Synthesis and characterisation of diketopyrrolopyrrole-based hydrogels

Valentina Gauci,[a] Annela Seddon[b] and Dave Adams [a].

a School of Chemistry, University of Glasgow, Glasgow, G12 8QQ, U.K.

Email: dave.adams@glasgow.ac.uk

b School of Physics, HH Wills Physics Laboratory, University of Bristol, Tyndall Avenue, Bristol, BS8 1TL, U.K.

Supplementary Information

General Experimental Details

Synthesis

Starting materials and reagents were used as purchased (Merck, Fluorochem or TCI) without further purification. Unless otherwise specified, reactions were carried out in air and at room temperature. Mass spectrometry was obtained from the mass spectrometry service at the University of Glasgow, using a Bruker MicroTOF-Q for electrospray mass. NMRs were recorded on Bruker Avance III 400 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 101 MHz, respectively, with chemical shift values reported in ppm referenced to the deuterated DMSO solvent peaks at 2.50 ppm (^{1}H) and 39.52 ppm (^{13}C). Multiplicity of peaks is reported according to the follow abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet and br, broad, with coupling constants, *J*, reported in Hz. NMR spectra were analysed using Mestrenova v14.2. Compound names were generated with IUPAC nomenclature using Marvin Sketch v20.11.

Gel preparation

Gelator solutions were prepared by adding the DTDPP-derivative powder to deionised water with 2 molar equivalents of 1 M NaOH. Solutions were stirred overnight to provide a homogeneous solution. The resulting solutions had a pH of 10.5. To prepare gels, GdL was pre-weighed in a vial to which the gelator solution was added. The vial was then swirled to dissolve the GdL and left overnight to allow gelation to occur undisturbed. The minimum gelation concentrations (mgc) for the four DTDPP-derivative solutions are 5 mg/mL for DTDPP-F-OH and DTDPP-A-OH, 10 mg/mL for DTDPP-V-OH, and 15 mg/mL for DTDPP-L-OH. The concentration of GdL used was 5 mg/mL for DTDPP-F, 8 mg/mL for DTDPP-A, 16 mg/mL for DTDPP-V-OH, and 24 mg/mL for DTDPP-L. The resulting gels had a pH of 3.5±0.2.

The mgc was determined by preparing samples at a starting concentration of 5 mg/mL of solution. Higher concentrations were tested until adequate rheology data was recorded and the gel samples were invertible and the minimum concentration at which this happened was determined to be the mgc.

pH measurements

A calibrated FC200 Hanna pH probe was used to measure the pH of solutions and gels. The accuracy of the recorded values, as stated by the supplier, is ±0.1.

To determine the apparent pK_a of the DTDPP-derivatives (as seen in Figure S7), a titration of the gelator solution with 0.1 M HCl was carried out. To 2 mL of the gelator solution (as prepared in the 'Gel preparation' section above), aliquots of 0.1 M HCl (10 µL and 5 µL) were added until a final pH solution of ≈ 2 was achieved. The solution was left to stir vigorously during and between addition of HCl to prevent localised gel formation and to obtain a solution that is close to homogenous as possible.

To carry out pH measurements during gel formation (as seen in Figure 5, and S8-S10), a custom-made pH data logger attached to a pH probe was used. 2 mL of gelator solution was added to pre-weighed GdL in a Sterilin vial (as described in the 'Gel preparation' section above) and placed in a water bath at 25°C with the pH probe suspended in the sample. The pH was recorded every minute over 16 hours.

Photophysical measurements

UV-Vis absorption spectra were recorded using a Agilent Cary 60 spectrophotometer. Measurements were obtained using a 10 mm path length quartz cell for solutions, and a 0.01 mm path length quartz cell for gels and the corresponding sol. For the gels, a mixture of solution and GdL was prepared in vial, which was then pipetted onto the cell and allowed to gel overnight (wrapped in parafilm to prevent drying).

Fluorescence emission spectra were recorded using an Agilent Cary Eclipse fluorescence spectrophotometer. Measurements were obtained using a 10 mm path length quartz cell.

Rheology measurements

Dynamic rheology data was recorded using an Anton Paar Physica MCR301 rheometer. Measurements were performed using a vane geometry (ST10-4V-8.8/97.5) and the cup rheometer plate, with a gap distance between the geometry and the bottom of the sample vial set to 1.8 mm. Samples were prepared in Sterilin vials unless otherwise stated. The temperature was set to 25 ºC unless otherwise stated.

Gels for strain and frequency sweeps were prepared as described in the 'Gel preparation' section above with 2 mL of pH 10.5 gelator solution and the appropriate amount of GdL. Strain sweeps were performed at an angular frequency of 10 rad/s. Frequency sweeps were performed under a strain of 0.125% for DTDPP-V and DTDPP-L, and 0.5% for DTDPP-F and DTDPP-A. Measurements were performed in triplicate, with a fresh sample for each run. The values for the data points were averaged, and the standard deviation is calculated and shown as error bars on the graphs.

For time sweeps, samples were prepared as described in the 'Gel preparation' section above with 2 mL of pH 10.5 gelator solution and the appropriate amount of GdL. Immediately after, the vial was placed into the cup rheometer plate and data was recorded for 16 hours. The angular frequency for time sweeps was set at 10 rad/s. The strain was set at 0.125% for DTDPP-V and DTDPP-L, and 0.5% for DTDPP-F and DTDPP-A.

For thixotopy measurements, samples were prepared as described in the 'Gel preparation' section above with 2 mL of pH 10.5 gelator solution and the appropriate amount of GdL. Data points were recorded at 25 ºC for 2 minutes at 0.5% strain and 10 rad/s frequency, followed by 10 seconds at 300% strain and 10 rad/s frequency. To measure the gel recovery, data points were subsequently recorded for 3.5 minutes at 0.5% strain and 10 rad/s frequency.

For heat-cool temperature sweeps, samples were prepared as described in the 'Gel preparation' section above with 2 mL of pH 10.5 gelator solution and the appropriate amount of GdL in a rheometer aluminium cup. Strain and frequency parameters were set at 0.5% and 10 rad/s respectively. Data points were recorded at 25 ºC for 1 minute before increasing the temperature to 80 ºC at a rate of 1 ºC/min. After 56 minutes of heating, the temperature was decreased to 25 ºC at a rate of 1 ºC/min, followed by a constant temperature of 25 ºC for 5 minutes.

Viscosity data was recorded using an Anton Paar Physica MCR101 rheometer. Measurements were performed using a 50 mm cone geometry (CP50 – cone angle = 0.994 º) with gap distance between the geometry and the flat rheometer plate set to 0.1 mm. Samples (pH 10.5 solutions) were poured onto the flat plate for measurement directly from the falcon tube. The temperature was set to 25 ºC. Measurements were performed in triplicate, with a fresh sample for each run. The values for the data points were averaged, and the standard deviation is calculated and shown as error bars on the graphs.

^{1}H NMR spectroscopy to determine the amount of free molecule

^{1}H NMR spectra were collected using a Bruker 500 MHz spectrometer. A sealed capillary tube with 0.1% polydimethylsiloxane (PDMS) in tetrachloroethylene solution was used as an internal standard inside the NMR tube with the DTDPP-R-OH samples prepared with D_2O and with 2 molar equivalents of 1M NaOD.

A 'time zero' (t = 0 minutes) run was done with DTDPP-R-OH solution at the mgc at a pD of 10.5. To prepare gel samples, DTDPP-R-OH solution (at mgc, at pD of 10.5) was added to a Sterilin vial with the required amount of GdL. The vial was swirled to dissolve the GdL and immediately after was transferred into an NMR tube. ^{1}H NMR spectra were recorded every 5 minutes for 16 hours.

To measure the changes in the percentage of free molecule over the 16 hours, the ratios of the integral of the PDMS peak and the integral of a DTDPP-R-OH peak were used (as seen below). The ratio of the 'time zero' run was set at 100% free molecule.

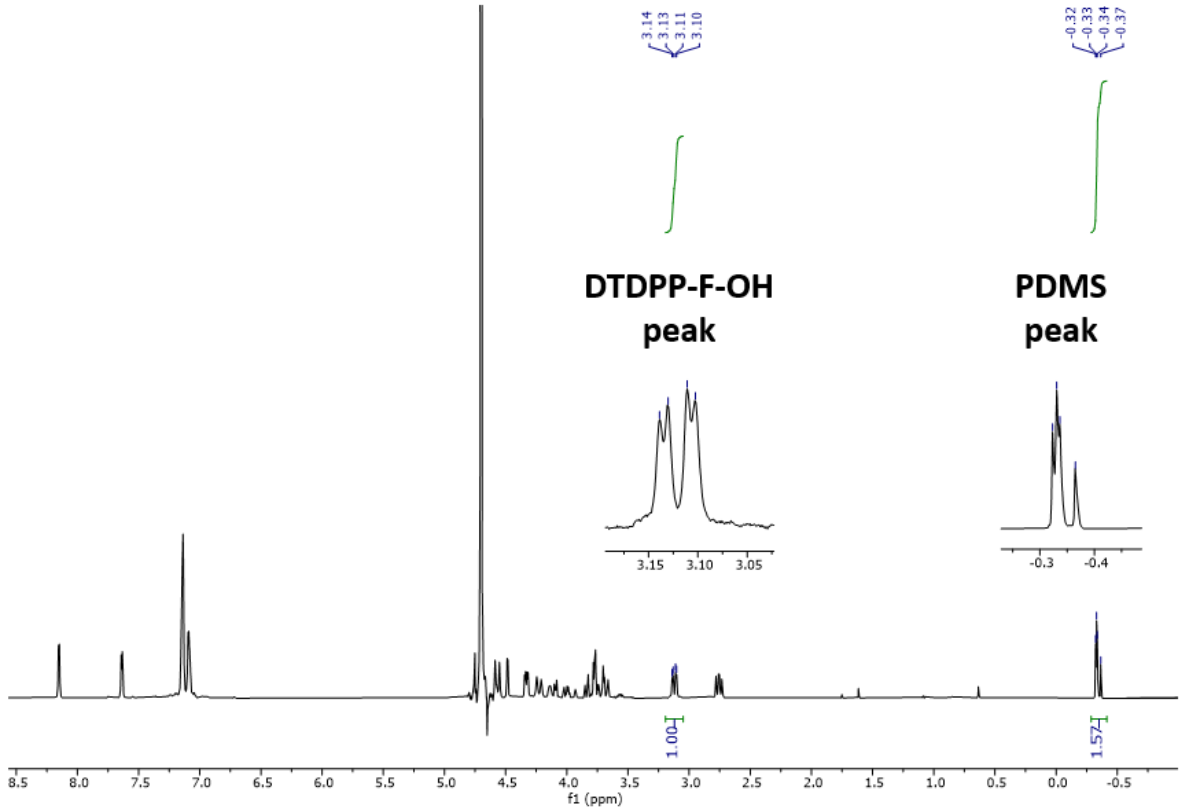


Figure S1. Example ^{1}H NMR spectra for DTDPP-F-OH %free molecule analysis in D_2O with PDMS as an internal standard.

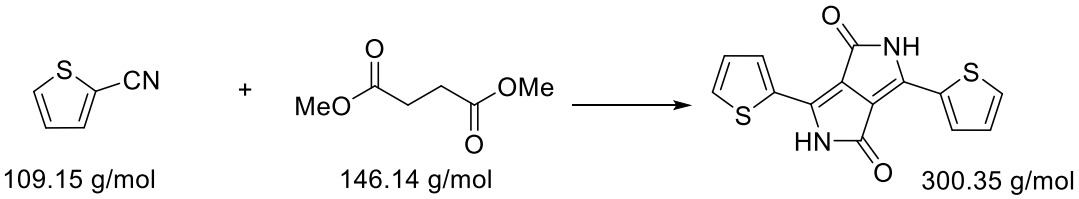
Small-angle X-Ray Scattering

Samples of gelator solutions and gels were prepared as described in the 'Gel preparation' section above. All samples were loaded into 3.5 mm borosilicate glass capillaries (Capillary Tube Supplies Ltd) and sealed using 2-part fast curing epoxy (Araldite) for 30 minutes; since the gelling time is slow using GdL, there is sufficient time to load the solutions after mixing with GdL before a gel is formed such that this loading does not lead to any issues.

SAXS data were collected on a Ganesha 300XL instrument (Xenocs). SAXS data were collected at room temperature over a Q range of 0.007 – 0.25Å^{-1} for an exposure time of 3600 seconds. All measurements were corrected for transmission and absolute intensity and had the solvent background and empty capillary scattering subtracted before processing. Data were reduced using SAXSGUI, and model fits were performed using SASView 4.0.[1]

Synthetic Procedures

3,6-Bis(thiophen-2-yl)-1H,2H,4H,5H-pyrrolo[3,4-c]pyrrole-1,4-dione (**DTDPP**):

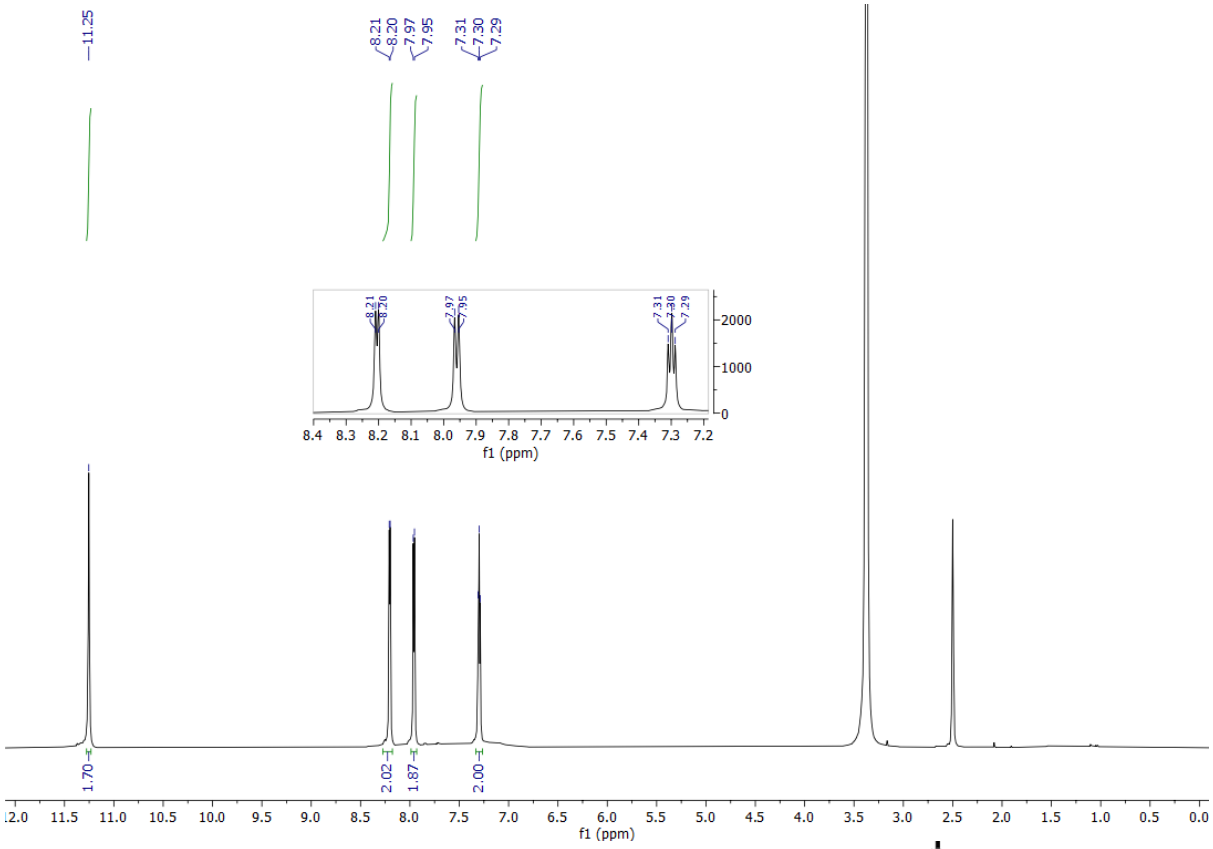


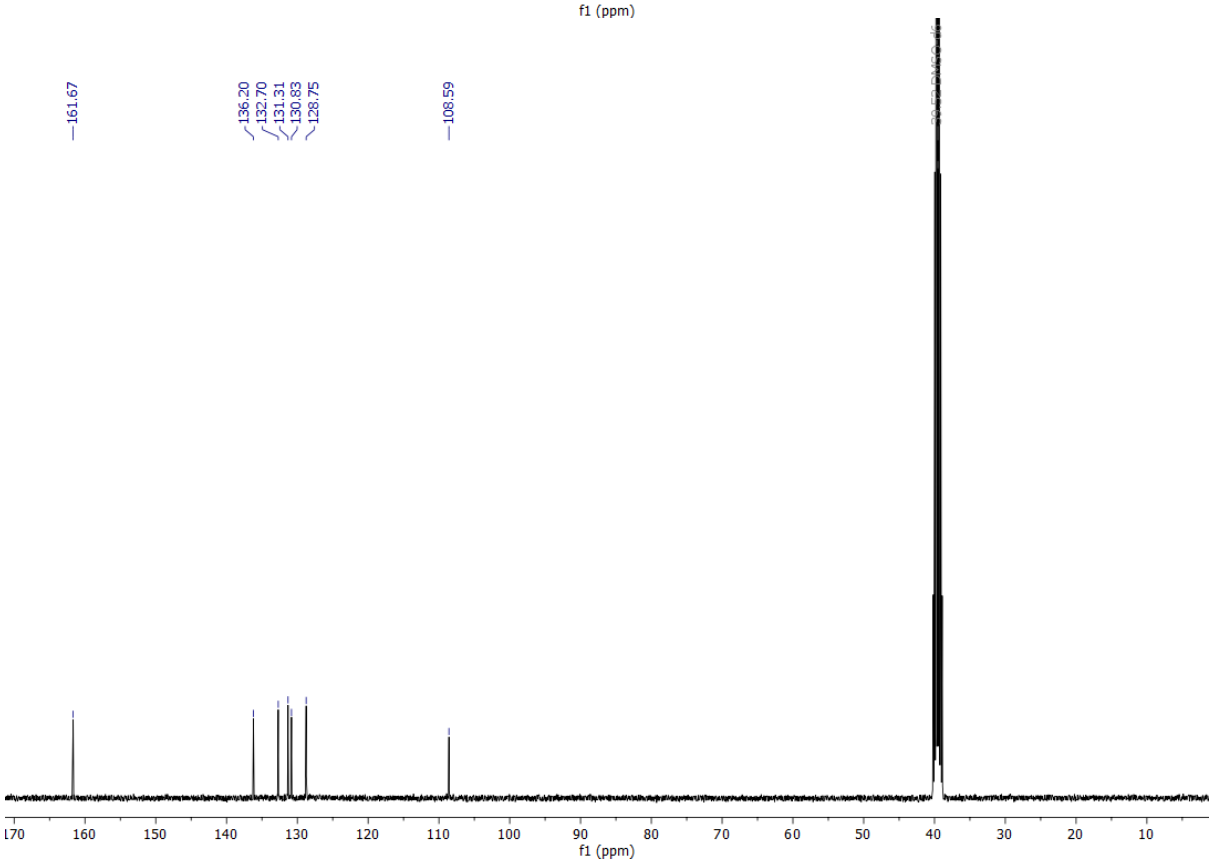
109.15 g/mol 146.14 g/mol 300.35 g/mol

DTDPP

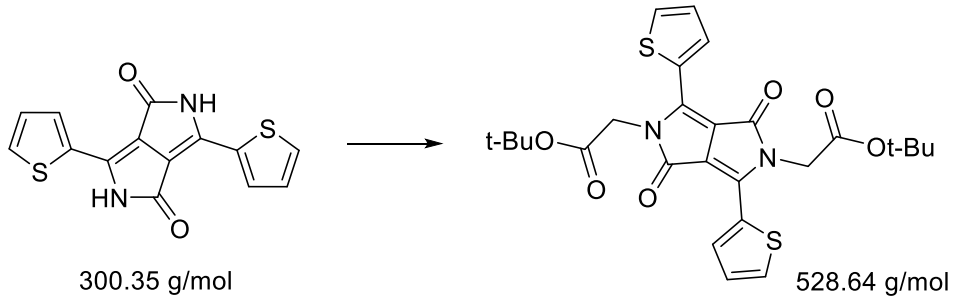
All glassware was dried in an oven and flushed with nitrogen prior to starting the reaction. Potassium *tert*-butoxide (53.13 g, 464.1 mmol, 3.57 eq.) was added to the flask and flushed with nitrogen. A solution of thiophene-2-carbonitrile (36.2 mL, 390 mmol, 3 eq.) in *tert*-amyl alcohol (325 mL) was added and the mixture was heated to 105 ºC. Following this, a solution of dimethyl succinate (17 mL, 130 mmol, 1 eq.) in *tert*-amyl alcohol (104 mL) was added slowly from a dropping funnel for approximately 1 hour. The progress of the reaction was monitored by TLC (1:9 EtOAc:DCM). After 3 hours, the reaction mixture was allowed to cool to 80 ºC above the oil bath. Methanol (650 mL) was added in portions to dilute the reaction mixture, followed by neutralisation with the addition of glacial acetic acid (52 mL) in portions. The mixture was then heated at reflux for 15 minutes, after which the heating was stopped, and the reaction was allowed to cool with stirring overnight. The reaction mixture was then filtered by vacuum and the residue was rinsed with hot methanol (150 mL) and hot water (150 mL) twice in successive portions. After drying in a vacuum oven at 60 ºC overnight, the title compound **DTDPP** was obtained as a purple-black solid at 58% yield (22.85827 g, 75.18 mmol).

δH (400 MHz, DMSO-d_6) 11.25 (2H, s), 8.20 (2H, d, *J* 3.8), 7.96 (2H, d, *J* 5.0), 7.30 (2H, t, *J* 4.4). δC (101 MHz, DMSO-d_6) δ 161.67, 136.20, 132.70, 131.31, 130.83, 128.75, 108.59. HRMS ESI (+ve) m/z: 322.9913 $[M\text{-}Na]^+$.


11.25
8.21
8.20
7.97
7.95
7.31
7.30
7.29
1.70
2.02
1.87
2.00
f1 (ppm)


161.67
136.20
132.70
131.31
130.83
128.75
108.59
f1 (ppm)

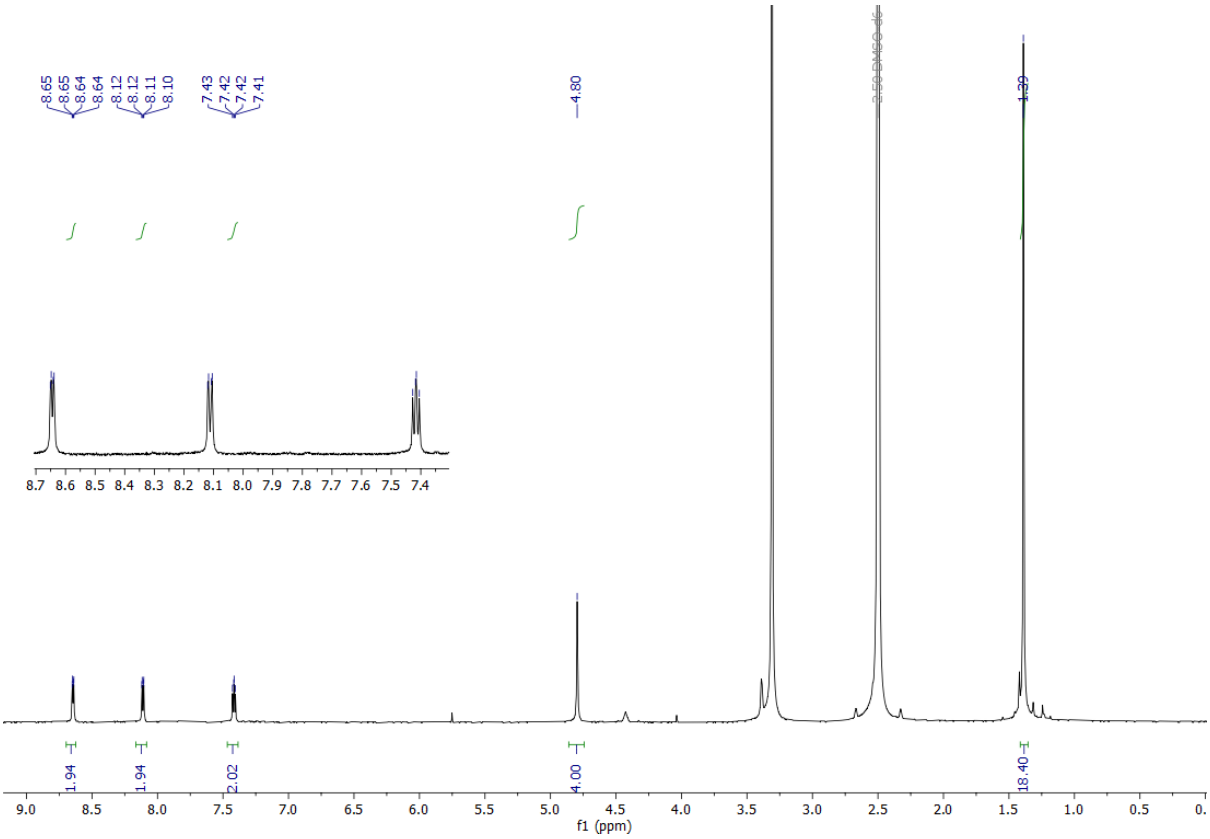
tert-Butyl-2-{5-[2-(tert-butoxy)-2-oxoethyl]-1,4-dioxo-3,6-bis(thiophen-2-yl)pyrrolo[3,4-c]pyrrol-2-yl}acetate (**DTDPP-O^{t}Bu**):



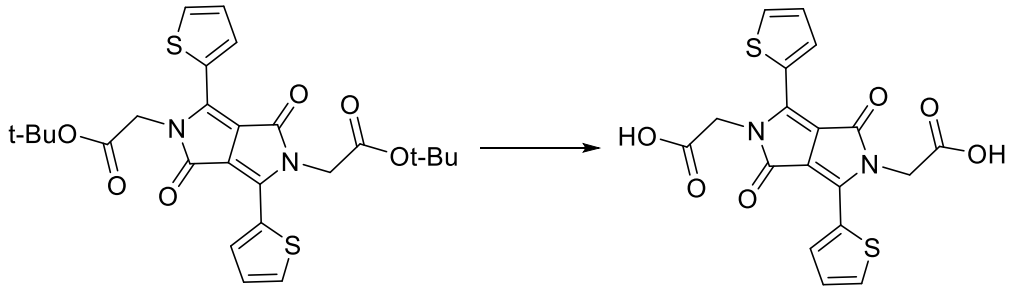
300.35 g/mol — **DTDPP** — 528.64 g/mol — **DTDPP-O^{t}Bu**

To the flask, **DTDPP** (20.36 g, 67.14 mmol, 1 eq.), K_2CO_3 (56 g, 405.8 mmol, 6 eq.) and acetone (800 mL) were added and heating was initiated. After 2 hours, tert-butyl bromoacetate (30 mL, 202.92 mmol, 3 eq) was added. The progress of the reaction was monitored by TLC (1:1 EtOAc:n-Hex) over one week. Upon completion, the reaction was allowed to cool to room temperature and evaporated under reduced pressure. The residue was partitioned between dichloromethane and water, and the organic phases were washed (brine), dried ($MgSO_4$), filtered, and evaporated to dryness under reduced pressure. The crude was purified on a flash column (1:20 product:silica, 1:99 EtOAc/DCM) and the product **DTDPP-O^{t}Bu** was obtained as a brown solid (6.6 g, 12.48 mmol, 18.6% yield).

δ_H (400 MHz, DMSO) 8.64 (2 H, dd, *J* 3.9, 1.2), 8.11 (2 H, dd, *J* 4.9, 1.2), 7.42 (2 H, dd, *J* 5.0, 3.9), 4.80 (4 H, s), 1.39 (18 H, s). The title product was too insoluble to obtain a ^{13}C NMR. HRMS ESI (+ve) m/z: 529.1451 $[M-H]^+$.



2-[5-(Carboxymethyl)-1,4-dioxo-3,6-bis(thiophen-2-yl)-1H,2H,4H,5H-pyrrolo[3,4-c]pyrrol-2-yl]acetic acid (**DTDPP-OH**):



528.64 g/mol

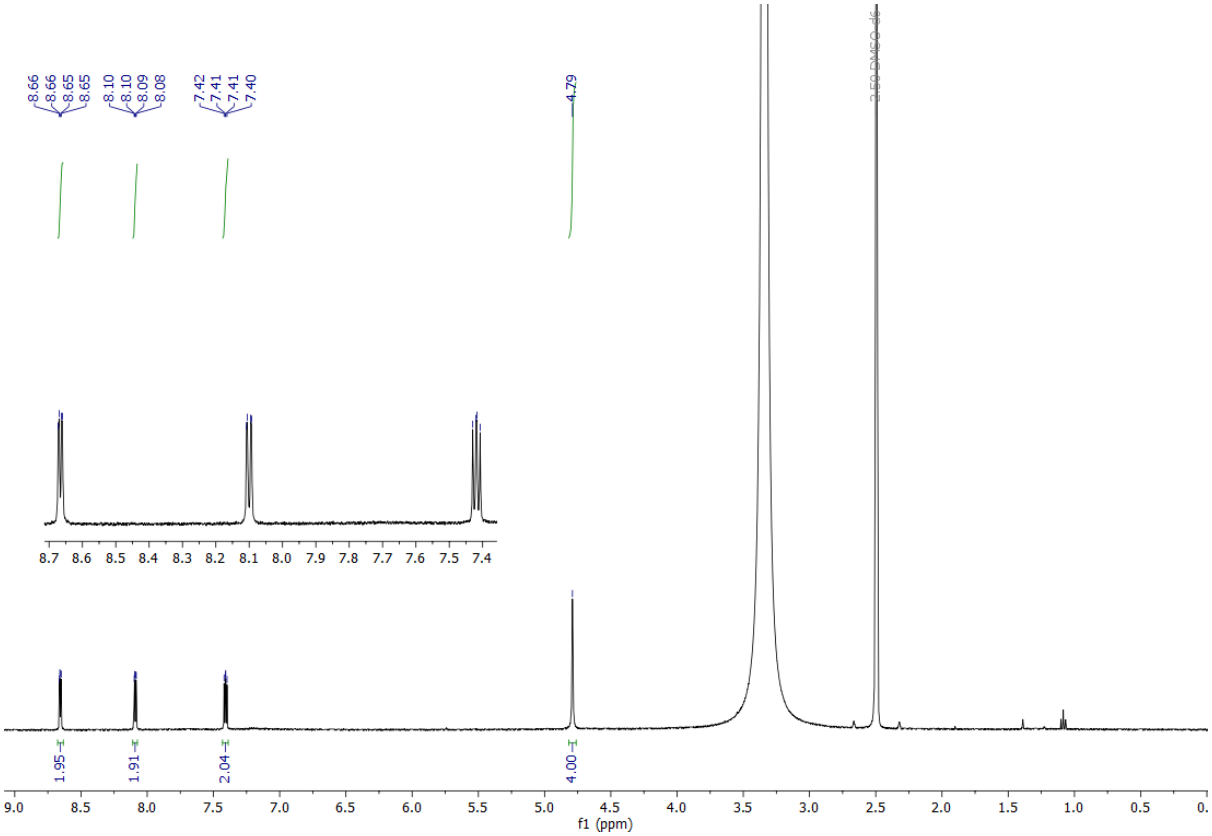
DTDPP-O^{t}Bu

416.42 g/mol

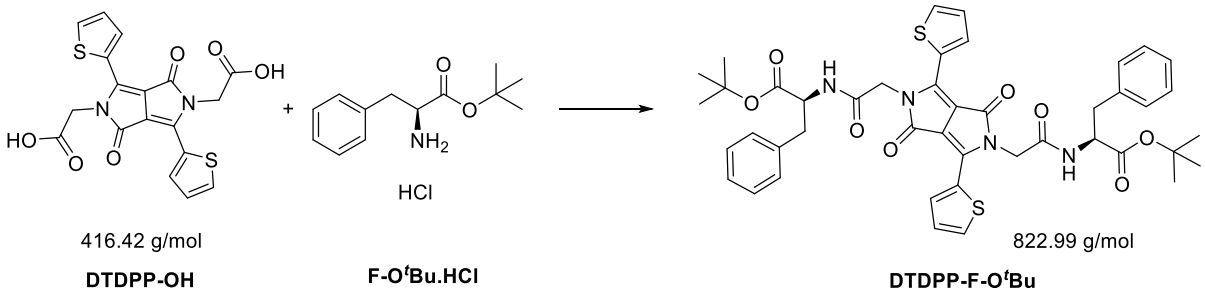
DTDPP-OH

DTDPP-O^{t}Bu (0.7017 g, 1.32 mmol, 1 eq.) was dissolved in DCM (20 mL). TFA (10 mL, 130.6 mmol, 99 eq) was added and the reaction mixture was left to stir overnight at room temperature. The reaction mixture was then poured into Et_2O (75 mL), stirred for 30 mins, filtered and washed the residue with Et_2O and dried in a vacuum oven overnight. The title compound **DTDPP-OH** was obtained as a purple solid at 98% yield (0.537 g, 1.29 mmol).

δH (400 MHz, DMSO-d_6) 8.67 (2H, dd, *J* 3.9, 1.2), 8.10 (2H, dd, *J* 5.0, 1.2), 7.42 (2H, dd, *J* 5.0, 3.9), 4.80 (4H, s). The title product was too insoluble to obtain a ^{13}C NMR. HRMS ESI (+ve) m/z: 439.0032 [M-Na]$^+$.



tert-Butyl-2-{2-[5-({[1-(*tert*-butoxy)-1-oxo-3-phenylpropan-2-yl]carbamoyl}methyl)-1,4-dioxo-3,6-bis(thiophen-2-yl)-1H,2H,4H,5H-pyrrolo[3,4-c]pyrrol-2-yl]acetamido}-3-phenylpropanoate (**DTDPP-F-O^{t}Bu**):



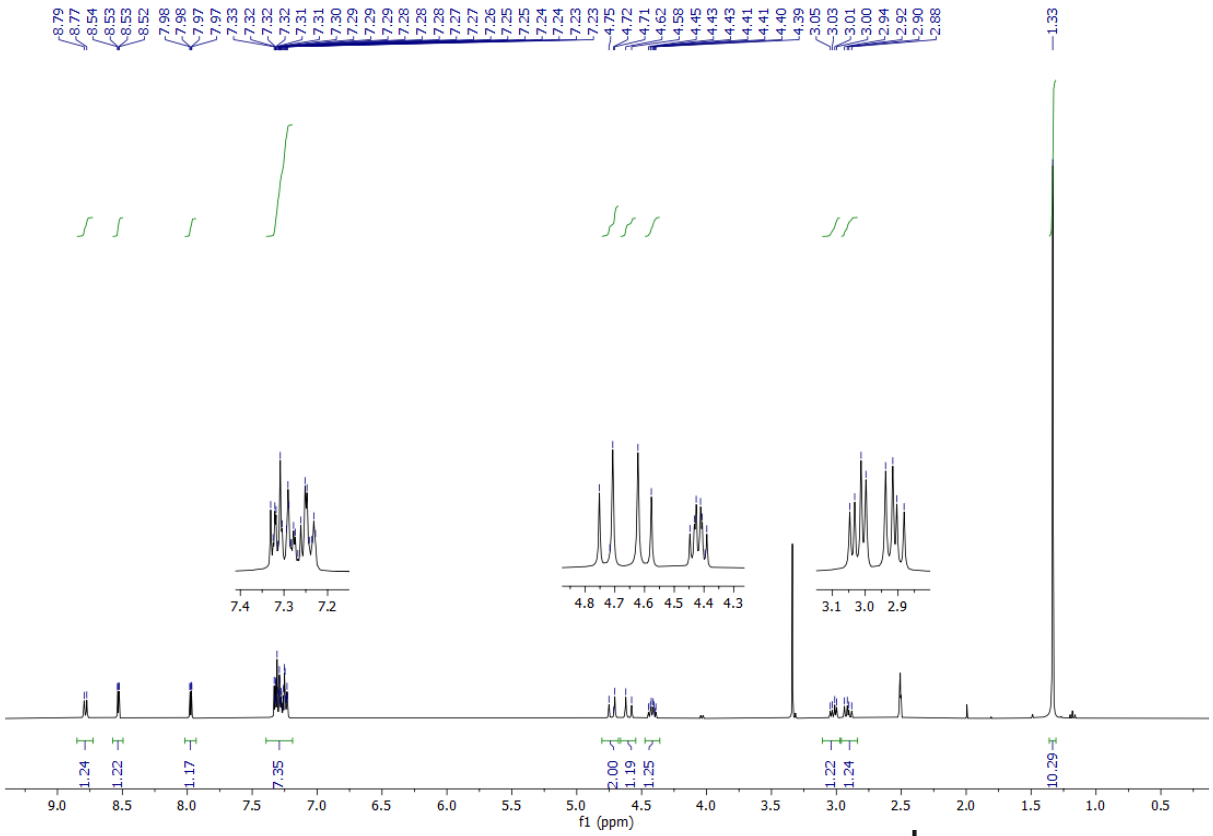
416.42 g/mol — **DTDPP-OH**

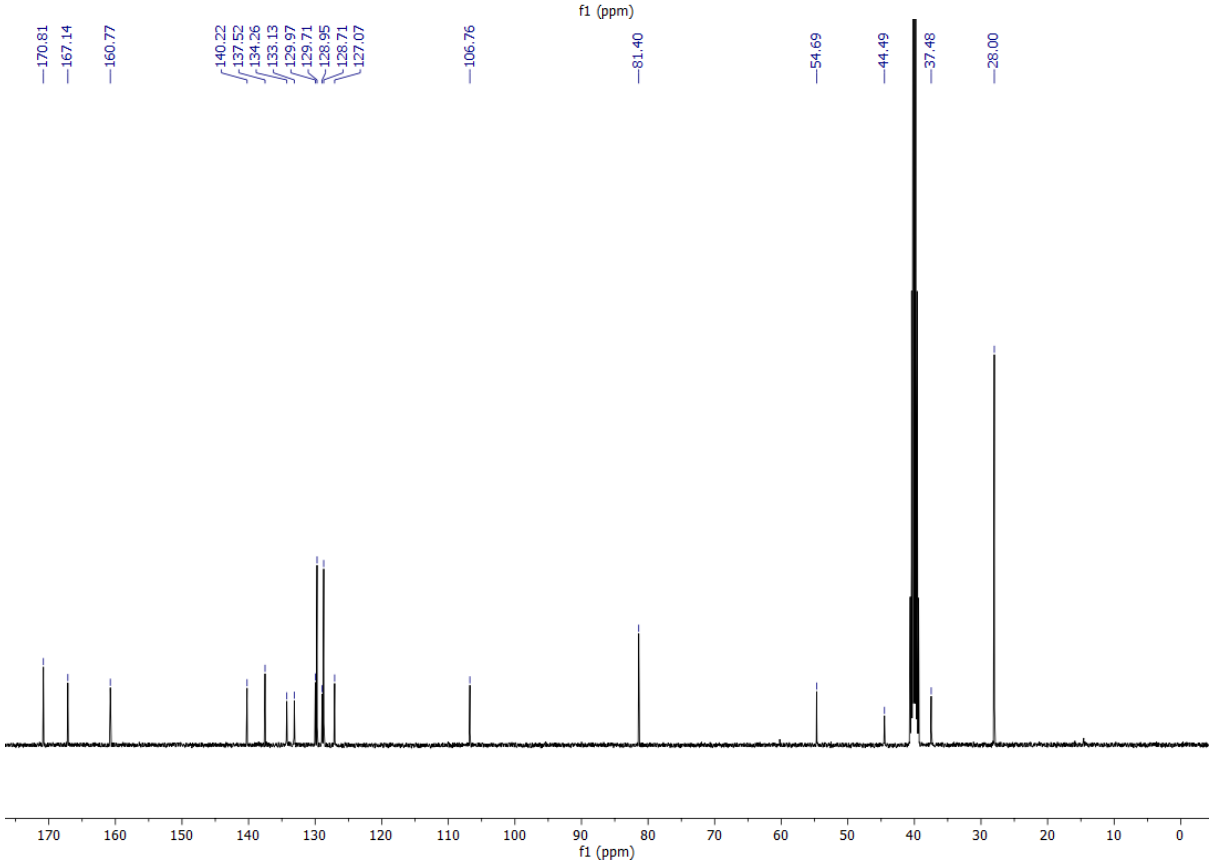
F-O^{t}Bu.HCl

822.99 g/mol — **DTDPP-F-O^{t}Bu**

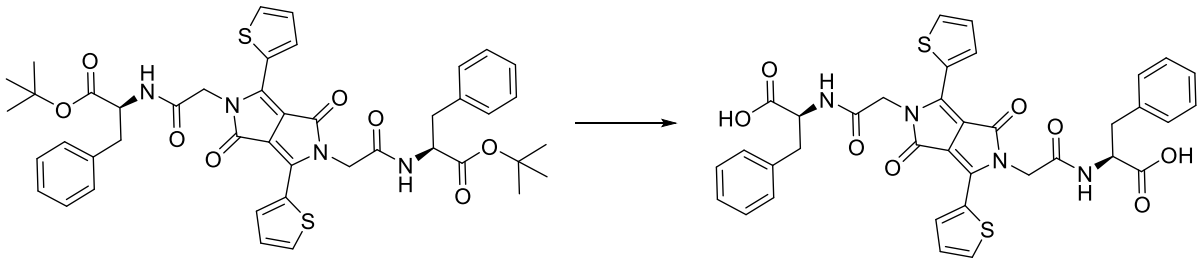
DTDPP-OH (1.45 g, 3.4 mmol, 1 eq.) was dissolved in $CHCl_3$ (35 mL) and left to stir for a few minutes. The flask was placed in an ice bath and NMM (1.87 mL, 17 mmol, 5 eq.) was added to the reaction mixture and left to stir for ten minutes. IBCF (0.97 mL, 7.5 mmol, 2.2 eq.) was added and left to stir for five minutes. Phenylalanine *tert*-butyl ester hydrochloride (1.77 g, 6.9 mmol, 2 eq.) was dissolved in $CHCl_3$ (15 mL) and NMM (1.5 mL), and was added to the reaction mixture and left to stir overnight. To quench the reaction, water (25 mL) was added. The organic and aqueous phases were separated, and the organic phase was washed with 1 M HCl and saturated aqueous brine, dried with $MgSO_4$ and then concentrated under vacuum. Column chromatography (4 cm x 27 cm, 1:9 EtOAc/DCM) was used for purification, which yielded the title compound **DTDPP-F-O^{t}Bu** as a purple solid at 92% yield (2.58 g, 3.13 mmol).

δ_H (400 MHz, DMSO-d_6) 8.78 (2 H, d, *J* 7.9), 8.53 (2 H, dd, *J* 3.9, 1.2), 7.97 (2 H, dd, *J* 5.0, 1.2), 7.35 – 7.20 (12 H, m), 4.73 (2 H, d, *J* 18.0), 4.60 (2 H, d, *J* 18.0), 4.42 (2 H, td, *J* 8.5, 6.0), 3.02 (2 H, dd, *J* 13.8, 6.0), 2.91 (2 H, dd, *J* 13.8, 8.8), 1.33 (18 H, s). δC (101 MHz, DMSO) δ 170.33, 166.66, 160.28, 139.74, 137.04, 133.78, 132.65, 129.49, 129.23, 128.47, 128.23, 126.59, 106.28, 80.92, 54.21, 44.01, 37.00, 27.52. HRMS ESI (+ve) m/z: 823.2817 $[M-H]^+$.


8.79 8.77 8.54 8.53 8.53 8.52 7.98 7.98 7.97 7.97 7.33 7.32 7.32 7.32 7.31 7.30 7.29 7.29 7.29 7.28 7.28 7.28 7.27 7.27 7.26 7.25 7.25 7.24 7.24 7.23 7.23 4.75 4.72 4.71 4.62 4.58 4.45 4.43 4.43 4.41 4.41 4.40 4.39 3.05 3.03 3.01 3.00 2.94 2.92 2.90 2.88 1.33
7.4 7.3 7.2
4.8 4.7 4.6 4.5 4.4 4.3
3.1 3.0 2.9
1.24 1.22 1.17 7.35 2.00 1.19 1.25 1.22 1.24 10.29
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


170.81 167.14 160.77 140.22 137.52 134.26 133.13 129.97 129.71 128.95 128.71 127.07 106.76 81.40 54.69 44.49 37.48 28.00
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

2-[2-(5-{[(1-Carboxy-2-phenylethyl)carbamoyl]methyl}-1,4-dioxo-3,6-bis(thiophen-2-yl)-1H,2H,4H,5H-pyrrolo[3,4-c]pyrrol-2-yl)acetamido]-3-phenylpropanoic acid (**DTDPP-F-OH**):



822.99 g/mol

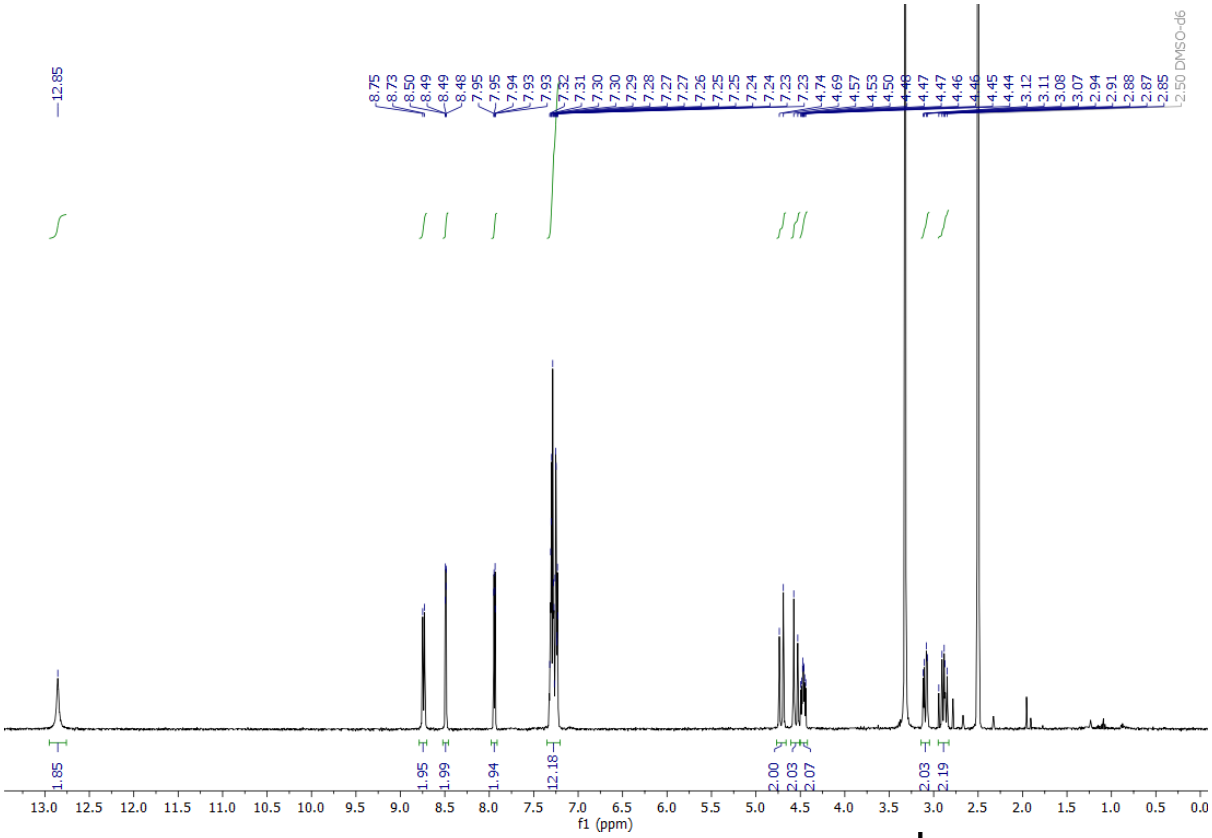
DTDPP-F-O^{t}Bu

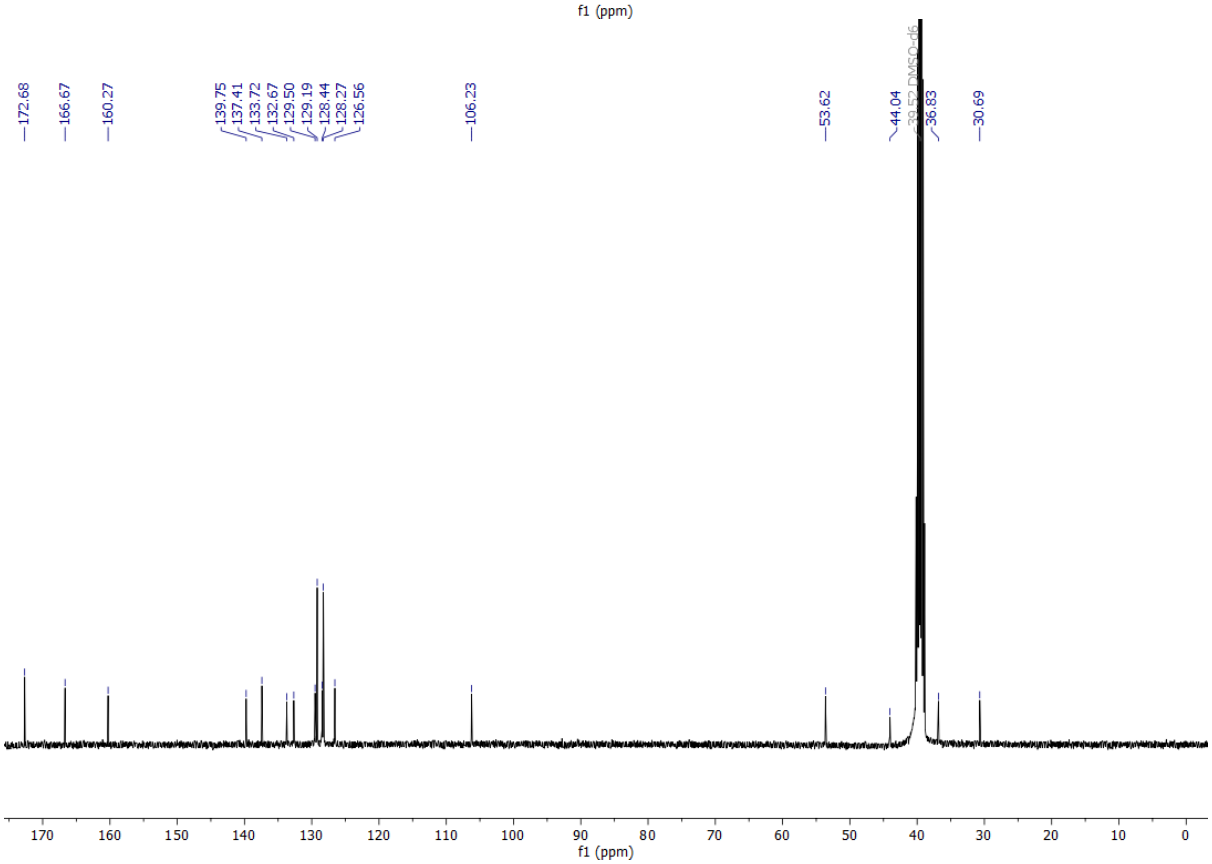
710.78 g/mol

DTDPP-F-OH

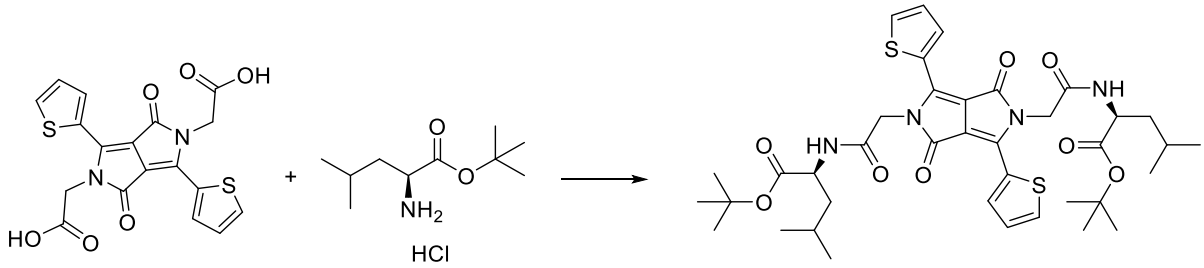
DTDPP-F-O^{t}Bu (0.4830 g, 0.58 mmol, 1eq.) was dissolved in DCM (50 mL). TFA (35 mL, 457 mmol, excess) was added and the reaction mixture was left to stir at ambient temperature overnight. The reaction mixture was poured into Et_2O (250 mL), stirred for 30 minutes, filtered and washed with Et_2O once more. The solid residue was dried in a vacuum oven, and the title compound **DTDPP-F-OH** was isolated at 92% yield (0.3839 g, 0.54 mmol).

δ_H (400 MHz, DMSO-d_6) 12.85 (2H, br), 8.74 (2 H, d, *J* 8.2), 8.49 (2 H, dd, *J* 4.0, 1.1), 7.97 – 7.91 (2 H, m), 7.35 – 7.20 (12 H, m), 4.71 (2 H, d, *J* 18.0), 4.55 (2 H, d, *J* 18.0), 4.47 (2 H, ddd, *J* 9.7, 8.3, 4.7), 3.09 (2 H, dd, *J* 13.8, 4.7), 2.97 – 2.81 (2 H, m). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.68, 166.67, 160.27, 139.75, 137.41, 133.72, 132.67, 129.50, 129.19, 128.44, 128.27, 126.56, 106.23, 53.62, 44.04, 36.83, 30.69. HRMS ESI (+ve) m/z: 733.1371 $[M\text{-}Na]^+$.


12.85
8.75
8.73
8.50
8.49
8.49
8.48
7.95
7.95
7.94
7.93
7.93
7.32
7.31
7.30
7.30
7.29
7.28
7.27
7.27
7.26
7.25
7.25
7.24
7.24
7.23
7.23
4.74
4.69
4.57
4.53
4.50
4.48
4.47
4.47
4.46
4.46
4.45
4.44
3.12
3.11
3.08
3.07
2.94
2.91
2.88
2.87
2.85
2.50 DMSO-d6
1.85
1.95
1.99
1.94
12.18
2.00
2.03
2.07
2.03
2.19
f1 (ppm)


172.68
166.67
160.27
139.75
137.41
133.72
132.67
129.50
129.19
128.44
128.27
126.56
106.23
53.62
44.04
39.52 DMSO-d6
36.83
30.69
f1 (ppm)

tert-Butyl-2-{2-[5-({[1-(*tert*-butoxy)-4-methyl-1-oxopentan-2-yl]carbamoyl}methyl)-1,4-dioxo-3,6-bis(thiophen-2-yl)-1H,2H,4H,5H-pyrrolo[3,4-c]pyrrol-2-yl]acetamido}-4-methylpentanoate (**DTDPP-L-O^{t}Bu**):



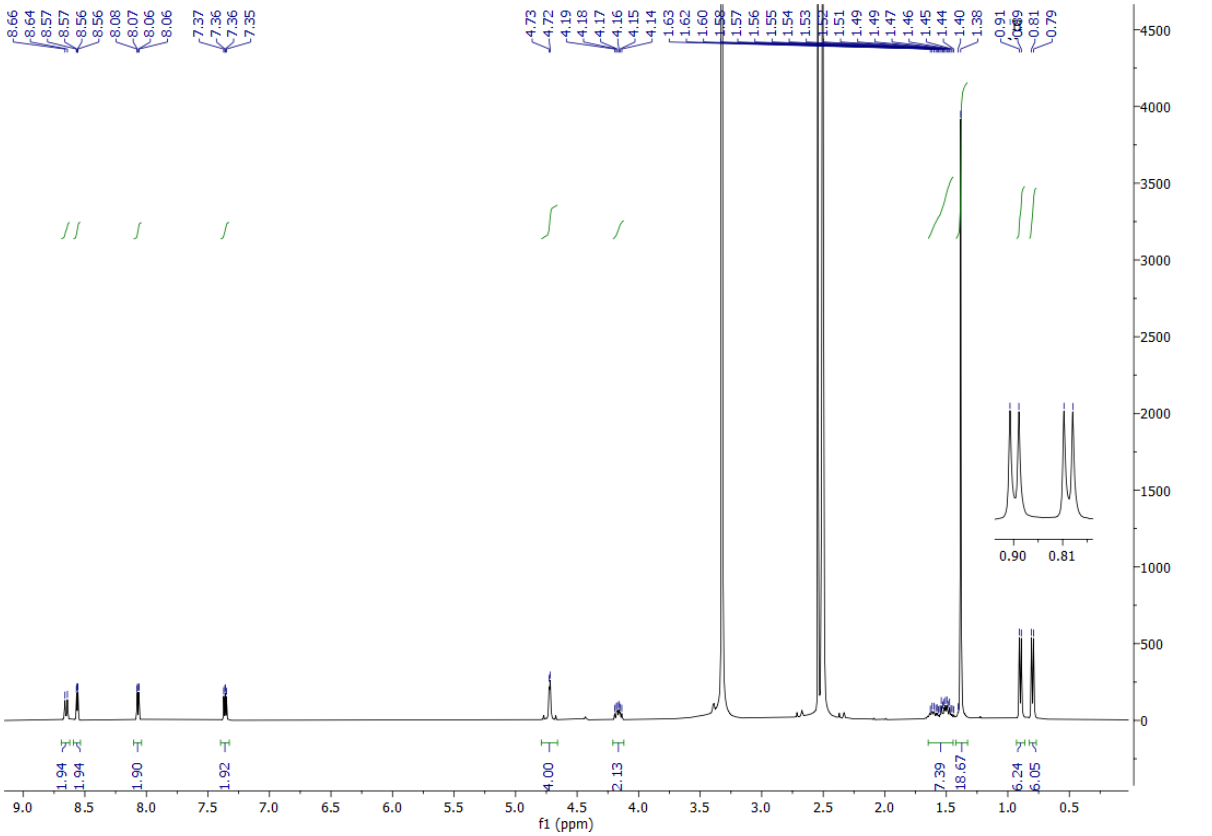
416.42 g/mol
DTDPP-OH

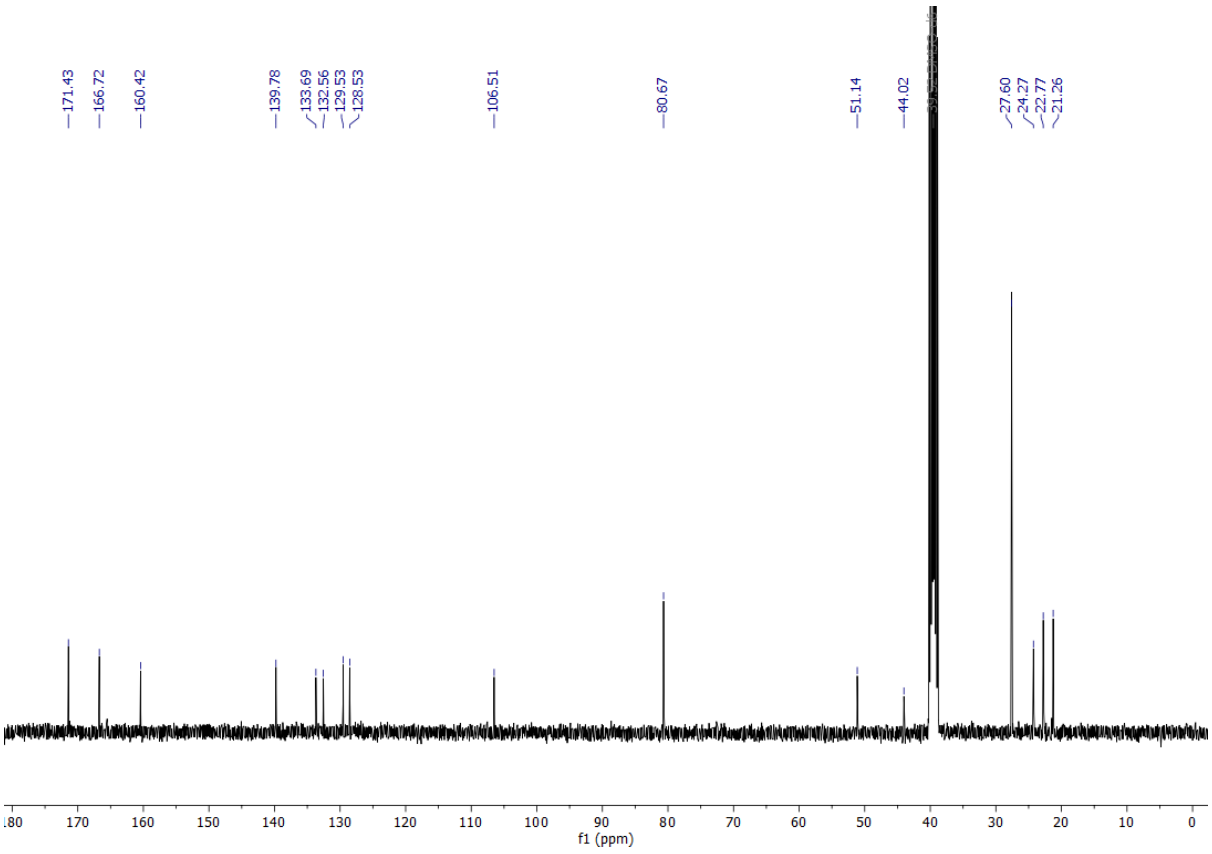
L-O^{t}Bu.HCl

754.96 g/mol
DTDPP-L-O^{t}Bu

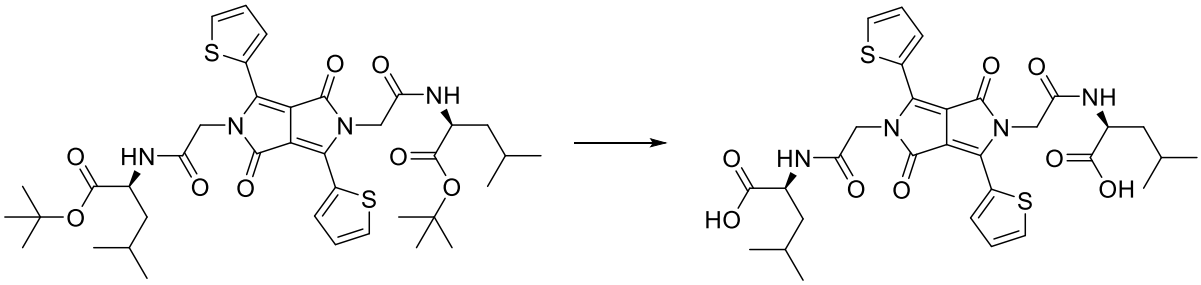
DTDPP-OH (0.298 g, 0.7 mmol, 1 eq.) was dissolved in $CHCl_3$ (10 mL) and left to stir for a few minutes. The flask was placed in an ice bath and NMM (0.38 mL, 3.5 mmol, 5 eq.) was added to the reaction mixture and left to stir for ten minutes. IBCF (0.2 mL, 1.54 mmol, 2.2 eq.) was added and left to stir for five minutes. Leucine *tert*-butyl ester hydrochloride (0.31 g, 1.4 mmol, 2 eq.), dissolved in $CHCl_3$ (1 mL) and NMM (0.1 mL), was added to the mixture and left to stir overnight. To quench the reaction, water (10 mL) was added. The organic and aqueous phases were separated, and the organic phase was washed with 1M HCl and saturated aqueous brine, dried with $MgSO_4$ and then concentrated under vacuum. The title compound **DTDPP-L-O^{t}Bu** was obtained at 72.3% yield (0.382 g, 0.506 mmol).

δH (400 MHz, DMSO-d_6) 8.65 (2H, d, *J* 7.92 Hz), 8.56 (2H, dd, *J* 3.86, 1.04 Hz), 8.06 (2H, dd, *J* 5.00, 1.03 Hz), 7.36 (2H, dd, *J* 4.93, 3.96 Hz), 4.72 (4H, d, *J* 2.81 Hz), 4.16 (2H, m), 2.54 (16H, s), 1.61 (3H, m), 1.50 (5H, m), 1.38 (19H, s), 0.89 (6H, d, *J* 6.51 Hz), 0.79 (6H, d, *J* 6.46 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.43, 166.72, 160.42, 139.78, 133.69, 132.56, 129.53, 128.53, 106.51, 80.67, 51.14, 44.02, 27.61, 24.27, 22.77, 21.26. HRMS ESI (+ve) m/z: 777.2708 $[M\text{-}Na]^+$.


8.66
8.64
8.57
8.57
8.56
8.56
8.08
8.07
8.06
8.06
7.37
7.36
7.36
7.35
4.73
4.72
4.19
4.18
4.17
4.16
4.15
4.14
1.63
1.62
1.60
1.58
1.57
1.56
1.55
1.54
1.53
1.52
1.51
1.49
1.49
1.47
1.46
1.45
1.44
1.40
1.38
0.91
0.89
0.81
0.79
0.90
0.81
1.94
1.94
1.90
1.92
4.00
2.13
7.39
18.67
6.24
6.05
f1 (ppm)


171.43
166.72
160.42
139.78
133.69
132.56
129.53
128.53
106.51
80.67
51.14
44.02
27.60
24.27
22.77
21.26
f1 (ppm)

2-[2-(5-{[(1-Carboxy-3-methylbutyl)carbamoyl]methyl}-1,4-dioxo-3,6-bis(thiophen-2-yl)-1H,2H,4H,5H-pyrrolo[3,4-c]pyrrol-2-yl)acetamido]-4-methylpentanoic acid (**DTDPP-L-OH**):

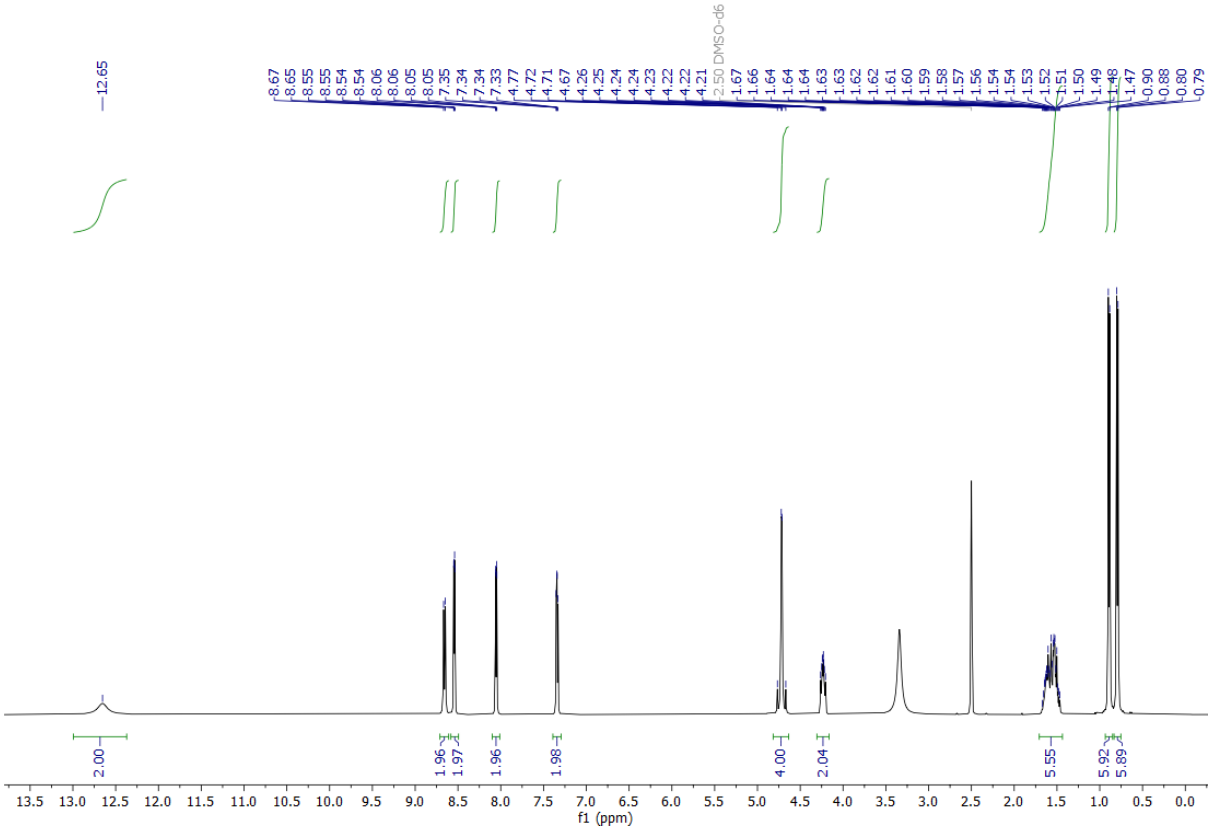


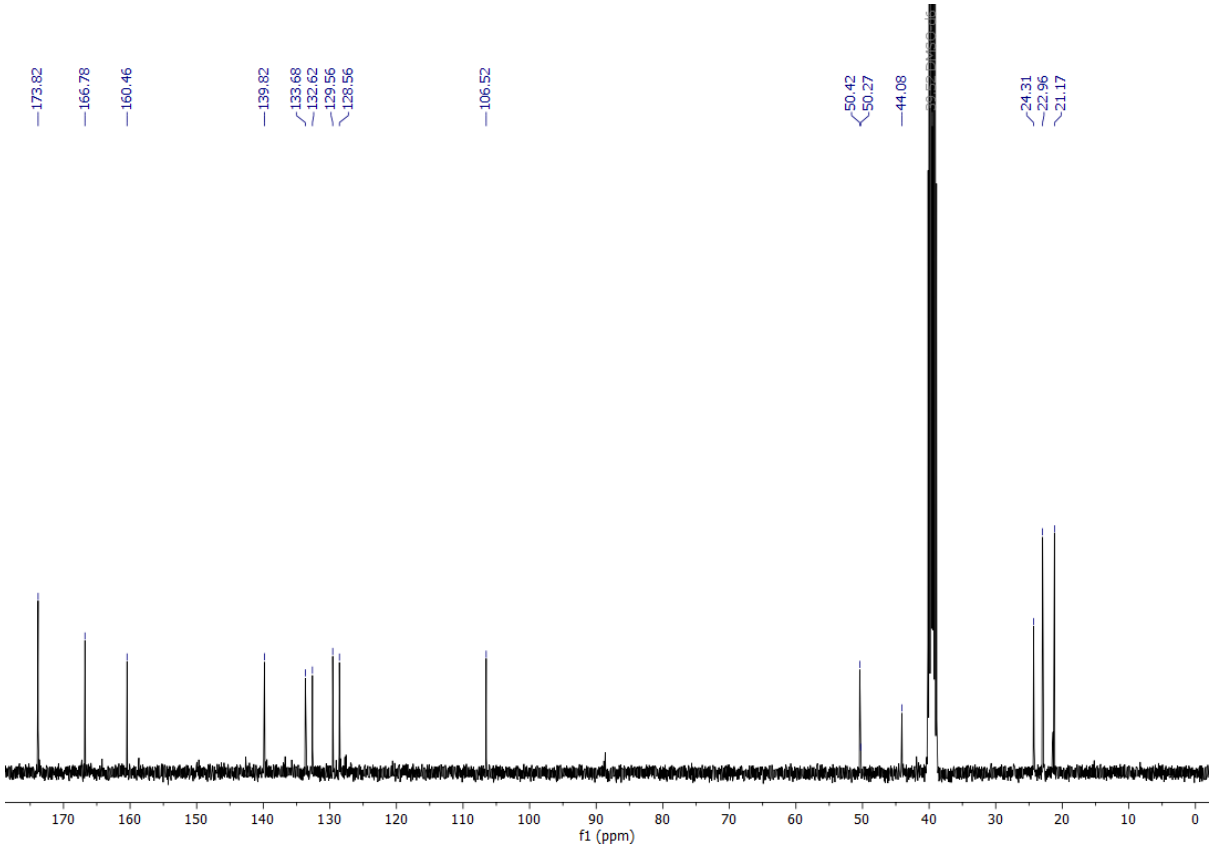
754.96 g/mol
DTDPP-L-O^{t}Bu

642.74 g/mol
DTDPP-L-OH

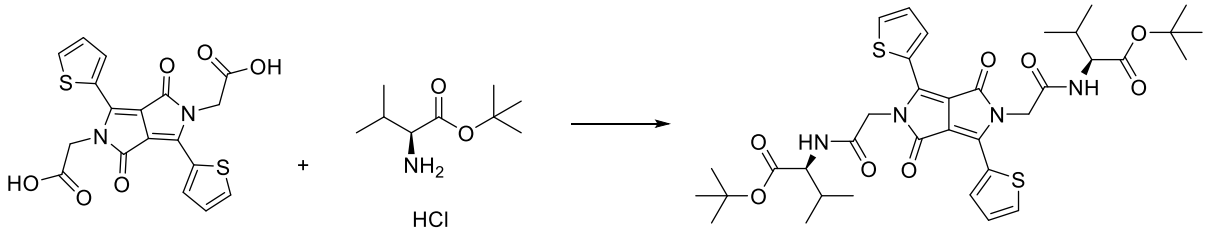
DPP-L-O^{t}Bu (1 g, 1.3 mmol, 1eq.) was dissolved in DCM (70 mL). TFA (30.61 mL, 397.37 mmol, 300 eq.) was added and the reaction mixture was left to stir at ambient temperature overnight. The reaction mixture was poured into Et_2O (700 mL), stirred for 30 mins, filtered and washed with Et_2O. The solid residue was dried in a vacuum oven overnight, and the title compound **DTDPP-L-OH** was isolated at 100% yield (0.8746 g, 1.3 mmol).

δ_H (400 MHz, DMSO-d_6) 12.65 (2 H, s), 8.66 (2 H, d, *J* 8.1), 8.54 (2 H, dd, *J* 3.9, 1.2), 8.05 (2 H, dd, *J* 5.0, 1.2), 7.34 (2 H, dd, *J* 5.0, 3.9), 4.81 – 4.63 (4 H, m), 4.23 (2 H, ddd, *J* 9.8, 8.0, 5.0), 1.70 – 1.44 (6 H, m), 0.89 (6 H, d, *J* 6.4), 0.79 (6 H, d, *J* 6.4). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.82, 166.78, 160.46, 139.82, 133.68, 132.62, 129.56, 128.56, 106.52, 50.42, 50.27, 44.08, 24.31, 22.96, 21.17.
HRMS ESI (+ve) m/z: 643.1896 $[M-H]^+$.




173.82
166.78
160.46
139.82
133.68
132.62
129.56
128.56
106.52
50.42
50.27
44.08
24.31
22.96
21.17
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

tert-Butyl-2-{2-[5-({[1-(*tert*-butoxy)-3-methyl-1-oxobutan-2-yl]carbamoyl}methyl)-1,4-dioxo-3,6-bis(thiophen-2-yl)-1H,2H,4H,5H-pyrrolo[3,4-c]pyrrol-2-yl]acetamido}-3-methylbutanoate (**DTDPP-V-O^{t}Bu**):



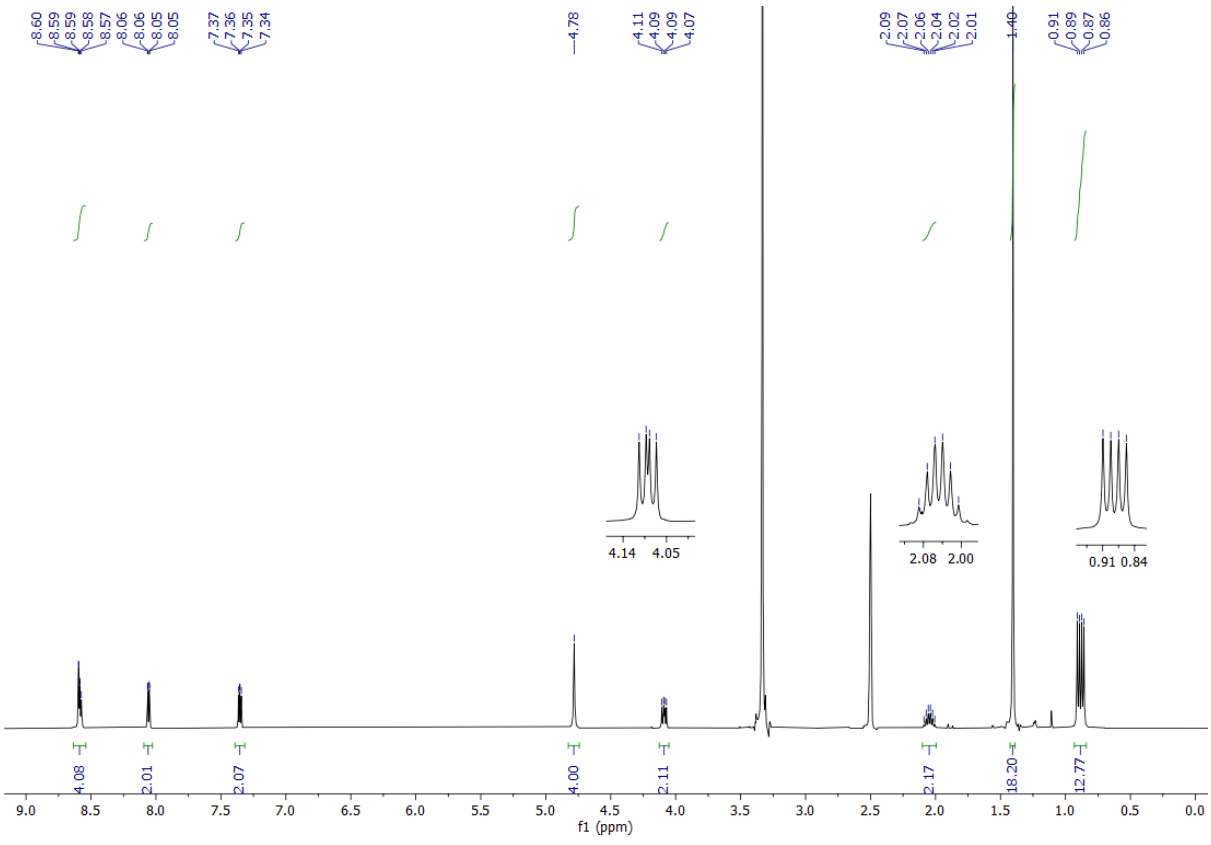
416.42 g/mol
DTDPP-OH

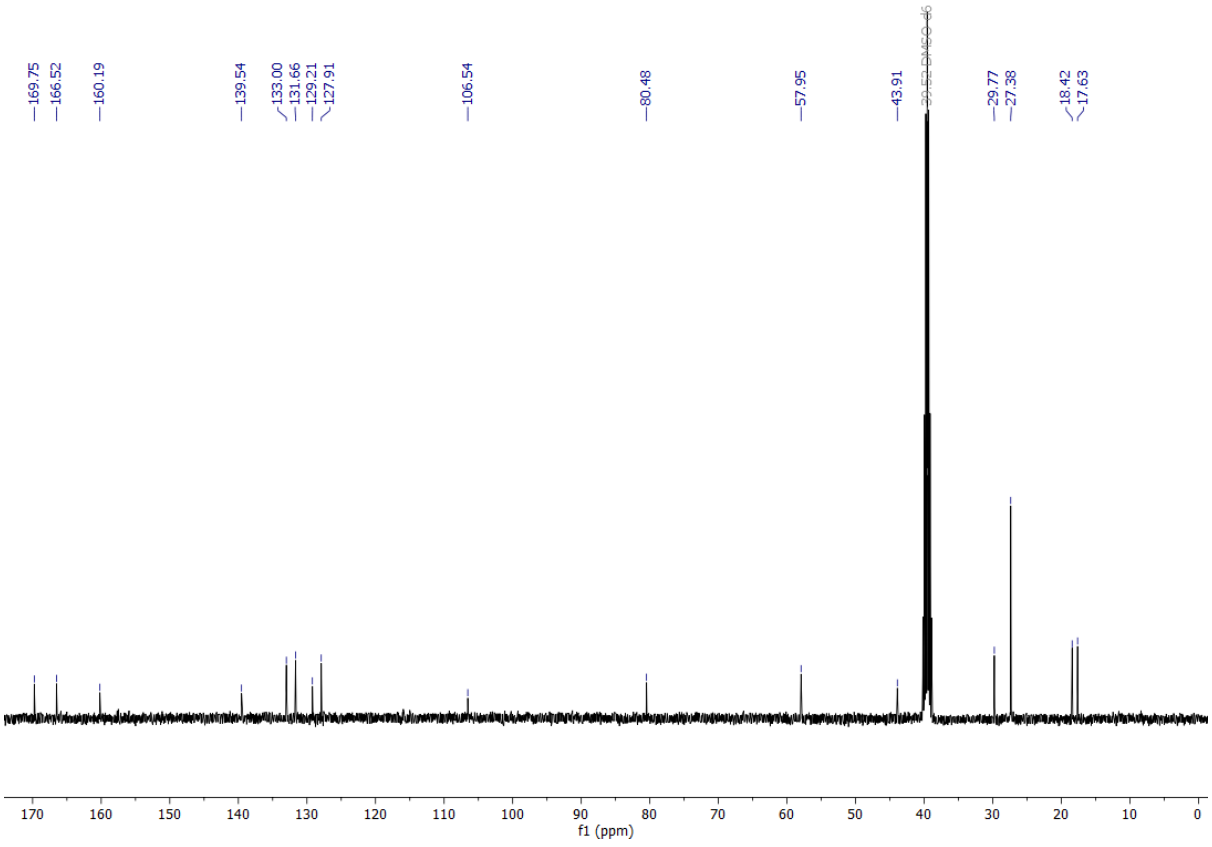
V-O^{t}Bu.HCl

726.90 g/mol
DTDPP-V-O^{t}Bu

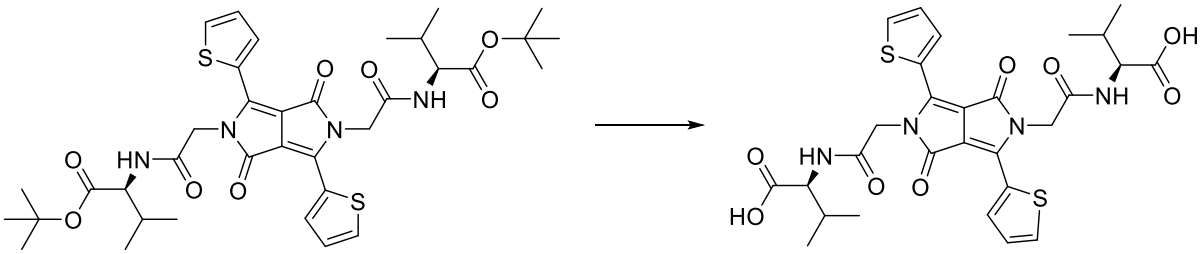
DTDPP-OH (0.3077 g, 0.73 mmol, 1 eq.) was dissolved in $CHCl_3$ (10 mL) and left to stir for a few minutes. The flask was placed in an ice bath and NMM (0.41 mL, 3.7 mmol, 5 eq.) was added to the reaction mixture and left to stir for ten minutes. IBCF (0.2 mL, 1.5 mmol, 2.2 eq.) was added and left to stir for five minutes. Valine *tert*-butyl ester hydrochloride (0.306 g, 1.46 mmol, 2 eq.), dissolved in $CHCl_3$ (1 mL) and NMM (0.1 mL), was added to the mixture and left to stir overnight. To quench the reaction, water (10 mL) was added. The organic and aqueous phases were separated, and the organic phase was washed with 1M HCl and saturated aqueous brine, dried with $MgSO_4$ and then concentrated under vacuum. The title compound **DTDPP-V-O^{t}Bu** was obtained at 91% yield (0.4865 g, 0.669 mmol).

δ_H (400 MHz, DMSO-d_6) 8.64 – 8.54 (4 H, m), 8.06 (2 H, dd, *J* 5.0, 1.1), 7.35 (2 H, dd, *J* 5.0, 3.9), 4.78 (4 H, s), 4.09 (2 H, dd, *J* 8.5, 5.8), 2.05 (2 H, dq, *J* 13.5, 6.8), 1.40 (18 H, s), 0.88 (13 H, dd, *J* 13.7, 6.8). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.75, 166.52, 160.19, 139.54, 133.00, 131.66, 129.21, 127.91, 106.54, 80.48, 57.95, 43.91, 29.77, 27.38, 18.42, 17.63. HRMS ESI (+ve) m/z: 727.2852 $[M-H]^+$.




169.75
166.52
160.19
139.54
133.00
131.66
129.21
127.91
106.54
80.48
57.95
43.91
29.77
27.38
18.42
17.63
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

2-[2-(5-{[(1-Carboxy-2-methylpropyl)carbamoyl]methyl}-1,4-dioxo-3,6-bis(thiophen-2-yl)-1H,2H,4H,5H-pyrrolo[3,4-c]pyrrol-2-yl)acetamido]-3-methylbutanoic acid (**DTDPP-V-OH**):

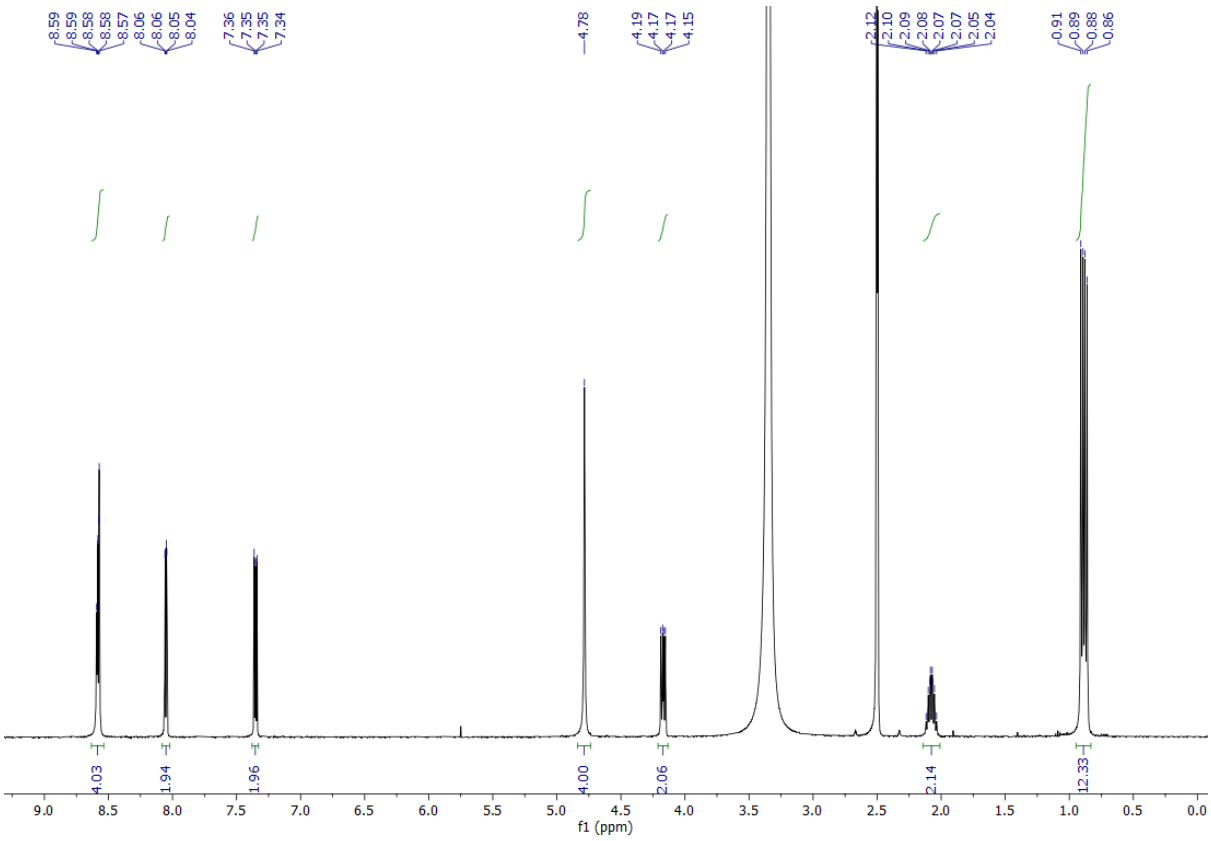


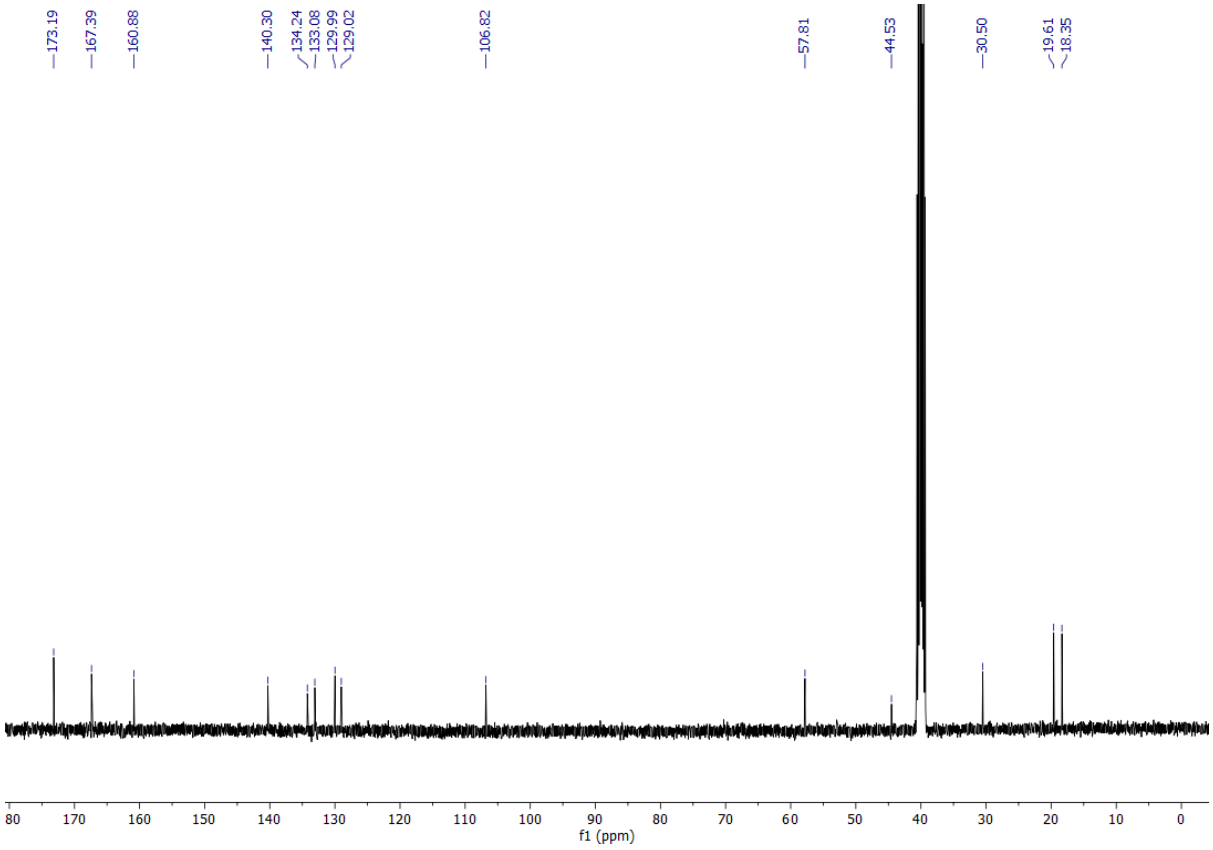
726.90 g/mol
DTDPP-V-O^{t}Bu

614.69 g/mol
DTDPP-V-OH

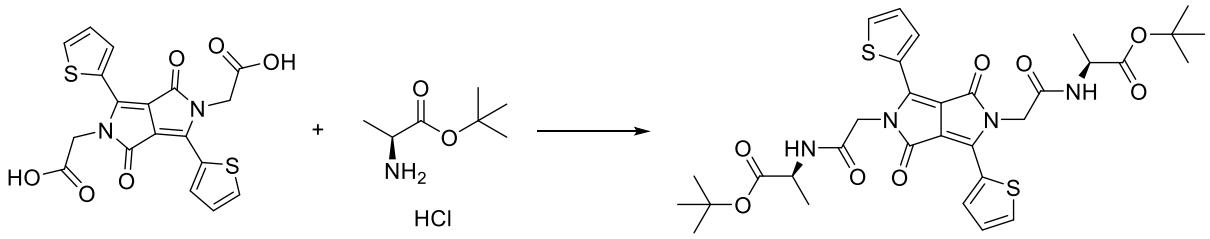
DTDPP-V-O^{t}Bu (0.5473 g, 0.753 mmol, 1 eq.) was dissolved in DCM (20 mL). TFA (10 mL, 130.59 mmol, 173 eq.) was added and the reaction mixture was left to stir at room temperature overnight. The reaction mixture was poured into Et_2O (150 mL), stirred for 30 minutes, filtered and the residue was washed with Et_2O, and filtered again. The residue was dried in a vacuum oven overnight, and the title compound **DTDPP-V-OH** was isolated as a purple solid at 89 % yield (0.4125 g, 0.671 mmol).

δ_H (400 MHz, DMSO-d_6) 8.71 – 8.45 (4 H, m), 8.05 (2 H, dd, *J* 5.0, 1.2), 7.35 (2 H, dd, *J* 5.0, 3.9), 4.78 (4 H, s), 4.17 (2 H, dd, *J* 8.7, 5.6), 2.14 – 2.01 (2 H, m), 0.89 (12 H, dd, *J* 12.7, 6.8). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.19, 167.39, 160.88, 140.30, 134.24, 133.08, 129.99, 129.02, 106.82, 57.81, 44.53, 30.50, 19.61, 18.35. HRMS ESI (+ve) m/z: 637.1387 [M-Na]$^+$.




173.19
167.39
160.88
140.30
134.24
133.08
129.99
129.02
106.82
57.81
44.53
30.50
19.61
18.35
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

tert-Butyl-2-{2-[5-({[1-(*tert*-butoxy)-1-oxopropan-2-yl]carbamoyl}methyl)-1,4-dioxo-3,6-bis(thiophen-2-yl)-1H,2H,4H,5H-pyrrolo[3,4-c]pyrrol-2-yl]acetamido}propanoate (**DTDPP-A-O^{t}Bu**):



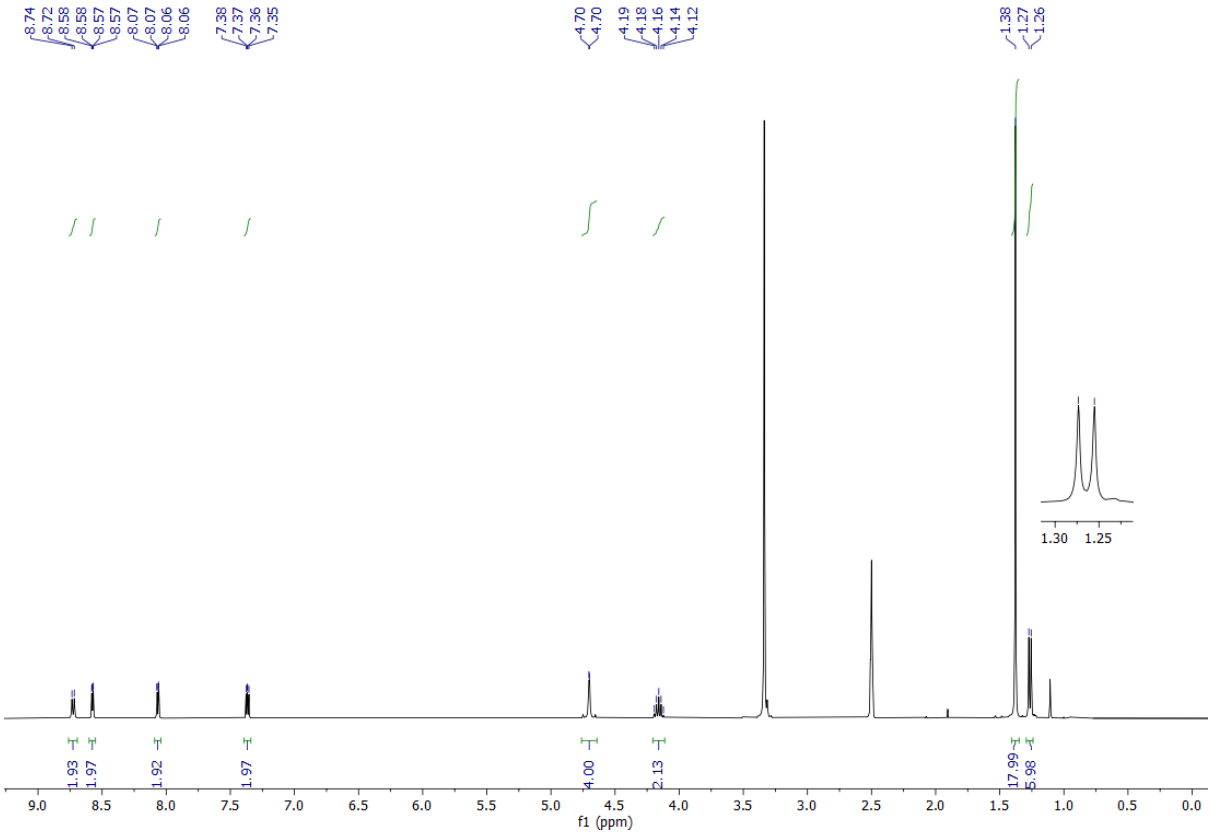
416.42 g/mol
DTDPP-OH

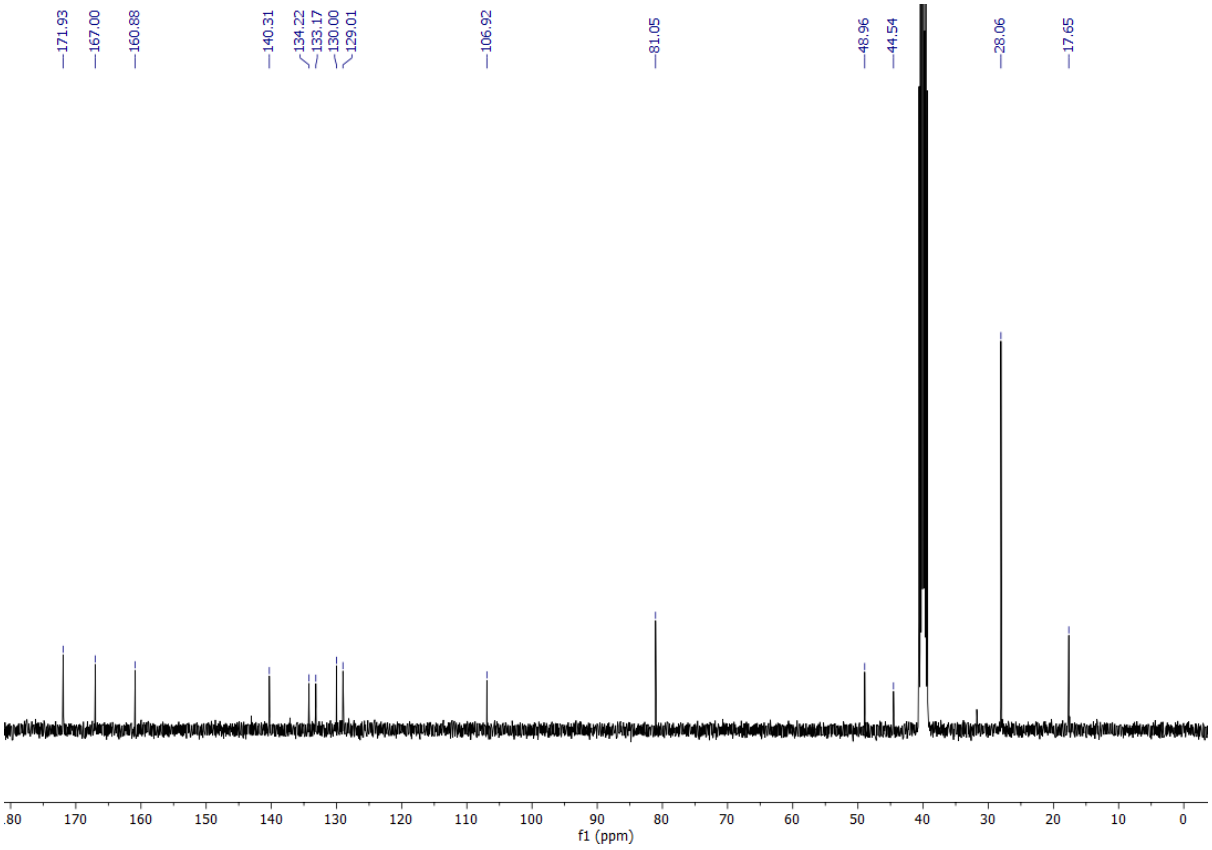
145.20 g/mol
A-O^{t}Bu.HCl

670.80 g/mol
DTDPP-A-O^{t}Bu

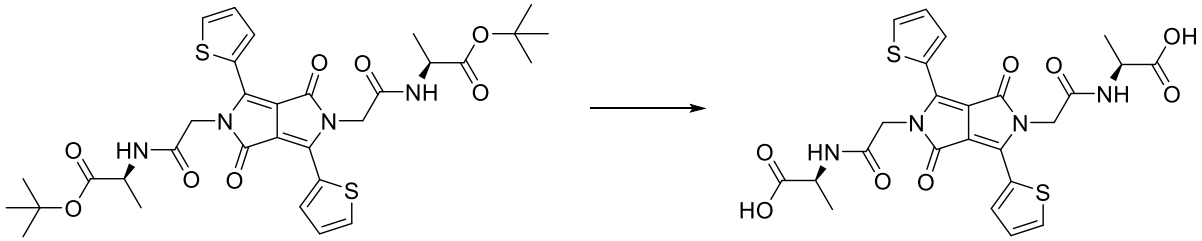
DTDPP-OH (1 g, 2.4 mmol, 1 eq.) was dissolved in $CHCl_3$ (45 mL) and left to stir for a few minutes. The flask was placed in an ice bath and NMM (1.33 mL, 12 mmol, 5 eq.) was added to the reaction mixture and left to stir for 10 minutes. IBCF (0.62 mL, 5.3 mmol, 2.2 eq.) was added and left to stir for 5 minutes. Alanine *tert*-butyl ester hydrochloride (0.89 g, 4.8 mmol, 2 eq.), dissolved in $CHCl_3$ (5 mL) and NMM (1 mL), was added to the mixture and left to stir overnight. To quench the reaction, water (50 mL) was added. The organic and aqueous phases were separated, and the organic phase was washed with 1M HCl (100 mL), water, and saturated brine (100 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude was purified on a flash column (4 cm x 10 cm silica, 1:9 EtOAc/DCM) and the title product **DTDPP-A-O^{t}Bu** was obtained as a red solid at 41% yield (0.66079 g, 0.98 mmol).

δ_H (400 MHz, DMSO-d_6) 8.73 (2 H, d, *J* 7.2), 8.57 (2 H, dd, *J* 3.9, 1.2), 8.07 (2 H, dd, *J* 5.0, 1.2), 7.37 (2 H, dd, *J* 5.0, 3.9), 4.16 (2 H, p, *J* 7.0), 1.38 (20 H, s), 1.26 (7 H, d, *J* 7.3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.93, 167.00, 160.88, 140.31, 134.22, 133.17, 130.00, 129.01, 106.92, 81.05, 48.96, 44.54, 28.06, 17.65. HRMS ESI (+ve) m/z: 693.1949 $[M\text{-}Na]^+$.




171.93
167.00
160.88
140.31
134.22
133.17
130.00
129.01
106.92
81.05
48.96
44.54
28.06
17.65
f1 (ppm)

2-[2-(5-{[(1-Carboxyethyl)carbamoyl]methyl}-1,4-dioxo-3,6-bis(thiophen-2-yl)-1H,2H,4H,5H-pyrrolo[3,4-c]pyrrol-2-yl)acetamido]propanoic acid (**DTDPP-A-OH**):



670.80 g/mol

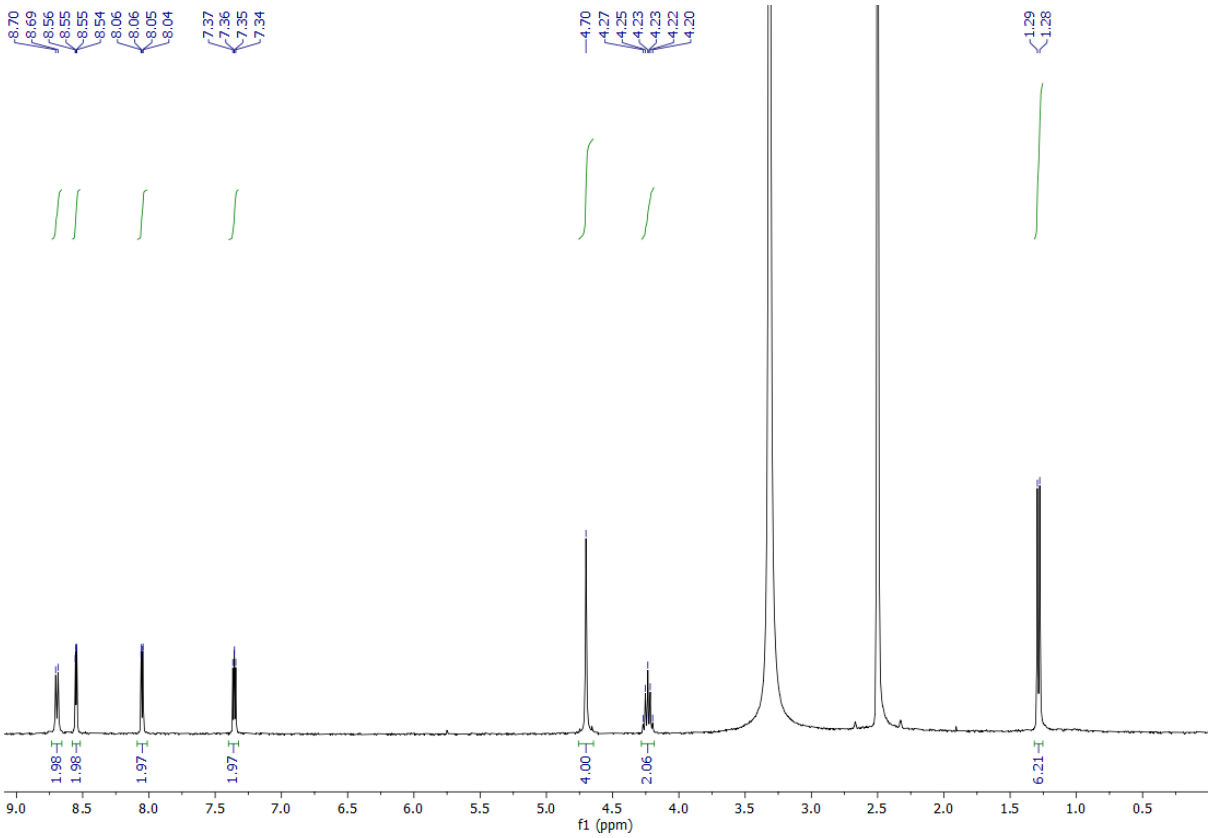
DTDPP-A-O^{t}Bu

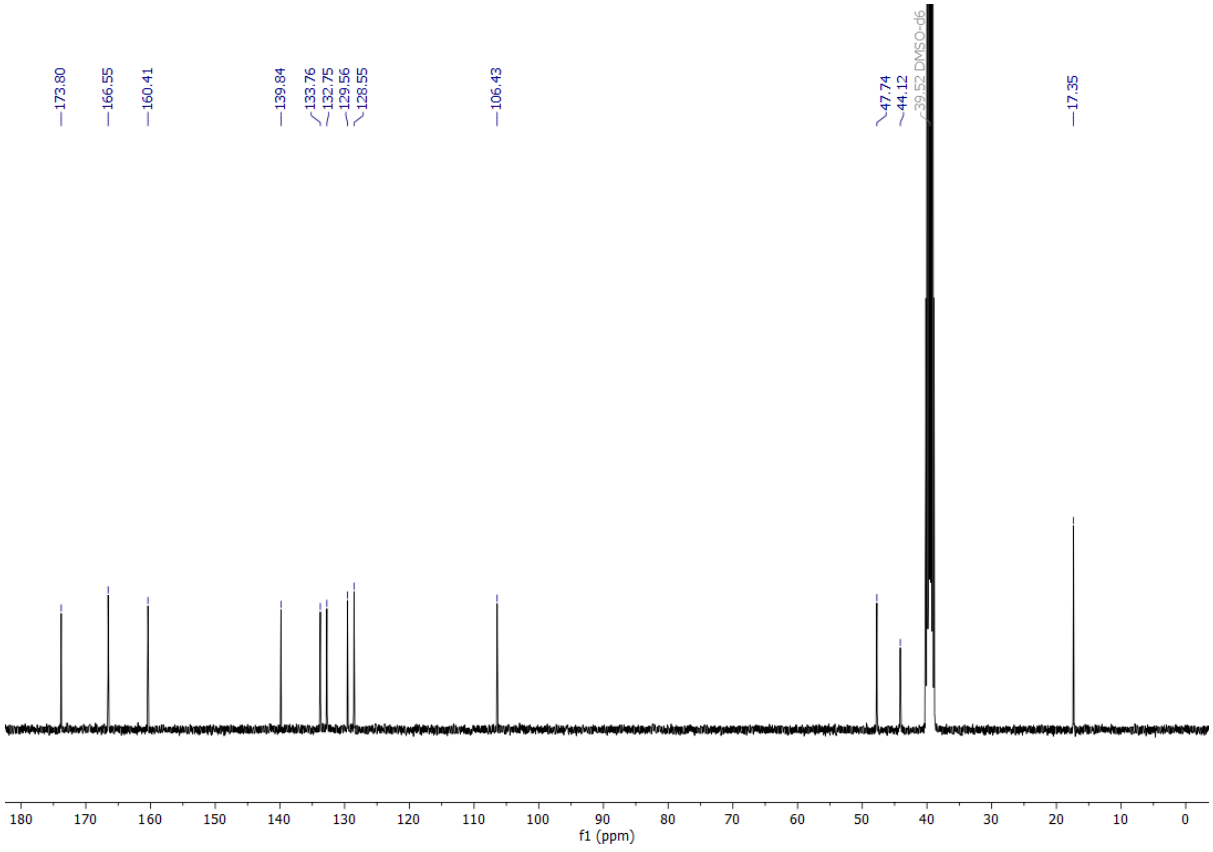
558.58 g/mol

DTDPP-A-OH

DTDPP-A-O^{t}Bu (0.1877 g, 0.28 mmol, 1 eq.) was dissolved in DCM (35 mL). TFA (15 mL, 195 mmol, 552 eq.) was added and the reaction mixture was left to stir at room temperature overnight. The reaction mixture was poured into Et_2O (200 mL), stirred for 30 minutes, filtered and the residue was washed with Et_2O, and filtered again. The residue was dried in a vacuum oven overnight, and the title compound **DTDPP-A-OH** was isolated as a purple solid at 89 % yield (0.1387 g, 0.25 mmol).

δ_H (400 MHz, DMSO) 8.55 (1 H, dd, *J* 3.9, 1.2), 8.05 (1 H, dd, *J* 5.0, 1.1), 7.36 (1 H, dd, *J* 5.0, 3.9), 4.70 (2 H, s), 4.23 (1 H, p, *J* 7.3), 1.29 (3 H, d, *J* 7.3). ^{13}C NMR (101 MHz, DMSO) δ 173.80, 166.55, 160.41, 139.84, 133.76, 132.75, 129.56, 128.55, 106.43, 47.74, 44.12, 17.35. HRMS ESI (+ve) m/z: 559.0953 $[M-H]^+$.




173.80
166.55
160.41
139.84
133.76
132.75
129.56
128.55
106.43
47.74
44.12
39.52 DMSO-d6
17.35
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Optical Studies

For DTDPP-R-O^{t}Bu, the solvents acetonitrile (MeCN), ethanol (EtOH), tetrahydrofuran (THF), chloroform ($CHCl_3$), and toluene (PhMe) were used to prepare the solutions. For DTDPP-R-OH, the solvents EtOH, THF and H_2O (at pH 10.5) were used.

The stock solution in the ten-fold dilution concentration series was aimed at 2 mg/mL (≈ 2.75 x10^{-3} M) for each sample. In solvents where the powder did not dissolve, the next concentration in the series (2 x10^{-1} mg/mL) was attempted. Solutions were prepared till 2x10^{-6} mg/mL (≈ 2.75 x10^{-9} M).

Table S1. Solvent and stock solution concentration for DTDPP-R-OtBu's and DTDPP-R-OH's.

	H_2O	MeCN	EtOH	THF	$CHCl_3$	PhMe
DTDPP-F-O^{t}Bu	-	2x10^{-1} mg/mL	2x10^{-1} mg/mL	2 mg/mL	2 mg/mL	2x10^{-1} mg/mL
DTDPP-F-OH	2x10^{-1} mg/mL	-	2x10^{-2} mg/mL	2x10^{-1} mg/mL	-	-
DTDPP-V-O^{t}Bu	-	2x10^{-1} mg/mL	2x10^{-1} mg/mL	2 mg/mL	2 mg/mL	2x10^{-2} mg/mL
DTDPP-V-OH	2x10^{-1} mg/mL	-	2x10^{-1} mg/mL	2 mg/mL	-	-
DTDPP-L-O^{t}Bu	-	2 mg/mL	2x10^{-1} mg/mL	2 mg/mL	2 mg/mL	2x10^{-1} mg/mL
DTDPP-L-OH	2x10^{-1} mg/mL	-	2x10^{-1} mg/mL	2 mg/mL	-	-
DTDPP-A-O^{t}Bu	-	2 mg/mL	2x10^{-1} mg/mL	2 mg/mL	2 mg/mL	2x10^{-1} mg/mL
DTDPP-A-OH	2x10^{-1} mg/mL	-	2x10^{-1} mg/mL	2 mg/mL	-	-

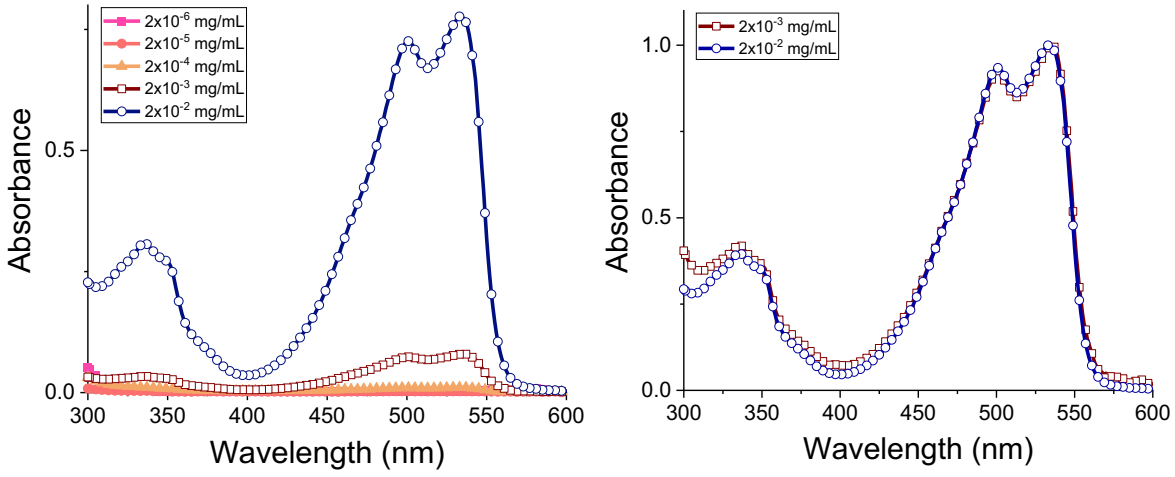


Figure S2. Absorption spectra for the concentration series of DTDPP-V-O^{t}Bu in EtOH – (left) full concentration series (right) normalised spectra for 2 x10^{-2} mg/mL and 2 x 10^{-3} mg/mL samples.

All other DTDPP derivatives in the different organic solvents show the same observations and hence the data plots for those samples are not shown here.

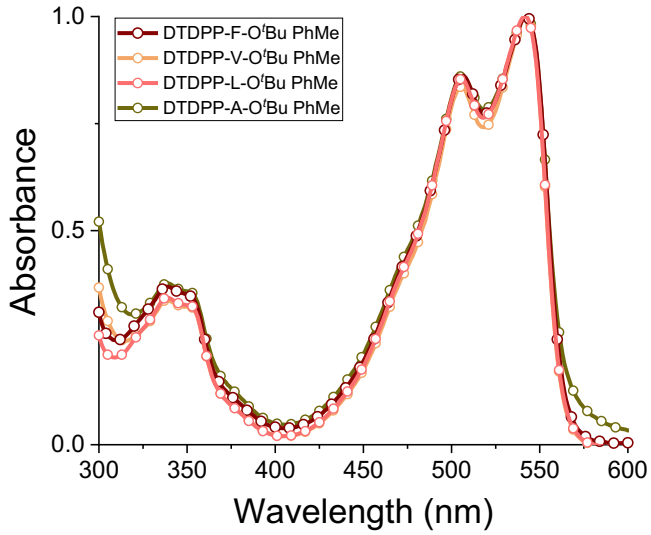


Figure S3. Normalised absorption spectrum for DTDPP-A-O*t*Bu, DTDPP-V-O*t*Bu, DTDPP-F-O*t*Bu and DTDPP-L-O*t*Bu in PhMe at ≈ 2 x10^{-3} mg/mL.

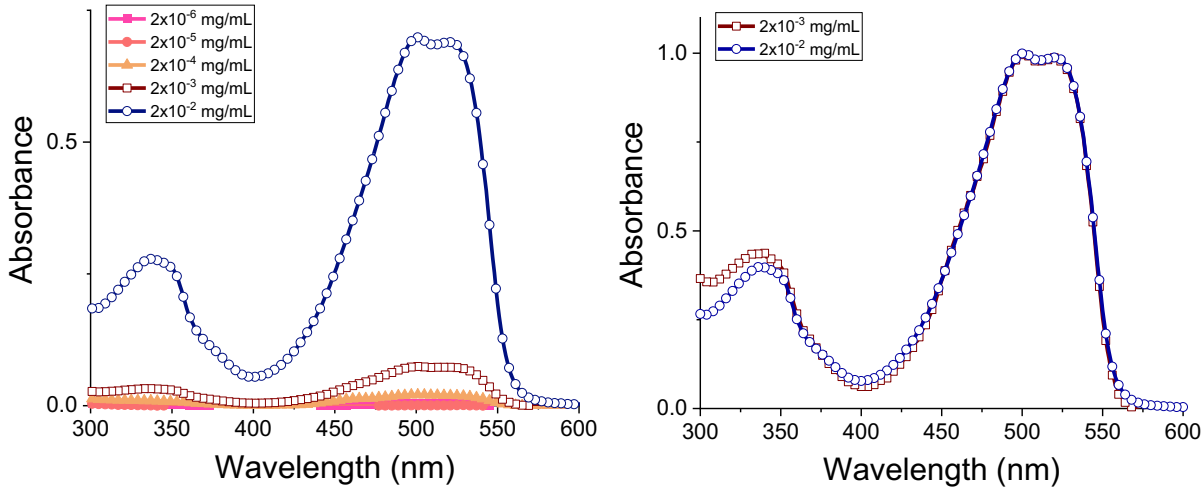


Figure S4. Absorption spectra for the concentration series of DTDPP-L-OH in H_2O (pH 10.5) – (left) full concentration series (right) normalised spectra for 2 x10^{-3} mg/mL and 2 x 10^{-4} mg/mL samples.

All other DTDPP derivatives in H_2O (pH 10.5) show similar trends and hence the data plots for those samples are not shown here.

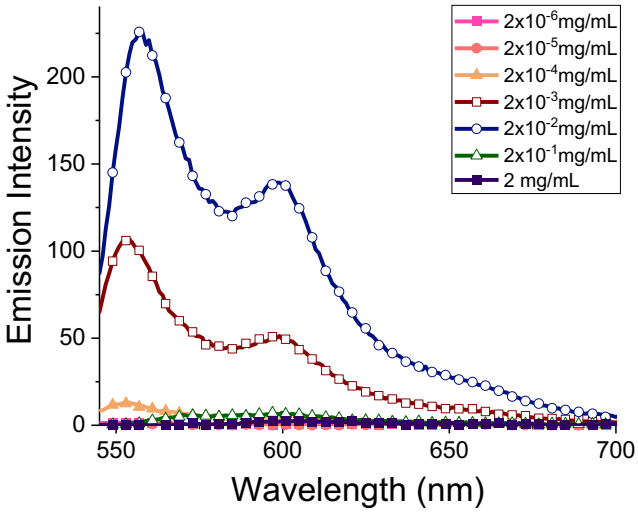


Figure S5. Emission spectrum for the concentration series of DTDPP-V-O*n*Bu in $CHCl_3$.

All other DTDPP derivatives in the different organic solvents show similar observations and hence the data plots for those samples are not shown here.

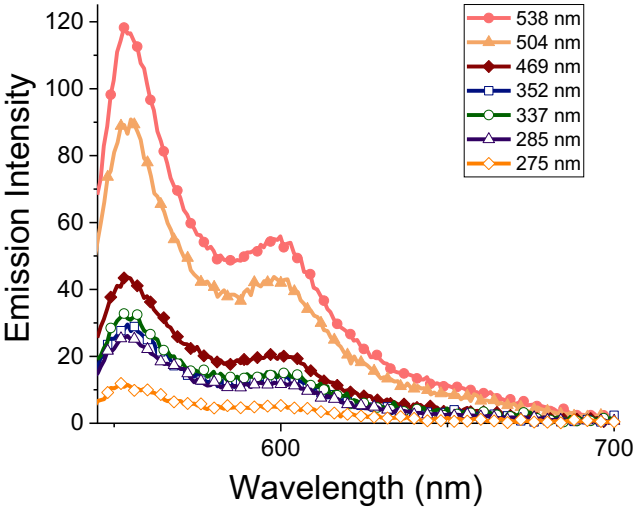


Figure S6. Emission spectrum of the irradiation series for DTDPP-F-O*n*Bu in $CHCl_3$ at $2x10^{-4}$ mg/mL.

All other DTDPP derivatives in the different organic solvents show similar observations and hence the data plots for those samples are not shown here.

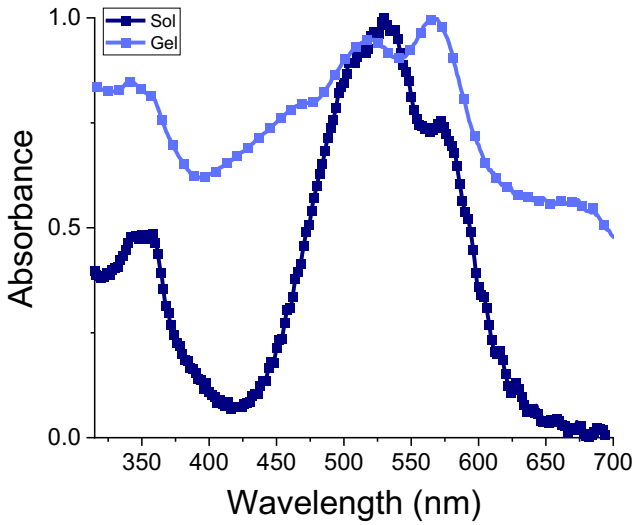


Figure S7. Normalised absorption spectrum for DTDPP-F-OH sol in water (at pH 10.5) and gel, both at 5 mg/mL using a 0.01 mm path length cuvette.

All other DTDPP derivatives in the sol and gel phases show similar observations and hence the data plots for those samples are not shown here.

Rheology studies

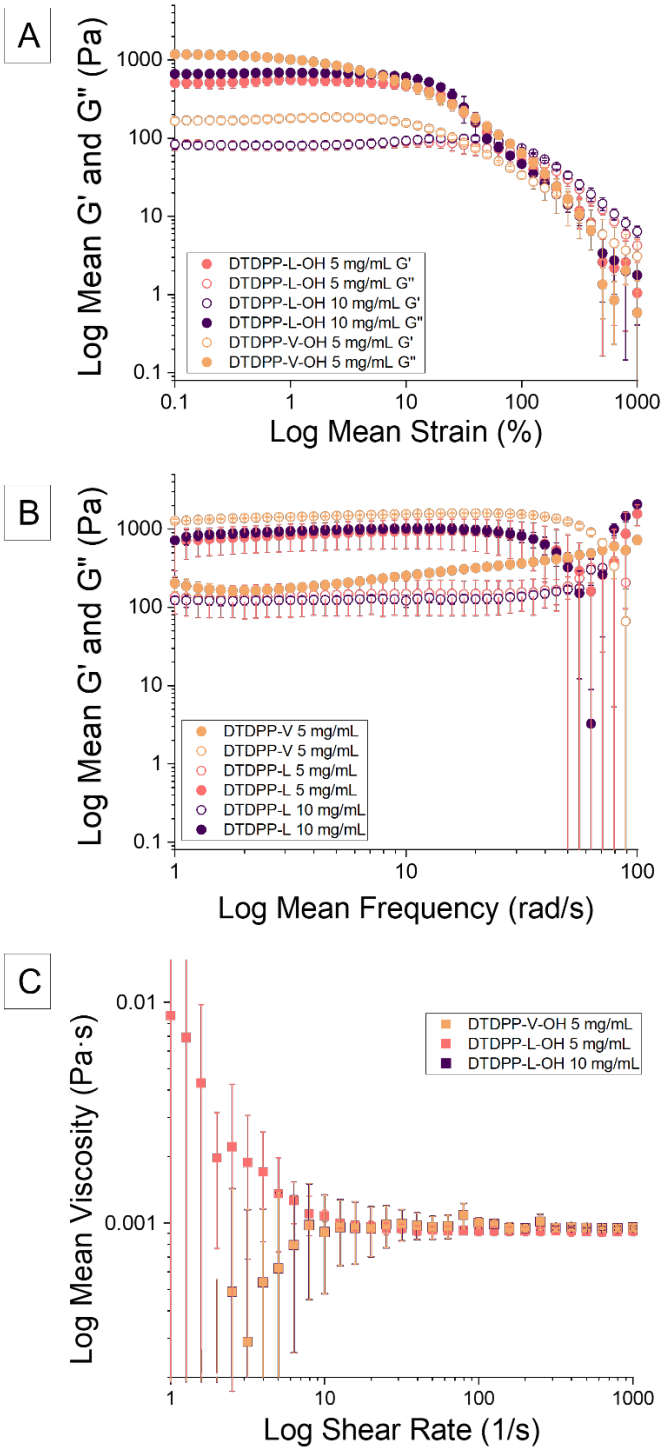


Figure S8. (A) Strain, (B) frequency, and (C) viscosity sweeps for DTDPP-L-OH (5 mg/mL with 8 mg/mL GdL and 10 mg/mL with 16 mg/mL GdL) and DTDPP-V-OH (5 mg/mL with 8 mg/mL GdL).

Table S2. The pH values obtained for DTDPP-F-OH gels with different GdL concentrations.

1 mg/mL	2 mg/mL	3 mg/mL	4 mg/mL	5 mg/mL	6 mg/mL	7 mg/mL	8 mg/mL
pH 6.2	pH 4.9	pH 4.0	pH 3.8	pH 3.5	pH 3.4	pH 3.3	pH 3.2

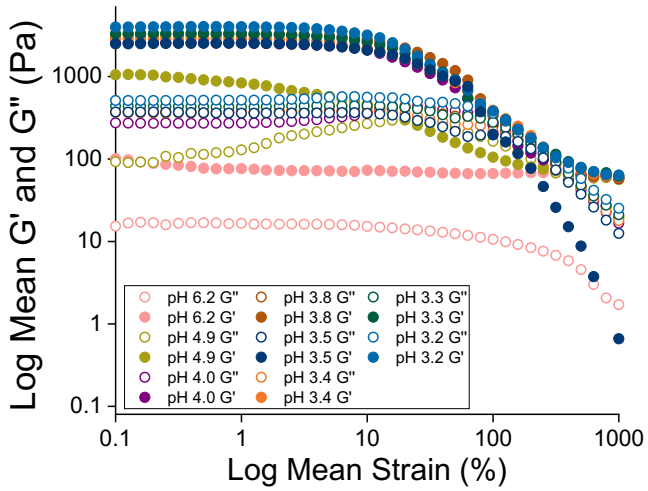


Figure S9. Strain sweeps for DTDPP-F-OH 5 mg/mL with gel samples at different pHs and different GdL concentrations.

pH studies

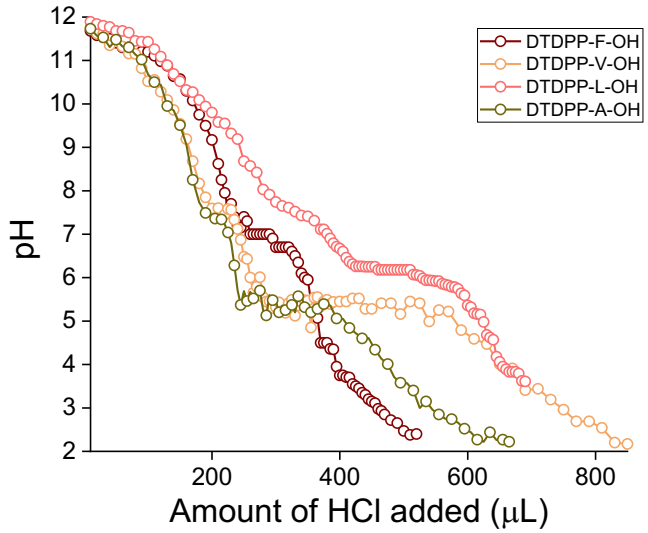


Figure S10. The apparent p*Ka* titrations for the four DTDPP-R-OH derivatives at the mgc (5 mg/mL for DTDPP-F-OH and -A-OH, 10 mg/mL for DTDPP-V-OH, and 15 mg/mL for DTDPP-L-OH).

Gel formation studies

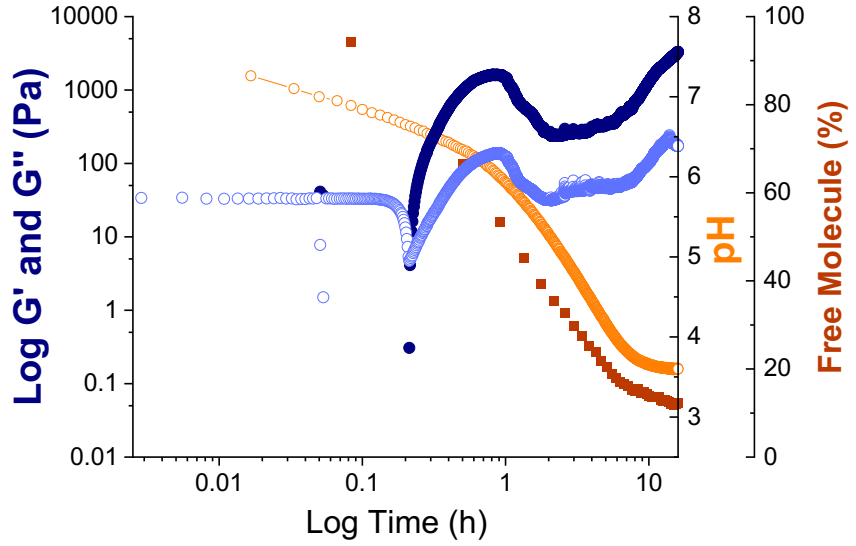


Figure S11. Gelation process of DTDPP-F-OH at 5 mg/mL showing rheology time sweep (G´ in dark blue closed circles and G″ in light blue open circles), pH logging (orange open circles) and % free molecule by NMR (dark red squares).

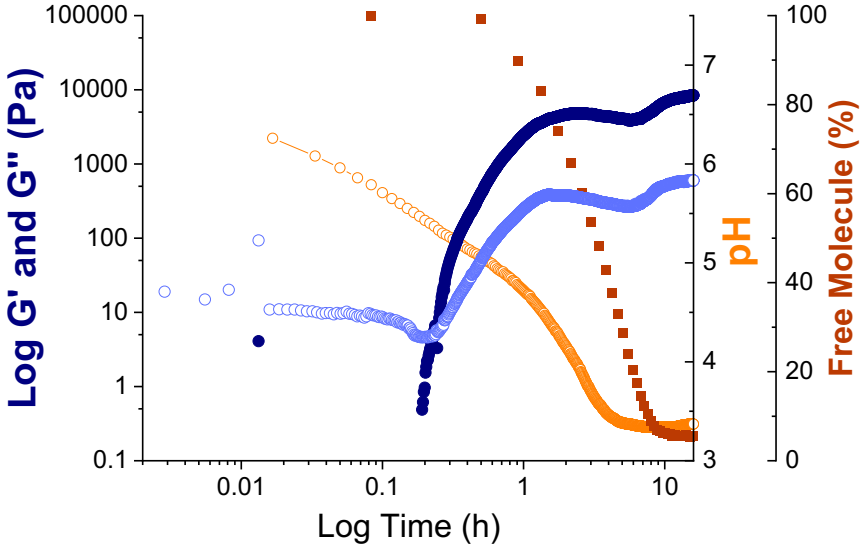


Figure S12. Gelation process of DTDPP-V-OH at 10 mg/mL showing rheology time sweep (G´ in dark blue closed circles and G″ in light blue open circles), pH logging (orange open circles) and % free molecule by NMR (dark red squares).

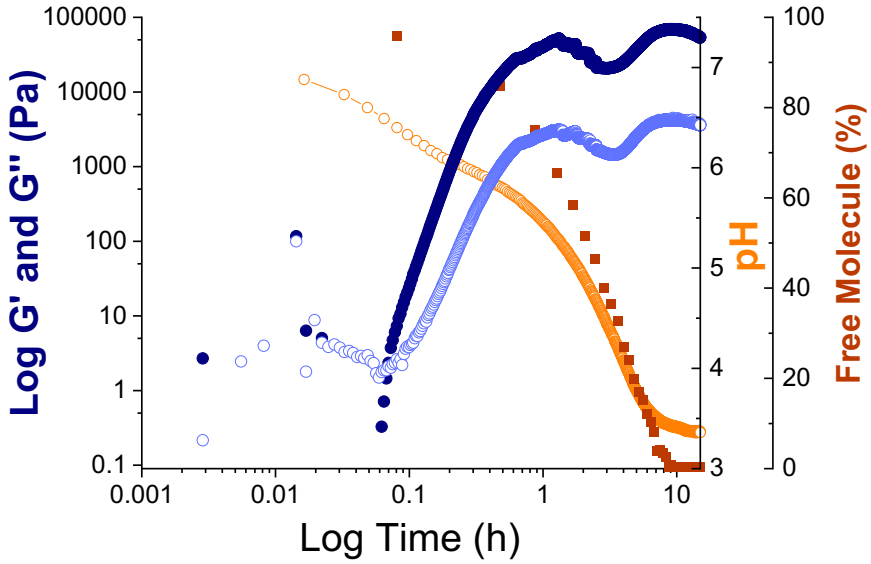


Figure S13. Gelation process of DTDPP-L-OH at 15 mg/mL showing rheology time sweep (G´ in dark blue closed circles and G″ in light blue open circles), pH logging (orange open circles) and % free molecule by NMR (dark red squares).

Small-angle X-ray Scattering studies

Table S3. Parameter values in nm with fitting error.

Sample		Model	Scale	Background	Length / Å	Kuhn Length / Å	Radius / Å	Axis Ratio	Power Law Scale	Power Law	χ^2
DTDPP-F-OH (at 5 mg/mL)	pH 10.5 sol	Power Law	5.4 x 10^{-9} ± 9.8 x 10^{-10}	0.006 ± 0.0003	-	-	-	-		4.2 ± 0.04	2.24
	gel	Flexible Elliptical Cylinder	0.0002 ± 9.8 x 10-7	0.008 ± 0.0004	>1000	13.8 ± 0.1	13.6 ± 0.05	2.5 ± 0.009	-	-	3.66
DTDPP-V-OH (at 10 mg/mL)	pH 10.5 sol	Power Law	3.3 x 10^{-14} ± 6.5 x 10^{-14}	0.03 ± 0.0004	-	-	-	-		6.2 ± 0.4	4.03
	gel	Flexible Elliptical Cylinder + Power Law	0.0008 ± 0.0001	0.01 ± 0.0006	-	48.1 ± 6.7	19.1 ± 1.3	2.8 ± 0.3	0.004 ± 0.0003	3.4 ± 0.03	2.63
DTDPP-L-OH (at 15 mg/mL)	pH 10.5 sol	Power Law	2.14 x 10^{-8} ± 8.8 x 10^{-9}	0.02 ± 0.0003	-	-	-	-		3.7 ± 0.09	5.21
	gel	Flexible Cylinder + Power Law	0.0003 ± 3.4 x 10^{-5}	0.01 ± 0.0005	>1000	109.6 ± 23.7	64.8 ± 1.5		0.002 ± 0.0003	3.8 ± 0.04	2.37
DTDPP-A-OH (at 5 mg/mL)	pH 10.5 sol	Power Law	4.4 x 10^{-6} ± 2.5 x 10^{-6}	0.02 ± 0.0004	-	-	-	-		2.3 ± 0.1	2.87
	gel	Flexible Elliptical Cylinder	0.0002 ± 1.1 x 10^{-6}	0.006 ± 0.0003	>1000	16.1 ± 0.1	13.5 ± 0.04	2.7 ± 0.08	-	-	2.39

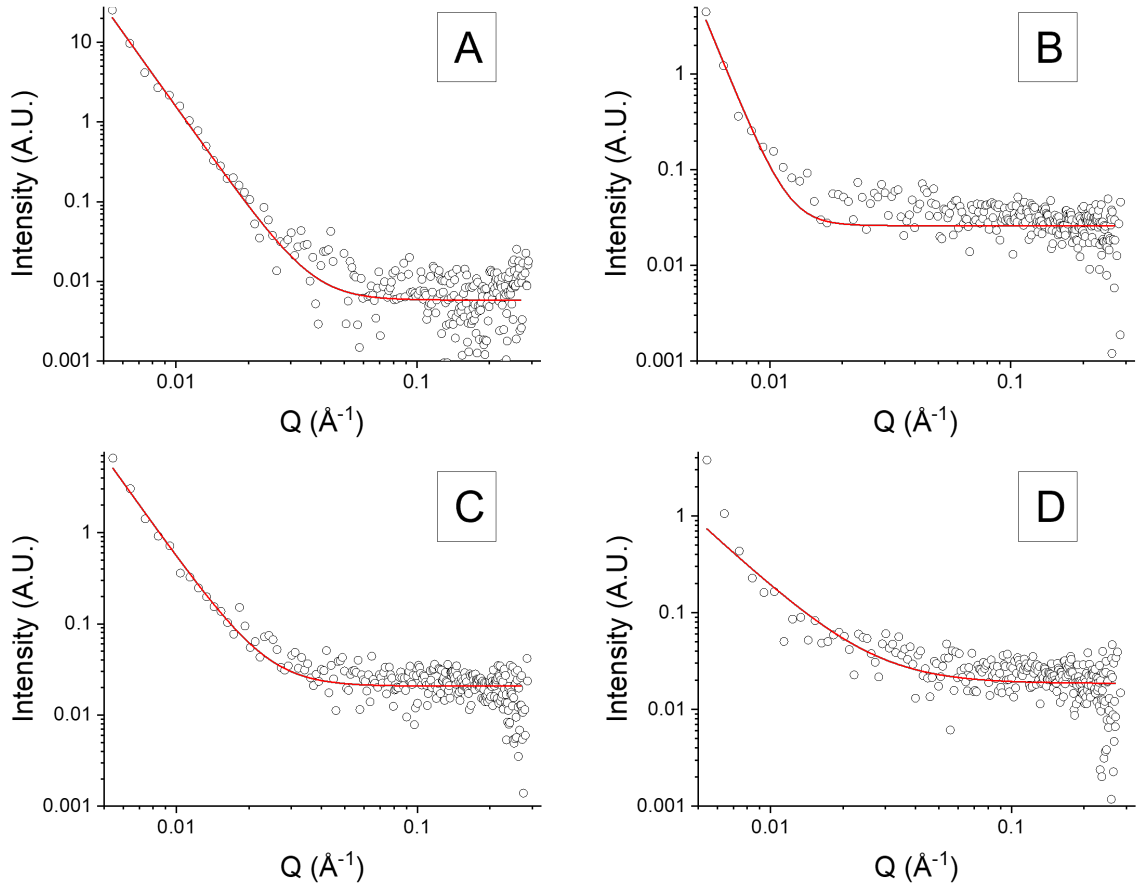


Figure S14. SAXS data collected on DTDPP-R-OH solutions (shown as open black circles) with a fit to a power law overlaid (red line) (A) DTDPP-F-OH; (B) DTDPP-V-OH; (C) DTDPP-L-OH; (D) DTDPP-A-OH.

References

1. www.sasview.org/