Electronic Supplementary Information

Ester vs. amide on folding: A case study with a 2-residue synthetic peptide

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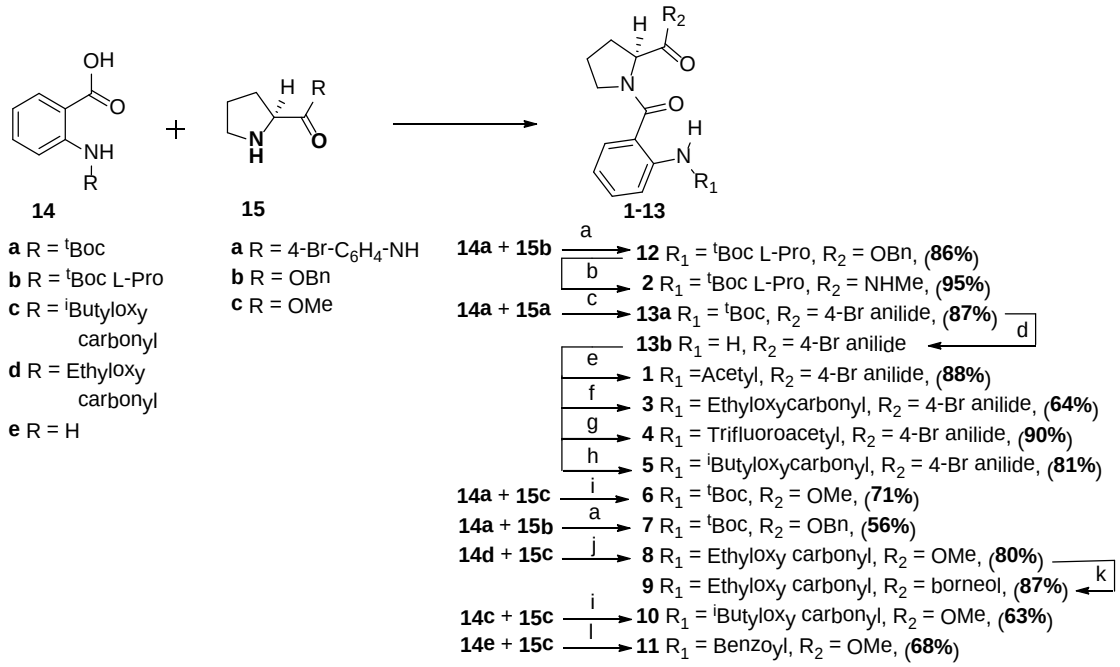
Contents	S1
General methods	S2
Synthetic Scheme	S3
Experimental procedures	S4-S12
Mass spectra of compounds	S13-S19
^{1}H NMR spectra of compounds	S20-S26
^{13}C and DEPT-135 spectra of compounds	S27-S39
2D COSY and TOCSY spectra of compounds **1** and **5** (amides)	S40-S43
2D COSY and TOCSY spectra of compounds **6** and **10** (esters)	S44-S48
2D NOESY spectra of compounds **1** and **5** (amides)	S49-S50
2D NOESY spectra of compound **6** and **10** (esters)	S51-S52
NMR titration studies of compounds **1**, **5**, **10**	S53-S55
Crystal Data Table-Hydrogen bonding parameters and Crystal Data	S56- S61
References	S61

General Methods.

Unless otherwise stated, all the 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 or 230-400 Mesh Silica gel. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 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 as singlet (s), doublet (d), quartet (q), broad singlet (bs), and multiplet (m). The DMSO-d_6 titration studies were done in $CDCl_3$. 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. Electron Scattered Ionization (ESI) Mass Spectrometric measurements were done with API QSTAR Pulsar mass Spectrometer. Single crystal X-ray data were collected on a *Bruker SMART APEX* CCD Area diffractometer with graphite monochromatized (Mo Ka = 0.71073Å) radiation at room temperature or less.

Synthetic Scheme

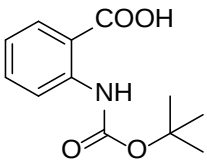


Reagents and Conditions

(a) DCC, HOBt, DCM, rt, 12h; (b) methanolic $MeNH_2$, rt, 3h; (c) EDC.HCl, HOBt, DCM, rt, 12h; (d) TFA, DCM, rt, 3h; (e) AcCl, Et_3N, DCM, rt, 12h; (f) Ethyl chloroformate, Et_3N, DCM, rt, 12h; (g) Trifluoroacetic anhydride, Et_3N, DCM, rt, 12h; EDC.HCl, HOBt, DCM, rt-12h; (h) Isobutyl chloroformate, Et_3N, DCM, rt, 12h; (i) EDC.HCl, DMAP, DCM, rt, 12h; (j) HBTU, DIPEA, MeCN, rt, 12h; (k) (i) $LiOH.H_2O$, MeOH, H_2O, rt, 12h, (ii) DCC, DMAP, Borneol, rt, 12h; (l) (i) Na_2CO_3, BzCl, THF, rt, 12h, (ii) DBU, DMF, 4A mol. sieves, rt, 3h.

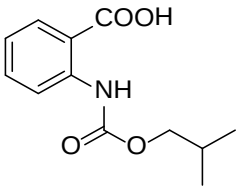
Experimental Procedures

2-(Tert-butoxycarbonylamino)benzoic acid, 14a:[1]



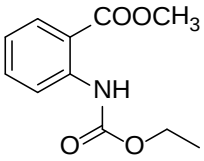
To a solution of anthranilic acid (1g, 6.6mmoles) in dioxane (15mL) and water (7.5mL), NaOH (0.528, 13.2 mmoles) was added followed by the addition of ^{t}Boc-anhydride (1.7g, 7.9mmoles). The reaction mixture was stirred at room temperature for 3 hours. The solvents were evaporated under reduced pressure. The residue was acidified with saturated potassium bisulphate solution, followed by extraction with DCM (10mL X 3). Evaporation under reduced pressure afforded the crude product **14a**, which was used for further reactions, without purification.

2-((Isobutoxycarbonyl)amino)benzoic acid, 14c:[2]



To a solution of anthranilic acid (1g, 6.6mmoles) in dioxane (15mL) and water (7.5mL), NaOH (0.528, 13.2 mmoles) was added followed by the addition of isobutyl chloroformate (1.7g, 7.9mmoles). The reaction mixture was stirred at room temperature for 3 hours, after which the solvents were evaporated under reduced pressure. The residue was acidified with saturated potassium bisulphate solution, followed by extraction with DCM (10mL X 3). Evaporation under reduced pressure afforded the crude product **14c**, which was used for further reactions, without purification.

Methyl 2-((ethoxycarbonyl)amino)benzoate, 16:



To a solution of anthranilic methyl ester (0.5g, 3.3mmoles) in dry DCM (10mL) containing DIPEA (1.25g, 1.7mL, 9.92 mmoles) was added ethyl chloroformate (0.43g, 3.92 mmoles), drop wise with vigorous stirring. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with DCM and the organic layer was washed sequentially with saturated sodium bicarbonate, potassium bisulphate and water. The organic layer was dried over anhydrous Na_2SO_4 solution and evaporated under reduced pressure to furnish the crude product which was purified by column chromatography, (85:15 pet. ether/ethyl acetate, R_f: 0.5) affording **16** as a white solid (0.63g**,** 93%), mp: 60-61^{o}C; IR ($CHCl_3$, ν (cm^{-1}): 3310, 3021, 2401, 1731, 1694,

1591, 1529, 1453, 1315, 1245, 1216; ^{1}H NMR ($CDCl_3$/200MHz): δ ppm 10.47 (s, 1H), 8.42-8.46 (d, *J*=8.23Hz, 1H), 7.97-8.01 (dd, *J*=7.98Hz, *J*=1.63Hz 1H), 7.47-7.56 (m, 1H), 6.96-7.05 (m, 1H), 4.17-4.27 (q, 2H), 3.90 (s, 3H), 1.28-1.35 (t, 1H, *J*=7.07), ^{13}C NMR ($CDCl_3$,125MHz): δ ppm 168.4, 153.6, 141.8, 134.5, 130.8, 121.3, 118.7, 114.3, 61.1, 52.1, 14.4; LC-MS: 247.06 $(M+23)^+$; Elemental Analysis calculated for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27; Found: 58.65; H, 5.16; N, 5.94.

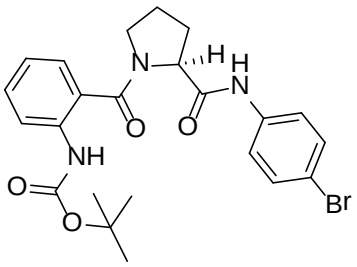
Representative procedure for ester hydrolysis:

2-((Ethoxycarbonyl)amino)benzoic acid, 14d

To a solution of **16** (0.5g) in methanol (5mL), LiOH (0.18, 0.008mmol) in water (5mL) was added. After stirring for 12h, the reaction mixture was stripped of the solvent under reduced pressure, acidified using saturated $KHSO_4$ solution and then extracted with ethyl acetate (3x5mL). The organic layer was evaporated under reduced pressure to obtain the free acid **14d** which was used for next reaction, without further purification.

Representative procedure for peptide coupling (for specific coupling agents, see scheme-1):

(S)-tert-butyl 2-(2-(4-bromophenylcarbamoyl)pyrrolidine-1-carbonyl)phenylcarbamate, 13a:

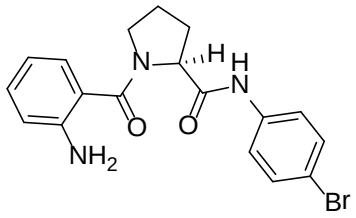


To a solution of **15a** (0.25g, 0.9949mmole) in dry DCM (5mL), Boc-Ant-OH (0.5g, 1.8903mmoles), EDC.HCl (0.286g, 1.4924) and HOBt (0.062g, 25wt %) were added. After stirring at room temperature for 12 hours, the reaction mixture was diluted with DCM and washed sequentially with saturated sodium bicarbonate, potassium bisulphate solution and water. The washings were extracted with DCM (10mLx2) and dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude residue thus obtained was purified by column chromatography, (50:50 pet ether/ethyl acetate, R_f: 0.5) furnishing **13a** as a white solid (0.4181g, 87%), mp: 97-101^{o}C; $[\alpha]^{28}_{D}$: -28.89° (*c* = 1.066, $CHCl_3$); IR ($CHCl_3$, ν (cm^{-1}): 3279, 3018, 2359, 1730, 1681, 1614, 1537, 1429, 1367, 1300, 1247, 1159, 1074; ^{1}H NMR ($CDCl_3$/500MHz): δ ppm 9.59 (s, 1H), 8.46(s, 1H), 8.26-8.28 (d, *J*=8.26Hz, 1H), 7.43 (t, *J*=7.43Hz, 1H), 7.36-7.37 (d, *J*=7.43Hz, 1H), 7.25-7.26 (d, *J*=8.8Hz,2H), 7.15-7.16 (d, 2H, *J*=8.8Hz), 7.07 (t,

1H, *J*=7.43Hz), 5.01-5.04 (m, 1H), 3.60-3.65 (m, 1H), 3.49-3.53(m, 1H), 2.23-2.37 (m, 2H) 2.03-2.11 (m, 1H) 1.85-1.93 (m, 1H) 1.55(s, 9H); ^{13}C NMR ($CDCl_3$,125MHz): δ ppm 169.7, 153.1, 137.2, 136.7, 131.3, 131.1, 126.8, 123.9, 122.0, 120.8, 120.1, 116.1, 80.6, 60.7, 50.5, 28.9, 25.1; ESI-MS: 490.3465 $(M+2H)^+$; 510.3085 $(M+Na)^+$; 428.2927 $(M+K)^+$; Elemental Analysis calculated for $C_{23}H_{26}BrN_3O_4$: C, 56.56; H, 5.37; N, 8.60; Found: C, 56.18; H, 5.87; N, 8.10.

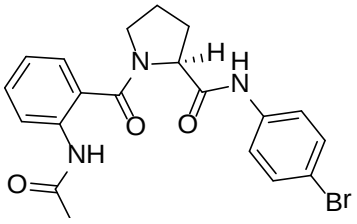
Representative procedure for ^{t}Boc deprotection using TFA/DCM.

(S)-1-(2-aminobenzoyl)-N-(4-bromophenyl)pyrrolidine-2-carboxamide, 13b:



To a solution of **13a** (0.1, 0.2577mmol) in DCM (1mL) maintained at 0^{o}C, trifluoroaceticacid (1 mL) was added drop wise. The reaction mixture was stirred at 0^{o}C for 10 minutes and then at RT for 3 h. The residue obtained after evaporating the volatiles was neutralized using saturated solution of sodium bicarbonate and extracted repeatedly using DCM (3x5mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the amine **13b** which was used for next reaction, without further purification.

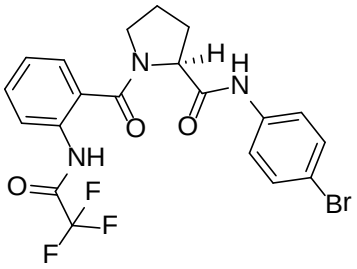
(S)-1-(2-acetamidobenzoyl)-N-(4-bromophenyl)pyrrolidine-2-carboxamide, 1:



To a solution of **13b** (0.1 gm, 0.2583mmol) in DCM (5 mL), Et_3N (0.11mL, 0.77507mmol) and acetyl chloride (0.03mL, 0.3875mmol) were added. After stirring for 12 hours, the reaction mixture was diluted with DCM (5 mL) and the organic layer was washed with saturated sodium bicarbonate (5mL), potassium bisulphate (5mL) and water (5mL). The organic layer was dried over anhydrous Na_2SO_4 solution and evaporated under reduced pressure to get the crude product which was purified by column chromatography, (20:80 pet. ether/ethyl acetate, R_f: 0.5) affording **1** as a white solid (0.98g, 88%), crystallized from a solution of methanol and dichloromethane, mp: 226-229^{o}C; $[\alpha]^{24}_D$: -90° (*c* = 0.4, $CHCl_3$); IR ($CHCl_3$) ν (cm-1) 3261, 3020, 2401, 2360, 2343, 1716, 1697, 1683, 1653, 1647, 1635, 1620; ^{1}H NMR($CDCl_3$/200MHz): δ ppm 9.47 (s, 1H), 9.29 (s, 1H), 8.35-8.39 (d,

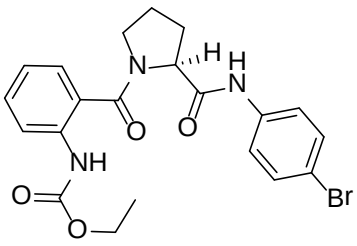
1H, *J*=8.06Hz), 7.38-7.47 (dd, 1H, *J*=15.62 Hz, *J*=1.59 Hz), 7.11-7.32 (m, 6H), 4.95-5.01 (m, 1H), 3.39-3.63 (m, 2H), 2.24 (s, 3H), 1.87-2.46 (m, 4H), ^{13}C NMR (DMSO-d_6,100MHz): δ ppm 171.3, 168.9, 167.5, 138.4, 135.0, 131.9, 129.9, 128.5, 126.8, 123.9, 121.9, 121.5, 115.4, 60.4, 49.3, 30.2, 24.9, 24.1; LC-MS: 454.05 $(M+Na)^+$; Elemental Analysis calculated for $C_{20}H_{20}BrN_3O_3$: C, 55.83; H, 4.68; N, 9.77; Found: C, 57.36; H, 5.14; N, 8.96.

(S)-1-(2-Trifluroacetamidobenzoyl)-N-(4-bromophenyl)pyrrolidine-2-carboxamide, 4:



Compound **4**, obtained by following the procedure used for preparation of **1** (*vide supra*), except using trifluoro acetic anhydride as the acylating agent, was purified by column chromatography (20:80 pet. ether/ethyl acetate, R_f: 0.5), white solid (0.112g, 90%), crystallized from methanol, mp: 210-217^{o}C; $[\alpha]^{27}_D$: -199° (*c* = 0.1, $CHCl_3$); IR ($CHCl_3$) ν (cm-1) 3310, 3020, 2400, 1733, 1698, 1621, 1531, 1422, 1215; ^{1}H NMR($CDCl_3$/200MHz): δ ppm 10.63 (s, 1H), 9.04 (s, 1H), 8.33-8.38 (d, 1H, *J*=8.03Hz), 7.52-7.60 (m, 2H), 7.26-7.42 (m, 6H), 4.90-4.97 (m, 1H), 3.61-3.80 (m, 2H), 1.87-2.55 (m, 4H), ^{13}C NMR (50 MHz, $CDCl_3$) δ : ppm 169.6, 168.7, 136.8, 134.5, 131.9, 131.7, 128.1, 125.0, 124.4, 122.3, 121.2, 116.8, 61.0, 51.2, 27.8, 25.4; ESI-MS: 508.6183 $(M+Na)^+$; 524.6121 $(M+K)^+$. Elemental Analysis calculated for $C_{20}H_{17}BrF_3N_3O_3$: C, 49.60; H, 3.54; N, 8.68; Found: C, 47.37; H, 6.46; N, 8.16.

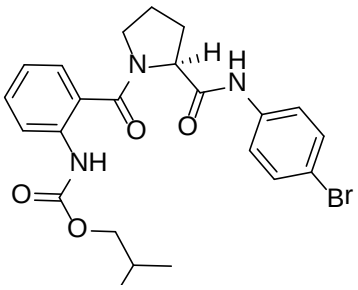
(S)-ethyl 2-(2-(4-bromophenylcarbamoyl)pyrrolidine-1-carbonyl)phenylcarbamate, 3:



Compound **3**, obtained by following the procedure used for preparation of **1** (*vide supra*), except using ethyl chloroformate as the acylating agent, was purified by column chromatography (30:70 pet. ether/ethyl acetate, R_f: 0.5), white solid (0.076g, 64%), crystallized from a solution of methanol and dichloromethane, mp: 201-203^{o}C; $[\alpha]^{26}_D$: -141° (*c* = 0.1, $CHCl_3$); IR ($CHCl_3$, ν (cm^{-1}): 3421, 3020, 2400, 1733, 1687, 1616, 1541, 1427, 1398, 1302, 1215; ^{1}H NMR ($CDCl_3$/400MHz): δ ppm 9.58 (s,

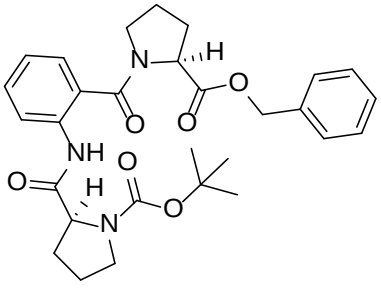
1H), 8.66(s, 1H), 8.25-8.27 (d, *J*=8.18Hz, 1H), 7.43-1.47 (t, *J*=7.77Hz, 1H), 7.38-7.39 (d, *J*=7.40Hz, 1H), 7.25-7.27 (d, *J*=8.7Hz,2H), 7.15-7.18 (d, 2H, *J*=8.51Hz), 7.08-7.12 (t, 1H, *J*=7.40Hz), 5.00-5.03 (m, 1H), 4.22-4.27 (m, 2H), 3.60-3.70 (m, 1H), 3.50-3.56 (m, 1H), 2.23-2.39 (m, 2H), 2.04-2.14 (m, 1H) 1.84-1.94 (m, 1H), 1.32-1.35 (t, 3H, *J*=7.15); ^{13}C NMR ($CDCl_3$,125MHz): δ ppm 169.8, 153.9, 137.2, 136.5, 131.3, 131.2, 126.8, 123.9, 122.3, 120.8, 120.3, 116.2, 61.3, 60.9, 50.7, 28.9, 25.1, 14.4; LC-MS: 482.08 $(M+Na)^+$; Elemental Analysis calculated for $C_{21}H_{22}BrN_3O_4$: C, 54.79; H, 4.82; 9.13; Found: C, 58.16; H, 4.38; N, 8.92.

(S)-Isobutyl 2-(2-(4-bromophenylcarbamoyl)pyrrolidine-1-carbonyl)phenyl Carbamate, 5:



Compound **5**, obtained by following the procedure used for preparation of **1** (*vide supra*), except using isobutyl chloroformate as the acylating agent, was purified by column chromatography (30:70 pet. ether/ethyl acetate, R_f: 0.55), white solid (0.102g, 81%), mp: 200-203^{o}C; $[\alpha]^{27}_D$: -142° (*c* = 0.1, $CHCl_3$); IR ($CHCl_3$, ν (cm^{-1}): 3316, 3020, 2400, 1734, 1686, 1617, 1541, 1457, 1398, 1302, 1215; ^{1}H NMR ($CDCl_3$/200MHz): δ ppm 9.45 (s, 1H), 8.61 (s, 1H), 8.19-8.23 (d, *J*=8.27Hz, 1H), 6.99-7.41 (m, 7H), 4.91-4.97 (m, 1H), 3.89-3.92 (d, 1H, *J*=6.54), 3.36-3.61 (m, 2H), 1.75-2.25 (m, 5H), 0.91-0.94 (d, 6H, *J*=6.54; ^{13}C NMR ($CDCl_3$,125MHz): δ ppm 169.7, 153.1, 137.2, 136.7, 131.3, 131.1, 126.8, 123.9, 122.0, 120.8, 120.1, 116.1, 80.6, 60.7, 50.5, 28.9, 25.1; ESI-MS: 488.4006 $(M+H)^+$; 510.2612; $(M+Na)^+$; Elemental Analysis calculated for $C_{23}H_{26}BrN_3O_4$: C, 56.56; H, 5.37; Br, 16.36; N, 8.60; Found: C, 56.19; H, 5.85; N, 8.98.

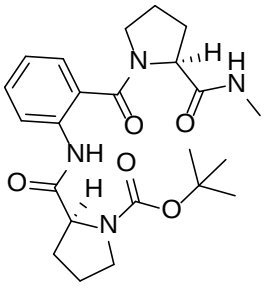
(S)-Tert-butyl 2-(2-((S)-2-(benzyloxycarbonyl)pyrrolidine-1-carbonyl)phenyl carbamoyl)pyrrolidine-1-carboxylate, 12



Compound **12**, obtained by following the coupling procedure used for the preparation of **13a** (*vide supra*), was purified by column chromatography (50% ethyl acetate/pet. ether, R_f: 0.4), waxy liquid (1.34 g, 86%); $[\alpha]^{26}_D$: -74.6° (*c* 0.34, $CHCl_3$); IR (ν) neat (cm^-

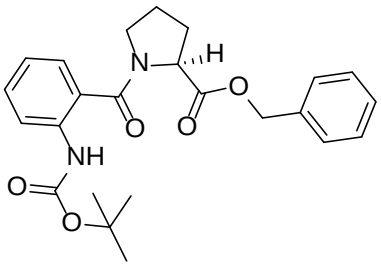
[1]) 3307, 3066, 2978, 1743, 1692, 1627, 1596, 1525, 1404, 1215, 1165, 1121, 1088, 1031; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.76$_{rotamer}$ (0.55H), 9.67$_{rotamer}$ (0.45H), 8.50-8.35 (m, 1H), 7.5-7.0 (m, 8H), 5.28-5.19 (m,1H), 4.78-4.75 (m, 1H), 4.43$_{rotamer}$ (0.55H), 4.26 $_{rotamer}$ (0.45H), 3.80-3.42 (m, 4H), 2.38-1.8 (m, 8H), 1.48$_{rotamer}$ (4.3H), 1.40$_{rotamer}$ (4.7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.6, 171.3, 168.1, 154.7, 153.7, 136.6, 135.97, 135.3, 130.9, 130.5, 128.2, 127.98, 127.7, 127.1, 126.9, 124.4, 123.3, 122.9, 122.5, 122.8, 122.5, 121.3, 120.6, 79.5, 66.7, 66.6, 61.9, 61.1, 58.7, 49.8, 49.6, 46.8, 46.4, 31.0, 29.9, 28.8, 28.1, 27.9, 24.8, 24.0, 23.5; ESI MS: 522.5042 $(M+H)^+$, 544.5149 $(M+Na)^+$, 560.5602 $(M+K)^+$; Elemental analyses calculated for $C_{29}H_{35}N_3O_6$: C, 66.78; H, 6.76; N, 8.06; Found: C, 67.01; H, 6.93; N, 7.69.

(S)-tert-butyl 2-(2-((S)-2-(methylcarbamoyl)pyrrolidine-1-carbonyl) phenyl carbamoyl)pyrrolidine-1-carboxylate, 2:



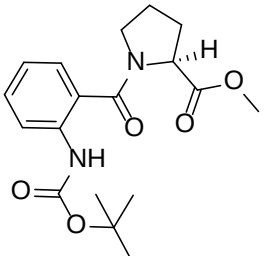
The ester **12** (0.45 g, 0.86 mmol) was converted into its corresponding methyl amide **2** by stirring the compound in methanolic methyl amine at room temperature. After completion of the reaction (3 h), the solvent was stripped off and the product was taken in dichloromethane, washed with water and the organic layer was dried over anhydrous sodium sulfate. Evaporation under reduced pressure and purification by column chromatography afforded **12** (5% methanol /ethyl acetate, R_f: 0.5), 0.36 g, 95%, ; mp: 185-187 ^{o}C; $[\alpha]^{26}_D$: -120° (*c* 0.2, $CHCl_3$); IR (ν) nujol (cm^{-1}): 3273, 2726, 1698, 1655, 1618, 1586, 1460, 1377, 1307, 1215, 1156; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.01$_{rotamer}$ (0.5H), 9.71-9.56$_{rotamer}$ (0.5H), 8.44-8.13 (m, 1H), 7.41 (b, 2H), 7.13-7.09 (t, *J* = 7.41 Hz, 1H), 6.70 (bs, 1H), 4.7-4.63 (b, 1H), 4.42$_{rotamer}$ (0.4H), 4.29$_{rotamer}$ (0.6H), 3.8-3.4 (m, 4H), 4.85-4.84 (d, *J* = 4.72 Hz, 3H), 2.4-1.8 (m, 8H), 1.48$_{rotamer}$ (s, 4H), 1.38$_{rotamer}$ (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.2, 171.9, 171.8, 169.2, 168.9, 155, 154.2, 136.6, 136.0, 135.3, 131.1, 130.5, 130.3, 126.8, 123.9, 123.5, 123.3, 122.9, 122.5, 120.9, 80.1, 79.9, 62.0, 60.96, 60.1, 50.3, 49.7, 47.1, 46.7, 31.8, 31.3, 29.9, 28.9, 28.2, 26.2, 25.1, 24.3, 23.7, 22.8; ESI MS: 445.3834 $(M+H)^+$, 467.3785 $(M+Na)^+$, 483.36 $(M+K)^+$; Elemental analyses calculated for $C_{23}H_{32}N_4O_5$: C, 62.14; H, 7.26; N, 12.60; Found: C, 61.86; H, 7.14; N,12.98.

(S)-Benzyl 1-(2-(*tert*-butoxycarbonylamino)benzoyl)pyrrolidine-2-carboxylate, 7:



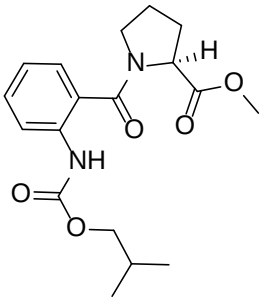
Preparation of this compound is reported.[1] **7** was crystallized from a mixture of ethylacetate and pet. ether.

(S)-Methyl 1-(2-(*tert*-butoxycarbonylamino)benzoyl)pyrrolidine-2-carboxylate, 6:



Compound **6**, obtained by following the coupling procedure used for the preparation of **13a** (*vide supra*), was purified by column chromatography (30:70 pet. ether/ethyl acetate, R_f: 0.5), 3.7 g, 71%, white solid, crystallized from a solution of methanol and dichloromethane; mp: 94-96 °C; $[\alpha]^{27}_D$: -91° (*c* = 0.1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}) 3368, 3020, 2982, 1724, 1625, 1596, 1522, 1454, 1414, 1216, 1159, 1052, 1026; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.33 (s,1H), 8.13-8.18 (d, *J* = 8.36 Hz, 1H), 7.32-7.39 (m, 2H), 6.95-7.03 (t, *J* = 7.22 Hz, 1H), 4.63-4.70 (m, 1H), 3.77 (s, 3H) 3.40-3.65 (m, 2H), 2.25-2.42 (m, 1H), 1.79-2.10 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ□: 172.4, 168.7, 152.9, 137.2, 130.9, 128.6, 127.1, 123.3, 121.5, 120.0, 80.2, 59.0, 52.3, 49.9, 29.2, 28.2, 25.2; LC-MS: 371.02 $(M+Na)^+$; Elemental analyses calculated for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04; Found: C, 61.99; H, 7.07; N, 8.58.

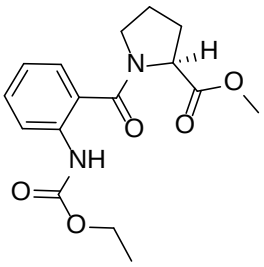
(S)-Methyl 1-(2-(*iso*-butoxycarbonylamino)benzoyl)pyrrolidine-2-carboxylate, 10:



Compound **10**, obtained by following the coupling procedure used for the preparation of **13a** (*vide supra*), was purified by column chromatography (35:65 pet. ether/ethyl acetate, R_f: 0.5), 0.32g, 63%, white solid, crystallized from a solution of diethyl ether and pet-ether; mp: 76-80 °C; $[\alpha]^{27}_D$: -92° (*c* = 0.1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}) 3366, 3020, 2959, 1733, 1625, 1597, 1524, 1456, 1415, 1216, 1113, 1058; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (s,1H), 8.17-8.21 (d, *J* = 8.28 Hz, 1H), 7.31-7.43 (m, 2H), 7.00-

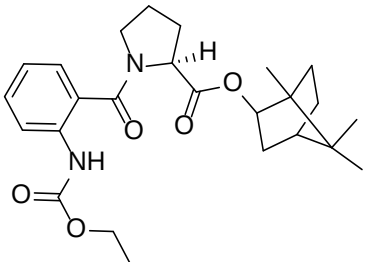
7.08 (m, 1H), 4.66-4.73 (m, 1H), 3.91-3.95 (m, 2H), 3.79 (s, 3H), 3.42-3.65 (m, 2H), 2.27-2.44 (m, 1H), 1.78-2.16 (m, 4H), 0.95-0.98 (d, J=6.61, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ□: 172.6, 168.7, 153.9, 136.9, 131.1, 127.1, 123.7, 121.9, 120.1, 71.2, 59.0, 52.4, 49.9, 29.3, 27.9, 25.2, 18.9; LC-MS: 371.11 $(M+Na)^+$; Elemental analyses calculated for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04; Found: C, 62.37; H, 6.67; N, 8.35.

(S)-Methyl 1-(2-(Ethyloxycarbonylamino)benzoyl)pyrrolidine-2-carboxylate, 8:



Compound **8**, obtained by following the coupling procedure used for the preparation of **13a** (*vide supra*), was purified by column chromatography (50:50 pet. ether/ethyl acetate, R_f: 0.5), 0.32g, 80%, white solid, crystallized from a solution of ethyl acetate and pet-ether; mp: 76-80 °C; $[\alpha]^{26}_D$: -103° (*c* = 0.1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}) 3378, 3020, 2400, 1732, 1626, 1597, 1525, 1416, 1215; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.49 (s,1H), 8.14-8.19 (d, *J* = 8.58 Hz, 1H), 7.33-7.41 (m, 2H), 6.98-7.05 (t, *J* = 7.20 Hz, 1H), 4.63-4.70 (m, 1H), 4.12-4.23 (m, 2H), 3.77 (s, 3H), 3.40-3.64 (m, 2H), 2.25-2.46 (m, 1H), 1.79-2.10 (m, 3H), 1.23-1.30 (t, *J*=7.18, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.4, 168.6, 153.7, 136.8, 131.0, 127.1, 123.4, 121.9, 120.0, 61.01, 59.0, 52.3, 49.9, 29.3, 25.2, 14.3; LC-MS: 343.06 $(M+Na)^+$; Elemental analyses calculated for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.24; N, 8.74; Found: C, 59.37; H, 5.67; N, 9.12.

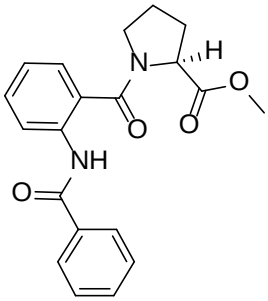
(2S)-((2R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl) 1-(2-(ethoxycarbonylamino) benzoyl)pyrrolidine-2-carboxylate, 9:



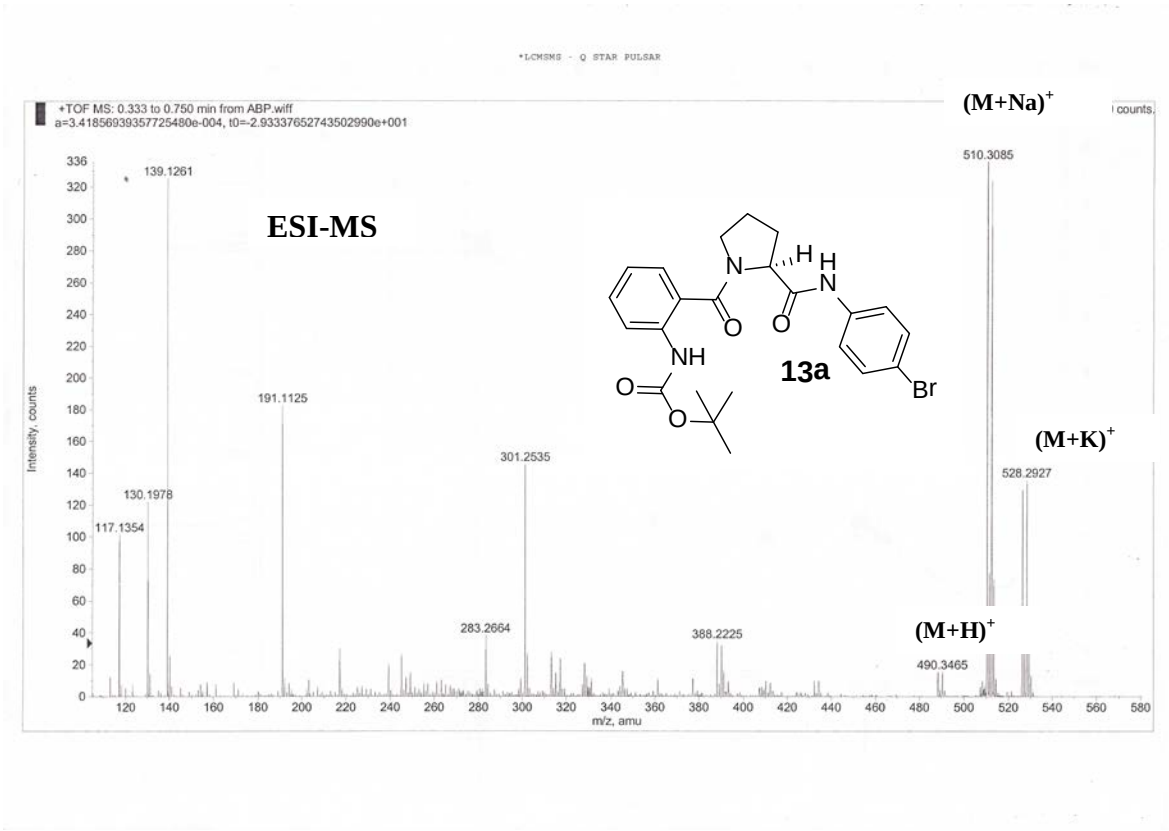
Compound **8** (0.2 g, 0.625 mmol) was first subjected to ester hydrolysis following the general procedure (*vide supra*). The free acid thus obtained was subjected to peptide coupling as mentioned in the representative procedure for **13a** (70:30 pet. ether/ethyl acetate, R_f: 0.5) to afford **9** (0.242g, 87%) as a white solid, crystallized from a solution of ethyl acetate and pet-ether; mp: 127-128 °C; $[\alpha]^{27}_D$: -93° (*c* = 0.1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}) 3448, 3020, 1726, 1626, 1597, 1524, 1455, 1418, 1216; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.70 (s,1H), 8.13-8.29 (m, 1H), 7.36-7.43 (m, 2H), 6.93-7.06 (m, 1H), 4.99-5.06 (m, 1H), 4.67-4.83 (m, 1H), 4.13-4.23 (m, 2H), 3.48-3.86

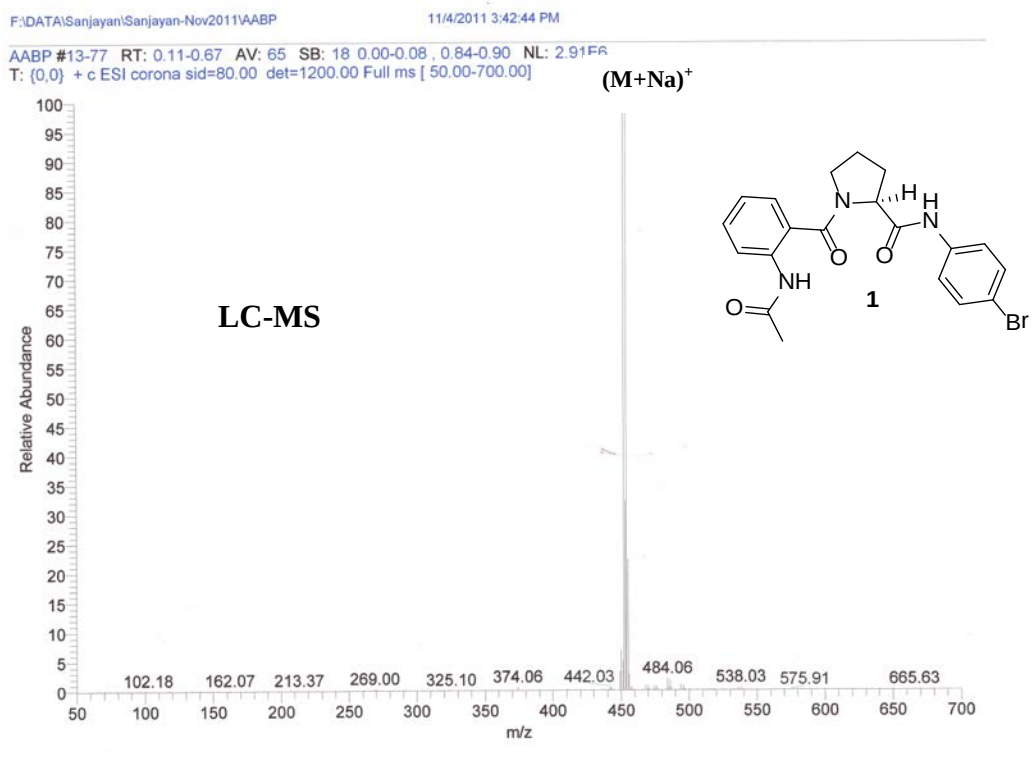
(m, 2H), 2.28-2.47 (m, 2H), 1.85-2.11 (m, 4H), 1.63-1.82 (m, 3H), 1.12-1.40 (m, 5H), 0.84-0.91 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.2, 168.5, 153.8, 137.3, 131.1, 127.2, 123.2, 121.7, 120.0, 80.7, 61.0, 59.5, 50.0, 49.0, 47.9, 44.8, 36.4, 29.3, 27.9, 27.1, 25.3, 19.6, 18.7, 14.4, 13.5; LC-MS: 465.23 $(M+Na)^+$, 481.21 $(M+K)^+$; Elemental analyses calculated for $C_{25}H_{34}N_2O_5$: 67.85; H, 7.74; N, 6.33; Found: 67.69; H, 7.52; N, 6.52.

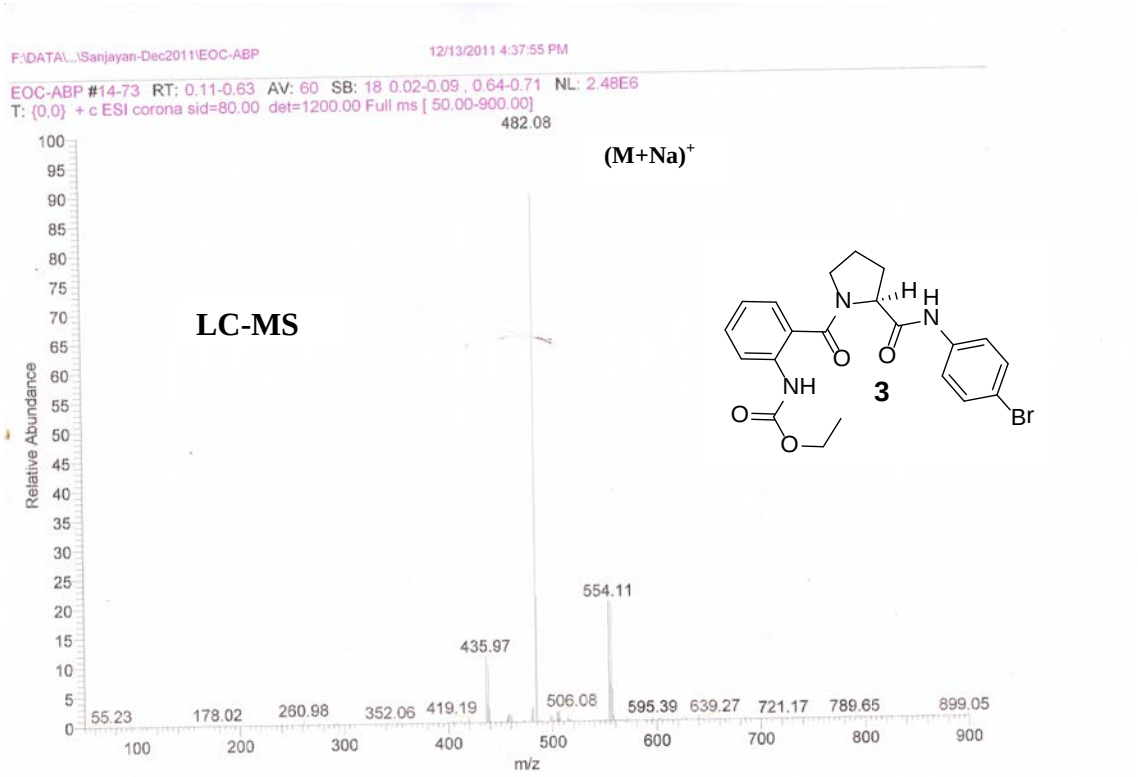
(S)-Methyl 1-(2-benzamidobenzoyl)pyrrolidine-2-carboxylate, 11:



To an ice cold solution of 2-phenyl benzoxazinone[3] (1 g, 4.48 mmol) and proline methyl ester (1 g, 5.83 mmol) in dry DMF (20 ml) containing 4Å molecular sieves, DBU (2.05g, 2ml, 13.44mmol) was added drop wise. The reaction mixture was allowed to stir at 0 °C for 10 minutes and then for 3 h at room temperature. The reaction mixture was diluted with DCM, and the organic layer was washed with water and dried using an.Na_2SO_4. The crude product obtained after the removal of solvent under reduced pressure was purified by column chromatography (50:50 pet. ether/ethyl acetate, R_f: 0.5) to afford **11** (1.08 g, 68%), white solid, crystallized from a solution of diethyl ether and pet-ether; mp: 116-120 °C; $[\alpha]^{25}_D$: -50° (*c* = 0.1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}) 3337, 3015, 2445, 1743, 1668, 1594, 1520, 1416, 1216; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.32 (s,1H), 8.53-8.57 (d, *J* = 8.49 Hz, 1H), 7.90-7.95 (m, 2H), 7.34-7.53 (m, 5H), 7.06-7.13 (m, 1H), 4.61-4.67 (m, 1H), 3.51-3.73 (m, 2H), 3.66 (s, 3H), 2.20-2.38 (m, 1H), 1.73-2.06 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ : 172.2, 168.9, 165.2, 162.4, 137.2, 134.3, 131.7, 131.2, 128.4, 127.4, 127.2, 123.6, 122.6, 121.7, 59.1, 52.1, 50.3, 36.3, 31.2, 29.0, 25.0; LC-MS: 375.05 $(M+Na)^+$; Elemental analyses calculated for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95; Found: C, C, 68.43; H, 5.43; N, 7.68.



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12/13/2011 4:37:55 PM
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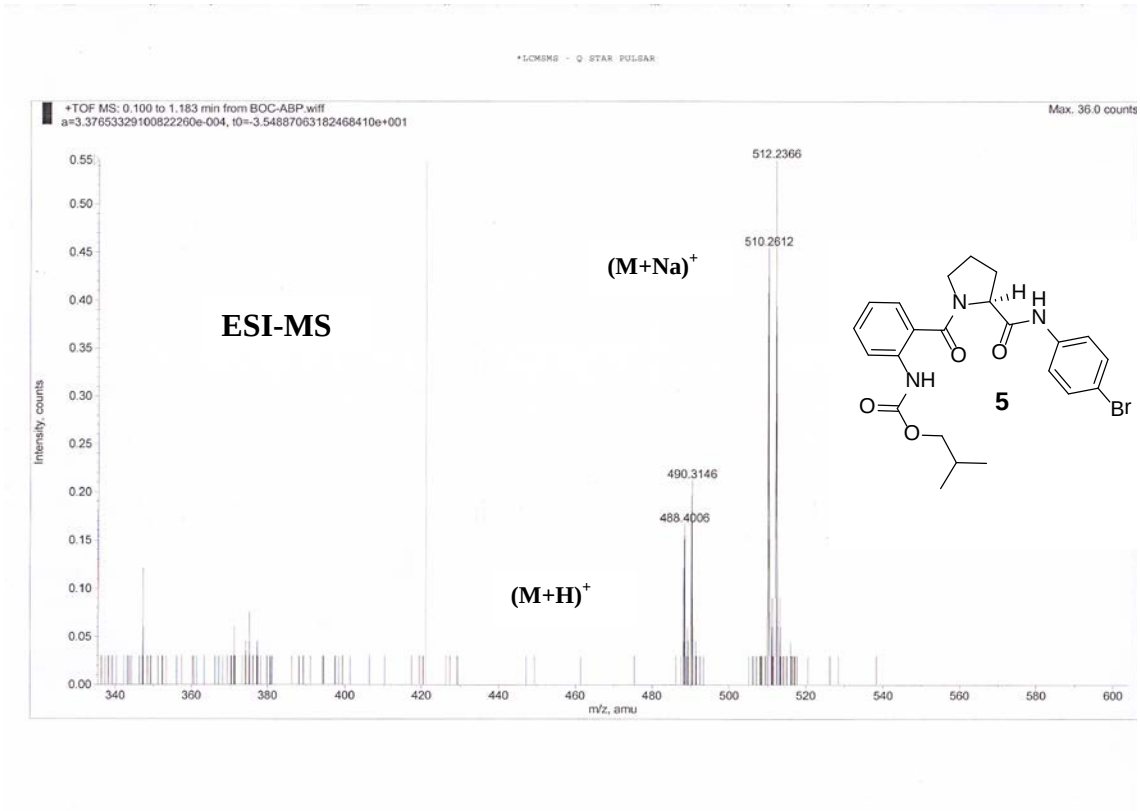
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [50.00-900.00]
LC-MS
(M+Na)+
482.08
554.11
435.97
506.08
595.39
639.27
721.17
789.65
899.05
55.23
178.02
260.98
352.06
419.19
Relative Abundance
m/z
3
NH
Br


*LCMSMS - Q STAR PULSAR
+TOF MS: 0.100 to 1.183 min from BOC-ABP.wiff
Max. 36.0 counts
ESI-MS
(M+Na)+
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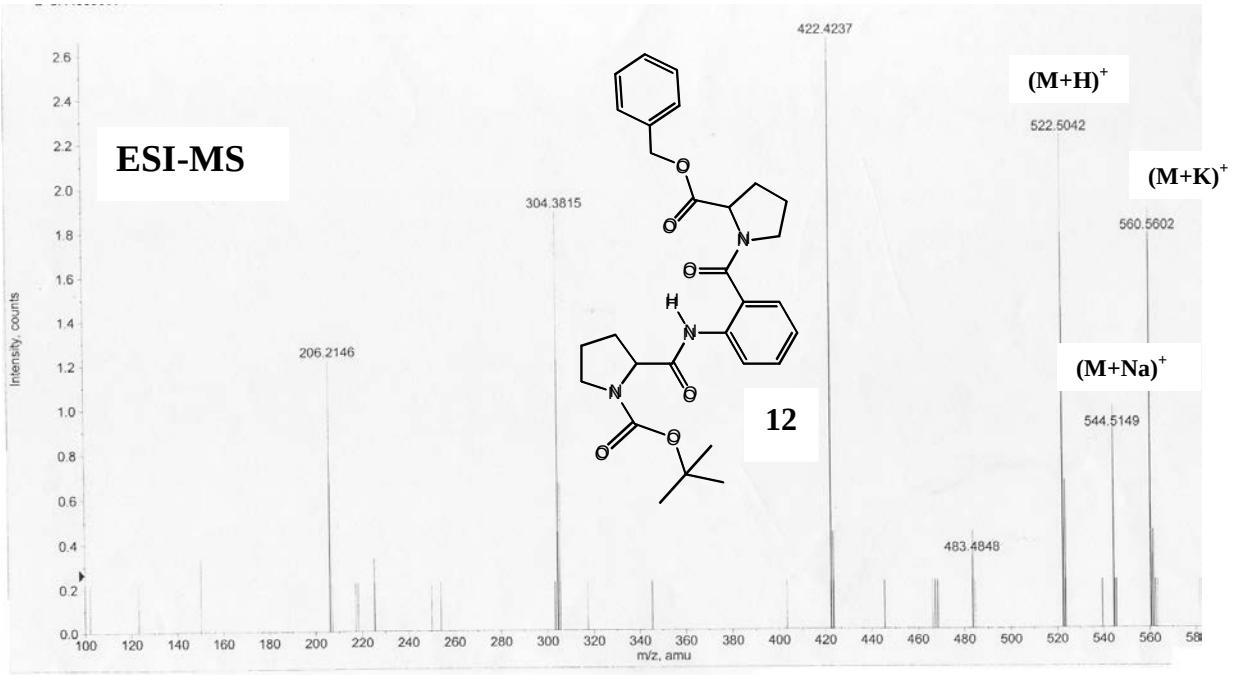
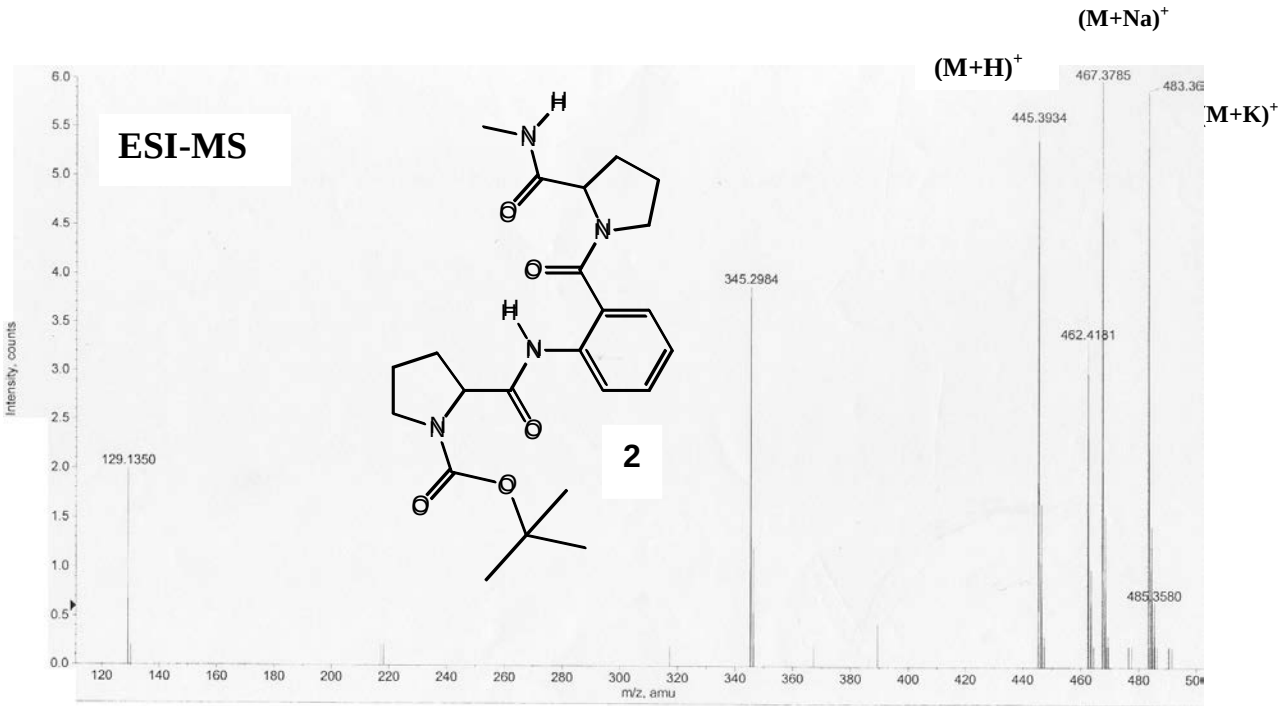
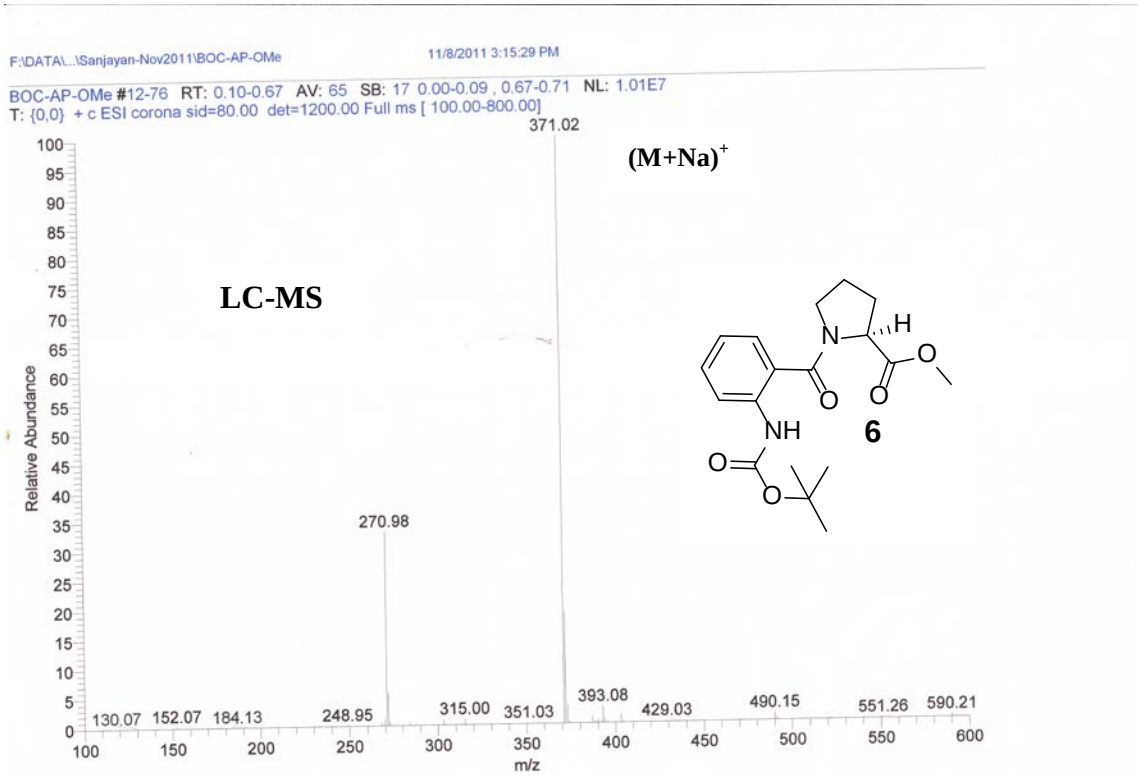
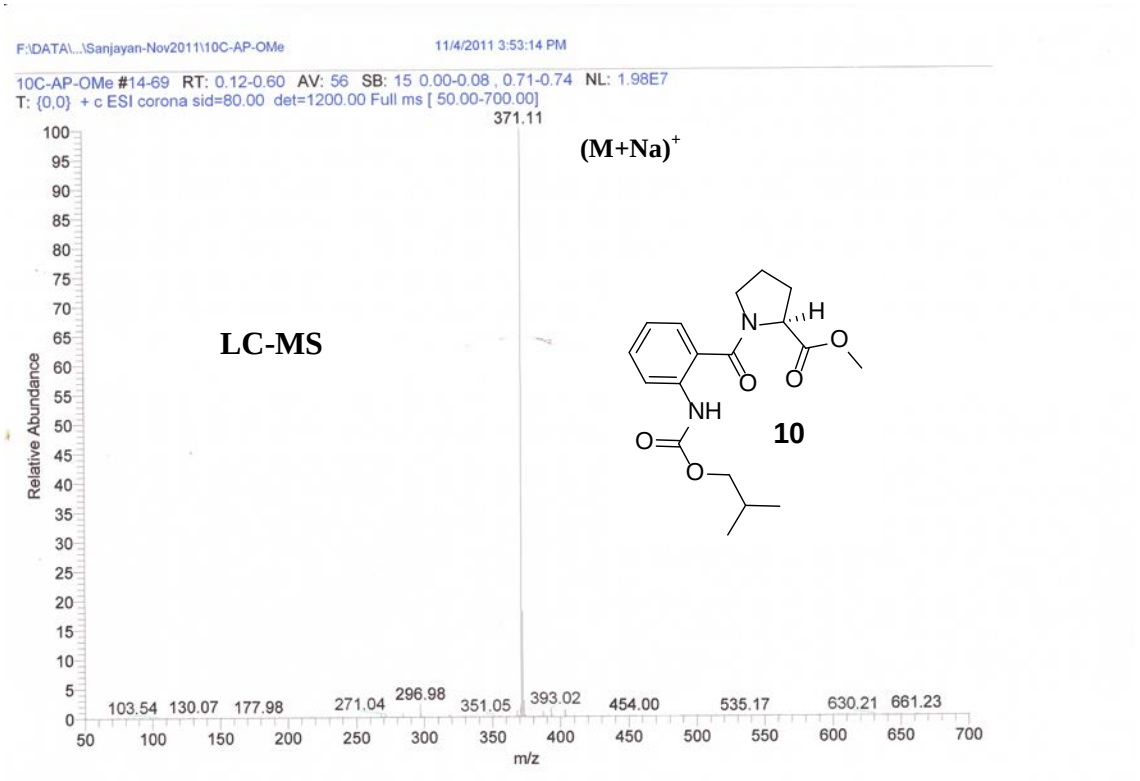
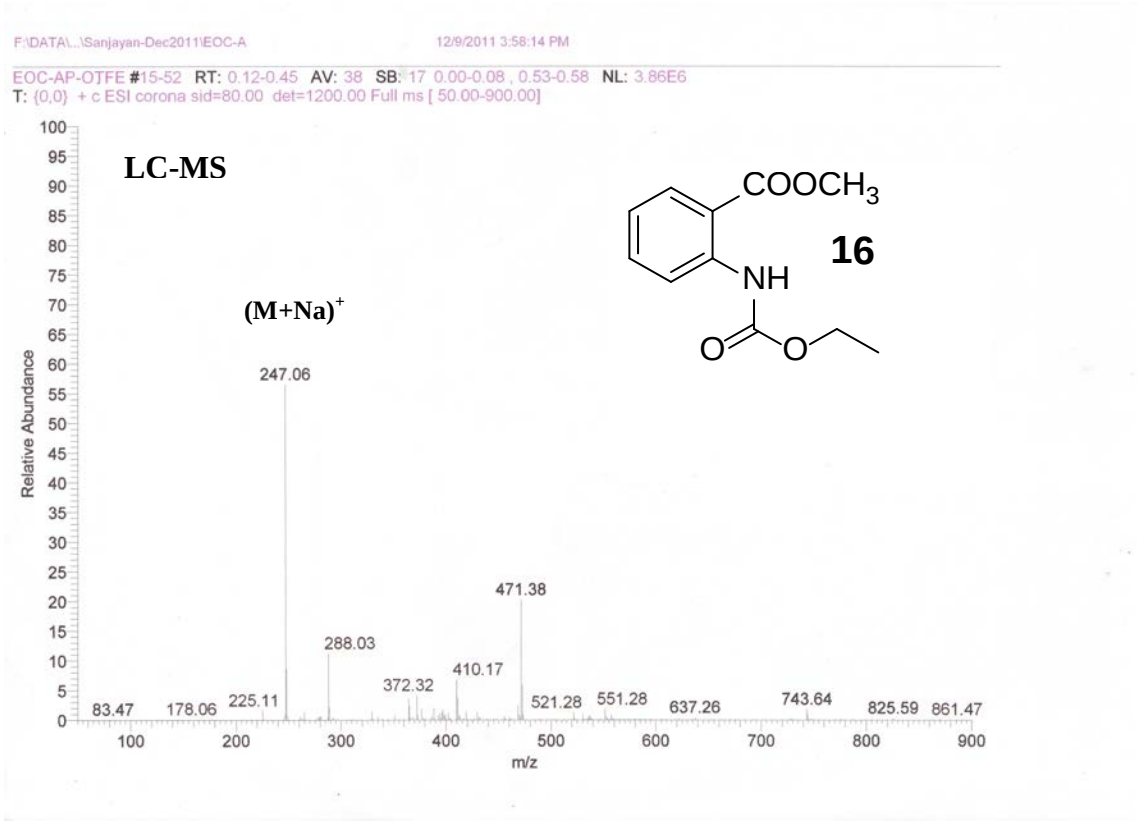
510.2612
490.3146
488.4006
(M+H)+
Intensity, counts
m/z, amu
5
NH
Br







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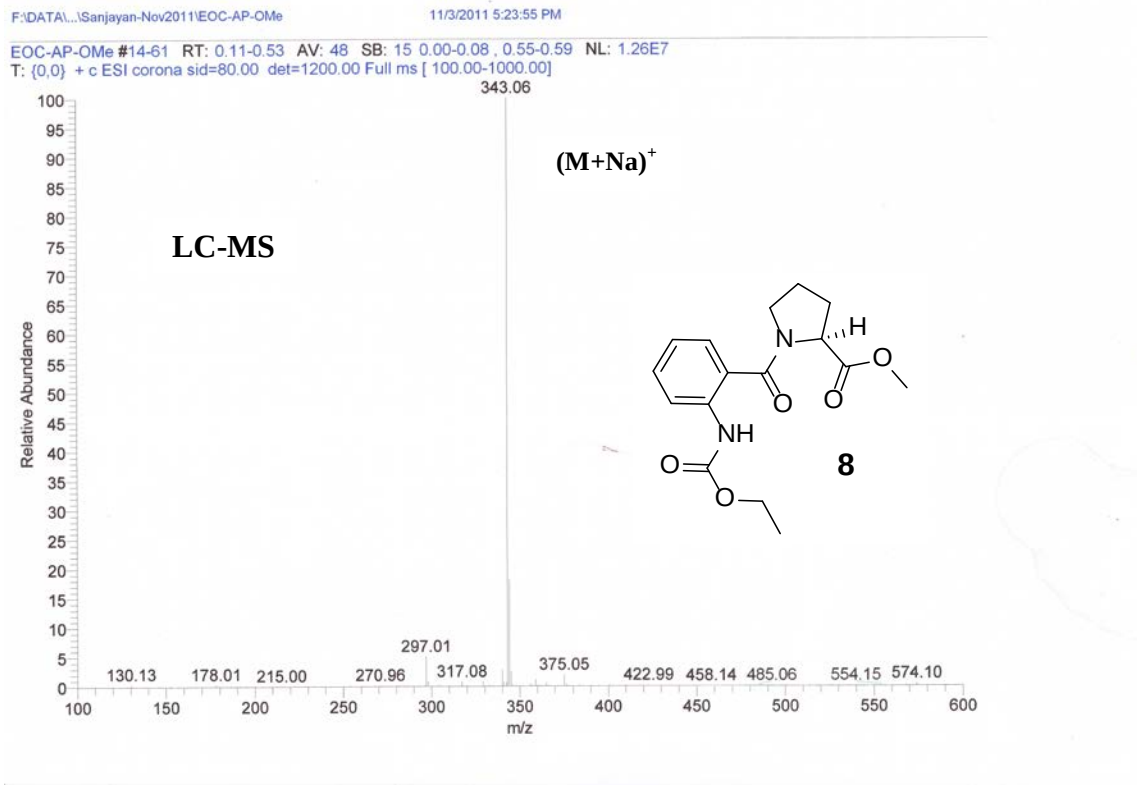
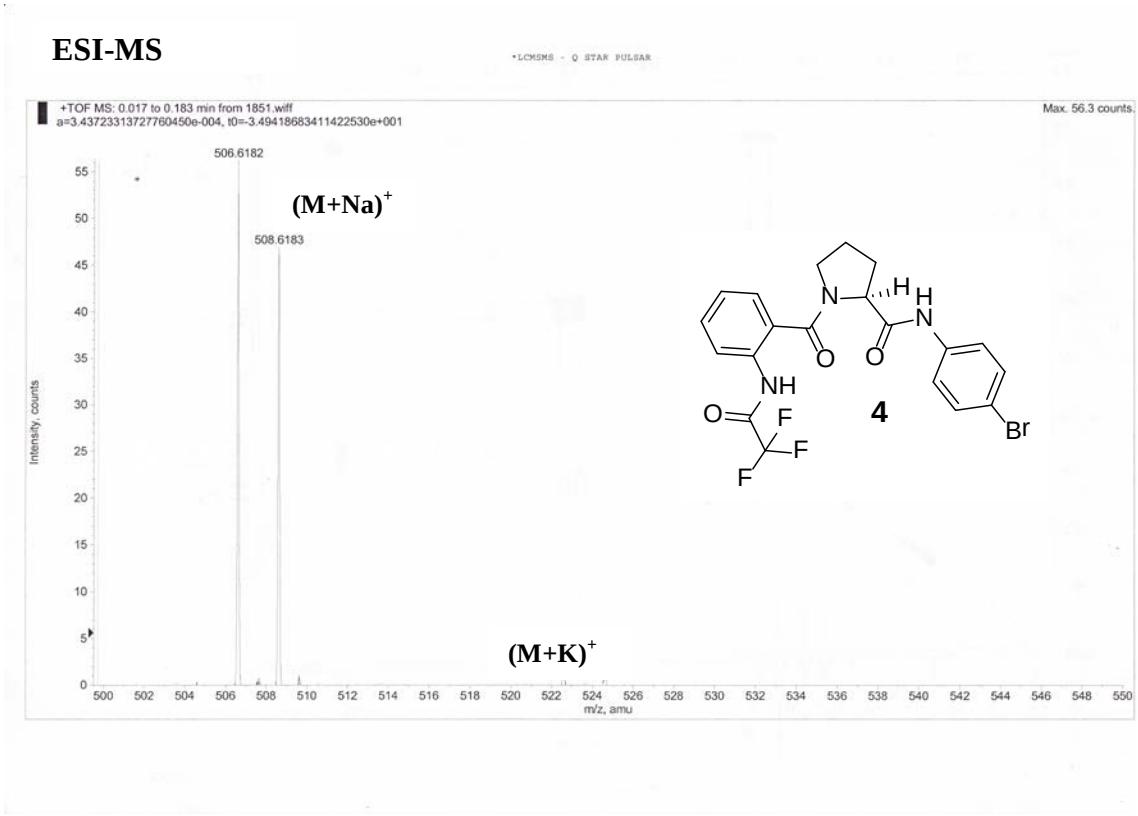
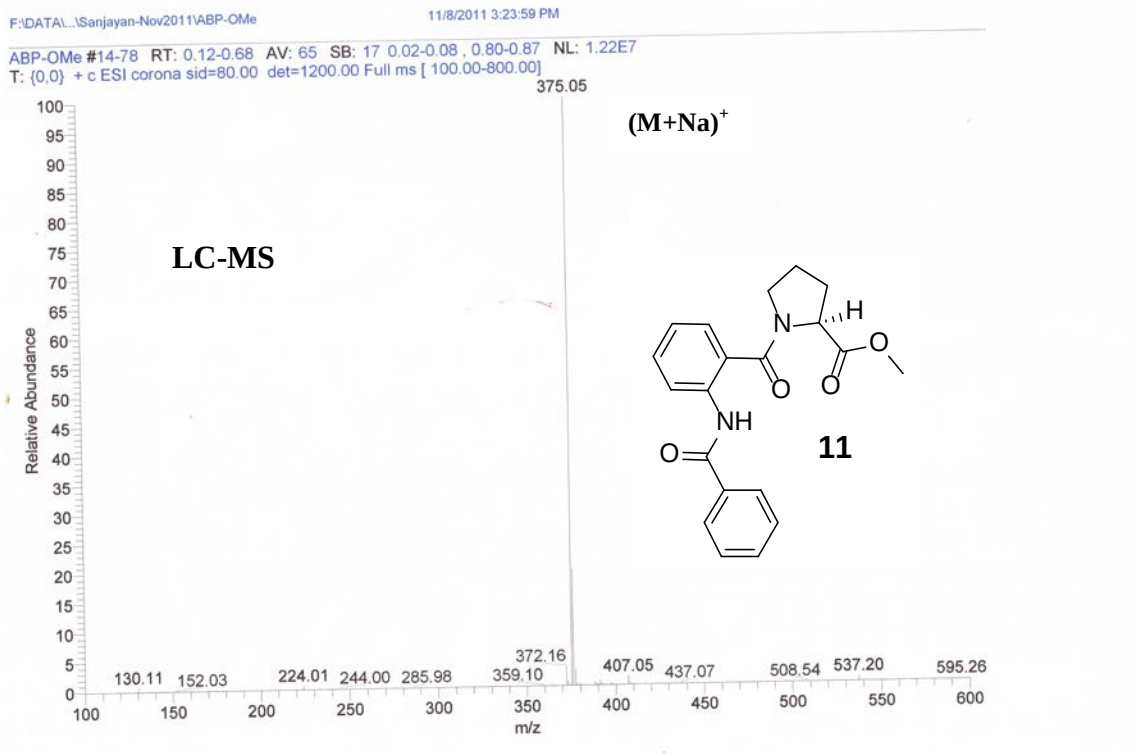
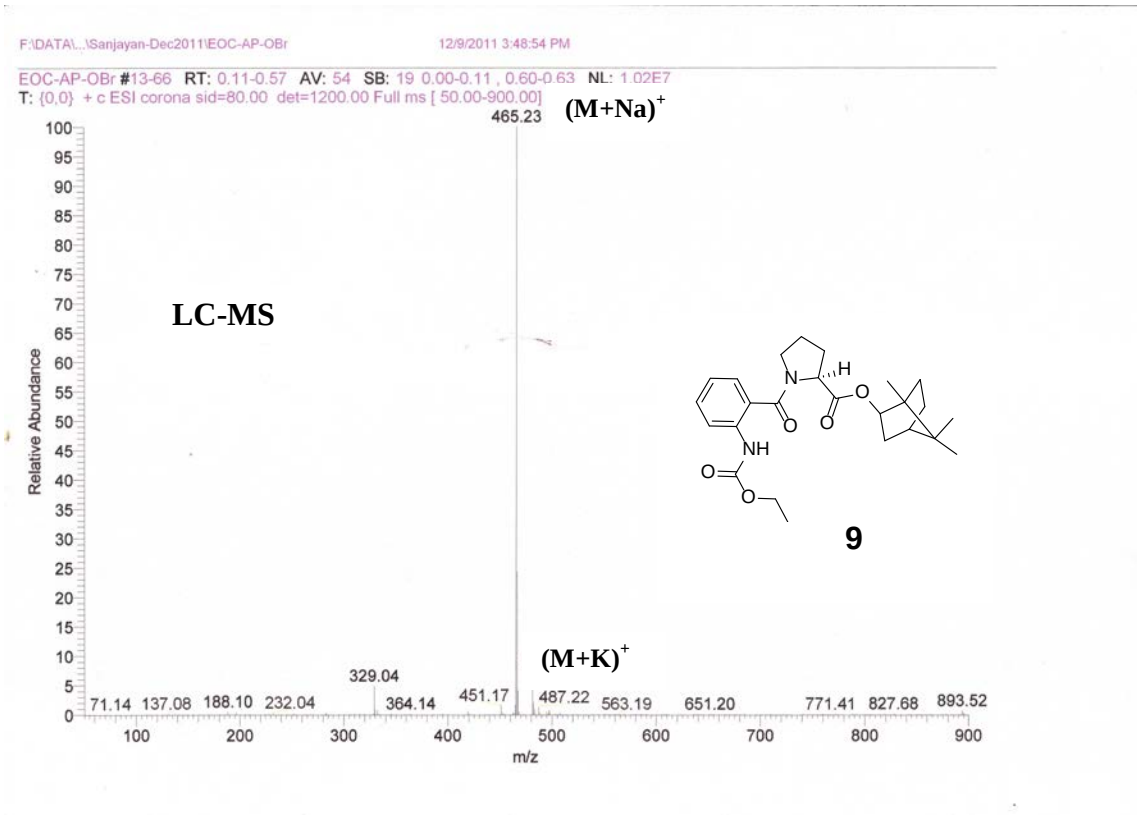
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [50.00-900.00]
LC-MS
(M+Na)+
COOCH3
NH
O
O
16
247.06
471.38
288.03
410.17
372.32
83.47
178.06
225.11
521.28
551.28
637.26
743.64
825.59
861.47
Relative Abundance
m/z

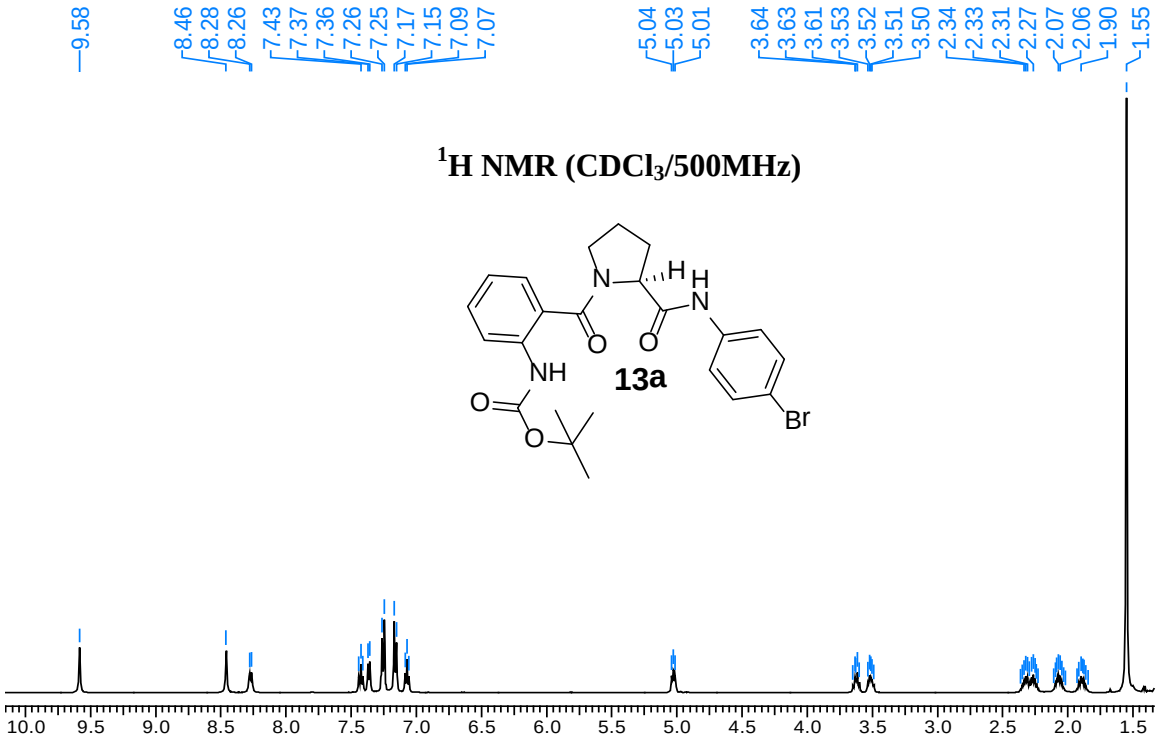

F:\DATA\...\Sanjayan-Nov2011\EOC-AP-OMe 11/3/2011 5:23:55 PM
EOC-AP-OMe #14-61 RT: 0.11-0.53 AV: 48 SB: 15 0.00-0.08 , 0.55-0.59 NL: 1.26E7
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-1000.00]
343.06
(M+Na)+
LC-MS
N
H
O
O
O
NH
O
O
8
297.01
130.13
178.01
215.00
270.96
317.08
375.05
422.99
458.14
485.06
554.15
574.10
Relative Abundance
m/z

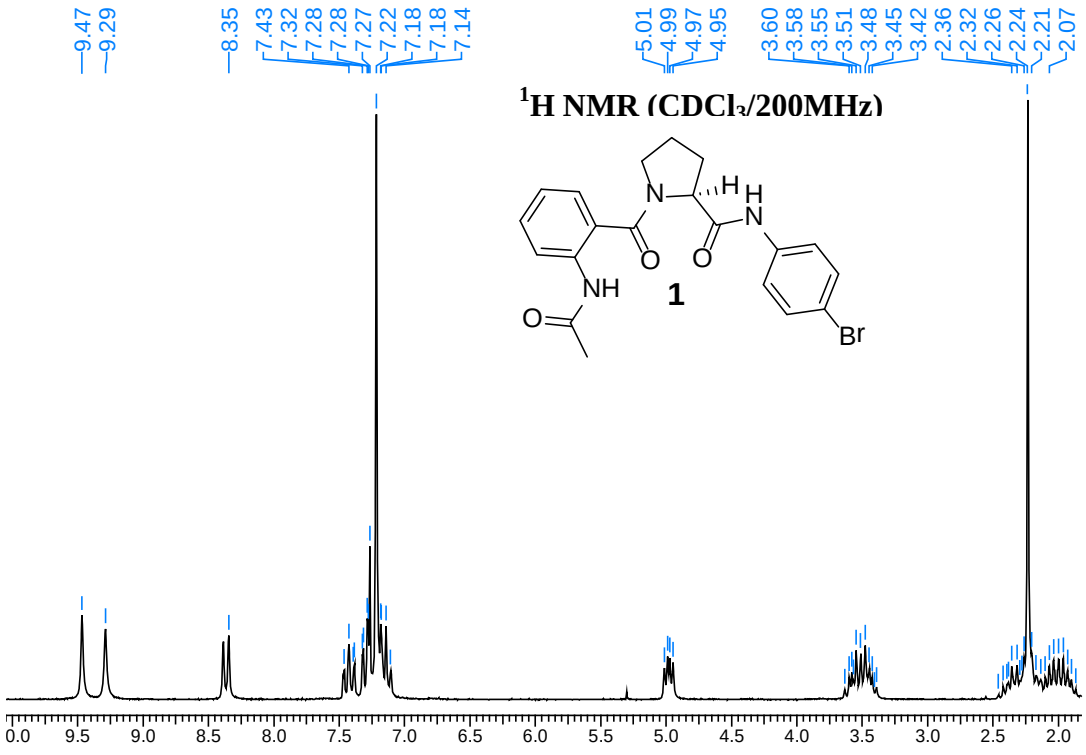
ESI-MS

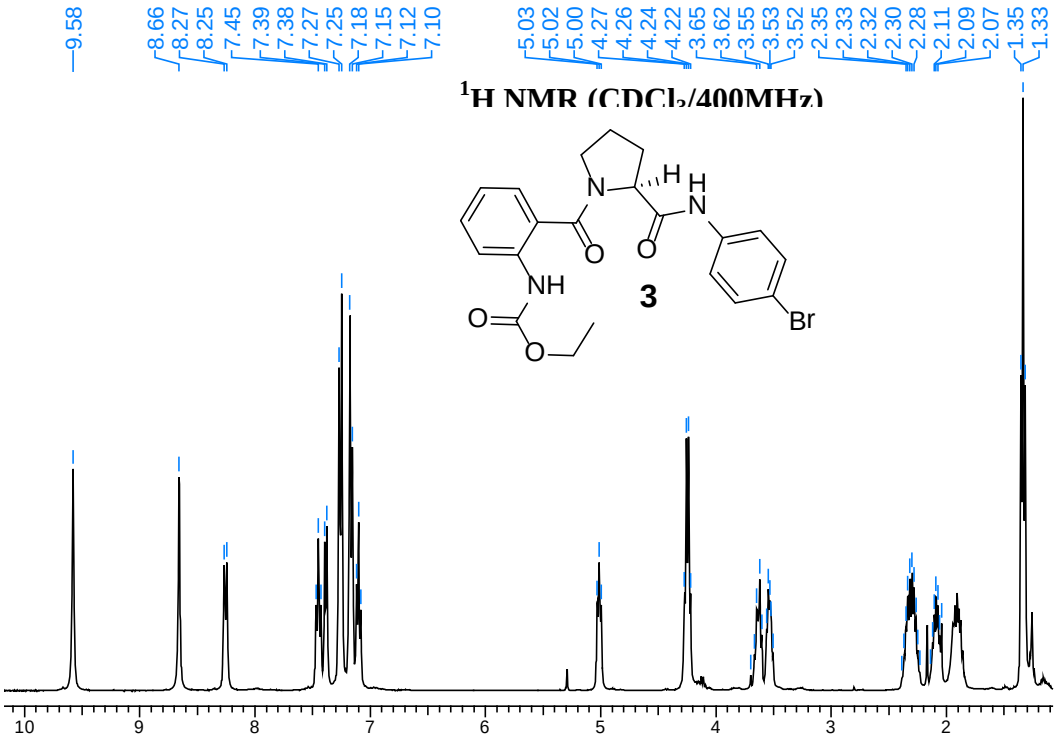

+TOF MS: 0.017 to 0.183 min from 1851.wiff
Max. 56.3 counts.
506.6182
508.6183
(M+Na)+
(M+K)+
Intensity, counts
m/z, amu
4
Br

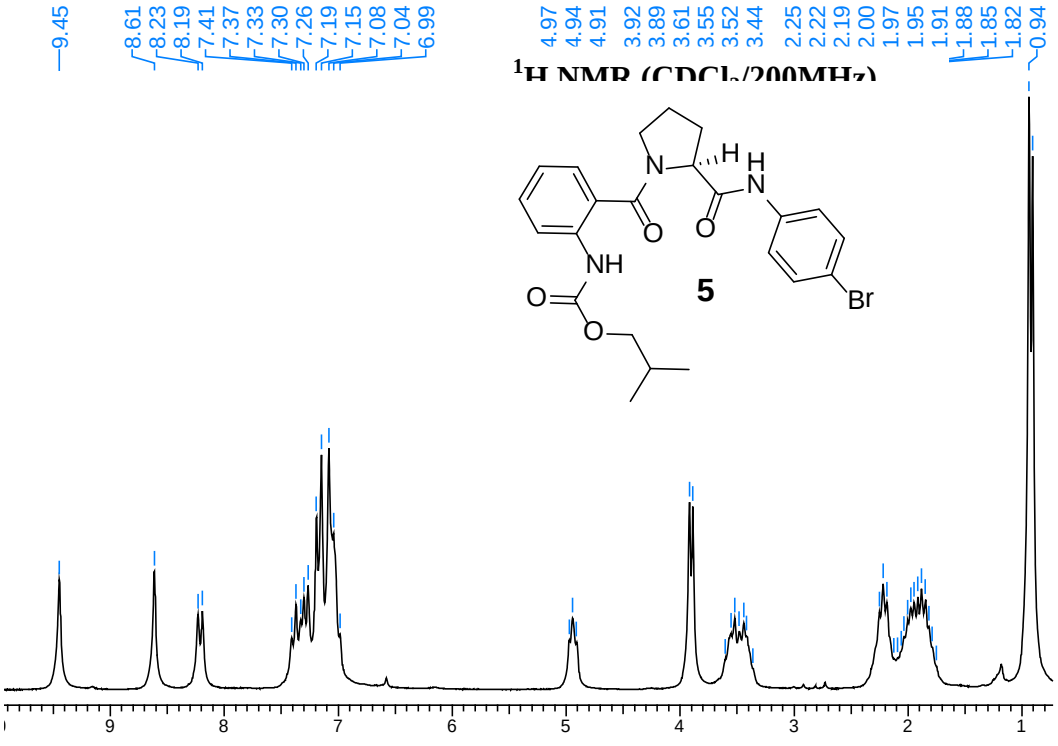

F:\DATA\...\Sanjayan-Nov2011\ABP-OMe
11/8/2011 3:23:59 PM
ABP-OMe #14-78 RT: 0.12-0.68 AV: 65 SB: 17 0.02-0.08 , 0.80-0.87 NL: 1.22E7
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [100.00-800.00]
375.05
(M+Na)+
LC-MS
Relative Abundance
m/z
11

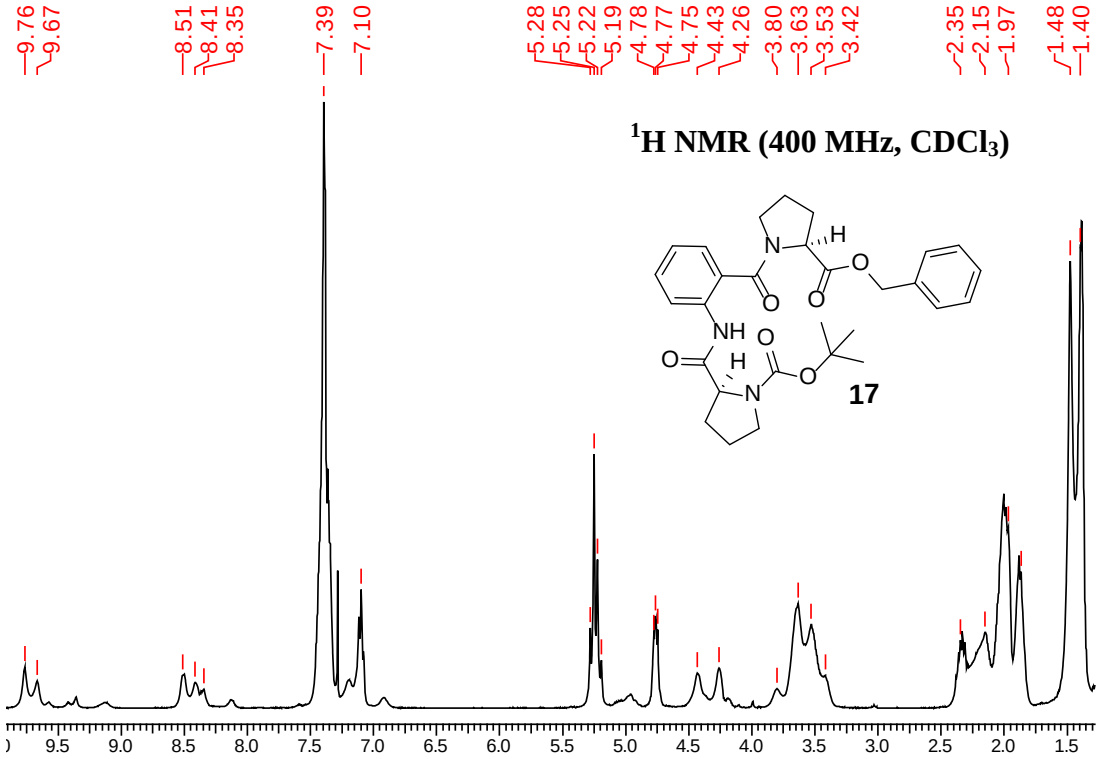


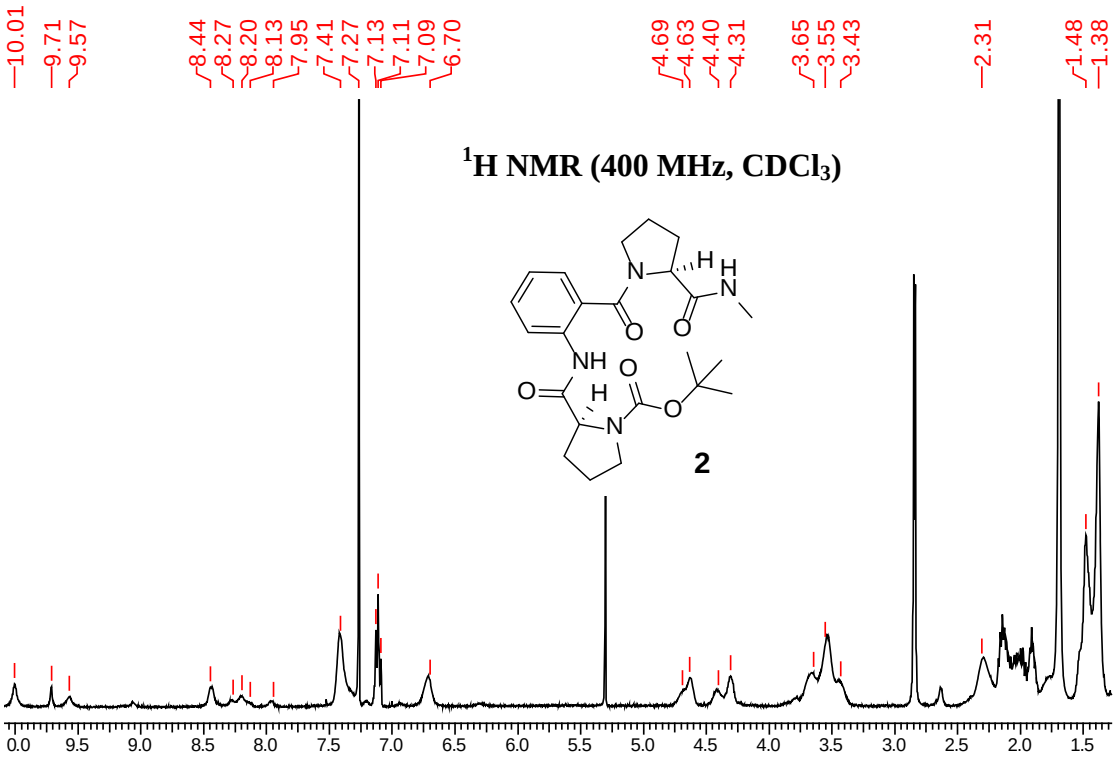


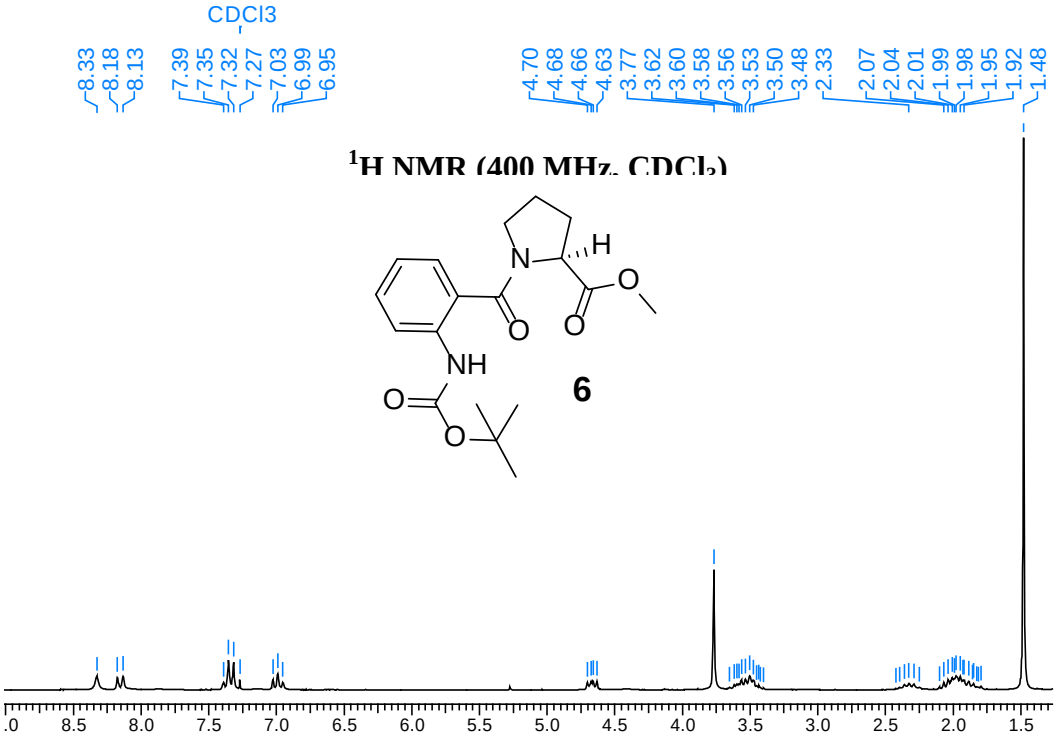


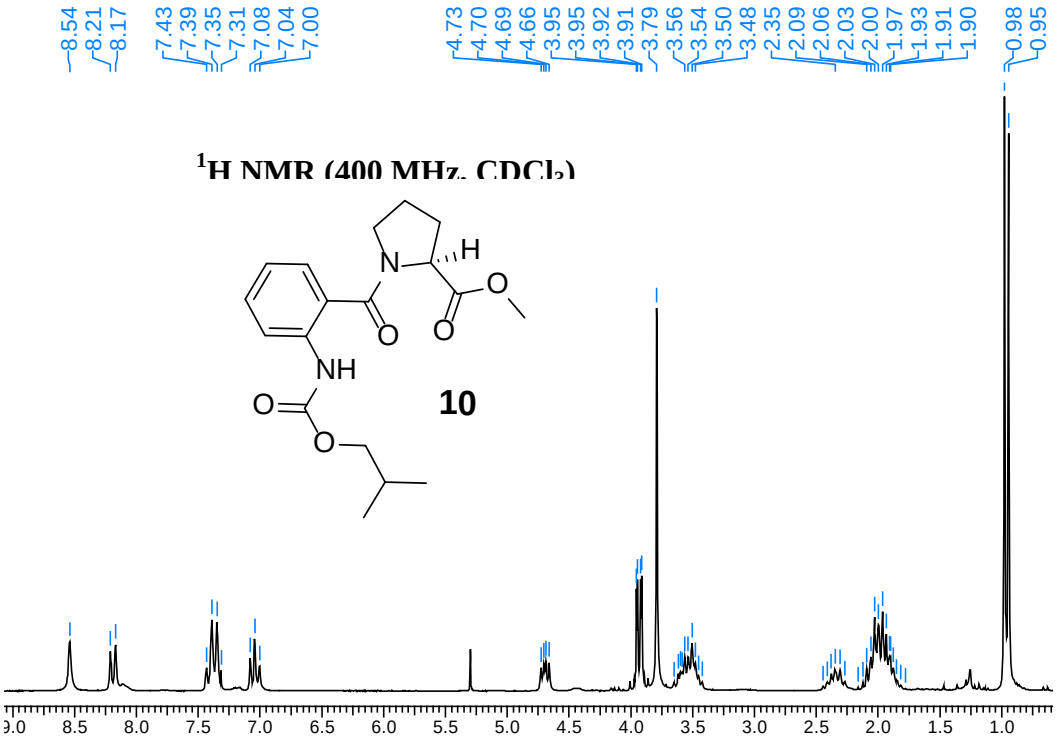


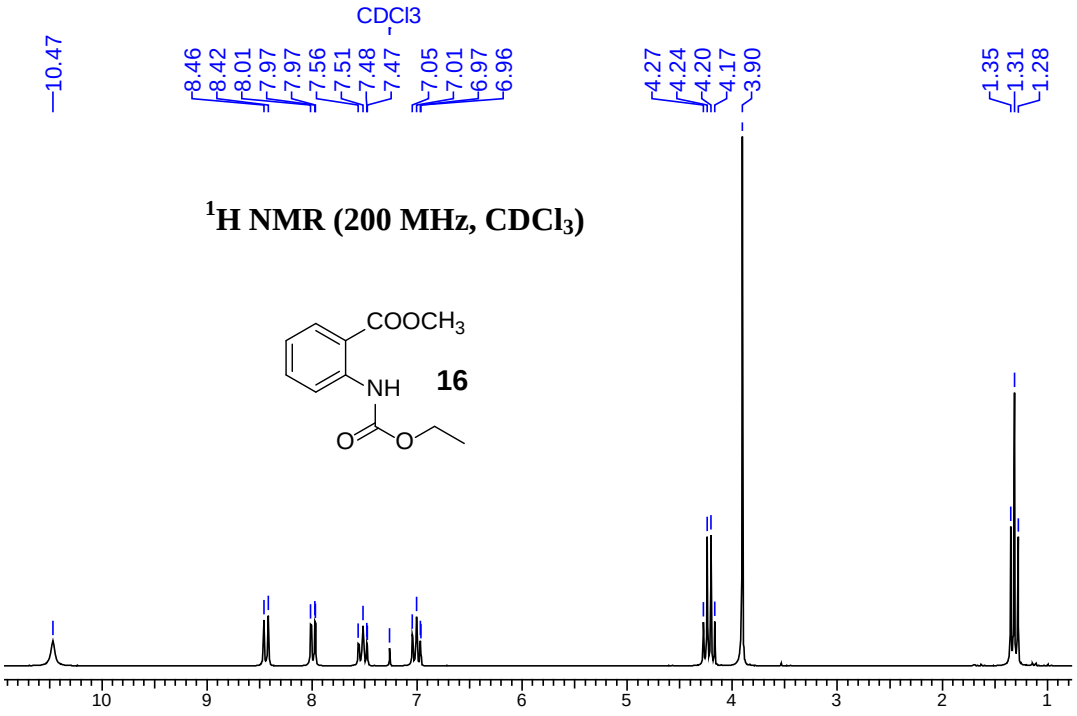






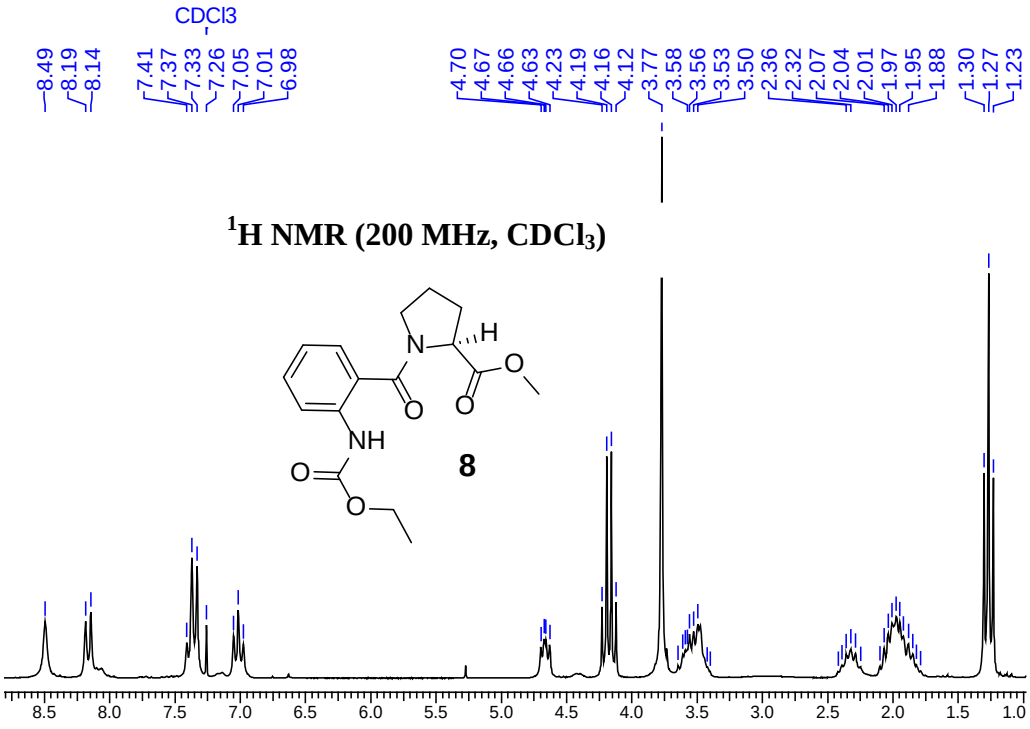






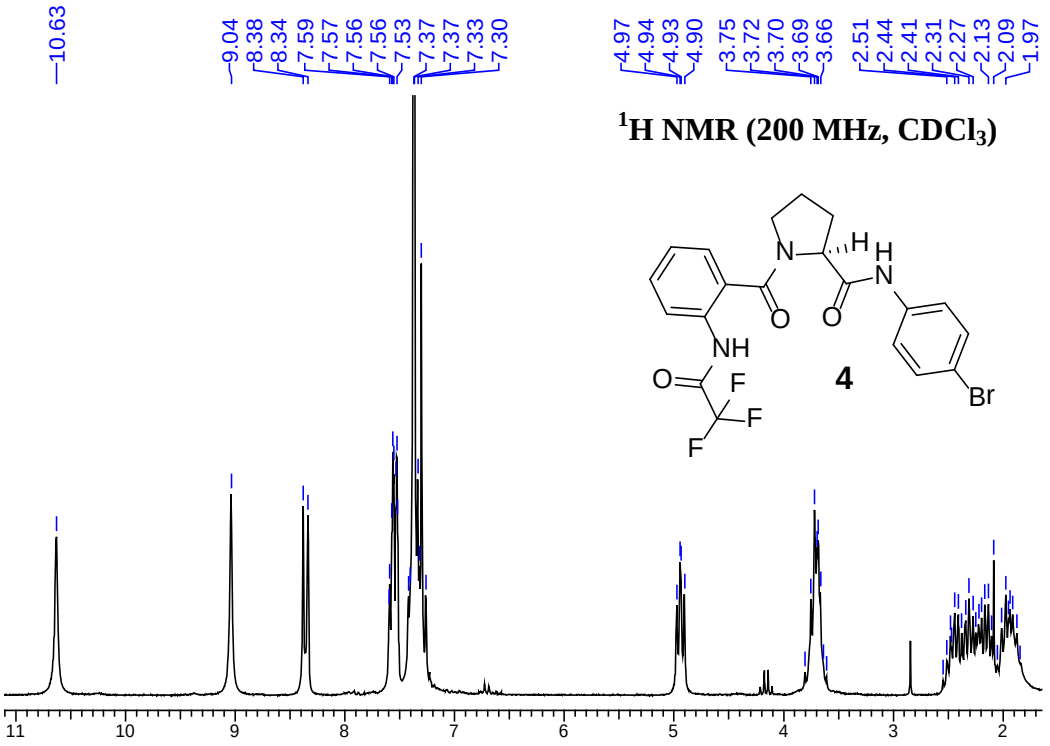
^{1}H NMR (200 MHz, $CDCl_3$)

16



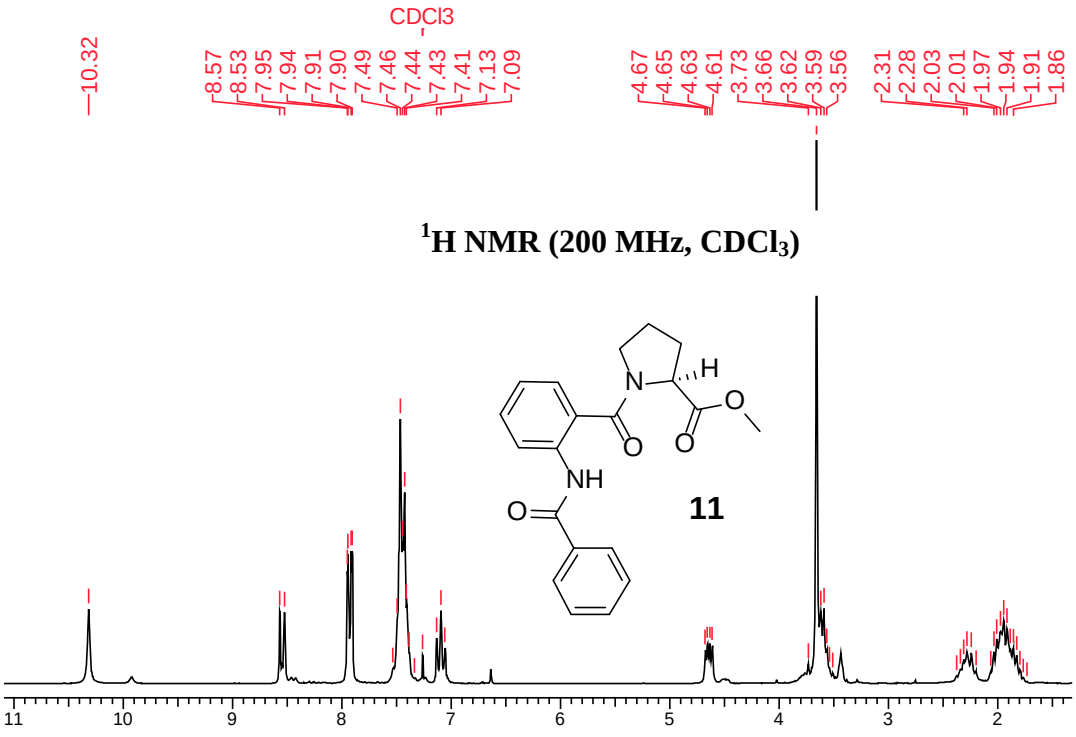
^{1}H NMR (200 MHz, $CDCl_3$)

8



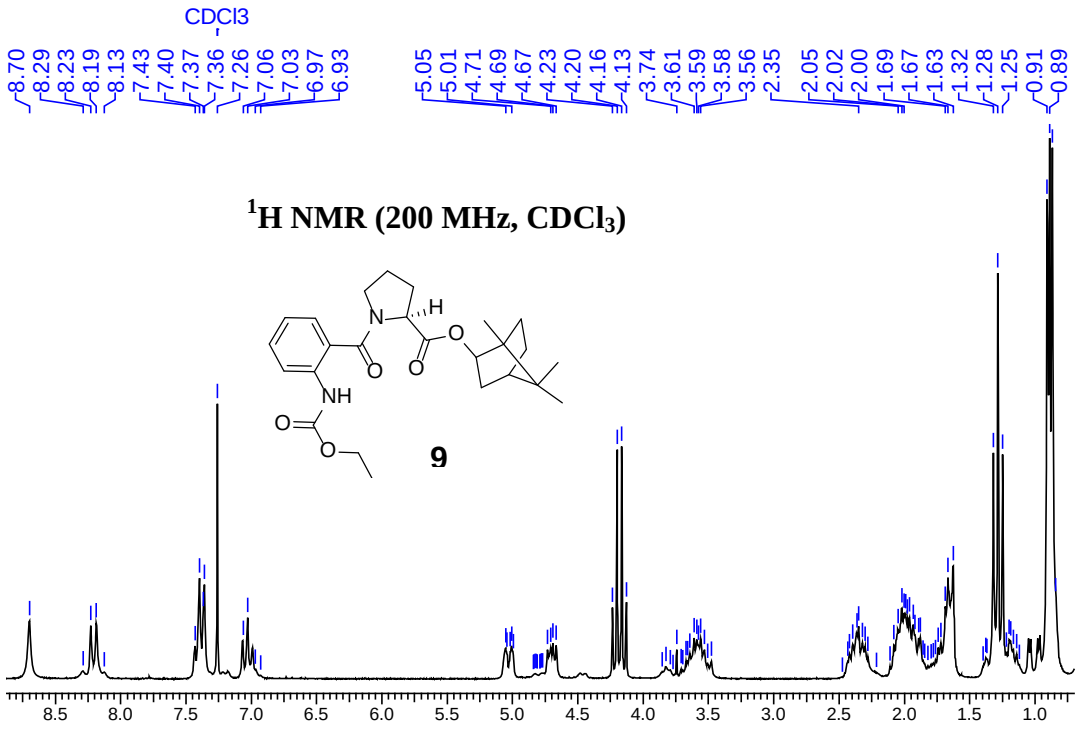
^{1}H NMR (200 MHz, $CDCl_3$)

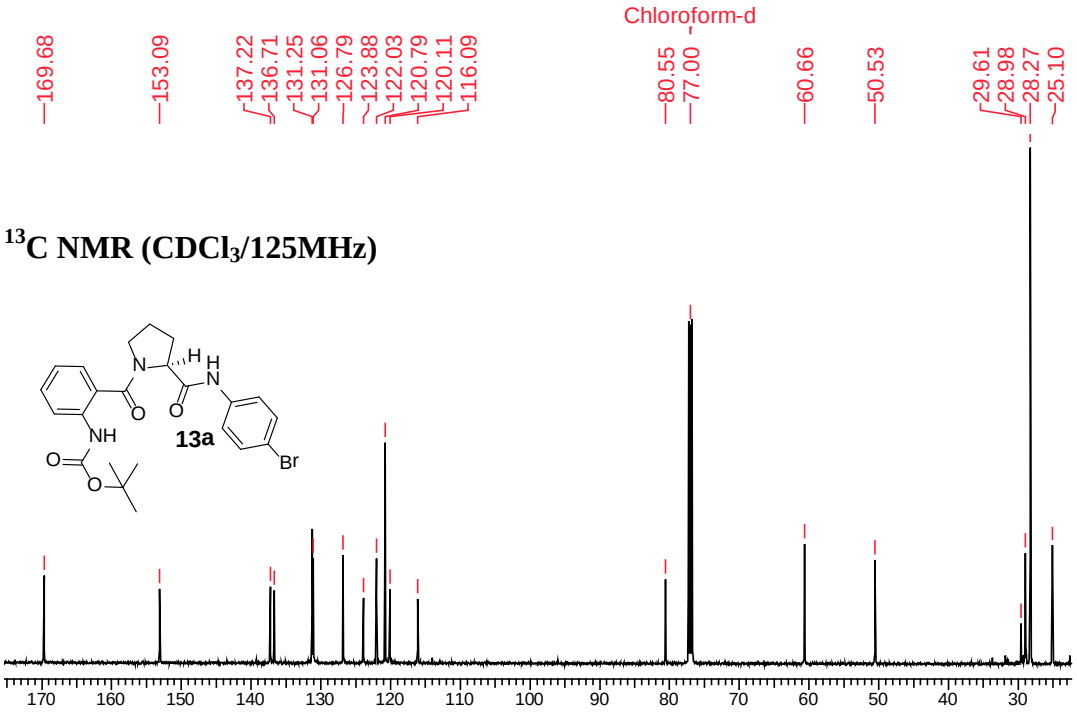
4



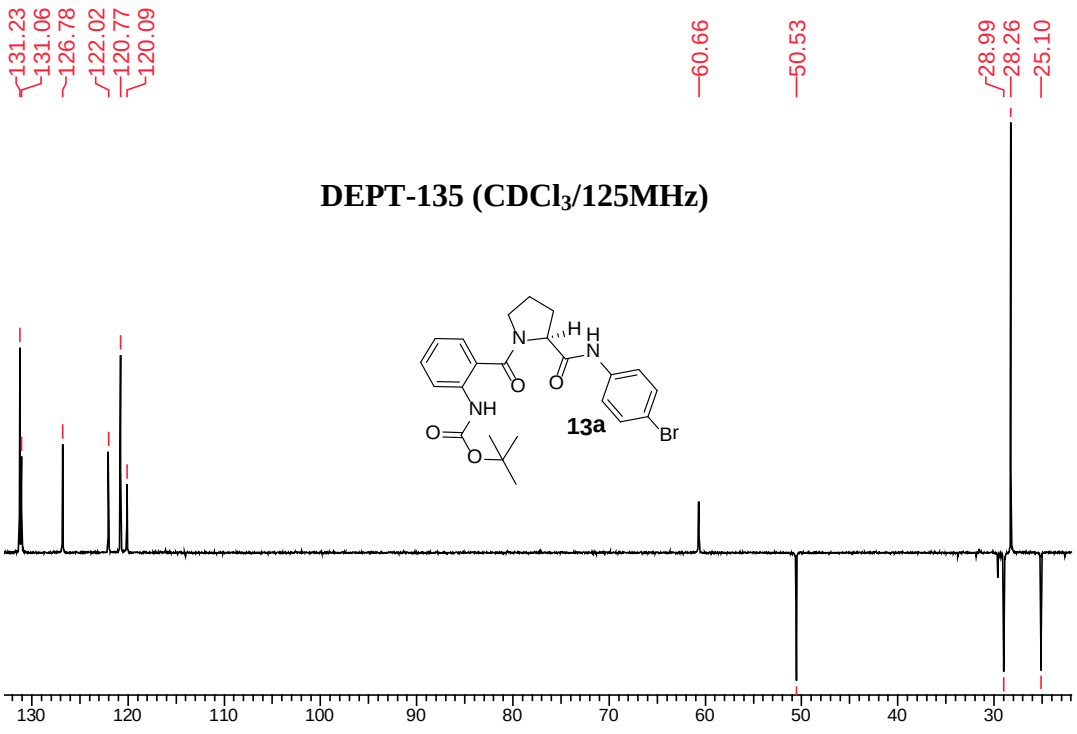
^{1}H NMR (200 MHz, $CDCl_3$)

11

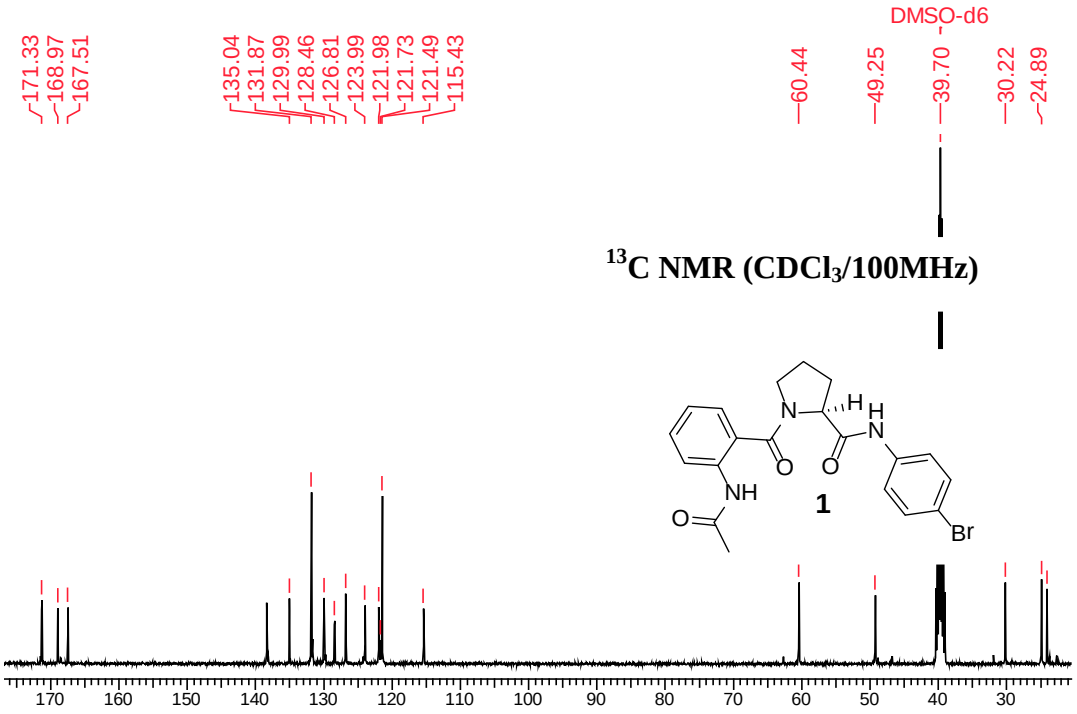




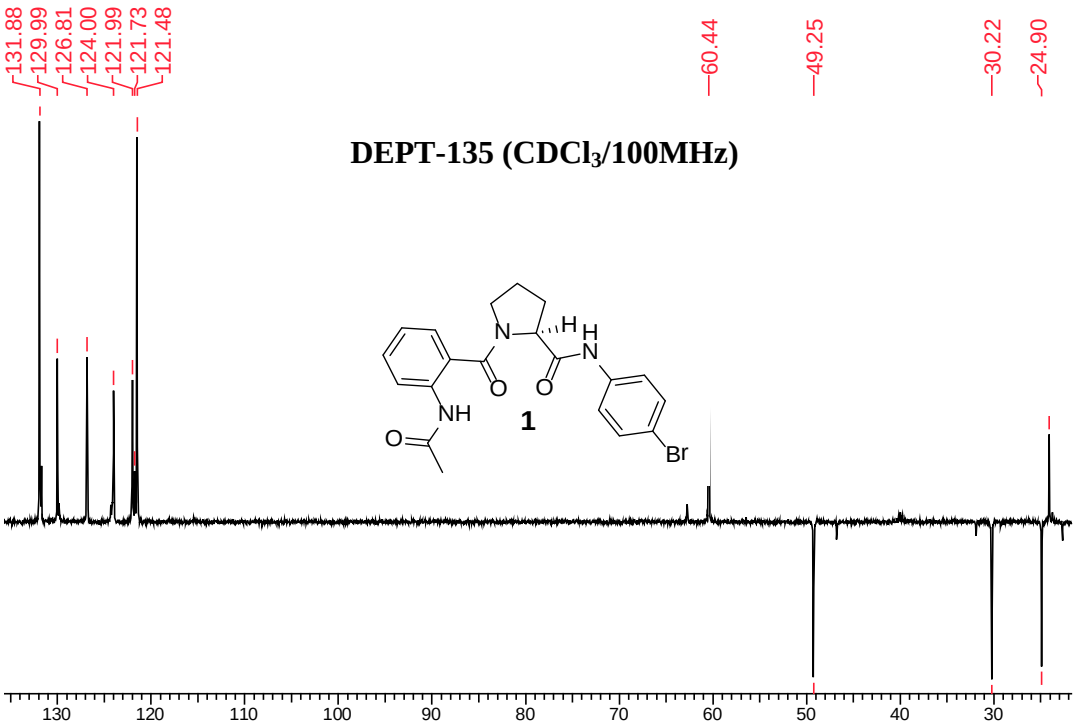
^{13}C NMR ($CDCl_3$/125MHz)



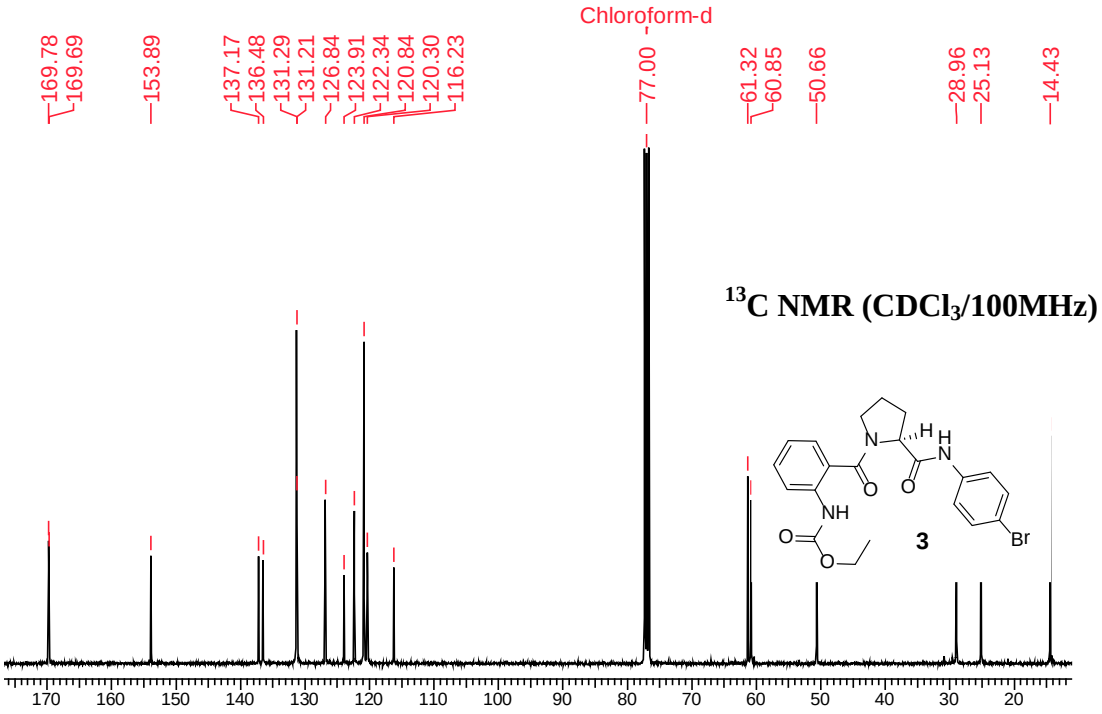
DEPT-135 ($CDCl_3$/125MHz)



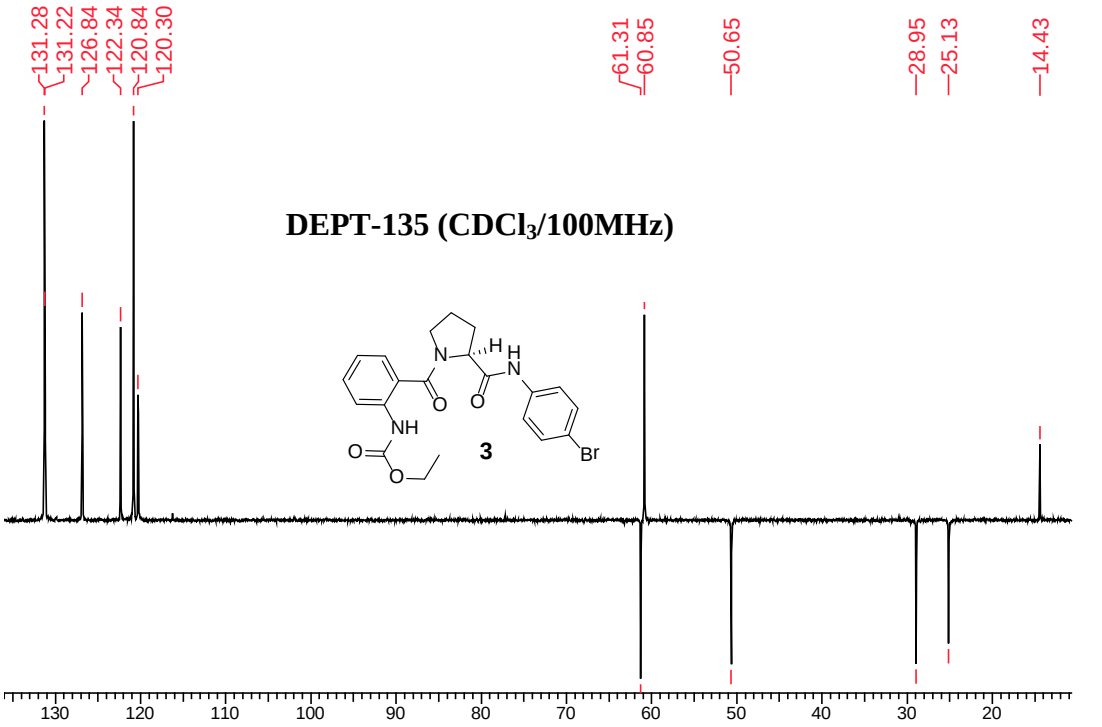
^{13}C NMR ($CDCl_3$/100MHz)



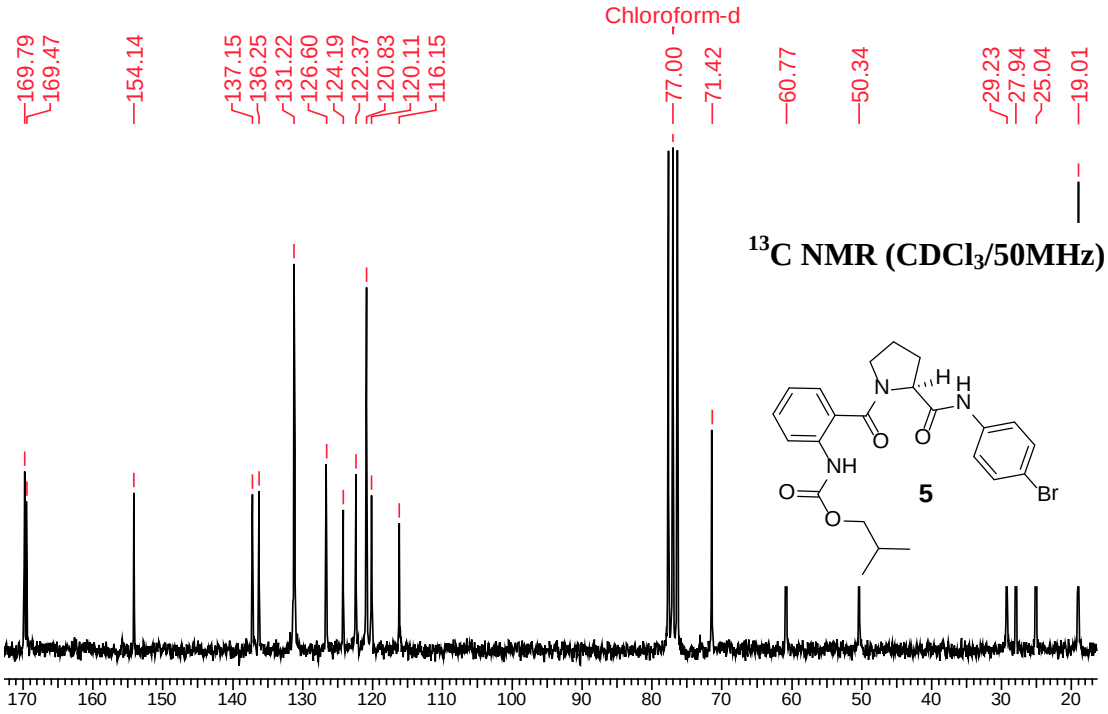
DEPT-135 ($CDCl_3$/100MHz)



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

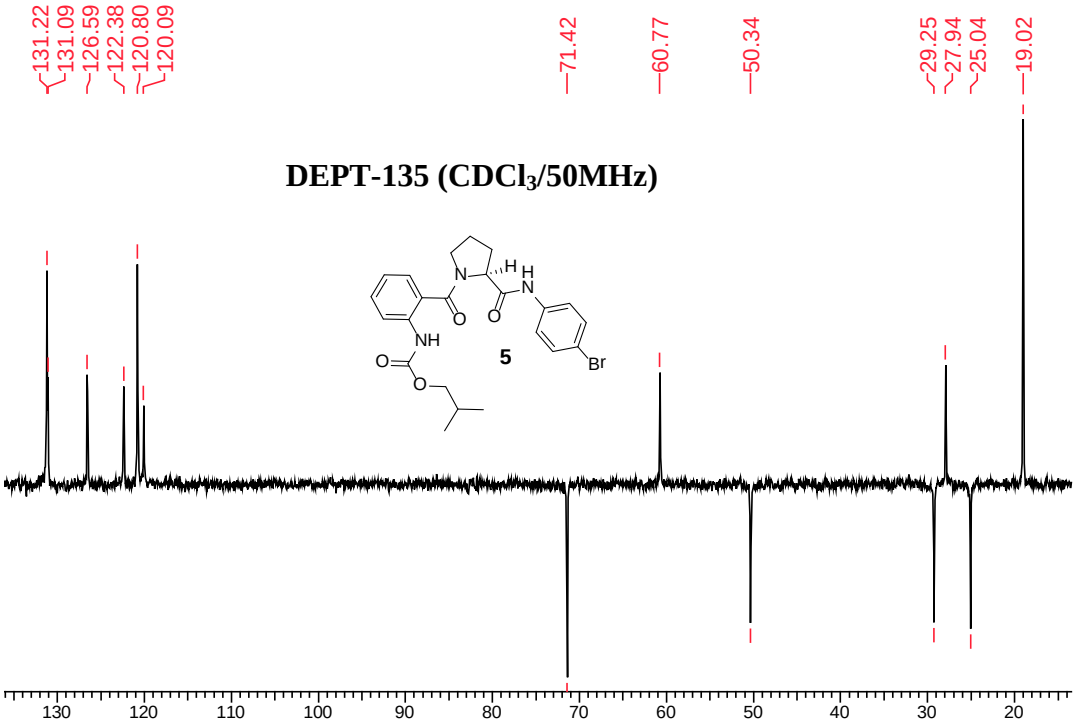


DEPT-135 ($CDCl_3$/100MHz)



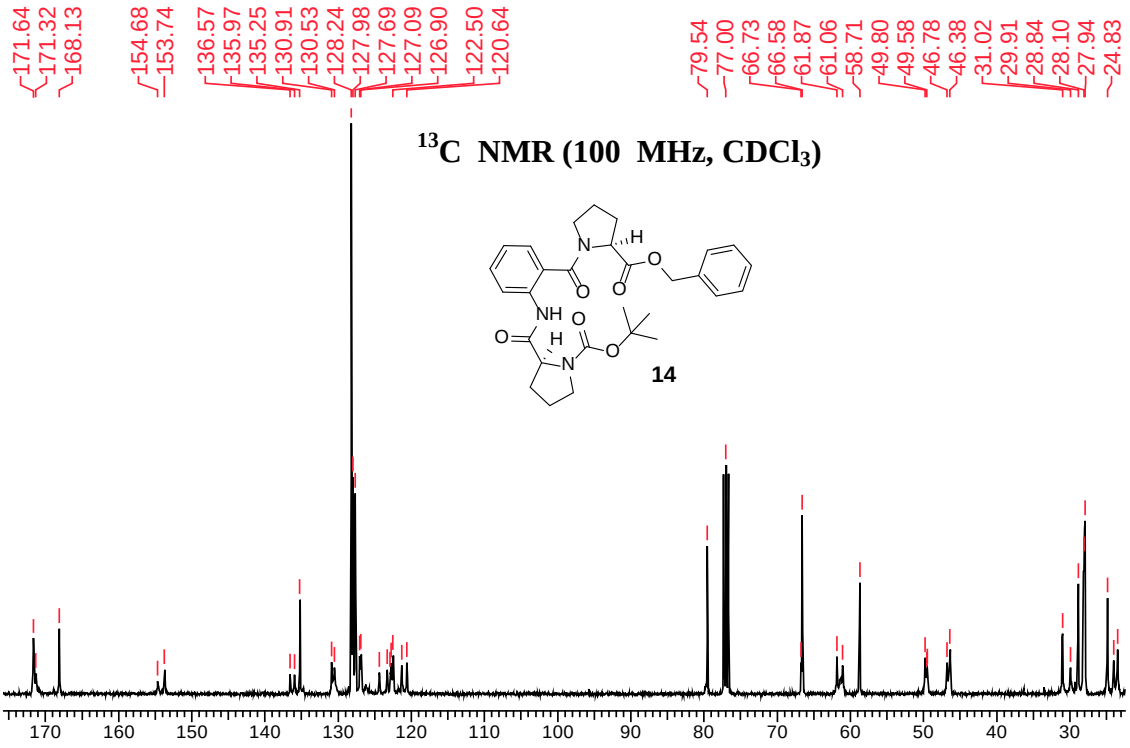
^{13}C NMR ($CDCl_3$/50MHz)

5



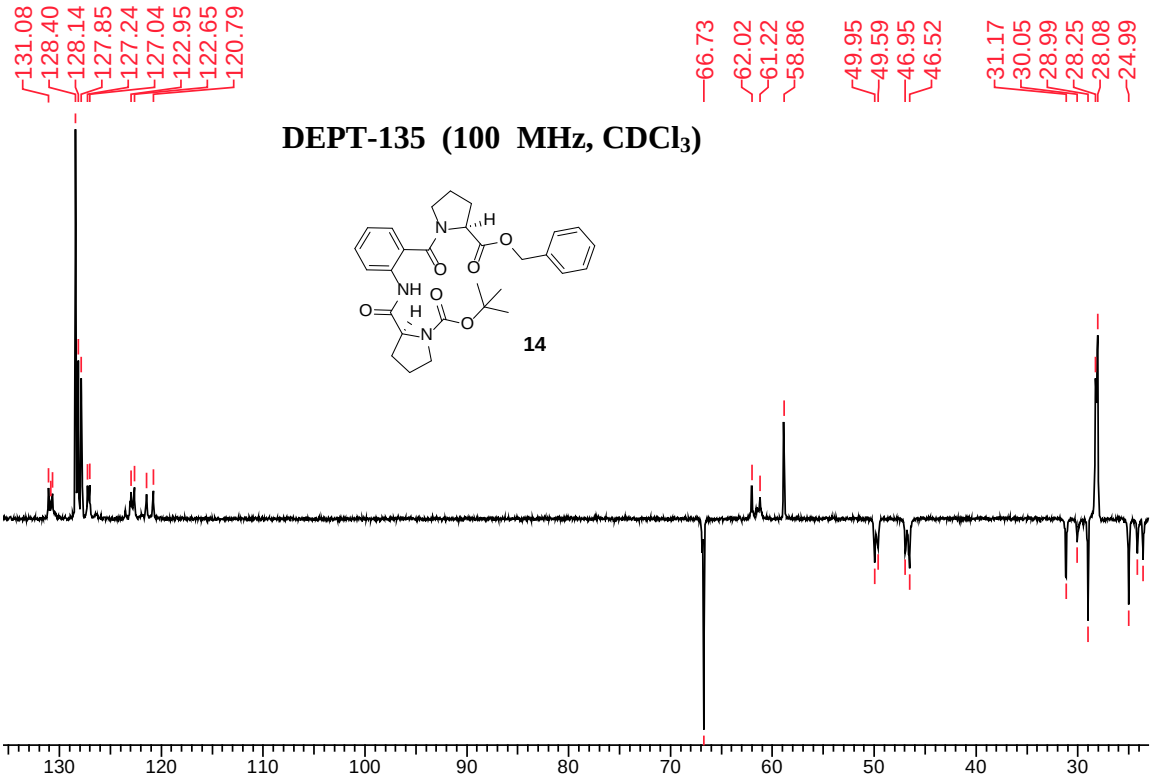
DEPT-135 ($CDCl_3$/50MHz)

5



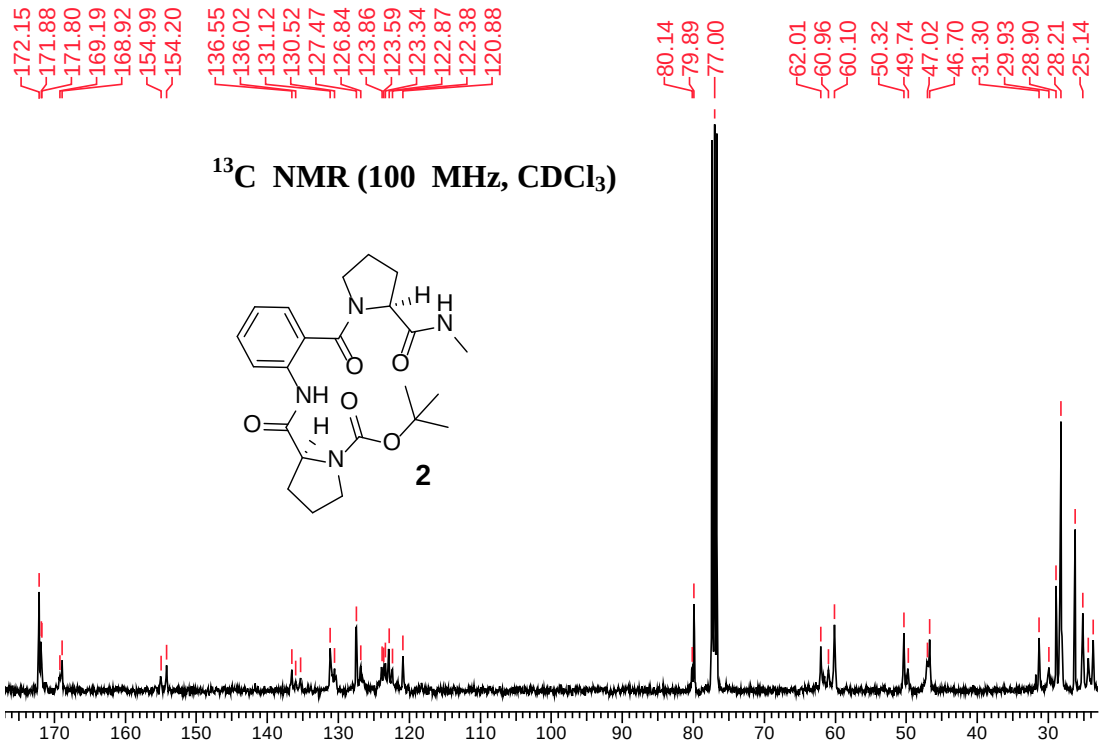
^{13}C NMR (100 MHz, $CDCl_3$)

14



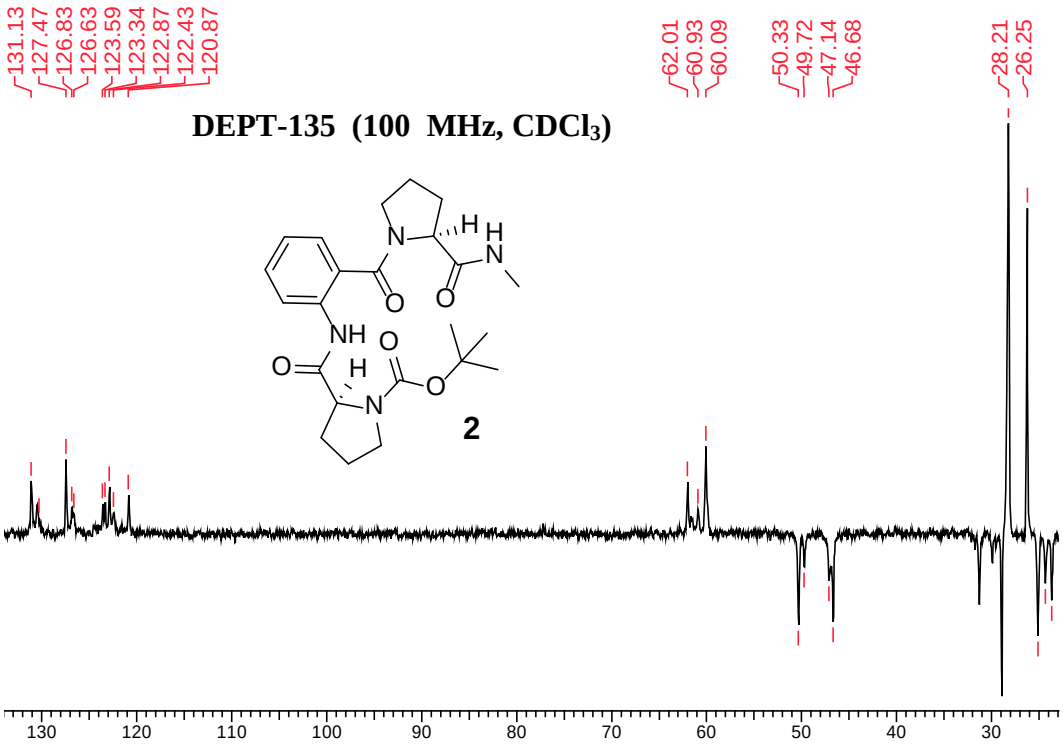
DEPT-135 (100 MHz, $CDCl_3$)

14



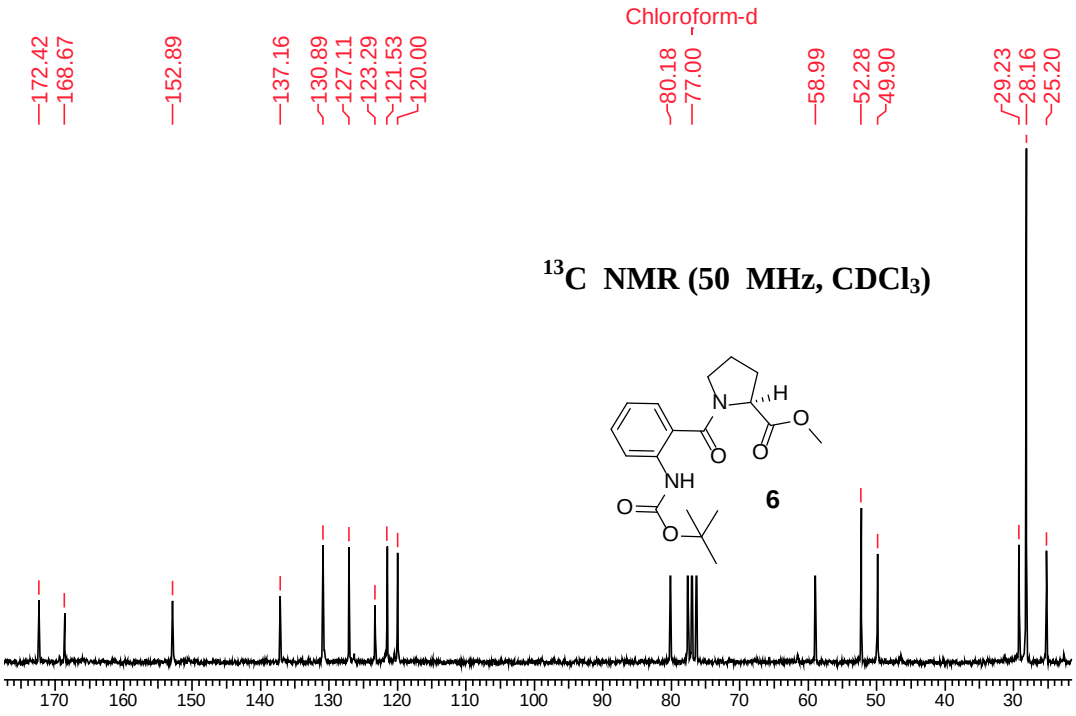
^{13}C NMR (100 MHz, $CDCl_3$)

2



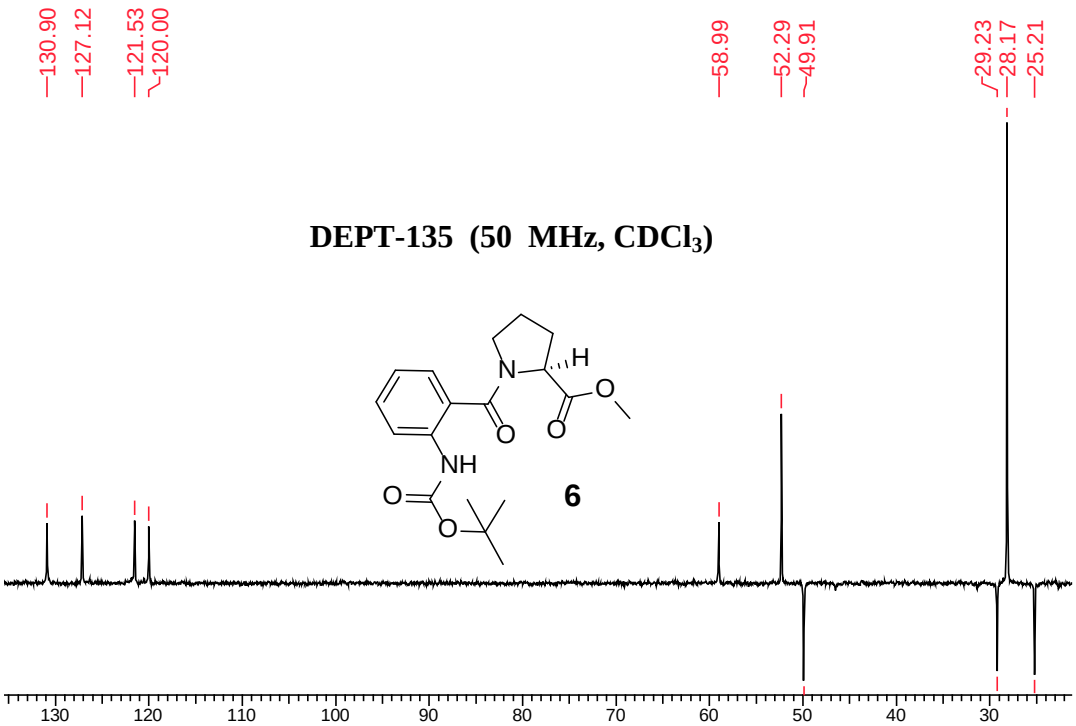
DEPT-135 (100 MHz, $CDCl_3$)

2



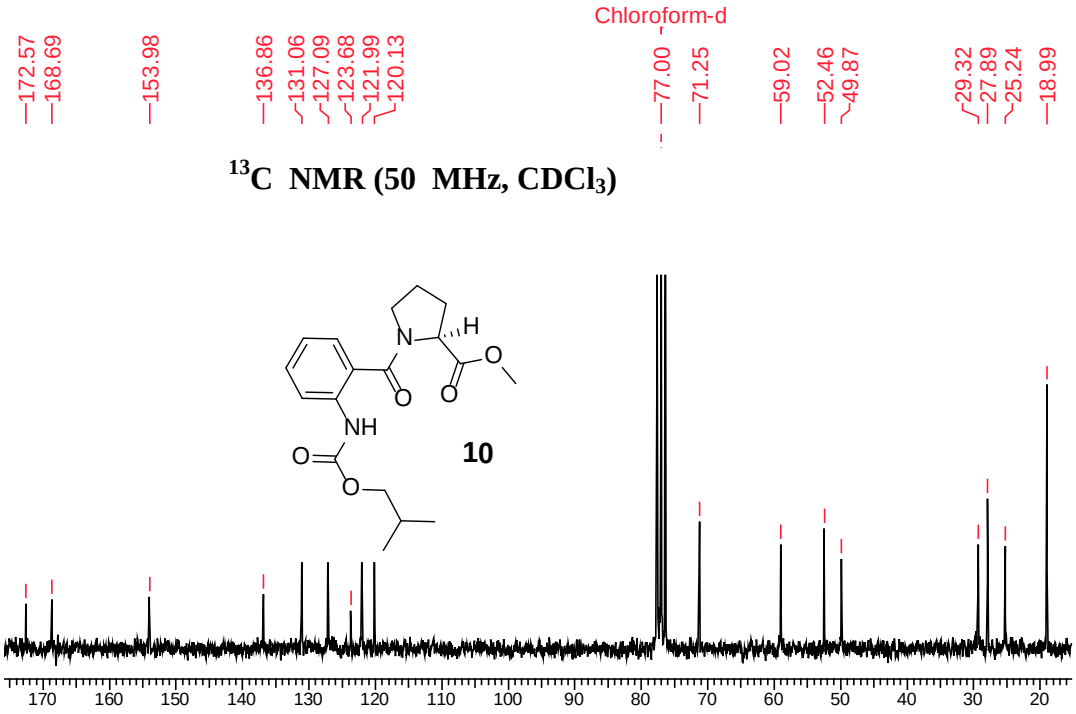
^{13}C NMR (50 MHz, $CDCl_3$)

6

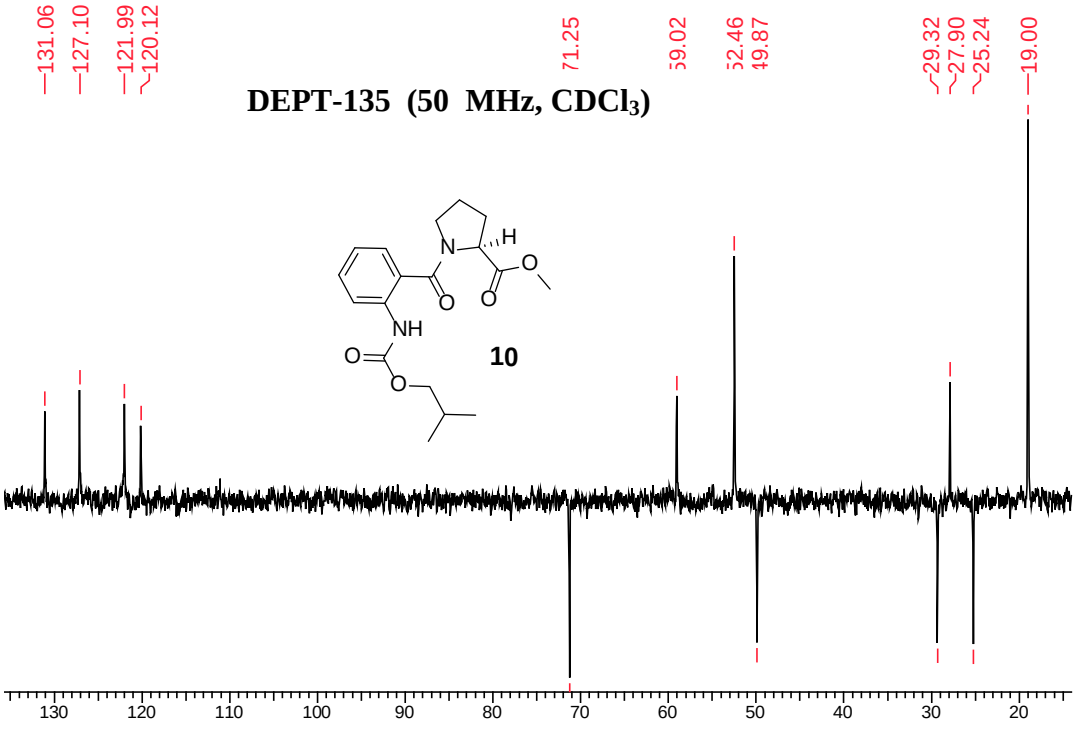


DEPT-135 (50 MHz, $CDCl_3$)

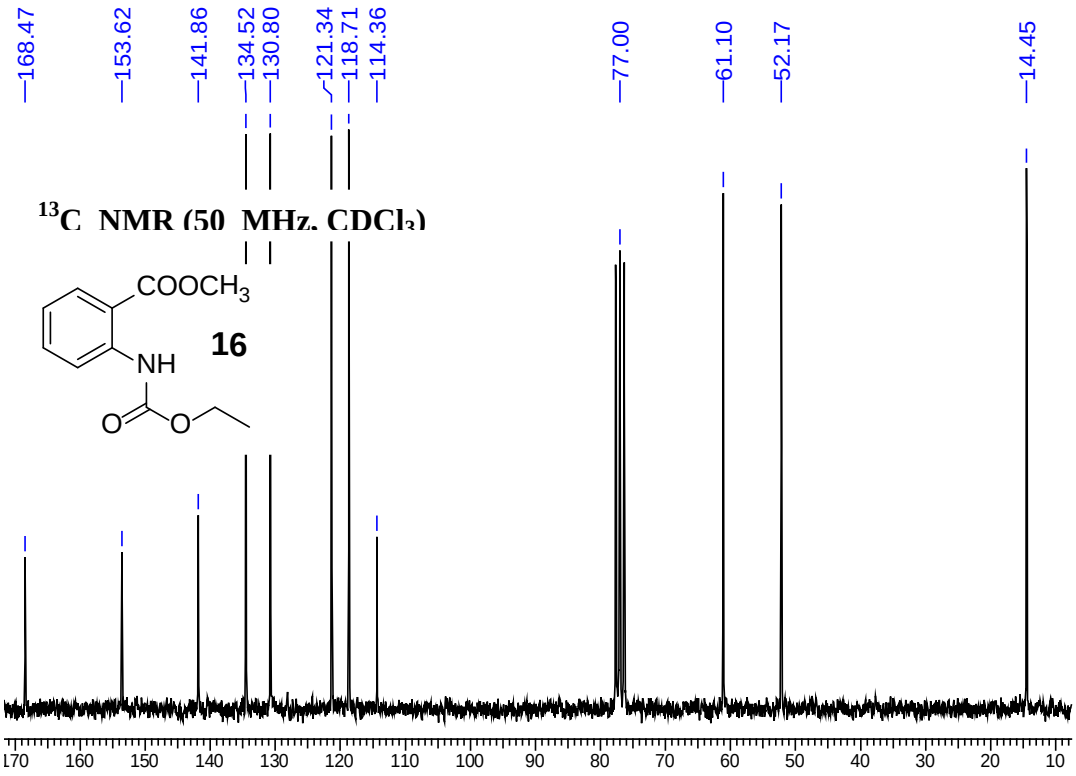
6

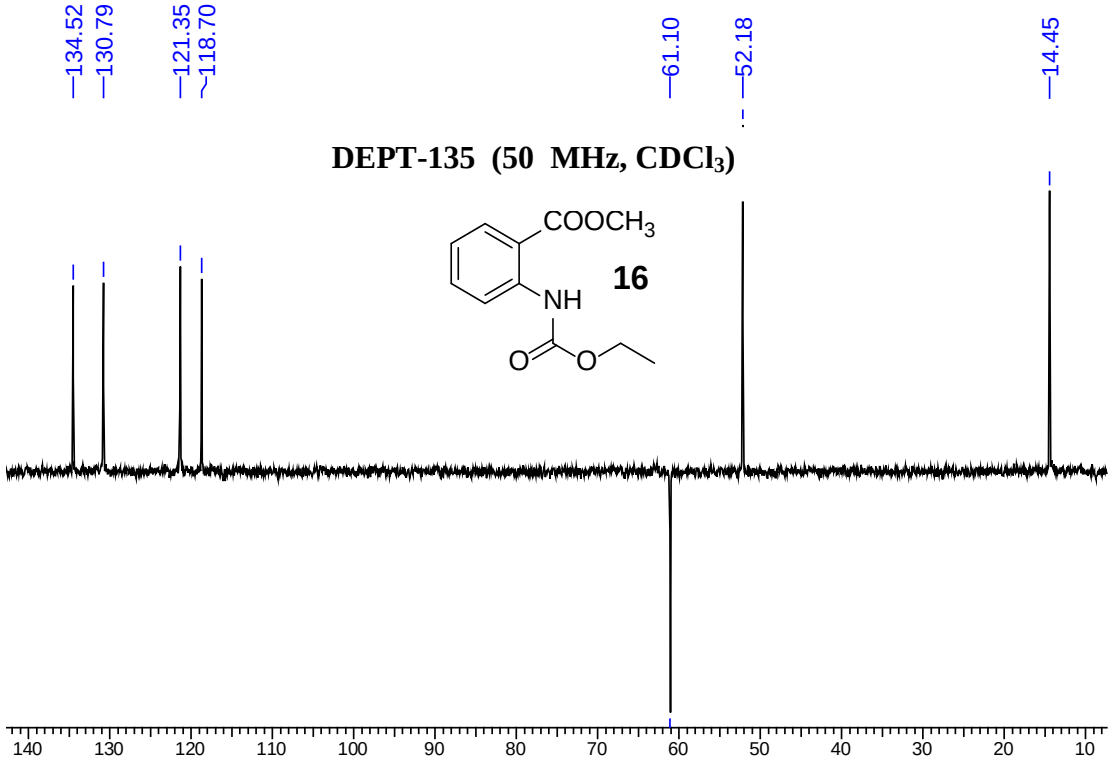


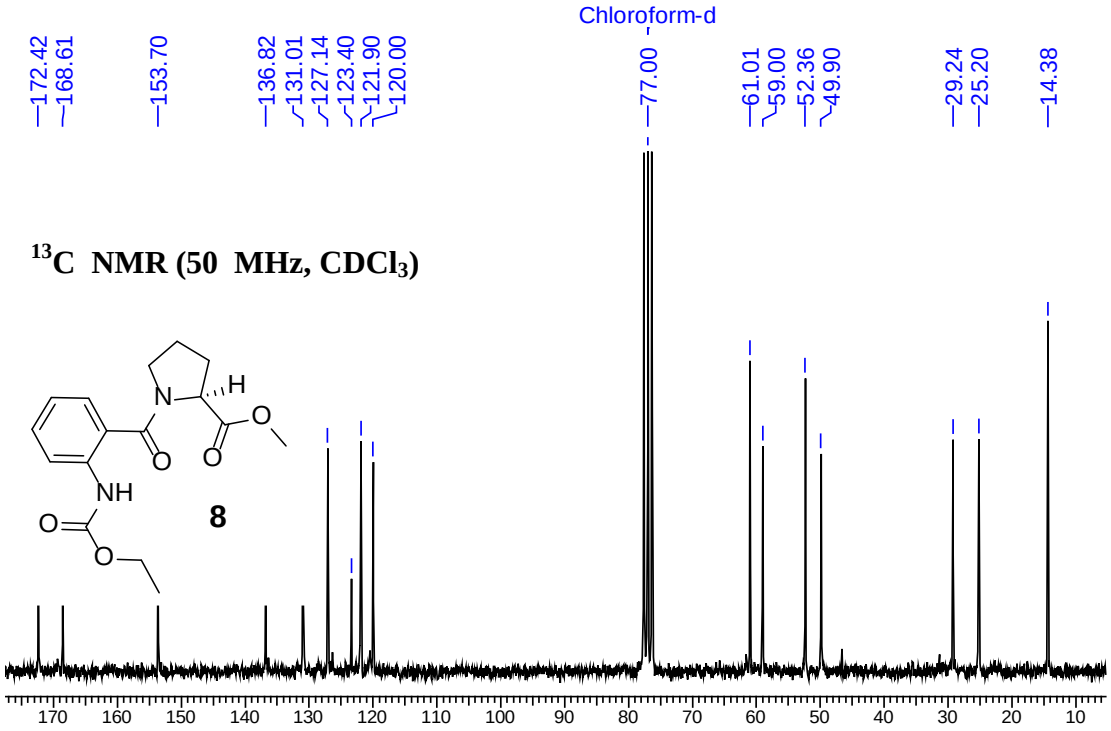
^{13}C NMR (50 MHz, $CDCl_3$)

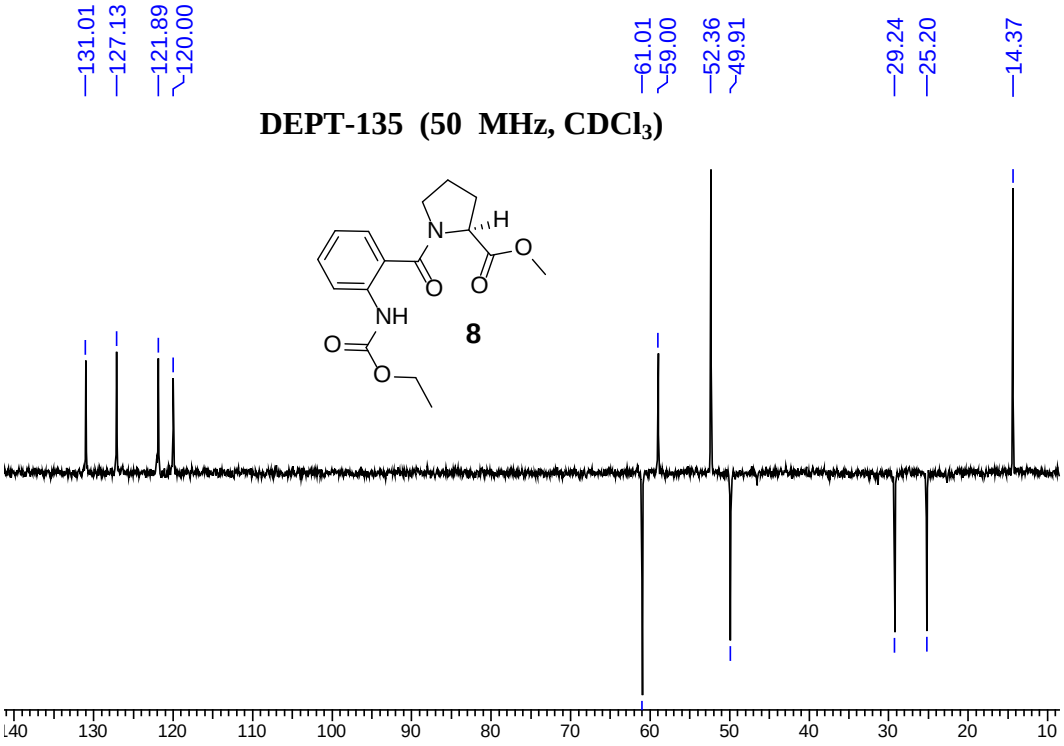


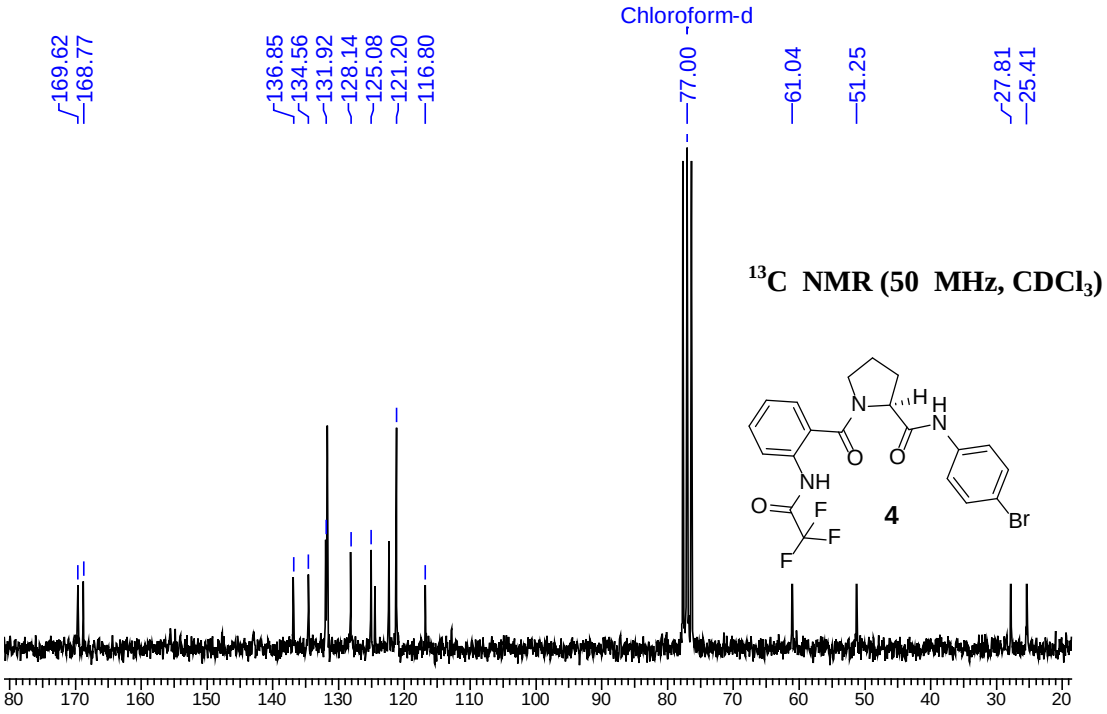
DEPT-135 (50 MHz, $CDCl_3$)



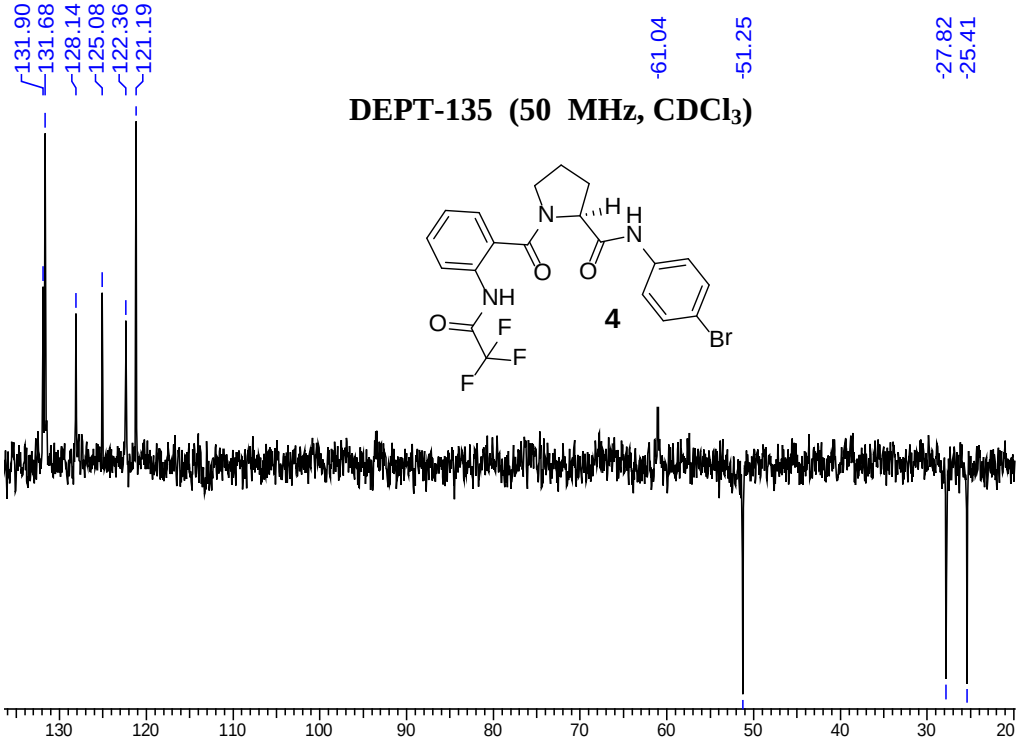




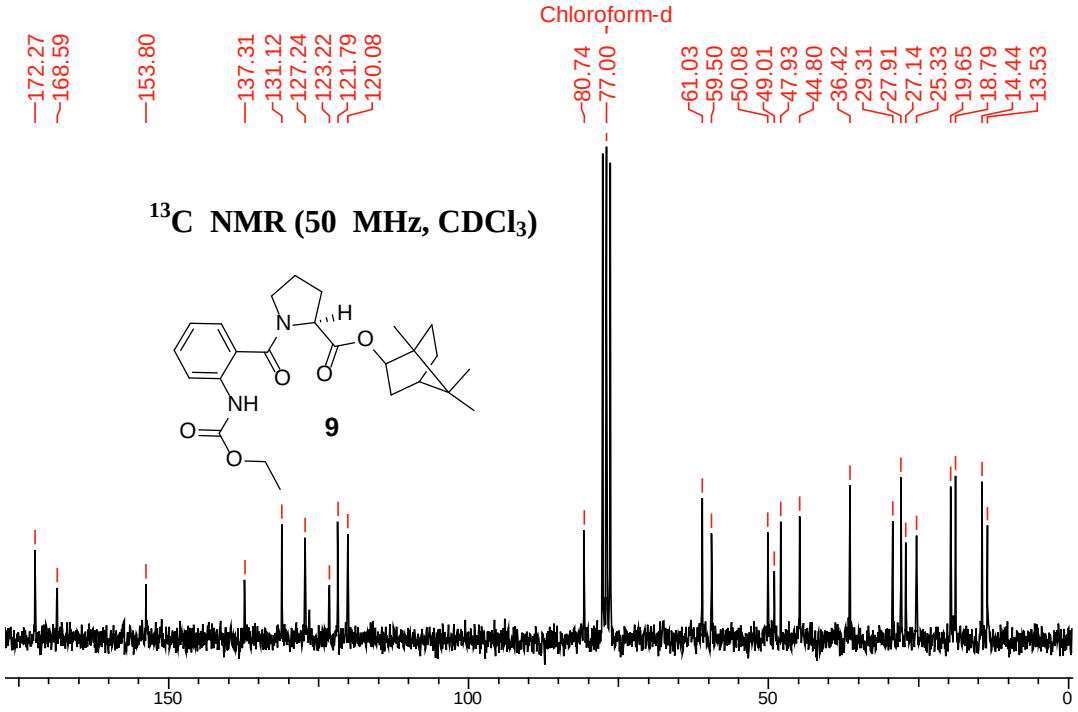




^{13}C NMR (50 MHz, $CDCl_3$)

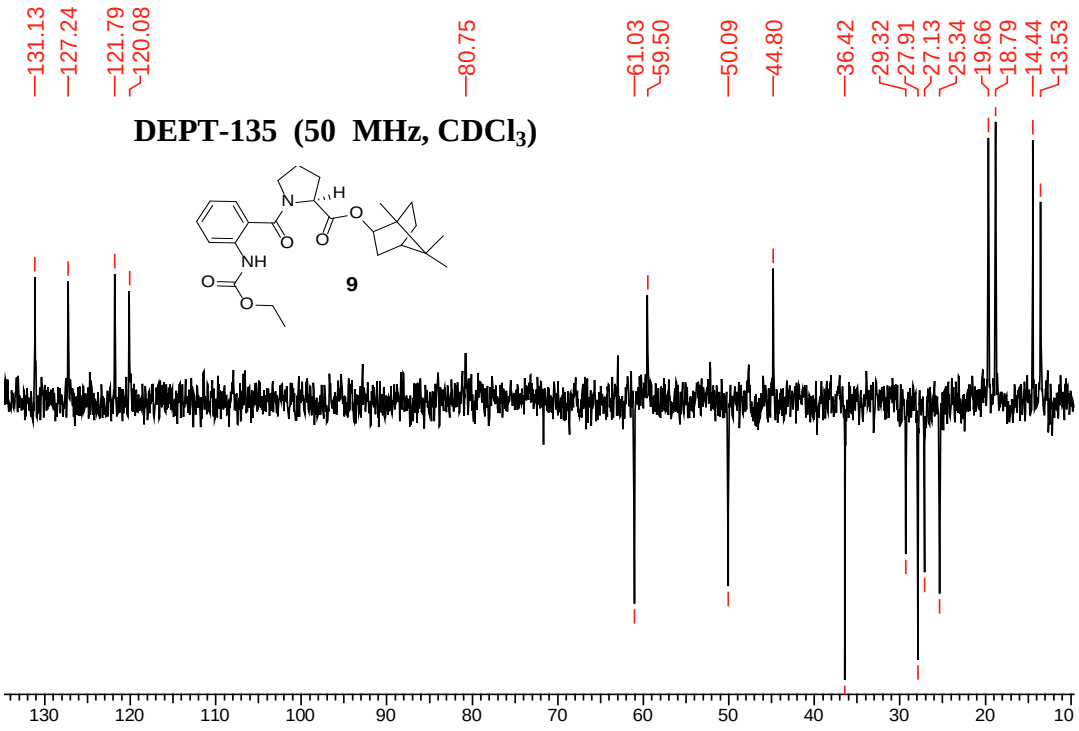


DEPT-135 (50 MHz, $CDCl_3$)



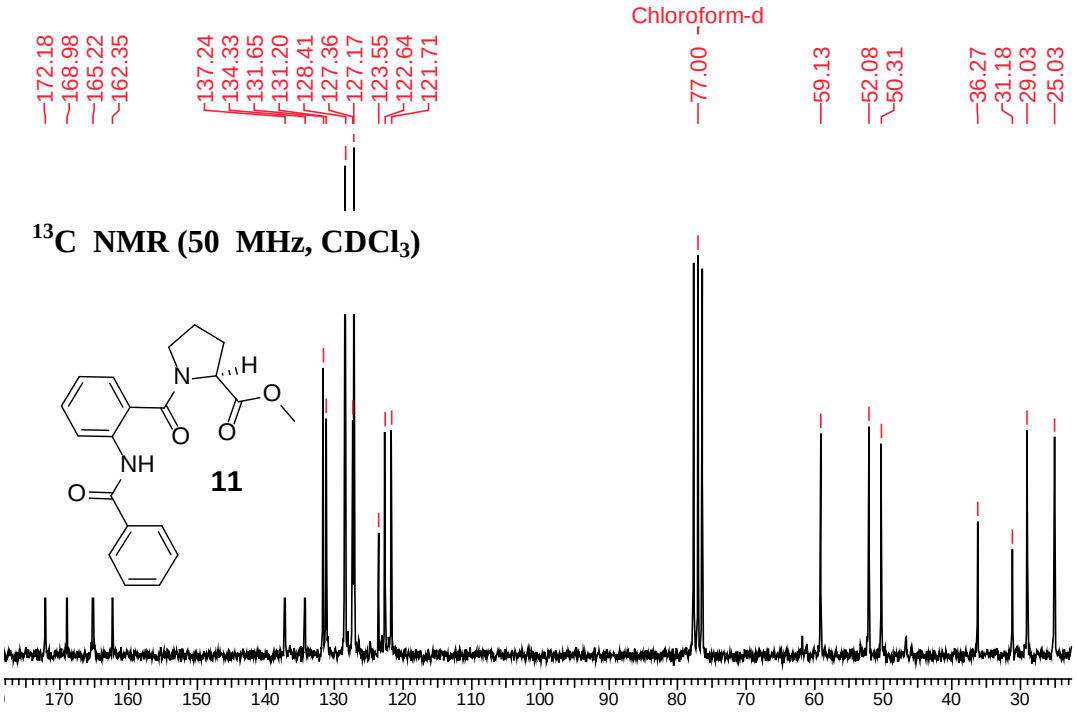
^{13}C NMR (50 MHz, $CDCl_3$)

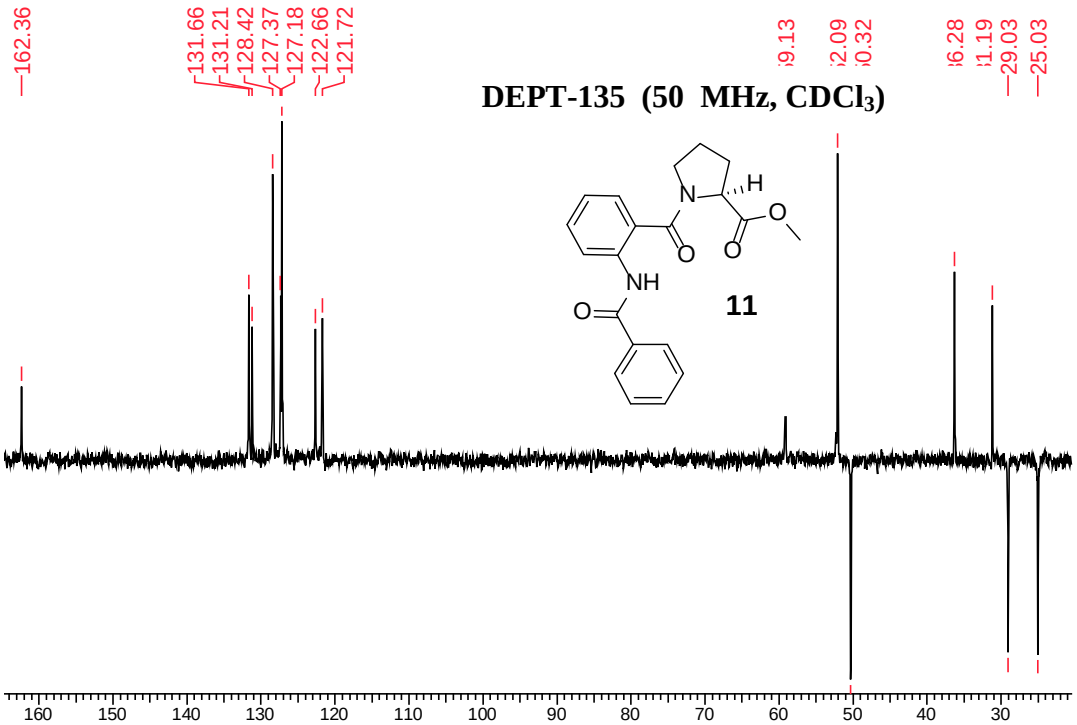
9



DEPT-135 (50 MHz, $CDCl_3$)

9





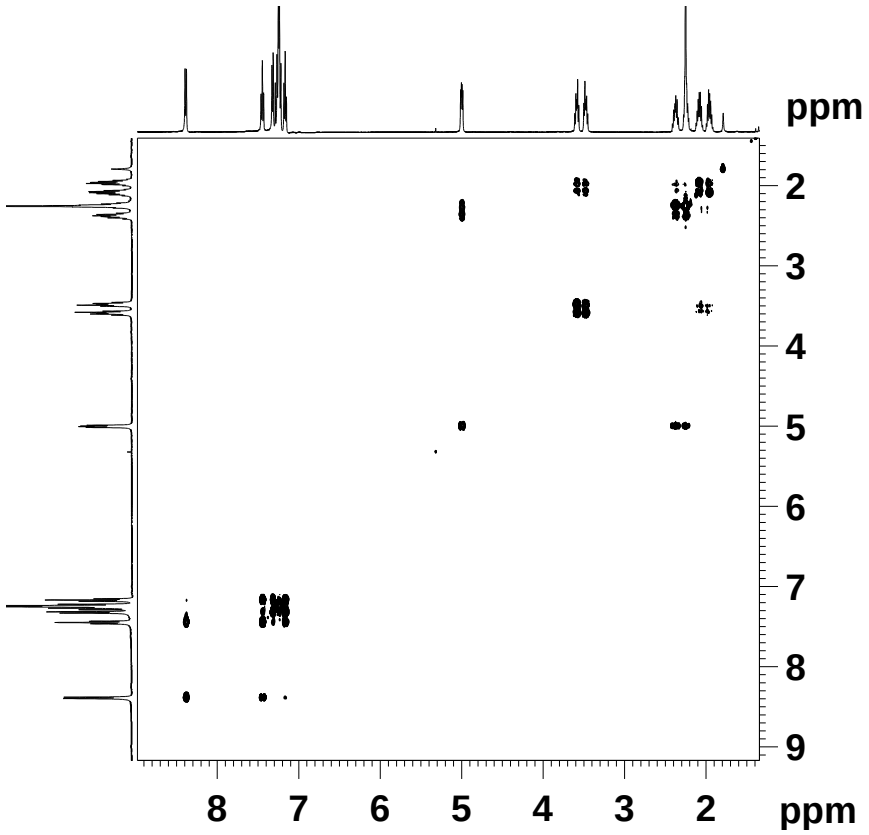


Figure 1: COSY spectra of amide **1** (400MHz, $CDCl_3$)

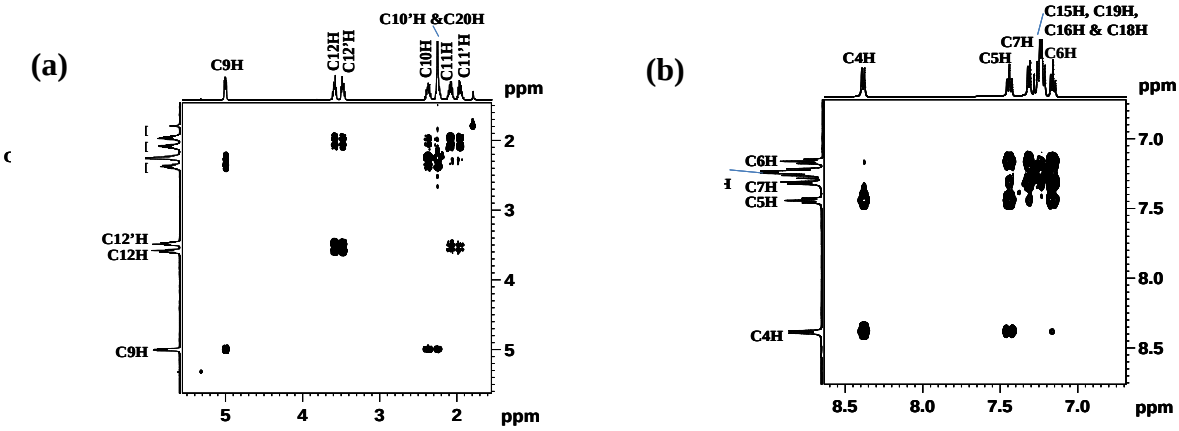


Figure 2: Partial COSY spectra of amide **1** (400MHz, $CDCl_3$): aromatic **(a)** and aliphatic regions **(b)**.

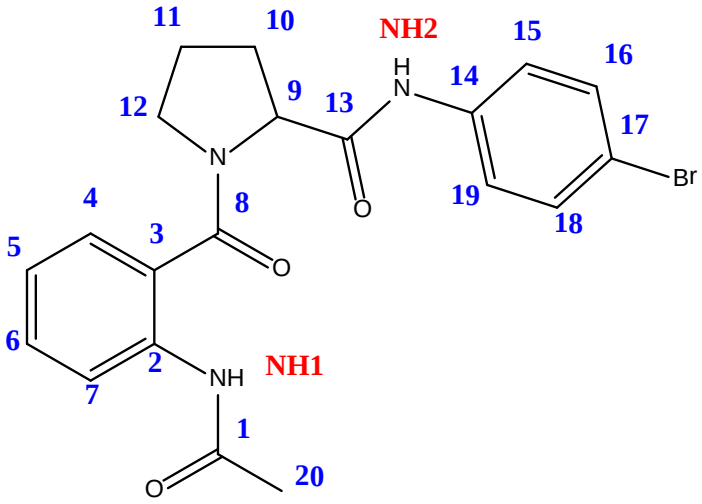


Figure 3: Molecular structure of Compound **1** (amide)

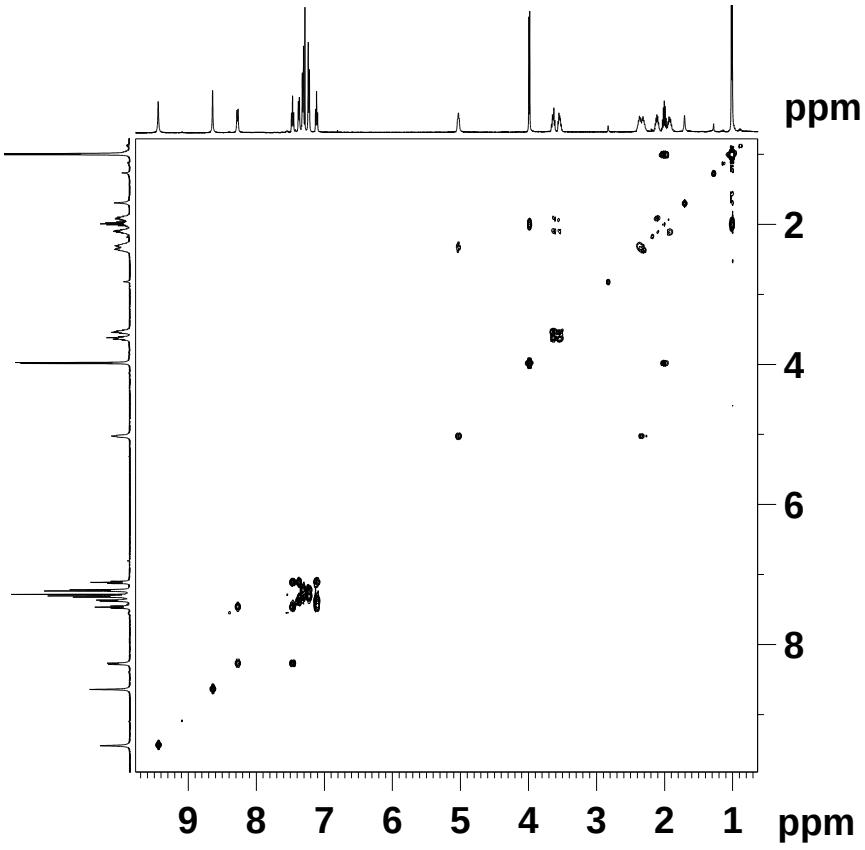


Figure 4: COSY spectra of amide **5** (400MHz, $CDCl_3$)

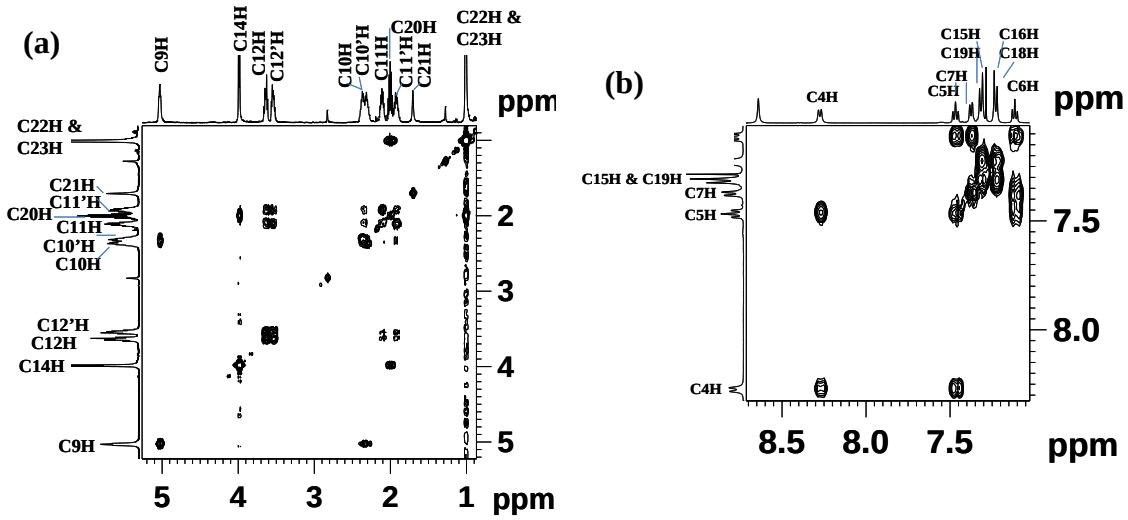


Figure 5: Partial COSY spectra of amide **5** (400MHz, C_6D_6): aromatic **(a)** and aliphatic regions **(b)**.

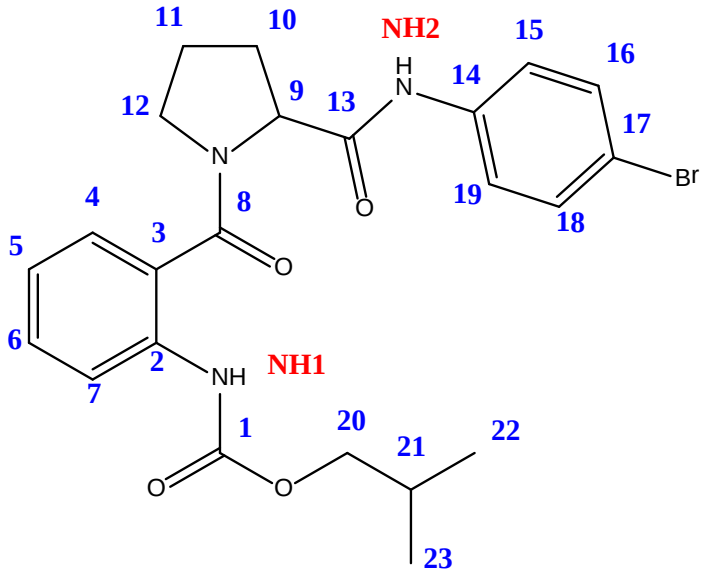


Figure 6: Molecular structure of Compound **5** (amide)

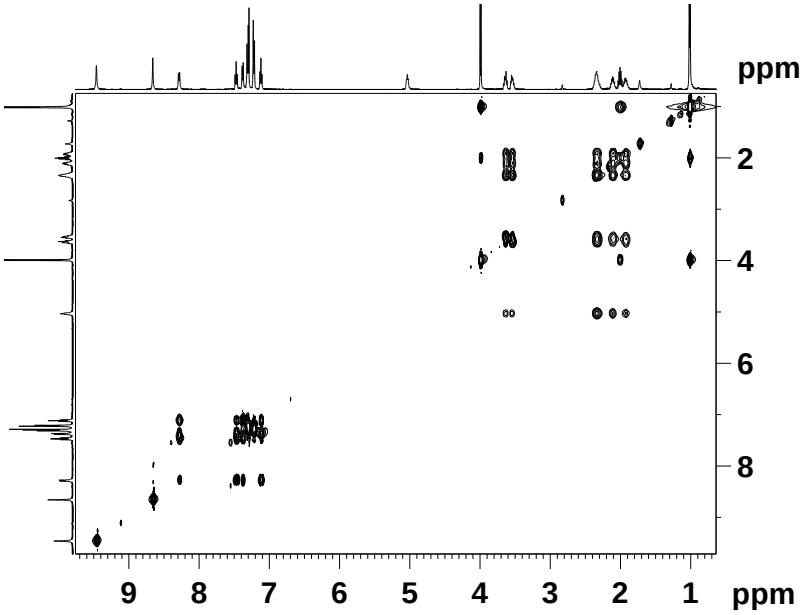


Figure 7: TOCSY spectra of amide **5** (400MHz, $CDCl_3$)

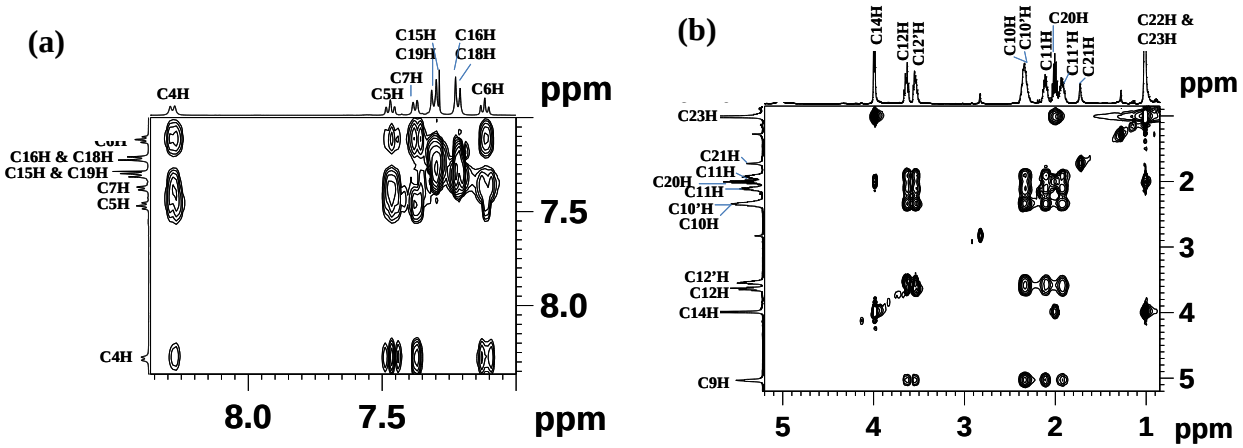


Figure 8: Partial TOCSY spectra of amide **5** (400MHz, $CDCl_3$): aromatic **(a)** and aliphatic regions **(b)**.

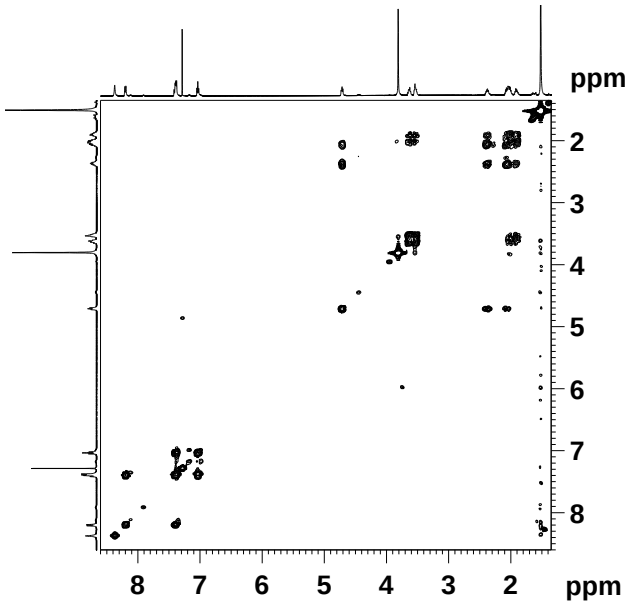


Figure 9: COSY spectra of ester **6** (400MHz, $CDCl_3$)

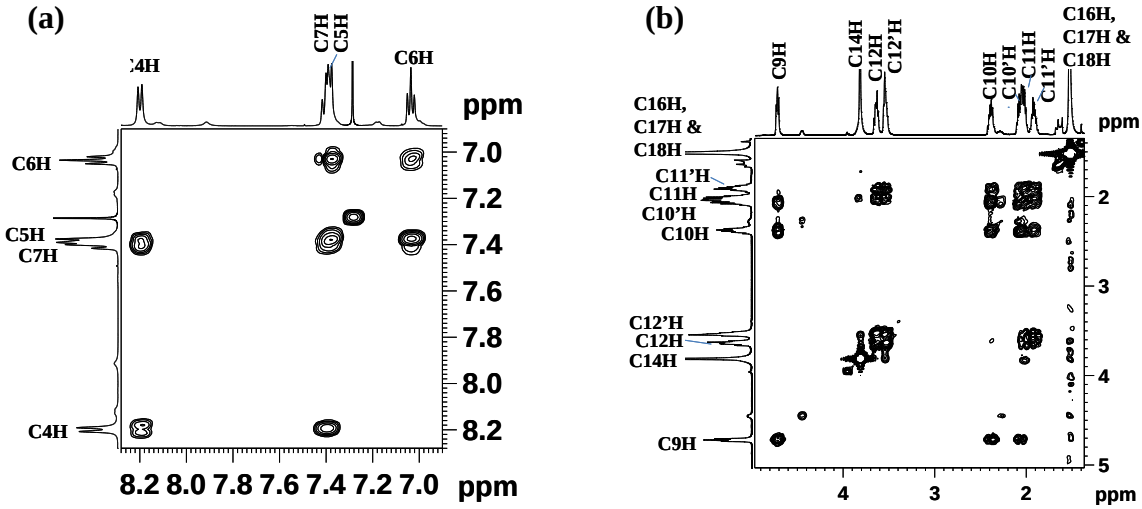


Figure 10: Partial COSY spectra of ester **6** (400MHz, $CDCl_3$): aromatic **(a)** and aliphatic regions **(b)**.

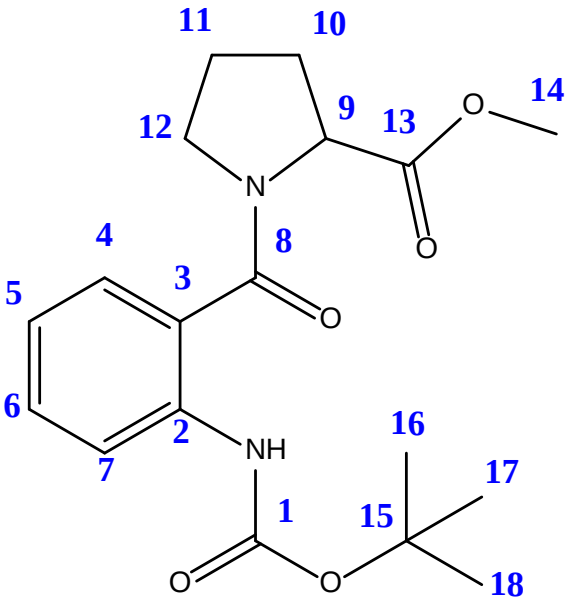


Figure 11: Molecular structure of Compound **6** (ester)

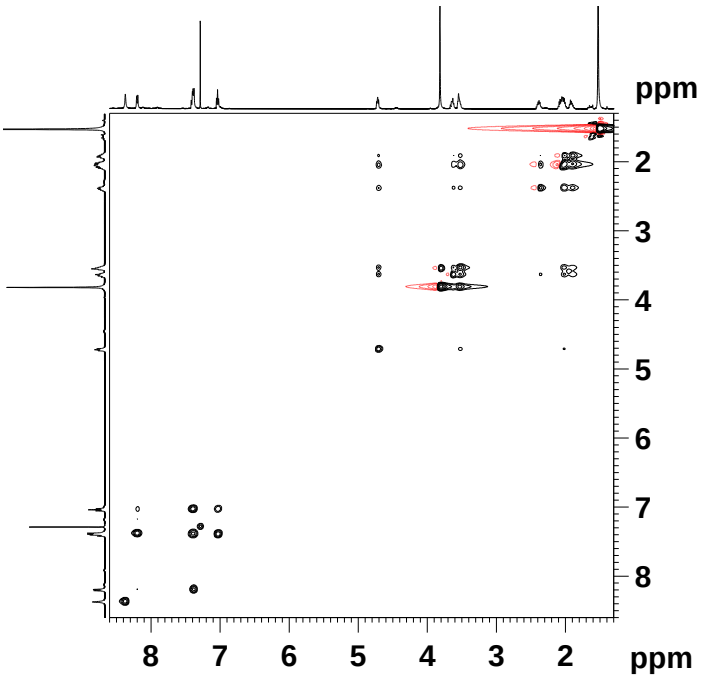


Figure 12: TOCSY spectra of ester **6** (400MHz, $CDCl_3$)

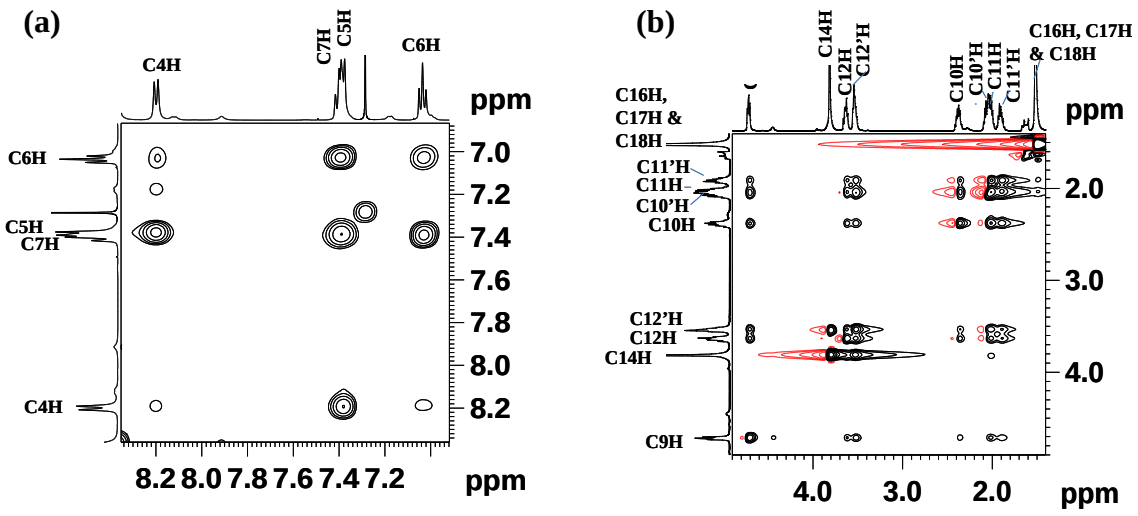


Figure 13: Partial TOCSY spectra of ester **6** (400MHz, $CDCl_3$): aromatic **(a)** and aliphatic regions **(b)**.

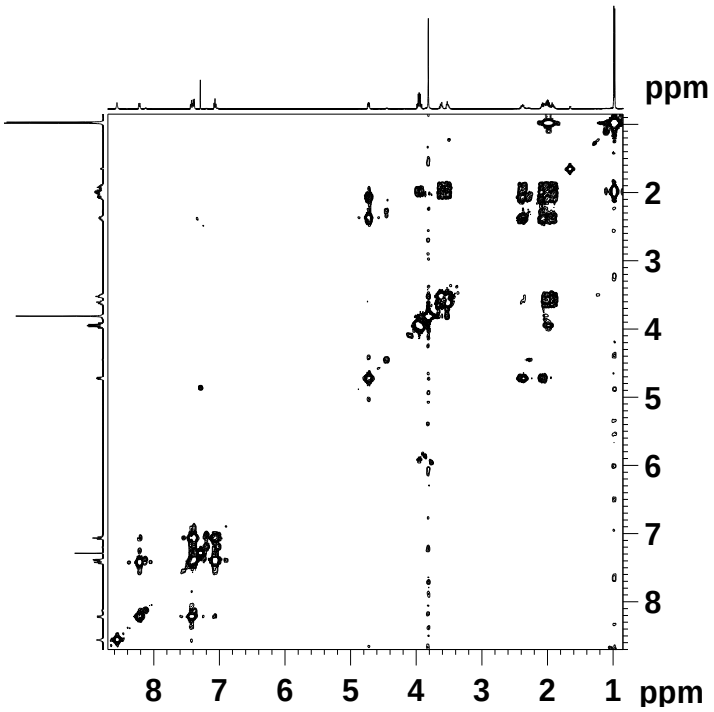


Figure 14: COSY spectra of ester **10** (400MHz, $CDCl_3$):

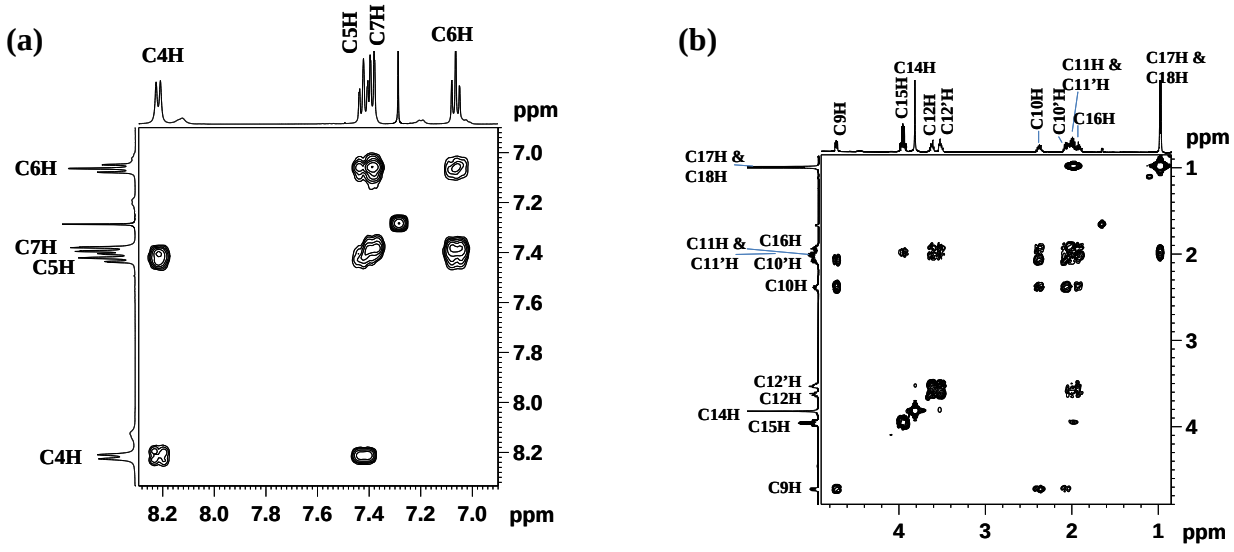


Figure 15: Partial COSY spectra of ester **10** (400MHz, $CDCl_3$): aromatic **(a)** and aliphatic regions **(b)**.

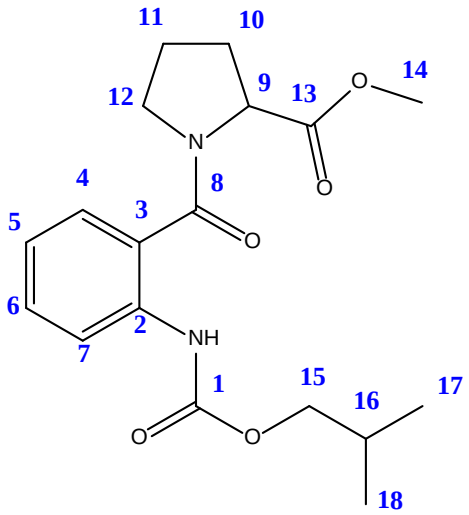


Figure 16: Molecular structure of Compound **10** (ester)

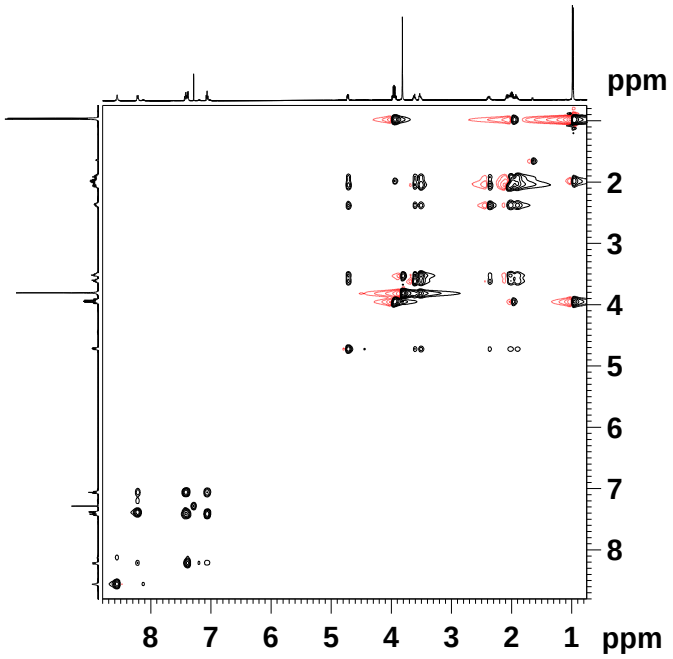


Figure 17: TOCSY spectra of ester **10** (400MHz, $CDCl_3$):

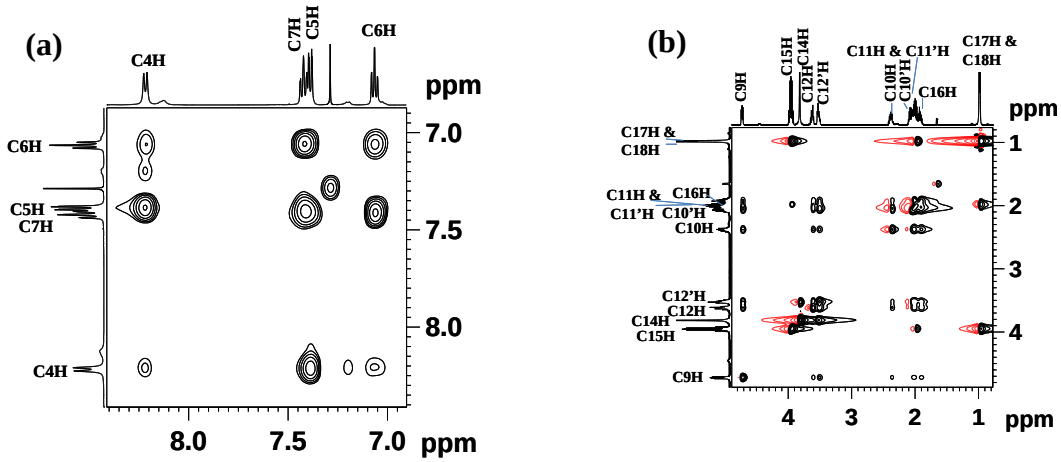


Figure 18: Partial TOCSY spectra of ester **10** (400MHz, $CDCl_3$): aromatic **(a)** and aliphatic regions **(b)**.

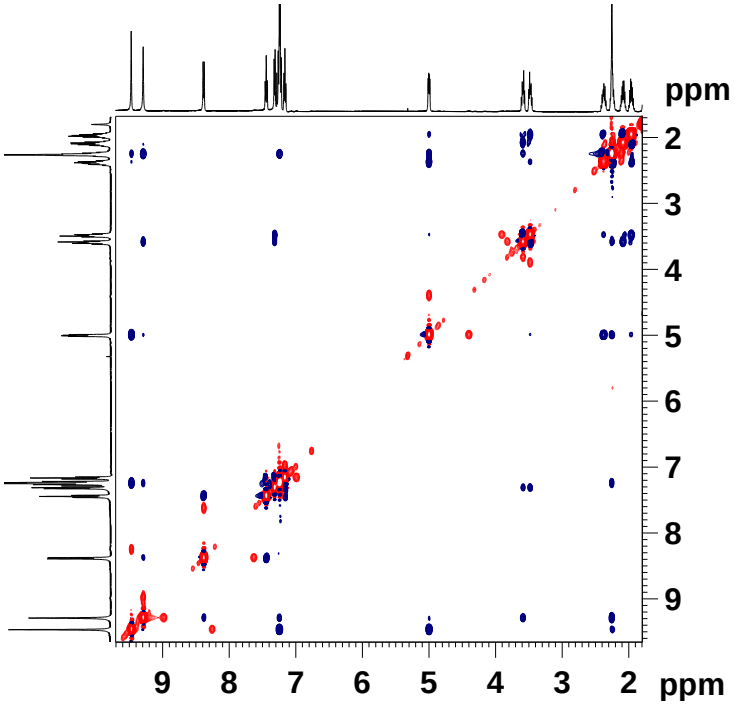


Figure 19: NOESY spectra of amide **1** (400MHz, $CDCl_3$)

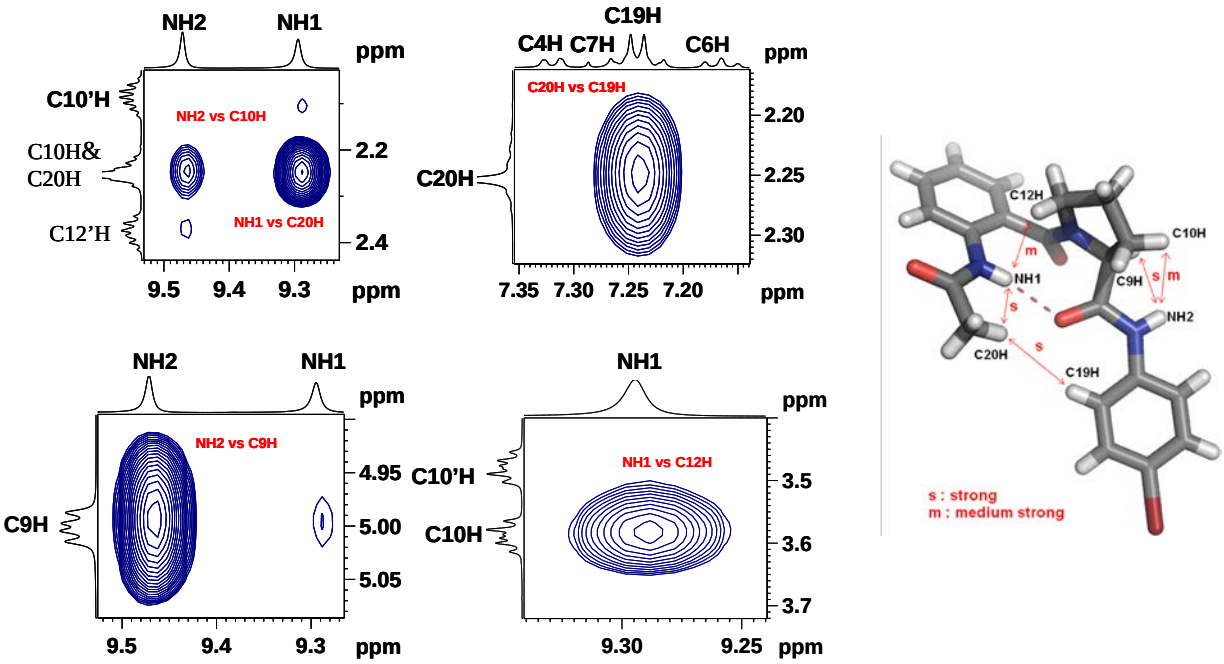


Figure 20: 2D NOESY extracts of amide **1** (400MHz, $CDCl_3$)

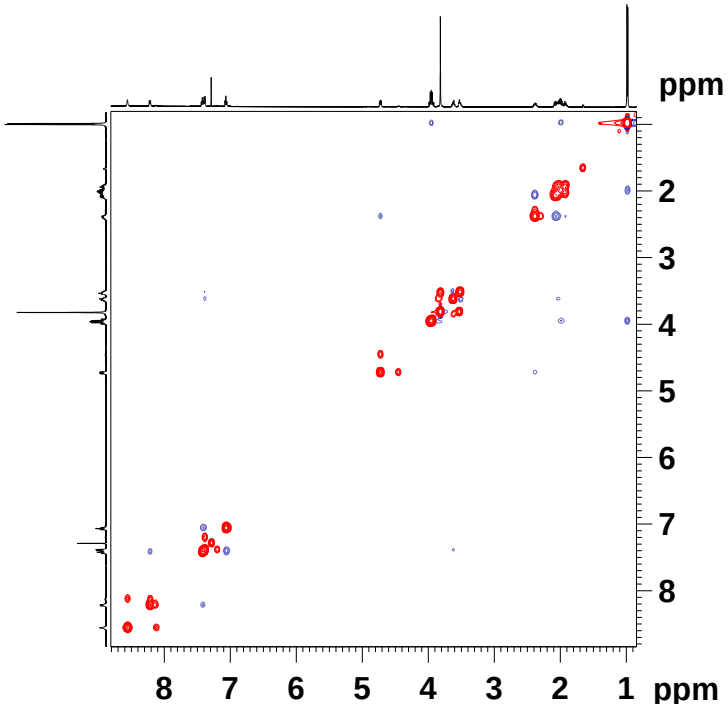
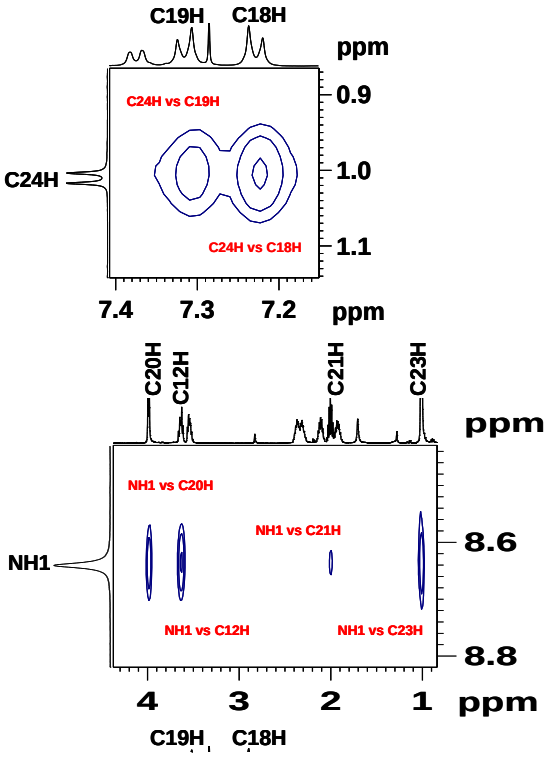


Figure 21: NOESY spectra of amide **5** (400MHz, $CDCl_3$)



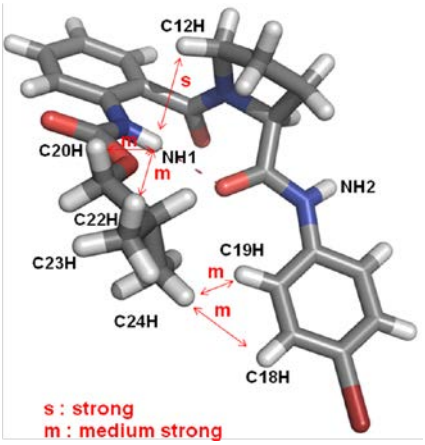


Figure 22: 2D NOESY extracts of amide **5** (400MHz, $CDCl_3$)

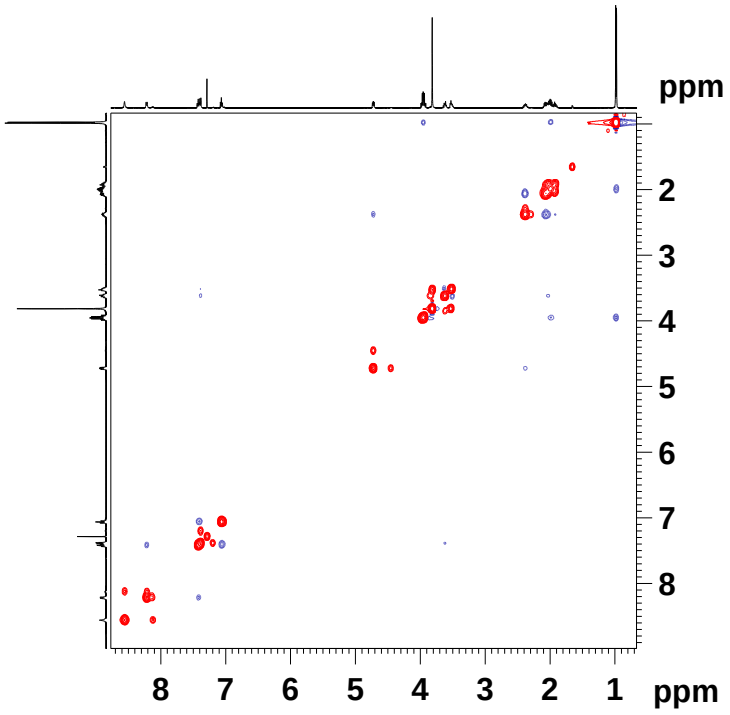


Figure 23: NOESY spectra of ester **10** (400MHz, $CDCl_3$)

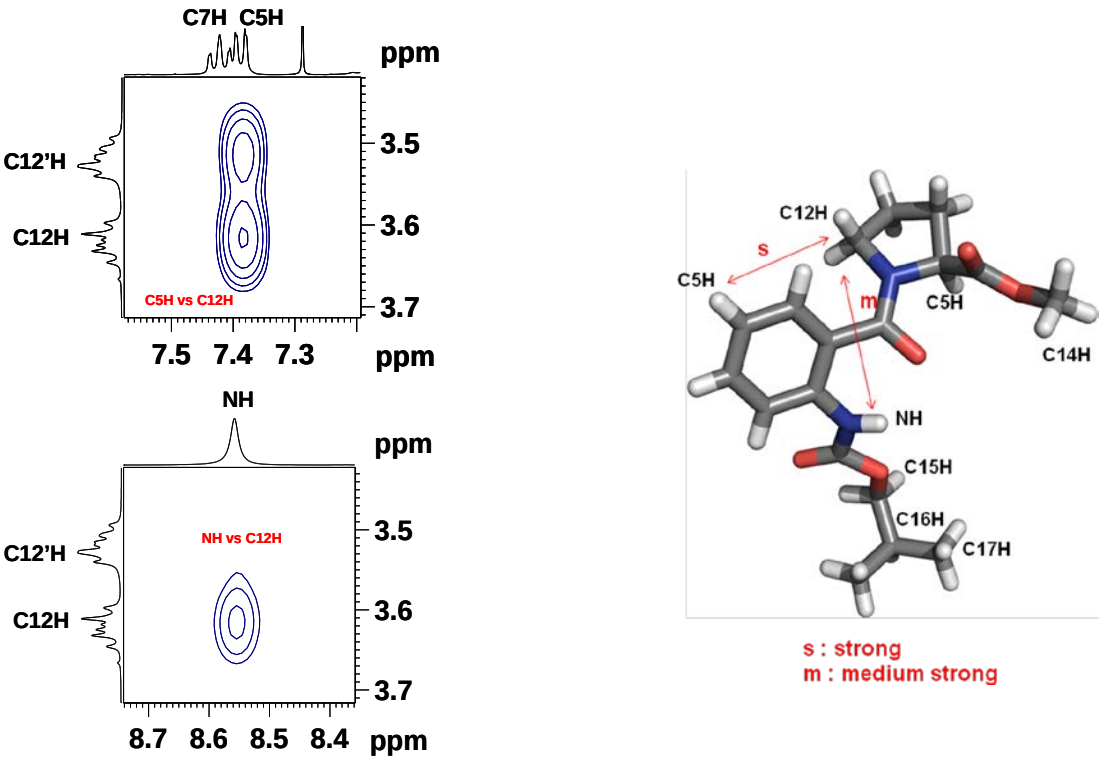


Figure 24: 2D NOESY extracts of ester **10** (400MHz, $CDCl_3$)

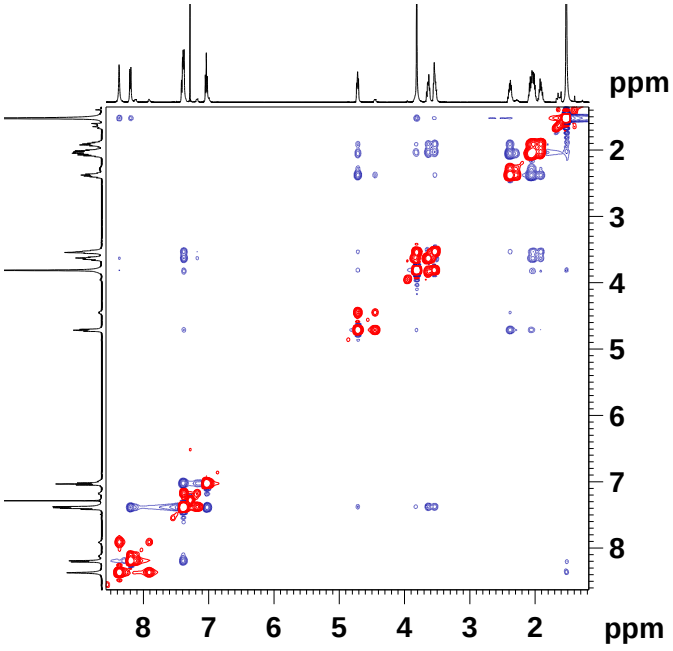


Figure 25: NOESY spectra of ester **6** (400MHz, $CDCl_3$)

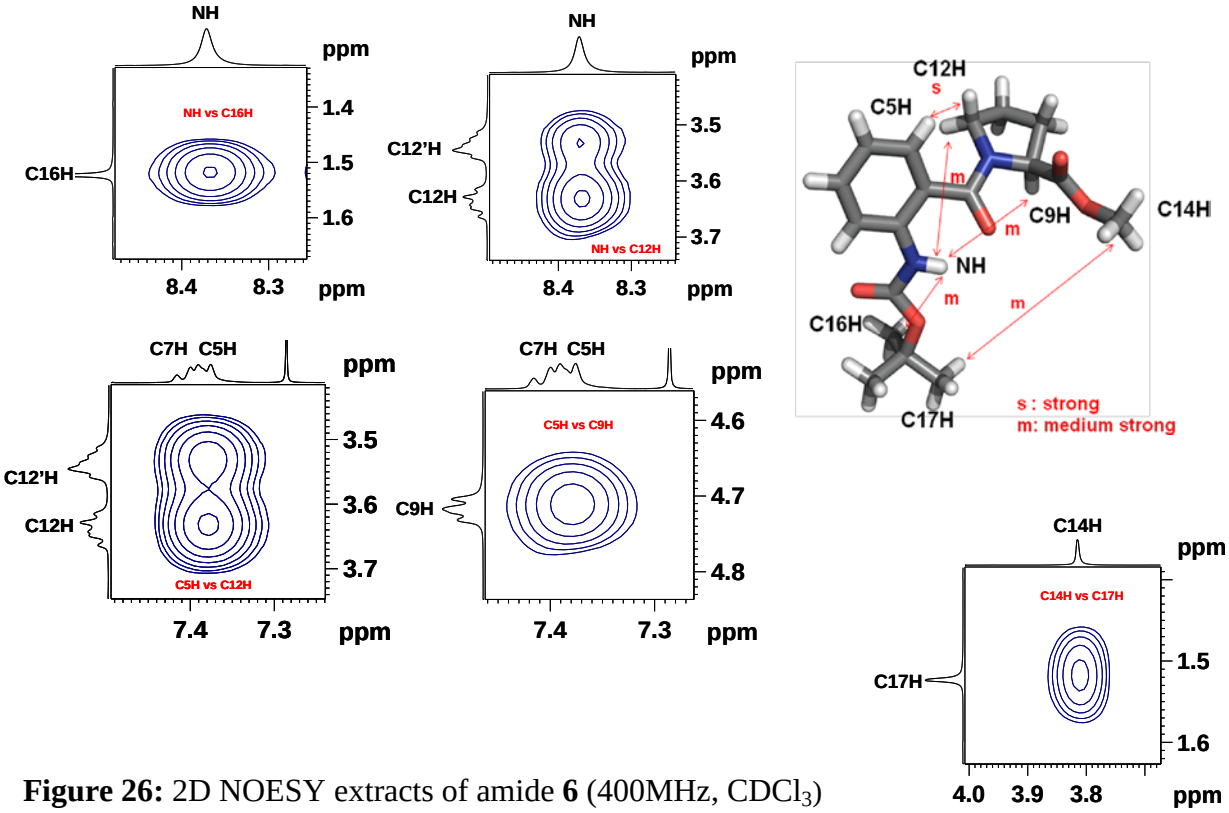
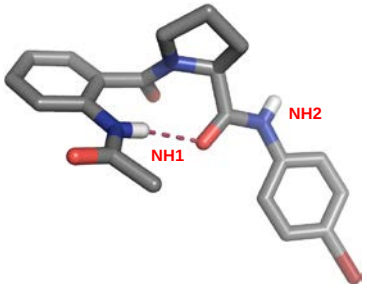


Figure 26: 2D NOESY extracts of amide **6** (400MHz, $CDCl_3$)

No:	$V_{DMSO\text{-}d6}$ (in μ lit)	δ_{NH2}	δ_{NH1}
1	0	9.15	9.15
2	5	9.36	9.18
3	10	9.48	9.2
4	15	9.57	9.21
5	20	9.63	9.21
6	25	9.67	9.22
7	30	9.71	9.21
8	35	9.73	9.21
9	40	9.75	9.2
10	45	9.77	9.19
11	50	9.77	9.18



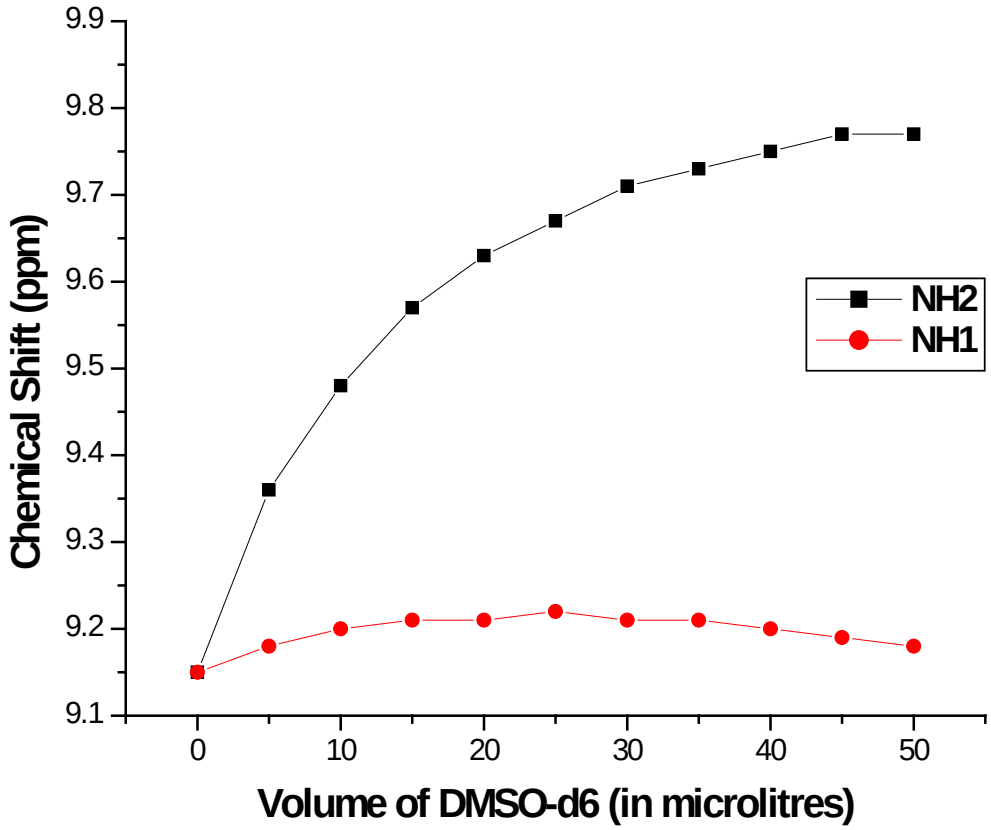
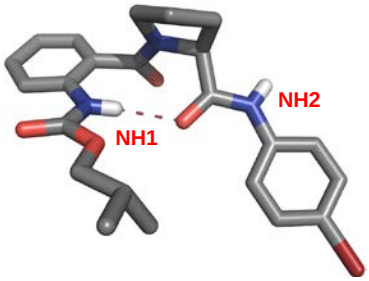


Figure 27: Titration study of 1 in $CDCl_3$ (5 mmol) with DMSO-d_6 (Volume of DMSO-d_6 added at each addition = 5 μl)

No:	$V_{DMSO\text{-}d6}$ (in μ lit)	δ_{NH2}	δ_{NH1}	Concentration in mMs
1	0	9.19	8.47	2
2	5	9.34	8.55	1.9802
3	10	9.42	8.59	1.9608
4	15	9.48	8.62	1.9418
5	20	9.54	8.64	1.9231
6	25	9.58	8.66	1.9048
7	30	9.6	8.66	1.8868
8	35	9.62	8.66	1.8692
9	40	9.64	8.66	1.8519
10	45	9.65	8.65	1.8349
11	50	9.66	8.65	1.8182



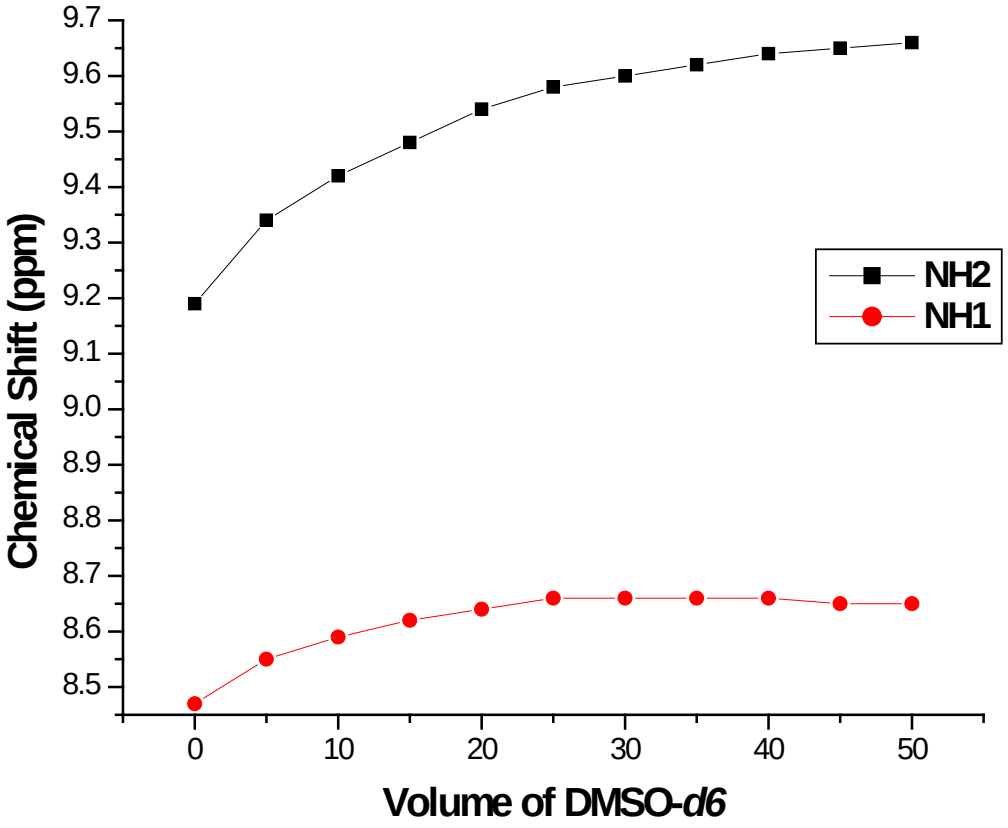
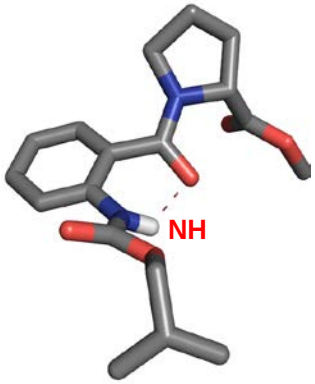


Figure 28: Titration study of 5 in $CDCl_3$ (2 mmol) with DMSO-d_6 (Volume of DMSO-d_6 added at each addition = 5 μl)

No:	**$V_{DMSO\text{-}d6}$ (in μ lit)**	**δ_{NH}**	Concentration in mM
1	0	8.55	2
2	5	8.53	1.9802
3	10	8.51	1.9608
4	15	8.49	1.9418
5	20	8.47	1.9231
6	25	8.45	1.9048
7	30	8.43	1.8868
8	35	8.41	1.8692
9	40	8.39	1.8519
10	45	8.38	1.8349
11	50	8.36	1.8182



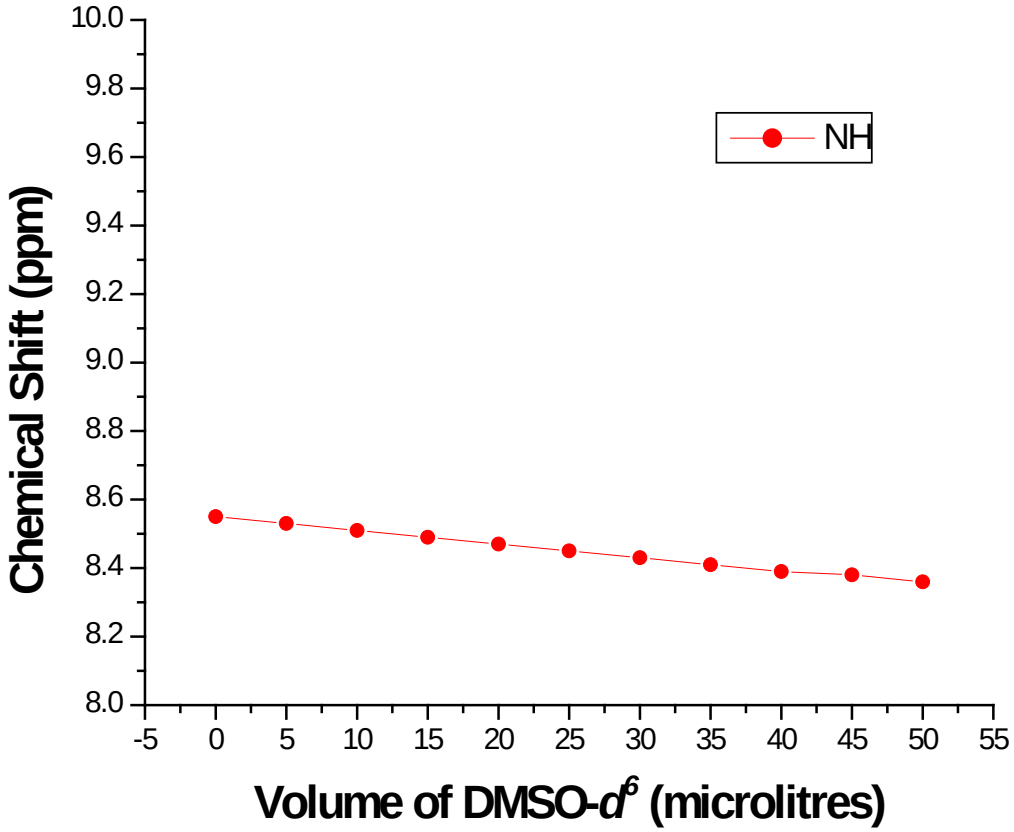


Figure 29: Titration study of 10 in $CDCl_3$ (2 mmol) with DMSO-d_6 (Volume of DMSO-d_6 added at each addition = 5 μl)

Crystal Data Table 1: Hydrogen bonding Parameters

Compound No.	Tortion angles (Deg,)				Hydrogen bonding Parameters			
	Ant		Pro		Distances (Å)		Angles (Deg.)	
	φ	ψ	φ	ψ	O...H	N...O	C=O..N	NH..O
Amides								
1	173.40	-65.37	-55.97	164.59	2.173	3.025	127.28	170.80
2	170.23	-69.58	-60.64	174.04	2.030	2.881	131.10	169.81
3	-172.38	-70.08	-58.82	164.32	2.259	3.075	123.31	158.34
4	176.23	-72.66	-55.94	166.62	2.108	2.960	132.15	171.33
5	166.51	-71.89	-56.49	162.41	2.178	3.033	127.17	172.17
Esters								
6	153.97	150.75	-61.60	-139.47	5.263	5.842	65.58	128.93
7	-177.80	140.07	-69.70	153.71	5.452	5.930	72.70	120.03
8	-144.62	146.41	-57.70	135.55	5.237	5.790	64.08	125.28
9	167.51	-144.35	-56.68	-38.27	4.737	5.552	48.65	156.00
10	-138.63	146.28	-59.04	134.8	5.366	5.874	62.70	122.65
11	-177.28	-130.50	-59.62	156.72	3.177	4.510	111.12	148.44

Crystal Data Table 2: Potential Hydrogen bonding parameters

Analysis of Potential Hydrogen Bonds for Compound **1**

Donor --- H....Acceptor		D - H	H...A	D...A	D - H...A
1 C(12A) --H(12A) ..O(1)	Inter	0.97	2.649	3.452	140
2 C(11A) --H(11A) ..N(1)	Inter	0.97	2.705	3.453	134
3 N(3) --H(3) ..O(2)	Inter	0.86	2.038	2.877	165
4 N(1) --H(1) ..O(3)	Intra	0.86	2.173	3.025	170

Analysis of Potential Hydrogen Bonds for Compound **2**

Donor --- H....Acceptor		D - H	H...A	D...A	D - H...A
1 C(23) --H(23B) ..N(1)	Inter	0.96	2.72	3.556	145
2 C(5) --H(5A) ..O(3)	Inter	0.97	2.37	3.169	138
3 N(4) --H(4) ..O(3)	Inter	0.86	2.06	2.859	154
4 N(2) --H(2) ..O(5)	Intra	0.93	2.03	2.881	170

Analysis of Potential Hydrogen Bonds for Compound **3**

Donor --- H....Acceptor		D - H	H...A	D...A	D - H...A
1 C(21) --H(21B) ..O(1)	intra	0.96	2.65	3.606	173
2 N(1) --H(1) ..O(4)	Intra	0.86	2.26	3.075	158
3 C(9) --H(9) ..O(3)	inter	0.98	2.63	3.178	115
4 N(3) –H(3) ..O(3)	Intra	0.86	2.08	2.911	161

Analysis of Potential Hydrogen Bonds for Compound **4**

Donor --- H....Acceptor		D - H	H...A	D...A	D - H...A
1C(20) --F(3) ..O(1)	Halogen bonding	1.334	2.898	3.607	111
2 N(1) --H(1) ..O(3)	intra	0.86	2.108	2.960	171
3 C(12) --H(12A) ..O(1)	inter	0.97	2.529	3.447	158
4 N(3) --H(3) ..O(2)	Inter	0.86	2.020	2.857	164
5 C(27) --Br(1) ..F(3)	Halogen bonding	1.895	3.020	4.867	163

Analysis of Potential Hydrogen Bonds for Compound **5**

Donor --- H....Acceptor		D - H	H...A	D...A	D - H...A
1 N(1) --H(1) ..O(3)	Intra	0.86	2.17	3.033	172
2 C(9) --H(9) ..O(2)	inter	0.98	2.63	3.193	116
3 C(12) --H(12B) ..O(1)	inter	0.97	2.32	3.140	141
4 N(3) --H(3) ..O(2)	Inter	0.86	2.06	2.87	157

Analysis of Potential Hydrogen Bonds for Compound **6**

Donor --- H....Acceptor		D - H	H...A	D...A	D - H...A
1 C(6) --H(6) ..O(1)	Inter	0.93	2.53	3.425	160
2 C(4) --H(4) ..O(3)	Inter	0.93	2.71	3.551	150
3 C(11) –H(11A) ..O(5)	inter	0.97	2.71	3.623	158
4 C(12) –H(12B) ..O(2)	inter	0.97	2.29	3.351	136
5 C(14) --H(14A) ..O(3)	Inter	0.96	3.15	3.205	84
6 C(14) --H(14B) ..O(3)	Inter	0.96	2.84	3.205	103
7 C(14) --H(14C) ..O(3)	Inter	0.96	3.09	3.205	88
8 N(1) --H(1) ..O(3)	Intra	0.86	2.02	2.685	133

Analysis of Potential Hydrogen Bonds for Compound **7**

Donor --- H....Acceptor		D - H	H...A	D...A	D - H...A
1 C(5) --H(5) ..O(2)		0.93	2.68	3.416	137
2 C(20) --H(20) ..O(3)	Intra	0.93	2.74	3.641	163
3 N(1) --H(1) ..O(3)	Intra	0.86	2.17	2.806	131

Analysis of Potential Hydrogen Bonds for Compound **8**

Donor --- H....Acceptor		D - H	H...A	D...A	D - H...A
1 C(16) --H(16B) ..O(3)	Inter	0.98	2.63	3.577	163
2 C(6) --H(6) ..O(1)	Inter	0.95	2.35	3.291	151

3	C(4) --H(4) ..O(3)	Inter	0.95	2.46	3.322	174
4	C(11) --H(11A) ..O(5)	Inter	0.99	2.65	3.533	148
5	C(12) --H(12A) ..O(3)	Inter	0.99	2.65	3.623	165
6	C(12) --H(12B) ..O(2)	Inter	0.99	2.46	3.285	141
7	C(14) --H(14A) ..O(3)	Inter	0.98	3.16	3.152	81
8	C(14) --H(14B) ..O(3)	Inter	0.98	2.76	3.152	105
9	C(14) --H(14C) ..O(3)	Inter	0.98	3.02	3.152	105
10	N(1) --H(1) ..O(2)	Intra	0.88	2.07	2.681	126

Analysis of Potential Hydrogen Bonds for Compound **9**

	Donor --- H....Acceptor		D - H	H...A	D...A	D - H...A
1	C(25) --H(25C) ..O(3)	Inter	0.98	2.51	3.346	143
2	C(4) --H(4) ..O(2)	Inter	0.95	2.38	3.284	158
3	C(23) --H(23B) ..O(1)	Inter	0.98	2.60	3.468	148
4	C(15) --H(15A) ..O(2)	Inter	0.99	2.65	3.938	145
5	C(18) --H(18B) ..O(4)	Intra	0.99	2.41	2.818	104
6	C(14) --H(14) ..O(3)	Intra	1.00	2.50	2.691	90
7	C(17) --H(17A) ..O(5)	Intra	0.99	2.62	3.432	139
8	N(1) --H(1) ..O(2)	Intra	0.88	2.02	2.711	134

Analysis of Potential Hydrogen Bonds for Compound **10**

	Donor --- H....Acceptor		D - H	H...A	D...A	D - H...A
1	C(12) --H(12A) ..O(3)	inter	0.97	2.67	3.634	171
2	C(12) --H(12B) ..O(2)	Inter	0.97	2.64	3.382	133
3	N(1) –H(1) ..O(2)	Intra	0.86	2.14	2.710	123

Analysis of Potential Hydrogen Bonds for Compound **11**

	Donor --- H....Acceptor		D - H	H...A	D...A	D - H...A
1	C(17) --H(17) ..O(4)	inter	0.93	2.668	3.488	148
2	C(16) --H(16) ..O(3)	intra	0.93	2.589	3.486	162
3	N(1) --H(1) ..O(3)	Intra	0.86	3.177	3.936	148
4	N(1) --H(1) ..O(2)	Intra	0.86	2.185	2.798	128
5	C(5) --H(5) ..O(1)	inter	0.93	2.634	3.367	136

Single Crystal X-ray Crystallographic Data.

Crystal Data for the compounds **1-11** were collected at *T* = 293 K, on SMART APEX CCD Single Crystal X-ray diffractometer using Mo KR radiation (λ) 0.7107 Å). The structures were solved by direct methods using SHELXTL. All the data were corrected for Lorentz polarization and absorption effects. SHELX-97 (ShelxTL) was used for structure solution and full matrix least-squares refinement on *F*2. Hydrogen atoms were included in the refinement in the riding mode. The refinements were carried out using SHELXL-97.[4]

Crystal Data for 1. Single crystals of **1** were grown by slow evaporation of the mixture of methanol and dichloromethane. Colorless prism crystals of approximate size 0.31 x 0.21 x 0.12 mm, was used for data collection. Temperature = 297 K, Wave length = 0.71073 Å, Hemisphere acquisition. Total scans = 4, F(000) = 440, θ range = 1.90 to 25.00, completeness to θ of 25.00º is 99.6 %, SADABS correction applied, Goodness-of-fit on F2 = 0.990, $C_{20}H_{20}Br\ N_3O_3$, *M* = 430.30. Crystals belong to Monoclinic, space group P21, *a* = 11.1418(8), *b* = 7.1748(5), *c* = 12.9148(10) Å, *V* = 994.55(13) Å^3, *Z* = 2, D_c = 1.437 mg m^{-3}, μ (Mo-K$_\alpha$) = 2.091 mm^{-1}, 5062 reflections measured, 2888 unique [I>2σ(I)], R value 0.0297, wR2 = 0.0714.

Crystal Data for 2. Single crystals of **2** were grown by slow evaporation of the mixture of ethyl acetate and pet. ether. Colorless needle of approximate size 0.17 x 0.12 x 0.12 mm, was used for data collection. Temperature = 295 K, Wave length = 0.71073 Å, Hemisphere acquisition. Total scans = 3, F(000) = 952, θ range = 2.11 to 24.99º, completeness to θ of 24.99º is 100.0 %. SADABS correction applied, Goodness-of-fit on F2 = 0.999 $C_{23}H_{32}N_4O_5$, *M* = 444.53. Crystals belong to Orthorhombic, space group $P2_12_12_1$, *a* = 8.9732 (8), *b* = 10.4292 (9), *c* = 25.653 (2) Å, *V* = 2400.7 (4) Å^3, *Z* = 4, D_c = 1.230 mg m^{-3}, μ (Mo-K$_\alpha$) = 0.088 mm^{-1}, 12181 reflections measured, 4239 unique [I>2σ(I)], R value 0.0467, wR2 = 0.1223.

Crystal Data for 3. Single crystals of **3** were grown by slow evaporation of the mixture of methanol and dichloromethane. Colorless plate of approximate size 0.17 x 0.12 x 0.02 mm, was used for data collection. Temperature = 296 K, Wave length = 0.71073 Å, Total scans = 4, F(000) = 944, θ range = 1.62 to 25.00º, completeness to θ of 24.99º is 100.0 %. SADABS correction applied, Goodness-of-fit on F2 = 1.203, $C_{21}H_{22}BrN_3O_4$, *M* = 460.33. Crystals belong to Orthorhombic, space group $P2_12_12_1$, *a* = 7.1599(7), *b* = 11.8460(11), *c* = 25.160(2) Å, *V* = 2134.0(4) Å^3, *Z* = 4, D_c = 1.433 mg m^{-3}, μ (Mo-K$_\alpha$) = 1.958 mm^{-1}, 17385 reflections measured, 3754 unique [I>2σ(I)], R value 0.0749, wR2 = 0.1330.

Crystal Data for 4. Single crystals of **4** were grown by slow evaporation of the mixture of methanol. Colorless thin plate of approximate size 0.48 x 0.14 x 0.02 mm, was used for data collection. Temperature = 297 K, Wave length = 0.71073 Å, Total scans = 4, F(000) = 488, θ range = 1.89 to 25.00º, completeness to θ of 25.00º is 99.7 %. SADABS correction applied, Goodness-of-fit on F2 = 0.985, $C_{20}H_{17}BrF_3N_3O_3$, *M* = 484.28. Crystals belong to monoclinic, space group P21, *a* = 11.016(5), *b* = 7.612(3), *c* = 12.920(5) Å, *V* = 1059.2(7) Å^3, *Z* = 2, D_c = 1.518 mg m^{-3}, μ (Mo-K$_\alpha$) = 1.992 mm^{-1}, 5304 reflections measured, 3754 unique [I>2σ(I)], R value 0.0469, wR2 = 0.0954.

Crystal Data for 5. Single crystals of **5** were grown by slow evaporation of the mixture of methanol. Colorless needle of approximate size 0.62 x 0.15 x 0.11 mm, was used for data collection. Temperature = 297 K, Wave length = 0.71073 Å, Total scans = 4, F(000) = 504, θ range = 2.19 to 25.00º, completeness to θ of 25.00º is 98.7 %. SADABS correction applied, Goodness-of-fit on F2 = 1.203, $C_{23}H_{26}BrN_3O_4$, *M* = 488.38. Crystals belong to monoclinic, space group P21, *a* = 12.8420(19), *b* = 7.0231(10), *c* = 13.3863(19) Å, *V* = 1207.3(3) $Å^3$, *Z* = 2, D_c = 1.343 mg m^{-3}, μ (Mo-K_α) = 1.734 mm^{-1}, 9259 reflections measured, 4152 unique [I>2σ(I)], R value 0.1045, wR2 = 0.1533.

Crystal Data for 6. Single crystals of **6** were grown by slow evaporation of the mixture of methanol and dichloromethane. Colorless needle of approximate size 1.37 x 0.54 x 0.47 mm, was used for data collection. Temperature = 297 K, Wave length = 0.71073 Å, Total scans = 4, F(000) = 744, θ range = 2.28 to 25.00º, completeness to θ of 25.00º is 99.8 %. SADABS correction applied, Goodness-of-fit on F2 = 1.042, $C_{18}H_{24}N_2O_5$, *M* = 348.39. Crystals belong to orthorhombic, space group P2(1)2(1)2(1), *a* = 8.547(5), *b* = 9.694(5), *c* = 22.943(12) Å,. *V* = 1900.9(18) $Å^3$, *Z* = 4, D_c = 1.217 mg m^{-3}, μ (Mo-K_α) = 0.089 mm^{-1}, 18354 reflections measured, 3348 unique [I>2σ(I)], R value 0.0479, wR2 = 0.1257.

Crystal Data for 7. Single crystals of **7** were grown by slow evaporation of the mixture of ethylacetate and pet. ether. Colorless rectangular crystals of approximate size 0.43 x 0.31 x 0.14 mm, was used for data collection. Temperature = 296 K, Wave length = 0.71073 Å, Total scans = 4, F(000) = 904, θ range = 2.09 to 25.00º, completeness to θ of 25.00º is 100 %. SADABS correction applied, Goodness-of-fit on F2 = 1.066, $C_{24}H_{28}N_2O_5$, *M* = 424.48. Crystals belong to orthorhombic, space group P2(1)2(1)2(1), *a* = 10.6231(7), *b* = 10.9569(7), *c* = 19.5280(12) Å, *V* = 2273.0(3) $Å^3$, *Z* = 4, D_c = 1.240 mg m^{-3}, μ (Mo-K_α) = 0.087 mm^{-1}, 11578 reflections measured, 4004 unique [I>2σ(I)], R value 0.0402, wR2 = 0.0946.

Crystal Data for 8. Single crystals of **8** were grown by slow evaporation of the mixture of ethylacetate and pet. ether. Colorless thick plate crystals of approximate size 0.50 x 0.27 x 0.22 mm, was used for data collection. Temperature = 173 K, Wave length = 0.71073 Å, Total scans = 4, F(000) = 680, θ range = 2.318 to 28.349º, completeness to θ of 28.41º is 99.1 %. SADABS correction applied, Goodness-of-fit on F2 = 1.031, $C_{16}H_{20}N_2O_5$, M = 320.34. Crystals belong to orthorhombic, space group P2(1)2(1)2(1), a = 8.111(2), b = 9.756(2), c = 20.126(6) Å, V = 1592.6(7) Å3, Z = 4, Dc = 1.336 mg m-3, μ (Mo-K_α) = 0.100 mm-1, 8457 reflections measured, 3901 unique [I>2s(I)], R value 0.0353, wR2 = 0.0823.

Crystal Data for 9. Single crystals of **9** were grown by slow evaporation of the mixture of ethylacetate and pet. ether. Colorless block crystals of approximate size 0.62 x 0.59 x 0.27 mm, was used for data collection. Temperature = 100 K, Wave length = 0.71073 Å, Total scans = 4, F(000) = 952, θ range = 2.10 to 25.00º, completeness to θ of 25.00º is 99.8 %. SADABS correction applied, Goodness-of-fit on F2 = 1.090, $C_{25}H_{34}N_2O_5$, *M* = 442.54. Crystals belong to orthorhombic, space group P2(1)2(1)2(1), *a* = 7.4115(4), *b* = 16.5480(9), *c* = 19.3577(11) Å, *V* = 2374.1(2) $Å^3$, *Z* = 4, D_c = 1.238 mg m^{-3}, μ (Mo-K_α) = 0.086 mm^{-1}, 17494 reflections measured, 4176 unique [I>2σ(I)], R value 0.0442, wR2 = 0.1054.

Crystal Data for 10. Single crystals of **10** were grown by slow evaporation of the mixture of ethylacetate and pet. ether. Colorless plate crystals of approximate size 0.44 x 0.34 x 0.14 mm, was used for data collection. Temperature = 297 K, Wave length = 0.71073 Å, Total scans = 4, F(000) = 744, θ range = 1.77 to 25.00º, completeness to θ of 25.00º is 100 %. SADABS correction applied, Goodness-of-fit on F2 = 1.062, $C_{18}H2_4N_2O_5$, *M* = 348.39. Crystals belong to orthorhombic, space group P2(1)2(1)2(1), *a* = 8.3515(8), *b* = 9.6398(9), *c* = 22.979(2) Å, *V* = 1850.0(3) $Å^3$, *Z* = 4, D_c = 1.251 mg m^{-3}, μ (Mo-K_α) = 0.092 mm^{-1}, 9400 reflections measured, 3251 unique [I>2σ(I)], R value 0.0430, wR2 = 0.1150.

Crystal Data for 11. Single crystals of **11** were grown by slow evaporation of the mixture of diethylether and pet. ether. Colorless plate crystals of approximate size 0.24 x 0.12 x 0.03 mm, was used for data collection. Temperature = 297 K, Wave length = 0.71073 Å, Total scans = 4, F(000) = 744, θ range = 1.96 to 25.99º, completeness to θ of 25.99º is 99.9 %. SADABS correction applied, Goodness-of-fit on F2 = 1.117, $C_{40}H_{40}N_4O_8$, *M* = 704.76. Crystals belong to orthorhombic, space group P2(1)2(1)2(1), *a* = 8.173(5), *b* = 13.001(8), *c* = 17.350(11) Å, *V* = 1843.5(19) $Å^3$, *Z* = 2, D_c = 1.270 mg m^{-3}, μ (Mo-K_α) = 0.089 mm^{-1}, 10075 reflections measured, 3616 unique [I>2σ(I)], R value 0.0488, wR2 = 0.1084.

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