Electronic Supplementary Information

Methionine and seleno-methionine type peptide and peptoid building blocks by five-component five-center reactions

Goran N. Kaluđerović,[a] Muhammad Abbas,[a,b] Hans Christian Kautz,[a] Mohammad A. M. Wadaan[b], Claudia Lennicke,[c] Barbara Seliger[c] and Ludger A. Wessjohann[a,*]

[a]Leibniz-Institute of Plant Biochemistry, Bioorganic Chemistry, Weinberg 3, 06120, Halle (Saale), Germany. E-mail: wessjohann@ipb-halle.de, [b]Chair of Advanced Proteomics and Cytomics Research, Faculty of Science - Department of Zoology, King Saud University, P.O. Box 2455, 11415 Riyadh - Saudi Arabia; [c]Institute of Medical Immunology, Martin-Luther-University Halle-Wittenberg, Magdeburger Str. 2, 06112, Halle (Saale), Germany.

Table of contents

1. General information S2
2.1. Ugi-5CR with isopropylamine S2
2.2. Ugi-5CR with aniline S5
2.3. Ugi-5CR with ammonium carbonate S8
2.4. Syntheses of peptoids and peptides by Ugi-4CR S11
2.5. Syntheses of peptoids and peptides by Ugi-5CR S15
2.5.1. Amine component: aniline S15
2.5.1. Amine component: ammonium carbonate S15
3. Analytical data of all compounds S19
4. *In vitro* studies S38
4.1. Reagents and cells S38
4.2. XTT assay S38
4.3. GPx1 mRNA expression assay S39
5. References S39
6. NMR copies of all compounds S40

1. General information

^{1}H NMR and ^{13}C NMR spectra were recorded at 25°C on the Varian Mercury 300 and 400, using $CDCl_3$, CD_3OD or pyridin-d_5 as solvents. Chemical shifts are reported in ppm in relation to TMS (δ = 0 ppm, ^{1}H) and $CDCl_3$, CD_3OD or pyridin-d_5 (δ = 77.0, 49.1 or 150.3/135.9/123.9 ppm, respectively, ^{13}C). Coupling constant *J* is quoted in Hz. The high resolution ESI mass spectra were obtained from a Bruker Apex III Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer (Bruker Daltonics, Billerica, USA) equipped with an Infinity™ cell, a 7.0 Tesla superconducting magnet (Bruker, Karlsruhe, Germany), an RF-only hexapole ion guide and an APOLLO electrospray ion source (Agilent, off axis spray). Nitrogen was used as drying gas at 150°C. The sample solutions were introduced continuously via a syringe pump with a flow rate of 120 µL h^{-1}. Thin layer chromatography (TLC) was performed on silica gel (Kieselgel® 60 F254) from Merck. The detection was performed by fluorescence quenching at UV-light (254 nm) or molybdatophosphoric acid (5% w/v) in ethanol. Column chromatography was performed on Kieselgel® 60 (40–60 µm).

2. General experimental procedures

(For yields and analytical data of the products see chapters 3 and 6)

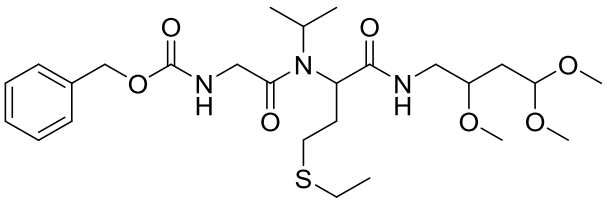
2.1. Ugi-5CR with isopropylamine

Thiol (2.2 equiv.) was slowly added dropwise to a solution of acrolein (1.5 equiv.) in trifluoroethanol (0.7 M) at room temperature. After 10 min isopropylamine (1.5 equiv.) was introduced to the solution and stirred for 2 hr at room temperature. Afterwards, subsequently acid (1.0 equiv.) suspended in trifluoroethanol (0.5 M) and isocyanide (1.25 equiv.) were added to the solution. Then, the reaction mixture was stirred at room temperature for 12 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under vacuum and the crude product was purified by column chromatography.

4-(ethylthio)-2-(*N*-isopropylacetamido)-*N*-(2,4,4-trimethoxybutyl)butanamide (1a)

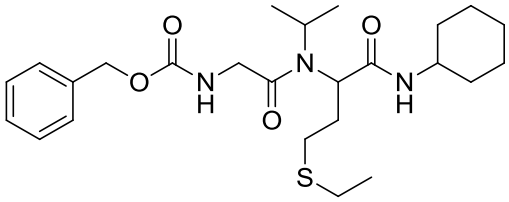
This compound was synthesized using acroleine (100 µL, 1.5 mmol), allylthiol (181 µL, 2.2 mmol), ethaneamine (122 µL, 1.5 mmol), acetic acid (57 µL, 1.0 mmol) and IPB (216 mg, 1.25 mmol).

Benzyl (2-((4-(ethylthio)-1-oxo-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)(isopropyl)amino)-2-oxoethyl)carbamate (1b)



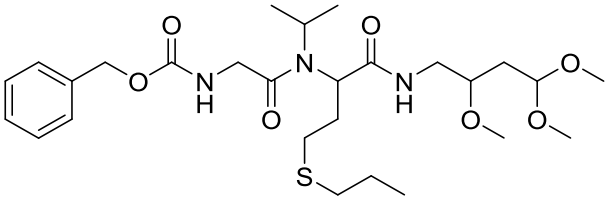
This compound was synthesized using acroleine (100 µL, 1.5 mmol), ethanethiol (158 µL, 2.2 mmol), isopropylamine (122 µL, 1.5 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and 4-isocyano-1,1,3-trimethoxybutane (IPB, 216 mg, 1.25 mmol).

Benzyl (2-((1-(cyclohexylamino)-4-(ethylthio)-1-oxobutan-2-yl)(isopropyl)amino)-2-oxoethyl)carbamate (1c)



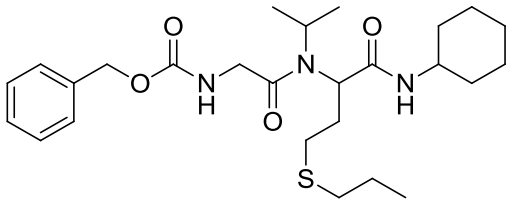
This compound was synthesized using acroleine (100 µL, 1.5 mmol), ethanethiol (158 µL, 2.2 mmol), isopropylamine (122 µL, 1.5 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and cyclohexyl isocyanide (155 µL, 1.25 mmol).

Benzyl (2-(isopropyl(1-oxo-4-(propylthio)-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)amino)-2-oxoethyl)carbamate (1d)



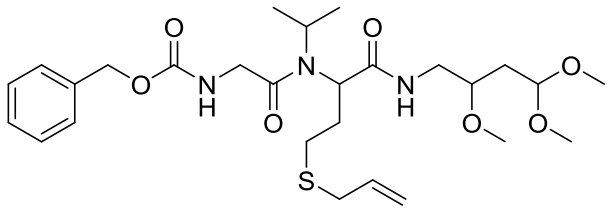
This compound was synthesized using acroleine (100 µL, 1.5 mmol), propanethiol (199 µL, 2.2 mmol), isopropylamine (122 µL, 1.5 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and IPB (216 mg, 1.25 mmol).

Benzyl (2-((1-(cyclohexylamino)-1-oxo-4-(propylthio)butan-2-yl)(isopropyl)amino)-2-oxoethyl)carbamate (1e)



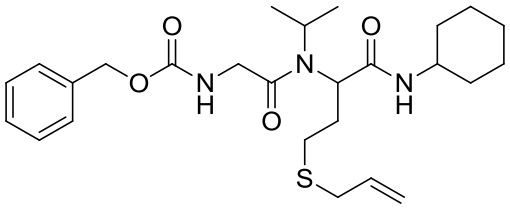
This compound was synthesized using acroleine (100 μL, 1.5 mmol), propanethiol (199 μL, 2.2 mmol), isopropylamine (122 μL, 1.5 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and cyclohexyl isocyanide (155 μL, 1.25 mmol).

Benzyl (2-((4-(allylthio)-1-oxo-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)(isopropyl)amino)-2-oxoethyl)carbamate (1f)



This compound was synthesized using acroleine (100 μL, 1.5 mmol), allylthiol (181 μL, 2.2 mmol), isopropylamine (122 μL, 1.5 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and IPB (216 mg, 1.25 mmol).

Benzyl (2-((4-(allylthio)-1-(cyclohexylamino)-1-oxobutan-2-yl)(isopropyl)amino)-2-oxoethyl)carbamate (1g)

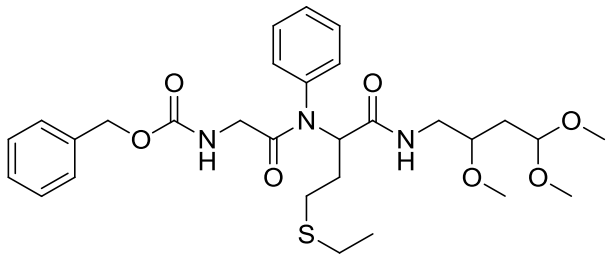


This compound was synthesized using acroleine (100 μL, 1.5 mmol), allylthiol (181 μL, 2.2 mmol), isopropylamine (122 μL, 1.5 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and cyclohexyl isocyanide (155 μL , 1.25 mmol).

2.2. Ugi-5CR with aniline

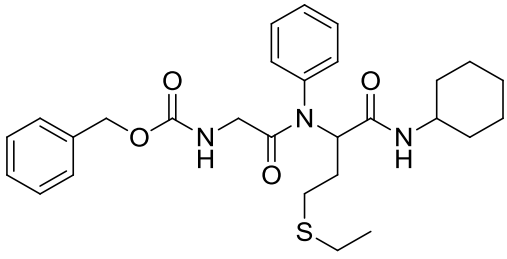
Thiol (3.0 equiv.) was slowly added dropwise to a solution of acroleine (1.5 equiv.) in trifluoroethanol (0.7 M) at room temperature. After 10 min the reaction mixture was cooled to 0°C and aniline (1.5 equiv.) was introduced dropwise over a period of 5 min. The mixture was stirred for 30 min at 0°C. Afterwards, subsequently were added acid (1.0 equiv.) suspended in trifluoroethanol (0.5 M) and isocyanide (1.25 equiv.) at 0°C. Then, the reaction was allowed to warm up and stirred for 12 h at room temperature. After completion of the reaction, the solvent was removed under vacuum and the crude product was purified by column chromatography.

Benzyl (2-((4-(ethylthio)-1-oxo-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)(phenyl)amino)-2-oxoethyl)carbamate (2a)



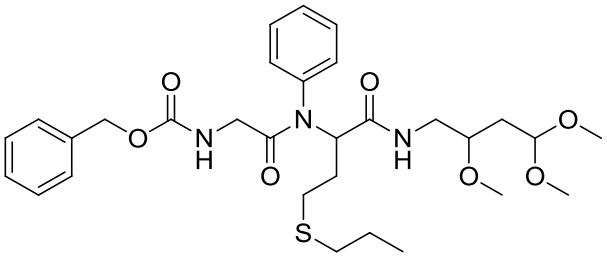
This compound was synthesized using acroleine (100 μL, 1.5 mmol), ethanethiol (216 μL, 3.0 mmol), aniline (137 μL, 1.5 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and IPB (216 mg, 1.25 mmol).

Benzyl (2-((1-(cyclohexylamino)-4-(ethylthio)-1-oxobutan-2-yl)(phenyl)amino)-2-oxoethyl)carbamate (2b)



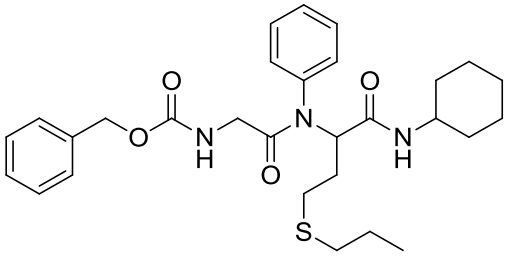
This compound was synthesized using acroleine (100 μL, 1.5 mmol), ethanethiol (216 μL, 3.0 mmol), aniline (137 μL, 1.5 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and cyclohexyl isocyanide (155 μL, 1.25 mmol).

Benzyl (2-oxo-2-((1-oxo-4-(propylthio)-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)(phenyl)amino)ethyl)carbamate (2c)



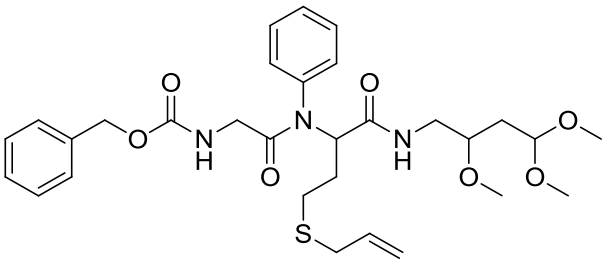
This compound was synthesized using acroleine (100 μL, 1.5 mmol), propanethiol (271 μL, 3.0 mmol), aniline (137 μL, 1.5 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and IPB (216 mg, 1.25 mmol).

Benzyl (2-((1-(cyclohexylamino)-1-oxo-4-(propylthio)butan-2-yl)(phenyl)amino)-2-oxoethyl)carbamate (2d)



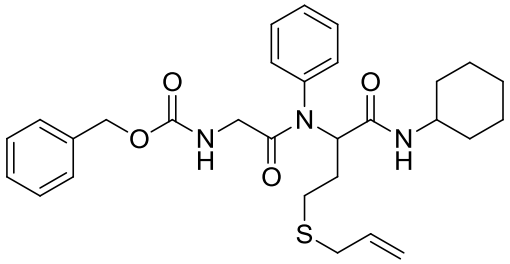
This compound was synthesized using acroleine (100 μL, 1.5 mmol), allylthiol (271 μL, 3.0 mmol), aniline (137 μL, 1.5 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and cyclohexyl isocyanide (155 μL, 1.25 mmol).

Benzyl (2-((4-(allylthio)-1-oxo-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)(phenyl)amino)-2-oxoethyl)carbamate (2e)



This compound was synthesized using acroleine (100 μL, 1.5 mmol), allylthiol (247 μL, 3.0 mmol), aniline (137 μL, 1.5 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and IPB (216 mg, 1.25 mmol).

Benzyl (2-((4-(allylthio)-1-(cyclohexylamino)-1-oxobutan-2-yl)(phenyl)amino)-2-oxoethyl)carbamate (2f)

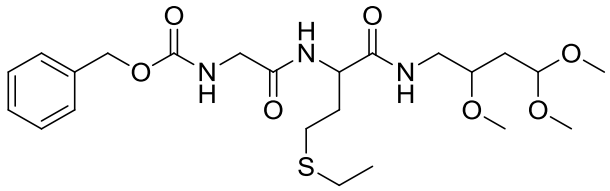


This compound was synthesized using acroleine (100 µL, 1.5 mmol), allylthiol (247 µL, 3.0 mmol), aniline (137 µL, 1.5 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and cyclohexyl isocyanide (155 µL, 1.25 mmol).

2.3. Ugi-5CR with ammonium carbonate

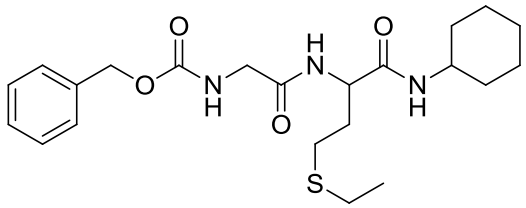
To a solution of acroleine (1.5 equiv.) in trifluoroethanol (1 M), thiol (3.0 equiv.) was added dropwise at room temperature. After 40 min ammonium carbonate (1.7 equiv.) was introduced to the solution and stirred for 1 h at room temperature. Then, acid (1.0 equiv.) suspended in trifluoroethanol (0.7 M) was added to the stirred mixture. After 10 min isocyanide (1.25 equiv.) was added to the solution. The reaction mixture was stirred for 12 h at room temperature. Reaction was followed by TLC. Afterwards solvent was removed under vacuum and the crude product was purified by column chromatography.

Benzyl (2-((4-(ethylthio)-1-oxo-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)amino)-2-oxoethyl)carbamate (3a)



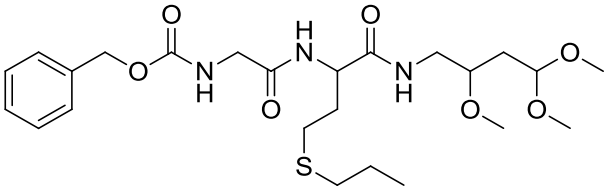
This compound was synthesized using acroleine (100 μL, 1.5 mmol), ethanethiol (216 μL, 3.0 mmol), ammonium carbonate (163 mg, 1.7 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and IPB (216 mg, 1.25 mmol).

Benzyl (2-((1-(cyclohexylamino)-4-(ethylthio)-1-oxobutan-2-yl)amino)-2-oxoethyl)carbamate (3b)



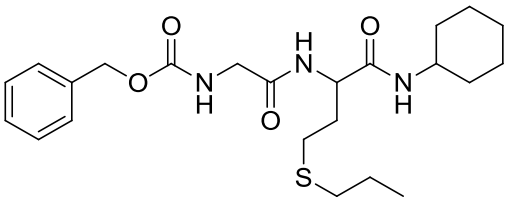
This compound was synthesized using acroleine (100 μL, 1.5 mmol), ethanethiol (216 μL, 3.0 mmol), ammonium carbonate (163 mg, 1.7 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and cyclohexyl isocyanide (155 μL, 1.25 mmol).

Benzyl (2-oxo-2-((1-oxo-4-(propylthio)-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)amino)ethyl)carbamate (3c)



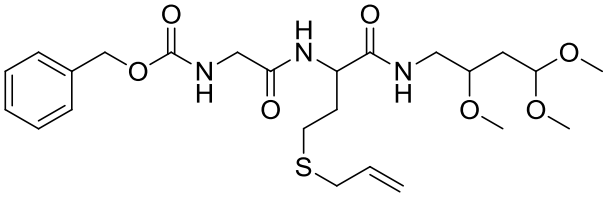
This compound was synthesized using acroleine (100 μL, 1.5 mmol), propanethiol (271 μL, 3.0 mmol), ammonium carbonate (163 mg, 1.7 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and IPB (216 mg, 1.25 mmol).

Benzyl (2-((1-(cyclohexylamino)-1-oxo-4-(propylthio)butan-2-yl)amino)-2-oxoethyl)carbamate (3d)



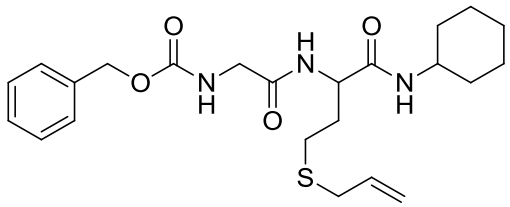
This compound was synthesized using acroleine (100 μL, 1.5 mmol), propaneethiol (271 μL, 3.0 mmol), ammonium carbonate (163 mg, 1.7 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and cyclohexyl isocyanide (155 μL, 1.25 mmol).

Benzyl (2-((4-(allylthio)-1-oxo-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)amino)-2-oxoethyl)carbamate (3e)



This compound was synthesized using acroleine (100 μL, 1.5 mmol), allylthiol (247 μL, 3.0 mmol), ammonium carbonate (163 mg, 1.7 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and IPB (216 mg, 1.25 mmol).

Benzyl (2-((4-(allylthio)-1-(cyclohexylamino)-1-oxobutan-2-yl)amino)-2-oxoethyl)carbamate (3f)



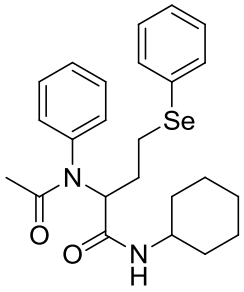
This compound was synthesized using acroleine (100 µL, 1.5 mmol), allylthiol (247 µL, 3.0 mmol), ammonium carbonate (163 mg, 1.7 mmol), *N*-carbobenzyloxyglycine (209 mg, 1.0 mmol) and cyclohexyl isocyanide (155 µL, 1.25 mmol).

2.4. Syntheses of peptoids and peptides by Ugi-4CR

At 0°C of dimethyl diselenide or diphenyl diselenide (15 mmol) was dissolved in 100 mL ethanol. $NaBH_4$ (40 mmol) was slowly added in portions for 30 min until the solution turns clear or slightly yellow. The mixture is warmed to 25°C for 30 min and recooled to 0°C, whereupon of 3-bromopropanaldehyde acetal (28 mmol) was added. The solution was stirred at room temperature for 2 h. Afterwards the solution was filtered, the solvent evaporated and residue dissolved in water (50 mL). The crude product was extracted with diethylether (3 × 50 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated. The residue was chromatographed on silica gel (petroleum ether : ethyl acetate = 10 : 1; yield: 80 %). The acetal was added to 1M HCOOH (40 mL) and heated to 55°C for 4 h. Reaction mixture was cooled to room temperature and extracted with diethyl ether (3 × 50 mL). Organic phase was evaporated yielding selenenylaldehyde as yellow oil (65 %) which was directly used for the further reactions without purification.

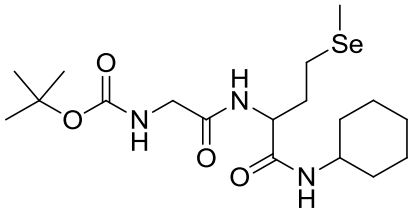
Selenenylaldehyde (1.5 equiv.) and ammonium carbonate (1.1 equiv.) were added in trifluoroethanol (4–5 mL) at 0°C and stirred for 10 min. Afterwards, amino acid (1.0 equiv.) and isonitrile (1.1 equiv.) were added and the reaction mixture and initially stirred at 0°C for 1 h, afterwards 8 h at room temperature. The solvent was removed by rotary evaporation and the obtained crude product was purified by column chromatography using petroleum ether : ethyl acetate.

_N_-cyclohexyl-2-(_N_-phenylacetamido)-4-(phenylselenyl)butanamide (4a)



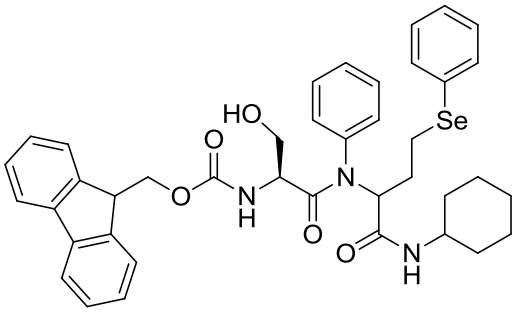
3-(Phenylselenyl)-propanal (320 mg, 1.5 mmol), aniline (136 µL, 1.5 mmol), acetic acid (57 µL, 1.0 mmol) and cyclohexyl isocyanide (137 µL, 1.1 mmol).

***Tert*-butyl (2-((1-(cyclohexylamino)-4-(methylselenyl)-1-oxobutan-2-yl)amino)-2-oxoethyl)carbamate (4b)**



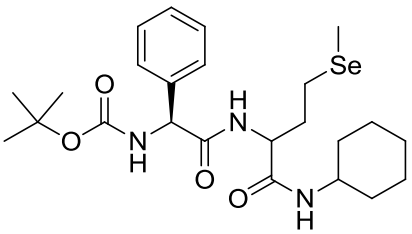
3-(Methylselenyl)-propanal (228 mg, 1.5 mmol), ammonium carbonate (106 mg, 1.1 mmol), *N*-Boc-glycine (175 mg, 1.0 mmol) and cyclohexyl isocyanide (137 μL, 1.1 mmol) were used.

(9*H*-fluoren-9-yl)methyl ((2*S*)-1-((1-(cyclohexylamino)-1-oxo-4-(phenylselenyl)butan-2-yl)(phenyl)amino)-3-hydroxy-1-oxopropan-2-yl)carbamate (4c)



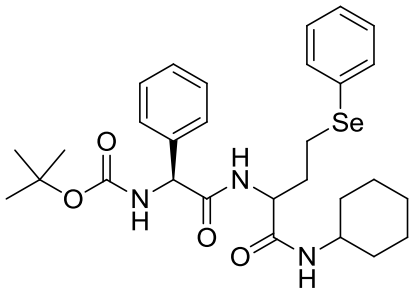
3-(Phenylselenyl)-propanal (320 mg, 1.5 mmol), aniline (136 μL, 1.5 mmol), *N*-Fmoc-L-serine (327 mg, 1.0 mmol) and cyclohexyl isocyanide (137 μL, 1.1 mmol) were used.

***Tert*-butyl ((1*S*)-2-((1-(cyclohexylamino)-4-(methylselenyl)-1-oxobutan-2-yl)amino)-2-oxo-1-phenylethyl)carbamate (4d)**



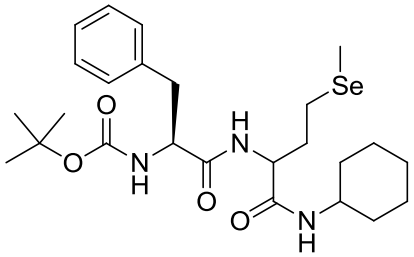
3-(methylselenyl)-propanal (228 mg, 1.5 mmol), ammonium carbonate (106 mg, 1.1 mmol), (*S*)-2-((*tert*-butoxycarbonyl)amino)-2-phenylacetic acid (251 mg, 1 mmol) and cyclohexyl isocyanide (137 μL, 1.1 mmol) were used.

***Tert*-butyl ((1*S*)-2-((1-(cyclohexylamino)-1-oxo-4-(phenylselenyl)butan-2-yl)amino)-2-oxo-1-phenylethyl)carbamate (4e)**



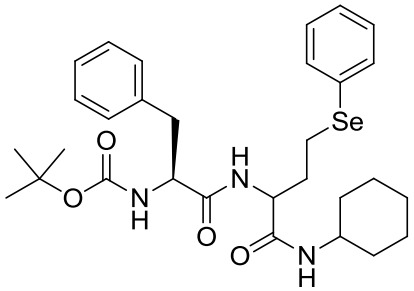
3-(Phenylselenyl)-propanal (320 mg, 1.5 mmol), ammonium carbonate (106 mg, 1.1 mmol), (*S*)-2-((*tert*-butoxycarbonyl)amino)-2-phenylacetic acid (251 mg, 1 mmol) and cyclohexyl isocyanide (137 μL, 1.1 mmol) were used.

***Tert*-butyl ((2*S*)-1-((1-(cyclohexylamino)-4-(methylselenyl)-1-oxobutan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (4f)**



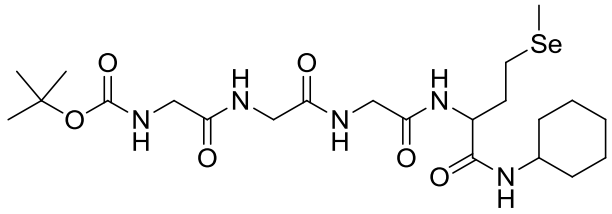
3-(Methylselenyl)-propanal (228 mg, 1.5 mmol), ammonium carbonate (106 mg, 1.1 mmol), *N*-Boc-L-phenylalanine (265 mg, 1.0 mmol) and cyclohexyl isocyanide (137 μL, 1.1 mmol) were used.

***Tert*-butyl ((2*S*)-1-((1-(cyclohexylamino)-1-oxo-4-(phenylselenyl)butan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (4g)**



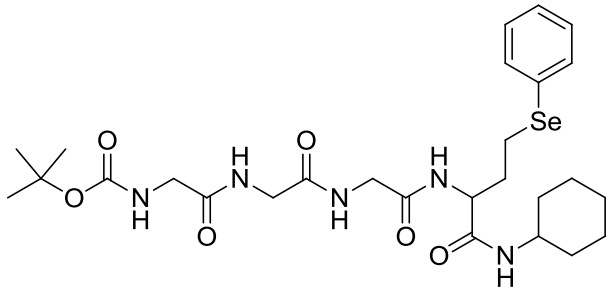
3-(Phenylselenyl)-propanal (320 mg, 1.5 mmol), ammonium carbonate (106 mg, 1.1 mmol), *N*-Boc-L-phenylalanine (265 mg, 1.0 mmol) and cyclohexyl isocyanide (137 μL, 1.1 mmol) were used.

***Tert*-butyl (5-(cyclohexylcarbamoyl)-7,10,13-trioxo-2-selena-6,9,12-triazatetradecan-14-yl)carbamate (4h)**



3-(Methylselenyl)-propanal (228 mg, 1.5 mmol), ammonium carbonate (106 mg, 1.1 mmol), *N*-Boc-Gly-Gly-Gly-OH (289 mg, 1.0 mmol) and cyclohexyl isocyanide (137 μL, 1.1 mmol) were used.

***Tert*-butyl (2-((2-((2-((1-(cyclohexylamino)-1-oxo-4-(phenylselenyl)butan-2-yl)amino)-2-oxoethyl)amino)-2-oxoethyl)amino)-2-oxoethyl)carbamate (4i)**



3-(Phenylselenyl)-propanal (320 mg, 1.5 mmol), ammonium carbonate (106 mg, 1.1 mmol), *N*-Boc-Gly-Gly-Gly-OH (289 mg, 1.0 mmol) and cyclohexyl isocyanide (137 μL, 1.1 mmol) were used

2.5. Syntheses of peptoids and peptides by Ugi-5CR

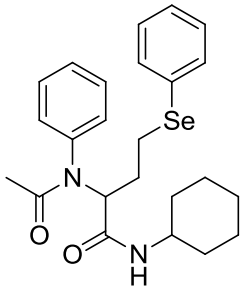
2.5.1. Amine component: aniline

Dimethyldiselenide or diphenyldiselenide (0.6 equiv.) was dissolved in ethanol (5 mL) at 0°C. Then, $NaBH_4$ (1.5 equiv.) was slowly added in portions (10 min), until the solution turned to clear or slightly yellow. The mixture was warmed up to 25°C for 20 min and recooled to 0°C, whereupon acid (2 equiv.) and after 5 min acroline (3 equiv.) and trifluoroethanol (10 mL) were added. The solution was stirred at 0°C for 30 min and then amine (1 equiv.) was introduced and stirred for 10 min at room temperature. Subsequently, isonitrile (1.2 equiv.) was added and the reaction mixture was stirred for 8 h at room temperature. Afterwards, the reaction mixture was concentrated and purified by column chromatography.

2.5.1. Amine component: ammonium carbonate

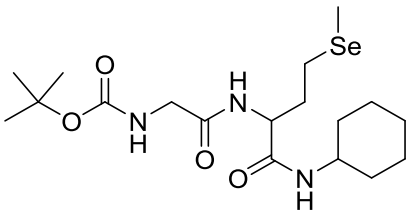
Dimethyl diselenide or diphenyl diselenide (1 equiv.) was dissolved in ethanol (2 mL) and $NaBH_4$ (2.6 equiv.) was added in portions (10 min) at 0°C and stirred for 20 min. Then, acid (2 equiv.) and after 5 min acroline (3 equiv.) were added to the reaction mixture and stirred for further 10 min at 0°C. Trifluoroethanol (10 mL) was added to the reaction mixture followed by ammonium carbonate (1.5 equiv.) in one portion. After 20 min, isonitrile (1 equiv.) was introduced. The reaction mixture was stirred at room temperature for 8 h then concentrated and purified by column chromatograph by using petroleum ether : ethyl acetate.

***N*-cyclohexyl-2-(*N*-phenylacetamido)-4-(phenylselenyl)butanamide (4a)**



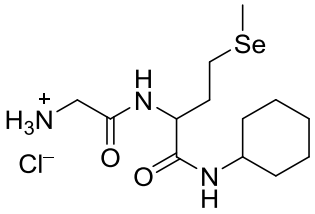
Acrolein (120 μL, 1.8 mmol), diphenyldiselenide (187 mg, 0.6 mmol), sodium borohydride (100 mg, 2.7 mmol), aniline (137 μL, 1.8 mmol), acetic acid (114 μL, 2.0 mmol) and cyclohexyl isocyanide (149 μL, 1.2 mmol) were used.

***Tert*-butyl (2-((1-(cyclohexylamino)-4-(methylselenyl)-1-oxobutan-2-yl)amino)-2-oxoethyl)carbamate (4b)**



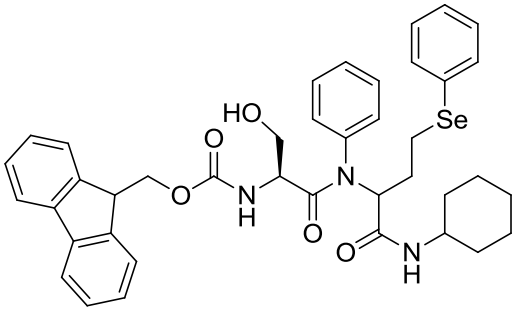
Acrolein (200 μL, 3.0 mmol), dimethyldiselenide (95 μL, 1 mmol), sodium borohydride (100 mg, 2.7 mmol), ammonium carbonate (140 mg, 1.5 mmol), *N*-Boc-glycine (350 mg, 2 mmol) and cyclohexyl isocyanide (125 μL, 1 mmol) were used.

2-((1-(Cyclohexylamino)-4-(methylselanyl)-1-oxobutan-2-yl)amino)-2-oxoethan-1-aminium chloride (4bd)



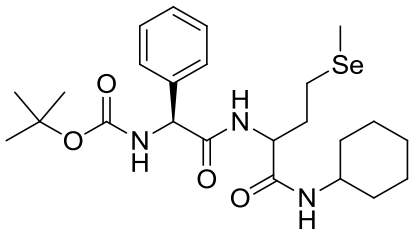
4b (100 mg, 0.23 mmol) was dissolved HCl/dioxan (2 M, 10 mL) and stirred at room temperature. Deprotection of **4b** was followed by TLC, which was completed within 30 min. Solvent was evaporated and pure product was obtained.

(9*H*-fluoren-9-yl)methyl ((2*S*)-1-((1-(cyclohexylamino)-1-oxo-4-(phenylselenyl)butan-2-yl)(phenyl)amino)-3-hydroxy-1-oxopropan-2-yl)carbamate (4c)



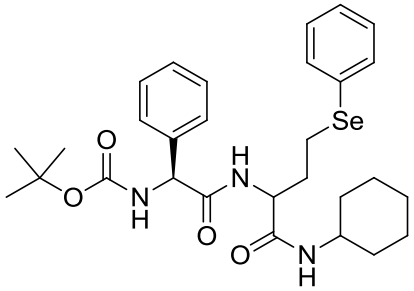
Acrolein (120 μL, 1.8 mmol), diphenyldiselenide (188 mg, 0.6 mmol), sodium borohydride (37 mg, 1 mmol), aniline (91 μL, 1 mmol), *N*-Fmoc-L-serine (654 mg, 2 mmol) and cyclohexyl isocyanide (150 μL, 1.2 mmol) were used.

***Tert*-butyl ((1*S*)-2-((1-(cyclohexylamino)-4-(methylselenyl)-1-oxobutan-2-yl)amino)-2-oxo-1-phenylethyl)carbamate (4d)**



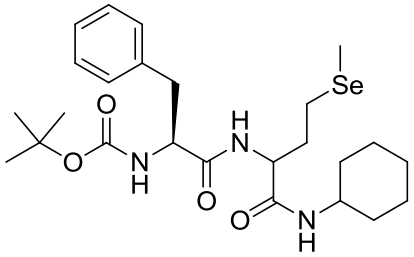
Acrolein (200 μL, 3.0 mmol), dimethyldiselenide (95 μL, 1 mmol), sodium borohydride (100 mg, 2.7 mmol), ammonium carbonate (140 mg, 1.5 mmol), (*S*)-2-((*tert*-butoxycarbonyl)-amino)-2-phenylacetic acid (456 mg, 2 mmol) and cyclohexyl isocyanide (125 μL, 1 mmol) were used.

***Tert*-butyl ((1*S*)-2-((1-(cyclohexylamino)-1-oxo-4-(phenylselenyl)butan-2-yl)amino)-2-oxo-1-phenylethyl)carbamate (4e)**



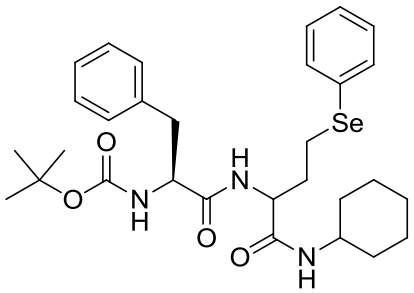
Acrolein (200 μL, 3.0 mmol), diphenyldiselenide (95 μL, 1 mmol), sodium borohydride (100 mg, 2.7 mmol), ammonium carbonate (140 mg, 1.5 mmol), (*S*)-2-((*tert*-butoxycarbonyl)-amino)-2-phenylacetic acid (456 mg, 2 mmol) and cyclohexyl isocyanide (125 μL, 1 mmol) were used.

***Tert*-butyl ((2*S*)-1-((1-(cyclohexylamino)-4-(methylselenyl)-1-oxobutan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (4f)**



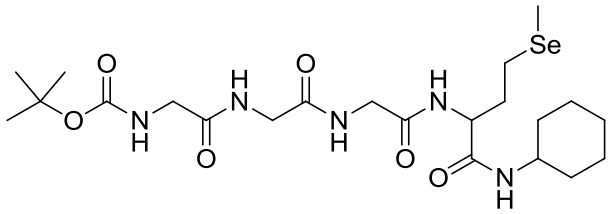
Acrolein (200 μL, 3.0 mmol), dimethyldiselenide (95 μL, 1 mmol), sodium borohydride (100 mg, 2.7 mmol), ammonium carbonate (140 mg, 1.5 mmol), *N*-Boc-L-phenylalanine (530 mg, 2 mmol) and cyclohexyl isocyanide (125 μL, 1 mmol) were used.

***Tert*-butyl ((2*S*)-1-((1-(cyclohexylamino)-1-oxo-4-(phenylselenyl)butan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (4g)**



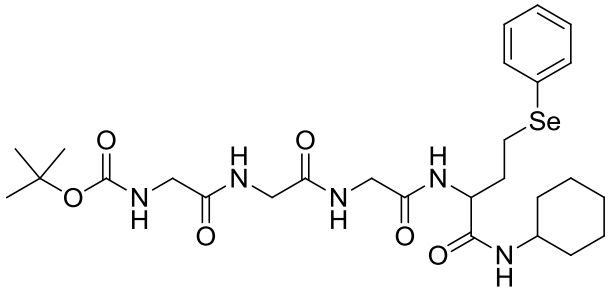
Acrolein (200 μL, 3.0 mmol), diphenyldiselenide (312 mg, 1 mmol), sodium borohydride (100 mg, 2.7 mmol), ammonium carbonate (140 mg, 1.5 mmol), *N*-Boc-L-phenylalanine (530 mg, 2 mmol) and cyclohexyl isocyanide (125 μL, 1 mmol) were used.

***Tert*-butyl (5-(cyclohexylcarbamoyl)-7,10,13-trioxo-2-selena-6,9,12-triazatetradecan-14-yl)carbamate (4h)**



Acrolein (200 μL, 3.0 mmol), dimethyldiselenide (95 μL, 1 mmol), sodium borohydride (100 mg, 2.7 mmol), ammonium carbonate (140 mg, 1.5 mmol), *N*-Boc-Gly-Gly-Gly-OH (578 mg, 2 mmol) and cyclohexyl isocyanide (125 μL, 1 mmol) were used.

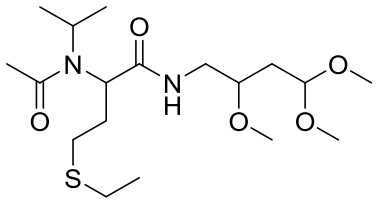
***Tert*-butyl (2-((2-((2-((1-(cyclohexylamino)-1-oxo-4-(phenylselenyl)butan-2-yl)amino)-2-oxoethyl)amino)-2-oxoethyl)amino)-2-oxoethyl)carbamate (4i)**



Acrolein (200 μL, 3.0 mmol), diphenyldiselenide (312 mg, 1 mmol), sodium borohydride (100 mg, 2.7 mmol), ammonium carbonate (140 mg, 1.5 mmol), *N*-Boc-Gly-Gly-Gly-OH (578 mg, 2 mmol) and cyclohexyl isocyanide (125 μL, 1 mmol) were used.

3. Analytical data of all compounds

4-(ethylthio)-2-(*N*-isopropylacetamido)-N-(2,4,4-trimethoxybutyl)butanamide (1a)



Yield: 50% (196 mg)

Nature: slightly yellow oil

Rf: 0.34 (ethyl acetate)

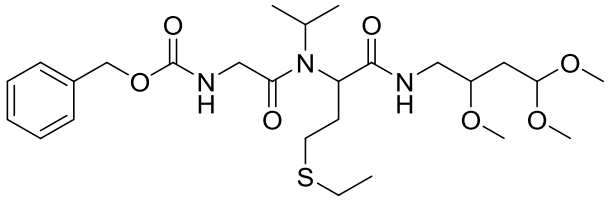
Flash chromatography: gradient: 4 : 1 (ethyl acetate : petroleum ether) to 95 : 5 (ethyl acetate : methanol)

^{1}H NMR (CD_3OD, 400 MHz): δ 4.506 (t, 1 H, *J* = 5.2 Hz), 4.180 (sep, 1 H, *J* = 6 Hz), 3.958 (t, 1 H, *J* = 5.2 Hz), 3.390 – 3.200 (m, 3 H), 3.360 (s, 3 H, OCH_3), 3.315 (s, 6 H, OCH_3), 2.680 – 2.500 (m, 4 H), 2.174 (s, 3 H), 1.712 (m, 2 H), 1.328 (m, 2 H), 1.276 (d, 6 H, *J* = 6 Hz, ^{i}Pr), 1.234 (t, 3 H, *J* = 7.6 Hz, S-CH_2-CH_3).

^{13}C NMR (CD_3OD, 125 MHz): δ 174.25, 174.19, 173.62, 103.49, 77.67, 58.16, 58.13, 57.62, 53.57, 53.54, 53.48, 52.08, 42.81, 42.64, 36.70, 36.54, 31.95, 30.25, 26.64, 22.85, 21.50, 20.99, 15.11.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{18}H_{36}O_5N_2NaS$: 415.2243, found: 415.2234.

Benzyl (2-((4-(ethylthio)-1-oxo-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)(isopropyl)amino)-2-oxoethyl)carbamate (1b)



Yield: 60% (325 mg)

Nature: slightly yellow oil

Rf: 0.65 (ethyl acetate)

Flash chromatography: gradient: 2 : 1 (ethyl acetate : petroleum ether) to ethyl acetate

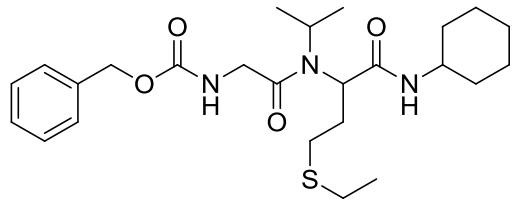
^{1}H NMR (CD_3OD, 400 MHz): δ 7.390 – 7.264 (m, 5 H, CH), 5.104 (s, 2 H, Ph-CH_2), 4.503 (t, 1 H, *J* = 6 Hz), 4.200 – 3.925 (m , 5 H), 3.305 (s, 9 H, OCH_3), 3.250 – 3.200 (m, 1 H),

2.685 – 2.455 (m, 5 H), 2.140 – 2.042 (m, 1 H), 1.772 – 1.625 (m, 2 H), 1.380 – 1.195 (m, 9 H).

^{13}C H NMR (CD_3OD, 125 MHz): δ 174.10, 171.49, 159.05, 138.21, 129.46, 129.01, 128.87, 103.54, 77.67, 77.61, 67.78, 58.26, 57.67, 53.49, 50.13, 44.36, 42.80, 36.80, 31.96, 30.76, 26.49, 21.54, 15.12.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{26}H_{43}O_7N_3NaS$: 564.2719, found: 564.2714.

Benzyl (2-((1-(cyclohexylamino)-4-(ethylthio)-1-oxobutan-2-yl)(isopropyl)amino)-2-oxoethyl)carbamate (1c)



Yield: 78% (372 mg)

Nature: white solid

Rf: 0.56 (1 : 1 ethyl acetate : petroleum ether)

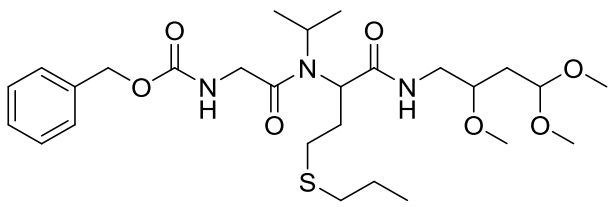
Flash chromatography: gradient: 1 : 2 (ethyl acetate : petroleum ether) to 2 : 1 (ethyl acetate : petroleum ether)

^{1}H NMR (CD_3OD, 400 MHz): δ 7.385 – 7.260 (m, 5 H, CH), 5.185 – 5.100 (bs, 2 H, Ph-CH_2), 4.200 – 3.890 (m, 4 H), 2.651 – 2.395 (m, 6 H), 2.180 (q, 1 H, *J* = 6 Hz), 1.923 – 1.545 (m, 8 H), 1.382 – 1.151 (m, 11 H).

^{13}C NMR (CD_3OD, 125 MHz): δ 173.15, 172.99, 171.97, 159.18, 138.23, 129.46, 128.99, 128.78, 67.71, 61.53 , 58.91, 50.27, 44.37, 33.36, 31.87, 30.11, 26.62, 26.47, 25.91, 20.86, 15.11.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{25}H_{39}O_4N_3NaS$: 500.2559, found: 500.2553.

Benzyl (2-(isopropyl(1-oxo-4-(propylthio)-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)amino)-2-oxoethyl)carbamate (1d)



Yield: 55% (305 mg)

Nature: slightly yellow oil

Rf: 0.68 (ethyl acetate)

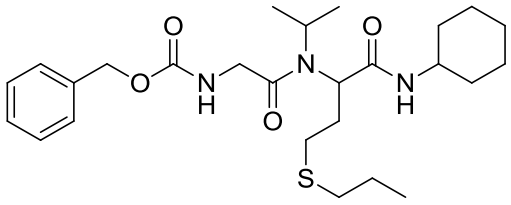
Flash chromatography: gradient: 2 : 1 (ethyl acetate : petroleum ether) to ethyl acetate

^{1}H NMR (CD_3OD, 400 MHz): δ 7.385 – 7.265 (m, 5 H, CH), 5.106 (s, 2 H, Ph-CH_2), 4.503 (t, 1 H, *J* = 6 Hz), 4.182 – 3.918 (m, 5 H), 3.344 (s, 3 H, OCH_3), 3.31 (s, 6 H, OCH_3), 3.250 – 3.165 (m, 2 H), 2.602 (t, 2 H, *J* = 11.2 Hz), 2.492 (t, 2 H, *J* = 7.2 Hz), 2.098 (m, 1 H), 1.765 – 1.662 (m, 2 H), 1.594 (hex, 2 H, *J* = 7.2 Hz, S-CH_2-CH_2), 1.375 – 1.152 (m, 2 H), 1.284 (d, 6 H, *J* = 4.8 Hz, ^{i}Pr), 0.976 (t, 3 H, *J* = 7.2 Hz, S-CH_2-CH_2-CH_3).

^{13}C NMR (CD_3OD, 125 MHz): δ 174.11, 174.06, 171.54, 171.49, 159.06, 138.20, 129.46, 129.01, 128.88, 103.54, 103.51, 77.67, 77.61, 67.78, 58.25, 57.67, 53.50, 50.19, 44.31, 42.85, 36.81, 34.86, 32.05, 30.71, 23.95, 21.55, 13.74.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{27}H_{45}O_7N_3NaS$: 578.2876, found: 578.2870.

Benzyl (2-((1-(cyclohexylamino)-1-oxo-4-(propylthio)butan-2-yl)(isopropyl)amino)-2-oxoethyl)carbamate (1e)



Yield: 66% (324 mg)

Nature: white solid

Rf: 0.60 (1 : 1 ethyl acetate : petroleum ether)

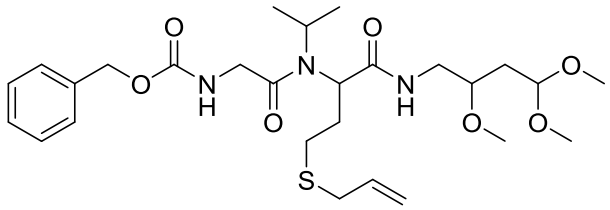
Flash chromatography: gradient: 1 : 2 (ethyl acetate : petroleum ether) to 2 : 1 (ethyl acetate : petroleum ether)

^{1}H NMR (CD_3OD, 400 MHz): δ 7.388 – 7.262 (m, 5 H, CH), 5.128 – 5.081 (bs, 2 H, Ph-CH_2), 4.438 (t, 1 H, *J* = 7.2 Hz), 4.242 – 4.046 (m, 1 H), 3.975 – 3.864 (m, 1 H), 3.708 – 3.585 (bs, 2 H), 2.615 – 2.435 (m, 6 H), 2.175 (q, 1 H, *J* = 4.4 Hz), 1.885 – 1.665 (m, 6 H), 1.590 (sex, 2 H, *J* = 6.8 Hz), 1.380 – 1.164 (m, 10 H), 0.976 (t, 3 H, *J* = 6.8 Hz, S-CH_2-CH_2-CH_3).

^{13}C NMR (CD_3OD, 125 MHz): δ 173.15, 171.96, 159.16, 138.29, 129.46, 128.99, 128.78, 67.71, 61.53, 58.92, 50.27, 49.89, 44.38, 34.85, 33.36, 31.95, 30.51, 26.63, 25.96, 23.94, 20.86, 13.73.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{26}H_{41}O_4N_3NaS$: 514.2716, found: 514.2710.

Benzyl (2-((4-(allylthio)-1-oxo-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)(isopropyl)amino)-2-oxoethyl)carbamate (1f)



Yield: 43% (237 mg)

Nature: slightly yellow oil

Rf: 0.62 (ethyl acetate)

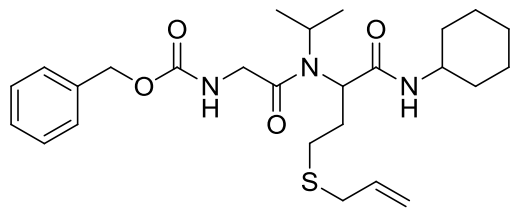
Flash chromatography: gradient: 2 : 1 (ethyl acetate : petroleum ether) to ethyl acetate

^{1}H NMR (CD_3OD, 400 MHz): δ 7.294 – 7.166 (m, 5 H, CH), 5.685 (ddt, 1 H, *J* = 13.2, 7.2, 3.2 Hz, S-CH_2-$CHCH_2$), 5.011 (s, 2 H), 4.970 (dd, 2 H, *J* = 13, 7 Hz, S-CH_2-$CHCH_2$), 4.409 (t, 1 H, *J* = 6.4 Hz), 4.098 – 3.805 (m, 4 H), 3.215 – 3.197 (bs, 9 H, OCH_3), 3.358 – 2.995 (m, 5 H), 2.560 – 2.342 (m, 4 H), 1.675 – 1.542 (m, 2 H), 1.271 – 1.092 (m, 2 H), 1.183 (d, 6 H, *J* = 5.6 Hz, ^{i}Pr).

^{13}C NMR (CD_3OD, 125 MHz): δ 174.01, 171.48, 159.06, 138.19, ,135.83, 129.47, 129.02, 128.88, 117.33, 103.56, 77.66, 64.79, 58.13, 57.67, 53.52, 50.20, 44.36, 42.87, 36.81, 35.29, 31.61, 30.26, 20.82.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{27}H_{43}O_7N_3NaS$: 576.2719, found: 576.2704.

Benzyl (2-((4-(allylthio)-1-(cyclohexylamino)-1-oxobutan-2-yl)(isopropyl)amino)-2-oxoethyl)carbamate (1g)



Yield: 60% (322 mg)

Nature: slightly yellow oil

Rf: 0.55 (1 : 1 ethyl acetate : petroleum ether)

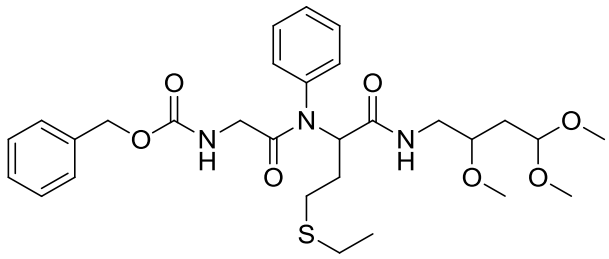
Flash chromatography: gradient: 1 : 2 (ethyl acetate : petroleum ether) to 2 : 1 (ethyl acetate : petroleum ether)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.384 – 7.294 (m, 5 H, CH), 6.458 (bs, 1 H, NH), 5.778 (ddt, 1H, *J* = 13.2, 7.2, 3.2 Hz, S-CH_2-$CHCH_2$), 5.751 (t, 1 H, *J* = 3.2 Hz), 5.135 (s, 2 H, Ph-CH_2), 5.090 (dd, 2 H, *J* = 7.2 Hz), 4.072 (qd, 2 H, *J* = 23.2, 4 Hz), 3.915 (s, 1*H*, *J* = 6 Hz), 3.695 (t, 1 H, *J* = 14 Hz), 3.116 (d, 2 H, *J* = 6.8 Hz), 2.651 – 2.402 (m, 4 H), 2.208 – 2.104 (m, 1H), 1.938 – 1.518 (m, 6 H), 1.400 – 1.075 (m, 4 H), 1.268 (d, 6 H, *J* = 6 Hz, ^{i}Pr).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.63, 168.91, 156.17, 136.29, 134.12, 128.50, 128.15, 128.02, 117.14, 66.96, 59.47, 59.29, 49.08, 47.93, 43.63, 34.56, 32.66, 32.55, 29.95, 27.75, 25.49, 24.52, 20.89, 20.80.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{26}H_{39}O_4N_3NaS$: 512.2559, found: 512.2555.

Benzyl (2-((4-(ethylthio)-1-oxo-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)(phenyl)amino)-2-oxoethyl)carbamate (2a)



Yield: 43% (247 mg)

Nature: slightly yellow oil

Rf: 0.65 (ethyl acetate)

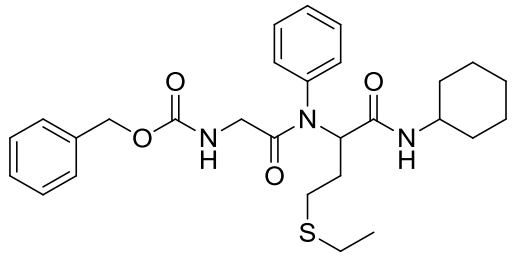
Flash chromatography: gradient: 1 : 2 (ethyl acetate : petroleum ether) to 1 : 1 (ethyl acetate : petroleum ether)

^{1}H NMR (CD_3OD, 400 MHz): δ 7.515 – 7.254 (m, 10 H, CH), 5.165 (t, 1 H, *J* = 7.2 Hz), 5.067 (s, 2 H, Ph-CH_2), 4.528 (t, 1 H, *J* = 6 Hz), 3.505 – 3.401 (m, 2 H), 3.381 (d, 2 H, *J* = 4.8 Hz), 3.329 (d, 2 H, *J* = 2 Hz), 3.316 – 3.294 (m, 9 H, OCH_3), 2.503 (t, 2 H, *J* = 7.6 Hz), 2.435 (q, 2 H, *J* = 7.6 Hz, S-CH_2), 1.922 (q, 1 H, *J* = 7.2 Hz), 1.835 – 1.702 (m, 4 H), 1.167 (t, 3 H, *J* = 7.6 Hz, S-CH_2-CH_3).

^{13}C NMR (CD_3OD, 125 MHz): δ 172.51, 171.77, 159.01, 139.25, 138.16, 130.92, 130.82, 130.34, 129.45, 129.00, 128.82, 103.65, 103.61, 77.67, 67.74, 60.33, 57.64, 57.58, 53.82, 53.75, 53.51, 53.49, 44.74, 42.88, 42.71, 36.91, 36.82, 30.56, 28.95, 28.92, 26.41, 15.16.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{29}H_{41}O_7N_3NaS$: 598.2563, found: 598.2556.

Benzyl (2-((1-(cyclohexylamino)-4-(ethylthio)-1-oxobutan-2-yl)(phenyl)amino)-2-oxoethyl)carbamate (2b)



Yield: 47% (240 mg)

Nature: slightly yellow solid

Rf: 0.52 (1 : 1 ethyl acetate : petroleum ether)

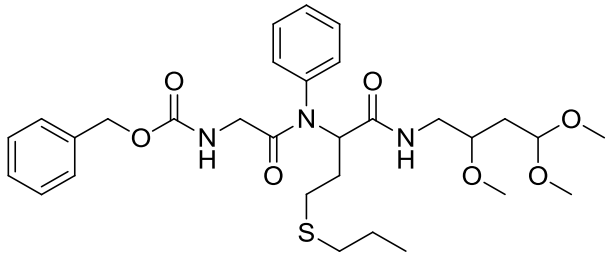
Flash chromatography: gradient: 1 : 2 (ethyl acetate : petroleum ether) to 1 : 1 (ethyl acetate : petroleum ether)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.423 – 7.154 (m, 10 H, CH), 6.545 (d, 1 H, *J* = 8.4, NH), 5.672 (t, *J* = 4.4 Hz), 5.145 (t, 1 H, *J* = 7.6 Hz), 5.070 (s, 2 H, PH-CH_2), 3.370 (dd, 1 H, *J* = 18, 5.2 Hz), 3.502 (dd, 1 H, *J* = 18, 5.2 Hz), 2.526 (sex, 1 H, *J* = 6 Hz, CH), 2.450 (q, 2 H, *J* = 7.2 Hz, S-CH_2), 2.480 – 2.390 (m, 1H), 1.980 – 1.840 (m, 3 H), 1.745 – 1.660 (m, 2H), 1.640 – 1.551 (m, 2 H), 1.426 – 1.294 (m, 2 H), 1.272 – 1.152 (m, 4 H), 1.190 (t, 3 H, *J* = 7.2 Hz, S-CH_2-CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.76, 168.72, 156.07, 136.83, 136.24, 129.71, 129.22, 129.12, 128.34, 127.96, 127.85, 66.72, 57.89, 48.20, 43.88, 32.67, 32.64, 28.54, 27.93, 25.64, 25.36, 24.61, 24.57, 14.54.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{28}H_{37}O_4N_3NaS$: 534.2402, found: 534.2402.

Benzyl (2-oxo-2-((1-oxo-4-(propylthio)-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)(phenyl)amino)ethyl)carbamate (2c)



Yield: 43% (253 mg)

Nature: slightly yellow oil

Rf: 0.70 (ethyl acetate)

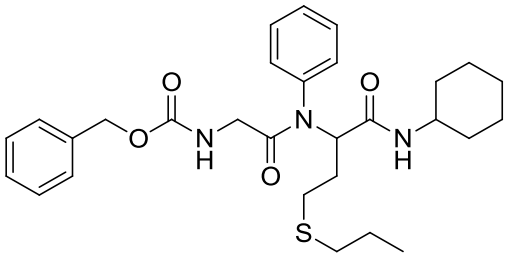
Flash chromatography: gradient: 1 : 2 (ethyl acetate : petroleum ether) to 1 : 1 (ethyl acetate : petroleum ether)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.435 – 7.178 (m, 10 H, CH), 5.644 (bs, 1 H), 5.168 (q, 1 H, *J* = 6.4 Hz), 5.065 (s, 2 H, Ph-CH_2), 4.518 (tdt, 1 H, *J* = 5.6, 4.4, 2.8 Hz), 3.810 (dt, 1 H, *J* = 18.4, 5.6 Hz), 3.598 (dt, 1 H, *J* = 18.4, 5.6 Hz), 3.444 – 3.940 (m, 4 H), 3.387, 3.380 (s, 3 H, OCH_3), 3.340 – 3.300 (m, 6 H, OCH_3), 2.518 (t, 1 H, *J* = 5.6 Hz), 2.499 (t, 1 H, *J* = 5.6 Hz), 2.405 (t, 2 H, *J* = 7.2 Hz, S-CH_2), 1.950 – 1.580 (m, 6 H), 1.538 (sex, 2 H, *J* = 7.2 Hz, S-CH_2-CH_2), 0.943 (t, 3 H, *J* = 7.2 Hz, S-CH_2-CH_2-CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.12, 170.09, 169.88, 169.81, 156.20, 136.95, 136.91, 136.40, 136.36, 129.85, 129.36, 129.28, 128.46, 128.09, 128.00, 101.98, 101.87, 76.20, 76.09, 66.84, 57.97, 57.15, 57.05, 53.34, 53.21, 53.11, 52.99, 44.01, 41.62, 41.25, 35.48, 35.32, 34.02, 33.99, 28.64, 28.44, 28.41, 22.79, 13.39.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{30}H_{43}O_7N_3NaS$: 612.2719, found: 612.2713.

Benzyl (2-((1-(cyclohexylamino)-1-oxo-4-(propylthio)butan-2-yl)(phenyl)amino)-2-oxoethyl)carbamate (2d)



Yield: 60% (315 mg)

Nature: slightly yellow solid

Rf: 0.48 (1 : 1 ethyl acetate : petroleum ether)

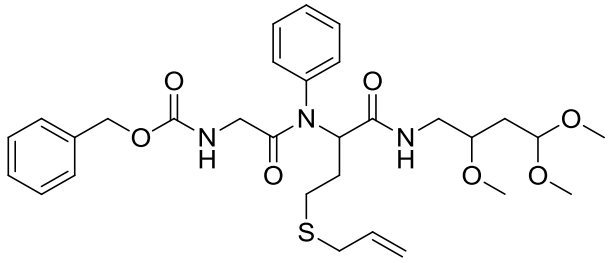
Flash chromatography: gradient: 1 : 2 (ethyl acetate : petroleum ether) to 1 : 1 (ethyl acetate : petroleum ether)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.438 – 7.154 (m, 10 H, CH), 6.506 (d, *J* = 8.4 Hz), 5.629 (t, *J* = 4.4 Hz), 5.141 (t, 1 H, *J* = 6.8 Hz), 5.068 (s, 2 H, Ph-CH_2), 3.380 – 3.724 (m, 1 H), 3.740 (dd, 1 H, *J* = 18, 4.4 Hz), 3.501 (dd, 1 H, *J* = 18, 4.4 Hz), 2.510 (sex, 1 H, *J* = 7.2 Hz), 2.455 – 2.396 (m, 1 H), 2.405 (t, 2 H, *J* = 7.2 Hz, S-CH_2), 1.964 – 1.842 (m, 4 H), 1.748 – 1.661 (m, 2 H), 1.638 – 1.561 (m, 2 H), 1.538 (sex, 2 H, *J* = 7.2 Hz, S-CH_2-CH_2), 1.430 – 1.298 (m, 2 H), 1.274 – 1.137 (m, 4 H), 0.941 (t, 3 H, *J* = 7.2 Hz, S-CH_2-CH_2-CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.77, 168.78, 156.08, 136.85, 136.28, 129.75, 129.27, 129.18, 128.39, 128.01, 127.90, 66.77, 57.93, 48.23, 43.93, 33.95, 32.71, 28.66, 28.40, 25.40, 24.64, 24.60, 22.73, 13.33.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{29}H_{39}O_4N_3NaS$: 548.2559, found: 548.2555.

Benzyl (2-((4-(allylthio)-1-oxo-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)(phenyl)amino)-2-oxoethyl)carbamate (2e)



Yield: 20% (117 mg)

Nature: slightly yellow oil

Rf: 0.60 (ethyl acetate)

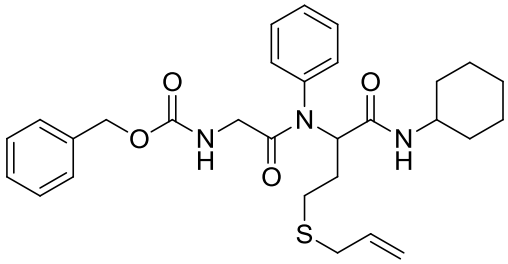
Flash chromatography: gradient: 1 : 2 (ethyl acetate : petroleum ether) to 1 : 1 (ethyl acetate : petroleum ether)

^{1}H NMR (CD_3OD, 400 MHz): δ 7.506 – 7.249 (m, 10 H, CH), 5.732 (ddt, 1 H, *J* = 13.2, 7.2, 3.2 Hz, S-CH_2-$CHCH_2$), 5.160 (t, 1 H, *J* = 7.2 Hz), 5.066 (s, 2 H, Ph-CH_2), 5.055 (dd, 2 H, *J* = 13, 7 Hz, S-CH_2-$CHCH_2$), 4.529 (t, 1 H, *J* = 5.6 Hz), 3.680 – 3.400 (m, 4 H), 3.386, 3.375 (s, 3H, OCH_3), 3.335 – 3.294 (m, 6 H, OCH_3), 3.066 (d, 2 H, *J* = 7.2 Hz), 2.450 (t, 2 H, *J* = 7.2 Hz), 1.970 – 1.682 (m, 4 H).

^{13}C NMR (CD_3OD, 125 MHz): δ 172.41, 171.76, 172.73, 158.99, 139.26, 138.15, 136.01, 135.82, 130.83, 130.34, 129.45, 129.00, 128.82, 117.33, 117.12, 103.64, 103.60, 67.74, 60.27, 57.65, 57.59, 53.82, 53.50, 44.74, 42.2, 42.73, 36.91, 36.83, 35.26, 30.17, 28.16, 28.12.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{30}H_{41}O_7N_3NaS$: 610.2563, found: 610.2558.

Benzyl (2-((4-(allylthio)-1-(cyclohexylamino)-1-oxobutan-2-yl)(phenyl)amino)-2-oxoethyl)carbamate (2f)



Yield: 18% (94 mg)

Nature: slightly yellow oil

Rf: 0.42 (1 : 1 ethyl acetate : petroleum ether)

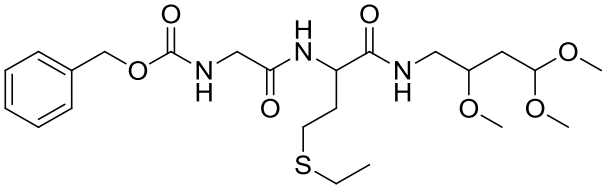
Flash chromatography: gradient: 1 : 2 (ethyl acetate : petroleum ether) to 1 : 1 (ethyl acetate : petroleum ether)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.431 – 7.086 (m, 10 H, CH), 6.496 (t, 1 H, *J* = 7.6 Hz), 5.731 (ddt, 1 H, *J* = 18, 8.8, 7.2 Hz, S-CH_2-$CHCH_2$), 5.616 (bs), 5.180 – 5.021 (m, 2 H), 5.068 (s, 2 H, Ph-CH_2), 3.822 – 3.730 (m, 1 H), 3.734 (dd, 1 H, *J* = 17.6, 4.4 Hz), 3.502 (dd, 1 H, *J* = 17.6, 4.4 Hz), 3.058 (d, 2 H, *J* = 6 .8 Hz), 2.604 – 2.345 (m, 2 H), 2.516 (q, 2 H, *J* = 6.8 Hz), 1.934 – 1.834 (m, 2 H), 1.770 (sex, 1 H, *J* = 7.2 Hz), 1.742 – 1.653 (m, 2 H), 1.648 – 1.515 (m, 2H), 1.434 – 1.301 (m, 2 H), 1.284 – 1.221 (m, 4 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.79, 168.73, 168.70, 156.08, 136.84, 136.81, 136.28, 134.23, 134.04, 129.77, 129.29, 129.13, 128.40, 128.02, 127.91, 117.09, 116.89, 66.78, 57.95,57.83, 48.24, 43.93, 34.60, 34.53, 32.71, 30.77, 30.65, 29.32, 28.74, 27.09, 25.41, 24.64, 24.60.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{29}H_{37}O_4N_3NaS$: 546.2403, found: 546.2398.

Benzyl (2-((4-(ethylthio)-1-oxo-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)amino)-2-oxoethyl)carbamate (3a)



Yield: 33% (164 mg)

Nature: colorless oil

Rf: 0.45 (ethyl acetate)

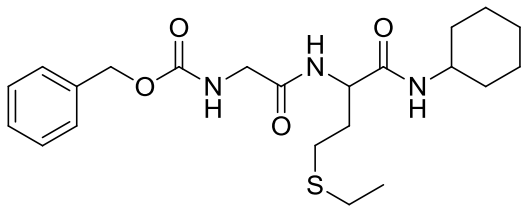
Flash chromatography: ethyl acetate

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.392 – 7.288 (m, 5 H, CH), 6.900 (t, 1 H, *J* = 6 Hz, NH), 6.583 (d, 1 H, *J* = 15.6 Hz), 5.510 (dd, 1 H, *J* = 6, 6 Hz, NH), 5.133 (s, 2 H, Ph-CH_2), 4.609 (q, 1 H, *J* = 7.6 Hz, double signal), 4.505 (t, 1 H, *J* = 5.6 Hz), 3.883 (dd, 2 H, *J* =6.6, 4.8 Hz), 3.508 – 3.242 (m, 4 H), 3.355 (s, 3 H, OCH_3), 3.324 (s, 6 H, OCH_3), 2.538 (q, 2 H, *J* = 7.2 Hz, S-CH_2), 2.091 – 1.932 (m, 2 H), 1.781 – 1.691 (m, 3 H), 1.240 (t, 3 H, *J* = 7.2 Hz, S-CH_2-CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.73, 168.91, 136.05, 128.57, 128.28, 128.14, 101.87, 76.03, 67.31, 57.08, 57.03, 53.18, 52.35, 44.61, 41.61, 41.56, 35.34, 35.18, 31.73, 31.56, 27.52, 27.46, 25.65, 25.59, 14.56.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{23}H_{37}O_7N_3NaS$: 522.2250, found: 522.2240.

Benzyl (2-((1-(cyclohexylamino)-4-(ethylthio)-1-oxobutan-2-yl)amino)-2-oxoethyl)carbamate (3b)



Yield: 30% (130 mg)

Nature: white solid

Rf: 0.60 (2 : 1 ethyl acetate : petroleum ether)

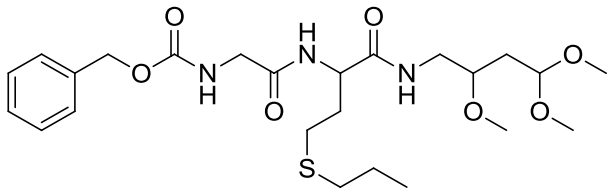
Flash chromatography: 2 : 1 (ethyl acetate : petroleum ether)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.385 – 7.290 (m, 5 H, CH), 7.021 (d, 1 H, *J* = 8 Hz, NH), 6.328 (d, 1 H, *J* = 7.2 Hz, NH), 5.559 (t, 1 H, *J* = 5.2 Hz, NH), 5.127 (s, 2 H, Ph-CH_2), 4.562 (q, 1 H, *J* = 8 Hz, NH-CH), 3.882 (d, 2 H, *J* = 5.2 Hz, NH-CH_2), 3.786 – 3.676 (m, 1 H, CH(Cy)), 2.640 – 2.454 (m, 2 H, CH_2), 2.534 (q, 2 H, *J* = 7.2 Hz, S-CH_2), 2.075 – 1.551 (m, 8 H), 1.451 – 1.100 (m, 4 H), 1.239 (t, 3 H, *J* = 7.2 Hz, SCH_2-CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.48, 168.79, 156.61, 136.05, 128.56, 128.26, 128.09, 67.25, 52.31, 48.46, 33.58, 32.86, 32.78, 31.74, 27.57, 25.58, 25.42, 24.70, 14.57.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{22}H_{33}O_4N_3NaS$: 458.2089, found: 458.2090.

Benzyl (2-oxo-2-((1-oxo-4-(propylthio)-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)amino)ethyl)carbamate (3c)



Yield: 31% (159 mg)

Nature: colorless oil

Rf: 0.48 (ethyl acetate)

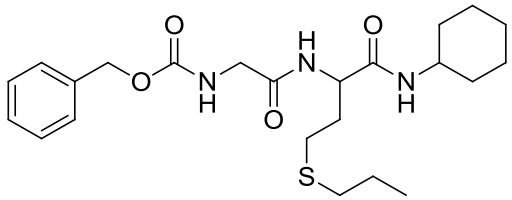
Flash chromatography: ethyl acetate

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.383 – 7.288 (m, 5H, CH), 7.178 (t, 1 H, *J* = 6.8 Hz, NH), 6.878 – 6.772 (m, 1 H, NH), 5.820 (1 H), 5.120 (s, 2 H, Ph-CH_2), 4.624 (q, 1 H, *J* = 6.8 Hz), 4.503 (t, 1 H, *J* = 5.6 Hz), 3.916 - 3.861 (m, 2 H), 3.424 – 3.274 (m, 4 H), 3.343 (s, 3 H, OCH_3), 3.313 (s, 6 H, OCH_3), 2.475 (t, 2 H, *J* = 7.6 Hz, S-CH_2), 2.105 – 1.891 (m, 2 H), 1.793 (t, 1 H, *J* = 6.4 Hz), 1.755 – 1.664 (m, 2 H), 1.578 (hex, 2 H, *J* = 7.6 Hz, S-CH_2-CH_2), 0.968 (t, 3 H, *J* = 7.6 Hz, S-CH_2-CH_2-CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.73, 168.91, 136.05, 128.57, 128.28, 128.14, 101.87, 76.03, 67.31, 57.08, 57.03, 53.18, 52.35, 44.61, 41.61, 41.56, 35.34, 35.18, 31.73, 31.56, 27.52, 27.46, 25.65, 25.59, 14.56.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{24}H_{39}O_7N_3NaS$: 536.2406, found: 536.2398.

Benzyl (2-((1-(cyclohexylamino)-1-oxo-4-(propylthio)butan-2-yl)amino)-2-oxoethyl)carbamate (3d)



Yield: 33% (148 mg)

Nature: slightly yellow solid

Rf: 0.65 (2 : 1 ethyl acetate : petroleum ether)

Flash chromatography: 2 : 1 (ethyl acetate : petroleum ether)

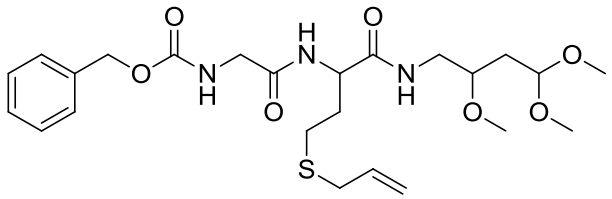
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.385 – 7.290 (m, 5 H, CH), 6.982 (d, 1 H, *J* = 7.6 Hz, NH), 6.292 (d, 1 H, *J* = 8 Hz, NH), 5.520 (t, 1 H, *J* = 4.8 Hz, NH), 5.128 (s, 2 H, Ph-CH_2), 4.560 (q, 1 H, *J* = 7.6 Hz, NH-CH-), 3.881 (d, 2 H, *J* = 4.8 Hz, NH-CH_2), 3.790 – 3.681 (m, 1 H,

CH(Cy)), 2.585 (dt, 1 H, *J* = 15.2, 7.6 Hz), 2.532 – 2.432 (m,1 H), 2.488 (t, 2 H, *J* = 7.2 Hz, S-CH_2), 2.064 – 1.934 (m, 2 H, CH_2), 1.918 – 1.812 (m, 2 H, CH_2), 1.743 – 1.649 (m, 2 H), 1.590 (sex, 2 H, *J* = 7.2 Hz, SCH_2-CH_2-CH_3), 1.410 – 1.278 (m, 2 H), 1.226 – 1.100 (m,2 H), 0.978 (t, 3 H, *J* = 7.2 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.44, 168.72, 156.60, 136.05, 128.56, 128.27, 128.09, 67.27, 52.33, 48.45, 44.59, 33.81, 32.87, 32.80, 31.82, 28.00, 25.42, 24.70, 22.72, 13.44.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{23}H_{36}O_4N_3NaS$: 472.2246, found: 472.2248

Benzyl (2-((4-(allylthio)-1-oxo-1-((2,4,4-trimethoxybutyl)amino)butan-2-yl)amino)-2-oxoethyl)carbamate (3e)



Yield: 24% (122 mg)

Nature: colorless oil

Rf: 0.44 (ethyl acetate)

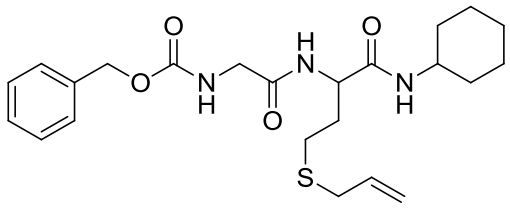
Flash chromatography: ethyl acetate

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.368 – 7.293 (m, 5 H, CH), 6.948 – 6.875 (m, 1 H, NH), 6.666 – 6.544 (m, 1 H, NH), 5.756 (ddt, 1 H, *J* = 17.2, 9.6, 7.2, S-CH_2-$CHCH_2$), 5.630 – 5.534 (m, 1 H,NH), 5.129 (s, 2 H, Ph-CH_2), 5.121 – 5.058 (m, 2 H, S-CH_2-$CHCH_2$), 4.602 (q, 1 H, *J* = 7.2 Hz), 4.502 (t, 1 H, *J* = 5.2 Hz), 3.914 – 3.860 (m, 2 H), 3.502 – 3.248 (m, 4 H), 3.350 (s, 3 H, OCH_3), 3.321 (m, 6 H, OCH_3), 3.126 (dd, 2 H, *J* = 7.2 Hz, 2.4 Hz, S-CH_2), 2.582 – 2.395 (m, 2 H), 2.093 – 1.655 (m, 4 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.74, 168.95, 198.91, 136.07, 133.96, 128.55, 128.26, 128.12, 117.34, 101.25, 76.02, 67.27, 57.07, 57.05, 53.16, 52.31, 44.56, 41.61, 41.57, 35.18, 34.40, 34.33, 31.45, 26.52, 26.45.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{24}H_{37}O_7N_3NaS$: 534.2250, found: 534.2244.

Benzyl (2-((4-(allylthio)-1-(cyclohexylamino)-1-oxobutan-2-yl)amino)-2-oxoethyl)carbamate (3f)



Yield: 27% (120 mg)

Nature: slightly yellow oil

Rf: 0.65 (2 : 1 ethyl acetate : petroleum ether)

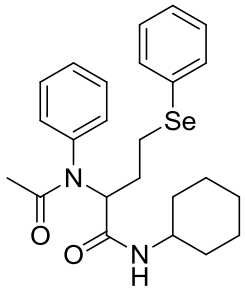
Flash chromatography: 2 : 1 (ethyl acetate : petroleum ether)

^{1}H NMR ($CDCl_3$, 400 MHz):) δ 7.539 (d, 1 H, *J* = 8 Hz, NH), 7.376 – 7.231 (m, 5 H, CH), 6.808 (d, 1 H, *J* = 8 Hz, NH), 6.073 (t, 1 H, *J* = 5.2 Hz, NH), 5.733 (ddt, 1 H, *J* = 17.6, 9.6, 7.2 Hz, S-CH_2-$CHCH_2$), 5.104 (s, 2 H, Ph-CH_2), 5.073 (dd, 2 H, *J* = 9.6, 7.2 Hz, S-CH_2-$CHCH_2$), 4.606 (q, 1 H, *J* = 7.2 Hz, NH-CH), 3.919 (d, 2 H, *J* = 5.2 Hz, NH-CH_2), 3.757 – 3.629 (m, 1 H, CH(Cy)), 3.090 (d, 2 H, *J* = 6.8 Hz, S-CH_2-$CHCH_2$), 2.665 – 2.358 (m, 4 H), 2.804 – 1.749 (m, 4 H), 1.667 (d, 2 H, *J* = 13.2 Hz), 1.580 (dt, 1 H, *J* = 13.2, 3.2 Hz), 1.394 – 1.230 (m, 2 H), 1.214 – 1.061 (m, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.72, 169.16, 156.53, 136.14, 133.91, 128.38, 128.02, 127.87, 117.11, 66.89, 52.25, 48.33, 34.29, 32.56, 30.50, 29.32, 28.65, 27.88.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{23}H_{23}O_4N_3NaS$: 470.2089, found: 470.2088.

***N*-cyclohexyl-2-(*N*-phenylacetamido)-4-(phenylselenyl)butanamide (4a)**



Yield: 4CR 48% (220 mg)

5CR 27 % (152 mg)

Nature: white solid

Rf: 0.35 (2 : 8 ethyl acetate : petroleum ether)

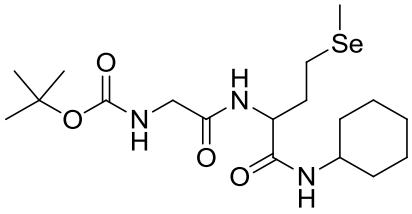
Flash chromatography: 2 : 8 (ethyl acetate : petroleum ether)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28 – 7.05 (m, 10H), 6.68 – 6.65 (m, 1H), 5.27 – 5.20 (m, 2H), 3.81 – 3.68(m, 1H), 2.98 – 2.86 (m, 2H), 2.10 – 1.86 (m, 2H), 2.82 (s, 3H), 2.80 – 1.22 (m, 11H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.9, 169.2, 139.2, 132.8, 129.4, 129.0, 129.0, 128.6, 126.9, 57.8, 48.0, 32.8, 32.7, 29.4, 25.4, 24.6, 24.5, 23.1.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{24}H_{31}O_2N_2Se$: 459,1545, found: 459.1540.

***Tert*-butyl (2-((1-(cyclohexylamino)-4-(methylselenyl)-1-oxobutan-2-yl)amino)-2-oxoethyl)carbamate (4b)**



Yield: 4CR 30% (131 mg)

5CR 34 % (148 mg)

Nature: white solid

Rf: 0.1 (3 : 7 ethyl acetate petroleum ether)

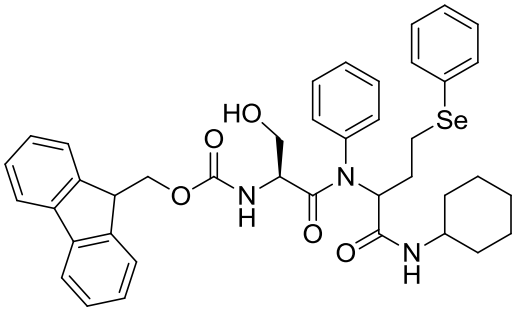
Flash chromatography: : 3 : 7 (ethyl acetate petroleum ether)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.54 – 7.48 (m, 1H), 6.96 – 6.90 (m, 1H), 5.71 (br s, 1H), 4.66 – 4.56 (m, 1 H), 3.92 – 3.62 (m, 3H), 2.57 – 2.47 (m, 2H), 2.19 – 1.53 (m, 10H), 1.46 (s, 9H), 1.42 – 1.09 (m, 5H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 169.7, 169.6, 155.8, 79.8, 53.0, 48.3, 32.9, 32.8, 32.6, 28.2, 25.3, 24.7, 20.5, 3.9.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{18}H_{33}O_4N_3NaSe$: 458.1534, found: 458.1525.

(9*H*-fluoren-9-yl)methyl ((2*S*)-1-((1-(cyclohexylamino)-1-oxo-4-(phenylselenyl)butan-2-yl)(phenyl)amino)-3-hydroxy-1-oxopropan-2-yl)carbamate (4c)



Yield: 4CR 45% (326 mg) yield.

5CR 38 % (295 mg) yield.

Nature: white solid

Rf: 0.55 (3 : 7 ethyl acetate : petroleum ether)

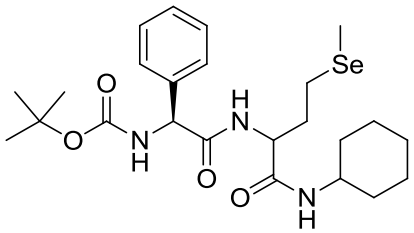
Flash chromatography: 3 : 7 (ethyl acetate : petroleum ether)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80 – 7.12 (m, 18H), 6.68 – 6.65 (m, 1H), 6.05 – 5.96 (m, 1H), 5.20 – 5.05 (m, 1H) 4.51 – 4.07 (m, 5H), 3.83 – 3.43 (m, 3H), 2.97 – 2.93 (m, 2H), 2.26 – 0.81 (m, 12H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.5, 171.2, 169.3, 168.5, 156.0, 143.7, 143.6, 141.2, 141.2, 132.9, , 129.7, 129.1, 129.0, 129.0, 127.7, 127.1, 127.0, 125.1, 119.9, 67.2, 63.0, 60.4, 59.4, 53.9, 48.7, 47.0, 32.8, 32.7, 29.1, 25.4, 24.8, 24.3, 21.0.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{40}H_{44}O_5N_3NaSe$: 748,2260, found: 748,2255.

***Tert*-butyl ((1*S*)-2-((1-(cyclohexylamino)-4-(methylselenyl)-1-oxobutan-2-yl)amino)-2-oxo-1-phenylethyl)carbamate (4d)**



Yield: 4CR 40% (204 mg)

5CR 33% (169 mg)

Nature: white solid

Rf: 0.35 (3: 7 ethyl acetate : petroleum ether)

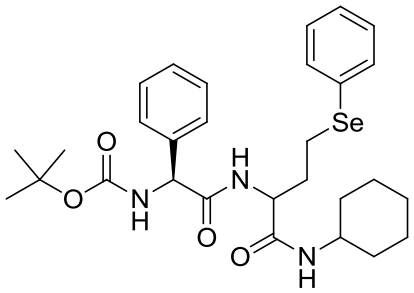
Flash chromatography: : 3: 7 (ethyl acetate : petroleum ether)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61 – 7.48 (m, 1H), 7.40 – 7.20 (m, 5H), 6.43 – 6.40 (m, 1H), 5.59 – 5.93 (m, 1H), 5.40 – 5.25 (m, 1H), 4.68– 4.48 (m, 1H), 3.76 – 3.54 (m, 1H), 2.54– 0.81 (m, 29H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.5, 169.4, 155.0, 138.0, 128.7, 128.1, 126.8, 80.0, 58.4, 53.3, 48.3, 32.7, 32.6, 32.4, 28.3, 24.7, 20.6, 20.3, 4.0.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{24}H_{37}O_4N_3NaSe$: 534.1841, found: 534.1837.

***Tert*-butyl ((1*S*)-2-((1-(cyclohexylamino)-1-oxo-4-(phenylselenyl)butan-2-yl)amino)-2-oxo-1-phenylethyl)carbamate (4e)**



Yield: 4CR43% (229 mg)

5CR 36 % (208 mg)

Nature: white solid

Rf: 0.39 (3 : 7 ethyl acetate : petroleum ether)

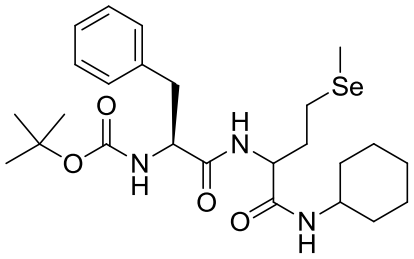
Flash chromatography: 2 : 8 (ethyl acetate : petroleum ether)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.60 – 7.12 (m, 11H), 6.36 – 6.31 (m, 1H), 5.92– 5.90 (m, 1H), 4.67 – 4.45 (m, 1H), 3.73 – 3.39 (m, 1H), 2.88 – 2.80 (m, 1H), 2.70 – 2.65 (m, 1H), 2.29 – 1.46 (m, 6H), 1.40 (s, 9H), 1.33 – 0.80 (m, 7H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.5, 169.0, 168.7, 132.3, 129.4, 129.0, 128.9, 128.7, 128.8, 128.1, 80.1, 58.4, 53.2, 48.3, 32.7, 32.6, 32.5, 28.3, 25.4, 24.7, 23.2, 22.7.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{29}H_{39}O_4N_3NaSe$: 596.1998, found: 596.1994.

***Tert*-butyl ((2*S*)-1-((1-(cyclohexylamino)-4-(methylselenyl)-1-oxobutan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (4f)**



Yield: 4CR 64% (366 mg)

5CR 55 % (289 mg)

Nature: white solid

Rf: 0.30 (3 : 7 ethyl acetate petroleum ether)

Flash chromatography: : 3 : 7 (ethyl acetate petroleum ether)

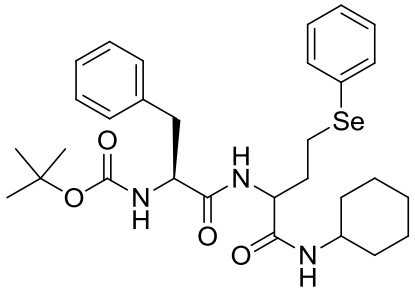
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31 – 7.15 (m, 6H), 6.96 – 6.93 (m, 1H), 6.86 – 6.83 (m, 1H), 4.61 – 4.36 (m, 2H), 3.78 – 3.63 (m, 1H), 3.13 – 2.96 (m, 2H), 2.50 – 2.43 (m, 1H), 2.31

– 2.20 (m, 1H), 2.17 – 1.94 (m, 2H), 1.94 (s, 3H), 1.91 – 1.50 (m, 5H), 1.39 (s, 9H), 1.35 – 1.05 (m, 5H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.2, 169.2, 155.2, 136.2, 129.0, 128.6, 126.6, 79.9, 55.4, 53.1, 48.3, 38.1, 32.8, 28.2, 25.4, 24.7, 20.4, 20.3, 3.9.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{25}H_{39}O_4N_3NaSe$: 548.1998, found: 548.1992.

***Tert*-butyl ((2*S*)-1-((1-(cyclohexylamino)-1-oxo-4-(phenylselenyl)butan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (4g)**



Yield: 4CR 40% (234 mg) yield.

5CR 28 % (165 mg)

Nature: white solid

Rf: 0.35 (3 : 7 ethyl acetate : petroleum ether)

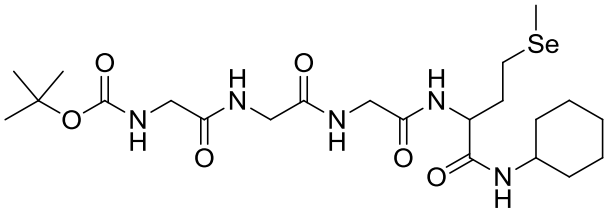
Flash chromatography: 3 : 7 (ethyl acetate : petroleum ether)

^{1}H NMR (pyridine-d_5, 300 MHz): δ 9.36 – 9.32 (m, 1H), 8.49 – 8.44 (m, 1H), 8.12 – 8.06 (m, 1H), 7.59 – 7.49 (m, 2H), 7.36 – 7.15 (m, 8H), 5.15 – 5.00 (m, 2H), 4.03 – 3.86 (m, 1H), 3.51 – 3.40 (m, 1H), 3.31 – 3.03 (m, 2H), 2.80 – 2.69 (m, 1H), 2.67 – 2.47 (m, 1H), 2.42 – 2.04 (m, 1H), 2.04 – 1.90 (m, 2H), 1.67 – 1.53 (m, 2H), 1.46 (s, 9H), 1.32 – 0.94 (m, 6H).

^{13}C NMR (pyridine-d_5, 75.5 MHz): δ 172.4, 170.4, 170.3, 156.4, 138.2, 132.6, 132.1, 130.6, 129.8, 129.5, 128.6, 127.1, 126.9, 126.7, 79.1, 54.0, 49.7, 48.8, 38.9, 34.5, 33.4, 33.2, 28.6, 25.9, 25.5, 23.6.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{30}H_{41}O_4N_3NaSe$: 610.2154, found: 610.2150.

***Tert*-butyl (5-(cyclohexylcarbamoyl)-7,10,13-trioxo-2-selena-6,9,12-triazatetradecan-14-yl)carbamate (4h)**



Yield: 4CR 44% (242 mg)

5CR 41 % (225 mg)

Nature: white solid

Rf: 0.50 (20 : 1 dichloromethane : methanol)

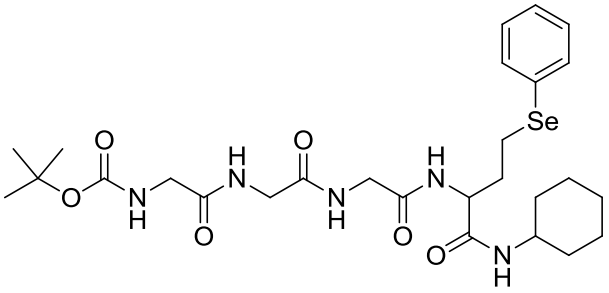
Flash chromatography: : 20 : 1 (dichloromethane : methanol)

^{1}H NMR (CD_3OD, 300 MHz): δ 4.46 – 4.38 (m, 1H), 3.98 – 3.70 (m, 7H), 2.64 – 2.41 (m, 2H), 2.20 – 2.02 (m, 2H), 1.97 (s, 3H), 1.86 – 1.53 (m, 4H), 1.44 (s, 9H), 1.39 – 1.10 (m, 6H).

^{13}C NMR (CD_3OD, 75.5 MHz): δ 173.0, 172.8, 172.6, 172.3, 158.0, 80.1, 52.7, 49.8, 44.8, 43.9, 43.6, 33.8, 33.6, 33.5, 28.7, 26.5, 26.1, 21.6, 3.8.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{22}H_{39}O_6N_5NaSe$: 572.1958, found: 572.1958.

***Tert*-butyl (2-((2-((2-((1-(cyclohexylamino)-1-oxo-4-(phenylselenyl)butan-2-yl)amino)-2-oxoethyl)amino)-2-oxoethyl)amino)-2-oxoethyl)carbamate (4i)**



Yield: 4CR 35% (214 mg)

5CR 31 % (190 mg)

Nature: white solid

Rf: 0.15 (20 : 1 dichloromethane : methanol)

Flash chromatography: : 20: 1 (dichloromethane : methanol)

^{1}H NMR (CD_3OD, 300 MHz): δ 7.51 – 7.47 (m, 2H), 7.29 – 7.21 (m, 3H), 4.47 – 4.42 (m, 1H), 3.96 – 3.93 (br s, 1H), 3.89 – 3.86 (br s, 4H), 3.75 (s, 2H), 3.66 – 3.52 (m, 1H), 3.34 (s,

4H) 3.32 – 3.29 (m, 1H), 3.22 – 3.15 (q, 1H), 3.01 – 2.82 (m, 2H), 2.22 – 1.99 (m, 2H), 1.84 – 1.55 (m, 4H), 1.43 (s, 9H), 1.36 – 1.29 (m, 4H).

^{13}C NMR (CD_3OD, 75.5 MHz): δ 173.3, 172.2, 172.0, 171.3, 158.4, 133.8, 133.5, 131.0, 130.2, 128.0, 80.8, 54.7, 49.8, 44.9, 43.9, 43.6, 34.0, 33.6, 33.5, 28.7, 26.5, 26.0, 24.2.

HRMS (ESI-FTICR, MeOH): Calcd. for $C_{27}H_{41}O_6N_5NaSe$: 634.2114, found: 634.2113.

4. *In vitro* studies

4.1. Reagents and cells

Phosphate-buffered saline (PBS), L-glutamine, dimethyl sulfoxide (DMSO) were obtained from Sigma (St. Louis, MO), while DMEM and fetal calf serum (FCS) from GIBCO and PanBioteck, respectively. The human colon carcinoma SW480 cell line, purchased from the German Collection of Microorganisms and Cell Cultures (Leibniz-DSMZ, Germany), was routinely maintained as monolayers in nutrient medium (DMEM supplemented with 10% FCS, 2 mM L-glutamine) at 37 °C in a humidified atmosphere with 5% CO_2. Stock solutions of investigated compounds were prepared in DMSO at a concentration of 20 mM, filtered through Millipore filter, 0.22 μm, before use, and diluted by nutrient medium to various working concentrations. After standard trypsinization, cells were seeded at 2.5×10^3 cells/well in 96-well plates for viability determination.

4.2. XTT assay

The viability of adherent viable cells was measured by XTT assay as described in the literature.[1] The absorbance of the dissolved dyes was measured in an automated microplate reader (add reader) at 540 nm with a reference wavelength of 670 nm. The results are presented as a percentage of control values obtained from untreated cultures.

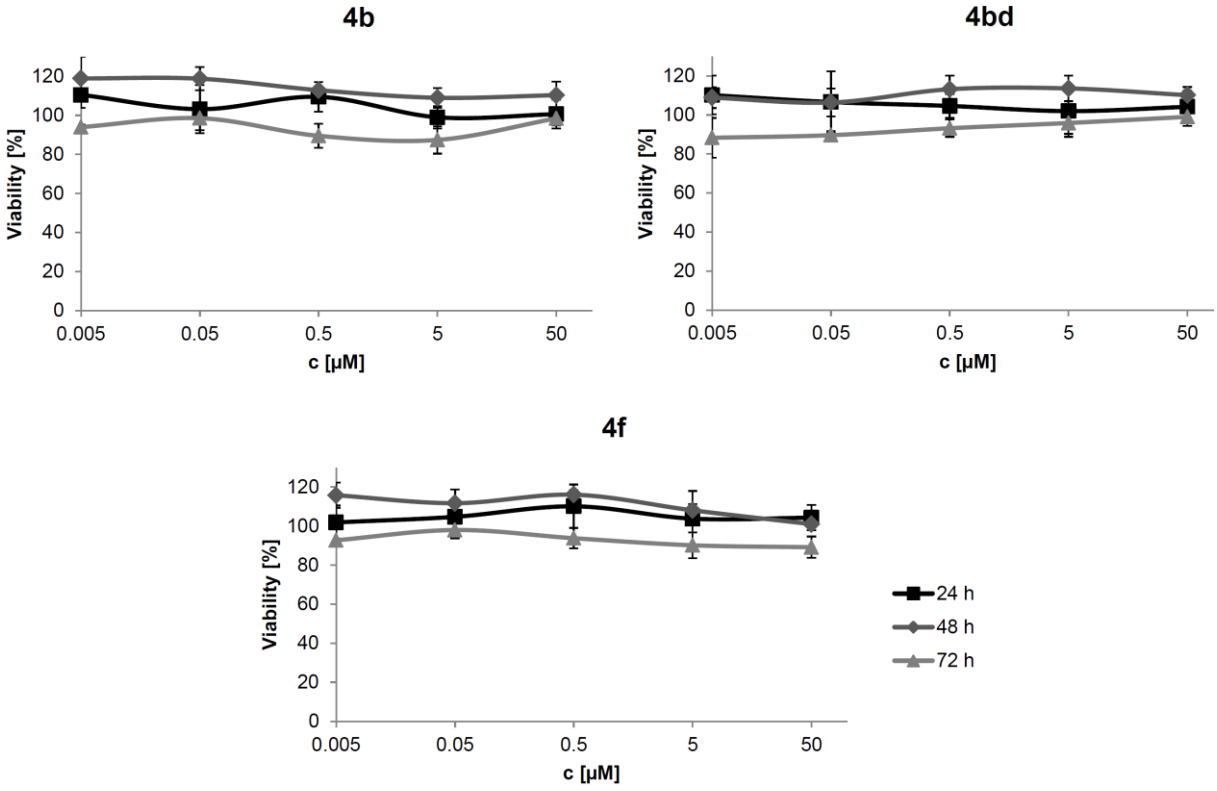


Fig. S1. Viability of SW480 cells treated with **4b**, **4bd** and **4f**.

4.3. GPx1 mRNA expression assay

The assay was performed as described in the literature.[2] The following GPx1 primers were used fw: CCAGTCGGTGTATGCCTTCT; rev: CAAACTGGTTGCACGGGAAG.

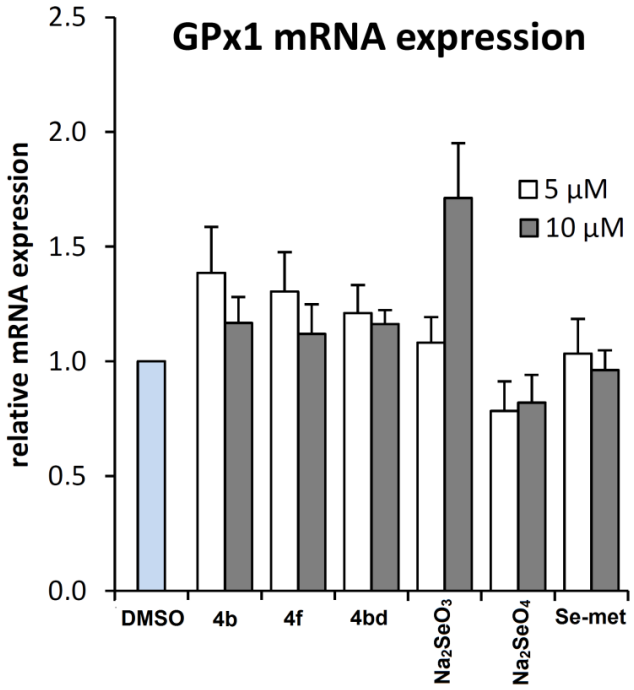


Fig. S2. GPx1 mRNA expression in SW480 cells treated with **4b**, **4bd** and **4f.**

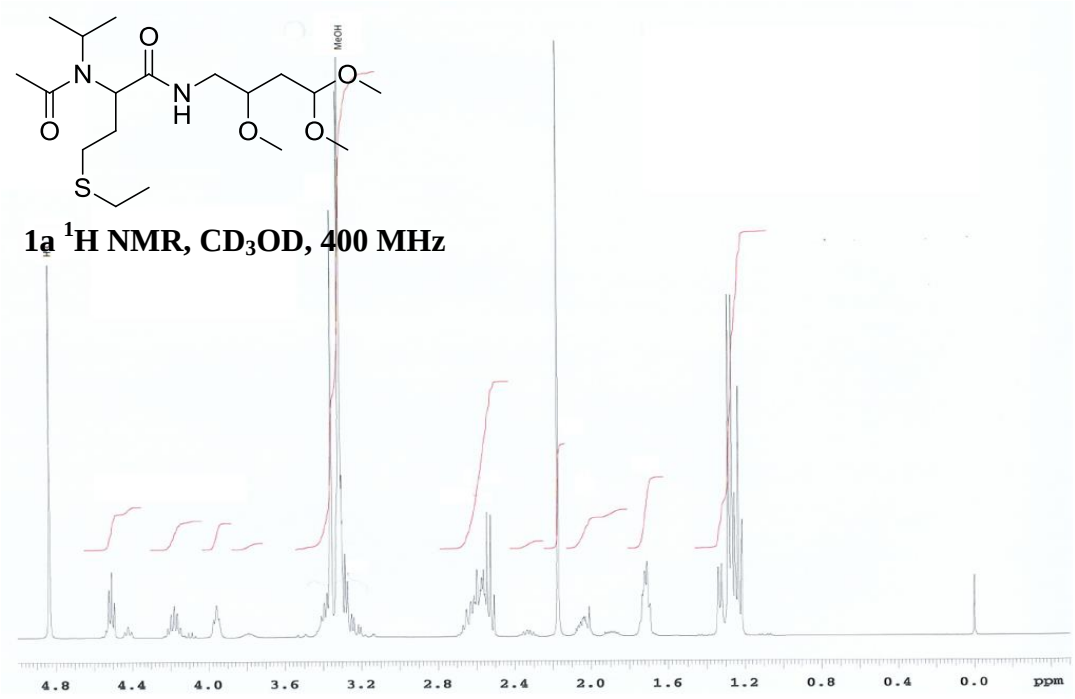
5. References

1 L. M. Jost, J. M. Kirkwood and T. L. Whiteside, *J. Immunol. Methods*, 1992, **147**, 153–165.

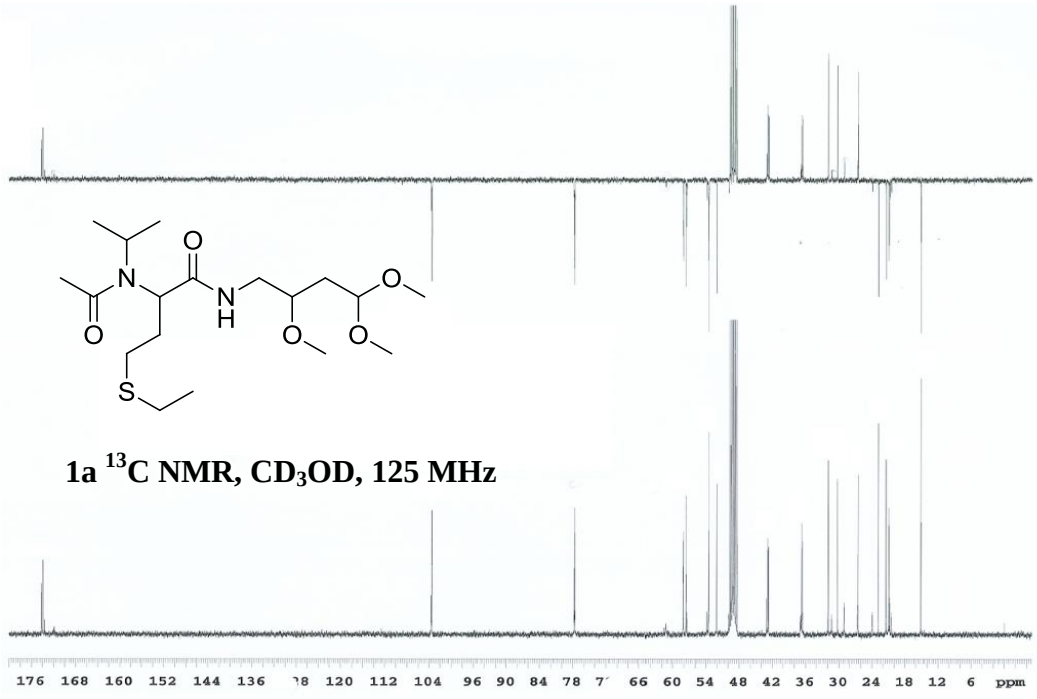
2 C. Lennicke, J. Rahn, A. P. Kipp, B. P. Dojčinović, A. S. Müller, L. A. Wessjohann, R. Lichtenfels and B. Seliger, *Biochim. Biophys. Acta*, 2017, **1861**, 3323–3334.

6. NMR copies of all compounds

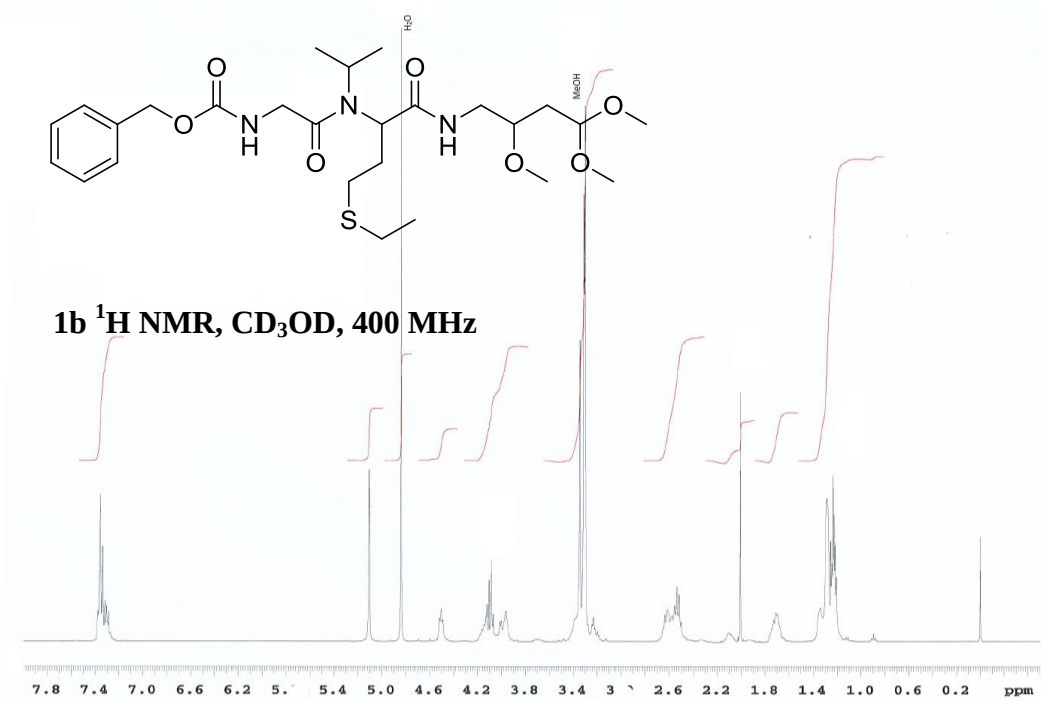
(Please note that peptoids show a mixture of *s-cis* and *s-trans* tertiary amide in the NMR time scale with equilibria dependent on the substituents and temperature. Thus peak doubling or broadening is normal in their spectra and no impurity)



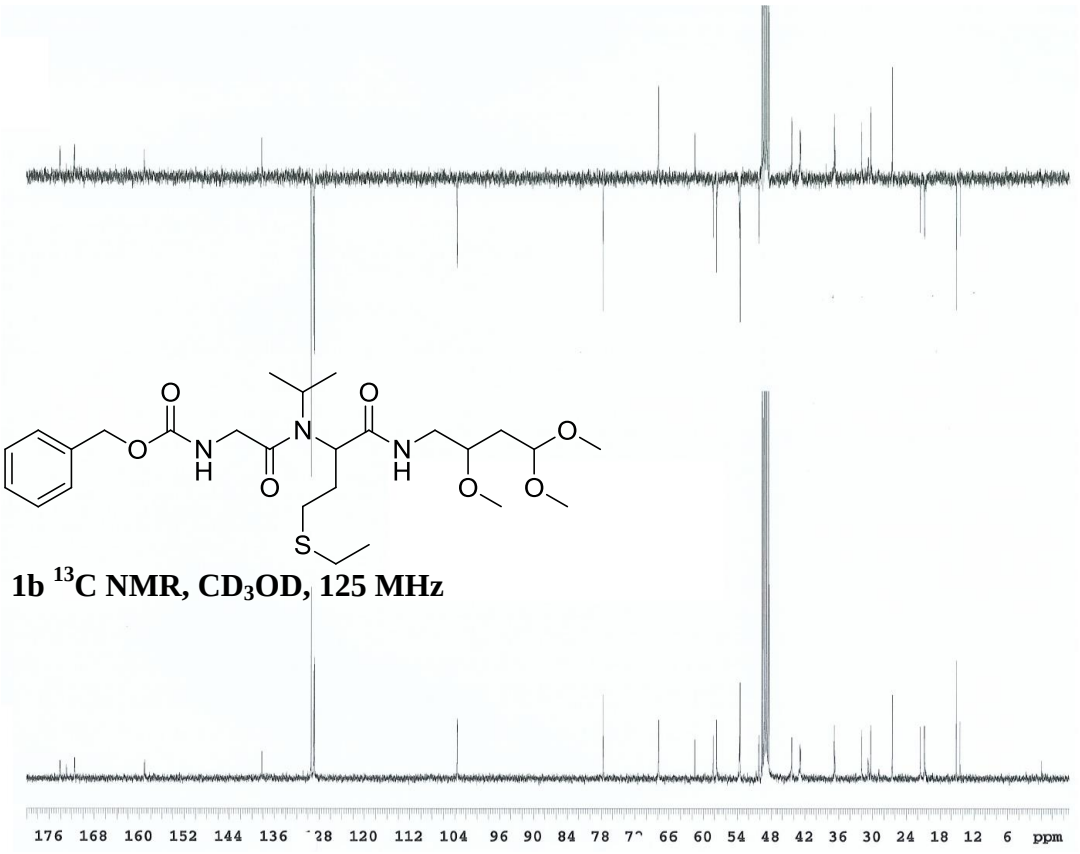
1a ^{1}H NMR, CD_3OD, 400 MHz



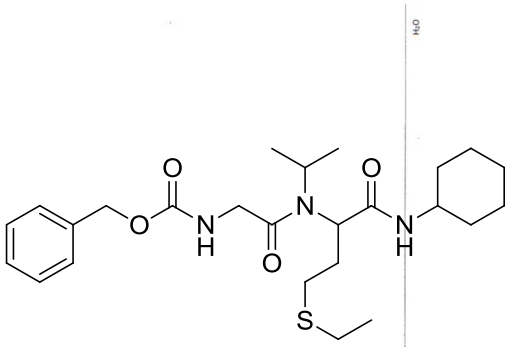
1a ^{13}C NMR, CD_3OD, 125 MHz



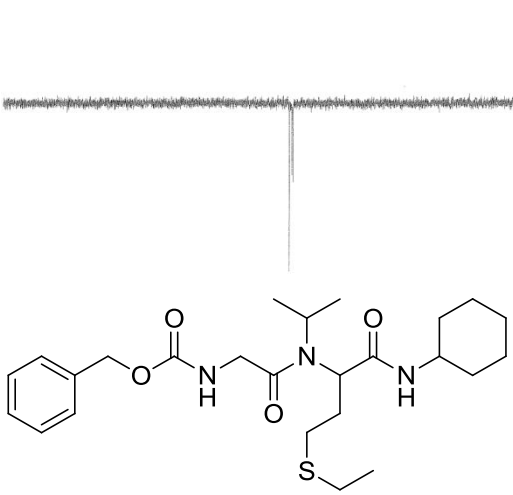
1b ^{1}H NMR, CD_3OD, 400 MHz



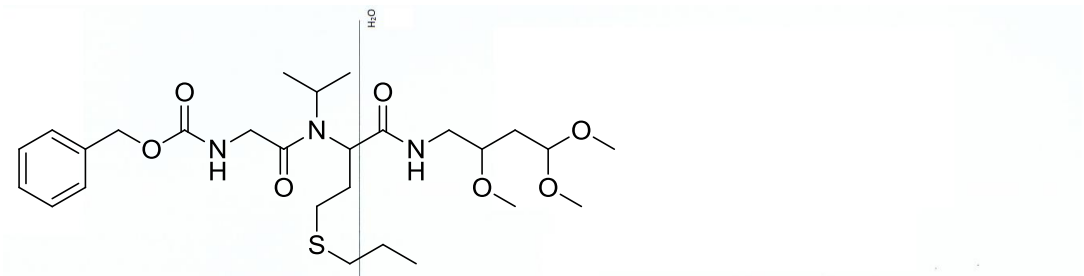
1b ^{13}C NMR, CD_3OD, 125 MHz



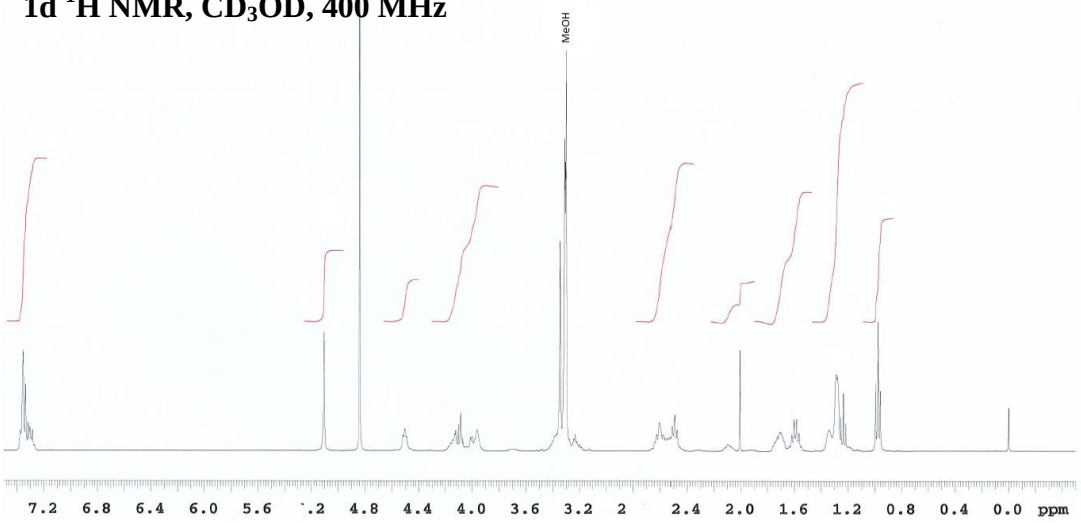
1c ^{1}H NMR, CD_3OD, 400 MHz

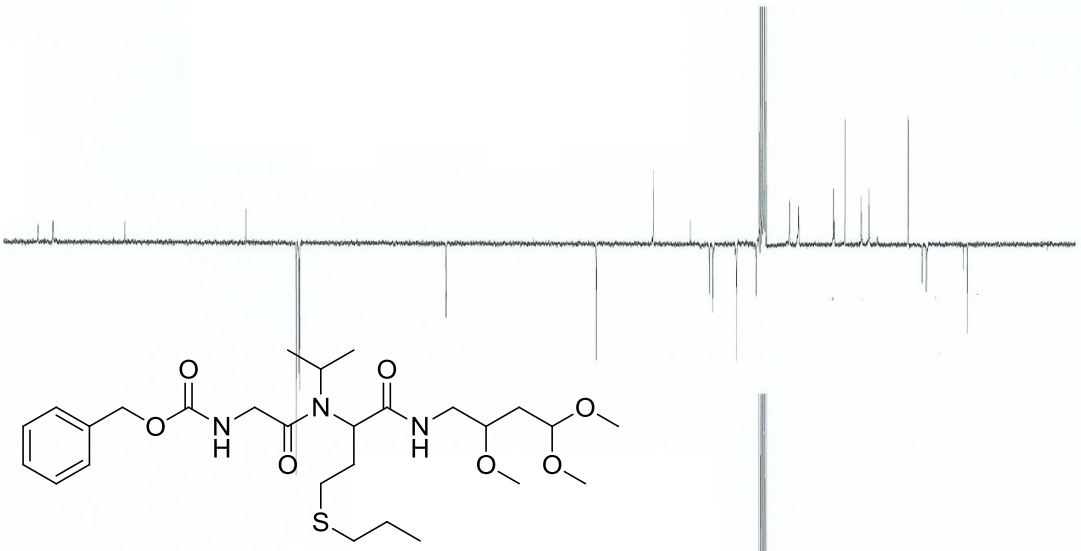


1c ^{13}C NMR, CD_3OD, 125 MHz

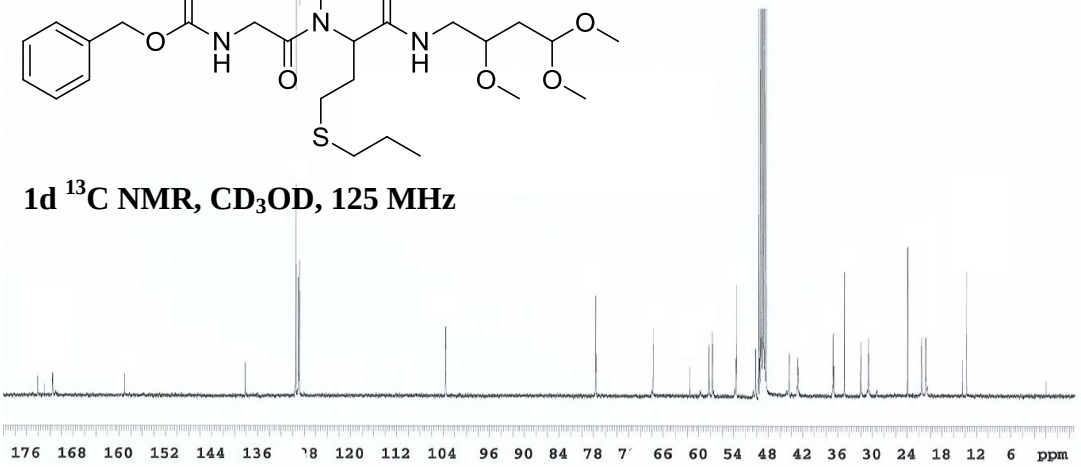


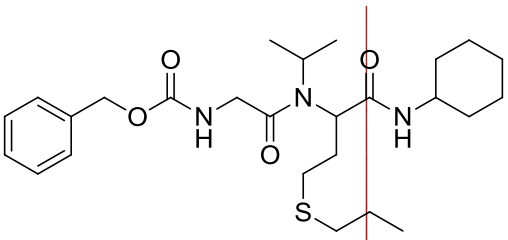
1d ^{1}H NMR, CD_3OD, 400 MHz



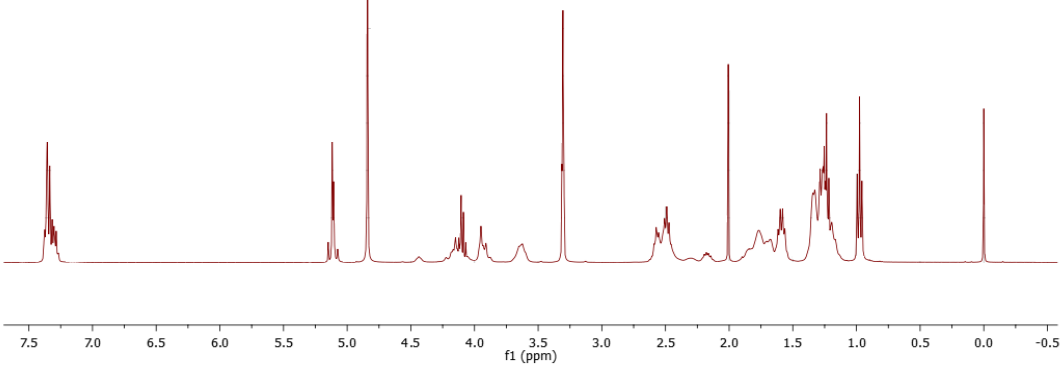


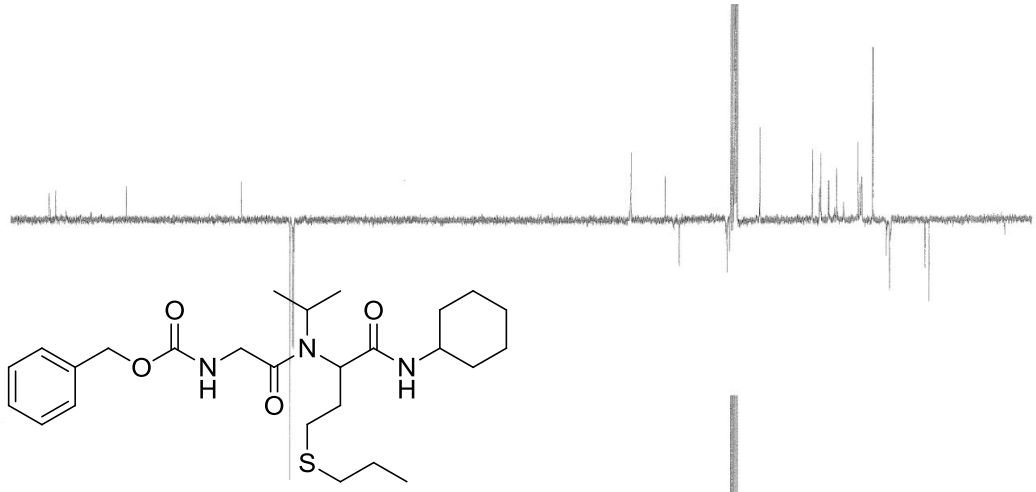
1d ^{13}C NMR, CD_3OD, 125 MHz



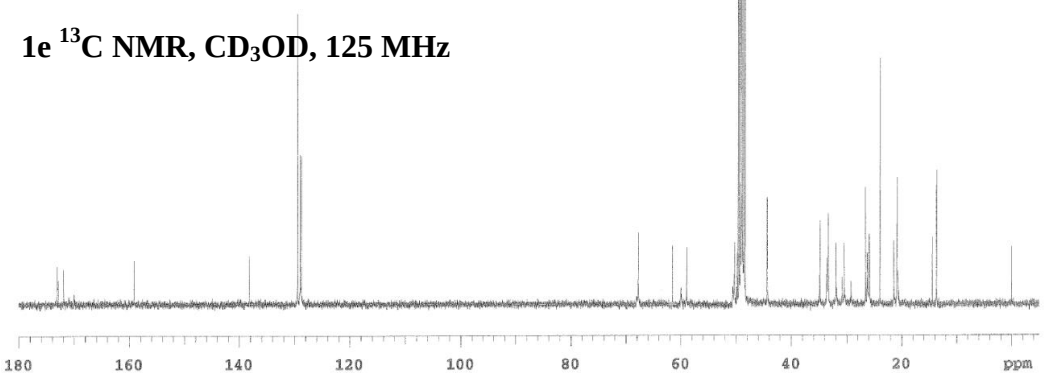


1e ^{1}H NMR, CD_3OD, 400 MHz

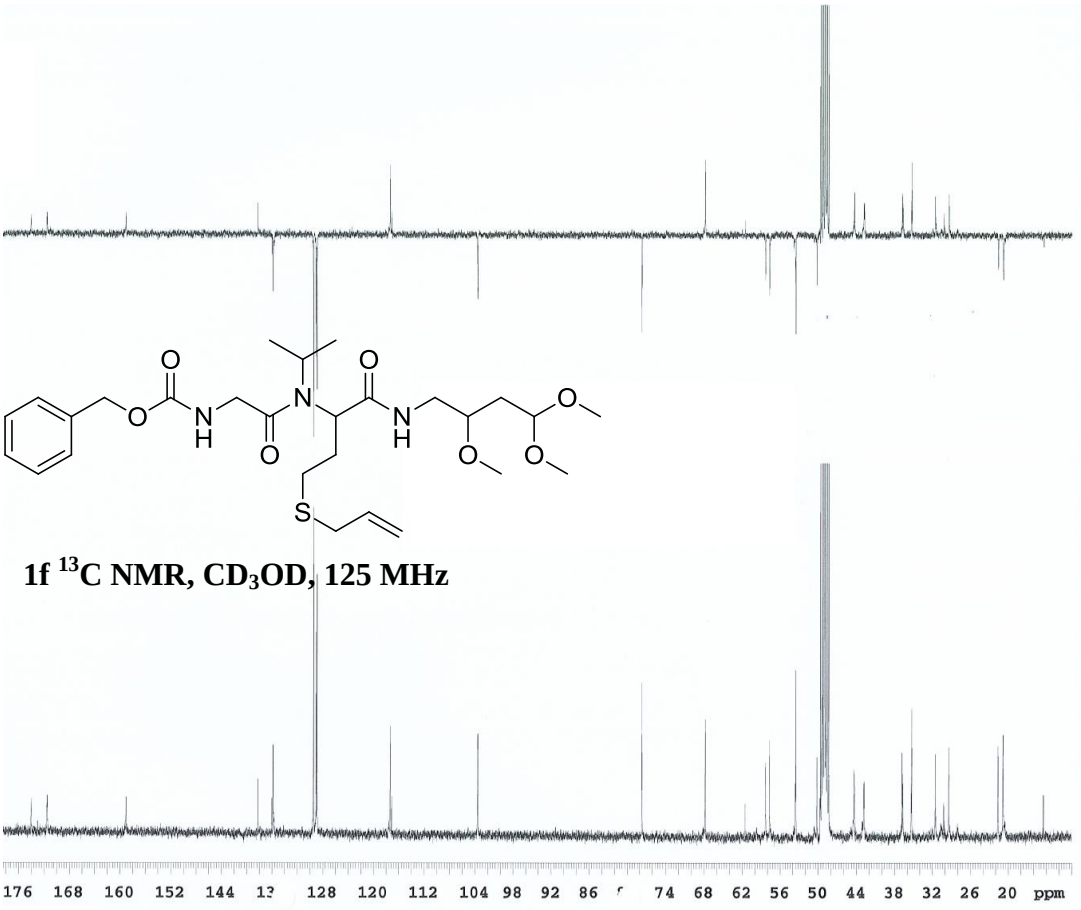




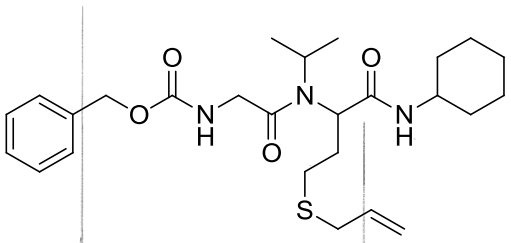
1e ^{13}C NMR, CD_3OD, 125 MHz



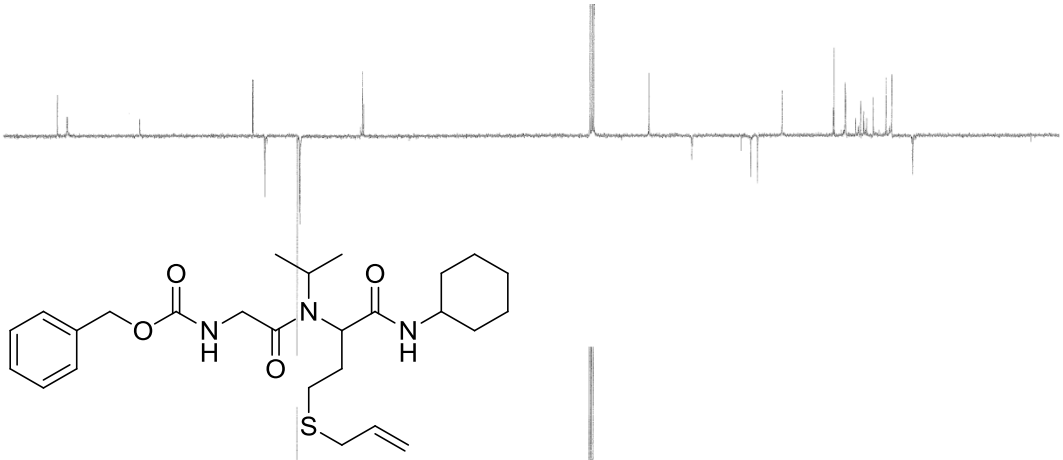
1f ^{1}H NMR, CD_3OD, 400 MHz



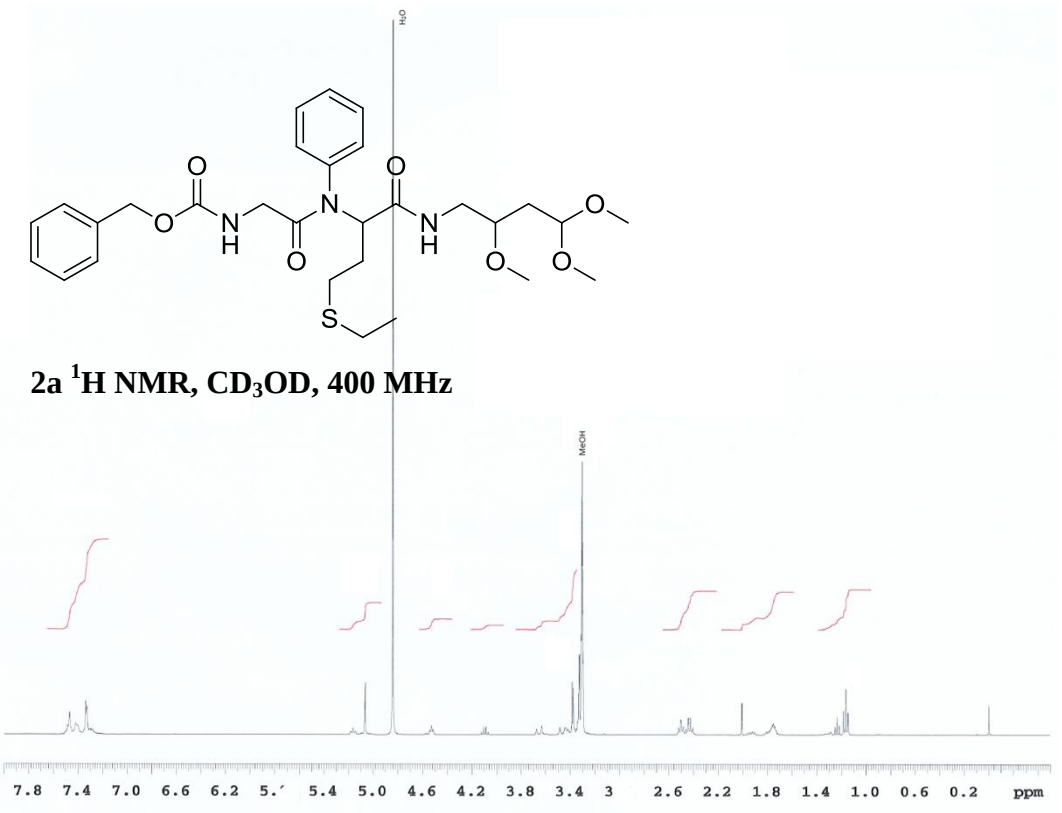
1f ^{13}C NMR, CD_3OD, 125 MHz



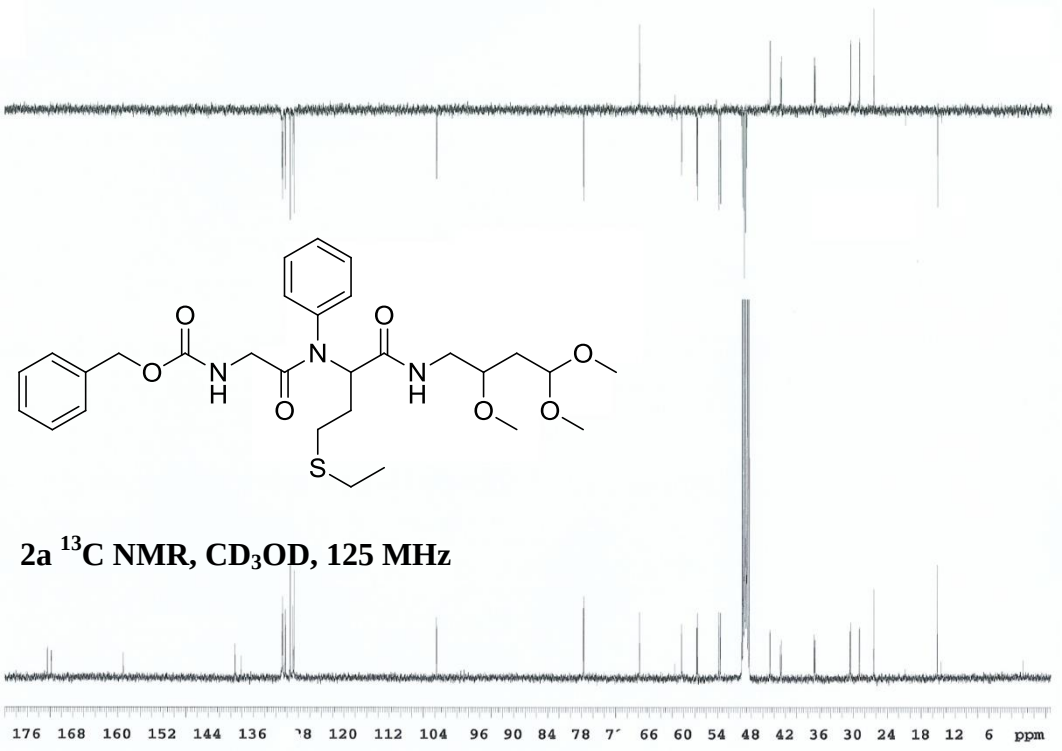
1g ^{1}H NMR, CD_3OD, 400 MHz



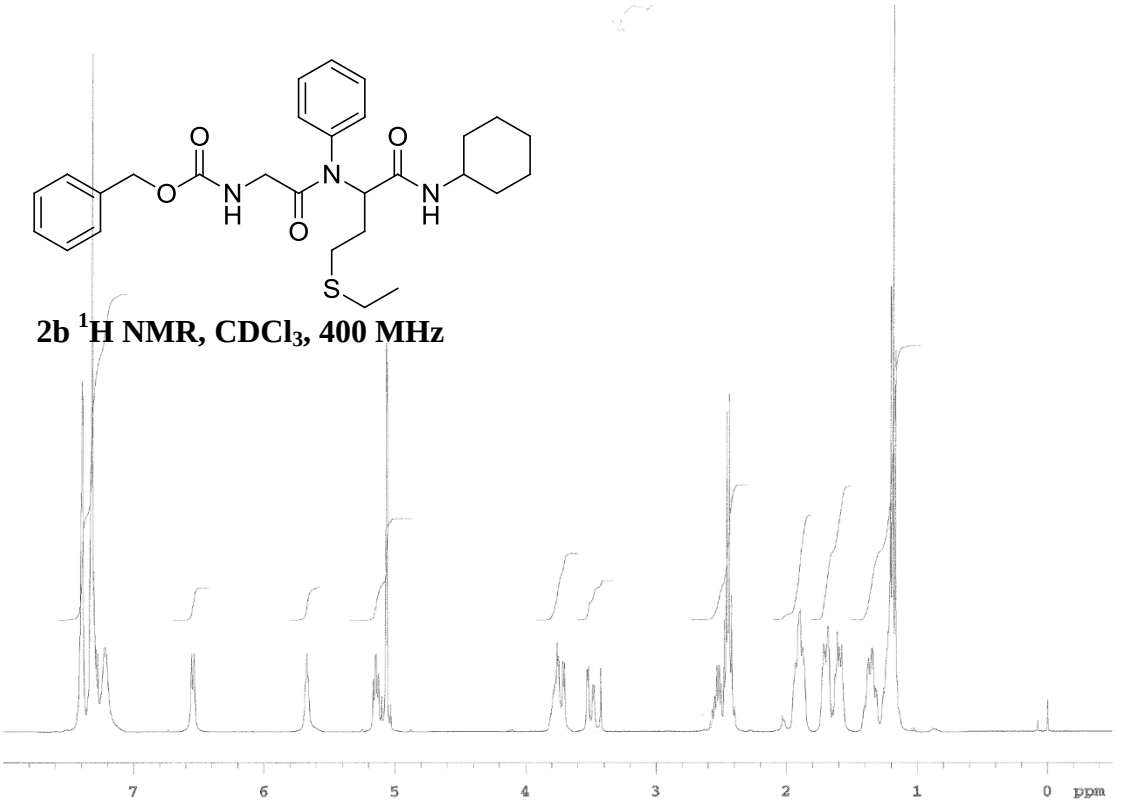
1g ^{13}C NMR, CD_3OD, 125 MHz



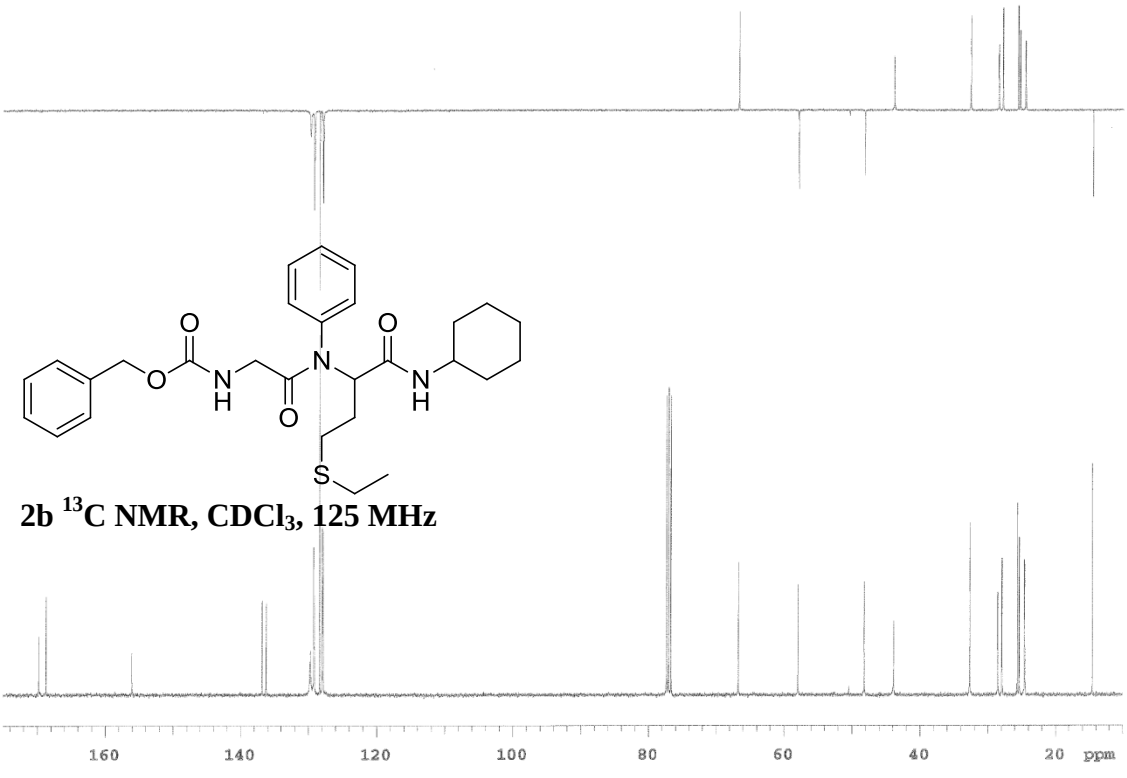
2a ^{1}H NMR, CD_3OD, 400 MHz



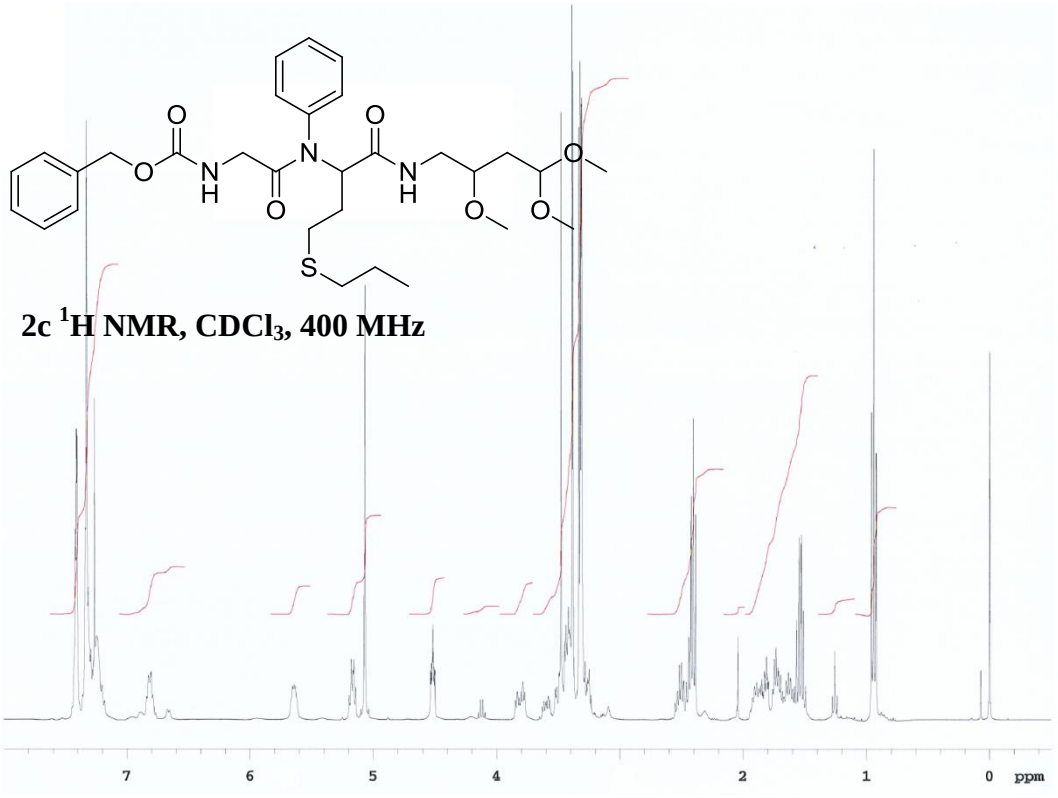
2a ^{13}C NMR, CD_3OD, 125 MHz



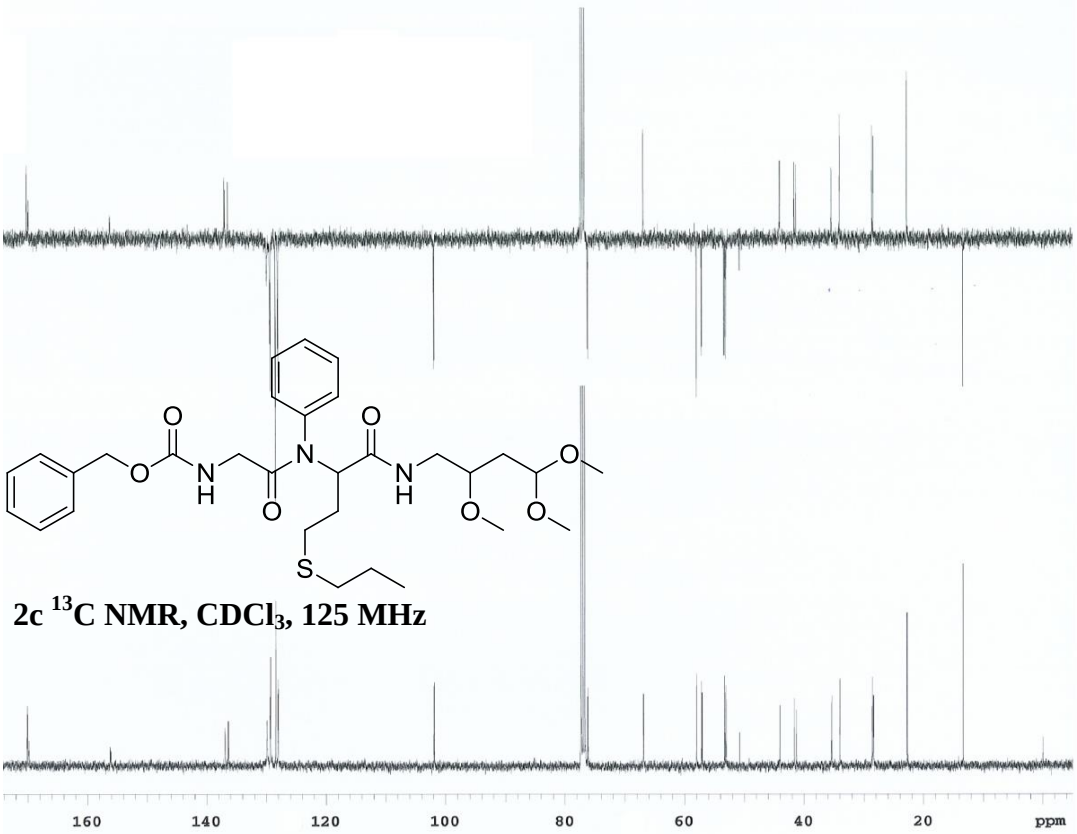
2b ^{1}H NMR, $CDCl_3$, 400 MHz



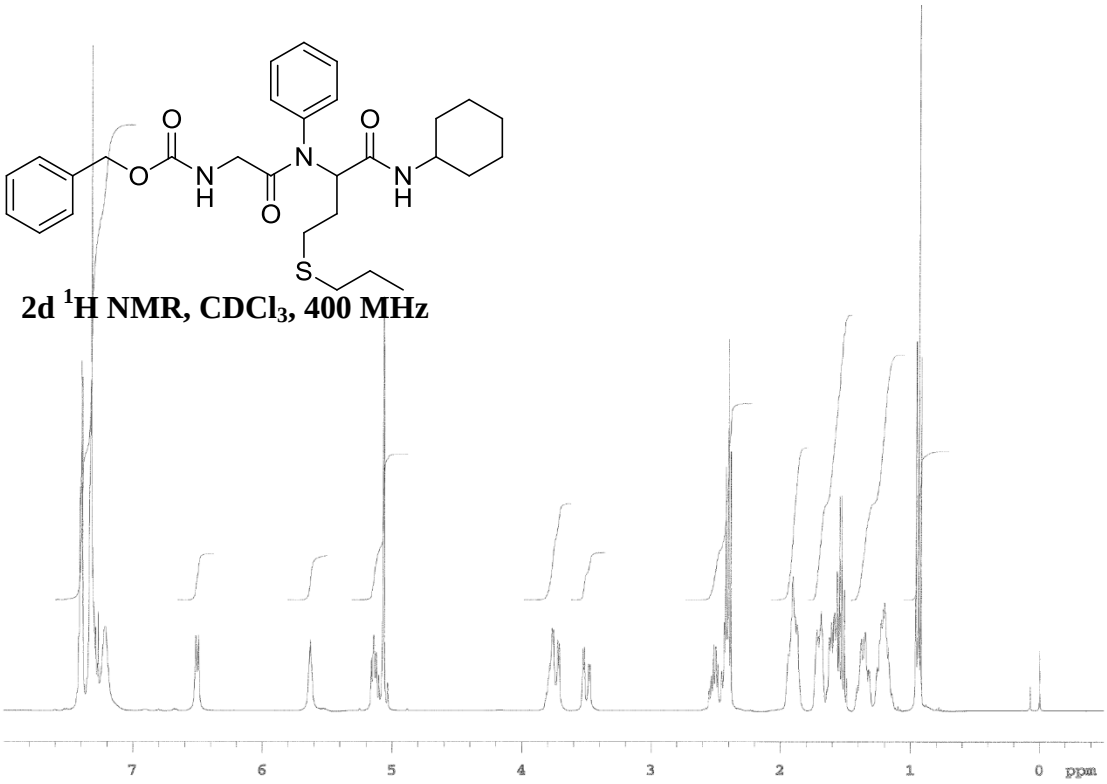
2b ^{13}C NMR, $CDCl_3$, 125 MHz



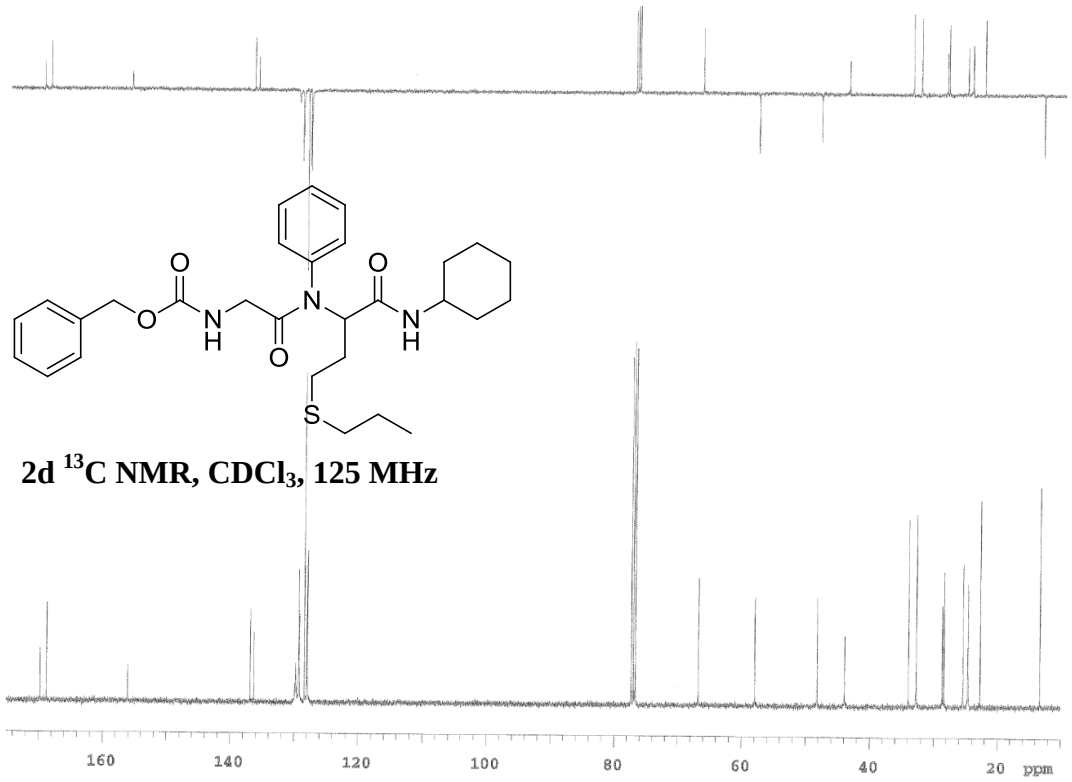
2c ^{1}H NMR, $CDCl_3$, 400 MHz



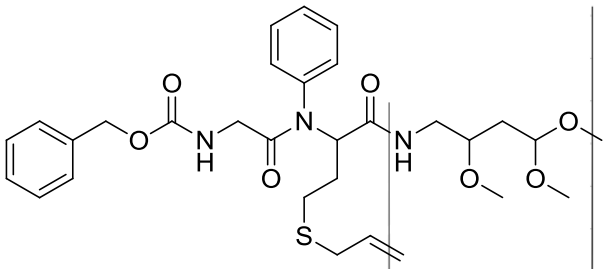
2c ^{13}C NMR, $CDCl_3$, 125 MHz



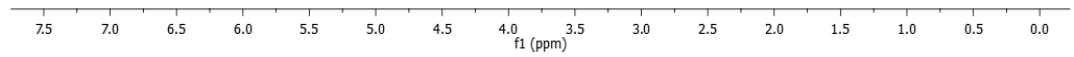
2d ^{1}H NMR, $CDCl_3$, 400 MHz

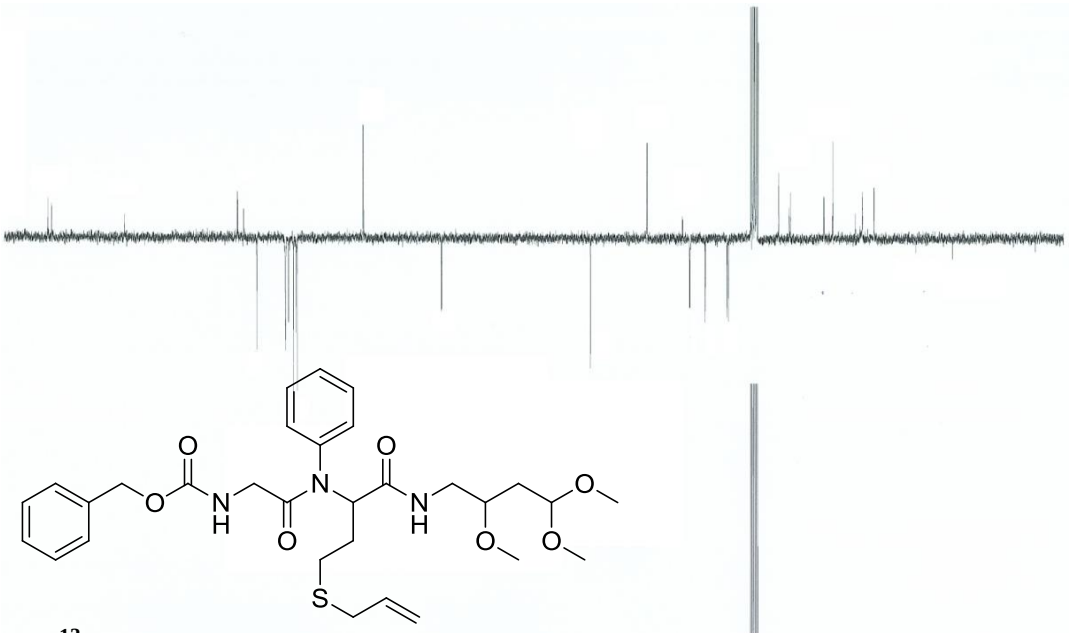


2d ^{13}C NMR, $CDCl_3$, 125 MHz

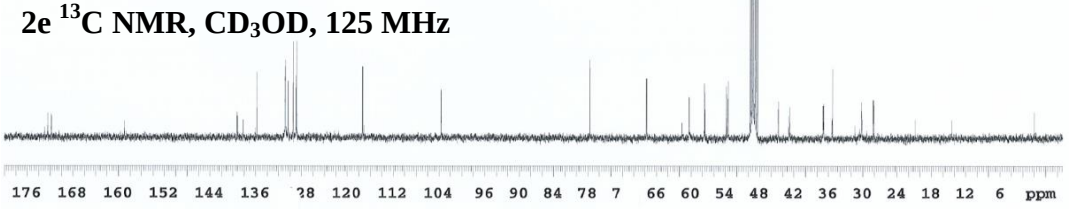


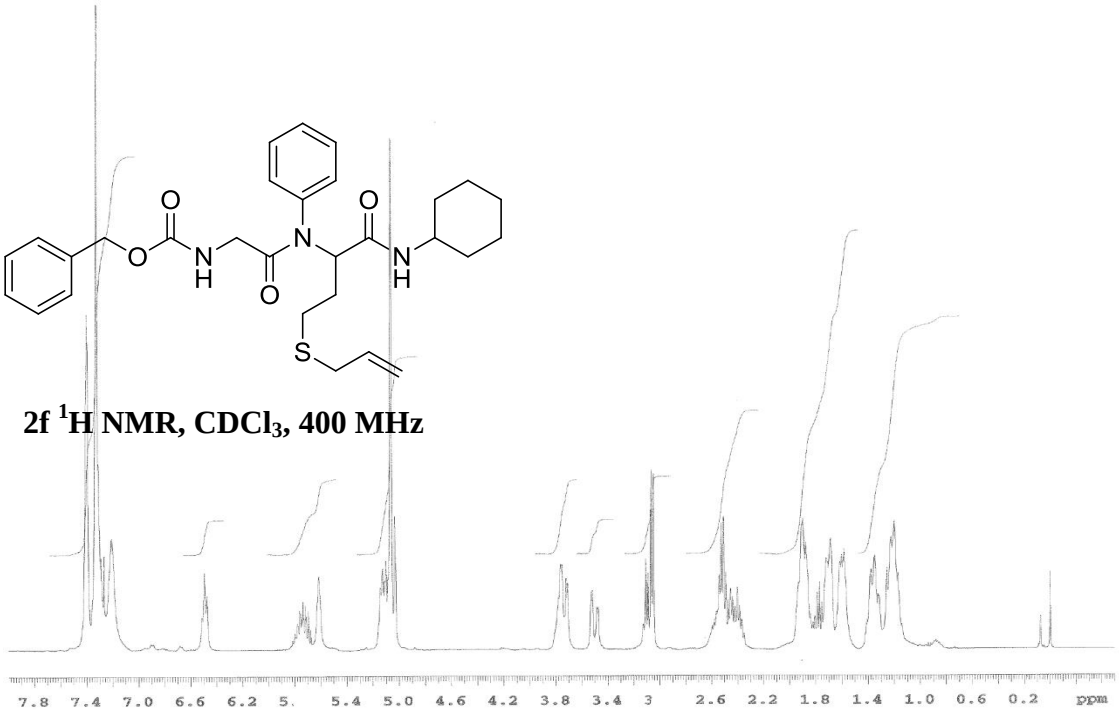
2e ^{1}H NMR, CD_3OD, 400 MHz



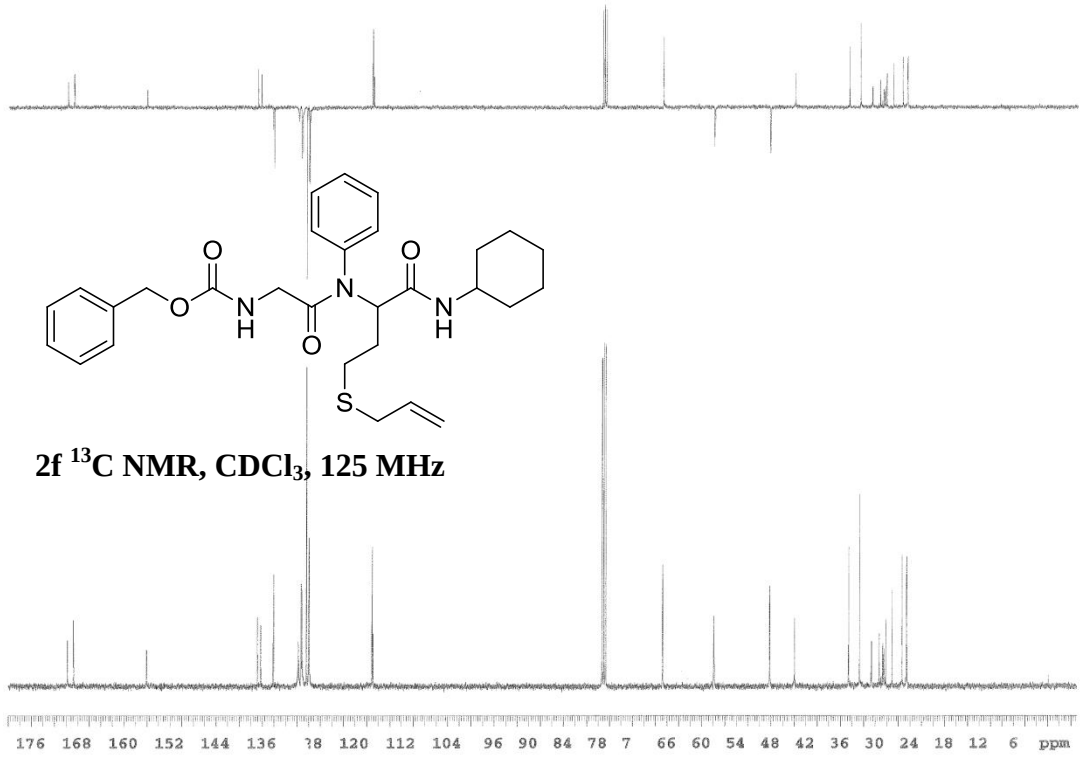


2e ^{13}C NMR, CD_3OD, 125 MHz

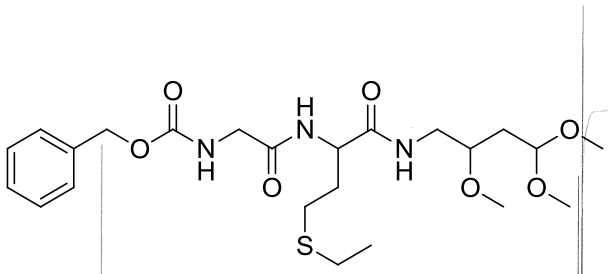




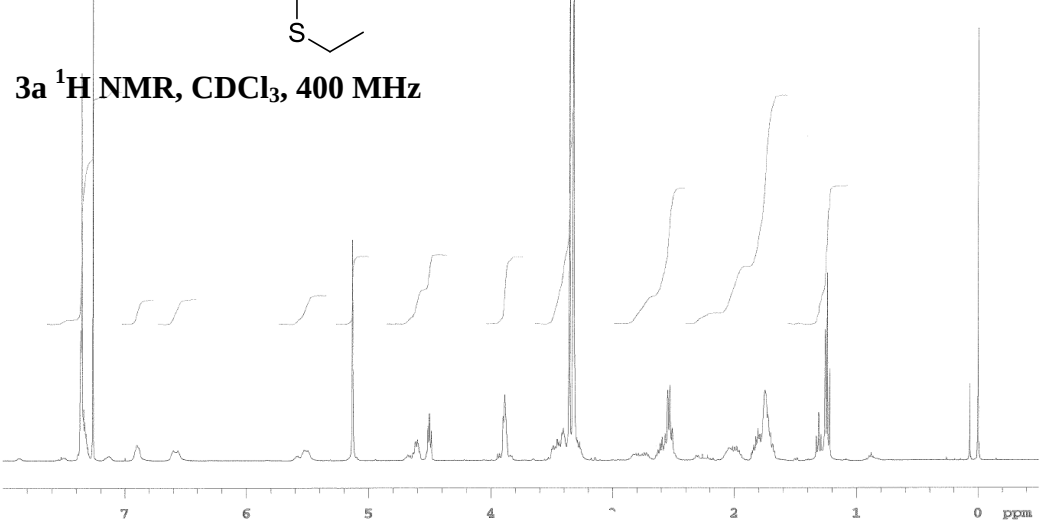
2f ^{1}H NMR, $CDCl_3$, 400 MHz

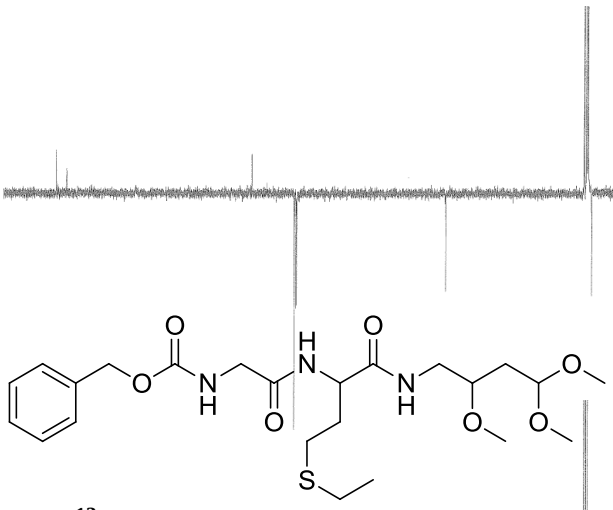


2f ^{13}C NMR, $CDCl_3$, 125 MHz

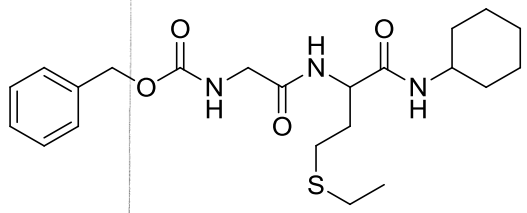


3a ^{1}H NMR, $CDCl_3$, 400 MHz

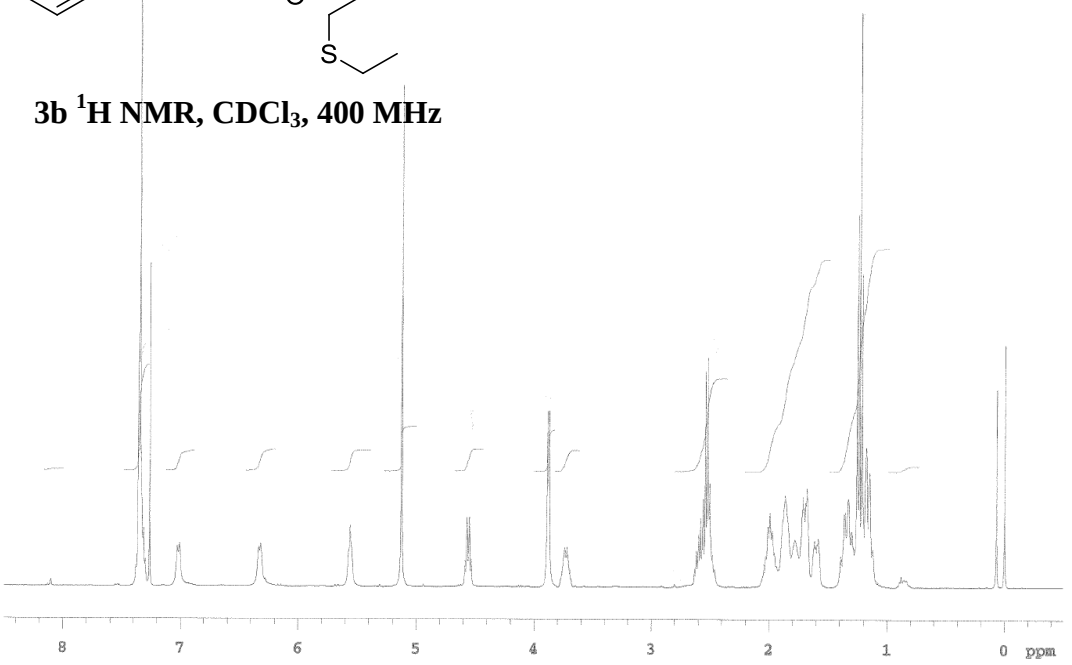


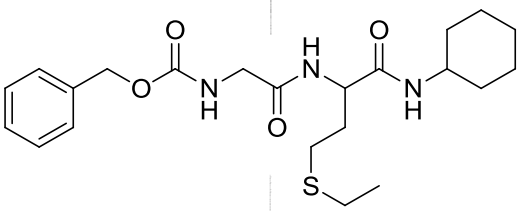


3a ^{13}C NMR, $CDCl_3$, 125 MHz

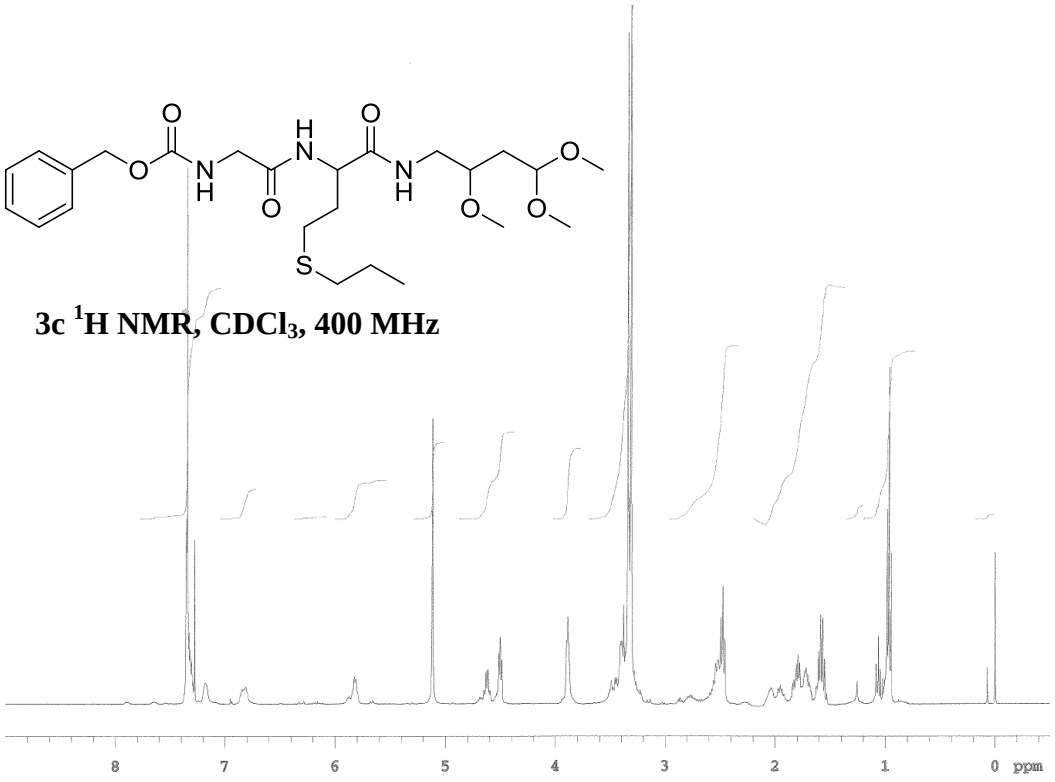


3b ^{1}H NMR, $CDCl_3$, 400 MHz

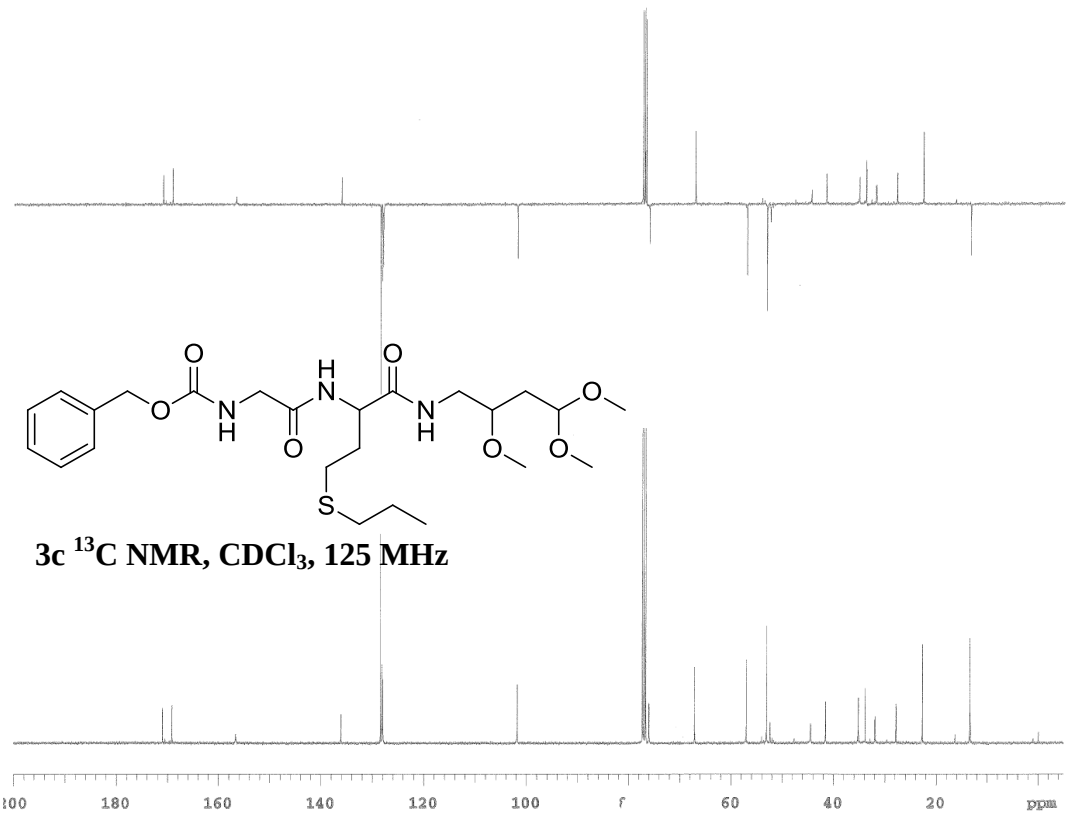




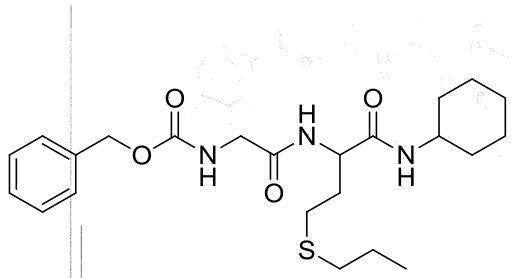
3b ^{13}C NMR, $CDCl_3$, 125 MHz



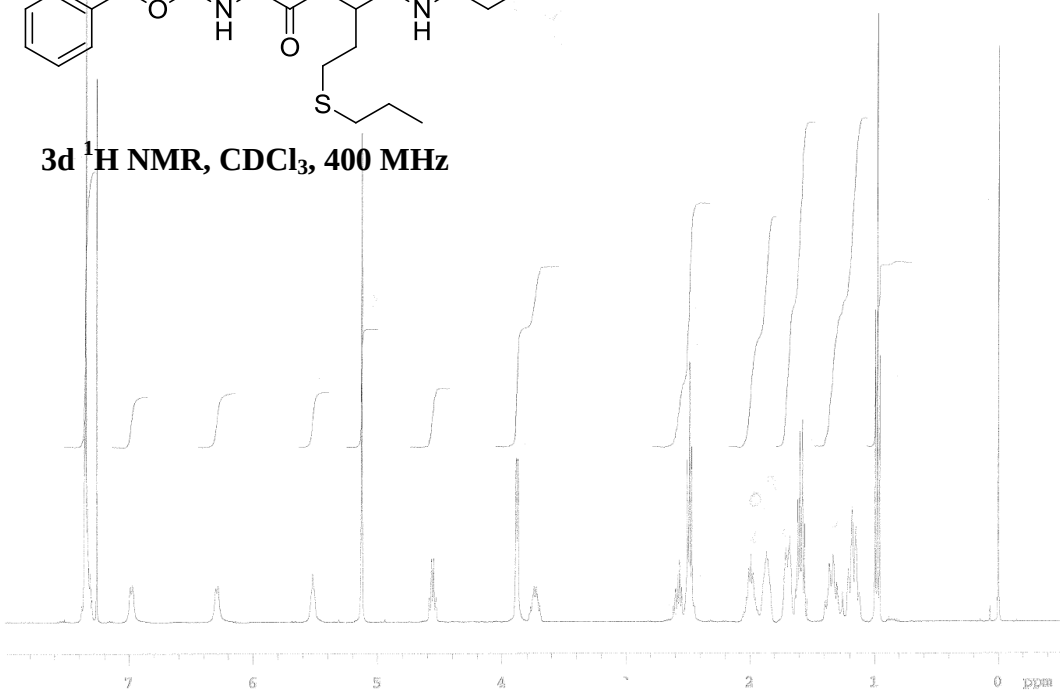
3c ^{1}H NMR, $CDCl_3$, 400 MHz

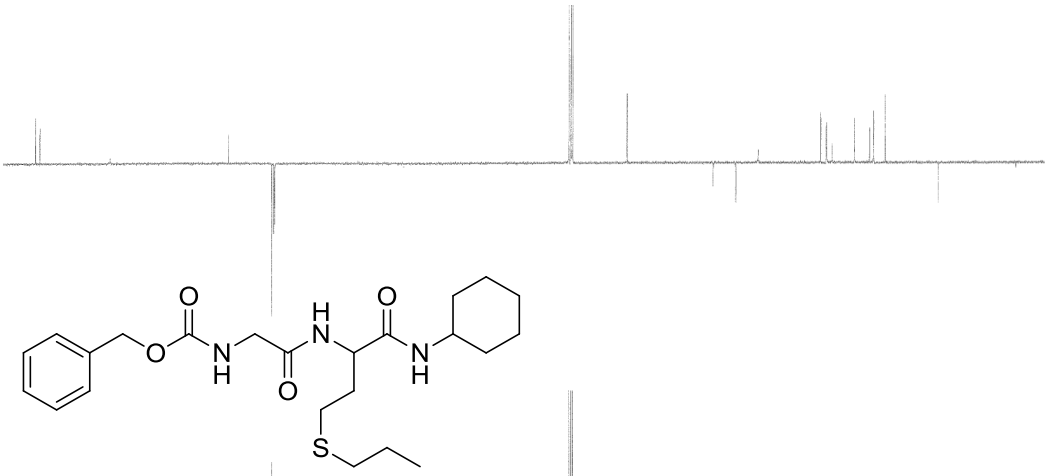


3c ^{13}C NMR, $CDCl_3$, 125 MHz

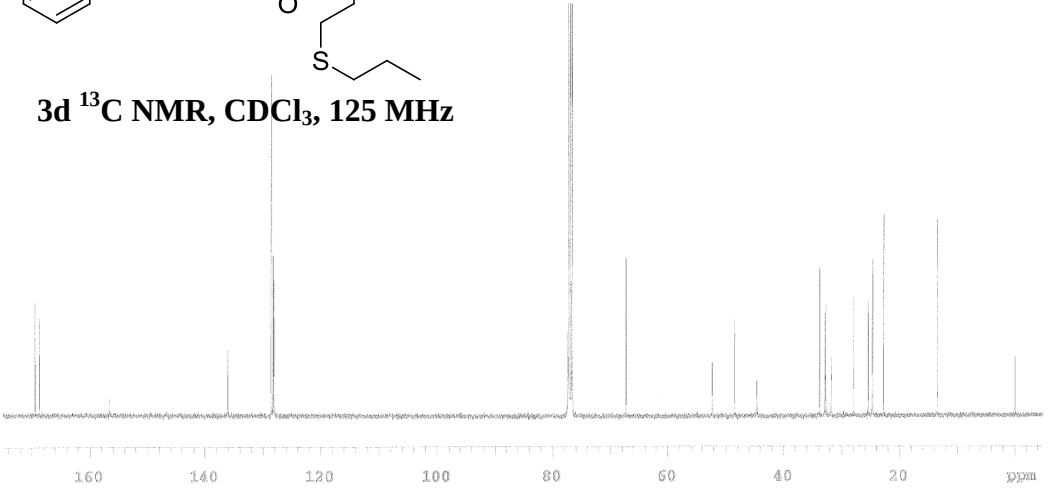


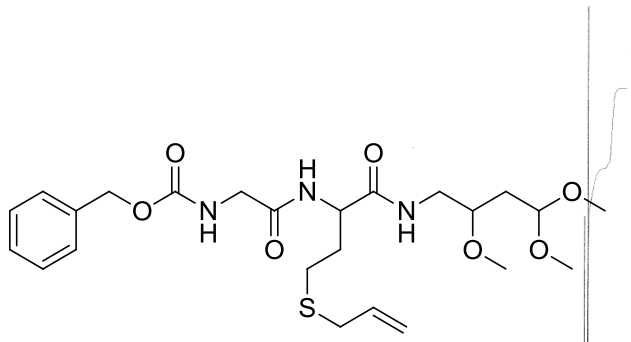
3d ^{1}H NMR, $CDCl_3$, 400 MHz



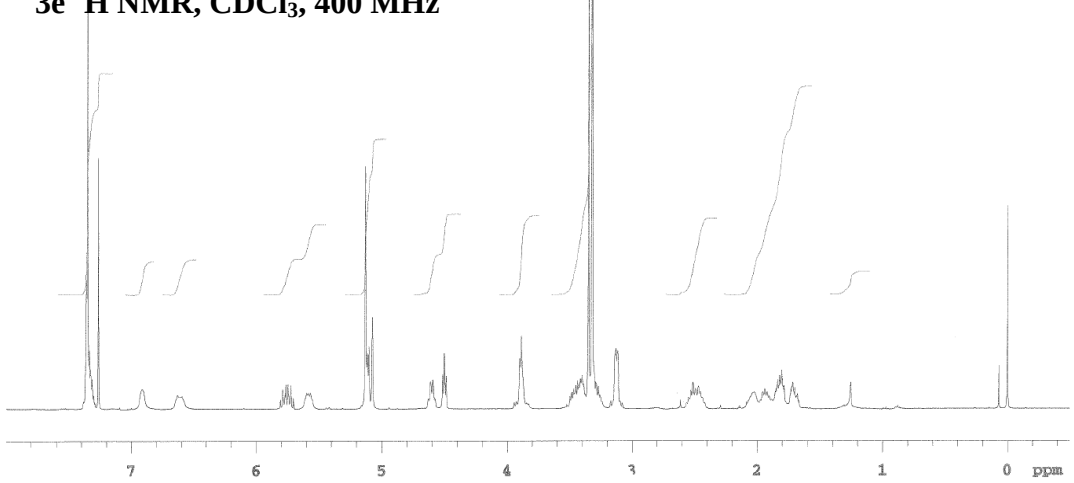


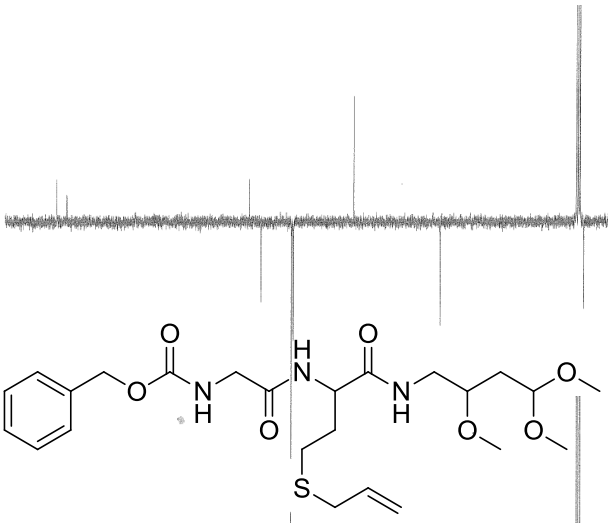
3d ^{13}C NMR, $CDCl_3$, 125 MHz



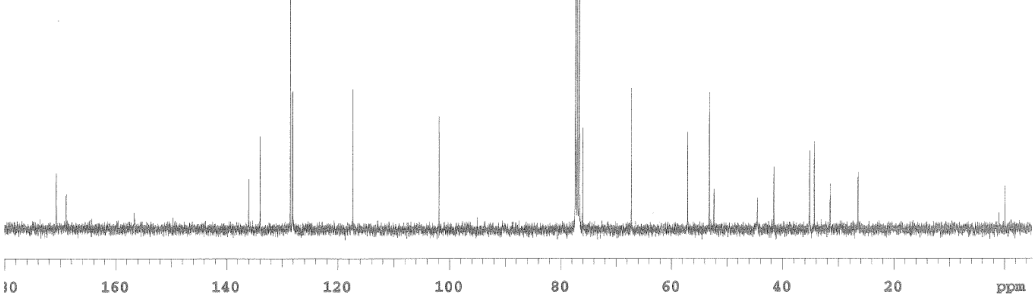


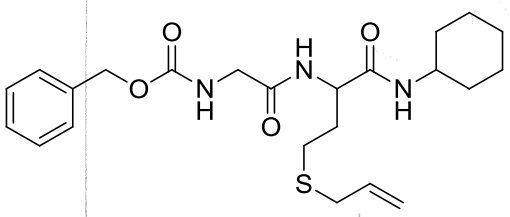
3e ^{1}H NMR, $CDCl_3$, 400 MHz



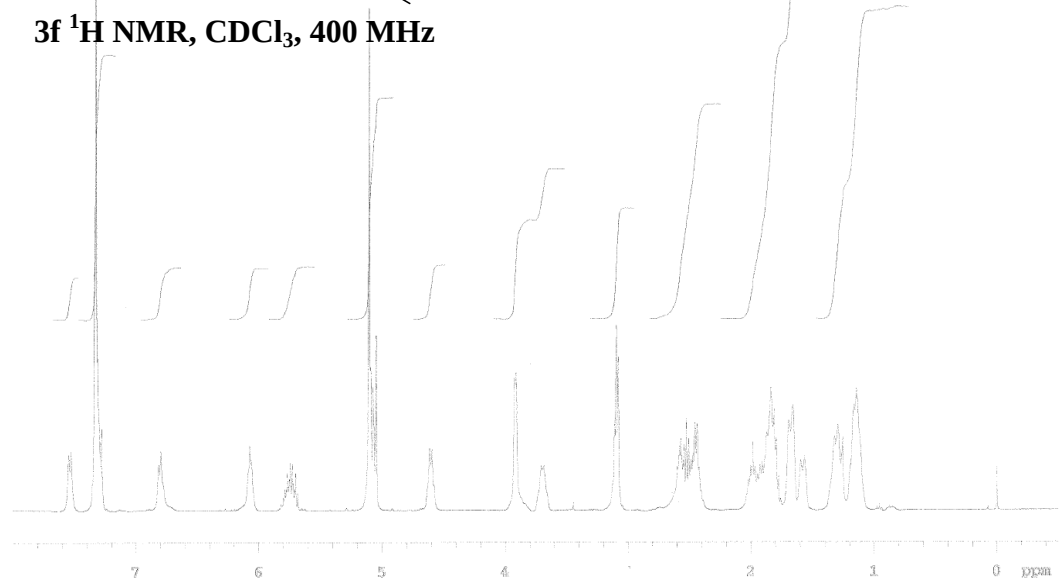


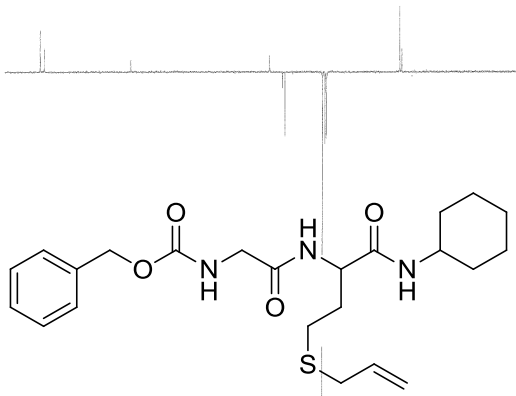
3e ^{13}C NMR, $CDCl_3$, 125 MHz



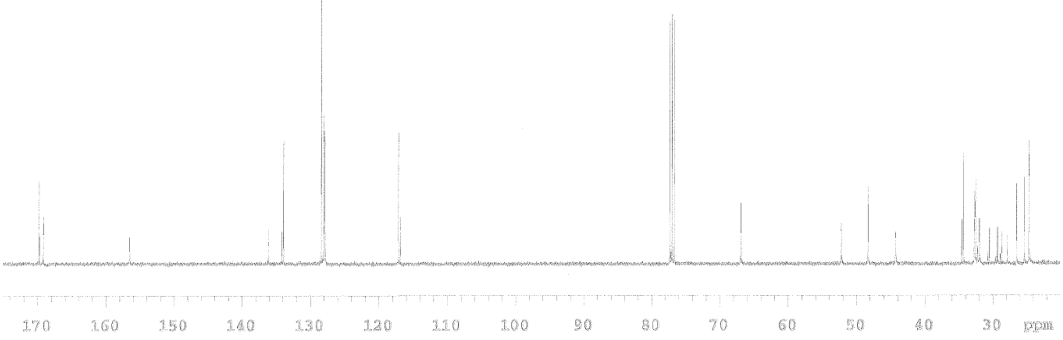


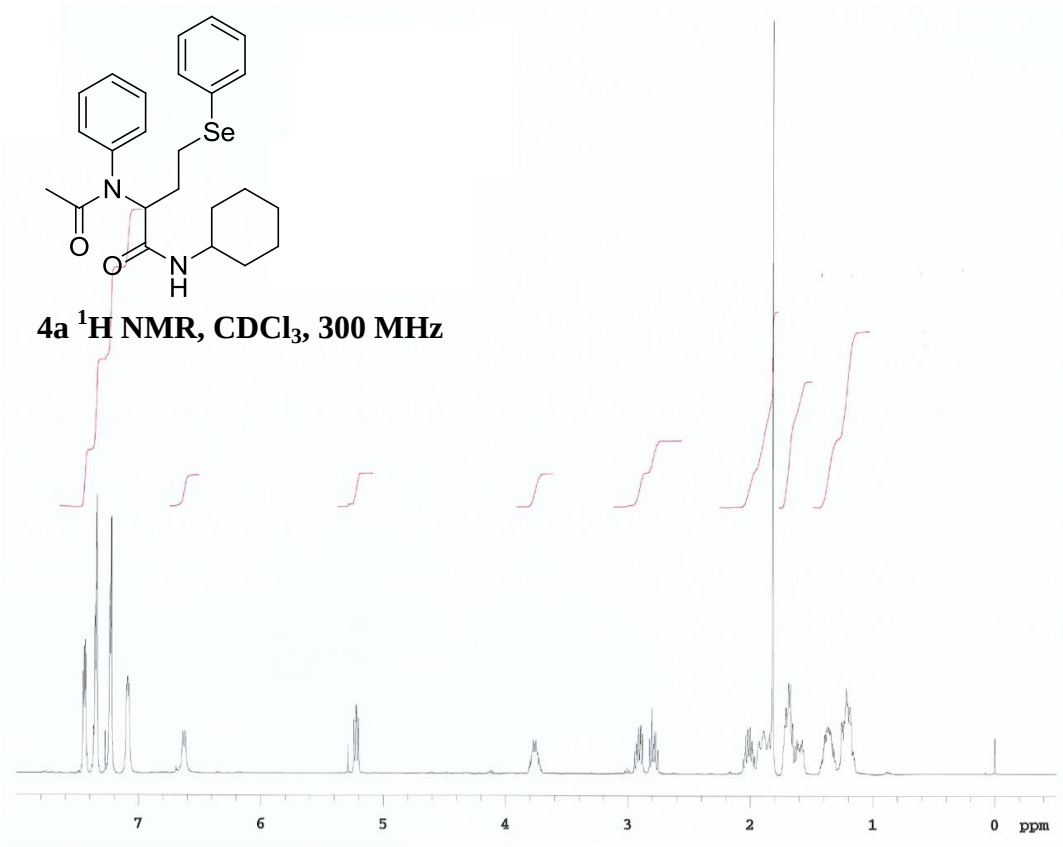
3f ^{1}H NMR, $CDCl_3$, 400 MHz



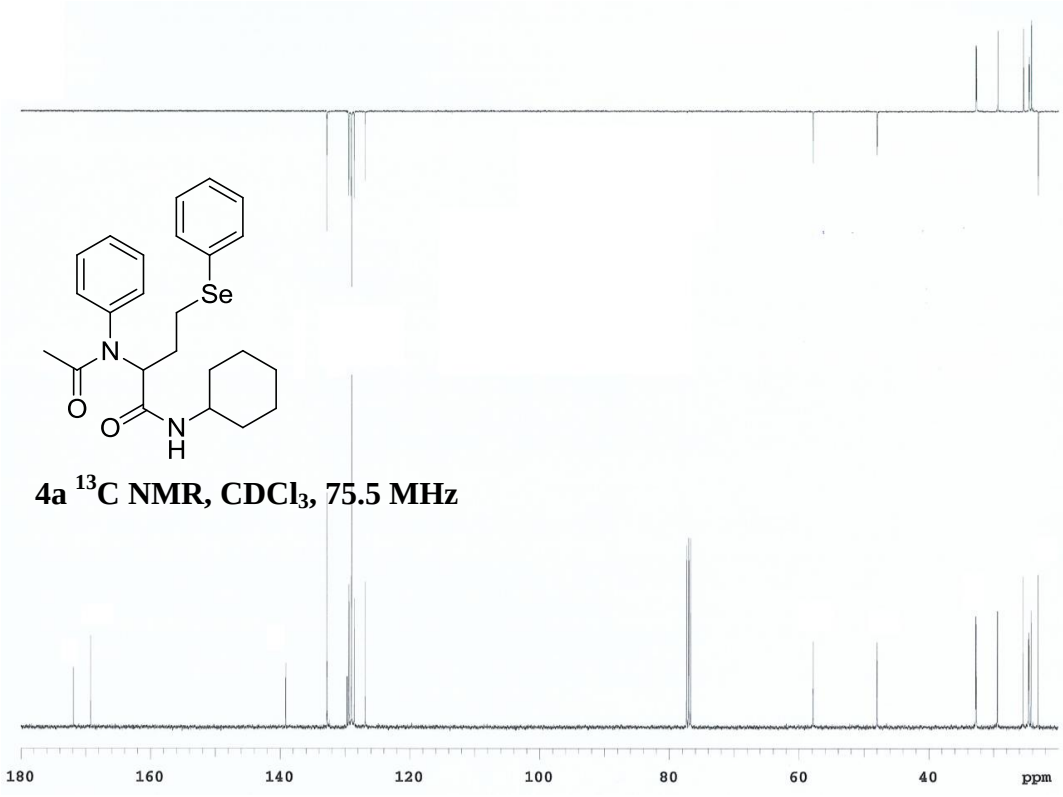


3f ^{13}C NMR, $CDCl_3$, 125 MHz

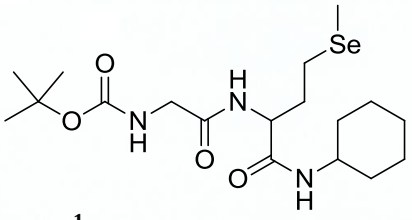




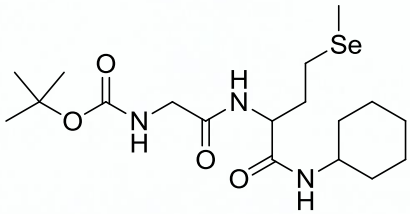
4a ^{1}H NMR, $CDCl_3$, 300 MHz



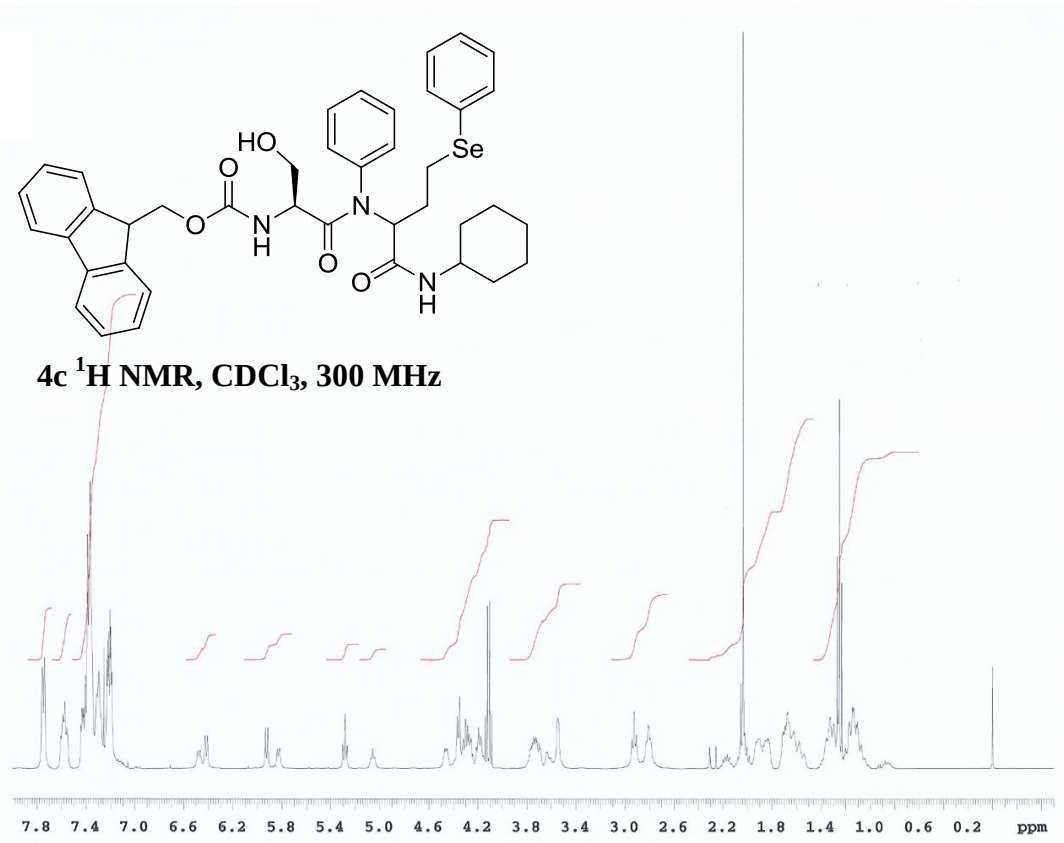
4a ^{13}C NMR, $CDCl_3$, 75.5 MHz



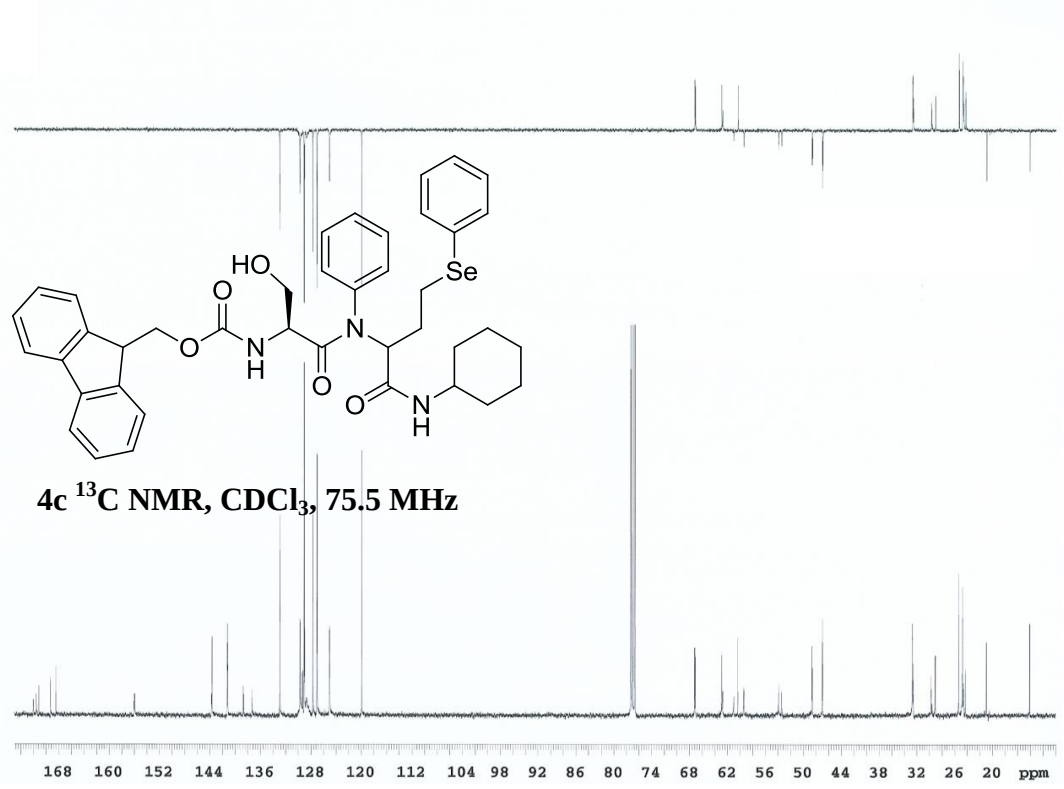
4b ^{1}H NMR, $CDCl_3$, 300 MHz



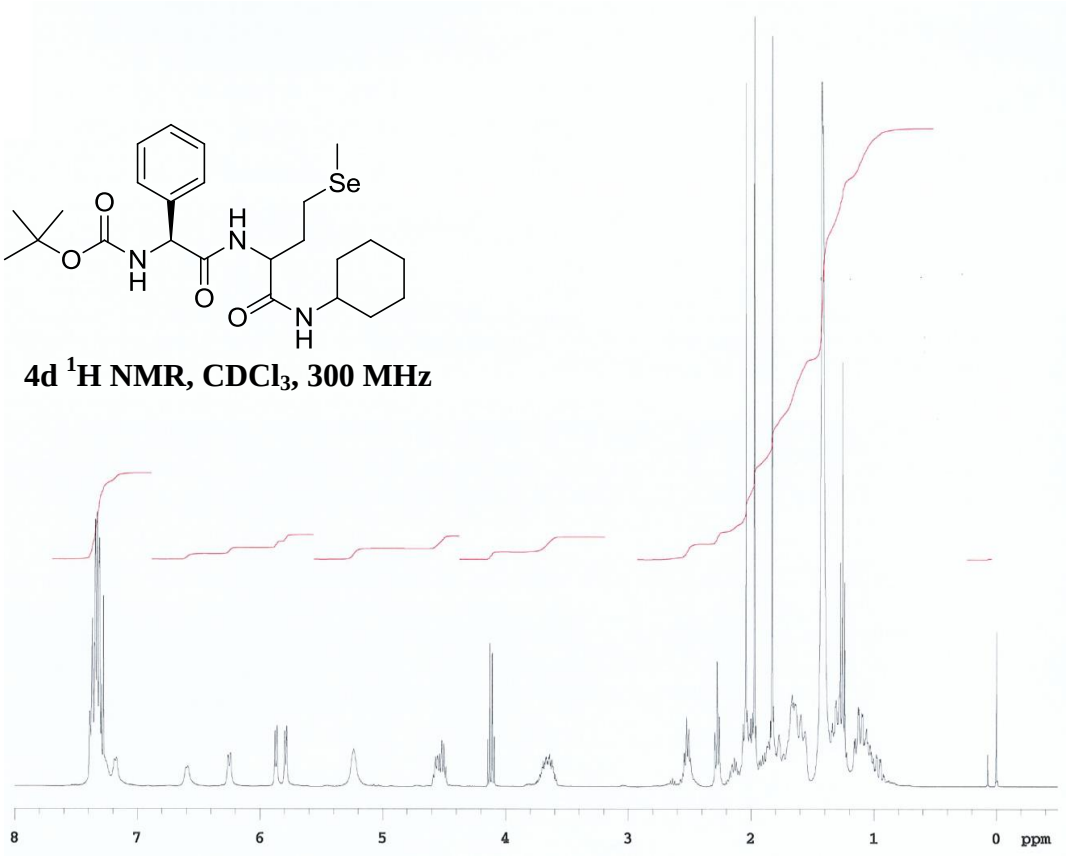
4b ^{13}C NMR, $CDCl_3$, 75.5 MHz



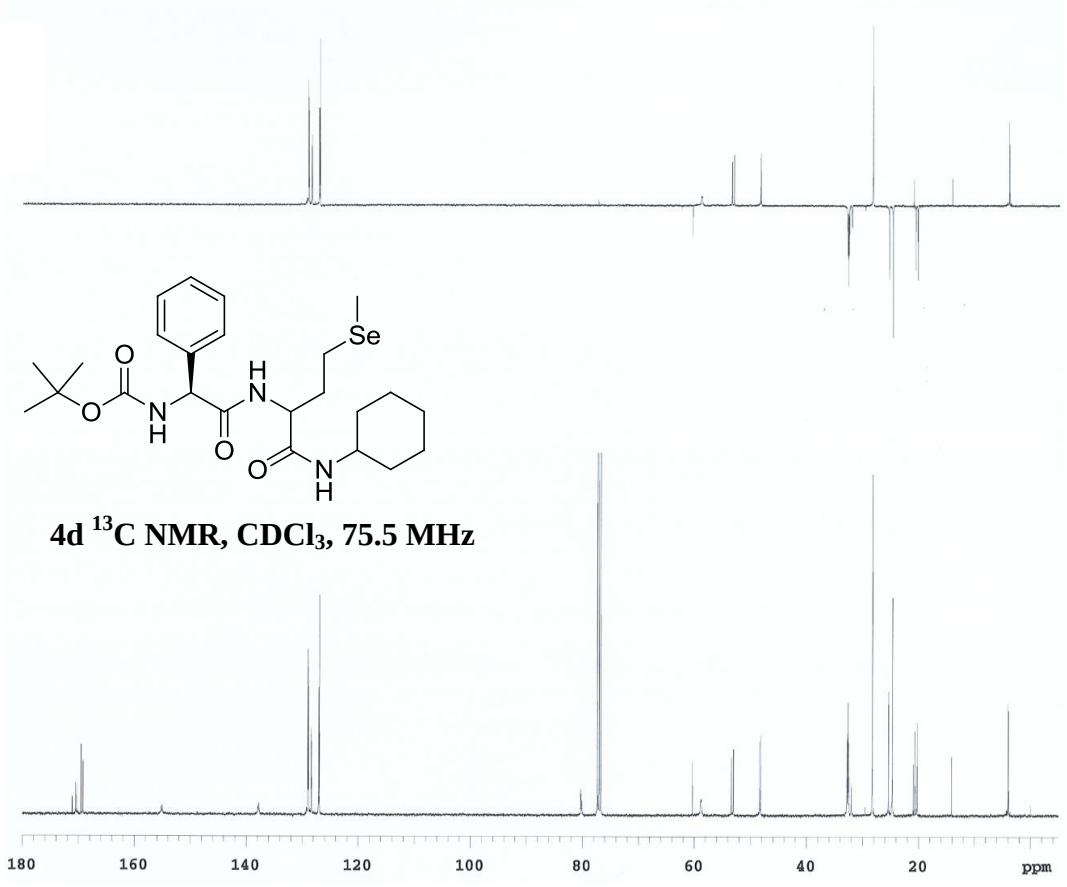
4c ^{1}H NMR, $CDCl_3$, 300 MHz



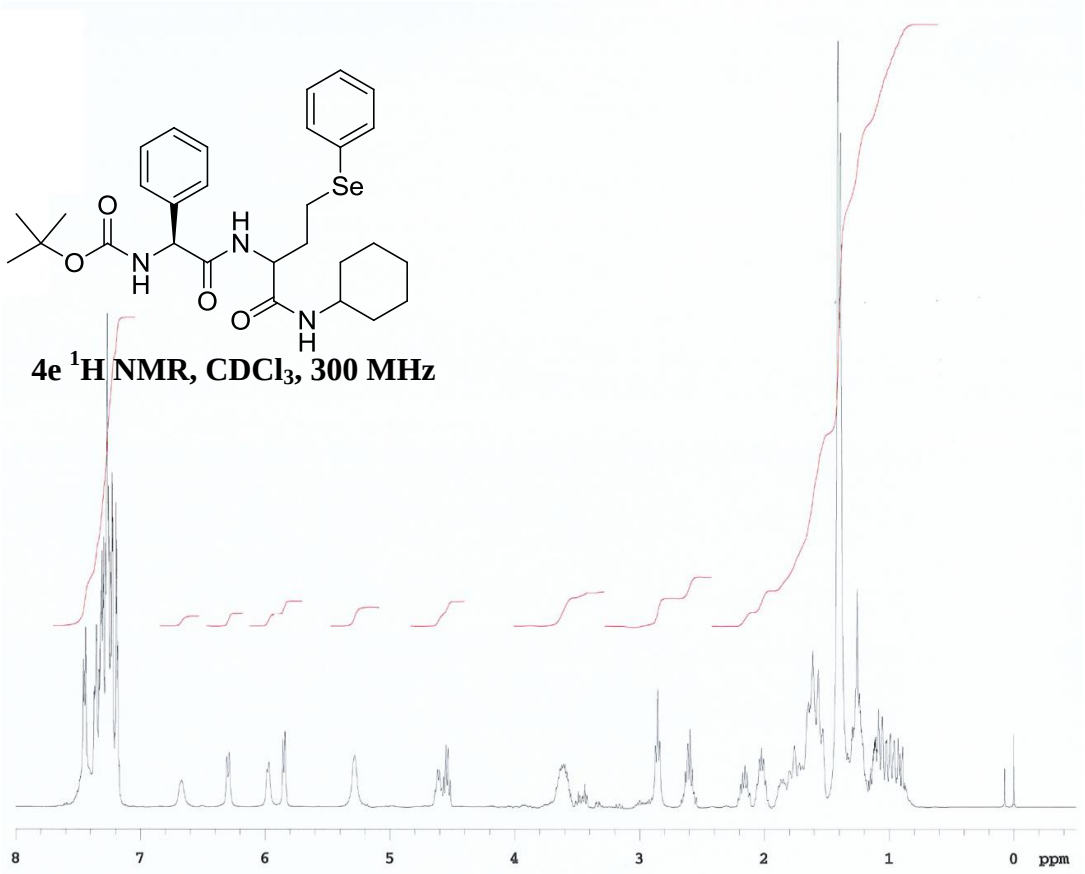
4c ^{13}C NMR, $CDCl_3$, 75.5 MHz



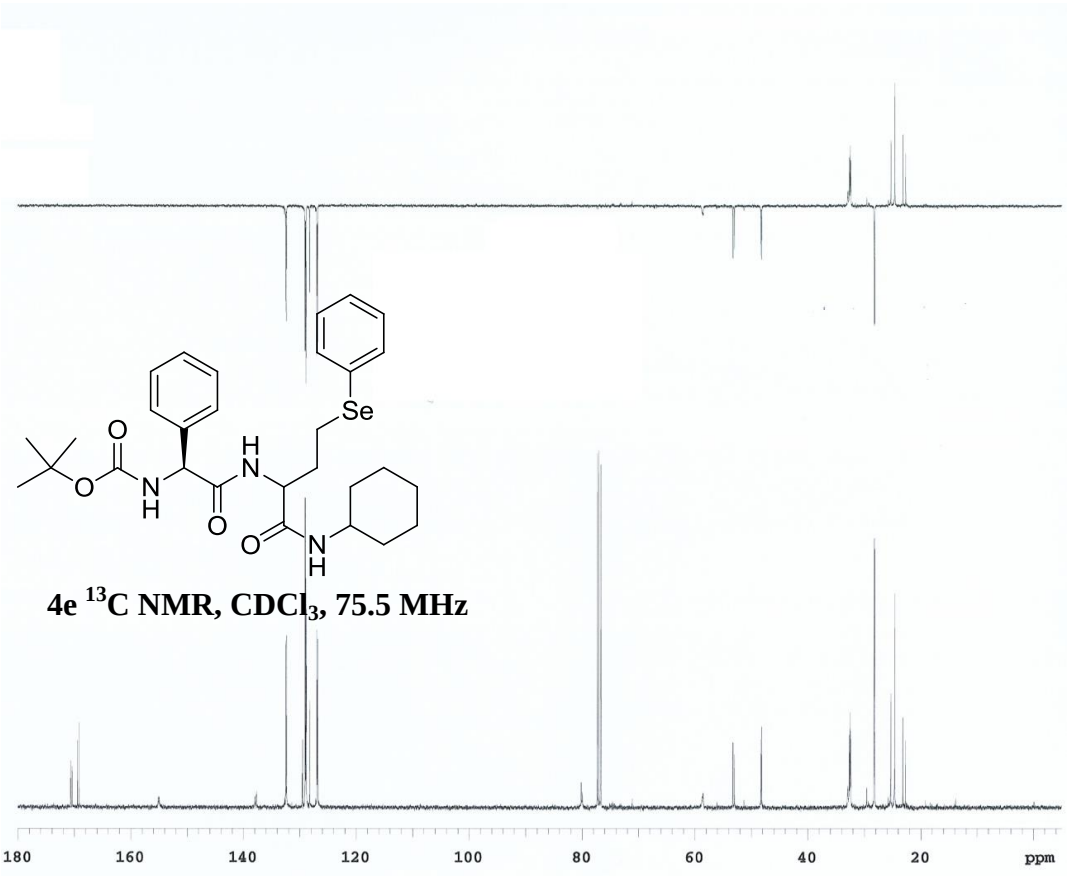
4d ^{1}H NMR, $CDCl_3$, 300 MHz



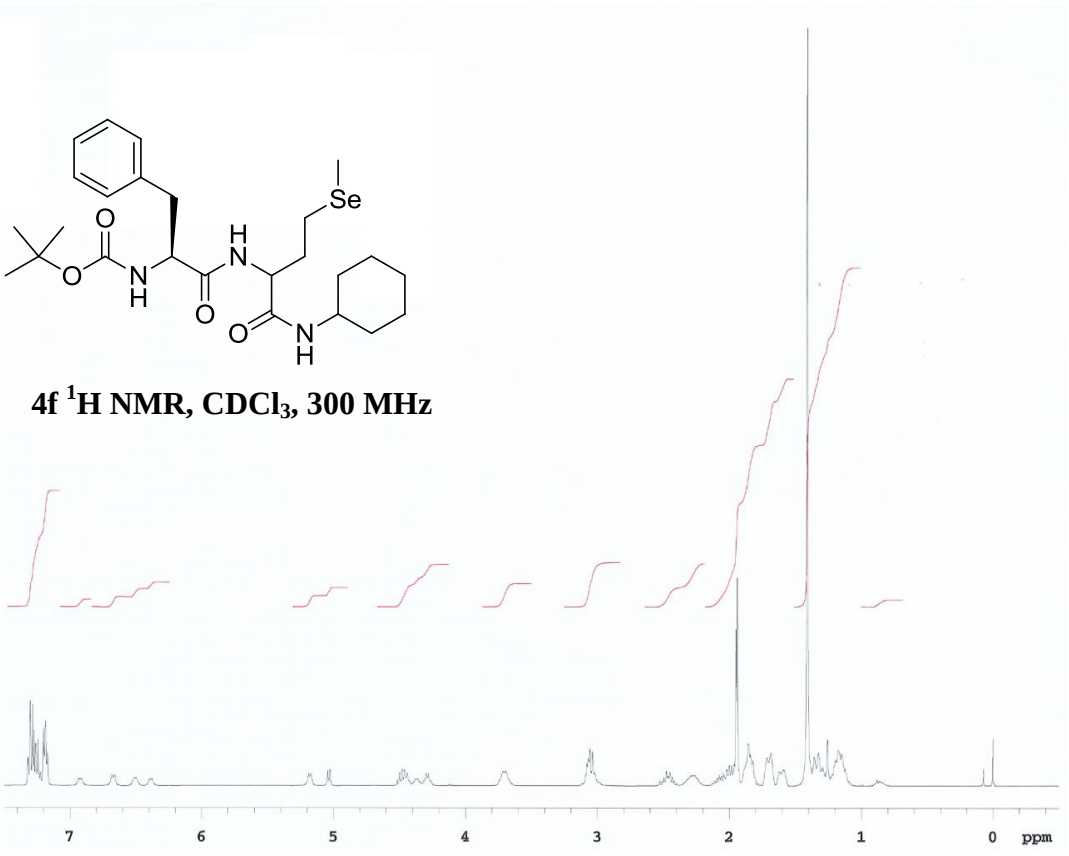
4d ^{13}C NMR, $CDCl_3$, 75.5 MHz



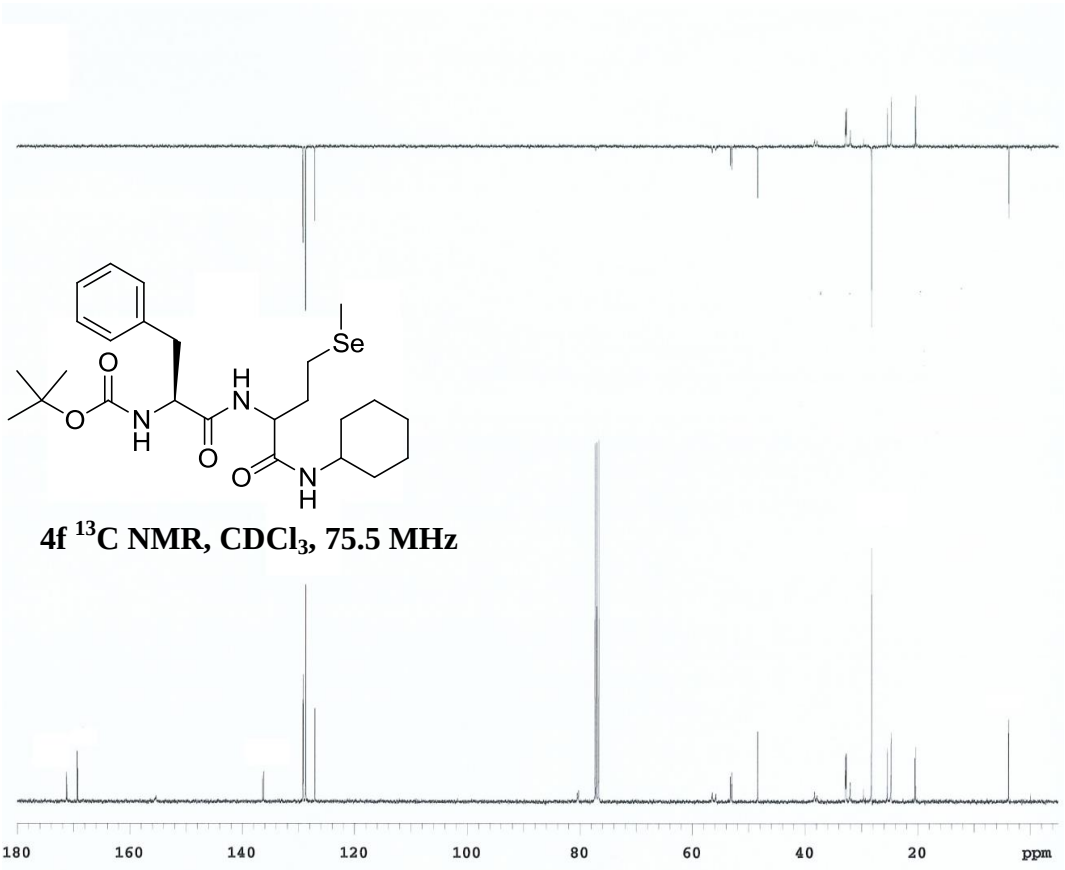
4e ^{1}H NMR, $CDCl_3$, 300 MHz



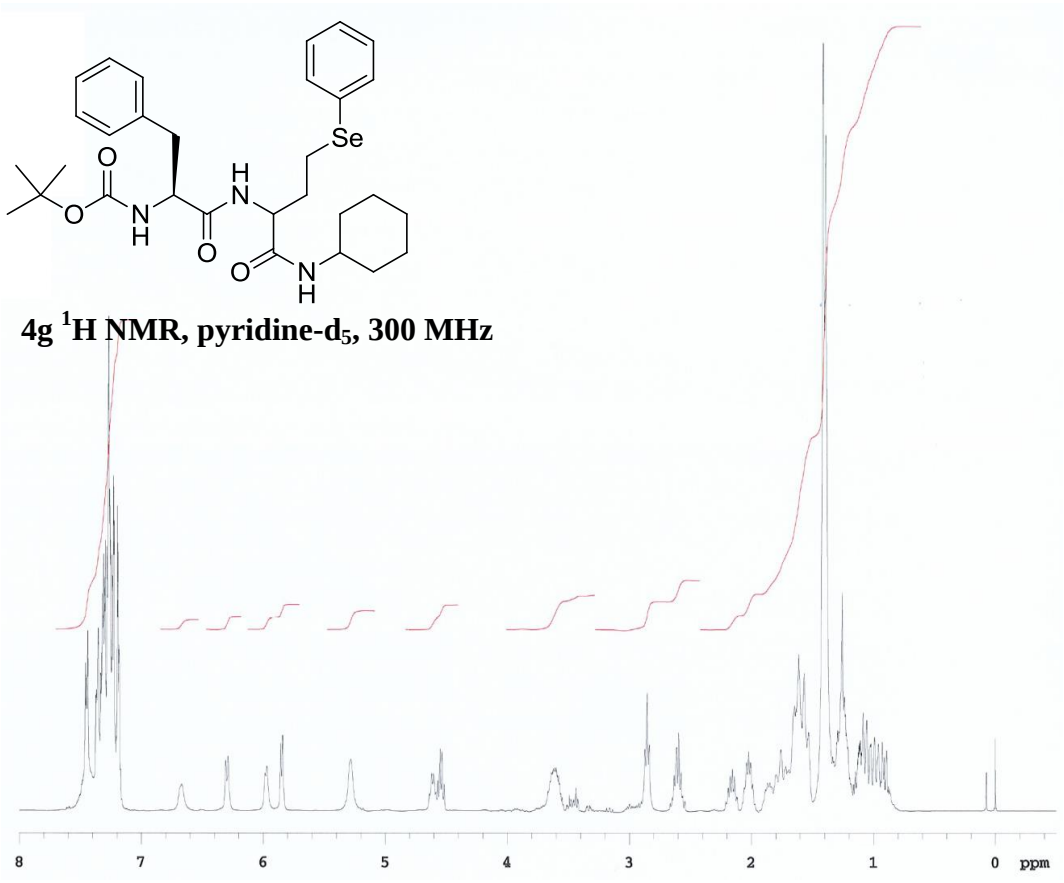
4e ^{13}C NMR, $CDCl_3$, 75.5 MHz



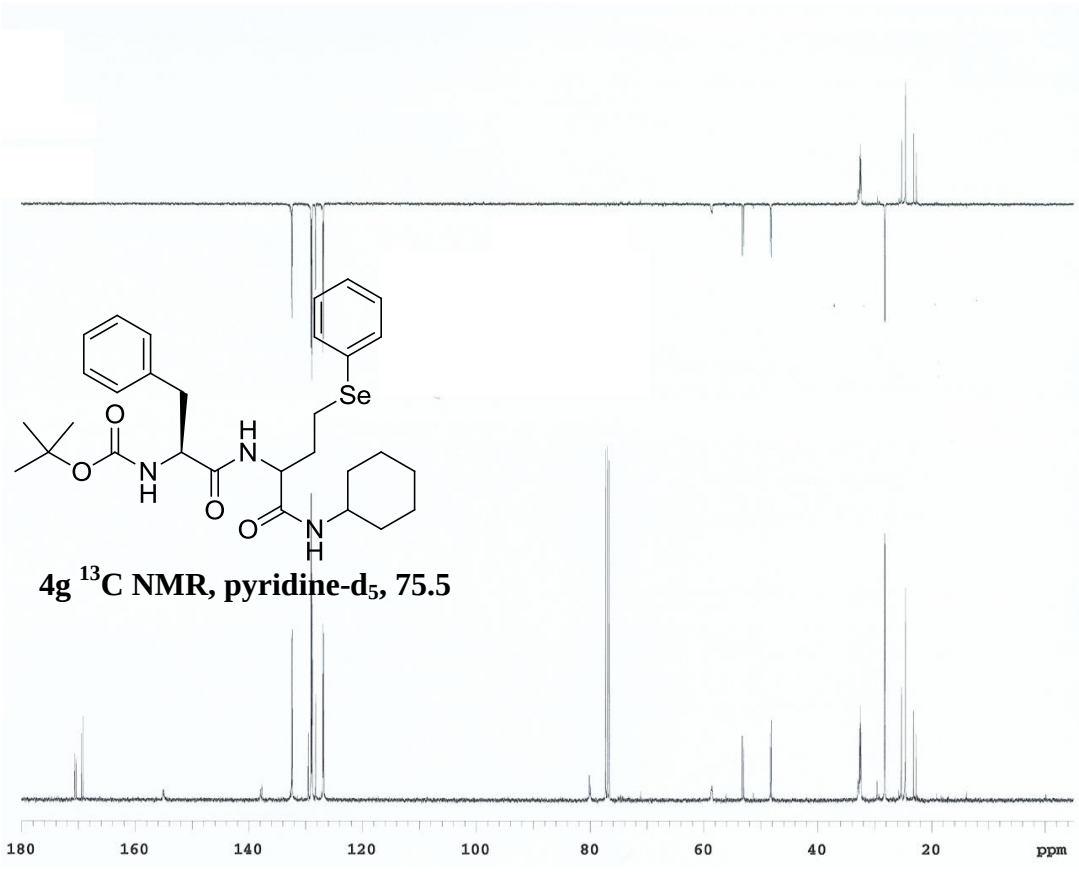
4f ^{1}H NMR, $CDCl_3$, 300 MHz



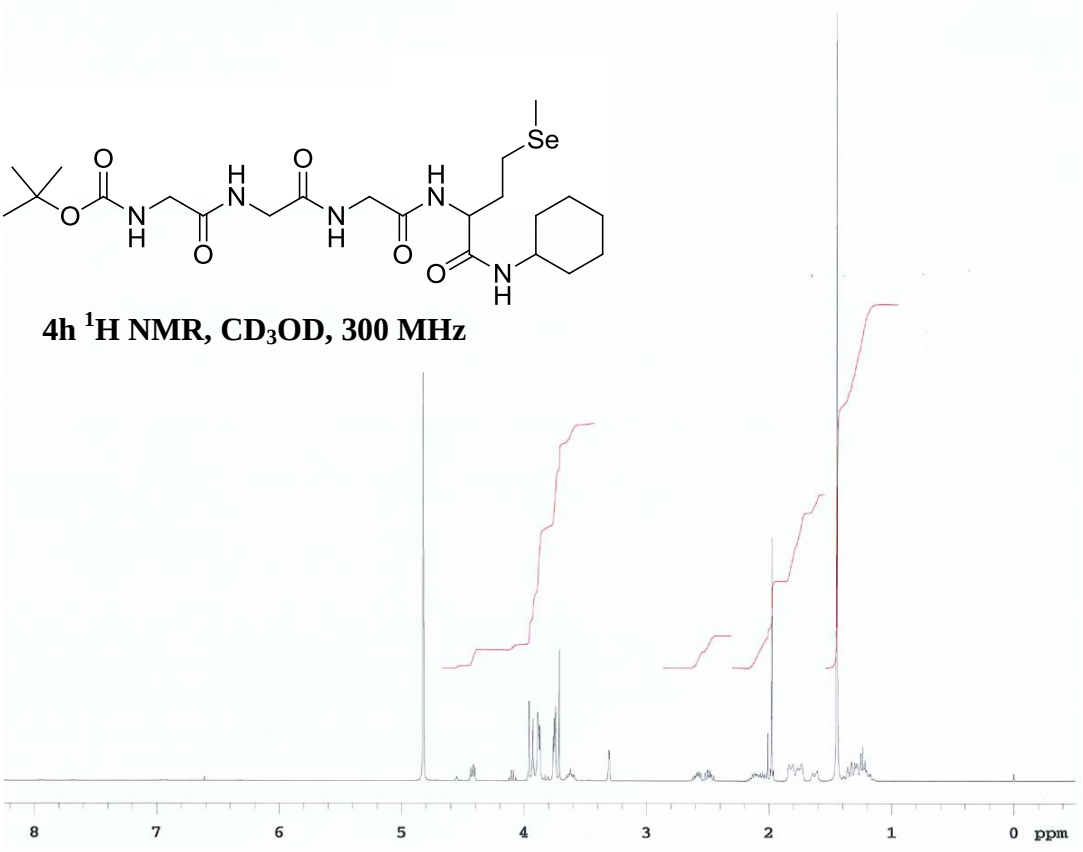
4f ^{13}C NMR, $CDCl_3$, 75.5 MHz



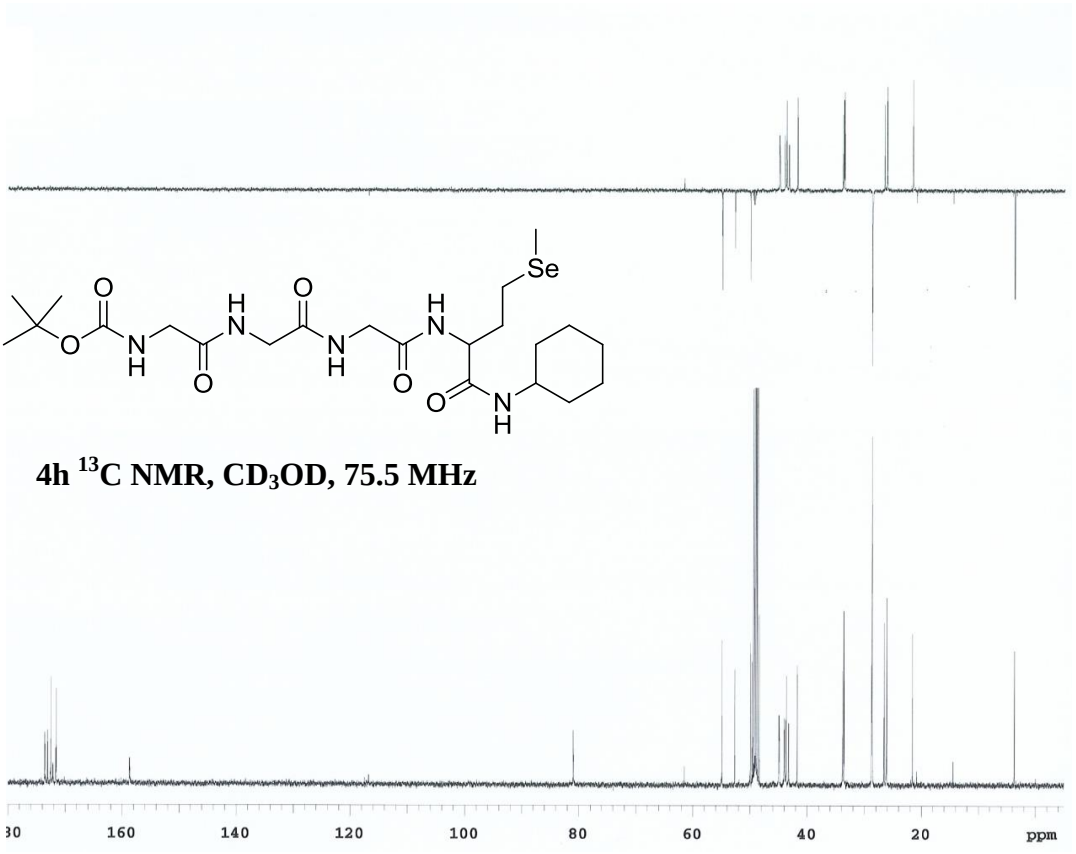
4g ^{1}H NMR, pyridine-d$_5$, 300 MHz



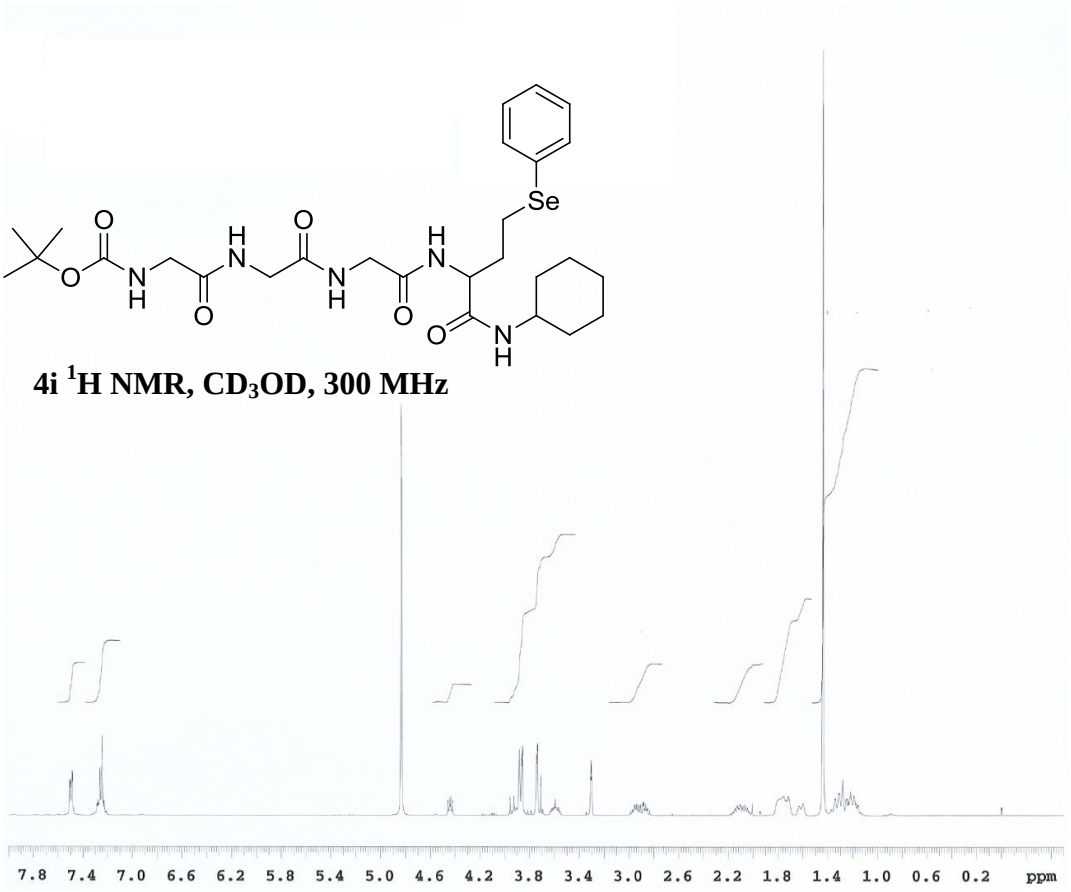
4g ^{13}C NMR, pyridine-d$_5$, 75.5



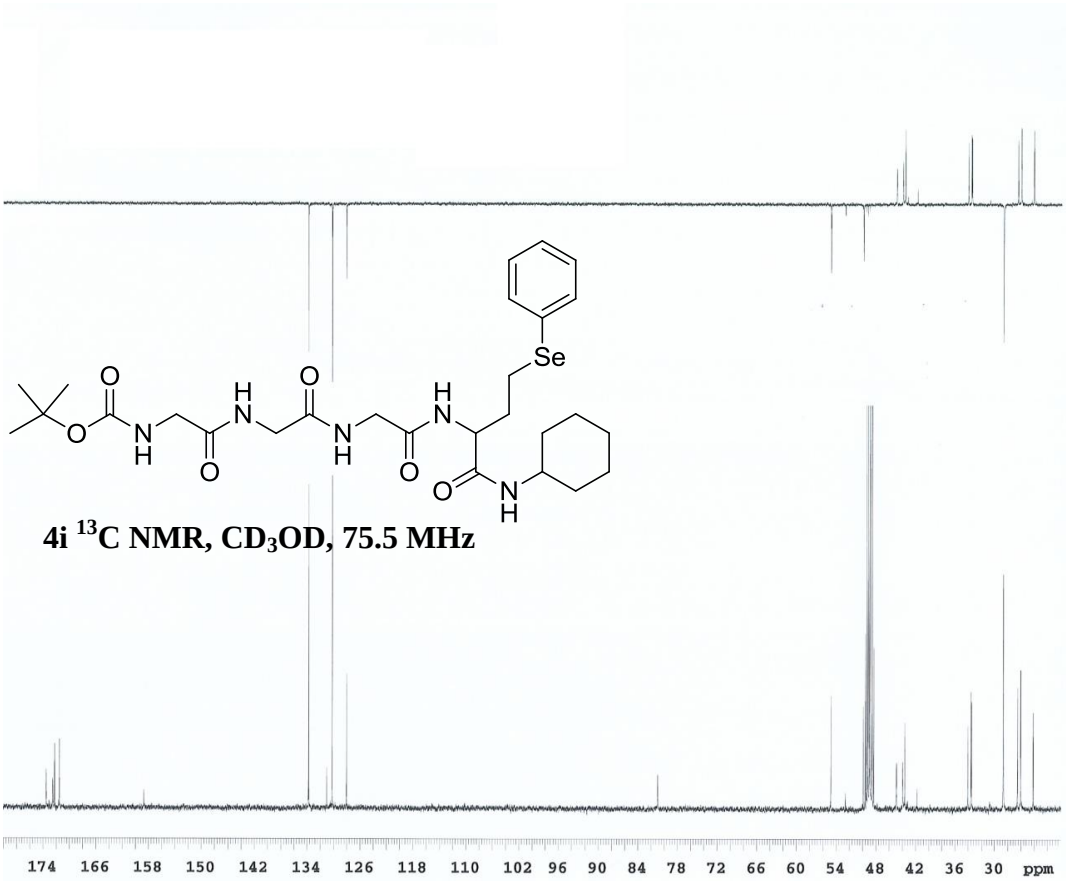
4h ^{1}H NMR, CD_3OD, 300 MHz



4h ^{13}C NMR, CD_3OD, 75.5 MHz



4i ^{1}H NMR, CD_3OD, 300 MHz



4i ^{13}C NMR, CD_3OD, 75.5 MHz