Microwave-assisted synthesis of pomalidomide building blocks for rapid PROTAC and molecular glue development.

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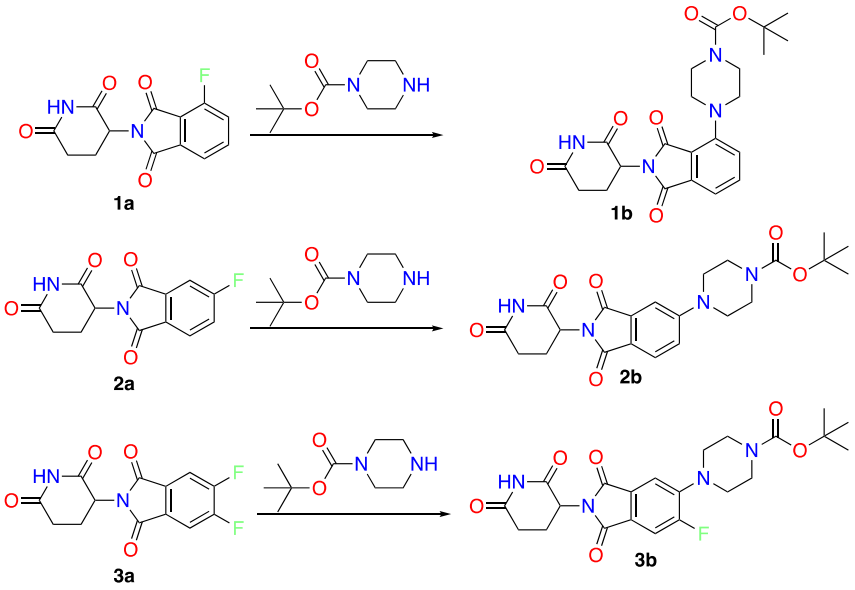
2. General materials and procedures

All reagents were purchased from Combi-blocks and used as received unless otherwise noted. Anhydrous solvents were obtained from Sigma-Aldrich in 100 mL Sure/Seal™ bottles, and were handled using standard inert syringe techniques. All reactions were conducted in anhydrous conditions under nitrogen or argon atmospheres unless otherwise noted. Biotage® Initiator+ (Fourth Generation Microwave Synthesizer) was used in all microwave-assisted syntheses unless otherwise noted. Purification of intermediates and final compounds was carried out using Biotage automated flash chromatography instrumentation (Isolera One and Isolera Prime). Biotage HC Duo cartridges (sizes of 12G, 25G, 50G, and 100G) were prepacked with 40−60 µm silica gel from VWR International (average pore size, 60 Å) and crude mixtures were eluted with the indicated solvent ratios at a rate of 40−100 mL/min depending on cartridge size. Compounds were identified using auto-detection by monitoring the UV absorbance at 254 and 289 nm, and pure fractions were collected. All spectra for this manuscript were collected in DMSO-d6 as the NMR solvent. All ^{1}H and ^{13}C NMR experiments for final compounds were acquired on a 500 MHz Agilent DD2 NMR spectrometer equipped with an Xsens Cold Probe, and all ^{19}F NMR experiments for final compounds were acquired on a 600 MHz Agilent DD2 NMR spectrometer equipped with HFX Probe, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual NMR solvent (^{1}H NMR: DMSO-d_5, δ 2.50; ^{13}C NMR: DMSO-d_5, δ 39.52).

2.1. Optimization of the microwave-assisted synthesis of pomalidomide analogs



Scheme 1: Fluorinated thalidomide substrates investigated in the development of Microwave-assisted pomalidomide synthesis.

2.1.1. Solvent screen

x-Fluorothalidomide (**1a/2a/3a** – 1.0 equiv., 150mg) and amine (1-boc-piperazine – 1.2 equiv.) were added into a VWR 5mL microwave reaction vial equipped with a stir bar. The reaction vessel was capped, evacuated, and

backfilled with nitrogen gas before the appropriate solvent (0.2M) was added (DMF/DMSO/NMP). Finally, diisopropylethylamine (3.0 equiv.) was added to the reaction vessel and the headspace was purged with nitrogen gas to maintain anhydrous inert conditions. The vessel was enclosed in the Biotage® Initiator+ microwave and was heated to 150°C for 1 hour, after which, the vessel was allowed to cool down to room temperature before performing a workup. The reaction mixture was poured into a solution of 0.1M HCl and was extracted 3 times with ethyl acetate. The combined organic layers were washed 2 times with water and once with brine. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product..

2.1.2. Kinetic (microwave reaction time) screen

x-Fluorothalidomide (**1a/2a/3a** – 1.0 equiv., 150mg) and amine (1-boc-piperazine – 1.2 equiv.) were added into a VWR 5mL microwave reaction vial equipped with a stir bar. The reaction vessel was capped then vacuum dried and backfilled with DMSO (0.2M). Finally, diisopropylethylamine (3.0 equiv.) was added to the reaction vessel and the headspace was purged with nitrogen gas to maintain anhydrous inert conditions. The vessel was enclosed in the Biotage® Initiator+ microwave and was heated to 150°C for the appropriate reaction time for the screen. (15min/30min/1 h), after which, the vessel was allowed to cool down to room temperature before performing a workup. The reaction mixture was poured into a solution of 0.1M HCl and was extracted 3 times with ethyl acetate. The combined organic layers were washed 2 times with water and once with brine to ensure removal of any residual reaction solvent. The organic layer was dried over sulfates and the crude product was concentrated under reduced pressure.

2.1.3. Temperature screen

x-Fluorothalidomide (**1a/2a/3a** – 1.0 equiv., 150mg) and amine (1-boc-piperazine – 1.2 equiv.) were added into a VWR 5mL microwave reaction vial equipped with a stir bar. The reaction vessel was capped then vacuum dried and backfilled with DMSO (0.2M). Finally, diisopropylethylamine (3.0 equiv.) was added to the reaction vessel and the headspace was purged with nitrogen gas to maintain anhydrous inert conditions. The vessel was enclosed in the Biotage® Initiator+ microwave and was heated to the appropriate temperature (150°C/180°C/210°C) for the screen for 15 minutes, after which, the vessel was allowed to cool down to room temperature before performing a workup. The reaction mixture was poured into a solution of 0.1M HCl and was extracted 3 times with ethyl acetate. The combined organic layers were washed 2 times with water and once with brine to ensure removal of any residual reaction solvent. The organic layer was dried over sulfates and the crude product was concentrated under reduced pressure.

2.1.4. Optimized procedures for the synthesis of palmolidomide analogues

2.1.4.1. Optimized microwave-assisted synthesis procedure 1 (method A)

This synthesis procedure was used for all substrate scope experiments and the gram scale experiments:

x-Fluorothalidomide (**1a** – 1.0 equiv.) and amine (1.2 equiv.) were added into a VWR 5mL microwave reaction vial equipped with a stir bar. The reaction vessel was capped then vacuum dried and backfilled with DMSO (0.2M).

Finally, diisopropylethylamine (3.0 equiv.) was added to the reaction vessel and the headspace was purged with nitrogen gas to maintain anhydrous inert conditions. The vessel was enclosed in the Biotage® Initiator+ microwave and was heated to 150°C for 15 minutes, after which, the vessel was allowed to cool down to room temperature before performing a workup. The reaction mixture was poured into a solution of 0.1M HCl and was extracted 3 times with ethyl acetate. The combined organic layers were washed 2 times with water and once with brine to ensure removal of any residual reaction solvent. The organic layer was dried over sulfates and the crude product was concentrated under reduced pressure.

2.1.4.2. Optimized microwave-assisted synthesis procedure 2 (method B)

This synthesis procedure was used for the gram scale experiments:

x-Fluorothalidomide (**1a** – 1.0 equiv.) and amine (1.2 equiv.) were added into a VWR 5mL microwave reaction vial equipped with a stir bar. The reaction vessel was capped then vacuum dried and backfilled with NMP (0.2M). Finally, diisopropylethylamine (3.0 equiv.) was added to the reaction vessel and the headspace was purged with nitrogen gas to maintain anhydrous inert conditions. The vessel was enclosed in the Biotage® Initiator+ microwave and was heated to 150°C for 30 minutes, after which, the vessel was allowed to cool down to room temperature before performing a workup. The reaction mixture was poured into a solution of 0.1M HCl and was extracted 3 times with ethyl acetate. The combined organic layers were washed 2 times with water and once with brine to ensure removal of any residual reaction solvent. The organic layer was dried over sulfates and the crude product was concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluting with the indicated solvent system to afford the pure product.

2.1.4.3. General procedure for oil bath synthesis of pomalidomide analogs (traditional procedure – method C)

This synthesis procedure was used the gram scale experiments:

x-Fluorothalidomide (**1a** – 1.0 equiv.) and amine (1.2 equiv.) were added into a 50-mL round bottom flask equipped with a stir bar. The reaction vessel was capped then vacuum dried and backfilled with DMSO (0.2M). Finally, diisopropylethylamine (3.0 equiv.) was added to the reaction vessel and the headspace was purged with nitrogen gas to maintain anhydrous inert conditions. The vessel was in an oil bath and was heated to 90°C for the screen for 16 hours, after which, the vessel was allowed to cool down to room temperature before performing a workup. The reaction mixture was poured into a solution of 0.1M HCl and was extracted 3 times with ethyl acetate. The combined organic layers were washed 2 times with water and once with brine to ensure removal of any residual reaction solvent. The organic layer was dried over sulfates and the crude product was concentrated under reduced pressure.

2.1.4.4. General procedure for oil bath synthesis of pomalidomide analogs (traditional procedure – method D)

This synthesis procedure was used the gram scale experiments:

x-Fluorothalidomide (**1a** – 1.0 equiv.) and amine (1.2 equiv.) were added into a 50-mL round bottom flask equipped with a stir bar. The reaction vessel was capped then vacuum dried and backfilled with DMSO (0.2M). Finally, diisopropylethylamine (3.0 equiv.) was added to the reaction vessel and the headspace was purged with nitrogen gas to maintain anhydrous inert conditions. The vessel was in an oil bath and was heated to 150°C for the screen for 16 hours, after which, the vessel was allowed to cool down to room temperature before performing a workup. The reaction mixture was poured into a solution of 0.1M HCl and was extracted 3 times with ethyl acetate. The combined organic layers were washed 2 times with water and once with brine to ensure removal of any residual reaction solvent. The organic layer was dried over sulfates and the crude product was concentrated under reduced pressure.

2.2. NMR sample preparation and general experimental procedure

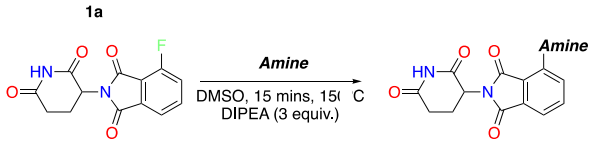
All NMR samples for "crude purity" and yield determinations from the screens and substrate scope were prepared by dissolving 5.0 mg (0.030 mmol) of 1,3,5-trimethoxybenzene (NMR standard) and a theoretical equimolar amount of the crude isolate (ie. if the crude mixture were assumed to contain 100% pure product) in 500μL of DMSO-d6. The purity of the crude material can then be determined by the ratio product:1,3,5-trimethoxybenzene, and a ratio of 1 = 100% crude purity. The yield can than be determined based on the crude recovery mass and the NMR purity (from abobe) used the following equation:

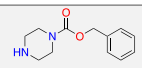
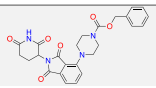
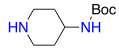
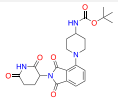
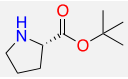
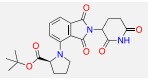
$$Final\ product\ yield\ \% = Amount\ of\ crude\ material\ x\ NMR\ purity\ of\ crude\ sample$$

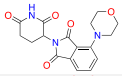
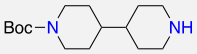
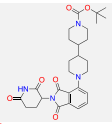
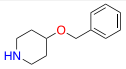
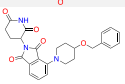
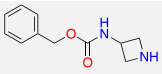
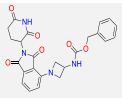
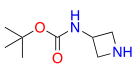
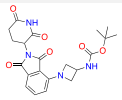
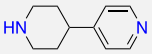
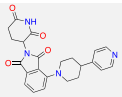
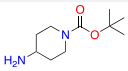
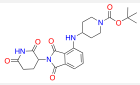
^{1}H NMR spectra of reactions from the solvent, kinetic, and temperature screens, as well as substrate scope product were acquired on 500 MHz Varian Unity-Inova spectrometer equipped with Varian 5-mm direct detect broadband probe and the product peaks were integrated against the normalized 1,3,5-trimethoxybenzene signals to determine yield of the product. Quantitative 1D NMRs were set up using 10 s relaxation delay, 4.5 s acquisition time, 60 degree excitation angle, 16 scans, and 16 ppm spectral window centered at 6 ppm.

3. Substrate Scope

Table S1: *Summary of amine substrates appended onto* ***1a*** *using the optimized MAS method. Yields were measured by NMR using the internal NMR standard 1,3,5-trimethoxybenzene.*



Entry	Amine	Product	Yield (%)
1c			93
1d			98
1e			70

1f			66
1g			63
1h			83
1i			84
1j			69
1k			77
1l			67
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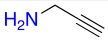
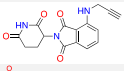
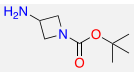
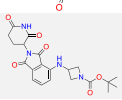
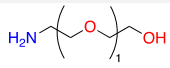
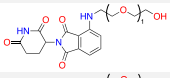
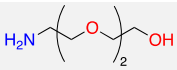
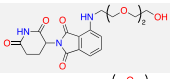
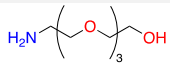
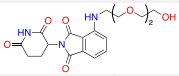
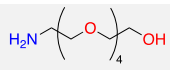
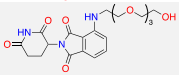
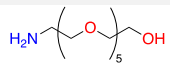
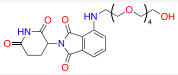
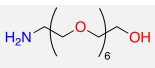
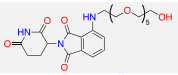
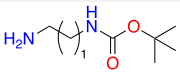
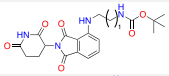
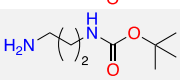
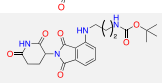
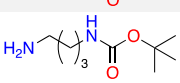
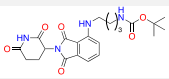
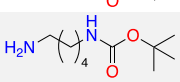
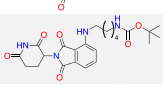
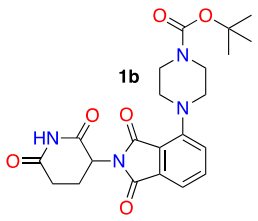
1n			60
1o			64
1p			51
1q			80
1r			57
1s			81
1t			96
1u			76
1v			41
1w			60
1x			76
1y			70
1z			69

4. Characterization of final compounds

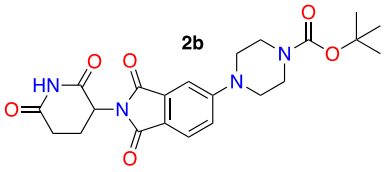
All ^{1}H and ^{13}C NMR experiments for final compounds were acquired on a 500 MHz Agilent DD2 NMR spectrometer equipped with an Xsens Cold Probe, and all ^{19}F NMR experiments for final compounds were acquired on a 600 MHz Agilent DD2 NMR spectrometer equipped with HFX Probe, unless otherwise noted. Only final compounds were purified via silica gel chromatography using a Biotage Isolera. This resulted in residual ethyl acetate in some spectra, which is labelled on the ^{1}H NMR.

4.1. Compound characterization

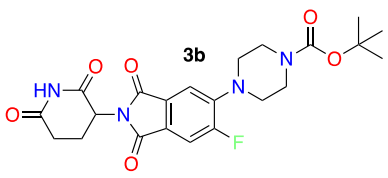
An analytically pure sample of the respective compounds was obtained by flash chromatography – the NMR data reported below originated from the purified materials.



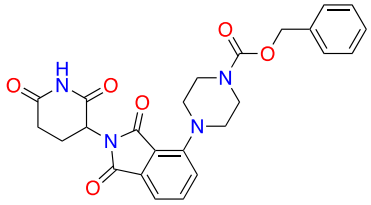
***tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)piperazine-1-carboxylate (1b)** was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (500 MHz, dmso) δ 11.08 (s, 1H), 7.69 (dd, *J* = 8.4, 7.1 Hz, 1H), 7.37 (d, *J* = 7.1 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 5.09 (dd, *J* = 12.7, 5.5 Hz, 1H), 3.49 (t, *J* = 5.0 Hz, 4H), 3.23 (t, *J* = 5.0 Hz, 4H), 2.86 (ddd, *J* = 16.7, 13.7, 5.4 Hz, 1H), 2.62 – 2.49 (m, 2H), 2.07 – 1.95 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (126 MHz, dmso) δ 173.2, 167.4, 166.8, 154.3, 150.0, 136.4, 134.0, 124.3, 117.4, 115.7, 79.5, 50.8, 49.3, 31.4, 28.5, 22.5. TOF MS ESI+ calcd for $C_{22}H_{27}N_4O_6^+$ $[M + H]^+$, 443.1925; found, 443.1956.



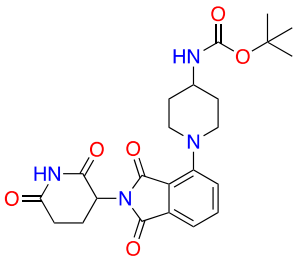
***tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazine-1-carboxylate (2b)** was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (500 MHz, dmso) δ 11.06 (s, 1H), 7.73 – 7.64 (m, 1H), 7.31 (d, *J* = 2.3 Hz, 1H), 7.21 (dd, *J* = 8.6, 2.4 Hz, 1H), 5.06 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.49 – 3.40 (m, 8H), 2.93 – 2.81 (m, 1H), 2.63 – 2.46 (m, 2H), 2.06 – 1.97 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (126 MHz, dmso) δ 173.2, 168.0, 167.4, 155.4, 154.3, 134.3, 125.3, 119.0, 118.3, 108.5, 79.6, 49.2, 47.0, 46.3, 31.4, 31.4, 28.5, 22.6. TOF MS ESI+ calcd for $C_{22}H_{27}N_4O_6^+$ $[M + H]^+$, 443.1925; found, 443.1956.



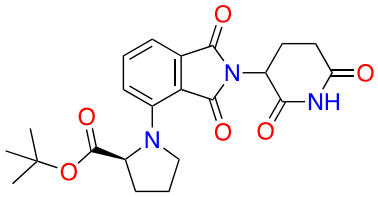
***tert*-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1,3-dioxoisoindolin-5-yl)piperazine-1-carboxylate (3b)** was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (500 MHz, dmso) δ 11.09 (s, 1H), 7.73 (d, *J* = 11.1 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 5.09 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.47 (t, *J* = 5.1 Hz, 4H), 3.19 (t, *J* = 5.0 Hz, 4H), 2.87 (ddd, *J* = 16.9, 13.8, 5.4 Hz, 1H), 2.62 – 2.49 (m, 2H), 2.06 – 1.97 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (126 MHz, dmso) δ 173.2, 167.0, 166.6, 156.9, 154.2, 145.7, 145.7, 129.1, 124.4, 114.6, 112.5, 79.6, 49.8, 49.5, 31.4, 28.5, 22.5. TOF MS ESI+ calcd for $C_{22}H_{26}FN_4O_6^+$ [M + H]$^+$, 461.1831; found, 461.1833.



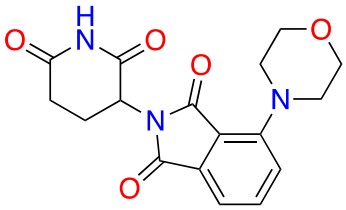
benzyl 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)piperazine-1-carboxylate (1c) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.8 (dd, J = 8.4, 7.2 Hz, 1H), 7.5 – 7.4 (m, 6H), 7.4 – 7.3 (m, 1H), 5.2 (s, 2H), 5.2 – 5.1 (m, 1H), 3.6 (s, 4H), 3.3 (t, J = 5.1 Hz, 4H), 2.9 (ddd, J = 17.4, 14.1, 5.5 Hz, 1H), 2.7 – 2.5 (m, 2H), 2.1 – 2.0 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.4, 167.5, 166.8, 154.9, 150.0, 137.3, 136.4, 134.1, 128.9, 128.3, 128.0, 124.4, 117.5, 115.8, 66.8, 60.2, 50.8, 49.3, 43.9, 31.4, 22.5, 21.2, 14.6. TOF MS ESI+ calcd for $C_{25}H_{25}N_4O_6^+$ [M + H]$^+$, 477.1769; found, 477.1831.



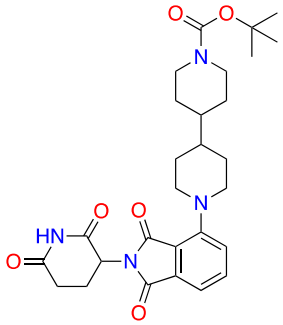
***tert*-butyl (1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)piperidin-4-yl)carbamate (1d)** was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.7 – 7.6 (m, 1H), 7.3 (d, J = 7.4 Hz, 2H), 6.9 (d, J = 7.8 Hz, 1H), 5.1 (dd, J = 12.9, 5.4 Hz, 1H), 3.7 (d, J = 12.1 Hz, 2H), 3.5 – 3.4 (m, 1H), 3.0 – 2.8 (m, 3H), 2.7 – 2.5 (m, 2H), 2.0 (ddq, J = 7.6, 5.5, 3.3 Hz, 1H), 1.8 (d, J = 12.2 Hz, 2H), 1.7 – 1.5 (m, 2H), 1.4 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.5, 167.5, 166.8, 155.4, 150.4, 136.2, 134.1, 124.4, 116.9, 115.0, 78.0, 50.4, 49.3, 47.5, 32.2, 31.4, 28.8, 22.5. TOF MS ESI+ calcd for $C_{23}H_{29}N_4O_6^+$ [M + H]$^+$, 457.2082; found, 457.2140.



***tert*-butyl (2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-*L*-prolinate (1e)** was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (d, J = 3.9 Hz, 1H), 7.7 – 7.5 (m, 1H), 7.2 – 7.0 (m, 2H), 5.1 (ddd, J = 22.7, 7.8, 4.7 Hz, 1H), 5.1 – 5.0 (m, 1H), 4.0 (q, J = 7.1 Hz, 0H), 3.7 – 3.5 (m, 2H), 3.5 (s, 1H), 3.0 – 2.8 (m, 1H), 2.7 – 2.4 (m, 2H), 2.4 – 2.3 (m, 1H), 2.1 – 1.9 (m, 4H), 1.3 (d, J = 6.4 Hz, 7H), 1.2 (t, J = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 173.3, 173.2, 171.9, 171.8, 170.8, 170.6, 170.4, 170.3, 170.1, 167.6, 167.5, 167.4, 167.2, 167.1, 167.0, 146.5, 145.8, 145.8, 135.5, 135.5, 135.2, 134.4, 134.1, 122.8, 122.7, 121.7, 112.6, 111.7, 111.4, 111.3, 110.4, 81.0, 80.9, 63.6, 63.5, 60.2, 51.8, 51.6, 49.6, 49.2, 31.4, 30.9, 30.8, 27.9, 27.9, 25.7, 23.7, 23.7, 22.6, 22.6, 22.3, 21.2, 14.6. TOF MS ESI+ calcd for $C_{22}H_{26}N_3O_6^+$ $[M + H]^+$, 428.1816; found, 428.1833.

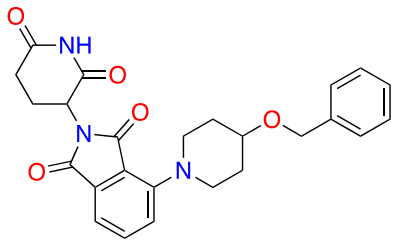


2-(2,6-dioxopiperidin-3-yl)-4-morpholinoisoindoline-1,3-dione (1f) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.7 (dd, J = 8.4, 7.1 Hz, 1H), 7.4 – 7.3 (m, 2H), 5.1 (dd, J = 12.9, 5.4 Hz, 1H), 3.8 (dd, J = 5.7, 3.5 Hz, 4H), 3.3 (t, J = 4.6 Hz, 4H), 2.9 (ddd, J = 17.4, 14.0, 5.4 Hz, 1H), 2.6 – 2.5 (m, 2H), 2.0 (dtd, J = 13.2, 6.0, 3.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.4, 167.5, 166.8, 150.2, 136.4, 134.1, 124.0, 117.2, 115.6, 66.6, 51.3, 49.3, 31.4, 22.5. TOF MS ESI+ calcd for $C_{17}H_{18}N_3O_5^+$ $[M + H]^+$, 344.1241; found, 344.1031.

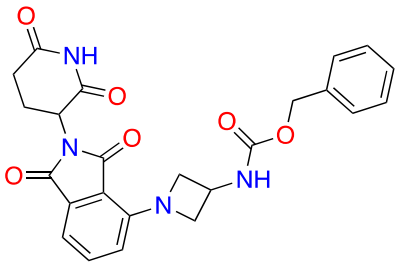


***tert*-butyl 1'-(2-(2,4-dioxocyclohexyl)-1,3-dioxoisoindolin-4-yl)-[4,4'-bipiperidine]-1-carboxylate (1g)** was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.7 (t, J = 7.8 Hz, 1H), 7.3 (d, J = 7.7 Hz, 2H), 5.1 (dd, J = 12.9, 5.4 Hz, 1H), 4.0 (dd, J = 21.3, 9.9 Hz, 2H), 3.7 (d, J = 11.7 Hz, 2H), 3.0 – 2.8 (m, 3H), 2.7 – 2.5 (m, 4H), 2.1 – 2.0 (m,

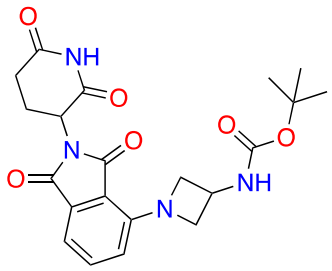
1H), 1.8 (d, J = 12.2 Hz, 2H), 1.7 (d, J = 12.4 Hz, 2H), 1.4 (s, 9H), 1.4 (s, 1H), 1.3 – 1.1 (m, 3H), 1.1 – 1.0 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.5, 167.6, 166.8, 154.3, 150.6, 136.2, 134.1, 124.3, 116.8, 114.9, 78.9, 60.2, 51.8, 49.2, 40.8, 31.4, 29.4, 29.3, 28.6, 22.6. TOF MS ESI+ calcd for $C_{28}H_{37}N_4O_6^+$ [M + H]$^+$, 525.2708; found, 525.2750.



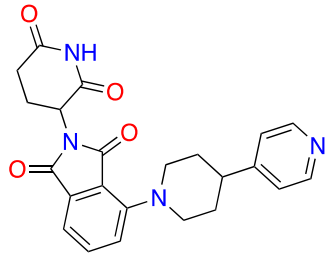
4-(4-(benzyloxy)piperidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (1h) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.7 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.4 – 7.4 (m, 6H), 7.4 – 7.3 (m, 1H), 5.1 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.6 (s, 2H), 3.7 (tt, *J* = 7.9, 3.7 Hz, 1H), 3.6 (dt, *J* = 11.2, 4.6 Hz, 2H), 3.1 (ddd, *J* = 12.1, 8.8, 3.1 Hz, 2H), 2.9 (ddd, *J* = 17.2, 14.0, 5.5 Hz, 1H), 2.7 – 2.6 (m, 2H), 2.6 – 2.5 (m, 1H), 2.1 – 2.0 (m, 2H), 1.8 (dtt, *J* = 12.2, 8.1, 3.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.5, 167.6, 166.8, 150.3, 139.5, 136.2, 134.1, 128.7, 127.9, 127.7, 124.4, 116.9, 115.0, 73.5, 69.4, 60.2, 49.3, 48.9, 48.9, 31.4, 22.6, 21.2, 14.6. TOF MS ESI+ calcd for $C_{25}H_{26}N_3O_5^+$ [M + H]$^+$, 449.1940; found, 449.1966.



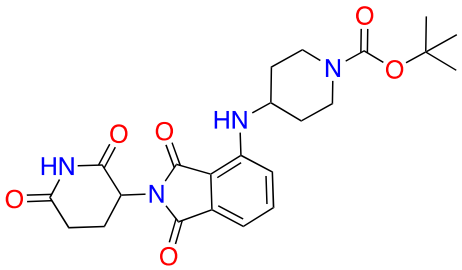
benzyl (1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)azetidin-3-yl)carbamate (1i) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 8.0 (d, J = 6.1 Hz, 1H), 7.6 (dd, J = 8.5, 7.0 Hz, 1H), 7.4 – 7.3 (m, 5H), 7.1 (dd, J = 7.1, 0.7 Hz, 1H), 6.8 (d, J = 8.5 Hz, 1H), 5.1 – 5.0 (m, 1H), 4.5 – 4.4 (m, 4H), 4.0 – 4.0 (m, 2H), 2.9 (ddd, J = 17.3, 14.1, 5.4 Hz, 1H), 2.6 – 2.5 (m, 2H), 2.0 (td, J = 6.0, 3.4 Hz, 1H), 1.2 (t, J = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.5, 167.7, 167.0, 156.0, 148.1, 137.4, 135.5, 133.7, 128.9, 128.3, 120.6, 112.4, 110.8, 66.0, 61.2, 60.2, 49.1, 41.5, 31.4, 22.6, 21.2, 14.6. TOF MS ESI+ calcd for $C_{24}H_{23}N_4O_6^+$ [M + H]$^+$, 463.1612; found, 463.1678.



tert-butyl (1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)azetidin-3-yl)carbamate (1j) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.6 (dt, *J* = 8.5, 5.5 Hz, 2H), 7.2 (dd, *J* = 7.0, 0.7 Hz, 1H), 6.9 – 6.8 (m, 1H), 5.1 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.5 (t, *J* = 8.2 Hz, 2H), 4.4 – 4.4 (m, 1H), 4.0 (dd, *J* = 8.7, 5.1 Hz, 2H), 2.9 (ddt, *J* = 17.4, 14.4, 4.6 Hz, 1H), 2.7 – 2.6 (m, 2H), 2.1 – 2.0 (m, 1H), 1.4 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 173.2, 170.5, 170.1, 167.7, 166.9, 155.4, 148.1, 135.4, 133.7, 120.6, 112.3, 110.7, 78.7, 61.2, 60.2, 49.6, 49.1, 41.0, 31.4, 31.4, 28.6, 22.6, 21.2, 14.6. TOF MS ESI+ calcd for $C_{21}H_{26}N_4O_6^+$ [M + H]$^+$, 430.1841; found, 430.1805.

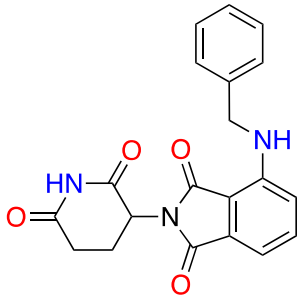


2-(2,6-dioxopiperidin-3-yl)-4-(4-(pyridin-4-yl)piperidin-1-yl)isoindoline-1,3-dione (1k) was synthesized using OP1. *Note: the 1 M HCl wash was excluded from thr work-up procedure in this case. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 8.5 (d, *J* = 5.1 Hz, 2H), 7.7 (dd, *J* = 8.4, 7.1 Hz, 1H), 7.4 – 7.3 (m, 3H), 7.3 (d, *J* = 1.6 Hz, 1H), 5.1 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.8 (d, *J* = 11.9 Hz, 2H), 3.0 (td, *J* = 11.6, 2.9 Hz, 2H), 3.0 – 2.7 (m, 2H), 2.7 – 2.5 (m, 2H), 2.1 (dtd, *J* = 12.9, 6.7, 4.0 Hz, 1H), 2.0 – 1.9 (m, 2H), 1.9 – 1.8 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.5, 167.6, 166.8, 154.9, 150.5, 150.1, 136.3, 134.1, 124.5, 122.9, 117.0, 115.1, 51.7, 49.3, 40.8, 32.5, 31.4, 22.6. TOF MS ESI+ calcd for $C_{23}H_{23}N_4O_4^+$ [M + H]$^+$, 419.1714; found, 419.2138.

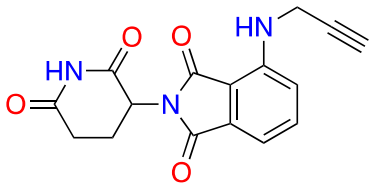


tert-butyl 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)piperidine-1-carboxylate (1l) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.6 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.2 (d, *J* = 8.6 Hz, 1H), 7.1 (d, *J* = 7.0

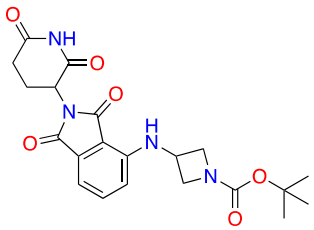
Hz, 1H), 6.3 (d, *J* = 8.3 Hz, 1H), 5.1 (dd, *J* = 12.8, 5.4 Hz, 1H), 3.9 (d, *J* = 13.2 Hz, 2H), 3.8 (tt, *J* = 8.1, 5.5 Hz, 1H), 2.9 (ddt, *J* = 17.1, 14.0, 5.6 Hz, 1H), 2.7 – 2.5 (m, 2H), 2.5 (dt, *J* = 3.7, 1.8 Hz, 1H), 2.1 – 2.0 (m, 1H), 2.0 – 1.9 (m, 2H), 1.4 (s, 11H), 1.4 – 1.3 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 173.2, 170.5, 170.1, 169.5, 167.7, 154.3, 145.8, 136.8, 132.7, 118.2, 111.3, 109.8, 79.2, 60.2, 49.6, 49.0, 49.0, 31.9, 31.4, 31.4, 28.5, 22.6, 22.3, 21.2, 14.6. TOF MS ESI+ calcd for $C_{23}H_{29}N_4O_6^+$ $[M + H]^+$, 457.2082; found, 357.1603.



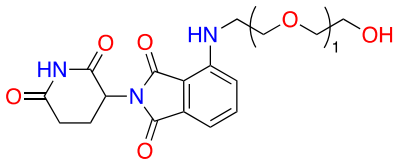
4-(benzylamino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (1m) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.5 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.4 – 7.3 (m, 4H), 7.3 – 7.2 (m, 2H), 7.1 – 7.0 (m, 1H), 7.0 (d, *J* = 8.4 Hz, 1H), 5.1 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.6 (d, *J* = 6.2 Hz, 2H), 2.9 (ddd, *J* = 17.3, 14.0, 5.4 Hz, 1H), 2.7 – 2.5 (m, 2H), 2.1 – 2.0 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.6, 169.3, 167.8, 146.6, 139.4, 136.6, 132.7, 129.0, 127.5, 127.4, 118.1, 111.2, 110.0, 60.2, 49.1, 45.9, 31.5, 22.6, 21.2, 14.6. TOF MS ESI+ calcd for $C_{20}H_{18}N_3O_4^+$ $[M + H]^+$, 364.1292; found, 364.1335.



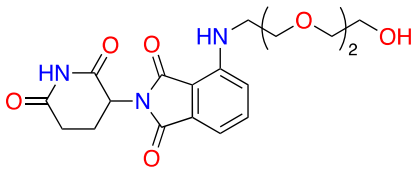
2-(2,6-dioxopiperidin-3-yl)-4-(prop-2-yn-1-ylamino)isoindoline-1,3-dione (1n) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.7 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.2 – 7.1 (m, 2H), 6.9 (t, *J* = 6.2 Hz, 1H), 5.1 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.2 (dd, *J* = 6.2, 2.5 Hz, 2H), 3.2 – 3.1 (m, 1H), 2.9 (tdd, *J* = 14.0, 5.8, 2.7 Hz, 1H), 2.7 – 2.5 (m, 2H), 2.2 – 2.0 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 173.2, 170.8, 170.5, 170.2, 169.1, 167.7, 145.7, 138.5, 136.5, 132.6, 118.4, 111.8, 110.8, 81.4, 74.2, 60.2, 49.6, 49.1, 32.0, 31.5, 31.4, 22.6, 22.3, 21.2, 14.6. TOF MS ESI+ calcd for $C_{16}H_{14}N_3O_4^+$ $[M + H]^+$, 312.0979; found, 312.1024.



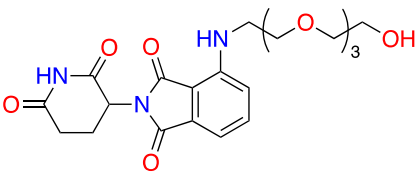
tert-butyl 3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)azetidine-1-carboxylate (1o) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.2 (s, 1H), 7.6 (dd, *J* = 8.5, 7.2 Hz, 1H), 7.2 (dd, *J* = 7.2, 0.6 Hz, 1H), 7.0 (d, *J* = 8.5 Hz, 1H), 6.9 (d, *J* = 6.6 Hz, 1H), 5.1 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.5 (dtd, *J* = 12.3, 7.1, 5.4 Hz, 1H), 4.3 (t, *J* = 8.0 Hz, 2H), 3.9 (t, *J* = 7.2 Hz, 2H), 2.9 (ddd, *J* = 17.1, 13.9, 5.3 Hz, 1H), 2.7 – 2.5 (m, 2H), 2.1 – 2.0 (m, 1H), 1.4 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.5, 168.9, 167.7, 156.1, 145.1, 136.8, 132.8, 118.1, 112.2, 110.9, 79.2, 60.2, 49.1, 42.2, 31.4, 28.5, 22.6, 21.2, 14.6. TOF MS ESI+ calcd for $C_{21}H_{25}N_4O_6^+$ [M + H]$^+$, 429.1769; found, 429.1792.



2-(2,6-dioxopiperidin-3-yl)-4-((2-(2-hydroxyethoxy)ethyl)amino)isoindoline-1,3-dione (1p) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.6 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.1 (d, *J* = 8.6 Hz, 1H), 7.0 (d, *J* = 7.0 Hz, 1H), 6.6 (t, *J* = 5.8 Hz, 1H), 5.1 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.6 (d, *J* = 4.6 Hz, 1H), 3.6 (t, *J* = 5.4 Hz, 2H), 3.6 – 3.4 (m, 6H), 2.9 (ddd, *J* = 17.0, 13.9, 5.3 Hz, 1H), 2.7 – 2.5 (m, 2H), 2.0 (ddt, *J* = 13.1, 5.6, 2.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.6, 169.4, 167.8, 146.9, 136.7, 132.6, 117.9, 111.1, 109.7, 72.7, 69.3, 60.7, 60.2, 49.0, 42.2, 31.5, 22.6, 14.6. TOF MS ESI+ calcd for $C_{17}H_{20}N_3O_6^+$ [M + H]$^+$, 362.1347; found, 362.1404.

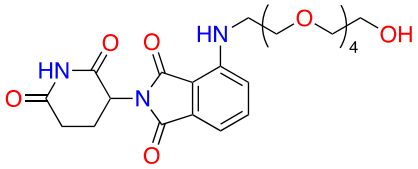


2-(2,6-dioxopiperidin-3-yl)-4-((2-(2-(2-hydroxyethoxy)ethoxy)ethyl)amino)isoindoline-1,3-dione (1q) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.6 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.1 (d, *J* = 8.6 Hz, 1H), 7.0 (d, *J* = 7.0 Hz, 1H), 6.6 (t, *J* = 5.8 Hz, 1H), 5.1 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.6 (t, *J* = 5.4 Hz, 1H), 3.7 – 3.4 (m, 12H), 2.9 (ddd, *J* = 17.4, 14.1, 5.4 Hz, 1H), 2.7 – 2.5 (m, 2H), 2.1 – 2.0 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.6, 169.4, 167.8, 146.9, 136.7, 132.6, 117.9, 111.2, 109.7, 72.9, 70.3, 69.4, 60.7, 49.0, 42.2, 31.5, 22.6. TOF MS ESI+ calcd for $C_{19}H_{24}N_3O_7^+$ [M + H]$^+$, 406.1609; found, 406.1334.

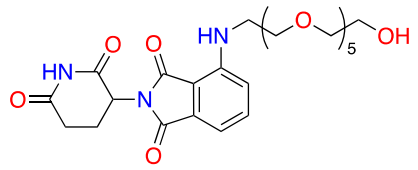


2-(2,6-dioxopiperidin-3-yl)-4-((2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl)amino)isoindoline-1,3-dione (1r) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.6 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.1 (d, *J* = 8.6 Hz, 1H), 7.0 (d, *J* =

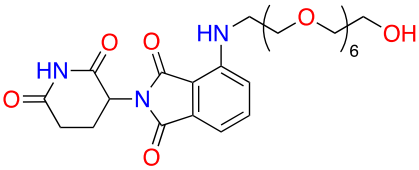
7.0 Hz, 1H), 6.6 (t, *J* = 5.8 Hz, 1H), 5.0 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.5 (t, *J* = 5.4 Hz, 1H), 3.6 (t, *J* = 5.4 Hz, 2H), 3.6 (ddd, *J* = 5.5, 3.2, 1.3 Hz, 2H), 3.5 – 3.4 (m, 10H), 3.4 – 3.3 (m, 2H), 2.9 (ddd, *J* = 16.9, 13.8, 5.2 Hz, 1H), 2.6 – 2.5 (m, 2H), 2.1 – 2.0 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.5, 169.4, 167.8, 146.9, 136.7, 132.6, 117.9, 111.1, 109.7, 72.8, 70.3, 70.3, 70.3, 70.2, 69.4, 60.7, 49.0, 42.2, 31.5, 22.6. TOF MS ESI+ calcd for $C_{21}H_{28}N_3O_8^+$ [M + H]$^+$, 450.1871; found, 450.2253.



2-(2,6-dioxopiperidin-3-yl)-4-((14-hydroxy-3,6,9,12-tetraoxatetradecyl)amino)isoindoline-1,3-dione (1s) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.6 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.2 (d, *J* = 8.5 Hz, 1H), 7.1 – 7.0 (m, 1H), 6.6 (t, *J* = 5.8 Hz, 1H), 5.1 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.6 (t, *J* = 5.5 Hz, 1H), 3.7 – 3.6 (m, 3H), 3.6 – 3.5 (m, 7H), 3.5 (s, 5H), 3.5 (ddd, *J* = 6.2, 5.1, 2.8 Hz, 3H), 3.4 (ddd, *J* = 5.7, 4.7, 0.8 Hz, 2H), 2.9 (ddd, *J* = 17.4, 14.0, 5.4 Hz, 1H), 2.7 – 2.5 (m, 2H), 2.0 (ddt, *J* = 12.9, 5.5, 2.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.5, 169.4, 167.8, 146.9, 136.7, 132.6, 117.9, 111.2, 109.7, 72.8, 70.3, 70.3, 70.3, 70.2, 70.2, 69.4, 60.7, 49.0, 42.2, 31.5, 22.6. TOF MS ESI+ calcd for $C_{23}H_{32}N_3O_9^+$ [M + H]$^+$, 494.2133; found, 494.2563.

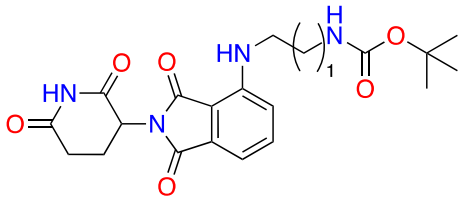


2-(2,6-dioxopiperidin-3-yl)-4-((17-hydroxy-3,6,9,12,15-pentaoxaheptadecyl)amino)isoindoline-1,3-dione (1t) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.6 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.1 (d, *J* = 8.5 Hz, 1H), 7.0 (dd, *J* = 7.1, 0.6 Hz, 1H), 6.6 (t, *J* = 5.8 Hz, 1H), 5.0 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.5 (t, *J* = 5.5 Hz, 1H), 3.7 – 3.3 (m, 15H), 3.5 (s, 5H), 3.3 (s, 4H), 2.9 (ddd, *J* = 17.4, 14.1, 5.4 Hz, 1H), 2.6 – 2.4 (m, 2H), 2.1 – 2.0 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.5, 169.4, 167.8, 146.9, 136.7, 132.6, 117.9, 111.1, 109.7, 72.8, 70.3, 70.3, 70.3, 70.2, 69.4, 60.7, 49.0, 42.2, 31.5, 22.6. TOF MS ESI+ calcd for $C_{25}H_{36}N_3O_{10}^+$ [M + H]$^+$, 538.2395; found, 538.2830.

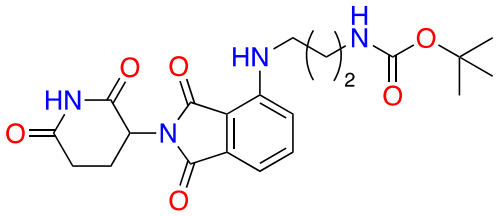


2-(2,6-dioxopiperidin-3-yl)-4-((20-hydroxy-3,6,9,12,15,18-hexaoxaicosyl)amino)isoindoline-1,3-dione (1u) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.6 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.1 (d, *J* = 8.6 Hz, 1H), 7.0 (d, *J* = 7.0 Hz, 1H), 6.6 (t, *J* = 5.8 Hz, 1H), 5.0 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.5 (t, *J* = 5.4 Hz, 1H), 3.6 (t, *J* = 5.4 Hz, 2H), 3.6 – 3.5

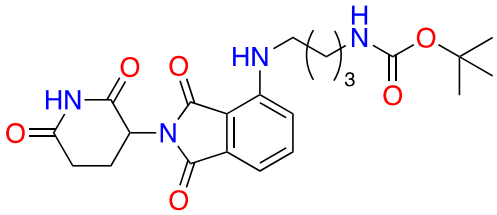
(m, 5H), 3.5 (s, 5H), 3.5 – 3.4 (m, 7H), 3.4 (s, 1H), 3.4 – 3.4 (m, 2H), 3.3 (d, *J* = 0.9 Hz, 6H), 2.9 – 2.8 (m, 1H), 2.6 – 2.4 (m, 2H), 2.1 – 2.0 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.5, 169.4, 167.8, 146.9, 136.7, 132.6, 117.9, 111.1, 109.7, 72.8, 70.3, 70.3, 70.3, 70.3, 70.2, 69.4, 60.7, 49.0, 42.2, 31.5, 22.6. TOF MS ESI+ calcd for $C_{27}H_{40}N_3O_{11}^+$ [M + H]$^+$, 582.2657; found, 582.3144.



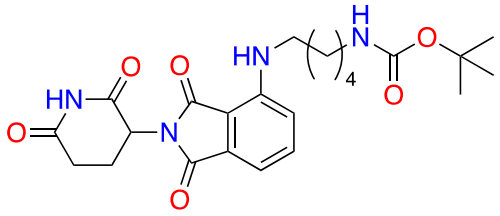
tert-butyl (2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)carbamate (1v) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.6 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.2 (d, *J* = 8.6 Hz, 1H), 7.0 (dd, *J* = 11.0, 6.3 Hz, 2H), 6.7 (t, *J* = 6.2 Hz, 1H), 5.1 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.4 – 3.4 (m, 2H), 3.2 (q, *J* = 6.1 Hz, 2H), 2.9 (dddd, *J* = 16.9, 14.0, 5.5, 3.1 Hz, 1H), 2.7 – 2.5 (m, 2H), 2.1 (dddd, *J* = 21.4, 9.7, 6.3, 2.2 Hz, 1H), 1.4 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 173.2, 170.5, 170.1, 169.2, 167.8, 156.4, 146.9, 138.6, 136.6, 132.7, 123.6, 123.4, 120.5, 117.5, 111.0, 109.7, 78.3, 60.2, 49.6, 49.0, 42.1, 31.4, 31.4, 28.7, 22.7, 22.3, 21.2, 14.6. TOF MS ESI+ calcd for $C_{20}H_{25}N_4O_6^+$ [M + H]$^+$, 417.1769; found, 417.1796.



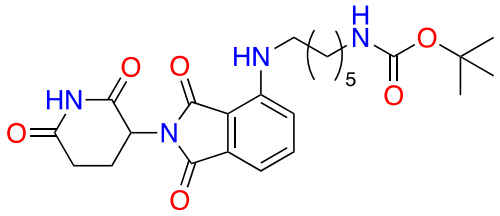
tert-butyl (3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)carbamate (1w) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.6 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.1 (d, *J* = 8.6 Hz, 1H), 7.0 (d, *J* = 7.0 Hz, 1H), 6.9 (t, *J* = 5.8 Hz, 1H), 6.7 (t, *J* = 6.2 Hz, 1H), 5.1 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.3 (t, *J* = 6.6 Hz, 2H), 3.0 (q, *J* = 6.4 Hz, 2H), 2.9 (ddd, *J* = 17.4, 14.0, 5.5 Hz, 1H), 2.7 – 2.5 (m, 2H), 2.1 – 2.0 (m, 1H), 1.7 (p, *J* = 6.6 Hz, 2H), 1.4 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.6, 169.3, 167.8, 156.2, 146.8, 136.7, 132.7, 117.5, 110.8, 109.6, 78.0, 60.2, 49.0, 37.7, 31.5, 29.4, 28.7, 22.6, 21.2, 14.5. TOF MS ESI+ calcd for $C_{21}H_{27}N_4O_6^+$ [M + H]$^+$, 431.1925; found, 431.1914.



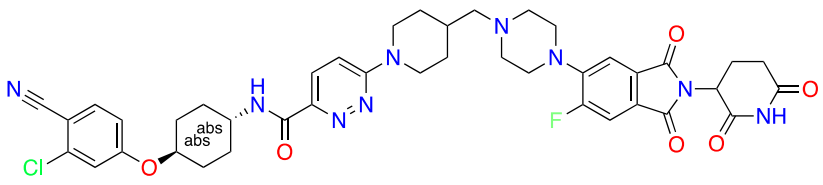
tert-butyl (4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)carbamate (1x) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.6 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.1 (d, *J* = 8.6 Hz, 1H), 7.0 (dd, *J* = 7.1, 0.6 Hz, 1H), 6.8 (t, *J* = 5.7 Hz, 1H), 6.6 (t, *J* = 6.1 Hz, 1H), 5.1 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.3 (q, *J* = 6.7 Hz, 2H), 3.0 – 2.8 (m, 3H), 2.7 – 2.5 (m, 2H), 2.1 – 2.0 (m, 1H), 1.6 – 1.4 (m, 4H), 1.4 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.6, 169.4, 167.8, 156.1, 146.9, 136.7, 132.7, 117.7, 110.8, 109.5, 77.9, 60.2, 49.0, 42.0, 31.4, 28.7, 27.4, 26.6, 22.6, 14.6. TOF MS ESI+ calcd for $C_{22}H_{29}N_4O_6^+$ [M + H]$^+$, 445.2082; found, 445.2102.



tert-butyl (5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentyl)carbamate (1y) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.6 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.1 (d, *J* = 8.6 Hz, 1H), 7.0 (d, *J* = 7.0 Hz, 1H), 6.8 (t, *J* = 5.8 Hz, 1H), 6.5 (t, *J* = 5.9 Hz, 1H), 5.1 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.3 (q, *J* = 6.7 Hz, 2H), 2.9 (s, 1H), 2.9 (s, 1H), 2.9 – 2.8 (m, 1H), 2.7 – 2.5 (m, 2H), 2.1 (ddt, *J* = 12.8, 5.4, 2.6 Hz, 1H), 1.6 (p, *J* = 7.3 Hz, 2H), 1.5 – 1.4 (m, 2H), 1.4 (s, 10H), 1.4 – 1.3 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.6, 169.4, 167.8, 156.1, 146.9, 136.7, 132.7, 117.6, 110.8, 109.5, 77.8, 60.2, 49.0, 42.3, 31.5, 29.7, 28.9, 28.7, 24.1, 22.6, 14.6. TOF MS ESI+ calcd for $C_{23}H_{31}N_4O_6^+$ [M + H]$^+$, 459.2238; found, 459.2250.



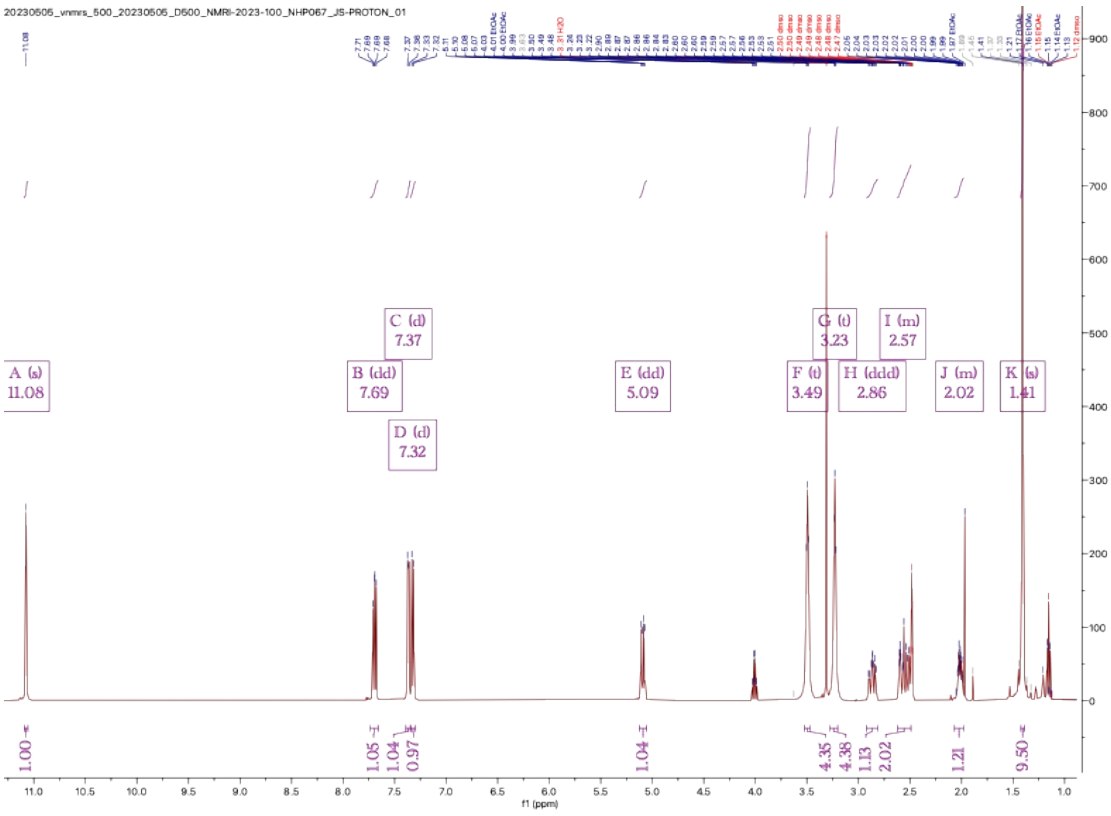
tert-butyl (6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)carbamate (1z) was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.6 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.1 (d, *J* = 8.6 Hz, 1H), 7.1 (d, *J* = 7.0 Hz, 1H), 6.8 (t, *J* = 5.8 Hz, 1H), 6.6 (t, *J* = 5.9 Hz, 1H), 5.1 (dd, *J* = 13.0, 5.4 Hz, 1H), 3.3 (q, *J* = 6.7 Hz, 2H), 2.9 (td, *J* = 13.7, 6.1 Hz, 3H), 2.7 – 2.5 (m, 2H), 2.1 – 2.0 (m, 1H), 1.6 (p, *J* = 7.1 Hz, 2H), 1.4 (s, 14H), 1.1 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 170.6, 169.4, 167.8, 156.1, 146.9, 136.7, 132.7, 117.6, 110.8, 109.5, 77.8, 60.2, 49.0, 42.2, 40.6, 31.5, 29.9, 29.1, 28.7, 26.5, 26.5, 25.4, 22.6. TOF MS ESI+ calcd for $C_{24}H_{33}N_4O_6^+$ [M + H]$^+$, 473.2395; found, 473.2389.



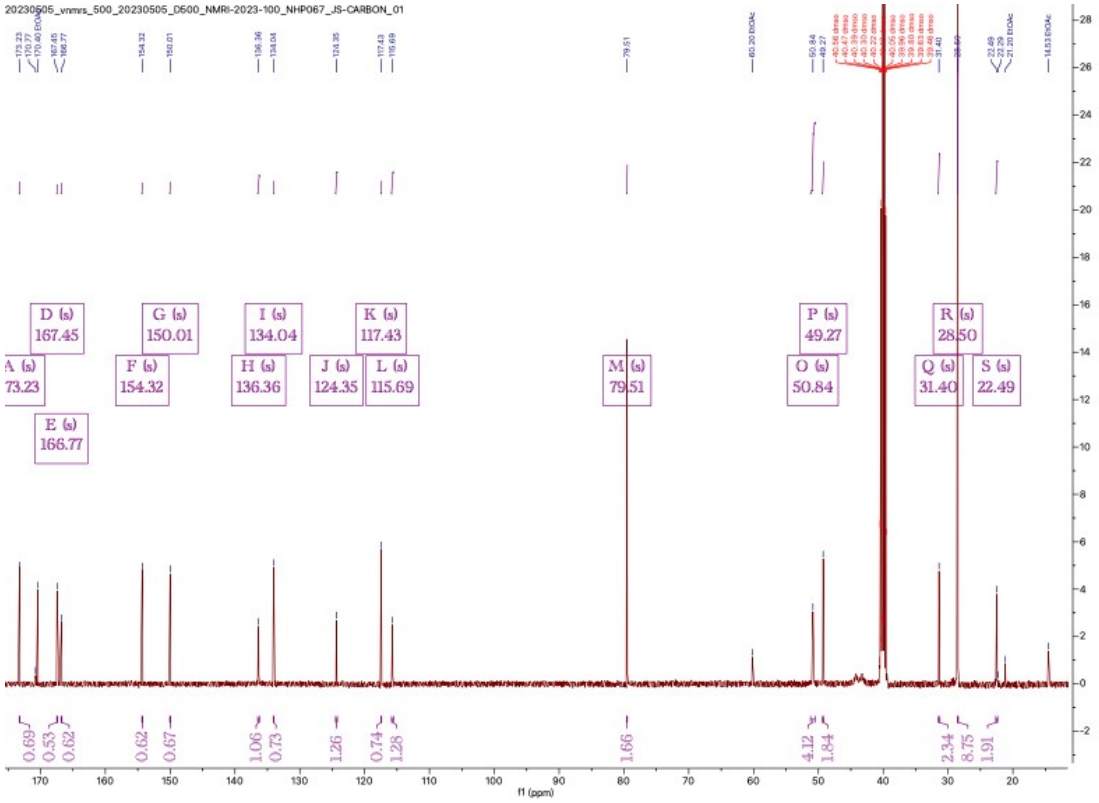
***N*-((1*r*,4*r*)-4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-((4-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)pyridazine-3-carboxamide (4)** was synthesized using OP1. The product was isolated via Biotage Isolera (gradient: 0 – 50% ethyl acetate in DCM) as a yellow solid. ^{1}H NMR (500 MHz, dmso) δ 11.10 (s, 1H), 8.54 (d, *J* = 8.1 Hz, 1H), 7.80 (dd, *J* = 14.8, 9.1 Hz, 2H), 7.67 (d, *J* = 11.4 Hz, 1H), 7.41 (d, *J* = 7.3 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.29 (d, *J* = 9.6 Hz, 1H), 7.09 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.09 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.50 (dt, *J* = 9.1, 3.9 Hz, 1H), 4.46 (s, 1H), 4.44 (s, 1H), 3.83 (dtd, *J* = 11.4, 7.6, 4.2 Hz, 1H), 3.25 – 3.20 (m, 3H), 2.98 (t, *J* = 12.3 Hz, 2H), 2.88 (ddt, *J* = 16.6, 12.2, 5.4 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.57 – 2.48 (m, 5H), 2.18 (d, *J* = 6.9 Hz, 2H), 2.11 – 1.98 (m, 4H), 1.91 – 1.84 (m, 3H), 1.80 (d, *J* = 12.7 Hz, 2H), 1.61 (td, *J* = 14.0, 7.0 Hz, 2H), 1.53 – 1.42 (m, 2H), 1.16 – 1.04 (m, 2H). ^{13}C NMR (126 MHz, dmso) δ 173.2, 170.3, 167.1, 166.6, 166.6, 163.0, 162.2, 160.4, 158.8, 156.7, 145.8, 145.7, 144.7, 137.4, 136.2, 129.2, 129.2, 126.7, 123.8, 123.7, 117.2, 116.8, 115.8, 114.0, 112.8, 112.4, 112.2, 103.7, 76.0, 64.0, 53.3, 50.0, 49.5, 47.5, 44.9, 40.9, 33.1, 31.4, 30.3, 30.2, 30.1, 29.9, 22.5. ^{19}F NMR (564 MHz, dmso) δ -111.86. TOF MS ESI+ calcd for $C_{41}H_{44}ClFN_9O_6^+$ [M + H]$^+$, 812.3082; found, 812.3640.

4.2. ^{1}H, ^{13}C, and ^{19}F NMR spectra

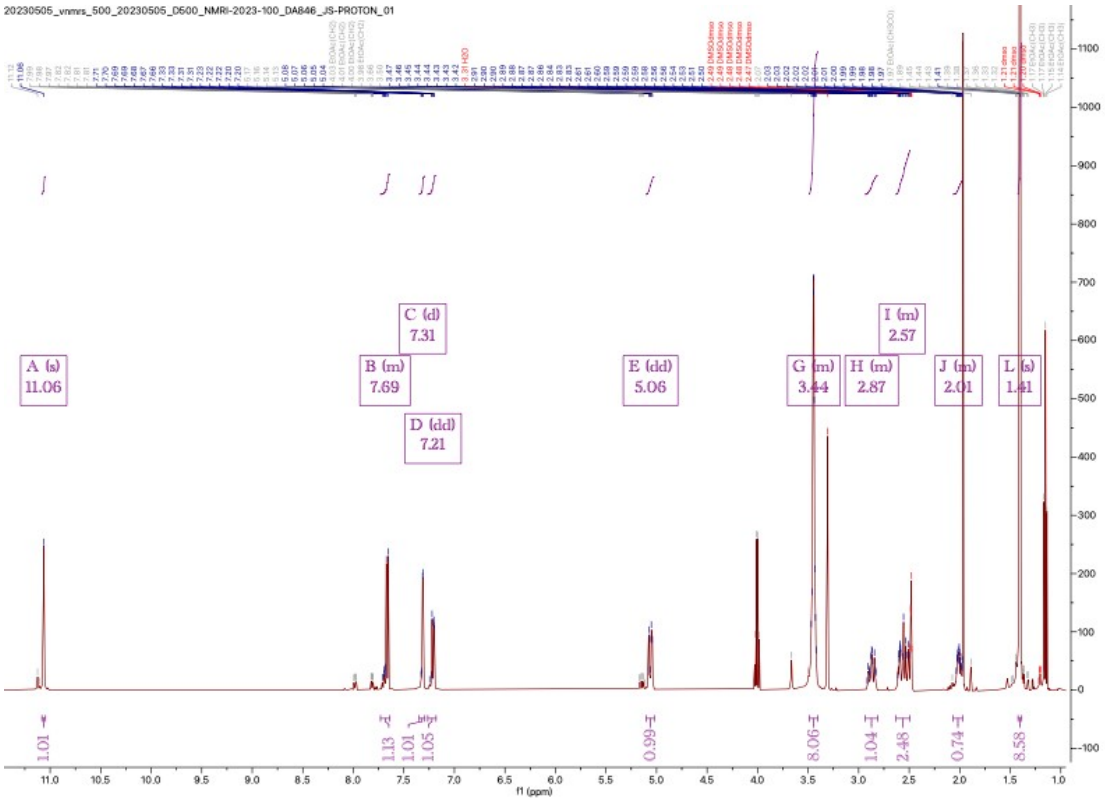
1b ^{1}H-NMR (500MHz, DMSO-d6)



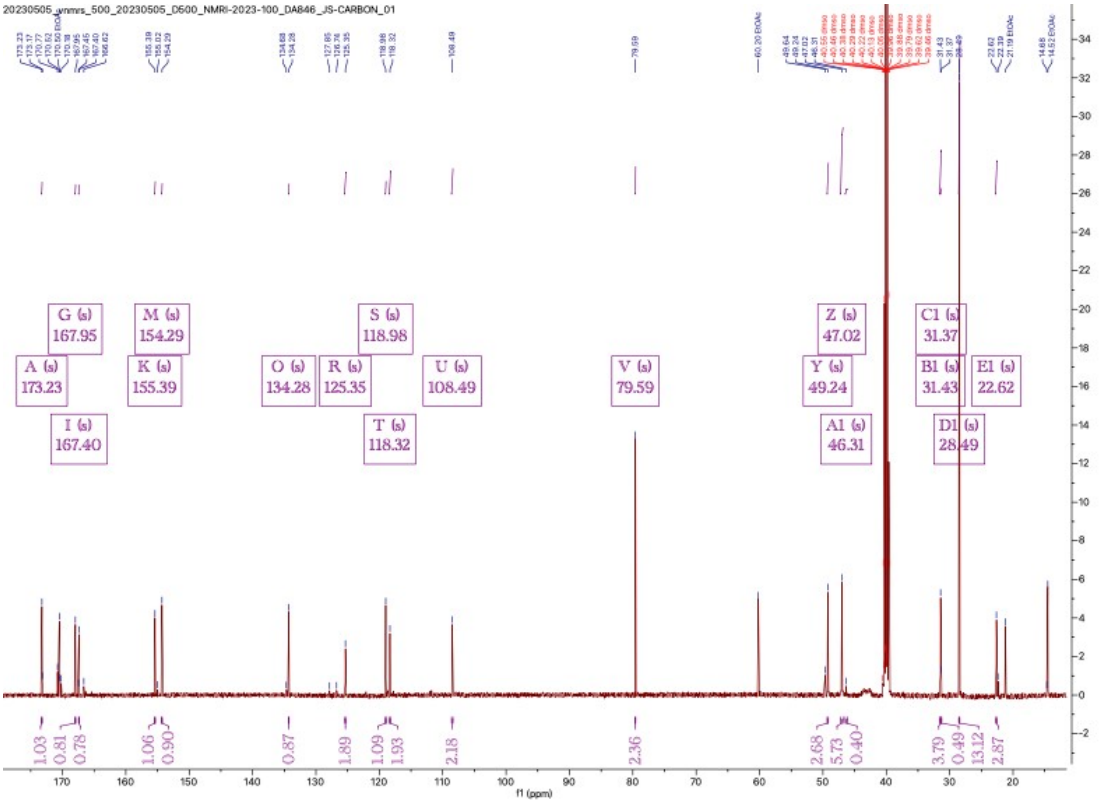
1b ^{13}C-NMR (125MHz, DMSO-d6)



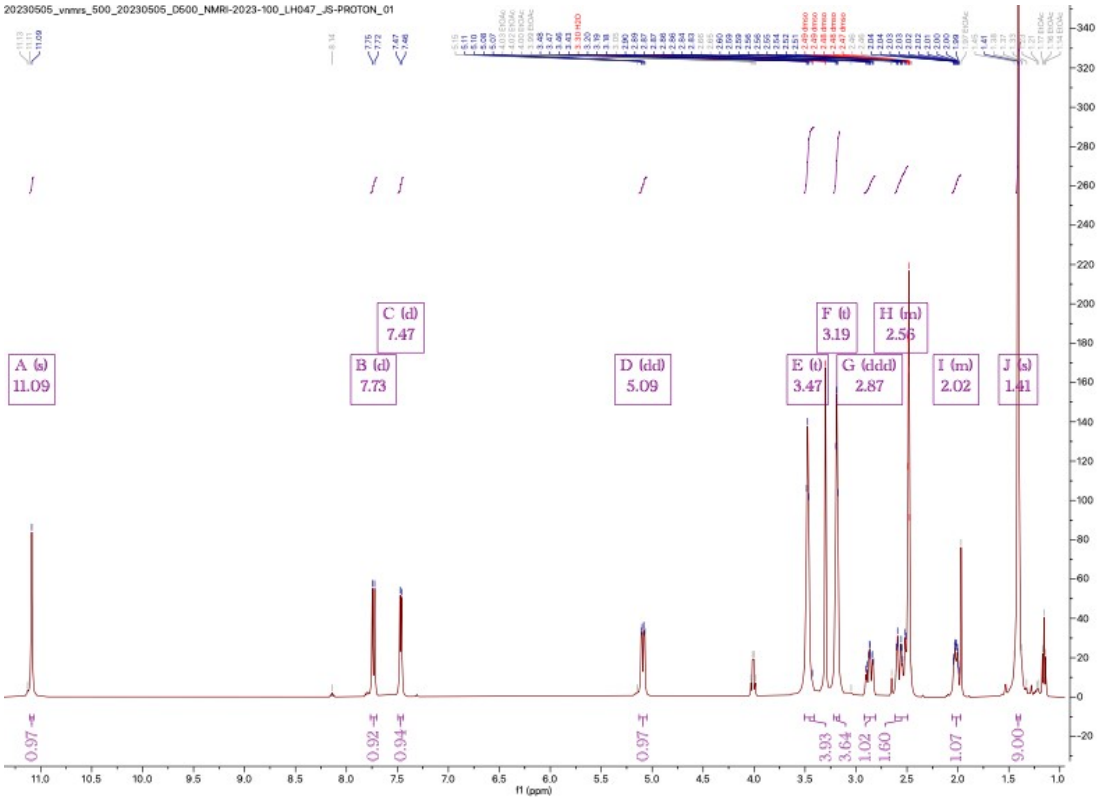
2b ^{1}H-NMR (500MHz, DMSO-d6)



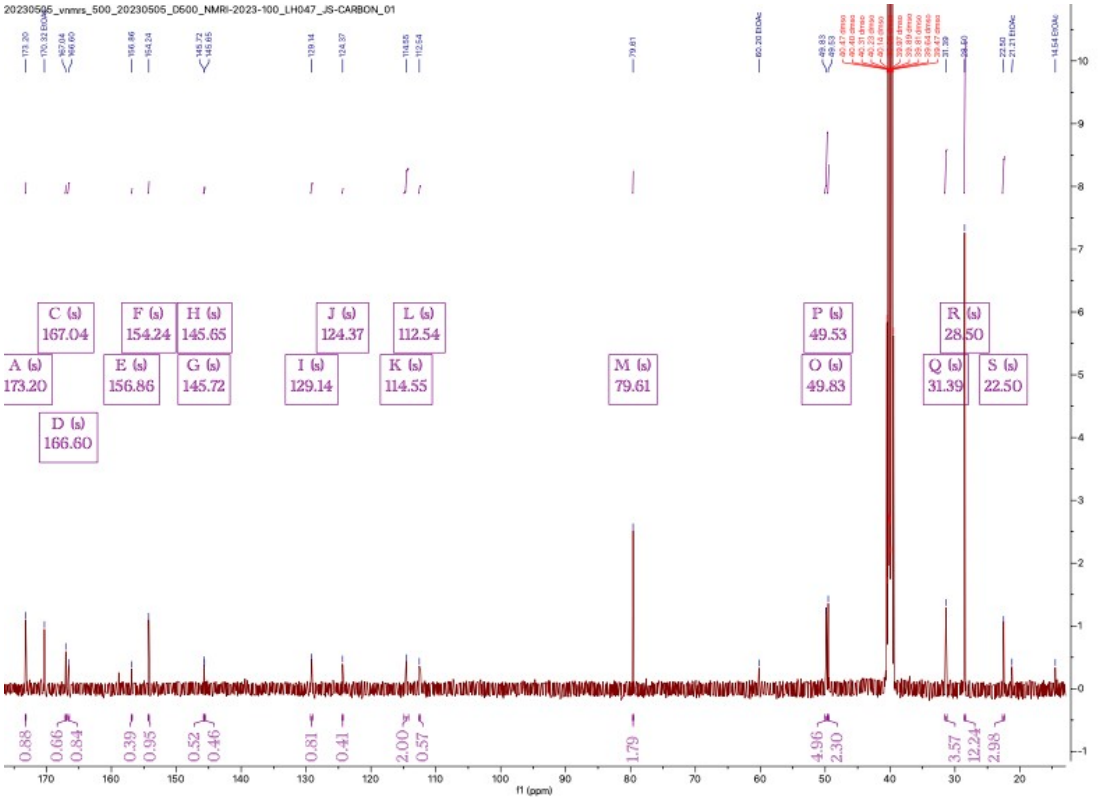
2b ^{13}C-NMR (125MHz, DMSO-d6)



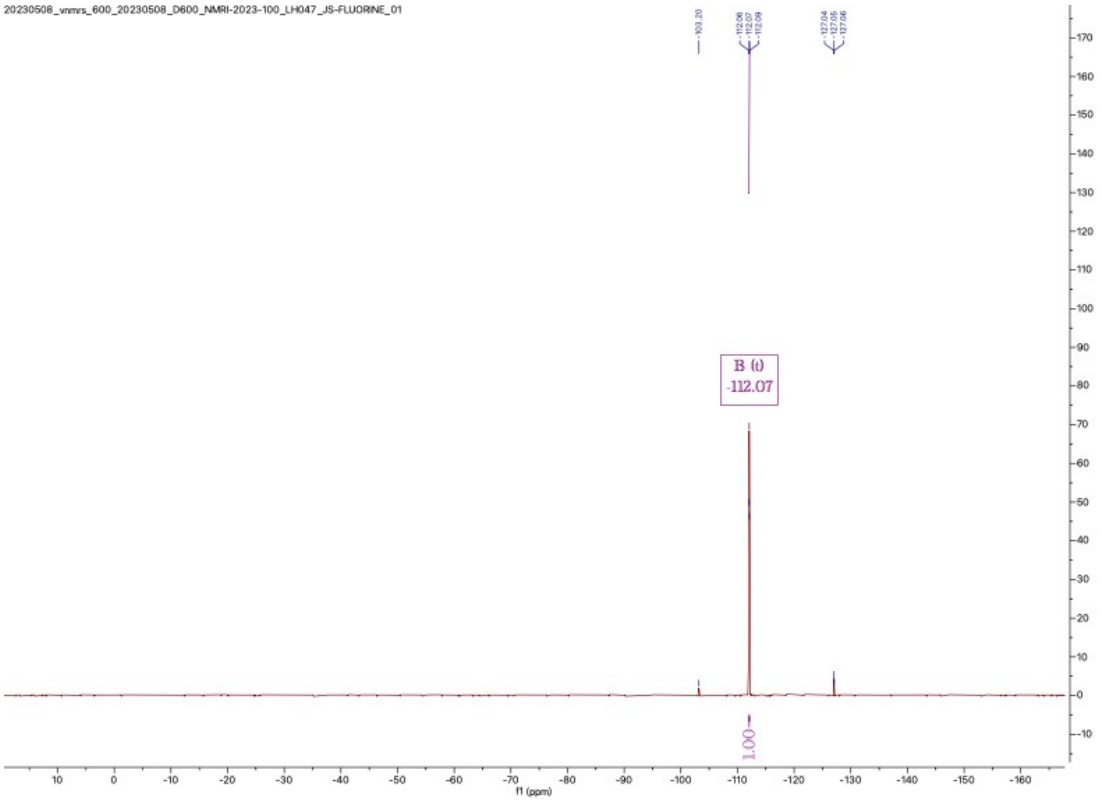
3b ^{1}H-NMR (500MHz, DMSO-d6)



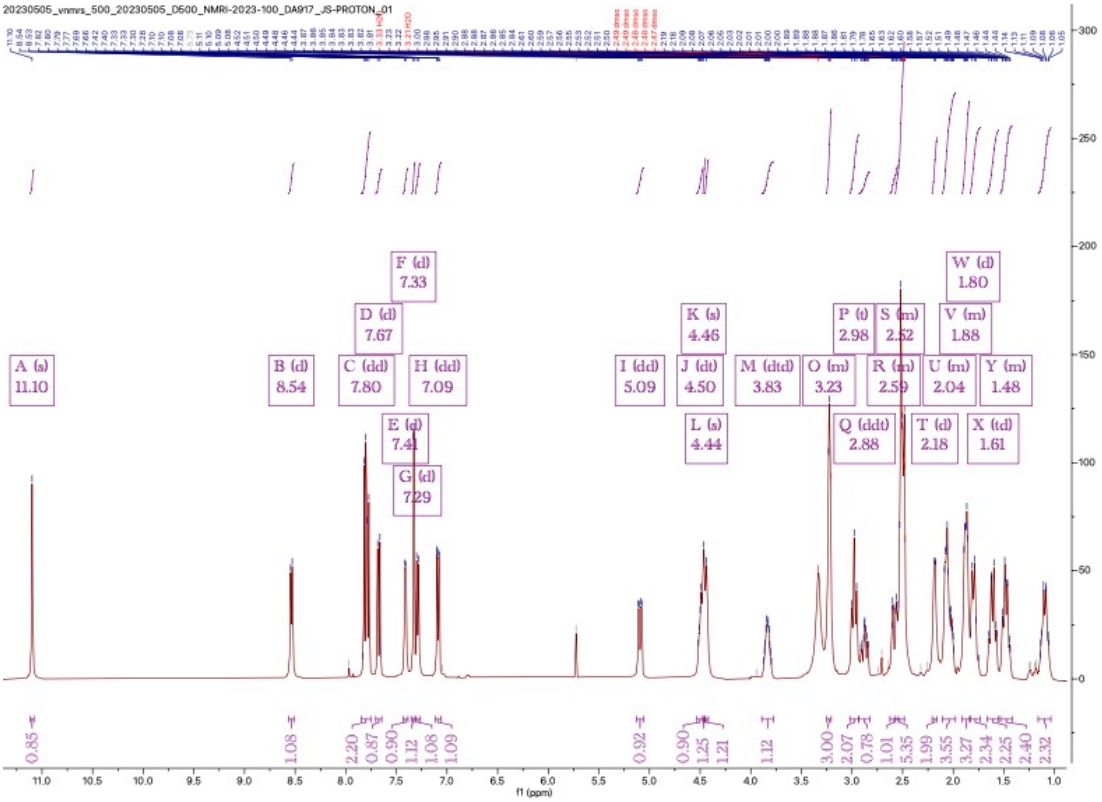
3b ^{13}C-NMR (125MHz, DMSO-d6)



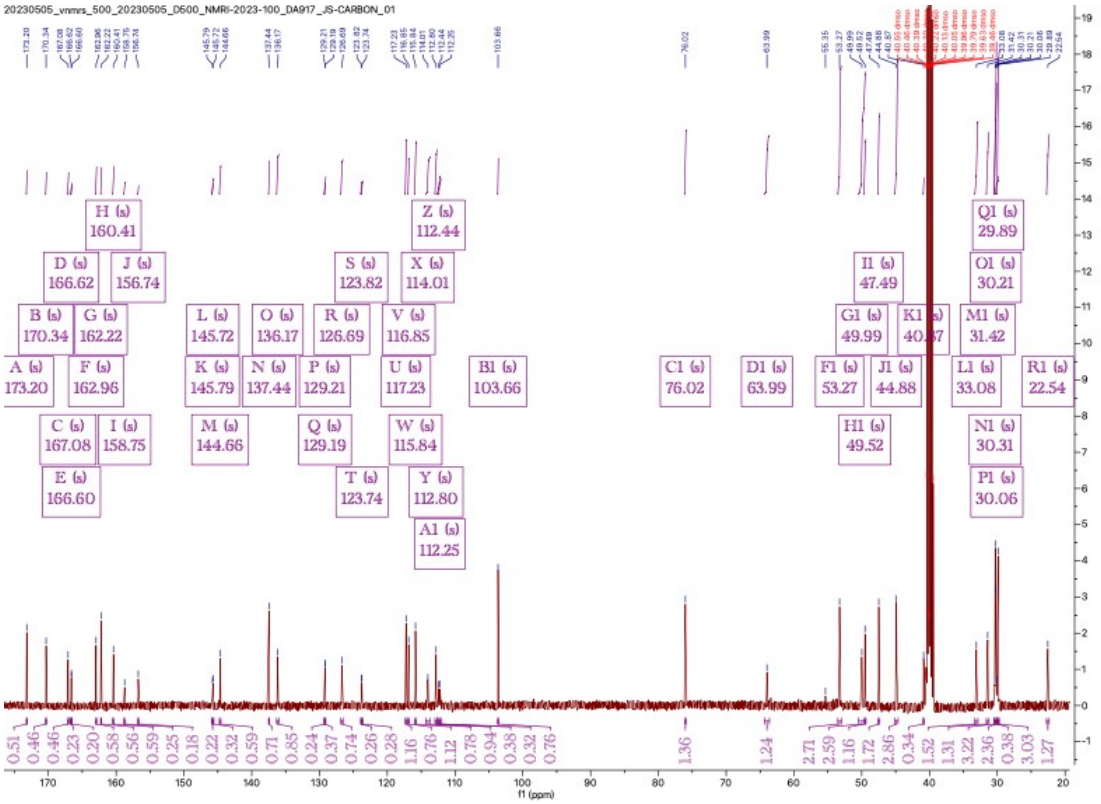
3b ^{19}F-NMR (564MHz, DMSO-d6)



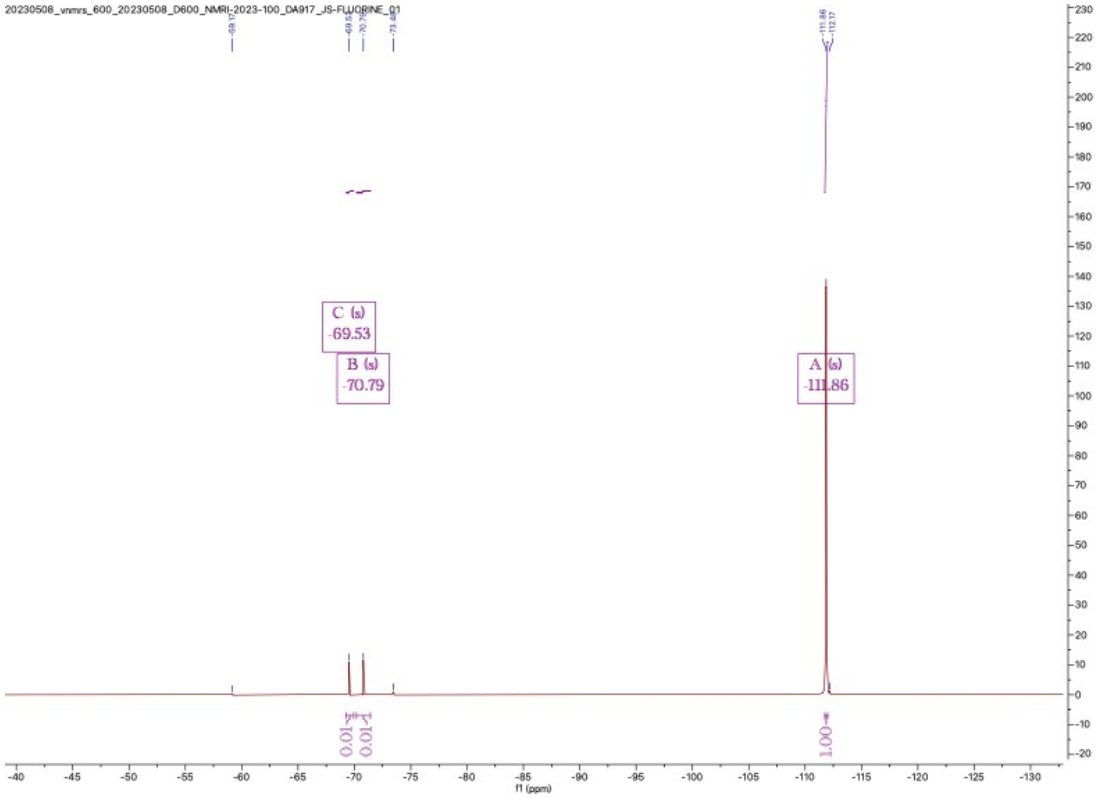
4 ^{1}H-NMR (500MHz, DMSO-d6)



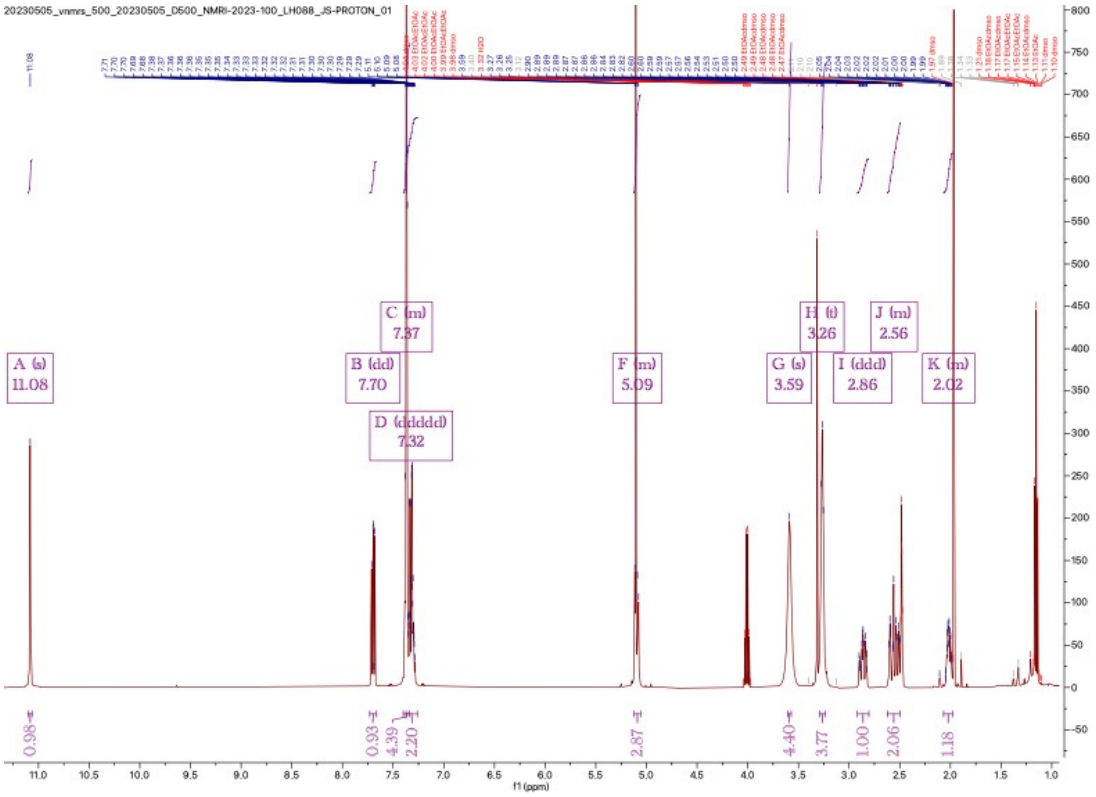
4 ^{13}C-NMR (125MHz, DMSO-d6)



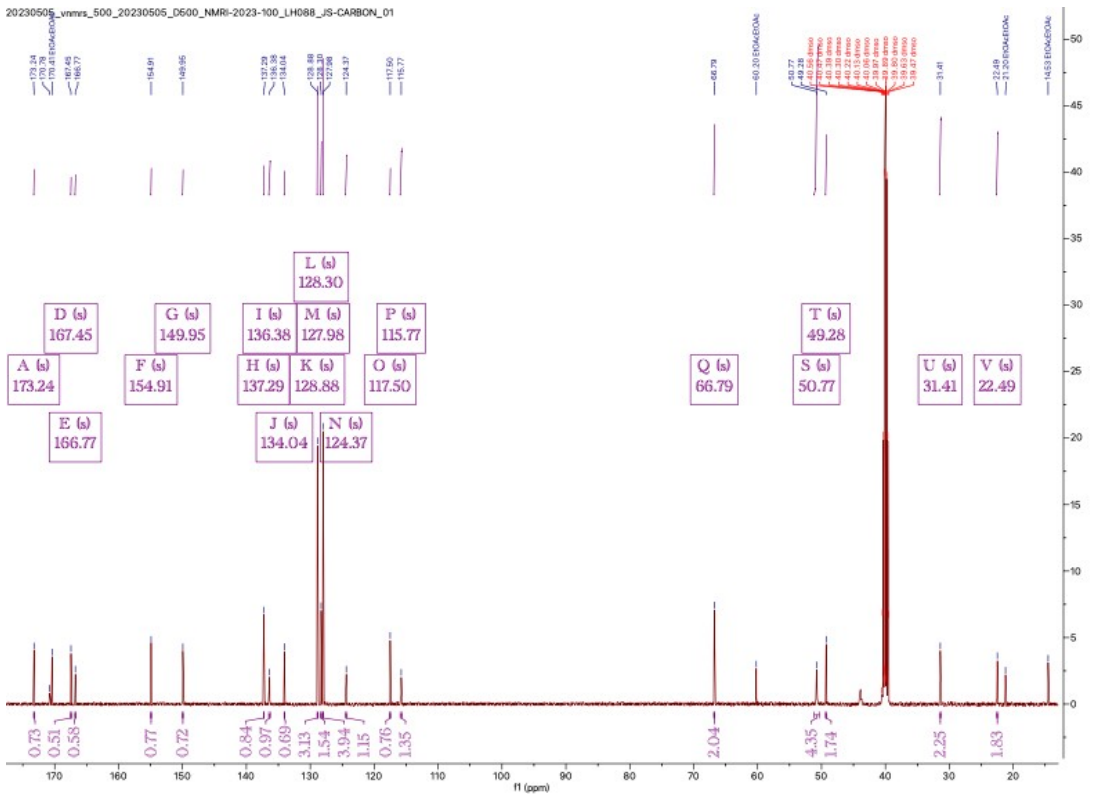
4 ^{19}F-NMR (564MHz, DMSO-d6)



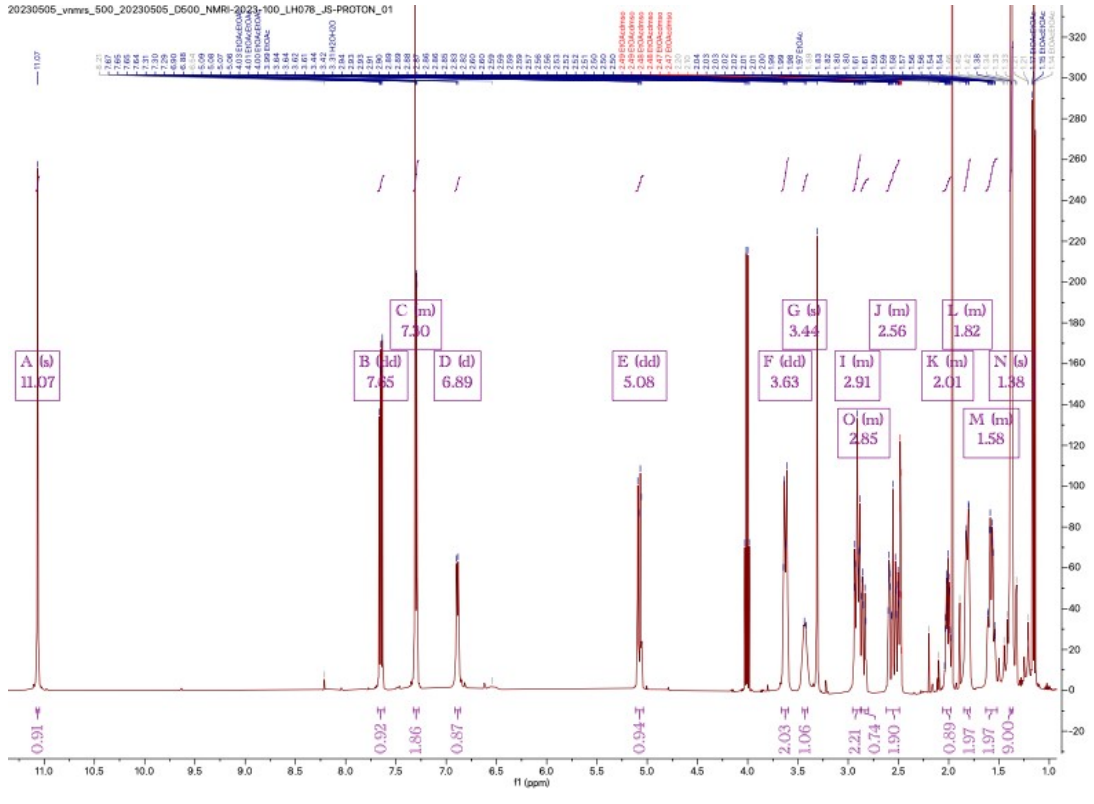
1c ^{1}H-NMR (500MHz, DMSO-d6)



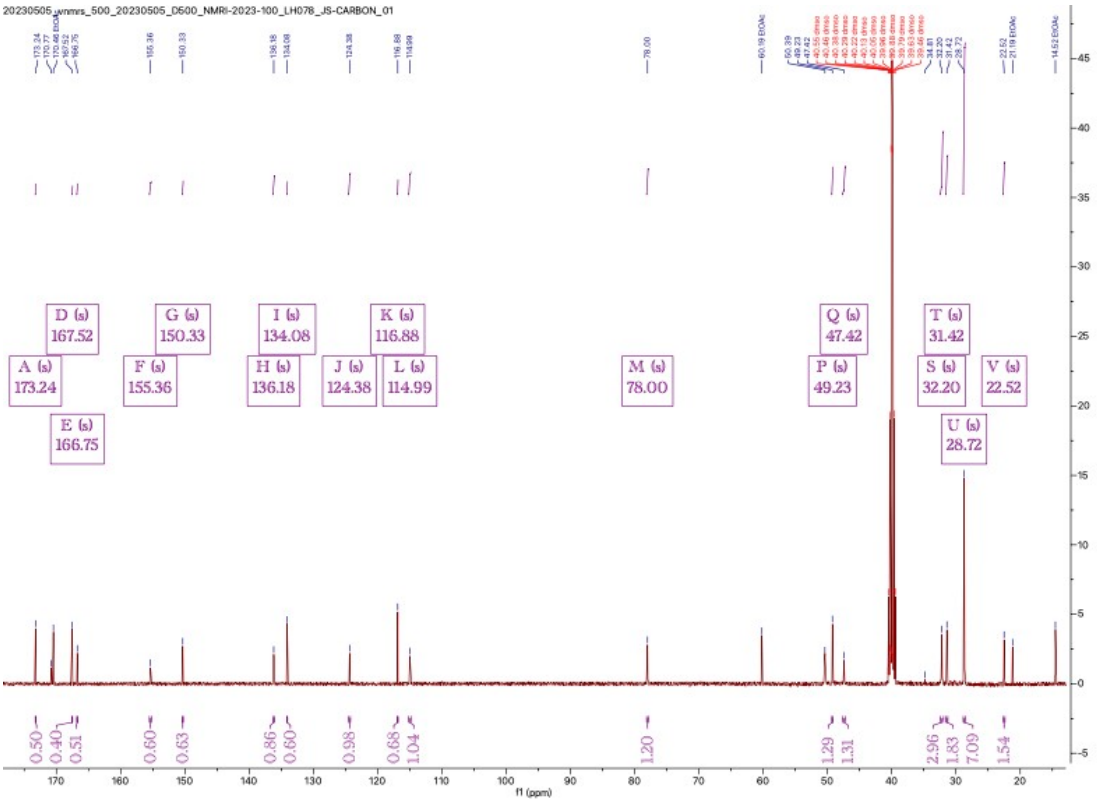
1c ^{13}C-NMR (125MHz, DMSO-d6)



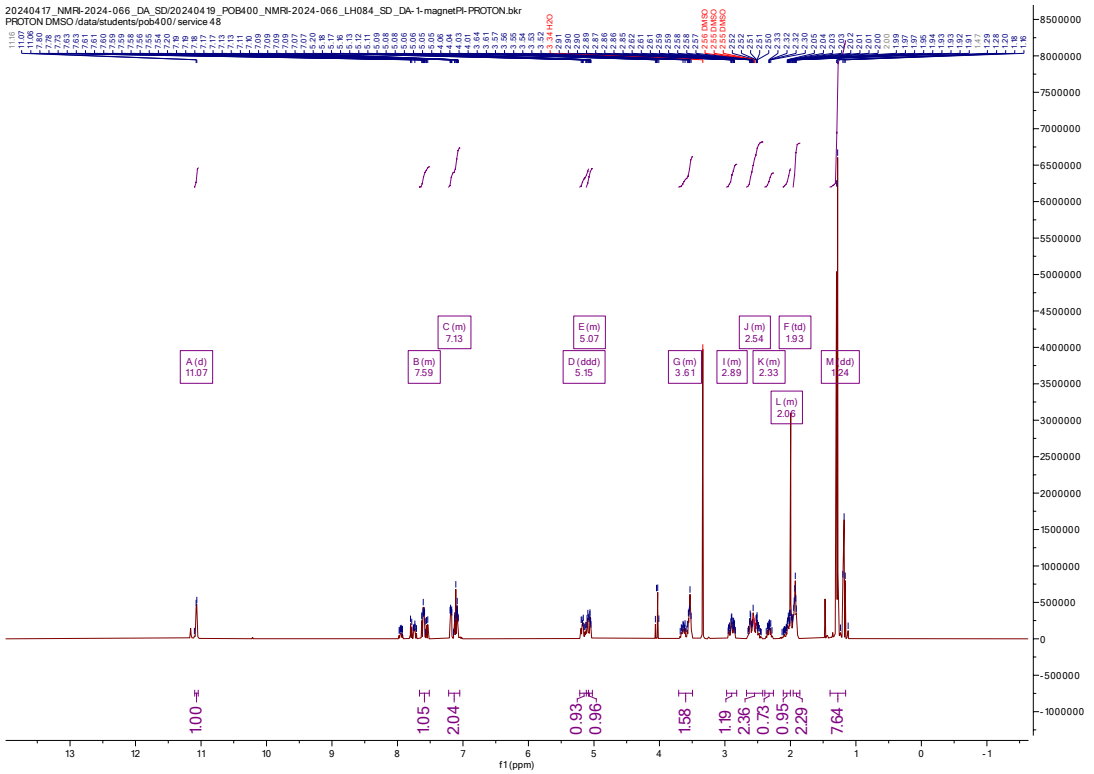
1d ^{1}H-NMR (500MHz, DMSO-d6)



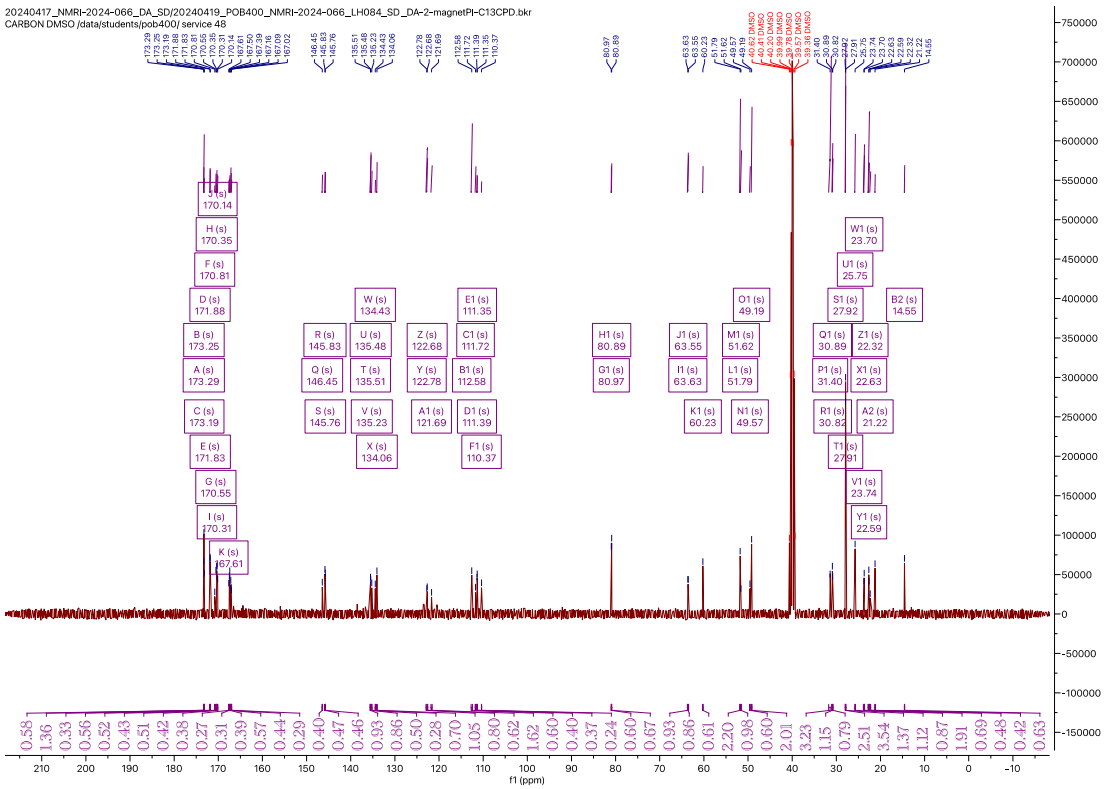
1d ^{13}C-NMR (125MHz, DMSO-d6)



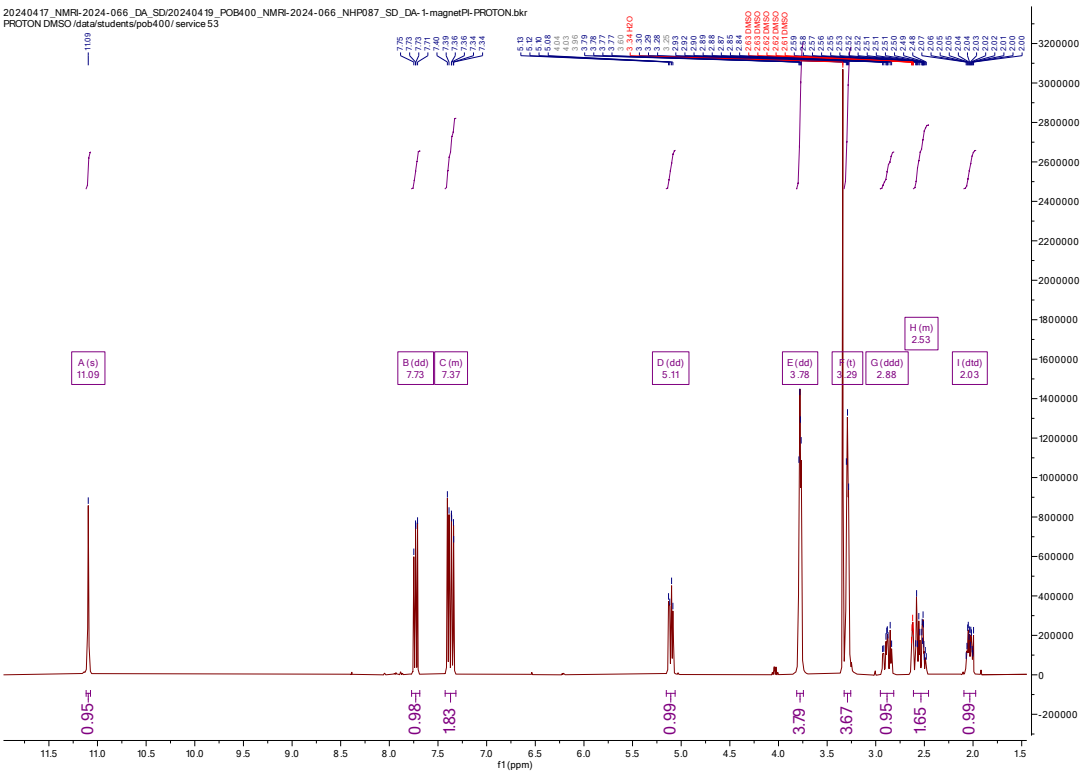
1e ^{1}H-NMR (500MHz, DMSO-d6)



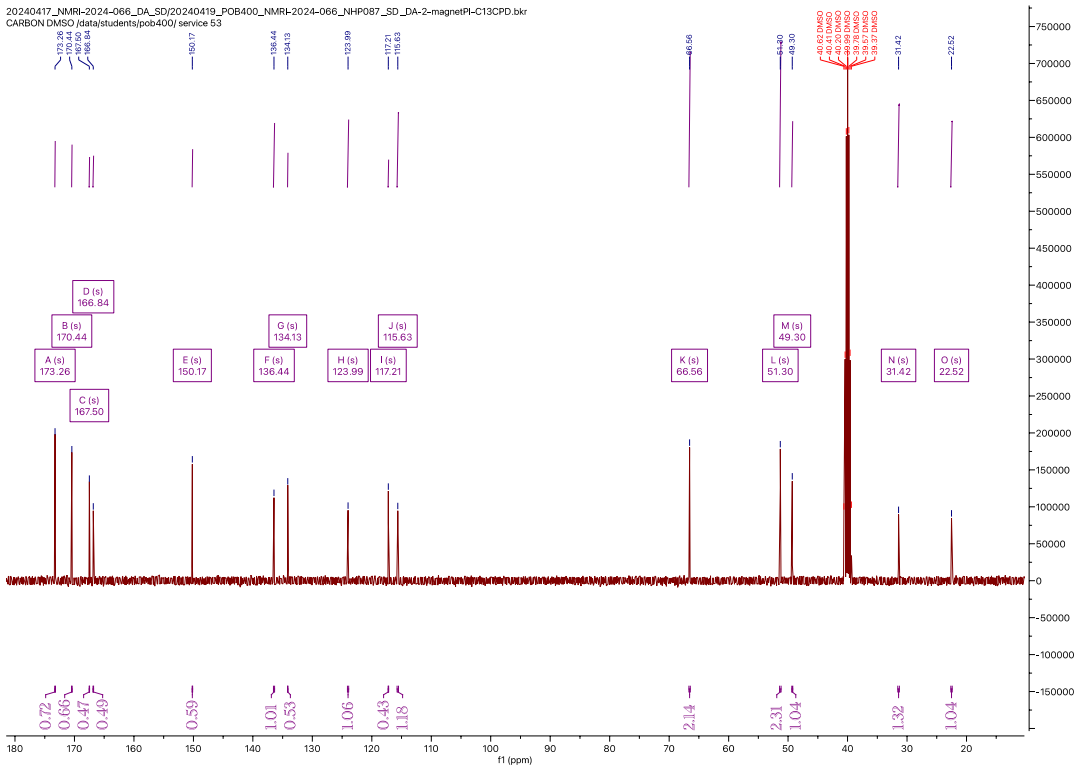
1e ^{13}C-NMR (125MHz, DMSO-d6)



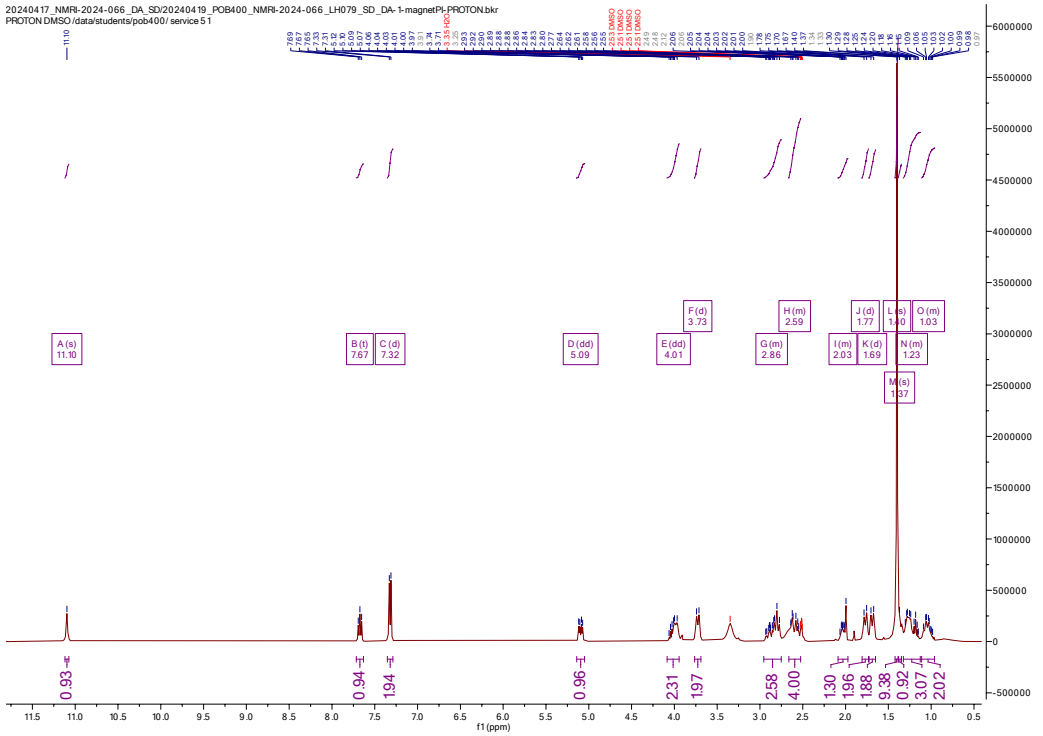
1f ^{1}H-NMR (500MHz, DMSO-d6)



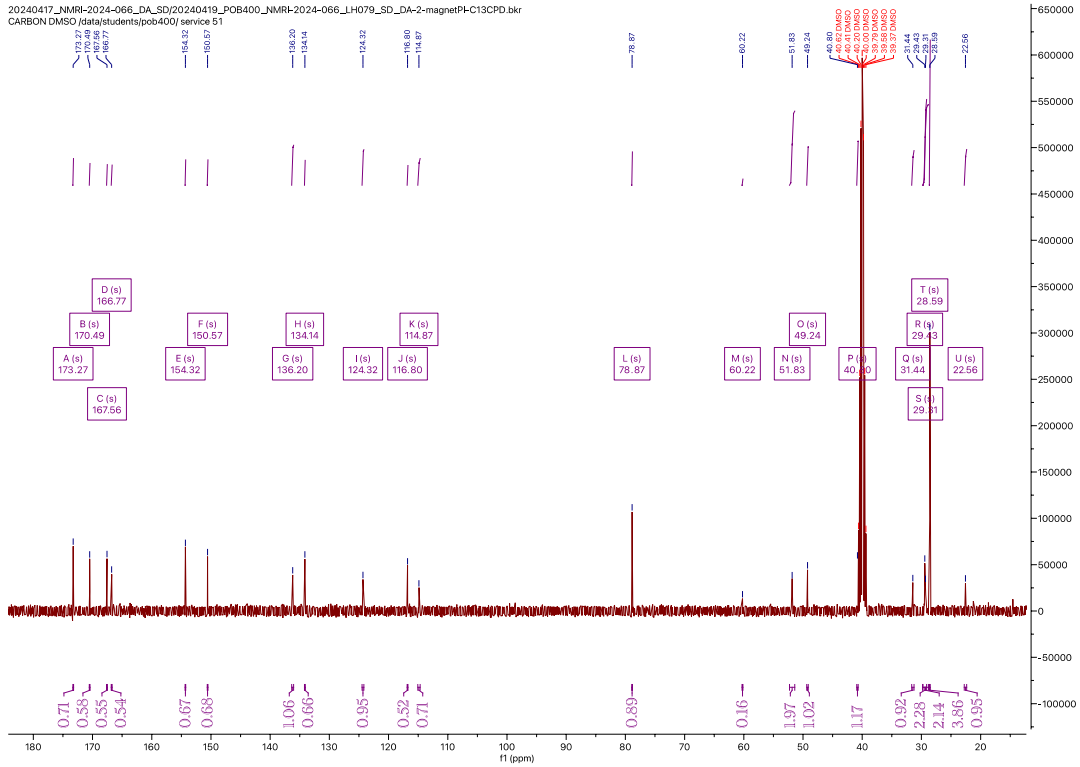
1f ^{13}C-NMR (125MHz, DMSO-d6)



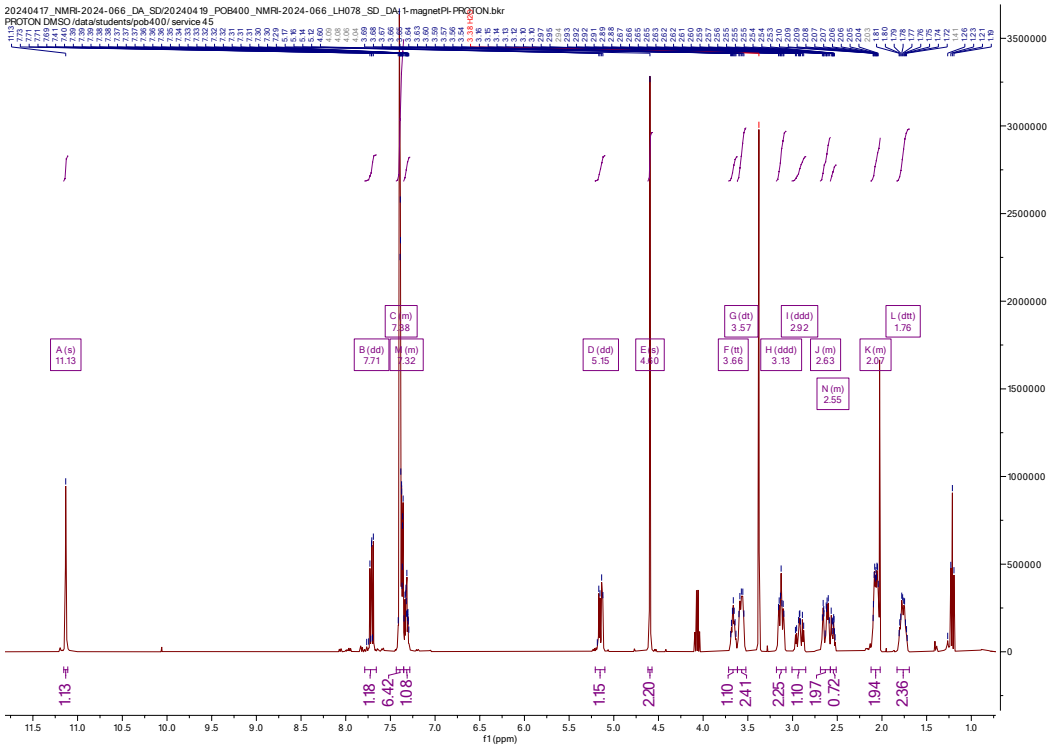
1g ^{1}H-NMR (500MHz, DMSO-d6)



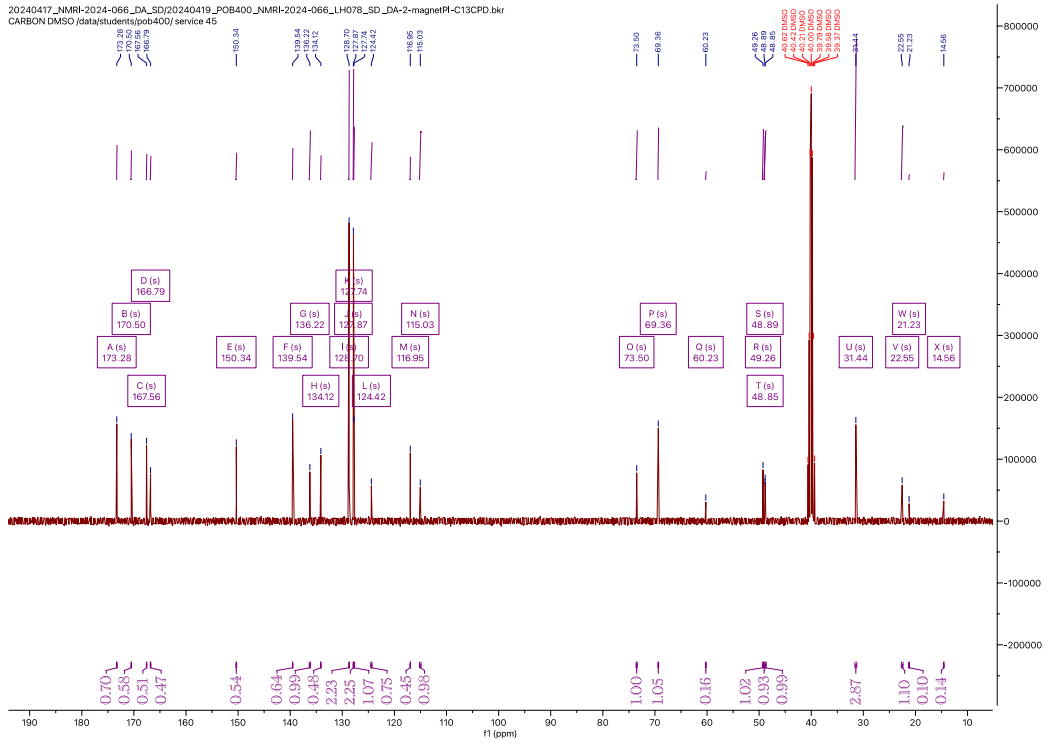
1g ^{13}C-NMR (125MHz, DMSO-d6)



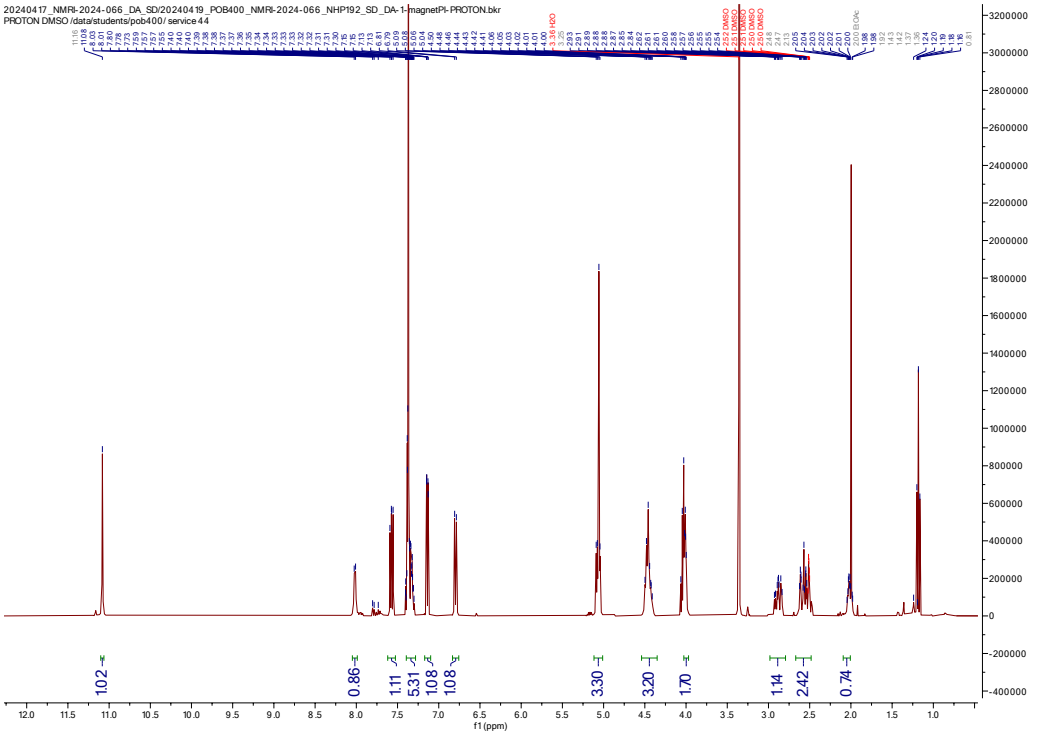
1h ^{1}H-NMR (500MHz, DMSO-d6)



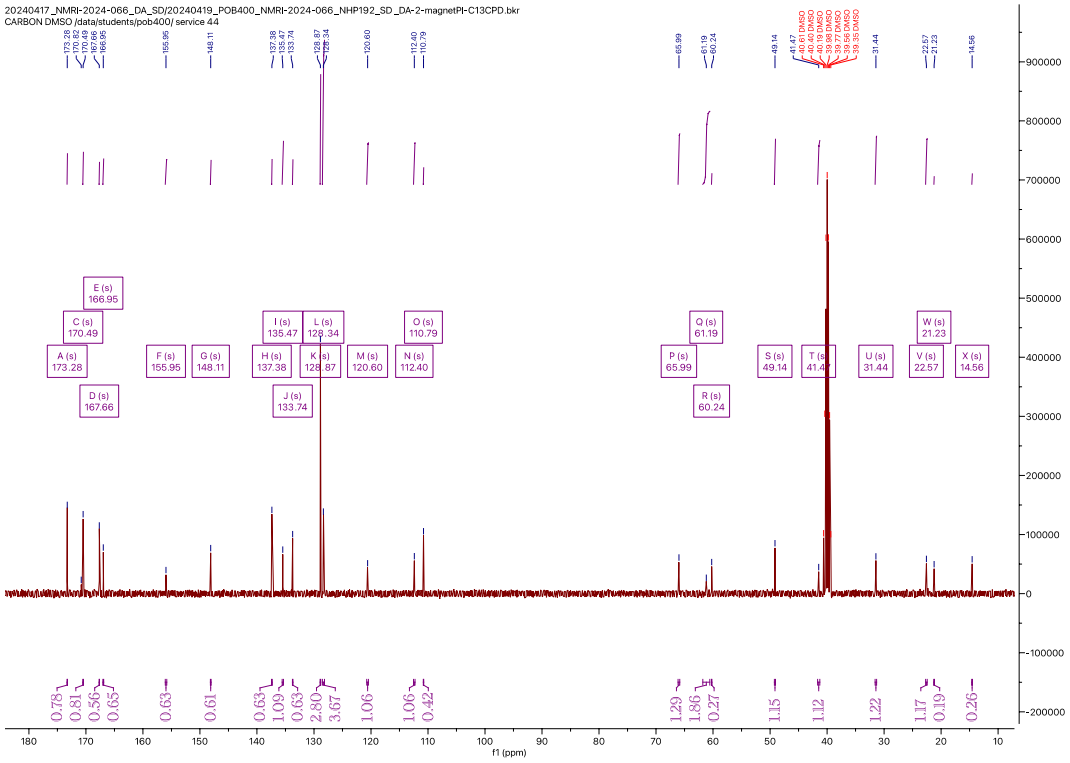
1h ^{13}C-NMR (125MHz, DMSO-d6)



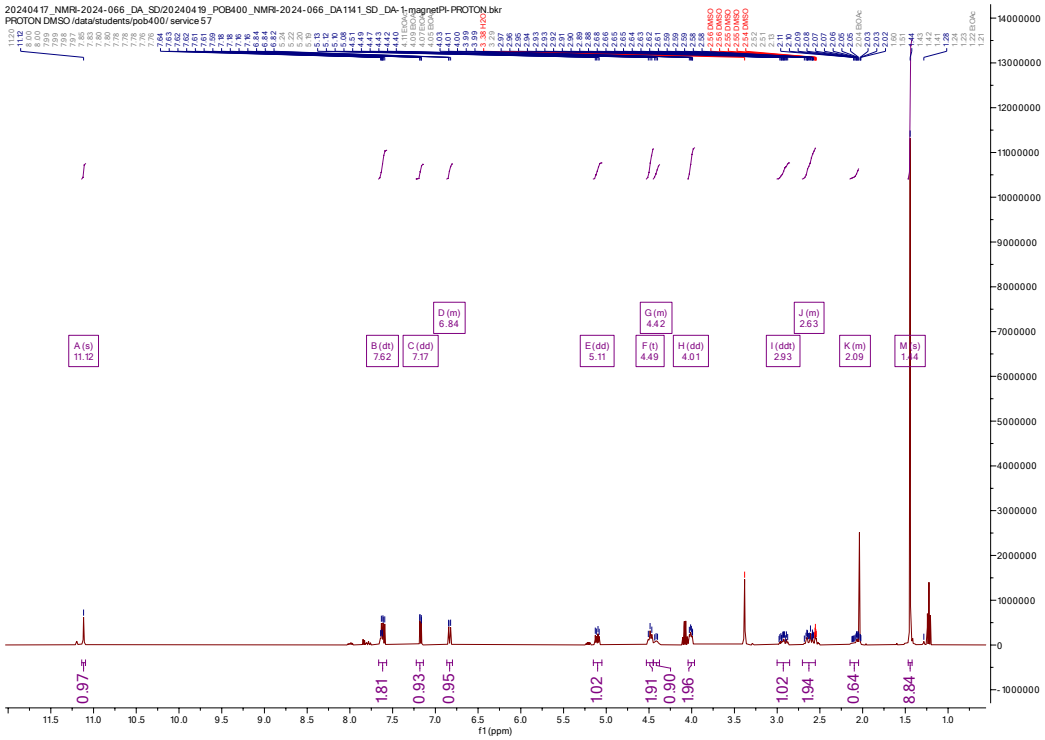
1i ^{1}H-NMR (500MHz, DMSO-d6)



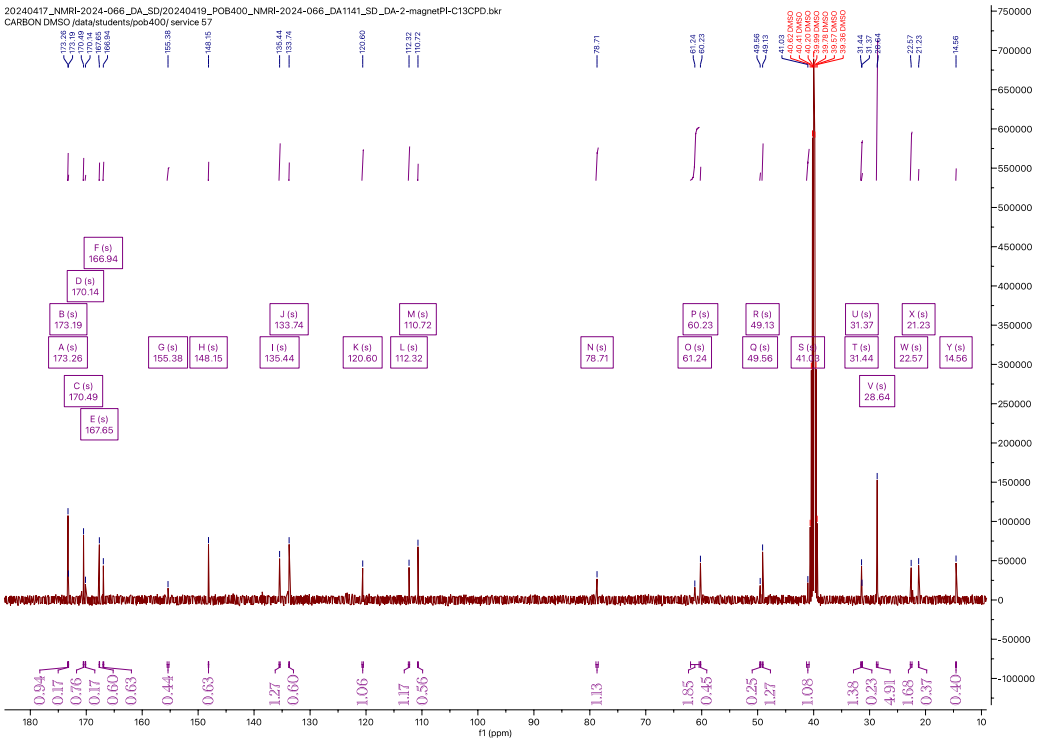
1i ^{13}C-NMR (125MHz, DMSO-d6)



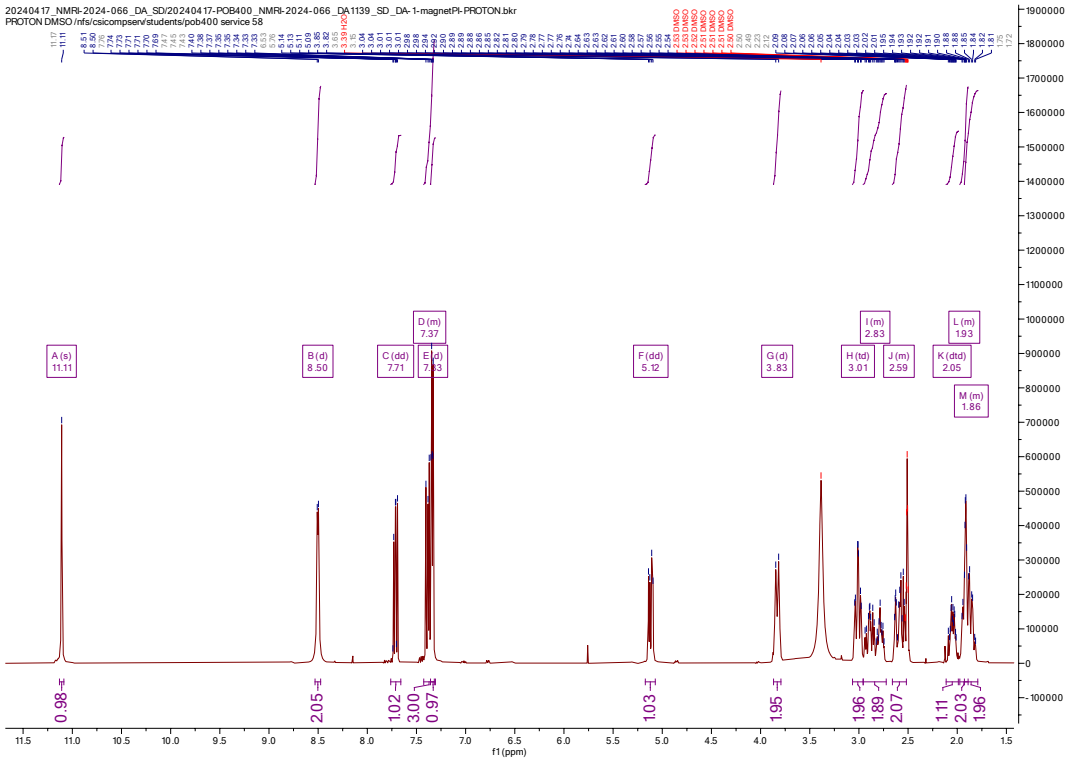
1j ^{1}H-NMR (500MHz, DMSO-d6)



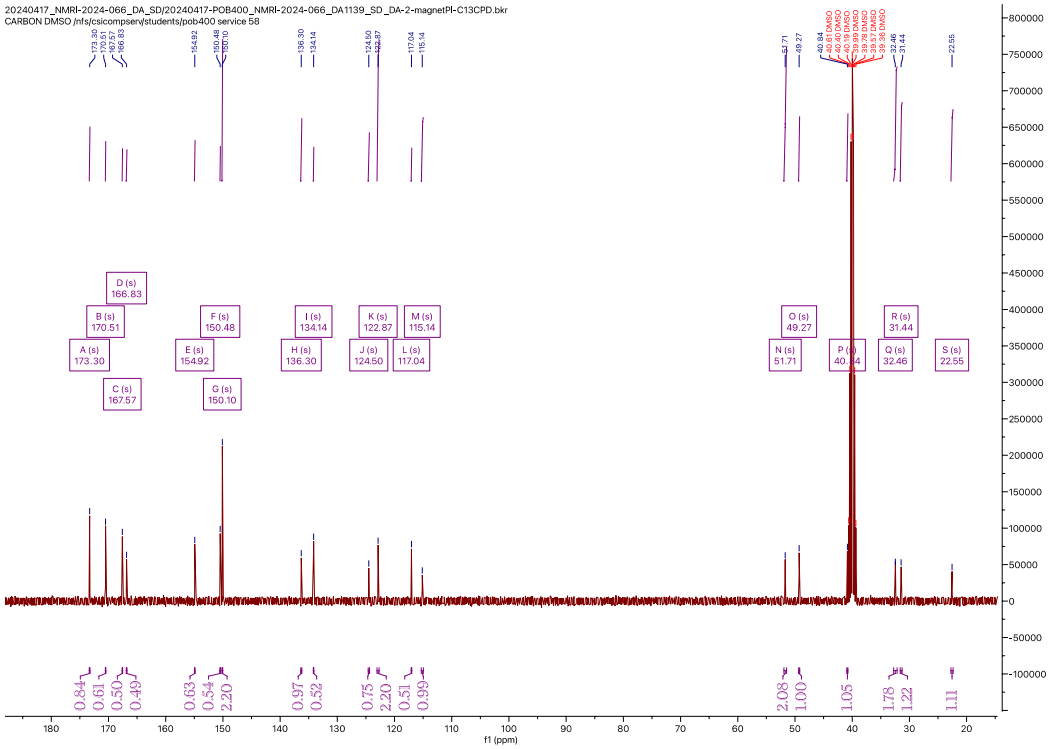
1j ^{13}C-NMR (125MHz, DMSO-d6)



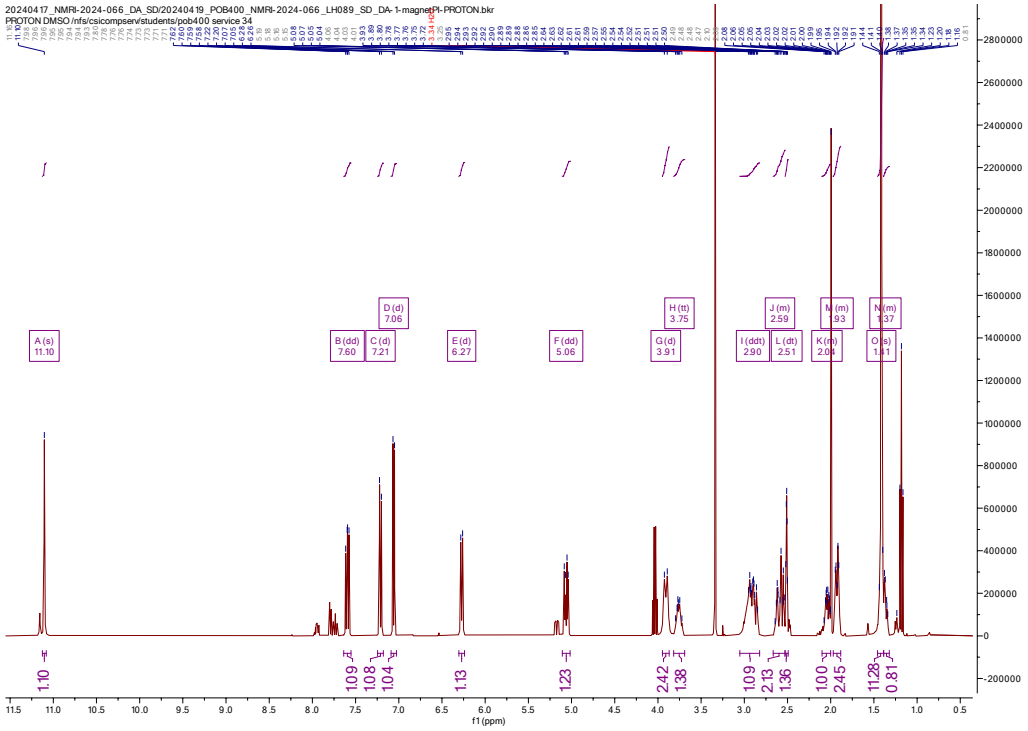
1k ^{1}H-NMR (500MHz, DMSO-d6)



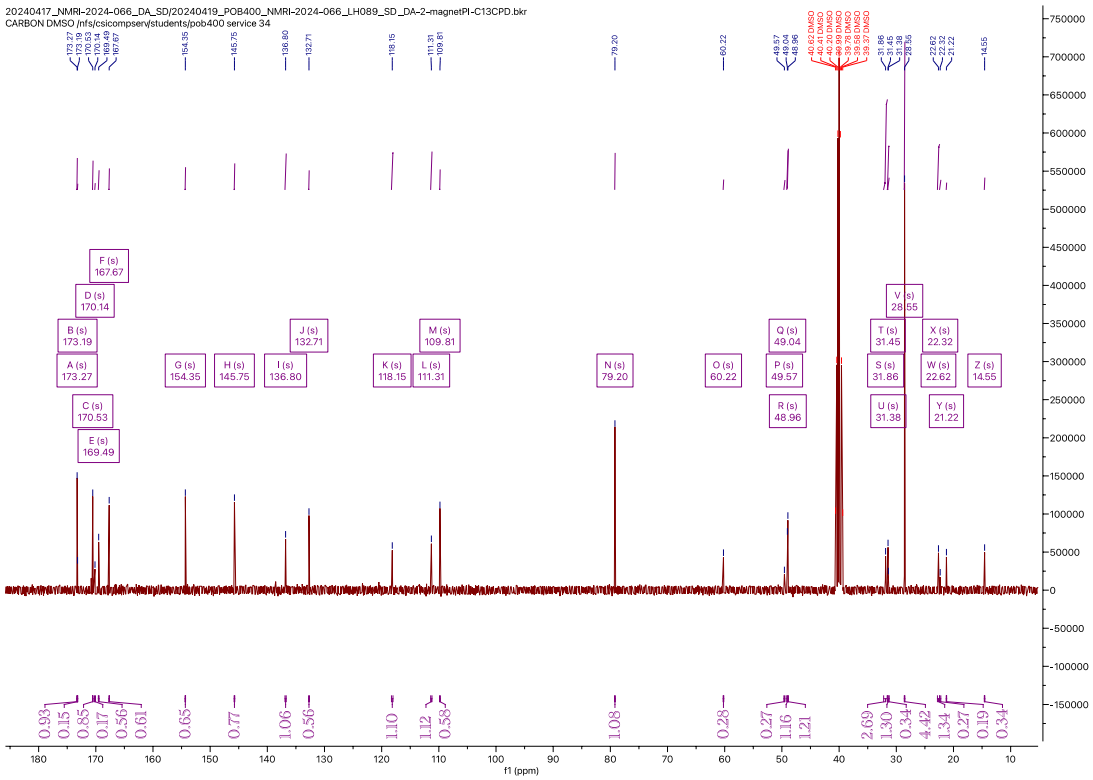
1k ^{13}C-NMR (125MHz, DMSO-d6)



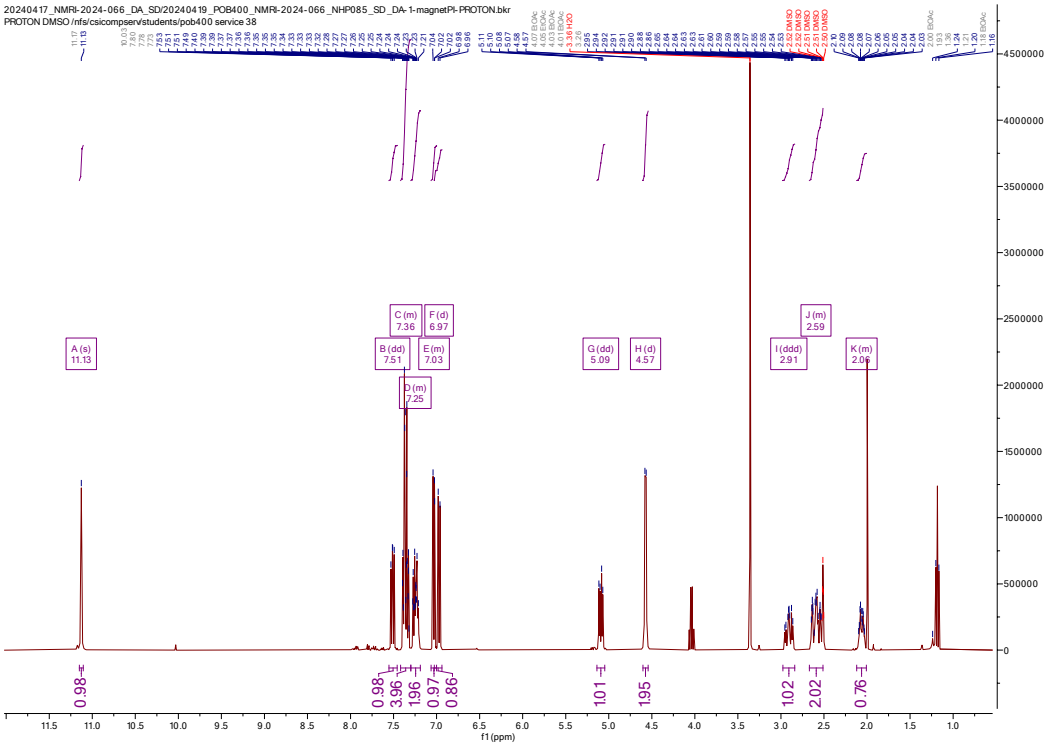
1l ^{1}H-NMR (500MHz, DMSO-d6)



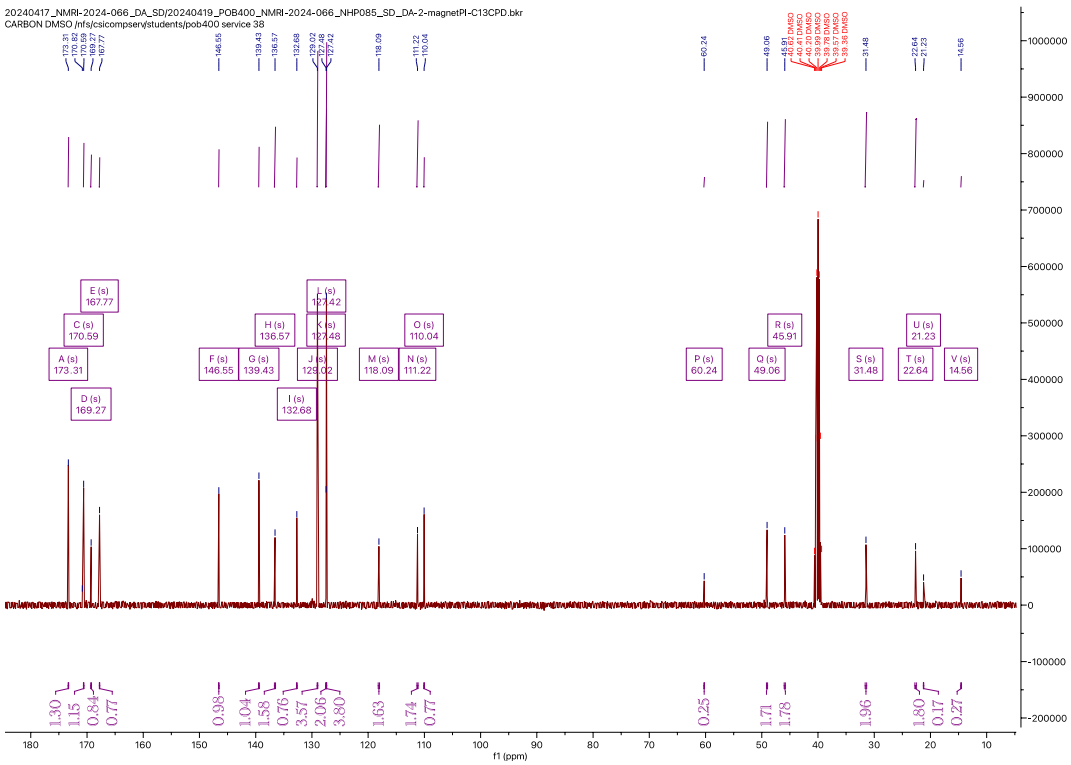
1l ^{13}C-NMR (125MHz, DMSO-d6)



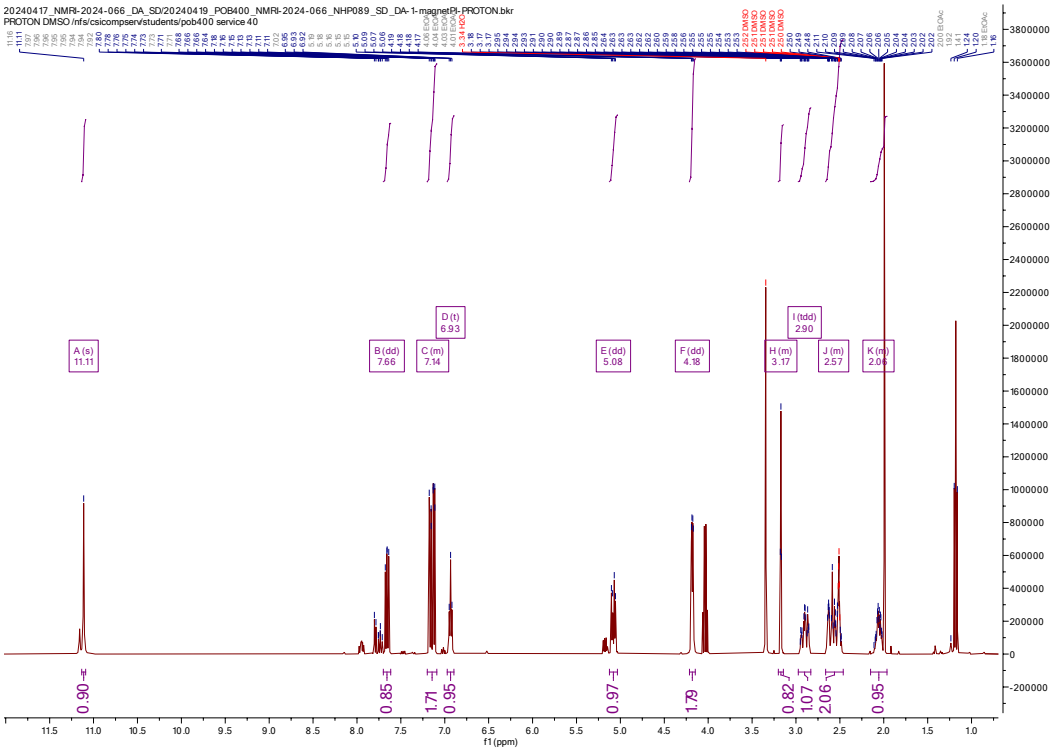
1m ^{1}H-NMR (500MHz, DMSO-d6)



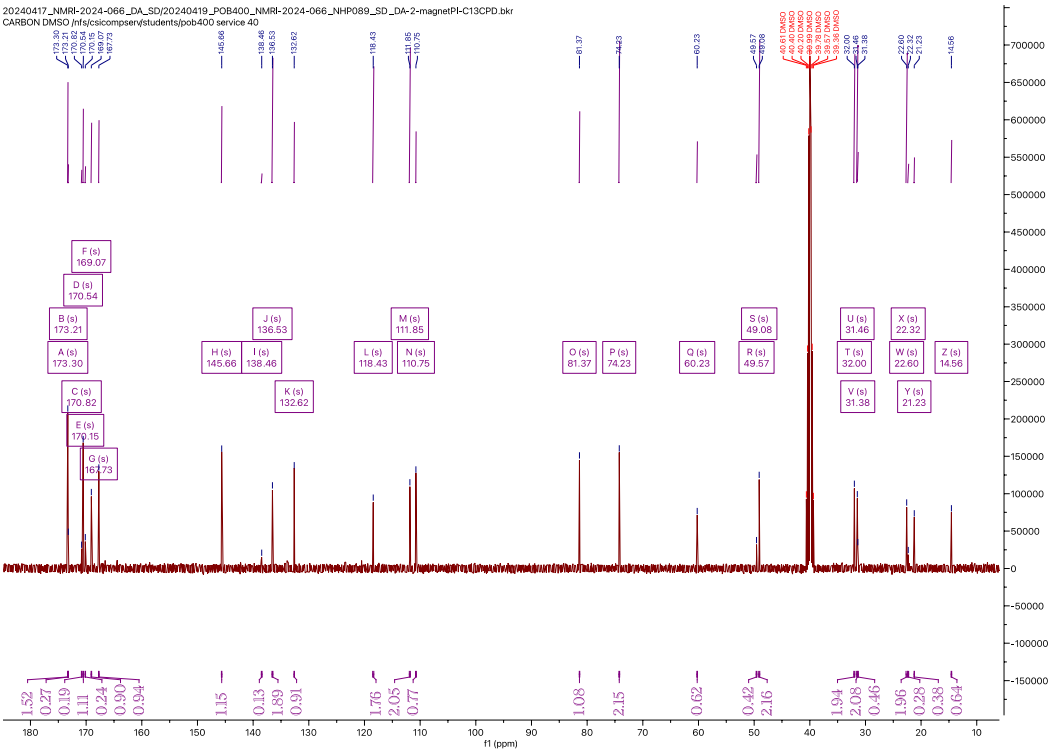
1m ^{13}C-NMR (125MHz, DMSO-d6)



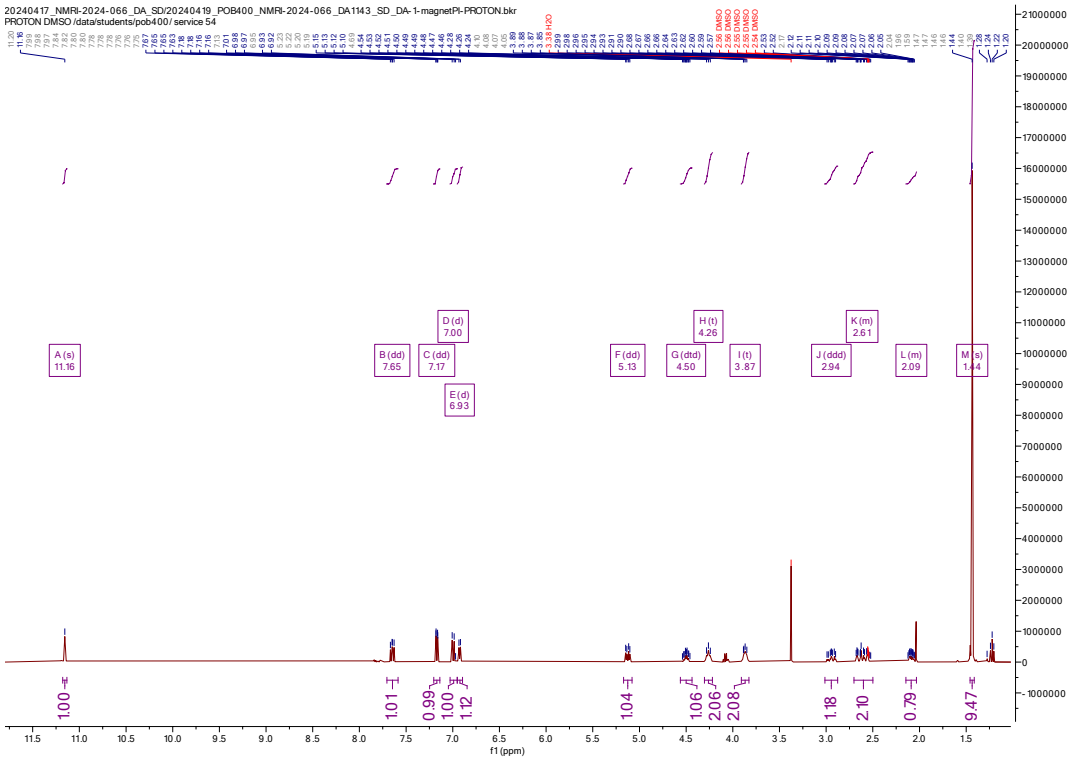
1n ^{1}H-NMR (500MHz, DMSO-d6)



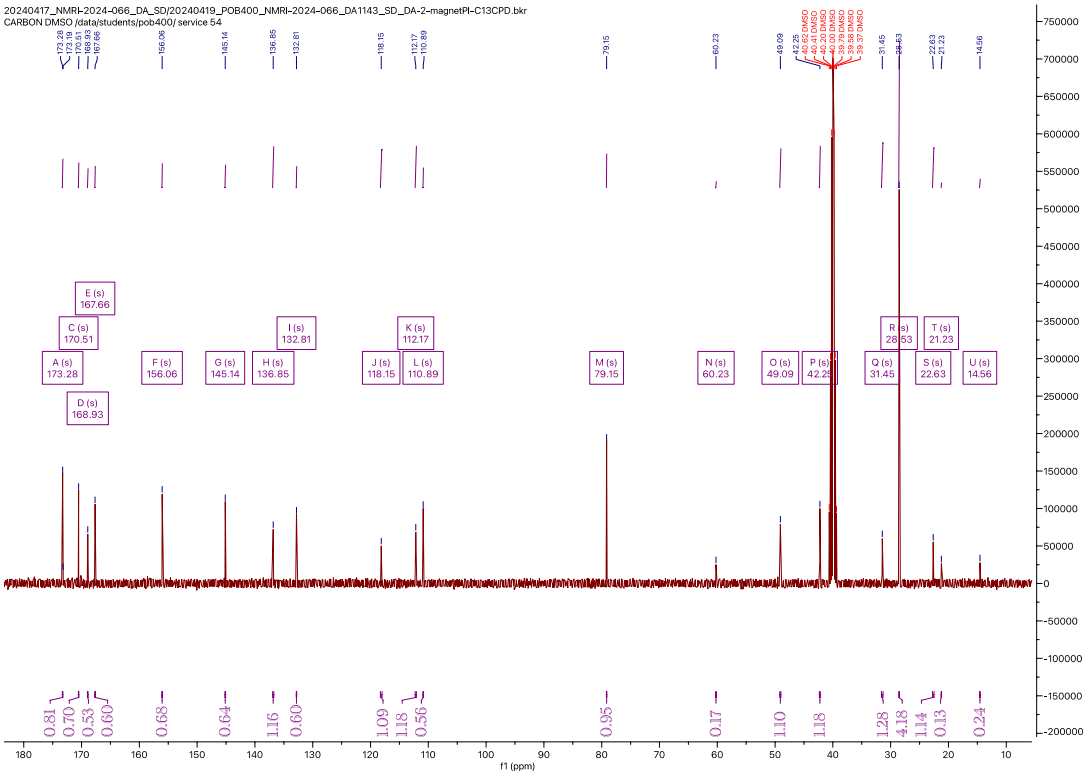
1n ^{13}C-NMR (125MHz, DMSO-d6)



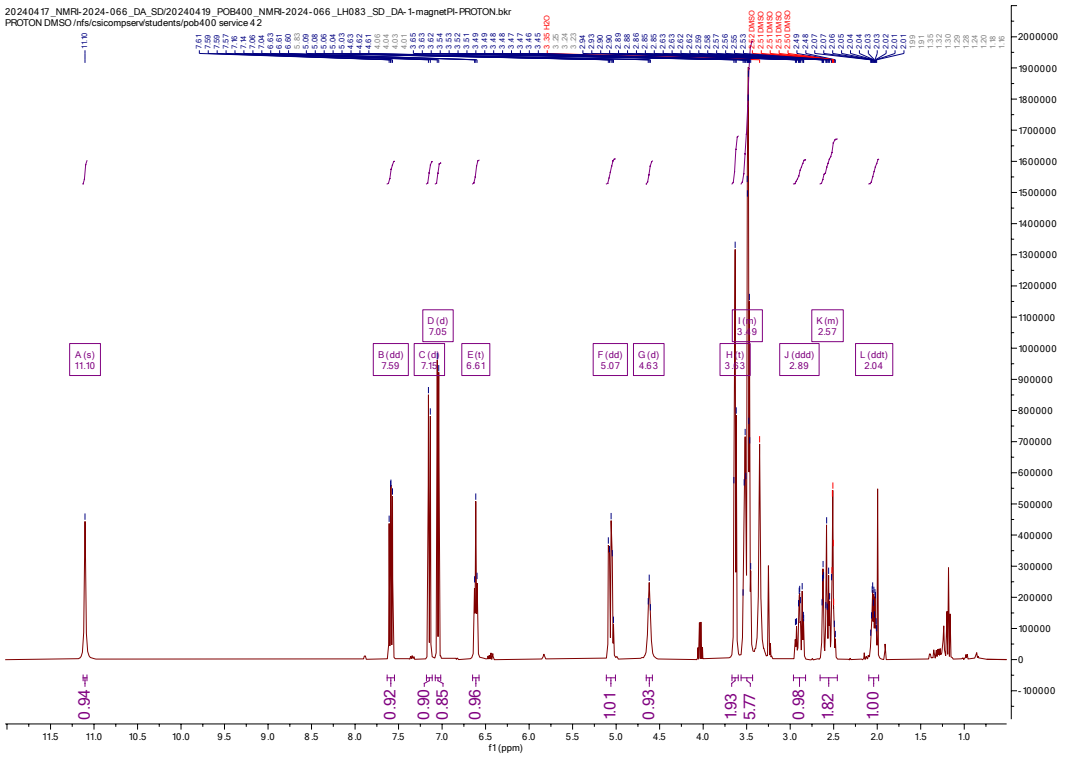
1o ^{1}H-NMR (500MHz, DMSO-d6)



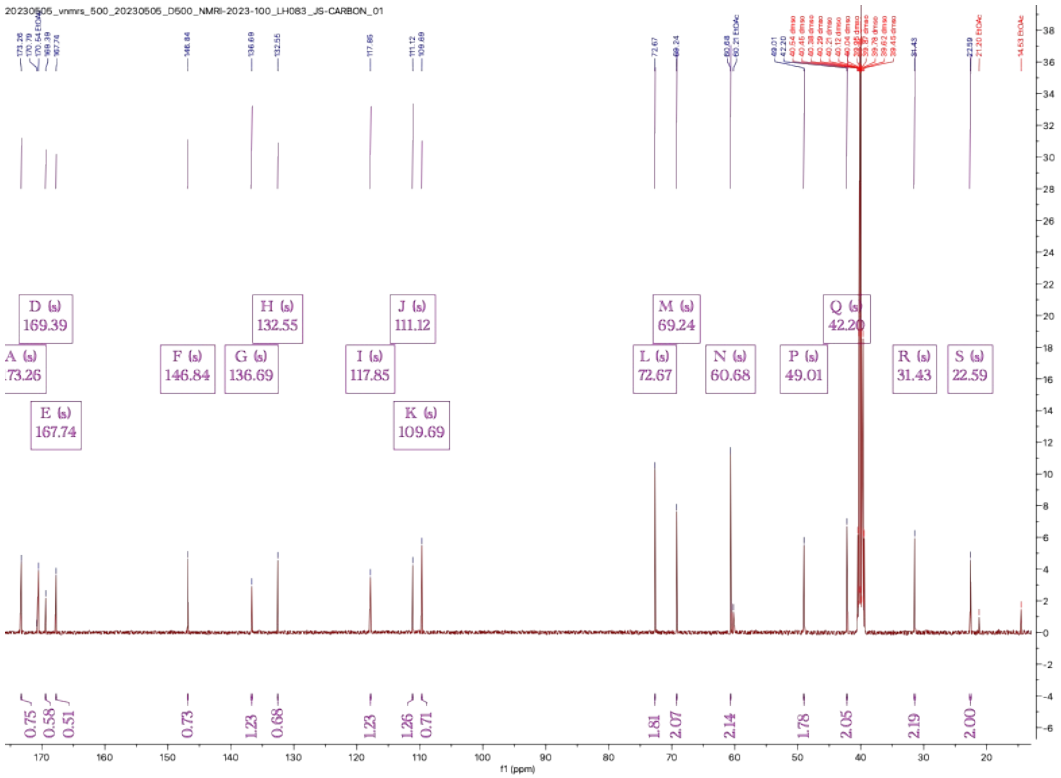
1o ^{13}C-NMR (125MHz, DMSO-d6)



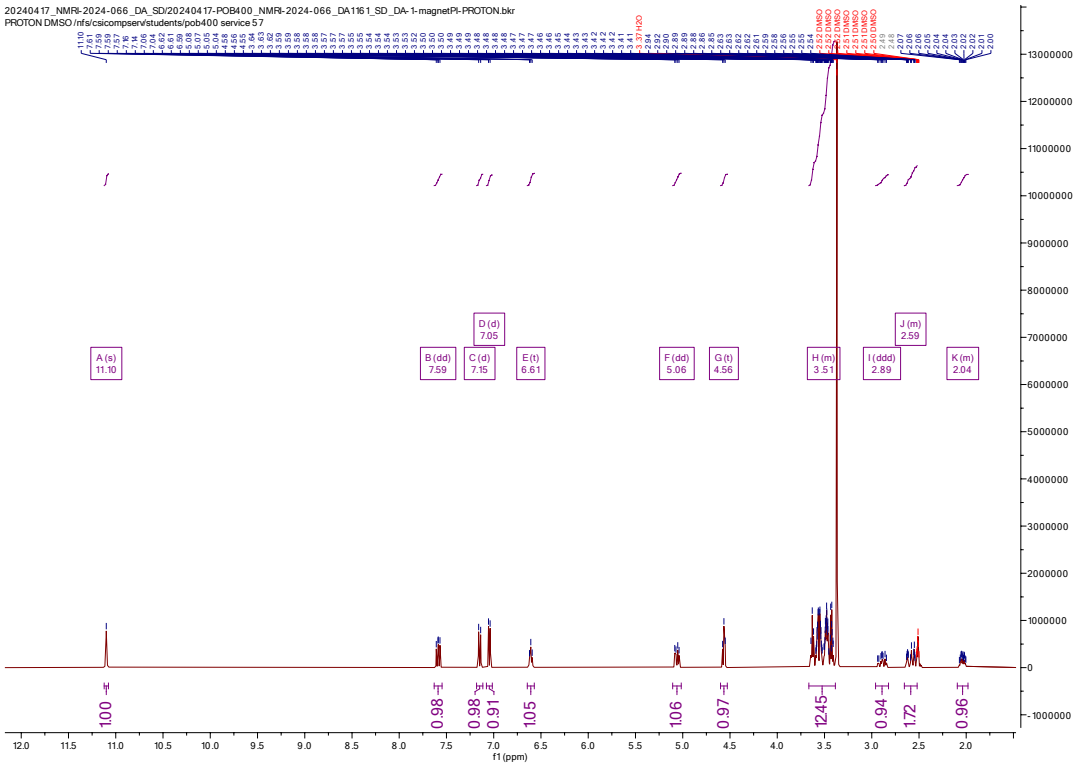
1p ^{1}H-NMR (500MHz, DMSO-d6)



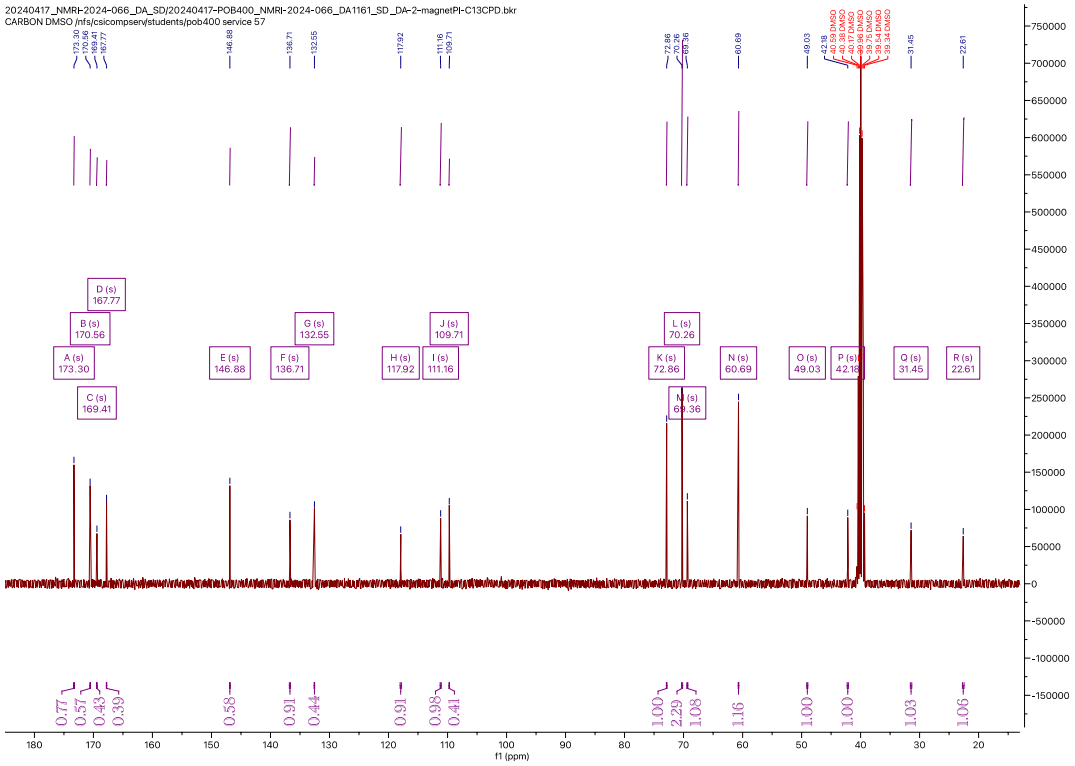
1p ^{13}C-NMR (125MHz, DMSO-d6)



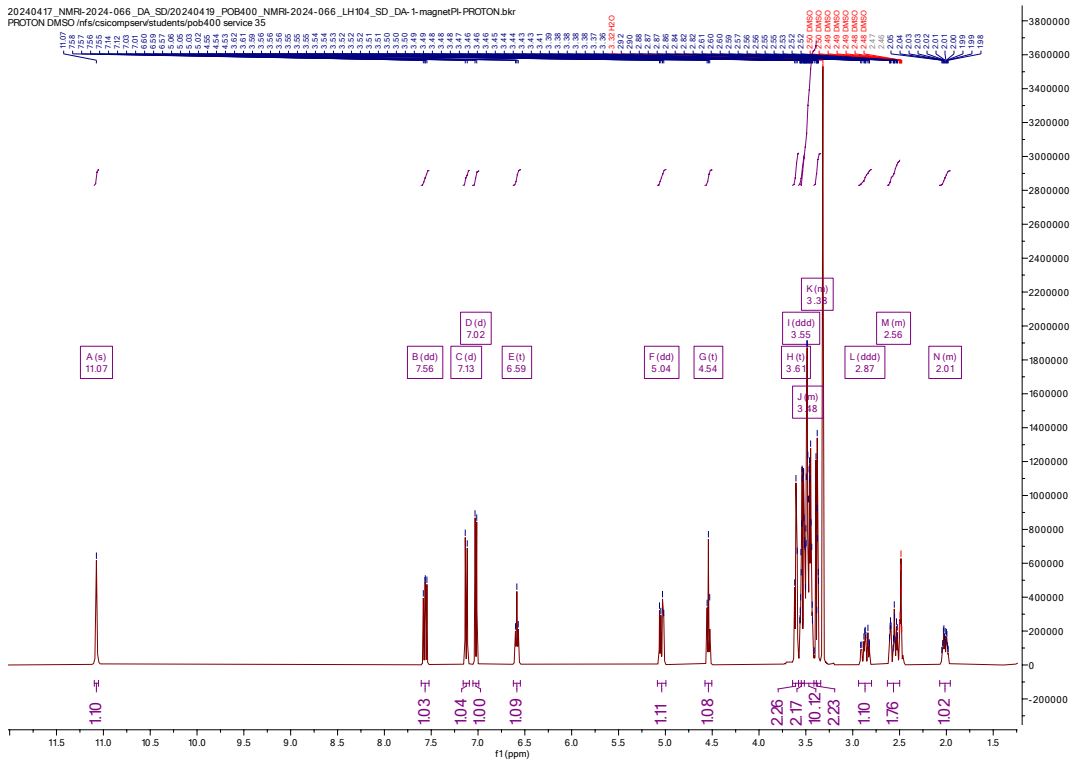
1q ^{1}H-NMR (500MHz, DMSO-d6)



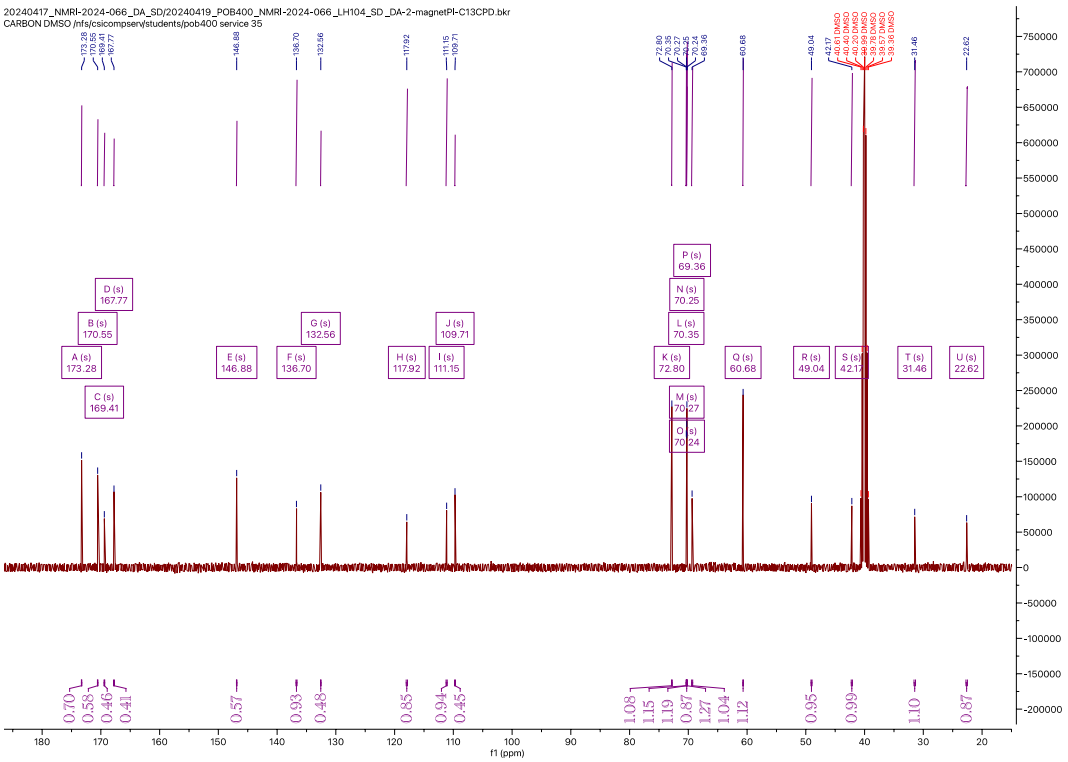
1q ^{13}C-NMR (125MHz, DMSO-d6)



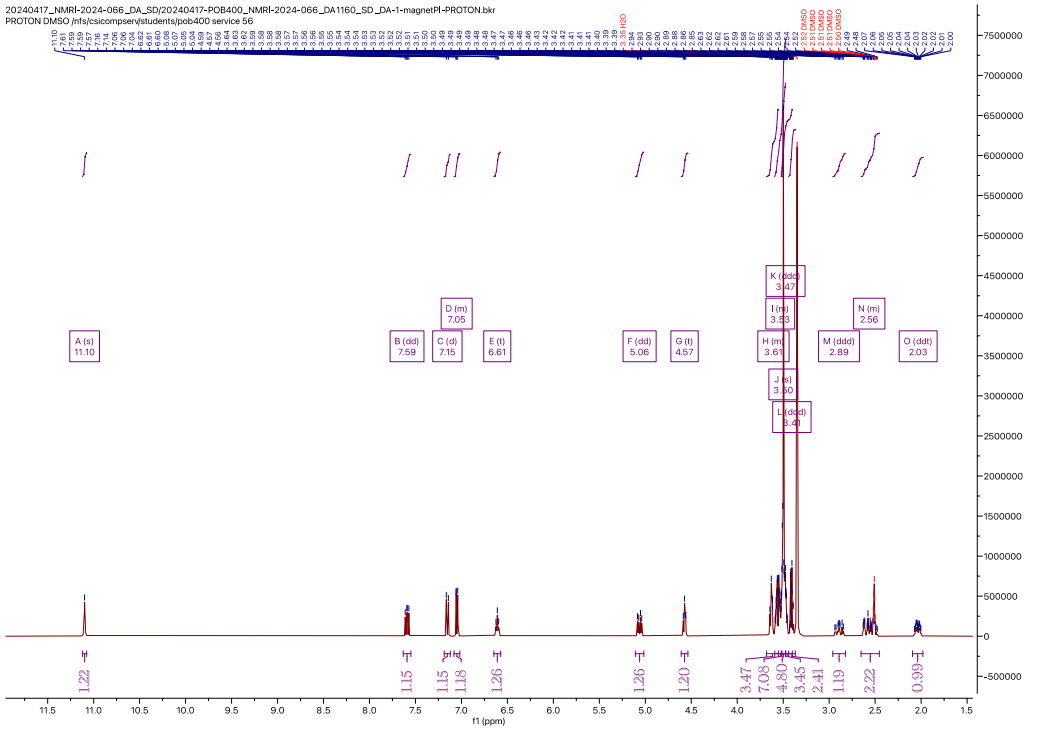
1r ^{1}H-NMR (500MHz, DMSO-d6)



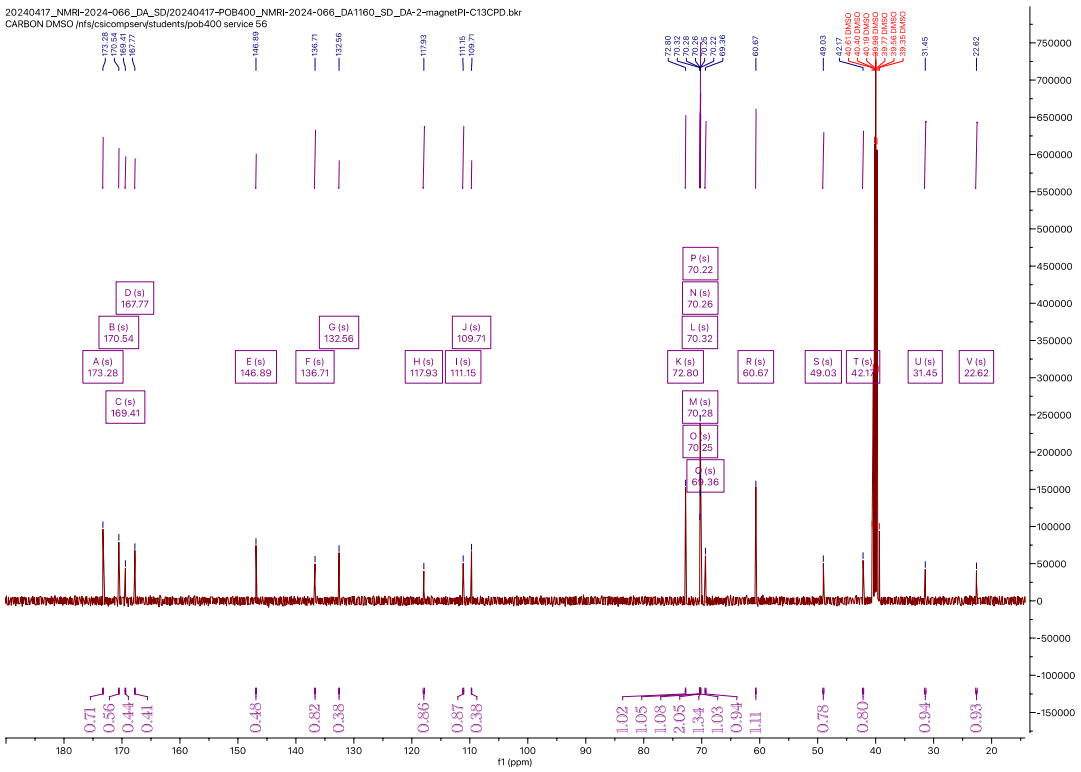
1r ^{13}C-NMR (125MHz, DMSO-d6)



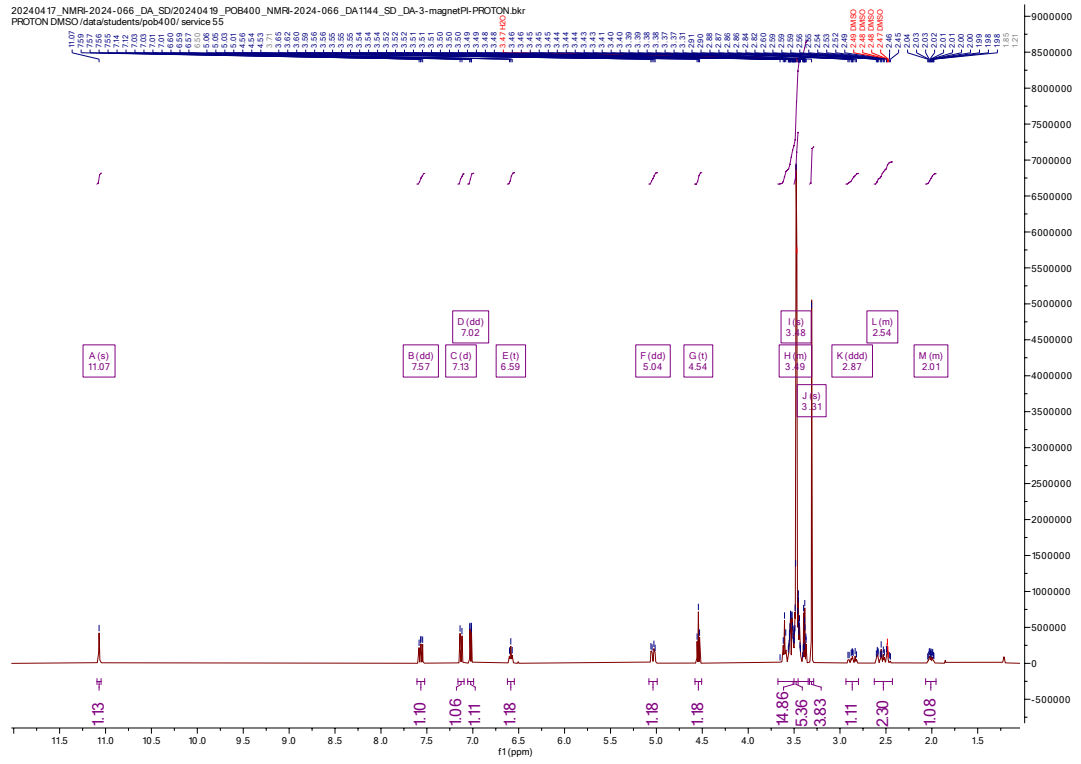
1s ^{1}H-NMR (500MHz, DMSO-d6)



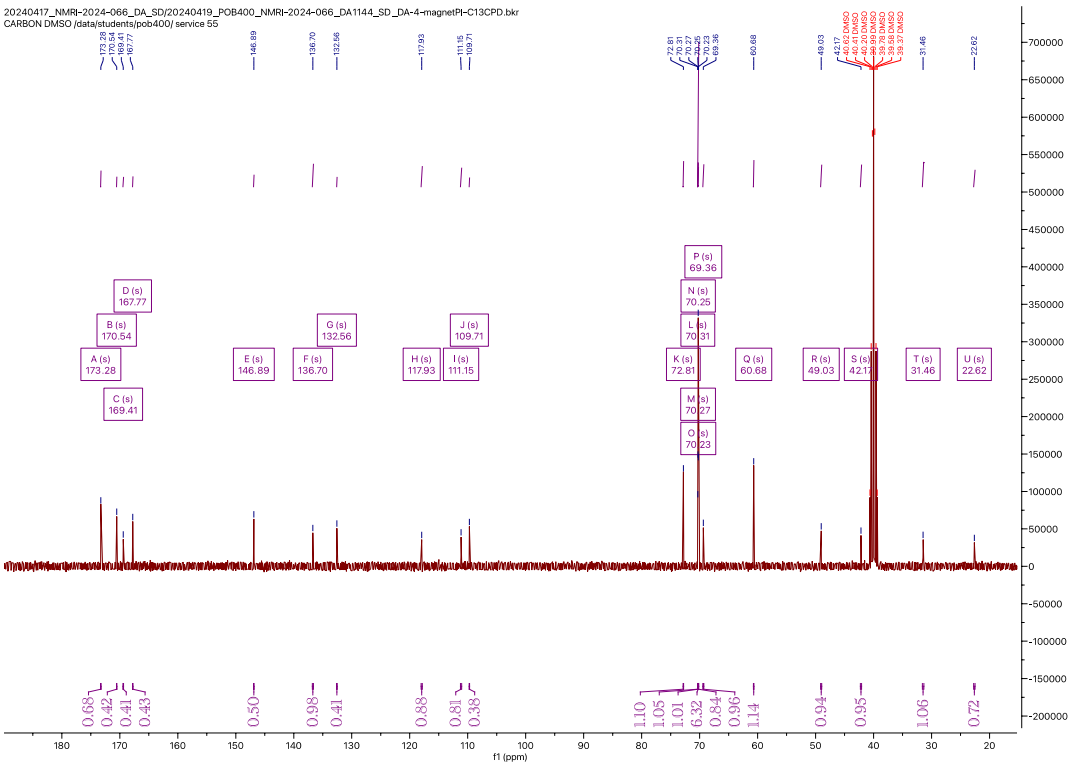
1s ^{13}C-NMR (125MHz, DMSO-d6)



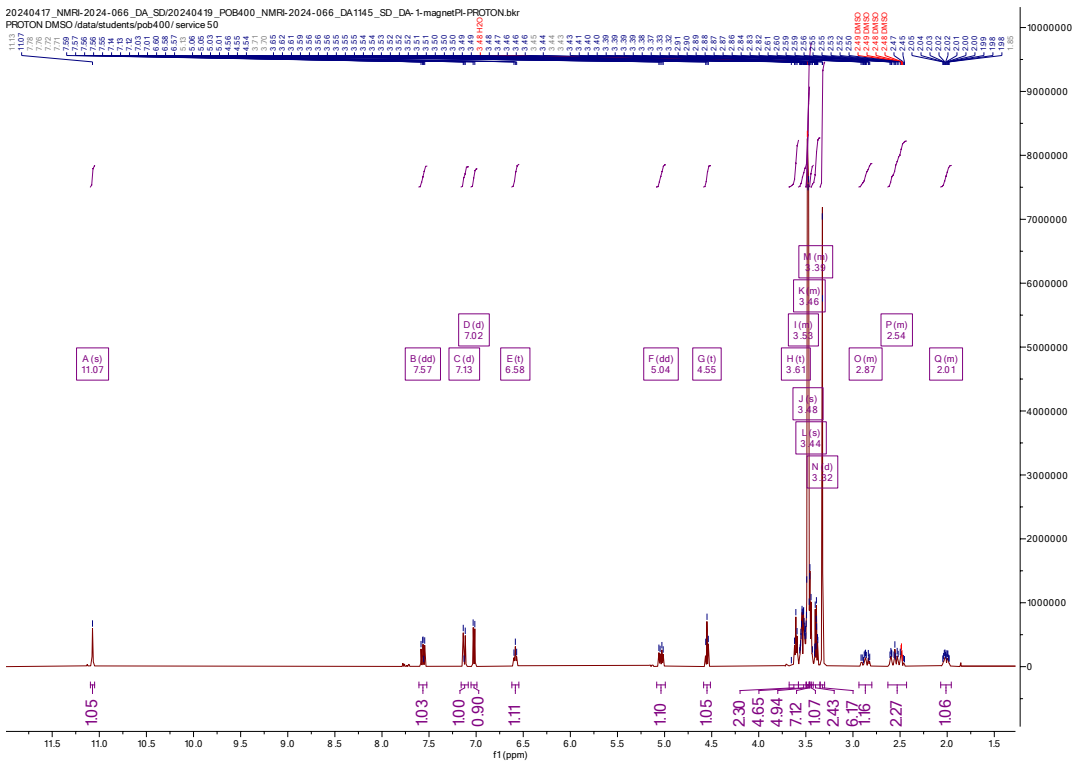
1t ^{1}H-NMR (500MHz, DMSO-d6)



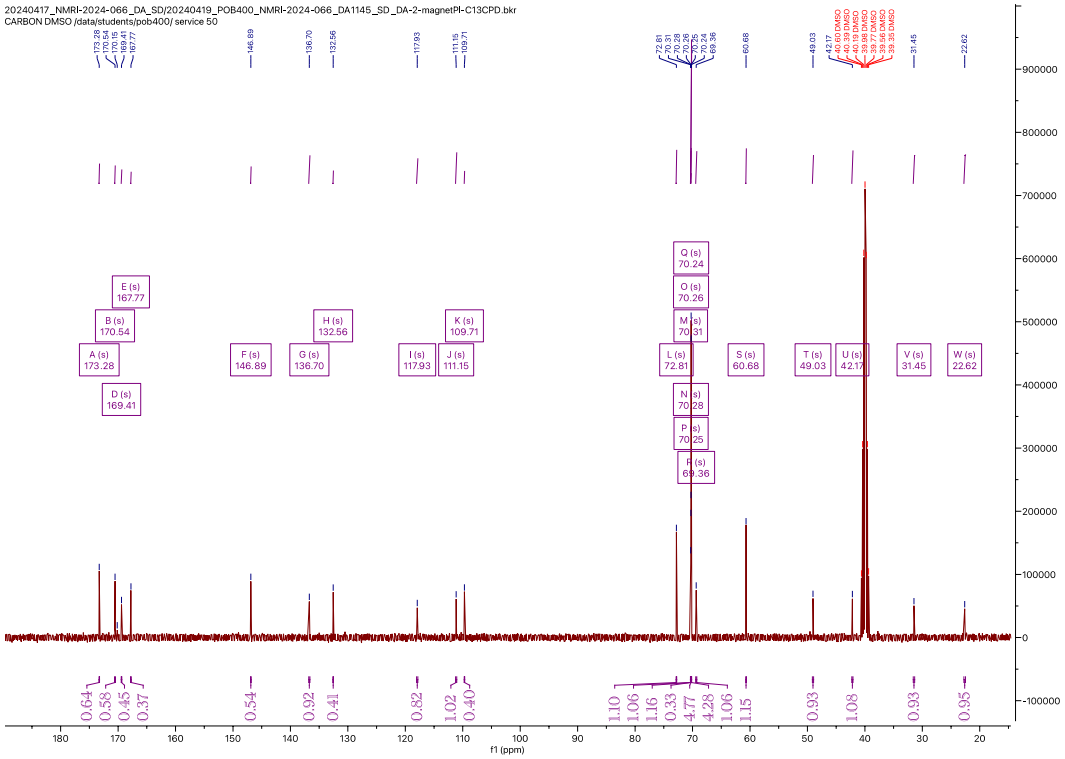
1t ^{13}C-NMR (125MHz, DMSO-d6)



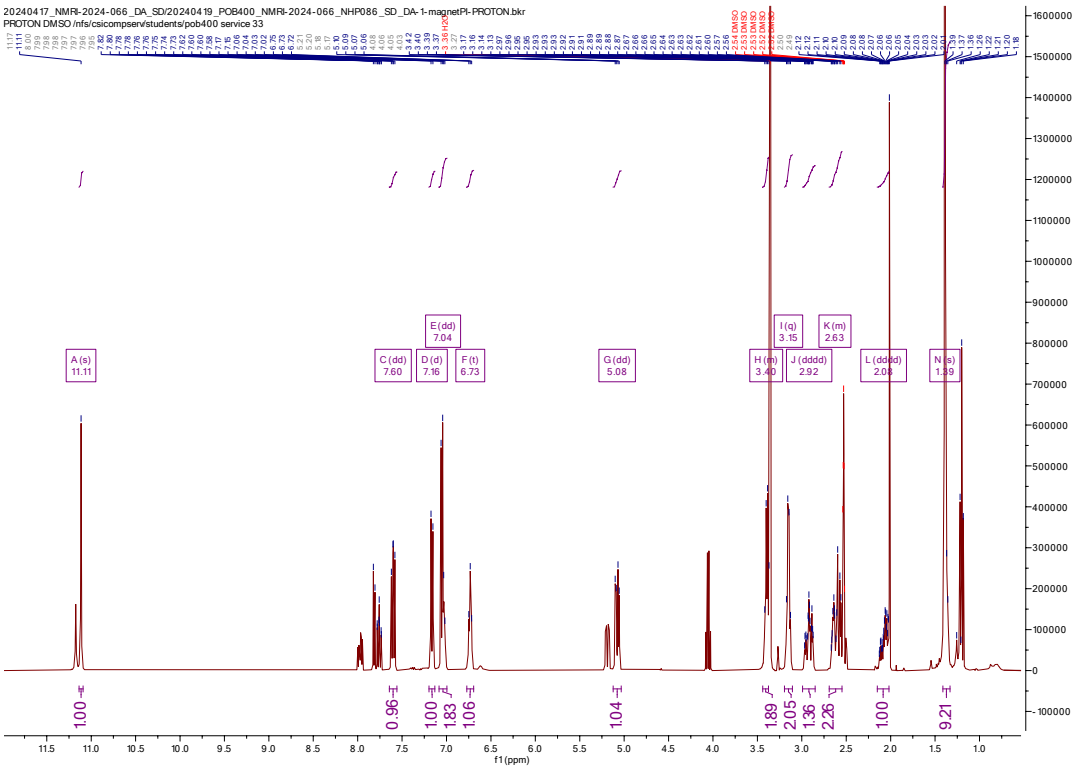
1u ^{1}H-NMR (500MHz, DMSO-d6)



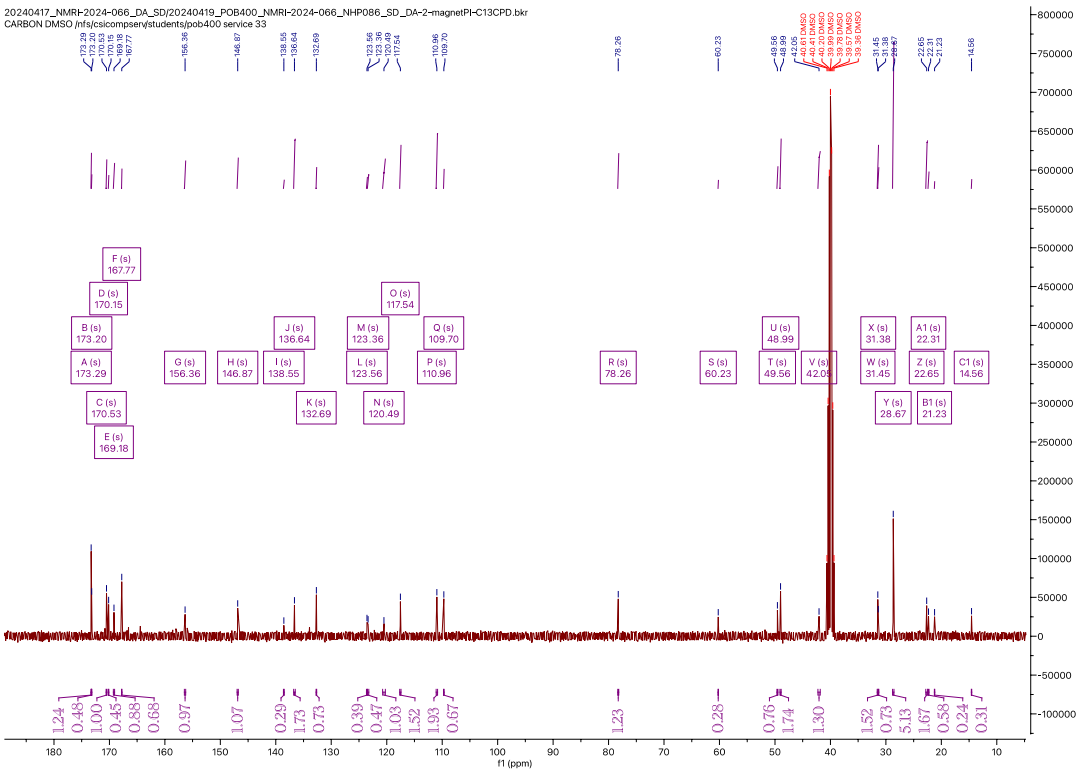
1u ^{13}C-NMR (125MHz, DMSO-d6)



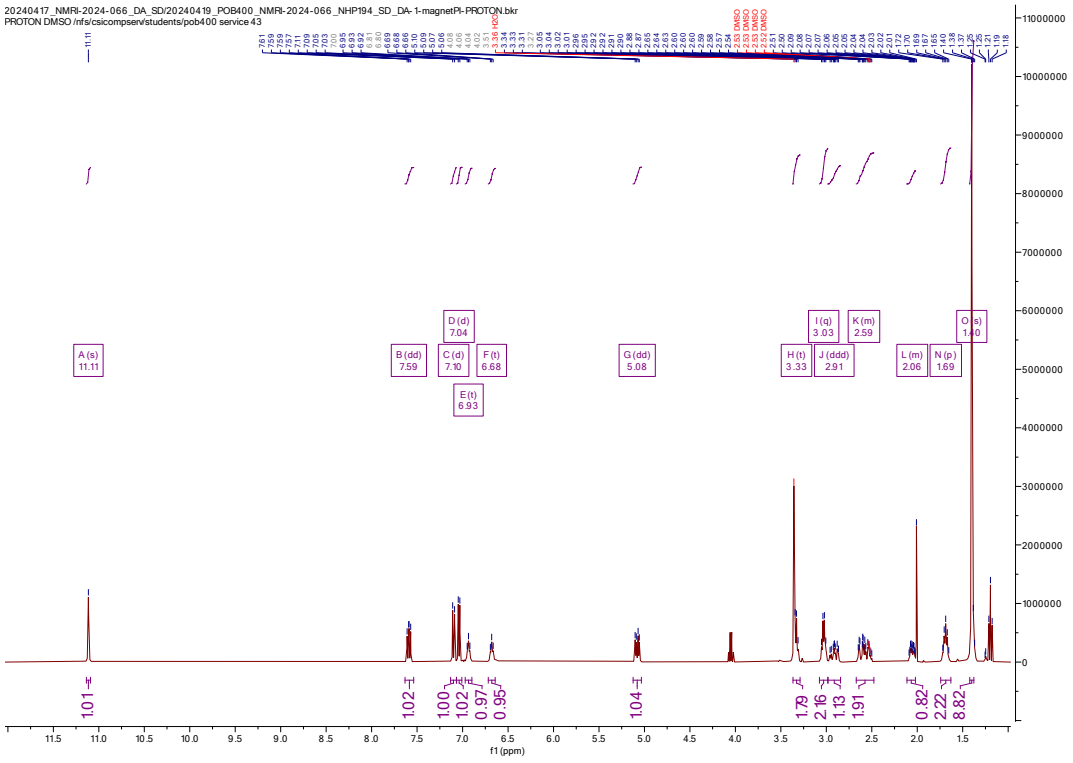
1v ^{1}H-NMR (500MHz, DMSO-d6)



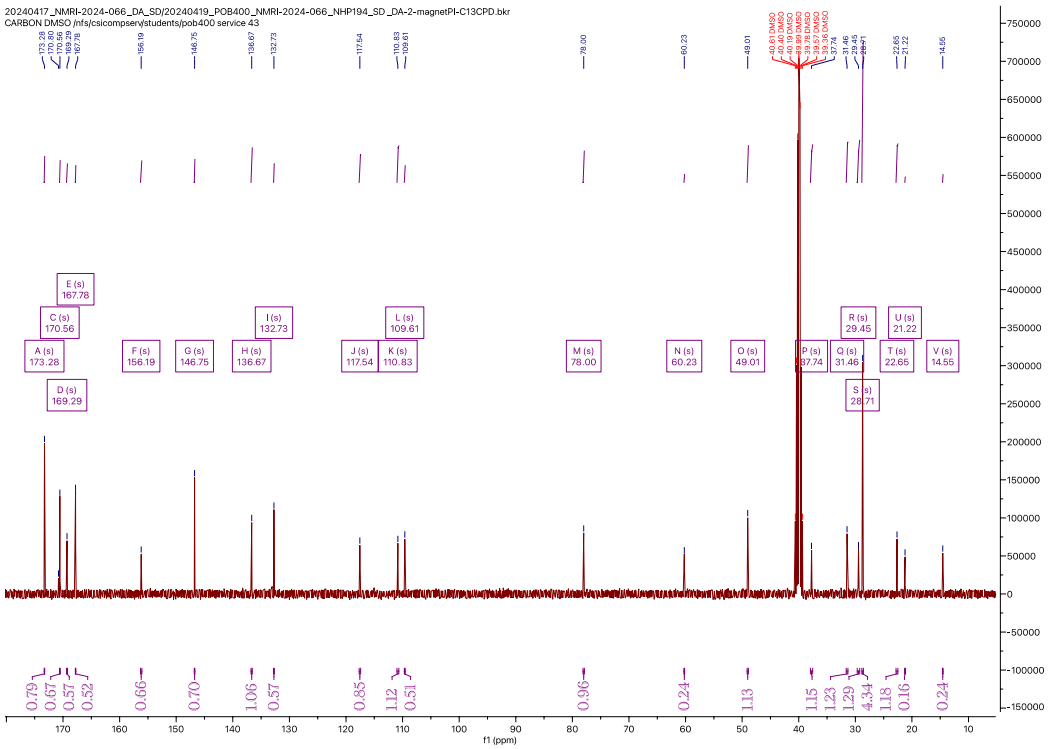
1v ^{13}C-NMR (125MHz, DMSO-d6)



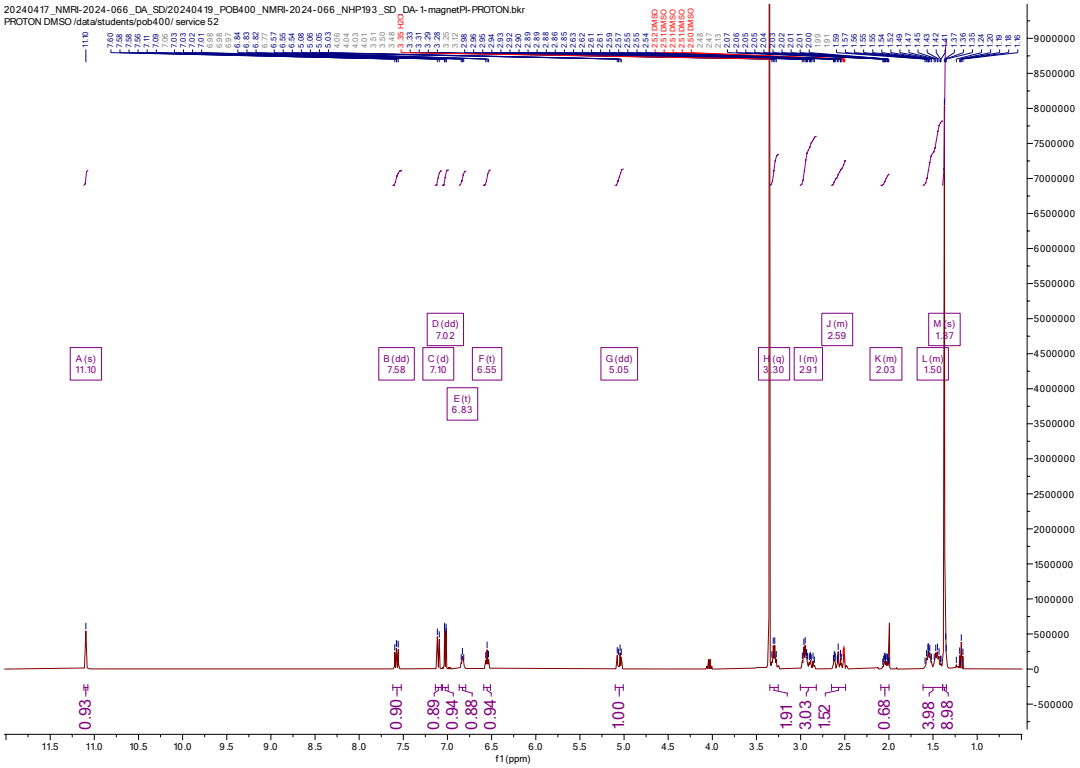
1w ^{1}H-NMR (500MHz, DMSO-d6)



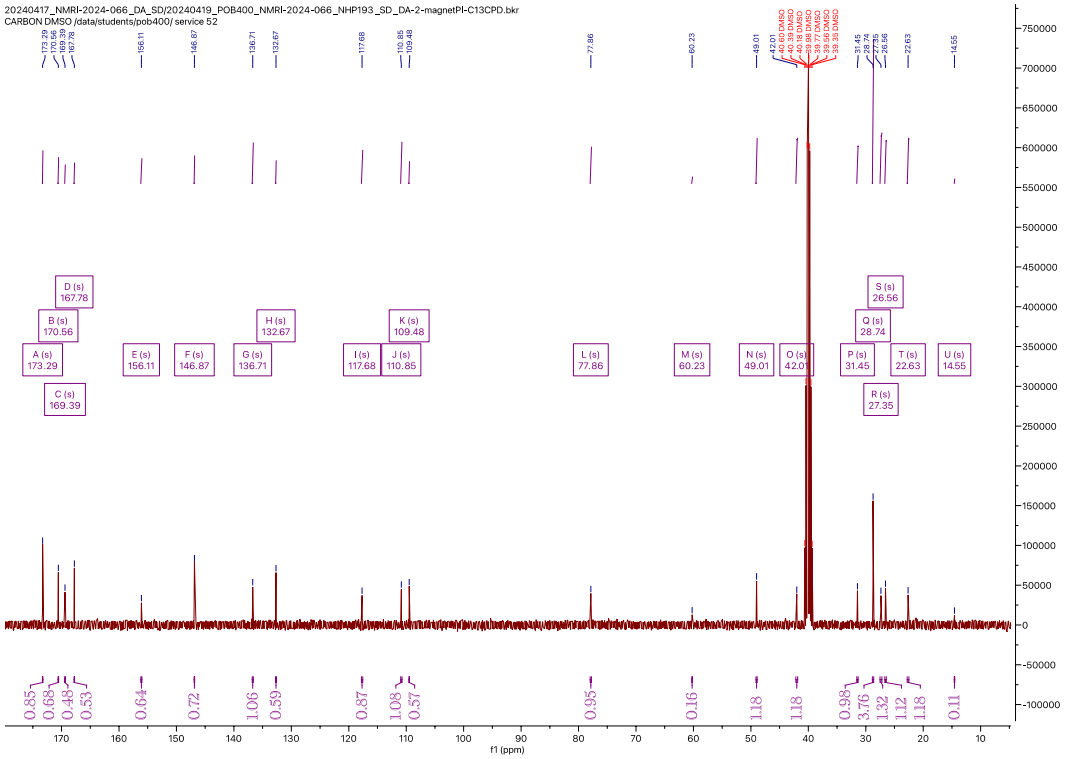
1w ^{13}C-NMR (125MHz, DMSO-d6)



1x ^{1}H-NMR (500MHz, DMSO-d6)

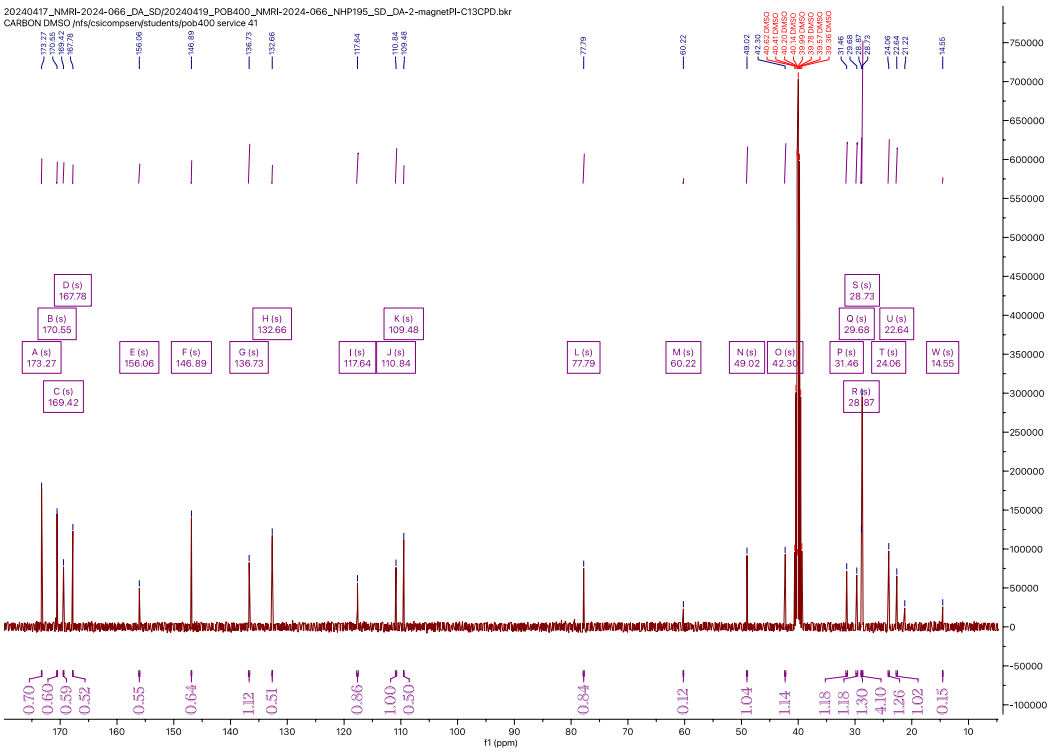


1x ^{13}C-NMR (125MHz, DMSO-d6)



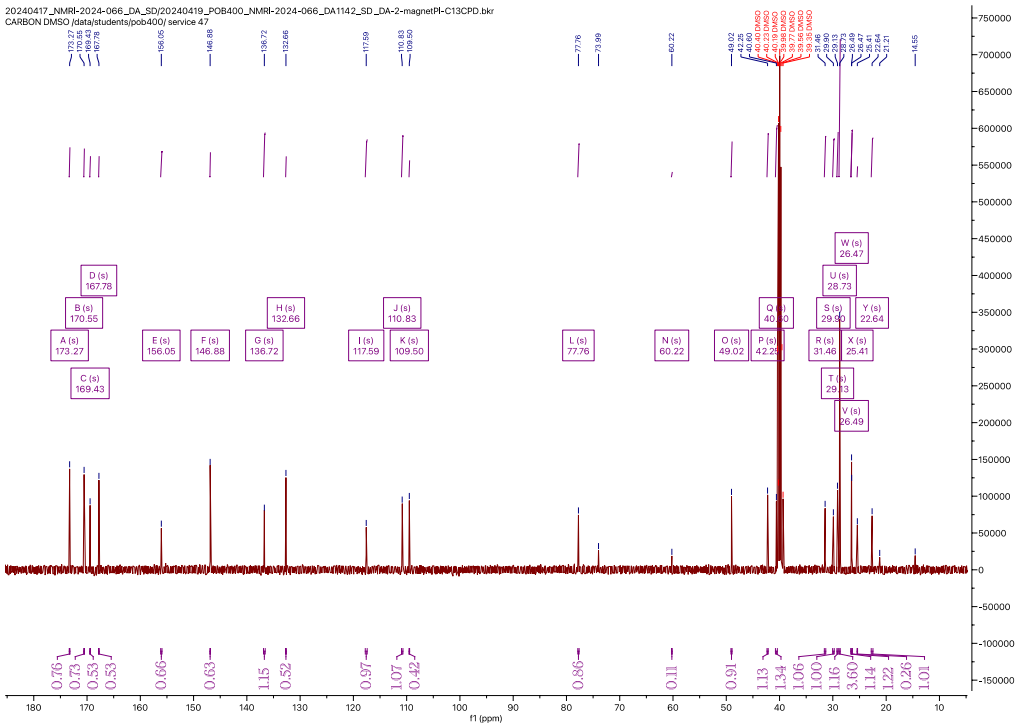
1y ^{1}H-NMR (500MHz, DMSO-d6)

1y ^{13}C-NMR (125MHz, DMSO-d6)



1z ^{1}H-NMR (500MHz, DMSO-d6)

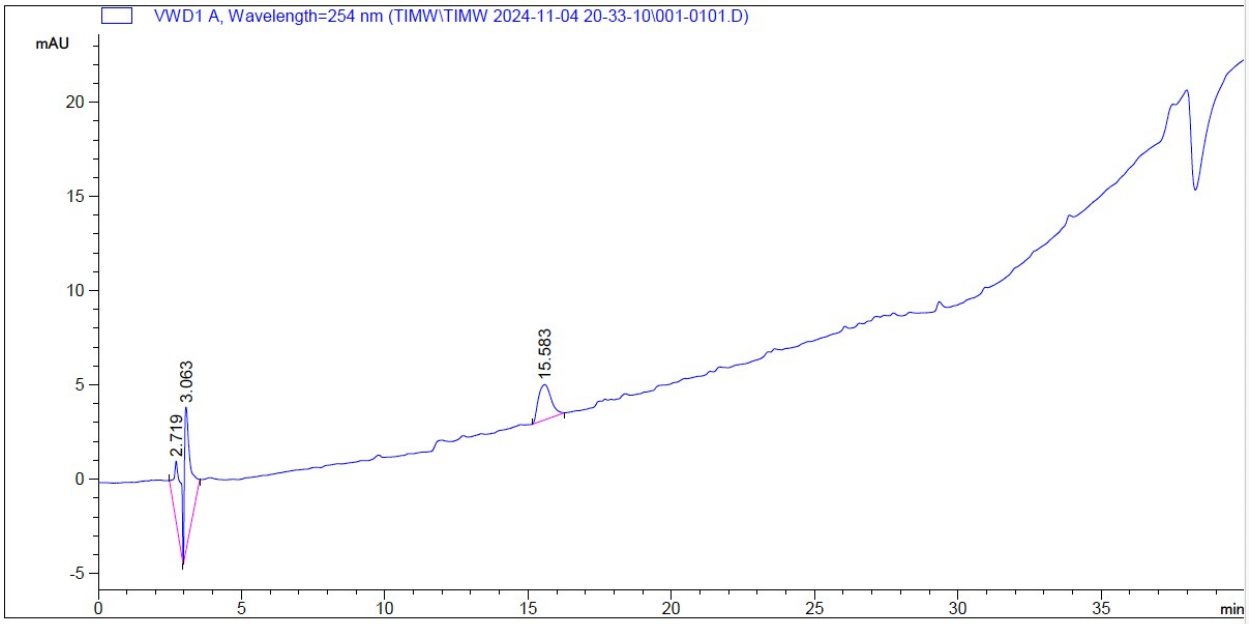
1z ^{13}C-NMR (125MHz, DMSO-d6)



4.3. Analytical HPLC traces (post-workup reaction purity)

Analytical HPLC profiles were obtained for each synthesized compound in this study. Peak integration was conducted automatically, and the software generated a report detailing the relative purity of each sample. Peaks eluting at the start (2.6–3.1 min), middle (15.5 min), and end (37–39 min) of each run were manually excluded, as a blank run confirmed these consistent minor impurities were derived from the column itself as well as baseline drift. This analysis was performed on An HP 1100 series analytical HPLC fitted with a reverse-phase (C18) analytical column, using a gradient of 5–100% acetonitrile in water (both components modified with 0.1% formic acid) over 35 min followed by a 5 min hold with 100% acetonitrile.

BLANK analytical HPLC trace

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=====================================================================
                        Area Percent Report
=====================================================================

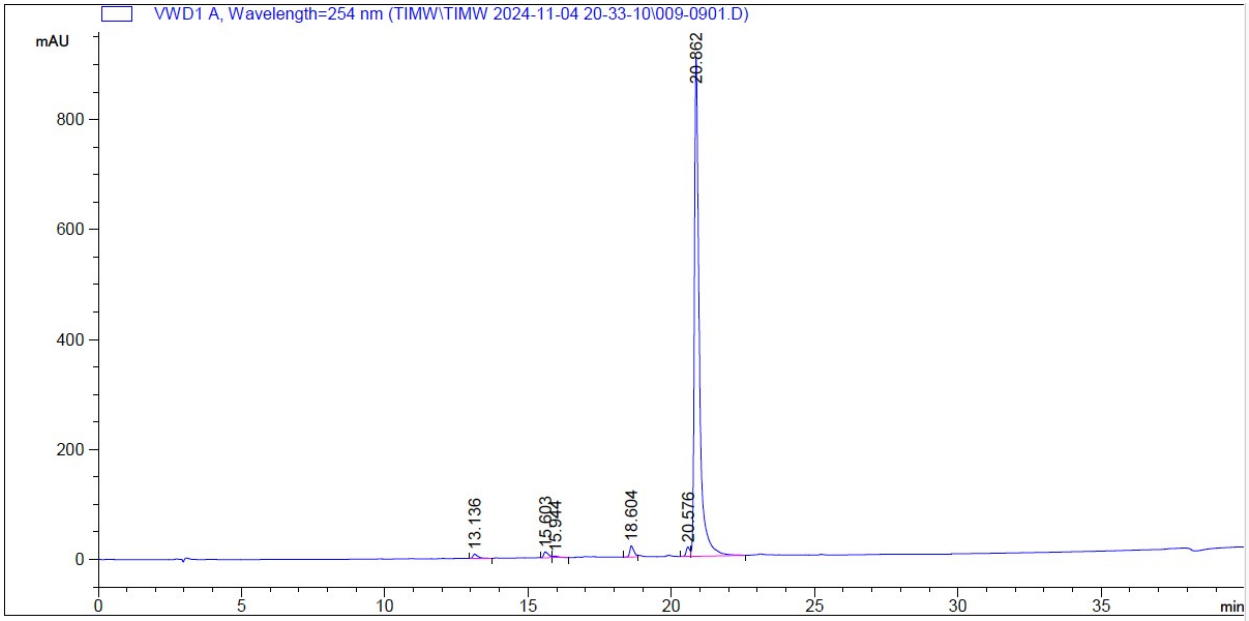
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   2.719 BB    0.2504   63.04268    3.19776  27.7303
   2   3.063 BB    0.2009  106.47383    7.61680  46.8341
   3  15.583 BB    0.4877   57.82583    1.86891  25.4356

Totals :                  227.34234   12.68347
```

1b analytical HPLC trace

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======================================================================
                        Area Percent Report
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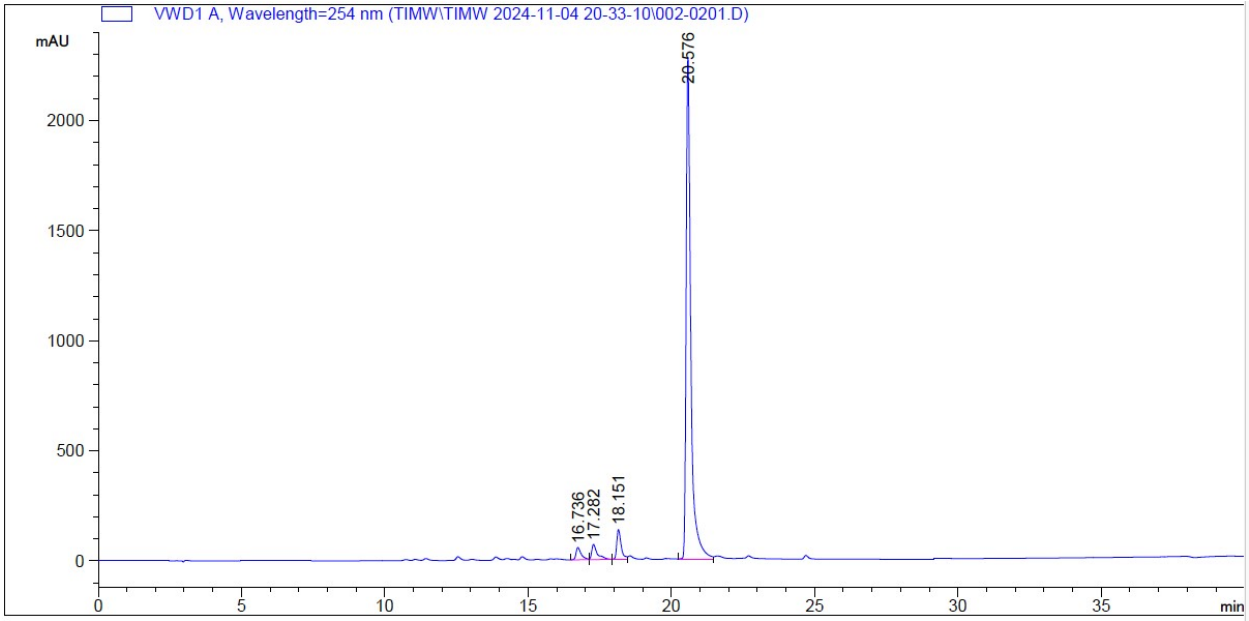
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  13.136 BB    0.1683   91.88400    7.78123   0.8042
   2  15.603 VV    0.1651  126.63076   10.86479   1.1083
   3  15.944 VB    0.2090   40.54279    2.78719   0.3548
   4  18.604 BV    0.1525  211.76591   20.27161   1.8534
   5  20.576 BV    0.1369  153.07501   17.03749   1.3397
   6  20.862 VB    0.1723 1.08020e4   907.62347  94.5396

Totals :                  1.14259e4   966.36578
```

2b analytical HPLC trace

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=====================================================================
                        Area Percent Report
=====================================================================

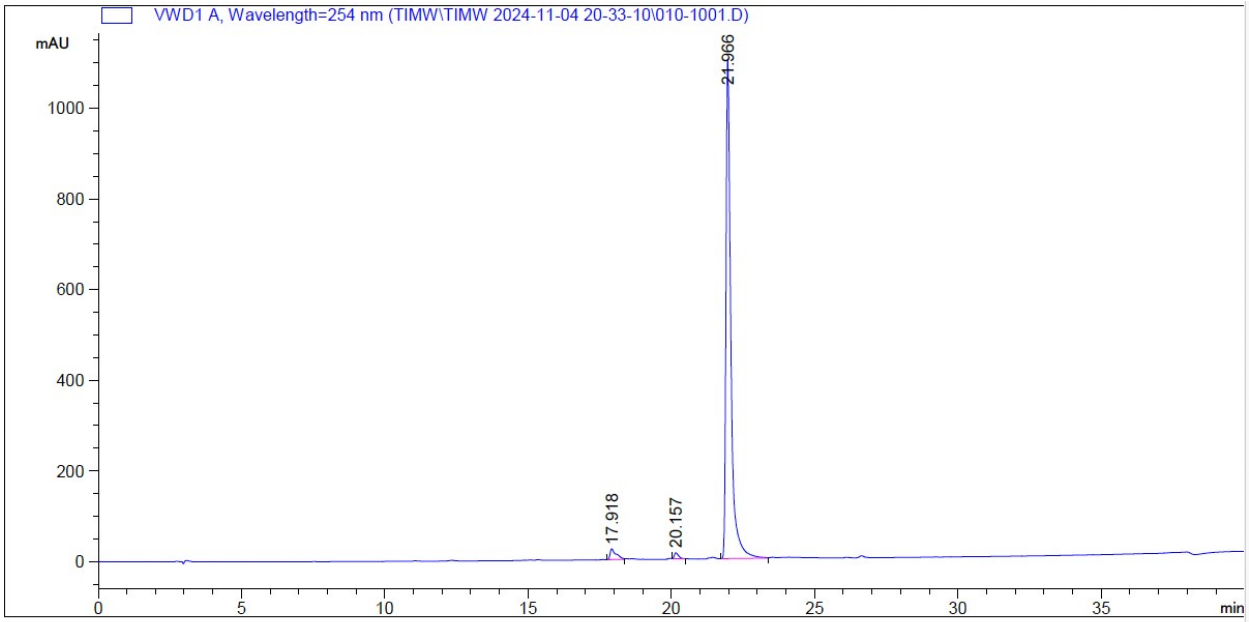
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  16.736 BV    0.1812  685.12659   55.75567   2.3443
   2  17.282 VB    0.1967  935.45105   68.72783   3.2008
   3  18.151 BV    0.1639 1439.62451  134.78552   4.9260
   4  20.576 BV    0.1718 2.61650e4  2279.56128  89.5289

Totals :                  2.92252e4  2538.83030
```

3b analytical HPLC trace

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=====================================================================
                        Area Percent Report
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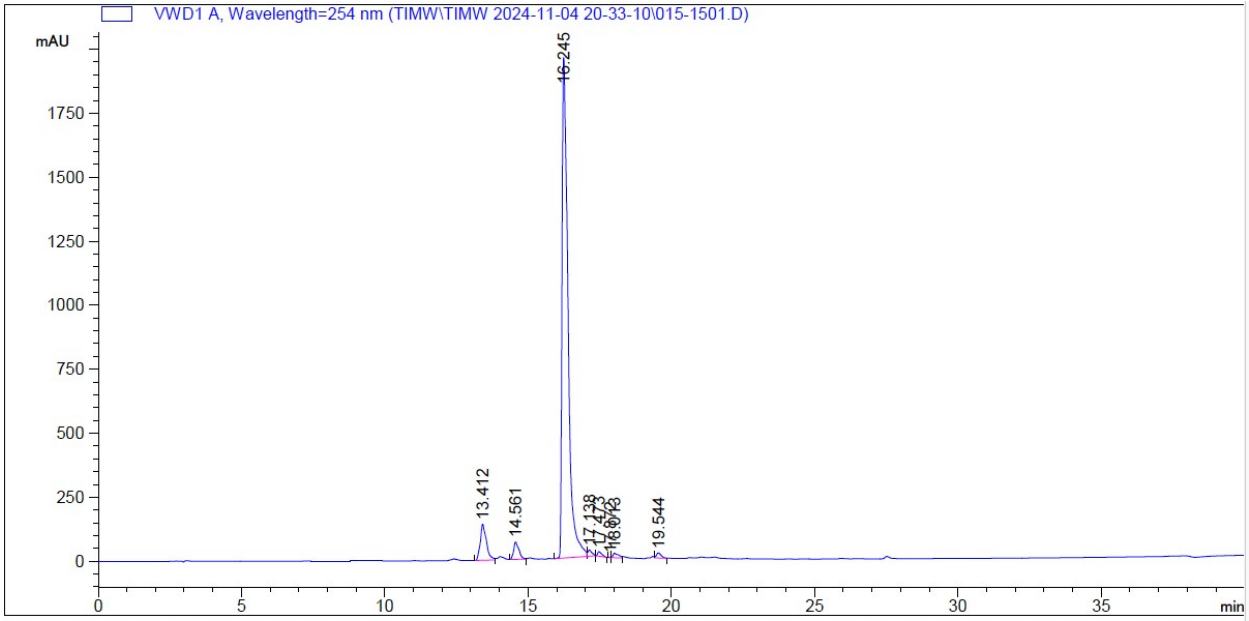
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  17.918 BV    0.2036  351.86600   23.52817   2.5978
   2  20.157 VV    0.1698  159.39249   14.09032   1.1768
   3  21.966 BV    0.1744 1.30336e4  1102.09485  96.2254

Totals :                  1.35448e4  1139.71333
```

4 analytical HPLC trace

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=====================================================================
                        Area Percent Report
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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  13.412 BV    0.1991 2097.79346  141.53775   6.5119
   2  14.561 BV    0.1750  879.81848   68.31993   2.7311
   3  16.245 BV    0.2026 2.83398e4  1955.47534  87.9713
   4  17.138 VB    0.1400  246.37233   24.62713   0.7648
   5  17.473 BB    0.1424  179.72682   18.04281   0.5579
   6  17.872 BV    0.0726    9.00447    1.95579   0.0280
   7  18.013 VV    0.1758  237.81387   18.01835   0.7382
   8  19.544 VB    0.1559  224.48834   20.65748   0.6968

Totals :                  3.22149e4  2248.63458
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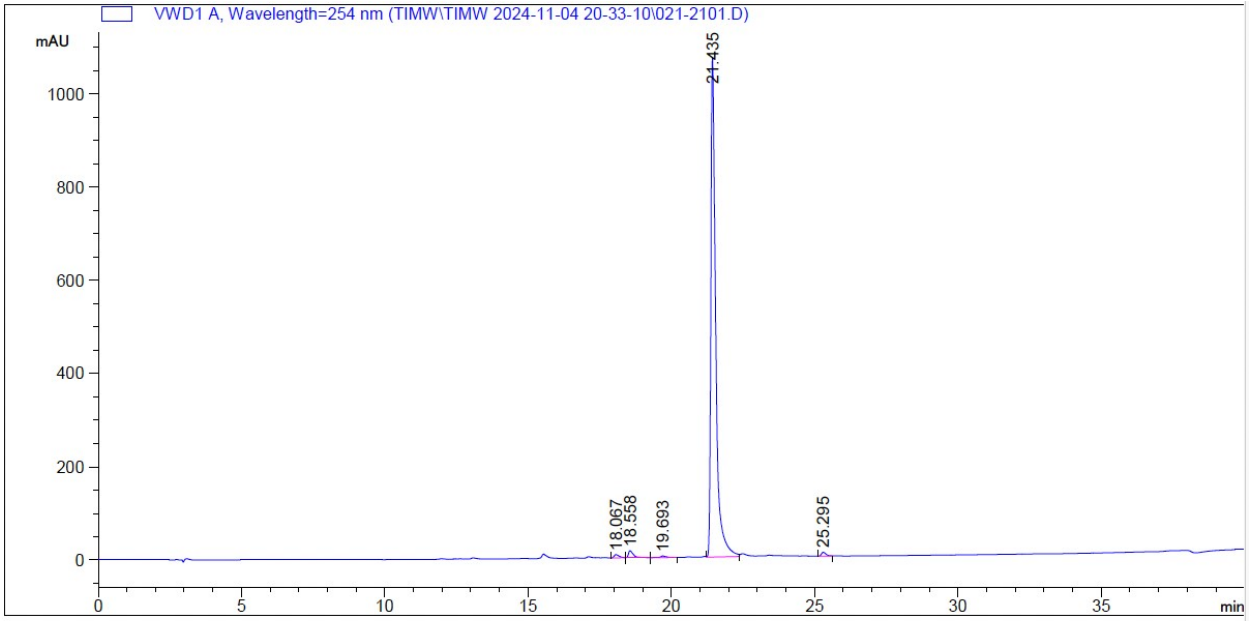
1c analytical HPLC trace

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=====================================================================
                        Area Percent Report
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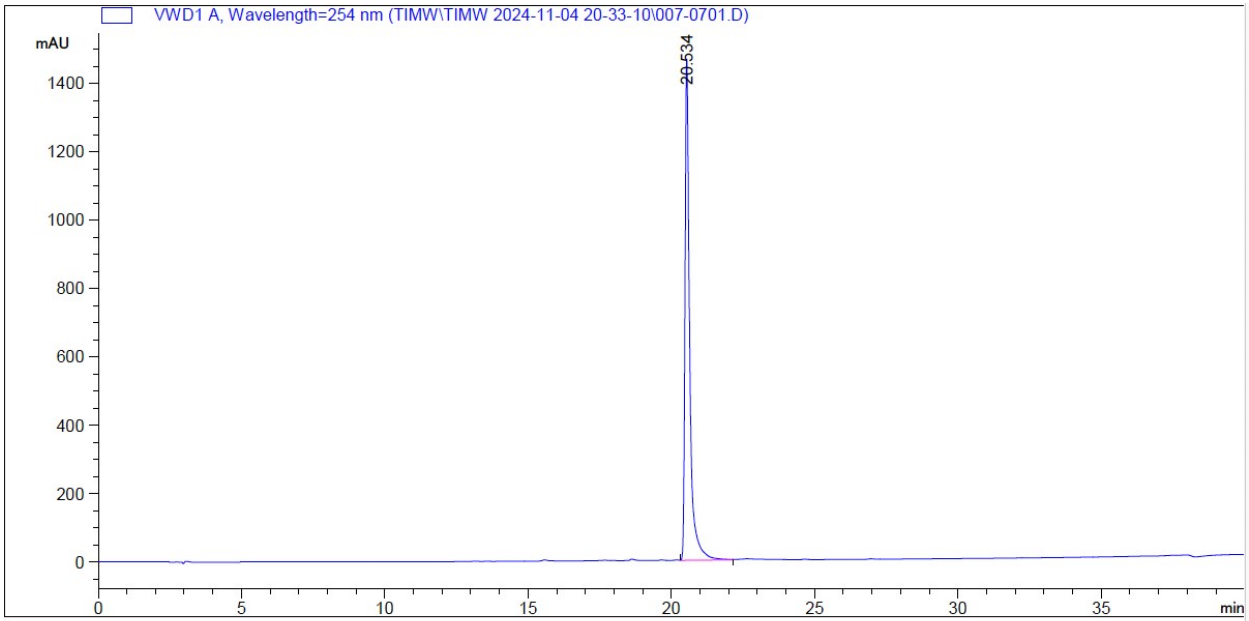
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  18.067 BV    0.1907   86.29153    6.98784   0.6599
   2  18.558 VV    0.1715  185.73372   15.37649   1.4204
   3  19.693 VB    0.1921   47.75234    3.41882   0.3652
   4  21.435 VV    0.1683 1.26681e4  1072.74097  96.8770
   5  25.295 BB    0.1671   88.59805    8.27499   0.6775

Totals :                  1.30765e4  1106.79912
```

1d analytical HPLC trace

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=====================================================================
                        Area Percent Report
=====================================================================

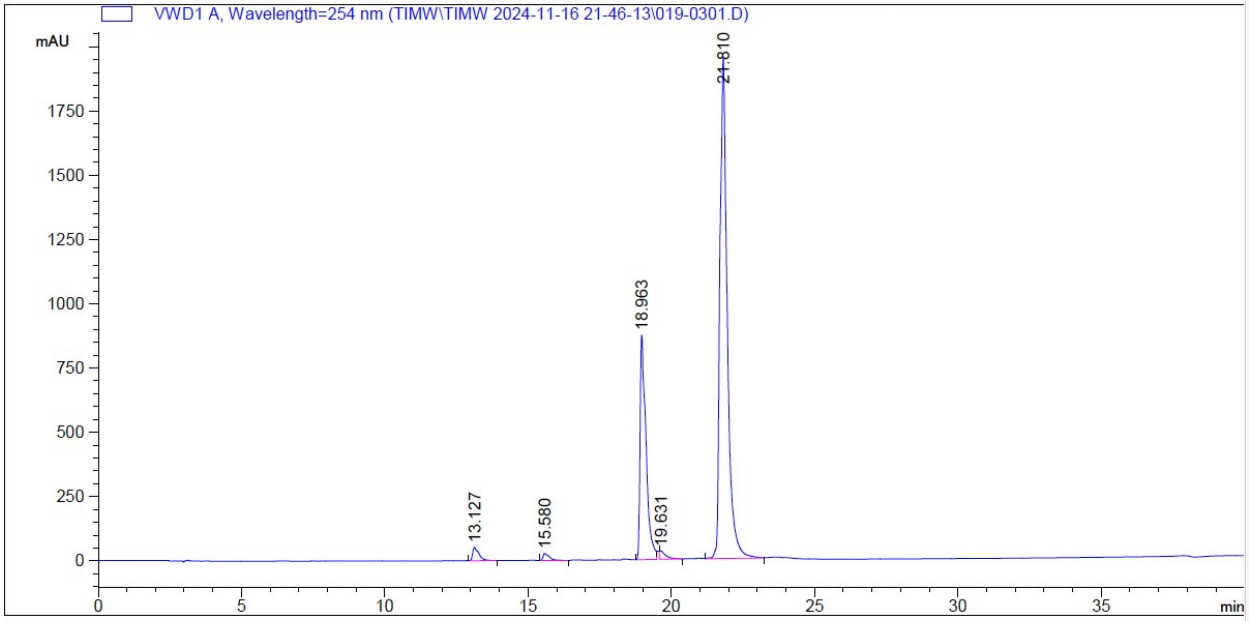
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  20.534 VV    0.1661 1.68505e4  1466.21130 100.0000

Totals :                  1.68505e4  1466.21130
```

1e analytical HPLC trace

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=====================================================================
                        Area Percent Report
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Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  13.127 VV    0.2026  777.18365   52.25653   1.5872
   2  15.580 VB    0.1971  401.94092   27.66934   0.8209
   3  18.963 BV    0.1949 1.25385e4   874.63409  25.6065
   4  19.631 VB    0.1970  483.20377   32.73068   0.9868
   5  21.810 BV    0.2371 3.47652e4  1949.73047  70.9987

Totals :                  4.89660e4  2937.02111
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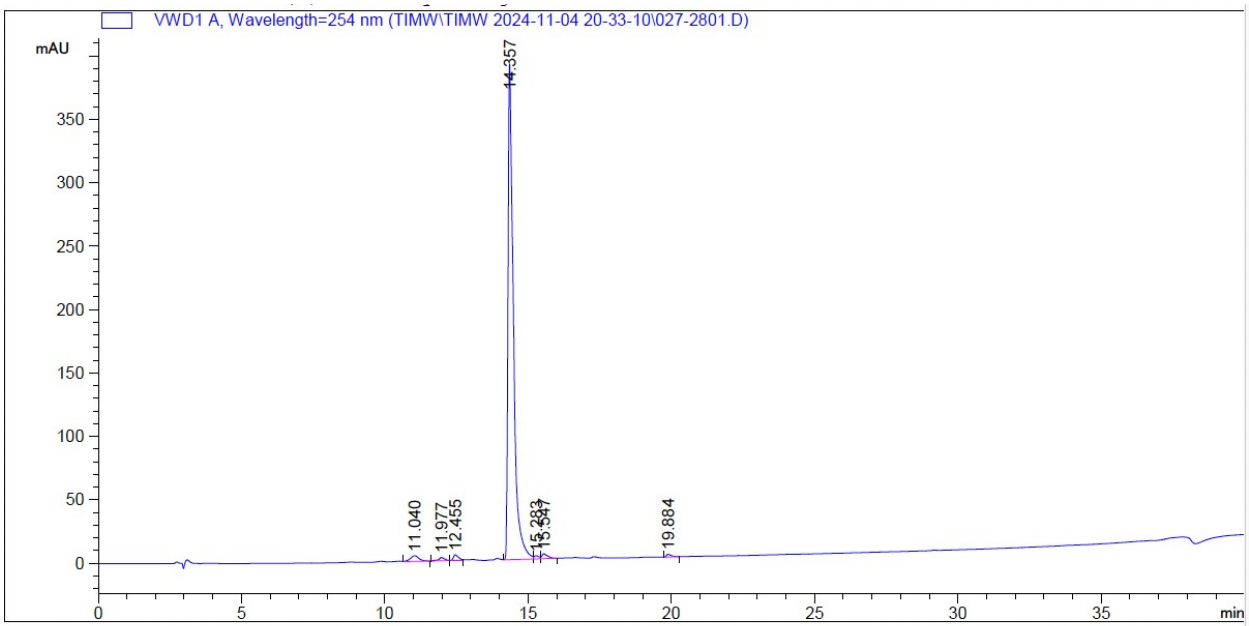
1f analytical HPLC trace

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=====================================================================
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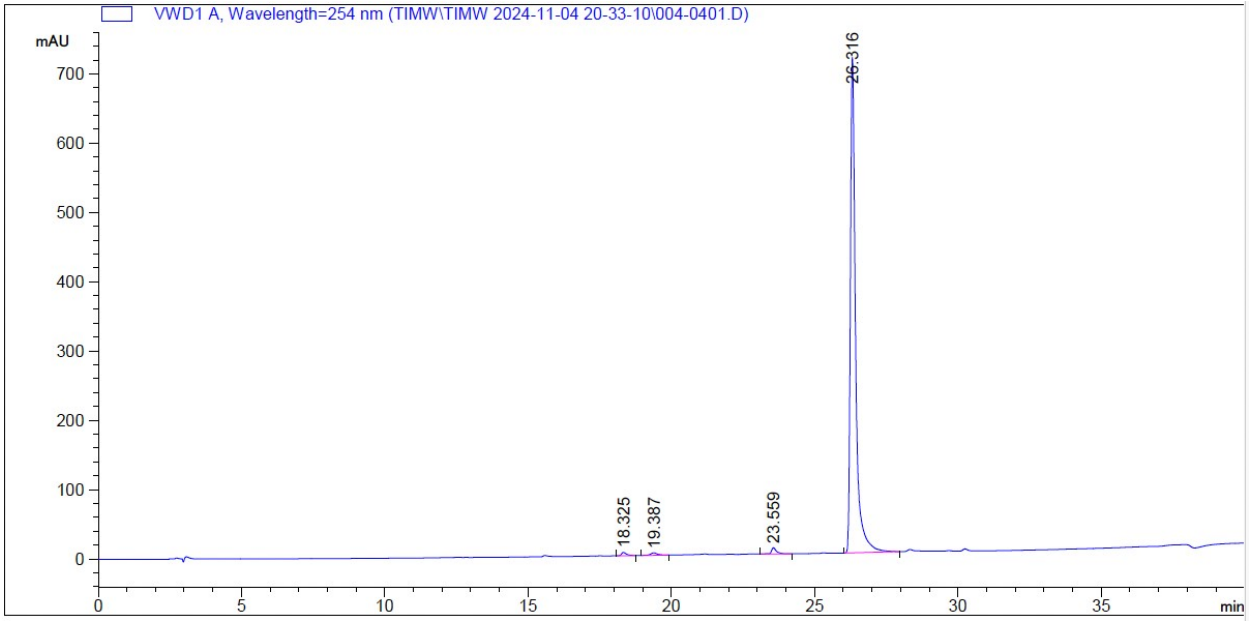
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  11.040 VB    0.3079   91.05147    4.46237   1.6949
   2  11.977 BB    0.1903   34.67086    2.50922   0.6454
   3  12.455 BV    0.1694   54.81179    4.51123   1.0203
   4  14.357 BV    0.1793 5081.67041  390.87256  94.5932
   5  15.283 VV    0.1594   29.50432    2.58450   0.5492
   6  15.547 VB    0.1886   55.56598    3.95578   1.0343
   7  19.884 BB    0.1654   24.85466    2.12817   0.4627

Totals :                  5372.12949  411.02383
```

1g analytical HPLC trace




```
=====================================================================
                        Area Percent Report
=====================================================================

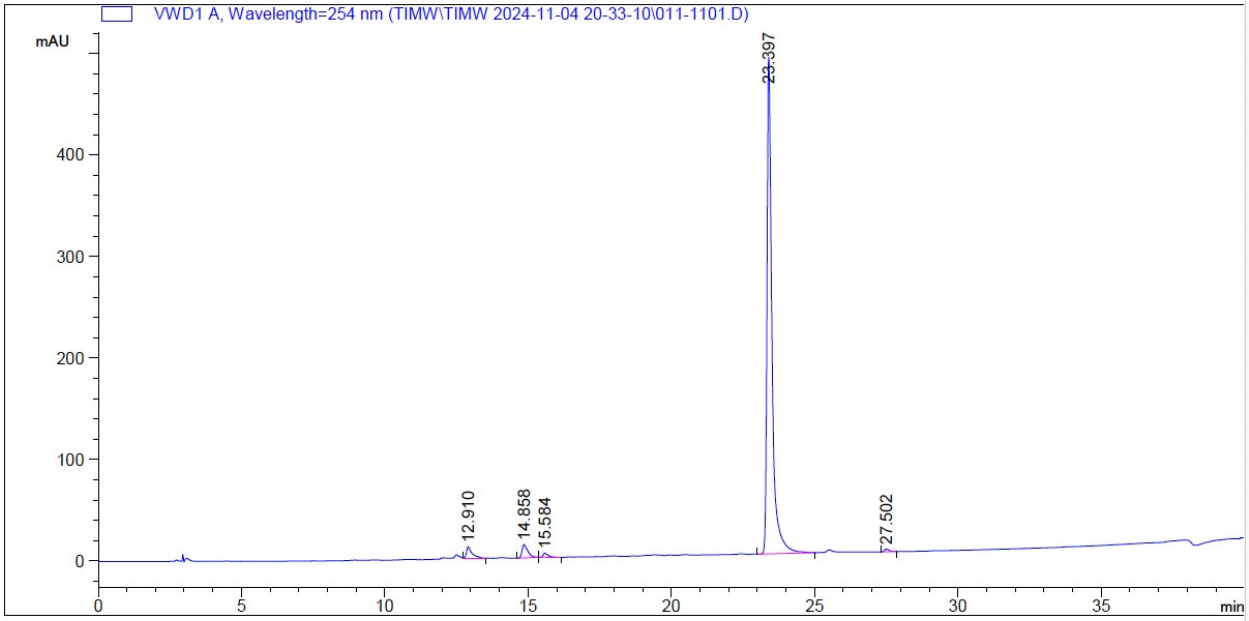
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  18.325 BB    0.1710   58.63103    5.02878   0.6357
   2  19.387 BB    0.2457   61.49929    3.71153   0.6668
   3  23.559 VB    0.1828  112.23994    8.94398   1.2170
   4  26.316 BB    0.1874 8990.19824  715.39337  97.4804

Totals :                  9222.56851  733.07766
```

1h analytical HPLC trace




```
=====================================================================
                        Area Percent Report
=====================================================================

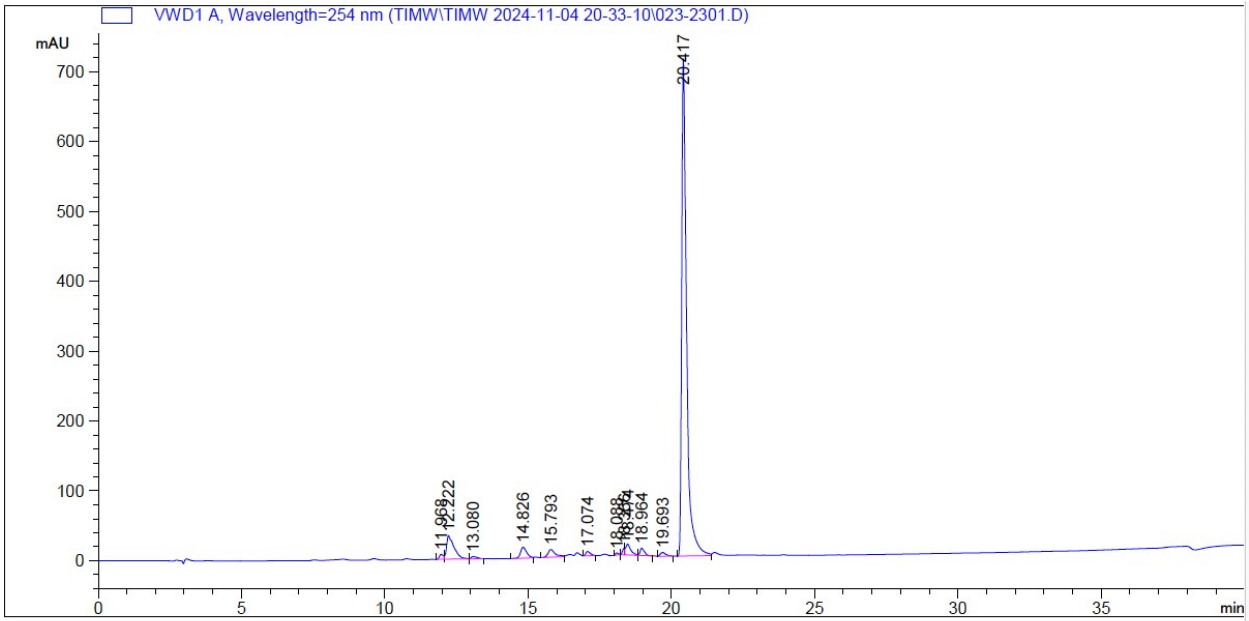
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.910 VB    0.1877  154.47833   11.26104   2.4287
   2  14.858 BB    0.1957  180.54602   13.09936   2.8385
   3  15.584 BB    0.1676   50.53587    4.21301   0.7945
   4  23.397 BB    0.1783 5947.72656  488.95206  93.5101
   5  27.502 BB    0.1678   27.23260    2.50125   0.4282

Totals :                  6360.51939  520.02672
```

1i analytical HPLC trace




```
=====================================================================
                        Area Percent Report
=====================================================================

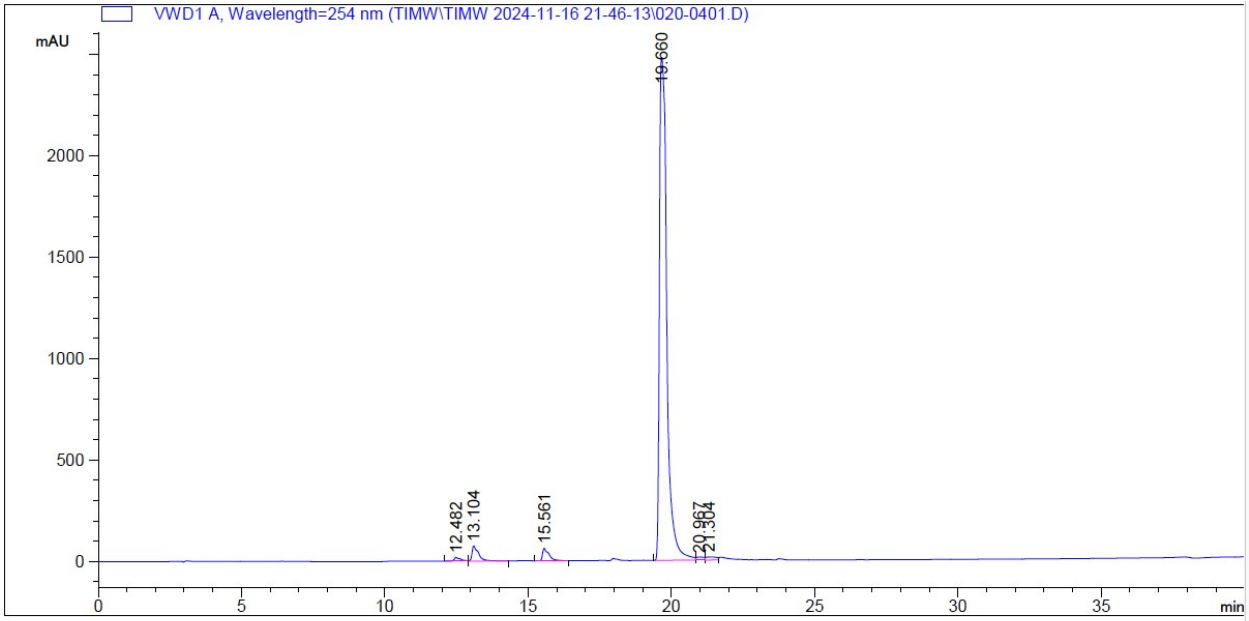
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  11.968 BV    0.1382   65.04644    7.04831   0.6475
   2  12.222 VV    0.2378  606.76483   33.68616   6.0404
   3  13.080 VB    0.2286   43.12968    3.08511   0.4294
   4  14.826 BV    0.2225  232.79527   15.56682   2.3175
   5  15.793 BV    0.2510  193.25539   11.02925   1.9239
   6  17.074 BV    0.1641   68.77467    6.14184   0.6847
   7  18.088 BB    0.1121   22.78741    3.20333   0.2269
   8  18.356 BV    0.0794   45.07846    9.13117   0.4488
   9  18.474 VV    0.1752  194.20952   15.51537   1.9334
  10  18.964 VB    0.1525  111.58939   10.67639   1.1109
  11  19.693 BB    0.1945   66.87139    5.32714   0.6657
  12  20.417 BV    0.1667 8394.74805  711.84369  83.5710

Totals :                 1.00451e4   832.25457
```

1j analytical HPLC trace




```
=====================================================================
                        Area Percent Report
=====================================================================

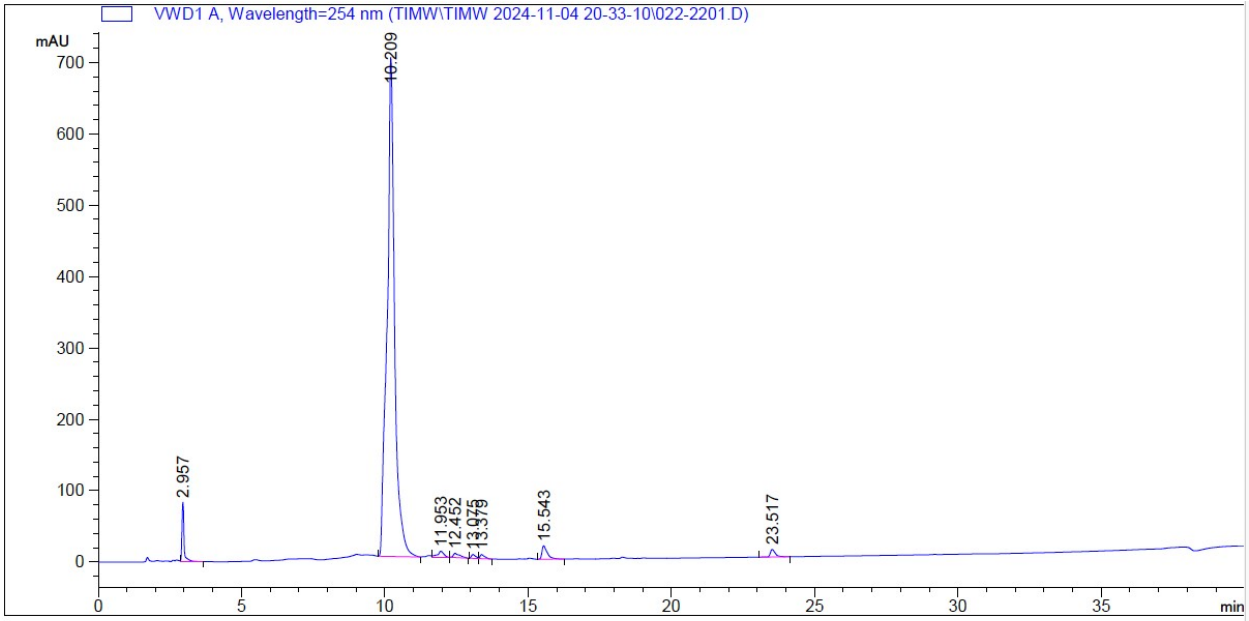
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.482 BV    0.2041  270.99020   17.91602   0.5740
   2  13.104 VB    0.2071 1139.83850   74.10852   2.4143
   3  15.561 BV    0.2019  919.18903   61.03940   1.9470
   4  19.660 BV    0.2488 4.42102e4  2478.87988  93.6424
   5  20.967 VV    0.2486  283.12466   15.25168   0.5997
   6  21.304 VV    0.3275  388.37720   15.04063   0.8226

Totals :                  4.72117e4  2662.23613
```

1k analytical HPLC trace




```
======================================================================
                        Area Percent Report
======================================================================

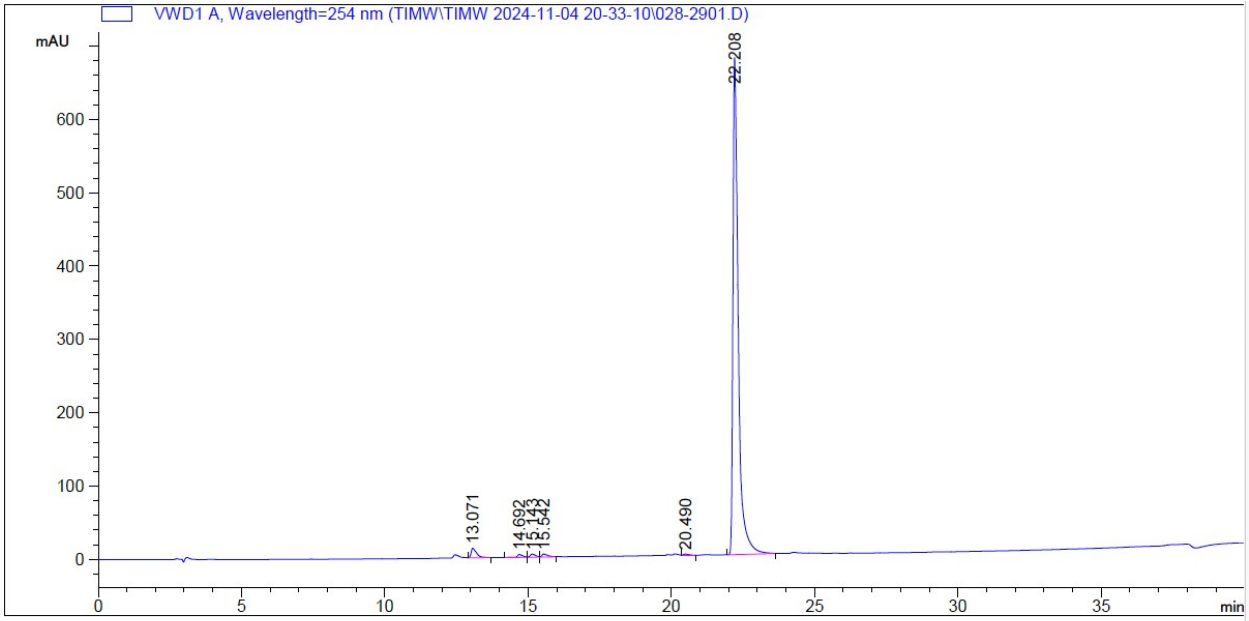
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   2.957 VB    0.0799  424.07346   83.08048   3.0272
   2  10.209 BB    0.2627 1.28737e4   699.78131  91.8965
   3  11.953 VB    0.2086  126.99967    8.46180   0.9066
   4  12.452 BB    0.2128   97.63343    6.15371   0.6969
   5  13.075 BV    0.1534   57.83768    5.49492   0.4129
   6  13.379 VB    0.1553   63.99104    5.78140   0.4568
   7  15.543 VB    0.1769  238.39702   18.82023   1.7018
   8  23.517 BB    0.1850  126.28115   10.53703   0.9014

Totals :                  1.40089e4   838.11088
```

1l analytical HPLC trace




```
=====================================================================
                        Area Percent Report
=====================================================================

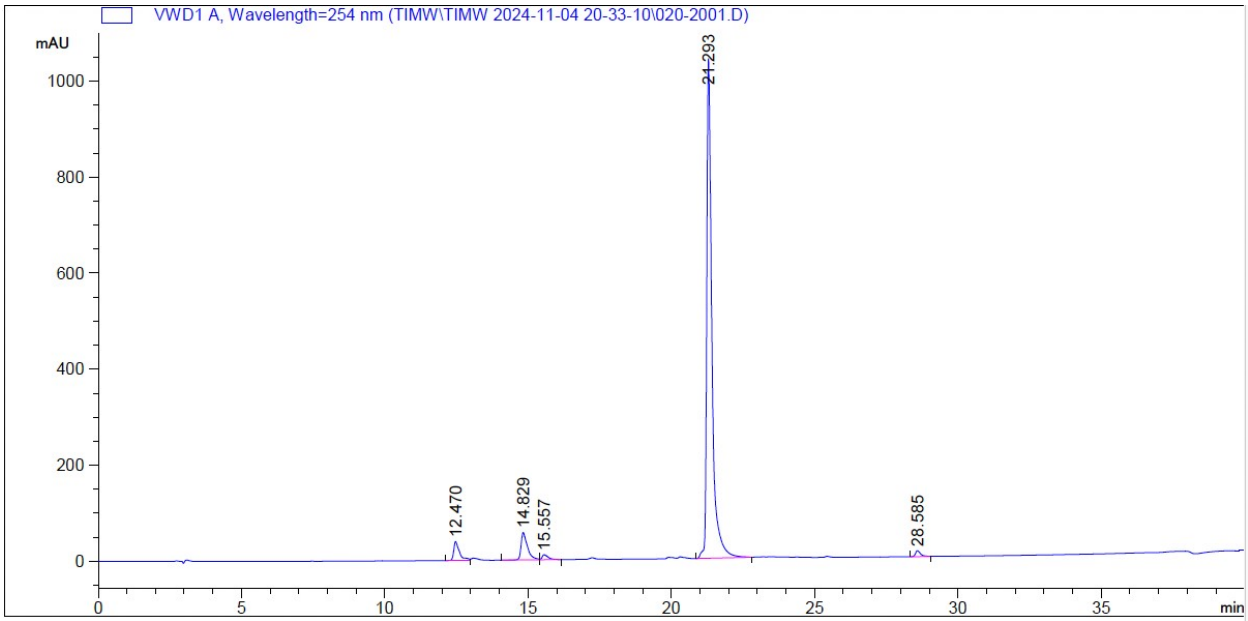
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  13.071 VB    0.1842  176.89848   13.30445   1.9362
   2  14.692 BV    0.1737   50.03774    3.99636   0.5477
   3  15.143 VV    0.1830   54.14396    4.22635   0.5926
   4  15.542 VV    0.1933   58.44632    4.08041   0.6397
   5  20.490 VB    0.1678   20.84258    1.73487   0.2281
   6  22.208 BV    0.2034 8776.16309  678.25037  96.0557

Totals :                  9136.53216  705.59281
```

1m analytical HPLC trace




```
======================================================================
                        Area Percent Report
======================================================================

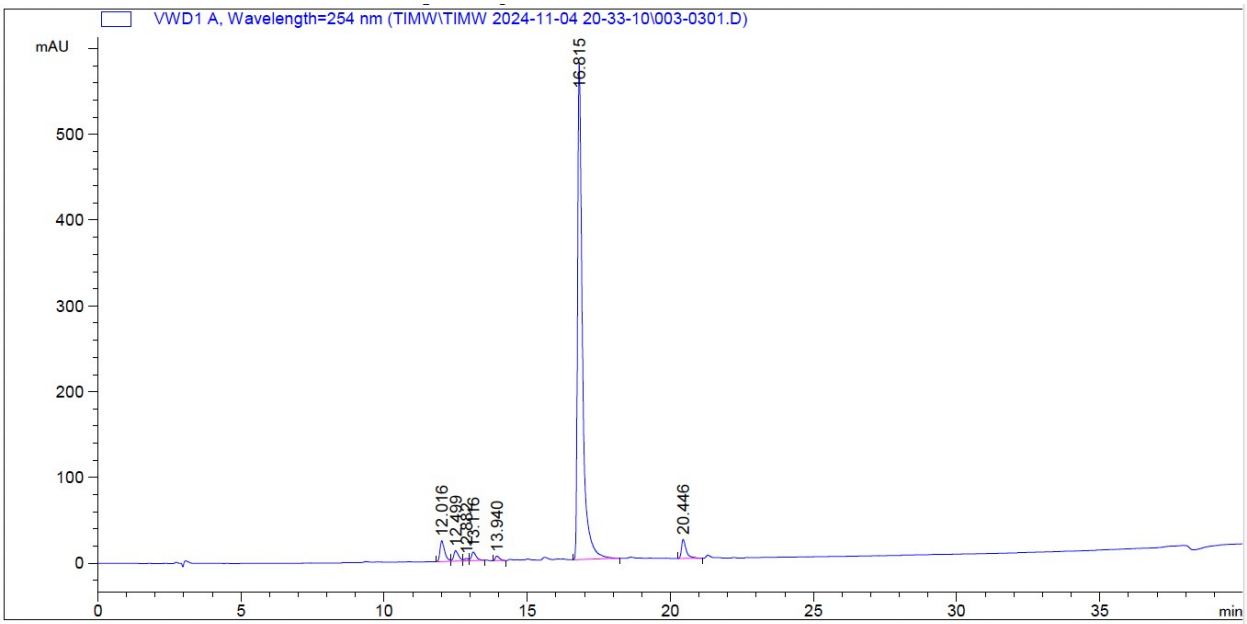
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.470 BV    0.1909  540.46240   39.33079   3.6677
   2  14.829 BV    0.2166  882.84100   57.14428   5.9912
   3  15.557 VV    0.2075  162.47949   10.62868   1.1026
   4  21.293 BB    0.1777 1.29955e4  1040.67957  88.1912
   5  28.585 BV    0.1896  154.31342   12.34141   1.0472

Totals :                  1.47356e4  1160.12473
```

1n analytical HPLC trace




```
=====================================================================
                        Area Percent Report
=====================================================================

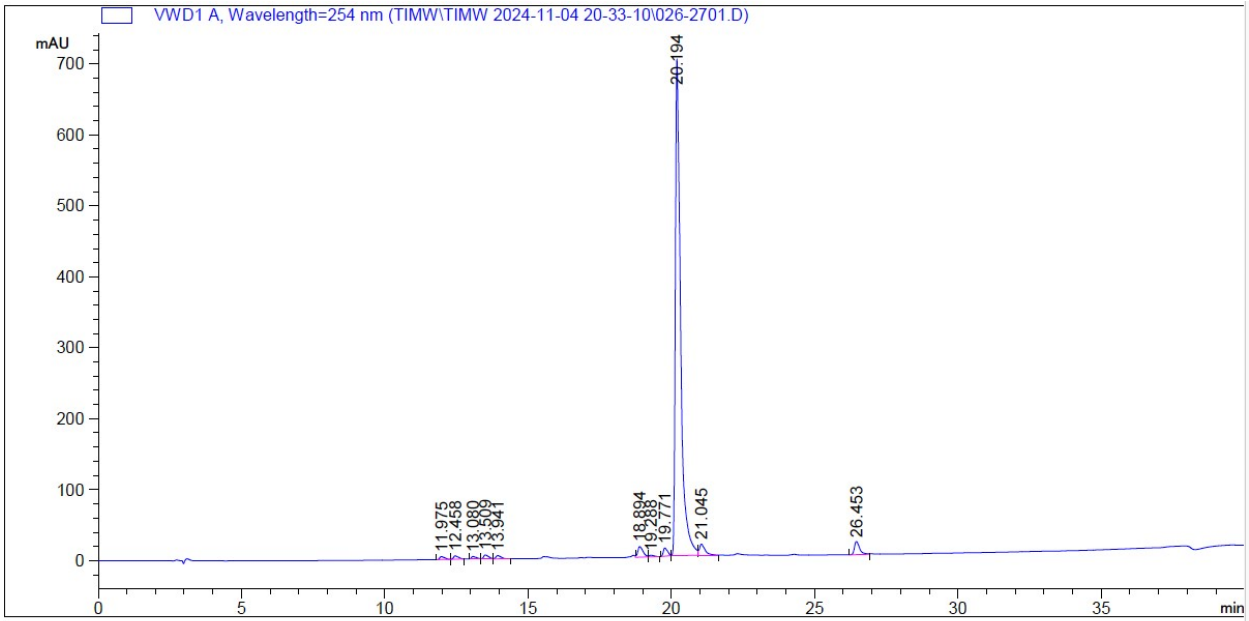
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.016 BV    0.1700  276.76321   24.17098   3.5634
   2  12.499 VV    0.1845  146.15868   12.36291   1.8818
   3  12.882 VV    0.1634   29.60714    2.71931   0.3812
   4  13.116 VB    0.1708  116.46101   10.00132   1.4995
   5  13.940 BB    0.1541   54.90276    5.31246   0.7069
   6  16.815 BB    0.1722 6889.69092  579.55756  88.7071
   7  20.446 BV    0.1687  253.20621   22.08117   3.2601

Totals :                  7766.78992  656.20570
```

1o analytical HPLC trace




```
=====================================================================
                        Area Percent Report
=====================================================================

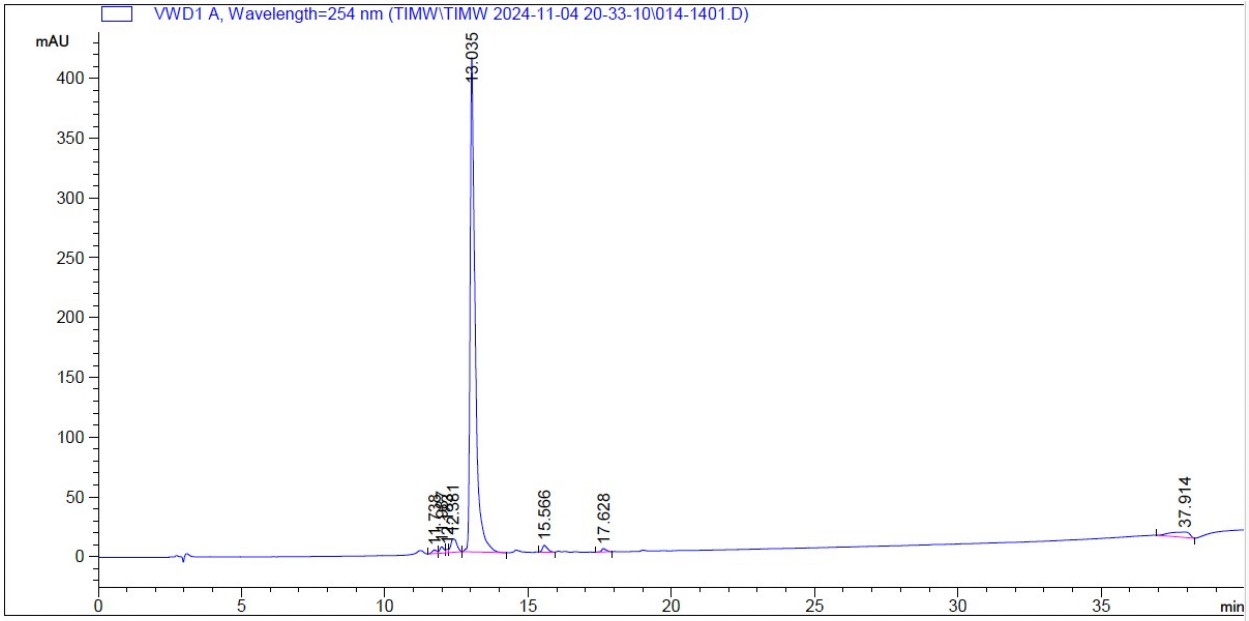
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  11.975 BV    0.1719   51.90578    4.24062   0.5180
   2  12.458 VV    0.1678   58.63097    4.88007   0.5851
   3  13.080 BV    0.1608   38.71159    3.39291   0.3863
   4  13.509 VV    0.1684   65.21254    5.46312   0.6508
   5  13.941 VB    0.1786   55.38382    4.45396   0.5527
   6  18.894 VV    0.2028  190.41206   14.91857   1.9003
   7  19.288 VB    0.1711   28.73897    2.31426   0.2868
   8  19.771 BB    0.1451  117.76134   11.69525   1.1752
   9  20.194 BV    0.1769 8952.43359  699.81042  89.3445
  10  21.045 VV    0.1940  226.53906   16.02662   2.2608
  11  26.453 BV    0.1964  234.39478   18.43004   2.3392

Totals :                  1.00201e4   785.62586
```

1p analytical HPLC trace




```
=====================================================================
                        Area Percent Report
=====================================================================

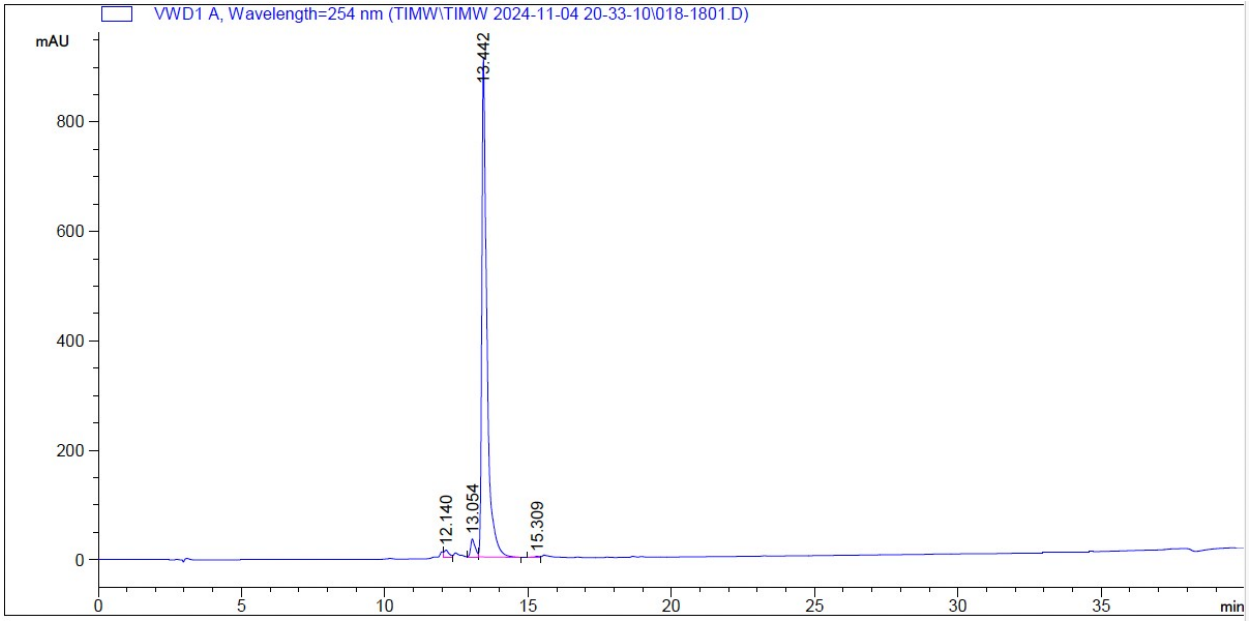
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  11.738 BV    0.1616   33.55567    3.05586   0.5906
   2  11.987 VV    0.1503   54.07996    5.26906   0.9519
   3  12.183 VV    0.0911   18.28724    2.89617   0.3219
   4  12.381 VB    0.1968  167.64368   11.27226   2.9508
   5  13.035 BB    0.1731 5101.80469  413.49130  89.8014
   6  15.566 VV    0.1818   75.87608    5.90932   1.3356
   7  17.628 BB    0.1559   29.93395    2.72313   0.5269
   8  37.914 BB    0.6072  200.02745    4.46447   3.5209

Totals :                  5681.20872  449.08157
```

1q analytical HPLC trace




```
=====================================================================
                        Area Percent Report
=====================================================================

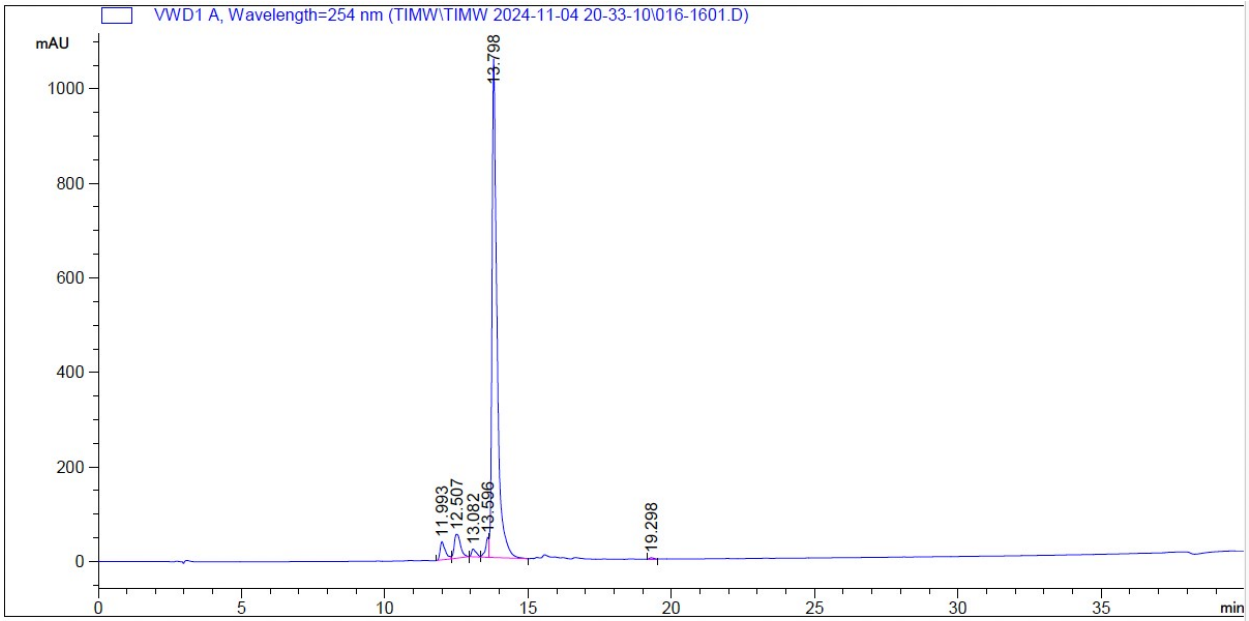
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.140 VV    0.1596  148.70094   13.00949   1.2597
   2  13.054 BV    0.1563  356.93628   32.75309   3.0238
   3  13.442 VB    0.1718 1.12768e4   913.06622  95.5326
   4  15.309 BV    0.1715   21.70555    1.77818   0.1839

Totals :                  1.18041e4   960.60699
```

1r analytical HPLC trace




```
=====================================================================
                        Area Percent Report
=====================================================================

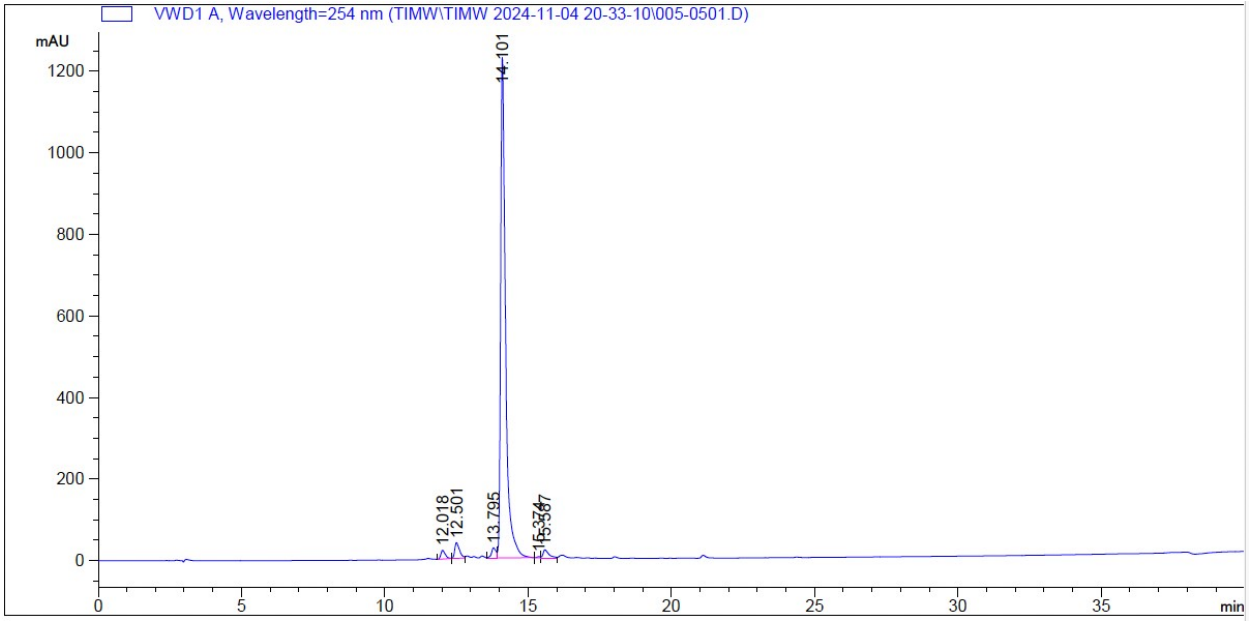
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  11.993 BV    0.1755  478.42151   38.51036   3.2491
   2  12.507 VB    0.2364  770.48334   50.46367   5.2327
   3  13.082 BV    0.1613  190.70491   16.65389   1.2952
   4  13.596 VV    0.1112  323.33258   42.19950   2.1959
   5  13.798 VB    0.1707 1.29318e4  1054.44373  87.8248
   6  19.298 BV    0.1528   29.80196    2.87836   0.2024

Totals :                  1.47245e4  1205.14950
```

1s analytical HPLC trace




```
======================================================================
                        Area Percent Report
======================================================================

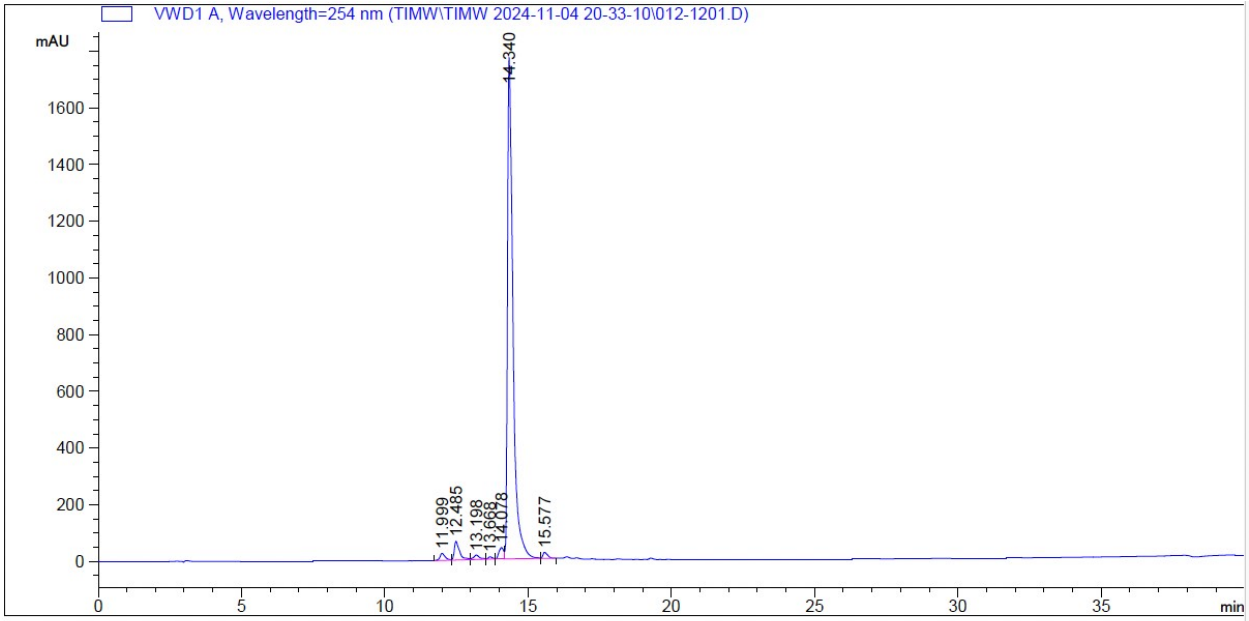
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.018 BB    0.1550  223.79337   21.22754   1.4162
   2  12.501 BV    0.1654  439.63718   38.45368   2.7820
   3  13.795 BV    0.1538  259.67529   24.58323   1.6432
   4  14.101 VB    0.1693 1.45917e4  1227.48865  92.3353
   5  15.374 BV    0.1272   20.79762    2.54878   0.1316
   6  15.587 VV    0.1876  267.33337   19.85876   1.6917

Totals :                  1.58029e4  1334.16063
```

1t analytical HPLC trace




```
======================================================================
                        Area Percent Report
======================================================================

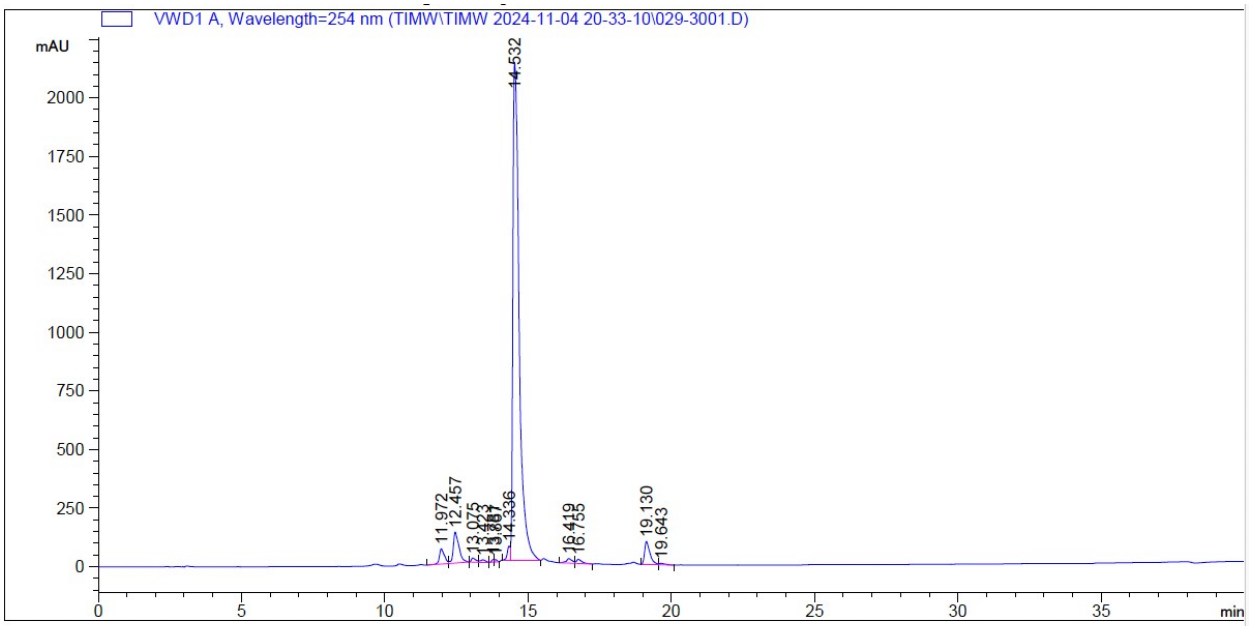
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  11.999 BV    0.1771  310.23492   24.95726   1.2198
   2  12.485 VV    0.1743  828.77734   65.94231   3.2585
   3  13.198 VV    0.2126  224.14392   15.09365   0.8813
   4  13.668 VB    0.1362   75.97928    8.06152   0.2987
   5  14.078 BV    0.1823  442.13522   39.72058   1.7384
   6  14.340 VV    0.1844 2.33188e4  1768.44299  91.6830
   7  15.577 VB    0.1575  234.07867   21.51027   0.9203

Totals :                  2.54342e4  1943.72858
```

1u analytical HPLC trace




```
=====================================================================
                        Area Percent Report
=====================================================================

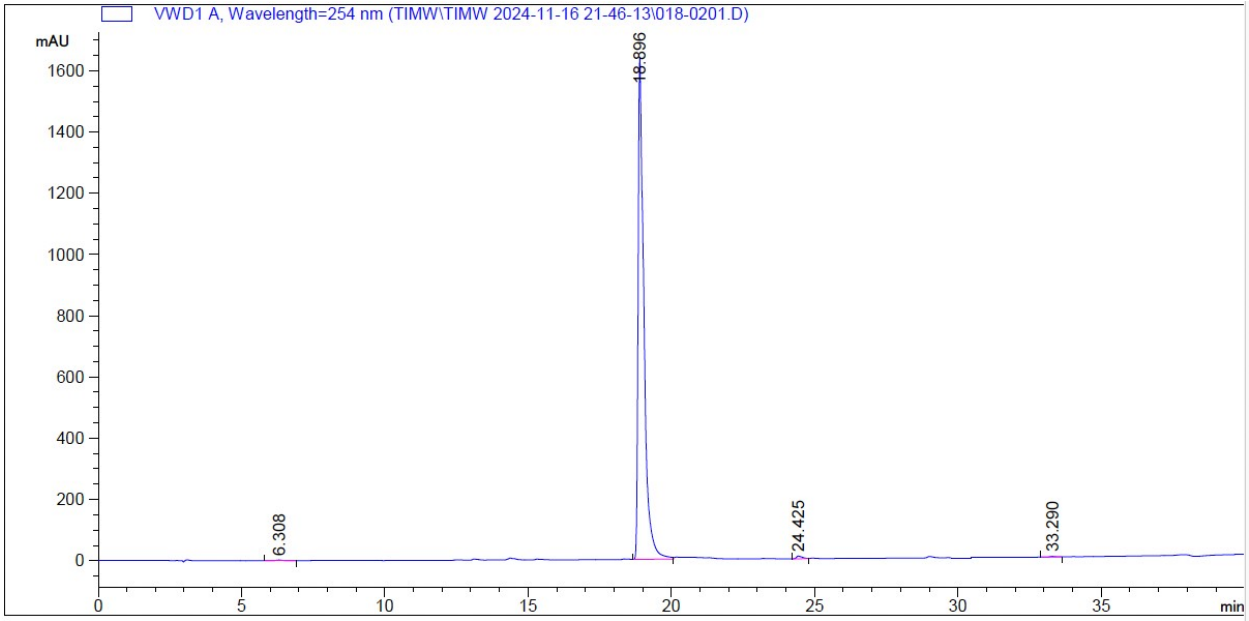
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  11.972 BV    0.1723  801.94891   65.34789   2.1256
   2  12.457 VB    0.1887 1807.01794  132.13037   4.7896
   3  13.075 BV    0.1531  187.72488   17.87331   0.4976
   4  13.423 VB    0.1727  126.50639   10.17937   0.3353
   5  13.781 BV    0.0931   63.95338   10.46394   0.1695
   6  13.867 VB    0.0897   53.86511    9.26203   0.1428
   7  14.336 BV    0.0928  374.96680   60.44315   0.9939
   8  14.532 VB    0.2392 3.24109e4  2123.15210  85.9072
   9  16.419 BV    0.1918  273.75577   19.45308   0.7256
  10  16.755 VB    0.1781  227.00983   17.43128   0.6017
  11  19.130 VV    0.1850 1303.70776   99.45521   3.4556
  12  19.643 VB    0.2024   96.43952    6.65990   0.2556

Totals :                 3.77278e4  2571.85162
```

1v analytical HPLC trace




```
=====================================================================
                        Area Percent Report
=====================================================================

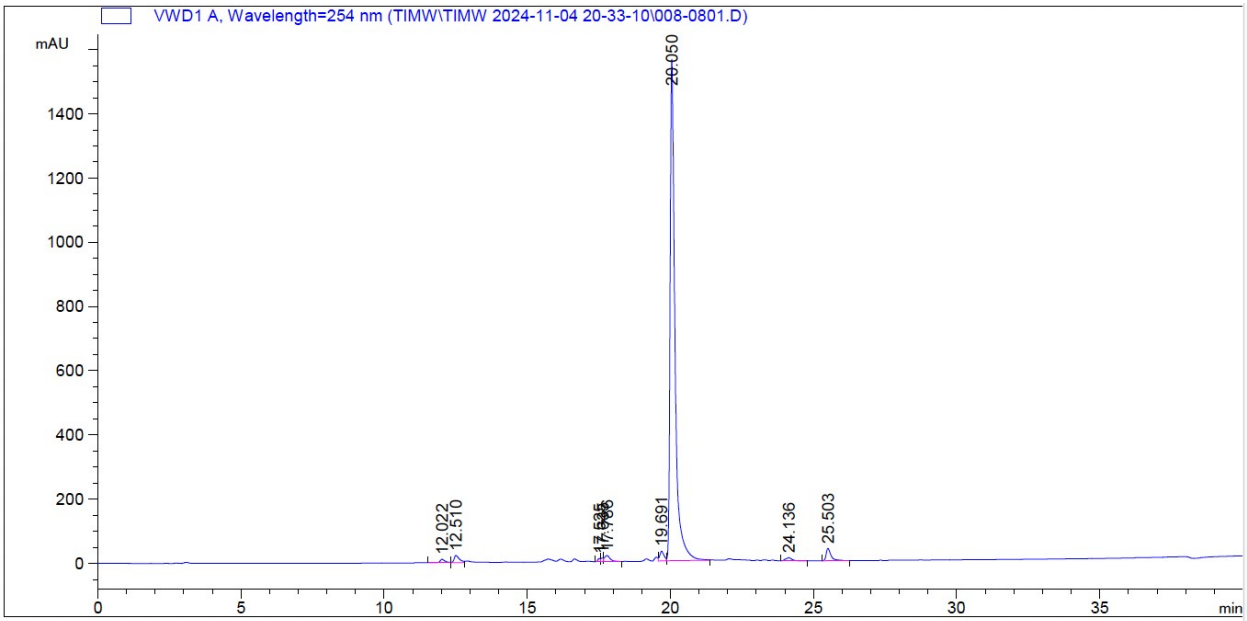
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   6.308 BB    0.2416   39.09727    2.35621   0.1681
   2  18.896 BV    0.1903 2.30779e4  1640.37585  99.1971
   3  24.425 BV    0.1922  120.44388    8.61639   0.5177
   4  33.290 BB    0.2147   27.25100    1.97702   0.1171

Totals :                  2.32647e4  1653.32547
```

1w analytical HPLC trace




```
=====================================================================
                        Area Percent Report
=====================================================================

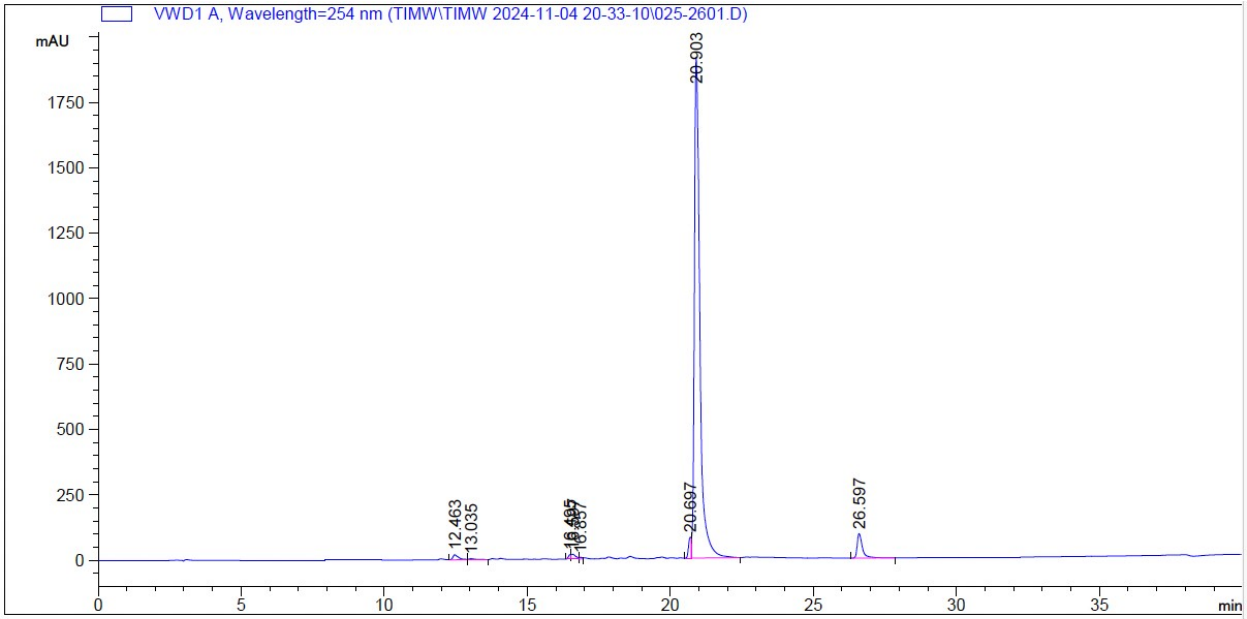
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.022 BV    0.1717  130.38286   10.78009   0.6489
   2  12.510 VV    0.1803  294.03116   22.90978   1.4634
   3  17.525 BV    0.0926   58.33535    9.81421   0.2903
   4  17.635 VV    0.0892   69.63125   11.31820   0.3466
   5  17.786 VB    0.1898  252.09818   18.99890   1.2547
   6  19.691 VV    0.1509  308.90079   29.94032   1.5375
   7  20.050 VV    0.1710 1.84037e4  1561.60388  91.5985
   8  24.136 BB    0.1960  132.46274    9.42524   0.6593
   9  25.503 BV    0.1718  442.16699   38.10089   2.2007

Totals :                  2.00918e4  1712.89150
```

1x analytical HPLC trace




```
=====================================================================
                        Area Percent Report
=====================================================================

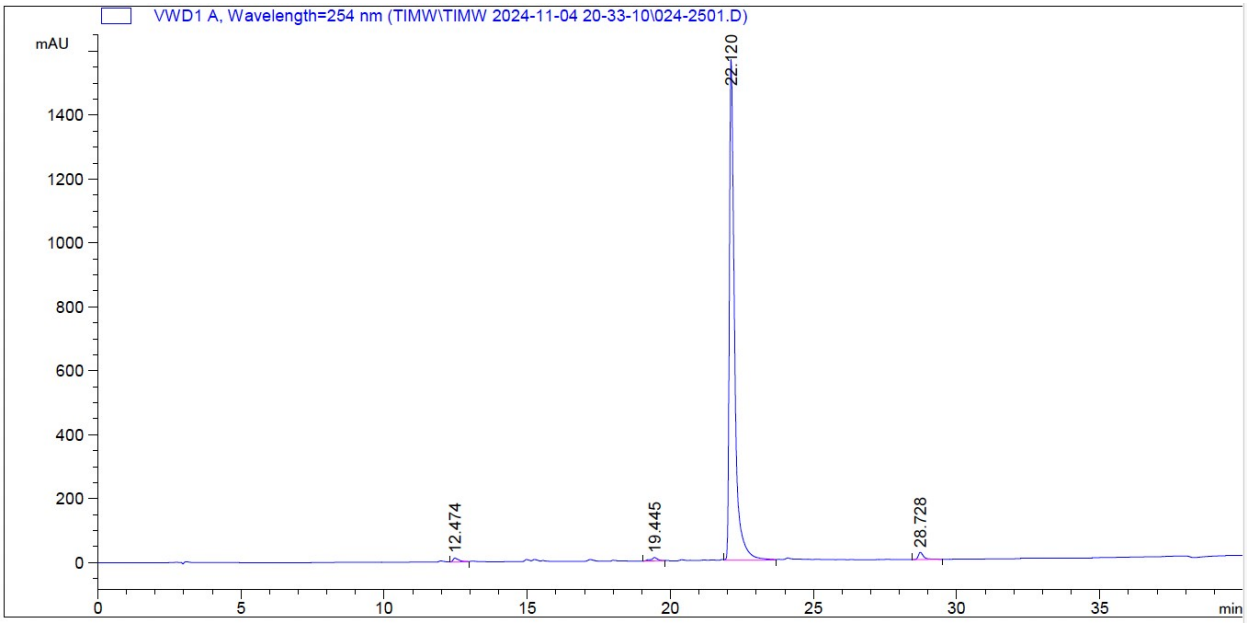
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.463 VV    0.1924  265.13339   18.93957   0.9465
   2  13.035 VB    0.2282   63.76819    3.76372   0.2276
   3  16.495 BV    0.0947  102.36372   16.72006   0.3654
   4  16.597 VV    0.1545  195.21571   17.96206   0.6969
   5  16.857 VV    0.1113   49.95175    6.41120   0.1783
   6  20.697 BV    0.0904  470.82309   80.07509   1.6808
   7  20.903 VB    0.2120 2.56935e4  1913.34302  91.7241
   8  26.597 BB    0.1920 1170.95886   93.01003   4.1802

Totals :                  2.80117e4  2150.22476
```

1y analytical HPLC trace




```
=====================================================================
                        Area Percent Report
=====================================================================

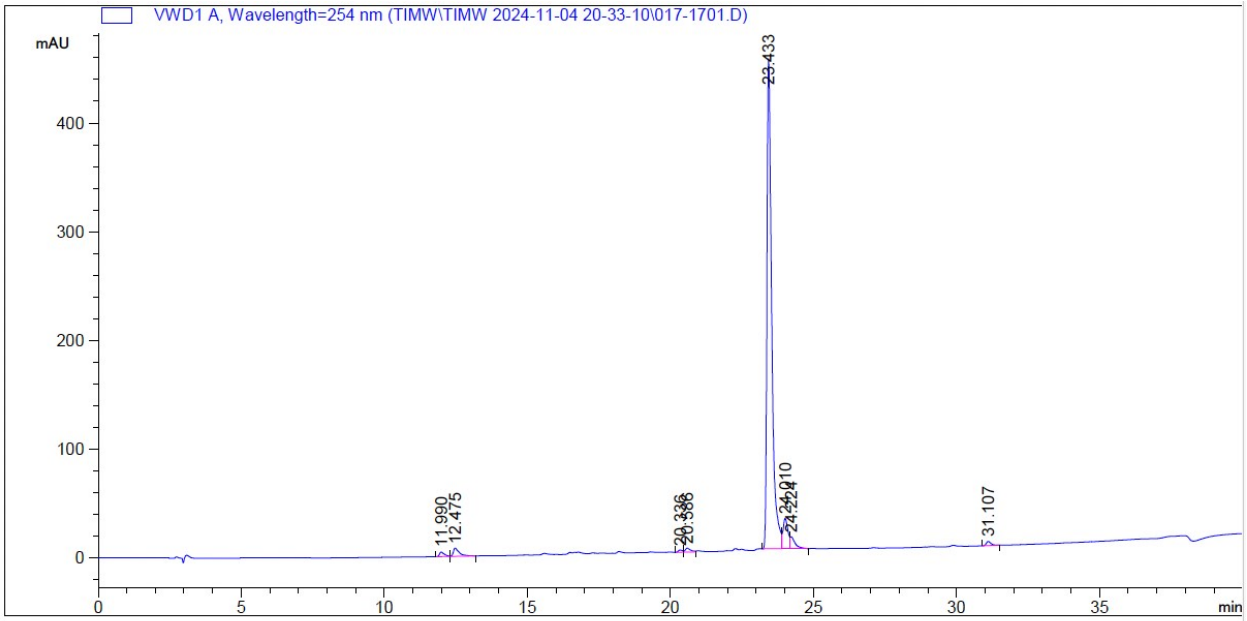
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.474 VV    0.2128  190.59886   12.30252   0.9290
   2  19.445 BB    0.2122  160.32056   10.37987   0.7814
   3  22.120 VV    0.1946 1.98870e4  1567.22266  96.9322
   4  28.728 BB    0.1897  278.48093   22.02693   1.3574

Totals :                  2.05164e4  1611.93199
```

1z analytical HPLC trace




```
================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  11.990 BV    0.1690   49.92919    4.20690   0.8401
   2  12.475 VB    0.1933  106.52960    7.57194   1.7924
   3  20.336 BV    0.1413   19.63781    2.06852   0.3304
   4  20.586 VV    0.1819   47.37438    3.65355   0.7971
   5  23.433 BV    0.1684 5209.40576  450.51926  87.6502
   6  24.010 VV    0.1747  339.21667   28.02105   5.7074
   7  24.224 VB    0.1620  126.64729   10.87714   2.1309
   8  31.107 BB    0.1770   44.66100    3.82518   0.7514

Totals :                  5943.40171  510.74353
```

5. ^{19}F NMR kinetic analysis – general procedure and experimental setup

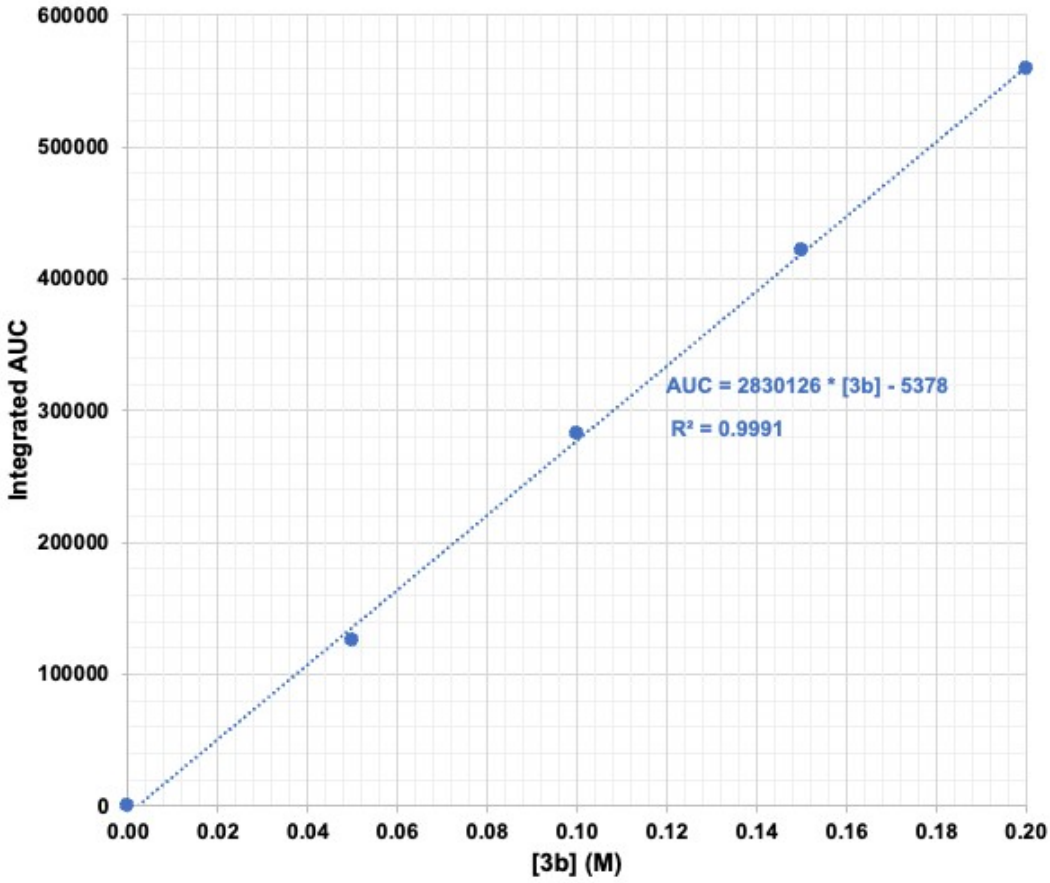
Prior to running kinetic experiments, a calibration curve was constructed to allow the conversion of ^{19}F-NMR signal intensity into concentration. More specifically, ^{19}F-NMR spectra were recorded for 0-0.20 M concentrations of pure product **3b**, and the integration of the -111 ppm peak was found to show excellent linearity with the concentration of **3b** (see Figure S1).

For kinetic runs, starting material **3a** was combined with Boc-piperazine in 1 mL of deuterated DMSO in a reaction vessel and 25 µL of DIPEA was added. The synthetically relevant final concentrations of reactants were 0.05 M for 3a and 0.06 M for Boc-piperazine. The reaction vessel was then heated either by submersion in a pre-heated oil bath (90^{o}C) or by 10-s pre-stir heating (150^{o}C) in a microwave reactor. After incubation for various reaction times, ranging from 2 min to 120 min, the reaction vessel was removed, cooled, and a 500-µL aliquot was removed for NMR analysis. An ^{19}F-NMR spectrum was recorded, the -111 pm peak was integrated, and the AUC value was converted to concentration of product **3b** according to the calibration curve (Figure S1). A different reaction mixture was treated in this manner for every time point, and each time point was performed in duplicate.

The kinetic data of **3b** concentration vs time were then analysed to give second order rate constants for the reactions. An explicit equation for the second order reaction was derived as shown in Scheme S1. Under these reaction conditions, reactants are not equimolar, nor is one in large excess over the other, so the explicit equation cannot be simplified to the typical simple second order or first-order equations, respectively. Rather, the full equation was used to fit the product concentration vs time data sets, by non-linear least squares regression in GraphPad Prism (Figure 4).

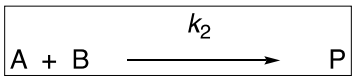
The rate constants measured in this way are shown in Table S2, along with their associated errors. These values were shown to be statistically significantly distinct according to an unpaired Student's t-test at the $\alpha = 0.5$ level (P = 0.0029, see Figure S3). The ratio of k_2^{MW}/ k_2^{OB} was calculated to be 7.01 ± 2.85, where the error represents the propagation of the uncertainties in the second order rate constants through to the ratio.

Figure S1: Calibration curve for conversion of NMR integration values to concentration for addition product LH047


600000
500000
400000
300000
200000
100000
0
Integrated AUC
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0.14
0.16
0.18
0.20
[3b] (M)
AUC = 2830126 * [3b] - 5378
R² = 0.9991

Scheme S1: Derivation of explicit equation for fitting of second order rate data

For a second order reaction:



the rate law can be written as:

$$\frac{d[\mathrm{P}]}{dt} = k_2[\mathrm{A}][\mathrm{B}] = k_2([\mathrm{A}]_0 - [\mathrm{P}])([\mathrm{B}]_0 - [\mathrm{P}])$$

and rearranged:

$$\frac{d[\mathrm{P}]}{([\mathrm{A}]_0 - [\mathrm{P}])([\mathrm{B}]_0 - [\mathrm{P}])} = k_2 dt$$

then integrated:

$$\int_0^{\mathrm{P}} \frac{d[\mathrm{P}]}{([\mathrm{A}]_0 - [\mathrm{P}])([\mathrm{B}]_0 - [\mathrm{P}])} = k_2 \int_0^t dt$$

to give the general linear equation:

$$\frac{1}{[\mathrm{B}]_0 - [\mathrm{A}]_0}\left(ln\left(\frac{[\mathrm{A}]_0([\mathrm{B}]_0 - [\mathrm{P}])}{[\mathrm{B}]_0([\mathrm{A}]_0 - [\mathrm{P}])}\right)\right) = k_2 t$$

This equation can in turn be rearranged:

$$ln\left(\frac{[\mathrm{A}]_0([\mathrm{B}]_0 - [\mathrm{P}])}{[\mathrm{B}]_0([\mathrm{A}]_0 - [\mathrm{P}])}\right) = k_2 t([\mathrm{B}]_0 - [\mathrm{A}]_0)$$

$$ln\left(\frac{[\mathrm{A}]_0}{[\mathrm{B}]_0}\right) + ln\left(\frac{([\mathrm{B}]_0 - [\mathrm{P}])}{([\mathrm{A}]_0 - [\mathrm{P}])}\right) = k_2 t([\mathrm{B}]_0 - [\mathrm{A}]_0)$$

$$ln\left(\frac{([\mathrm{B}]_0 - [\mathrm{P}])}{([\mathrm{A}]_0 - [\mathrm{P}])}\right) = k_2 t([\mathrm{B}]_0 - [\mathrm{A}]_0) - ln\left(\frac{[\mathrm{A}]_0}{[\mathrm{B}]_0}\right)$$

$$\frac{([\mathrm{B}]_0 - [\mathrm{P}])}{([\mathrm{A}]_0 - [\mathrm{P}])} = e^{\left(k_2 t([\mathrm{B}]_0 - [\mathrm{A}]_0) - ln\left(\frac{[\mathrm{A}]_0}{[\mathrm{B}]_0}\right)\right)}$$

$$[\mathrm{B}]_0 - [\mathrm{P}] = ([\mathrm{A}]_0 - [\mathrm{P}])e^{\left(k_2 t([\mathrm{B}]_0 - [\mathrm{A}]_0) - ln\left(\frac{[\mathrm{A}]_0}{[\mathrm{B}]_0}\right)\right)}$$

$$[\mathrm{P}]e^{\left(k_2 t([\mathrm{B}]_0-[\mathrm{A}]_0)-ln\left(\frac{[\mathrm{A}]_0}{[\mathrm{B}]_0}\right)\right)}-[\mathrm{P}]=[\mathrm{A}]_0 e^{\left(k_2 t([\mathrm{B}]_0-[\mathrm{A}]_0)-ln\left(\frac{[\mathrm{A}]_0}{[\mathrm{B}]_0}\right)\right)}-[\mathrm{B}]_0$$

$$[\mathrm{P}]\left(e^{\left(k_2 t([\mathrm{B}]_0-[\mathrm{A}]_0)-ln\left(\frac{[\mathrm{A}]_0}{[\mathrm{B}]_0}\right)\right)}-1\right)=[\mathrm{A}]_0 e^{\left(k_2 t([\mathrm{B}]_0-[\mathrm{A}]_0)-ln\left(\frac{[\mathrm{A}]_0}{[\mathrm{B}]_0}\right)\right)}-[\mathrm{B}]_0$$

to isolate an explicit equation for [P] :

$$[\mathrm{P}]=\frac{[\mathrm{A}]_0 e^{\left(k_2 t([\mathrm{B}]_0-[\mathrm{A}]_0)-ln\left(\frac{[\mathrm{A}]_0}{[\mathrm{B}]_0}\right)\right)}-[\mathrm{B}]_0}{\left(e^{\left(k_2 t([\mathrm{B}]_0-[\mathrm{A}]_0)-ln\left(\frac{[\mathrm{A}]_0}{[\mathrm{B}]_0}\right)\right)}-1\right)}$$

This explicit equation for [P] was then re-written in simple text, for use in fitting software such as GraphPad Prism:

Y=((A0*exp((k2*X*(B0-A0))-ln(A0/B0))-B0)/((exp((k2*X*(B0-A0))-ln(A0/B0)))-1))

where Y is [P], X is time, and A0 and B0 are the initial concentrations of reactants, entered as constants prior to fitting each X-Y data set.

Figure S2: Kinetic data for duplicate reactions of 0.05 M A and 0.06 M B, heated in a microwave oven (panel A) or in an oil bath (panel B). The data were fitted by non-linear regression to the explicit second order equation derived in Scheme S1.

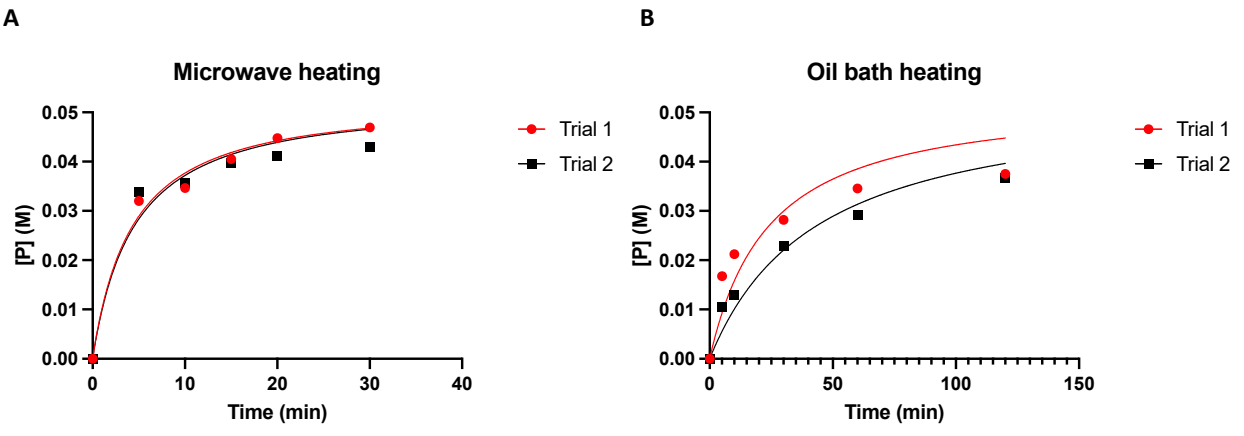


Table S2: Second order rate constants calculated for the reaction of 3a with Boc-piperazine, heated in a microwave reactor (k_2^{MW}) or in an oil bath (k_2^{OB}) (see Figure S2). For individual trial values, the standard errors of the fitting are shown. For the mean values, the errors reported are the standard deviation of the mean.

	k_2^{MW} ($M^{-1}min^{-1}$)	**k_2^{OB} ($M^{-1}min^{-1}$)**
Trial 1	4.12 ± 0.38	0.741 ± 0.180
Trial 2	3.95 ± 0.59	0.411 ± 0.271
Mean	4.02 ± 0.12	0.576 ± 0.233