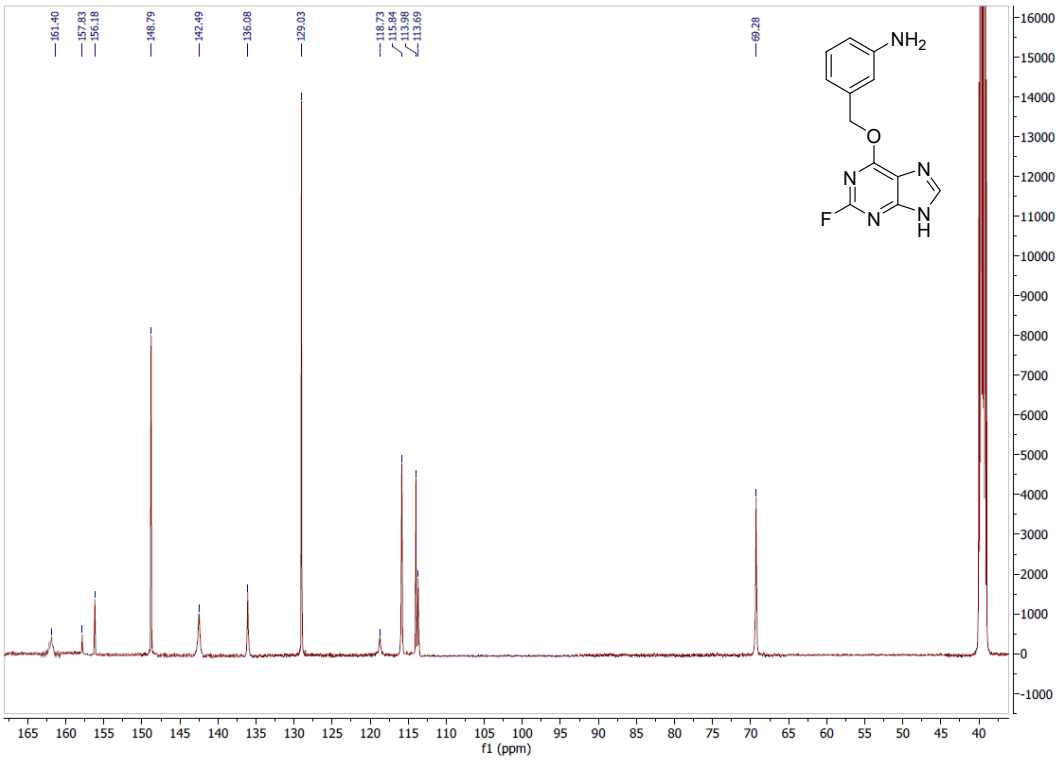


Figure S6. ^{19}F NMR (470 MHz, DMSO-d_6) of Compound 4b.

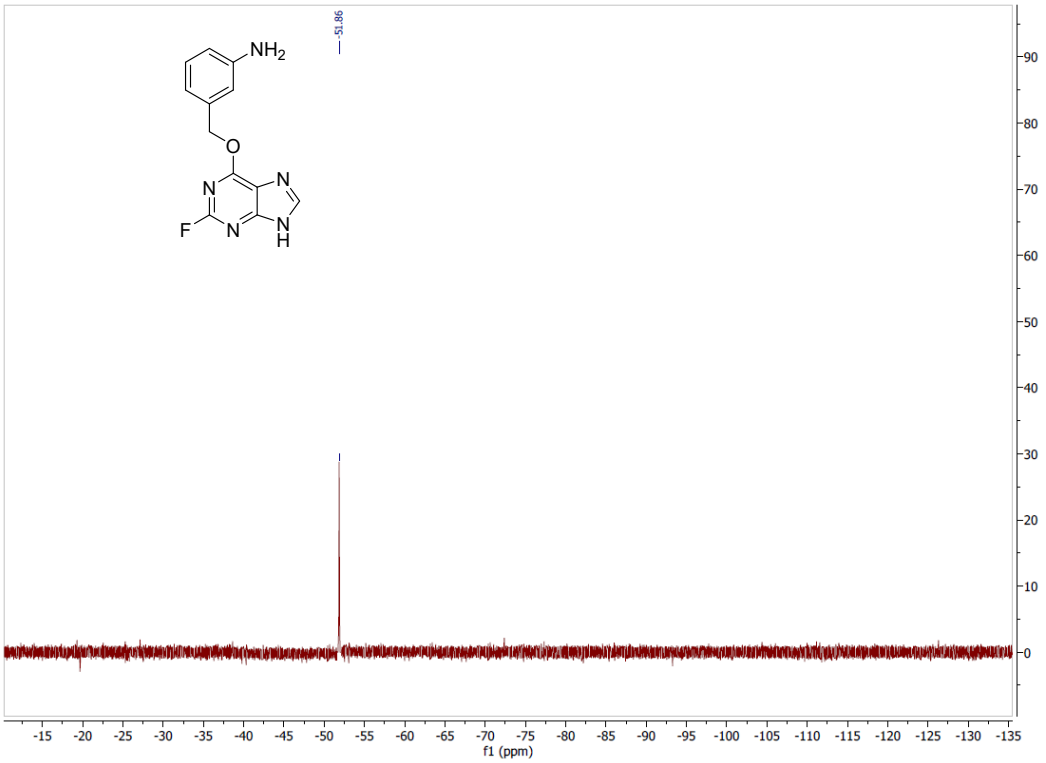


Figure S7. ^{1}H NMR (300 MHz, CD_3OD) of Compound 6.

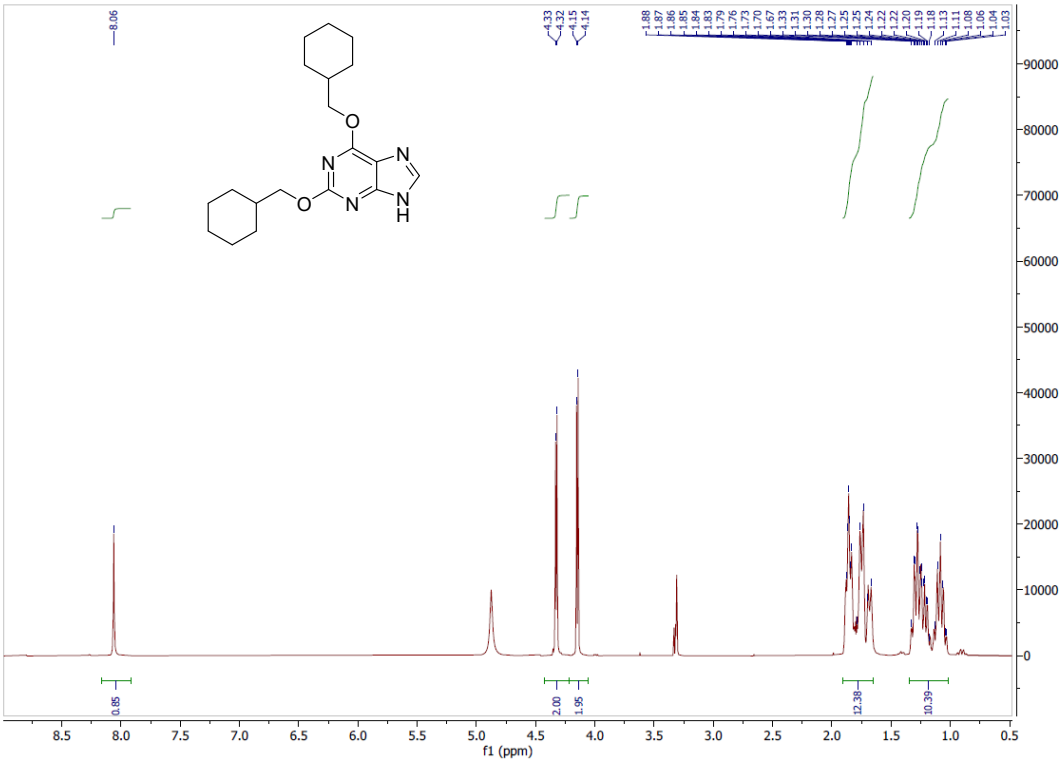


Figure S8. ^{13}C NMR (75 MHz, CD_3OD) of Compound 6.

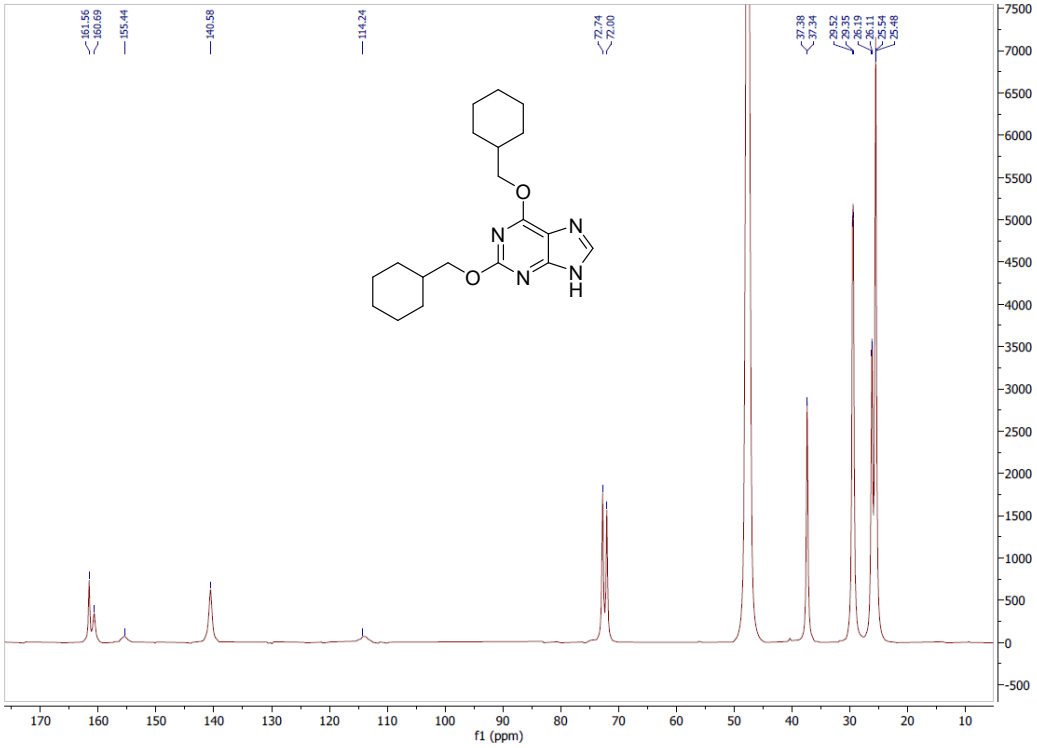


Figure S9. ^{1}H NMR (300 MHz, $CDCl_3$) of Compound 7

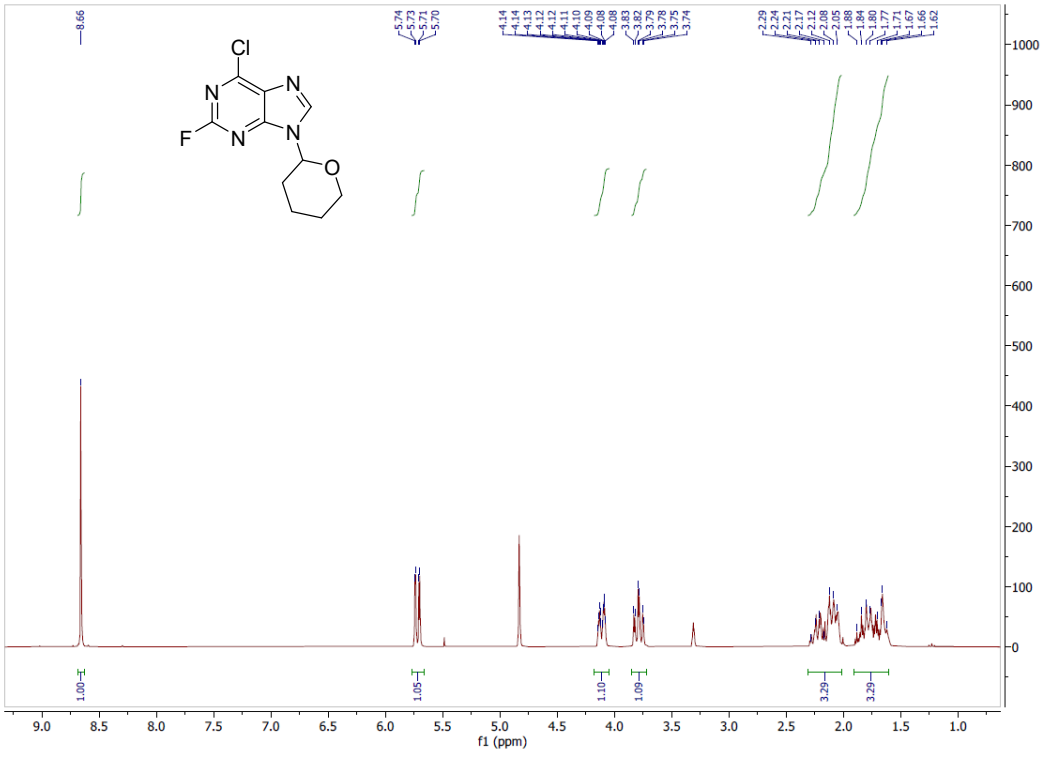


Figure S10. ^{1}H NMR (300 MHz, D_2O) of Compound 8.

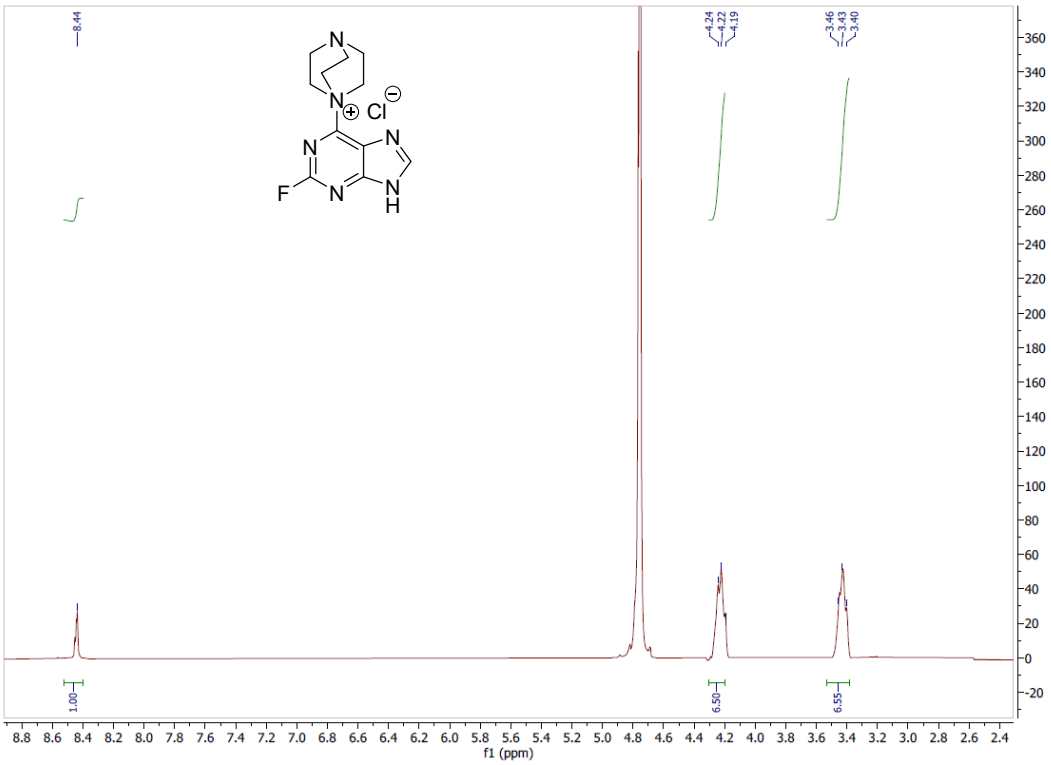


Figure S11. ^{13}C NMR (125 MHz, DMSO-d_6) of Compound 8.

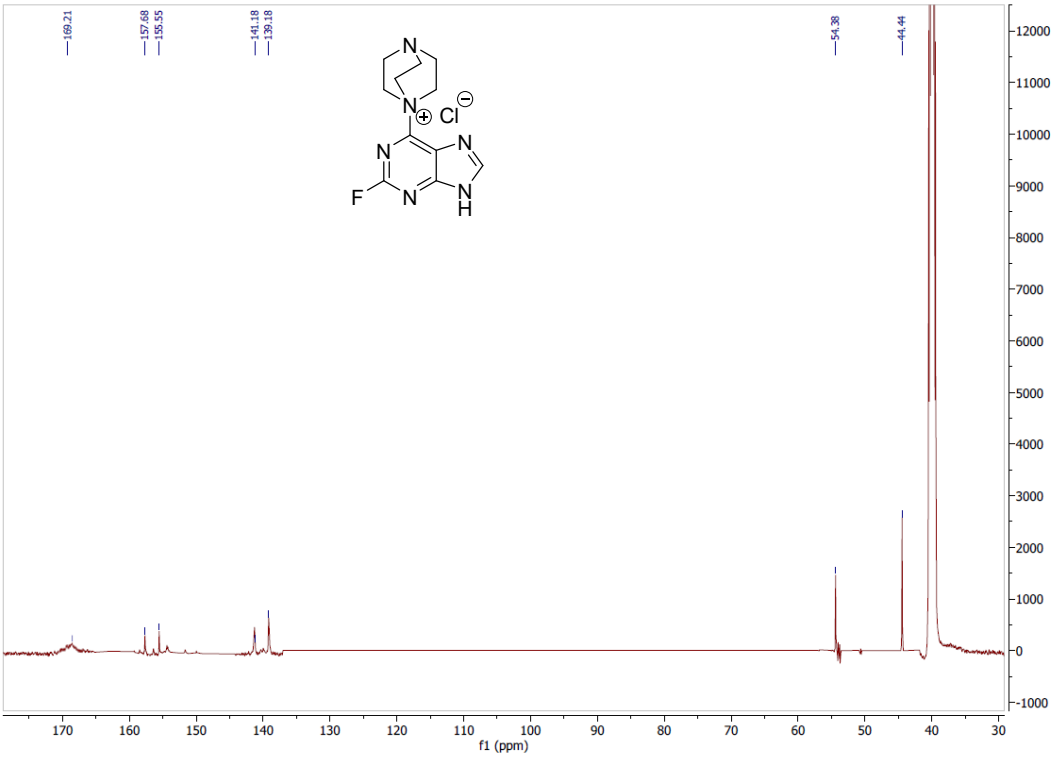


Figure S12. ^{19}F NMR (470 MHz, DMSO-d_6) of Compound 8.

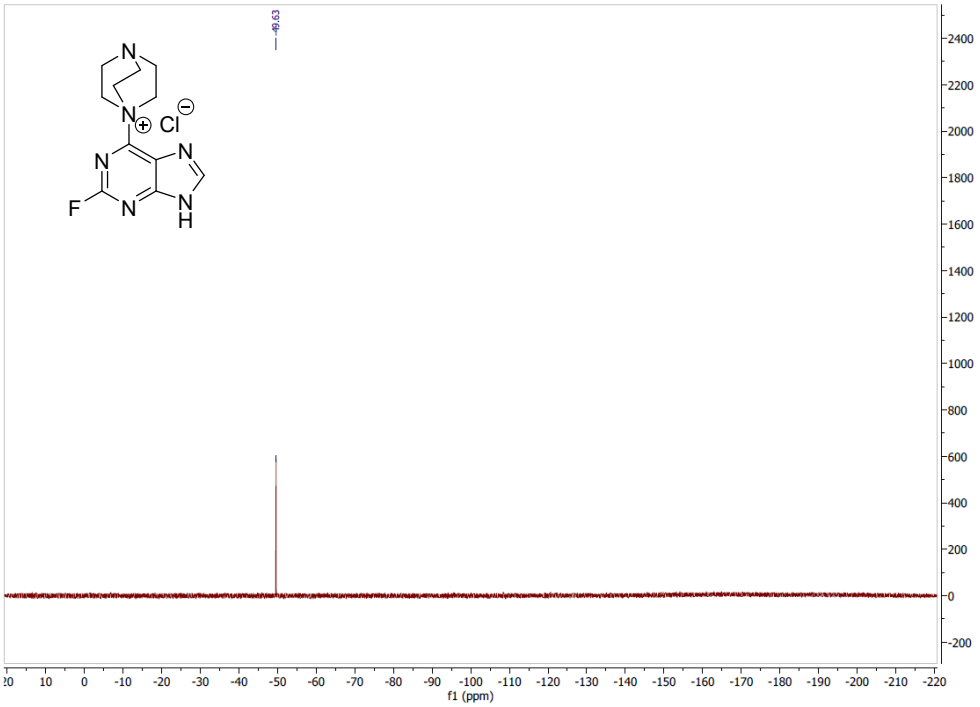


Figure S13. ^{1}H NMR (300 MHz, DMSO-d_6) of Compound 9 (NU6102)

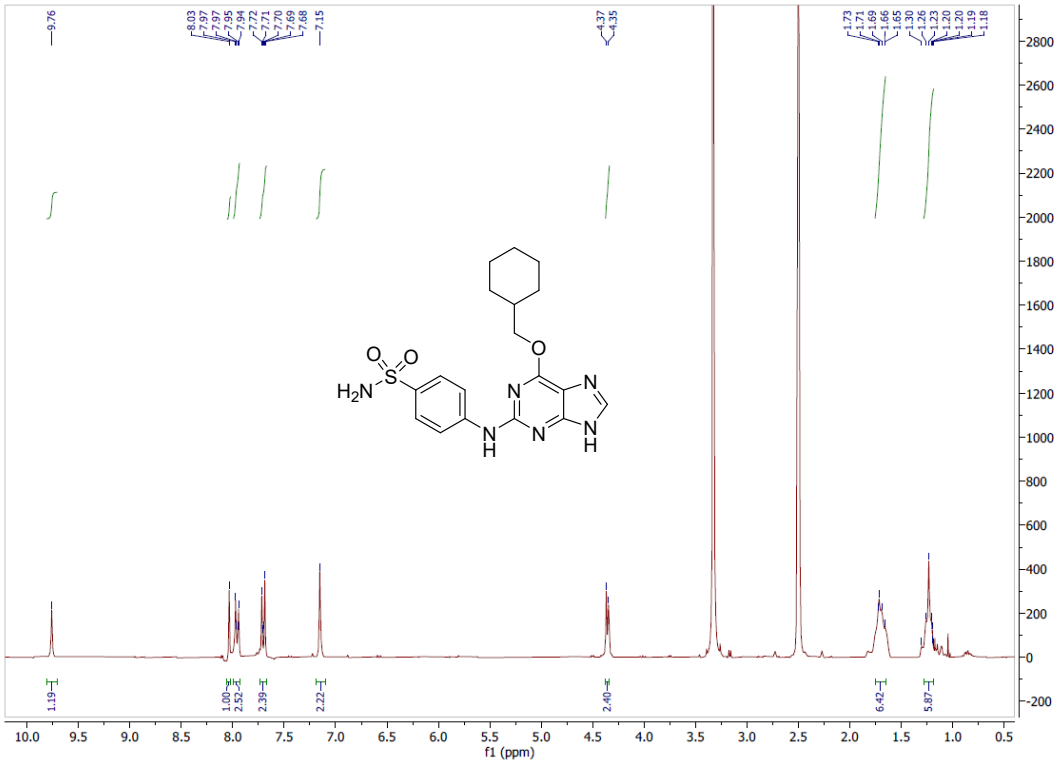


Figure S14. ^{1}H NMR (300 MHz, DMSO-d_6) of Compound 11.

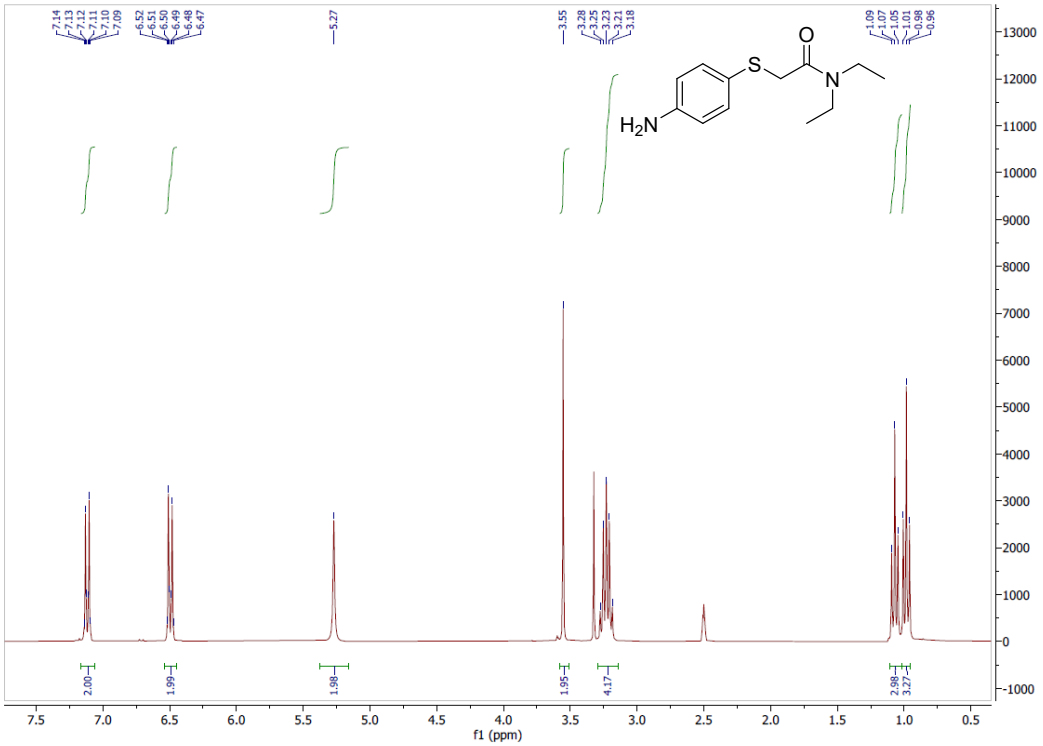


Figure S15. ^{13}C NMR (75 MHz, DMSO-d_6) of Compound 11.

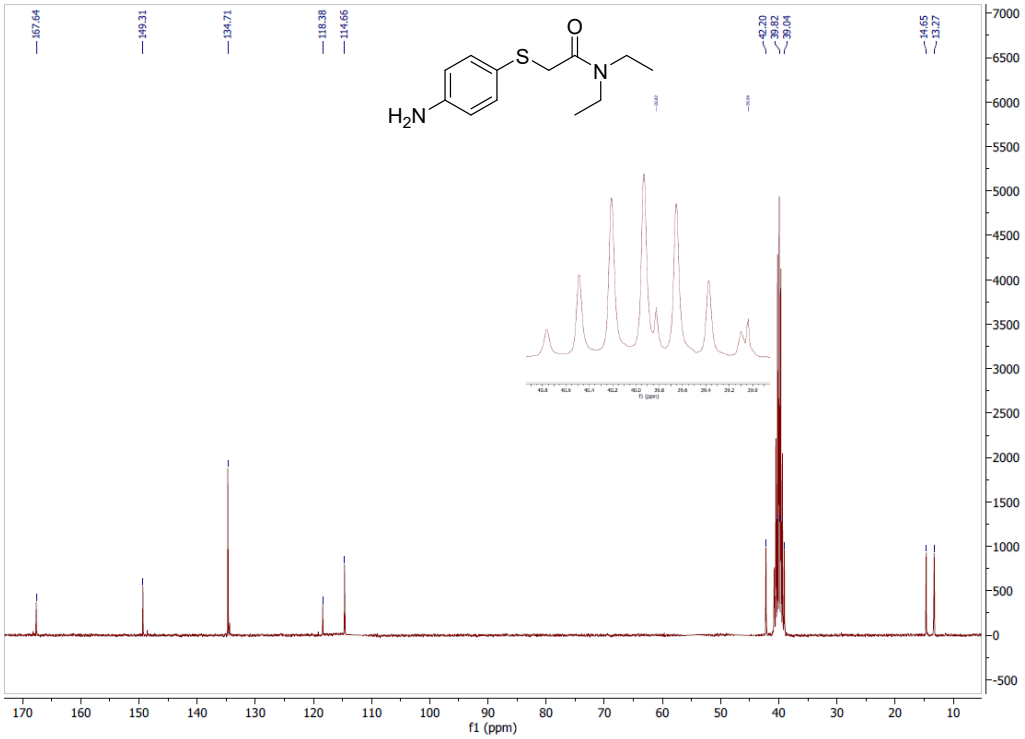


Figure S16. ^{1}H NMR (300 MHz, CD_3OD) of Compound 12

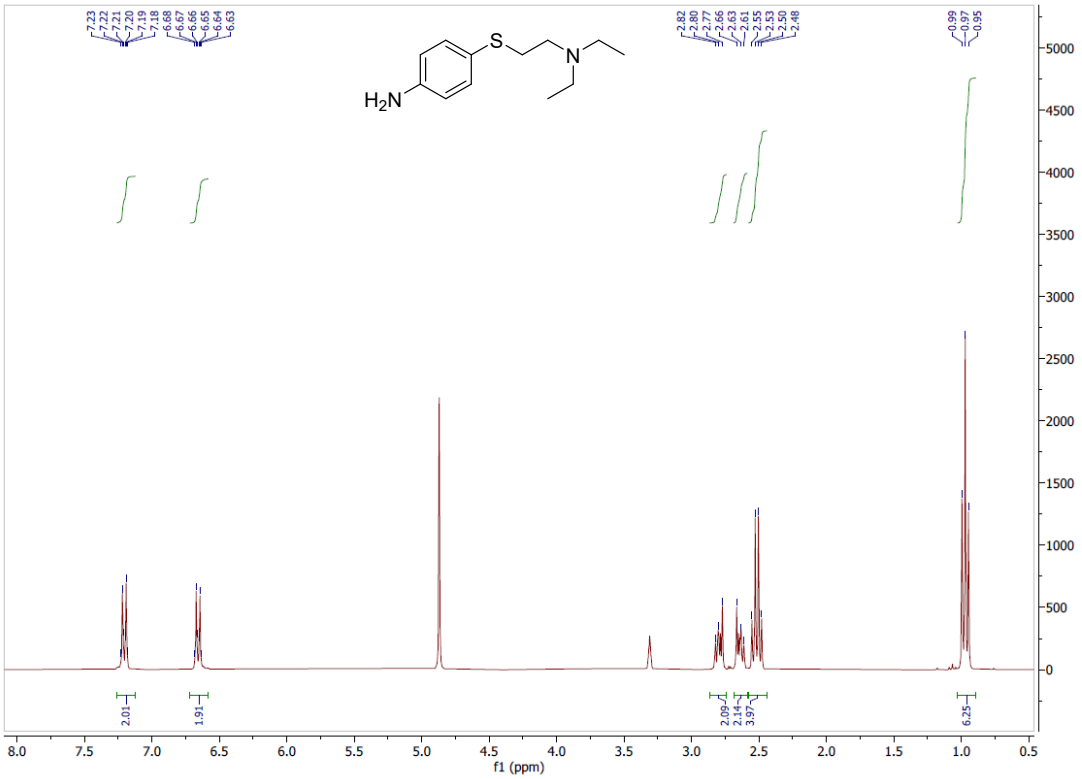


Figure S17. ^{1}H NMR (300 MHz, CD_3OD) of Compound 13

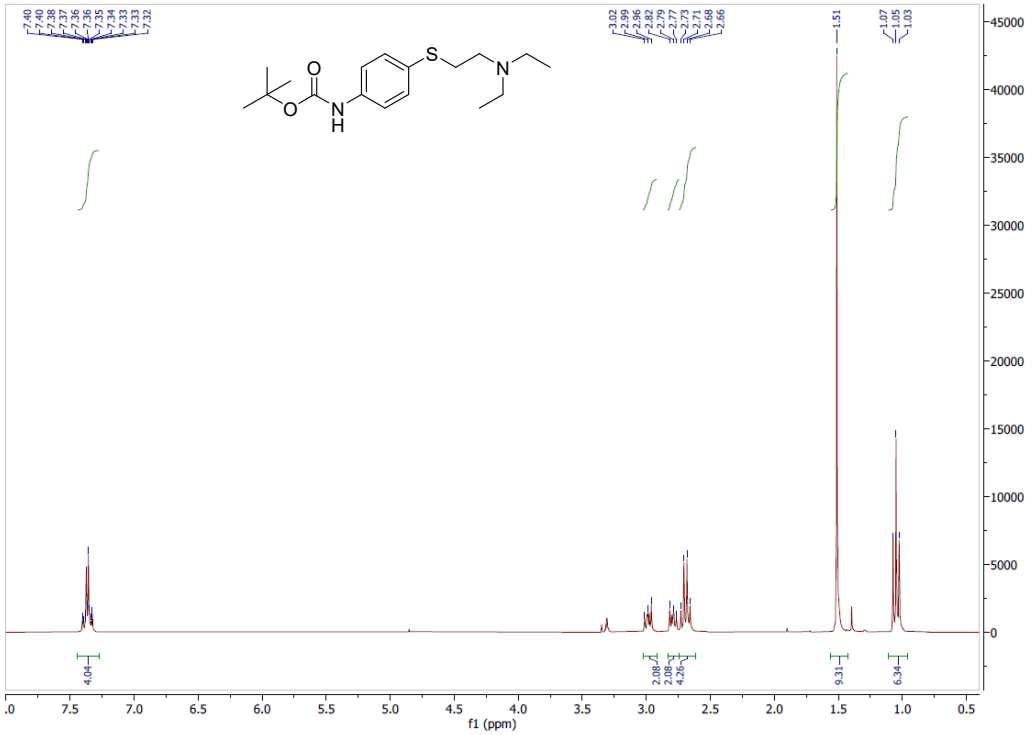


Figure S18.^{13}C NMR (75 MHz, CD_3OD) of Compound 13

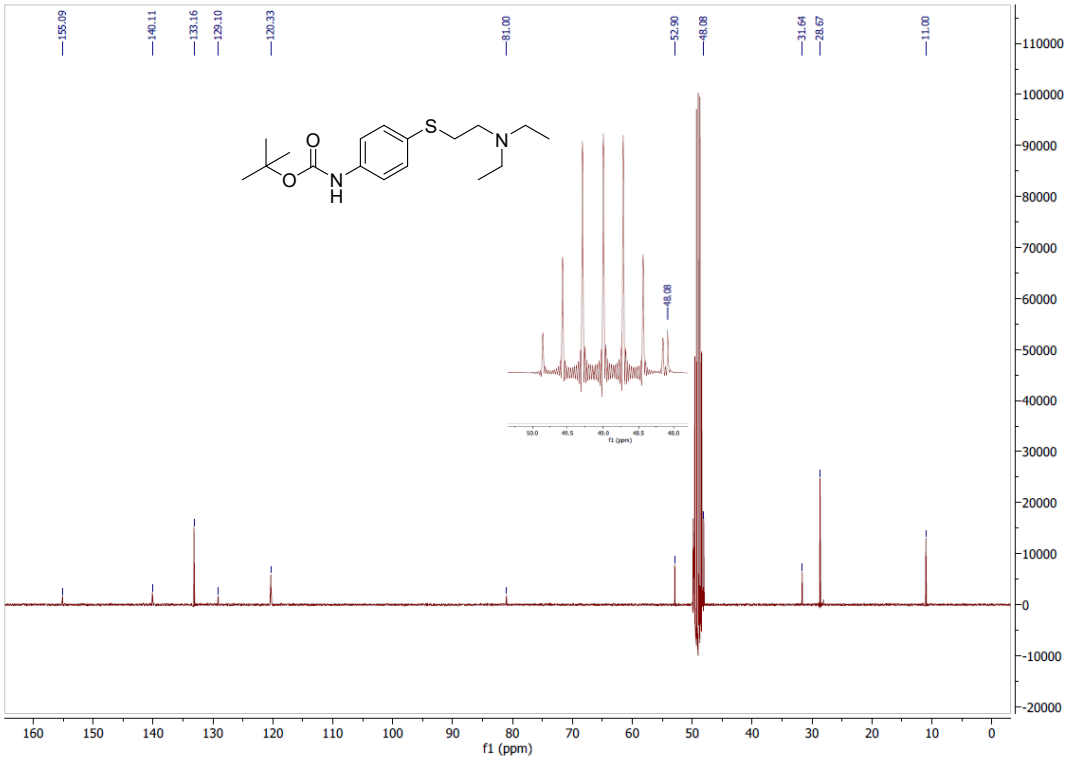


Figure S19. ^{1}H NMR (300 MHz, $CDCl_3$) of Compound 14

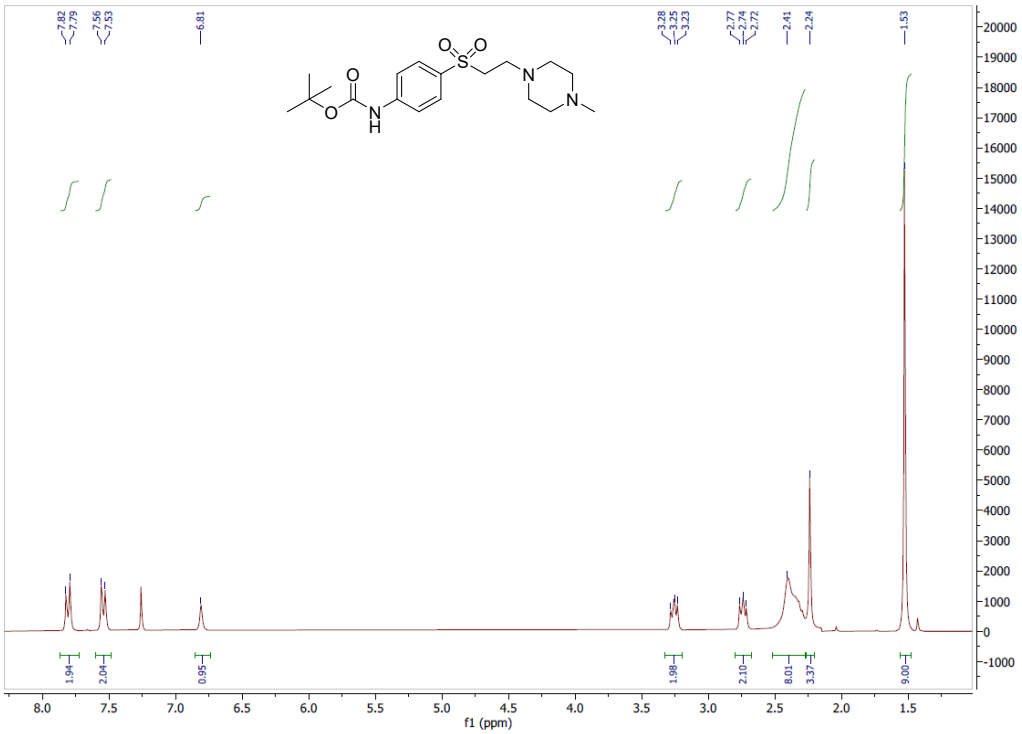


Figure S20. ^{13}C NMR (75 MHz, $CDCl_3$) of Compound 14

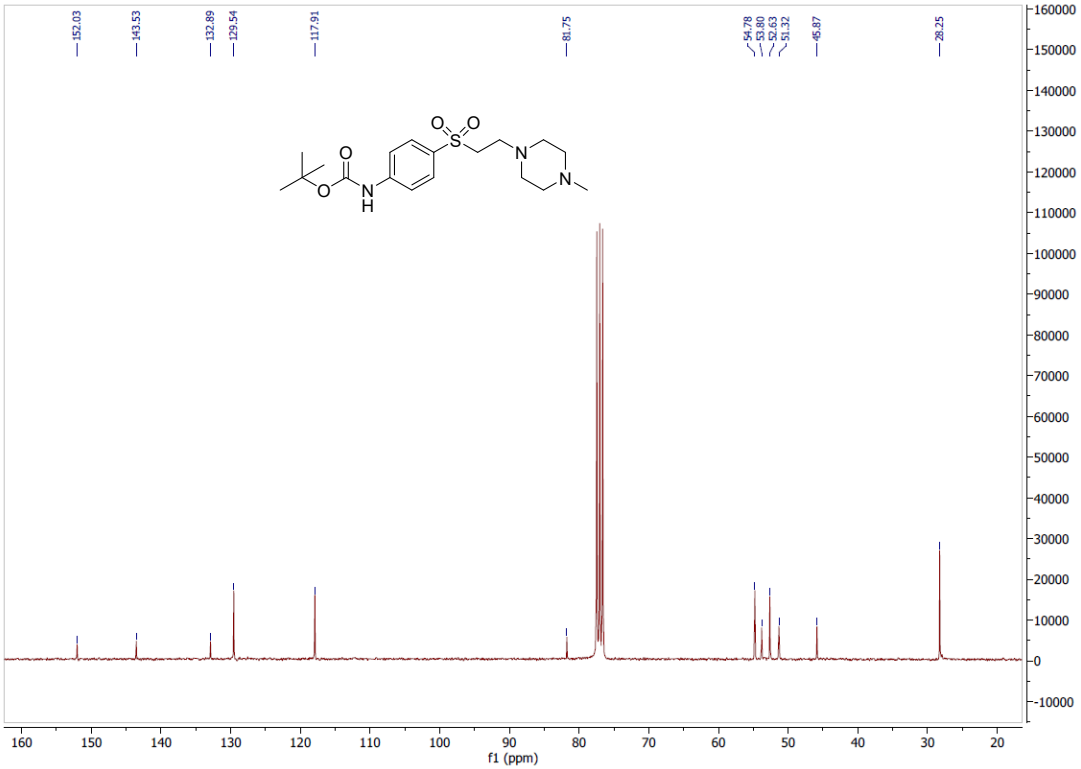


Figure S21. ^{1}H NMR (300 MHz, $CDCl_3$) of Compound 15 (NU6247)

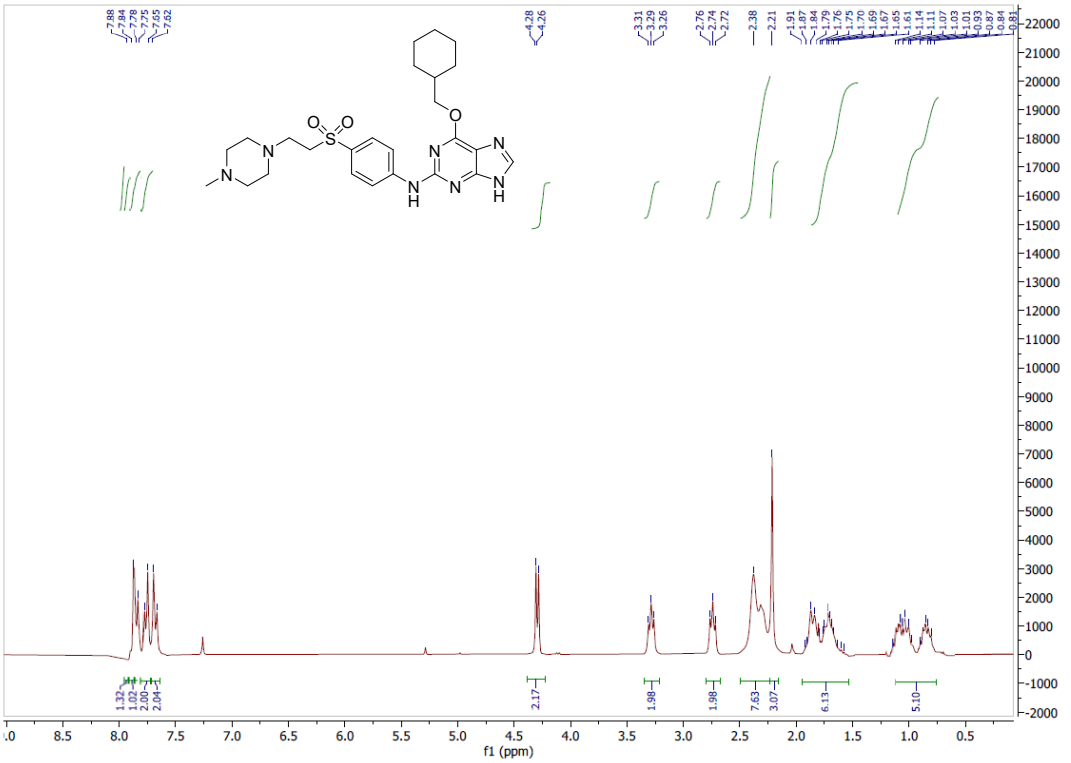


Figure S22. ^{13}C NMR (125 MHz, $CDCl_3$) of Compound 15 (NU6247)

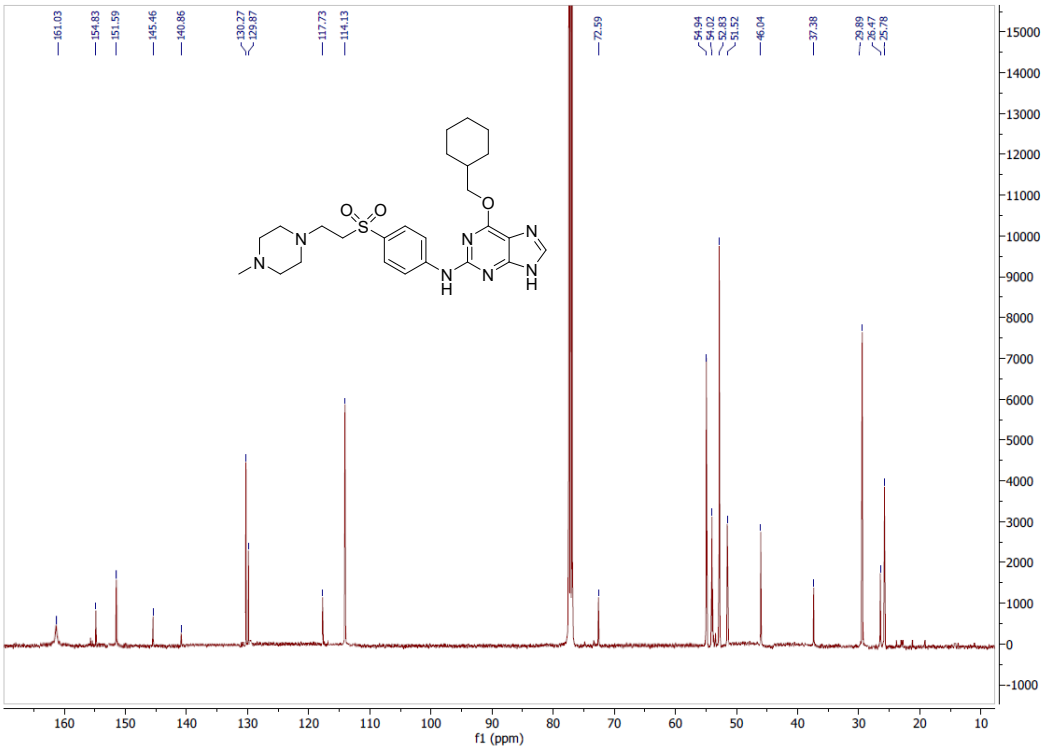


Figure S23. ^{1}H NMR (300 MHz, $CDCl_3$) of Compound 16

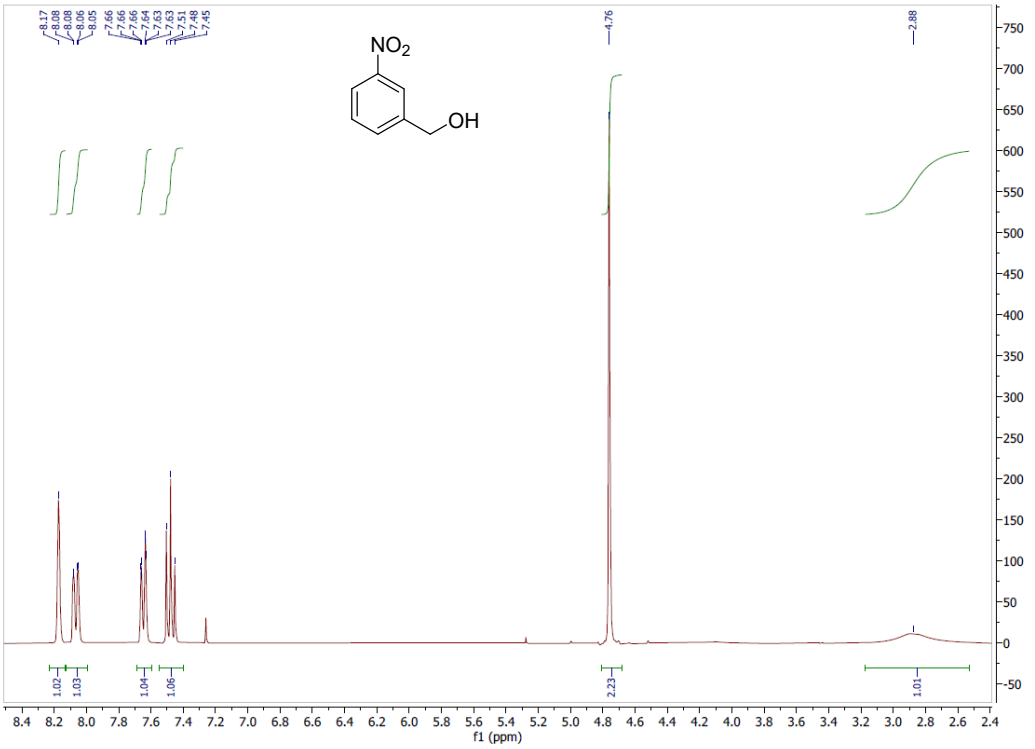
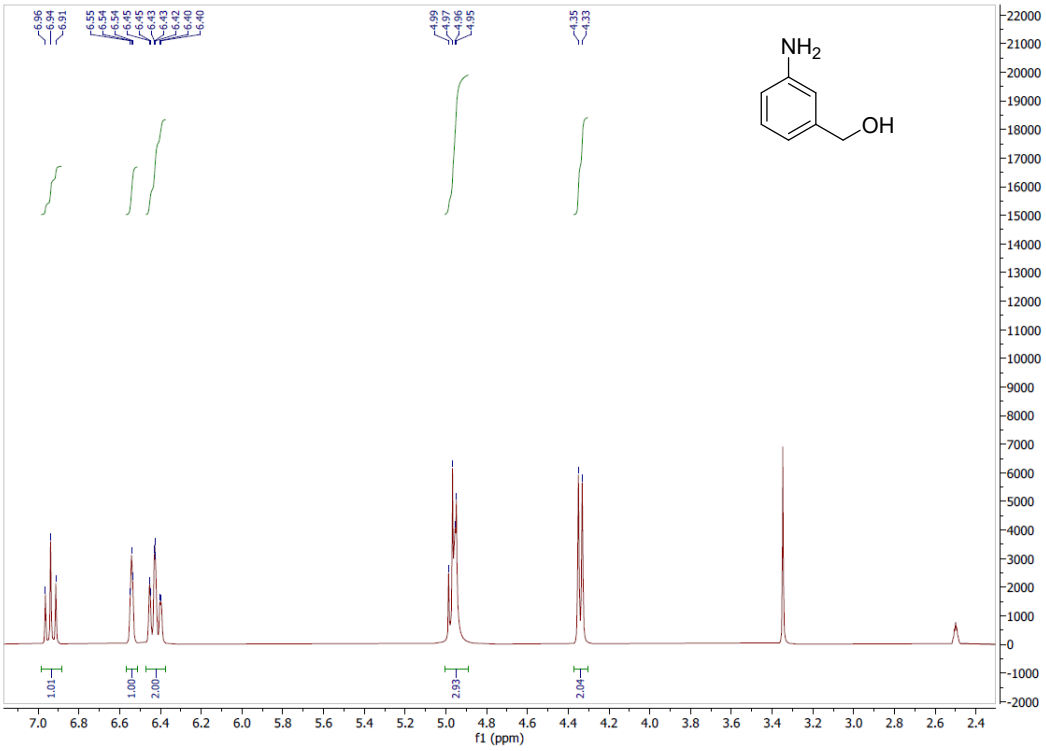


Figure S24. ^{1}H NMR (300 MHz, DMSO-d_6) of Compound 17.



NMR (500 MHz, CD_3OD) of Compound 18.

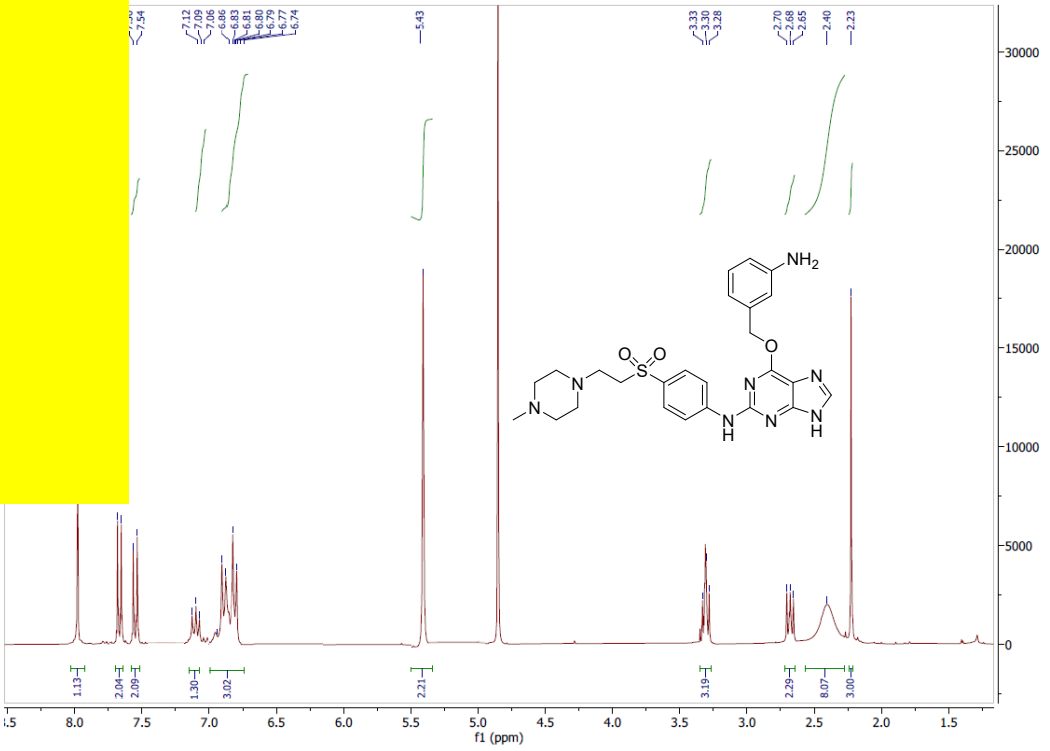
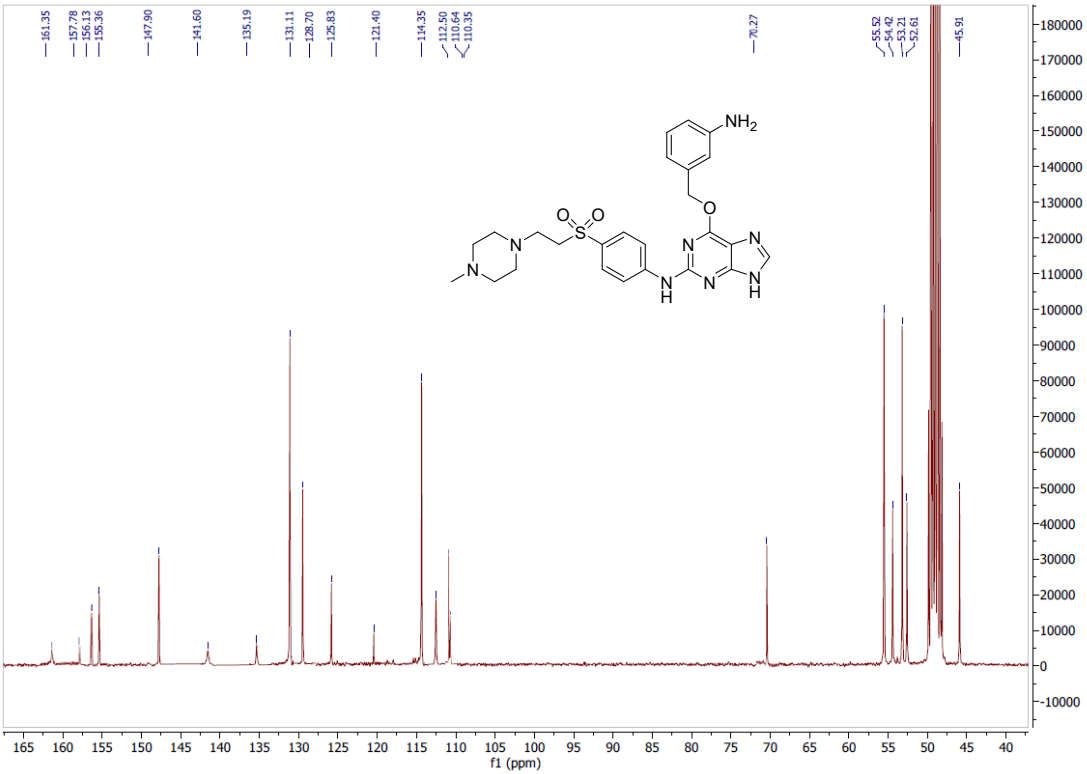


Figure S26. ^{13}C NMR (125 MHz, CD_3OD) of Compound 18.



References

1. R. J. Griffin, A. Henderson, N. J. Curtin, A. Echalier, J. A. Endicott, I. R. Hardcastle, D. R. Newell, M. E. M. Noble, L.-Z. Wang and B. T. Golding, *J. Am. Chem. Soc*, 2006, **128**, 6012-6013.
2. P. J. Monsen and F. A. Luzzio, *Tet. Lett.*, 2020, **61**, 152575.
3. M.-U. Hung, S.-T. Yang, M. Ramanathan and S.-T. Liu, *Appl. Organometal. Chem.*, 2018, **32**, e3976.