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Supporting Information (SI)

Aldehyde-mediated bioconjugation via *in-situ* generated ylides

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I. General information

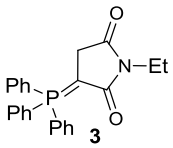
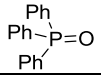
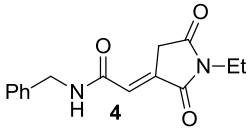
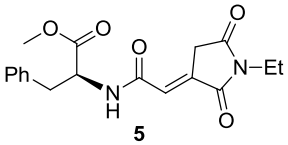
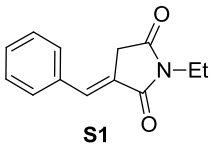
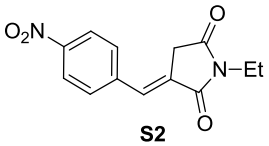
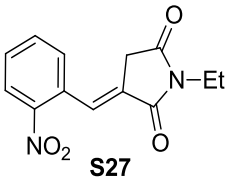
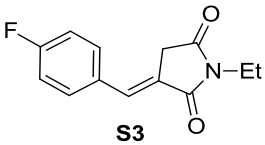
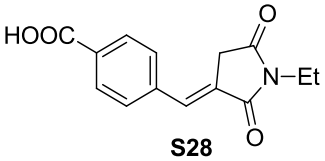
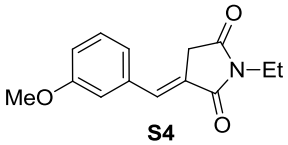
All reactions were performed in oven-dried glassware and under inert atmosphere (nitrogen or argon) unless specified. Reagents and solvents used for organic synthesis were purchased from Sigma-Aldrich, Merck, Spectrochem, Alfa Aesar, Avra or Sisco Research Laboratories (SRL) and were used without any further purification. Dichloromethane (CH_2Cl_2) and *N*,*N*-diisopropylethylamine (DIPEA) were dried and distilled over calcium hydride (CaH_2). The progress of reactions was monitored by thin-layer chromatography (TLC) using 0.25 mm Merck pre-coated (60 F254) silica gel plates. Visualization of spots on the TLC plates was performed using UV of wavelengths 254 nm (for UV active compounds) and 365 nm (for fluorescent compounds). For visualizing UV inactive compounds on TLC, staining solutions $KMnO_4$, vanillin, ninhydrin and phosphomolybdic acid (PMA) were used. Compound purification was performed using column chromatography on silica gel (100-200 mesh) and distilled solvents such as ethyl acetate (EtOAc) and hexane were used. Photo-sensitive reactions and column purification of light-sensitive compounds containing dansyl substituent were performed in dark conditions, by wrapping reaction vessels and columns with aluminum foil. Ozonolysis was performed inside an efficient fume hood using Faraday ozone L10G. Reagents for bioconjugation viz peptides (glutathione reduced (GSH), glutathione oxidized (GSSG) and TRAP6)), protein (myoglobin), pyridoxal-5′-phosphate (PLP), sodium periodate ($NaIO_4$), chemicals for buffer preparation and HPLC solvents were purchased from Sigma-Aldrich. Ultrapure Type 1 water from Millipore was used for buffer preparations and HPLC mobile phase.

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 and 500 MHz spectrometers. Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane (TMS) as internal standard and coupling constants (*J* values) in Hertz (Hz). Multiplicities are indicated as follow: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), td (triplet of doublets), dq (doublet of quartet) and m (multiplet). High-resolution mass spectra (HRMS) were recorded on Bruker microTOF QII mass spectrometer equipped with Waters Acquity UPLC system. MALDI mass spectrometry was performed on Nano-LC MALDI TOF/TOF spectrometer by using 2,6-dihydroxyacetophenone (DHAP)/diammonium hydrogen citrate (DAHC) matrix for protein and 2,5-dihydroxybenzoic acid as a matrix for small molecules. HPLC analyses were performed on Agilent 1260 Infinity LC instrument using ZorbaxODS C18 column (4.6 × 250 mm, 5 μm). The mobile phase was water-acetonitrile containing 0.1% TFA; solvent elution profile employed: first 5 min elution with 100% water followed by a linear increase to 100% acetonitrile over 30 min. The flow rate was 1 mL/min and UV absorbance was monitored at 215 nm unless specified. Circular dichroism (CD) data were acquired on a JASCO CD (J-1500) instrument.

Bacterial strains, *Escherichia coli* BL21 and *Staphylococcus aureus* were gifts from Dr. Ishu Saraogi (IISER Bhopal) and Prof. Milind Watve (IISER Pune) respectively. Bacterial cultures were grown in sterile LB media using a standard protocol. Fluorescence imaging of bacterial cells was performed with a Zeiss LSM 780 inverted confocal microscope using a 100× oil objective.

II. Supplementary tables

Table S1. Masses (MALDI/HRMS) of peaks isolated from HPLC

S. No.	Compound	Location	Expected mass	Mass obtained	Molecular formula
1	 **3**	Figure 2	388.1466	388.1474	$C_{24}H_{23}NO_2P$ $[M+H]^+$
2		Figure 2	279.0939	279.0935	$C_{18}H_{16}OP$ $[M+H]^+$
3	 **4**	Figure 2	273.1239	273.1225	$C_{15}H_{17}N_2O_3$ $[M+H]^+$
4	 **5**	Figure 2	345.1450 367.1270	345.1437 367.1265	$C_{18}H_{21}N_2O_5$ $[M+H]^+$ $C_{18}H_{20}N_2NaO_5$ $[M+Na]^+$
5	 **S1**	Figure S5	238.0844	238.0824	$C_{13}H_{13}NNaO_2$ $[M+Na]^+$
6	 **S2**	Figure S5	261.0875	261.0874	$C_{13}H_{13}N_2O_4$ $[M+H]^+$
7	 **S27**	Figure S5	261.0875	261.0906	$C_{13}H_{13}N_2O_4$ $[M+H]^+$
8	 **S3**	Figure S5	234.0930	234.0959	$C_{13}H_{13}FNO_2$ $[M+H]^+$
9	 **S28**	Figure S5	260.0923	260.0952	$C_{14}H_{14}NO_4$ $[M+H]^+$
10	 **S4**	Figure S5	246.1130	246.1155	$C_{14}H_{16}NO_3$ $[M+H]^+$

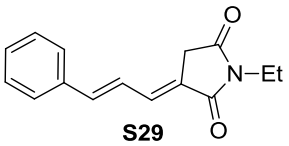
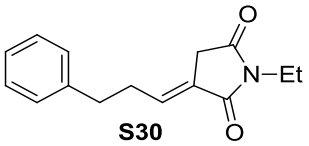
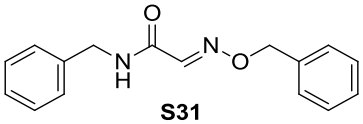
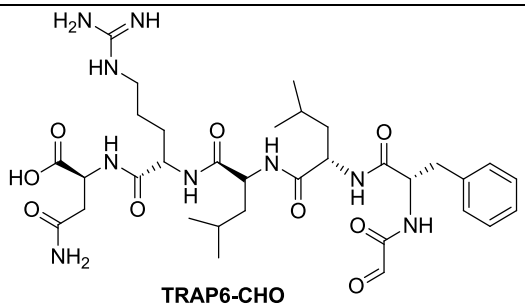
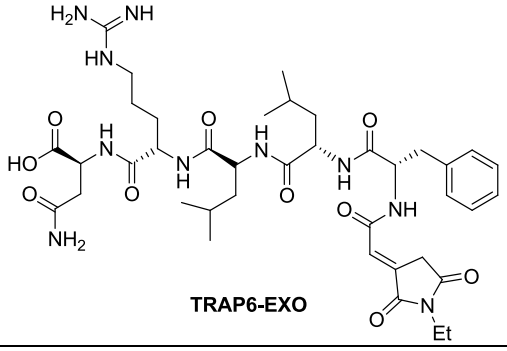
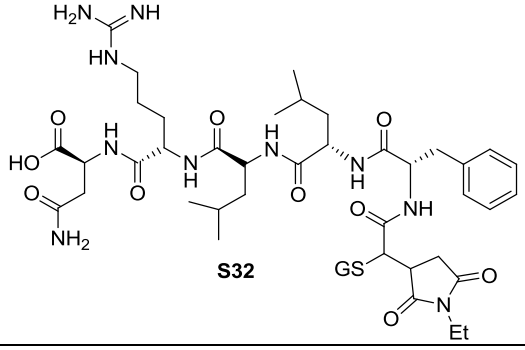
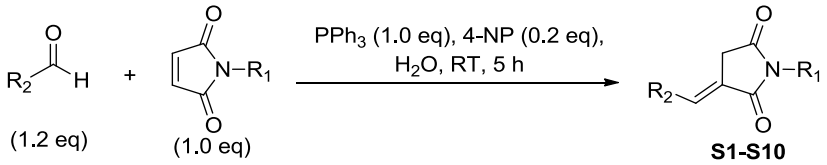
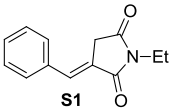
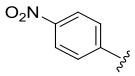
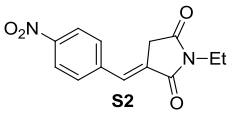
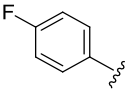
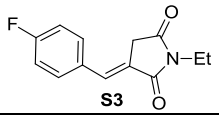
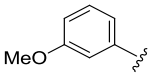
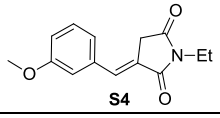
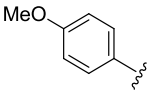
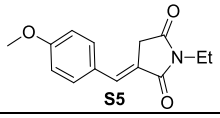
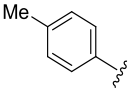
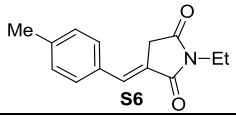
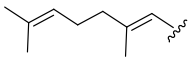
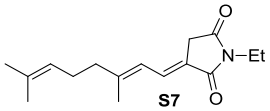
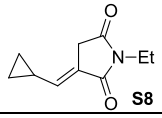
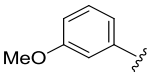
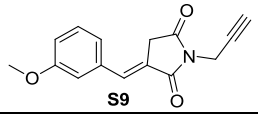
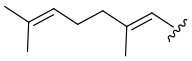
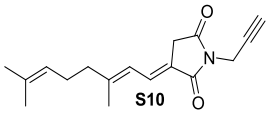
11	 **S29**	Figure S5	242.1181	242.1168	$C_{15}H_{16}NO_2$ $[M+H]^+$
12	 **S30**	Figure S5	244.1338	244.1368	$C_{15}H_{18}NO_2$ $[M+H]^+$
13	 **S31**	Figure S9	269.1290	269.1294	$C_{16}H_{17}N_2O_2$ $[M+H]^+$
14	 **TRAP6-CHO**	Figure 3	736.3994	736.3993	$C_{33}H_{54}N_9O_{10}$ $[M+H]^+$ (hydrate)
15	 **TRAP6-EXO**	Figure 3	827.4416	827.4415	$C_{39}H_{59}N_{10}O_{10}$ $[M+H]^+$
16	 **S32**	Figure S11	1134.5254	1134.5200	$C_{49}H_{76}N_{13}O_{16}S$ $[M+H]^+$

Table S2. Synthesis of exocyclic olefinic maleimides under aqueous conditions.



S No	R^1	R^2-CHO	Catalyst	Yield (%)[a]	Product
1a	Et		--	37	 S1
1b			4-nitrophenol	76	
1c			2,4-dinitrophenol	54	
1d			2,4,6-trinitrophenol	41	
2a	Et		--	25	 S2
2b			4-nitrophenol	78	
2c			2,4-dinitrophenol	53	
2d			2,4,6-trinitrophenol	66	
3a	Et		--	44 (67)[b]	 S3
3b			4-nitrophenol	71 (84)[b]	
3c			2,4-dinitrophenol	62	
3d			2,4,6-trinitrophenol	54	
4a	Et		--	47	 S4
4b			4-nitrophenol	84	
4c			2,4-dinitrophenol	64	
4d			2,4,6-trinitrophenol	64	
5a	Et		--	55	 S5
5b			4-nitrophenol	78 (84)[b]	
5c			2,4-dinitrophenol	71	
5d			2,4,6-trinitrophenol	51	
6a	Et		--	57	 S6
6b			4-nitrophenol	76	
6c			2,4-dinitrophenol	61	
6d			2,4,6-trinitrophenol	63	
7a	Et		--	66 (60)[b]	 S7
7b			4-nitrophenol	77 (71)[b]	
7c			2,4-dinitrophenol	70	
7d			2,4,6-trinitrophenol	67	
8a	Et		--	58	 S8
8b			4-nitrophenol	77	
8c			2,4-dinitrophenol	70	
8d			2,4,6-trinitrophenol	58	
9a			--	32	 S9
9b			4-nitrophenol	77	
9c			2,4-dinitrophenol	58	
9d			2,4,6-trinitrophenol	56	
10a			--	44	 S10
10b			4-nitrophenol	80	
10c			2,4-dinitrophenol	57	
10d			2,4,6-trinitrophenol	48	

[a]All yields obtained after product purification via column chromatography. [b]Reaction performed in sodium phosphate buffer (150 mM, pH 7).

General procedure: To a stirred solution of aldehyde (0.38 mmoL, 1.2 eq) and CH_3CN (0.2 mL) in water (6 mL) was added a freshly prepared CH_3CN (1.2 mL) solution containing PPh_3 (0.32 mmoL, 1.0 eq), maleimide (0.32 mmol, 1.0 eq) and 4-NP (0.064 mmol, 0.2 eq) at room temperature. After 5 h, the reaction mixture was concentrated *in vacuo* on rotary evaporator to remove CH_3CN and the aqueous solution was extracted with CH_2Cl_2 (2 × 8 mL). The organic layers were

combined, dried (anhyd. Na_2SO_4) and concentrated *in vacuo* and the crude mixture was purified on silica gel chromatography using EtOAc/hexane as a solvent system to yield desired exocyclic olefinic maleimides.

(*E*)-3-benzylidene-1-ethylpyrrolidine-2,5-ione (S1): R_f 0.6 in EtOAc/hexane 1:4, white solid, eluent for column chromatography EtOAc/hexane 1:9. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (t, *J* = 2.4 Hz, 1H), 7.53 – 7.41 (m, 5H), 3.71 (q, *J* = 7.3 Hz, 2H), 3.58 (d, *J* = 2.3 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 170.8, 134.1, 134.1, 130.1, 130.1, 129.1, 123.6, 34.1, 33.8, 13.2. HRMS (TOF MS ES+) *m/z* calcd. for $C_{13}H_{14}NO_2$ $[M+H]^+$ 216.1025 and found 216.1026.

(*E*)-1-ethyl-3-(4-nitrobenzylidene)pyrrolidine-2,5-dione (S2)[1]: R_f 0.3 in EtOAc/hexane 1:4, white solid, eluent for column chromatography EtOAc/hexane 3:17. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 2.6 Hz, 2H), 7.66 (s, 1H), 3.74 (q, *J* = 7.2 Hz, 2H), 3.62 (d, *J* = 2.5 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H).

(*E*)-1-ethyl-3-(4-fluorobenzylidene)pyrrolidine-2,5-dione (S3): R_f 0.45 in EtOAc/hexane 1:4, white solid, eluent for column chromatography EtOAc/hexane 1:9. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (t, *J* = 2.4 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.18 – 7.12 (m, 2H), 3.70 (q, *J* = 7.3 Hz, 2H), 3.53 (d, *J* = 2.4 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 170.7, 164.7, 162.2, 132.7, 132.0, 130.4, 123.2, 116.3, 33.8, 13.1; HRMS (TOF MS ES+) *m/z* calcd. for $C_{13}H_{13}FNO_2$ $[M+H]^+$ 234.0930 and found 234.0930.

(*E*)-1-ethyl-3-(3-methoxybenzylidene)pyrrolidine-2,5-dione (S4): R_f 0.5 in EtOAc/hexane 1:4, white solid, eluted for column chromatography EtOAc/hexane 1:9. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (t, *J* = 2.4 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.08 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.00 – 6.94 (m, 2H), 3.84 (s, 3H), 3.69 (q, *J* = 7.2 Hz, 2H), 3.54 (d, *J* = 2.5 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 170.7, 159.8, 135.4, 133.9, 130.0, 123.9, 122.5, 115.6, 115.4, 55.3, 34.0, 33.8, 13.1. HRMS (TOF MS ES+) *m/z* calcd. for $C_{14}H_{16}NO_3$ $[M+H]^+$ 246.1130 and found 246.1134.

(*E*)-1-ethyl-3-(4-methoxybenzylidene)pyrrolidine-2,5-dione (S5): R_f 0.3 in EtOAc/hexane 1:4, white solid, eluent for column chromatography EtOAc/ hexane 1:9. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (t, *J* = 2.4 Hz, 1H), 7.50 – 7.39 (m, 2H), 7.00 – 6.94 (m, 2H), 3.86 (s, 3H), 3.68 (q, *J* = 7.2 Hz, 2H), 3.51 (d, *J* = 2.4 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 171.1, 161.0, 133.7, 131.9, 126.8, 120.8, 114.6, 55.4, 34.0, 33.7, 13.2. HRMS (TOF MS ES+) *m/z* calcd. for $C_{14}H_{16}NO_3$ $[M+H]^+$ 246.1130 and found 246.1133.

(*E*)-1-ethyl-3-(4-methylbenzylidene)pyrrolidine-2,5-dione (S6): R_f 0.45 in EtOAc/hexane 1:4, white solid, eluent for column chromatography EtOAc/hexane 1:9. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (t, *J* = 2.4 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 3.69 (q, *J* = 7.2 Hz, 2H), 3.54 (d, *J* = 2.4 Hz, 2H), 2.40 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 171.0, 140.6, 134.0, 131.4, 130.1, 129.8, 122.4, 34.1, 33.7, 21.4, 13.1. HRMS (TOF MS ES+) *m/z* calcd. for $C_{14}H_{16}NO_2$ $[M+H]^+$ 230.1181 and found 230.1185.

(*E*)-3-((*E*)-3,7-dimethylocta-2,6-dien-1-ylidene)-1-ethylpyrrolidine-2,5-dione (S7)[1]: R_f 0.55 in EtOAc/hexane 1:4, white solid, eluent for column chromatography EtOAc/hexane 2:23. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (ddt, *J* = 12.6, 8.2, 2.3 Hz, 1H), 5.96 – 5.84 (m, 1H), 5.10 (dddd, *J* = 13.8, 6.8, 3.7, 1.6 Hz, 1H), 3.65 (q, *J* = 7.1 Hz, 2H), 3.28 (d, *J* = 2.2

Hz, 2H), 2.39 – 2.08 (m, 4H), 1.96 (d, *J* = 1.3 Hz, 3H), 1.70 (d, *J* = 1.5 Hz, 3H), 1.63 (d, *J* = 1.3 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H).

(*E*)-3-(cyclopropylmethylene)-1-ethylpyrrolidine-2,5-dione (S8): R_f 0.5 in EtOAc/hexane 1:4, colorless liquid, eluent for column chromatography EtOAc/ hexane 2:23. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.64 (q, *J* = 7.2 Hz, 2H), 3.33 (d, *J* = 2.2 Hz, 2H), 1.47 (dt, *J* = 7.8, 3.9 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.07 (dd, *J* = 4.6, 4.2 Hz, 2H), 0.75 (dd, *J* = 4.5, 2.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 169.7, 143.3, 122.8, 33.4, 32.1, 13.1, 12.8, 9.0; HRMS (TOF MS ES+) *m/z* calcd. for $C_{10}H_{14}NO_2$ $[M+H]^+$ 180.1025 and found 180.1029.

(*E*)-3-(3-methoxybenzylidene)-1-(prop-2-yn-1-yl)pyrrolidine-2,5-dione (S9): R_f 0.3 in EtOAc/hexane 1:4, white solid, eluent for column chromatography EtOAc/hexane 1:9. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (t, *J* = 2.4 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.05 – 6.98 (m, 2H), 4.43 (d, *J* = 2.6 Hz, 2H), 3.87 (s, 3H), 3.65 (d, *J* = 2.4 Hz, 2H), 2.24 (t, *J* = 2.5 Hz, 1H), 1.28 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 169.5, 159.9, 135.1, 130.1, 123.1, 122.6, 118.4, 115.9, 115.6, 71.5, 55.3, 34.1, 28.8, 27.8. HRMS (TOF MS ES+) *m/z* calcd. for $C_{15}H_{14}NO_3$ $[M+H]^+$ 256.0974 and found 256.0974.

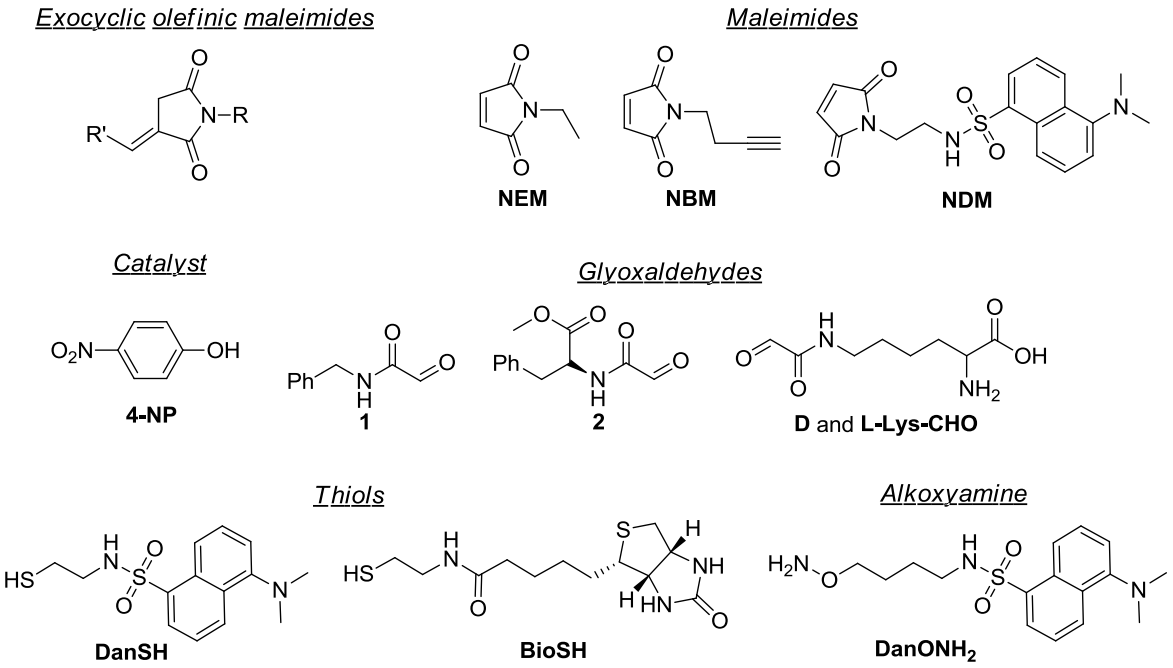
(*E*)-3-((*E*)-3,7-dimethylocta-2,6-dien-1-ylidene)-1-(prop-2-yn-1-yl)pyrrolidine-2,5-dione (S10): R_f 0.4 in EtOAc/hexane 1:4, white solid, eluent for column chromatography EtOAc/hexane 1:9. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (ddt, *J* = 11.7, 7.1, 2.3 Hz, 1H), 5.91 (dtd, *J* = 12.1, 2.8, 1.4 Hz, 1H), 5.17 – 5.00 (m, 1H), 4.36 (d, *J* = 2.5 Hz, 2H), 3.34 (d, *J* = 2.2 Hz, 2H), 2.38 (t, *J* = 7.7 Hz, 1H), 2.27 – 2.14 (m, 4H), 1.97 (d, *J* = 1.2 Hz, 3H), 1.70 (dd, *J* = 4.6, 1.4 Hz, 3H), 1.63 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 169.5, 153.9, 153.7, 131.1, 130.8, 123.0, 121.1, 120.3, 71.2, 40.6, 33.0, 32.3, 27.6, 26.9, 26.3, 25.7, 24.9, 17.7. HRMS (TOF MS ES+) *m/z* calcd. for $C_{17}H_{22}NO_2$ $[M+H]^+$ 272.1651 and found 272.1653.

(*E*)-*N*-benzyl-2-(1-ethyl-2,5-dioxopyrrolidin-3-ylidene)acetamide (4): Following the procedure described, aldehyde **1** (90 mg, 0.55 mmol), NEM (56 mg, 0.46 mmol), PPh_3 (121 mg, 0.46 mmol) and 4-NP (13 mg, 0.091 mmol) afforded compound **4** (0.11 g, 84%). R_f 0.35 in EtOAc/hexane 1:4, off-white solid, eluent for column chromatography EtOAc/hexane 1:4. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 7.25 – 7.20 (m, 3H), 6.79 (t, *J* = 2.5 Hz, 1H), 6.60 (t, *J* = 5.8 Hz, 1H), 4.45 (d, *J* = 5.7 Hz, 2H), 3.70 (d, *J* = 2.6 Hz, 2H), 3.49 (q, *J* = 7.2 Hz, 2H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 169.7, 163.6, 137.5, 137.3, 128.8, 127.8, 127.8, 123.7, 43.9, 34.2, 33.9, 13.0; HRMS (TOF MS ES+) m/z calcd. for $C_{15}H_{17}N_2O_3$ $[M+H]^+$ 273.1239 and found 273.1239.

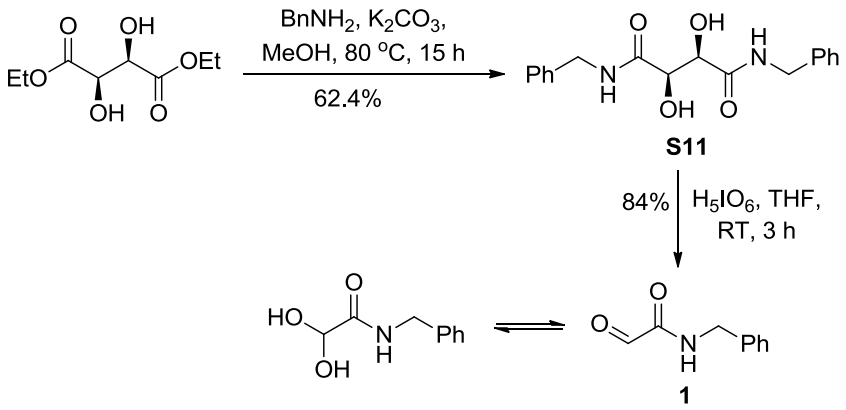
(*R*,*E*)-methyl2-(2-(1-ethyl-2,5-dioxopyrrolidin-3-ylidene)acetamido)-3-phenylpropanoate (5): Following the procedure described, aldehyde **2** (0.148 g, 0.63 mmol), NEM (66 mg, 0.52 mmol), PPh_3 (0.137 g, 0.52 mmol) and 4-NP (15 mg, 0.1 mmol) afforded compound **5** (0.109 g, 61%). R_f 0.5 in EtOAc/hexane 1:1, off-white solid, eluent for column chromatography (EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 3H), 7.16 – 7.07 (m, 2H), 6.82 (t, *J* = 2.6 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 4.97 (dt, *J* = 8.0, 5.9 Hz, 1H), 3.77 (s, 3H), 3.72 (d, *J* = 2.5 Hz, 2H), 3.67 (q, *J* = 7.2 Hz, 2H), 3.26 – 3.09 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 171.7, 169.6, 163.4, 138.1, 135.5, 129.3, 128.8, 127.4, 123.3, 53.4, 52.7, 37.9, 34.3, 34.0, 13.1. HRMS (QTOF MS ESI+) *m/z* calcd. for $C_{18}H_{20}NaN_2O_5[M+Na]^+$ 367.1270 and found 367.1264.

III. Synthetic schemes and procedures (Schemes S1-S8)

Structure of compounds described in the main article



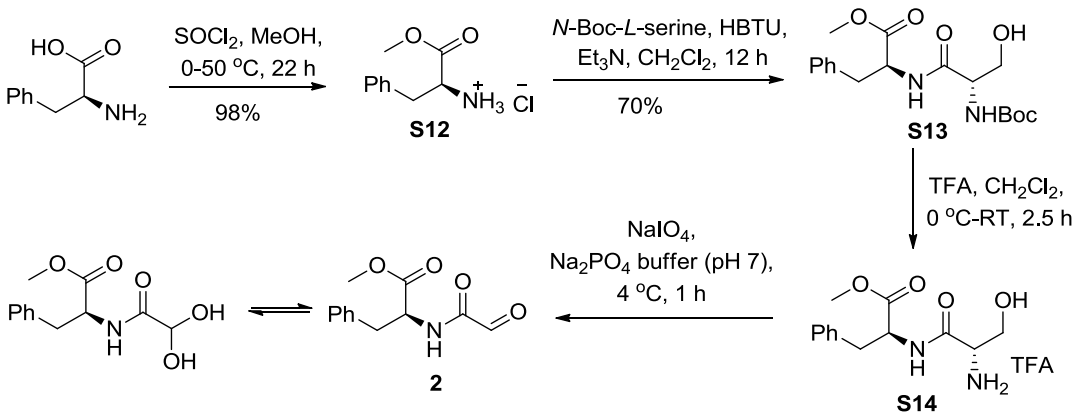
Scheme S1. Synthesis of glyoxaldehyde **1**



(2*R*,3*R*)-*N*^{1},*N*^{4}-dibenzyl-2,3-dihydroxysuccinamide (S11)[2]: To a stirred suspension of (+)-diethyl *L*-tartrate (12 mL, 69.8 mmoL) in MeOH (160 mL) was added benzylamine (12.5 mL, 114.3 mmoL) followed by the addition of anhydrous K_2CO_3 (1.34 g, 9.7 mmoL) at room temperature under nitrogen atmosphere. The reaction mixture was slowly heated and refluxed for 15 h. Upon cooling the reaction mixture, white crystalline solid appeared which was filtered, and the resultant solid was washed thoroughly with cold water. Recrystallization of the crude solid with ethanol:water (1:1, 4 mL) gave analytically pure **S11** as white crystalline solid (14.3 g, 62.4%, R_f 0.1 in 100% EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (t, *J* = 6.4 Hz, 2H), 7.34 – 7.28 (m, 8H), 7.27 – 7.20 (m, 2H), 5.77 – 5.72 (m, 2H), 4.42 – 4.30 (m, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.6, 139.9, 128.5, 127.6, 127.5, 127.0, 73.2, 42.3; HRMS (QTOF MS ESI+) *m/z* calcd. for $C_{18}H_{20}NaN_2O_4$ $[M+Na]^+$ 351.1321 and found 351.1315.

***N*-benzyl-2-oxoacetamide (1)[3]:** To a stirred suspension of compound **S11** (1 g, 3.05 mmoL) in THF (20 mL) was added periodic acid (0.834 g, 3.66 mmoL) at room temperature under argon atmosphere in dark. After 3 h, the reaction mixture centrifuged, and the clear pale color supernatant was decanted from the white inorganic precipitate. Concentration of the supernatant *in vacuo* on rotary evaporator at room temperature gave the crude mixture that was purified on silica gel column chromatography (EtOAc/hexane 1:1) to give a mixture of aldehyde **1** as clear gummy liquid (0.42 g, 84.5 %, R_f 0.45 in EtOAc/hexane 1:1). Compound **1** was stored at -30 ^oC and was used within a week. ^1H NMR (500 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.41 – 7.29 (m, 6H), 4.55 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 188.2, 159.7, 136.5, 128.9, 128.0, 127.9, 43.3; HRMS (QTOF MS ESI+) *m/z* calcd. for $C_{18}H_{20}NaN_2O_4$ $[M+Na]^+$ 351.1321 and found 351.1315.

Scheme S2. Synthesis of glyoxaldehyde **2**



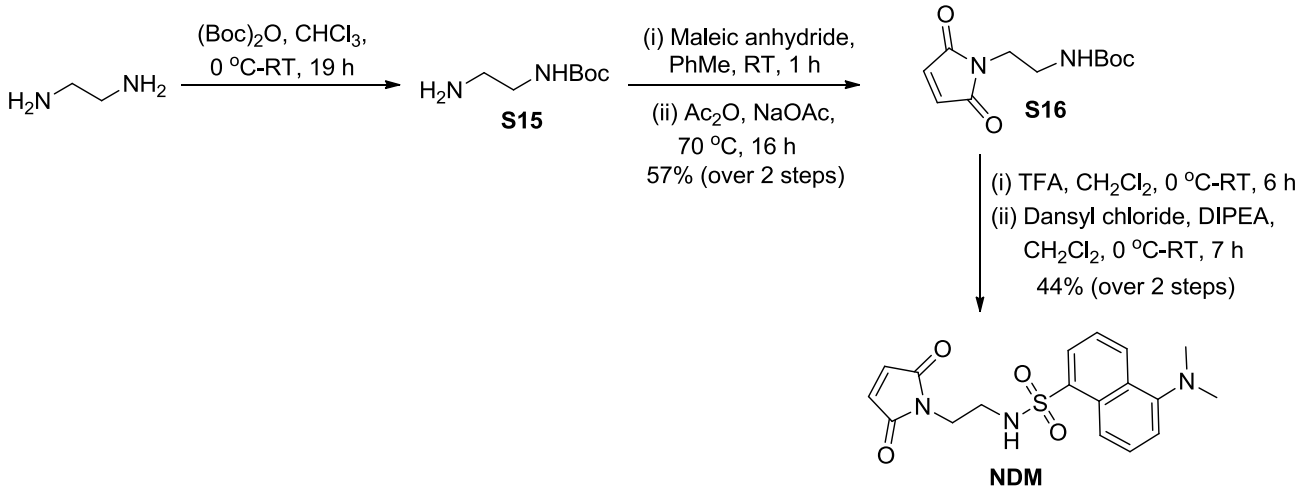
(*S*)-methyl 2-amino-3-phenylpropanoate. HCl (S12): To a stirred solution of *L*-phenylalanine (2.5 g, 15.2 mmoL) in methanol (38 mL) was added dropwise thionyl chloride (3.64 mL) at 0 ^oC under nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and then slowly heated to 50 ^oC. After 22 h, the reaction mixture was concentrated *in vacuo* on rotary evaporator and the resultant crude was washed with diethyl ether (3 × 20 mL) to yield analytically pure **S12** as white solid (3.2 g, 98%, R_f 0.55 in 100% EtOAc). ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.26 – 7.21 (m, 1H), 7.21 – 7.16 (m, 2H), 3.73 (dd, *J* = 8.0, 5.2 Hz, 1H), 3.71 (s, 3H), 3.09 (dd, *J* = 13.5, 5.2 Hz, 1H), 2.85 (dd, *J* = 13.5, 7.9 Hz, 1H), 1.53 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 137.2, 129.3, 128.6, 126.8, 55.8, 52.0, 41.1; HRMS (QTOF MS ESI+) *m/z* calcd. for $C_{10}H_{14}NO_2$ $[M+H]^+$ 180.1025; found 180.1028.

(*S*)-methyl 2-((*S*)-2-((tert-butoxycarbonyl)amino)-3-hydroxypropanamido)-3-phenylpropanoate (S13): To a stirred solution of compound **S12** (1.71 g, 7.94 mmoL) in anhydrous CH_2Cl_2 (30 mL) was added *N*-Boc-*L*-serine (1.94 g, 9.53 mmol), Et_3N (2.21 mL, 15.9 mmoL) and HBTU (3.61 g, 9.52 mmoL) at room temperature under argon atmosphere. After 12 h, the reaction mixture was concentrated *in vacuo* on rotary evaporator. The crude mixture was re-dissolved in EtOAc (20 mL) and was sequentially washed with saturated citric acid (20 mL) and saturated sodium bicarbonate (20 mL). The organic layer was finally washed with brine (20 mL), separated, dried (anhyd. Na_2SO_4), filtered and concentrated *in vacuo* on rotary evaporator to give yellow sticky liquid. Purification of crude mixture by column chromatography (EtOAc/hexane 1:1) on silica gel gave compound **S13** (2.05 g, 70.4%, R_f 0.7 in 100% EtOAc) as clear sticky liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 3H), 7.15 – 7.10 (m, 2H), 6.95 (d, *J* = 8.1 Hz, 1H), 5.52 – 5.36 (m, 1H), 4.85

(q, *J* = 6.8 Hz, 1H), 4.14 (d, *J* = 8.6 Hz, 1H), 4.01 (d, *J* = 11.3 Hz, 1H), 3.74 (s, 3H), 3.68 – 3.52 (m, 1H), 3.18 (dd, *J* = 14.0, 5.5 Hz, 1H), 3.05 (dd, *J* = 14.0, 6.9 Hz, 1H), 2.87 (s, 1H), 1.73 (s, 1H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 171.1, 135.7, 129.2, 128.7, 127.2, 77.2, 63.0, 54.9, 53.4, 52.5, 37.7, 28.3; HRMS (QTOF MS ESI+) *m/z* calcd. for $C_{18}H_{26}N_2NaO_6$ $[M+Na]^+$ 389.1689; found 389.1695.

(*S*)-methyl 2-(2-oxoacetamido)-3-phenylpropanoate (2): To a cooled (0 °C) and stirred solution of compound **S13** (1.026 g, 2.81 mmoL) in anhydrous CH_2Cl_2 (2 mL) was added 20% TFA solution in CH_2Cl_2 (8.0 mL) under argon atmosphere. The reaction mixture was allowed to warm to room temperature. After 2.5 h, the reaction mixture was concentrated *in vacuo* on rotary evaporator and the crude mixture was further rotavaped with toluene (50 mL) to remove excess TFA to give analytically pure compound **S14** (R_f 0.2 in 100% EtOAc) as thick liquid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.32 – 7.26 (m, 2H), 7.22 (td, *J* = 6.5, 1.6 Hz, 3H), 4.74 (dd, *J* = 8.7, 5.5 Hz, 1H), 3.94 (dd, *J* = 11.1, 4.2 Hz, 1H), 3.89 (dd, *J* = 6.7, 4.2 Hz, 1H), 3.77 (dd, *J* = 11.1, 6.7 Hz, 1H), 3.71 (s, 3H), 3.21 (dd, *J* = 14.0, 5.5 Hz, 1H), 3.02 (dd, *J* = 14.0, 8.8 Hz, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ 171.6, 166.8, 136.5, 128.8, 128.2, 126.6, 60.3, 54.7, 54.1, 51.5, 36.8. The crude **S14** was dissolved in sodium phosphate buffer (10 mL, 250 mM, pH 7) and the pH was adjusted to 7 by adding more buffer, if required. To this was added $NaIO_4$ (1.2 g, 5.62 mmoL) and the reaction mixture was stirred at room temperature under argon atmosphere in dark. After 60 min, the reaction mixture was extracted with EtOAc (2 ×15 mL). The combined organic layers were washed with brine (10 mL), separated, dried (anhyd. Na_2SO_4) and concentrated *in vacuo* on rotary evaporator. Purification of crude mixture by column chromatography (EtOAc/hexane 2:3) on silica gel to give compound **2** as its hydrate (0.42 g, 63.5% (over two steps), R_f 0.3 in EtOAc/hexane 3:2) as clear sticky liquid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.21 – 7.06 (m, 5H), 4.71 (d, *J* = 5.3 Hz, 1H), 4.61 (ddd, *J* = 10.1, 8.0, 5.6 Hz, 1H), 3.60 (d, *J* = 3.2 Hz, 3H), 3.24 (d, *J* = 3.9 Hz, 1H), 3.08 (dt, *J* = 13.9, 5.8 Hz, 1H), 2.96 (ddd, *J* = 13.7, 8.0, 5.2 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 171.6, 170.0, 136.5, 129.0, 128.2, 126.7, 93.6, 53.4, 51.5, 36.9. HRMS (QTOF MS ESI+) *m/z* calcd. for $C_{12}H_{14}NO_4$ $[M+H]^+$ 236.0923 and found 236.0917.

Scheme S3. Synthesis of *N*-dansylmaleimide (**NDM**)

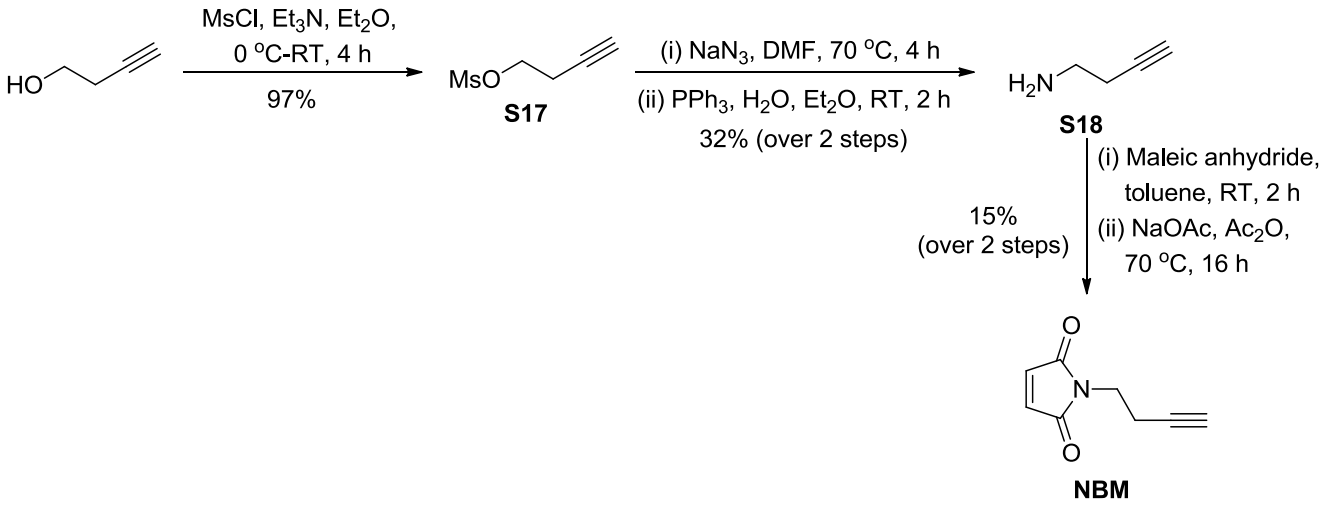


***tert*-butyl (2-aminoethyl)carbamate (S15)[4]:** To a stirred solution of 1,2-diaminoethane (6.0 mL, 89.6 mmoL) in $CHCl_3$ (30 mL) was added a solution of *di-tert*-butyl-bicarbonate (2.06 mL, 8.96 mmoL) in $CHCl_3$ (50 mL) dropwise at 0 ^oC over a period of 2 h under nitrogen atmosphere. After 17 h, the white precipitate in the reaction mixture was filtered, and the residue was washed with $CHCl_3$ (25 mL × 2). To the combined $CHCl_3$ fractions was added water (80 mL) and the two layers were separated. The organic layer was washed with brine (50 mL), separated, dried (anhyd. Na_2SO_4), filtered and concentrated *in vacuo* on a rotary evaporator to give compound **S15** (1.3 g, 90%, R_f 0.5 in MeOH/$CHCl_3$ 1:1) as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 4.91 (s, 1H), 3.19 (t, *J* = 6.0 Hz, 2H), 2.81 (t, *J* = 5.9 Hz, 2H), 1.46 (s, 9H).

***tert*-butyl (2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl)carbamate (S16):** To a stirred solution of **S15** (1.39 g, 8.67 mmoL) in toluene (20 mL) was added maleic anhydride (0.85 g, 8.67 mmoL) at room temperature under argon atmosphere After 1h, the reaction mixture was concentrated *in vacuo* on rotary evaporator to give crude acid (R_f 0.1 in 100% EtOAc). To the resultant acid was added Ac_2O (15 mL) and NaOAc (0.78 g, 9.54 mmoL) at room temperature. The reaction mixture was heated to 70 ^oC and stirred for 16 h. Subsequently, the reaction was cooled to room temperature and poured over to the ice-cold water (50 mL) and extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine (20 mL), separated, dried (anhyd. Na_2SO_4), filtered and concentrated *in vacuo* on a rotary evaporator to give brown crude. Purification of the crude mixture by column chromatography (EtOAc/hexane 7:13) on silica gel gave maleimide **S16** (1.18 g, 56.7% (over two steps), R_f 0.5 in EtOAc/hexane 1:1) as yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 2H), 4.76 (s, 1H), 3.71 – 3.5 (m, 2H), 3.30 (q, *J* = 5.8 Hz, 2H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 156.0, 134.2, 79.6, 39.4, 38.1, 28.4; HRMS (TOF MS ES+) *m/z* calcd. for $C_{11}H_{16}N_2NaO_4$ $[M+Na]^+$ 263.1008 and $C_6H_9N_2O_2$ $[M\text{-}Boc]^+$ 141.0664; found 263.1007 and 141.0668 respectively.

***N*-dansyl maleimide (NDM):** To a stirred solution of **S16** (0.2 g, 0.79 mmoL) in CH_2Cl_2 (1 mL) was added a 20% TFA in CH_2Cl_2 (3 mL) at room temperature under argon atmosphere. After 6 h, the reaction mixture was concentrated *in vacuo* on rotary evaporator to give the TFA salt of the deprotected amine (R_f 0.1 in 100% EtOAc). To the resultant amine was added anhydrous CH_2Cl_2 (5 mL) under argon atmosphere followed by the addition of DIPEA (0.463 mL, 2.63 mmoL). The reaction mixture was stirred and cooled to 0 ^oC. Subsequently, a solution of dansyl chloride (0.199 g, 0.737 mmoL) in CH_2Cl_2 (5 mL) was added to the reaction mixture dropwise in dark. After addition, the reaction was allowed to warm to room temperature. After 7 h, the reaction mixture was concentrated *in vacuo* on rotary evaporator to give pale yellow crude. Purification of crude by column chromatography (EtOAc/hexane 3:7) on silica gel gave **NDM** (0.12 g, 44.4% (over two steps), R_f 0.5 in EtOAc/hexane 1:1) as yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.51 (dt, *J* = 8.6, 1.1 Hz, 1H), 8.19 (ddd, *J* = 10.0, 7.5, 1.2 Hz, 2H), 7.53 (ddd, *J* = 15.7, 8.6, 7.4 Hz, 2H), 7.16 (dd, *J* = 7.6, 0.9 Hz, 1H), 6.35 (s, 2H), 5.10 (t, *J* = 6.2 Hz, 1H), 3.57 – 3.50 (m, 2H), 3.17 (q, *J* = 6.0 Hz, 2H), 2.88 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 152.1, 134.1, 133.4, 130.6, 130.1, 129.9, 129.4, 128.5, 123.3, 119.0, 115.2, 45.5, 41.8, 37.0; HRMS (QTOF MS ESI+) *m/z* calcd. for $C_{18}H_{20}N_3O_4S$ $[M+H]^+$ 374.1175 and $C_{18}H_{19}N_3O_4SNa$ $[M+Na]^+$ 396.0994; found 374.1175 and 396.0994 respectively.

Scheme S4. Synthesis of *N*-butynylmaleimide (**NBM**)



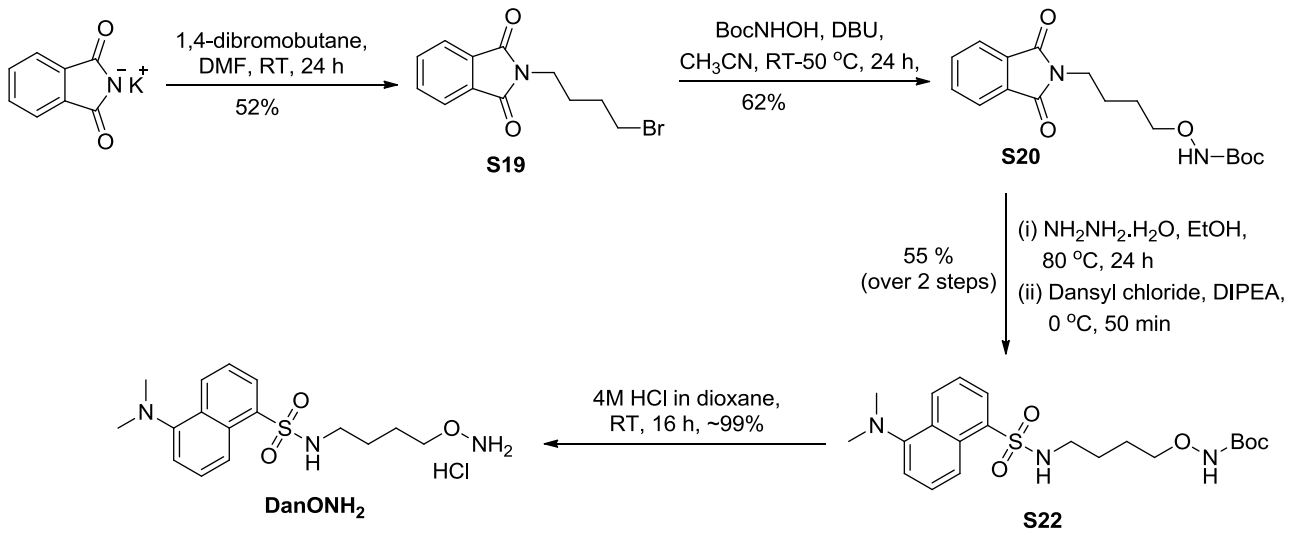
But-3-yn-1-yl methanesulfonate (S17)[5]: To a cooled (0 °C) solution of 3-butyn-1-ol (3 mL, 39.6 mmoL) and Et_3N (8.3 mL, 59.5 mmol) in anhydrous Et_2O (40 mL) was added methane sulfonyl chloride (4.6 mL, 59.5 mmoL) dropwise under argon atmosphere. After 4 h, the insoluble white precipitate was filtered, and the filtrate was washed with brine (20 mL). The organic layer was separated, dried (anhyd. Na_2SO_4) and concentrated *in vacuo* on a rotary evaporator to give compound **S17** (5.7 g, 97%, R_f 0.45 in EtOAc/hexane 1:3) as a faint yellow liquid. The crude product was used for the next reaction without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (t, *J* = 6.7 Hz, 2H), 3.05 (s, 3H), 2.65 (td, *J* = 6.7, 2.7 Hz, 2H), 2.06 (t, *J* = 2.7 Hz, 1H).

But-3-yn-1-amine (S18)[5]: To a stirred solution of **S17** (5.7 g, 38.4 mmoL) in anhydrous DMF (30 mL) was added NaN_3 (6.25 g, 96.1 mmoL) portion-wise at room temperature under argon atmosphere. The reaction mixture was slowly heated to 70 °C. After 4 h, the reaction mixture was poured into cold water (25 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layer was dried (anhyd. Na_2SO_4) and filtered. Subsequently, the organic layer was cooled to 0 °C and PPh_3 (8.05 g, 30.7 mmol) was added to it with stirring under argon atmosphere. After 2 h, water (6 mL) was added and the reaction was warmed to room temperature. After 20 h, the reaction was poured into 10% HCl (30 mL) and stirred for 10 min. The aqueous layer was separated from the biphasic solution and washed with CH_2Cl_2 (3 × 75 mL). The resultant aqueous layer was concentrated to dryness *in vacuo* to yield a sticky, hygroscopic **S18.HCl** salt (5.26 g). 2.0 g of the salt was re-dissolved in water and the aqueous solution was basified to pH ~10 with 6N NaOH (~4 mL). The free base amine was extracted with CH_2Cl_2 (3 × 100 mL), washed with water (100 mL), dried (anhyd. Na_2SO_4) and concentrated *in vacuo* on a rotary evaporator to give **S18** (0.84 g (crude yield 32%, over two steps)). This amine was used for further reaction without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (t, *J* = 6.4 Hz, 2H), 2.25 (td, *J* = 6.3, 2.6 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 82.3, 69.6, 40.8, 23.3.

***N*-butynylmaleimide (NBM):** To the stirred solution of amine **S18** (0.84 g (77% purity by NMR), 12.12 mmoL) in toluene (15 mL) was added maleic anhydride (1.19 g, 12.12 mmoL) at room temperature under argon atmosphere. After 2 h, the reaction mixture was concentrated *in vacuo* on a rotary evaporator. To the resultant crude was added acetic anhydride (15 mL) and NaOAc (0.105 g, 1.28 mmoL) at room temperature under argon atmosphere. The reaction mixture

was slowly heated to 70 °C. After 16 h, the reaction was poured on to the ice and stirred for 10 min. The aqueous solution was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (50 mL), separated, dried (anhyd. Na_2SO_4), filtered and concentrated *in vacuo* on a rotary evaporator to give yellow crude. Purification by column chromatography on silica gel (EtOAc/hexane 7:43) gave **NBM** (0.204 g, 14.6%, R_f 0.2 in EtOAc/Hexane 1:4). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 (s, 2H), 3.71 (t, *J* = 7.0 Hz, 2H), 2.51 (td, *J* = 7.0, 2.7 Hz, 2H), 1.95 (t, *J* = 2.7 Hz, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 134.1, 80.0, 70.3, 36.3, 18.3; HRMS (TOF MS ES+) *m/z* calcd. for $C_8H_8NO_2$ $[M+H]^+$ 150.0555; found 150.0557.

Scheme S5. Synthesis of dansyl alkoxyamine (**DanONH$_2$**)



2-(4-bromobutyl)isoindoline-1,3-dione (S19): To a stirred solution of potassium phthalimide (6.7 g, 36.17 mmoL) in anhydrous DMF (50 mL) was added 1,4-dibromobutane (5.2 mL, 43.17 mmoL) at room temperature under nitrogen atmosphere. After 24 h, the reaction mixture was diluted with water (150 mL) and extracted with CH_2Cl_2 (200 mL × 2). The organic layers were combined and washed with brine (50 mL), dried (anhyd. Na_2SO_4), filtered and concentrated *in vacuo* on rotary evaporator to give yellow crude. Purification of the crude mixture by column chromatography (EtOAc/hexane 1:6) on silica gel gave compound **S19** (5.32 g, 52.2%, R_f 0.4 in EtOAc/Hexane 1:4) as white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.77 – 7.69 (m, 2H), 3.75 (t, *J* = 6.7 Hz, 2H), 3.47 (t, *J* = 6.4 Hz, 2H), 2.00 – 1.79 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 131.6, 129.6, 120.9, 74.9, 74.6, 74.3, 34.61, 30.4, 27.4, 24.8. HRMS (QTOF MS ESI+) *m/z* calcd. for $C_{12}H_{13}BrNO_2$ $[M+H]^+$ 282.0130 and found 282.0124.

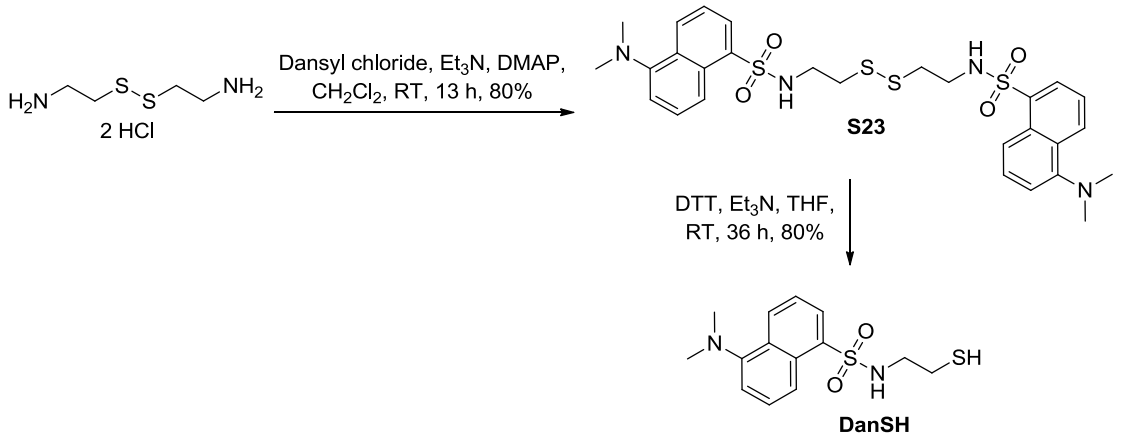
***tert*-butyl 4-(1,3-dioxoisoindolin-2-yl)butoxycarbamate phthalimide (S20):** To a stirred solution of *N*-Boc hydroxylamine (1 g, 7.51 mmoL) and **S19** (1.49 g, 5.29 mmoL) in anhydrous CH_3CN (2 mL) was added DBU (1.2 mL, 7.94 mmoL) dropwise at room temperature under nitrogen atmosphere. The resultant yellow reaction mixture was slowly heated at 50 °C. After 24 h, the reaction was cooled to 4 °C with ice-water mixture and quenched by adding cooled 1N

HCl (20 mL) solution. The mixture was then extracted with EtOAc (30 mL × 2). The organic layers were combined and washed with brine (20 mL), dried (anhyd. Na_2SO_4), filtered and concentrated *in vacuo* on rotary evaporator to give yellow crude. Purification of the crude mixture by column chromatography (EtOAc/hexane/CH_2Cl_2 1:3:2) on silica gel gave compound **S20** (1.1 g, 62.3%, R_f 0.5 in EtOAc/hexane/CH_2Cl_2 2:2:1) as white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.92 (s, 1H), 7.90 – 7.81 (m, 4H), 3.68 (t, *J* = 6.3 Hz, 2H), 3.59 (t, *J* = 6.9 Hz, 2H), 1.72 – 1.61 (m, 2H), 1.56 – 1.46 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.4, 156.5, 134.8, 132.0, 123.4, 79.8, 75.1, 37.6, 28.4, 25.5, 25.2. HRMS (QTOF MS ESI+) *m/z* calcd. for $C_{17}H_{22}N_2NaO_5$ $[M+Na]^+$ 357.1426 and found 357.1404.

***tert*-butyl 4-(5-(dimethylamino)naphthalene-1-sulfonamido)butoxycarbamate (S22):** To a stirred solution of **S20** (0.31 g, 0.93 mmoL) in EtOH (1 mL) was added hydrazine hydrate (0.74 mL, 23.7 mmoL) at room temperature under nitrogen atmosphere. The reaction mixture was slowly heated to refluxed at 80 ^{o}C. After 24 h, the reaction mixture was cooled to room temperature and concentrated *in vacuo* on rotary evaporator. To the resultant pink residue was added ethanol (20 mL) and the insoluble solid was filtered. The filtrate was concentrated *in vacuo* on rotary evaporator and to the resultant crude was added CH_2Cl_2 and an aqueous solution of K_2CO_3 (1 g in 14 mL). The organic layer from the biphasic solution was separated and washed with brine (10 mL), dried (anhyd. Na_2SO_4), filtered and concentrated *in vacuo* on rotary evaporator to give *N*-Boc amine **S21** as yellow oil (131 mg, 69%) and was used for the next step without further purification. Data for **S21**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.62 (t, *J* = 6.5 Hz, 2H), 3.29 (br s, 1H), 2.50 – 2.47 (m, 2H), 1.46 (dq, *J* = 8.7, 6.7 Hz, 2H), 1.28-1.35 (m, 11 H). To a cooled (0 ^{o}C) and stirred solution of crude amine **S21** (125 mg, 0.612 mmoL) and DIPEA (0.24 mL, 1.39 mmoL) in anhydrous CH_2Cl_2 (10 mL) was added a solution of dansyl chloride (92 mg, 0.34 mmol) in CH_2Cl_2 (2 mL) slowly and dropwise under argon atmosphere. After 50 min, the reaction was quenched with MeOH (2 mL) followed by concentrating it *in vacuo* on rotary evaporator. Purification of the crude mixture by column chromatography EtOAc/hexane 1:4) on silica gel gave compound **S22** (119 mg, 80%, R_f 0.3 in EtOAc/hexane 3:7) as a green solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dt, *J* = 8.6, 1.1 Hz, 1H), 8.35 (dt, *J* = 8.7, 0.9 Hz, 1H), 8.27 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.56 (ddd, *J* = 14.3, 8.6, 7.4 Hz, 2H), 7.21 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.13 (s, 1H), 5.16 (bs, 1H), 3.82 – 3.71 (m, 2H), 2.97 (dd, *J* = 8.0, 4.6 Hz, 2H), 2.92 (s, 6H), 1.57 (dt, *J* = 5.5, 2.6 Hz, 4H), 1.50 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 151.9, 134.8, 130.2, 129.9, 129.6, 129.6, 128.2, 123.2, 118.8, 115.1, 81.9, 76.1, 42.9, 28.2, 26.2, 25.0. HRMS (QTOF MS ESI+) *m/z* calcd. for $C_{21}H_{31}N_3NaO_5S$ $[M+Na]^+$ 460.1882 and found 460.1895.

***tert*-butyl 4-(5-(dimethylamino)naphthalene-1-sulfonamido)butoxycarbamate hydroxylamine.HCl (DanONH$_2$):** A solution of **S22** (18 mg, 0.041 mmoL) in 4M HCl in dioxane (1 mL) was stirred at room temperature under argon atmosphere. After 16 h, the reaction mixture was concentrated *in vacuo* on rotary evaporator to give analytically pure compound **DanONH$_2$** as its hydrochloride salt (15 mg) in quantitative yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (br s, 1H), 8.72 (d, *J* = 8.6 Hz, 1H), 8.52 (d, *J* = 8.5 Hz, 1H), 8.16 (dd, *J* = 7.3, 1.0 Hz, 1H), 8.07 (t, *J* = 5.7 Hz, 1H), 7.82 – 7.68 (m, 2H), 7.64 (br s, 1H), 3.89 (t, *J* = 6.1 Hz, 2H), 3.04 (s, 6H), 2.80 (q, *J* = 6.5 Hz, 2H), 1.49 (dq, *J* = 11.2, 6.3 Hz, 2H), 1.45 – 1.35 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 136.4, 128.8, 128.5, 128.5, 127.6, 124.7, 117.3, 73.4, 45.7, 41.9, 25.5, 24.2; HRMS (QTOF MS ESI+) *m/z* calcd. for $C_{16}H_{24}N_3O_3S$ $[M+H]^+$ 338.1538 and found 338.1354.

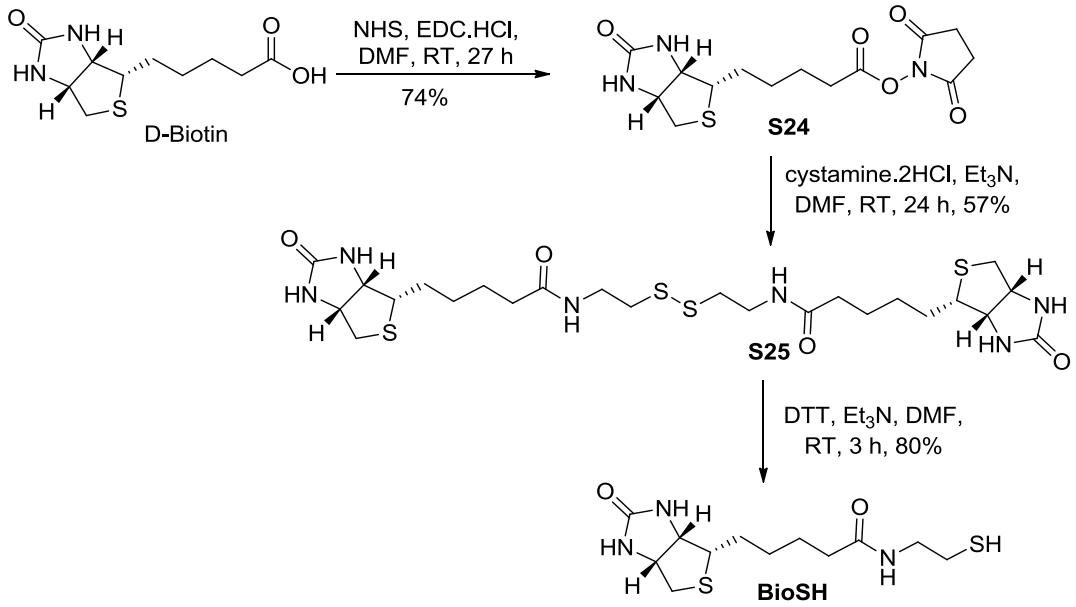
Scheme S6. Synthesis of dansyl thiol (**DanSH**)



***N,N'*-(disulfanediylbis(ethane-2,1-diyl))bis(5-(dimethylamino)naphthalene-1-sulfonamide) (S23):** To a stirred suspension of cystamine dihydrochloride (42 mg, 0.19 mmoL) in CH_2Cl_2 (5 mL) was added Et_3N (0.21 mL, 1.48 mmoL) dansyl chloride (0.1 g, 0.37 mmoL) and DMAP (5 mg, 0.037 mmol), sequentially at room temperature under argon atmosphere in dark. After 13 h, the reaction mixture was diluted with saturated ammonium chloride (10 mL). The organic layer was separated from the biphasic solution, dried (anhyd. Na_2SO_4), filtered and concentrated *in vacuo* on rotary evaporator to give yellow crude. Purification of crude mixture by column chromatography (EtOAc/hexane 3:7) on silica gel gave disulfide **S23** (94 mg, 80.3%, R_f 0.35 in EtOAc/Hexane 2:3). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (dt, *J* = 8.5, 1.1 Hz, 2H), 8.29 – 8.18 (m, 4H), 7.53 (ddd, *J* = 17.5, 8.6, 7.4 Hz, 4H), 7.18 (dd, *J* = 7.6, 0.9 Hz, 2H), 5.21 (t, *J* = 6.3 Hz, 2H), 3.10 (q, *J* = 6.3 Hz, 4H), 2.89 (s, 12H), 2.49 (t, *J* = 6.3 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.0, 134.3, 130.6, 129.8, 129.6, 129.4, 128.5, 123.1, 118.5, 115.3, 45.4, 41.5, 37.7; HRMS (QTOF MS ESI+) *m/z* calcd. for $C_{28}H_{35}N_4O_4S_4$ $[M+H]^+$ 619.1541 and $C_{28}H_{34}N_4NaO_4S_4$ $[M+Na]^+$ 641.1361; found 619.1542 and 641.1357 respectively.

5-(dimethylamino)-N-(2-mercaptoethyl)naphthalene-1-sulfonamide (DanSH): To a stirred solution of **S23** (87 mg, 0.14 mmoL) and Et_3N (47 µL, 0.34 mmoL) in THF (5 mL) was added DTT (69 mg, 0.45 mmoL) at room temperature under argon atmosphere in dark. After 36 h, the reaction mixture was diluted with brine (10 mL). The organic layer was separated from the biphasic solution, dried (anhyd. Na_2SO_4), filtered and concentrated *in vacuo* on rotary evaporator to give yellow crude. Purification of the crude mixture by column chromatography (EtOAc/hexane 3:20) on silica gel gave **DanSH** (35 mg, 79.8%, R_f 0.6 in EtOAc/hexane 3:2) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (dt, *J* = 8.6, 1.1 Hz, 1H), 8.29 (ddd, *J* = 8.8, 8.1, 1.1 Hz, 2H), 7.58 (ddd, *J* = 22.8, 8.6, 7.4 Hz, 2H), 7.22 (dd, *J* = 7.6, 0.9 Hz, 1H), 5.19 (t, *J* = 6.4 Hz, 1H), 3.11 (q, *J* = 6.3 Hz, 2H), 2.92 (s, 6H), 2.53 (ddd, *J* = 8.7, 6.7, 5.9 Hz, 2H), 1.23 (t, *J* = 8.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1, 134.6, 130.7, 129.9, 129.6, 129.5, 128.6, 123.2, 118.5, 115.3, 45.8, 45.4, 24.8; HRMS (QTOF MS ESI+) *m/z* calcd. for $C_{14}H_{19}N_2O_2S_2$ $[M+H]^+$ 311.0888 and $C_{14}H_{18}N_2NaO_2S_2$ $[M+Na]^+$ 333.0707; found 311.0888 and 333.0706 respectively.

Scheme S7. Synthesis of biotin thiol (**BioSH**)



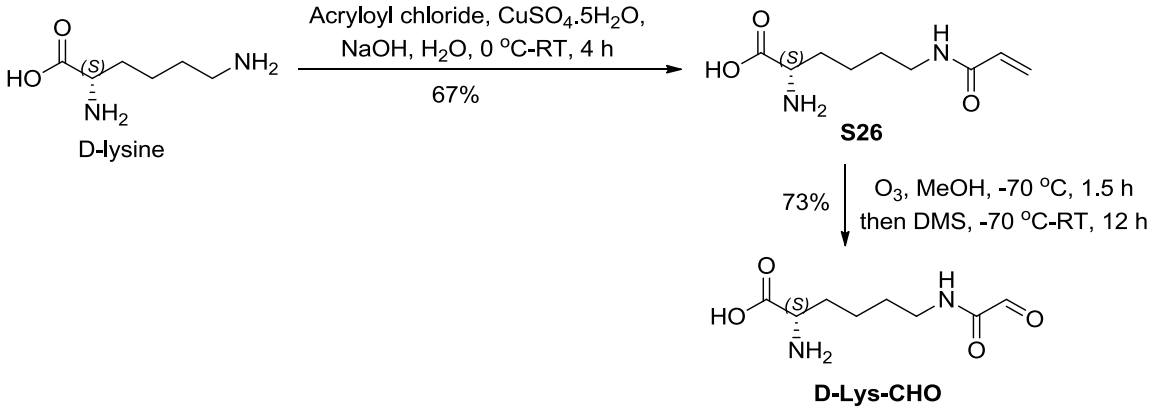
Biotin-NHS ester (S24): To a stirred solution of *D*-Biotin (0.25 g, 1.03 mmoL) and *N*-hydroxy succinimide, NHS (0.13 g, 1.13 mmoL) in DMF (12 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride, EDC.HCl (0.24 g, 1.24 mmoL) at room temperature under argon atmosphere. After 27 h, the reaction mixture was concentrated *in vacuo* on rotary evaporator followed by drying the resultant crude under high vacuum for 2-3 h. To the resultant white solid was added methanol (8 mL× 5) and the analytically pure **S24** (0.26 g, 74.4%) was obtained as white solid upon filtration. ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.43 (s, J = 1.8 Hz, 1H), 6.37 (s, 1H), 4.36 – 4.26 (m, 1H), 4.15 (ddd, J = 7.6, 4.4, 1.8 Hz, 1H), 3.11 (ddd, J = 8.2, 6.3, 4.4 Hz, 1H), 2.86 – 2.82 (m, 1H), 2.82 – 2.79 (m, 4H), 2.67 (dd, J = 8.0, 6.8 Hz, 2H), 2.58 (d, J = 12.4 Hz, 1H), 1.70 – 1.36 (m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.7, 169.3, 163.1, 61.4, 59.6, 55.6, 40.3, 30.4, 28.3, 28.0, 25.9, 24.7. HRMS (TOF MS ES+) *m/z* calcd. for $C_{14}H_{20}N_3O_5S$ $[M+H]^+$ 342.1124 and found 342.1121.

Biotin disulphide (S25): To a stirred solution of Biotin-NHS ester **S24** (0.33 g, 0.96 mmoL) in DMF (10 mL) was added cystamine dihydrochloride (0.11 g, 0.48 mmoL) and Et_3N (0.4 mL, 2.88 mmoL) at room temperature under argon atmosphere. After 24 h, the reaction mixture was concentrated *in vacuo* on rotary evaporator followed by drying the resultant crude under high vacuum for 2-3 h. The resultant white solid was washed with water (20 mL× 5) and dried under high vacuum give **S25** (0.17 g, 57.2%) as a white solid that was used for next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (t, J = 5.7 Hz, 2H), 6.41 (s, J = 2.1 Hz, 2H), 6.36 (s, 2H), 4.31 (dd, J = 7.7, 5.0 Hz, 2H), 4.14 (ddd, J = 7.4, 4.5, 1.9 Hz, 2H), 3.11 (ddd, J = 8.7, 6.3, 4.5 Hz, 2H), 2.87 – 2.71 (m, 8H), 2.59 (d, J = 12.7 Hz, 4H), 2.14 – 2.02 (m, 4H), 1.69 – 1.27 (m, 12H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.7, 163.2, 61.5, 59.6, 55.8, 38.3, 37.7, 35.6, 28.6, 28.4, 25.7; HRMS (TOF MS ES+) *m/z* calcd. for $C_{24}H_{41}N_6O_4S_4$ $[M+H]^+$ 605.2072 and found 605.2080.

Biotin thiol (BioSH): DMF (3 mL) was added to biotin disulphide **S25** (50 mg, 0.083 mmoL) under argon atmosphere. The resultant mixture was stirred and warmed to 50 ^{o}C to dissolve **S25**. Subsequently, the reaction mixture was cooled to room temperature followed by the sequential addition of DTT (78 mg, 0.51 mmoL) and Et_3N (5 µL, 0.036 mmoL) and a

light pink color appeared in the reaction. After 3 h, the reaction mixture was concentrated *in vacuo* on rotary evaporator followed by drying the resultant crude under high vacuum for 2 h. To the resultant semi-solid crude was added CH_2Cl_2 (3 mL × 3) and filtered. The filtrate was concentrated *in vacuo* on rotary evaporator and dried under high vacuum to give sticky solid and gave analytically pure **BioSH** (20 mg, 80%) as white solid upon trituration with diethyl ether. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (t, *J* = 5.7 Hz, 1H), 6.38 (s, 1H), 6.32 (s, 1H), 4.26 (dd, *J* = 7.7, 5.1 Hz, 1H), 4.08 (ddd, *J* = 7.5, 4.6, 1.7 Hz, 1H), 3.19 – 3.09 (m, 2H), 3.05 (ddd, *J* = 8.7, 6.1, 4.4 Hz, 1H), 2.78 (dd, *J* = 12.4, 5.1 Hz, 1H), 2.59 – 2.48 (m, 2H), 2.33 – 2.26 (m, 1H), 2.02 (t, *J* = 7.4 Hz, 2H), 1.62 – 1.20 (m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.5, 163.1, 61.5, 59.6, 55.8, 42.5, 35.6, 28.6, 28.4, 25.7, 24.0; HRMS (TOF MS ES+) *m/z* calcd. for $C_{12}H_{22}N_3O_2S_2$ $[M+H]^+$ 304.1153 and found 304.1156.

Scheme S8. Synthesis of **D-Lys-CHO**



(*S*)-6-acrylamido-2-aminohexanoic acid (S26): To a cooled (0 °C) and stirred solution D-lysine monohydrochloride (0.5 gm, 2.73 mmoL), $CuSO_4.5H_2O$ (0.34 g, 1.36 mmoL), NaOH (0.22 g, 5.47 mmoL), Na_2CO_3 (0.29 g, 2.73 mmoL) in water (12 mL) was added acryloyl chloride (0.3 mL, 3.28 mmoL) dropwise over the course of 15 min. After addition, the reaction mixture was allowed to warm to room temperature and stirred for 4 h. The blue precipitate formed in the reaction was filtered and sequentially washed with water (30 mL), acetone (12 mL), diethyl ether (6 mL) and water (6 mL). The resultant solid was air-dried and then resuspended in water (12 mL) and chloroform (12 mL) mixture. To this solution was added 8-hydroxyquinoline (2 g, 13.65 mmoL) portion-wise over 30 min with vigorous stirring. After 1 h, the green solid appeared and was filtered, followed by the washing of the resultant solid with additional water (6 mL). The filtrate was separated into two layers and the aqueous layer was washed with $CHCl_3$ (4 ×12 mL) until no yellow color due to 8-hydroxyquinoline appeared in the organic layer. The aqueous layer was separated and lyophilized to give the desired product (*S*)-**S26** as white solid (0.37 g, 67.3%). ^{1}H NMR (500 MHz, D_2O) δ 6.15 (dd, *J* = 17.1, 10.2 Hz, 1H), 6.13 (d, *J* = 10.2 Hz, 1H), 6.06 (dd, *J* = 17.1, 1.3 Hz, 1H), 3.62 (t, *J* = 6.1 Hz, 1H), 3.17 (t, *J* = 6.9 Hz, 2H), 1.77 (m, 2H), 1.49 (p, *J* = 7.2 Hz, 2H), 1.41 – 1.19 (m, 2H). ^{13}C NMR (126 MHz, D_2O) δ 174.8, 168.5, 129.9, 126.9, 54.6, 38.9, 30.0, 27.9, 21.7; HRMS (QTOF MS ESI+) *m/z* calcd. for $C_9H_{17}N_2O_3$ $[M+H]^+$ 201.1239 and found 201.1234.

(*S*)-2-amino-6-(2-oxoacetamido)hexanoic acid (D-Lys-CHO)[6, 7]: (Caution! Ozone is a highly toxic gas and therefore, ozonolysis must be done inside an efficient fume hood). To a cooled (-70 °C) solution of compound (*S*)-**S26** (86 mg, 0.42

mmoL) in anhydrous MeOH (20 mL) was bubbled ozone gas for 1.5 h. Before quenching, the excess ozone was removed by passing argon gas through the reaction mixture for 30 min at -70 ºC. The reaction was quenched by adding dimethyl sulfide, DMS (2 mL) at -70 ºC and the reaction was allowed to slowly warm to room temperature and stirred overnight. The reaction mixture was concentrated *in vacuo* on a rotary evaporator and the sticky crude was dissolved in distilled water (5 mL). Lyophilization of the aqueous solution gave analytically pure glyoxaldehyde, **D-Lys-CHO** (62 mg, 73%) as a white solid. ^{1}H NMR (500 MHz, D_2O) δ 5.26 (s, 1H), 3.73 (t, *J* = 6.1 Hz, 1H), 3.24 (t, *J* = 6.9 Hz, 2H), 1.95 – 1.78 (m, 2H), 1.62 – 1.50 (m, 2H), 1.48 – 1.30 (m, 2H). ^{13}C NMR (126 MHz, D_2O) Aldehyde form: δ 174 (*C*OOH), 172.1 (NH*C*O), 166.7 (*C*HO), 54 (α-*C*H), 38 (ε-*C*H_2), 30 (β-*C*H_2), 27 (δ-*C*H_2), 21 (γ-*C*H_2). Hydrate form: δ 174 (*C*OOH), 172.1 (NH*C*O), 86.7 (*C*HOH), 54 (α-*C*H), 38 (ε-*C*H_2), 30 (β-*C*H_2), 27 (δ-*C*H_2), 21 (γ-*C*H_2).

(*R*)-6-acrylamido-2-aminohexanoic acid (S26): Following the procedure described above, L-lysine monohydrochloride (0.5 gm, 2.73 mmoL), $CuSO_4.5H_2O$ (0.34 g, 1.36 mmoL), NaOH (0.22 g, 5.47 mmoL), Na_2CO_3 (0.29 g, 2.73 mmoL) and acryloyl chloride (0.3 mL, 3.28 mmoL) afforded *R* isomer of compound **S26** as white solid (0.31 g, 45.3%). All other spectroscopic data (^{1}H, ^{13}C-NMR and HRMS) matched with the (*S*)-**S26**.

(*R*)-2-amino-6-(2-oxoacetamido)hexanoic acid (L-Lys-CHO)[6, 7]: Following the procedure described above, the ozonolysis of *R* isomer of **S26** (90 mg, 0.45 mmoL) afforded *R* isomer of compound **L-Lys-CHO** as white solid (65 mg, 71%). All other spectroscopic data (^{1}H, ^{13}C-NMR and HRMS) matched with the (*S*)-**D-Lys-CHO**.

IV. Procedures for the HPLC experiments

(A) Kinetics of formation of exocyclic olefinic maleimides

Case 1. Aldehyde **1** (1.5 mM) : NEM : PPh_3 : 4-NP = 1 : 1 : 1 : 0.2

To a solution of sodium phosphate buffer at pH 7 (500 µL, 50 mM), aldehyde **1** (20 µL, 50 mM solution in MeOH, 1.0 eq) and CH_3CN (57 µL) was added a freshly prepared solution (88 µL) containing NEM (40 µL, 25 mM solution in CH_3CN), Ph_3P (40 µL, 25 mM solution in CH_3CN) and 4-NP (8 µL, 25 mM solution in CH_3CN). The reaction mixture was thoroughly mixed by pipetting up and down and kept at room temperature. Aliquots (5 µL) from the mixture was periodically withdrawn and subjected to HPLC. Peaks were collected and characterized by MALDI (Table S1). The traces of the experiment are depicted in **Figure S1**.

Case 2. Aldehyde (1.5 mM) : NEM : PPh_3 : 4-NP = 1 : 2 : 2 : 0.4 (Aldehyde = **1**, **2**, benzaldehyde, 4-nitrobenzaldehyde, 2-nitrobenzaldehyde, 4-fluorobenzaldehyde, 4-carboxybenzaldehyde, 3-methoxybenzaldehyde, cinnamaldehyde and hydrocinnamaldehyde)

Similar procedures were followed as described above for various aldehydes, except 50 mM stock solutions of NEM, Ph_3P and 4-NP were used to obtain their respective ratios in the reaction mixture. The HPLC traces obtained from the experiment with aldehydes **1** and **2** are depicted in **Figure 2** (left panel for **1** and right panel for **2**) of the main text. The HPLC traces obtained from the experiment with other aldehydes (benzaldehyde, 4-nitrobenzaldehyde, 2-nitrobenzaldehyde, 4-fluorobenzaldehyde, 4-carboxybenzaldehyde, 3-methoxybenzaldehyde, cinnamaldehyde and

hydrocinnamaldehyde) are depicted in **Figure S5**. The MALDI/HRMS characterization of the peaks observed was summarized in Table S1 and their spectral data is summarized in section IX.

Case 3. Aldehyde **1** (1.5 mM) : GSSG : NEM : PPh_3 : 4-NP = 1 : 5 : 2 : 2 : 0.4

To a solution of sodium phosphate buffer of pH 7 (400 µL, 50 mM), GSSG (100 µL, 50 mM solution in sodium 50 mM phosphate buffer, pH 7), aldehyde **1** (20 µL, 50 mM solution in MeOH, 1.0 eq) and CH_3CN (57 µL) was added a freshly prepared solution (88 µL) containing NEM (40 µL, 50 mM solution in CH_3CN), Ph_3P (40 µL, 50 mM solution in CH_3CN) and 4-NP (8 µL, 25 mM solution in CH_3CN). The reaction mixture was thoroughly mixed by pipetting up and down and kept at room temperature. Aliquots (5 µL) from the mixture was periodically withdrawn and subjected to HPLC. Peaks were collected and characterized by MALDI (Table S1). The traces of the experiment are depicted in **Figure S3**.

Case 4: Aldehyde **1** (0.05 mM) : NEM : PPh_3 : 4-NP = 1 : 2-10 : 2-10 : 0.4-2

Condition A (**1** : NEM : PPh_3 : 4-NP = 1 : 2 : 2 : 0.4): To a solution of sodium phosphate buffer of pH 7 (750 µL, 50 mM), CH_3CN (196 µL) and aldehyde **1** (10 µL, 5 mM solution in MeOH) was added a freshly prepared solution (44 µL) containing NEM (20 µL, 5 mM solution in CH_3CN), Ph_3P (20 µL, 5 mM solution in CH_3CN) and 4-NP (4 µL, 5 mM solution in CH_3CN). The reaction mixture was mixed thoroughly by pipetting up and down at room temperature. Aliquots (200 µL) from this reaction mixture was injected to HPLC and reaction was monitored at different time intervals. The traces of the experiment are depicted in **Figure S2a**.

Condition B (**1** : NEM : PPh_3 : 4-NP = 1 : 6 : 6 : 1.2): Similar procedure was followed for condition **B** except for 15 mM stock solutions of NEM, PPh_3 and 4-NP were used. The traces of the experiment are depicted in **Figure S2b**.

Condition C (**1** : NEM : PPh_3 : 4-NP = 1 : 10 : 10 : 2): Similar procedure was followed for condition **C** except for 25 mM stock solutions of NEM, PPh_3 and 4-NP were used. The traces of the experiment are depicted in **Figure S2c.**

(B) Kinetics of oxime formation reaction

Case 1. Aldehyde **1** (1.5 mM) : $BnONH_2$: 1,4-diaminobenzene = 1 : 2 : 0.4

To a solution of sodium phosphate buffer at pH 7 (500 µL, 50 mM), aldehyde **1** (20 µL, 50 mM solution in MeOH, 1.0 eq) and CH_3CN (89 µL) was added a solution of benzyloxyamine hydrochloride, $BnONH_2$.HCl (40 µL, 50 mM solution in H_2O, 2.0 eq) and 1,4-diaminobenzene (16 µL, 25 mM solution in CH_3CN, 0.4 eq). The reaction mixture was thoroughly mixed by pipetting and kept at room temperature in the dark. Aliquots (5 µL) from the mixture were periodically withdrawn and subjected to HPLC. Peaks were collected and characterized by MALDI (Table S1). The HPLC traces obtained for the experiment are depicted in **Figure S9** (left panel).

Case 2. Aldehyde **1** (1.5 mM) : $BnONH_2$: 1,4-diaminobenzene = 1 : 2 : 5

Similar procedure as described above was followed except 16 µL of 312 mM solution of the 1,4-diaminobenzene catalyst in CH_3CN was used. The HPLC traces obtained for the experiment are depicted in **Figure S9** (right panel).

(C) Stability of exocyclic olefinic maleimides in sodium phosphate buffers (pH 5-8)

Exocyclic olefinic maleimide **4** (20 µL, 25 mM in CH_3CN) in sodium phosphate buffer of various pH (5-8) (320 µL, 50 mM) and CH_3CN (120 µL) was incubated for 2 d at room temperature. Aliquots (5 µL) from the solution at obtained at different time intervals were injected into the HPLC to give the traces depicted in **Figure S4**.

(D) Procedure for peptide, TRAP6 labelling

Preparation of TRAP-6 CHO: To a solution of TRAP6 (0.8 mg, 1 eq) in sodium phosphate buffer of pH 6.5 (50 mM, 897.5 µL) was added freshly prepared solution of $NaIO_4$ (42.5 µL, 50 mM solution in water, 2 eq) under ice-cold condition 4 ^oC. The reaction mixture was thoroughly mixed by pipetting up and down and kept at 4 ^oC in dark. After 30 min, the reaction was subjected to HPLC purification to isolate TRAP6 CHO (0.5 mg, 65.3%) and was characterized by MALDI (Table S1). The purified TRAP-6 CHO was stored at -30 ^oC and utilized for the further reactions within 1-2 days. The HPLC traces of the experiment are depicted in **Figure 3**.

Procedure for the kinetics of TRAP6-EXO formation from TRAP6-CHO: To a solution of sodium phosphate buffer of pH 7 (250 µL, 50 mM), CH_3CN (20 µL), TRAP6-CHO (10 µL, 16.25 mM solution in water, 1.0 eq) was added a freshly prepared solution (45 µL) containing NEM (20 µL, 16.25 mM solution in CH_3CN, 2 eq), PPh_3 (20µL, 16.25 mM solution in CH_3CN, 2 eq) and 4-NP (4 µL, 16.25 mM solution in CH_3CN, 0.4 eq). The reaction mixture was thoroughly mixed by pipetting up and down and kept at room temperature. Aliquots (5 µL) from the incubation mixture was periodically withdrawn and subjected to HPLC. Peaks were collected and characterized by MALDI (Table S1). The traces of the experiment are depicted in **Figure 3** of the main text.

*Procedure for the synthesis of GSH adduct of TRAP6-EXO peptide (**S32**)*

To a solution of sodium phosphate buffer of pH 7 (250 µL, 50 mM), CH_3CN (40 µL) and GSH (40 µL, 125 mM solution in H_2O, 5.0 eq) was added a solution of TRAP6-EXO (40 µL, 25 mM solution in 1:5 CH_3CN/H_2O, 1.0 eq). The reaction mixture was thoroughly mixed by pipetting and kept at room temperature. Aliquots (15 µL) from the incubation mixture were periodically withdrawn and subjected to HPLC. Peaks were collected and characterized by MALDI (Table S1). The traces obtained from this experiment are depicted in **Figure S11** (left panel).

*Procedure for evaluating the stability of thiol conjugate **S32** in the presence of N-acetyl cysteine (NAC)*

To a solution of sodium phosphate buffer of pH 7 (180 µL, 50 mM), CH_3CN (30 µL) and **S32** (40 µL, 10 mM solution in H_2O, 1.0 eq) was added a solution of NAC (80 µL, 100 mM solution H_2O, 20 eq). The reaction mixture was thoroughly mixed by pipetting and kept at room temperature. Aliquots (40 µL) from the incubation mixture was periodically withdrawn and subjected to HPLC. The traces obtained from this experiment are depicted in **Figure S11** (right panel).

V. Procedures for the protein labelling experiments

(A) General procedure for the generation of MbCHO:

To a solution of myoglobin (120 µL, 0.25 mM solution in 25 mM sodium phosphate buffer, pH 6.5) and sodium phosphate buffer (180 µL, 25 mM, pH 6.5) was added a solution of pyridoxal-5′-phosphate, PLP (300 µL, 20 mM solution in 25 mM sodium phosphate buffer, pH 6.5) at room temperature. The reaction mixture was gently mixed by pipetting up and down. The final pH of the mixture was adjusted to 6.5 with 1M NaOH solution and kept at 37 ^oC in the dark without agitation. After 18 h, the reaction mixture (120 µL) was desalted using 7K MWCO spin column to give MbCHO that was used for further labelling experiments.

(B) General procedure for the generating mono-labelled myoglobin conjugate

To a solution of MbCHO (28 μL, 0.09 mM in water) in sodium phosphate buffer of pH 7 (53 μL, 50 mM) was added a freshly prepared acetonitrile solution (10 μL) containing *N*-substituted maleimide (2.52 μL, 25 mM solution in CH_3CN), PPh_3 (2.52 μL, 25 mM solution in CH_3CN) and 4-NP (0.84 μL, 25 mM solution in CH_3CN). The reaction mixture was gently mixed by pipetting up and down and kept at room temperature in the dark. After 2 h, the reaction mixture was desalted using a 7K MWCO spin column. Protein modification was monitored by subjecting a desalted sample to SDS-PAGE on 15% polyacrylamide and MALDI analysis. The gel was imaged with a fluorimager in case fluorescent, NDM is used and then stained with coomassie.

(C) General procedure for generating dually-labelled myoglobin conjugate

To a solution of mono-labelled Mb conjugate (20 μL, 0.06 mM in water) in sodium phosphate buffer of pH 7 (35 μL, 50 mM) was added either Dansyl thiol, DanSH (6 μL, 5 mM in CH_3CN) or Biotin thiol, BioSH (6 μL, 5 mM in DMF). The reaction mixture was gently mixed by pipetting up and down and kept at room temperature in dark. After 5 h, the reaction mixture was diluted with water (40 μL) and desalted using 7K MWCO spin column. Dual labelling of protein was monitored by subjecting desalted samples to SDS-PAGE on 15% polyacrylamide and MALDI analysis. The gel was imaged with a fluorimager in case fluorescent mono-labelled conjugate or fluorescent thiol is used and then stained with coomassie.

(D) Procedure for trypsin digestion

All solutions were prepared in type-1water before use. In a 1.5 mL microfuge tube, a solution of myoglobin conjugate **7** (80 μL, 32.5 μM in water, 45 μg) was treated sequentially with a solution of NH_4HCO_3 (15 μL, 0.1 M in water), trifluoroethanol (15 μL) and DTT (1.5 μL, 0.2 M in water). The mixture was vortexed briefly and heated at 90 ^oC for 20 min. To this solution was added a solution of iodoacetamide (6 μL, 0.2 M in water). The mixture was vortexed briefly and incubated at 27 ^oC for 1 h in dark. The excess iodoacetamide was quenched by adding a solution of DTT (1.5 μL, 0.2 M in water) to the mixture. After incubating at 27 ^oC for 1 h in dark, the mixture was diluted with water (180 μL) and treated with a solution of NH_4HCO_3 (60 μL, 0.1 M in water) to attain a pH value between ~7.5- 8.0. To this solution, was added a solution of trypsin enzyme (2.25 μL, 1μg/μL stock in 50 mM acetic acid, 2.25 μg) at 1:20 enzyme:substrate ratio. The mixture was incubated at 37 ^oC for 10 h and the digestion was quenched by the addition of trifluoroacetic acid (0.8 μL). The final pH of the mixture should be less than 6. Subsequently, the sample was purified using a zip-tip and analyzed by MALDI and MS-MS sequencing (**Figure S7**).

VI. Bacterial cell wall labelling experiments

Bacterial cell culture and peptidoglycan labelling: For each strain, bacterial cells from a single colony were picked and was inoculated in a sterile LB broth media (5 mL). The resulting culture was grown at 37 ^oC under agitation at 250 rpm for 10 h. Subsequently, an aliquot (50 μL) of this culture was added into a fresh broth (5 mL) and cultured for another 3.5 until the cells reached the beginning of logarithmic growth phase (OD_{600} ~ 0.3-0.4). D-Lys-CHO (50 μL, 40 mM in PBS, final concentration 2 mM) was added to the aliquots (1 mL) of bacterial cultures. The cultures were allowed to grow at 37 ^oC with agitation at 250 rpm. After 6 h, the aliquots were centrifuged at 4 ^oC (g = 5000 rcf) for 3 min and the resulting cell

pellet was washed with sterile PBS (1 ml × 2). The cell pellet was then resuspended in PBS (1 mL) and to this was added a freshly prepared acetonitrile solution (10 μL) containing NDM (3 μL, 18 mM solution in CH_3CN), PPh_3 (3 μL, 18 mM solution in CH_3CN) and 4-NP (1 μL, 10 mM solution in CH_3CN) and kept at 37 ^oC. After 30 min, the cells were centrifuged, and the resultant cell pellet was washed with sterile PBS (1 mL × 3) as described above, resuspended in 200 μL PBS and used for microscopic analysis.

A similar procedure was followed for the control experiments in which the D-Lys-CHO as described above was replaced with the L-Lys-CHO.

Competitive fluorescent labelling of bacterial cell walls: For competitive fluorescent labelling, the cell pellets obtained after the treatment with D-Lys-CHO (as described above) were suspended in sterile PBS (1 mL) containing different concentrations of hydroxylamine hydrochloride and 1,4-diaminobenzene catalyst (1:20). After incubating the cell suspensions at room temperature for 90 min, the cells were centrifuged and the resultant pellet was washed with sterile PBS (1 mL × 2). The pellet was resuspended in PBS (1 mL) and to this was added a freshly prepared acetonitrile solution (10 μL) containing NDM (3 μL, 18 mM solution in CH_3CN), PPh_3 (3 μL, 18 mM solution in CH_3CN) and 4-NP (1 μL, 10 mM solution in CH_3CN) and kept at 37 ^oC. After 30 min, the cells were centrifuged and the resultant pellet was washed with PBS (1 mL × 3) and resuspended in 200 μL PBS for microscopic analysis (**Figure S13**).

Microscopic analysis of bacterial cells: For confocal microscopic analysis, 4 μL of the bacterial cell suspensions as prepared above were placed on a coverslip (Axiva, 22 mm × 22 mm). A glass slide (Borosil, 76 mm × 26 mm × 1 mm) was pressed down on the cell droplet on a coverslip and sealed with a sealing agent. Images were taken on a Zeiss LSM 780 inverted confocal microscope equipped with a filter (405 nm excitation, 450-550 nm emission) suitable for the detection of dansyl fluorescence and a 100× oil objective was used to visualize the bacterial cells.

VII. Supplementary figures (Figures S1-S13)

Figure S1. Kinetics of exocyclic olefinic maleimide (**4**) formation in 50 mM sodium phosphate buffer (pH 7) at room temperature with aldehyde **1** (1.5 mM) : NEM : PPh_3 : 4-NP = 1 : 1 : 1 : 0.2. Stacked HPLC chromatograms of the reaction at 3 min showed 95% conversion of the **1** (retention time 15.7 min) to the desired exocyclic maleimide **4** (retention time 21.6 min).

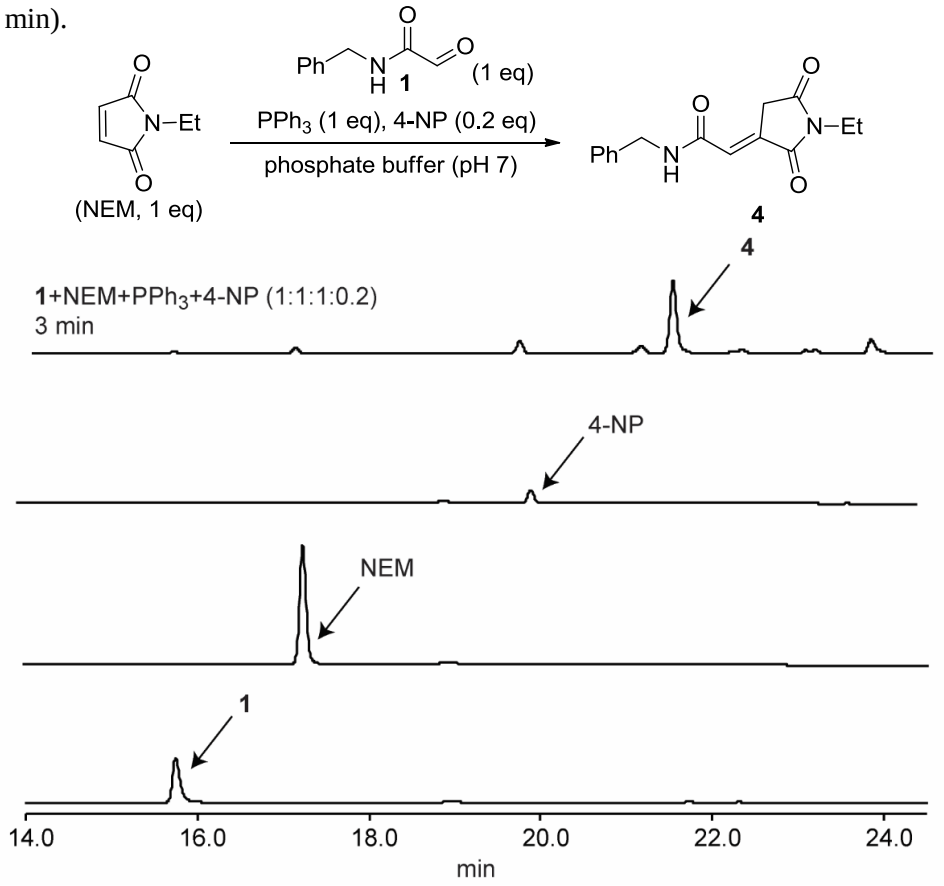
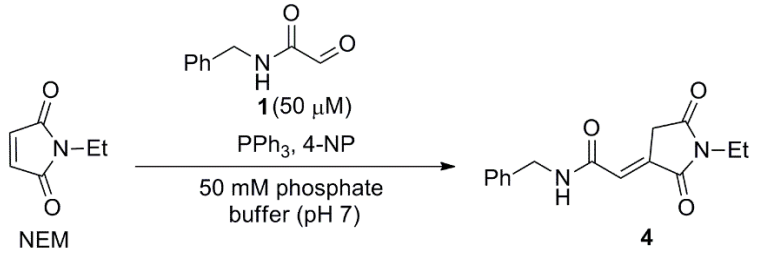
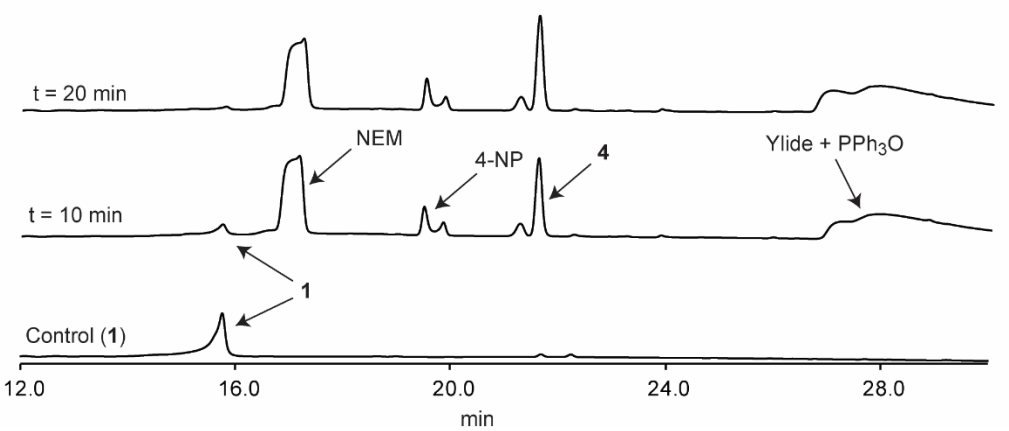


Figure S2. Kinetics of exocyclic olefinic maleimide (**4**) formation with 50 μM of aldehyde **1**. The reaction was performed under three conditions in sodium phosphate buffer (pH 7) (a) Condition **A**; **1** : NEM : PPh_3 : 4-NP = 1 : 2 : 2 : 0.4; (b) Condition **B**; **1** : NEM : PPh_3 : 4-NP = 1 : 6 : 6 : 1.2 and (c) Condition **C**; **1** : NEM : PPh_3 : 4-NP = 1 : 10 : 10 : 2. The results of the experiment are summarized in the table below. Percentage conversion of **1** to product **4** was determined from the area under the peaks in the HPLC chromatograms. The results demonstrate that the reaction proceeded in quantitative conversion within 10 min under conditions **B** and **C**.

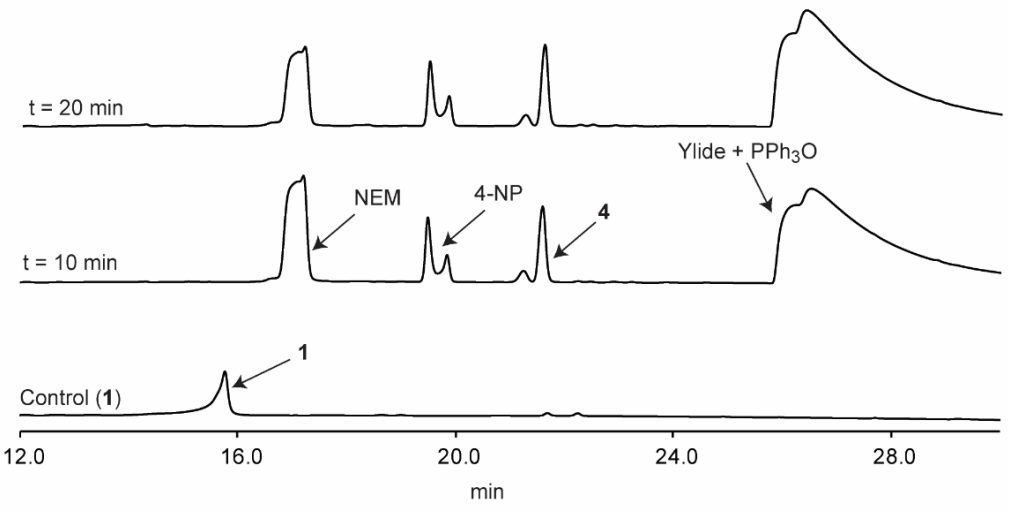


1 (μM)	Condition	NEM (μM)	PPh_3 (μM)	4-NP (μM)	% conversion of **1** to **4** at 1 min	% conversion of **1** to **4** at 10 min	% conversion of **1** to **4** at 20 min
50 μM	**A**	100	100	20	7	67	83
	B	300	300	60	40	100	99
	C	500	500	100	72	99	99

(a) Condition **A**; **1** : NEM : PPh_3 : 4-NP = 1 : 2 : 2 : 0.4



(b) Condition **B**; **1** : NEM : PPh_3 : 4-NP = 1 : 6 : 6 : 1.2



(c) Condition **C**; **1** : NEM : PPh_3 : 4-NP = 1 : 10 : 10 : 2

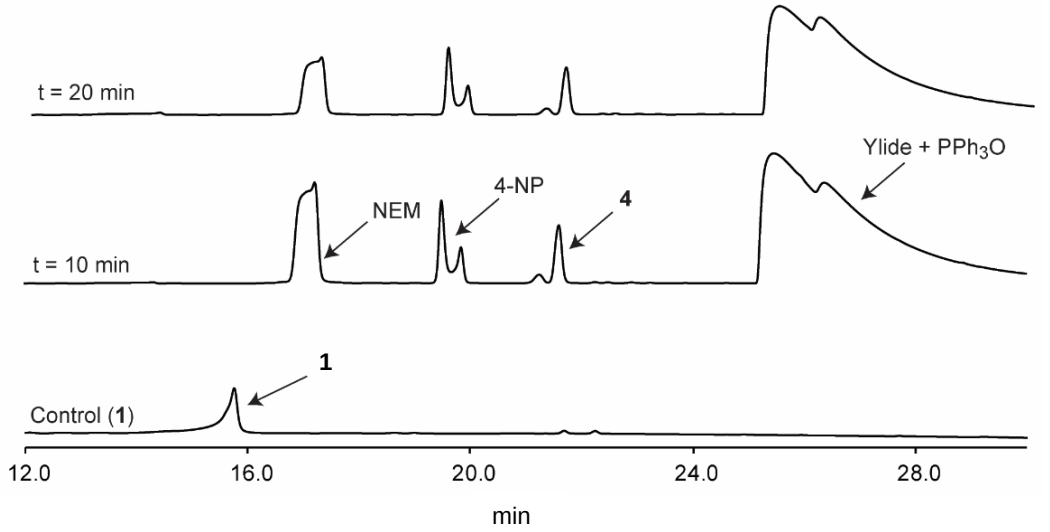


Figure S3. Kinetics of exocyclic olefinic maleimide (**4**) formation in presence of GSSG. The reaction was performed in sodium phosphate buffer (50 mM, pH 7) at room temperature with **1** (1.5 mM) : GSSG : NEM : PPh_3 : 4-NP = 1 : 5 : 2 : 2 : 0.4. Stacked HPLC chromatograms of the reaction showed that the reaction proceeded to completion within 5 min and GSSG retained integrity (area of peak for GSSG in control = 11436 and its area after 45 min = 11281).

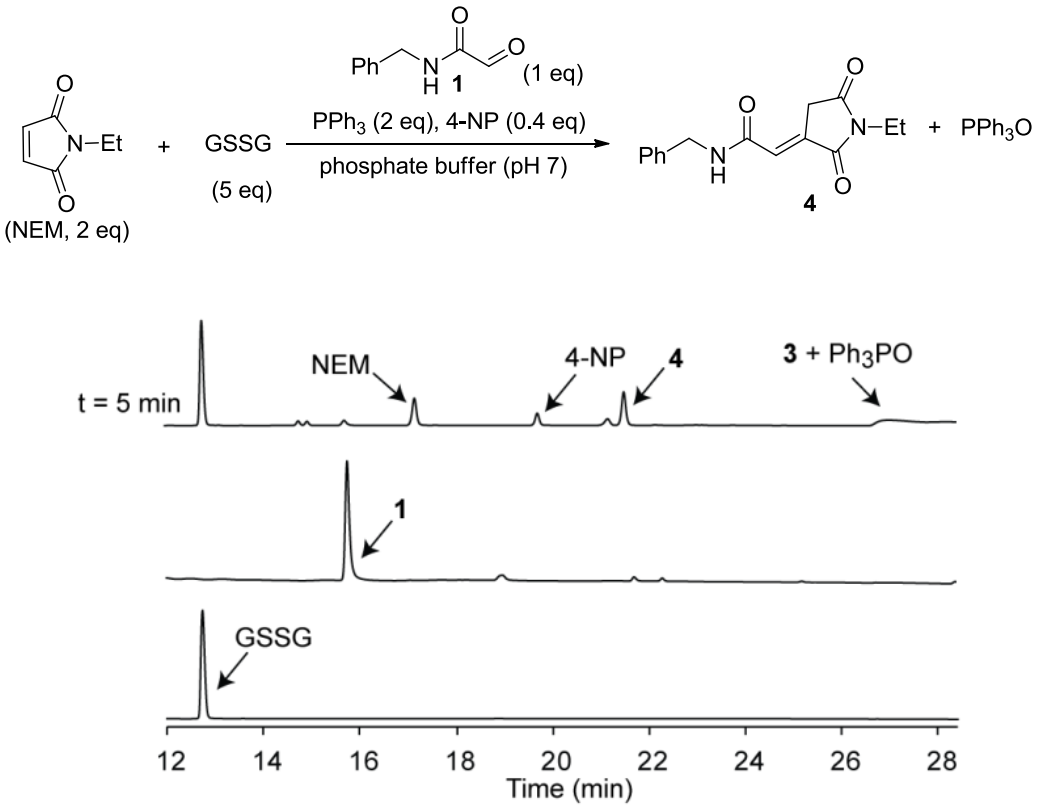


Figure S4. Stability of exocyclic olefinic maleimide (**4**) in sodium phosphate buffer at (a) pH 7 (b) pH 5 and (c) pH 8. The stacked HPLC chromatograms showed that the **4** is stable under acidic, neutral and basic pH.

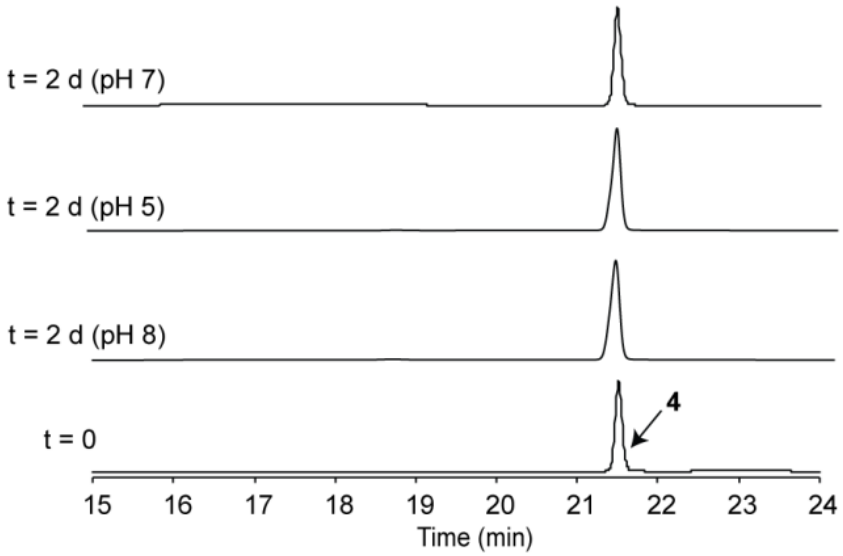


Figure S5. Kinetics of exocyclic olefinic maleimide formation with various aldehydes. (a) Benzaldehyde, (b) 4-nitrobenzaldehyde, (c) 2-nitrobenzaldehyde, (d) 4-fluorobenzaldehyde, (e) 4-carboxybenzaldehyde, (f) 3-methoxybenzaldehyde, (g) Cinnamaldehyde and (h) Hydrocinnamaldehyde. The reactions were performed in 50 mM sodium phosphate buffer (pH 7) at room temperature with aldehyde (1.5 mM) : NEM : PPh_3 : 4-NP = 1 : 2 : 2 : 0.4. Stacked HPLC chromatograms of these reactions showed >90% conversion of reactant aldehydes into the desired corresponding exocyclic olefinic maleimides.

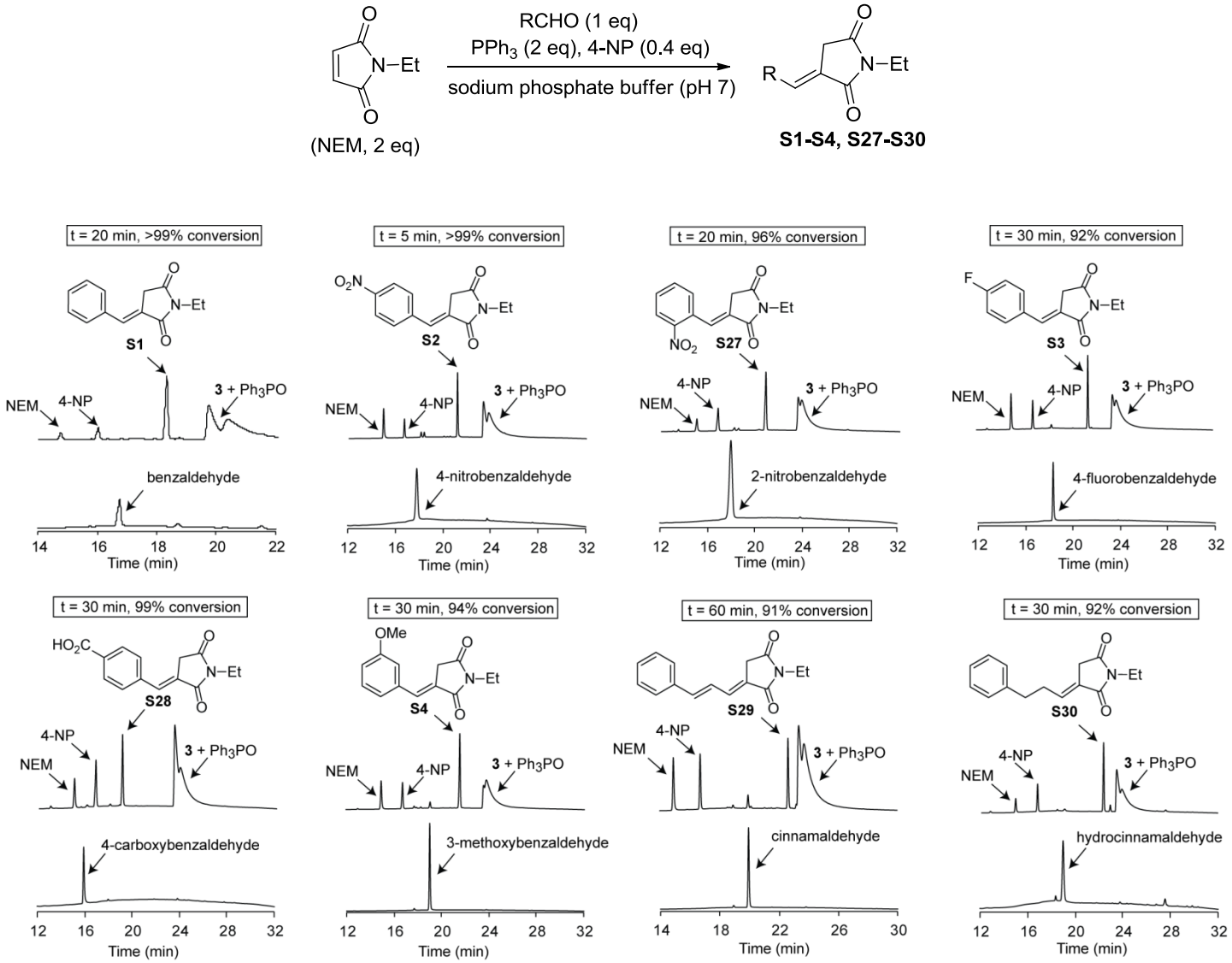
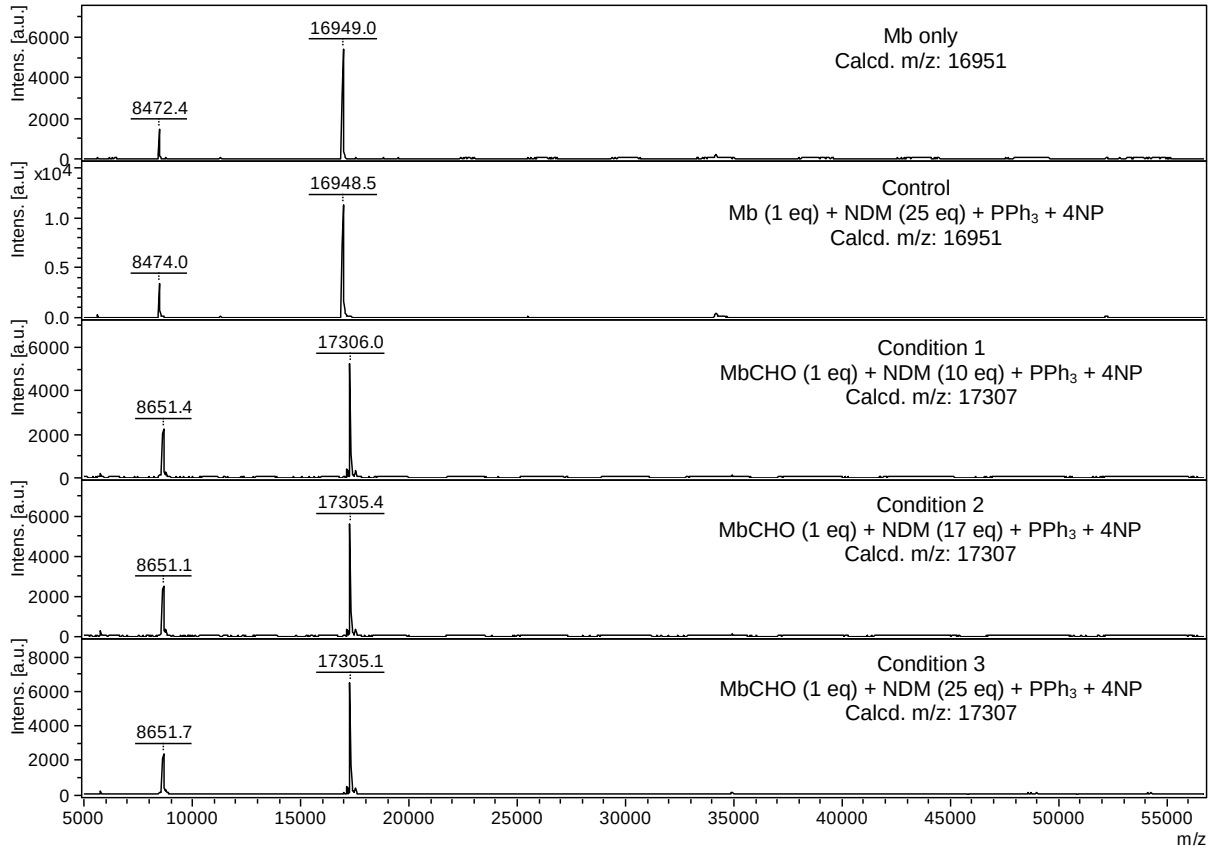


Figure S6. Fluorescent labelling of MbCHO with different equivalents of labelling reagents. The reactions were monitored and analyzed by (a) MALDI and (b) Tricine SDS-PAGE. Reactions were performed with MbCHO (30 μM) in sodium phosphate buffer (50 mM, pH 7) at room temperature for 2 h following the procedure described above in Section V (B). Condition 1 = MbCHO : NDM : PPh_3 : 4-NP = 1 : 10 : 10 : 2; Condition 2 = MbCHO : NDM : PPh_3 : 4-NP = 1 : 17 : 17 : 3.4 and Condition 3 = MbCHO : NDM : PPh_3 : 4-NP = 1 : 25 : 25 : 5. The results demonstrate that there is no labeling in the control sample and the labeling proceeded efficiently even with 10-fold excess of reagents (Condition 1).

(a)



(b)

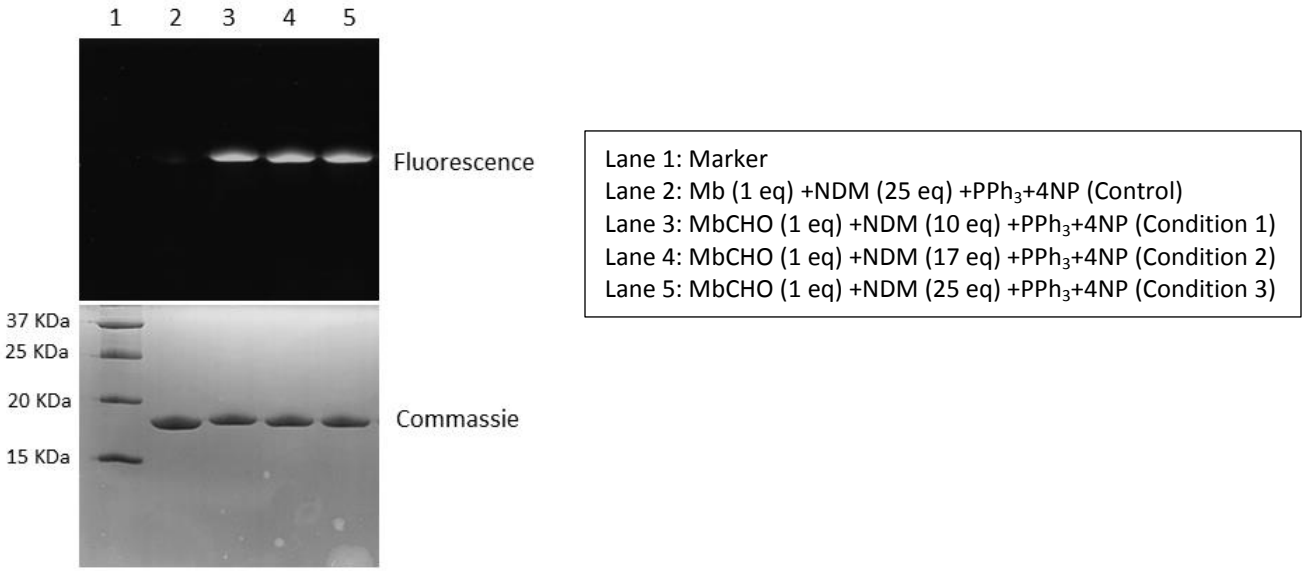


Figure S7. Mass spectra of myoglobin conjugate **7** tryptic digest. (a) MALDI analysis of trypsin digestion and (b) MS-MS fragmentation of modified peptide fragment (Label-LSDGEWQQVLNVWGK; m/z 2189 $[M+NH_4]^+$) of conjugate **7** obtained after trypsinization. Spectral data confirmed *N*-terminus labelling. The expected mass for the *N*-terminal peptide fragment of conjugated **7** = 2189 $[M+NH_4]^+$ and the mass obtained = 2189.2 $[M+NH_4]^+$. The MS-MS fragmentation verified the MALDI data of trypsin digested **7** by the presence of several modified masses such as B4, B5 and B6. (For B4 expected mass = 769 $[M+Na]^+$, obtained mass = 769, for B5 expected mass = 826 $[M+Na]^+$, obtained mass = 826.4 and for B6 expected mass = 955 $[M+Na]^+$, obtained mass = 955.1).

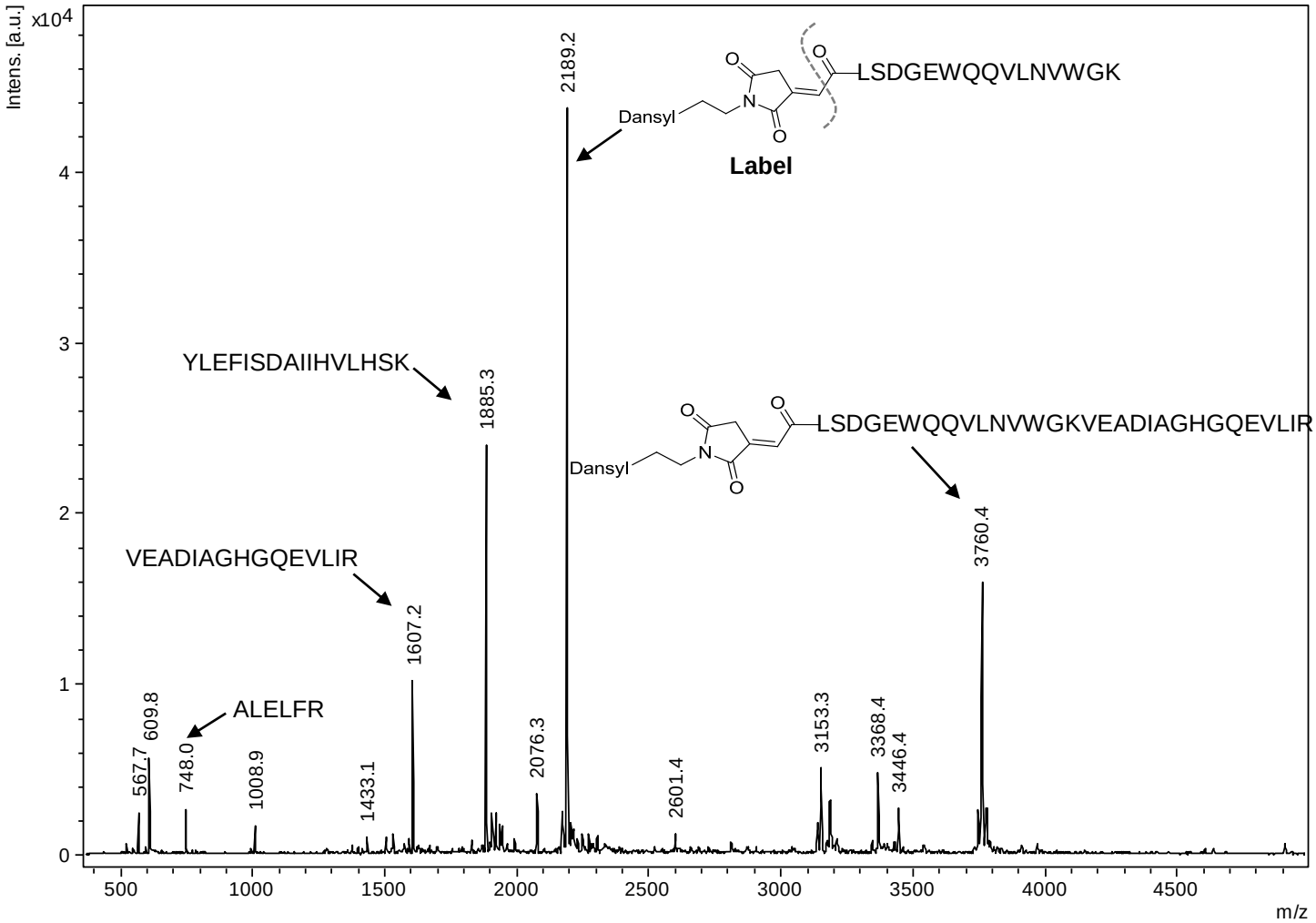
Sequence of myoglobin conjugate **7:**

Label-*LSDGEWQQVLNVWGKVEADIAGHGQEVLIRLFTGHPETLEKFDKFKHLKTEAEMKASEDLKK
HGTVVLTALGGILKKKGHHEAELKPLAQSHATKHKIPIKYLEFISDAIIHVLHSKHPGDFGADAQGAMTK
ALELFRNDIAAKYKELGFQG
(*Second amino acid residue)

Calculated (*m/z*)$^{\#}$	Sequence range	Peptide sequence
748 $[M+H]^+$	134-139	ALELFR
1607 $[M+H]^+$	17-31	VEADIAGHGQEVLIR
1885 $[M+H]^+$	103-118	YLEFISDAIIHVLHSK
2189 $[M+NH_4]^+$	1-16	**Label**-LSDGEWQQVLNVWGK
3760 $[M+H]^+$	1-31	**Label**-LSDGEWQQVLNVWGKVEADIAGHGQEVLIR

$^{\#}$Masses of observed m/z are shown.

(a)



(b)

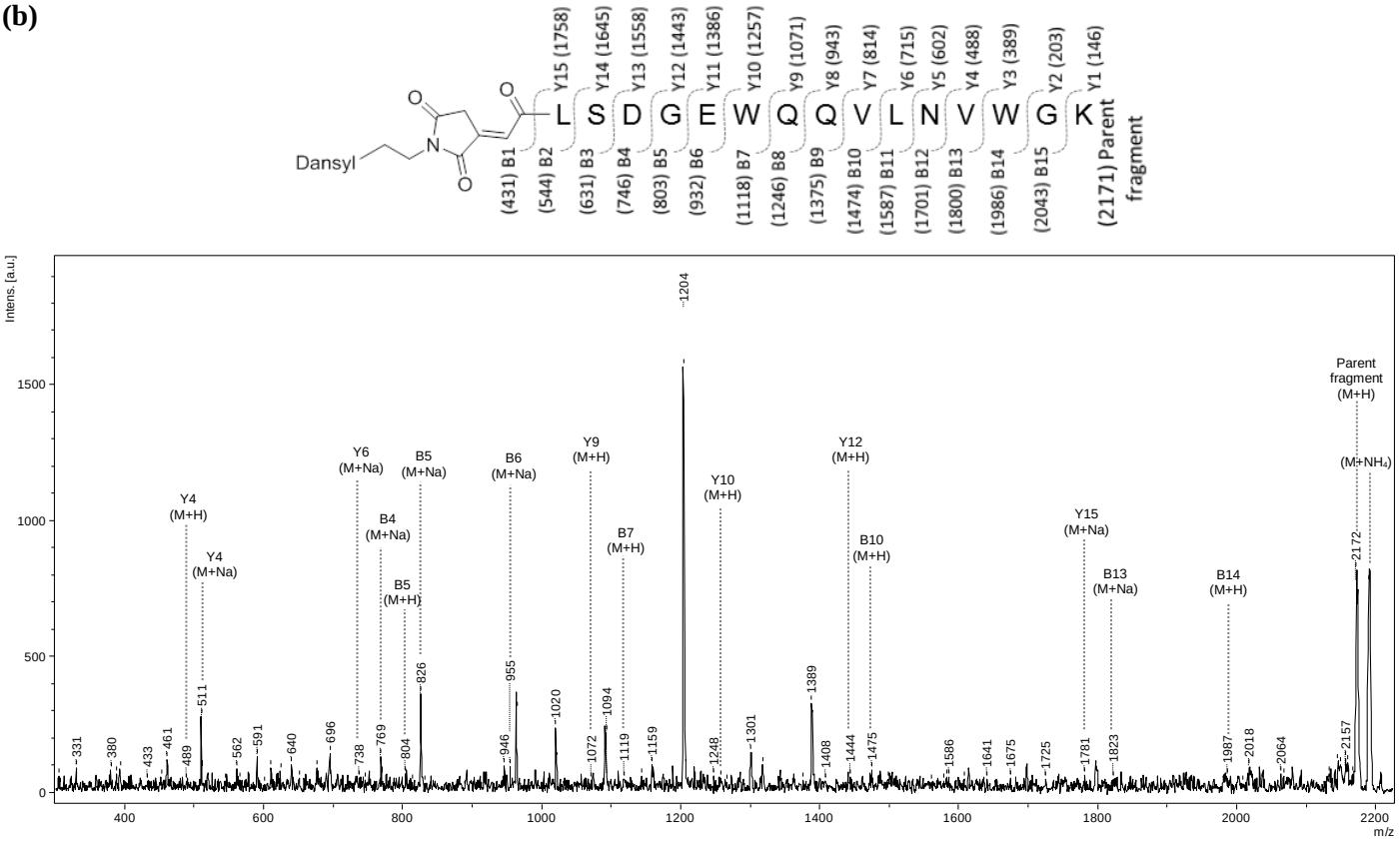


Figure S8. The overlay circular dichroism (CD) spectra for myoglobin before and after modification. Data was acquired with 7 μM protein solution in water at 25 ºC using a quartz cuvette of 1 mm pathlength. The results demonstrate that the labelling conditions are mild, well-tolerated, and modified proteins (conjugates **6** and **7**) retains the secondary structure of the wild-type protein.

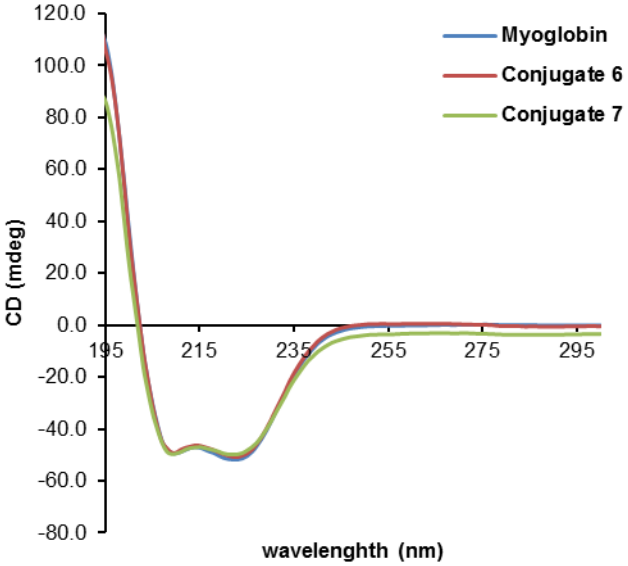


Figure S9. Kinetics of oxime formation in the presence of a 1,4-diaminobenzene catalyst. The reaction was performed in sodium phosphate buffer (50 mM, pH 7) at room temperature with **1** (1.5 mM) : $BnONH_2$ = 1 : 2 and 0.4 eq (left panel) and 5.0 eq (right panel) of catalyst. Stacked HPLC chromatograms of the reactions showed a 20% conversion of **1** into oxime **S31** in 8.5 h with 0.4 eq of catalyst and 55% conversion in 7.5 h with 5.0 eq of catalyst.

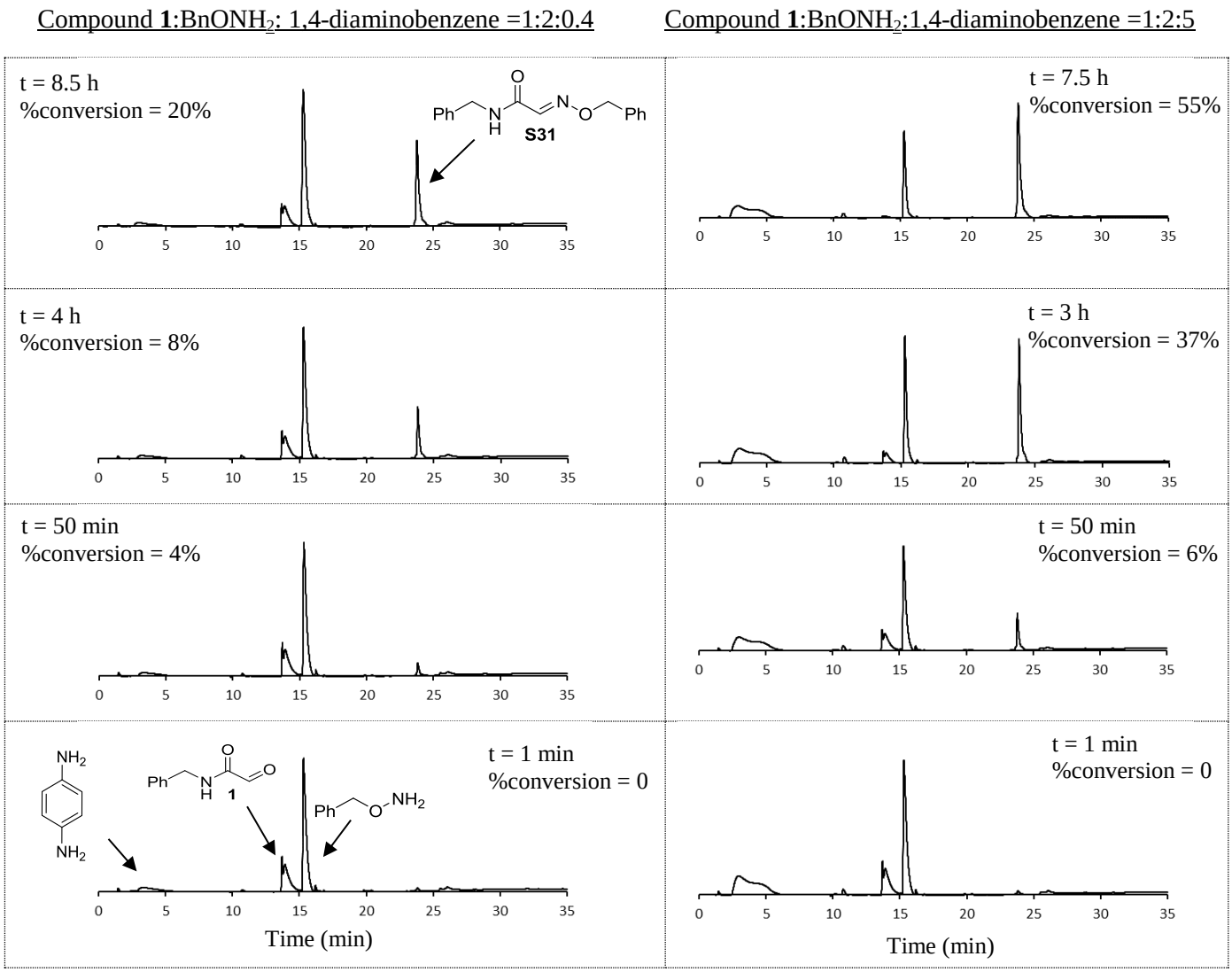


Figure S10. SDS-PAGE analysis of fluorescent labelling of MbCHO using two different methods. Bioconjugation reactions were performed with MbCHO (30 μM) in sodium phosphate buffer (50 mM, pH 7) at room temperature for 2 h following the procedure described above in Section V (B). Method 1 (our method) = MbCHO : NDM : PPh_3 : 4-NP = 1 : 25 : 25 : 5 and Method 2 (oxime formation) = MbCHO : $DanONH_2$: 1,4-diaminobenzene = 1 : 25 : 5 or 25. No fluorescence was observed in the reactions of MbCHO with $DanONH_2$ (lanes 5 and 6) whereas our method gave a fluorescent band for the myoglobin conjugate **7** (lane 7) demonstrating efficient labelling.

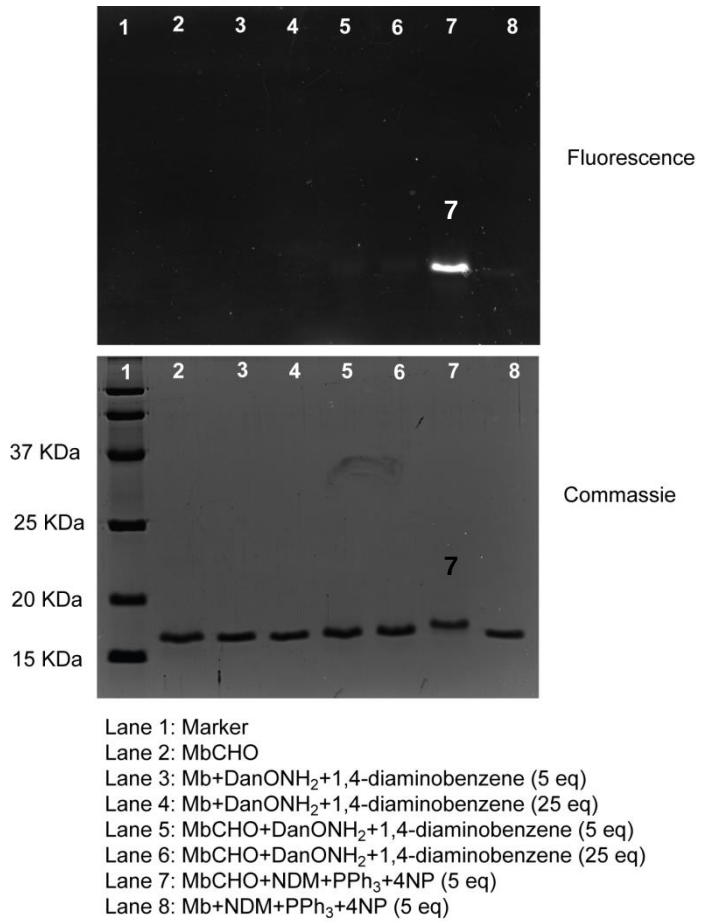


Figure S11. Synthesis and stability of GSH adduct of TRAP6-EXO peptide (**S32**). (a) Formation of GSH conjugate of TRAP6-EXO peptide (**S32**), (b) Stability of **S32** in presence of *N*-acetylcysteine (NAC, 20 eq) in sodium phosphate buffer (pH 7). Both the reactions were performed in 50 mM sodium phosphate buffer (pH 7) and monitored by HPLC analysis. The thiol addition of GSH to TRAP6-EXO to give **S32** was completed in 1.5 h to give a diastereomeric peaks. Stability of the resultant thioether adduct showed that the conjugate was extremely stable and no decomposition/thiol exchange was observed upon in presence of NAC over the course of 2 days.

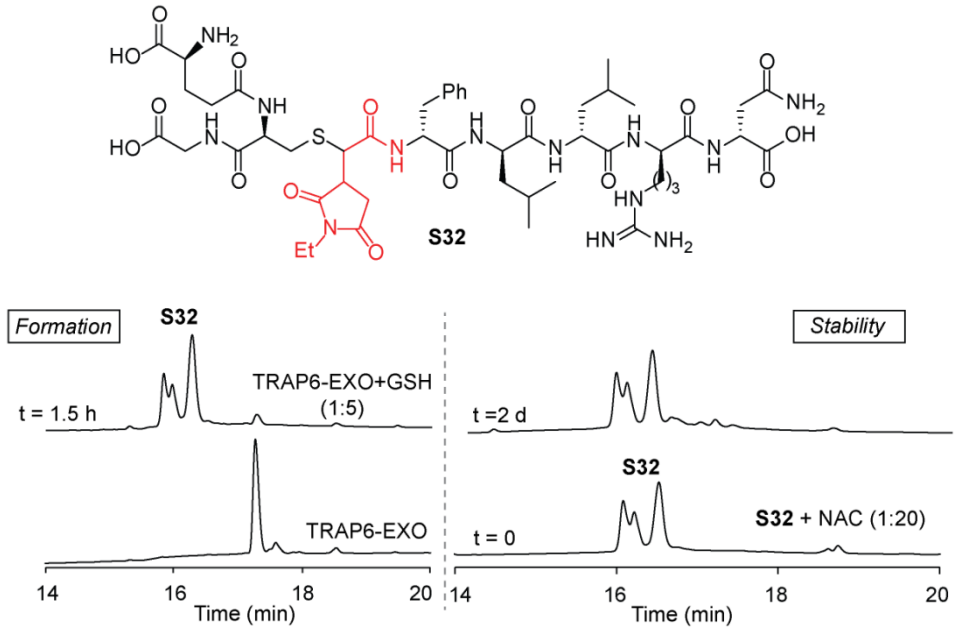


Figure S12. Enlarged version of the Figure 5c of the main text.

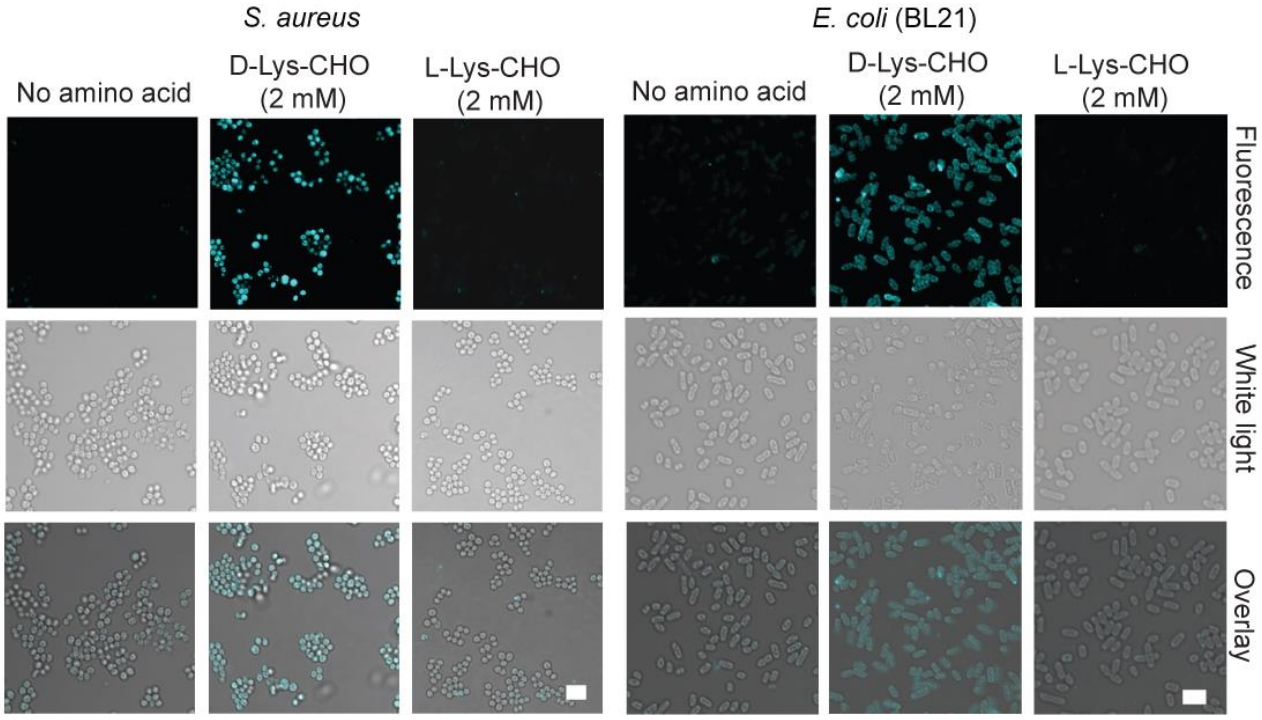
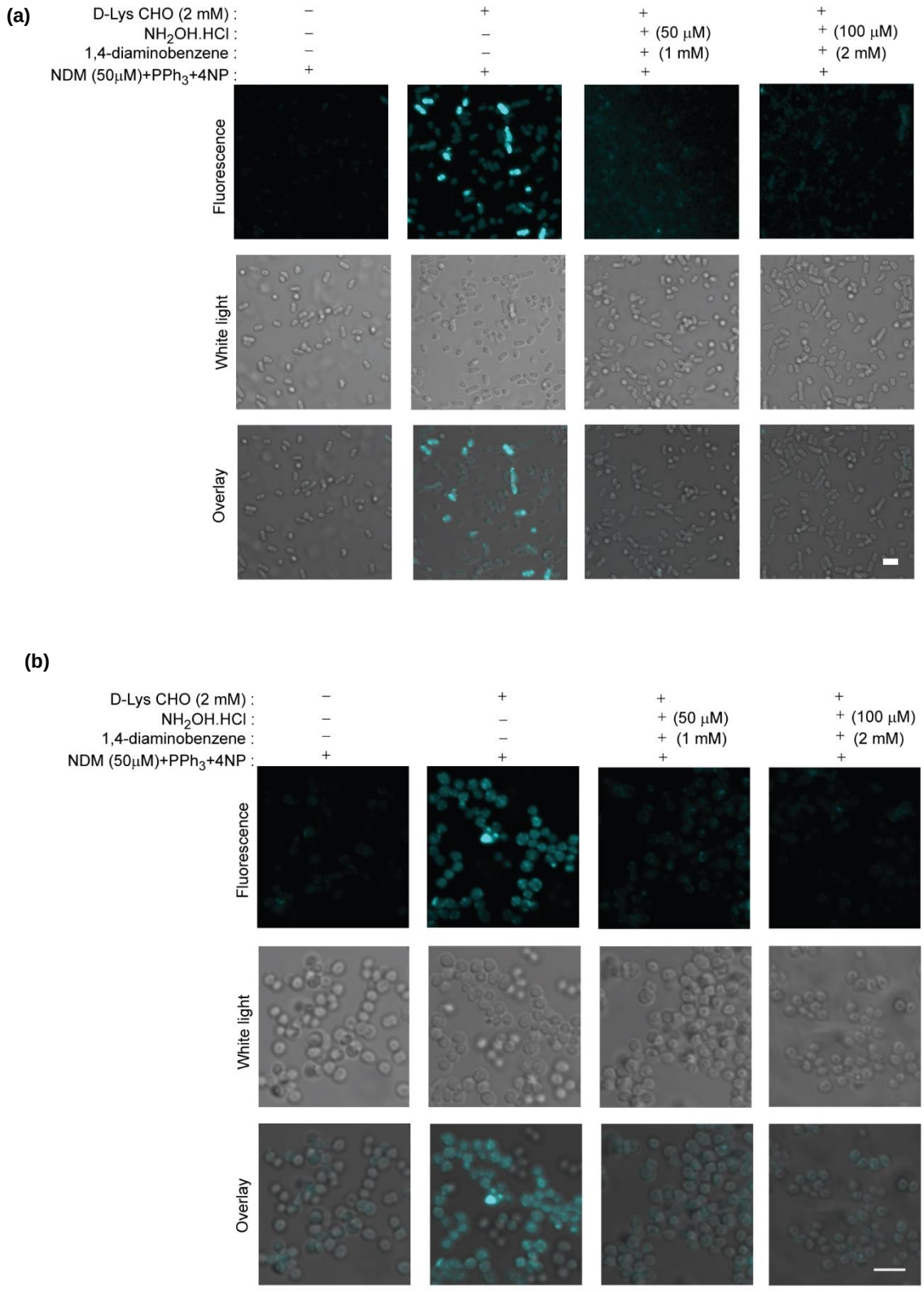
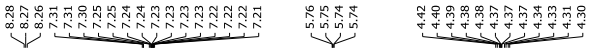
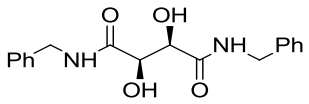


Figure S13. Competitive fluorescent labelling of bacterial cell walls of (a) *E. coli* and (b) *S. aureus*. The results demonstrate that the fluorescent labelling of the cell walls is significantly reduced in hydroxylamine hydrochloride and aniline catalyst-treated cells. These results support the conclusion that our method of *in-situ* generation of maleimido-phosphonium ylide is selective to the aldehyde functional group and the reduced labelling in the treated cells is due to the formation of non-fluorescent oxime adducts with the aldehydes. Scale bars represent 3 μm in both the images.

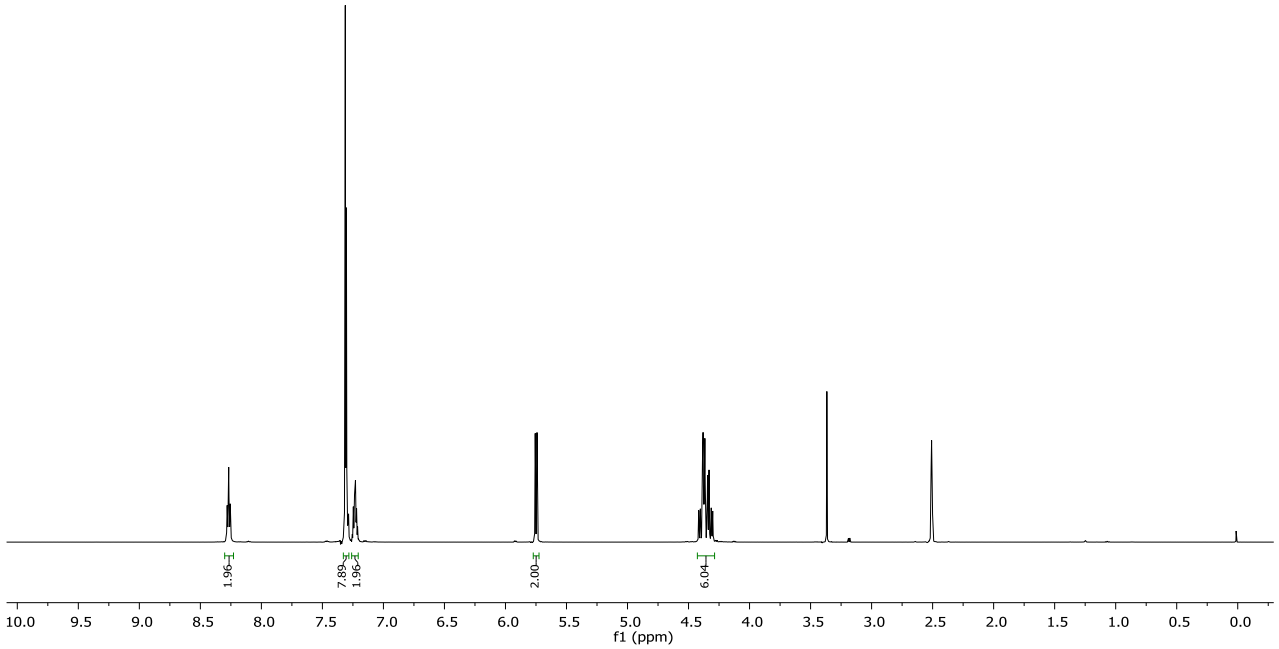


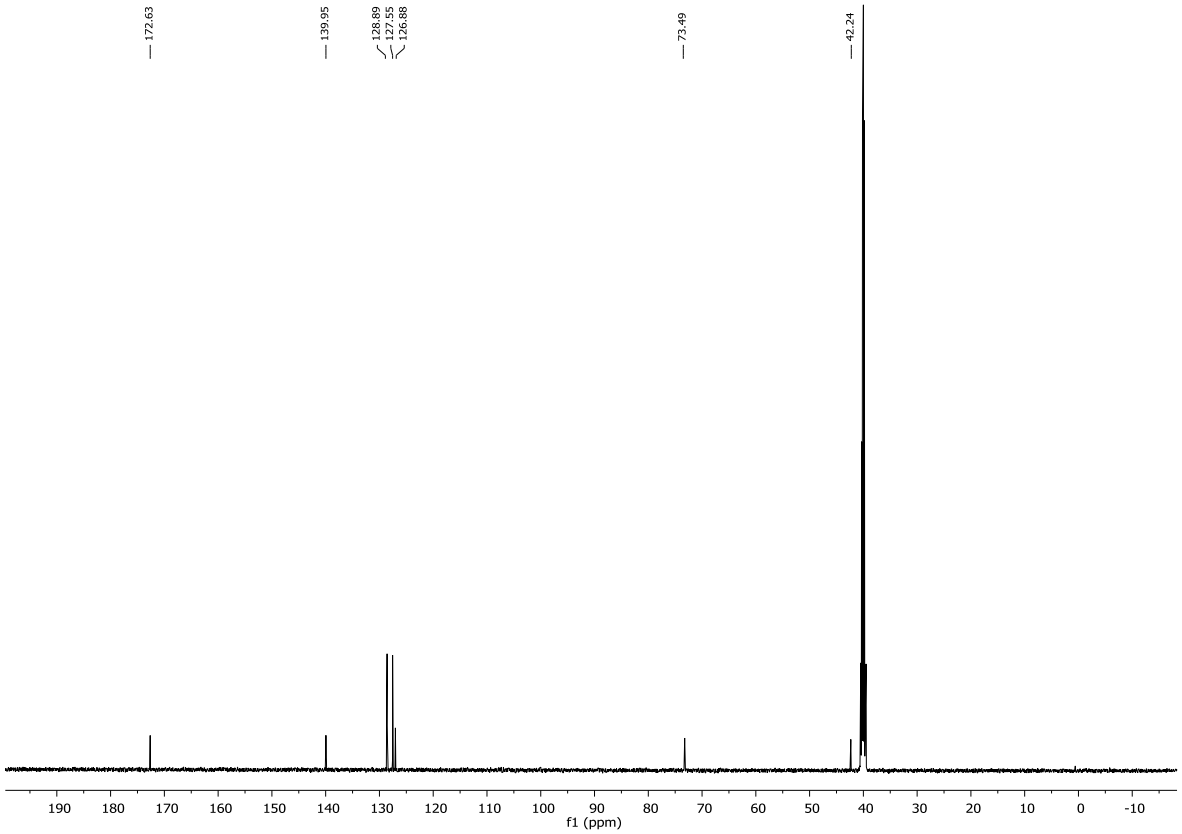
VIII. NMR spectral data

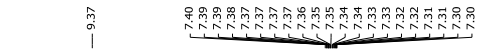




S11



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7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.30
7.30
4.55
4.54
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1.88
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1.87
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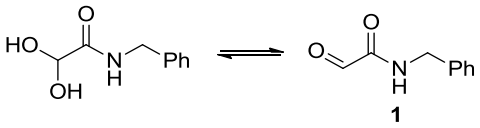
1.87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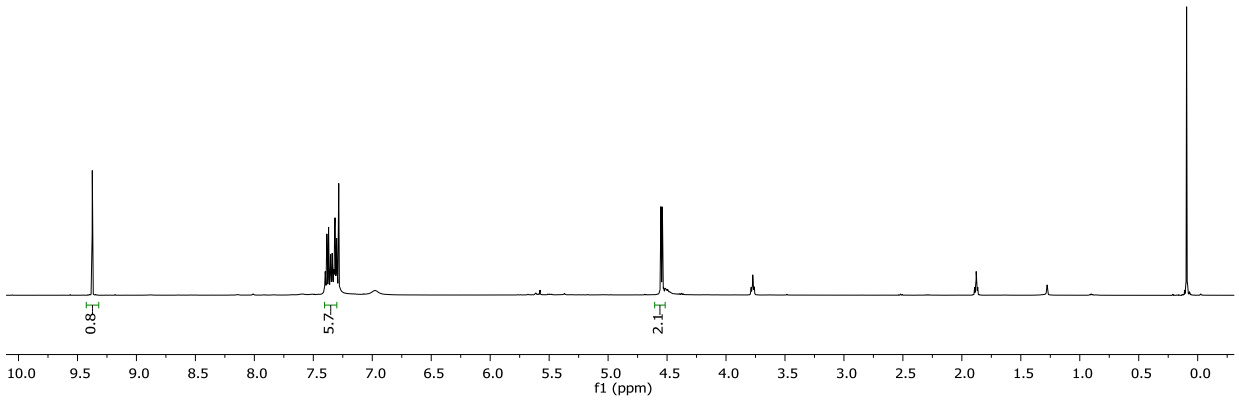
N
H
Ph
OH
O
O
N
H
Ph

1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9.5
9.0
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7.0
6.5
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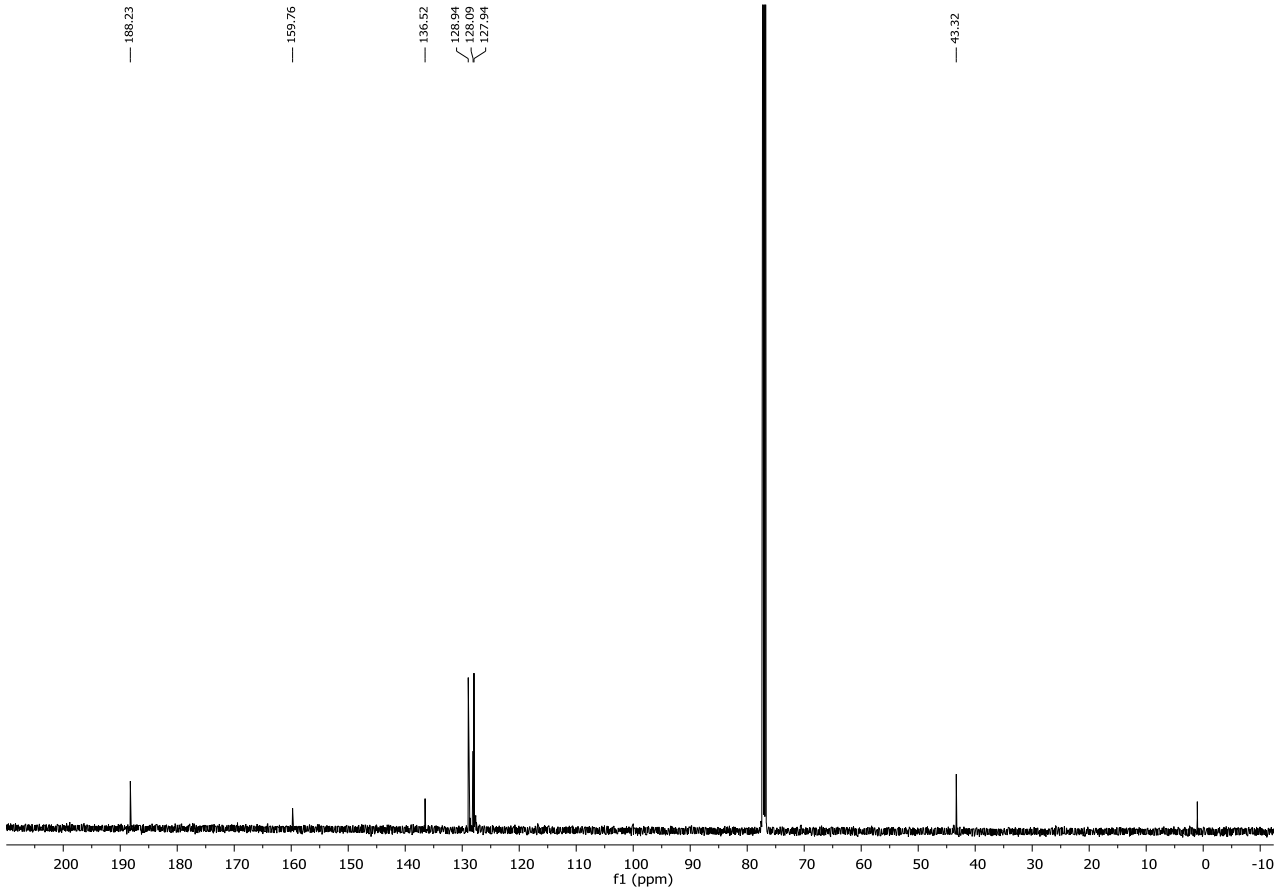
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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128.94
128.09
127.94
43.32
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.32
7.32
7.31
7.30
7.30
7.30
7.29
7.29
7.28
7.26
7.25
7.25
7.25
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7.19
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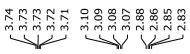
7.17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3.08
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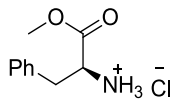
2.88
2.86
2.85
2.83

1.53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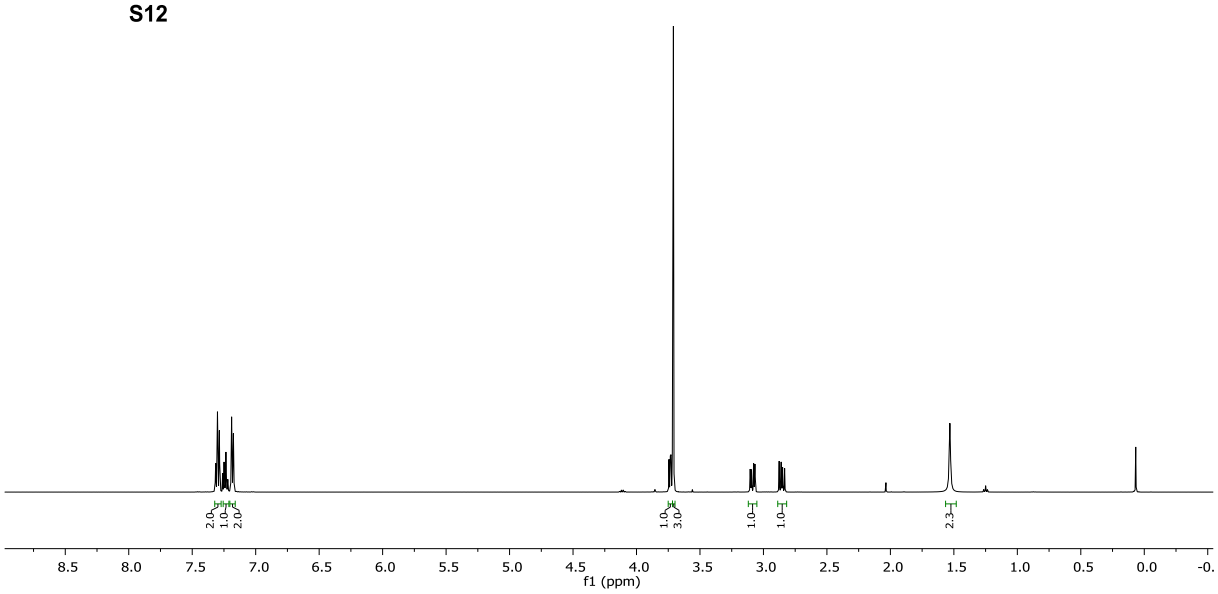
Ph
NH3
Cl

S12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3.0
1.0
1.0
2.3
8.5
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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
0.0
-0.
f1 (ppm)


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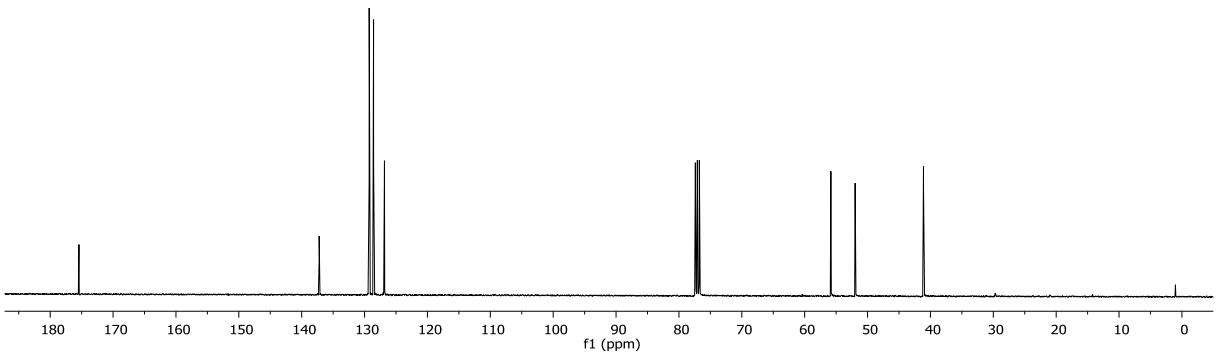
129.3
128.6
126.8


55.8
52.0
41.1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160
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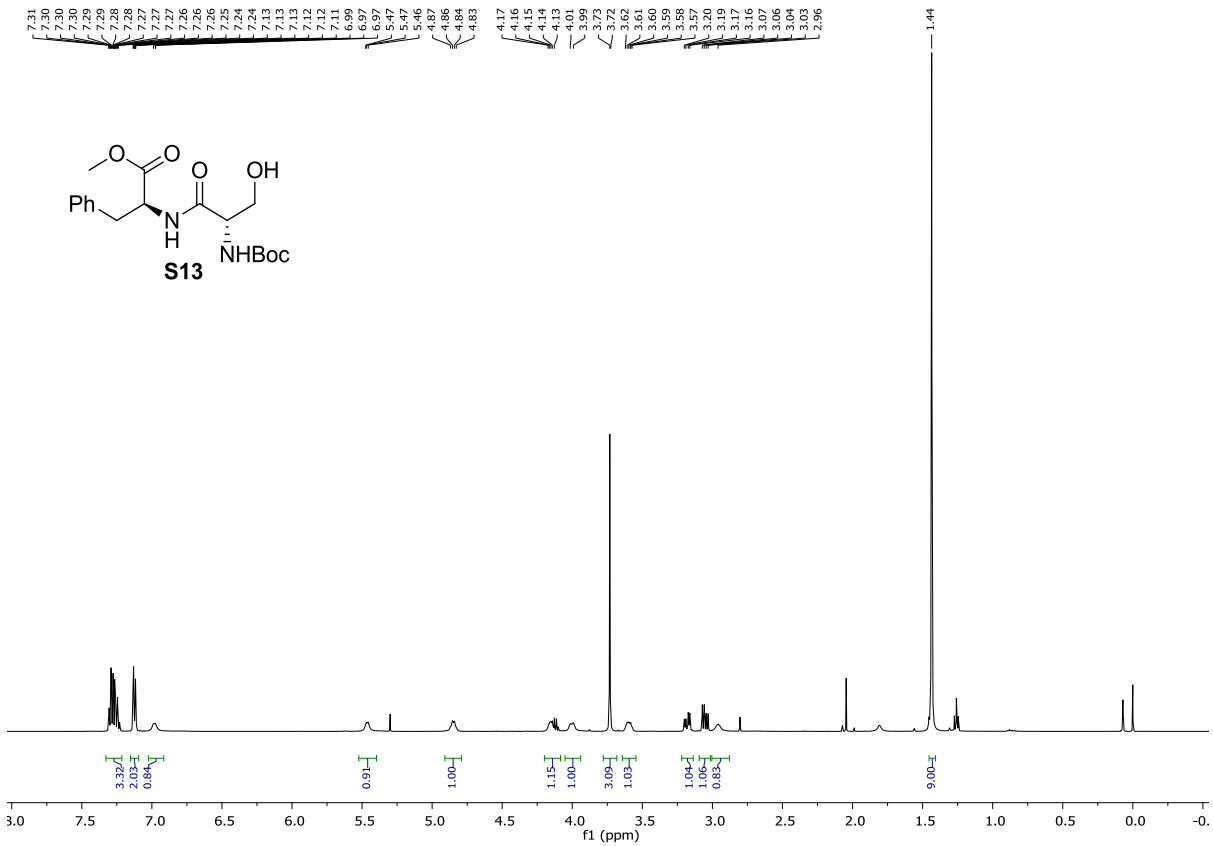
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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O
O
O
OH
Ph
N
H
NHBoc
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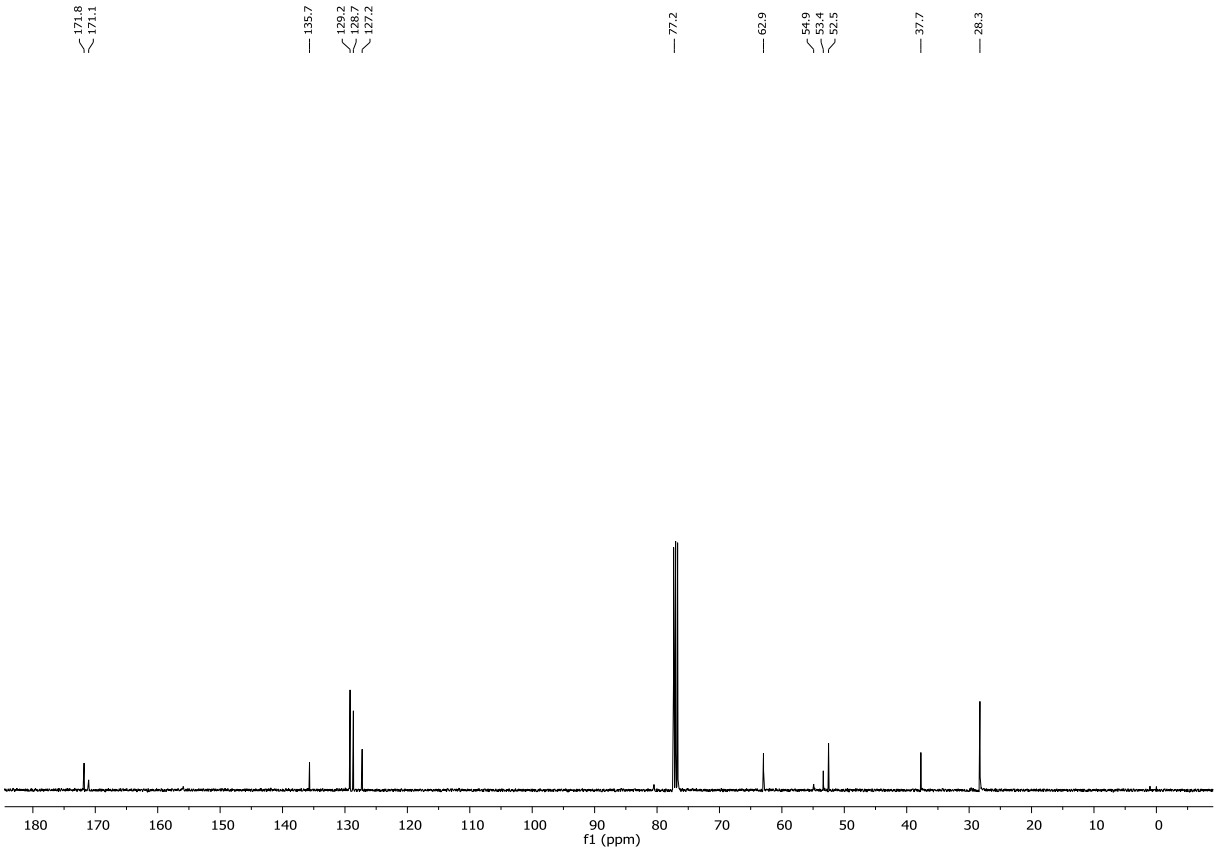
3.32 2.03 0.84 0.91 1.00 1.15 1.00 3.09 1.03 1.04 1.06 0.83 9.00
f1 (ppm)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62.9
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53.4
52.5
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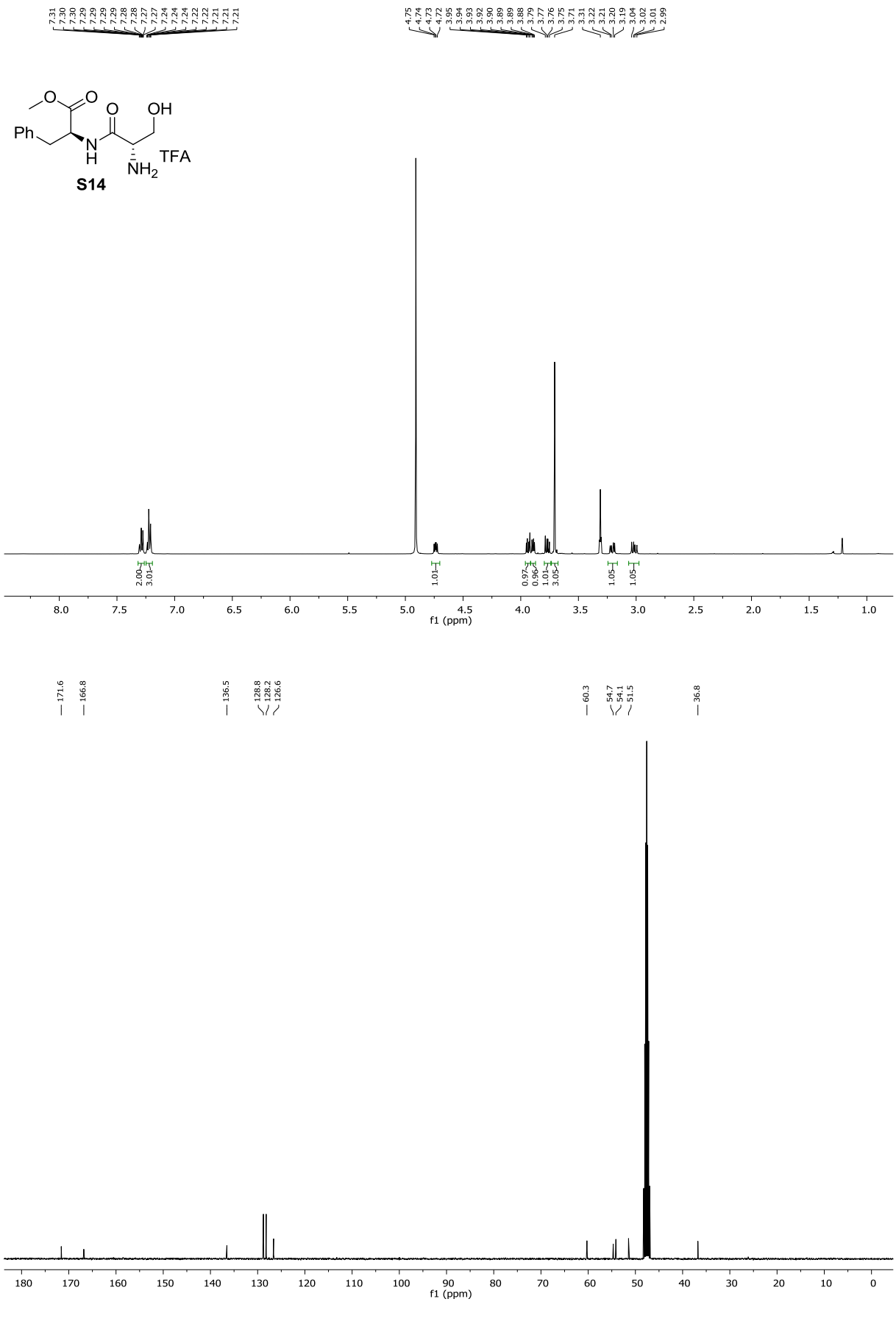
28.3
f1 (ppm)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O
O
O
OH
Ph
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H
NH2
TFA
S14
2.00
3.01
1.01
0.97
0.96
1.01
3.05
1.05
1.05
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)
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166.8
136.5
128.8
128.2
126.6
60.3
54.7
54.1
51.5
36.8
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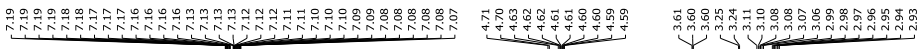
f1 (ppm)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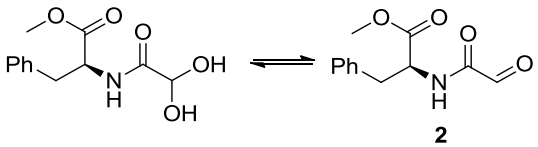
4.71 4.70 4.63 4.62 4.62 4.61 4.61 4.60 4.60 4.60 4.59 4.59
3.61 3.60 3.60 3.25 3.24 3.11 3.10 3.08 3.08 3.07 3.06 2.99 2.98 2.97 2.96 2.95 2.94 2.93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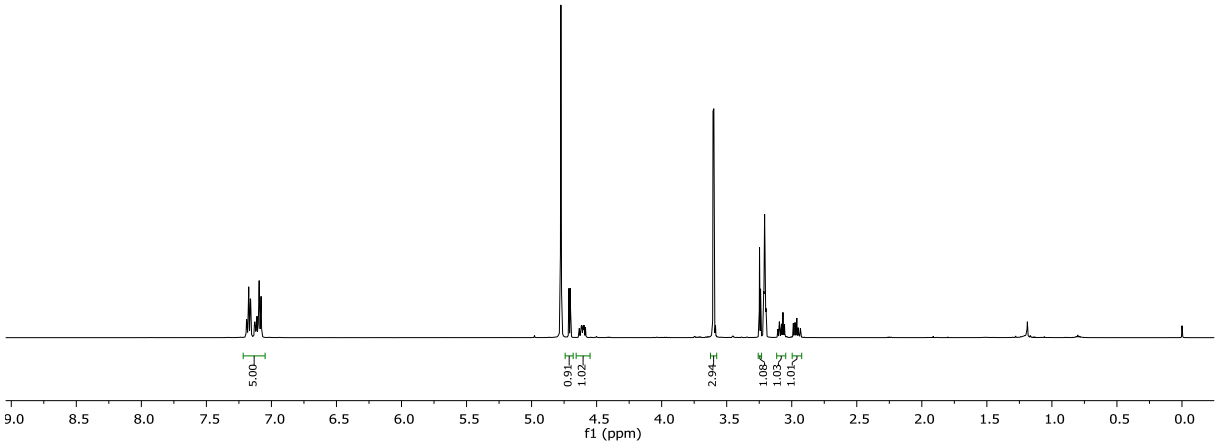
H
O
OH
OH
O
O
Ph
N
H
O
O

2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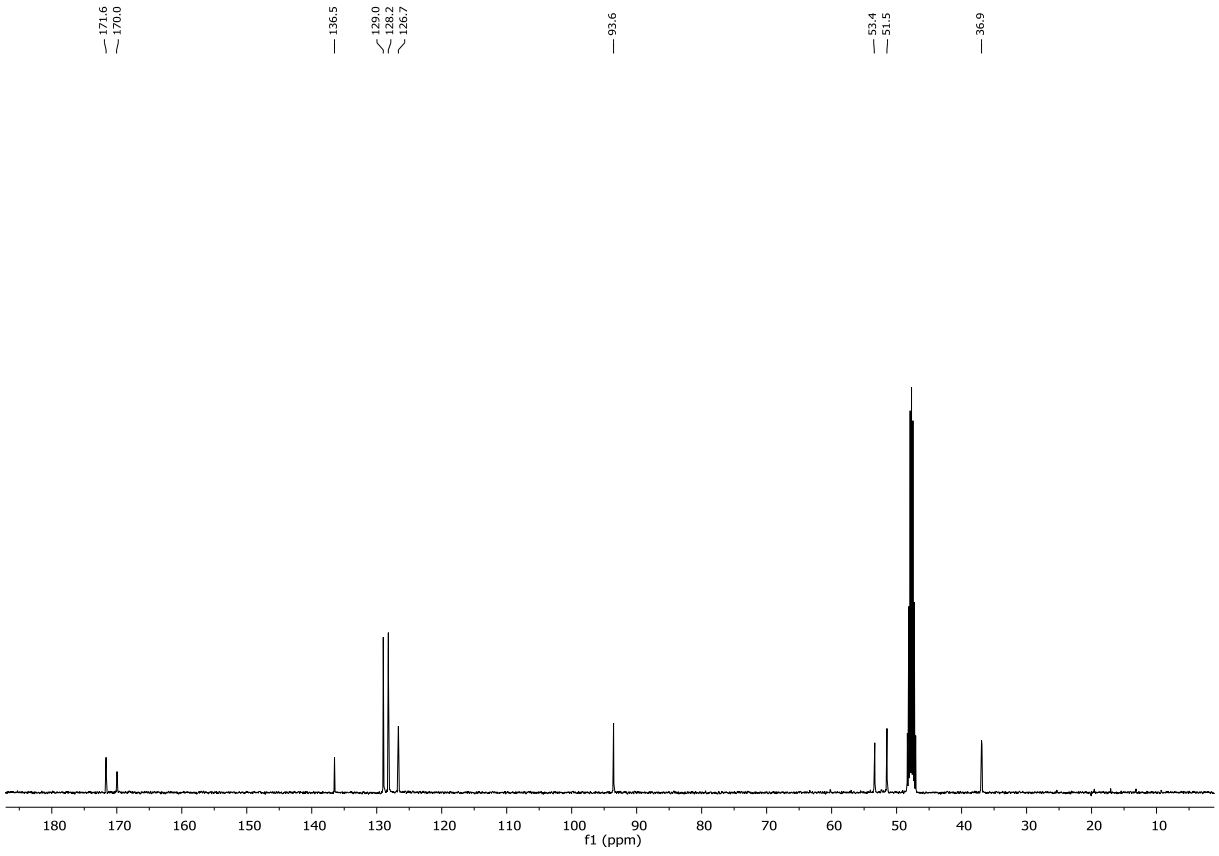
1.08
1.03
1.01
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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51.5
36.9
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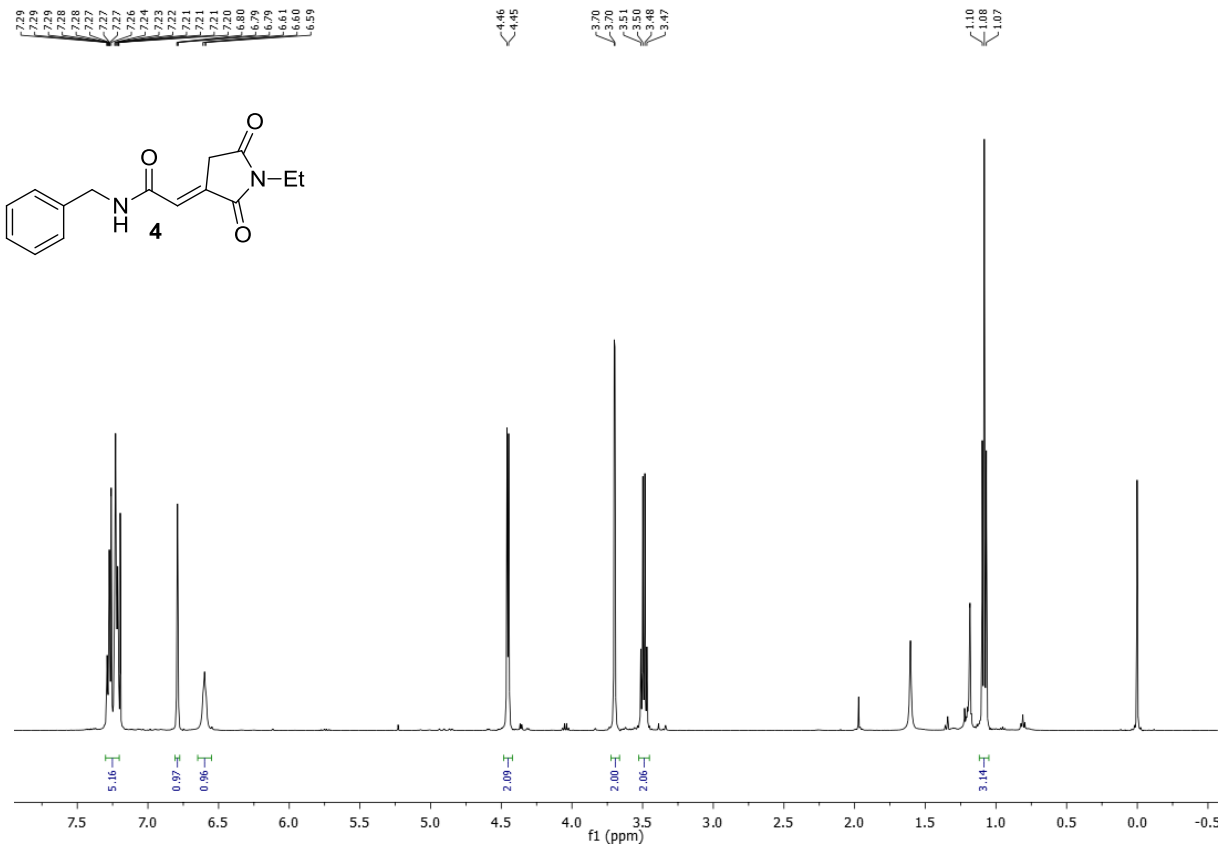
f1 (ppm)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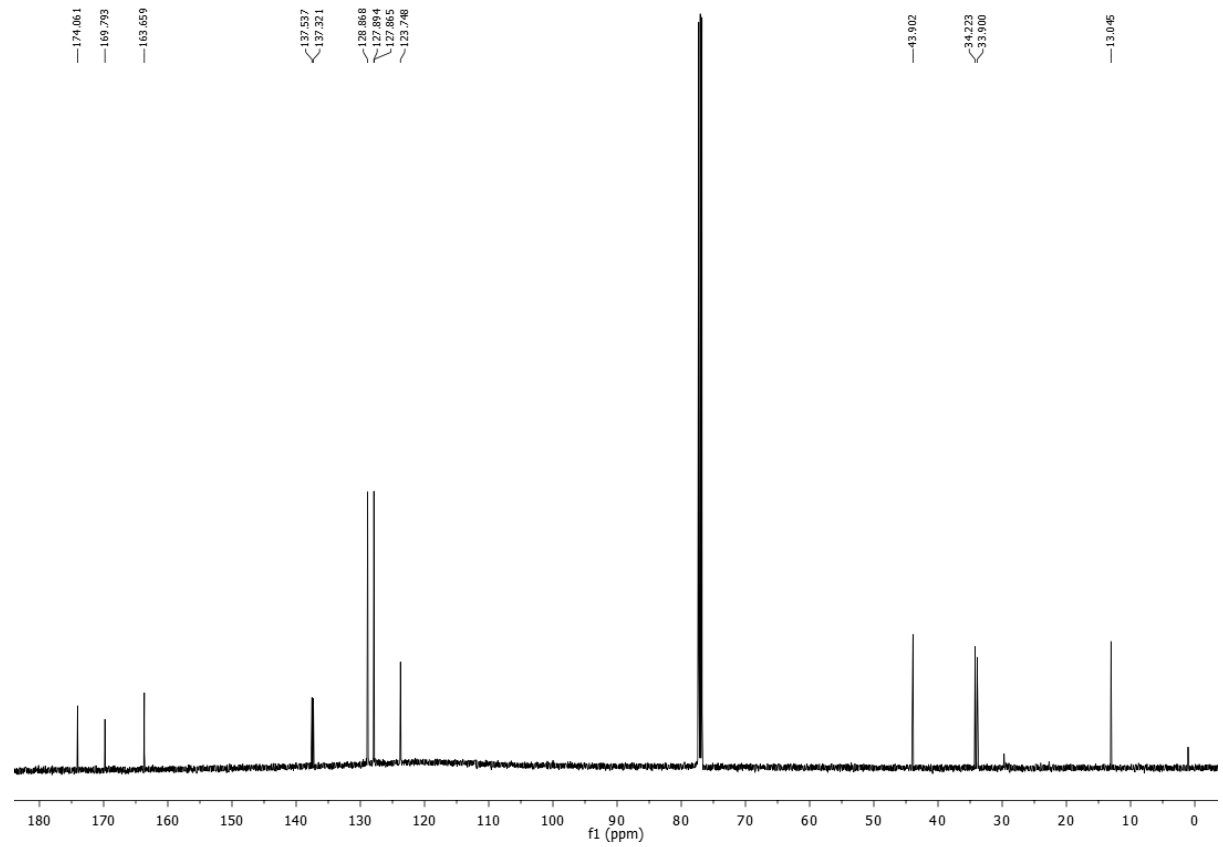
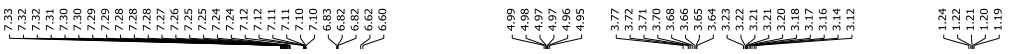
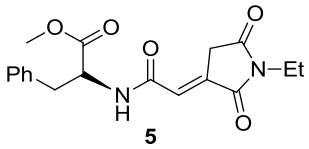
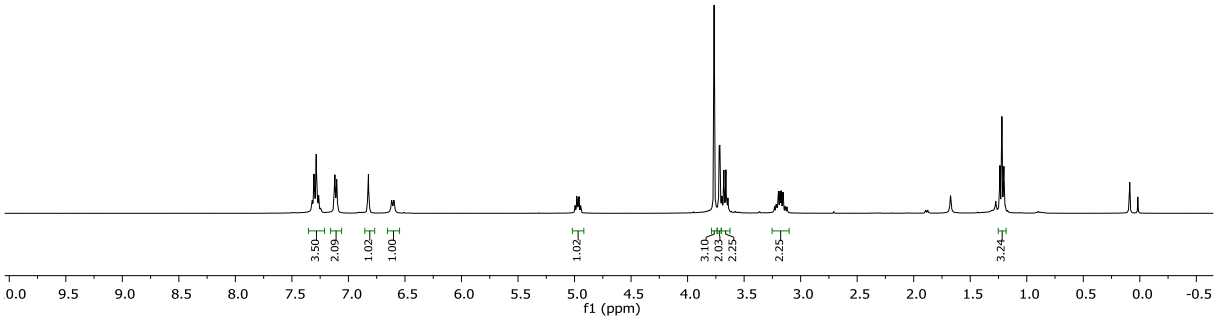
7.21
7.21
7.20
6.80
6.79
6.79
6.61
6.60
6.59
4.46
4.45
3.70
3.70
3.51
3.50
3.48
3.47
1.10
1.08
1.07
O
O
N–Et
N
H
O
4
5.16
0.97
0.96
2.09
2.00
2.06
3.14
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


174.061
169.793
163.659
137.537
137.321
128.868
127.894
127.865
123.748
43.902
34.223
33.900
13.045
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

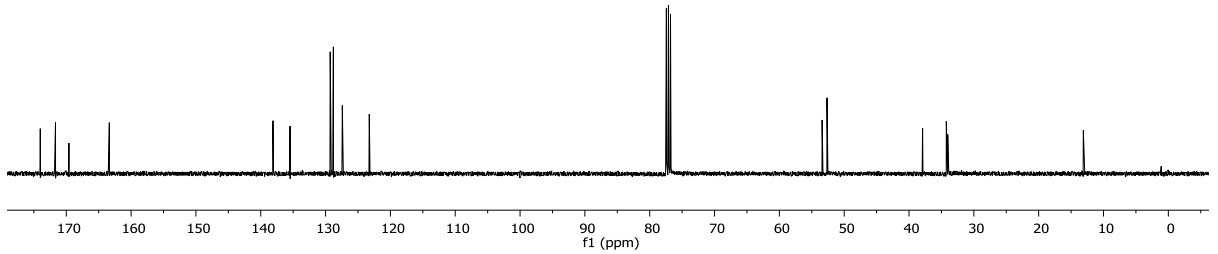

7.33 7.32 7.32 7.31 7.30 7.30 7.29 7.29 7.28 7.28 7.28 7.27 7.26 7.25 7.25 7.24 7.24 7.12 7.12 7.11 7.11 7.10 7.10 6.83 6.82 6.82 6.62 6.60
4.99 4.98 4.97 4.97 4.97 4.96 4.95
3.77 3.72 3.71 3.70 3.68 3.66 3.65 3.64 3.23 3.22 3.21 3.21 3.20 3.18 3.17 3.16 3.14 3.12
1.24 1.22 1.21 1.20 1.19

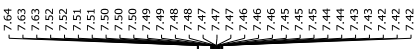

O
O
O
Ph
N
H
O
N–Et
O

5


3.50
2.09
1.02
1.00
1.02
3.10
2.03
2.25
2.25
3.24
0.0 9.5 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 0.0 -0.5
f1 (ppm)

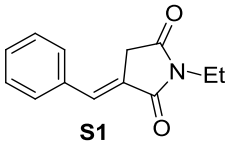

174.01
171.66
169.59
163.36
138.12
135.48
129.28
128.80
127.42
123.26
53.41
52.66
37.91
34.25
34.03
13.11


170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

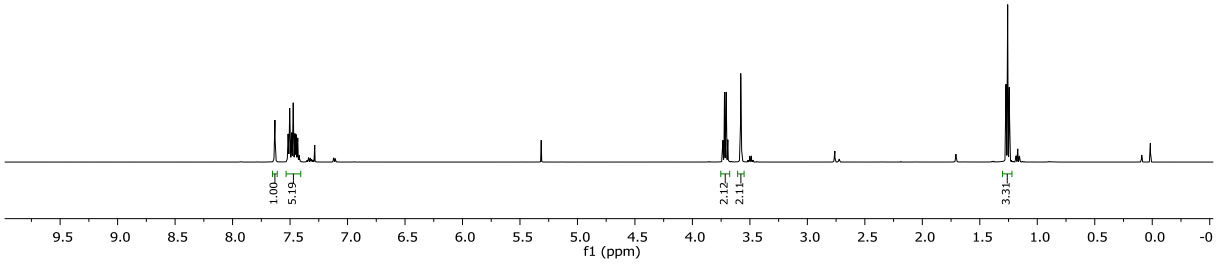

7.64
7.63
7.63
7.52
7.52
7.51
7.51
7.50
7.50
7.50
7.49
7.49
7.48
7.48
7.47
7.47
7.47
7.46
7.46
7.46
7.45
7.45
7.45
7.44
7.44
7.43
7.43
7.42
7.42
7.42


3.74
3.72
3.71
3.69
3.58
3.58


1.27
1.26
1.24

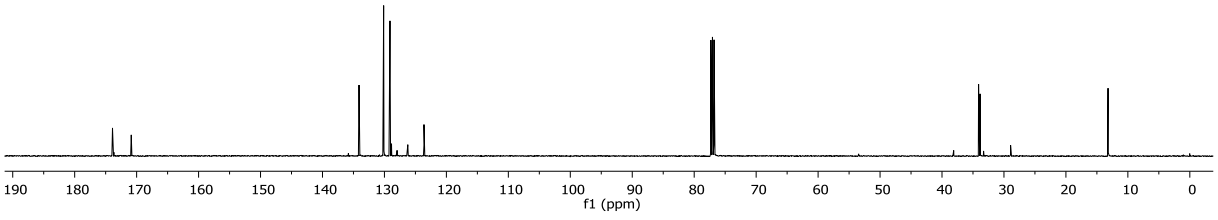

O
N
Et
O

S1


1.00
5.19
2.12
2.11
3.31
9.5
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
0.0
-0
f1 (ppm)

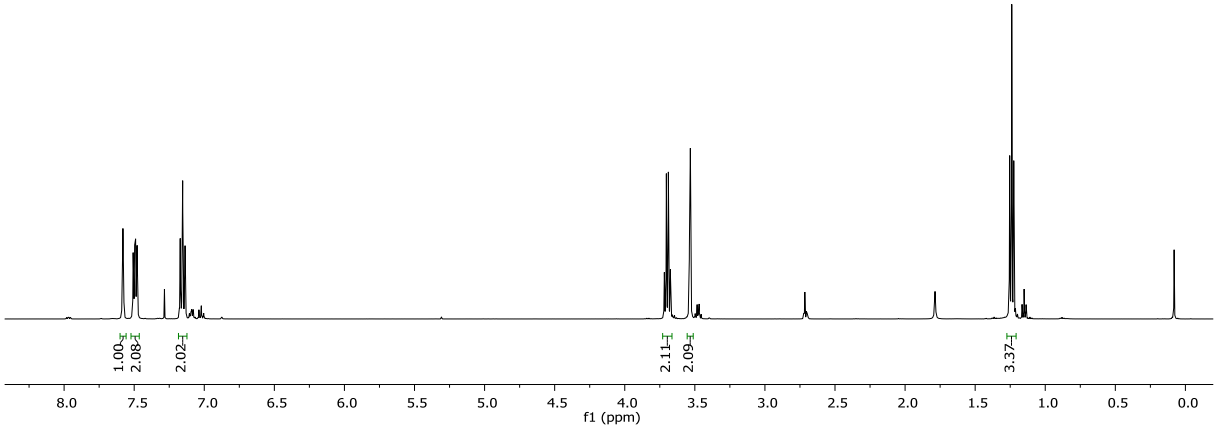

173.89
170.87
134.14
134.10
130.13
130.11
129.11
123.62

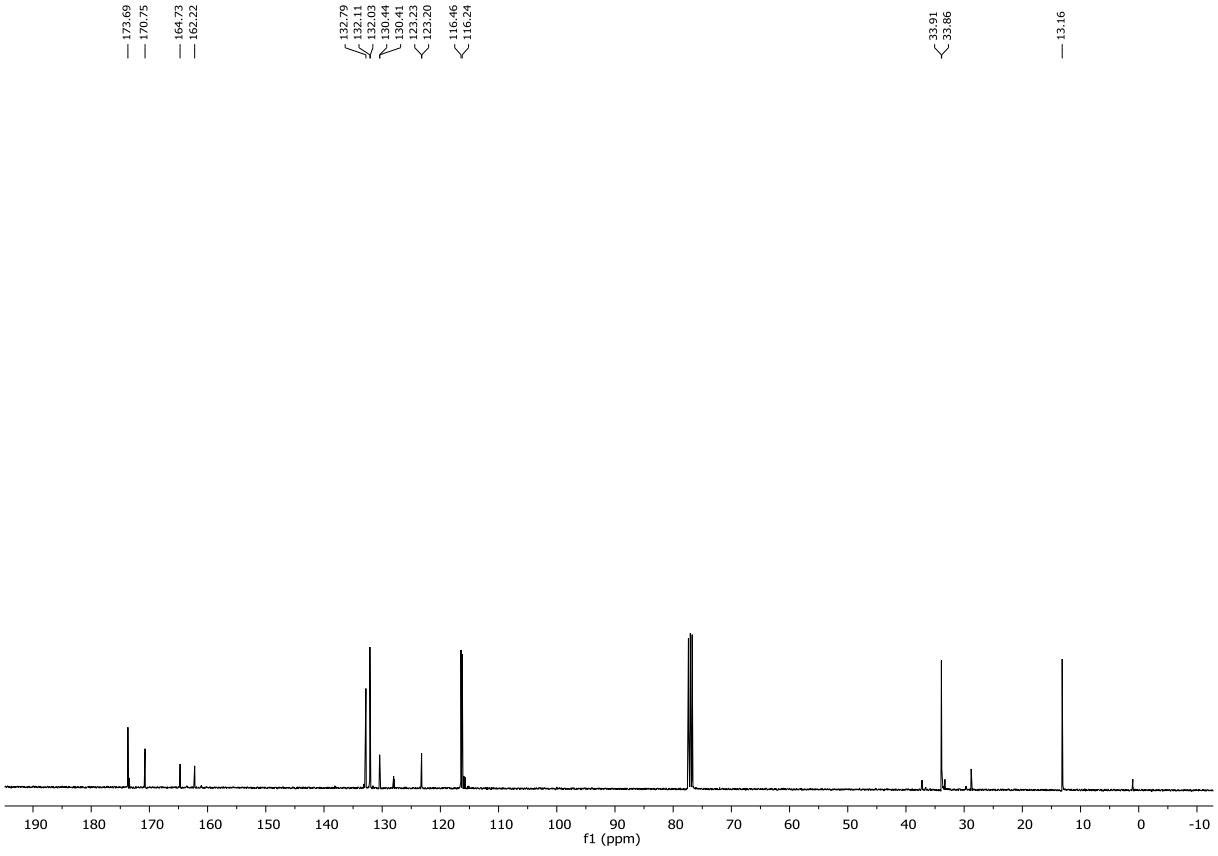

34.10
33.85
13.20


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

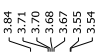

8.34
8.33
7.68
7.68
7.66
3.76
3.75
3.74
3.72
3.62
3.61
1.29
1.27
1.26
O2N
N−Et
O
O
S2
1.95
2.00
1.00
2.06
2.04
3.57
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


7.59
7.58
7.58
7.51
7.50
7.50
7.49
7.48
7.48
7.17
7.17
7.16
7.16
7.15
7.15
7.15
7.14
7.14
3.72
3.70
3.69
3.67
3.54
3.53
1.25
1.24
1.22
F
O
N−Et
O
S3

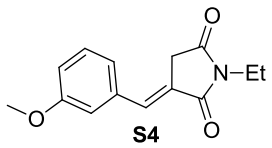

1.00
2.08
2.02
2.11
2.09
3.37
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


173.69
170.75
164.73
162.22
132.79
132.11
132.03
130.44
130.41
123.23
123.20
116.46
116.24
33.91
33.86
13.16
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

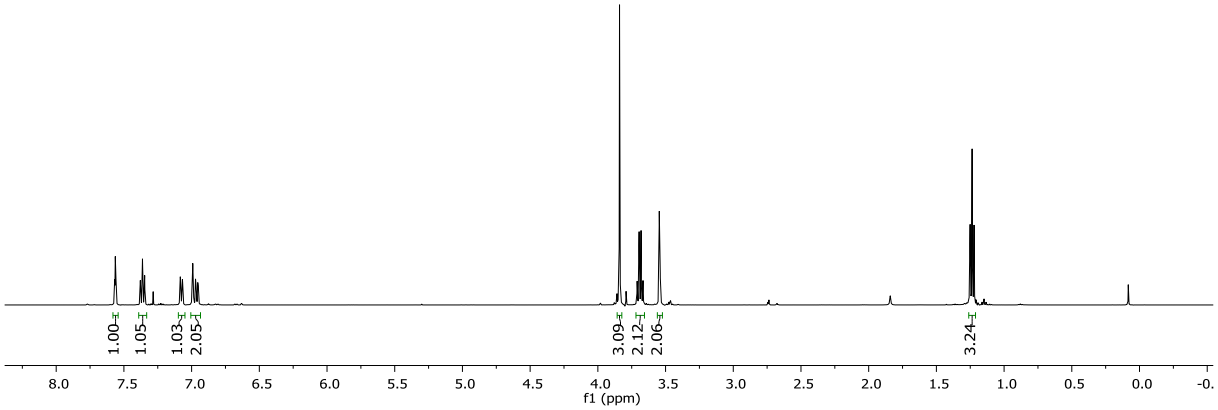

7.57
7.56
7.56
7.38
7.36
7.35
7.09
7.08
7.08
7.07
7.07
7.07
7.00
6.99
6.99
6.97
6.97
6.97
6.96
6.95
6.95
6.95


3.84
3.71
3.70
3.68
3.67
3.55
3.54

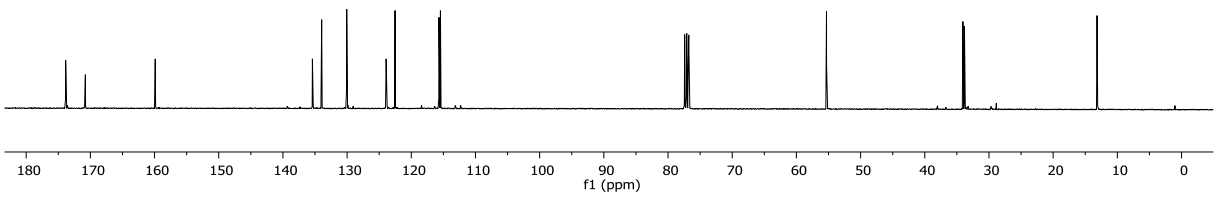

1.25
1.24
1.22

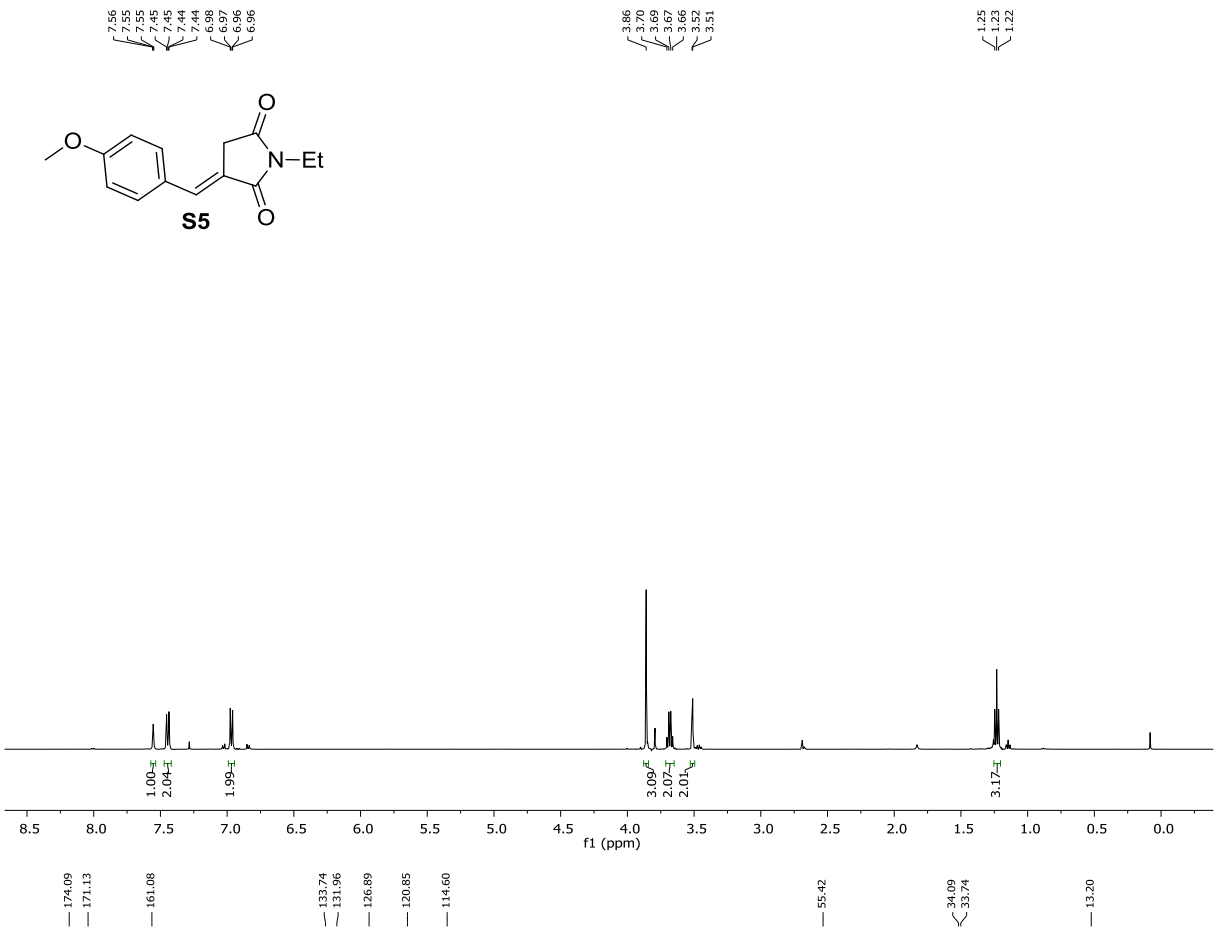

O
N–Et
O
O

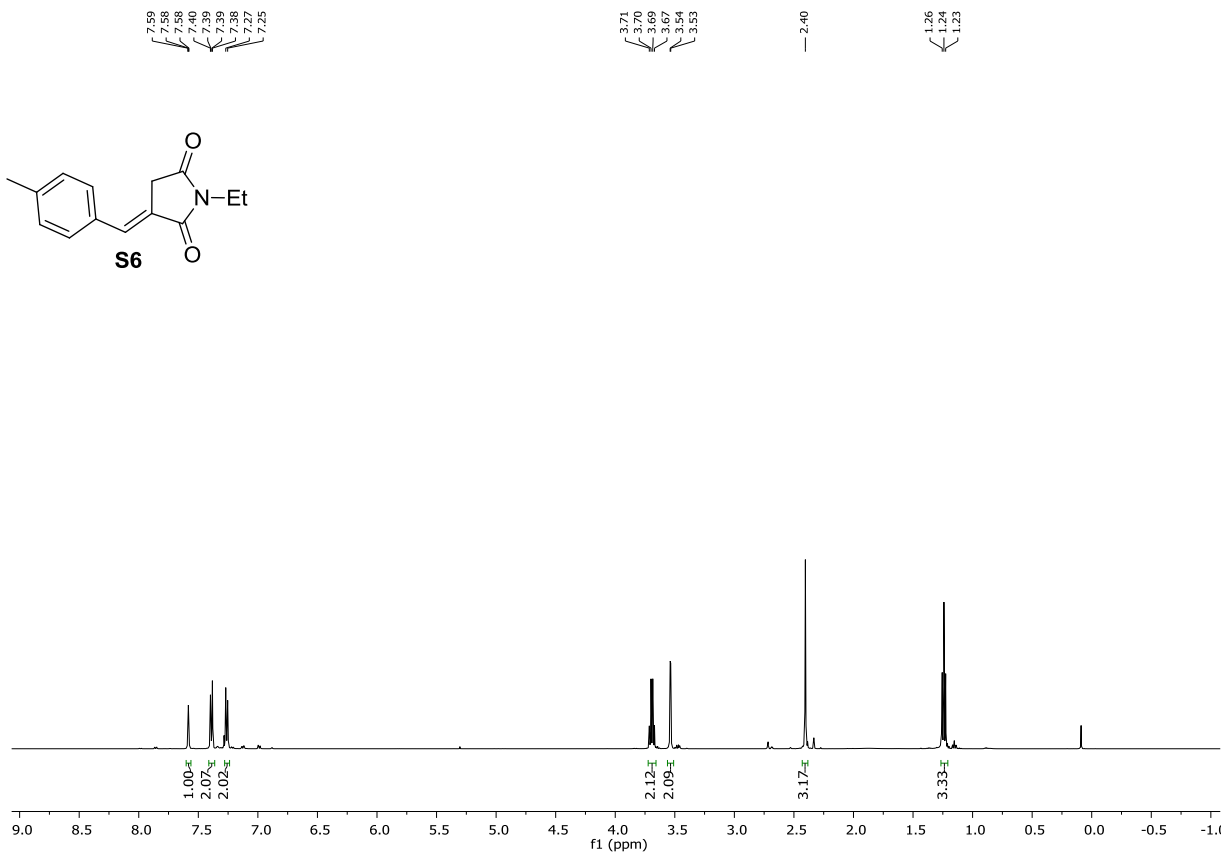
S4

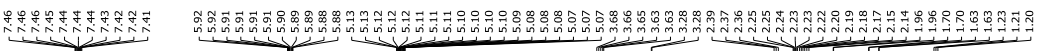

1.00
1.05
1.03
2.05
3.09
2.12
2.06
3.24
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

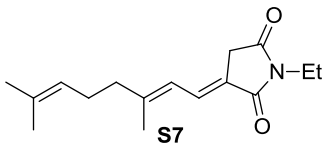

173.85
170.78
159.89
135.41
133.96
130.06
123.92
122.53
115.69
115.46
55.31
34.06
33.82
13.16


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

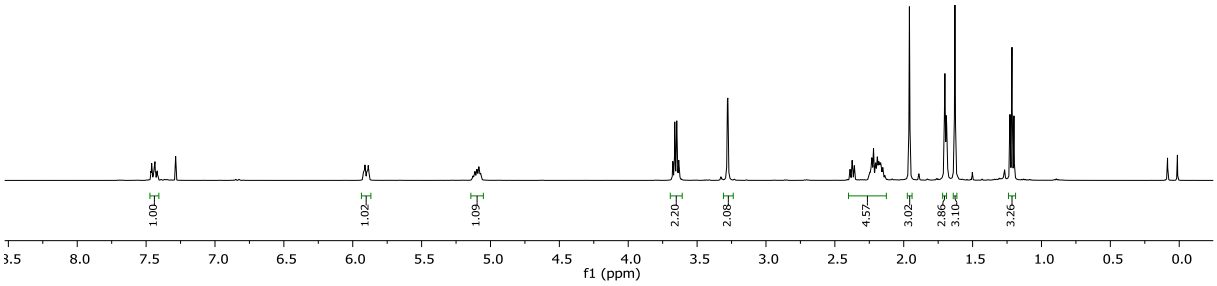

7.56
7.55
7.55
7.45
7.45
7.44
7.44
6.98
6.97
6.96
6.96
3.86
3.70
3.69
3.67
3.66
3.52
3.51
1.25
1.23
1.22
O
O
N–Et
O
S5
1.00
2.04
1.99
3.09
2.07
2.01
3.17
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
174.09
171.13
161.08
133.74
131.96
126.89
120.85
114.60
55.42
34.09
33.74
13.20
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

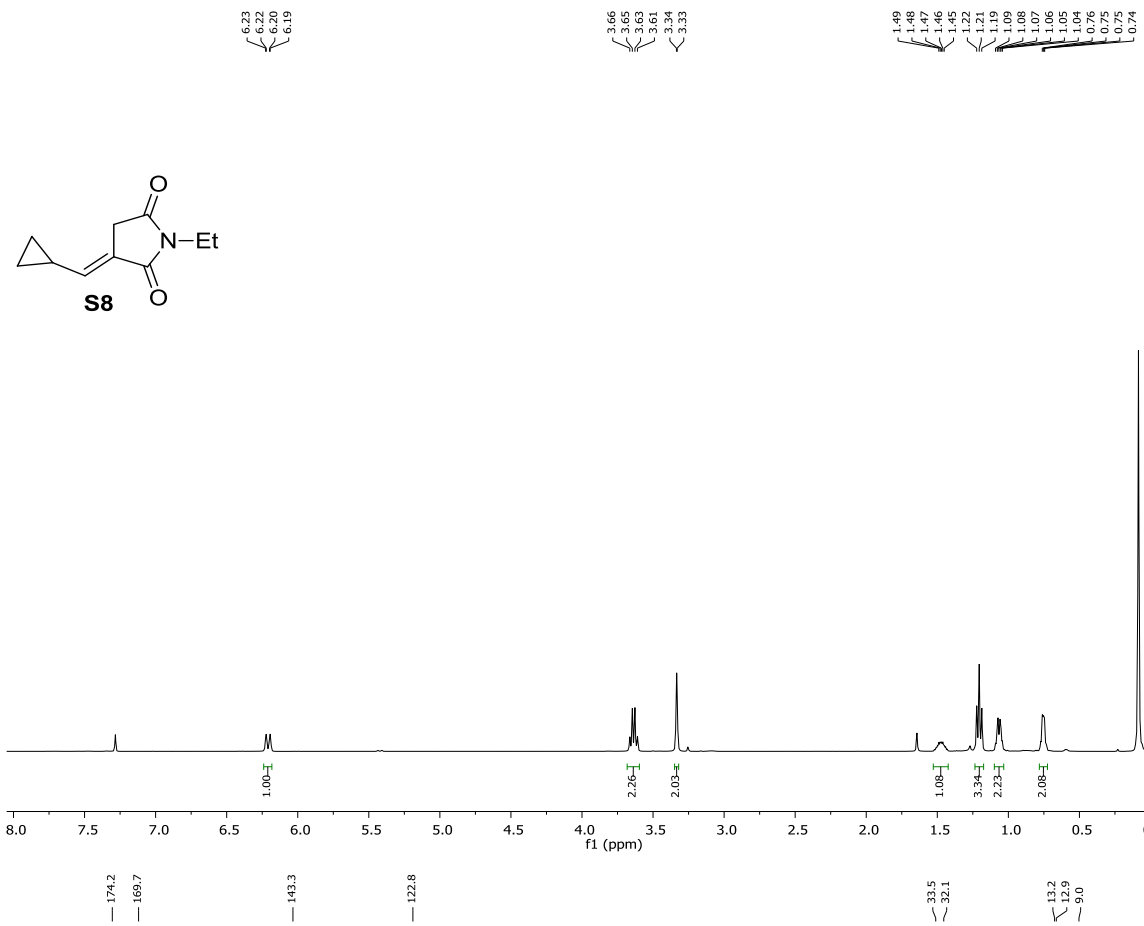

7.59
7.58
7.58
7.40
7.39
7.39
7.38
7.27
7.25
3.71
3.70
3.69
3.67
3.54
3.53
2.40
1.26
1.24
1.23
O
N–Et
O
S6
1.00
2.07
2.02
2.12
2.09
3.17
3.33
f1 (ppm)
174.01
171.00
140.65
134.07
131.41
130.18
129.84
122.49
34.12
33.78
21.49
13.19
f1 (ppm)

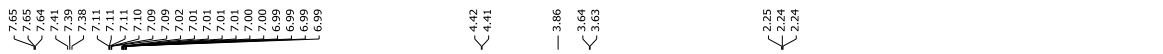


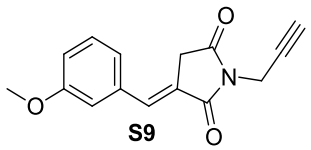

O
N–Et
O

S7

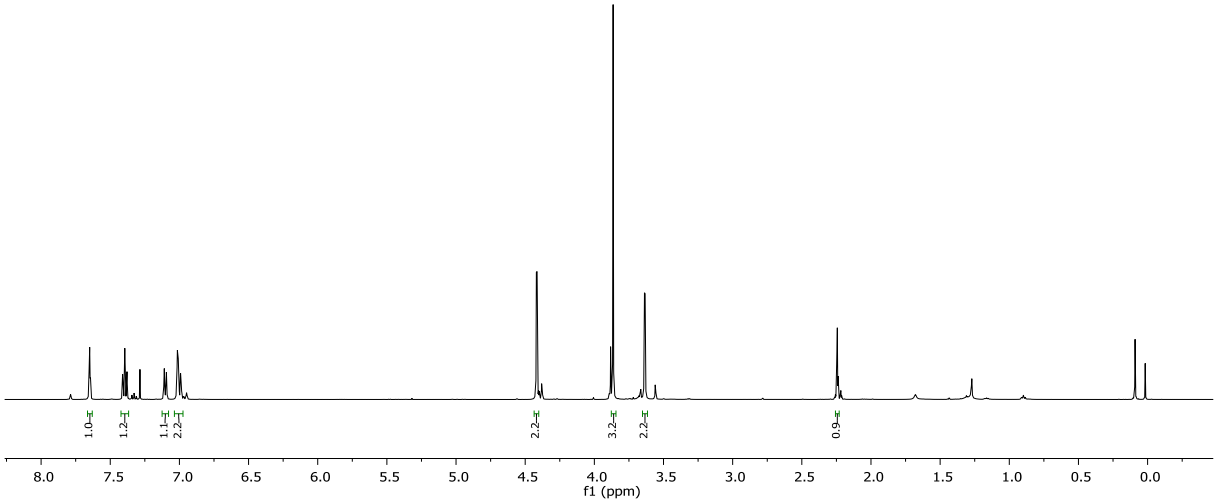

1.00
1.02
1.09
2.20
2.08
4.57
3.02
2.86
3.10
3.26
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


6.23
6.22
6.20
6.19
3.66
3.65
3.63
3.61
3.34
3.33
1.49
1.48
1.47
1.46
1.45
1.22
1.21
1.19
1.09
1.08
1.07
1.06
1.05
1.04
0.76
0.75
0.75
0.74
O
N–Et
O
S8
1.00
2.26
2.03
1.08
3.34
2.23
2.08
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
0.0
f1 (ppm)
174.2
169.7
143.3
122.8
33.5
32.1
13.2
12.9
9.0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

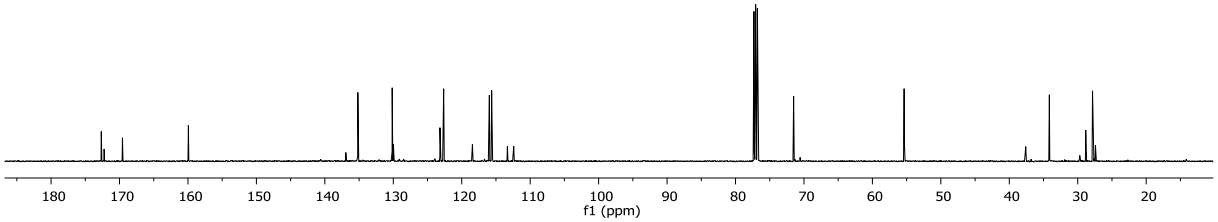

7.65
7.65
7.64
7.41
7.39
7.38
7.11
7.11
7.11
7.10
7.09
7.09
7.02
7.01
7.01
7.01
7.01
7.00
7.00
6.99
6.99
6.99
4.42
4.41
3.86
3.64
3.63
2.25
2.24
2.24

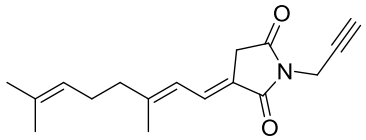

O
N
O
O

S9

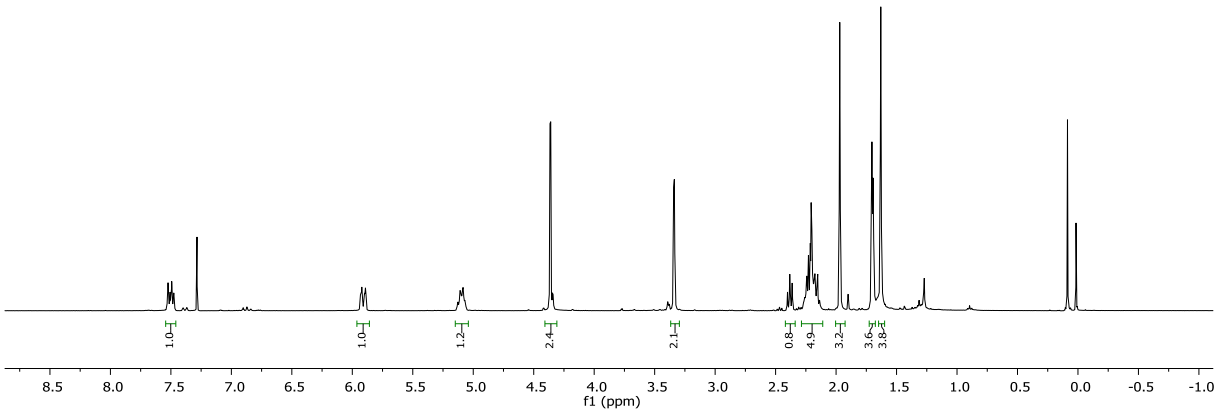

1.0
1.2
1.1
2.2
2.2
3.2
2.2
0.9
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

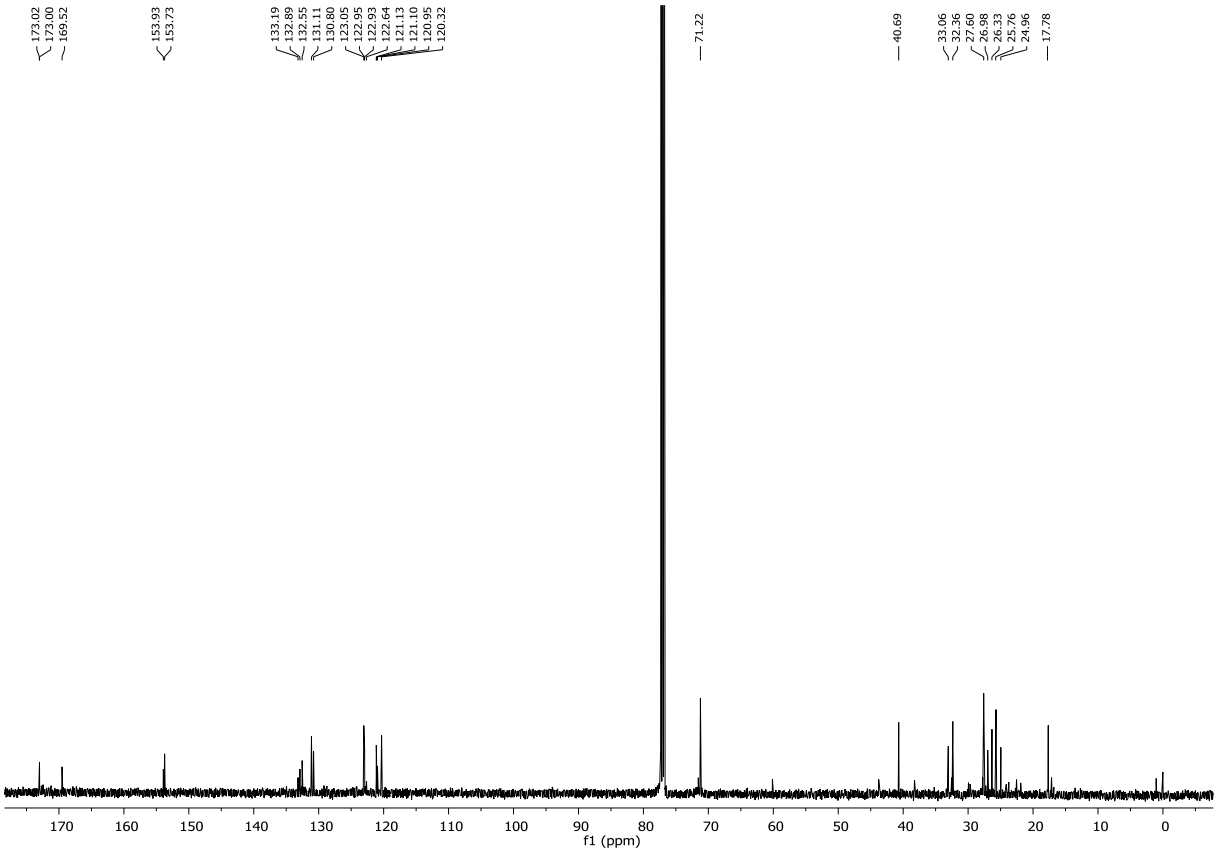

172.7
169.6
159.9
135.2
130.2
130.0
123.2
122.6
118.4
116.0
115.6
113.3
112.4
71.5
55.4
34.1
28.8
27.8

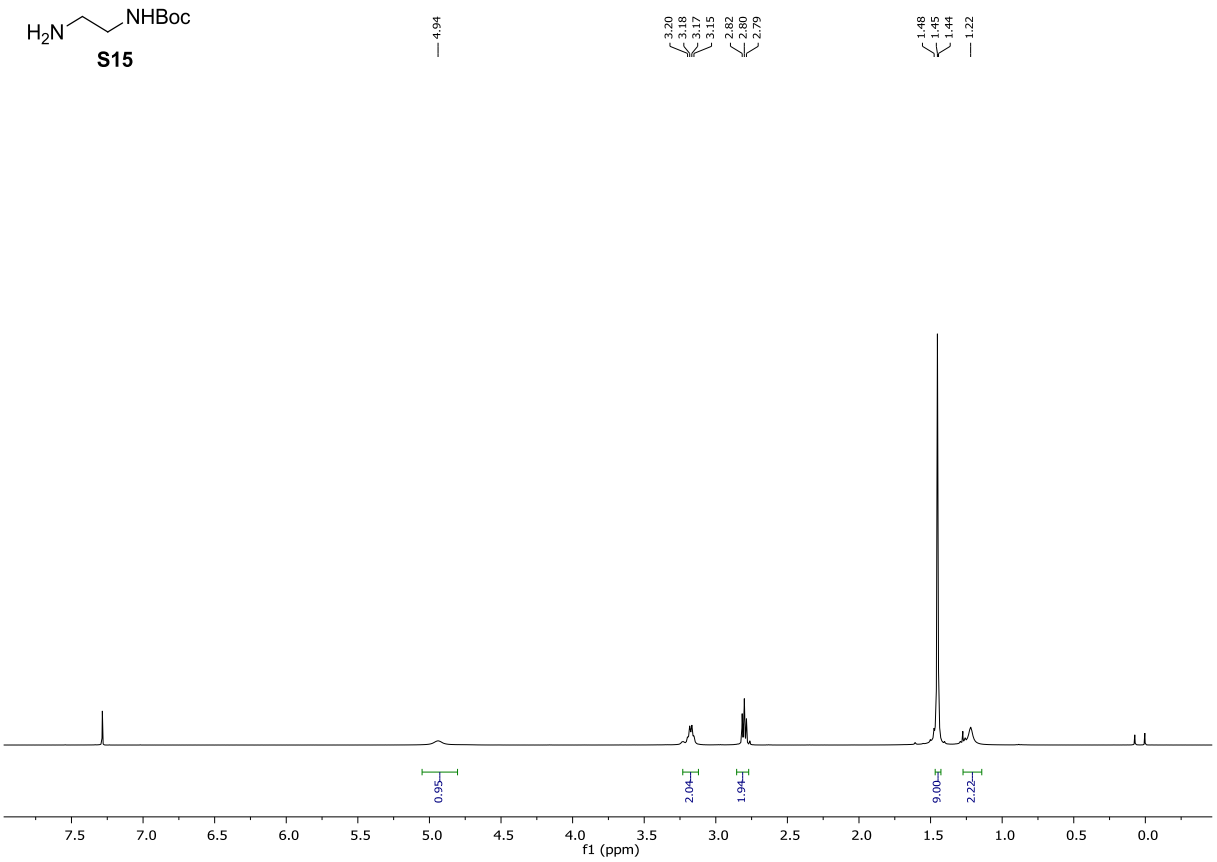

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

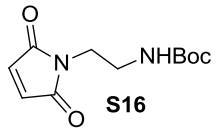


S10



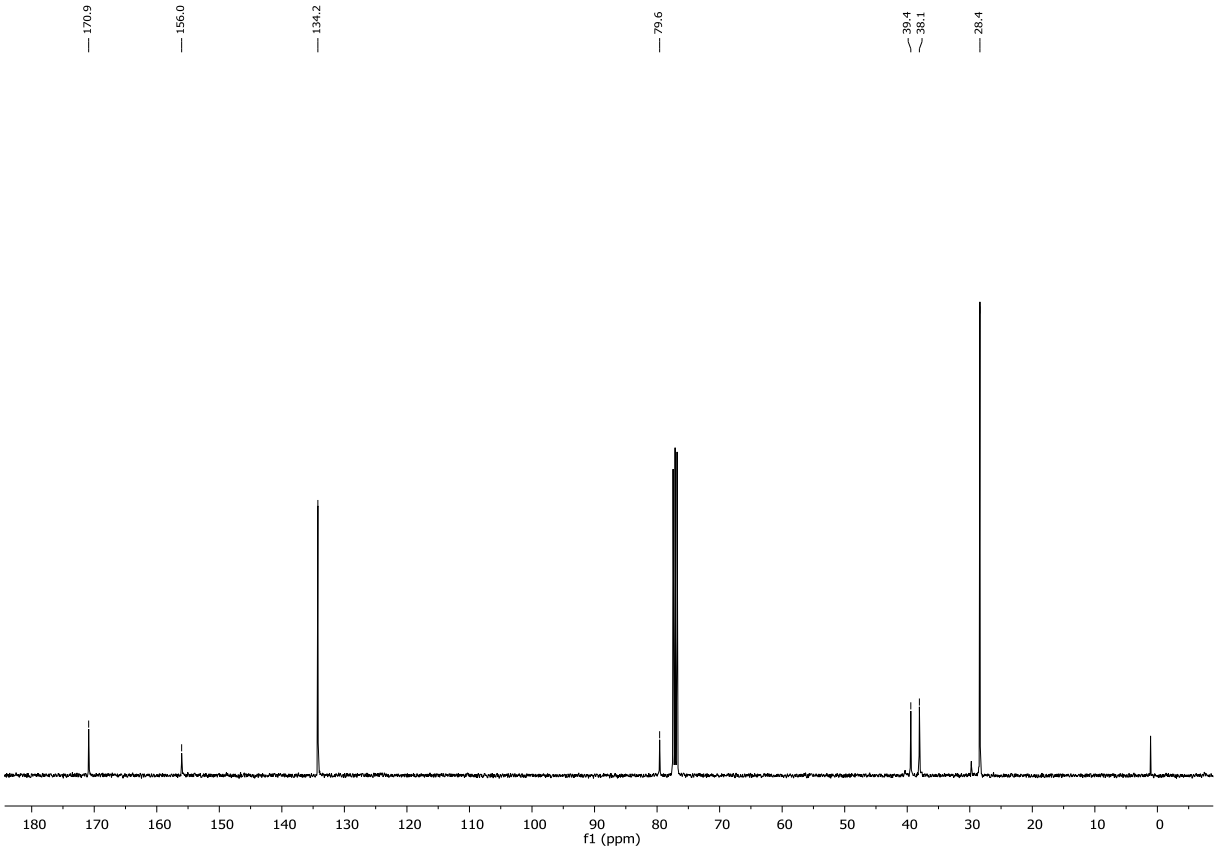


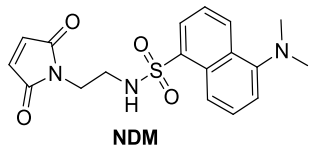

H2N
NHBoc
S15
4.94
3.20
3.18
3.17
3.15
2.82
2.80
2.79
1.48
1.45
1.44
1.22
0.95
2.04
1.94
9.00
2.22
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
N
NHBoc
O

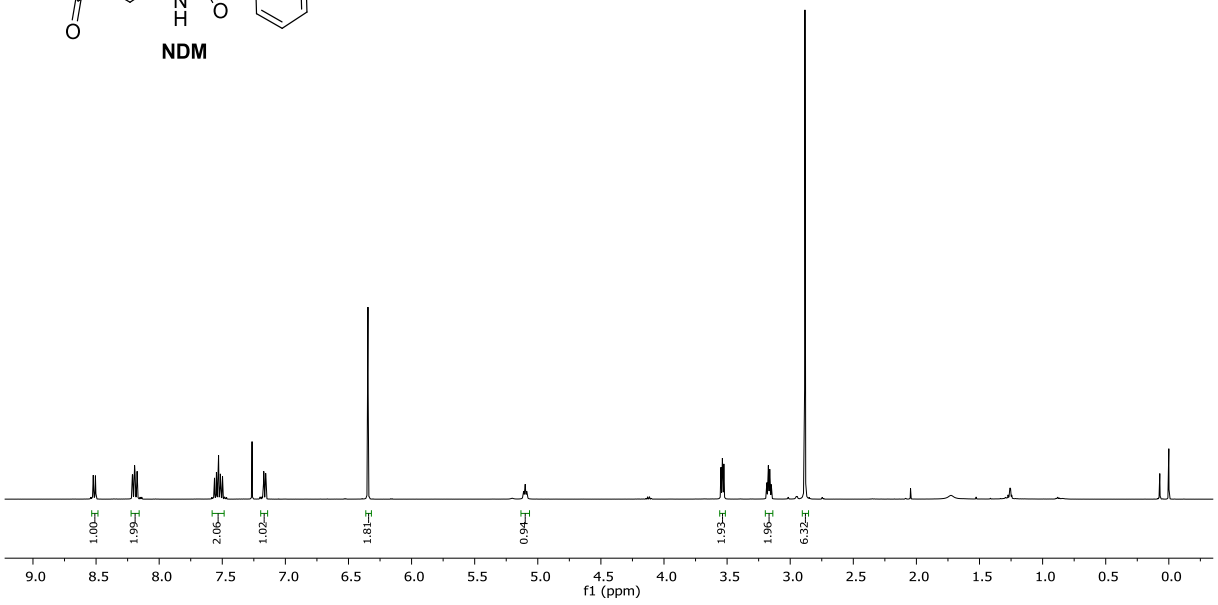
S16

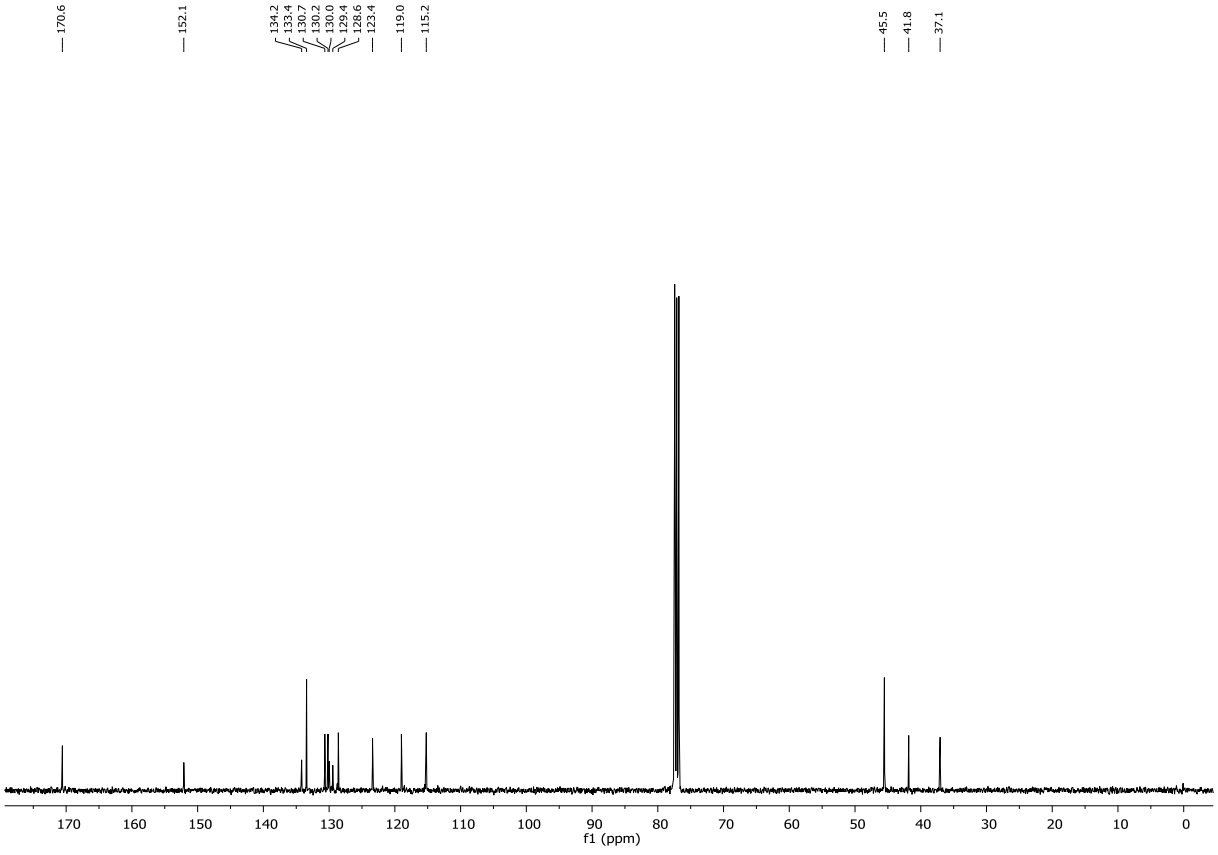
6.68
4.76
3.64
3.63
3.61
3.31
3.29
3.28
1.37
2.00
0.93
2.13
2.08
9.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

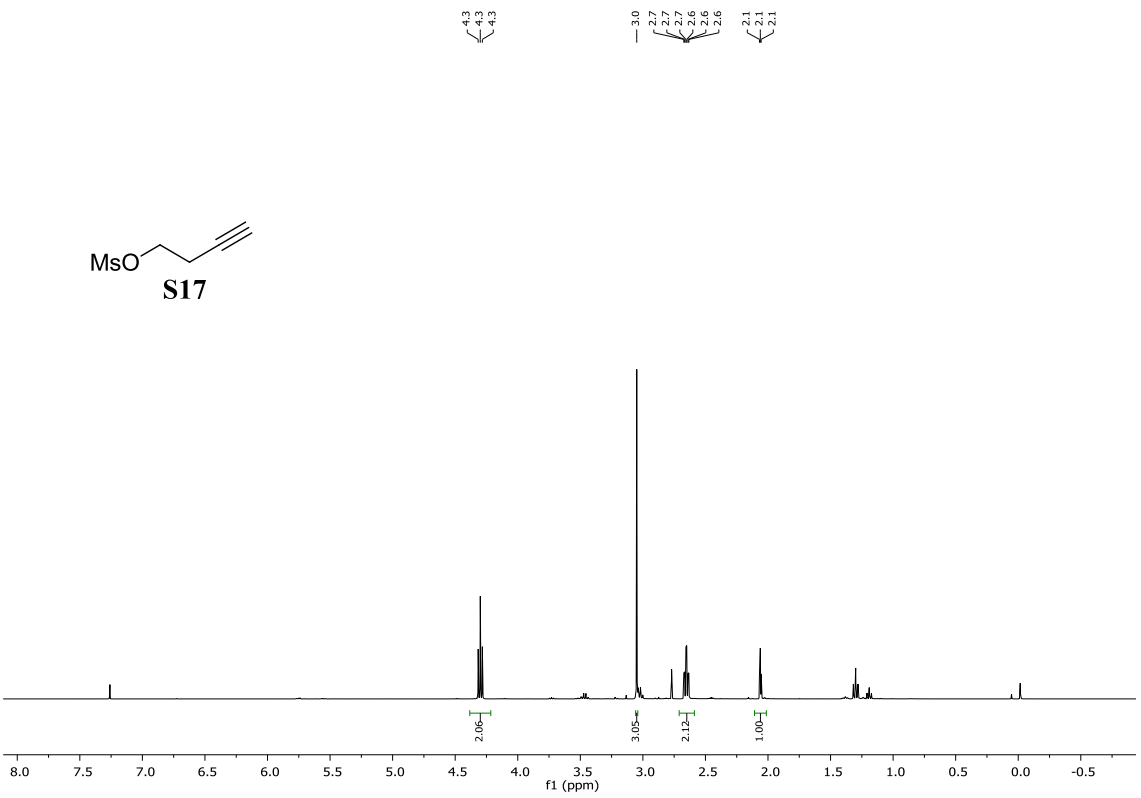

170.9
156.0
134.2
79.6
39.4
38.1
28.4
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



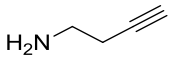
NDM


1.00
1.99
2.06
1.02
1.81
0.94
1.93
1.96
6.32
f1 (ppm)

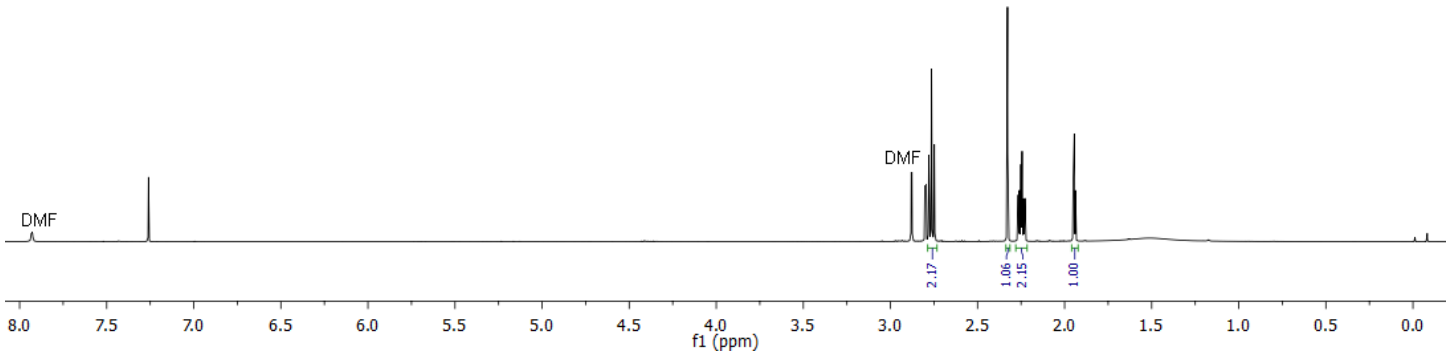

170.6
152.1
134.2
133.4
130.7
130.2
130.0
129.4
128.6
123.4
119.0
115.2
45.5
41.8
37.1
f1 (ppm)

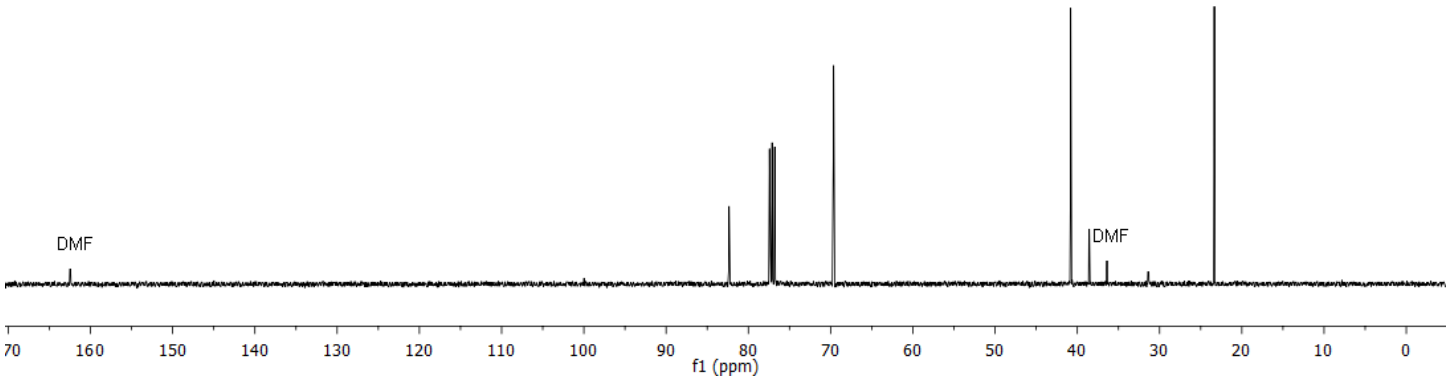

4.3
4.3
4.3
3.0
2.7
2.7
2.7
2.6
2.6
2.6
2.1
2.1
2.1
MsO
2.06
3.05
2.12
1.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

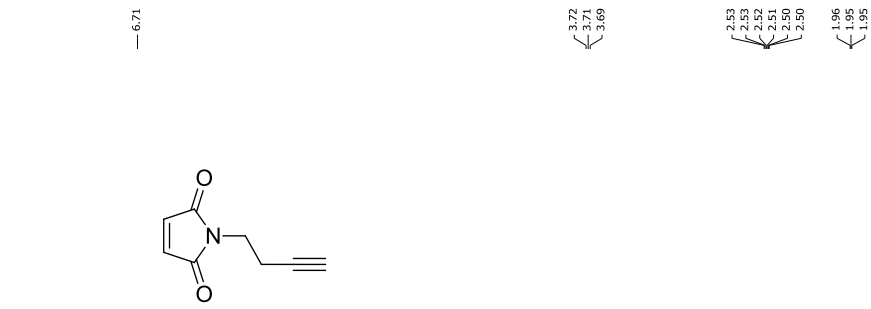
S17



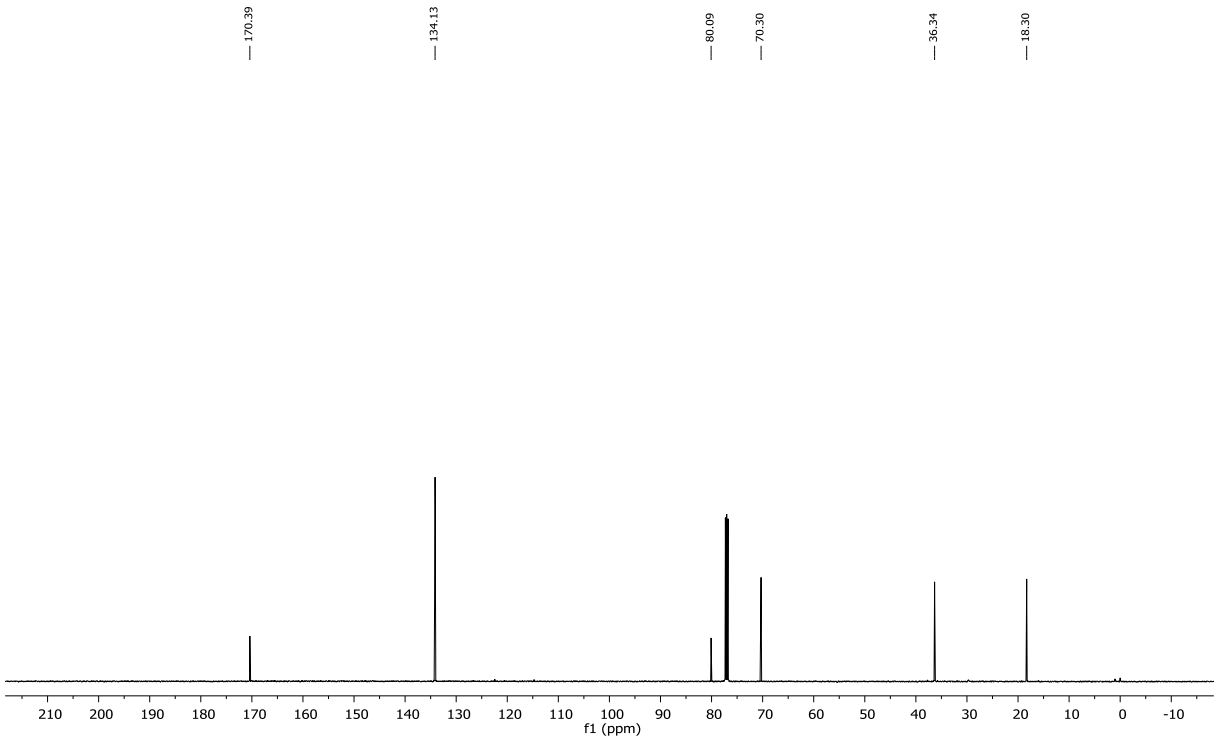
S18





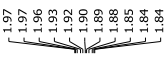

6.71
3.72
3.71
3.69
2.53
2.53
2.52
2.51
2.50
2.50
1.96
1.95
1.95
O
N
O
2.00
2.16
2.13
0.95
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

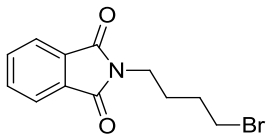
NBM


170.39
134.13
80.09
70.30
36.34
18.30
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

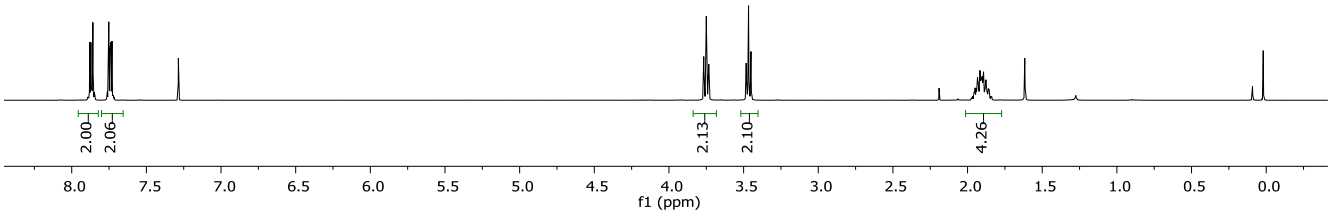

7.88
7.87
7.87
7.86
7.75
7.74
7.74
7.73

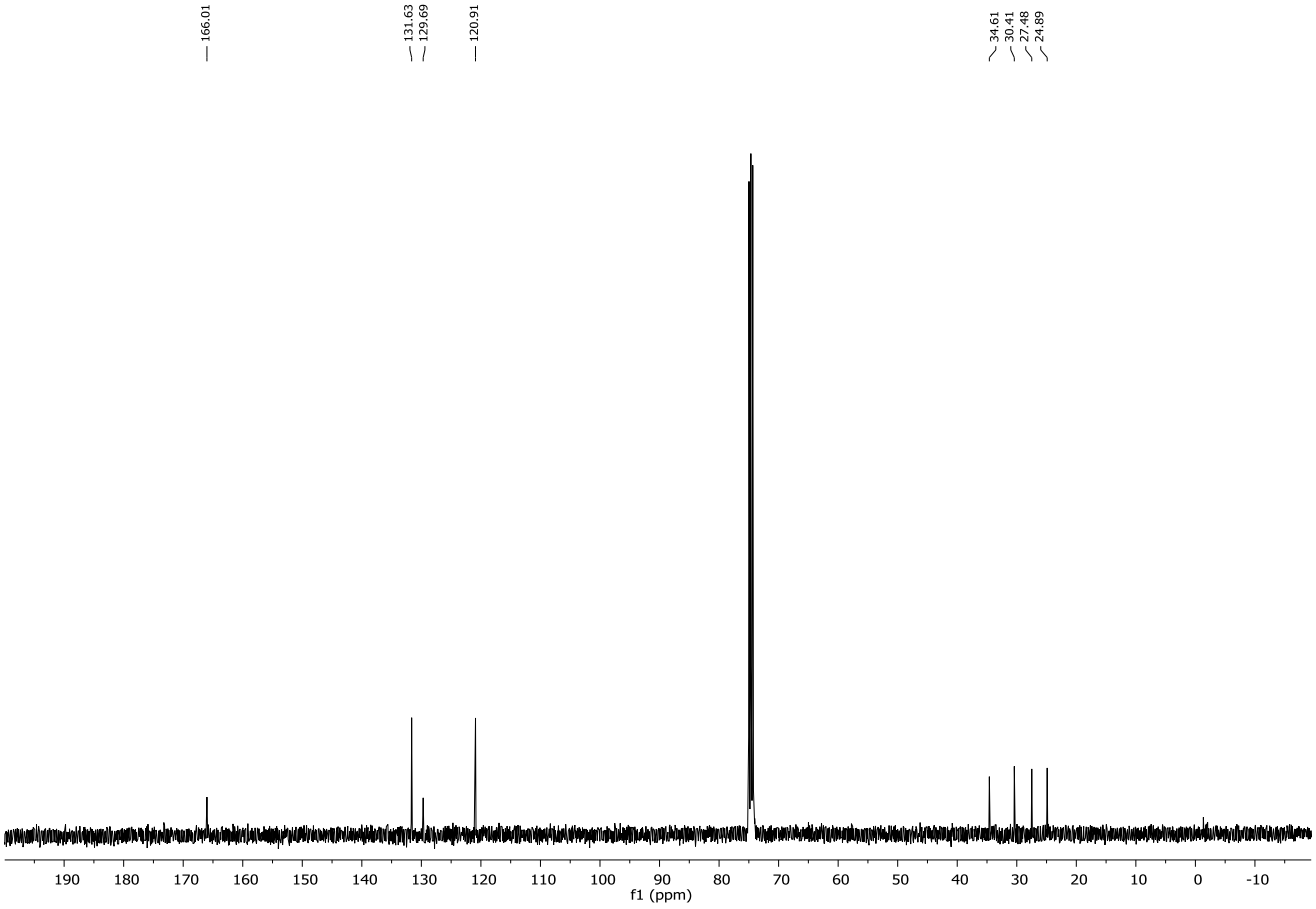

3.77
3.75
3.73
3.48
3.47
3.45

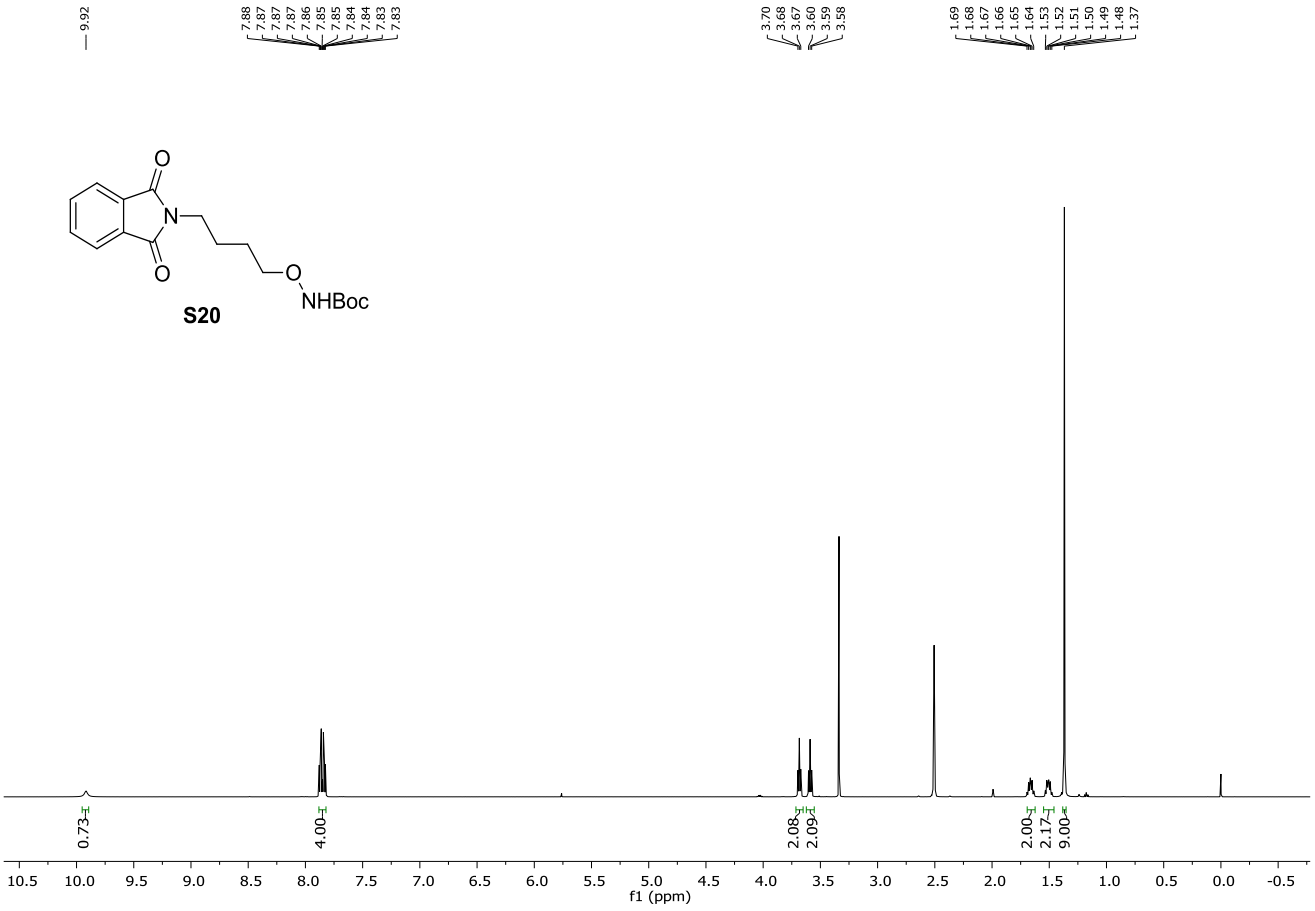

1.97
1.97
1.96
1.93
1.92
1.90
1.89
1.88
1.85
1.84
1.84

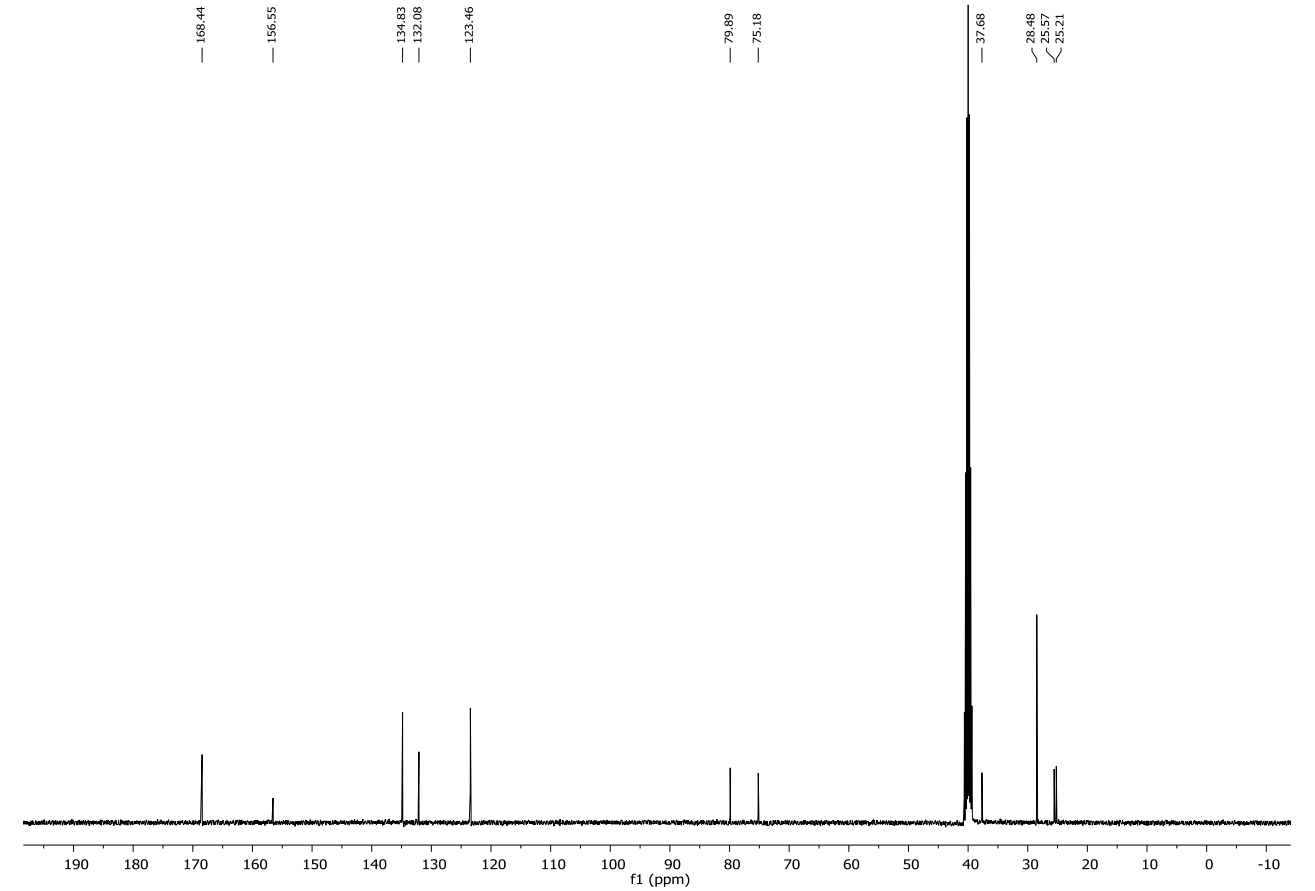

O
N
O
Br

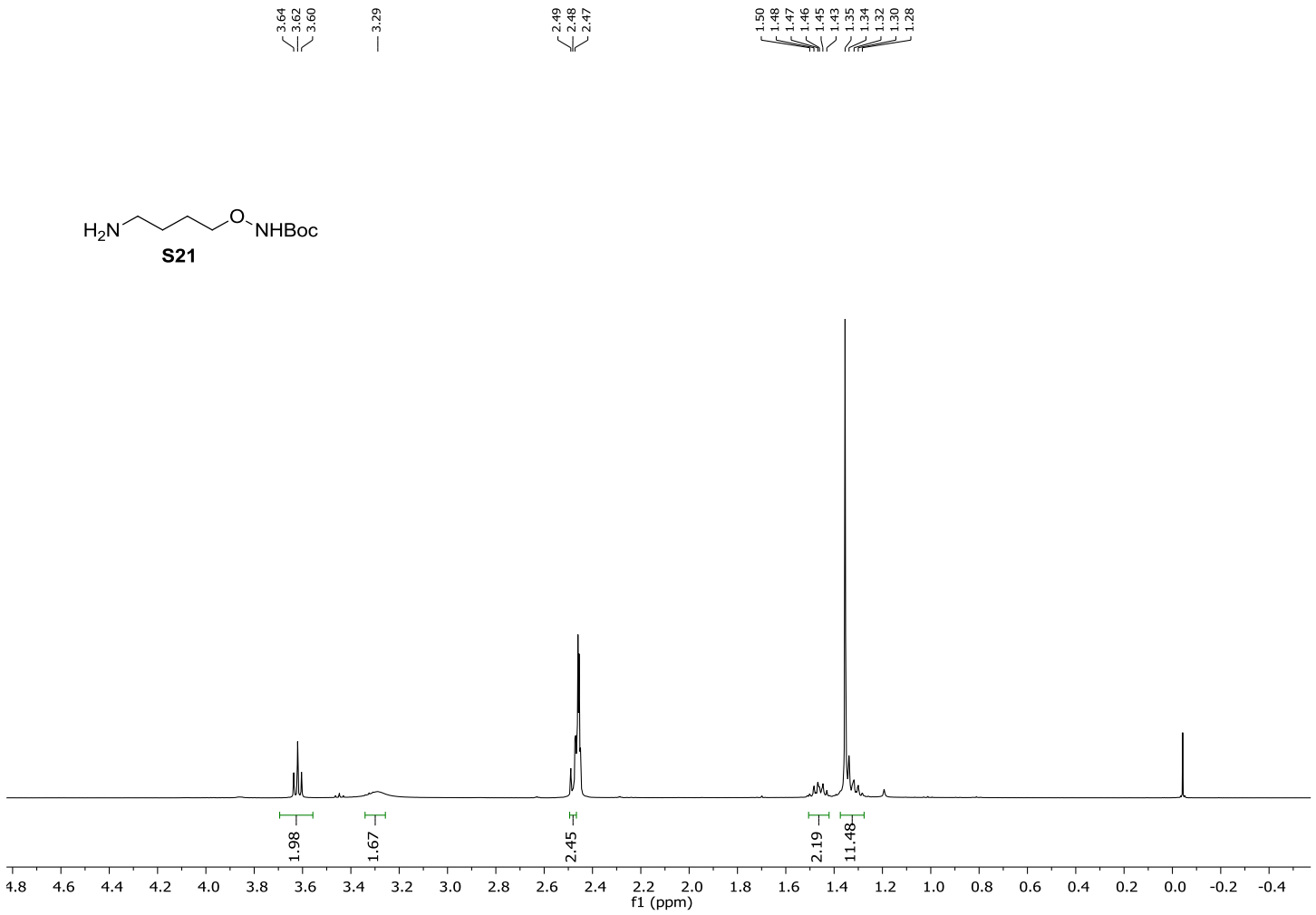
S19


2.00
2.06
2.13
2.10
4.26
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
0.0
f1 (ppm)

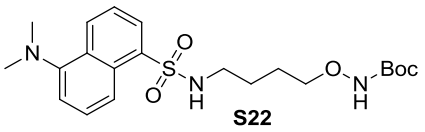

166.01
131.63
129.69
120.91
34.61
30.41
27.48
24.89
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


9.92
7.88
7.87
7.87
7.87
7.86
7.85
7.85
7.84
7.84
7.83
7.83
3.70
3.68
3.67
3.60
3.59
3.58
1.69
1.68
1.67
1.66
1.65
1.64
1.53
1.52
1.51
1.50
1.49
1.48
1.37
O
N
O
O
NHBoc
S20
0.73
4.00
2.08
2.09
2.00
2.17
9.00
f1 (ppm)


168.44
156.55
134.83
132.08
123.46
79.89
75.18
37.68
28.48
25.57
25.21
f1 (ppm)


3.64
3.62
3.60
3.29
2.49
2.48
2.47
1.50
1.48
1.47
1.46
1.45
1.43
1.35
1.34
1.32
1.30
1.28
H2N
O
NHBoc
S21
1.98
1.67
2.45
2.19
11.48
f1 (ppm)

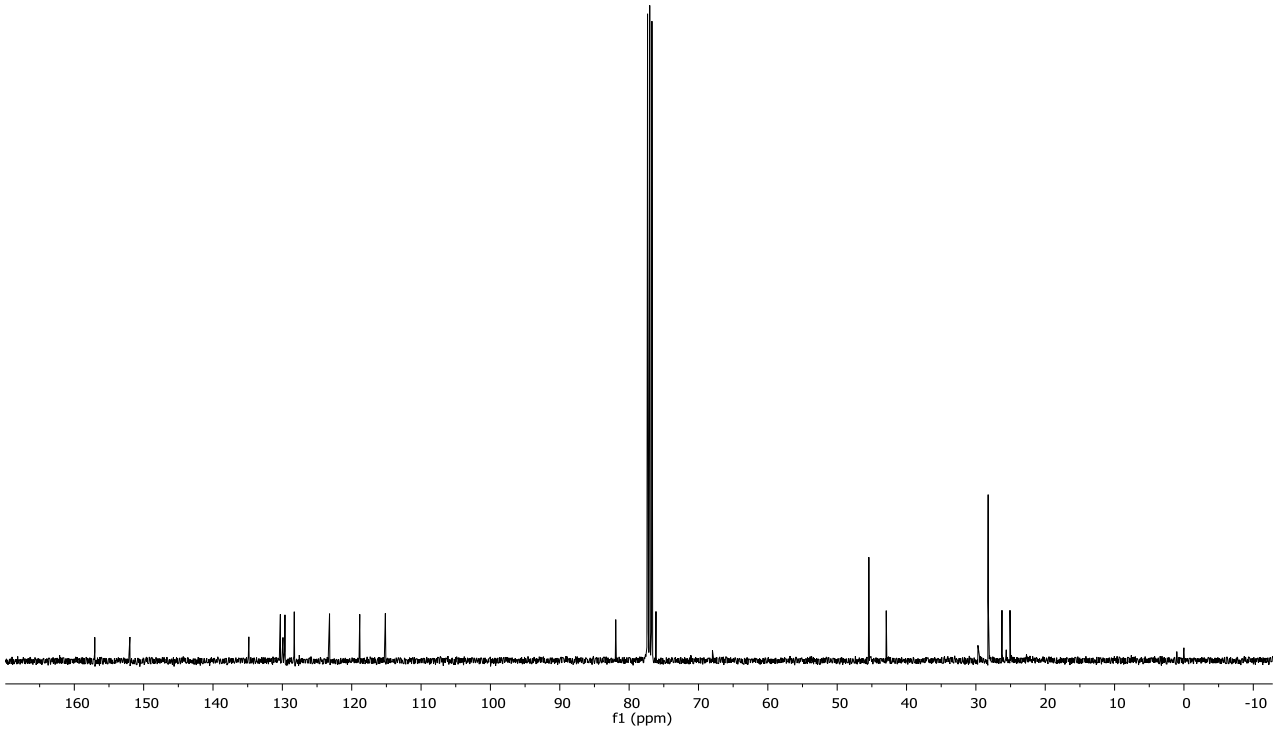

8.57
8.55
8.36
8.33
8.28
8.28
8.26
8.26
7.60
7.58
7.58
7.56
7.56
7.55
7.54
7.52
7.22
7.20
7.13
5.17
5.16
5.14
3.78
3.77
3.75
2.99
2.97
2.96
2.94
2.92
1.59
1.58
1.58
1.57
1.56
1.50

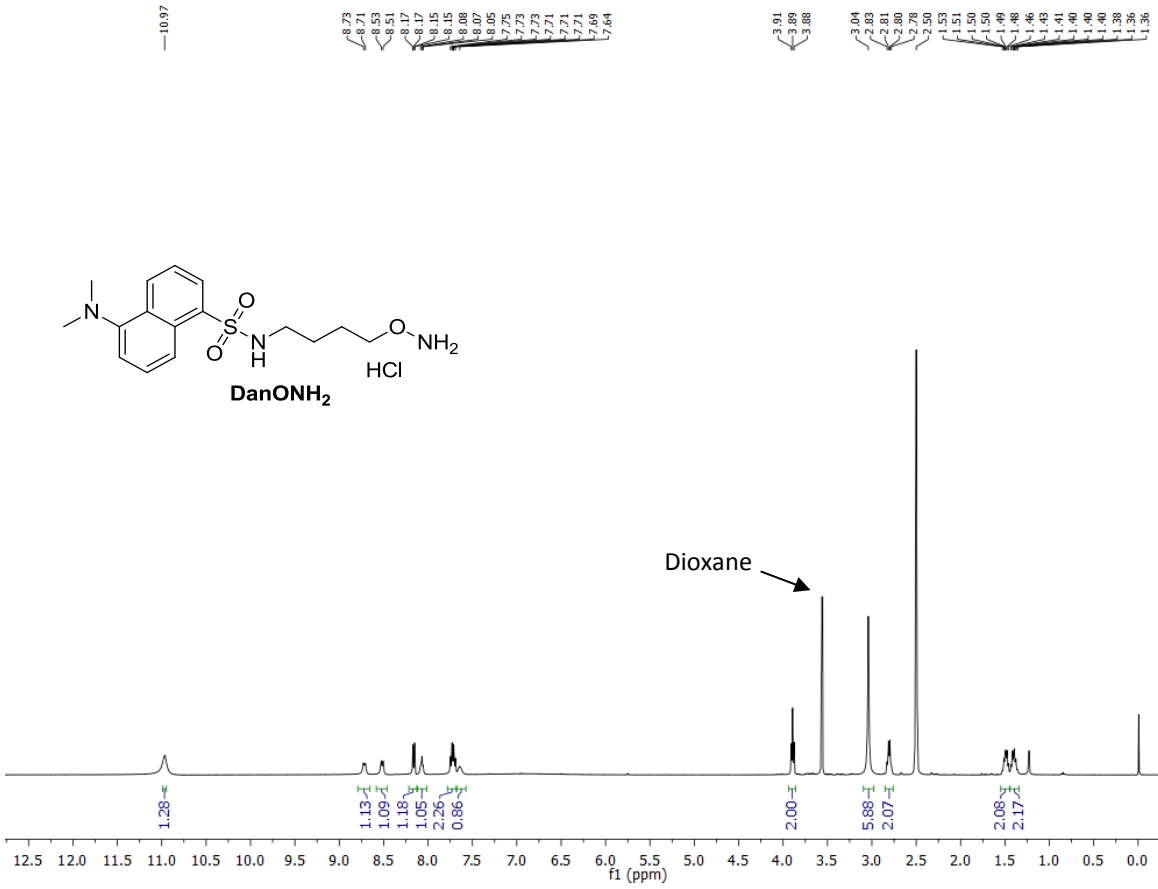

N
O
S
O
N
H
O
N
Boc
H

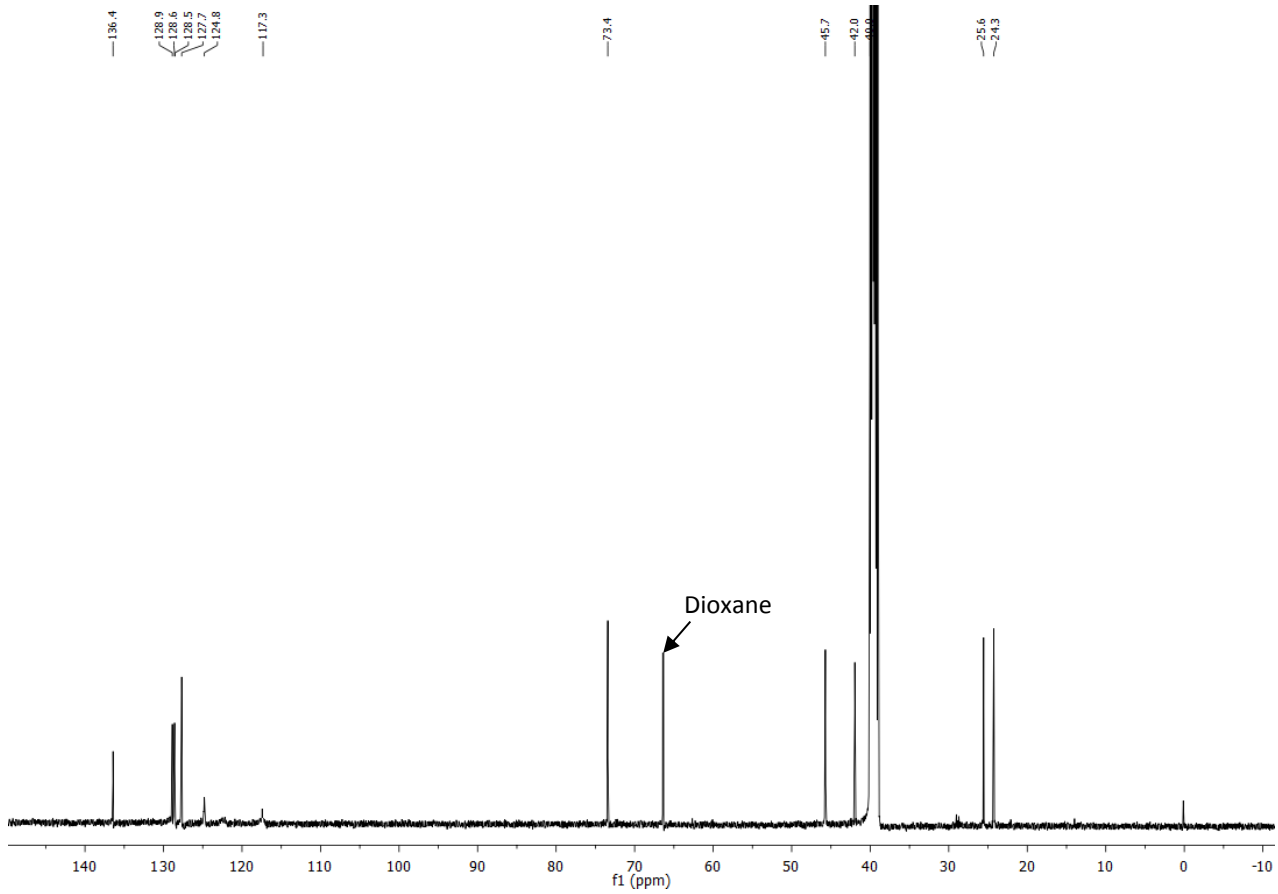
S22

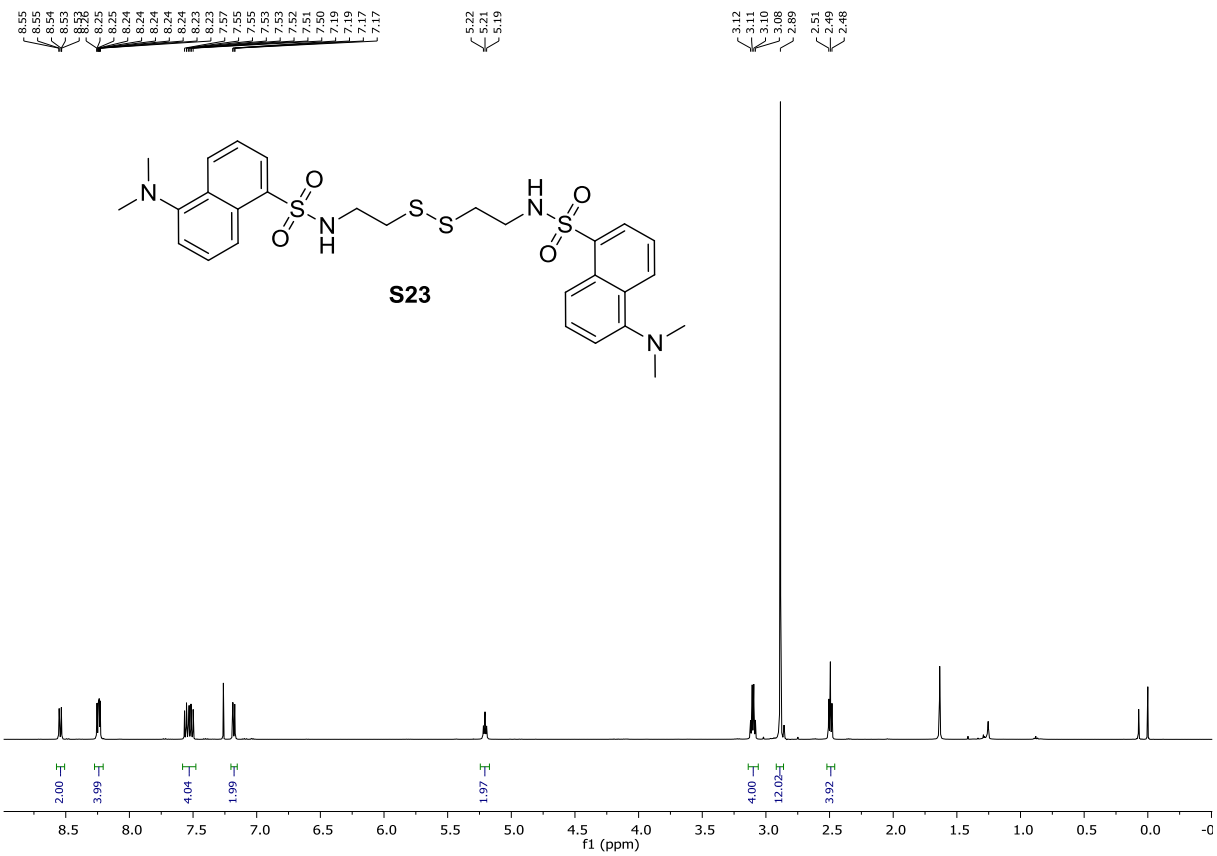
1.00
1.02
0.95
2.01
1.01
0.91
0.98
2.08
7.94
4.64
9.16
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

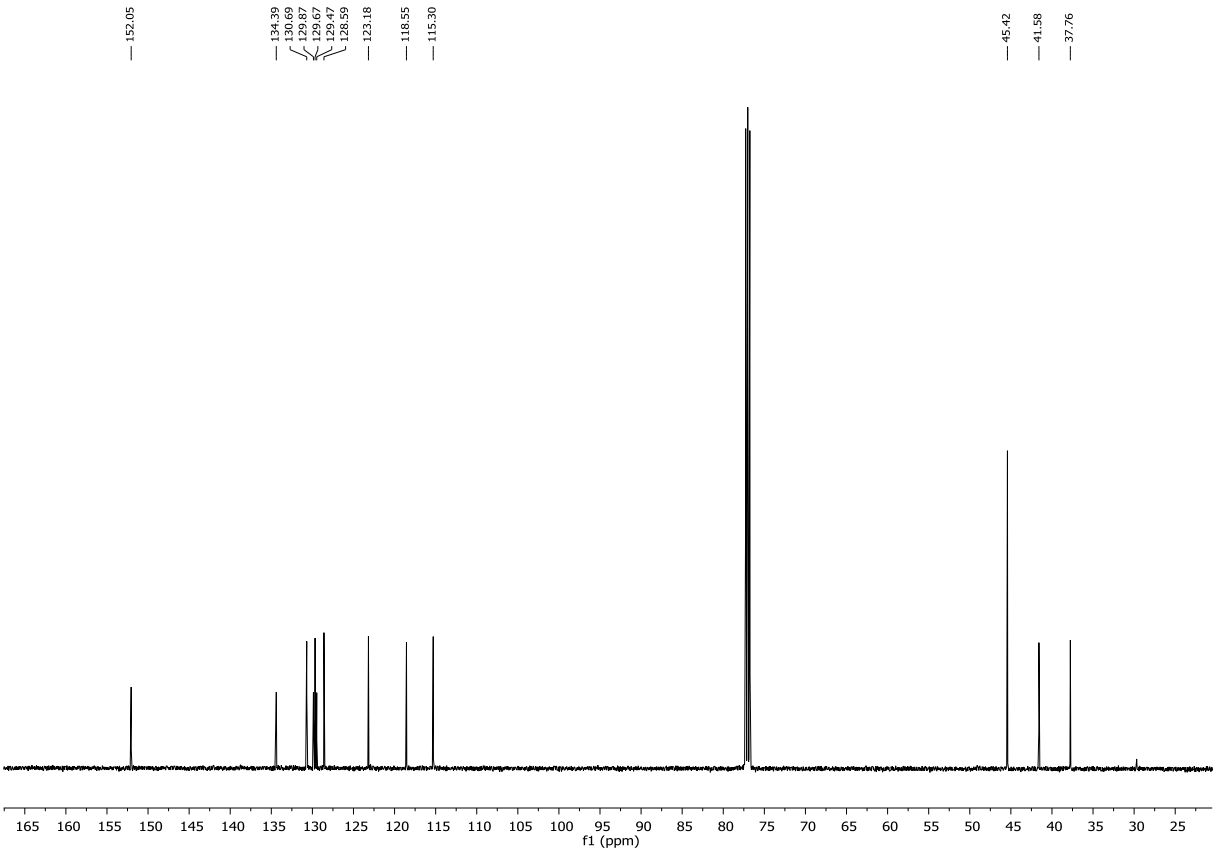

157.05
151.98
134.83
130.43
130.29
129.91
129.66
129.63
128.29
123.20
118.84
115.15
81.93
76.13
45.43
42.92
28.23
26.24
25.08

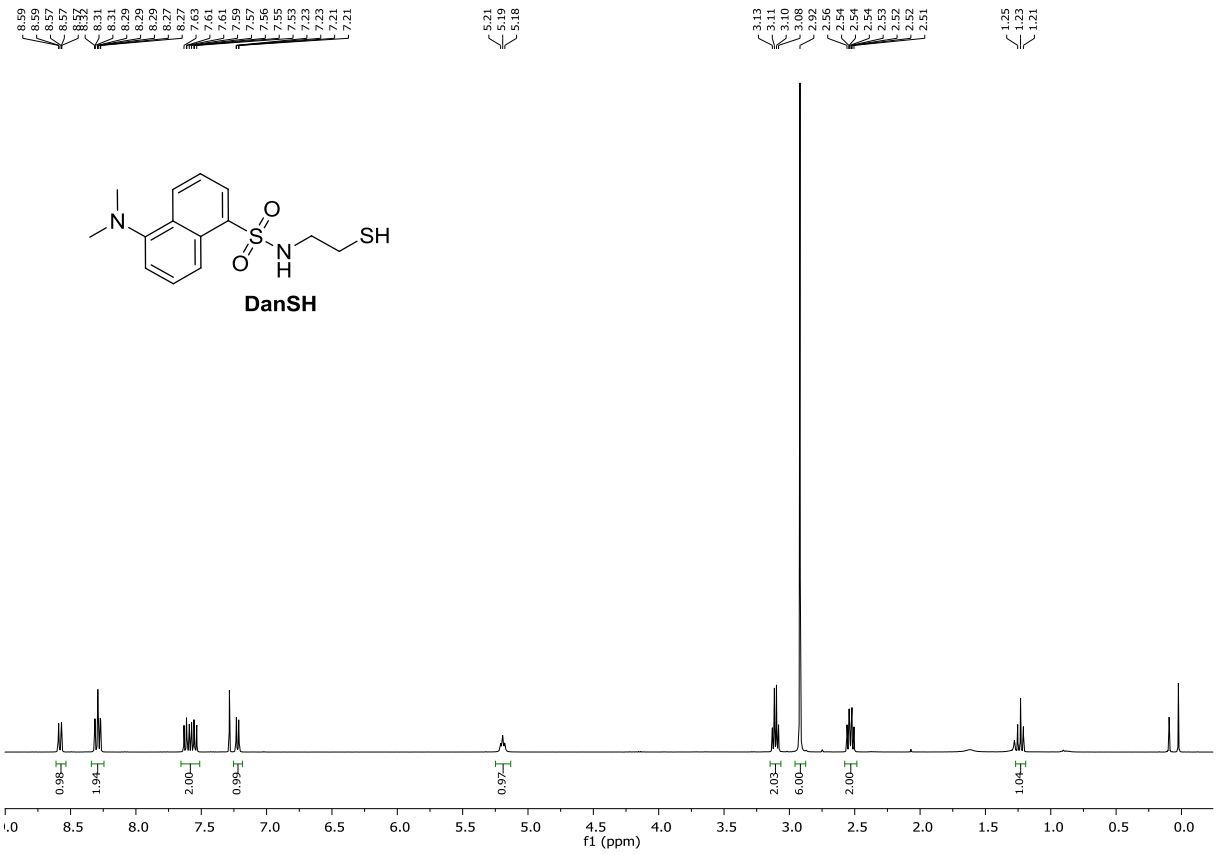

160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

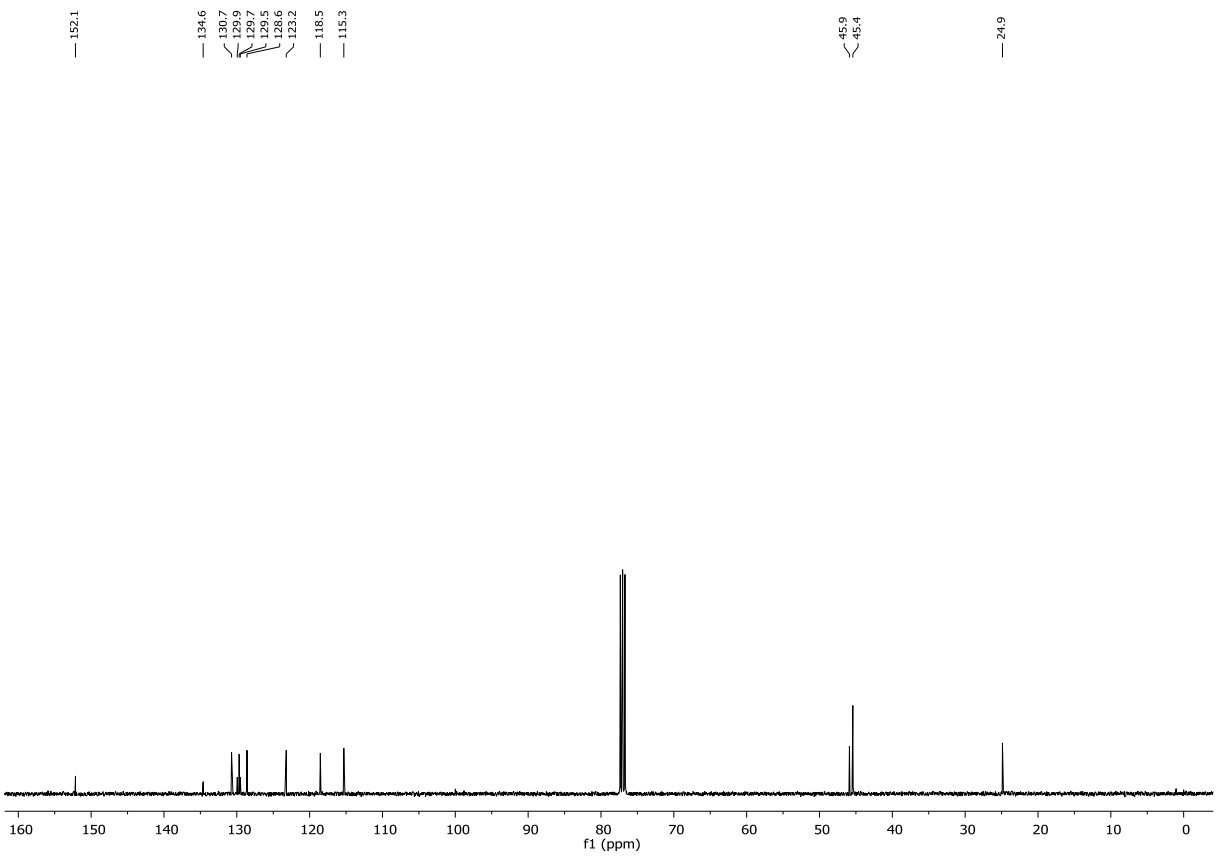

DanONH2
HCl
Dioxane
f1 (ppm)

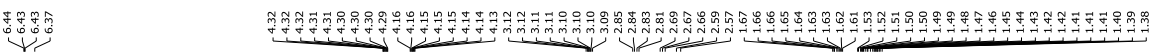

Dioxane
f1 (ppm)

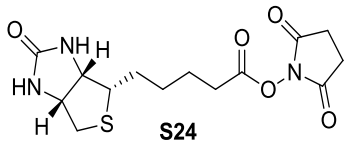

8.55
8.55
8.54
8.53
8.26
8.25
8.24
8.24
8.24
8.24
8.23
7.57
7.55
7.55
7.53
7.52
7.51
7.50
7.19
7.19
7.17
7.17
5.22
5.21
5.19
3.12
3.11
3.10
3.08
2.89
2.51
2.49
2.48
S23
2.00
3.99
4.04
1.99
1.97
4.00
12.02
3.92
f1 (ppm)


152.05
134.39
130.69
129.87
129.67
129.47
128.59
123.18
118.55
115.30
45.42
41.58
37.76
f1 (ppm)

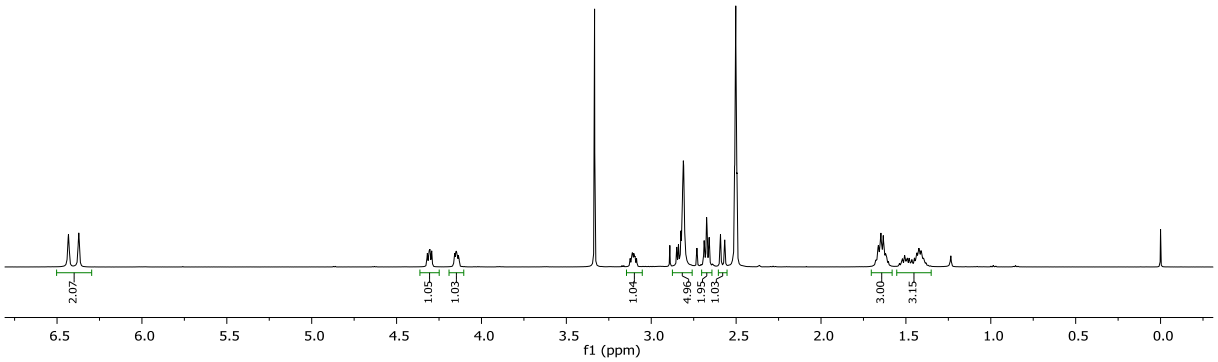

8.59
8.59
8.57
8.57
8.32
8.31
8.31
8.29
8.29
8.29
8.27
8.27
7.63
7.61
7.61
7.59
7.57
7.56
7.55
7.53
7.23
7.23
7.21
7.21
5.21
5.19
5.18
3.13
3.11
3.10
3.08
2.92
2.56
2.54
2.54
2.54
2.53
2.52
2.52
2.51
1.25
1.23
1.21
N
S
O
O
N
H
SH
DanSH
0.98
1.94
2.00
0.99
0.97
2.03
6.00
2.00
1.04
f1 (ppm)

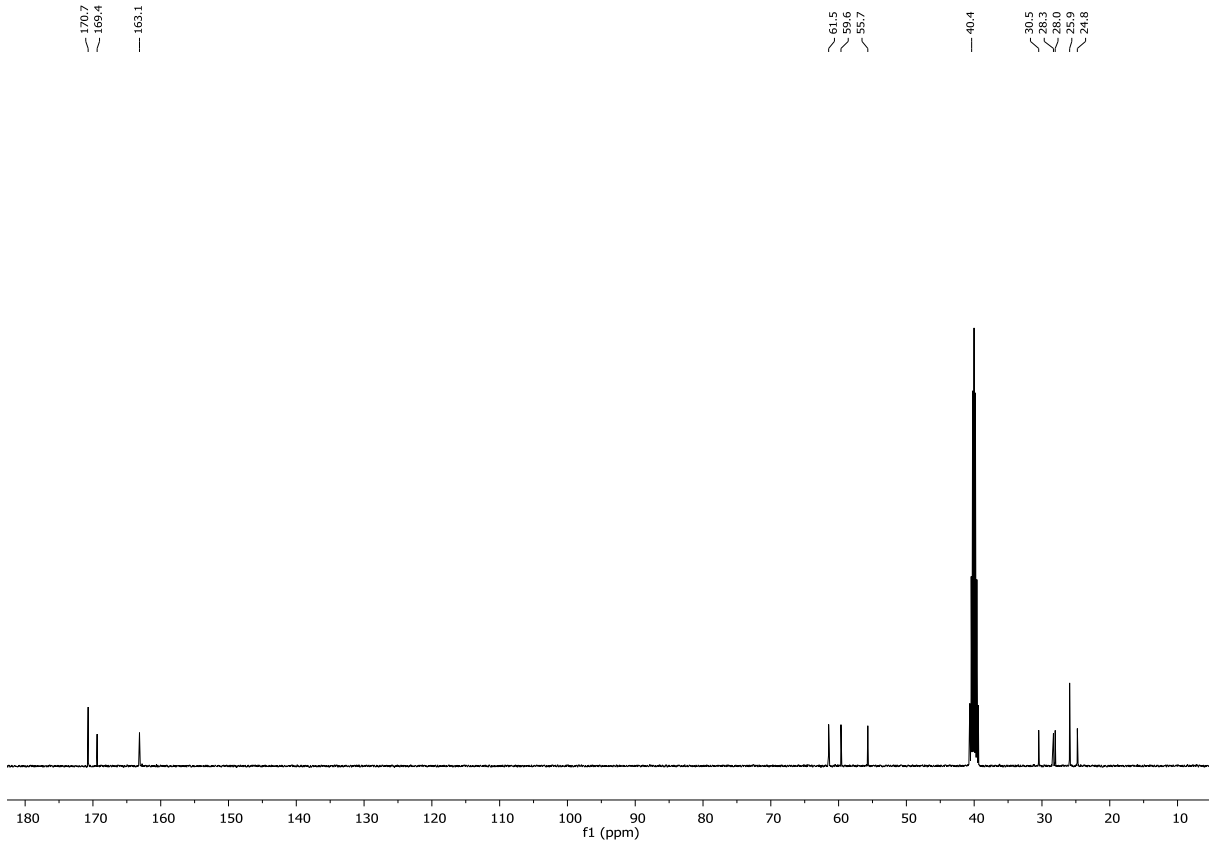

152.1
134.6
130.7
129.9
129.7
129.5
128.6
123.2
118.5
115.3
45.9
45.4
24.9
f1 (ppm)

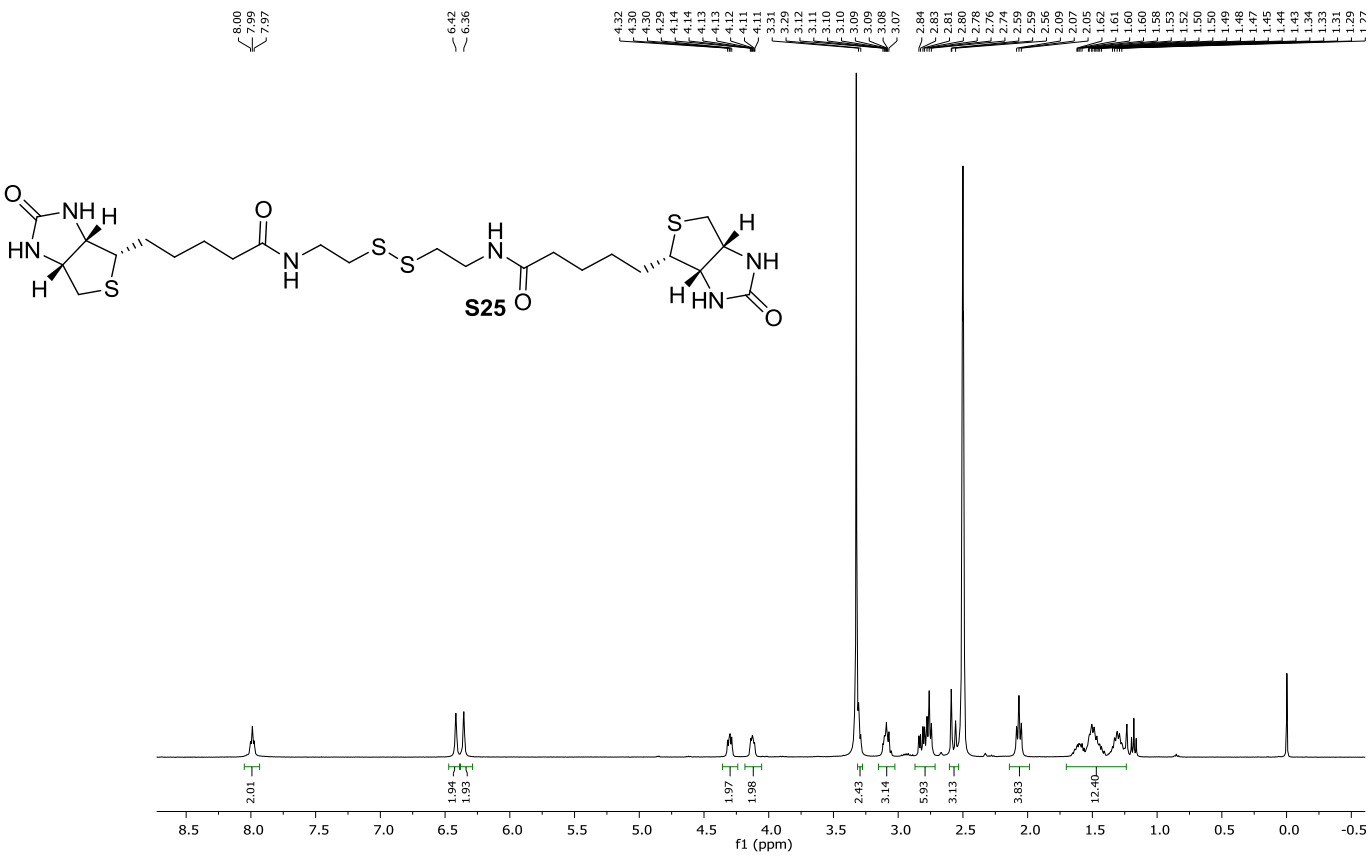

6.44
6.43
6.43
6.37
4.32
4.32
4.32
4.31
4.31
4.30
4.30
4.30
4.29
4.16
4.16
4.15
4.15
4.14
4.14
4.13
3.12
3.12
3.11
3.11
3.10
3.10
3.10
3.09
2.85
2.84
2.83
2.81
2.69
2.67
2.66
2.59
2.57
1.67
1.66
1.66
1.65
1.64
1.63
1.63
1.62
1.61
1.53
1.52
1.51
1.50
1.50
1.49
1.49
1.48
1.47
1.46
1.45
1.44
1.43
1.42
1.42
1.41
1.41
1.41
1.40
1.39
1.38

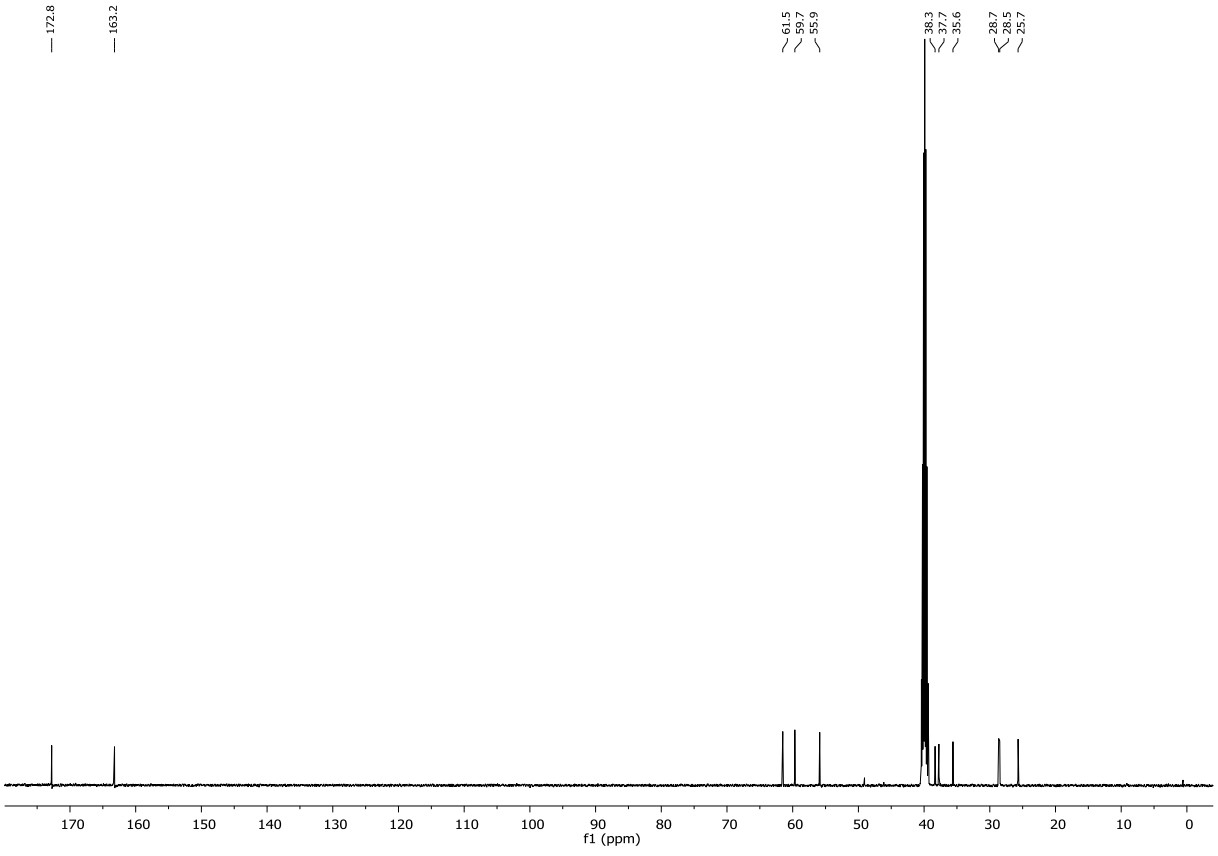

O
NH
H
HN
H
S
O
O
N
O
O

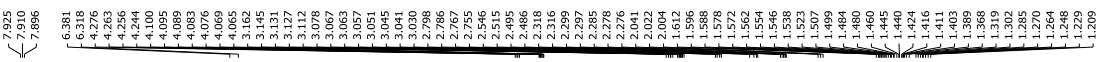
S24

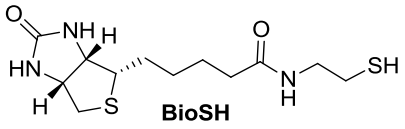

2.07
1.05
1.03
1.04
4.96
1.95
1.03
3.00
3.15
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


170.7
169.4
163.1
61.5
59.6
55.7
40.4
30.5
28.3
28.0
25.9
24.8
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

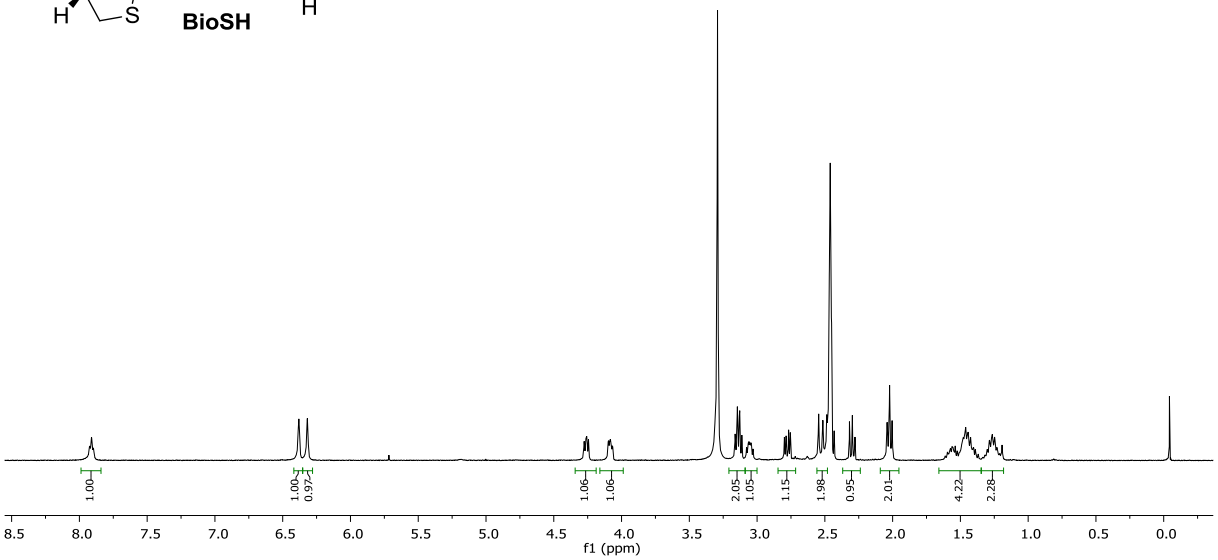

S25

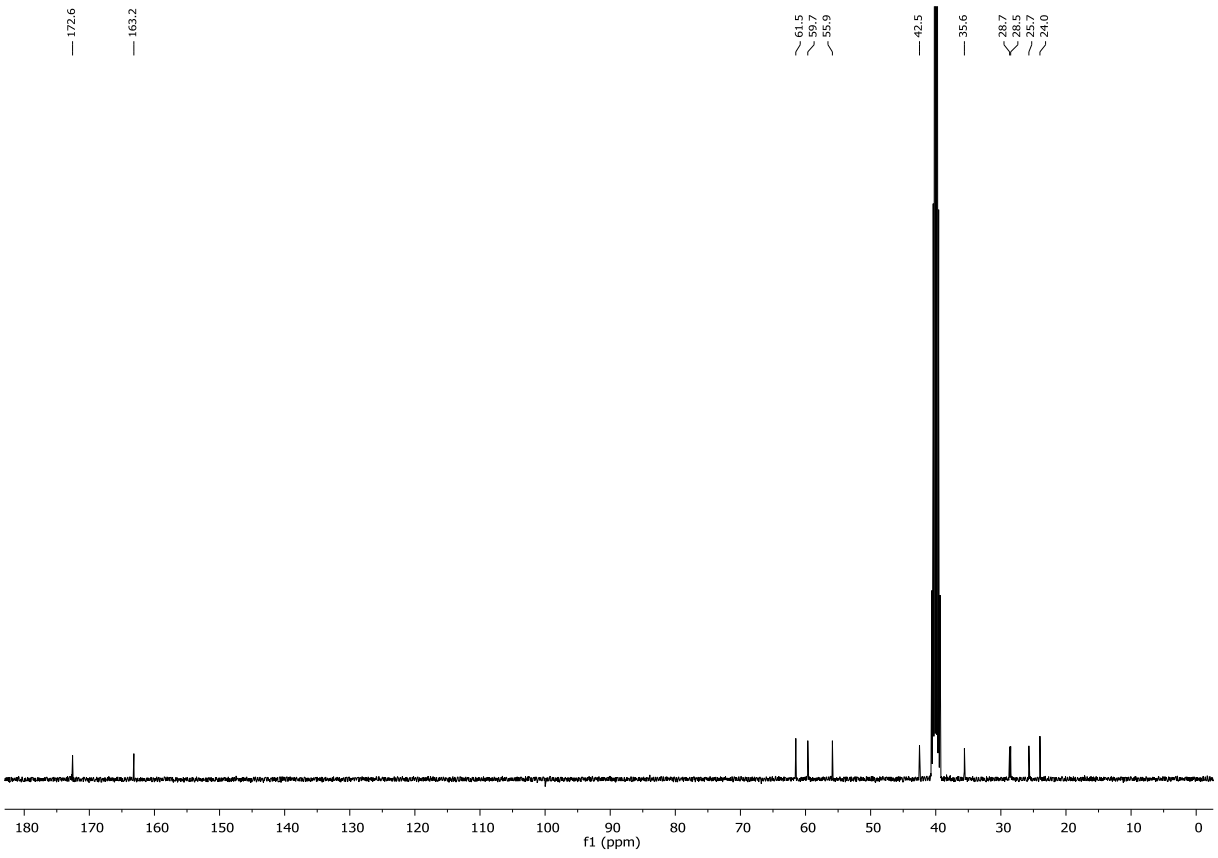


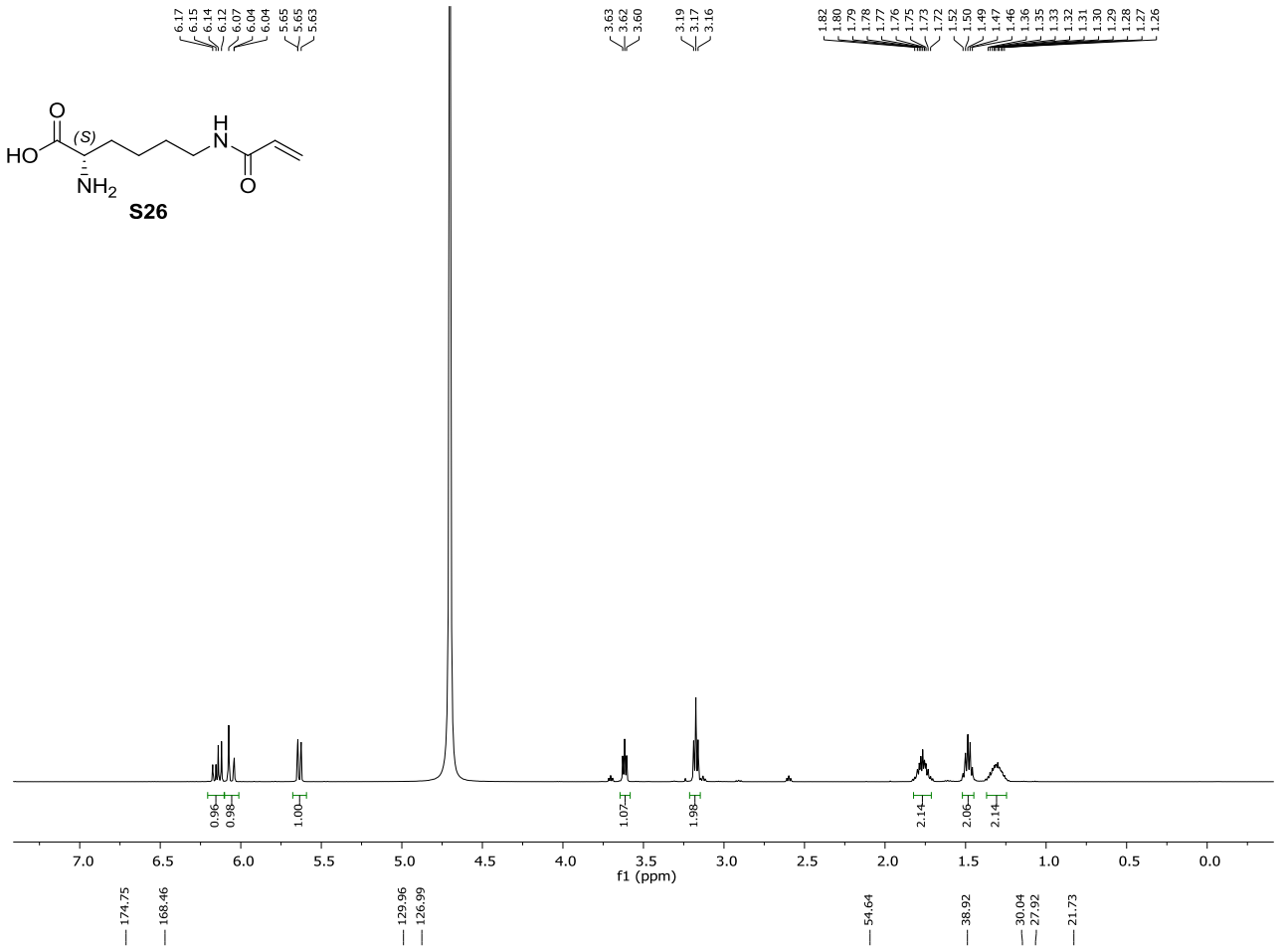


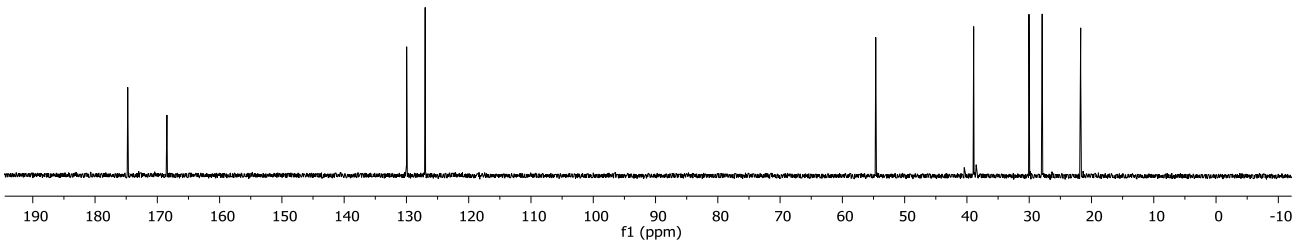

O
NH
H
HN
H
S
O
N
H
SH

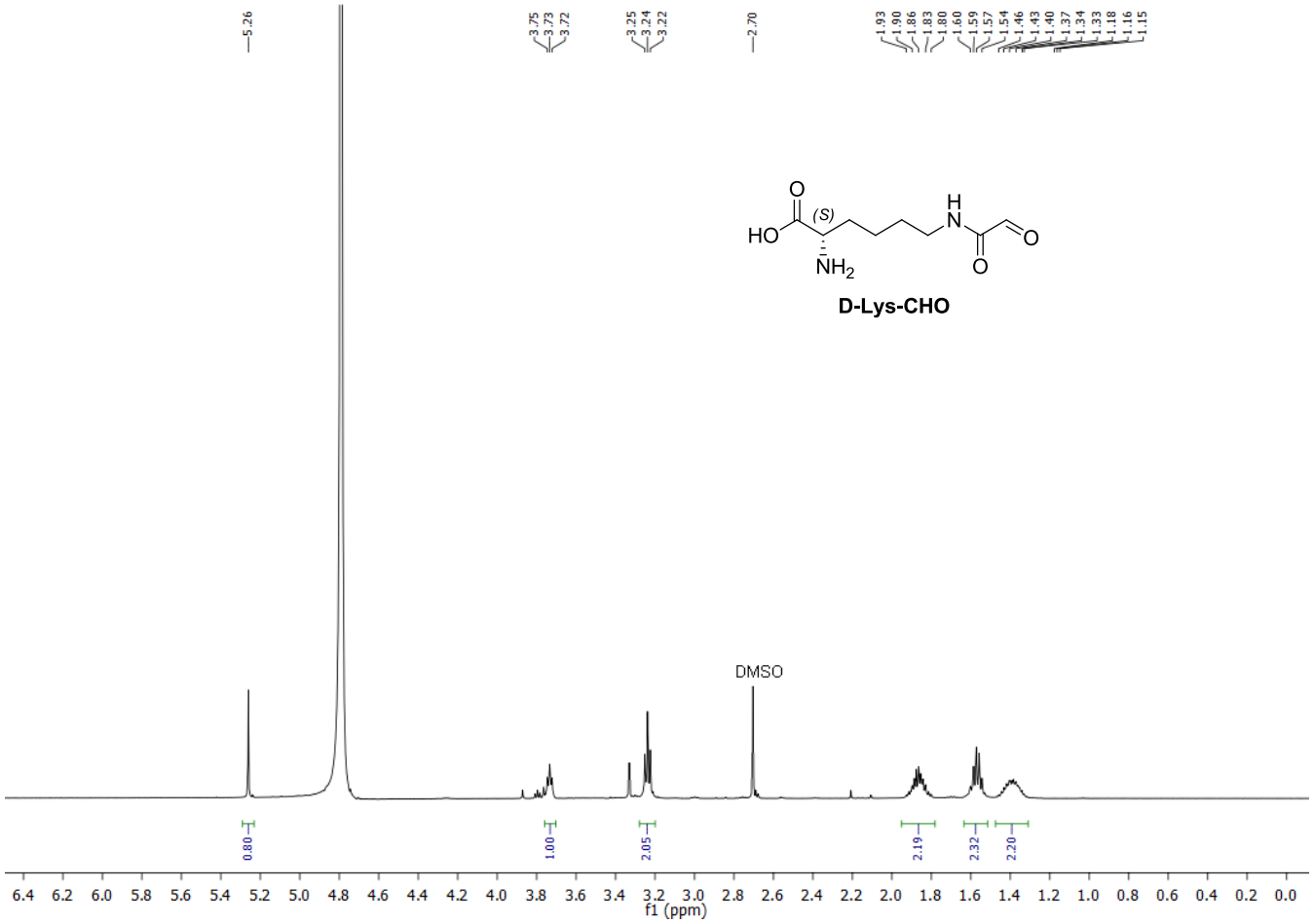
BioSH


1.00
1.00
0.97
1.06
1.06
2.05
1.05
1.15
1.98
0.95
2.01
4.22
2.28
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
0.0
f1 (ppm)


172.6
163.2
61.5
59.7
55.9
42.5
35.6
28.7
28.5
25.7
24.0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

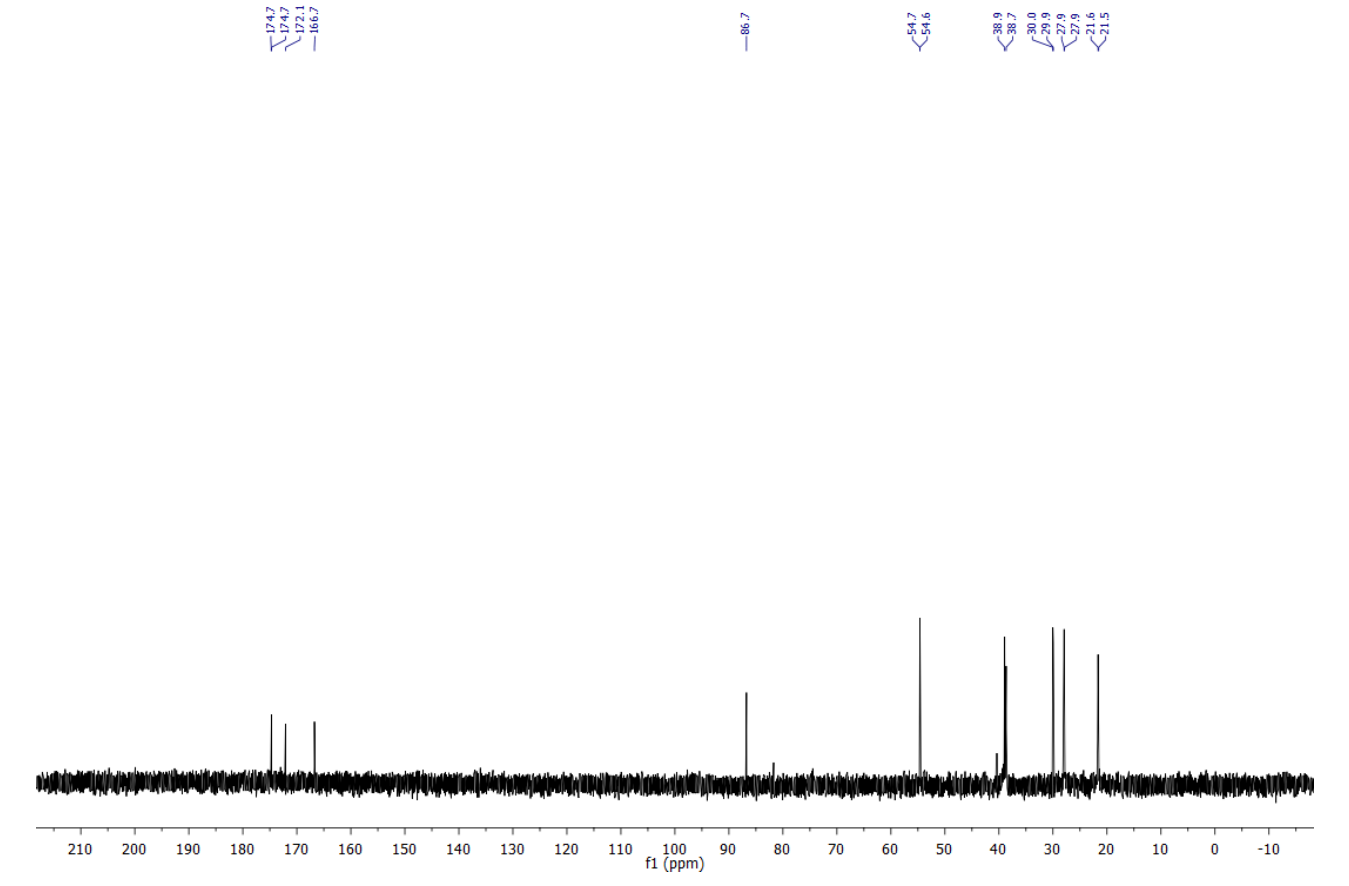

6.17
6.15
6.14
6.12
6.07
6.04
6.04
5.65
5.65
5.63
3.63
3.62
3.60
3.19
3.17
3.16
1.82
1.80
1.79
1.78
1.77
1.76
1.75
1.73
1.72
1.52
1.50
1.49
1.47
1.46
1.36
1.35
1.33
1.32
1.31
1.30
1.29
1.28
1.27
1.26
HO
(S)
NH2
H
N
O
O
S26
0.96
0.98
1.00
1.07
1.98
2.14
2.06
2.14
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
174.75
168.46
129.96
126.99
54.64
38.92
30.04
27.92
21.73


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

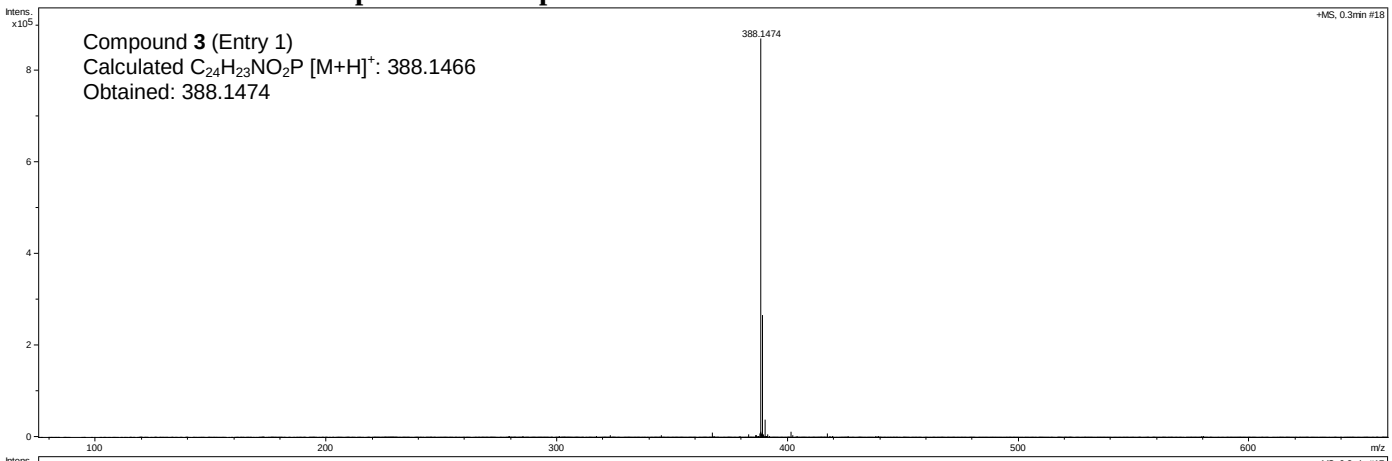

5.26
3.75
3.73
3.72
3.25
3.24
3.22
2.70
1.93
1.90
1.86
1.83
1.80
1.60
1.59
1.57
1.54
1.46
1.43
1.40
1.37
1.34
1.33
1.18
1.16
1.15
DMSO
0.80
1.00
2.05
2.19
2.32
2.20
f1 (ppm)

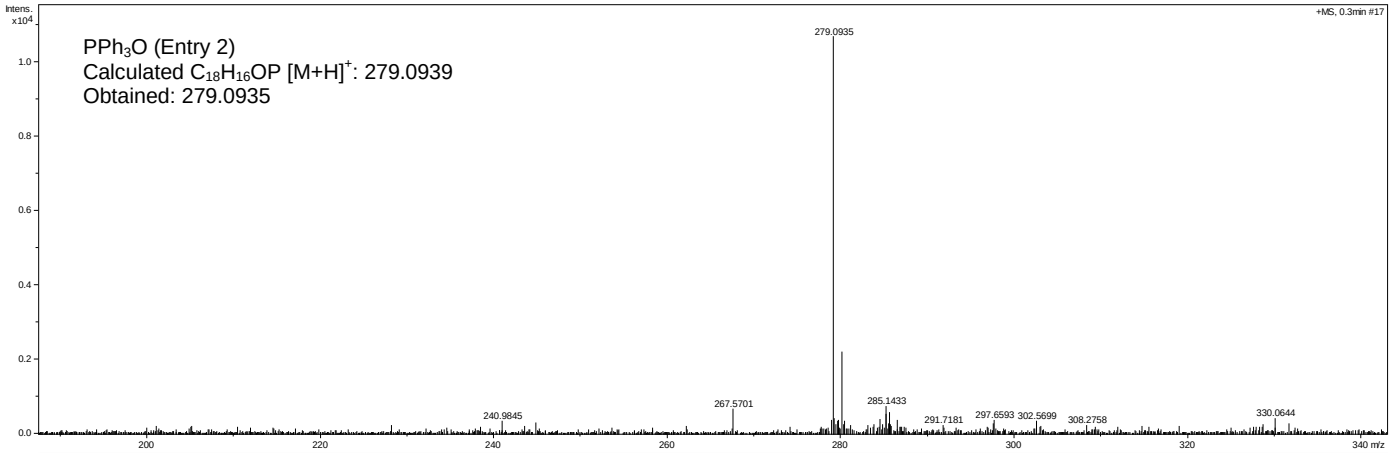
O
(S)
HO
NH2
H
N
O
O

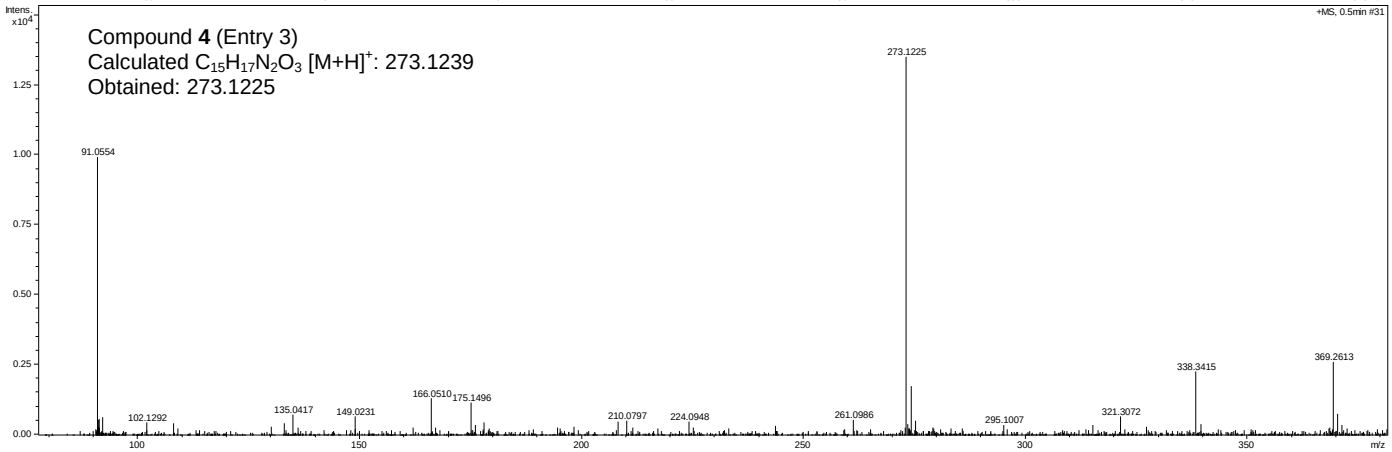
D-Lys-CHO

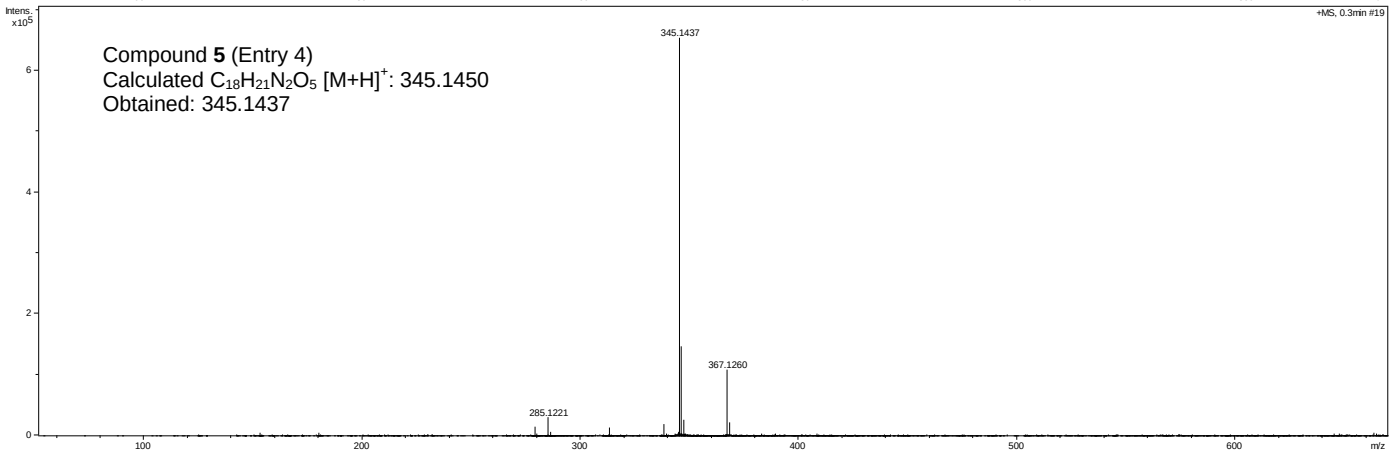

174.7
174.7
172.1
166.7
86.7
54.7
54.6
38.9
38.7
30.0
29.9
27.9
27.9
21.6
21.5
f1 (ppm)

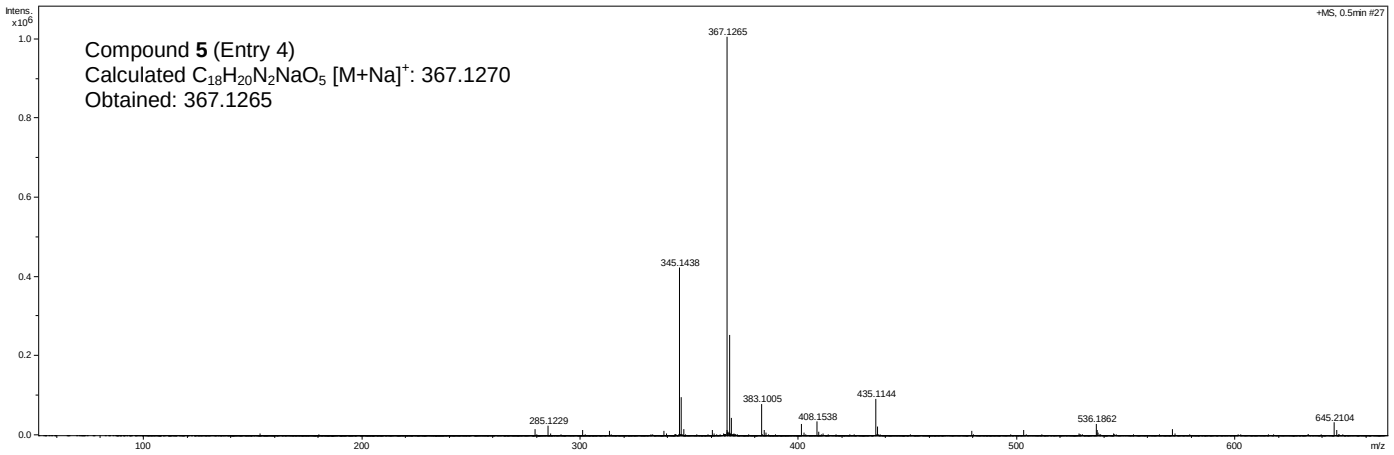
IX. HRMS/MALDI spectra for compounds in Table S1.

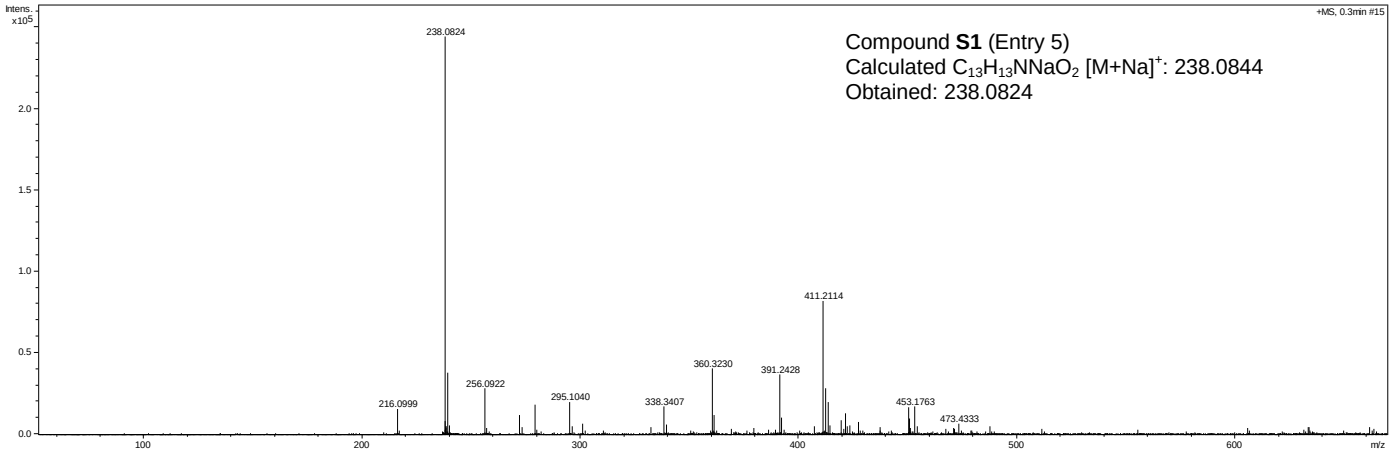


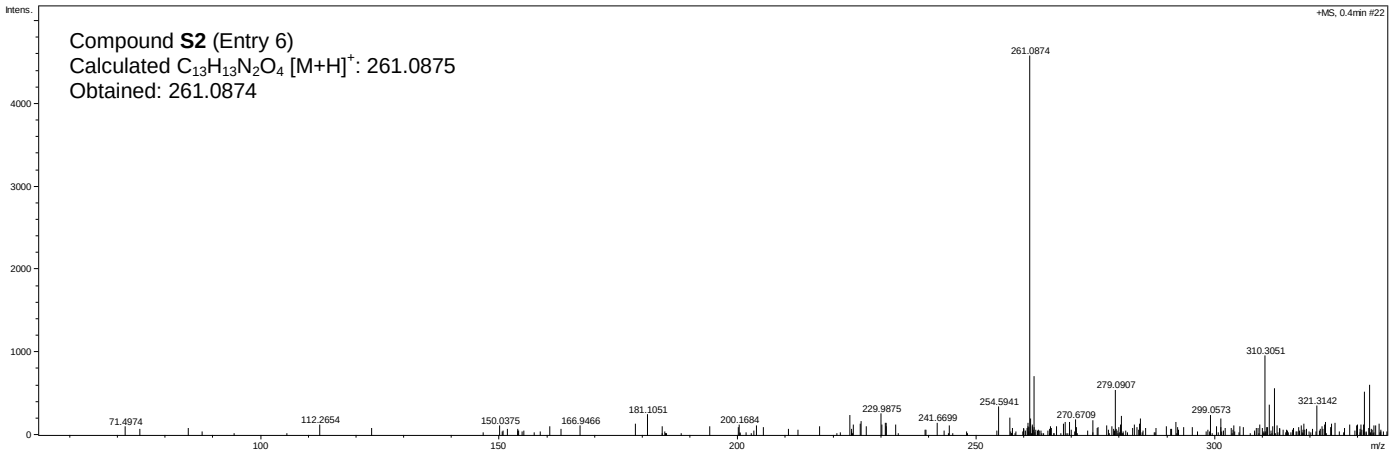


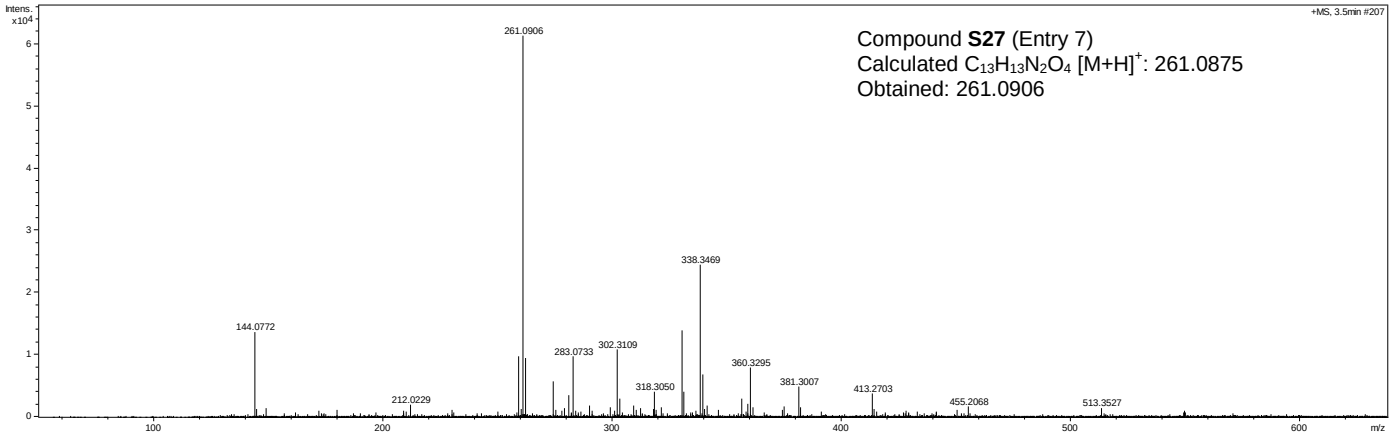


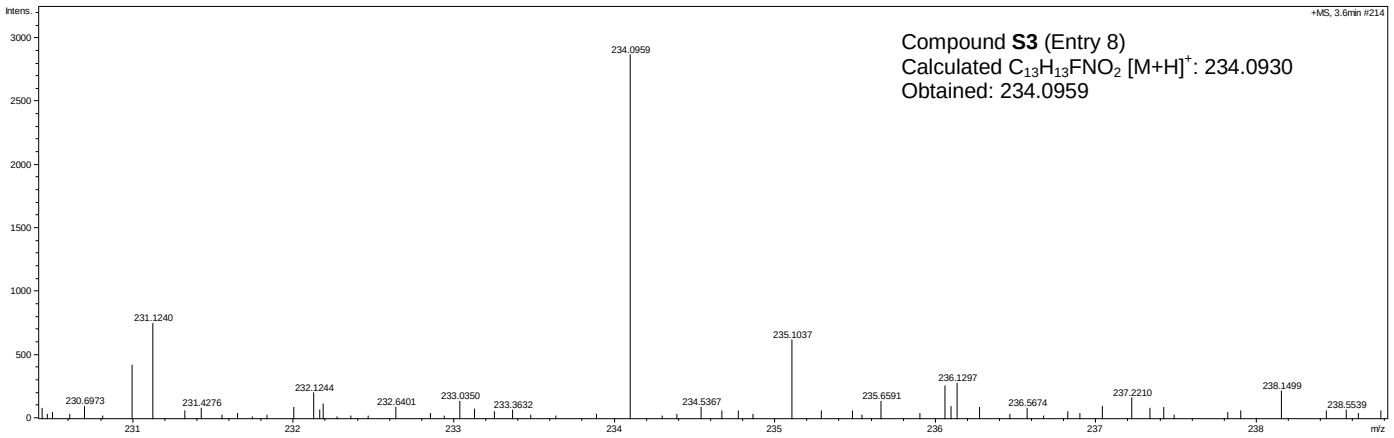


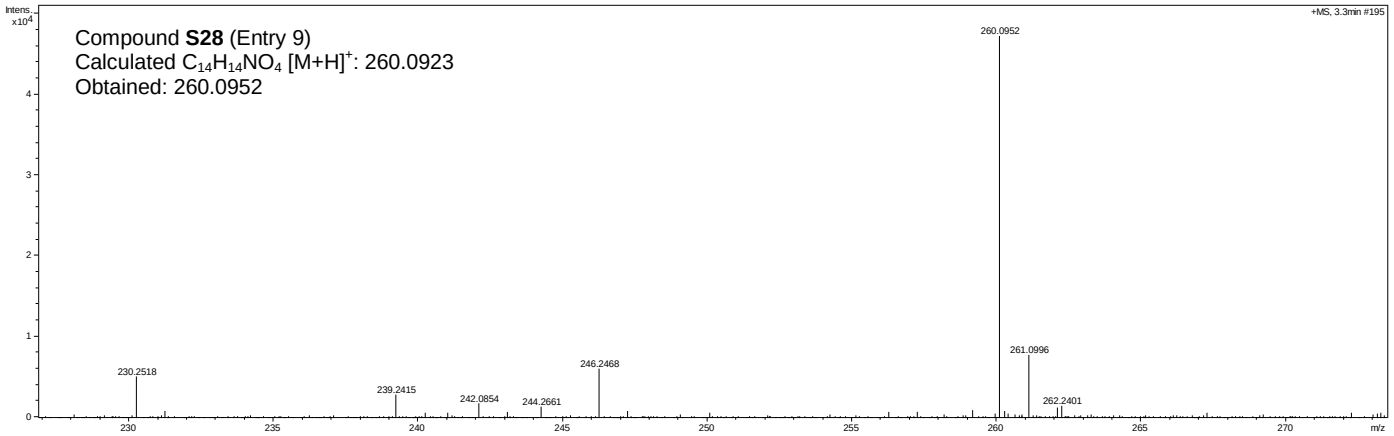

Intens.
x10^6
+MS, 0.5min #27
Compound **5** (Entry 4)
Calculated $C_{18}H_{20}N_2NaO_5$ $[M+Na]^+$: 367.1270
Obtained: 367.1265
367.1265
345.1438
383.1005
435.1144
285.1229
408.1538
536.1862
645.2104
m/z

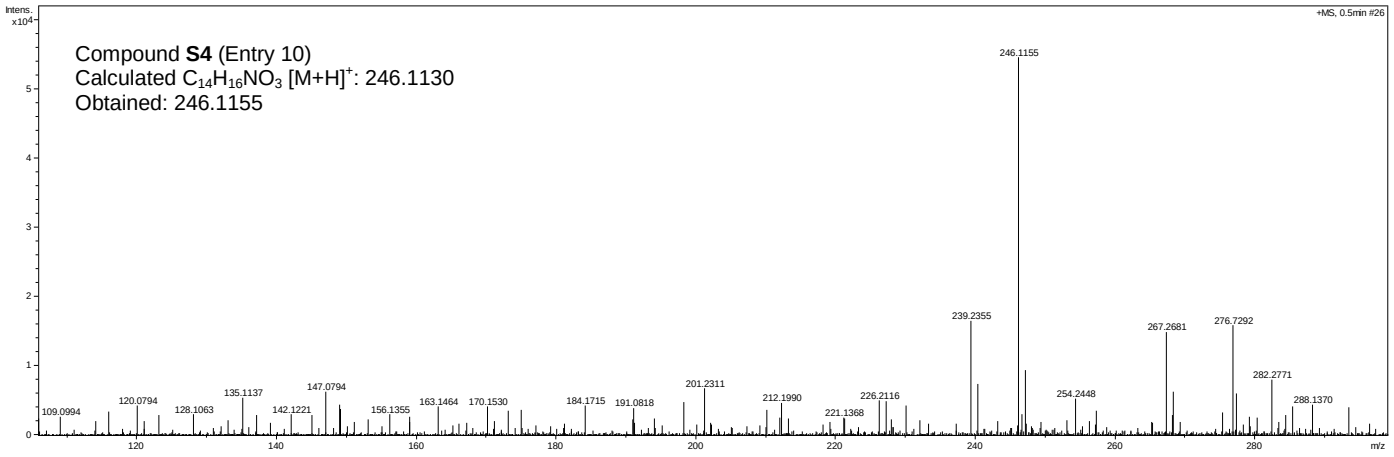

Intens.
x10^5
+MS, 0.3min #15
Compound **S1** (Entry 5)
Calculated $C_{13}H_{13}NNaO_2$ $[M+Na]^+$: 238.0844
Obtained: 238.0824
238.0824
411.2114
360.3230
391.2428
256.0922
216.0999
295.1040
338.3407
453.1763
473.4333
m/z

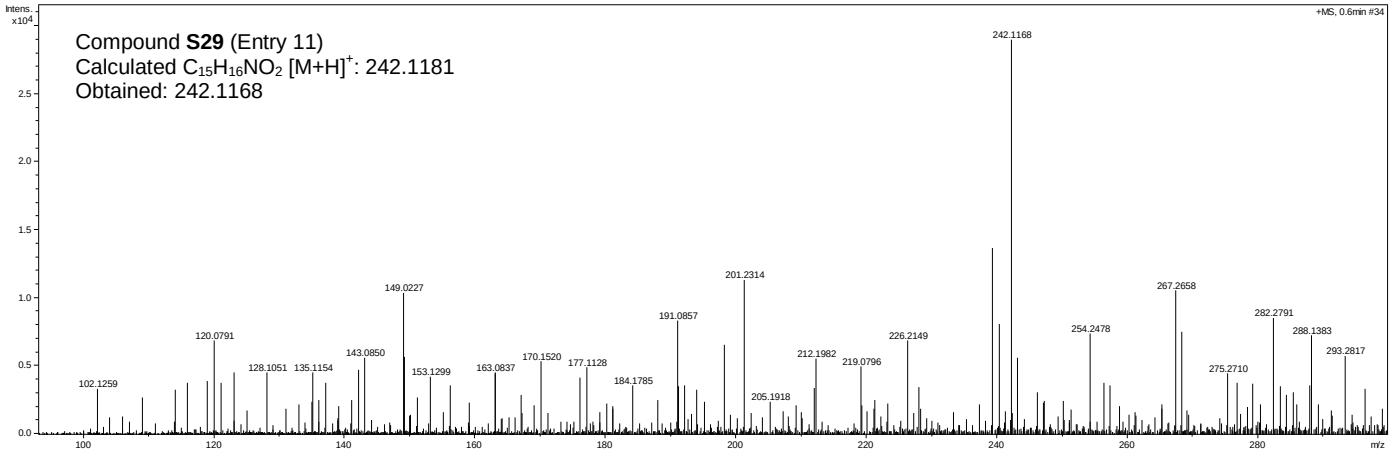

Intens.
+MS, 0.4min #22
Compound **S2** (Entry 6)
Calculated $C_{13}H_{13}N_2O_4$ $[M+H]^+$: 261.0875
Obtained: 261.0874
261.0874
310.3051
279.0907
321.3142
254.5941
229.9875
181.1051
241.6699
270.6709
299.0573
200.1684
71.4974
112.2654
150.0375
166.9466
m/z

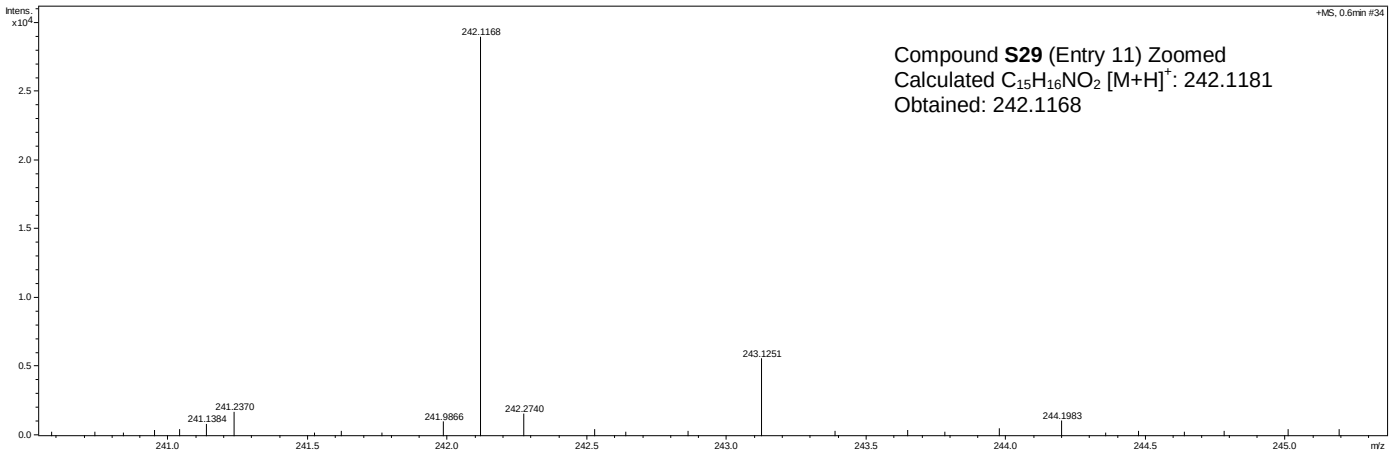

Intens.
x10^4
+MS, 3.5min #207
Compound **S27** (Entry 7)
Calculated $C_{13}H_{13}N_2O_4$ $[M+H]^+$: 261.0875
Obtained: 261.0906
261.0906
338.3469
144.0772
283.0733
302.3109
360.3295
318.3050
381.3007
413.2703
212.0229
455.2068
513.3527
m/z


+MS, 3.6min #214
Compound **S3** (Entry 8)
Calculated $C_{13}H_{13}FNO_2$ $[M+H]^+$: 234.0930
Obtained: 234.0959
234.0959
231.1240
235.1037
236.1297
232.1244
238.1499
230.6973
231.4276
232.6401
233.0350
233.3632
234.5367
235.6591
236.5674
237.2210
238.5539
m/z

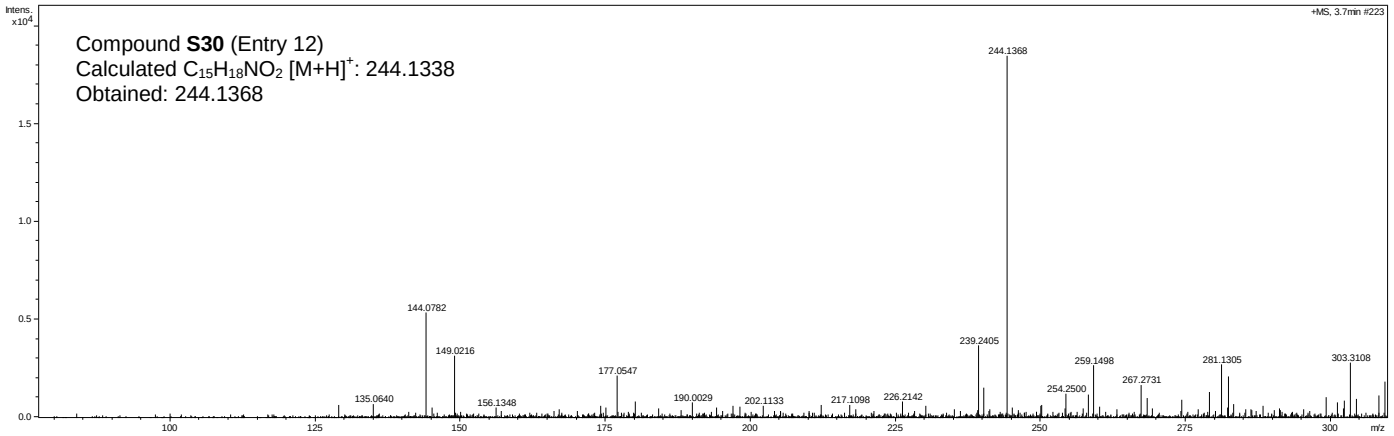

+MS, 3.3min #195
Compound **S28** (Entry 9)
Calculated $C_{14}H_{14}NO_4$ $[M+H]^+$: 260.0923
Obtained: 260.0952
260.0952
261.0996
246.2468
230.2518
239.2415
242.0854
244.2661
262.2401
m/z


+MS, 0.5min #26
Compound **S4** (Entry 10)
Calculated $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.1130
Obtained: 246.1155
246.1155
239.2355
267.2681
276.7292
282.2771
288.1370
254.2448
201.2311
147.0794
135.1137
120.0794
128.1063
142.1221
156.1355
163.1464
170.1530
184.1715
191.0818
212.1990
226.2116
221.1368
109.0994
m/z

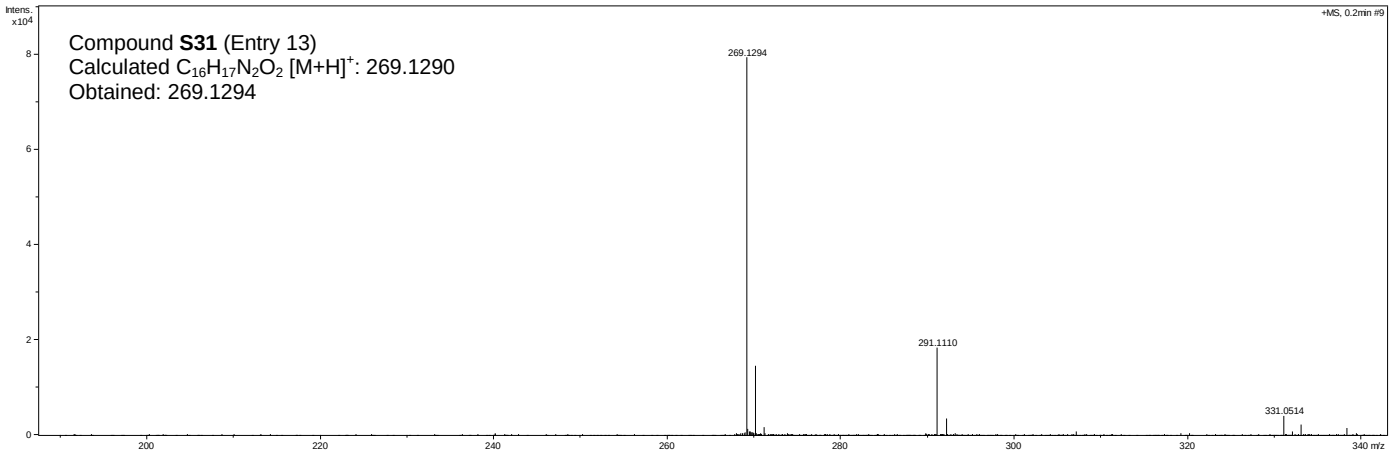

+MS, 0.6min #34
Compound **S29** (Entry 11)
Calculated $C_{15}H_{16}NO_2$ $[M+H]^+$: 242.1181
Obtained: 242.1168
242.1168
201.2314
267.2658
149.0227
191.0857
282.2791
120.0791
254.2478
288.1383
226.2149
143.0850
293.2817
170.1520
177.1128
212.1982
219.0796
153.1299
163.0837
275.2710
128.1051
135.1154
184.1785
102.1259
205.1918
m/z



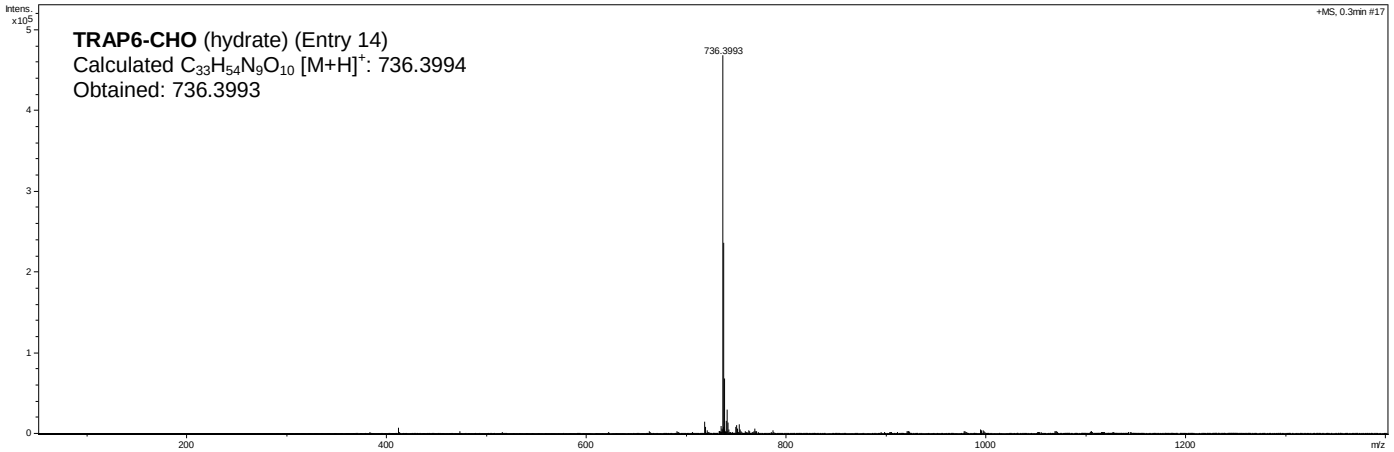
Compound **S29** (Entry 11) Zoomed
Calculated $C_{15}H_{16}NO_2$ $[M+H]^+$: 242.1181
Obtained: 242.1168



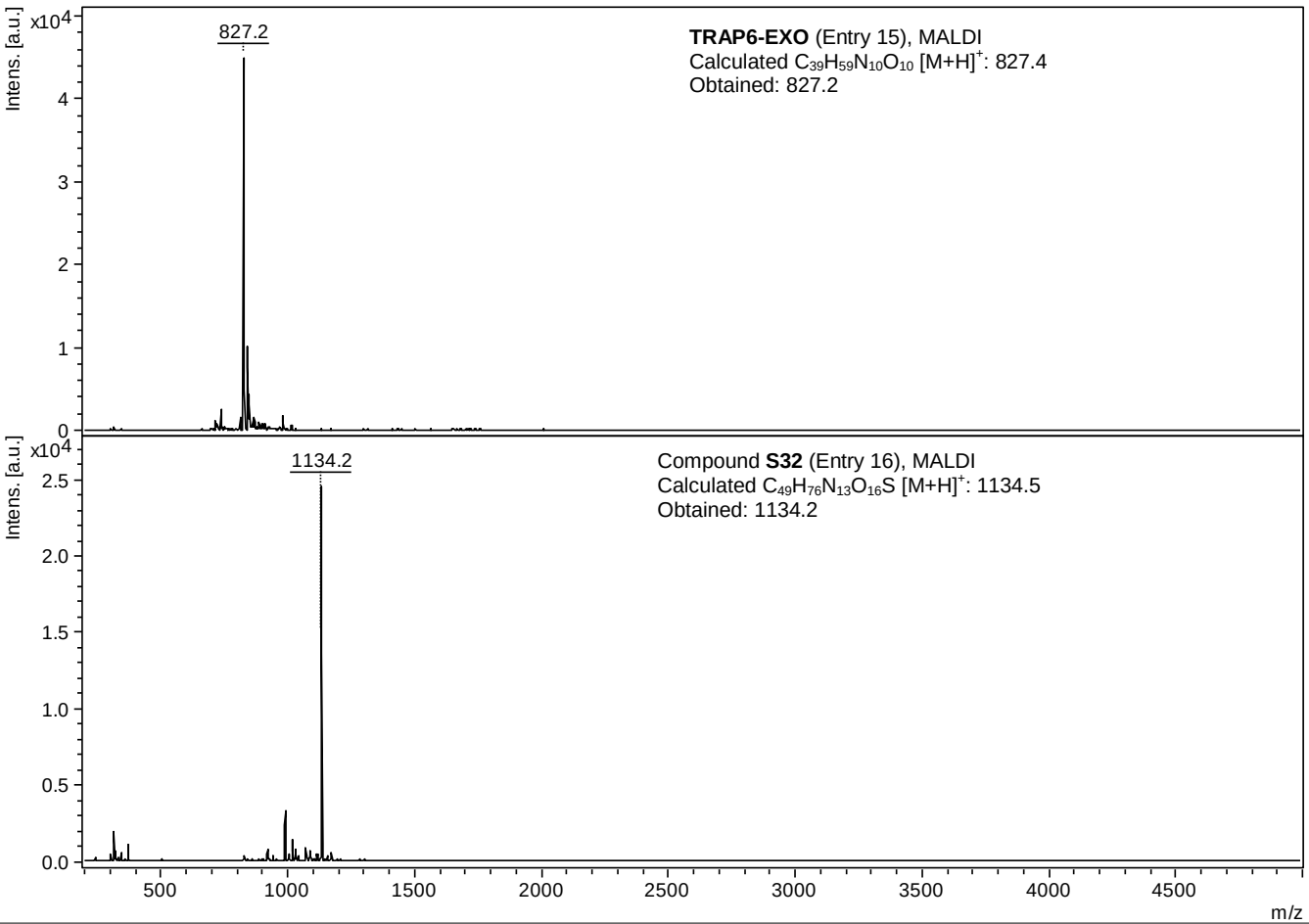
Compound **S30** (Entry 12)
Calculated $C_{15}H_{18}NO_2$ $[M+H]^+$: 244.1338
Obtained: 244.1368

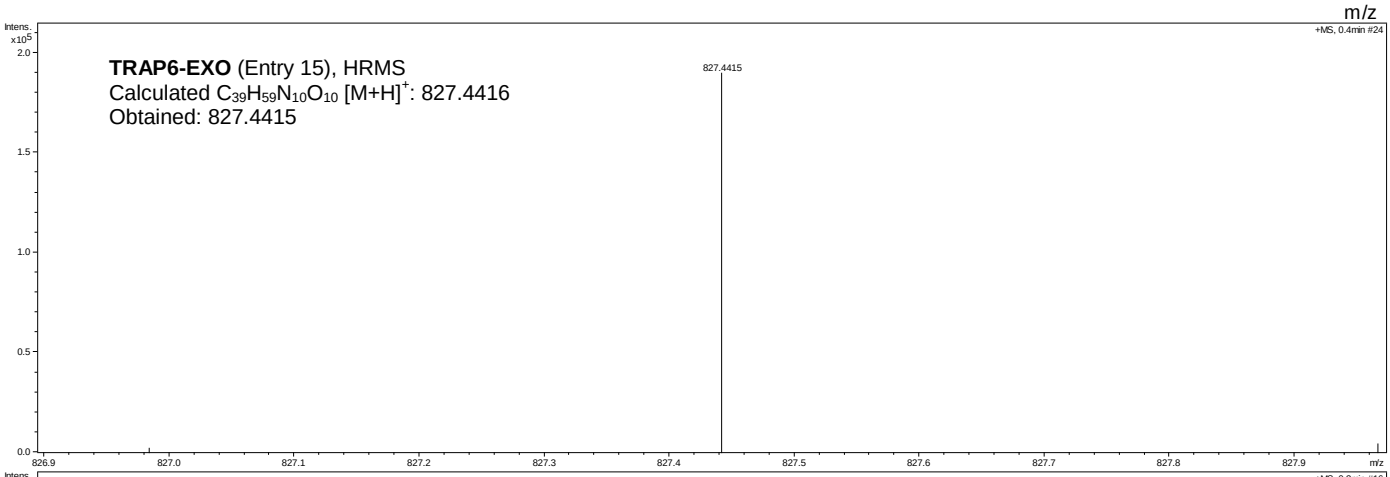


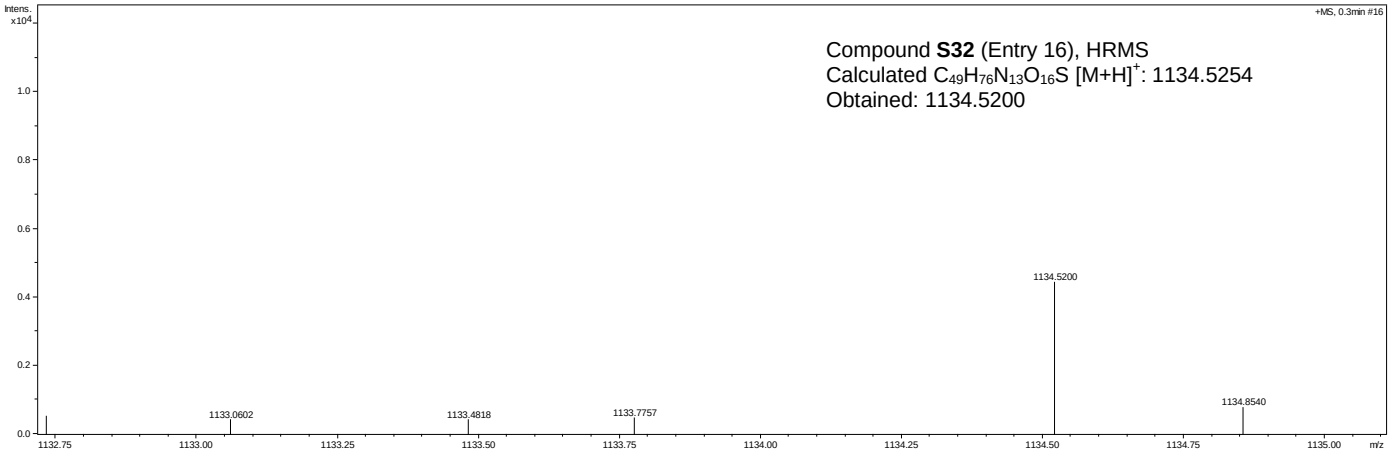
Compound **S31** (Entry 13)
Calculated $C_{16}H_{17}N_2O_2$ $[M+H]^+$: 269.1290
Obtained: 269.1294



TRAP6-CHO (hydrate) (Entry 14)
Calculated $C_{33}H_{54}N_9O_{10}$ $[M+H]^+$: 736.3994
Obtained: 736.3993


827.2
TRAP6-EXO (Entry 15), MALDI
Calculated $C_{39}H_{59}N_{10}O_{10}$ $[M+H]^+$: 827.4
Obtained: 827.2
1134.2
Compound **S32** (Entry 16), MALDI
Calculated $C_{49}H_{76}N_{13}O_{16}S$ $[M+H]^+$: 1134.5
Obtained: 1134.2
Intens. [a.u.]
m/z


TRAP6-EXO (Entry 15), HRMS
Calculated $C_{39}H_{59}N_{10}O_{10}$ $[M+H]^+$: 827.4416
Obtained: 827.4415
827.4415
+MS, 0.4min #24


Compound **S32** (Entry 16), HRMS
Calculated $C_{49}H_{76}N_{13}O_{16}S$ $[M+H]^+$: 1134.5254
Obtained: 1134.5200
1134.5200
1133.0602
1133.4818
1133.7757
1134.8540
+MS, 0.3min #16

X. References:

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