Supporting Information

Switching the H-Bonding Network of a Foldamer by Modulating Backbone Chirality and Constitutional Ratio of Amino Acids

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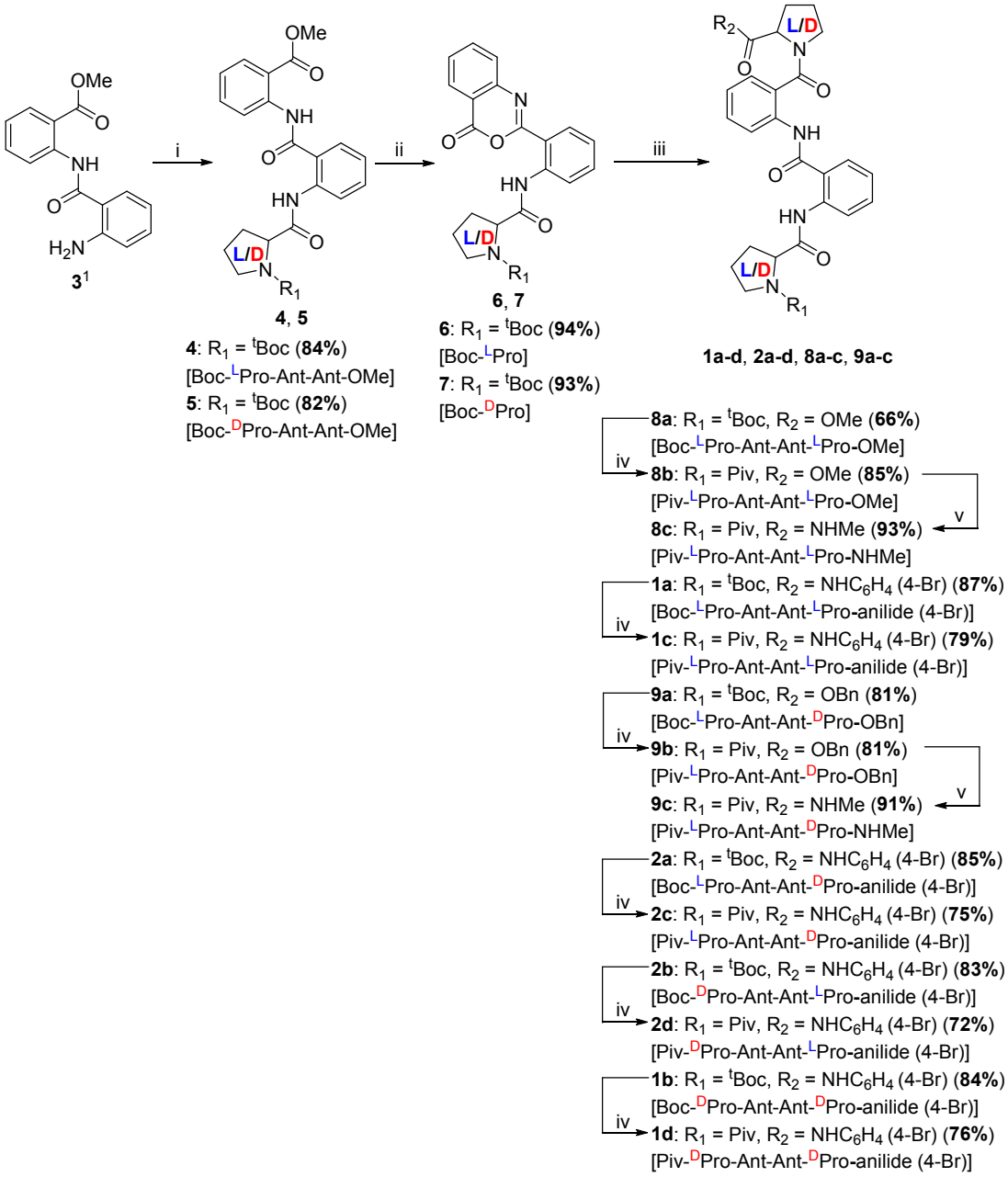
General Methods:

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). 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.

Synthetic Scheme:



Scheme 1. *Reagents and conditions*: (i) a. Boc-$^{L/D}$Pro-OH, ethylchloroformate, Et_3N, THF, 0 °C, 15 min.; b. H-Ant-Ant-OMe, THF, 0 °C then reflux, 8 h; (ii) a. aq. $LiOH.H_2O$, MeOH, rt, 12 h; b. EDC.HCl, HOBt, DCM, 10 min.; (iii) amine [H-^{L}Pro-OMe for **8a**, H-^{L}Pro-anilide (4-Br) for **1a**, **2b**; H-^{D}Pro-OBn for **9a** and H-^{D}Pro-anilide (4-Br) for **2a**, **1b**], DBU, DMF, 4Å MS, 0 °C then rt, 2 h; (vi) a. TFA:DCM (1:1), rt, 1h; b. Piv-Cl, Et_3N, DCM, 0 °C then rt, 5 h; (v) methanolic $MeNH_2$, rt, 5 h.

Experimental Procedures:

Methyl 2-(2-aminobenzamido)benzoate 3[1]:

Compound **3** was synthesized following the reported procedure[1]

***General method for synthesis of* 4 *and* 5 *using active ester method*:**

(S)-tert-butyl 2-((2-((2-(methoxycarbonyl)phenyl)carbamoyl)phenyl)carbamoyl) pyrrolidine-1-carboxylate 4:

Representative procedure: To a solution of Boc-(L)-Proline (1.1 equiv) in dry THF, TEA (1.2 equiv) was added followed by the addition of ethyl chloroformate (1.2 equiv) dropwise over a period of 10 min. After 15 min, amine **3**[1] (1 equiv) in THF was added and refluxed for 8 h. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane and water. The organic layer was washed sequentially with saturated $NaHCO_3$ solution and saturated brine solution. The organic layer was then dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to obtain the crude product which was then purified by column chromatography.

The product **4** was obtained as a white solid (5.24 g, 84%). mp: 92-94 °C; $[\alpha]^{24}_D$: -88.84° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3264, 2979, 1690, 1584, 1523, 1271, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 12.09 (s, 0.55H), $12.05_{rotamer}$ (s, 0.45H), $11.81_{rotamer}$ (s, 0.4H), 11.75 (s, 0.6H), 8.89 (d, *J* = 8.46 Hz, 1H), 8.82-8.71 (m, 1H), 8.11 (dd, *J* = 1.39 Hz, 8.09 Hz, 1H), 7.92 (t, *J* = 7.45 Hz, 1H), 7.68-7.49 (m, 2H), 7.29-7.11 (m, 2H), $4.49\text{-}4.44_{rotamer}$ (m, 0.45H), 4.32-4.26 (m, 0.55H), 3.96 (s, 3H), 3.85-3.74 (m, 1H), 3.65-3.41 (m, 1H), 2.36-2.10 (m, 2H), 2.07-1.87 (m, 2H), $1.45_{rotamer}$ (s, 4H), 1.32 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.1, 171.7, 168.8, 167.3, 154.8, 154.0, 141.0, 139.8, 134.8, 134.3, 132.9, 130.8, 126.9, 123.1, 123.0, 121.1, 120.5, 115.4, 115.2, 80.0, 62.5, 61.9, 52.4, 46.9, 46.6, 31.4, 30.4, 28.2, 28.1, 24.2, 24.1, 23.7, 23.6; ESI-MS: 468.4953 $(M+H)^+$; 490.3769 $(M+Na)^+$; 506.3938 $(M+K)^+$; Anal. Calcd. for $C_{25}H_{29}N_3O_6$: C, 64.23; H, 6.25; N, 8.99; Found: C, 64.35; H, 6.13; N, 9.13.

(R)-tert-butyl 2-((2-((2-(methoxycarbonyl)phenyl)carbamoyl)phenyl)carbamoyl) pyrrolidine-1-carboxylate 5:

The product **5** was obtained from **3**[1], following the procedure for **4,** as a white solid (1.99 g, 82%). mp: 101-103 °C; $[\alpha]^{24}_D$: +188.04° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3264, 2979, 1690, 1584, 1523, 1271, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 12.07 (s,

0.6H), 12.04$_{rotamer}$ (s, 0.4H), 11.79$_{rotamer}$ (s, 0.4H), 11.73 (s, 0.6H), 8.89 (d, *J* = 8.46 Hz, 1H), 8.81 $_{rotamer}$ (d, *J* = 8.72 Hz, 0.4H), 8.74 (d, *J* = 8.46 Hz, 0.6H), 8.11 (dd, *J* = 1.39, 7.96 Hz, 1H), 7.91 (d, *J* = 7.33 Hz, 1H), 7.67-7.51 (m, 2H), 7.22 (t, *J* = 7.83 Hz, 1H), 7.19 (t, *J* = 6.95 Hz, 1H), 4.48-4.43$_{rotamer}$ (m, 0.4H), 4.32-4.26 (m, 0.6H), 3.95 (s, 3H), 3.83-3.68 (m, 1H), 3.64-3.40 (m, 1H), 2.40-2.10 (m, 2H), 2.06-1.86 (m, 2H), 1.44$_{rotamer}$ (s, 4H), 1.31 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.2, 171.8, 168.9, 167.5, 167.3, 154.1, 141.2, 141.1, 134.9, 134.4, 133.0, 130.9, 127.0, 123.2, 123.0, 121.1, 120.6, 115.4, 115.3, 80.0, 79.9, 62.5, 61.9, 52.5, 46.9, 46.7, 31.4, 30.4, 28.2, 28.1, 24.2, 23.7; LC-MS: 490.16 $(M+Na)^+$; 506.18 $(M+K)^+$; Anal. Calcd. for $C_{25}H_{29}N_3O_6$: C, 64.23; H, 6.25; N, 8.99; Found: C, 64.05; H, 6.41; N, 9.15.

***General method for preparation of oxazinones* 6 *and* 7:**

(S)-tert-butyl 2-((2-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)phenyl)carbamoyl) pyrrolidine-1-carboxylate 6:

Representative procedure: To a solution of the ester **4** (1 equiv) in methanol, $LiOH·H_2O$ (3 equiv) in water was added and stirred for 12 h. The solvent was evaporated under reduced pressure and the residue was neutralized with the addition of dilute HCl, filtered and washed repeatedly with water. The precipitate (free carboxylic acid) was then dried over P_2O_5 and was carried forward for the next reaction, without any further purification.

To a solution containing the crude acid in dry DCM, EDC.HCl (1.1 equiv) was added followed by the addition of HOBt (0.2 equiv) and stirred for 10 minutes. It was then diluted with DCM and the organic layer was washed sequentially with saturated $NaHCO_3$, water and brine solutions. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the crude product, which was purified by column chromatography yielding the product **6**.

The product **6** was obtained as a white solid (3.07 g, 94%). mp: 107-109 °C; $[\alpha]^{24}_D$: +10.52.° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3240, 1768, 1693, 1681, 1606, 1573, 1519, 759; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 12.06 (s, 1H), 8.92 (d, *J* = 8.08 Hz, 1H), 8.27 (d, *J* = 7.83 Hz, 2H), 8.08 (d, *J* = 7.33 Hz, 1H), 7.96 (t, *J* = 7.07 Hz, 1H), 7.61 (t, *J* = 7.96 Hz, 2H), 7.25 (t, *J* = 7.71 Hz, 1H), 4.53-4.35 (m, 1H), 3.73-3.53 (m, 2H), 2.45-2.32 (m, 1H), 2.20-2.04 (m, 1H), 1.94-1.87 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.3, 158.3, 157.0, 155.0, 145.5, 139.6, 137.0, 133.8, 129.7, 128.8, 128.5, 127.2, 123.1, 120.8, 116.5, 115.8, 80.6, 62.9, 47.58, 31.8, 28.1, 24.1; ESI-MS:

436.7123 $(M+H)^+$; 458.3249 $(M+Na)^+$; Anal. Calcd. for $C_{24}H_{25}N_3O_5$: C, 66.19; H, 5.79; N, 9.65; Found: C, 65.00; H, 5.95; N, 9.81.

(R)-tert-butyl 2-((2-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)phenyl)carbamoyl) pyrrolidine-1-carboxylate 7:

The compound **7** was obtained from **5**, following the procedure for **6**. White solid (1.60 g, 93%). mp: 115-117 °C; $[\alpha]^{24}_D$: -4.06° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3242, 3018, 1767, 1686, 1606, 1216, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 12.06 (s, 1H), 8.91 (d, *J* = 8.08 Hz, 1H), 8.26 (d, *J* = 7.71 Hz, 2H), 8.07 (d, *J* = 6.57 Hz, 1H), 7.96 (t, *J* = 6.95 Hz, 1H), 7.60 (t, *J* = 7.96 Hz, 2H), 7.24 (t, *J* = 7.71 Hz, 1H), 4.53-4.38 (m, 1H), 3.73-3.70 $_{rotamer}$ (m, 0.8H), 3.64-3.52 (m, 1.2H), 2.48-2.26 (m, 1H), 2.20-2.04 (m, 1H), 1.94-1.88 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.3, 158.3, 157.0, 155.0, 145.5, 139.5, 137.0, 133.7, 129.6, 128.7, 128.5, 127.1, 123.1, 120.8, 116.5, 115.8, 80.6, 62.9, 47.58, 31.8, 28.1, 24.1; LC-MS: 458.15 $(M+Na)^+$; 490.19 $(M+K)^+$; Anal. Calcd. for $C_{24}H_{25}N_3O_5$: C, 66.19; H, 5.79; N, 9.65; Found: C, 66.36; H, 5.92; N, 9.47.

***General method for the ring opening of oxazinone* (6 *and* 7) *with proline amines* [H-^{L}Pro-CO_2Me *for* 8a; H-^{L}Pro-$CONHC_6H_4$ (4-Br) *for* 1a, 2b; H-^{D}Pro-CO_2Bn *for* 9a *and* H-^{D}Pro-$CONHC_6H_4$ (4-Br) *for* 2a, 1b]: *Synthesis of* 8a, 1a, 9a, 2a, 2b *and* 1b:**

(S)-tert-butyl 2-((2-((2-((S)-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)phenyl) carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate 8a:

Representative procedure: To a solution of oxazinone **6** (1 equiv) in dry DMF, amine (1 equiv) was added followed by the addition of 4Å molecular sieves (0.2 g) and DBU (1 equiv). The reaction mixture was stirred at room temperature for 2 h and quenched with saturated $KHSO_4$ solution. The organic layer was repeatedly washed with water, brine solution and dried over anhydrous Na_2SO_4. It was then evaporated under reduced pressure to obtain the crude product which was purified by column chromatography to yield **8a**.

The product **8a** was obtained as a colourless fluffy liquid (1.02 g, 66%). $[\alpha]^{24}_D$: -100.21° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 1747, 1734, 1697, 1683, 1585, 1539, 1521, 1508, 758; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.72 (s, 0.6H), 11.66$_{rotamer}$ (s, 0.4H), 10.42 (s, 0.6H), 10.27$_{rotamer}$ (s, 0.4H), 8.71 (d, *J* = 8.33 Hz, 1H), 8.56-8.50 (m, 1H), 7.75-7.65 (m, 1H), 7.55-7.41 (m, 3H), 7.20-7.12 (m, 2H), 4.71-4.67 (m, 1H),

4.46-4.41$_{rotamer}$ (m, 0.4H), 4.31-4.25$_{rotamer}$ (m, 0.6H), 3.72 (s, 1.7H), 3.70$_{rotamer}$ (s, 1.3H), 3.65-3.40 (m, 4H), 2.33-1.90 (m, 8H), 1.45$_{rotamer}$ (s, 3H), 1.33 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.0, 166.9, 139.8, 136.9, 132.9, 131.5, 131.0, 127.5, 127.3, 123.2, 123.0, 122.1, 120.9, 120.3, 80.0, 59.2, 52.3, 50.5, 50.4, 46.7, 31.4, 29.1, 28.2, 25.2, 24.2, 23.7; ESI-MS: 587.7821 $(M+Na)^+$; 603.7756 $(M+K)^+$; Anal. Calcd. for $C_{30}H_{36}N_4O_7$: C, 63.82; H, 6.43; N, 9.92; Found: C, 64.01; H, 6.49; N, 10.05.

General method for the pivolyl protection: Synthesis of* 8b, 1c, 9b, 2c, 2d *and* 1d*:

(S)-methyl 1-(2-(2-((S)-1-pivaloylpyrrolidine-2-carboxamido)benzamido) benzoyl) pyrrolidine-2-carboxylate 8b:

Representative procedure: **8a** was subjected to ^{t}Boc deprotection using TFA to obtain its free amine. To a solution of amine, Et_3N (1.5 equiv) was added followed by the addition of Piv-Cl (1.5 equiv). The reaction mixture was stirred for 5 h and diluted with DCM. It was then washed sequentially with dilute HCl solution, brine, saturated $NaHCO_3$ solution and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the crude product which was purified by column chromatography affording **8b**.

The product **8b** was obtained as a white solid (0.45 g, 85%). mp: 67-69 °C; $[\alpha]^{24}_D$: -39.34° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3321, 1745, 1681, 1622, 1531, 1518, 1415, 769; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.30 (s, 1H), 10.29 (s, 1H), 8.64 (d, *J* = 7.96 Hz, 1H), 8.38 (d, *J* = 8.08 Hz, 1H), 7.70 (dd, *J* = 1.26 Hz, 7.95 Hz, 1H), 7.49-7.40 (m, 3H), 7.18-7.05 (m, 2H), 4.69-4.55 (m, 2H), 3.97-3.72 (m, 2H), 3.67 (s, 3H), 3.62-3.45 (m, 2H), 2.37-1.90 (m, 8H), 1.27 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.2, 172.1, 171.4, 168.8, 167.0, 139.7, 136.6, 132.6, 130.9, 127.4, 127.1, 124.3, 123.2, 122.8, 122.1, 121.3, 120.5, 63.9, 59.1, 52.1, 50.3, 48.4, 38.9, 29.0, 28.7, 27.3, 25.5, 25.0; ESI-MS: 549.5628 $(M+H)^+$; 571.5337 $(M+Na)^+$; 587.5027 $(M+K)^+$; Anal. Calcd. for $C_{30}H_{36}N_4O_6$: C, 65.68; H, 6.61; N, 10.21; Found: C, 65.79; H, 6.45; N, 10.40.

***General method for C-terminal amidation: Synthesis of* 8c *and* 9c:**

(S)-N-methyl-1-(2-(2-((S)-1-pivaloylpyrrolidine-2-carboxamido) benzamido) benzoyl) pyrrolidine-2-carboxamide 8c:

Representative procedure: The ester **8b** was taken in saturated methanolic methylamine solution and stirred at room temperature for 5 h. The solvent was

removed under reduced pressure, and the residue was purified by column chromatography to yield pure **8c**.

The product **8c** was obtained as a white solid (0.28 g, 93%). mp: 83-85 °C; $[\alpha]^{24}_{D}$: -71.43° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3321, 1666, 1651, 1519, 1514, 767; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.20 (s, 1H), 10.37 (s, 1H), 8.56 (d, *J* = 8.34 Hz, 1H), 8.14 (d, *J* = 8.08 Hz, 1H), 7.72 (dd, *J* = 1.01 Hz, 7.84 Hz, 1H), 7.49-7.33 (m, 3H), 7.17-7.04 (m, 2H), 6.89-6.86 (d, *J* = 4.80 Hz, 1H), 4.59-4.49 (m, 2H), 3.94-3.57 (m, 4H), 2.73-2.69 (m, 3H), 2.21-1.89 (m, 8H), 1.26 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.2, 171.7, 171.2, 169.8, 169.3, 167.2, 139.3, 135.9, 134.6, 132.5, 130.7, 129.7, 128.0, 127.5, 127.4, 125.7, 123.6, 122.9, 122.7, 121.2, 120.5, 63.8, 60.3, 50.6, 48.4, 38.8, 28.8, 28.6, 27.2, 26.6, 26.0, 25.1; ESI-MS: 548.5326 $(M+H)^+$; 570.5035 $(M+Na)^+$; 586.4995 $(M+K)^+$; Anal. Calcd. for $C_{30}H_{37}N_5O_5$: C, 65.79; H, 6.81; N, 12.79; Found: C, 65.97; H, 7.01; N, 12.64.

(S)-tert-butyl 2-((2-((2-((S)-2-((4-bromophenyl)carbamoyl)pyrrolidine-1-carbonyl)phenyl)carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate 1a:

The product **1a** was obtained from **6**, following the procedure for **8a**, as a white solid (0.42 g, 87%). mp: 224-225 °C; $[\alpha]^{24}_{D}$: -210.33° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3269, 1693, 1681, 1672, 1587, 1537, 1519, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.55 (s, 0.5H), $11.49_{rotamer}$ (s, 0.5H), 10.06 (s, 1H), 9.32 (s, 1H), 8.66 (q, 1H), 8.42 (d, *J* = 8.21 Hz, 0.5H), $8.22_{rotamer}$ (d, *J* = 8.46 Hz, 0.5H), 7.72 (d, *J* = 6.57 Hz, 1H), 7.51-7.18 (m, 8H), 6.90-6.76 (m, 1H), 4.75 (t, *J* = 5.68 Hz, 1H), $4.40\text{-}4.35_{rotamer}$ (m, 0.45H), 4.30-4.23 (m, 0.55H), 3.76-3.36 (m, 4H), 2.31-1.81 (m, 8H), $1.41_{rotamer}$ (s, 4H), 1.31 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.0, 171.4, 169.6, 169.4, 169.3, 169.3, 167.4, 167.1, 154.8, 154.1, 139.4, 139.3, 137.0, 136.0, 135.7, 132.7, 132.6, 131.4, 130.8, 127.6, 127.2, 126.0, 124.8, 123.9, 123.7, 123.0, 122.4, 121.1, 120.9, 120.4, 116.3, 80.0, 79.9, 62.4, 61.7, 60.9, 50.7, 47.0, 46.6, 31.3, 30.4, 28.9, 28.8, 28.7, 28.2, 28.1, 25.0, 24.1, 23.6; ESI-MS: 726.3931 $(M+Na)^+$; 728.3964 $(M+2+Na)^+$; Anal. Calcd. for $C_{35}H_{38}BrN_5O_6$: C, 59.66; H, 5.44; N, 9.94; Found: C, 59.82; H, 5.38; N, 10.07.

(S)-N-(4-bromophenyl)-1-(2-(2-((S)-1-pivaloylpyrrolidine-2-carboxamido) benzamido)benzoyl)pyrrolidine-2-carboxamide 1c:

The product **1c** was obtained from **1a**, following the procedure for **8b**, was obtained as a white solid (0.27 g, 79%). mp: 115-117 °C; $[\alpha]^{24}_{D}$: -153.21° (*c* = 1, $CHCl_3$); IR

($CHCl_3$) ν (cm^{-1}): 3275, 1697, 1687, 1681, 1602, 1591, 1537, 1519, 759; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.24 (s, 1H), 10.18 (s, 1H), 9.33 (s, 1H), 8.55 (d, *J* = 8.54 Hz, 1H), 8.07 (d, *J* = 6.71 Hz, 1H), 7.70 (d, *J* = 7.63 Hz, 1H), 7.44-7.41 (m, 2H), 7.39-7.33 (m, 3H), 7.29-7.27 (m, 2H), 7.19 (t, *J* = 7.63 Hz, 1H), 6.87 (t, *J* = 7.02 Hz, 1H), 4.75 (t, *J* = 6.41 Hz, 1H), 4.56-4.54 (m, 1H), 3.94-3.89 (m, 1H), 3.81-3.77 (m, 1H), 3.63-3.62 (m, 2H), 2.22-2.08 (m, 3H), 2.07-1.98 (m, 2H), 1.97-1.92 (m, 2H), 1.88-1.83 (m, 1H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.4, 171.2, 169.8, 169.3, 167.5, 162.5, 139.5, 137.1, 135.8, 132.7, 131.6, 130.9, 127.4, 127.4, 126.2, 124.0, 123.2, 122.9, 121.4, 121.2, 120.4, 116.4, 63.9, 61.1, 50.9, 48.6, 38.9, 28.7, 28.6, 28.5, 27.4, 25.7, 25.2; ESI-MS: 710.4007 $(M+Na)^+$; 712.4042 $(M+2+Na)^+$; Anal. Calcd. for $C_{35}H_{38}BrN_5O_5$: C, 61.05; H, 5.56; N, 10.17; Found: C, 60.96; H, 5.39; N, 10.29.

(S)-tert-butyl 2-((2-((2-((R)-2-((benzyloxy)carbonyl)pyrrolidine-1-carbonyl)phenyl)carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate 9a:

The product **9a** was obtained from **6**, following the procedure for **8a**, as a colourless liquid (1.01 g, 81%). $[\alpha]^{24}_D$: +25.43° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3308, 3016, 2980, 1741, 1691, 1625, 1584, 1216, 758; ^{1}H NMR (500 MHz, $CDCl_3$) δ: $11.76_{rotamer}$ (s, 0.4H), 11.74 (s, 0.6H), 10.41 (s, 0.6H), $10.37_{rotamer}$ (s, 0.4H), $8.76_{rotamer}$ (d, *J* = 8.55 Hz, 0.3H), 8.72 (d, *J* = 8.24 Hz, 0.7H), 8.58-8.55 (m, 1H), 7.77 (d, *J* = 7.93 Hz, 0.6H), $7.72_{rotamer}$ (d, *J* = 7.93 Hz, 0.4H), 7.55-7.47 (m, 4H), 7.36-7.32 (m, 5H), 7.18 (d, *J* = 7.63 Hz, 1H), 7.09 (d, *J* = 7.63 Hz, 1H), 5.25-5.17 (m, 2H), 4.76-4.74 (m, 1H), $4.46\text{-}4.44_{rotamer}$ (m, 0.4H), 4.30-4.27 (m, 0.6H), 3.88-3.74 (m, 1H), 3.64 (m, 1.6H), 3.61-3.56 (m, 1H), $3.50\text{-}3.44_{rotamer}$ (m, 0.4H), 2.38-2.25 (m, 2H), 2.23-2.13 (m, 2H), 2.07-1.96 (m, 2H), 1.95-1.91 (m, 1.6H), 1.82-1.74 (m, 0.4H), $1.42_{rotamer}$ (s, 4H), 1.33 (s, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.2, 171.7, 171.6, 169.1, 169.0, 167.1, 167.0, 154.9, 154.1, 139.9, 136.9, 135.4, 132.9, 131.6, 131.1, 128.6, 128.3, 127.9, 127.4, 123.2, 123.0, 122.2, 121.0, 120.8, 120.2, 80.0, 79.8, 66.8, 62.6, 62.6, 62.0, 59.4, 59.3, 50.5, 47.0, 46.7, 31.5, 30.5, 29.1, 28.3, 28.2, 25.2, 25.1, 24.2, 23.7; LC-MS: 663.23 $(M+Na)^+$; 679.30 $(M+K)^+$; Anal. Calcd. for $C_{36}H_{40}N_4O_7$: C, 67.48; H, 6.29; N, 8.74; Found: C, 67.66; H, 6.10; N, 8.89.

(R)-benzyl 1-(2-(2-((S)-1-pivaloylpyrrolidine-2-carboxamido)benzamido)benzoyl) pyrrolidine-2-carboxylate 9b:

The product **9b** was obtained from **9a**, following the procedure for **8b**, as a colourless liquid (0.51 g, 81%). $[\alpha]^{24}_{D}$: +8.22° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3306, 3013, 1742, 1660, 1548, 1448, 1216, 755; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.42 (s, 1H), 10.35 (s, 1H), 8.72 (d, *J* = 8.34 Hz, 1H), 8.48 (d, *J* = 8.46 Hz, 1H), 7.22 (d, *J* = 7.58 Hz, 1H), 7.52-7.42 (m, 3H), 7.34 (s, 5H), 7.19 (t, *J* = 7.71 Hz, 1H), 7.09 (t, *J* = 7.71 Hz, 1H), 5.17 (s, 2H), 4.78-4.71 (m, 1H), 4.65-4.60 (m, 1H), 4.02-3.92 (m, 1H), 3.86-3.76 (m, 1H), 3.71-3.55 (m, 2H), 2.40-2.22 (m, 1H), 2.18-1.88 (m, 7H), 1.29 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.4, 171.5, 168.9, 167.0, 139.9, 136.8, 135.4, 132.7, 131.0, 128.5, 128.2, 127.9, 127.5, 127.1, 124.0, 123.1, 122.8, 122.0, 121.3, 120.2, 66.8, 64.1, 59.2, 50.4, 48.4, 39.0, 29.0, 27.4, 25.5, 25.1; LC-MS: 625.34 $(M+H)^+$; 647.34 $(M+Na)^+$; 663.33 $(M+K)^+$; Anal. Calcd. for $C_{36}H_{40}N_4O_6$: C, 69.21; H, 6.45; N, 8.97; Found: C, 69.40; H, 6.29; N, 9.13.

(R)-N-methyl-1-(2-(2-((S)-1-pivaloylpyrrolidine-2-carboxamido)benzamido) benzoyl)pyrrolidine-2-carboxamide 9c:

The product **9c** was obtained from **9b**, following the procedure for **8c**, as a white solid (0.32 g, 91%). mp: 115-117 °C; $[\alpha]^{24}_{D}$: +110.03° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3326, 3017, 1660, 1610, 1592, 1520, 1216, 755; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.64 (s, 1H), 10.24 (s, 1H), 8.37 (d, *J* = 8.55 Hz, 1H), 7.94 (d, *J* = 7.63 Hz, 1H), 7.67 (d, *J* = 7.63 Hz, 1H), 7.47-7.44 (m, 2H), 7.42 (d, *J* = 7.93 Hz, 1H), 7.20 (t, *J* = 7.63 Hz, 1H), 7.15 (t, *J* = 7.63 Hz, 1H), 6.90 (bs, 1H), 4.60-4.58 (m, 1H), 4.51-4.49 (m, 1H), 3.87-3.83 (m, 1H), 3.76-3.68 (m, 2H), 3.64-3.59 (m, 1H), 2.46 (d, *J* = 4.27 Hz, 3H), 2.26-2.10 (m, 5H), 2.07-2.03 (m, 1H), 2.01-1.94 (m, 1H), 1.92-1.83 (m, 1H), 1.19 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.0, 171.7, 171.6, 169.6, 167.7, 138.1, 136.0, 132.3, 130.7, 127.8, 127.3, 124.0, 123.5, 122.9, 122.6, 63.8, 60.6, 50.4, 48.5, 38.8, 29.0, 28.6, 27.2, 24.9 ; LC-MS: 625.34 $(M+H)^+$; 647.34 $(M+Na)^+$; 663.33 $(M+K)^+$; Anal. Calcd. for $C_{30}H_{37}N_5O_5$: C, 65.79; H, 6.81; N, 12.79; Found: C, 35.62; H, 7.00; N, 12.85.

(S)-tert-butyl 2-((2-((2-((R)-2-((4-bromophenyl)carbamoyl)pyrrolidine-1-carbonyl)phenyl)carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate 2a:

The product **2a** was obtained from **6**, following the procedure for **8a**, as a white solid (0.55 g, 85%). mp: 229-231 °C; $[\alpha]^{24}_{D}$: +54.42° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}):

3315, 1693, 1681, 1585, 1519, 1514, 769; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.60-11.37 (m, 1H), $10.24_{rotamer}$ (s, 0.1H), 10.13 (s, 0.9H), 9.28 (s, 0.9H), $9.10_{rotamer}$ (s, 0.1H), 8.66-8.59 (m, 1H), 8.26 (d, *J* = 7.96 Hz, 1H), 7.75-7.62 (m, 1H), 7.51-7.14 (m, 8H), 6.95-6.81 (m, 1H), 4.77-4.74 (m, 1H), $4.43\text{-}4.38_{rotamer}$ (m, 0.4H), 4.28-4.24 (m, 0.6H), 3.73-3.35 (m, 4H), 2.35-1.88 (m, 8H), $1.47_{rotamer}$ (s, 2H), $1.34_{rotamer}$ (s, 3H), 1.27 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.0, 171.7, 169.6, 169.4, 167.3, 167.3, 154.8, 154.0, 139.3, 139.0, 136.9, 136.1, 135.8, 132.8, 132.5, 131.4, 131.2, 130.9, 127.5, 127.4, 127.2, 125.2, 123.7, 123.1, 122.9, 122.7, 121.3, 121.0, 120.9, 120.4, 116.5, 80.0, 79.8, 62.4, 61.8, 61.0, 58.8, 50.7, 47.0, 46.8, 46.6, 31.3, 30.4, 28.8, 28.3, 28.1, 24.9, 24.2, 23.65; ESI-MS: 726.4358 $(M+Na)^+$; 728.4542 $(M+2+Na)^+$; Anal. Calcd. for $C_{35}H_{38}BrN_5O_6$: C, 59.66; H, 5.44; N, 9.94; Found: C, 59.54; H, 5.49; N, 9.81.

(R)-N-(4-bromophenyl)-1-(2-(2-((S)-1-pivaloylpyrrolidine-2-carboxamido) benzamido)benzoyl)pyrrolidine-2-carboxamide 2c:

The product **2c** was obtained from **2a**, following the procedure for **8b**, as a white solid. (0.29 g, 75%). mp: 169-171 °C; $[\alpha]^{24}_{D}$: +132.11° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3308, 1697, 1681, 1614, 1539, 1519, 769; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.78 (s, 1H), 10.12 (s, 1H), 9.22 (s, 1H), 8.50 (d, *J* = 8.24 Hz, 1H), 8.08 (d, *J* = 7.93 Hz, 1H), 7.57 (d, *J* = 7.63 Hz, 1H), 7.43 (t, *J* = 7.93 Hz, 1H), 7.39 (t, *J* = 7.93 Hz, 1H), 7.27 (d, *J* = 8.54 Hz, 2H), 7.20 (t, *J* = 8.54 Hz, 1H), 7.17 (t, *J* = 7.63 Hz, 1H), 6.94 (t, *J* = 7.63 Hz, 1H), 4.75-4.73 (m, 1H), 4.62-4.59 (m, 1H), 3.92-3.87 (m, 1H), 3.80-3.75 (m, 1H), 3.69-3.64 (m, 1H), 3.59-3.55 (m, 1H), 2.28-2.23 (m, 1H), 2.21-2.16 (m, 2H), 2.13-2.10 (m, 1H), 2.06-1.99 (m, 2H), 1.97-1.92 (m, 1H), 1.88-1.83 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.3, 171.6, 169.8, 169.3, 167.7, 138.7, 136.9, 135.9, 132.3, 131.4, 130.9, 127.4, 125.7, 123.8, 123.1, 121.7, 121.5, 116.4, 63.9, 61.1, 50.7, 48.5, 38.9, 28.7, 27.3, 25.7, 25.0; ESI-MS: 710.5039 $(M+Na)^+$; 712.4886 $(M+2+Na)^+$; Anal. Calcd. for $C_{35}H_{38}BrN_5O_5$: C, 61.05; H, 5.56; N, 10.17; Found: C, 60.89; H, 5.63; N, 10.33.

(R)-tert-butyl 2-((2-((2-((S)-2-((4-bromophenyl)carbamoyl)pyrrolidine-1-carbonyl)phenyl)carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate 2b:

The product **2b** was obtained from **7**, following the procedure for **8a**, as a white solid. (0.60 g, 83%). mp: 230-232 °C; $[\alpha]^{24}_{D}$: -78.07° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3317, 1691, 1624, 1584, 1410, 755; ^{1}H NMR (200 MHz, $CDCl_3$) δ: $11.58_{rotamer}$ (s, 0.1H), 11.46 (s, 0.5H), $11.31_{rotamer}$ (s, 0.4H), 10.11 (s, 1H), 9.13-8.98 (m, 1H), 8.66 (t,

J = 7.45 Hz, 1H), 8.30 (d, *J* = 8.34 Hz, 1H), 7.73-7.57 (m, 1H), 7.48-7.42 (m, 3H), 7.36-7.13 (m, 5H), 6.99-6.85 (m, 1H), 4.80-4.76 (m, 1H), 4.47-4.37 (m, 0.6H), 4.28-4.22$_{rotamer}$ (m, 0.4H), 3.71-3.39 (m, 4H), 2.29-1.90 (m, 8H), 1.38$_{rotamer}$ (s, 1H), 1.34$_{rotamer}$ (s, 4H), 1.28 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.1, 171.8, 169.9, 169.2, 167.3, 154.8, 154.1, 139.4, 139.0, 136.9, 136.3, 136.0, 132.9, 132.6, 131.5, 131.2, 127.4, 125.0, 123.7, 123.1, 122.7, 122.5, 121.3, 120.4, 116.5, 80.0, 79.8, 64.3, 62.5, 61.8, 61.0, 50.7, 47.0, 46.7, 31.4, 30.5, 28.3, 28.1, 25.0, 24.2, 23.6; LC-MS: 726.31 $(M+Na)^+$; 728.32 $(M+2+Na)^+$; 742.28 $(M+K)^+$; 744.25 $(M+2+K)^+$;Anal. Calcd. for $C_{35}H_{38}BrN_5O_6$: C, 59.66; H, 5.44; N, 9.94; Found: C, 59.48; H, 5.31; N, 10.08.

(S)-N-(4-bromophenyl)-1-(2-(2-((R)-1-pivaloylpyrrolidine-2-carboxamido) benzamido)benzoyl)pyrrolidine-2-carboxamide 2d:

The product **2d** was obtained from **2b**, following the procedure for **8b**, as a white solid (0.28 g, 72%). mp: 140-142 °C; $[\alpha]^{24}_D$: -128.24° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3279, 3018, 1669, 1614, 1588, 1520, 1215, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 10.82 (s, 1H), 10.14 (s, 1H), 9.31 (s, 1H), 8.52 (d, *J* = 8.34 Hz, 1H), 8.09 (d, *J* = 8.21 Hz, 1H), 7.58 (d, *J* = 7.45 Hz, 1H), 7.43-7.29 (m, 4H), 7.25-7.10 (m, 4H), 6.93 (t, *J* = 7.45 Hz, 1H), 4.75-4.68 (t, *J* = 6.69 Hz, 1H), 4.63-4.57 (m, 1H), 3.94-3.71 (m, 2H), 3.68-3.48 (m, 2H), 2.21-1.78 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.3, 171.5, 169.4, 167.6, 162.4, 138.8, 137.0, 135.8, 132.2, 131.3, 130.8, 127.3, 125.7, 123.7, 123.0, 122.8, 121.5, 121.4, 116.3, 63.9, 61.1, 50.6, 48.5, 38.9, 31.3, 28.9, 28.8, 25.6, 24.9; LC-MS: 710.30 $(M+Na)^+$; 712.30 $(M+2+Na)^+$; 726.30 $(M+K)^+$; 728.29 $(M+2+K)^+$; Anal. Calcd. for $C_{35}H_{38}BrN_5O_5$: C, 61.05; H, 5.56; N, 10.17; Found: C, 60.93; H, 5.69; N, 9.99.

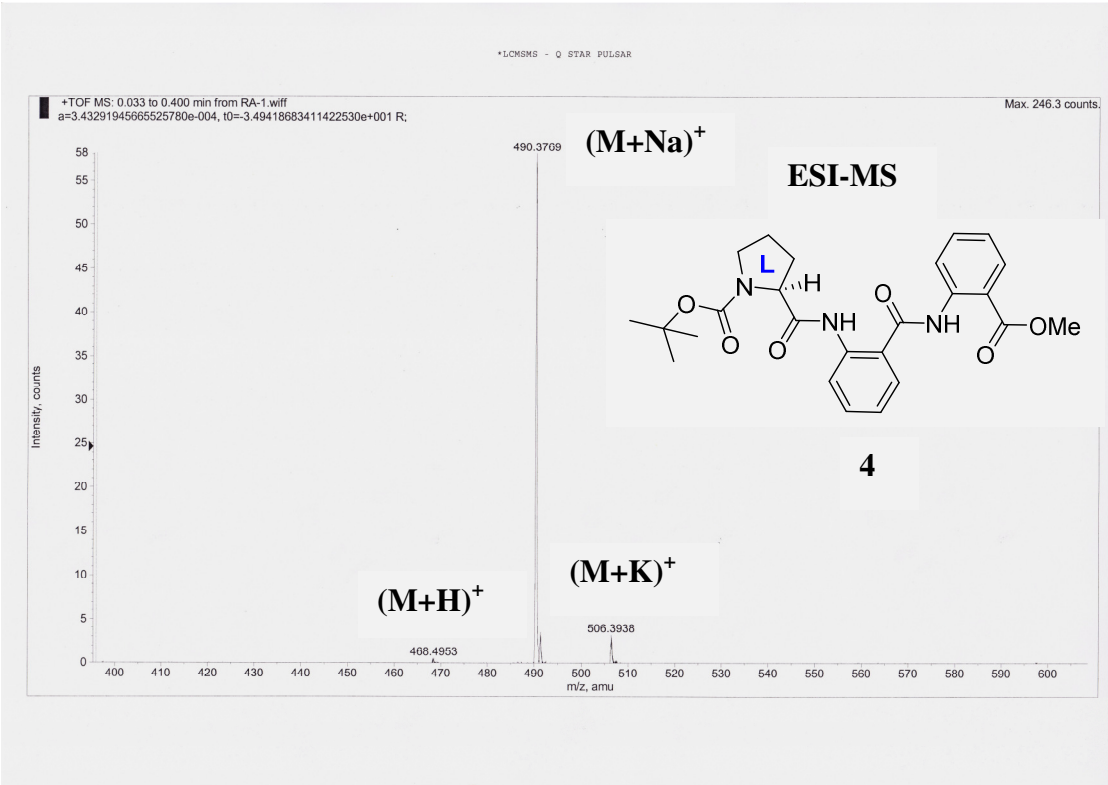
(R)-tert-butyl 2-((2-((2-((R)-2-((4-bromophenyl)carbamoyl)pyrrolidine-1-carbonyl) phenyl)carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate 1b:

The product **2b** was obtained from **7**, following the procedure for **8a**, as a white solid (0.47 g, 84%). mp: 223-225 °C; $[\alpha]^{24}_D$: +214.14° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3267, 3019, 1685, 1586, 1522, 1215, 756; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.56 (s, 0.5H), 11.44$_{rotamer}$ (s, 0.5H), 10.10 (s, 1H), 9.21 (s, 1H), 8.68 (t, *J* = 8.72 Hz, 1H), 8.44 (d, *J* = 8.34 Hz, 0.5H), 8.26$_{rotamer}$ (d, *J* = 8.21 Hz, 0.5H), 7.72 (d, *J* = 7.83 Hz, 1H), 7.53-7.42 (m, 3H), 7.33-7.29 (m, 4H), 7.22 (t, *J* = 7.83 Hz, 1H), 6.95-6.84 (m, 1H), 4.81 (dd, *J* = 5.56, 7.07 Hz, 1H), 4.43-4.36$_{rotamer}$ (m, 0.4H), 4.30-4.24 (m, 0.6H),

3.77-3.77 (m, 4H), 2.37-2.02 (m, 5H), 1.96-1.75 (m, 3H), $1.42_{rotamer}$ (s, 4H), 1.32 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.1, 171.5, 169.9, 169.7, 169.2, 169.1, 167.4, 167.1, 162.5, 154.8, 154.0, 139.6, 137.0, 136.2, 136.0, 132.9, 136.0, 132.9, 132.7, 131.5, 130.9, 127.4, 127.4, 125.7, 124.5, 123.8, 123.6, 123.0, 122.4, 121.2, 121.0, 120.6, 120.4, 116.4, 80.8, 79.9, 62.5, 61.79, 60.9, 50.9, 47.0, 46.7, 31.3, 30.5, 28.3, 28.1, 25.1, 24.2, 23.7; LC-MS: 726.30 $(M+Na)^+$; 728.30 $(M+2+Na)^+$; 742.31 $(M+K)^+$; 744.31 $(M+2+K)^+$; Anal. Calcd. for $C_{35}H_{38}BrN_5O_6$: C, 59.66; H, 5.44; N, 9.94; Found: C, 59.84; H, 5.25; N, 10.12.

(R)-N-(4-bromophenyl)-1-(2-(2-((R)-1-pivaloylpyrrolidine-2-carboxamido) benzamido)benzoyl)pyrrolidine-2-carboxamide 1d:

The product **1d** was obtained from **1b**, following the procedure for **8b**, as a white solid (0.26 g, 76%). mp: 226-228 °C; $[\alpha]^{24}_D$: +156.12° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3271, 2976, 1684, 1659, 1602, 1415, 1300, 755; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 11.27 (s, 1H), 10.19 (s, 1H), 9.40 (s, 1H), 8.55 (d, *J* = 8.34 Hz, 1H), 8.06 (d, *J* = 8.46 Hz, 1H), 7.71 (d, *J* = 7.45 Hz, 1H), 7.45-7.36 (m, 2H), 7.31-7.24 (m, 4H), 7.21 (t, *J* = 8.08 Hz, 1H), 6.86 (t, *J* = 7.45 Hz, 1H), 4.74 (t, *J* = 6.69 Hz, 1H), 4.56-4.52 (m, 1H), 3.95-3.73 (m, 2H), 3.65 (t, *J* = 6.1 Hz, 2H), 2.13-1.79 (m, 8H), 1.28 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.4, 171.1, 169.5, 167.5, 139.5, 137.1, 135.6, 132.6, 131.4, 130.8, 127.4, 127.3, 126.4, 124.0, 123.1, 122.9, 121.3, 121.1, 120.2, 116.3, 63.9, 61.1, 50.8, 48.5, 38.9, 28.9, 28.7, 27.3, 25.6, 25.1; LC-MS: 710.32 $(M+Na)^+$; 712.34 $(M+2+Na)^+$; 726.29 $(M+K)^+$; 728.30 $(M+2+K)^+$; Anal. Calcd. for $C_{35}H_{38}BrN_5O_5$: C, 61.05; H, 5.56; N, 10.17; Found: C, 59.89; H, 5.69; N, 9.99.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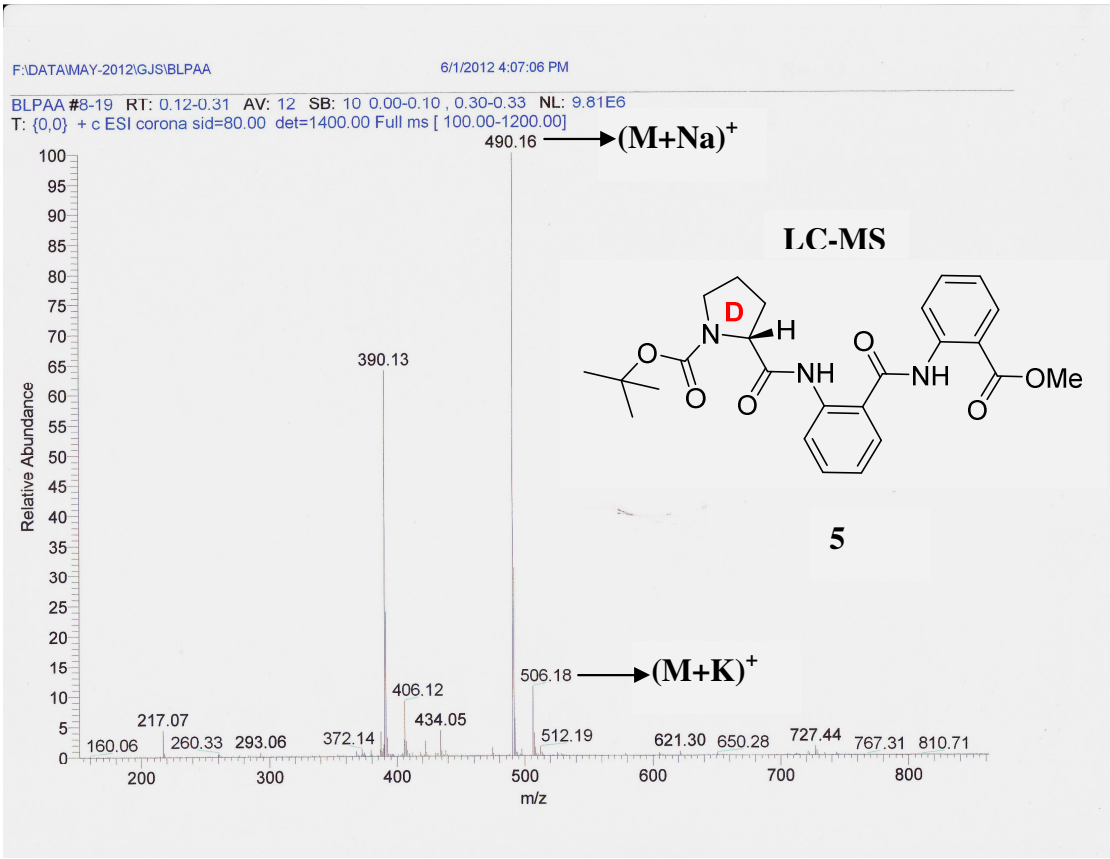
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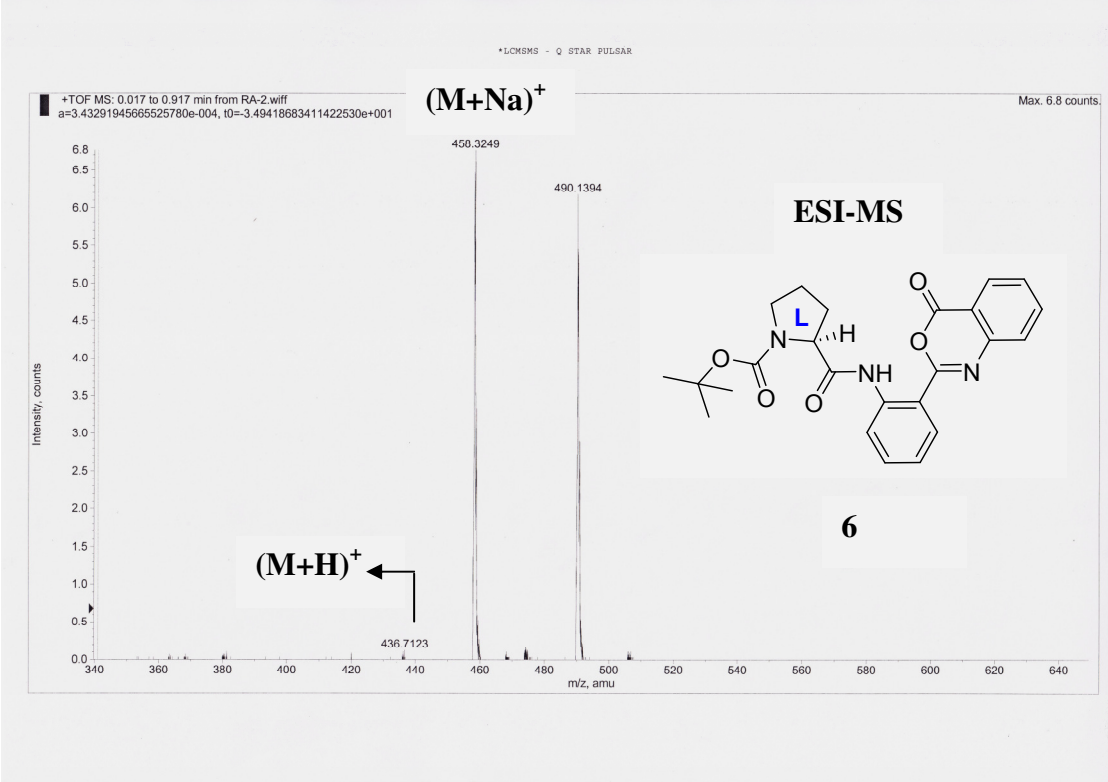
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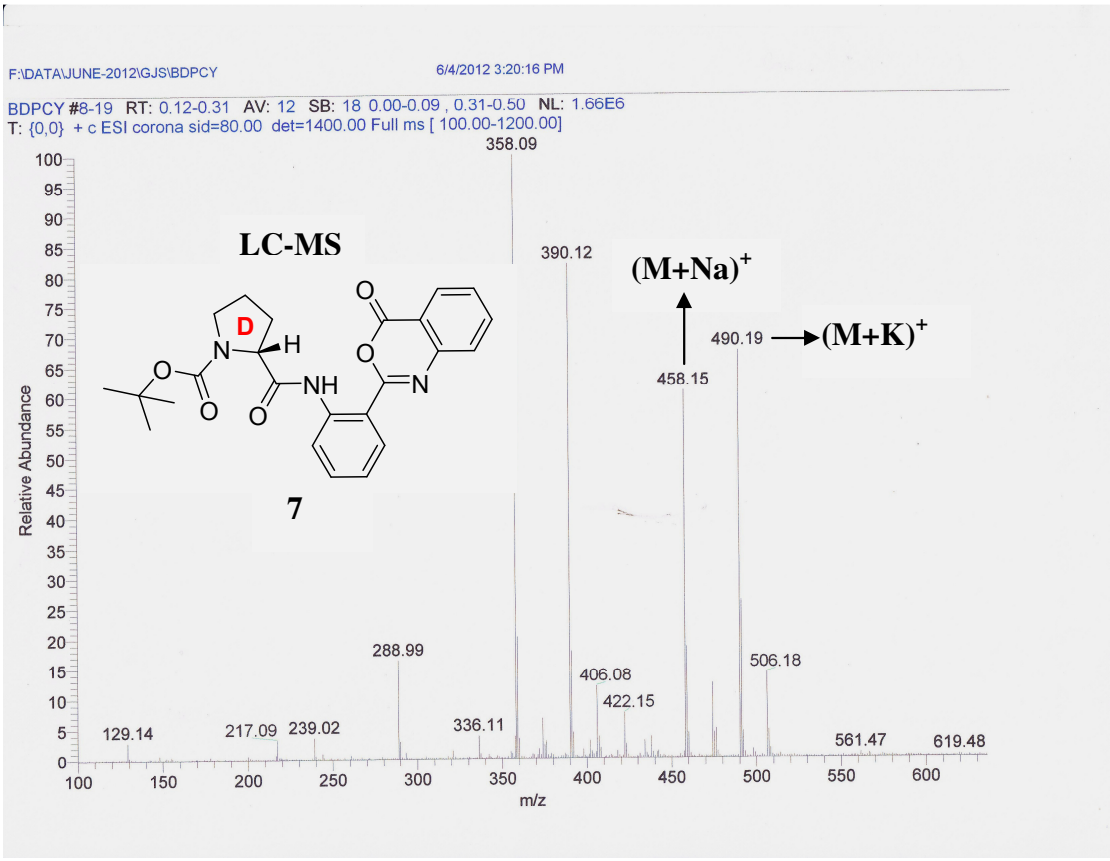
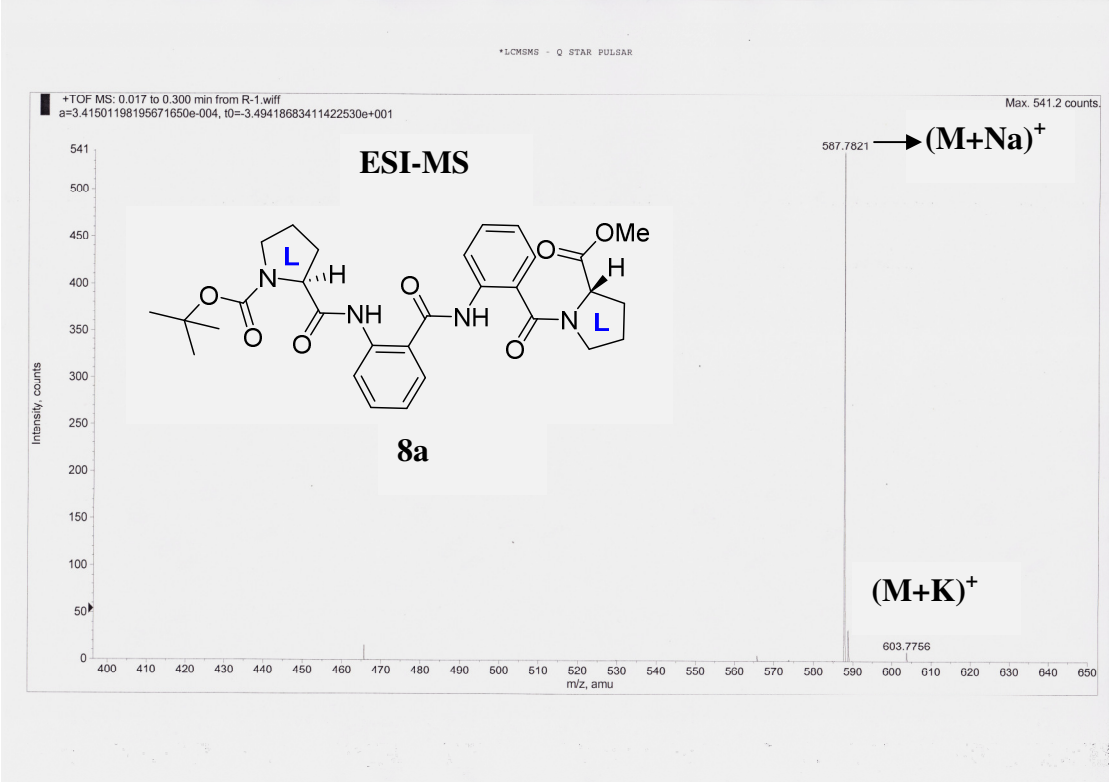
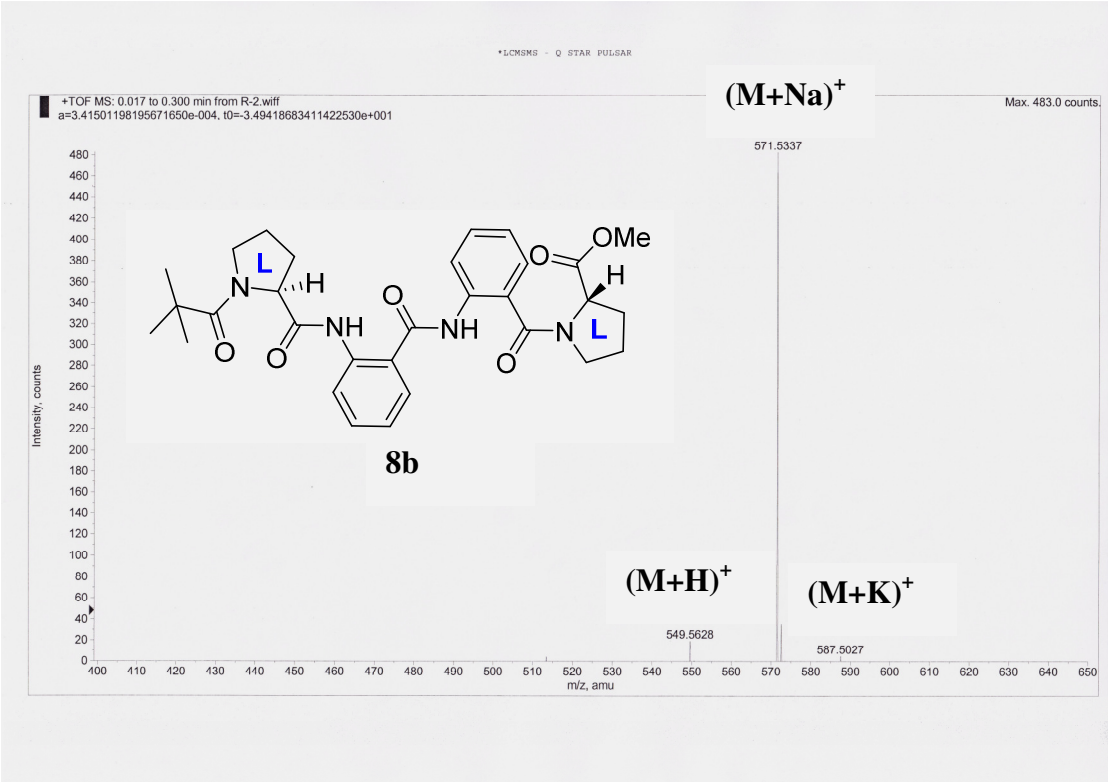
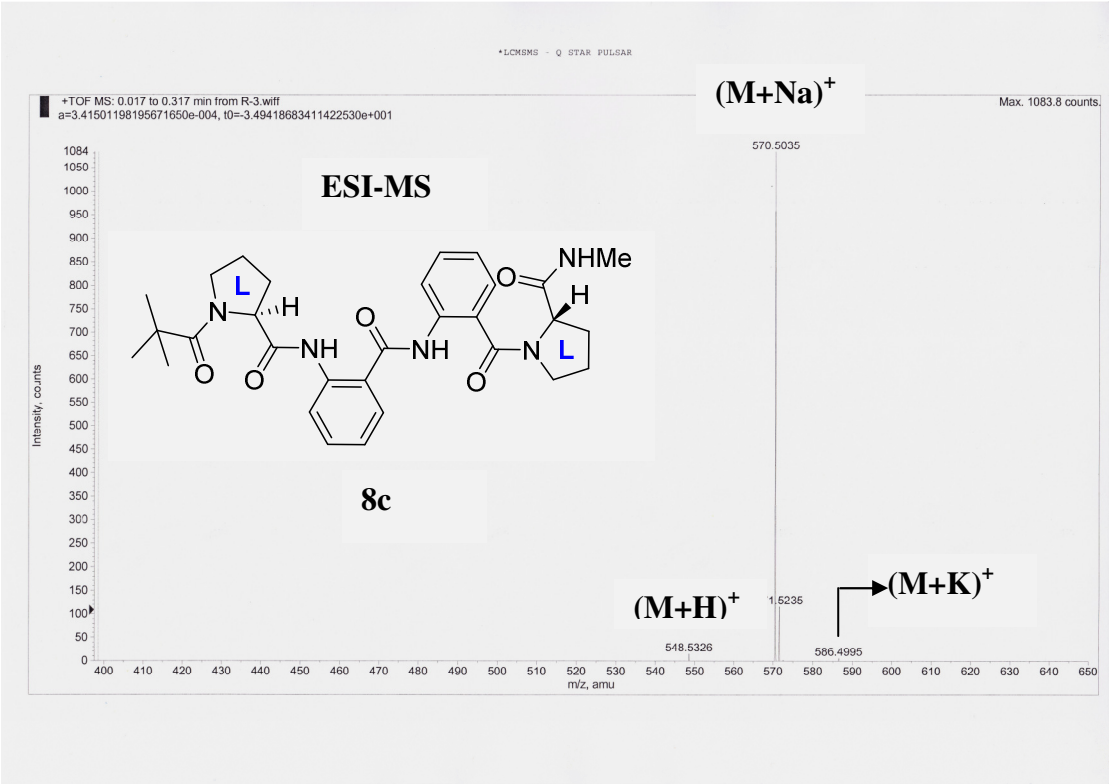
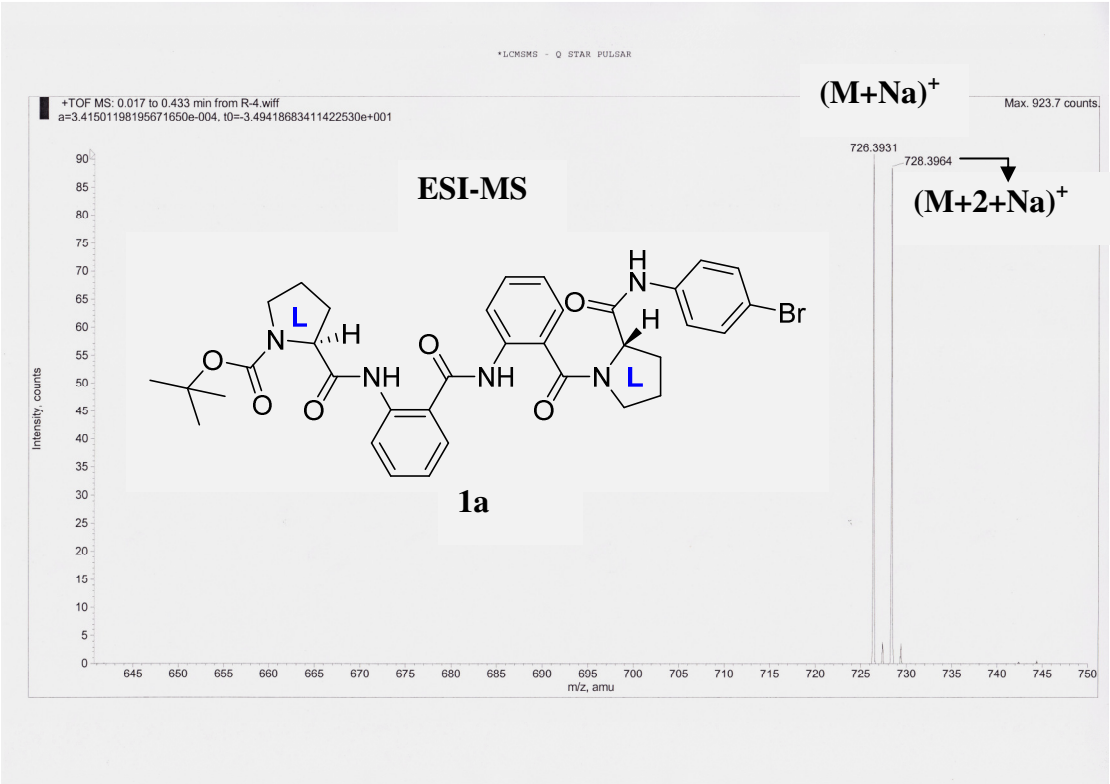
Intensity, counts
m/z, amu

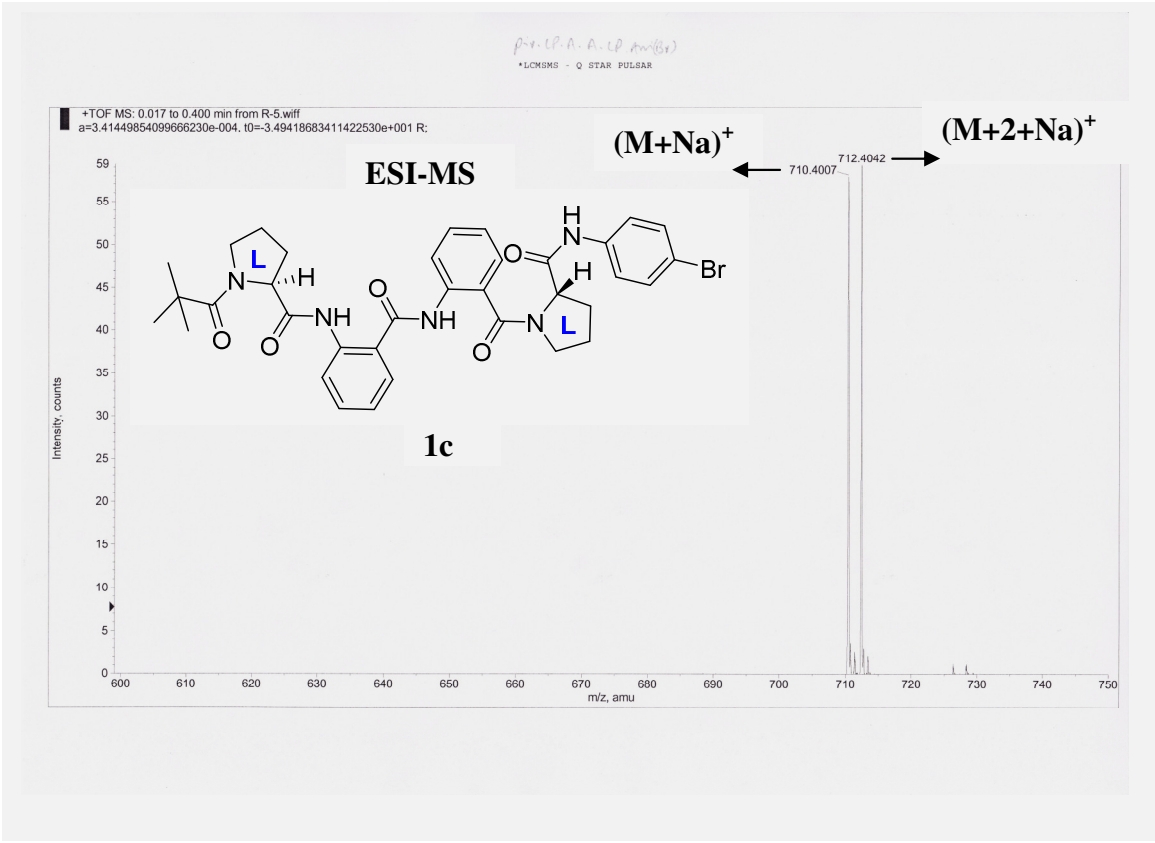

F:\DATA\JUNE-2012\GJS\BDPCY
6/4/2012 3:20:16 PM
BDPCY #8-19 RT: 0.12-0.31 AV: 12 SB: 18 0.00-0.09 , 0.31-0.50 NL: 1.66E6
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
LC-MS
358.09
390.12
(M+Na)+
490.19
(M+K)+
458.15
7
288.99
406.08
422.15
506.18
129.14
217.09
239.02
336.11
561.47
619.48
Relative Abundance
m/z

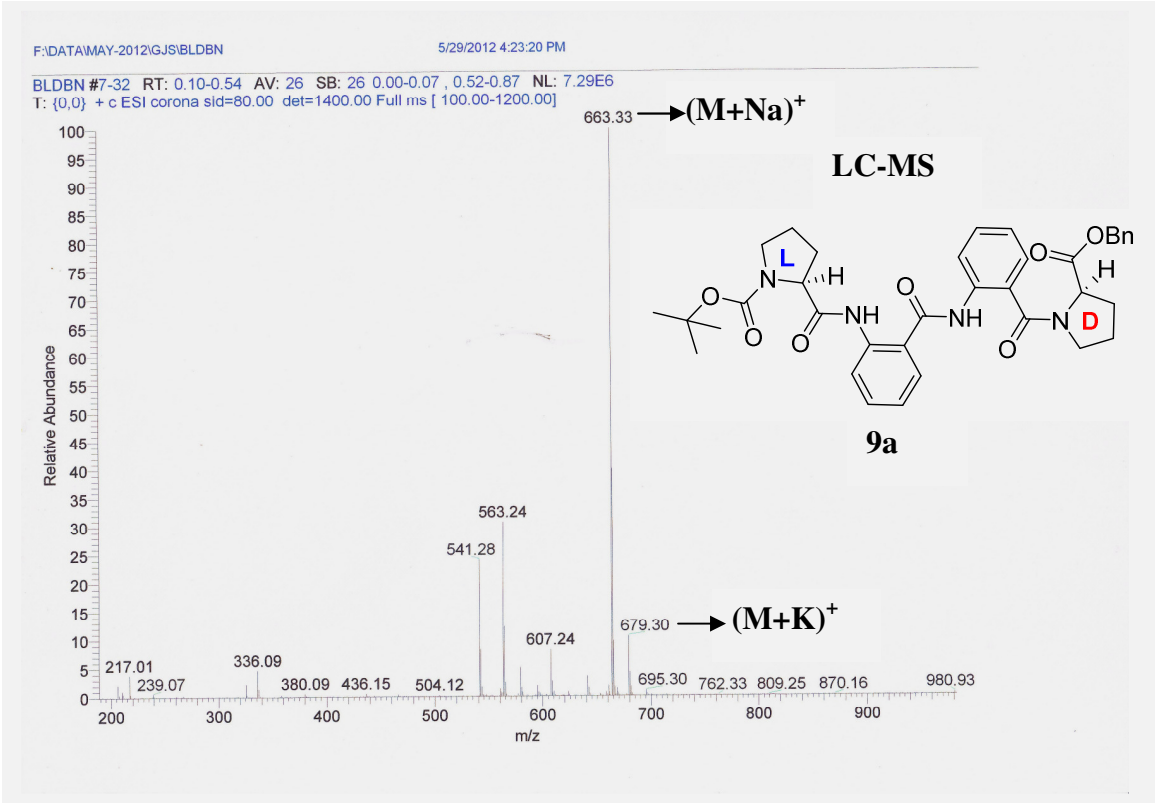


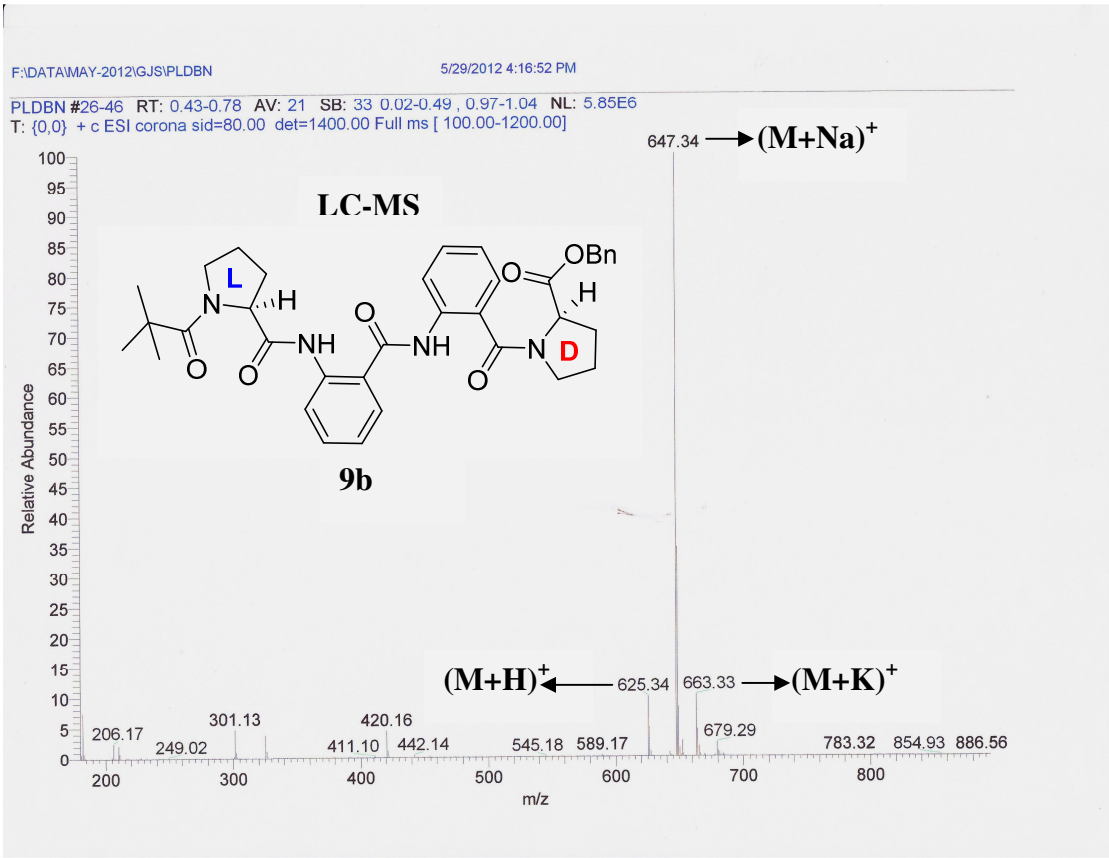


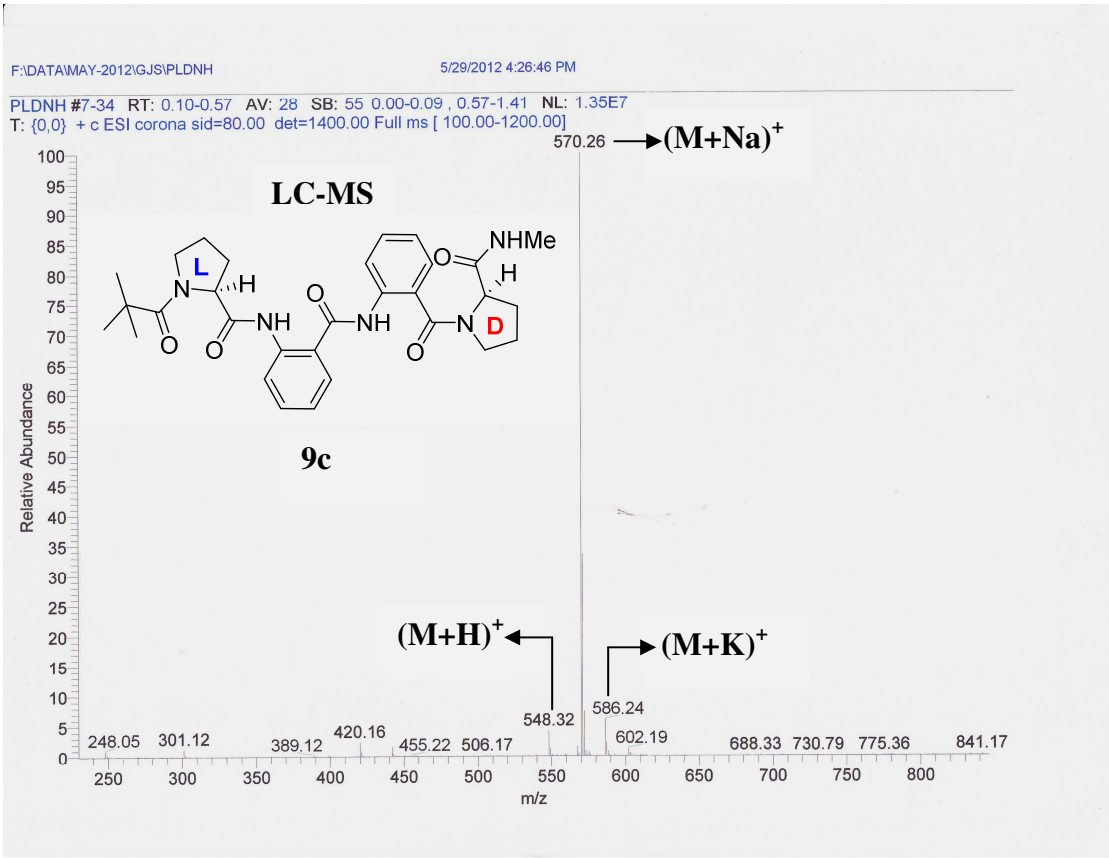

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.317 min from R-3.wiff
a=3.41501198195671650e-004, t0=-3.49418683411422530e+001
Max. 1083.8 counts.
(M+Na)+
570.5035
ESI-MS
NHMe
8c
(M+H)+
548.5326
1.5235
(M+K)+
586.4995
Intensity, counts
m/z, amu

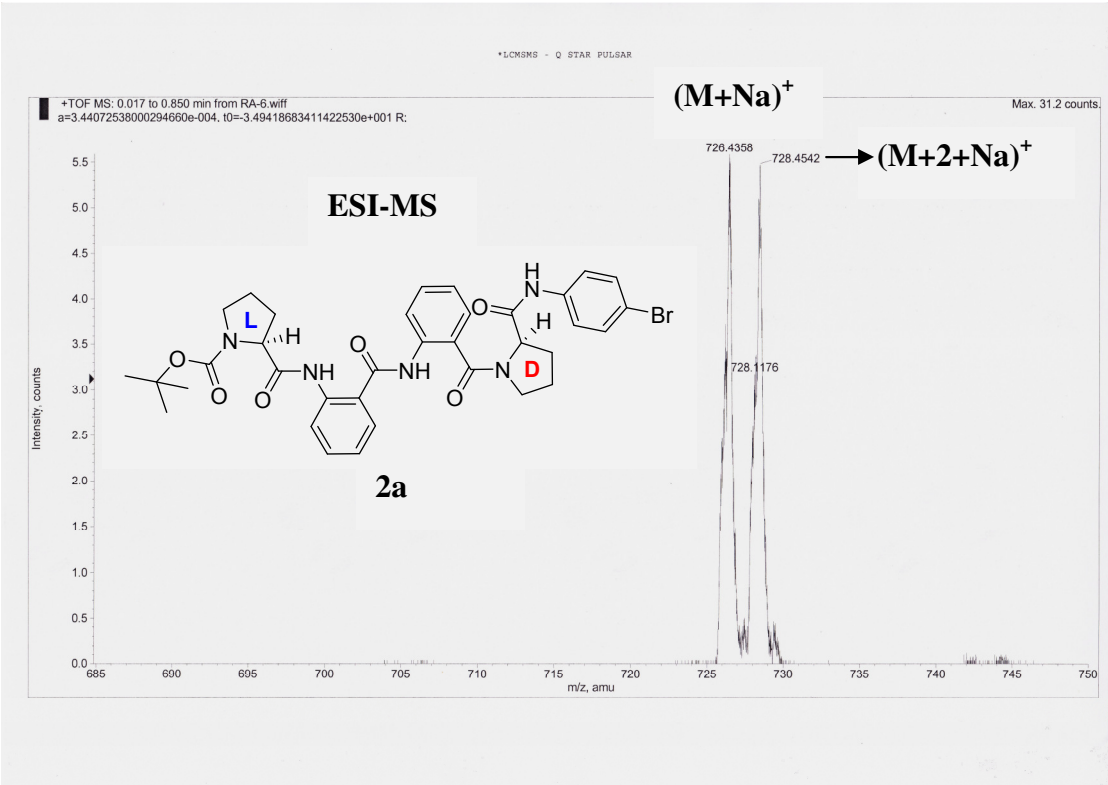

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.433 min from R-4.wiff
a=3.41501198195671650e-004, t0=-3.49418683411422530e+001
Max. 923.7 counts.
(M+Na)+
726.3931
728.3964
(M+2+Na)+
ESI-MS
Br
1a
Intensity, counts
m/z, amu

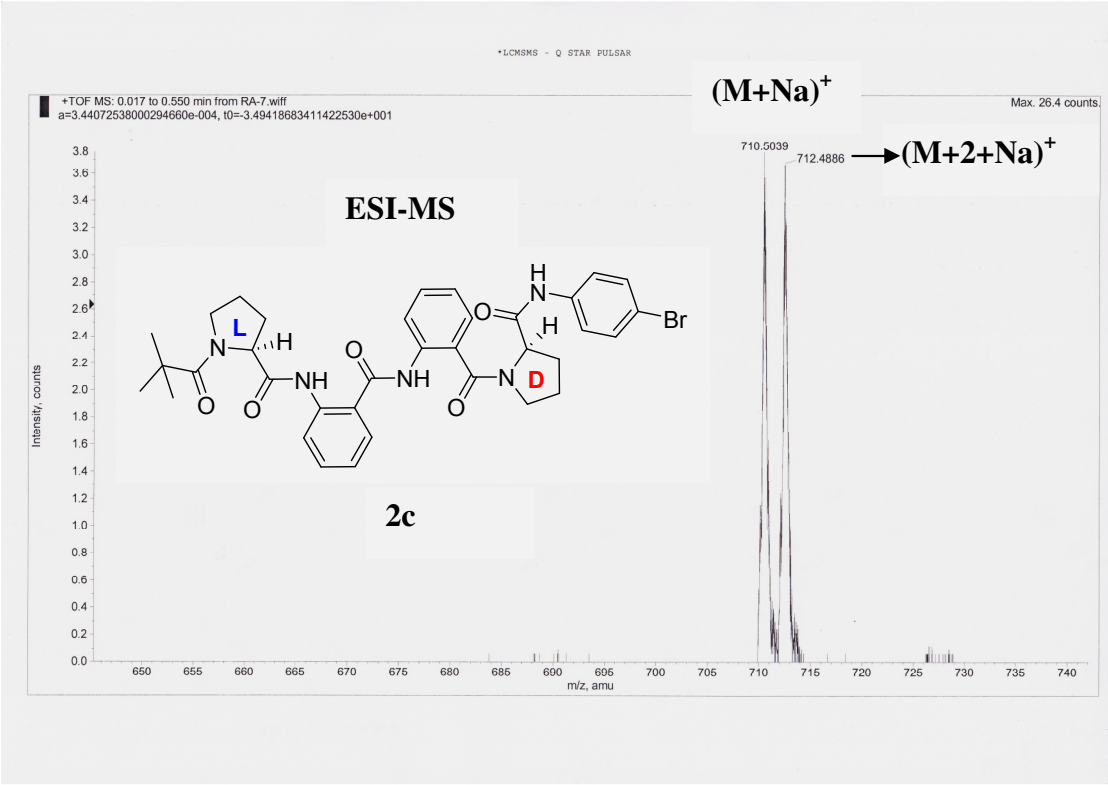

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.400 min from R-5.wiff
a=3.41449854099666230e-004, t0=-3.49418683411422530e+001 R;
ESI-MS
(M+Na)+
(M+2+Na)+
710.4007
712.4042
1c
Intensity, counts
m/z, amu

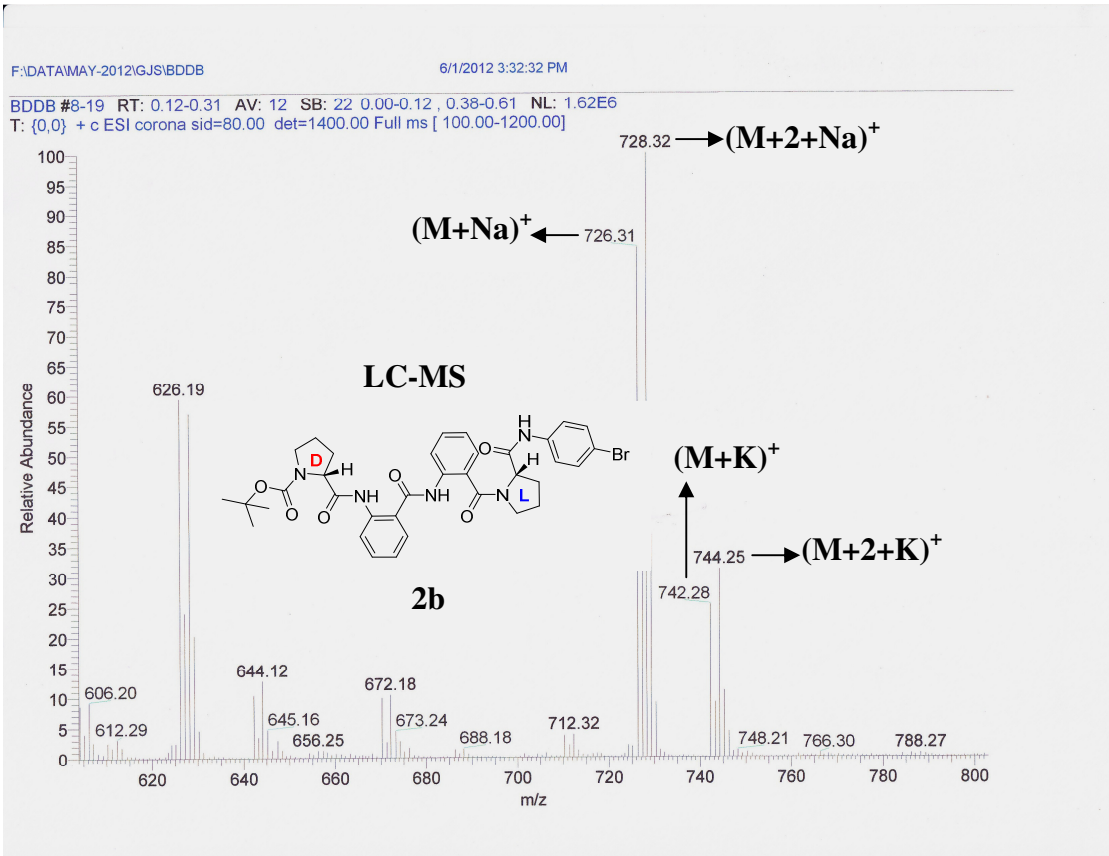

F:\DATA\MAY-2012\GJS\BLDBN
5/29/2012 4:23:20 PM
BLDBN #7-32 RT: 0.10-0.54 AV: 26 SB: 26 0.00-0.07 , 0.52-0.87 NL: 7.29E6
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
663.33
(M+Na)+
LC-MS
9a
563.24
541.28
679.30
(M+K)+
607.24
217.01
239.07
336.09
380.09
436.15
504.12
695.30
762.33
809.25
870.16
980.93
Relative Abundance
m/z

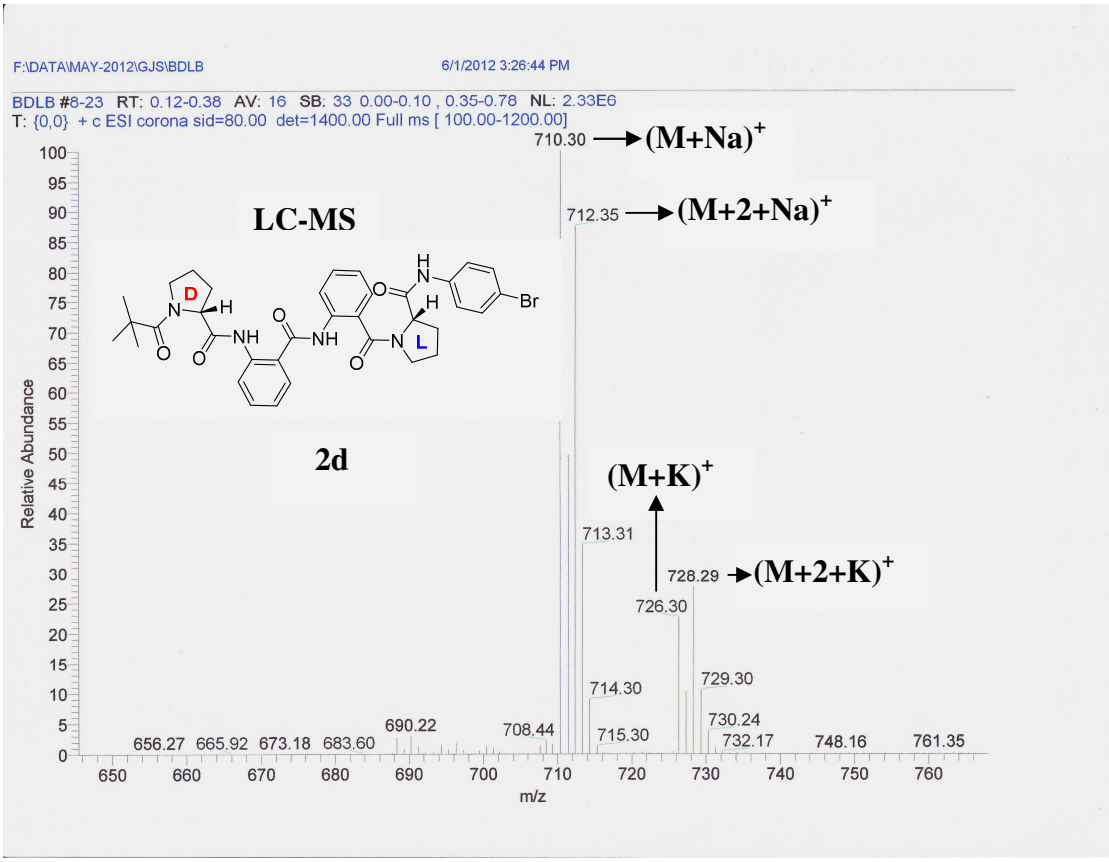

F:\DATA\MAY-2012\GJS\PLDBN
5/29/2012 4:16:52 PM
PLDBN #26-46 RT: 0.43-0.78 AV: 21 SB: 33 0.02-0.49 , 0.97-1.04 NL: 5.85E6
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
LC-MS
9b
647.34 (M+Na)+
(M+H)+
625.34
663.33 (M+K)+
Relative Abundance
m/z

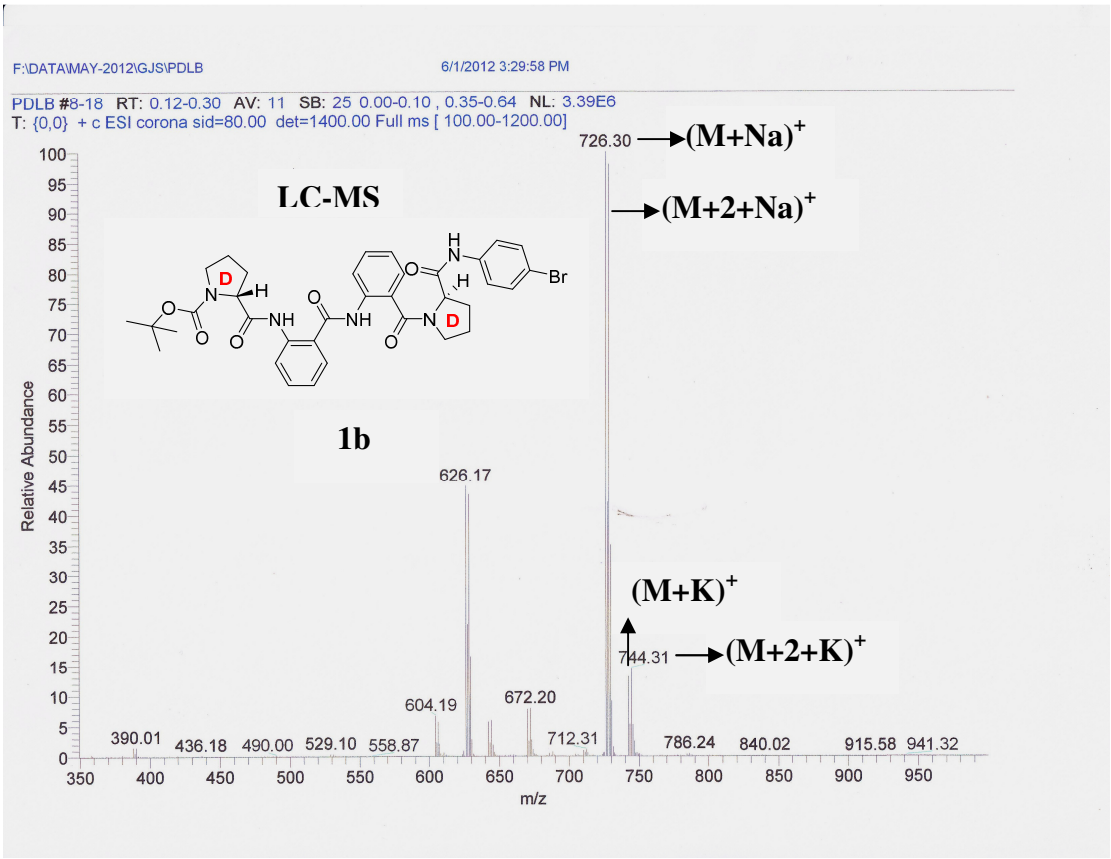

F:\DATA\MAY-2012\GJS\PLDNH
5/29/2012 4:26:46 PM
PLDNH #7-34 RT: 0.10-0.57 AV: 28 SB: 55 0.00-0.09 , 0.57-1.41 NL: 1.35E7
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
LC-MS
9c
570.26 (M+Na)+
(M+H)+
548.32
(M+K)+
586.24
Relative Abundance
m/z

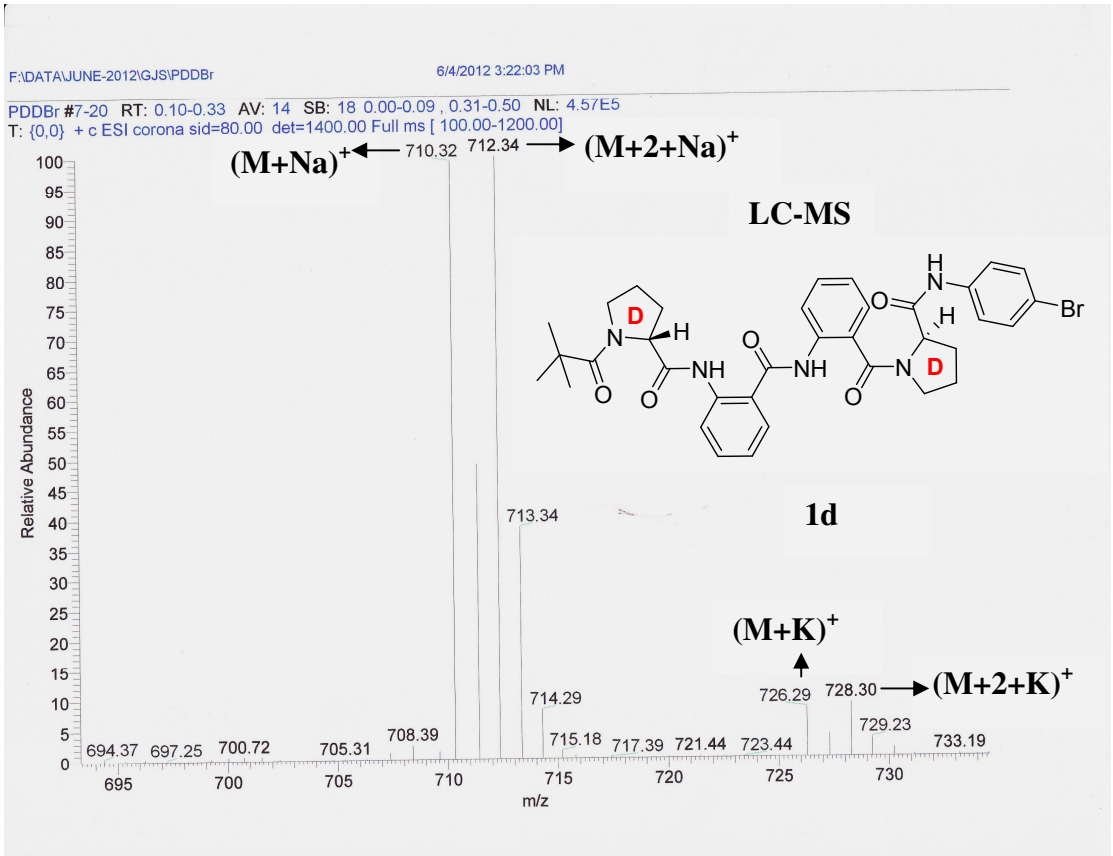

*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.850 min from RA-6.wiff
a=3.44072538000294660e-004, t0=-3.49418683411422530e+001 R:
Max. 31.2 counts.
(M+Na)+
726.4358
728.4542
(M+2+Na)+
728.1176
ESI-MS
2a
Intensity, counts
m/z, amu


*LCMSMS - Q STAR PULSAR
+TOF MS: 0.017 to 0.550 min from RA-7.wiff
a=3.44072538000294660e-004, t0=-3.49418683411422530e+001
Max. 26.4 counts.
(M+Na)+
710.5039
712.4886
(M+2+Na)+
ESI-MS
2c
Intensity, counts
m/z, amu

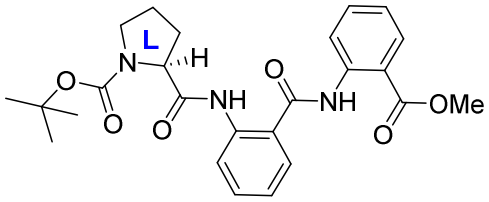

F:\DATA\MAY-2012\GJS\BDDB
6/1/2012 3:32:32 PM
BDDB #8-19 RT: 0.12-0.31 AV: 12 SB: 22 0.00-0.12 , 0.38-0.61 NL: 1.62E6
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
728.32 (M+2+Na)+
(M+Na)+ 726.31
LC-MS
626.19
(M+K)+
744.25 (M+2+K)+
742.28
2b
644.12
672.18
606.20
612.29
645.16
656.25
673.24
688.18
712.32
748.21
766.30
788.27
Relative Abundance
m/z


F:\DATA\MAY-2012\GJS\BDLB
6/1/2012 3:26:44 PM
BDLB #8-23 RT: 0.12-0.38 AV: 16 SB: 33 0.00-0.10 , 0.35-0.78 NL: 2.33E6
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
710.30 (M+Na)+
712.35 (M+2+Na)+
LC-MS
2d
(M+K)+
713.31
728.29 (M+2+K)+
726.30
714.30
729.30
730.24
690.22
708.44
715.30
732.17
656.27
665.92
673.18
683.60
748.16
761.35
Relative Abundance
m/z


F:\DATA\MAY-2012\GJS\PDLB
6/1/2012 3:29:58 PM
PDLB #8-18 RT: 0.12-0.30 AV: 11 SB: 25 0.00-0.10 , 0.35-0.64 NL: 3.39E6
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
LC-MS
1b
726.30 (M+Na)+
(M+2+Na)+
626.17
(M+K)+
744.31 (M+2+K)+
604.19
672.20
390.01
436.18
490.00
529.10
558.87
712.31
786.24
840.02
915.58
941.32
Relative Abundance
m/z


F:\DATA\JUNE-2012\GJS\PDDBr
6/4/2012 3:22:03 PM
PDDBr #7-20 RT: 0.10-0.33 AV: 14 SB: 18 0.00-0.09 , 0.31-0.50 NL: 4.57E5
T: {0,0} + c ESI corona sid=80.00 det=1400.00 Full ms [100.00-1200.00]
(M+Na)+ 710.32 712.34 (M+2+Na)+
LC-MS
1d
713.34
(M+K)+
726.29 728.30 (M+2+K)+
714.29
694.37
697.25
700.72
705.31
708.39
715.18
717.39
721.44
723.44
729.23
733.19
Relative Abundance
m/z

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



4

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

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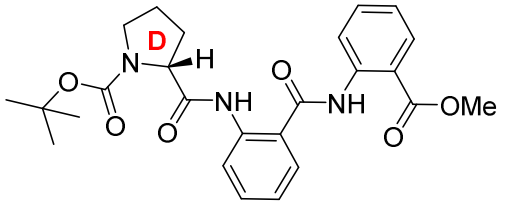
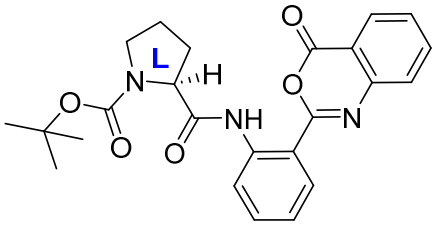
^{1}H NMR ($CDCl_3$, 200 MHz)



5

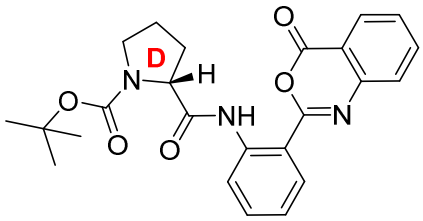
^{1}H NMR ($CDCl_3$, 200 MHz)



6

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

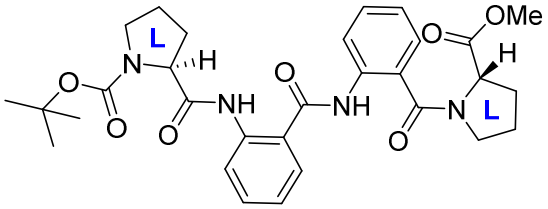
^{1}H NMR ($CDCl_3$, 200 MHz)



7

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

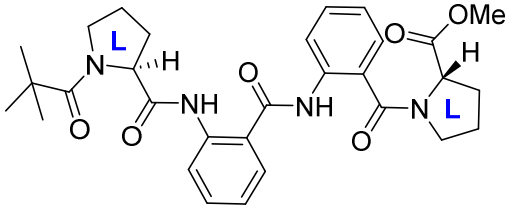
^{1}H NMR ($CDCl_3$, 200 MHz)



8a

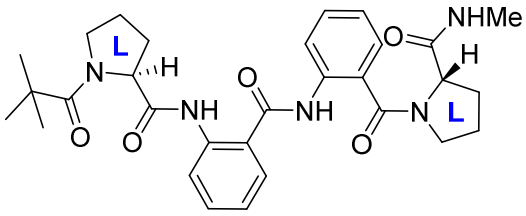
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

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



8b

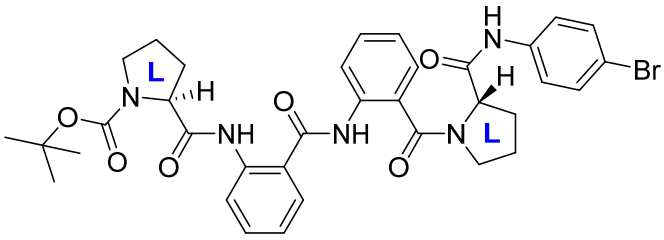
^{1}H NMR ($CDCl_3$, 200 MHz)



8c

 # DMF

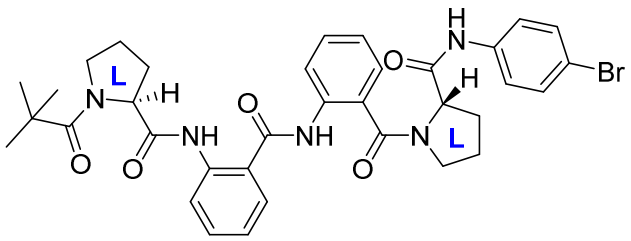
^{1}H NMR ($CDCl_3$, 200 MHz)



1a

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

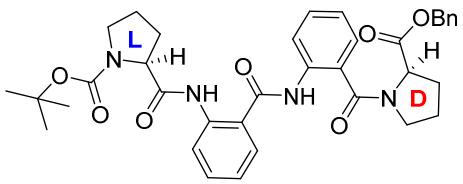
^{1}H NMR ($CDCl_3$, 200 MHz)



1c

 # DMF

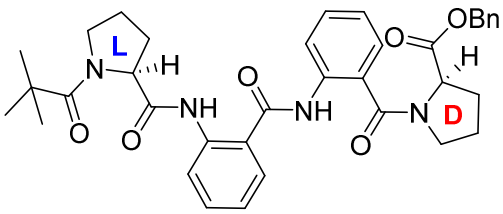
^{1}H NMR ($CDCl_3$, 500 MHz)



9a

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

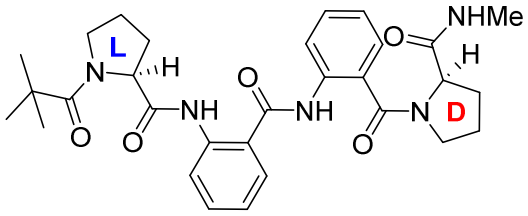
^{1}H NMR ($CDCl_3$, 200 MHz)



9b

 # DMF

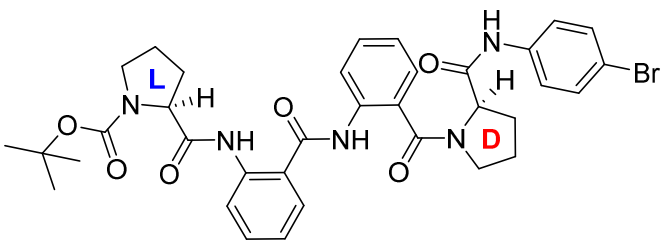
^{1}H NMR ($CDCl_3$, 500 MHz)



9c

 # DMF

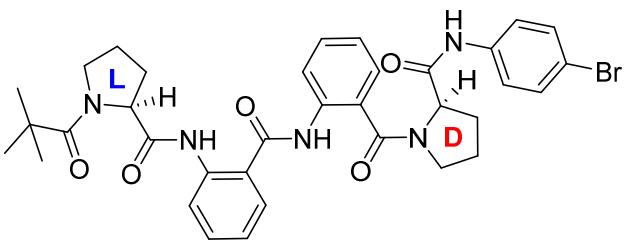
^{1}H NMR ($CDCl_3$, 200 MHz)



2a

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

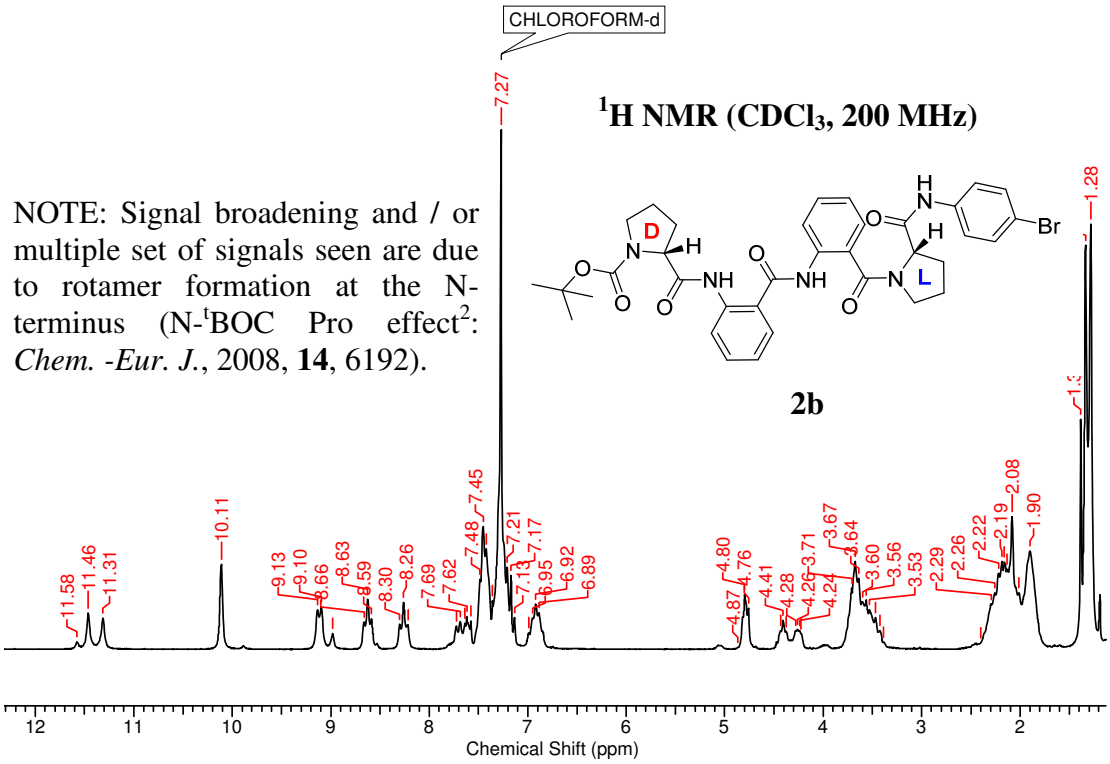
^{1}H NMR ($CDCl_3$, 500 MHz)

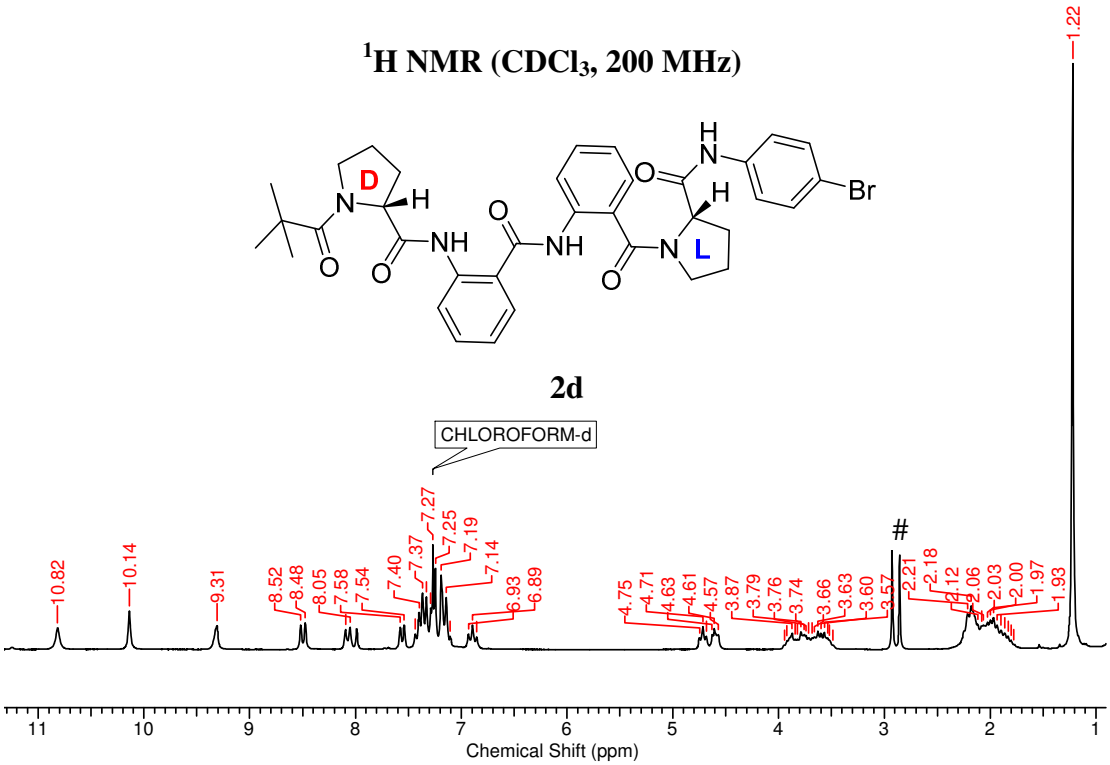


2c

 # DMF

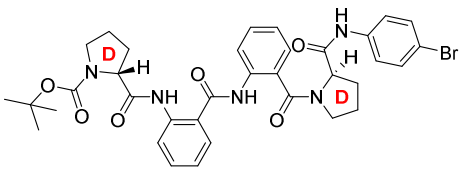
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).





DMF

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

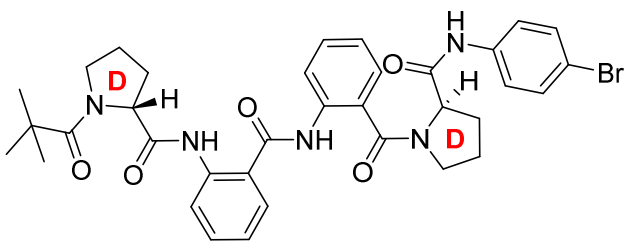


1b

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

 # DMF

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

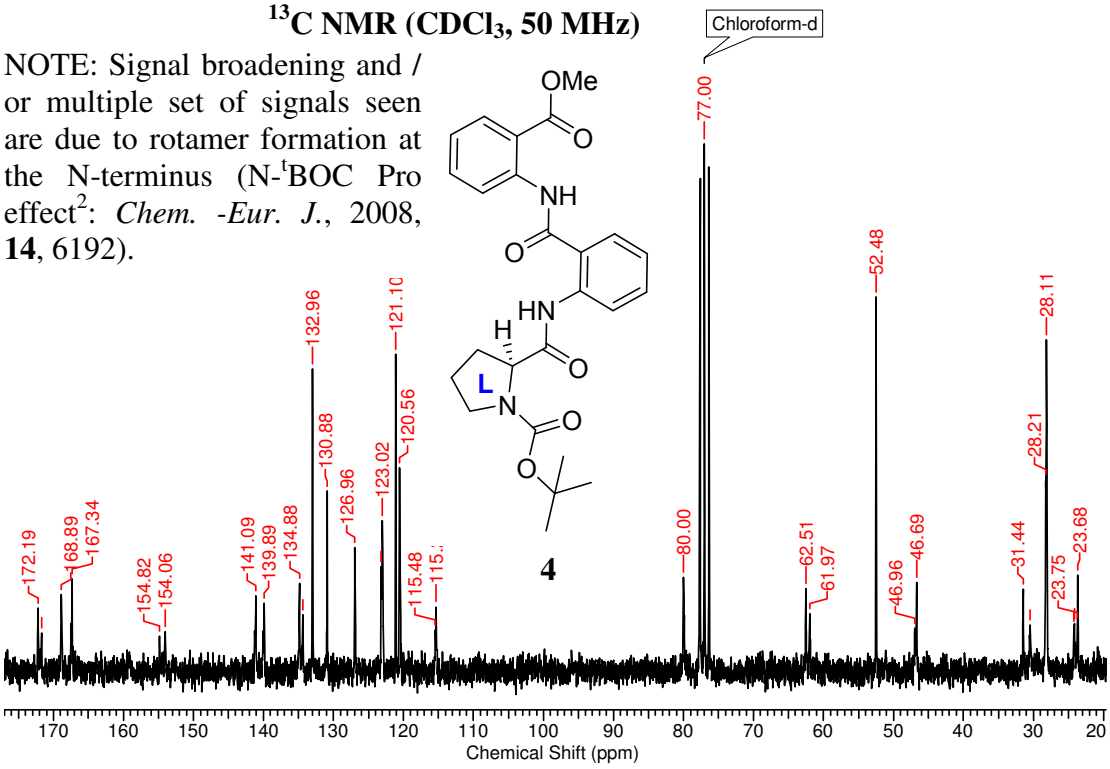


1d

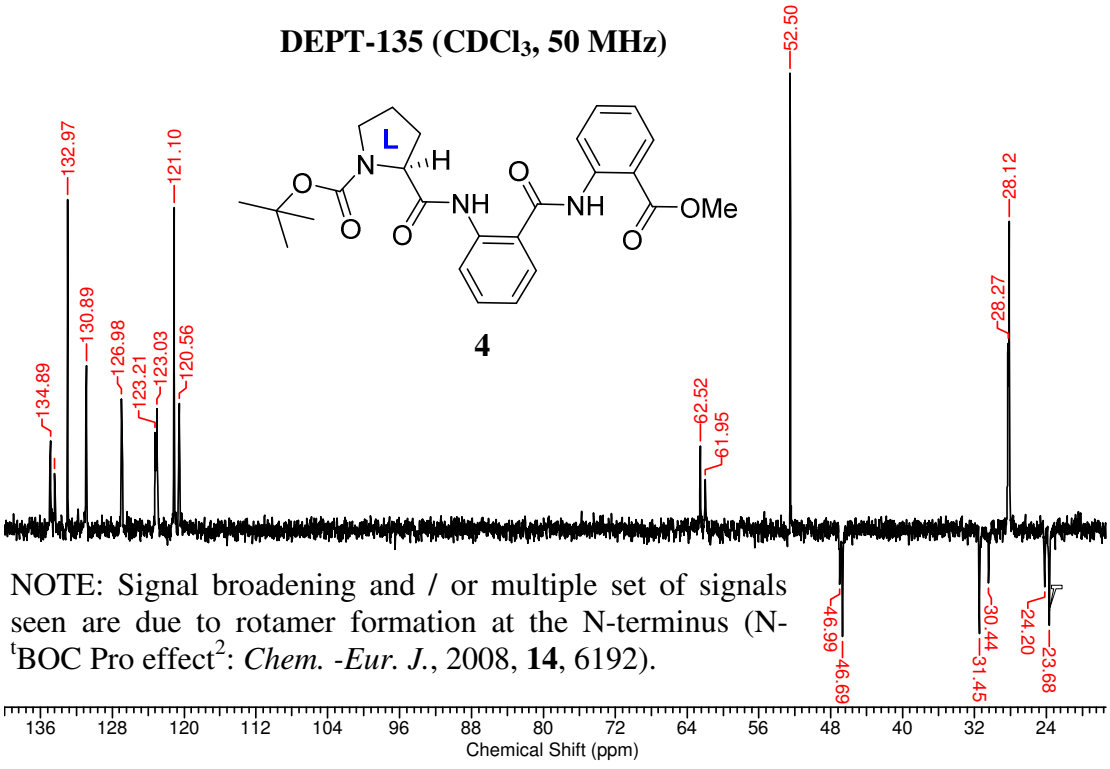
 # DMF

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

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).



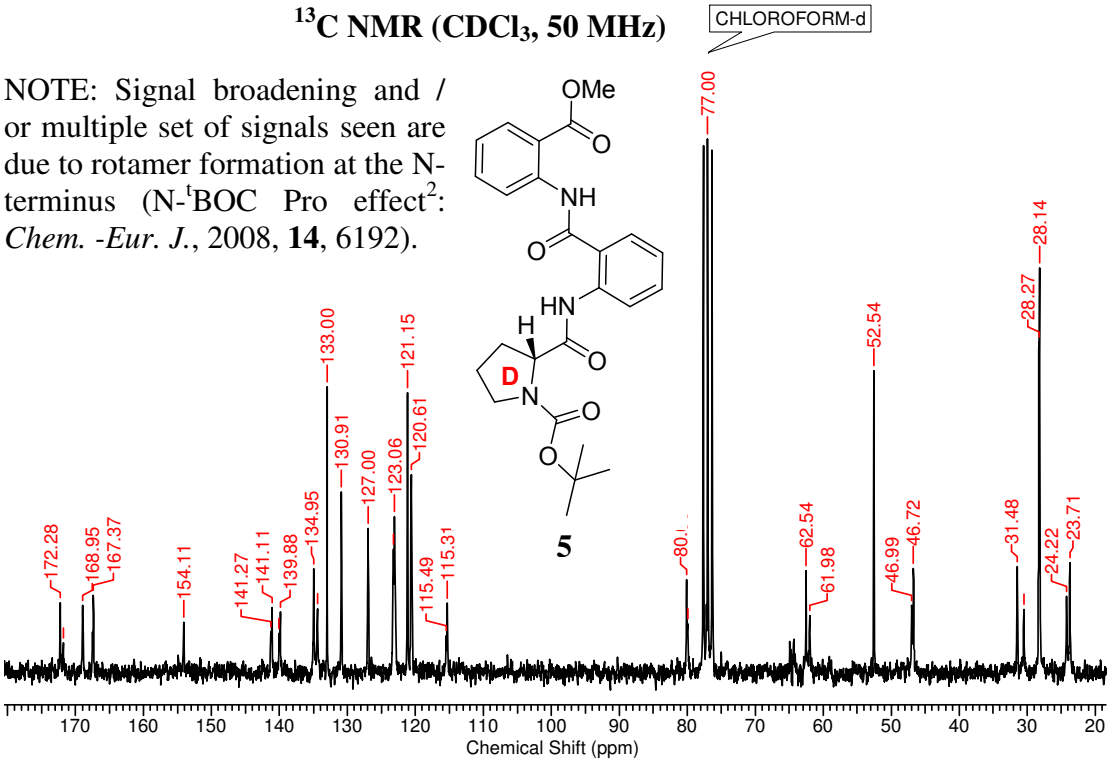
DEPT-135 ($CDCl_3$, 50 MHz)



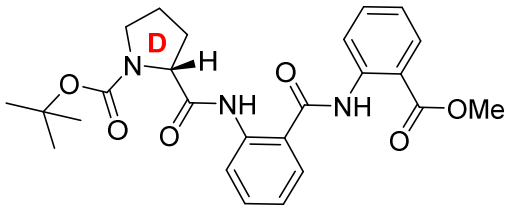
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

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

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

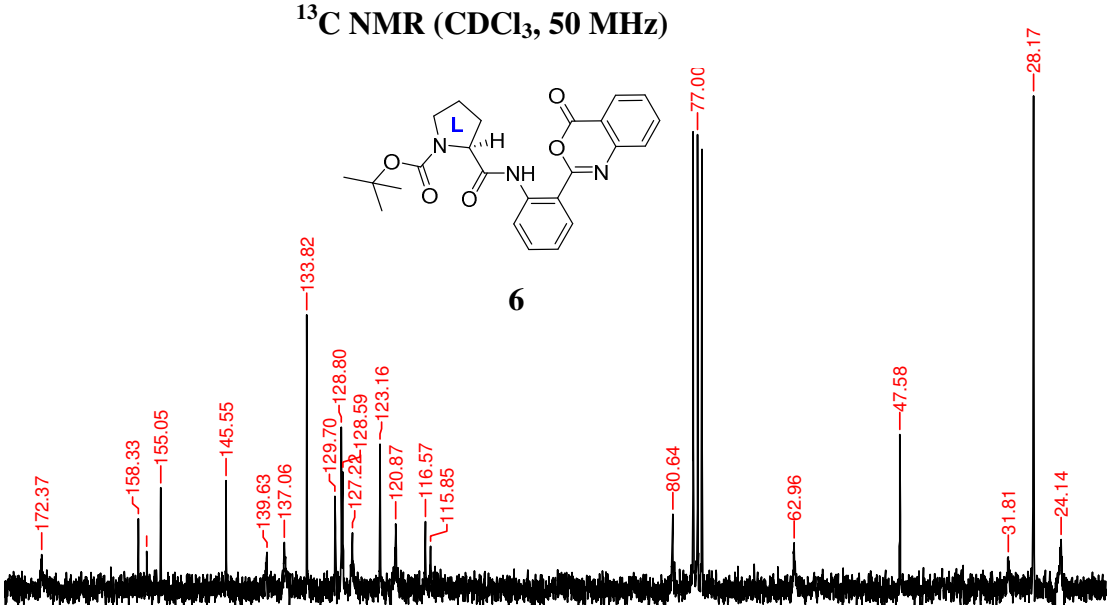


DEPT-135 ($CDCl_3$, 50 MHz)



NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

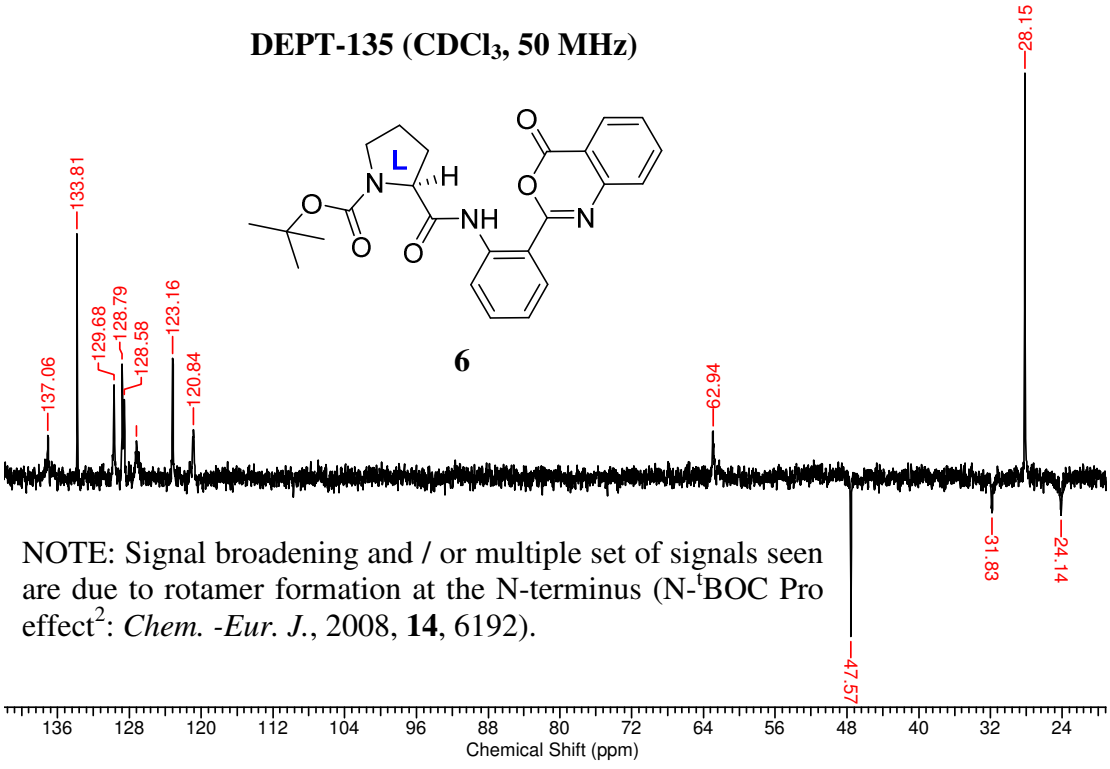
^{13}C NMR ($CDCl_3$, 50 MHz)



6

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

DEPT-135 ($CDCl_3$, 50 MHz)

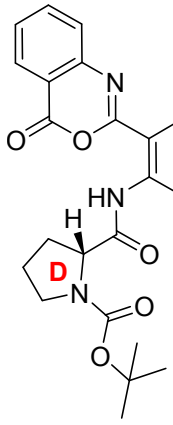


6

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

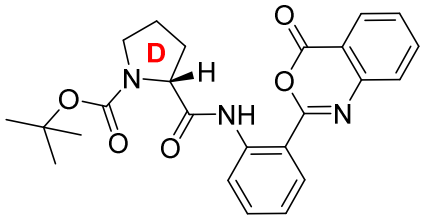
^{13}C NMR ($CDCl_3$, 50 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).



7

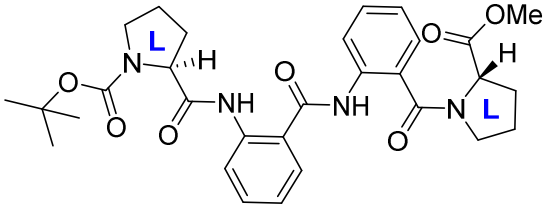
DEPT-135 ($CDCl_3$, 50 MHz)



7

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

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

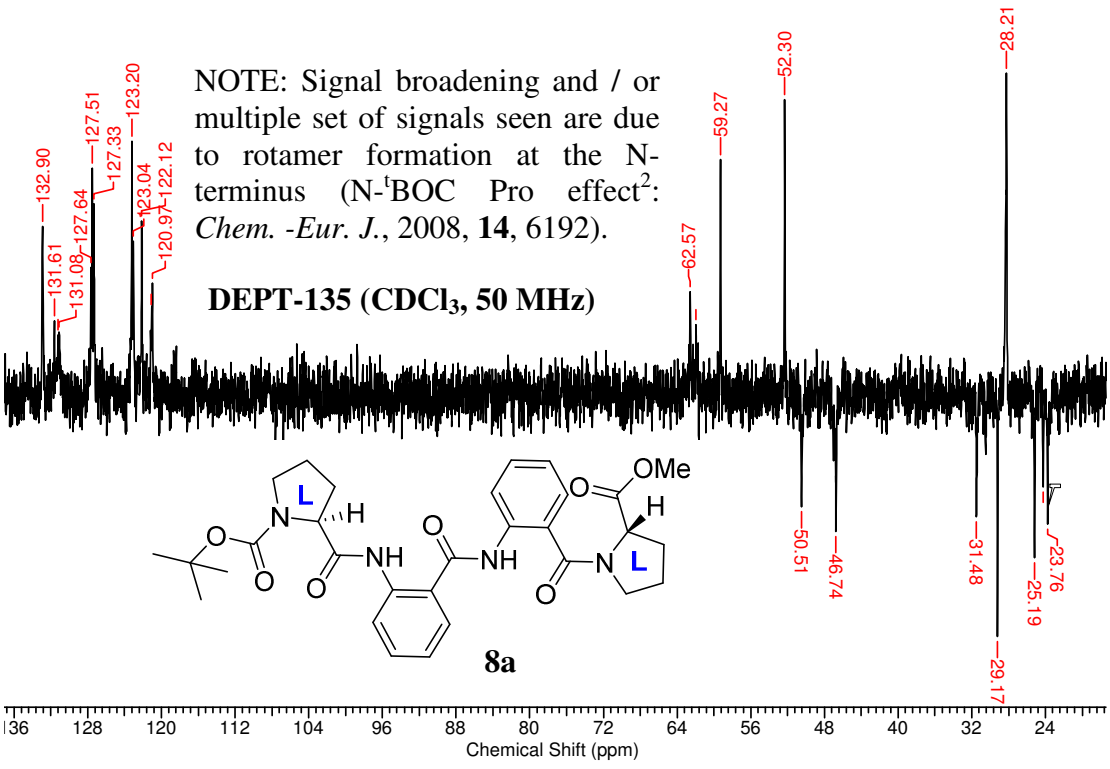


8a

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

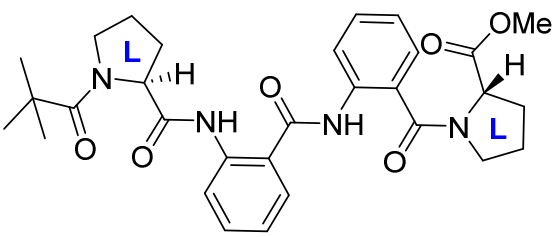
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

DEPT-135 ($CDCl_3$, 50 MHz)



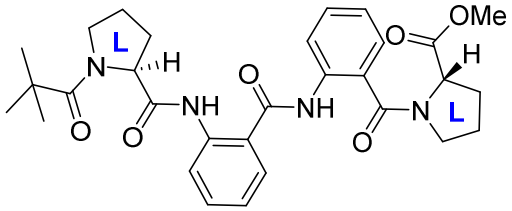
8a

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



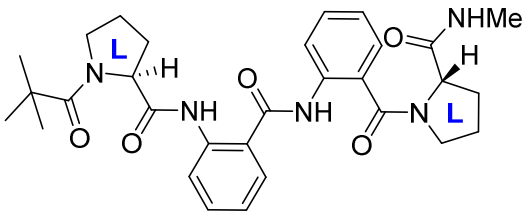
8b

DEPT-135 ($CDCl_3$, 50 MHz)



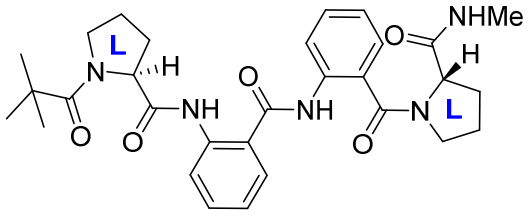
8b

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



8c

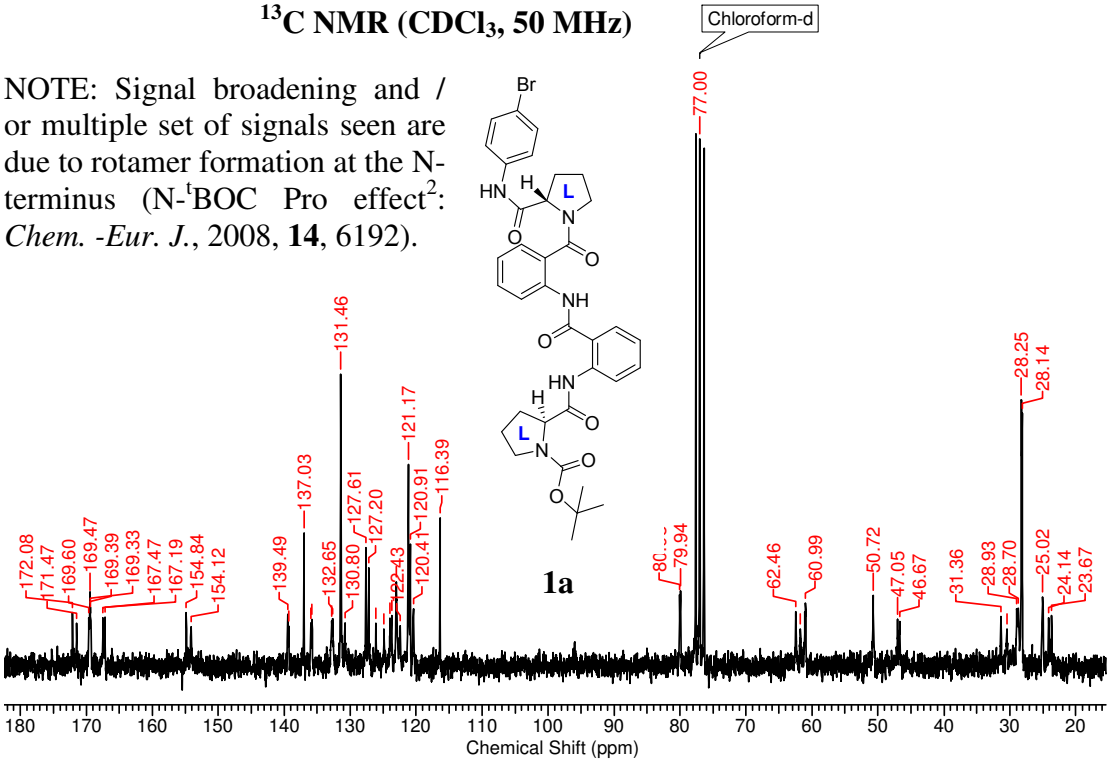
DEPT-135 ($CDCl_3$, 50 MHz)



8c

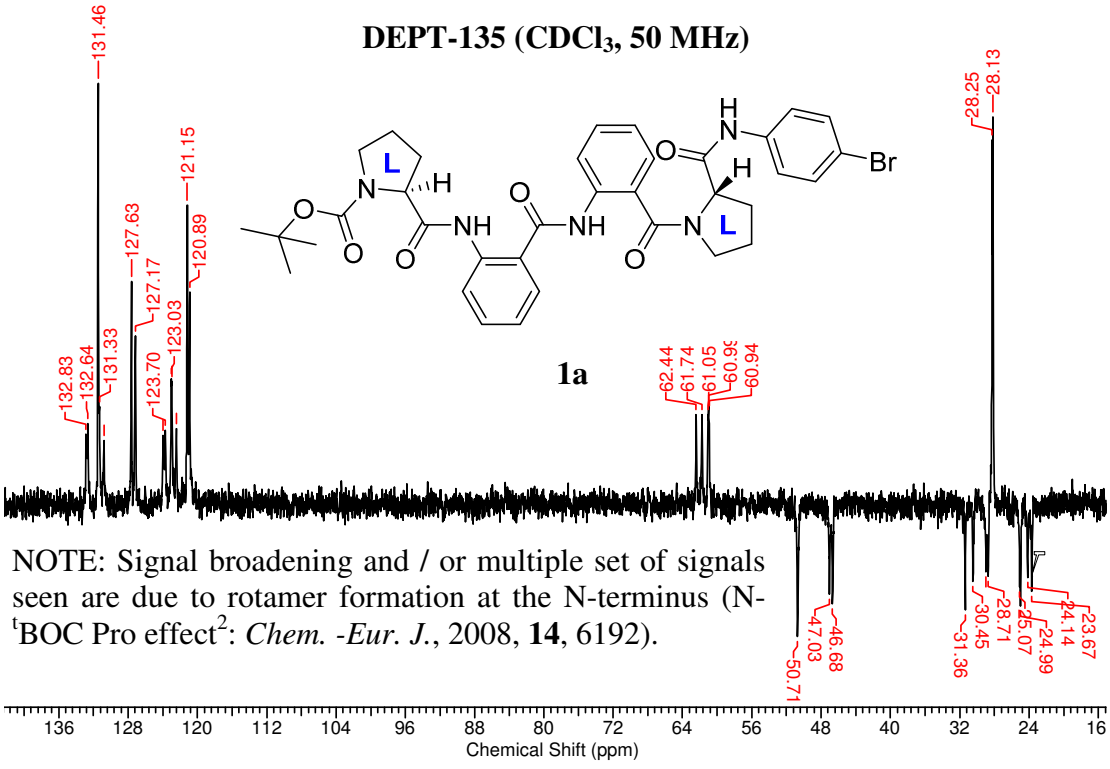
^{13}C NMR ($CDCl_3$, 50 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).



1a

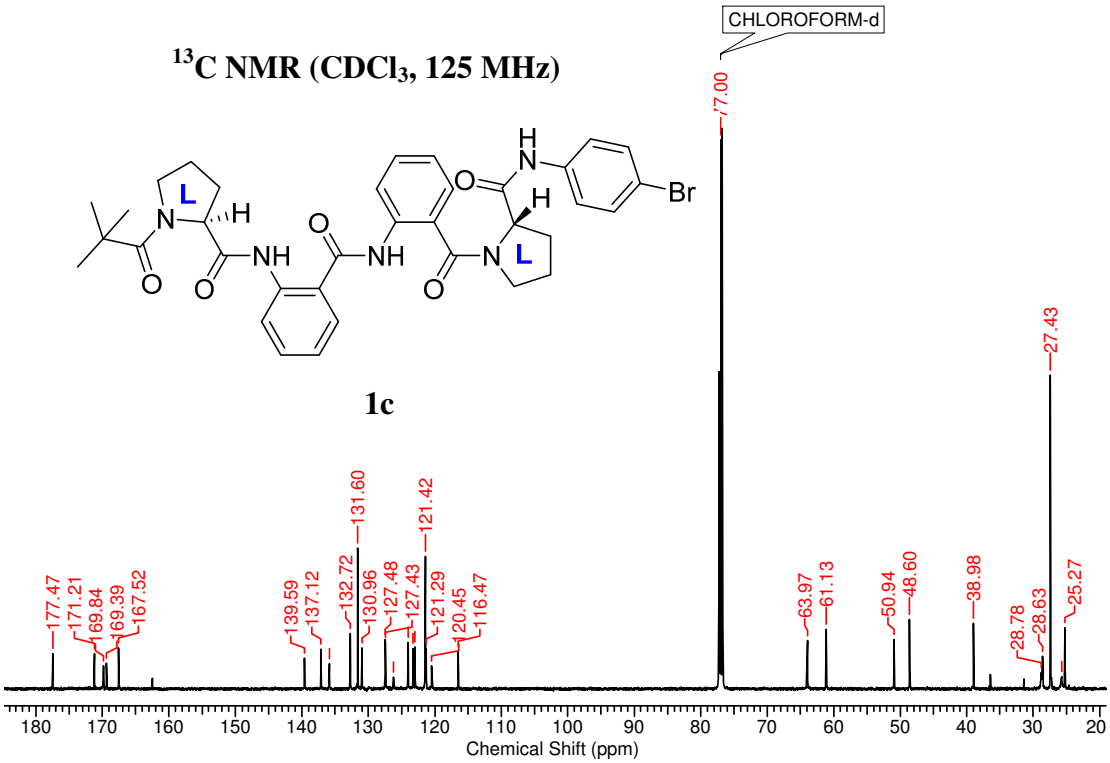
DEPT-135 ($CDCl_3$, 50 MHz)



1a

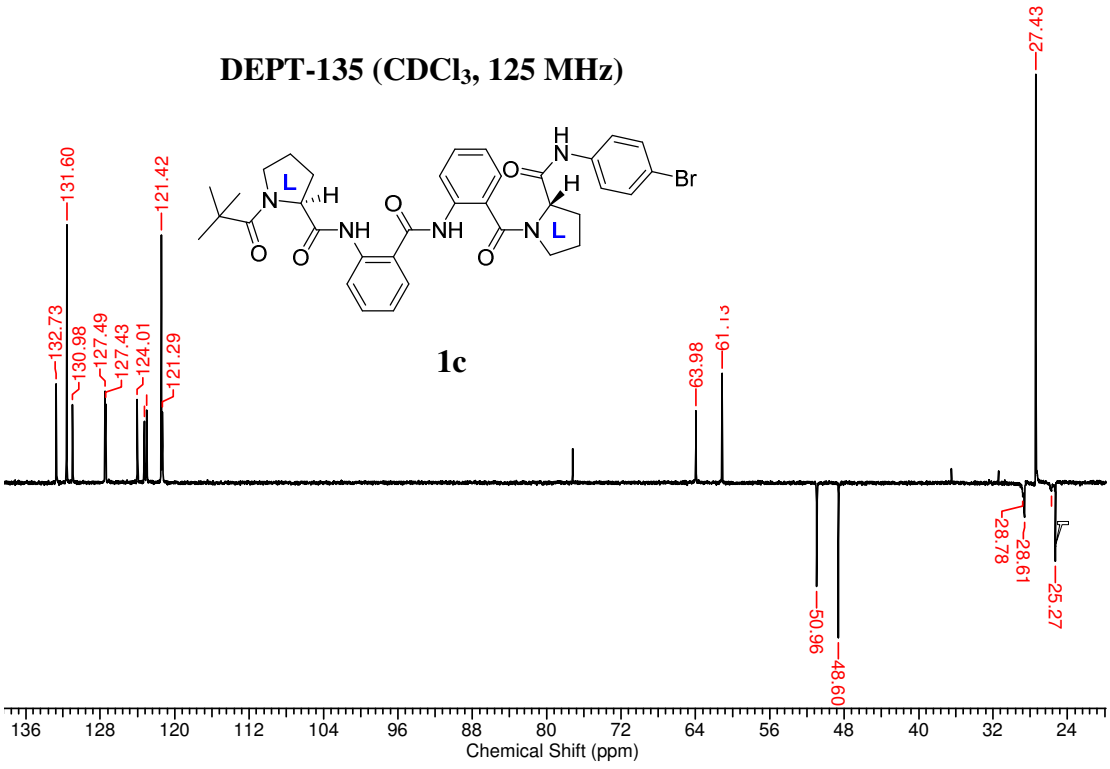
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

^{13}C NMR ($CDCl_3$, 125 MHz)



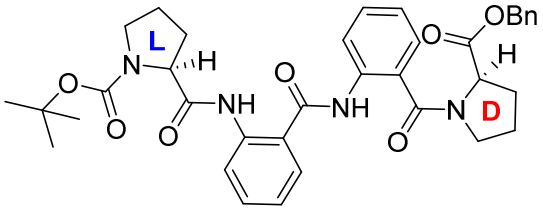
1c

DEPT-135 ($CDCl_3$, 125 MHz)



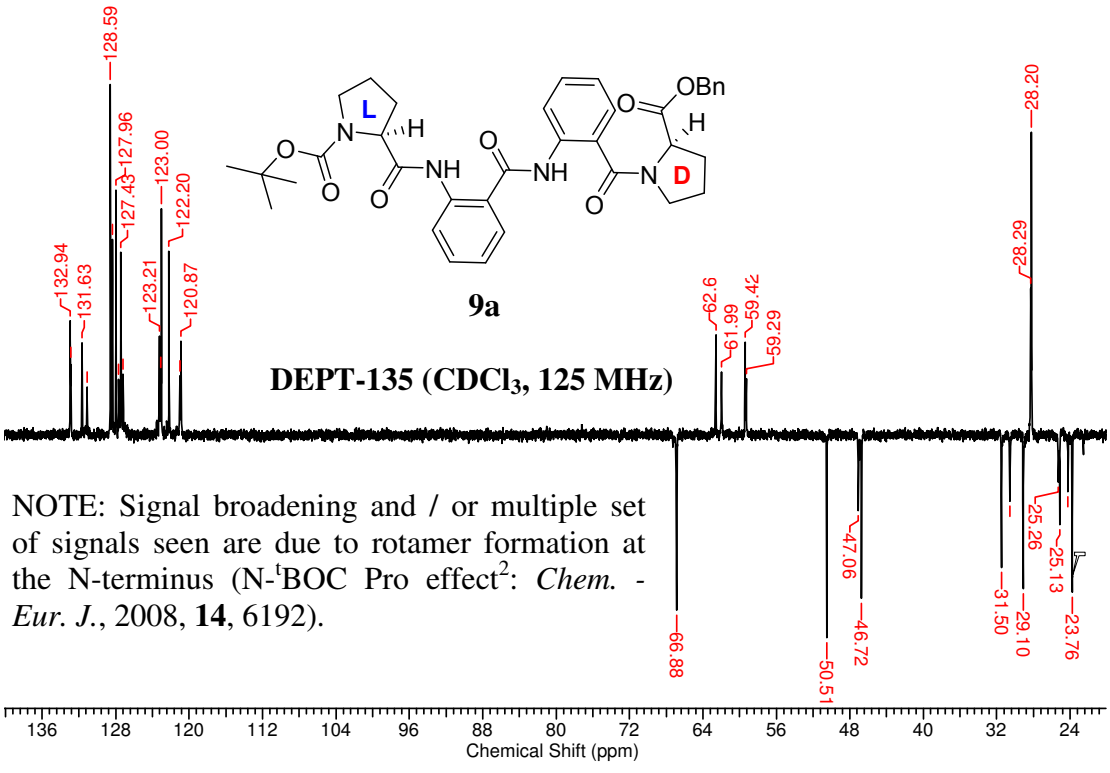
1c

^{13}C NMR ($CDCl_3$, 125 MHz)



9a

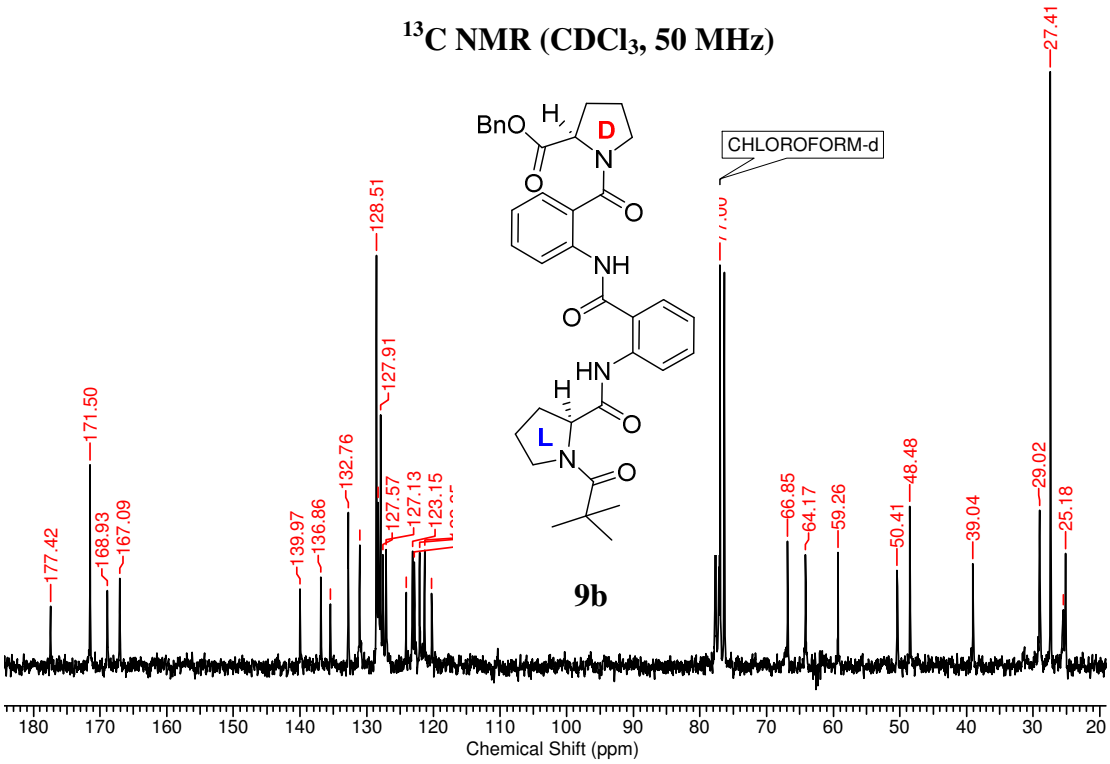
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

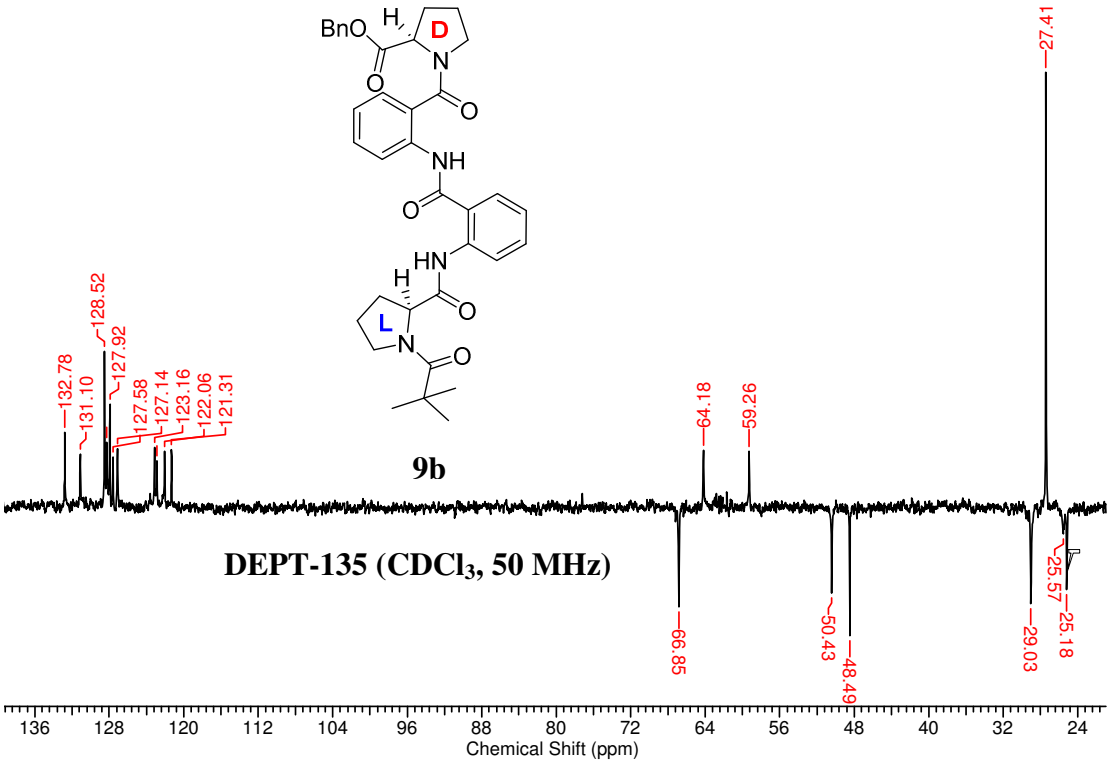


9a

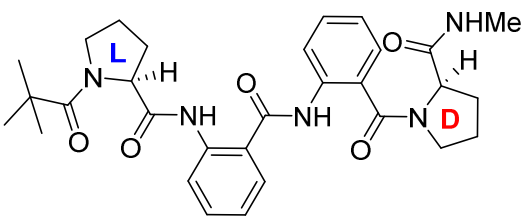
DEPT-135 ($CDCl_3$, 125 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

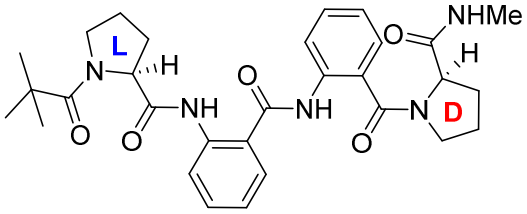

13C NMR (CDCl3, 50 MHz)
BnO
H
D
N
O
O
NH
O
HN
H
L
N
O
O
9b
CHLOROFORM-d
177.42
171.50
168.93
167.09
139.97
136.86
132.76
128.51
127.91
127.57
127.13
123.15
66.85
64.17
59.26
50.41
48.48
39.04
29.02
27.41
25.18
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
Chemical Shift (ppm)


BnO
H
D
N
O
O
NH
O
HN
H
L
N
O
O
9b
132.78
131.10
128.52
127.92
127.58
127.14
123.16
122.06
121.31
64.18
59.26
27.41
DEPT-135 (CDCl3, 50 MHz)
99.85
50.43
48.49
29.03
25.57
22.18
136 128 120 112 104 96 88 80 72 64 56 48 40 32 24
Chemical Shift (ppm)

^{13}C NMR ($CDCl_3$, 125 MHz)



9c

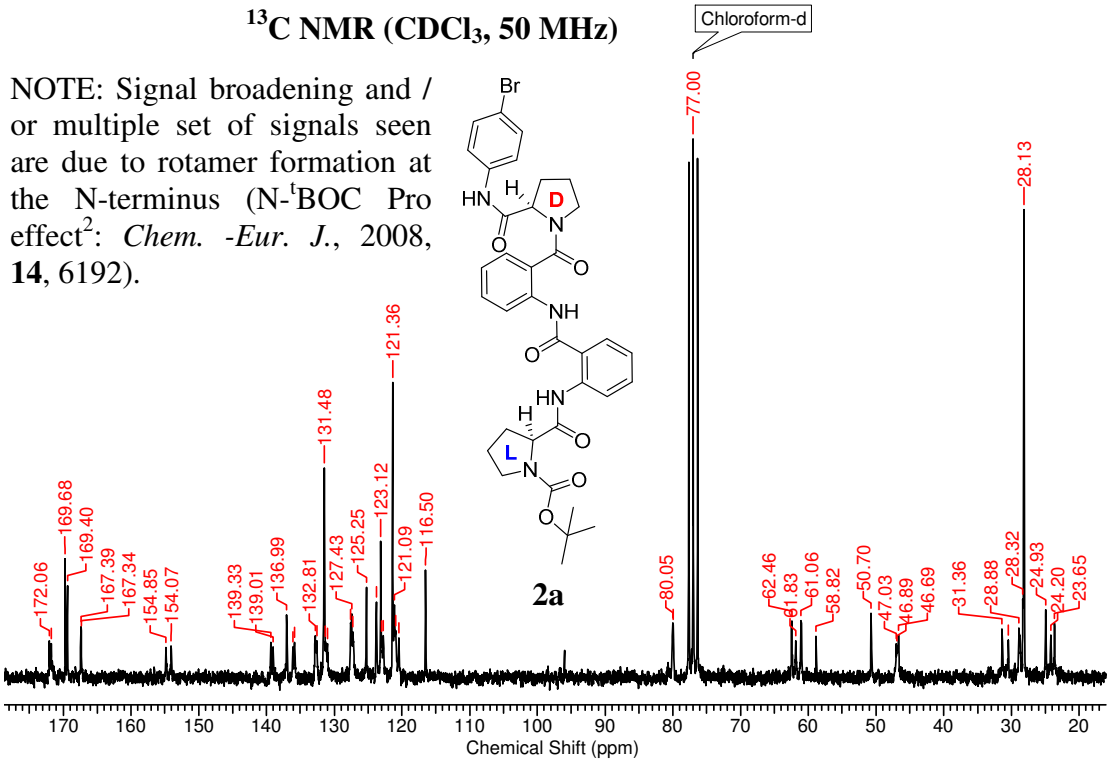


9c

DEPT-135 ($CDCl_3$, 125 MHz)

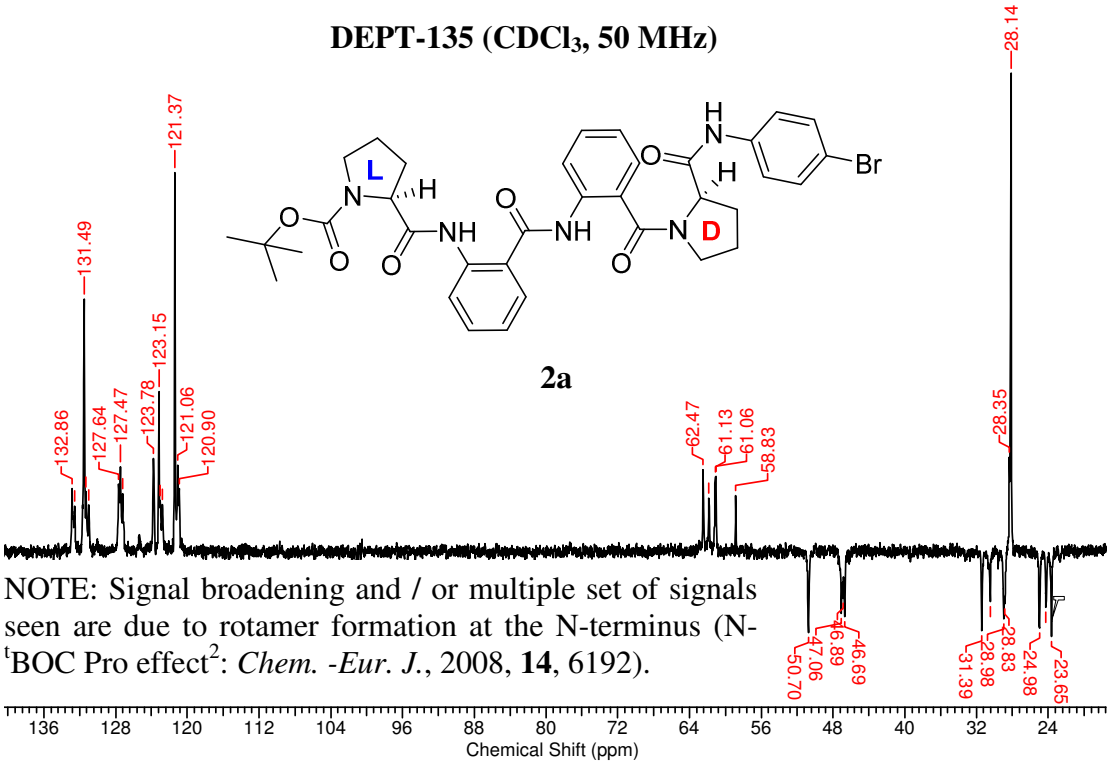
^{13}C NMR ($CDCl_3$, 50 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).



2a

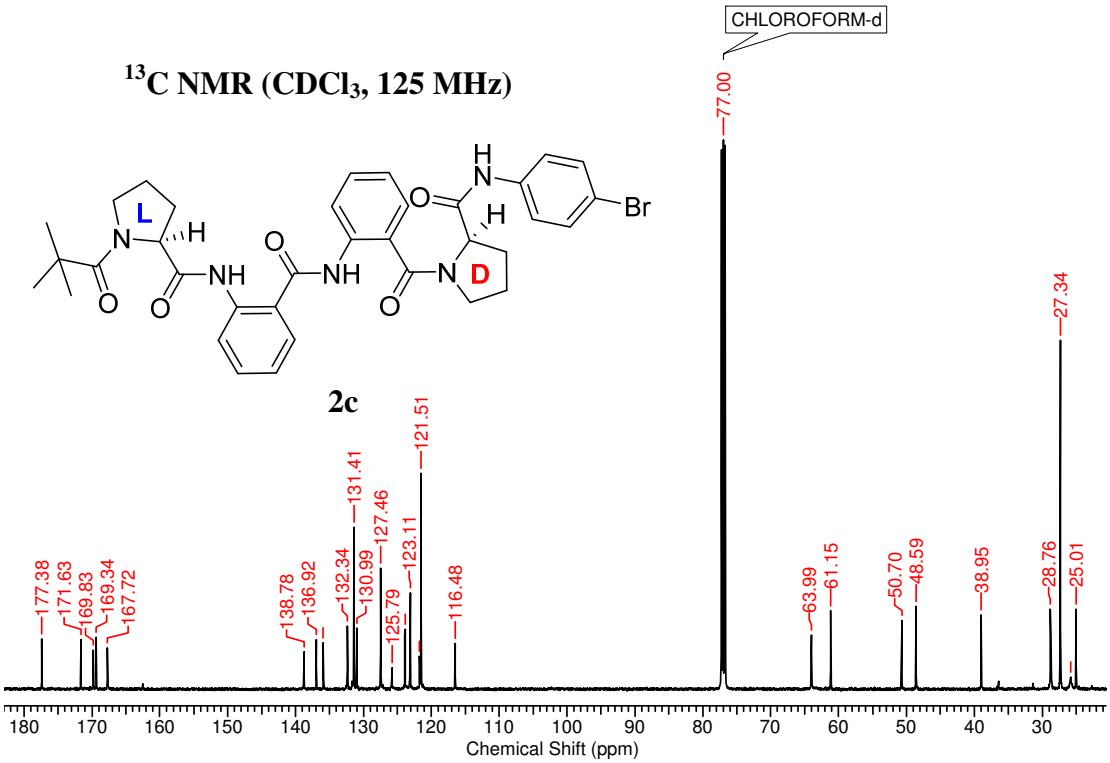
DEPT-135 ($CDCl_3$, 50 MHz)



2a

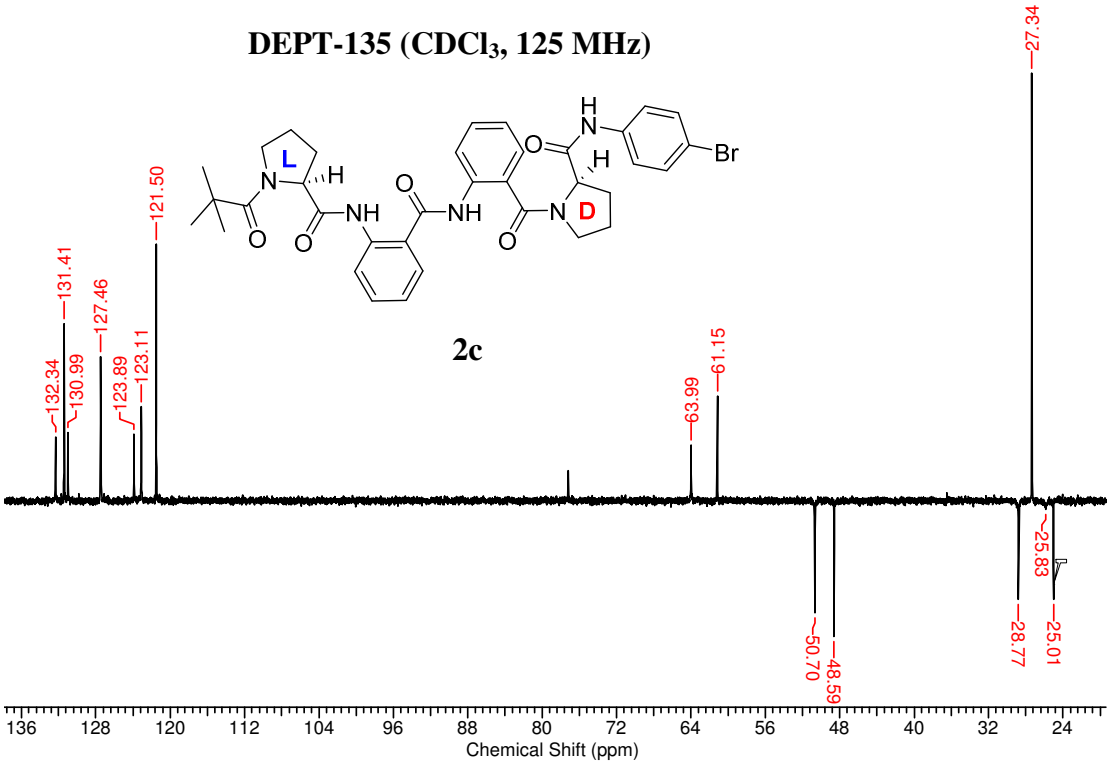
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

^{13}C NMR ($CDCl_3$, 125 MHz)



2c

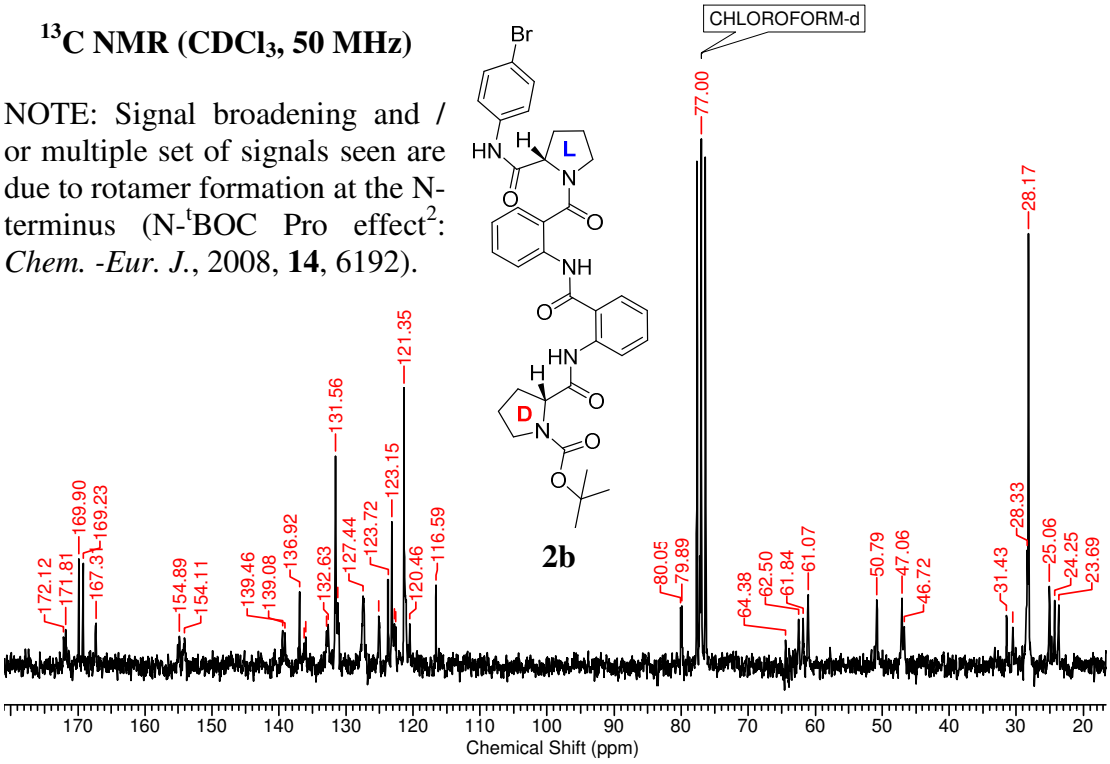
DEPT-135 ($CDCl_3$, 125 MHz)



2c

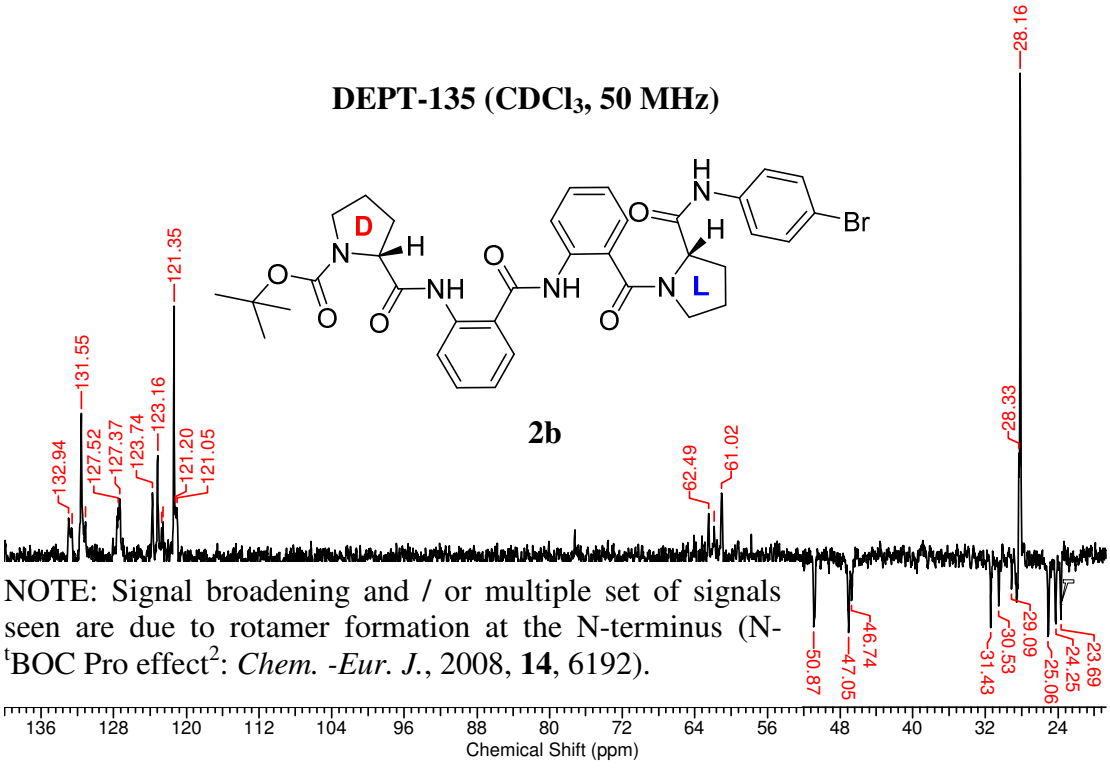
^{13}C NMR ($CDCl_3$, 50 MHz)

NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).



2b

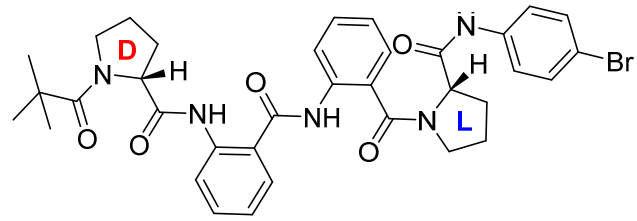
DEPT-135 ($CDCl_3$, 50 MHz)



2b

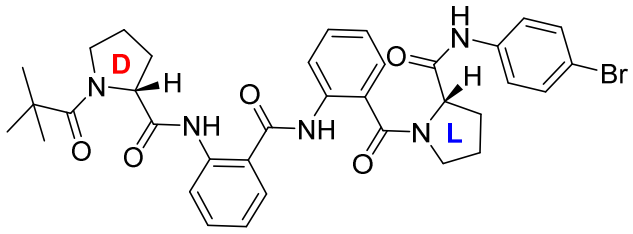
NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

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



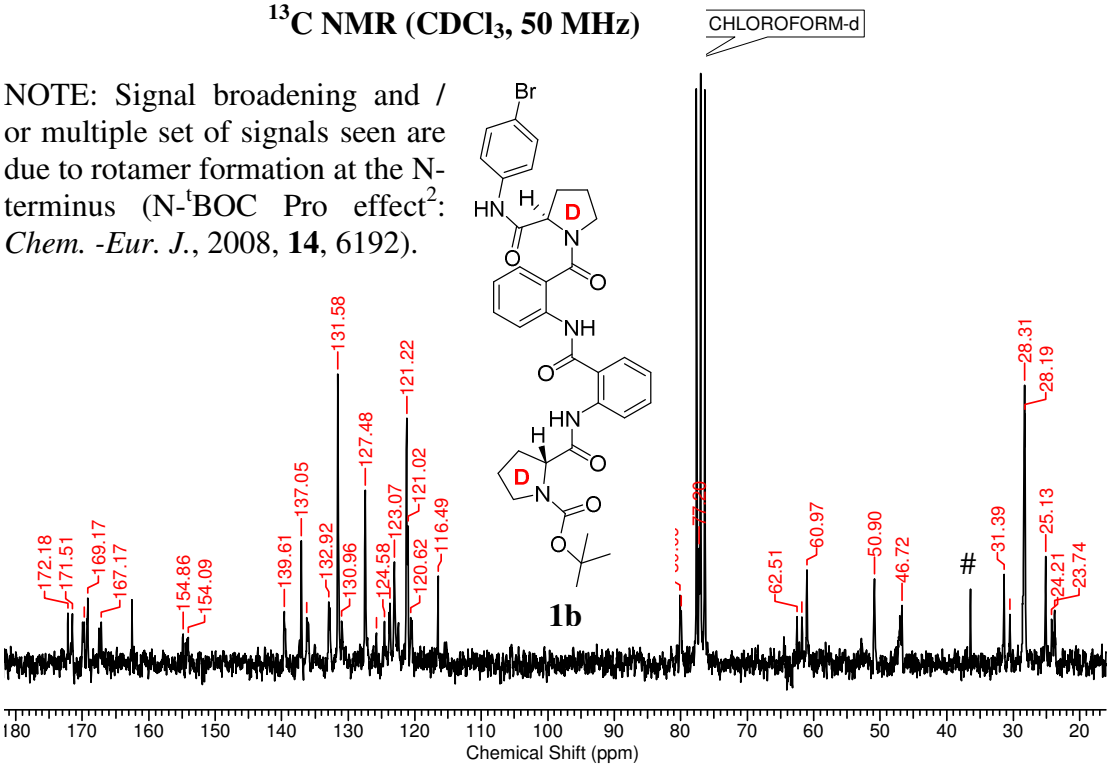
2d

DEPT-135 ($CDCl_3$, 50 MHz)



2d

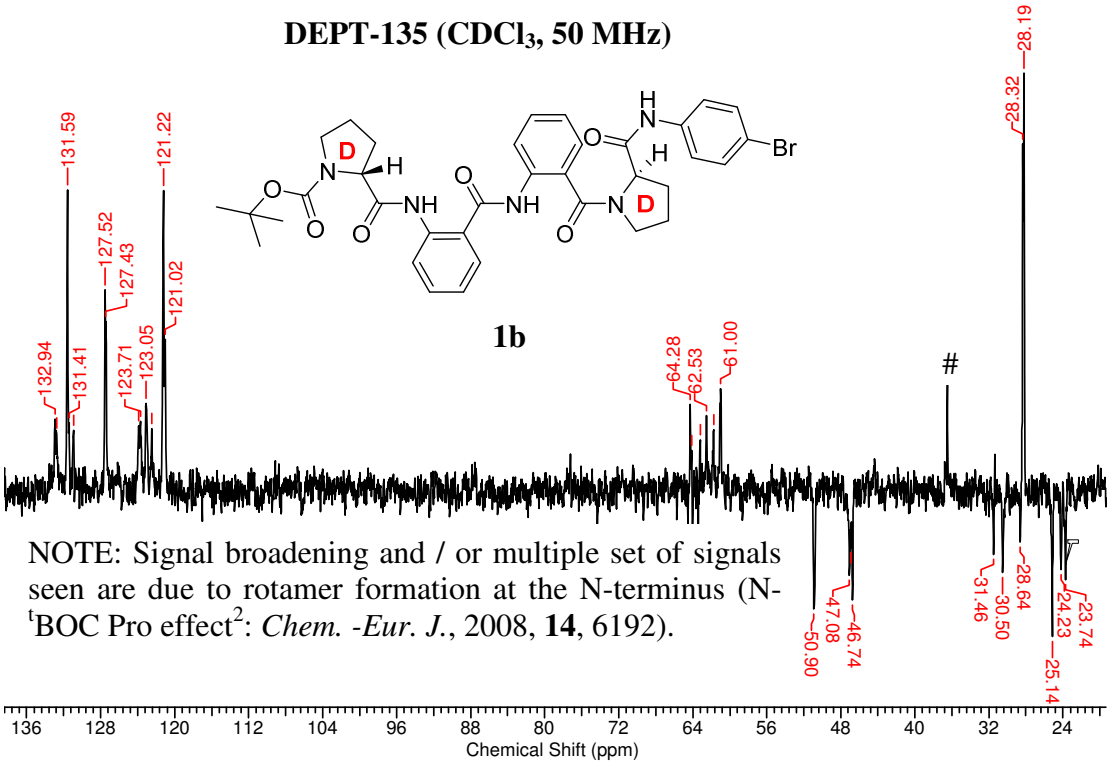
^{13}C NMR ($CDCl_3$, 50 MHz)



NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

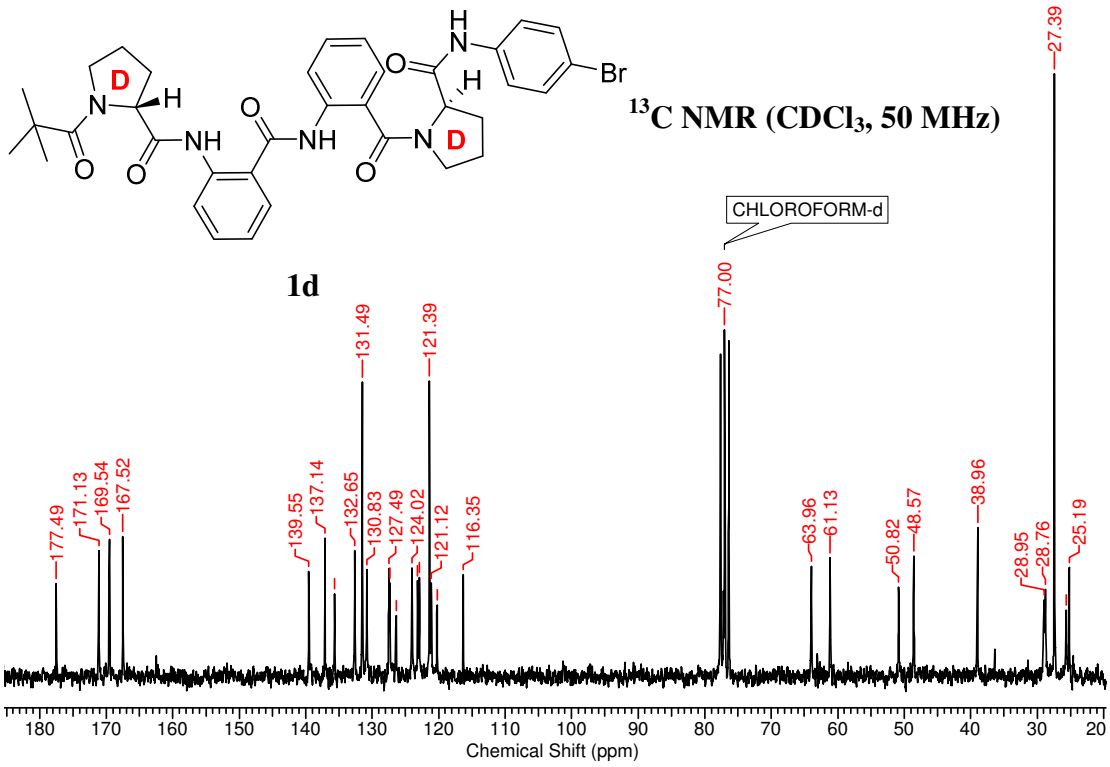
 # DMF

DEPT-135 ($CDCl_3$, 50 MHz)



NOTE: Signal broadening and / or multiple set of signals seen are due to rotamer formation at the N-terminus (N-^{t}BOC Pro effect[2]: *Chem. -Eur. J.*, 2008, **14**, 6192).

DMF



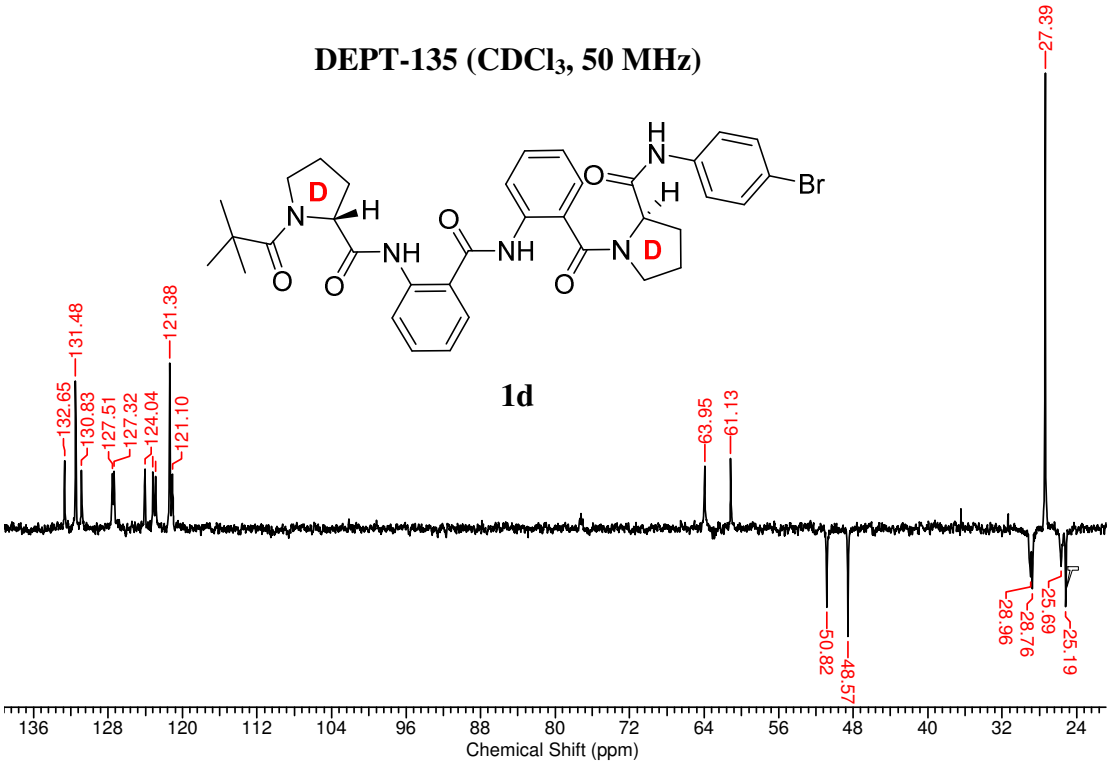
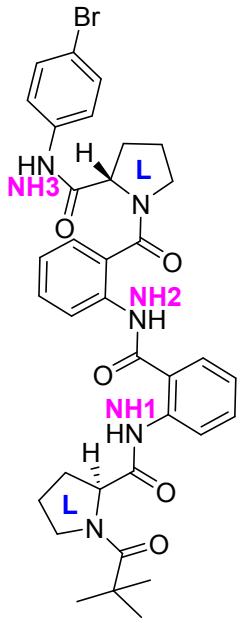


Table S1. NMR titration study of tetrapeptide 1c in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d6 (volume of DMSO-d6 added at each addition = 5 µl)

Volume of DMSO-d6 added (in µL)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
0	11.19	10.21	9.13
5	11.17	10.25	9.28
10	11.14	10.27	9.39
15	11.12	10.27	9.47
20	11.11	10.27	9.52
25	11.09	10.26	9.56
30	11.07	10.25	9.59
35	11.06	10.23	9.61
40	11.04	10.21	9.63
45	11.02	10.20	9.64
50	11.00	10.18	9.64



1c

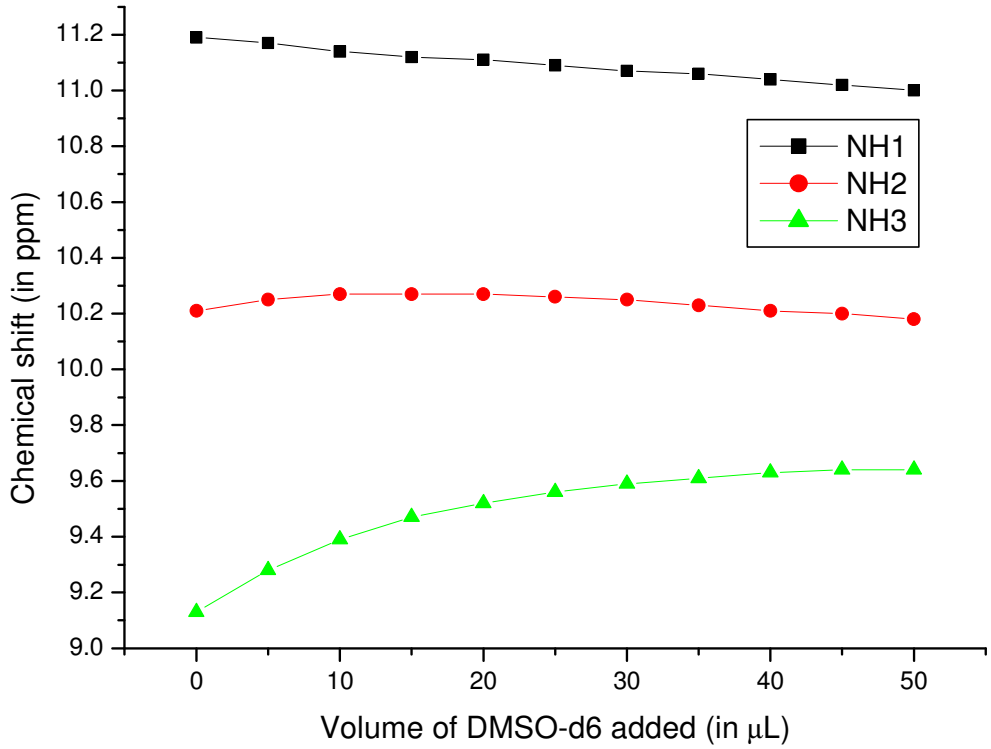
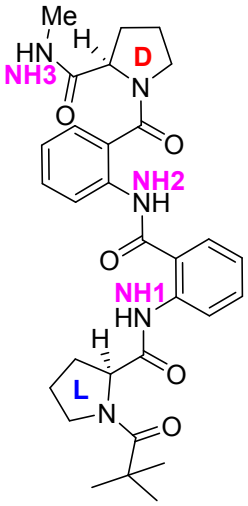


Table S2. NMR titration study of tetrapeptide 9c in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d6 (volume of DMSO-d6 added at each addition = 5 µl)

Volume of DMSO-d6 added (in µL)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
0	10.59	10.22	6.80
5	10.63	10.24	6.86
10	10.66	10.26	6.91
15	10.68	10.26	6.95
20	10.69	10.27	7.00
25	10.70	10.26	7.02
30	10.70	10.26	7.04
35	10.69	10.25	7.07
40	10.69	10.24	7.09
45	10.68	10.23	7.10
50	10.67	10.22	7.12



9c

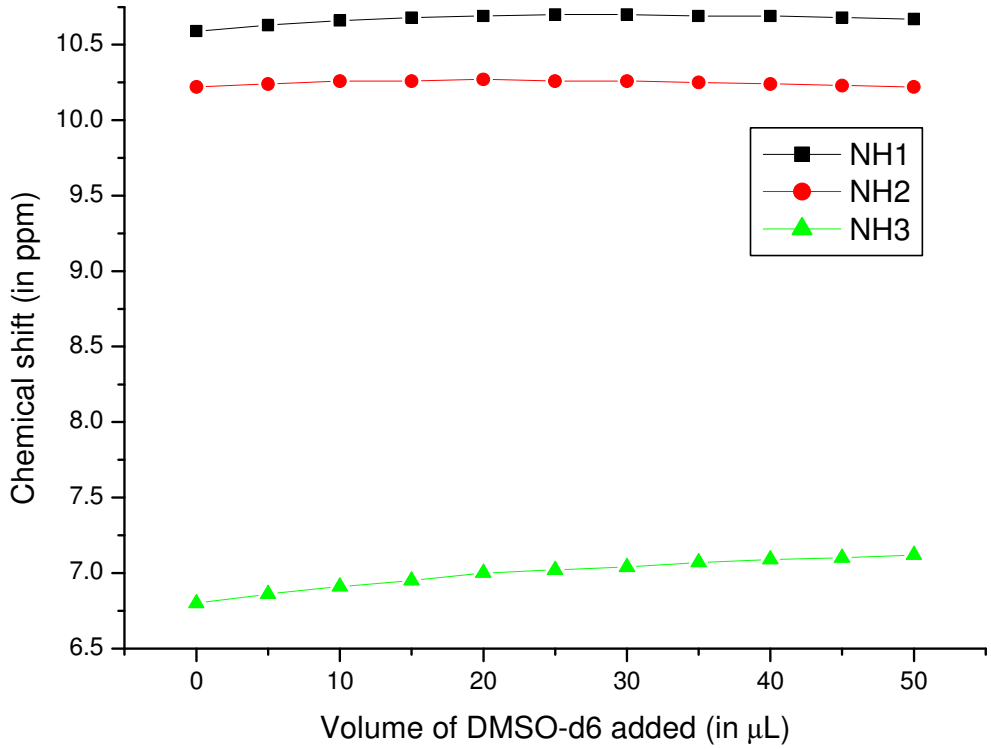
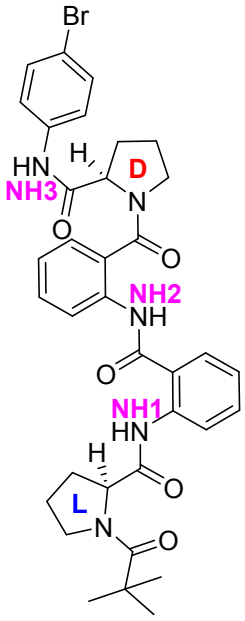


Table S3. NMR titration study of tetrapeptide 2c in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d6 (volume of DMSO-d6 added at each addition = 5 µl)

Volume of DMSO-d6 added (in µL)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
0	10.82	10.14	9.02
5	10.88	10.21	9.19
10	10.92	10.25	9.32
15	10.94	10.26	9.43
20	10.94	10.26	9.49
25	10.94	10.25	9.54
30	10.93	10.24	9.57
35	10.92	10.23	9.58
40	10.91	10.21	9.60
45	10.90	10.20	9.61
50	10.88	10.18	9.62



2c

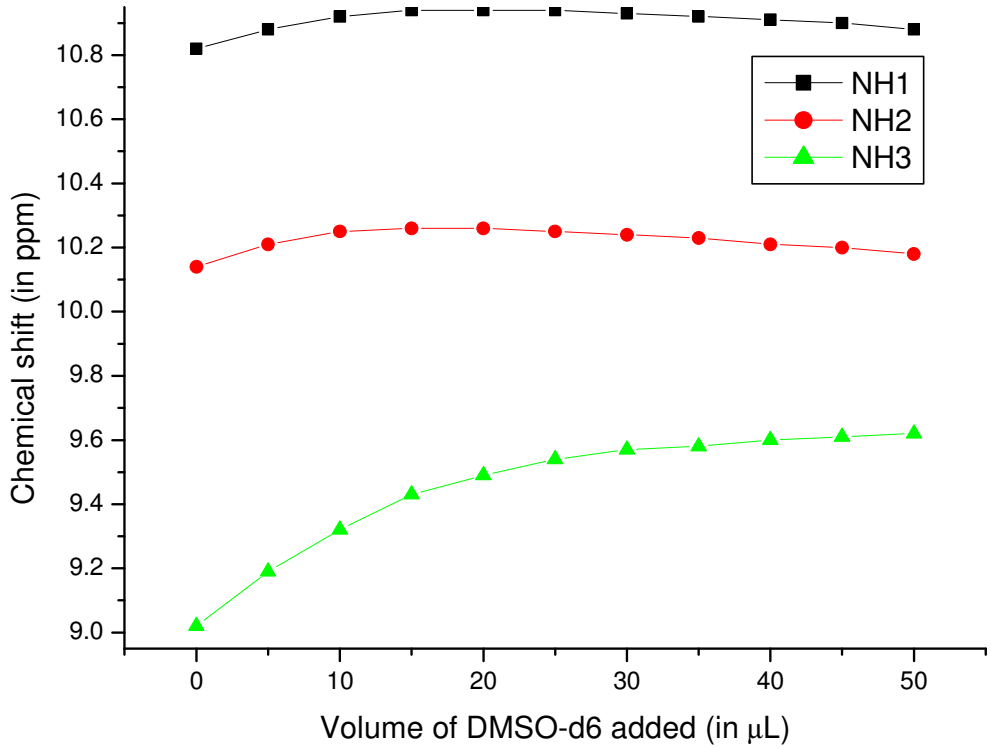
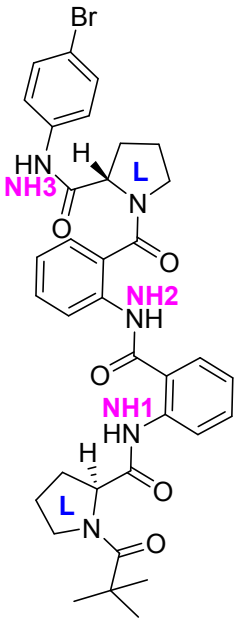


Table S4. NMR dilution study of tetrapeptide 1c in $CDCl_3$, 400 MHz (Concentration from 120 to 2 mmol)

Concentration (in ppm)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
120	11.27	10.20	9.44
100	11.25	10.19	9.41
80	11.25	10.20	9.37
60	11.24	10.20	9.32
40	11.22	10.21	9.27
20	11.20	10.21	9.15
10	11.17	10.21	9.06
5	11.15	10.22	9.00
4	11.15	10.21	8.98
2	11.14	10.21	8.93



1c

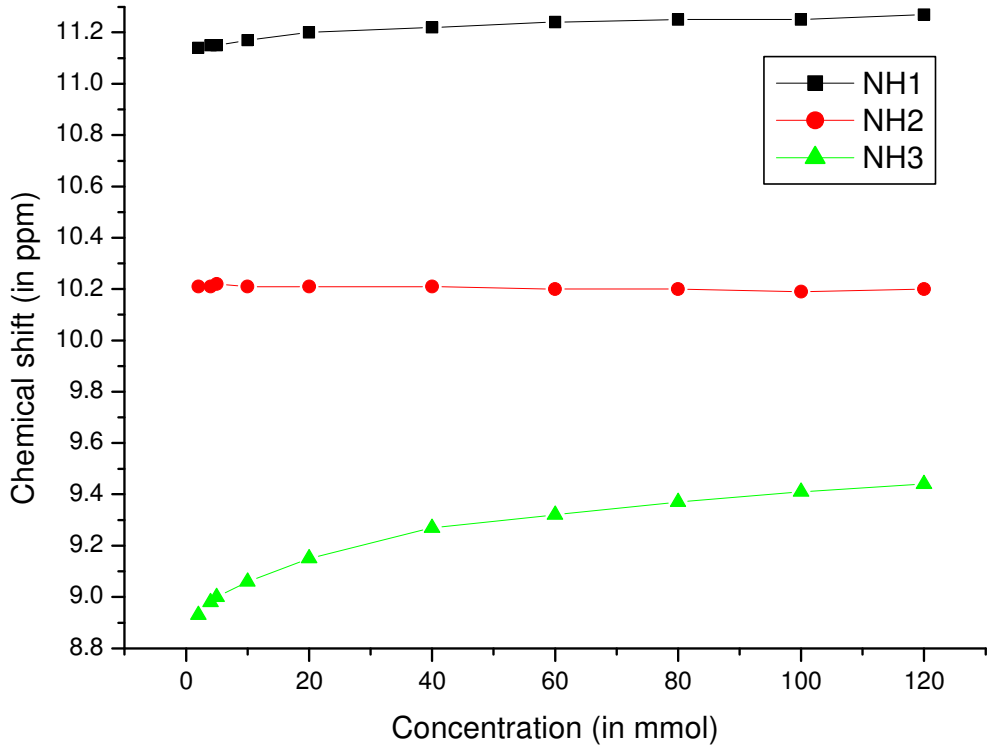
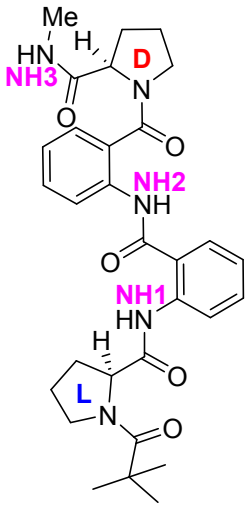


Table S5. NMR dilution study of tetrapeptide 9c in $CDCl_3$, 400 MHz (Concentration from 120 to 2 mmol)

Concentration (in ppm)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
120	10.60	10.27	6.95
100	10.59	10.27	6.93
80	10.59	10.26	6.90
60	10.58	10.26	6.88
40	10.57	10.24	6.85
20	10.57	10.23	6.82
10	10.58	10.22	6.80
5	10.58	10.22	6.78
4	10.58	10.21	6.77
2	10.58	10.21	6.77



9c

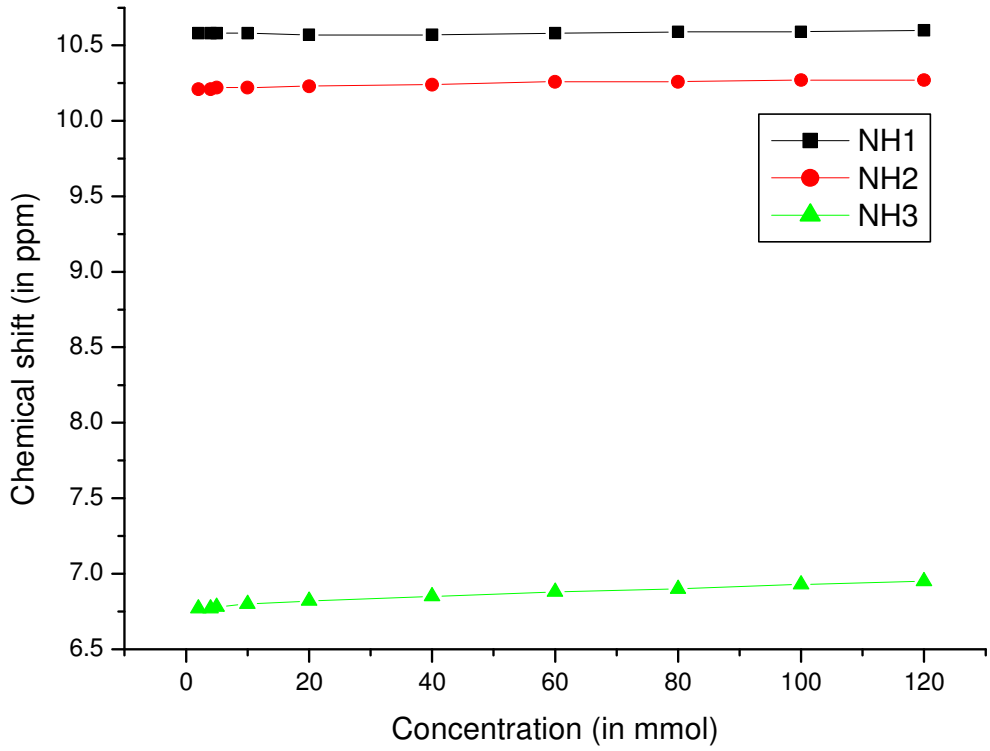
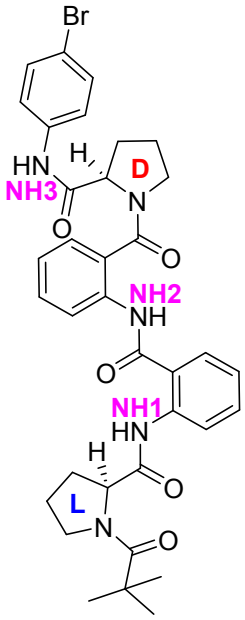


Table S6. NMR dilution study of tetrapeptide 2c in $CDCl_3$, 400 MHz (Concentration from 120 to 2 mmol)

Concentration (in ppm)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
120	10.80	10.16	9.30
100	10.78	10.13	9.24
80	10.79	10.15	9.23
60	10.78	10.14	9.17
40	10.79	10.14	9.10
20	10.81	10.14	9.02
10	10.84	10.15	8.94
5	10.86	10.15	8.90
4	10.86	10.15	8.89
2	10.88	10.15	8.86



2c

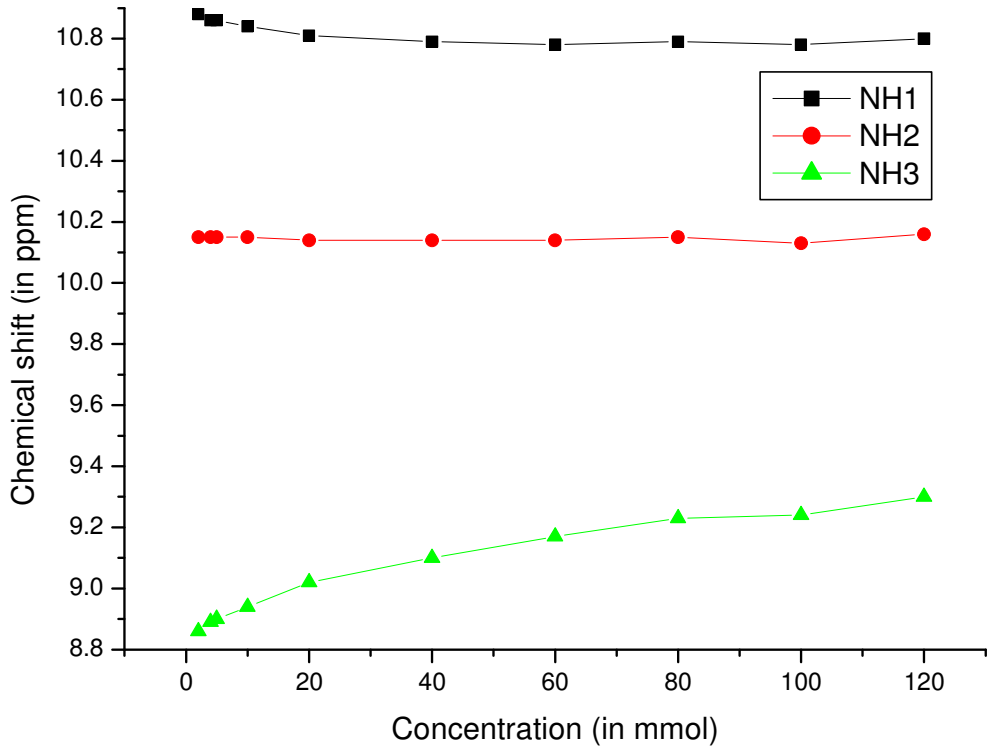
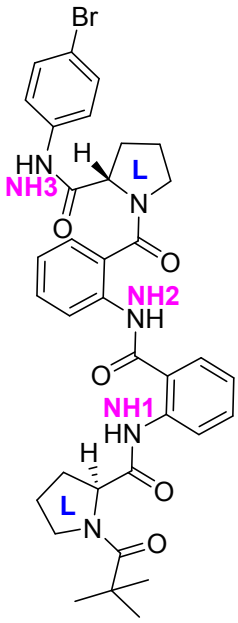


Table S7. Variable Temperature NMR study of tetrapeptide 1c (20 mmol, 400 MHz, $CDCl_3$)

Temperature (in K)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
268	11.25	10.29	9.39
273	11.24	10.27	9.34
278	11.23	10.27	9.29
283	11.22	10.25	9.25
288	11.21	10.23	9.20
293	11.19	10.21	9.15
298	11.17	10.19	9.10
303	11.16	10.16	9.07
308	11.14	10.14	9.04
313	11.12	10.11	9.00
318	11.10	10.09	8.97
323	11.08	10.06	8.94



1c

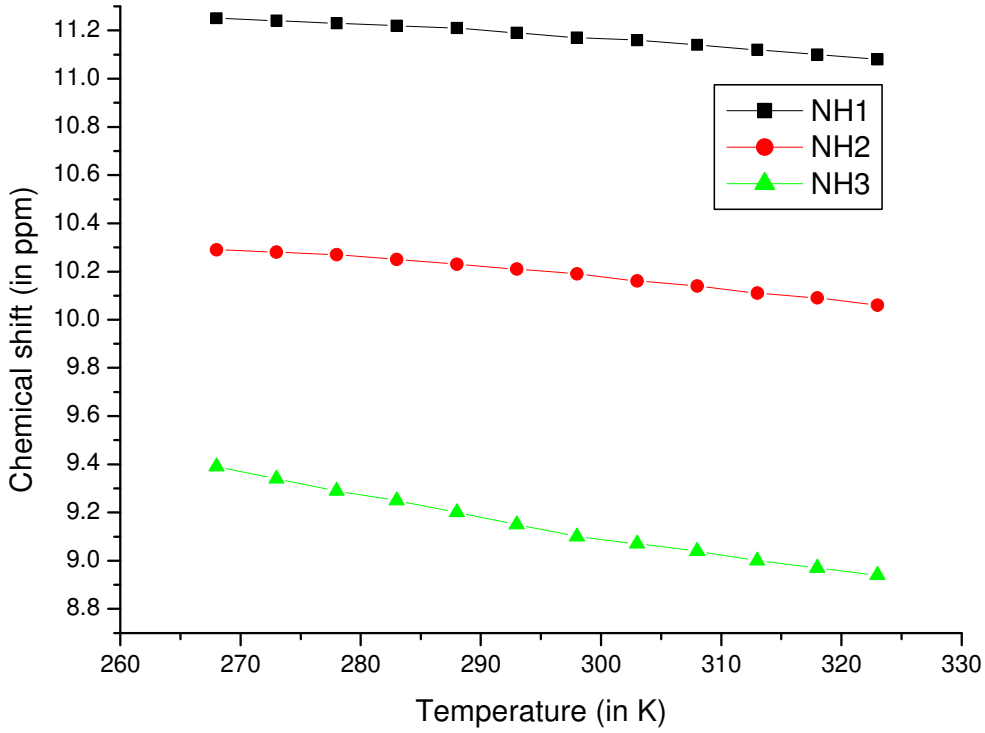
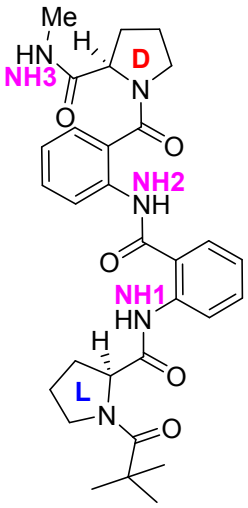


Table S8. Variable Temperature NMR study of tetrapeptide 9c (20 mmol, 400 MHz, $CDCl_3$)

Temperature (in K)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
268	10.39	10.31	6.94
273	10.43	10.29	6.91
278	10.46	10.28	6.88
283	10.50	10.26	6.85
288	10.53	10.24	6.82
293	10.57	10.22	6.79
298	10.59	10.21	6.78
303	10.63	10.20	6.75
308	10.65	10.18	6.73
313	10.67	10.16	6.71
318	10.69	10.15	6.68
323	10.71	10.13	6.66



9c

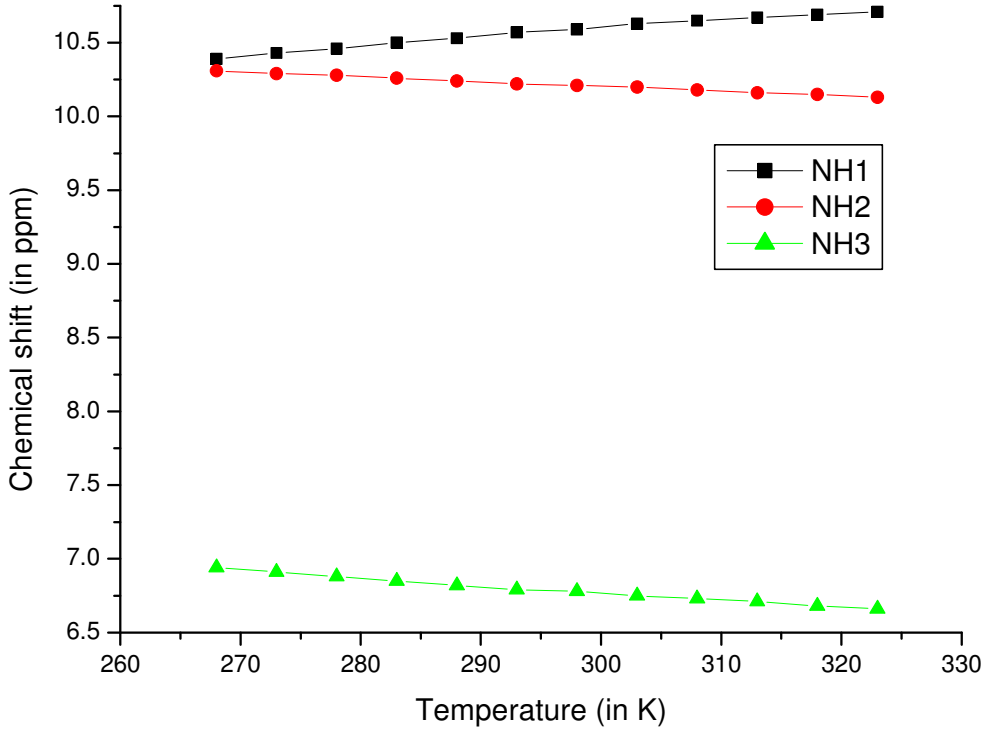
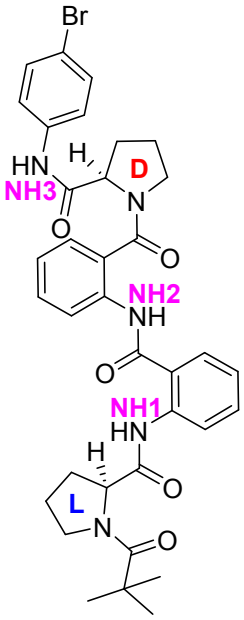
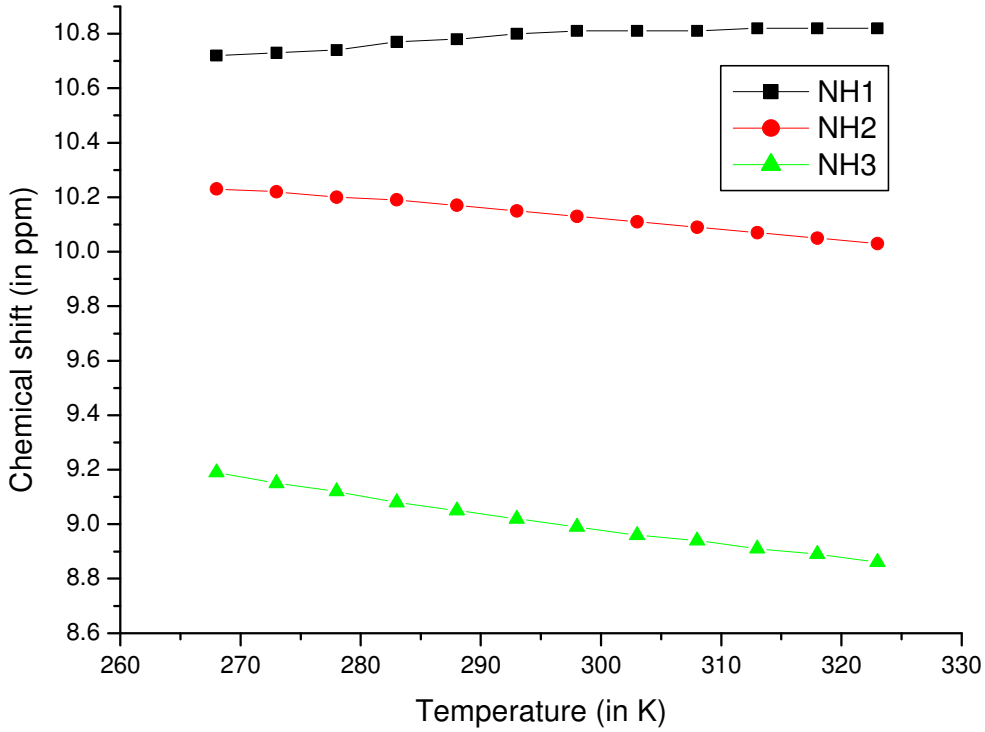


Table S9. Variable Temperature NMR study of tetrapeptide 2c (20 mmol, 400 MHz, $CDCl_3$)

Temperature (in K)	Chemical Shift (in ppm)		
	NH1	NH2	NH3
268	10.72	10.23	9.19
273	10.73	10.22	9.15
278	10.74	10.20	9.12
283	10.77	10.19	9.08
288	10.78	10.17	9.05
293	10.80	10.15	9.02
298	10.81	10.13	8.99
303	10.81	10.11	8.96
308	10.81	10.09	8.94
313	10.82	10.07	8.91
318	10.82	10.05	8.89
323	10.82	10.03	8.86



2c



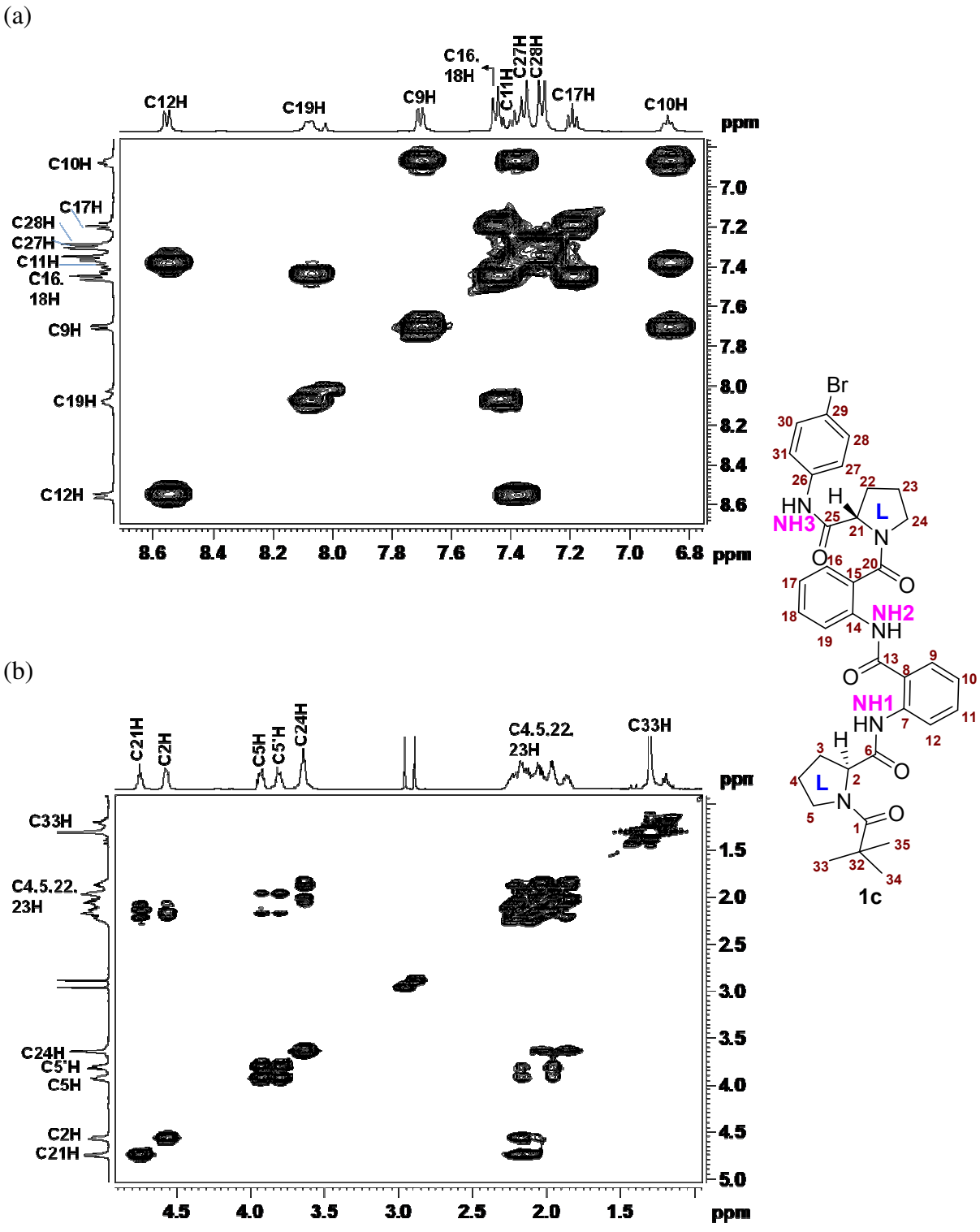


Fig. S1: 2D COSY NMR of 1c: Partial COSY spectra of 1c (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions

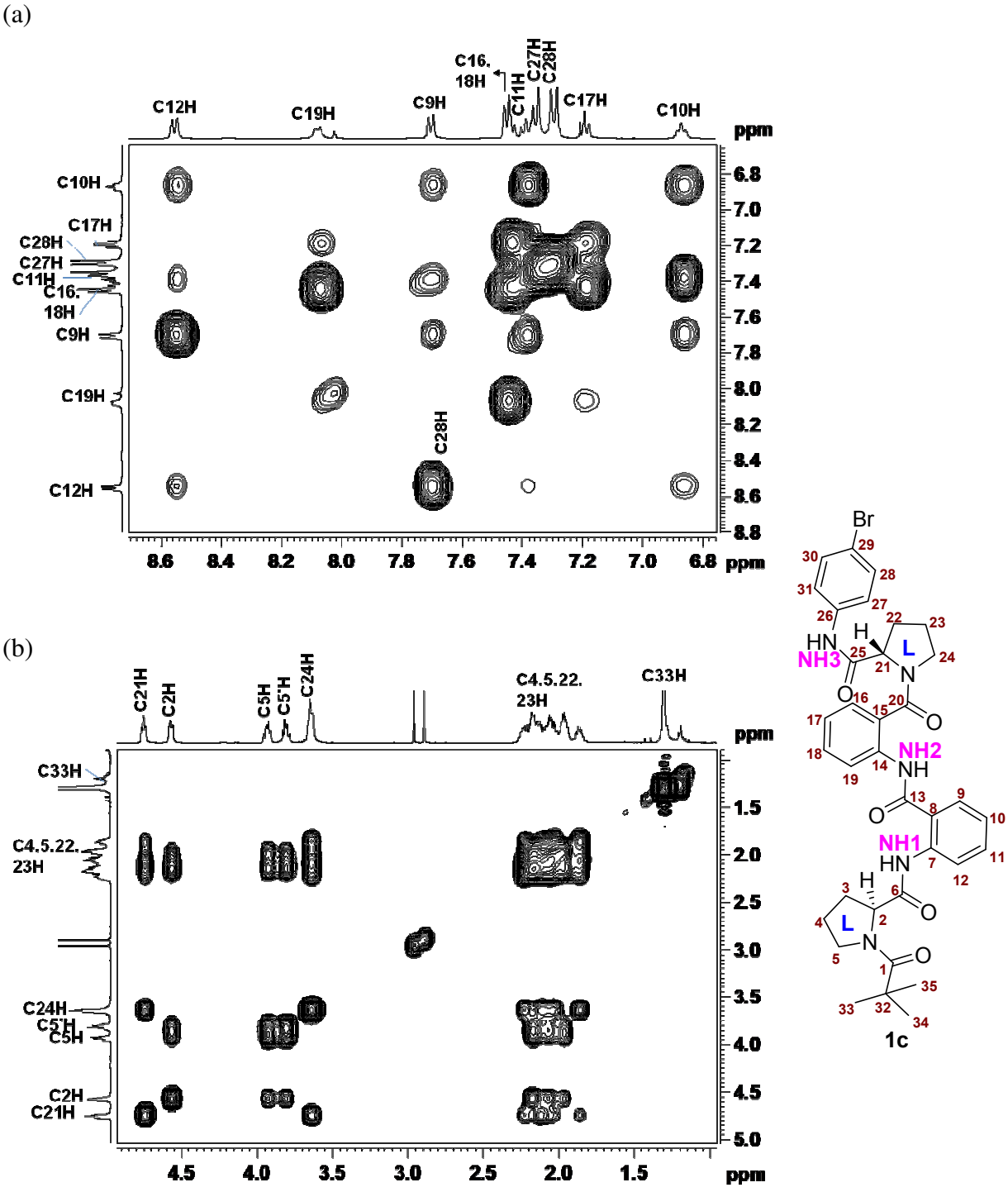


Fig. S2: 2D TOCSY NMR of 1c: Partial TOCSY spectra of 1c (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions

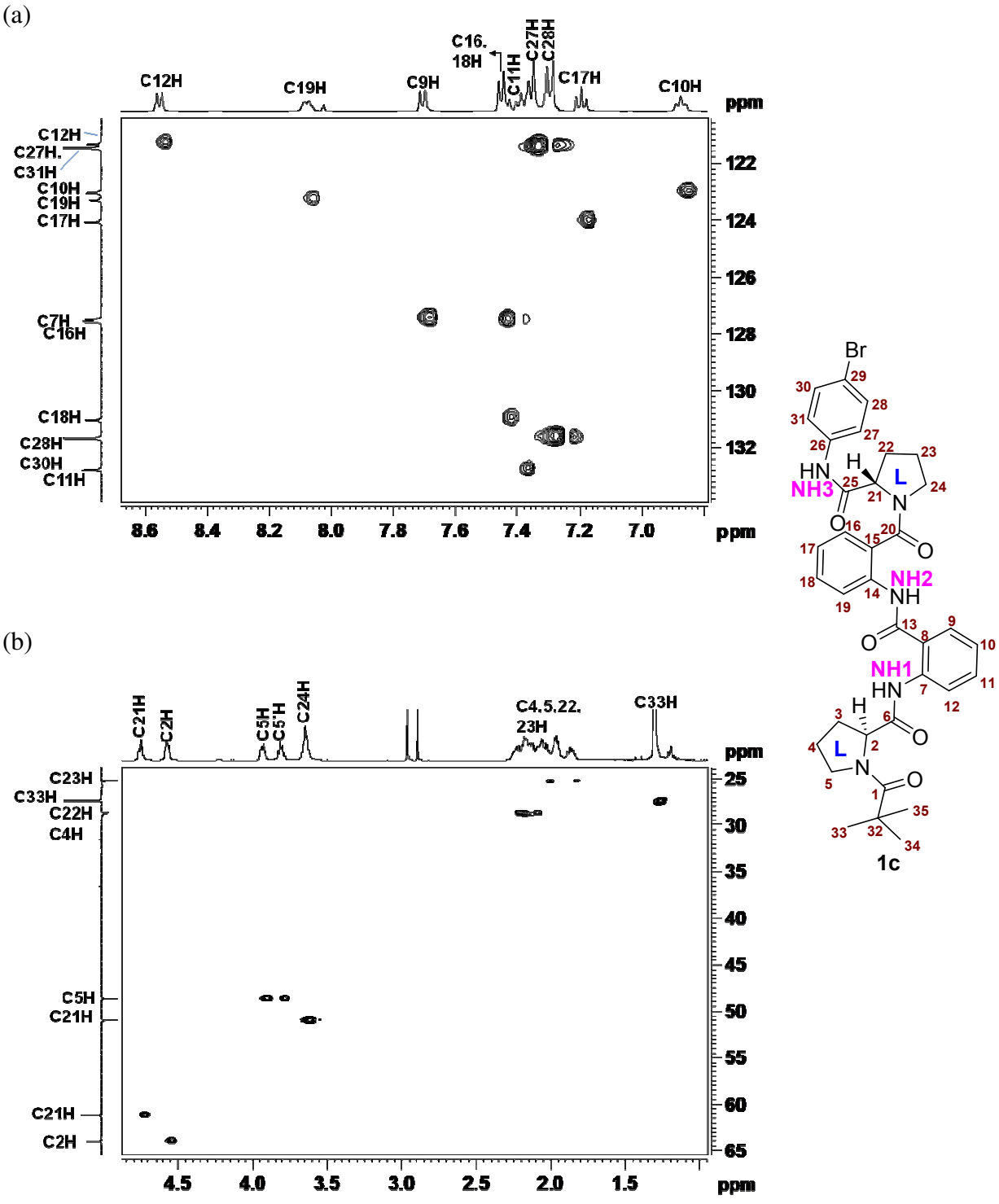


Fig. S3: 2D HSQC NMR of 1c: Partial HSQC spectra of 1c (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions

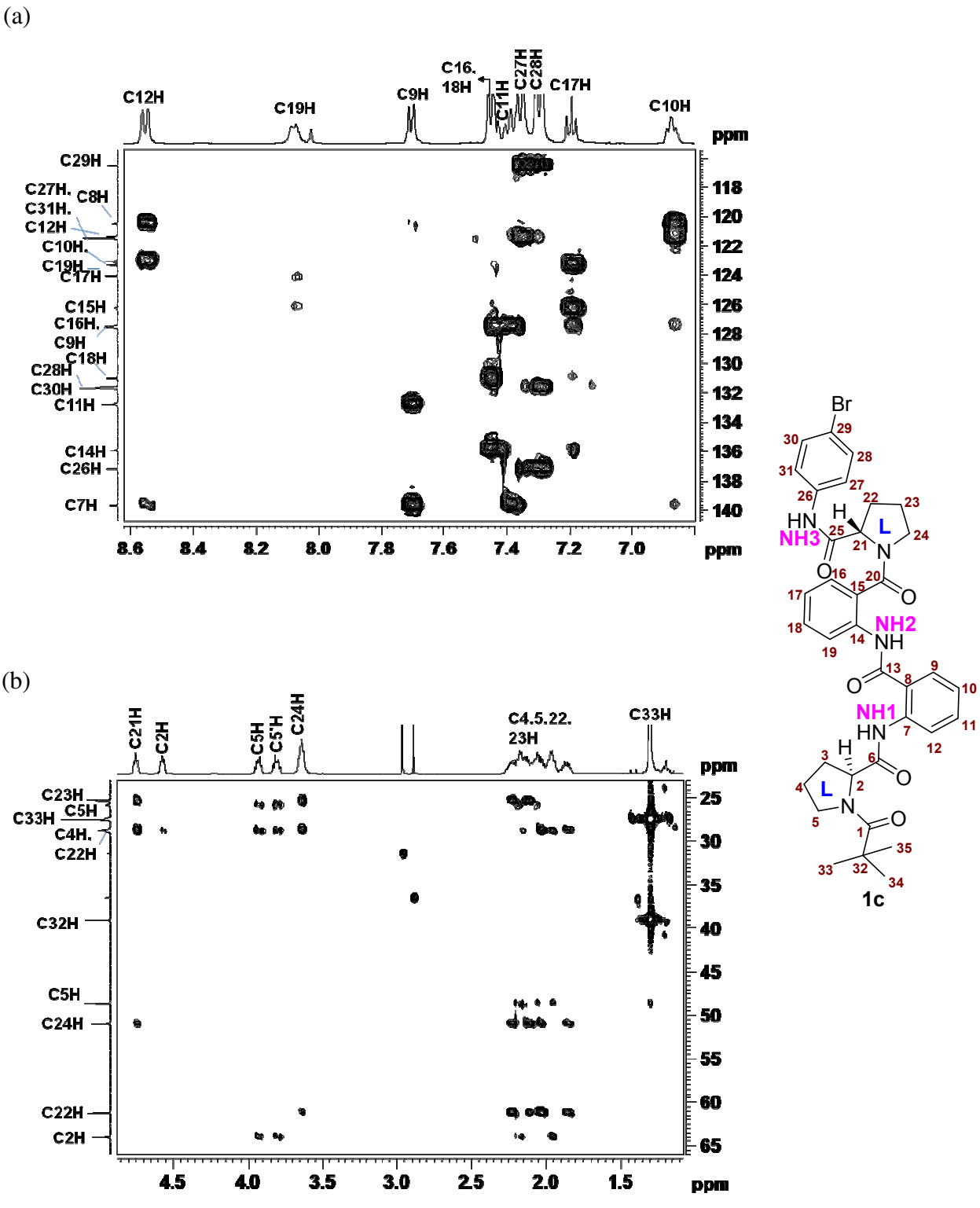


Fig. S4: 2D HMBC NMR of 1c: Partial HMBC spectra of 1c (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions

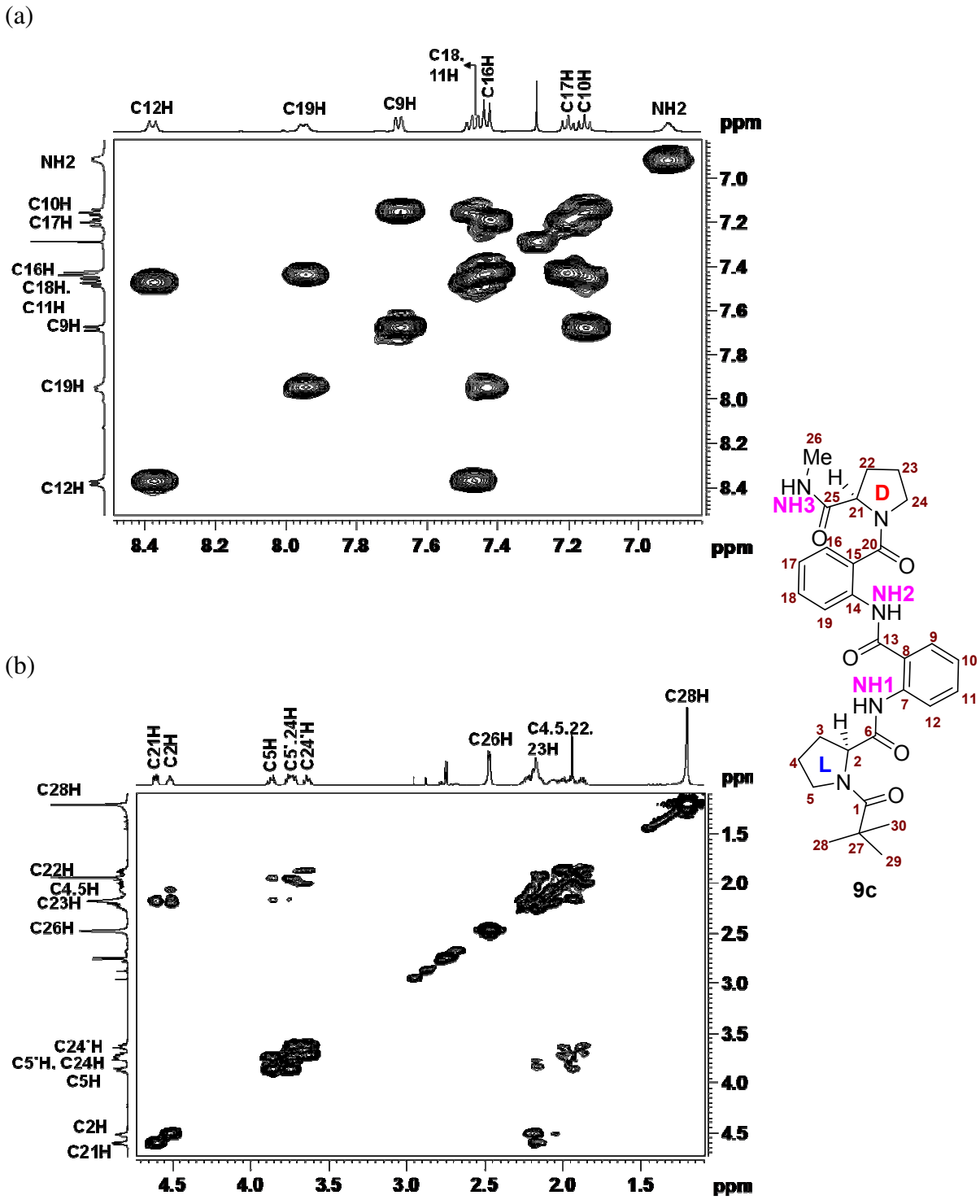


Fig. S5: 2D COSY NMR of 9c: Partial COSY spectra of 9c (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions

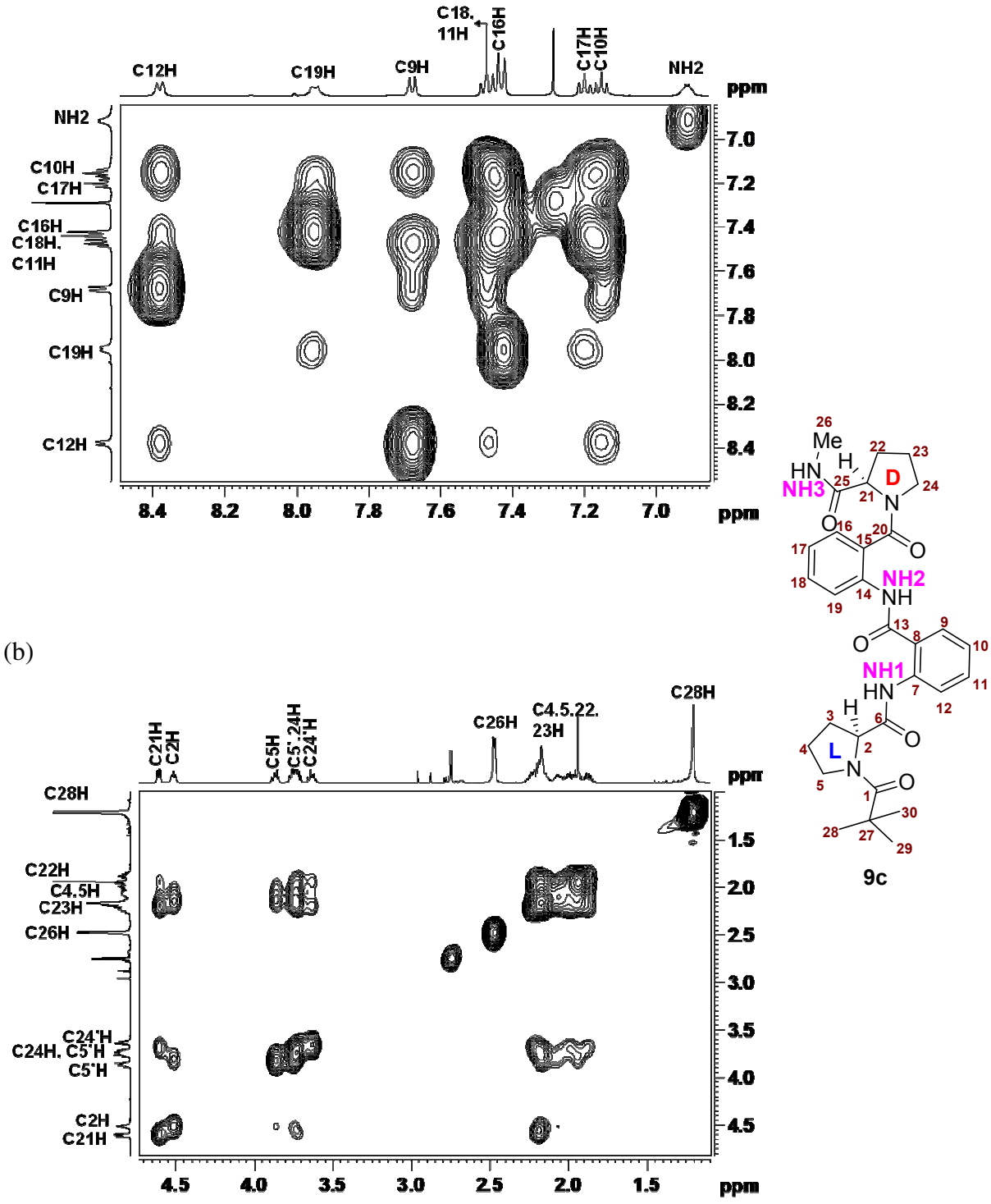


Fig. S6: 2D TOCSY NMR of 9c: Partial TOCSY spectra of 9c (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions

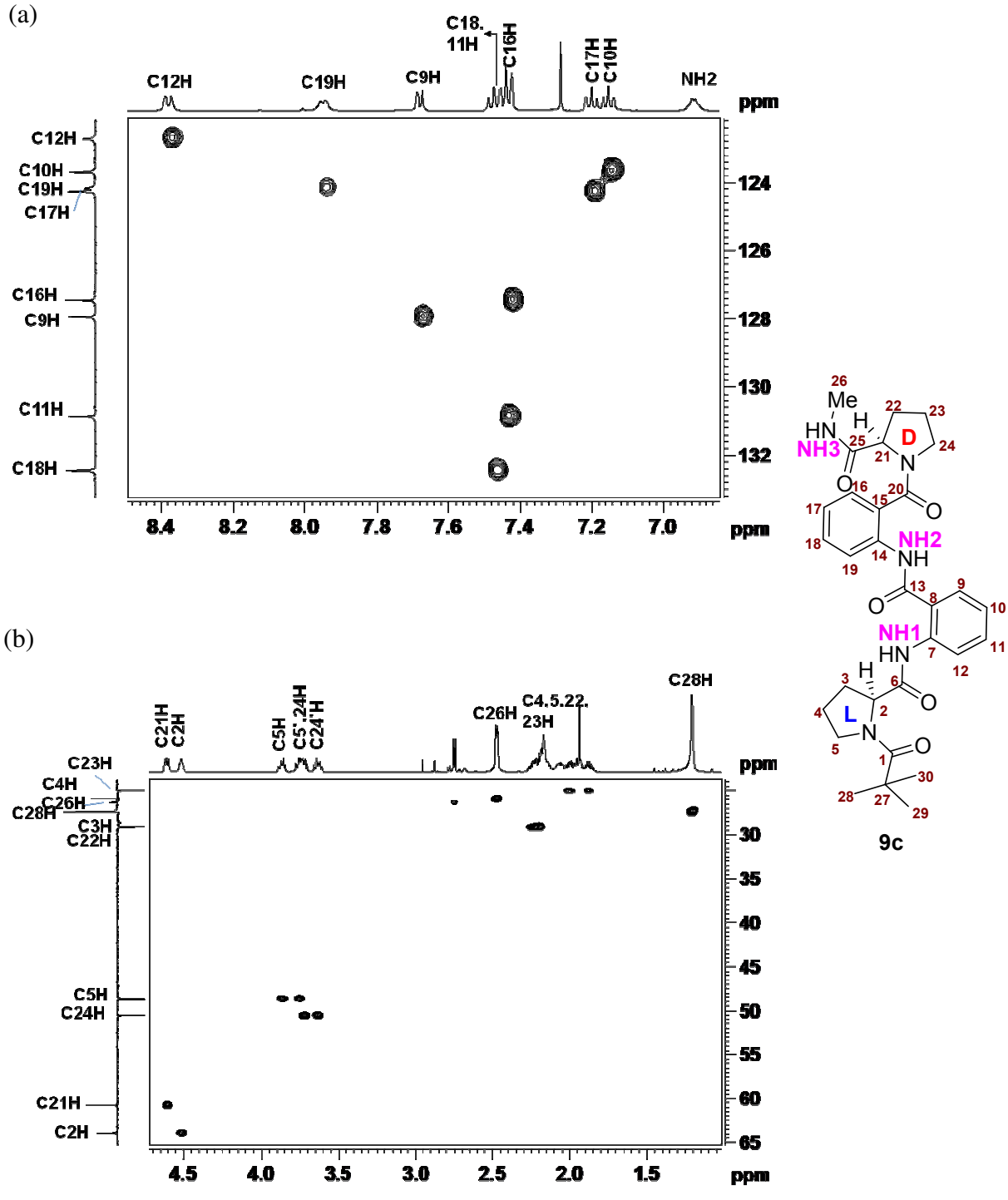


Fig. S7: 2D HSQC NMR of 9c: Partial HSQC spectra of 9c (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions

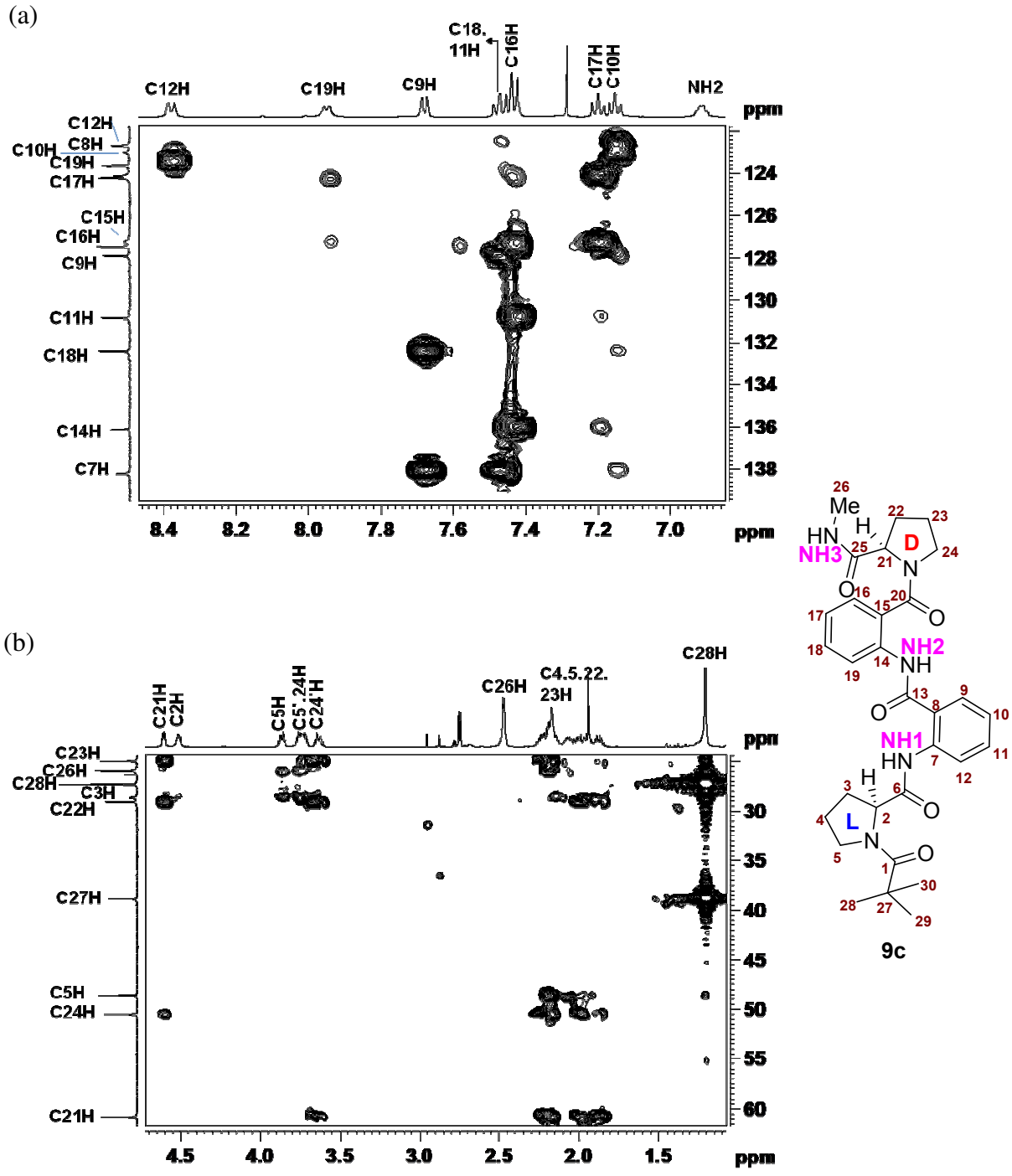


Fig. S8: 2D HMBC of 9c: Partial HMBC spectra of 9c (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions

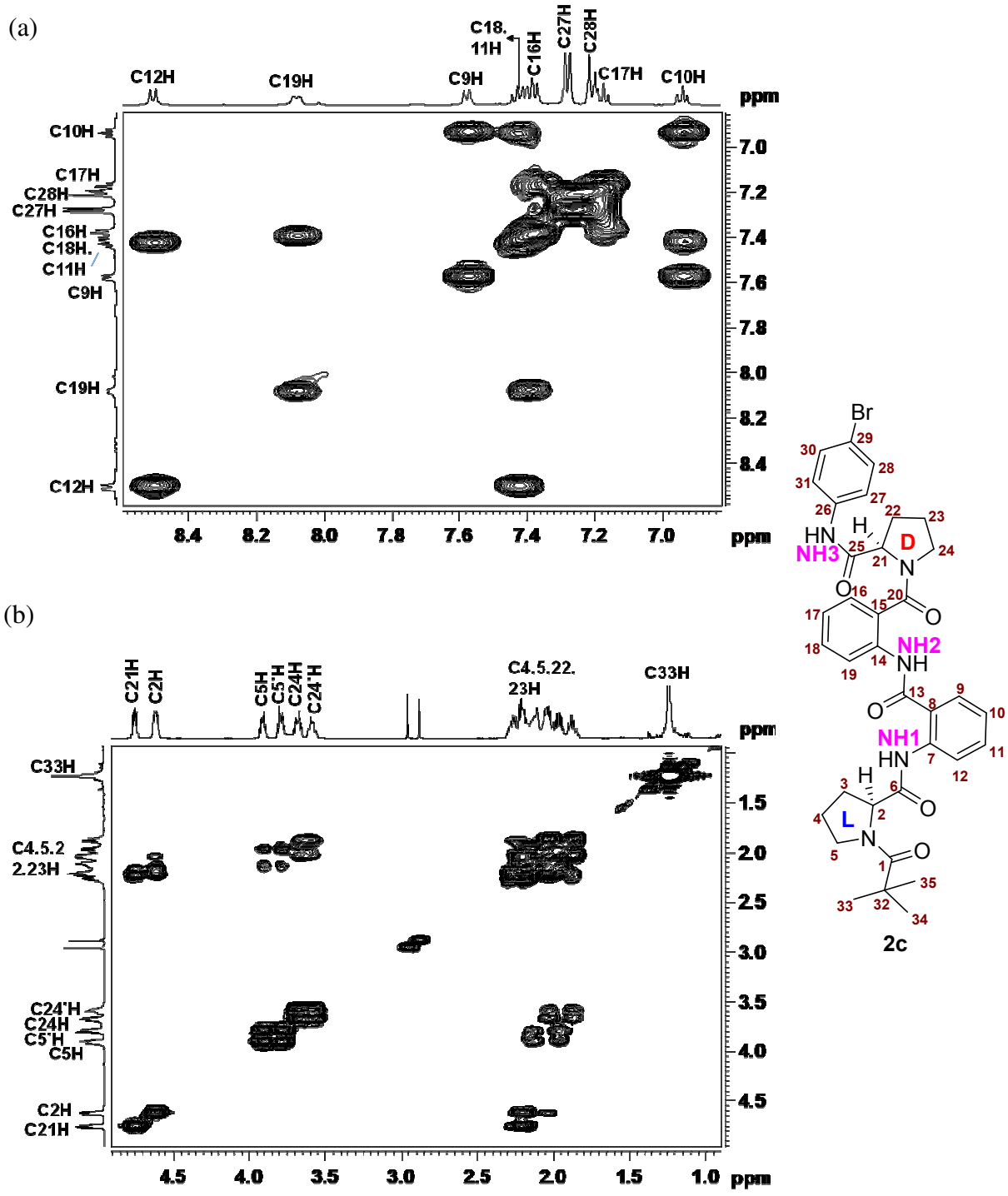


Fig. S9: 2D COSY of 2c: Partial COSY spectra of 2c (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions

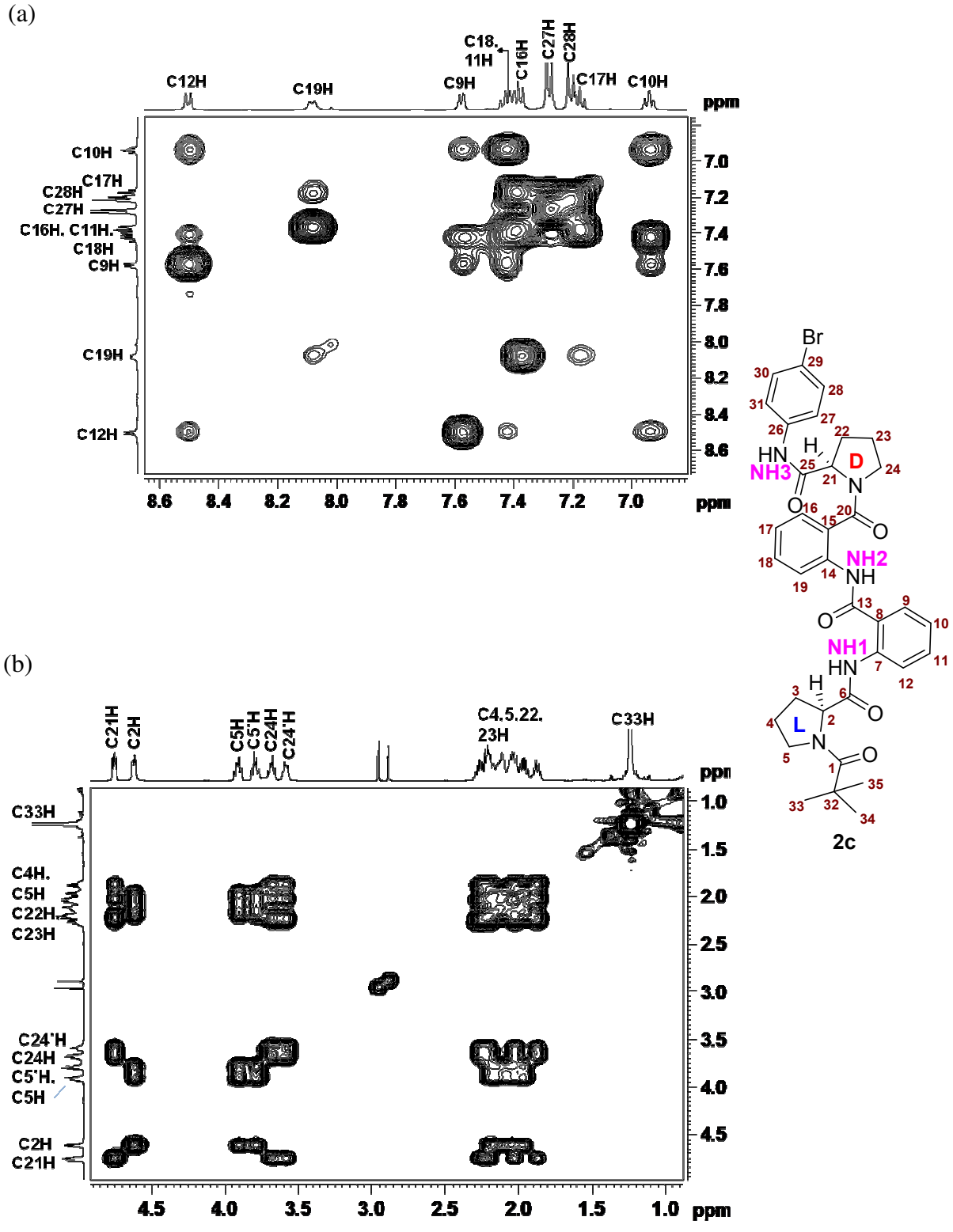


Fig. S10: 2D TOCSY of 2c: Partial TOCSY spectra of 2c (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions

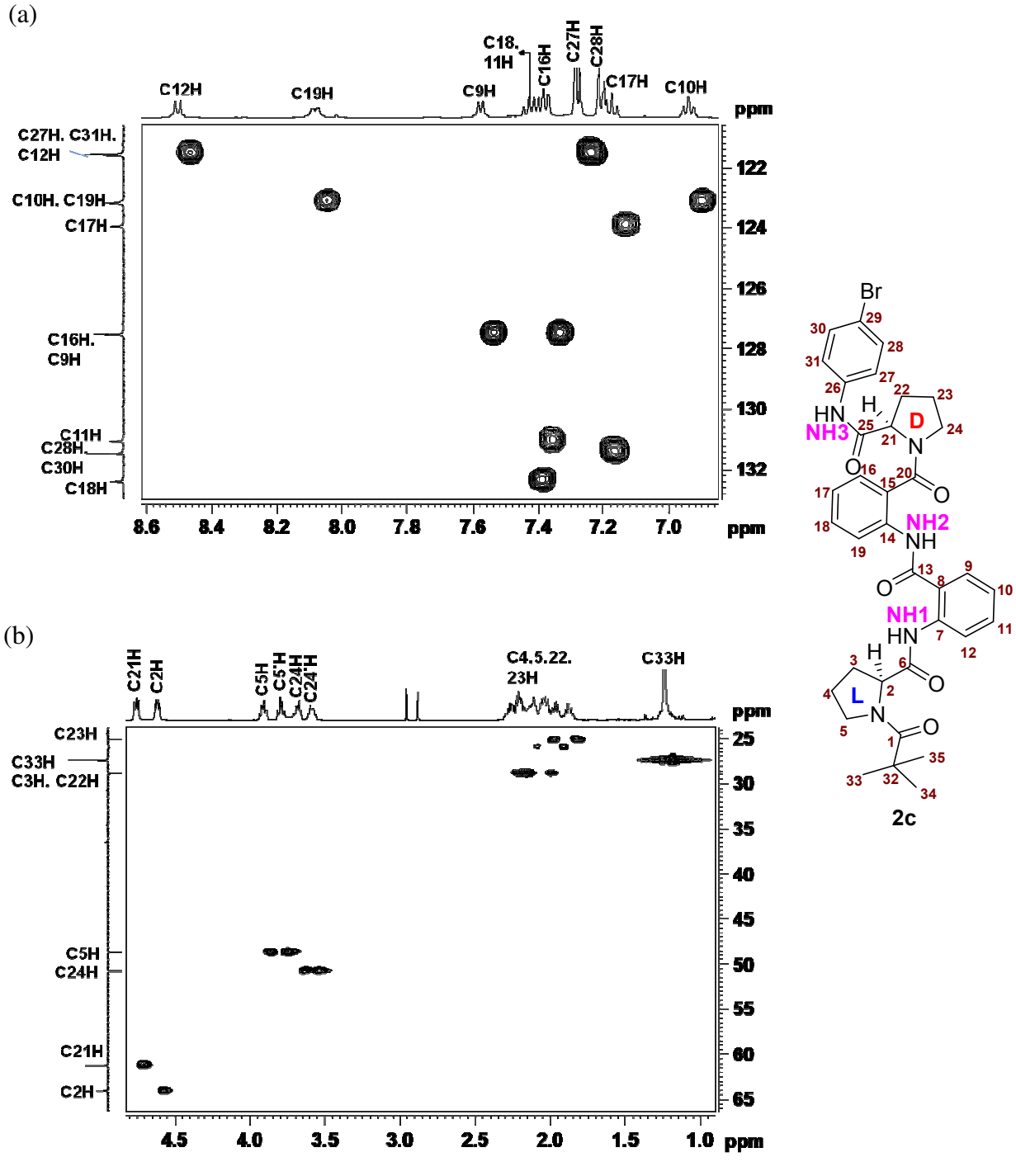


Fig. S11: 2D HSQC of 2c: Partial HSQC spectra of 2c (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions

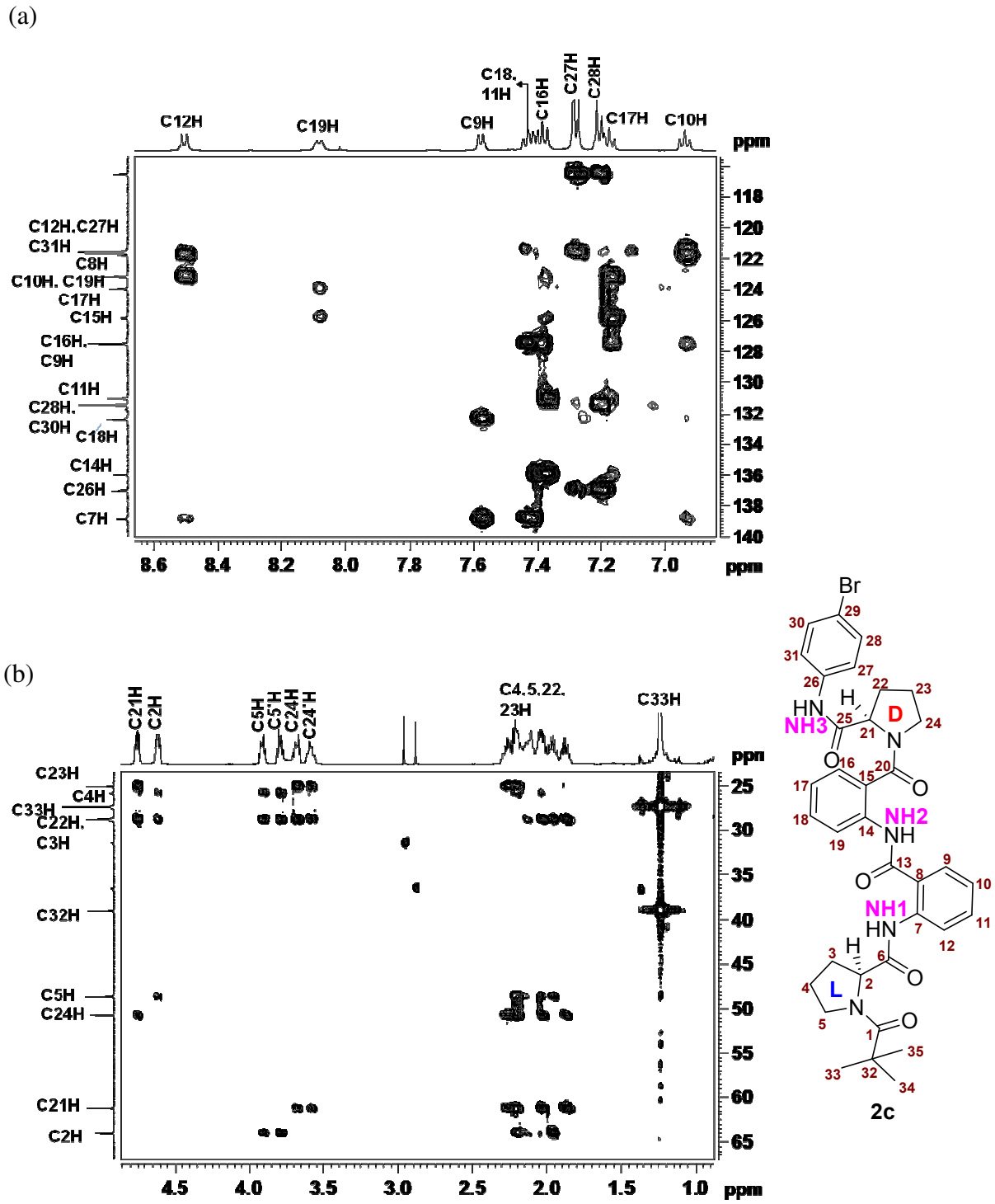


Fig. S12: 2D HMBC of 2c: Partial HMBC spectra of 2c (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions

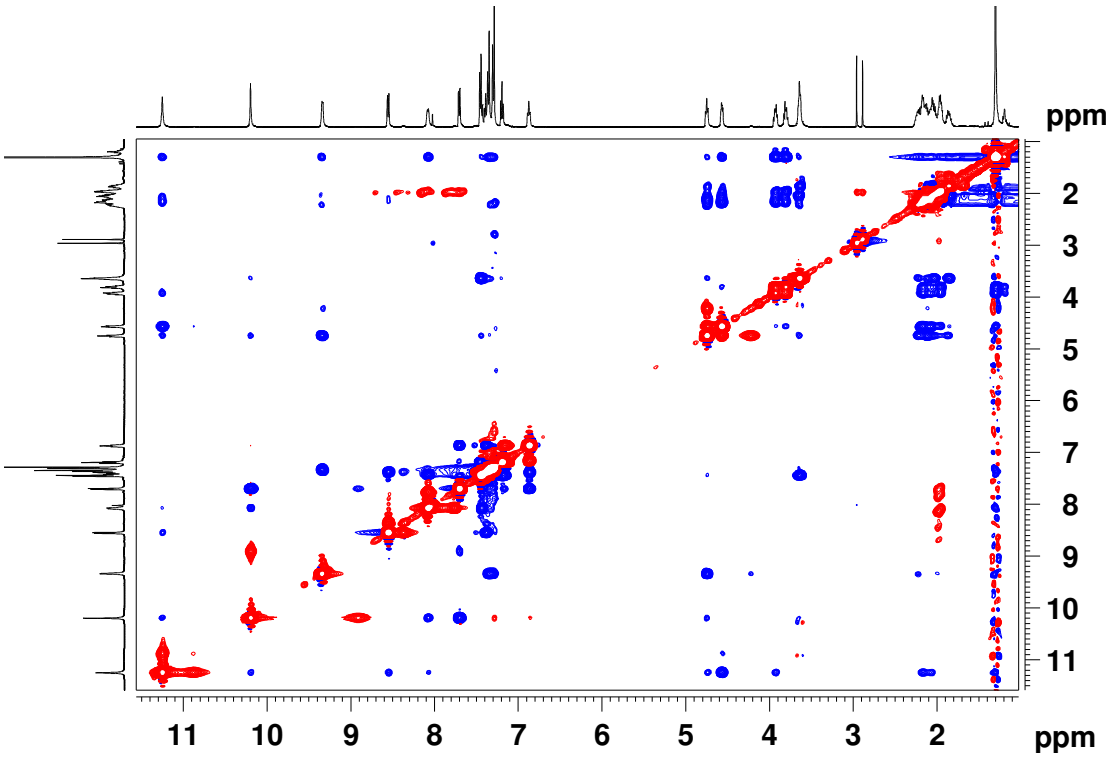


Fig. S13: 2D NOESY full spectra of 1c (500 MHz, $CDCl_3$)

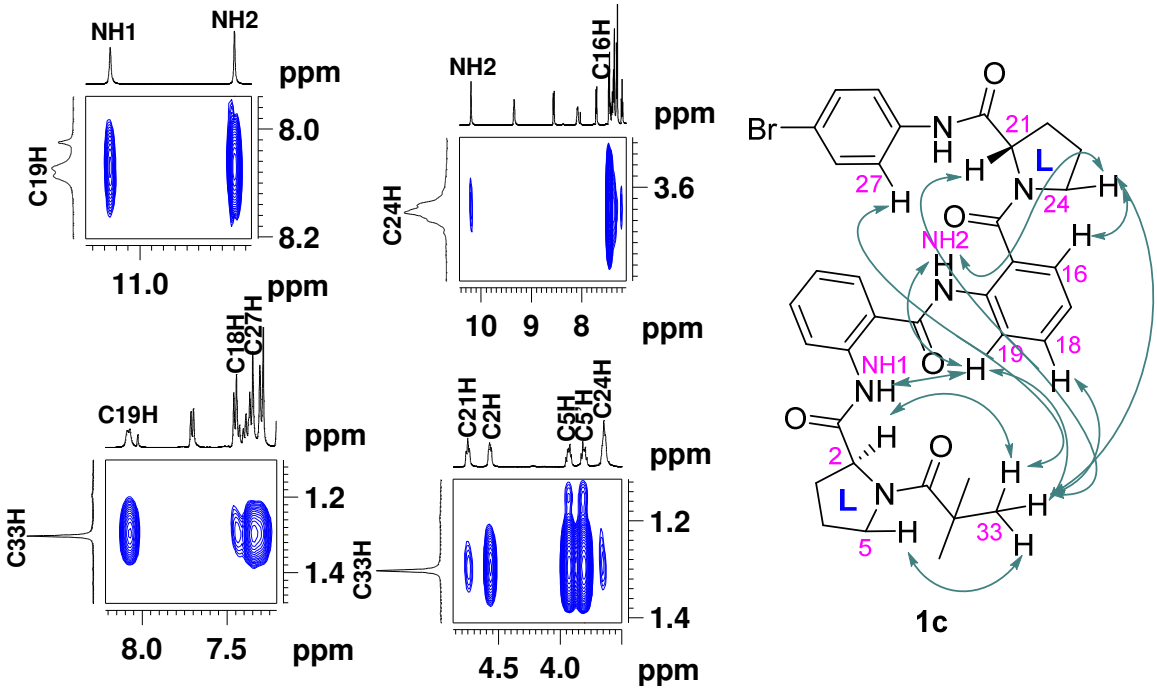


Fig. S14: 2D NOESY excerpts of 1c (500 MHz, $CDCl_3$)

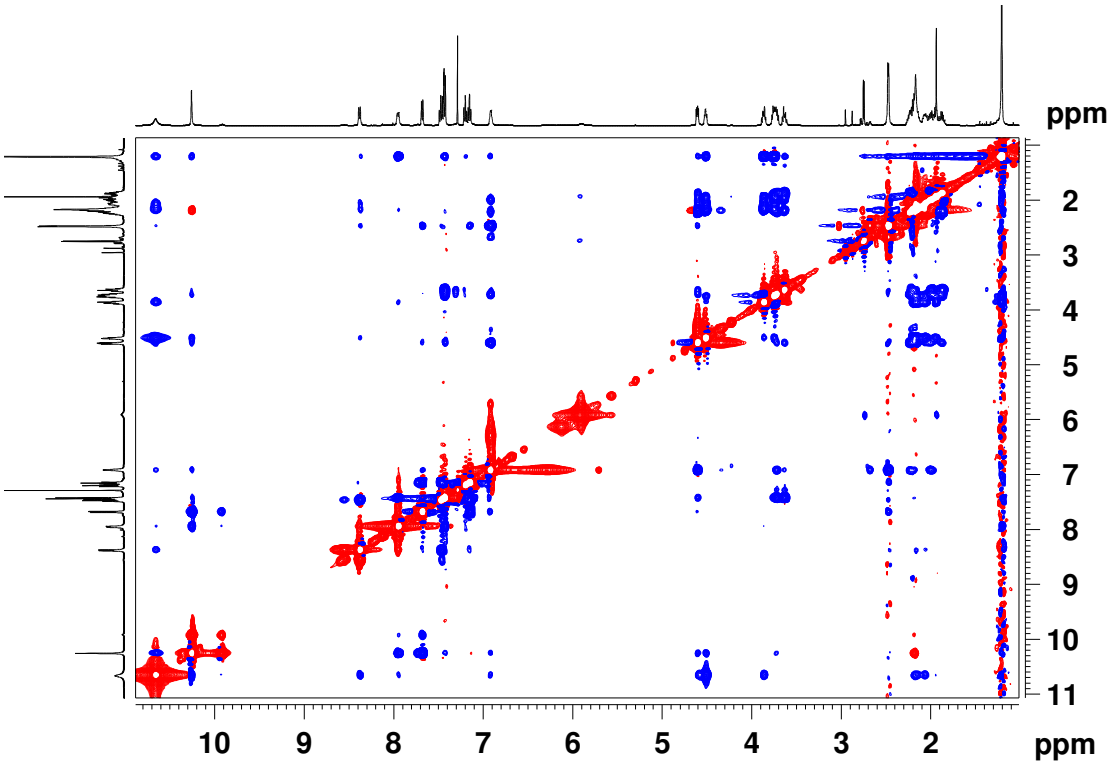


Fig. S15: 2D NOESY full spectra of 9c (500 MHz, $CDCl_3$)

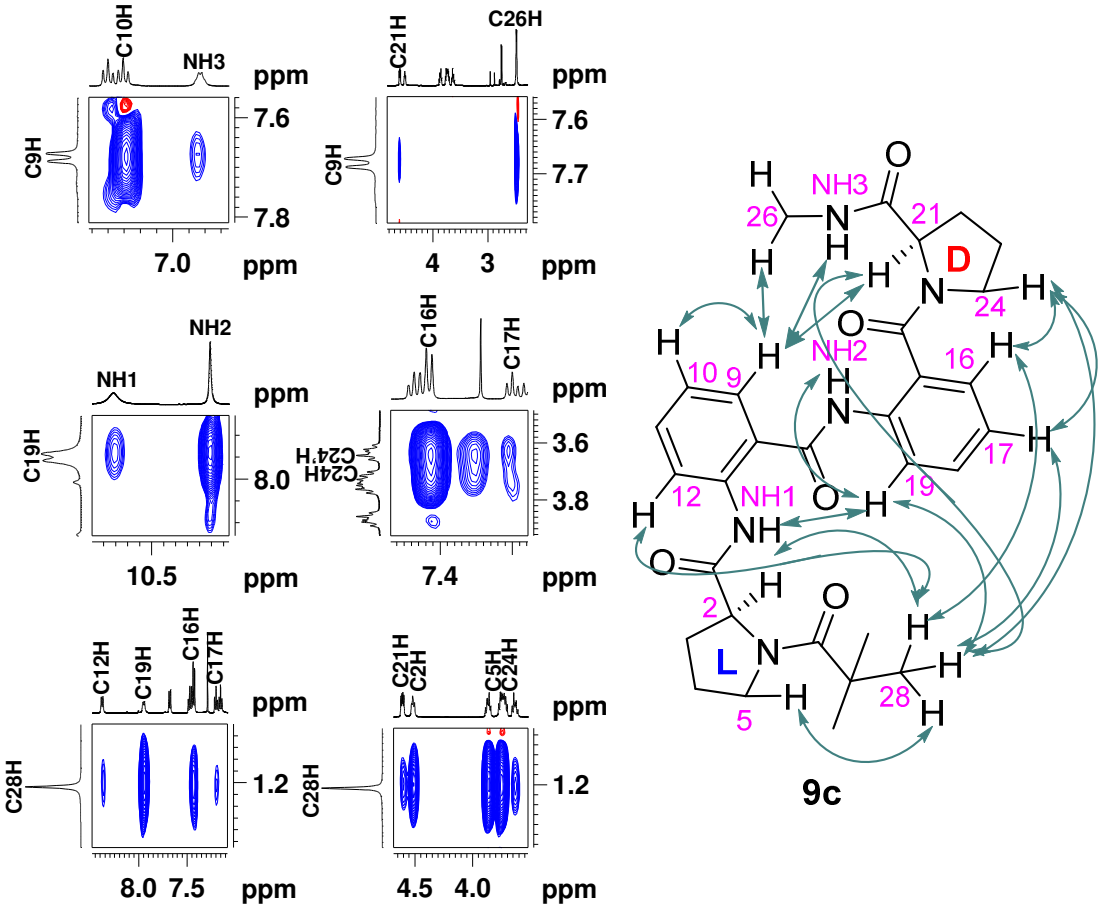


Fig. S16: 2D NOESY excerpts of 9c (500 MHz, $CDCl_3$)

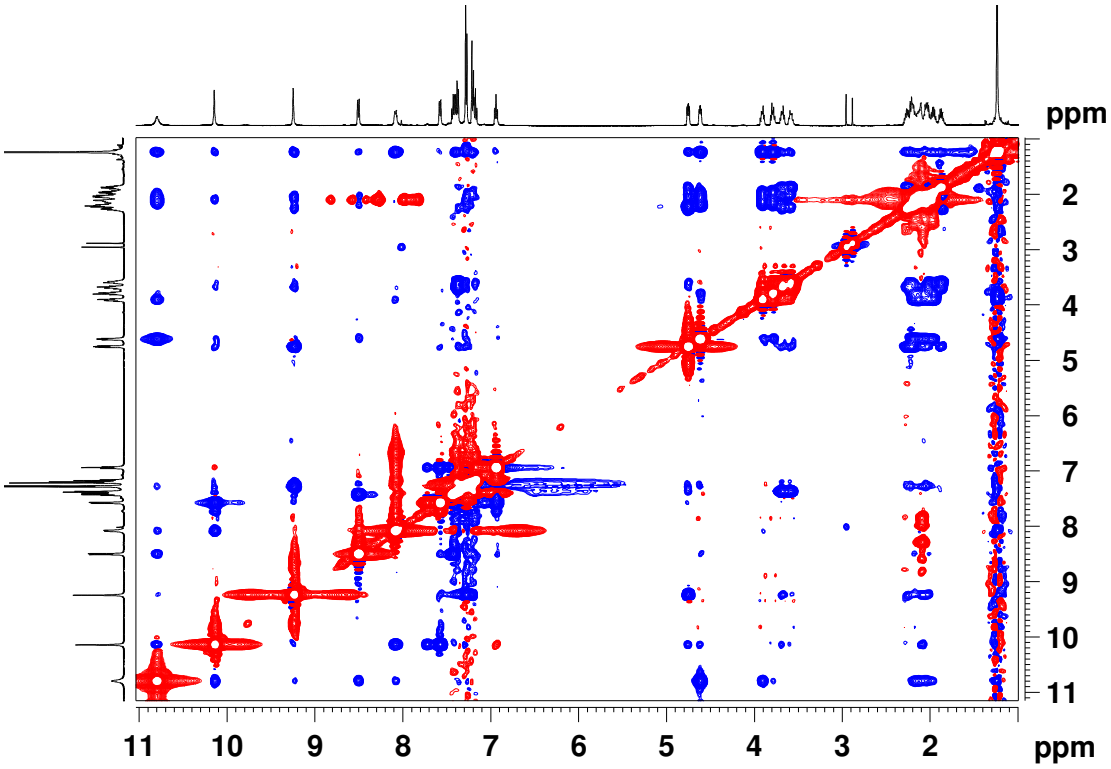


Fig. S17: 2D NOESY full spectra of 2c (500 MHz, $CDCl_3$)

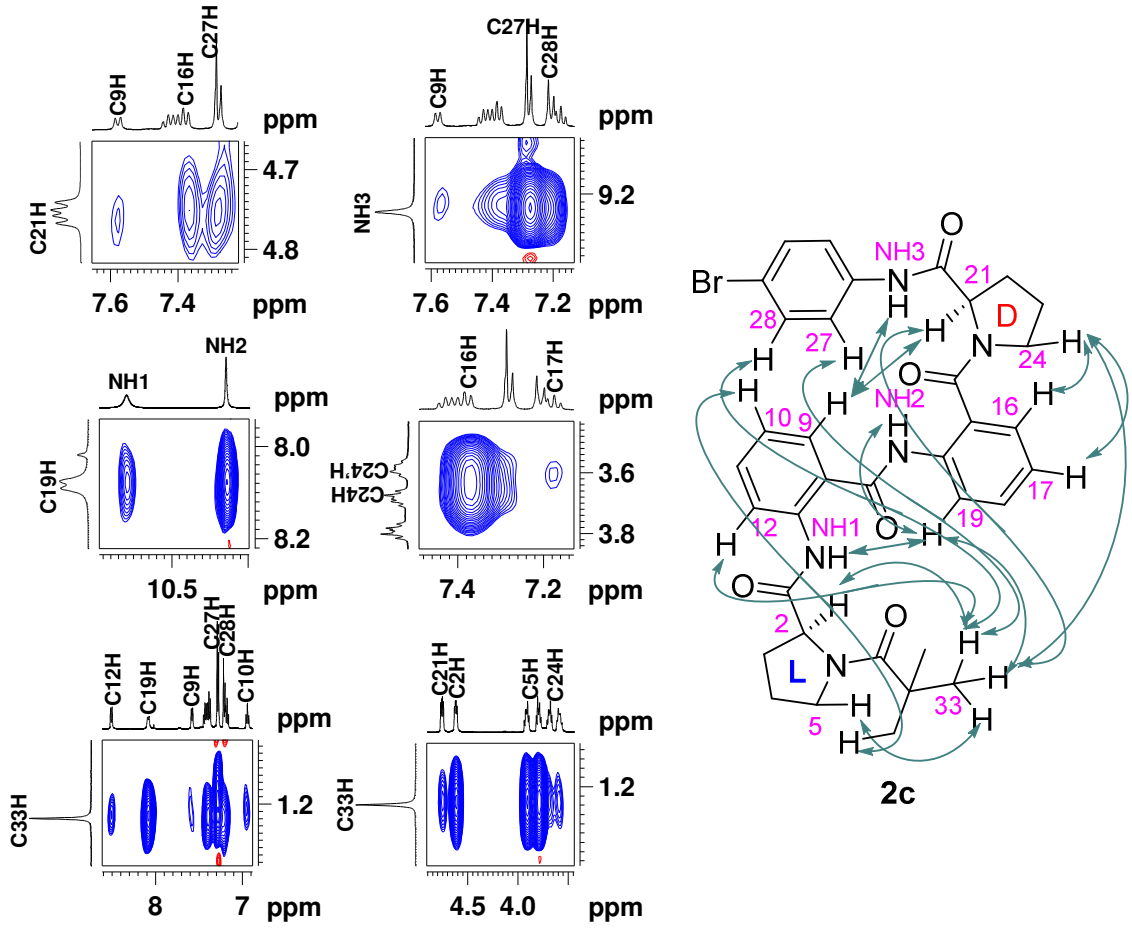


Fig. S18: 2D NOESY excerpts of 2c (500 MHz, $CDCl_3$)

Crystal Data

Crystal Data[3]**:** X-ray intensity data measurements of all the compounds (**1a**, **1b** and **2a**) were carried out on a Bruker SMART APEX I CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation. The X-ray generator was operated at 50 kV and 30 mA. Data were collected with ω scan width of 0.3° at different settings of φ (0°, 90°, 180° and 270°) keeping the sample-to-detector distance fixed at 6.145 cm and the detector position (2θ) fixed at -28°. The X-ray data collection was monitored by SMART program (Bruker, 2006).[4]

X-ray intensity data measurements of all the compounds (**2b**) was carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation at 100 (2) K. The X-ray generator was operated at 50 kV and 30 mA. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX 2 program (Bruker, 2006).[4]

All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2006).[4] SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2. Hydrogen atoms for all the compounds were placed in geometrically idealized position and constrained to ride on their parent atoms. Molecular and packing diagrams were generated using Mercury-3 and Pymol.[5] Geometrical calculations were performed using SHELXTL (Bruker, 2006) and PLATON.

Crystal data for 1a:

Colorless crystals of **1a** were grown by slow evaporation of a mixture of methanol and chloroform. $C_{35}H_{38}BrN_5O_6 \cdot 0.25(H_2O)$, M = 708.61, colorless prism, 0.28 x 0.16 x 0.10 mm^3, monoclinic, space group $P2_1$, a = 14.1444(14), b = 15.9217(16), c = 16.0940(16) Å, β = 112.638(2)°, V = 3345.2(6) $Å^3$, Z = 4, T = 100(2) K, $2\theta_{max}$ = 50.00°, D_{calc} (g cm^{-3}) = 1.407, $F(000)$ = 1472, μ (mm^{-1}) = 1.283, 16915 reflections collected, 11007 unique reflections (R_{int} = 0.0214), 10069 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.715, T_{max} = 0.882, 862 refined parameters, S = 0.962, $R1$ = 0.0316, $wR2$ = 0.0714 (all data R = 0.0360, $wR2$ = 0.0872), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.628, $\Delta\rho_{min}$= -0.242 $eÅ^{-3}$.

Crystal data for 1b:

Colorless crystals of **1b** were grown by slow evaporation of a mixture of methanol and chloroform. $C_{35}H_{38}BrN_5O_6 \cdot 0.25(H_2O)$, M = 708.61, colorless plate, 0.41 x 0.35 x 0.13 mm^3, monoclinic, space group $P2_1$, a = 14.1383(3), b = 15.9256(3), c = 16.0775(4) Å, β = 112.5560(10)°, V = 3343.11(13) $Å^3$, Z = 4, T = 100(2) K, $2\theta_{max}$ = 52.00°, D_{calc} (g cm^{-3}) = 1.400, $F(000)$ = 1464, μ (mm^{-1}) = 1.283, 52660 reflections collected, 13040 unique reflections (R_{int} = 0.0275), 12007 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.621, T_{max} = 0.851, 862 refined parameters, S = 1.044, $R1$ = 0.0265, $wR2$ = 0.0602 (all data R = 0.0310, $wR2$ = 0.0615), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.748, $\Delta\rho_{min}$= -0.477 $eÅ^{-3}$.

Crystal data for 2a:

Colorless crystals of **2a** were grown by slow evaporation of a mixture of methanol and chloroform. $C_{35}H_{38}BrN_5O_6$, M = 704.61, colorless prism, 0.40 x 0.10 x 0.09 mm^3, monoclinic, space group $P2_1$, a = 11.2385(14), b = 9.2310(11), c = 32.800(4) Å, β = 99.779(2)°, V = 3353.3(7) $Å^3$, Z = 4, T = 100(2) K, $2\theta_{max}$ = 50.00°, D_{calc} (g cm^{-3}) = 1.396, $F(000)$ = 1464, μ (mm^{-1}) = 1.279, 24538 reflections collected, 11731 unique reflections (R_{int} = 0.0438), 11012 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.629, T_{max} = 0.894, 853 refined parameters, S = 1.051, $R1$ = 0.0402, $wR2$ = 0.0921 (all data R = 0.0438, $wR2$ = 0.0942), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.547, $\Delta\rho_{min}$= -0.319 $eÅ^{-3}$.

Crystal data for 2b:

Colorless crystals of **2b** were grown by slow evaporation of a mixture of methanol and chloroform. $C_{35}H_{38}BrN_5O_6$, M = 704.61, colorless prism, 0.70 x 0.11 x 0.09 mm^3, monoclinic, space group $P2_1$, a = 11.2356(6), b = 9.2098(5), c = 32.8244(16) Å, β = 99.779(2)°, V = 3347.3(3) $Å^3$, Z = 4, T = 100(2) K, $2\theta_{max}$ = 52.00°, D_{calc} (g cm^{-3}) = 1.398, $F(000)$ = 1464, μ (mm^{-1}) = 1.281, 41276 reflections collected, 13026 unique reflections (R_{int} = 0.0303), 11766 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.468, T_{max} = 0.893, 853 refined parameters, S = 0.987, $R1$ = 0.0271, $wR2$ = 0.0516 (all data R = 0.0329, $wR2$ =

0.0529), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.418, $\Delta\rho_{min}$= -0.327 eÅ^{-3}.

Discussion on Crystal Structure

All the compounds **1a**, **2a**, **2b** and **1b** have crystallized in monoclinic chiral space group $P2_1$ where assymetric unit having two symmetry independent molecules. Crystal structure of **1a** and **1b** also contained one molecule of water having occupancy 25%, thus the ratio of host moelecule to water is 8:1. In crystal structures of **1a** and **1b**, the both proline moieties have S and R configuration respectively while in **2a** the configuration of the proline moieties are S (at N-terminal) and R (at C-terminal) whereas it is reverse in **2b**, i.e the configuration is R (at N-terminal) and S (at C-terminal).

The conformation of the molecule as observed in the crystal structure of **1a** and **1b** (homochiral tetramer) reveals very similar structure as the only change is in the handedness at the Pro1 and Pro2 moieties, in **1a** it is S whereas in **1b** it is R. All the torsions angles ψ, ϕ, θ and ω (Fig. S19) showed similar values (Table S11). In contrast, significant difference were noticed in the torsion angles at Pro2 moieties of **1a** and **2a** while at Pro1 of both the compounds showed similar torsion angles. This is due to the change of chirality at Pro2 moiety of **1a** and **2a** (Pro2 moiety has S configuration in **1a** and R configuration in **2a**). In a similar way, torsion angles at Pro1 moieties of **1a** and **2b** also differ extensively again due to configuration change at Pro1 moieties (Pro1 has S configuration in **1a** and R configuration in **2b**); at Pro2, torsion angles of **1a** and **2b** have similar values.

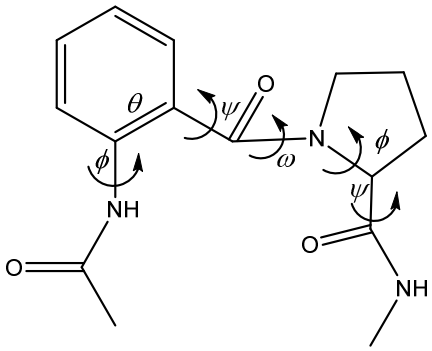


Fig. S19: Dihedral angle of Ant-Pro moiety. The dihedral angle θ has been shown for the Ant, which is a constrained β-amino acids.[6]

In crystal structures of **1a** and **1b** (the homochiral tetramer), both molecules revealed formation of C_9 and C_6 intramolecular hydrogen bonding network {graph set **S**(9) and **S**(6) respectively}. The C_6 hydrogen bonding interactions (N2-

H2N…O3, N2'-H2'N…O3') are stronger whereas the other C_9 and C_6 hydrogen bonding interactions (N3-H3N…O5, N3'-H3N'…O5', N3-H3N…O4, N3-H3'N…O4') (Table S10) are very long and non-linear (Fig. S20).

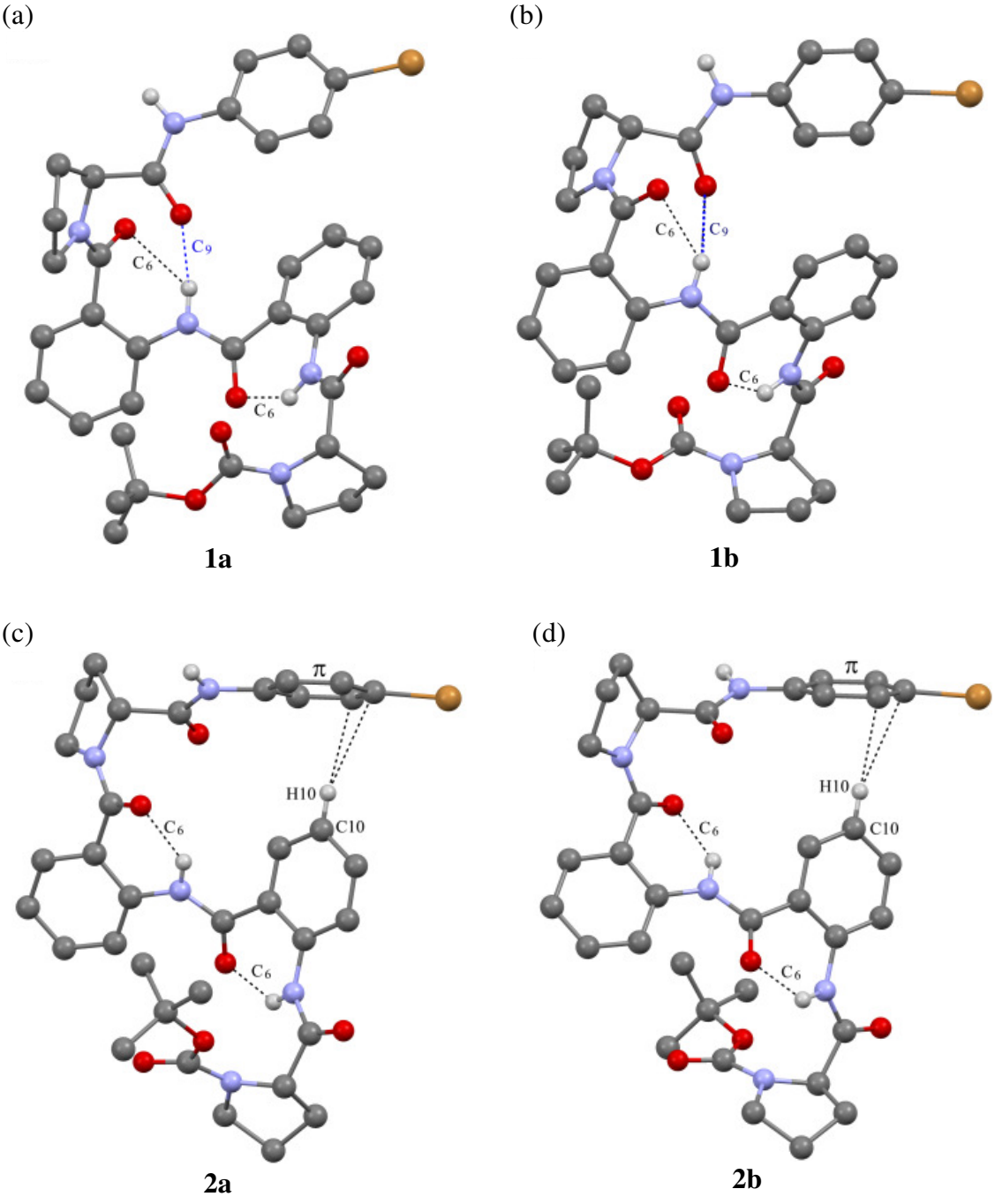


Fig. S20: Intramolecular geometry of **1a** (a), **1b** (b), **2a** (c) and **2b** (d).

Crystal structures of **2a** and **2b** also displays the C_6 intramolecular hydrogen bonding network. The configuration change at Pro1 and Pro2 of these structures do not seem to alter the C_6 network because of the rigid conformation at Ant1 and Ant2 positions (θ). However, crystal structures of **2a** and **2b** did not

exhibit C_9 intramolecular hydrogen bonding network because of the significant torsional change (ψ at Ant2 and Pro2, ~30° and ~15° respectively, Table S11) with respect to **1a** and **1b**. Surprisingly, even the change of charility at Pro2, in **2a** (R) and **2b** (S) did not have any effect on the the ψ values, thus exhibitting similar torsions. This significant conformation change at Ant2 and Pro2 (ψ) of **2a** and **2b**, could be due to the involvement of anilide (4-Br) group in intra and intramolecular C-H···π, intermolecular C-Br···O=C halogen bonding interaction and intermolecular dipolar C-Br···C=O contact of perpendicular motif. The benzene ring of anilide group is engaged with aromatic C-H from the Ant1 ring and C-H (CH_2) from Pro2 to generate intra and intermolecular C-H···π interactions respectively, while the bromine atom makes very short and linear C-Br···O=C halogen bonding contact with the carbonyl oxygen of the C-terminus of the Pro1. In addition to this the C-Br of the anilide groups is engaged in dipolar C-Br···C=O interaction (antiparallel motif)[7] with C=O of the N-terminus of the Pro1. All these interactions tightly hold the 4-anilide group, thus preventing the formation of C_9-hydrogen bonding network (Fig. S20).

Molecular Packing

(a) (b)

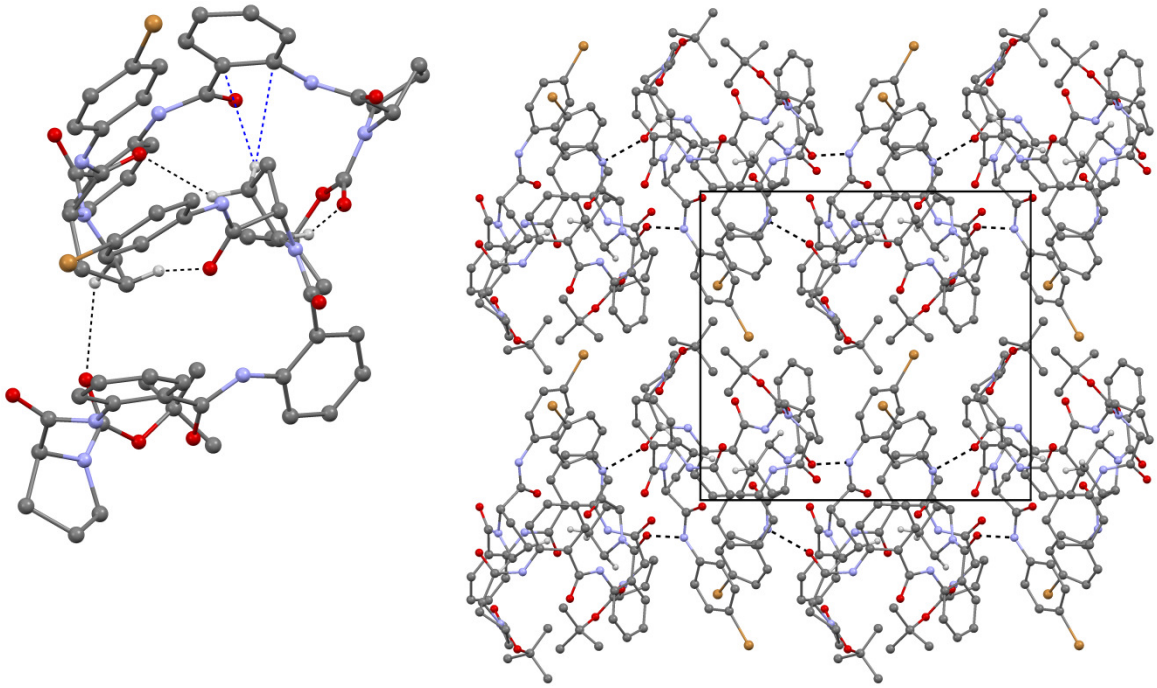


Fig. S21: (a) Molecules in the asymmetric unit of **1a**, linked via C-H…O and C-H…π interaction to generate a capsule and (b) helical aggregation of capsules along the crystalographic 2_1 screw axis mainly via N-H…O interactions. *Note*: Molecules of **1b** also exhibits similar packing arrangement.

Two molecules in the asymmetric units of **1a** and **1b** form a capsule type aggregation linked via four C-H···O (C23-H23B…O5', C24-H24B···O1', C23'-H23D···O5 and C24'-H24C···O1) and one offcentered C-H···π (C23-H23A···π(C7'-C12')) interactions. Along the *b*-axis these capsules are connected mainly via intermolecular N-H···O (N5-H5N···O2 and N5'-H5'N···O4) interactions to generate the helical network. Additionally, some C-H···O interactions namely C21-H21···O2, C21'-H21'···O4 and C31-H31···O1, also supports this helical architecture. The adjacent helices along the *a* and *c*-axis are loosely associated via van der waal's interactions (Fig. S21).

The molecular packing in crystals of **2a** and **2b** is quite different. Here also molecules are involved in helical arrangement but with a difference. Each molecule in the asymmetric unit forms its own helical architecture along the crystallographic 2_1-screw axis and both these neighboring helices are linked either via Br···O=C halogen bonding interactions or by C-H···O (C2-H2···O2', C4-H4A···O2', C2'-H2'···O2, C11-H11···O2') interactions (Fig. S22).

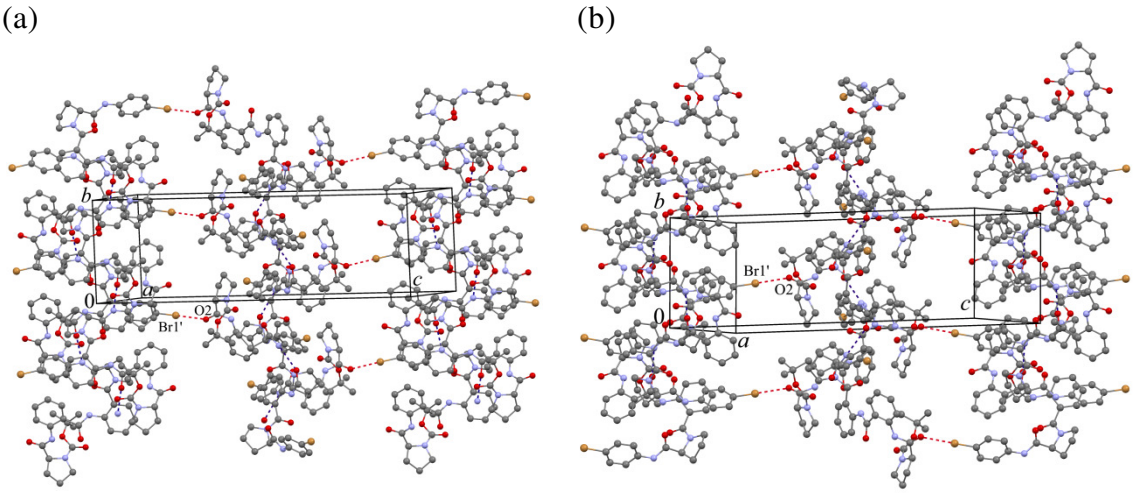


Fig. S22: View of molecular packing in **2a** (a) and **2b** (b) along the *a*-axis.

Table S10. Geometrical parameters of intra and intermolecular interactions in crystals of **1a**, **1b**, **2a** and **2b**.

No.	Contacts	D-H (Å)	H···A (Å)	D··A (Å)	N-H···O (°)	*Symmetry codes*
1a	C24'-H24C···O1	0.99	2.58	3.367(4)	136	*x, y, z*
	C23'-H23*D*···O5	0.99	2.49	3.328(4)	142	*x, y, z*

	C23-H23*B*···O5'	0.99	2.36	3.156(4)	137	*x, y, z*
	C24-H24*B*···O1'	0.99	2.19	3.101(4)	152	*x, y, z*
	N3'-H3'N···O5'	0.88	2.84	3.464(3)	129	*x, y, z*
	N3'-H3'N···O4'	0.88	2.45	3.078(4)	129	*x, y, z*
	N2'-H2'N···O3'	0.88	2.01	2.668(3)	131	*x, y, z*
	N3-H3N···O5	0.88	2.42	3.105(4)	134	*x, y, z*
	N3-H3N···O4	0.88	2.44	3.059(4)	128	*x, y, z*
	N2-H2N···O3	0.88	1.97	2.672(3)	136	*x, y, z*
	C11-H11···O7	0.95	2.72	3.531(14)	144	*1-x, -1/2+y, -z*
	C31-H31···O1	0.95	2.54	3.377(4)	147	*1-x, 1/2+y, -z*
	C3'-H3'*A*···O4'	0.99	2.46	3.305(5)	143	*2-x, 1/2+y, -z*
	C9'-H9'···O2'	0.95	2.37	3.230(4)	150	*2-x, -1/2+y, -z*
	C21-H21···O2	1.00	2.62	3.250(4)	121	*1-x, 1/2+y, -z*
	N5'-H5'N···O4	0.88	1.89	2.757(3)	167	*1-x, -1/2+y, -z*
	N5-H5N···O2	0.88	2.02	2.858(3)	159	*1-x, 1/2+y, -z*
1b	C23'-H23*C*···O5	0.99	2.49	3.326(3)	142	*x, y, z*
	C24-H24*A*···O7	0.99	2.62	3.260(11)	122	*x, y, z*
	C23-H23*A*···O5'	0.99	2.36	3.150(3)	137	*x, y, z*
	C24-H24*A*···O1'	0.99	2.18	3.090(3)	152	*x, y, z*
	C24'-H24*C*···O1	0.99	2.58	3.362(2)	136	*x, y, z*
	N3'-H3'N···O5'	0.88	2.86	3.472(2)	128	*x, y, z*
	N3'-H3'N···O4'	0.88	2.45	3.078(2)	129	*x, y, z*

	N2'-H2'N···O3'	0.88	2.00	2.666(2)	131	*x, y, z*
	N3-H3N···O5	0.88	2.42	3.102(2)	134	*x, y, z*
	N3-H3N···O4	0.88	2.42	3.041(2)	128	*x, y, z*
	N2-H2N···O3	0.88	1.97	2.674(2)	136	*x, y, z*
	C21'-H21'···O4	1.00	2.61	3.140(2)	113	*-x, 1/2+y, -z*
	C9'-H9'···O2'	0.95	2.37	3.227(2)	150	*1-x, 1/2+y, -z*
	C3'-H3'*B*···O4'	0.99	2.45	3.312(3)	146	*1-x, -1/2+y, -z*
	C31-H31···O1	0.95	2.55	3.390(3)	147	*-x, -1/2+y, -z*
	C21-H21···O2	1.00	2.61	3.238(2)	121	*-x, -1/2+y, -z*
	C11-H11···O7	0.95	2.70	3.514(12)	144	*-x, 1/2+y, -z*
	N5'-H5'N···O4	0.88	1.89	2.756(2)	167	*-x, 1/2+y, -z*
	N5-H5N···O2	0.88	2.01	2.854(2)	160	*-x, -1/2+y, -z*
2a	C4'-H4*D*···O2	0.99	2.60	3.355(4)	133	*x, y, z*
	C2'-H2'···O2	1.00	2.45	3.248(4)	137	*x, y, z*
	N3'-H3'N···O4'	0.88	1.91	2.636(4)	139	*x, y, z*
	N2'-H2'N···O3'	0.88	2.03	2.722(4)	135	*x, y, z*
	N3-H3N···O4	0.88	1.91	2.640(4)	139	*x, y, z*
	N2-H2N···O3	0.88	2.05	2.738(4)	135	*x, y, z*
	N5'-H5'N···O3'	0.88	2.22	3.042(4)	156	*x, 1+y, z*
	N5-H5N···O3	0.88	2.16	2.991(4)	158	*x, -1+y, z*
	C5-H5*A*···O4	0.99	2.58	3.320(4)	131	*x, 1+y, z*
	C11-H11···O2'	0.95	2.52	3.324(4)	143	*x, -1+y, z*

	C16-H16···O1	0.95	2.44	3.152(4)	132	*1-x, -1/2+y, 1-z*
	C22-H22*A*···O5	0.99	2.30	3.219(5)	154	*-1-x, --1.5+y, 1-z*
	C31-H31···O3	0.95	2.60	3.370(4)	139	*x, -1+y, z*
	C31-H31···N2	0.95	2.69	3.588(5)	159	*x, -1+y, z*
	C5'-H5*C*···O4'	0.99	2.61	3.313(4)	128	*x, -1+y, z*
	C16'-H16'···O1'	0.95	2.48	3.216(4)	134	*1-x, -1/2+y, 2-z*
	C22'-H22*C*···O5'	0.99	2.43	3.349(5)	153	*-x, 1/2+y, 2-z*
	C31'-H31'···O3'	0.95	2.51	3.310(4)	143	*x, 1+y, z*
	C31'-H31'···N2'	0.95	2.66	3.534(5)	154	*x, 1+y, z*
	C10-H10···π (C26-C31)	0.95	2.62	3.542(4)	163	*x, y, z*
	C10'-H10'···π (C26'-C31')	0.95	2.64	3.547(4) Å	161	*x, y, z*
	C24-H24B···π (C26'-C31')	0.99	3.01	3.860	144	*-x, -1/2+y,2-z*
	C24'-H24D···π (C26'-C31')	0.99	2.81	3.703(4)	150	*-x, -1/2+y,2-z*
	C29'-Br1'···O2=C6		2.958(2)		178.7(1)	*-1+x,1+y,z*
	C-Br1···C1=O1 / C-Br1'···C1'=O1'/		3.544 (4)/ 3.545 (4)		∠Br = 92.3° ∠C = 88.5°/ ∠Br = 96.2° ∠C = 84.1°	

2b	N2-H2N···O3	0.88	2.02	2.722(2)	135	*x, y, z*
	N3-H3N···O4	0.88	1.91	2.633(2)	139	*x, y, z*
	N2'-H2'N···O3'	0.88	2.04	2.734(2)	135	*x, y, z*
	N3'-H3'N···O4'	0.88	1.92	2.643(2)	139	*x, y, z*
	C11'-H11'···O2	0.95	2.51	3.318(3)	142	*x, y, z*
	C2-H2···O2'	1.00	2.45	3.249(2)	137	*x, 1+y, z*
	C4-H4*A*···O2'	0.99	2.61	3.362(3)	133	*x, 1+y, z*
	C5-H5*B*···O4	0.99	2.61	3.313(2)	128	*x, 1+y, z*
	C16-H16···O1	0.95	2.49	3.219(2)	134	*1-x, -1/2+y, 2-z*
	C22-H22*A*···O5	0.99	2.42	3.332(3)	153	*-x, -1/2+y, 2-z*
	C31-H31···O3	0.95	2.51	3.310(2)	142	*x, -1+y, z*
	C31-H31···N2	0.95	2.65	3.533(3)	154	*x, -1+y, z*
	C5'-H5'*B*···O4'	0.99	2.58	3.318(2)	132	*x, -1+y, z*
	C16'-H16'···O1'	0.95	2.44	3.152(2)	131	*1-x, 1/2+y, 1-z*
	C22'-H22*C*···O5'	0.99	2.29	3.209(3)	154	*-x, 1/2+y, 1-z*
	C31'-H31'···O3'	0.95	2.60	3.371(2)	139	*x, 1+y, z*
	C31'-H31'···N2'	0.95	2.68	3.583(3)	159	*x, 1+y, z*
	C10-H10···π (C26-C31)	0.95	2.64	3.546(2)	160	*x, y, z*
	C10'-H10'···π (C26'-C31')	0.95	2.62	3.539(2)	163	*x, y, z*
	C24-H24A···π (C26'-	0.99	2.82	3.708(2)	150	*-x,1/2+y,2-z*

	C31')					
	C24'-H24D···π (C26'-C31')	0.99	3.025	3.866	144	*-x, 1/2+y, 1-z*
	C-Br···O=C		2.9637(14)		178.7(1)	*-1+x, y, z*
	C-Br1···C1=O1/ C-Br1'···C1'=O1'		3.546(2)/ 3.545 (2)		∠Br = 96.0° ∠C = 84.0°/ ∠Br = 91.8° ∠C = 88.7°	

Table S11: Backbone torsion angles observed in the crystals **1a**, **1b**, **2a** and **2b**.

Compound No	Torsion angle parameters											
	Pro1		Ant1				Ant2				Pro2	
	ϕ	ψ	ϕ	θ	ψ	ω	ϕ	θ	ψ	ω	ϕ	ψ
1a	-70.90	-29.38	-156.95	2.88	153.84	-176.20	156.85	2.88	-111.93	174.90	-61.92	164.44
1a	-76.19	-29.40	-161.42	0.94	148.33	178.97	166.98	3.08	-108.96	167.74	-62.52	165.77
1b	70.93	29.14	157.30	-3.03	-153.82	175.79	-156.30	-2.94	112.57	-175.38	61.84	-163.98
1b	75.98	29.94	161.12	-1.11	-148.15	-178.89	-166.63	-3.81	110.33	-168.25	62.52	-165.92
2a	-62.38	-32.88	-157.36	0.56	142.57	-178.27	-171.42	0.38	142.04	-170.44	59.21	-149.56
2a	-64.36	-28.86	-157.50	-2.75	146.39	-178.74	-170.87	0.94	143.57	-170.14	58.14	-148.70
2b	62.51	32.80	157.29	-0.55	-142.77	178.40	171.27	-0.15	-142.44	170.70	-58.92	149.43
2b	64.35	28.55	157.92	2.98	-146.25	178.81	170.44	-0.77	-143.47	170.09	-58.43	148.42

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3. Crystal structure was solved by direct method and refined by full matrix least squares on *F*2 for all data using SHELXTL software (SHELX-97). The hydrogen atom of hydroxy group was located on the difference map and refined isotropically. Other hydrogen atoms were refined in the riding mode. Crystallographic data of **1a**, **1b**, **2a** and **2b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 948398-948401 respectively. Copies of the

data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

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