Electronic Supplementary Information

Multifaceted Folding in a Foldamer Featuring Highly Cooperative Folds

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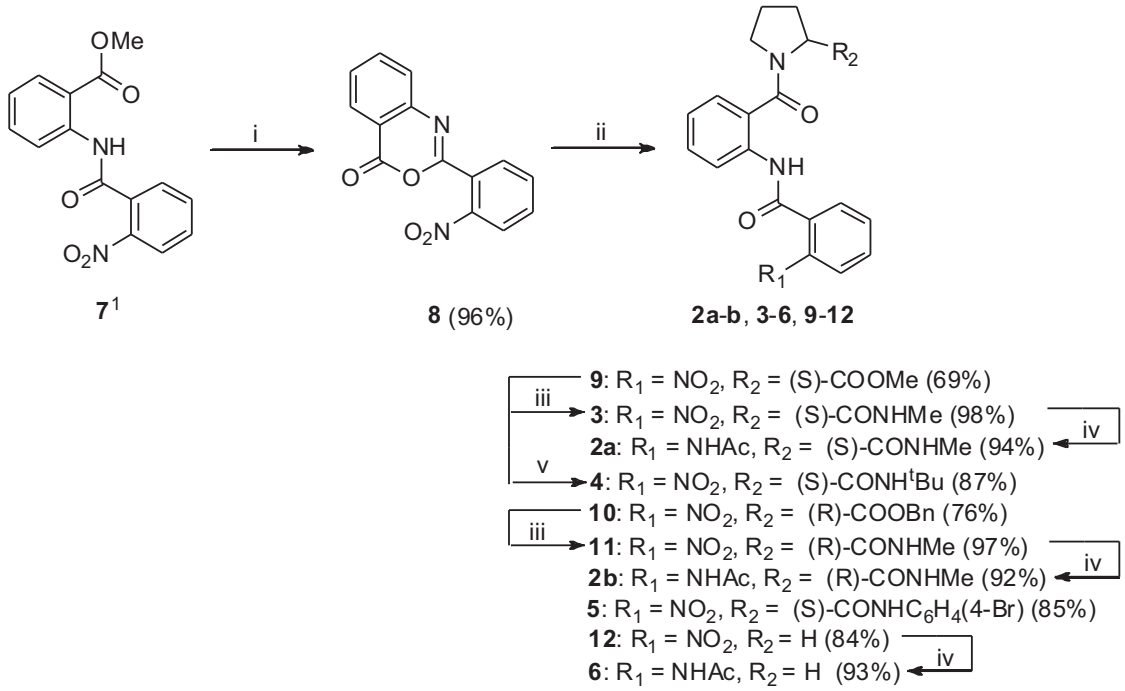
General Methods.

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.

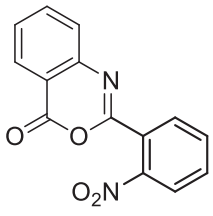


Scheme 1. Reagents and conditions: (i) a. aq. $LiOH.H_2O$, MeOH, rt, 12h; b. Ac_2O, pyridine, DCM, rt, 30 min.; (ii) DBU, DMF, 4 Å molecular sieves, amine [H-^{L}Pro-CO_2Me for **9**; H-^{D}Pro-CO_2Bn for **10**; H-^{L}Pro-$CONHC_6H_4$(4-Br) for **5**, pyrrolidine for **6**], rt, 2h; (iii) methanolic $MeNH_2$, rt, 5h; (iv) a. Pd-C, H_2, 1 atm., rt, 2h; b. Ac_2O, pyridine, DMAP, DCM, rt, 5h; (v) a. aq. $LiOH.H_2O$, MeOH, rt, 12h; b. $^{t}BuNH_2$, EDC.HCl, HOBt, DCM, rt, 8h.

References:

1. Y. Hamuro, S. J. Geib, A. D. Hamilton, *J. Am. Chem. Soc.* **1996**, *118*, 7529 – 7541.

2-(2-nitrophenyl)-4H-benzo[d][1,3]oxazin-4-one 8:



8

To a solution of the ester **7**[1] (5 g, 16.6 mmol) in methanol (35 mL), $LiOH \cdot H_2O$ (2.09 g, 49.9 mmol) in water (15 mL) was added 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 precipitated with the addition of dil. 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.

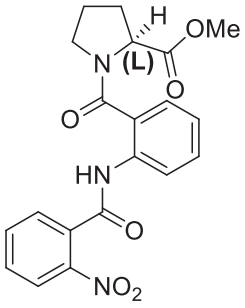
A solution containing the crude acid in dry DCM (40 mL) was cooled to 0 °C. The reaction mixture was then treated with acetic anhydride (1.88 mL, 19.9 mmol), pyridine (1.61 mL, 19.9 mmol) and was stirred at 0 °C for 30 min. The reaction mixture was diluted with DCM and the organic layer was washed sequentially with sat. $NaHCO_3$, 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 on purification by column chromatography (80:20 pet. ether/ethyl acetate, *Rf*: 0.5) afforded **8** as a white solid (4.28 g, 96%). mp: 193-195 °C; IR ($CHCl_3$) ν (cm^{-1}): 3501, 1770, 1635, 1606, 1574, 1531, 1472, 1346, 1216, 770, 669; ^{1}H NMR (500 MHz, DMSO-*d6*) δ: 8.22 (d, *J* = 7.93 Hz, 1H), 8.17 (d, *J* = 7.93 Hz, 1H), 8.11 (d, *J* = 7.33 Hz, 1H), 8.03 (t, *J* = 7.63 Hz, 1H), 7.97 (t, *J* = 7.33 Hz, 1H), 7.92 (t, *J* = 7.94 Hz, 1H), 7.74-7.70 (m, 2H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ: 158.4, 154.7, 148.3, 145.7, 137.4, 133.8, 133.1, 131.3, 129.8, 128.4, 127.2, 125.1, 124.7, 116.8; LC-MS: 268.98 $(M)^+$; Elemental analysis calculated for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.01; N, 10.44; Found: C, 62.60; H, 3.12; N, 10.32.

General method for the ring opening of 2-(2-nitrophenyl)-4H-benzo[d][1,3]oxazin-4-one 8 with proline amines [H-^{L}Pro-CO_2Me for 9; H-^{D}Pro-CO_2Bn for 10; H-^{L}Pro-$CONHC_6H_4$(4-Br) for 5 and pyrrolidine for 12]:

Representative procedure: To a solution containing the oxazinone **8** (1 equiv), amine (1.1 equiv) and 4Å molecular sieves (0.2 g) in dry DMF (10 mL) at 0 °C, DBU (1.1 equiv) were added. The solution was stirred at room temperature for 2 h. The reaction

mixture was quenched with dil. HCl solution and diluted with DCM (50 mL). The organic layer was repeatedly washed with water followed by brine solution and was dried over anhydrous Na_2SO_4. It was then evaporated under reduced pressure to obtain the crude product which was purified by column chromatography.

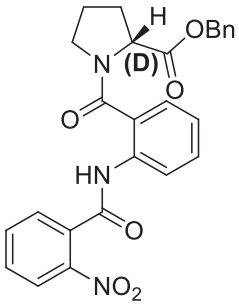
(S)-methyl 1-(2-(2-nitrobenzamido)benzoyl)pyrrolidine-2-carboxylate 9:



9

The product **9** was obtained as sticky substance (2.55 g, 69%). $[\alpha]^{24}_D$: -44° (*c* = 0.9, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3325, 1740, 1687, 1626, 1597, 1532, 1418, 1349, 1215, 755, 668; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.50 (s, 1H), 8.46 (d, *J* = 8.34 Hz, 1H), 8.08 (d, *J* = 7.96 Hz, 1H), 7.69-7.64 (m, 2H), 7.62-7.55 (m, 1H), 7.53-7.47 (m, 1H), 7.43-7.36 (m, 1H), 7.21 (dt, *J* = 0.76 Hz, *J* = 7.45 Hz, 1H), 4.64-4.58 (m, 1H), 3.66-3.54 (m, 1H), 3.58 (s, 3H), 3.50-3.42 (m, 1H), 2.40-2.25 (m, 1H), 2.06-1.85 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.5, 168.3, 164.7, 146.2, 135.4, 133.6, 132.7, 130.8, 130.4, 128.9, 126.5, 125.5, 124.2, 123.9, 122.1, 58.7, 52.2, 49.6, 29.1, 24.8; LC-MS: 420.07 $(M+Na)^+$; Elemental analysis calculated for $C_{20}H_{19}N_3O_6$: C, 60.45; H, 4.82; N, 10.57; Found: C, 60.28; H, 5.01; N, 10.41.

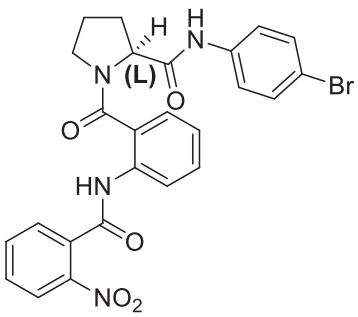
(R)-benzyl 1-(2-(2-nitrobenzamido)benzoyl)pyrrolidine-2-carboxylate 10:



10

The product **10** was isolated as a white solid (0.93 g, 76%). mp: 122-124 °C; $[\alpha]^{24}_D$: +22° (*c* = 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3336, 1739, 1687, 1626, 1598, 1532, 1420, 1349, 1215, 759, 669; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.39 (s, 1H), 8.41 (d, *J* = 8.21 Hz, 1H), 7.98 (d, *J* = 7.45 Hz, 1H), 7.61-7.55 (m, 2H), 7.52-7.04 (m, 9H), 5.06-4.86 (m, 2H), 4.63-4.57 (m, 1H), 3.70-3.33 (m, 2H), 2.32-2.13 (m, 1H), 2.03-1.74 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.9, 168.3, 164.7, 146.2, 135.4, 135.2, 133.6, 132.8, 130.8, 130.3, 128.9, 128.4, 128.2, 127.8, 126.4, 125.7, 124.2, 123.9, 122.1, 66.8, 58.8, 49.6, 29.1, 24.8; LC-MS: 496.16 $(M+Na)^+$; Elemental analysis calculated for $C_{26}H_{23}N_3O_6$: C, 65.95; H, 4.90; N, 8.87; Found: C, 66.11; H, 5.13; N, 8.68.

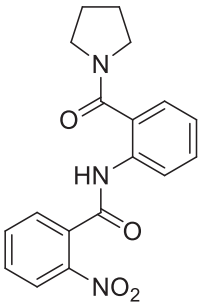
(S)-N-(4-bromophenyl)-1-(2-(2-nitrobenzamido)benzoyl)pyrrolidine-2-carboxamide 5:



5

The product **5** was obtained as white solid (0.51 g, 85%). mp: 210-212 °C; $[\alpha]^{24}_{D}$: +50° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3310, 1677, 1618, 1542, 1534, 1427, 1350, 1218, 771, 669; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.71 (s, 1H), 9.11 (s, 1H), 8.68 (d, *J* = 8.24 Hz, 1H), 8.09 (d, *J* = 7.93 Hz, 1H), 7.77 (t, *J* = 7.02 Hz, 1H), 7.67 (d, *J* = 7.01 Hz, 1H), 7.63 (t, *J* = 7.63 Hz, 1H), 7.54 (t, *J* = 7.63 Hz, 1H), 7.31 (d, *J* = 6.71 Hz, 1H), 7.24 (t, *J* = 7.02 Hz, 1H), 7.00 (d, *J* = 7.63 Hz, 1H), 6.66 (d, *J* = 7.32 Hz, 1H), 4.90-4.78 (m, 1H), 3.61-3.59 (m, 1H), 3.42-3.41 (m, 1H), 2.27-2.26 (m, 1H), 2.07-1.92 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.0, 169.0, 165.7, 146.0, 136.7, 135.1, 133.8, 133.2, 131.0, 130.0, 129.4, 126.0, 125.7, 124.3, 124.3, 121.6, 120.5, 116.0, 60.8, 49.8, 29.8, 24.8; LC-MS: 559.08 $(M+Na)^+$; 561.06 $(M+2+Na)^+$; 574.98 $(M+K)^+$; 576.98 $(M+2+K)^+$; Elemental analysis calculated for $C_{25}H_{21}BrN_4O_5$: C, 55.88; H, 3.94; N, 10.43; Found: C, 56.01; H, 4.11; N, 10.24.

2-nitro-N-(2-(pyrrolidine-1-carbonyl)phenyl)benzamide 12:



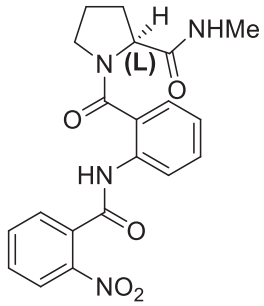
12

The product **12** was isolated as white solid (0.63 g, 84%). mp: 149-151 °C; IR ($CHCl_3$) ν (cm^{-1}): 3310, 1682, 1621, 1594, 1532, 1423, 1348, 1216, 755, 668; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.97 (s, 1H), 8.34 (d, *J* = 7.96 Hz, 1H), 8.07 (d, *J* = 7.70 Hz, 1H), 7.76-7.56 (m, 3H), 7.51-7.38 (m, 2H), 7.21-7.13 (m, 1H), 3.59-3.54 (m, 4H), 2.01-1.93 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.3, 164.2, 146.5, 136.0, 133.7, 132.6, 130.8, 130.6, 128.5, 127.3, 125.8, 124.5, 123.7, 123.0, 50.1, 46.2, 26.2, 24.2; LC-MS: 361.92 $(M+Na)^+$; Elemental analysis calculated for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38; Found: C, 63.89; H, 4.88; N, 12.49.

General method for C-terminal amidation: Synthesis of 3 and 11

Representative procedure*:* The esters **9** and **10** were taken in saturated methanolic methylamine solution (10 mL) 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 **3** and **11**, respectively.

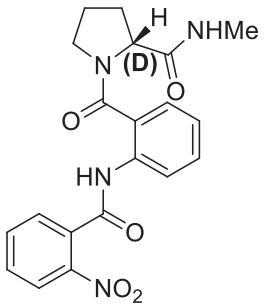
(S)-N-methyl-1-(2-(2-nitrobenzamido)benzoyl)pyrrolidine-2-carboxamide 3:



3

The amide **3** was obtained as a white solid (1.12 g, 98%). mp: 153-155 °C; $[\alpha]^{24}_{D}$: -90° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3346, 1673, 1621, 1590, 1532, 1417, 1350, 1215, 756, 669; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.87 (s, 1H), 8.35 (d, *J* = 8.24 Hz, 1H), 8.10 (d, *J* = 8.24 Hz, 1H), 7.71-7.66 (m, 2H), 7.60 (t, *J* = 7.94 Hz, 1H), 7.50 (t, *J* = 7.93 Hz, 1H), 7.33 (t, *J* = 7.63 Hz, 1H), 7.21 (t, *J* = 7.63 Hz, 1H), 6.59 (bs, 1H), 4.60 (t, *J* = 5.50 Hz, 1H), 3.61-3.56 (m, 1H), 3.48-3.43 (m, 1H), 2.55 (s, 3H), 2.24-2.17 (m, 1H), 2.11-2.07 (m, 1H), 1.99-1.93 (m, 1H), 1.91-1.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.9, 168.8, 165.5, 146.2, 135.0, 133.6, 132.9, 130.6, 130.2, 129.1, 126.9, 126.3, 124.2, 124.0, 122.4, 60.0, 49.6, 29.4, 25.8, 24.7; LC-MS: 418.99 $(M+Na)^+$; Elemental analysis calculated for $C_{20}H_{20}N_4O_5$: C, 60.60; H, 5.09; N, 14.13; Found: C, 60.43; H, 4.91; N, 14.31.

(R)-N-methyl-1-(2-(2-nitrobenzamido)benzoyl)pyrrolidine-2-carboxamide 11:



11

The amide **11** was isolated as a white solid (0.60 g, 97%). mp: 159-161 °C; $[\alpha]^{24}_{D}$: +120° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3338, 1671, 1618, 1588, 1534, 1420, 1350, 1216, 756, 668; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 10.05 (s, 1H), 8.32 (d, *J* = 8.34 Hz, 1H), 8.07 (d, *J* = 7.83 Hz, 1H), 7.69-7.51 (m, 3H), 7.46 (t, *J* = 7.45 Hz, 1H), 7.27-7.24 (m, 1H), 7.19 (t, *J* = 7.20 Hz, 1H), 6.78 (bs, 1H), 4.53-4.49 (m, 1H), 3.71-3.32 (m, 1H), 2.40 (s, 3H), 2.19-2.10 (m, 1H), 1.98-1.78 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.9, 168.7, 165.5, 146.1, 134.9, 133.5, 132.8, 130.5, 130.1, 129.1, 126.9, 126.2, 124.2, 124.0, 122.4, 60.0, 49.6,

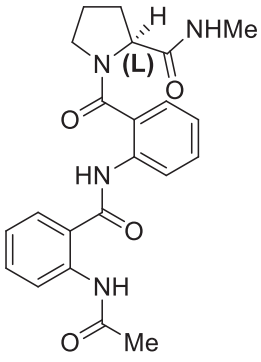
29.5, 25.8, 24.6; LC-MS: 418.98 $(M+Na)^+$; Elemental analysis calculated for $C_{20}H_{20}N_4O_5$: C, 60.60; H, 5.09; N, 14.13; Found: C, 60.75; H, 4.91; N, 13.98.

General method for N-acetylation: Synthesis of 2a, 2b and 6:

Representative procedure*:* A solution of the tripeptides **3**, **11** and **12** in ethyl acetate (5 ml) were subjected to hydrogenolysis using catalytic amount of 10 % Pd/C and H_2 (1 atm). After complete reduction, the reaction mixture was filtered over celite and the filtrate was evaporated under reduced pressure to yield the corresponding free amines, which were subjected to acetylation without further purification.

The free amines obtained thus were taken in dry DCM (5 mL) and cooled to 0 °C. To the reaction mixture, acetic anhydride (1.1 equiv) was added followed by pyridine (1.1 equiv) and catalytic amount of DMAP (0.1 equiv). The reaction mixture was stirred at rt for 5 h. It was then diluted with DCM and the organic layer was washed sequentially with sat. $NaHCO_3$, 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 further purified by column chromatography.

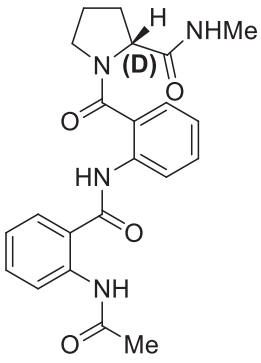
(S)-1-(2-(2-acetamidobenzamido)benzoyl)-N-methylpyrrolidine-2-carboxamide 2a:



2a

The product **2a** was obtained as a white solid (0.86 g, 94%). mp: 225-227 °C; $[\alpha]^{24}_D$: -110° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3330, 1702, 1644, 1621, 1603, 1522, 1421, 1215, 759, 669; ^1H NMR (500 MHz, $CDCl_3$) δ: 11.00 (s, 1H), 10.32 (s, 1H), 8.60 (d, *J* = 8.39 Hz, 1H), 8.31 (d, *J* = 8.22 Hz, 1H), 7.72 (d, *J* = 7.40 Hz, 1H), 7.53 (t, *J* = 7.40 Hz, 2H), 7.49 (d, *J* = 8.05 Hz, 1H), 7.22 (t, *J* = 7.57 Hz, 1H), 7.18 (t, *J* = 7.89 Hz, 1H), 6.51 (s, 1H), 4.68 (t, *J* = 7.40 Hz, 1H), 3.70-3.67 (m, 1H), 3.65-3.60 (m, 1H), 2.78 (d, *J* = 4.11 Hz, 3H), 2.37-2.31 (m, 1H), 2.21 (s, 1H), 2.18-2.12 (m, 1H), 2.10-2.03 (m, 1H), 1.86-1.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.4, 169.8, 169.0, 167.5, 139.9, 136.5, 132.9, 131.4, 128.0, 127.3, 124.9, 123.7, 123.1, 122.6, 121.6, 120.6, 60.2, 51.0, 28.11, 26.3, 25.3, 25.2; LC-MS: 431.10 $(M+Na)^+$; 447.07 $(M+K)^+$; Elemental analysis calculated for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72; Found: C, 64.55; H, 6.09 ; N, 13.85.

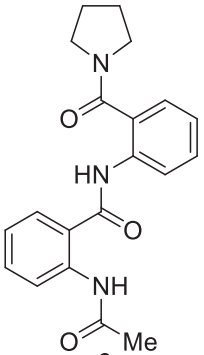
(R)-1-(2-(2-acetamidobenzamido)benzoyl)-N-methylpyrrolidine-2-carboxamide 2b:



2b

The product **2b** was isolated as a white solid (0.37 g, 92%). mp: 232-234 °C; $[\alpha]^{24}_{D}$: +130° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3330, 1701, 1654, 1640, 1618, 1603, 1523, 1424, 1215, 757, 669; ^{1}H NMR (500 MHz, DMSO-*d6*) δ: 10.47 (s, 0.8H), $10.36_{rotamer}$ (s, 0.2H), 10.20 (s, 1H), $8.28_{rotamer}$ (d, *J* = 7.93 Hz, 0.2H), 8.22 (d, *J* = 7.93 Hz, 0.8H), $7.91\text{-}7.90_{rotamer}$ (m, 0.2H), 7.78-7.77 (m, 0.8H), 7.70-7.64 (m, 2H), 7.60-7.59 (m, 1H), 7.55-7.42 (m, 2H), 7.30-7.25 (m, 2H), 7.23-7.16 (m, 1H), 4.32-4.27 (m, 1H), 3.57-3.50 (m, 2H), 2.48-2.48 (m, 3H), 2.19-2.11 (m, 1H), $2.08_{rotamer}$ (s, 0.7H), 2.06 (s, 2.3H), 1.83-1.80 (m, 3H); ^{13}C NMR (125 MHz, DMSO-*d6*) δ: $172.7_{rotamer,}$ 171.9, 168.6, $168.5_{rotamer}$, 167.1, $166.8_{rotamer}$, 138.2 $_{rotamer}$, 137.9, 135.0, $134.6_{rotamer}$, $131.9_{rotamer}$, 131.7, $131.3_{rotamer}$, 130.2, 129.9, 128.4, $128.3_{rotamer}$, 127.7, $126.5_{rotamer}$, $125.1_{rotamer}$, $125.0_{rotamer}$, 124.8, 124.2, $124.1_{rotamer}$, 123.2, 121.3, $62.6_{rotamer}$, 60.4, 50.0, $46.7_{rotamer}$, $31.6_{rotamer}$, 30.0, $25.8_{rotamer}$, 25.5, 24.8, $24.6_{rotamer}$, 24.5, $22.5_{rotamer}$; LC-MS: 431.13 $(M+Na)^+$; 447.09 $(M+K)^+$; Elemental analysis calculated for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72; Found: C, 64.81; H, 6.15; N, 13.53.

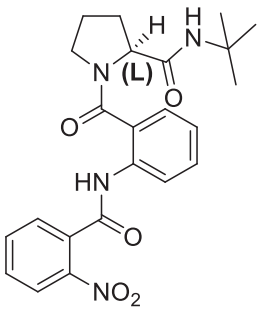
2-acetamido-N-(2-(pyrrolidine-1-carbonyl)phenyl)benzamide 6:



6

The product **6** was obtained as a white solid (0.47 g, 93%). mp: 132-134 °C; IR ($CHCl_3$) ν (cm^{-1}): 3290, 1688, 1652, 1621, 1587, 1519, 1449, 1416, 1298, 1216, 754, 669; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.24 (s, 1H), 10.82 (s, 1H), 8.63 (d, *J* = 8.54 Hz, 1H), 8.36 (d, *J* = 8.24 Hz, 1H), 7.77 (dd, *J* = 0.91 Hz, *J* = 7.93 Hz, 1H), 7.53-7.48 (m, 2H), 7.48 (dd, *J* = 1.22 Hz, *J* = 7.63 Hz, 1H), 7.19 (dt, *J* = 2.14 Hz, *J* = 7.33 Hz, 1H), 3.66 (bs, 2H), 3.57 (bs, 2H), 2.22 (s, 3H), 1.99 (bs, 2H), 1.91 (bs, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: $169.0_{rotamer}$, 168.7, 167.3, 140.2, 136.9, 133.0, 131.1, 127.9, 127.0, 124.9, 123.3, 123.2, 122.4, 121.5, 120.1, 50.3, $49.2_{rotamer}$, 46.5, $45.7_{rotamer}$, 26.4, $26.1_{rotamer}$, 25.3, $24.2_{rotamer}$, 24.2; LC-MS: 374.04 $(M+Na)^+$; 390.05 $(M+K)^+$; Elemental analysis calculated for $C_{20}H_{21}N_3O_3$: C, 63.71; H, 5.05; N, 12.38; Found: C, 68.17; H, 5.94; N, 12.15.

(S)-N-tert-butyl-1-(2-(2-nitrobenzamido)benzoyl)pyrrolidine-2-carboxamide 4:



4

To the solution of ester **9** (1 g, 2.5 mmol) in methanol (15 mL), $LiOH \cdot H_2O$ (0.31 g, 7.55 mmol) in water (5 mL) was added at 0 °C and the reaction mixture was stirred for 12 h. After the completion of reaction, the solvent was evaporated under reduced pressure, and the residue was neutralized with dil. HCl solution. The aqueous layer was then extracted with DCM (2 X 25 mL) and evaporated under reduced pressure to obtain the free acid which was then used for the next reaction without further purification.

To a solution of crude acid in dry DCM, tert-butyl amine (0.36 g, 5.0 mmol) was added followed by EDC.HCl (0.58 g, 3.0 mmol), and a catalytic amount of HOBt (0.03 g, 0.2 mmol) at 0 ^{o}C. The reaction mixture was then stirred at 15 min at room temperature for 8 hrs. The reaction mixture was diluted with DCM and washed sequentially with saturated solutions of $NaHCO_3$, $KHSO_4$, water and brine. The organic layer was then dried with anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the crude product which was purified by column chromatography (eluent: pet. ether/ethyl acetate 30:70, *Rf*: 0.6) to afford **4** as a white solid (0.95 g, 87%). mp: 178-180 °C; $[\alpha]^{24}_{D}$: +10° (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3310, 1673, 1624, 1589, 1531, 1456, 1421, 1350, 1215, 669; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.94 (s, 1H), 8.64 (d, *J* = 8.24 Hz, 1H), 8.11 (d, *J* = 8.24 Hz, 1H), 7.71-7.66 (q, 1H), 7.67 (d, *J* = 7.02 Hz, 1H), 7.58 (t, *J* = 7.94 Hz, 1H), 7.49 (t, *J* = 7.94 Hz, 1H), 7.30 (d, *J* = 7.32 Hz, 1H), 7.19 (t, *J* = 7.33 Hz, 1H), 5.75 (bs, 1H), 4.39-4.35 (m, 1H), 3.56-3.52 (m, 1H), 3.35-3.32 (m, 1H), 2.19-2.18 (m, 1H), 1.97-1.89 (m, 2H), 1.87-1.83 (m, 1H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.8, 168.4, 165.5, 146.0, 135.3, 133.6, 133.4, 130.5, 129.9, 129.3, 126.3, 126.0, 124.1, 123.9, 121.4, 60.4, 51.3, 49.4, 29.6, 28.3, 24.8; LC-MS: 439.09 $(M+H)^+$; 461.14 $(M+Na)^+$; 477.12 $(M+K)^+$; Elemental analysis calculated for $C_{23}H_{26}N_4O_5$: C, 63.00; H, 5.98; N, 12.78; Found: C, 62.85; H, 6.15; N, 12.60.

Crystal Data: X-ray intensity data measurements of all the compounds (**2a**, **2b**, **3**, **4**, **5** and **6**) 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, 2003).

All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2003). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2. Hydrogen atoms for compounds **2a**, **2b** and **3** were located in difference Fourier map and refined isotropically whereas for compounds **4** and **6**, they were placed in geometrically idealized position and constrained to ride on their parent atoms. Most of H-atoms in compound **5** were located in difference Fourier map and refined isotropically except for the proline H-atoms, which were placed in geometrically idealized position and constrained to ride on their parent atoms. Molecular and packing diagrams were generated using ORTEP-32 and Mercury-3. Geometrical calculations were performed using SHELXTL (Bruker, 2003) and PLATON.

Crystal data for 2a:

Colorless crystals of **2a** were grown by slow evaporation of a mixture of solvents methanol and chloroform. $C_{22}H_{24}N_4O_4$, M=408.45, colorless plate, 0.31 x 0.21 x 0.16 mm^3, orthorhombic, space group $P2_12_12_1$, a =10.4632(17), b=11.4185(19), c=16.753(3) Å, V = 2001.5(6) $Å^3$, Z = 4, T = 133(2) K, $2\theta_{max}$=50.00°, D_{calc} (g cm^{-3}) = 1.355, $F(000)$ = 864, μ (mm^{-1}) = 0.095, 10141 reflections collected, 3525 unique reflections (R_{int}=0.0217), 3416 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.971, T_{max} = 0.985, 367 refined parameters, S = 1.117, $R1$=0.0340, $wR2$=0.0793 (all data R =

0.0354, *wR*2 = 0.0800), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.196, $\Delta\rho_{min}$= -0.167 (eÅ^{-3}).

Colorless crystals of **2a** were grown by slow evaporation of a mixture of solvents dimethylsulfoxide-D6. $C_{22}H_{24}N_4O_4$, M=408.45, colorless plate, 0.16 x 0.14 x 0.13 mm^3, orthorhombic, space group $P2_12_12_1$, a = 10.4631(6), b= 11.4137(6), c= 16.7221(9) Å, V = 1997.00(19) Å^3, Z = 4, T = 100(2) K, $2\theta_{max}$=56.92°, D_{calc} (g cm^{-3}) = 1.359, $F(000)$ = 864, μ (mm^{-1}) = 0.095, 18043 reflections collected, 4995 unique reflections (R_{int}=0.0682), 4151 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.985, T_{max} = 0.988, 282 refined parameters, S = 1.027, R1=0.0463, *wR*2=0.0940 (all data R = 0.0602, *wR*2 = 0.1006), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.281, $\Delta\rho_{min}$= -0.219 (eÅ^{-3}).

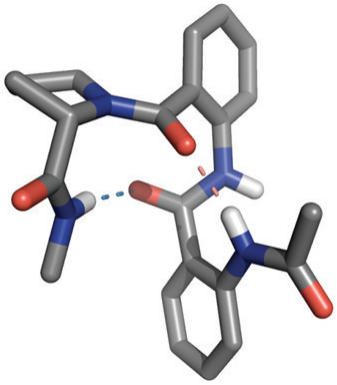


Figure 1: Crystal Structure of **2a** obtained in DMSO-*D*6

Crystal data for 2b:

Colorless crystals of **2b** were grown by slow evaporation of a mixture of solvents methanol and chloroform. $C_{22}H_{24}N_4O_4$, M=408.45, colorless prism, 0.17 x 0.13 x 0.09 mm^3, orthorhombic, space group $P2_12_12_1$, a = 10.4654(8), b= 11.4224(9), c= 16.7268(13) Å, V = 1999.5(3) Å^3, Z = 4, T = 100(2) K, $2\theta_{max}$=50.00°, D_{calc} (g cm^{-3}) = 1.357, $F(000)$ = 864, μ (mm^{-1}) = 0.095, 14600 reflections collected, 3518 unique reflections (R_{int}=0.0295), 3459 observed ($I > 2\sigma(I)$) reflections multi-scan absorption correction, T_{min} = 0.984, T_{max} = 0.992, 367 refined parameters, S = 1.114, R1=0.0308, *wR*2=0.0700 (all data R = 0.0316, *wR*2 = 0.0704, maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.187, $\Delta\rho_{min}$= -0.165 (eÅ^{-3}).

Crystal data for 3:

Colorless crystals of **3** were grown by slow evaporation of diethyl ether solution. $C_{20}H_{20}N_4O_5$, M=396.40, colorless needle, 0.78 x 0.16 x 0.10 mm^3, monoclinic, space group $P2_1$, a = 10.9252(7), b= 8.9395(6), c= 11.2908(7) Å, β = 116.821(2)°, V = 984.09(11) Å^3, Z = 2, T = 100(2) K, $2\theta_{max}$=57.64°, D_{calc} (g cm^{-3}) = 1.338, $F(000)$ = 416,

μ (mm^{-1}) = 0.098, 13960 reflections collected, 4884 unique reflections (R_{int}=0.0287), 4452 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.927, T_{max} = 0.990, 343 refined parameters, S = 1.054, $R1$=0.0386, $wR2$=0.0808 (all data R = 0.0443, $wR2$ = 0.0833, maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.302, $\Delta\rho_{min}$= -0.193 ($eÅ^{-3}$).

Crystal data for 4:

Single crystals of **4** were grown by slow evaporation of $CDCl_3$ solution. $C_{23}H_{26}N_4O_5$, M=438.48, colorless needle, 0.37 x 0.06 x 0.04 mm^3, orthorhombic, space group $P2_12_12_1$, a =7.564(3), b=15.725(7), c=18.913(8) Å, V = 2249.7(16) $Å^3$, Z = 4, T = 100(2) K, $2\theta_{max}$=50.00°, D_{calc} (g cm^{-3}) = 1.295, $F(000)$ = 928, μ (mm^{-1}) = 0.093, 16193 reflections collected, 3957 unique reflections (R_{int}=0.0510), 3787 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.967, T_{max} = 0.997, 365 refined parameters, S = 1.190, $R1$=0.0420, $wR2$=0.0871 (all data R = 0.0447, $wR2$ = 0.0882, maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.197, $\Delta\rho_{min}$= -0.162 ($eÅ^{-3}$).

Crystal data for 5:

Colorless crystals of **5** were grown by slow evaporation of a mixture of benzene and chloroform. $C_{25}H_{21}BrN_4O_5$. C_6H_6, M=615.48, colorless plate, 0.29 x 0.20 x 0.14 mm^3, monoclinic, space group $P2_1$, a =9.628(3), b=11.943(4), c=12.282(4)Å, β = 91.847(6)°, V = 1411.5(8) $Å^3$, Z = 2, T = 133(2) K, $2\theta_{max}$=51.00°, D_{calc} (g cm^{-3}) = 1.448, $F(000)$ = 632, μ (mm^{-1}) = 1.504, 7184 reflections collected, 4873 unique reflections (R_{int}=0.0215), 4521 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.669, T_{max} = 0.817, 382 refined parameters, 49 restraints applied, S = 1.000, $R1$=0.0300, $wR2$=0.0717 (all data R = 0.0326, $wR2$ = 0.0730), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.706, $\Delta\rho_{min}$= -0.307 ($eÅ^{-3}$).

Crystal data for 6:

Colorless crystals of **6** were grown by slow evaporation a mixture of dichloromethane and acetonitrile. $C_{20}H_{21}N_3O_3$, M=351.40, colorless needle, 0.61 x 0.20 x 0.09 mm^3, monoclinic, space group $P2_1/c$, a =21.610(3), b=8.6706(12), c=21.210(3) Å, β = 118.719(2)°, V = 3485.2(8) $Å^3$, Z = 8, T = 100(2) K, $2\theta_{max}$=50.00°, D_{calc} (g cm^{-3}) =

1.339, *F*(*000*) = 1488, □ (mm^{-1}) = 0.092, 17077 reflections collected, 6121 unique reflections (R_{int}=0.0619), 5518 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.947, T_{max} = 0.992, 480 refined parameters, *S* = 1.054, *R*1=0.0511, *wR*2=0.1208 (all data *R* = 0.0561, *wR*2 = 0.1240, maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.343, $\Delta\rho_{min}$= -0.335 ($eÅ^{-3}$). C18' atoms of the proline moiety in this compound showed positional disorder over two positions (C18' and C18") which have been refined with occupancies 0.6 and 0.4 respectively.

Discussion on Crystal Structure

Compound **2a** crystallized in orthorhombic chiral space group $P2_12_12_1$ irrespective of the different solvents (methanol and DMSO) used for crystallization. The conformation of the molecule as observed in the crystal structure reveals doubly folded conformation solely due to the two strong intramolecular N-H···O hydrogen bonds featuring two distinctly different folds - one towards the N-terminus with a C_{10}-hydrogen-bonded network [graph set- S(10)] through short and linear intramolecular N-H···O [N1-H1N···O3; H1N···O3 = 2.11(2) Å, N1···O3 = 2.977(2) Å, ∠N1-H1N···O3 = 162(2)°] interaction engaging two Ant residues, and the other one at the C-terminus displaying a C_{11}-hydrogen-bonded network [graph set- S(11)] *via* another short and linear intramolecular N-H···O [N4-H4N···O2; H4N···O2 = 2.12(2) Å, N4···O2 = 2.948(2) Å, ∠N4-H4N···O2 = 165(2)°] interaction involving replacement of H-bonding donor group by nitro group at the N-terminus. Neighboring molecules form helical assemblies across the crystallographic two-fold screw axis, dictated exclusively by intermolecular strong N-H···O hydrogen bond engrossing C=O group of the Pro residue and N-H of the Ant moiety [N2-H2N···O4; H2N···O4 = 1.94(2) Å, N2···O4 = 2.783(2)Å, ∠N2-H2N···O4 = 165(2)°; symmetry code: ½-*x*, 1-*y*, ½+*z;* graph set: C(9)]. The aggregation of these helices *via* various weak interactions led to crystal formation.

Molecular packing viewed down the *c*-axis reveals the bridging of neighboring helices *via* two C-H···O interactions namely, C12-H12···O1 (along *b*-

axis) and C11-H11···O2 (along *a*-axis). The former contact is shorter than the latter whereas the angle of approach in both the contacts is close to linearity [C12-H12···O1; H12···O1 = 2.48(2) Å, C12···O1 = 3.426(2)Å, ∠C12-H12···O1 = 162(2)°; symmetry code: *x*, 1+*y*, *z* and C11-H11···O2; H11···O2 = 2.63(2) Å, C11···O2 = 3.456(2)Å, ∠C11-H11···O2 = 153(2)°; symmetry code: -½+*x*, 1.5-*y*, -*z*].

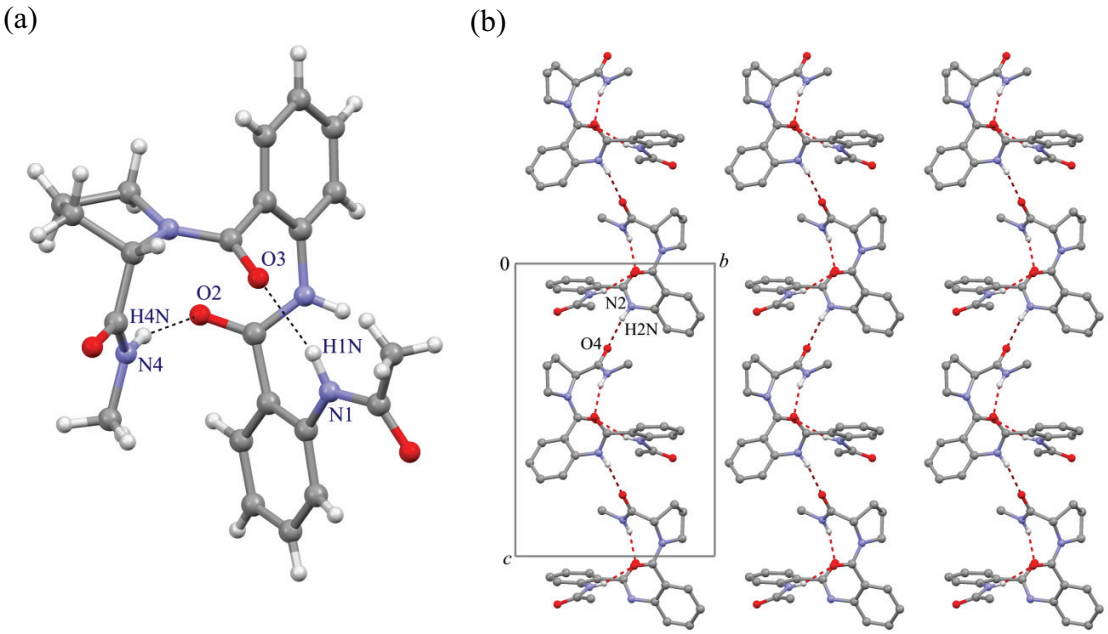


Figure S1. (a) Intramolecular geometry exhibited by **2a** with the help of two N-H···O interactions and (b) Molecular packing viewed down *a*-axis in crystals of **2a** displaying helical architecture of molecules linked *via* N-H···O interactions.

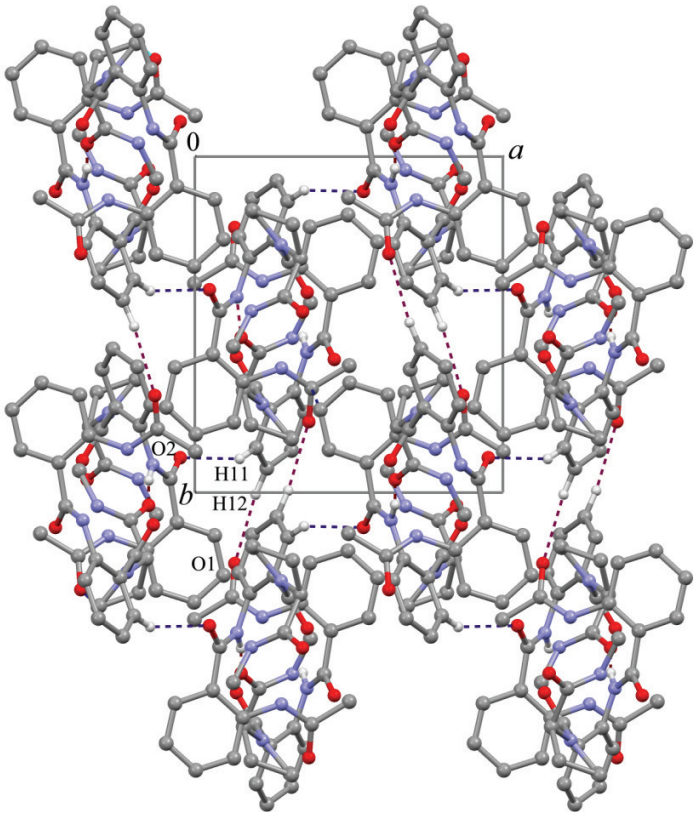


Figure S2. Networking of the neighboring helices through C-H···O interactions, leading to compact packing in crystal.

The crystal structure of **2b** is exactly similar to **2a**, as both are L and D enantiomers of the same chiral molecule.

Crystal structures of 3, 4 and 5

Compounds **3**, **4** and **5** have a similar backbone structure as that of **2**, except that they are devoid of the H-bond donor at the N-terminus. In place of the crucial N-acetyl group, the oligoamides **3**, **4** and **5** possess nitro group - devoid of H-bond donor ability. The substituent's at C-terminus were varied (N-Me in **3**, N-^{t}Bu in **4**, and *p*-Br-anilide in **5**), keeping the N-terminus nitro group constant, in order to judge the substituent effects on intramolecular geometry and folding behavior. Crystal structures of **3** and **5** were belonging to monoclinic $P2_1$ space group with **5** as benzene solvate whereas compound **4** crystallized in orthorhombic $P2_12_12_1$ space group. Conformation of the molecules as

observed in the crystal structure of **3**, **4** and **5** reveals short and linear intramolecular N-H···O [graph set S(9)] C_9 hydrogen bonding network involving N-H group of the Ant residue and C=O of the Pro moiety. This is in contrast to the C_{10} and C_{11} member N-H···O hydrogen bonding network observed in **2** due to the absence of H-bonding donor at the N-terminus in these compounds. The omission of H-bonding donor at the N-terminus not only demolished C_{10} N-H···O hydrogen bond, but also the C_{11} N-H···O bonding structure. The geometry of intramolecular N-H···O hydrogen bond is short and linear in **3** and **4** whereas it deviates in **5** (Table 1).

Closely associated molecules in **3** form a helical architecture [graph set: C(4)] across the crystallographic 2-fold screw axis (*b*-axis) *via* N3-H3N···O2 interactions involving N-H of the Pro residue and C=O of the Ant residue. This contact is longer than the intramolecular N-H···O interactions, however the angle of approach is very linear in this case (Table 1). This helical arrangements also brings the nitrobenzene C20-H20 of Ant residue close to the carbonyl oxygen O2 of Pro residue and C11-H11A of the proline moiety in close proximity to the carbonyl oxygen O1 of the Ant residue in the next molecule of the helical chain generating two moderate C-H···O interactions, C20-H20···O2 and C11-H11A···O1 thereby supporting the helical assembly. Molecular packing viewed down the helical axis reveals association of neighboring helices *via* two C-H···O interactions, C7-H7···O4 and C6-H6···O5, thereby providing tight binding of the helices in the crystal lattice.

(a) (b)

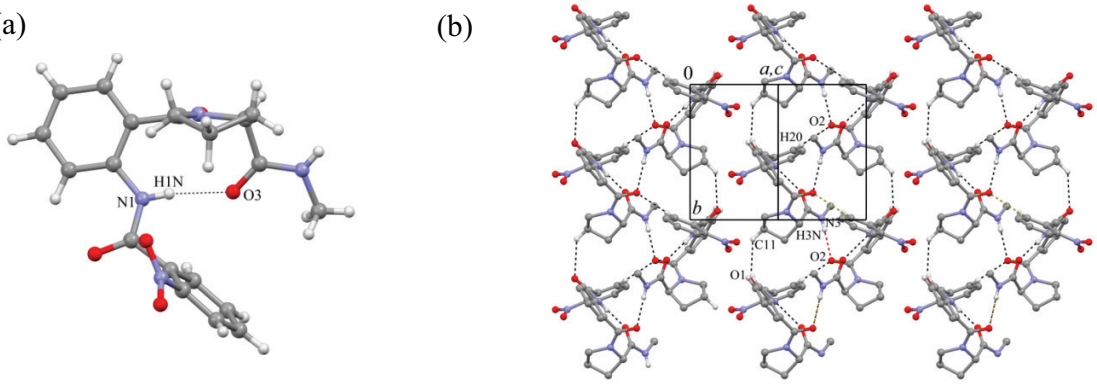


Figure S3. (a) Ball and stick view of **3** displaying intramolecular N-H···O interactions, (b) Molecular packing viewed along *b*-axis in crystals of **3** displaying helical architecture of molecules linked *via* N-H···O and C-H···O interactions.

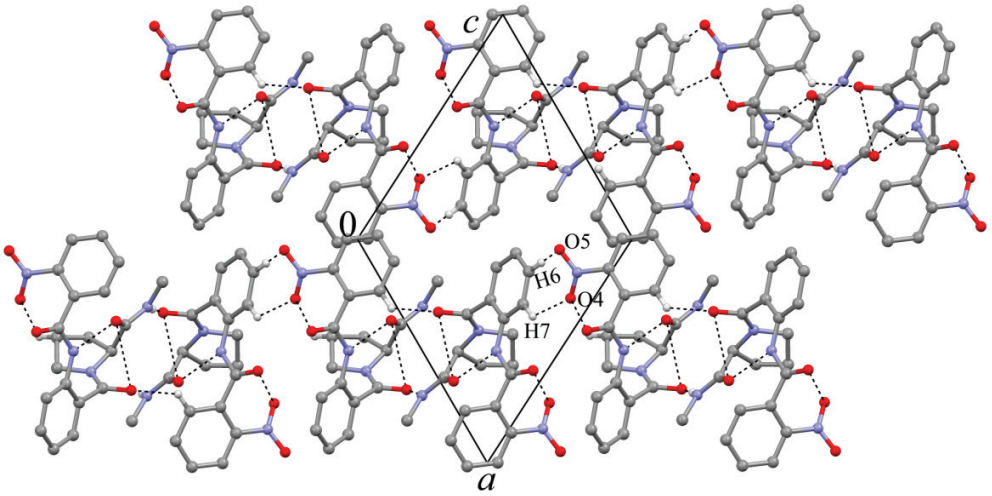


Figure S4. View of the packing of the closely related helices through C-H···O interactions leading to compact packing in the crystal.

Crystal Structure of 4

The molecular conformation dictated by intramolecular N-H···O hydrogen bond was further supported by two short and linear C-H···O interactions, C12-H12A···O4 and C10-H10A···O5, thus stabilizing the geometry (Figure S5a, and Table S1). The neighboring molecules are associated *via* trifurcated interactions involving one N-H···O (N3-H3N···O2) and two C-H···O's (C9-H9···O2 and C10-H10B···O2), consequently generating helical architecture about a crystallographic two-fold screw axis (Figure S5b, and Table 1). The unit translated molecules within the helical chain are further connected through C22-H22···O5 contact. No significant interactions were observed between the adjacent helices along the *b*-axis. Molecular view down *a*-axis reveals linking of closely associated helices through catemeric C4-H4···O1 interaction to generate compact packing of molecules.

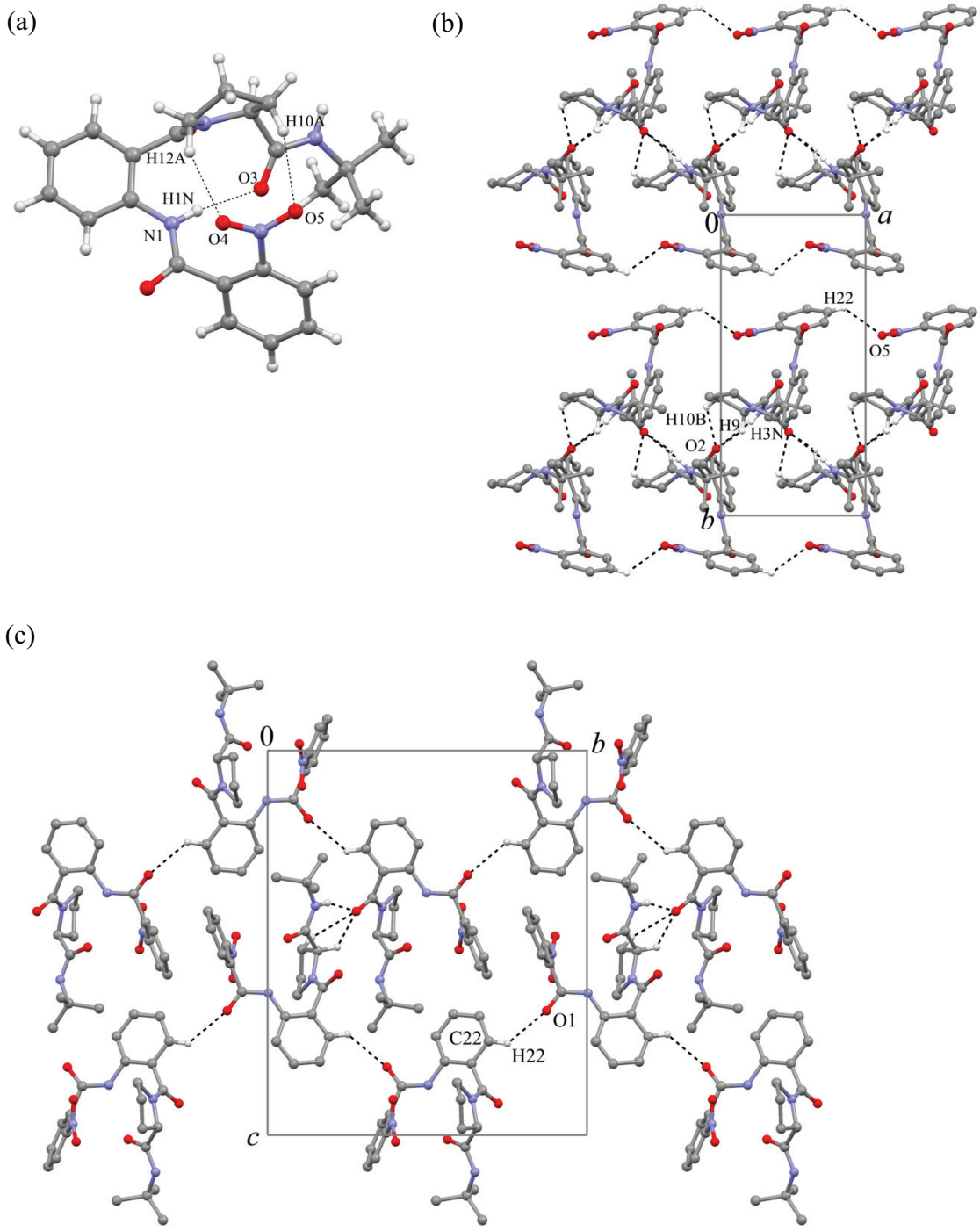


Figure S5. (a) Ball and stick view of **4** displaying molecular conformation dictated solely by intramolecular N-H···O and C-H···O interactions, (b) Molecular packing viewed along *c*-axis in crystals of **4** showing helical architecture of molecules linked *via* trifurcated N-H···O and C-H···O interactions, (c) Packing of the closely related helices through catemeric C-H···O interactions leading to compact packing in crystal.

Crystal Structure of 5

Crystal of **5** is the inclusion complex containing benzene as solvate with host-guest ratio is 1:1. As mentioned earlier, the intramolecular geometry of **5** is similar to **3** and **4,** except, the N-H···O interaction is somewhat longer (Figure S6a, Table 1). Notable difference is noticed in the association of neighboring molecules in crystals of **5** compared to **2**, **3** and **4**. Here, strong intermolecular N-H···O (N3-H3N···O1) interactions do not direct the helical assembly of molecules, and instead, it helps in generating one-dimensional molecular chain. The neighboring chains are connected through two C-H···Br (C4-H4···Br1 and C6-H6···Br1) and one C-Br···C=O (Br1···C8 = 3.495Å, ∠ Br1···C8=O2 = 86.0°) contact generating two-dimensional corrugated sheet structure (Figure S6b). Helical assembly in the crystals of **5** are directed by short and linear C-H···O (C23-H23···O5) interaction involving nitro group oxygen and nitrobenzene C-H group. These closely associated helical chains are stitched *via* another short and linear C-H···O (C5-H5···O2) interaction (Figure S7a). Molecular packing viewed down the *a*-axis reveals host guest association. The occluded benzene molecules in the lattice are just making weak off-centered C-H···π contact with the host molecule and lie along the helical axis in between the neighboring helices (Figure S7b). It indicates that the benzene molecules only fill the space created by the host molecules and do not direct the molecular assembly.

(a) (b)

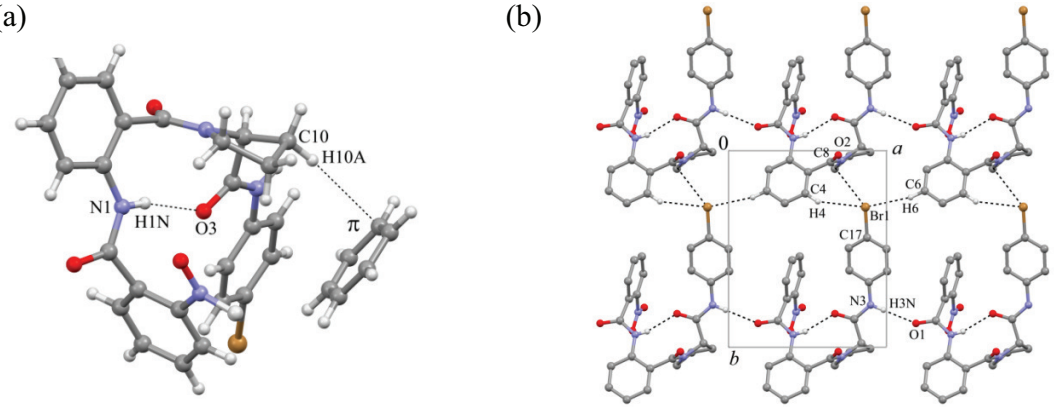


Figure S6. (a) View of **5** displaying molecular conformation dictated solely by intramolecular N-H···O interaction. The association of guest benzene solvent with the host *via* C-H···π contact is also displayed, (b) Molecular packing viewed along *c*-axis in crystals of **5** showing sheet architecture of molecules.

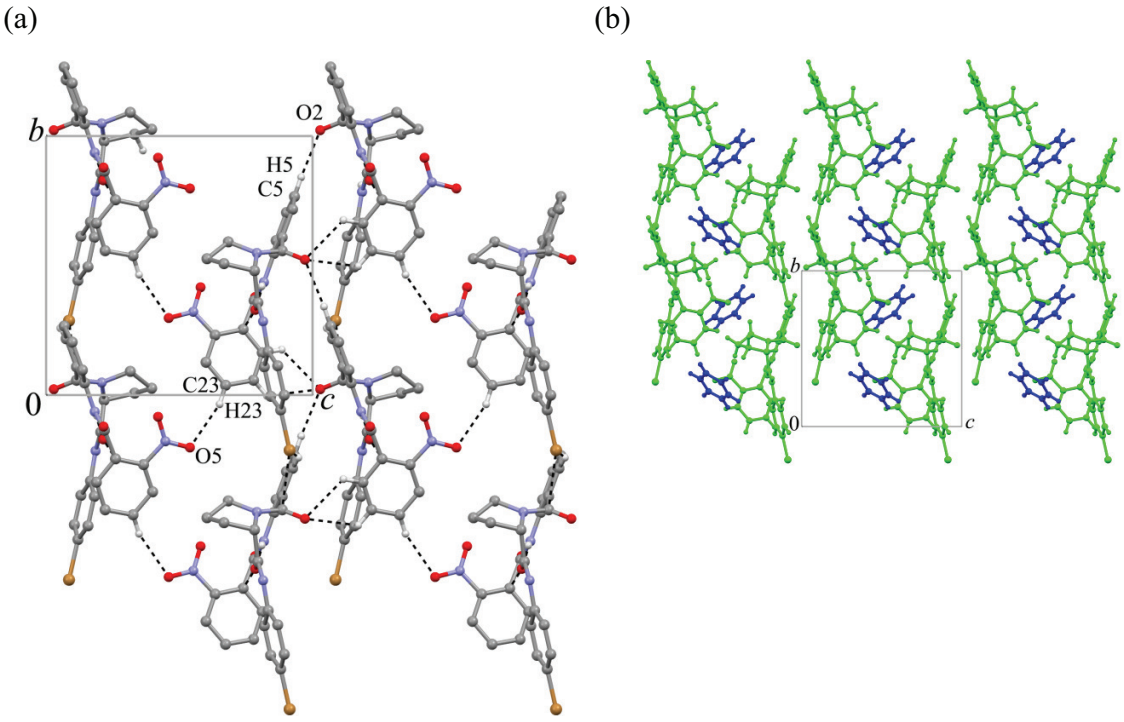


Figure S7. (a) Packing of the closely related helices through catemeric C-H···O interactions leading to compact molecular arrangement in crystals of **5**, (b) Molecular organization viewed down *a*-axis showing host guest association.

Crystal structure of 6

Compound **6**, which lacks the amide group at Pro moiety was made in an attempt to verify the individual contribution of the C-terminus H-bond donor in the stabilization of the entire intramolecular geometry. Crystals of **6** belong to monoclinic $P2_1/c$ space group containing two molecules in the asymmetric unit. Pyrrolidine group of the prime molecule revealed orientational disorder over two positions with occupancies 0.6 and 0.4. The conformation of the molecule of **6** as observed in its crystal strcuture revealed the absence of not only the C_{11} but also the C_{10} H-bonded networks – with the consequence of complete breakdown of the entire folded architecture of the peptide. The only H-bonding observed in this case was the Hamilton-type C_6 bonding - characteristic of consecutive Ant rings. Close look at the molecular structure of both symmetry independent molecules reveals that although six

membered (C_6) N-H···O interaction is short but it deviates too much from linearity (Figure S8a and Table S1). These two symmetry independent molecules form *pseudo* centrosymmeric dimeric structure *via* strong N-H···O interactions involving N-H of the Ant residue and C=O of the pyrrolidine ring (N2-H2N···O3' and N2'-H2N'···O3). These adjacent dimers are connected to each other *via* C20-H20C···O3 contact engaging only the unprimed molecules. There is direct connection between primer molecule in this view. The unprime molecules are further connected to each other *via* C18-H18B···O3 contact, thus O3 is acting as a bifurcated acceptor (Figure S8b).

Each symmetry independent molecule forms its own helical architecture and are placed alternately along *ac* diagonal. Prime lebelled molecules form helical arraangement *via* short C17-H17···O3' interaction, whereas unprimed molecules assembled helically merely *via* van der Waal's forces. These two different helices linked *via* C13-H13···O1'and off-centered C12'-H12'···π interactions (Figure S9). There are other various weak C-H···O's and C-H···π's interactions which help in compact arrangement of the molecules in crystals of **6.**

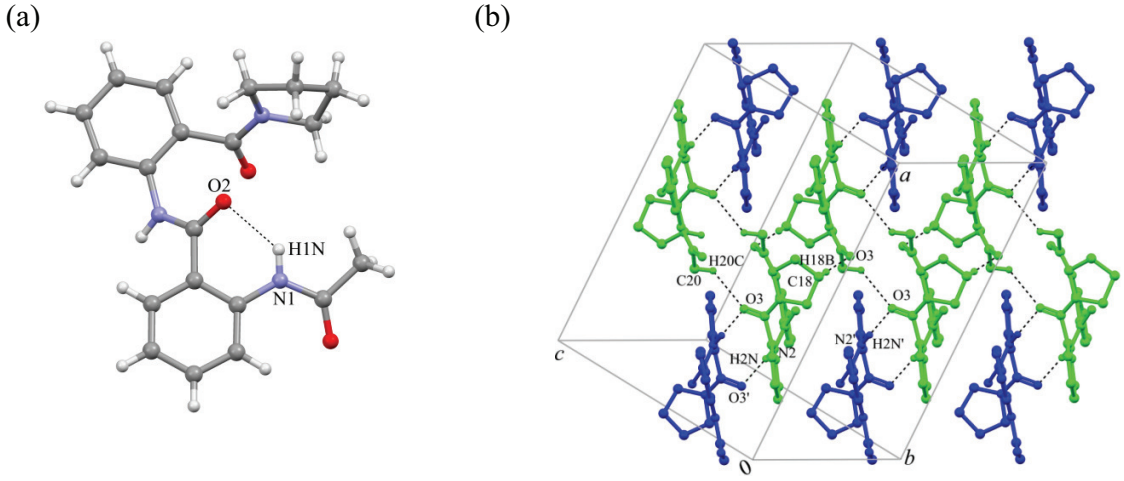


Figure S8. (a) View of unprimed molecule of **6** displaying molecular conformation, (b) Molecular packing viewed along *ac*-diagonal in crystals of **6** showing adhering of *pseudo* centrosymmetric dimers *via* C-H···O interactions.

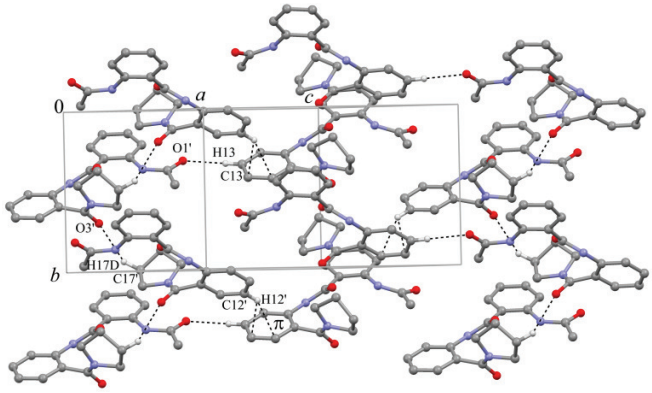


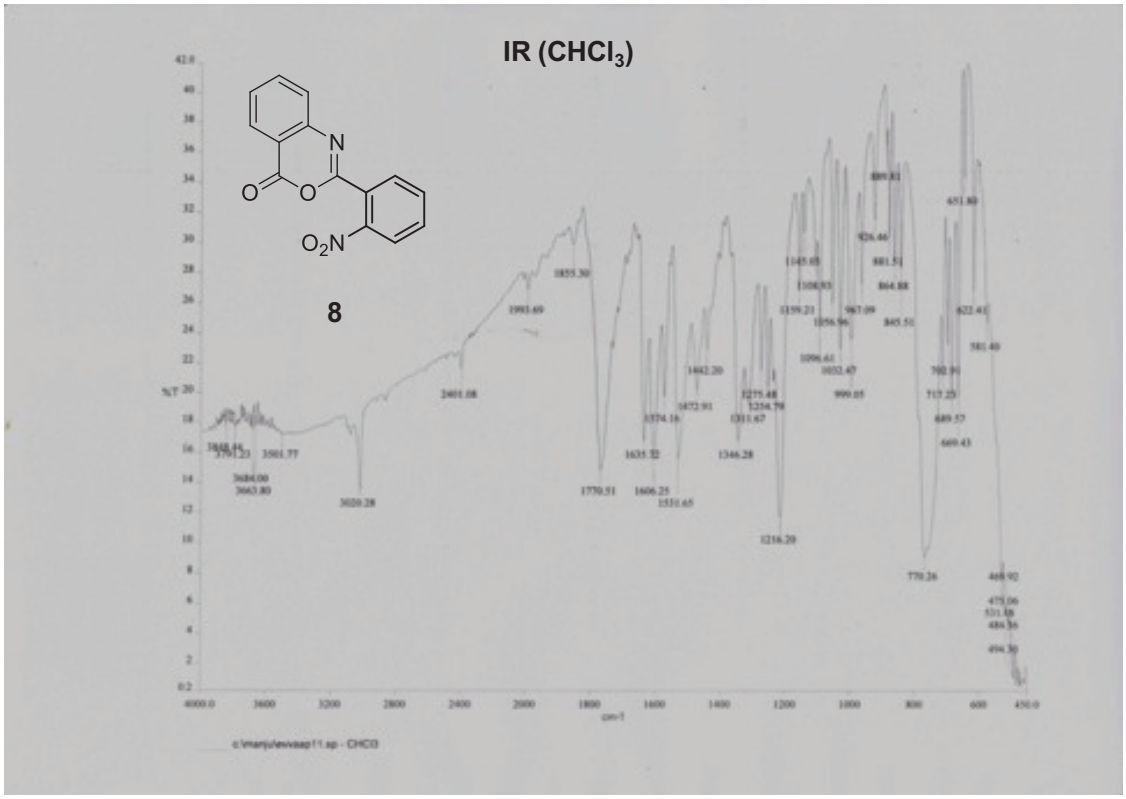
Figure S9. Packing of the closely related helices along *ac*-diagonal through C-H···O interactions leading to compact molecular arrangement in crystals of **6**.

Table S1. Geometrical parameters of intra and intermolecular interactions in crystals of **3**, **4**, **5**, and **6**.

No.	Contacts	D-H (Å)	H···A(Å)	D··A (Å)	N-H···O (°)	Symmetry codes
3	N1-H1N···O3	0.83(2)	1.98(2)	2.809(2)	170(2)	*x*, *y*, *z*
	N3-H3N···O2	0.81(2)	2.10(2)	2.902(2)	177(2)	1-*x*, 1/2+*y*, 2-*z*
	C11-H11A···O1	1.00(3)	2.62(3)	3.400(2)	135(2)	*x*, 1+*y*, *z*
	C20-H20···O2	0.95(2)	2.38(2)	3.109(2)	134(1)	1-*x*, -1/2+*y*, 2-*z*
	C7-H7···O4	0.98(2)	2.51(2)	3.225(2)	129(1)	-*x*, -1/2+*y*, 1-*z*
	C6-H6···O5	0.95(2)	2.55(2)	3.451(2)	159(1)	-*x*, -1/2+*y*, 1-*z*
4	N1-H1N···O3	0.88(3)	2.07(3)	2.941(3)	171(2)	*x*, *y*, *z*
	C10-H10A···O5	0.99	2.51	3.459(3)	162	*x*, *y*, *z*

	C12-H12A···O4	0.99	2.43	3.349(3)	155	*x*, *y*, *z*
	N3-H3N···O2	0.87(3)	2.34(3)	3.167(3)	159(2)	-1/2+*x*,1.5-*y*,2-*z*
	C9-H9···O2	1.00	2.41	3.103(3)	126	-1/2+*x*,1.5-*y*,2-*z*
	C4-H4···O1	0.98(2)	2.53(2)	3.224(3)	128(1)	1-*x*,1/2+*y*,1.5-*z*
	C22-H22···O5	0.91(3)	2.54(3)	3.124(3)	122(2)	1+*x*, *y*, *z*
	C10-H10B···O2	0.99	2.60	3.265(3)	125	-1/2+*x*,1.5-*y*,2-*z*
5	N1-H1N···O3	0.76(3)	2.14(3)	2.870(3)	165(3)	*x*, *y*, *z*
	N3-H3N···O1	0.84(2)	2.17(2)	2.995(3)	167(2)	1+*x*, *y*, *z*
	C5-H5···O2	0.95	2.36	3.312(3)	176	1-*x*, 1/2+*y*, -*z*
	C16-H16···O2	0.95	2.69	3.436(3)	136	2-*x*, -1/2+*y*, -*z*
	C23-H23···O5	0.95	2.47	3.392(4)	163	1-*x*, -1/2+*y*, 1-*z*
	C4-H4···Br1	0.95	2.94	3.751(3)	168	*x*, 1+*y*, *z*
	C6-H6···Br1	0.95	2.82	3.752(3)	145	-1+*x*, 1+*y*, *z*
6	N1-H1N···O2	0.88	2.08	2.7634(19)	134	*x*, *y*, *z*
	N1'-H1N'···O2'	0.88	2.16	2.7956(19)	129	*x*, *y*, *z*
	N2-H2N···O3'	0.88	2.02	2.8547(19)	158	*x*, -1+*y*, *z*

	N2'-H2N'···O3	0.88	1.93	2.7693(19)	159	*x*, 1+*y*, *z*
	C13-H13···O1’	0.95	2.52	3.467(2)	175	-*x*, 1-*y*, -*z*
	C18-H18*B*···O1	0.99	2.64	3.628(2)	173	1-*x*, 1-*y*, 1-*z*
	C19-H19*B*···O1	0.99	2.48	3.340(2)	145	*x*, 1/2-*y*, -1/2+*z*
	C20-H20*C*···O3	0.98	2.55	3.318(2)	136	1-*x*, -*y*, 1-*z*
	C20’-H20*D*···O1’	0.98	2.68	3.413(3)	132	-*x*, 2-*y*, -*z*
	C17'-H17D···O3'	0.99	2.48	3.371(2)	149	-*x*, -1/2+*y*, 1/2-*z*
	C18”-H18F···O1'	0.99	2.60	3.553(5)	162	-*x*, 1/2+*y*, 1/2-*z*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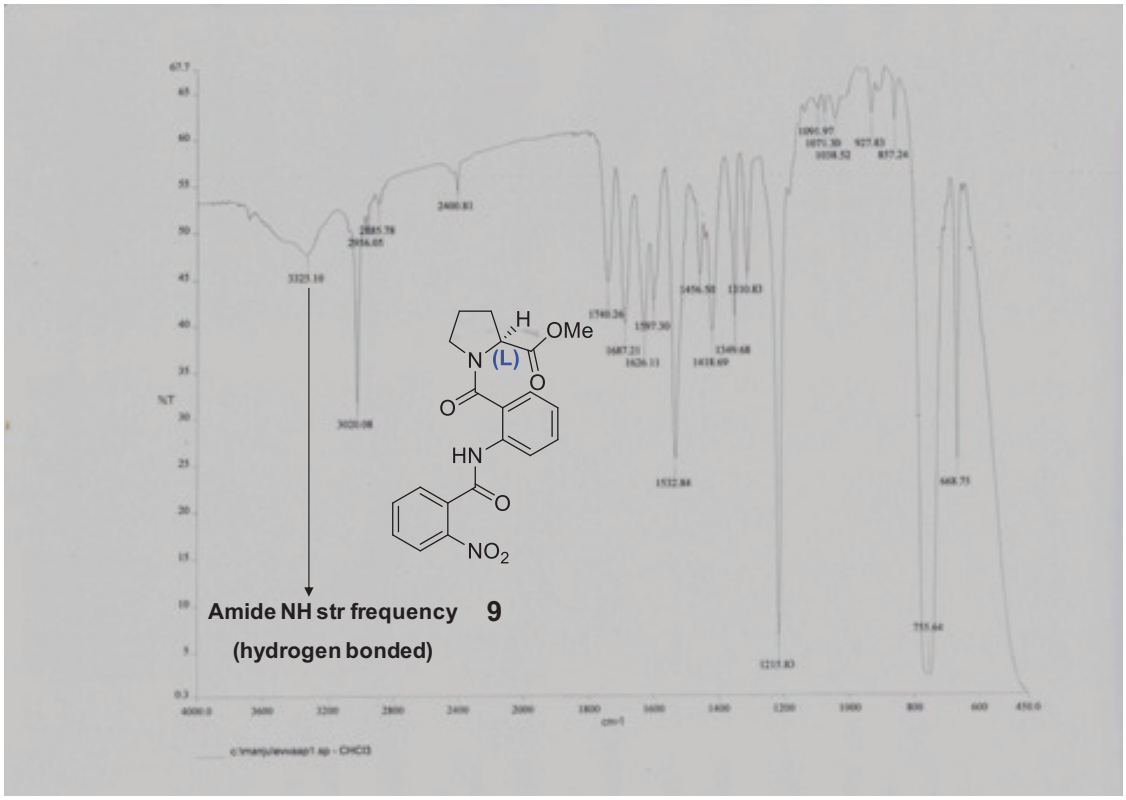
Amide NH str frequency
(hydrogen bonded)
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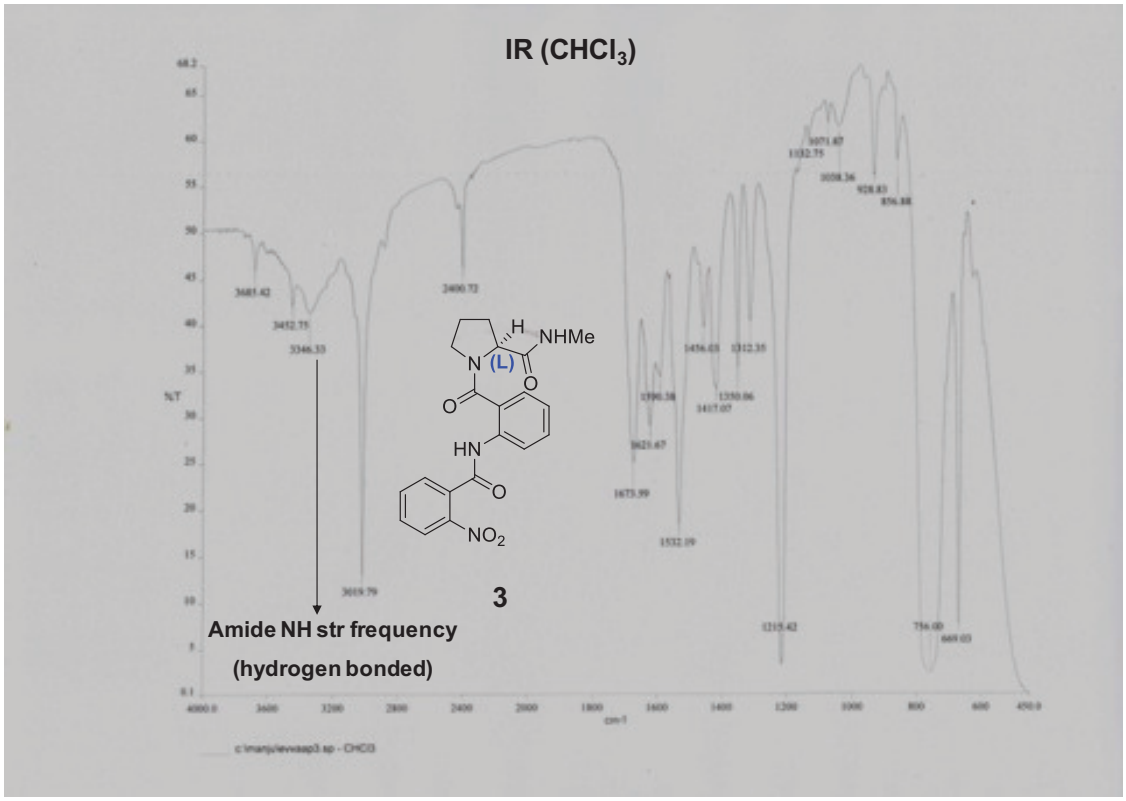
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3
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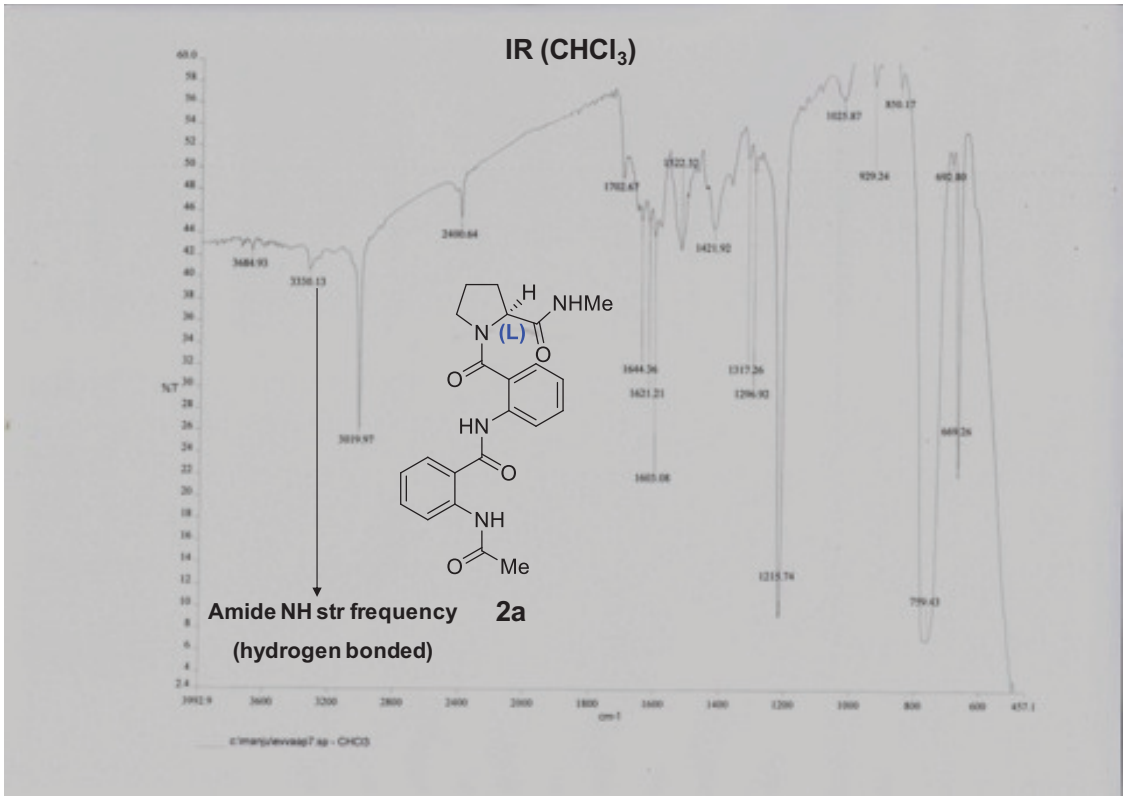
(hydrogen bonded)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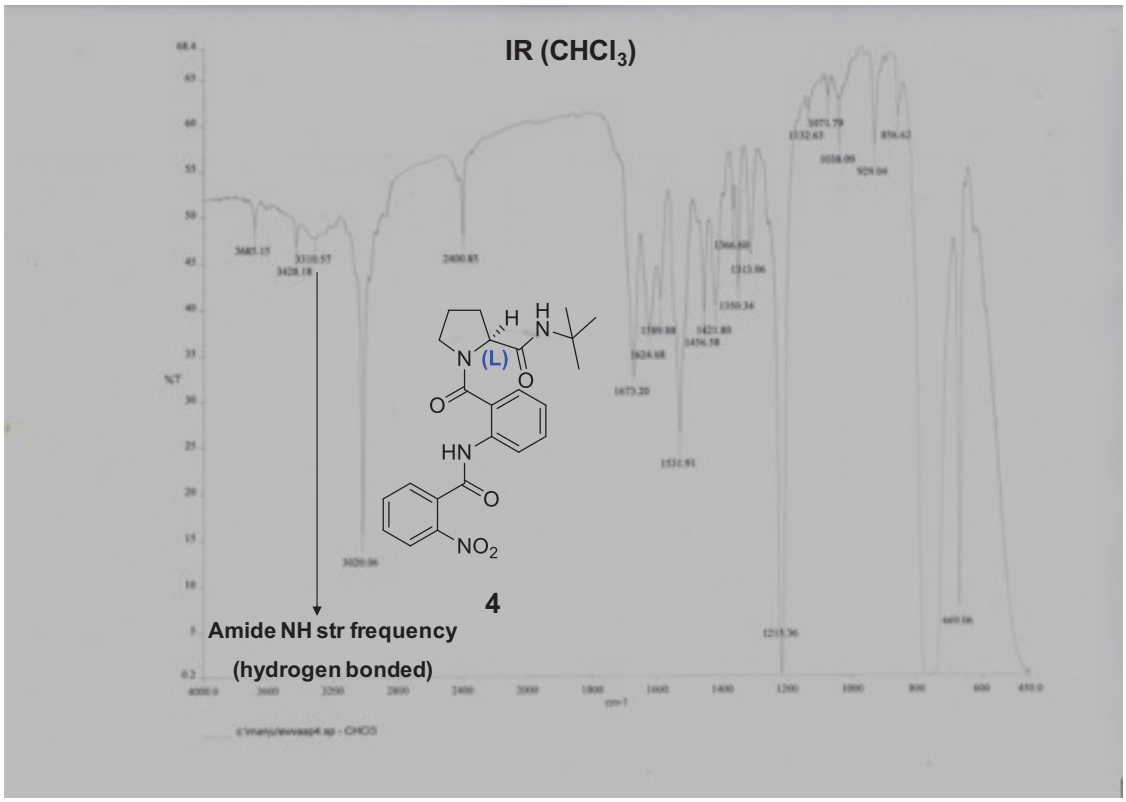
(L)
HN
NH
Me
2a
Amide NH str frequency
(hydrogen bonded)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(L)
4
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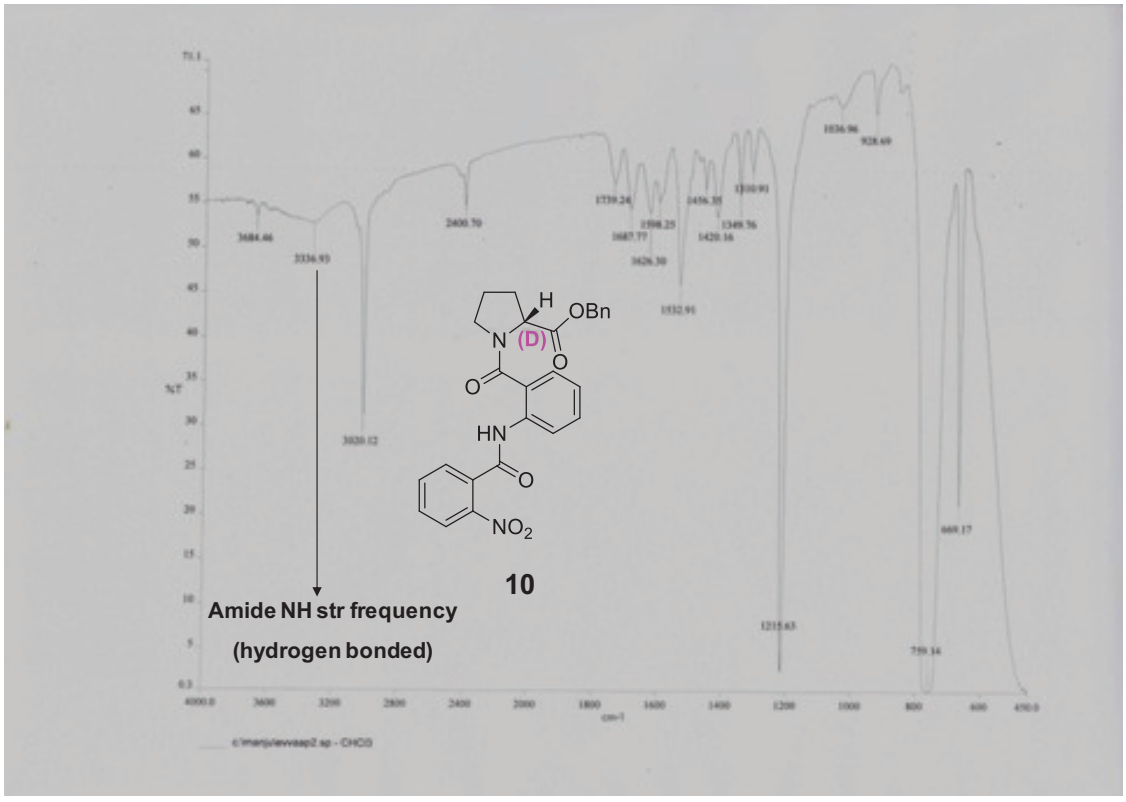
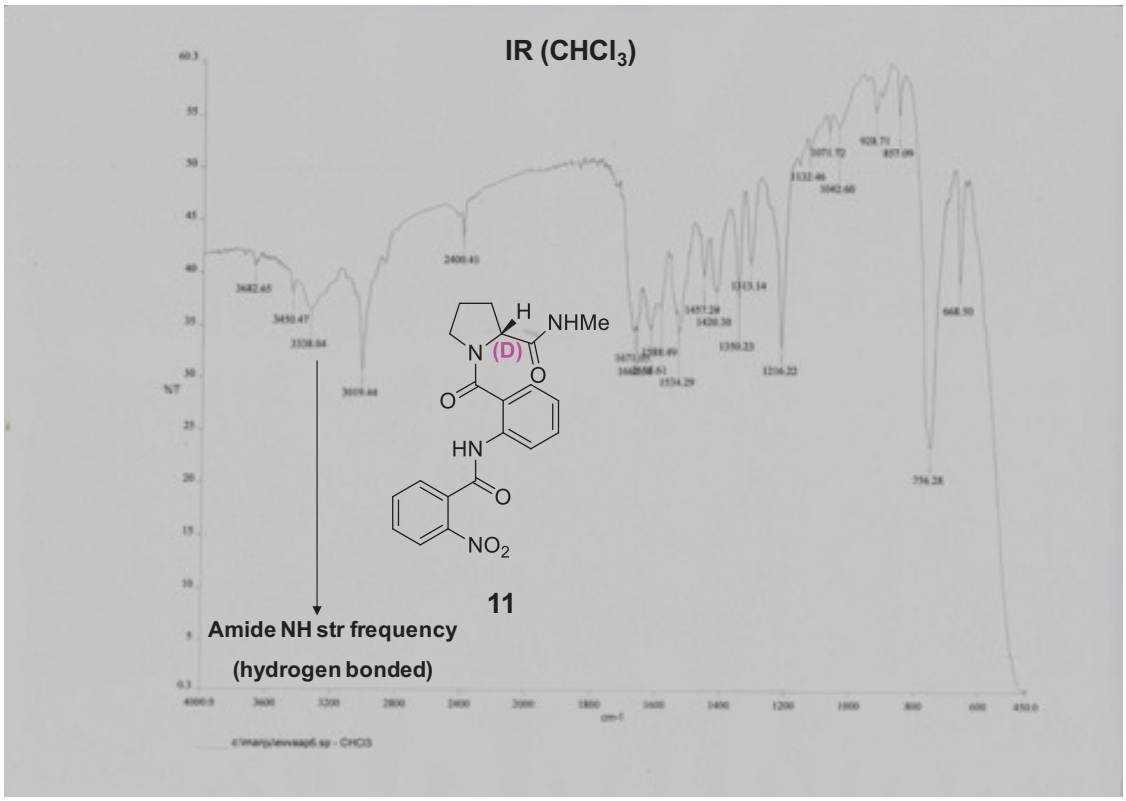
(hydrogen bonded)


(D)
OBn
10
Amide NH str frequency
(hydrogen bonded)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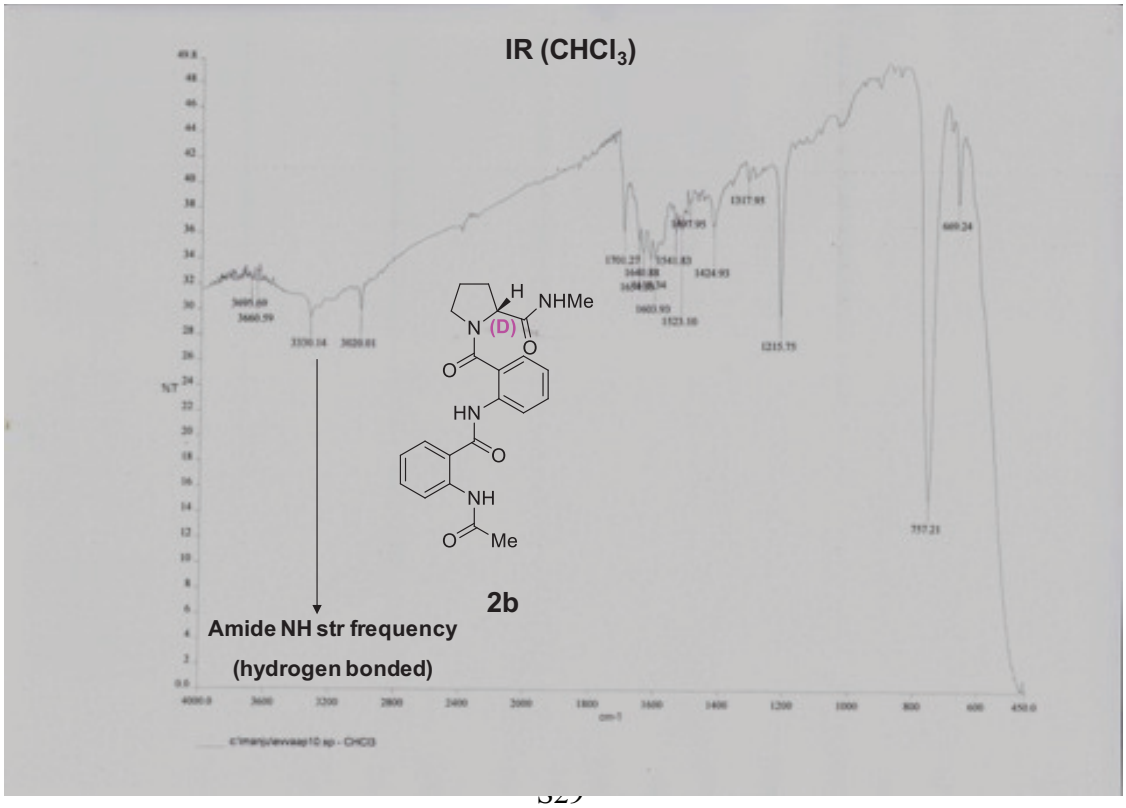
NHMe
N
(D)
O
O
HN
O
NO_2
11
Amide NH str frequency
(hydrogen bonded)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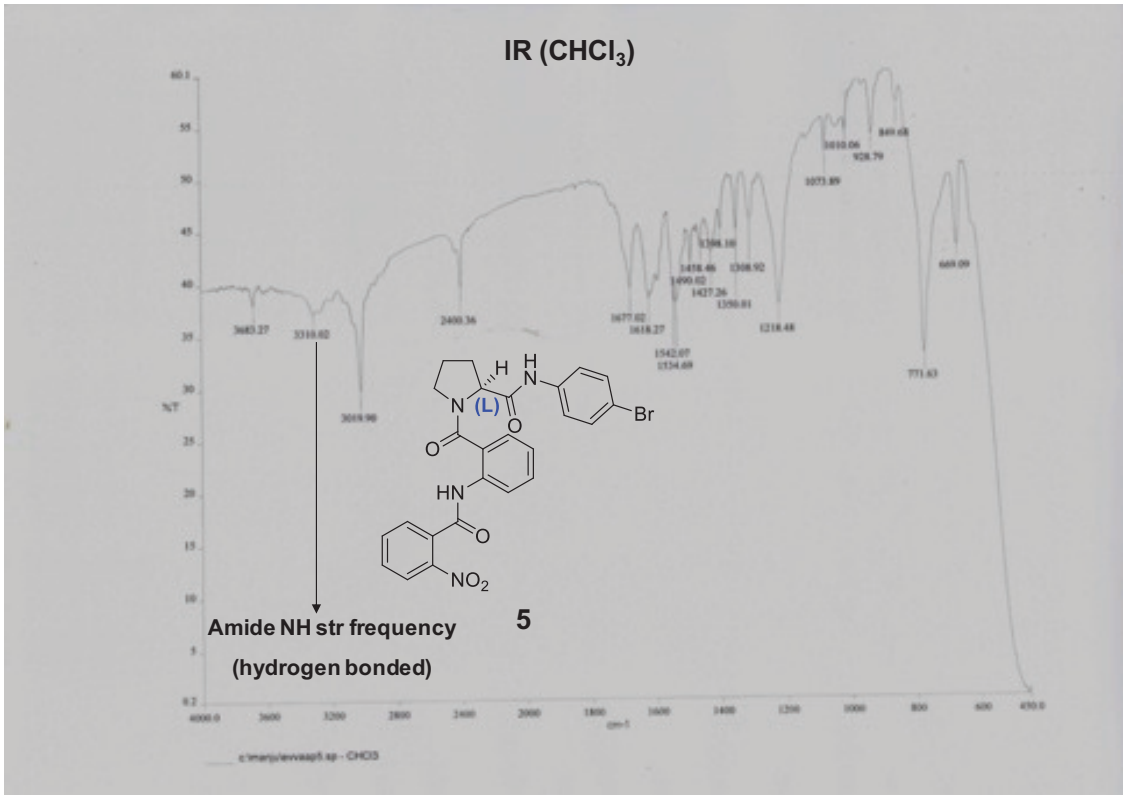
NHMe
N
(D)
O
O
HN
O
NH
O
Me
2b
Amide NH str frequency
(hydrogen bonded)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Amide NH str frequency
(hydrogen bonded)
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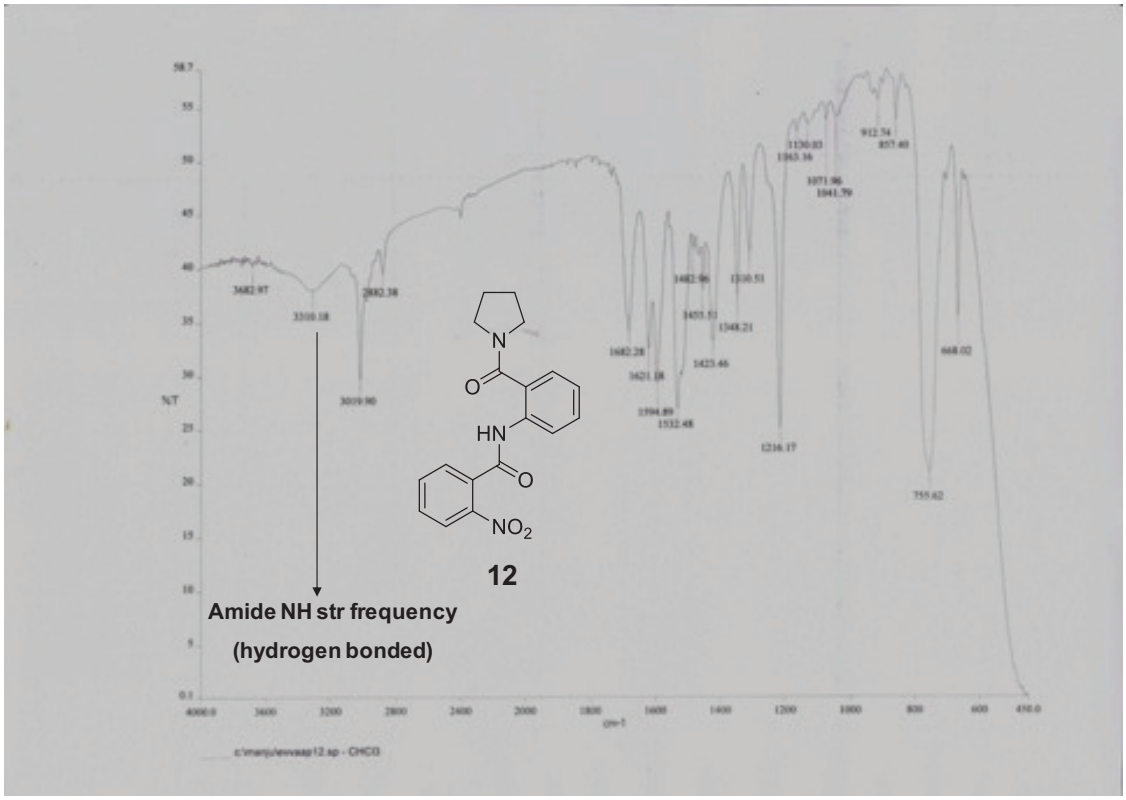
(L)
Br
HN
NO_2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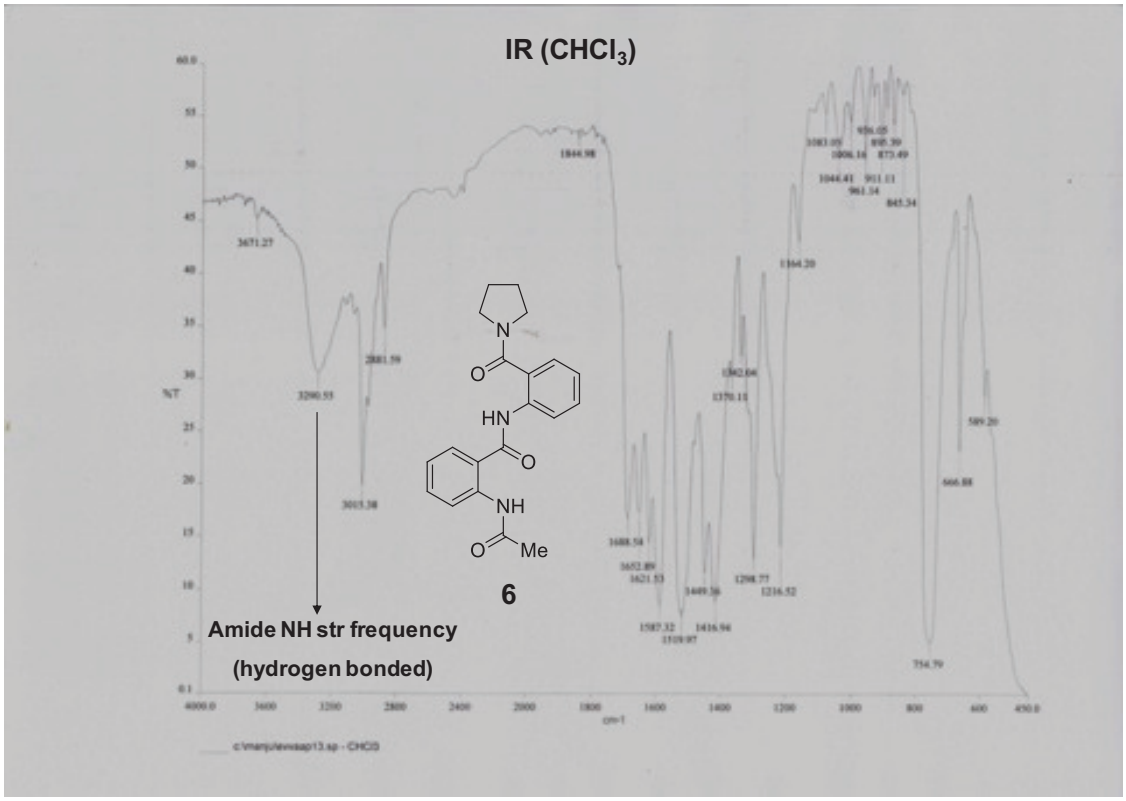
HN
NO_2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Amide NH str frequency
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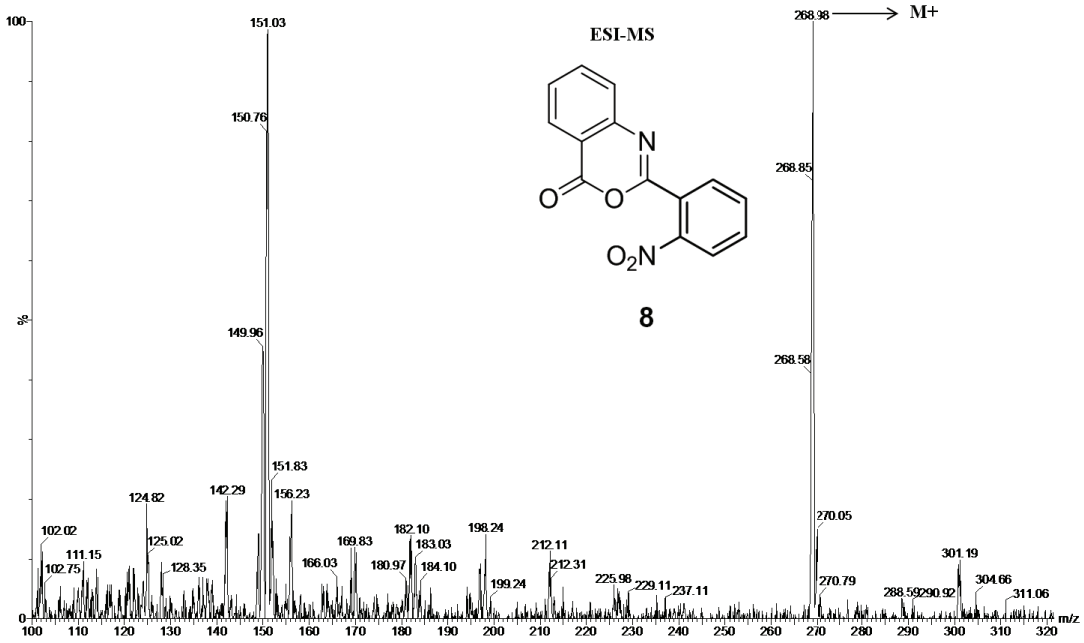
6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M+
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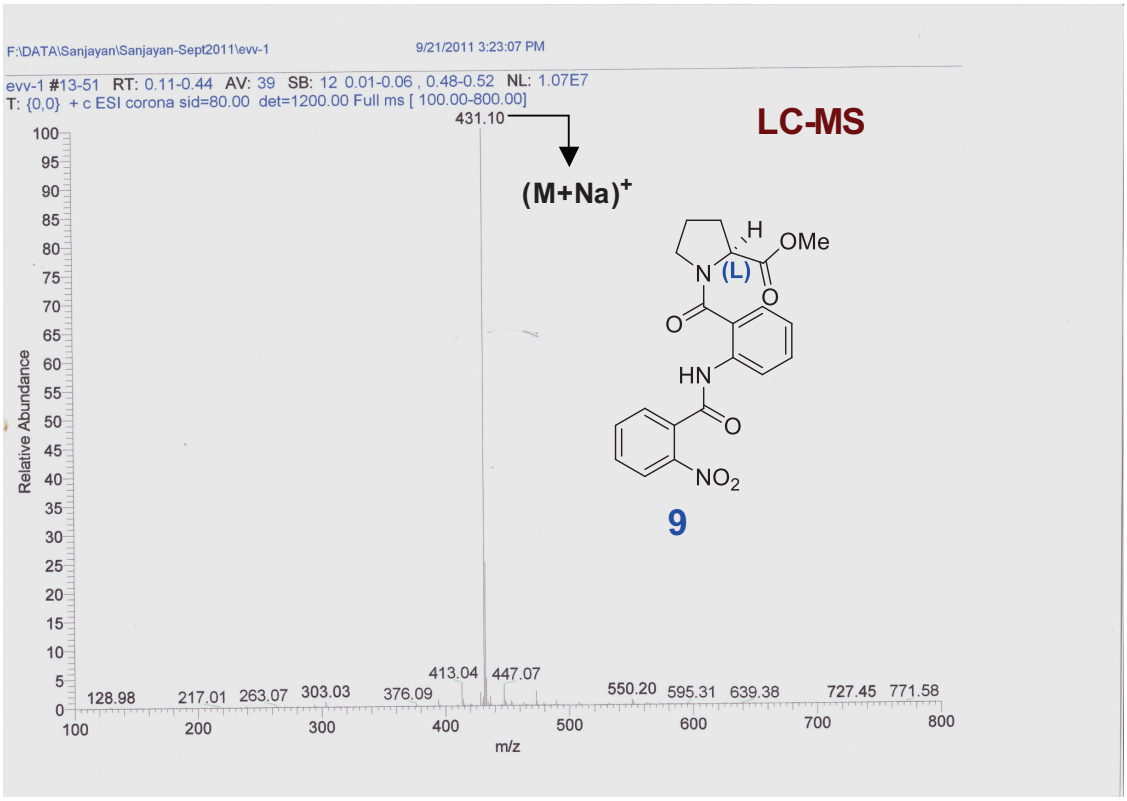
150.76
149.96
268.38
268.85
268.58
151.83
156.23
142.29
124.82
102.02
125.02
111.15
102.75
128.35
166.03
169.83
180.97
182.10
183.03
184.10
198.24
199.24
212.11
212.31
225.98
229.11
237.11
270.05
270.79
288.59
290.92
301.19
304.66
311.06
%
m/z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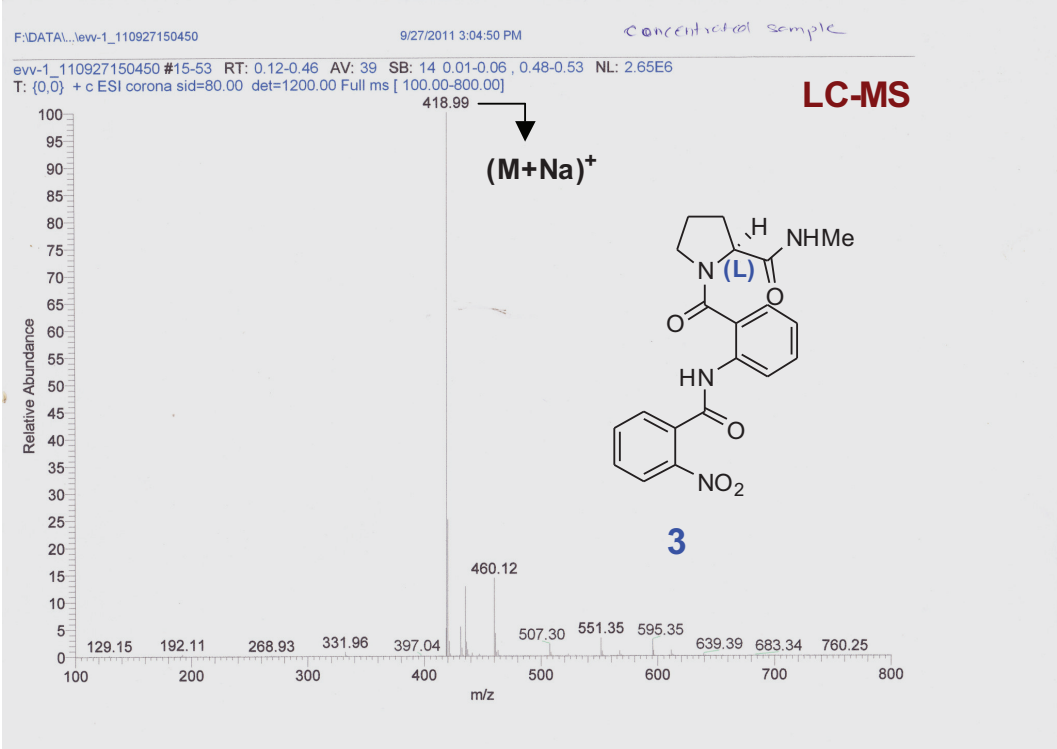
LC-MS
431.10
(M+Na)+
OMe
(L)
HN
NO2
9
Relative Abundance
413.04
447.07
128.98
217.01
263.07
303.03
376.09
550.20
595.31
639.38
727.45
771.58
m/z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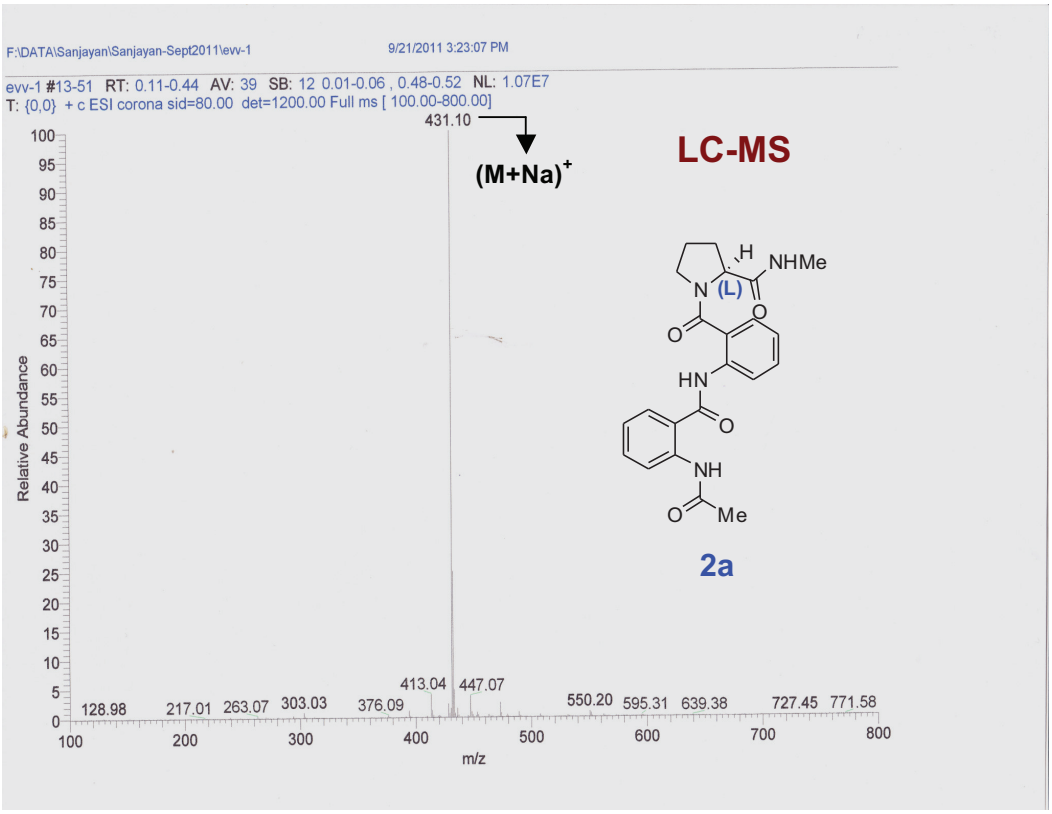
LC-MS
418.99
(M+Na)+
NHMe
N (L)
O
HN
NO2
3
460.12
129.15
192.11
268.93
331.96
397.04
507.30
551.35
595.35
639.39
683.34
760.25
Relative Abundance
m/z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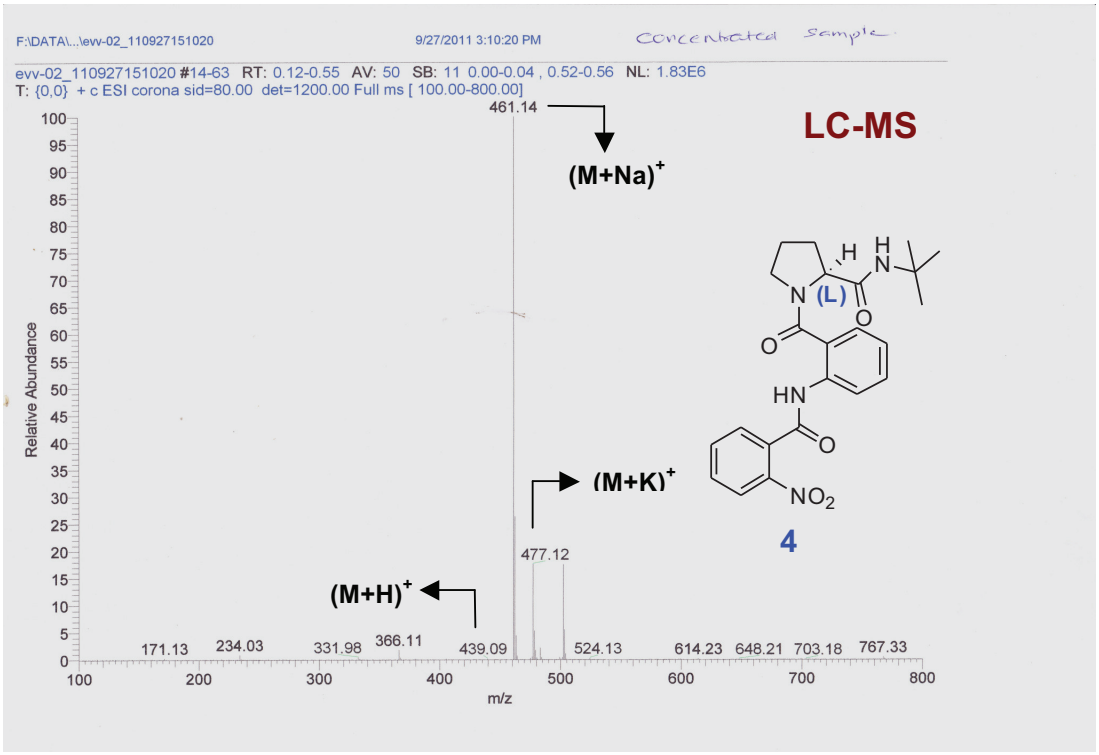
LC-MS
431.10
(M+Na)+
NHMe
N (L)
O
HN
NH
Me
2a
413.04
447.07
128.98
217.01
263.07
303.03
376.09
550.20
595.31
639.38
727.45
771.58
Relative Abundance
m/z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LC-MS
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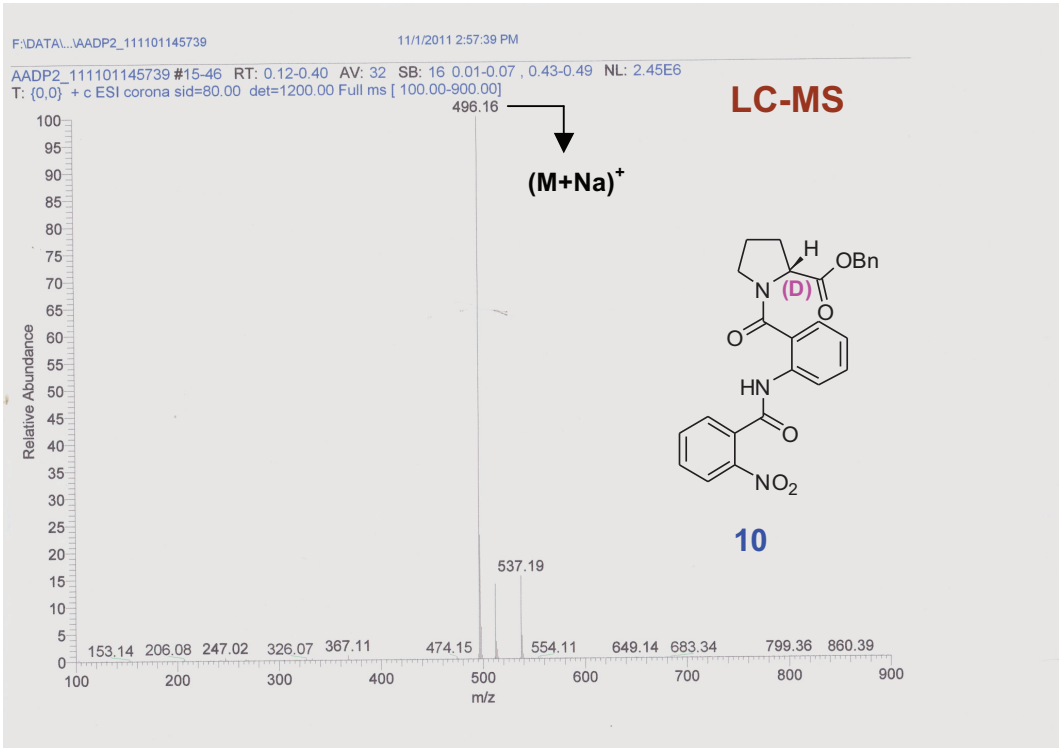
(M+Na)+
(M+K)+
477.12
(M+H)+
Relative Abundance
m/z
171.13 234.03 331.98 366.11 439.09 524.13 614.23 648.21 703.18 767.33
(L)
4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LC-MS
496.16
(M+Na)+
537.19
Relative Abundance
m/z
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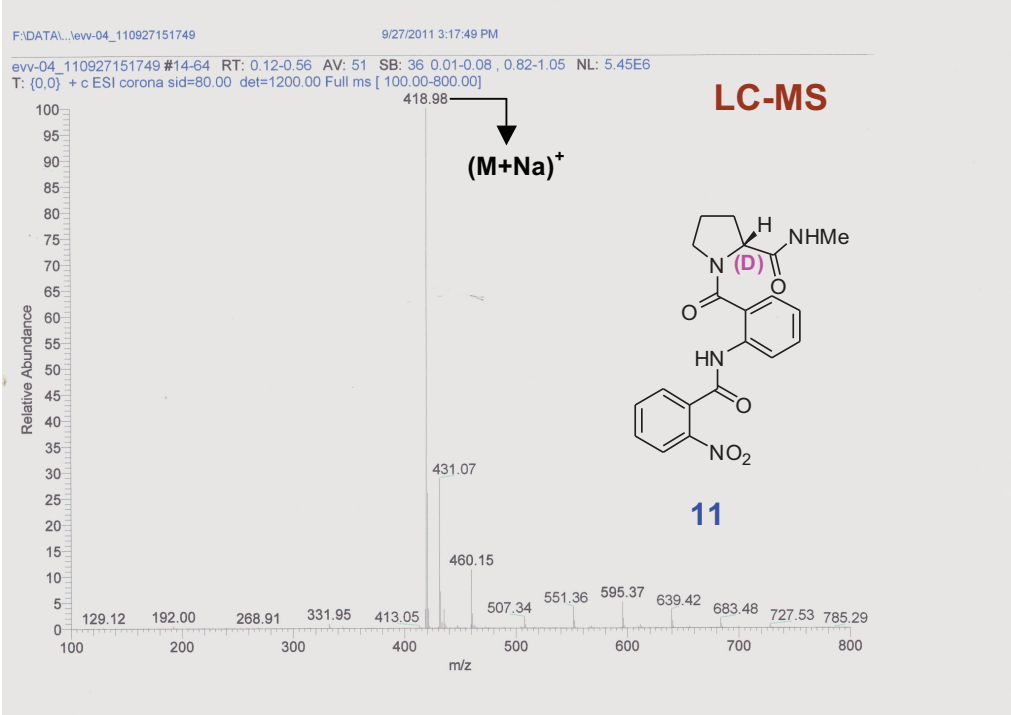
(D)
OBn
10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(M+Na)+
NHMe
H
N
(D)
O
HN
NO2
431.07
11
460.15
129.12
192.00
268.91
331.95
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507.34
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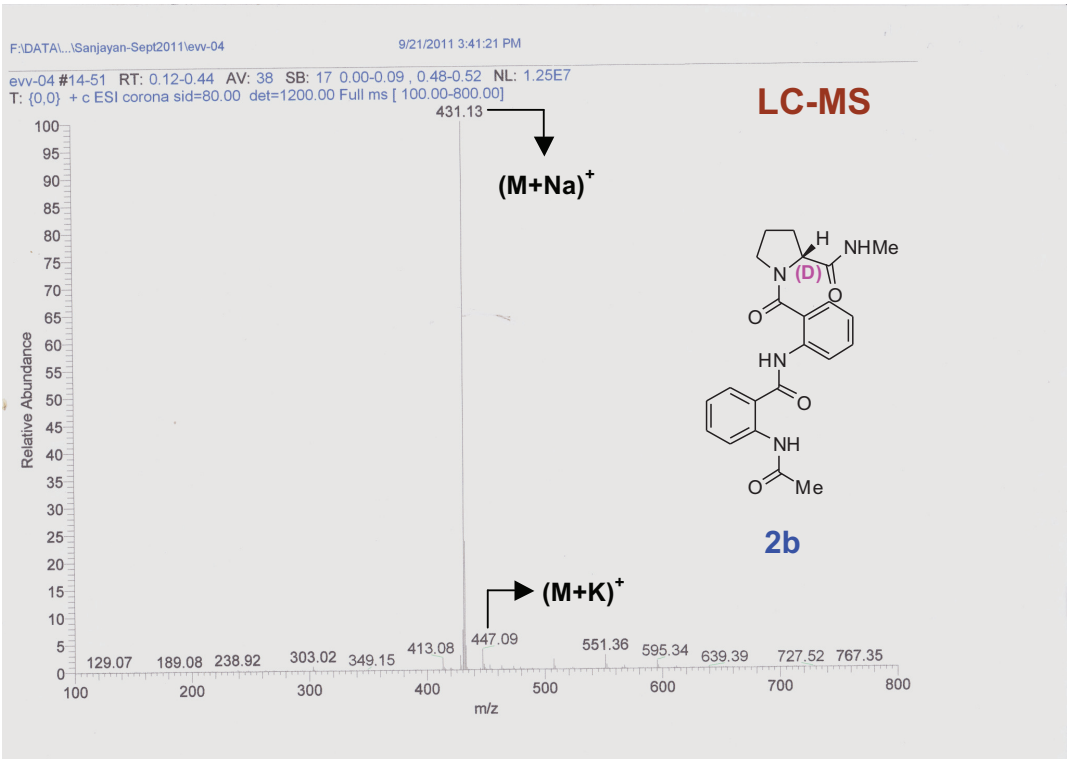
639.42
683.48
727.53
785.29
Relative Abundance
m/z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LC-MS
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(M+Na)+
NHMe
H
N
(D)
O
HN
NH
Me
2b
(M+K)+
447.09
129.07
189.08
238.92
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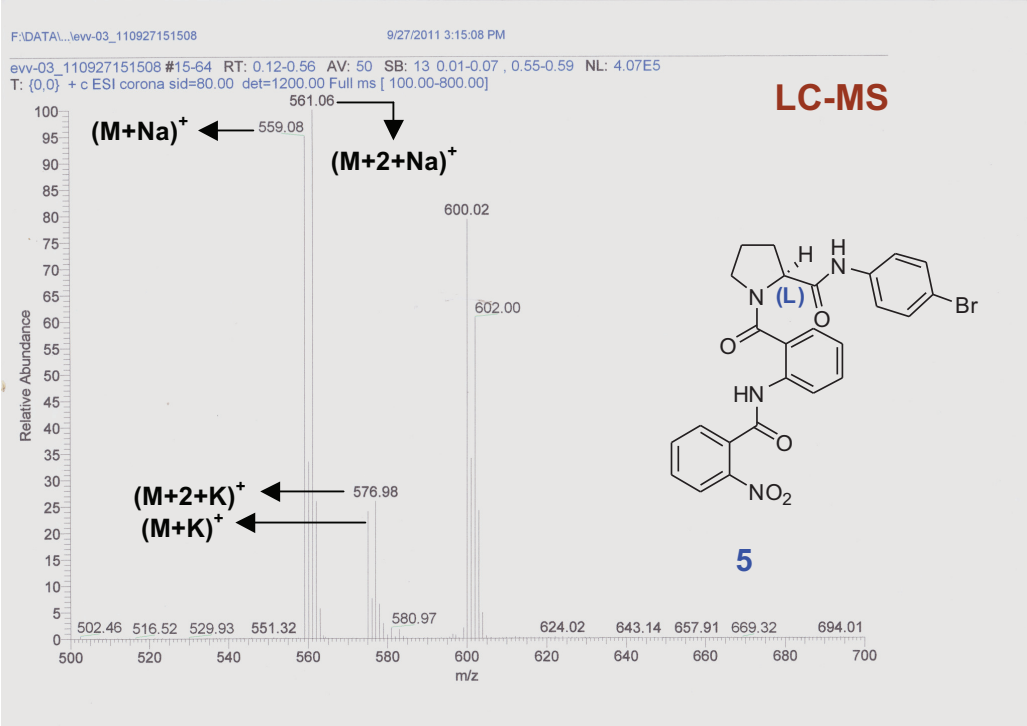
349.15
413.08
551.36
595.34
639.39
727.52
767.35
Relative Abundance
m/z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LC-MS
(M+Na)+
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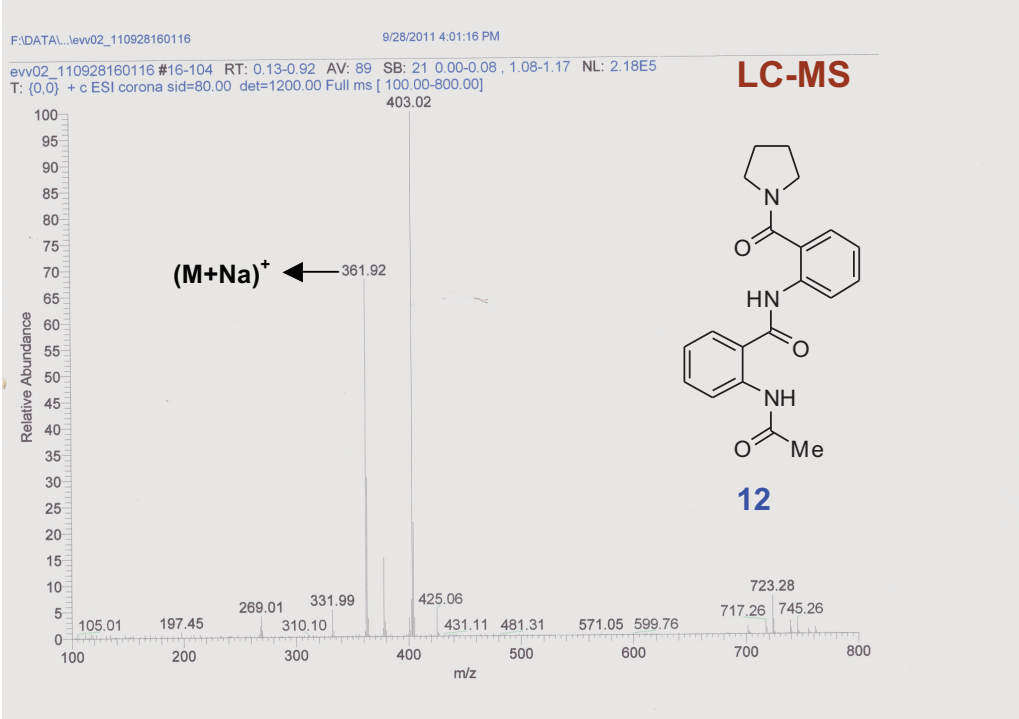
561.06
(M+2+Na)+
600.02
602.00
(M+2+K)+
(M+K)+
576.98
580.97
Relative Abundance
m/z
5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LC-MS
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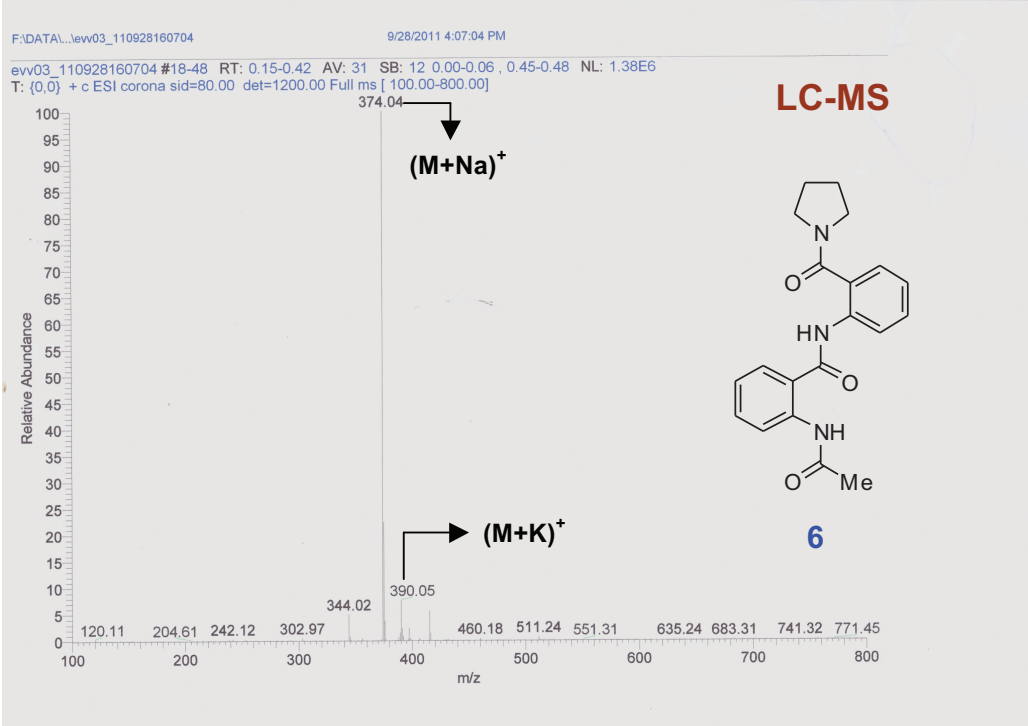
(M+Na)+
361.92
Relative Abundance
m/z
12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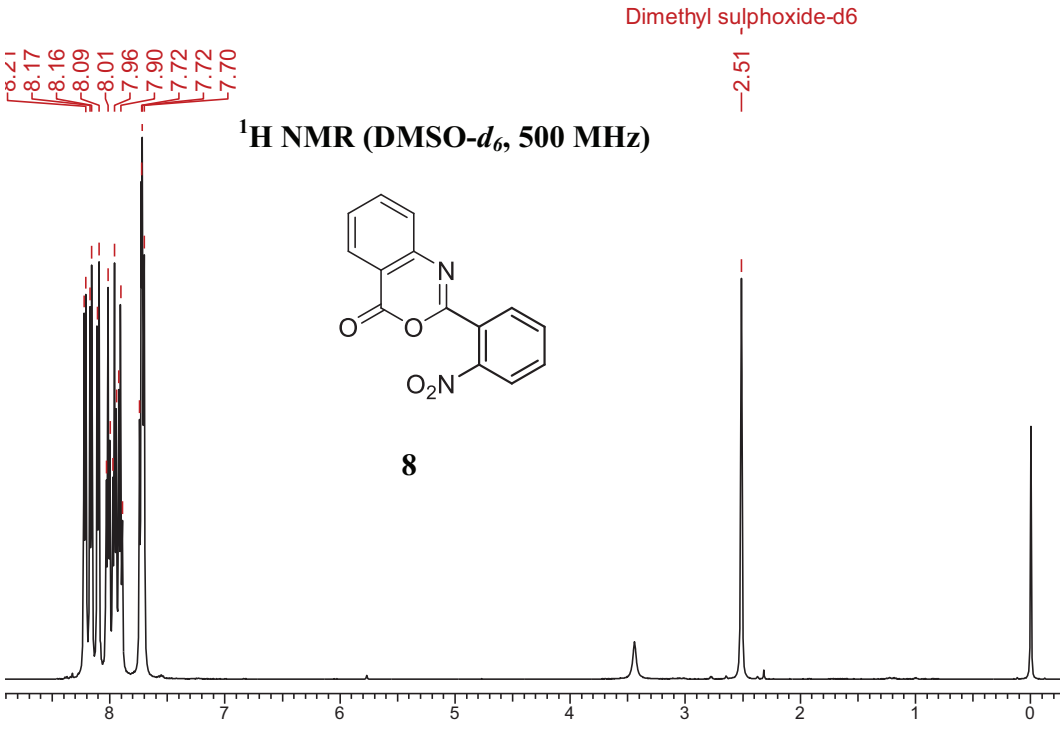
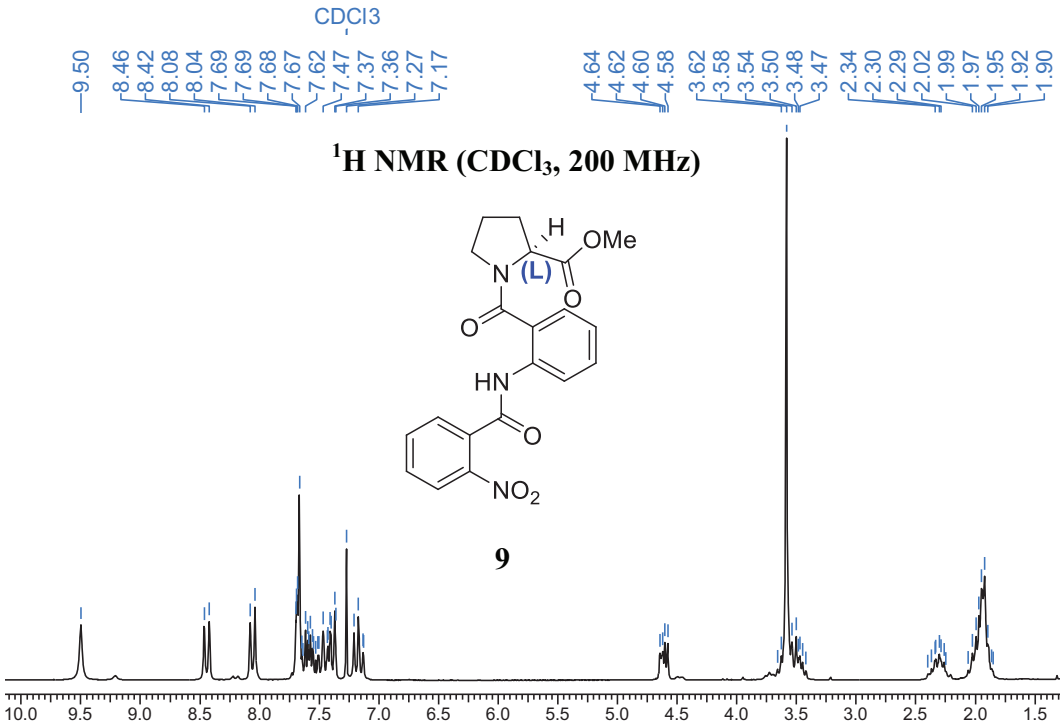
(M+K)+
390.05
344.02
120.11
204.61
242.12
302.97
460.18
511.24
551.31
635.24
683.31
741.32
771.45
Relative Abundance
m/z
6



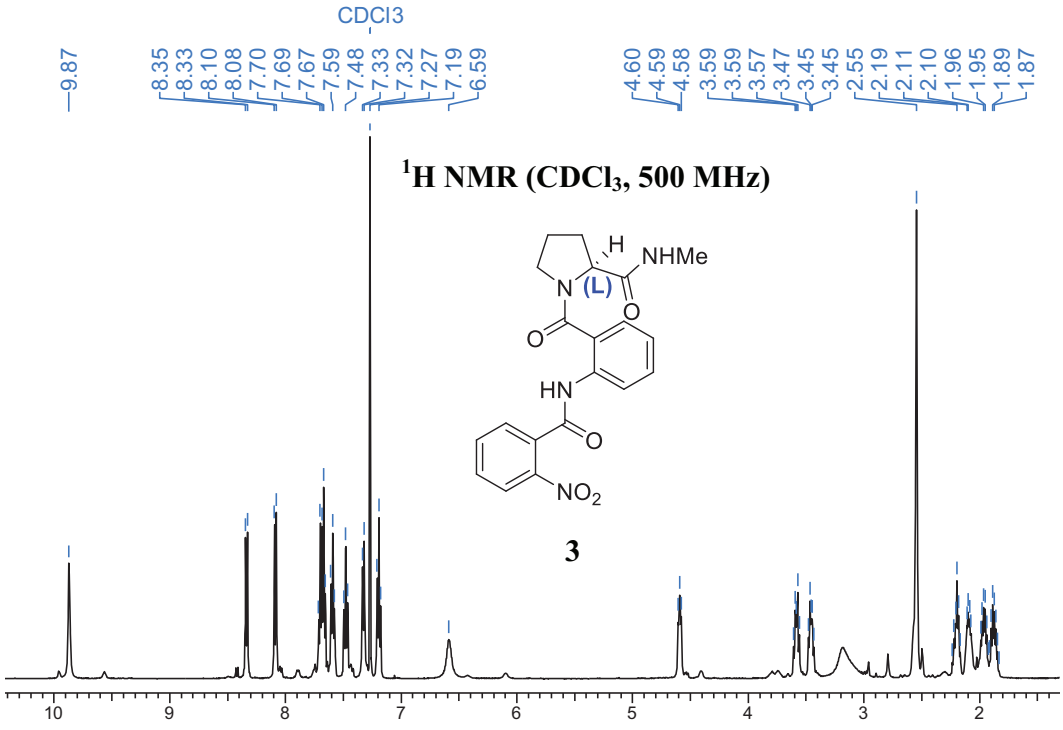
^{1}H NMR (DMSO-d_6, 500 MHz)

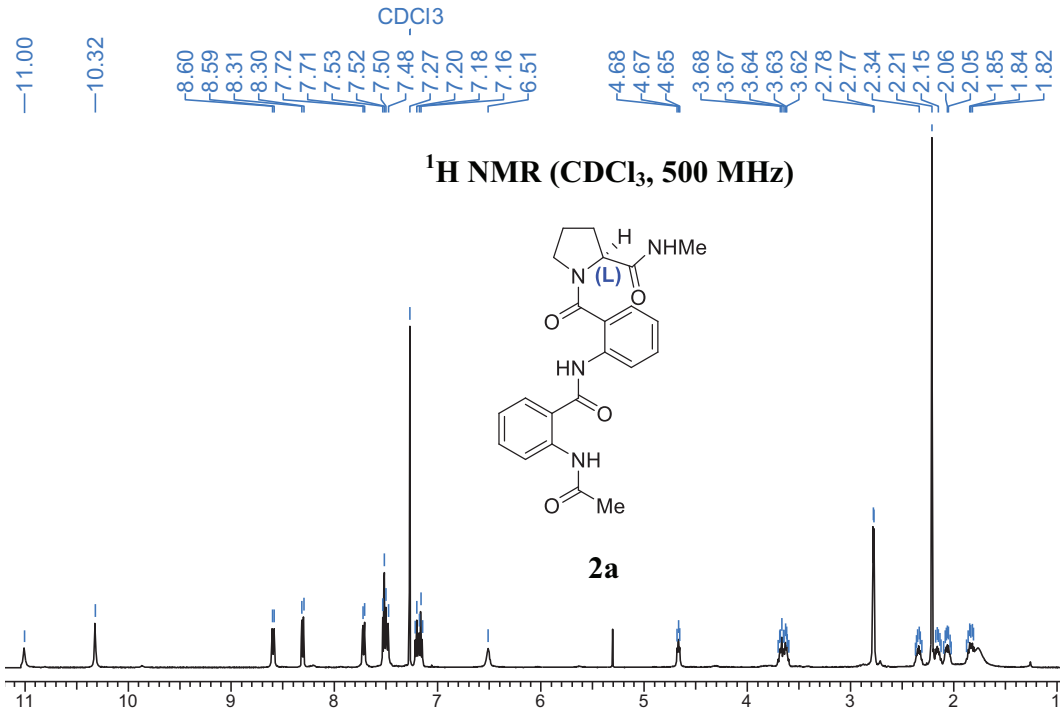
8

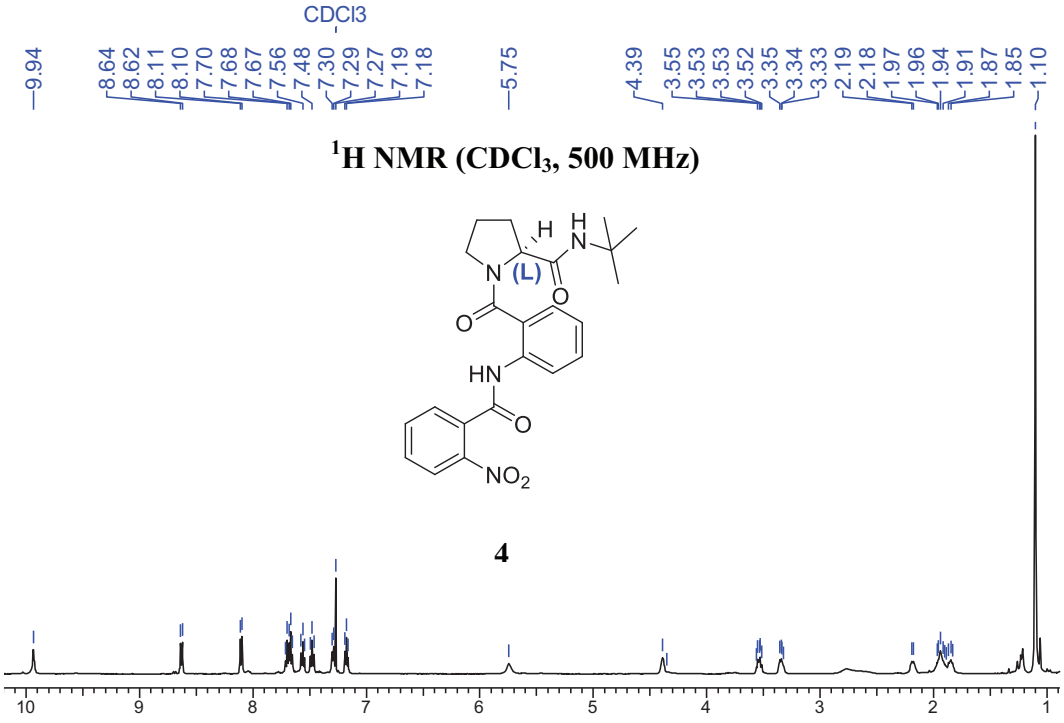


^{1}H NMR ($CDCl_3$, 200 MHz)

9

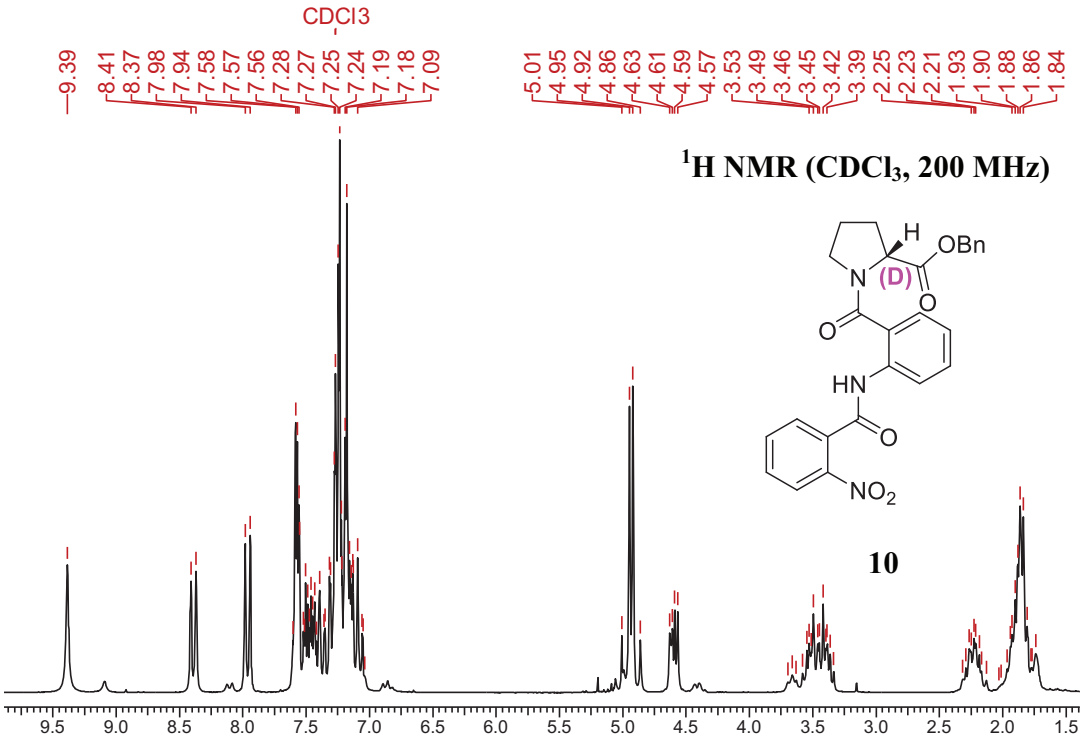

CDCl3
9.87
8.35
8.33
8.10
8.08
7.70
7.69
7.67
7.59
7.48
7.33
7.32
7.27
7.19
6.59
4.60
4.59
4.58
3.59
3.59
3.57
3.47
3.45
3.45
2.55
2.19
2.11
2.10
1.96
1.95
1.89
1.87
1H NMR (CDCl3, 500 MHz)
H
NHMe
N
(L)
O
O
HN
O
NO2
3
10
9
8
7
6
5
4
3
2


CDCl3
11.00
10.32
8.60
8.59
8.31
8.30
7.72
7.71
7.53
7.52
7.50
7.48
7.27
7.20
7.18
7.16
6.51
4.68
4.67
4.65
3.68
3.67
3.64
3.63
3.62
2.78
2.77
2.34
2.21
2.15
2.06
2.05
1.85
1.84
1.82
1H NMR (CDCl3, 500 MHz)
H
NHMe
N
(L)
O
O
HN
O
NH
O
Me
2a
11
10
9
8
7
6
5
4
3
2
1



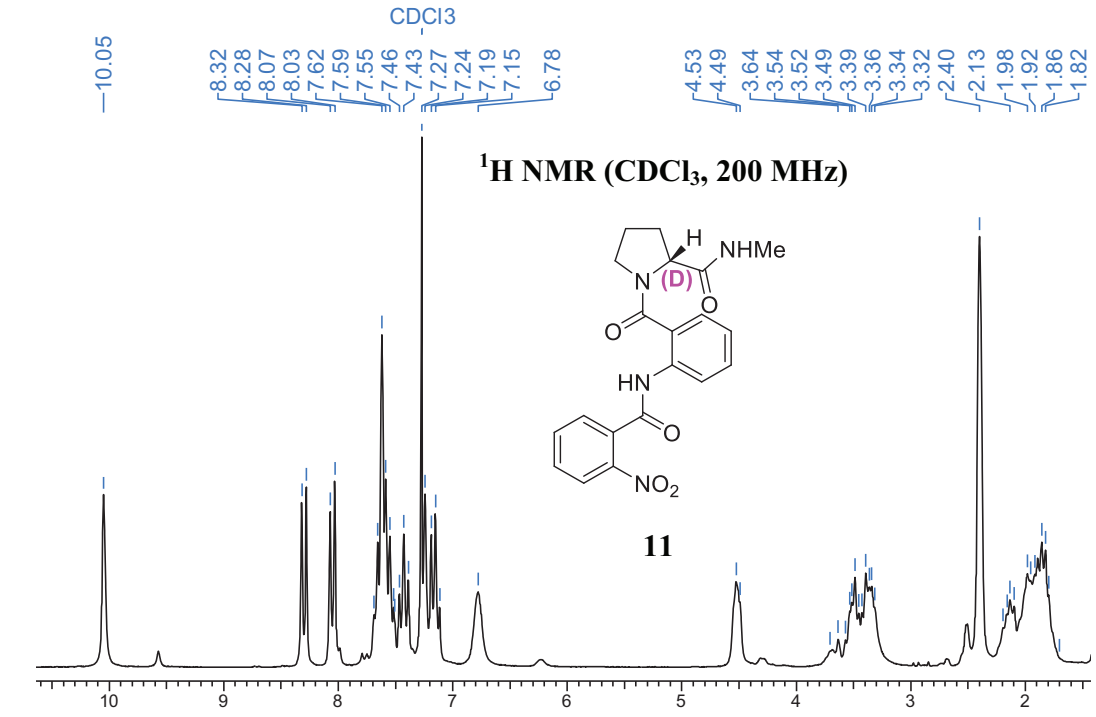
^{1}H NMR ($CDCl_3$, 500 MHz)

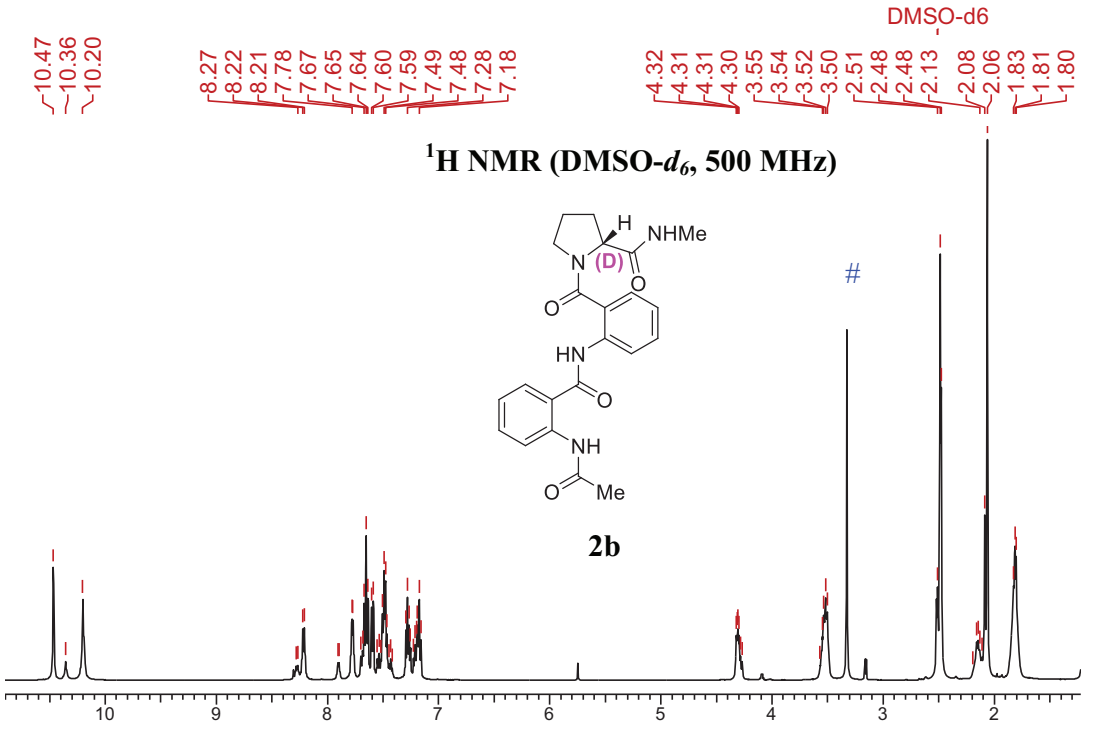
4



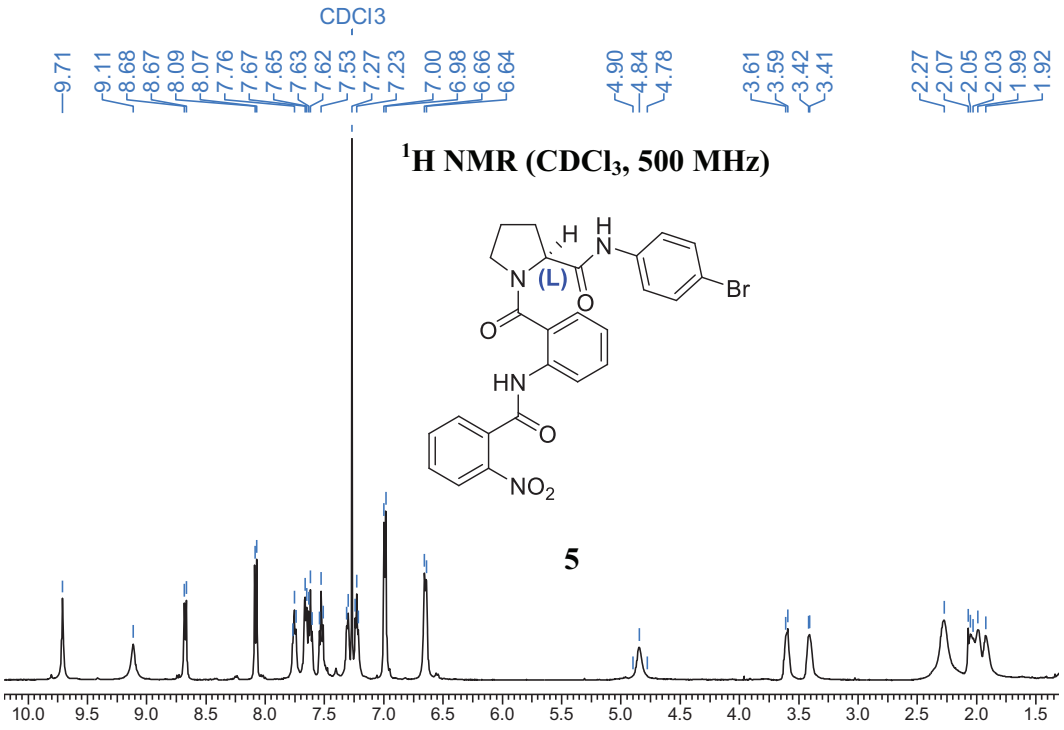
^{1}H NMR ($CDCl_3$, 200 MHz)

10



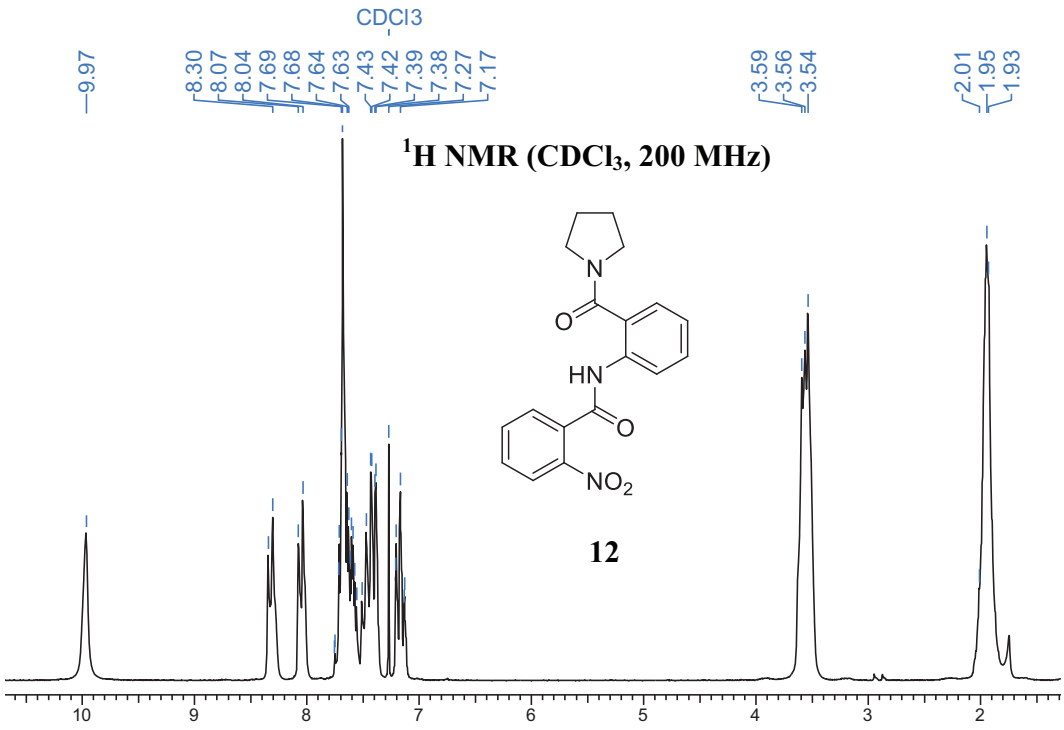


Notes: Small sister peaks are due to rotamer formation in DMSO-d_6. # DMSO-d_6 H_2O



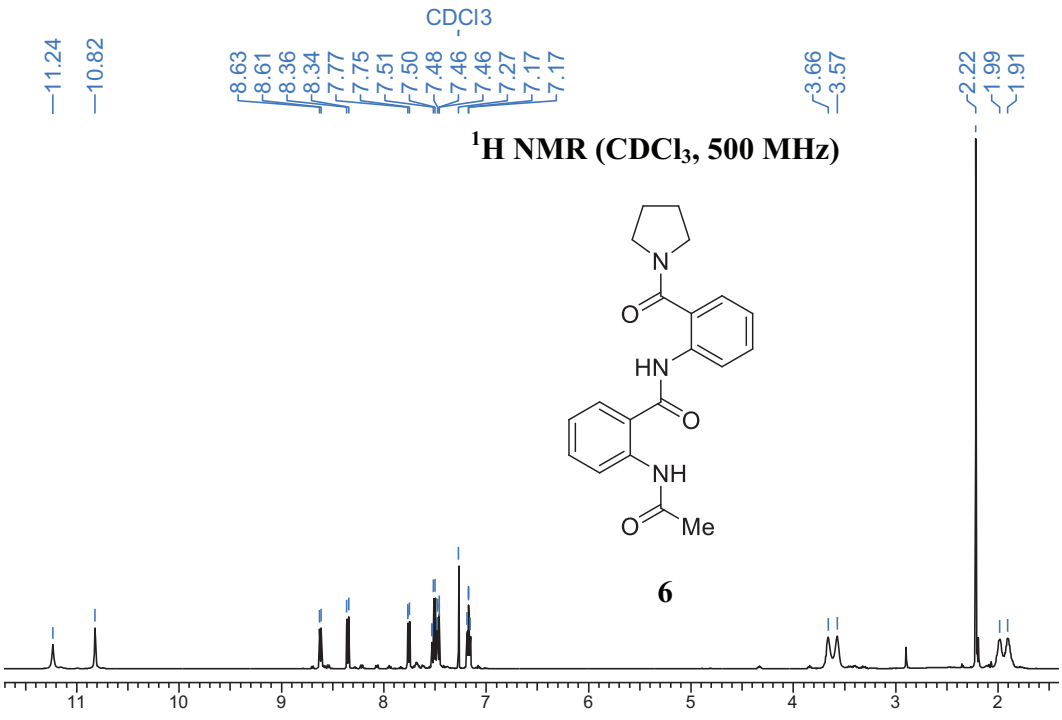
^{1}H NMR ($CDCl_3$, 500 MHz)

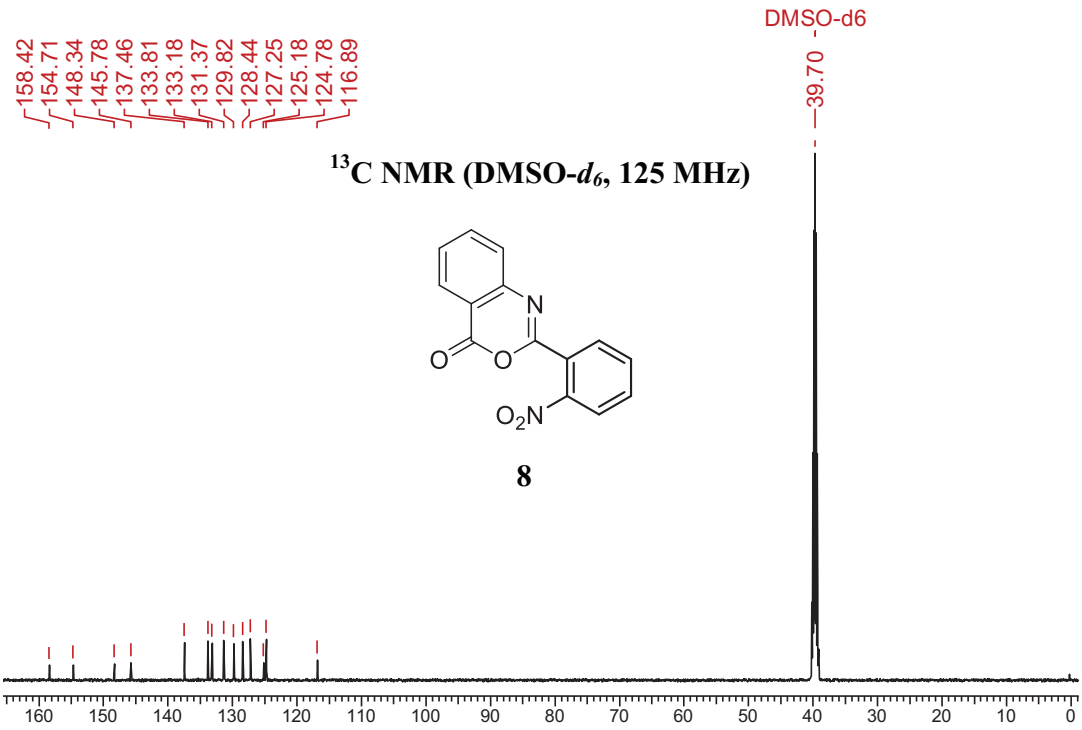
5



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

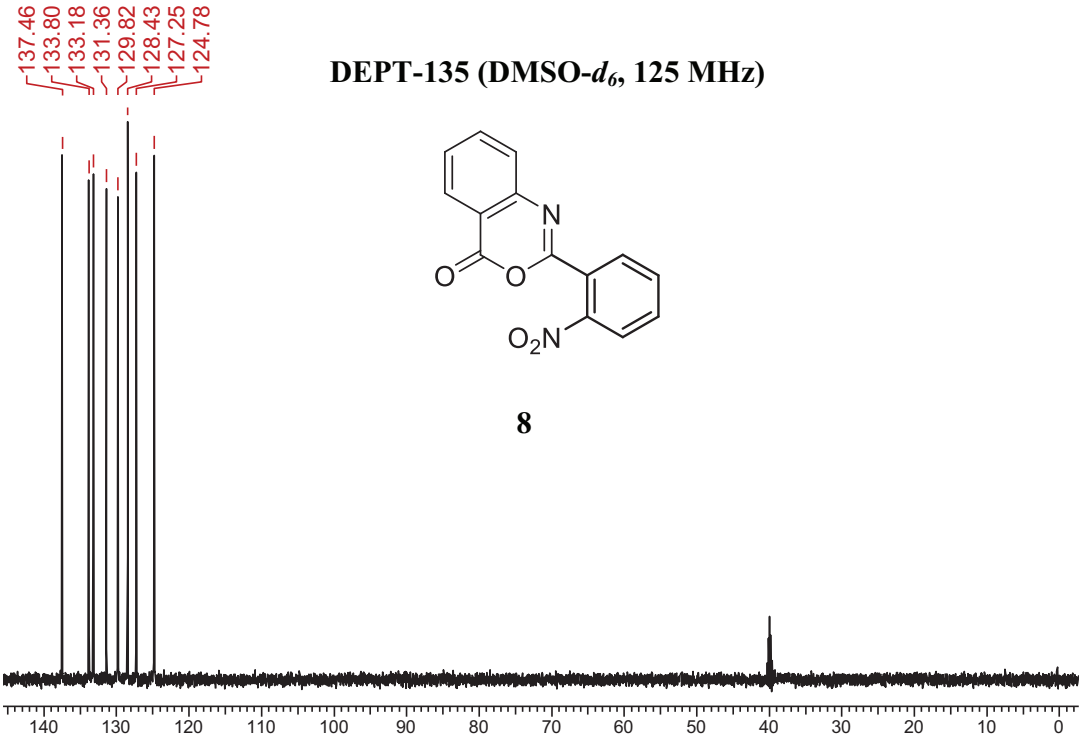
12


CDCl3
11.24
10.82
8.63
8.61
8.36
8.34
7.77
7.75
7.51
7.50
7.48
7.46
7.46
7.27
7.17
7.17
3.66
3.57
2.22
1.99
1.91
^{1}H NMR (CDCl$_3$, 500 MHz)
N
O
HN
O
NH
O
Me
6
11
10
9
8
7
6
5
4
3
2



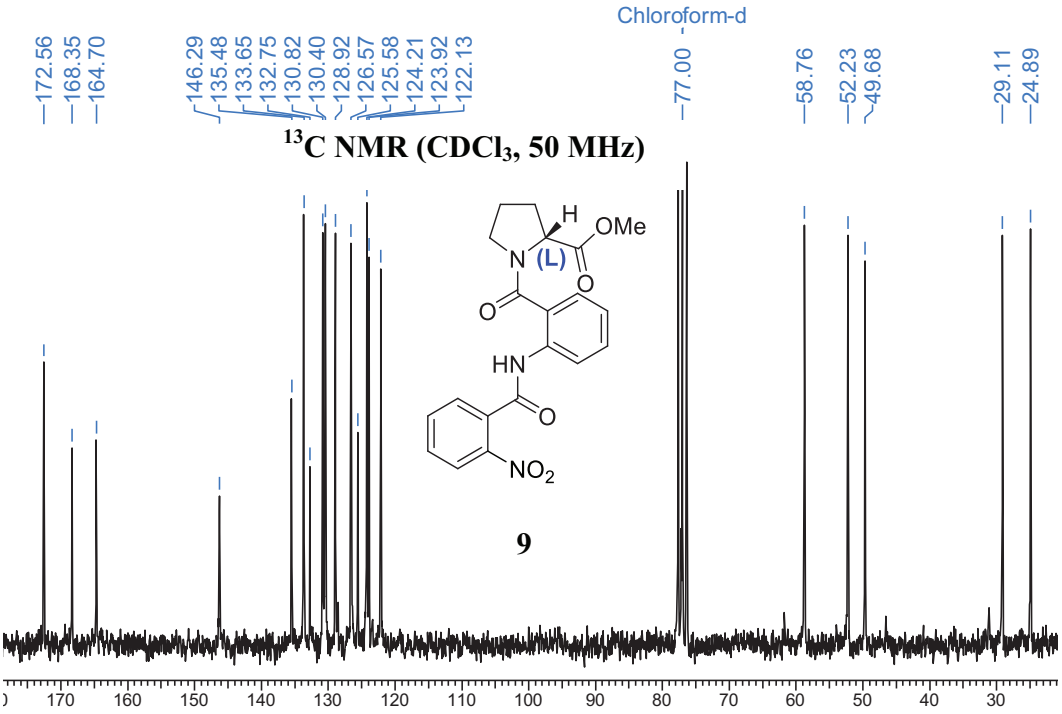
^{13}C NMR (DMSO-d_6, 125 MHz)

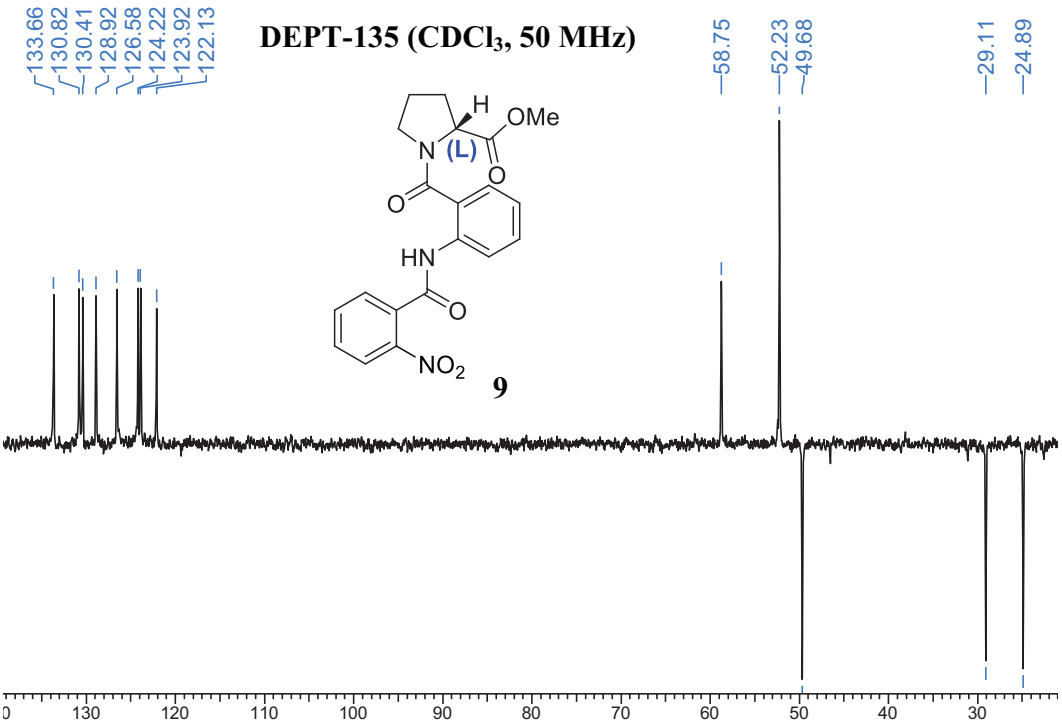
8

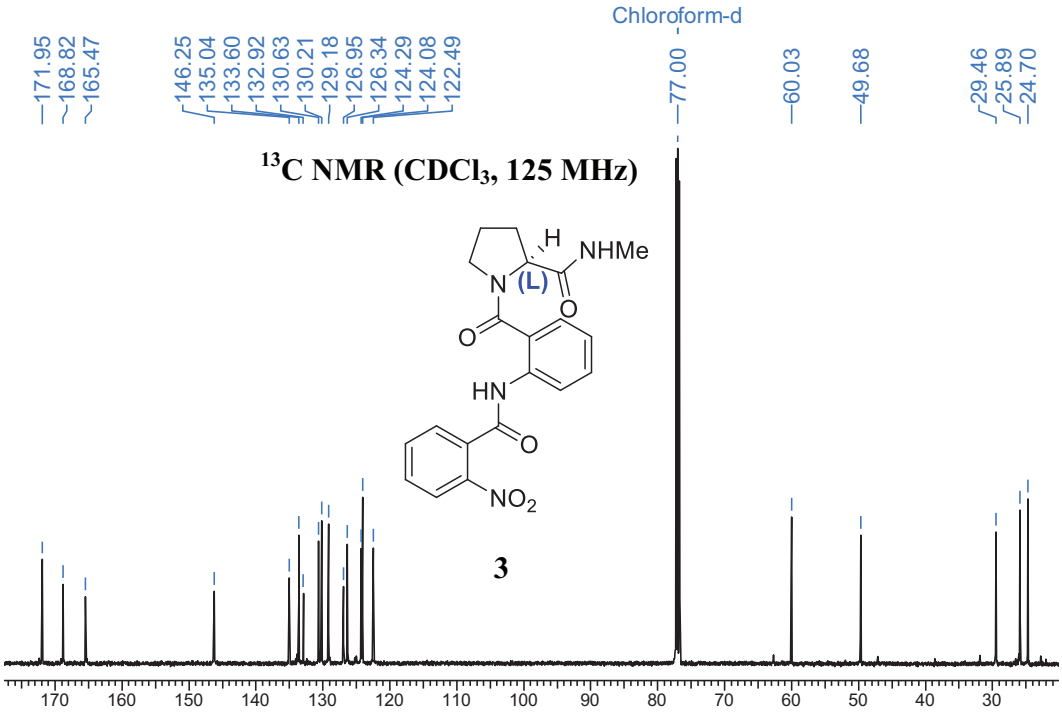


DEPT-135 (DMSO-d_6, 125 MHz)

8

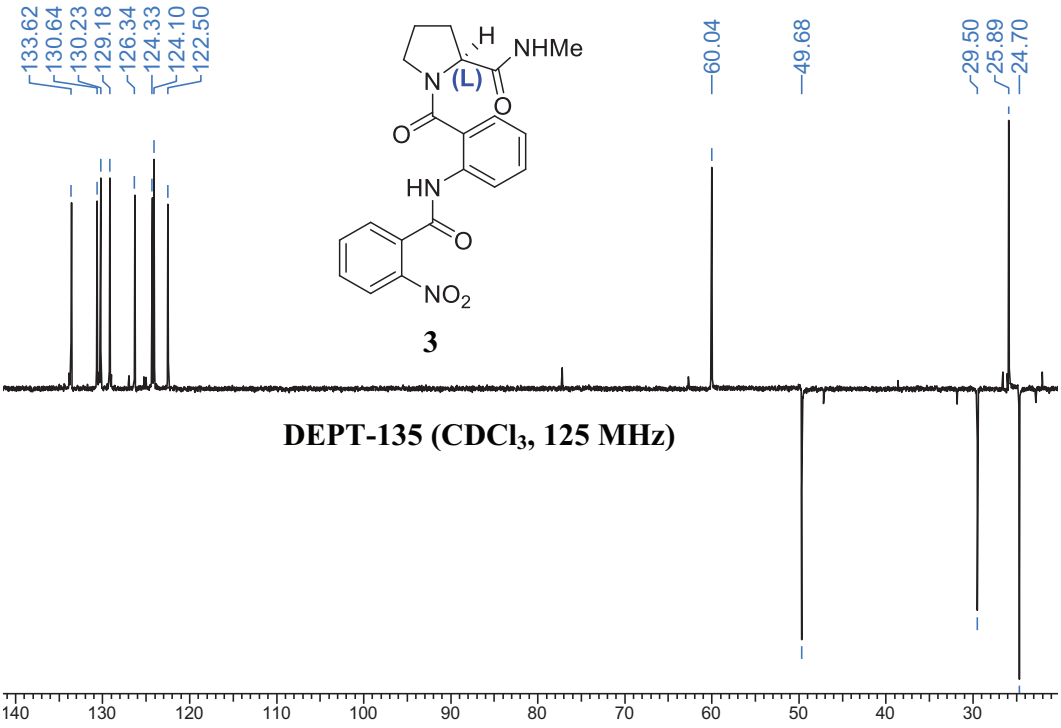

Chloroform-d
172.56
168.35
164.70
146.29
135.48
133.65
132.75
130.82
130.40
128.92
126.57
125.58
124.21
123.92
122.13
77.00
58.76
52.23
49.68
29.11
24.89
13C NMR (CDCl3, 50 MHz)
H
OMe
N
(L)
O
O
HN
O
NO2
9


133.66
130.82
130.41
128.92
126.58
124.22
123.92
122.13
DEPT-135 (CDCl3, 50 MHz)
58.75
52.23
49.68
29.11
24.89
H
OMe
N
(L)
O
O
HN
O
NO2
9



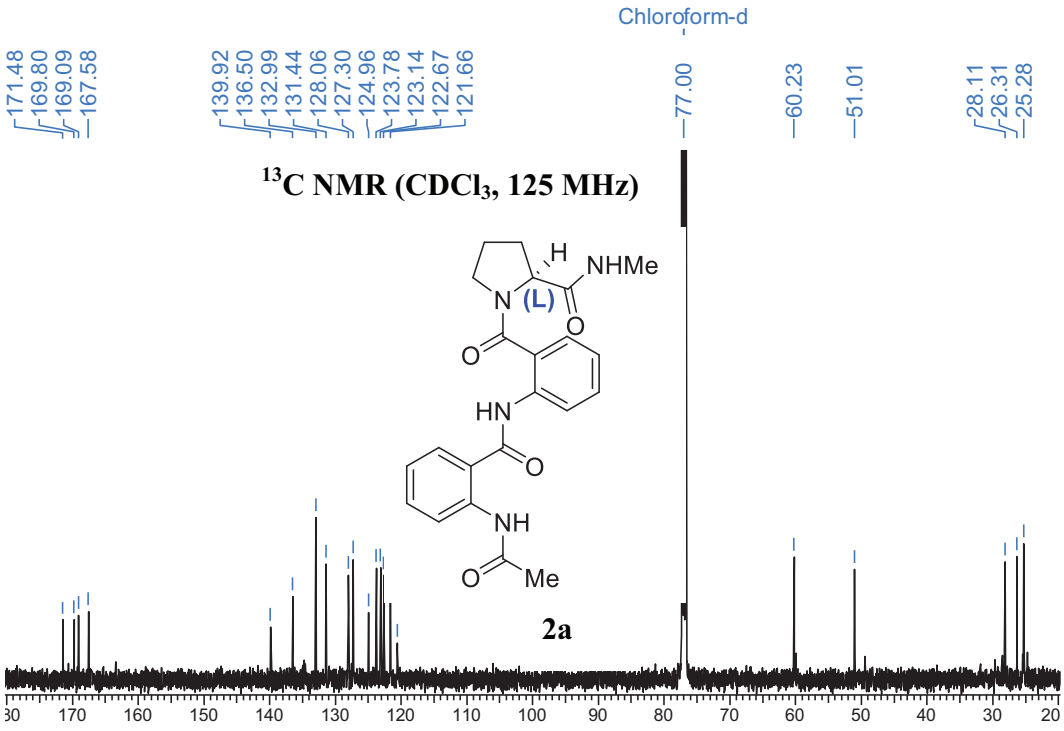
^{13}C NMR ($CDCl_3$, 125 MHz)

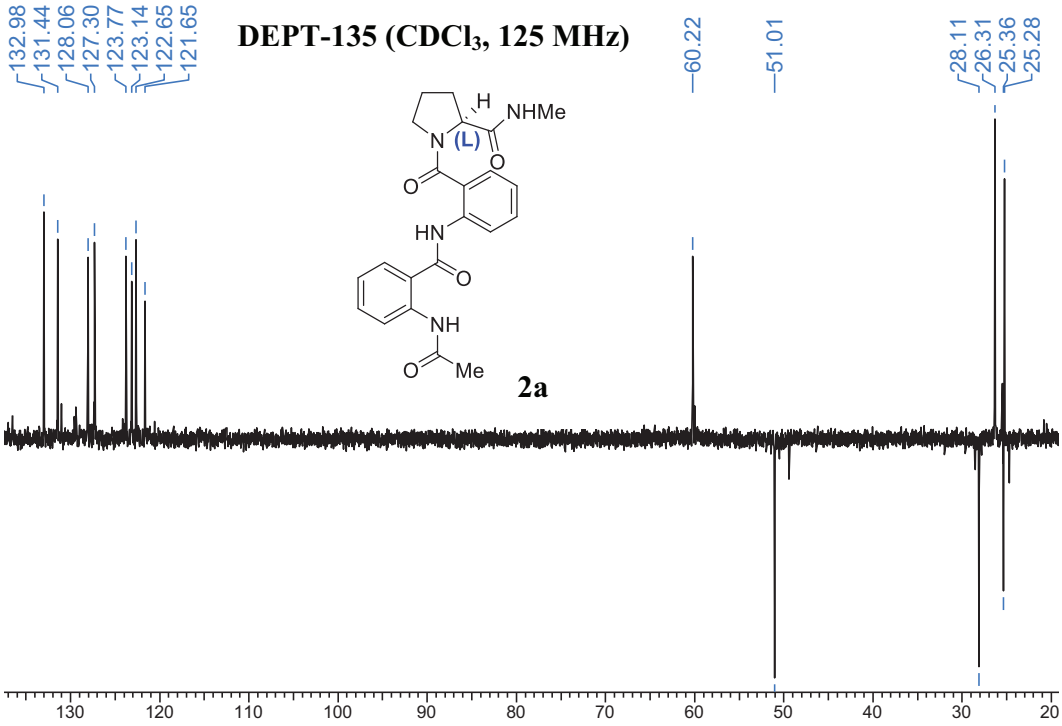
3

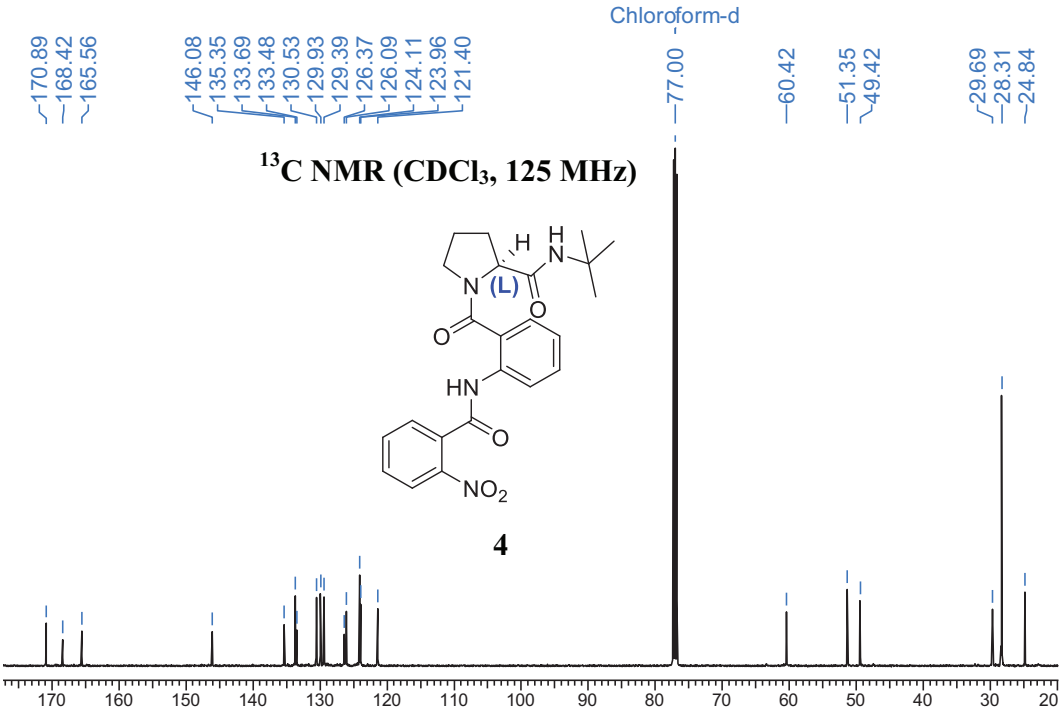


3

DEPT-135 ($CDCl_3$, 125 MHz)

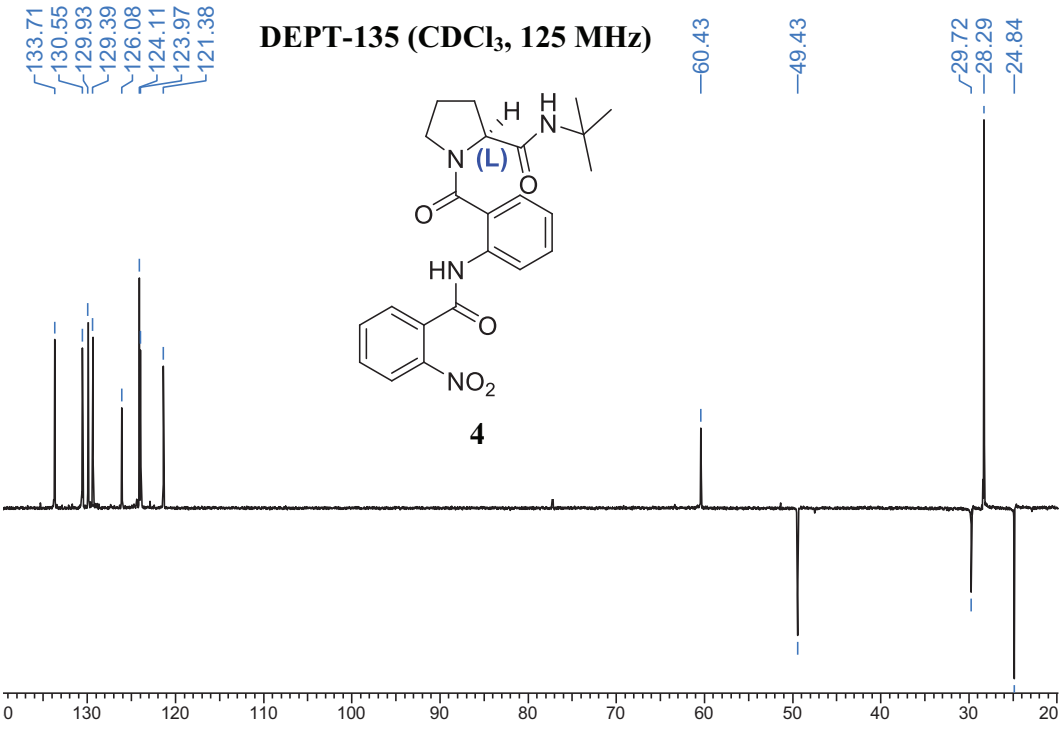






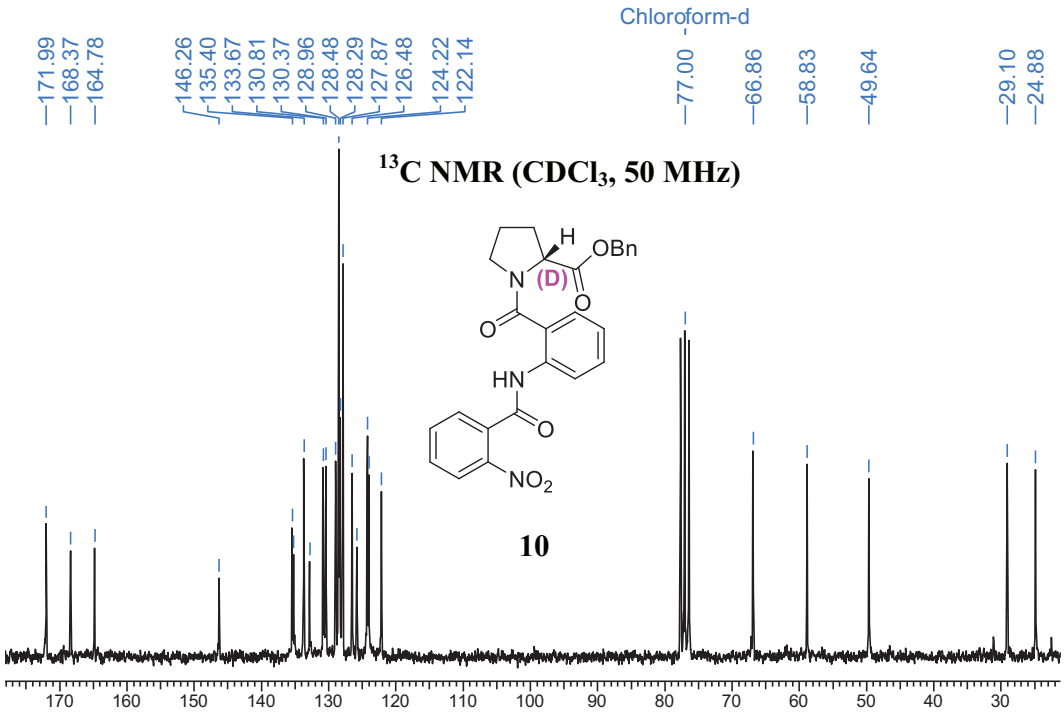
^{13}C NMR ($CDCl_3$, 125 MHz)

4



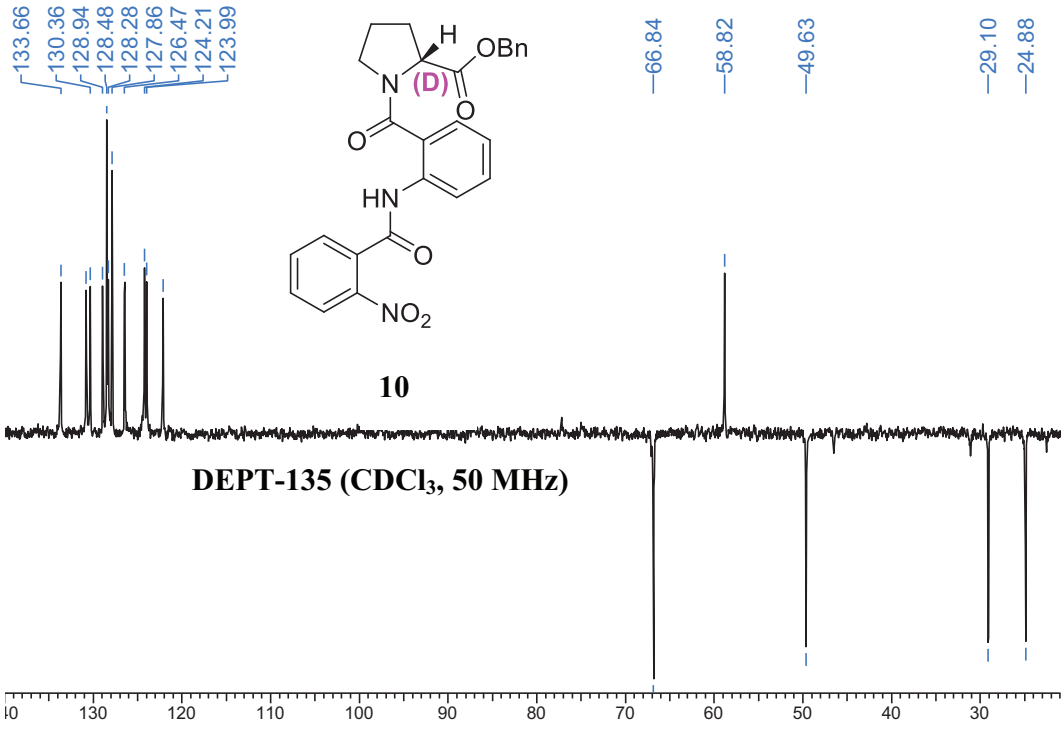
DEPT-135 ($CDCl_3$, 125 MHz)

4



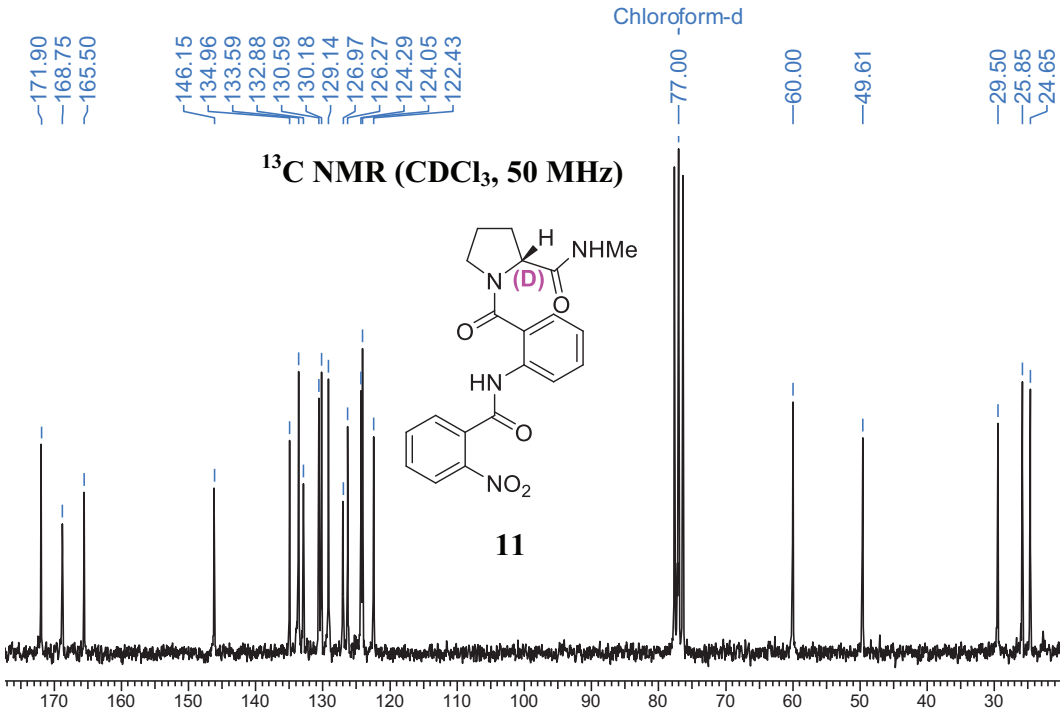
^{13}C NMR ($CDCl_3$, 50 MHz)

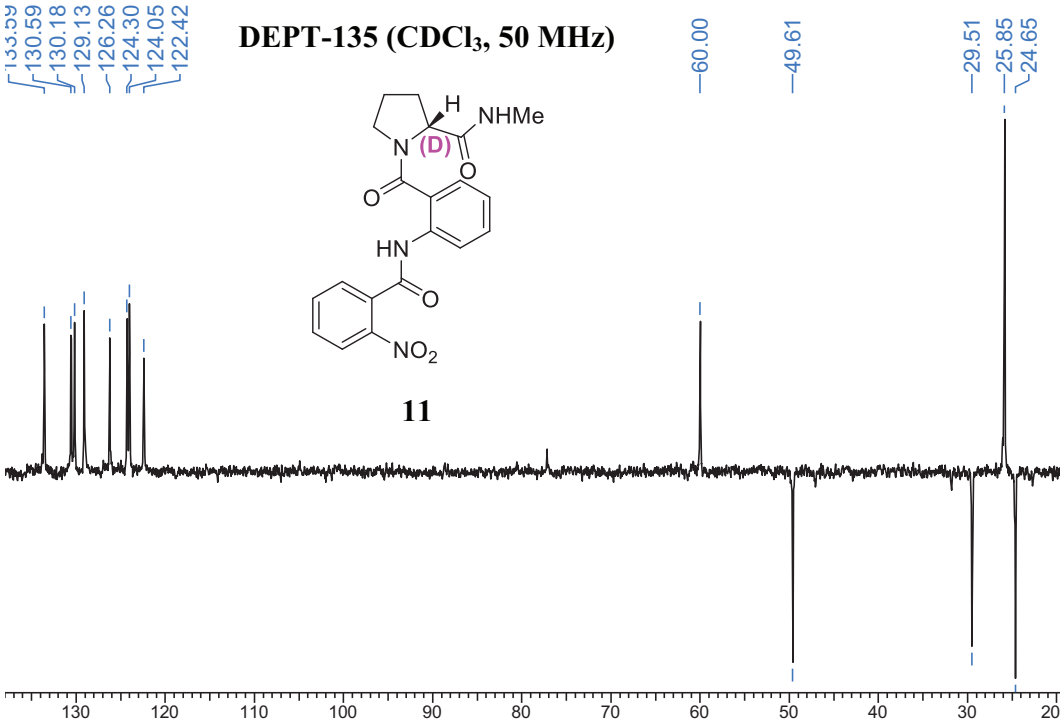
10

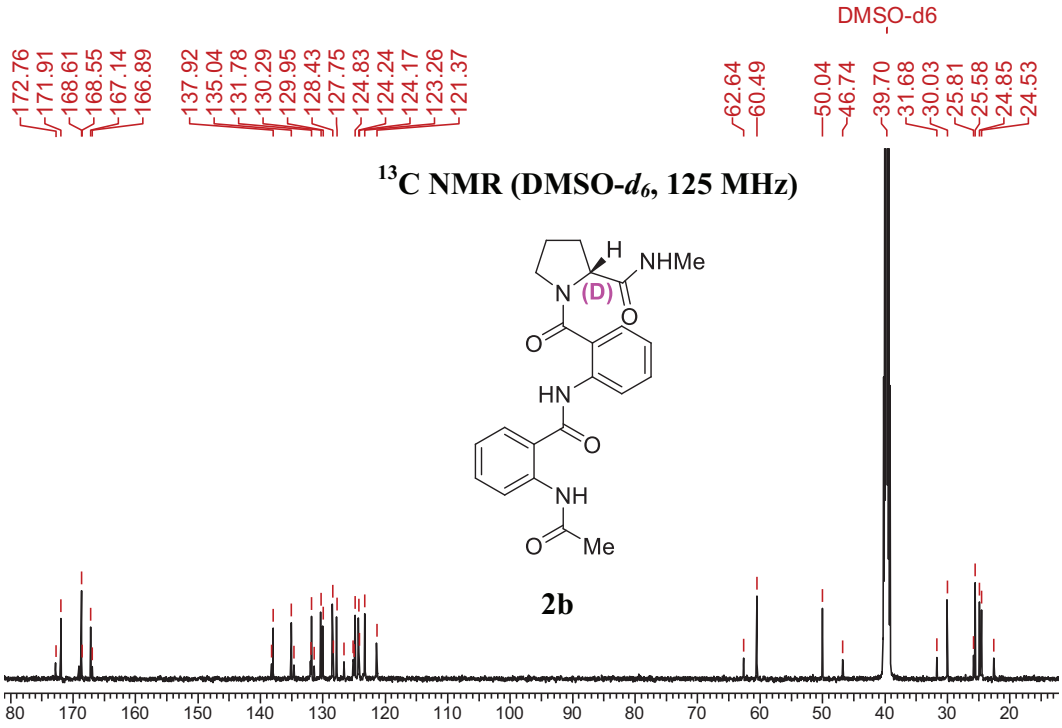


10

DEPT-135 ($CDCl_3$, 50 MHz)

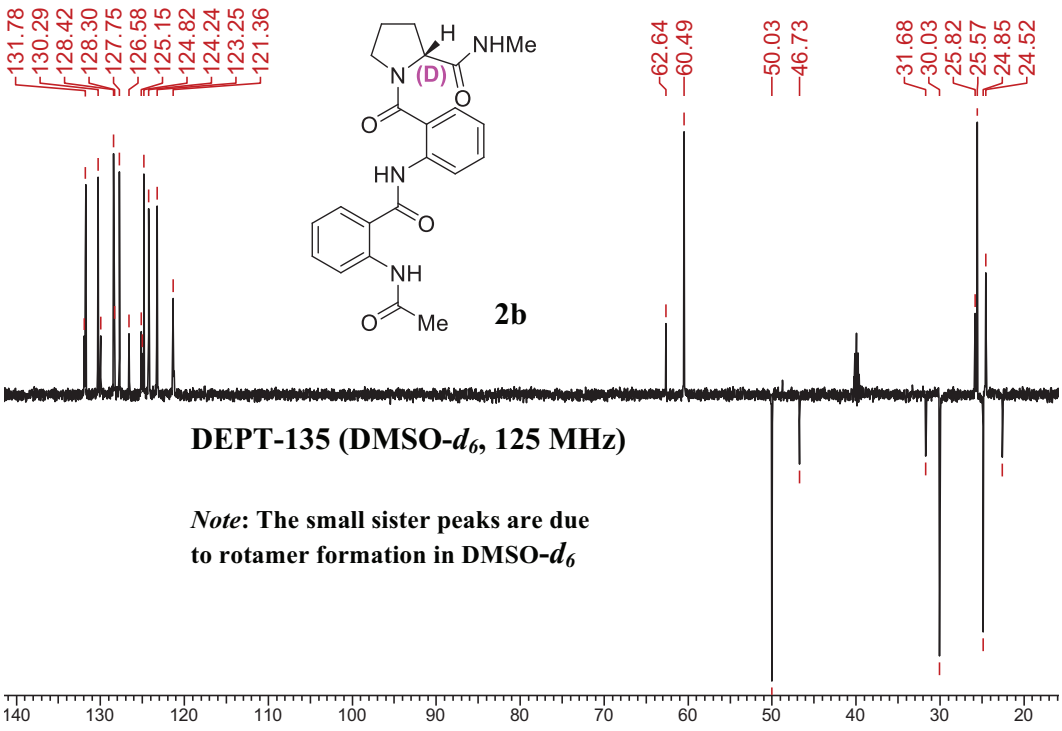

Chloroform-d
171.90
168.75
165.50
146.15
134.96
133.59
132.88
130.59
130.18
129.14
126.97
126.27
124.29
124.05
122.43
77.00
60.00
49.61
29.50
25.85
24.65
13C NMR (CDCl3, 50 MHz)
H
NHMe
N
(D)
O
O
HN
O
NO2
11


133.59
130.59
130.18
129.13
126.26
124.30
124.05
122.42
DEPT-135 (CDCl3, 50 MHz)
60.00
49.61
29.51
25.85
24.65
H
NHMe
N
(D)
O
O
HN
O
NO2
11



^{13}C NMR (DMSO-d_6, 125 MHz)

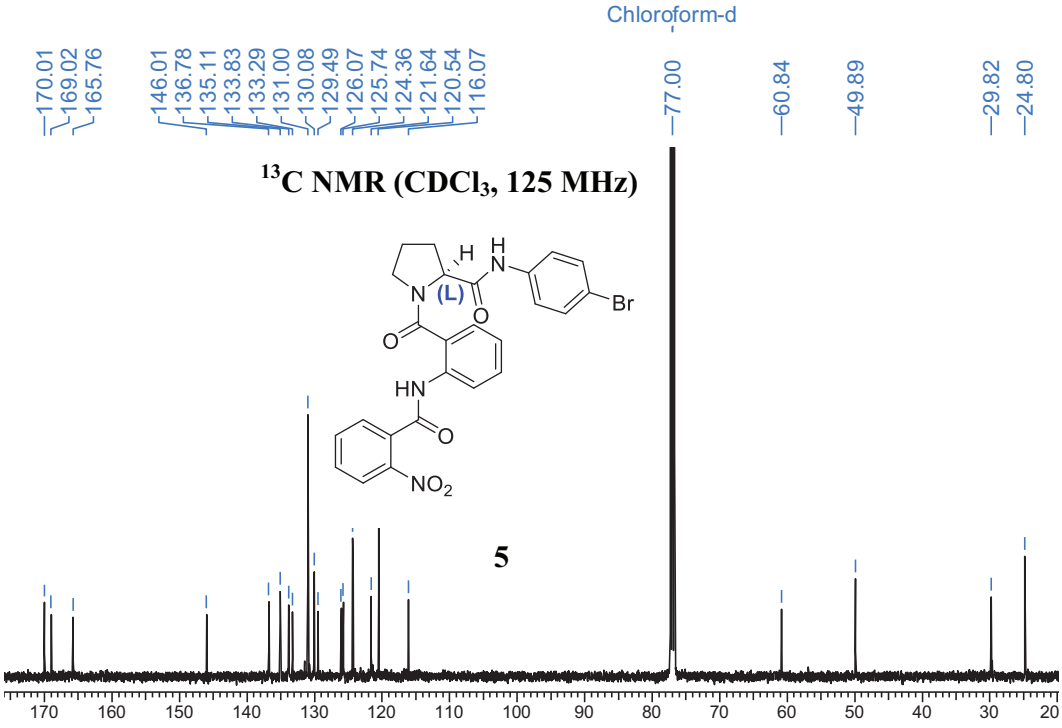
2b

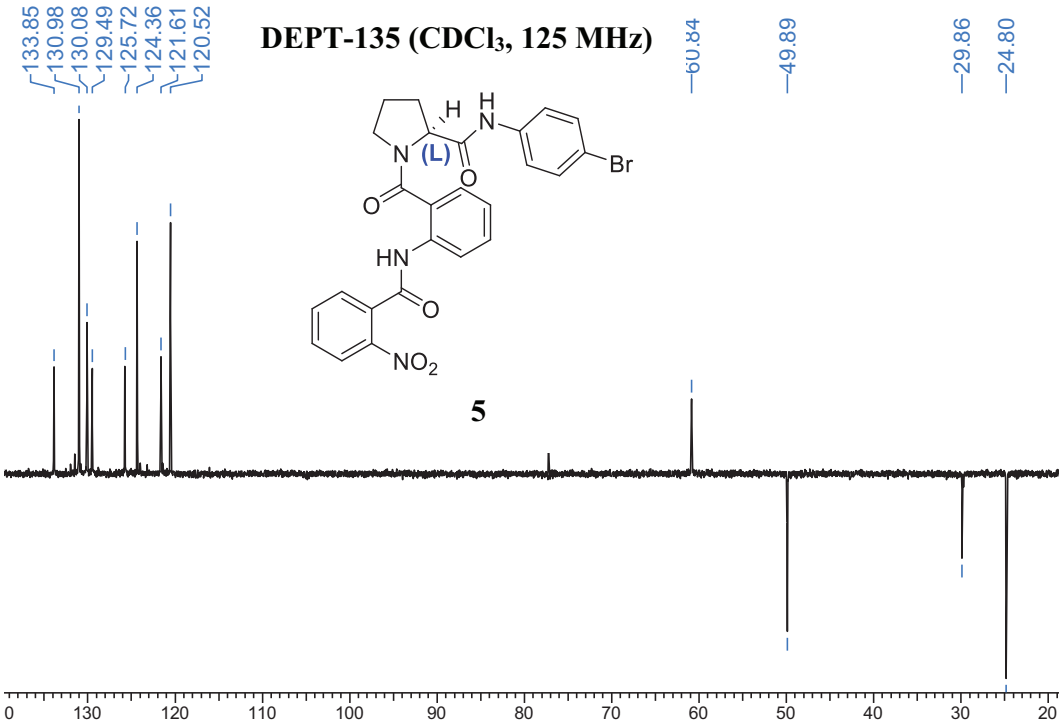


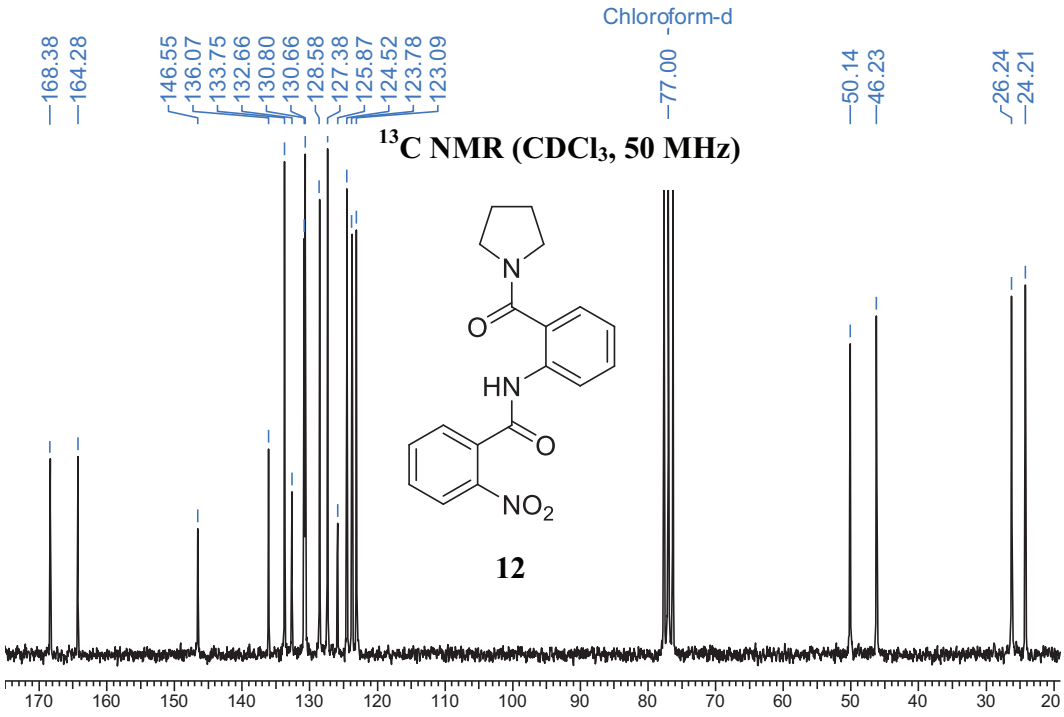
2b

DEPT-135 (DMSO-d_6, 125 MHz)

***Note*: The small sister peaks are due to rotamer formation in DMSO-d_6**

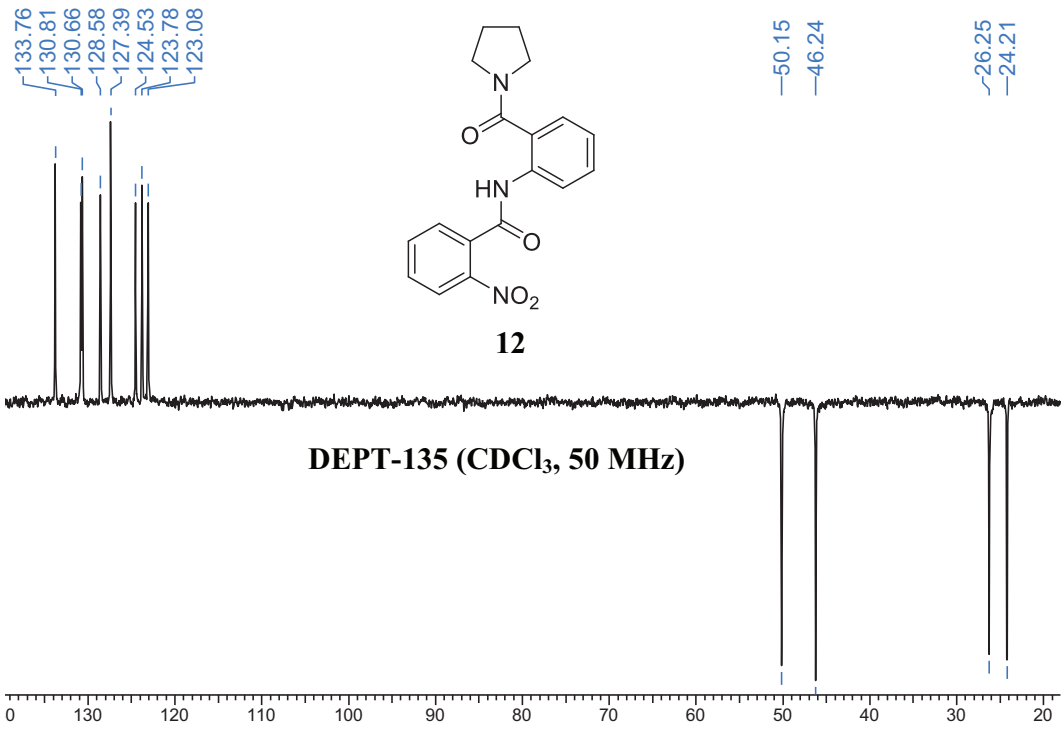

Chloroform-d
170.01
169.02
165.76
146.01
136.78
135.11
133.83
133.29
131.00
130.08
129.49
126.07
125.74
124.36
121.64
120.54
116.07
77.00
60.84
49.89
29.82
24.80
13C NMR (CDCl3, 125 MHz)
(L)
Br
HN
NO2
5
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20


133.85
130.98
130.08
129.49
125.72
124.36
121.61
120.52
60.84
49.89
29.86
24.80
DEPT-135 (CDCl3, 125 MHz)
(L)
Br
HN
NO2
5
0
130
120
110
100
90
80
70
60
50
40
30
20



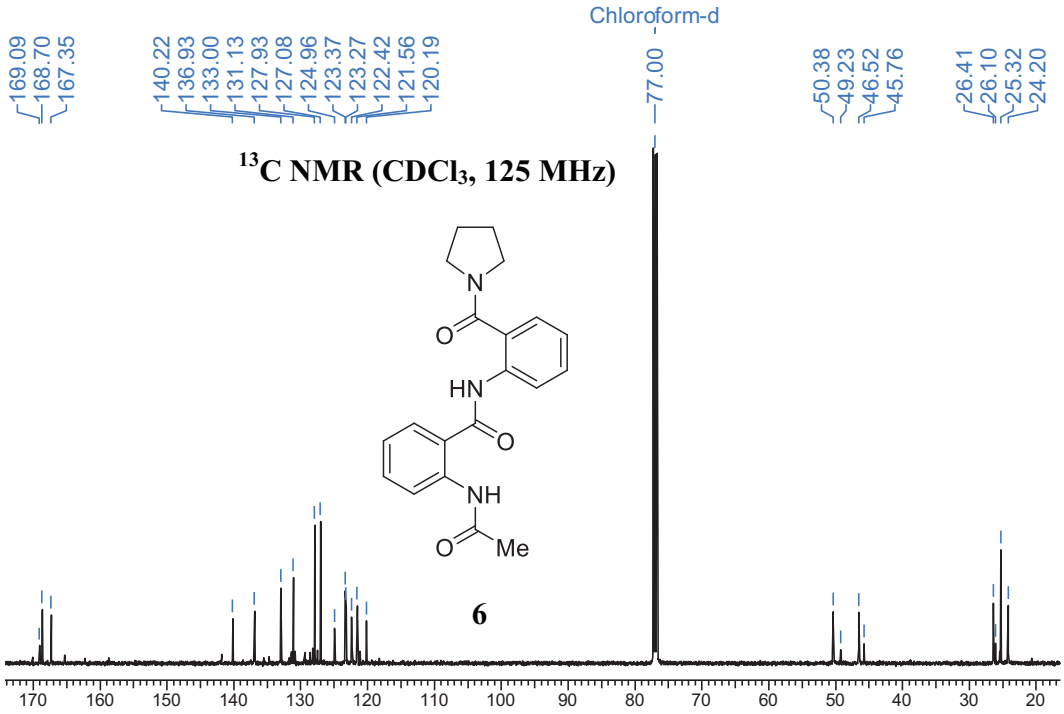
^{13}C NMR ($CDCl_3$, 50 MHz)

12



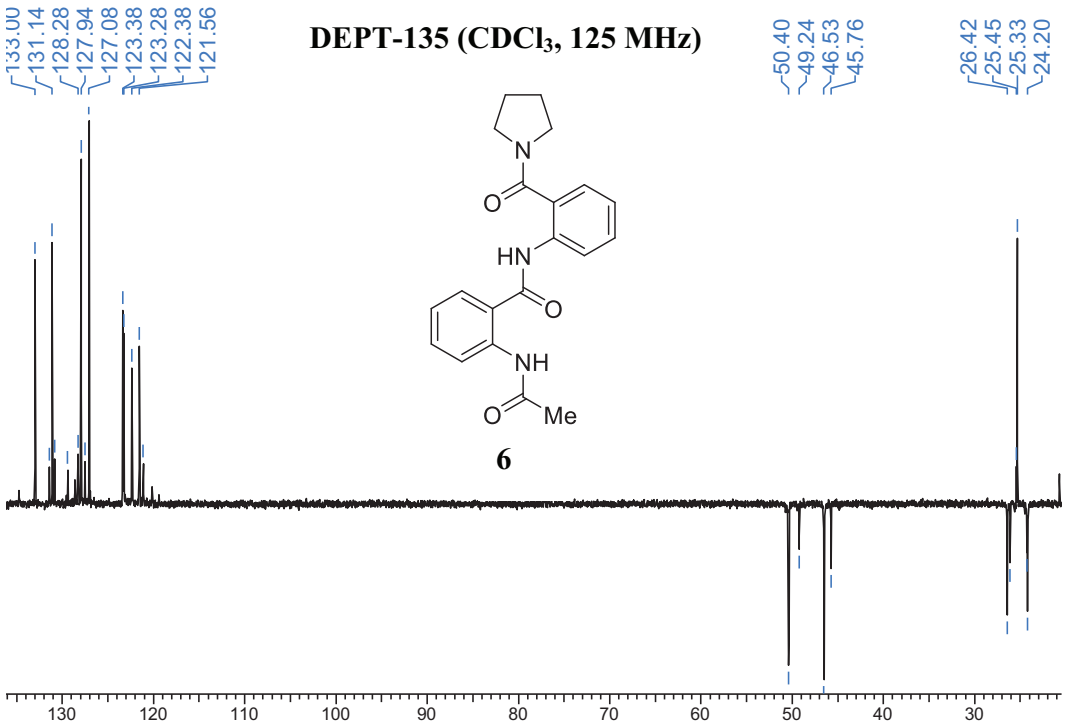
12

DEPT-135 ($CDCl_3$, 50 MHz)



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

6

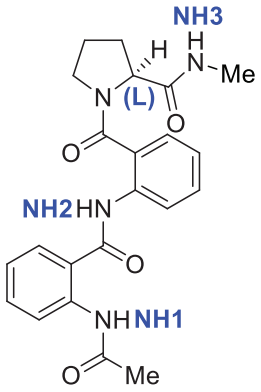


DEPT-135 ($CDCl_3$, 125 MHz)

6

Table S2. Titration study of tripeptide 2a 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	11.02	10.34	6.49
5	10.97	10.36	6.60
10	10.90	10.37	6.72
15	10.85	10.37	6.81
20	10.82	10.37	6.86
25	10.77	10.37	6.92
30	10.73	10.37	6.97
35	10.73	10.37	6.97
40	10.70	10.36	7.01
45	10.66	10.35	7.03
50	10.63	10.34	7.06



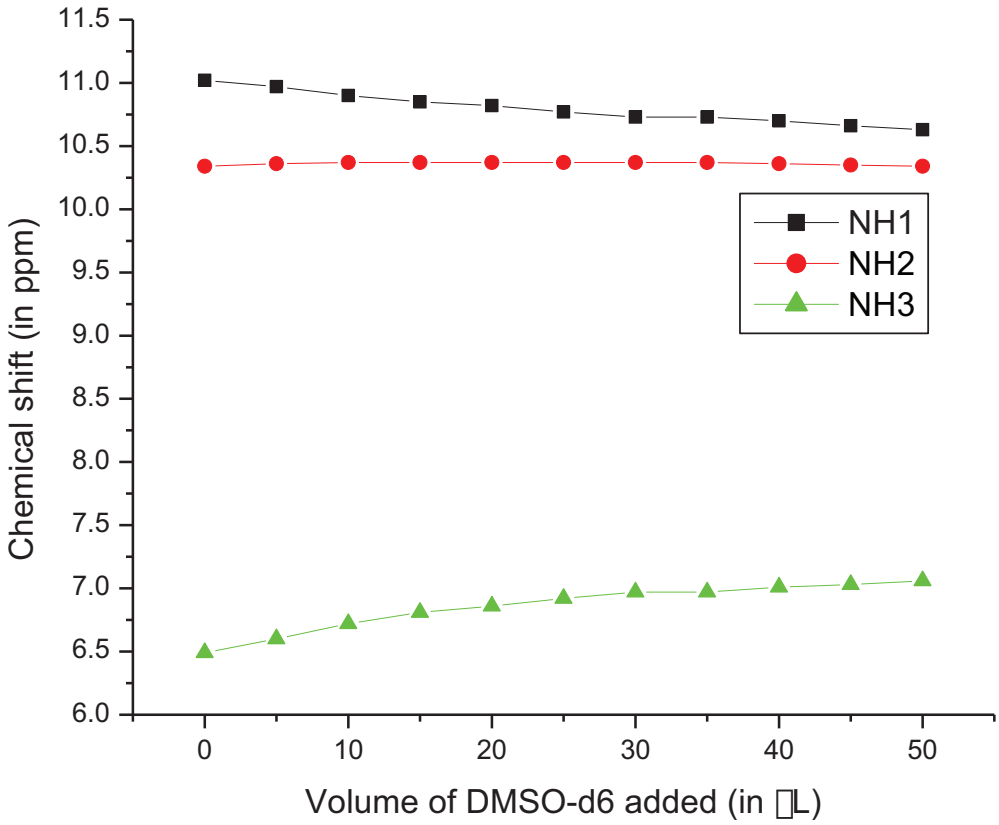
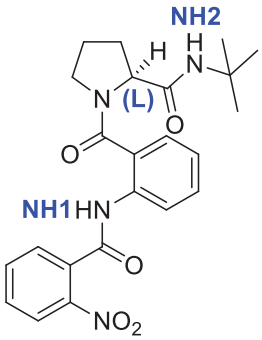


Table S3. Titration study of tripeptide 4 in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d6 (volume of DMSO-d6 added at each addition = 5 μl)

Volume of DMSO-d6 added (in μL)	Chemical Shift (in ppm)	
	NH1	NH2
0	9.93	5.61
5	9.96	5.72
10	9.98	5.78
15	10.01	5.89
20	10.04	5.97
25	10.06	6.04
30	10.07	6.12
35	10.09	6.19
40	10.10	6.25
45	10.11	6.30
50	10.12	6.35



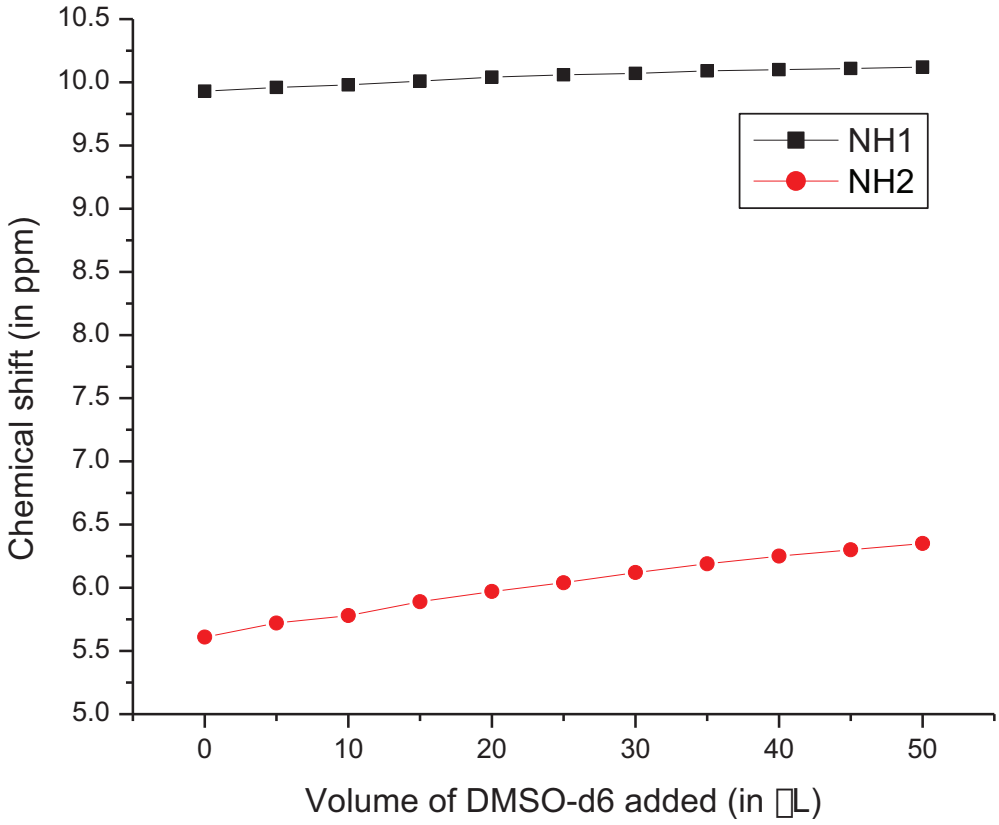
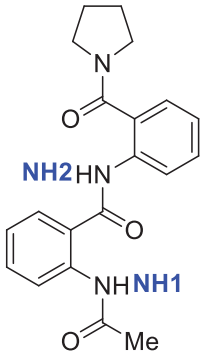


Table S4. Titration study of tripeptide 6 in $CDCl_3$, 400 MHz (20 mmol) with DMSO-d6 (volume of DMSO-d6 added at each addition = 5 μl)

Volume of DMSO-d6 added (in μL)	Chemical Shift (in ppm)	
	NH1	NH2
0	11.24	10.86
5	11.22	10.84
10	11.20	10.83
15	11.17	10.81
20	11.15	10.79
25	11.13	10.78
30	11.10	10.76
35	11.08	10.74
40	11.05	10.72
45	11.02	10.70
50	11.00	10.69



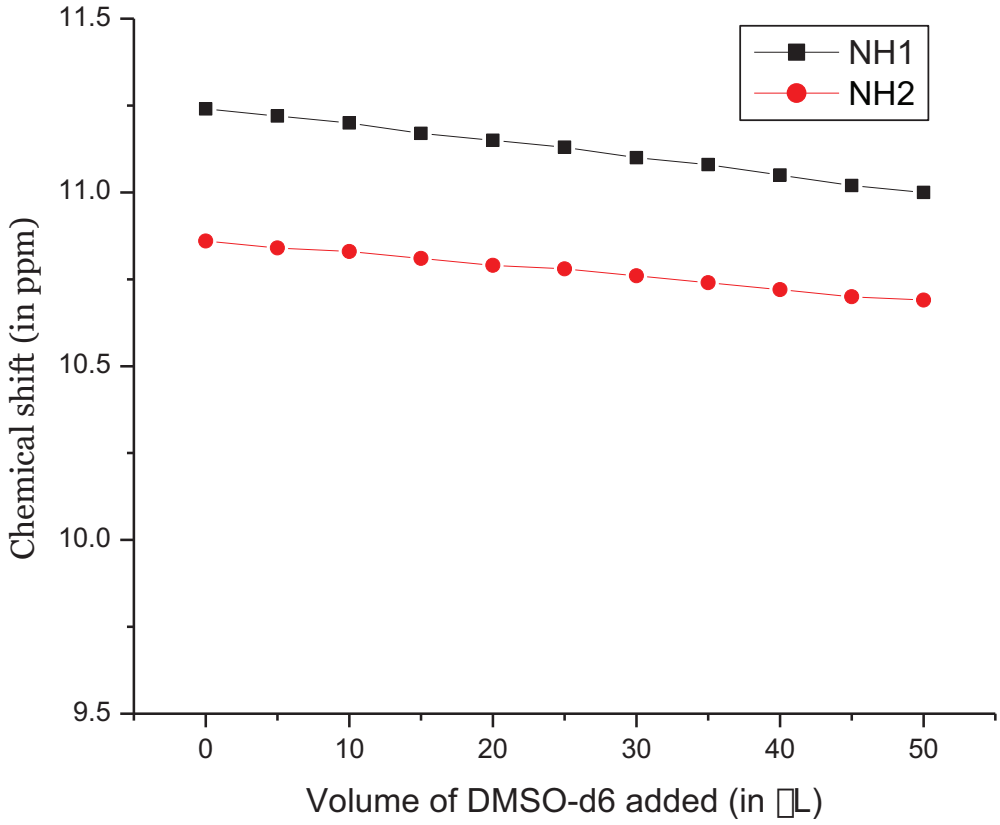
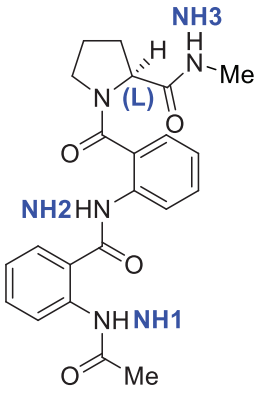


Table S5. Variable temperature study of tripeptide 2a (20 mmol, 400 MHz, $CDCl_3$)

Temperature (in K)	Chemical shift (in ppm)		
	NH1	NH2	NH3
268	11.00	10.41	6.55
273	11.00	10.40	6.54
278	11.01	10.38	6.53
283	11.02	10.37	6.51
288	11.02	10.35	6.50
293	11.02	10.34	6.48
298	11.02	10.32	6.47
303	11.02	10.30	6.46
308	11.02	10.28	6.45
313	11.01	10.26	6.43
318	11.01	10.24	6.43
323	11.00	10.22	6.41



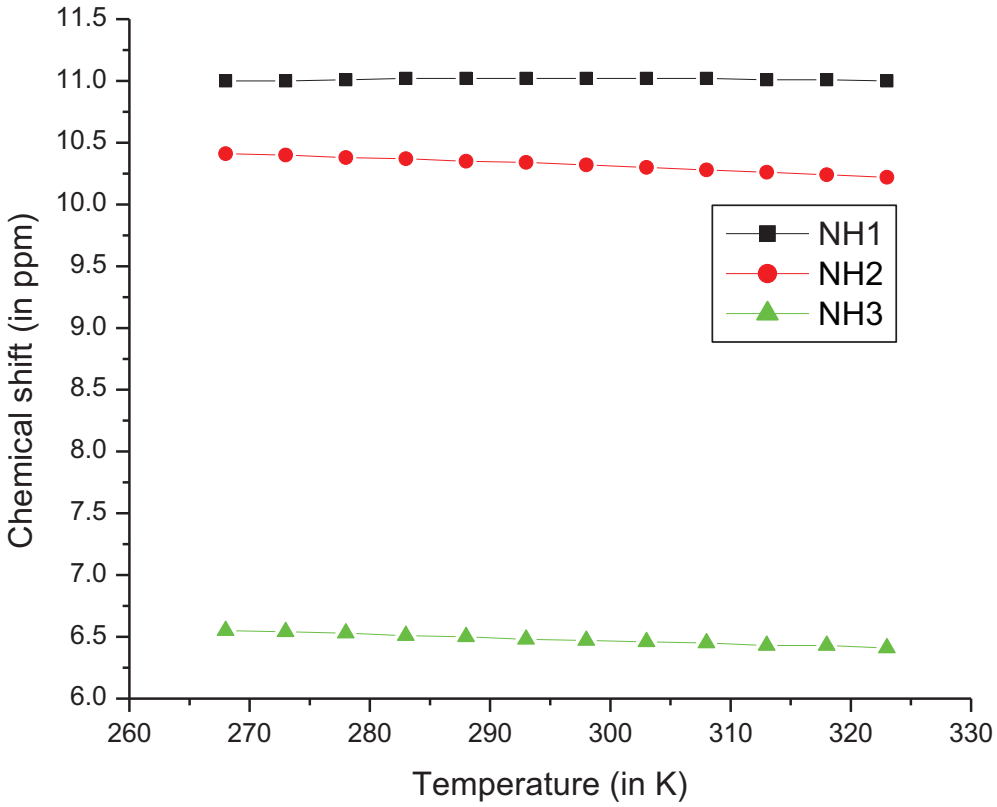
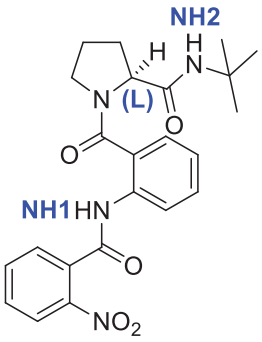


Table S6. Variable temperature study of tripeptide 4 (20 mmol, 400 MHz, $CDCl_3$)

Temperature (in K)	Chemical shift (in ppm)	
	NH1	NH2
268	10.06	5.66
273	10.03	5.67
278	10.01	5.68
283	9.98	5.68
288	9.96	5.67
293	9.92	5.65
298	9.90	5.64
303	9.87	5.63
308	9.85	5.63
313	9.82	5.63
318	9.79	5.63
323	9.77	5.63



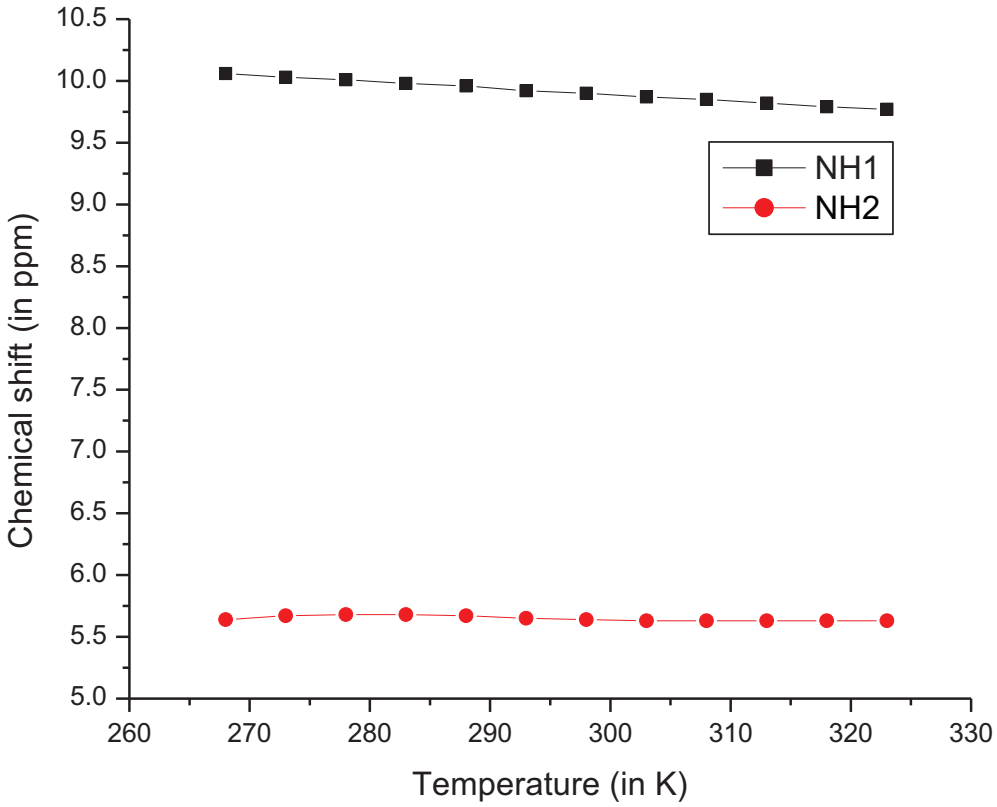
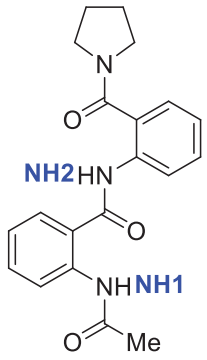
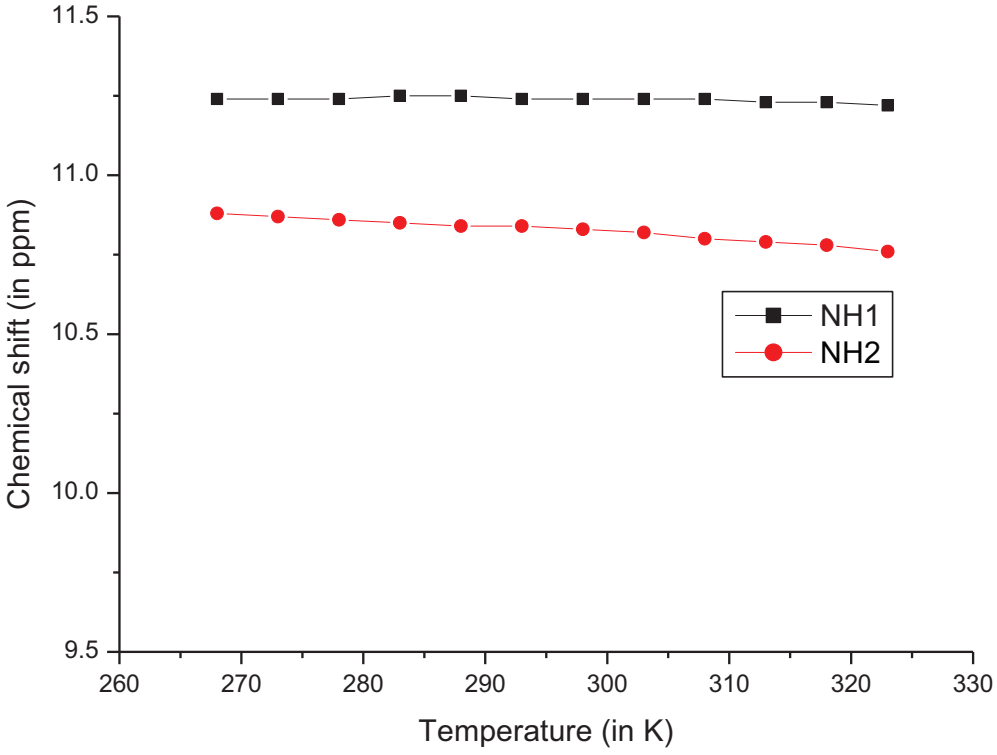
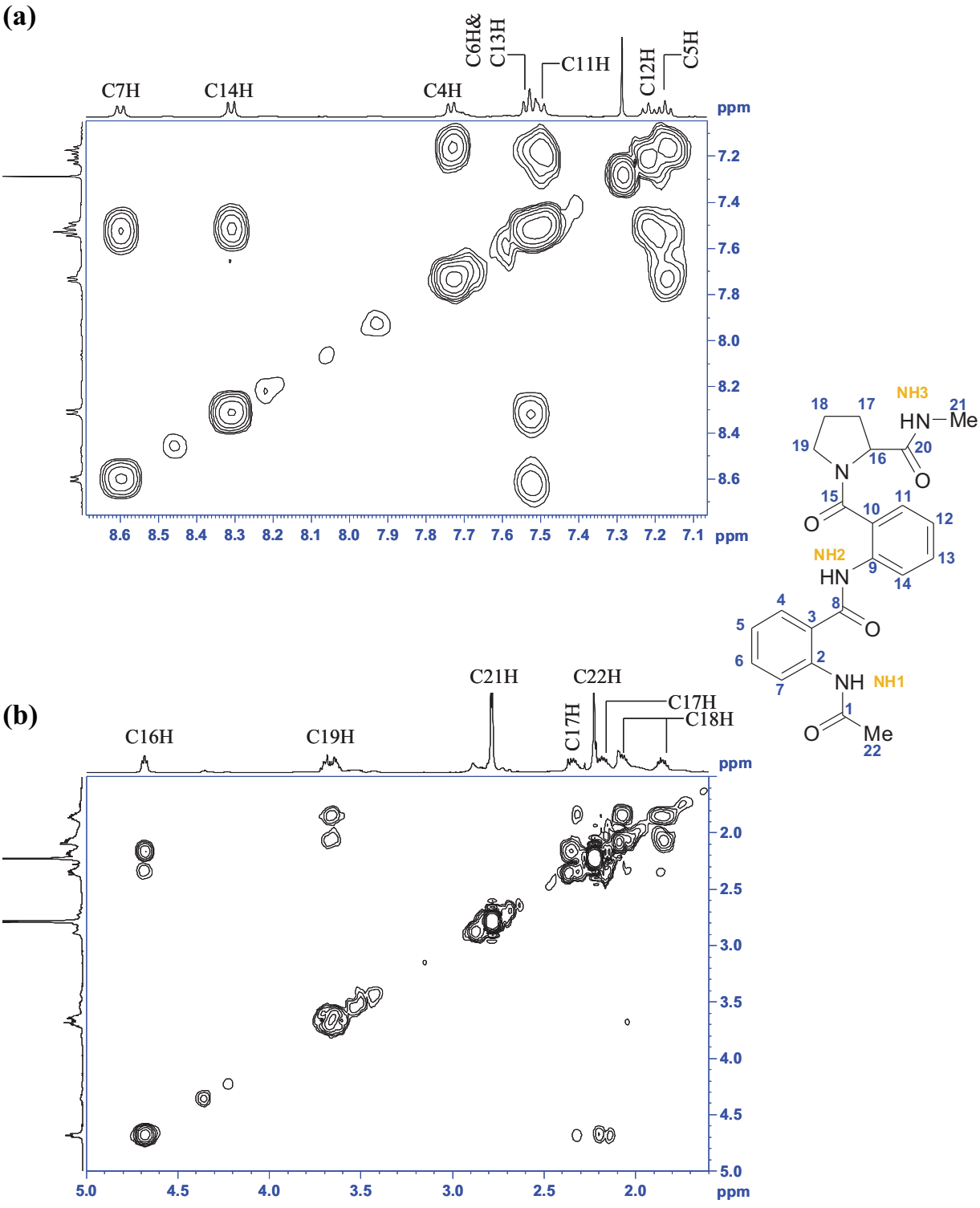


Table S7. Variable temperature study of tripeptide 6 (20 mmol, 400 MHz, $CDCl_3$)

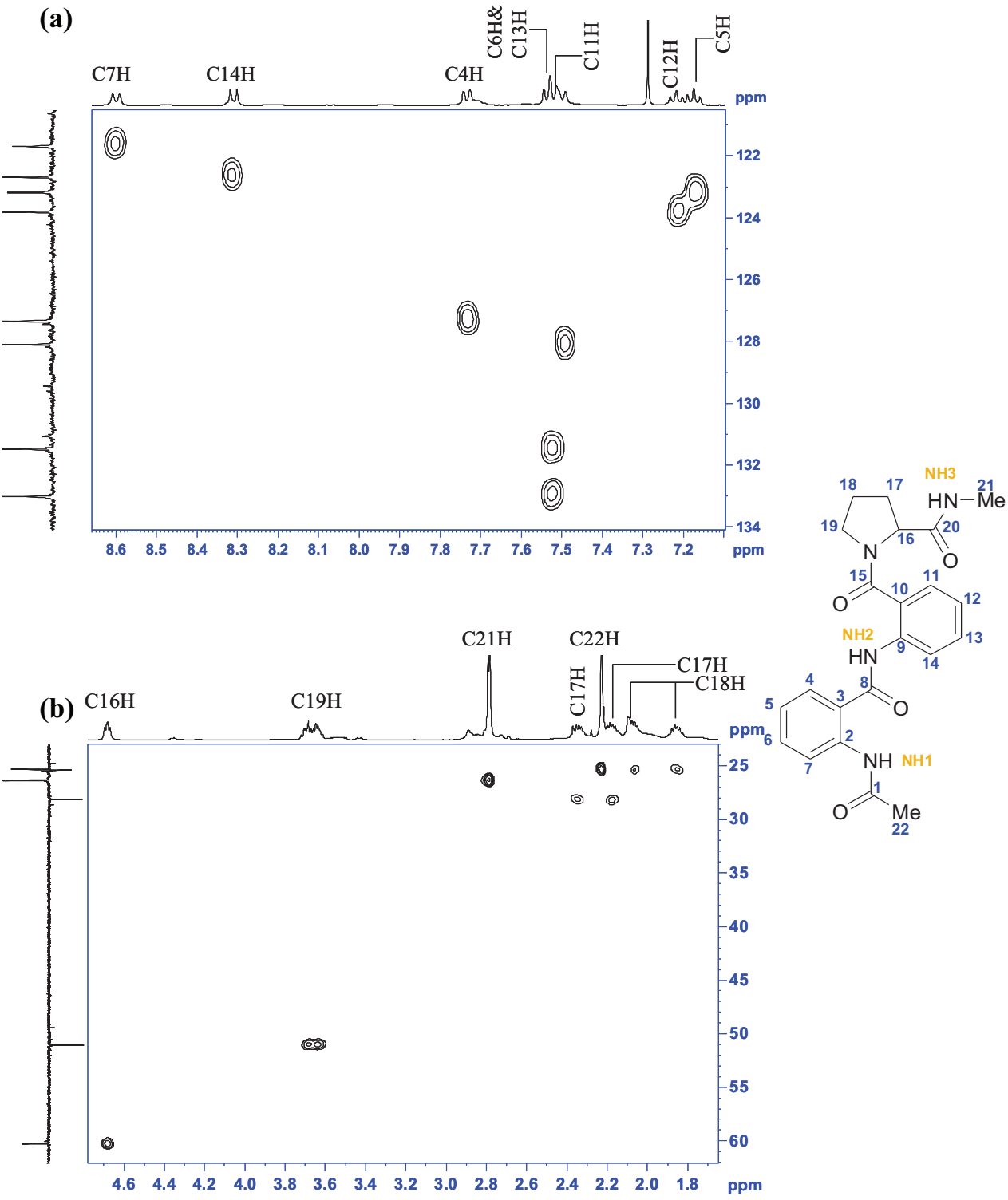
Temperature (in K)	Chemical shift (in ppm)	
	NH1	NH2
268	11.24	10.88
273	11.24	10.84
278	11.24	10.86
283	11.25	10.85
288	11.25	10.84
293	11.24	10.87
298	11.24	10.83
303	11.24	10.82
308	11.24	10.80
313	11.23	10.79
318	11.23	10.78
323	11.22	10.76



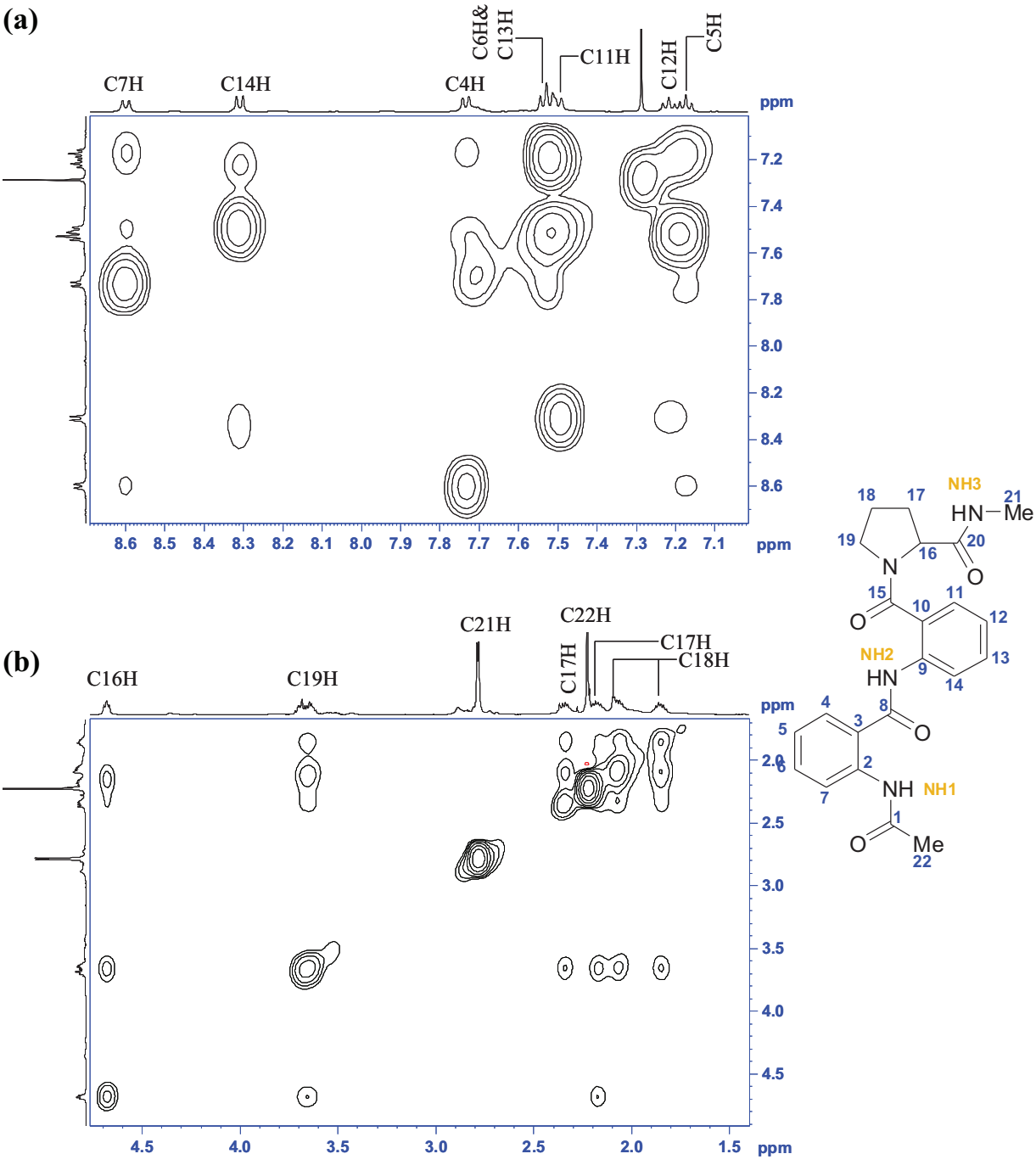




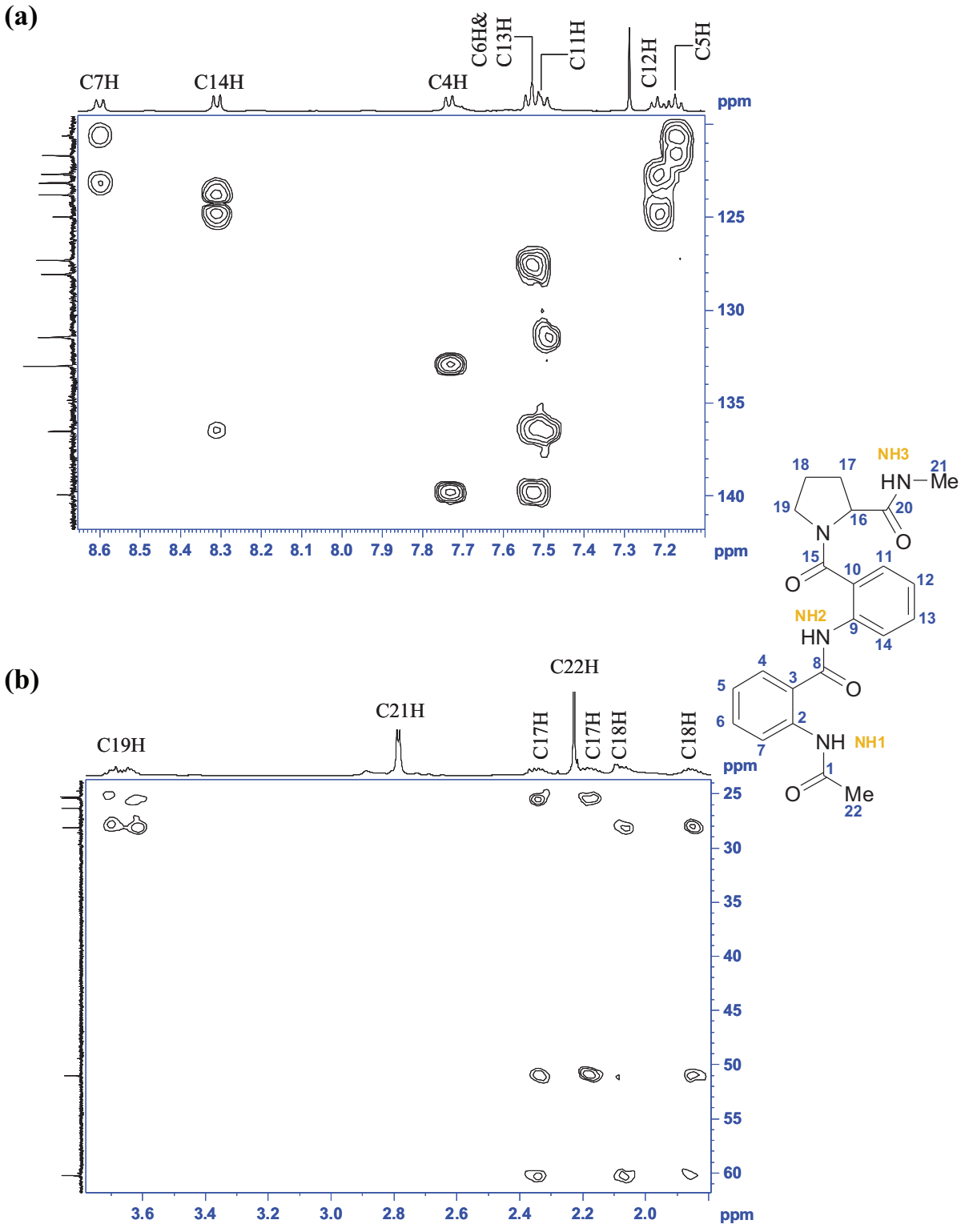
Partial COSY spectra of 2a (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions



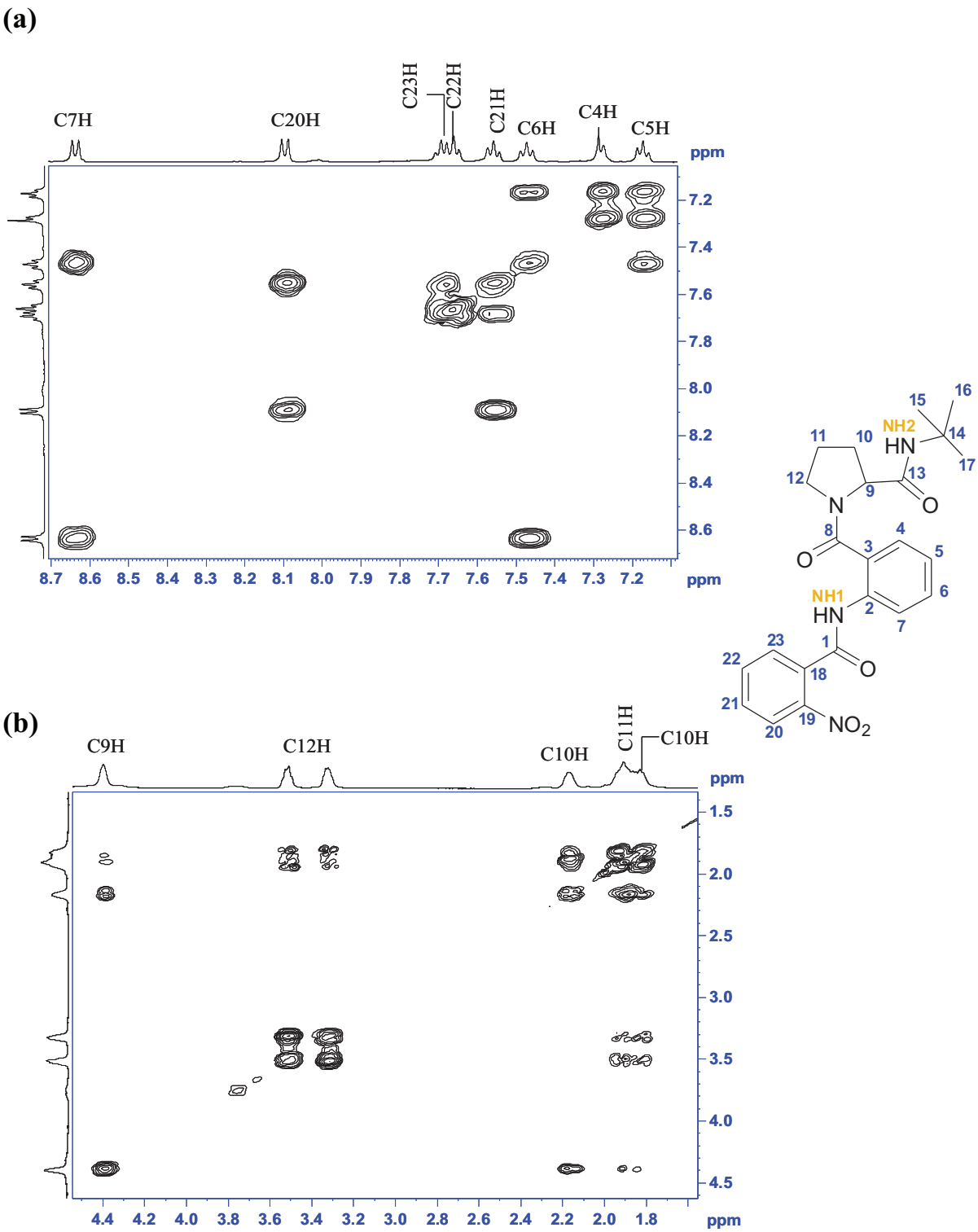
Partial HSQC spectra of 2a (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions.



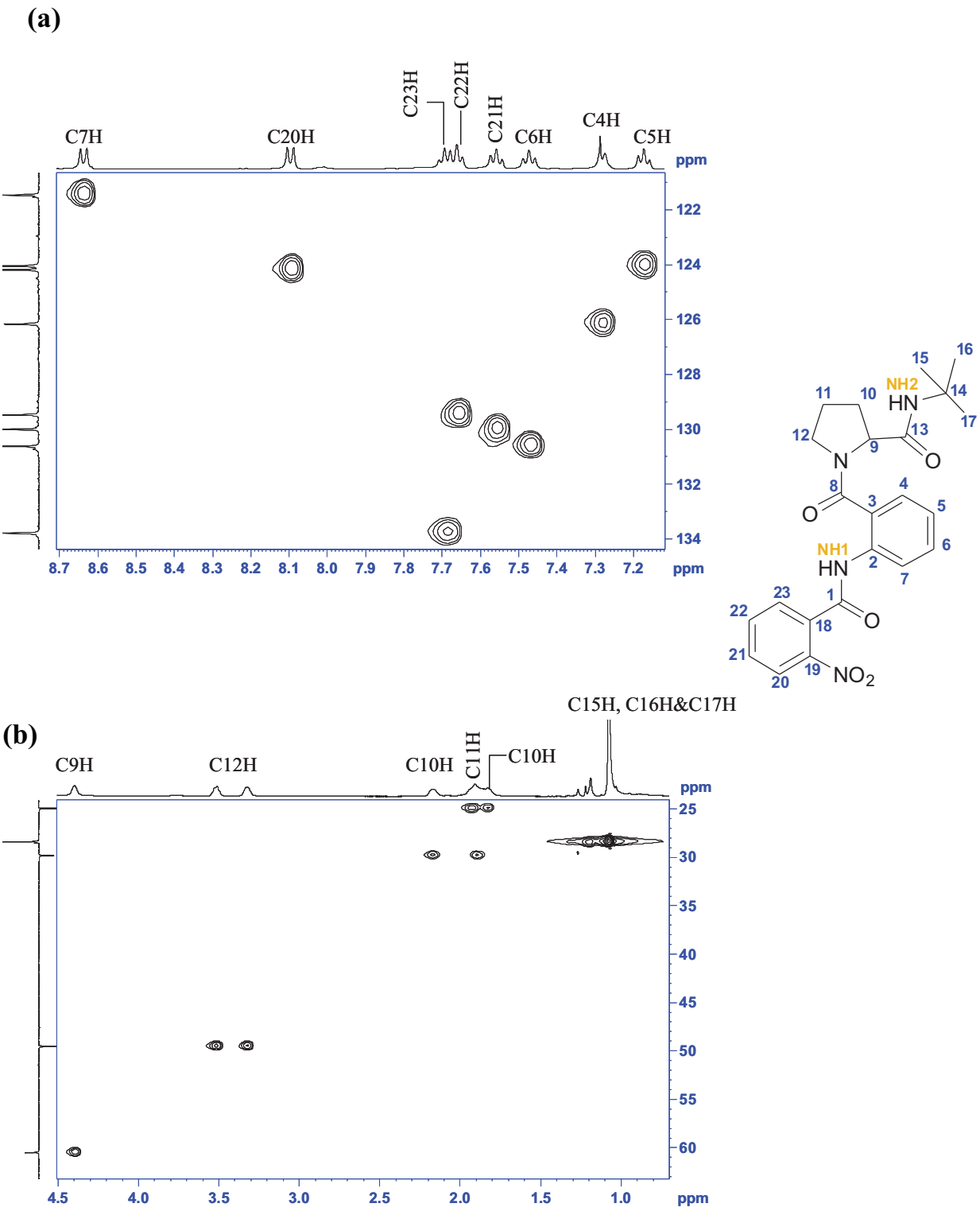
Partial TOCSY spectra of 2a (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions.



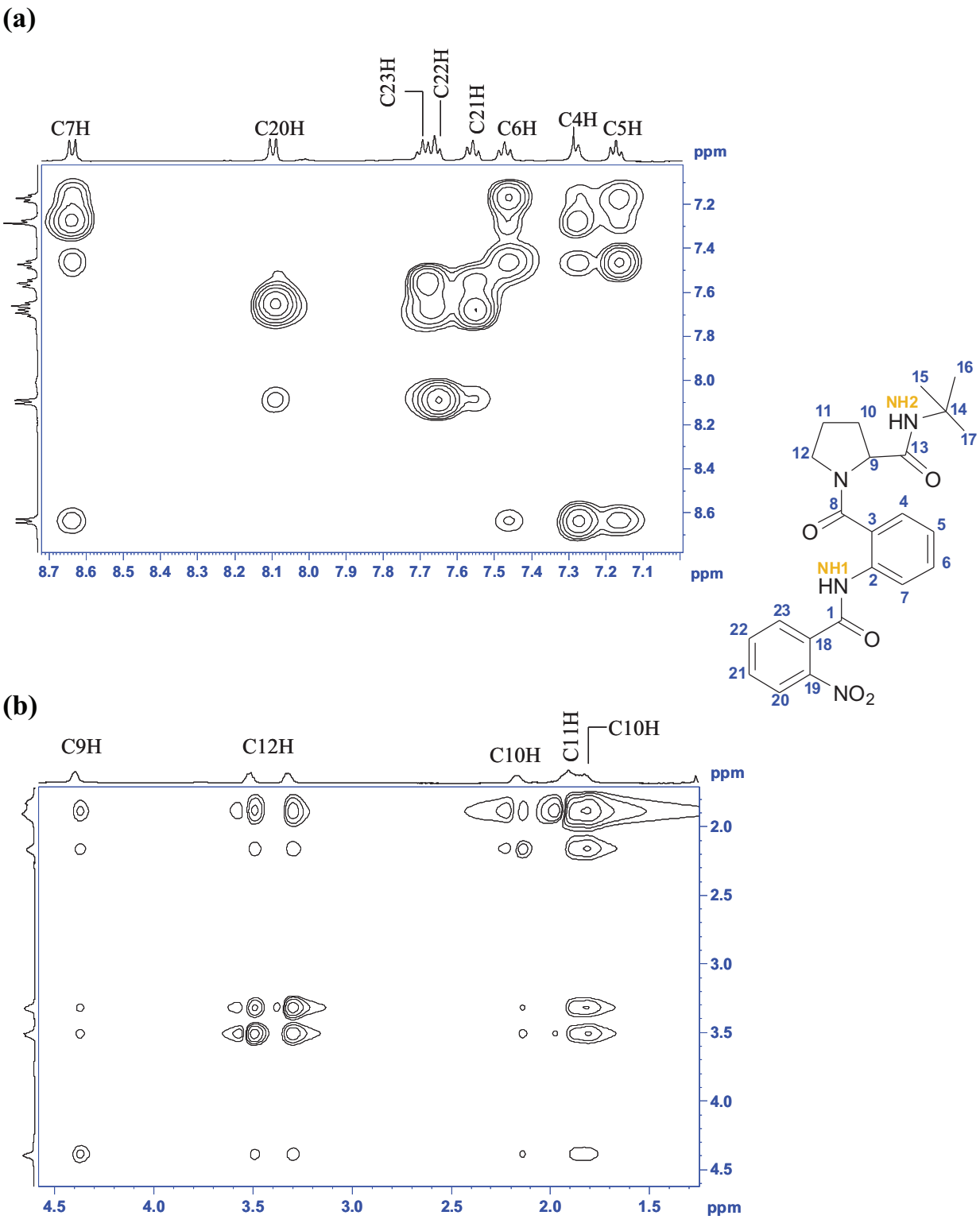
Partial HMBC spectra of 2a (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions



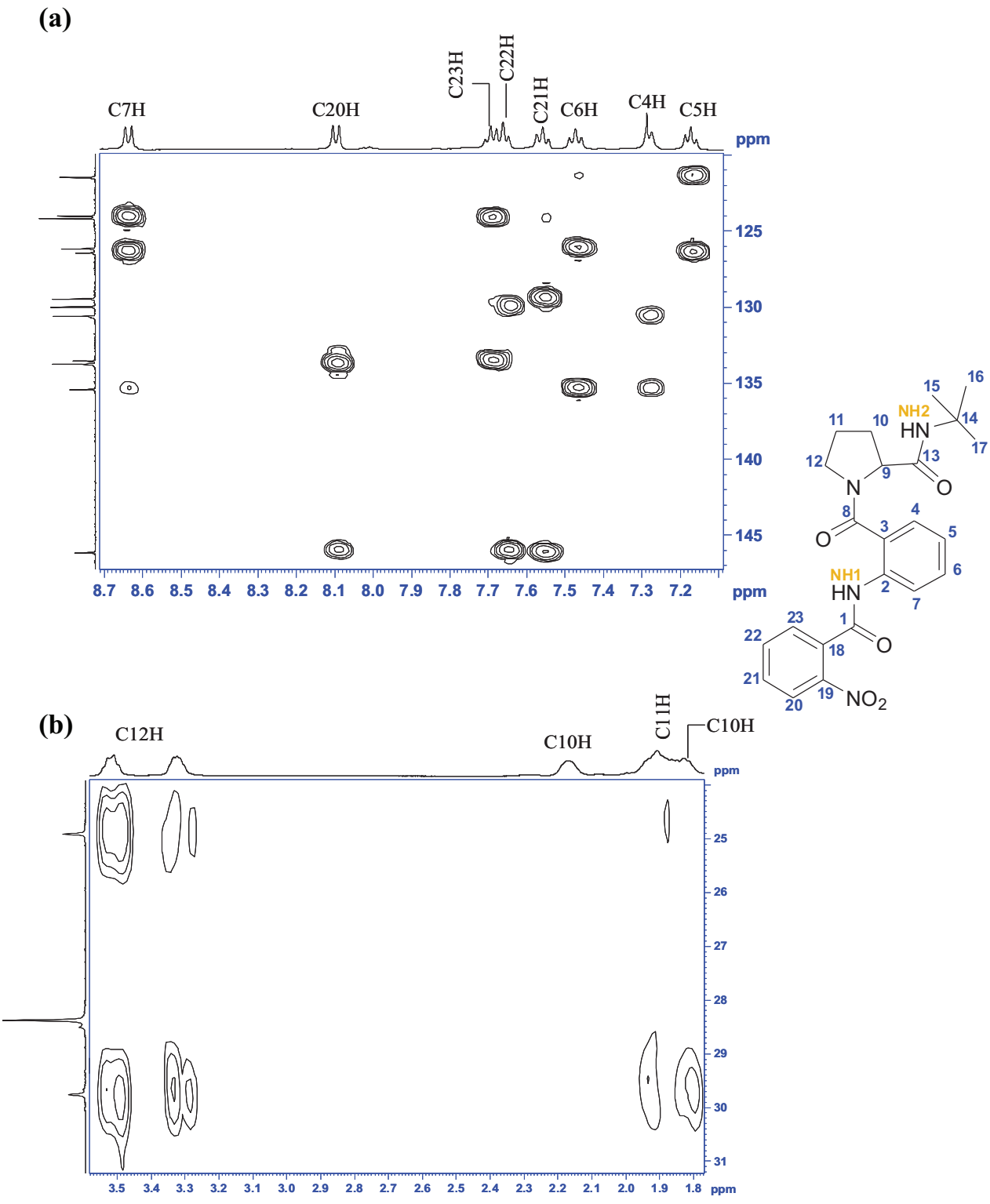
Partial COSY spectra of 4 (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions.



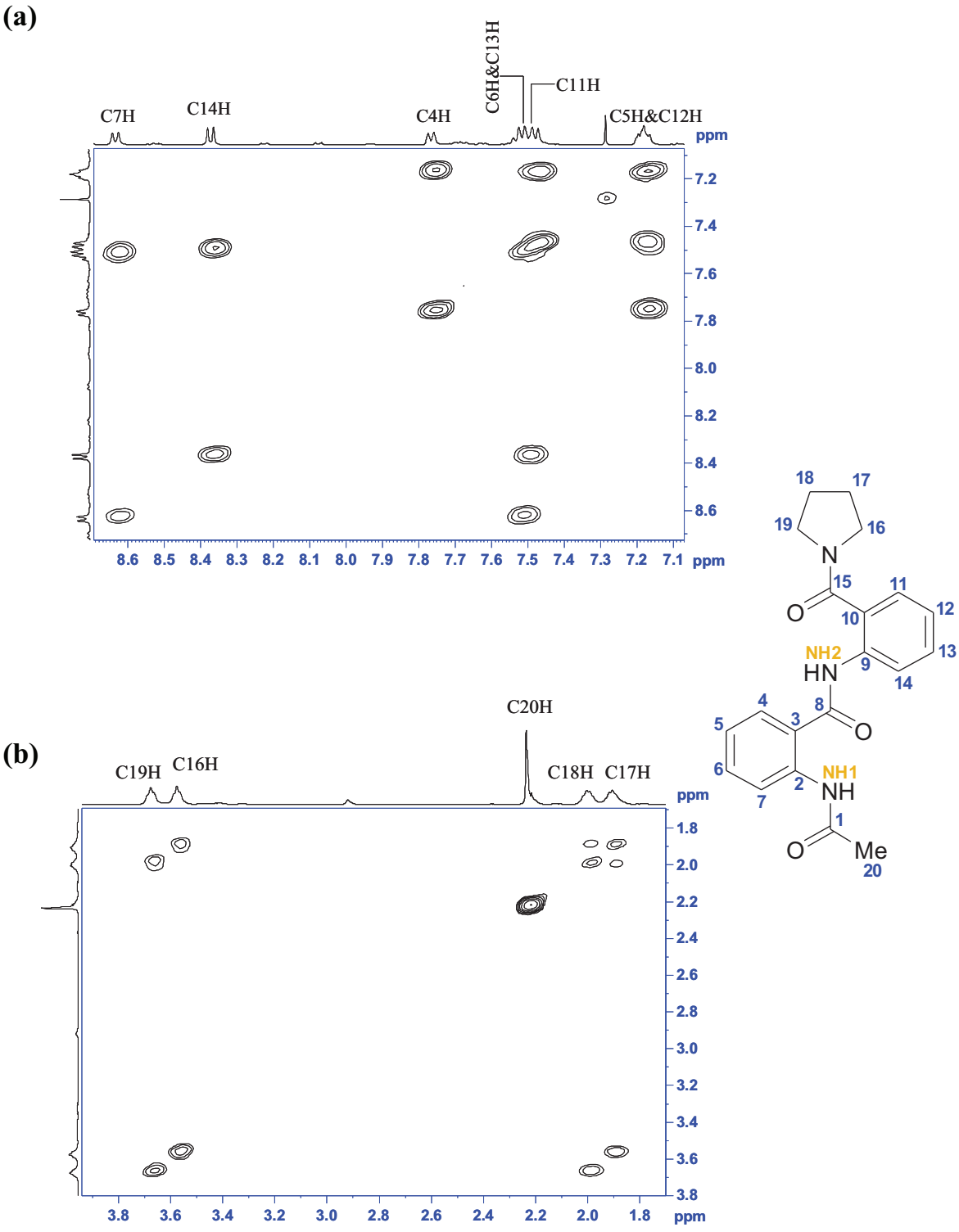
Partial HSQC spectra of 4 (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions.



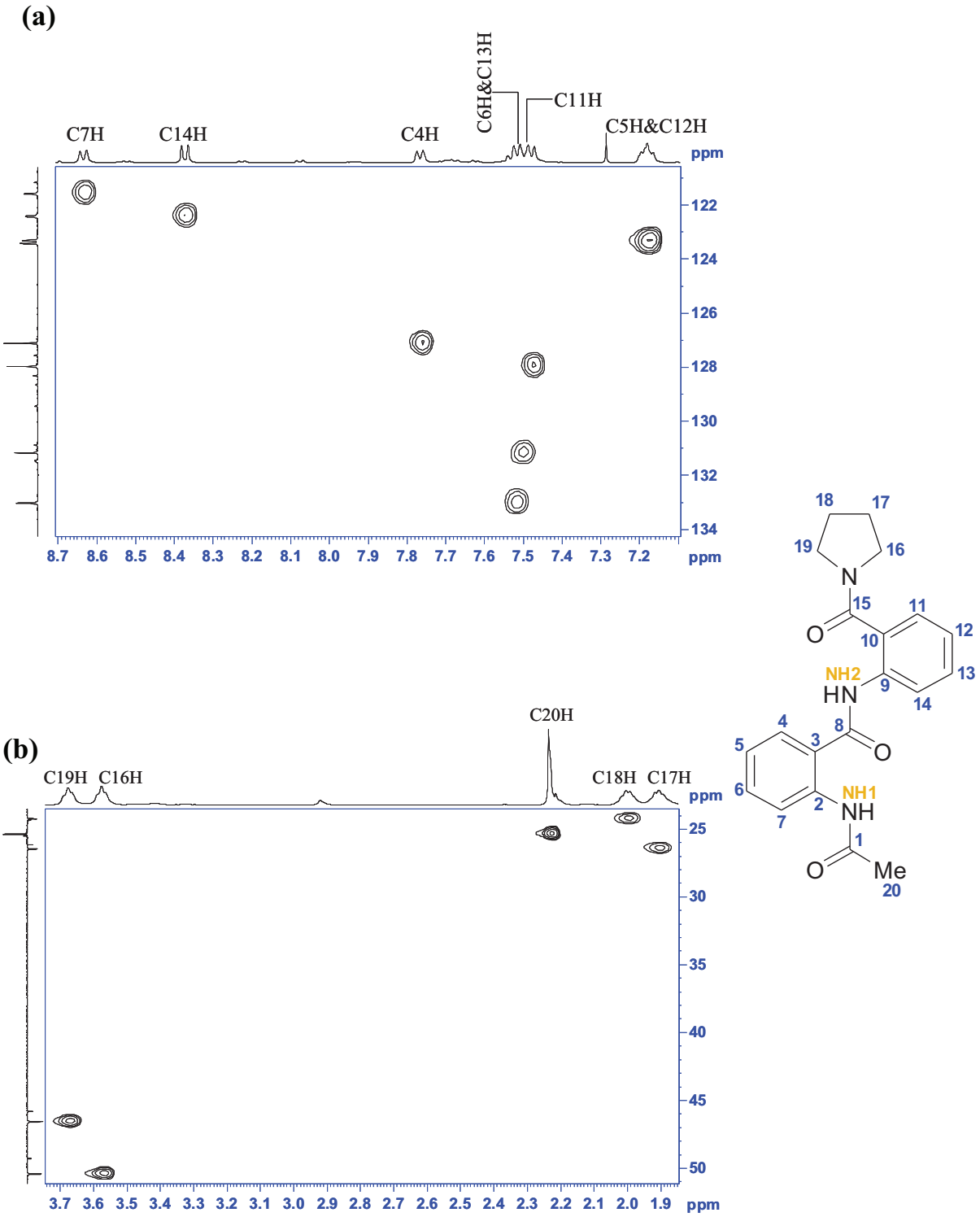
Partial TOCSY spectra of 4 (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions.



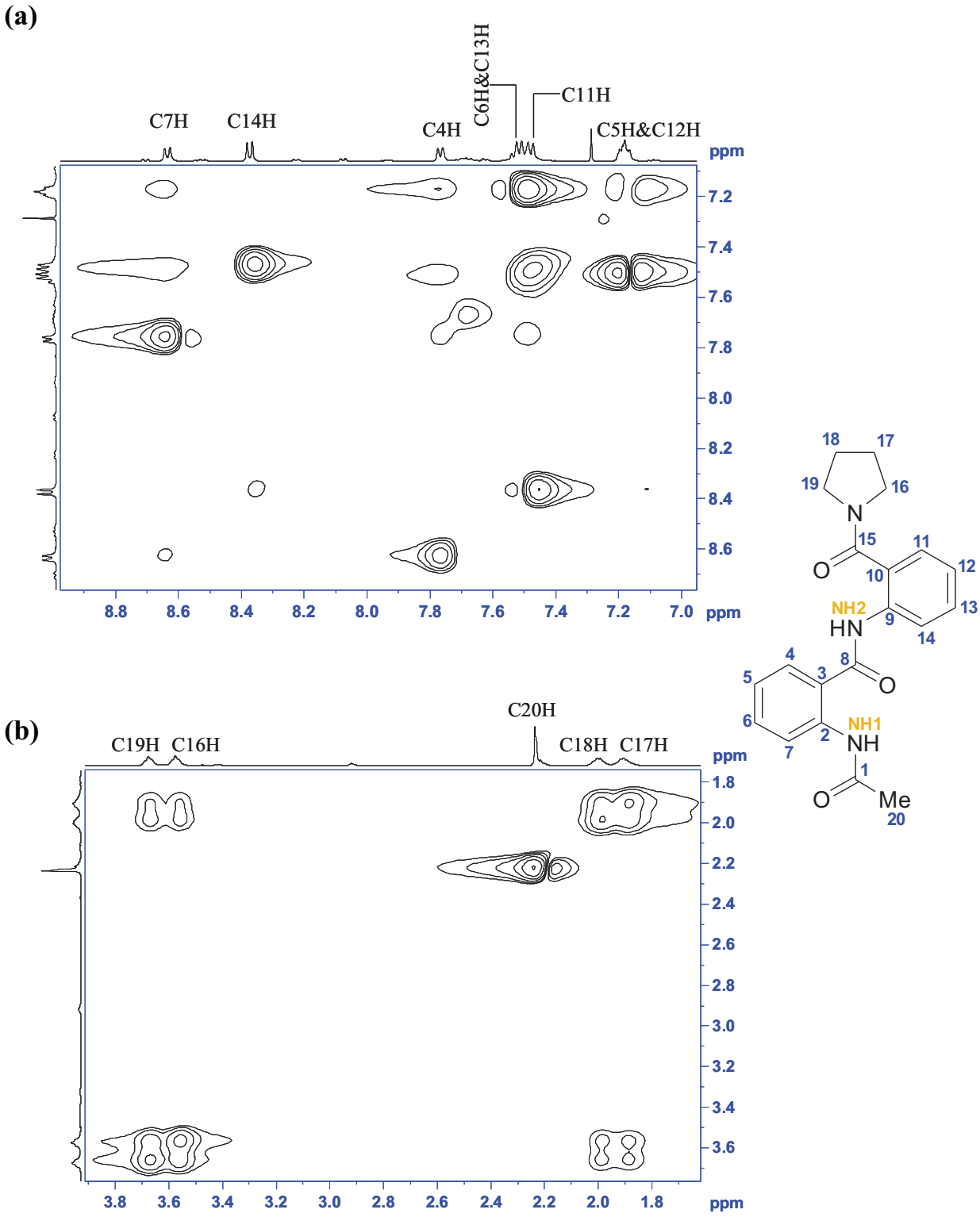
Partial HMBC spectra of 4 (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions.



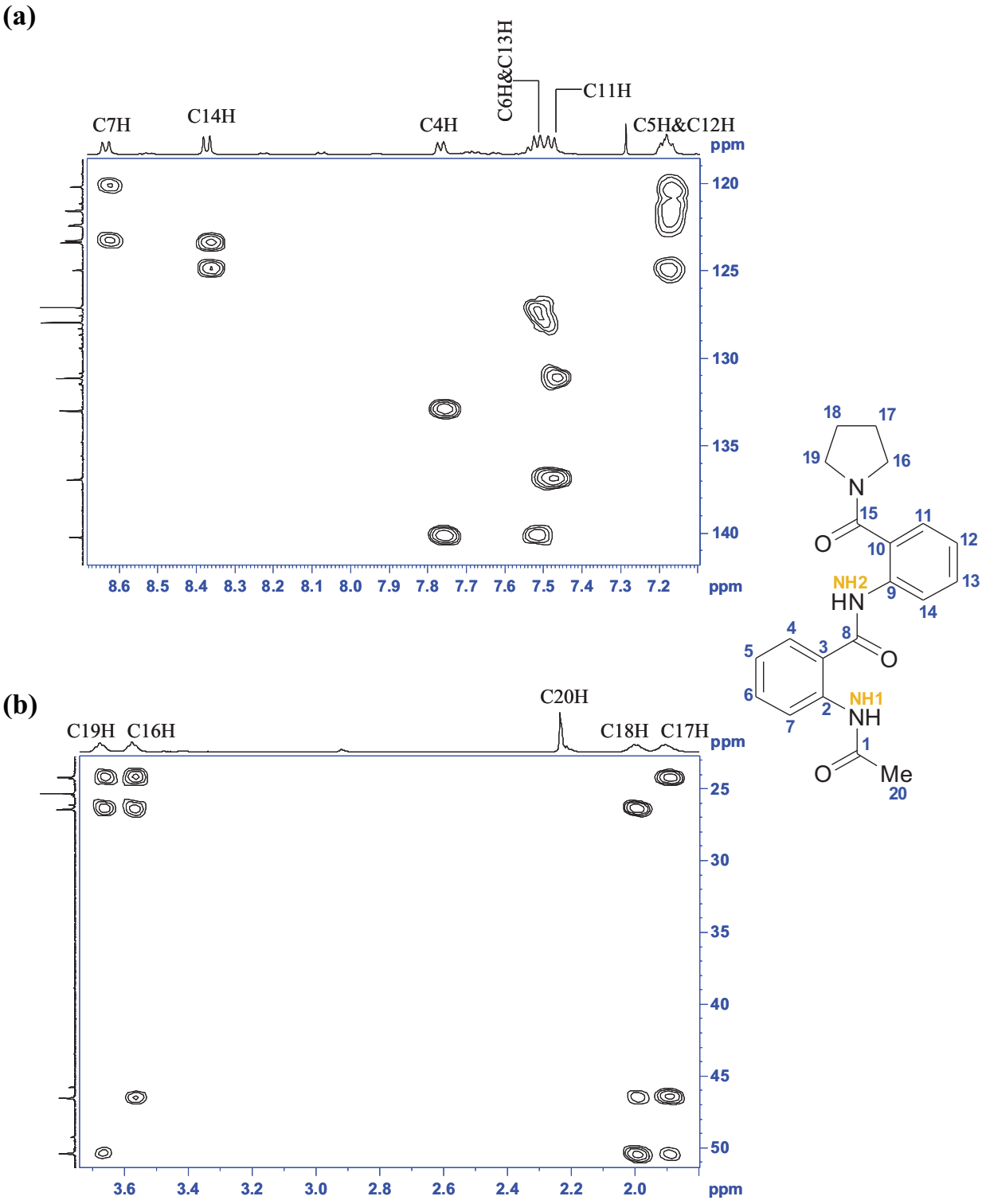
Partial COSY spectra of 6 (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions



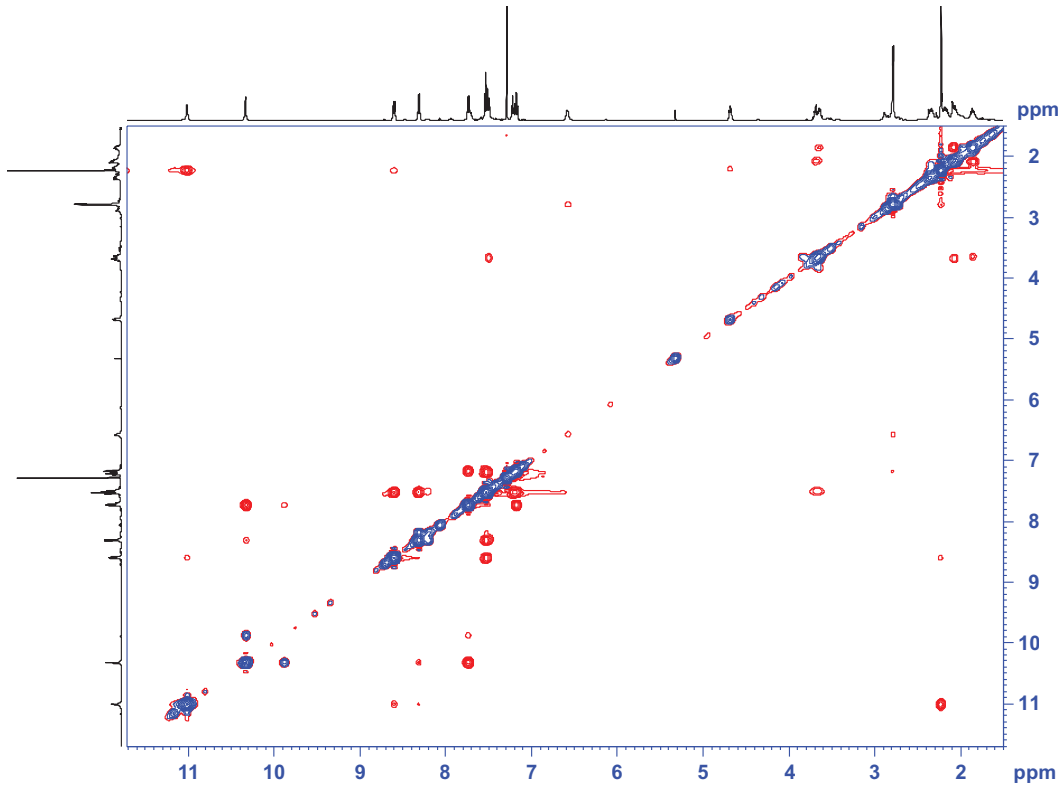
Partial HSQC spectra of 6 (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions.



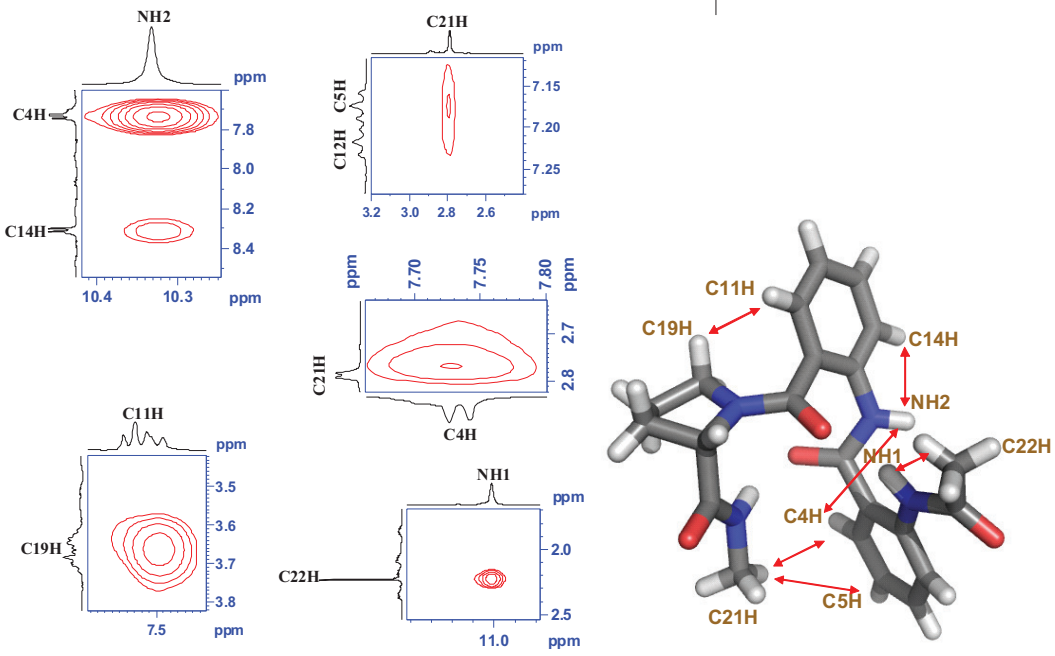
Partial TOCSY spectra of 6 (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions.



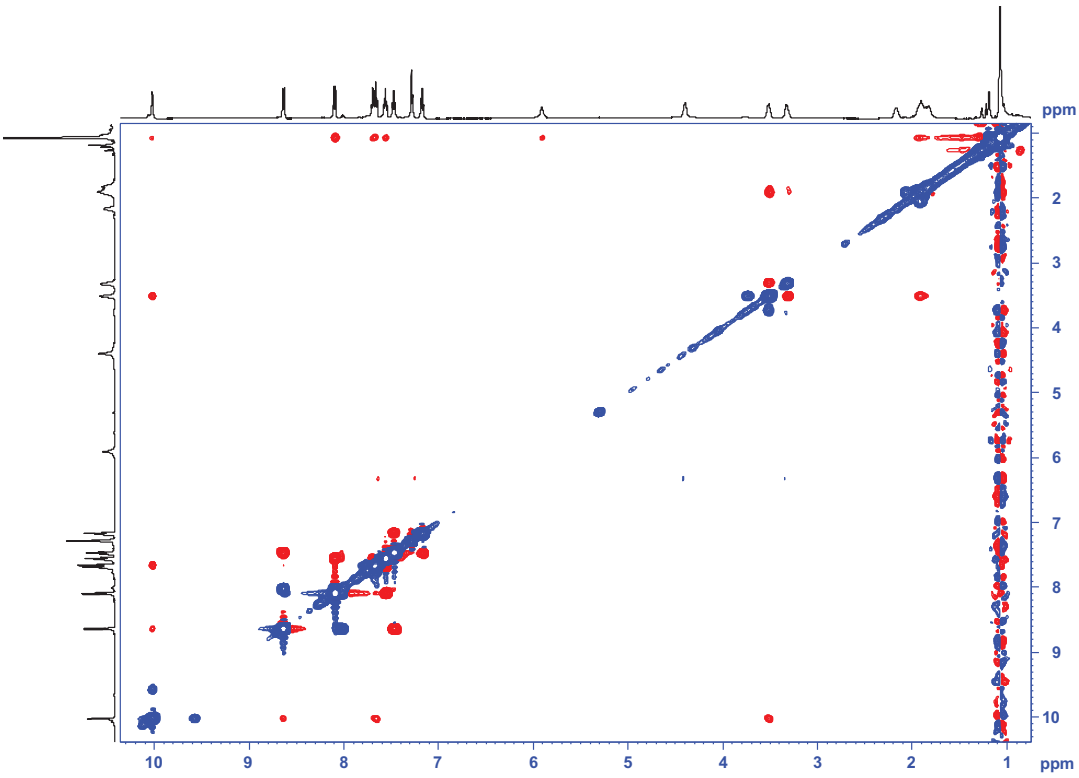
Partial HMBC spectra of 6 (500 MHz, $CDCl_3$): Aromatic (a) and aliphatic (b) regions.



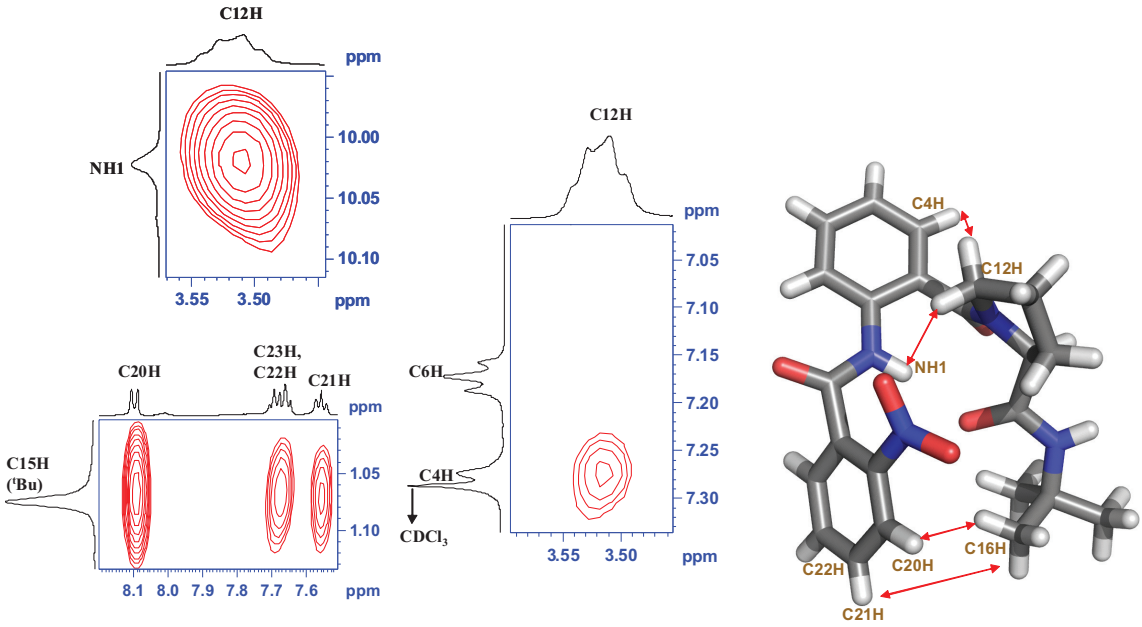
2D NOESY full spectrum of 2a (500 MHz, $CDCl_3$).



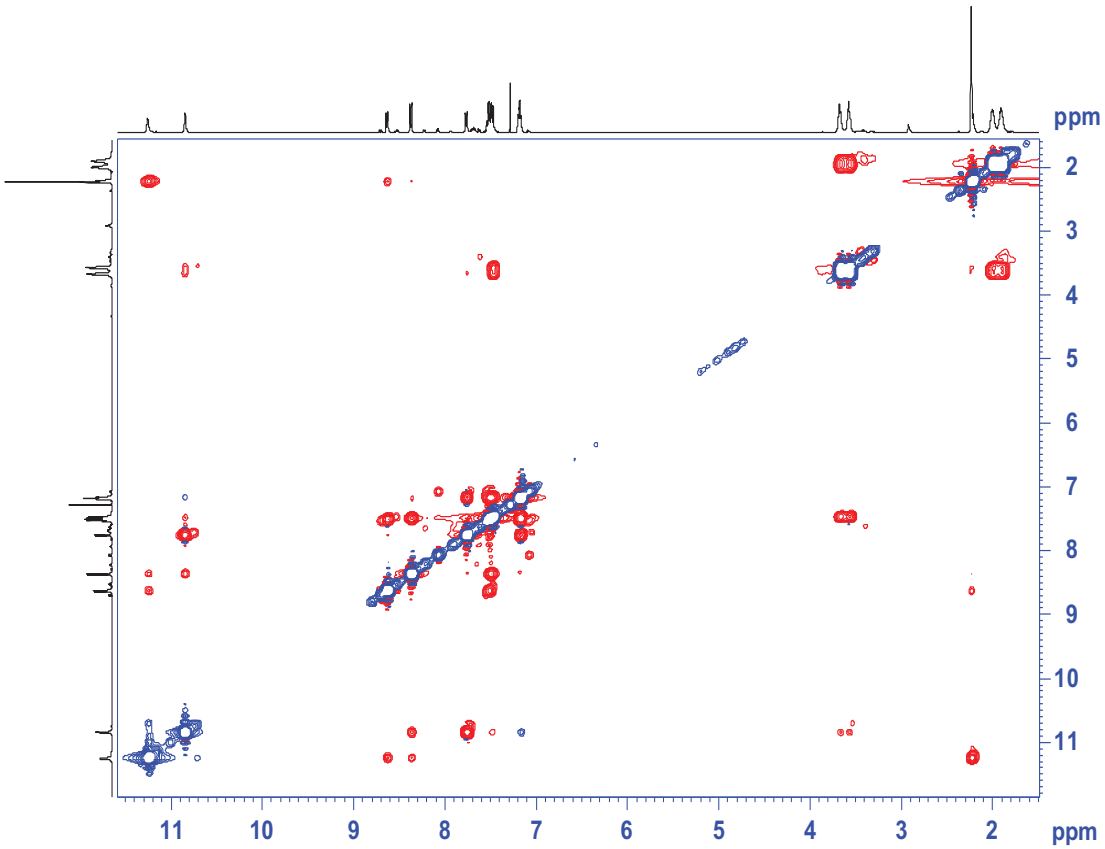
2D NOESY excerpts of 2a (500 MHz, $CDCl_3$), suggestive of folded conformation as seen in the crystal structure (representative nOes are highlighted).



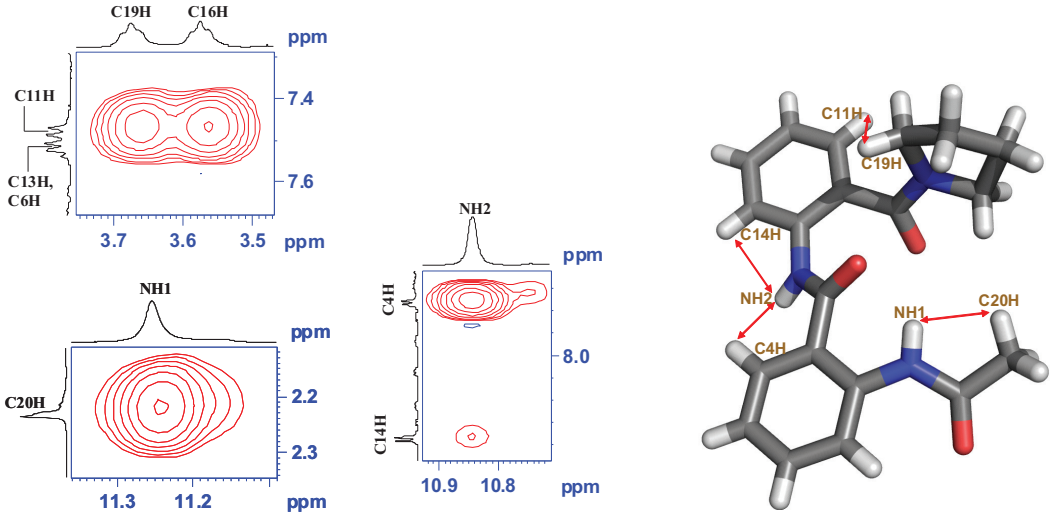
2D NOESY spectrum of 4 (500MHz, $CDCl_3$)



2D NOESY excerpts of 4 (500 MHz, $CDCl_3$). Representative nOes are highlighted on the crystal structure, using red double-headed arrows.



2D NOESY spectrum of 6 (500MHz, $CDCl_3$)



2D NOESY excerpts of 6 (500 MHz, $CDCl_3$). Representative nOes are highlighted on the crystal structure, using red double-headed arrows.