Electronic Supplementary Information (ESI)

Design and synthesis of galactose-conjugated fluorinated and non-fluorinated proline oligomers: Towards antifreeze molecules

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General Information:

All reactions were performed in oven-dried glassware under a positive pressure of nitrogen. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel (60-F_{254}). The TLC plates were visualized with UV light and phosphomolybdic acid solution (phosphomolybdic acid: 25 g, EtOH: 500 mL) or acidic *p*-anisaldehyde solution (*p*-anisaldehyde: 25 mL, *c*-H_2SO_4: 25 mL, AcOH: 5 mL, EtOH: 425 mL) with subsequent heating. Column chromatography was carried out on a column packed with silica gel 60N spherical neutral size 63-210 μm or reverse phase silica gel (nacalai cosmosil 75C18-OPN). The ^{1}H NMR (300, 700 MHz), ^{19}F NMR (282 MHz) and ^{13}C NMR (126, 176 MHz) spectra were recorded on a Varian Mercury 300, a Bruker Avance 500 and a JEOL ECZ-700R. Chemical shifts (δ) are expressed in ppm downfield from $CDCl_3$ (7.26 ppm for ^{1}H NMR), D_2O (4.79 ppm for ^{1}H NMR), C_6F_6 (−162.2 ppm for ^{19}F NMR) or $CDCl_3$ (77.0 ppm for ^{13}C NMR). Mass spectra were recorded on a SHIMAZU LCMS-2020EV (ESI-MS). High resolution mass spectrometry were recorded on a Waters Synapt G2 HDMS (ESI-MS). Infrared spectra were recorded on a JASCO FT/IR-4100 spectrometer. Circular dichroism spectra was recorded on a JASCO J-820 spectrometer.

1. General Procedure for the synthesis of compounds

General procedure (a): Condensation of amine and carboxylic acid

To a solution of amine (1.0 equiv) and carboxylic acid (1.1 equiv) in CH_2Cl_2 was added EDCI (1.3 equiv), and the whole mixture was stirred at rt for 12 h. Saturated $NaHCO_3$ aq was added the mixture and the whole mixture was extracted with CH_2Cl_2. Removal of the solvent from the extract under reduced pressure gave a crude product, which was purified by SiO_2 column to give product.

General procedure (b): Removal of Boc group

TFA (TFA:CH_2Cl_2 = 1:3) was added to a solution of *N*-Boc compound in CH_2Cl_2 (0.1 M) at 0 °C, and the whole mixture was stirred at rt for 2 h. The solvent was removed under reduced pressure, and saturated $NaHCO_3$ aq was carefully added to the resulting mixture until pH = 9. The whole mixture was extracted with CH_2Cl_2, and the organic phase was washed with brine. Removal of the solvent from the extract under reduced pressure gave a crude product, which was used for the next reaction without further purification.

General procedure (c): Base hydrolysis of methyl ester

1N LiOH aq (2.0 equiv) was added to a solution of methyl ester (1.0 equiv) in THF-MeOH (2:1, 0.3 M), and the whole mixture was stirred at rt for 4 h. 4N HCl was added to the mixture until pH = 2, and the whole mixture was extracted with EtOAc. Removal of the solvent from the extract under reduced pressure gave a crude product, which was used for the next reaction without further

purification.

General procedure (d): Acetylation of amine

To a solution of secondary amine in CH_2Cl_2, Ac_2O (5.0 equiv) and pyridine (5.0 equiv) were added at 0 ℃, and the whole mixture was stirred at rt for 12 h. Removal of the solvent from the extract under reduced pressure gave a crude product, which was purified by SiO_2 column to give acetyl product.

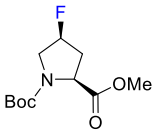
General procedure (e): Click reaction

To a solution of azide (1.0 equiv) and *O*-propargyl galactose **29** (4.0 equiv) in ^{t}BuOH, $CuSO_4$ (0.05 M solution, 1.5 equiv) and sodium ascorbate (0.05 M solution, 3.0 equiv) were added, and the whole mixture was stirred at rt for 24 h. Removal of the solvent from the extract under reduced pressure gave a crude product, which was purified by reverse phase SiO_2 column to give triazole product.

2. Synthesis of 12 and 13

2.1. Synthesis of galactose-conjugated fluorinated proline oligomer 12a

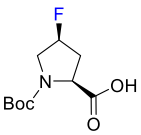
1-(*tert*-Butyl) 2-methyl (2*S*,4*S*)-4-fluoropyrrolidine-1,2-dicarboxylate (SI-1)[1]



DBU (1.83 mL, 12.3 mmol, 1.2 equiv) was added to a solution of *trans*-4-hydroxy-*N*-Boc-L-proline (2.50 g, 10.2 mmol) in CH_2Cl_2 (40 mL), the mixture was cooled to –78 ℃ and Xtalfluor-E® (2.81 g, 12.3 mmol, 1.2 equiv) was added to the mixture. The whole mixture was stirred at –78 ℃ for 1 h, and stirred with gently warming to rt for 12 h. Saturated $NaHCO_3$ aq was added to the mixture and the mixture was extracted with CH_2Cl_2. Removal of the solvent from the extract under reduced pressure gave a crude product, which was purified by SiO_2 column chromatography (*n*-hexane:AcOEt = 4:1) to give title compond (1.91 g, 76%) as a white solid.

Mixture of rotamer. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.20 (dd, *J* = 52.6, 3.7 Hz, 1H), 4.55 (d, *J* = 9.8 Hz, 0.5H), 4.43 (d, *J* = 9.6 Hz, 0.5H), 3.75 (s, 3H), 3.85–3.60 (m, 2H), 2.51–2.46 (m, 1H), 2.44–2.28 (m, 1H), 1.48 (s, 4H), 1.43 (s, 5H) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz) δ: –173.8 (brd, 1F) ppm; IR (KBr): 2978, 2881, 1759, 1703, 1402, 1367, 1163, 1120, 1072, 768 cm^{-1}; MS (ESI) *m*/*z*: 270 $[M+Na]^+$.

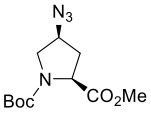
(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (14)[2]



According to the general procedure (c), **SI-1** (1.43 g, 5.78 mmol), in THF-MeOH (2:1, 19.3 mL) and LiOH aq (1.0 M, 11.6 mL, 11.6 mmol, 2.0 equiv) gave the title compound (1.27 g, 94%) as a white solid. The crude compound was used for the next reaction without column purification.

Mixture of rotamer. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 9.62 (brd, 1H), 5.20 (dt, *J* = 52.4, 3.9 Hz, 1H), 4.55 (d, *J* = 9.4 Hz, 0.5H), 4.44 (d, *J* = 9.6 Hz, 0.5H), 3.87–3.82 (m, 0.5H), 3.78–3.72 (m, 0.5H), 3.69–3.57 (m, 1H), 2.70 (t, *J* = 16.2 Hz, 0.5H), 2.54 (t, *J* = 16.6 Hz, 0.5H), 2.45–2.28 (m, 1H), 1.48 (s, 4.5H), 1.43 (s, 4.5H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ: –173.5 (m, 0.5F), –174.7 (m, 0.5F) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 177.0, 174.6, 155.4, 153.8, 91.9 (d, *J* = 128.0 Hz), 90.9 (d, *J* = 127.2 Hz), 81.6, 80.9, 57.5, 57.4, 53.5 (d, *J* = 24.3 Hz), 52.9 (d, *J* = 23.4 Hz), 37.3 (d, *J* = 22.6 Hz), 35.6 (d, *J* = 20.9 Hz), 28.3, 28.2 ppm; IR (KBr): 2983, 1738, 1701, 1423, 1369, 1165, 1128, 1072, 849, 765 cm^{-1}; MS (ESI) *m*/*z*: 232 $[M–H]^–$.

1-(*tert*-Butyl) 2-methyl (2*S*,4*S*)-4-azidopyrrolidine-1,2-dicarboxylate (SI-2)[3]

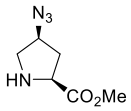


Et_3N (2.16 mL, 24.5 mmol, 2.0 equiv) and MsCl (1.14 mL, 14.7 mmol, 1.2 equiv) were added to a solution of *trans*-4-hydroxy-*N*-Boc-L-proline (3.01 g, 12.2 mmol) in CH_2Cl_2 (41 mL) at 0 ℃, and the whole mixture was stirred at 0 ℃ for 2 h. H_2O was added to the mixture and the mixture was extracted with CH_2Cl_2. Removal of the solvent from the extract under reduced pressure gave a crude product, which was used for the next reaction without column purification.

To a solution of mesylate intermediate in DMF (61 mL) was added sodium azide (2.39 g, 36.7 mmol, 3.0 equiv), and the whole mixture was stirred at 65 ℃ for 12 h. H_2O was added to the mixture and the mixture was extracted with organic solvent (EtOAc:*n*-hexane = 1:1). Removal of the solvent from the extract under reduced pressure gave a crude product, which was purified by SiO_2 column chromatography (*n*-hexane:AcOEt = 2:1) to give title compound (3.46 g, quant) as colorless oil.

^{1}H NMR ($CDCl_3$, 700 MHz) δ: 4.43 (q, *J* = 4.2 Hz, 0.45H), 4.32 (q, *J* = 4.4 Hz, 0.55H), 4.17–4.12 (m, 1H), 3.74 (t, *J* = 6.8 Hz, 3.55H), 3.70–3.67 (m, 0.45H), 3.51–3.44 (m, 1H), 2.50–2.42 (m, 1H), 2.18–2.15 (m, 1H), 1.47 (s, 4H), 1.41 (s, 5H) ppm; IR (KBr): 2978, 2889, 2106, 1753, 1707, 1400, 1203, 1163, 893, 769 cm^{-1}; MS (ESI) *m*/*z*: 293 $[M+Na]^+$.

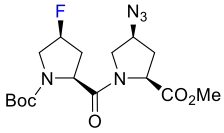
Methyl (2*S*,4*S*)-4-azidopyrrolidine-2-carboxylate (AZP-OMe,16)



According to the general procedure (b), **SI-2** (3.18 g, 11.8 mmol) in CH_2Cl_2 (118 mL) and TFA (39.3 mL) gave the title compound (1.91 g, 94%) as colorless oil. The crude compound was used for the next reaction without column purification.

^{1}H NMR ($CDCl_3$, 700 MHz) δ: 4.10–4.07 (m, 1H), 3.82–3.79 (m, 1H), 3.77 (s, 3H), 3.14–3.11 (m, 1H), 3.00 (dd, *J* = 11.9, 4.9 Hz, 1H), 2.37 (ddd, *J* = 14.8, 8.7, 5.3 Hz, 1H), 2.12–2.09 (m, 1H) ppm; IR (KBr): 3458, 2954, 2883, 2106, 1743, 1672, 1743, 1267 cm^{-1}; MS (ESI) *m*/*z*: 171 $[M+Na]^+$.

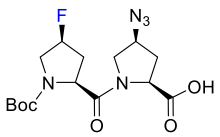
***tert*-Butyl (2*S*,4*S*)-2-((2*S*,4*S*)-4-azido-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)-4-fluoropyrrolidine-1-carboxylate (SI-3)**



According to the general procedure (a), **14** (4.38 g, 18.8 mmol, 1.0 equiv), **16** (3.96 g, 20.7 mmol, 1.1 equiv) and EDCI (4.68 g, 24.4 mmol, 1.3 equiv) gave the title compound (6.71 g, 92%) as a white solid. The title compound was purified by SiO_2 column chromatography (*n*-hexane:AcOEt = 1:2).

Mixture of rotamer. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.21 (d, *J* = 53.7 Hz, 1H), 4.75–4.73 (m, 1H), 4.54 (q, *J* = 4.0 Hz, 1H), 4.28–4.25 (m, 1H), 3.98 (dd, *J* = 10.5, 6.1 Hz, 1H), 3.87–3.73 (m, 2H), 3.72 (s, 1H), 3.71 (s, 2H), 3.48–3.45 (m, 1H), 2.52–2.37 (m, 3H), 2.17–2.14 (m, 1H), 1.44 (s, 6.6H), 1.40 (s, 2.4H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ: –173.63– –173.06 (m, 0.72F), –174.67 (m, 0.28F) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 171.1, 170.9, 170.0, 169.5, 165.6, 154.2, 153.4, 91.2 (major, d, *J* = 180.7 Hz), 90.5 (minor, d, *J* = 180.7 Hz), 80.5, 59.6, 58.3, 58.1, 57.7, 57.4, 57.3, 56.7, 53.2 (major, d, *J* = 25.9 Hz), 52.9 (minor, d, *J* = 25.1 Hz), 52.5, 52.4, 51.02, 50.96, 50.4, 36.5 (minor, d, *J* = 21.8 Hz), 35.5 (major, d, *J* = 21.8 Hz), 33.8, 33.7, 28.3, 28.2 ppm; IR (KBr): 2976, 2108, 1755, 1701, 1400, 1173, 769 cm^{-1}; MS (ESI) *m*/*z*: 408 $[M+Na]^+$; HRMS (ESI) *m*/*z*: 408.1659 calcd. for $C_{16}H_{24}N_5O_5FNa$, found: 408.1658.

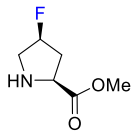
(2*S*,4*S*)-4-Azido-1-((2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carbonyl)pyrrolidine-2-carboxylic acid (17)



According to the geberal procedure (b), **SI-3** (6.71 g, 17.4 mmol) in THF-MeOH (2:1, 58 mL) and LiOH aq (1.0 M, 34.8 mL, 34.8 mmol, 2.0 equiv) gave the title compound (6.46 g, quant) as a white solid. The crude compound was used for the next reaction without column purification.

Mixture of rotamer. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.85 (brd, 1H), 5.25–5.15 (m, 1H), 4.73–4.68 (m, 1H), 4.59 (dd, *J* = 9.8, 2.2 Hz, 1H), 4.32–4.26 (m, 1H), 3.98 (dd, *J* = 10.5, 5.9 Hz, 1H), 3.86–3.68 (m, 2H), 3.40 (dd, *J* = 10.5, 3.9 Hz, 1H), 2.54–2.32 (m, 4H), 1.44 (s, 6.7H), 1.39 (s, 2.3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ: –173.2– –172.6 (major), –174.7– –174.0 (minor) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 172.3, 171.5, 154.4, 91.3 (major, d, *J* = 181.5 Hz), 90.6 (minor, d, *J* = 179.9 Hz), 81.0, 80.8, 67.9, 59.5, 59.4, 58.3, 57.5, 57.4, 56.8, 53.3 (major, d, *J* = 25.1 Hz), 53.0 (minor, d, *J* = 24.3 Hz), 51.6, 51.4, 36.5 (minor, d, *J* = 21.8 Hz), 35.6 (major, d, *J* = 21.8 Hz), 33.0, 32.8, 31.5, 28.3, 28.2, 25.5, 22.6 ppm; IR (KBr): 2979, 2877, 2108, 1749, 1678, 1410, 1217, 1169, 1072, 764 cm^{-1}; MS (ESI) *m*/*z*: 394 $[M+Na]^+$, 370 $[M–H]^–$; HRMS (ESI) *m*/*z*: 394.1503 calcd. for $C_{15}H_{22}N_5O_5FNa$, found: 394.1508.

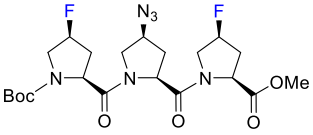
Methyl (2*S*,4*S*)-4-fluoropyrrolidine-2-carboxylate (19)[4]



According to the general procedure (b), **SI-1** (1.05 g, 4.25 mmol) in CH_2Cl_2 (20 mL) and TFA (6.6 mL) gave the title compound (435 mg, 70%) as yellowish volatile oil. The crude compound was used for the next reaction without column purification.

^{1}H NMR ($CDCl_3$, 700 MHz) δ: 5.19–5.11 (m, 1H), 3.83–3.81 (m, 1H), 3.76 (s, 3H), 3.40 (dd, *J* = 21.7, 13.7 Hz, 1H), 2.92 (ddd, *J* = 37.5, 13.4, 3.4 Hz, 1H), 2.33 (dd, *J* = 7.6, 3.4 Hz, 1H), 2.29–2.27 (m, 1H) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz) δ: –174.73– 174.24 (m, 1F) ppm; IR (KBr): 3647, 3320, 2956, 1739, 1437, 1344, 1227, 1113, 1041, 958, 856 cm^{-1};MS (ESI) *m*/*z*: 148 $[M+H]^+$.

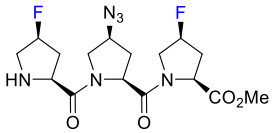
***tert*-Butyl (2*S*,4*S*)-2-((2*S*,4*S*)-4-azido-2-((2*S*,4*S*)-4-fluoro-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluoropyrrolidine-1-carboxylate (21)**



According to the general procedure (a), **17** (933 mg, 2.51 mmol), **19** (441 mg, 3.0 mmol) and EDCI (625 mg, 3.26 mmol, 1.3 equiv) in CH_2Cl_2 (8.4 mL) gave the title compound (941 mg, 74%) as a white solid. The title compound was purified by SiO_2 column chromatography (CH_2Cl_2:MeOH = 10:1).

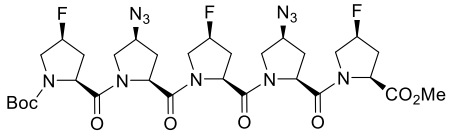
Mixture of rotamer. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.32–5.22 (m, 1H), 5.20–5.09 (m, 1H), 4.83–4.80 (m, 1H), 4.69 (t, *J* = 7.9 Hz, 0.75H), 4.62 (t, *J* = 7.8 Hz, 0.25H), 4.54–4.52 (m, 0.75H), 4.46–4.44 (m, 0.25H), 4.18–4.05 (m, 2.75H), 3.99–3.97 (m, 0.25H), 3.85–3.74 (m, 2H), 3.70 (s, 3H), 3.70–3.63 (m, 1H), 3.45 (t, *J* = 9.0 Hz, 1H), 2.67–2.62 (m, 1H), 2.48–2.32 (m, 3H), 2.12–2.08 (m, 1H), 1.96 (s, 1H), 1.42 (s, 7H), 1.39 (s, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ: –173.0– –172.4 (m, 1F), –173.9– –173.3 (m, 0.75F), –174.5– –174.3 (m, 0.25F) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.9, 170.0, 169.6, 169.5, 169.4, 154.2, 153.3, 92.5 (d, *J* = 178.2 Hz, 1C), 91.2 (d, *J* = 181.5 Hz, 0.75C), 90.4 (d, *J* = 181.5 Hz, 0.25C), 80.4, 80.3, 58.9, 58.8, 57.0, 56.6 (d, *J* = 18.4 Hz, 1C), 53.2 (d, *J* = 24.3 Hz, 0.75C), 52.9 (d, *J* = 25.1 Hz, 0.25C), 52.4, 50.9, 50.8, 36.0 (d, *J* = 21.8 Hz, 0.25C), 35.4 (d, *J* = 21.8 Hz, 1C), 35.1 (d, *J* = 22.6 Hz, 0.75C), 33.0, 31.5, 28.3, 28.2, 22.6 ppm; IR (KBr): 2976, 2877, 2106, 1745, 1664, 1427, 1404, 1213, 1173, 752 cm^{-1}; MS (ESI) *m/z*: 523 $[M+Na]^+$; HRMS (ESI) *m/z*: 523.2093 calcd. for $C_{21}H_{30}N_6O_6F_2Na$, found: 523.2089.

Methyl
(2*S*,4*S*)-1-((2*S*,4*S*)-4-azido-1-((2*S*,4*S*)-4-fluoropyrrolidine-2-carbonyl)pyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2-carboxylate (23)



According to the general procedure (b), **21** (941 mg, 1.88 mmol) in CH_2Cl_2 (18.8 mL) and TFA (6.3 mL) gave the title compound (644 mg, 85%) as a white solid. The crude compound was used for the next reaction without column purification.
^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.31 (dt, *J* = 52.5, 4.0 Hz, 1H), 5.16 (dt, *J* = 53.9, 3.7 Hz, 1H), 4.87 (d, *J* = 9.6 Hz, 1H), 4.64 (t, *J* = 7.9 Hz, 1H), 4.20–4.15 (m, 1H), 4.09 (dq, *J* = 35.1, 5.4 Hz, 1H), 3.99 (dd, *J* = 10.0, 7.0 Hz, 1H), 3.86–3.80 (m, 2H), 3.72 (s, 3H), 3.46 (dd, *J* = 10.0, 8.4 Hz, 1H), 3.43–3.39 (m, 1H), 2.78–2.68 (m, 2H), 2.53–2.49 (m, 2H), 2.41–2.27 (m, 2H), 2.22–2.15 (m, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ: –173.0– –172.4 (m, 1F), –174.0– –173.4 (m, 1F) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 171.2, 170.9, 169.3, 94.1 (d, *J* = 176.5 Hz), 92.4 (d, *J* = 179.0 Hz), 58.9, 58.6, 57.1, 56.5, 54.8 (d, *J* = 23.4 Hz), 53.2 (d, *J* = 24.3 Hz), 52.5, 50.8, 37.2 (d, *J* = 22.6 Hz), 35.4 (d, *J* = 21.8 Hz), 33.2 ppm; IR (KBr): 2952, 2108, 1759, 1655, 1431, 1406, 1200 cm^{-1}; MS (ESI) *m/z*: 401 $[M+H]^+$; HRMS (ESI) *m/z*: 401.1749 calcd. for $C_{16}H_{23}N_6O_4F_2$, found: 401.1749.

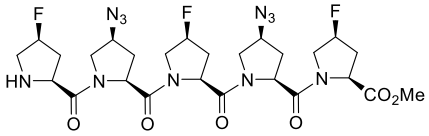
***tert*-Butyl**
(2*S*,4*S*)-2-((2*S*,4*S*)-4-azido-2-((2*S*,4*S*)-2-((2*S*,4*S*)-4-azido-2-((2*S*,4*S*)-4-fluoro-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluoropyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluoropyrrolidine-1-carboxylate (25)



According to the general procedure (a), **23** (649 mg, 1.61 mmol), **17** (657 mg, 1.77 mmol, 1.1 equiv) and EDCI (401 mg, 2.09 mmol, 1.3 equiv) in CH_2Cl_2 (8.1 mL) gave the title compound (1.18 g, 96%) as a white solid. The title compound was purified by SiO_2 column chromatography (AcOEt:MeOH = 10:1).

Mixture of rotamer. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.30–5.13 (m, 3H), 4.82 (d, *J* = 9.8 Hz, 1H), 4.78–4.75 (m, 1H), 4.69 (t, *J* = 8.0 Hz, 0.8H), 4.65 (t, *J* = 7.8 Hz, 1H), 4.61 (t, *J* = 7.9 Hz, 0.2H), 4.52 (dd, *J* = 9.4, 2.8 Hz, 0.8H), 4.44 (d, *J* = 9.6 Hz, 0.2H), 4.22–4.03 (m, 4.6H), 3.99 (dd, *J* = 12.0, 4.2 Hz, 0.4H), 3.87–3.75 (m, 3H), 3.69 (s, 3H), 3.71–3.65 (m, 1H), 3.44–3.37 (m, 2H), 2.66–2.59 (m, 2H), 2.48–2.31 (m, 5H), 2.11–2.05 (m, 2H), 1.92 (br s, 2H), 1.43 (s, 7H), 1.39 (s, 2H) ppm; ^{19}F NMR (659 MHz, $CDCl_3$) δ: –172.7– –172.4 (m, 2F), –173.6– –173.3 (m, 0.8F), –174.3– –174.1 (m, 0.2F) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 170.9, 169.9, 169.6, 169.5, 169.4, 168.6, 154.1, 153.3, 92.6 (d, *J* = 132.2 Hz), 91.6 (d, *J* = 136.4 Hz), 91.3 (d, *J* = 180.7 Hz), 80.4, 80.3, 58.9, 58.8, 57.1, 57.0, 56.9, 56.7, 56.6, 53.4, 53.3, 53.2, 53.11, 53.05, 52.9, 52.8, 52.4, 51.1, 51.02, 50.9, 36.0 (d, *J* = 22.6 Hz), 35.4 (d, *J* = 21.8 Hz), 35.1 (d, *J* = 22.6 Hz), 34.0 (d, *J* = 21.8 Hz), 33.0 (d, *J* = 19.2 Hz), 28.3, 28.2 ppm; IR (KBr): 2978, 2108, 1747, 1658, 1433, 1363, 1336, 1255, 1213 cm^{-1}; MS (ESI) *m*/*z*: 776 $[M+Na]^+$; HRMS (ESI) *m*/*z*: 776.3068 calcd. for $C_{31}H_{42}N_{11}O_8NaF_3$, found: 776.3052.

Methyl (2*S*,4*S*)-1-((2*S*,4*S*)-4-azido-1-((2*S*,4*S*)-1-((2*S*,4*S*)-4-azido-1-((2*S*,4*S*)-4-fluoropyrrolidine-2-carbonyl)pyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2-carbonyl)pyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2-carboxylate (SI-4)

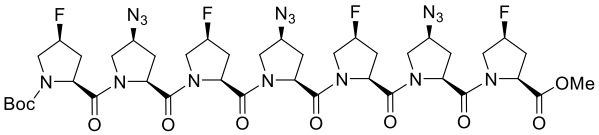


According to the general procedure (b), **25** (475 mg, 0.635 mmol) in CH_2Cl_2 (6.4 mL) and TFA (2.1 mL) gave the title compound (387 mg, 93%) as a white solid. The crude compound was used for the next reaction without column purification.

^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.33–5.22 (m, 2H), 5.16 (d, *J* = 54.1 Hz, 1H), 4.83–4.81 (m, 2H), 4.68–4.62 (m, 2H), 4.23–4.19 (m, 1H), 4.17–3.94 (m, 5H), 3.89–3.84 (m, 1H), 3.80–3.75 (m, 2H), 3.70 (s, 3H), 3.45–3.37 (m, 3H), 2.78–2.63 (m, 3H), 2.52–2.26 (m, 6H), 2.19–2.08 (m, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ: –173.2– –172.1 (m, 2F), –173.9– –173.3 (m, 1F) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 171.1, 170.9, 169.32, 169.27, 168.6, 94.1 (d, *J* = 175.7 Hz), 92.4 (d, *J* = 178.2 Hz), 91.6 (d, *J* = 172.3 Hz), 58.9, 58.6, 57.1, 57.0, 56.64, 56.62, 54.7 (d, *J* = 22.6 Hz), 53.3 (d, *J* = 25.1

Hz), 53.1 (d, *J* = 24.3 Hz), 51.0 (d, *J* = 30.1 Hz), 37.2 (d, *J* = 20.9 Hz), 35.4 (d, *J* = 21.8 Hz), 34.0 (d, *J* = 21.8 Hz), 33.1 (d, *J* = 11.7 Hz) ppm; IR (KBr): 2952, 2108, 1751, 1658, 1433, 1333, 1265, 1213, 1059, 964, 856, 760 cm^{-1}; MS (ESI) *m/z*: 654 $[M+H]^+$; HRMS (ESI) *m/z*: 654.2724 calcd. for $C_{26}H_{35}N_{11}O_6F_3$, found: 654.2720.

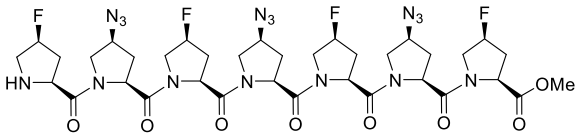
***tert*-Butyl**
(2*S*,4*S*)-2-((2*S*,4*S*)-4-azido-2-((2*S*,4*S*)-2-((2*S*,4*S*)-4-azido-2-((2*S*,4*S*)-2-((2*S*,4*S*)-4-azido-2-((2*S*,4*S*)-4-fluoro-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluoropyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluoropyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluoropyrrolidine-1-carboxylate (SI-5)



According to the general procedure (a), **SI-4** (811 mg, 1.24 mmol), **17** (553 mg, 1.49 mmol, 1.2 equiv) and EDCI (309 mg, 1.61 mmol, 1.3 equiv) in CH_2Cl_2 (6.2 mL) gave the title compound (370 mg, 68%) as a white solid. The title compound was purified by SiO_2 column chromatography (AcOEt:MeOH = 10:1 to 8:1 to 5:1).

Mixture of rotamer. ^1H NMR (700 MHz, $CDCl_3$) δ: 5.31–5.29 (m, 1.5H), 5.24–5.23 (m, 2H), 5.14 (s, 0.5H), 4.83 (d, *J* = 9.8 Hz, 1H), 4.79–4.75 (m, 2H), 4.70 (t, *J* = 7.8 Hz, 1H), 4.67–4.64 (m, 2H), 4.52 (dd, *J* = 9.6, 2.8 Hz, 0.78H), 4.46–4.44 (m, 0.22H), 4.22–3.95 (m, 9H), 3.87–3.65 (m, 5H), 3.70 (s, 3H), 3.44–3.35 (m, 3H), 2.66–2.59 (m, 3H), 2.49–2.32 (m, 8H), 2.12–2.07 (m, 3H), 1.44 (s, 7H), 1.40 (s, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ: –172.9– –172.2 (m, 3F), –173.7– –173.2 (m, 0.8F), –174.6– –174.0 (m, 0.2F) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 171.0, 169.6, 169.5, 169.4, 169.3, 168.63, 168.60, 154.2, 92.5 (d, *J* = 178.2 Hz), 91.8 (d, *J* = 181.5 Hz), 91.7 (d, *J* = 181.5 Hz), 91.3 (d, *J* = 180.7 Hz), 80.4, 80.3, 58.90, 58.86, 57.1, 57.0, 56.9, 56.7, 56.6, 53.39, 53.35, 53.3, 53.2, 53.13, 53.06, 52.4, 51.2, 51.1, 51.04, 50.97, 35.5, 35.4, 35.2, 35.1, 34.1, 34.0, 33.9, 33.1, 33.04, 32.98, 28.4, 28.3 ppm; IR (KBr): 2976, 2108, 1745, 1662, 1433, 1367, 1325, 1252, 1212, 1072, 964, 760 cm^{-1}; MS (ESI) *m/z*: 1029 $[M+Na]^+$; HRMS (ESI) *m/z*: 1029.4043 calcd. for $C_{41}H_{54}N_{16}O_{10}F_4Na$, found: 1029.4032.

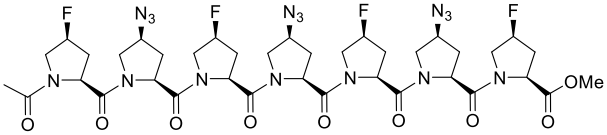
Methyl
(2*S*,4*S*)-1-((2*S*,4*S*)-4-azido-1-((2*S*,4*S*)-1-((2*S*,4*S*)-4-azido-1-((2*S*,4*S*)-1-((2*S*,4*S*)-4-azido-1-((2*S*,4*S*)-4-fluoropyrrolidine-2-carbonyl)pyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2-carbonyl)pyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2-carbonyl)pyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2-carboxylate (SI-6)



According to the general procedure (b), **SI-5** (1.07 g, 1.06 mmol) in CH_2Cl_2 (10.6 mL) and TFA (3.5 mL) gave the title compound (856 mg, 89%) as a white solid. The crude compound was used for the next reaction without column purification.

^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.33–5.22 (m, 3H), 5.15 (d, *J* = 53.7 Hz, 1H), 4.82–4.78 (m, 3H), 4.68–4.62 (m, 3H), 4.23–3.94 (m, 8H), 3.87–3.75 (m, 4H), 3.70 (s, 3H), 3.43–3.31 (m, 4H), 2.79–2.62 (m, 4H), 2.51–2.30 (m, 9H), 2.18–2.05 (m, 4H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ: –173.1– –172.2 (m, 3F), –174.0– –173.3 (m, 1F) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 171.2, 171.1, 170.9, 169.4, 169.33, 169.29, 168.6, 94.2 (d, *J* = 176.5 Hz), 92.5 (d, *J* = 178.2 Hz), 91.8 (d, *J* = 181.5 Hz), 91.7 (d, *J* = 182.4 Hz), 58.92, 58.85, 58.8, 58.6, 57.1, 57.0, 56.8, 56.7, 56.6, 54.8, 54.6, 53.3, 53.24, 53.17, 53.15, 53.1, 53.0, 52.4, 51.2, 51.1, 50.9, 37.3 (d, *J* = 21.8 Hz), 35.4 (d, *J* = 20.9 Hz), 34.1 (d, *J* = 22.6 Hz), 33.9 (d, *J* = 22.6 Hz), 33.1, 33.0 ppm; IR (KBr): 2954, 2108, 1749, 1658, 1431, 1331, 1263, 1215, 1059, 964, 758 cm^{-1}; MS (ESI) *m/z*: 907 $[M+H]^+$; HRMS (ESI) *m/z*: 907.3699 calcd. for $C_{36}H_{47}N_{16}O_8F_4$, found: 907.3680.

Methyl (2*S*,4*S*)-1-((2*S*,4*S*)-1-((2*S*,4*S*)-1-((2*S*,4*S*)-1-((2*S*,4*S*)-1-((2*S*,4*S*)-1-((2*S*,4*S*)-1-acetyl-4-fluoropyrrolidine-2-carbonyl)-4-azidopyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2-carbonyl)-4-azidopyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2-carbonyl)-4-azidopyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2-carboxylate (27)

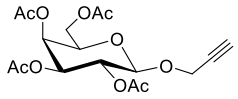


According to the general procedure (d), **SI-6** (63.1 mg, 0.0696 mmol), Ac_2O (32.8 µL, 0.348 mmol, 5.0 equiv) and pyridine (28.1 µL, 0.348 mmol, 5.0 equiv) in CH_2Cl_2 (0.7 mL) gave the title compound (54 mg, 81%) as a white solid. The title compound was purified by SiO_2 column chromatography (CH_2Cl_2:MeOH = 10:1).

^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.31–5.29 (m, 2H), 5.23–5.21 (m, 2H), 4.82 (d, *J* = 9.8 Hz, 1H), 4.78 (td, *J* = 9.4, 2.9 Hz, 2H), 4.69–4.64 (m, 4H), 4.23–4.02 (m, 8H), 3.99–3.72 (m, 6H), 3.70 (s, 3H), 3.43–3.34 (m, 3H), 2.67–2.60 (m, 3H), 2.49–2.30 (m, 8H), 2.11–2.05 (m, 3H), 2.07 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ: –172.98– –172.40 (m, 3F), –174.49– –174.17 (m, 1F) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.93, 169.42, 169.33, 169.29, 168.95, 168.56, 168.53, 93.21, 92.54, 92.46, 91.99, 91.79, 91.10, 91.02, 90.54, 58.87, 58.84, 57.05, 57.00, 56.96, 56.70, 56.63, 56.47, 54.08, 53.88, 53.30, 53.19, 53.10, 52.99, 52.46, 51.32, 51.19, 51.03, 35.45, 35.29, 34.67, 34.50, 34.11,

34.01, 33.94, 33.84, 33.06, 33.02, 33.01 ppm; IR (KBr): 2952, 2866, 2108, 1738, 1658, 1433, 1325, 1263, 1213, 1072, 752 cm^{-1}; MS (ESI) *m/z* : 971 $[M+Na]^+$; HRMS (ESI) *m/z*: 971.3624 calcd. for $C_{38}H_{48}N_{16}O_9F_4Na$, found: 971.3599.

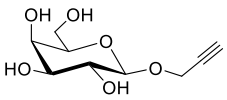
(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (SI-7)[5]



BF_3•Et_2O (1.71 mL, 13.6 mmol, 2.0 equiv) was added to the mixture of D-galactose pentaacetate[6] (2.66 g, 6.80 mmol) in CH_2Cl_2 (15 mL) and propargyl alcohol (0.981 mL, 17.0 mmol, 2.5 equiv), and the whole mixture was stirred at rt for 2 days. Saturated $NaHCO_3$ aq was added the mixture and the mixture was extracted with CH_2Cl_2 and the organic phase was washed with brine. Removal of the solvent from the extract under reduced pressure gave a crude product, which was purified by SiO_2 column chromatography (Et_2O:*n*-hexane = 3:1 to 4:1) to give the title compound (2.60 g, quant) as colorless oil.

^1H NMR ($CDCl_3$, 300 MHz) δ: 5.40 (dd, *J* = 3.5, 1.1 Hz, 1H), 5.25–5.21 (m, 1H), 5.06 (dd, *J* = 10.5, 3.5 Hz, 1H), 4.74 (d, *J* = 8.0 Hz, 1H), 4.38 (dd, *J* = 2.4, 0.8 Hz, 2H), 4.19 (dd, *J* = 11.3, 6.5 Hz, 1H), 4.13 (dd, *J* = 11.3, 6.9 Hz, 1H), 3.94 (td, *J* = 6.7, 1.1 Hz, 1H), 2.46 (t, *J* = 2.4 Hz, 1H), 2.15 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H) ppm; IR (KBr): 3278, 2976, 2937, 2121, 1745, 1427, 1279, 1244, 1061 cm^{-1}; MS (ESI) *m/z*: 409 $[M+Na]^+$.

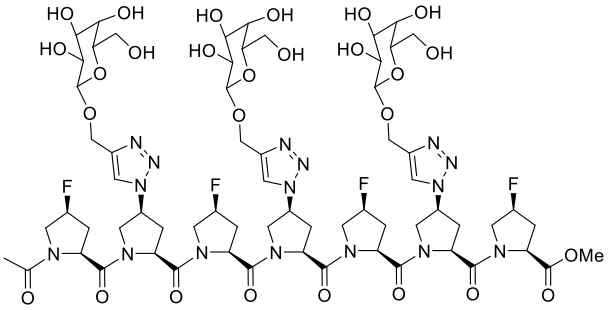
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Hydroxymethyl)-6-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran-3,4,5-triol (29)[5]



NaOMe (12.8 mg, 0.237 mmol, 0.1 equiv) was added to a solution of **SI-7** (915 mg, 2.37 mmol) in MeOH (20 mL) at 0 °C, and the whole mixture was stirred at rt for 12 h. Dowex was added the mixture, the mixture was filtered. The filtrate was concentrated *in vacuo* to give the crude product, which was purified by SiO_2 column chromatography (CH_2Cl_2:MeOH = 10:1 to 6:1) to give the *O*-propargyl galactose (**29**) (540 mg, quant) as a white solid.

^1H NMR (D_2O, 700 MHz) δ: 4.58 (d, *J* = 8.0 Hz, 1H), 4.50 (d, *J* = 15.8 Hz, 1H), 4.46 (d, *J* = 15.8 Hz, 1H), 3.93 (d, *J* = 3.2 Hz, 1H), 3.79–3.72 (m, 2H), 3.72–3.70 (m, 1H), 3.66 (dd, *J* = 9.8, 3.4 Hz, 1H), 3.53 (t, *J* = 8.9 Hz, 1H); IR (KBr):3307, 2949, 2858, 1726, 1456, 1281, 1124, 1061 cm^{-1}; MS (ESI) *m/z*: 241$[M+Na]^+$.

Galactose-conjugated fluorinated proline oligomer 12a



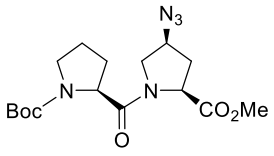
According to the general procedure (e), **27** (25 mg, 0.0276 mmol), *O*-propargyl galactose **29** (24.1 mg, 0.110 mmol, 4.0 equiv), $CuSO_4$ aq (0.05 M, 0.828 mL, 0.0414 mmol, 1.5 equiv) and sodium ascorbate aq (0.05 M, 1.66 mL, 0.0828 mmol, 3.0 equiv) in ^{t}BuOH (1.38 mL) gave the title compound (28.1 mg, 65%) as a white solid. The title compound was purified by reverse phase SiO_2 column chromatography (100% H_2O to 10% MeOH).

^{1}H NMR (700 MHz, D_2O) δ: 8.26–8.21 (m, 3H), 5.52–5.43 (m, 7H), 5.12 (d, *J* = 12.6 Hz, 1H), 5.03–4.96 (m, 6H), 4.94–4.89 (m, 6H), 4.58 (s, 3H), 4.50 (d, *J* = 7.8 Hz, 3H), 4.18–3.93 (m, 14H), 3.81–3.71 (m, 11H), 3.65–3.52 (m, 7H), 3.27–3.20 (m, 3H), 2.68–2.43 (m, 11H), 2.14 (s, 3H) ppm; ^{19}F NMR (282 MHz, D_2O) δ: –170.9– –170.1 (m, 3F), –172.4– –171.8 (m, 1F) ppm; ^{13}C NMR (176 MHz, D_2O) δ: 174.5, 172.7, 172.4, 171.7, 170.4, 170.3, 170.2, 143.7, 124.6, 124.5, 106.9, 102.1, 82.9, 81.34, 81.29, 76.8, 75.3, 72.8, 70.8, 68.7, 62.8, 61.93, 61.88, 61.1, 60.2, 59.6, 58.8, 58.3, 58.2, 58.0, 57.3, 53.0, 51.5, 51.3, 49.0, 48.7, 47.7, 47.5, 33.01, 32.97, 32.9, 28.7, 28.6, 28.0, 24.62, 24.59, 24.3, 21.3 ppm; IR (KBr): 3431, 2952, 1647, 1442, 1034 cm^{-1}; MS (ESI) *m/z* : 825 $[(M+Na+H)/2]^{2+}$; HRMS (ESI) *m/z*: 1625.5995 calcd. for $C_{65}H_{90}N_{16}O_{27}Na\ F_4$, found: 1625.6006.

2.2. Synthesis of galactose-conjugated non-fluorinated proline oligomer 13a

***tert*-Butyl**

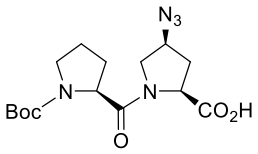
(*S*)-2-((2*S*,4*S*)-4-azido-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate (SI-8)[7]



According to the general procedure (a), *N*-Boc-L-proline **15** (2.65 g, 12.3 mmol, 1.1 equiv), **16** (1.91 g, 11.2 mmol, 1.0 equiv) and EDCI (2.79 g, 14.6 mmol, 1.3 equiv) in CH_2Cl_2 (37.3 mL) gave the title compound (3.90 g, 94%) as a white solid. The title compound was purified by SiO_2 column chromatography (*n*-hexane:AcOEt = 3:7 to AcOEt 100%).

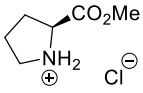
Mixture of rotamer. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.66–4.62 (m, 1H), 4.39 (dd, *J* = 8.5, 3.1 Hz, 0.7H), 4.30 (dd, *J* = 8.5, 3.7 Hz, 0.3H), 4.25–4.21 (m, 1H), 4.06 (dd, *J* = 10.6, 6.0 Hz, 0.7H), 3.87 (dd, *J* = 10.6, 6.2 Hz, 0.3H), 3.69 (s, 0.9H), 3.68 (s, 2.1H), 3.51–3.47 (m, 2H), 3.43–3.39 (m, 0.3H), 3.36–3.32 (m, 0.7H), 2.44–2.36 (m, 1H), 2.19–1.97 (m, 4H), 1.86–1.78 (m, 1H), 1.39 (s, 6.4H), 1.33 (s, 2.6H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 171.5, 171.3, 171.2, 170.9, 154.5, 153.4, 79.5, 79.4, 59.5, 59.4, 57.6, 57.5, 57.1, 52.34, 52.25, 51.1, 51.0, 46.7, 46.5, 33.90, 33.85, 30.0, 29.1, 28.3, 28.2, 24.0, 23.4 ppm; IR (KBr): 2976, 2883, 2106, 1751, 1693, 1666, 1433, 1400, 1165, 752 cm^{-1}; MS (ESI) *m*/*z*: 390 $[M+Na]^+$.

(2*S*,4*S*)-4-Azido-1-((*tert*-butoxycarbonyl)-L-prolyl)pyrrolidine-2-carboxylic acid (18)[7]



According to the general procedure (c), **SI-8** (3.90 g, 10.6 mmol) in THF-MeOH (2:1, 35.3 mL) and LiOH aq. (1.0 M, 21.2 mL, 21.2 mmol, 2.0 equiv) gave the title compound (3.74 g, quant) as a white solid. The crude compound was used for the next reaction without column purification.
^{1}H NMR (700 MHz, $CDCl_3$) δ: 8.78 (br s, 1H), 4.62–4.59 (m, 1H), 4.40 (dd, *J* = 8.6, 3.4 Hz, 0.7H), 4.28–4.25 (m, 1H), 4.22 (t, *J* = 4.3 Hz, 0.3H), 4.05–4.02 (m, 0.8H), 3.82 (dd, *J* = 10.6, 6.0 Hz, 0.2H), 3.51–3.44 (m, 1.4H), 3.41–3.38 (m, 1H), 3.33–3.30 (m, 0.6H), 2.45–2.41 (m, 0.7H), 2.38–2.34 (m, 0.3H), 2.27–2.23 (m, 0.3H), 2.19–2.07 (m, 1.7H), 2.02–1.93 (m, 2H), 1.82–1.74 (m, 1H), 1.36 (s, 6.6H), 1.30 (s, 2.4H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 172.7, 172.4, 172.3, 172.1, 154.7, 153.5, 80.0, 79.7, 59.32, 59.26, 57.7, 57.6, 57.5, 51.31, 51.26, 46.83, 46.75, 46.5, 33.4, 33.3, 29.8, 29.0, 28.2, 28.1, 23.9, 23.3 ppm; IR (KBr): 2978, 2883, 2106, 1743, 1664, 1408, 1165, 756 cm^{-1}; MS (ESI) *m*/*z*: 376 $[M+Na]^+$.

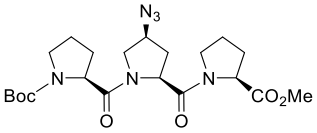
Methyl L-prolinate hydrochloride salt (SI-9)



$SOCl_2$ (0.69 mL, 9.55 mmol, 1.1 equiv) was added to a solution of L-proline (1.00 g, 8.68 mmol) in MeOH (8.7 mL) at 0 °C, and the whole mixture was stirred under reflux for 3 h. The resulting mixture was evaporated under reduced pressure to give the crude product (1.37 g, 8.25 mmol, 82%) as yellowish oil, which was used for the next reaction without further purification.

***tert*-Butyl**

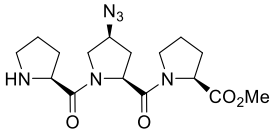
(*S*)-2-((2*S*,4*S*)-4-azido-2-((*S*)-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate (22)



According to the general procedure (a), **18** (827 mg, 2.34 mmol), Proline methyl ester hydrochloride **SI-9** (426 mg, 2.57 mmol, 1.1 equiv), Et_3N (0.36 mL, 2.57 mmol, 1.1 equiv) and EDCI (583 mg, 3.04 mmol, 1.3 equiv) in CH_2Cl_2 (12 mL) gave the title compound (743 mg, 68%) as a white solid. The title compound was purified by SiO_2 column chromatography (*n*-hexane:AcOEt = 1:9 to 100% AcOEt).

^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.69 (t, *J* = 7.9 Hz, 0.7H), 4.63 (t, *J* = 7.8 Hz, 0.3H), 4.53–4.50 (m, 1H), 4.40 (dd, *J* = 8.5, 3.3 Hz, 0.7H), 4.32 (dd, *J* = 8.5, 3.9 Hz, 0.3H), 4.16–4.11 (m, 1.4H), 4.07 (t, *J* = 7.7 Hz, 0.3H), 3.99 (t, *J* = 8.5 Hz, 0.3H), 3.79–3.71 (m, 1H), 3.66 (s, 0.8H), 3.65 (s, 2.2H), 3.56–3.36 (m, 3H), 3.33–3.30 (m, 1H), 2.61–2.54 (m, 1H), 2.18–1.89 (m, 8H), 1.79–1.74 (m, 1H), 1.39 (s, 6.6H), 1.34 (s, 2.4H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 172.4, 171.3, 170.8, 169.4, 169.1, 154.5, 153.4, 79.4, 79.2, 58.7, 58.6, 58.5, 57.63, 57.55, 56.4, 56.3, 52.1, 50.9, 50.8, 46.7, 46.5, 46.5, 33.0, 32.9, 29.8, 28.8, 28.6, 28.34, 28.27, 24.7, 24.1, 23.4 ppm; IR (KBr): 2976, 2879, 2106, 1745, 1693, 1435, 1365, 1171, 756 cm^{-1}; MS (ESI): *m*/*z*: 487 $[M+Na]^+$; HRMS (ESI) *m/z*: 487.2281 calcd. for $C_{21}H_{32}N_6O_6Na$, found: 487.2281.

Methyl ((2*S*,4*S*)-1-(L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolinate (24)

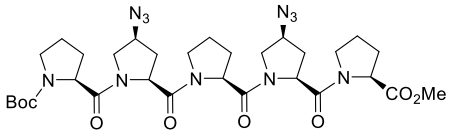


According to the general procedure (b), **22** (743 mg, 1.60 mmol) in CH_2Cl_2 (16 mL) and TFA (5.3 mL) gave the title compound (445 mg, 76%) as a white solid. The crude compound was used for the next reaction without column purification.

^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.70 (t, *J* = 8.0 Hz, 1H), 4.59 (dd, *J* = 8.7, 4.1 Hz, 1H), 4.21–4.14 (m, 2H), 4.02–3.99 (m, 1H), 3.78 (q, *J* = 10.6 Hz, 1H), 3.72 (s, 3H), 3.62–3.58 (m, 2H), 3.45–3.43 (m, 1H), 3.17–3.14 (m, 1H), 3.05–3.02 (m, 1H), 2.74–2.66 (m, 2H), 2.25–2.21 (m, 2H), 2.08–1.80 (m, 6H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 172.4, 171.2, 169.0, 58.9, 58.8, 58.7, 56.9, 52.4, 51.0, 47.1, 46.7, 38.8, 33.2, 30.5, 29.8, 29.6, 29.0, 28.9, 26.1, 24.9, 23.8, 23.0 ppm; IR (KBr): 3460, 2956, 2883, 2106, 1743, 1649, 1439, 1277, 1200 cm^{-1}; MS (ESI) *m*/*z* : 365 $[M+H]^+$; HRMS (ESI) *m/z*: 365.1937 calcd. for $C_{16}H_{25}N_6O_4$, found: 365.1932.

***tert*-Butyl**

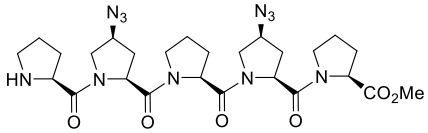
(*S*)-2-((2*S*,4*S*)-4-azido-2-((*S*)-2-((2*S*,4*S*)-4-azido-2-((*S*)-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate (26)



According to the general procedure (a), **24** (445 mg, 1.22 mmol), **18** (474 mg, 1.34 mmol, 1.1 equiv) and EDCI (280 mg, 1.46 mmol, 1.2 equiv) in CH_2Cl_2 (6.1 mL) gave the title compound (754 mg, 88%) as a white solid. The title compound was purified by SiO_2 column chromatography (CH_2Cl_2:MeOH = 20:1).

Mixture of Rotamer. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.72–4.64 (m, 3H), 4.55 (dd, *J* = 8.7, 3.9 Hz, 1H), 4.42 (dd, *J* = 8.5, 3.1 Hz, 0.7H), 4.33 (dd, *J* = 8.6, 3.8 Hz, 0.3H), 4.20–4.13 (m, 2.8H), 4.08 (dd, *J* = 15.1, 7.5 Hz, 0.2H), 3.75−3.70 (m, 2H), 3.68 (s, 3H), 3.56−3.35 (m, 6H), 2.62−2.55 (m, 2H), 2.18−1.90 (m, 14H), 1.84−1.77 (m, 1H), 1.41 (s, 6.3H), 1.37 (s, 2.7H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 172.5, 172.44, 171.38, 171.0, 170.1, 170.0, 169.3, 169.23, 169.19, 169.0, 154.6, 153.5, 79.5, 79.4, 58.9, 58.8, 58.7, 58.0, 57.9, 57.7, 57.5, 56.7, 56.6, 56.5, 52.2, 51.2, 51.1, 51.0, 46.93, 46.86, 46.8, 46.6, 46.5, 33.03, 33.00, 31.5, 29.9, 29.0, 28.7, 28.43, 28.36, 27.7, 24.8, 24.7, 24.2, 23.5, 22.6 ppm; IR (KBr): 2979, 2879, 2106, 1743, 1657, 1437, 1265, 1215, 1171, 754 cm^{-1}; MS (ESI) *m*/*z*: 722 $[M+Na]^+$; HRMS (ESI) *m*/*z*: 722.3250 calcd. for $C_{31}H_{45}N_{11}O_8Na$, found: 722.3339.

Methyl ((2*S*,4*S*)-1-(((2*S*,4*S*)-1-(L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolinate (SI-10)

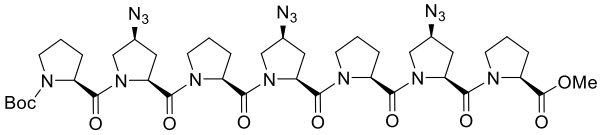


According to the general procedure (b), **26** (724 mg, 1.03 mmol) in CH_2Cl_2 (10 mL) and TFA (3.4 mL) gave the title compound (604 mg, 98%) as white solid. The crude compound was used for the next reaction without column purification.

^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.70–4.64 (m, 3H), 4.54 (dd, *J* = 8.7, 3.9 Hz, 1H), 4.19–4.11 (m, 3H), 3.95 (t, *J* = 8.4 Hz, 1H), 3.86 (br s, 1H), 3.75–3.70 (m, 1H), 3.68 (s, 3H), 3.57–3.50 (m, 2H), 3.44–3.41 (m, 1H), 3.38 (t, *J* = 9.1 Hz, 1H), 3.10–3.06 (m, 3H), 2.86 (br s, 1H), 2.63–2.56 (m, 2H), 2.19–1.92 (m, 11H), 1.86–1.73 (m, 3H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 172.5, 172.4, 169.9, 169.2, 169.1, 59.4, 58.8, 58.7, 58.6, 58.5, 58.0, 56.7, 56.6, 52.2, 51.0, 50.9, 47.6, 46.9, 46.4, 33.03, 33.01, 29.8, 28.7, 27.7, 26.3, 24.9, 24.8, 24.7 ppm; IR (KBr): 2956, 2877, 2106, 1743, 1651, 1439, 1265, 1201, 756 cm^{-1}; MS (ESI) *m*/*z*: 600 $[M+H]^+$; HRMS (ESI) *m*/*z*: 600.3007 calcd. for

$C_{26}H_{38}N_{11}O_6$, found: 600.2996.

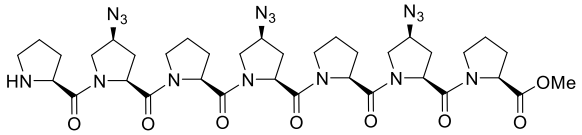
***tert*-Butyl**
(*S*)-2-((2*S*,4*S*)-4-azido-2-((*S*)-2-((2*S*,4*S*)-4-azido-2-((*S*)-2-((2*S*,4*S*)-4-azido-2-((*S*)-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate (SI-11)



According to the general procedure (a), **SI-10** (793 mg, 1.32 mmol), **18** (512 mg, 1.45 mmol, 1.1 equiv) and EDCI (330 mg, 1.72 mmol, 1.3 equiv) in CH_2Cl_2 (5.0 mL) gave the title compound (1.15 g, 92%) as a white solid. The title compound was purified by SiO_2 column chromatography (CH_2Cl_2:MeOH = 10:1).

Mixture of rotamer. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.72–4.63 (m, 5H), 4.54 (dd, *J* = 8.8, 4.0 Hz, 1H), 4.42 (dd, *J* = 8.5, 3.1 Hz, 0.7H), 4.33 (dd, *J* = 8.5, 3.7 Hz, 0.3H), 4.19–4.12 (m, 5.6H), 4.11–4.06 (m, 0.2H), 3.99 (dd, *J* = 9.8, 7.2 Hz, 0.2H), 3.80–3.69 (m, 2H), 3.68 (s, 3H), 3.59–3.47 (m, 4H), 3.45–3.34 (m, 4H), 2.60–2.53 (m, 3H), 2.19–1.92 (m, 19H), 1.83–1.79 (m, 1H), 1.41 (s, 6.6H), 1.37 (s, 2.4H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 172.5, 171.5, 171.0, 170.10, 170.06, 170.02, 169.99, 169.3, 169.2, 169.11, 169.08, 169.0, 154.6, 153.5, 79.5, 79.4, 58.84, 58.76, 58.7, 57.9, 57.8, 57.7, 57.5, 56.7, 56.5, 52.2, 51.3, 51.2, 51.1, 51.0, 46.93, 46.87, 46.82, 46.77, 46.6, 46.5, 33.0, 31.5, 29.9, 29.0, 28.7, 28.42, 28.36, 27.8, 27.7, 24.8, 24.7, 24.2, 23.5, 22.6 ppm; IR (KBr): 2979, 2877, 2106, 1655, 1437, 1269, 1213, 760 cm^{-1}; MS (ESI) *m*/*z*: 957 $[M+Na]^+$; HRMS (ESI) *m*/*z*: 957.4420 calcd. for $C_{41}H_{58}N_{16}O_{10}Na$, found: 957.4418.

Methyl
((2*S*,4*S*)-1-(((2*S*,4*S*)-1-(((2*S*,4*S*)-1-(L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolinate (SI-12)

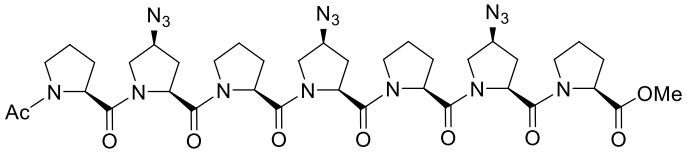


According to the general procedure (b), **SI-11** (747 mg, 0.799 mmol) in CH_2Cl_2 (8.0 mL) and TFA (2.7 mL) gave the title compound (616 mg, 93%) as a white solid. The crude compound was used for the next reaction without column purification.

^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.70–4.65 (m, 5H), 4.55 (dd, *J* = 8.6, 4.0 Hz, 1H), 4.20–4.11 (m, 5H), 3.96 (dd, *J* = 10.1, 7.1 Hz, 1H), 3.91 (t, *J* = 7.4 Hz, 1H), 3.77–3.66 (m, 3H), 3.69 (s, 3H), 3.59–3.51 (m, 3H), 3.44–3.38 (m, 3H), 3.14–3.12 (m, 1H), 3.00 (s, 1H), 2.93–2.89 (m, 1H), 2.64–2.54 (m, 3H),

2.20–1.76 (m, 19H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 172.5, 171.9, 170.0, 169.9, 169.2, 169.1, 168.9, 59.4, 58.9, 58.8, 58.7, 58.6, 57.94, 57.93, 56.8, 56.7, 56.6, 52.2, 51.3, 51.03, 50.97, 47.5, 46.9, 46.8, 46.5, 33.0, 31.5, 29.7, 28.7, 27.8, 27.7, 26.2, 24.8, 24.7, 22.6 ppm; IR (KBr): 2983, 2877, 2106, 1743, 1651, 1435, 1267, 1209, 762 cm^{-1}; MS (ESI) *m/z*: 835 $[M+H]^+$; HRMS (ESI) *m/z*: 835.4076 calcd. for $C_{36}H_{51}N_{16}O_8$, found: 835.4050.

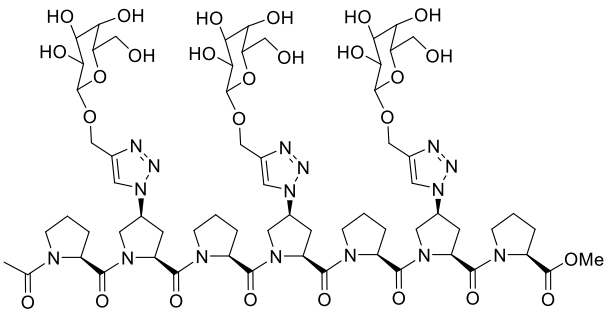
Methyl ((2*S*,4*S*)-1-(((2*S*,4*S*)-1-(((2*S*,4*S*)-1-(acetyl-L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolinate (28)



According to the general procedure (d), **SI-12** (123 mg, 0.147 mmol), Ac_2O (0.068 mL, 0.719 mmol, 5.0 equiv) and pyridine (0.059 mL, 0.982 mmol, 6.7 equiv) in CH_2Cl_2 (1.4 mL) gave the title compound (80.5 mg, 63%) as a white solid. The title compound was purified by SiO_2 column chromatography (CH_2Cl_2:MeOH = 20:1 to 5:1).

^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.69–4.65 (m, 5H), 4.55–4.53 (m, 2H), 4.28 (dd, *J* = 9.7, 7.1 Hz, 1H), 4.21–4.12 (m, 5H), 3.75–3.66 (m, 3H), 3.68 (s, 3H), 3.63–3.60 (m, 1H), 3.56–3.45 (m, 3H), 3.43–3.38 (m, 3H), 2.59–2.55 (m, 3H), 2.04 (s, 3H), 2.18–1.88 (m, 20H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 172.5, 170.7, 170.1, 170.0, 169.3, 169.20, 169.16, 169.1, 58.84, 58.80, 58.77, 58.7, 57.9, 57.8, 57.4, 56.68, 56.66, 56.5, 52.2, 51.5, 51.3, 51.0, 48.0, 46.9, 46.8, 46.4, 33.1, 33.0, 28.70, 28.66, 27.9, 27.7, 24.9, 24.7, 22.2 ppm; IR (KBr): 2978, 2877, 2106, 1743, 1649, 1437, 1329, 1267, 1217, 754 cm^{-1}; MS (ESI) *m/z*: 899 $[M+Na]^+$; HRMS (ESI) *m/z*: 899.4001 calcd. for $C_{38}H_{52}N_{16}O_9Na$, found: 899.3979.

Galactose-conjugated non-fluorinated proline oligomer 13a



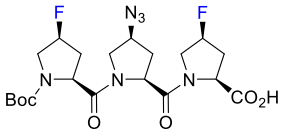
According to the general procedure (e), **28** (32.4 mg, 0.037 mmol), *O*-propargyl galactose **29** (32.3 mg, 0.148 mmol, 4.0 equiv), $CuSO_4$ aq (0.05 M solution, 1.11 mL, 0.056 mmol, 1.5 equiv) and

sodium ascorbate aq (0.05 M, 2.22 mL, 0.111 mmol, 3.0 equiv) in ^{t}BuOH (1.85 mL) gave the title compound (12.7 mg, 22%) as a white solid. The title compound was purified by reverse phase SiO_2 column chromatography (20% MeOH).

^{1}H NMR (700 MHz, D_2O) δ: 8.21–8.18 (m, 3H), 5.49–5.45 (m, 3H), 5.02–5.00 (m, 3H), 4.96–4.94 (m, 2H), 4.90–4.87 (m, 2H), 4.82–4.76 (m, 2H), 4.64–4.59 (m, 3H), 4.49–4.45 (m, 4H), 4.08–4.01 (m, 4H), 3.92 (s, 3H), 3.97–3.63 (m, 23H), 3.54–3.52 (m, 3H), 3.22–3.14 (m, 3H), 2.47 (d-like, *J* = 7.0 Hz, 4H), 2.36–2.29 (m, 4H), 2.12 (s, 3H), 2.09–1.97 (m, 13H) ppm; ^{13}C NMR (176 MHz, D_2O) δ: 174.5, 172.7, 172.4, 171.7, 170.4, 170.3, 170.2, 143.7, 124.6, 124.5, 106.9, 102.1, 82.9, 81.34, 81.29, 76.8, 75.3, 72.8, 70.8, 68.7, 62.8, 61.93, 61.88, 61.1, 60.2, 59.6, 58.8, 58.3, 58.2, 58.0, 57.3, 53.0, 51.5, 51.3, 49.0, 48.7, 47.7, 47.5, 33.01, 32.97, 32.9, 28.7, 28.6, 28.0, 24.6, 24.6, 24.3, 21.3 ppm; IR (KBr): 3390, 2941, 1651, 1456, 1336, 1045 cm^{-1}; MS (ESI) *m/z*: 789 $[(M+Na+H)/2]^{2+}$; HRMS (ESI) *m/z*: 1553.6372 calcd. for $C_{65}H_{94}N_{16}O_{27}$, found: 1553.6400.

2.3. Synthesis of galactose-conjugated fluorinated proline oligomer 12b

(2*S*,4*S*)-1-((2*S*,4*S*)-4-Azido-1-((2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carbonyl)pyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid (30)



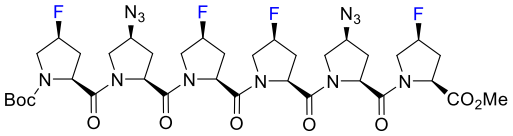
According to the general procedure (c), **21** (4.0 g, 8.0 mmol) in THF-MeOH (2:1, 27 mL) and LiOH aq. (1.0 M, 16.0 mL, 16.0 mmol, 2.0 equiv) gave the title compound (3.89 g, quant) as a white solid. The crude compound was used for the next reaction without column purification.

Mixture of rotamer. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.28 (d, *J* = 52.3 Hz, 1H), 5.16 (d, *J* = 53.1 Hz, 1H), 4.77 (d, *J* = 10.2 Hz, 1H), 4.68 (t, *J* = 8.0 Hz, 1H), 4.62 (dd, *J* = 9.2, 2.6 Hz, 1H), 4.20–4.06 (m, 3H), 3.83–3.75 (m, 2H), 3.69–3.62 (m, 1H), 3.47–3.40 (m, 1H), 2.65–2.56 (m, 2H), 2.44–2.37 (m, 3H), 2.07–2.03 (m, 1H), 1.43 (s, 7H), 1.39 (s, 2H) ppm (one protone of COOH group is not observed); ^{19}F NMR (282 MHz, $CDCl_3$) δ: –173.8– –172.9 (m, 1.72F), –174.7– –174.2 (m, 0.28F) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 172.3, 170.7, 169.7, 154.4, 92.5 (d, *J* = 178.2 Hz), 91.2 (d, *J* = 181.5 Hz), 80.8, 80.5, 58.9, 58.7, 57.6, 56.7 (d, *J* = 20.1 Hz), 53.6 (d, *J* = 24.3 Hz), 53.3 (d, *J* = 25.1 Hz), 50.9, 35.1 (d, *J* = 21.8 Hz), 34.7 (d, *J* = 21.8 Hz), 33.00, 32.95, 28.3, 28.2 ppm; IR (KBr): 2979, 2889, 2108, 1745, 1666, 1408, 1367, 1221, 1169, 1076, 760 cm^{-1}; MS (ESI) *m/z*: 509 $[M+Na]^+$, 485 $[M–H]^–$; HRMS (ESI) *m/z*: 509.1936 calcd. for $C_{20}H_{28}N_6O_6F_2Na$, found: 509.1931.

***tert*-Butyl**

(2*S*,4*S*)-2-((2*S*,4*S*)-4-azido-2-((2*S*,4*S*)-2-((2*S*,4*S*)-2-((2*S*,4*S*)-4-azido-2-((2*S*,4*S*)-4-fluoro-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluoropyrrolidine-1-carbonyl)-4-

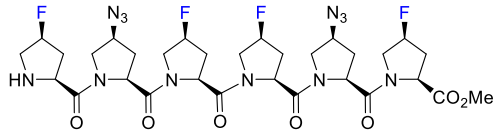
fluoropyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluoropyrrolidine-1-carboxylate (32)



According to the general procedure (a), **30** (106 mg, 0.219 mmol), **23** (87.6 mg, 0.219 mmol, 1.0 equiv) and EDCI (46.1 mg, 0.241 mmol, 1.1 equiv) in CH_2Cl_2 (2.0 mL) gave the title compound (159 mg, 82%) as a white solid. The title compound was purified by SiO_2 column chromatography (CH_2Cl_2:MeOH = 10:1).

Mixture of rotamer. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.26 (d, *J* = 52.9 Hz, 3H), 5.16 (d, *J* = 53.5 Hz, 1H), 4.81–4.77 (m, 2H), 4.73–4.65 (m, 2H), 4.52 (dd, *J* = 9.6, 2.6 Hz, 1H), 4.21–3.95 (m, 6H), 3.86–3.74 (m, 4H), 3.70 (s, 3H), 3.42 (dd, *J* = 9.8, 7.8 Hz, 1H), 3.38 (t, *J* = 8.9 Hz, 1H), 2.67–2.62 (m, 2H), 2.47–2.38 (m, 8H), 2.06 (t, *J* = 11.8 Hz, 1H), 1.96 (br s, 4H), 1.43 (s, 7H), 1.38 (s, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ: –173.4– –172.0 (m, 3.7F), –174.5– –173.7 (m, 0.3F) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 171.0, 169.6, 169.44, 169.36, 169.0, 168.7, 154.1, 92.5 (d, *J* = 177.3 Hz), 91.9 (d, *J* = 180.7 Hz), 91.7 (d, *J* = 182.4 Hz), 91.4 (d, *J* = 180.7 Hz), 80.4, 80.2, 58.9, 58.8, 57.1, 57.0, 56.73, 56.71, 56.66, 53.4, 53.3, 53.2, 53.14, 53.08, 53.0, 52.9, 52.4, 51.14, 51.10, 35.4 (d, *J* = 20.9 Hz), 35.2 (d, *J* = 21.8 Hz), 34.3 (d, *J* = 21.8 Hz), 33.9 (d, *J* = 21.8 Hz), 33.0 (d, *J* = 23.4 Hz), 28.3, 28.2 ppm; IR (KBr): 2978, 2881, 2108, 1751, 1664, 1433, 1367, 1213, 1074, 964, 754 cm^{-1}; MS (ESI) *m/z*: 891 $[M+Na]^+$; HRMS (ESI) *m/z*: 891.3501 calcd. for $C_{36}H_{48}N_{12}O_9F_4Na$, found: 891.3524.

Methyl
(2*S*,4*S*)-1-((2*S*,4*S*)-4-azido-1-((2*S*,4*S*)-1-((2*S*,4*S*)-1-((2*S*,4*S*)-4-azido-1-((2*S*,4*S*)-4-fluoropyrrolidine-2-carbonyl)pyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2-carbonyl)pyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2-carboxylate (SI-13)



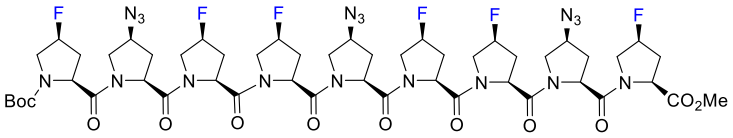
According to the general procedure (b), **32** (143 mg, 0.161 mmol) in CH_2Cl_2 (2.0 mL) and TFA (0.6 mL) gave the title compound (118 mg, 92%) as a white solid. The crude compound was used for the next reaction without column purification.

^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.36–5.23 (m, 3H), 5.16 (dt, *J* = 54.2, 3.7 Hz, 1H), 4.84–4.80 (m, 2H), 4.77 (dd, *J* = 9.9, 3.3 Hz, 1H), 4.67 (td, *J* = 14.4, 6.7 Hz, 2H), 4.22–4.15 (m, 3H), 4.09–3.95 (m, 3H), 3.89–3.75 (m, 4H), 3.71 (s, 3H), 3.46–3.44 (m, 1H), 3.42–3.39 (m, 2H), 2.75 (dq, *J* = 37.6, 5.5 Hz, 1H), 2.69–2.63 (m, 2H), 2.56–2.34 (m, 8H), 2.20–2.08 (m, 4H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$,) δ: –172.7– –172.1 (m, 1F), –174.0– –173.0 (m, 3F) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ:

171.3, 171.0, 169.30, 169.28, 168.9, 168.6, 92.5 (d, *J* = 178.2 Hz), 94.2 (d, *J* = 176.5 Hz), 91.61 (d, *J* = 182.4 Hz), 91.57 (d, *J* = 183.2 Hz), 58.90, 58.89, 58.7, 57.1, 57.0 (d, *J* = 5.0 Hz), 56.7 (d, *J* = 4.2 Hz), 54.8 (d, *J* = 23.4 Hz), 53.3, 53.2, 53.1, 53.03, 52.97, 52.5, 51.0 (d, *J* = 26.8 Hz), 37.4 (d, *J* = 21.8 Hz), 35.4 (d, *J* = 20.9 Hz), 34.3 (d, *J* = 21.8 Hz), 34.0 (d, *J* = 21.8 Hz), 33.1 ppm; IR (KBr): 2949, 2877, 2106, 1747, 1657, 1431, 1329, 1213, 1059, 964, 746 cm^{-1}; MS (ESI) *m/z*: 769 $[M+H]^+$; HRMS (ESI) *m/z*: 769.3157 calcd. for $C_{31}H_{41}N_{12}O_7F_4$, found: 769.3142.

***tert*-Butyl**

(2*S*,4*S*)-2-((2*S*,4*S*)-4-azido-2-((2*S*,4*S*)-2-((2*S*,4*S*)-2-((2*S*,4*S*)-4-azido-2-((2*S*,4*S*)-2-((2*S*,4*S*)-2-((2*S*,4*S*)-4-azido-2-((2S,4S)-4-fluoro-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluoropyrrolidine-1-carbonyl)-4-fluoropyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluoropyrrolidine-1-carbonyl)-4-fluoropyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluoropyrrolidine-1-carboxylate (SI-14)



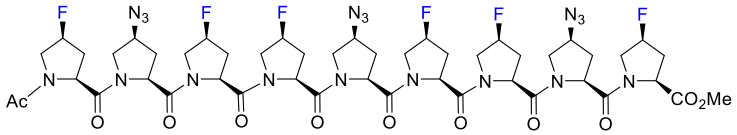
According to the general procedure (a), **SI-13** (101 mg, 0.131 mmol), **23** (63.8 mg, 0.131 mmol, 1.0 equiv) and EDCI (27.7 mg, 0.144 mmol, 1.1 equiv) in CH_2Cl_2 (1.5 mL) gave the title compound (40.9 mg, 25%) as a white solid. The title compound was purified by SiO_2 column chromatography (CH_2Cl_2:MeOH = 10:1 to 5:1).

Mixture of rotamer. ^1H NMR (700 MHz, $CDCl_3$) δ: 5.31–5.13 (m, 6H), 4.78–4.62 (m, 8H), 4.52 (d-like, *J* = 9.8 Hz, 1H), 4.28–4.20 (m, 3H), 4.07–4.00 (m, 6H), 3.80–3.70 (m, 5H), 3.70 (s, 3H), 3.41–3.31 (m, 3H), 2.70 (br s, 5H), 2.54–2.20 (m, 9H), 2.07–2.02 (m, 3H), 1.72 (br s, 5H), 1.43 (s, 7.3H), 1.39 (s, 1.7H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$,) δ: –171.50– –170.82 (m, 1F), –173.57– –171.81 (m, 4F) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ: 218.27, 218.26, 171.0, 169.8, 169.6, 169.3, 169.0, 168.8, 168.6, 168.3, 154.1, 153.4, 132.1, 131.0, 129.5, 128.9, 128.8, 93.5, 93.4, 93.3, 93.2, 93.1, 92.7, 92.4, 92.3, 92.1, 91.7, 91.5, 91.4, 91.0, 80.2, 80.1, 65.6, 59.0, 58.9, 57.3, 57.1, 56.9, 56.8, 56.7, 53.6, 53.5, 53.3, 53.0, 52.4, 51.9, 51.5, 51.3, 51.1, 51.0, 35.6, 35.5, 35.4, 35.3, 35.2, 34.44, 34.36, 34.2, 34.0, 33.8, 32.9, 32.7, 31.9, 29.7, 29.3, 28.4, 28.3 ppm; IR (KBr): 2952, 2870, 2106, 1658, 1435, 1367, 1034, 1018 cm^{-1}; MS (ESI) *m/z*: 1259 $[M+Na]^+$; HRMS (ESI) *m/z*: 1259.4909 calcd. for $C_{51}H_{66}N_{18}O_{12}F_6Na$, found: 1259.4930.

Methyl

(2*S*,4*S*)-1-((2*S*,4*S*)-1-((2*S*,4*S*)-1-((2*S*,4*S*)-1-((2*S*,4*S*)-1-((2*S*,4*S*)-1-((2*S*,4*S*)-1-((2*S*,4*S*)-1-((2*S*,4*S*)-1-acetyl-4-fluoropyrrolidine-2-carbonyl)-4-azidopyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2-carbonyl)-4-azidopyrrolidine-2-carbonyl)-4-fluoropyrrolidine-2

-carbonyl)-4-fluoropyrrolidine-2-carbonyl)-4-azidopyrrolidine-2-carbonyl)-4-fluoropyrrolidine -2-carboxylate (34)

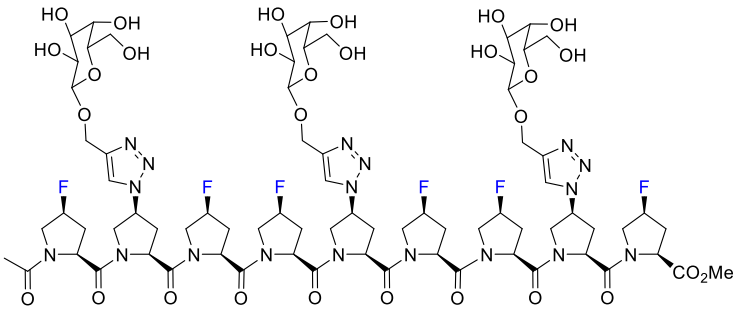


According to the general procedure (b), **SI-14** (40.9 mg, 0.033 mmol) in CH_2Cl_2 (1.0 mL) and TFA (0.3 mL) gave the title compound (37.6 mg, quant) as a white solid. The crude compound was used for the next reaction without column purification.

According to the general procedure (d), previous crude product (37.6 g, 0.033 mmol), Ac_2O (15.6 µL, 0.165 mmol, 5.0 equiv) and pyridine (13.2 µL, 0.165 mmol, 5.0 equiv) in CH_2Cl_2 (1.0 mL) gave the title compound (38.9 mg, quant) as a white solid. The crude **34** was used for next reaction without column purification.

^{1}H NMR (700 MHz, $CDCl_3$) δ: 5.33–5.22 (m, 4H), 4.84 (d, *J* = 10.2 Hz, 1H), 4.81–4.79 (m, 1H), 4.74 (dd, *J* = 9.7, 3.5 Hz, 1H), 4.70–4.67 (m, 3H), 4.33–3.98 (m, 17H), 3.94–3.73 (m, 6H), 3.71 (s, 3H), 3.46–3.42 (m, 2H), 2.67–2.62 (m, 2H), 2.51–2.31 (m, 12H), 2.17–2.07 (m, 5H), 2.08 (s, 3H) ppm; IR (KBr): 2956, 2108, 1734, 1657, 1414, 1335, 1203, 1061, 958, 904, 802 cm^{-1}; MS (ESI) *m/z*: 1201 $[M+Na]^+$; HRMS (ESI) *m/z*: 1201.4491 calcd. for $C_{48}H_{60}N_{18}O_{11}F_6Na$, found: 1201.4512.

Galactose-conjugated fluorinated proline oligomer 12b



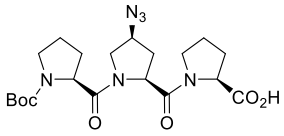
According to the general procedure (e), **34** (13.0 mg, 0.0110 mmol), *O*-propargyl galactose **29** (9.6 mg, 0.0441 mmol, 4.0 equiv), $CuSO_4$ aq (0.05 M, 0.331 mL, 0.0165 mmol, 1.5 equiv) and sodium ascorbate aq (0.05 M, 0.662 mL, 0.0331 mmol, 3.0 equiv) in ^{t}BuOH (1.5 mL) gave the title compound (14.2 mg, 70%) as a white solid. The title compound was purified by reverse phase SiO_2 column chromatography (5% MeOH to 50% MeOH).

^{1}H NMR (700 MHz, D_2O) δ: 8.24–8.21 (m, 3H), 5.51–5.36 (m, 11H), 5.10 (d, *J* = 10.2 Hz, 1H), 5.03–4.83 (m, 14H), 4.59–4.56 (m, 2H), 4.50–4.47 (m, 2H), 4.20–3.89 (m, 18H), 3.75 (s, 3H), 3.83–3.61 (m, 11H), 3.55–-3.51 (m, 3H), 3.23–3.16 (m, 3H), 2.77–2.44 (m, 16H), 2.14 (s, 3H) ppm; ^{19}F NMR (D_2O, 282 MHz) δ: –171.1– –170.0 (m, 5F), –172.7– –172.1 (m, 1F) ppm; ^{13}C NMR (176 MHz, D_2O) δ: 173.4, 173.1, 170.91, 170.87, 170.69, 170.65, 170.4, 170.3, 143.8, 124.6, 124.5, 106.9,

102.1, 94.1, 93.7, 93.5, 93.2, 92.6, 92.5, 82.9, 81.33, 81.29, 76.8, 75.3, 72.8, 70.8, 68.7, 68.6, 62.8, 61.9, 61.1, 60.2, 58.2, 58.0, 57.8, 57.5, 57.3, 57.2, 55.0, 54.9, 54.3, 54.2, 54.1, 53.8, 53.7, 53.60, 53.56, 53.2, 51.3, 35.1, 35.01, 34.95, 34.8, 34.7, 34.6, 34.5, 34.2, 34.1, 33.1, 33.0, 23.4, 21.4, 20.2 ppm; IR (KBr): 3431, 2956, 2922, 1658, 1435, 1205, 1034 cm^{-1}; MS (ESI) *m/z* : 940 $[(M+Na+H]/2]^{2+}$; HRMS (ESI) *m/z*: 1855.6862 calcd. For $C_{75}H_{102}N_{18}O_{29}F_6Na$, found: 1855.6858.

2.4. Synthesis of galactose-conjugated non-fluorinated proline oligomer 13b

((2*S*,4*S*)-4-Azido-1-((*tert*-butoxycarbonyl)-L-prolyl)pyrrolidine-2-carbonyl)-L-proline (31)[8]

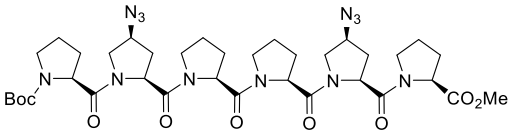


According to the general procedure (c), **22** (4.24 g, 9.13 mmol) in THF-MeOH (2:1, 23 mL) and LiOH aq (1.0 M, 18.3 mL, 18.3 mmol, 2.0 equiv) gave the title compound (4.12 g, quant) as a white solid. The crude title compound was used for the next reaction without column purification.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.31 (brd, 1H), 4.69 (t, *J* = 8.0 Hz, 0.7H), 4.64 (t, *J* = 8.1 Hz, 0.3H), 4.53–4.50 (m, 1H), 4.43 (dd, *J* = 8.6, 3.2 Hz, 0.7H), 4.33–4.31 (m, 0.3H), 4.19–4.15 (m, 1.4H), 4.07 (t, *J* = 7.8 Hz, 0.3H), 3.98 (t, *J* = 8.5 Hz, 0.3H), 3.78–3.72 (m, 1H), 3.54–3.30 (m, 4H), 2.59–2.54 (m, 1H), 2.19–1.92 (m, 8H), 1.81–1.76 (m, 1H), 1.39 (s, 6.5H), 1.35 (s, 2.5H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.0, 171.7, 171.1, 170.3, 170.0, 154.6, 153.5, 79.8, 79.5, 59.0, 58.7, 57.7, 57.6, 57.5, 56.54, 56.48, 50.9, 46.8, 46.5, 32.9, 31.4, 28.8, 28.34, 28.26, 28.2, 24.7, 24.1, 22.5 ppm; IR (KBr): 2979, 2881, 2106, 1689, 1655, 1404, 1167, 756 cm^{-1}; MS (ESI) *m/z*: 473 $[M+Na]^+$, 449 $[M–H]^–$; HRMS (ESI) *m/z*: 473.2125 calcd. for $C_{20}H_{30}N_6O_6Na$, found: 473.2129.

***tert*-Butyl**

(*S*)-2-((2*S*,4*S*)-4-azido-2-((*S*)-2-((*S*)-2-((2*S*,4*S*)-4-azido-2-((*S*)-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate (33)

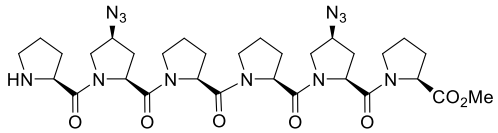


According to the general procedure (a), **31** (357 mg, 0.980 mmol), **24** (486 mg, 1.08 mmol, 1.1 equiv) and EDCI (225 mg, 1.18 mmol, 1.2 equiv) in CH_2Cl_2 (5.0 mL) gave the title compound (603 mg, 77%) as a white solid. The title compound was purified by SiO_2 column chromatography (CH_2Cl_2:MeOH = 20:1).

Mixture of rotamer. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.74–4.63 (m, 4H), 4.55 (dd, *J* = 8.8, 3.8 Hz, 1H), 4.43 (dd, *J* = 8.4, 3.2 Hz, 1H), 4.20–4.12 (m, 3H), 3.77–3.67 (m, 3H), 3.69 (s, 3H), 3.58–3.41

(m, 5H), 3.37–3.35 (m, 1H), 2.60–2.56 (m, 2H), 2.17–1.79 (m, 20H), 1.42 (s, 7H), 1.37 (s, 2H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 172.5, 172.4, 171.4, 170.9, 170.3, 170.1, 169.4, 169.1, 168.9, 154.6, 153.5, 79.5, 79.4, 58.9, 58.80, 58.75, 58.68, 58.65, 58.0, 57.9, 57.8, 57.7, 57.6, 57.5, 56.7, 56.6, 56.5, 52.2, 51.24, 51.19, 51.14, 51.08, 47.0, 46.9, 46.83, 46.80, 46.59, 46.55, 46.4, 33.1, 33.0, 31.5, 30.0, 29.6, 29.0, 28.9, 28.7, 28.64, 28.58, 28.44, 28.37, 27.83, 27.77, 24.8, 24.7, 24.2, 23.5, 22.6 ppm; IR (KBr): 2974, 2877, 2106, 1743, 1655, 1435, 1169, 758 cm^{-1}; MS (ESI) *m/z*: 819 $[M+Na]^+$; HRMS (ESI) *m/z*: 819.3878 calcd. for $C_{36}H_{52}N_{12}O_9Na$, found: 819.3876.

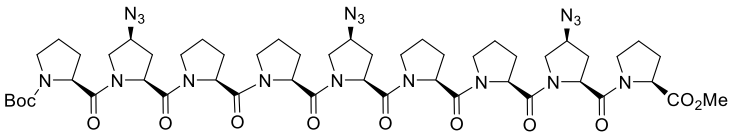
Methyl ((2*S*,4*S*)-1-(((2*S*,4*S*)-1-(L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolyl-L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolinate (SI-15)



According to the general procedure (b), **33** (559 mg, 0.702 mmol) in CH_2Cl_2 (5.0 mL) and TFA (1.7 mL) gave the title compound (487 mg, quant) as a white solid. The crude compound was used for the next reaction without column purification.

^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.74 (dd, *J* = 8.7, 3.9 Hz, 1H), 4.69 (dd, *J* = 14.7, 7.1 Hz, 2H), 4.65 (dd, *J* = 8.1, 3.5 Hz, 1H), 4.56 (dd, *J* = 8.7, 3.9 Hz, 1H), 4.20–4.12 (m, 3H), 4.00 (dd, *J* = 8.6, 6.6 Hz, 1H), 3.96 (dd, *J* = 10.1, 7.1 Hz, 1H), 3.77–3.67 (m, 3H), 3.69 (s, 3H), 3.59–3.51 (m, 3H), 3.42 (qd, *J* = 11.5, 6.1 Hz, 2H), 3.16–3.12 (m, 1H), 2.98–2.93 (m, 3H), 2.66–2.58 (m, 2H), 2.19–1.79 (m, 18H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 172.43, 171.36, 170.9, 170.3, 170.02, 170.00, 169.14, 169.12, 168.9, 168.8, 154.6, 153.5, 79.5, 79.4, 58.91, 58.89, 58.8, 58.6, 58.0, 57.9, 57.82, 57.79, 57.7, 57.6, 56.70, 56.68, 56.6, 56.5, 52.2, 51.4, 51.2, 51.14, 51.08, 47.0, 46.9, 46.8, 46.8, 46.7, 46.6, 46.4, 33.1, 33.0, 31.5, 30.3, 30.0, 29.6, 29.0, 28.9, 28.6, 28.44, 28.38, 27.9, 27.82, 27.76, 24.84, 24.79, 24.72, 24.66, 24.2, 23.7, 23.5, 23.0, 22.6 ppm; IR (KBr): 2981, 2879, 2106, 1743, 1651, 1439, 1331, 1267, 1201, 758 cm^{-1}; MS (ESI) *m/z*: 697 $[M+H]^+$; HRMS (ESI) *m/z*: 697.3534 calcd. for $C_{31}H_{45}N_{12}O_7Na$, found: 697.3505.

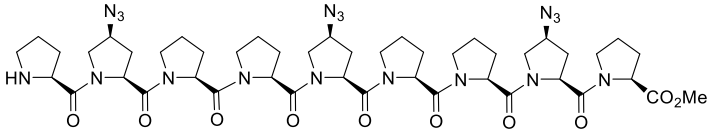
***tert*-Butyl (*S*)-2-((2*S*,4*S*)-4-azido-2-((*S*)-2-((*S*)-2-((2*S*,4*S*)-4-azido-2-((*S*)-2-((*S*)-2-((2*S*,4*S*)-4-azido-2-((*S*)-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate (SI-16)**



According to the general procedure (a), **SI-15** (487 mg, 0.699 mmol), **24** (346 mg, 0.769 mmol) and EDCI (161 mg, 0.840 mmol, 1.2 equiv) in CH_2Cl_2 (5.0 mL) gave the title compound (430 mg, 54% for 2 steps) as a white solid. The title compound was purified by SiO_2 column chromatography (CH_2Cl_2:MeOH = 20:1 to 10:1 to 6:1).

Mixture of rotamer. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.74–4.64 (m, 7H), 4.56 (dd, *J* = 8.7, 3.9 Hz, 1H), 4.43 (dd, *J* = 8.4, 3.2 Hz, 0.7H), 4.35 (dd, *J* = 8.6, 3.8 Hz, 0.3H), 4.21–4.08 (m, 6H), 3.77–3.67 (m, 4H), 3.70 (s, 3H), 3.57–3.52 (m, 4H), 3.45–3.36 (m, 4H), 2.60–2.53 (m, 3H), 2.18–1.93 (m, 27H), 1.82–1.78 (m, 3H), 1.42 (s, 6.6H), 1.38 (s, 2.4H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 172.5, 171.0, 170.4, 170.0, 169.2, 169.1, 168.90, 168.86, 154.6, 153.6, 79.5, 79.4, 58.93, 58.90, 58.8, 58.7, 58.0, 57.9, 57.84, 57.81, 57.7, 57.6, 56.72, 56.70, 56.60, 56.56, 52.2, 51.4, 51.3, 51.2, 51.1, 47.0, 46.9, 46.84, 46.82, 46.78, 46.75, 46.6, 46.4, 33.1, 33.0, 31.5, 30.3, 30.0, 29.7, 29.0, 28.7, 28.5, 28.4, 27.9, 27.84, 27.77, 24.9, 24.8, 24.74, 24.68, 24.3, 23.5, 22.9, 22.6 ppm; IR (KBr): 2987, 2879, 2108, 1655, 1439, 1213, 1161, 762 cm^{-1}; MS (ESI) *m*/*z*: 1157 $[M+Na]^+$; HRMS (ESI) *m*/*z*: 1151.5475 calcd. for $C_{51}H_{72}N_{18}O_{12}Na$, found: 1151.5457.

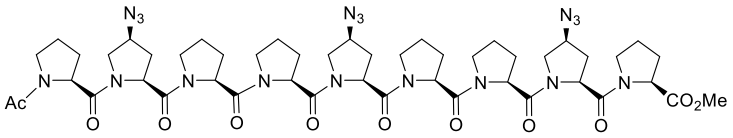
Methyl ((2*S*,4*S*)-1-(((2*S*,4*S*)-1-(L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolyl-L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolinate (SI-17)



According to the general procedure (b), **SI-16** (152 mg, 0.133 mmol) in CH_2Cl_2 (1.3 mL) and TFA (0.4 mL) gave the title compound (137mg, quant) as a white solid. The crude compound was used for the next reaction without column purification.

^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.74–4.63 (m, 7H), 4.55 (dd, *J* = 8.8, 4.0 Hz, 1H), 4.20–4.17 (m, 2H), 4.14–4.09 (m, 3H), 3.95 (dd, *J* = 10.0, 7.2 Hz, 1H), 3.89 (s, 1H), 3.76–3.66 (m, 4H), 3.69 (s, 3H), 3.58–3.51 (m, 5H), 3.41 (q, *J* = 8.4 Hz, 2H), 3.12 (s, 1H), 2.88 (s, 1H), 2.63–2.55 (m, 3H), 2.46 (s, 3H), 2.17–1.93 (m, 25H), 1.90–1.70 (m, 3H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 172.4, 172.0, 170.34, 170.28, 170.0, 169.9, 169.2 168.9, 168.8, 59.3, 58.9, 58.8, 58.7, 58.6, 58.0, 57.94, 57.85, 56.8, 56.7, 56.6, 52.2, 51.4, 51.1, 51.0, 47.4, 46.9, 46.82, 46.78, 46.7, 46.4, 33.04, 32.98, 33.0, 31.5, 29.7, 28.6, 27.84, 27.81, 27.76, 27.7, 24.82, 24.78, 24.73, 24.66, 22.6 ppm; IR (KBr): 2960, 2106, 1741, 1649, 1433, 1273, 1211, 758 cm^{-1}; MS (ESI) *m*/*z*: 1029 $[M+H]^+$; HRMS (ESI) *m*/*z*: 1051.4951 calcd. for $C_{46}H_{65}N_{18}O_{10}Na$, found: 1051.4928.

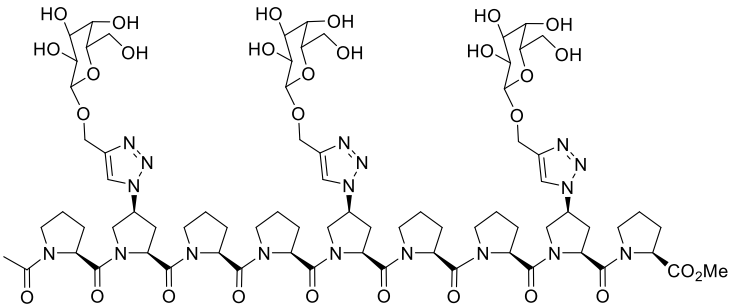
Methyl ((2*S*,4*S*)-1-(((2*S*,4*S*)-1-(((2*S*,4*S*)-1-(acetyl-L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolyl-L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolyl-L-prolyl)-4-azidopyrrolidine-2-carbonyl)-L-prolinate (35)



According to the general procedure (d), **SI-17** (139 mg, 0.133 mmol), Ac_2O (62.8 µL, 0.664 mmol, 5.0 equiv) and pyridine (53.6 µL, 0.664 mmol, 5.0 equiv) in CH_2Cl_2 (1.3 mL) gave the title compound (128 mg, 90%) as a white solid. The title compound was used for the next reaction without column purification.

^{1}H NMR (700 MHz, $CDCl_3$) δ: 4.72–4.68 (m, 5H), 4.64–4.63 (m, 2H), 4.57–4.54 (m, 2H), 4.28 (t, *J* = 8.3 Hz, 1H), 4.22–4.17 (m, 3H), 4.15–4.11 (m, 2H), 3.75–3.68 (m, 4H), 3.69 (s, 3H), 3.63–3.61 (m, 1H), 3.57–3.54 (m, 5H), 3.48–3.39 (m, 4H), 2.61–2.55 (m, 3H), 2.05 (s, 3H), 2.19–1.89 (m, 28H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ: 173.4, 172.5, 170.7, 170.4, 170.13, 170.11, 169.5, 169.2, 169.1, 169.0, 58.9, 58.83, 58.79, 58.7, 58.0, 57.88, 57.85, 57.5, 56.8, 56.6, 52.2, 51.5, 51.4, 51.1, 48.1, 46.93, 46.87, 46.82, 46.78, 46.4, 33.08, 33.06, 33.0, 28.68, 28.66, 27.9, 27.84, 27.79, 27.76, 24.9, 24.80, 24.75, 24.7, 22.2, 20.6 ppm; IR (KBr): 2981, 2877, 2106, 1743, 1649, 1437, 1327, 1267, 1209, 758 cm^{-1}; MS (ESI) *m/z*: 1093 $[M+Na]^+$; HRMS (ESI) *m/z*: 1093.5056 calcd. for $C_{48}H_{66}N_{18}O_{11}Na$, found: 1093.5050.

Galactose-conjugated non-fluorinated proline oligomer 13b



According to the general procedure (e), **35** (25.0 mg, 0.0233 mmol), *O*-propargyl galactose **29** (20.3 mg, 0.0933 mmol, 4.0 equiv), $CuSO_4$ aq (0.05 M solution, 0.70 mL, 0.035 mmol, 1.5 equiv) and sodium ascorbate aq (0.05 M, 1.40 mL, 0.070 mmol, 3.0 equiv) in ^{t}BuOH (1.1 mL) gave the title compound (40.2 mg, quant) as a white solid. The title compound was purified by reverse phase SiO_2 column chromatography (20% MeOH).

^{1}H NMR (700 MHz, D_2O) δ: 8.24–8.19 (m, 3H), 5.50–5.45 (m, 3H), 5.10–5.08 (m, 1H), 5.03–4.94

(m, 6H), 4.90–4.87 (m, 2H), 4.77–4.76 (m, 4H), 4.65–4.62 (m, 3H), 4.50–4.46 (m, 3H), 4.13–3.99 (m, 4H), 3.73 (s, 3H), 3.93–3.51 (m, 29H), 3.19–3.14 (m, 3H), 2.47–2.30 (m, 11H), 2.12 (s, 3H), 2.09–1.91 (m, 18H) ppm; ^{13}C NMR (176 MHz, D_2O) δ: 174.6, 172.7, 172.3, 171.9, 171.8, 171.6, 170.4, 170.23, 170.16, 143.8, 124.6, 124.5, 124.4, 124.3, 106.9, 102.1, 95.0, 94.9, 75.3, 73.9, 73.5, 72.8, 70.7, 68.7, 68.2, 65.6, 65.0, 63.6, 62.9, 61.9, 61.1, 60.2, 59.6, 58.8, 58.6, 58.3, 58.2, 57.9, 57.3, 57.2, 54.7, 53.9, 53.9, 53.0, 51.5, 50.1, 48.7, 47.9, 47.8, 47.7, 47.6, 47.5, 44.3, 33.1, 33.0, 28.7, 28.5, 28.0, 27.9, 24.6, 24.3, 21.3, 20.9 ppm; IR (KBr): 3431, 2952, 2877, 1639, 1442, 1329, 1030 cm^{-1}; MS (ESI) *m/z*: 886 $[(M+Na+H)/2]^{2+}$; HRMS (ESI) *m/z*: 1747.7427 calcd. for $C_{75}H_{108}N_{18}O_{29}Na$, found: 1747.7424.

3. Measurement of Circular dichroism (CD) spectra

The all CD spectra measurements for all synthetic compounds were performed using JASCO J-820 spectrometer, cell length 2 mm with the wavelength from 185 nm to 300 nm. The concentration of all compounds were adjusted to 1.0 mM for one amide bond in PBS (phosphate-buffered saline) (pH = 7.0).

3-1. CD spectra of proline oligomers

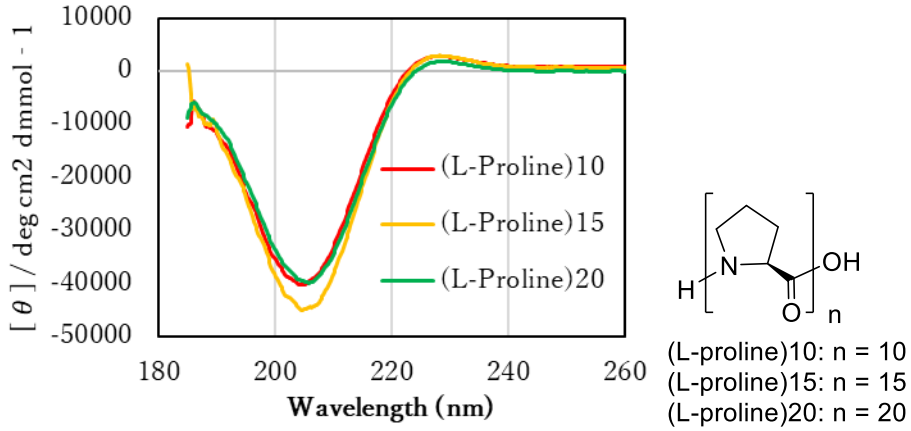


Fig. SI-1 CD spectra of proline oligomers (n = 10, 15, 20).

4. Ice recrystallization Inhibition (IRI) activity

The assay for the inhibition of ice recrystallization (IRI) was performed by the modified method of Smallwood and co-workers.[9] Each sample contained a known dilution of the AFP preparation and 30% sucrose in water. This mixture (1.5 μL) was "sandwiched" between two labeled, circular glass cover slips, 13 mm in diameter. The sandwich was cooled to –80°C using the programming unit and then maintained at –6 °C. The sandwich was observed using the Olympus phase-contrast microscope with a 10X objective. Visual assessments of recrystallization were made by comparing the test

sample with the control sample (30% sucrose solution without AFP) after 30 min. Photographs of the test sample and the control sample after being kept at –6 ºC for 30 min were analyzed for the average area (pixels) of one crystal using Image Factory (Ruka International Co., Japan). The value of IRI was calculated as the relative rate of the average area of one crystal in the control to that in the test samples. IRI activity increased in proportion to decreases in IRI value. Also, one unit of IRI activity was defined as the activity with IRI = 0.5.

5. Refferences

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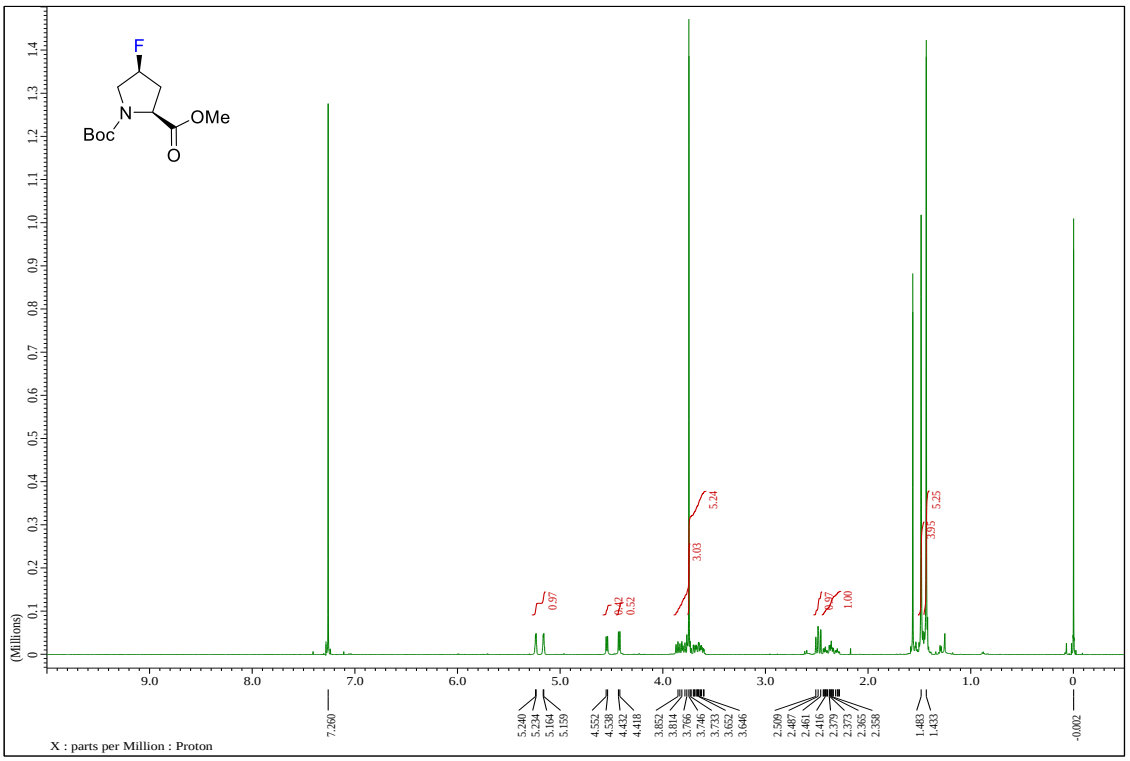
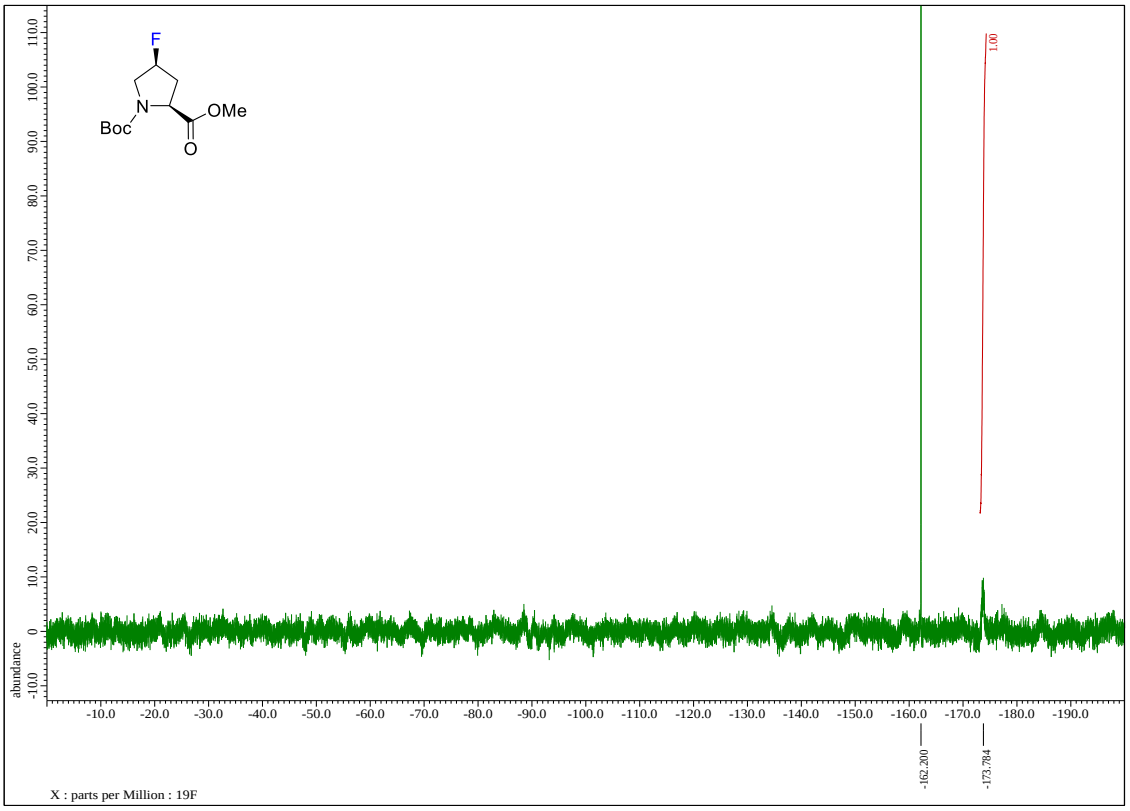
6. ^{1}H, ^{19}F, and ^{13}C NMR Spectra

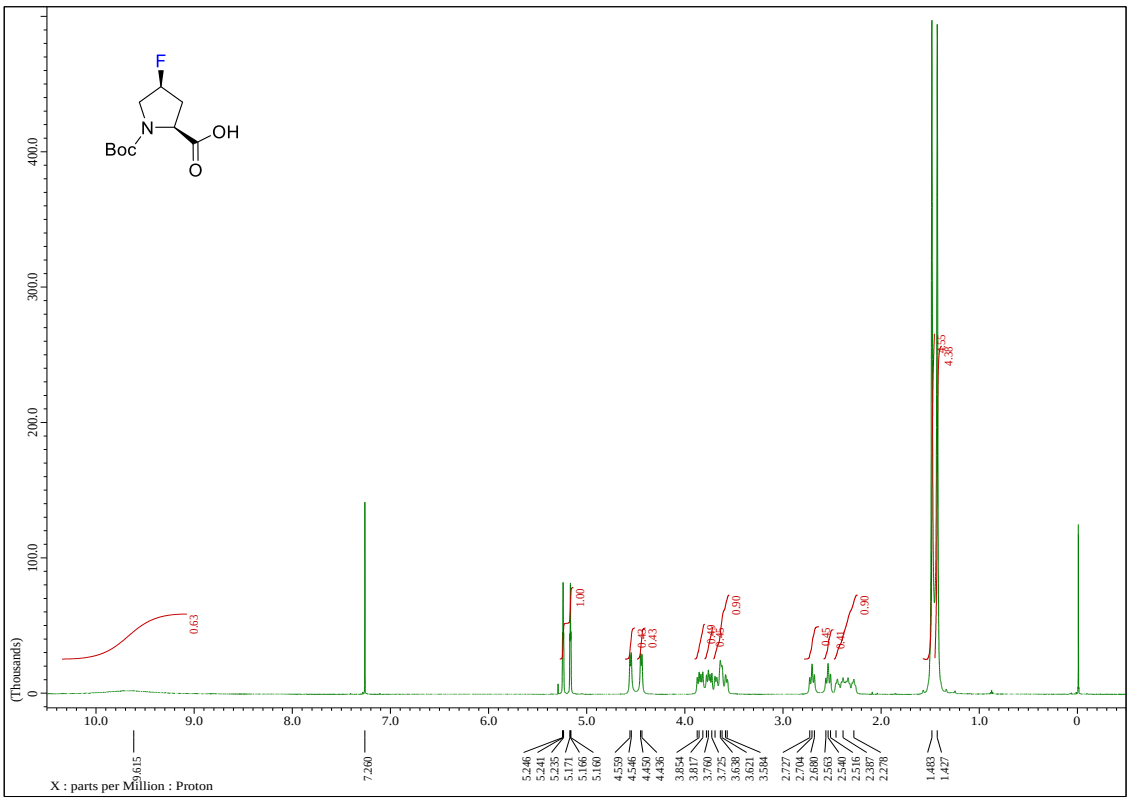
^{1}H NMR of **SI-1**



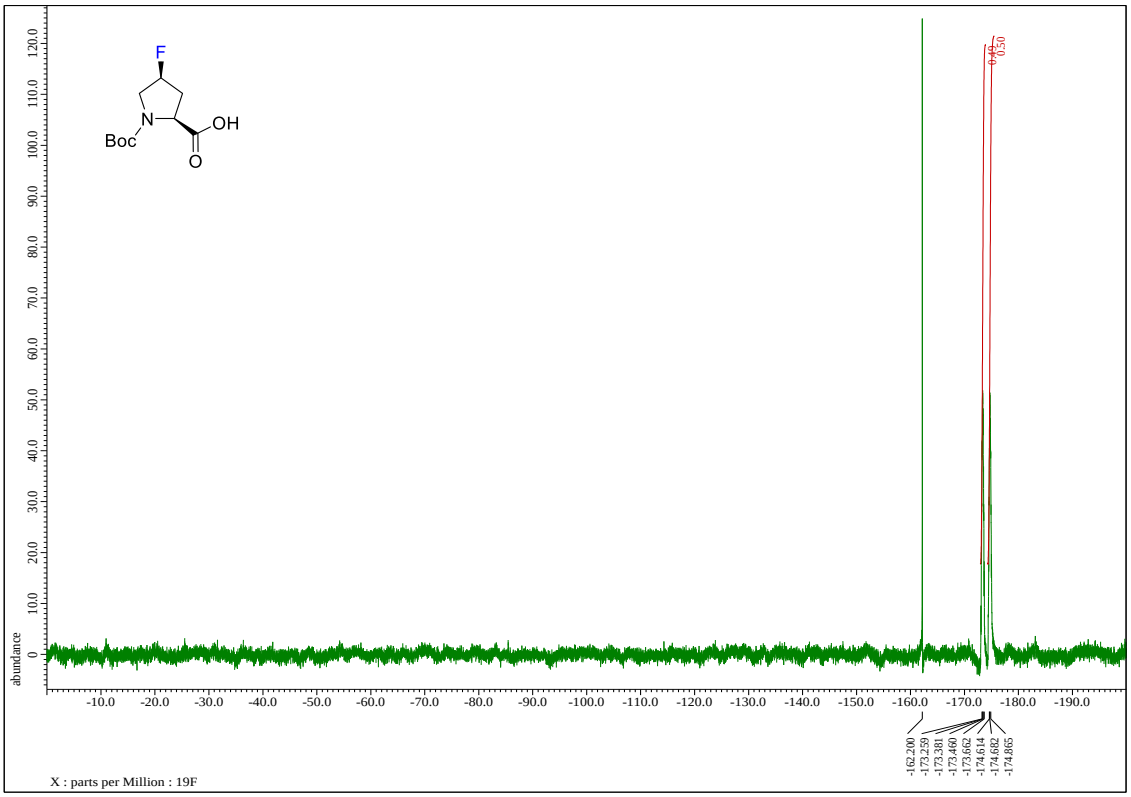
^{19}F NMR of **SI-1**



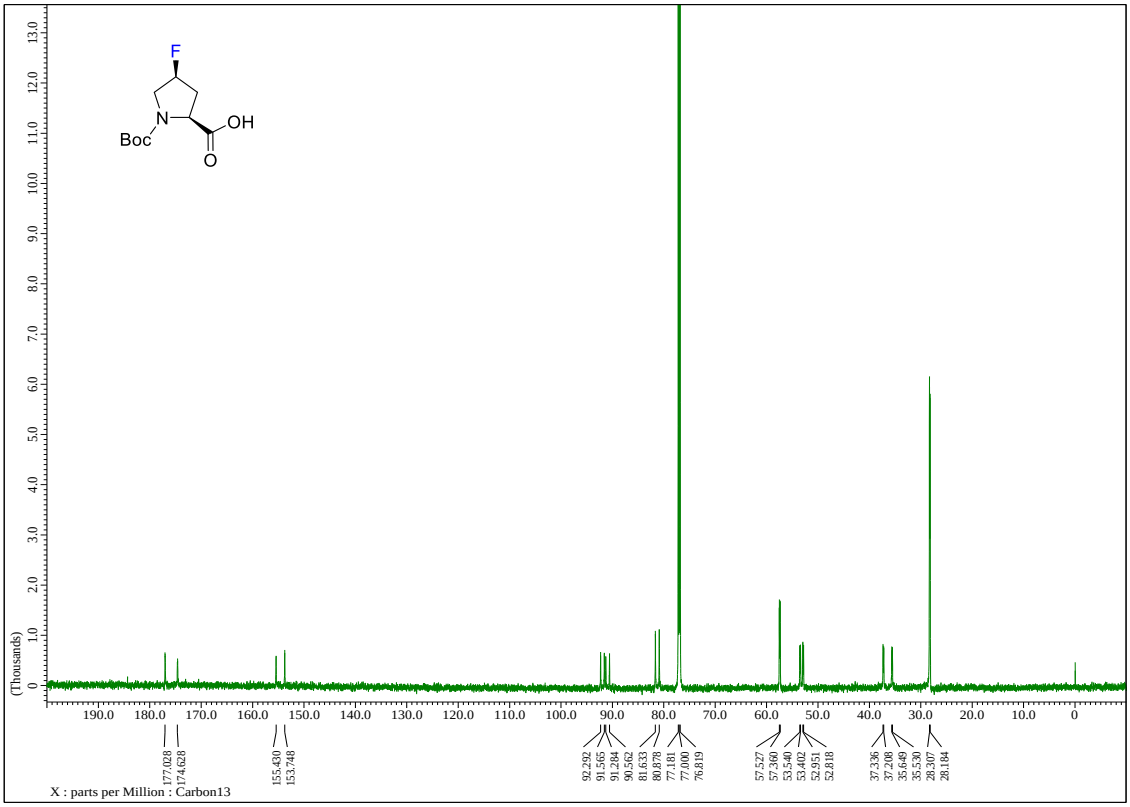
^{1}H NMR of **14**



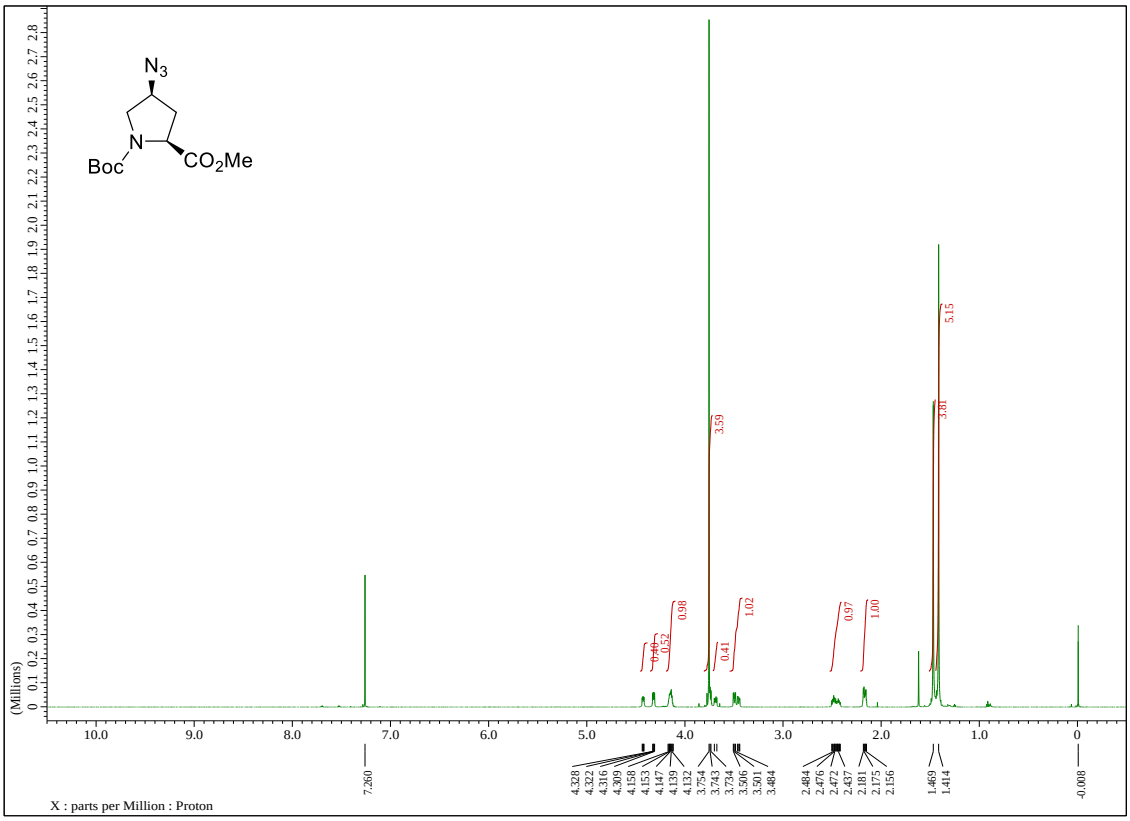
^{19}F NMR of **14**



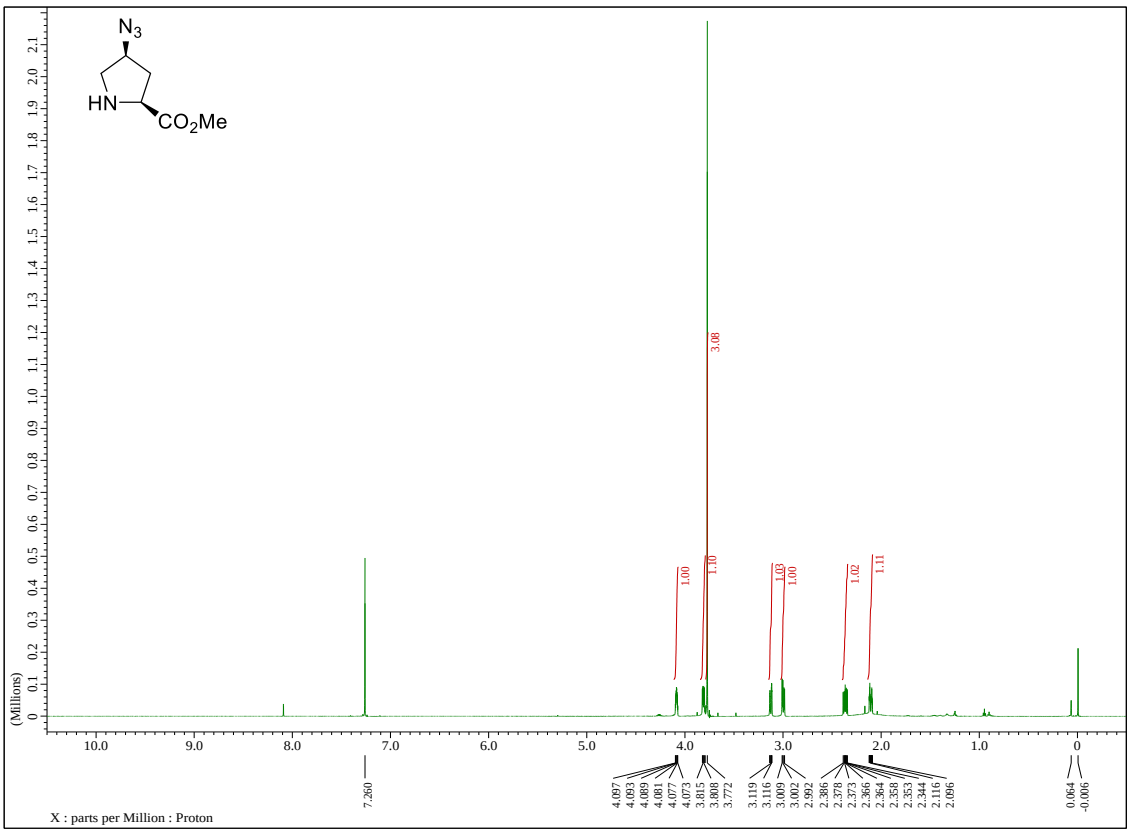
^{13}C NMR of **14**



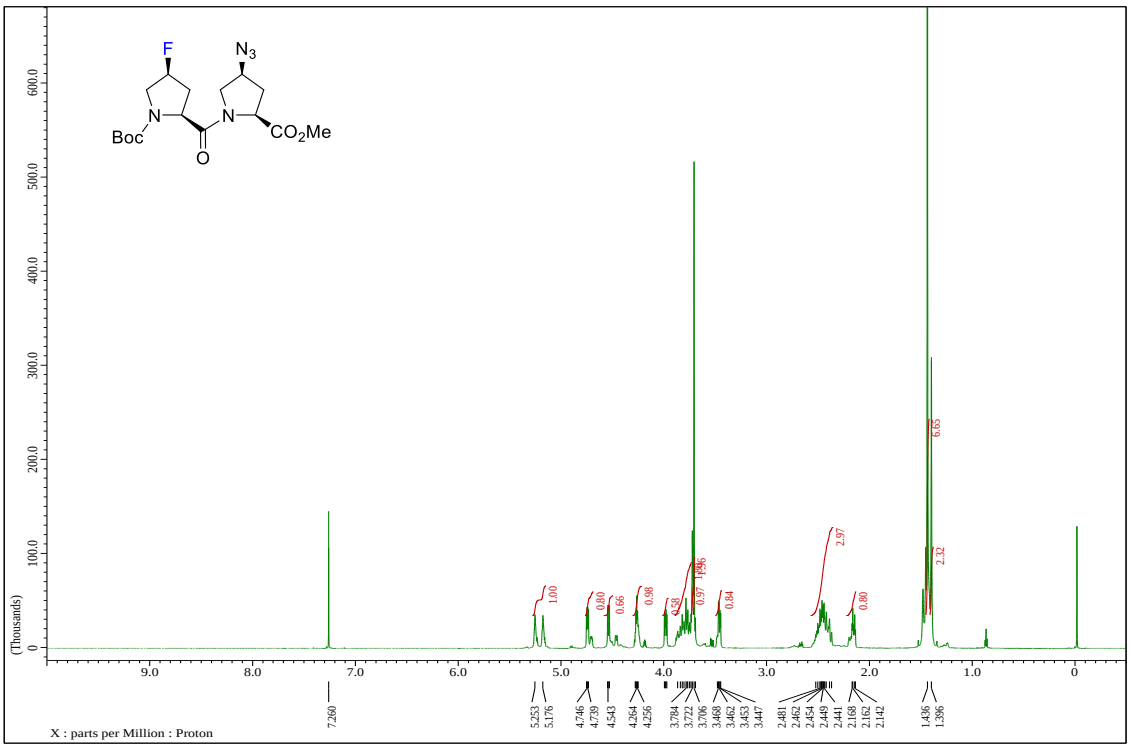
^{1}H NMR of **SI-2**



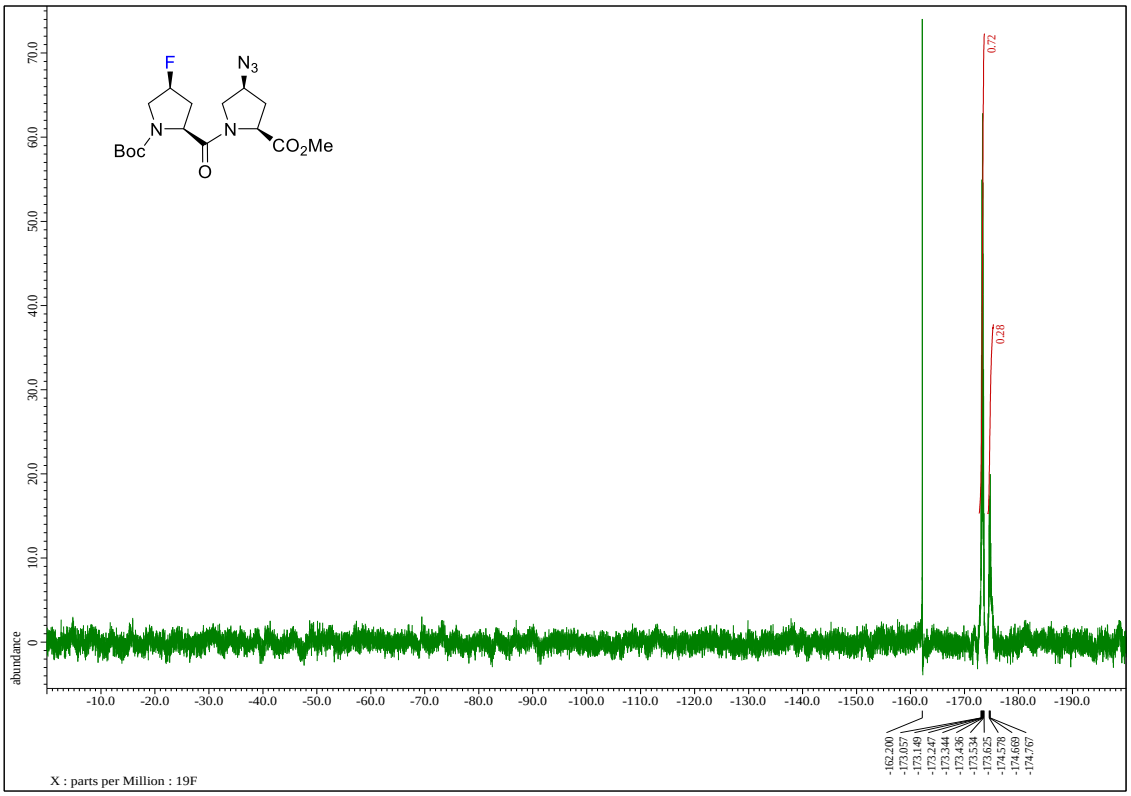
^{1}H NMR of **16**



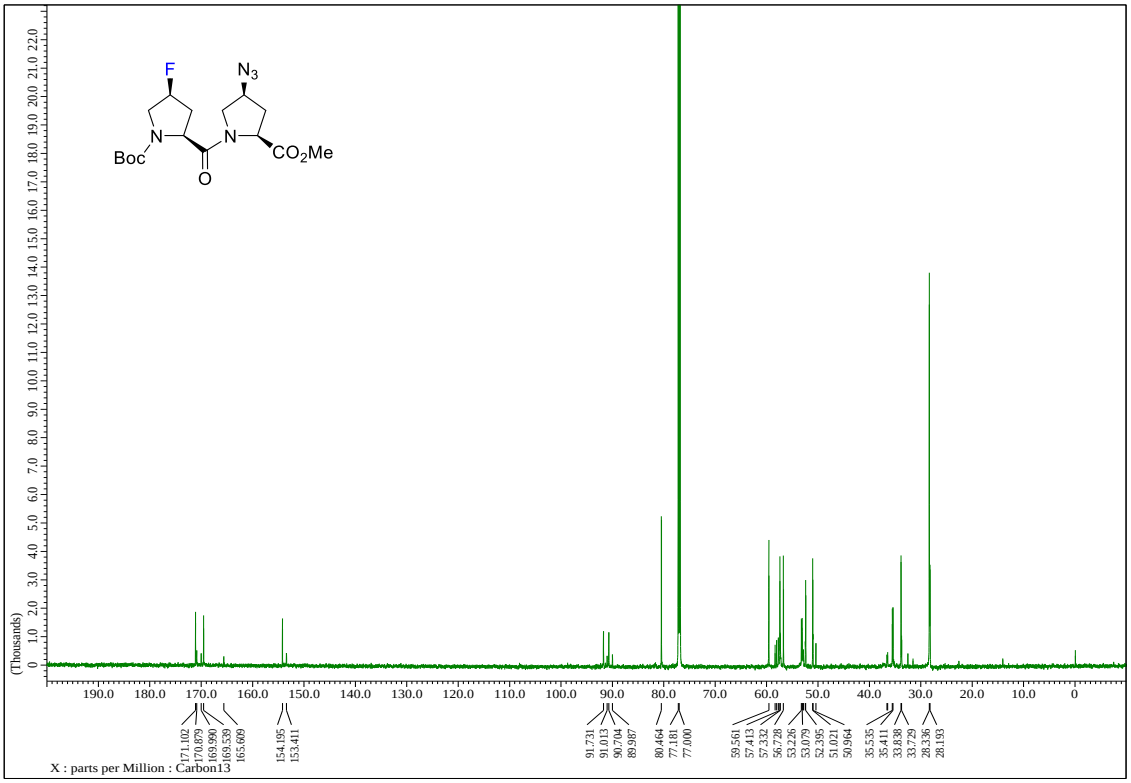
^{1}H NMR of **SI-3**



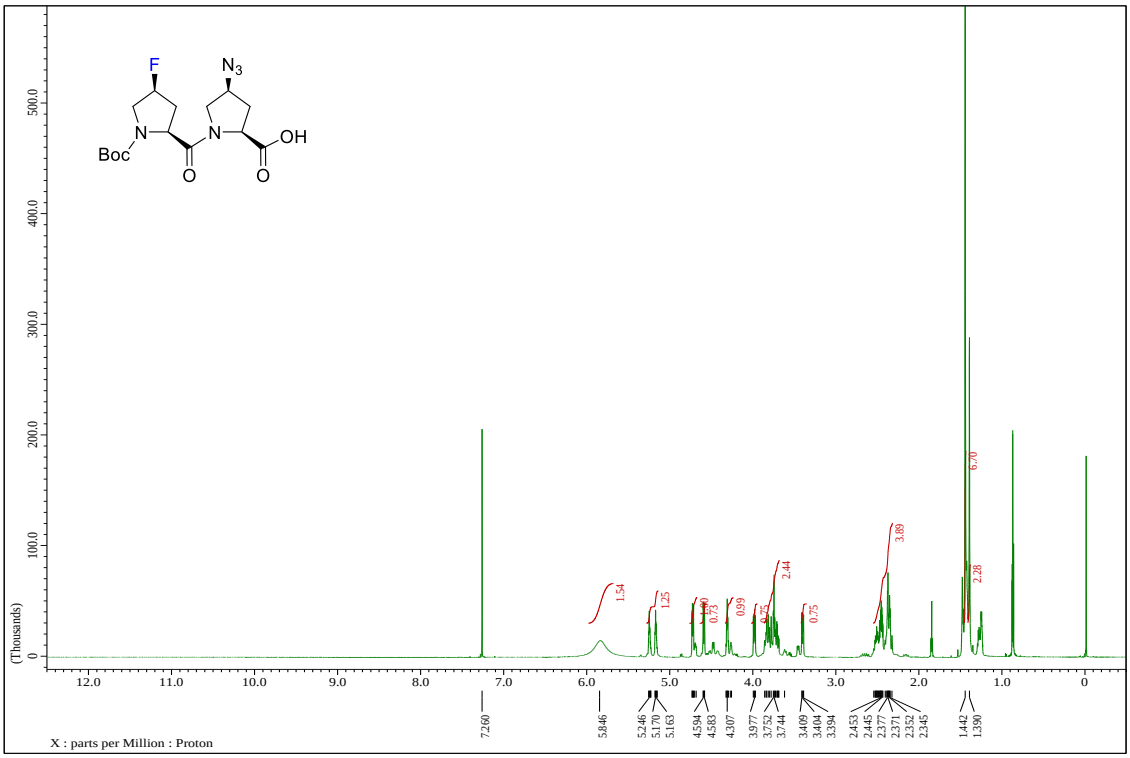
^{19}F NMR of **SI-3**



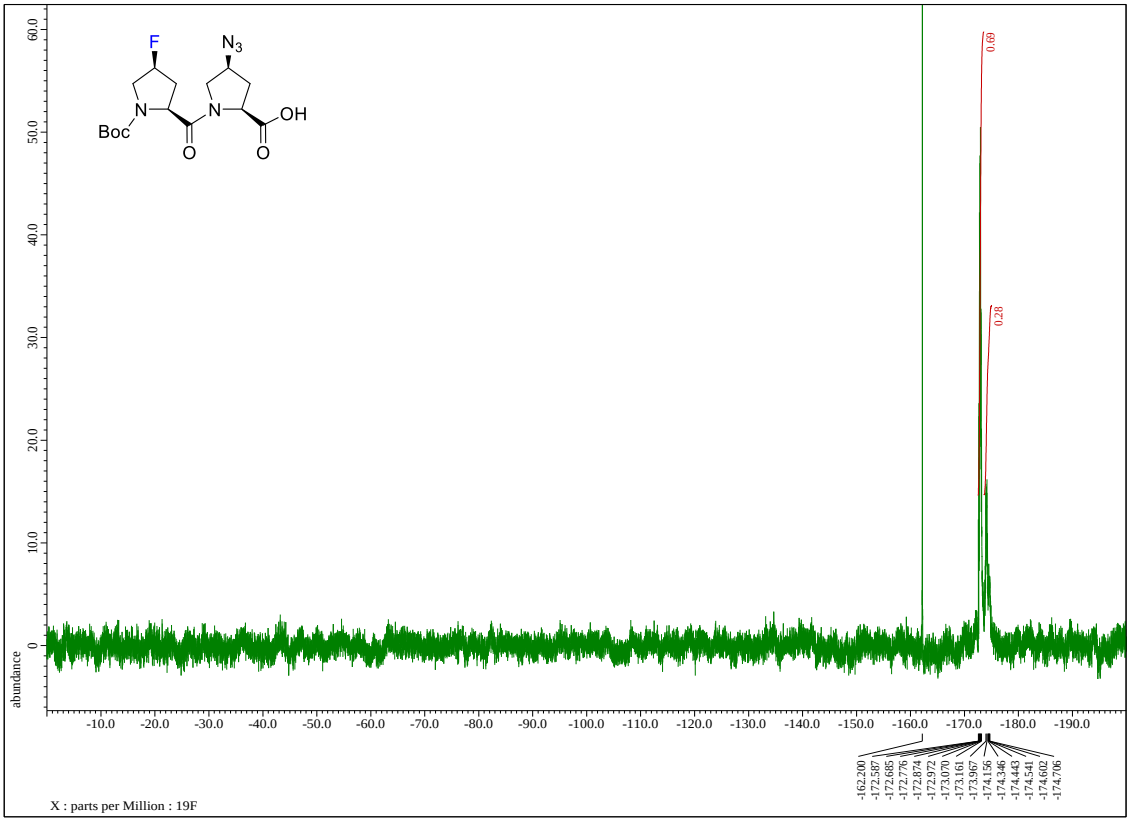
^{13}C NMR of **SI-3**



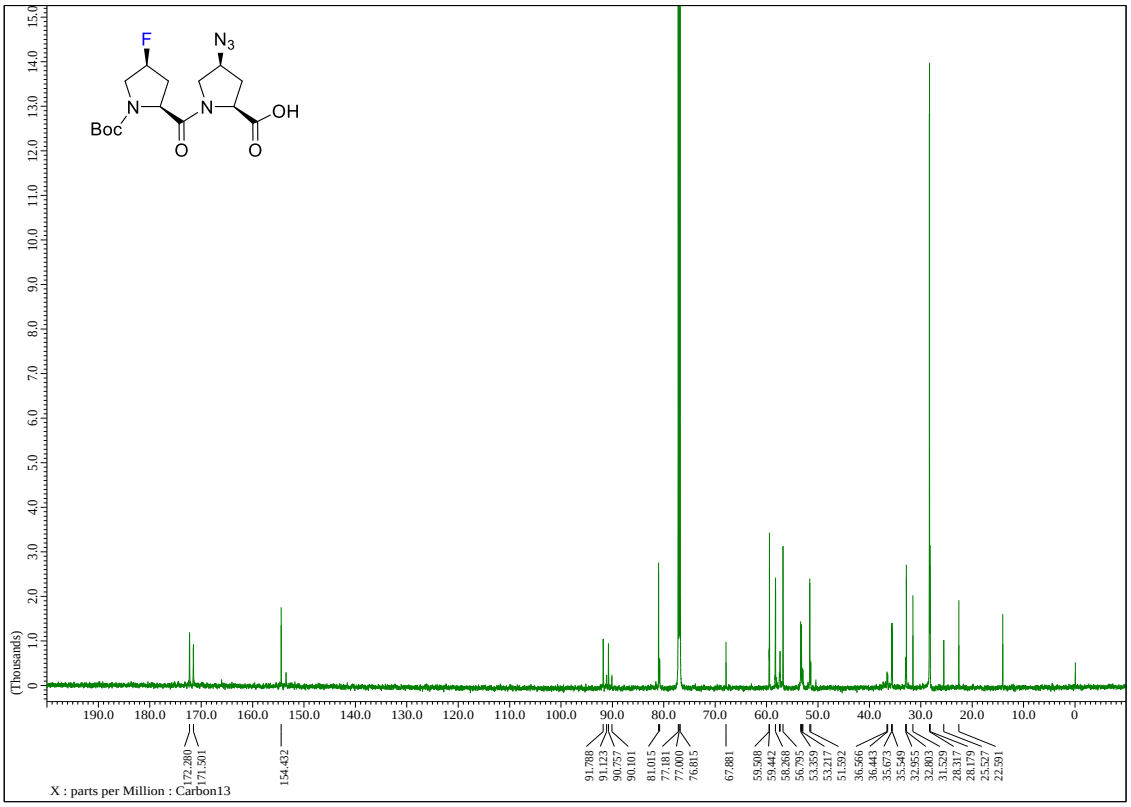
^{1}H NMR of **17**



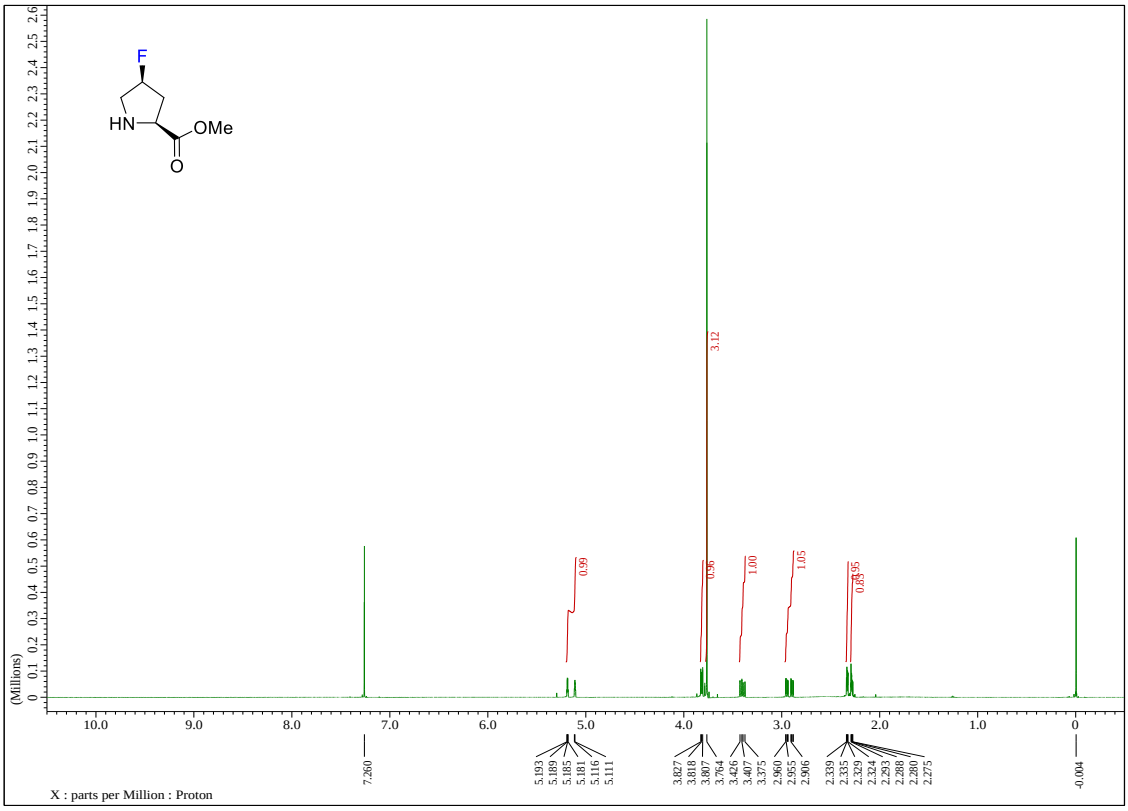
^{19}F NMR of **17**



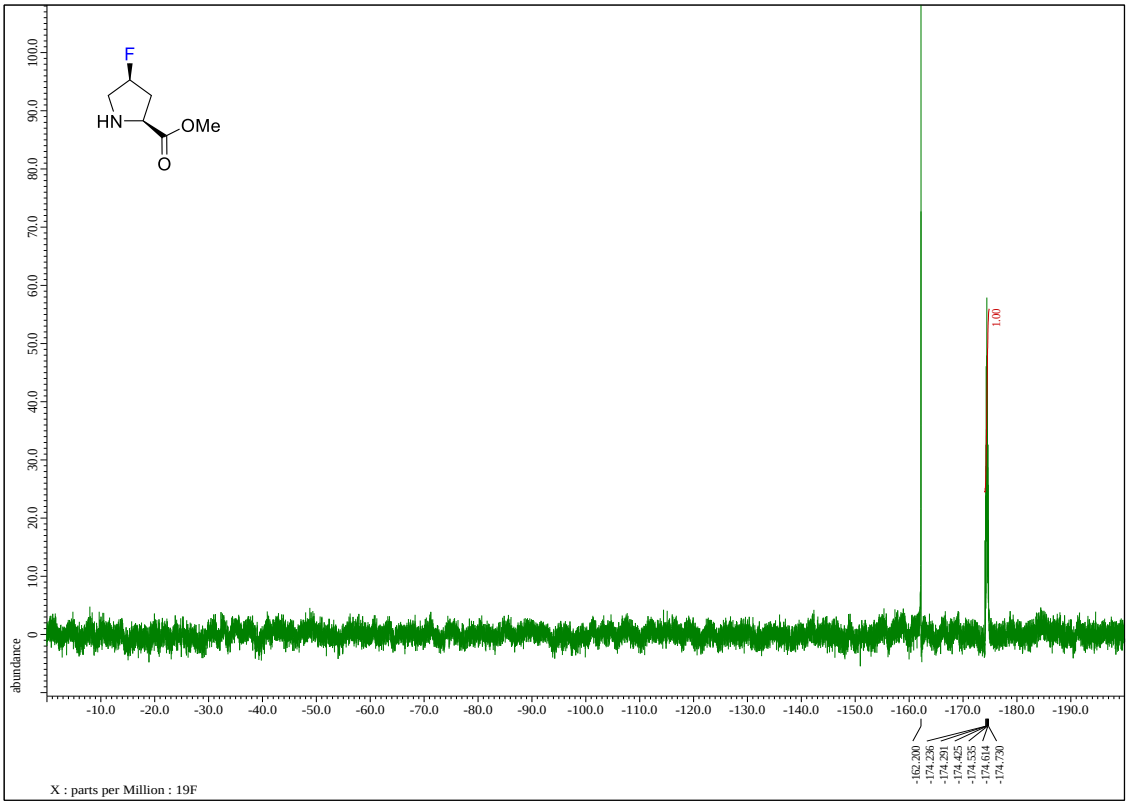
^{13}C NMR of **17**



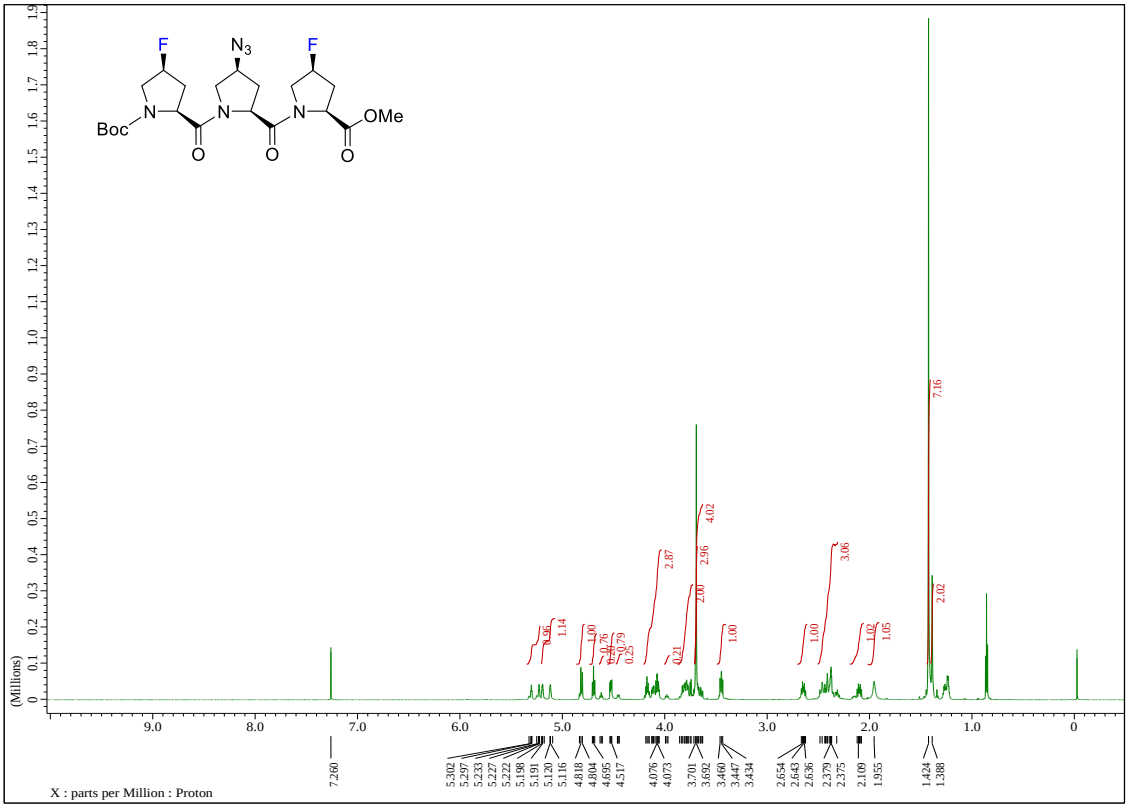
^{1}H NMR of **19**



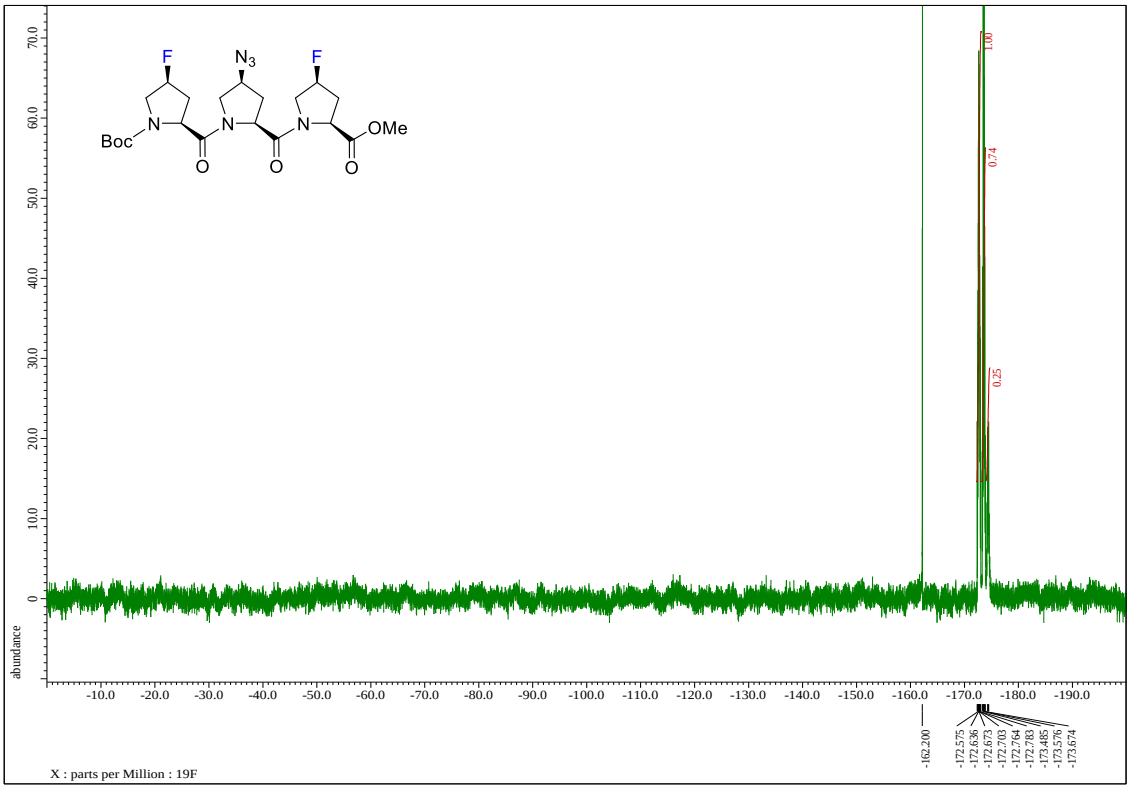
^{19}F NMR of **19**



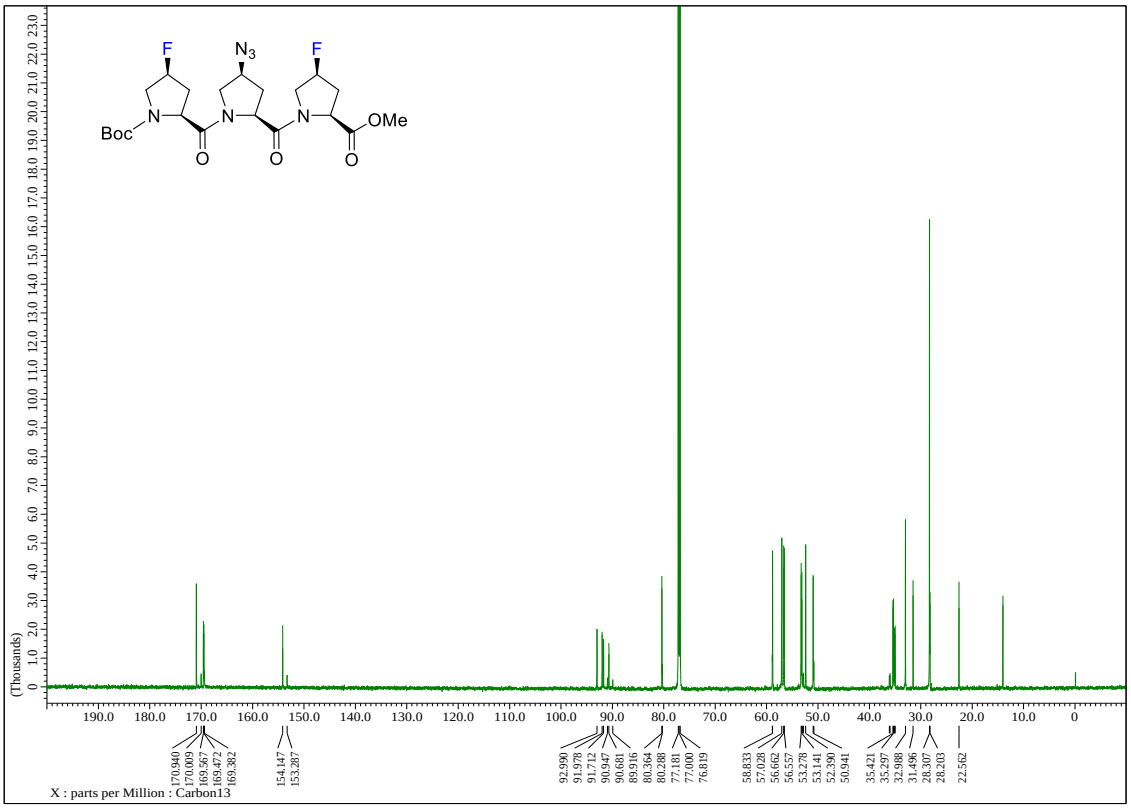
^{1}H NMR of **21**



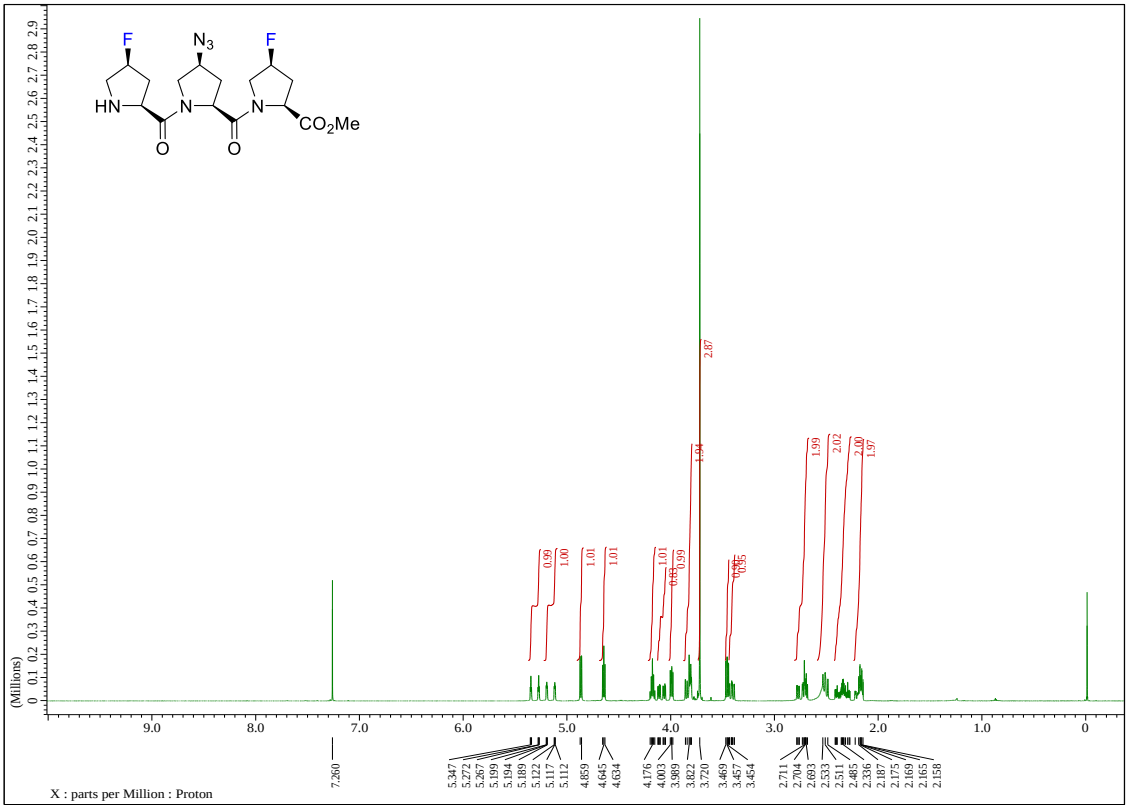
^{19}F NMR of **21**



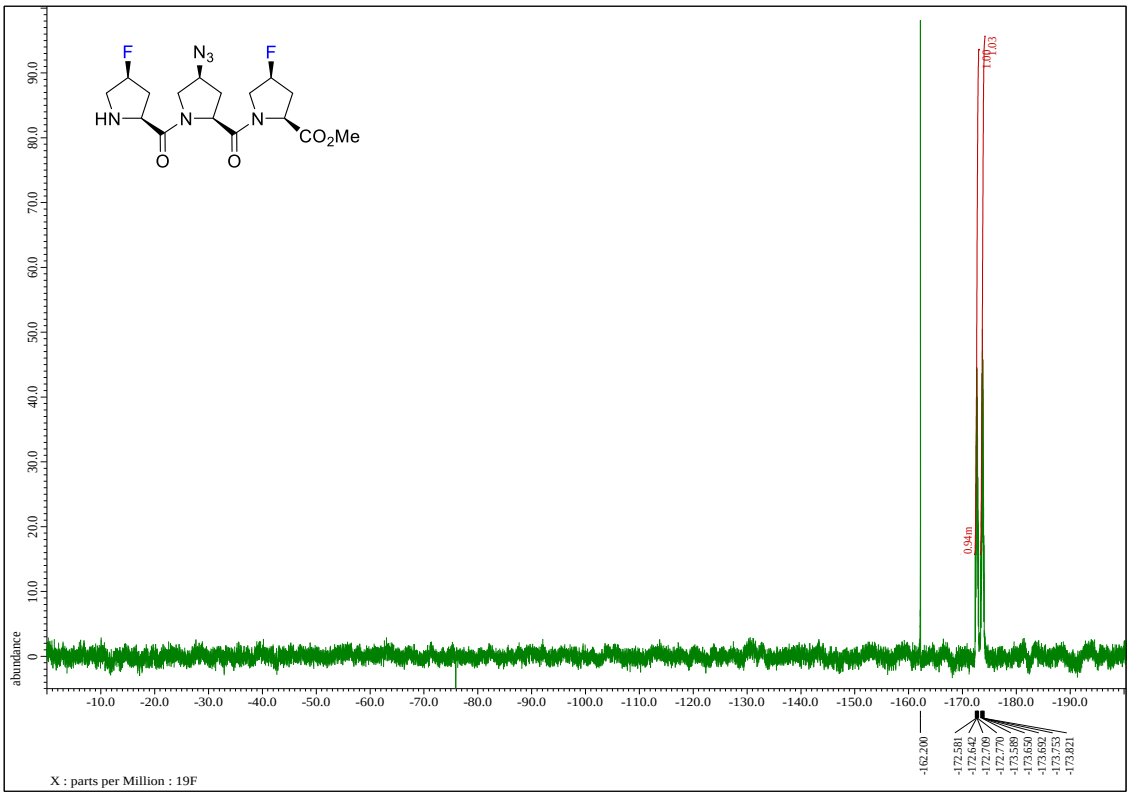
^{13}C NMR of **21**



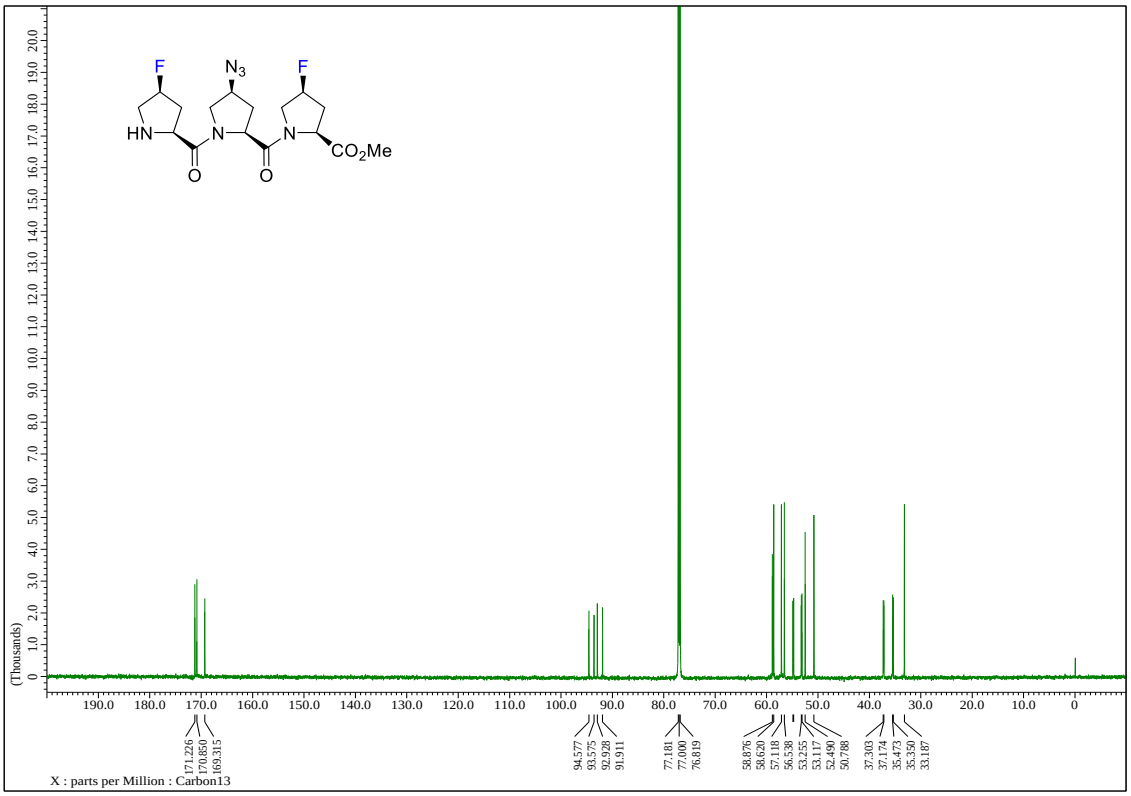
^{1}H NMR of **23**



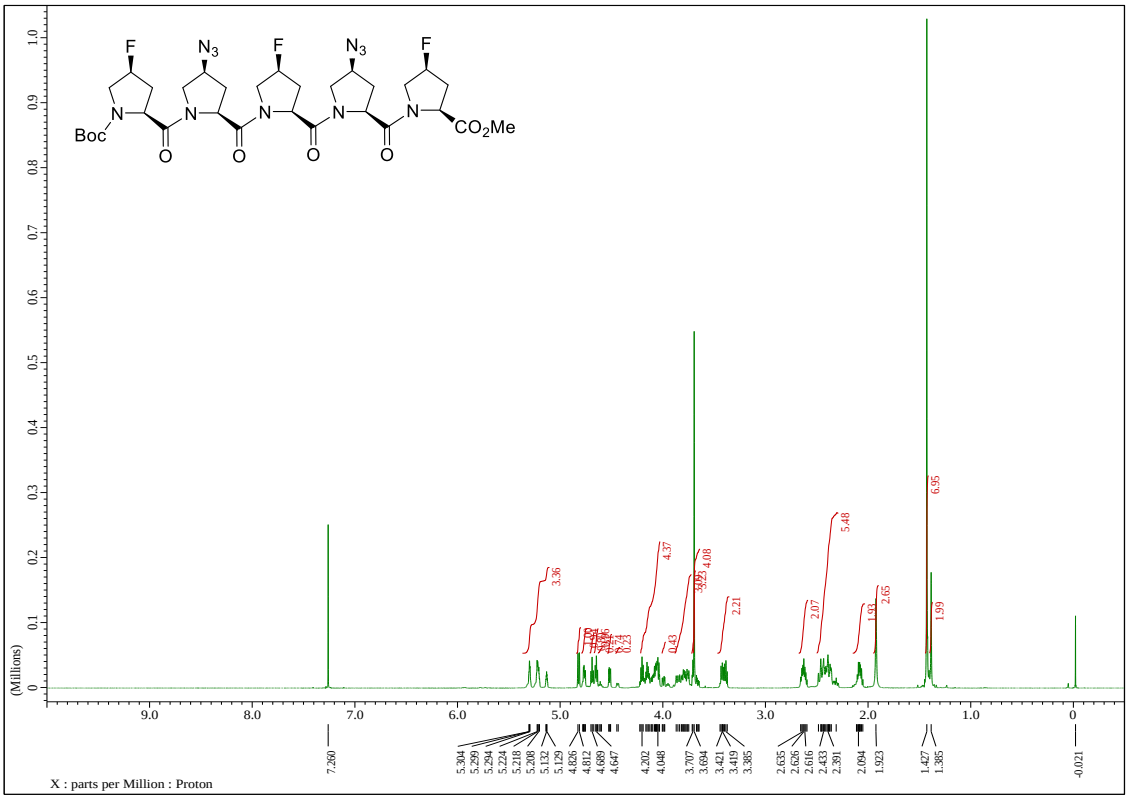
^{19}F NMR of **23**



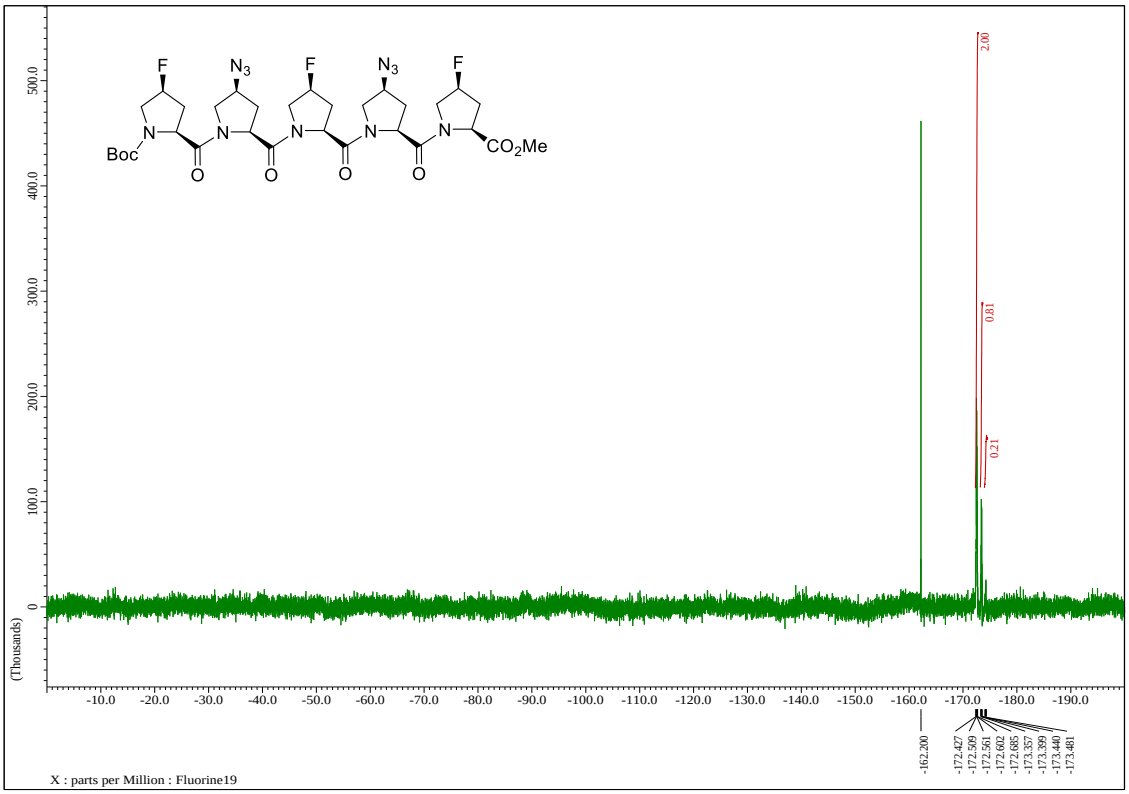
^{13}C NMR of **23**



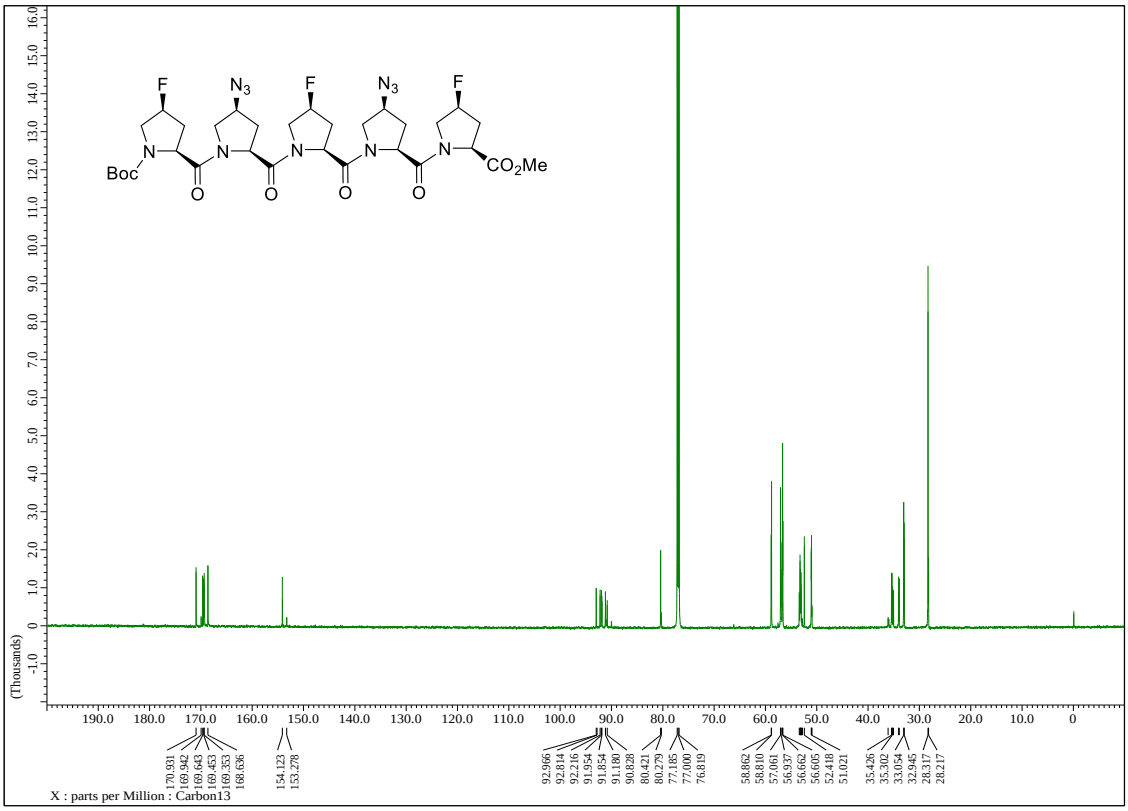
^{1}H NMR of **25**



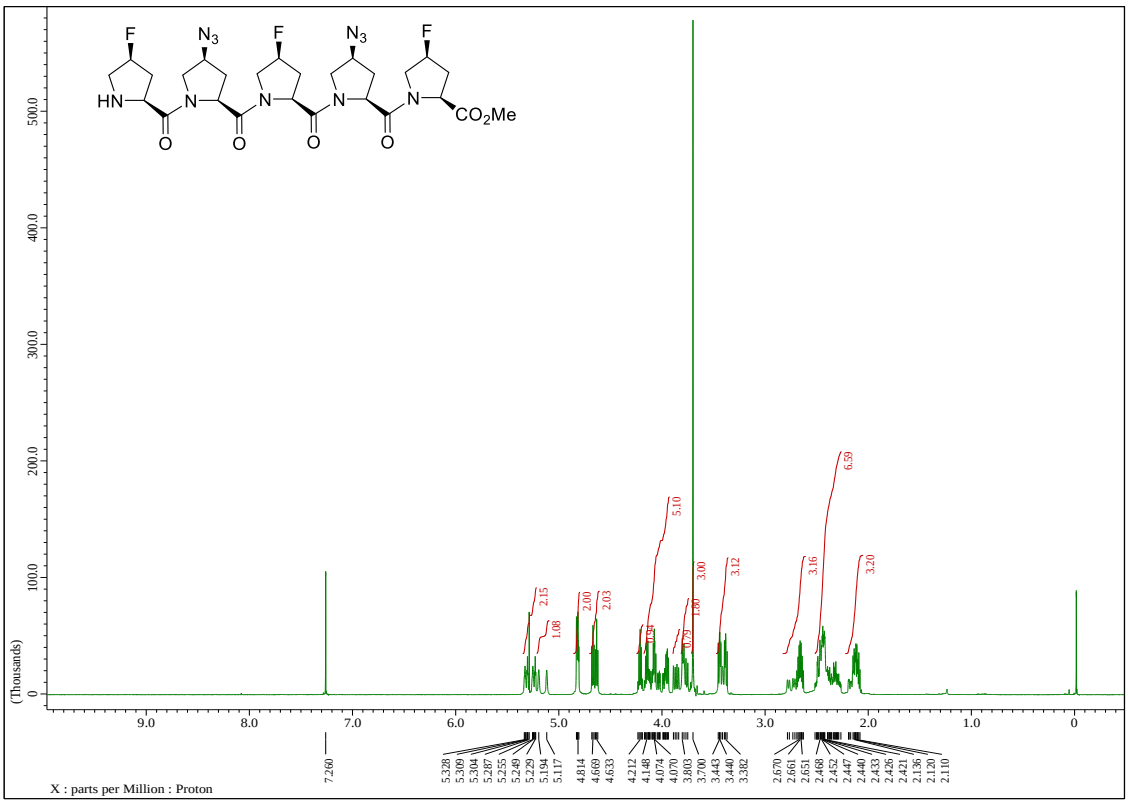
^{19}F NMR of **25**



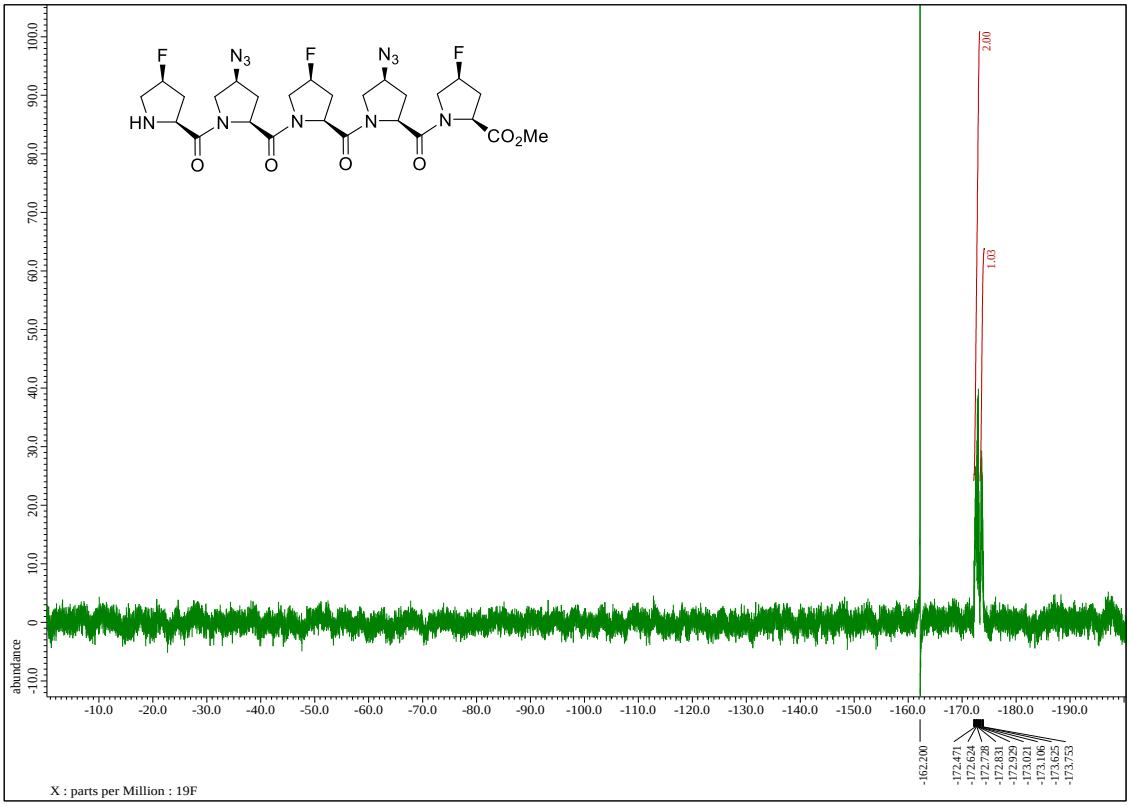
^{13}C NMR of **25**



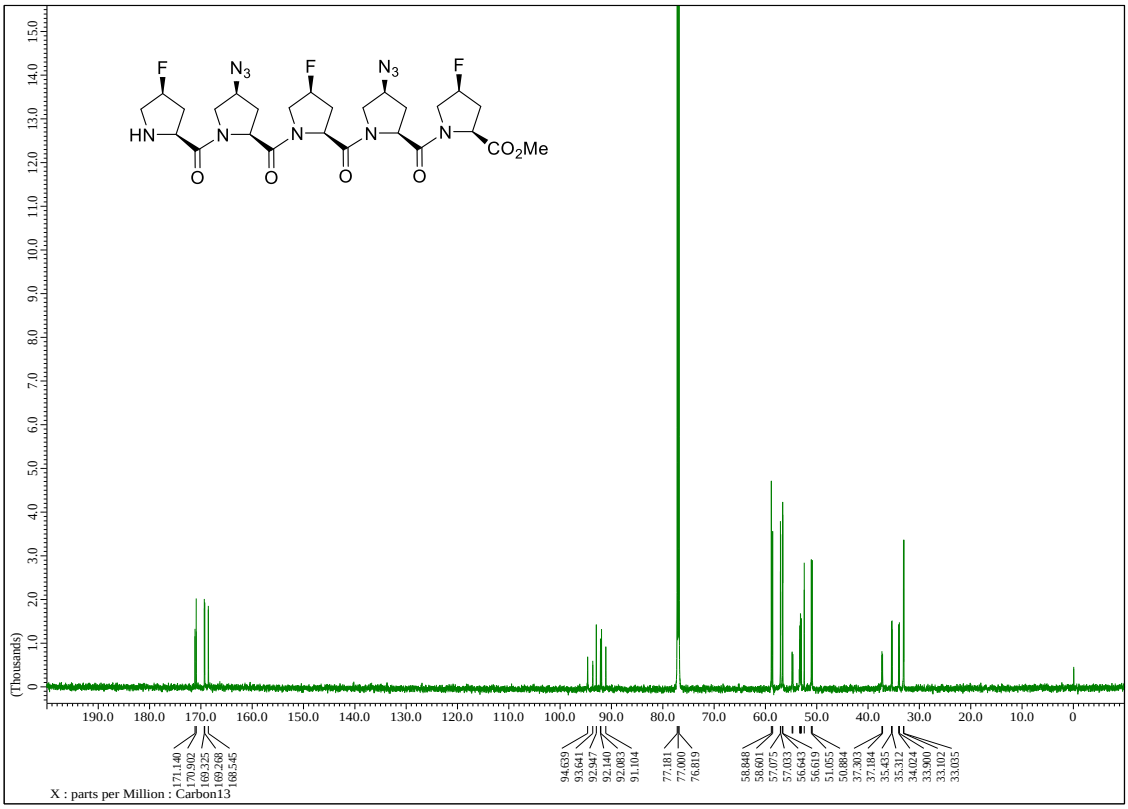
^{1}H NMR of **SI-4**



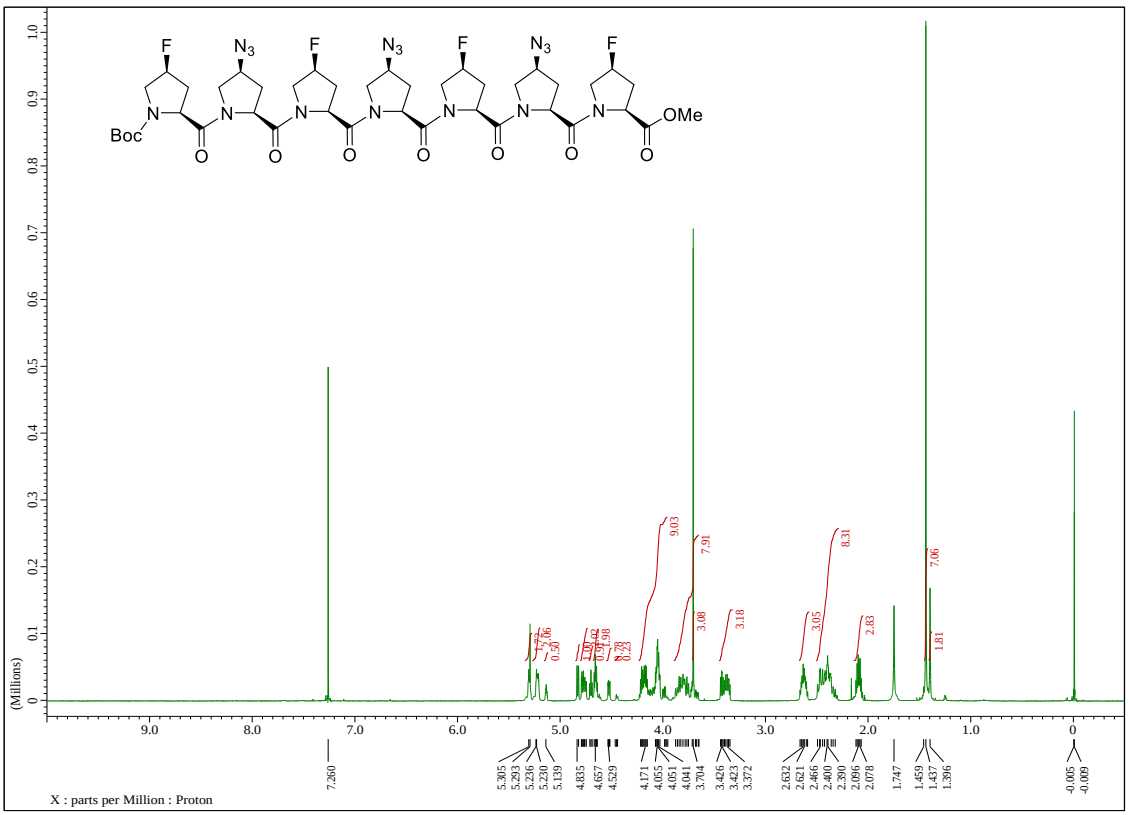
^{19}F NMR of **SI-4**



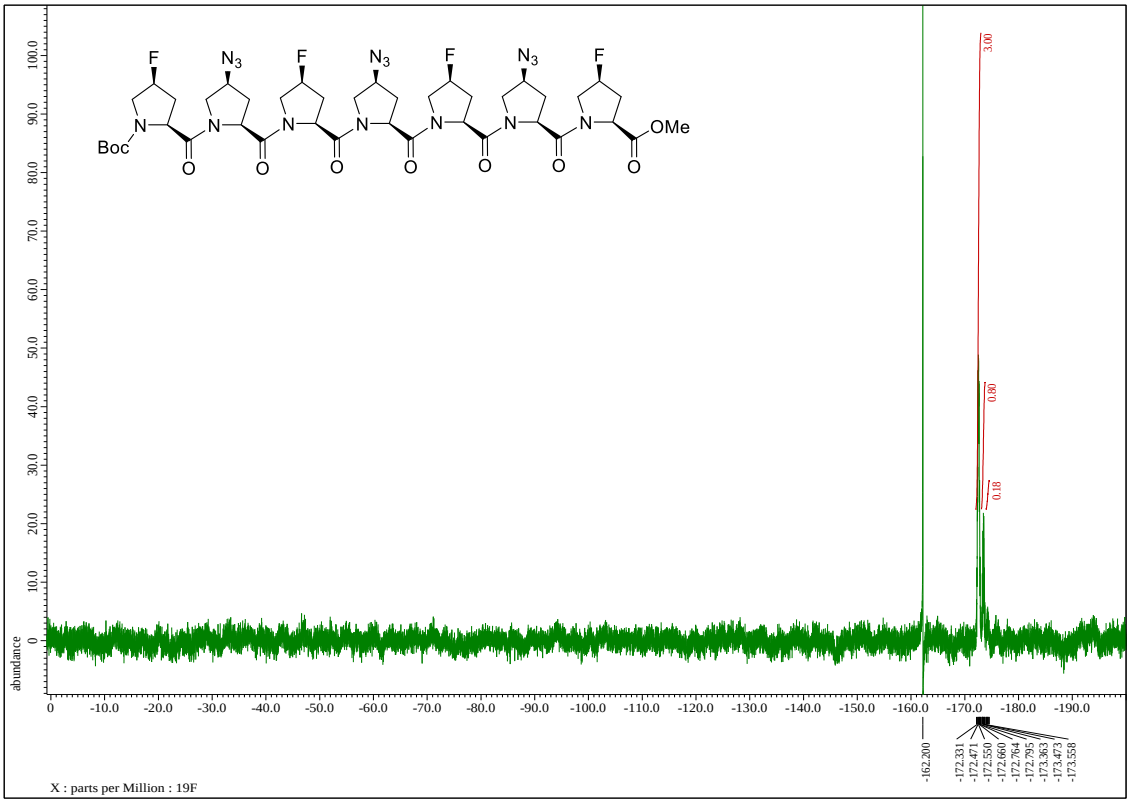
^{13}C NMR of **SI-4**



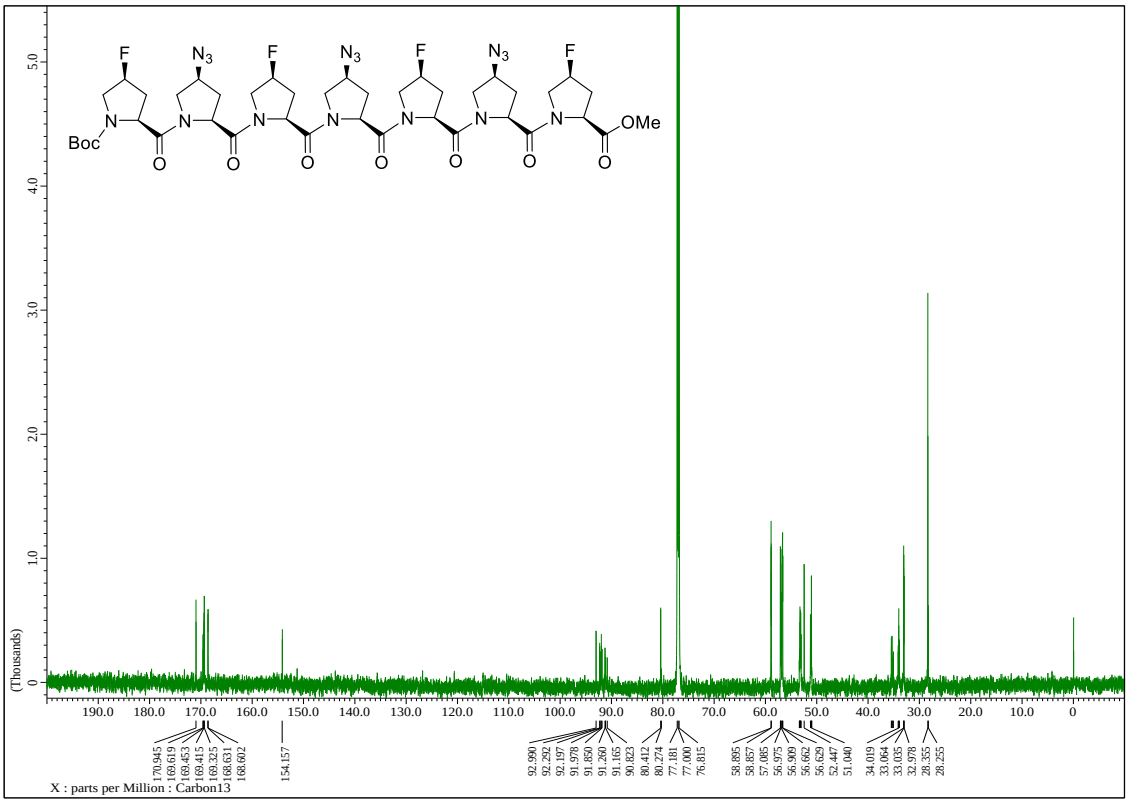
^{1}H NMR of **SI-5**



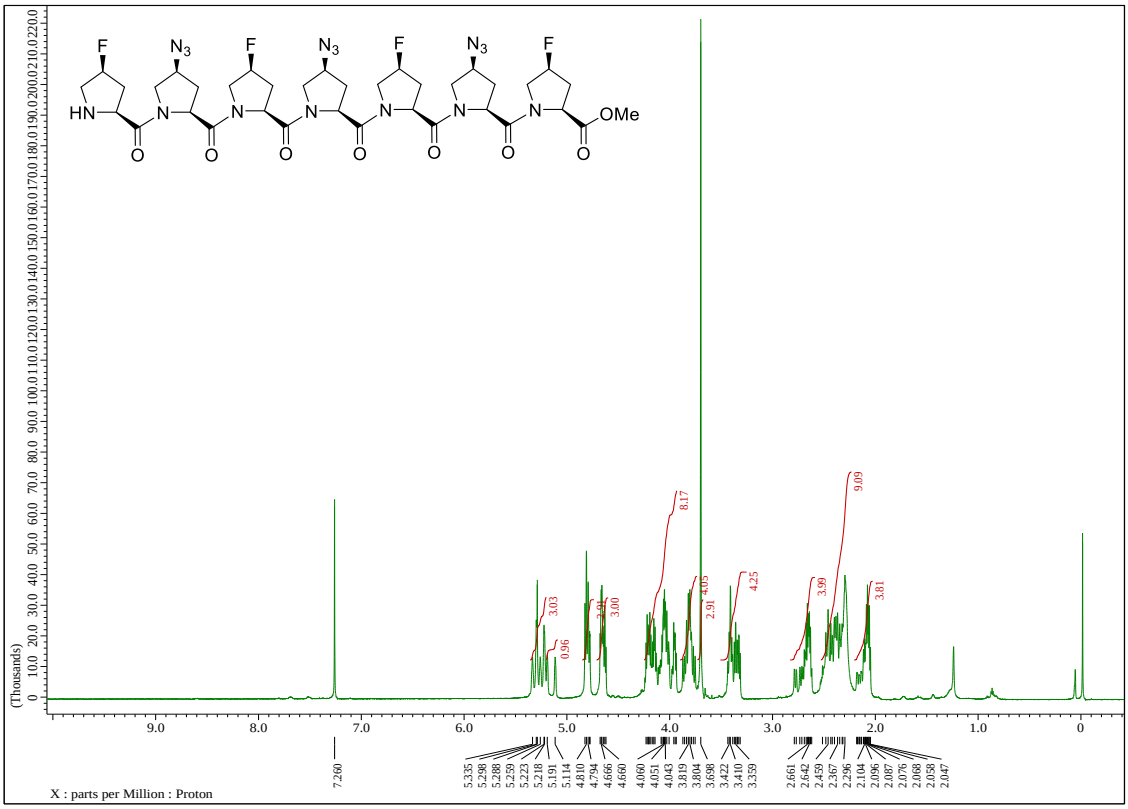
^{19}F NMR of **SI-5**



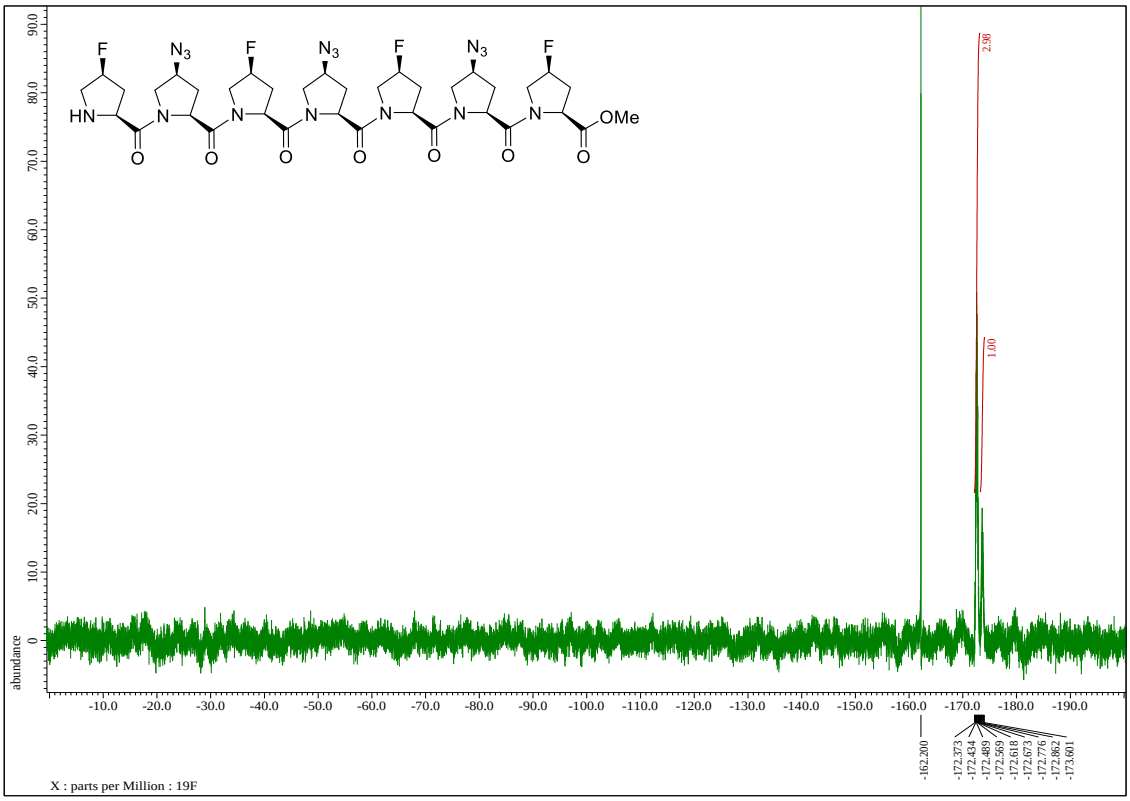
^{13}C NMR of **SI-5**



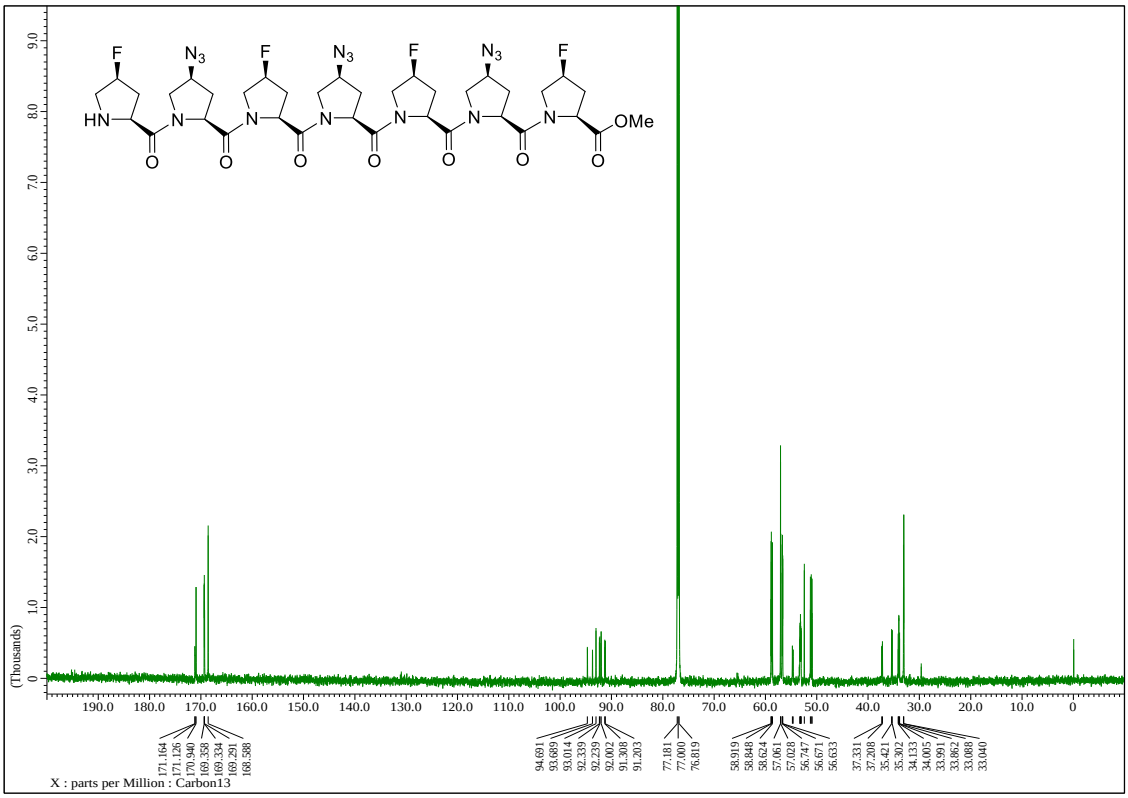
^{1}H NMR of **SI-6**



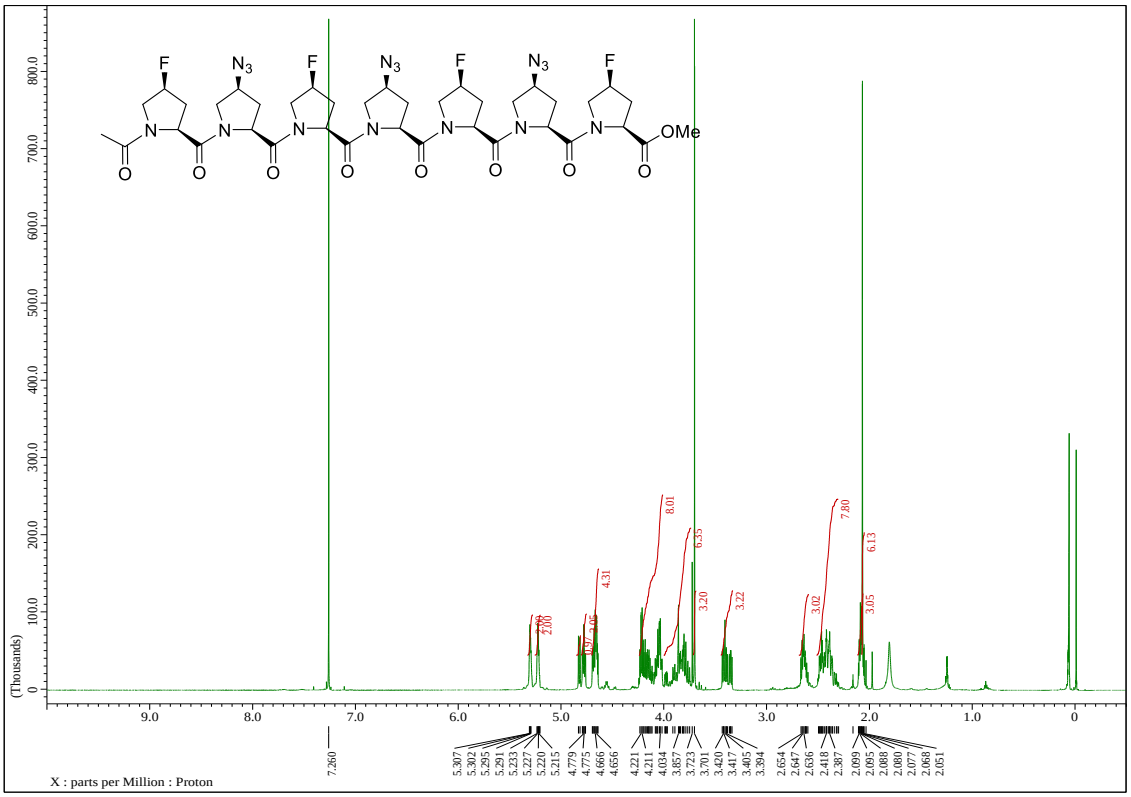
^{19}F NMR of **SI-6**



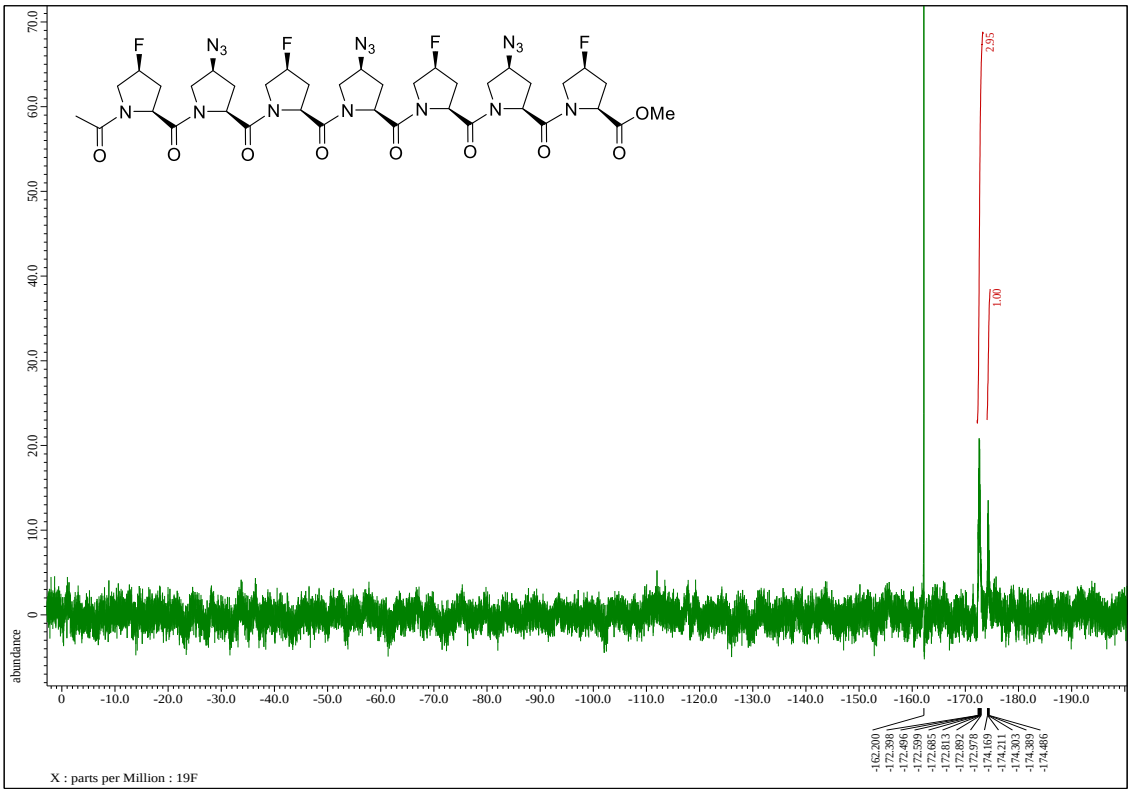
^{13}C NMR of **SI-6**



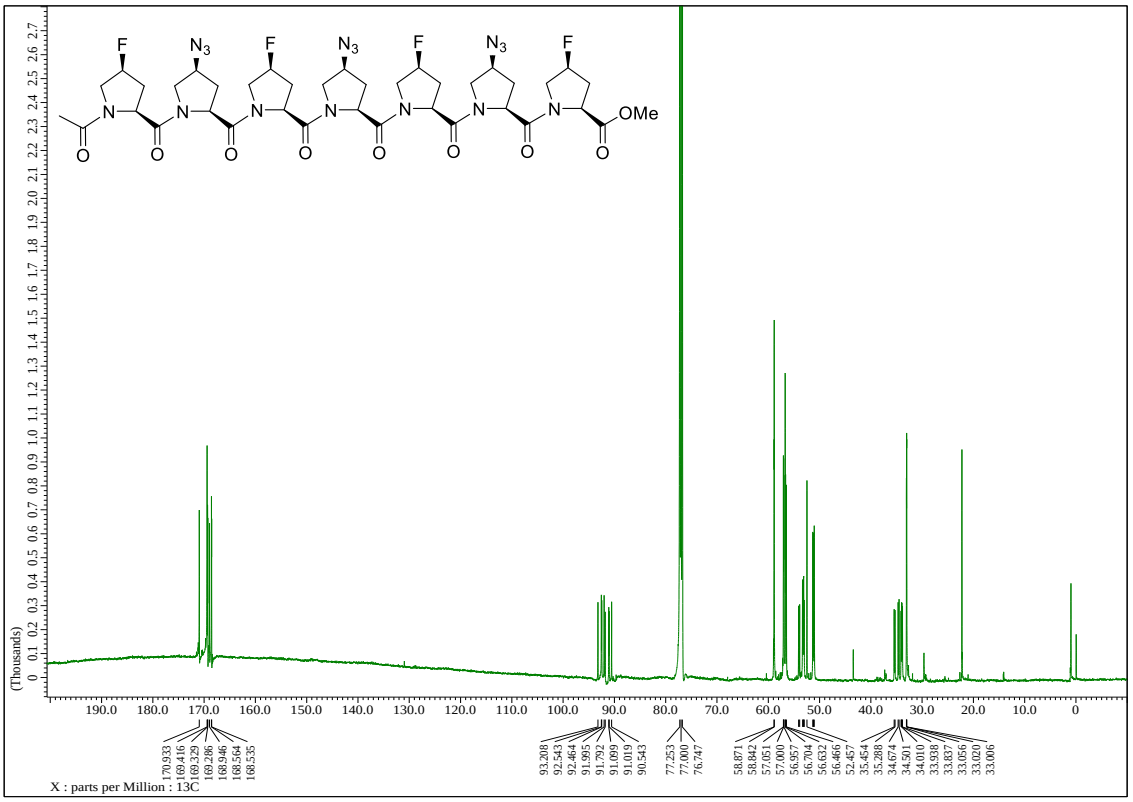
^{1}H NMR of **27**



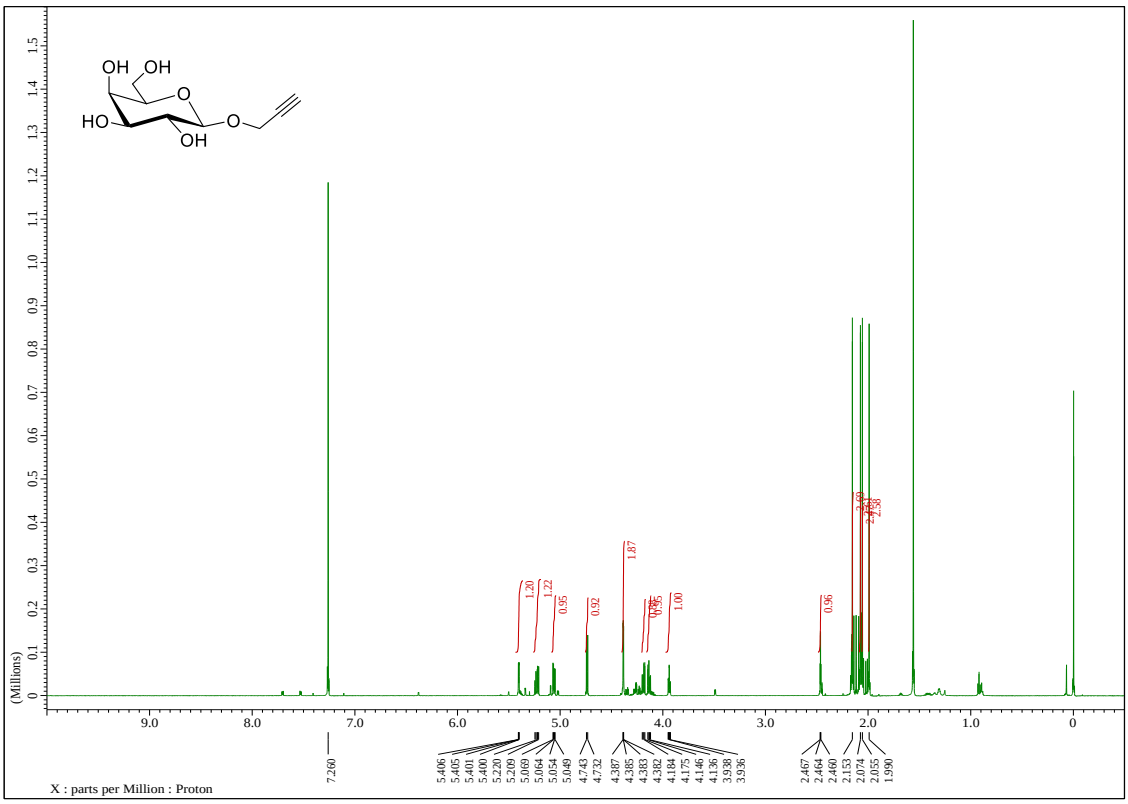
^{19}F NMR of **27**



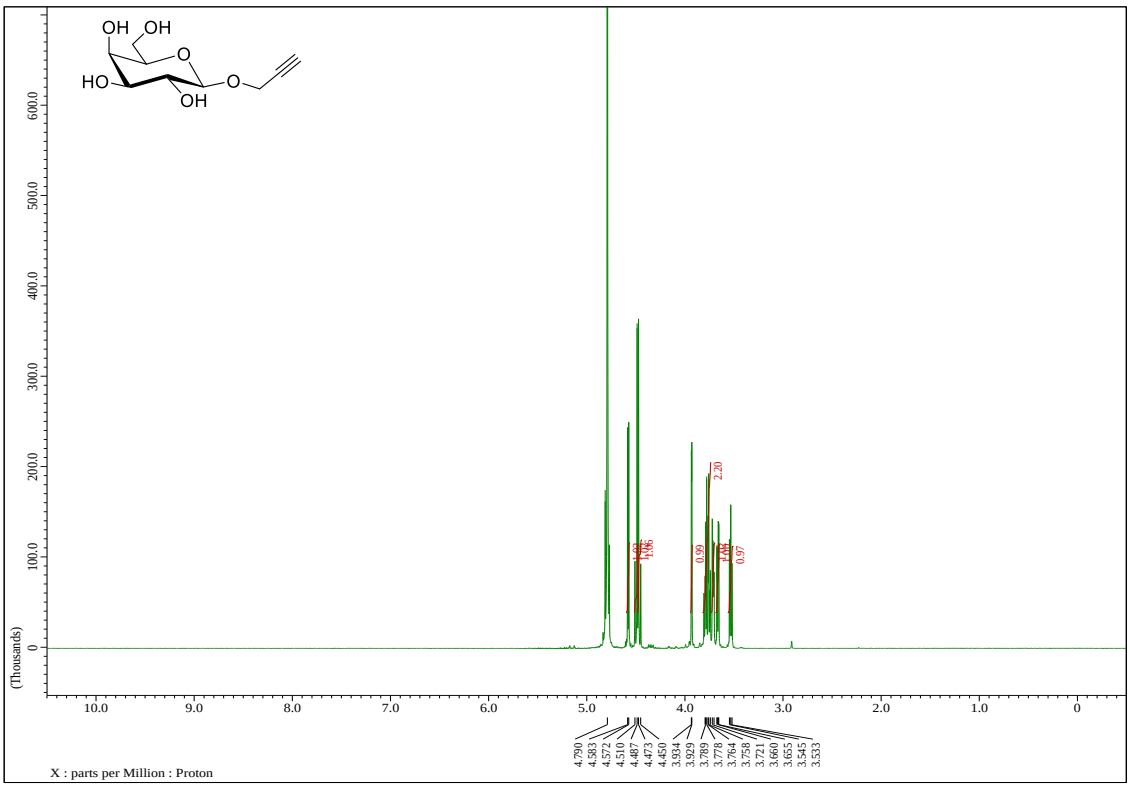
^{13}C NMR of **27**



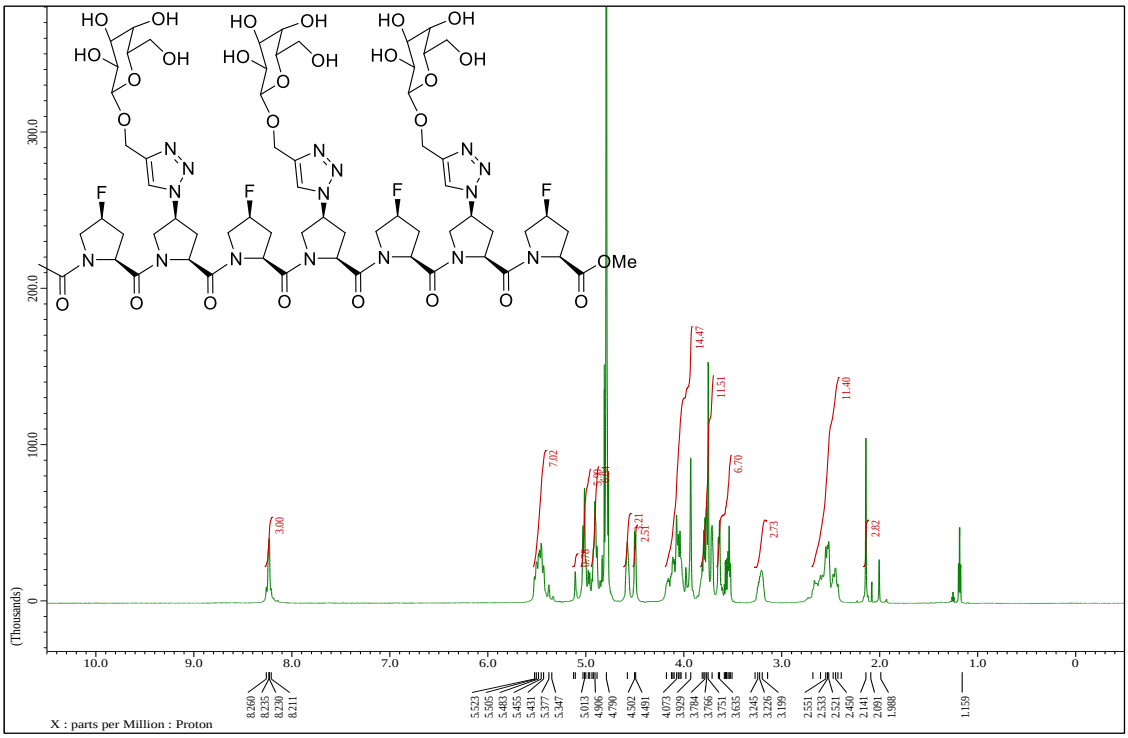
^{1}H NMR of **29**



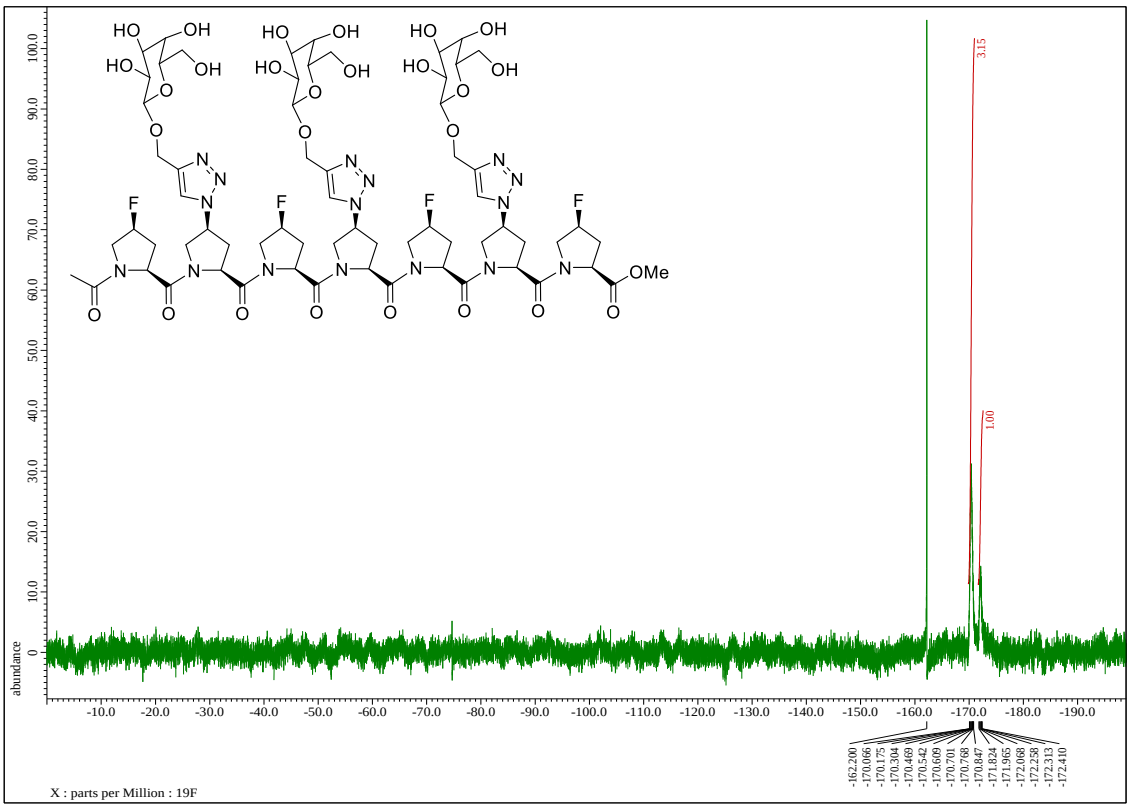
^{13}C NMR of **29**



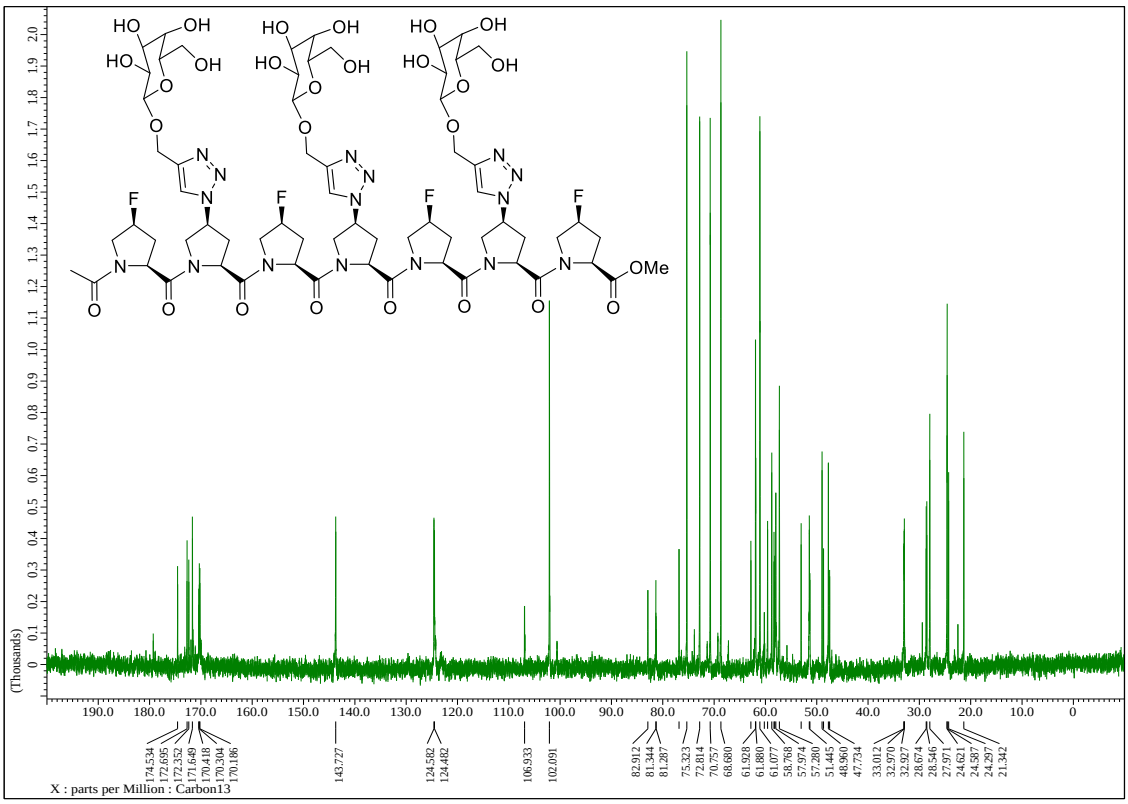
^{1}H NMR of **12a**



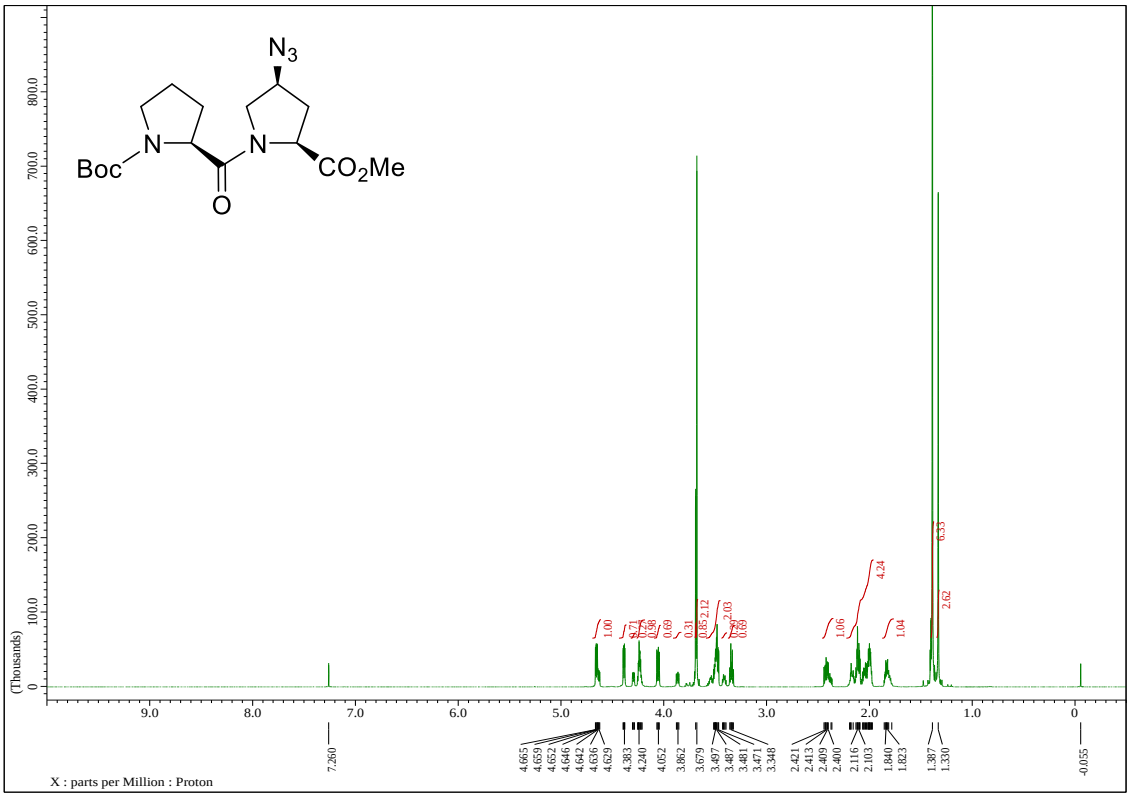
^{19}F NMR of **12a**



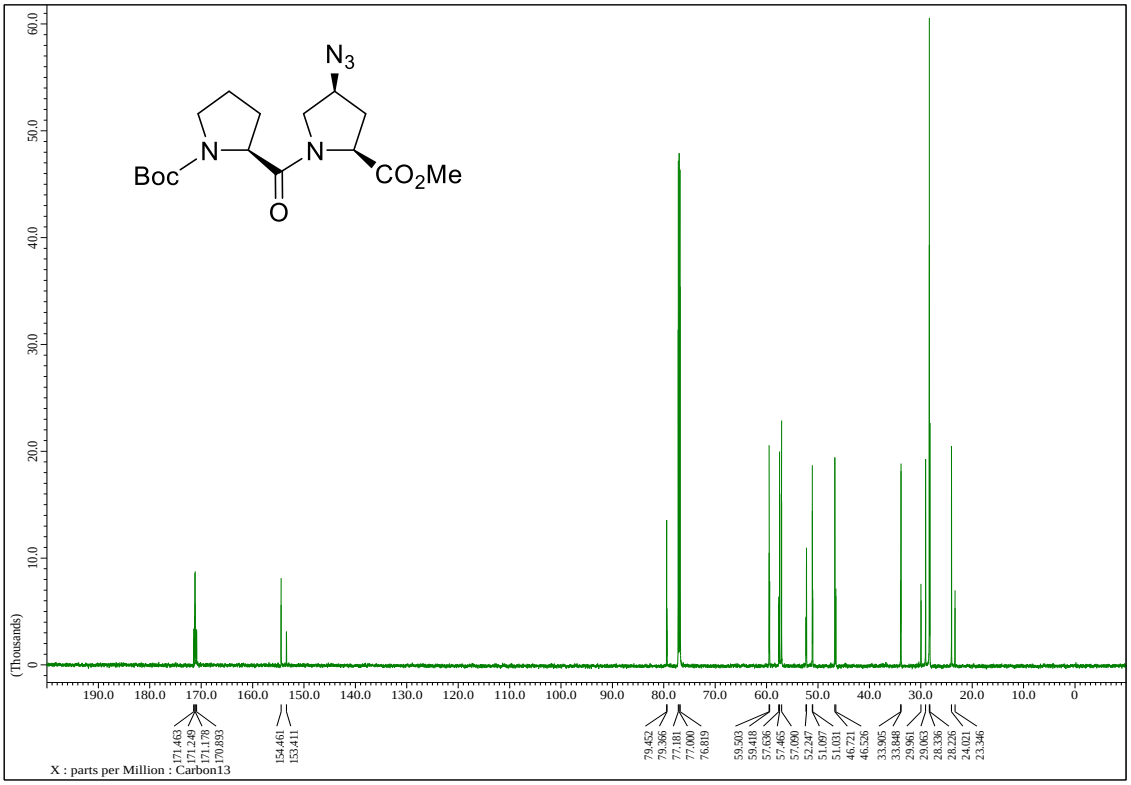
^{13}C NMR of **12a**



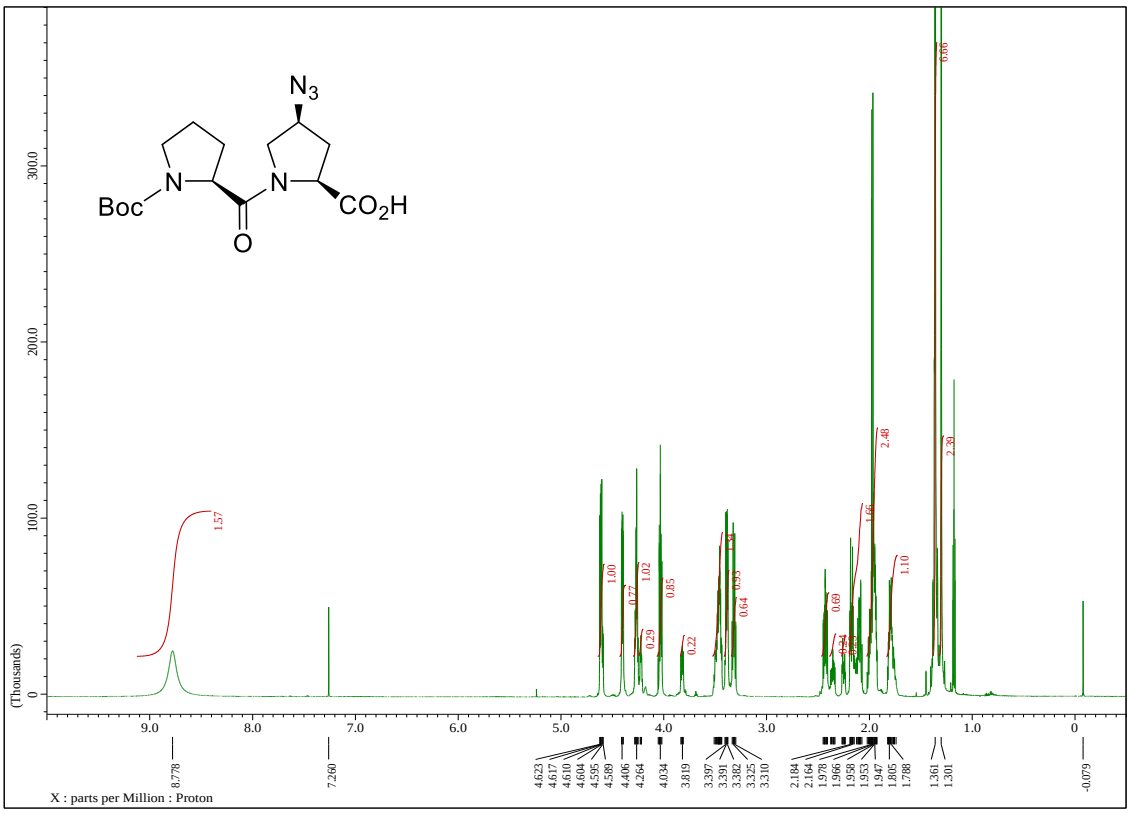
^{1}H NMR of **SI-8**



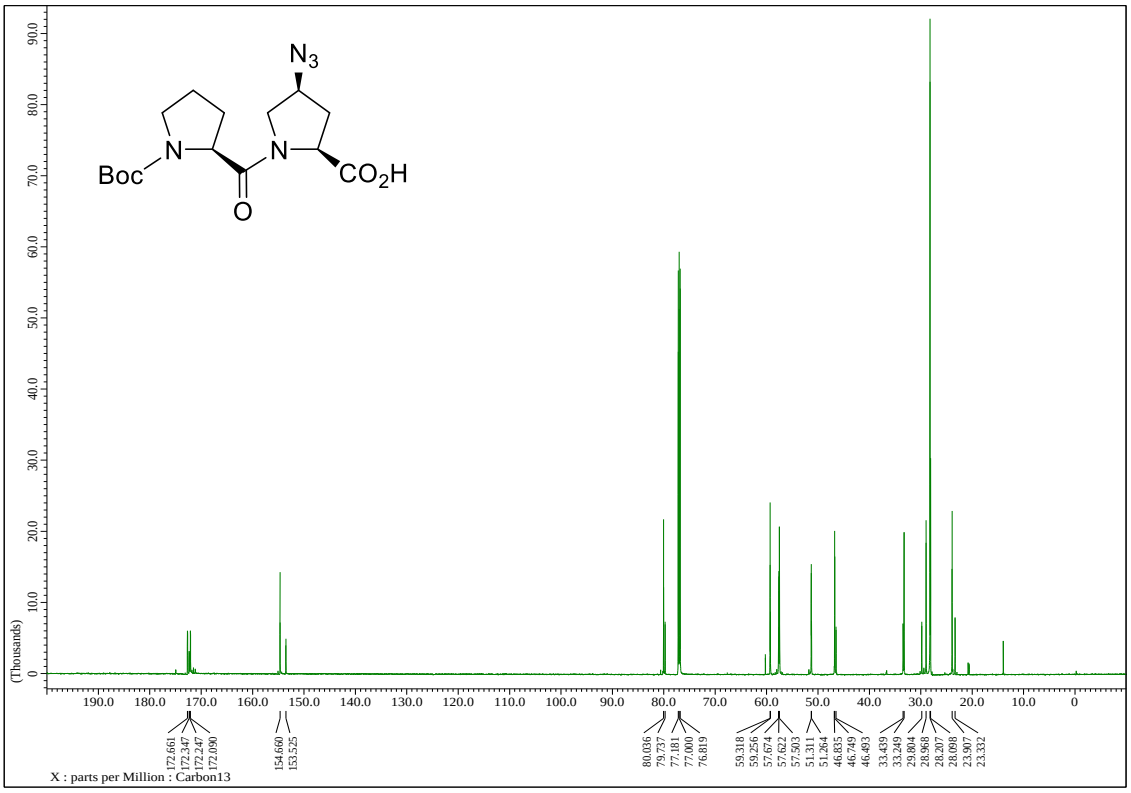
^{13}C NMR of **SI-8**



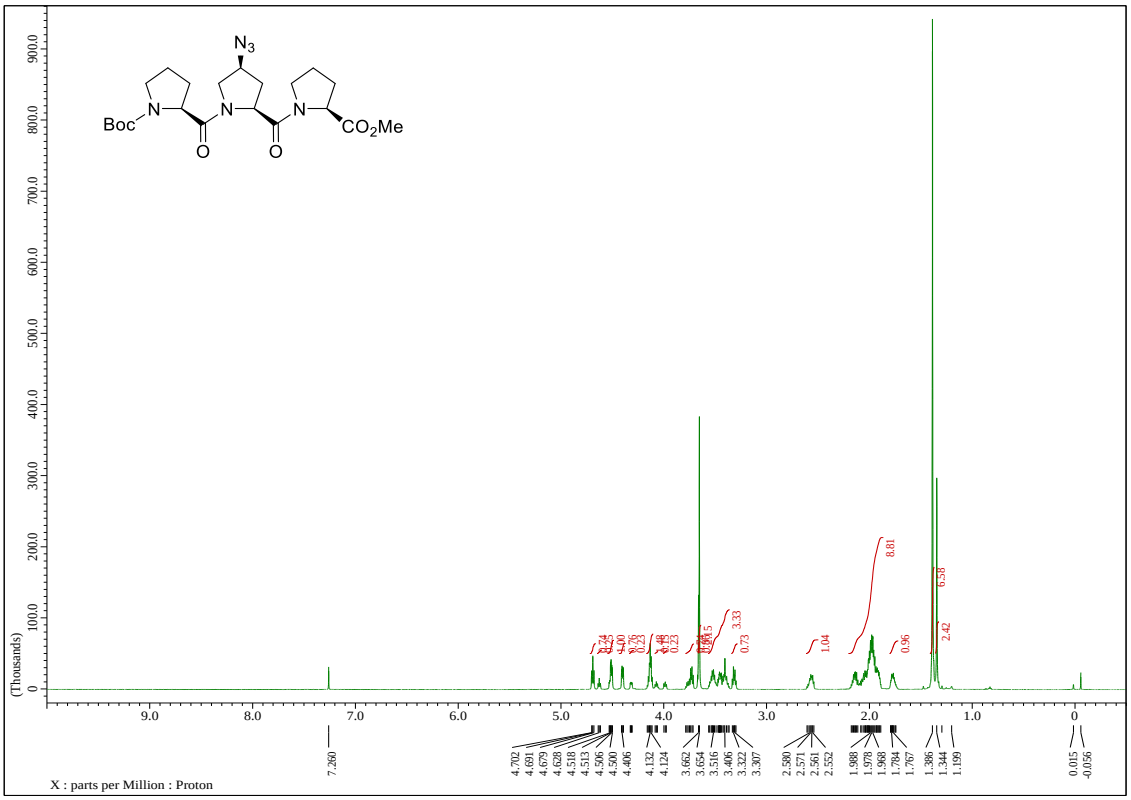
^{1}H NMR of **18**



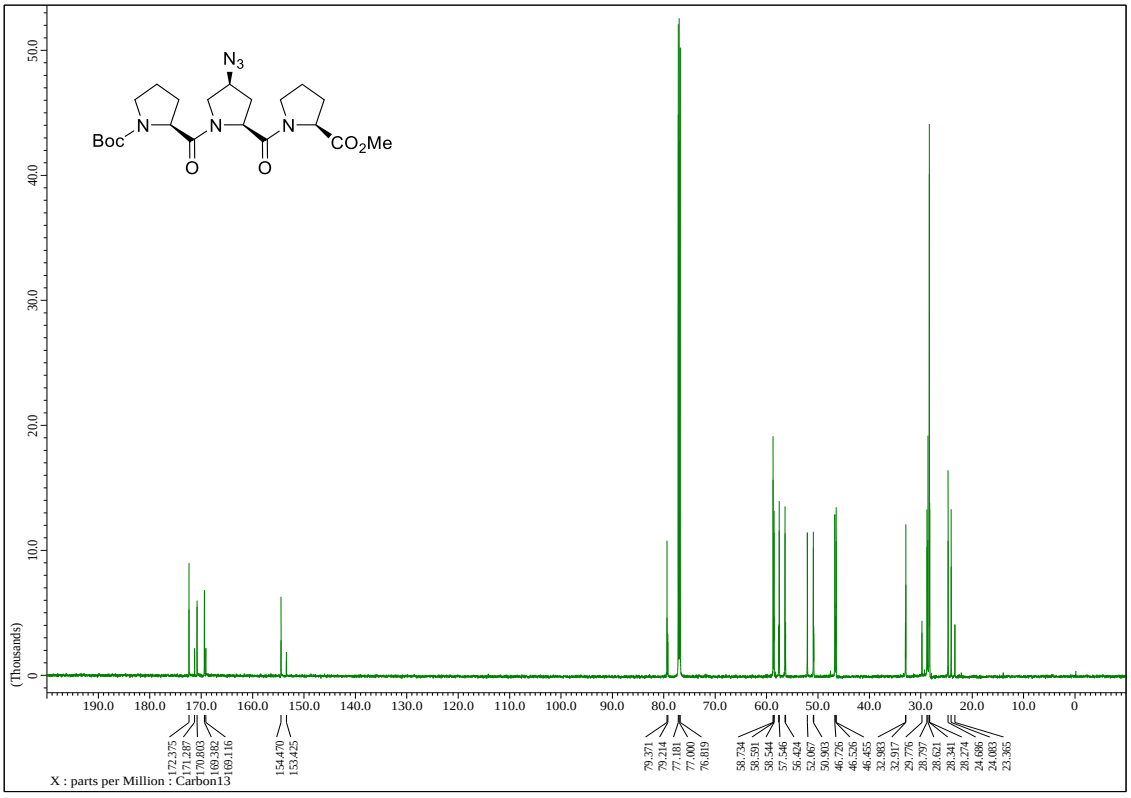
^{13}C NMR of **18**



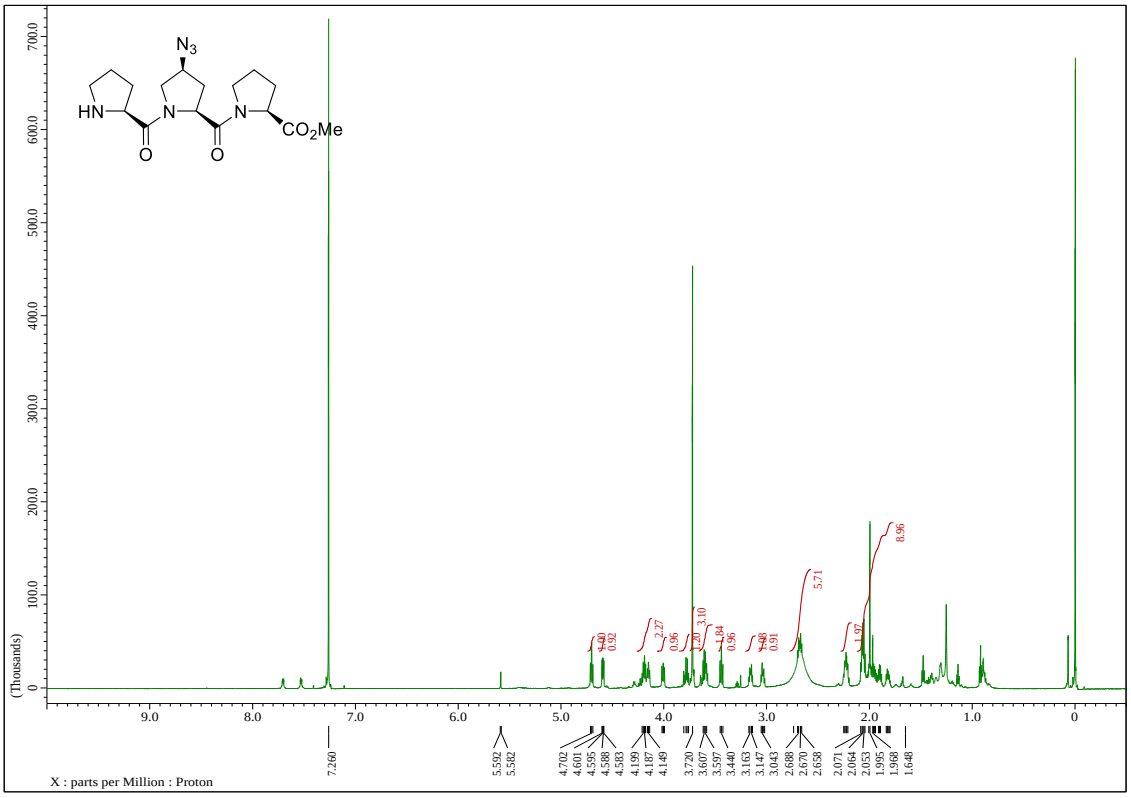
^{1}H NMR of **22**



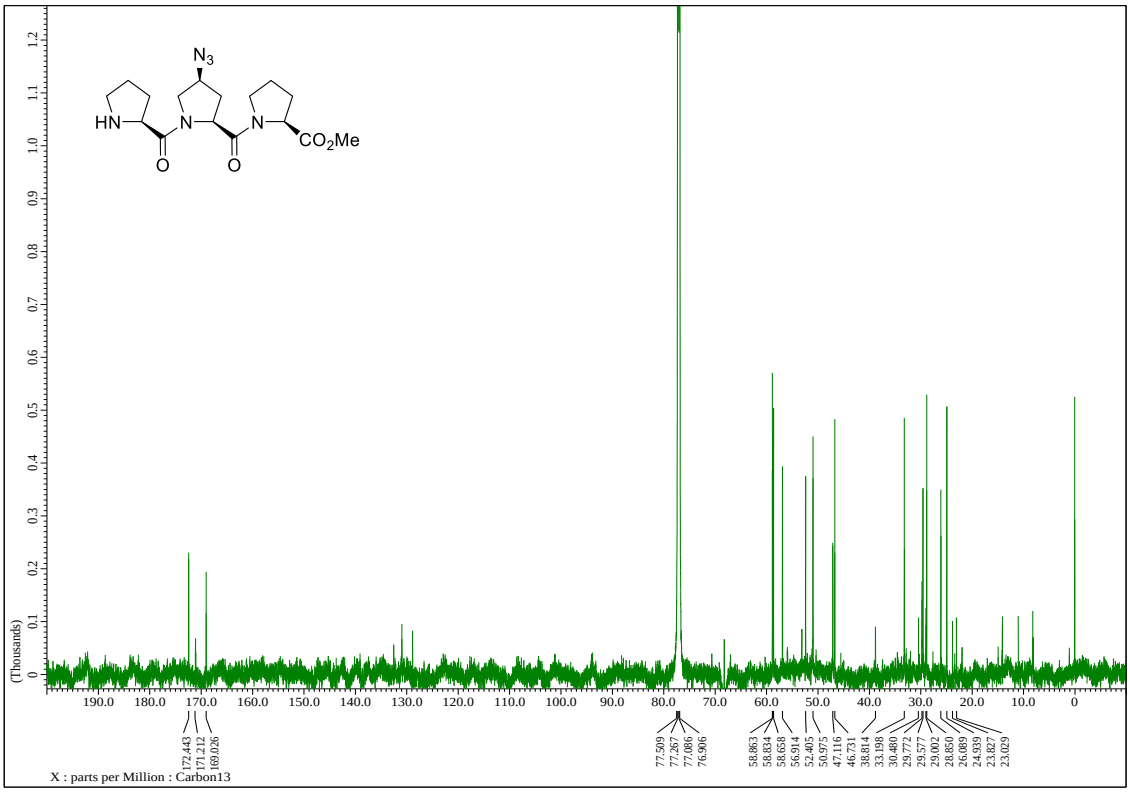
^{13}C NMR of **22**



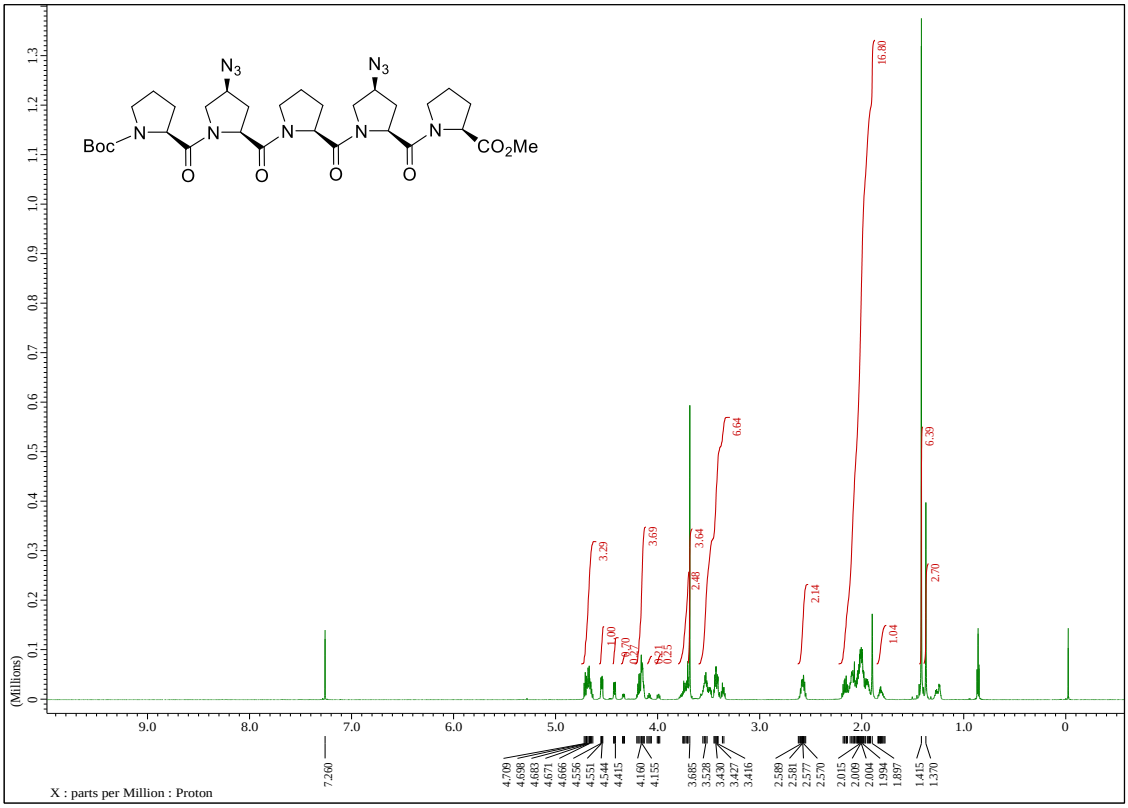
^{1}H NMR of **24**



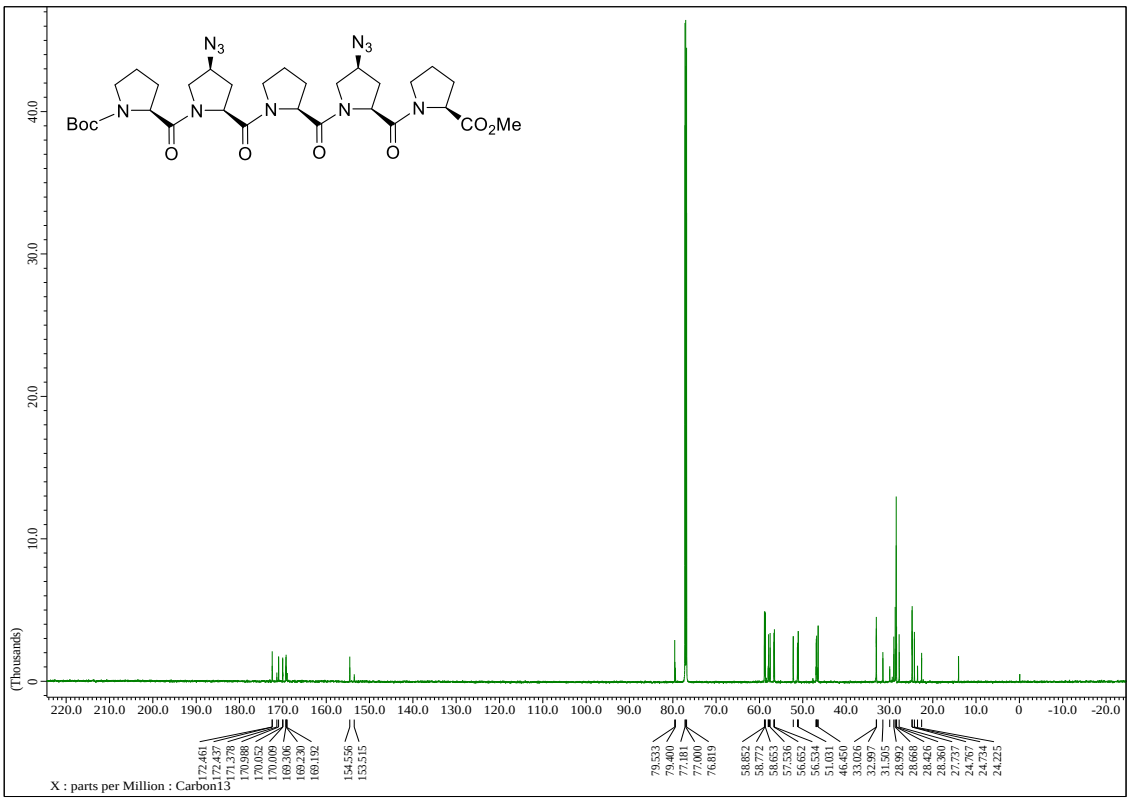
^{13}C NMR of **24**



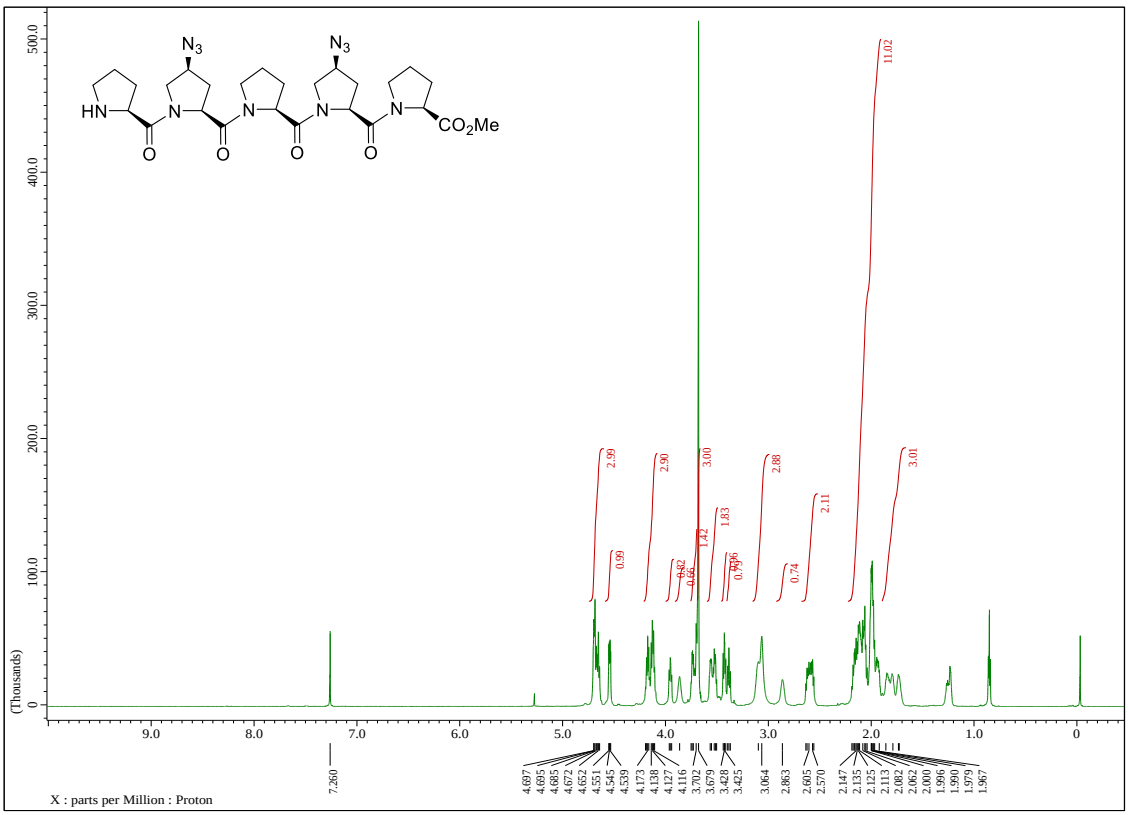
^{1}H NMR of **26**



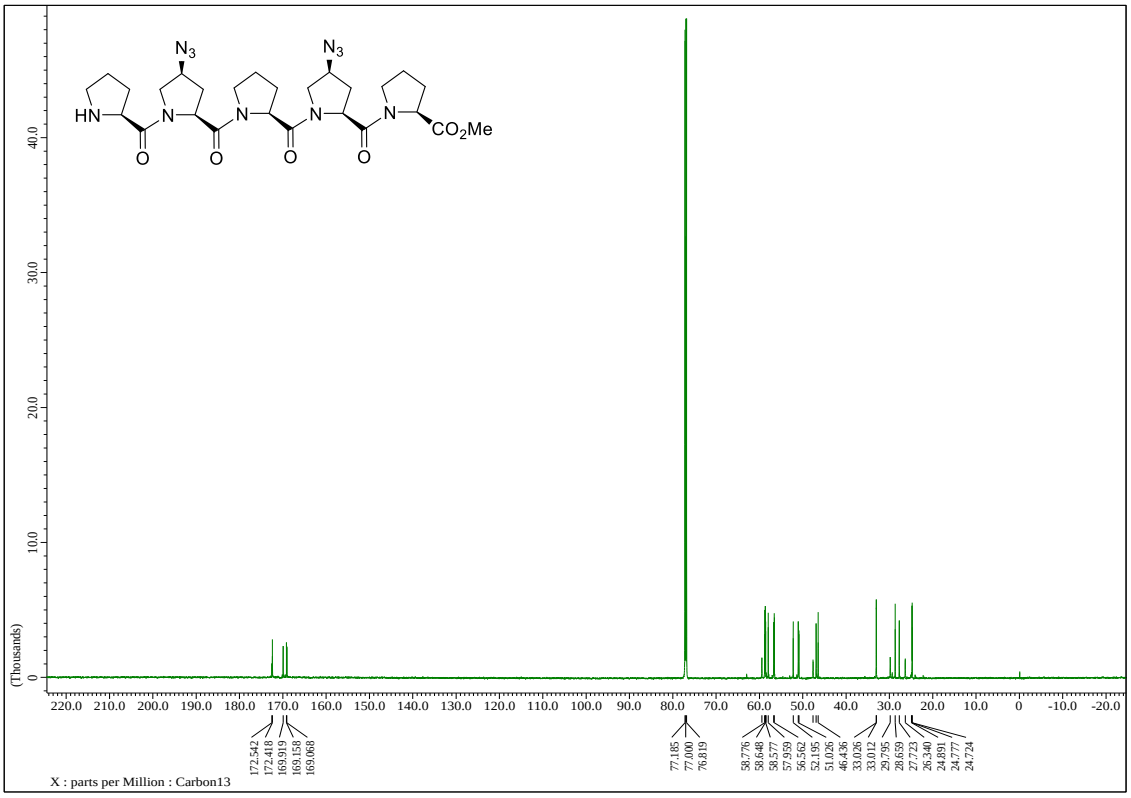
^{13}C NMR of **26**



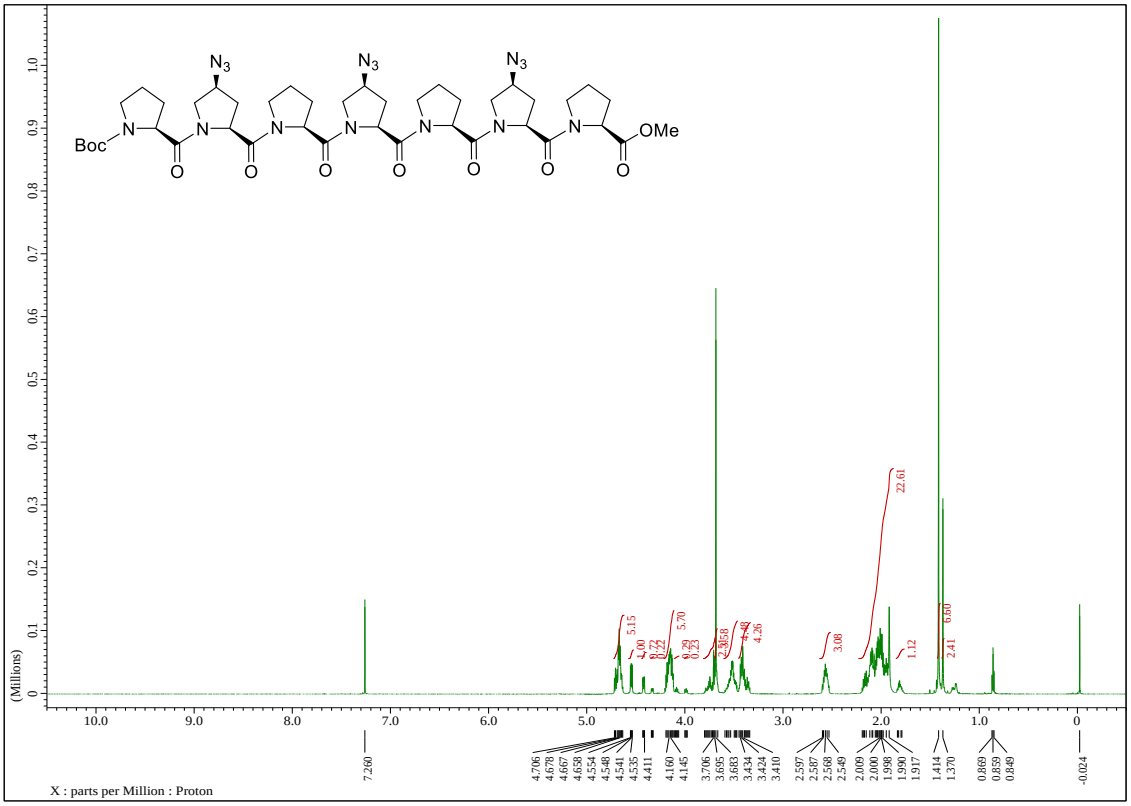
^{1}H NMR of **SI-10**



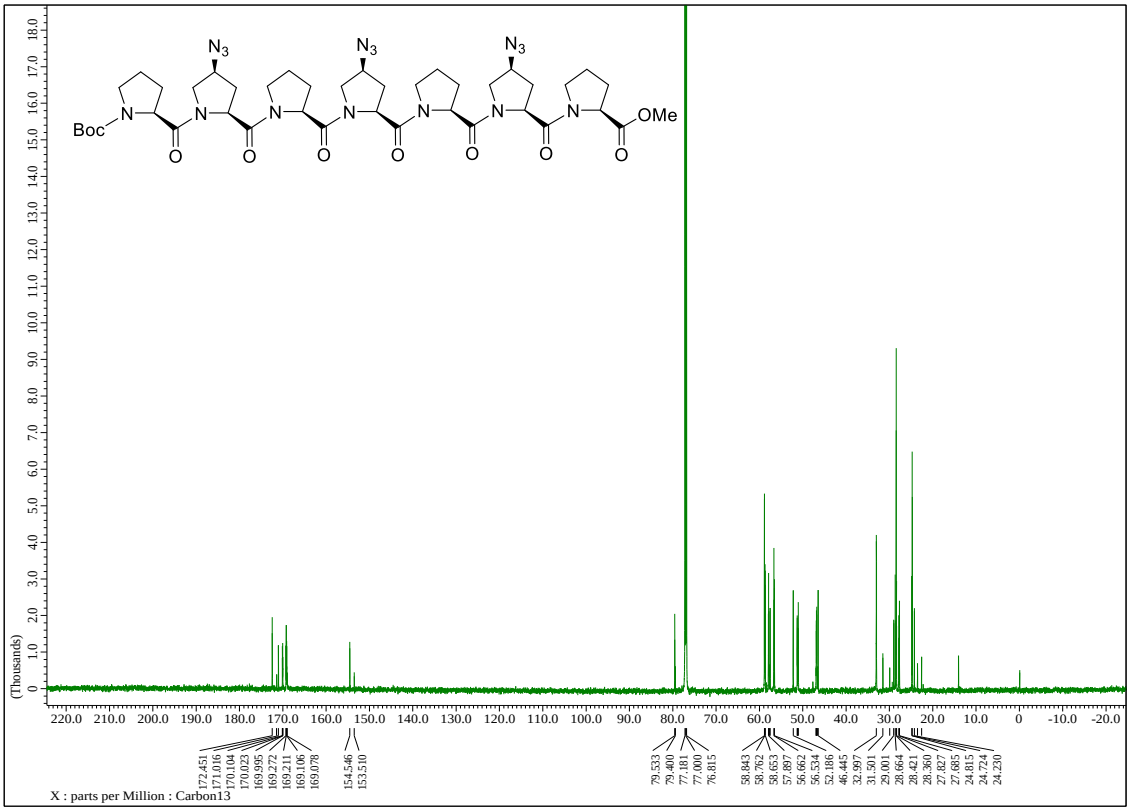
^{13}C NMR of **SI-10**



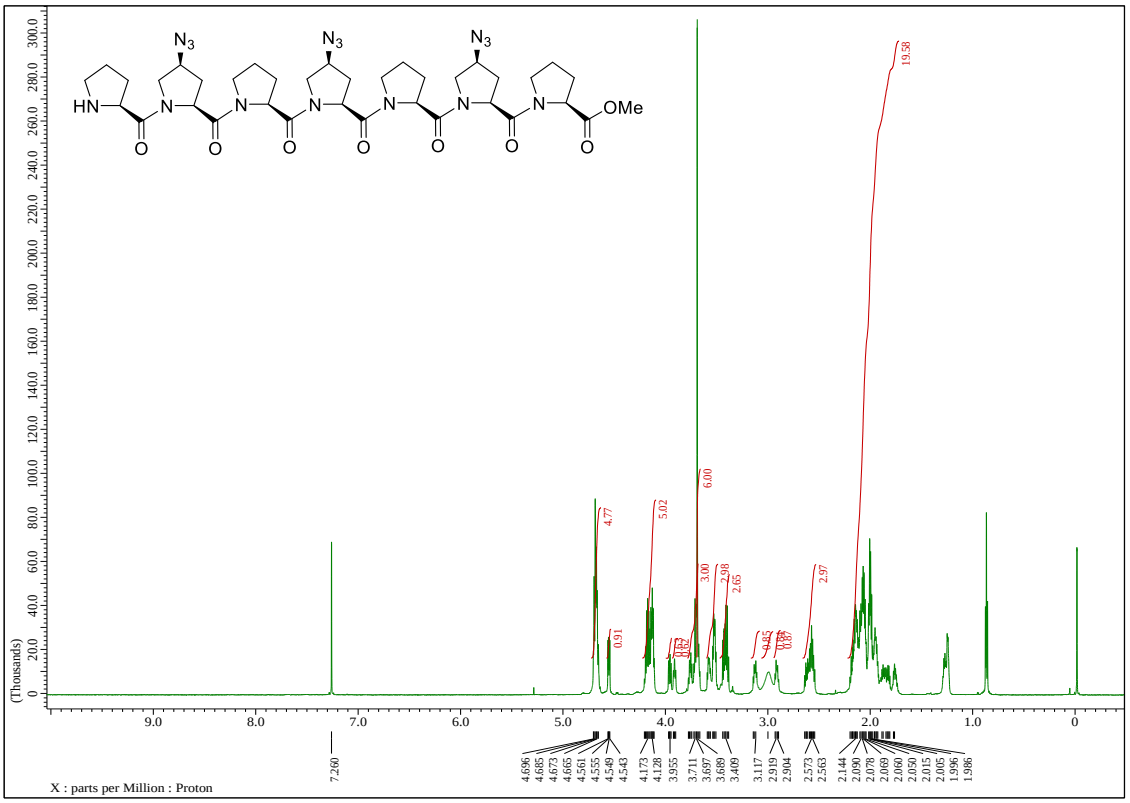
^{1}H NMR of **SI-11**



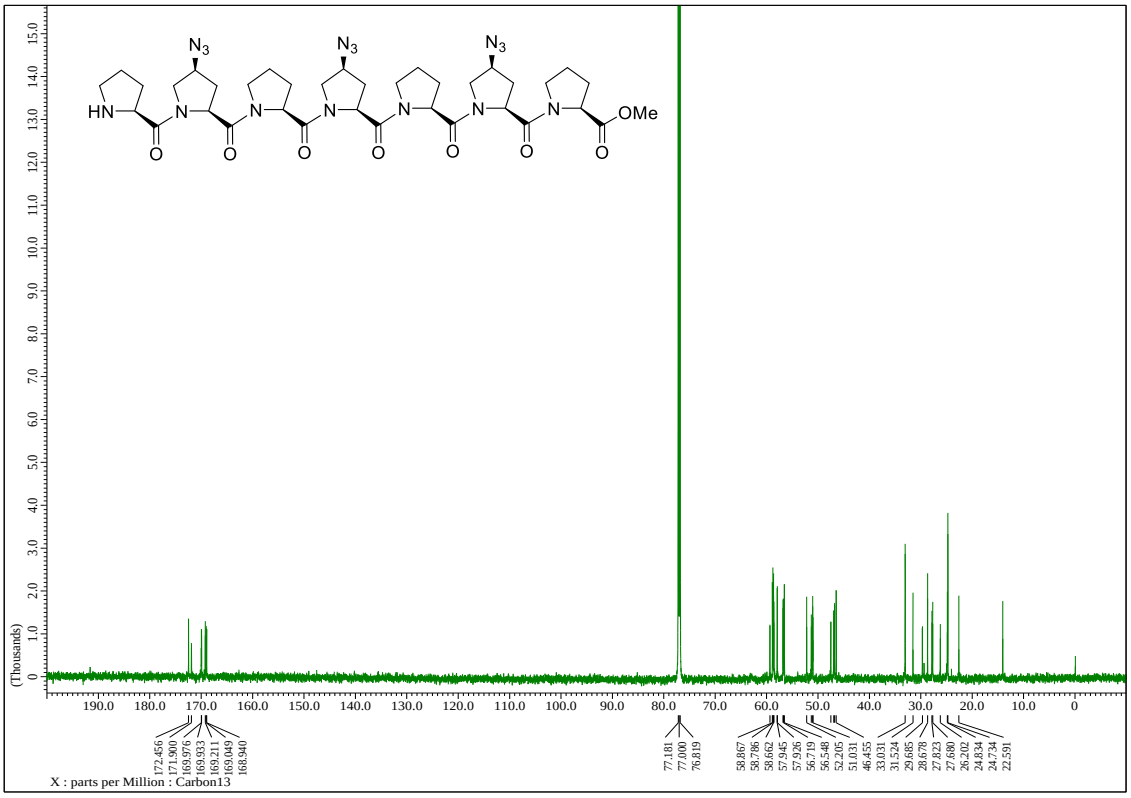
^{13}C NMR of **SI-11**



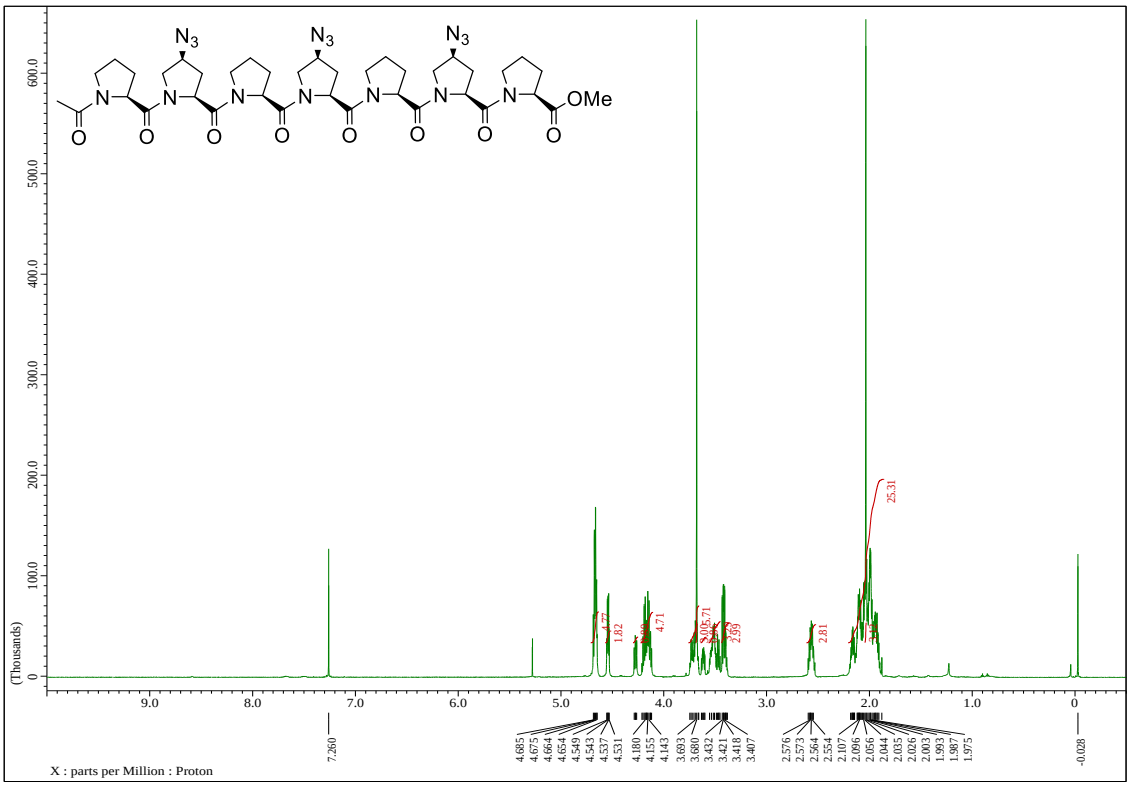
^{1}H NMR of **SI-12**



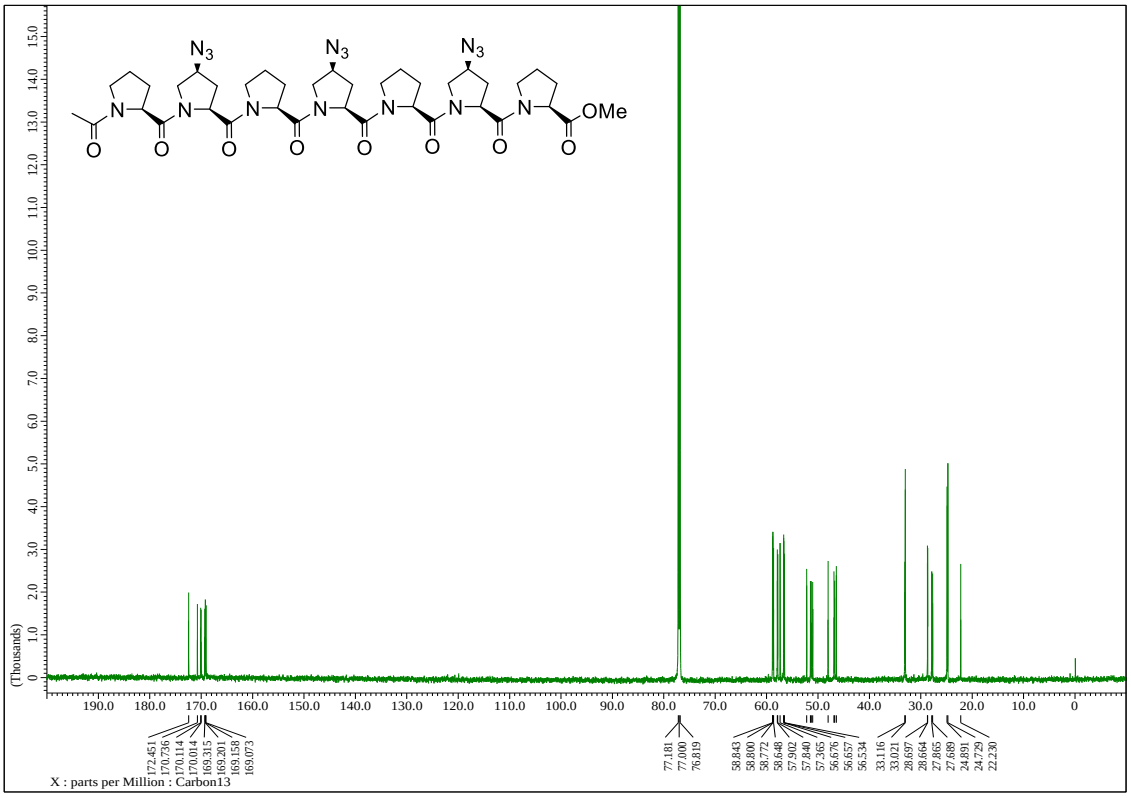
^{13}C NMR of **SI-12**



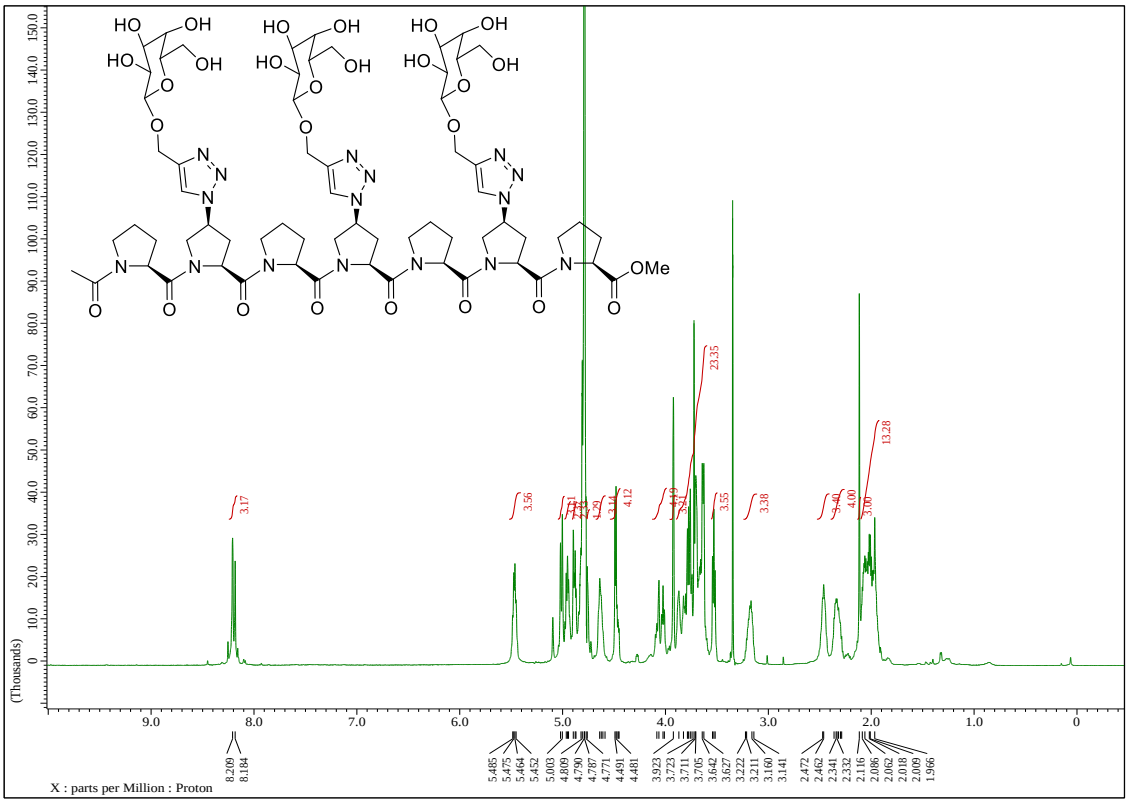
^{1}H NMR of **28**



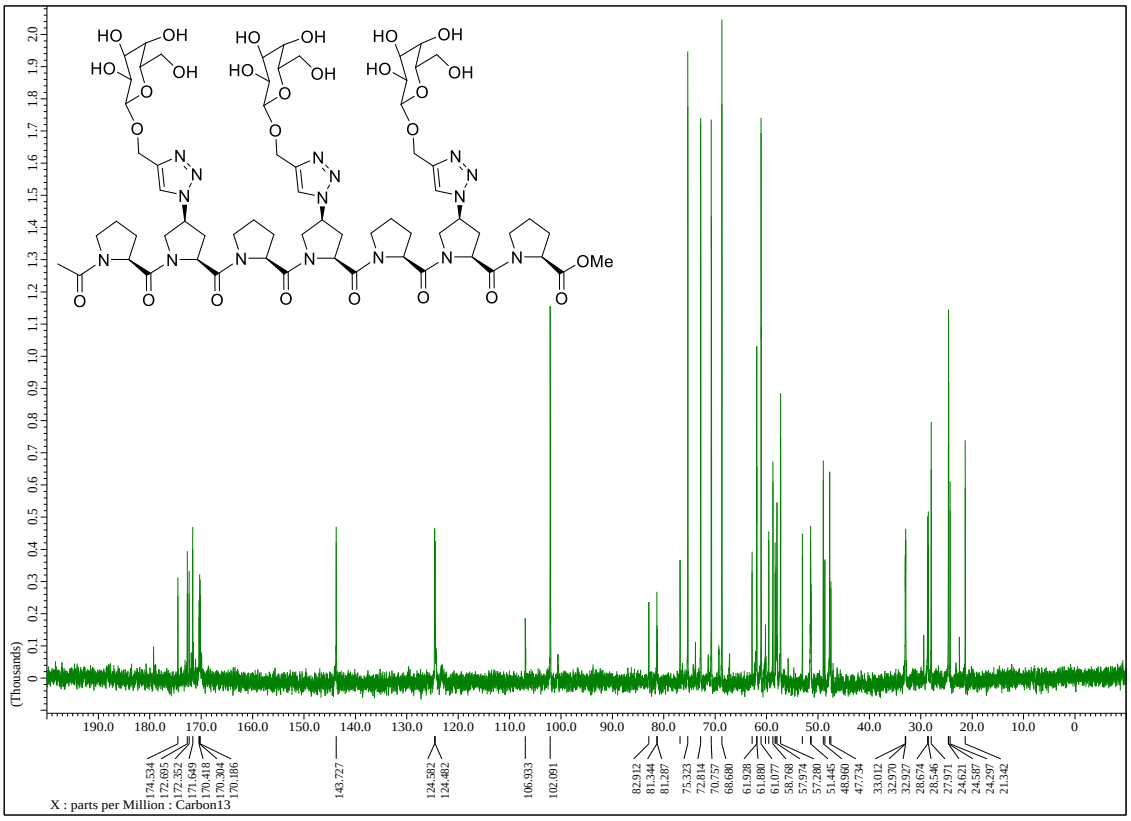
^{13}C NMR of **28**



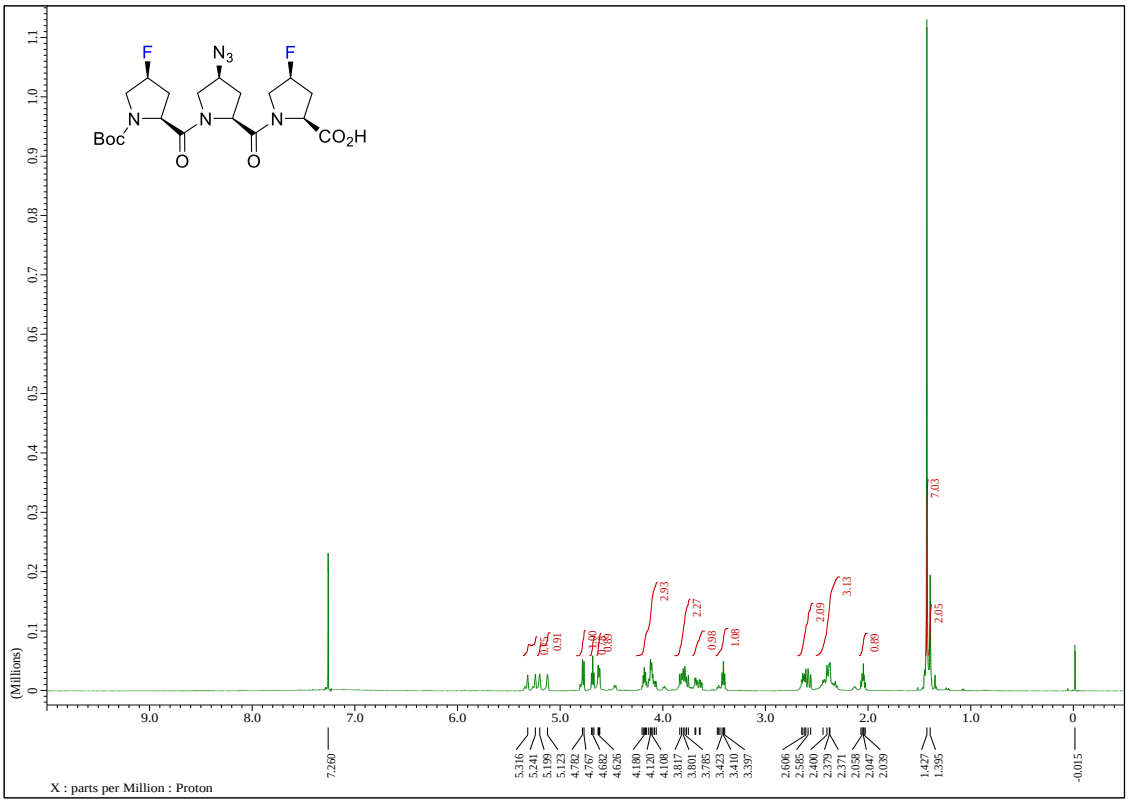
^{1}H NMR of **13a**



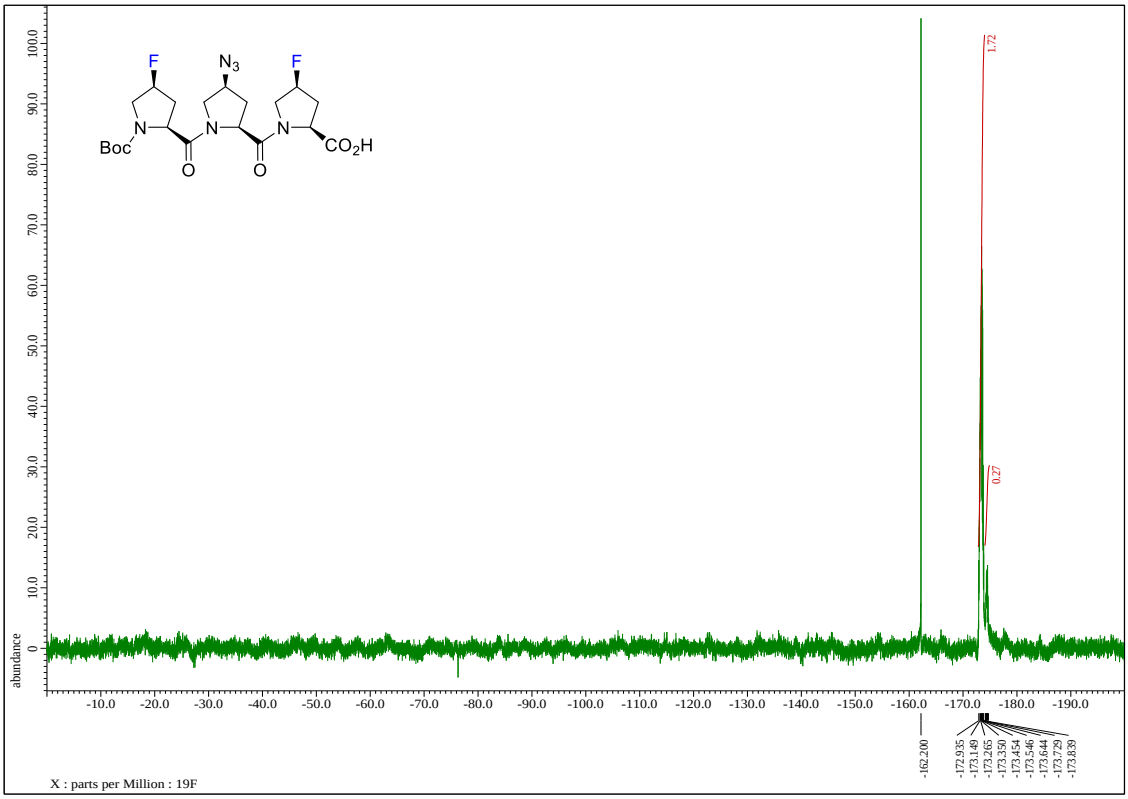
^{13}C NMR of **13a**



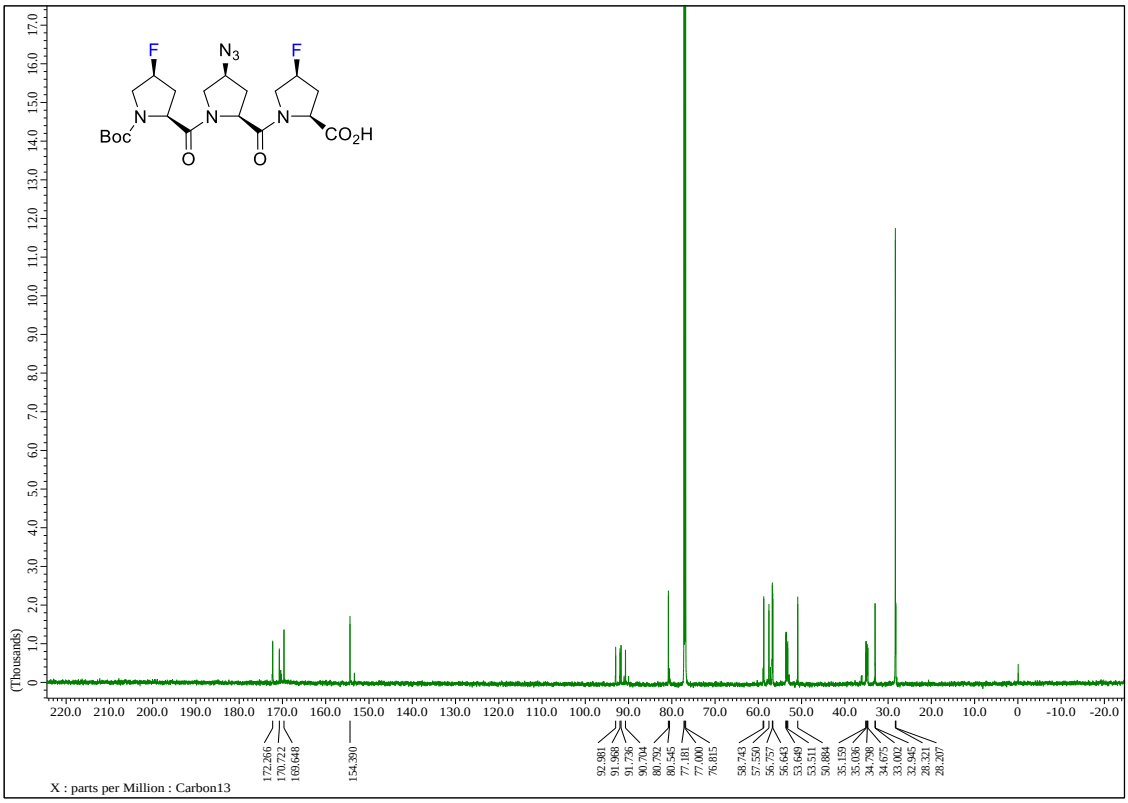
^{1}H NMR of **30**



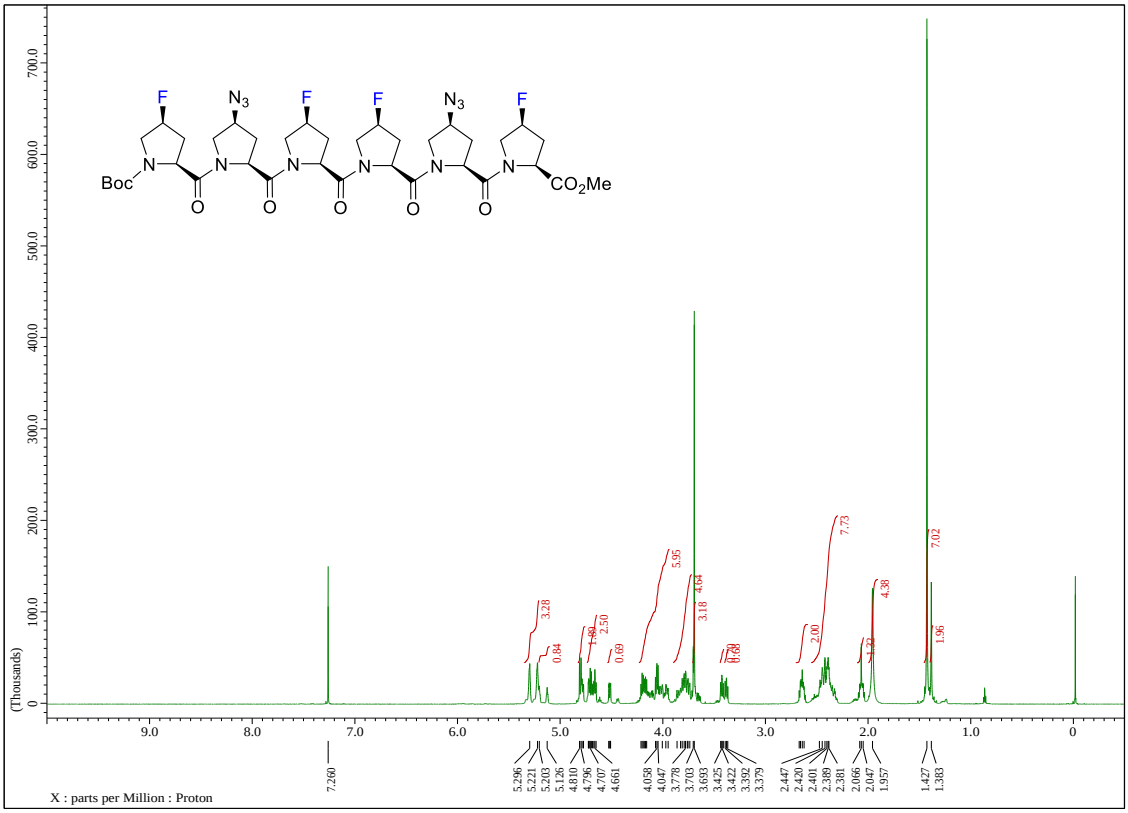
^{19}F NMR of **30**



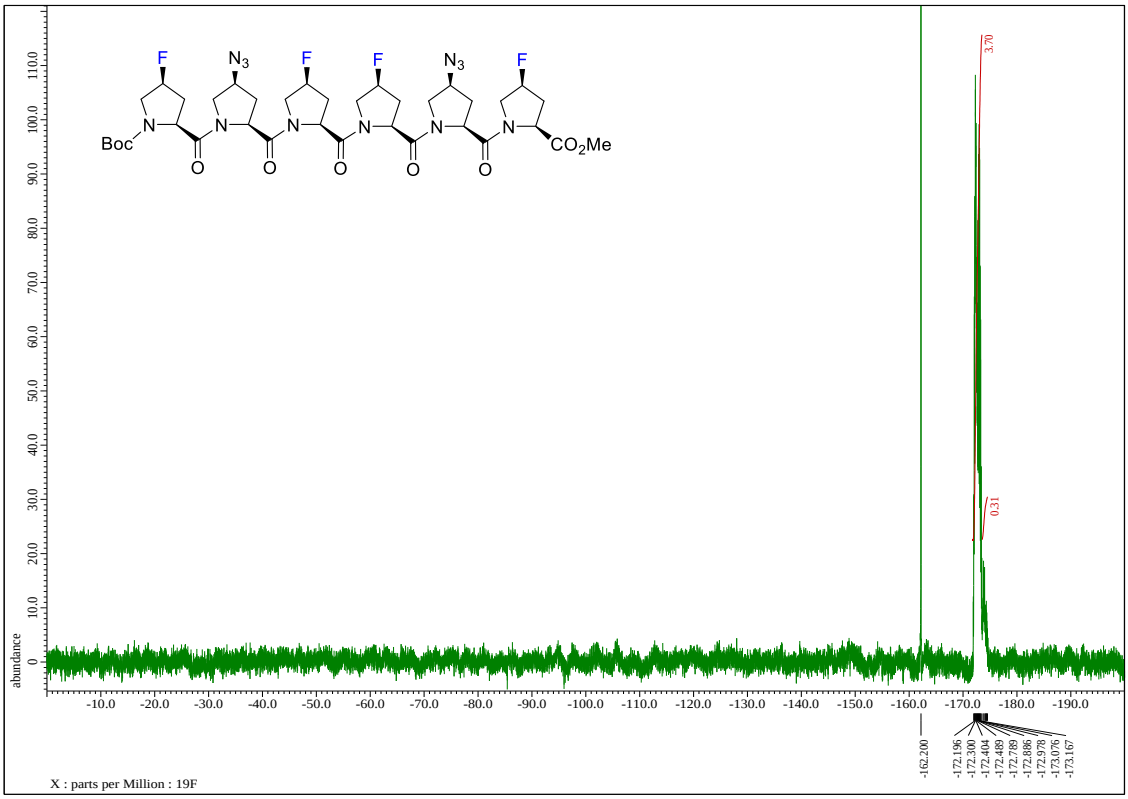
^{13}C NMR of **30**



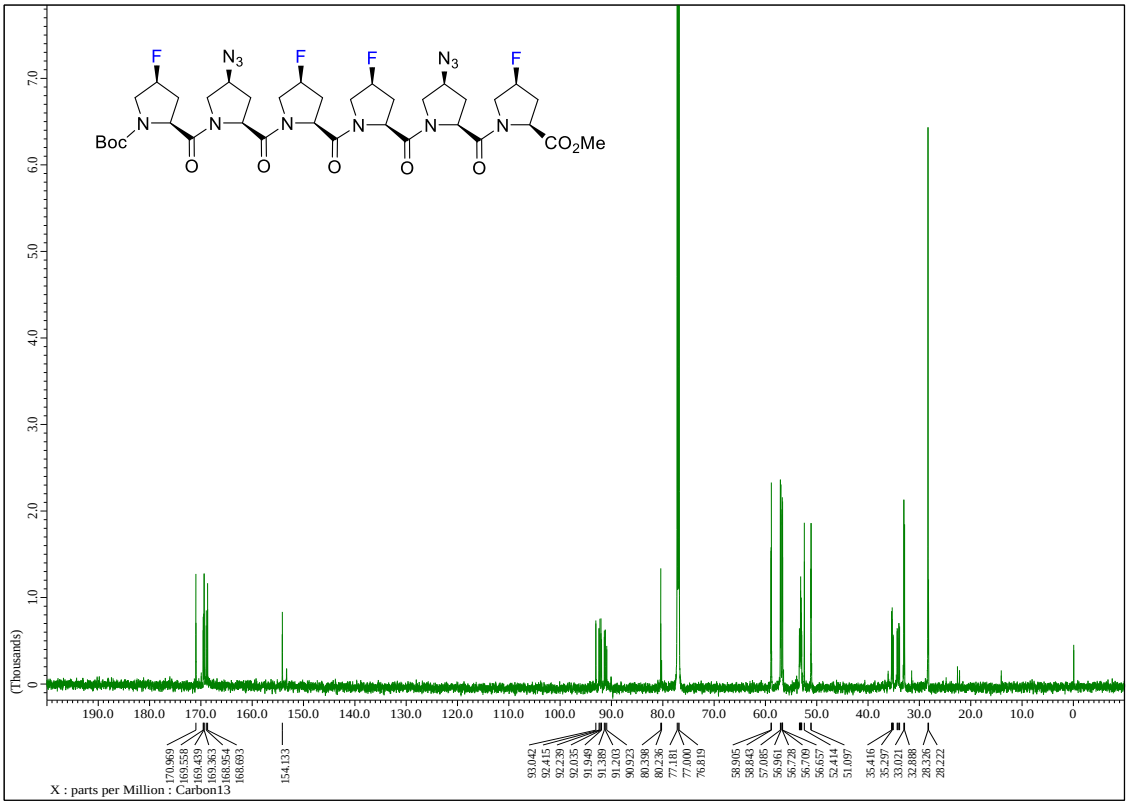
^{1}H NMR of **32**



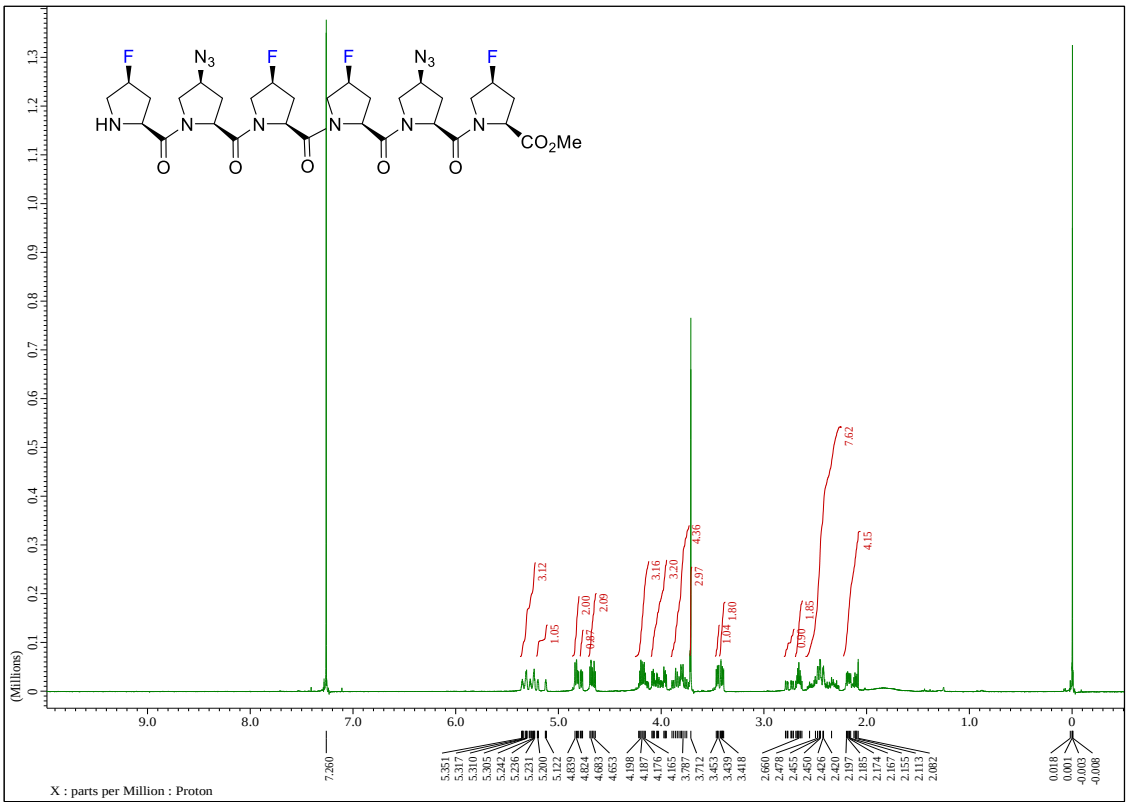
^{19}F NMR of **32**



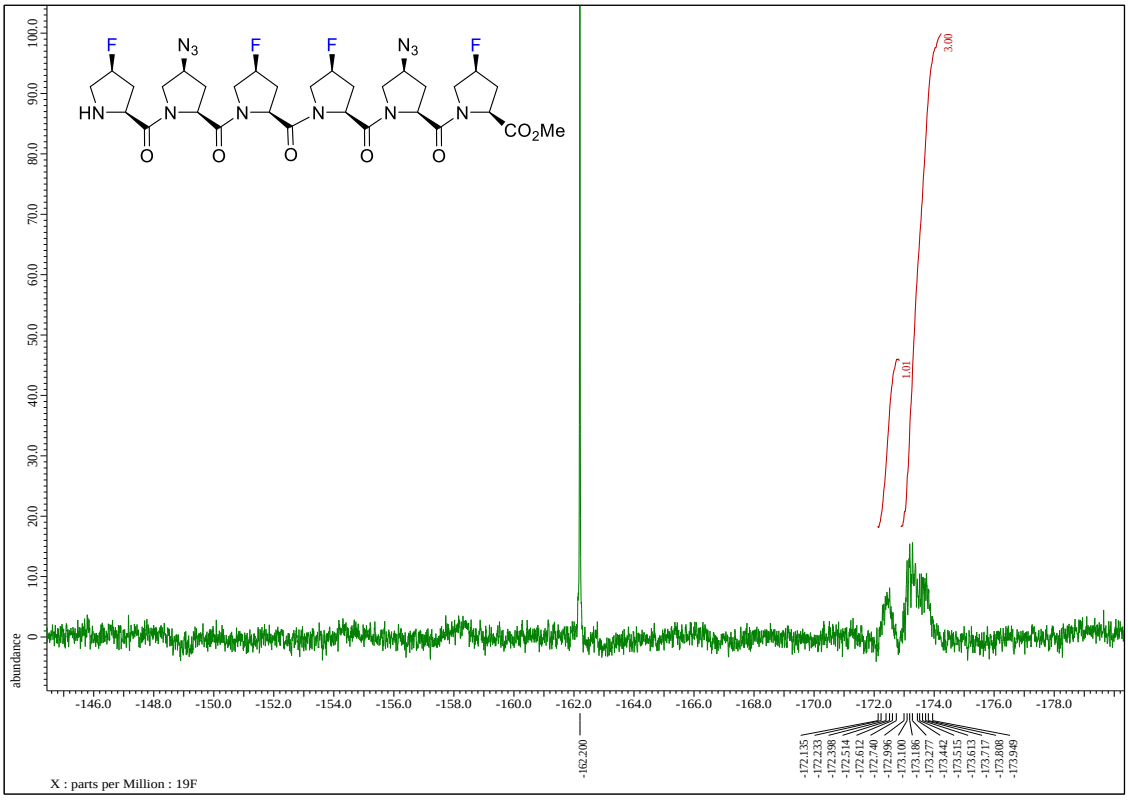
^{13}C NMR of **32**



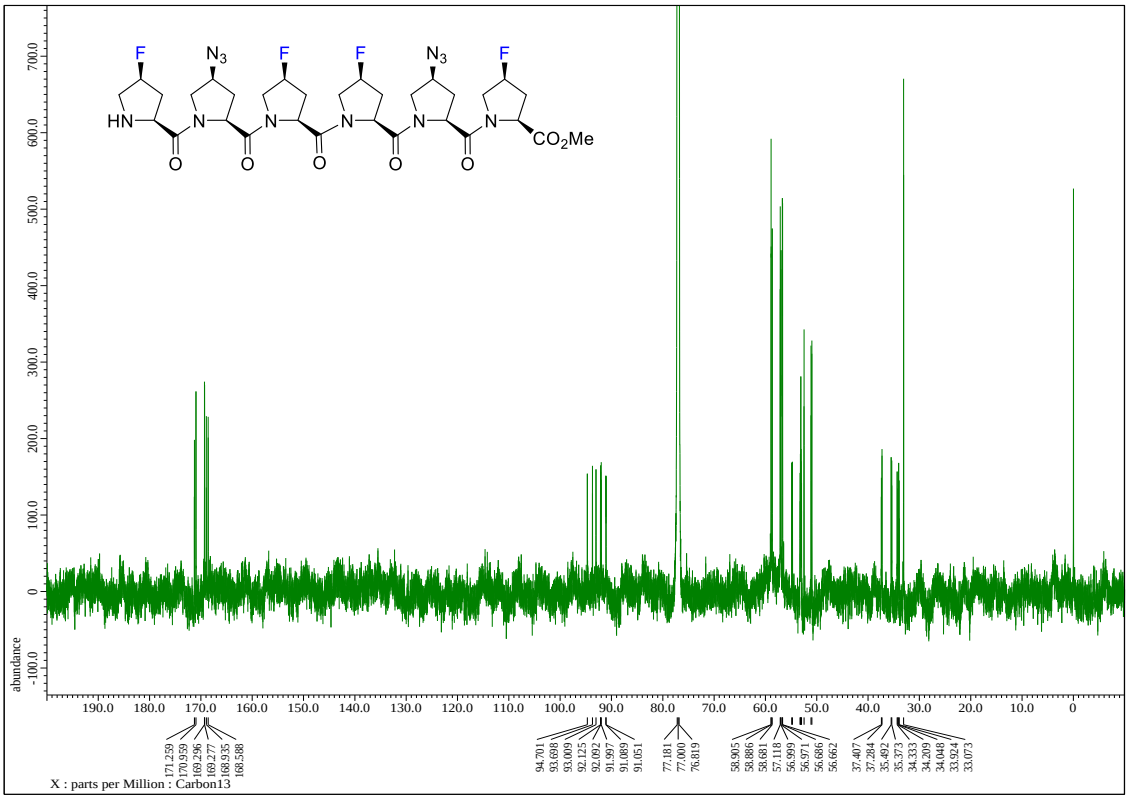
^{1}H NMR of **SI-13**



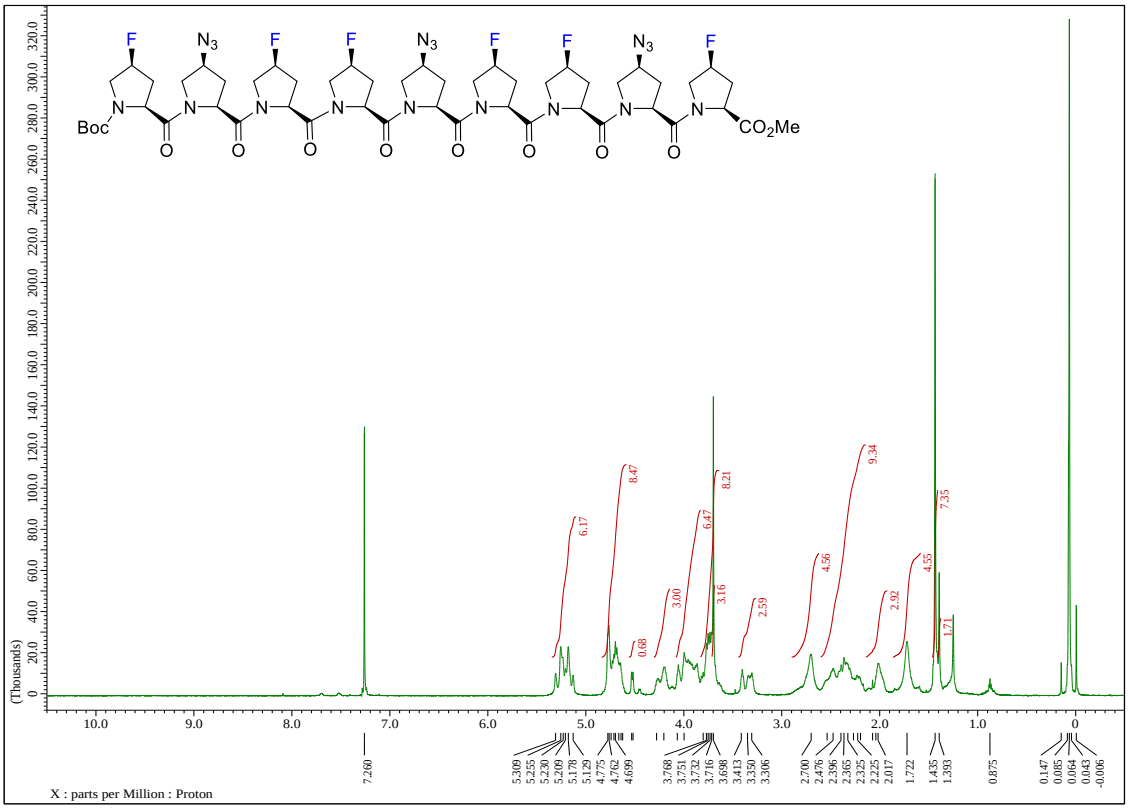
^{19}F NMR of **SI-13**



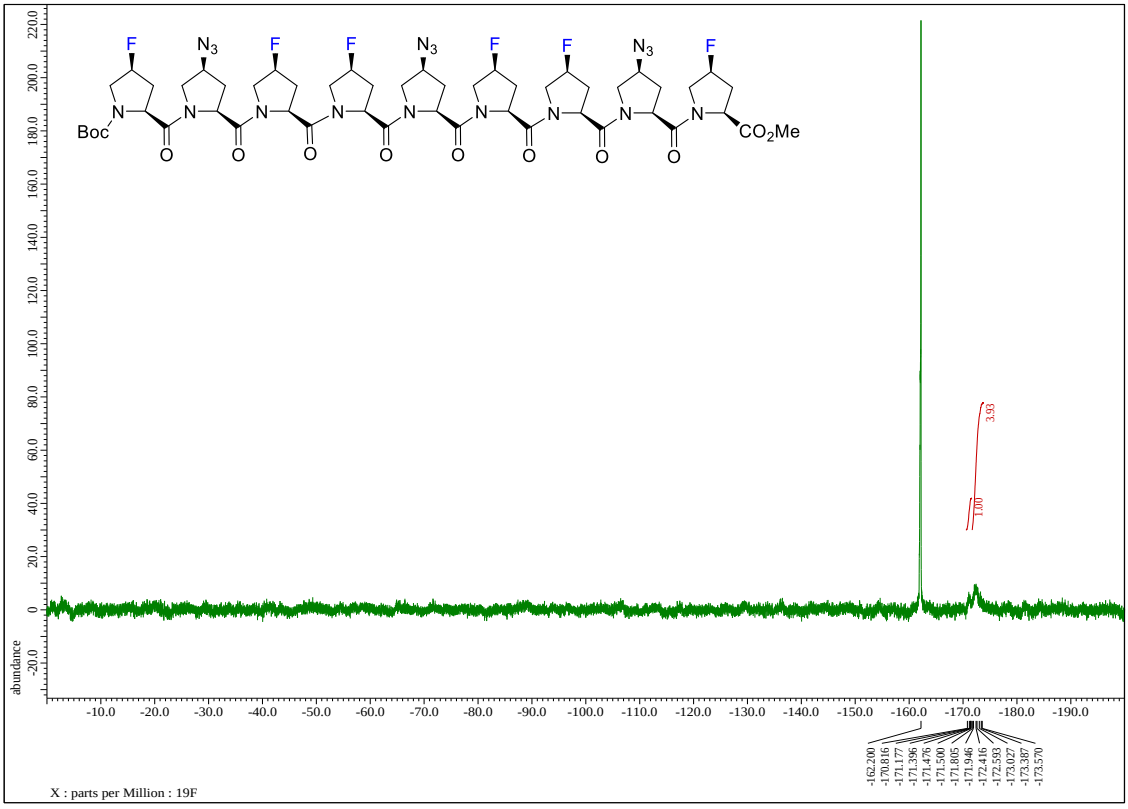
^{13}C NMR of **SI-13**



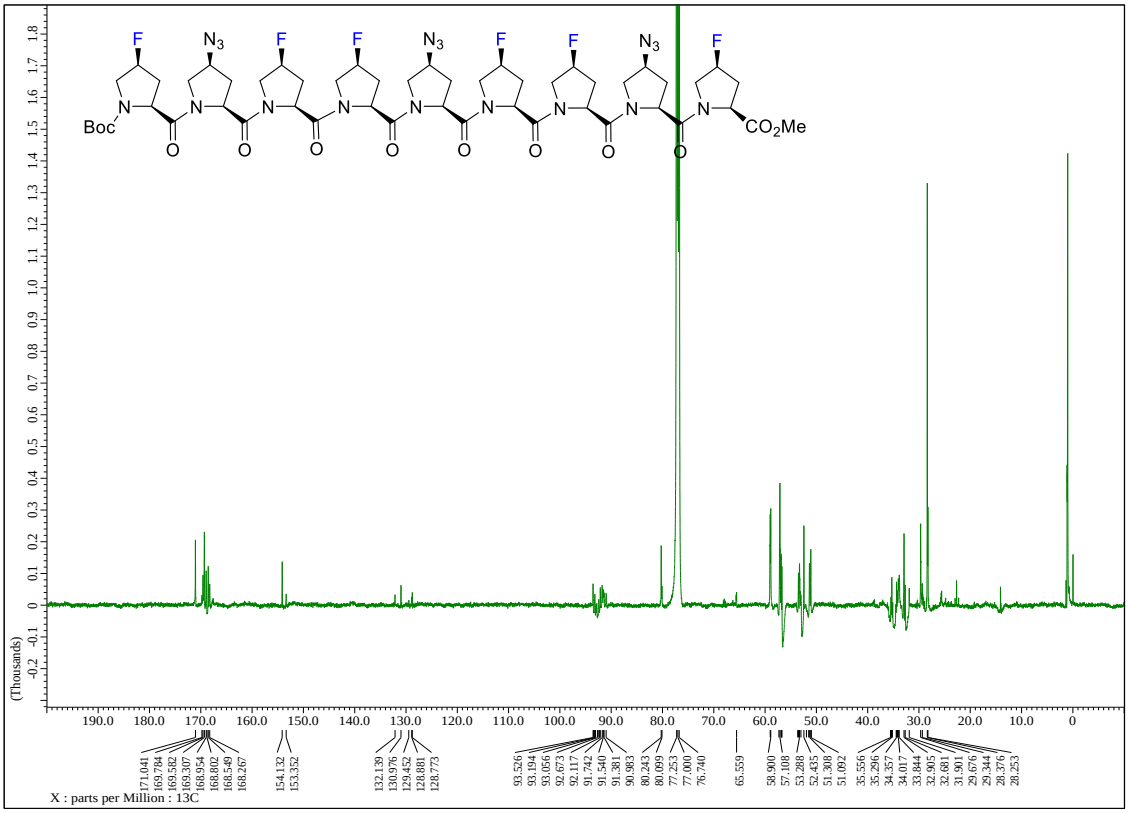
^{1}H NMR of **SI-14**



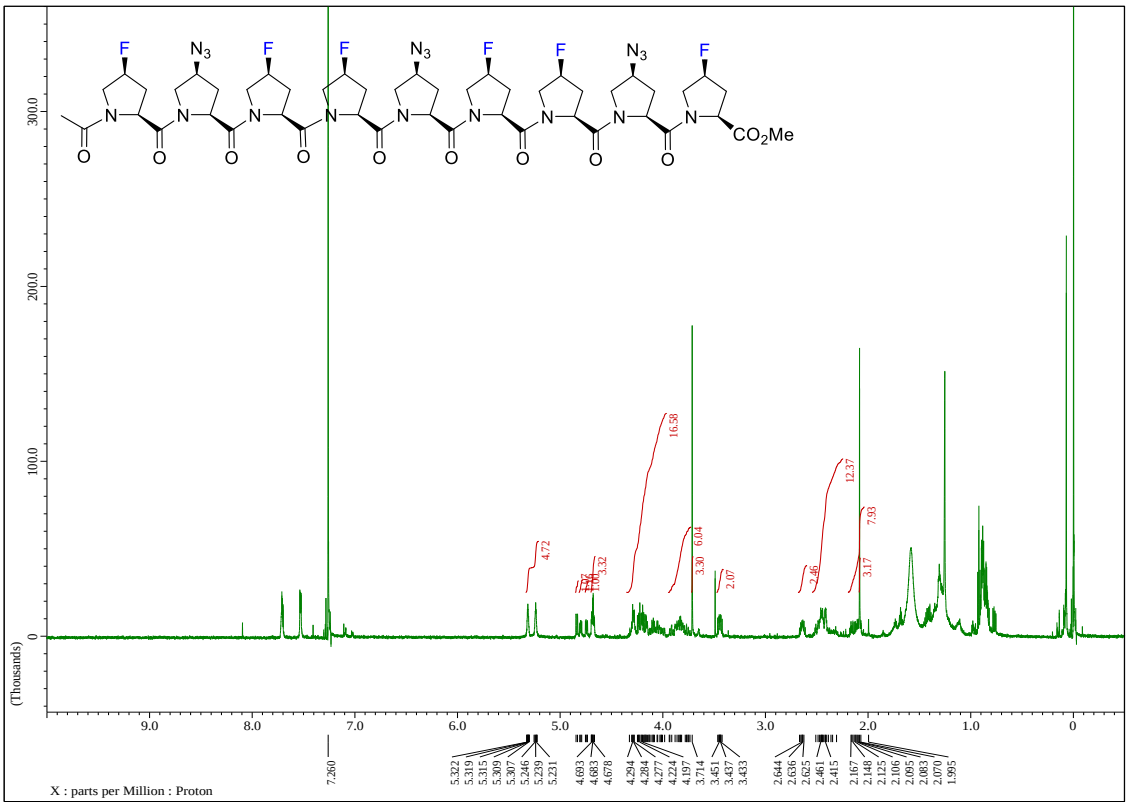
^{19}F NMR of **SI-14**



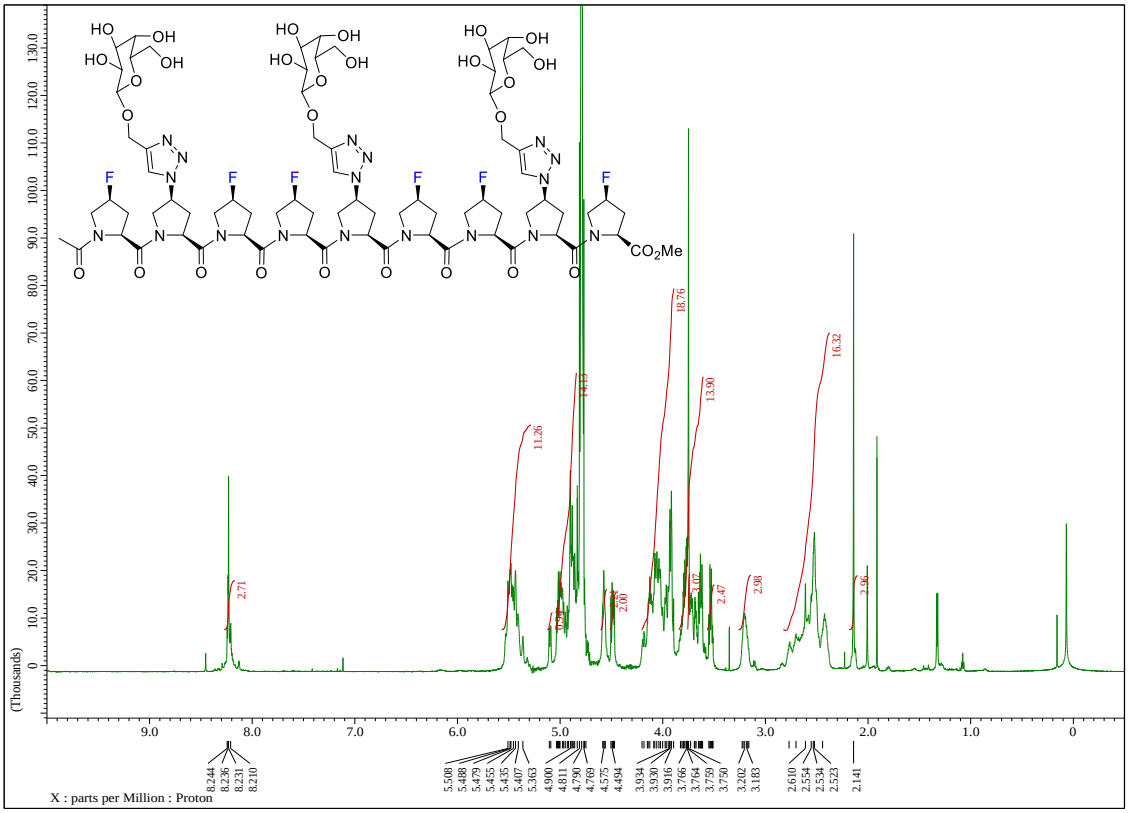
^{13}C NMR of **SI-14**



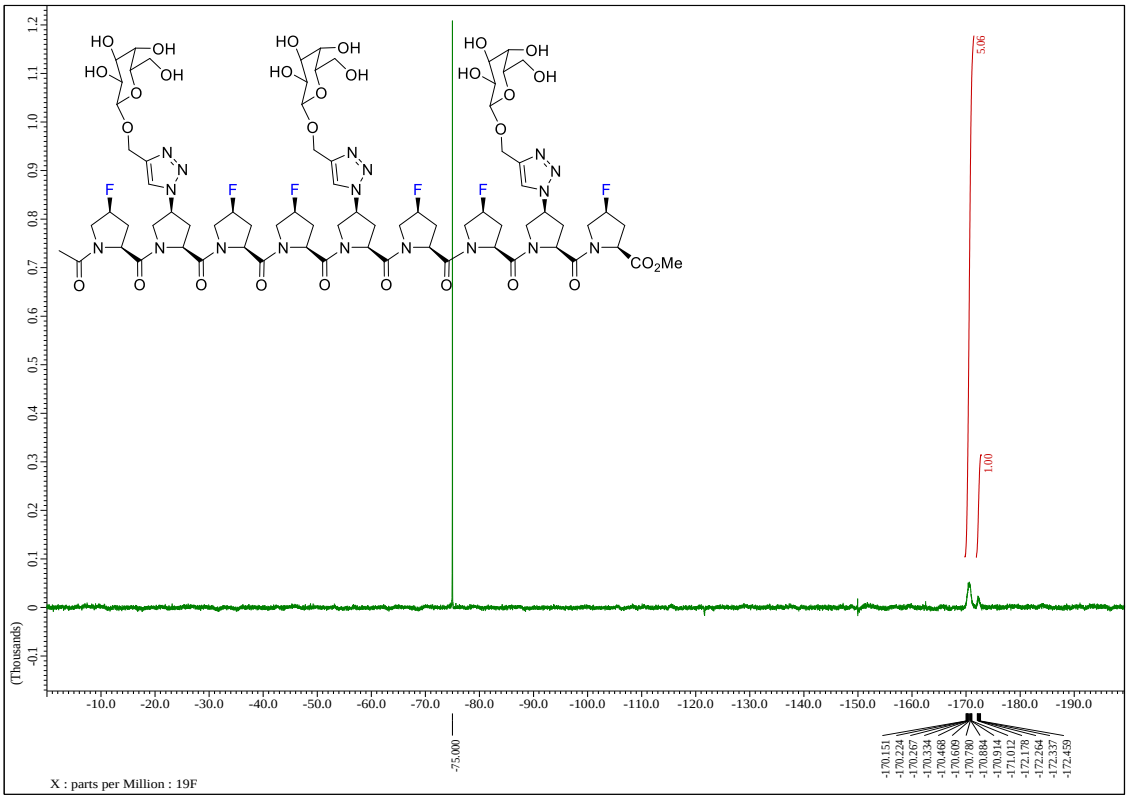
^{1}H NMR of **34** (crude)



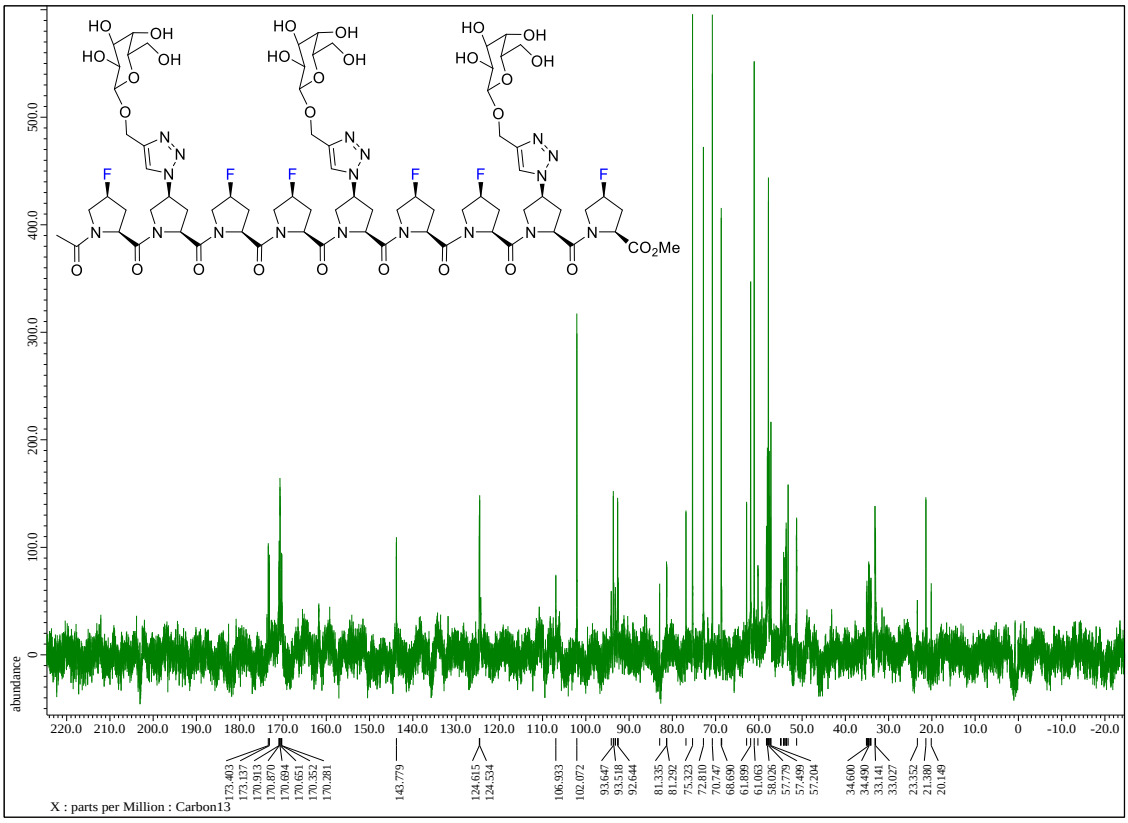
^{1}H NMR of **12b**



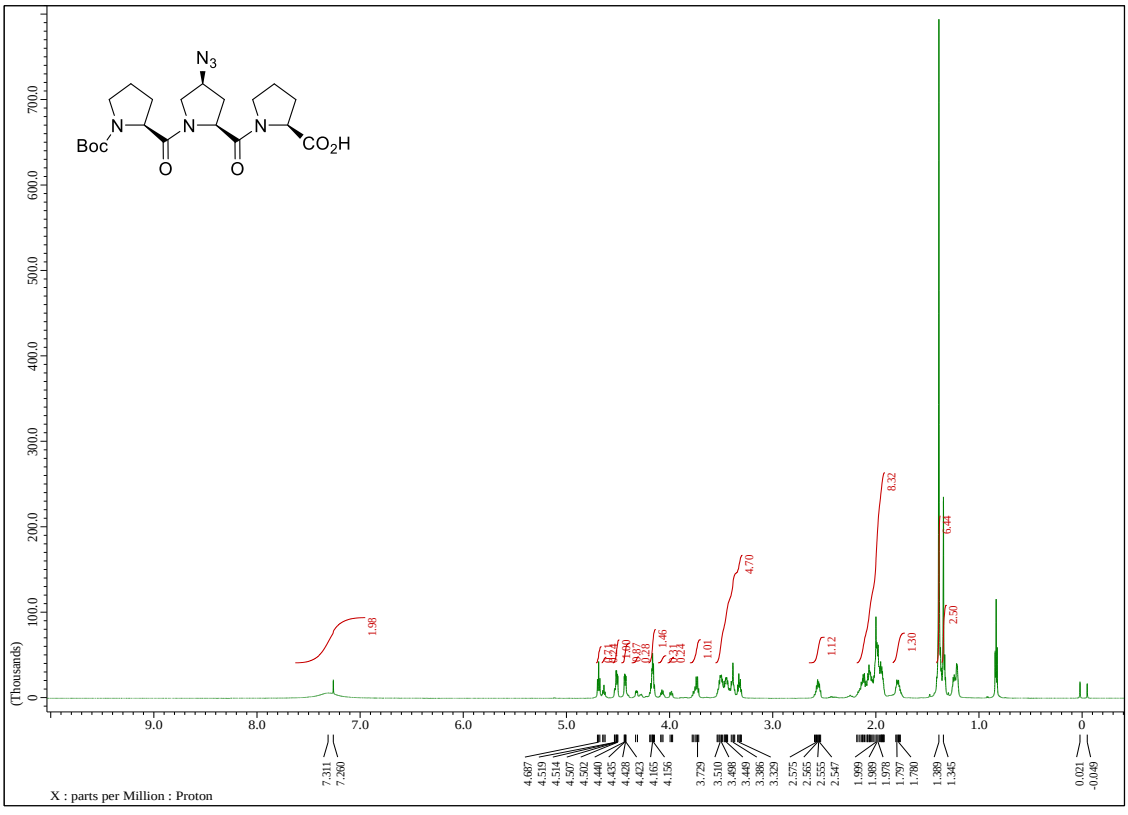
^{19}F NMR of **12b**



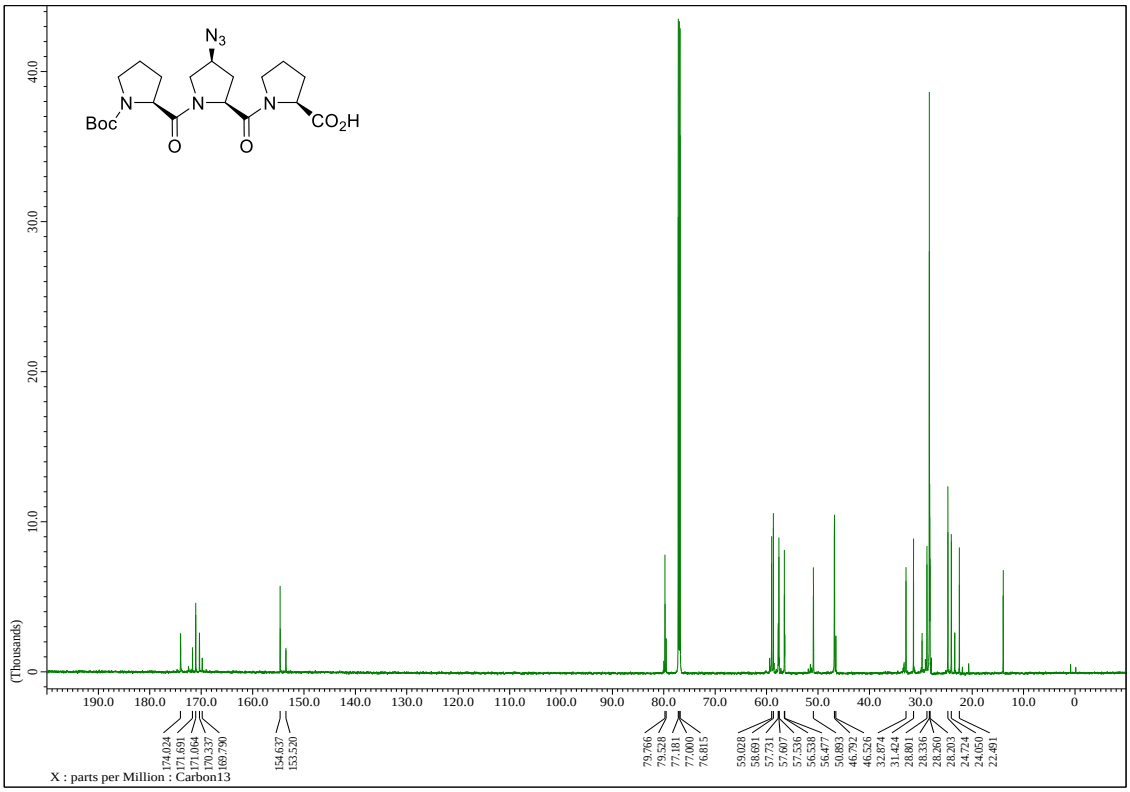
^{13}C NMR of **12b**



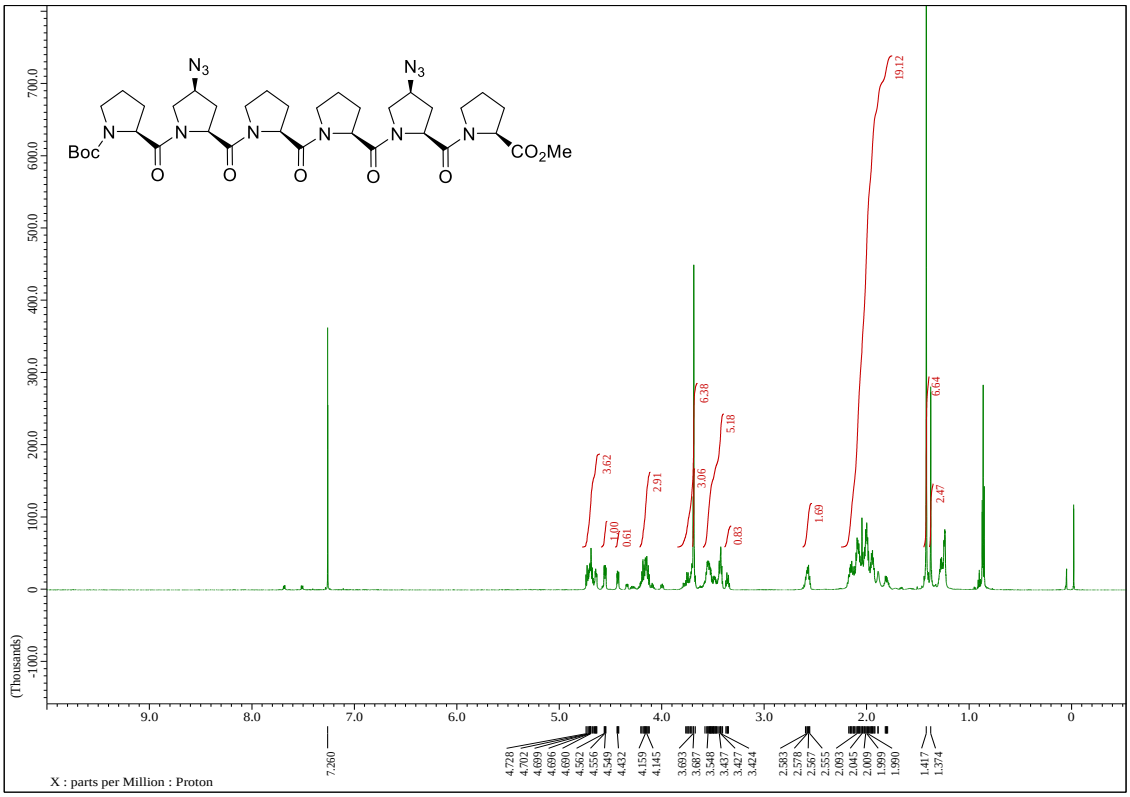
^{1}H NMR of **31**



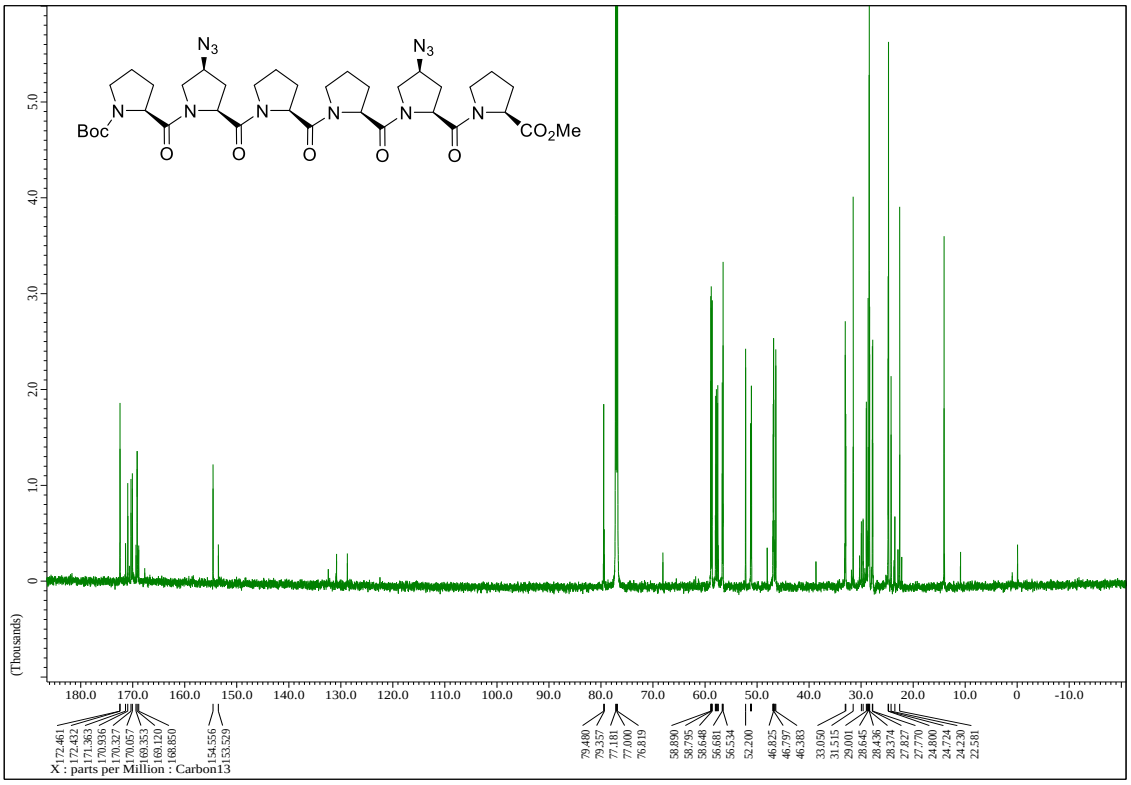
^{13}C NMR of **31**



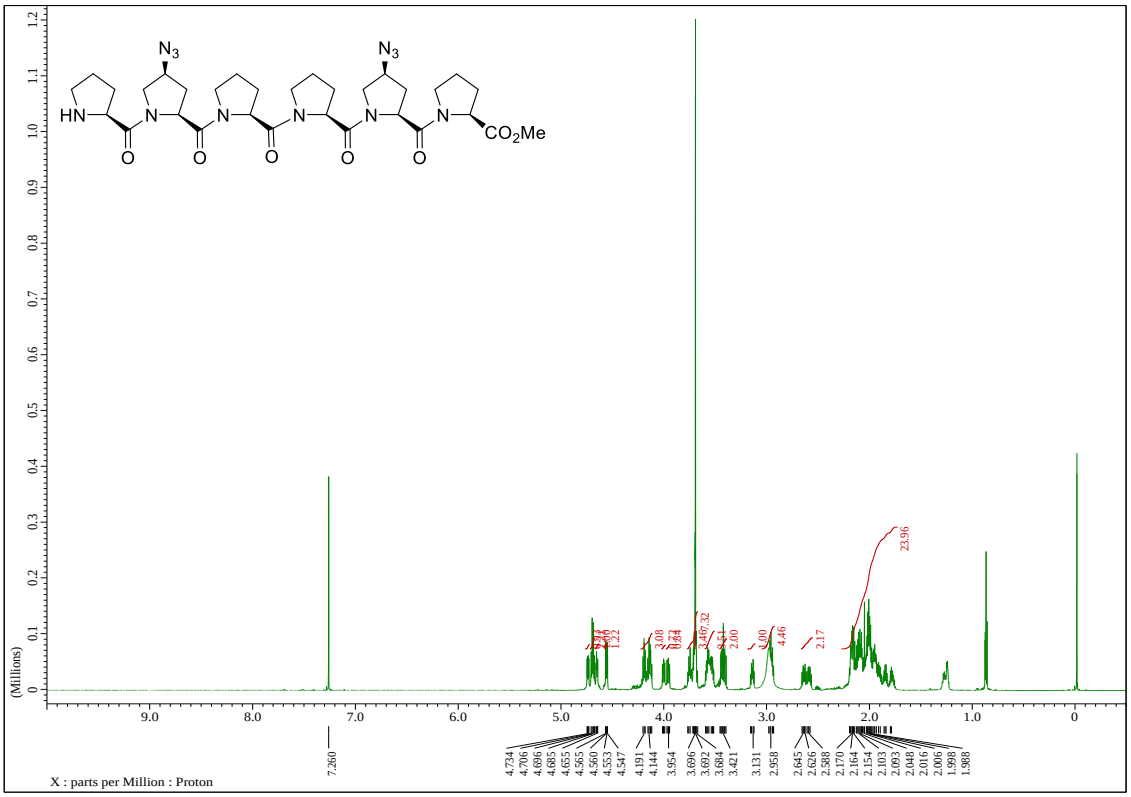
^{1}H NMR of **33**



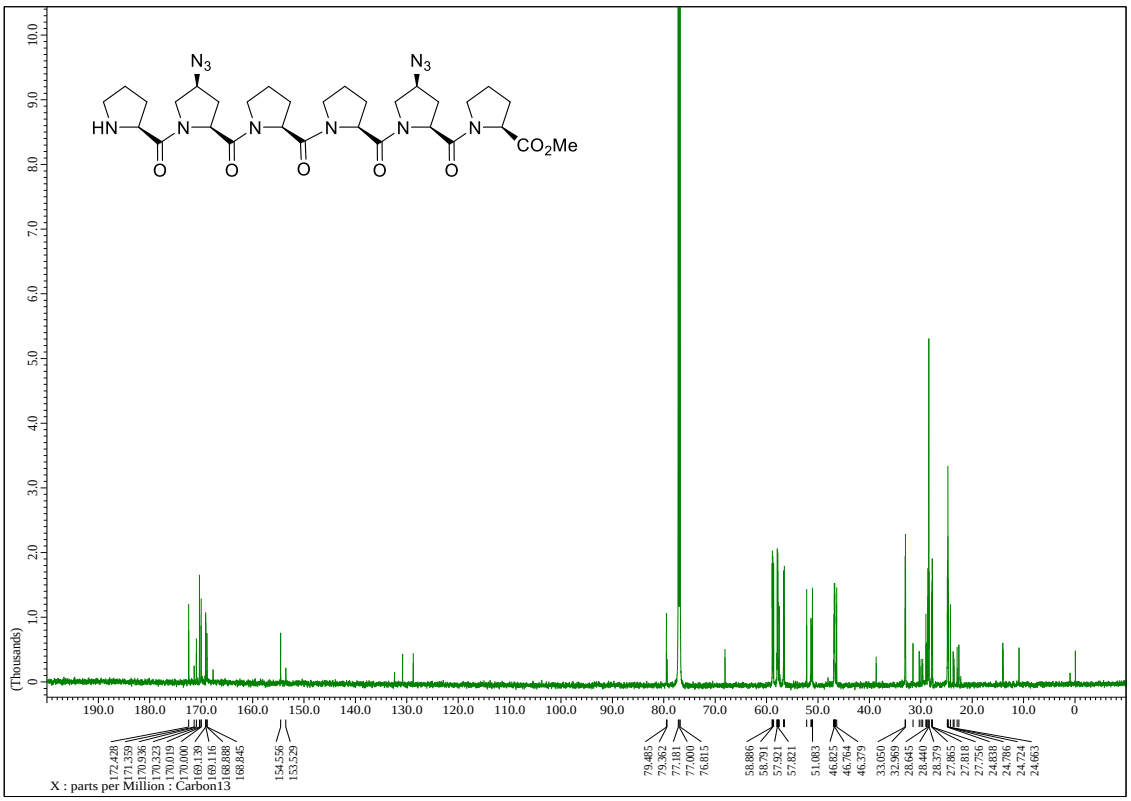
^{13}C NMR of **33**



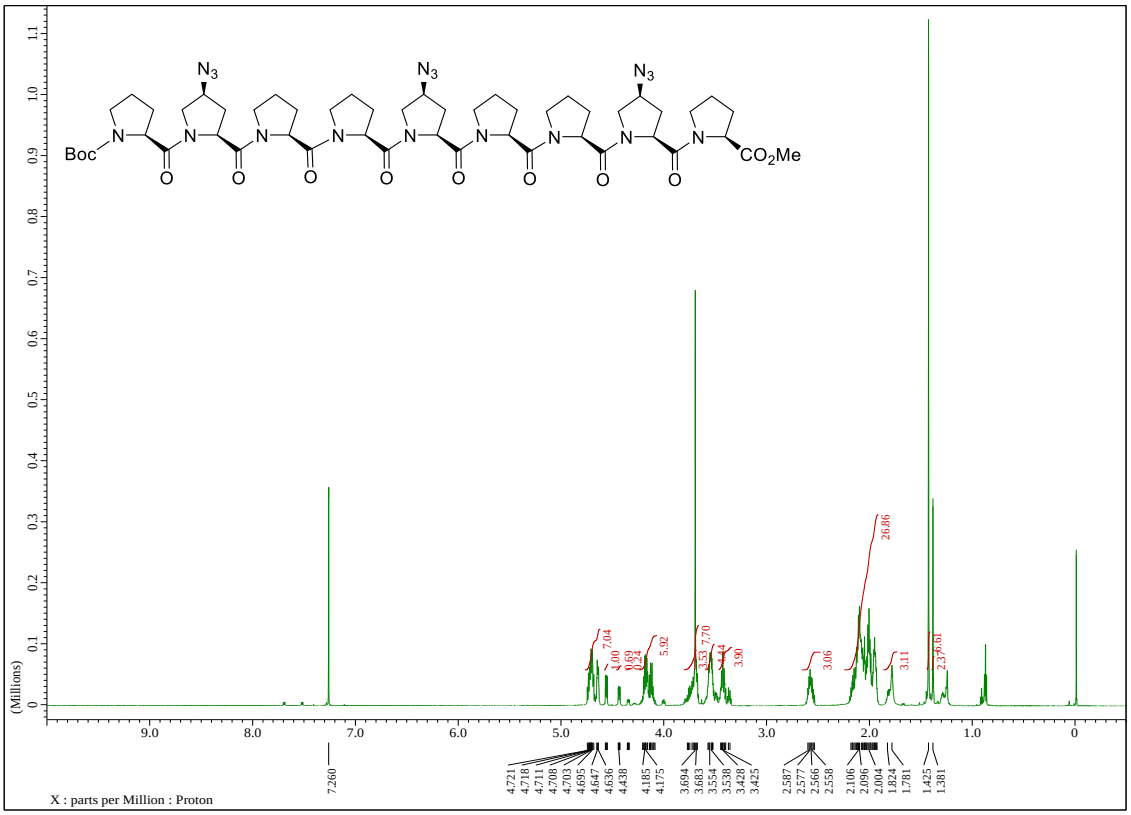
^{1}H NMR of **SI-15**



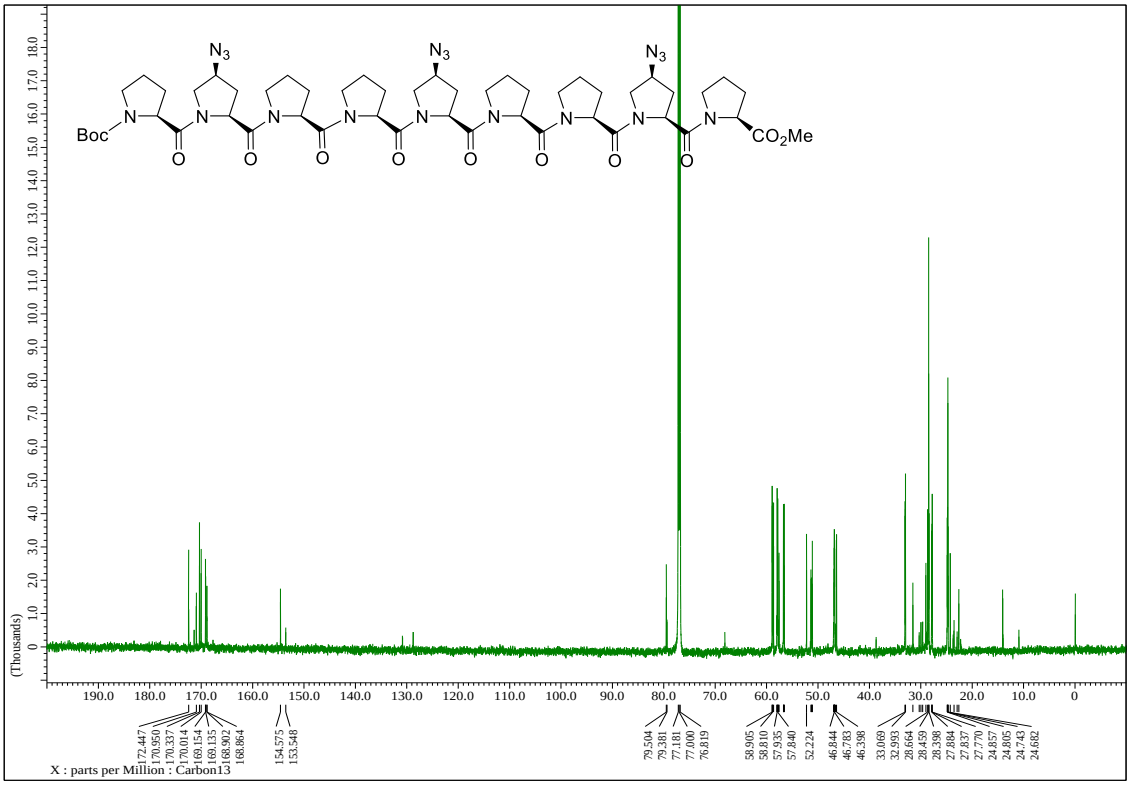
^{13}C NMR of **SI-15**



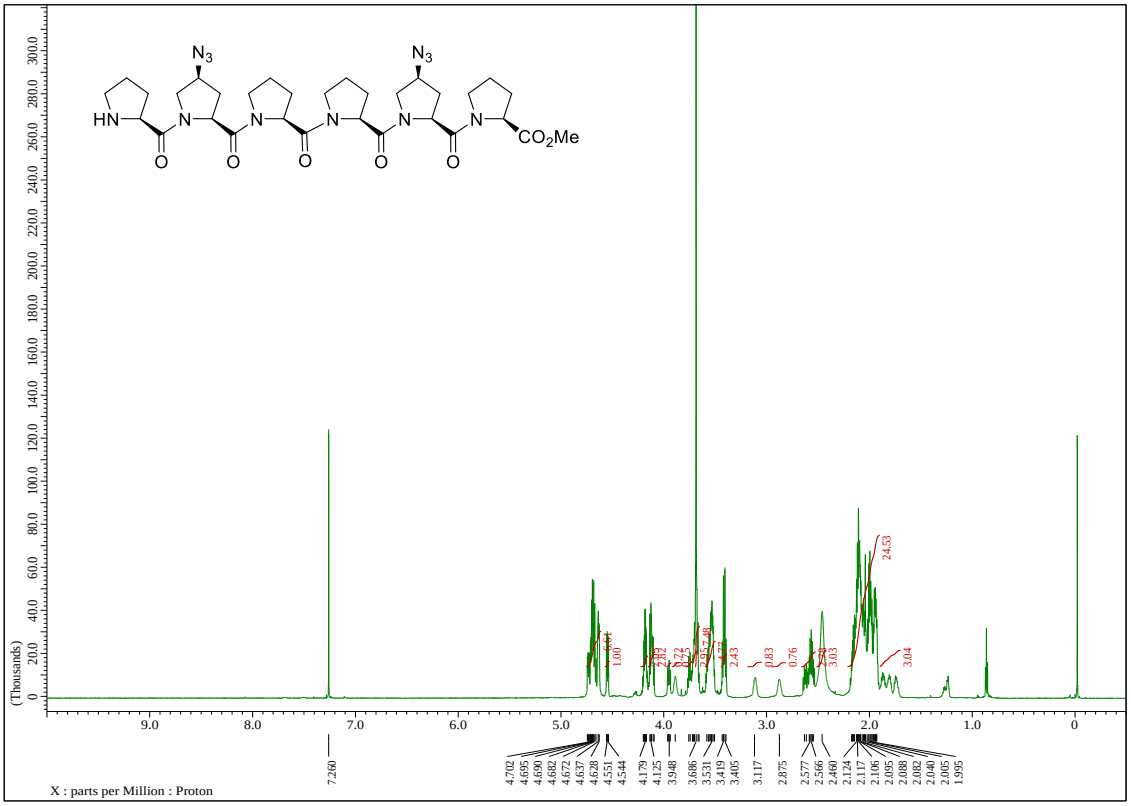
^{1}H NMR of **SI-16**



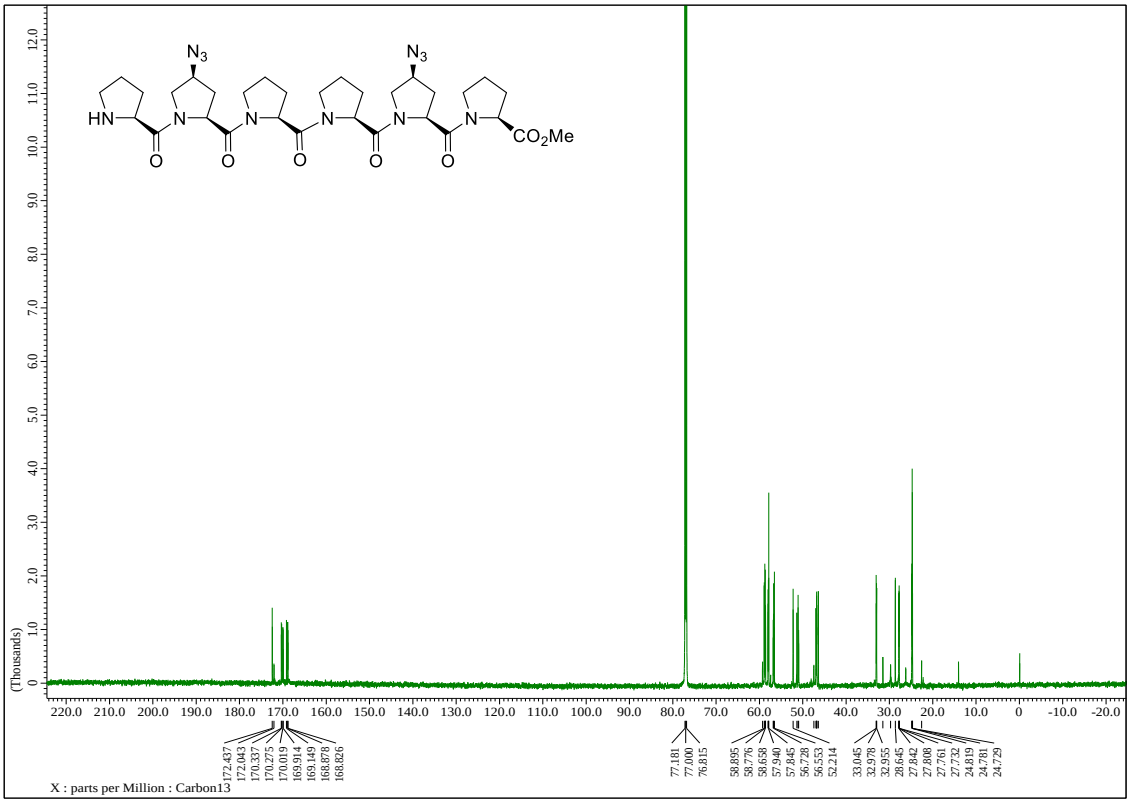
^{13}C NMR of **SI-16**



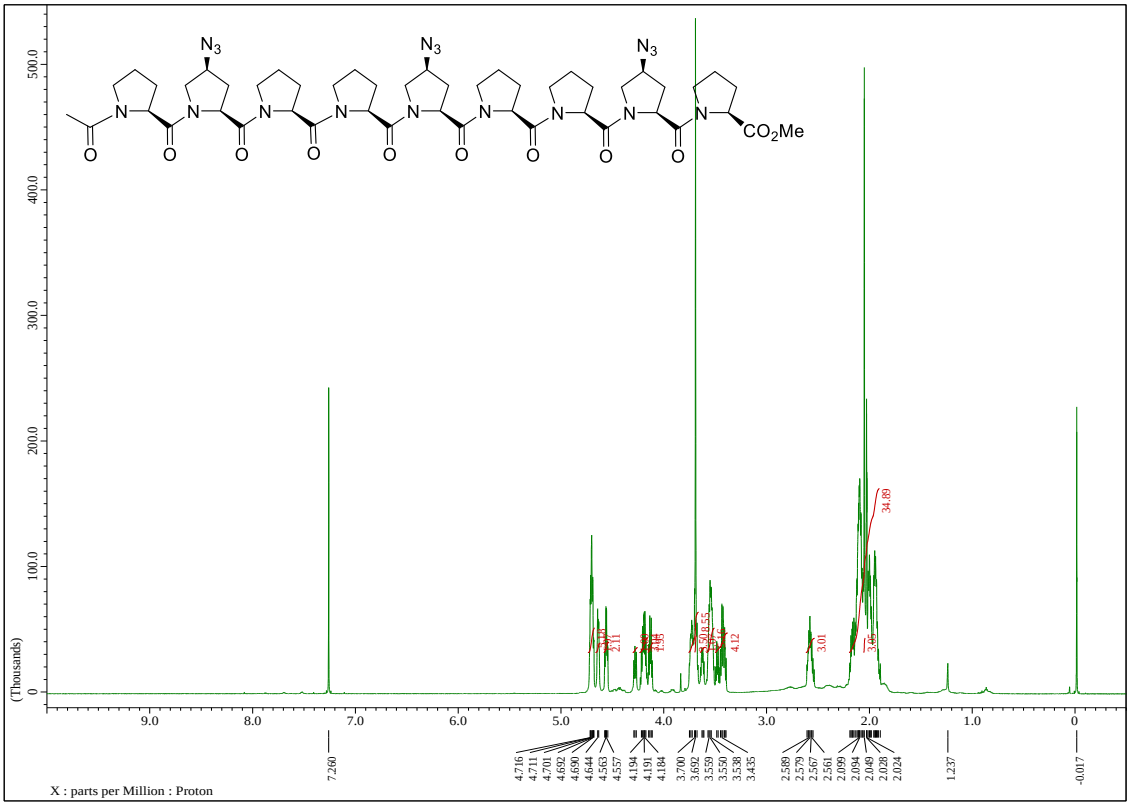
^{1}H NMR of **SI-17**



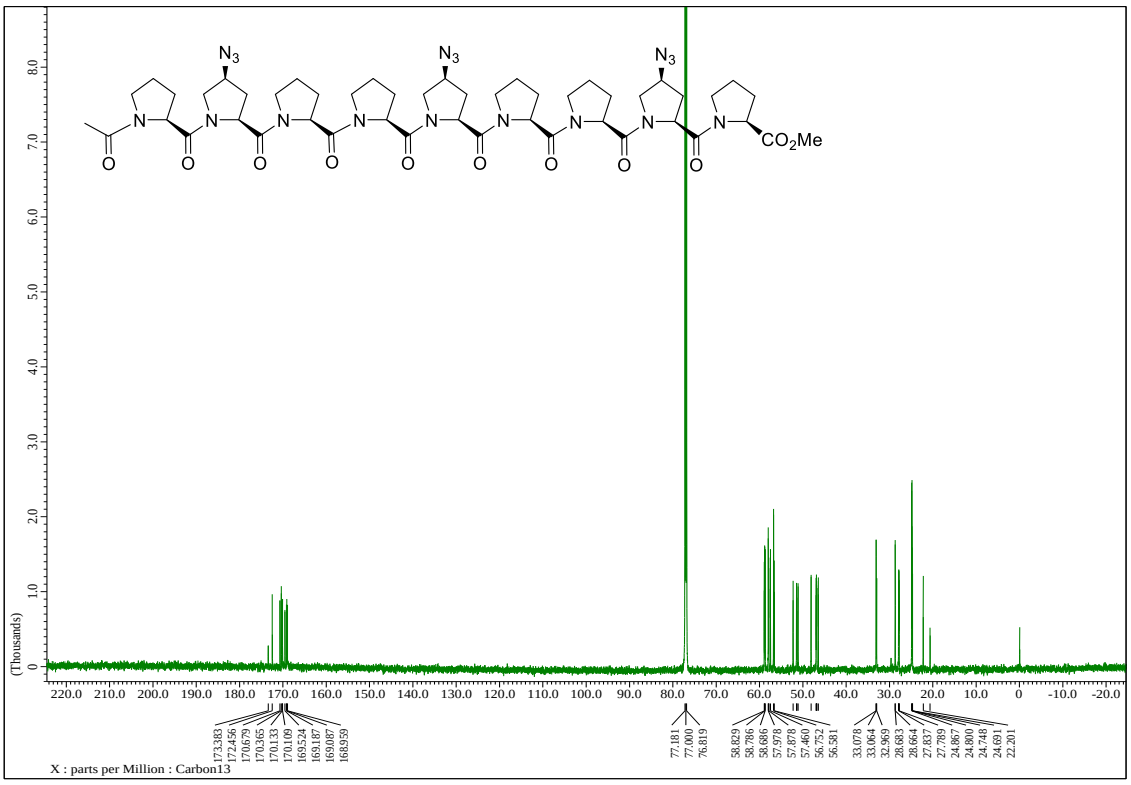
^{13}C NMR of **SI-17**



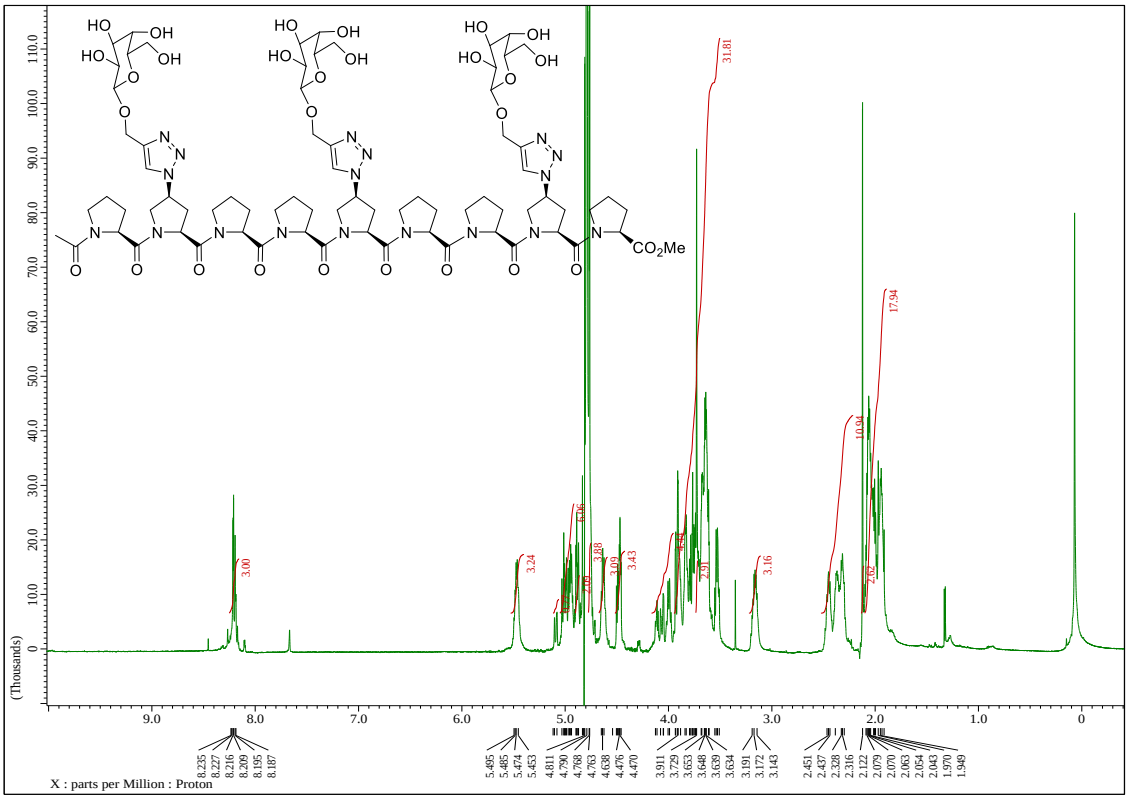
^{1}H NMR of **35**



^{13}C NMR of **35**



^{1}H NMR of **13b**



^{13}C NMR of **13b**