Electronic Supplementary Material (ESI) for Green Chemistry.


Supporting Information

# Radical-mediated thiol-ene 'click' reactions in deep eutectic solvents for bioconjugation

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**Contents:**

## 1. General Information

Commercial materials were obtained from Sigma-Aldrich, Fluorochem, Alfa-Aesar or Fisher Scientific and used without further purification. Chromatographic separation was performed on Silica gel Florisil (200 mesh; Aldrich). Thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates and visualised by UV light, molybdenum, ninhydrin or sulfuric acid staining. Dry solvents were obtained from a Pure Solv Micro Solvent Purification System. Deuterated solvents for use in NMR were purchased from Apollo Scientific. NMR data was obtained using a Bruker Advance 400 spectrometer and Bruker Ultrashield 600 and processed using Bruker TopSpin software. High-resolution mass spectrometry (HRMS) analysis was performed on a Q-Tof Premier Waters Maldi-quadropole time-of-flight (Q-Tof) spectrometer fitted with Z-spray electrospray ionisation (ESI), electron ionisation (EI), atmospheric-pressure chemical ionisation and matrix-assisted laser desorption ionisation (MALDI) sources. UV reactions were performed in a Luzchem LZC-EDU (110 V/ 60 Hz) photoreactor housing 3 UV lamps centred at 365 nm.

## 2. Methods for Assessing DES Properties

### 2.1 Thermal analysis - Thermogravimetric analysis (TGA)

The thermal stability of DES was investigated by thermal gravimetric analysis (TG) conducted in a TA Instruments Q500 TGA (weighing Precision ± 0.01%, sensitivity 0.1 µg, baseline dynamic drift < 50 µg). The temperature calibration was performed using curie point of nickel and Alumel standards and for mass calibration weight standards of 1 g, 500 mg, and 100 mg were used. All the standards were supplied by TA Instruments Inc. 12-15 mg of each sample were heated in a platinum crucible as sample holder. First, the heating mode was set to isothermal at 40 °C in $N_2$ (80 mL/min) for 30 min. Then, the sample was heated from 40 °C to 500 °C at 10 °C/min under $N_2$ (80 mL/min) and maintained at 500 °C for 3 min. Mass change was recorded as a function of temperature and time. $T_{deg}$ was taken as the first temperature peak on the derivative TG (DTG) curve. TGA experiments were carried out in duplicate.

### 2.2 Differential scanning calorimetry (DSC)

The thermal behavior of DES was analyzed by a differential scanning calorimeter (TA DSC, Q250, USA, temperature accuracy ± 0.05 °C, temperature precision ± 0.008 °C, enthalpy precision ± 0.08%). Dry high purity $N_2$ gas with a flow rate of 50 mL/min was purged through the sample. 1-5 mg of each sample was loaded in pinhole hermetic aluminum crucibles and

the phase behavior was explored under nitrogen atmosphere in the temperature range from -90 to 120 °C with a heating rate of 10 °C/min. The temperature calibration was performed considering the heating rate dependence of the onset temperature of the melting peak of indium. The enthalpy was also calibrated using indium (melting enthalpy $\Delta H_m$=28.71 J g-1). DSC experiments were carried out in duplicate. $T_g$ was obtained by taking the midpoint of the heat capacity change on heating from a glass to a liquid. $T_m$ was taken as the peak temperature of the endothermic peak on the heating run. The peak temperatures were chosen instead of the onset temperatures due to the complexity of the thermograms.

### 2.3 Viscosity

Viscosity of DES as a function of temperature was measured using a rheometer model MCR 302 Anton Paar (Anton Paar GmbH, Graz, Austria), with a torque range from 0.5 nNm to 230 mNm. The measurements were carried out at 25 °C, controlled by a Peltier thermostat with an accuracy of 0.1 °C. Viscosity (η) was determined applying a shear rate of 100 $s^{-1}$.

### 2.4 Density

Density was measured with 0.0001 g/$cm^3$ resolution and 0.001 g/$cm^3$ accuracy by use of a density-meter model DMA35 Anton Paar (Anton Paar GmbH, Graz, Austria). This instrument exploits a U-shaped oscillating tube as a sensing element. Measurements were collected at 25 °C.

## 3. General Synthetic Procedures

### 3.1 General Procedure A: UV-Initiated TEC in DESs

A solution of alkene, thiol, DPAP (0.2 equiv.) and MAP (0.2 equiv.) in DES was stirred under UV irradiation for 1 hour. The reaction was then minimally diluted with $H_2O$ to reduce viscosity of the aqueous layer and extracted with EtOAc. Organics were dried using $MgSO_4$, filtered and concentrated *in vacuo*. The product was then purified *via* flash chromatography on silica gel.

### 3.2 General Procedure B: UV-initiated ATE in DESs

A solution of alkene, thioacid, DPAP (0.2 equiv.) and MAP (0.2 equiv.) in DES was stirred under UV irradiation for 1 hour. The reaction was then minimally diluted with $H_2O$ to reduce viscosity of the aqueous layer and extracted with EtOAc. Organics were dried using $MgSO_4$, filtered and concentrated *in vacuo*. The product was then purified *via* flash chromatography on silica gel.

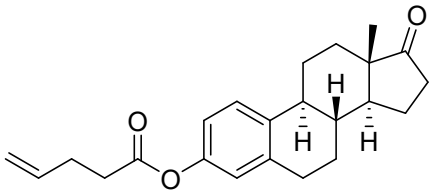
### 3.3 General Procedure C: $O_2$-Initiated TEC in DESs

A solution of alkene and thiol in DES was heated to 64 °C with rapid stirring for 16-24 h. The reaction was cooled, minimally diluted with $H_2O$ to reduce viscosity of the aqueous layer and extracted with EtOAc. Organics were dried using $MgSO_4$, filtered and concentrated *in vacuo*. The product was then purified *via* flash chromatography on silica gel.

### 3.4 General Procedure D: $O_2$-Initiated ATE in DESs

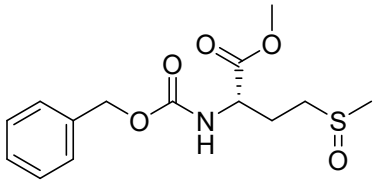
A solution of alkene and thioacid in DES was heated to 64 °C with rapid stirring for 16-24 h. The reaction was cooled, minimally diluted with $H_2O$ to reduce viscosity of the aqueous layer and extracted with EtOAc. Organics were dried using $MgSO_4$, filtered and concentrated *in vacuo*. The product was then purified *via* flash chromatography on silica gel.

## 4. Preparation of Alkene Starting Materials



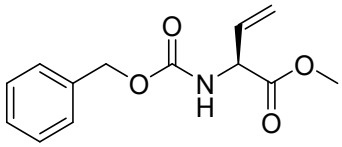
**(8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl pent-4-enoate (26)**

To a solution of 4-pentenoic acid (1.9 mmol, 0.190 g, 0.194 mL) in dry DCM (12 mL) at 0 °C, EDC•HCl (1.9 mmol, 0.364 g) was added and stirred for 15 min. DMAP (0.4 mmol, 0.049 g) and estrone (1.5 mmol 0.406 g) was then added. The solution was warmed to rt and stirred for 24 h. The solvent was then removed *in vacuo*. The product was purified by silica gel flash chromatography using 25% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (333 mg, 66%). The isolated product was in agreement with the literature.[1]



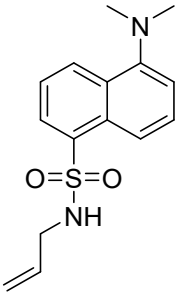
**Methyl (2*S*)-2-(((benzyloxy)carbonyl)amino)-4-(methylsulfinyl)butanoate (27)**

To a solution of Cbz-Met-OMe (16.8 mmol, 5.00 g) in MeOH (25 mL) at 0 °C, NaIO4 (1.1 equiv., 18.8 mmol, 4.02 g) in $H_2O$ (25 mL) was added dropwise. The mixture was stirred under $N_2$ for 16 hours. The mixture was then filtered through celite and concentrated under reduced pressure to remove MeOH. The solution was extracted with chloroform (3 x 25 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give the product as a colourless oil (5.15 g, 98%). The isolated product was in agreement with the literature.[2]



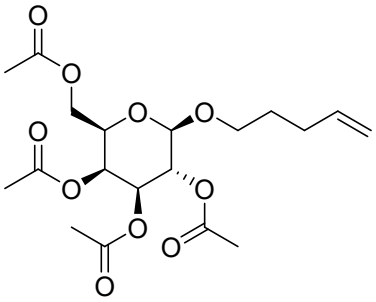
**Methyl (*S*)-2-(((benzyloxy)carbonyl)amino)but-3-enoate (28)**

A solution of **27** (16.3 mmol, 5.10 g) in xylene (50 mL) was heated to reflux for 72 h. The mixture was concentrated *in vacuo* to give a brown oil (4.22 g) which was purification by silica gel flash chromatography using 10-20% EtOAc/Hexane (v/v) to afford the desired product as a colourless oil (0.81 g, 20%). The isolated product was in agreement with the literature.[2]



***N*-allyl-5-(dimethylamino)naphthalene-1-sulfonamide (29)**

To allylamine (0.37 mmol, 0.021 g, 0.028 mL) and *N,N*-diisopropylethylamine (1.85 mmol, 0.239 g, 0.322 mL) in DCM (5 mL), dansyl chloride (0.37 mmol, 0.100 g) in DCM (3 mL) was added. The mix was stirred at rt for 18h and then concentrated *in vacuo*. The product was purified by silica gel flash chromatography using 10-20% EtOAc/Hexane (v/v) to afford the desired product as a yellow solid (0.08 g, 75%). The isolated product was in agreement with the literature.[3]



**(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(pent-4-en-1-yloxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (30)**

To a stirred solution of peracetylated galactose (0.390 g, 1.0 mmol) and 4-penten-1-ol (0.399 mL, 0.3325 g, 4.0 mmol) in dry DCM (6 mL), $BF_3 \bullet Et_2O$ (0.494 mL, 0.5677 g, 5.0 mmol) was added dropwise. The reaction was stirred overnight and then quenched by addition of $H_2O$. Organics were filtered through celite and then washed with 1.0 M HCl, $NaHCO_3$ and brine, followed by concentration in vacuo. The product was purified by silica gel flash chromatography using 20-40% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (175 mg, 42%). $\mathbf{R_f}$ = 0.41 (40% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 5.86-5.75 (m, 1H), 5.40 (dd, *J* = 3.4 Hz, *J* = 1.1 Hz, 1H), 5.22 (dd, *J* = 10.5 Hz, *J* = 7.94 Hz, 1H), 5.06-4.97 (m, 3H), 4.47 (d, *J* = 7.97 Hz, 1H), 4.23-4.12 (m, 2H), 3.94-3.89 (m, 2H), 3.55-3.49 (m, 1H), 3.08 (s, 3H), 2.13-2.11 (m, 2H), 2.07 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H), 1.77-1.63 (m, 2H). $\delta_C$ (151 MHz, $CDCl_3$) 170.4, 170.3, 170.2, 169.4, 137.8, 115.1, 101.4, 71.0, 70.6, 69.4, 69.0, 67.1, 61.3, 29.8, 28.6, 20.8, 20.7, 20.6. **HRMS**: ($ESI^+$) *m/z* calcd. for $C_{19}H_{28}NaO_{10}$

([M+Na]$^+$): 439.1575; found: 439.1587. $\upsilon_{max}$ (film), cm$^{-1}$: 2970 (alkene stretch) 2905 (C-H stretch), 1741 (C=O stretch), 1214 (C-O stretch), 1173 (C-O stretch).

## 5. DES Thiol-Ene Compatibility Screen

Allyl acetate (0.25 mmol, 0.025 g, 0.027 mL) and thioacetic acid (0.25 mmol, 0.019 g, 0.018 mL) was dissolved in a sample of DES (2.0 g). DPAP (0.05 mmol, 0.013 g) and MAP (0.05 mmol, 0.008 g) were added and the mix was irradiated under UV for 1 hour. The mix was minimally diluted with $H_2O$ to reduce viscosity of the aqueous layer and extracted with EtOAc (3 x 3 mL). Organics were dried over $MgSO_4$ and concentrated *in vacuo*. Extracts were analysed by $^1H$ NMR for presence of DES components.

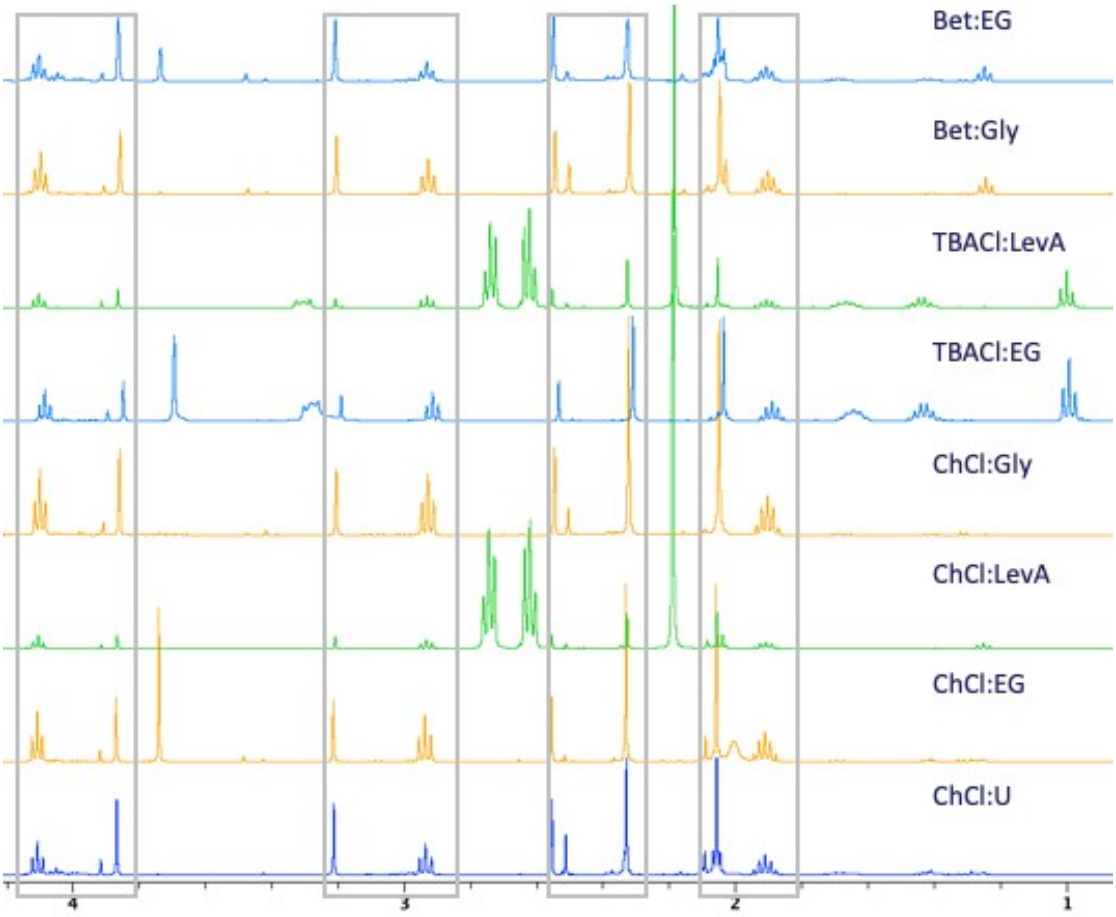
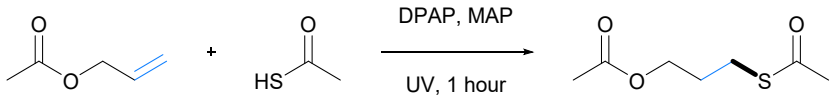



**Figure S1:** $^1$HNMR ($CDCl_3$) spectra of crude extracts. Peaks assigned to product or DPAP/MAP and their products are shown in boxes. Additional peaks are due to DES components.

## 6. Recycling Study




Diethyl 2-allylmalonate (1.0 mmol, 0.200 g, 0.197 mL) was reacted with thioacetic acid (1.2 mmol, 0.091 g, 0.084 mL) in ChCl:Gly in the presence of DPAP (0.2 mmol, 0.051 g) and MAP (0.2 mmol, 0.031 g) according to general procedure B. The aqueous layer was concentrated *in vacuo* to give the DES for re-use in the next repeat. The reaction was performed six times in the same DES sample.

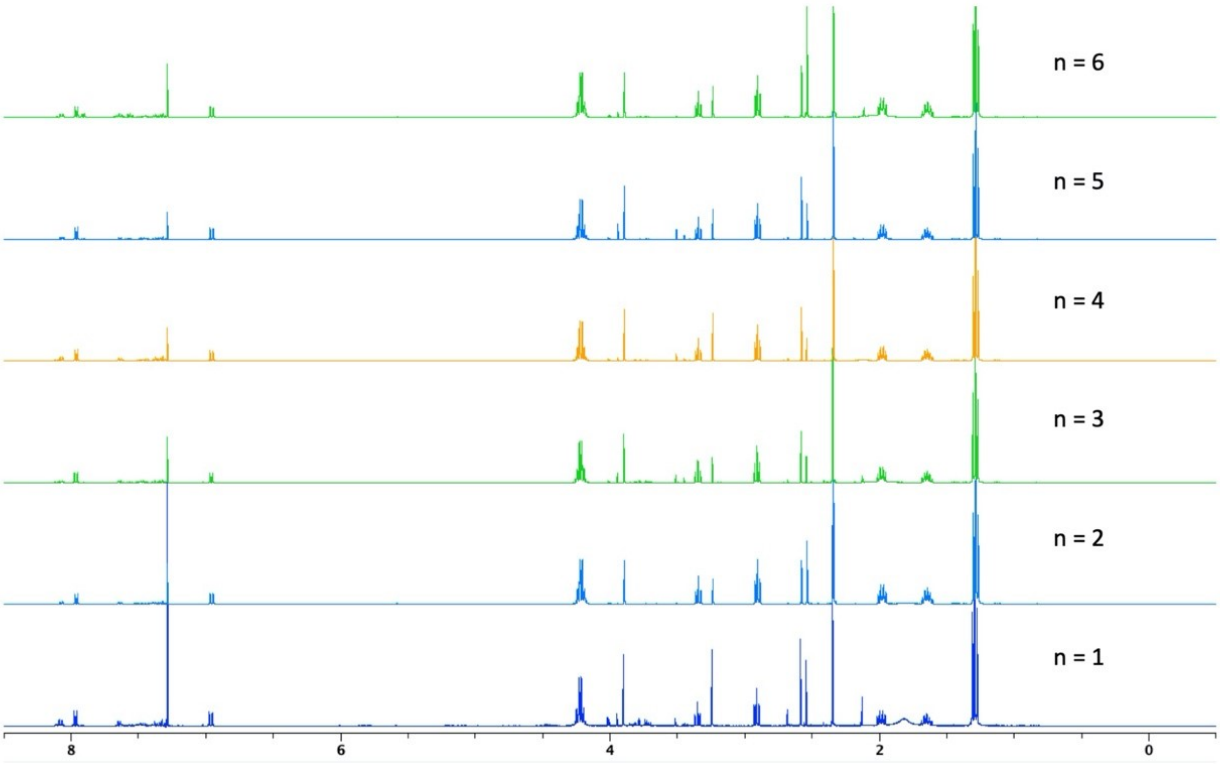



**Figure S2:** NMR spectra ($CDCl_3$) of crude products obtained from recycling study (n = no. reactions).

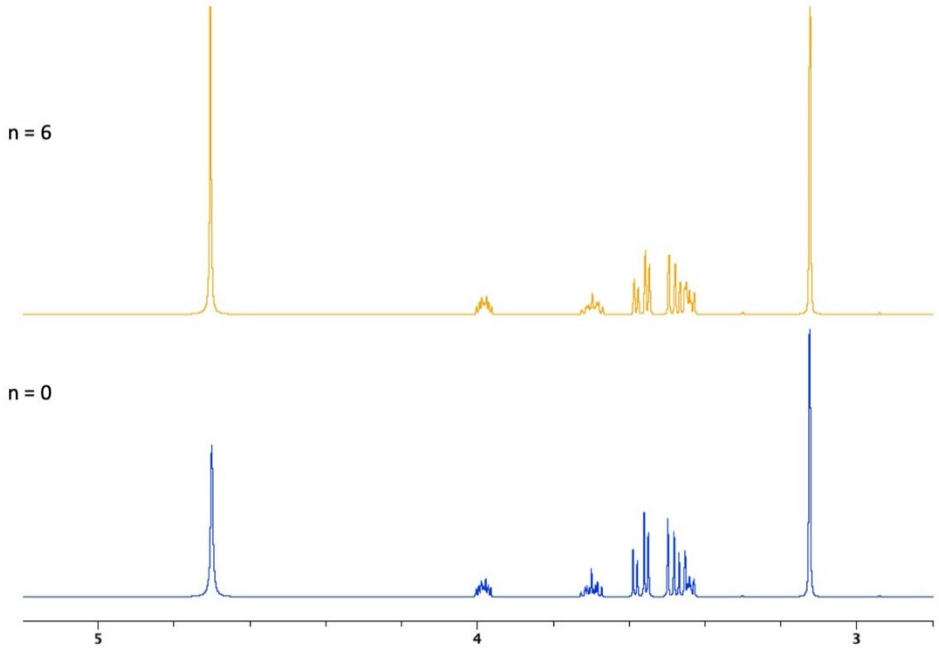
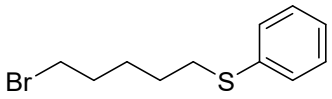


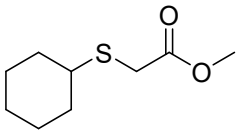

**Figure S3:** NMR spectra ($D_2O$) of DES before use and after 6 reaction repeats (n = no. reactions).

## 7. Scope for UV-Initiated TEC in DESs



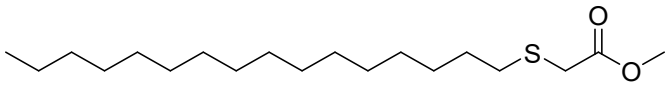

**(5-bromopentyl)(phenyl)sulfane (7)**

5-bromopent-1-ene (1.0 mmol, 0.149 g, 0.118 mL) was reacted with thiophenol (1.2 mmol, 0.132 g, 0.122 mL) in ChCl:Gly in the presence of DPAP (0.2 mmol, 0.051 g) and MAP (0.2 mmol, 0.031 g) according to general procedure A. The product was purified by silica gel flash chromatography using 0-15% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (223 mg, 86%). The isolated product was in agreement with the literature.[4] $\mathbf{R_f}$ = 0.73 (15% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 7.36-7.14 (m, 5H), 3.39 (t, *J* = 6.7 Hz, 2H), 2.93 (t, *J* = 7.1 Hz, 2H), 1.92-1.82 (m, 2H), 1.73-1.54 (m, 4H).




**Methyl 2-(cyclohexylthio)acetate (8)**

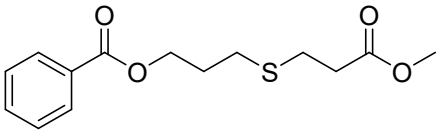
Cyclohexene (1.0 mmol, 0.082 g, 0.101 mL) was reacted with methyl 2-mercaptoacetate (1.2 mmol, 0.128 g, 0.111 mL) in ChCl:Gly in the presence of DPAP (0.2 mmol, 0.051 g) and MAP (0.2 mmol, 0.031 g) according to general procedure A. The product was purified by silica gel flash chromatography using 10% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (117 mg, 63%). The isolated product was in agreement with the literature.[5] $\mathbf{R_f}$ = 0.50 (10% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 3.73 (s, 3H), 3.27 (s, 2H), 2.85-2.75 (m, 1H), 2.04-2.19 (m, 2H), 1.82-1.72 (m, 2H), 1.67-1.57 (m, 1H), 1.38-1.20 (m, 5H).




**Methyl 2-(hexadecylthio)acetate (9)**

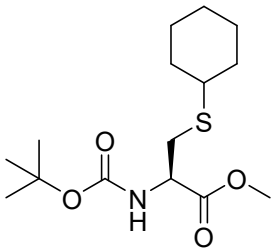
Cyclohexene (1.0 mmol, 0.082 g, 0.101 mL) was reacted with methyl 2-mercaptoacetate (1.2 mmol, 0.128 g, 0.111 mL) in ChCl:Gly in the presence of DPAP (0.2 mmol, 0.051 g) and MAP (0.2 mmol, 0.031 g) according to general procedure A. The product was purified by silica gel flash chromatography using 10% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (117 mg, 63%). The isolated product was in agreement with the literature.[6] $\mathbf{R_f}$ = 0.71 (10% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 3.76 (s, 3H), 3.25 (s, 2H), 2.65 (t, *J* =

7.4 Hz, 2H), 1.66-1.56 (m, 2H), 1.46-1.21 (m, 26H), 0.90 (t, *J* = 6.9 Hz, 3H). **HRMS**: (ESI$^+$) *m/z* calcd. for $C_{19}H_{38}NaO_2S$ ([M+Na]$^+$): 353.2485; found: 353.2489.



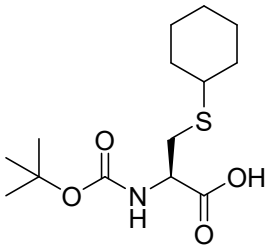
**3-((3-methoxy-3-oxopropyl)thio)propyl benzoate (10)**

Allyl benzoate (0.4 mmol, 0.065 g, 0.064 mL) was reacted with methyl 3-mercaptopropionate (0.6 mmol, 0.072 g, 0.066 mL) in the presence of DPAP (0.04 mmol, 0.010 g) and MAP (0.04 mmol, 0.006 g) according to general procedure A. The product was purified by silica gel flash chromatography using 10-15% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (0.1023 g, 91%). $\mathbf{R_f}$ = 0.48 (20% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 8.06 (d, *J* = 8.5 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 4.44 (t, *J* = 6.2 Hz, 2H), 3.72 (s, 3H), 2.85 (t, *J* = 7.0 Hz, 2H), 2.72 (t, *J* = 7.3 Hz, 2H), 2.65 (t, *J* = 7.3 Hz, 2H), 2.09 (p, *J* = 6.8 Hz, 2H). $\delta_C$ (151 MHz, $CDCl_3$) 172.3, 166.5, 133.0, 130.2, 129.6, 128.4, 63.5, 51.8, 34.6, 28.8, 27.0 .**HRMS**: (APCI$^+$) *m/z* calcd. for $C_{14}H_{18}NaO_4S$ ([M+Na]$^+$): 305.0818; found: 305.0819. $\upsilon_{max}$ (film), cm$^{-1}$: 2952 (C-H stretch), 1734, 1714 (C=O stretch), 1457 (C-H bend), 1248, 1110 (C-O stretch).



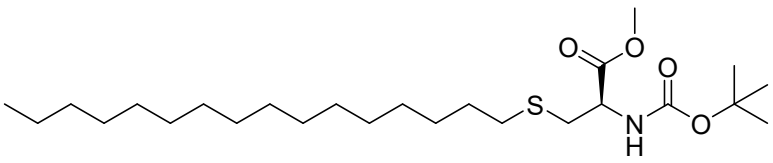
**Methyl *N*-(tert-butoxycarbonyl)-*S*-cyclohexyl-L-cysteinate (11)**

Cyclohexene (2.0 mmol, 0.164 g, 0.202 mL) was reacted with Boc-Cys-OMe (1.0 mmol, 0.235 g, 0.206 mL) in ChCl:Gly in the presence of DPAP (0.2 mmol, 0.051 g) and MAP (0.2 mmol, 0.031 g) according to general procedure A. The product was purified by silica gel flash chromatography using 20% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (212 mg, 67%). $\mathbf{R_f}$ = 0.46 (20% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 5.37 (d, *J* = 5.8 Hz, 1H), 4.55 (d, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 3.00 (d, *J* = 4.7 Hz, 2H), 2.71-2.61 (m, 1H), 2.02-1.91 (m, 2H), 1.84-1.73 (m, 2H), 1.65 (s, 2H), 1.47 (s, 9H), 1.37-1.21 (m, 4H). $\delta_C$ (151 MHz, $CDCl_3$) 171.7, 155.2, 80.1, 53.4, 52.5, 44.0, 33.6, 33.6, 32.3, 28.3, 26.0, 25.7. **HRMS**: (APCI$^+$) *m/z* calcd. for $C_{15}H_{27}NNaO_4S$ ([M+Na]$^+$): 340.1553; found: 340.1553. $\upsilon_{max}$ (film), cm$^{-1}$: 2934 (N-H stretch), 1747, 1713 (C=O stretch), 1497 (C-H bend), 1208, 1161 (C-O stretch).



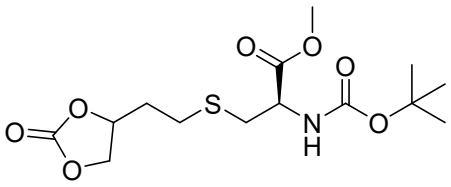
**_N_-(tert-butoxycarbonyl)-_S_-cyclohexyl-L-cysteine (12)**

Cyclohexene (0.700 mmol, 0.058 g, 0.072 mL) was reacted with Boc-Cys-OH (0.350 mmol, 0.077 g) in ChCl:Gly in the presence of DPAP (0.035 mmol, 0.009 g) and MAP (0.035 mmol, 0.005 g) according to general procedure A. The product was purified by back-extraction to yield the desired product as a viscous, colourless oil (74 mg, 70%). $\delta_H$ (400 MHz, $CDCl_3$) 5.44-5.36 (m, 1H), 4.64-4.52 (m, 1H), 3.02-2.93 (m, 2H), 3.02-2.93 (m, 1H), 1.95 (s, 2H), 1.75 (s, 2H), 1.61-1.58 (m, 1H), 1.45 (s, 11H), 1.31-1.24 (4H). $\delta_C$ (151 MHz, $CDCl_3$) 175.3, 155.5, 54.6, 53.2, 44.1, 33.5, 33.5, 28.3, 27.0, 26.0, 25.7. **HRMS**: ($ESI^-$) *m/z* calcd. for $C_{14}H_{24}NO_4S$ ($[M-H]^-$): 302.1432; found 302.1436. $\upsilon_{max}$ (film), $cm^{-1}$: 3433 (O-H stretch), 2930 (N-H stretch), 1710 (C=O stretch), 1501 (C-H bend), 1159 (C-O stretch).



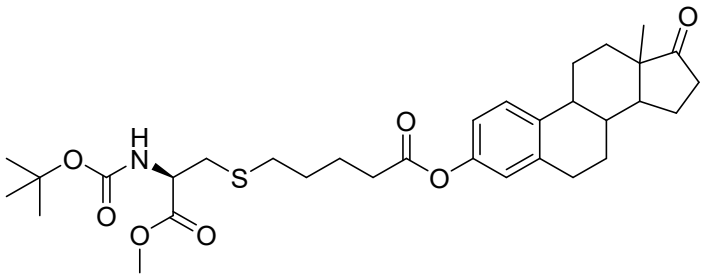
**Methyl _N_-(tert-butoxycarbonyl)-_S_-hexadecyl-L-cysteinate (13)**

Hexadec-1-ene (0.36 mmol, 0.071 g, 0.091 mL) was reacted with Boc-Cys-OMe (0.30 mmol, 0.081 g, 0.071 mL) in ChCl:Gly in the presence of DPAP (0.06 mmol, 0.016 g) and MAP (0.06 mmol, 0.010 g) according to general procedure A. The product was purified by silica gel flash chromatography using 0-10% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil, later forming white crystals (108 mg, 78%). $\mathbf{R_f}$ = 0.51 (15% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 5.37 (d, *J* = 7.1 Hz, 1H), 4.55 (d, *J* = 6.9 Hz, 1H), 3.78 (s, 3H), 2.98 (d, *J* = 4.6 Hz, 2H), 2.53 (t, *J* = 7.4 Hz, 2H), 1.62-1.51 (m, 2H), 1.47 (s, 9H), 1.41-1.22 (m, 26H), 0.90 (t, *J* = 6.8 Hz, 3H). ). $\delta_C$ (151 MHz, $CDCl_3$) 171.7, 155.1, 80.1, 53.3, 52.5, 34.5, 32.8, 31.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.2, 28.8, 28.3, 22.7, 14.1. **HRMS**: ($APCI^+$) *m/z* calcd. for $C_{25}H_{49}NNaO_4S$ ($[M+Na]^+$): 482.3275; found: 482.3281. $\upsilon_{max}$ (film), $cm^{-1}$: 2916, 2847 (N-H stretch), 1751, 1683 (C=O stretch), 1497 (C-H bend), 1203, 1168 (C-O stretch).



**Methyl *N*-(tert-butoxycarbonyl)-*S*-(2-(2-oxo-1,3-dioxolan-4-yl)ethyl)-L-cysteinate (14)**

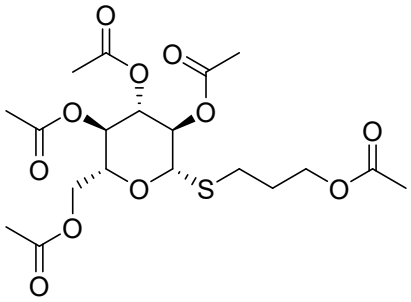
4-vinyl-1,3-dioxolan-2-one (1.0 mmol, 0.057 g, 0.048 mL) was reacted with Boc-Cys-OMe (0.5 mmol, 0.117 g, 0.103 mL) in ChCl:Gly in the presence of DPAP (0.1 mmol, 0.026 g) and MAP (0.1 mmol, 0.016 g) according to general procedure A. The product was purified by silica gel flash chromatography using 20-60% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (103 mg, 59%). $\mathbf{R_f}$ = 0.19 (40% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 5.35 (s, 1H), 4.93-4.84 (m, 1H), 4.63-4.55 (m, 2H), 3.80 (s, 3H), 3.08-2.92 (m, 2H), 2.82-2.63 (m, 2H), 2.18-2.06 (m, 1H), 2.00-1.82 (m, 2H), 1.47 (s, 9H). $\delta_C$ (151 MHz, $CDCl_3$) 171.3, 154.6, 80.4, 75.2, 69.1, 53.3, 52.7, 34.9, 33.9, 28.3, 27.8. **HRMS**: (APCI$^+$) *m/z* calcd. for $C_{14}H_{23}NNaO_7S$ ([M+Na]$^+$): 372.1087; found: 372.1095. $\upsilon_{max}$ (film), cm$^{-1}$: 2978, 2928 (N-H stretch), 1793,. 1741, 1705 (C=O stretch), 1503 (C-H bend), 1215, 1157 (C-O stretch).



**13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 5-(((*R*)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)thio)pentanoate (15)**

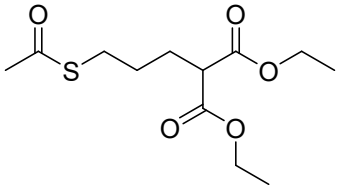
**26** (0.30 mmol, 0.106 g) was reacted with Boc-Cys-OMe (0.33 mmol, 0.078 g, 0.069 mL) in 20% $H_2O$/ChCl:Gly (v/v) in the presence of DPAP (0.6 mmol, 0.016 g) and MAP (0.06 mmol, 0.010 g) according to general procedure A. The product was purified by silica gel flash chromatography using 25-30% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (36 mg, 20%). $\mathbf{R_f}$ = 0.26 (30% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 7.28 (d, *J* = 8.4 Hz, 1H), 6.88-6.79 (m, 2H), 5.46-5.34 (m, 1H), 4.65-4.50 (m, 1H), 3.77 (s, 3H), 3.03-2.87 (m, 4H), 2.63-2.46 (m, 4H), 2.44-2.36 (m, 1H), 2.33-2.24 (m, 1H), 2.21-1.92 (m, 4H), 1.89-1.79 (m, 2H), 1.75-1.39 (m, 17H), 0.91 (s, 3H). $\delta_C$ (151 MHz, $CDCl_3$) 220.7, 172.0, 171.6, 155.1, 148.5, 138.0, 137.4, 126.4, 121.5, 118.7, 53.3, 52.6, 50.4, 47.9, 44.1, 38.0, 35.8, 34.5, 33.8, 32.3, 31.6, 29.4, 28.8, 28.3, 26.3, 25.8, 23.9, 21.6, 13.8. **HRMS**: (APCI$^+$) *m/z* calcd. for

$C_{32}H_{45}NNaO_7S$ ([M+Na]$^+$): 610.2809; found: 610.2813. $\upsilon_{max}$ (film), cm$^{-1}$: 2934 (N-H stretch), 1737, 1712 (C=O stretch), 1493 (C-H bend), 1208, 1159 (C-O stretch).



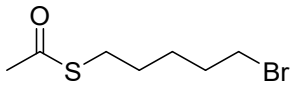
**(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((3-acetoxypropyl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (16)**

Allyl acetate (0.5 mmol, 0.050 g, 0.054 mL) was reacted with 1-thio-β-D-glucose tetraacetate (0.6 mmol, 0.182 g) in 20% $H_2O$/ChCl:Gly (v/v) in the presence of DPAP (0.1 mmol, 0.026 g) and MAP (0.1 mmol, 0.016 g) according to general procedure A. The product was purified by silica gel flash chromatography using 50% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (174 mg, 75%). The isolated product was in agreement with the literature.[7] $\mathbf{R_f}$ = 0.54 (60% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 5.18 (app-t, 1H), 5.07-4.95 (m, 2H), 4.45 (d, *J* = 10 Hz, 1H), 4.20 (dd, *J* = 12.2 Hz, *J* = 5.1 Hz, 1H), 4.16-4.09 (m, 3H), 3.71-3.64 (m, 1H), 2.79-2.61 (m, 2H), 2.06 (s, 3H), 2.03 (s, 6H), 2.01 (s, 3H), 1.99 (s, 3H), 1.93-1.85 (m, 2H). **HRMS**: (APCI$^+$) *m/z* calcd. for $C_{19}H_{27}O_{11}S$ ([M+H]$^+$): 463.1279; found: 463.1275.



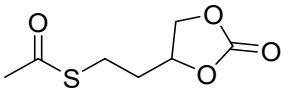
**Diethyl 2-(3-(acetylthio)propyl)malonate (17)**

Diethyl 2-allylmalonate (1.0 mmol, 0.200 g, 0.197 mL) was reacted with thioacetic acid (1.2 mmol, 0.091 g, 0.084 mL) in ChCl:Gly in the presence of DPAP (0.2 mmol, 0.051 g) and MAP (0.2 mmol, 0.031 g) according to general procedure B. The product was purified by silica gel flash chromatography using 10% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (161 mg, 71%). $\mathbf{R_f}$ = 0.24 (20% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 4.22 (m, 4H), 3.35 (t, *J* = 7.5 Hz, 1H), 2.91 (t, *J* = 7.2 Hz, 2H), 2.35 (s, 3H), 1.19 (m, 2H), 1.64 (m, 2H), 1.29 (t, *J* = 7.1, 6H). ). **HRMS**: (APCI$^+$) *m/z* calcd. for $C_{12}H_{21}O_5S$ ([M+H]$^+$): 277.1104; found: 277.1107.



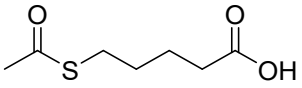
**_S_-(5-bromopentyl) ethanethioate (18)**

5-bromo-pent-1-ene (1.5 mmol, 0.240 g, 0.190 mL) was reacted with thioacetic acid (1.8 mmol, 0.137 g, 0.127 mL) in ChCl:Gly in the presence of DPAP (0.3 mmol, 0.077 g) and MAP (0.3 mmol, 0.057 g) according to general procedure B. The product was purified by silica gel flash chromatography using 15% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (161 mg, 71%). The isolated product was in agreement with the literature.[8] $\mathbf{R_f}$ = 0.56 (15% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 3.40 (t, *J* = 6.7 Hz, 2H), 2.87 (t, *J* = 7.1 Hz, 2H). 2.32 (s, 3H), 1.87 (q, *J* = 7.2 Hz, 2H), 1.65-1.46 (m, 4H).



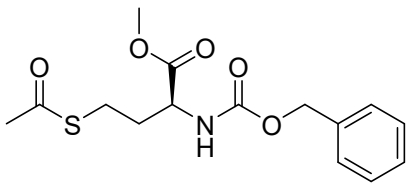
**_S_-(2-(2-oxo-1,3-dioxolan-4-yl)ethyl) ethanethioate (19)**

4-vinyl-1,3-dioxolan-2-one (0.5 mmol, 0.057 g, 0.048 mL) was reacted with thioacetic acid (0.6 mmol, 0.046 g, 0.043 mL) in ChCl:Gly in the presence of DPAP (0.1 mmol, 0.026 g) and MAP (0.1 mmol, 0.016 g) according to general procedure B. The product was purified by silica gel flash chromatography using 20-60% EtOAc/Hexane (v/v) to yield the desired product as a pale yellow oil (76 mg, 80%). The isolated product was in agreement with the literature.[7] $\mathbf{R_f}$ = 0.59 (60% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 4.81-4.73 (m, 1H), 4.57 (t, *J* = 8.2 Hz, 1H), 4.14 (dd, *J* = 8.5, J = 6.9 Hz), 3.08-2.99 (m, 1H), 2.96-2.87 (m, 1H), 2.35 (s, 3H), 2.15-1.93 (m, 2H). **HRMS**: ($ESI^+$) *m/z* calcd. for $C_7H_{10}NaO_4S$ ($[M+Na]^+$): 213.0192; found: 213.0194.



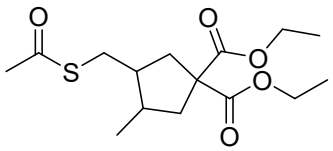
**5-(acetylthio)pentanoic acid (20)**

Pentenoic acid (0.6 mmol, 0.601 g, 0.0613 mL) was reacted with thioacetic acid (0.9 mmol, 0.069 g, 0.064 mL) in the presence of DPAP (0.06 mmol, 0.015 g) and MAP (0.06 mmol, 0.009 g) according to general procedure B. The product was purified by back-extraction to yield the desired product as a white crystalline solid (97 mg, 91%). The isolated product was in agreement with the literature.[9] $\delta_H$ (400 MHz, $CDCl_3$) 2.91 (t, *J* = 7.0 Hz, 2H), 2.40 (t, *J* = 7.0 Hz, 2H), 2.35 (s, 3H), 1.78-1.62 (m, 4H). $\delta_H$ (400 MHz, $CDCl_3$) 195.9, 178.9, 33.3, 30.6, 28.9, 28.6, 23.7. $\delta_C$ (151 MHz, $CDCl_3$) 172.3, 166.5, 133.0, 130.2, 129.6, 128.4, 63.5, 51.8, 34.6, 28.8, 27.0. **HRMS**: ($APCI^+$) *m/z* calcd. for $C_7H_{11}O_3S$ ($[M+H]^+$): 175.0434; found: 175.0434.



**Methyl *S*-acetyl-*N*-((benzyloxy)carbonyl)-L-homocysteinate (21)**

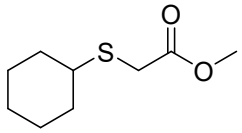
**28** (0.30 mmol, 0.075 g) was reacted with thioacetic acid (0.36 mmol, 0.027 g, 0.025 mL) in ChCl:Gly in the presence of DPAP (0.06 mmol, 0.016 g) and MAP (0.10 mmol, 0.010 g) according to general procedure B. The product was purified by silica gel flash chromatography using 20% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (57 mg, 58%). The isolated product was in agreement with the literature.[10] $\mathbf{R_f}$ = 0.23 (20% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 7.41-7.32 (m, 5H), 5.43 (d, *J* = 5.1 Hz, 1H), 5.14 (s, 2H), 4.46 (q, *J* = 4.6, 1H), 3.78 (s, 3H), 3.01-2.94 (m, 1H), 2.91-2.85 (m, 1H), 2.34 (s, 3H), 2.19-2.14 (m, 1H), 1.99-1.93 (m, 1H). **HRMS**: (APCI$^+$) *m/z* calcd. for $C_{15}H_{19}NNaO_5S$ ([M+Na]$^+$): 348.0876; found: 348.0881.



**Diethyl 3-((acetylthio)methyl)-4-methylcyclopentane-1,1-dicarboxylate (22)**

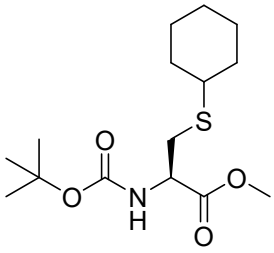
Diethyl 2,2-diallylmalonate (0.5 mmol, 0.121 g, 0.122 mL) was reacted with thioacetic acid (0.6 mmol, 0.046 g, 0.043 mL) in ChCl:Gly in the presence of DPAP (0.1 mmol, 0.026 g) and MAP (0.1 mmol, 0.016 g) at a concentration of 0.1 M, according to general procedure B. The product was purified by silica gel flash chromatography using 95% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (83 mg, 53%, 1:6 d.r.). The isolated product was in agreement with the literature. The isolated product was in agreement with the literature.[11] $\delta_H$ (400 MHz, $CDCl_3$) 4.19 (qd *J* = 7.1 Hz, J = 3.2, 4H), 2.96 (dd, *J* = 13.4 Hz, *J* = 6.5 Hz), 2.81 (dd, *J* = 13.4 Hz, *J* = 8.5 Hz), 2.50-2.39 (m, 2H), 2.34 (s, 3H), 2.30-2.17 (m, 2H), 2.09 (dd, *J* = 13.3 Hz, *J* = 8.8 Hz, 1H), 2.01 (dd, *J* = 13.3 Hz, *J* = 5.6 Hz, 1H), 1.25 (td, *J* = 7.1 Hz, *J* = 2.0 Hz, 6H), 1.06 (d, *J* = 6.5 Hz, 0.44H), 0.94 (d, *J* = 6.5 Hz, 2.56H). **HRMS**: (APCI$^+$) *m/z* calcd. for $C_{15}H_{25}O_5S$ ([M+H]$^+$): 317.1417; found: 317.1420.

## 8. Scope for $O_2$-Initiatied TEC in DESs



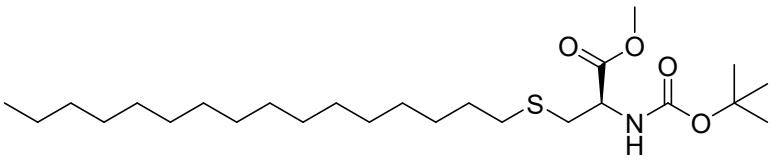
**Methyl 2-(cyclohexylthio)acetate (8)**

Cyclohexene (1.0 mmol, 0.082 g, 0.101 mL) was reacted with methyl 2-mercaptoacetate (0.5 mmol, 0.053 g, 0.046 mL) in ChCl:Gly according to general procedure D. The product was purified by silica gel flash chromatography using 10% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (61 mg, 32%). The isolated product was in agreement with the literature.[5] $\mathbf{R_f}$ = 0.57 (10% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 3.73 (s, 3H), 3.27 (s, 2H), 2.85-2.75 (m, 1H), 2.04-2.19 (m, 2H), 1.82-1.72 (m, 2H), 1.67-1.57 (m, 1H), 1.38-1.20 (m, 5H).



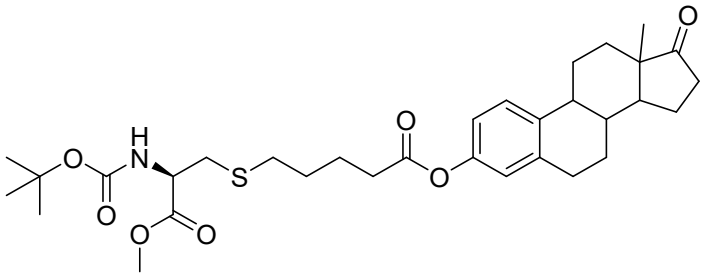
**Methyl *N*-(tert-butoxycarbonyl)-*S*-cyclohexyl-L-cysteinate (11)**

Cyclohexene (1.0 mmol, 0.082 g, 0.101 mL) was reacted with Boc-Cys-OMe (0.5 mmol, 0.118 g, 0.103 mL) in ChCl:Gly according to general procedure D. The product was purified by silica gel flash chromatography using 20% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (67 mg, 73%). $\mathbf{R_f}$ = 0.46 (20% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 5.37 (d, *J* = 5.8 Hz, 1H), 4.55 (d, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 3.00 (d, *J* = 4.7 Hz, 2H), 2.71-2.61 (m, 1H), 2.02-1.91 (m, 2H), 1.84-1.73 (m, 2H), 1.65 (s, 2H), 1.47 (s, 9H), 1.37-1.21 (m, 4H). $\delta_C$ (151 MHz, $CDCl_3$) 171.7, 155.2, 80.1, 53.4, 52.5, 44.0, 33.6, 33.6, 32.3, 28.3, 26.0, 25.7. **HRMS**: (APCI$^+$) *m/z* calcd. for $C_{15}H_{27}NNaO_4S$ ([M+Na]$^+$): 340.1553; found: 340.1553. $\upsilon_{max}$ (film), cm$^{-1}$: 2934 (N-H stretch), 1747, 1713 (C=O stretch), 1497 (C-H bend), 1208, 1161 (C-O stretch).



**Methyl *N*-(tert-butoxycarbonyl)-*S*-hexadecyl-L-cysteinate (13)**

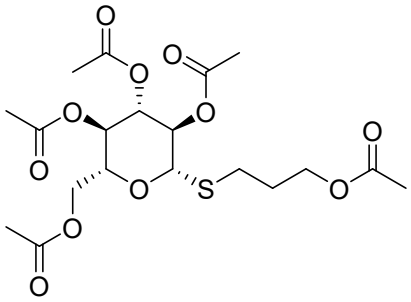
Hexadec-1-ene (0.6 mmol, 0.135 g, 0.173 mL) was reacted with Boc-Cys-OMe (0.30 mmol, 0.081 g, 0.071 mL) in ChCl:Gly according to general procedure D. The product was purified by silica gel flash chromatography using 0-10% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil, later forming white crystals (90 mg, 65%). $\mathbf{R_f}$ = 0.51 (15% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 5.37 (d, *J* = 7.1 Hz, 1H), 4.55 (d, *J* = 6.9 Hz, 1H), 3.78 (s, 3H), 2.98 (d, *J* = 4.6 Hz, 2H), 2.53 (t, *J* = 7.4 Hz, 2H), 1.62-1.51 (m, 2H), 1.47 (s, 9H), 1.41-1.22 (m, 26H), 0.90 (t, *J* = 6.8 Hz, 3H). ). $\delta_C$ (151 MHz, $CDCl_3$) 171.7, 155.1, 80.1, 53.3, 52.5, 34.5, 32.8, 31.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.2, 28.8, 28.3, 22.7, 14.1. **HRMS**: (APCI$^+$) *m/z* calcd. for $C_{25}H_{49}NNaO_4S$ ([M+Na]$^+$): 482.3275; found: 482.3281. $\upsilon_{max}$ (film), cm$^{-1}$: 2916, 2847 (N-H stretch), 1751, 1683 (C=O stretch), 1497 (C-H bend), 1203, 1168 (C-O stretch).



**13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 5-(((*R*)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)thio)pentanoate (15)**

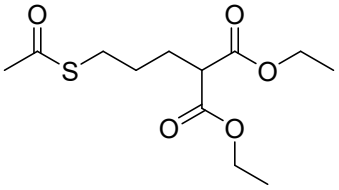
**26** (0.3 mmol, 0.106 g) was reacted with Boc-Cys-OMe (0.33 mmol, 0.078 g, 0.069 mL) in 20% $H_2O$/ChCl:Gly (v/v) according to general procedure D. The product was purified by silica gel flash chromatography using 25-30% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (95 mg, 54%). $\mathbf{R_f}$ = 0.26 (30% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 7.28 (d, *J* = 8.4 Hz, 1H), 6.88-6.79 (m, 2H), 5.46-5.34 (m, 1H), 4.65-4.50 (m, 1H), 3.77 (s, 3H), 3.03-2.87 (m, 4H), 2.63-2.46 (m, 4H), 2.44-2.36 (m, 1H), 2.33-2.24 (m, 1H), 2.21-1.92 (m, 4H), 1.89-1.79 (m, 2H), 1.75-1.39 (m, 17H), 0.91 (s, 3H). $\delta_C$ (151 MHz, $CDCl_3$) 220.7, 172.0, 171.6, 155.1, 148.5, 138.0, 137.4, 126.4, 121.5, 118.7, 53.3, 52.6, 50.4, 47.9, 44.1, 38.0, 35.8, 34.5, 33.8, 32.3, 31.6, 29.4, 28.8, 28.3, 26.3, 25.8, 23.9, 21.6, 13.8. **HRMS**: (APCI$^+$) *m/z* calcd. for

$C_{32}H_{45}NNaO_7S$ ([M+Na]$^+$): 610.2809; found: 610.2813. $\upsilon_{max}$ (film), cm$^{-1}$: 2934 (N-H stretch), 1737, 1712 (C=O stretch), 1493 (C-H bend), 1208, 1159 (C-O stretch).



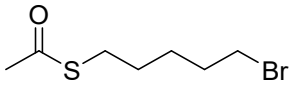
**(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((3-acetoxypropyl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (16)**

Allyl acetate (0.3 mmol, 0.030 g, 0.033 mL) was reacted with 1-thio-β-D-glucose tetraacetate (0.33 mmol, 0.120 g) in 20% $H_2O$/ChCl:Gly (v/v) according to general procedure D. The product was purified by silica gel flash chromatography using 50% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (100 mg, 72%). The isolated product was in agreement with the literature.[7] $\mathbf{R_f}$ = 0.54 (60% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 5.18 (app-t, 1H), 5.07-4.95 (m, 2H), 4.45 (d, *J* = 10 Hz, 1H), 4.20 (dd, *J* = 12.2 Hz, *J* = 5.1 Hz, 1H), 4.16-4.09 (m, 3H), 3.71-3.64 (m, 1H), 2.79-2.61 (m, 2H), 2.06 (s, 3H), 2.03 (s, 6H), 2.01 (s, 3H), 1.99 (s, 3H), 1.93-1.85 (m, 2H). **HRMS**: (APCI$^+$) *m/z* calcd. for $C_{19}H_{27}O_{11}S$ ([M+H]$^+$): 463.1279; found: 463.1275.



**Diethyl 2-(3-(acetylthio)propyl)malonate (17)**

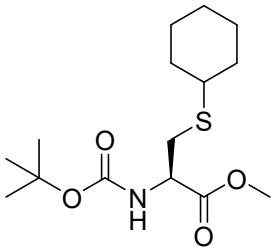
Diethyl 2-allylmalonate (1.0 mmol, 0.200 g, 0.197 mL) was reacted with thioacetic acid (2.0 mmol, 0.152 g, 0.141 mL) in ChCl:Gly according to general procedure D. The product was purified by silica gel flash chromatography using 10% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (83 mg, 37%). $\mathbf{R_f}$ = 0.24 (20% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 4.21 (m, 4H), 3.35 (t, *J* = 7.5 Hz, 1H), 2.91 (t, *J* = 7.2 Hz, 2H), 2.35 (s, 3H), 1.20 (m, 2H), 1.64 (m, 2H), 1.29 (t, *J* = 7.1, 6H). **HRMS**: (APCI$^+$) *m/z* calcd. for $C_{12}H_{21}O_5S$ ([M+H]$^+$): 277.1104; found: 277.1107.




**_S_-(5-bromopentyl) ethanethioate (18)**

5-bromo-pent-1-ene (0.75 mmol, 0.112 g, 0.089 mL) was reacted with thioacetic acid (1.5 mmol, 0.114 g, 0.106 mL) in ChCl:Gly in the presence of DPAP (0.3 mmol, 0.077 g) and MAP (0.3 mmol, 0.057 g) according to general procedure B. The product was purified by silica gel flash chromatography using 15% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (81 mg, 67%). The isolated product was in agreement with the literature.[8] $\mathbf{R_f}$ = 0.56 (15% EtOAc/Hexane (v/v)). $\delta_H$ (400 MHz, $CDCl_3$) 3.40 (t, *J* = 6.7 Hz, 2H), 2.87 (t, *J* = 7.1 Hz, 2H). 2.32 (s, 3H), 1.87 (q, *J* = 7.2 Hz, 2H), 1.65-1.46 (m, 4H).

Multi-gram Scale Reaction:

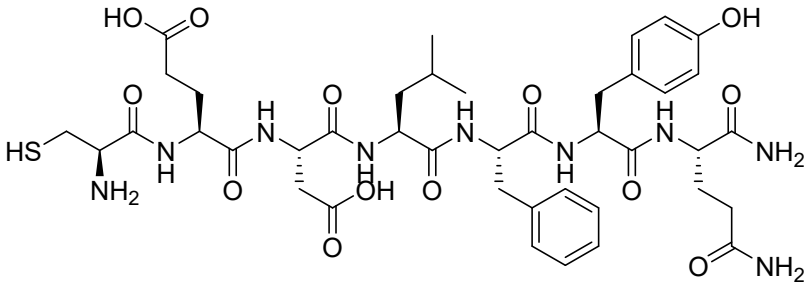



**Methyl _N_-(tert-butoxycarbonyl)-_S_-cyclohexyl-L-cysteinate (11)**

Cyclohexene (6.50 mmol, 0.534 g, 0.658 mL) was reacted with Boc-Cys-OMe (9.75 mmol, 2.294 g, 2.007 mL) in ChCl:Gly according to general procedure D for 72h. Peroxide levels in the reaction mixture were quantified using MerkQuant colorimetric peroxide tests (0.5-25 mg/L) at t = 0, 0.5, 1, 1.5, 2, 3, 5, 24, 30, 48 and 72 hours. The product was purified by silica gel flash chromatography using 5-20% EtOAc/Hexane (v/v) to yield the desired product as a colourless oil (0.964 g, 47%).

## 9. Peptide Bioconjugation in DESs

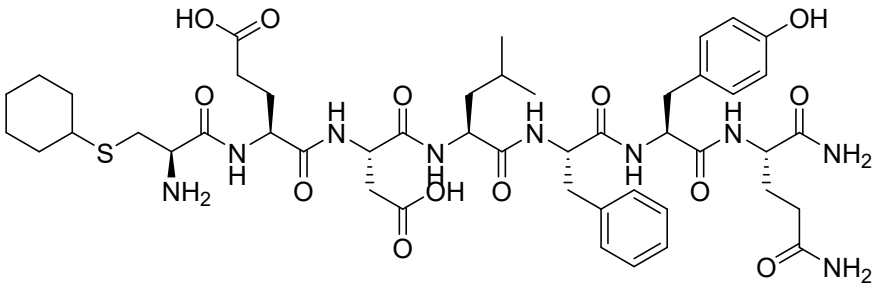
### 9.1 Peptide Synthesis



**Cys-Glu-Asp-Leu-Phe-Tyr-Gln-$NH_2$ (23)**

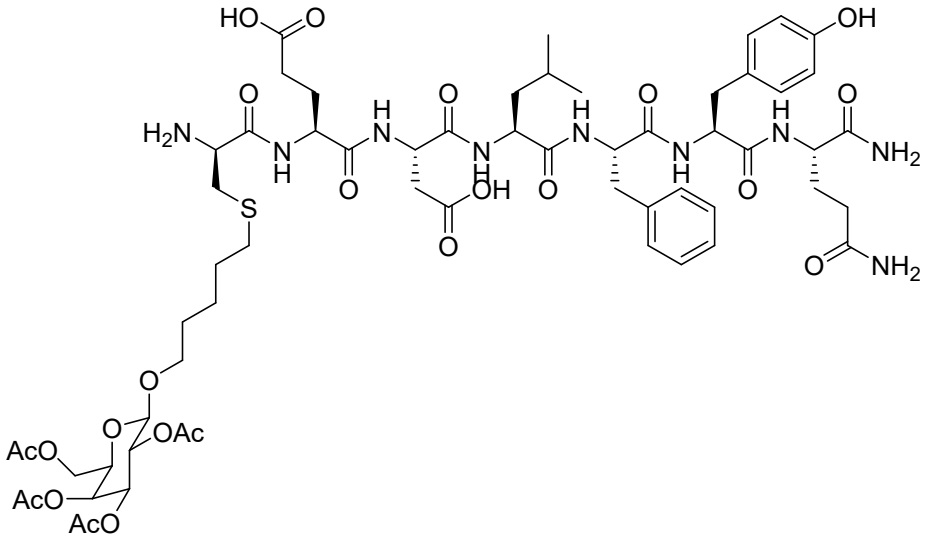
The desired sequence was prepared by standard Fmoc SPPS using 20% piperidine in DMF (2 x 10 min) for deprotection. A coupling mix consisting of Fmoc-AA (4 equiv.), PyBop (4 equiv.) and NMM (8 equiv.) in DMF was used to couple the first residue to the resin. Further couplings used Fmoc-AA (3 equiv.), PyBop (3 equiv.) and NMM (6 equiv.) in DMF. All couplings were complete after 45 min. The peptide was cleaved from the resin using TFA:$H_2O$:EDT:TES (94:2.5:2.5:1) cleavage cocktail. The TFA was removed under Ar flow, the peptide precipitated using cold ether and lyophilised. The product was analysed by RP-HPLC and used without further purification. $\mathbf{t_R}$ (RP-HPLC) = 15.19 min (5-95% ACN in $H_2O$ with 0.1% TFA, 25 min). **HRMS**: (ESI$^+$) *m/z* calcd. for $C_{41}H_{58}N_9O_{13}S$ ([M+H]$^+$): 916.3888; found: 916.3870. **$^1$H NMR (600 MHz, DMSO-$d_6$)** $\delta_H$ 9.15 (brs, 1H, Tyr OH), 8.72-8.59 (m, 1H, Glu NH), 8.50-8.35 (m, 1H, Asp NH), 8.04-7.84 (m, 3H, Tyr NH, Leu NH, Phe NH), 7.28-7.13 (m, 8H, Gln $NH_2$ x 1, Phe Ar CH x 5, Gln $NH_2$ x 1), 7.07 (s, 1H, Gln $NH_2$ x 1), 7.02 (d, *J* = 8.5 Hz, 2H, Tyr Ar CH x 2), 6.76 (s, 1H, Gln $NH_2$ x 1), 6.64 (d, *J* = 8.46 Hz, 2H, Tyr Ar CH x 2), 4.58-4.53 (m, 1H, Asp αH), 4.50-4.31 (m, 3H, Phe αH, Tyr αH, Glu αH), 4.24-4.13 (m, 2H, Leu αH, Gln αH), 4.02-3.99 (m, 1H, Cys αH), 3.03-2.84 (m, 4H, Phe βH x 1, Cys βH x 2, Tyr βH), 2.80-2.70 (m, Phe βH x 1, Tyr βH x 1), 2.68-2.61 (m, 1H, Asp βH x 1), 2.34-2.21 (m, 2H, Glu γH), 2.08 (t, *J* = 8.3, 2H, Gln γH), 1.95-1.84 (m, 2H, Glu βH x 1, Gln βH x 1), 1.81-1.71 (m, 2H, Glu βH x 1, Gln βH x 1), 1.55-1.46 (m, 1H, Leu γH), 1.36-1.28 (m, 1H Leu βH), 0.82 (d, *J* = 6.5 Hz, 3H, Leu $CH_3$), 0.77 (d, *J* = 6.5 Hz, 3H, Leu $CH_3$). **$^{13}$C NMR (151 MHz, DMSO-$d_6$)** $\delta_C$ 173.8 (Glu COOH), 173.8 (Tyr CO), 173.7 (Gln $CONH_2$), 173.0 (Glu CO), 173.0 (Gln CHCONH2), 171.7 (Asp CO), 171.6 (Leu CO), 170.8 (Phe CO), 170.1 (Asp COOH), 155.8 (Tyr Ar-COH), 137.6 (Phe qC-Ar) 130.0 (Tyr Ar), 129.2 (Phe Ar), 127.9 (Phe Ar), 127.5 (Tyr qC-Ar), 126.1 (Phe Ar), 114.9 (Tyr Ar), 54.3 (Tyr αC), 53.9 (Cys αC), 53.6 (Phe αC), 52.1 (Gln αC), 51.9 (Glu αC), 51.1 (Leu αC), 49.3 (Asp αC), 49.1 (Leu βC), 39.7 (Asp βC), 37.2 (Phe βC), 36.5 (Tyr βC), 35.8 (Glu γC), 31.4 (Gln γC), 28.1 (Gln βC), 27.7 (Glu βC), 25.2 (Cys βC), 24.0 (Leu γC), 23.0 (Leu δC), 21.4 (Leu δC).

9.2 Peptide Modification via TEC in DES



***S*-cyclohexyl-Cys-Glu-Asp-Leu-Phe-Tyr-Gln-$NH_2$ (24)**

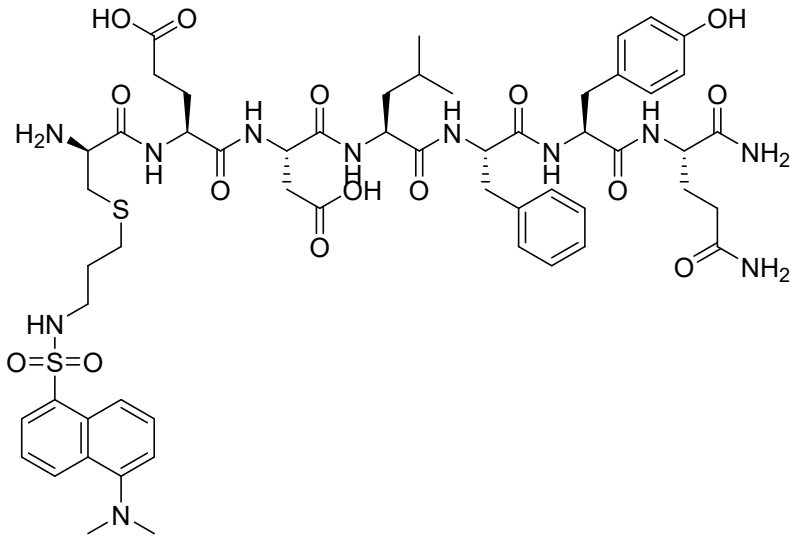
To degassed ChCl:Gly/$H_2O$ was added peptide **22** (0.0090 g, 0.01 mmol, 1 equiv.), cyclohexene (0.0050 mL, 0.0040 g, 0.05 mmol, 5 equiv.), DPAP (0.0026 g, 0.01 mmol, 1 equiv.), MAP (0.0015 g, 0.01 mmol, 1 equiv.) and TES (0.0020 mL, 0.0012 g, 0.01 mmol, 1 equiv.). The mix was stirred under uv irradiation and Ar atmosphere for 3 hours. A 0.25 mL aliquot of reaction mix was added to 0.25 mL ACN and subjected to RP-HPLC analysis which confirmed the consumption of the peptide starting material. A 0.75 mL aliquot was then subjected to semi-preparative RP-HPLC to yield the desired product as a white solid after lyophilisation (1.4 mg, 48%). $\mathbf{t_R}$ (RP-HPLC) = 16.93 min (5-95% ACN in $H_2O$ with 0.1% TFA, 25 min). **HRMS**: (ESI$^+$) *m/z* calcd. for $C_{47}H_{68}N_9O_{13}S$ ([M+H]$^+$): 998.4652; found: 998.4633.



***S*-galactosyl-Cys-Glu-Asp-Leu-Phe-Tyr-Gln-$NH_2$ (25)**

To degassed ChCl:Gly/$H_2O$ was added peptide **22** (0.0090 g, 0.01 mmol, 1 equiv.), galactosyl alkene **26** (0.0208 g, 0.05 mmol, 5 equiv.), DPAP (0.0026 g, 0.01 mmol, 1 equiv.), MAP (0.0015 g, 0.01 mmol, 1 equiv.) and TES (0.0020 mL, 0.0012 g, 0.01 mmol, 1 equiv.). The mix was stirred under uv irradiation and Ar atmosphere for 3 hours. A 0.25 mL aliquot of reaction mix was added to 0.25 mL ACN and subjected to RP-HPLC analysis which confirmed the

consumption of the peptide starting material and formation of the desired product. $t_R$ (RP-HPLC) = 18.15 min (5-95% ACN in $H_2O$ with 0.1% TFA, 25 min). **HRMS**: (ESI$^+$) *m/z* calcd. for $C_{60}H_{85}N_9O_{23}S$ ([M+H]$^+$): 1332.5552; found: 1332.5418.



***S*-dansyl-Cys-Glu-Asp-Leu-Phe-Tyr-Gln-NH$_2$ (26)**

To degassed ChCl:Gly/$H_2O$ was added peptide **22** (0.0090 g, 0.01 mmol, 1 equiv.), dansyl alkene **25** (0.0145 g, 0.05 mmol, 5 equiv.), DPAP (0.0026 g, 0.01 mmol, 1 equiv.), MAP (0.0015 g, 0.01 mmol, 1 equiv.) and TES (0.0020 mL, 0.0012 g, 0.01 mmol, 1 equiv.). The mixture was stirred under uv irradiation and Ar atmosphere for 3 hours. A 0.25 mL aliquot of reaction mix was added to 0.25 mL ACN and subjected to RP-HPLC analysis which confirmed the consumption of the peptide starting material and formation of the desired product. $t_R$ (RP-HPLC) = 18.16 min (5-95% ACN in $H_2O$ with 0.1% TFA, 25 min). **HRMS**: (ESI$^+$) *m/z* calcd. for $C_{56}H_{77}N_{11}O_{15}S_2$ ([M+2H]$^{2+}$): 602.7455; found: 602.7437.

## 10. References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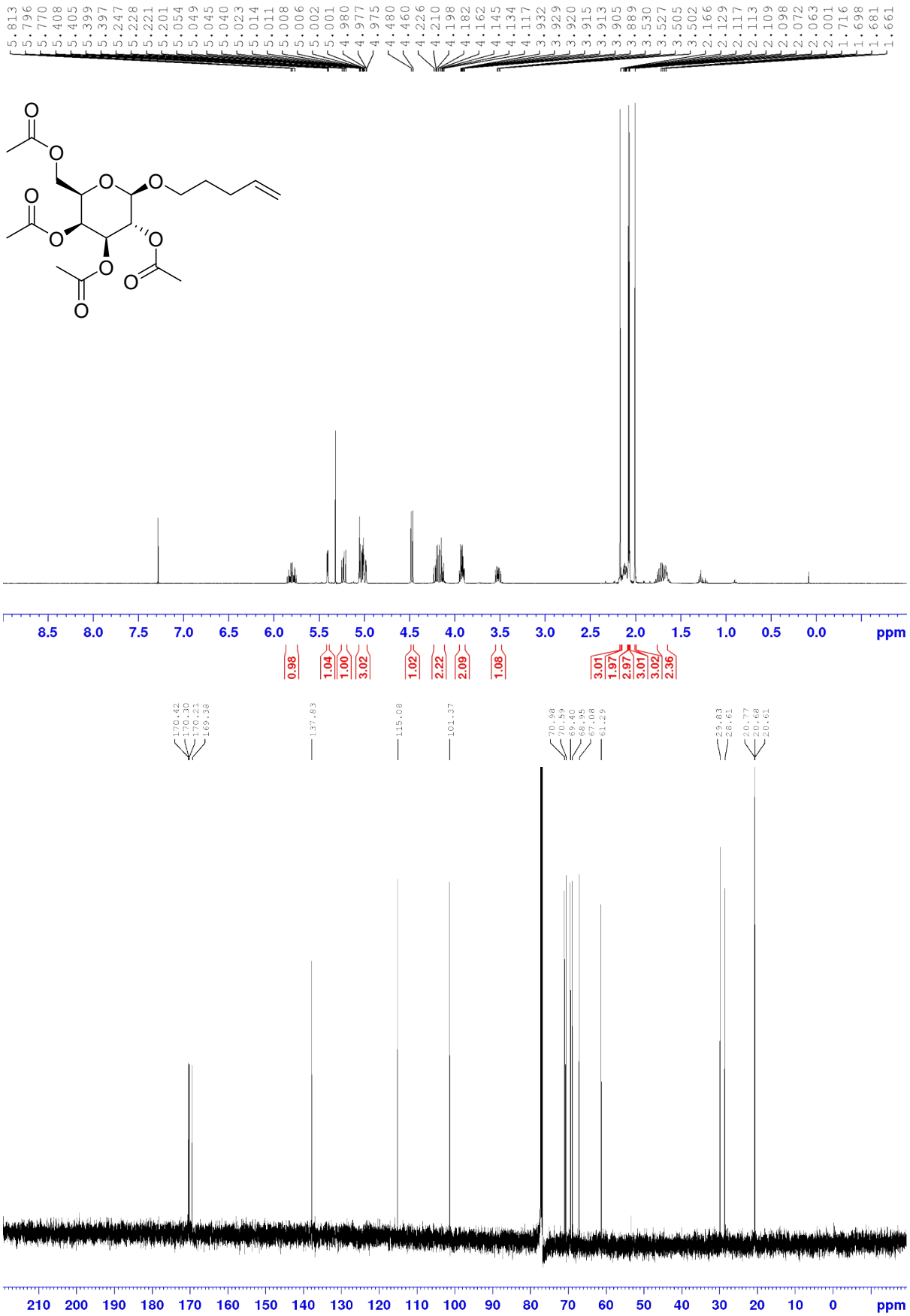
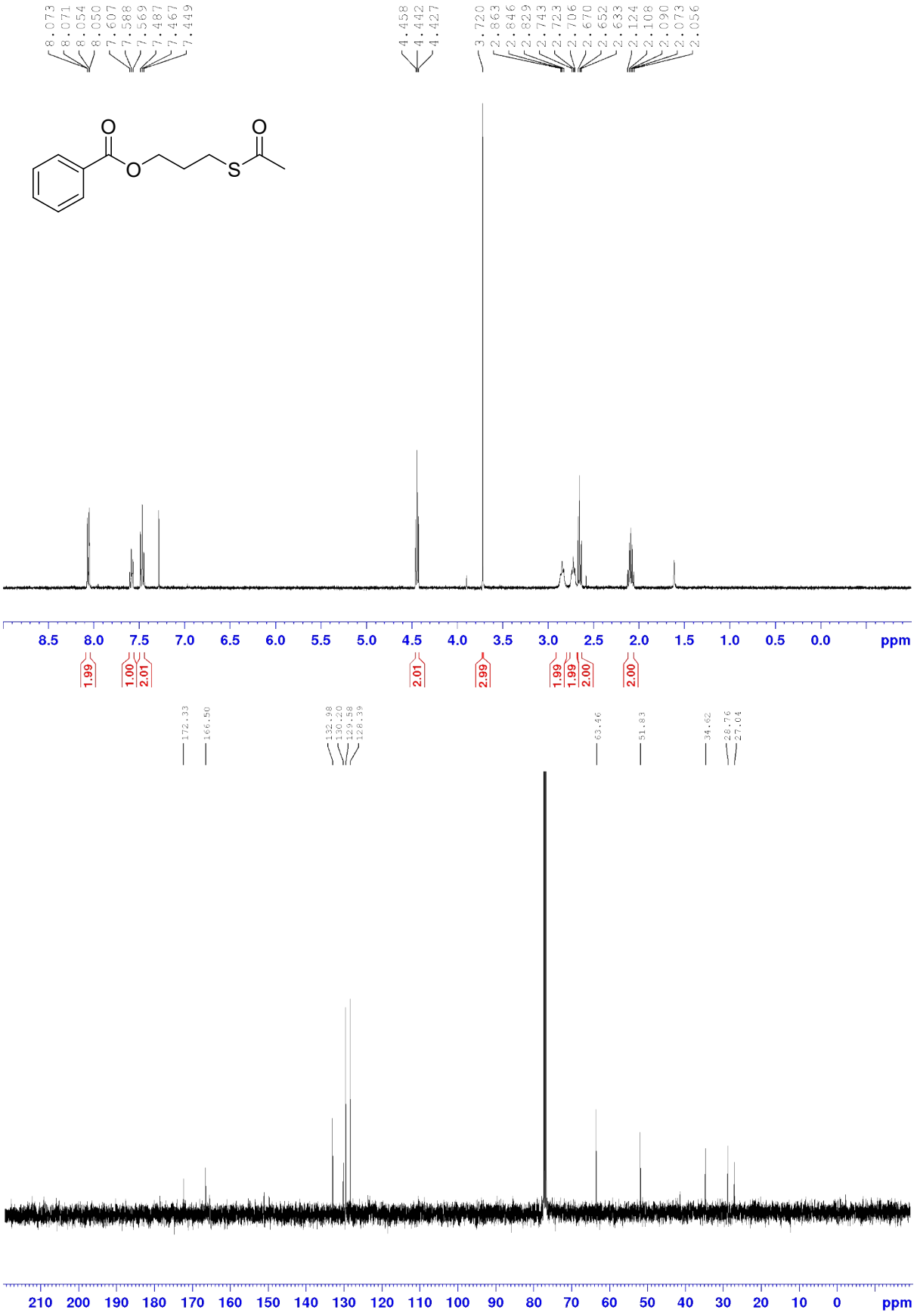
## 11. NMR Spectra for Novel Compounds

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1.99
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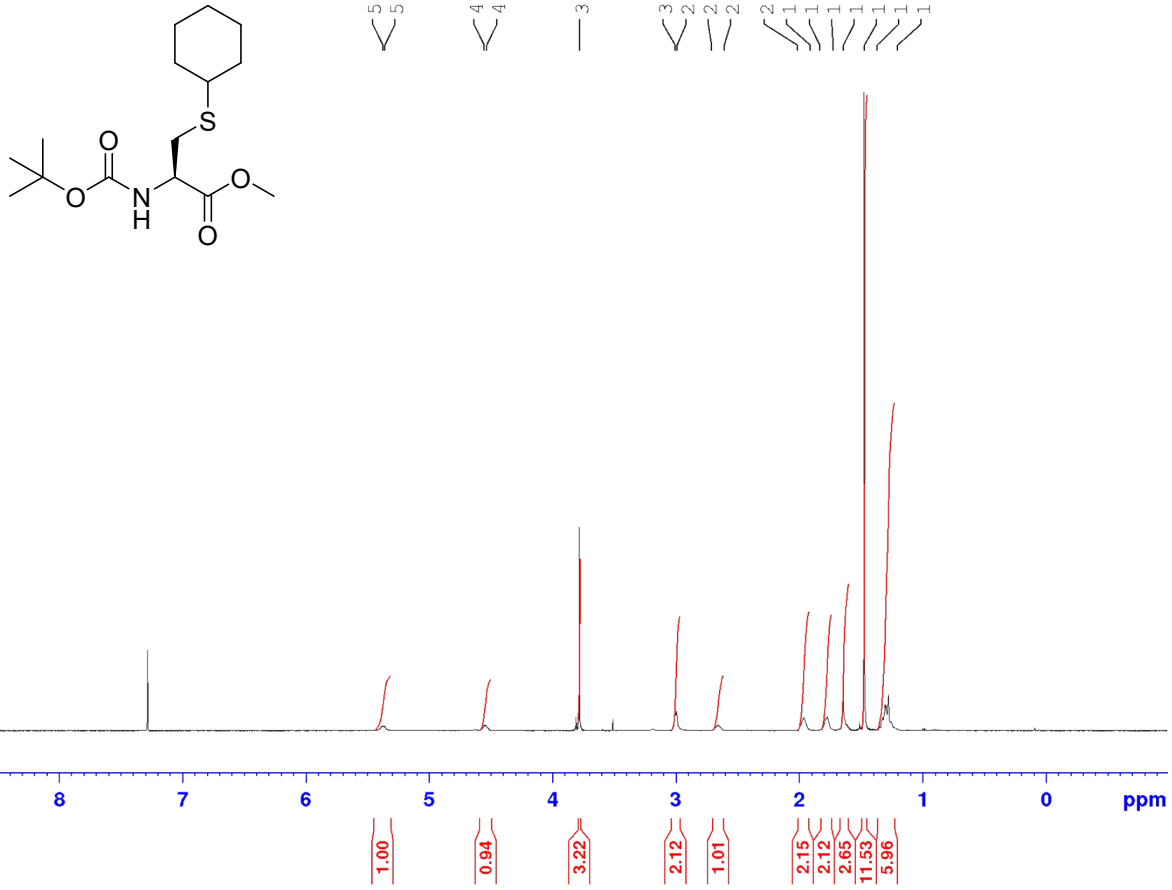
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O
O
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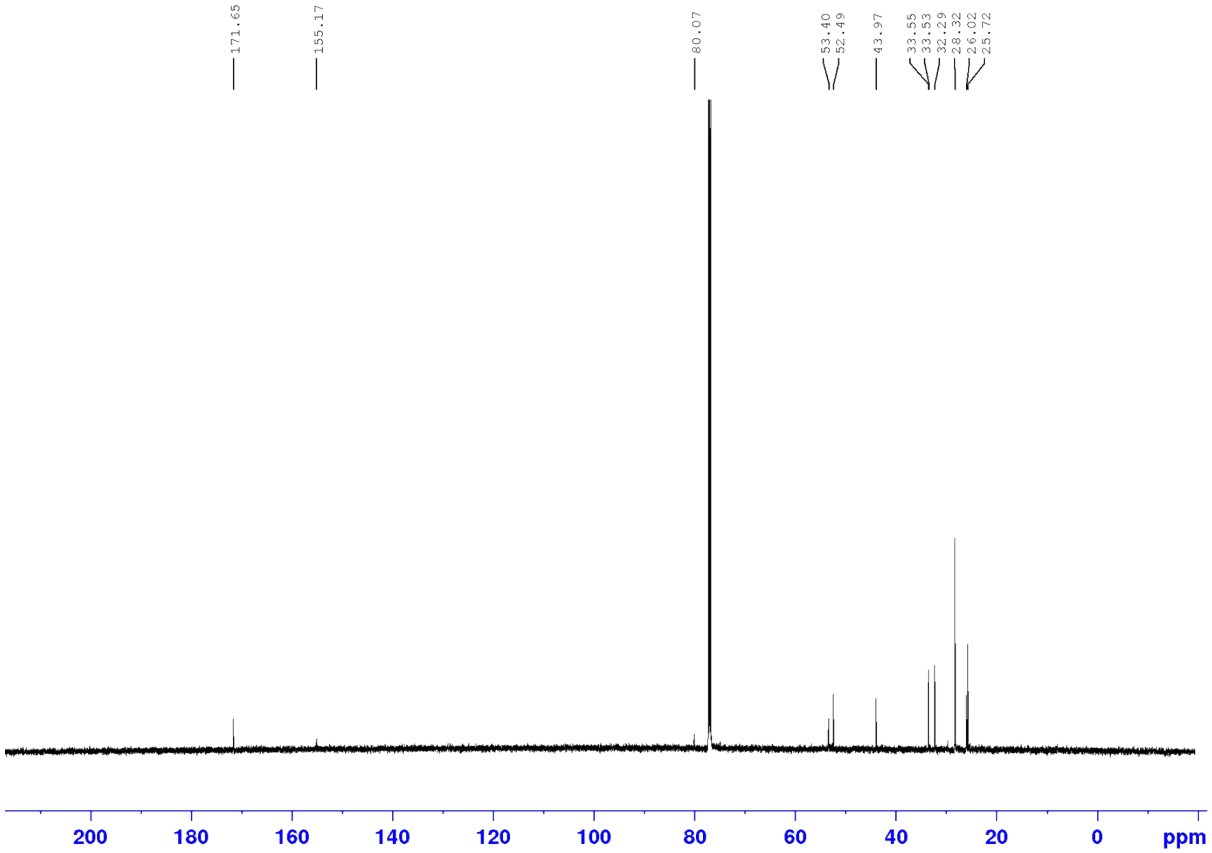
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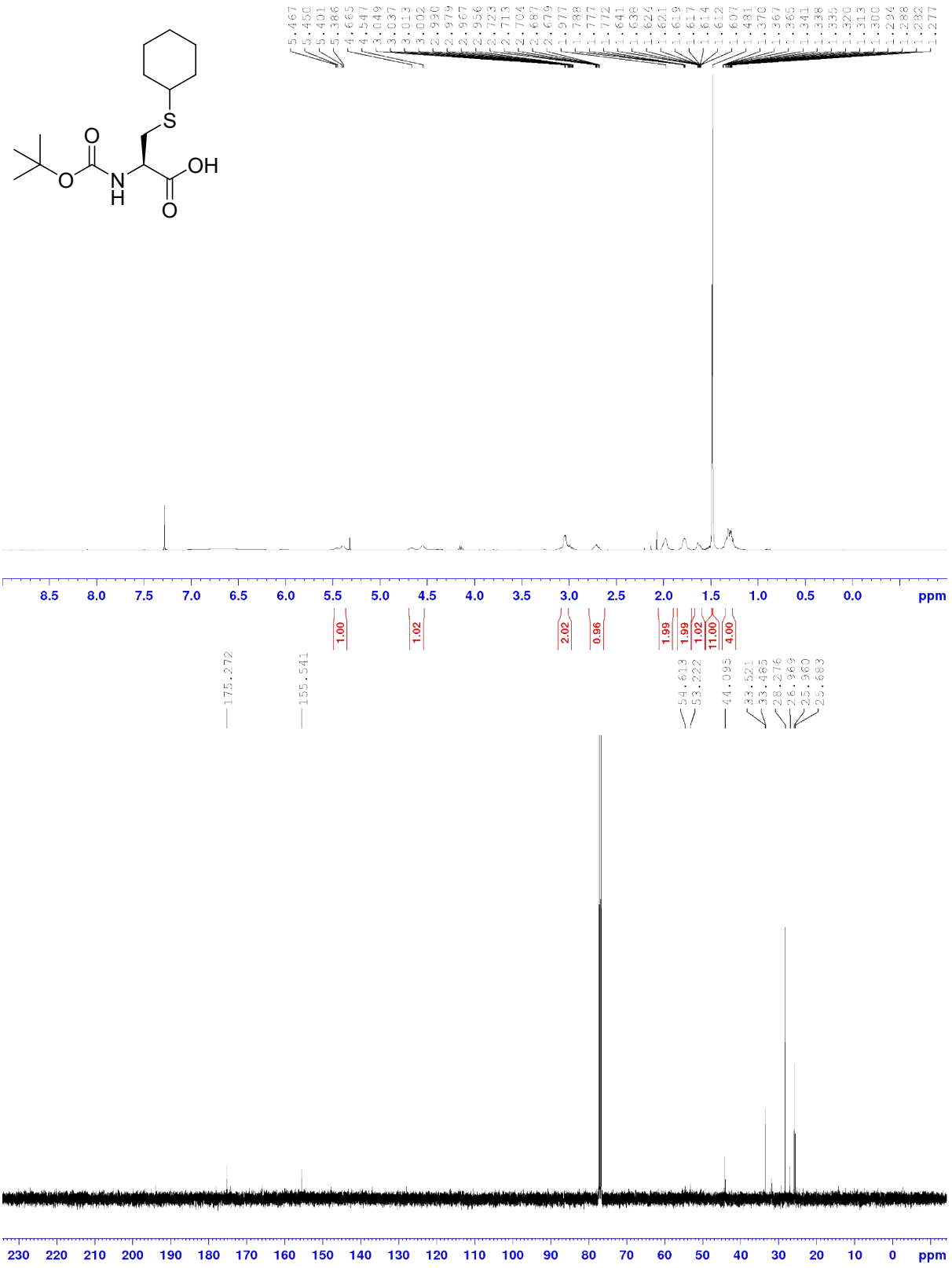
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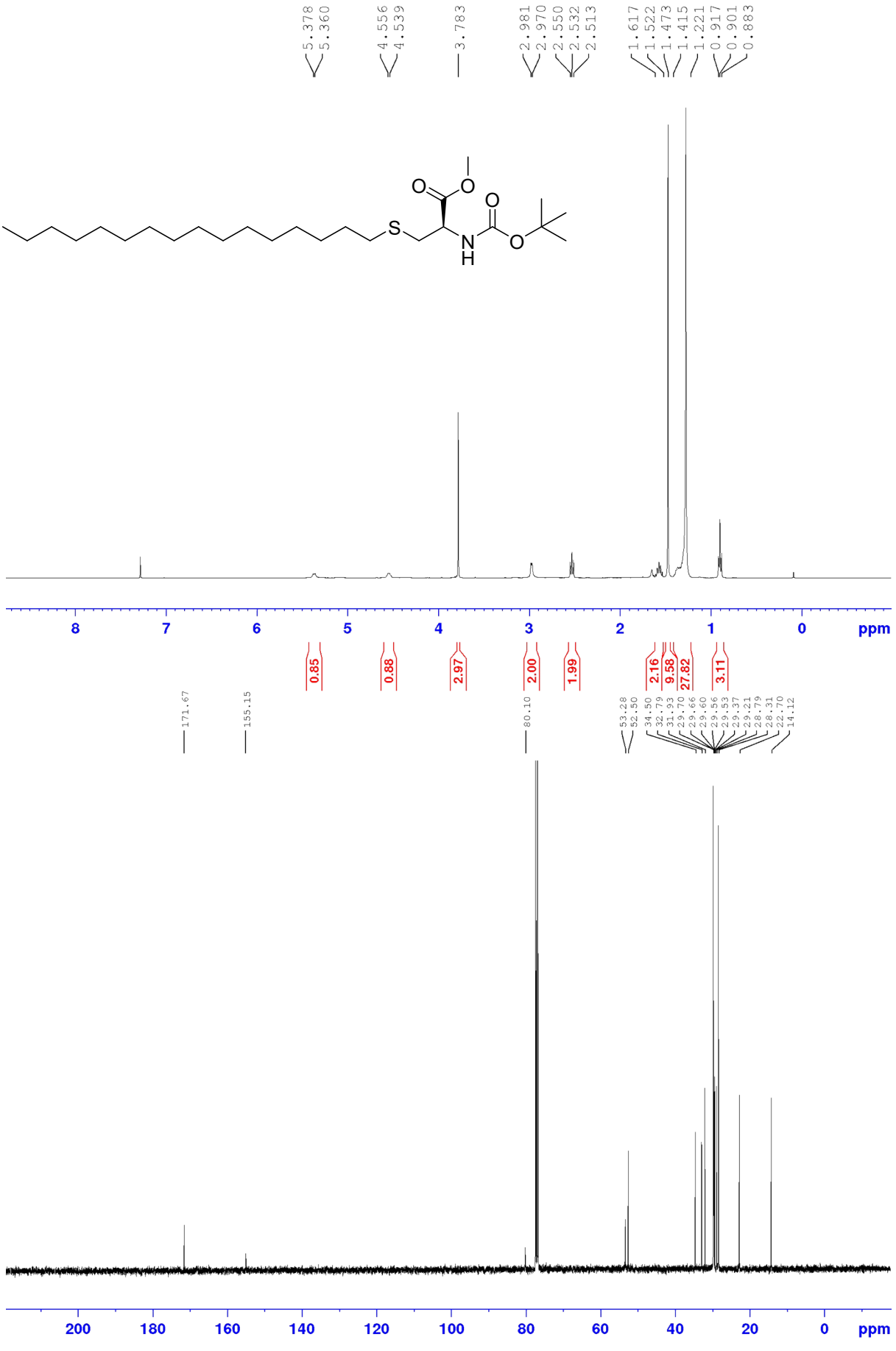
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H
O
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6
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ppm
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2.00
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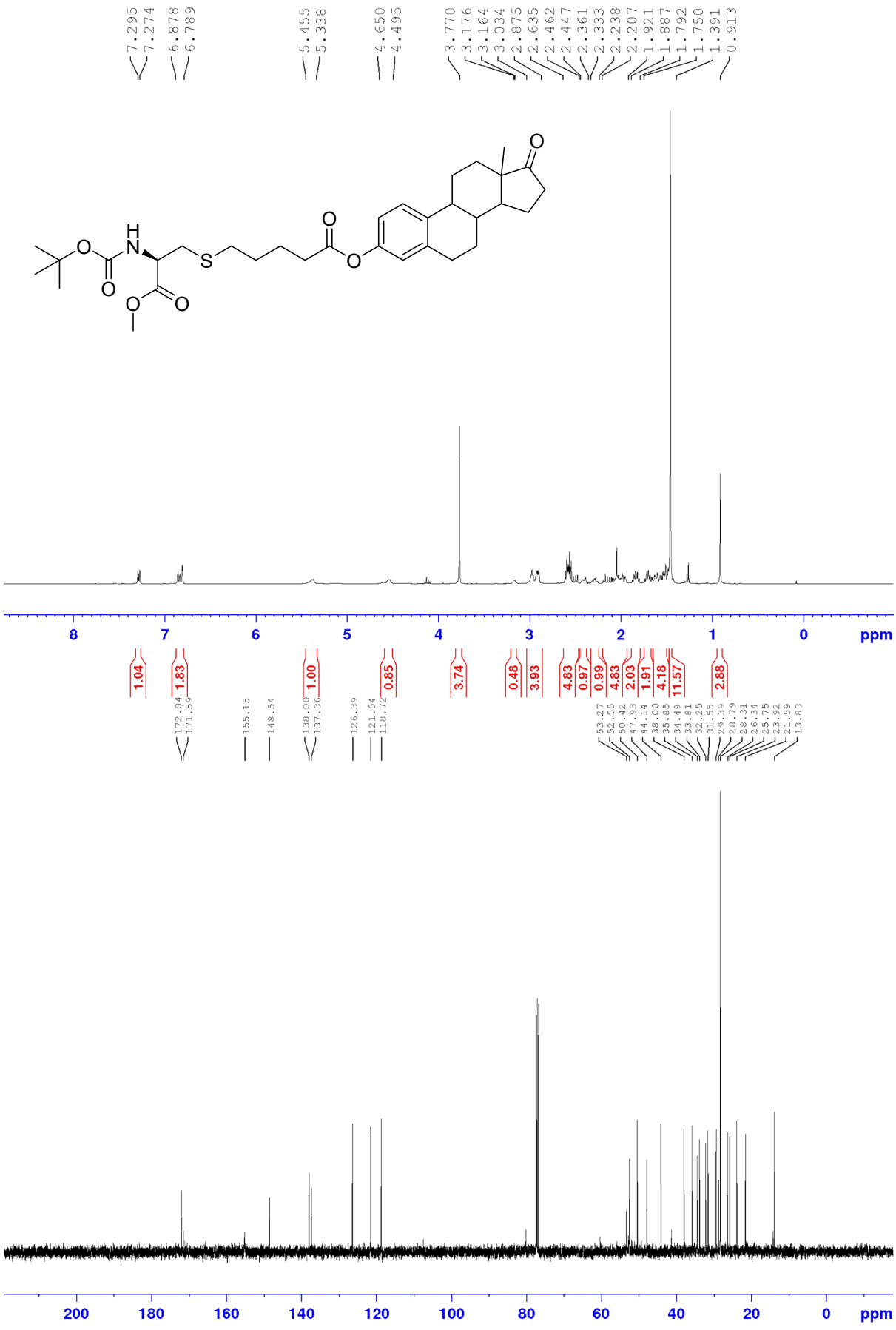
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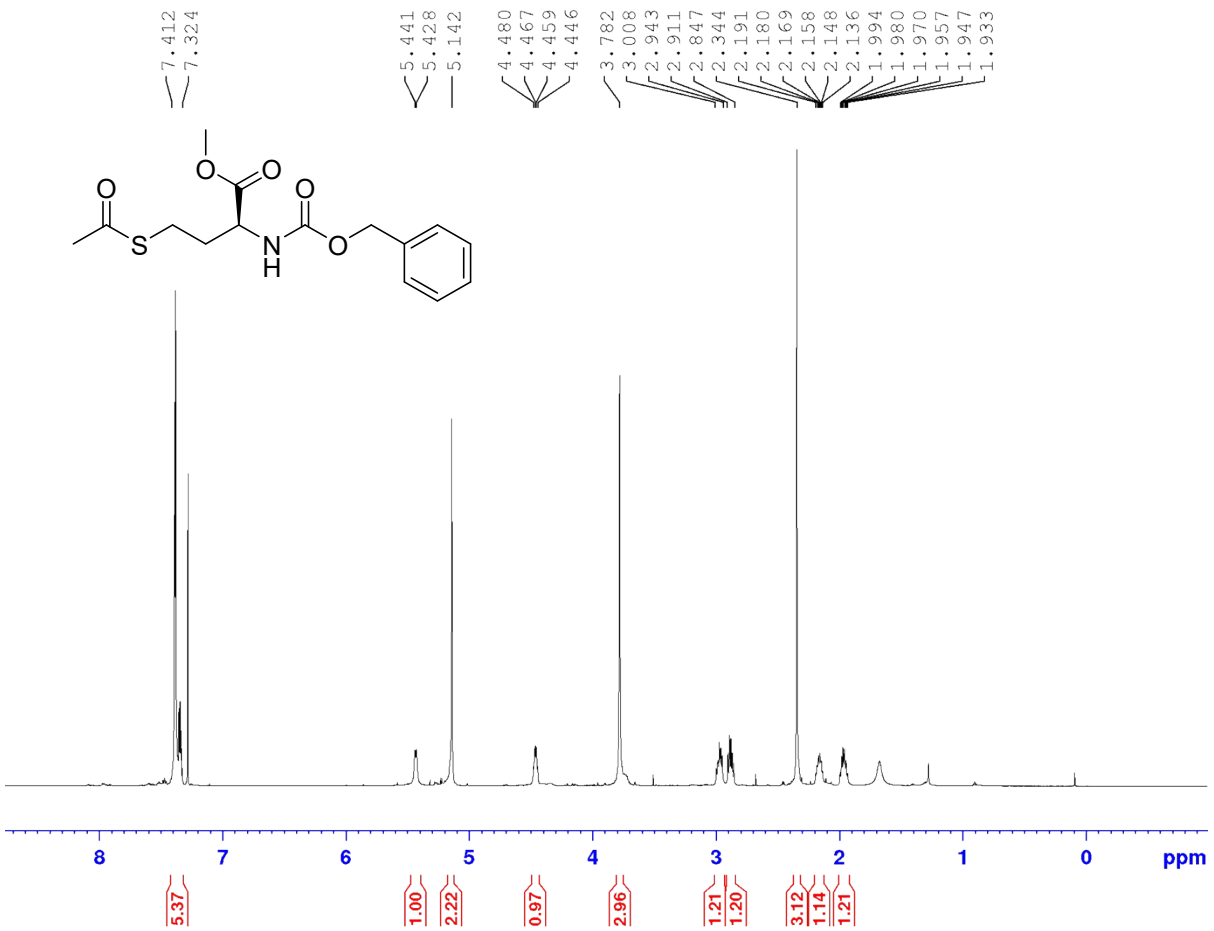
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S
N
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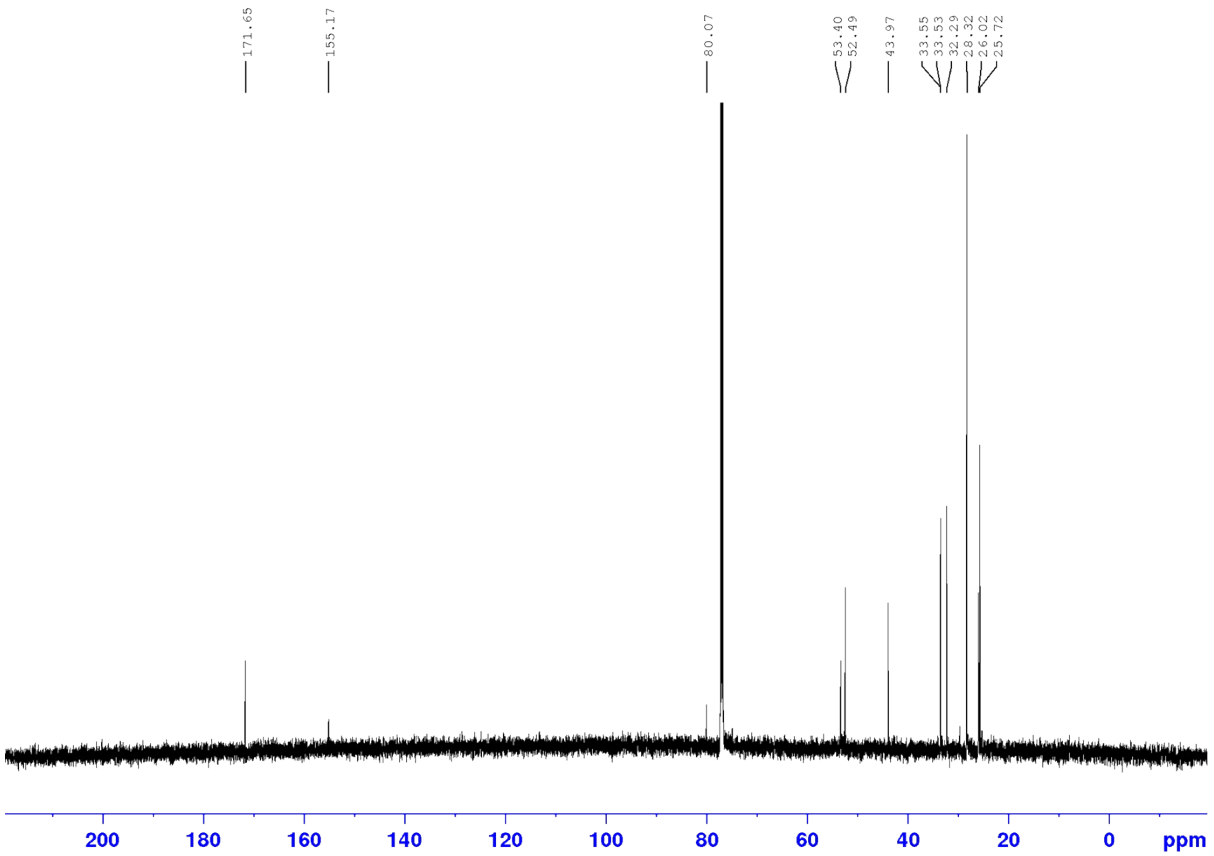
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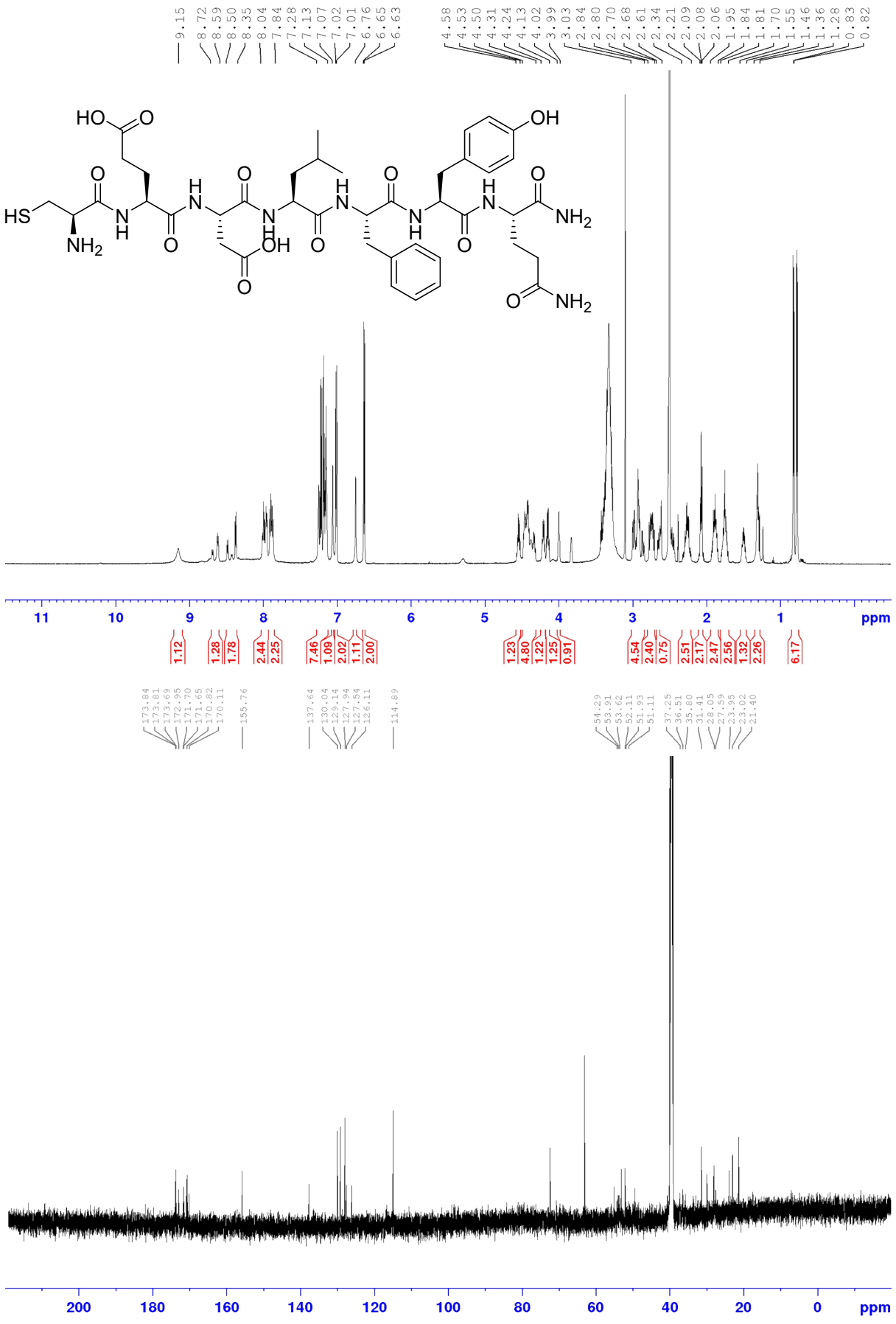
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6.63
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N
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OH
NH2
O
NH2
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9
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