Supporting Information for

New antimicrobial self-assembling short lipopeptides

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1. General experimental details.

Reagents obtained from Sigma-Aldrich, Alfa, Fluorochem and TCI suppliers were used directly as supplied. All anhydrous reactions were carried out in flame dried glassware and under an inert atmosphere of argon provided by a balloon.

Reaction monitoring was performed through TLC analyses using Merck Kiesegel 60 F_{254} 0.25 mm precoated silica plates and the analysis was carried out using UV lamps and staining with phosphomolybdic acid, potassium permanganate or KOH/$FeCl_3$. Flash column chromatography was performed using silica gel (60 Å, 0.033-0.070 mm, BDH).

^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz or 400 MHz spectrometer in $CDCl_3$, CD_3OD or D_2O and referenced to residual solvent peaks. Chemical shifts are quoted in ppm (parts per million) to the nearest 0.01 ppm with signal splitting recorded as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), septet (sept) and multiplet (m). Coupling constants, *J*, are measured in Hz to the nearest 0.1 Hz. ^{1}H and ^{13}C NMR spectra were recorded at room temperature.

Infrared spectra were acquired using an Agilent Cary 630 FTIR Spectrometer, on transmission mode. Spectra was acquired of dried samples. The spectra were recorded between 4000 and 650 cm^{-1} at 2 cm^{-1} resolution with 32 accumulations. All spectral measurements were recorded at room temperature. Spectral data was automatically smoothed, and was studied using Microlab FTIR Software.

High resolution mass spectra are given to four decimal places and were registered in a spectrometer GCT Agilent Technologies 6890N using Electronic Impact (E.I.) techniques at 70 eV, Fast Atom Bombardment and electrospray (ESI^+ or ESI^-). Optical rotation values ($[\alpha]^{20}_D$) were registered at room temperature with a 241MC *Perkin Elmer* polarimeter. Melting points (m.p.) were obtained from recrystallized samples using a Lecia VMTG heated-stage microscope and are uncorrected.

2. Synthesis and characterization of lipopeptides.

· Method A: coupling free amino acids and fatty acyl chlorides.[1]

The corresponding free aminoacid (1.0 equiv) and a base (1.5 – 2.5 equiv) were dissolved in the minimal amount of water for complete solvation, followed by 2.5 volumes of THF and the reaction was stirred vigorously at 0 ºC under Ar. Acyl chloride (1.1 – 1.2 equiv) was added dropwise in 4 portions during a 4-hour period, and the mixture was then stirred at

RT overnight. The reaction was monitored using TLC. The volatile solvent (THF) were evaporated and the solution was then acidified with 6N HCl.

Depending on the example a white solid or an oil will be formed. Solids were filtrated, and further recrystallized in warm diethyl ether yielded white solids. Oils were extracted from water with EtOAc, washed with brine, dried with anhydrous Na_2SO_4, filtered and evaporated, to yield a yellowish oil, that was further purified using column chromatography on silica gel using a slow gradient of the appropriate mixture of eluents to give the corresponding product.

· **Method B: coupling amino ester and carboxylic acids using EDC/HOBt.**[2]

A solution of free carboxylic acid (1.0 equiv), HOBt (1.1 equiv) in dry DMF or THF (0.5 mL/ mmol), previously dried using activated molecular sieves, was added dropwise to another solution of EDC (1.1 equiv) in dry DMF. The mixture was stirred at RT for 30 min under Ar and a solution of free amine (1.1 equiv), DIPEA (2.5 – 4.5 equiv) in dry DMF, previously dried using activated molecular sieves, was added. The mixture was stirred at RT for 18 – 24 h under Ar and the crude reaction was diluted with 2.5 volumes of distilled water and extracted three times with EtOAc. The pH of the aqueous phase was adjusted before the extraction (pH = 7 for dipeptides, pH = 9 for *N*-acyl-dipeptides and pH = 3 for C-amine-dipeptides). The organic phase was dried with Na_2SO_4 and the solvents were evaporated under reduced pressure. The crude was further purified using column chromatography on silica gel using a slow gradient of the appropriate mixture of eluents to give the corresponding product.

· **Method C: amide bond formation using HATU or HCTU.**

A solution of the free carboxylic acid (1.0 equiv), HATU or HCTU (1.1 equiv) and DIPEA (2.5 – 4.5 equiv) in dry DMF (0.5 mL/ mmol), previously dried using activated molecular sieves, was stirred at 0 ºC for 30 min under Ar. A solution of the free amine (1.1 equiv) in dry DMF (0.5 mL/ mmol), previously dried using activated molecular sieves, was added and the mixture was stirred at RT for 18 – 24 h under Ar.

The reaction mixture was diluted with 2.5 volumes of distilled water, and the product was extracted with EtOAc three times. The pH of the aqueous phase was adjusted before the extraction (pH = 7 for dipeptides, pH = 9 for *N*-acyl-dipeptides and pH = 3 for C-amine-dipeptides). The organic phase was dried with Na_2SO_4 and the solvents were evaporated under reduced pressure. The crude was further purified using column chromatography on silica gel using a slow gradient of the appropriate mixture of eluents to give the corresponding product.

· **Method D: deprotection of ester groups.**

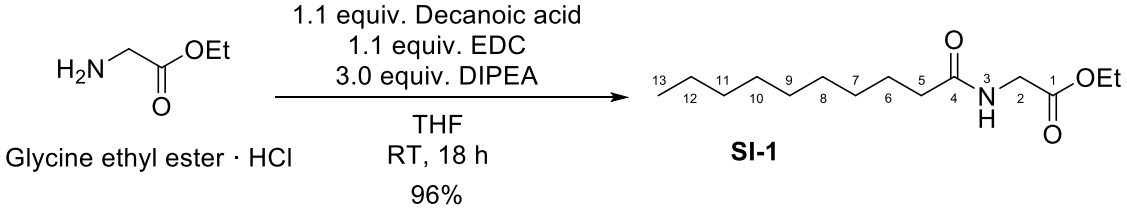
An aqueous solution of NaOH (4.0 equiv) was added dropwise to a solution of ester-protected lipoamino acid or lipopeptide (1.0 equiv) in MeOH (2.5 mL/mmol), and was stirred at RT for 1.5 – 2 h. The reaction was monitored using TLC until completion, when it was neutralized with HCl 2N until pH = 7. Water was evaporated under reduced pressure at 55 ºC. The resulting solid was re-dissolved in a 1 : 1 mixture of MeOH–CH_2Cl_2 and filtrated to remove solid salts. Finally, volatile solvents were evaporated under reduced pressure, yielding white powders or foams.

· **Method E: deprotection of NHBoc and O*t*-Bu groups**

A solution of the NHBoc and/or O*t*-Bu protected starting material (1.0 equiv), TFA (10.0 – 20.0 equiv), TIPS (10 mol%) and DTE (5 mol%) in CH_2Cl_2 (5.0 mL/mmol) were stirred at RT for 2 – 5 h and the reaction was monitored using TLC until completion. Volatile solvents (CH_2Cl_2) were evaporated under reduced pressure, and product was precipitated, and subsequently washed with cold (-18 ºC) Et_2O or Hexane.

If an oil is obtained, it was purified using column chromatography on silica gel sing a slow gradient of the appropriate mixture of eluents to give the corresponding product.

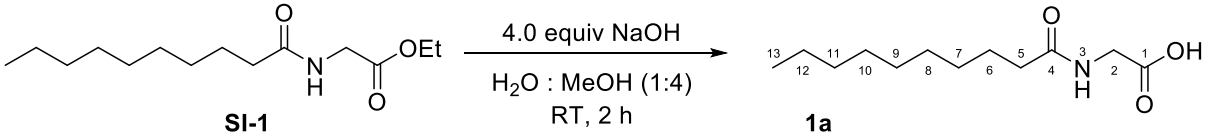
2.1. Synthesis of *N*-decanoyl-2-amino-ethylacetate, SI-1.



From glycine ethyl ester · HCl (1.2 g, 8.60 mmol), decanoic acid (1.77 g, 10.30 mmol), HATU (3.90 g, 10.30 mmol) and DIPEA (5.0 mL, 30.10 mmol) in 50.0 mL of THF, following the general procedure (**Method B**), amide **SI-1** (2.15 mg, 96 % yield) was obtained as a white solid. Spectroscopic properties matched those previously reported.[3]

Data for **SI-1**: $\mathbf{R_f}$ 0.60 (5% MeOH – DCM). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 6.21 (1H, t, *J* = 5.4 Hz, 3-H), 4.18 (2H, q, *J* = 7.2 Hz, CH_2 Et), 3.98 (2H, d, *J* = 5.2 Hz, 2-H_2), 2.21 (2H, t, *J* = 7.4 Hz, 5-H_2), 1.59 (2H, quint, *J* = 6.8 Hz, 6-H_2), 1.15-1.31 (15H, m, 7-H_2 and 8-H_2 and 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2 and CH_3 Et), 0.83 (3H, t, *J* = 7.1 Hz, 13-H_3).

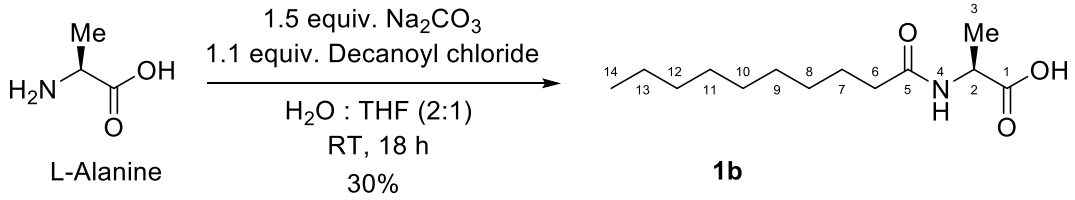
2.2. Synthesis of *N*-decanoyl-2-aminoacetic acid (*N*-decanoyl-glycine), 1a.



From amide **SI-1** (2.15 g, 8.36 mmol), and 4N NaOH (5.0 mL) in 20.0 mL of MeOH, following the general procedure (**Method D**), amide **1a** (1.7 g, 88 % yield) was obtained as a white solid. Spectroscopic properties matched those previously reported.[1]

Data for **1a**: $\mathbf{R_f}$ 0.80 (5% MeOH – DCM). **^{1}H-NMR** (300 MHz, CD_3OD): δ 3.86 (2H, s, 2-H_2), 2.24 (2H, t, J = 7.4 Hz, 5-H_2), 1.62 (2H, quint, J = 6.8 Hz, 6-H_2), 1.22-1.42 (12H, m, 7-H_2 and 8-H_2 and 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2), 0.86 (3H, t, J = 7.1 Hz, 13-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 176.7 (C-1), 173.0 (C-4), 41.7 (C-2), 36.8 (C-5), 33.0 (C-6), 30.6 and 30.42 and 30.40 and 30.2 and 26.8 and 23.7 (6C, C-7 and C-8 and C-9 and C-10 and C-11 and C-12), 14.4 (C-13). **IR** (solid): ν_{max} 3302, 2907, 1694, 1637, 1528, 1249 cm^{-1}.

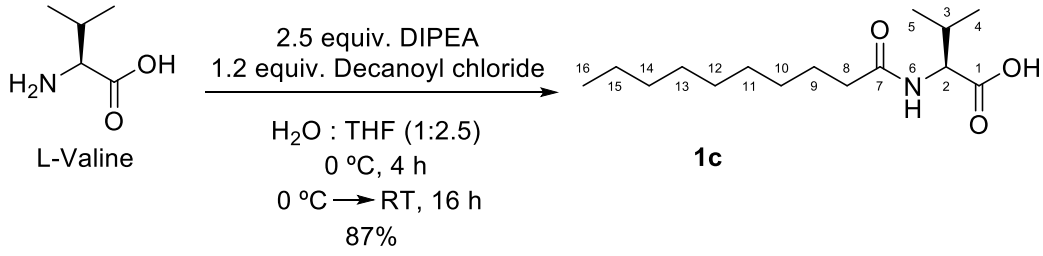
2.3. Synthesis of (2S)-*N*-decanoyl-2-aminopropionic acid, 1b.



From L-alanine (1.00 g, 11.22 mmol), decanoyl chloride (2.50 g, 12.34 mmol) and Na_2CO_3 (1.78 g, 22.44 mmol) in 30.0 mL of a 2:1 mixture of H_2O:THF, following the general procedure (**Method A**), amide **1b** (751 mg, 30 % yield) was obtained as a white solid. Spectroscopic properties matched those previously reported.[4]

Data for **1b**: $\mathbf{R_f}$ 0.15 (20% EtOAc – DCM). **[α]$^{20}_D$** +2.6 (c = 1.0, $CHCl_3$). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 11.54 (1H, s, COOH), 6.43 (1H, d, J = 7.1 Hz, 4-H), 4.52 (1H, quint, J = 7.2 Hz, 2-H), 2.18 (2H, t, J = 7.5 Hz, 6-H_2), 1.57 (2H, quint, J = 6.9 Hz, 7-H_2), 1.38 (3H, d, J = 7.2 Hz, 3-H_3), 1.12-1.29 (12H, m, 8-H_2 and 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2), 0.80 (3H, t, J = 6.7 Hz, 14-H_3). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 175.9 (C-1), 174.2 (C-5), 48.2 (C-2), 36.4 and 31.8 and 29.4 and 29.27 and 29.23 and 29.1 and 25.6 and 22.6 (8C, C-6 and C-7 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13), 18.1 (C-3), 14.0 (C-14). **IR** (solid): ν_{max} 3302, 2907, 1694, 1637, 1528, 1249 cm^{-1}.

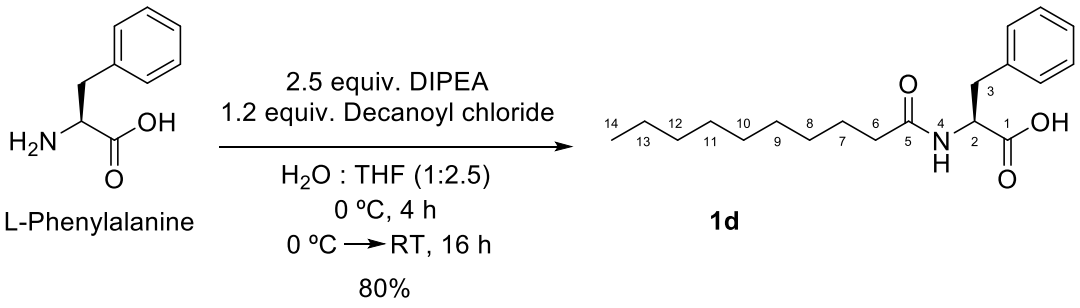
2.4. Synthesis of (2S)-N-decanoyl-2-aminopropionic acid, 1c.



From L-valine (1.00 g, 8.50 mmol), decanoyl chloride (1.2 mL, 10.20 mmol) and DIPEA (3.0 mL, 17.0 mmol) in 50.0 mL of a 1:2.5 mixture of H_2O:THF, following the general procedure (**Method A**), amide **1c** (2.00 g, 87 % yield) was obtained as a white solid. Spectroscopic properties matched those previously reported.[5]

Data for **1c**: $\mathbf{R_f}$ 0.25 (5% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ –11.4 (*c* = 1.0, $CHCl_3$). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 11.06 (1H, s, COOH), 6.24 (1H, d, *J* = 8.8 Hz, 6-H), 4.43-4.57 (1H, m, 2-H), 2.21 (2H, t, *J* = 9.9 Hz, 8-H_2), 2.05-2.15 (1H, m, 3-H), 1.56 (2H, quint, *J* = 6.9 Hz, 9-H_2), 1.08-1.27 (12H, m, 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 14-H_2 and 15-H_2), 0.90 (3H, d, *J* = 7.3 Hz, 4-H_3), 0.88 (3H, d, *J* = 7.3 Hz, 5-H_3), 0.85 (3H, t, *J* = 7.0 Hz, 16-H_3). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 175.1 (C-1), 174.3 (C-7), 57.0 (C-2), 36.6 (C-8), 31,8 and 31.0 (2C, C-3 and C-9), 29.4 and 29.29 and 29.23 and 29.20 and 25.8 and 22.6 (6C, C-10 and C-11 and C-12 and C-13 and C-14 and C-15), 18.9 and 17.6 (C-4 and C-5), 14.0 (C-16). **IR** (solid): ν_{max} 3302, 2907, 1701, 1629, 1529, 1235 cm^{-1}.

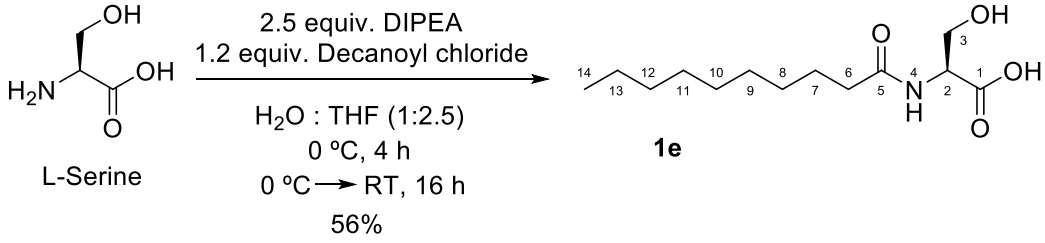
2.5. Synthesis of (2S)-*N*-decanoyl-2-amino-3-phenylpropionic acid, 1d.



From L-phenylalanine (1.00 g, 6.05 mmol), decanoyl chloride (1.5 mL, 7.26 mmol) and DIPEA (2.1 mL, 12.10 mmol) in 40.0 mL of a 1:2.5 mixture of H_2O:THF, following the general procedure (**Method A**), amide **1d** (1.52 g, 80 % yield) was obtained as a white solid. Spectroscopic properties matched those previously reported.[2]

Data for **1d**: $\mathbf{R_f}$ 0.25 (10% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ +41.1 (*c* = 1.0, $CHCl_3$). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 11.16 (1H, s, COOH), 7.00-7.24 (5H, m, Ar), 6.27 (1H, d, *J* = 7.3 Hz, 4-H), 4.74-4.86 (1H, m, 2-H), 3.16 (1H, dd, *J* = 14.0 and 5.3 Hz, 3-H_a), 3.03 (1H, dd, *J* = 14.2 and 6.2 Hz, 3-H_b), 2.09 (2H, t, *J* = 7.2 Hz, 6-H_2), 1.45 (2H, m, 7-H_2), 0.95-1.35 (12H, m, 8-H_2 and 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2), 0.79 (3H, t, *J* = 6.4 Hz, 14-H_3). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 174.7 (C-1), 174.2 (C-5), 135.9 (C-Ar), 129.4 (2C, 2 x CH Ar), 128.5 (2C, 2 x CH Ar), 127.0 (CH-Ar), 53.3 (C-2), 37.3 (C-3), 36.4 (C-6), 31.8 and 29.4 and 29.3 and 29.3 and 29.1 and 25.6 and 22.67 (7C, C-7 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13), 14.1 (C-14). **IR** (solid): ν_{max} 3295, 3037, 2914, 1715, 1615, 1543, 1242 cm^{-1}.

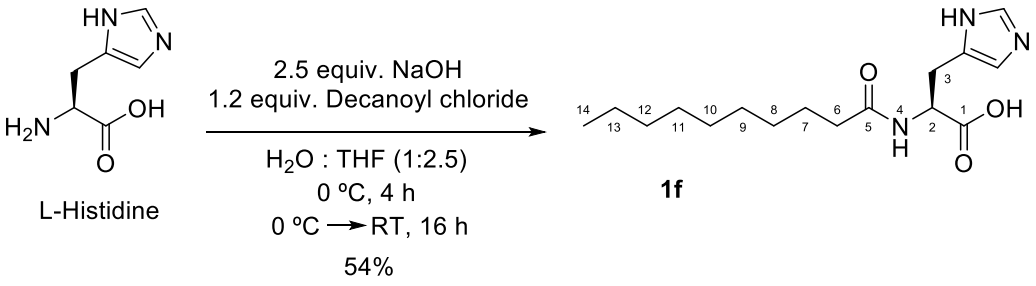
2.6. Synthesis of (2S)-*N*-decanoyl-2-amino-3-hydroxypropionic acid, 1e.



From L-serine (1.00 g, 9.44 mmol), decanoyl chloride (2.160 mL, 10.4 mmol) and DIPEA (3.3 mL, 19.00 mmol) in 18.0 mL of a 1:2.5 mixture of H_2O:THF, following the general procedure (**Method A**), amide **1e** (1.38 g, 56 % yield) was obtained as a white solid.

Data for **1e**: $\mathbf{R_f}$ 0.30 (20% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ +5.4 (*c* = 1.0, MeOH) **^{1}H-NMR** (300 MHz, CD_3OD): δ 4.45 (1H, t, *J* = 4.4 Hz, 2-H), 3.80 (1H, dd, *J* = 11.1 and 5.1 Hz, 3-H_a), 3.72 (1H, dd, *J* = 11.0 and 4.5 Hz, 3-H_b), 2.23 (2H, t, *J* = 7.5 Hz, 6-H_2), 1.52 (2H, quint, *J* = 7.0 Hz, 7-H_2), 1.13-1.31 (12H, m, 8-H_2 and 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2), 0.81 (3H, t, *J* = 6.5 Hz, 14-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 176.4 (C-1), 173.5 (C-5), 62.9 (C-3), 56.0 (C-2), 36.9 (C-6), 26.8 (C-7), 33.0 and 30.6 and 30.5 and 30.4 and 30.2 and 23.7 (6C, C-8 and C-9 and C-10 and C-11 and C-12 and C-13), 14.4 (C-14). **IR** (solid): ν_{max} 3316, 2907, 1730, 1608, 1522, 1206 cm^{-1}. **HRMS** (ESI): calculated for $C_{13}H_{26}N\,O_4$ $[M+H]^+$ requires *m*/*z* 260.1856, found *m*/*z* 260.1856.

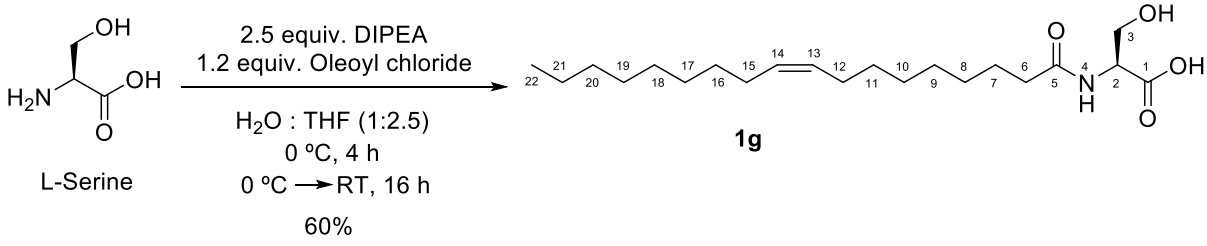
2.7. Synthesis of (2S)-*N*-decanoyl-2-amino-3-(1H-imidazol-4-yl)propionic acid, 1f.



From L-histidine (1.00 g, 6.44 mmol), decanoyl chloride (1.60 mL, 7.73 mmol) and NaOH (515 mg, 12.88 mmol) in 25.0 mL of a 1:2.5 mixture of H_2O:THF, following the general procedure (**Method A**), amide **1f** (1.07 g, 54 % yield) was obtained as a white solid.

Data for **1f**: $\mathbf{R_f}$ 0.30 (30% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ –8.5 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 7.64 (1H, s, Imidazole), 6.83 (1H, s, Imidazole), 4.60 (1H, dd, *J* = 8.7 and 5.3 Hz, 2-H), 3.03 (1H, dd, *J* = 14.9 and 5.3 Hz, 3-H_a), 2.90 (1H, dd, *J* = 14.9 and 8.8 Hz, 3-H_b), 2.09 (2H, t, *J* = 6.9 Hz, 6-H_2), 1.44 (2H, quint, *J* = 6.9 Hz, 7-H_2), 1.08-1.26 (12H, m, 8-H_2 and 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2), 0.79 (3H, t, *J* = 6.7 Hz, 14-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 176.2 (C-1), 173.3 (C-5), 136.2 and 134.2 and 118.2 (3C, 3 x Imidazole), 53.8 and 52.7 (2C, C-2 and C-6), 36.7 and 33.0 and 30.6 and 30.47 and 30.43 and 30.1 and 26.8 and 23.7 (8C, C-3 and C-7 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13), 14.5 (C-14). **IR** (solid): ν_{max} 3316, 3072, 2907, 1744, 1629, 1514, 1443, 1371, 1178 cm^{-1}. **HRMS** (ESI): calculated for $C_{16}H_{28}N_3O_3$ $[M+H]^+$ requires *m*/*z* 310.2125, found *m*/*z* 310.2124.

2.8. Synthesis of (2S)-*N*-oleyl-2-amino-3-hydroxypropionic acid, 1g.

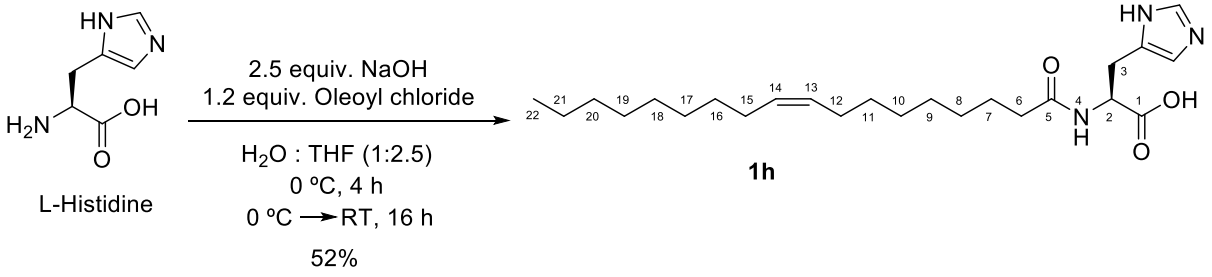


From L-serine (1.00 g, 9.44 mmol), oleoyl chloride 89% (3.86 mL, 10.4 mmol) and DIPEA (3.3 mL, 19.00 mmol) in 18.0 mL of a 1:2.5 mixture of H_2O:THF, following the general procedure (**Method A**), amide **1g** (2.09 g, 60 % yield) was obtained as a white solid.

Data for **1g**: $\mathbf{R_f}$ 0.40 (20% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ +8.1 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 5.30-5.42 (2H, m, 13-H and 14-H), 4.50 (1H, t, *J* = 4.5 Hz, 2-H), 3.90 (1H, dd, *J* = 11.2 and 4.9 Hz, 3-H_a), 3.81 (1H, dd, *J* = 11.2 and 4.8 Hz, 3-H_b), 2.28 (2H, t, *J* = 7.4

Hz, 6-H_2), 1.97-2.12 (4H, m, 12-H_2 and 15-H_2), 1.63 (2H, quint, J = 7.4 Hz, 7-H_2), 1.26-1.44 (20H, m, 8-H_2 and 9-H_2 and 10-H_2 and 11-H_2 and 16-H_2 and 17-H_2 and 18-H_2 and 19-H_2 and 20-H_2 and 21-H_2), 0.90 (3H, t, J = 6.5 Hz, 22-H_3).**^{13}C-NMR** (75 MHz, MeOD): δ 176.2 (C-1), 173.5 (C-5), 130.9 and 130.8 (2C, C-13 and C-14), 63.1 (C-3), 56.9 (C-2), 37.0 (C-6), 33.1 and 30.9 and 30.8 and 30.6 and 30.5 and 30.49 and 30.44 and 30.39 and 30.34 and 28.29 and 28.27 and 26.8 and 23.8 (13C, C-7 and C-8 and C-9 and C-10 and C-11 and C-12 and C-15 and C-16 and C-17 and C-18 and C-19 and C-20 and C-21, 14.7 (C-22). **IR** (solid): ν_{max} 3331, 2907, 1715, 1595, 1529, 1206 cm^{-1}. **HRMS** (ESI): calculated for $C_{21}H_{40}NO_4$ $[M+H]^+$ requires m/z 370.2957, found m/z 370.2960.

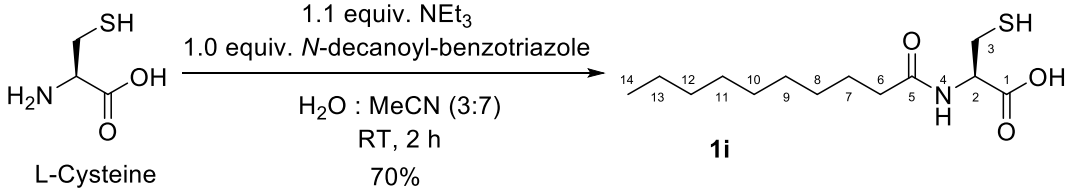
2.9. Synthesis of (2S)-*N*-oleyl-2-amino-3-(1H-imidazol-4-yl)propionic acid, 1h.



From L-histidine (1.00 g, 6.44 mmol), oleoyl chloride 89% (2.87 mL, 7.73 mmol) and NaOH (515 mg, 12.88 mmol) in 25.0 mL of a 1:2.5 mixture of H_2O:THF, following the general procedure (**Method A**), amide **1h** (1.41 g, 52 % yield) was obtained as a white solid.

Data for **1h**: **R_f** 0.40 (30% MeOH – DCM). **[α]$^{20}_D$** +4.9 (c = 1.0, MeOH). **^{1}H-NMR** (300 MHz, MeOD): δ 8.69 (1H, s, Imidazole), 7.29 (1H, s, Imidazole), 5.29-5.40 (2H, m, 13-H and 14-H), 4.58-4.68 (1H, m, 2-H), 3.24-3.30 (1H, m, 3-H_a), 3.04-3.16 (1H, m, 3-H_b), 2.21 (2H, t, J = 7.5 Hz, 6-H_2), 1.95-2.10 (4H, m, 12-H_2 and 15-H_2), 1.47-1.61 (2H, m, 7-H_2), 1.44-1.63 (20H, m, 8-H_2 and 9-H_2 and 10-H_2 and 11-H_2 and 16-H_2 and 17-H_2 and 18-H_2 and 19-H_2 and 20-H_2 and 21-H_2), 0.89 (3H, t, J = 6.5 Hz, 22-H_3). **^{13}C-NMR** (75 MHz, MeOD): δ 176.2 1 (C-1), 176. (C-5), 134.4 and 132.1 and 118.2 (3C, 3 x Imidazole), 130.88 and 130.83 (2C, C-13 and C-14), 68.2 (C-2), 54.3 (C-6), 37.0 and 33.1 and 30.93 and 30.90 and 30.6 and 30.49 and 30.46 and 30.40 and 30.38 and 30.34 and 28.25 and 28.21 and 26.9 and 23.7 (14C, C-3 and C-7 and C-8 and C-9 and C-10 and C-11 and C-12 and C-15 and C-16 and C-17 and C-18 and C-19 and C-20 and C-21), 14.6 (C-22). **IR** (solid): ν_{max} 3266, 2914, 1730, 1615, 1536 cm^{-1}. **HRMS** (ESI): calculated for $C_{24}H_{42}N_3O_3$ $[M+H]^+$ requires m/z 420.3226, found m/z 420.3230.

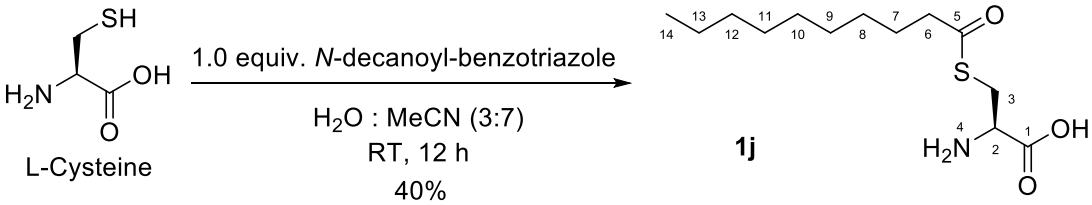
2.10. Synthesis of (2S)-*N*-decanoyl-2-amino-3-mercaptopropionic acid, 1i.



L-cysteine (183 mg, 1.5 mmol, 1.0 equiv), *N*-decanoyl-benzotriazole (413 mg, 1.5 mmol, 1.0 equiv) and triethylamine (0.230 mL, 1.6 mmol, 1.1 equiv) were dissolved in 6.0 mL of a 3:7 mixture of H_2O:MeCN. The reaction was stirred at RT and was monitored using TLC until completion (2 h). The volatile solvent (MeCN) were evaporated and the mixture was diluted with 2 volumes of EtOAc. The organic phase was washed with HCl 2N and brine, dried with anhydrous Na_2SO_4 and evaporated to yield amide **1i** as a yellowish oil. The crude reaction was purified by column chromatography on silica gel using 30% EtOAc – DCM to elute side products and 20% MeOH – CH_2Cl_2 to elute the desired product. Amide **1i** (290 mg, 70 % yield) was obtained as a yellow solid. [6]

Data for **1i**: $\mathbf{R_f}$ 0.10 (30% EtOAc – DCM). $\mathbf{[\alpha]^{20}_D}$ –11.4 (*c* =42.3, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 4.50-4.59 (1H, m, 2-H), 3.19-3.33 (1H, m, 3-H_a), 2.86 (1H, dd, *J* = 13.6 and 8.1 Hz, 3-H_b), 2.16 (2H, t, *J* = 7.3 Hz, 6-H_2), 1.47-1.57 (2H, m, 7-H_2), 1.12-1.30 (12H, m, 8-H_2 and 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2), 0.76-0.86 (3H, m, 14-H_3). **^{13}C-NMR** (75 MHz, CD_3OD – $CDCl_3$): δ 176.2 (C-1), 176.1 (C-5), 54.1 (C-2), 42.0 (C-6), 37.0 and 33.0 and 30.6 and 30.5 and 30.4 and 30.3 and (6C, C-3 and C-8 and C-9 and C-10 and C-11 and C-12) 26.9 (C-7), 23.7 (C-13), 14.52 (C-14). **IR** (solid): ν_{max} 3295, 1907, 1715, 1644, 1522, 1213 cm^{-1}. **HRMS** (ESI): calculated for $C_{26}H_{49}N_2O_6S_2$ $[2M\text{-}2H+H]^+$ requires *m/z* 549.3027, found *m/z* 549.3033.

2.11. Synthesis of (2S)-*S*-decanoyl-2-amino-3-mercaptopropionic acid, 1j.

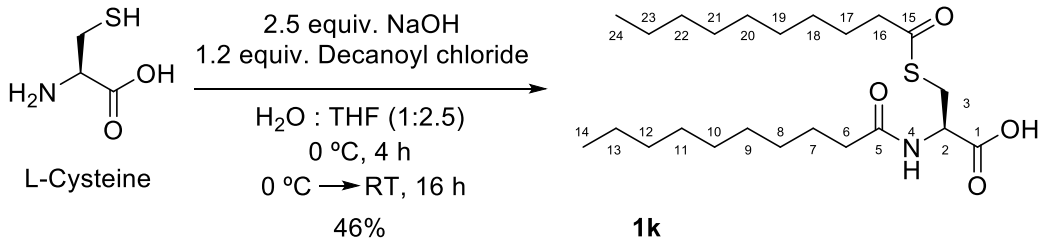


L-cysteine (230 mg, 1.9 mmol, 1.0 equiv) and *N*-decanoyl-benzotriazole (285 mg, 1.3 mmol, 1.0 equiv) in 10.0 mL of a 3:7 mixture of H_2O:MeCN. The reaction was stirred at RT and was monitored using TLC until completion (12 h). The heterogeneous mixture was filtered, and the white solid was then washed with 3 volumes of water, 3 volumes of EA and finally 3

volumes of diethyl ether. The resulting solid was vacuum dried, and amide **1j** (151 mg, 40 % yield) was obtained as a white solid.[6] Spectroscopic properties matched those previously reported.[7]

Data for **1j**: $\mathbf{R_f}$ 0.30 (5% TFA – DCM). $\mathbf{[\alpha]^{20}_D}$ –32.9 (*c* = 1.0, $CHCl_3$). **^{1}H-NMR** (300 MHz, 5% TFA - $CDCl_3$): δ 11.40 (1H, bs, COOH), 7.36-7.75 (2H, bs, NH_2), 4.45-4.54 (1H, m, 2-H), 3.52 (1H, dd, *J* = 15.4 and 3.7 Hz, 3-H_a), 3.35 (1H, dd, *J* = 15.4 and 6.8 Hz, 3-H_b), 2.56 (2H, t, *J* = 6.8 Hz, 6-H_2), 1.55 (2H, quint, *J* = 7.2 Hz, 7-H_2), 1.09-1.31 (12H, m, 8-H_2 and 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2), 0.78 (3H, t, *J* = 6.2 Hz, 14-H_3) . **^{13}C-NMR** (75 MHz, 5% TFA - $CDCl_3$): δ 204.5 (C-5), 169.9 (C-1), 54.3 (C-2), 43.8 (C-6), 31.7 and 29.2 and 29.13 and 29.00 and 28.78 and 28.6 (6C, C-3 and C-8 and C-9 and C-10 and C-11 and C-12), 25.2 (C-7), 22.5 (C-13) 13.9 (C-14). **IR** (solid): ν_{max} 3295, 1907, 1701, 1629, 1743, 1235 cm^{-1}. **HRMS** (ESI): calculated for $C_{13}H_{26}NO_3S$ $[M+H]^+$ requires *m/z* 276.1628, found *m/z* 276.1632.

2.12. Synthesis of (2S)-*N*-decanoyl-*S*-decanoyl-2-amino-3-mercaptopropionic acid, 1k.

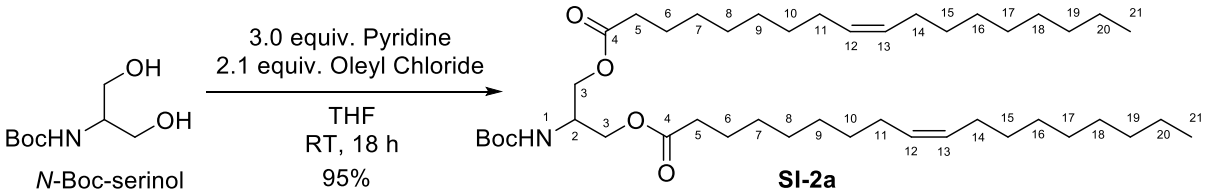


From L-cysteine (1.00 g, 8.25 mmol,), decanoyl chloride (3.80 mL, 18.16 mmol) and NaOH (660 mg, 16.5 mmol) in 20.0 mL of a 1:5 mixture of H_2O:THF, following the general procedure (**Method A**), amide **1k** (1.377 g, 46 % yield) was obtained as a yellow solid.

Data for **1k**: $\mathbf{R_f}$ 0.30 (10% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ –3.9 (*c* = 1.0, $CHCl_3$). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.10 (1H, d, *J* = 7.7 Hz, NH), 4.17-4.29 (1H, m, 2-H), 3.29-3.39 (1H, m, 3-H_a), 3.08 (1H, dd, *J* = 14.0 and 9.5 Hz, 3-H_b), 2.44 (2H, t, *J* = 7.8 Hz, 16-H_2), 2.09 (2H, t, *J* = 7.7 Hz, 6-H_2), 1.40-1.59 (4H, m, 7-H_2 and 17-H_2), 1.10-1.29 (24H, m, 8-H_2 and 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 18-H_2 and 19-H_2 and 20-H_2 and 21-H_2 and 22-H_2 and 23-H_2), 0.76-0,85 (6H, m, 14-H_3 and 24-H_3) . **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 201.0 (C-15), 176.3 (C-1), 174.5 (C-5), 54.8 (C-2), 44.1 (C-6), 36.6 (C-16), 32.0 and 31.9 and 31.1 and 29.8 and 29.7 and 29.63 and 29.60 and 29.5 and 29.4 and 29.3 and 29.2 and 22.7 and 22.6 (13C, C-3 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-18 and C-19 and C-20 and C-21 and C-22 and C-23), 25.9 and 25.7 (C-7 and C-17), 14.09 and 14.06 (C-14 and C-24). **IR**

(solid): ν_{max} 3345, 2907, 1723, 1680, 1594, 1536, 1192 cm^{-1}. **HRMS** (ESI): calculated for $C_{23}H_{44}NO_4S$ $[M+H]^+$ requires *m/z* 430.2986, found *m/z* 430.2988.

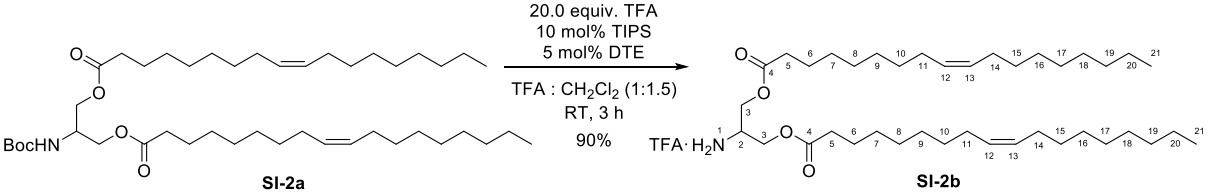
2.13. Synthesis of 2-((*tert*-butoxycarbonyl)amino)propane-1,3-diyl dioleate, SI-2a.



N-Boc-serinol (1.0 g, 5.23 mmol, 1.0 equiv) and pyridine (1.27 mL, 15.7 mmol, 3.0 equiv) were dissolved in 25.0 mL of anhydrous THF, and the solution was stirred at RT. Then, oleoyl chloride 89% (4.08 mL, 10.98 mmol, 2.1 equiv) was added dropwise, and the solution was stirred at RT for 18 h. The volatile solvent (THF) was evaporated, and the resulting crude was purified by column chromatography on silica gel (gradient elution: 2:98 → 8:92 Et_2O – cyclohexane). Diacylated **SI-2a** (3.58 g, 95% yield) was obtained as a yellow oil.

Data for **SI-2a**: $\mathbf{R_f}$ 0.40 (50% Et_2O – cyclohexane). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 5.24-5.41 (4H, m, 12-H and 13-H), 4.77 (1H, bs, NH), 4.00-4.25 (5H, m, 2-H and 3-H_2), 2.31 (4H, t, *J* = 7.5 Hz, 5-H_2), 1.92-2.10 (8H, m, 11-H_2 and 14-H_2), 1.56-1.69 (4H, m, 6-H_2), 1.45 (9H, s, 3 x CH_3 *t*Bu Boc), 1.19-1.39 (40H, m, 7-H_2 and 8-H_2 and 9-H_2 and 10-H_2 and 15-H_2 and 16-H_2 and 17-H_2 and 18-H_2 and 19-H_2 and 20-H_2), 0.87 (6H, t, *J* = 6.3 Hz, 21-H_3). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 173.4 (C-4), 155.0 (C=O Boc), 129.9 and 129.6 (2C, C-12 and C-13), 79.9 (3C, 3 x C *t*Bu Boc), 62.9 (C-3), 48.5 (C-2), 34.0 and 31.8 and 29.7 and 29.6 and 29.59 and 29.51 and 29.1 and 29.0 and 28.2 and 27.2 and 27.1 and 24.8 and 22.6 (13C, C-6 and C-7 and C-8 and C-9 and C-10 and C-11 and C-14 and C-15 and C-16 and C-17 and C-18 and C-19 and C-20), 29.3 (3C, 3 x CH_3 *t*Bu Boc), 14.0 (C-21). **HRMS** (ESI): calculated for $C_{44}H_{82}NO_6$ $[M+H]^+$ requires *m/z* 720.6137, found *m/z* 720.6136.

2.14. Synthesis of 1,3-bis(oleoyloxy)propan-2-amine SI-2b.

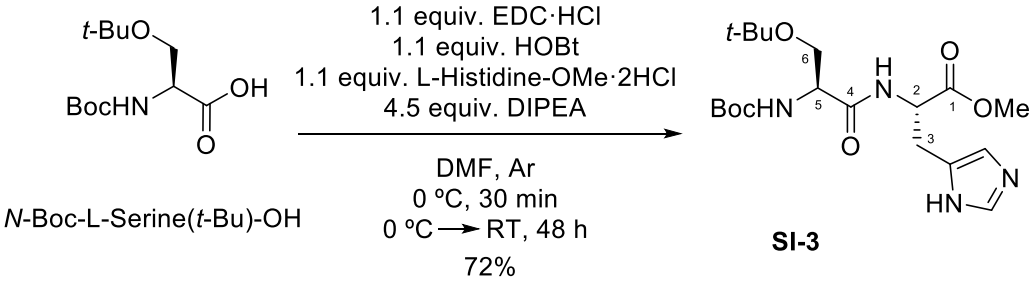


From carbamate **SI-2a** (3.0 g, 4.17 mmol), TFA (3.0 mL, 40.0 mmol), TIPS (90 µL, 0.42 mmol)

and DTE (42 mg, 0.20 mmol) in 5.0 mL of CH_2Cl_2, following the general procedure (**Method E**), amine **SI-2b** (2.75 g, 90 % yield) was obtained as a white foam.

Data for **SI-2b**: $\mathbf{R_f}$ 0.20 (10% MeOH – DCM). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 5.30-5.39 (4H, m, 12-H and 13-H), 4.22-4.43 (4H, m, 3-H_2), 3.71 (1H, bs, 2-H), 2.34 (4H, t, J = 7.6 Hz, 5-H_2), 1.89-2.06 (8H, m, 11-H_2 and 14-H_2), 1.49-1.66 (4H, m, 6-H_2), 1.15-1.39 (40H, m, 7-H_2 and 8-H_2 and 9-H_2 and 10-H_2 and 15-H_2 and 16-H_2 and 17-H_2 and 18-H_2 and 19-H_2 and 20-H_2), 0.77-0,92 (6H, m, 21-H_3). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 173.5 (2C, 2 x C-4), 129.98 and 129.95 (4C, 2 x C-12 and 2 x C-13), 60.8 (2C, 2 x C-3), 48.9 (C-2), 34.0 and 33.6 and 31.8 and 29.75 and 29.70 and 29.5 and 29.3 and 29.17 and 29.13 and 29.0 and 27.1 and 24.7 and 24.5 and 22.6 (28C, 2 x C-5 and 2 x C-6 and 2 x C-7 and 2 x C-8 and 2 x C-9 and 2 x C-10 and 2 x C-11 and 2 x C-14 and 2 x C-15 and 2 x C-16 and 2 x C-17 and 2 x C-18 and 2 x C-19 and 2 x C-20), 14.0 (2C, 2 x C-21). **HRMS** (ESI): calculated for $C_{39}H_{74}NO_4$ $[M+H]^+$ requires m/z 620.5612, found m/z 620.5608. Calculated for $C_{41}H_{75}F_3NO_6$ $[M+H+TFA]^+$ requires m/z 734.5541, found m/z 734.5543.

2.15. Synthesis of Methyl-*N*-(*tert*-butoxycarbonyl)-*O*-(*tert*-butyl)-L-seryl-L-histidinate, SI-3.



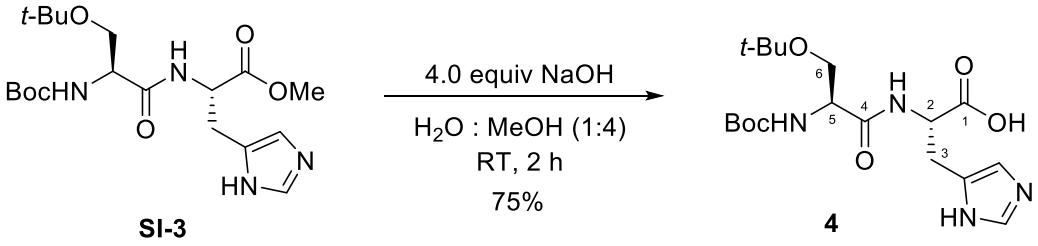
N-Boc-L-Serine(*t*-Bu)-OH

From *N*-Boc-L-Serine(*t*-Bu)-OH·HCl (2.0 g, 7.2 mmol), EDC·HCl (1.6 g, 8.4 mmol), HOBt·H_2O (1.2 g, 8.4 mmol) and DIPEA (6.0 mL, 34.0 mmol) in 25.0 mL of dry DMF, following the general procedure (**Method B**), dipeptide **SI-3** (2.5 g, 72 % yield) was obtained as a yellow foam.

Data for **SI-3**: $\mathbf{R_f}$ 0.40 (10% MeOH – DCM). **$[\alpha]^{20}_D$** +5.5 (c = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 7.58 (1H, s, Imidazole), 6.86 (1H, s, Imidazole), 4.71 (1H, t, J = 7.0 Hz, 2-H), 4.06-4.22 (1H, m, 5-H), 3.70 (3H, s, OMe), 3.50-3.63 (2H, m, 6-H_2), 2.99-3.17 (2H, m, 3-H_2), 1.45 (9H, s, 3 x CH_3 *t*Bu Boc), 1.16 (9H, s, 3 x CH_3 *t*-Bu). **^{13}C-NMR** (75 MHz, CD_3OD): δ 173.1 and 172.9 (C-1 and C-4), 157,7 (C=O Boc), 136.4 and 134.1 and 118.6 (3C, 3 x C-Imidazole), 80.9 and 56.4 (C *t*Bu Boc and C *t*Bu), 74.8 and 63.1 and 54.0 and 52.8 (C-2 and C-

5 and C-6 and OMe), 30.3 (C-3), 28.8 and 27.8 (6C, 3 x CH_3 *t*Bu Boc and 3 x CH_3 *t*Bu). **HRMS** (ESI): calculated for $C_{19}H_{33}N_4O_6$ $[M+H]^+$ requires *m*/*z* 413.2395, found *m*/*z* 413.2395.

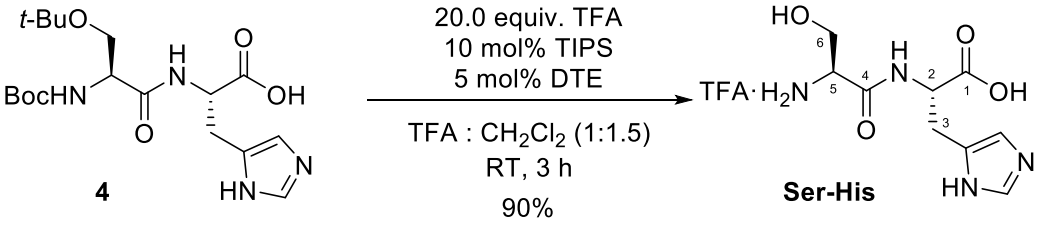
2.16. Synthesis of *N*-(*tert*-butoxycarbonyl)-*O*-(*tert*-butyl)-L-seryl-L-histidine, 4.



From amide **SI-3** (1.2 g, 2.9 mmol) and NaOH (470 mg, 11.8 mmol) in 10.0 mL of MeOH, following the general procedure (**Method D**), dipeptide **4** (900 mg, 75 % yield) was obtained as a white foam.

Data for **4**: $\mathbf{R_f}$ 0.20 (10% MeOH – DCM). **^{1}H-NMR** (300 MHz, CD_3OD): δ 8.54 (1H, s, Imidazole), 7.21 and 7.25 (1H, s, Imidazole, 2 tautomers), 4.43-4.50 (1H, m, 5-H), 4.10-4.17 (1H, m, 2-H), 3.60-3.68 (1H, m, 3-H_a), 3.53-3.58 (1H, m, 3-H_b), 3.25-3.30 (1H, m, 6-H_a), 3.08-3.20 (1H, m, 6-H_b), 1.45 (9H, s, 3 x CH_3 *t*Bu Boc), 1.17 (9H, s, 3 x CH_3 *t*-Bu). **^{13}C-NMR** (75 MHz, CD_3OD): δ 175.6 and 172.7 (2C, C-2 and C-4), 158.0 (C=O Boc), 134.7 and 132.0 and 118.6 (3C, 3 x C-Imidazole), 81.0 (3C, C *t*Bu Boc), 74.9 (C *t*Bu), 63.0 (C-6), 56.8 and 56.0 (2C, C-2 and C-5), 28.8 (C-3), 27.8 (3C, 3 x CH_3 *t*Bu Boc). **HRMS** (ESI): calculated for $C_{18}H_{31}N_4O_6$ $[M+H]^+$ requires *m*/*z* 399.2238, found *m*/*z* 399.2238.

2.17. Synthesis of L-seryl-L-histidine, Ser-His.

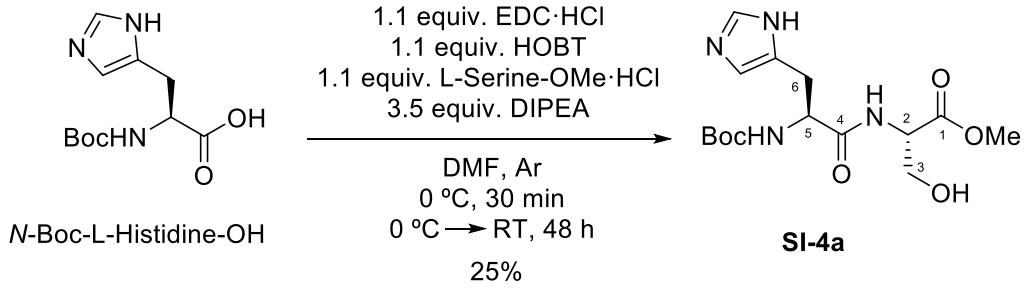


From amide **4** (397 mg, 1.0 mmol,), TFA (1.5 mL, 20.0 mmol), TIPS (20 µL, 0.1 mmol) and DTE (10 mg, 0.05 mmol) in 2.0 mL of CH_2Cl_2, following the general procedure (**Method E**), dipeptide **Ser-His** (217 mg, 90 % yield) was obtained as a white foam.

Data for **Ser-His**: $\mathbf{R_f}$ 0.10 (30% MeOH – DCM, with 1% AcOH). **$[\alpha]^{20}_D$** +3.6 (*c* = 1.0, $CHCl_3$). **^{1}H-NMR** (300 MHz, CD_3OD with TFA): δ 8.80 (1H, s, Imidazole), 7.38 (1H, s, Imidazole), 4.78-4.87 (1H, m, 2-H), 3.74-4.05 (3H, m, 5-H and 6-H_2), 3.35-3.44 (1H, m, 3-H_a),

3.15-3.27 (1H, m, 3-H_b). **^{13}C-NMR** (75 MHz, CD_3OD with TFA): δ 172.9 and 168.7 (2C, C-1 and C-4), 135.1 and 131.0 and 118.6 (3C, 3 x C-Imidazole), 61.6 (C-6), 56.2 (C-2), 53.2 (C-5), 27.8 (C-3). **HRMS** (ESI): calculated for $C_9H_{15}N_4O_4$ $[M+H]^+$ requires *m/z* 243.1088, found *m/z* 243.1090.

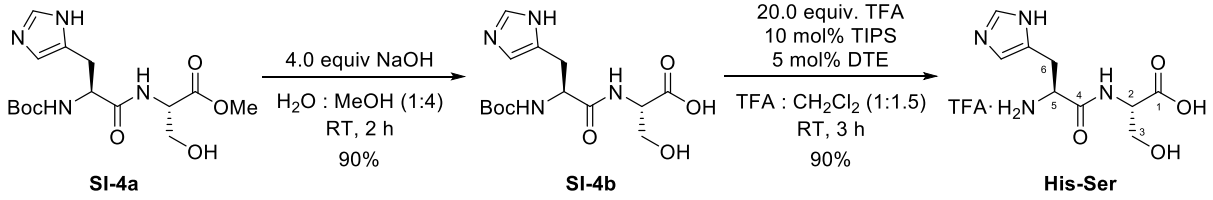
2.18. Synthesis of Methyl-(*tert*-butoxycarbonyl)-L-histidyl-L-serinate, SI-4a.



From *N*-Boc-L-His-OH·2HCl (1.0 g, 3.9 mmol), EDC·HCl (824 mg, 4.3 mmol), HOBt·H_2O (581 mg, 4.3 mmol), DIPEA (2.3 mL, 13.6 mmol) and L-Ser-OMe·HCl (669 mg, 4.3 mmol) in 30.0 mL of dry DMF, following the general procedure (**Method B**), dipeptide **SI-4a** (350 mg, 25 % yield) was obtained as a yellow foam.

Data for **SI-4a**: **R_f** 0.40 (10% MeOH – DCM). **$[\alpha]^{20}_D$** –2.9 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 7.90 (1H, s, Imidazole), 7.01 (1H, s, Imidazole), 4.55 (1H, t, *J* = 4.3 Hz, 5-H), 4.39 (1H, t, *J* = 4.4 Hz, 2-H), 3.92 (1H, dd, *J* = 11.6 and 4.5 Hz, 3-H_a), 3.80 (1H, dd, *J* = 11.6 and 4.4 Hz, 3-H_b), 3.73 (3H, s, OMe), 3.13 (1H, dd, *J* = 14.0 and 5.2 Hz, 6-H_a), 2.93 (1H, dd, *J* = 14.0 and 5.2 Hz, 6-H_b), 1.40 (9H, s, 3 x CH_3 *t*Bu Boc). **^{13}C-NMR** (75 MHz, CD_3OD): δ 174.0 and 172.1 (2C, C-1 and C-4), 157.7 (C=O Boc), 136.0 and 133.7 and 118.2 (3C, 3 x C-Imidazole), 81.0 (C *t*Bu Boc), 62.8 and 56.2 and 55.8 and 53.0 (4C, C-2 and C-3 and C-5 and OMe), 30.2 (C-6), 28.7 (3C, 3 x CH_3 *t*Bu Boc).

2.19. Synthesis of L-histidyl-L-serine, His-Ser.

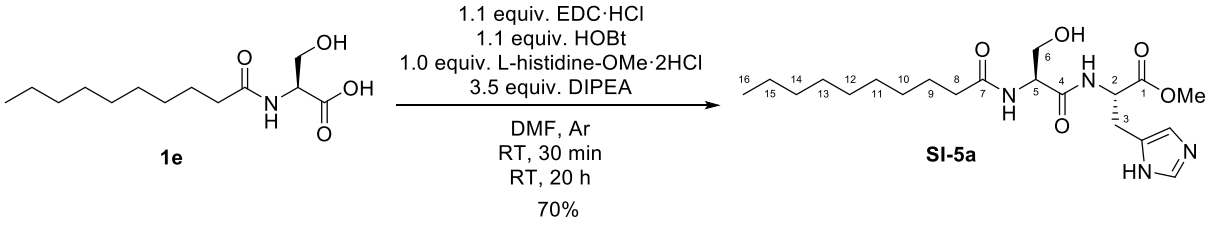


From amide **SI-4a** (350 mg, 1.0 mmol) and NaOH (160 mg, 4.0 mmol) in 4.0 mL of MeOH, following the general procedure (**Method D**), dipeptide **SI-4b** (302 mg, 90 % yield) was obtained as a white foam. This product was used without further purification.

From amide **SI-4b** (303 mg, 0.8 mmol), TFA (1.2 mL, 16.0 mmol), TIPS (16 μL, 0.08 mmol) and DTE (8 mg, 0.04 mmol) in 2.0 mL of CH_2Cl_2, following the general procedure (**Method E**), dipeptide **His-Ser** (192 mg, 90 % yield) was obtained as a yellowish foam.

Data for **His-Ser**: $\mathbf{R_f}$ 0.10 (30% MeOH – DCM, with 1% AcOH). $\mathbf{[\alpha]^{20}_D}$ –7.3 (*c* = 1.0, $CHCl_3$). **^{1}H-NMR** (300 MHz, CD_3OD): δ 8.54 (1H, s, Imidazole), 7.28 (1H, s, Imidazole), 4.38 (1H, q, *J* = 5.8 Hz, 5-H), 4.16 (1H, q, *J* = 4.5 Hz, 2-H), 3.72-3.84 (2H, m, 3-H_2), 3.17-3.27 (1H, m, 6-H_a), 3.01-3.13 (1H, m, 6-H_b). **^{13}C-NMR** (75 MHz, CD_3OD): δ 177.1 and 172.7 (C1 and C4), 133.3 and 129.8 and 117.0 (3C, 3 x C-Imidazole), 62.5 and 56.8 and 54.4 (C2 and C3 and C5), 28.1 (C6). **HRMS** (ESI): calculated for $C_9H_{15}N_4O_4$ $[M+H]^+$ requires *m*/*z* 243.1088, found *m*/*z* 243.1088.

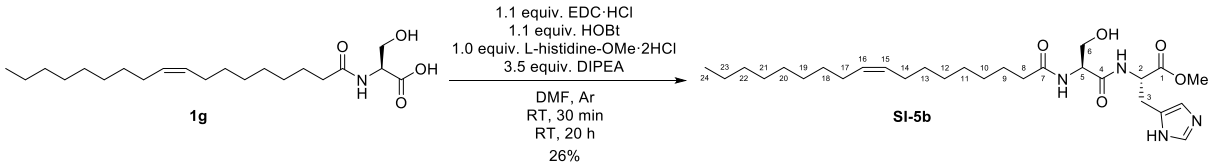
2.20. Synthesis of Methyl-decanoyl-L-seryl-L-histidinate, SI-5a.



From *N*-decanoyl-L-serine (230 mg, 0.8 mmol), EDC·HCl (187 mg, 0.9 mmol), HOBt·H_2O (131 mg, 0.9 mmol), L-histidine-OMe·2HCl (214 mg, 0.8 mmol) and DIPEA (0.5 mL, 2.8 mmol) in 15.0 mL of dry DMF, following the general procedure (**Method B**), lipopeptide **SI-5a** (252 mg, 70 % yield) was obtained as a white foam.

Data for **SI-5a**: $\mathbf{R_f}$ 0.20 (10% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ +3.6 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 7.57 (1H, s, Imidazole), 6.88 (1H, s, Imidazole), 4.65-4.71 (1H, m, 2-H), 4.21 (1H, q, *J* = 7.1 Hz, 5-H), 3.71-3.76 (2H, m, 6-H_2), 3.70 (3H, s, OMe), 3.01-3.17 (2H, m, 3-H_2), 2.27 (2H, t, *J* = 7.5 Hz, 8-H_2), 1.60 (2H, quint, *J* = 7.1 Hz, 9-H_2), 1.25-1.36 (12H, m, 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 14-H_2 and 15-H_2), 0.89 (3H, t, *J* = 6.8 Hz, 16-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 176.4 and 173.0 and 172.3 (3C, C-1 and C-4 and C-7), 136.4 and 134.2 and 118.3 (3C, 3 x C-Imidazole), 63.0 and 56.6 and 54.1 and 52.8 (4C, C-2 and C-5 and C-6 and OMe), 36.95 and 36.92 and 33.0 and 30.6 and 30.5 and 30.4 and 30.3 and 26.8 and 23.7 (9C, C-3 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-15), 14.4 (C-16).

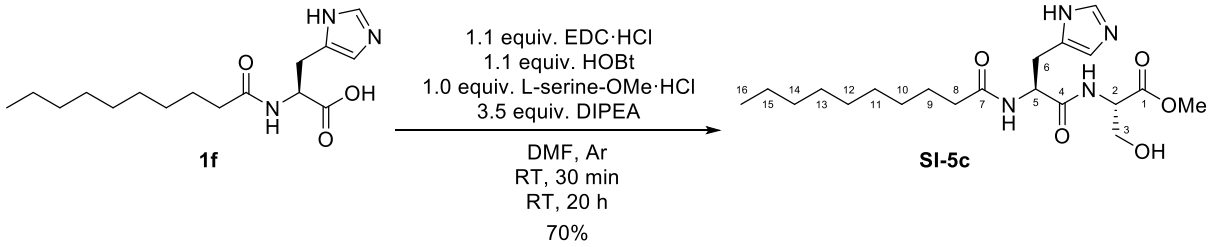
2.21. Synthesis of Methyl-oleoyl-L-seryl-L-histidinate, SI-5b.



From *N*-oleyl-L-serine (300 mg, 0.8 mmol), EDC·HCl (180 mg, 0.9 mmol), HOBt·H_2O (127 mg, 0.9 mmol), L-histidine-OMe·2HCl (206 mg, 0.8 mmol) and DIPEA (0.4 mL, 2.5 mmol) in 15.0 mL of dry DMF, following the general procedure (**Method B**), lipopeptide **SI-5b** (110 mg, 26 % yield) was obtained as a white foam.

Data for **SI-5b**: $\mathbf{R_f}$ 0.50 (10% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ –3.7 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 7.57 (1H, s, Imidazole), 6.87 (1H, s, Imidazole), 5.30-5.40 (2H, m, 15-H and 16-H), 4.68 (1H, t, *J* = 6.7 Hz, 2-H), 4.45 (1H, q, *J* = 5.9 Hz, 5-H), 3.64-3.86 (5H, m, 6-H_2 and OMe), 3.00-3.18 (2H, m, 3-H_2), 2.29 (2H, t, *J* = 7.7 Hz, 8-H_2), 1.97-2.09 (4H, m, 14-H_2 and 17-H_2), 1.56-1.68 (2H, m, 9-H_2), 1.24-1.44 (20H, m, 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 18-H_2 and 19-H_2 and 20-H_2 and 21-H_2 and 22-H_2 and 23-H_2), 0.86-0.95 (3H, m, 24-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 176.6 and 173.1 and 172.5 (3C, C-1 and C-4 and C-7), 136.5 and 134.4 and 118.5 (3C, 3 x C-Imidazole), 131.0 and 130.9 (2C, C-15 and C-16), 63.2 and 56.7 and 54.3 and 52.9 (4C, C-2 and C-5 and C-6 and OMe), 37.06 and 37.03 and 33.1 and 30.99 and 30.93 and 30.7 and 30.57 and 30.53 and 30.4 and 30.3 and 30.0 and 28.3 and 28.2 and 26.9 and 23.8 (15C, C-3 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-17 and C-18 and C-19 and C-20 and C-21 and C-22 and C-23), 14.5 (C-24).

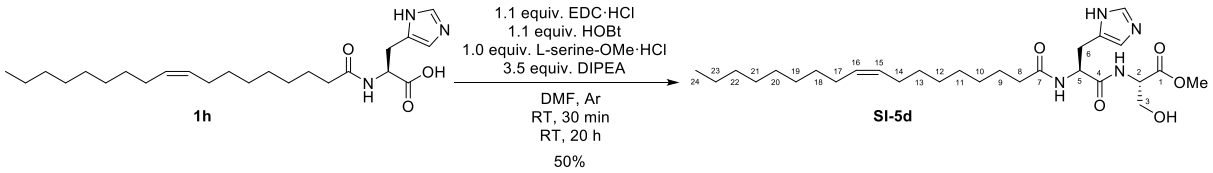
2.22. Synthesis of Methyl-decanoyl-L-histidyl-L-serinate, SI-5c.



From *N*-decanoyl-L-histidine (200 mg, 0.6 mmol), EDC·HCl (137 mg, 0.7 mmol), HOBt·H_2O (96 mg, 0.7 mmol), L-serine-OMe·HCl (101 mg, 0.6 mmol) and DIPEA (0.4 mL, 2.1 mmol) in 10.0 mL of dry DMF, following the general procedure (**Method B**), lipopeptide **SI-5c** (183 mg, 70 % yield) was obtained as a white foam.

Data for **SI-5c**: $\mathbf{R_f}$ 0.20 (10% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ +1.7 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ **^{1}H-NMR** (300 MHz, CD_3OD): δ 7.60 (1H, d, *J* = 3.9 Hz, Imidazole), 6.88 (1H, d, *J* = 3.9 Hz, Imidazole), 4.64-4.74 (1H, m, 5-H), 4.47-4.52 (1H, m, 2-H), 3.71-3.92 (5H, m, 3-H_2 and OMe), 3.06-3.15 (1H, m, 6-H_a), 2.88-2.98 (1H and 6-H_b), 2.15-2.24 (2H, m, 8-H_2), 1.48-1.58 (2H, m, 9-H_2), 1.22-1.35 (12H, m, 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 14-H_2 and 15-H_2), 0.86-0,93 (3H, m, 16-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 176.3 and 173.6 and 172.1 (3C, C-1 and C-4 and C-7), 136.4 and 134.5 and 118.7 (3C, 3 x C-Imidazole), 62.8 and 56.3 and 54.6 and 52.9 (4C, C-5 and C-2 and C-3 and OMe), 37.0 and 36.9 and 33.1 and 30.6 and 30.59 and 30.54 and 30.3 and 26.9 and 23.8 (9C, C-6 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-15), 14.4 (C-16).

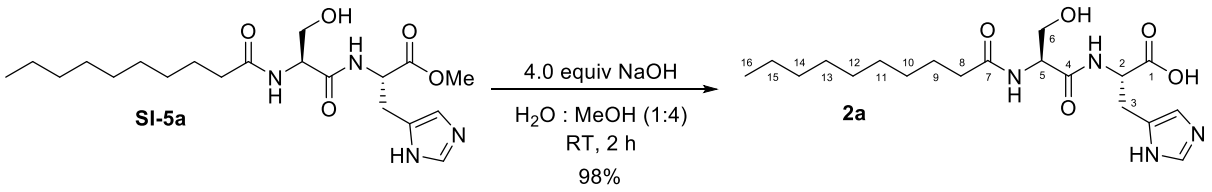
2.23. Synthesis of Methyl-oleoyl-L-histidyl-L-serinate, SI-5d.



From *N*-oleyl-L-histidine (155 mg, 0.4 mmol), EDC·HCl (80 mg, 0.4 mmol), HOBt·H_2O (55 mg, 0.4 mmol), L-serine-OMe·HCl (58 mg, 0.4 mmol) and DIPEA (0.3 mL, 1.4 mmol) in 10.0 mL of dry DMF, following the general procedure (**Method B**), lipopeptide **SI-5d** (97 mg, 50 % yield) was obtained as a white foam.

Data for **SI-5d**: $\mathbf{R_f}$ 0.50 (10% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ –5.3 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 7.59 (1H, s, Imidazole), 6.88 (1H, s, Imidazole), 5.34 (2H, t, *J* = 4.8 Hz, 15-H and 16-H), 4.64-4.73 (1H, m, 5-H), 4.51 (1H, t, *J* = 4.3 Hz, 2-H), 3.71-3.95 (5H, m, 3-H_2 and OMe), 3.06-3.16 (1H, m, 6-H_a), 2.88-2.98 (1H, m, 6-H_b), 2.16-2.25 (2H, m, 8-H_2), 1.98-2.08 (4H, m, 14-H_2 and 17-H_2), 1.50-1.60 (2H, m, 9-H_2), 1.22-1.40 (20H, m, 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 18-H_2 and 19-H_2 and 20-H_2 and 21-H_2 and 22-H_2 and 23-H_2), 0.85-0.94 (3H, m, 24-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 176.3 and 173.8 and 172.2 (3C, C-1 and C-4 and C-7), 136.4 and 134.9 and 118.4 (3C, 3 x C-Imidazole), 130.99 and 130.96 (2C, C-15 and C-16), 62.8 and 56.3 and 54.7 and 52.9 (4C, C-2 and C-5 and C-3 and OMe), 37.0 and 36.9 and 33.1 and 30.99 and 30.93 and 30.90 and 30.7 and 30.6 and 30.5 and 30.4 and 30.3 and 28.3 and 28.2 and 27.0 and 23.8 (15C, C-6 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-17 and C-18 and C-19 and C-20 and C-21 and C-22 and C-23), 14.6 (C-24).

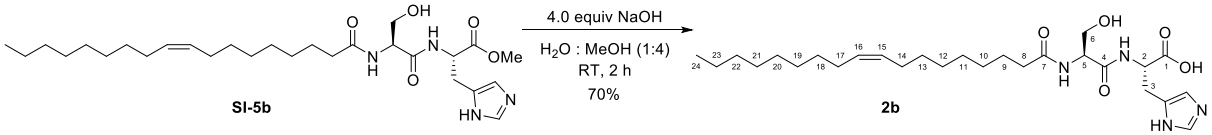
2.24. Synthesis of *N*-decanoyl-L-seryl-L-histidine, 2a.



From amide **SI-5a** (252 mg, 0.6 mmol) and NaOH (96 mg, 2.4 mmol) in 2.0 mL of MeOH, following the general procedure (**Method D**), lipopeptide **2a** (215 mg, 98 % yield) was obtained as a white foam.

Data for **2a**: $\mathbf{R_f}$ 0.20 (10% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ –10.5 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 8.81 (1H, s, Imidazole), 7.40 (1H, d, *J* = 7.9 Hz, Imidazole), 4.70-4.80 (1H, m, 2-H), 4.34-4.45 (1H, m, 5-H), 3.73-3.81 (2H, m, 6-H_2), 3.33-3.42 (1H, m, 3-H_a), 3.13-3.26 (1H, m, 3-H_b), 2.30 (2H, t, *J* = 7.3 Hz, 8-H_2), 1.56-1.67 (2H, m, 9-H_2), 1.25-1.39 (12H, m, 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 14-H_2 and 15-H_2), 0.90 (3H, t, *J* = 6.6 Hz, 16-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 176.7 and 172.8 and 172.0 (3C, C-1 and C-4 and C-7), 135.0 and 130.8 and 118.9 (3C, 3 x C-Imidazole), 63.0 and 57.1 and 53.0 (3C, C-2 and C-5 and C-6), 36.9 and 36.9 and 33.1 and 30.69 and 30.60 and 30.50 and 30.4 and 26.9 and 23.8 (9C, C-3 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-15), 14.5 (C-16). **IR** (solid): ν_{max} 3273, 2914, 1723, 1629, 1522, 1206 cm^{-1}. **HRMS** (ESI): calculated for $C_{19}H_{33}N_4O_5$ $[M+H]^+$ requires *m*/*z* 397.2445, found *m*/*z* 397.2453.

2.25. Synthesis of *N*-oleyl-L-seryl-L-histidine, 2b.

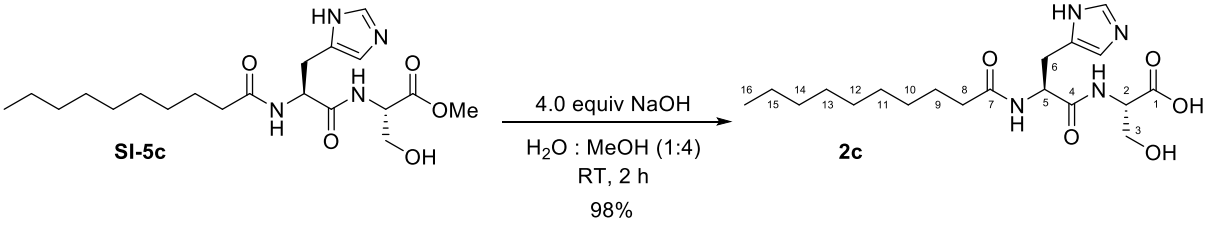


From amide **SI-5b** (110 mg, 0.2 mmol) and NaOH (32 mg, 0.8 mmol) in 1.5 mL of MeOH, following the general procedure (**Method D**), lipopeptide **2b** (74 mg, 70 % yield) was obtained as a white foam.

Data for **2b**: $\mathbf{R_f}$ 0.20 (10% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ –24.6 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 7.51 (1H, s, Imidazole), 6.82 (1H, s, Imidazole), 5.34 (2H, t, *J* = 5.0 Hz, 15-H and 16-H), 4.36-4.46 (2H, m, 2-H and 5-H), 3.66-3.86 (2H, m, 6-H_2), 3.13-2.23 (1H, m, 3-H_a), 2.98-3.07 (1H, m, 3-H_b), 2.28 (2H, t, *J* = 7.7 Hz, 8-H_2), 1.98-2.09 (4H, m, 14-H_2 and 17-H_2), 1.55-1.66 (2H, m, 9-H_2), 1.23-1.41 (20H, m, 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 18-H_2 and 19-H_2 and 20-H_2 and 21-H_2 and 22-H_2 and 23-H_2), 0.88-0.93 (3H, m, 24-H_3). **^{13}C-**

NMR (75 MHz, CD_3OD): δ 176.7 and 172.9 and 172.8 (3C, C-1 and C-4 and C-7), 135.50 and 131.0 and 118.8 (3C, 3 x C-Imidazole), 130.97 and 130.92 (2C, C-15 and C-16), 63.0 and 57.1 and 52.9 (3C, C-2 and C-5 and C-6), 36.98 and 36.95 and 33.1 and 30.97 and 30.94 and 30.8 and 30.7 and 30.5 and 30.4 and 30.3 and 30.2 and 28.28 and 28.24 and 26.9 and 23.8 (15C, C-3 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-17 and C-18 and C-19 and C-20 and C-21 and C-22 and C-23), 14.5 (C-24). **IR** (solid): ν_{max} 3231, 3007, 2914, 1737, 1629, 1522, 1221, 1070 cm^{-1}. **HRMS** (ESI): calculated for $C_{27}H_{47}N_4O_5$ $[M+H]^+$ requires *m/z* 507.3541, found *m/z* 507.3546.

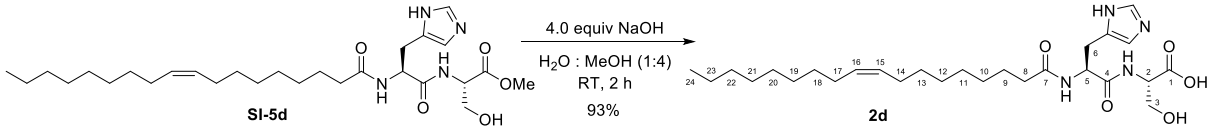
2.26. Synthesis of *N*-decanoyl-L-histidyl-L-serine, 2c.



From amide **SI-5c** (183 mg, 0.4 mmol) and NaOH (64 mg, 1.6 mmol) in 2.0 mL of MeOH, following the general procedure (**Method D**), lipopeptide **2c** (173 mg, 98 % yield) was obtained as a white foam.

Data for **2c**: $\mathbf{R_f}$ 0.20 (10% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ +6.2 (*c* = 1.0, $CHCl_3$). **^{1}H-NMR** (300 MHz, CD_3OD): δ 8.85 (1H, s, Imidazole), 7.41 (1H, s, Imidazole), 4.79-4.88 (1H, m, 5-H), 4.47-4.52 (1H, m, 2-H), 3.83-4.01 (2H, m, 3-H_2), 3.26-3.34 (1H, m, 6-H_a), 3.10-3.20 (1H, m, 6-H_b), 2.25 (2H, t, *J* = 7.5 Hz, 8-H_2), 1.48-1.60 (2H, m, 9-H_2), 1.20-1.35 (12H, m, 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 14-H_2 and 15-H_2), 0.83-0.94 (3H, m, 16-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 176.4 and 173.2 and 172.3 (C-1 and C-4 and C-7), 135.0 and 130.9 and 118.7 (3C, 3 x C-Imidazole), 62.7 and 56.3 and 53.4 (C-5 and C-2 and C-3), 36.99 and 36.92 and 33.0 and 30.6 and 30.5 and 30.4 and 30.3 and 26.9 and 23.8 (C-6 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-15), 14.5 (C-16). **IR** (solid): ν_{max} 3266, 2914, 1737, 1629, 1529, 1213 cm^{-1}. **HRMS** (ESI): calculated for $C_{19}H_{33}N_4O_5$ $[M+H]^+$ requires *m/z* 397.2445, found *m/z* 397.2449.

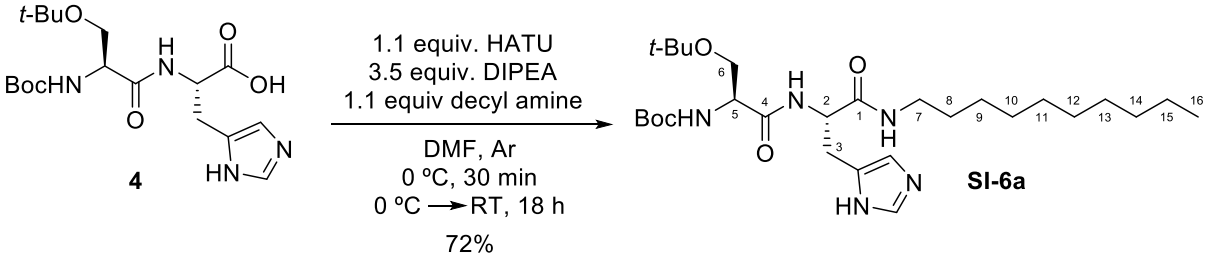
2.27. Synthesis of *N*-oleyl-L-histidyl-L-serine, 2d.



From amide **SI-5d** (97 mg, 0.2 mmol) and NaOH (30 mg, 0.8 mmol) in 1.5 mL of MeOH, following the general procedure (**Method D**), lipopeptide **2d** (90 mg, 93 % yield) was obtained as a white foam.

Data for **2d**: $\mathbf{R_f}$ 0.20 (10% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ –11.0 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 8.78 (1H, s, Imidazole), 7.37 (1H, s, Imidazole), 5.34 (2H, t, *J* = 4.8 Hz, 15-H and 16-H), 4.77-4.84 (1H, m, 5-H), 4.44-4.49 (1H, m, 2-H), 3.83-3.98 (2H, m, 3-H_2), 3.08-3.28 (2H, m, 6-H_2), 2.25 (2H, t, *J* = 6.9 Hz, 8-H_2), 1.98-2.08 (4H, m, 14-H_2 and 17-H_2), 1.52-1.63 (2H, m, 9-H_2), 1.24-1.40 (20H, m, 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 18-H_2 and 19-H_2 and 20-H_2 and 21-H_2 and 22-H_2 and 23-H_2), 0.90 (3H, t, *J* = 6.4 Hz, 24-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 176.4 and 174.1 and 172.3 (3C, C-1 and C-4 and C-7), 135.1 and 131.2 and 118.8 (3C, 3 x C-Imidazole), 130.96 and 130.91 (2C, C-15 and C-16), 62.9 and 56.7 and 53.5 (3C, C-2 and C-5 and C-3), 36.97 and 36.93 and 33.1 and 30.98 and 30.95 and 30.7 and 30.57 and 30.54 and 30.49 and 30.43 and 30.3 and 28.28 and 28.25 and 26.9 and 23.8 (15C, C-6 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-17 and C-18 and C-19 and C-20 and C-21 and C-22 and C-23), 14.6 (C-24). **IR** (solid): ν_{max} 3266, 3129, 2914, 1725, 1637, 1536, 1443 cm^{-1}. **HRMS** (ESI): calculated for $C_{27}H_{47}N_4O_5$ $[M+H]^+$ requires *m/z* 507.3541, found *m/z* 507.3539.

2.28. Synthesis of *tert*-butyl-((S)-3-(*tert*-butoxy)-1-(((S)-1-(decylamino)-3-(1H-imidazol-5-yl)-1-oxopropan-2-yl)amino)-1-oxopropan-2-yl)carbamate, SI-6a.

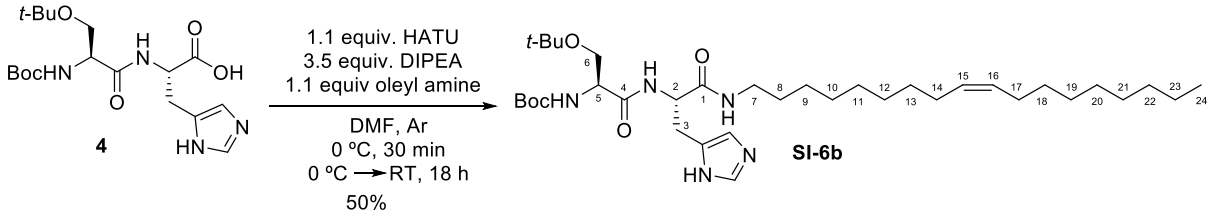


From amide **SI-3b** (150 mg, 0.4 mmol), HATU (157 mg, 0.4 mmol), DIPEA (0.3 mL, 1.3 mmol) and decyl amine (83 µL, 0.4 mmol), in 10.0 mL of dry DMF, following the general procedure (**Method C**), lipopeptide **SI-6a** (173 mg, 72 % yield) was obtained as a white foam.

Data for **SI-6a**: $\mathbf{R_f}$ 0.30 (10% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ –11.6 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 8.44 (1H, d, *J* = 4.8 Hz, Imidazole), 7.20 (1H, d, *J* = 4.7 Hz, Imidazole), 4.61-4.68 (1H, m, 2-H), 4.01-4.10 (1H, m, 5-H), 3.50-3.63 (2H, m, 6-H_2), 2.98-3.22 (4H, m, 3-H_2 and 7-H_2), 1.43-1.53 (11H, m, 8-H_2 and 3 x CH_3 *t*Bu Boc), 1.23-1.34 (14H, m, 9-H_2 and 10-

H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 14-H_2 and 15-H_2), 1.14 and 1.16 (9H, s, 3 x CH_3 *t*-Bu, 2 rotamers), 0.90 (3H, t, *J* = 6.4 Hz, 16-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 173.6 and 172.0 (2C, C-1 and C-4), 158.0 (C=O Boc), 135.4 and 132.3 and 118.3 (3C, 3 x C-Imidazole), 81.2 (C *t*Bu Boc), 75.0 and 62.8 and 57.2 and 54.0 (4C, C-2 and C-5 and C-6 and C *t*Bu), 40.7 (C-7), 33.1 and 30.8 and 30.7 and 30.52 and 30.50 and 30.46 and 30.41 and 28.0 and 23.8 (9C, C-3 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-15), 28.8 and 27.7 (6C, 3 x CH_3 *t*Bu Boc and 3 x CH_3 *t*Bu) 14.5 (C-16).

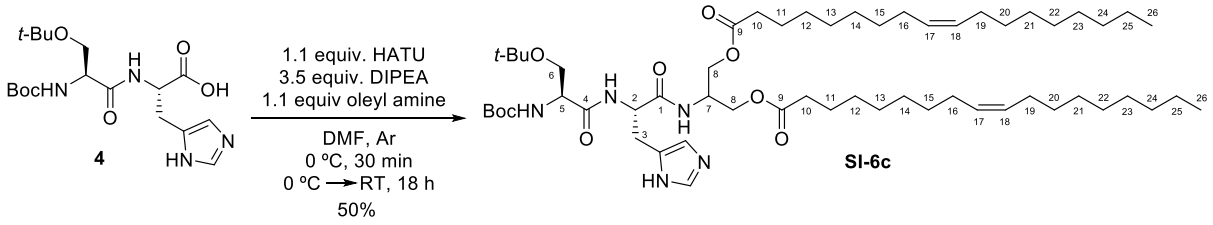
2.29. Synthesis of *tert*-butyl-((S)-1-(((S)-3-(1H-imidazol-5-yl)-1-(((Z)-octadec-9-en-1-yl)amino)-1-oxopropan-2-yl)amino)-3-(*tert*-butoxy)-1-oxopropan-2-yl)carbamate, SI-6b.



From amide **SI-3b** (150 mg, 0.4 mmol), HATU (157 mg, 0.4 mmol), DIPEA (0.3 mL, 1.3 mmol) and decyl amine (171 µL, 0.4 mmol) in 10.0 mL of dry DMF, following the general procedure (**Method C**), lipopeptide **SI-6b** (120 mg, 50 % yield) was obtained as a white foam.

Data for **SI-6b**: **R_f** 0.60 (10% MeOH – DCM). **$[\alpha]^{20}_D$** +8.8 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 7.68 (1H, s, Imidazole), 6.90 (1H, s, Imidazole), 5.30-5.40 (2H, m, 15-H and 16-H), 4.59 (1H, t, *J* = 6.1 Hz, 2-H), 4.05-4.10 (1H, m, 5-H), 3.49-3.65 (2H, m, 6-H_2), 3.02-3.18 (4H, m, 3-H_2 and 7-H_2), 1.94-2.07 (4H, m, 14-H_2 and 17-H_2), 1.39-1.50 (11H, m, 8-H_2 and 3 x CH_3 *t*Bu Boc), 1.23-1.38 (22H, m, 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 18-H_2 and 19-H_2 and 20-H_2 and 21-H_2 and 22-H_2 and 23-H_2), 1.15 (9H, d, *J* = 9.3 Hz, 3 x CH_3 *t*-Bu), 0.90 (3H, t, *J* = 6.5 Hz, 24-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 173.3 and 172.9 (2C, C-1 and C-4), 158.1 (C=O Boc), 136.3 and 131.6 and 118.3 (3C, 3 x C-Imidazole), 130.99 and 130.97 (2C, C-15 and C-16), 81.2 and 74.9 (2C, C *t*Bu Boc and C *t*-Bu), 62.9 and 57.2 and 54.9 (3C, C-2 and C-5 and C-6), 40.6 (C-7), 33.7 and 33.1 and 31.0 and 30.98 and 30.92 and 30.75 and 30.70 and 30.6 and 30.58 and 30.52 and 30.48 and 30.41 and 28.2 and 28.1 and 23.8 (15C, C-3 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-17 and C-18 and C-19 and C-20 and C-21 and C-22 and C-23), 28.8 and 27.8 (6C, 3 x CH_3 *t*Bu Boc and 3 x CH_3 *t*Bu) 14.6 (C-24).

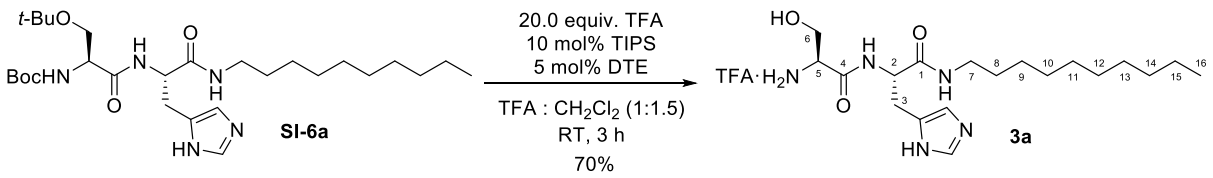
2.30. Synthesis of 2-((S)-2-((S)-3-(*tert*-butoxy)-2-((*tert*-butoxycarbonyl)amino) propanamido)-3-(1H-imidazol-5-yl)propanamido)propane-1,3-diyl dioleate, SI-6c.



From amide **SI-3b** (169 mg, 0.4 mmol), HATU (178 mg, 0.5 mmol), DIPEA (0.3 mL, 1.3 mmol) and decyl amine (300 mg, 0.5 mmol) in 15.0 mL of dry DMF, following the general procedure (**Method C**), lipopeptide **SI-6c** (190 mg, 50 % yield) was obtained as a yellowish oil.

Data for **SI-6c**: $\mathbf{R_f}$ 0.60 (5% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ –3.0 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 7.56 (1H, s, Imidazole), 6.87 (1H, s, Imidazole), 5.34 (4H, t, *J* = 4.9 Hz, 17-H and 18-H), 4.62 (1H, t, *J* = 6.8 Hz, 2-H), 4.26-4.36 (1H, m, 5-H), 4.04-4.14 (5H, m, 7-H and 8-H_2), 3.47-3.62 (2H, m, 6-H_2), 2.95-3.11 (2H, m, 3-H_2), 2.28-2.35 (4H, m, 10-H_2), 1.98-2.08 (8H, m, 16-H_2 and 19-H_2), 1.59 (4H, q, *J* = 7.3 Hz, 11-H_2), 1.45 (9H, s, 3 x CH_3 *t*Bu Boc), 1.25-1.39 (40H, m, 12-H_2 and 13-H_2 and 14-H_2 and 15-H_2 and 20-H_2 and 21-H_2 and 22-H_2 and 23-H_2 and 24-H_2 and 25-H_2), 1.15 (9H, d, *J* = 8.4 Hz, *t*-Bu), 0.90 (6H, t, *J* = 6.8 Hz, 26-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 175.0 and 171.9 and 168.9 (4C, C-1 and C-2 and 2 x C-9), 163.7 (C=O Boc), 135.6 and 131.6 and 118.7 (3C, 3 x C-Imidazole), 131.0 and 130.8 (4C, 2 x C-17 and 2 x C-18), 81.4 (C *t*Bu Boc), 63.5 (2C, 2 x C-8), 61.8 and 56.0 and 54.0 (3C, C-2 and C-5 and C-6), 52.1 (C-7), 34.97 and 34.95 and 33.1 and 30.98 and 30.91 and 30.74 and 30.72 and 30.5 and 30.48 and 30.46 and 30.34 and 30.32 and 28.5 and 26.0 and 23.8 (29C, C-3 and 2 x C-10 and 2 x C-11 and 2 x C-12 and 2 x C-13 and 2 x C-14 and 2 x C15 and 2 x C-16 and 2 x C-19 and 2 x C20 and 2 x C-21 and 2 x C-22 and 2 x C-23 and 2 x C-24 and 2 x C-25), 30.95 and 28.8 (6C, 3 x CH_3 *t*Bu Boc and 3 x CH_3 *t*Bu), 14.6 (2C, 2 x C-26).

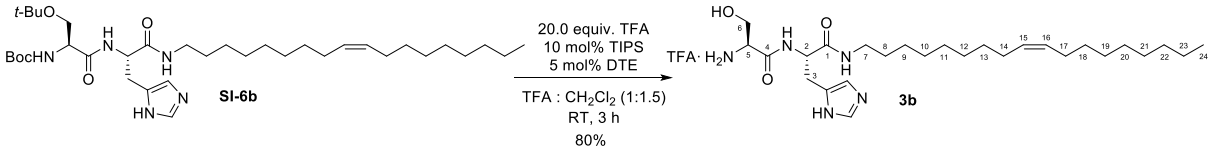
2.31. Synthesis of (S)-2-amino-N-((S)-1-(decylamino)-3-(1H-imidazol-5-yl)-1-oxopropan-2-yl)-3-hydroxypropanamide, 3a.



From amide **SI-6a** (120 mg, 0.1 mmol), TFA (0.2 mL, 2.4 mmol), TIPS (10 µL, 0.01 mmol) and DTE (5 mg, 0.01 mmol) in 0.4 mL of CH_2Cl_2, following the general procedure (**Method E**), dipeptide **3a** (35 mg, 70 % yield) was obtained as a white foam.

Data for **3a**: $\mathbf{R_f}$ 0.30 (10% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ –30.1 (*c* = 1.0, MeOH). **1H-NMR** (300 MHz, CD_3OD): δ 8.79 (1H, s, Imidazole), 7.34 (1H, s, Imidazole), 4.67-4.77 (1H, m, 2-H), 3.75-4.50 (3H, m, 5-H and 6-H_2), 3.26-3.34 (1H, m, 3-H_a), 3.03-3.21 (3H, m, 3-H_b and 7-H_2), 1.43-1.53 (2H, m, 8-H_2), 1.24-1.36 (14H, m, 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 14-H_2 and 15-H_2), 0.89 (3H, t, *J* = 6.5 Hz, 16-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 171.5 and 168.7 (2C, C-1 and C-4), 135.1 and 131.1 and 118.6 (3C, 3 x C-Imidazole), 61.7 and 57.2 and 54.0 (3C, C-2 and C-5 and C-6), 40.8 (C-7), 33.1 and 30.83 and 30.80 and 30.5 and 30.4 and 30.3 and 28.4 and 28.1 and 23.8 (9C, C-3 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-15) 14.5 (C-16).). **IR** (solid): ν_{max} 3266, 3104, 2921, 1658, 1551,1443, 1184 cm^{-1}. **HRMS** (ESI): calculated for $C_{19}H_{36}N_5O_3$ $[M+H]^+$ requires *m*/*z* 382.2813, found *m*/*z* 382.2812.

2.32. Synthesis of (S)-N-((S)-3-(1H-imidazol-5-yl)-1-(((Z)-octadec-9-en-1-yl)amino)-1-oxopropan-2-yl)-2-amino-3-hydroxypropanamide, 3b.

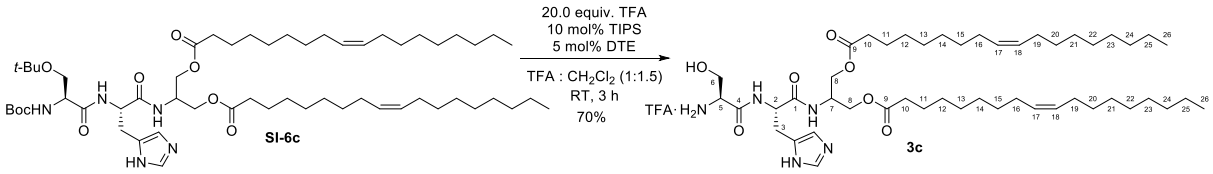


From amide **SI-6b** (120 mg, 0.2 mmol), TFA (0.3 mL, 4.0 mmol), TIPS (10 µL, 0.01 mmol) and DTE (5 mg, 0.01 mmol) in 0.6 mL of CH_2Cl_2, following the general procedure (**Method E**), dipeptide **3b** (74 mg, 80 % yield) was obtained as a white foam.

Data for **3b**: $\mathbf{R_f}$ 0.60 (10% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ –6.2 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 8.63 (1H, s, Imidazole), 7.29 (1H, s, Imidazole), 5.23-5.39 (2H, m, 15-H and 16-H), 4.66-4.77 (1H, m, 2-H), 3.65-4.07 (3H, m, 5-H and 6-H_2), 2.99-3.30 (4H, m, 3-H_2 and 7-H_2), 1.90-2.07 (4H, m, 14-H_2 and 17-H_2), 1.41-1.54 (2H, m, 8-H_2), 1.13-1.39 (22H, m, 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 18-H_2 and 19-H_2 and 20-H_2 and 21-H_2 and 22-H_2 and 23-H_2), 0.82-0.92 (3H, m, 24-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 171.7 and 168.7 (2C, C-1 and C-4), 135.6 and 131.6 and 118.7 (3C, 3 x C-Imidazole), 130.98 and 130.94 (2C, C-15 and C-16), 61.7 and 56.1 and 54.2 (3C, C-2 and C-5 and C-6), 40.8 (C-7), 33.7 and 33.1 and 30.98 and 30.95 and 30.89 and 30.80 and 30.7 and 30.5 and 30.48 and 30.44 and 30.35 and

30.31 and 28.2 and 28.1 and 23.8 (15C, C-3 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-17 and C-18 and C-19 and C-20 and C-21 and C-22 and C-23) 14.5 (C-24). **IR** (solid): ν_{max} 3273, 3079, 2914, 1651, 1551, 1436, 1141 cm^{-1}. **HRMS** (ESI): calculated for $C_{27}H_{50}N_5O_3$ $[M+H]^+$ requires *m/z* 492.3908, found *m/z* 492.3904.

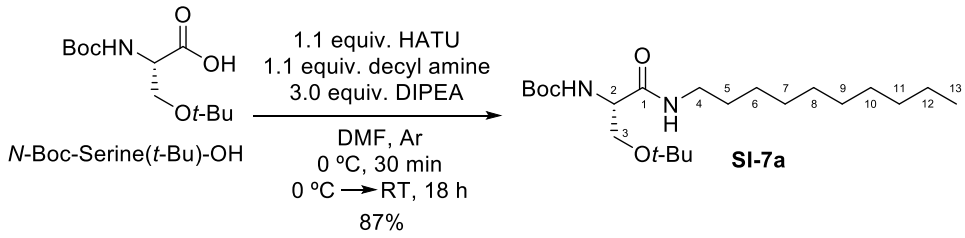
2.33. Synthesis of 2-((S)-2-((S)-2-amino-3-hydroxypropanamido)-3-(1H-imidazol-5-yl)propanamido)propane-1,3-diyl dioleate, 3c.



From amide **SI-6c** (190 mg, 0.2 mmol), TFA (0.4 mL, 4.2 mmol), TIPS (20 µL, 0.02 mmol) and DTE (8 mg, 0.01 mmol) in 0.8 mL of CH_2Cl_2, following the general procedure (**Method E**), dipeptide **3c** (110 mg, 70 % yield) was obtained as a white foam.

Data for **3c**: $\mathbf{R_f}$ 0.60 (5% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ – 4.2 (*c* = 1.0, $CHCl_3$). **^{1}H-NMR** (300 MHz, CD_3OD): δ 8.73 (1H, s, Imidazole), 7.35 (1H, s, Imidazole), 5.28-5.40 (2H, m, 17-H and 18-H), 4.75-4.82 (1H, m, 2-H), 4.35 (1H, t, *J* = 5.6 Hz, 5-H), 4.08-4.21 (4H, m, 8-H_2), 3.74-3.96 (2H, m, 6-H_2), 3.58-3.66 (1H, m, 7-H), 3.30-3.37 (1H, m, 3-H_a), 3.04-3.17 (1H, m, 3-H_b), 2.27-2.44 (4H, m, 10-H_2), 1.94-2.12 (8H, m, 16-H_2 and 19-H_2), 1.54-1.71 (4H, m, 11-H_2), 1.23-1.46 (40H, m, 12-H_2 and 13-H_2 and 14-H_2 and 15-H_2 and 20-H_2 and 21-H_2 and 22-H_2 and 23-H_2 and 24-H_2 and 25-H_2), 0.81-0.97 (6H, m, 26-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 175.05 and 175.00 and 171.8 (4C, C-1 and C-2 and 2 x C-9), 135.4 and 131.5 and 118.8 (3C, 3 x C-Imidazole), 130.9 and 130.8 (4C, 2 x C-17 and 2 x C-18), 63.5 (2C, 2 x C-8), 61.8 and 56.0 and 54.0 (3C, C-2 and C-5 and C-6), 52.1 (C-7), 34.9 and 33.1 and 30.96 and 30.93 and 30.7 and 30.57 and 30.54 and 30.47 and 30.44 and 30.33 and 30.30 and 28.27 and 28.25 and 26.0 and 23.8 (29C, C-3 and 2 x C-10 and 2 x C-11 and 2 x C-12 and 2 x C-13 and 2 x C-14 and 2 x C15 and 2 x C-16 and 2 x C-19 and 2 x C20 and 2 x C-21 and 2 x C-22 and 2 x C-23 and 2 x C-24 and 2 x C-25), 14.6 (2C, 2 x C-26). **IR** (solid): ν_{max} 3259, 3137, 2914, 1665, 1543, 1436, 1184 cm^{-1}. **HRMS** (ESI): calculated for $C_{48}H_{86}N_5O_7$ $[M+H]^+$ requires *m/z* 844.6522, found *m/z* 844.6520. Calculated for $C_{50}H_{87}F_3N_5O_9$ $[M+H+TFA]^+$ requires *m/z* 958.6450, found *m/z* 958.6451.

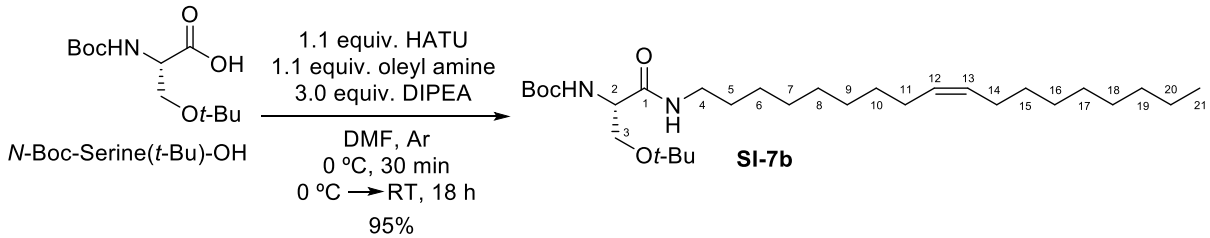
2.34. Synthesis of *tert*-butyl (S)-(3-(*tert*-butoxy)-1-(decylamino)-1-oxopropan-2-yl)carbamate, SI-7a.



From *N*-Boc-Ser(*t*-Bu)OH (750 mg, 2.8 mmol), HATU (1.2 g, 3.1 mmol), DIPEA (1.5 mL, 8.6 mmol) and decyl amine (630 µL, 3.1 mmol) in 25.0 mL of dry DMF, following the general procedure (**Method C**), lipopeptide **SI-7a** (1.0 g, 87 % yield) was obtained as a white foam.

Data for **SI-7a**: $\mathbf{R_f}$ 0.50 (20% EtOAc – DCM). $\mathbf{[\alpha]^{20}_D}$ +38.2 (*c* = 1.0, $CHCl_3$). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 6.53 (1H, bs, NH), 5.40 (1H, bs, NH), 4.01-4.09 (1H, m, 2-H), 3.72 (1H, dd, *J* = 8.6 and 3.9 Hz, 3-H_a), 3.32 (1H, t, *J* = 8.1 Hz, 3-H_b), 3.21 (2H, q, *J* = 6.6 Hz, 4-H_2), 1.38-1.48 (11H, m, 5-H_2 and 3 x CH_3 *t*Bu Boc), 1.19-1.28 (14H, m, 6-H_2 and 7-H_2 and 8-H_2 and 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2), 1.23 (9H, s, 3 x CH_3 *t*-Bu), 0.83 (3H, t, *J* = 6.6 Hz, 13-H_3). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 170.3 (C-1), 155.4 (C=O Boc), 79.7 (C *t*Bu Boc), 73.7 and 65.7 and 61.8 (C-2 and C-3 and C *t*-Bu), 39.3 (C-4), 31.7 and 29.4 and 29.3 and 29.2 and 29.1 and 26.7 and 22.5 and 15.1 (8C, C-5 and C-6 and C-7 and C-8 and C-9 and C-10 and C-11 and C-12), 28.2 and 27.3 (6C, 3 x CH_3 *t*Bu Boc and 3 x CH_3 *t*Bu) 13.9 (C-13). **HRMS** (ESI): calculated for $C_{22}H_{45}N_2O_4$ $[M+H]^+$ requires *m*/*z* 401.3374, found *m*/*z* 401.3375.

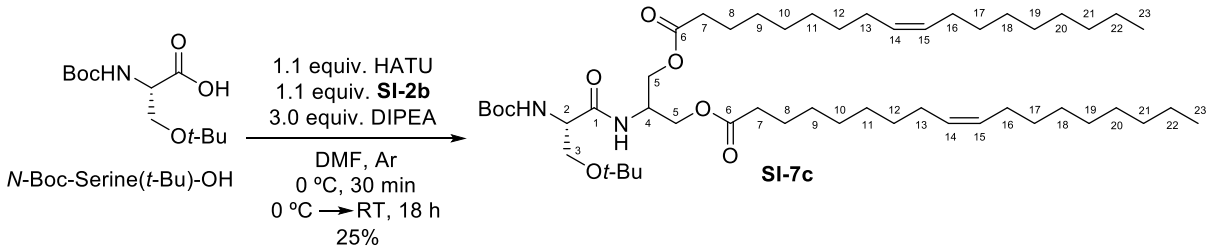
2.35. Synthesis of *tert*-butyl (S,Z)-(3-(*tert*-butoxy)-1-(octadec-9-en-1-ylamino)-1-oxopropan-2-yl)carbamate, SI-7b.



From *N*-Boc-Ser(*t*-Bu)OH (750 mg, 2.8 mmol), HATU (1.2 g, 3.1 mmol), DIPEA (1.5 mL, 8.6 mmol) and oleyl amine (1.3 mL, 3.1 mmol) in 25.0 mL of dry DMF, following the general procedure (**Method C**), lipopeptide **SI-7b** (1.39 g, 95 % yield) was obtained as a white foam.

Data for **SI-7b**: **R_f** 0.50 (30% EtOAc – DCM). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 6.53 (1H, bs, NH), 5.27-5.53 (3H, m, 12-H and 13-H and NH), 4.05-4.14 (1H, m, 2-H), 3.76 (1H, dd, *J* = 8.7 and 3.8 Hz, 3-H_a), 3.34 (1H, t, *J* = 8.0 Hz, 3-H_b), 3.25 (2H, q, *J* = 6.6 Hz, 4-H_2), 1.91-2.07 (4H, m, 11-H_2 and 14-H_2), 1.40-1.53 (11H, m, 5-H_2 and 3 x CH_3 *t*Bu Boc), 1.21-1.36 (14H, m, 6-H_2 and 7-H_2 and 8-H_2 and 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2), 1.17 (9H, s, 3 x CH_3 *t*-Bu), 0.87 (3H, t, *J* = 6.6 Hz, 13-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 170.4 (C-1), 155.4 (C=O Boc), 129.9 and 129.7 (2C, C-12 and C-13), 79.8 (C *t*Bu Boc), 73.8 and 65.8 and 61.9 (3C, C-2 and C-3 and C *t*-Bu), 39.4 (C-4), 31.8 and 29.73 and 29.71 and 29.65 and 29.61 and 29.52 and 29.48 and 29.42 and 29.28 and 29.24 and 29.22 and 27.1 and 26.8 and 22.6 (14C, C-5 and C-6 and C-7 and C-8 and C-9 and C-10 and C-11 and C-14 and C-15 and C-16 and C-17 and C-18 and C-19 and C-20), 28.3 and 27.4 (6C, 3 x CH_3 *t*Bu Boc and 3 x CH_3 *t*Bu), 14.0 (C-21). **HRMS** (ESI): calculated for $C_{30}H_{59}N_2O_4$ $[M+H]^+$ requires *m/z* 511.4469, found *m/z* 511.4466.

2.36. Synthesis of 2-((S)-3-(tert-butoxy)-2-((tert-butoxycarbonyl)amino)propanamido) propane-1,3-diyl dioleate, SI-7c.

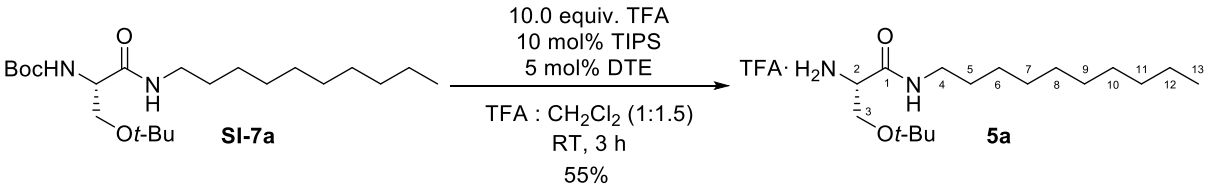


From *N*-Boc-Ser(*t*-Bu) (186 mg, 0.7 mmol), HATU (326 mg, 0.9 mmol), DIPEA (380 µL, 2.1 mmol) and amine **SI-2b** (500 mL, 0.8 mmol), in 15.0 mL of dry DMF, following the general procedure (**Method C**), lipopeptide **SI-7c** (160 mg, 25 % yield) was obtained as a white foam.

Data for **SI-7c**: **R_f** 0.30 (50% Et_2O – Cyclohexane). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 6.92 (1H, bs, NH), 5.24-5.40 (4H, m, 2 x 14-H and 2 x 15-H), 4.37-4.49 (1H, m, 2-H), 4.00-4.21 (5H, m, 4-H and 2 x 5-H_2), 3.75 (1H, dd, *J* = 8.7 and 4.0 Hz, 3-H_a), 3.34 (1H, t, *J* = 8.1 Hz, 3-H_b), 2.28 (4H, t, *J* = 7.6 Hz, 2 x 7-H_2), 1.91-2.04 (8H, m, 2 x 13-H_2 and 2 x 16-H_2), 1.58 (4H, quint, *J* = 7.5 Hz, 2 x 8-H_2), 1.43 (9H, s, 3 x CH_3 *t*Bu Boc), 1.19-1.35 (40H, m, 2 x 9-H_2 and 2 x 10-H_2 and 2 x 11-H_2 and 2 x 12-H_2 and 2 x 17-H_2 and 2 x 18-H_2 and 2 x 19-H_2 and 2 x 20-H_2 and 2 x 21-H_2 and 2 x 22-H_2), 1.16 (9H, s, 3 x CH_3 *t*Bu), 0.85 (6H, t, *J* = 6.5 Hz, 2 x 23-H_3). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 173.2 and 170.5 (3C, C-1 and 2 x C-6), 155.3 (C=O Boc),

129.8 and 129.5 (4C, 2x C-14 and 2 x C-15), 79.9 (C *t*Bu Boc), 73.9 and 62.3 and 61.7 (4C, C-2 and C-3 and 2 x C-5), 47.1 (C-4), 33.9 and 31.8 and 29.67 and 29.61 and 29.5 and 29.4 and 29.2 and 29.08 and 29.02 and 27.1 and 27.0 and 24.73 and 24.71 and 22.5 (28C, 2 x C-7 and 2 x C-8 and 2 x C-9 and 2 x C-10 and 2 x C-11 and 2 x C-12 and 2 x C-13 and 2 x C-16 and 2 x C-17 and 2 x C-18 and 2 x C-19 and 2 x C-20 and 2 x C-21 and 2 x C-22), 28.2 and 27.3 (6C, 3 x CH_3 *t*Bu Boc and 3 x CH_3 *t*Bu), 14.0 (2 x C-23). **HRMS** (ESI): calculated for $C_{51}H_{95}N_2O_8$ $[M+H]^+$ requires *m*/*z* 863.7083, found *m*/*z* 863.7081.

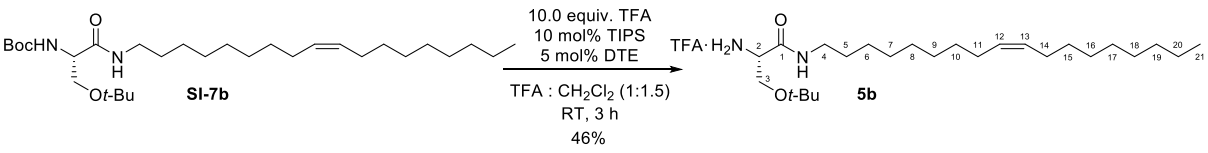
2.37. Synthesis of (S)-2-amino-3-(tert-butoxy)-N-decylpropanamide, 5a.



From amide **SI-7a** (1.0 g, 2.5 mmol), TFA (2.0 mL, 25.0 mmol), TIPS (40 µL, 0.2 mmol) and DTE (20 mg, 0.1 mmol) in 2.5 mL of CH_2Cl_2, following the general procedure (**Method E**), dipeptide **5a** (416 mg, 55 % yield) was obtained as a white foam.

Data for **5a**: $\mathbf{R_f}$ 0.20 (5% MeOH – DCM). **^{1}H-NMR** (300 MHz, CD_3OD): δ 3.63-3.96 (3H, m, 2-H and 3-H_2), 3.14-3.23 (2H, m, 4-H_2), 1.49 (2H, quint, *J* = 7.0 Hz, 5-H_2), 1.21-1.35 (14H, m, 6-H_2 and 7-H_2 and 8-H_2 and 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2), 1.18 (9H, s, 3 x CH_3 *t*-Bu), 0.85 (3H, t, *J* = 6.4 Hz, 13-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 168.2 (C-1), 75.3 and 61.8 (C-2 and C-3), 40.8 (C-4), 33.1 and 30.7 and 30.6 and 30.5 and 30.4 and 30.3 and 28.0 and 23.7 (8C, C-5 and C-6 and C-7 and C-8 and C-9 and C-10 and C-11 and C-12) 27.6 (3C, 3 x CH_3-*t*-Bu) 14.5 (C-13). **HRMS** (ESI): calculated for $C_{23}H_{44}N_5O_3$ $[M+H]^+$ requires *m*/*z* 438.3444, found *m*/*z* 438.3440. Calculated for $C_{19}H_{36}N_5O_3$ $[M-t\text{Bu}+H]^+$ requires *m*/*z* 382.2813, found *m*/*z* 382.2812.

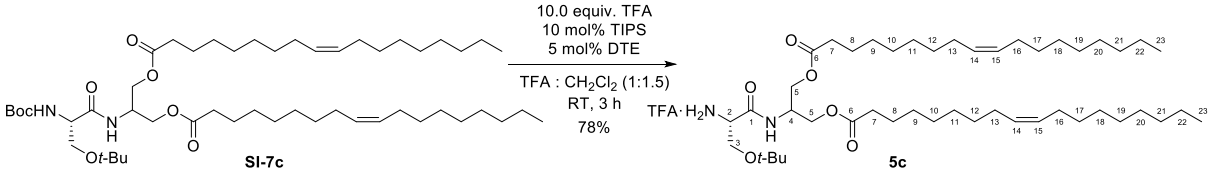
Synthesis of (S,Z)-2-amino-3-(tert-butoxy)-N-(octadec-9-en-1-yl)propanamide, 5b.



From amide **SI-7b** (1.39 g, 2.7 mmol), TFA (2.0 mL, 27.0 mmol), TIPS (40 µL, 0.2 mmol) and DTE (21 mg, 0.1 mmol) in 2.5 mL of CH_2Cl_2, following the general procedure (**Method E**), dipeptide **5b** (416 mg, 46 % yield) was obtained as a white foam.

Data for **5b**: $\mathbf{R_f}$ 0.20 (5% MeOH – DCM). **^{1}H-NMR** (300 MHz, $CDCl_3$): 5.23-5.33 (2H, m, 12-H and 13-H), 3.64-3.95 (3H, m, 2-H and 3-H_2), 3.12-3.18 (2H, m, 4-H_2), 1.90-2.03 (4H, m, 11-H_2 and 14-H_2), 1.49 (2H, quint, J = 7.1 Hz, 5-H_2), 1.20-1.37 (22H, m, 6-H_2 and 7-H_2 and 8-H_2 and 9-H_2 and 10-H_2 and 15-H_2 and 16-H_2 and 17-H_2 and 18-H_2 and 19-H_2 and 20-H_2), 1.17 (9H, s, 3 x CH_3 *t*-Bu), 0.85 (3H, t, J = 6.5 Hz, 13-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 168.2 (C-1), 130.8 and 130.8 (C-12 and C-13), 75.3 and 61.8 (C-2 and C-3), 40.8 (C-4), 33.7 and 33.1 and 30.9 and 30.88 and 30.80 and 30.73 and 30.70 and 30.5 and 30.46 and 30.40 and 30.3 and 28.0 and 27.7 and 23.8 (14C, C-5 and C-6 and C-7 and C-8 and C-9 and C-10 and C-11 and C-14 and C-15 and C-16 and C-17 and C-18 and C-19 and C-20), 27.7 (3C, 3 x CH_3-*t*-Bu), 14.6 (C-21). **HRMS** (ESI): calculated for $C_{31}H_{58}N_5O_3$ $[M+H]^+$ requires *m/z* 548.4540, found *m/z* 548.4536. Calculated for $C_{27}H_{49}N_5O_3$ $[M-t\text{Bu}+H]^+$ requires *m/z* 491.3908, found *m/z* 491.3903.

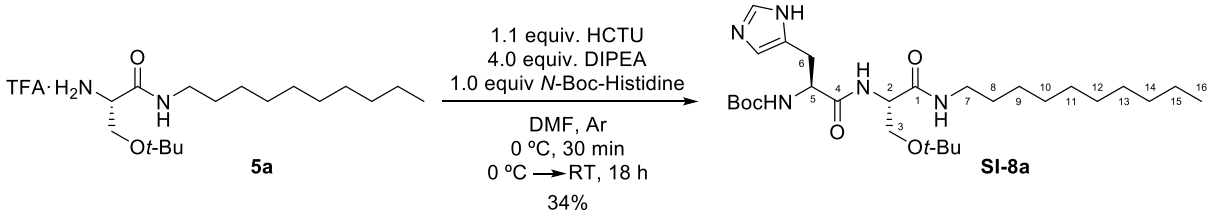
2.38. Synthesis of 2-((S)-2-amino-3-(tert-butoxy)propanamido)propane-1,3-diyl dioleate, 5c.



From amide **SI-7c** (160 mg, 0.2 mmol), TFA (160 µL, 2.0 mmol), TIPS (20 µL, 0.02 mmol) and DTE (8 mg, 0.01 mmol) in 0.5 mL of CH_2Cl_2, following the general procedure (**Method E**), dipeptide **5c** (120 mg, 78 % yield) was obtained as a white foam. This product was used without further purification.

Partial data for **5c**: **^{1}H-NMR** (300 MHz, CD_3OD): δ 5.34 (4H, t, J = 4.9 Hz, 2 x 14-H and 2 x 15-H), 4.33-4.40 (1H, m, 4-H), 4.09-4.26 (4H, m, 2 x 5-H_2), 3.64-4.04 (3H, m, 2H and 3-H_2), 2.35 (4H, t, J = 7.5 Hz, 2 x 7-H_2), 1.96-2.09 (8H, m, 2 x 13-H_2 and 2 x 16-H_2), 1.56-1.66 (4H, m, 2 x 8-H_2), 1.26-1.38 (40H, m, 2 x 9-H_2 and 2 x 10-H_2 and 2 x 11-H_2 and 2 x 12-H_2 and 2 x 17-H_2 and 2 x 18-H_2 and 2 x 19-H_2 and 2 x 20-H_2 and 2 x 21-H_2 and 2 x 22-H_2), 1.23 (9H, s, 3 x CH_3 *t*Bu), 0.90 (6H, t, J = 6.7 Hz, 2 x 23-H_3).

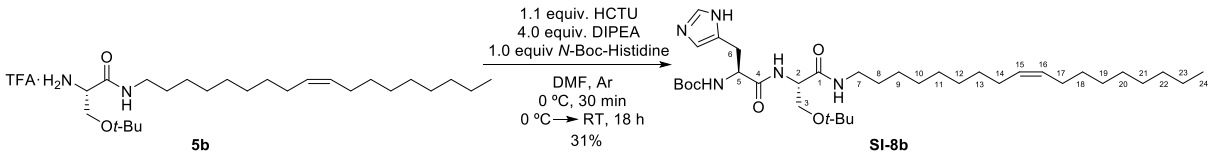
2.39. Synthesis of *tert*-butyl ((S)-1-(((S)-3-(*tert*-butoxy)-1-(decylamino)-1-oxopropan-2-yl)amino)-3-(1H-imidazol-5-yl)-1-oxopropan-2-yl)carbamate, SI-8a.



From amide **5a** (416 mg, 1.4 mmol), HCTU (600 mg, 1.5 mmol), DIPEA (0.9 mL, 5.4 mmol) and *N*-Boc-histidine (343 mg, 1.3 mmol) in 15.0 mL of dry DMF, following the general procedure (**Method C**), lipopeptide **SI-8a** (150 mg, 34 % yield) was obtained as a white foam.

Data for **SI-8a**: $\mathbf{R_f}$ 0.30 (10% MeOH – DCM). **^{1}H-NMR** (300 MHz, CD_3OD): δ 8.42 (1H, s, Imidazole), 7.21 (1H, s, Imidazole), 4.32-4.42 (2H, m, 2-H and 5-H), 3.69-3.77 (1H, m, 3-H_a), 3.51-3.58 (1H, m, 3-H_b), 3.02-3.27 (4H, m, 6-H_2 and 7-H_2), 1.46-1.55 (2H, m, 8-H_2), 1.42 (9H, s, 3 x CH_3 *t*Bu Boc), 1.25-1.34 (14H, 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 14-H_2 and 15-H_2), 1.18 (9H, s, 3 x CH_3 *t*-Bu), 0.89 (3H, t, J = 6.5 Hz, 16-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 173.1 and 172.3 (2C, C-1 and C-4), 157.9 (C=O Boc), 135.6 and 132.2 and 118.8 (3C, 3 x C-Imidazole), 81.3 (C *t*Bu Boc), 74.8 and 62.7 and 55.9 and 55.4 (4C, C-2 and C-3 and C-5 and C *t*Bu), 43.9 and 40.7 and 33.1 and 30.8 and 30.7 and 30.56 and 30.51 and 28.0 and 23.8 and 14.5 (10C, C-6 and C-7 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-15), 28.8 and 27.8 (6C, 3 x CH_3-Boc and 3 x CH_3-*t*-Bu), 13.2 (C-16).

2.40. Synthesis of *tert*-butyl ((S)-1-(((S)-3-(*tert*-butoxy)-1-(((Z)-octadec-9-en-1-yl)amino)-1-oxopropan-2-yl)amino)-3-(1H-imidazol-5-yl)-1-oxopropan-2-yl)carbamate, SI-8b.

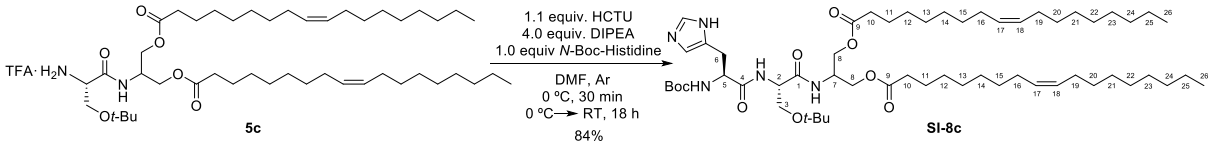


From amide **5b** (519 mg, 1.3 mmol), HCTU (600 mg, 1.5 mmol), DIPEA (0.9 mL, 5.4 mmol) and *N*-Boc-histidine (343 mg, 1.3 mmol) in 15.0 mL of dry DMF, following the general procedure (**Method C**), lipopeptide **SI-8b** (260 mg, 31 % yield) was obtained as a white foam.

Data for **SI-8b**: $\mathbf{R_f}$ 0.60 (10% MeOH – DCM). **^{1}H-NMR** (300 MHz, CD_3OD): δ 7.84 (1H, s, Imidazole), 6.99 (1H, s, Imidazole), 5.29-5.40 (2H, m, 15-H and 16-H), 4.26-4.36 (2H, m, 2-H and 5-H), 3.69-3.79 (1H, m, 3-H_a), 3.45-3.54 (1H, m, 3-H_b), 3.04-3.27 (3H, m, 6-H_a and 7-H_2), 2.91-3.00 (1H, m, 6-H_b), 1.93-2.03 (4H, m, 15-H_2 and 16-H_2), 1.47-1.57 (2H, m, 8-H_2),

1.48 (9H, s, Boc), 1.25-1.37 (22H, m, 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 18-H_2 and 19-H_2 and 20-H_2 and 21-H_2 and 22-H_2 and 23-H_2), 1.17 (9H, s, *t*-Bu), 0.90 (3H, t, J = 6.5 Hz, 24-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 173.8 and 172.2 (2C, C-1 and C-4), 158.2 (CO-Boc), 136.2 and 134.1 and 118.5 (3C, 3 x C-Imidazole), 130.98 and 130.96 (2C, C-15 and C-16), 81.2 (C-Boc), 74.7 and 62.6 and 56.6 and 56.4 (4C, C-2 and C-3 and C-5 and C-*t*-Bu), 40.7 (C-7), 33.1 and 31.0 and 30.97 and 30.90 and 30.8 and 30.74 and 30.72 and 30.58 and 30.52 and 30.5 and 29.8 and 28.29 and 28.27 and 28.0 and 23.8 (15C, C-6 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-17 and C-18 and C-19 and C-20 and C-21 and C-22 and C-23), 28.8 and 27.8 (6C, 3 x CH_3-Boc and 3 x CH_3-*t*-Bu), 14.6 (C-24).

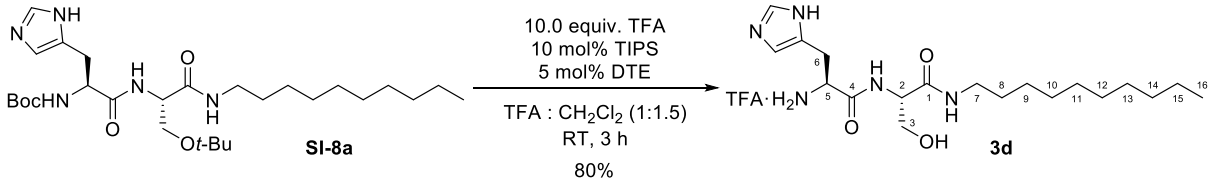
2.41. Synthesis of 2-((S)-3-(*tert*-butoxy)-2-((S)-2-((*tert*-butoxycarbonyl)amino)-3-(1H-imidazol-5-yl)propanamido)propanamido)propane-1,3-diyl dioleate, SI-8c.



From amide **5c** (160 mg, 0.2 mmol), HCTU (95 mg, 0.2 mmol), DIPEA (140 µL, 0.8 mmol) and *N*-Boc-histidine (60 mg, 0.2 mmol) in 10.0 mL of dry DMF, following the general procedure (**Method C**), lipopeptide **SI-8c** (175 mg, 84 % yield) was obtained as a white oil. This product was used without further purification.

Partial data for **SI-8c**: **R_f** 0.60 (5% MeOH – DCM). **^{1}H-NMR** (300 MHz, CD_3OD): δ 8.73 (1H, s, Imidazole), 7.70 (1H, s, Imidazole), 5.26-5.41 (4H, 2 x 17-H and 2 x 18-H), 4.34-4.50 (3H, m, 2-H and 5-H and 7-H), 4.10-4.26 (4H, m, 2 x 8-H_2), 3.67-3.73 (1H, m, 3-H_a), 3.53-3.65 (1H, m, 3-H_b), 3.19-3.29 (1H, m, 6-H_a), 3.05-3.14 (1H, m, 6-H_b), 2.33 (4H, t, J = 7.4 Hz, 2 x 10-H_2), 1.95-2.10 (8H, m, 2 x 16-H_2 and 2 x 19-H_2), 1.54-1.68 (4H, m, 2 x 11-H_2), 1.40 (9H, s, Boc), 1.24-1.36 (40H, m, 2 x 12-H_2 and 2 x 13-H_2 and 2 x 14-H_2 and 2 x 15-H_2 and 2 x 20-H_2 and 2 x 21-H_2 and 2 x 22-H_2 and 2 x 23-H_2 and 2 x 24-H_2 and 2 x 25-H_2), 1.19 (9H, s, *t*-Bu), 0.85-0.94 (6H, m, 2 x 26-H_3).

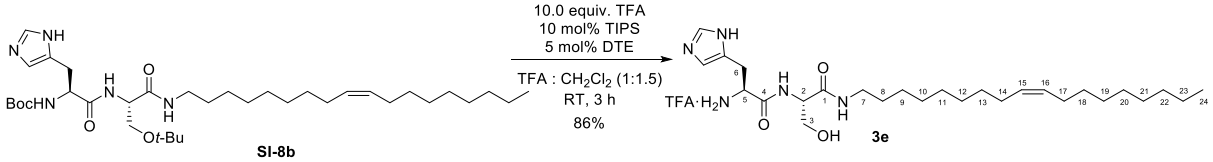
2.42. Synthesis of (S)-2-amino-N-((S)-1-(decylamino)-3-hydroxy-1-oxopropan-2-yl)-3-(1H-imidazol-5-yl)propanamide, 3d.



From amide **SI-8a** (150 mg, 0.3 mmol), TFA (360 µL, 4.6 mmol), TIPS (20 µL, 0.02 mmol) and DTE (8 mg, 0.01 mmol) in 0.5 mL of CH_2Cl_2, following the general procedure (**Method E**), dipeptide **3d** (97 mg, 80 % yield) was obtained as a white foam.

Data for **3d**: $\mathbf{R_f}$ 0.10 (10% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ +37.5 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 8.89 (1H, s, Imidazole), 7.54 (1H, s, Imidazole), 4.49 (2H, t , *J* = 5.5 Hz, 5-H), 4.39 (1H, t, *J* = 5.8 Hz, 2-H), 3.87-3.96 (2H, m, 3-H_2), 3.34-3.61 (4H, m, 6-H_2 and 7-H_2), 1.59 (2H, quint, *J* = 6.2 Hz, 8-H_2), 1.28-1.44 (14H, 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 14-H_2 and 15-H_2), 0.94 (3H, t, *J* = 6.8 Hz, 16-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 172.6 and 169.0 (2C, C-1 and C-4), 136.1 and 127.9 and 120.2 (3C, 3 x C-Imidazole), 62.9 and 57.5 and 53.1 (3C, C-2 and C-3 and C-5), 40.9 (C-7), 33.1 and 30.7 and 30.5 and 30.38 and 30.31 and 28.0 and 27.6 and 26.5 and 23.8 (9C, C-6 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-15), 14.5 (C-16). **IR** (solid): ν_{max} 3288, 3043, 2914, 1644, 1551, 1421, 1127 cm^{-1}. **HRMS** (ESI): calculated for $C_{19}H_{36}N_5O_3$ $[M+H]^+$ requires *m*/*z* 382.2813, found *m*/*z* 382.2812.

2.43. Synthesis of (S)-2-amino-N-((S)-3-hydroxy-1-(((Z)-octadec-9-en-1-yl)amino)-1-oxopropan-2-yl)-3-(1H-imidazol-5-yl)propanamide, 3e.

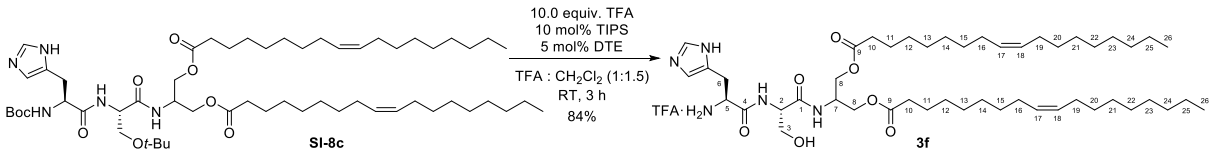


From amide **SI-8b** (260 mg, 0.5 mmol), TFA (750 µL, 9.7 mmol), TIPS (50 µL, 0.05 mmol) and DTE (10 mg, 0.01 mmol) in 1.5 mL of CH_2Cl_2, following the general procedure (**Method E**), dipeptide **3e** (120 mg, 86 % yield) was obtained as a white foam.

Data for **3e**: $\mathbf{R_f}$ 0.10 (10% MeOH – DCM). $\mathbf{[\alpha]^{20}_D}$ +38.6 (*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 8.85 (1H, s, Imidazole), 7.48 (1H, s, Imidazole), 5.30-5.40 (2H, m, 15-H and 16-H), 4.41 (1H, t, *J* = 5.3 Hz, 5-H), 4.30 (1H, t, *J* = 4.8 Hz, 2-H), 3.84-3.87 (2H, m, 3-

H_2), 3.17-3.53 (3H, m, 6-H_a and 7-H_2), 2.91-3.00 (1H, m, 6-H_b), 1.93-2.08 (4H, m, 14-H_2 and 17-H_2), 1.48-1.59 (2H, m, 8-H_2), 1.24-1.41 (22H, m, 9-H_2 and 10-H_2 and 11-H_2 and 12-H_2 and 13-H_2 and 18-H_2 and 19-H_2 and 20-H_2 and 21-H_2 and 22-H_2 and 23-H_2), 0.85-0.94 (3H, m, 24-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 172.7 and 169.0 (2C, C-1 and C-4), 136.1 and 131.0 and 120.3 (3C, 3 x C-Imidazole), 130.9 and 130.8 (2C, C-15 and C-16), 62.9 and 57.5 and 53.2 (3C, C-2 and C-3 and C-5), 41.0 (C-7), 33.1 and 31.0 and 30.96 and 30.92 and 30.8 and 30.7 and 30.5 and 30.49 and 30.46 and 30.42 and 28.2 and 28.1 and 27.6 and 23.86 and 23.82 (15C, C-6 and C-8 and C-9 and C-10 and C-11 and C-12 and C-13 and C-14 and C-17 and C-18 and C-19 and C-20 and C-21 and C-22 and C-23), 14.5 (C-24). **IR** (solid): ν_{max} 3280, 3086, 2921, 1651, 1536, 1436, 1134 cm^{-1}. **HRMS** (ESI): calculated for $C_{27}H_{50}N_5O_3$ $[M+H]^+$ requires *m*/*z* 492.3908, found *m*/*z* 492.3903.

2.44. Synthesis of 2-((S)-2-((S)-2-amino-3-(1H-imidazol-5-yl)propanamido)-3-hydroxypropanamido)propane-1,3-diyl dioleate, 3f.



From amide **SI-8c** (175 mg, 0.3 mmol), TFA (300 µL, 3.4 mmol), TIPS (30 µL, 0.03 mmol) and DTE (8 mg, 0.01 mmol) in 0.6 mL of CH_2Cl_2, following the general procedure (**Method E**), dipeptide **3f** (125 mg, 84 % yield) was obtained as a white foam.

Data for **3f**: **R_f** 0.20 (10% MeOH – DCM). **$[\alpha]^{20}_D$** +22.6(*c* = 1.0, MeOH). **^{1}H-NMR** (300 MHz, CD_3OD): δ 7.85-7.92 (1H, m, Imidazole), 7.39-7.46 (1H, m, Imidazole), 5.29-5.39 (4H, 2 x 17-H and 2 x 18-H), 4.38-4.47 (2H, m, 2-H and 5-H), 4.11-4.30 (5H, m, 7-H and 2 x 8-H_2), 3.80-3.87 (2H, m, 3-H_2), 3.35-3.50 (2H, m, 6-H_2), 2.30-2.39 (4H, m, 2 x 10-H_2), 1.93-2.07 (8H, m, 2 x 16-H_2 and 2 x 19-H_2), 1.57-1.66 (4H, m, 2 x 11-H_2), 1.24-1.38 (40H, m, 2 x 12-H_2 and 2 x 13-H_2 and 2 x 14-H_2 and 2 x 15-H_2 and 2 x 20-H_2 and 2 x 21-H_2 and 2 x 22-H_2 and 2 x 23-H_2 and 2 x 24-H_2 and 2 x 25-H_2), 0.87-0.93 (6H, m, 2 x 26-H_3). **^{13}C-NMR** (75 MHz, CD_3OD): δ 175.2 and 175.1 (4C, C-1 and C-4 and 2 x C-9), 136.5 and 131.5 and 120.0 (3C, 3 x C-Imidazole), 131.0 and 130.9 (4C, 2 x C-17 and 2 x C-18), 63.5 and 63.3 and 62.8 and 57.4 and 53.1 (6C, C-2 and C-3 and C-5 and C-7 and 2 x C-8), 34.9 and 33.2 and 30.98 and 30.96 and 30.92 and 30.7 and 30.6 and 30.5 and 30.48 and 30.46 and 30.3 and 28.8 and 26.1 and 25.1 and 23.8 (29C, C-6 and 2 x C-10 and 2 x C-11 and 2 x C-12 and 2 x C-13 and 2 x C-14 and 2 x C15

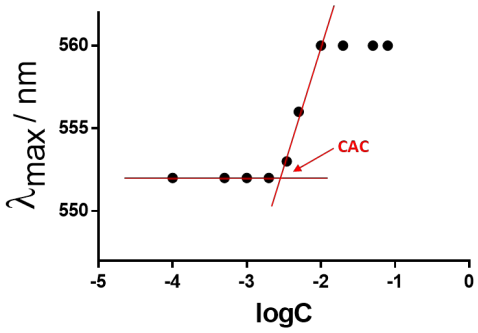
and 2 x C-16 and 2 x C-19 and 2 x C20 and 2 x C-21 and 2 x C-22 and 2 x C-23 and 2 x C-24 and 2 x C-25), 14.6 (2C, 2 x C-26). **IR** (solid): ν_{max} 3137, 2914, 1658, 1443, 1134 cm^{-1}. **HRMS** (ESI): calculated for $C_{48}H_{86}N_5O_7$ $[M+H]^+$ requires *m/z* 844.6522, found *m/z* 844.6522. Calculated for $C_{50}H_{87}F_3N_5O_9$ $[M+H+TFA]^+$ requires *m/z* 958.6450, found *m/z* 958.6450.

3. Determination of the Critical Aggregation Concentration (CAC).

The Critical Aggregation Concentration (CAC) of surfactants lipopeptides were determined using a stablished fluorimetric method,[8] that relies on the effect that the presence of supramolecular structures has on the maximum wavelength of fluorescence emission of an added fluorochrome.

Basic aqueous solution (pH = 8.5, Bicine) of surfactants were prepared, containing rhodamine 6G (1 μM), with a surfactant concentration ranging from 0.1 M to 0.01. Surfactant **1j** (*S*-decanoyl-L-cysteine) required and acidic medium, that was adjusted using TFA. Lipodipeptides **3c** and **3f** did not provide consistent results.

Analyses were performed using a *Cary Eclipse* Varian spectrofluorotometer with Rhodamine 6G as the probe. The excitation wavelength was 520 nm and the emission wawelength switched from 552 to 560nm. CAC values were obtained by plotting the maximum wavelength of emission (λ_{max} / nm) against the logarithm of the surfactant concentration (C / mM).



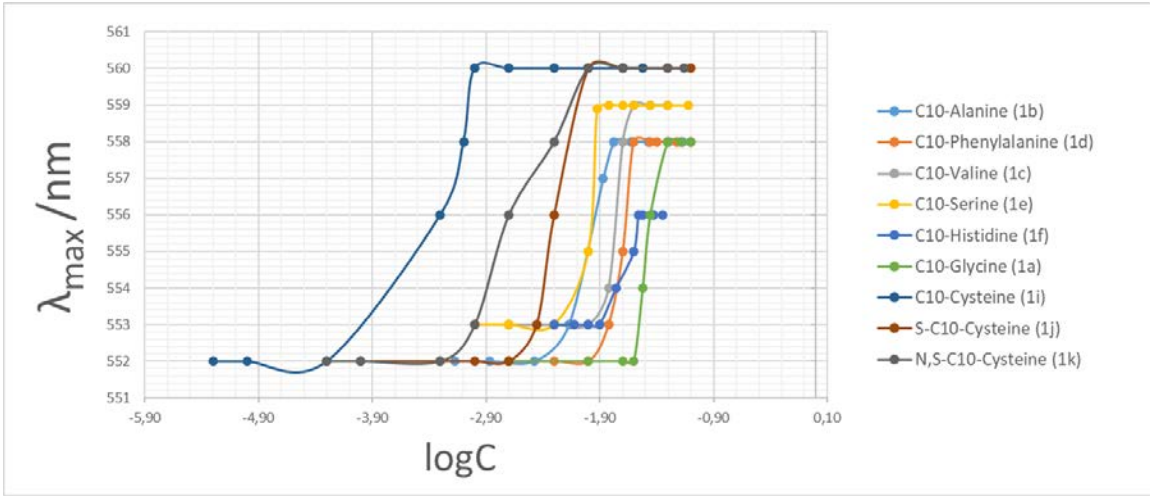


Figure S1: Maximum of fluorescence emission (λ) vs. lipoaminoacids concentration (logC)

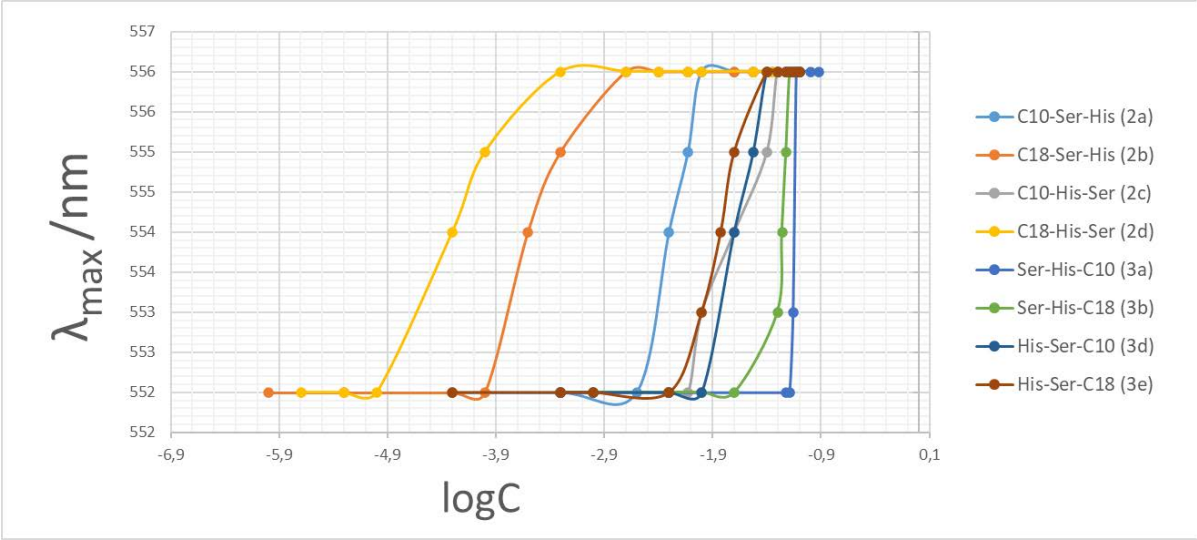


Figure S2: Maximum of fluorescence emission (λ) vs. lipodipeptides concentration (logC)

Compound	Code	CAC (mM)	CMC (mM) literature
N-decanoyl-glycine	**1a**	25.00 ±	25.1 [1]
N-decanoyl-alanine	**1b**	4.50 ±	24.5 [9]
N-decanoyl-valine	**1c**	12.00 ±	17.7 [5]
N-decanoyl-phenylalanine	**1d**	12.50 ±	-
N-decanoyl-serine	**1e**	8.90 ±	5.5 [10]
N-decanoyl-histidine	**1f**	9.90 ±	8.0 [11]
N-decanoyl-cysteine	**1i**	0.20 ±	-
S-decanoyl-cysteine	**1j**	3.00 ±	-
N,*S*-decanoyl-cysteine	**1k**	0.70 ±	-
C10-Ser-His	**2a**	0.01 ±	-
C18-Ser-His	**2b**	0.06 ±	-
C10-His-Ser	**2c**	5.96 ±	-
C18-His-Ser	**2d**	0.01 ±	-
Ser-His-C10	**3a**	68.40 ±	-
Ser-His-C18	**3b**	45.72 ±	-
His-Ser-C10	**3d**	8.88 ±	-
His-Ser-C18	**3e**	7.17 ±	-

Table S1: Values of CAC obtained for the lipoaminoacids and lipodipeptides analized.

4. Measurement of particle size and Zeta-potential using Dynamic Light Scattering.

Analysis were performed using a Malvern Zetasizer Nano ZS model system recording particle size and zeta-potential. Instrument control and data processing were performed using Zetasizer software. Disposable folded capillary cuvettes were used with 1.0 mL of sample solution, that were filtrated through a 0.45 µm nylon syringe filters. Measurements were done using an equilibrated probe at 25 ºC. For each sample, hydrodynamic radii and size distribution reflects the average of three measurements, and zeta potential accounts for the average of five measurements.

Extensive screening of multiple parameters, such as concentration, pH or effect of counterions has been made. An example of pH screening for C10-His (**1f**) is shown in Figure S3. Both, particle size and Zeta-potential were recorded at different pH, observing consistent uniform particle size (~100 nm) and more stable (higher absolute value of zeta potential) at basic pH (> 7).

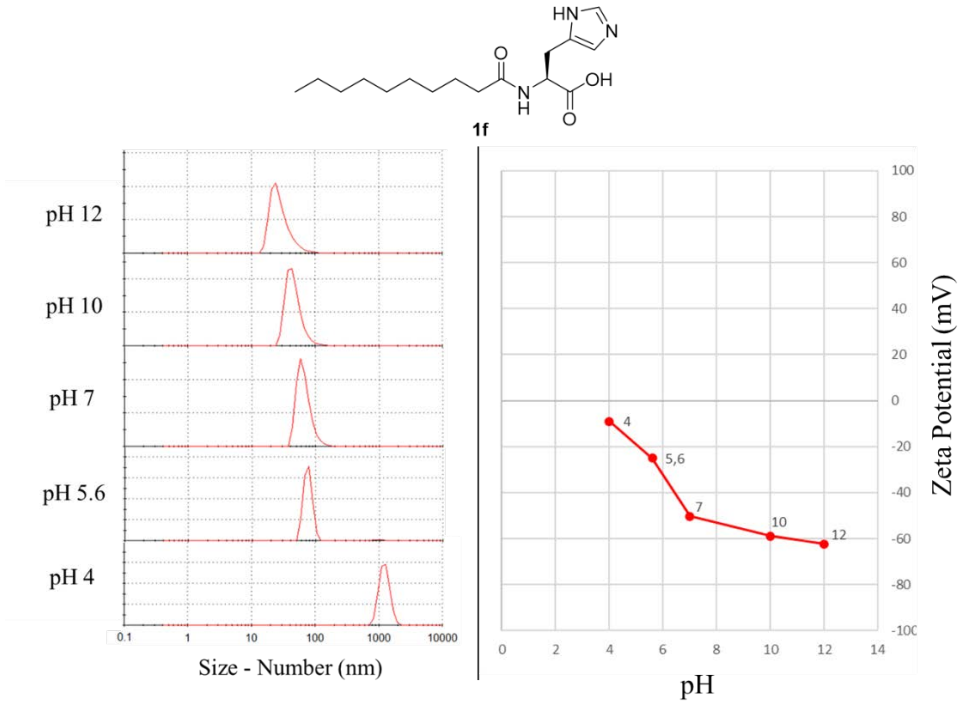


Figure S3: Variation of: a) particle size and b) zeta-potential for 1f at different pH.

Further examples of pH screening for His-Ser-C10 (**3d**) and His-Ser-C18 (**3e**) are shown in Figures S4 and S5 respectively. Both, particle size and Zeta-potential were recorded at different pH, observing more stable particles (higher absolute value of zeta potential) at neutral pH (> 6).

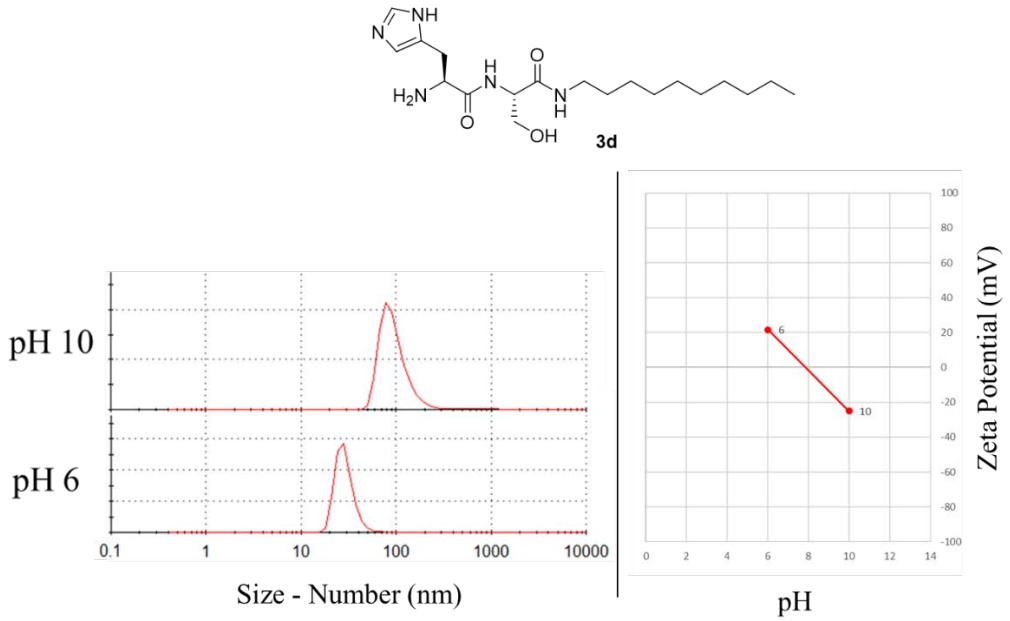


Figure S4: Variation of: a) particle size and b) zeta-potential for 1f at different pH.

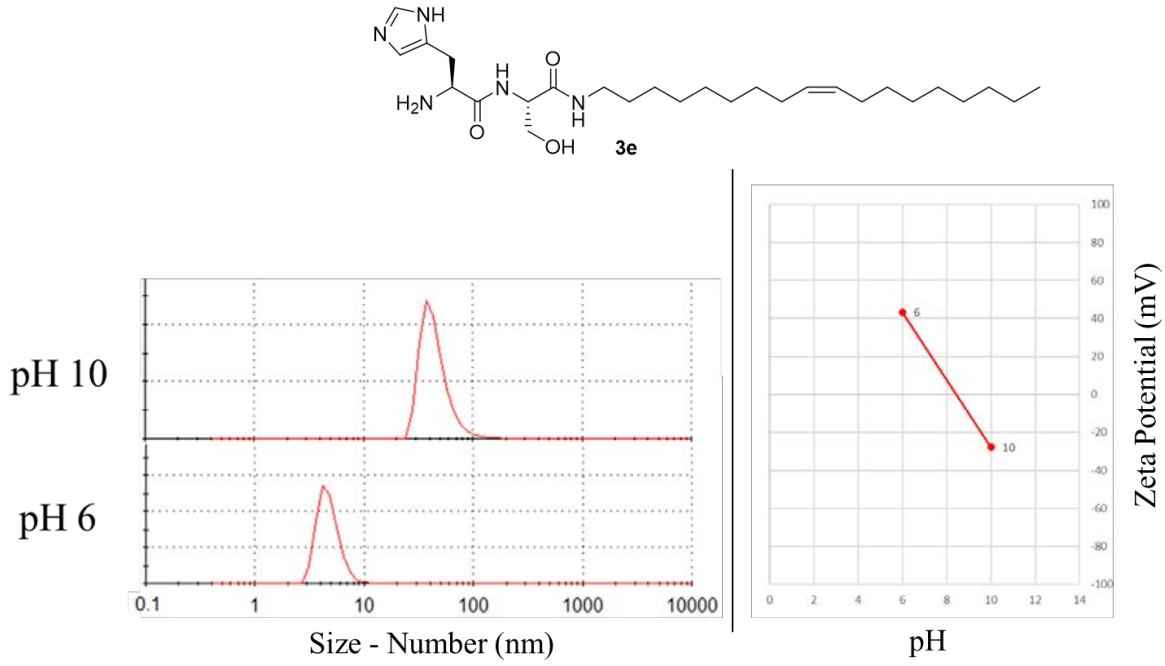
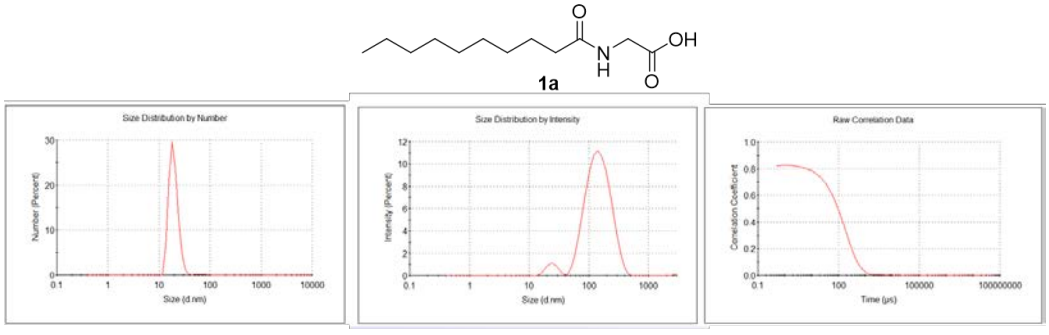


Figure S5: Variation of: a) particle size and b) zeta-potential for 1f at different pH.

In order to facilitate the study and to afford a general view, herein we provide data for every compound at the optimal concentration and pH: lipoaminoacids were used as potassium salts at pH = 11, and lipodipeptides were used at neutral pH = 6.

Compound	Code	Particle size Number, nm (population ratio)	Particle size Intensity, nm (population ratio)	Zeta-P (mV)
C10-Glycine	**1a**	18	24 and 142 (4:96)	—
C10-Alanine	**1b**	3	4 and 161 (42:58)	- 65.9 ± 4.2
C10-Valine	**1c**	4	196	- 60.0 ± 4.0
C10-Phenylalanine	**1d**	68	74 and 841 (6:94)	- 68.5 ± 4.0
C10-Serine	**1e**	28	164	- 85.3 ± 3.5
C10-Histidine	**1f**	32	120	- 62.3 ± 3.1
C10-Cysteine	**1i**	10	13, 68 and 712 (6:54:40)	- 67.3 ± 1.8
S-C10-Cysteine	**1j**	68	215	—
N,*S*-C10-Cysteine	**1k**	28 and 105 (80:20)	95	- 74.2 ± 2.4
C10-Ser-His	**2a**	10	15 and 210 (10:90)	+ 42.2 ± 0.9
C18-Ser-His	**2b**	37	105	+ 69.9 ± 0.8
C10-His-Ser	**2c**	11	22 and 255 (12:82)	+ 54.0 ± 1.5
C18-His-Ser	**2d**	190	220 and 1280 (13:87)	+ 55.9 ± 1.0
Ser-His-C10	**3a**	68	181	+ 61.3 ± 1.8
Ser-His-C18	**3b**	6	8, 54 and 278 (6:36:58)	+ 66.7 ± 0.7
Ser-His-DC	**3c**	32	137	+ 91.2 ± 2.4
His-Ser-C10	**3d**	28	32 and 236 (8:92)	+ 21.6 ± 1.6
His-Ser-C18	**3e**	5	7 and 190 (30:70)	+ 43.3 ± 1.5
His-Ser-DC	**3f**	68	130	+ 78.3 ± 2.1

Table S2: Values of particle size and Zeta-potential for lipoaminoacids and lipodipeptides.



0.025 M / pH 11

Figure S6: Particle size data for 1a.

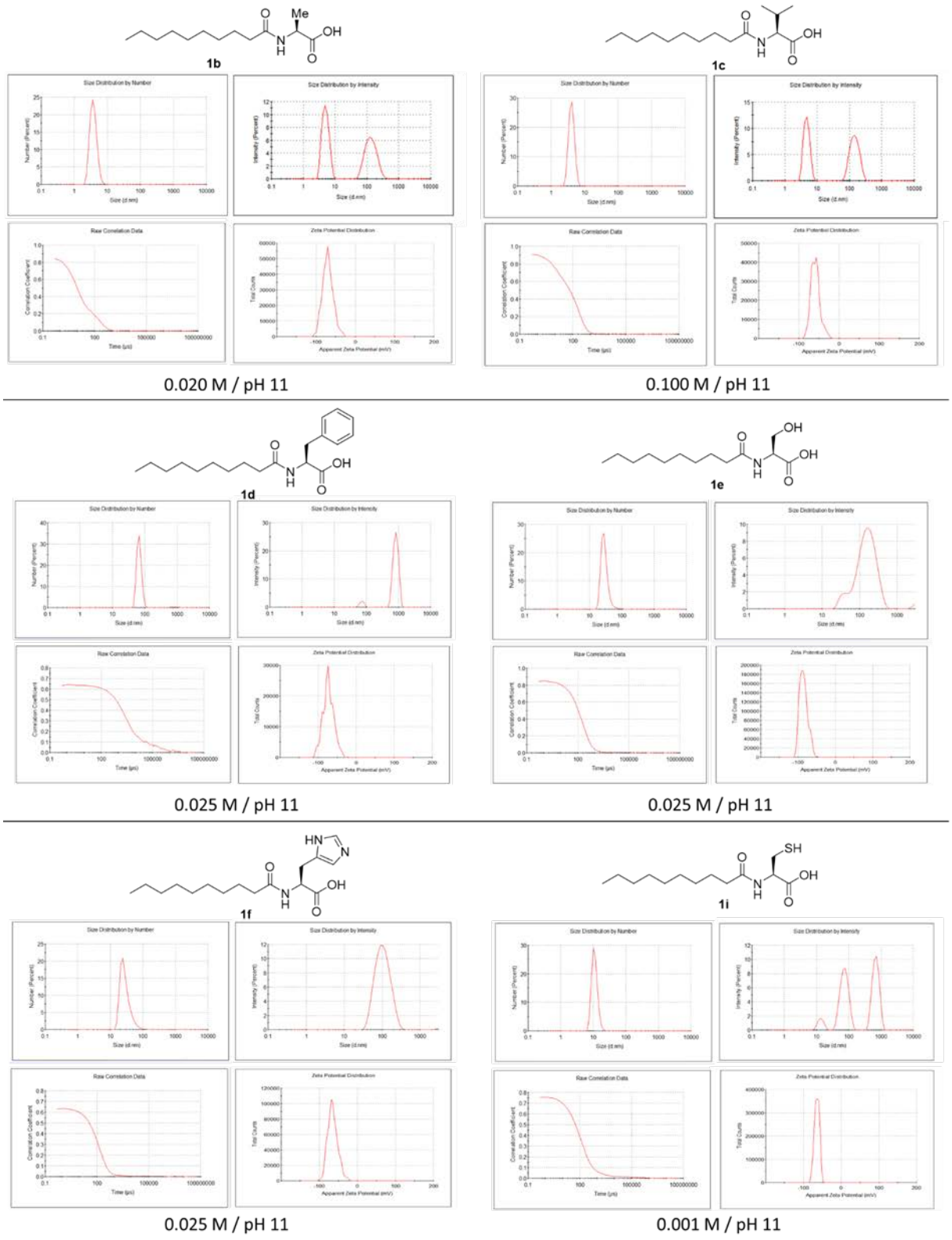


Figure S7: Particle size and Zeta-potential data for 1b, 1c, 1d, 1e, 1f and 1i.

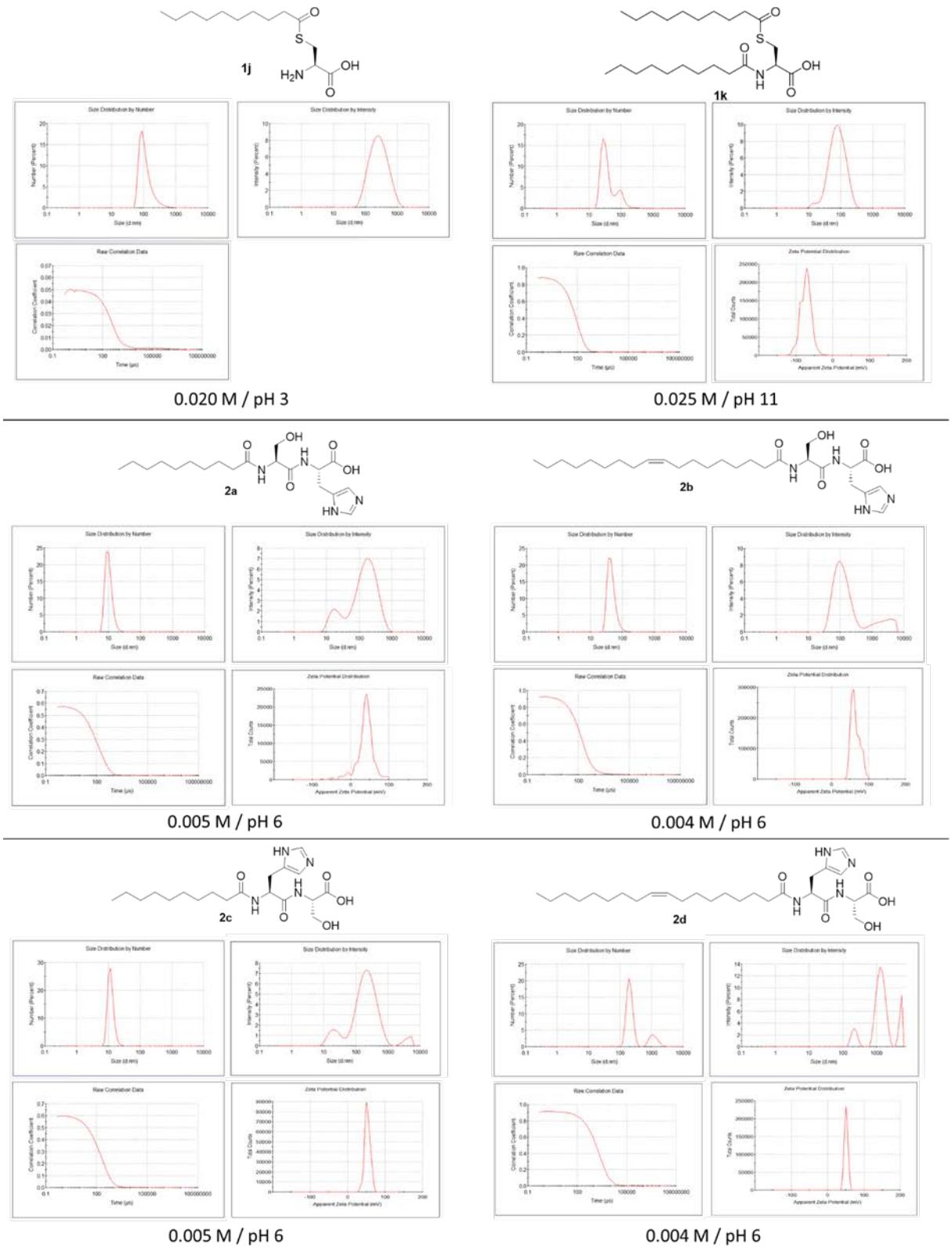


Figure S8: Particle size and Zeta-potential data for 1j, 1k, 2a 2b 2c and 2d.

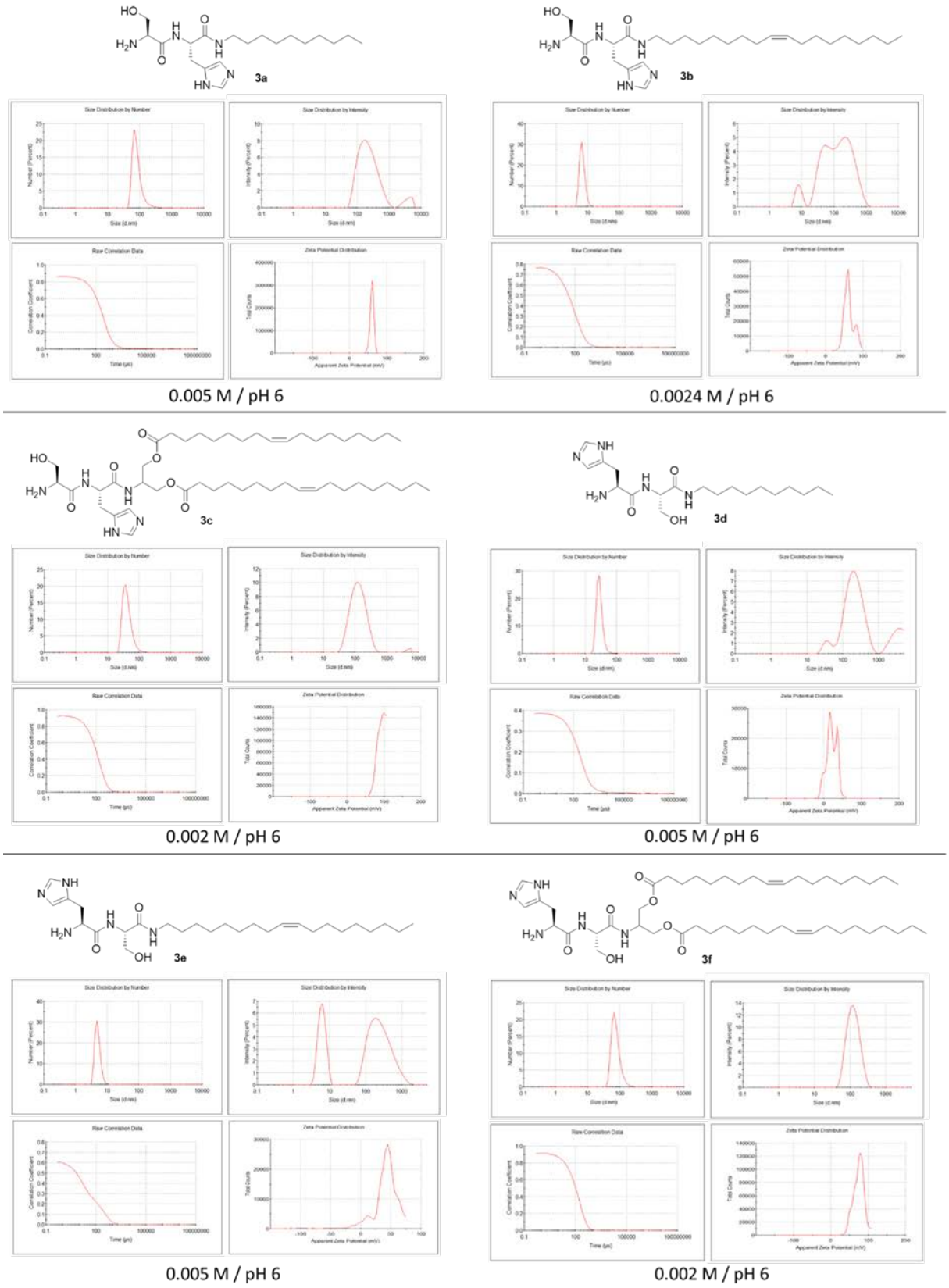


Figure S9: Particle size and Zeta-potential data for 3a-f.

5. Analysis of Infrared spectra

The analysis of the infrared spectra reveals the widespread presence of characteristic bands such as O-H and N-H stretching (3300 – 2500 cm^{-1}); C=C–H and C–C–H stretching (3200 – 3000 and 3000 – 2700 cm^{-1}, respectively); C=O stretching (1750 – 1630 cm^{-1}); C–O stretching (1200 – 1100 cm^{-1}); and C=C stretching (1600 – 1500 cm^{-1}) in case of **1g-h**; **2b**,**d**; **3b-c**; **3e-f**.

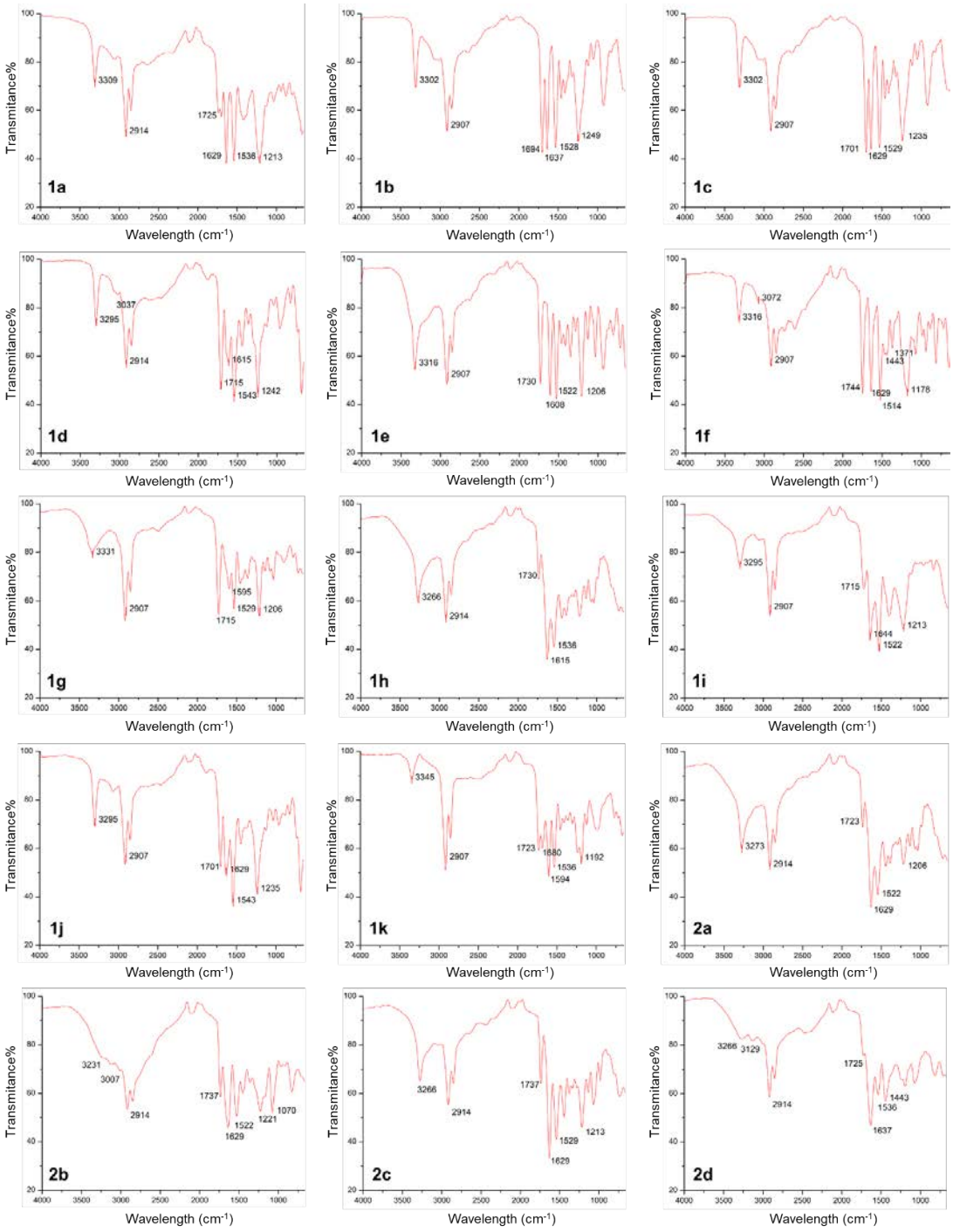


Figure S10: Infrared spectra of compounds 1a-2d in solid state.

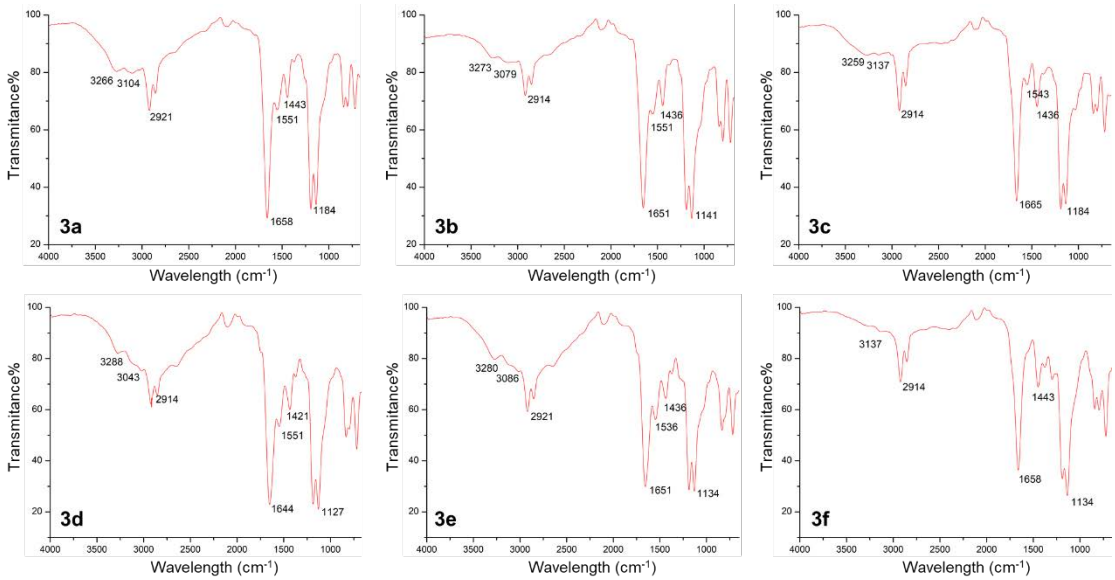


Figure S11: Infrared spectra of compounds 3a-3f in solid state.

6. Study of the shape and morphology using HR-TEM and FE-SEM.

Electron microscopy measurements were performed at the Advanced Microscopy Laboratory in the Institute for Nanoscience of Aragon at the University of Zaragoza (LMA-INA).

High Resolution Transmission Electron Microscopy (HR-TEM) analysis was performed in a Tecnai F30 microscope (Thermofisher, formerly FEI) at a working voltage of 300KV. High Resolution TEM images were obtained with a CCD camera (Gatan). Grids were negative stained with uranyl acetate. After 30 s, the excess was removed with a filter paper and grids were stored in a grid box inside a desiccator for 24 h.

Field Emission Scanning Electron Microscopy (FE-SEM) was performed on 10nm palladium- or gold-coated carbon adhesive discs in an Inspect F50 microscope (Thermofisher, formerly FEI) at a working voltage of 10KV.

Samples were prepared at the specified concentration indicated in each case and at pH = 9 for lipoamino acids, and pH = 6 for lipodipeptides.

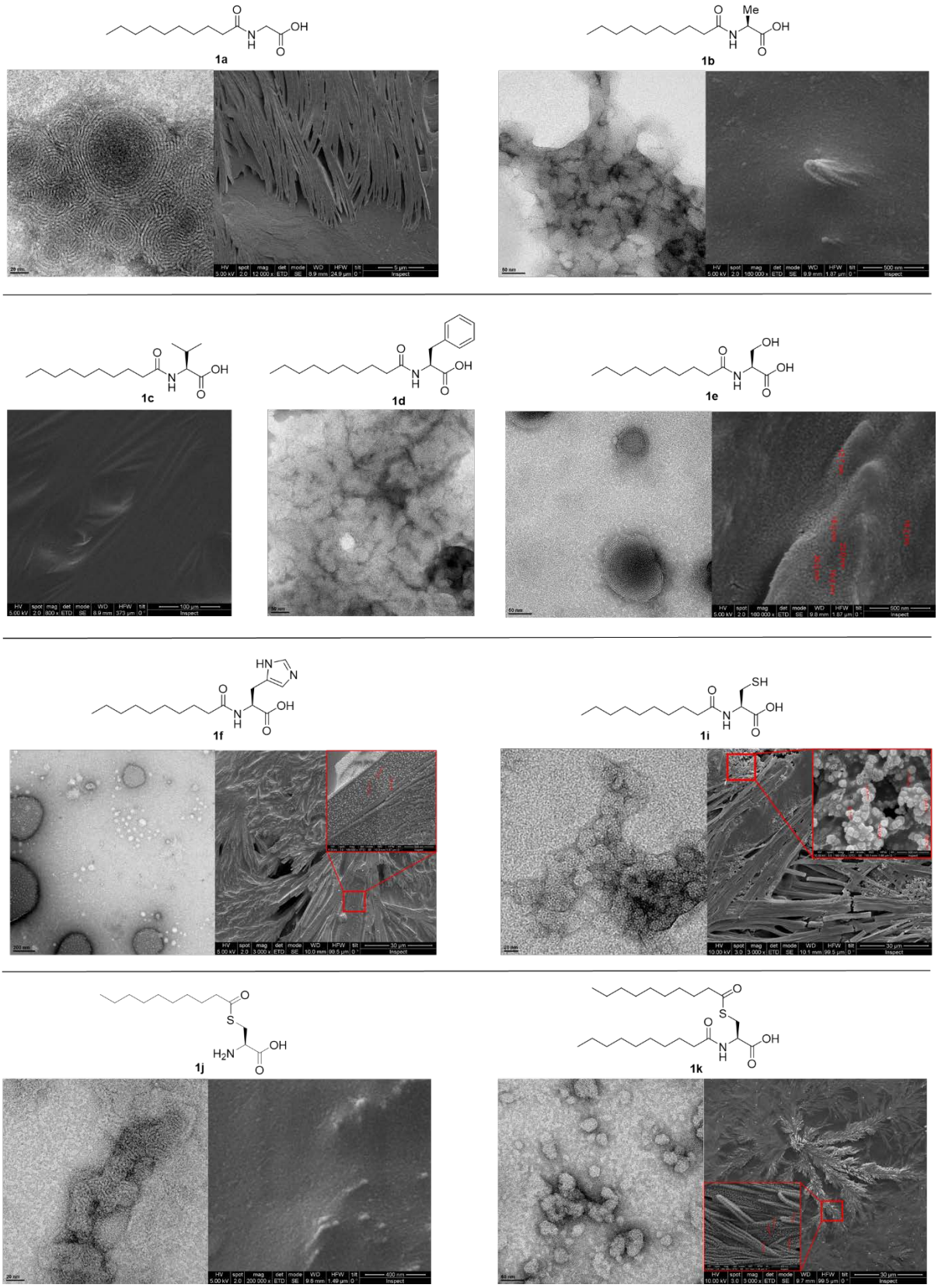


Figure S12: HR-TEM (left) and FE-SEM (right) for every lipoaminoacid, prepared from solutions at 0.1 M.

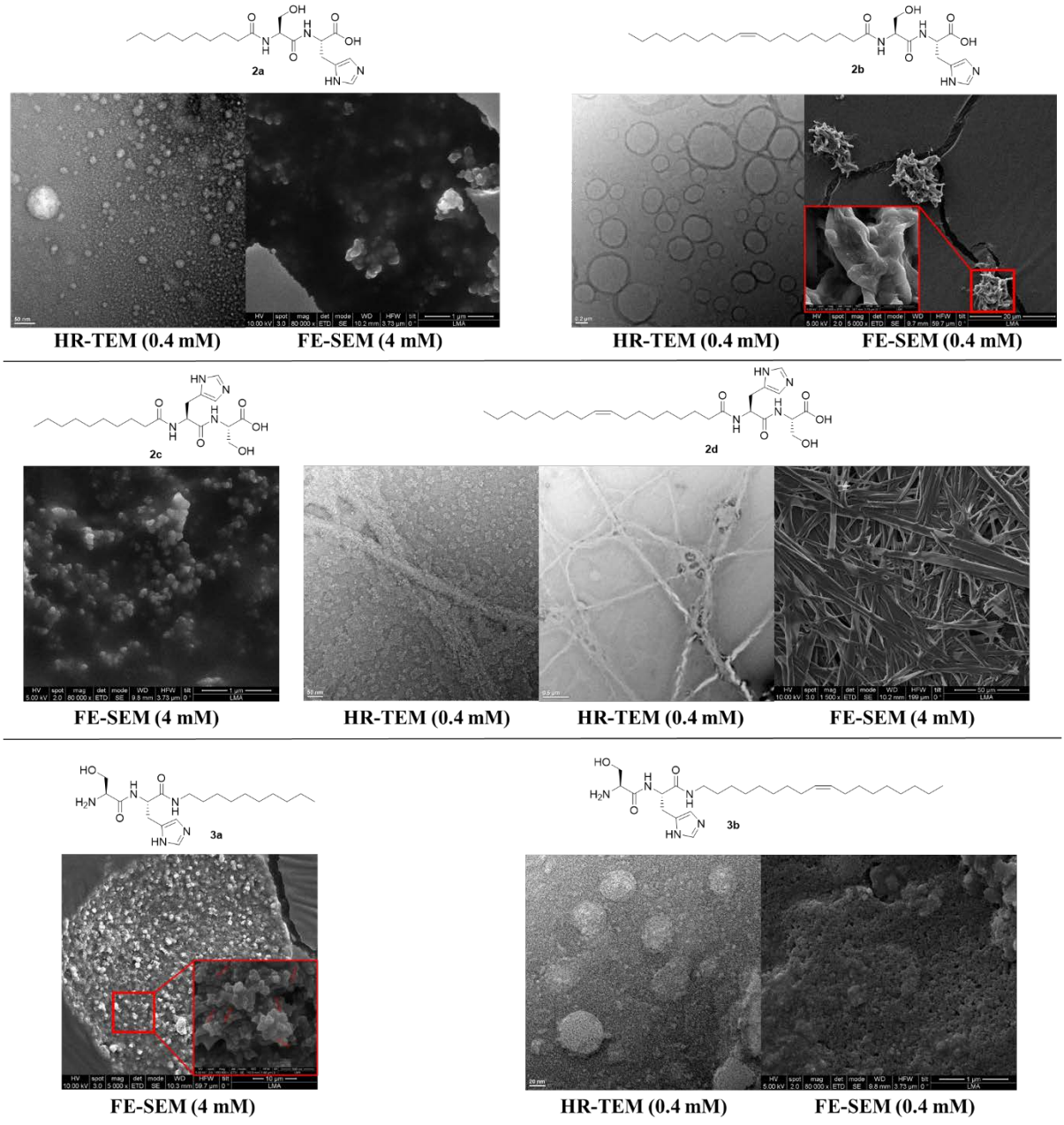


Figure S13: HR-TEM and FE-SEM for lipodipeptides.

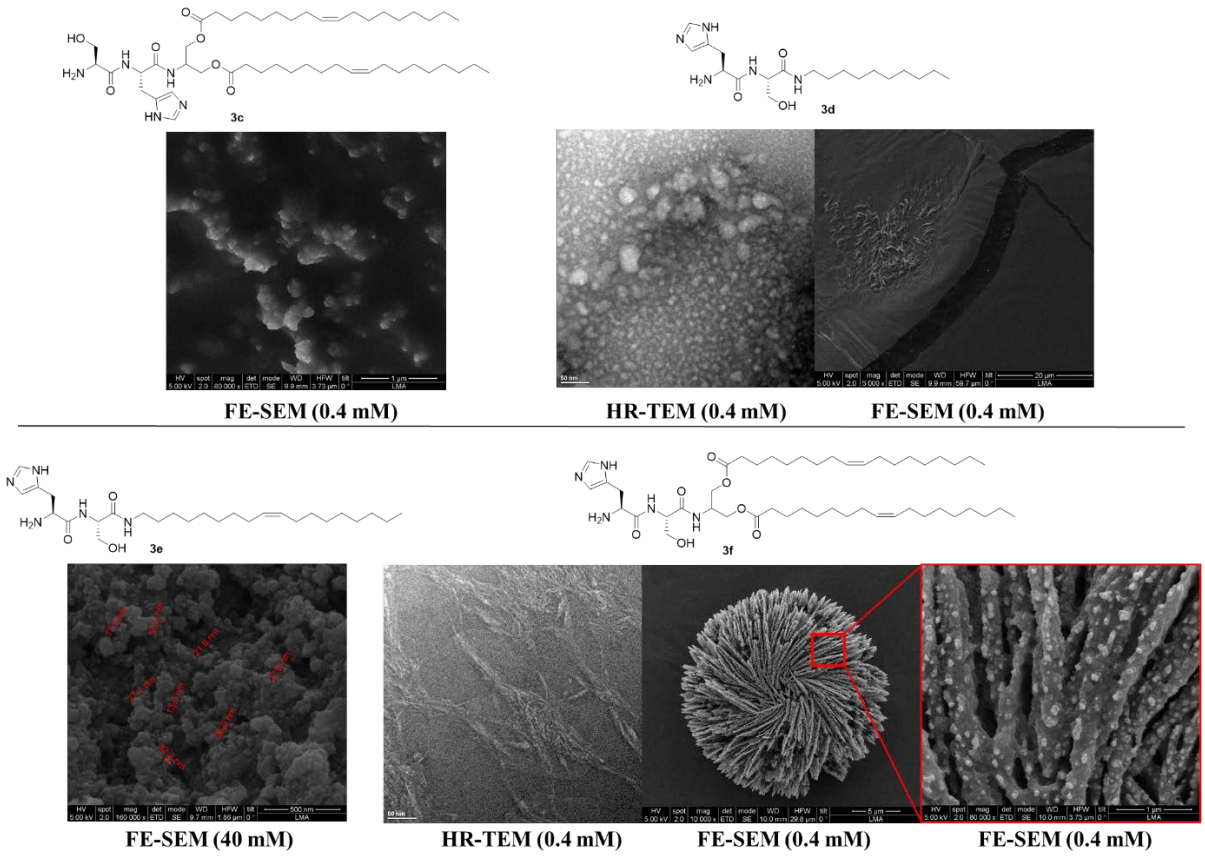


Figure S14: HR-TEM and FE-SEM for lipodipeptides.

7. Antibacterial Activity Assay.

The Minimal Inhibition Concentration (MIC) of the lipoaminoacids and lipodipeptides synthesized were determined using the broth microdilution method, following previously published protocols for CMDR.[12] The bacterial strains used in this study include Gram – and Gram + strains; *Escherichia coli* CECT 516 (highlighted in red boxes) and *Staphylococcus aureus* CECT 240 (highlighted in purple boxes) reference strains, respectively. Both bacteria strains were grown at 37 ºC in tryptone-beef broth medium. All experiments were run with three replicates and included both growth (highlighted in green boxes) and sterility (highlighted in black boxes) controls.

For each compound, a range of concentrations (5, 40, 125, 250, 500 and 1000 µg/mL) were prepared by serial dilution and added to an equal volume of bacterial solution (100 µL) in each well of a non-treated 96-well round bottom polystyrene microplates. The plates were incubated at 37 ºC for 18 h. The MIC (µg/mL and mM) was assigned to the lowest concentration of the compound that inhibited visual growth of the microorganisms (lack of turbidity in the culture).[13]

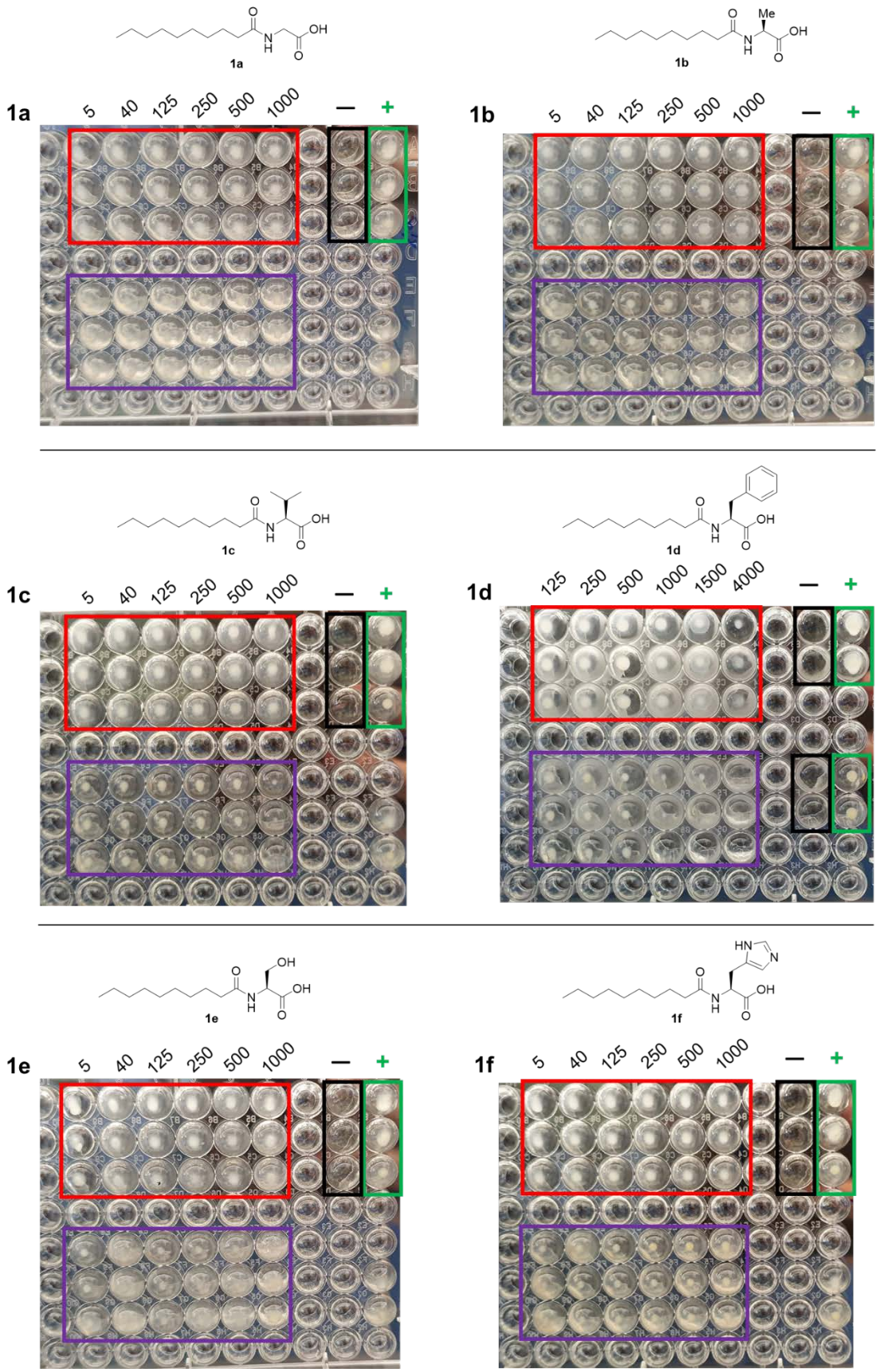


Figure S15: Antibacterial assays for lipoaminoacids 1a-f.

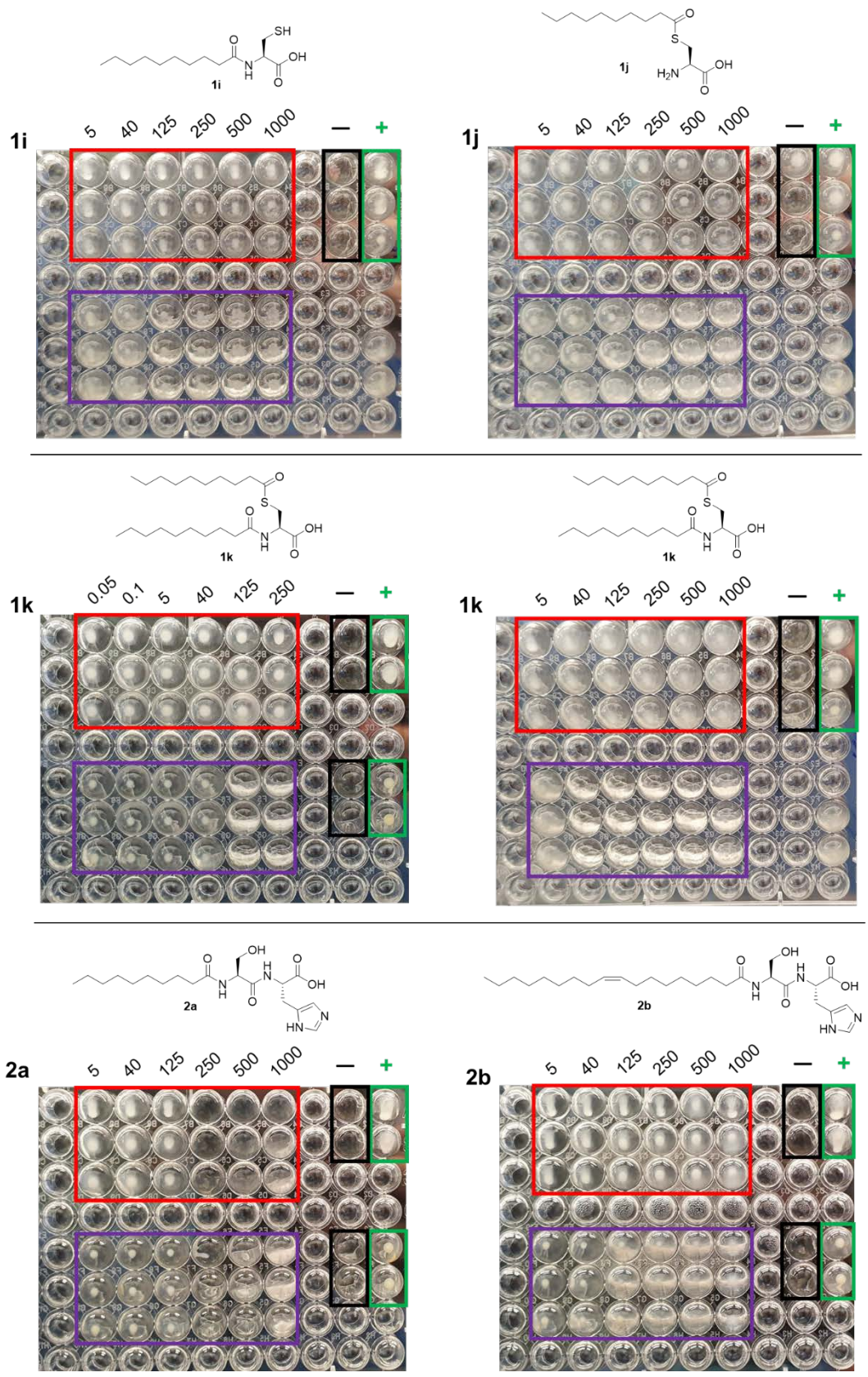


Figure S16: Antibacterial assays for lipoaminoacids 1i-k and lipodipeptides 2a-b.

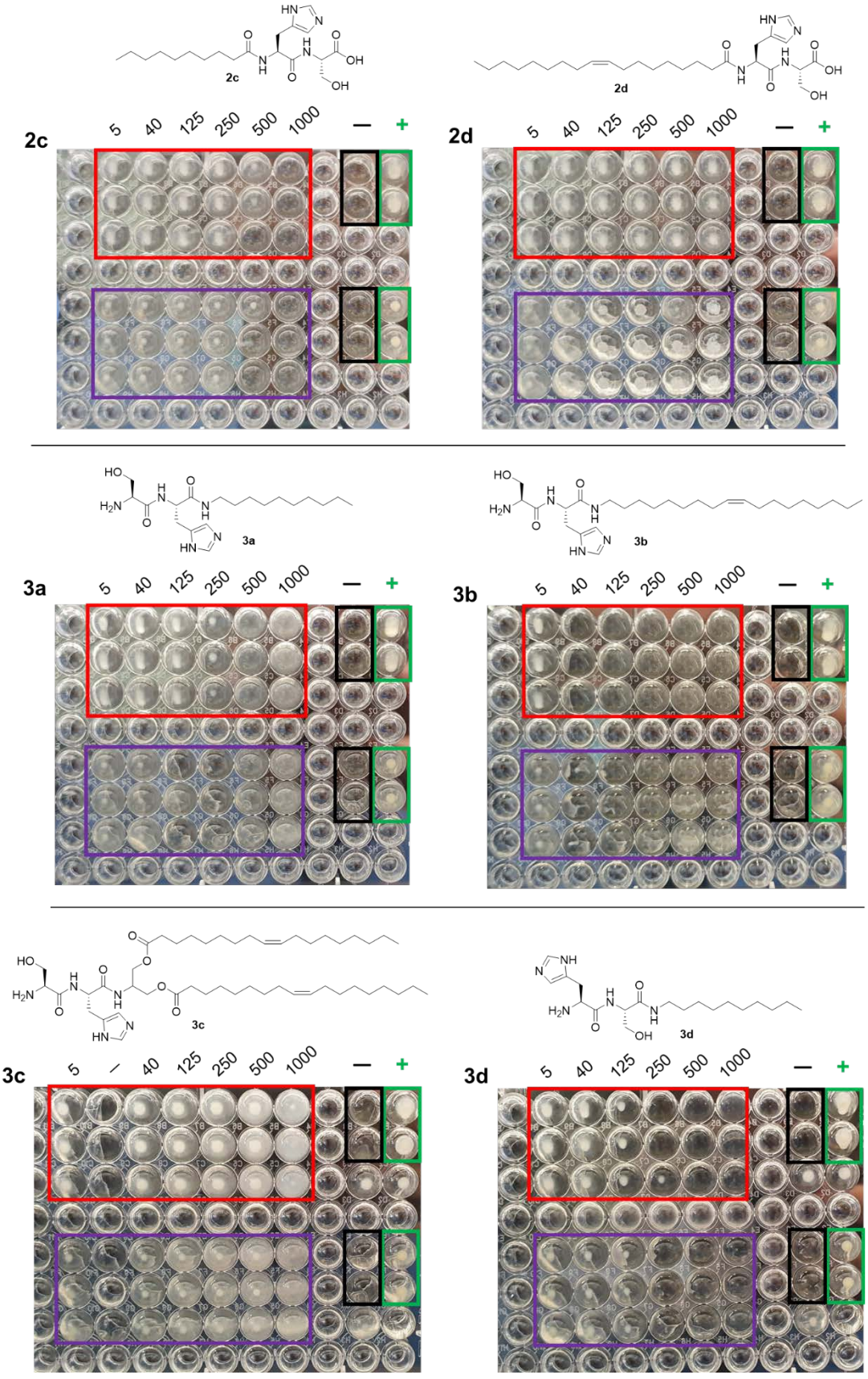


Figure S17: Antibacterial assays for lipodipeptides 2c-d and 3a-d.

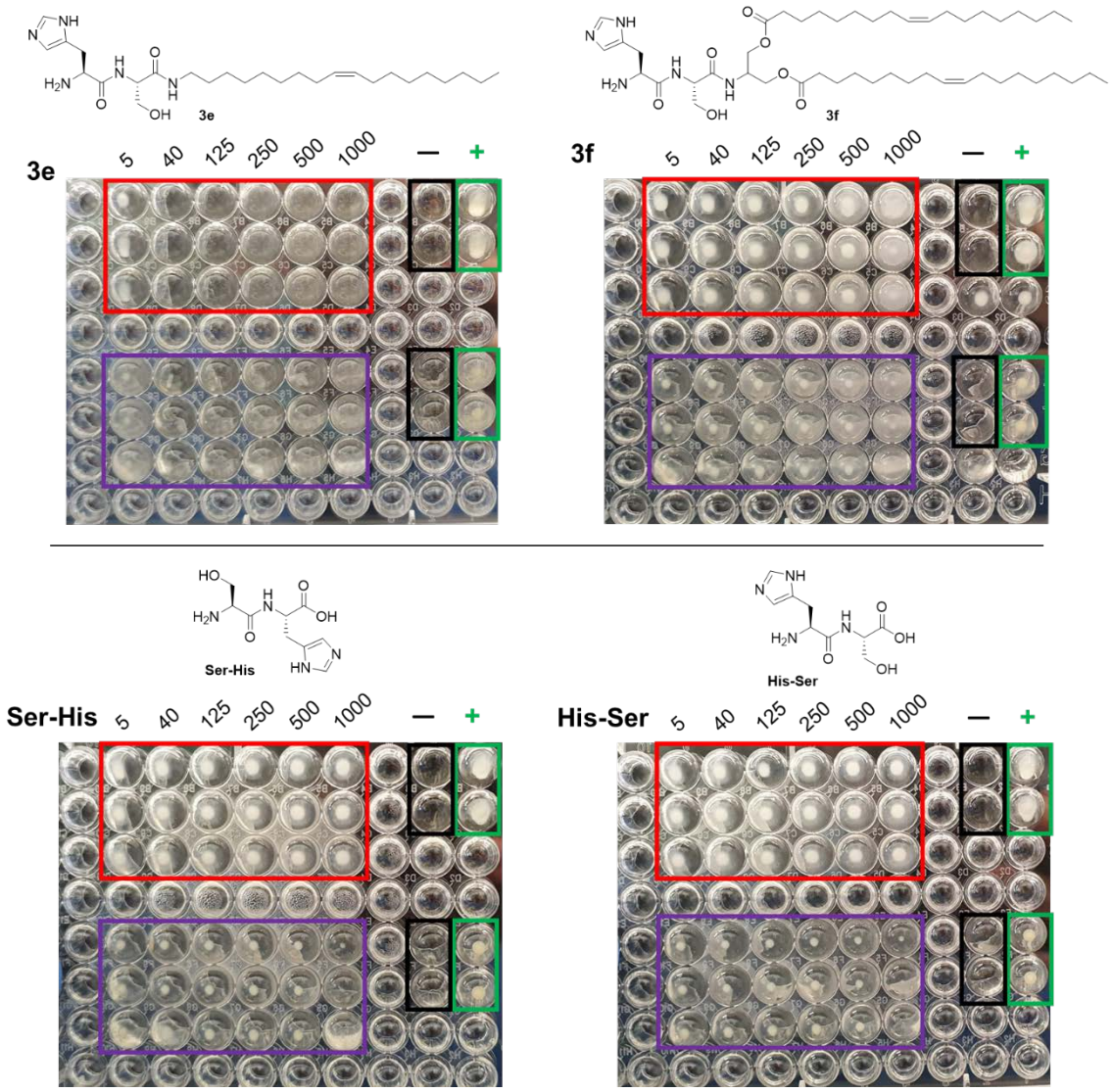


Figure S18: Antibacterial assays for lipodipeptides 3e-f and dipeptides Ser-His and His-Ser.

Non-lipidated Ser-His and His-Ser dipeptides were also tested for antibacterial activity, and were proved inactive against both strains (**Figure S16** and **Table S3**). All the antimicrobial data can be compared to those of a well-established antibiotic (Gentamicine), used against the same strains of both Gram – and Gram + bacteria (**Table S3**).[14,15]

	MIC (μg/mL) [a]	
Compound	***E. coli CECT 516***	***S. aureus CECT 240***
Ser-His	> 1000	1000
His-Ser	> 1000	1000
Gentamicin	4.0 [34a]	1.56 [34b]

[a] Minimum concentration that inhibits bacterial proliferation after overnight incubation.

Table S3: Antimicrobial data for non-lipidated dipeptides and antibiotic Gentamicin.

8. References.

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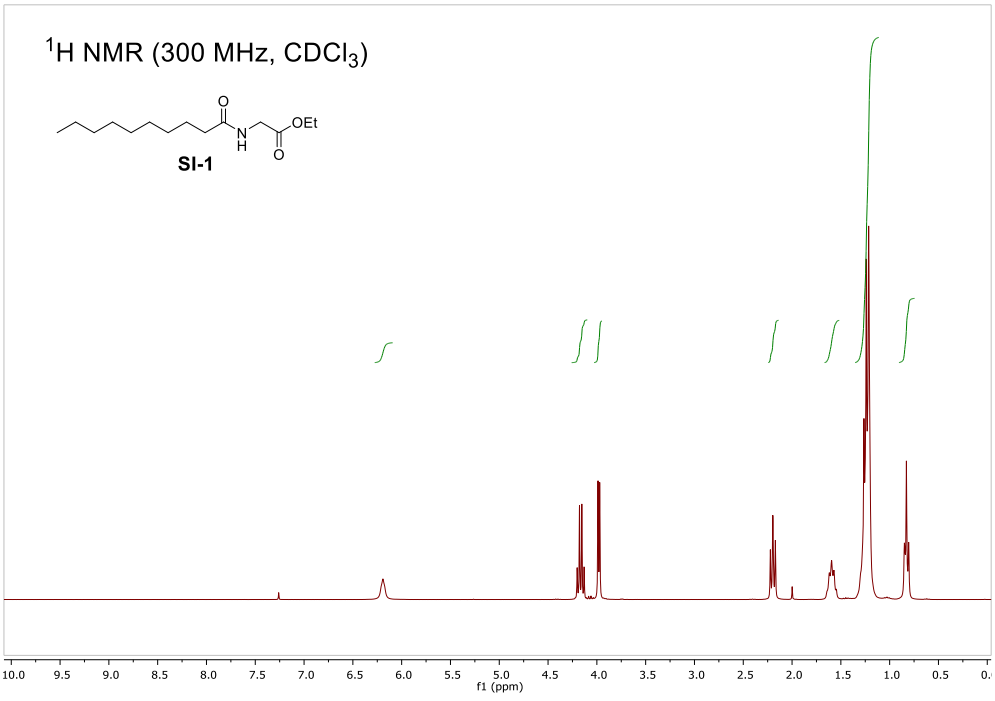
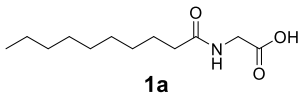
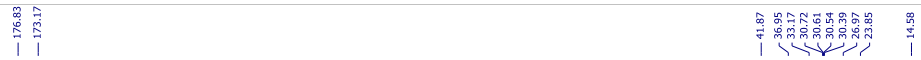
9. NMR spectra



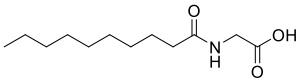
^{1}H NMR (300 MHz, CD_3OD)



1a

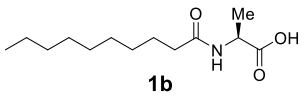


^{13}C NMR (75 MHz, MeOD)

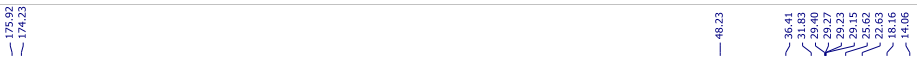


1a

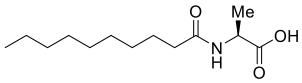
^{1}H NMR (300 MHz, $CDCl_3$)



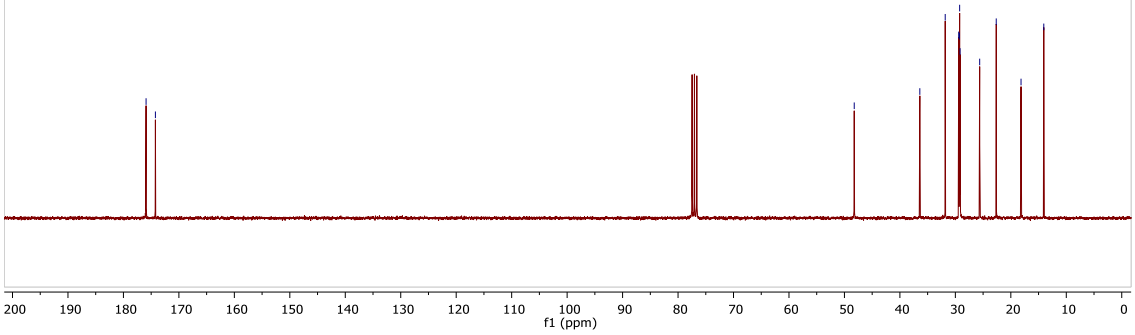
1b



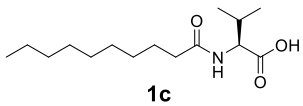
^{13}C NMR (75 MHz, $CDCl_3$)



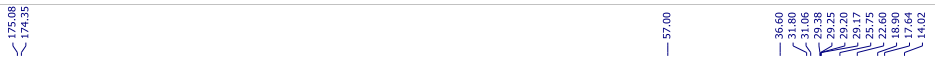
1b



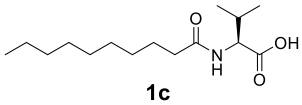
^{1}H NMR (300 MHz, $CDCl_3$)



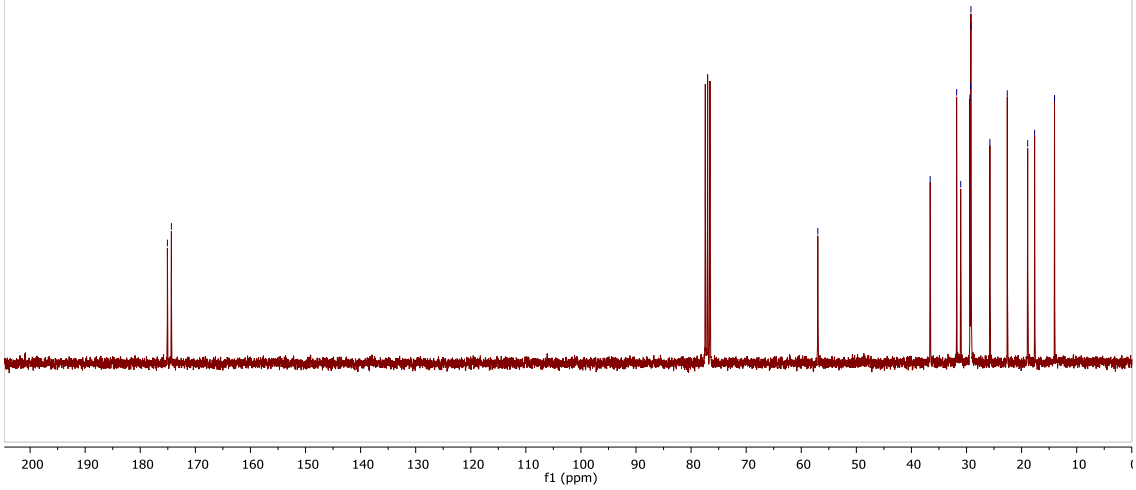
1c



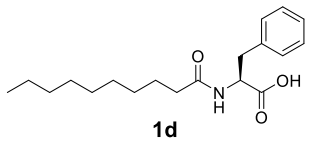
^{13}C NMR (75 MHz, $CDCl_3$)



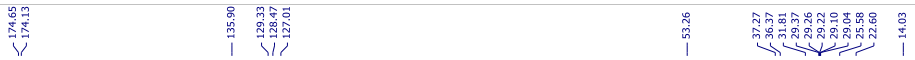
1c



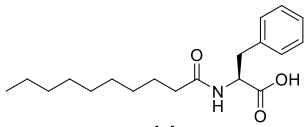
^{1}H NMR (300 MHz, $CDCl_3$)



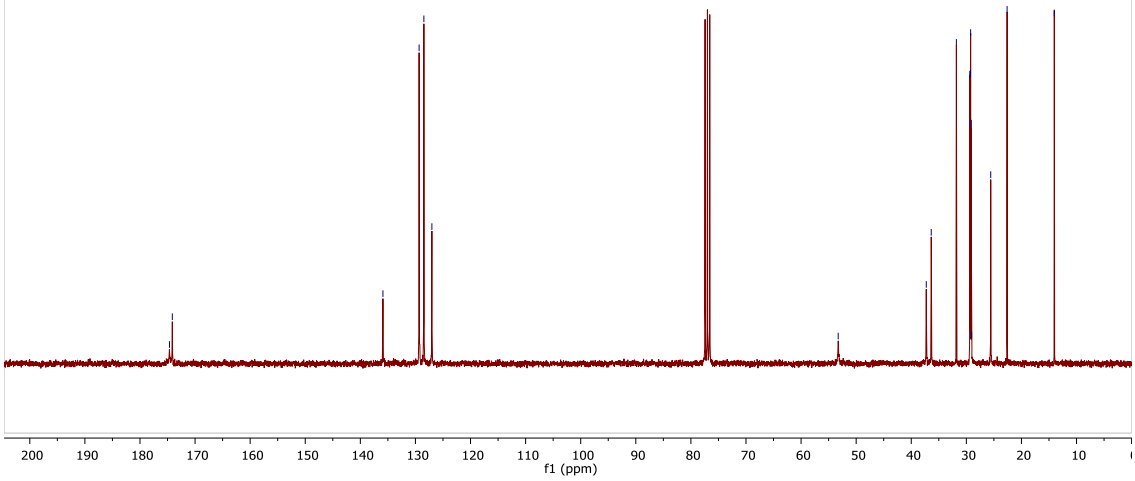
1d

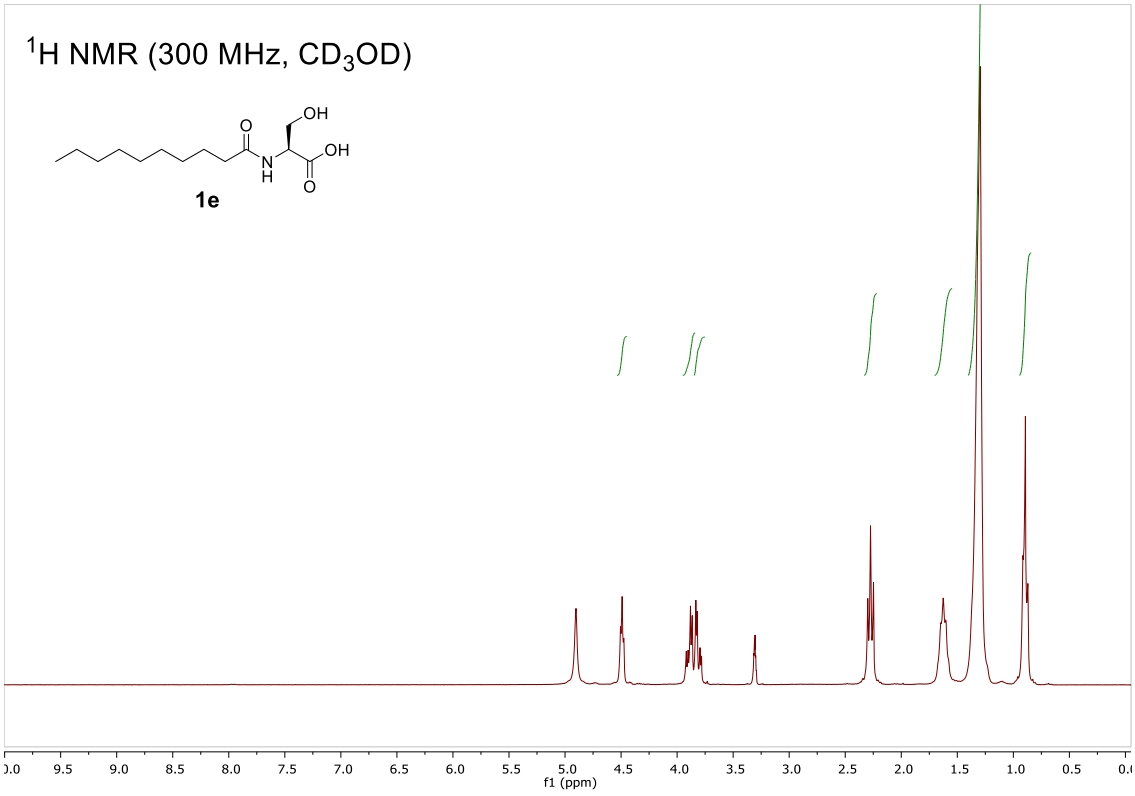


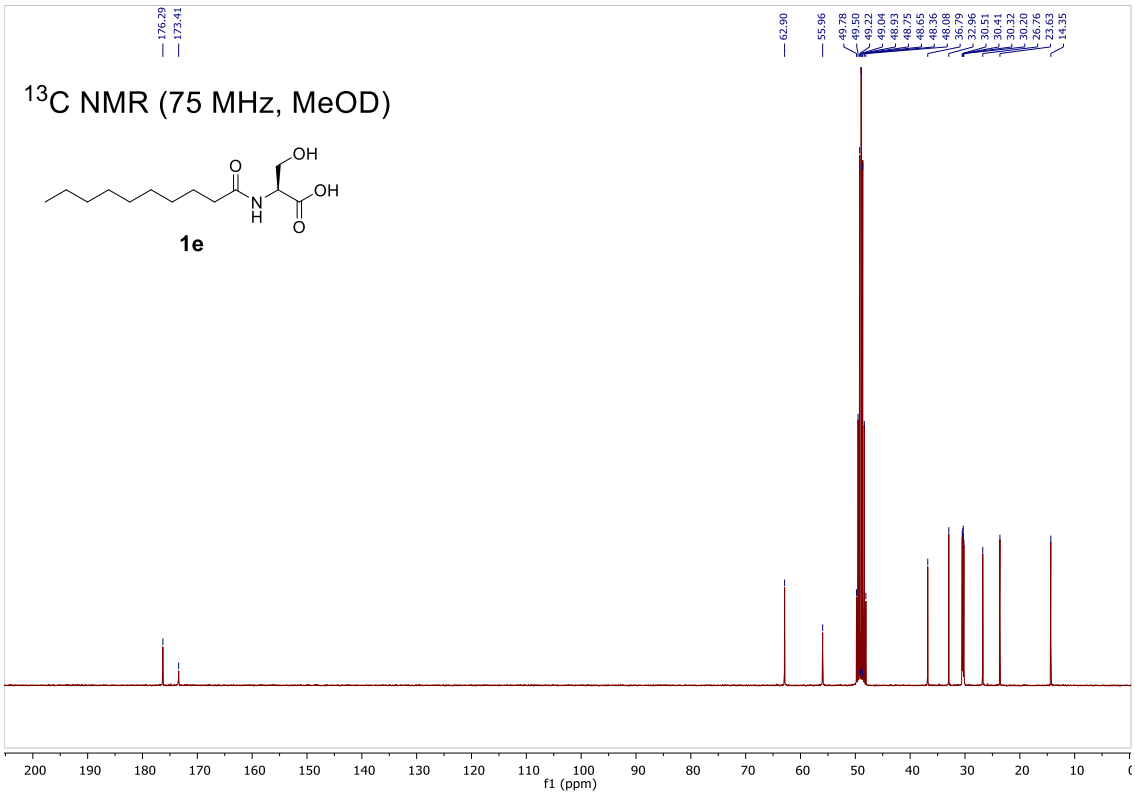
^{13}C NMR (75 MHz, $CDCl_3$)

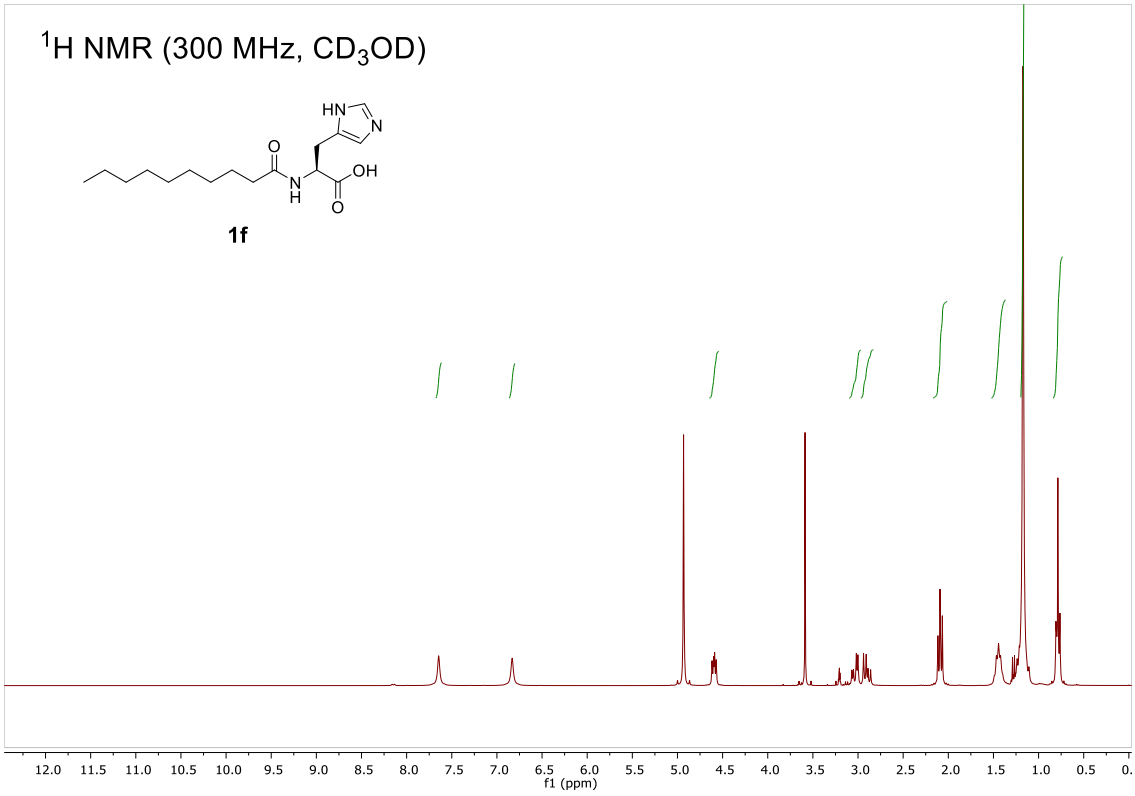


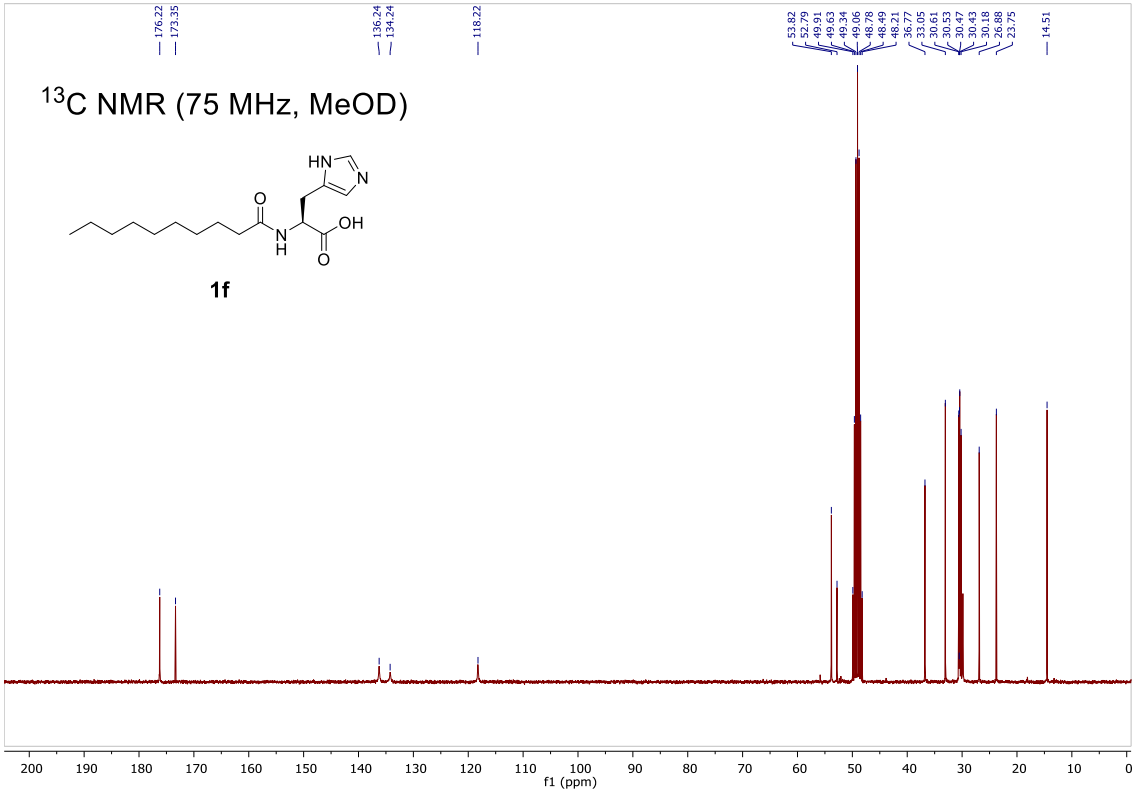
1d

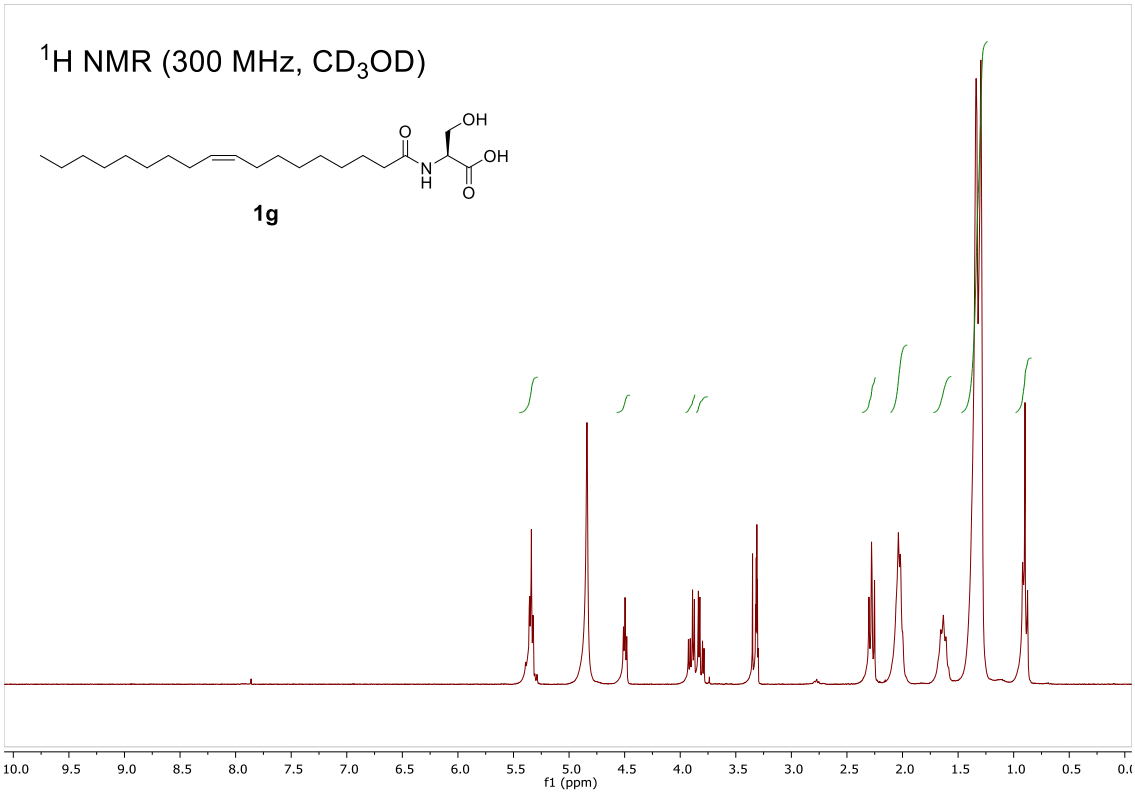


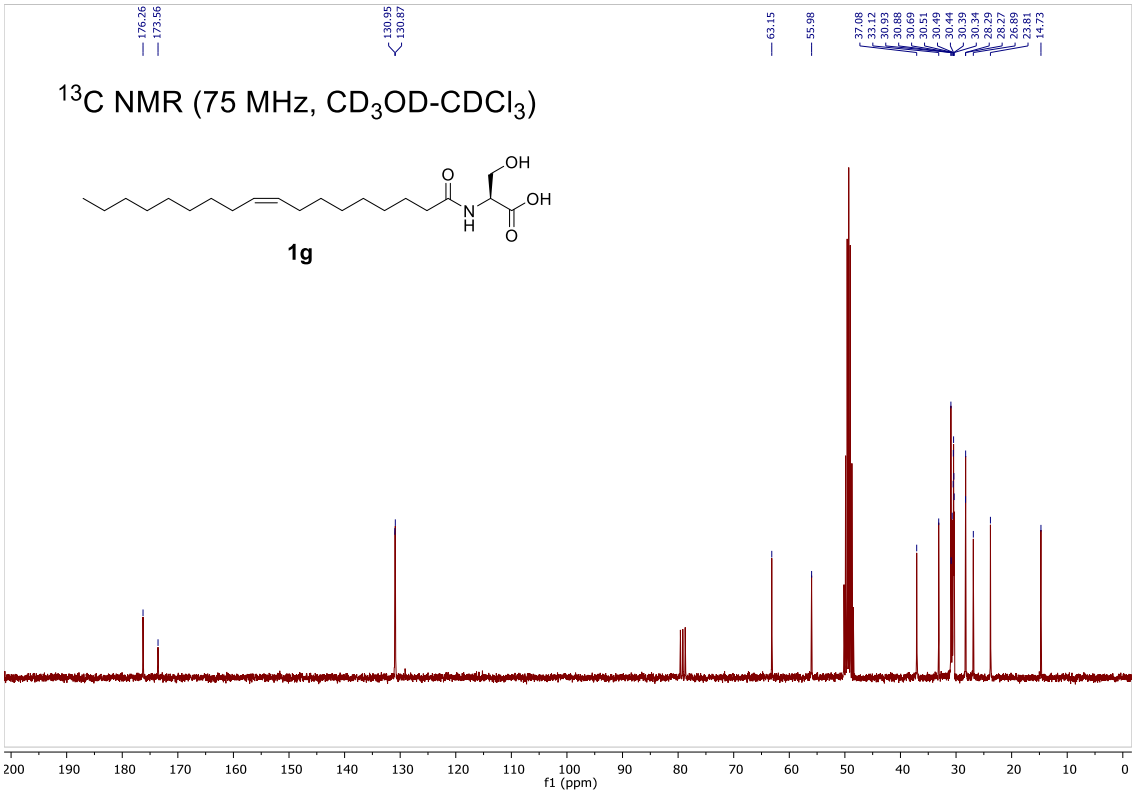

1H NMR (300 MHz, CD3OD)
OH
O
N
H
OH
O
1e
f1 (ppm)

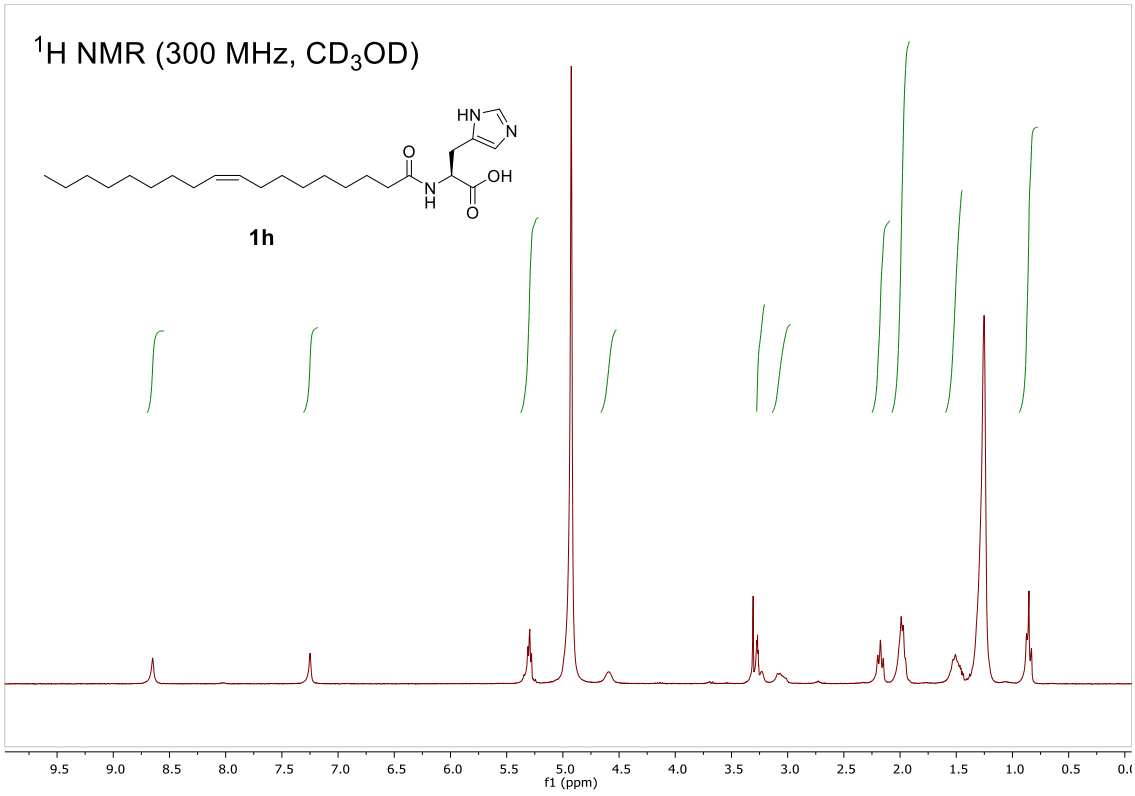

176.29
173.41
62.90
55.96
49.78
49.50
49.22
49.04
48.93
48.75
48.65
48.36
48.08
36.79
32.96
30.51
30.41
30.32
30.20
26.76
23.63
14.35
13C NMR (75 MHz, MeOD)
OH
O
N
H
OH
O
1e
f1 (ppm)

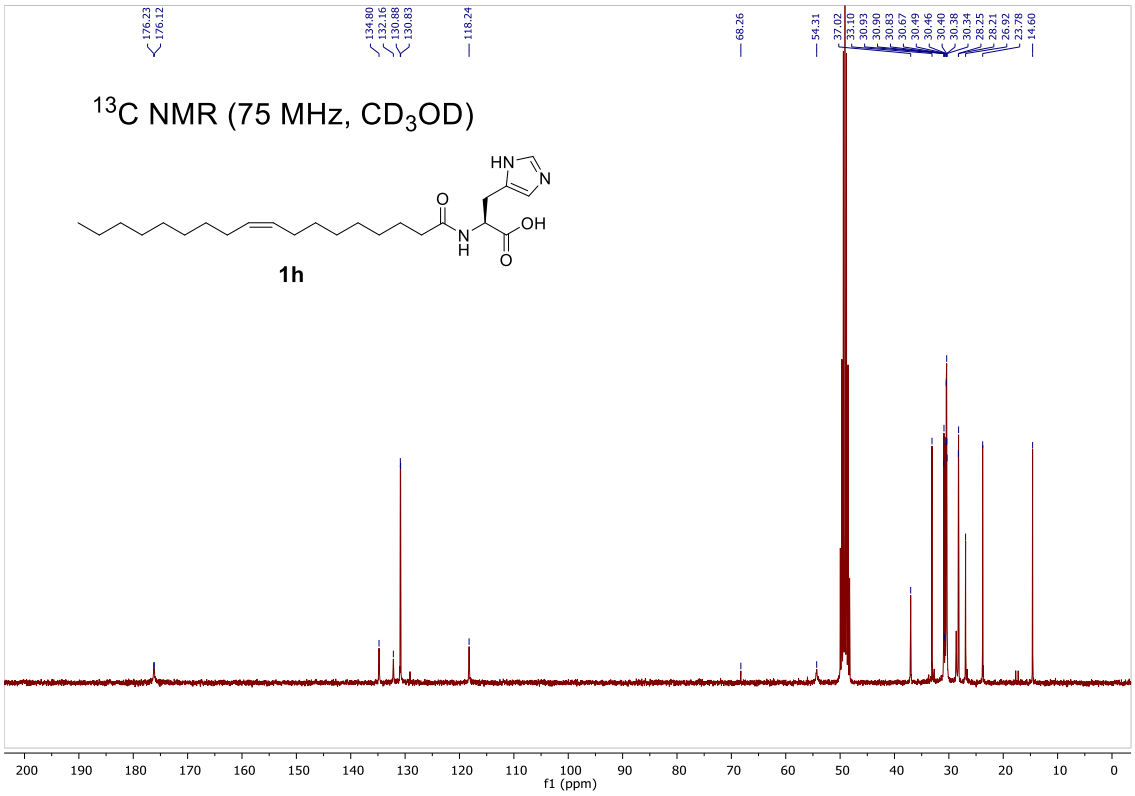

^{1}H NMR (300 MHz, CD_3OD)
HN
N
O
N
H
OH
O
1f
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)

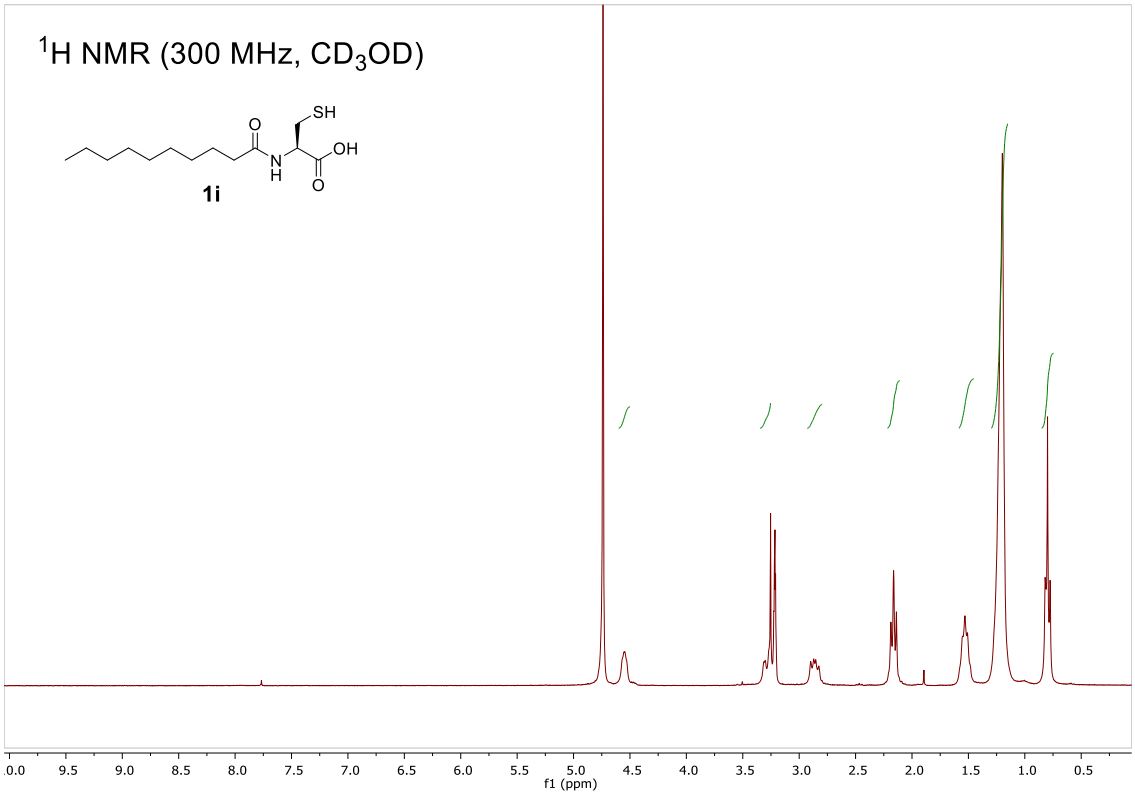

176.22
173.35
136.24
134.24
118.22
53.82
52.79
49.91
49.63
49.34
49.06
48.78
48.49
48.21
36.77
33.05
30.61
30.53
30.47
30.43
30.18
26.88
23.75
14.51
^{13}C NMR (75 MHz, MeOD)
HN
N
O
N
H
OH
O
1f
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

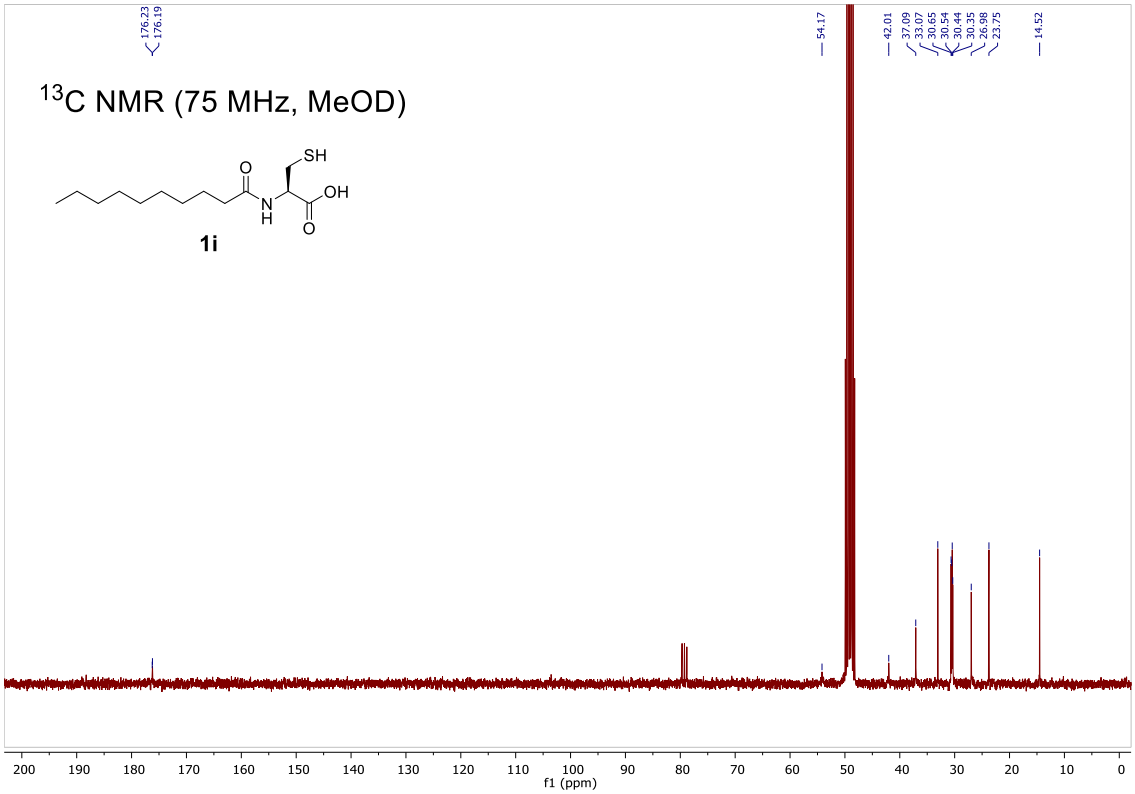

1H NMR (300 MHz, CD3OD)
OH
O
N
H
OH
O
1g
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

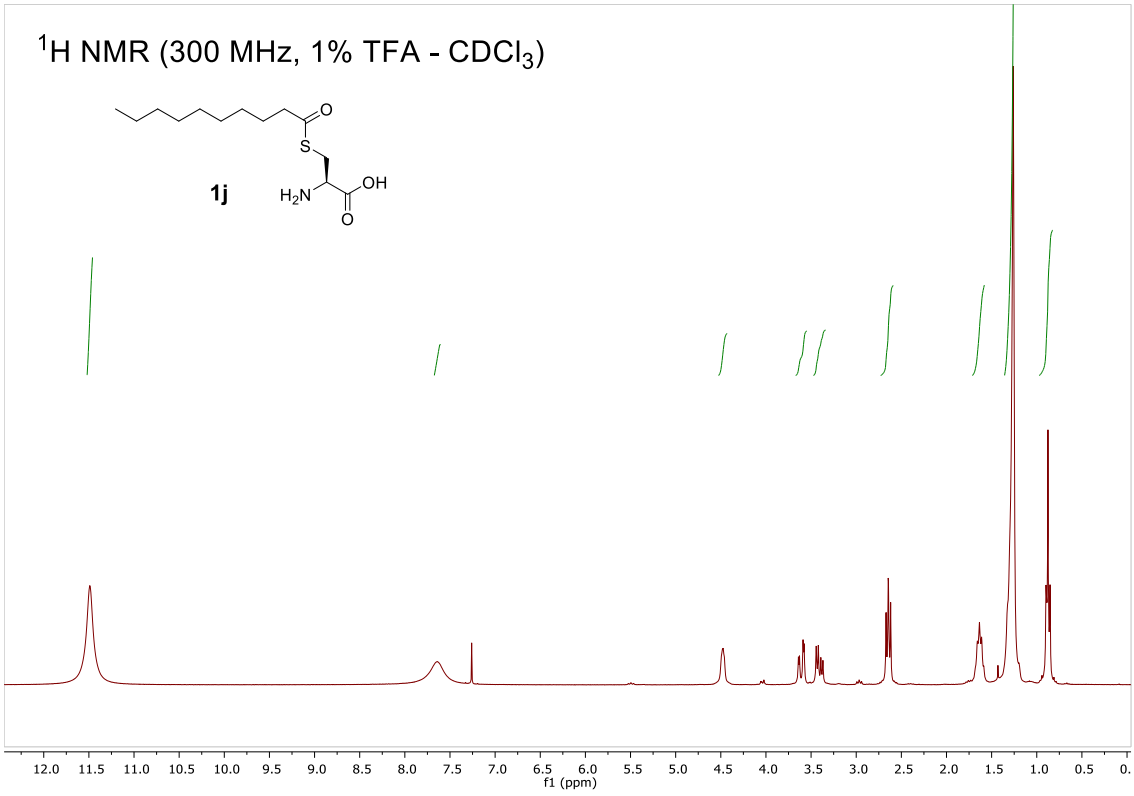

176.26
173.56
130.95
130.87
63.15
55.98
37.08
33.12
30.93
30.88
30.69
30.51
30.49
30.44
30.39
30.34
28.29
28.27
26.89
23.81
14.73
13C NMR (75 MHz, CD3OD-CDCl3)
OH
O
N
H
OH
O
1g
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

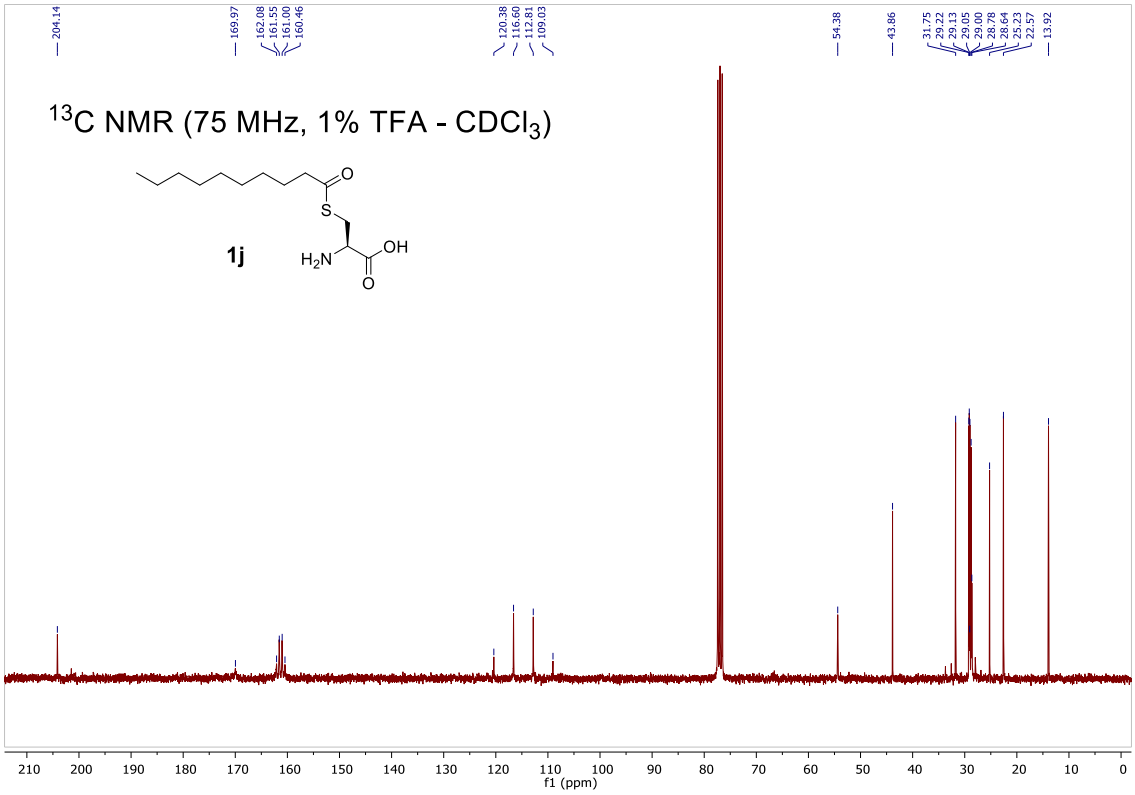

^{1}H NMR (300 MHz, CD_3OD)
HN
N
O
N
H
OH
O
1h
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

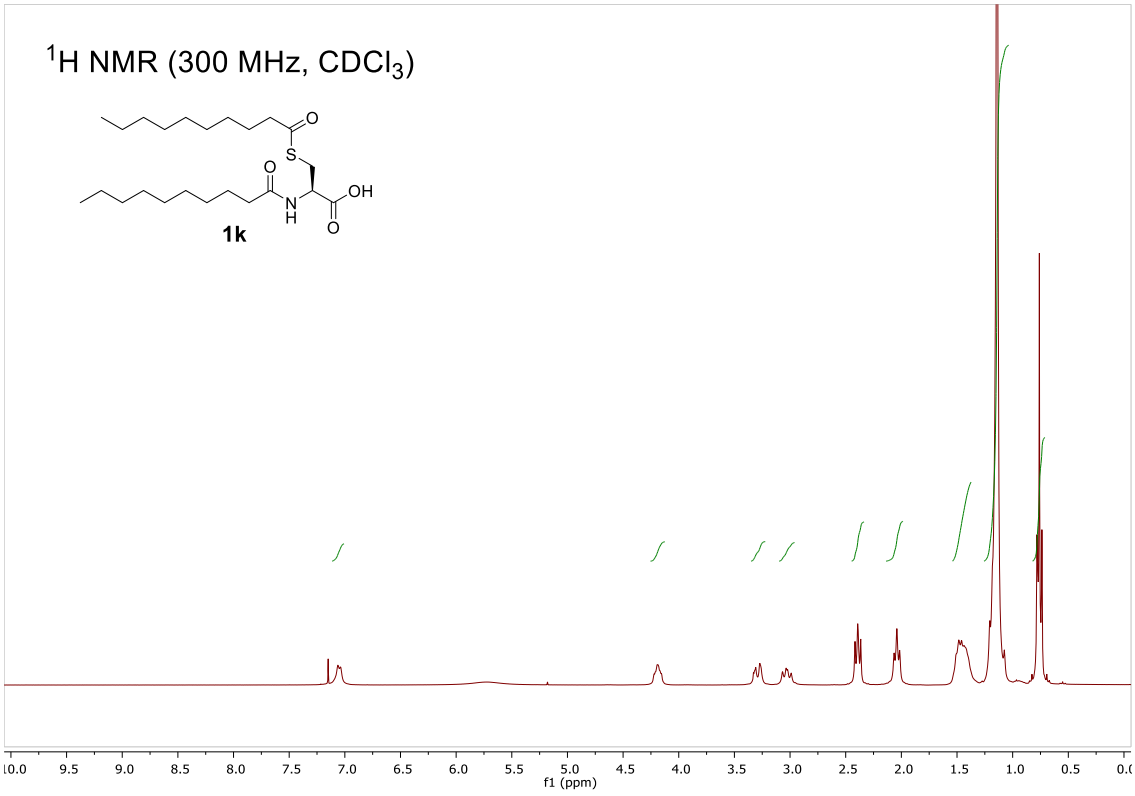

176.23
176.12
134.80
132.16
130.88
130.83
118.24
68.26
54.31
37.02
33.10
30.93
30.90
30.83
30.67
30.49
30.46
30.40
30.38
30.34
28.25
28.21
25.92
23.78
14.60
^{13}C NMR (75 MHz, CD_3OD)
HN
N
O
N
H
OH
O
1h
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

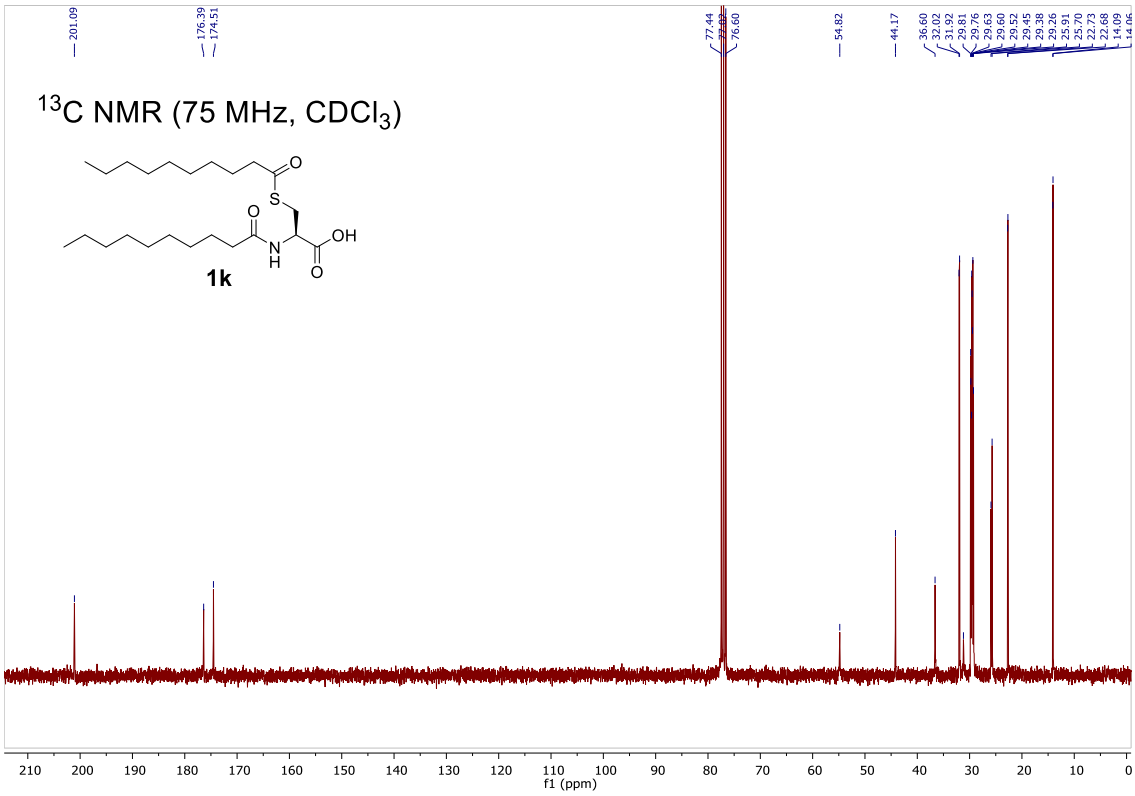

^{1}H NMR (300 MHz, CD_3OD)
SH
O
OH
N
H
O
1i
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

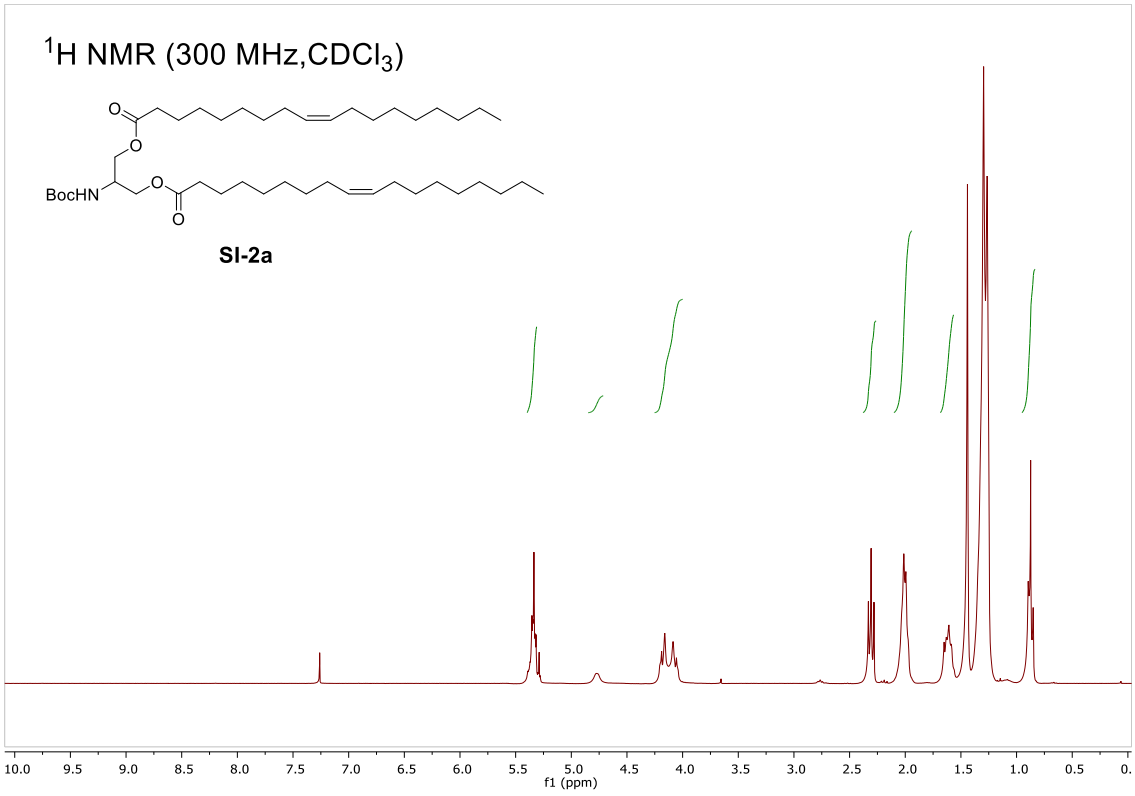

176.23
176.19
54.17
42.01
37.09
33.07
30.65
30.54
30.44
30.35
26.98
23.75
14.52
^{13}C NMR (75 MHz, MeOD)
SH
O
OH
N
H
O
1i
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

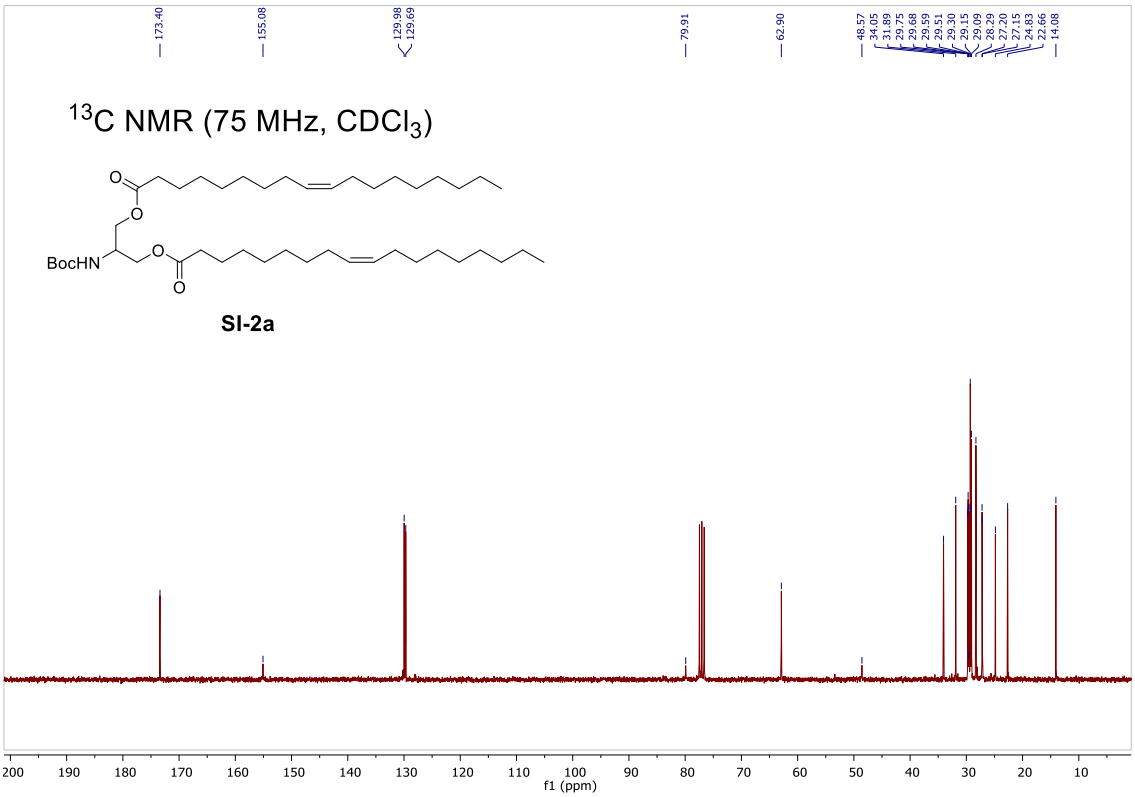

^{1}H NMR (300 MHz, 1% TFA - $CDCl_3$)
1j
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)


204.14
169.97
162.08
161.55
161.00
160.46
120.38
115.60
112.81
109.03
54.38
43.86
31.75
29.22
29.13
29.05
29.00
28.79
28.64
25.23
22.57
13.92
^{13}C NMR (75 MHz, 1% TFA - $CDCl_3$)
1j
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

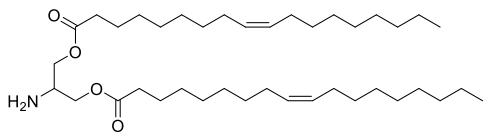

^{1}H NMR (300 MHz, $CDCl_3$)
1k
f1 (ppm)


^{13}C NMR (75 MHz, $CDCl_3$)
1k
f1 (ppm)

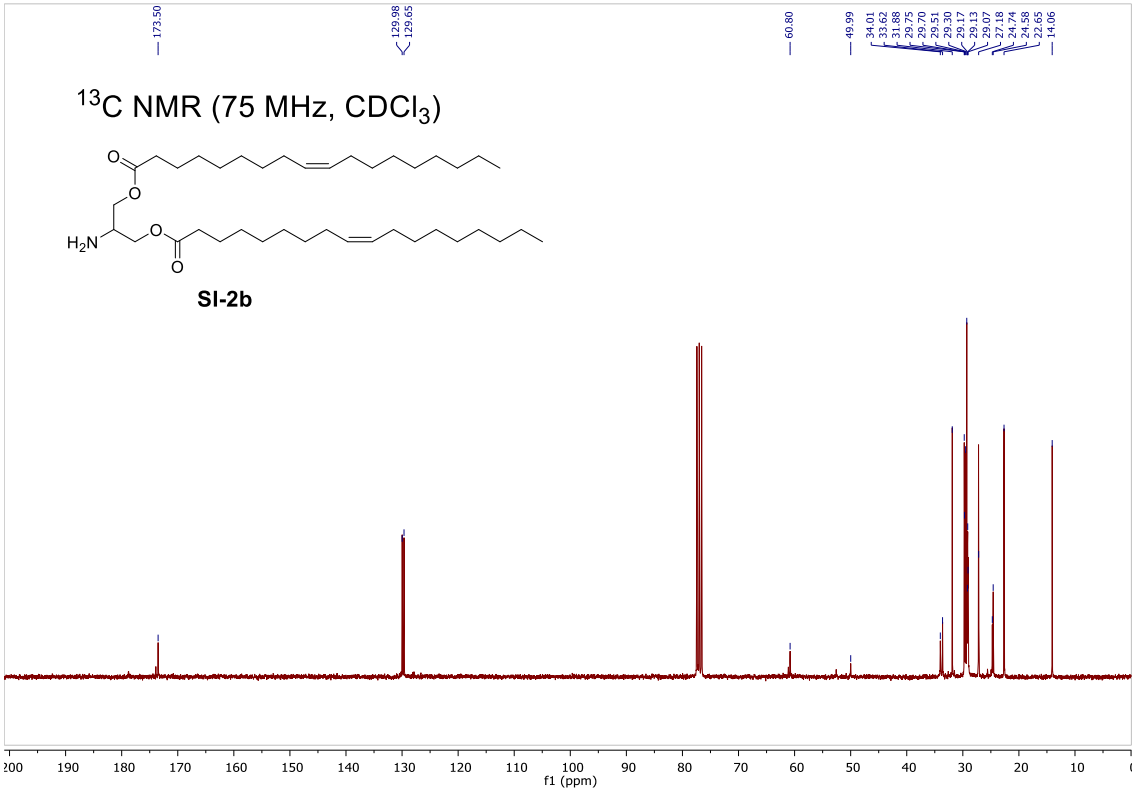

^{1}H NMR (300 MHz,$CDCl_3$)
BocHN
SI-2a
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)


173.40
155.08
129.98
129.69
79.91
62.90
48.57
34.05
31.89
29.75
29.68
29.59
29.51
29.30
29.15
29.09
28.29
27.20
27.15
24.83
22.66
14.08
^{13}C NMR (75 MHz, $CDCl_3$)
BocHN
SI-2a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

^{1}H NMR (300 MHz,$CDCl_3$)



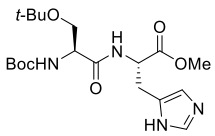
SI-2b



^{13}C NMR (75 MHz, $CDCl_3$)

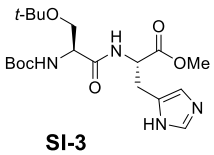
SI-2b

^{1}H NMR (300 MHz, CD_3OD)



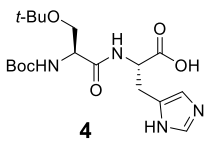
SI-3

^{13}C NMR (75 MHz, CD_3OD)



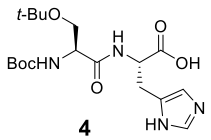
SI-3

^{1}H NMR (300 MHz, CD_3OD)



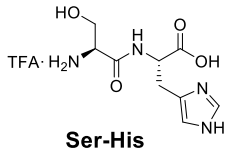
4

^{13}C NMR (75 MHz, CD_3OD)

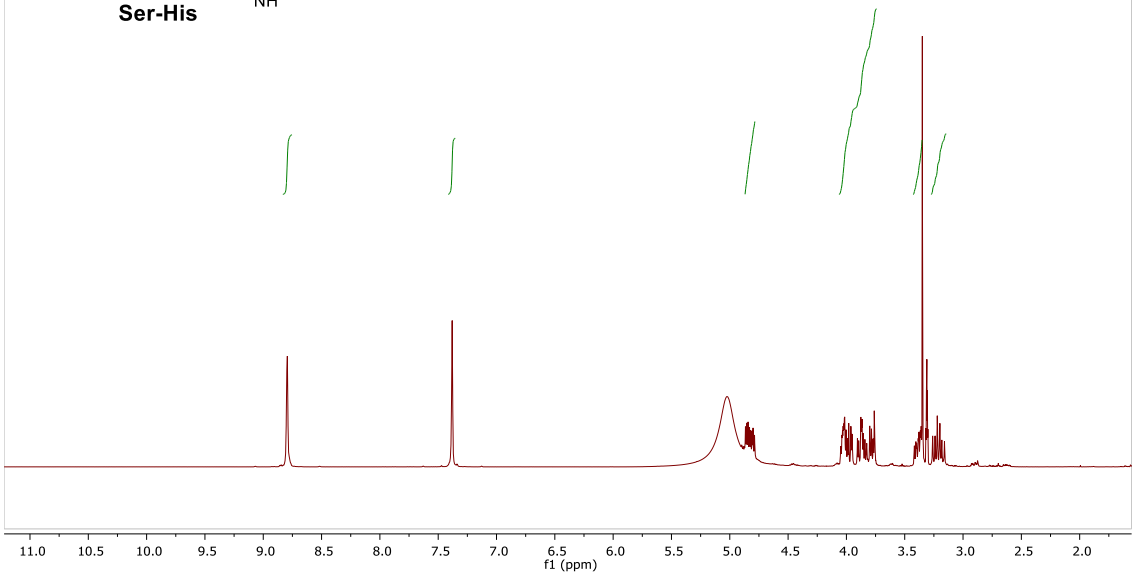


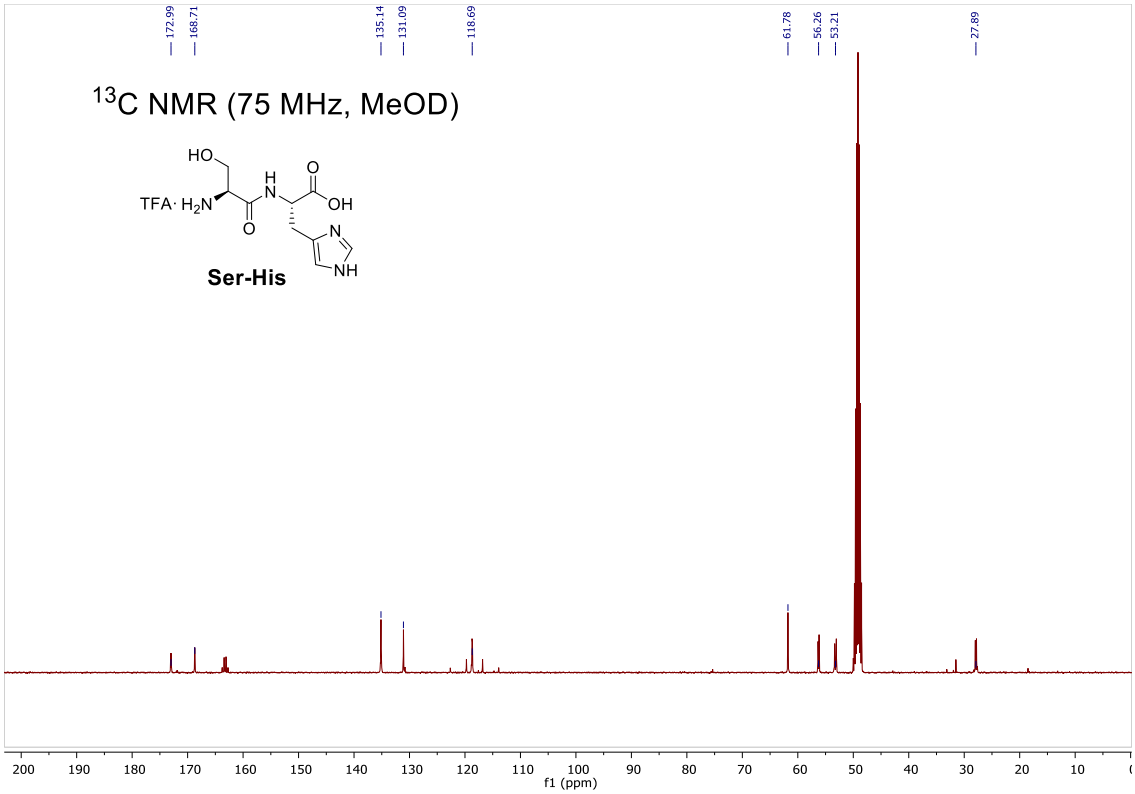
4

^{1}H NMR (300 MHz,MeOD)



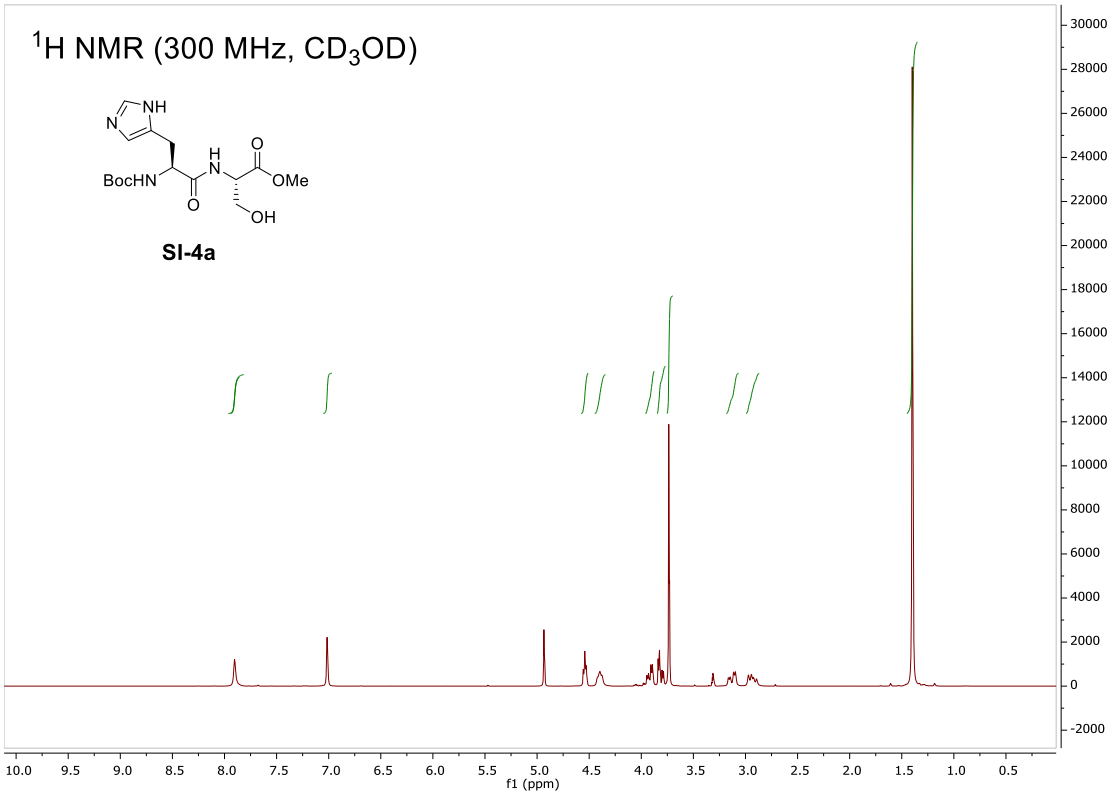
Ser-His

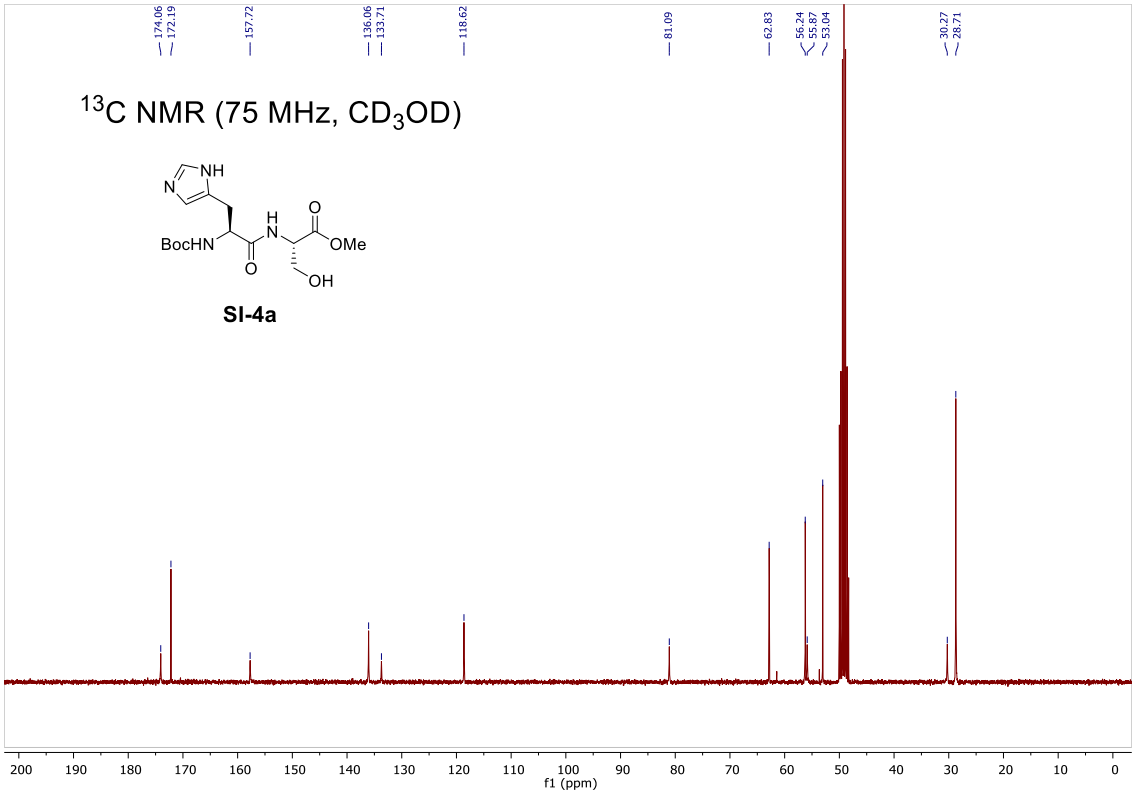


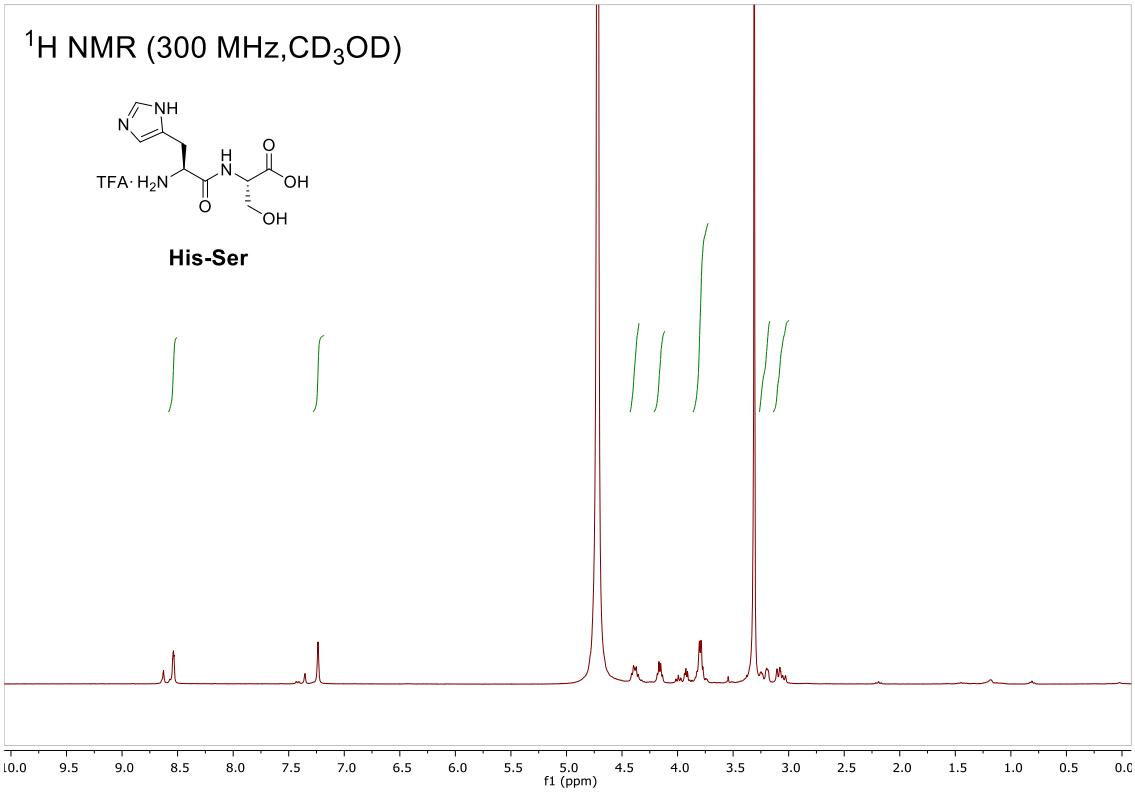


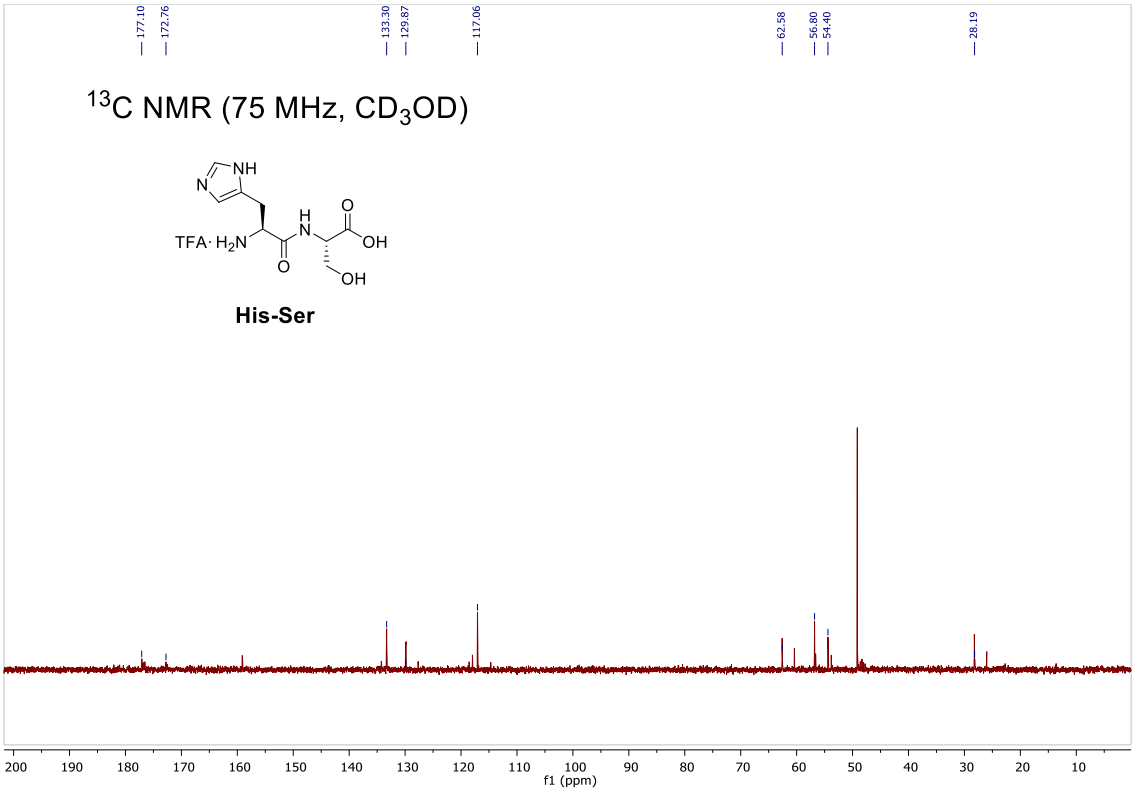
^{13}C NMR (75 MHz, MeOD)

Ser-His

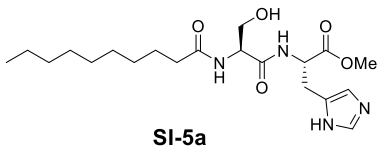

1H NMR (300 MHz, CD3OD)
NH
N
H
N
O
BocHN
O
OMe
OH
SI-4a
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


174.06
172.19
157.72
136.06
133.71
118.62
81.09
62.83
56.24
55.87
53.04
30.27
28.71
13C NMR (75 MHz, CD3OD)
NH
N
H
N
O
BocHN
O
OMe
OH
SI-4a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

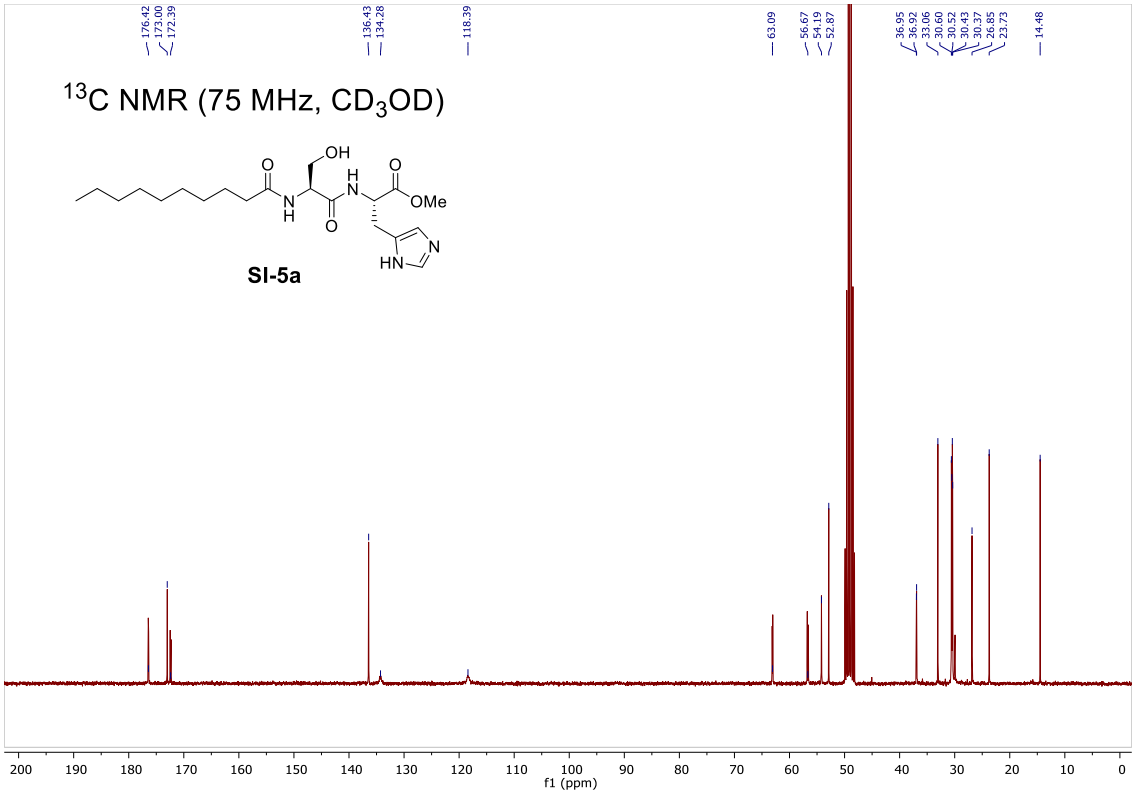

1H NMR (300 MHz,CD3OD)
TFA· H2N
His-Ser
f1 (ppm)


177.10
172.76
133.30
129.87
117.06
62.58
56.80
54.40
28.19
13C NMR (75 MHz, CD3OD)
TFA· H2N
His-Ser
f1 (ppm)

^{1}H NMR (300 MHz,MeOD)

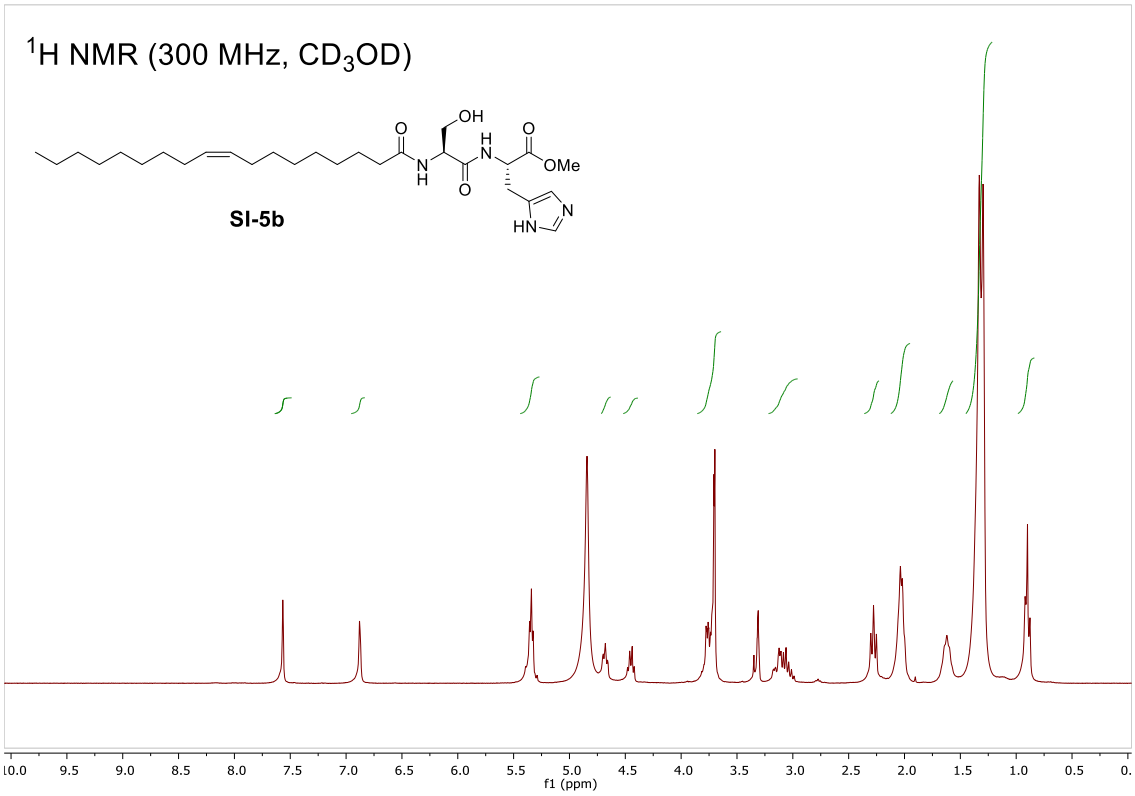


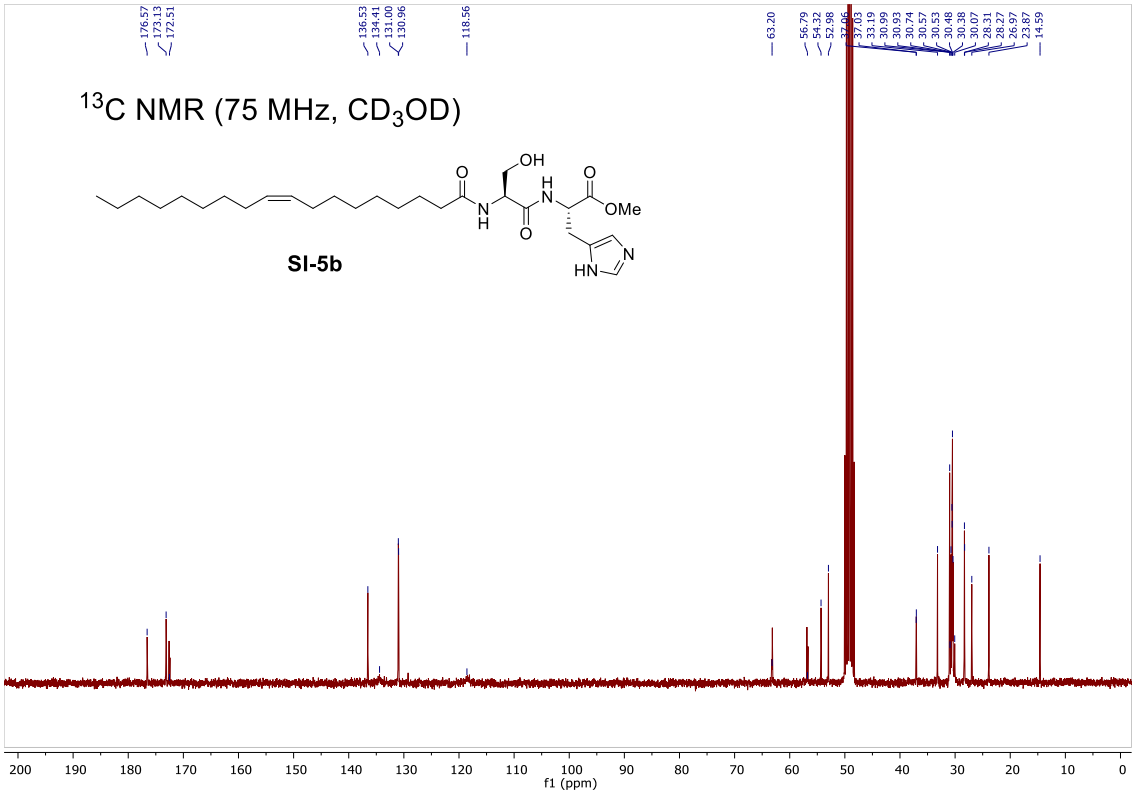
SI-5a



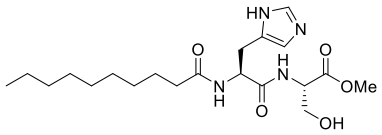
^{13}C NMR (75 MHz, CD_3OD)

SI-5a

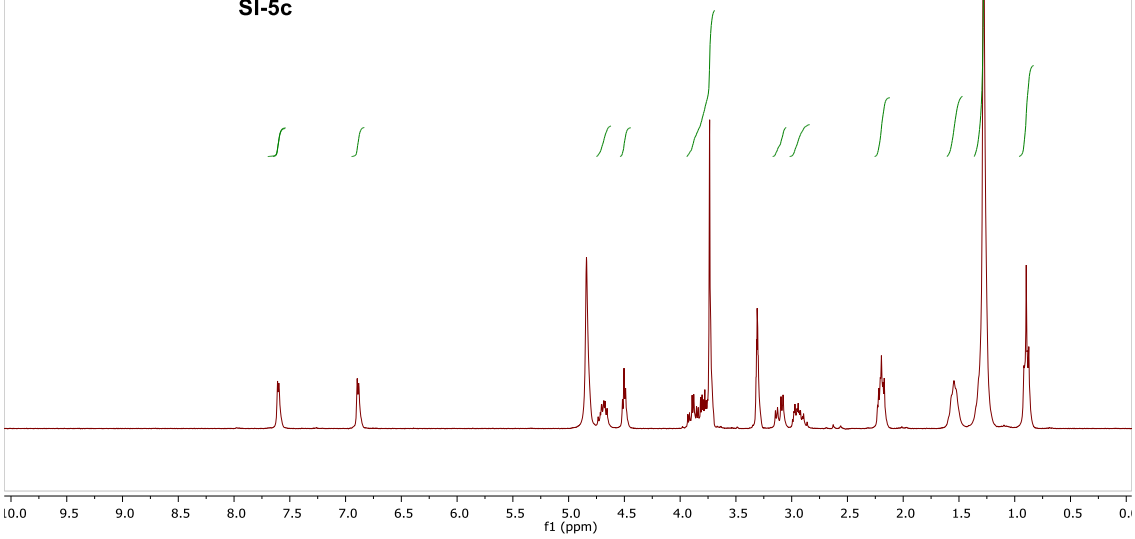

1H NMR (300 MHz, CD3OD)
SI-5b
f1 (ppm)

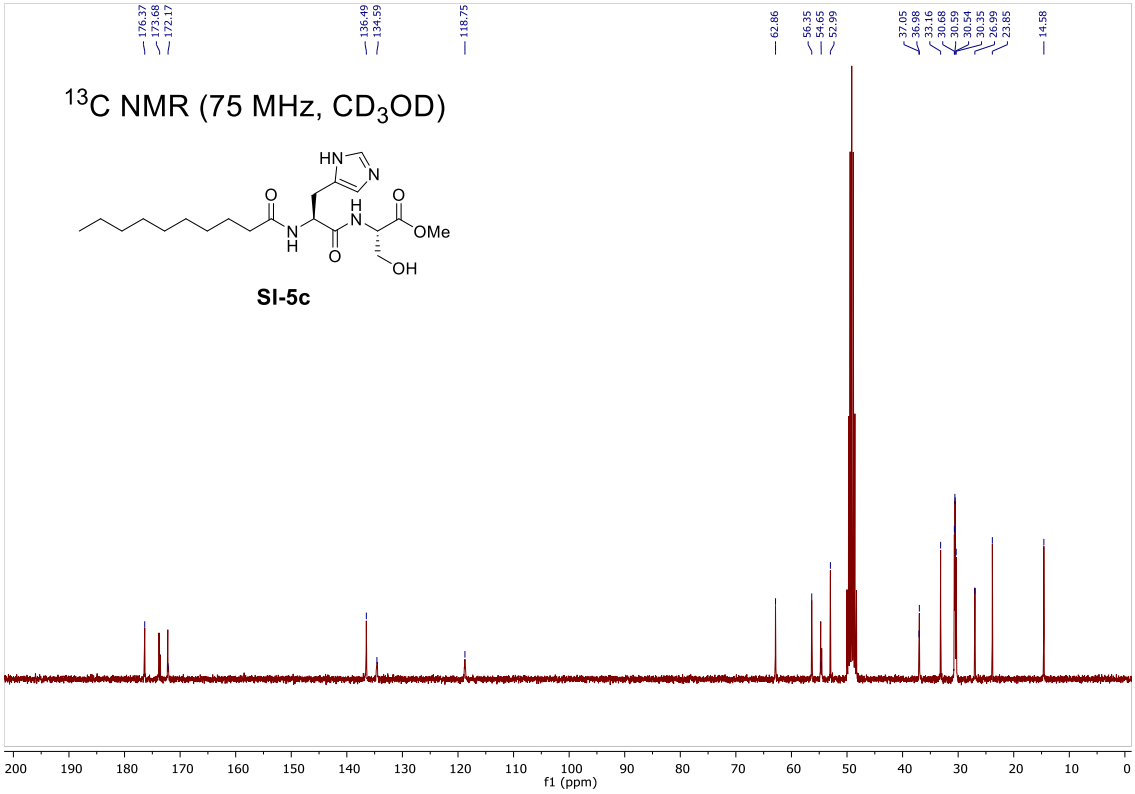

13C NMR (75 MHz, CD3OD)
SI-5b
f1 (ppm)

^{1}H NMR (300 MHz, CD_3OD)



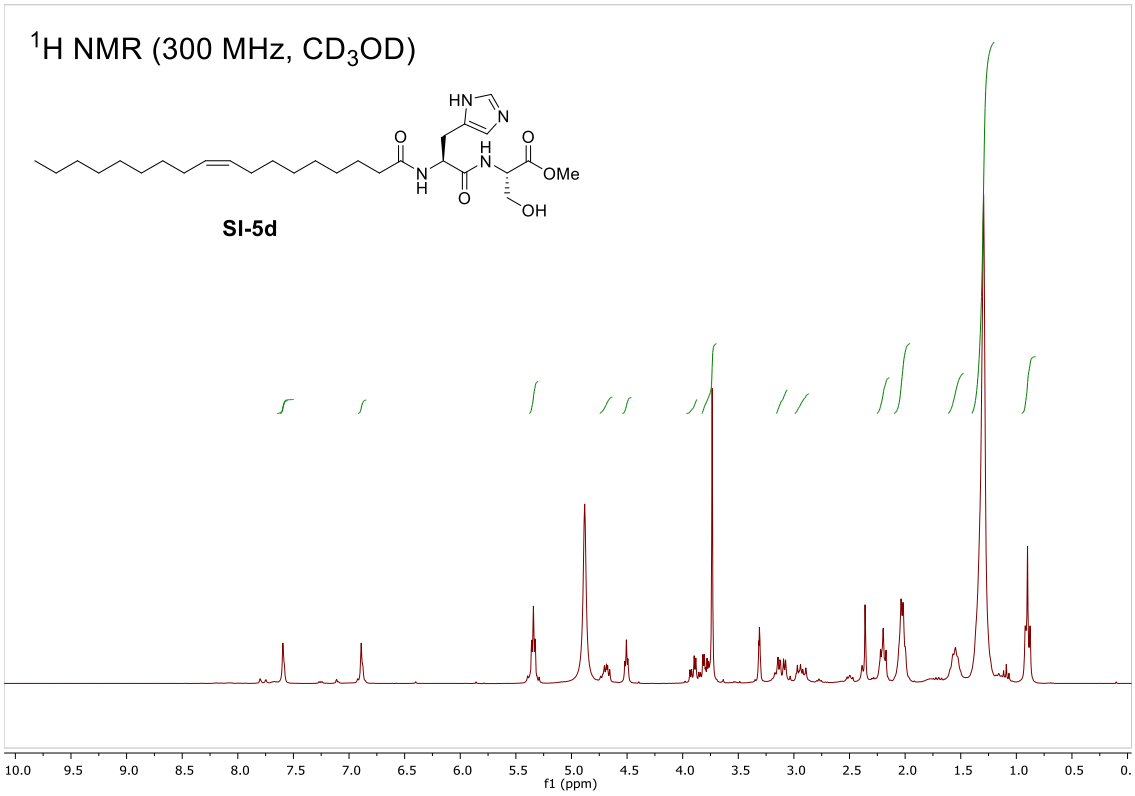
SI-5c

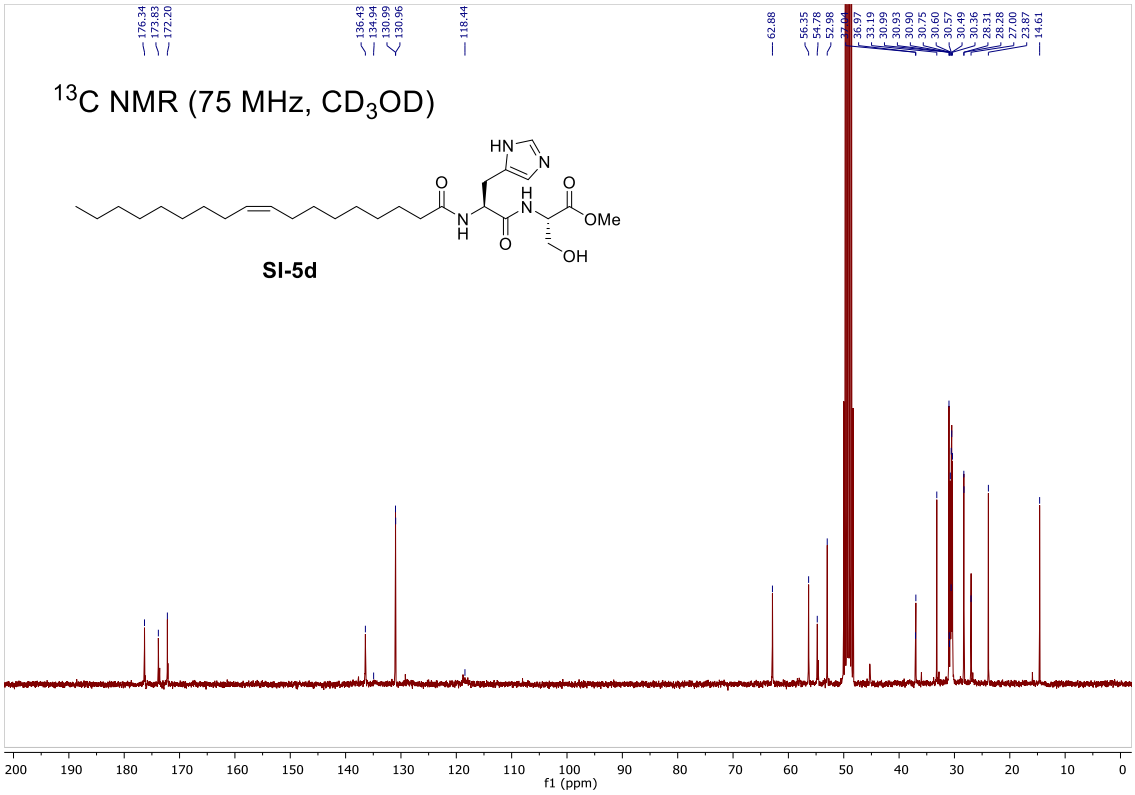


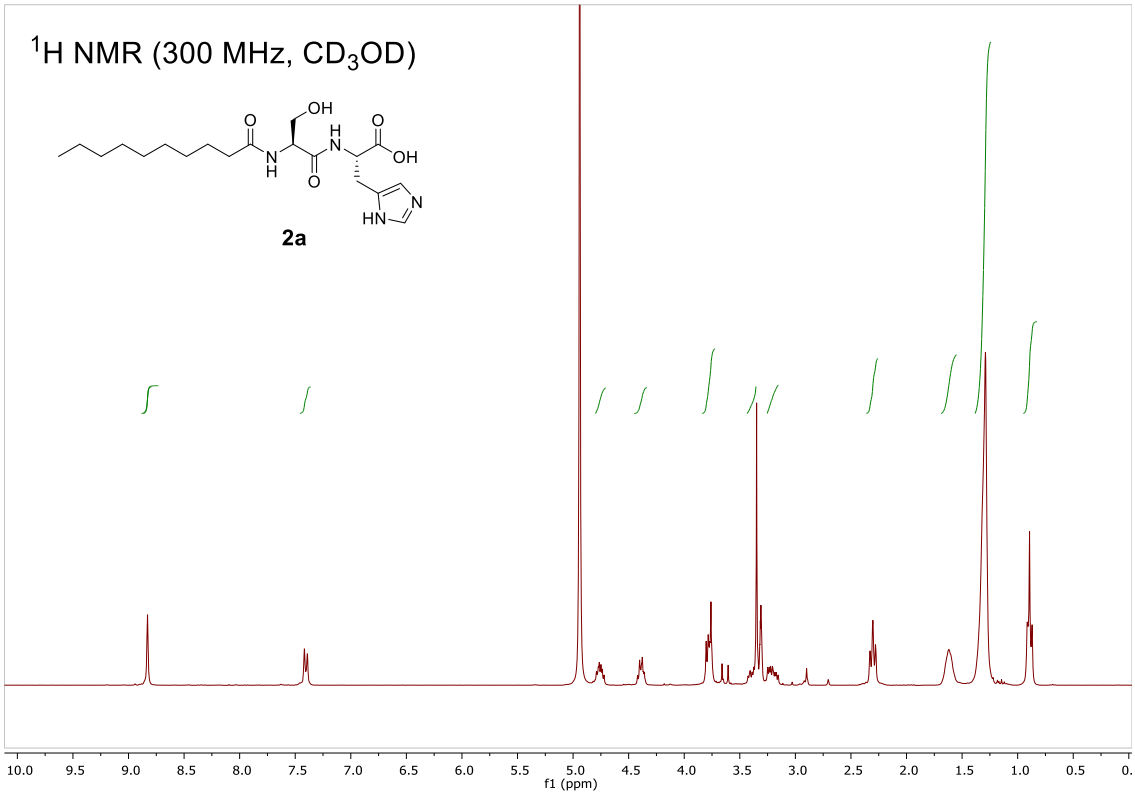


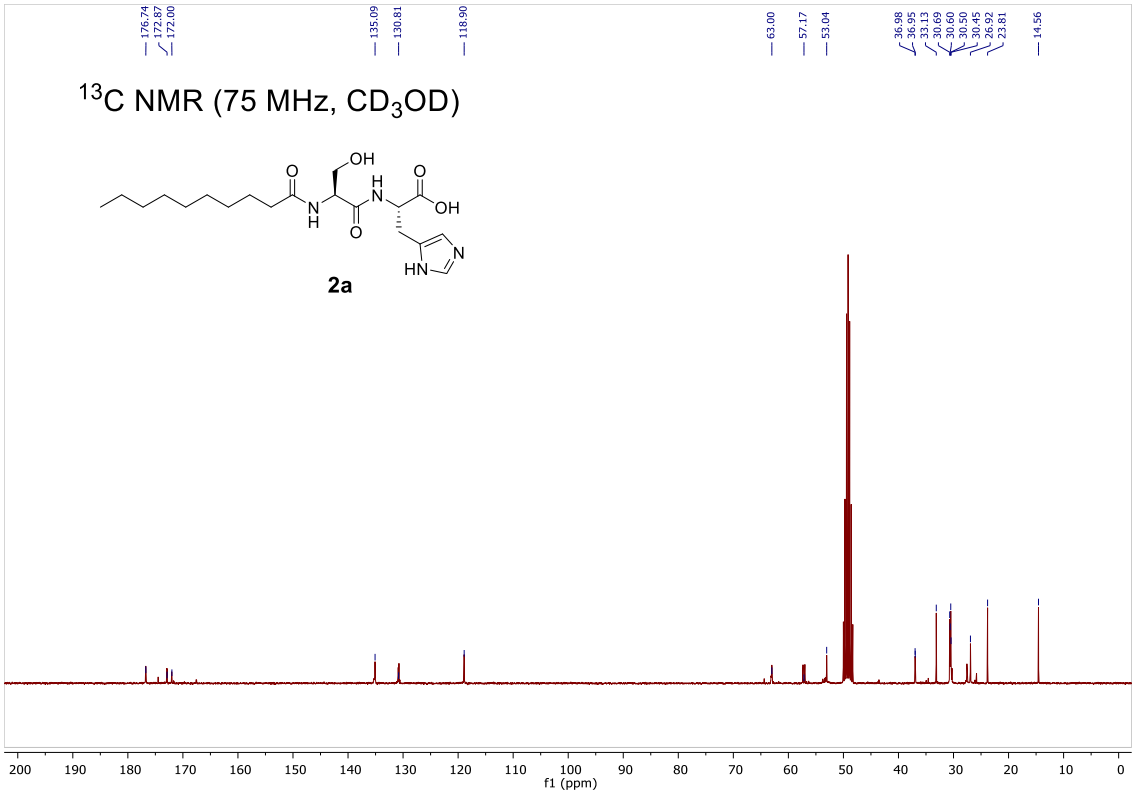
^{13}C NMR (75 MHz, CD_3OD)

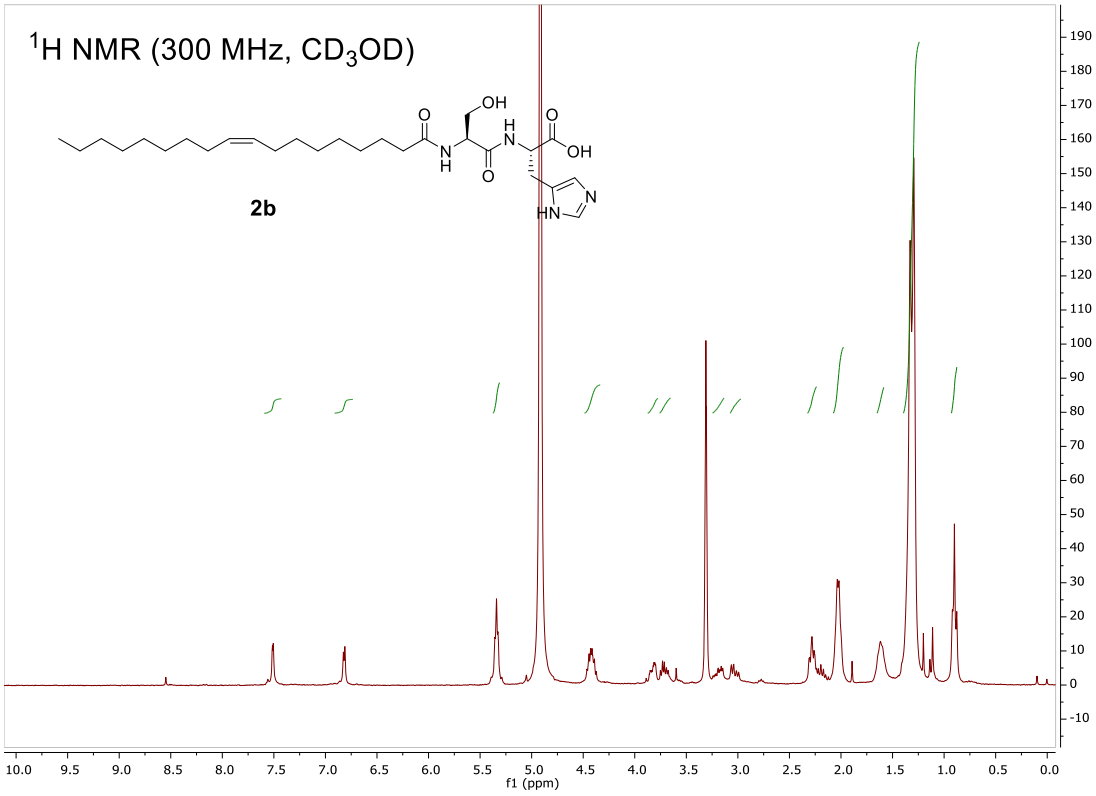
SI-5c

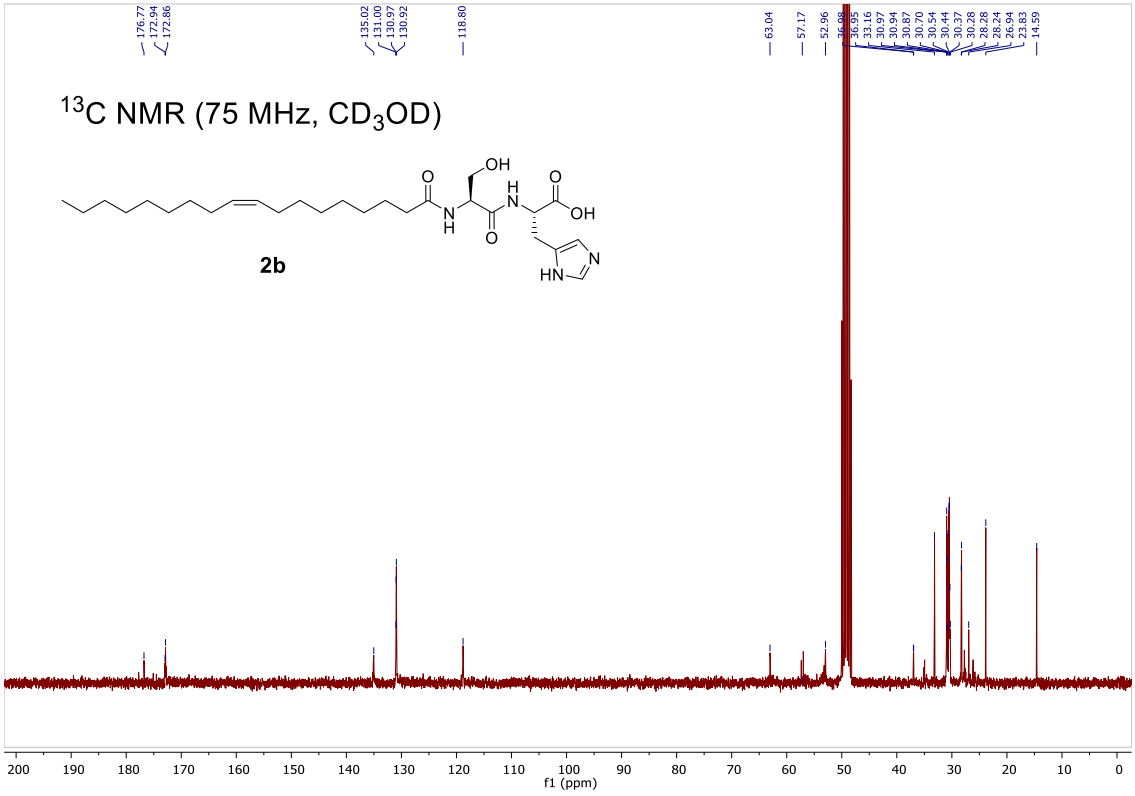

1H NMR (300 MHz, CD3OD)
HN
N
O
N
H
H
N
O
O
OMe
O
OH
SI-5d
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)

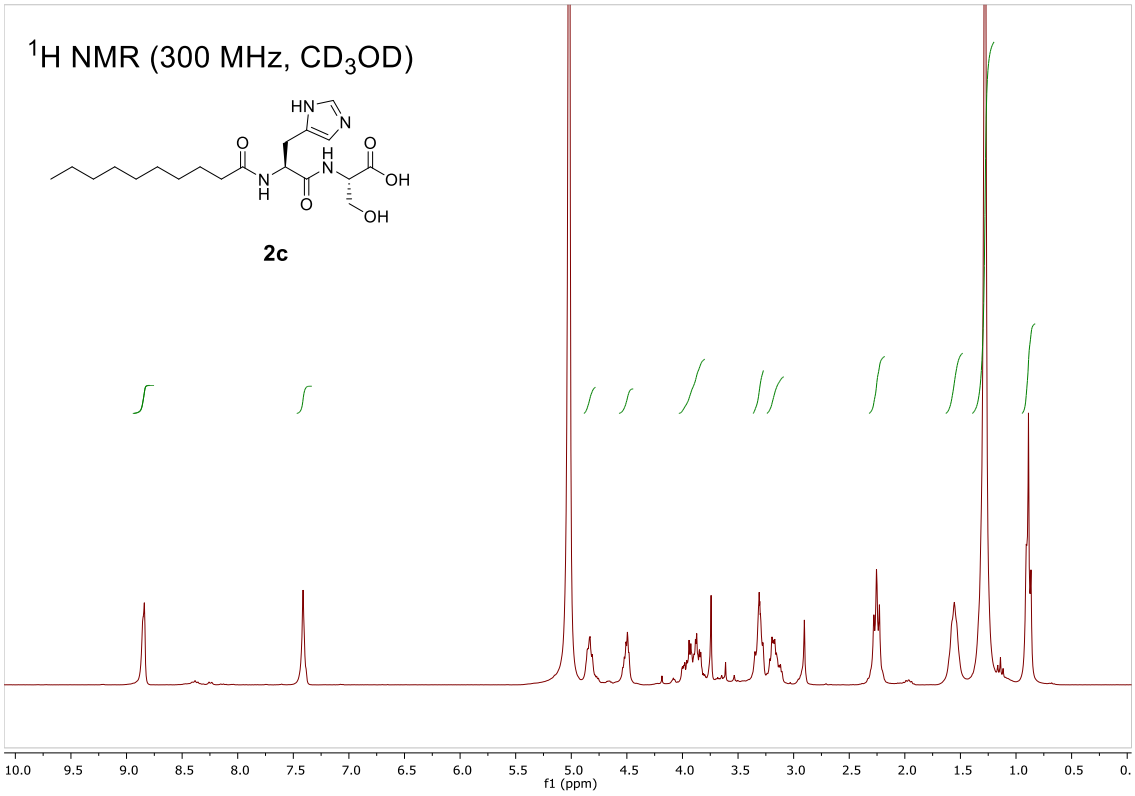

176.34
173.83
172.20
136.43
134.94
130.99
130.96
118.44
62.88
56.35
54.78
52.98
36.97
33.19
30.99
30.93
30.90
30.75
30.69
30.57
30.49
30.36
28.31
28.28
27.00
23.87
14.61
13C NMR (75 MHz, CD3OD)
HN
N
O
N
H
H
N
O
O
OMe
O
OH
SI-5d
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

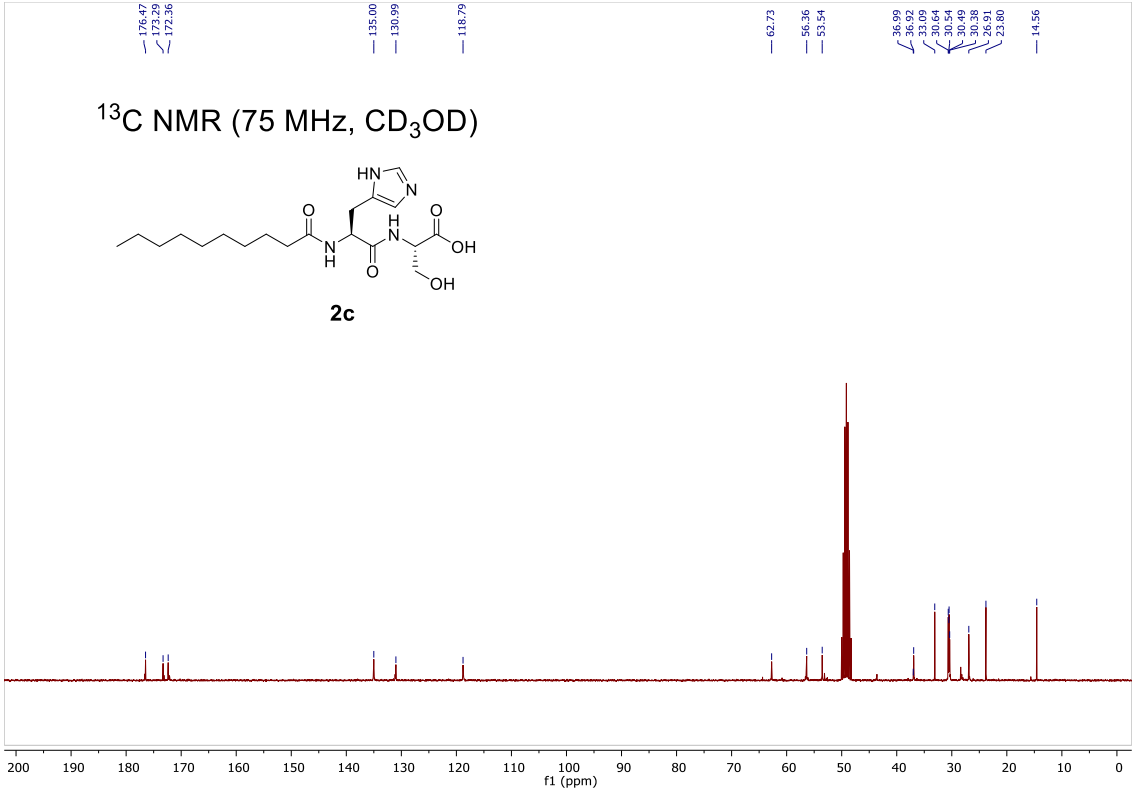

^{1}H NMR (300 MHz, CD_3OD)
2a
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)

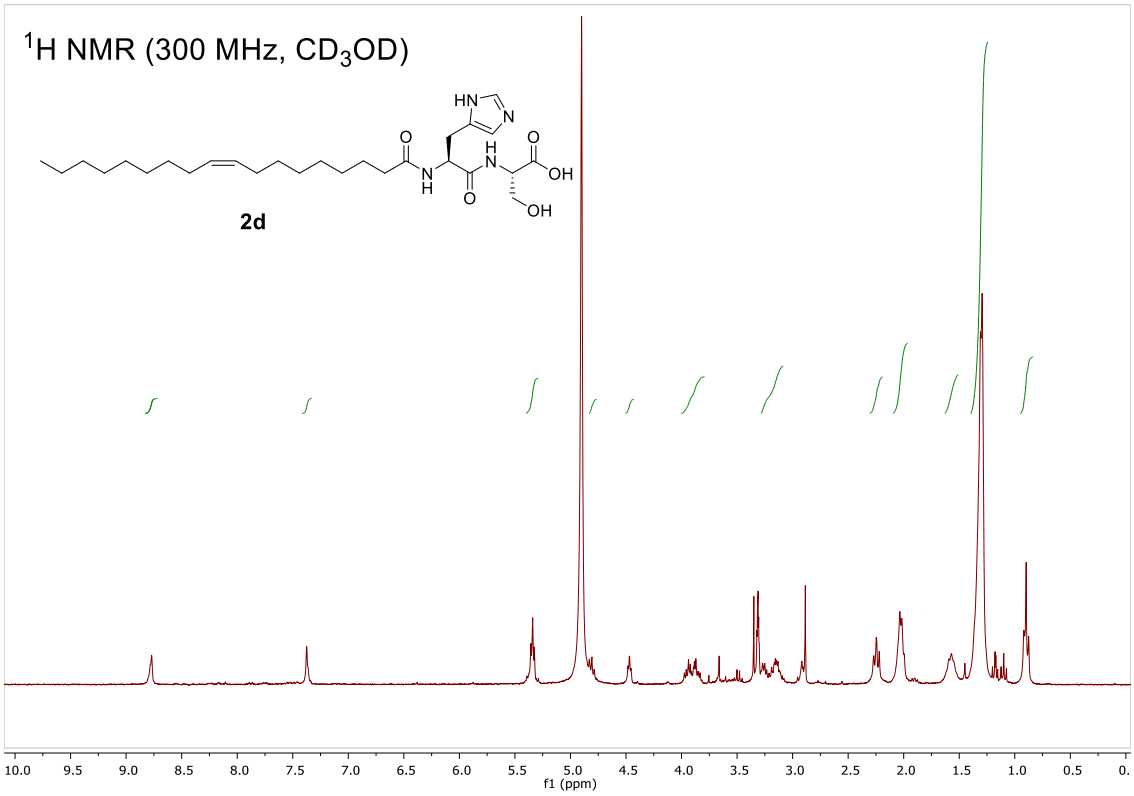

176.74
172.87
172.00
135.09
130.81
118.90
63.00
57.17
53.04
36.98
36.95
33.13
30.69
30.60
30.55
30.45
26.92
23.81
14.56
^{13}C NMR (75 MHz, CD_3OD)
2a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

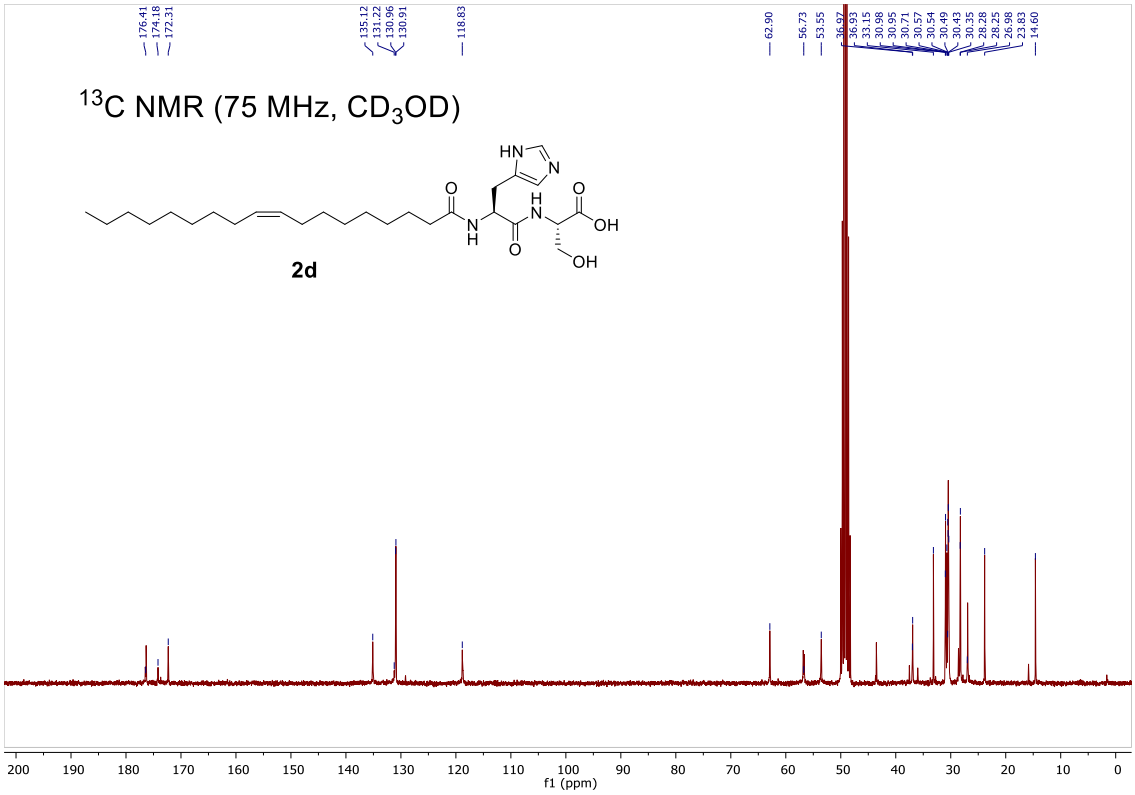

^{1}H NMR (300 MHz, CD_3OD)
2b
f1 (ppm)

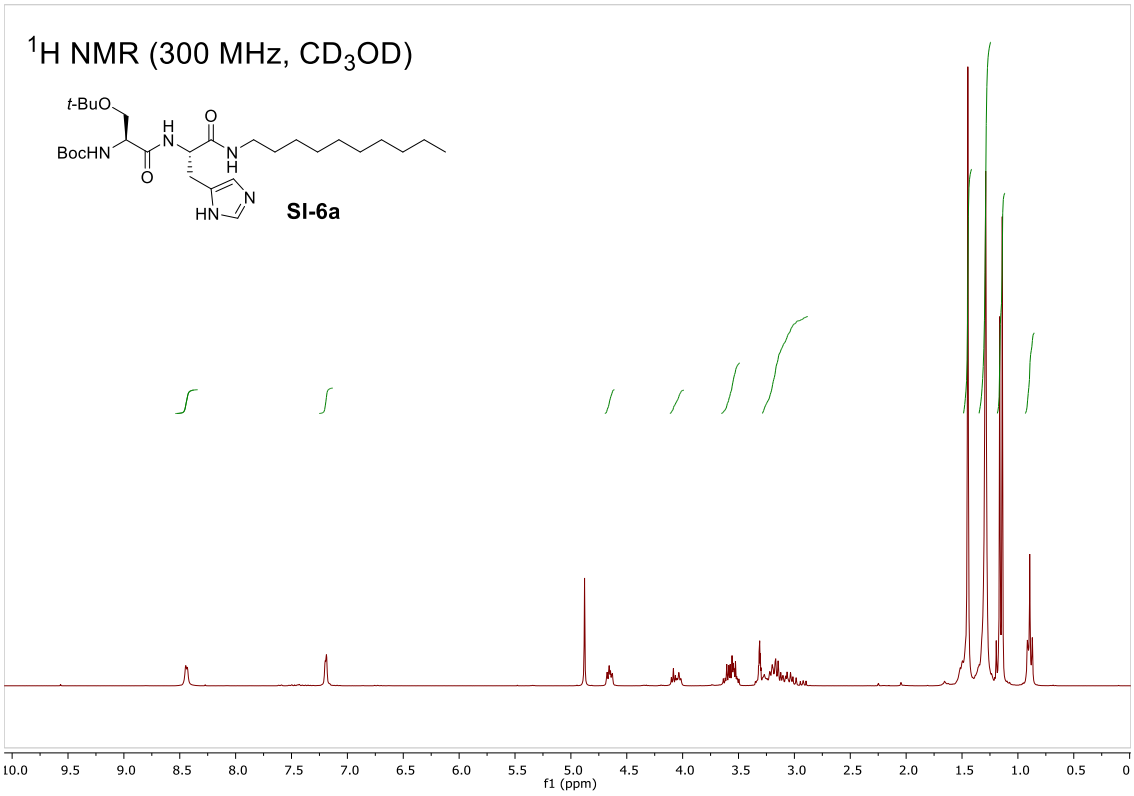

^{13}C NMR (75 MHz, CD_3OD)
2b
f1 (ppm)

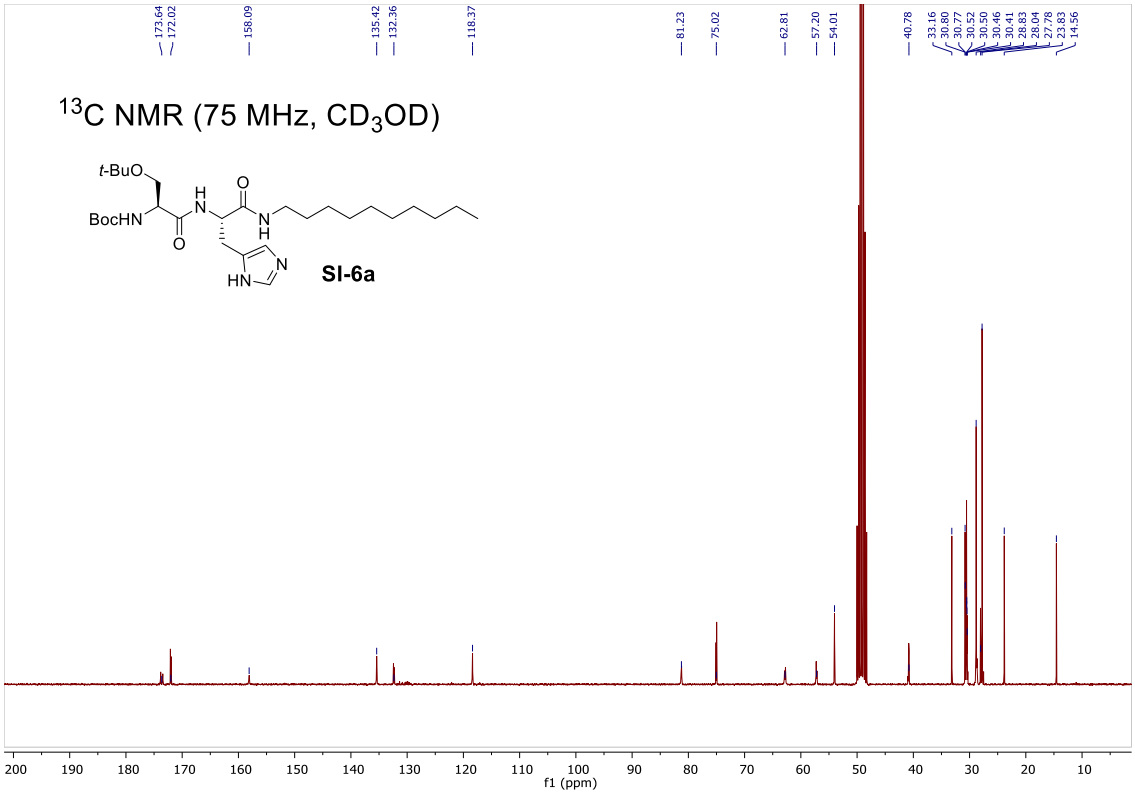

^{1}H NMR (300 MHz, CD_3OD)
HN
N
O
O
N
H
H
N
O
OH
O
OH
2c
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)

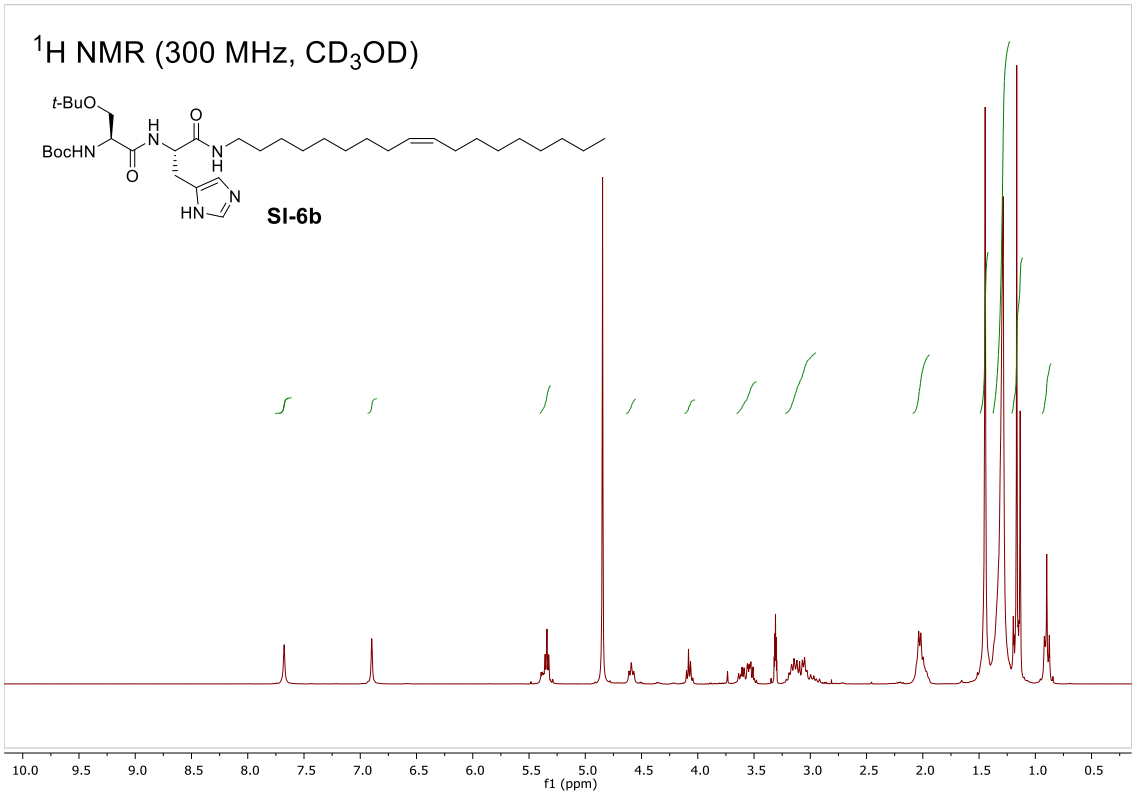

176.47
173.29
172.36
135.00
130.99
118.79
62.73
56.36
53.54
36.99
36.92
33.09
30.64
30.54
30.49
30.38
26.91
23.80
14.56
^{13}C NMR (75 MHz, CD_3OD)
HN
N
O
O
N
H
H
N
O
OH
O
OH
2c
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

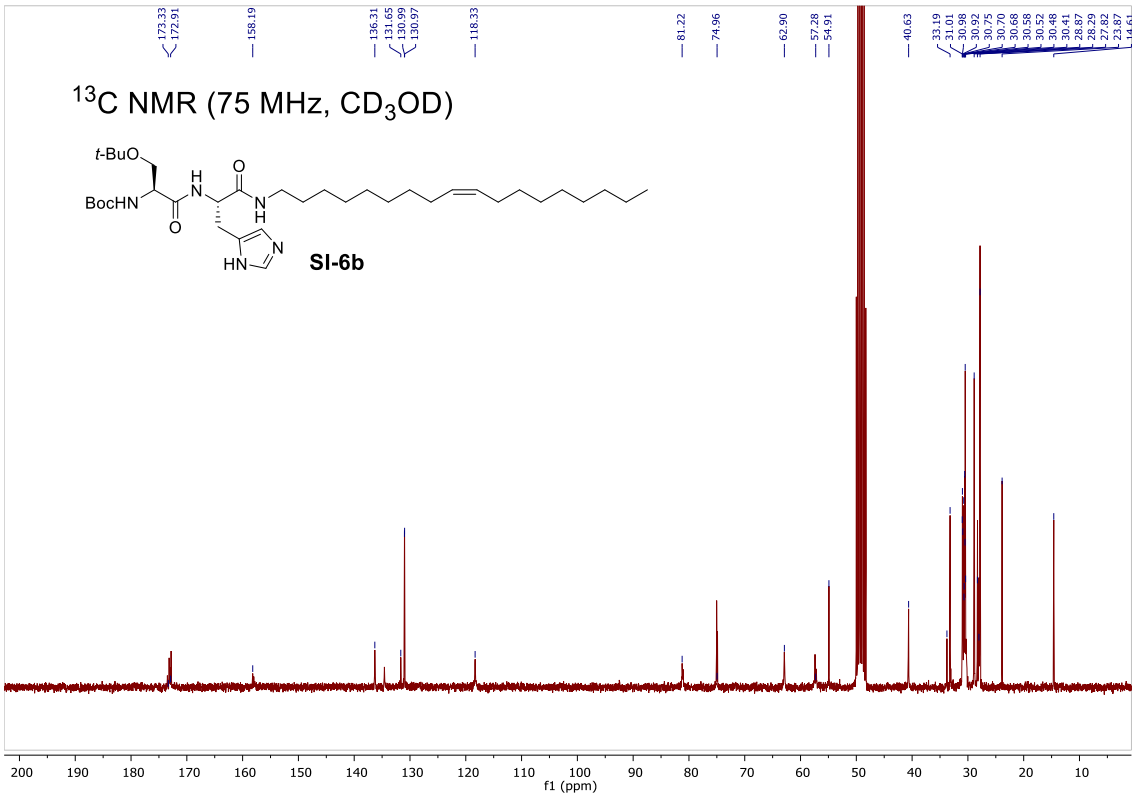

^{1}H NMR (300 MHz, CD_3OD)
2d
f1 (ppm)

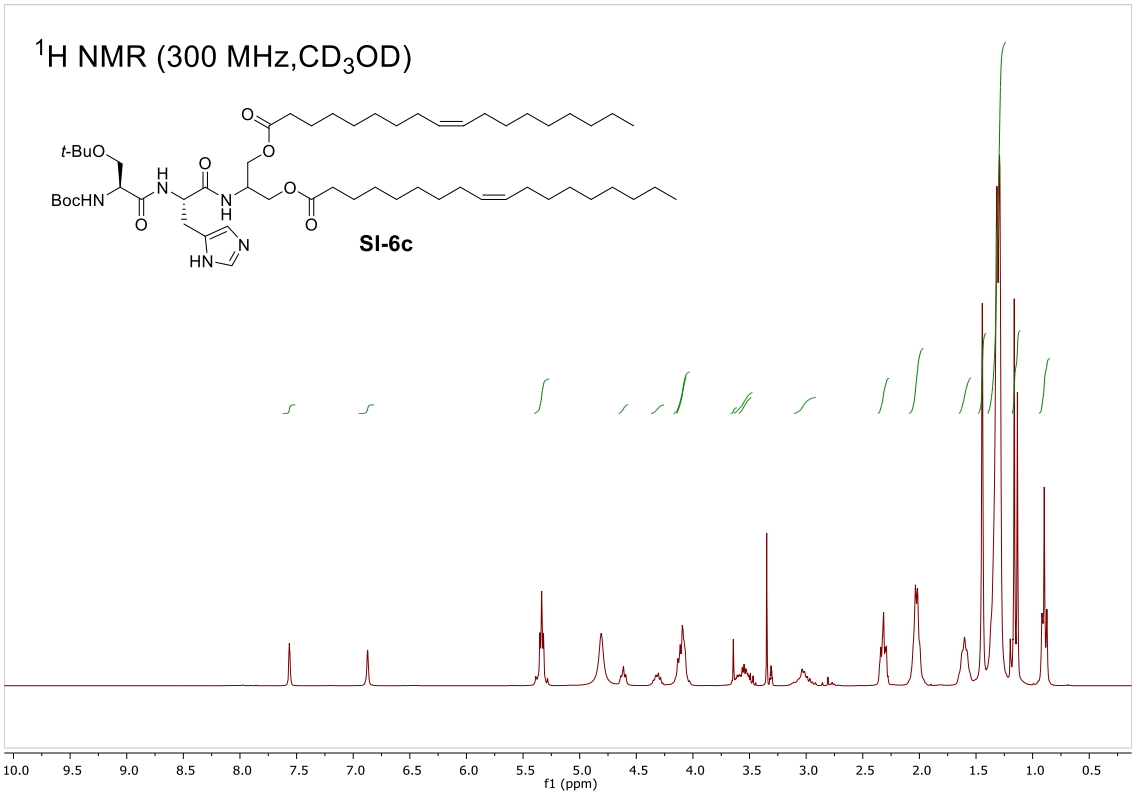

176.41
174.18
172.31
135.12
131.22
130.96
130.91
118.83
62.90
56.73
53.55
36.37
36.93
33.15
30.98
30.95
30.71
30.57
30.54
30.49
30.43
30.35
28.28
28.25
26.98
23.83
14.60
^{13}C NMR (75 MHz, CD_3OD)
2d
f1 (ppm)

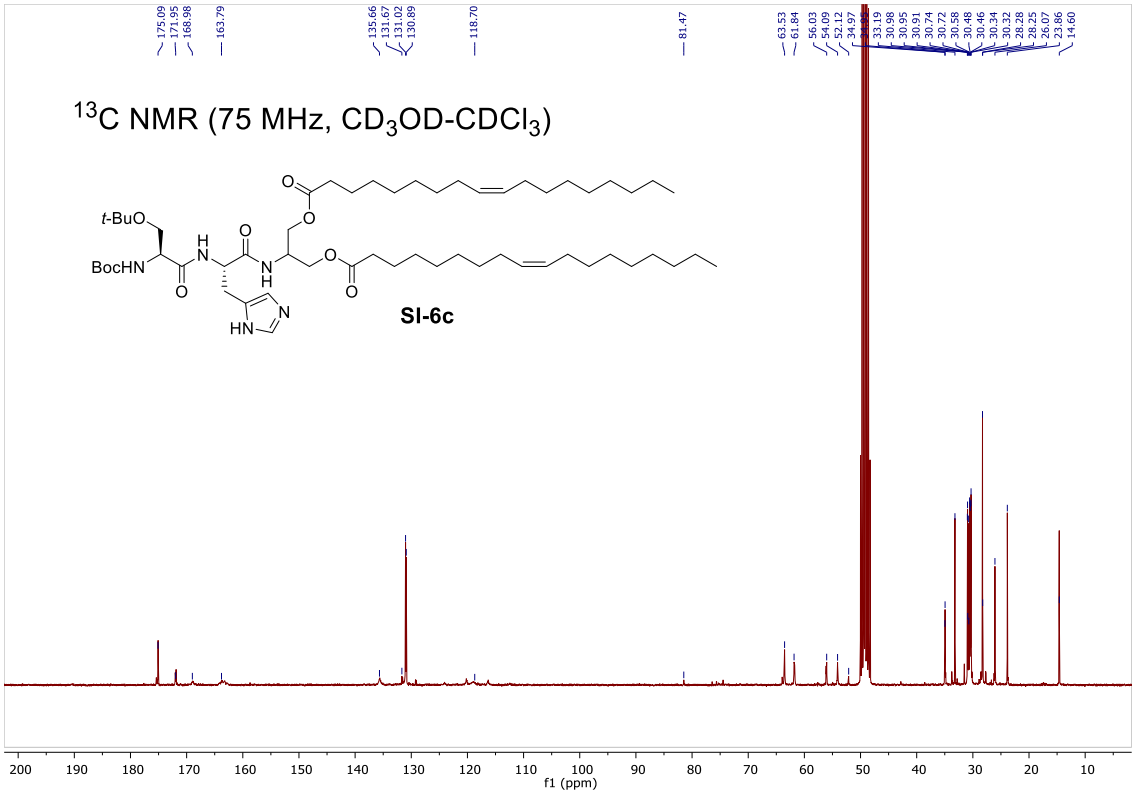

1H NMR (300 MHz, CD3OD)
t-BuO
BocHN
H
N
O
O
N
H
HN
N
SI-6a
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

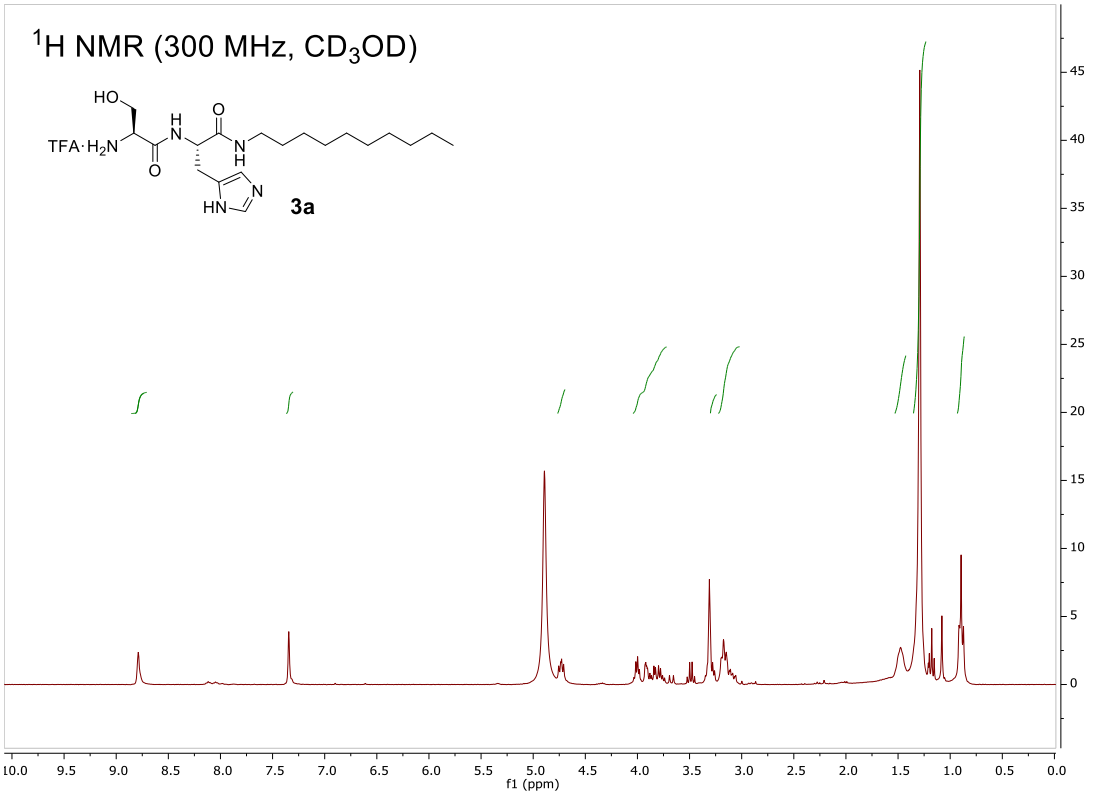

173.64
172.02
158.09
135.42
132.36
118.37
81.23
75.02
62.81
57.20
54.01
40.78
33.16
30.80
30.77
30.52
30.50
30.46
30.41
28.83
28.04
27.78
23.43
14.56
13C NMR (75 MHz, CD3OD)
t-BuO
BocHN
H
N
O
O
N
H
HN
N
SI-6a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

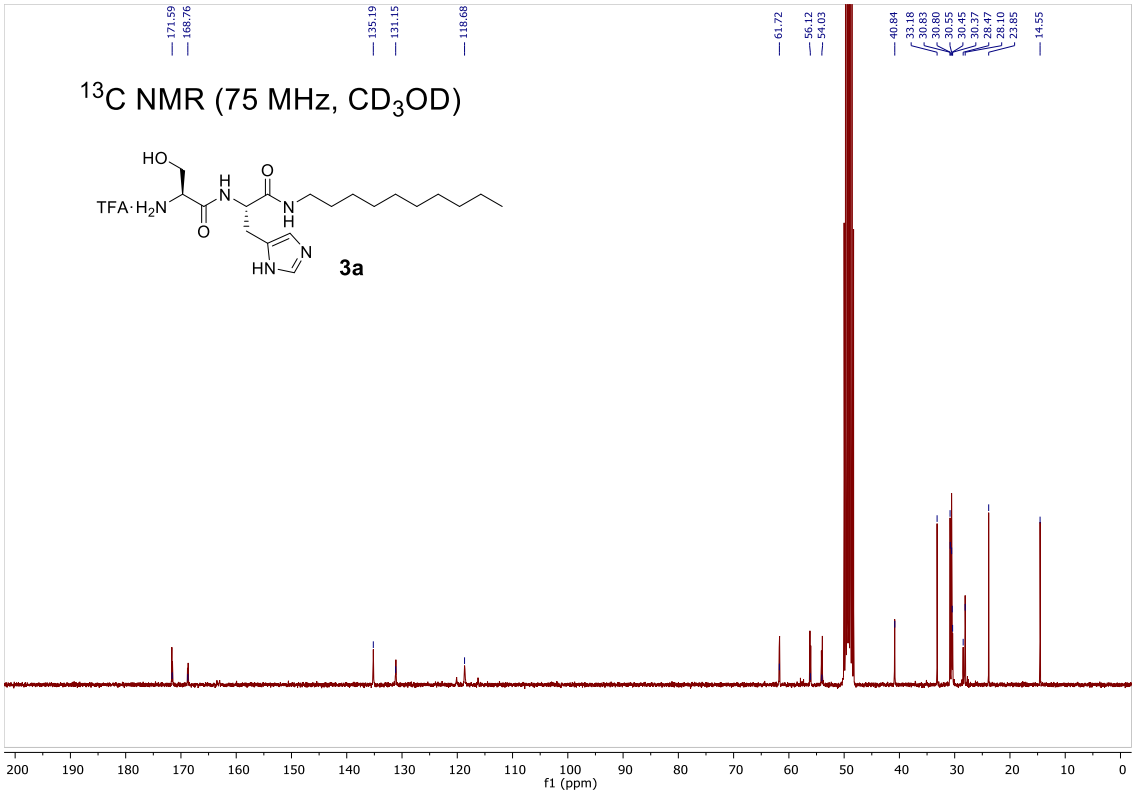

1H NMR (300 MHz, CD3OD)
t-BuO
BocHN
HN
N
SI-6b
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

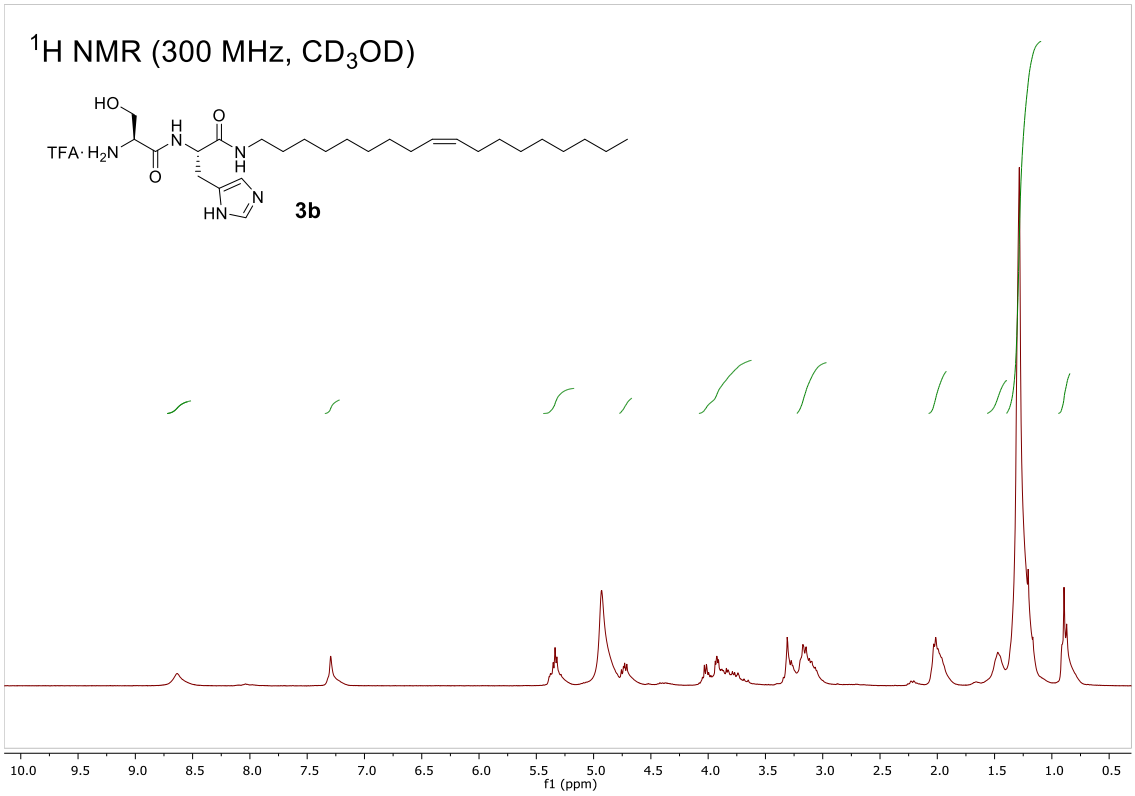

173.33
172.91
158.19
136.31
131.65
130.99
130.97
118.33
81.22
74.96
62.90
57.28
54.91
40.63
33.19
31.01
30.98
30.92
30.75
30.70
30.68
30.58
30.52
30.48
30.41
28.87
28.29
27.82
25.87
14.61
13C NMR (75 MHz, CD3OD)
t-BuO
BocHN
HN
N
SI-6b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

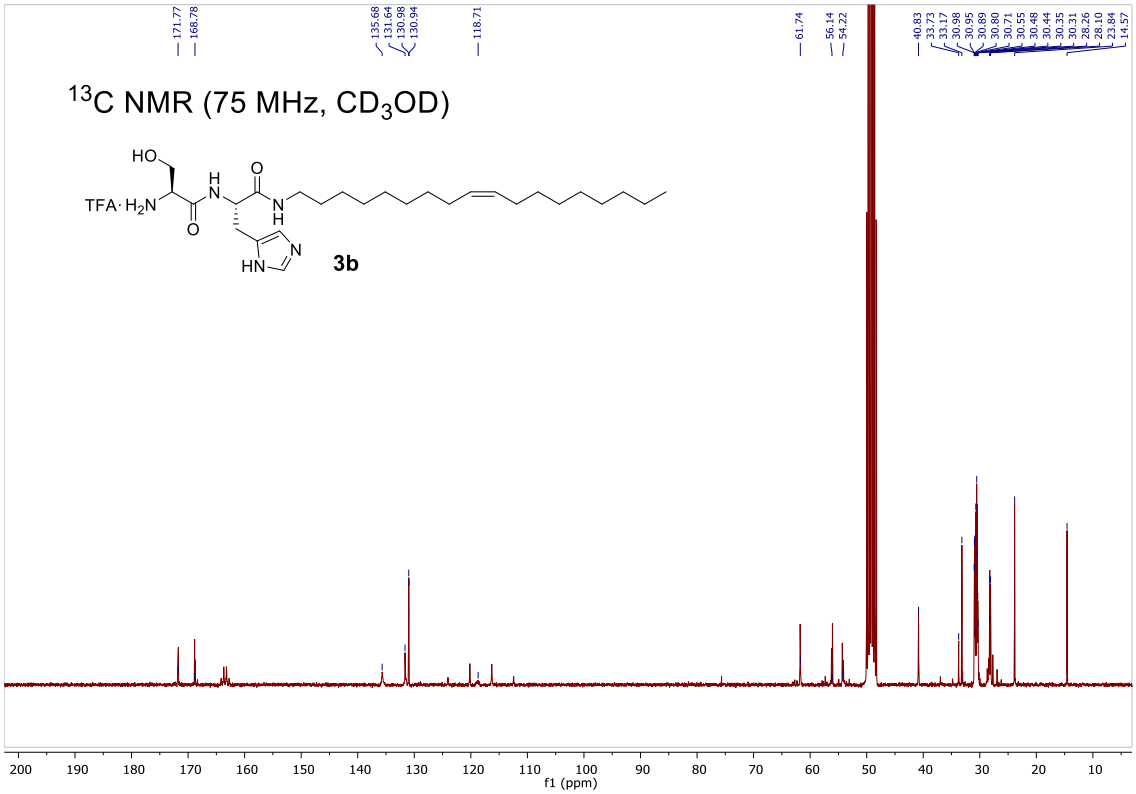

^{1}H NMR (300 MHz,CD_3OD)
t-BuO
BocHN
HN
SI-6c
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

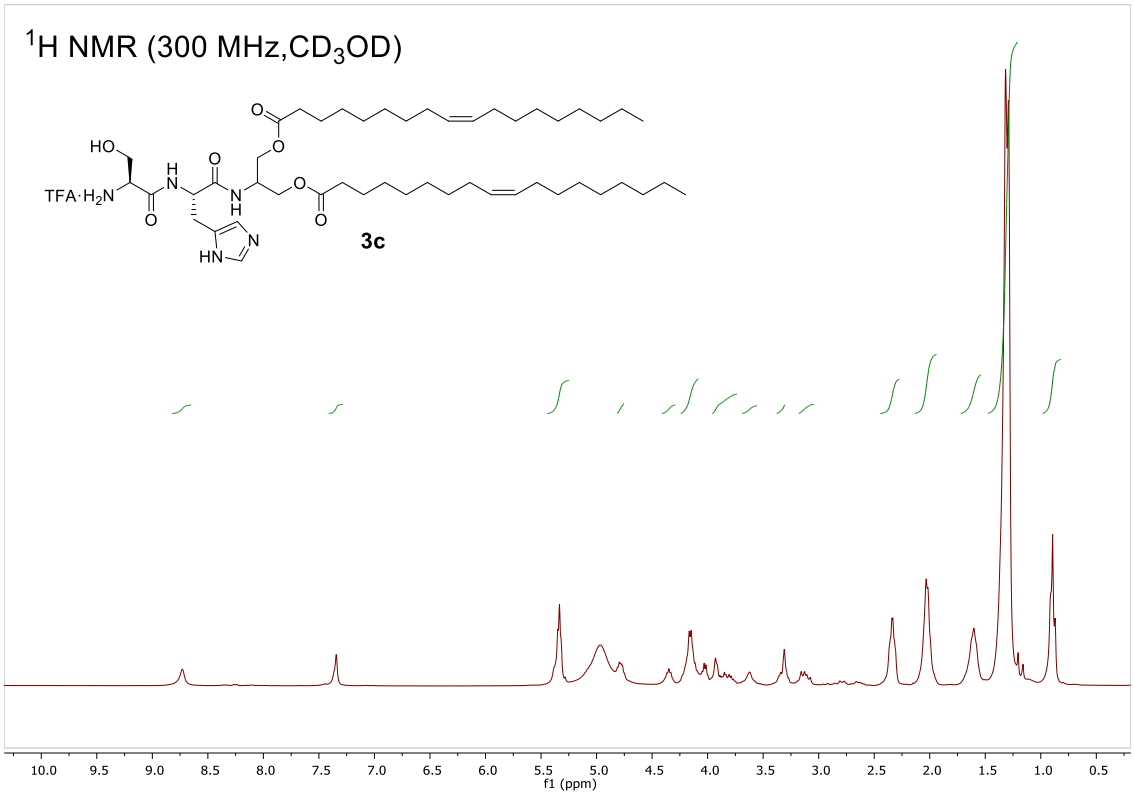

175.09
171.95
168.98
163.79
135.66
131.67
131.02
130.89
118.70
81.47
63.53
61.84
56.03
54.09
54.12
34.97
33.19
30.98
30.95
30.91
30.74
30.72
30.58
30.48
30.46
30.34
30.32
29.28
28.25
26.07
23.86
14.60
^{13}C NMR (75 MHz, CD_3OD-$CDCl_3$)
t-BuO
BocHN
HN
SI-6c
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

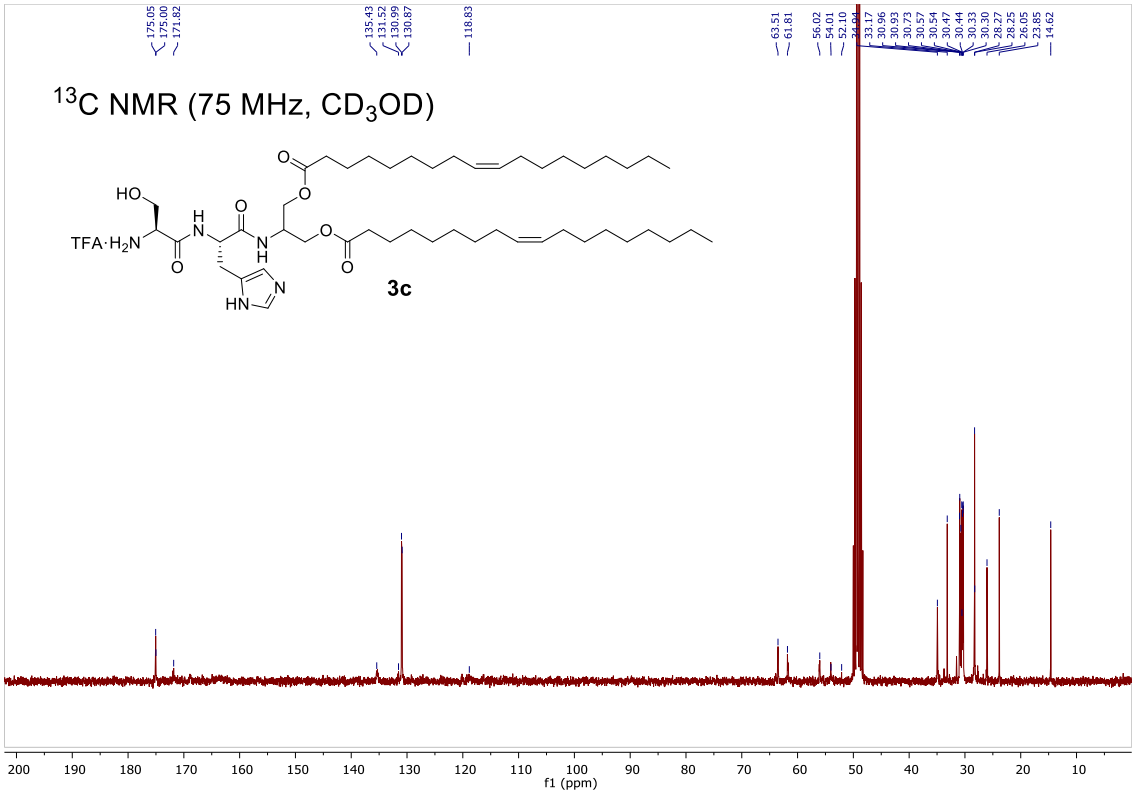

^{1}H NMR (300 MHz, CD_3OD)
HO
TFA·H2N
O
H
N
O
N
H
HN
N
3a
45
40
35
30
25
20
15
10
5
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


171.59
168.76
135.19
131.15
118.68
61.72
56.12
54.03
40.84
33.18
30.83
30.80
30.55
30.45
30.37
28.47
28.10
23.85
14.55
^{13}C NMR (75 MHz, CD_3OD)
HO
TFA·H2N
O
H
N
O
N
H
HN
N
3a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

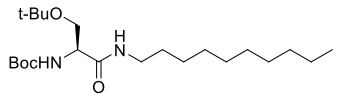

^{1}H NMR (300 MHz, CD_3OD)
HO
TFA·H2N
H
N
O
O
N
H
HN
N
3b
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


171.77
168.78
135.68
131.64
130.98
130.94
118.71
61.74
56.14
54.22
40.83
33.73
33.17
30.98
30.95
30.89
30.80
30.71
30.55
30.48
30.44
30.35
30.31
28.26
28.10
23.84
14.57
^{13}C NMR (75 MHz, CD_3OD)
HO
TFA·H2N
H
N
O
O
N
H
HN
N
3b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


^{1}H NMR (300 MHz,CD$_3$OD)
HO
TFA·H$_2$N
3c
10.0 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
f1 (ppm)

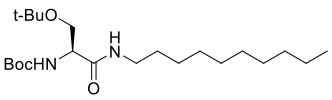

175.05
175.00
171.82
135.43
131.52
130.99
130.87
118.83
63.51
61.81
56.02
54.01
52.10
34.64
33.17
30.96
30.93
30.73
30.57
30.54
30.47
30.44
30.33
30.30
28.27
28.25
26.05
23.85
14.62
^{13}C NMR (75 MHz, CD$_3$OD)
HO
TFA·H$_2$N
3c
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

^{1}H NMR (300 MHz, $CDCl_3$)

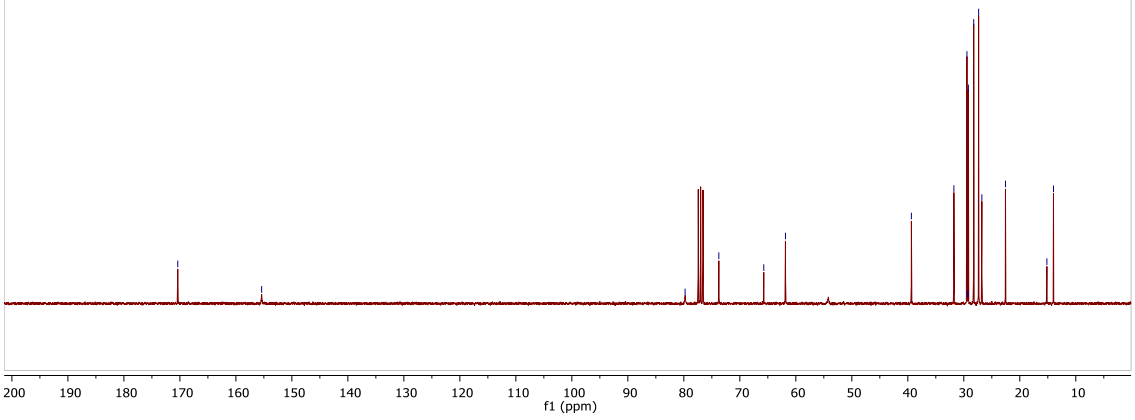


SI-7a

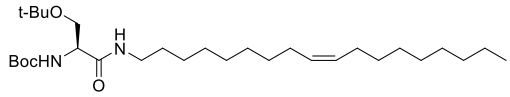
^{13}C NMR (75 MHz, $CDCl_3$)



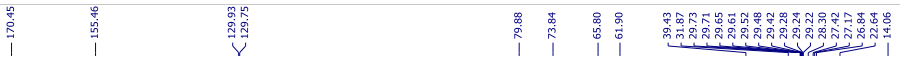
SI-7a



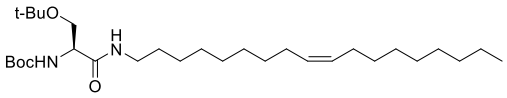
^{1}H NMR (300 MHz, $CDCl_3$)



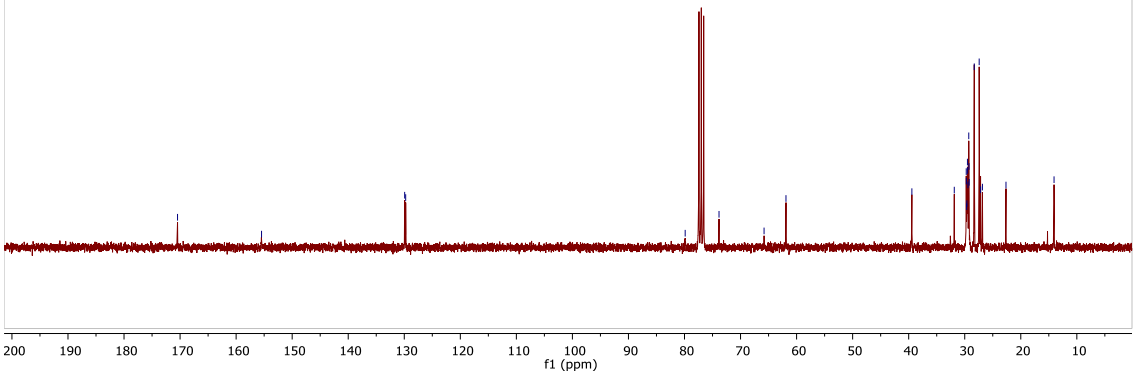
SI-7b

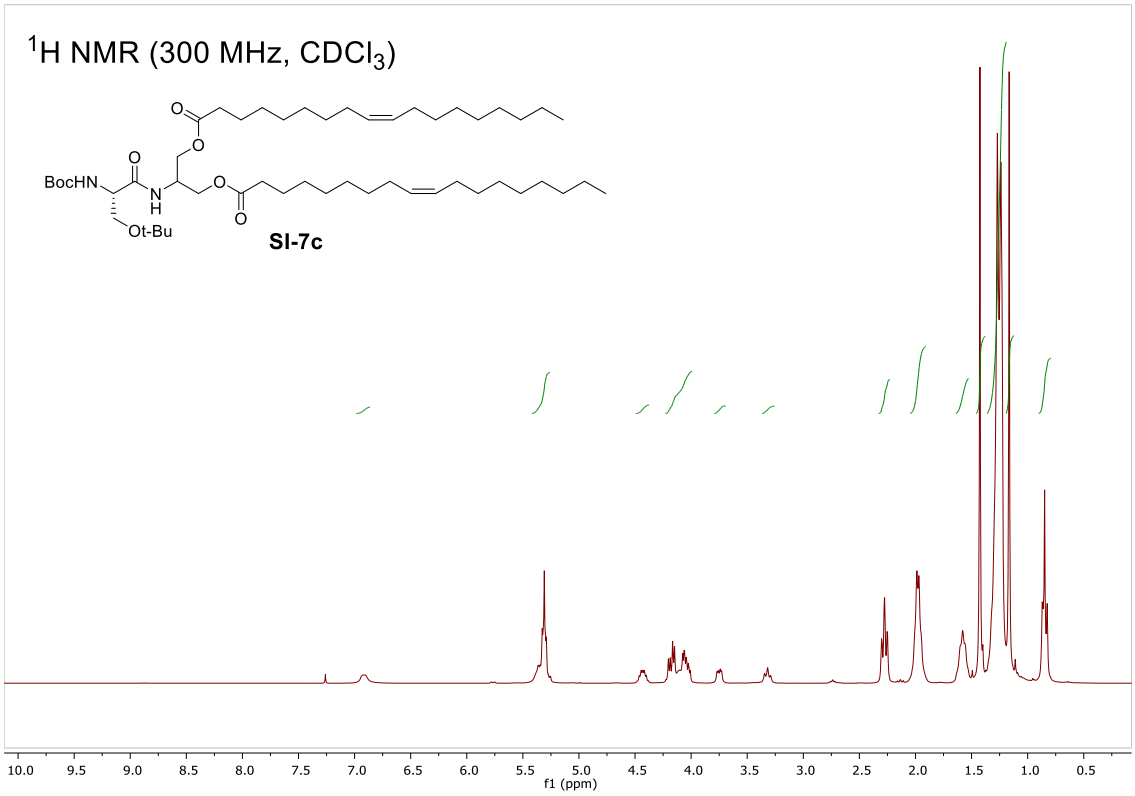


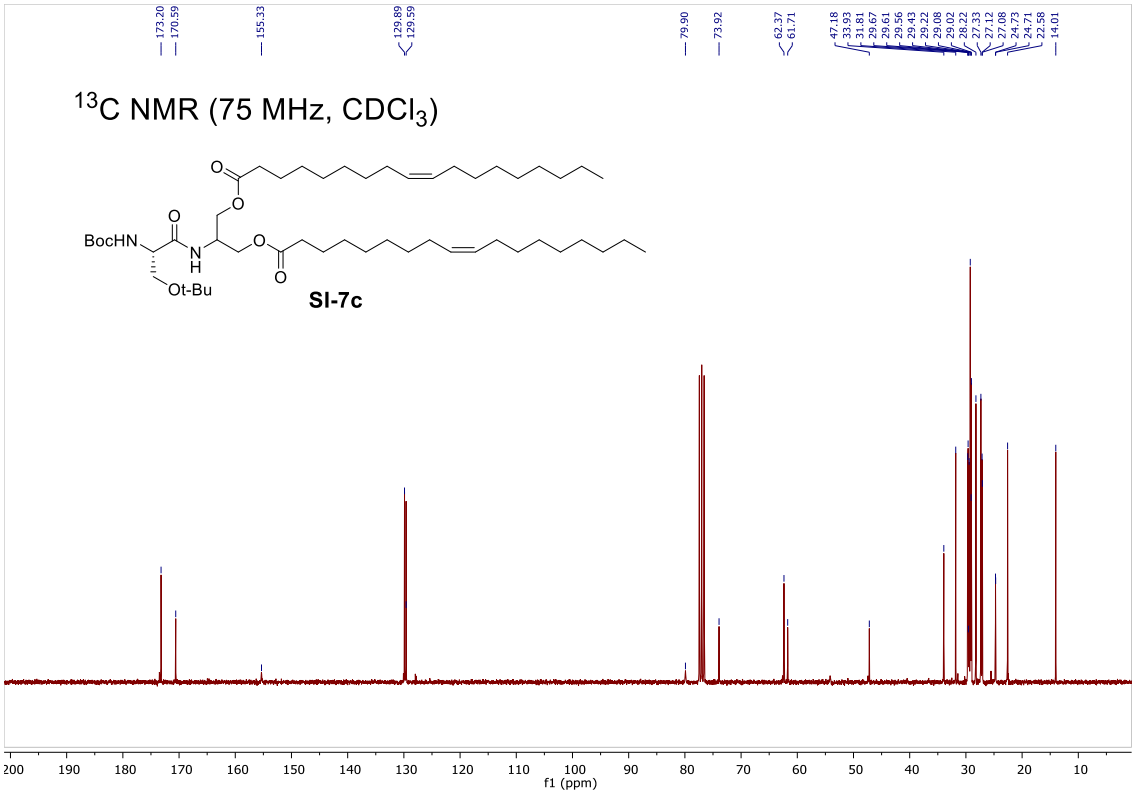
^{13}C NMR (75 MHz, $CDCl_3$)

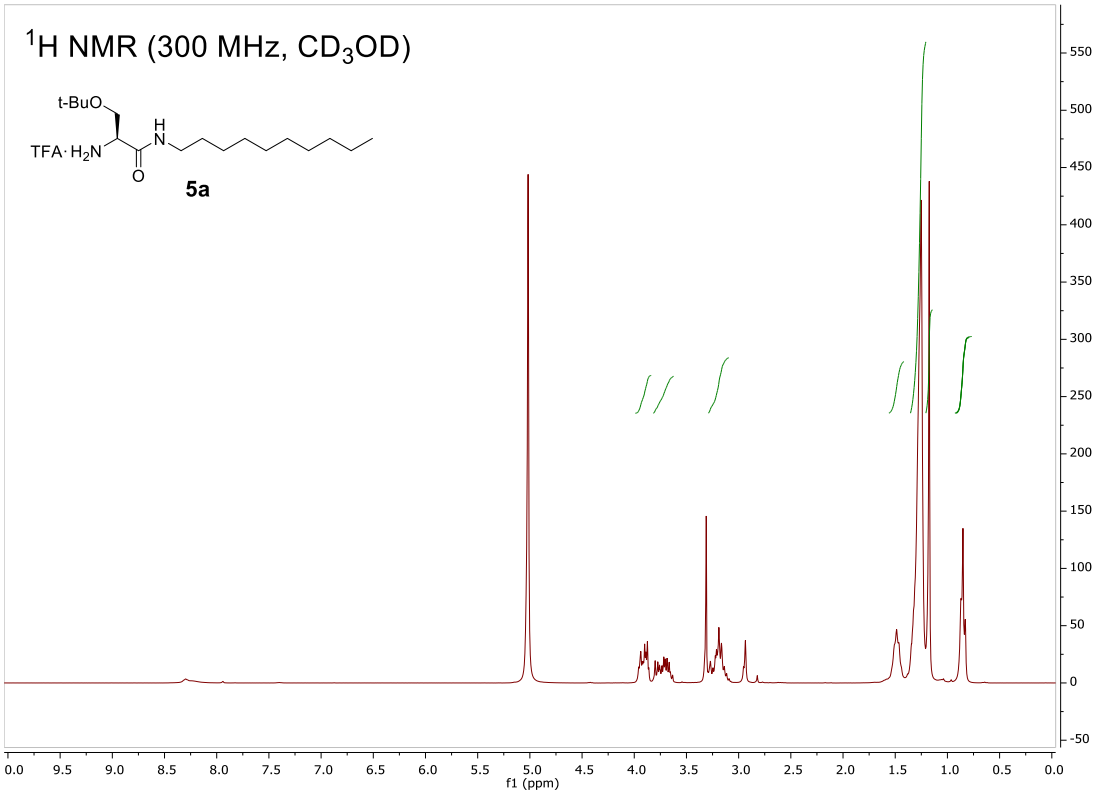


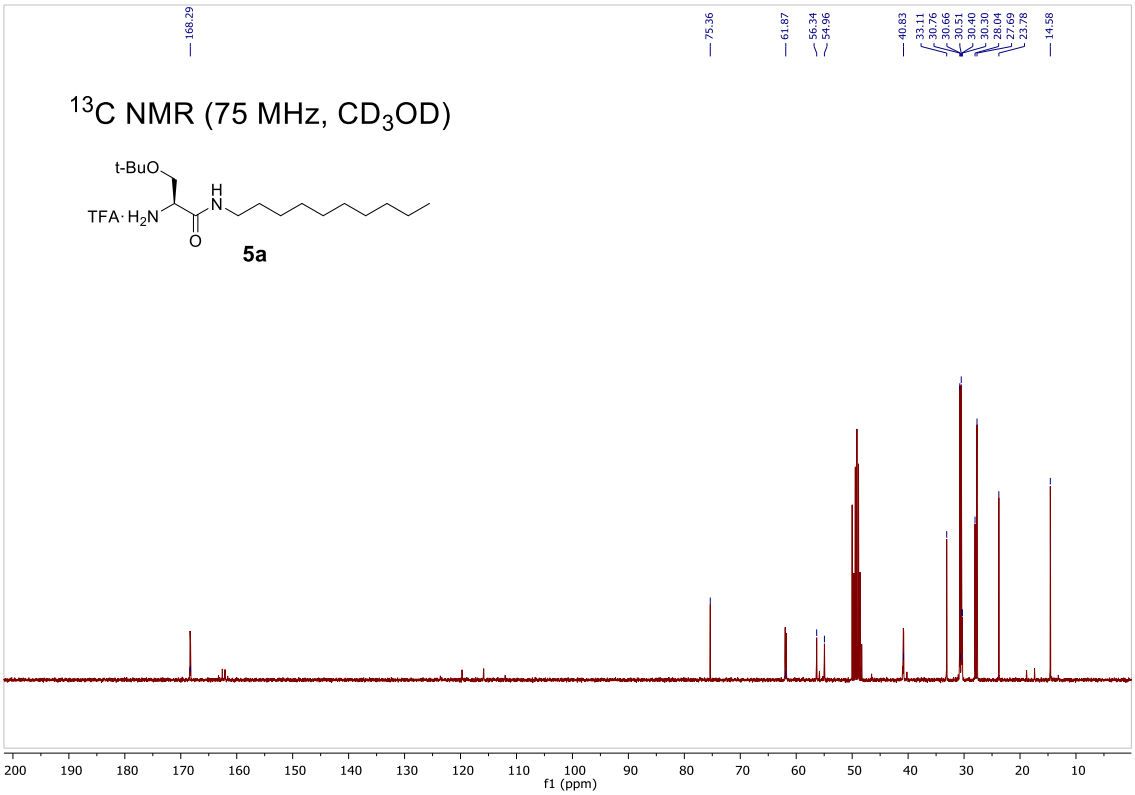
SI-7b



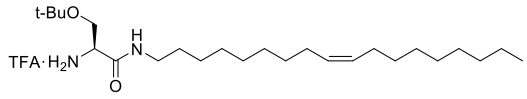

1H NMR (300 MHz, CDCl3)
BocHN
N
H
Ot-Bu
SI-7c
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


173.20
170.59
155.33
129.89
129.59
79.90
73.92
62.37
61.71
47.18
33.93
31.81
29.67
29.61
29.56
29.43
29.22
29.08
29.02
28.21
27.33
27.12
27.08
24.73
24.71
22.58
14.01
13C NMR (75 MHz, CDCl3)
BocHN
N
H
Ot-Bu
SI-7c
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

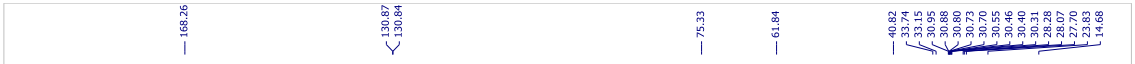

1H NMR (300 MHz, CD3OD)
t-BuO
TFA·H2N
H
N
O
5a
f1 (ppm)


168.29
75.36
61.87
56.34
54.96
40.83
33.11
30.76
30.66
30.51
30.40
30.30
28.04
27.69
23.78
14.58
13C NMR (75 MHz, CD3OD)
t-BuO
TFA·H2N
H
N
O
5a
f1 (ppm)

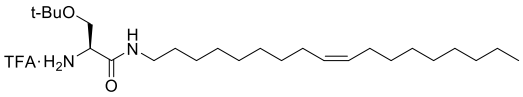
^{1}H NMR (300 MHz, CD_3OD)



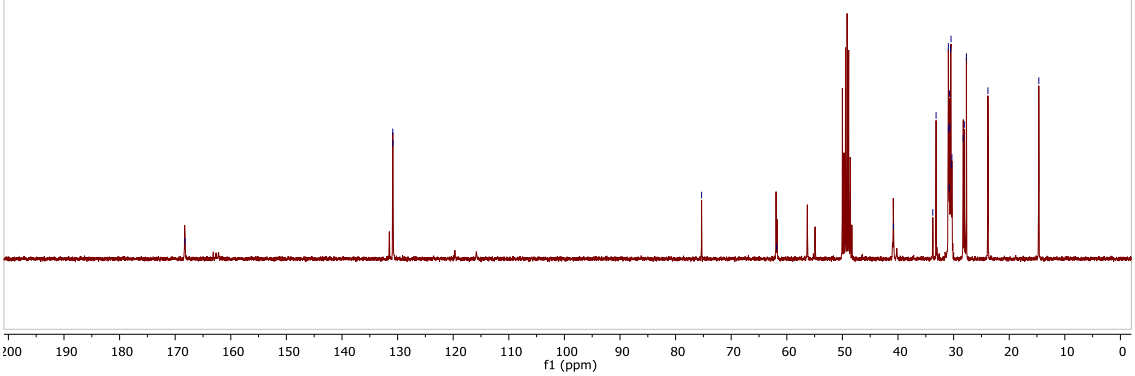
5b

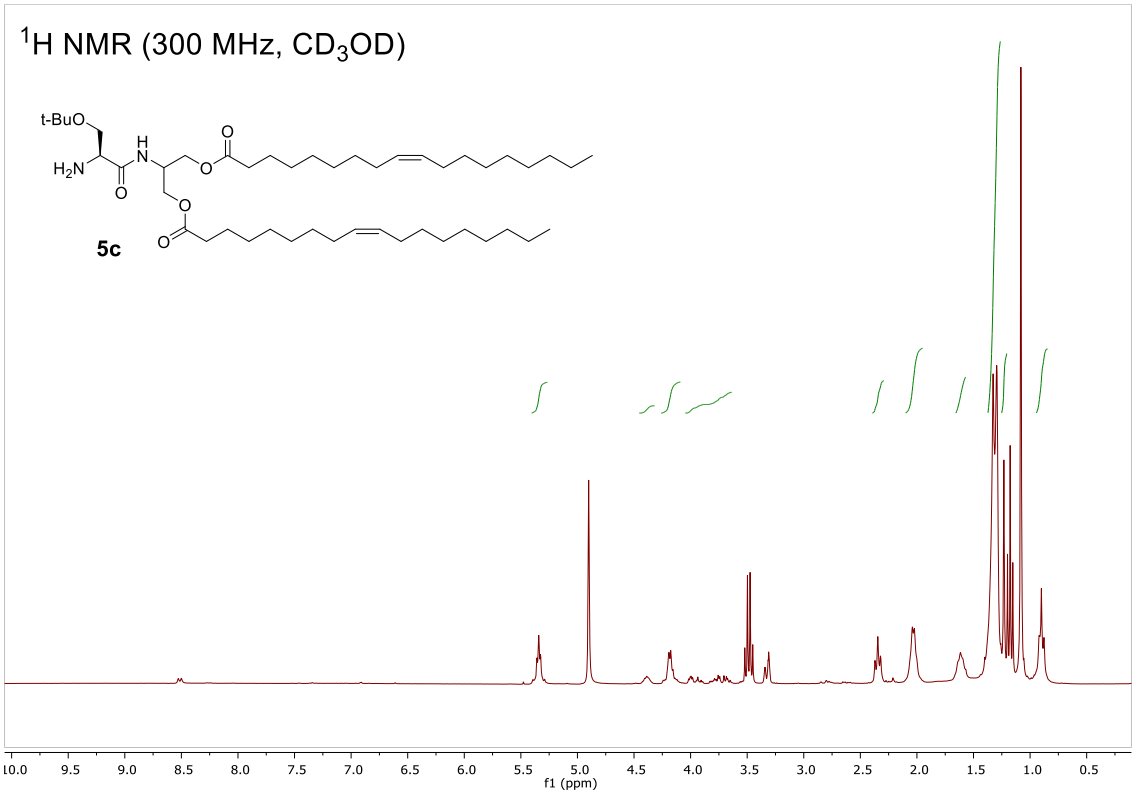


^{13}C NMR (75 MHz, CD_3OD)

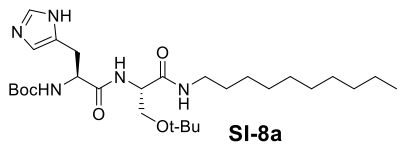


5b



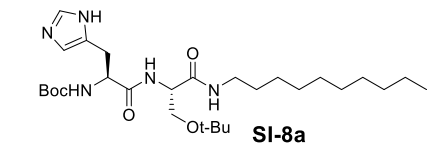

1H NMR (300 MHz, CD3OD)
t-BuO
H2N
H
N
O
O
O
O
O
5c
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

^{1}H NMR (300 MHz, CD_3OD)

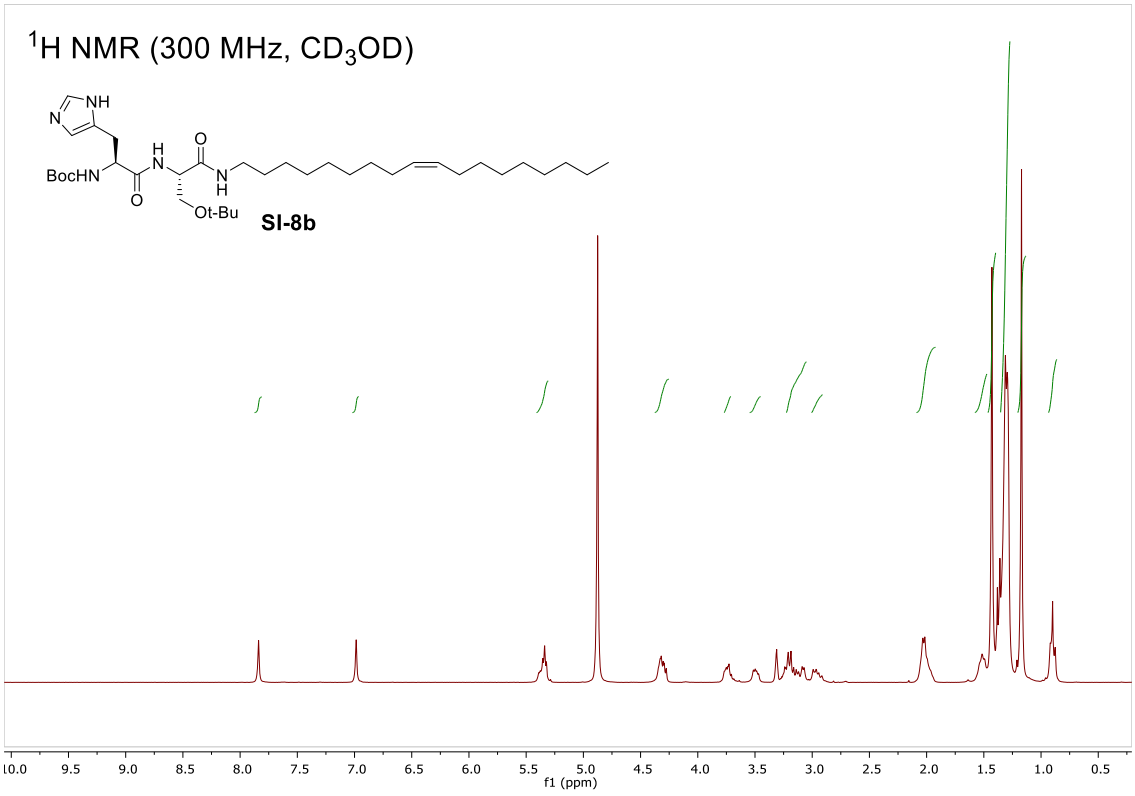


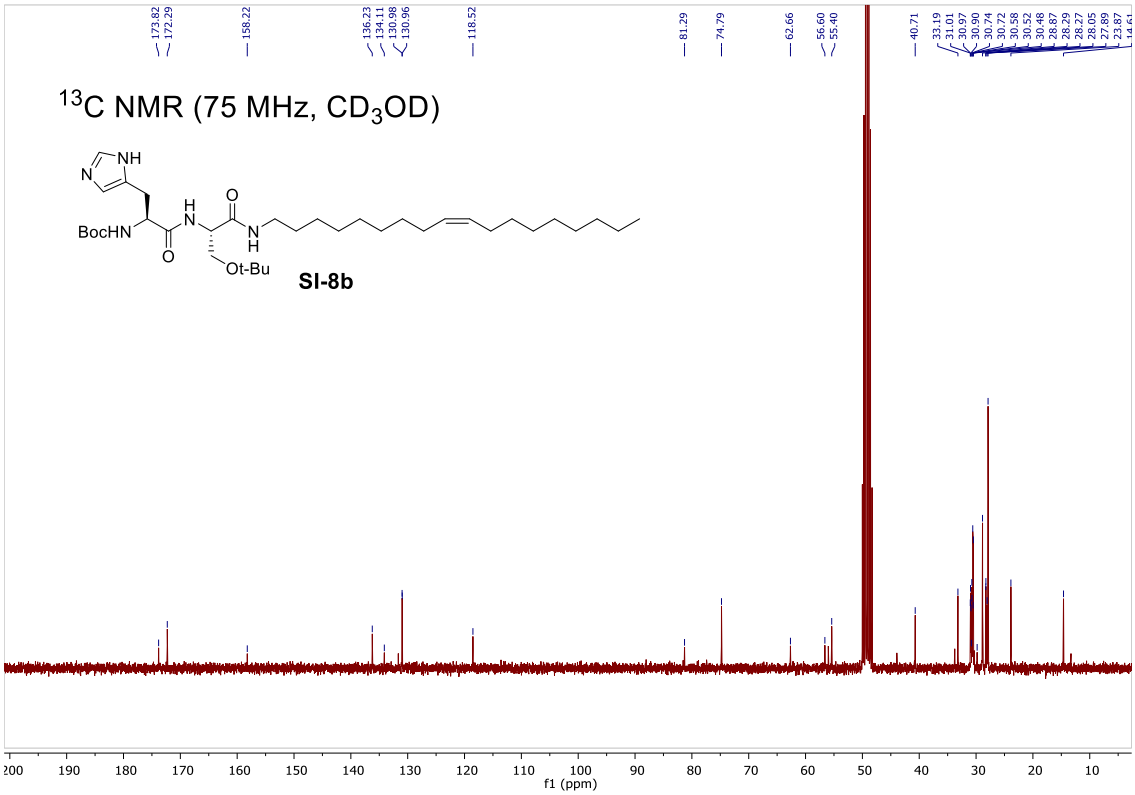
SI-8a

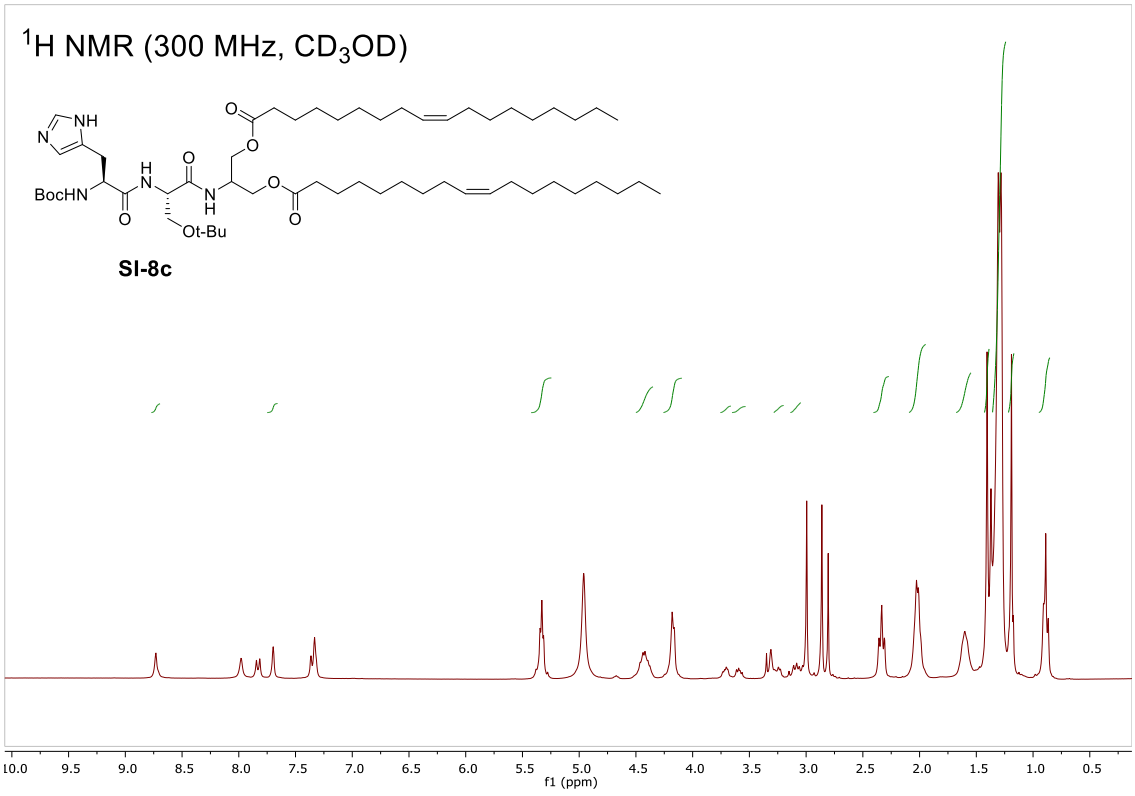
^{13}C NMR (75 MHz, CD_3OD)

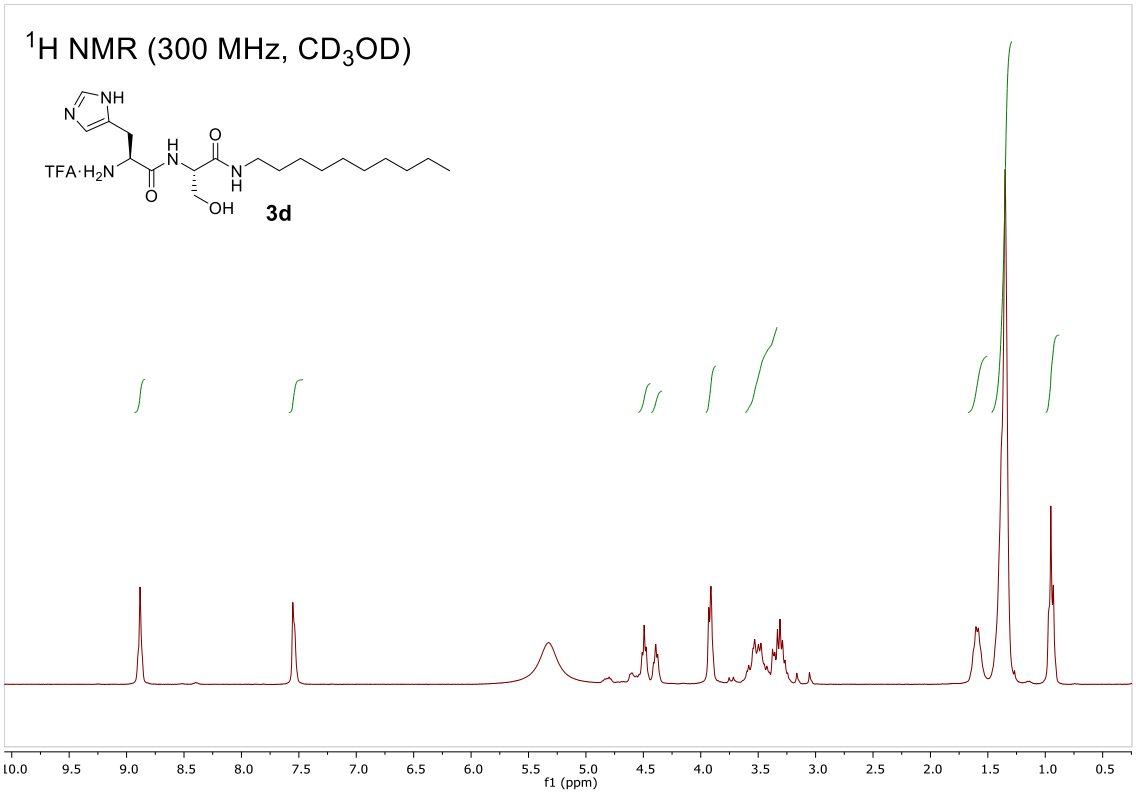


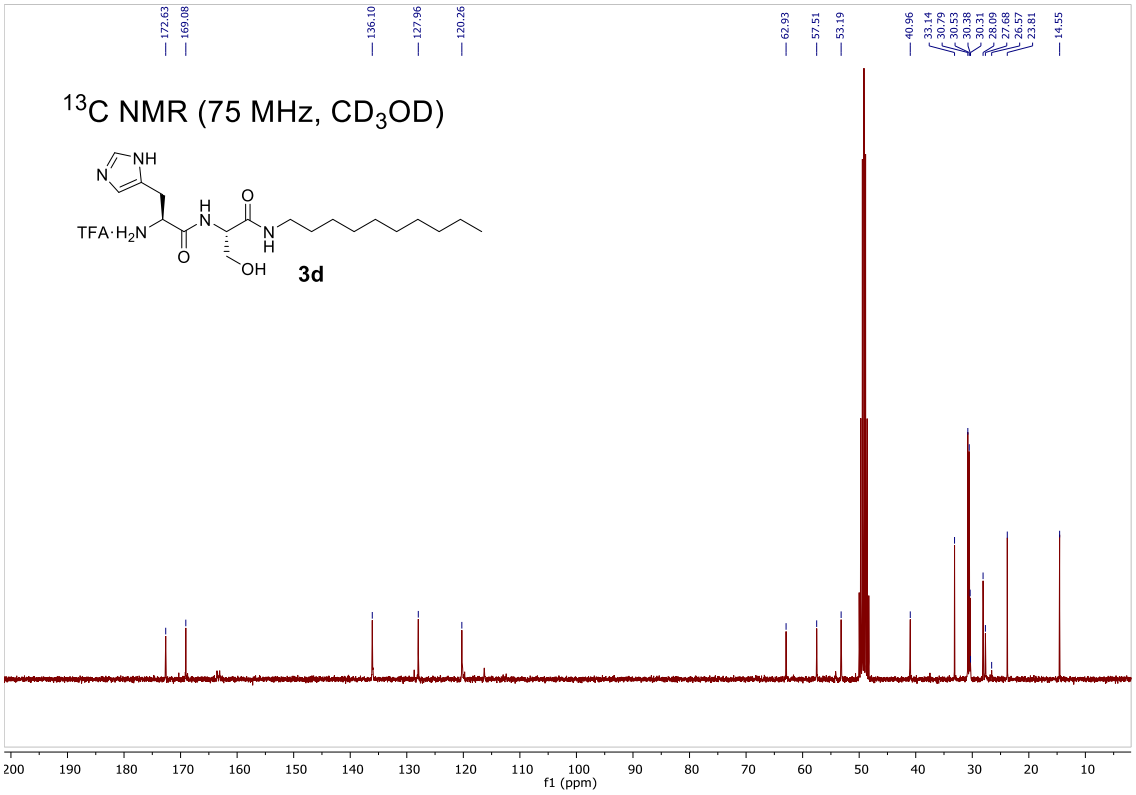
SI-8a

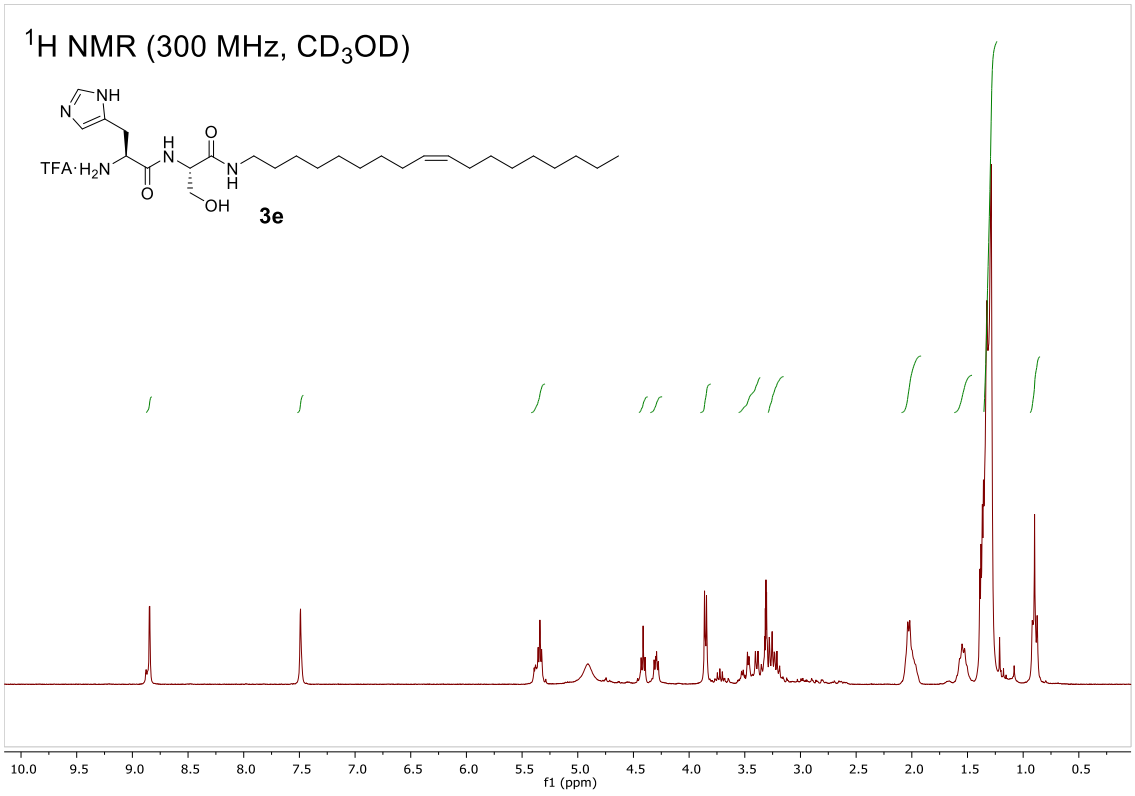

1H NMR (300 MHz, CD3OD)
NH
N
BocHN
H
N
O
O
N
H
Ot-Bu
SI-8b
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

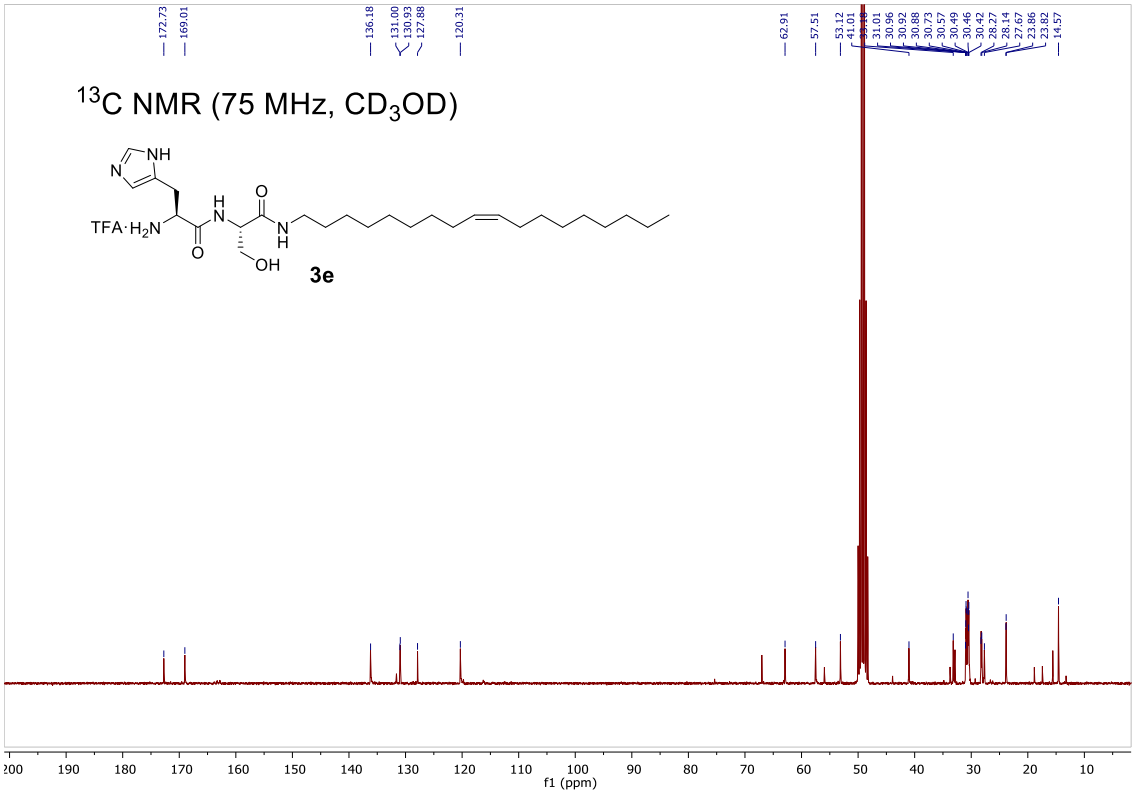

173.82
172.29
158.22
136.23
134.11
130.98
130.96
118.52
81.29
74.79
62.66
56.60
55.40
40.71
33.19
31.01
30.97
30.90
30.74
30.72
30.58
30.52
30.48
28.87
28.29
28.27
28.05
27.89
23.37
14.61
13C NMR (75 MHz, CD3OD)
NH
N
BocHN
H
N
O
O
N
H
Ot-Bu
SI-8b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

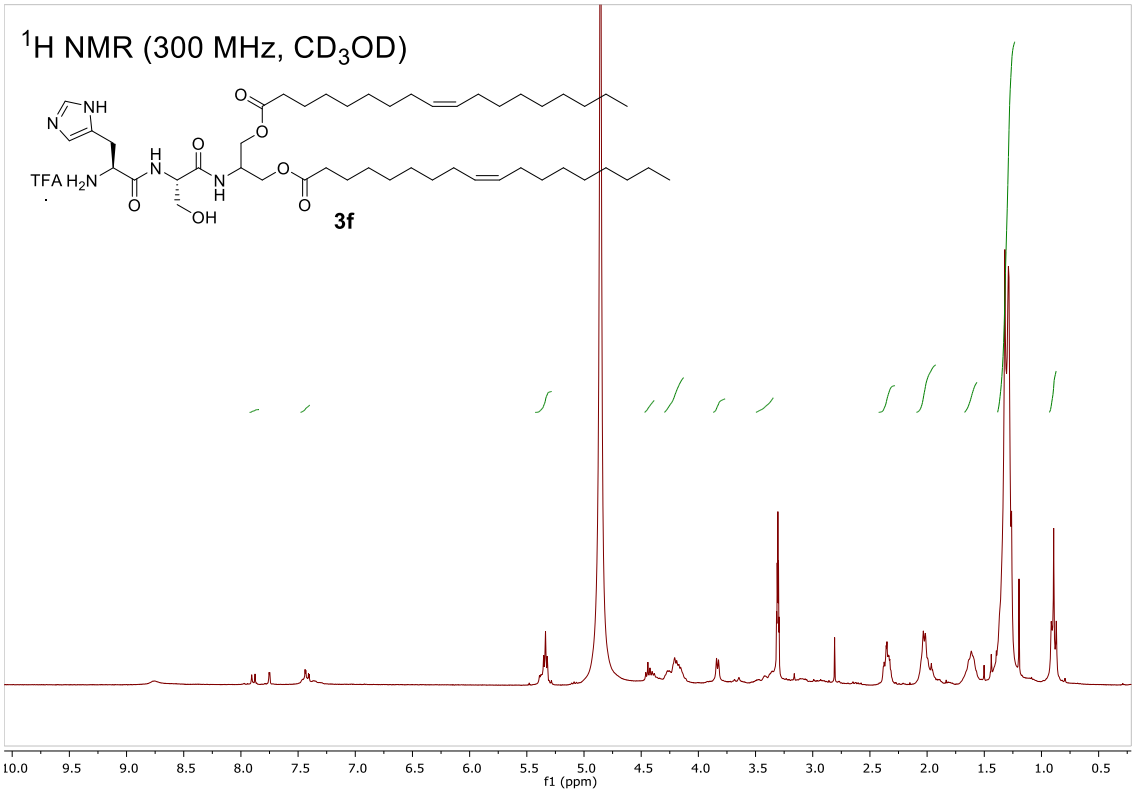

1H NMR (300 MHz, CD3OD)
BocHN
Ot-Bu
SI-8c
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

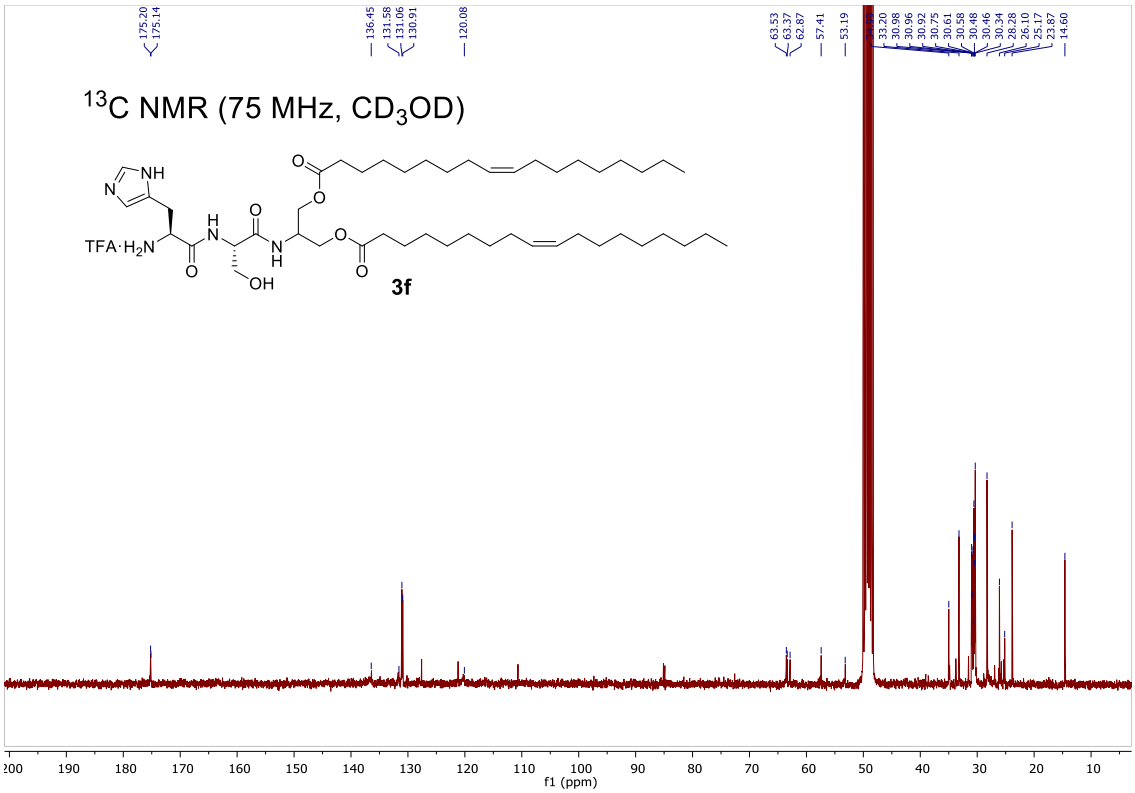

^{1}H NMR (300 MHz, CD_3OD)
TFA·H_2N
OH
3d
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


172.63
169.08
136.10
127.96
120.26
62.93
57.51
53.19
40.96
33.14
30.79
30.53
30.38
30.31
29.09
27.68
26.57
23.81
14.55
^{13}C NMR (75 MHz, CD_3OD)
TFA·H_2N
OH
3d
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


1H NMR (300 MHz, CD3OD)
TFA·H2N
NH
N
O
H
N
O
N
H
OH
3e
10.0 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
f1 (ppm)


172.73
169.01
136.18
131.00
130.93
127.88
120.31
62.91
57.51
53.12
41.01
31.01
30.96
30.92
30.88
30.73
30.57
30.49
30.46
30.42
28.27
28.14
27.67
23.86
23.82
14.57
13C NMR (75 MHz, CD3OD)
TFA·H2N
NH
N
O
H
N
O
N
H
OH
3e
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


^{1}H NMR (300 MHz, CD_3OD)
TFA H_2N
OH
3f
10.0 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
f1 (ppm)


175.20
175.14
136.45
131.58
131.06
130.91
120.08
63.53
63.37
62.87
57.41
53.19
33.20
30.98
30.96
30.92
30.75
30.61
30.58
30.48
30.46
30.34
28.28
26.10
25.17
23.87
14.60
^{13}C NMR (75 MHz, CD_3OD)
TFA·H_2N
OH
3f
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)