Synthesis

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Supporting Information

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Supporting Information

Synthesis of Anti-oxidant Steroids by Hybridisation with Nitroxides

Carl P. Soltau, Naomi E. Weir, Alexander Martyn & Steven E. Bottle

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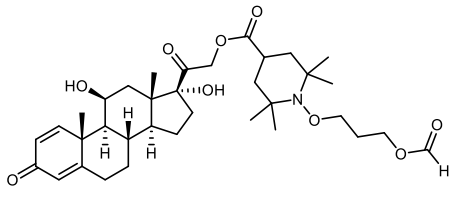
1. Isolation of N4-A



N4-A

To a stirred solution of 4-carboxy-TEMPO (100 mg, 1.0 eqv.), prednisolone (198 mg, 1.1 eqv.) and DMAP (12 mg, 0.2 eqv.) in dry THF (50 mL) at 0 °C under an atmosphere of Ar was added EDC•HCl (105 mg, 1.1 eqv.) in dry DCM (10 mL). The cooling bath was removed and the solution was stirred overnight. The solution was diluted into DCM (100 mL) and washed with 1M HCl (30 mL). The organic phase was then dried over anhydrous Na_2SO_4 and concentrated in vacuo to provide a crude material that was purified by normal-phase flash chromatography (DCM:Acetone) followed by reversed-phase flash chromatography (MeOH:H_2O) to afford N4-A as a white solid (176 mg, 65%).

M.p. = 181 – 183 °C; R_f: 0.65 (DCM-EtOAc, 70:30)

IR (neat): 3517 (w, O-H), 3488 (w, O-H), 2971 (w, C-H), 2931 (w, C-H), 1719 (s, C=O), 1653 (s, C=O), 1611 (m, C=O), 1600 (m, C=O).

^{1}H NMR (DMSO-d_6, 600 MHz) δ 8.23 (s, 1H), 7.32 (d, *J* = 10.1 Hz, 1H), 6.16 (dd, *J* = 10.1, 1.9 Hz, 1H), 5.91 (t, *J* = 1.6 Hz, 1H), 5.40 (s, 1H), 5.08 (d, *J* = 17.5 Hz, 1H), 4.75 (d, *J* = 17.5 Hz, 1H), 4.71 (d, *J* = 4.9 Hz, 1H), 4.28 (p, *J* = 3.6 Hz, 1H), 4.18 (t, *J* = 6.4 Hz, 2H), 3.76 (t, *J* = 6.2 Hz, 2H), 2.74 (tt, *J* = 12.9, 3.4 Hz, 1H), 2.56 – 2.44 (overlapped, 2H), 2.35 – 2.19 (m, 1H), 2.06 – 1.98 (m, 2H), 1.91 – 1.80 (overlapped, 3H), 1.76 – 1.70 (m, 2H), 1.69 – 1.57 (m, 3H), 1.51 (t, *J* = 12.9 Hz, 2H), 1.47 – 1.41 (m, 1H), 1.39 (s, 3H), 1.37 – 1.21 (m, 2H), 1.20 – 1.12 (overlapped, 1H), 1.14 (d, *J* = 1.8 Hz, 6H), 1.09 (d, *J* = 1.8 Hz, 6H), 1.00 (m, 1H), 0.89 (dd, *J* = 11.0, 3.5 Hz, 1H), 0.78 (s, 3H).

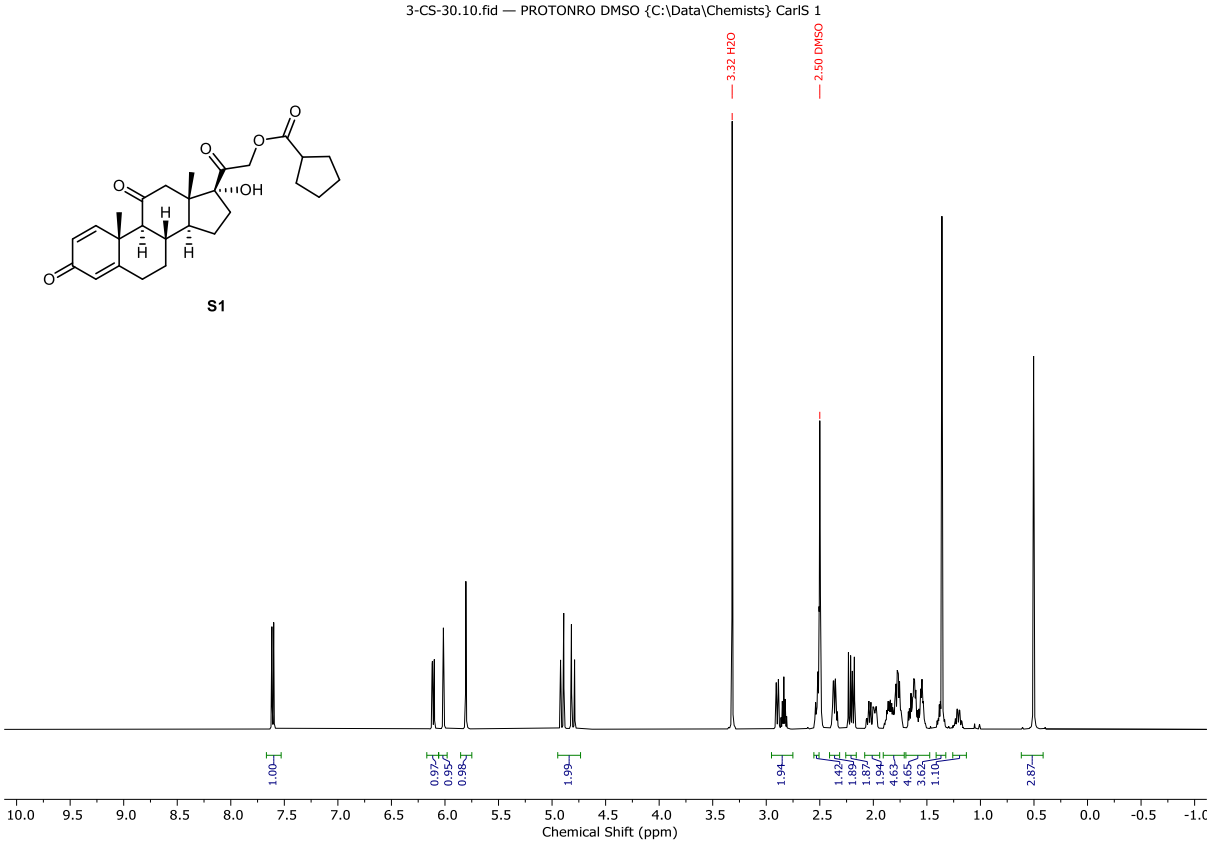
^{13}C NMR (DMSO-d_6, 150 MHz) δ 205.1, 185.1, 173.9, 170.5, 156.7, 127.0, 121.6, 88.6, 72.5, 68.3, 67.5, 60.7, 58.8, 58.8, 55.4, 51.0, 51.0, 47.1, 43.8, 41.5, 41.4, 38.6, 34.0, 33.9, 33.9, 33.8, 33.8, 33.0, 33.0, 32.6, 32.6, 32.6, 32.5, 31.3, 31.3, 30.9, 30.9, 27.6, 27.5, 23.5, 20.9, 19.9, 16.5.

HRMS (ESI): *m/z* [*M*+H]$^+$ calcd for $C_{35}H_{52}NO_9^+$: 630.3637; found: 630.3626.

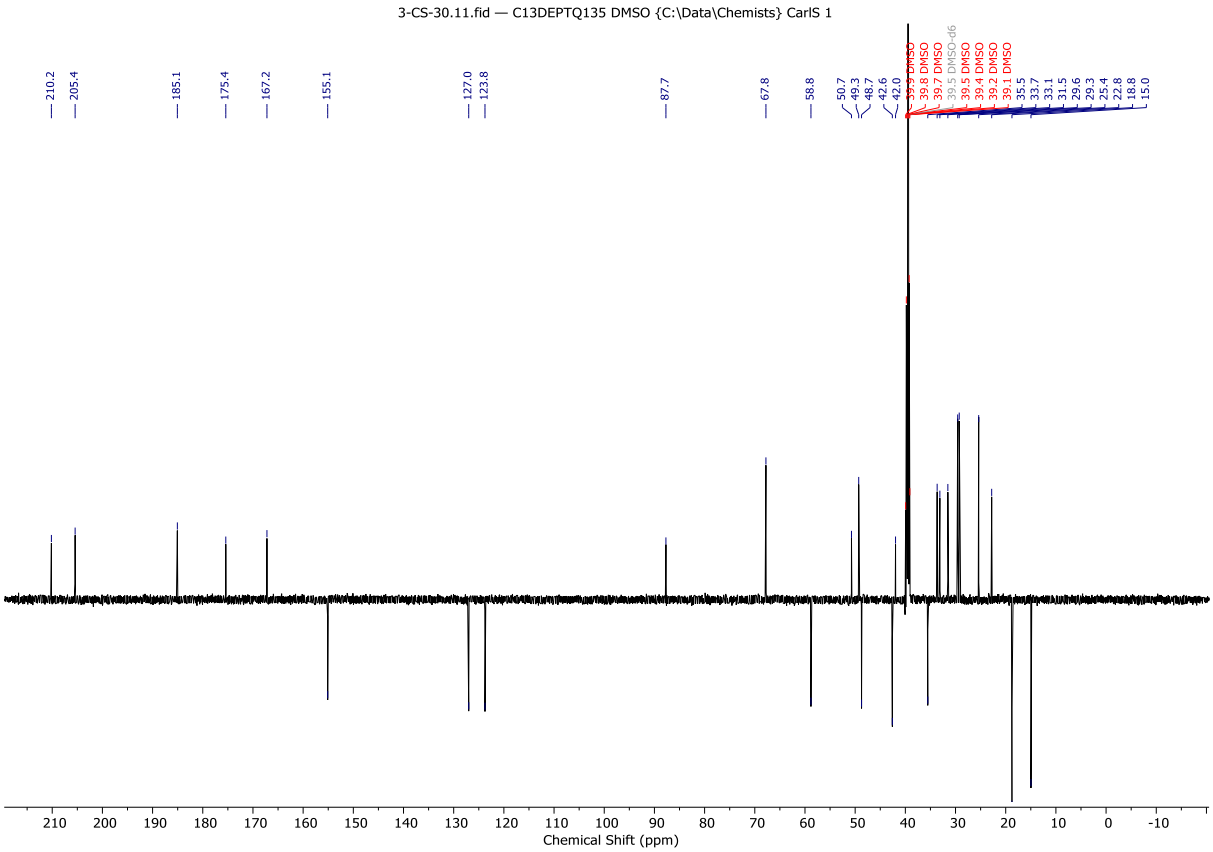
Notes: Immediately prior to commencing the experiment we conducted a peroxide test of the THF reagent bottle using a colorimetric QUANTOFIX® Peroxide 100 test strip which displayed a peroxide concentration of 10-30 mg/L.

N4 was also isolated from this reaction in 17% yield.

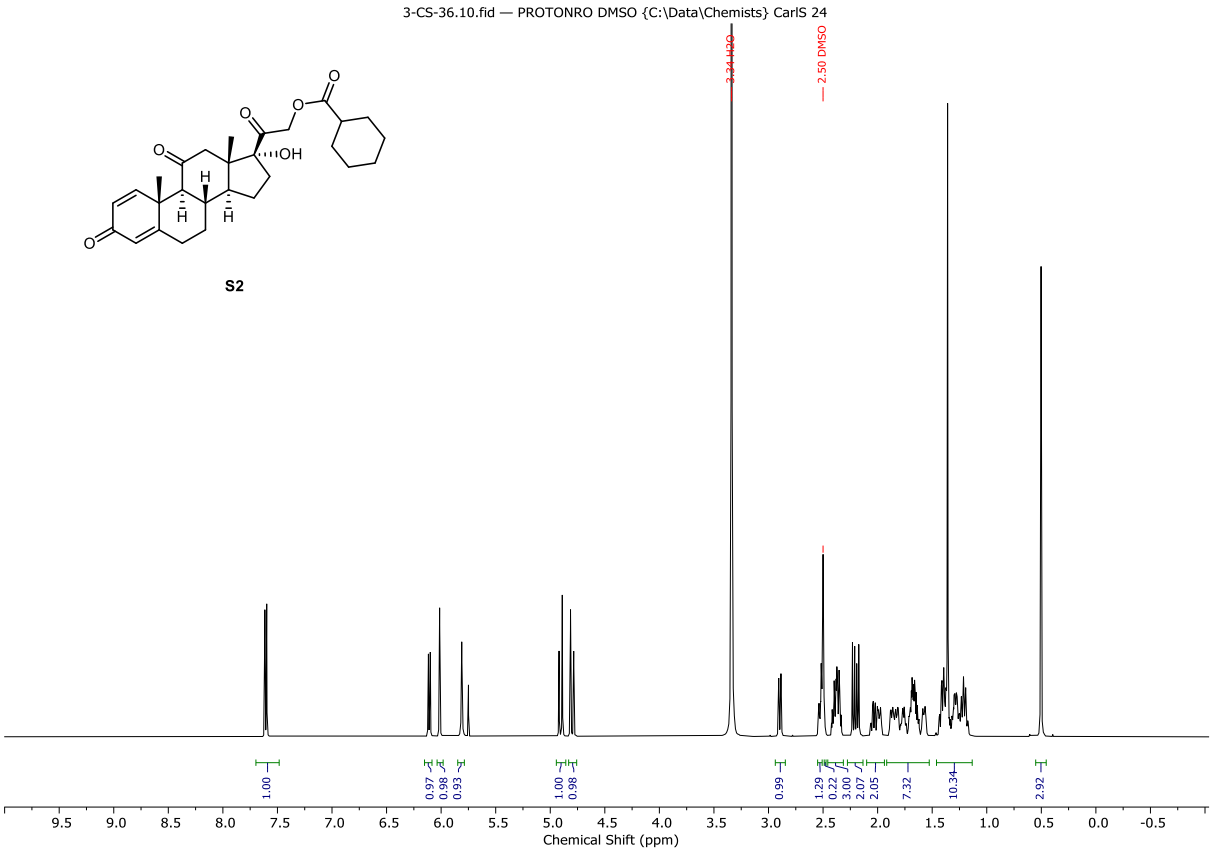
2. ^{1}H and ^{13}C NMR Data



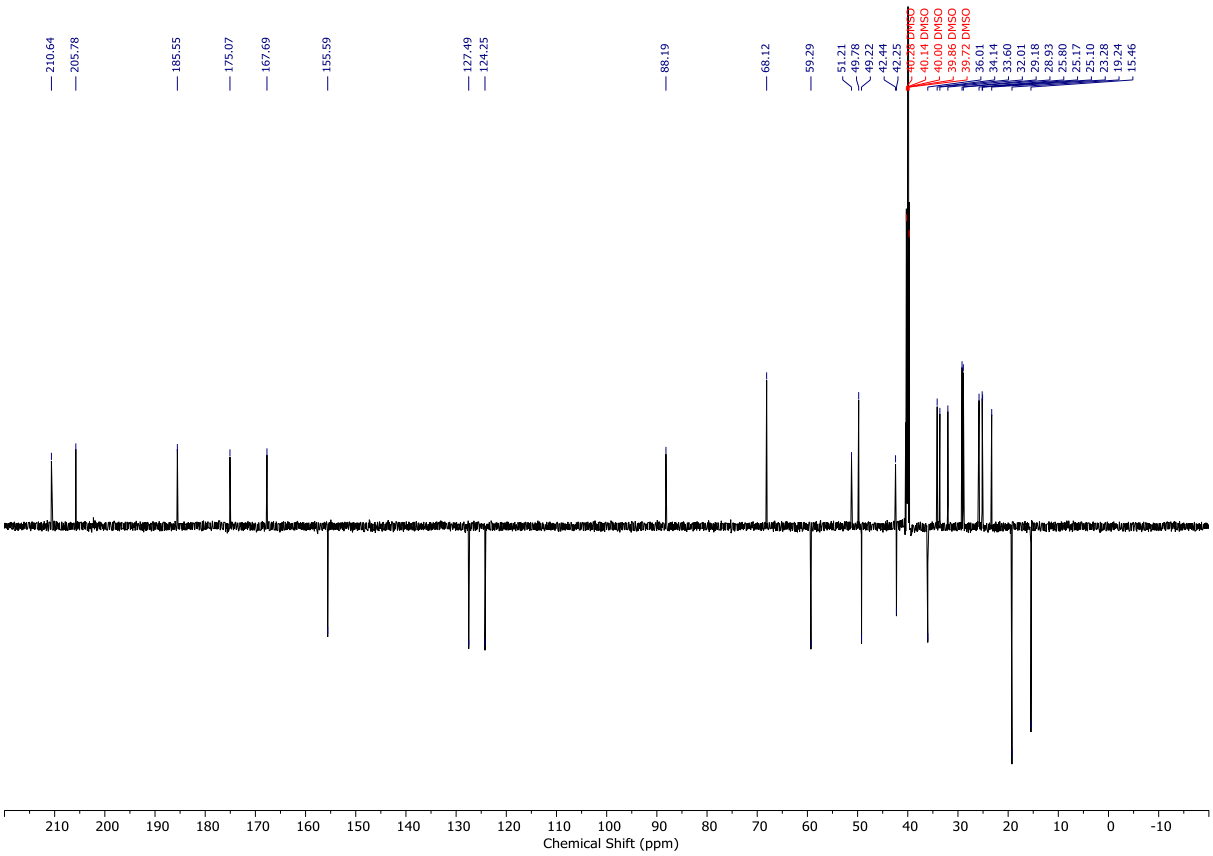
Supplementary Figure 1: ^{1}H NMR (DMSO-d_6, 600 MHz) of **S1**.



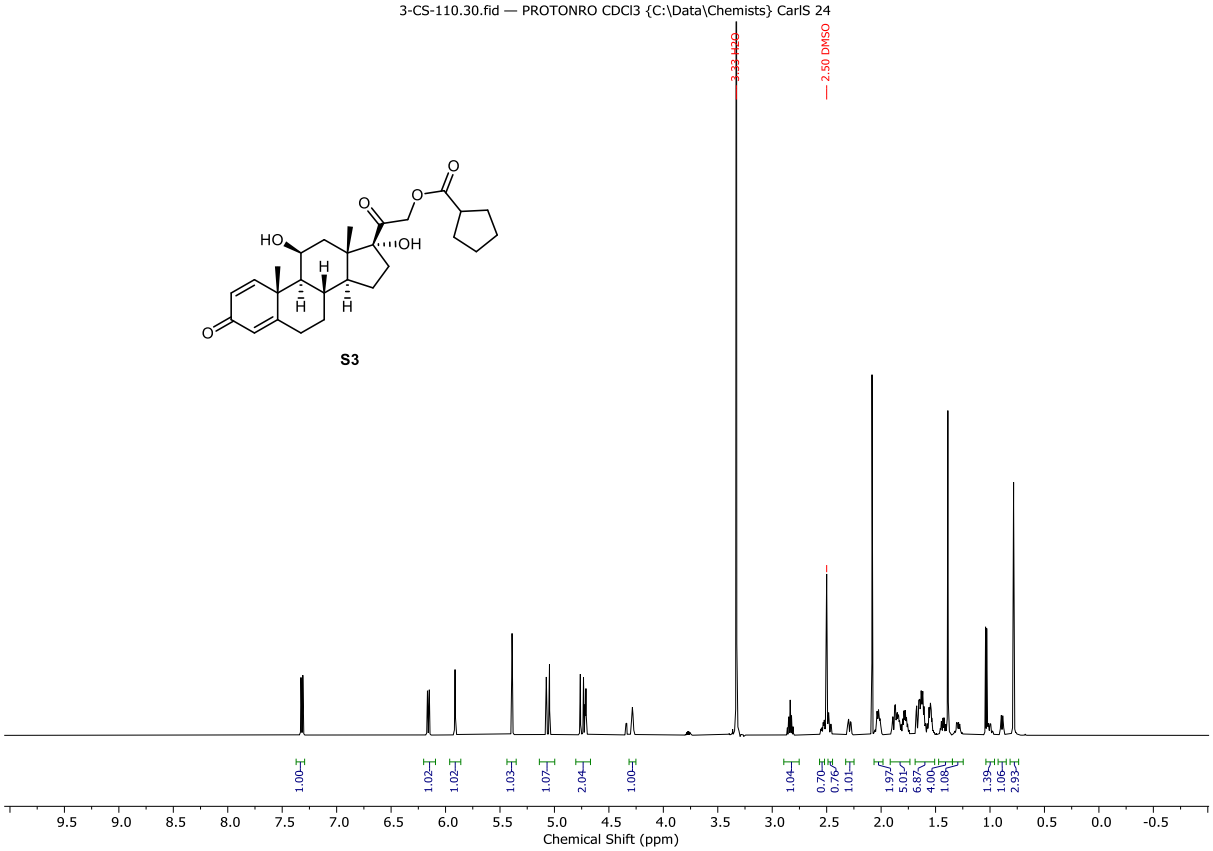
Supplementary Figure 2: ^{13}C DEPTQ135 NMR (DMSO-d_6, 150 MHz) of **S1**.



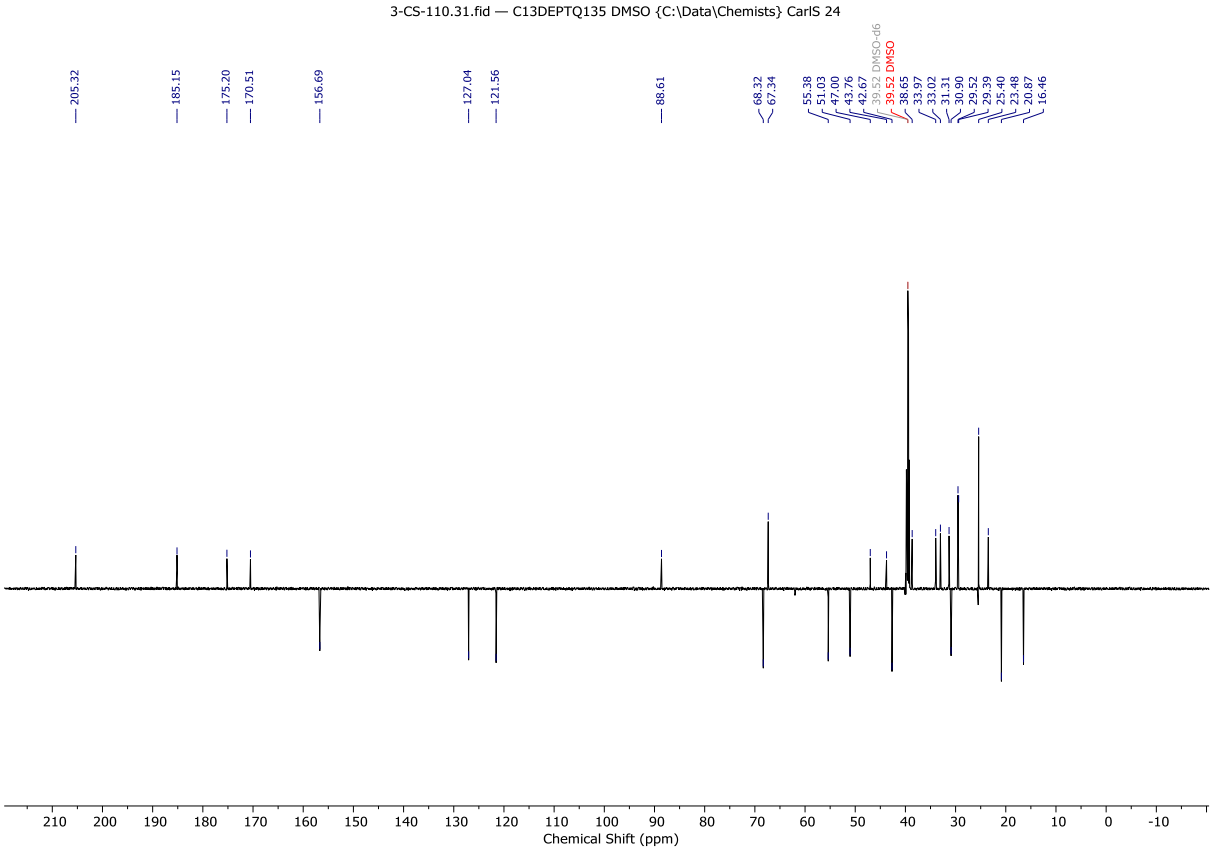
Supplementary Figure 3: ^{1}H NMR (DMSO-d_6, 600 MHz) of **S2**.



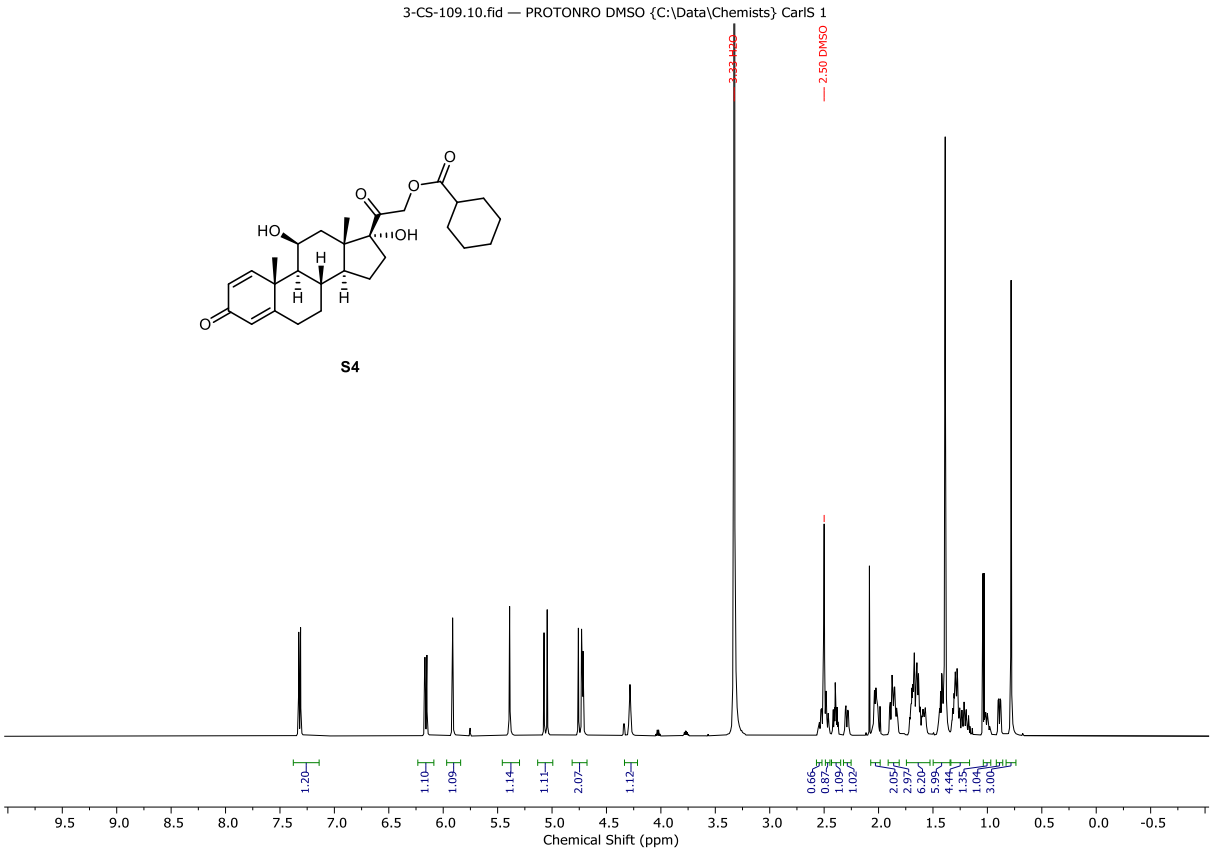
Supplementary Figure 4: ^{13}C DEPTQ135 NMR (DMSO-d_6, 150 MHz) of **S2**.



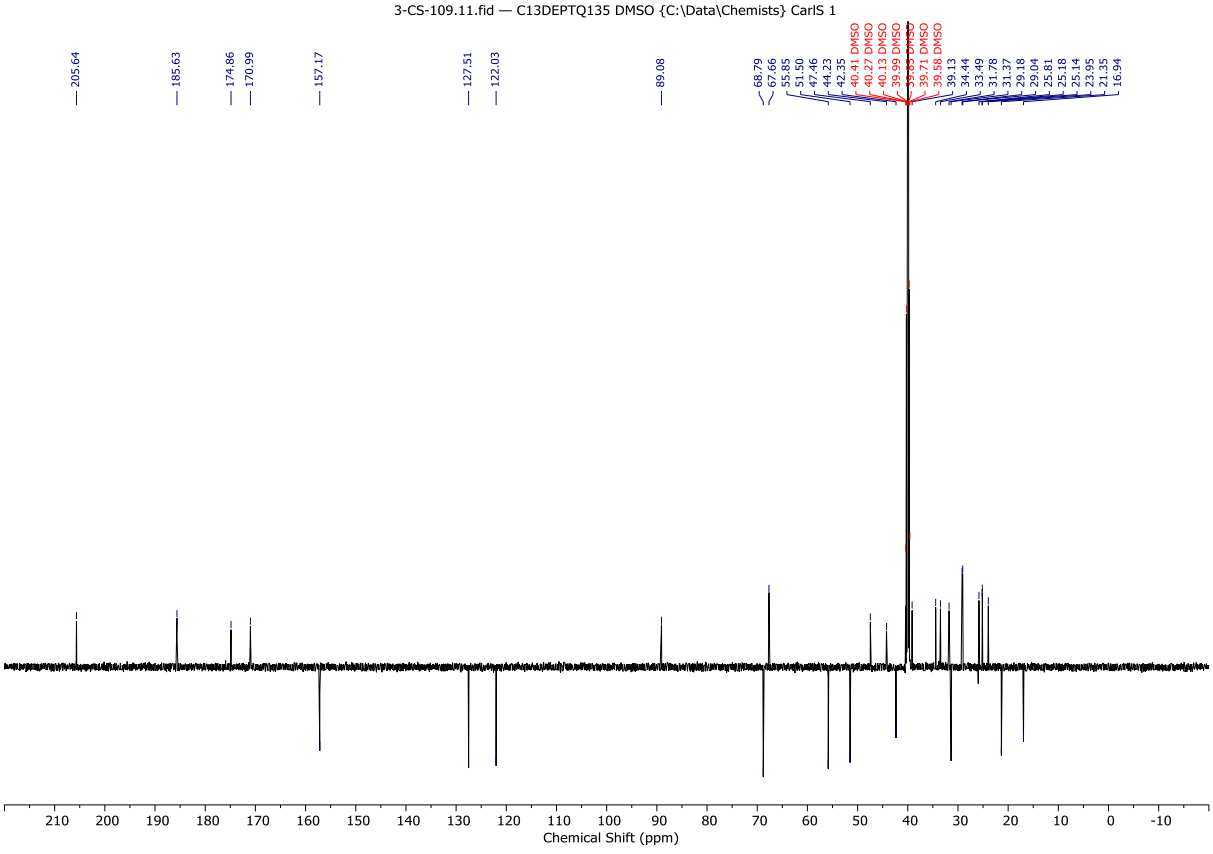
Supplementary Figure 5: ^{1}H NMR (DMSO-d_6, 600 MHz) of **S3**.



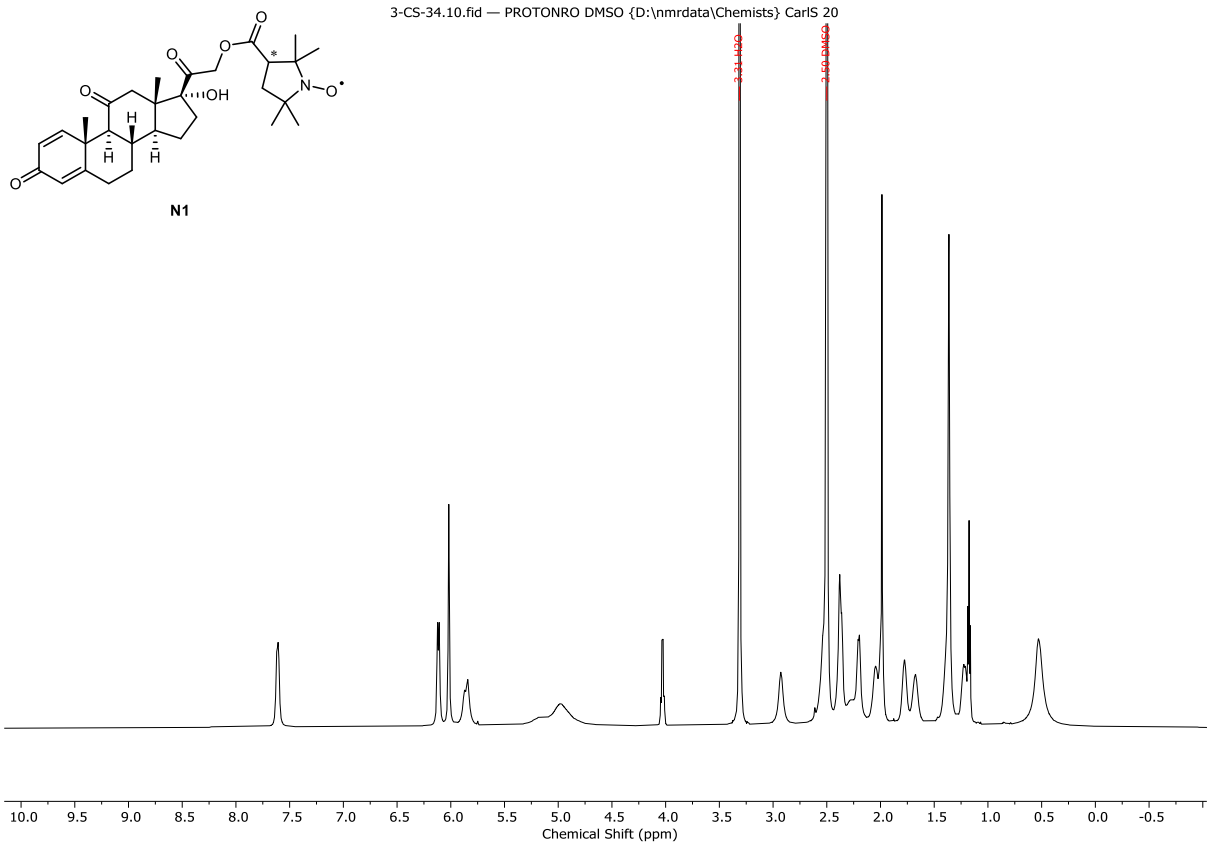
Supplementary Figure 6: ^{13}C DEPTQ135 NMR (DMSO-d_6, 150 MHz) of **S3**.



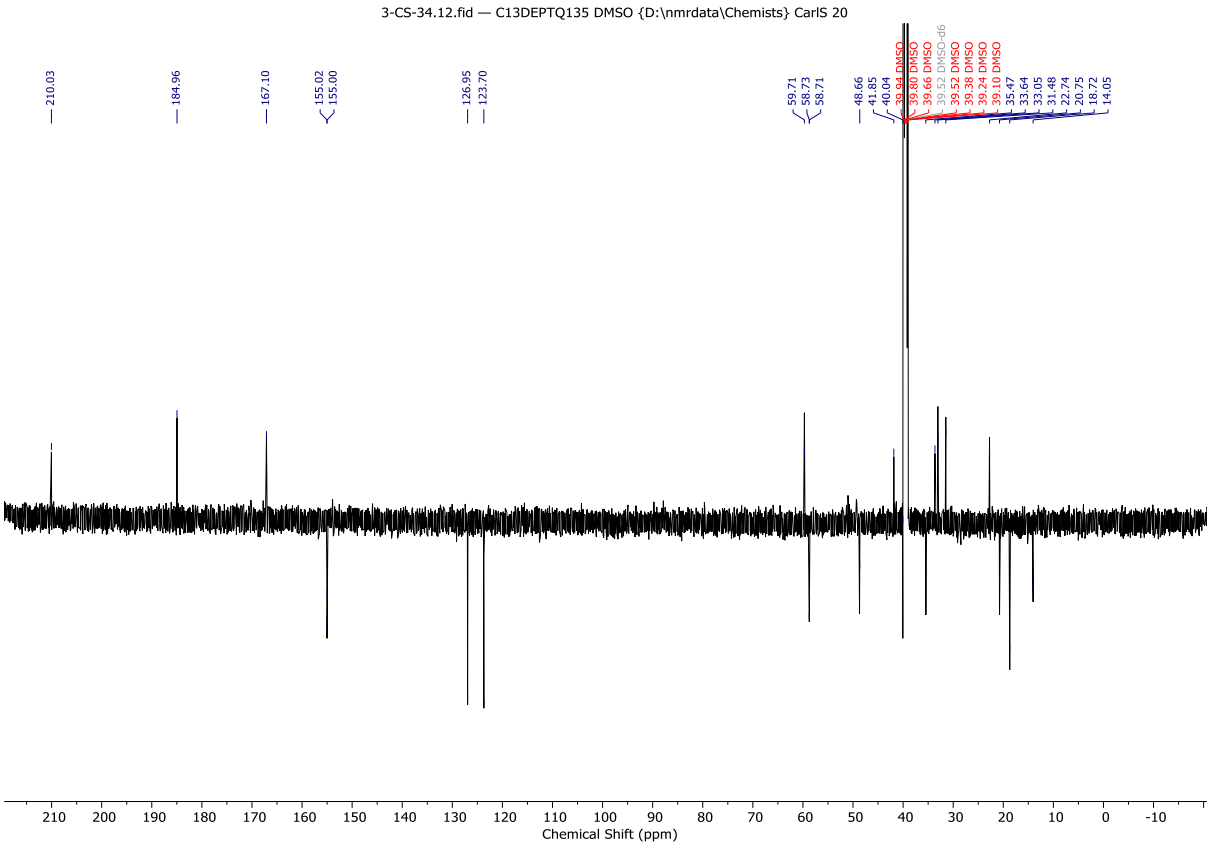
Supplementary Figure 7: ^{1}H NMR (DMSO-d_6, 600 MHz) of **S4**.



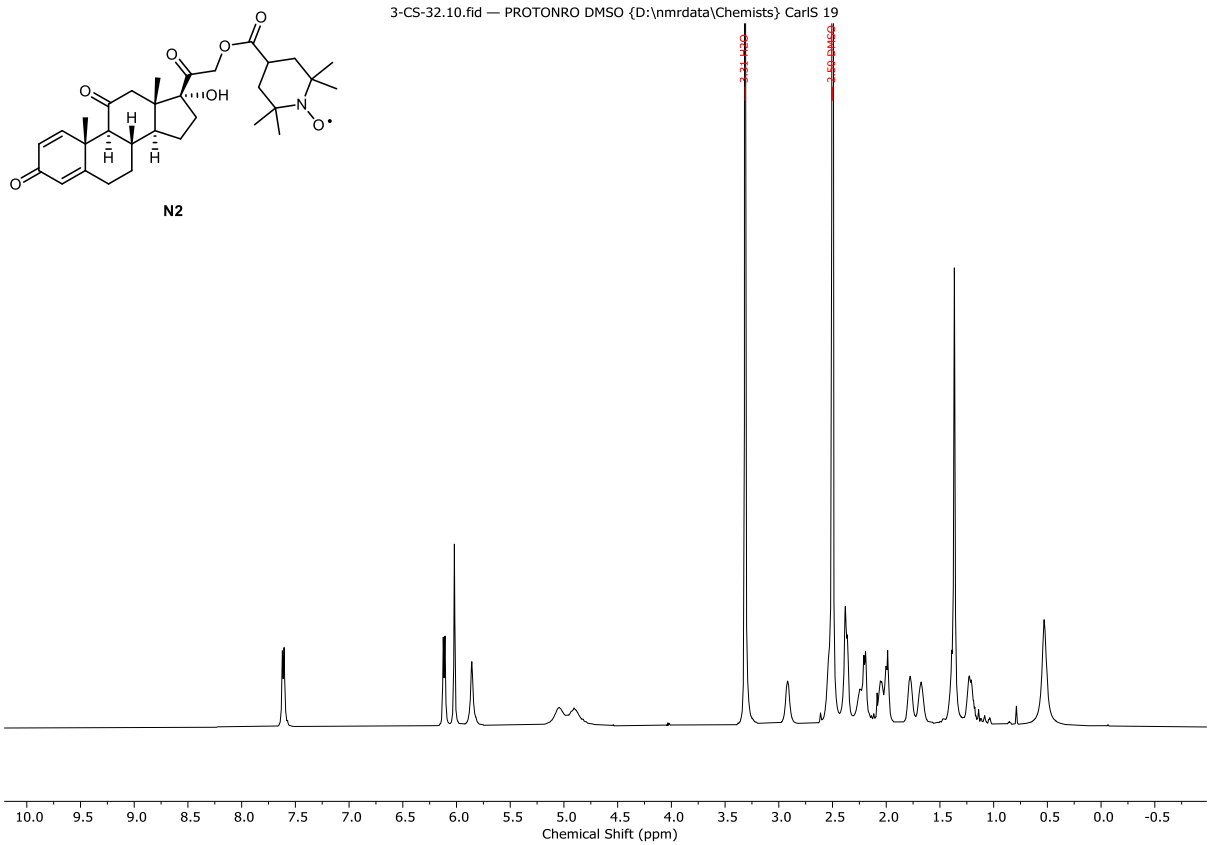
Supplementary Figure 8: ^{13}C DEPTQ135 NMR (DMSO-d_6, 150 MHz) of **S4**.



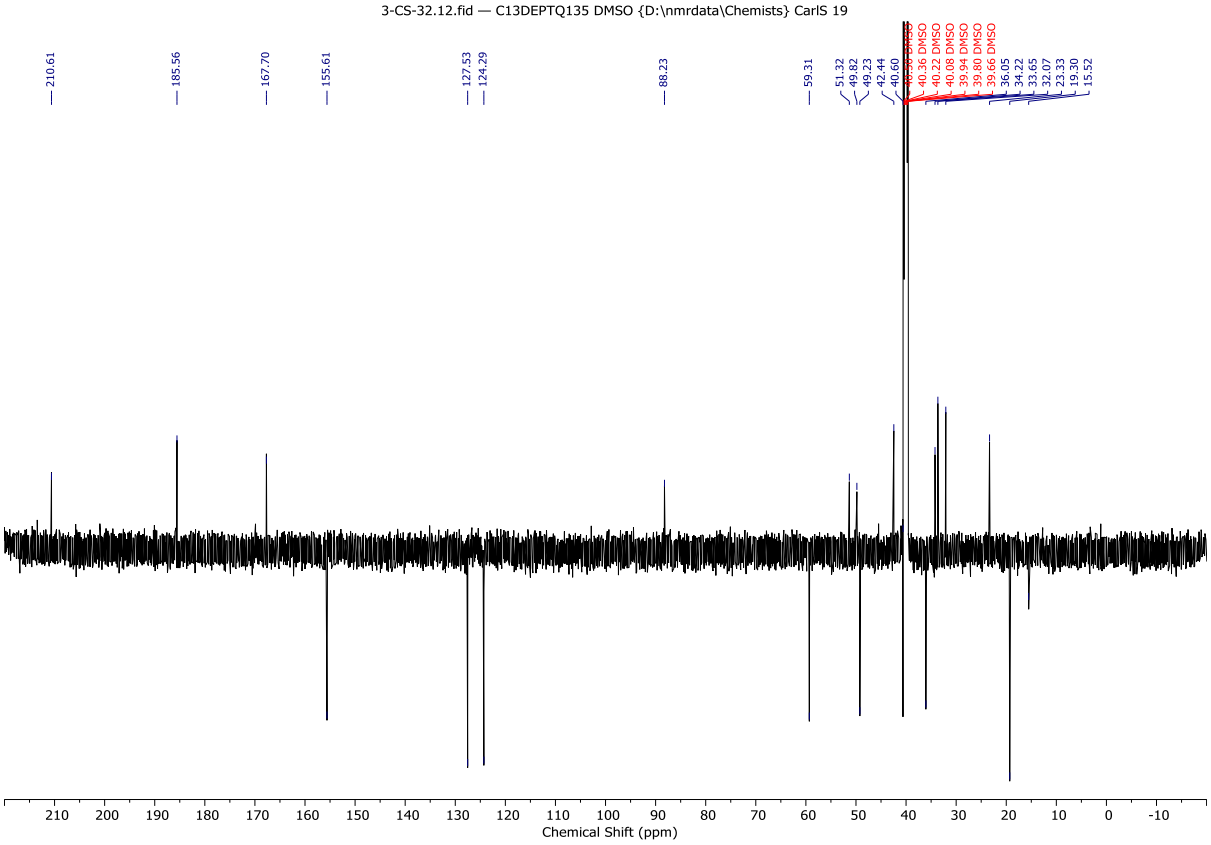
Supplementary Figure 9: ^{1}H NMR (DMSO-d_6, 600 MHz) of **N1**.



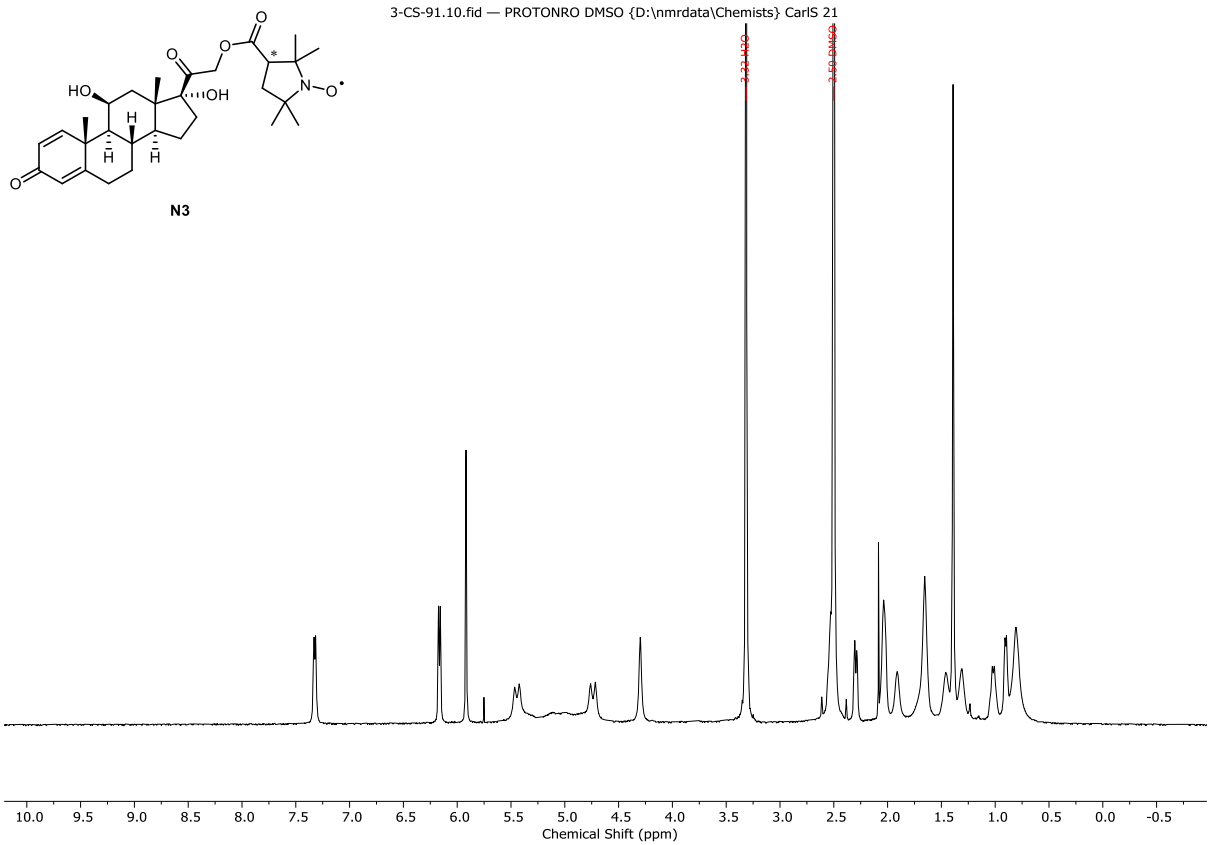
Supplementary Figure 10: ^{13}C DEPTQ135 NMR (DMSO-d_6, 150 MHz) of **N1**.



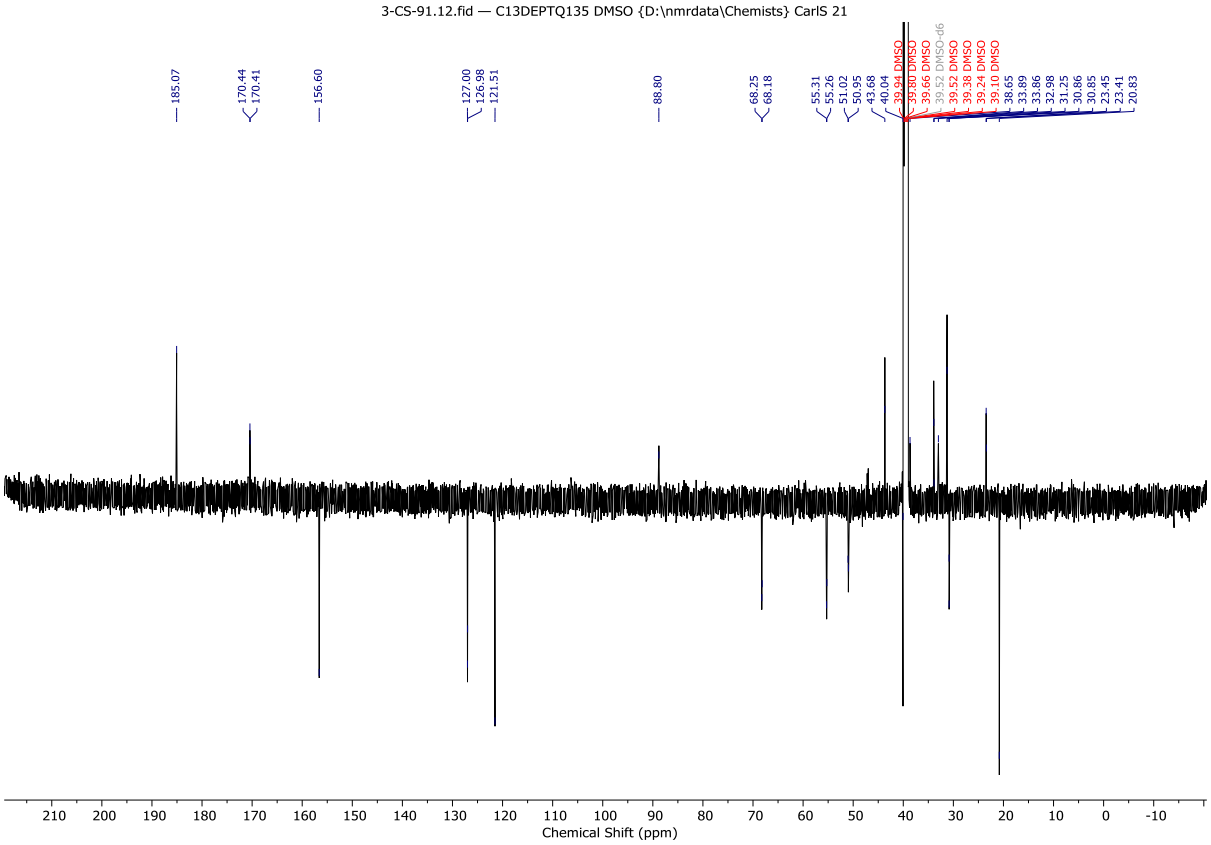
Supplementary Figure 11: ^{1}H NMR (DMSO-d_6, 600 MHz) of **N2**.



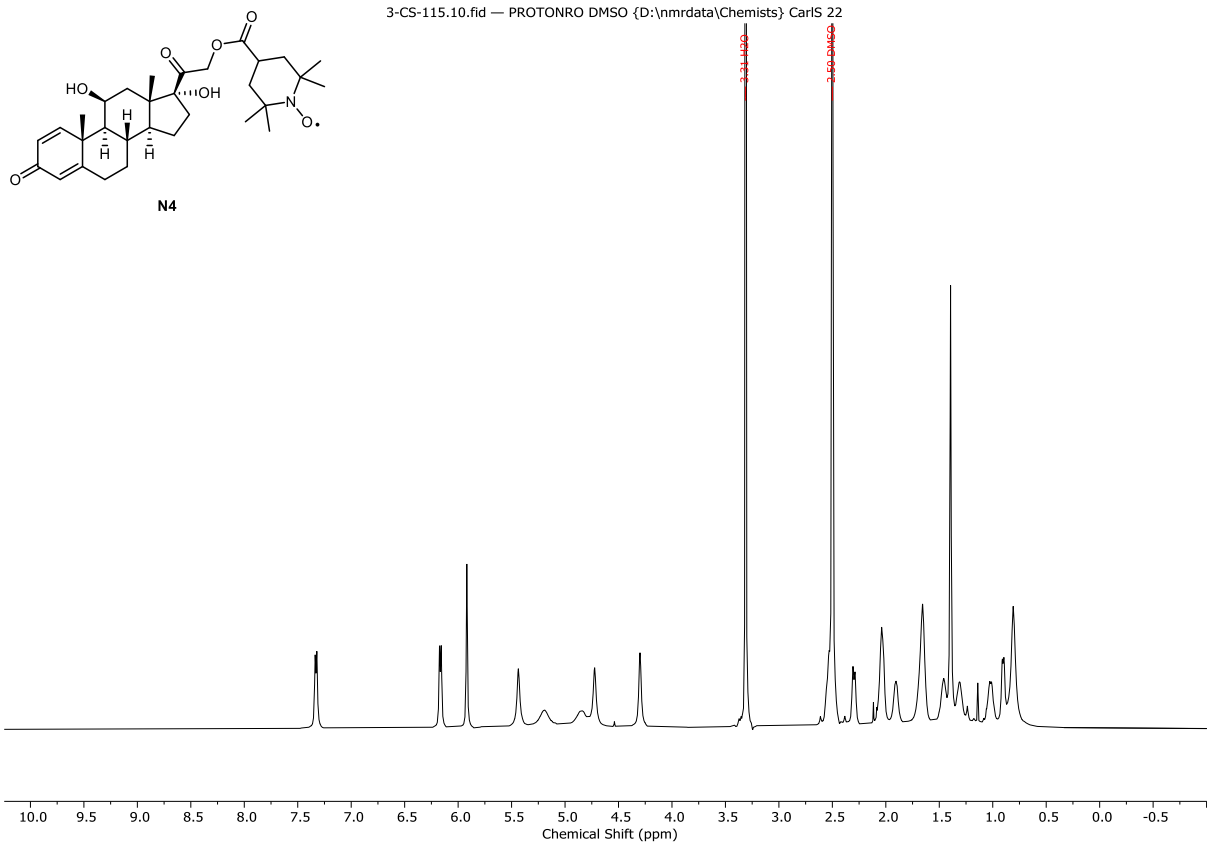
Supplementary Figure 12: ^{13}C DEPTQ135 NMR (DMSO-d_6, 150 MHz) of **N2**.



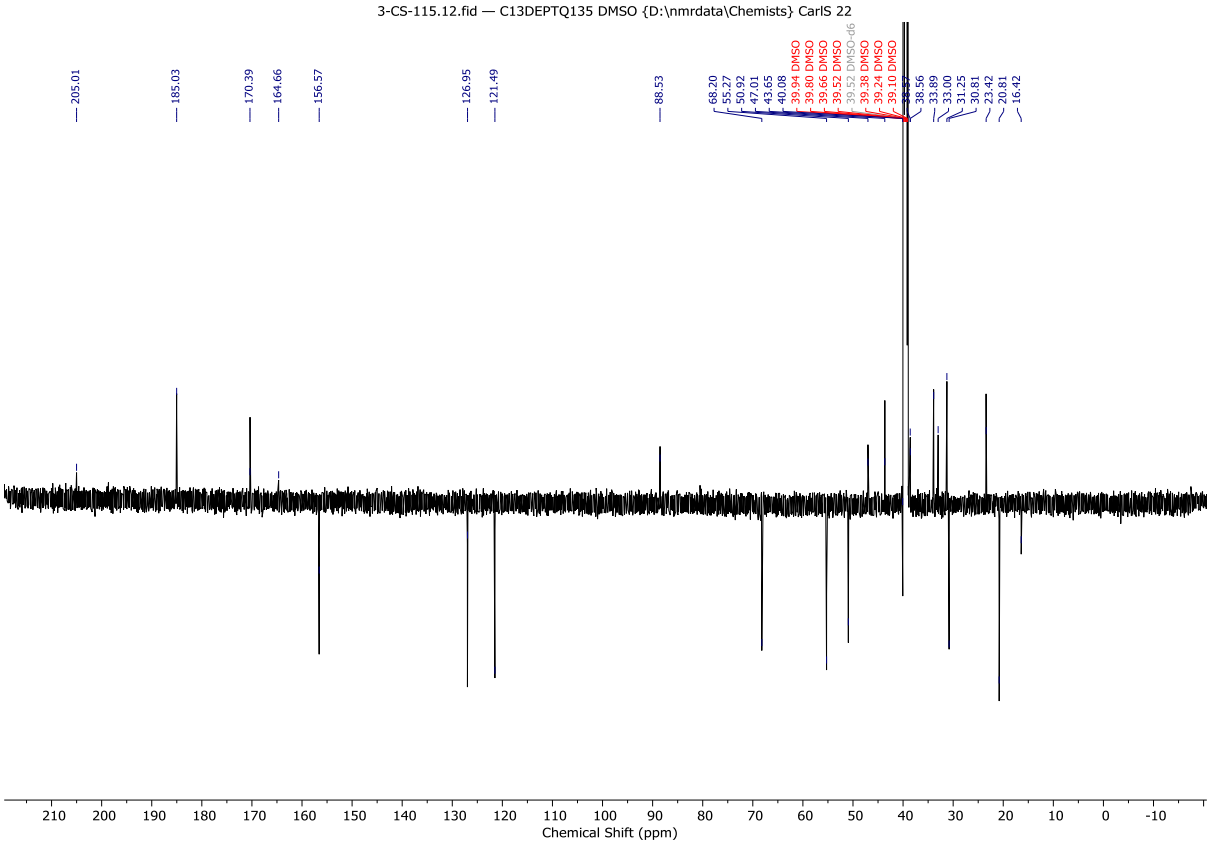
Supplementary Figure 13: ^{13}C DEPTQ135 NMR (DMSO-d_6, 150 MHz) of **N3**.



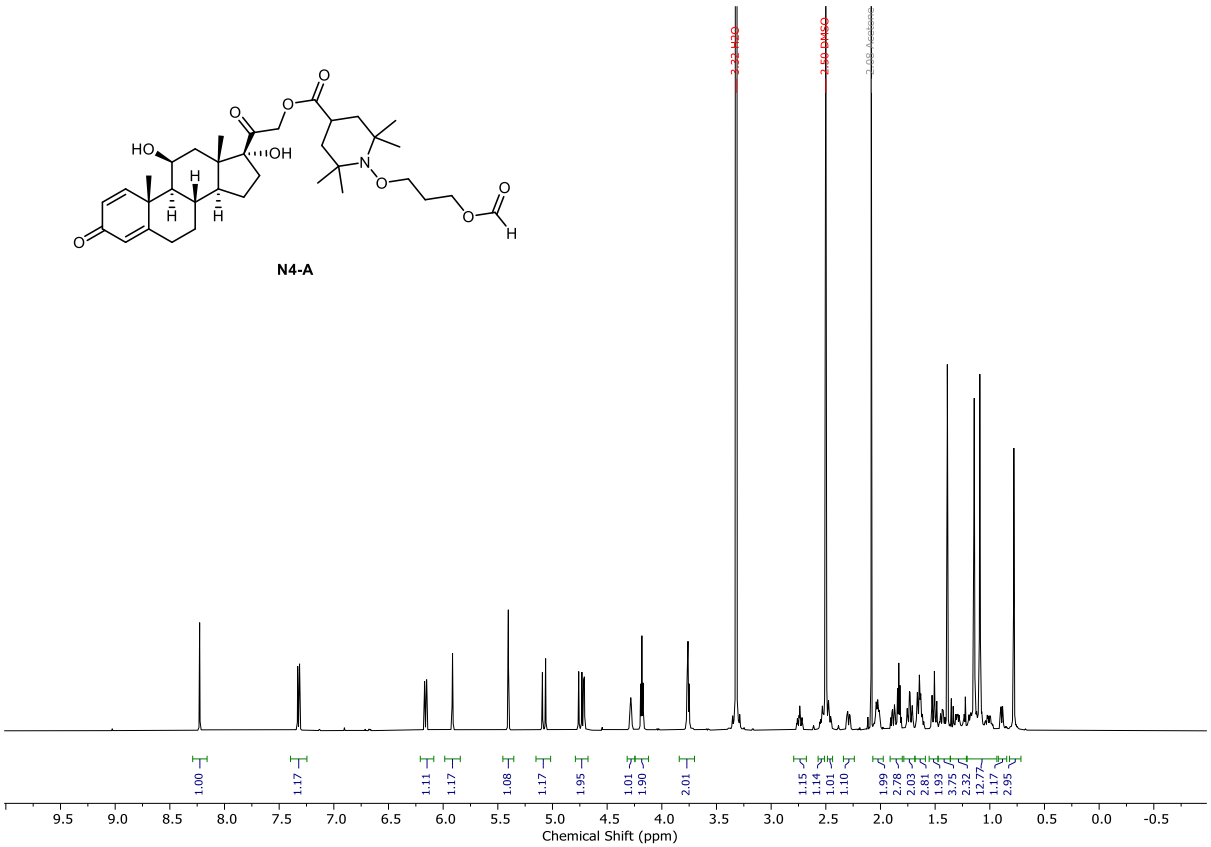
Supplementary Figure 14: ^{13}C DEPTQ135 NMR (DMSO-d_6, 150 MHz) of **N3**.



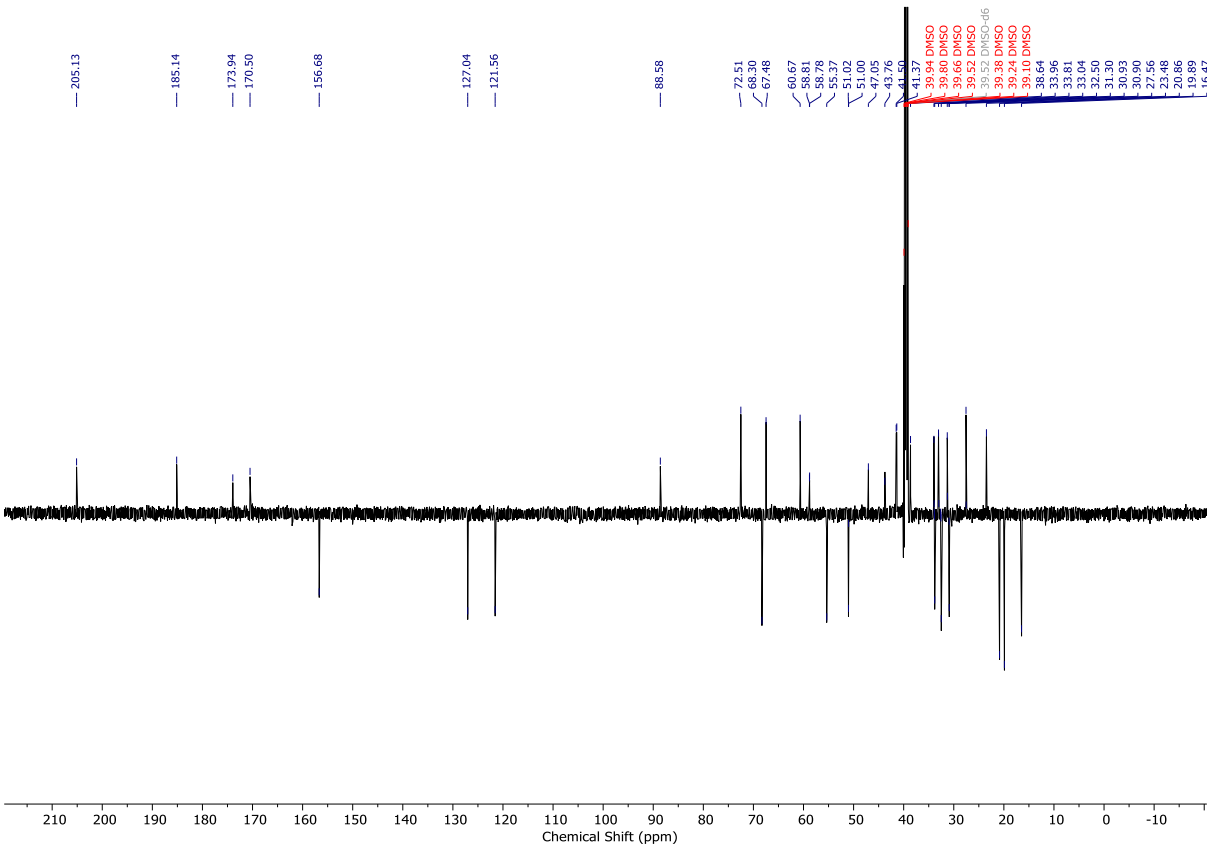
Supplementary Figure 15: ^{13}C DEPTQ135 NMR (DMSO-d_6, 150 MHz) of **N4**.



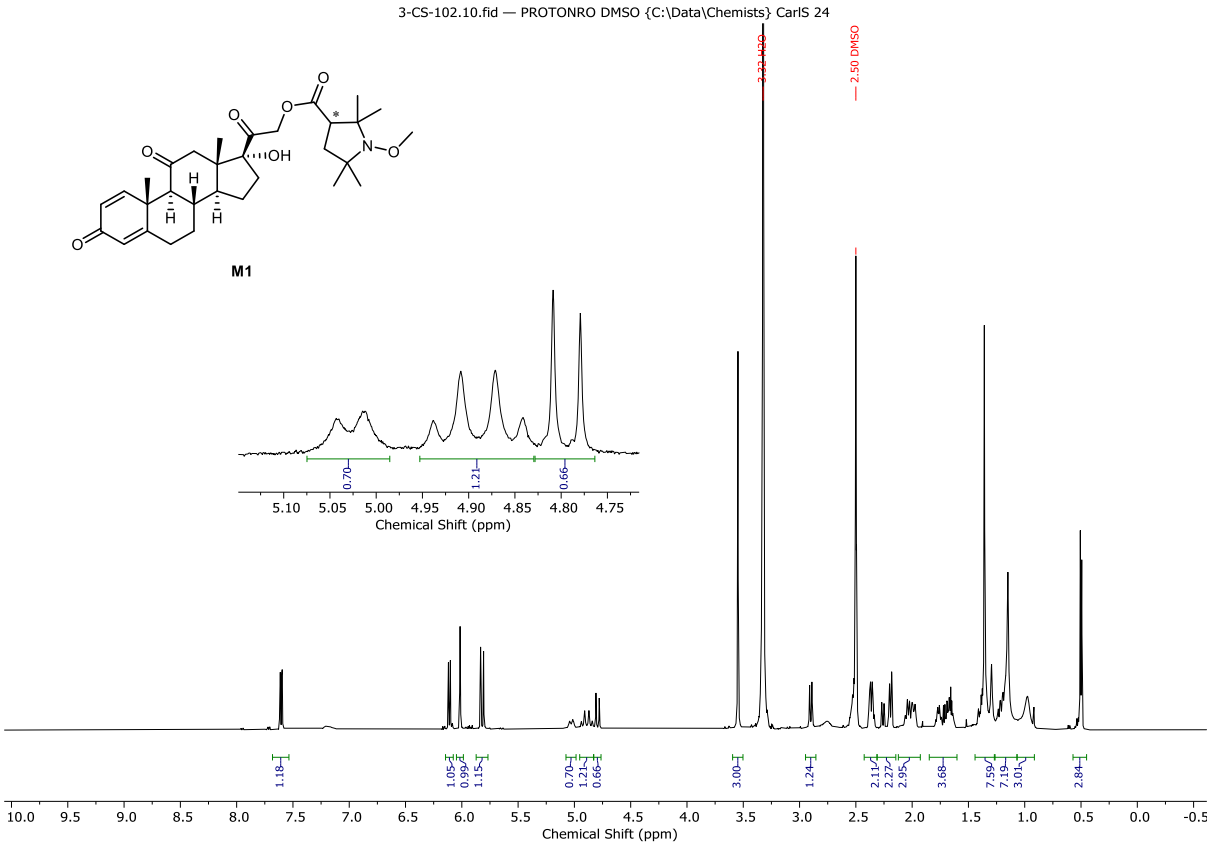
Supplementary Figure 16: ^{13}C DEPTQ135 NMR (DMSO-d_6, 150 MHz) of **N4**.



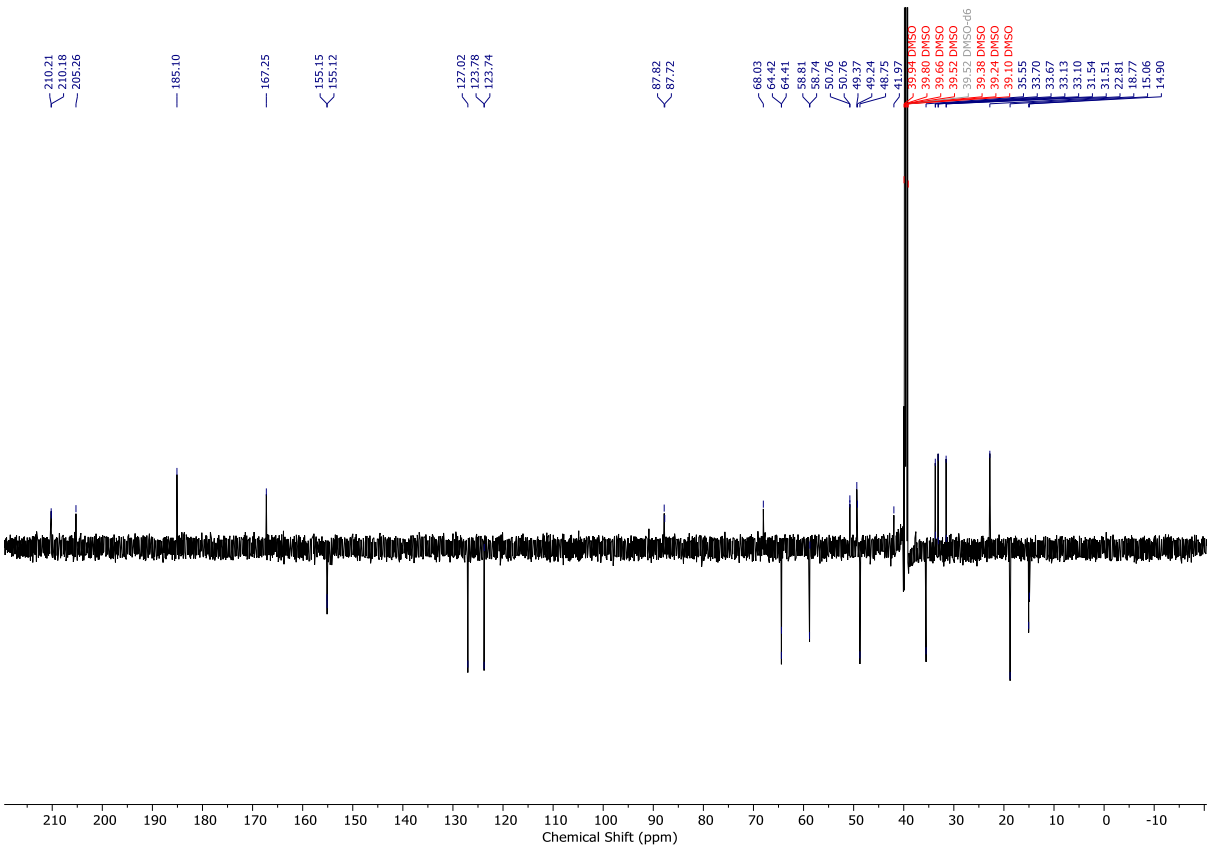
Supplementary Figure 17: ^{1}H NMR (DMSO-d_6, 600 MHz) of **N4-A**.



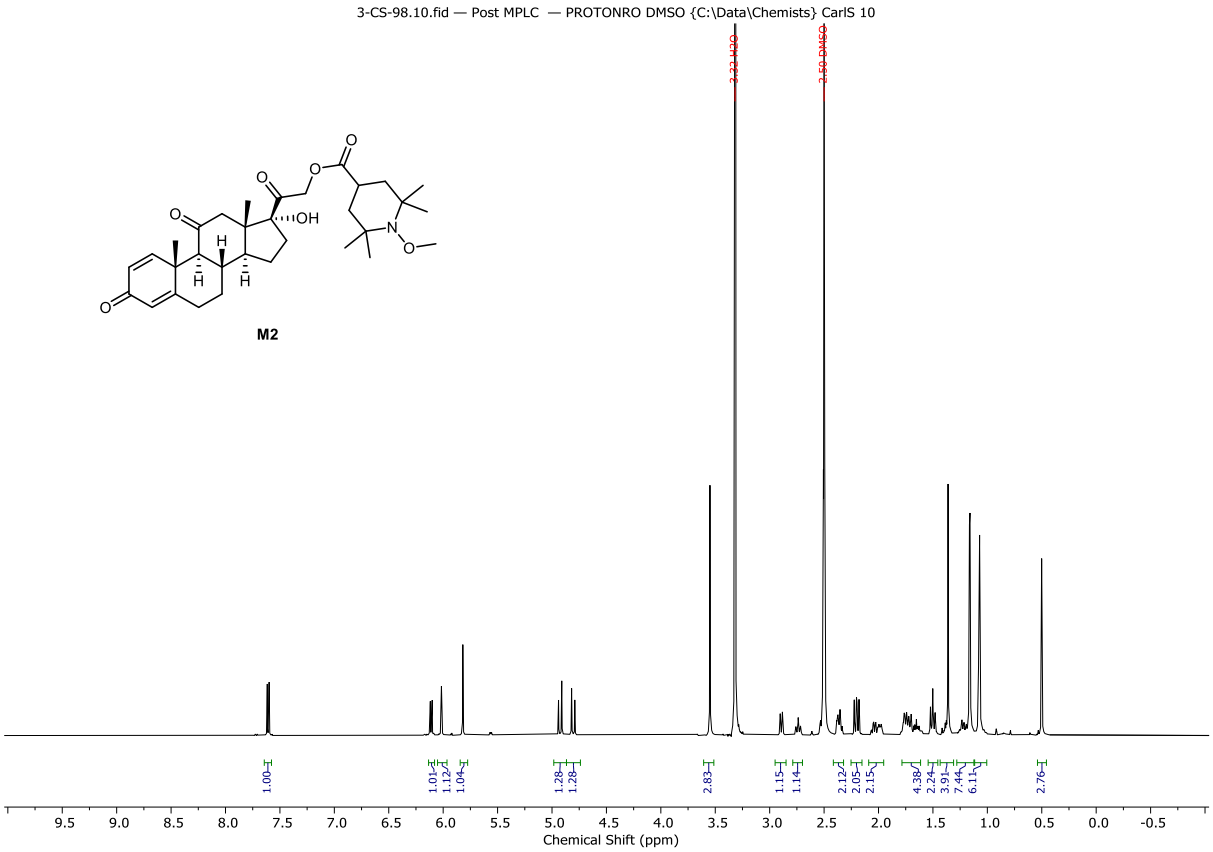
Supplementary Figure 18: ^{13}C DEPTQ135 NMR (DMSO-d_6, 150 MHz) of **N4-A**.



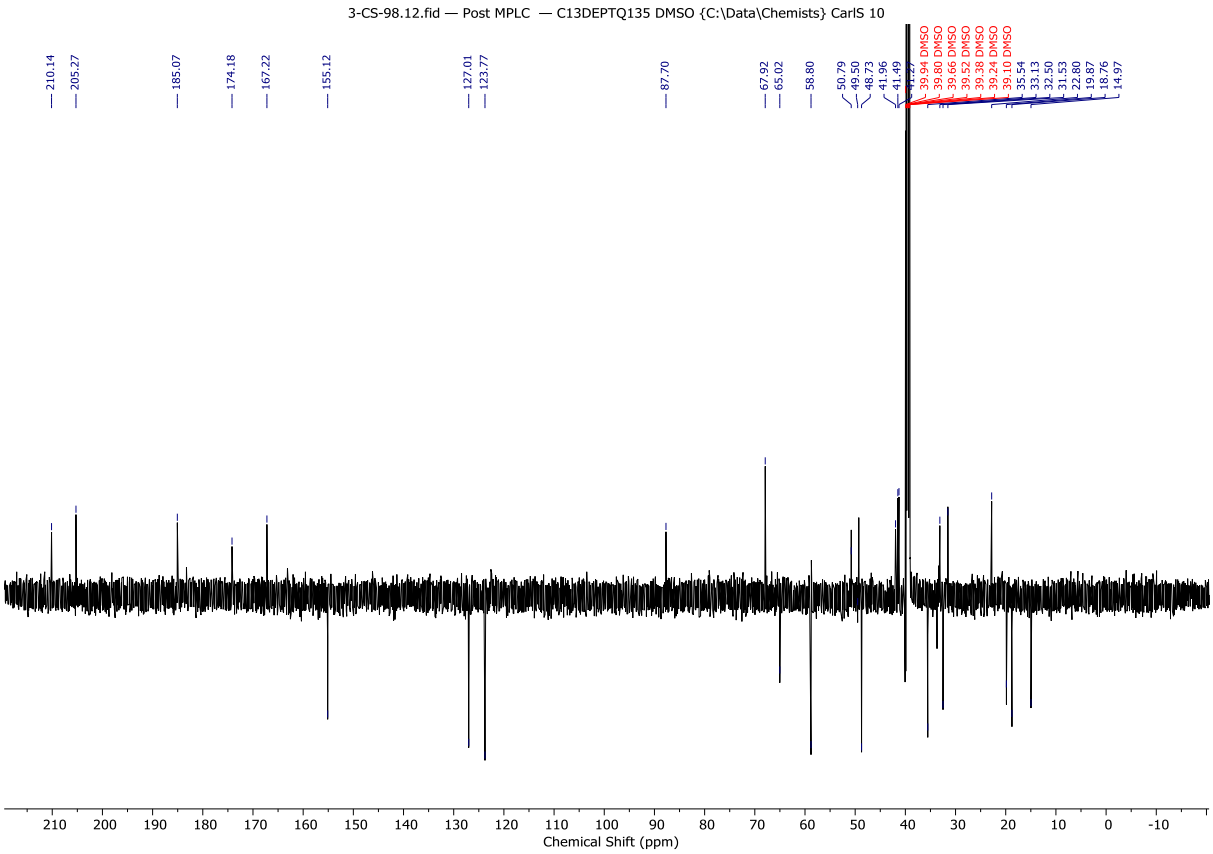
Supplementary Figure 19: ^{1}H NMR (DMSO-d_6, 600 MHz) of **M1**. '*' denotes undefined chirality.



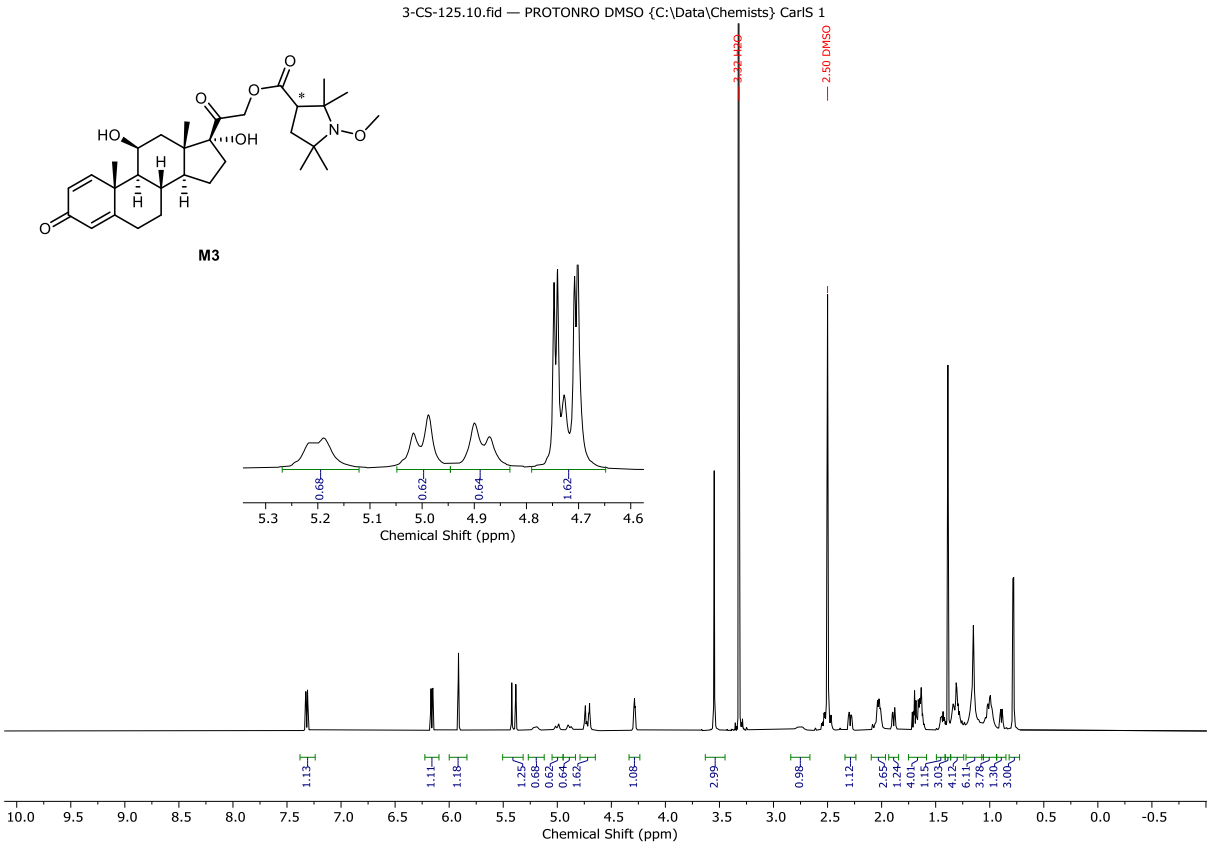
Supplementary Figure 20: ^{13}C DEPTQ135 NMR (DMSO-d_6, 150 MHz) of **M1**. '*' denotes undefined chirality.



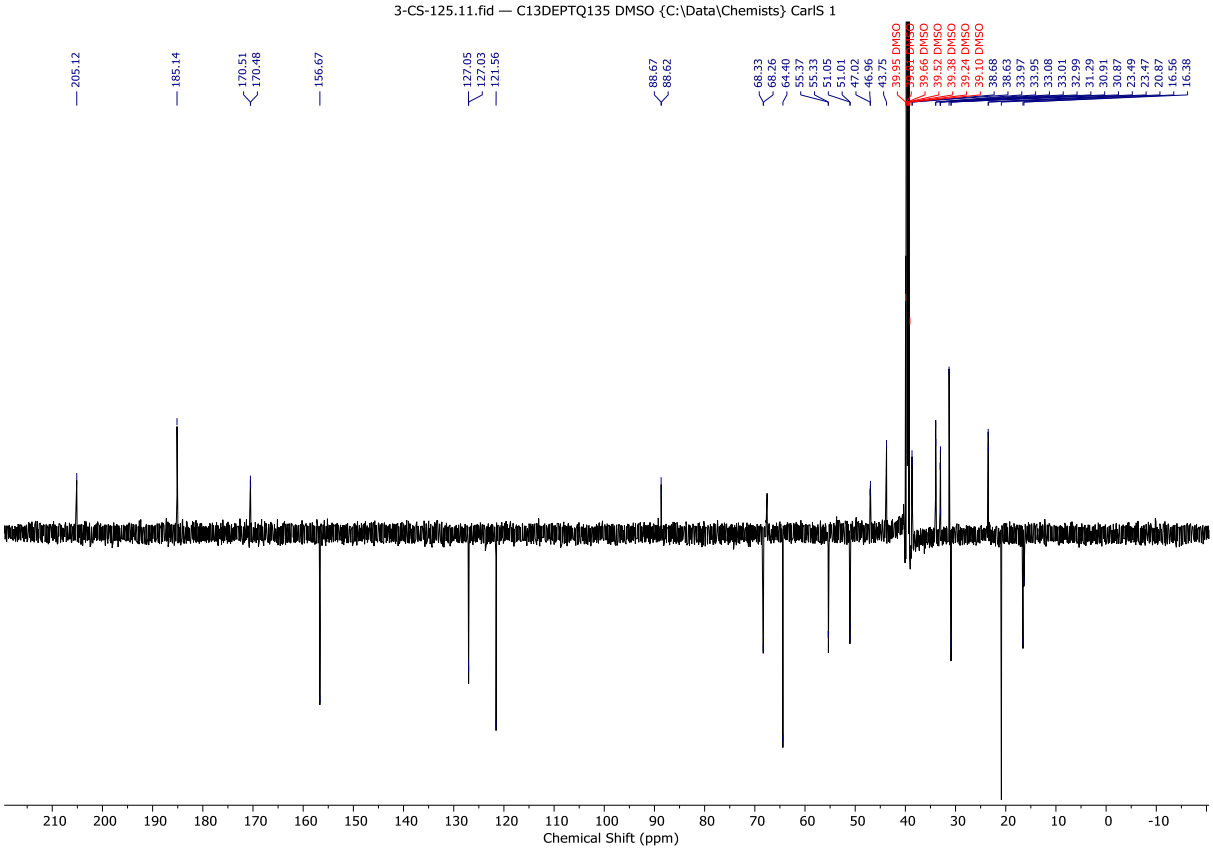
Supplementary Figure 21: ^{1}H NMR (DMSO-d_6, 600 MHz) of **M2**.



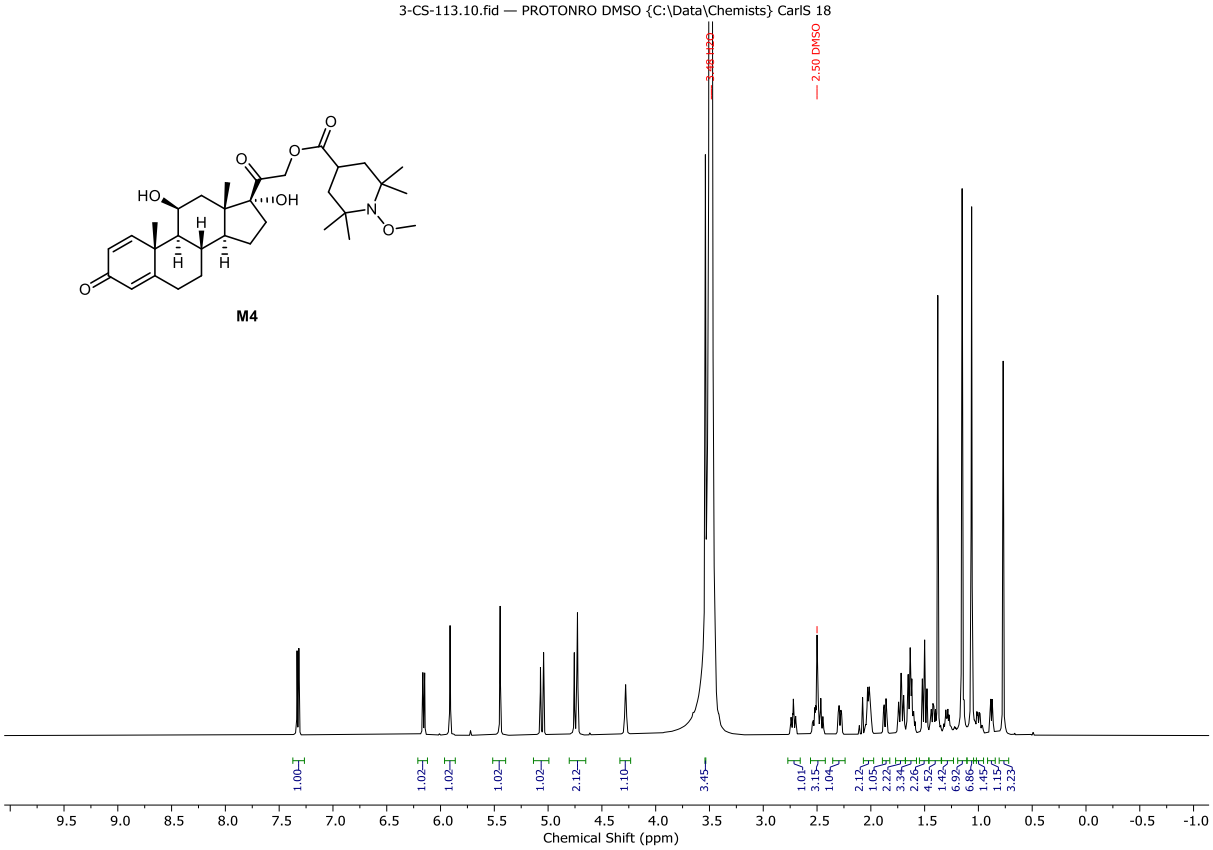
Supplementary Figure 22: ^{13}C DEPTQ135 NMR (DMSO-d_6, 150 MHz) of **M2**.



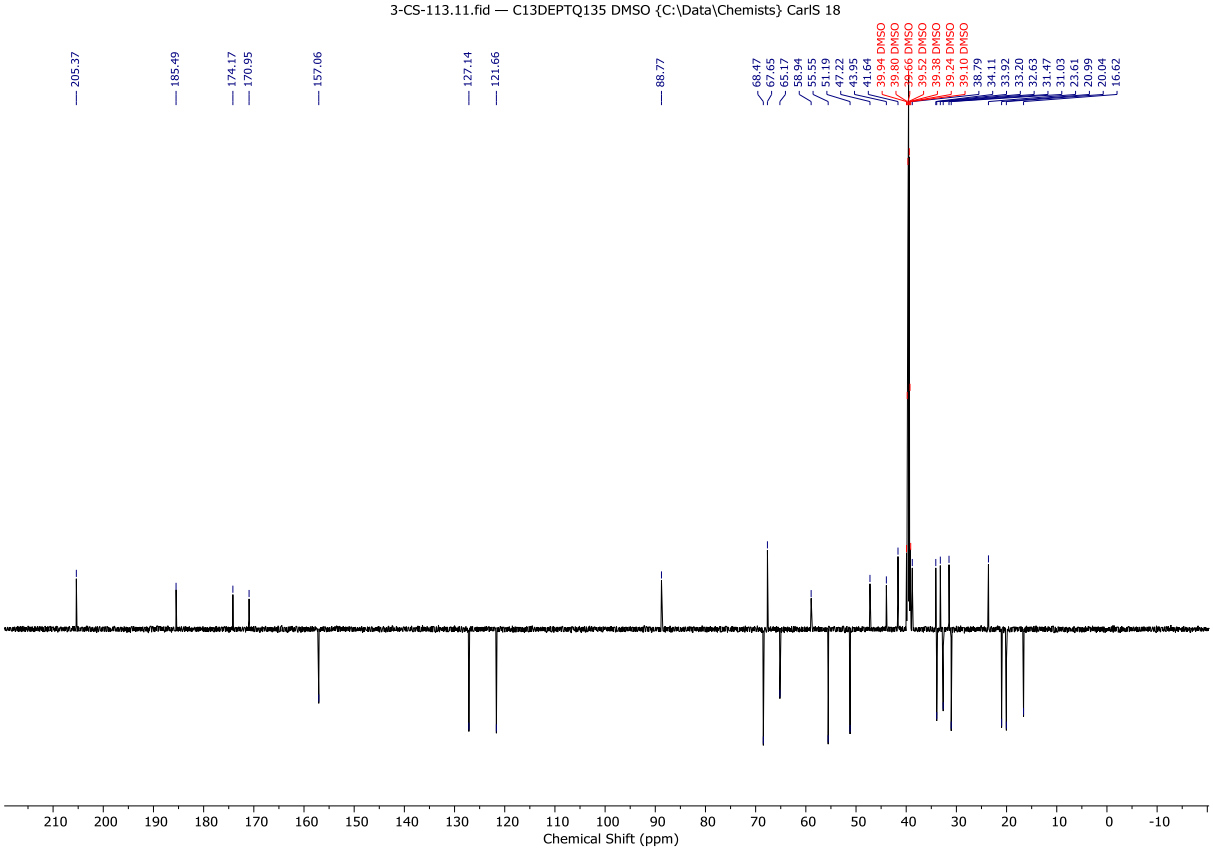
Supplementary Figure 23: ^{1}H NMR (DMSO-d_6, 600 MHz) of **M3**. '*' denotes undefined chirality.



Supplementary Figure 24: ^{13}C DEPTQ135 NMR (DMSO-d_6, 150 MHz) of **M3**. '*' denotes undefined chirality.

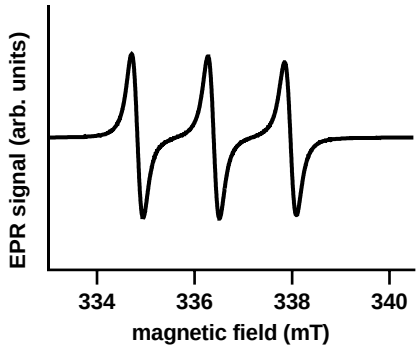


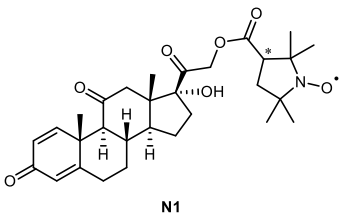
Supplementary Figure 25: ^{1}H NMR (DMSO-d_6, 600 MHz) of **M4**.



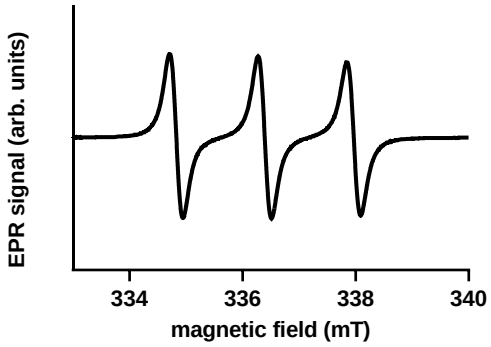
Supplementary Figure 26: ^{13}C DEPTQ135 NMR (DMSO-d_6, 150 MHz) of **M4**.

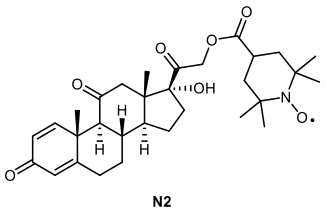
3. EPR Spectra



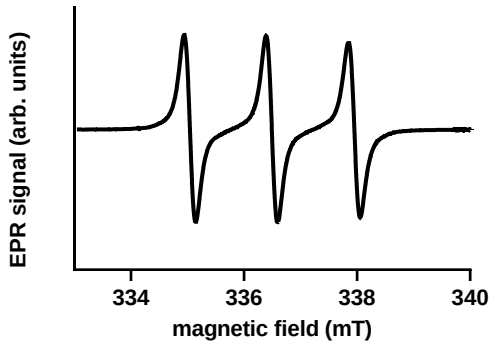


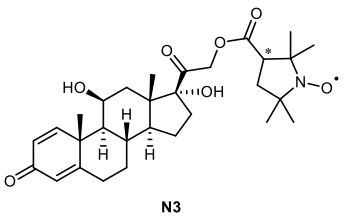
Supplementary Figure 27: EPR (DCM, 0.5 mg/mL) spectrum of **N1**. '*' denotes undefined chirality.



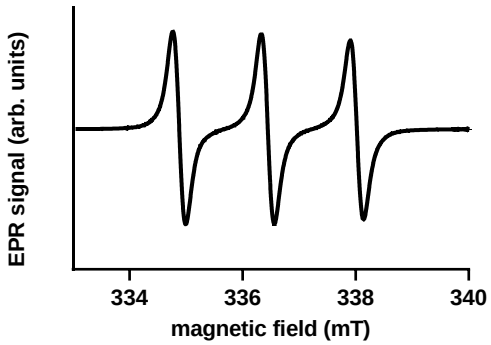


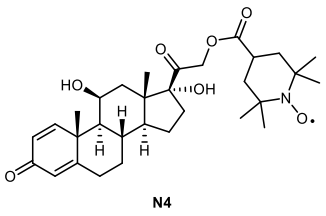
Supplementary Figure 28: EPR (DCM, 0.5 mg/mL) spectrum of **N2**.





Supplementary Figure 29: EPR (DCM, 0.5 mg/mL) spectrum of **N3**. '*' denotes undefined chirality.

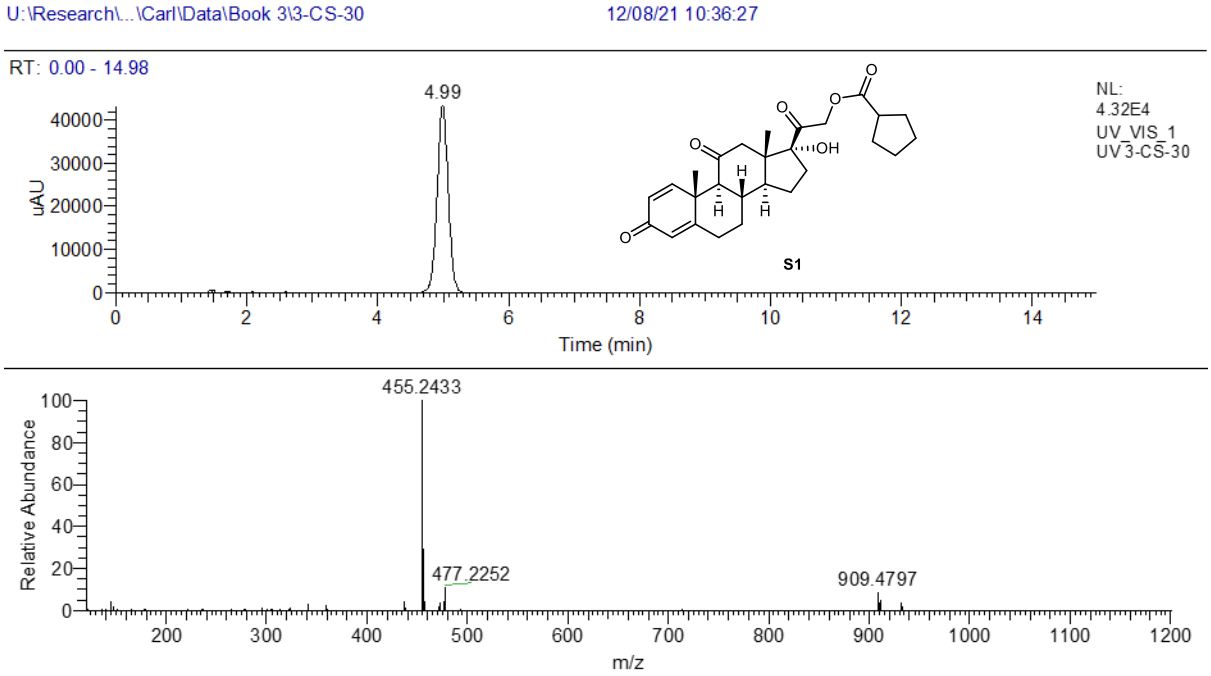




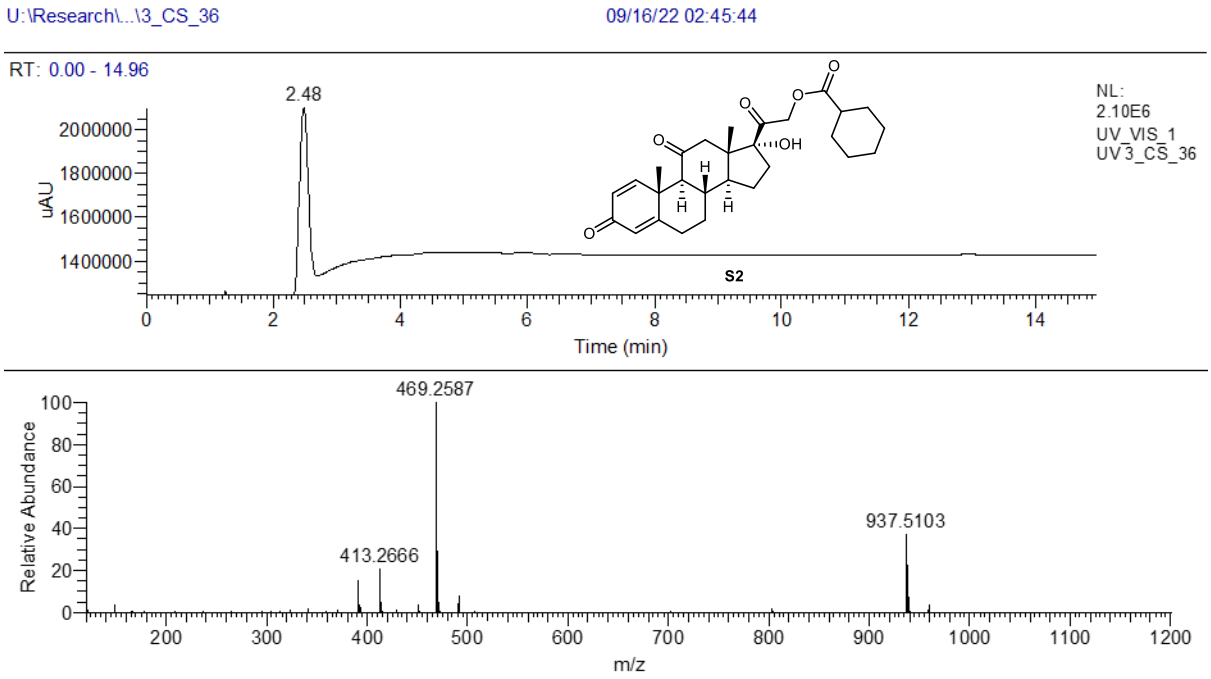
Supplementary Figure 30: EPR (DCM, 0.5 mg/mL) spectrum of **N4**.

4. LC-MS Data

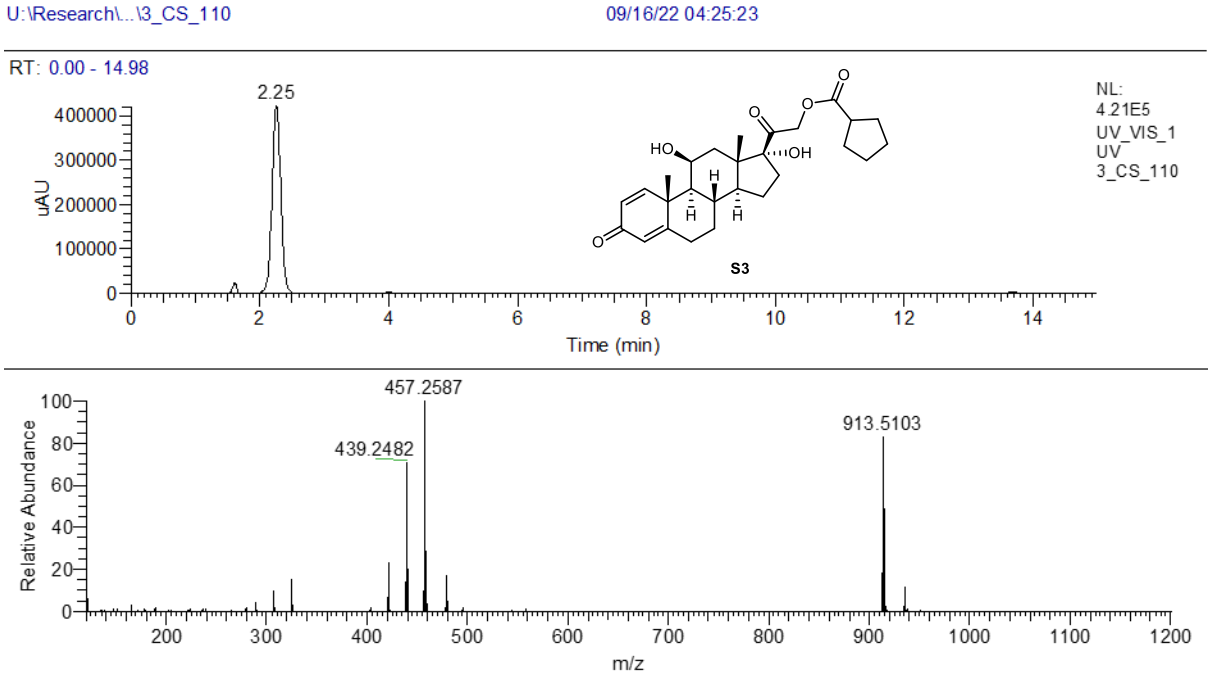
General: LC-MS was performed using an isocratic method of 70% acetonitrile:30% water with a flow rate of 0.8 mL/min at 40 °C measuring UV absorbance at 237 nm. High-resolution mass spectrometry (HRMS) was performed on a Thermo Scientific LTQ Orbitrap XL ETD Hybrid Ion Trap-Orbitrap Mass Spectrometer equipped with a heated electrospray ionization (ESI) source operating in positive ion mode at a mass resolution of 120,000 (at m/z 400). High-performance liquid chromatography (HPLC) was performed on a Thermo Scientific Dionex UltiMate 3000 RSLC using an Agilent Prep-C18 Scalar column (10 µ, 150 × 4.6 mm).



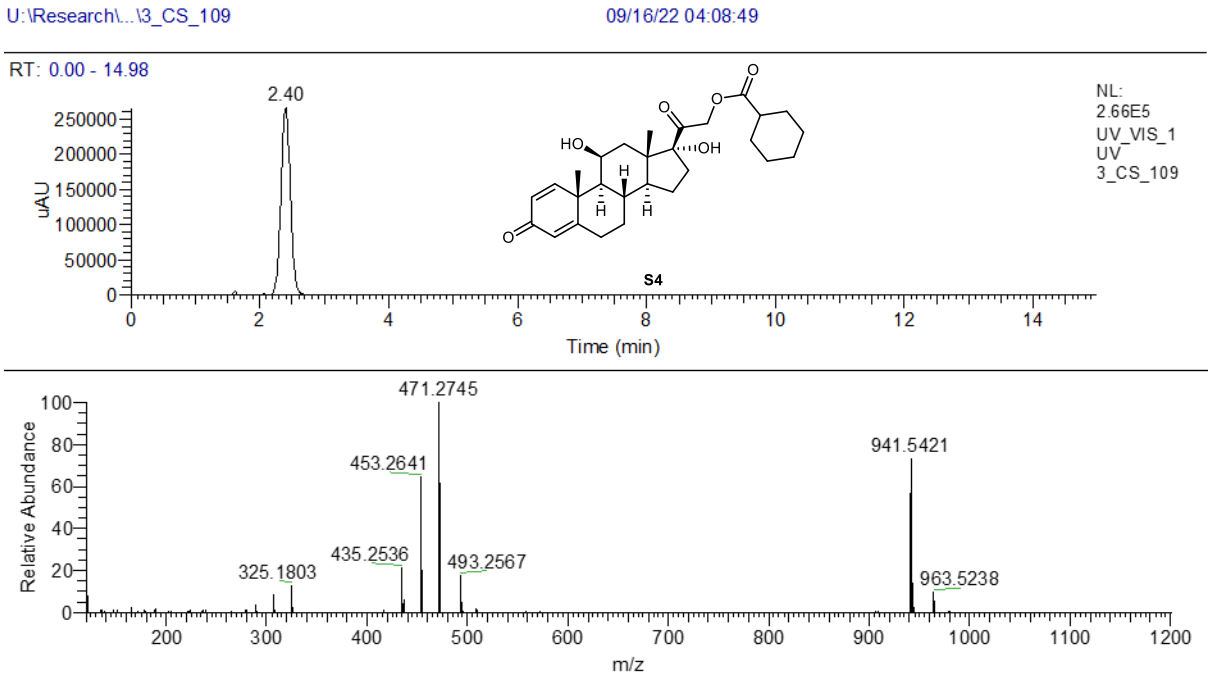
Supplementary Figure 31: LC-MS of **S1**.



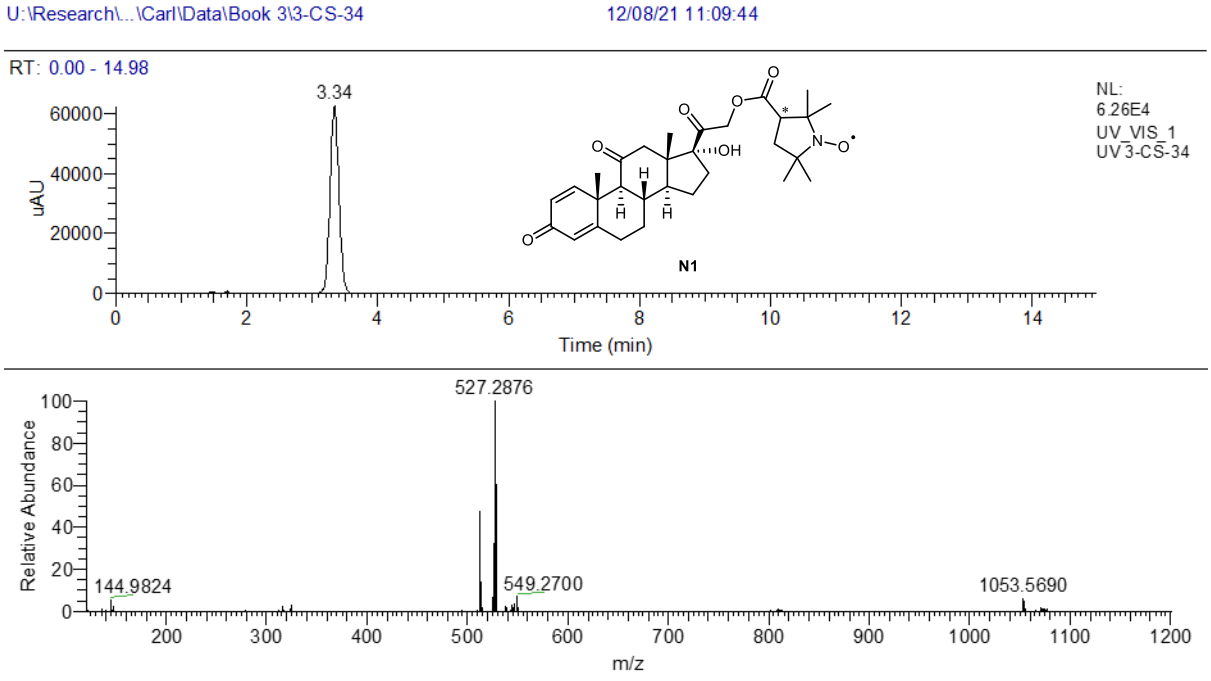
Supplementary Figure 32: LC-MS of **S2**.



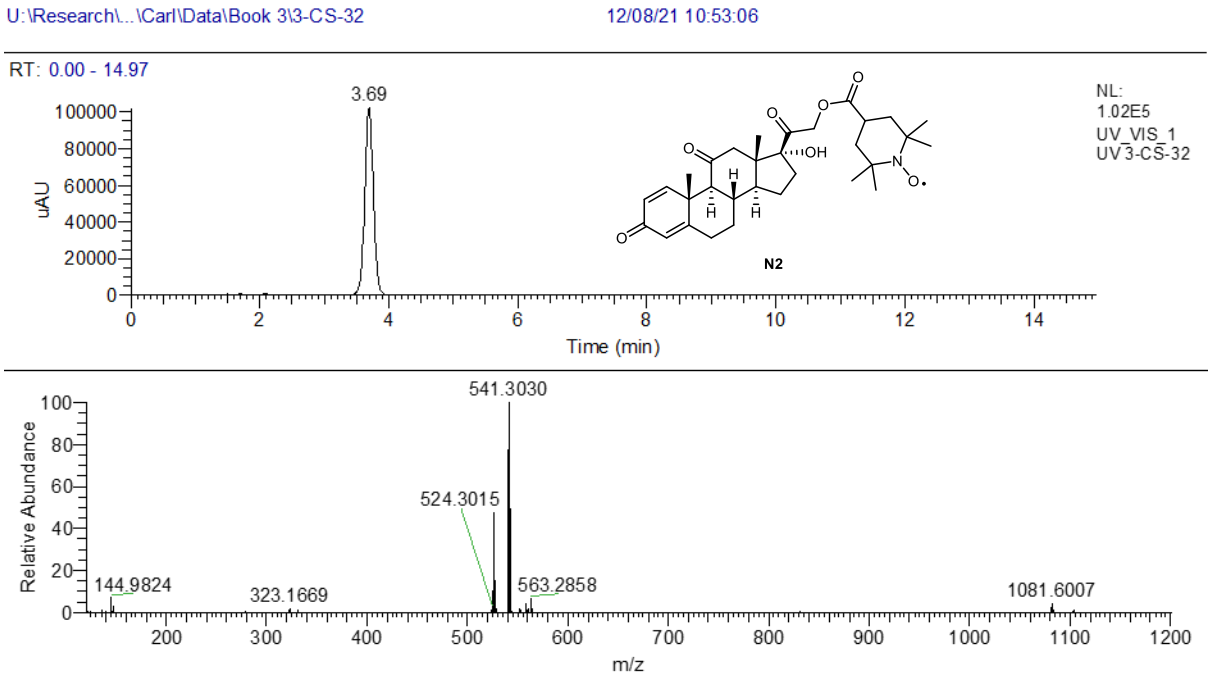
Supplementary Figure 33: LC-MS of **S3**.



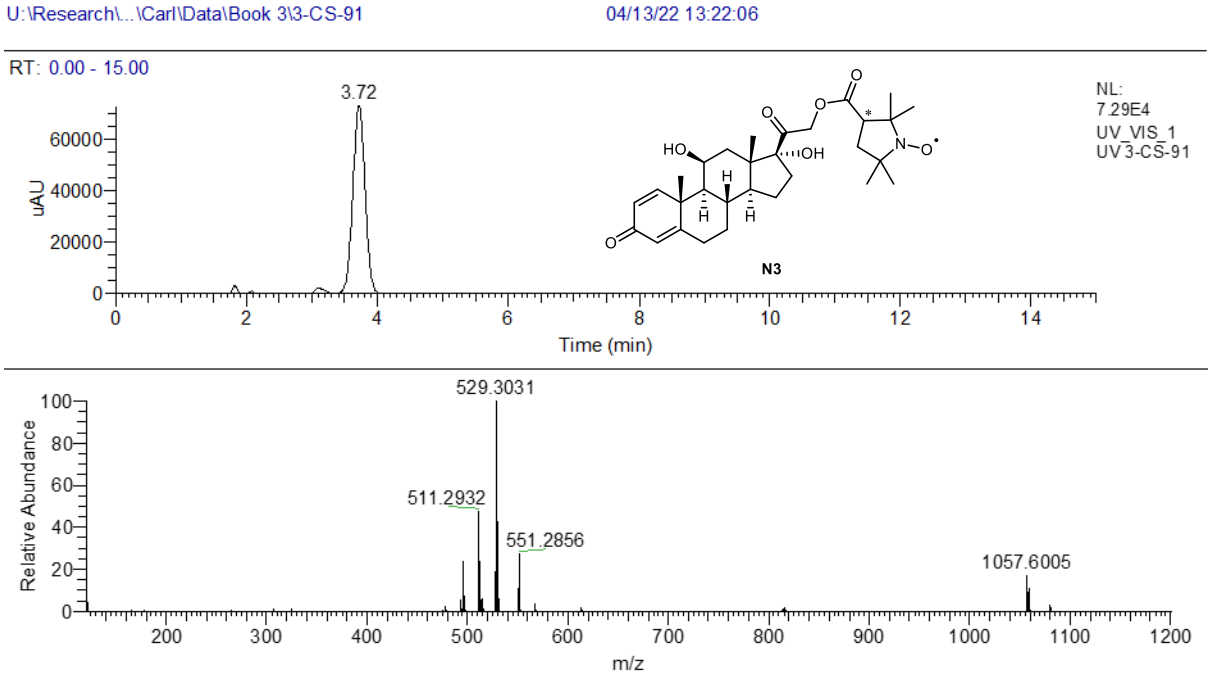
Supplementary Figure 34: LC-MS of **S4**.



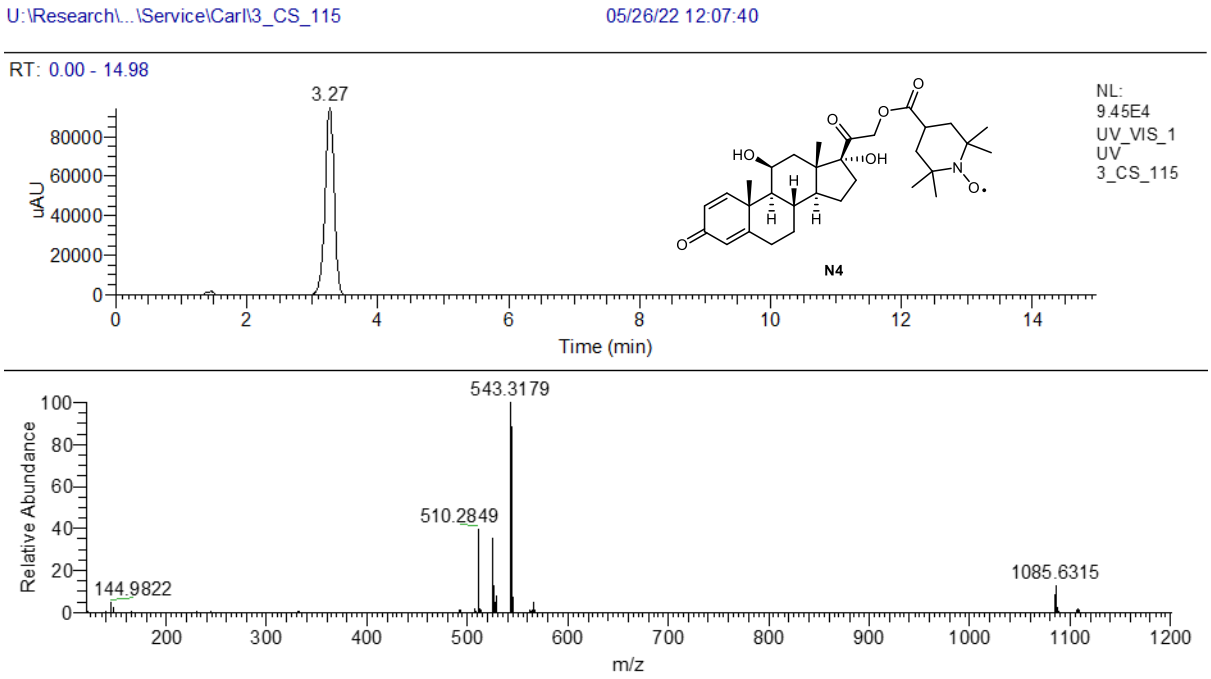
Supplementary Figure 35: LC-MS of **N1**. '*' denotes undefined chirality.



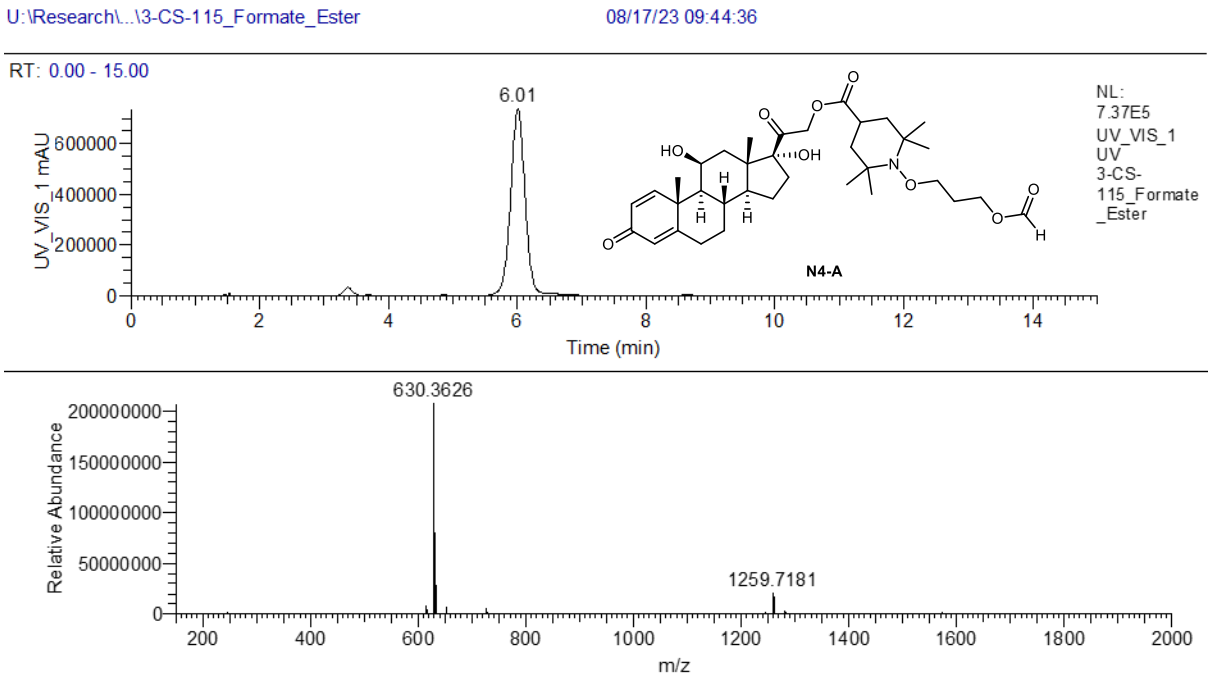
Supplementary Figure 36: LC-MS of **N2**.



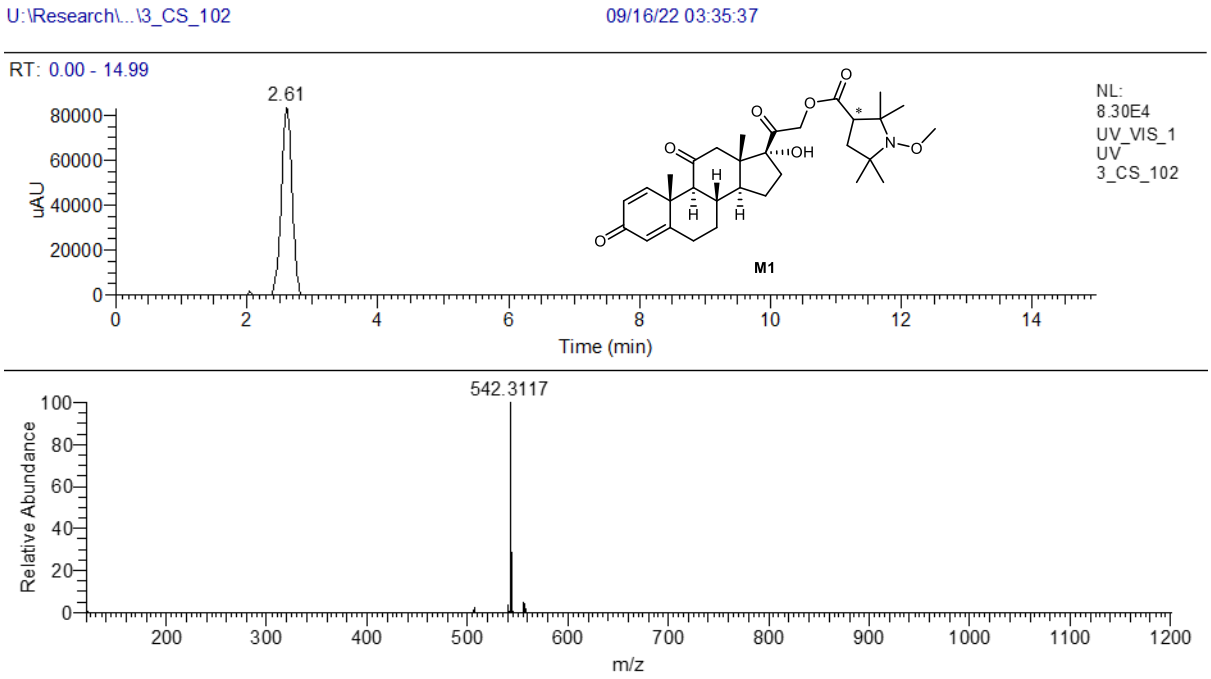
Supplementary Figure 37: LC-MS of **N3**. '*' denotes undefined chirality.



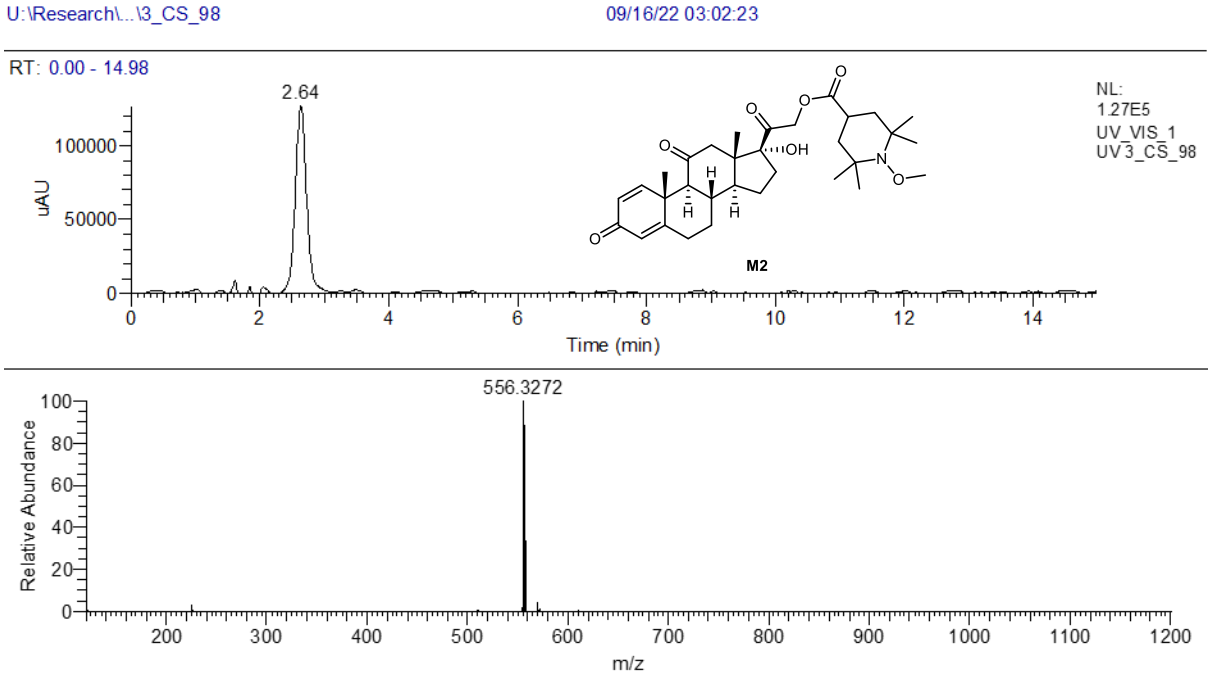
Supplementary Figure 38: LC-MS of **N4**.



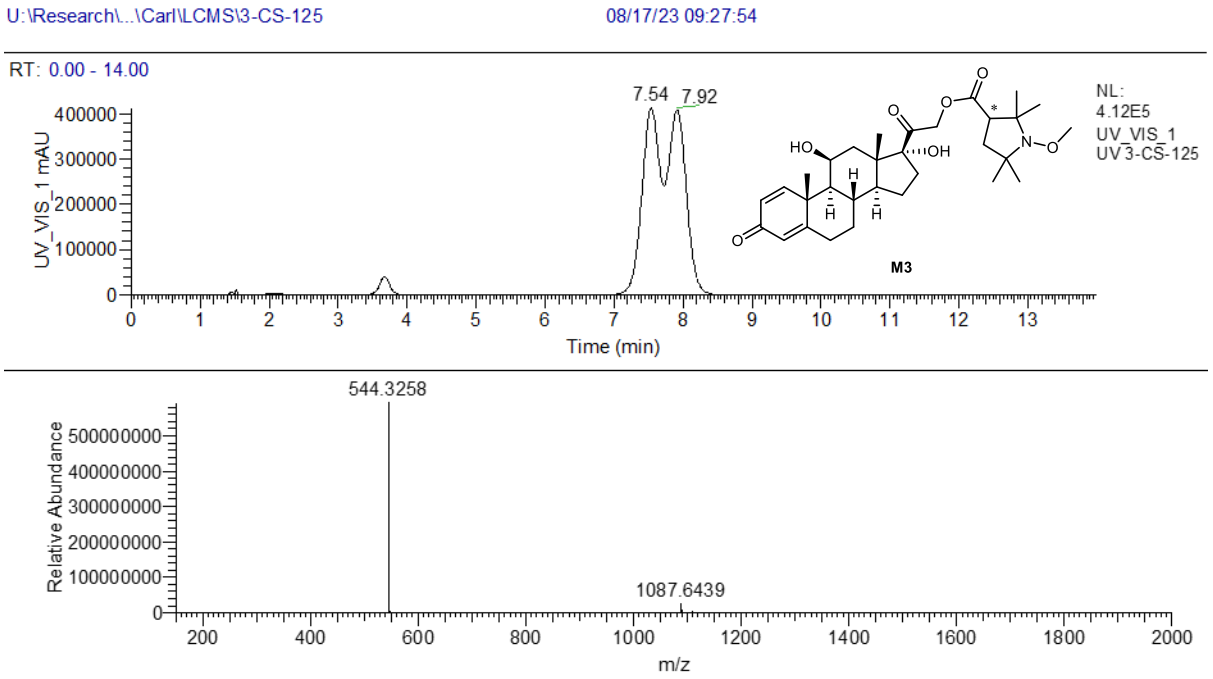
Supplementary Figure 39: LC-MS of **N4-A**.



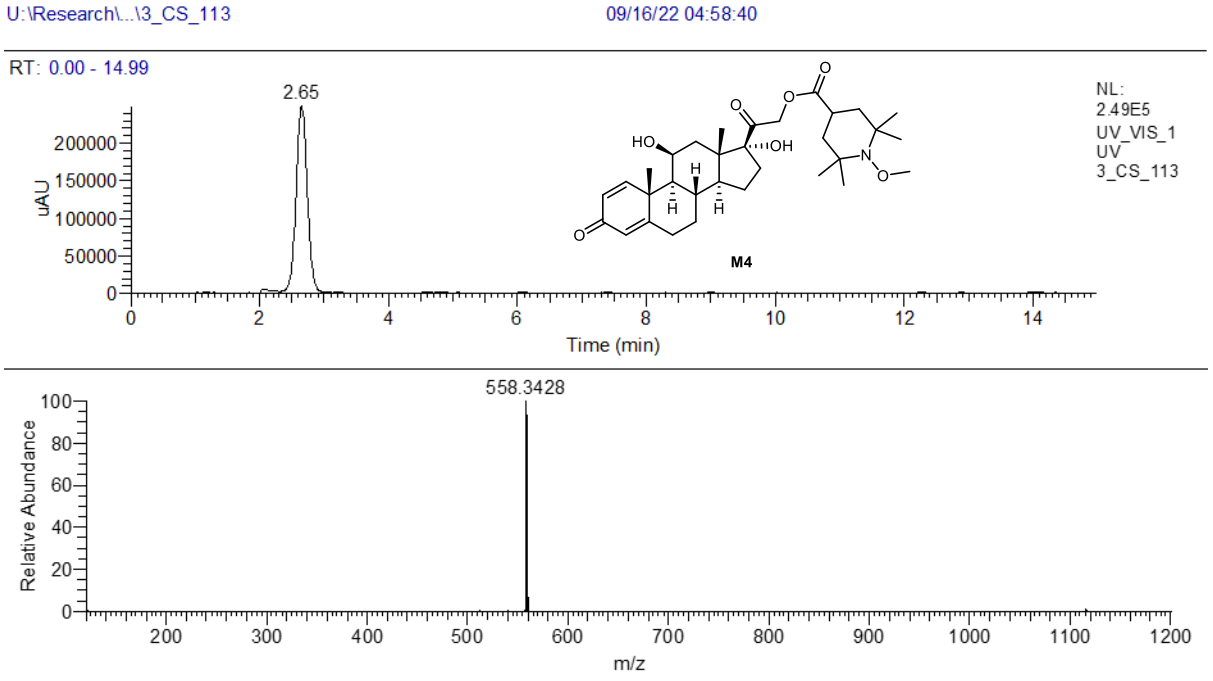
Supplementary Figure 40: LC-MS of **M1**. '*' denotes undefined chirality.



Supplementary Figure 41: LC-MS of **M2**.



Supplementary Figure 42: LC-MS of **M3**. '*' denotes undefined chirality.



Supplementary Figure 43: LC-MS of **M4**.