Electronic supplementary information

Helical Folding in α/β-hybrid peptides Without Inter-Residual backbone hydrogen bonding.

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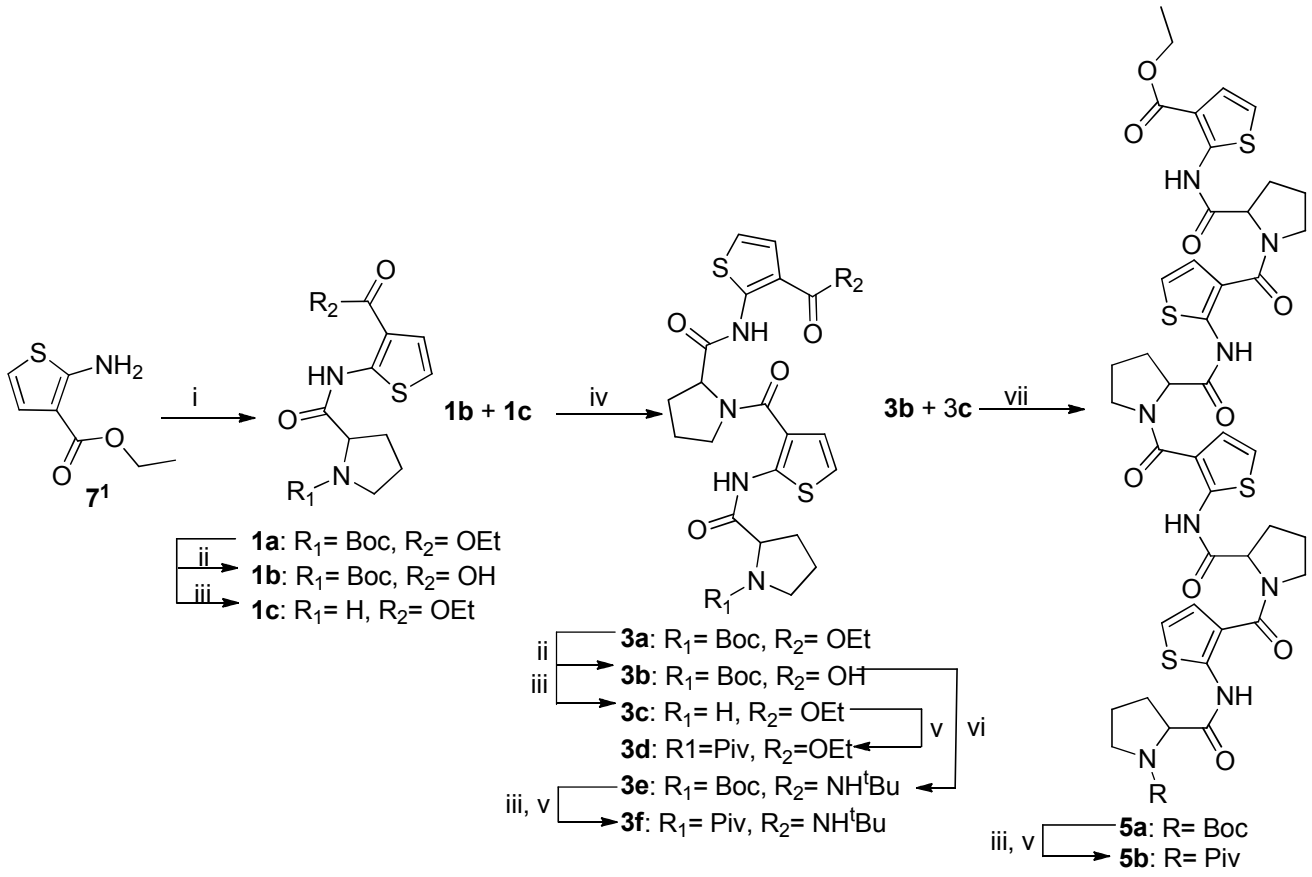
General Methods.

Unless otherwise stated, all chemicals and reagents were obtained commercially. Dry solvents were prepared by the standard procedures. Analytical thin layer chromatography was done on pre-coated silica gel plates (Kieselgel $60F_{254}$, Merck). Column chromatographic purifications were done with 100-200 mesh silica gel. NMR spectra were recorded in $CDCl_3$ on AV 200 MHz, AV 400 MHz or AV 500 MHz spectrometers. All chemical shifts are reported in δ ppm downfield to TMS and peak multiplicities are referred to as singlet (s), doublet (d), quartet (q), broad singlet (bs), and multiplet (m). The titration studies were done in $CDCl_3$. Elemental analyses were performed on an Elmentar-Vario-EL (Heraeus Company Ltd., Germany). Elemental analyses were performed on an Elmentar-Vario-EL (Heraeus Company Ltd., Germany). IR spectra were recorded in $CHCl_3$ using Shimadzu FTIR-8400 spectrophotometer. Melting points were determined on a Buchi melting point B-540 instrument. Electron Scattered Ionization (ESI) Mass Spectrometric measurements were done with API QSTAR Pulsar mass Spectrometer. Circular Dichroism studies have been carried out using JASCO-815 Spectro Photometer.

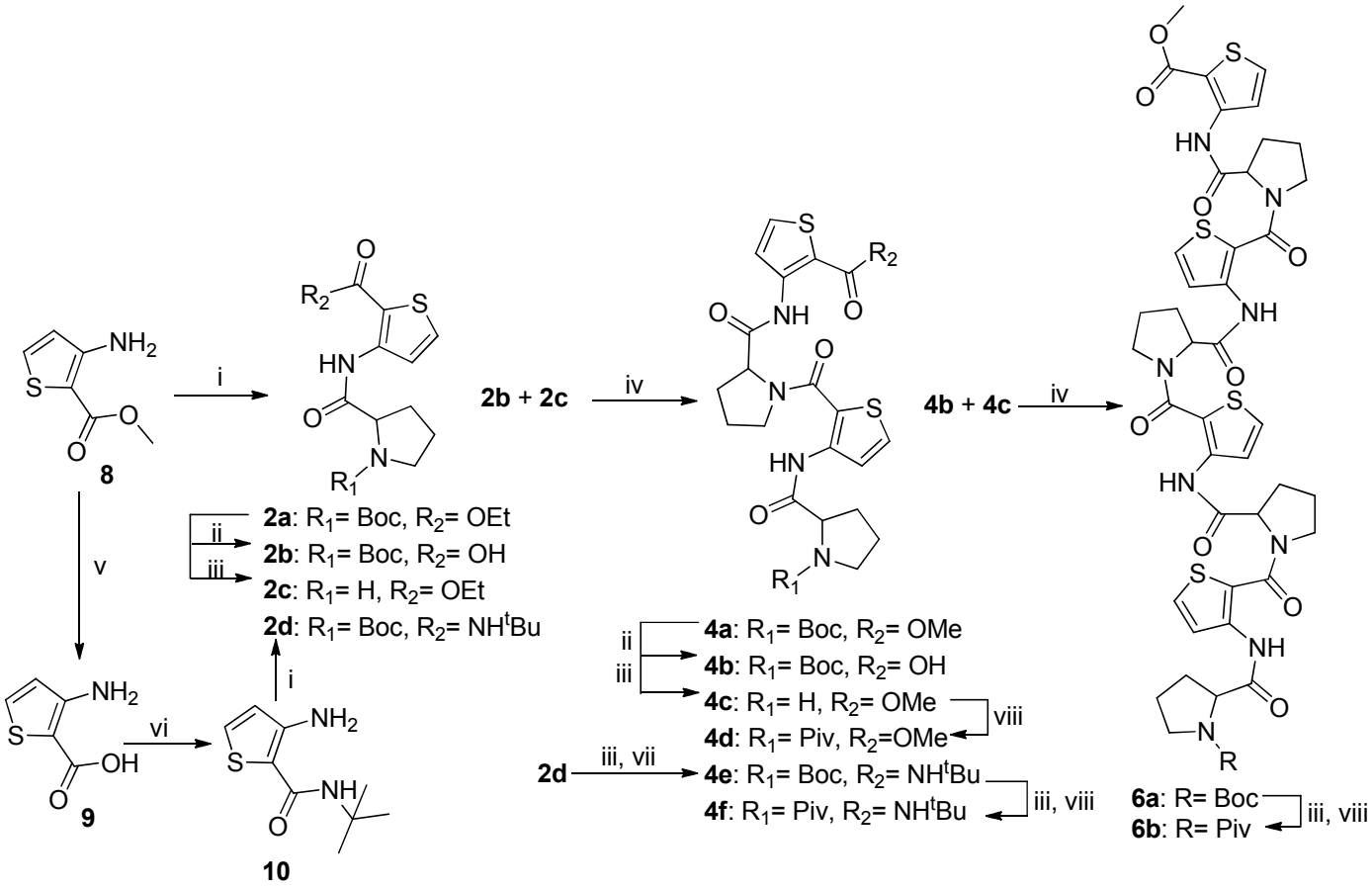


Scheme 1. Reagents and conditions: (i) Boc ^{L}Pro-OH, ethyl chloroformate, Et_3N, THF, 80 °C, 48 h; (ii) aq. LiOH, MeOH, rt, 4 h; (iii) TFA:DCM (1:1), rt, 2 h; (iv) DCC, HOBt, Et_3N, DCM, rt, 12h; (v) Piv-Cl, Et_3N, DCM, rt, 4 h; (vi) $^{t}BuNH_2$, Et_3N, EDC.HCl, CH_3CN, (vii) HBTU, HOBt, Et_3N, CH_3CN, rt, 12h.

Compound **7** was synthesized by the reported procedure.[1]

References:

(1) Gaschow, M.; Kuerschner, L.; Neumann, U.; Pietsch, M.; Laser, R.; Koglin, N.; Eger, K. *J. Med. Chem*. **1999**, *42*, 5437.

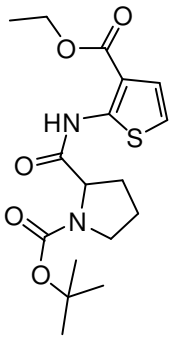


Scheme 2: Reagents and conditions: (i) Boc ^{L}Pro-OH, ethyl chloroformate, Et_3N, DCM, 80 °C, 48 h; (ii) aq. LiOH, MeOH, rt, 4 h; (iii)TFA:DCM (1:1), rt, 2 h; (iv) DCC, HOBt, Et_3N, DCM, rt, 12h; (v) 2N NaOH, 60 °C, 5h; (vi) $^{t}BuNH_2$, EDC.HCl, Et_3N, CH_3CN, rt, 12h; (vii) **2b**, DCC, HOBt, Et_3N, DCM, rt, 12h; (viii) Piv-Cl, Et_3N, DCM, rt, 4 h.

General Method for the preparation of Dipeptides 1a and 2a:

To a solution of Boc ^{L}Proline (0.2 g, 0.9 mmol, 1 equiv) in THF at 0 °C, ethyl chloroformate (0.11 g, 1.0 mmol, 1.2 equiv), Et_3N (0.14 mL, 1.0 mmol, 1.2 equiv) were added followed by the addition of amino esters **7** (0.15 g, 0.8 mmol, 1 equiv) in case of **1a** and **8** (0.17 g, 1.02 mmol, 1.1 equiv) in case of **2a**, respectively, and stirred for 30 min at 0 °C. Then the reaction mixture was refluxed for 48 h at 80 °C. Later, the reaction mixture was filtered and the solvent was stripped off under reduced pressure. The residue was taken into DCM and the organic layer was washed sequentially with sat. $KHSO_4$, brine, sat. $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude products which were purified by column chromatography.

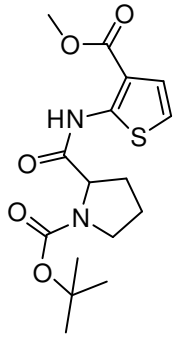
tert-butyl 2-((3-(ethoxycarbonyl)thiophen-2-yl)carbamoyl)pyrrolidine-1-carboxylate (1a):



1a

Compound **1a** was isolated as a yellow solid (0.3 g, 85%); m.p: 66-69 °C; $[\alpha]^{26}_{D}$: -120° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3276, 3019, 2982, 2400, 1685, 1550, 1498, 1478, 1238, 1215, 1034, 927, 747, 702, 668. ^{1}H NMR (400 MHz, $CDCl_3$) δ: $11.54_{rotamer}$(0.45H), $11.38_{rotamer}$(0.55H), 7.20-7.17 (d, *J* = 5.4 Hz, 1H), 6.73-6.71 (d, *J* = 4.5 Hz, 1H), $4.53_{rotamer}$ (0.45H), $4.50_{rotamer}$ (0.55H), 4.36-4.25 (q, *J* = 7.1 Hz, 2H), 3.61-3.45 (m, 2H), 2.24-2.14 (m, 4H), 1.95-1.88 (t, *J* = 6.8 Hz, 3H), $1.48_{rotamer}$ (4H), $1.33_{rotamer}$ (5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.4, 169.9, 164.9, 123.8, 115.9, 113.3, 80.5, 61.3, 60.6, 46.7, 31.2, 29.6, 28.2, 24.4, 23.8, 14.2; ESI-MS: 369.3233 $(M+H)^+$, 391.3003 $(M+Na)^+$, 407.2976 $(M+K)^+$; Elemental analysis calculated for $C_{17}H_{24}N_2O_5S$: C, 55.42; H, 6.65; N, 8.56; S, 8.70; Found: C, 55.6; H, 6.65; N, 8.56; S, 8.76.

tert-butyl 2-((3-(methoxycarbonyl)thiophen-2-yl)carbamoyl)pyrrolidine-1-carboxylate (2a):



2a

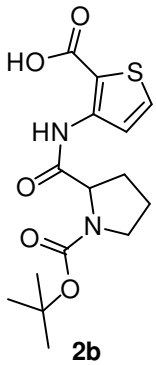
Compound **2a** was isolated as a white solid (0.3 g, 90%); m.p: 67-70 °C; $[\alpha]^{26}_{D}$: -138° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3308, 3015, 1684, 1570, 1388, 1282, 1216, 1160, 1095, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ: $10.75_{rotamer}$ (0.45H), $10.62_{rotamer}$ (0.55H), 8.15-8.12 (d, *J* = 5.6 Hz, 1H), 7.47 (bs, 1H), $4.44_{rotamer}$ (0.45H), $4.30_{rotamer}$ (0.55H), 4.16-4.06 (q, ethyl acetate), 3.87 (s, 3H), 3.64-3.58 (m, 2H), 2.20-2.17 (m, 2H), 2.04 (s, ethyl acetate), 1.93 (m,2H), $1.49_{rotamer}$ (4H), $1.33_{rotamer}$ (5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.0, 170.4, 164.1, 154.1, 143.8, 131.6, 122.0, 110.7, 80.4, 61.9, 61.3, 51.9, 46.8, 31.3, 30.0, 28.1 23.1, 14.0; ESI-MS:

355.3549 $(M+H)^+$, 377.3449 $(M+Na)^+$, 393.2878 $(M+K)^+$; Elemental analysis calculated for $C_{16}H_{22}N_2O_5S$: C, 54.22; H, 6.26; N, 7.90; S, 9.05; Found: C, 55.56; H, 6.50, N, 6.85; S, 10.66.

General method for ester hydrolysis:

To the solutions of esters **1a**, **2a**, **3a** and **4a** (10 mmol, 1 equiv) in methanol, $LiOH \cdot H_2O$ (40 mmol, 4 equiv) was added in water (12 mL) at 0 °C and the reaction mixture was stirred for 12 h. After the complete consumption of the starting material, the solvent was evaporated under reduced pressure and the residue was treated with sat. $KHSO_4$ solution followed by extraction with DCM (2 X 25 mL). The corresponding acid derivatives **1b**, **2b**, **3b** and **4b**, respectively, obtained after evaporation of the solvent were carried forward for the next reaction without any purification.

3-(1-(tert-butoxycarbonyl)pyrrolidine-2-carboxamido)thiophene-2-carboxylic acid (2b):



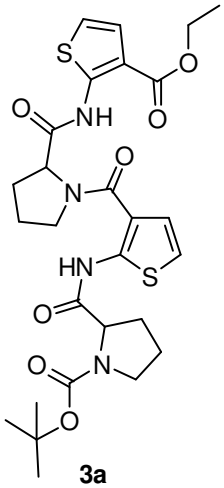
2b

Compound **2b** was isolated as a yellow solid; mp: 155-158 °C; $[\alpha]^{26}_D$: -110° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3684, 3303, 3018, 2980, 2621, 2401, 1681, 1566, 1409, 1216, 1161, 769, 667; ^1H NMR (400 MHz, $CDCl_3$) δ: $10.72_{rotamer}$ (0.45H), $10.68_{rotamer}$ (0.55H), 8.17-8.16 (d, *J* = 4.9 Hz, 1H), 7.57-7.50 (m, 1H), $4.64_{rotamer}$ (0.55H), $4.35_{rotamer}$ (0.45H), 3.64-3.47 (m, 2H), 2.32-2.24 (m, 1H), 2.18 (bs, 1H), 1.96 (bs, 2H), $1.49_{rotamer}$ (5H), $1.33_{rotamer}$ (4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 170.4, 167.8, 167.2, 155.2, 154.2, 145.0, 144.5, 132.8, 122.2, 110.7, 110.2, 80.9, 62.0, 61.1, 47.2, 46.8, 31.3, 30.4, 28.3, 24.3, 23.7; ESI-MS: 341.0 $(M+H)^+$, 362.54 $(M+Na-1)^+$, 363.87 $(M+Na+1)^+$, 364.94 $(M+Na+2)^+$, Elemental analysis calculated for $C_{15}H_{20}N_2O_5S$: C, 52.93; H, 5.92; N, 8.23; S, 9.42; Found: C, 53.65; H, 6.21, N, 7.99; S, 10.50.

General method for Boc deprotection:

The solutions of Boc-peptides **1a**, **2a**, **3a**, **4a**, **5a** and **6a** (3 mmol) were subjected to deprotection using DCM/TFA (1:1, 5 mL) at 0°C. After completion of the reaction (~2 h), the solvent was stripped off, the residue was taken into DCM (30 mL), washed with sat.$NaHCO_3$ solution (3x10 mL) and the product was repeatedly extracted. The organic layer was dried over anhydrous Na_2SO_4. The residues **1c**, **2c**, **3c**, **4c**, **5b** and **6b**, respectively, obtained after evaporation of the solvent were carried forward for the next step without any purification**.**

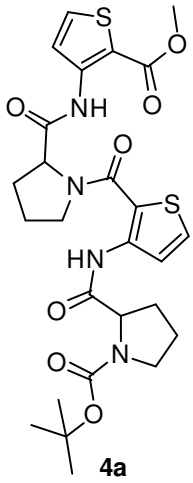
tert-butyl-2((3-(2-((3-(ethoxycarbonyl)thiophen-2-yl)carbamoyl)pyrrolidine-1-carbonyl) thiophen-2-yl)carbamoyl)pyrrolidine-1-carboxylate (3a):



3a

The acid **1b** (0.18 g, 0.5 mmol, 1 equiv) was coupled with the amine **1c** (0.14 g, 0.5 mmol, 1 equiv) using DCC (0.12 g, 0.5 mmol, 1.1 eqiv) and HOBt (0.01 g, 0.1 mmol, 0.2 equiv) in DCM . Work up, as that described for **1a** followed by column chromatographic purification yielded compound **3a** as a white solid (0.2 g, 63%); mp: 86-90 °C; $[\alpha]^{26}_{D}$: -190° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3272, 3019, 1681, 1551, 1399, 1215, 702, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.73 (s, 1H), 11.60 (s, 1H), 7.27-7.25 (bs, 1H), 7.21-7.18 (d, *J* = 5.8 Hz, 1H), 6.82-6.80 (m, 1H), 6.75-6.73 (d, *J* = 5.7 Hz, 1H), 4.97-4.91 (m, 1H), 4.51-4.48 (m, 1H), 4.34-4.24 (q, *J* = 6.9 Hz, 2H), 4.04-3.87 (m, 2H), 3.53-3.33 (m, 2H), 2.37-1.85 (m, 8H), $1.49_{rotamer}$ (4H), 1.40-1.33 (m, 3H), $1.29_{rotamer}$ (5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5, 169.9, 168.9, 166.6, 165.1, 155.0, 153.7, 148.0, 147.2, 123.7, 123.2, 115.9, 115.2, 113.4, 96.0, 80.2, 80.1, 79.4, 61.1, 60.5, 57.4, 50.0, 46.9, 46.5, 36.5, 31.2, 29.8, 28.3, 25.7, 25.1, 24.2, 23.7, 14.2; ESI-MS: 613.4067 $(M+Na)^+$; Elemental analysis calculated for $C_{27}H_{34}N_4O_7S_2$: C, 54.90; H, 5.80; N, 9.48; S, 10.86; Found: C, 52.54; H, 5.42; N, 10.01; S, 10.66.

tert-butyl-2-((2-(2-((2-(methoxycarbonyl)thiophen-3-yl)carbamoyl)pyrrolidine-1-carbonyl) thiophen-3-yl)carbamoyl)pyrrolidine-1-carboxylate (4a):

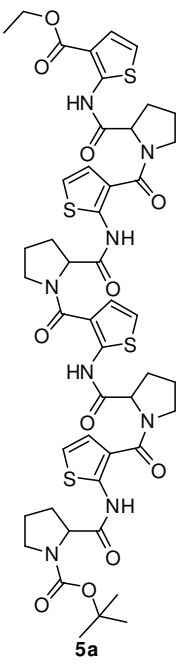


4a

The acid **2b** (0.28 g, 0.8 mmol, 1 equiv) was coupled with the amine **2c** (0.21 g, 0.8 mmol, 1 equiv) using DCC (0.19 g, 0.9 mmol, 1.1 eqiv) and HOBt (0.02 g, 0.1 mmol, 0.2 equiv) in DCM . Work up, as that described for **1a** followed by column chromatographic purification yielded compound **4a** as white solid (0.3 g, 62%); mp: 140-143 °C; $[\alpha]^{26}_{D}$: -120° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3309, 3019, 1557, 1422, 1446, 1403, 1355, 1283, 1246, 1215, 755, 668, 649; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.65-11.58 (m, 1H), 10.67 (s, 1H), 8.22-8.20 (m, 1H), 8.13-8.10 (m, 1H), 7.48-7.43 (m, 2H), $4.90_{rotamer}$ (0.4H), $4.83_{rotamer}$ (0.6H), $4.39_{rotamer}$ (0.5H), $4.23_{rotamer}$ (0.5H), 4.15 (bs, 1H), 4.0-3.97 (m, 1H), 3.82-3.80 (m, 3H), $3.60_{rotamer}$ (0.5H), 3.48-3.42 (m, 1H), $3.32_{rotamer}$ (0.5H), 2.24 (bs, 4H), 2.11 (bs,2H), $2.04_{rotamer}$ (0.55H), 1.94-1.89 (m, 0.45H) 1.79-1.74 (m, 1H), $1.47_{rotamer}$ (4H), $1.28_{rotamer}$

(5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.1, 170.6, 169.4, 164.7. 164.3, 154.8, 153.9. 144.8, 144.0, 131.4, 129.0, 128.7, 122.1, 112.1, 111.9, 110.9, 79.9, 62.7, 61.9, 61.3, 51.8, 48.9, 46.5, 31.3, 30.4, 28.3, 28.1, 24.1, 23.6; ESI-MS: 599.7709 $(M+Na)^+$; Elemental analysis calculated for $C_{26}H_{32}N_4O_7S_2$: C, 54.15; H, 5.59; N, 9.72; S, 11.12; Found: C, 55.2; H, 5.3; N, 9.1; S, 10.8.

tert-butyl-2-((3-(2-((3-(2-((3-(2-((3-(ethoxycarbonyl)thiophen-2-yl)carbamoyl)pyrrolidine-1-carbonyl)thiophen-2-yl)carbamoyl)pyrrolidine-1-carbonyl)thiophen-2-yl)carbamoyl) pyrrolidine-1-carbonyl)thiophen-2-yl)carbamoyl)pyrrolidine-1-carboxylate (5a):

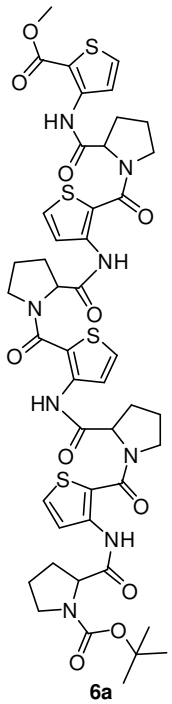


5a

The acid **3b** (0.19 g, 0.3 mmol, 1 equiv) was coupled with the amine **3c** (0.16 g, 0.3 mmol, 1 equiv) using HBTU (0.15 g, 0.4 mmol, 1.2 eqiv), DIPEA (0.08 mL, 0.5 mmol, 1.5 equiv) and HOBt (0.02 g, 0.1 mmol, 0.2 equiv) in dry CH_3CN. Work up, as that described for **1a** followed by column chromatographic purification yielded compound **5a** as white solid (0.21 g, 60%); mp: 180-184 °C; $[\alpha]^{26}_D$: -272° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3270, 3019, 2400, 1685, 1676, 1596, 1545, 1492, 1432, 1400, 1356, 1215, 1034, 927, 755, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.07 (s, 1H), 11.88, (bs, 1H), 11.61 (s, 1H), $11.54_{rotamer}$ (0.5H), $11.46_{rotamer}$ (0.5H), 7.39 (bs, 1H), 7.34-7.29 (m, 3H), 7.25-7.22 (d, *J* = 5.8 Hz, 1H), 6.86-6.84 (d, *J* = 5.8 Hz, 2H), 6.80-6.77 (d, *J* = 5.7 Hz, 1H), 5.01-4.90 (m, 1H), 4.82-4.75 (m, 2H), 4.52-4.48 (m, 1H), 4.39-4.28 (q, *J* = 7.1 Hz, 2H), 4.04-3.90 (m, 4H), 3.80-3.70 (m, 2H), 3.59-3.34 (m, 2H), 2.41-1.98 (m, 10H), 1.89 (bs, 6H), $1.50_{rotamer}$ (4H), 1.38 (t, J = 7.1 Hz, 3H), $1.31_{rotamer}$ (5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.0, 169.1, 166.5, 165.4, 153.8, 148.1, 147.3, 146.8, 123.8, 123.2, 116.0, 115.7, 115.5, 113.4, 80.1, 61.4, 61.0, 60.6, 60.2, 50.1, 49.9, 47.0, 46.6, 38.5, 31.1, 28.9, 28.2, 28.0, 25.7, 25.6, 23.7, 20.9, 20.4, 14.2, 14.1; MALDI-TOF: 1056.4635 $(M+Na-1)^+$, 1057.4781 $(M+Na)^+$, 1058.4454 $(M+Na+1)^+$, 1059.5731 $(M+Na+2)^+$, 1072.4297 $(M+K-1)^+$, 1073.4417 $(M+K)^+$, 1074.4271 $(M+K+1)^+$, 1075.3999 $(M+K+2)^+$; Elemental analysis calculated for $C_{47}H_{54}N_8O_{11}S_4$: C, 54.53; H, 5.26; N, 10.82; S, 12.39; Found: C, 56.6; H, 6.3; N, 10.5; S, 12.8.

tert-butyl 2-((2-(2-((2-(2-((2-(2-((2-(methoxycarbonyl)thiophen-3-yl)carbamoyl)pyrrolidine-1-carbonyl)thiophen-3-yl)carbamoyl)pyrrolidine-1-carbonyl)thiophen-3-yl)carbamoyl) pyrrolidine-1-carbonyl)thiophen-3-yl)carbamoyl)pyrrolidine-1-carboxylate (6a):

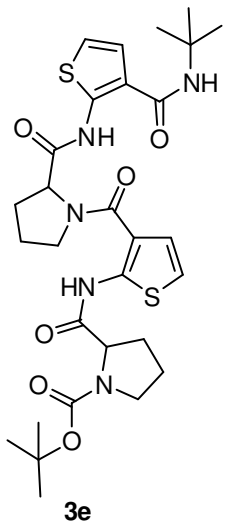
The acid **4b** (0.12 g, 0.2 mmol, 1 equiv) was coupled with the amine **4c** (0.14 g, 0.2 mmol, 1 equiv) using DCC (0.05 g, 0.2 mmol, 1.1 eqiv), HOBt (0.007 g, 0.05 mmol, 0.2 equiv) in dry DCM. Work up, as that described for **1a** followed by column chromatographic purification yielded compound **6a** as white solid (0.17 g, 65%); mp: 155-158 °C; $[\alpha]^{26}_{D}$: -154° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3610, 3445, 3308, 3131, 3018, 2934, 2858, 1694, 1682, 1574, 1567, 1557, 1435, 1446, 1403, 1366, 1283, 1246, 1215, 1435, 1446, 1403, 1366, 1283, 1246, 1215, 1062, 1025, 969, 889, 844, 771, 667, 648; ^{1}H NMR (400 MHz, $CDCl_3$) δ: $11.84_{rotamer}$ (0.5H), $11.80_{rotamer}$ (0.5), $11.76_{rotamer}$ (0.5), $11.74_{rotamer}$ (0.5H), $11.51_{rotamer}$ (0.5H), $11.38_{rotamer}$ (0.5H), 10.60 (s, 1H), 8.23-8.22 (d, *J* = 5.2 Hz, 1H), 8.14-8.09 (m, 2H), 8.04 (bs, 2H), 7.49-7.47 (m, 2H), 7.44-7.43 (m, 2H), $4.82_{rotamer}$ (0.5H), $4.77_{rotamer}$ (0.5H), 4.70-4.65 (m, 1H), 4.55-4.50 (m, 1H), $4.34_{rotamer}$ (0.5H), $4.17_{rotamer}$ (1.5H), 4.04-3.97, (m, 3H), 3.83 (s, 3H), 3.79 (bs, 1H), 3.72 (bs, 1H), $3.59_{rotamer}$ (0.5H), $3.52_{rotamer}$ (0.5H), $3.46_{rotamer}$ (0.5H), $3.33_{rotamer}$ (0.5H), 2.25-1.89 (m, 15H), 1.77-1.72 (m, 1H), $1.43_{rotamer}$ (4H), $1.27_{rotamer}$ (5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 169.4, 164.6, 164.3, 154.8, 153.9, 144.9, 144.2, 131.6, 129.1, 122.1, 121.7, 112.5, 111.9, 110.6, 110.4, 96.0. 79.9, 62.9, 61.8, 61.3. 51.9, 48.9, 48.6, 46.9, 46.5, 31.3, 30.4, 29.04, 28.3, 28.1, 25.4, 24.0, 23.6; MALDI-TOF: 1042.8814 $(M+Na-1)^+$, 1043.8922 $(M+Na)^+$, 1044.8918 $(M+Na+1)^+$, 1058.8540 $(M+K-1)^+$, 1059 $(M+K)^+$; Elemental analysis calculated for $C_{46}H_{52}N_8O_{11}S_4$: C, 54.96; H, 5.21; N, 11.15; S, 12.76; Found: C, 55.5; H, 5.8; N, 10.9; S, 12.8.



6a

tert-butyl 2-((3-(2-((3-(tert-butylcarbamoyl) thiophen-2-yl)carbamoyl)pyrrolidine-1-carbonyl)thiophen-2-yl)carbamoyl)pyrrolidine-1-carboxylate (4e):

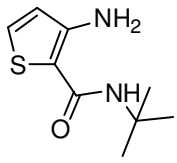
The acid **3b** (0.18 g, 0.33 mmol, 1equiv) was coupled with ^{t}BuNH$_2$ (0.1 mL, 1.01 mmol, using HBTU (0.19 g, 0.5 mmol, 1.5 equiv) and DIPEA (0.11 mL, 0.6 mmol, 2 equiv). Work up, as that described for **1a** followed by column chromatographic purification yielded compound **4e** (0.1 g, 50%) as brownish yellow solid; mp: 83-86 °C; $[\alpha]^{26}_{D}$: -142° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}):



3e

3368, 2976, 1682, 1548, 1453, 1313, 1216, 1161, 917, 853, 759, 694, 663; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.69$_{rotamer}$ (0.4H), 11.63 (s, 1H), 11.58, $_{rotamer}$ (0.6H), 8.20-8.17 (d, *J* = 5.6 Hz, 1H), 8.12-8.10 (m, 1H), 7.48-7.43 (m, 1H), 7.27-7.24 (d, J = 5.4 Hz, 1H), 5.44, (s, 1H), 4.90-4.82 (m, 1H), 4.41-4.36 (m, 1H), 4.28-4.18 (m, 1H), 4.04-3.96 (m, 1H), 3.66-3.23 (m, 2H), 2.23-1.62 (m, 8H), 1.47$_{rotamer}$ (4H), 1.34 (s, 9H), 1.28$_{rotamer}$ (5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.4, 166.5, 164.7, 146.4, 145.7, 123.7, 120.7, 115.9, 115.3, 80.1, 60.9, 51.5, 50.6, 49.9, 46.7, 38.4, 28.6, 28.0, 24.3; MALDI-TOF: 639.7768 $(M+Na-1)^+$, 640.7768 $(M+Na)^+$, 641.7773 $(M+Na+1)^+$, 655.7349 $(M+K-1)^+$, 656.7327 $(M+K)^+$, 657.7293 $(M+Na+1)^+$; Elemental analysis calculated for $C_{29}H_{39}N_5O_6S_2$: C, 54.96; H, 5.21; N, 11.15; S, 12.76; Found: C, 55.5; H, 5.8; N, 10.9; S, 12.8.

3-amino-N-(tert-butyl)thiophene-2-carboxamide (10):



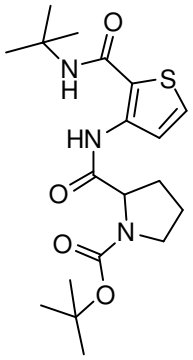
10

The amino ester **8** (0.1 g, 0.5 mmol, 1 equiv) was subjected to hydrolysis using 5N NaOH (4 mL) by heating the reaction mixture at 60 °C for 12 h. Later, the solvent was evaporated under reduced pressure, the residue obtained was taken into DCM, and washed with sat $KHSO_4$ solution (2x10 mL), The organic layer was dried over Na_2SO_4, and evaporated, which gave the free amino acid **9** as a yellow solid. This amino acid **9** (0.09 g, 0.58 mmol, 1 equiv) was coupled with $^{t}BuNH_2$ (0.3 mL, 2.92 mmol, 5 equiv) using HBTU (0.33 g, 0.87 mmol, 1.5 equiv) and DIPEA (0.2 mL, 1.16 mmol, 2 equiv).

Work up, as that described for **1a** followed by column chromatographic purification yielded compound **10** as a pasty mass (0.1 g, 80%); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.07-7.04 (d, *J* = 5.3Hz, 1H), 6.54-6.52 (d, *J* = 5.3 Hz, 1H), 5.26 (bs, 1H), 1.42 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 164.6, 152.0, 125.7, 121.4, 104.0, 51.4, 29.1; ESI-MS: 221.2014 $(M+Na)^+$; Elemental analysis calculated for $C_9H_{14}N_2OS$: C, 54.52; H, 7.12; N, 14.13; S, 16.17; Found: C, 53.5; H, 7.8; N, 15.9; S, 16.8.

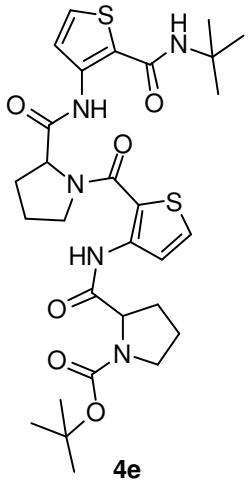
tert-butyl 2-((2-(tert-butylcarbamoyl)thiophen-3-yl)carbamoyl)pyrrolidine-1-carboxylate (2d):

To a solution of Boc ^{L}Proline (0.47 g, 2.22 mmol, 1.1 equiv) in THF at 0 °C, ethyl chloroformate (0.2 mL, 2.42 mmol, 1.2 equiv), Et_3N (0.33 mL, 2.42 mmol, 1.2 equiv) were


2d

added followed by the addition of **10** (0.4 g, 2.02 mmol, 1 equiv) and stirred for 30 min at 0 °C. Then the reaction mixture was refluxed for 48 h at 80 °C. Later, the reaction mixture was filtered and the solvent was stripped off under reduced pressure. The residue was taken into DCM and the organic layer was washed sequentially with sat. $KHSO_4$, brine, sat. $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude product which after purification by column chromatography gave **2d** as a brownish yellow solid; mp: 53-55 °C; $[\alpha]^{26}_D$: +2° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3681, 3483, 3423, 3352, 3012, 2967, 2400, 1629, 1535, 1475, 1364, 1306, 1218, 1096, 1082, 772, 669; ^{1}H NMR (200 MHz, $CDCl_3$) δ: $11.50_{rotamer}$ (0.4H), $11.42_{rotamer}$ (0.6H), 8.15-8.13 (d, *J* = 5.3 Hz, 1H), 7.24-7.20 (m, 1H), 5.46 (bs, 1H), 4.45-$4.40_{rotamer}$ (0.5H), 4.28-$4.22_{rotamer}$(0.5H), 3.68-3.42 (m, 2H), 2.25-1.83 (m, 4H), $1.49_{rotamer}$ (4H), $1.42_{rotamer}$ (5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 176.4, 175.1, 170.9, 170.4, 163.2, 154.7, 153.9, 142.2, 125.8, 125.4, 122.7, 113.7, 113.6, 79.8, 61.6, 61.1, 58.7, 52.0, 46.7, 46.4, 46.0, 31.2, 30.5, 28.6, 28.0, 24.0, 23.5, 23.4; ESI-MS: 418.7926 $(M+Na)^+$; Elemental analysis calculated for $C_{19}H_{29}N_3O_4S$: C, 57.70; H, 7.39; N, 10.62; S, 8.11; Found: C, 59.6; H, 8.4; N, 11.2; S, 7.9.

tert-butyl-2-((2-(2-((2-(tert-butylcarbamoyl)thiophen-3-yl)carbamoyl)pyrrolidine-1-carbonyl)thiophen-3-yl)carbamoyl)pyrrolidine-1-carboxylate (4e):


4e

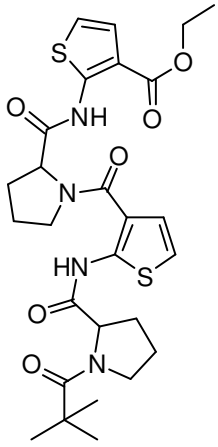
Compound **2d** was subjected to Boc deprotection following the similar procedure mentioned to obtain **2c**. The free amine obtained was coupled with **2b** (0.31 g, 0.93 mmol, 1.1 equiv) using DCC (0.19 g, 0.93 mmol, 1.1 equiv) and HOBt (0.02 g, 1.69 mmol, 0.2 equiv) in dry DCM. Later, the reaction mixture was dilute dwith DCM and washed sequentially with sat. $KHSO_4$, brine, sat. $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude product which was purified by column chromatography yielded **4e** as a white solid (0.31 g, 60%), mp: 116-119 °C; $[\alpha]^{26}_D$: -140° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3246, 3019, 2979, 1686, 1560, 1403, 1289, 1215, 1092, 890; ^{1}H NMR (400 MHz, $CDCl_3$) δ: $11.65_{rotamer}$ (0.4H), 11.59, (s, 1H), $11.56_{rotamer}$ (0.6H), 8.17-8.16 (d, *J* = 5.3 Hz) 8.09-8.08 (m, 1H), 7.45-7.39 (dd, *J* = 4.5Hz, 1H), 7.24-7.22 (d, *J* = 5.3 Hz,

1H), 5.44 (s, 1H), 4.88$_{rotamer}$ (0.5H), 4.80$_{rotamer}$ (0.5H), 4.36$_{rotamer}$ (0.5H), 4.19$_{rotamer}$ (1.5H), 3.96 (bs, 1H), 3.58$_{rotamer}$ (0.5H), 3.48-3.45 (m, 1H), 3.29$_{rotamer}$ (0.5H), 2.22-2.18 (bs, 4H), 2.10-2.07 (m, 2H), 1.90-1.87 (m, 1H), 1.76 (bs, 1H), 1.45$_{rotamer}$ (4H), 1.32 (s, 9H), 1.26$_{rotamer}$ (5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.0, 170.5, 169.3, 164.5, 163.4, 154.8, 153.9, 144.5, 142.5, 128.8, 125.8, 122.9, 121.9, 113.7, 112.6, 112.3, 79.9, 62.6, 61.8, 61.3, 52.1, 48.8, 46.8, 46.5. 31.2, 28.7, 28.0, 24.0, 23.6; ESI-MS: 640.6573 $(M+Na)^+$; Elemental analysis calculated for $C_{29}H_{39}N_5O_6S_2$: C, 56.38; H, 6.36; N, 11.34; S, 10.38; Found: C, 57.1; H, 6.9; N, 11.1; S, 10.1.

General Method for Pivolyl protection:

To the solutions of amines **3c**, **4c**, and the amines obtained from the Boc deprotection of **3e**, **4e**, **5a**, and **6a** (10 mmol, 1equiv) in DCM, Piv-Cl (12 mmol, 1.2 equiv) and Et_3N (15 mmol, 1.5 equiv) were added at 0 °C, and the reaction mixture was stirred for 12 h. After the complete consumption of the starting material, the reaction mixture was diluted with DCM and washed sequentially with sat. $KHSO_4$ solution, brine, sat. $NaHCO_3$ solution and water, the organic layer was dried over Na_2SO_4. Later, the solvent was evaporated and the residues obtained were purified by column chromatography to yield the products **3d**, **4d**, **3f**, **4f**, **5b** and **6b**, respectively.

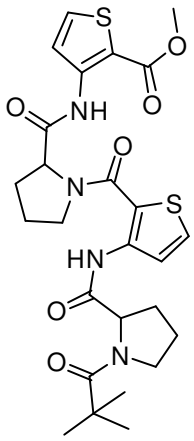
Ethyl 2-(1-(2-(1-pivaloylpyrrolidine-2-carboxamido)thiophene-3-carbonyl)pyrrolidine-2-carboxamido)thiophene-3-carboxylate (3d):



3d

Compound **3d** was isolated as a yellow solid (0.20 g, 70%), mp: 168-172 °C; $[\alpha]^{26}_D$: -102° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3018, 1671, 1616, 1542, 1405, 1290, 1215, 1089, 1033, 922, 853, 756, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.63 (s, 1H), 11.54 (s, 1H), 7.24 (bs, 1H), 7.21-7.20 (d, J = 5.8 Hz, 1H), 6.79-6.77, (d, J = 6.2 Hz, 1H), 6.75-6.74 (d, *J* = 5.8 Hz, 1H), 4.84-4.81 (m 1H), 4.74-4.70 (m, 1H), 4.33-4.27 (q, J = 7Hz, 2H), 4.0-3.94 (m, 1H), 3.90-3.85 (m,1H), 3.82-3.77 (m,1H), 3.73-3.67 (m, 1H), 2.36-2.29 (m,1H), 2.21-2.09 (m, 3H), 2.07-1.95 (m, 3H), 1.93-1.87 (m, 1H), 1.36-1.33 (t, J = 7Hz, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.8, 169.7, 169.1, 165.1, 148.0, 147.5, 123.7, 122.9, 115.9, 115.5, 115.0, 62.7, 60.5, 49.9, 48.2, 39.0, 28.4, 27.2, 25.6, 14.2; ESI-MS: 575.4474 $(M+H)^+$, 597.4312 $(M+Na)^+$; Elemental analysis calculated for $C_{27}H_{34}N_4O_6S_2$: C, 56.43; H, 5.96; N, 9.75; S, 11.16; Found: C, 55.93; H, 5.91; N, 10.70; S, 10.1.

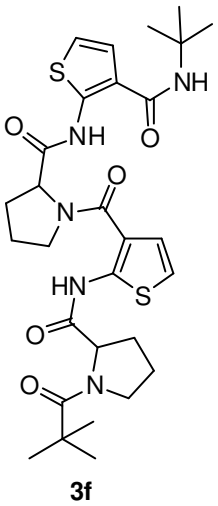
methyl 3-(1-(3-(1-pivaloylpyrrolidine-2-carboxamido)thiophene-2-carbonyl)pyrrolidine-2-carboxamido)thiophene-2-carboxylate (4d):



4d

Compound **4d** was isolated as a white solid (0.20 g, 70%), mp: 156-158 °C; $[\alpha]^{26}_{D}$: -128° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3309, 3017, 1680, 1572, 1445, 1361, 1282, 1246, 1215, 1088, 754, 667, 649; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.48 (s, 1H), 10.63 (s, 1H), 8.21-8.20 (d, *J* = 5.5 Hz, 1H), 8.12-8.10 (d, J = 5.5 Hz, 1H),7.47-7.46 (d, J = 5.5 Hz, 1H), 7.43-7.42 (d, *J* = 5.5 Hz, 1H), 4.77 (bs, 1H), 4.61-4.58 (dd, *J* = 8.7 Hz, 1H), 4.15-4.12 (m, 1H), 4.00-3.96 (m, 1H), 3.82 (s, 3H), 3.77-3.74 (m, 1H), 3.68-3.63 (m, 1H), 2.23 (bs, 3H), 2.11-2.07 (m, 2H), 2.03-1.94 (m, 2H), 1.85-1.80 (m, 1H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.6, 170.4, 169.4, 164.6, 164.4, 145.0, 144.0, 131.5, 128.7, 122.4, 122.1, 111.7, 63.6, 62.9, 51.9, 48.8, 48.2, 39.0, 28.6, 27.3, 25.5; ESI-MS: 583.5084 $(M+Na)^+$; Elemental analysis calculated for $C_{26}H_{32}N_4O_6S_2$: C, 55.70; H, 5.75; N, 9.99; S, 11.44; Found: C, 54.8; H, 5.5; N, 10.10; S, 10.9.

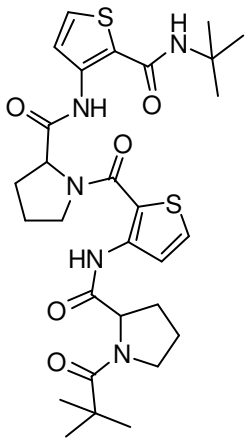
N-(3-(tert-butylcarbamoyl)thiophen-2-yl)-1-(2-(1-pivaloylpyrrolidine-2-carboxamido) thiophene-3-carbonyl)pyrrolidine-2-carboxamide (3f):



3f

Compound **3f** was isolated as a yellow solid (0.20 g, 70%), mp: 106-109 °C; $[\alpha]^{26}_{D}$: -102° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3019, 1674, 1626, 1547, 1485, 1405, 1361, 1215, 758, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.59 (s, 1H), 11.54 (s, 1H), 7.33 (bs, 1H), 6.87-6.86 (d, *J* = 5.8 Hz, 1H), 6.76-6.75 (d, *J* = 4.6 Hz, 2H), 5.73 (s, 1H), 4.84-4.82 (m, 1H), 4.73-4.71 (m, 1H), 4.04-4.01 (m, 1H), 3.89-3.84 (m, 1H), 3.81-3.77 (m, 1H), 3.72-3.67 (m, 1H), 3.50-3.46 (q, ethyl acetate), 2.37-2.32 (m, 1H), 2.17-2.10 (m, 3H), 2.07-2.01 (m, 1H), 2.0-1.94 (m, 2H), 1.91-1.87 (m, 1H), 1.41 (s, 9H), 1.30 (s. 9H), 1.24-1.23 (ethyl acetate); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.0, 169.7, 169.4, 166.5, 164.8, 147.1, 146.1, 123.4, 120.5, 116.2, 115.6, 115.3, 65.8, 62.8, 61.3, 51.7, 50.0, 48.3, 39.1, 28.9, 27.4, 25.7, 15.2; ESI-MS: 603.11 $(M+H)^+$, 624.04 $(M+Na)^+$; Elemental analysis calculated for $C_{29}H_{39}N_5O_5S_2$: C, 57.88; H, 6.53; N, 11.64; S, 10.66; Found: C, 58.2; H, 7.1; N, 10.30; S, 9.8.

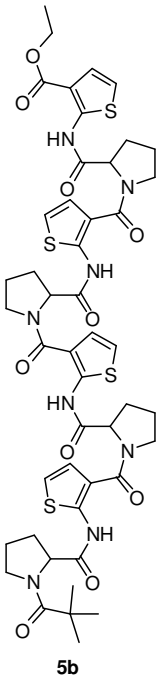
N-(2-(tert-butylcarbamoyl)thiophen-3-yl)-1-(3-(1-pivaloylpyrrolidine-2-carboxamido) thiophene-2-carbonyl)pyrrolidine-2-carboxamide (4f):



4f

Compound **4f** was isolated as a white solid (0.20 g, 70%), mp: 118-120 °C; $[\alpha]^{26}_{D}$: 158° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3019, 2400, 1685, 1628, 1559, 1423, 1404, 1365, 1289, 1215, 928, 771, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.55 (s, 1H), 11.51 (s, 1H), 8.18-8.17 (d, *J* = 5.5 Hz, 1H), 8.13-8.11 (d, *J* = 5.5 Hz, 1H), 7.40-7.39 (d, *J* = 5.3 Hz, 1H), 7.25-7.24 (d, *J* = 5.5 Hz, 1H), 5.45 (s, 1H), 4.74 (bs, 1H), 4.61-4.58 (dd, *J* = 8.5 Hz, 1H), 4.19-4.18 (m, 1H), 4.00-3.94 (m, 1H), 3.78-3.72 (m, 1H), 3.66-3.61 (m, 1H), 2.29-2.15 (m, 3H), 2.09-2.04 (m, 2H), 2.01—1.90 (m, 2H), 1.85-1.75 (m, 1H), 1.36 (s, 9H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.6, 170.3, 169.5, 164.4, 163.5, 144.7, 142.7, 128.4, 125.7, 123.0, 122.3, 113.5, 112.1, 63.6, 62.9, 52.1, 48.8, 48.2, 39.0, 28.8, 27.4, 25.5; ESI-MS: 601.84 $(M)^+$, 603.11 $(M+2H)^+$, 624.11 $(M+Na)^+$; Elemental analysis calculated for $C_{29}H_{39}N_5O_5S_2$: C, 57.88; H, 6.53; N, 11.64; S, 10.66; Found: C, 58.1; H, 6.5; N, 11.30; S, 9.91.

ethyl-2-(1-(2-(1-(2-(1-(2-(1-pivaloylpyrrolidine-2-carboxamido)thiophene-3-carbonyl) pyrrolidine-2-carboxamido)thiophene-3-carbonyl)pyrrolidine-2-carboxamido)thiophene-3-carbonyl)pyrrolidine-2-carboxamido)thiophene-3-carboxylate (5b):

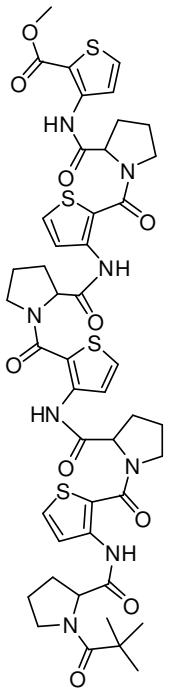


5b

Compound **5b** was isolated as a white solid (0.20 g, 70%), mp: 170-174 °C; $[\alpha]^{26}_{D}$: -266° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3439, 3263, 3114, 3015, 2982, 2447, 1674, 1600, 1489, 1435, 1403, 1357, 1179, 1097, 1033, 912, 876, 852, 833, 754, 699, 666; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.04 (s, 1H), 11.86 (s, 1H), 11.57 (s, 1H), 11.42 (s, 1H), 7.31-7.27 (m, 3H), 7.22-7.20 (d, *J* = 5.5 Hz, 1H), 6.83-6.81 (d, J = 5.8 Hz, 2H), 6.79-6.78 (d, *J* = 5.5 Hz, 1H), 6.77-6.75 (d, *J* = 5.8 Hz, 1H), 4.83-4.80 (t, *J* = 7.3 Hz, 1H), 4.77-4.74 (m, 1H), 4.72-4.68 (m, 1H), 4.67-4.64 (dd, *J* = 8.4 Hz, 3.9Hz, 1H), 4.33-4.20 (q, *J* = 7 Hz, 2H), 4.14-4.09 (q, ethyl acetate), 4.01-3.94 (m, 1H), 3.91-3.85 (m, 4H), 3.76-3.71 (m, 3H), 2.34-2.25 (m, 3H), 2.18-1.95 (m, 10H), 1.92-1.84 (m, 3H), 1.36-1.33 (t, *J* = 7.2 Hz, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.6, 169.6, 168.9, 166.4, 165.3, 148.0, 147.1, 147.0, 146.6, 123.7, 123.6, 123.1, 116.0 115.5, 115.3, 115.2, 62.7, 60.6, 50.0, 48.3, 38.9,

28.8, 28.3, 27.2, 25.6, 14.1; MALDI-TOF: 1018.7148 $(M)^+$, 1019.7191 $(M+H)^+$, 1020.7153 $(M+2H)^+$, 1043.7069 $(M+Na-1)^+$, 1041.7144 $(M+Na)^+$, 1042.7101 $(M+Na+1)^+$, 1043.7061 $(M+Na+2)^+$, 1056.6581 $(M+K-1)^+$, 1057.6554 $(M+K)^+$, 1058.6558 $(M+K+1)^+$, 1059.6614 $(M+K+2)^+$; Elemental analysis calculated for $C_{47}H_{54}N_8O_{10}S_4$: C, 55.38; H, 5.34; N, 10.99; S, 12.58; Found: C, 56.5; H, 5.8; N, 10.80; S, 12.60.

methyl-3-(1-(3-(1-(3-(1-(3-(1-pivaloylpyrrolidine-2-carboxamido)thiophene-2-carbonyl) pyrrolidine-2-carboxamido)thiophene-2-carbonyl)pyrrolidine-2-carboxamido)thiophene-2-carbonyl)pyrrolidine-2-carboxamido)thiophene-2-carboxylate (6b):



6b

Compound **6b** was isolated as a white solid (0.20 g, 70%), mp: 170-174 °C; $[\alpha]^{26}_D$: -158° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3243, 3131, 3019, 2400, 1681, 1563, 1557, 1444, 1404, 1360, 1283, 1246, 1215, 1096, 668, 648; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.83 (s, 1H), 11.76 (s, 1H), 11.38 (s, 1H), 10.60 (s, 1H), 8.23-8.22 (d, *J* = 5.5 Hz, 1H), 8.14-8.12 (d, *J* = 5.5 Hz, 1H), 8.10-8.08 (d, *J* = 5.5 Hz, 1H), 8.06-8.04 (d, J = 5.3 Hz, 1H), 7.49-7.48 (d, J = 5.3 Hz, 2H), 7.44-7.43 (d, *J* = 5 Hz, 2H), 4.69 (bs, 2H), 4.55-4.52 (dd, *J* = 8.3 Hz, 3.8 Hz, 2H), 4.17 (bs, 1H), 4.14-4.08 (q, ethyl acetate), 4.04-3.94 (m, 3H), 3.83 (s, 3H), 3.80-3.75 (m, 2H), 3.73-3.70 (m, 1H), 3.67-3.61 (m, 1H), 2.27-2.16 (m, 6H), 2.13-2.01 (m, 6H), 1.95-1.89 (m, 4H), 1.80-1.77 (m, 1H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.6, 170.3, 169.6, 169.4, 164.5, 164.5, 164.3, 144.9, 144.5, 144.1, 131.9, 129.2, 129.0, 122.1, 121.7, 112.3, 112.1, 111.8, 110.5, 63.6, 62.9, 60.3, 51.9, 48.8, 48.3, 38.9, 29.6, 29.0, 27.3, 25.5; MALDI-TOF: 1018.7148 $(M)^+$, 1019.7191 $(M+H)^+$, 1020.7153 $(M+2H)^+$, 1026.9773 $(M+Na-1)^+$, 1027.1059 $(M+Na)^+$, 1028.7229 $(M+Na+1)^+$, 1029.7169 $(M+Na+2)^+$, 1042.6831 $(M+K-1)^+$, 1043.6793 $(M+K)^+$, 1044.6777 $(M+K+1)^+$, 1047.6775 $(M+K+2)^+$; Elemental analysis calculated for $C_{46}H_{52}N_8O_{10}S_4$: C, 54.96; H, 5.21; N, 11.15; S, 12.76; Found: C, 56.2; H, 6.1; N, 10.6; S, 11.9.

Crystal Data: Data for the compounds **1a**, **2b**, **3a** and **4d** were collected on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 25.00°. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, Oscillation / frame -0.3º, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration with different exposure time per frame and SADABS correction applied.

Data for the compound **4f** was collected on SMART APEX-II CCD using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 25.00°. Crystal to detector distance 5.00 cm, 512 x 512 pixels / frame, Oscillation / frame -0.5º, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration with different exposure time per frame and SADABS correction applied.

All the structures were solved by direct methods using SHELXTL. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL) was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. The refinements were carried out using SHELXL-97.

Crystal data for 1a:

Single crystals of the compound **1a** were grown by slow evaporation of the solution a mixture of pet. ether and ethyl acetate. Pale yellow plate-like crystal of approximate size 0.42 x 0.17 x 0.04 mm^3, was used for data collection. Multi-run data acquisition. Total scans = 5, total frames = 2809, exposure / frame = 20.0 sec / frame, θ range = 1.75 to 25.50º, completeness to θ of 25.50º is 100.0 %. $C_{17}H_{24}N_2O_5S$, M = 368.44. Crystals belong to Tetragonal, space group $P4_32_12$, a = 9.2214(4), b = 9.2214 (4), c = 46.482(2) Å, V = 3952.6(3) $Å^3$, Z = 8, D_c = 1.238 g /cc, μ (Mo–Kα) = 0.191 mm^{-1}, 44585, reflections measured, 3674 unique [I>2σ(I)], R value 0.0454, wR2 = = 0.1193. Largest diff. peak and hole 0.159 and -0.173 e. $Å^{-3}$.

Crystal data for 2b:

Single crystals of the compound **2b** were grown by slow evaporation of a solution of ethyl acetate. Colorless plate-like crystal of approximate size 0.29 x 0.20 x 0.04 mm^3, was used for data collection. Multi-run data acquisition. Total scans = 5, total frames = 1271, exposure / frame = 20.0 sec / frame, θ range = 2.06 to 25º, completeness to θ of 25º is 100.0 %. $C_{15}H_{20}N_2O_5S$, M

= 340.39. Crystals belong to Orthorhombic, space group $P2_12_12_1$, a = 7.8940(7) Å b = 10.9470(9) Å, c = 19.7800(2) Å, V = 1709.3(2) Å^3, Z = 4, D_c = 1.323 g/cc, μ (Mo–Kα) = 0.215 mm^{-1}, 7939, reflections measured, 3001 unique [I>2σ(I)], R value 0.0436, wR2 = 0.0826. Largest diff. peak and hole 0.223 and -0.217 e.Å^{-3}.

Crystal data for 3a:

Single crystals of the compound **3a** were grown by slow evaporation of the solution a mixture of pet. ether and ethyl acetate. Colorless needle-like crystal of approximate size 0.14 x 0.04 x 0.04 mm^3, was used for data collection. Multi-run data acquisition. Total scans = 5, total frames = 1271, exposure / frame = 20.0 sec / frame, θ range = 2.18 to 25.00°, completeness to θ of 24.00º is 100.0 %. $C_{27}H_{34}N_4O_7S_2$, M = 590.70. Crystals belong to Orthorhombic, space group $P2_12_12_1$, a = 11.077(1) Å, b = 16.0203(2) Å, c = 17.3250(2) Å, V = 3074.4(6) Å^3, Z = 4, D_c = 1.276 g /cc, μ (Mo–Kα) = 0.221 mm^{-1}, 15654, reflections measured, 5415 unique [I>2σ(I)], R value 0.0586, wR2 = = 0.1467. Largest diff. peak and hole 0.345 and -0.275 e.Å^{-3}.

Crystal data for 4d:

Single crystals of the compound **4d** were grown by slow evaporation of the solution of methanol. Colorless plate-like crystal of approximate size 0.45 x 0.15 x 0.13 mm^3, was used for data collection. Multi-run data acquisition. Total scans = 5, total frames = 1271, exposure / frame = 20.0 sec / frame, θ range = 2.09 to 25.00°, completeness to θ of 25.00º is 99.8 %. $C_{26}H_{32}N_4O_6S_2$, M = 560.68. Crystals belong to Monoclinic space group $P2_1$, a = 7.3385(4)Å, b = 38.880(2)Å, c = 9.7776(6) Å, V = 2780.7(3) Å^3, Z = 4, D_c = 1.339 g /cc, μ (Mo–Kα) = 0.238 mm^{-1}, 14101, reflections measured, 9614 unique [I>2σ(I)], R value 0.0424, wR2 = = 0.0961. Largest diff. peak and hole 0.216 and -0.161 e.Å^{-3}. It has been observed that two molecules with a slight different conformation at the C terminus are packed in the unit cell of the molecule (see Fig-1).

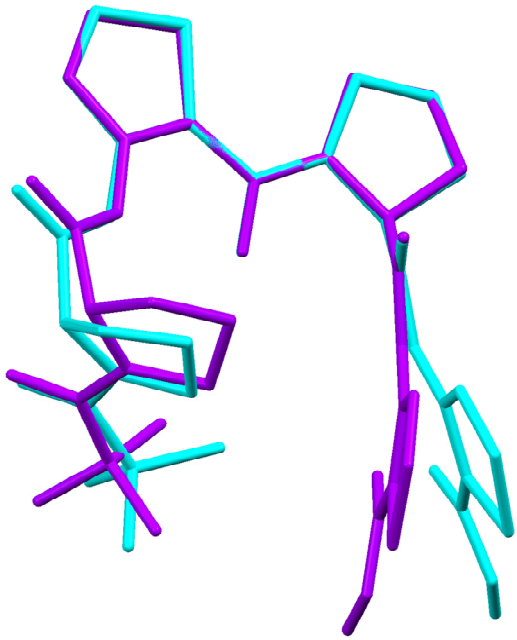
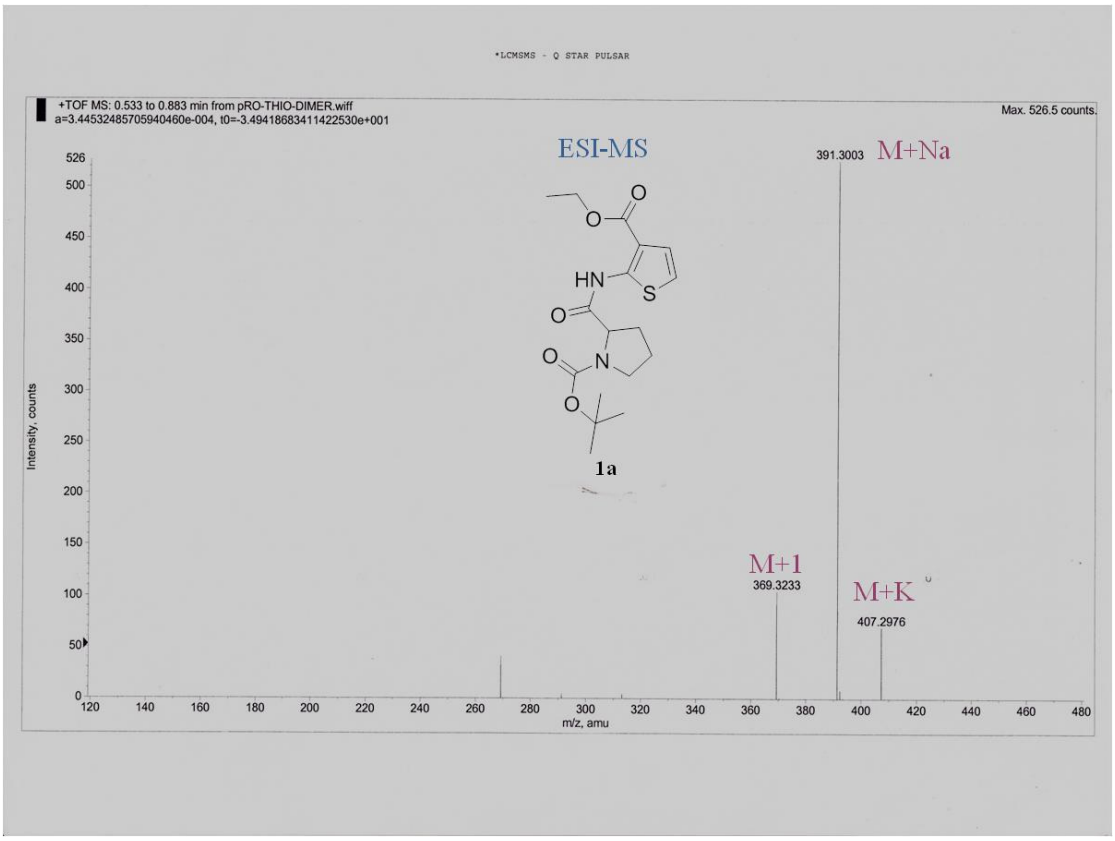


Figure-1: Overlay of the two molecules present in the unit cell of **4d**

Crystal data for 4f:

Single crystals of the compound **4f** were grown by slow evaporation of the solution of methanol. Colorless plate-like crystal of approximate size 0.45 x 0.31 x 0.14 mm^3, was used for data collection. Multi-run data acquisition. Total scans = 5, total frames = 669, exposure / frame = 20.0 sec / frame, θ range = 1.59 to 25.00°, completeness to θ of 25.00º is 100.0 %. $C_{29}H_{35}N_5O_5S_2$, M = 601.77. Crystals belong to Orthorhombic, space group $P2_12_12_1$, a = 9.3121(9) Å, b = 17.9909(2) Å, c = 18.1542(2) Å, V = 3041.4(5) $Å^3$, Z = 4, D_c = 1.314 g /cc, μ (Mo–Kα) = 0.221 mm^{-1}, 13111, reflections measured, 5244 unique [I>2σ(I)], R value 0.0317, wR2 = = 0.0766. Largest diff. peak and hole 0.164 and -0.177 e.$Å^{-3}$.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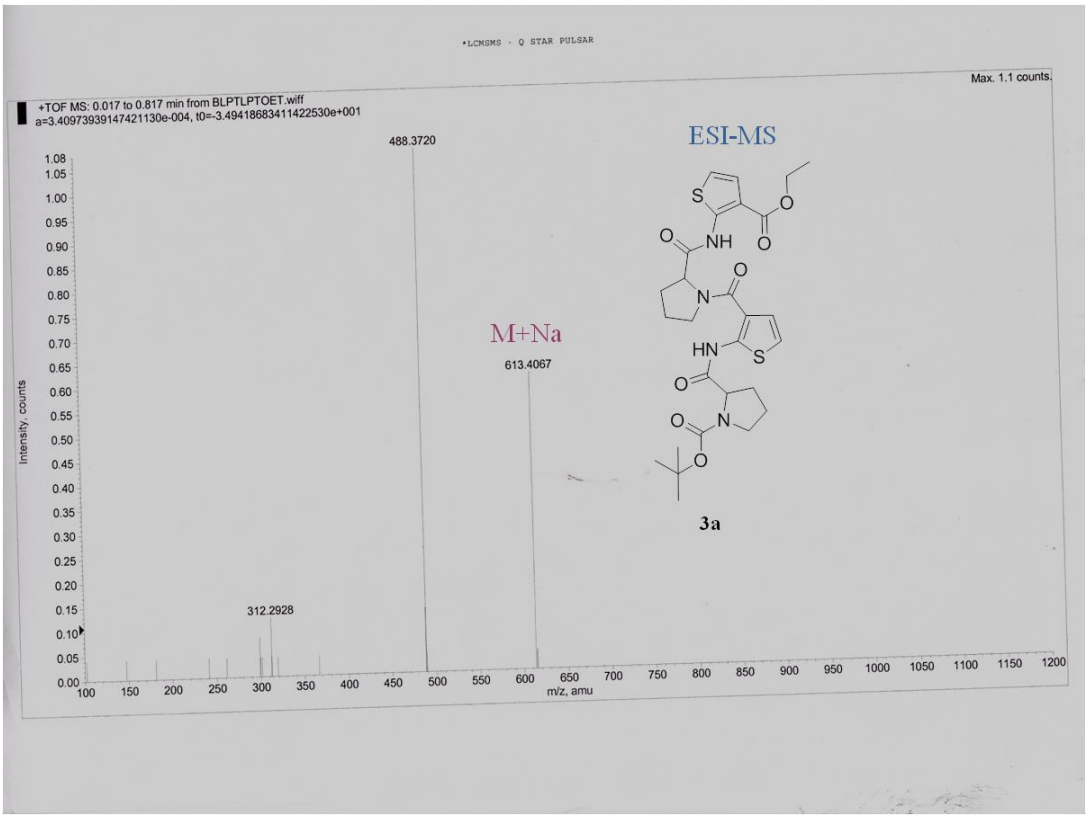
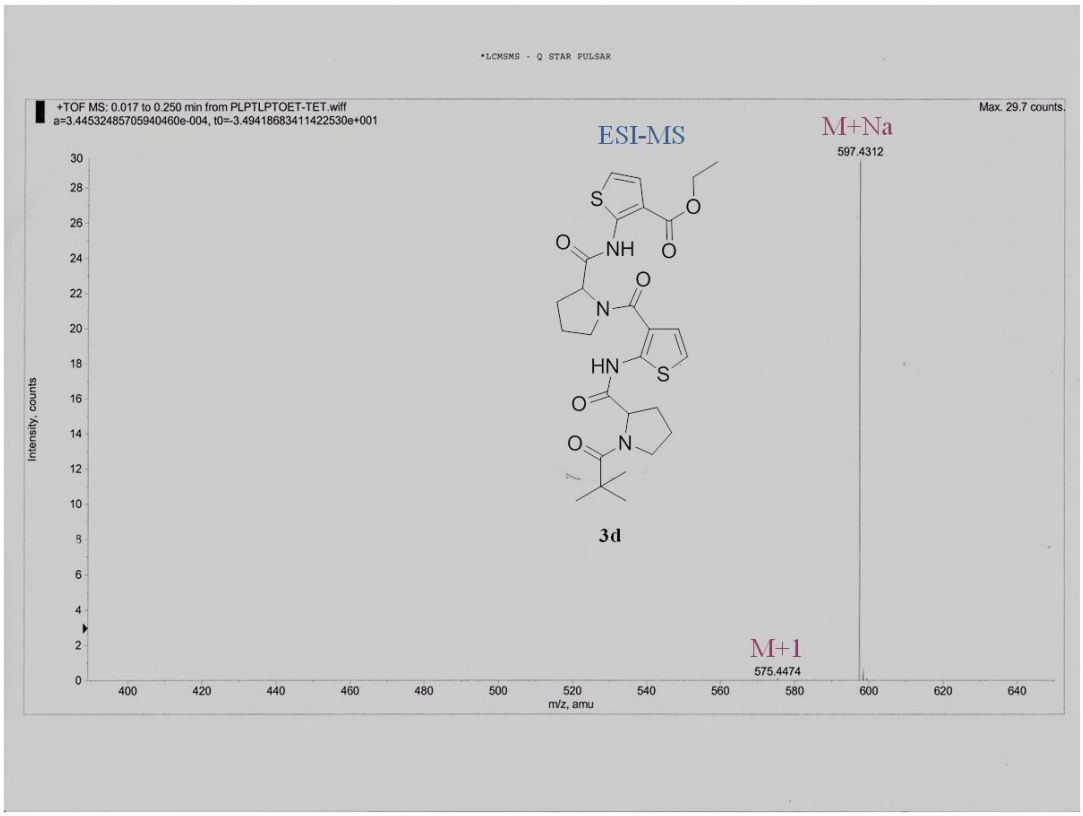
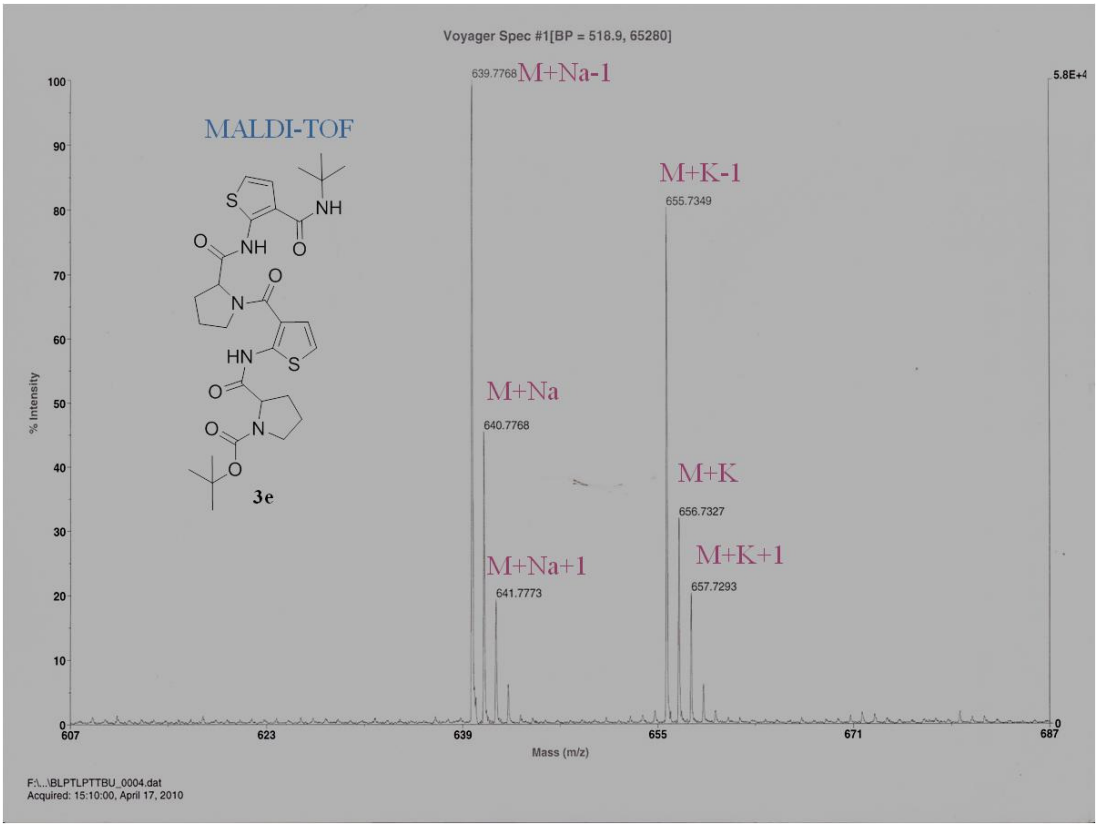
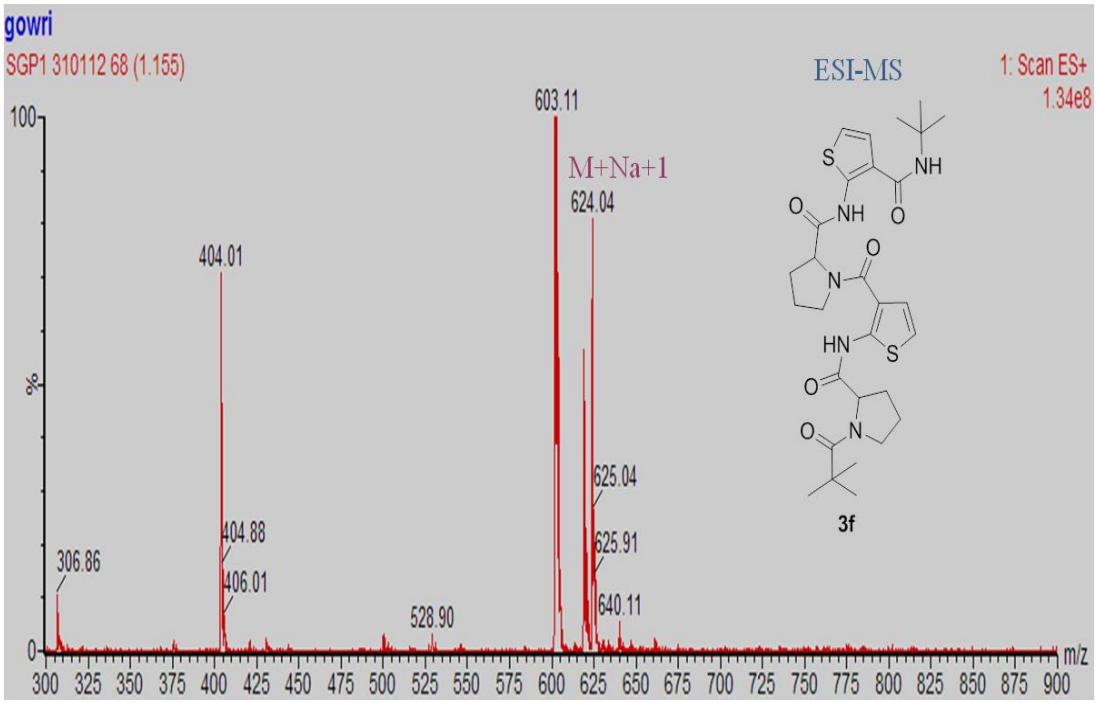
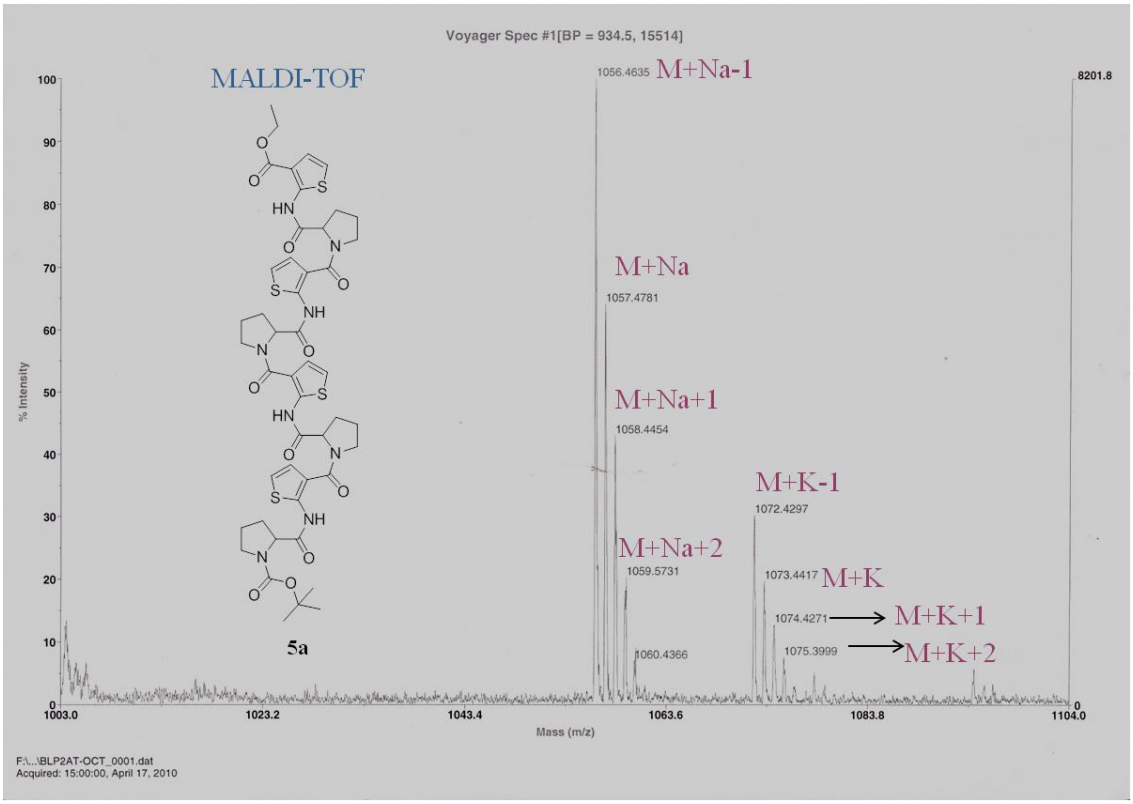
+TOF MS: 0.533 to 0.883 min from pRO-THIO-DIMER.wiff
a=3.44532485705940460e-004, t0=-3.49418683411422530e+001
Max. 526.5 counts.
ESI-MS
391.3003 M+Na
M+1
369.3233
M+K
407.2976
1a
Intensity, counts
m/z, amu

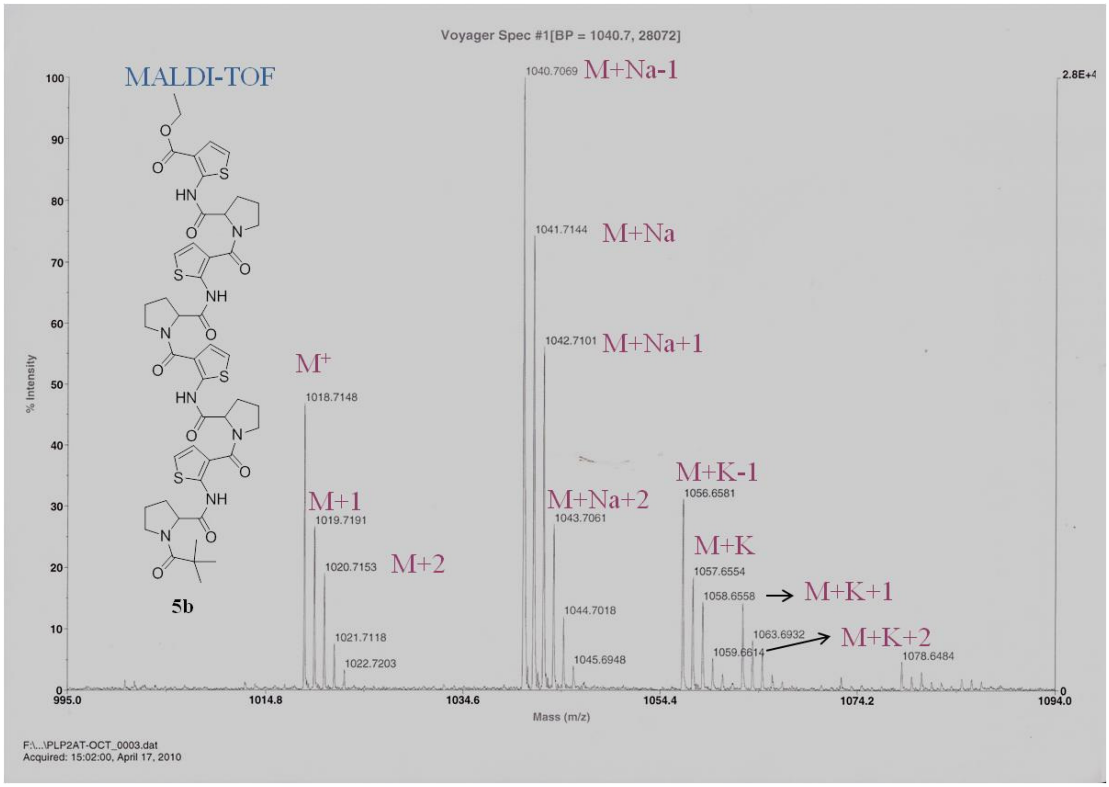

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.817 min from BLPTLPTOET.wiff
a=3.40973939147421130e-004, t0=-3.49418683411422530e+001
Max. 1.1 counts.
488.3720
ESI-MS
M+Na
613.4067
312.2928
3a
Intensity, counts
m/z, amu

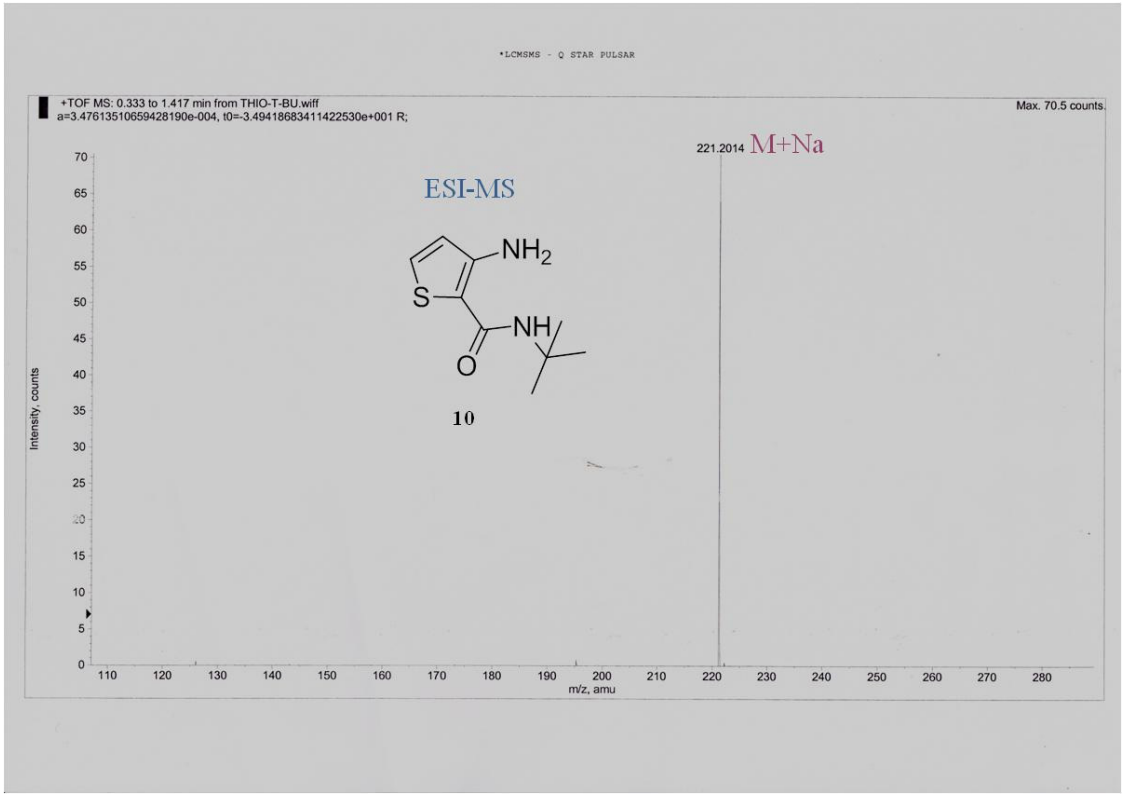

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.250 min from PLPTLPTOET-TET.wiff
a=3.44532485705940460e-004, t0=-3.49418683411422530e+001
Max. 29.7 counts.
ESI-MS
M+Na
597.4312
M+1
575.4474
Intensity, counts
m/z, amu
3d

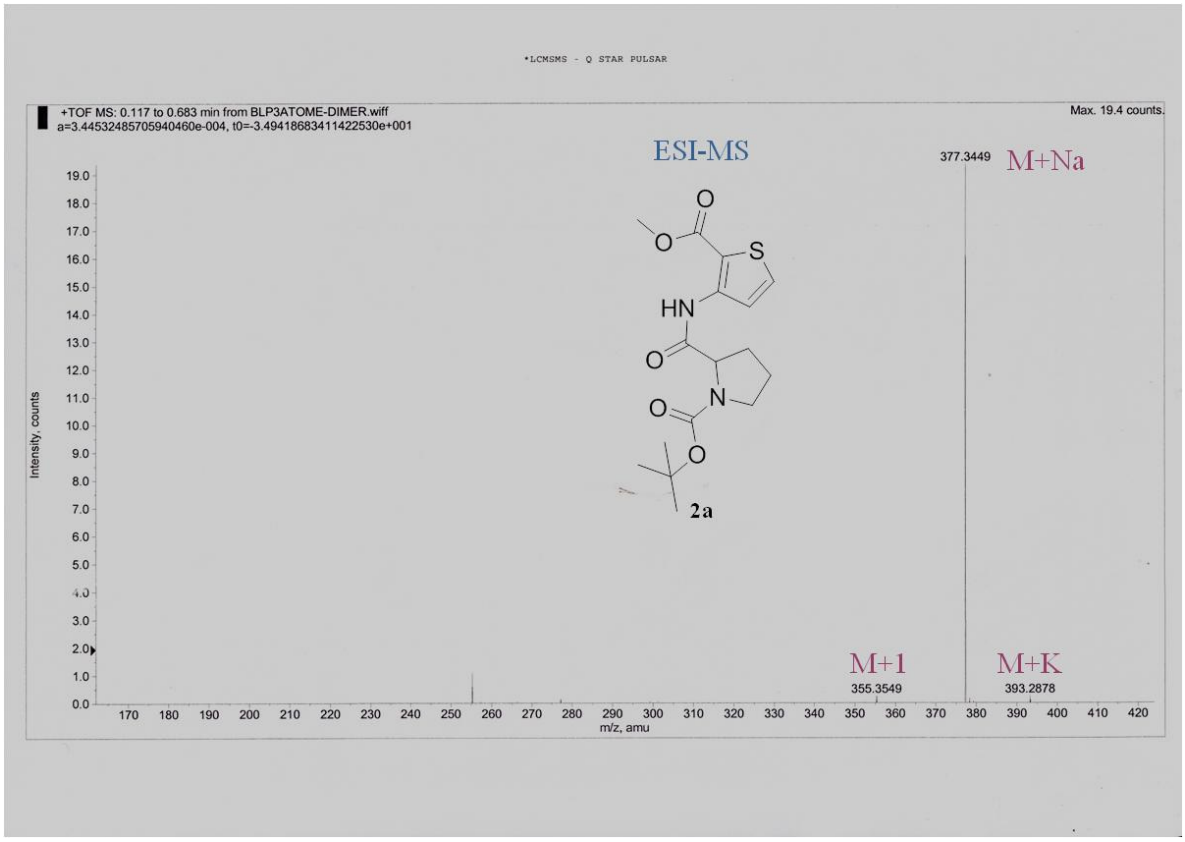

Voyager Spec #1[BP = 518.9, 65280]
MALDI-TOF
639.7768 M+Na-1
M+K-1
655.7349
M+Na
640.7768
M+K
656.7327
M+Na+1
641.7773
M+K+1
657.7293
5.8E+4
% Intensity
Mass (m/z)
F:\...\BLPTLPTTBU_0004.dat
Acquired: 15:10:00, April 17, 2010
3e

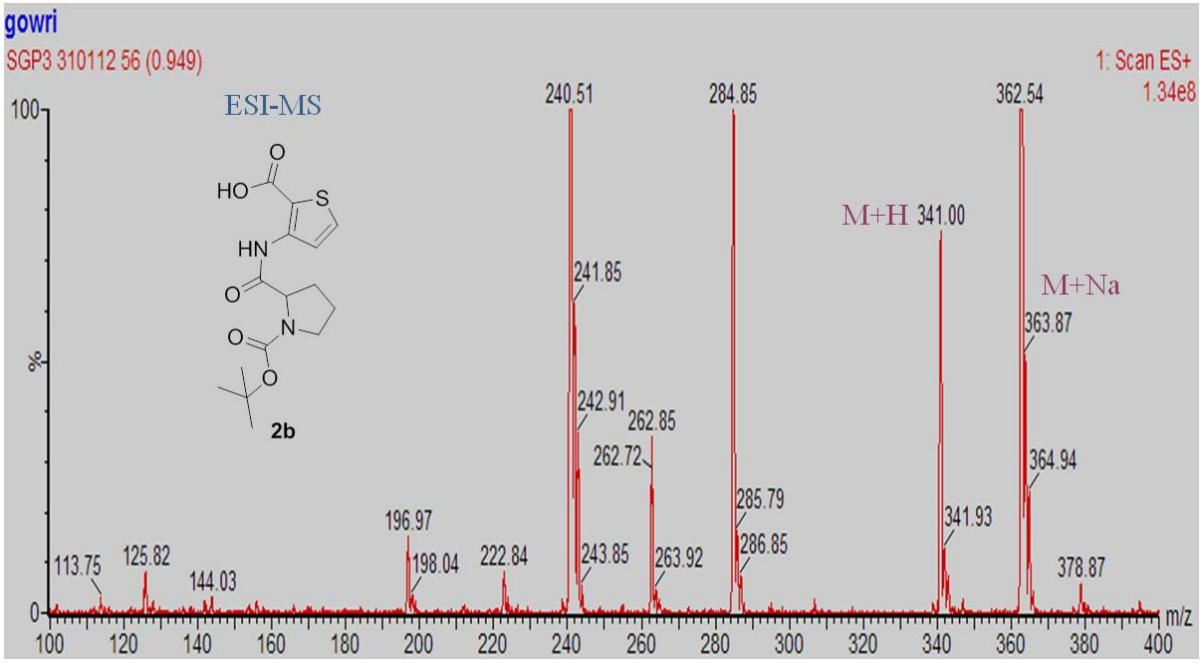

gowri
SGP1 310112 68 (1.155)
ESI-MS
1: Scan ES+
1.34e8
603.11
M+Na+1
624.04
404.01
625.04
625.91
640.11
404.88
406.01
306.86
528.90
3f
%
m/z

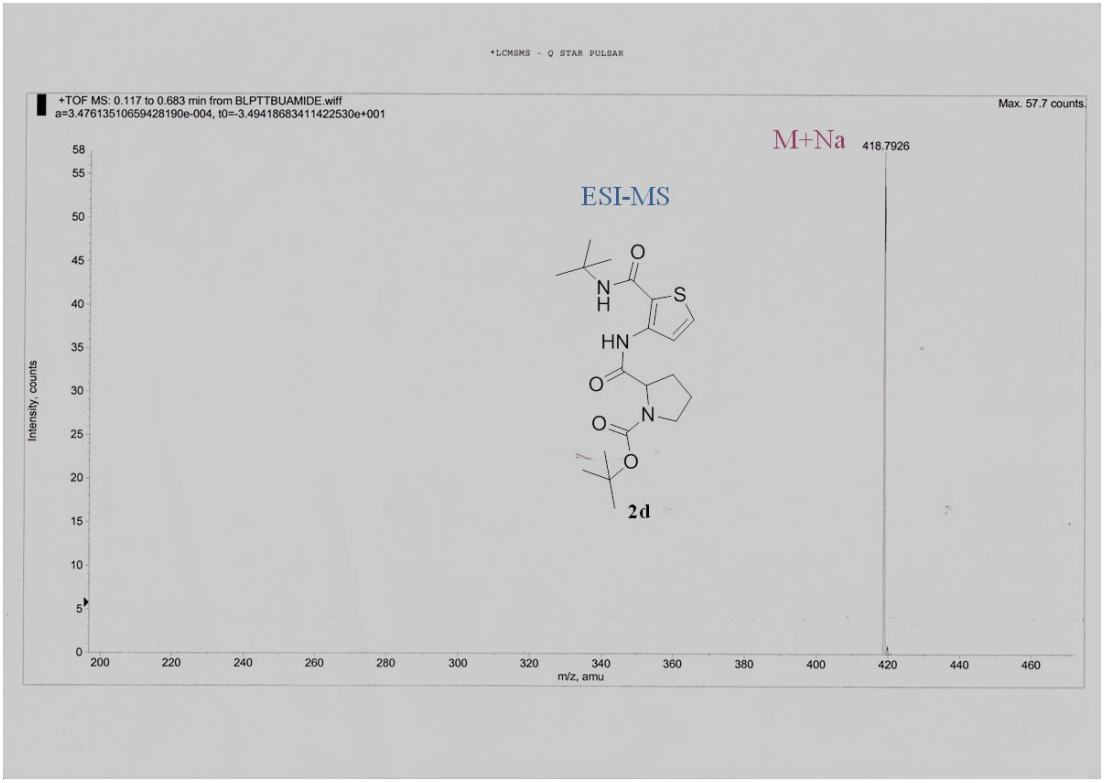

Voyager Spec #1[BP = 934.5, 15514]
MALDI-TOF
1056.4635 M+Na-1
8201.8
M+Na
1057.4781
M+Na+1
1058.4454
M+K-1
1072.4297
M+Na+2
1059.5731
1073.4417 M+K
1074.4271 M+K+1
1075.3999 M+K+2
1060.4366
5a
% Intensity
Mass (m/z)
F:\...\BLP2AT-OCT_0001.dat
Acquired: 15:00:00, April 17, 2010

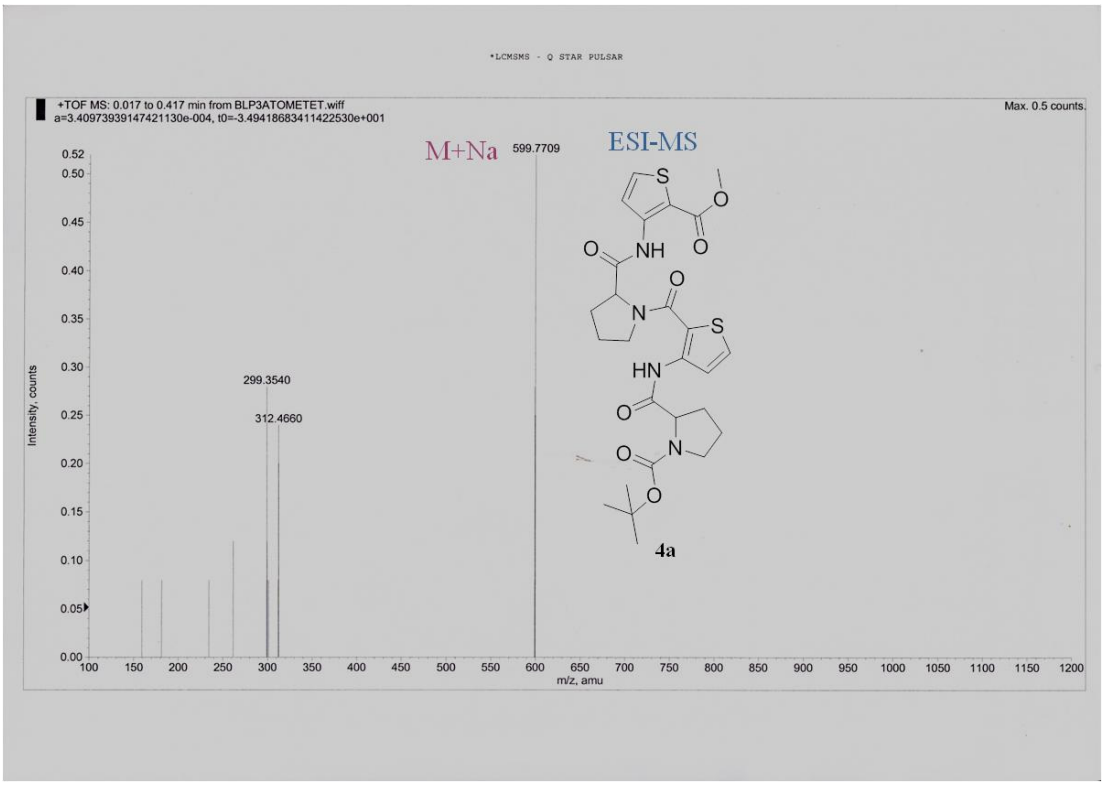

Voyager Spec #1[BP = 1040.7, 28072]
MALDI-TOF
5b
M+
1018.7148
M+1
1019.7191
1020.7153
M+2
1021.7118
1022.7203
1040.7069 M+Na-1
1041.7144 M+Na
1042.7101 M+Na+1
M+Na+2
1043.7061
1044.7018
1045.6948
M+K-1
1056.6581
M+K
1057.6554
1058.6558
M+K+1
1059.6614
1063.6932
M+K+2
1078.6484
% Intensity
Mass (m/z)
F:\...\PLP2AT-OCT_0003.dat
Acquired: 15:02:00, April 17, 2010

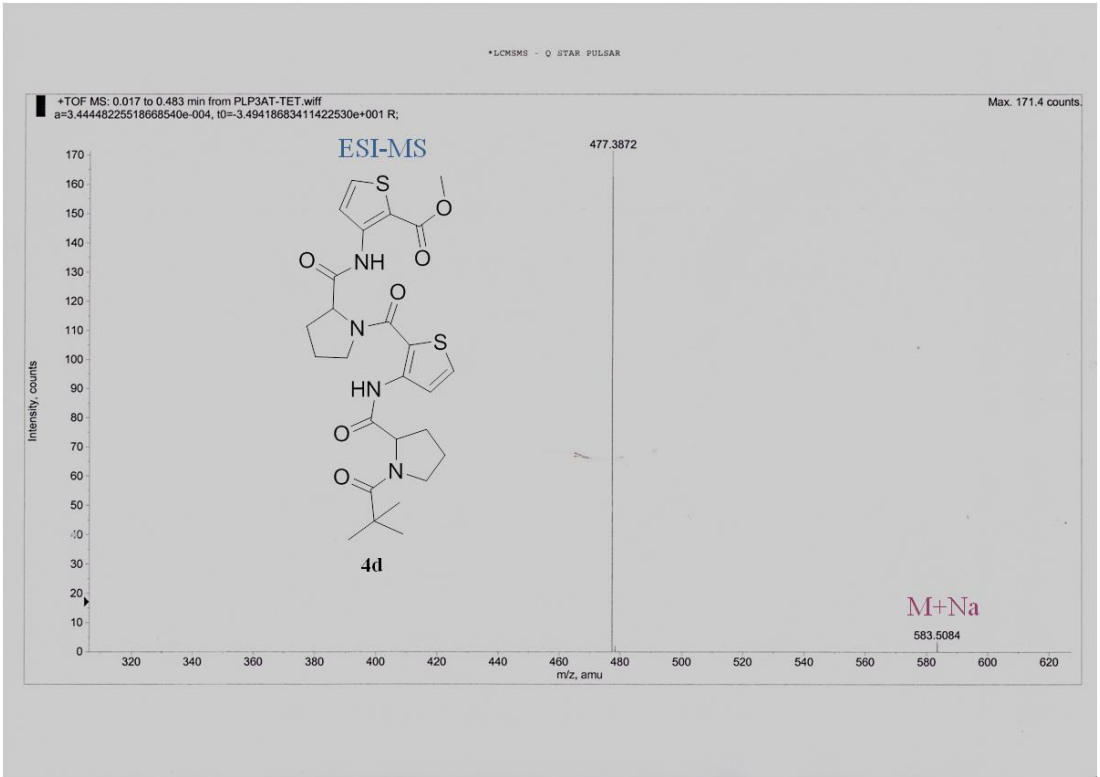

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.333 to 1.417 min from THIO-T-BU.wiff
a=3.47613510659428190e-004, t0=-3.49418683411422530e+001 R;
Max. 70.5 counts.
221.2014 M+Na
ESI-MS
10
Intensity, counts
m/z, amu


*LCMSMS - Q STAR PULSAR
+TOF MS: 0.117 to 0.683 min from BLP3ATOME-DIMER.wiff
a=3.44532485705940460e-004, t0=-3.49418683411422530e+001
Max. 19.4 counts.
ESI-MS
377.3449
M+Na
2a
M+1
355.3549
M+K
393.2878
Intensity, counts
m/z, amu


gowri
SGP3 310112 56 (0.949)
1: Scan ES+
1.34e8
ESI-MS
2b
240.51
284.85
362.54
M+H 341.00
M+Na
241.85
363.87
242.91
262.85
262.72
364.94
285.79
341.93
196.97
286.85
113.75
125.82
144.03
198.04
222.84
243.85
263.92
378.87
%
m/z


*LCMSMS - Q STAR PULSAR
+TOF MS: 0.117 to 0.683 min from BLPTTBUAMIDE.wiff
a=3.476135106594281 90e-004, t0=-3.494186834114225 30e+001
Max. 57.7 counts.
M+Na
418.7926
ESI-MS
2d
Intensity, counts
m/z, amu


*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.417 min from BLP3ATOMETET.wiff
a=3.409739391474211 30e-004, t0=-3.494186834114225 30e+001
Max. 0.5 counts.
M+Na
599.7709
ESI-MS
299.3540
312.4660
4a
Intensity, counts
m/z, amu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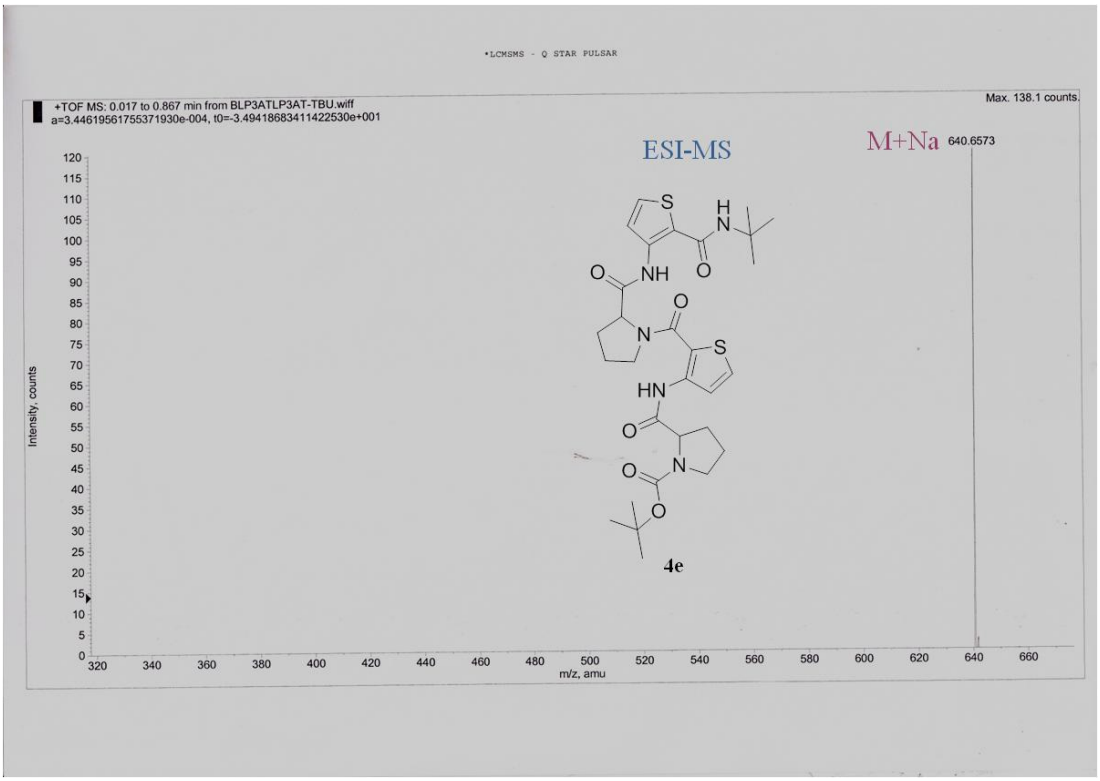
+TOF MS: 0.017 to 0.483 min from PLP3AT-TET.wiff
a=3.44448225518668540e-004, t0=-3.49418683411422530e+001 R;
Max. 171.4 counts.
ESI-MS
477.3872
4d
M+Na
583.5084
Intensity, counts
m/z, amu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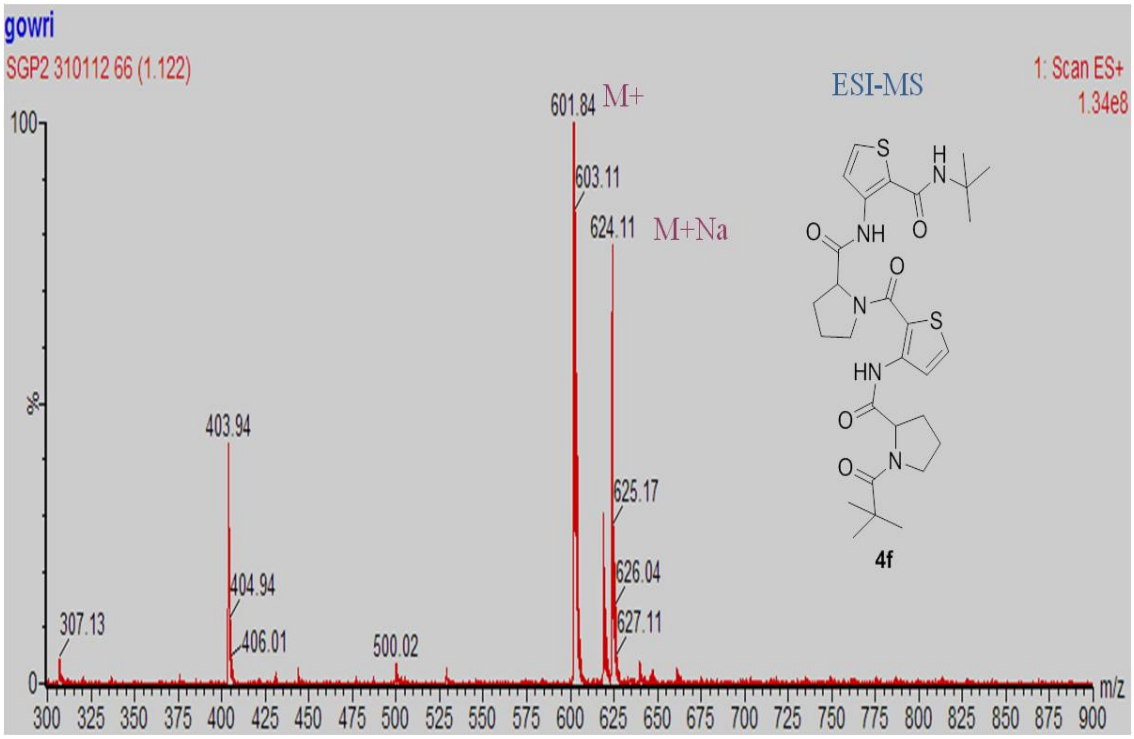
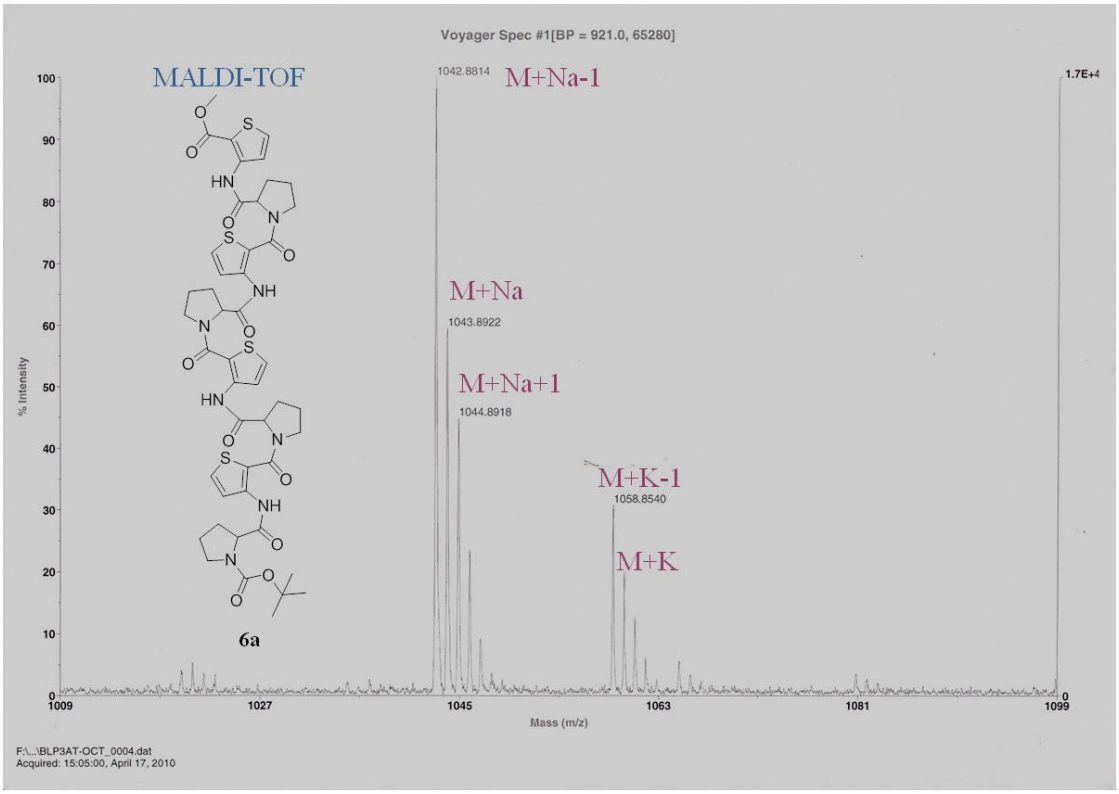
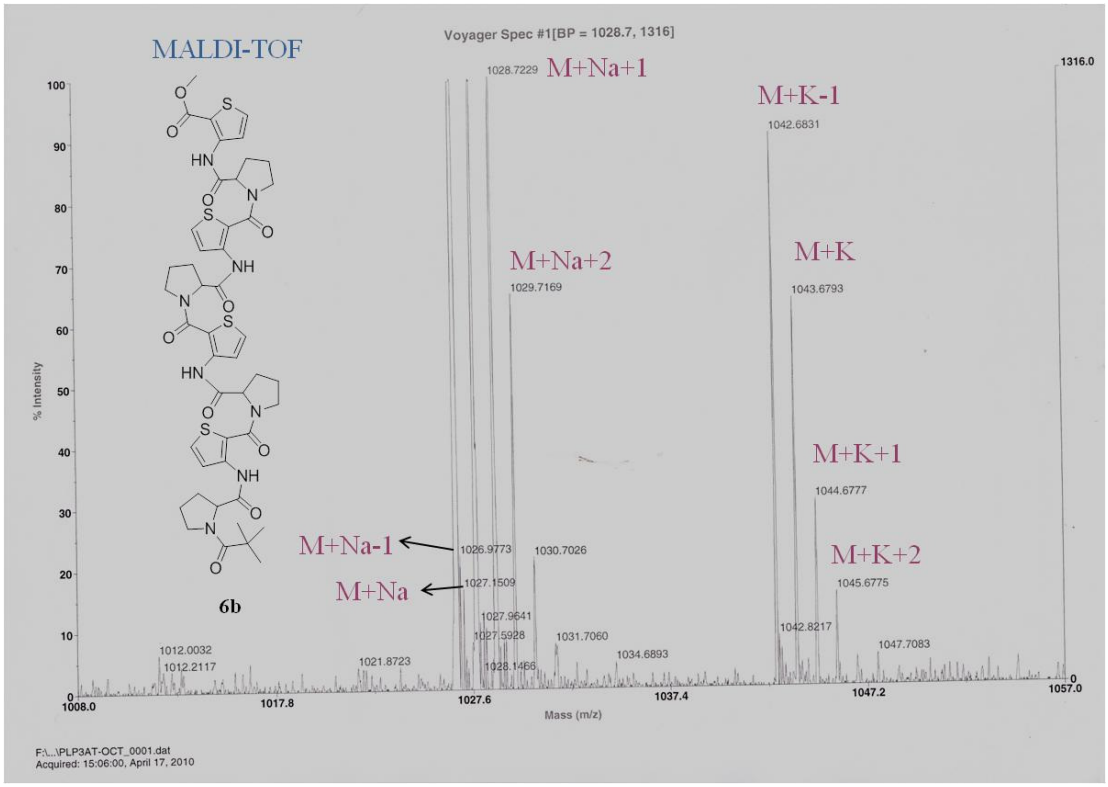
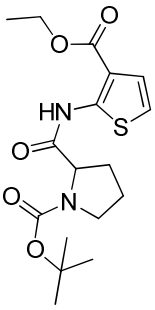
Max. 138.1 counts.
ESI-MS
M+Na 640.6573
4e
Intensity, counts
m/z, amu


gowri
SGP2 310112 66 (1.122)
1: Scan ES+
1.34e8
ESI-MS
601.84 M+
603.11
624.11 M+Na
403.94
625.17
626.04
627.11
404.94
406.01
307.13
500.02
4f
%
m/z


Voyager Spec #1[BP = 921.0, 65280]
MALDI-TOF
1042.8814 M+Na-1
M+Na
1043.8922
M+Na+1
1044.8918
M+K-1
1058.8540
M+K
6a
% Intensity
Mass (m/z)
F:\...\BLP3AT-OCT_0004.dat
Acquired: 15:05:00, April 17, 2010

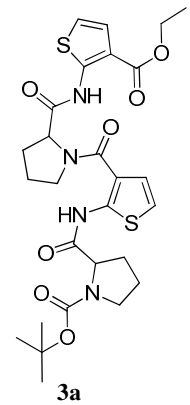

MALDI-TOF
Voyager Spec #1[BP = 1028.7, 1316]
1028.7229 M+Na+1
M+K-1
1042.6831
1316.0
M+Na+2
1029.7169
M+K
1043.6793
M+K+1
1044.6777
M+K+2
1045.6775
M+Na-1
1026.9773
M+Na
1027.1509
1030.7026
1027.9641
1027.5928
1031.7060
1034.6893
1042.8217
1047.7083
1012.0032
1012.2117
1021.8723
1028.1466
6b
% Intensity
Mass (m/z)
F:\...\PLP3AT-OCT_0001.dat
Acquired: 15:06:00, April 17, 2010



1a

^{1}H NMR(200MHz, $CDCl_3$)

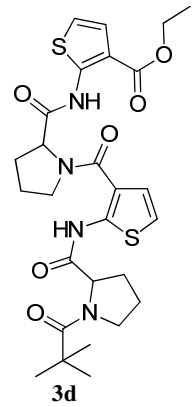
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, 14, 6192).



3a

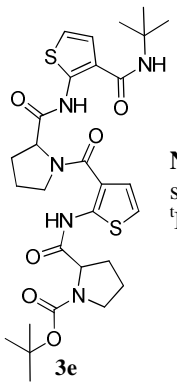
^{1}H NMR(400MHz, $CDCl_3$)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, 14, 6192).



3d

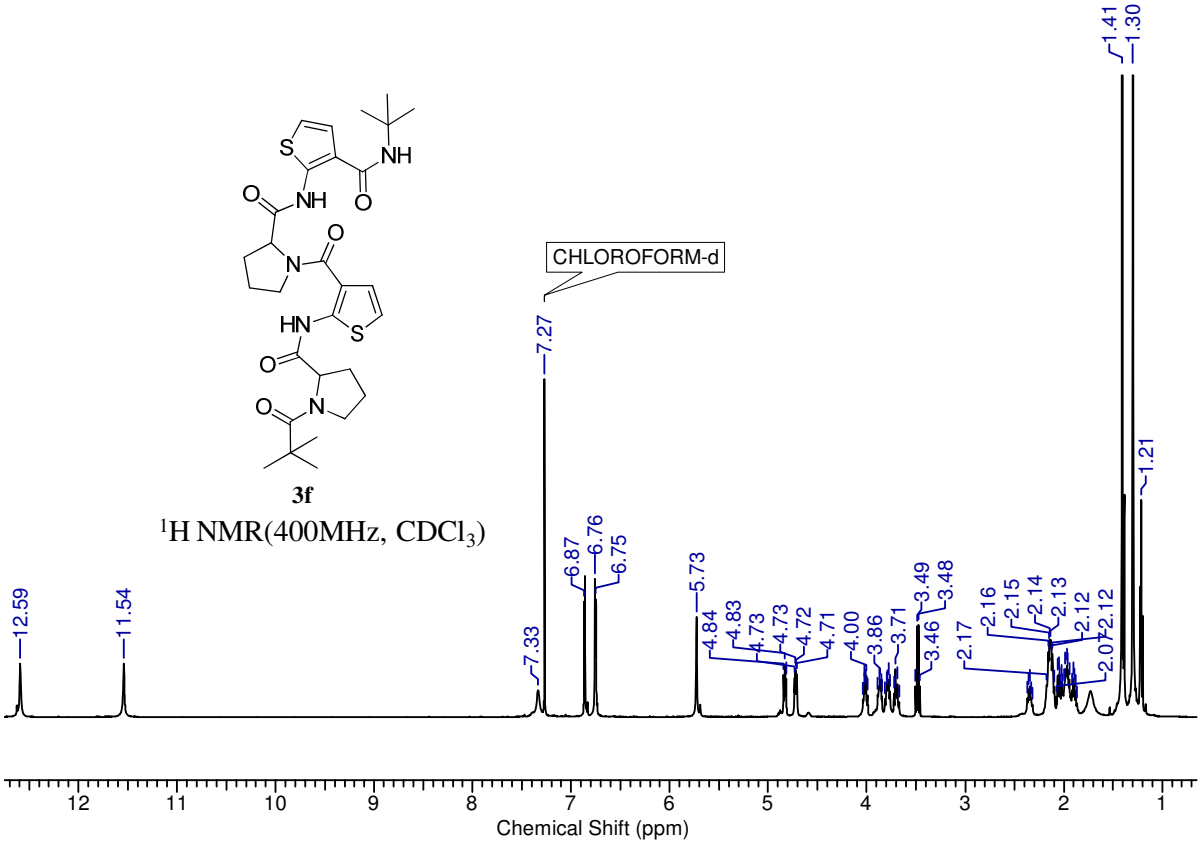
^{1}H NMR(400MHz, $CDCl_3$)



3e

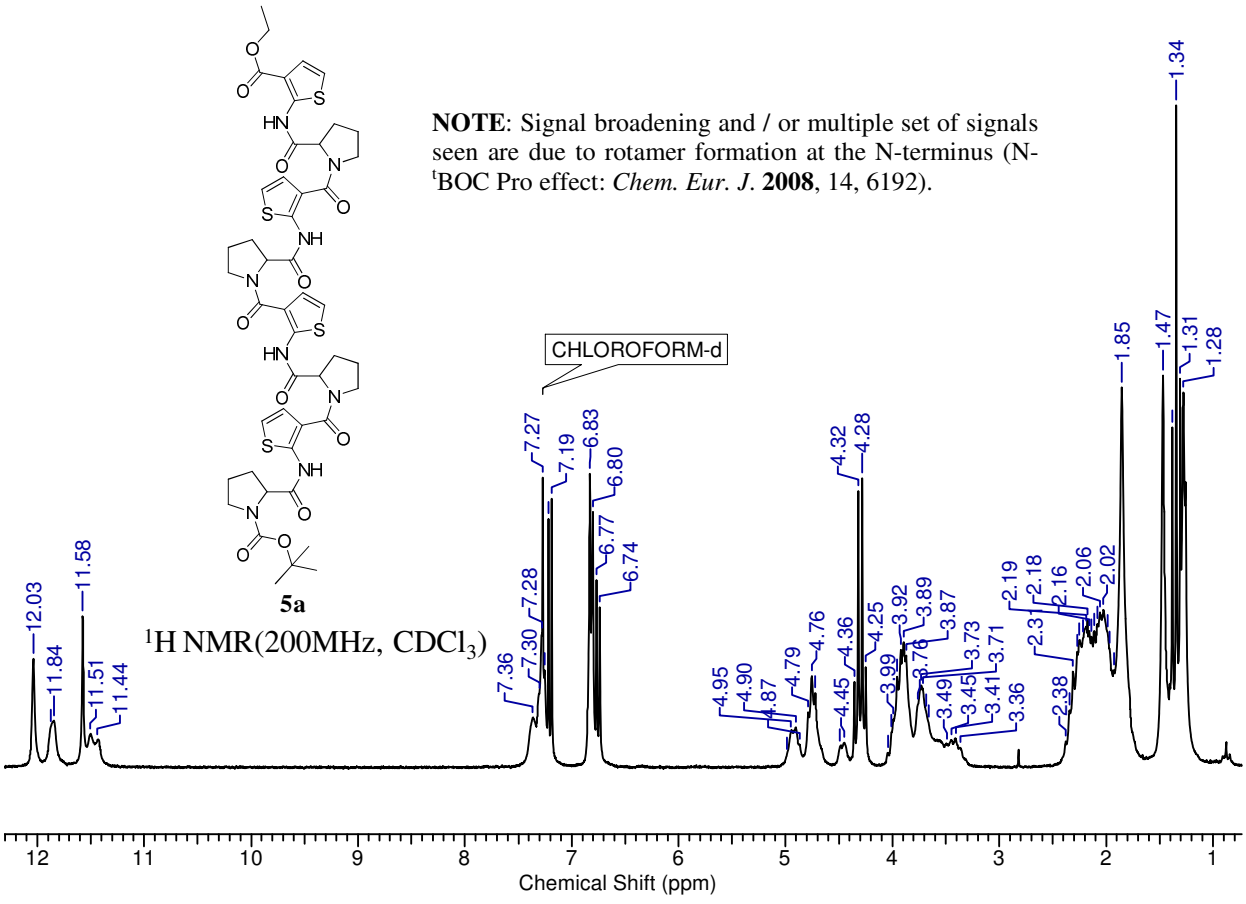
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, 14, 6192).

^{1}H NMR(200MHz, $CDCl_3$)



3f

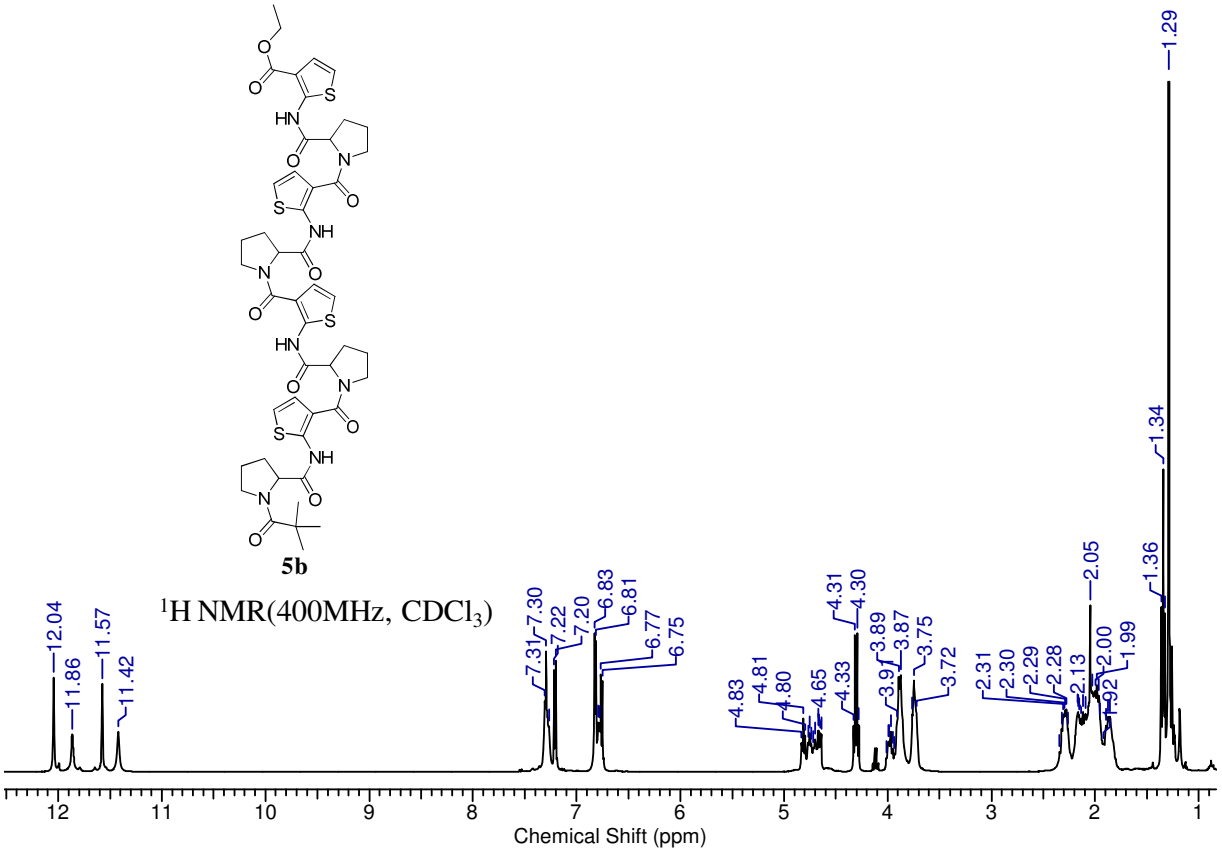
^{1}H NMR(400MHz, $CDCl_3$)



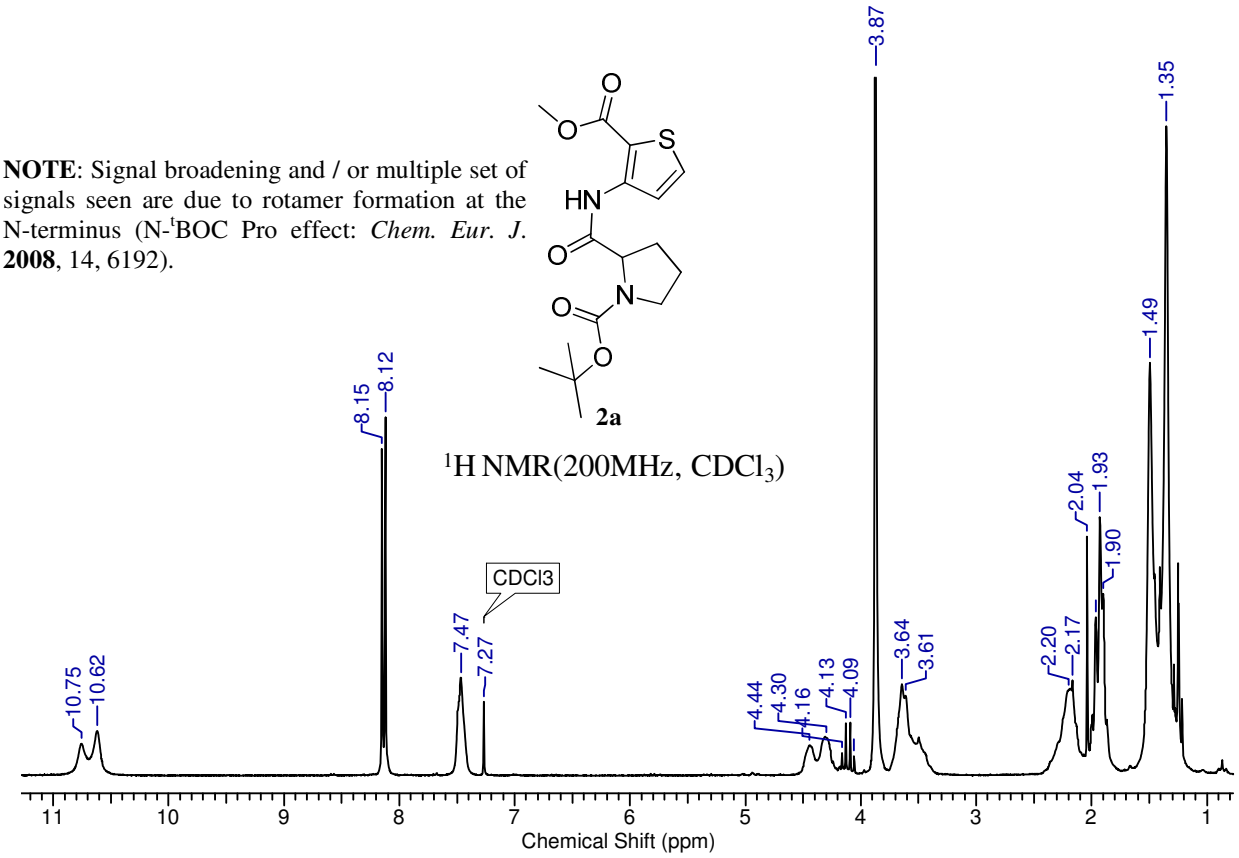
5a

^{1}H NMR(200MHz, $CDCl_3$)

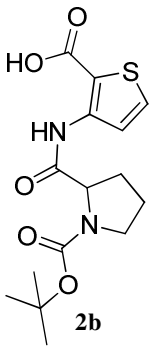
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, 14, 6192).



NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, 14, 6192).

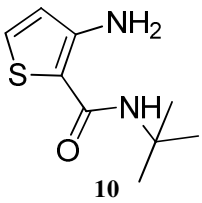


NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J*. **2008**, 14, 6192).



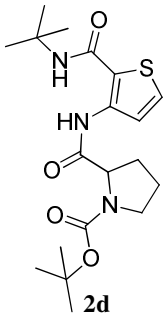
2b

^{1}H NMR(500MHz, $CDCl_3$)



10

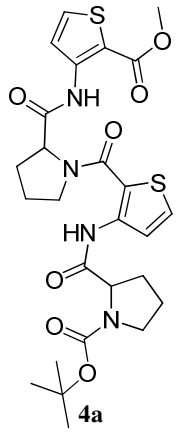
^{1}H NMR(200MHz, $CDCl_3$)



2d

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, 14, 6192).

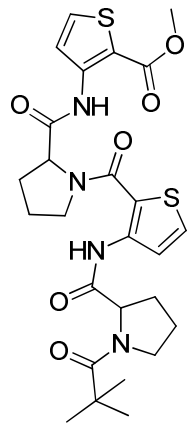
^{1}H NMR(200MHz, $CDCl_3$)



4a

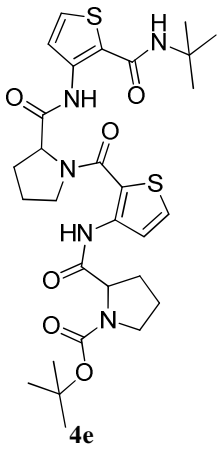
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, 14, 6192).

^{1}H NMR(400MHz, $CDCl_3$)



4d

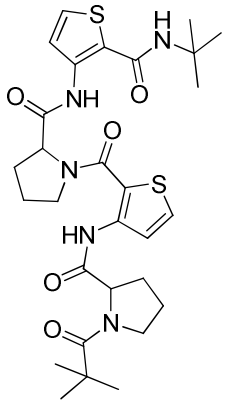
^{1}H NMR(400MHz, $CDCl_3$)



4e

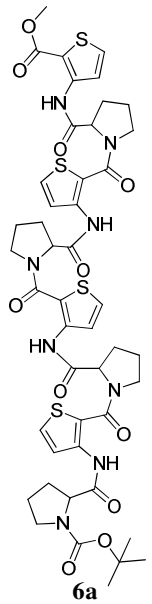
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, 14, 6192).

^{1}H NMR(400MHz, $CDCl_3$)



4f

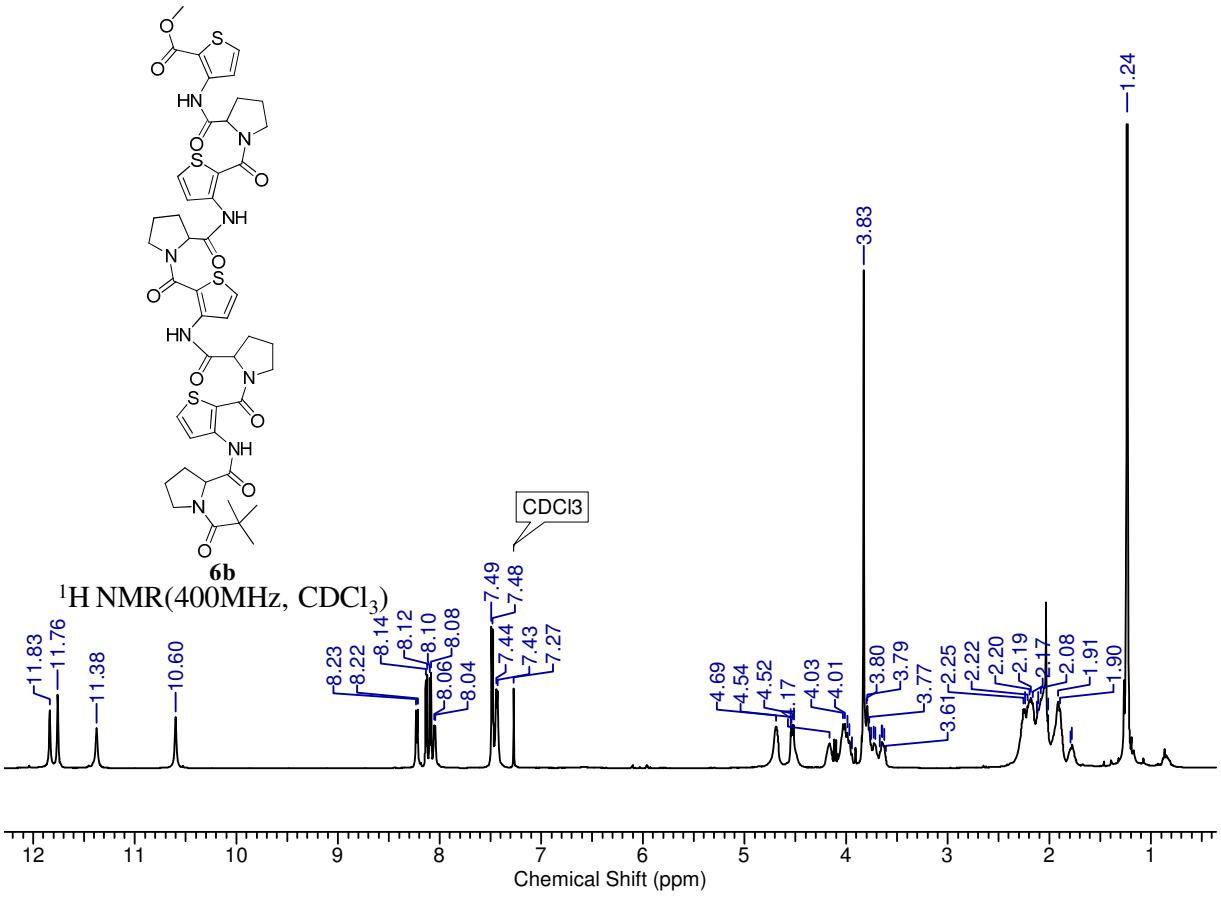
^{1}H NMR(400MHz, $CDCl_3$)

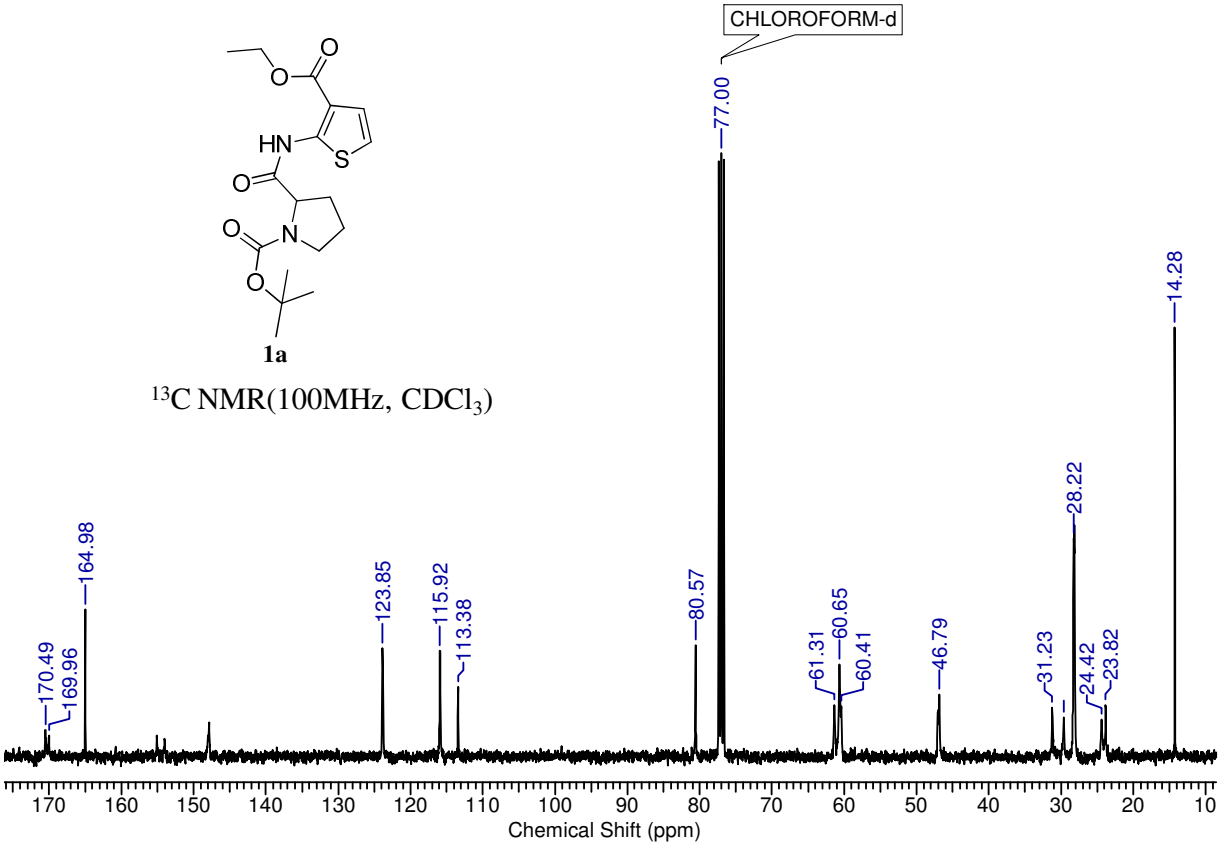


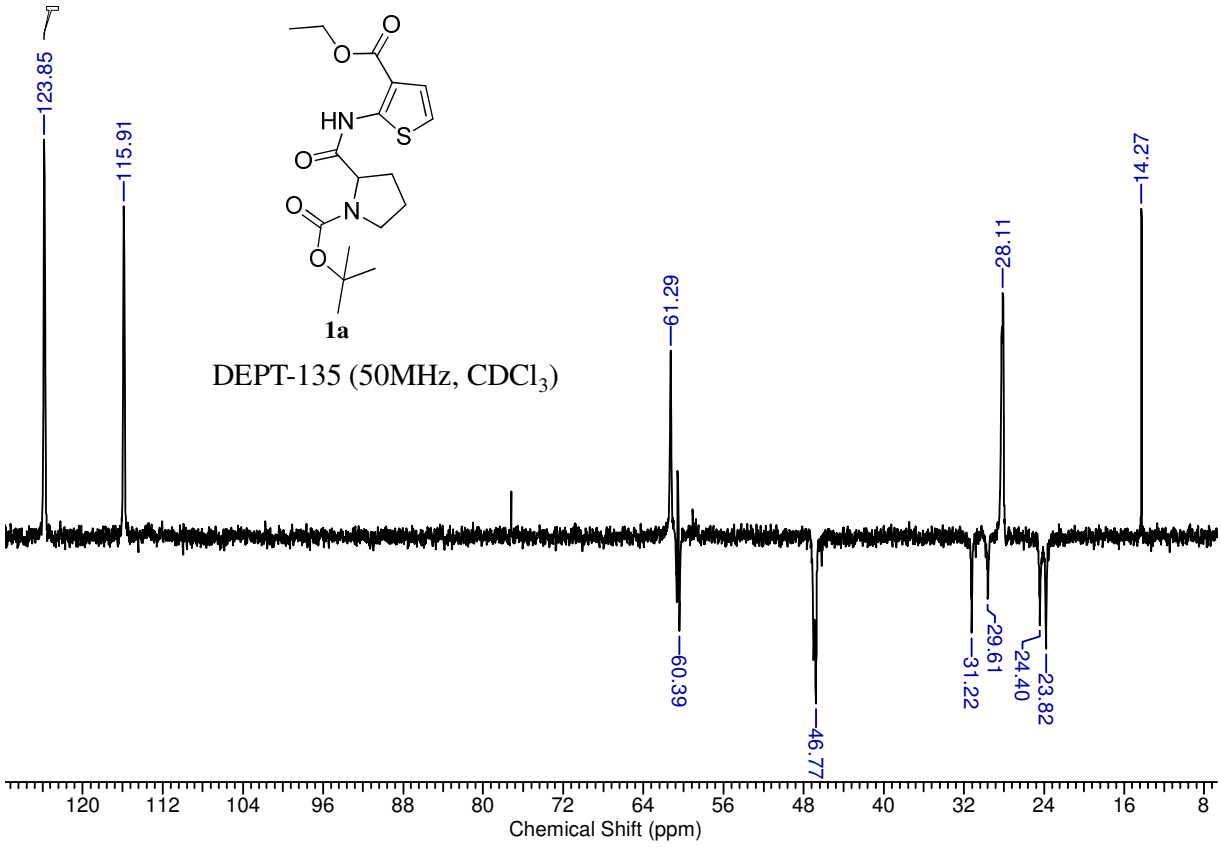
6a

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect: *Chem. Eur. J.* **2008**, 14, 6192).

^{1}H NMR(400MHz, $CDCl_3$)

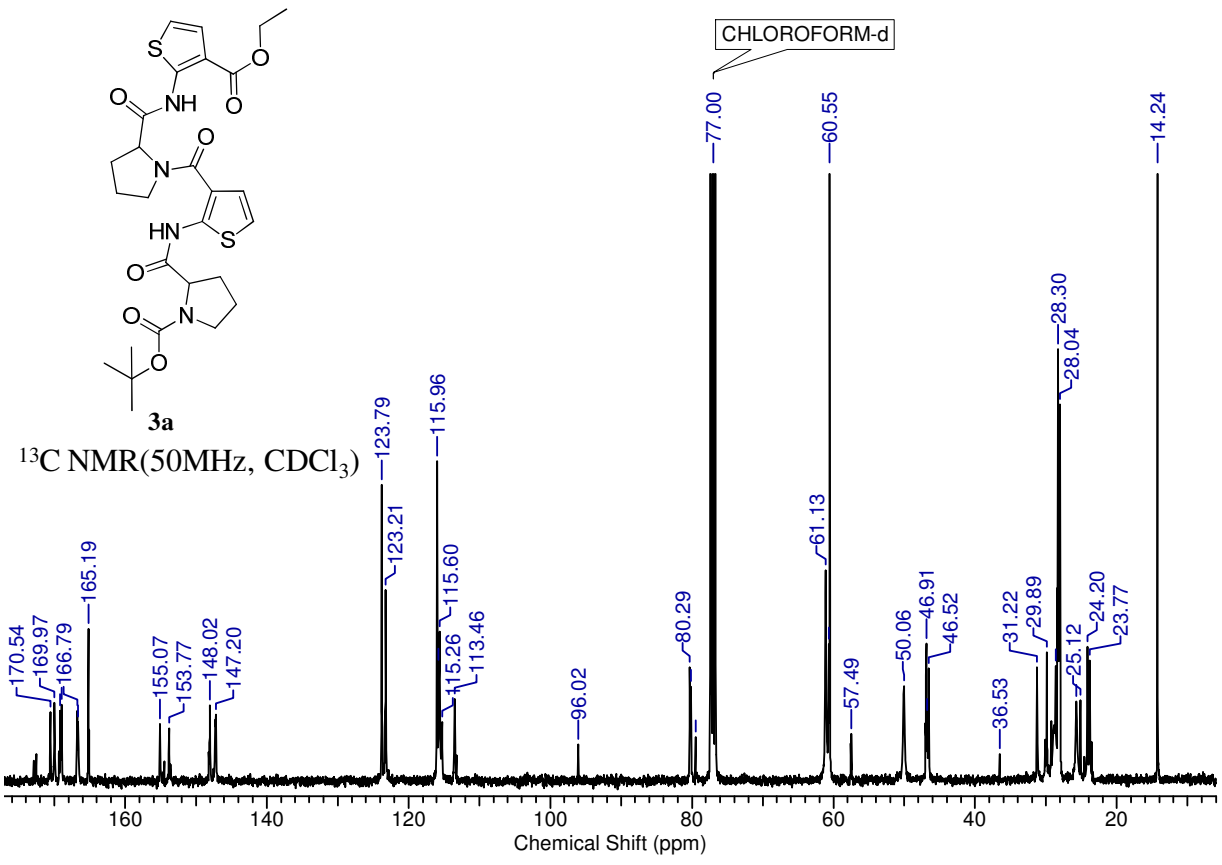

6b
^{1}H NMR(400MHz, CDCl$_3$)
CDCl3
11.83
11.76
11.38
10.60
8.23
8.22
8.14
8.12
8.10
8.08
8.06
8.04
7.49
7.48
7.44
7.43
7.27
4.69
4.54
4.52
4.17
4.03
4.01
3.83
3.80
3.79
3.77
3.61
2.25
2.22
2.20
2.19
2.17
2.08
1.91
1.90
1.24
Chemical Shift (ppm)


1a
^{13}C NMR(100MHz, CDCl$_3$)
CHLOROFORM-d
170.49
169.96
164.98
123.85
115.92
113.38
80.57
77.00
61.31
60.65
60.41
46.79
31.23
28.22
24.42
23.82
14.28
Chemical Shift (ppm)



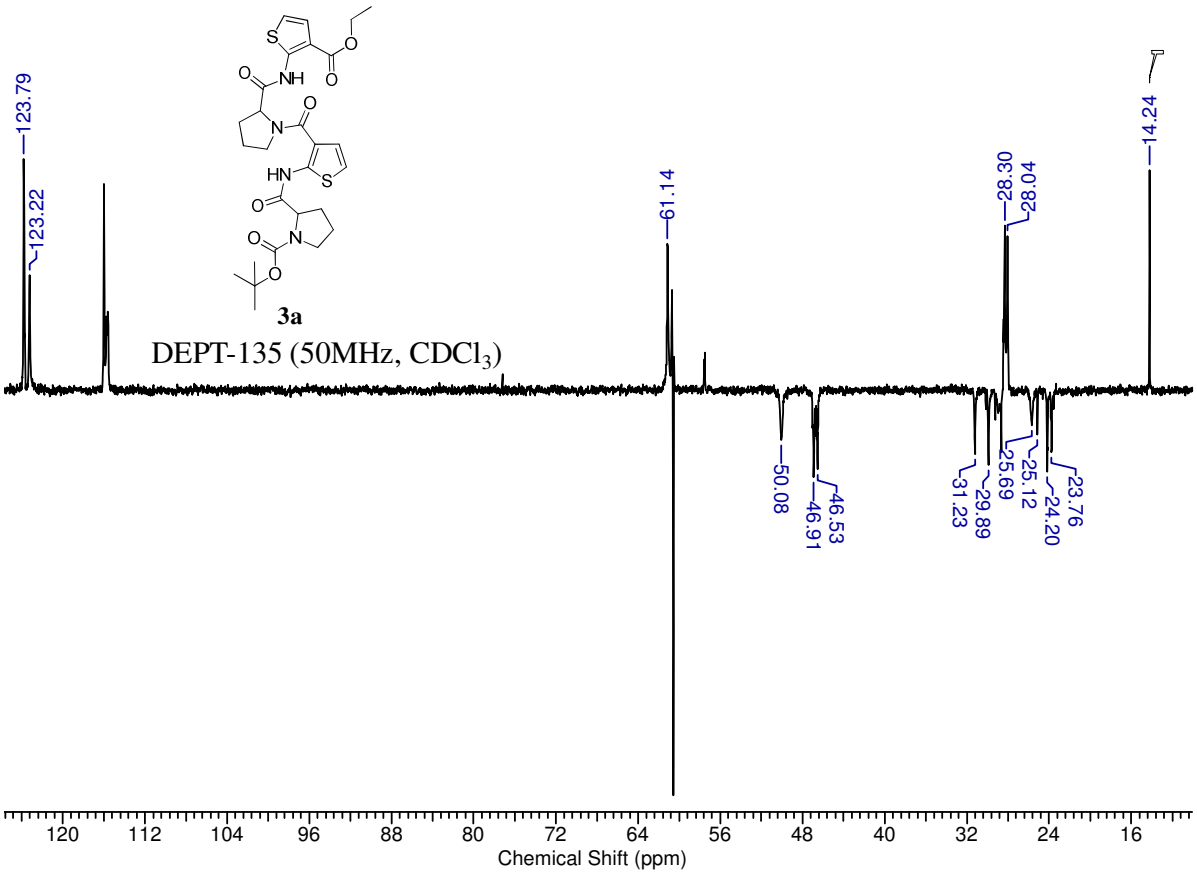
1a

DEPT-135 (50MHz, $CDCl_3$)



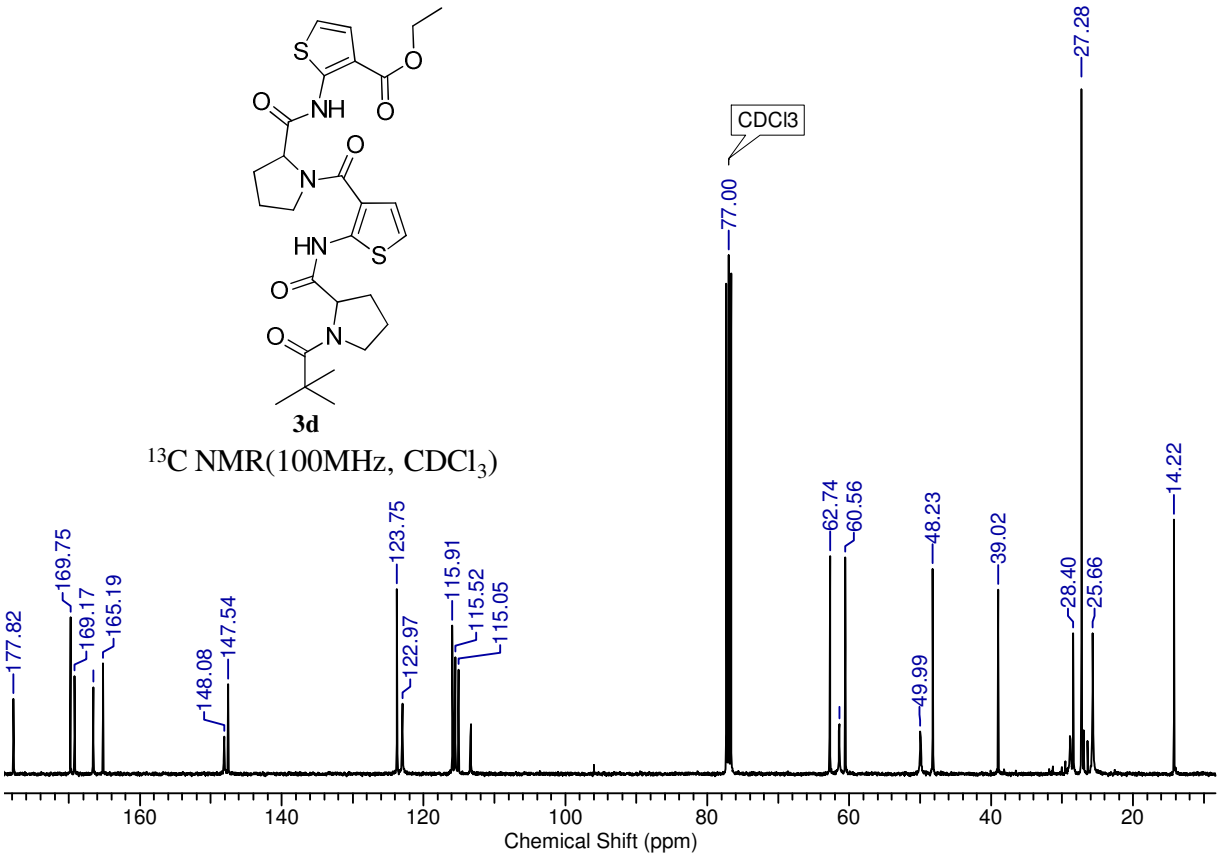
3a

^{13}C NMR(50MHz, $CDCl_3$)



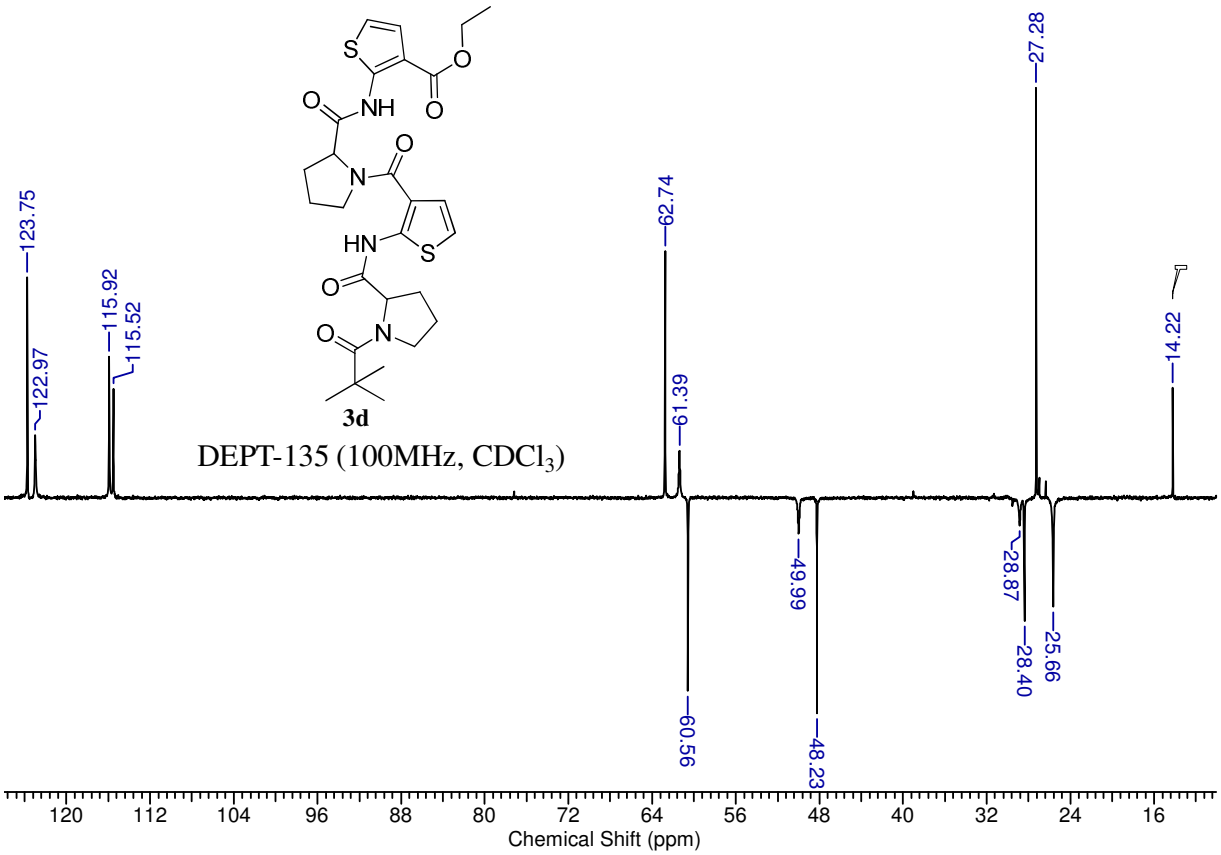
3a

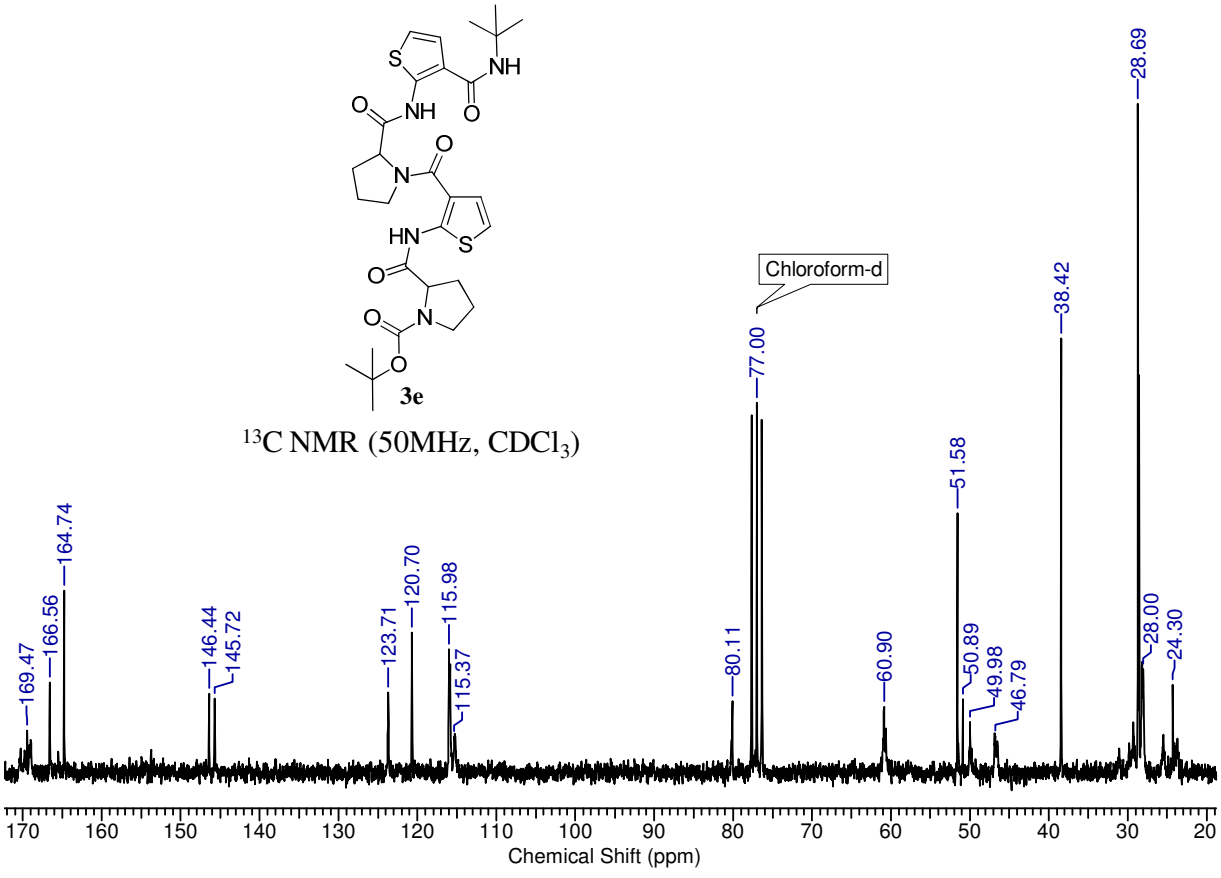
DEPT-135 (50MHz, $CDCl_3$)

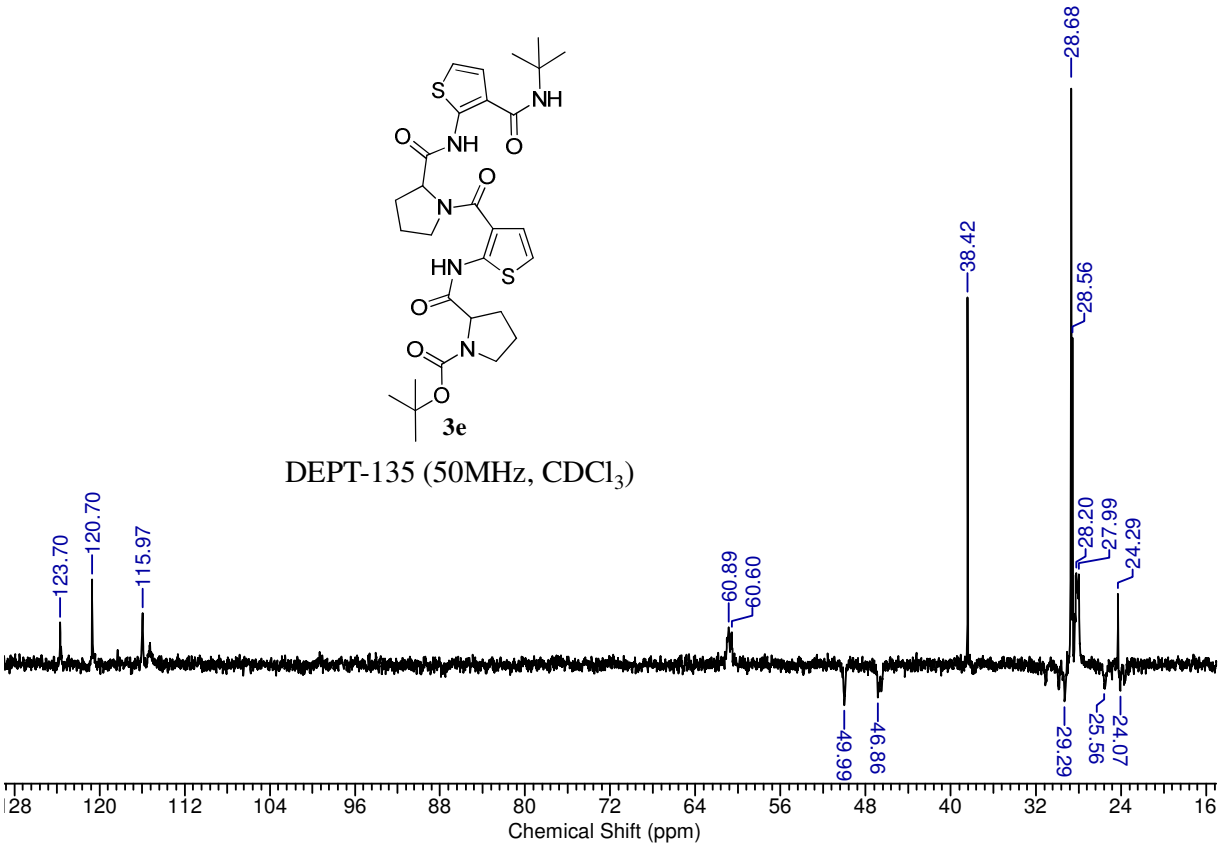


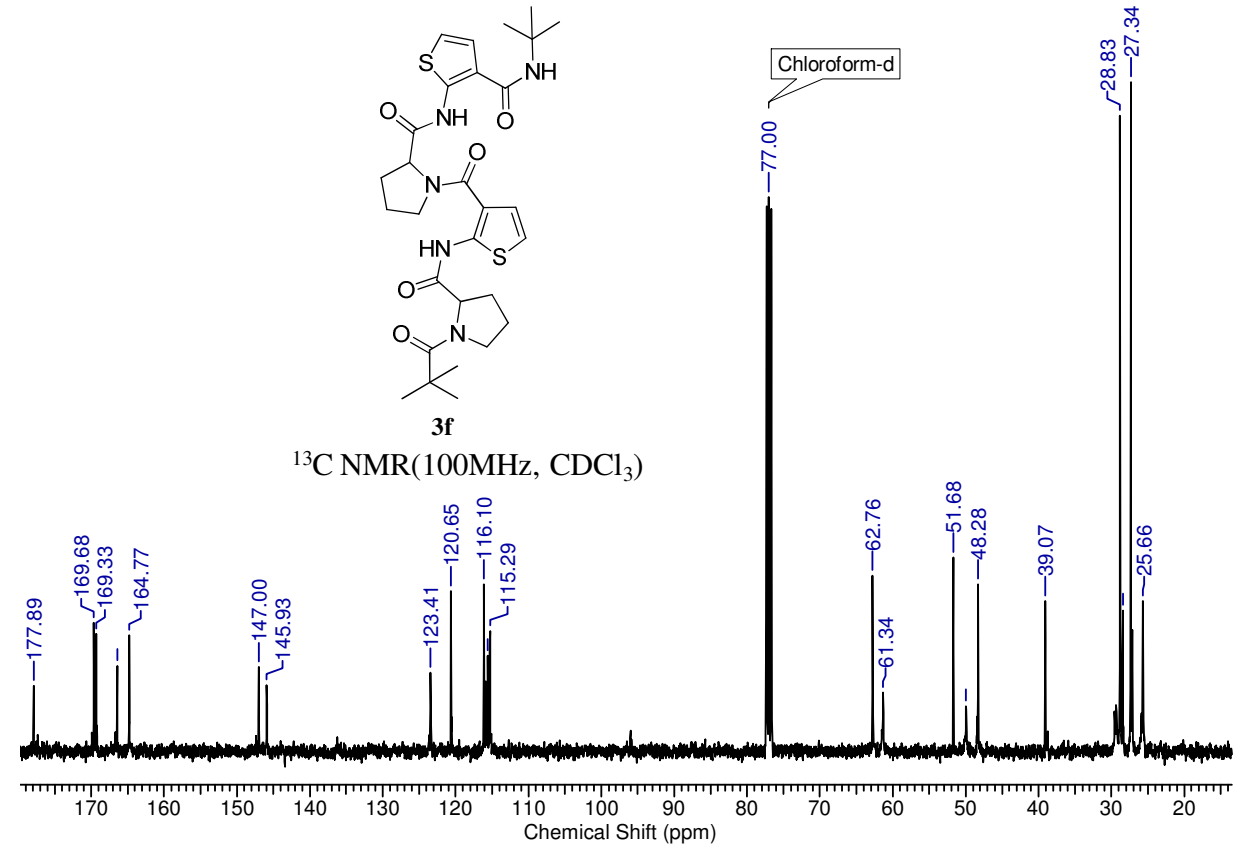
3d

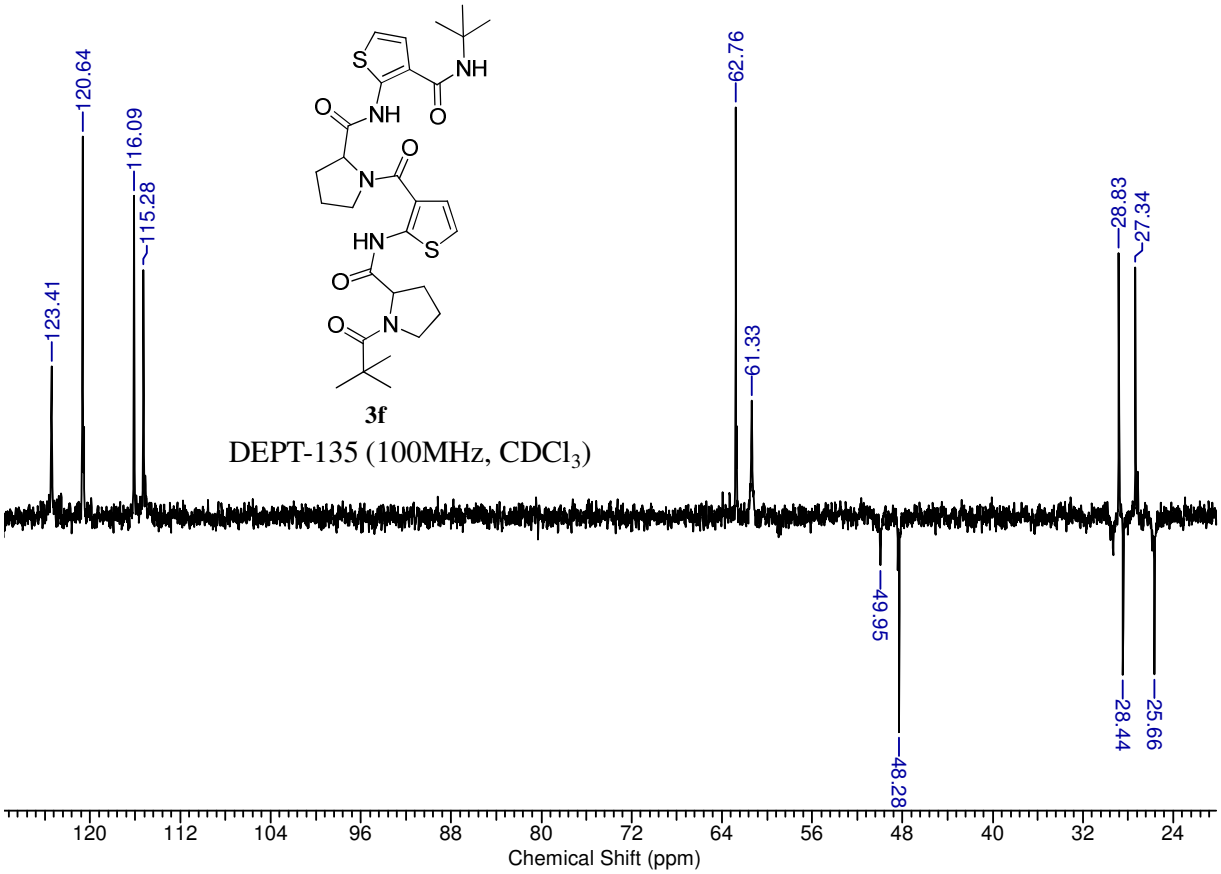
^{13}C NMR(100MHz, $CDCl_3$)

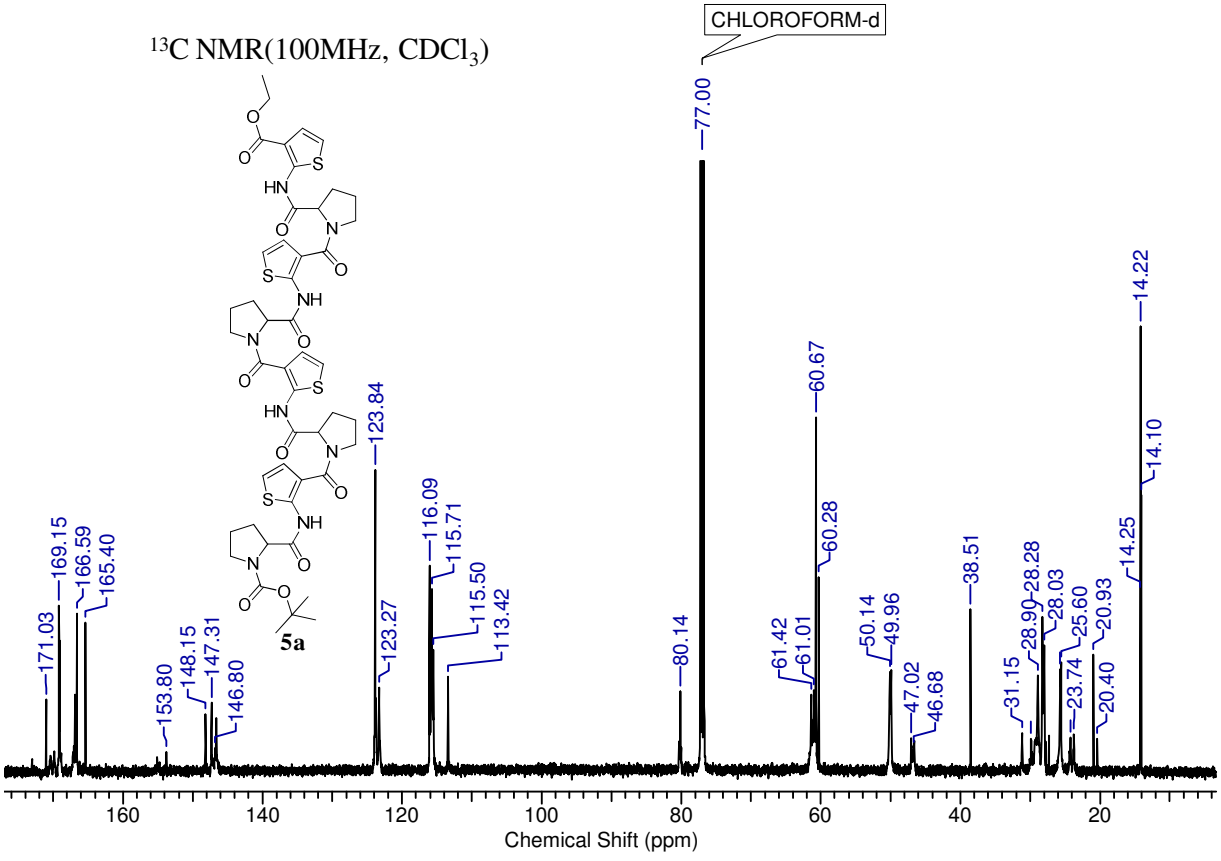

3d
DEPT-135 (100MHz, CDCl3)
123.75
122.97
115.92
115.52
62.74
61.39
60.56
49.99
48.23
28.87
28.40
25.96
27.28
14.22
Chemical Shift (ppm)


3e
13C NMR (50MHz, CDCl3)
Chloroform-d
169.47
166.56
164.74
146.44
145.72
123.71
120.70
115.98
115.37
80.11
77.00
60.90
51.58
50.89
49.98
46.79
38.42
28.69
28.00
24.30
Chemical Shift (ppm)

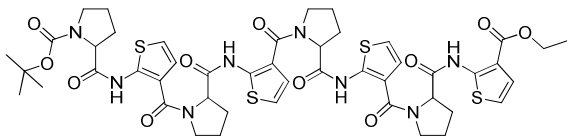

3e
DEPT-135 (50MHz, CDCl3)
123.70
120.70
115.97
60.89
60.60
49.99
46.86
38.42
29.29
28.68
28.56
28.20
27.99
25.56
24.29
24.07
Chemical Shift (ppm)


3f
13C NMR(100MHz, CDCl3)
Chloroform-d
177.89
169.68
169.33
164.77
147.00
145.93
123.41
120.65
116.10
115.29
77.00
62.76
61.34
51.68
48.28
39.07
28.83
27.34
25.66
Chemical Shift (ppm)


3f
DEPT-135 (100MHz, CDCl3)
120.64
116.09
115.28
123.41
62.76
61.33
28.83
27.34
49.95
48.28
28.44
25.66
Chemical Shift (ppm)

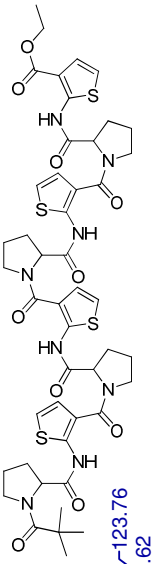

13C NMR(100MHz, CDCl3)
5a
CHLOROFORM-d
77.00
171.03
169.15
166.59
165.40
153.80
148.15
147.31
146.80
123.84
123.27
116.09
115.71
115.50
113.42
80.14
61.42
61.01
60.67
60.28
50.14
49.96
47.02
46.68
38.51
31.15
28.90
28.28
28.03
25.60
23.74
20.93
20.40
14.22
14.25
14.10
Chemical Shift (ppm)

DEPT-135 (100MHz, $CDCl_3$)



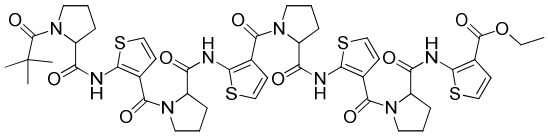
5a

^{13}C NMR(50MHz, $CDCl_3$)

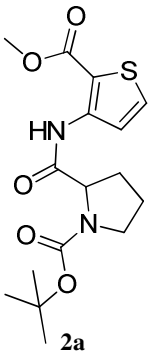


5b

DEPT-135 (50MHz, $CDCl_3$)

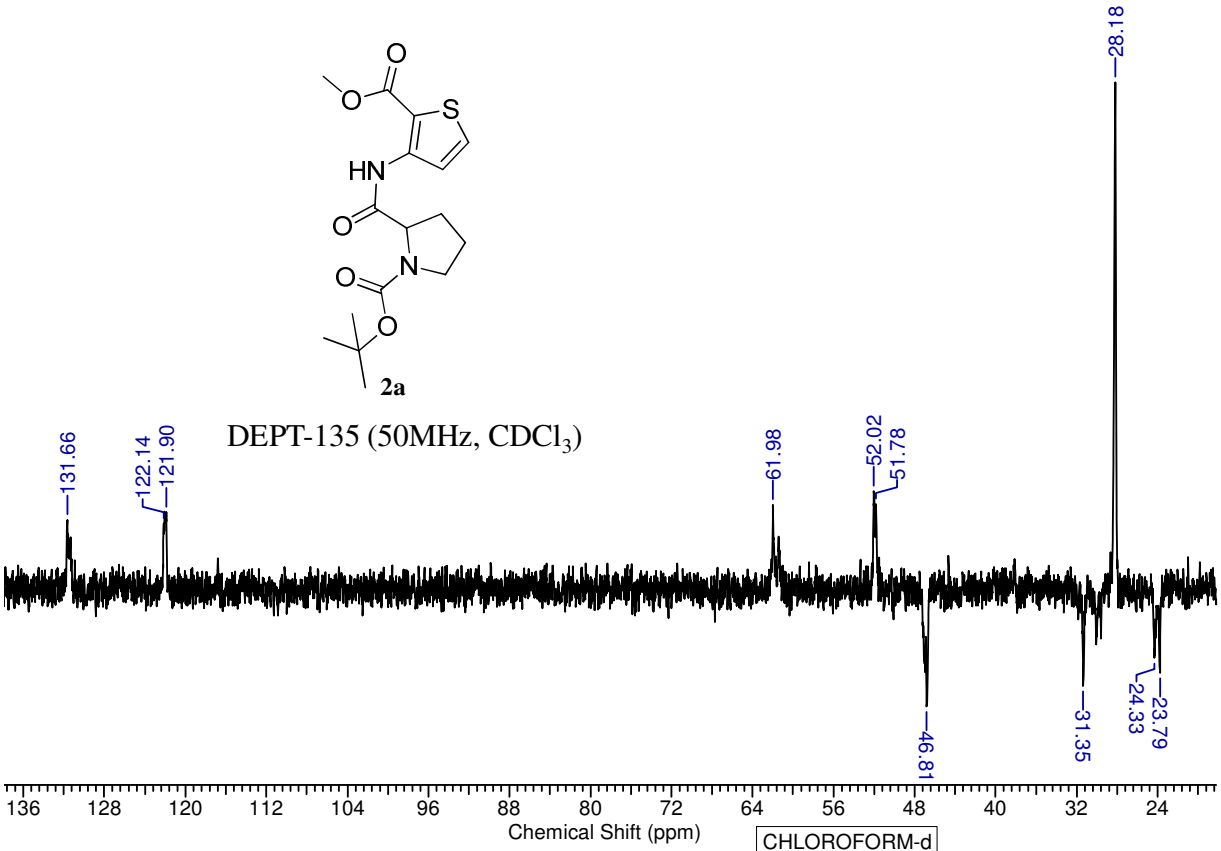


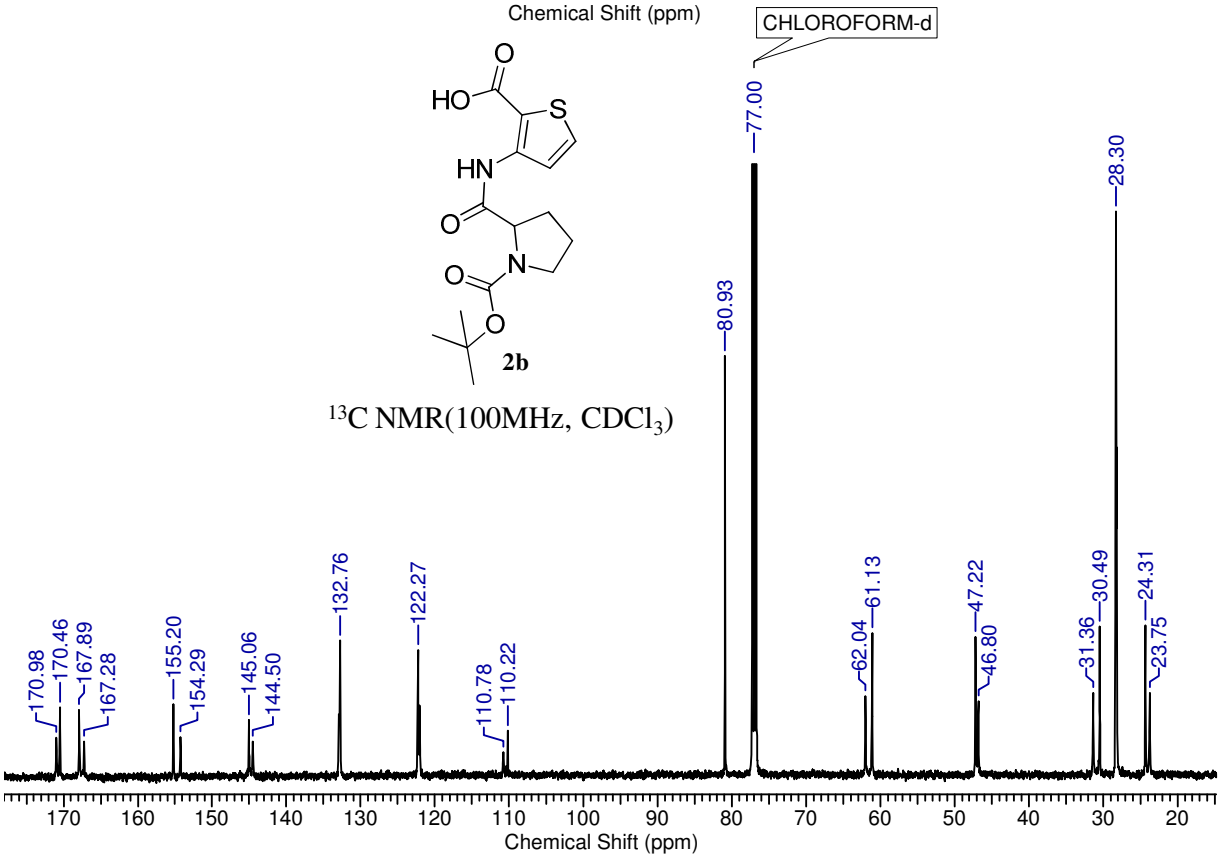
5b

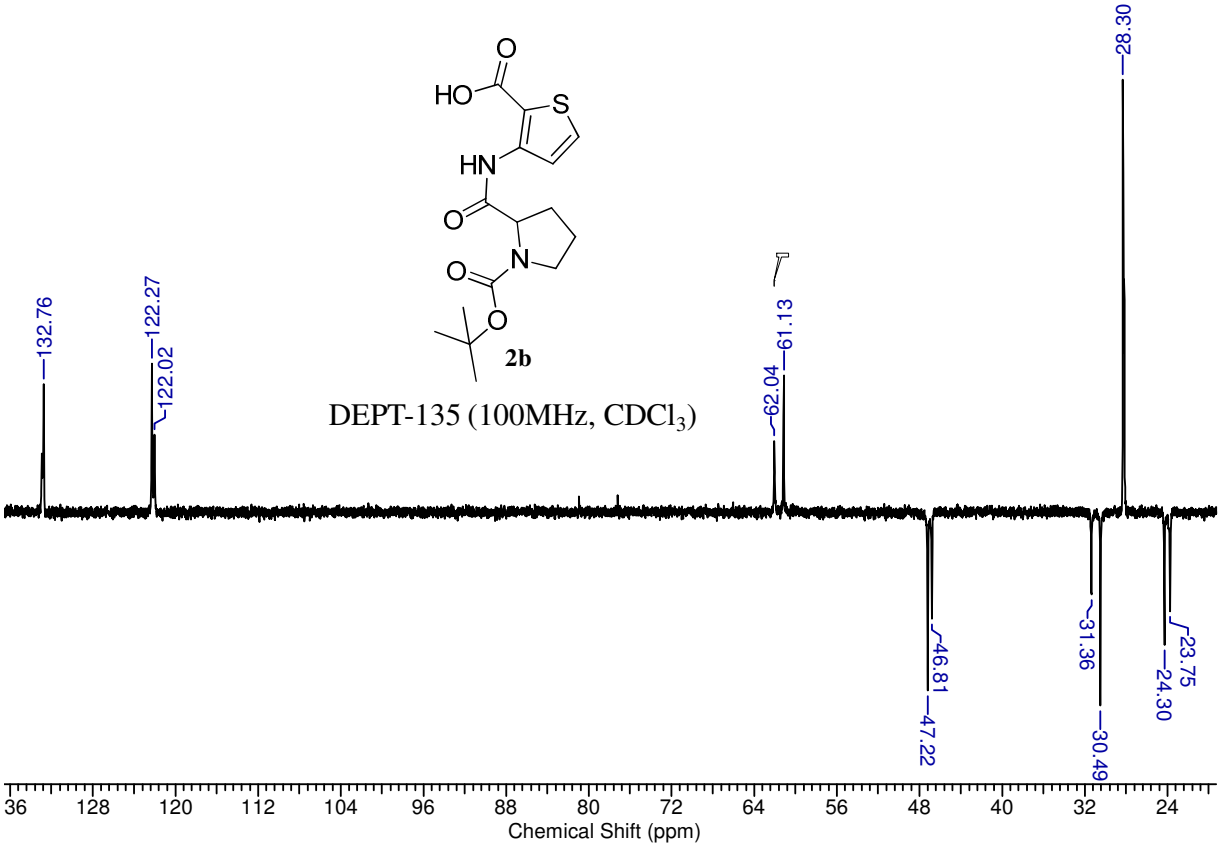


2a

^{13}C NMR(50MHz, $CDCl_3$)

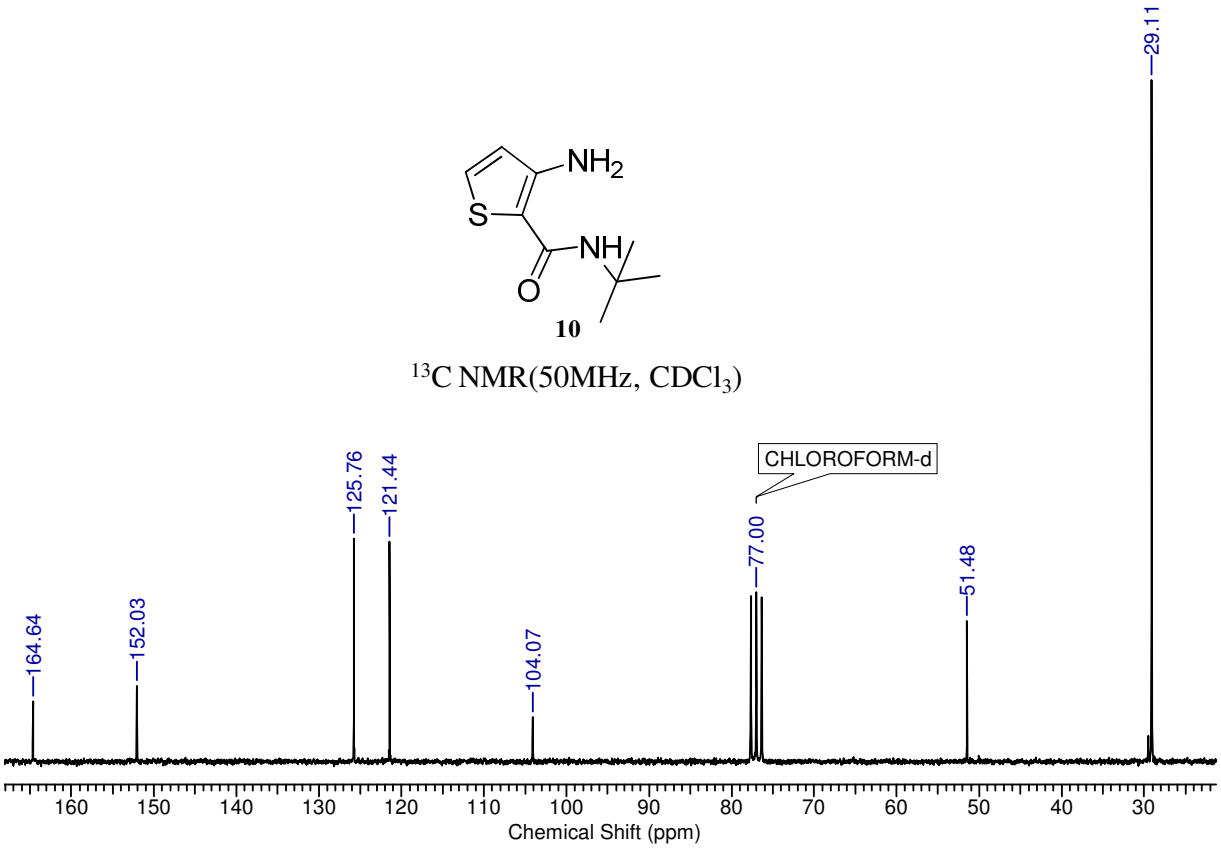

2a
DEPT-135 (50MHz, CDCl3)
131.66
122.14
121.90
61.98
52.02
51.78
28.18
49.81
31.35
24.33
23.79
Chemical Shift (ppm)


2b
13C NMR(100MHz, CDCl3)
CHLOROFORM-d
77.00
80.93
28.30
170.98
170.46
167.89
167.28
155.20
154.29
145.06
144.50
132.76
122.27
110.78
110.22
62.04
61.13
47.22
46.80
31.36
30.49
24.31
23.75
Chemical Shift (ppm)



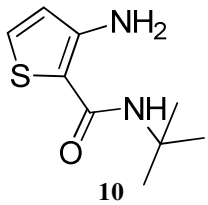
2b

DEPT-135 (100MHz, $CDCl_3$)



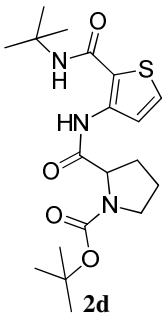
10

^{13}C NMR(50MHz, $CDCl_3$)



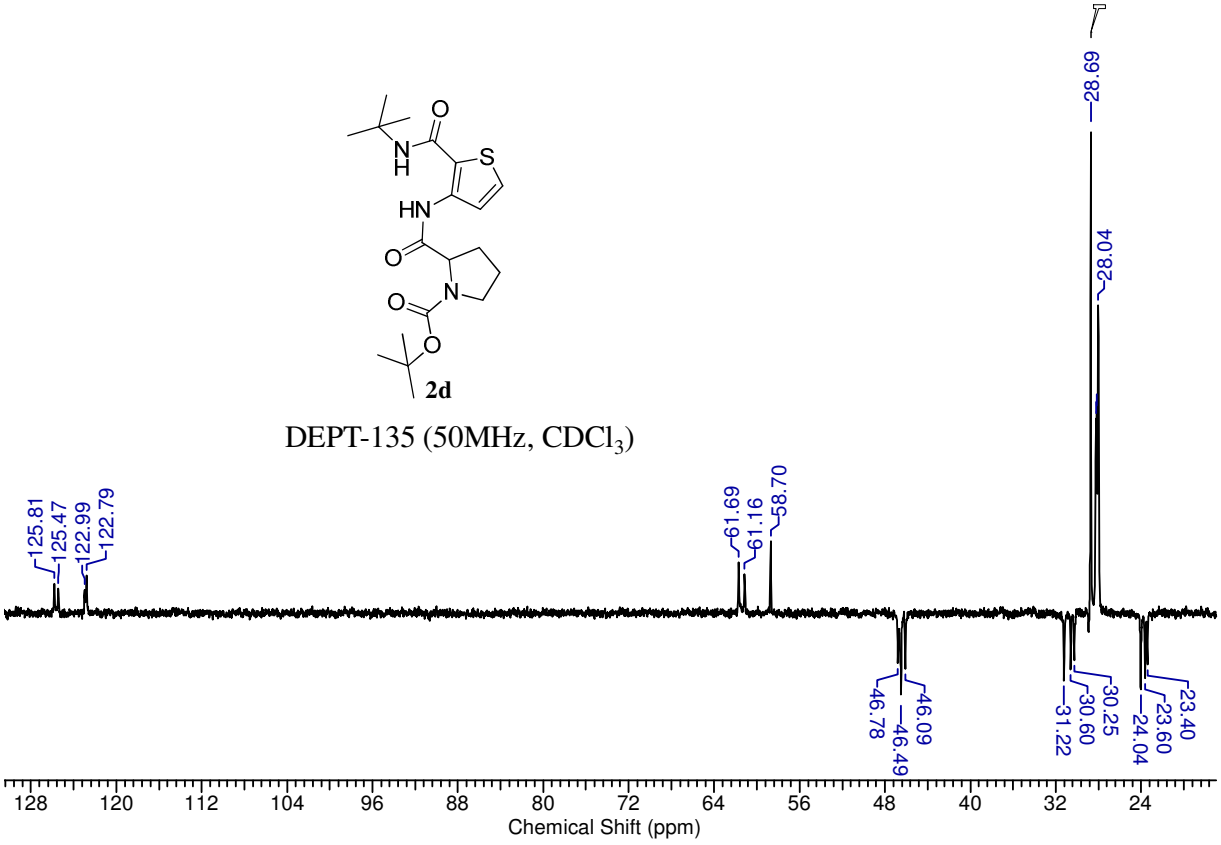
10

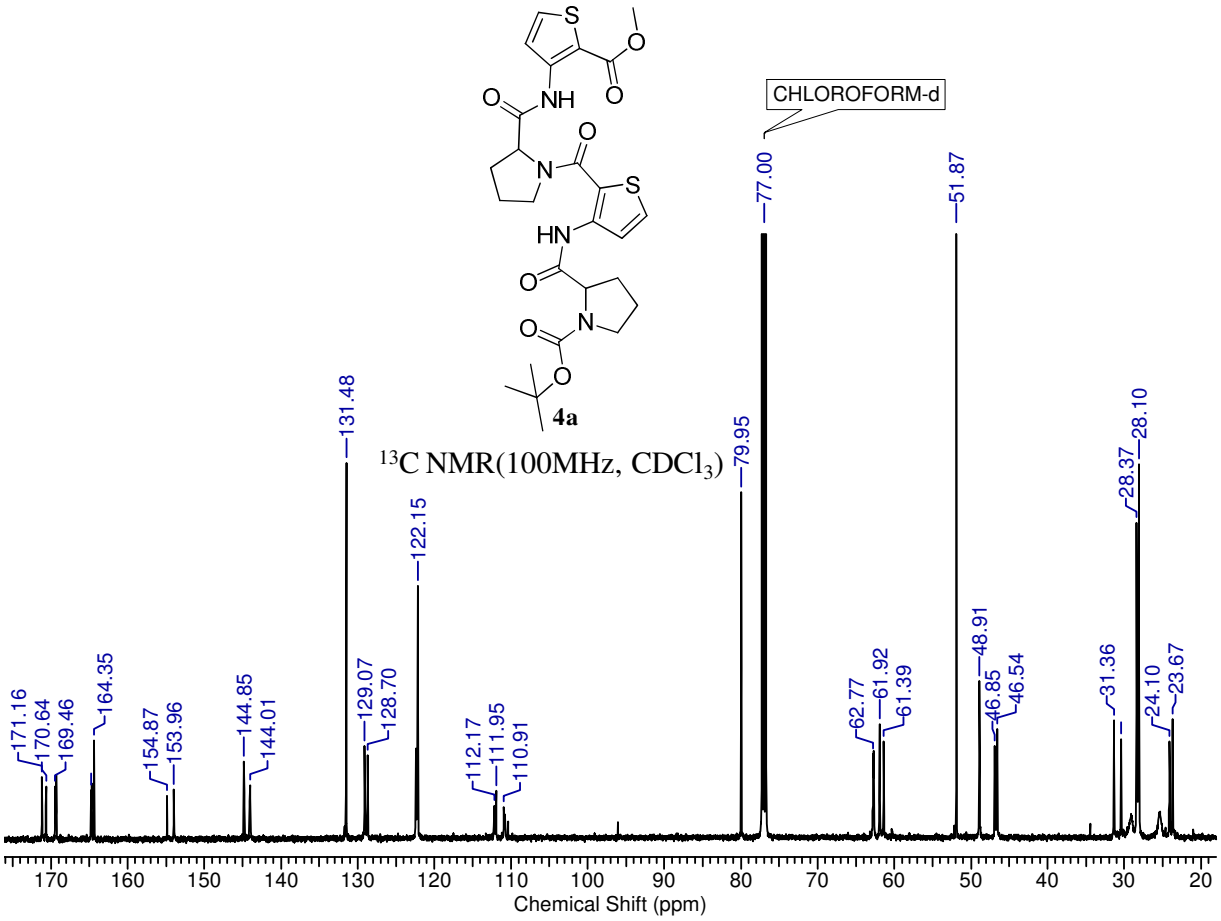
DEPT-135 (50MHz, $CDCl_3$)

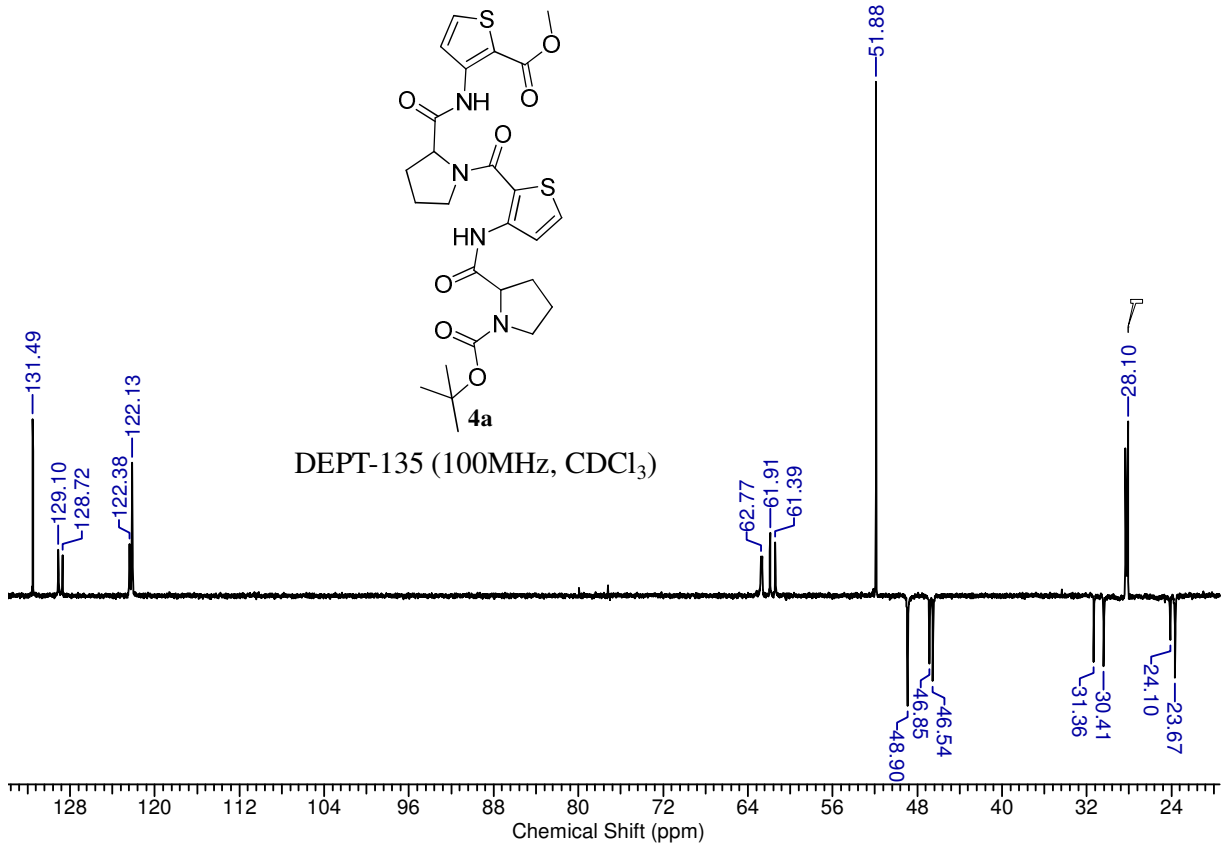


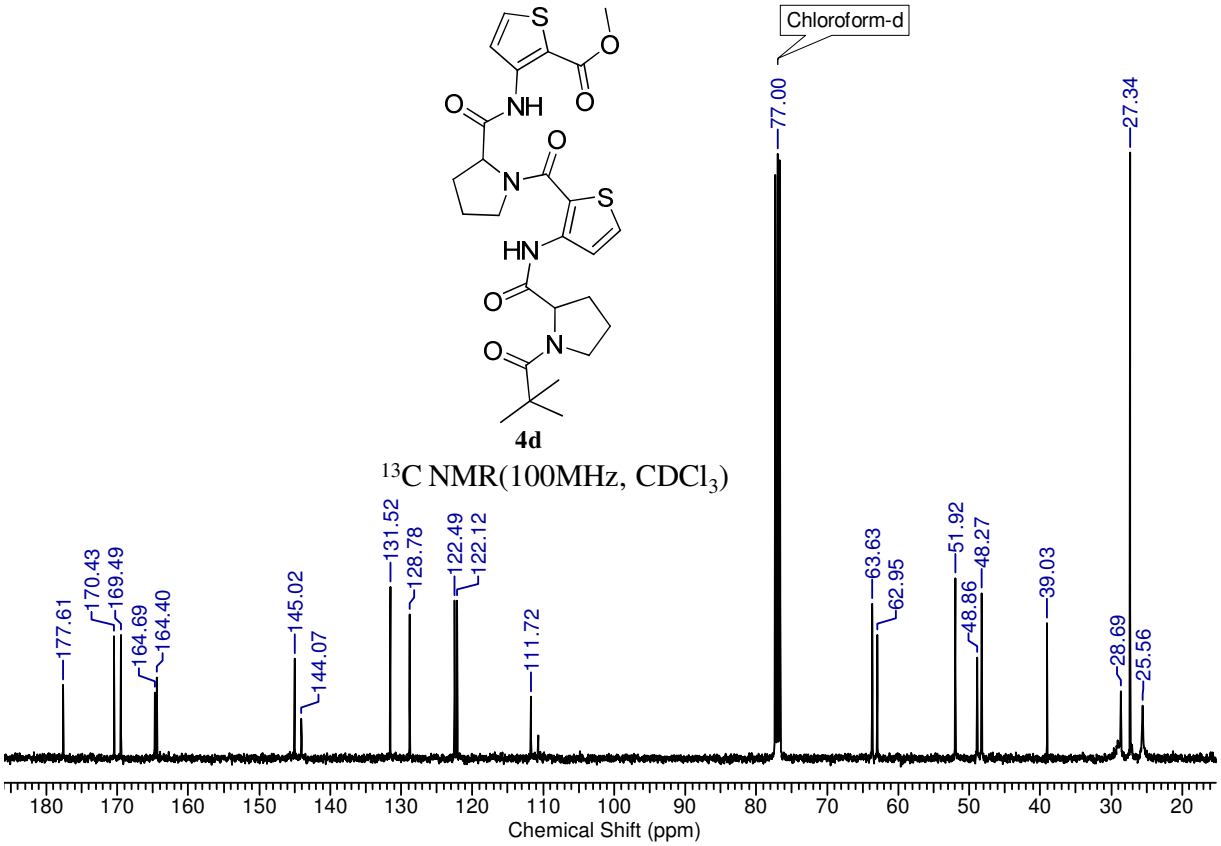
2d

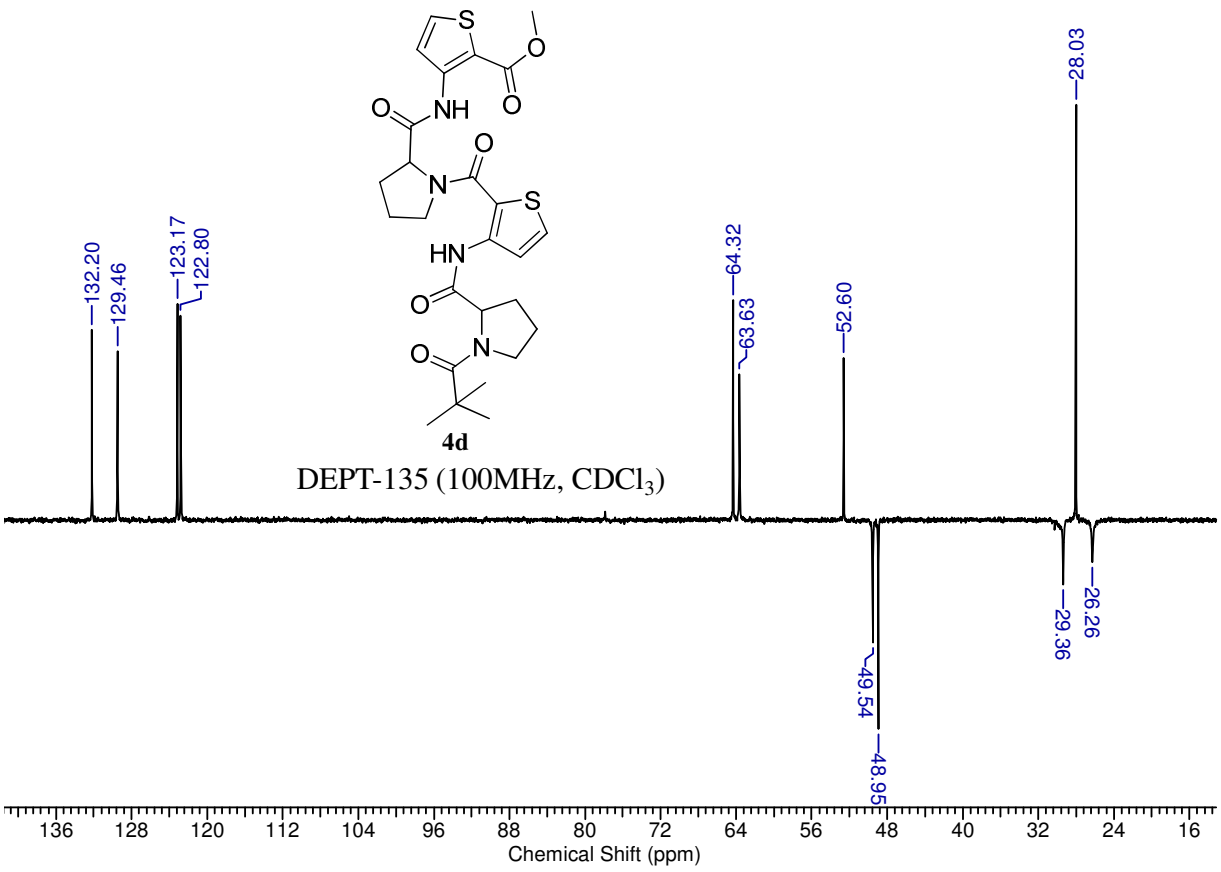
^{13}C NMR(50MHz, $CDCl_3$)

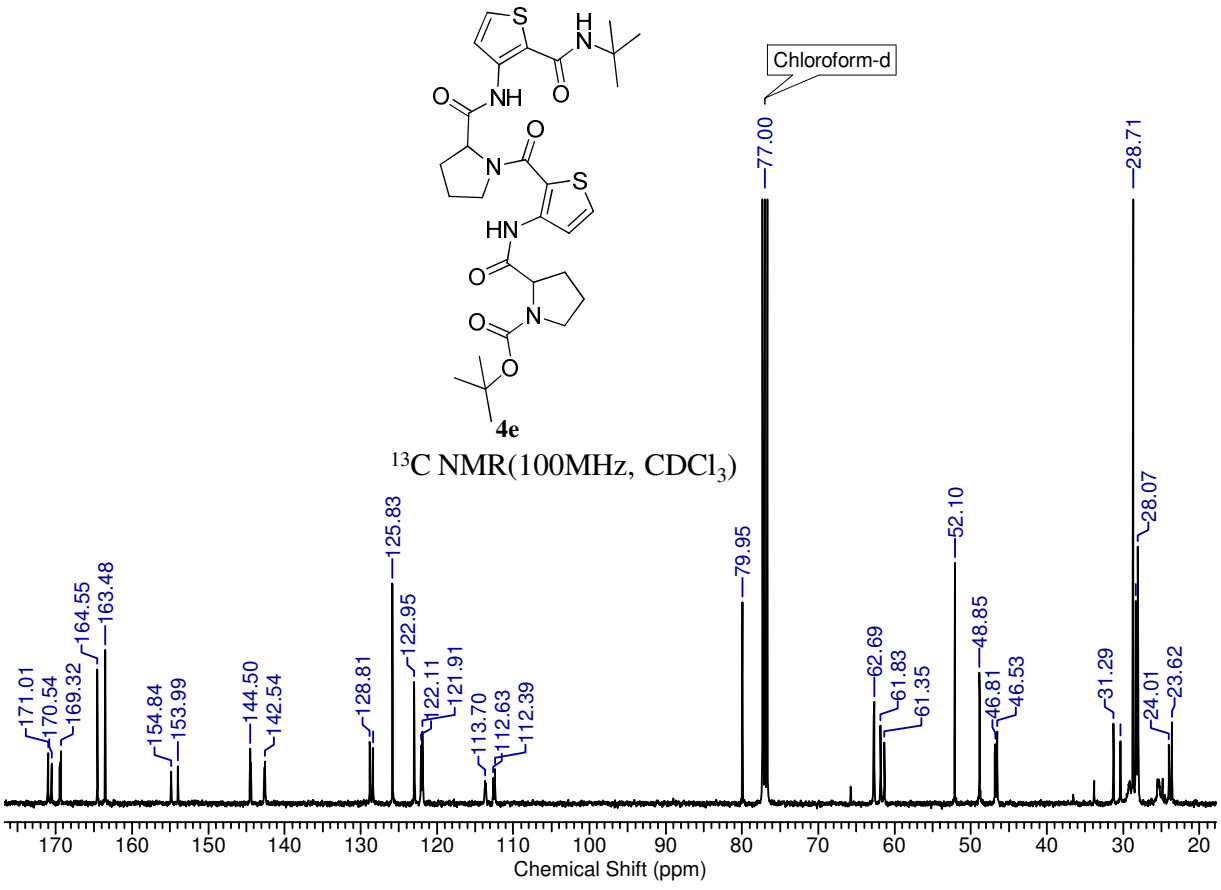

2d
DEPT-135 (50MHz, CDCl3)
28.69
28.04
125.81
125.47
122.99
122.79
61.69
61.16
58.70
49.78
49.49
49.09
31.22
30.60
30.25
24.04
23.60
23.40
Chemical Shift (ppm)

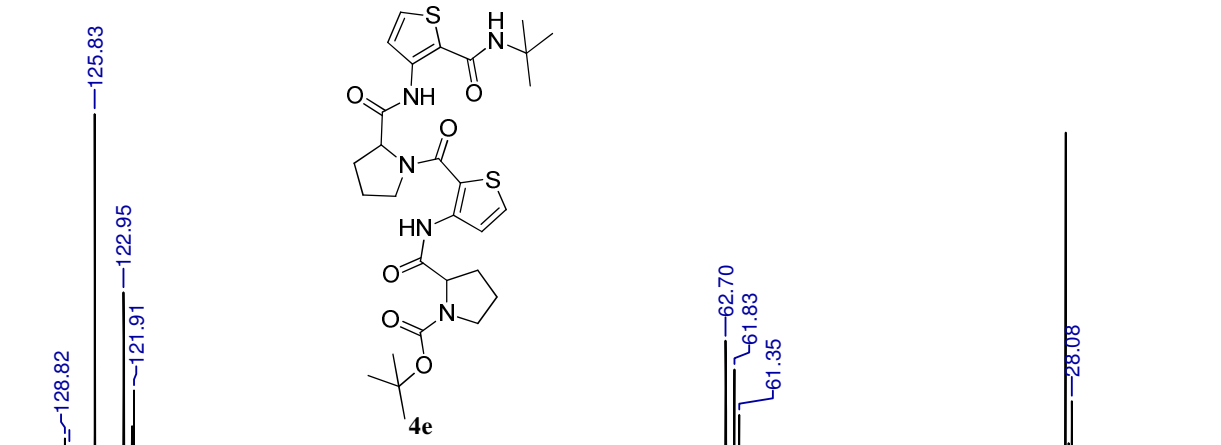

4a
13C NMR(100MHz, CDCl3)
CHLOROFORM-d
77.00
51.87
131.48
79.95
122.15
28.37
28.10
171.16
170.64
169.46
164.35
154.87
153.96
144.85
144.01
129.07
128.70
112.17
111.95
110.91
62.77
61.92
61.39
48.91
46.85
46.54
31.36
24.10
23.67
Chemical Shift (ppm)


4a
DEPT-135 (100MHz, CDCl3)
131.49
129.10
128.72
122.38
122.13
62.77
61.91
61.39
51.88
48.90
46.85
46.54
31.36
30.41
28.10
24.10
23.67
Chemical Shift (ppm)


4d
13C NMR(100MHz, CDCl3)
Chloroform-d
177.61
170.43
169.49
164.69
164.40
145.02
144.07
131.52
128.78
122.49
122.12
111.72
77.00
63.63
62.95
51.92
48.86
48.27
39.03
28.69
27.34
25.56
Chemical Shift (ppm)

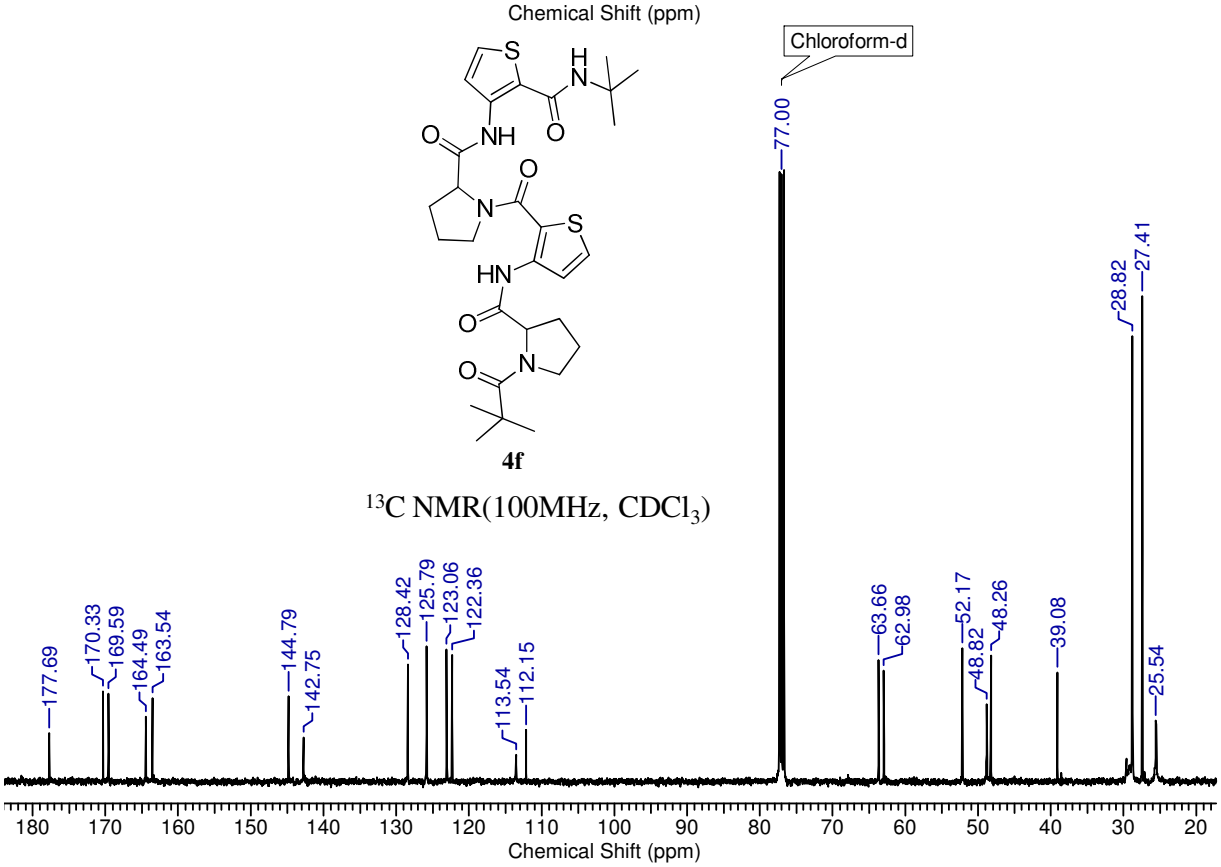

4d
DEPT-135 (100MHz, CDCl3)
132.20
129.46
123.17
122.80
64.32
63.63
52.60
28.03
29.36
26.26
49.54
48.95
Chemical Shift (ppm)


4e
13C NMR(100MHz, CDCl3)
Chloroform-d
77.00
28.71
125.83
79.95
28.07
52.10
163.48
164.55
169.32
171.01
170.54
154.84
153.99
144.50
142.54
128.81
122.95
122.11
121.91
113.70
112.63
112.39
62.69
61.83
61.35
48.85
46.81
46.53
31.29
24.01
23.62
Chemical Shift (ppm)



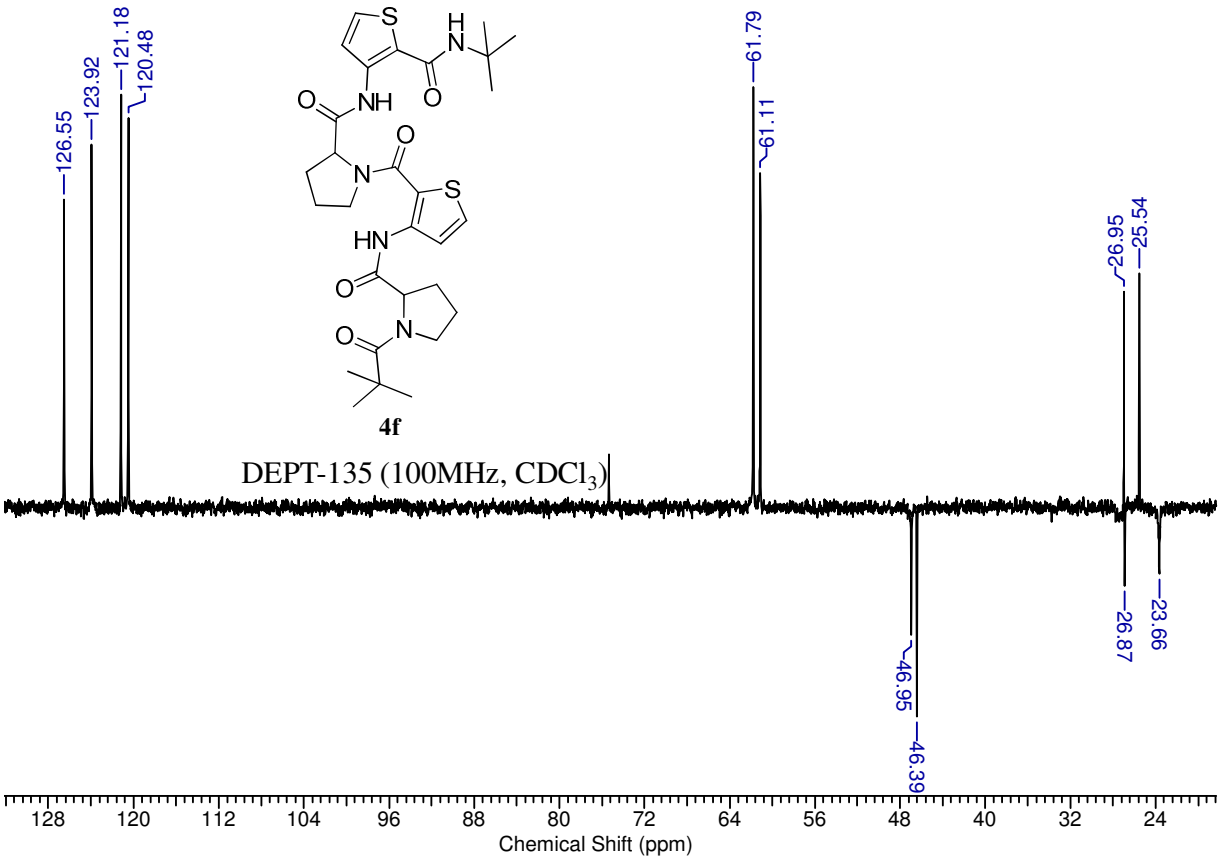
4e

DEPT-135 (100MHz, $CDCl_3$)

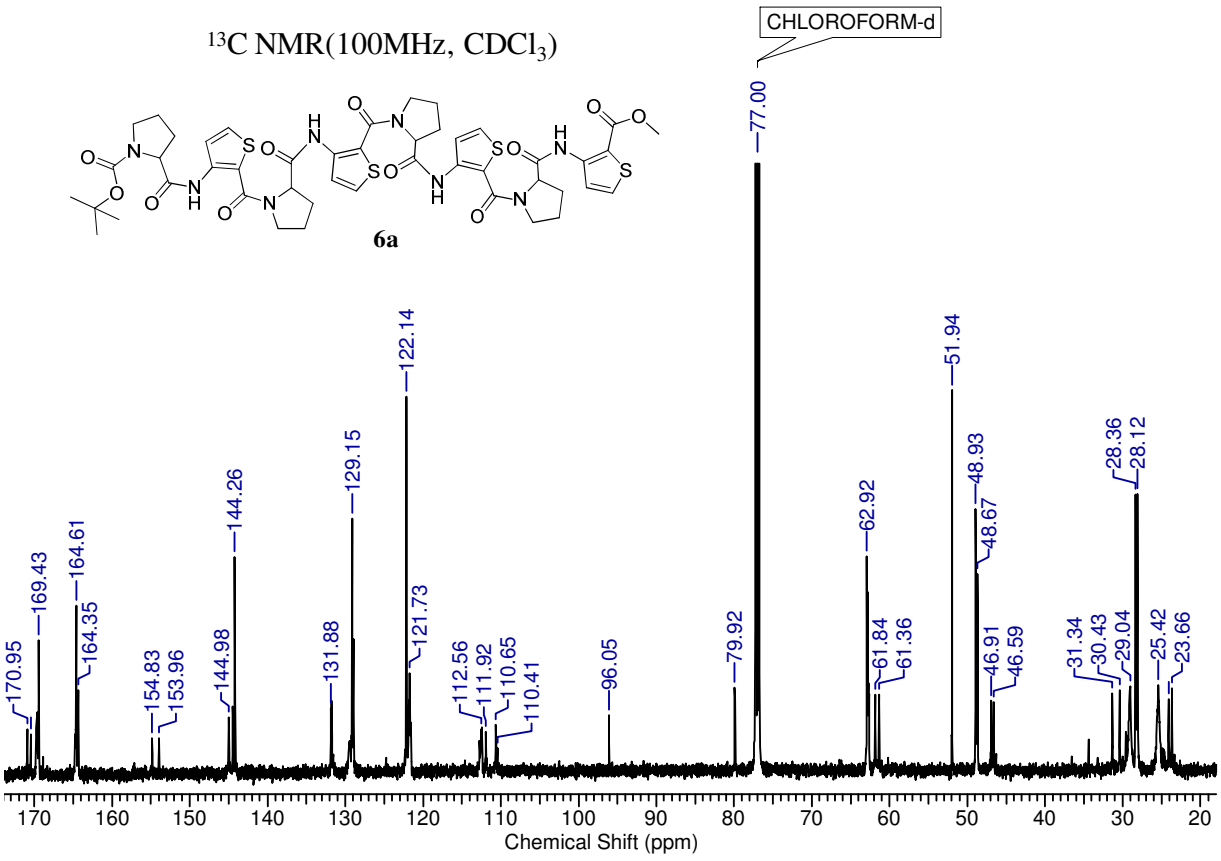


4f

^{13}C NMR(100MHz, $CDCl_3$)

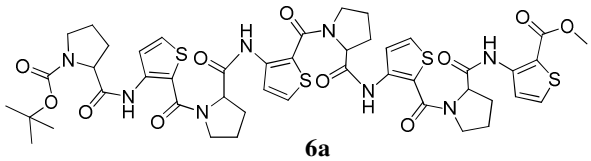

126.55
123.92
121.18
120.48
61.79
61.11
26.95
25.54
26.87
23.66
46.95
46.39
DEPT-135 (100MHz, CDCl3)
Chemical Shift (ppm)

4f


13C NMR(100MHz, CDCl3)
CHLOROFORM-d
77.00
170.95
169.43
164.61
164.35
154.83
153.96
144.98
144.26
131.88
129.15
122.14
121.73
112.56
111.92
110.65
110.41
96.05
79.92
62.92
61.84
61.36
51.94
48.93
48.67
46.91
46.59
31.34
30.43
29.04
28.36
28.12
25.42
23.66
Chemical Shift (ppm)

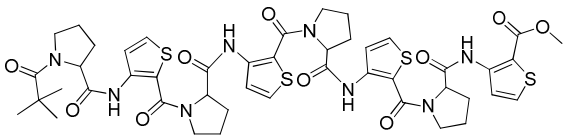
6a

DEPT-135 (100MHz, $CDCl_3$)



6a

^{13}C NMR(100MHz, $CDCl_3$)



6b

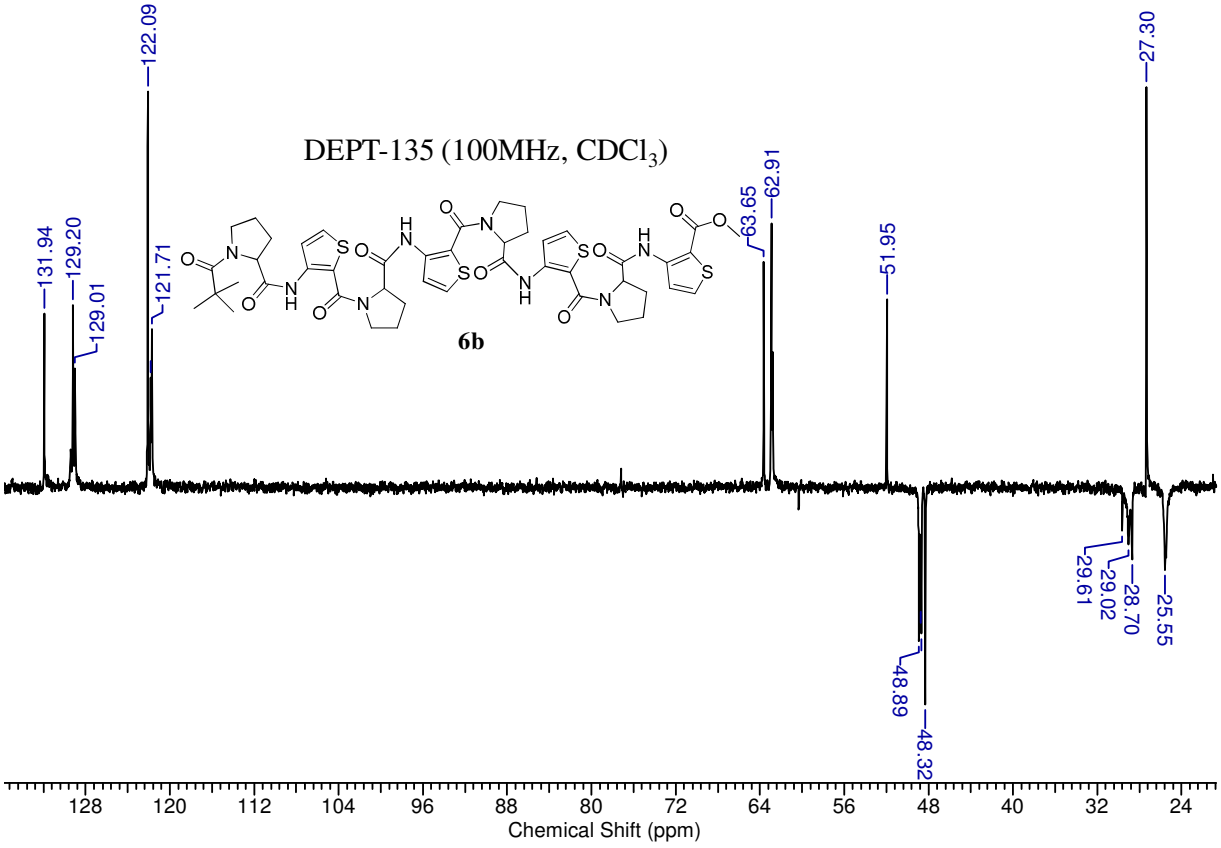

DEPT-135 (100MHz, CDCl3)
6b
131.94
129.20
129.01
122.09
121.71
63.65
62.91
51.95
48.89
48.32
29.61
29.02
28.70
27.30
25.55
128
120
112
104
96
88
80
72
64
56
48
40
32
24
Chemical Shift (ppm)

Table S1. Titration study of tetrapeptide 3f in $CDCl_3$ (10 mmol) with DMSO-d6 (volume of DMSO-$_{d6}$ added at each addition = 5 µl)

Volume of DMSO-d6 added (in µL)	Chemical Shift (in ppm)		
	δNH1	δNH2	δNH3
0	11.54	12.59	5.70
5	11.53	12.58	5.75
10	11.51	12.57	5.80
15	11.50	12.57	5.85
20	11.48	12.56	5.89
25	11.46	12.55	5.94
30	11.44	12.54	5.97
35	11.42	12.53	6.01
40	11.41	12.53	6.05
45	11.39	12.52	6.08
50	11.36	12.50	6.12

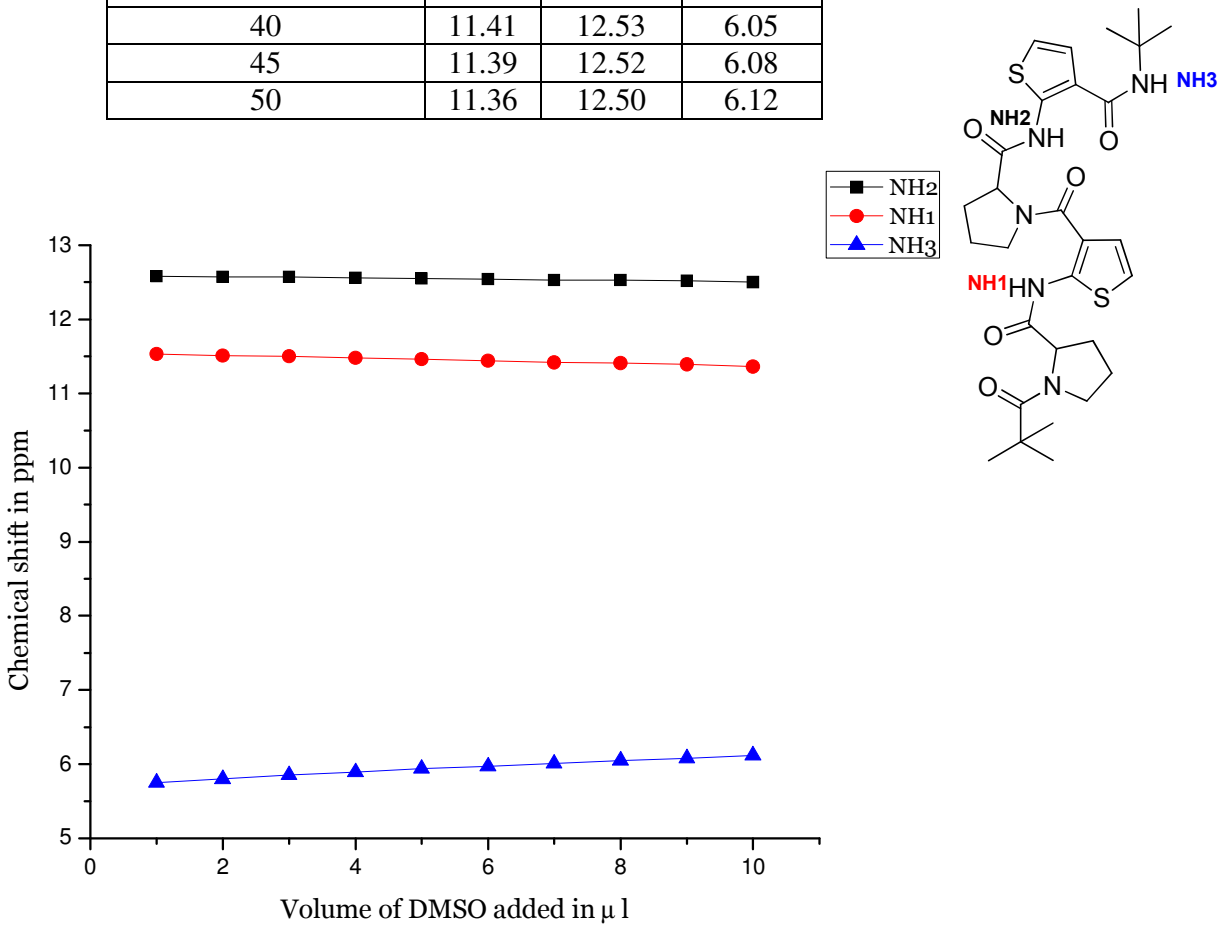
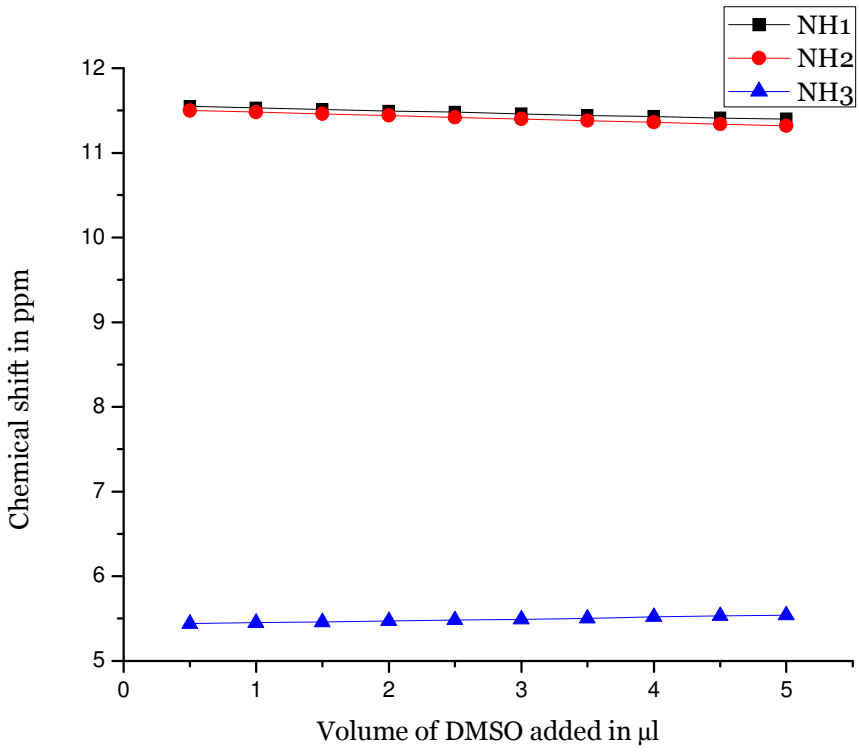


Table S2. Titration study of tetrapeptide 4f in $CDCl_3$ (10 mmol) with DMSO-d6 (volume of DMSO-d6 added at each addition = 5 µl)

Volume of DMSO-d6 added (in µL)	Chemical Shift (in ppm)		
	δNH1	δNH2	δNH3
0	11.57	11.52	5.43
5	11.55	11.50	5.44
10	11.53	11.48	5.45
15	11.51	11.46	5.46
20	11.49	11.44	5.47
25	11.48	11.42	5.48
30	11.46	11.40	5.49
35	11.44	11.38	5.50
40	11.43	11.36	5.52
45	11.41	11.34	5.53
50	11.40	11.32	5.54



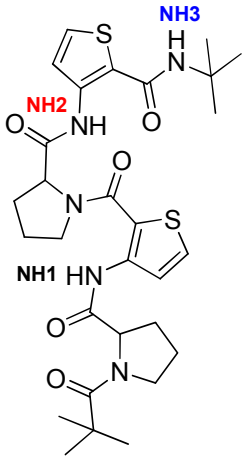
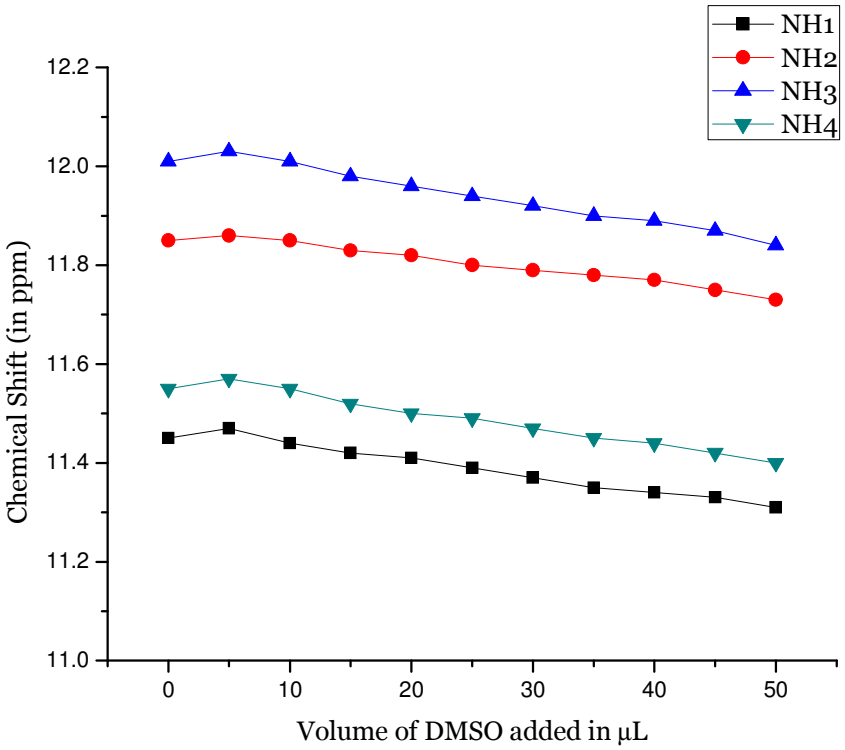
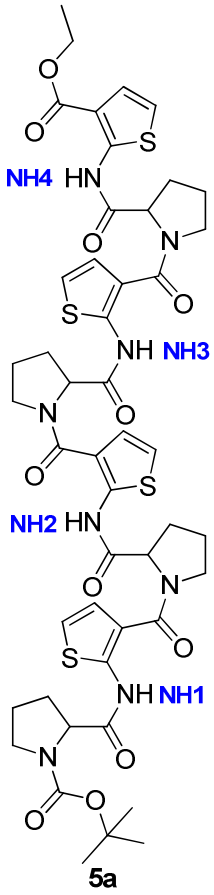


Table S3. Titration study of octapeptide 5a (10 mmol, 400 MHz, $CDCl_3$) with DMSO-d6 (volume of DMSO-d6 added at each addition = 5 µl)

Volume of DMSO-d6 added (in µL)	Chemical Shift (in ppm)			
	δNH1	δNH2	δNH3	δNH4
0	11.45	11.85	12.01	11.55
5	11.47	11.86	12.03	11.57
10	11.44	11.85	12.01	11.55
15	11.42	11.83	11.98	11.52
20	11.41	11.82	11.96	11.50
25	11.39	11.80	11.94	11.49
30	11.37	11.79	11.92	11.47
35	11.35	11.78	11.90	11.45
40	11.34	11.77	11.89	11.44
45	11.33	11.75	11.87	11.42
50	11.31	11.73	11.84	11.40

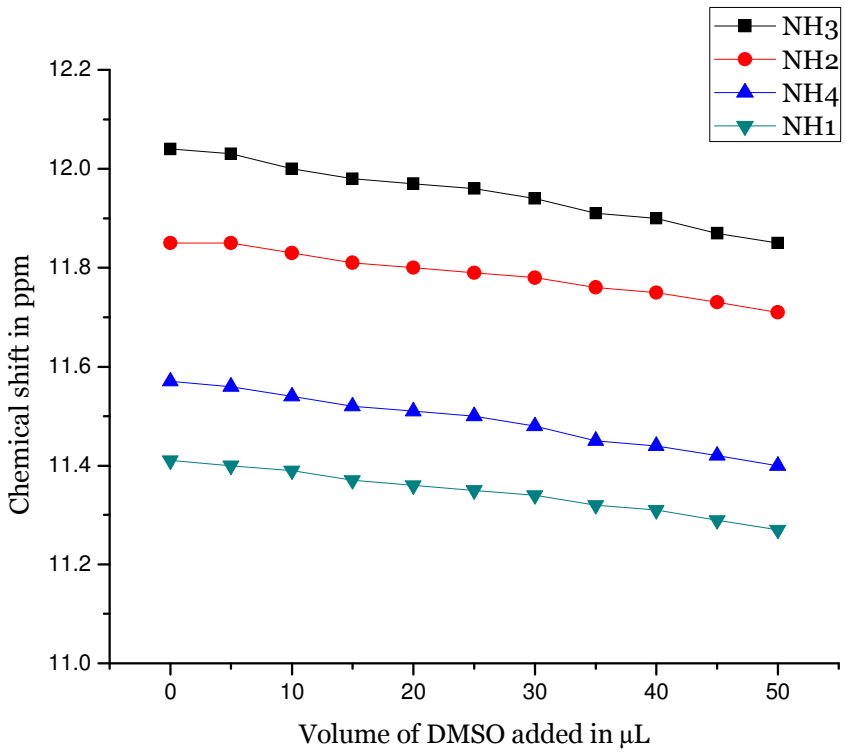


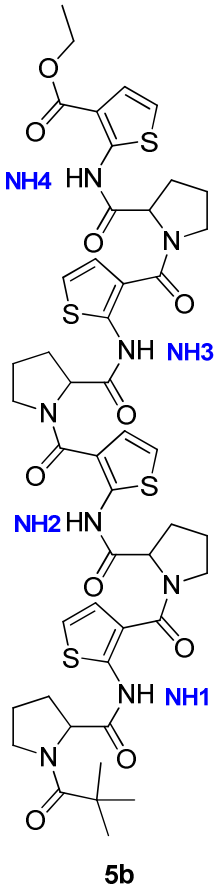


Table

Table S4. Titration study of octapeptide 5b (10 mmol, 400 MHz, $CDCl_3$) with DMSO-d6 (volume of DMSO-d6 added at each addition = 5 µl)

Volume of DMSO-d6 added (in µL)	Chemical Shift (in ppm)			
	δNH1	δNH2	δNH3	δNH4
0	11.41	11.85	12.04	11.57
5	11.40	11.85	12.03	11.56
10	11.39	11.83	12.00	11.54
15	11.37	11.81	11.98	11.52
20	11.36	11.80	11.97	11.51
25	11.35	11.79	11.96	11.50
30	11.34	11.78	11.94	11.48
35	11.32	11.76	11.91	11.45
40	11.31	11.75	11.90	11.44
45	11.29	11.73	11.87	11.42
50	11.27	11.71	11.85	11.40

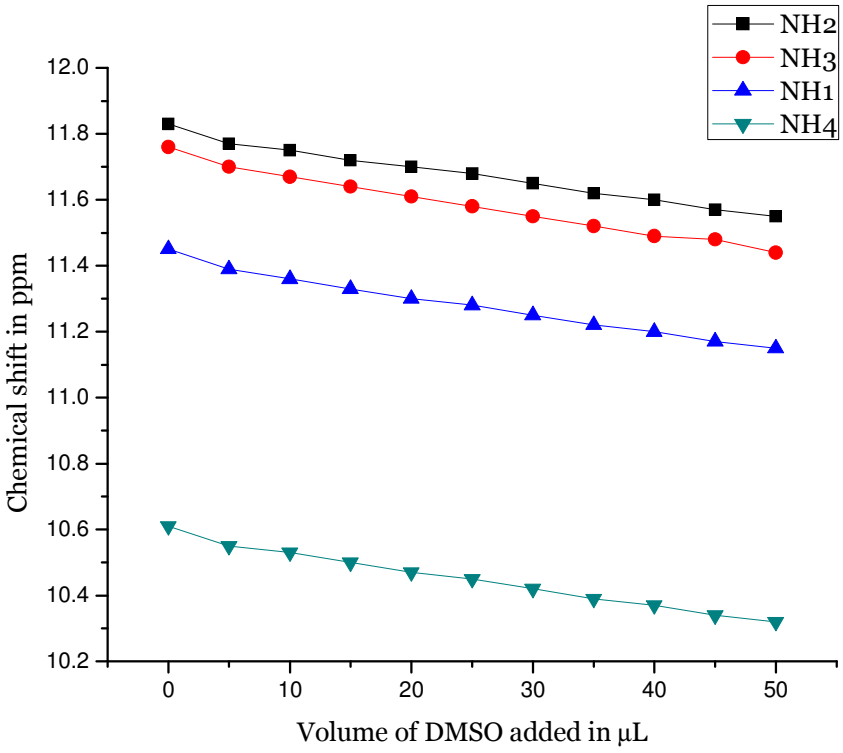




5b

Table S5. Titration study of octapeptide 6a (10 mmol, 400 MHz, $CDCl_3$) with DMSO-d6 (volume of DMSO-d6 added at each addition = 5 µl)

Volume of DMSO-d6 added (in µL)	Chemical Shift (in ppm)			
	δNH1	δNH2	δNH3	δNH4
0	11.45	11.83	11.76	10.61
5	11.39	11.77	11.70	10.55
10	11.36	11.75	11.67	10.53
15	11.33	11.72	11.64	10.50
20	11.30	11.70	11.61	10.47
25	11.28	11.68	11.58	10.45
30	11.25	11.65	11.55	10.42
35	11.22	11.62	11.52	10.39
40	11.20	11.60	11.49	10.37
45	11.17	11.57	11.48	10.34
50	11.15	11.55	11.44	10.32



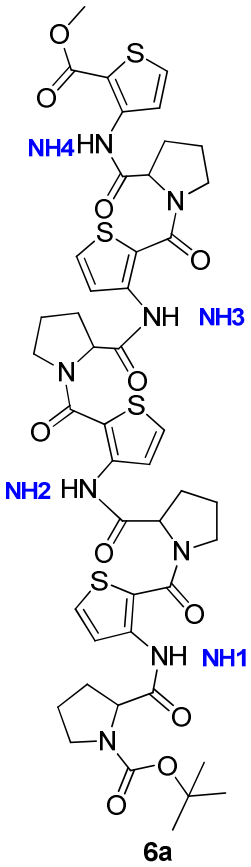
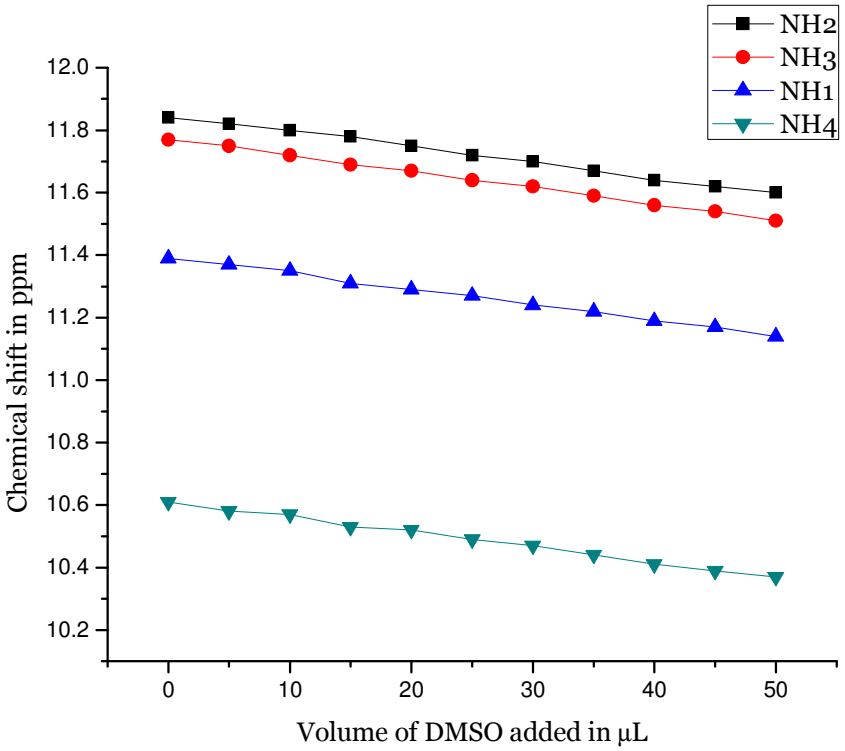


Table S6. Titration study of octapeptide 6b (10 mmol, 400 MHz, $CDCl_3$) with DMSO-d6 (volume of DMSO-d6 added at each addition = 5 µl)

Volume of DMSO-d6 added (in µL)	Chemical Shift (in ppm)			
	δNH1	δNH2	δNH3	δNH4
0	11.39	11.84	11.77	10.61
5	11.37	11.82	11.75	10.58
10	11.35	11.80	11.72	10.57
15	11.31	11.78	11.69	10.53
20	11.29	11.75	11.67	10.52
25	11.27	11.72	11.64	10.49
30	11.24	11.70	11.62	10.47
35	11.22	11.67	11.59	10.44
40	11.19	11.64	11.56	10.41
45	11.17	11.62	11.54	10.39
50	11.14	11.60	11.51	10.37



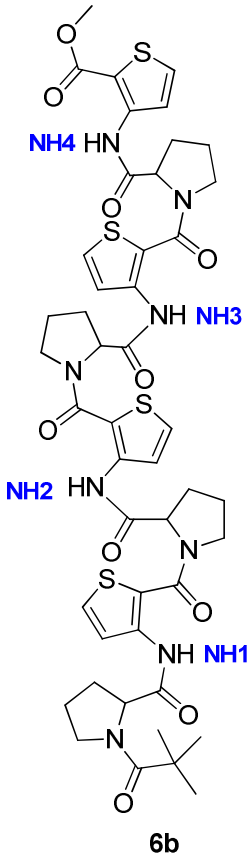
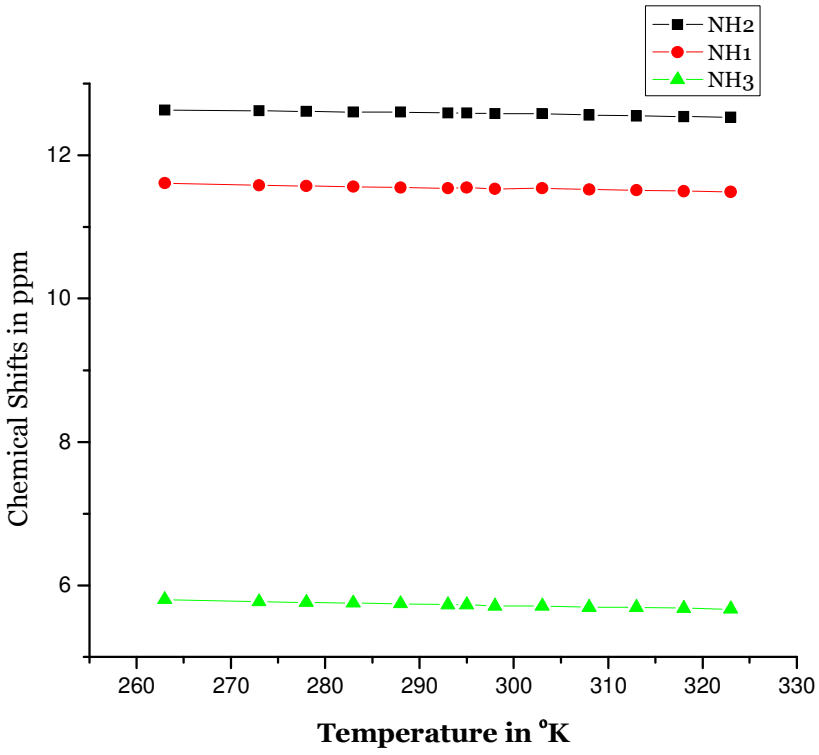
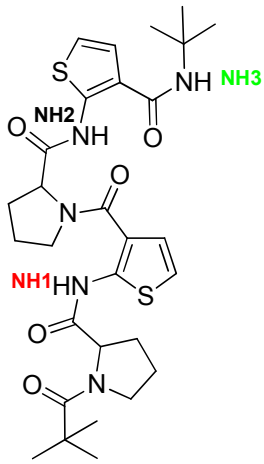
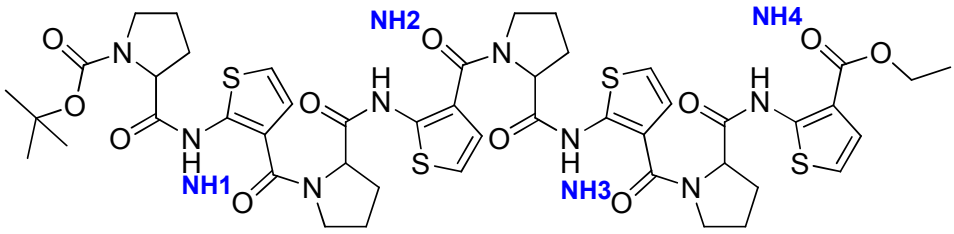


Table S7. Variable temperature study of tetrapeptide 3f (10 mmol, 400 MHz, $CDCl_3$)

Temperature (in K)	Chemical shift (in ppm)		
	δNH1	δNH2	δNH3
263	11.61	12.63	5.80
273	11.58	12.62	5.77
278	11.57	12.61	5.76
283	11.56	12.60	5.75
288	11.55	12.60	5.74
293	11.54	12.59	5.73
295	11.55	12.59	5.73
298	11.53	12.58	5.71
303	11.54	12.58	5.71
308	11.52	12.56	5.69
313	11.51	12.55	5.69
318	11.50	12.54	5.68
323	11.49	12.53	5.67







5a

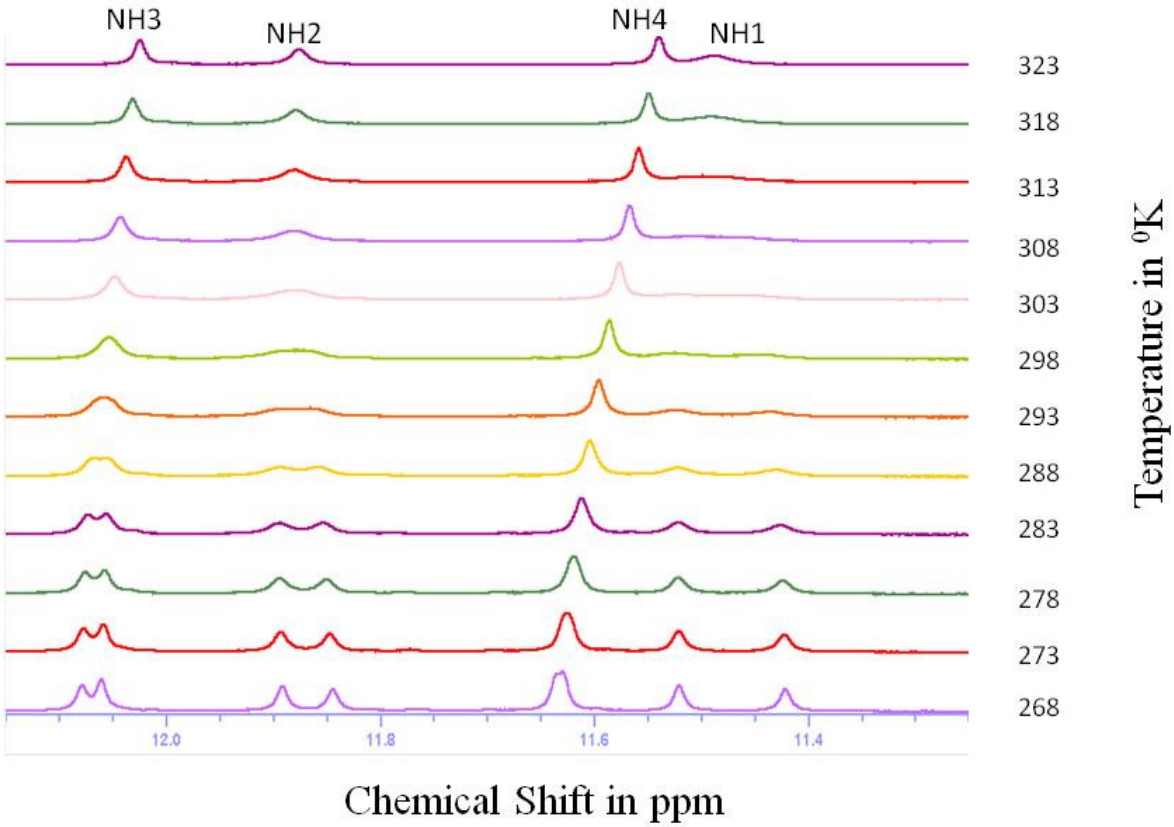
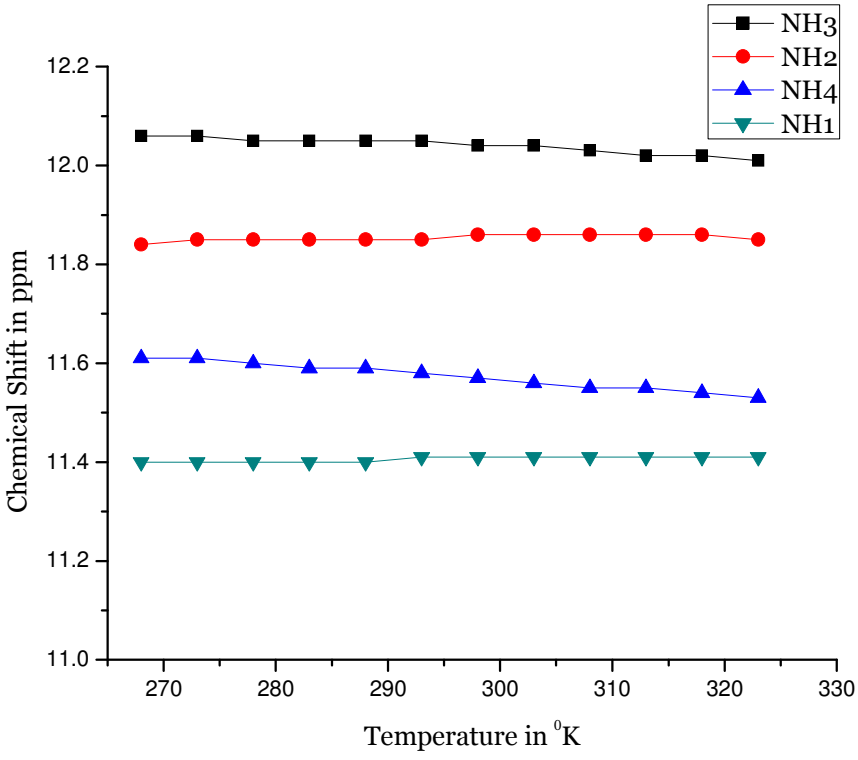
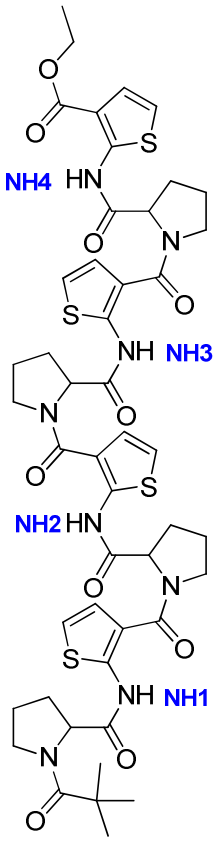


Figure-2. Variable temperature study of octapeptide **5a** (10 mmol, 400 MHz, $CDCl_3$)

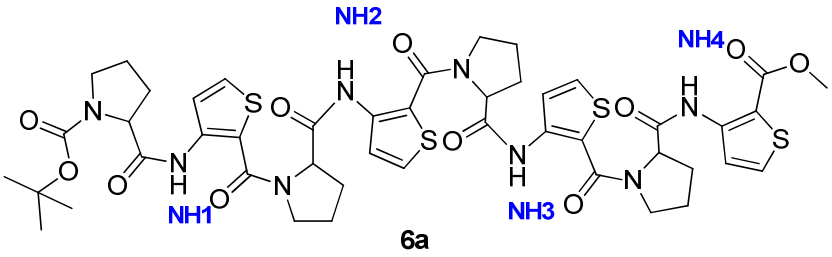
Table S8. Variable temperature study of octapeptide 5b (10 mmol, 400 MHz, $CDCl_3$)

Temperature (in K)	δNH1	δNH2	δNH3	δNH4
268	11.40	11.84	12.06	11.61
273	11.40	11.85	12.06	11.61
278	11.40	11.85	12.05	11.60
283	11.40	11.85	12.05	11.59
288	11.40	11.85	12.05	11.59
293	11.41	11.85	12.05	11.58
298	11.41	11.85	12.04	11.57
303	11.41	11.86	12.04	11.56
308	11.41	11.86	12.03	11.55
313	11.41	11.86	12.02	11.55
318	11.41	11.86	12.02	11.54
323	11.41	11.85	12.01	11.53





5b



6a

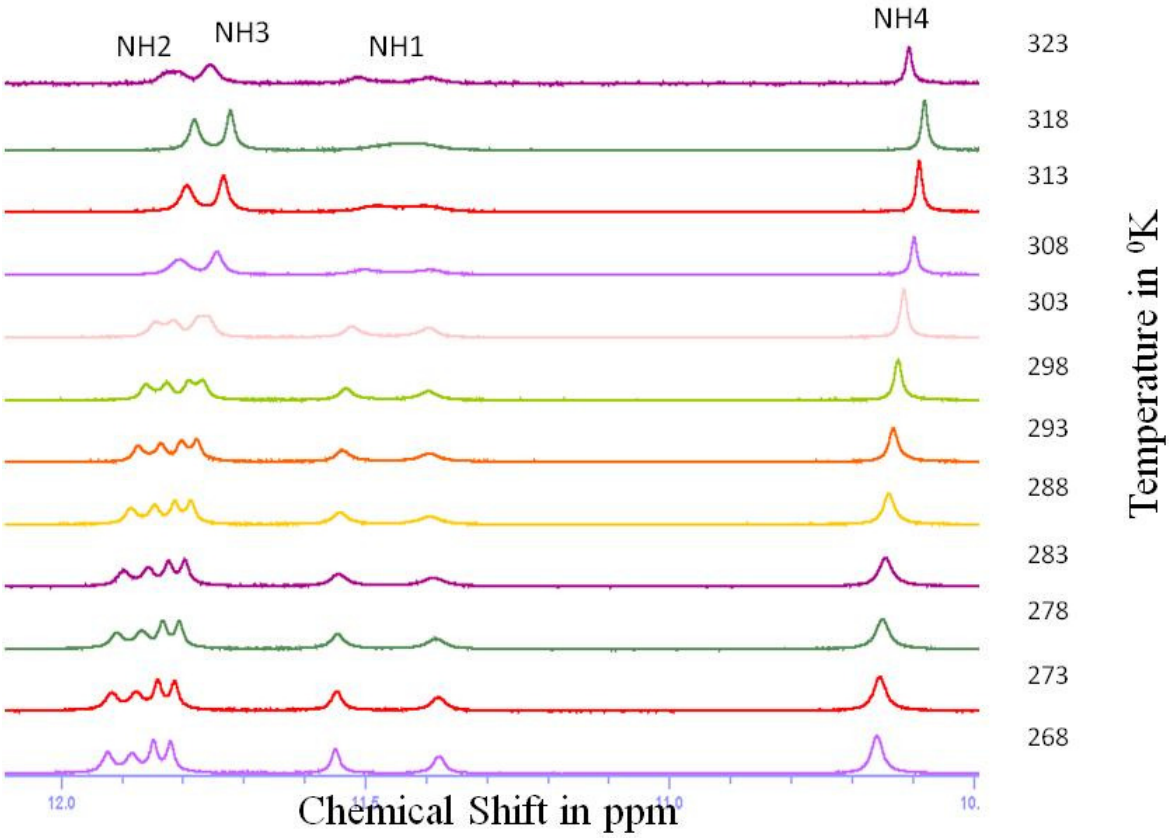
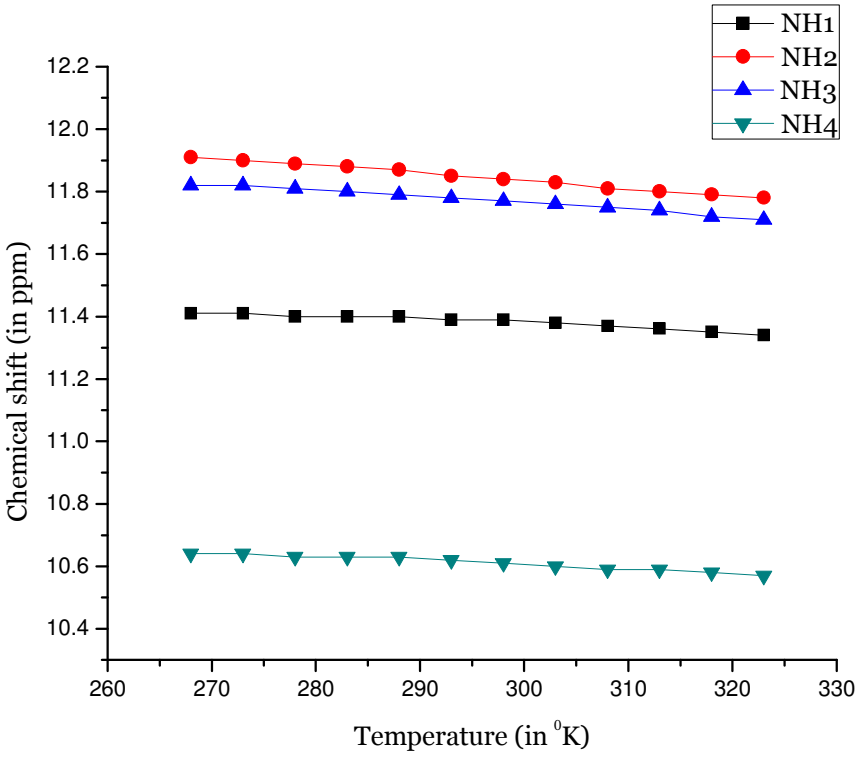
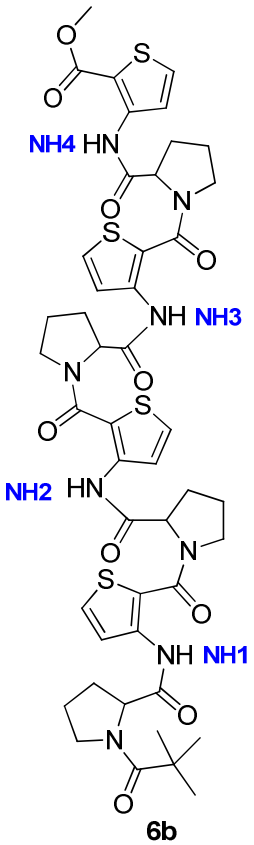


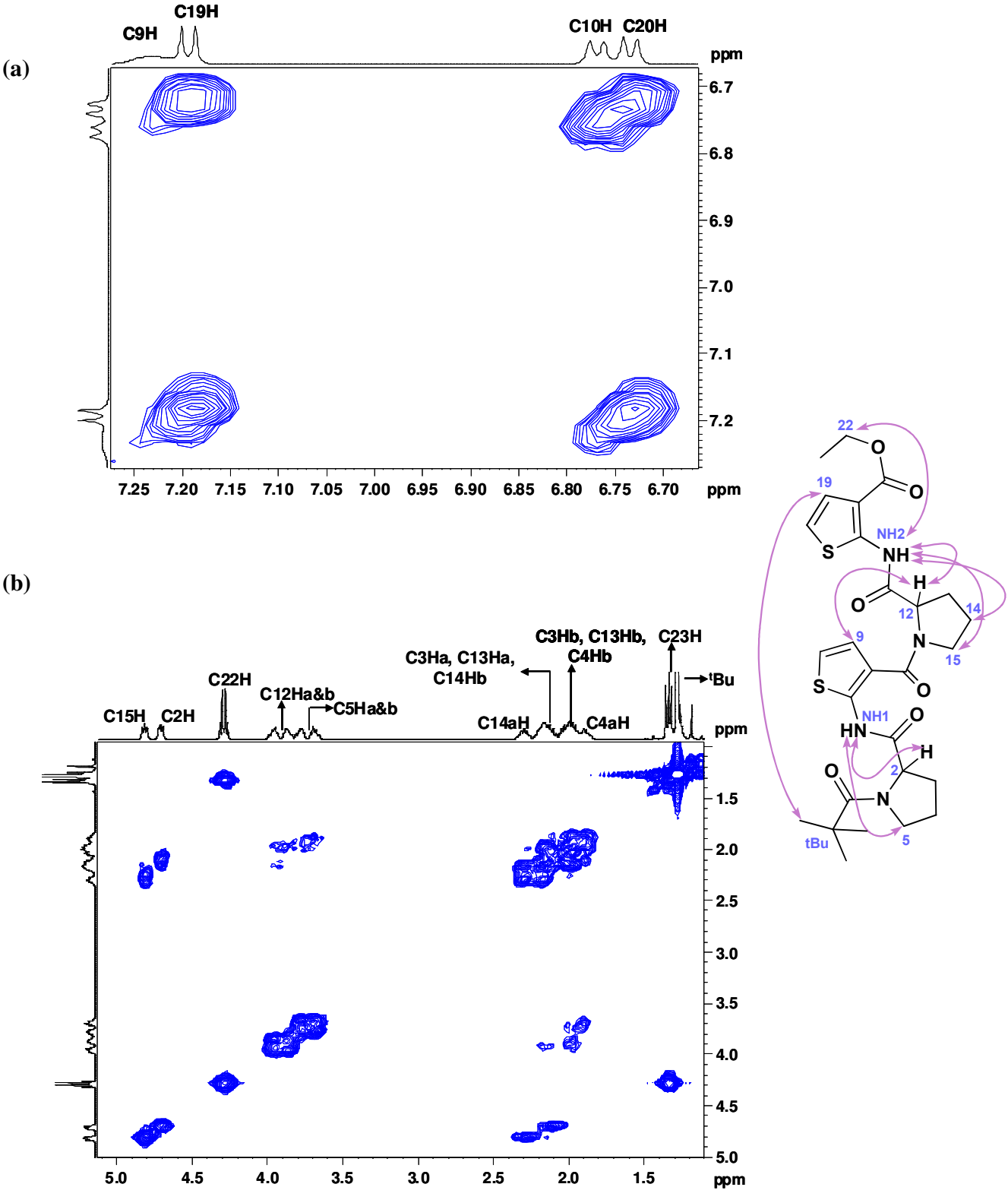
Figure-3. Variable temperature study of octapeptide **5a** (10 mmol, 400 MHz, $CDCl_3$)

Table S9. Variable temperature study of octapeptide 6b (10 mmol, 400 MHz, $CDCl_3$)

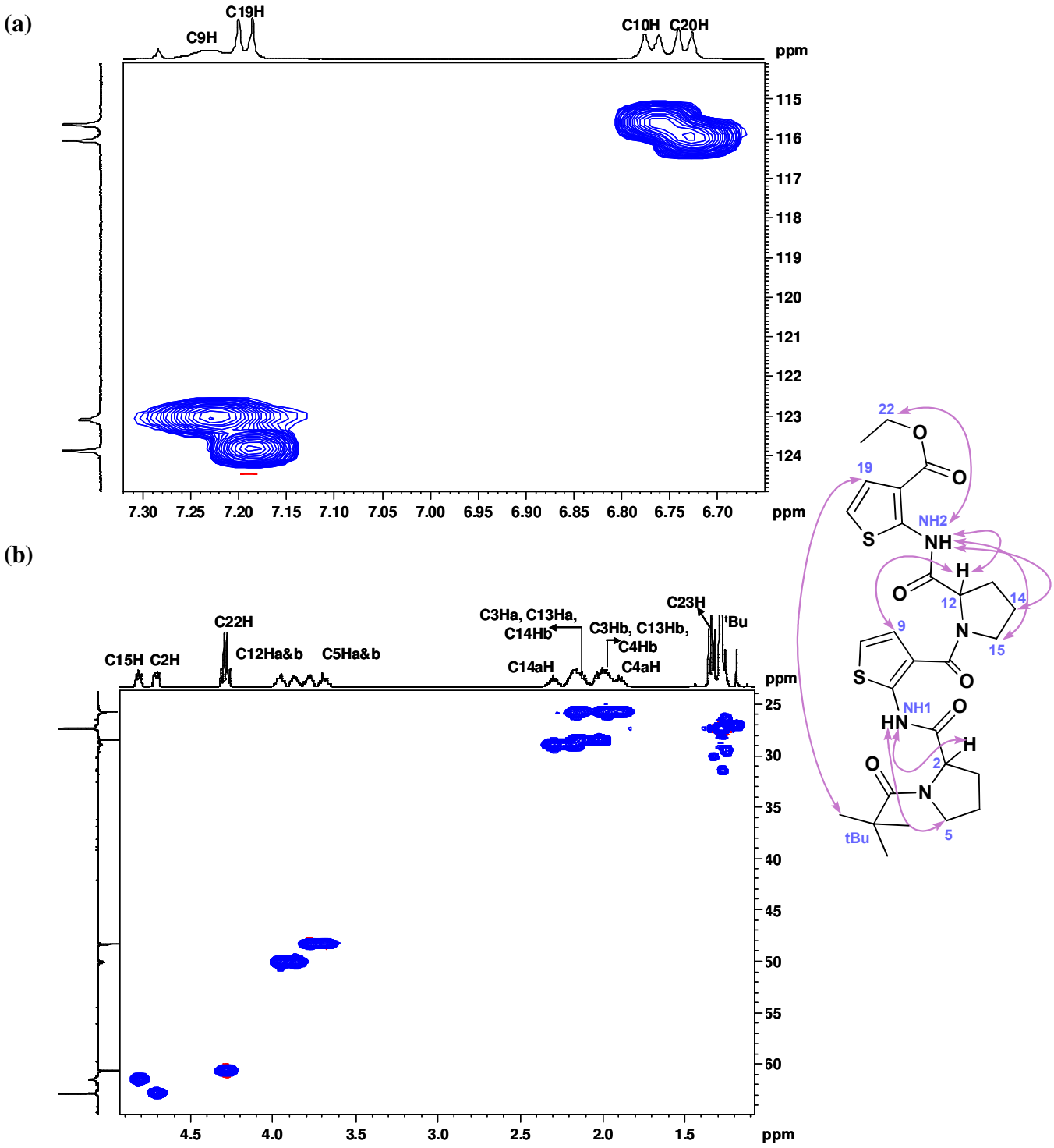
Temperature (in K)	δNH1	δNH2	δNH3	δNH4
268	11.41	11.91	11.82	10.64
273	11.41	11.90	11.82	10.64
278	11.40	11.89	11.81	10.63
283	11.40	11.88	11.80	10.63
288	11.40	11.87	11.79	10.63
293	11.39	11.85	11.78	10.62
298	11.39	11.84	11.77	10.61
303	11.38	11.83	11.76	10.60
308	11.37	11.81	11.75	10.59
313	11.36	11.80	11.74	10.59
318	11.35	11.79	11.72	10.58
323	11.34	11.78	11.71	10.57



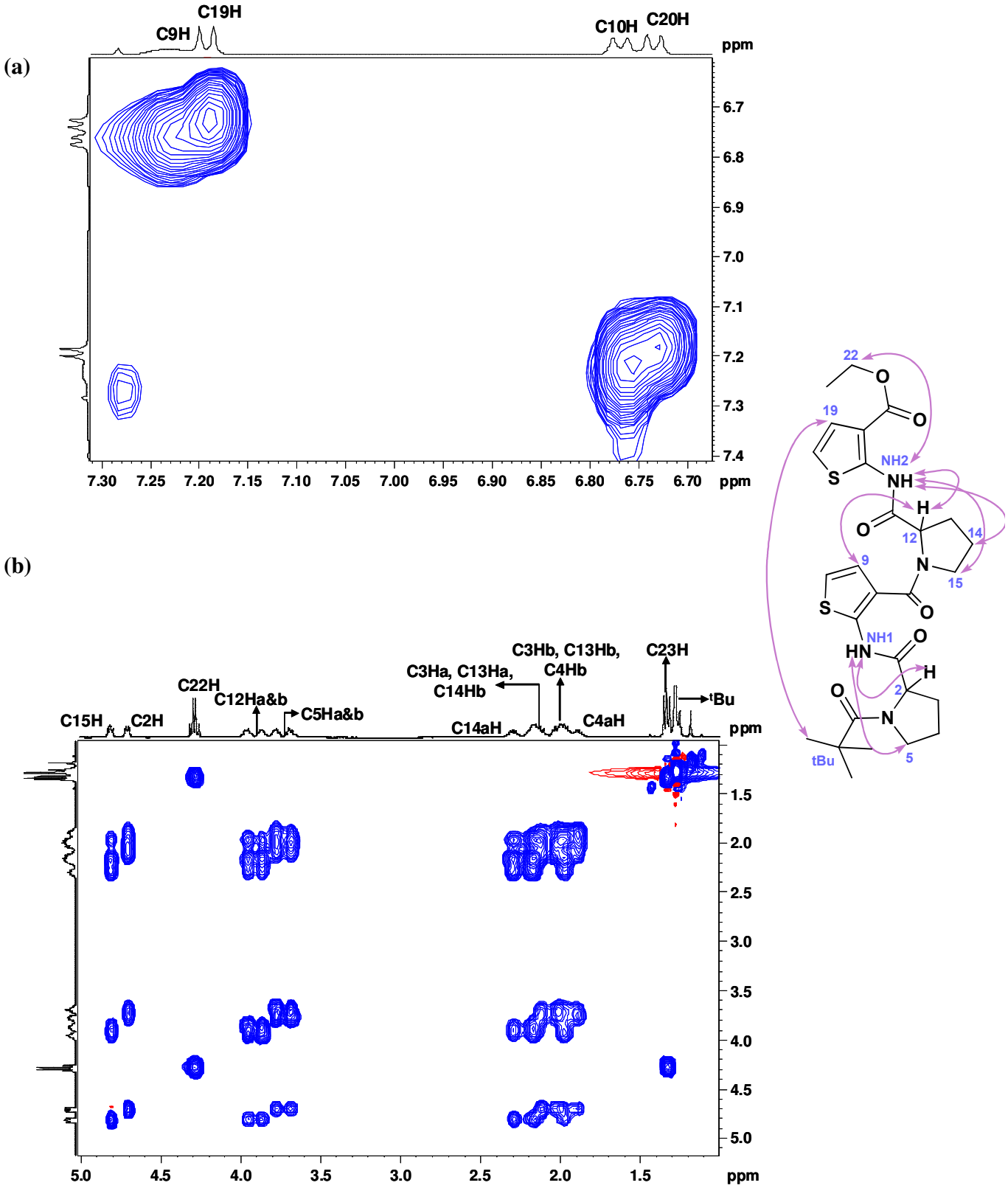




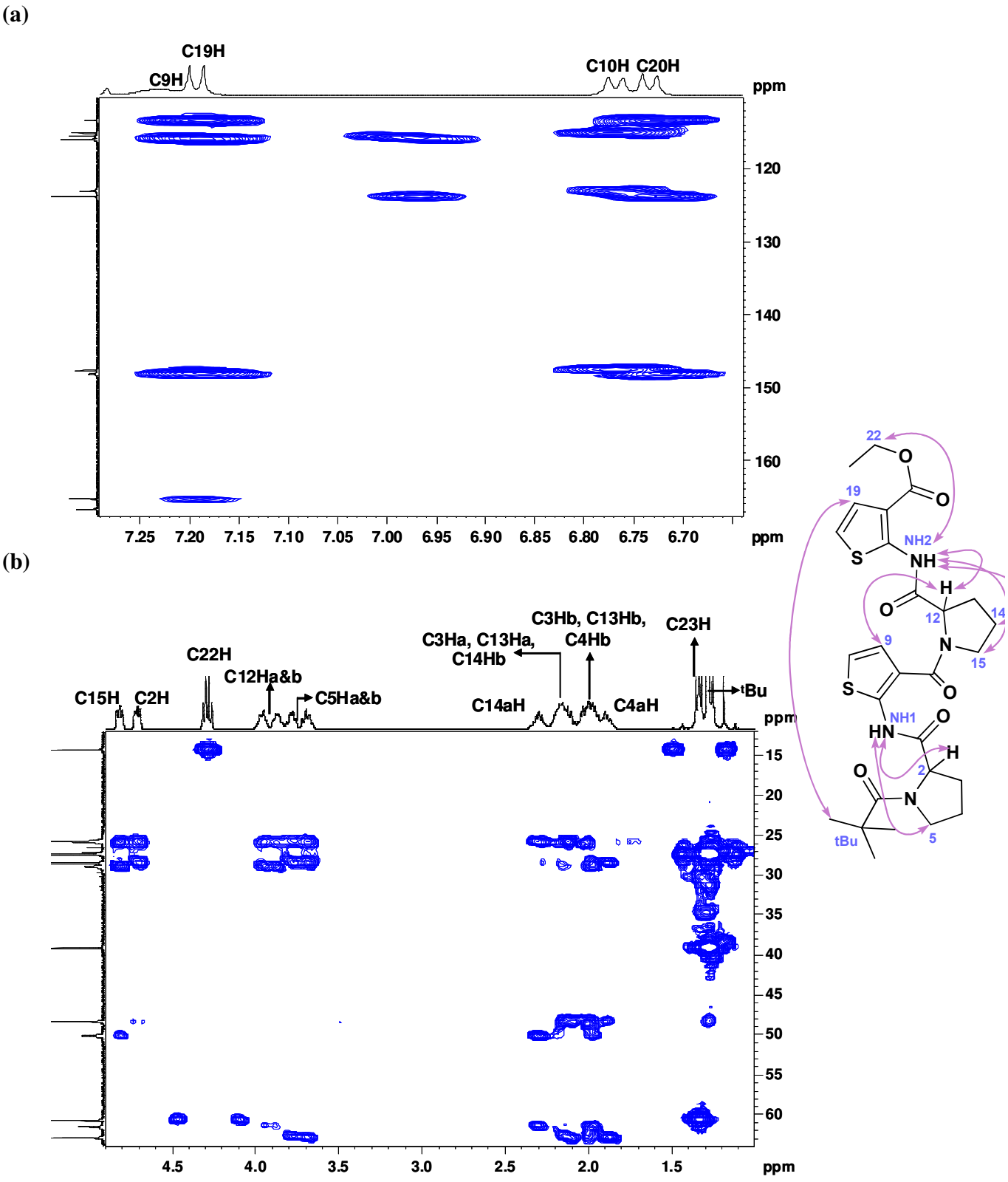
Partial COSY spectra of 3d (400MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions



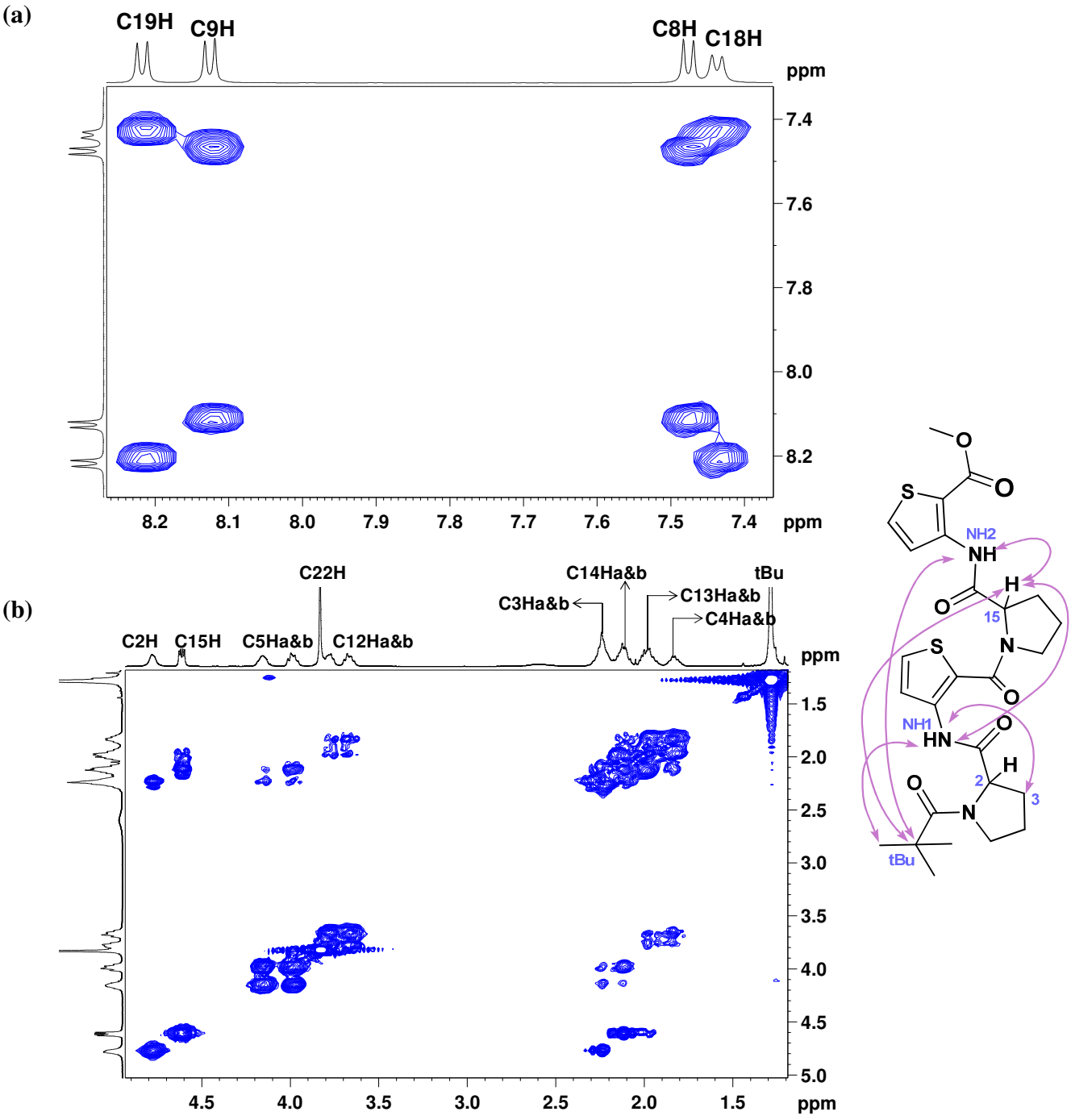
Partial HSQC spectra of 3d (400MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions



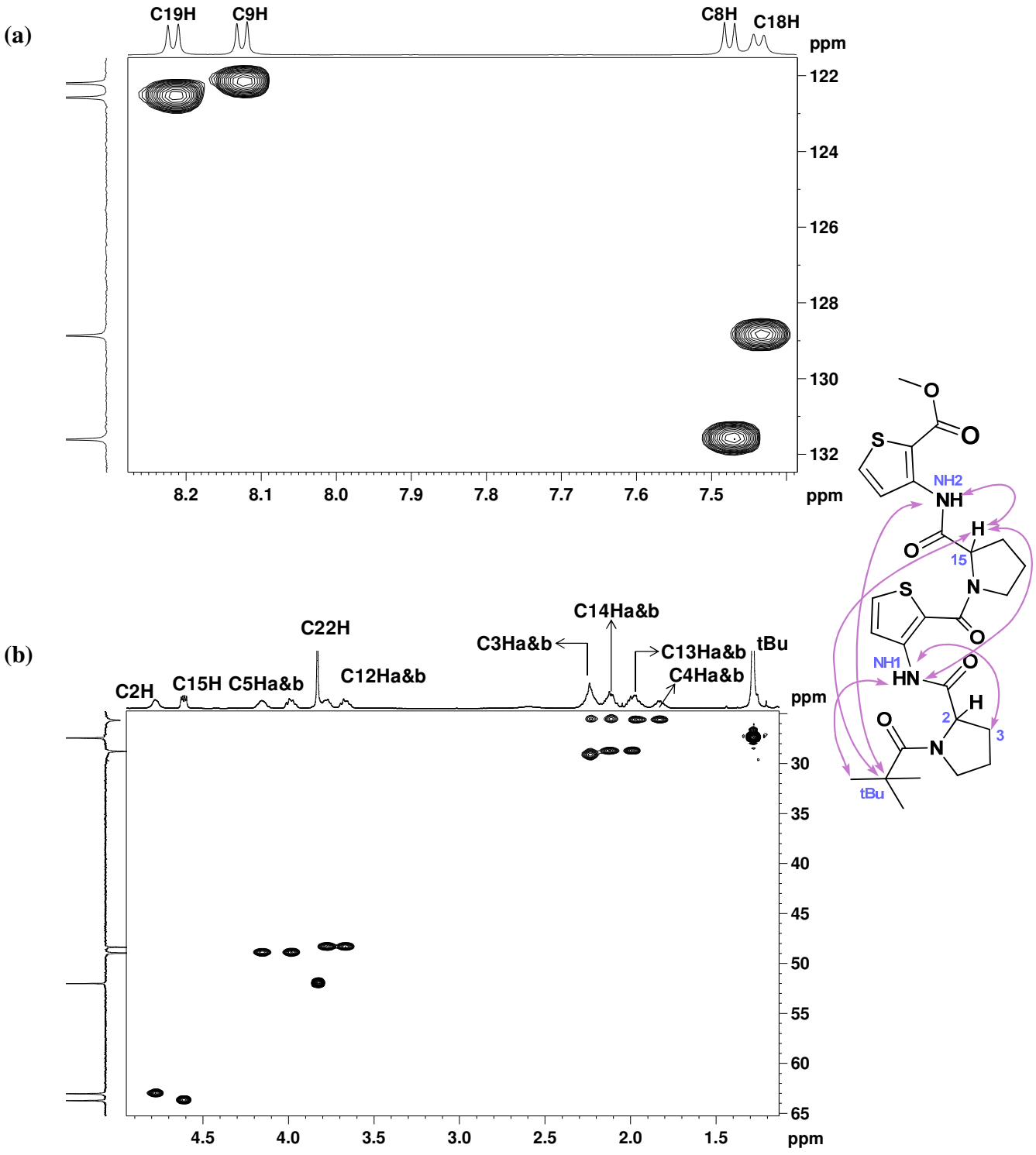
Partial TOCSY spectra of 3d (400MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions



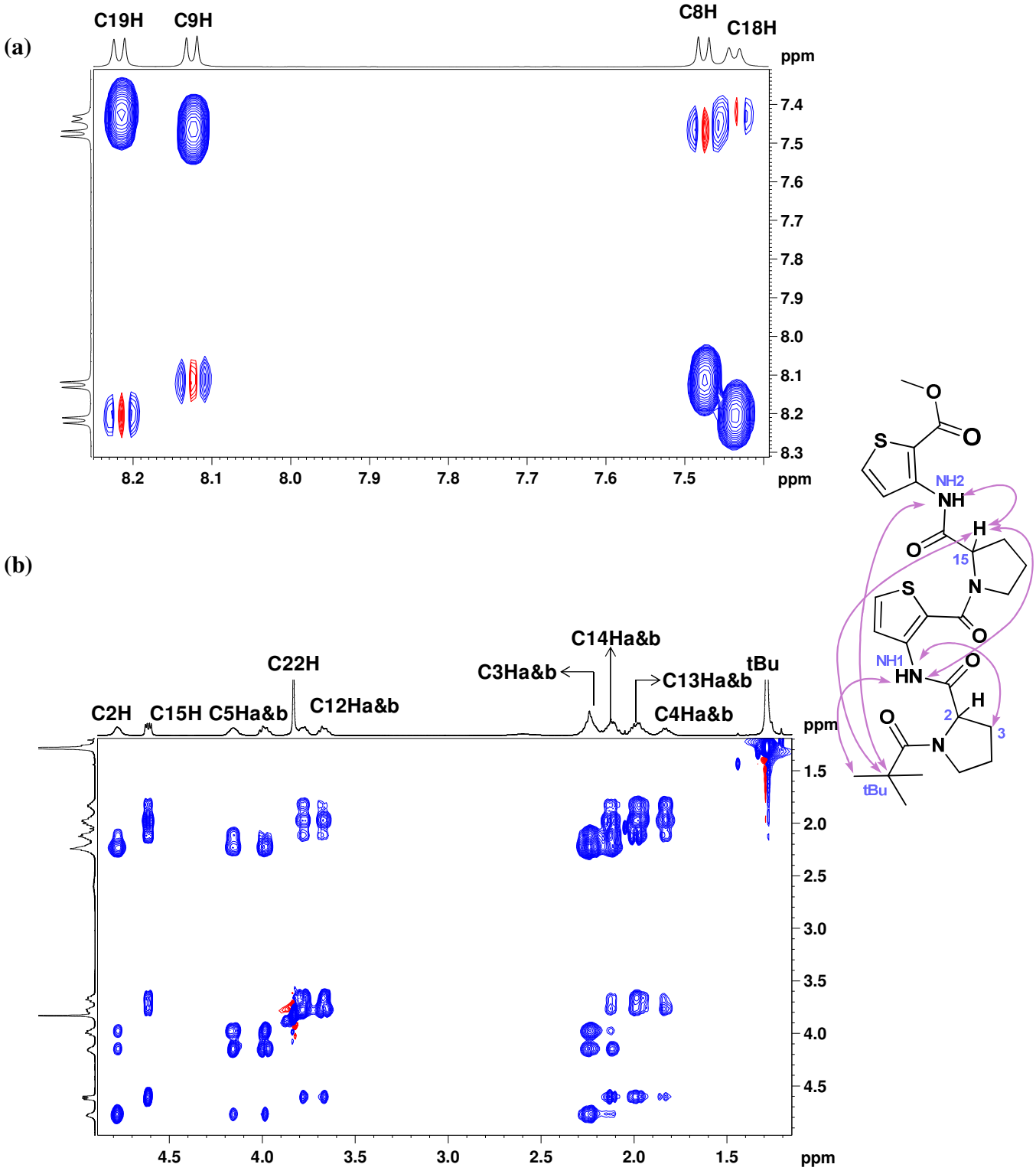
Partial HMBC spectra of 3d (400MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions



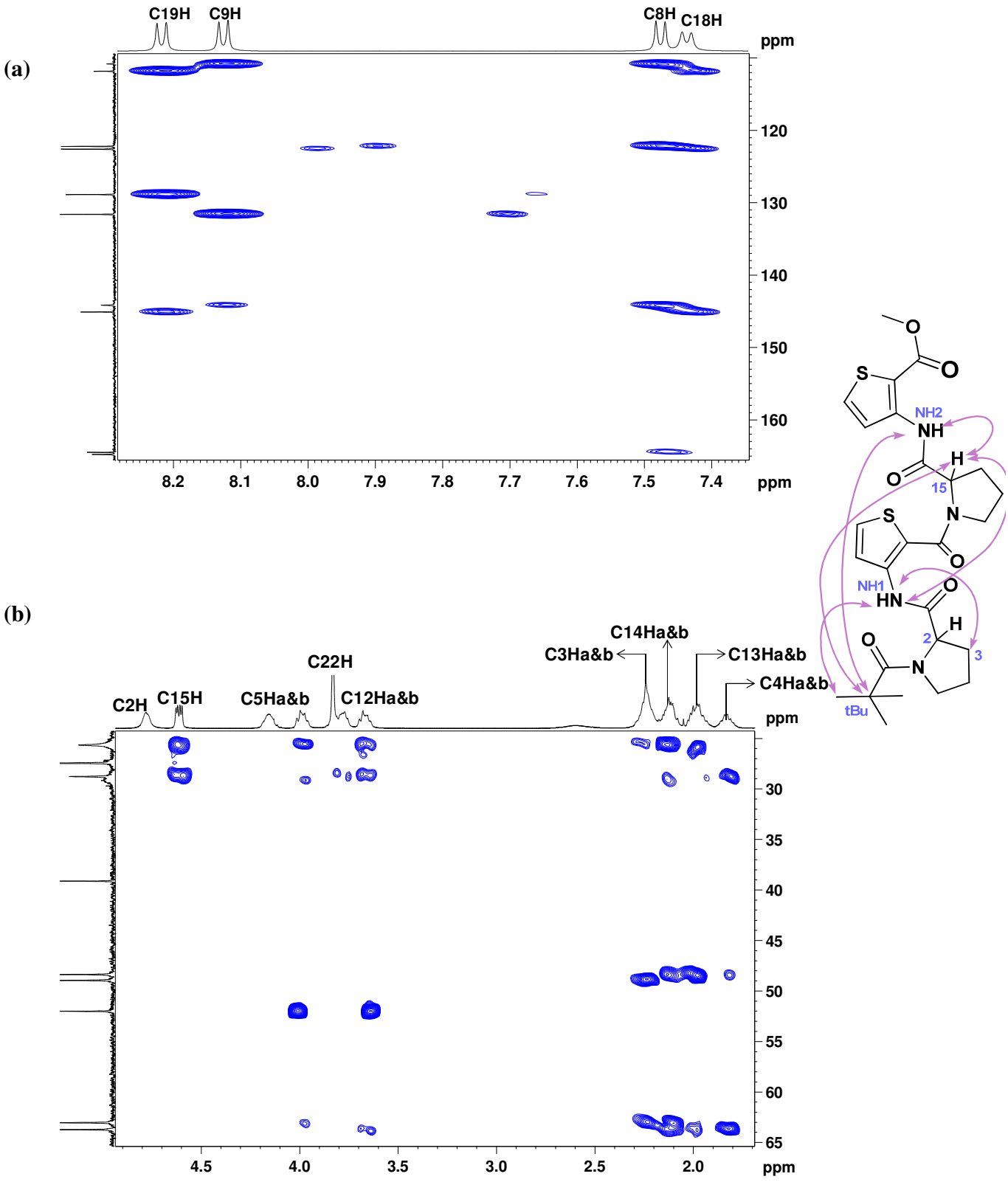
Partial COSY spectra of 4d (400MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions



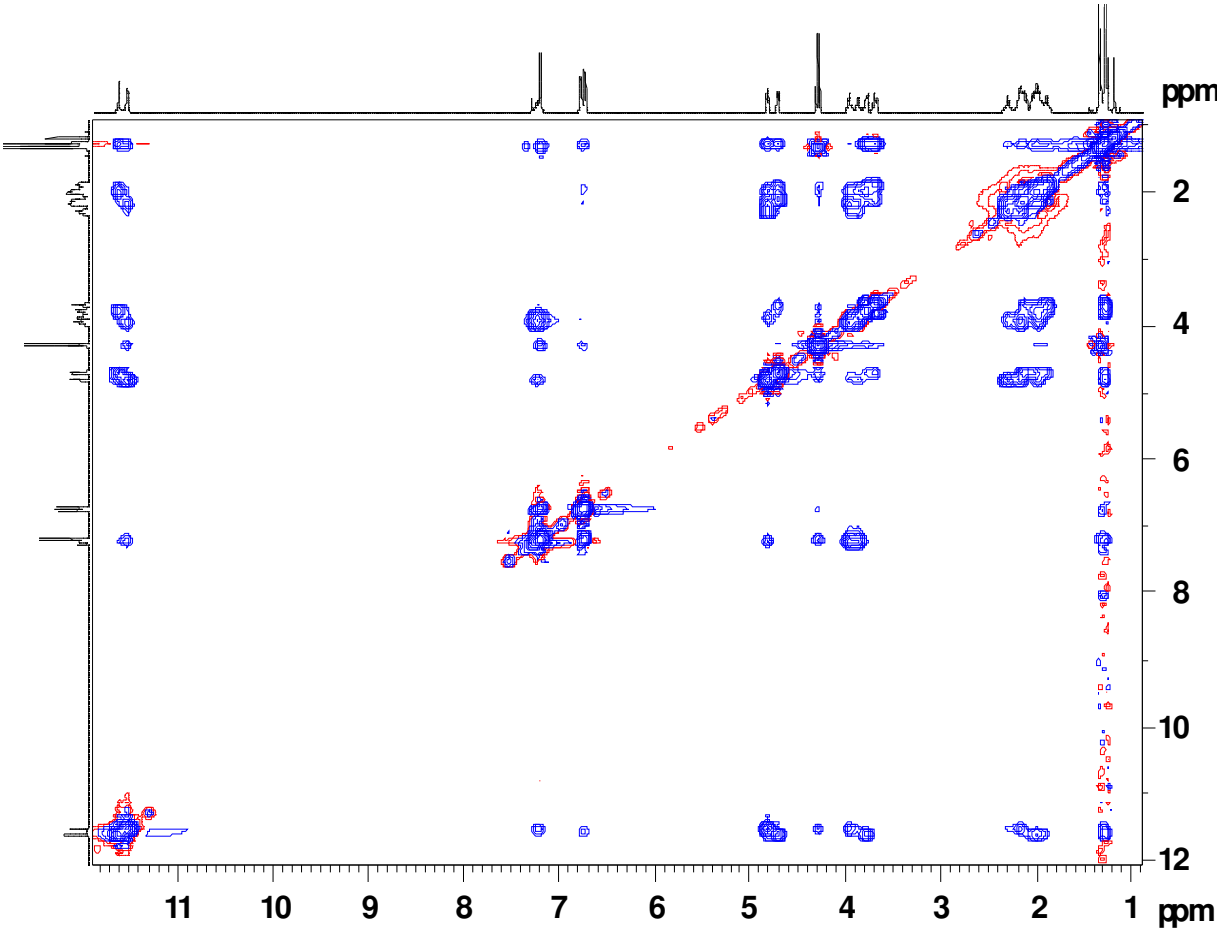
Partial HSQC spectra of 4d (400MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions



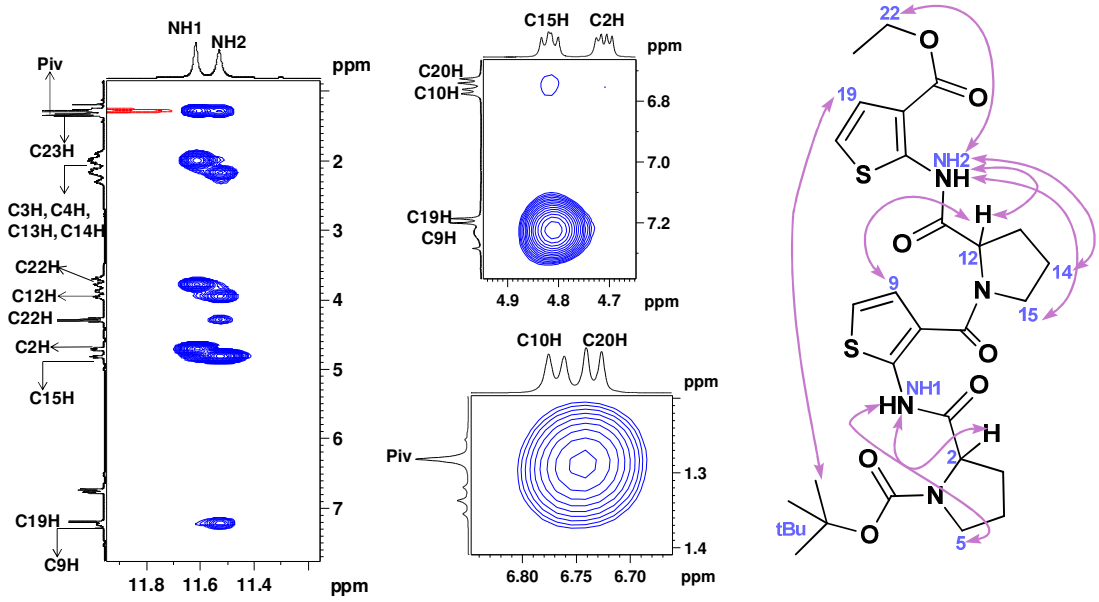
Partial TOCSY spectra of 4d (400MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions



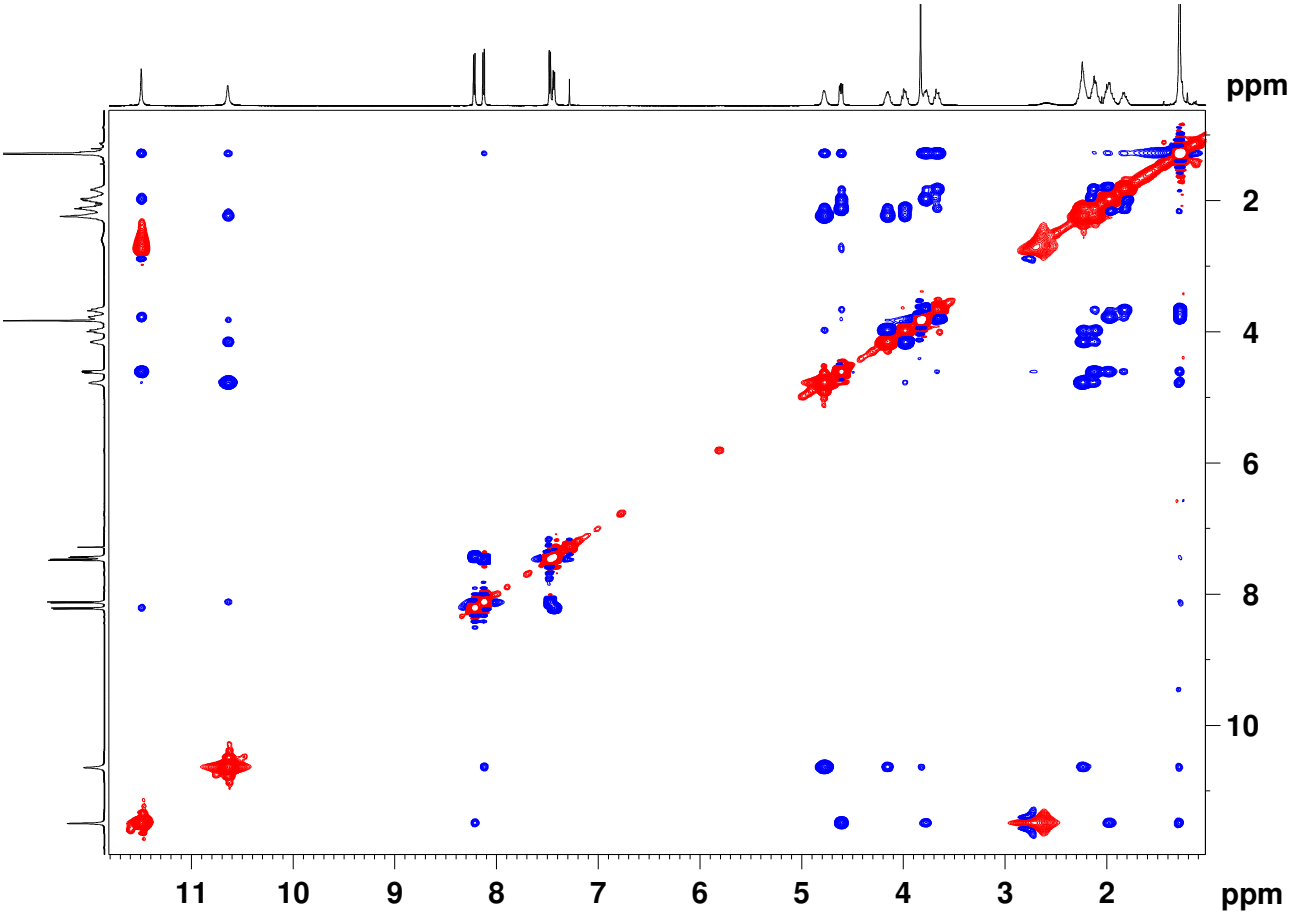
Partial HMBC spectra of 4d (400MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions



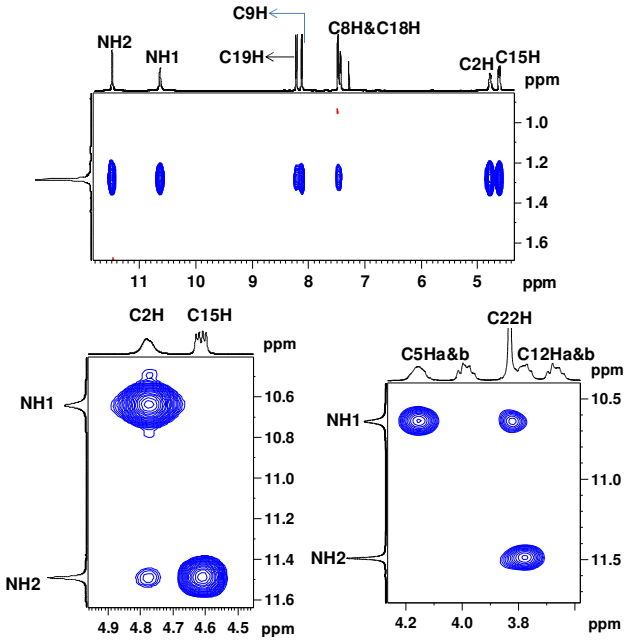
2D NOESY full spectrum of 3d (400MHz, $CDCl_3$).

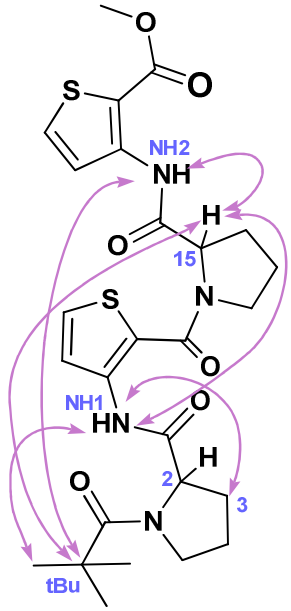


2D NOESY excerpts of 3d (400 MHz, $CDCl_3$).



2D NOESY full spectrum of 4d (400MHz, $CDCl_3$).





2D NOESY excerpts of 4d (400 MHz, $CDCl_3$).

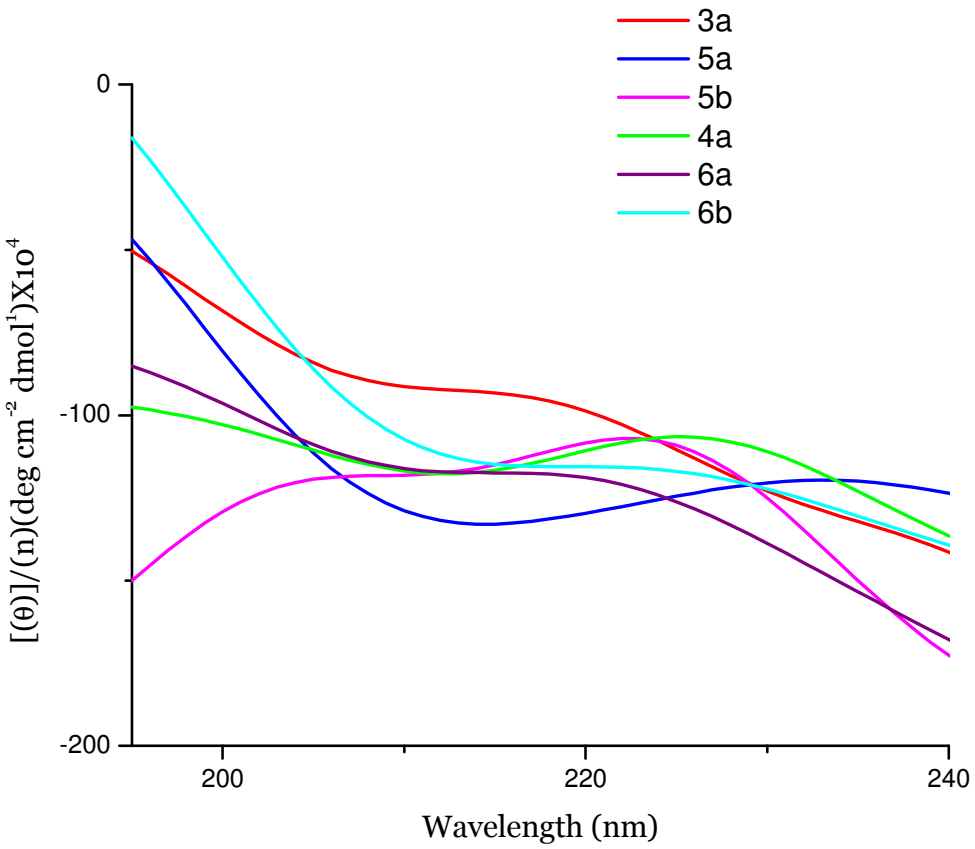


Figure-4. Circular dichroism (CD) spectra of tetrapeptides (**3a** and **4a**) and octapeptides (**5a**, **5b**, **6a** and **6b**); 0.2mmol solution in trifluoro ethanol.

Details of the quantum chemical calculations

All quantum chemical calculations were performed at the HF/6-31G**++ level of *ab initio* MO theory employing the Gaussian03 software package. The backbone torsion angles and total energies for the derivatives **3a**, **4a**, **5a** and **6a** are given below.

Table S10. Backbone Torsion Angles (in degrees)[a] for **3a** according to the HF/6-31G**++

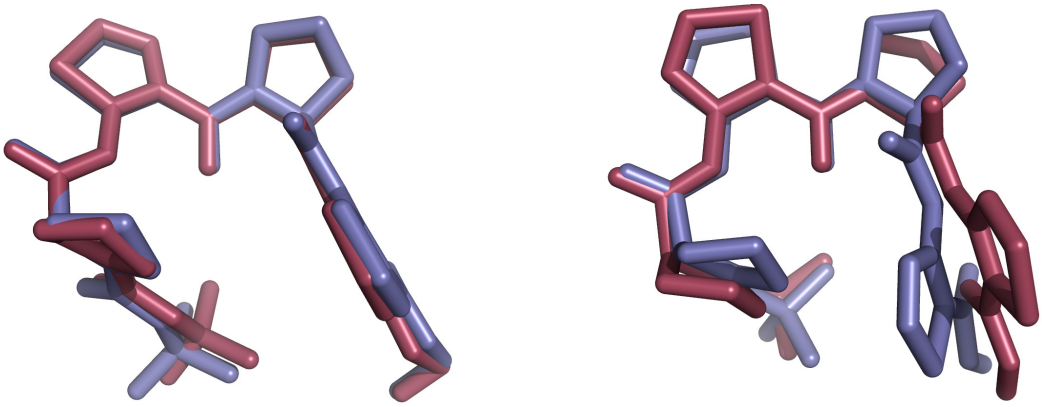
Pro1		Atc1			Pro2		Atc2		
ϕ	ψ	ϕ	θ	ψ	ϕ	ψ	ϕ	θ	ψ
-86.10	-5.76	179.21	-1.10	-157.37	-58.07	145.04	-178.99	1.39	178.46
-84.75	-12.27	173.33	-1.14	152.75	-61.57	148.15	-179.7	0.22	179.0

[a]First row includes the data of the crystal **3a**, second row includes the data of the model **3a** obtained using HF/6-31G**++. E_T(HF/6-31G**++) = -2579.3011 a.u

Table S11. Backbone Torsion Angles (in degrees)[a] for **4d** according to the HF/6-31G**++

Pro1		Atc1			Pro2		Atc2		
ϕ	ψ	ϕ	θ	ψ	ϕ	ψ	ϕ	θ	ψ
-83.35	-3.67	158.12	1.43	-165.69	-56.45	144.51	-170.90	0.35	176.34
-75.02	-24.65	179.2	-2.96	167.55	-62.62	140.20	-176.28	-0.32	179.30

[a]First row includes the data of the crystal **4d** , second row includes the data of the model **4a** obtained using HF/6-31G**++. E_T(HF/6-31G**++) = -2465.3680 a.u



A **B**

Figure-5. A: Overlay of crystal of **3a** (red) with its model (blue). **B**: Overlay of crystal of **4d** (red) with its model (blue). Hydrogens have been removed for clarity.

Table S12. Backbone Torsion Angles (in degrees) for **5a** according to the HF/6-31G**++

Pro1		Atc1			Pro2		Atc2		
ϕ	ψ	ϕ	θ	ψ	ϕ	ψ	ϕ	θ	ψ
-87.51	-7.62	173.92	-0.10	-151.79	-61.82	151.71	-178.97	0.16	-168.04
Pro3		Atc3			Pro4		Atc4		
ϕ	ψ	ϕ	θ	ψ	ϕ	ψ	ϕ	θ	ψ
-64.86	134.06	164.49	-2.64	-153.33	-62.01	142.16	178.62	-0.38	-179.19

The data of the model **5a** obtained using HF/6-31G**++. E_T(HF/6-31G**++) = -4660.7033 a.u.

Table S13. Backbone Torsion Angles (in degrees) for **6a** according to the HF/6-31G**++

Pro1		Atc1			Pro2		Atc2		
ϕ	ψ	ϕ	θ	ψ	ϕ	ψ	ϕ	θ	ψ
-88.33	-6.90	169.72	2.97	-159.85	-64.69	151.69	-179.92	2.24	-174.66
Pro3		Atc3			Pro4		Atc4		
ϕ	ψ	ϕ	θ	ψ	ϕ	ψ	ϕ	θ	ψ
-66.95	143.77	137.12	1.74	-158.57	-64.08	143.77	-178.37	0.06	179.75

The data of the model **6a** obtained using HF/6-31G**++. E_T(HF/6-31G**++) = -4621.6695 a.u.

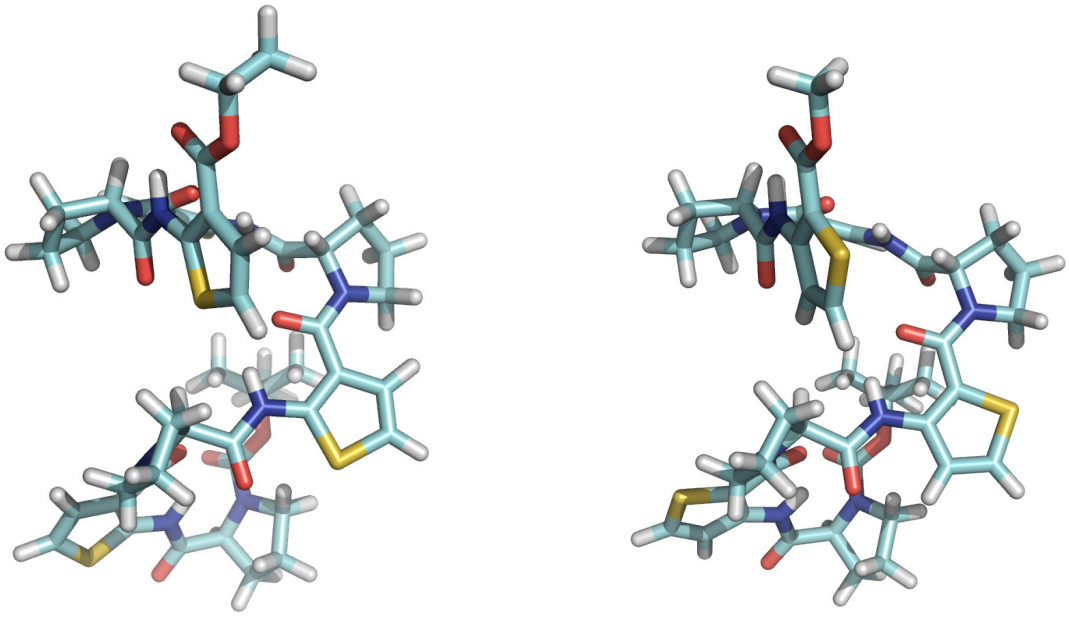


Figure-6. Models of octapeptides **5a** (left) and **6a** (right) obtained at HF/6-31G**++ level.