Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Evaluation of stereochemically dense morpholine-based scaffolds as proline surrogates in β-turn peptides

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ELECTRONIC SUPPLEMENTARY INFORMATION

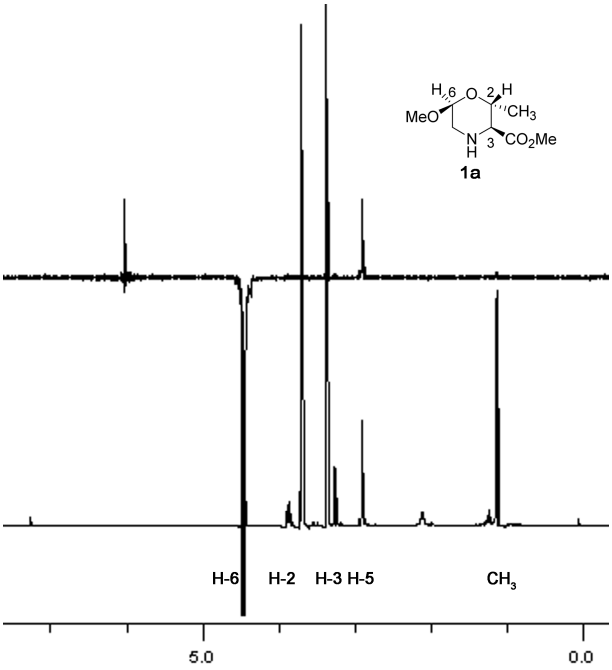


Fig. S1 NOe irradiation of H-6 of compound **1a** at 4.44 ppm (NOESY1D, mixing time of 500 ms): the nOe correlations between H-6 and H-2 are not present.

H-Gly-D-Leu-D-Val-OMe. Peptide H-Gly-D-Leu-D-Val-OMe was prepared using standard protocols for solution phase peptide synthesis using Boc-glycine Boc-D-leucine and D-valine methyl ester hydrochlorides as starting materials. δ_H (400 MHz, DMSO-d_6) 8.47 (d, J = 8.0 Hz, 1H, NH), 8.32 (d, J = 8.0 Hz, 1 H, NH), 8.02 (br, 3 H), 4.49 (q, J = 8.0 Hz, 1 H, D-Leu H-α), 4.11 (t, J = 7.2 Hz, 1 H, D-Val H-α), 3.59 (s, 3 H, OCH_3), 2.60 (m, 2 H, Gly H-α), 2.01 (septet, J = 7.2 Hz, 1 H, D-Val H-β), 1.59 (septet, J = 6.8 Hz, 1 H, D-Leu H-γ), 1.41 (t, J = 6.8 Hz, 2 H, D-Leu H-β), 0.88-0.84 (m, 12 H, D-Leu H-δ and D-Val H-γ).

H-Mor-Gly-D-Leu-D-Val-OMe (9a). Tripeptide H-Gly-D-Leu-D-Val-OMe (125 mg, 0.30 mmol) was suspended in CH_2Cl_2 (3 mL) and DIPEA (177 μL, 1.10 mmol) was added. The mixture was stirred until a clear solution was obtained, and Fmoc-amino acid **8** (100 mg, 0.27 mmol) and TBTU (96 mg, 0.30 mmol) were sequentially added. The reaction mixture was stirred 4 hours at room temperature and then CH_2Cl_2 was evaporated. The resultant oil was dissolved in EtOAc, washed with 1M HCl, 5% Na_2CO_3, brine and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated to dryness to yield a solid that was treated with a 30% Et_2NH in CH_3CN (3 mL). The Fmoc deprotection was monitored by

TLC. When complete conversion was obtained, volatiles were removed under reduced pressure and the residue was eluted over silica gel (Et_2O/MeOH 30:1 to pure MeOH) to yield amine **9a** as a white solid (110 mg, 95%). (Found: C, 56.18; H, 8.55; N, 12.98. $C_{20}H_{36}N_4O_6$ requires C, 56.06; H, 8.47; N, 13.07%). $[\alpha]_D^{21}$ = -44.6 (c 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.50 (br, 1 H, NH), 6.63 (br, 1 H, NH), 6.45 (d, *J* = 8.4 Hz, 1 H, NH), 4.53-4.43 (m, 2 H), 3.92 (dd, *J* = 15.6, 5.6 Hz, 1 H), 3.88-3.79 (m, 2 H), 3.73 (s, 3 H, OCH_3), 3.63 (t, *J* = 12.0 Hz, 1 H), 3.45 (m, 1 H), 3.17 (d, *J* = 8.0 Hz, 1 H), 2.97 (t, *J* = 12.0 Hz, 1 H), 2.1 (m, 1 H, D-Val H-β), 1.83 (br, 1 H, H-4), 1.55 (m, 2 H, D-Leu H-β), 1.53 (t, *J* = 8.0 Hz, 1 H, D-Leu H-γ), 1.23 (d, *J* = 5.6 Hz, 3 H, CH_3-C-2), 0.95-0.85 (m, 12 H, D-Leu H-δ and D-Val H-γ); δ_C (60 MHz, $CDCl_3$) 172.2 (s, CO), 172.1 (s, CO), 171.9 (s, CO), 168.7 (s, $\underline{C}O_2Me$), 74.8, (d), 67.3 (t), 65.4 (d, C-2), 57.2 (d), 52.1 (d), 51.9 (q, OCH_3), 44.2 (t), 42.6 (t), 41.2 (t), 31.1 (d), 24.6 (d), 22.8 (q, CH_3), 22.0 (q, CH_3), 18.9 (q, CH_3), 18.3 (q, CH_3), 17.9 (q, CH_3). ESI-MSMS *m*/*z* 429.47 (M^++1, 16), 397.19 (M^+-OMe, 28), 298.11 [M^+-(D-Val_2OMe), 100].

H-[(6*S*)-methoxy]-Mor-Gly-D-Leu-D-Val-OMe (9b). Tripeptide H-Gly-D-Leu-D-Val-OMe (120 mg, 0.29 mmol) was suspended in CH_2Cl_2 (3 mL) and DIPEA (181 μL, 1.06 mmol) was added. The mixture was stirred until a clear solution was obtained, then **4** (105 mg, 0.26 mmol) and TBTU (93 mg, 0.29 mmol) were sequentially added. The reaction mixture was stirred 4 hours at room temperature, then CH_2Cl_2 was evaporated. The resultant oil was dissolved in EtOAc, washed with 1M HCl, 5% Na_2CO_3, brine and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated to dryness to yield a solid that was treated with 30% Et_2NH in CH_3CN (3 mL). The Fmoc deprotection was monitored by TLC, and after complete conversion was obtained, volatiles were removed under reduced pressure and the residue was eluted over silica gel (Et_2O/MeOH 30:1 to pure MeOH) to yield amine **9b** as a white solid (114 mg, 96%). (Found: C, 55.12; H, 8.42; N, 12.13. $C_{21}H_{38}N_4O_7$ requires C, 55.00; H, 8.35; N, 12.22%). $[\alpha]_D^{21}$ = +46.0 (c 1.24, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.33 (t, *J* = 6.0 Hz, 1H, NH), 6.55 (d, *J* = 8.4 Hz, 1 H, NH), 6.44 (d, *J* = 8.8 Hz, 1 H, NH), 4.55 (s, 1 H, H-6), 4.50 (dd, *J* = 8.8, 4.0 Hz, 1 H), 4.46-4.41 (m, 1 H), 3.98 (dd, *J* = 16.0, 6.0 Hz, 1 H), 3.91 (m, 1 H), 3.84 (dd, *J* = 16.0, 6.0 Hz, 1 H), 3.73 (s, 3 H, CO_2CH_3), 3.39 (s, 3 H, OCH_3), 3.13 (d, *J* = 9.6 Hz, 1 H), 2.96 (dd, *J* = 13.2, 3.6 Hz, 1 H), 2.89 (d, *J* = 13.2 Hz, 1 H), 2.10 (m 1 H, D-Val H-β), 1.71 (br, 1 H, H-4), 1.69-1.61 (m, 2 H, D-Leu H-β), 1.55-1.50 (m, 1 H, D-Leu H-γ), 1.25 (d, *J* = 6.4 Hz, 3 H, CH_3-C-2), 0.94-0.88 (m, 12 H, D-Leu H-δ and D-Val H-γ); δ_C (60 MHz, $CDCl_3$) 172.0 (s, CO), 171.8 (s, CO), 171.4 (s, CO), 168.5 (s, $\underline{C}O_2Me$), 95.9 (d, C-6), 65.7 (t), 65.7 (d), 64.3 (d), 57.2 (d), 54.5 (q, OCH_3), 52.1 (d), 51.9 (d), 47.2 (t), 42.8 (t), 41.3

(t), 31.1 (d), 24.7 (d), 22.8 (q), 22.2 (q), 19.0 (q), 18.5 (q), 17.9 (q). ESI-MSMS *m*/*z* 459.46 (M^++1, 67), 427.00 (M^+-OMe, 100), 322.23 [M^+-(OMe)Mor+Na, 100].

H-[(6*R*)-methoxy]-Mor-Gly-D-Leu-D-Val-OMe (9c). Tripeptide H-Gly-D-Leu-D-Val-OMe (120 mg, 0.29 mmol) was suspended in CH_2Cl_2 (3 mL) and DIPEA (181 μL, 1.06 mmol) was added. The mixture was stirred until a clear solution was obtained and Fmoc-amino acid **5** (105 mg, 0.26 mmol) and TBTU (93 mg, 0.29 mmol) were sequentially added. The reaction mixture was stirred 4 hours at room temperature and then CH_2Cl_2 was evaporated. The resultant oil was dissolved in EtOAc, washed with 1M HCl, 5% Na_2CO_3, brine and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated to dryness to yield a solid that was treated with 30% Et_2NH in CH_3CN (3 mL). The Fmoc deprotection was monitored by TLC. When complete conversion was obtained, volatiles were removed under reduced pressure and the residue was eluted over silica gel (Et_2O/MeOH 30:1 to pure MeOH) to yield amine **9c** as a white solid (90 mg, 75%). (Found: C, 55.07; H, 8.39; N, 12.17. $C_{21}H_{38}N_4O_7$ requires C, 55.00; H, 8.35; N, 12.22%). $[\alpha]_D^{20}$ = -36.5 (c 0.84, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.34 (t, *J* = 7.2 Hz, 1 H, Gly NH), 6.54 (d, *J* = 12.4, 1 H, D-Leu NH), 6.39 (d, *J* = 12.4, 1 H, D-Val NH), 4.51 (dd, *J* = 8.7, 4.8 Hz, 1 H, D-Val H-α), 4.46-4.43 (m, 2 H, D-Leu H-α + H-6), 4.01 (dd, *J* = 15.9, 6.1, 1 H, Gly H-α), 3.81 (dd, *J* = 15.9, 5.5 Hz, 1 , Gly H-α), 3.72 (s, 3 H, CO_2CH_3), 3.61 (dq, *J* = 8.8, 6.2 Hz, 1 H, H-2), 3.50 (s, 3 H, OCH_3), 3.08 (d, *J* = 8.8 Hz, 1 H, H-3), 3.03 (dd, *J* = 11.7, 2.4 Hz, 1 H, H-5), 2.61 (dd, *J* = 11.6, 8.5, Hz, 1 H, H-5), 2.15 (m, 1 H, D-Val H-β), 1.66 (m, 3 H, D-Leu H-β/γ), 1.29 (d, *J* = 6.3 Hz, 3 H, CH_3-C-2), 0.95-0-88 (m, 12 H, D-Leu H-δ and D-Val H-γ). δ_C (50 MHz, $CDCl_3$) 172.2 (s, CO), 172.0 (s, CO), 171.4 (s, CO), 168.4 (s, $\underline{C}O_2Me$), 100.4 (d, C-6), 74.8, (d), 73.8 (d), 64.1 (d), 57.1 (d), 56.1 (q, OCH_3), 52.2 (d), 51.8 (d), 48.0 (t), 42.6 (t), 41.5 (t), 31.2 (d), 24.7 (d), 22.8 (q, CH_3), 22.2 (q, CH_3), 19.0 (q, CH_3), 18.1 (q, CH_3), 18.0 (q, CH_3). ESI-MSMS *m*/*z* 481.85 (M^++Na, 14), 449.33 (M^+-OMe+Na, 93), 322.23 [M^+-(OMe)Mor+Na, 100].

H-D-Val-Mor-Gly-D-Leu-D-Val-OMe (10a). 2,6-Lutidine (112 μL, 0.96 mmol) was added to a solution of peptide **9a** (135 mg, 0.32 mmol) in CH_2Cl_2 (3 mL). Solid Fmoc-D-Val-Cl (114 mg, 0.32 mmol) was added in small portions. The reaction mixture was stirred at room temperature for 3 hours and dichloromethane was then removed under reduced pressure. The resultant oil was dissolved in EtOAc, washed with 1M HCl, 5% Na_2CO_3, brine and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated to dryness to yield a solid that was treated with 30% Et_2NH in CH_3CN (3 mL). The Fmoc deprotection was monitored by TLC, until complete conversion was obtained, then volatiles were removed under reduced pressure and the residue was eluted over silica gel (Et_2O/MeOH 30:1 to

pure MeOH) to yield amine **10a** as a white solid (140 mg, 83%). (Found: C, 56.99; H, 8.56; N, 13.21. $C_{25}H_{45}N_5O_7$ requires C, 56.91; H, 8.60; N, 13.27%). $[\alpha]_D^{21}$ = +10.5 (c 1.00, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.15 (d, *J* = 7.6 Hz, 1H, NH), 7.06 (br, 1 H, NH), 6.55 (d, *J* = 8.4 Hz, 1 H, NH), 4.85 (m, 2 H), 4.34 (m, 1 H), 4.28 (d, *J* = 5.6 Hz, 1 H), 3.97 (d, *J* = 6.0 Hz, 2 H), 4.0-3.82 (m, 1 H), 3.80-3.62 (m, 2 H), 3.73 (s, 3H, CO_2CH_3), 3.63-3.57 (m, 1 H), 3.50 (d, *J* = 6.4 Hz, 1 H), 2.17-2.04 (m, 1 H), 1.97-1.82 (m, 4 H), 1.68-1.65 (m, 2 H), 1.32 (d, *J* = 6.4 Hz, 3 H), 1.02-0.88 (m, 18 H, D-Leu H-δ and D-Val H-γ). δ_C (60 MHz, $CDCl_3$) δ 176.3 (s, CO), 171.9 (s, CO), 171.8 (s, CO), 169.6 (s, CO), 169.1 (s, $\underline{C}O_2Me$), 69.3 (d), 61.1 (d), 59.9 (d), 57.3 (d), 56.6 (q, OCH_3), 52.1 (d), 52.0 (d), 43.1 (t), 42.5 (t), 40.3 (t), 31.8 (q, CH_3), 31.1 (d), 24.7 (d), 23.0 (q, CH_3), 22.0 (q, CH_3), 20.0 (q, CH_3), 19.0 (q, CH_3), 17.9 (q, CH_3), 17.1 (q, CH_3). ESI-MSMS *m*/*z* 527.52 (M^+, 18), 496 (18, M^+-OMe), 397.07 (M^+-D-Val$_2$OMe, 78), 269.25 [M^+-(D-Val$_2$OMe)-(C=O), 35], 284.15 [M^+-(D-Leu-D-Val$_2$OMe), 4], 227.04 [M^+-(Gly-D-Leu-D-Val$_2$OMe), 100].

H-D-Val-[(6*S*)-methoxy]-Mor-Gly-D-Leu-D-Val-OMe (10b). 2,6-Lutidine (85 μL, 0.73 mmol) was added to a solution of peptide **9b** (118 mg, 0.24 mmol) in CH_2Cl_2 (3 mL). Solid Fmoc-D-Val-Cl (86 mg, 0.24 mmol) was added in small portions. The reaction mixture was stirred at room temperature for 4 hours and dichloromethane was then removed under reduced pressure. The resultant oil was dissolved in EtOAc, washed with 1M HCl, 5% Na_2CO_3, brine and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated to dryness to yield a solid that was treated with 30% Et_2NH in CH_3CN (3 mL). The Fmoc deprotection was monitored by TLC. When complete conversion was obtained, volatiles were removed under reduced pressure and the residue was eluted over silica gel (Et_2O/MeOH 30:1 to pure MeOH) to yield amine **10b** as a white solid (114 mg, 85%). (Found: C, 56.21; H, 8.61; N, 12.45. $C_{26}H_{47}N_5O_8$ requires C, 56.00; H, 8.49; N, 12.56%). $[\alpha]_D^{21}$ = +7.5 (c 5.50, CH_3CN); δ_H (400 MHz, $CDCl_3$) 7.11 (d, *J* = 7.6 Hz, 2 H, NH), 6.56 (d, *J* = 8.8 Hz, 1 H, NH), 4.81 (dd, *J* = 7.6, 5.6 Hz, 1 H, H-6), 4.42 (m, 2 H), 4.31 (dt, *J* = 16.0, 6.4 Hz, 1 H), 4.05 (dd, *J* = 18.0, 9.6 Hz, 2 H), 3.98 (dd, *J* = 14.0, 5.6 Hz, 1 H), 3.85 (dd, *J* = 17.2, 6.0 Hz, 1 H), 3.71 (s, 3 H, CO_2CH_3), 3.53 (d, *J* = 5.6 Hz, 1 H), 3.42 (dd, *J* = 14.4, 8.4 Hz, 1 H), 3.41 (s, 3 H, CO_2CH_3), 2.07 (septet, *J* = 6.8 Hz, 1 H), 1.98 (br, 2 H, NH_2), 1.89 (septet, *J* = 6.4 Hz, 1 H), 1.67 (d, *J* = 6.4, 2 H, D-Leu H-β), 1.35 (d, *J* = 6.4 Hz, 3 H, CH_3-C-2), 0.99-0.86 (m, 18 H, D-Leu H-δ and D-Val H-γ). δ_C (60 MHz, $CDCl_3$) 175.3 (s, CO), 171.8 (s, CO), 171.7 (s, CO), 169.4 (s, CO), 169.0 (s, $\underline{C}O_2Me$), 97.2 (d, C-6), 63.9 (d), 63.0 (d), 57.3 (d), 56.4 (d), 55.0 (q, OCH_3), 52.0 (d), 51.7 (d), 44.1 (t), 42.9 (t), 40.0 (t), 31.8 (q, CH_3), 30.9 (d), 24.6 (d), 23.0 (q, CH_3), 22.0

(q, CH_3), 19.9 (q, CH_3), 19.0 (q, CH_3), 17.8 (q, CH_3), 17.0 (q, CH_3). ESI-MSMS *m*/*z* 557.92 (M^++1, 10), 526.23 (M^+-OMe+1, 100).

H-D-Val-[(6*R*)-methoxy]-Mor-Gly-D-Leu-D-Val-OMe (10c). 2,6-Lutidine (85 μL, 0.57 mmol) was added to a solution of peptide 9c (80 mg, 0.16 mmol) in CH_2Cl_2 (3 mL). Solid Fmoc-D-Val-Cl (57 mg, 0.16 mmol) was added in small portions. The reaction mixture was stirred at room temperature for 4 hours and dichloromethane was then removed under reduced pressure. The resultant oil was dissolved in EtOAc, washed with 1M HCl, 5% Na_2CO_3, brine and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated to dryness to yield a solid that was treated with 30% Et_2NH in CH_3CN (3 mL). The Fmoc deprotection was monitored by TLC. When complete conversion was obtained, volatiles were removed under reduced pressure and the residue was eluted over silica gel (Et_2O/MeOH 30:1 to pure MeOH) to yield amine 10c as a white solid (87 mg, 98%). (Found: C, 56.13; H, 8.53; N, 12.51. $C_{26}H_{47}N_5O_8$ requires C, 56.00; H, 8.49; N, 12.56%). $[\alpha]_D^{21}$ = +2.3 (c 1.0, CH_3CN); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.2 Hz, 1 H, NH), 6.71 (br, 1 H, NH), 4.80 (t, *J* = 2.8 Hz, 1 H, H-6), 4.45-4.39 (m, 2 H), 4.2 (q, *J* = 6.4 Hz, 1 H), 4.12 (d, *J* = 8.4 Hz, 1 H), 4.08 (d, *J* = 7.2 Hz, 1 H), 3.80 (dd, *J* = 17.2, 5.2 Hz, 1 H), 3.75-3.67 (m, 2 H), 3.71 (s, 3 H, CO_2CH_3), 3.42 (s, 3 H, CO_2CH_3),3.37 (d, *J* = 6.4 Hz, 1 H), 2.14 (septet, *J* = 6.8 Hz, 1 H), 2.04 (septet, *J* = 6.0 Hz, 1 H), 1.71 (br, 2 H, NH_2), 1.32 (d, *J* = 6.0 Hz, 3 H, CH_3-C-2), 0.96-0.80 (m, 18 H, D-Leu H-δ and D-Val H-γ). δ_C (60 MHz, $CDCl_3$) 176.5 (s, CO), 171.8 (s, CO), 171.7 (s, CO), 169.7 (s, CO), 169.2 (s, $\underline{C}O_2Me$), 97.1 (d, C-6), 68.1 (d), 61.9 (d), 57.2 (d), 56.7 (d), 55.2 (q, OCH_3), 52.0 (d), 51.8 (t), 45.2 (t), 43.0 (t), 39.7 (q, CH_3), 31.0 (d), 24.6 (d), 23.0 (q, CH_3), 21.9 (q, CH_3), 20.1 (q, CH_3), 19.3 (q, CH_3), 19.0 (q, CH_3), 17.8 (q, CH_3), 16.7 (q, CH_3). ESI-MSMS *m*/*z* 558.40 (M^++1, 15), 526.10 (M^+-OMe+1, 100).

Table S1. ^{1}H chemical shift data for peptides **I** – **IV** in $CDCl_3$ and CD_3CN

	I		**II**		**III**		**IV**	
	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN
Boc	1.48	1.42	1.48	1.42	1.46	1.42	1.49	1.43
D-Ala NH	5.32	5.71	5.29	5.63	5.32	5.67	5.27	5.73
D-Ala H-α	4.24	4.13	4.30	4.16	4.26	4.13	4.12	4.15
D-Ala H-β	1.32	1.23	1.31	1.20	1.32	1.20	1.32	1.22
D-Val_1 NH	7.65	7.37	7.79	7.60	7.68	7.55	7.50	7.23
D-Val_1 H-α	4.48	4.56	4.49	4.58	4.56	4.55	4.38	4.62
D-Val_1 H-β	2.16	2.06	2.16	2.07	2.19	2.14	2.15	2.12
D-Val_1 H-γ	1.03	0.96	0.97	0.87	0.98	0.88	0.97	0.97
H-2	4.42	3.87-3.66	4.35-4.14	4.15-4.01	4.27	4.18-4.13	5.13-4.49	5.00-4.97
CH_3-2	1.33	1.25	1.35	1.30	1.33	1.27	1.32	1.23
H-3	4.35	3.86-3.67	4.31	4.18	4.15	4.18-4.13	4.87	4.63
H-5	3.78-3.75	3.62-3.59	4.16-3.37	4.20-3.24	3.96-3.76	3.84-3.76	5.96	5.94
H-6	3.90-3.74	3.60	4.85	4.86	4.83	4.84	6.44	6.46
OCH_3-6	-	-	3.43	3.36	3.45	3.40	-	-
Gly NH	7.08	7.35	6.79	7.30	6.72	7.25	7.50	7.47
Gly H-α	3.99-3.91	3.76	4.15-3.72	3.85,3.55	4.07-3.78	3.80,3.64	3.72	3.78
D-Leu NH	7.11	7.13	7.16	7.28	7.40	7.40	6.53	6.61
D-Leu H-α	4.43	4.44	4.42	4.46	4.44	4.48	4.39	4.36
D-Leu H-β	1.69	1.68-1.53	1.70	1.73-1.60	1.72	1.72-1.59	1.70-1.59	1.55
D-Leu H-γ	1.69	1.68-1.53	1.70	1.73-1.58	1.72	1.71	1.59	1.41
D-Leu H-δ	0.98	0.92	0.95	0.92	0.96	0.90	0.94	0.91
D-Val_2 NH	6.69	7.01	6.71	7.02	6.62	7.03	6.74	6.92
D-Val_2 H-α	4.49	4.27	4.49	4.25	4.49	4.25	4.49	4.27
D-Val_2 H-β	2.18	2.10	2.18	2.07	2.31	2.09	2.19	2.10
D-Val_2 H-γ	0.94	0.90	0.94	0.90	0.94	0.90	0.94	0.91
CO_2CH_3	3.76	3.67	3.76	3.67	3.76	3.68	3.76	3.67

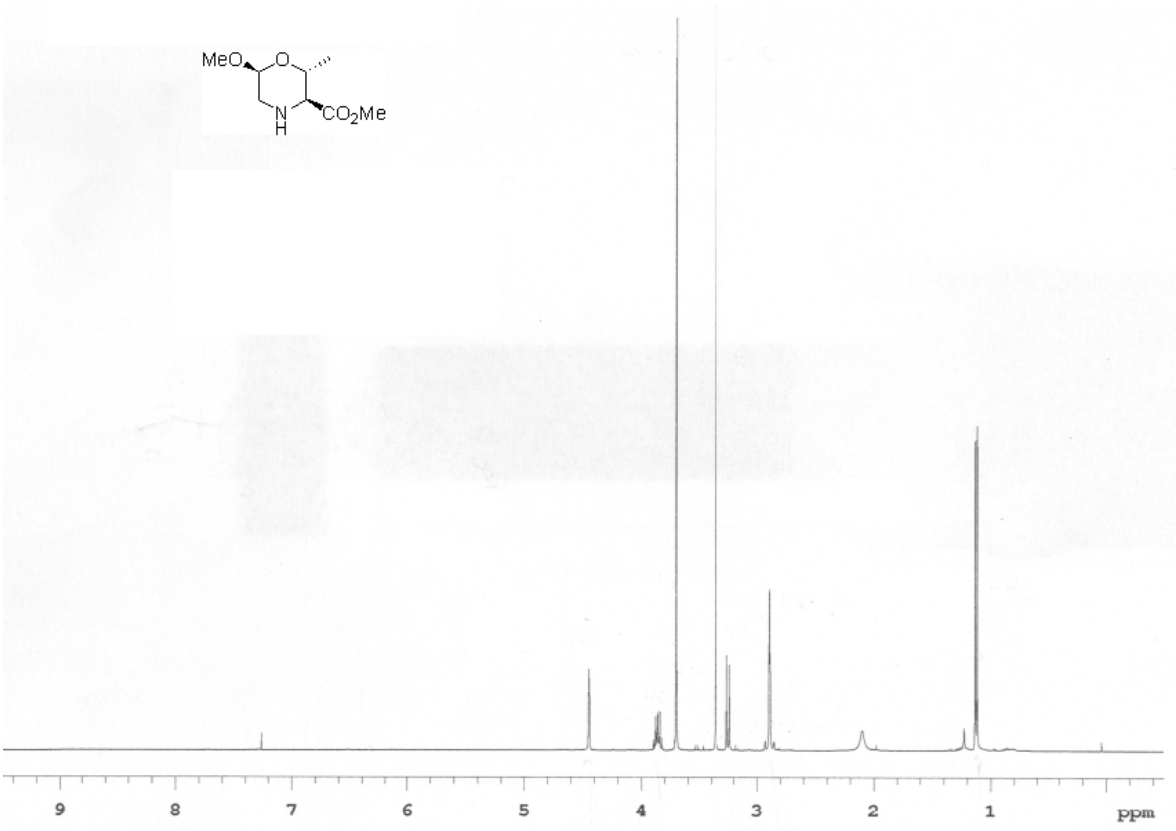
Table S2. ^{13}C chemical shift data for peptides **I** – **IV** in $CDCl_3$ and CD_3CN

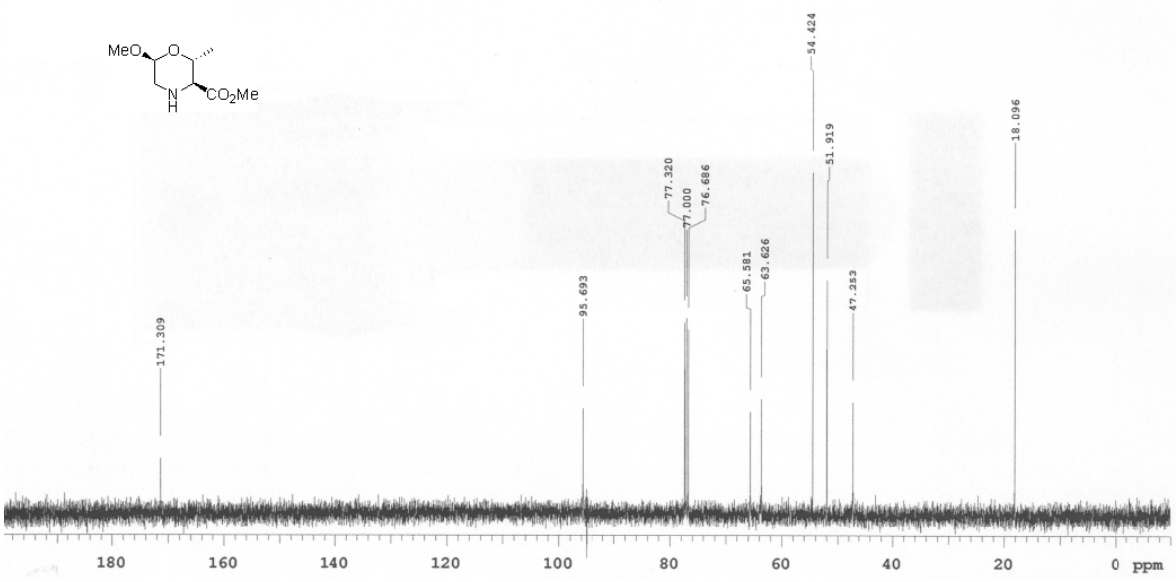
	I		**II**		**III**		**IV**	
	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN
Boc	28.2	27.5	27.8	27.5	27.8	27.6	28.5	27.5
D-Ala NH	-	-	-	-	-	-	-	-
D-Ala C-α	50.1	49.8	50.1	49.7	49.8	49.8	49.4	49.8
D-Ala C-β	17.9	16.9	19.2	17.5	18.5	17.6	16.5	16.6
D-Val_1 NH	-	-	-	-	-	-	-	-
D-Val_1 C-α	55.1	54.1	54.7	53.7	54.4	54.1	55.1	54.7
D-Val_1 C-β	30.8	30.1	30.8	30.1	30.2	29.8	29.5	29.8
D-Val_1 C-γ	18.2	18.5	18.6	18.7	22.5	17.9	21.5	22.2
C-2	68.7	60.4	62.7	63.0	67.3	67.3	57.7	69.7
CH_3-2	17.8	17.0	18.9	17.8	19.2	18.4	16.8	16.7
C-3	60.1	42.5	64.0	63.7	61.7	62.0	56.4	56.4
C-5	42.5	51.5	44.1	43.8	45.1	42.5	102.5	103.9
C-6	60.1	42.4	97.2	97.2	97.2	97.2	129.4	130.5
OCH_3	-	-	55.1	54.1	54.7	54.4	.	-
Gly NH	-	-	-	-	-	-	-	-
Gly C-α	43.1	42.5	43.1	42.1	42.8	42.5	42.7	42.8
D-Leu NH	-	-	-	-	-	-	-	-
D-Leu C-α	51.8	51.1	51.7	50.7	51.7	50.8	51.7	51.1
D-Leu C-β	39.8	24.2	39.8	40.1	39.4	40.1	39.8	40.5
D-Leu C-γ	24.5	17.5	24.5	24.2	24.2	24.2	24.2	27.5
D-Leu C-δ	19.2	17.3	19.5	22.2	17.9,17.5	20.5	18.5,17.5	17.9
D-Val_2 NH	-	-	-	-	-	-	-	-
D-Val_2 C-α	57.4	57.7	57.7	57.7	56.7	57.7	56.7	57.4
D-Val_2 C-β	30.8	29.8	30.8	30.1	30.2	29.8	30.5	29.8
D-Val_2 C-γ	22.8	20.9	22.8	20.9	21.5	20.6	21.5	20.5
CO_2CH_3	52.1	51.4	52.1	51.1	51.7	51.4	52.1	51.4

Table S3. ROESY data in CD_3CN for compounds **I-IV**.

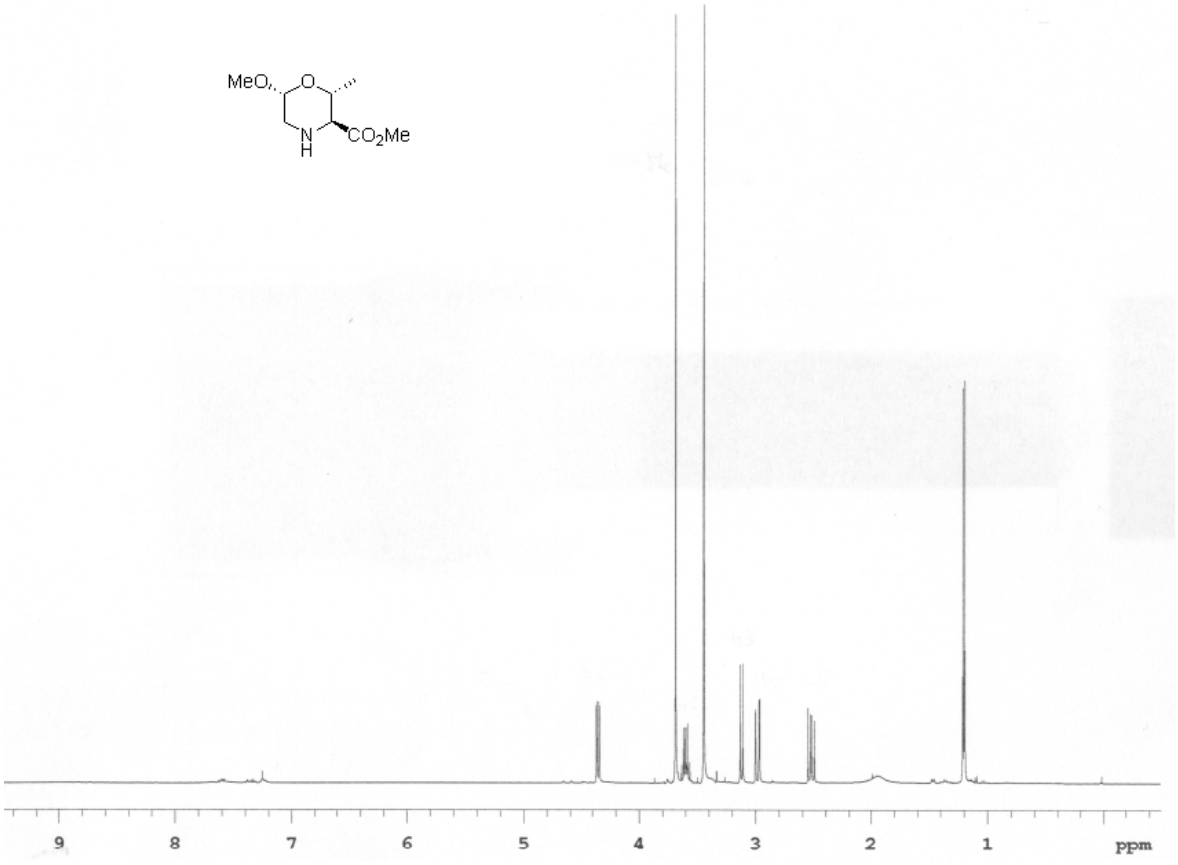
ROESY cross-peaks	I	II	III	IV
D-Val_1 H-α / H-5	4.56 / 3.62-3.59	4.58 / 4.20	4.55 / 3.84	-
D-Val_1 NH / D-Ala H-α	7.37 / 4.13	7.60 / 4.16	7.55 / 4.13	7.23 / 4.15
D-Val_1 NH / D-Ala H-β	-	7.60 / 1.20	7.55 / 1.20	-
H-2 / H-6	-	-	4.16 / 4.84	-
Gly NH / H-2	7.35 / 3.87	7.30 / 4.07	7.25 / 4.15	7.47 / 4.98
Gly NH / D Leu H-α	-	7.30 / 4.44	-	-
Gly H-α / H-3	-	-	3.81 / 4.18	-
Gly NH / CH_3-2	7.35 / 1.25	-	7.25 / 1.27	-
D-Leu NH / Gly H-α	-	7.28 / 3.57	7.40 / 3.80-3.65	6.61 / 3.78
D-Leu NH / Gly NH	-	-	7.40 / 7.25	6.61 / 7.47
D-Val_2 NH / D-Leu H-α	7.01 / 4.44	7.02 / 4.46	7.03 / 4.48	6.92 / 4.36

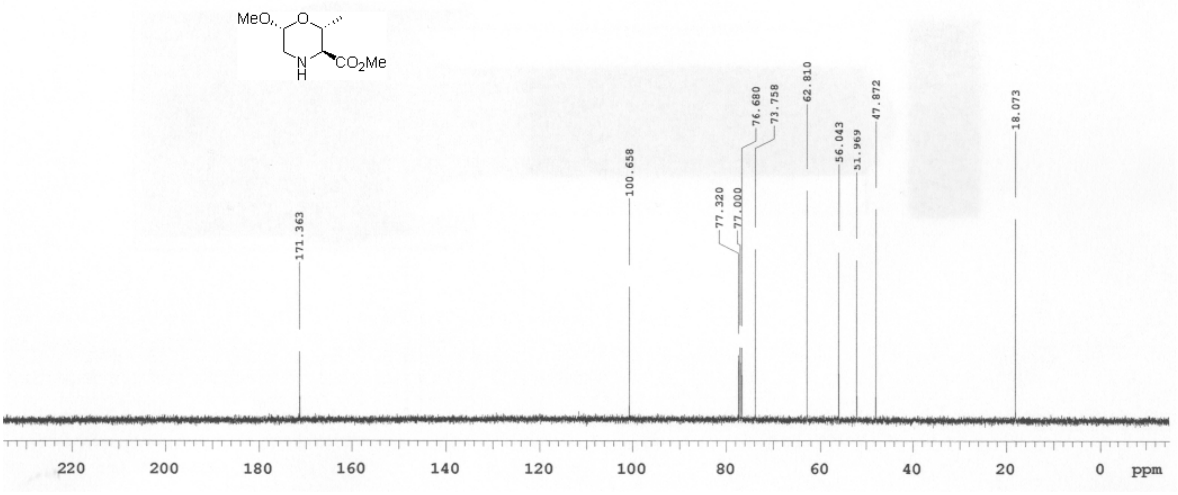
Compound 1a



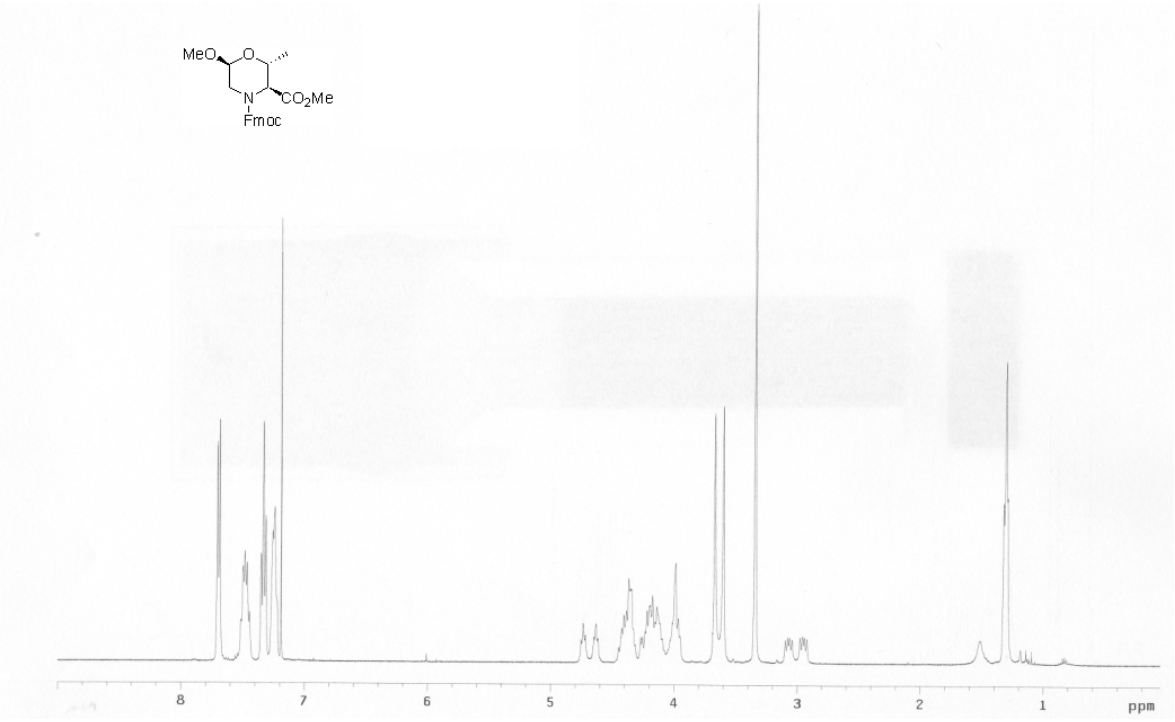


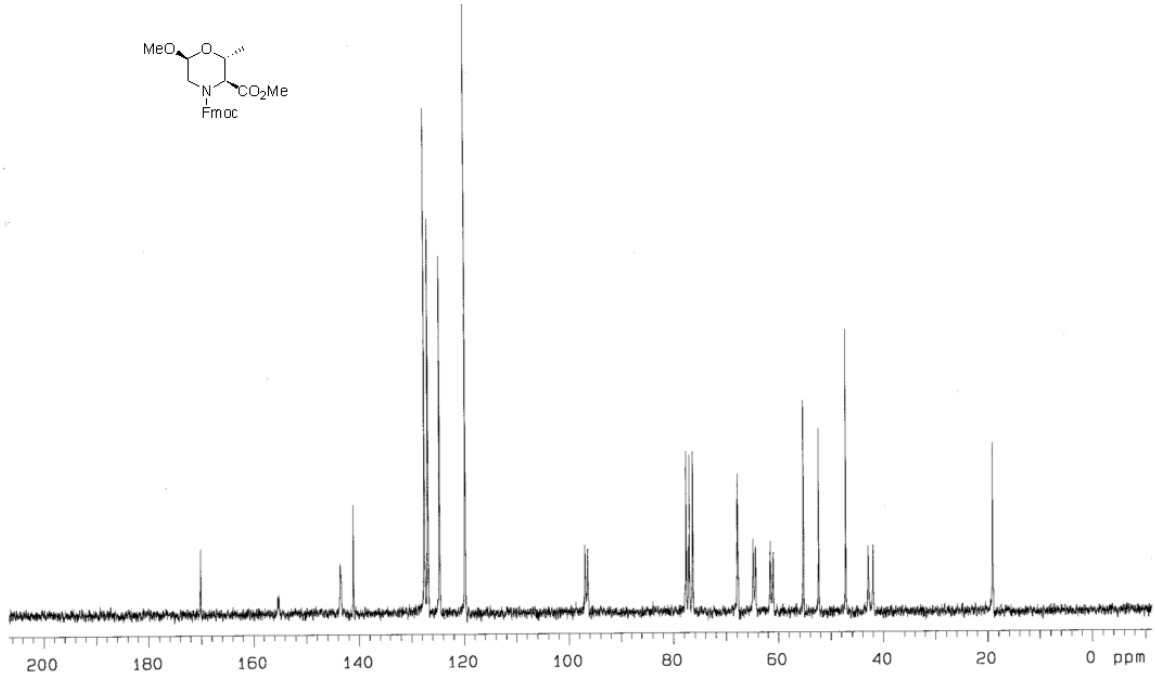
Compound 1b



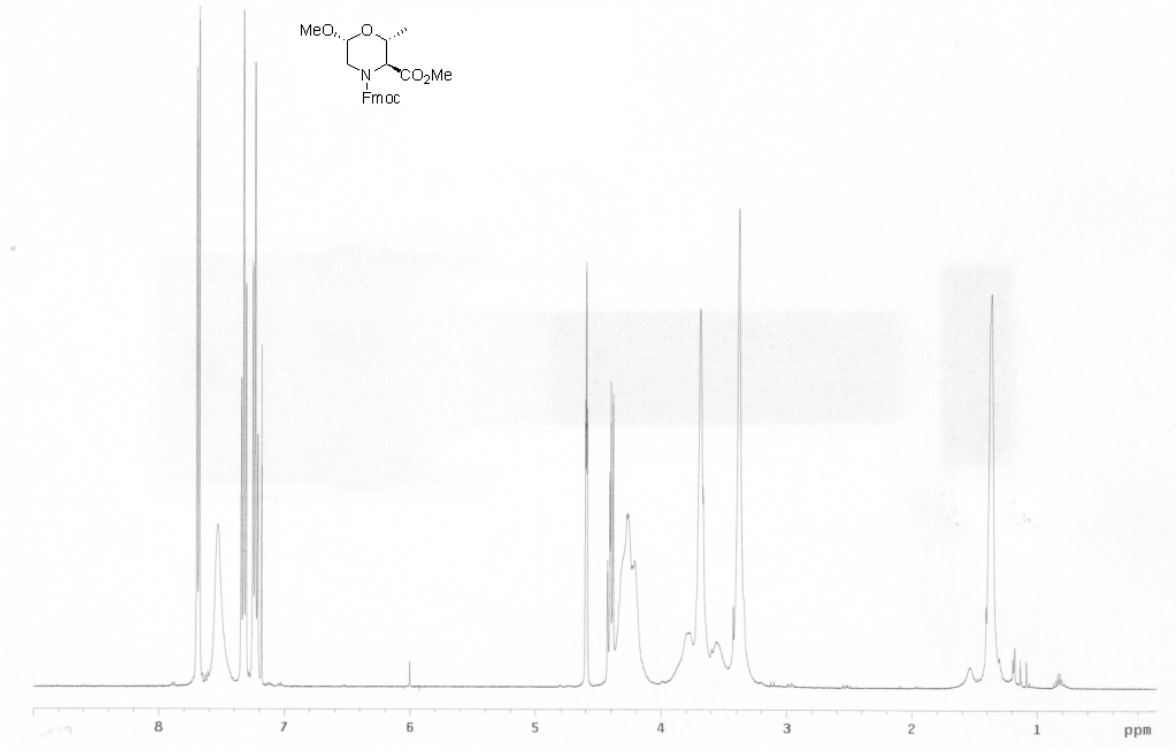


Compound 2





Compound 3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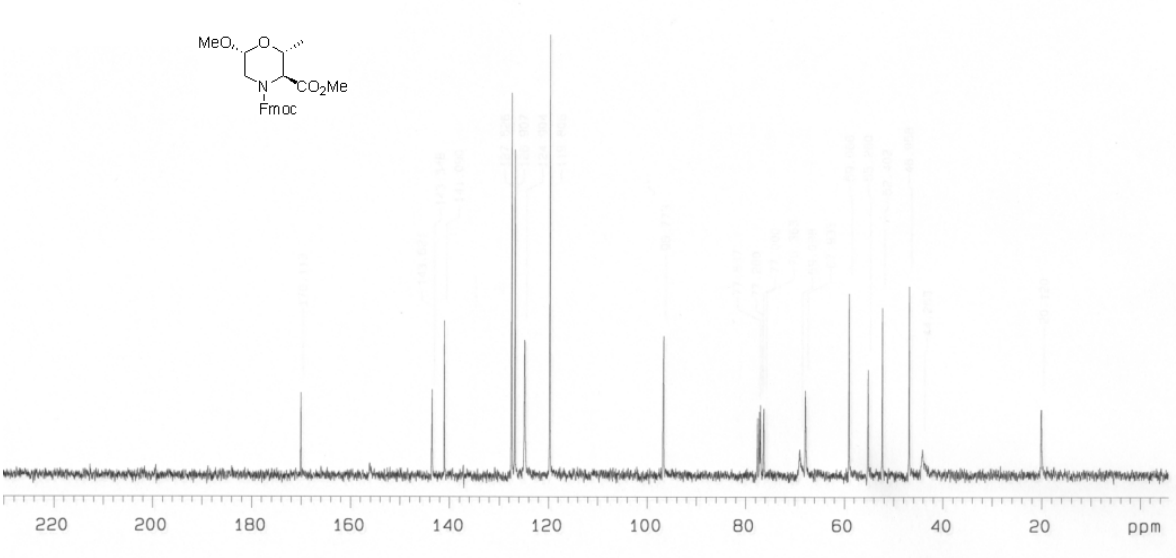
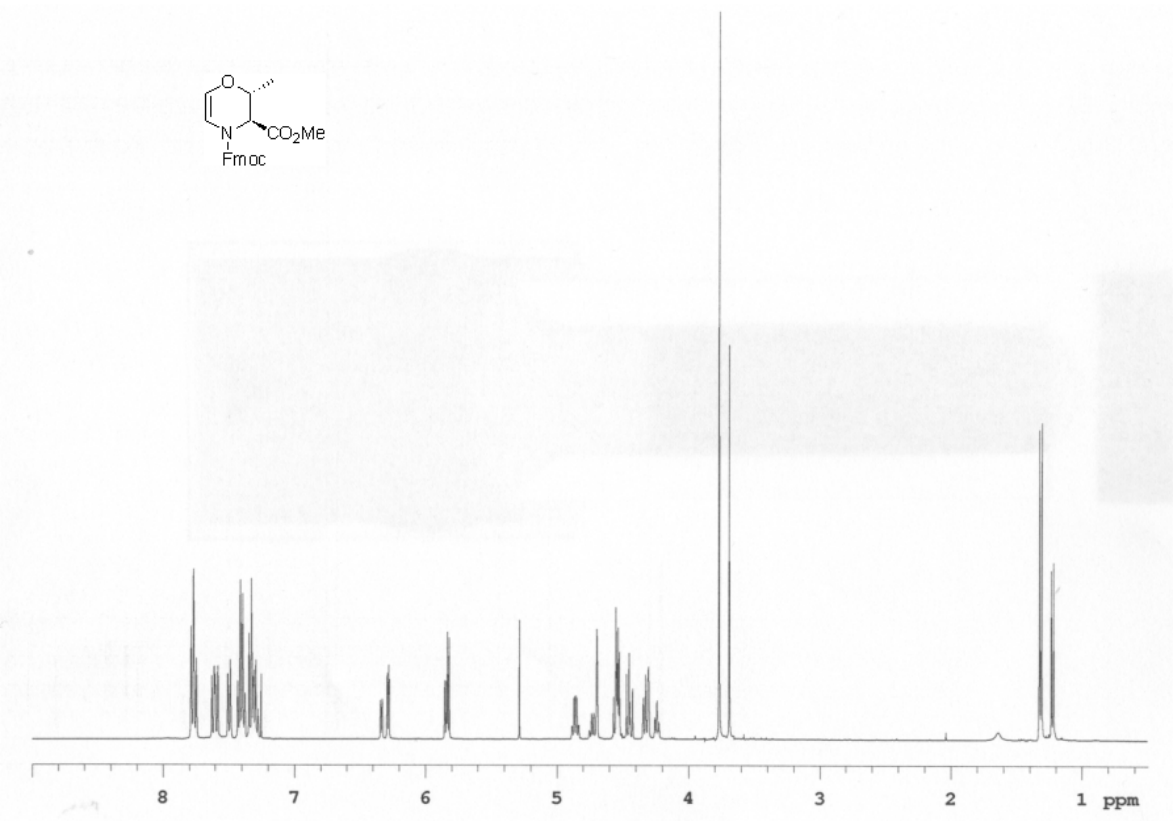
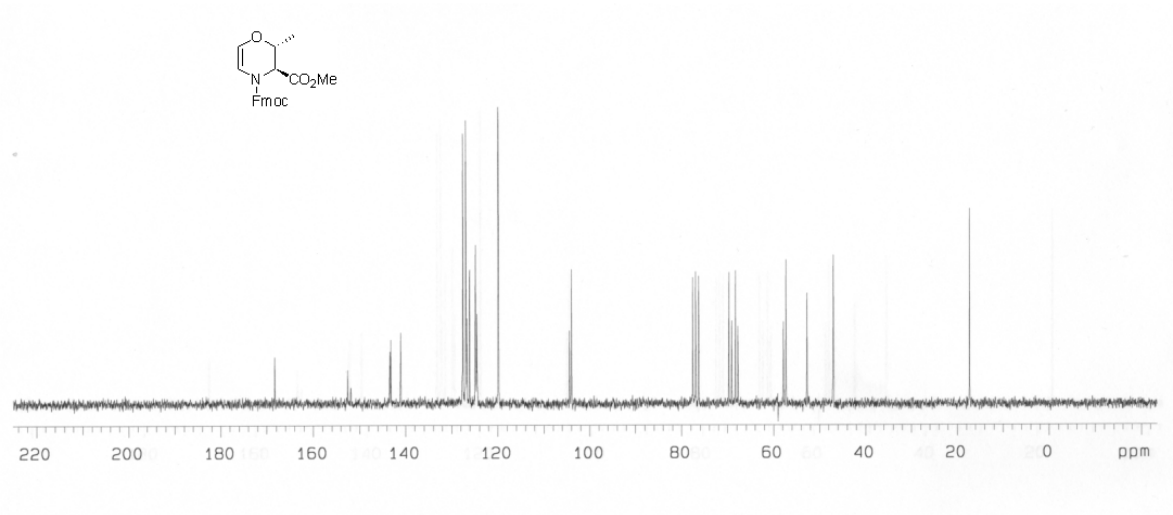
CO2Me
Fmoc
8
7
6
5
4
3
2
1
ppm

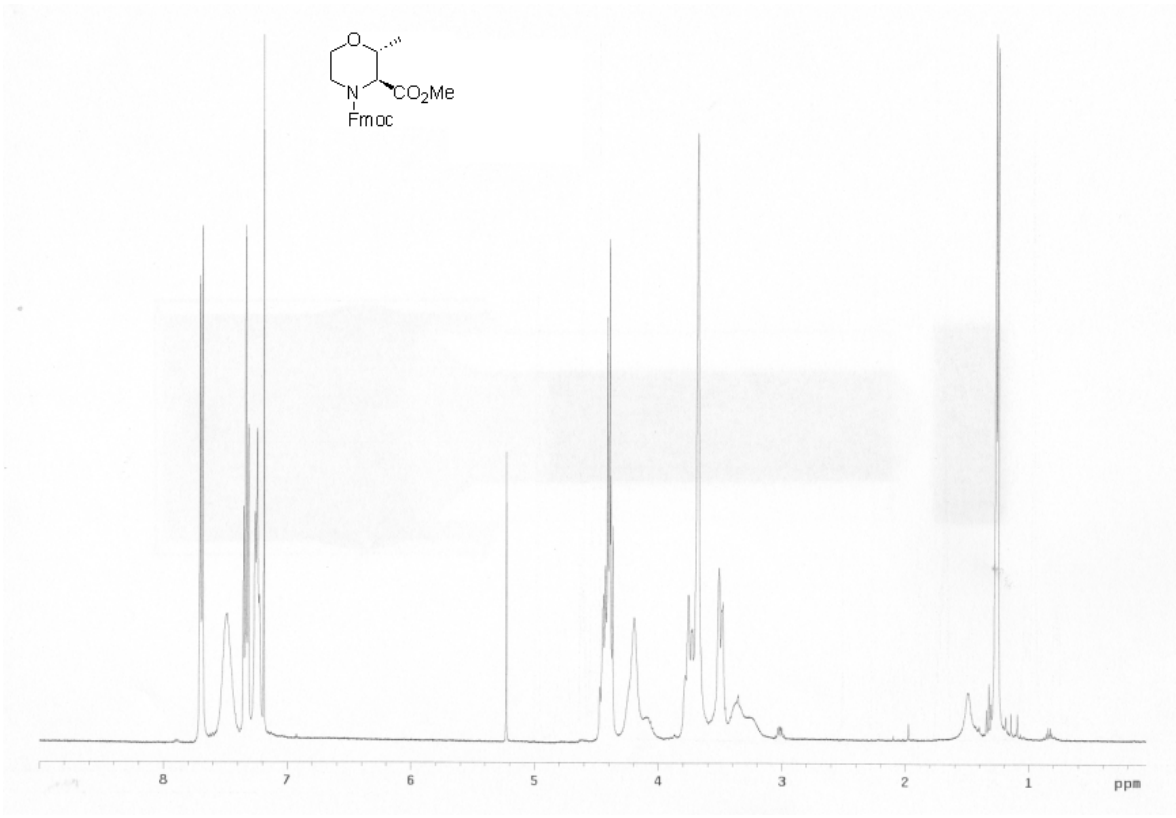

MeO
O
N
CO2Me
Fmoc
220
200
180
160
140
120
100
80
60
40
20
ppm

Compound 6





Compound 7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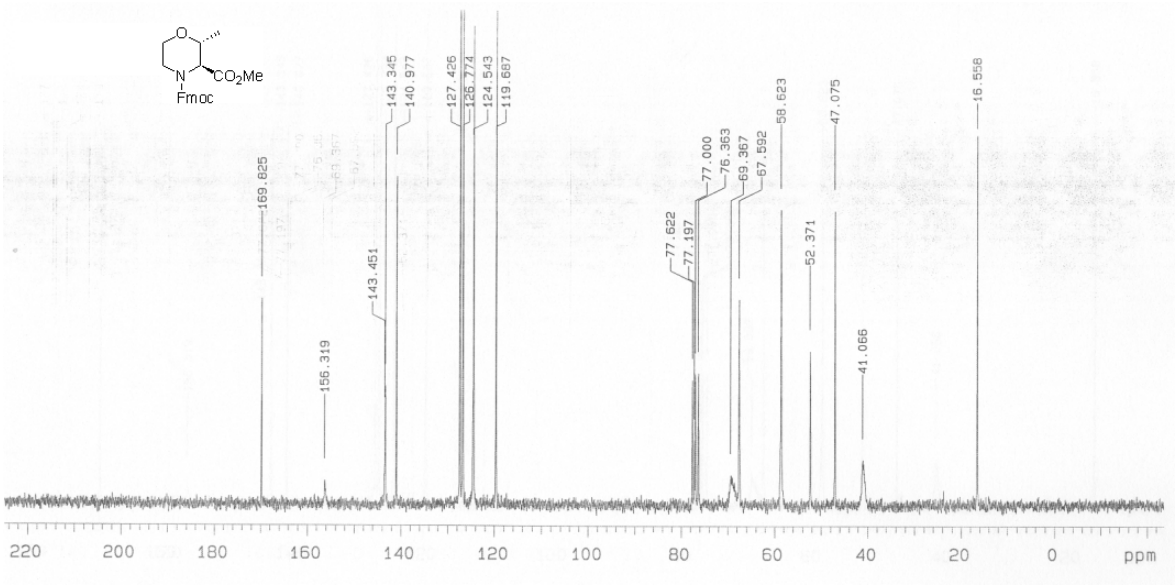
CO2Me
Fmoc
8
7
6
5
4
3
2
1
ppm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CO2Me
Fmoc
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156.319
143.451
143.345
140.977
127.426
126.774
124.543
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77.197
77.000
76.363
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67.592
58.623
52.371
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220
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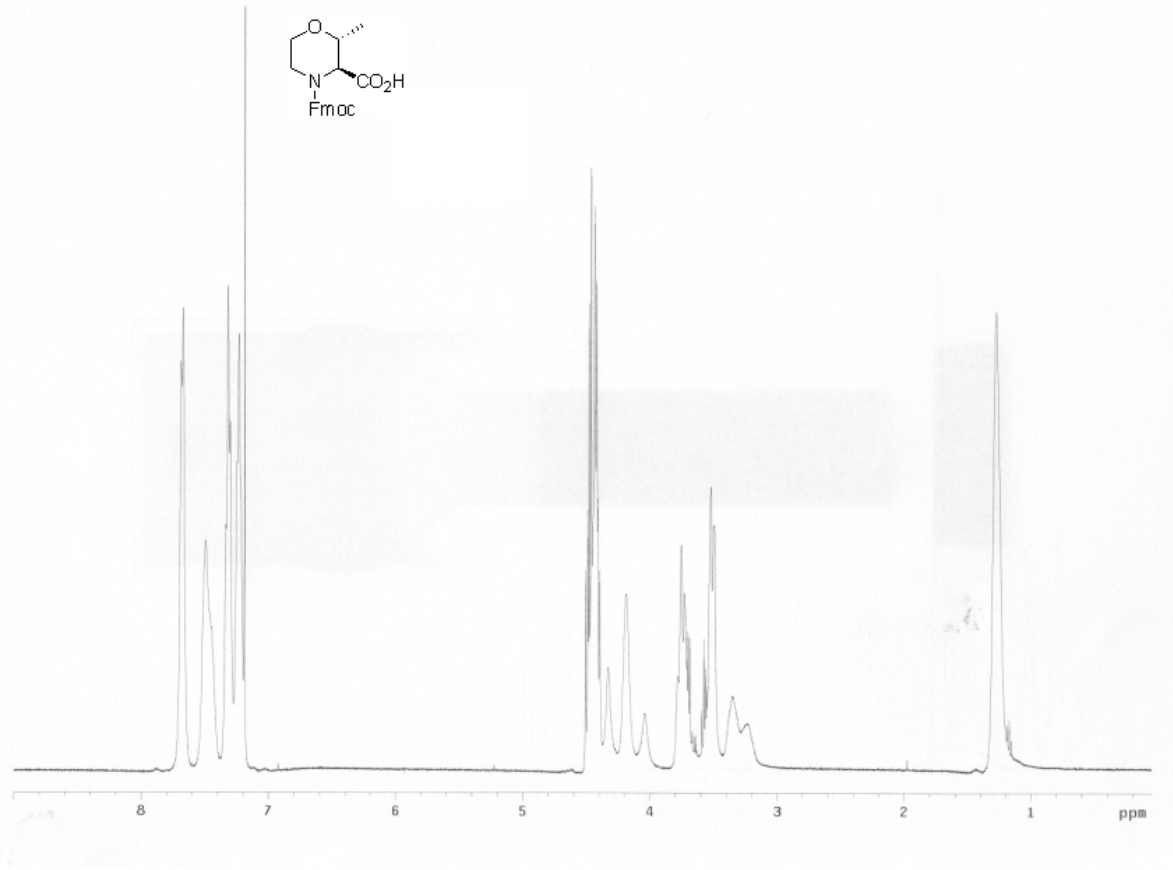
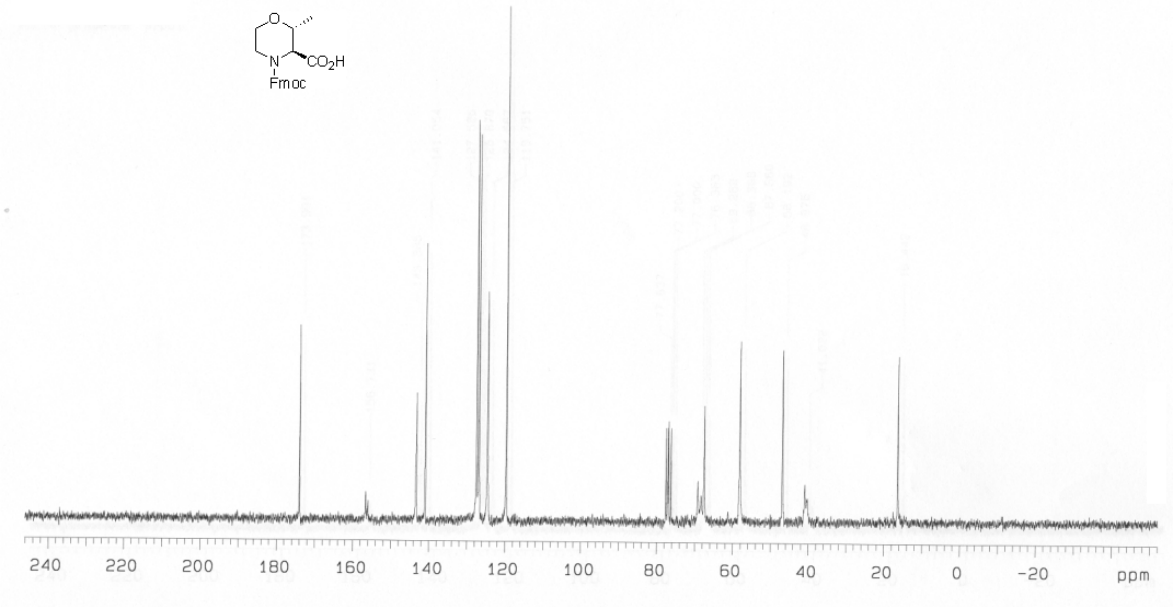
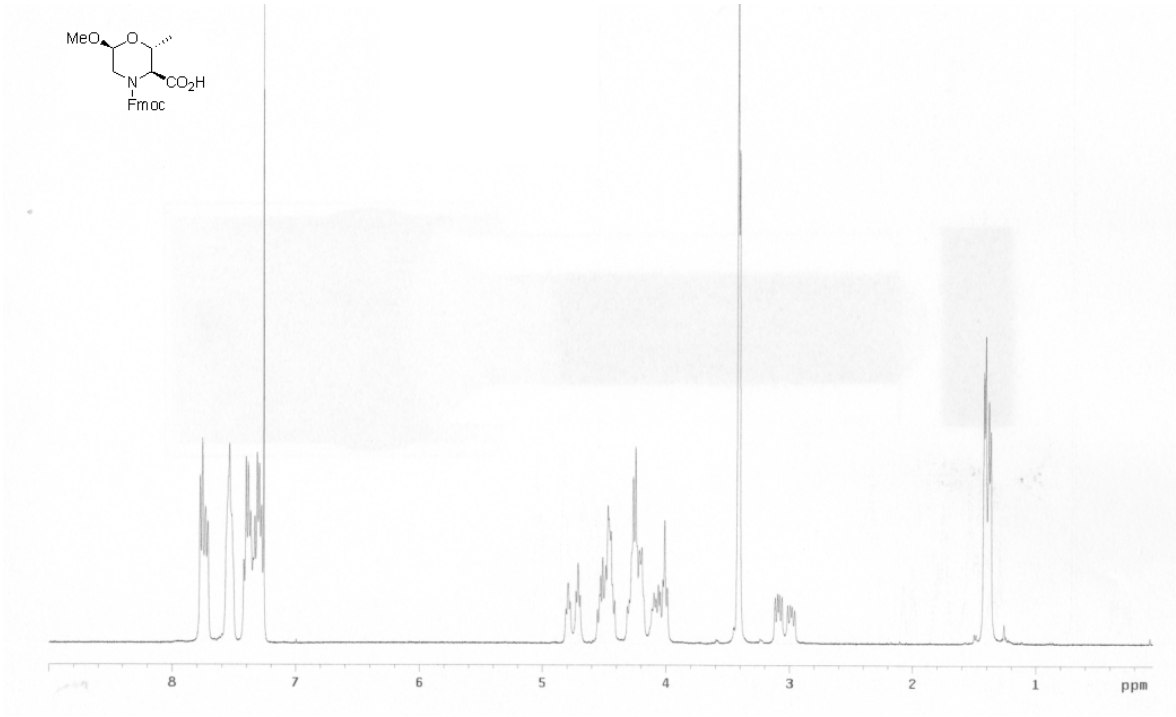
100
80
60
40
20
0
ppm

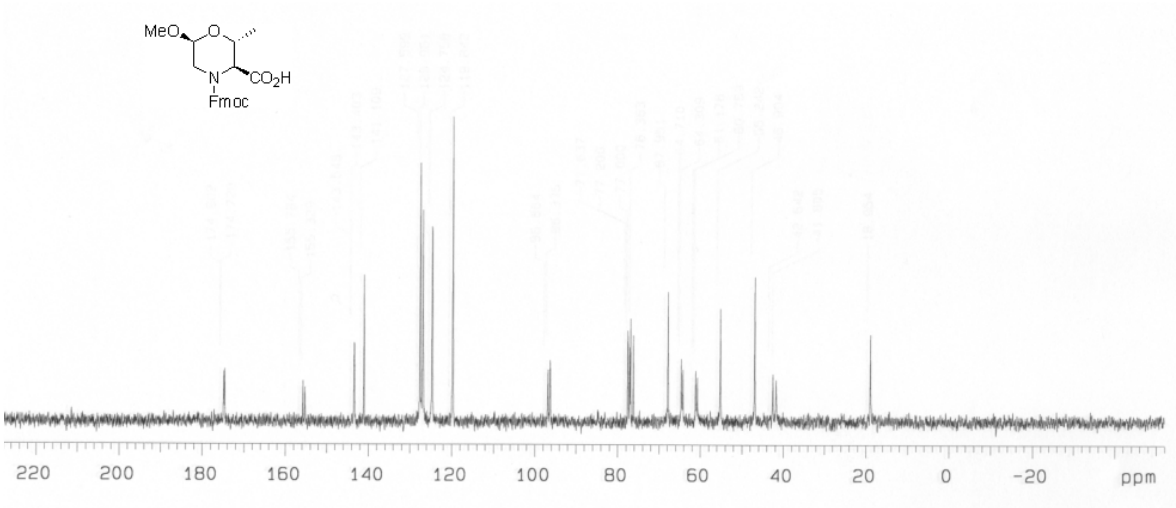
Compound 8



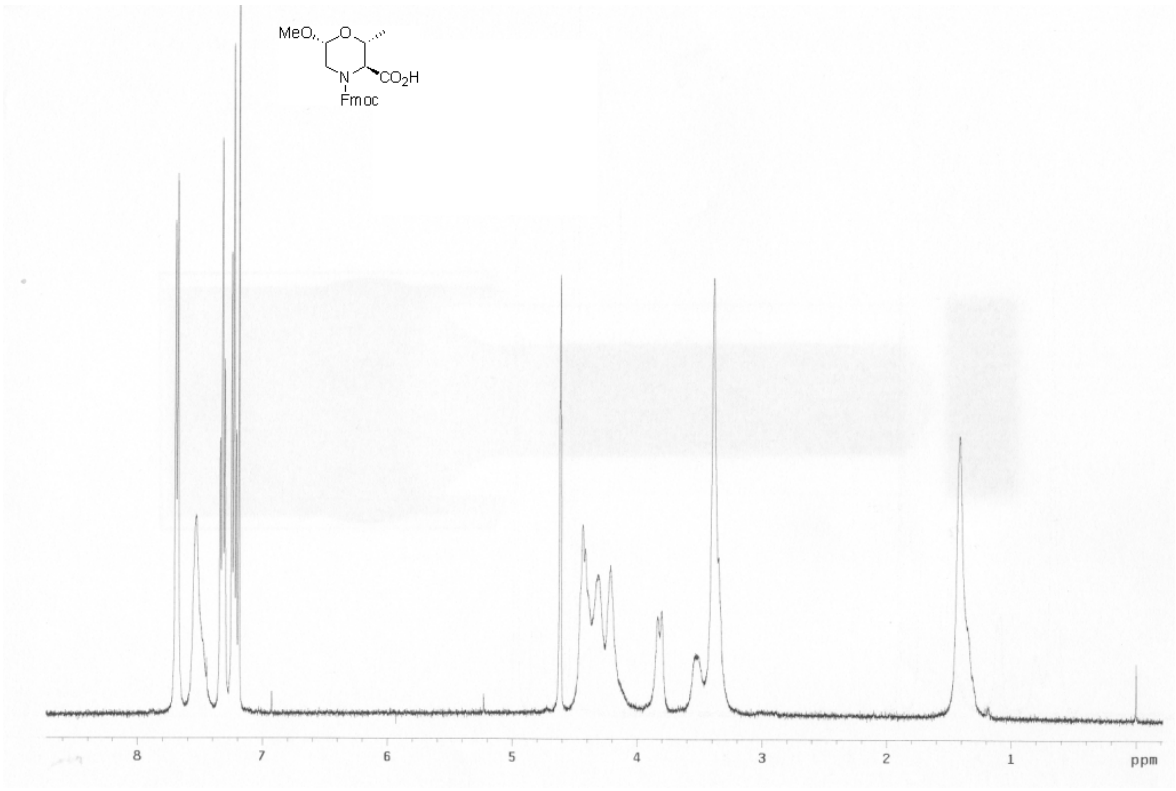


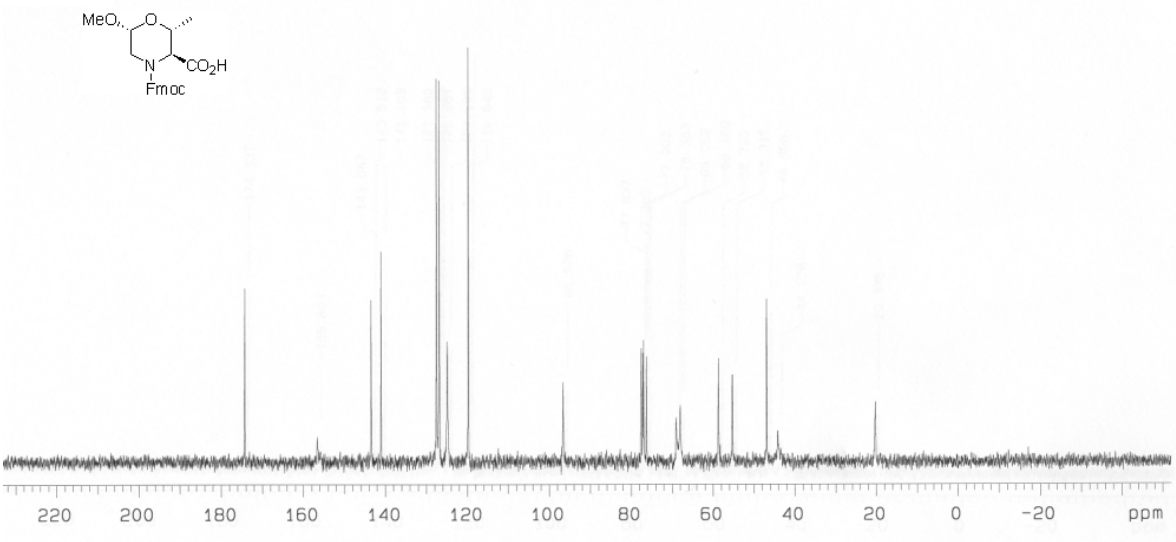
Compound 4



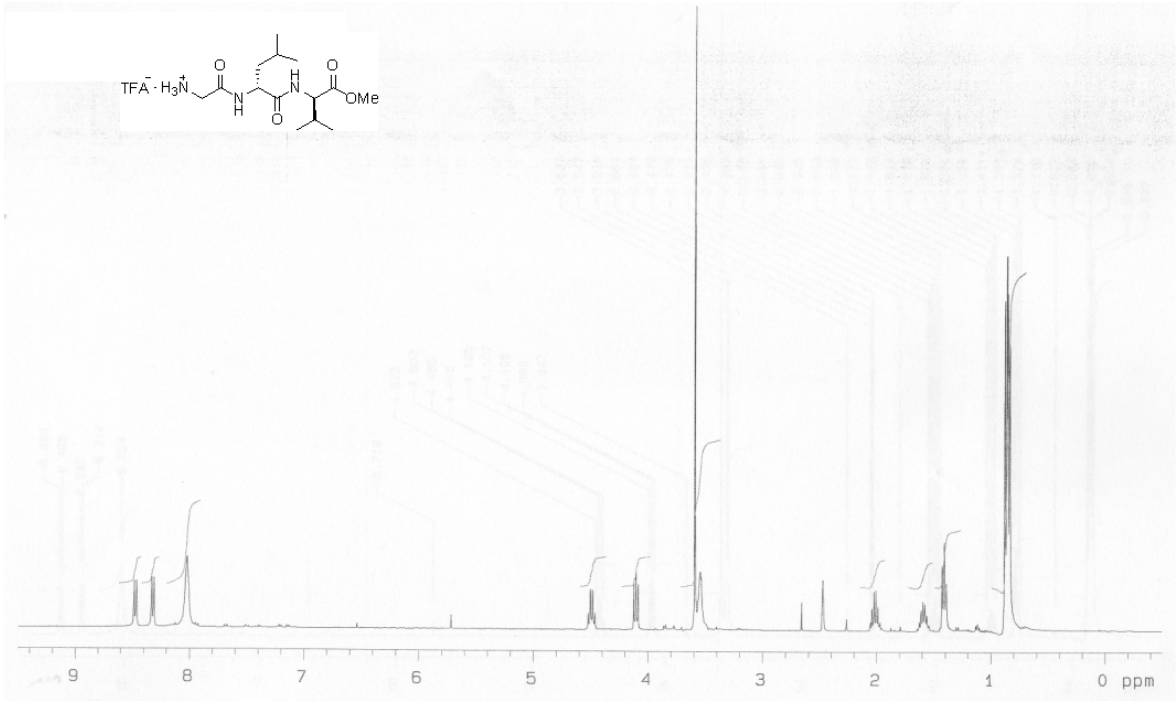


Compound 5

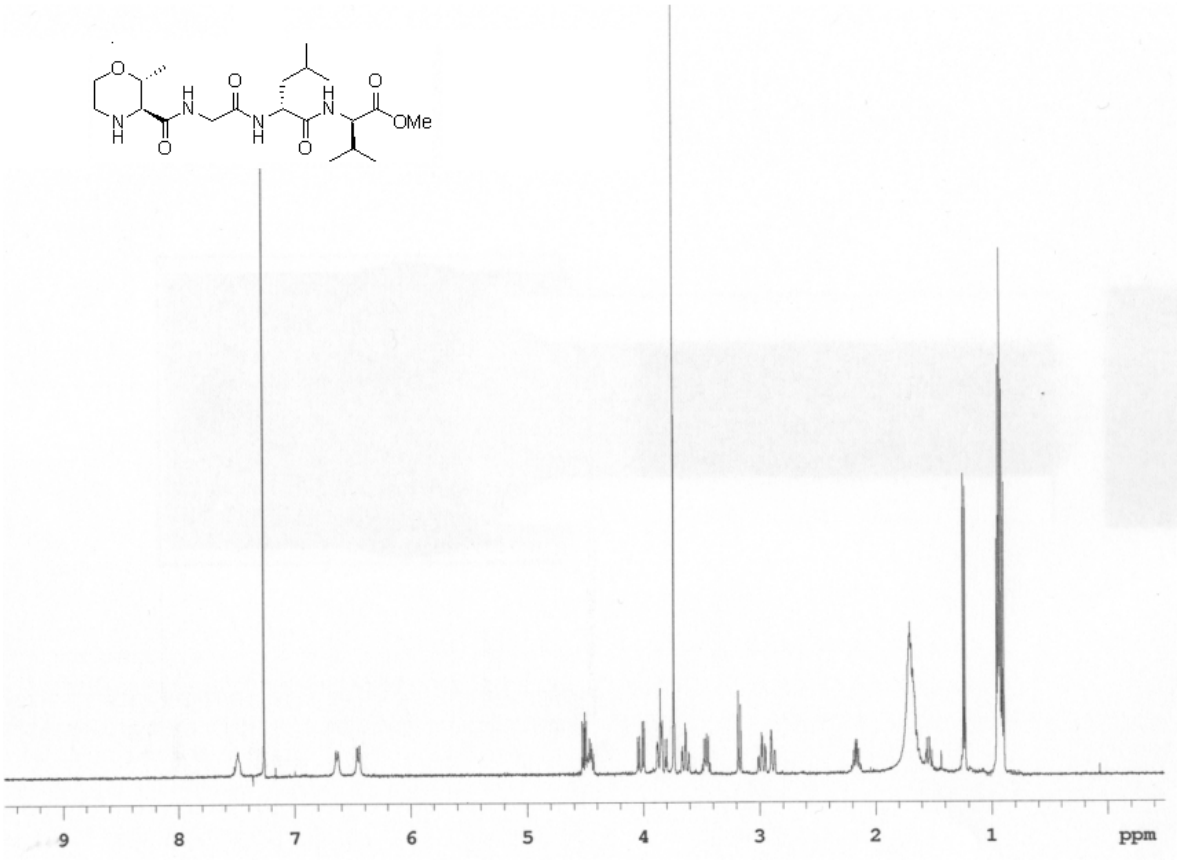


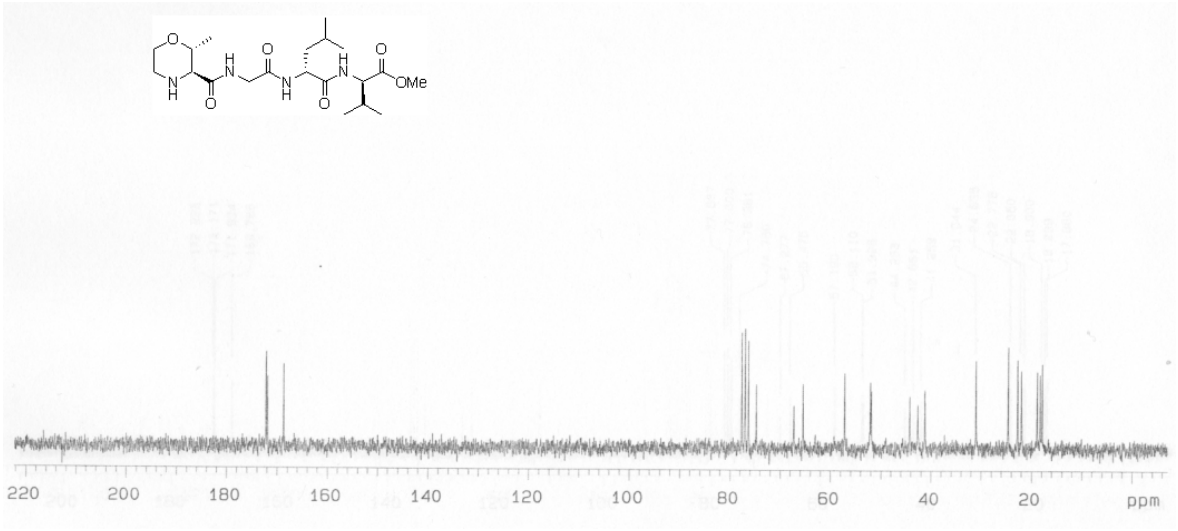


Peptide Gly-D-Leu-D-Val-OMe

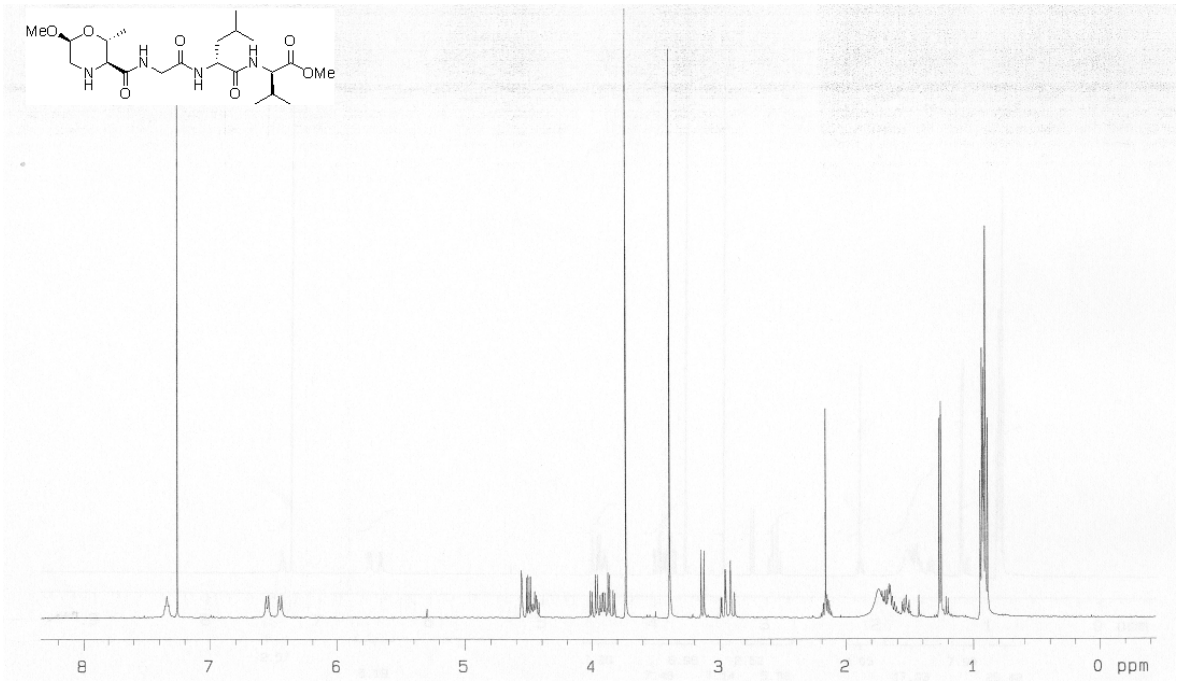


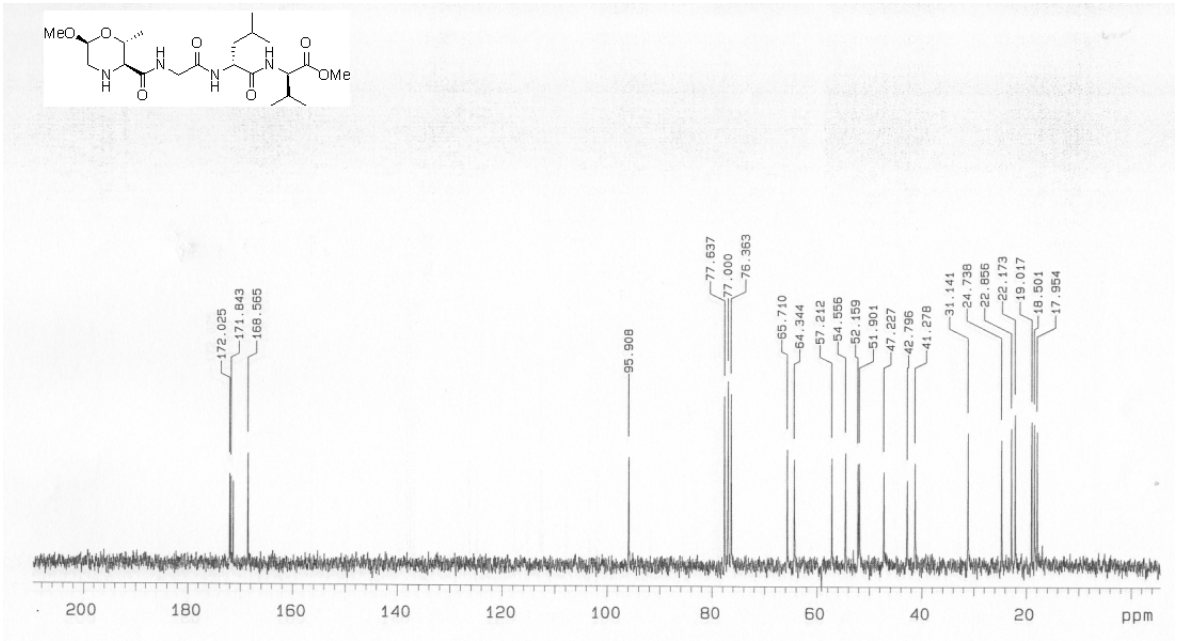
Compound 9a



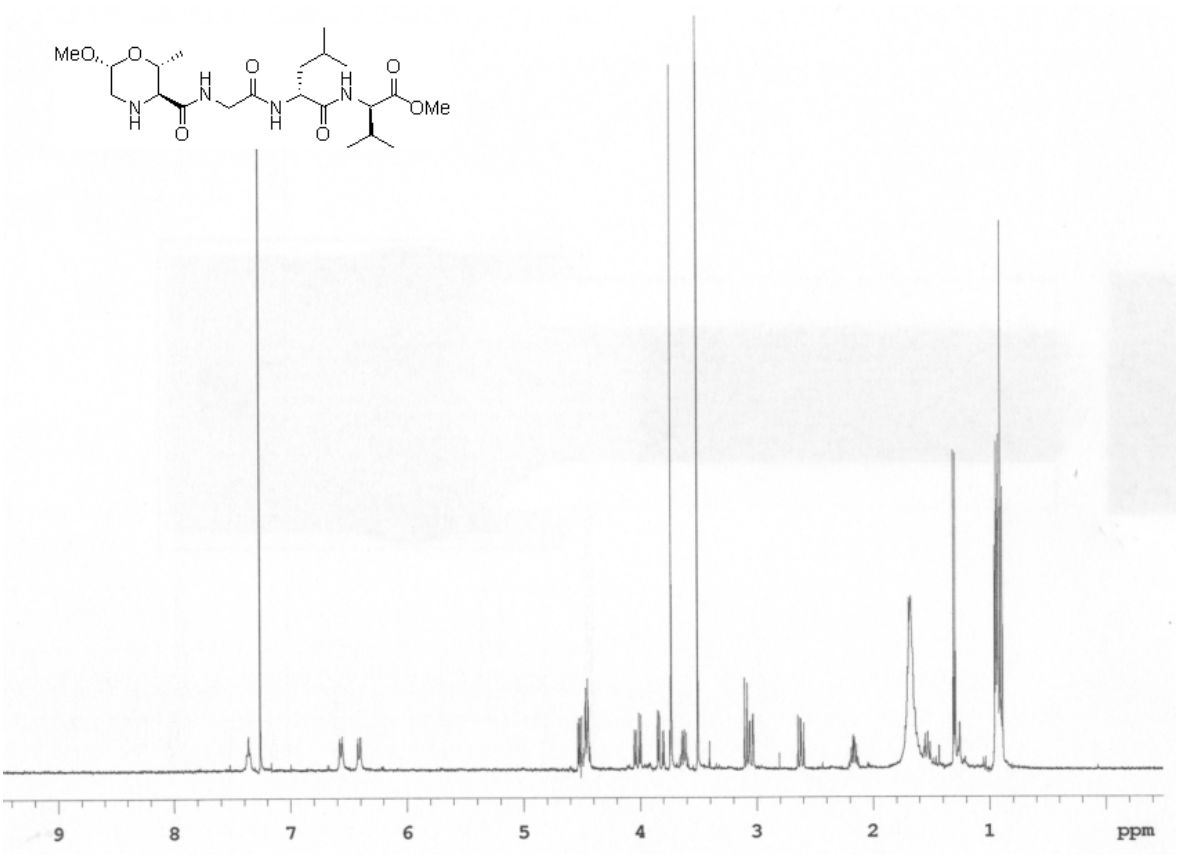


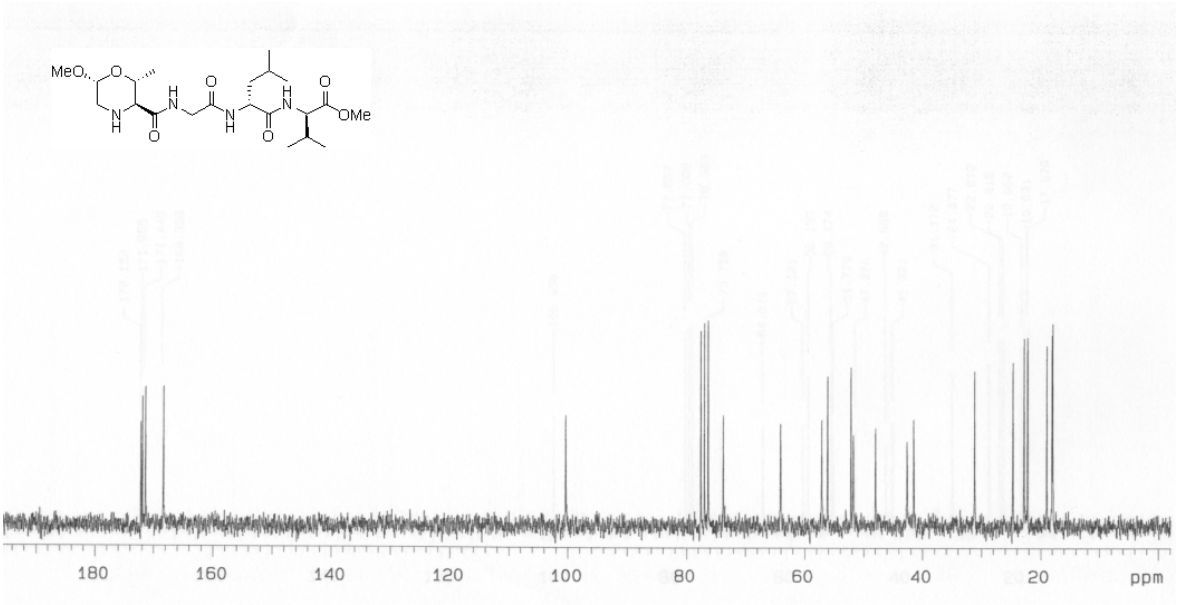
Compound 9b



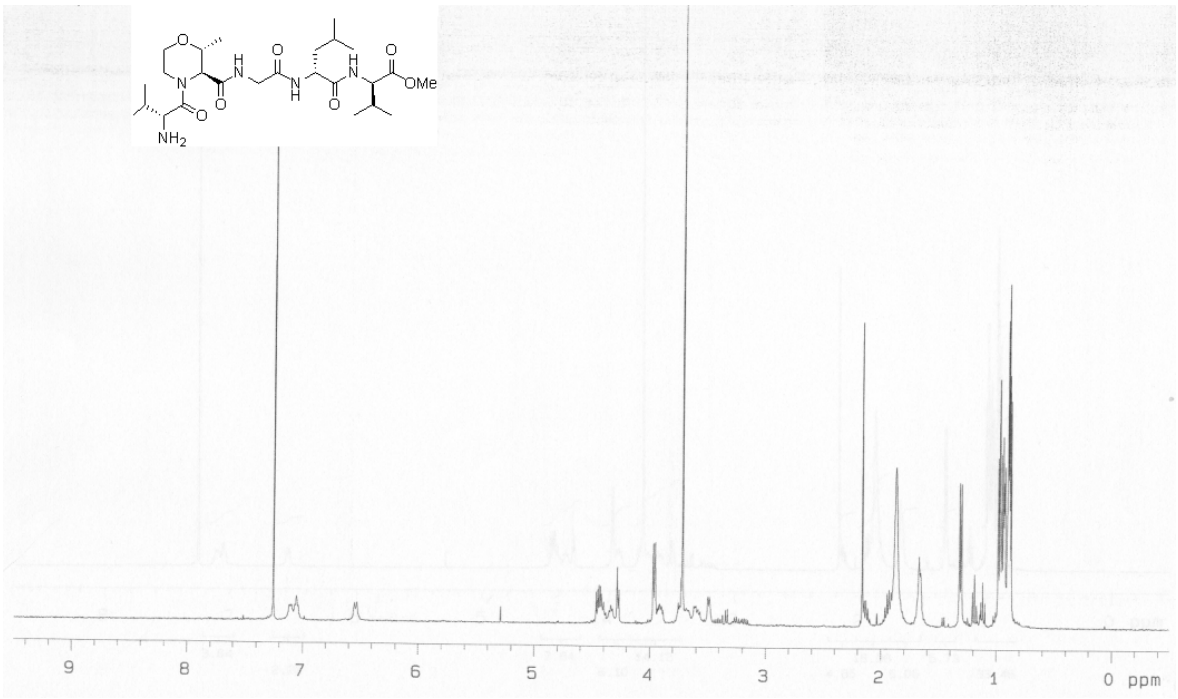


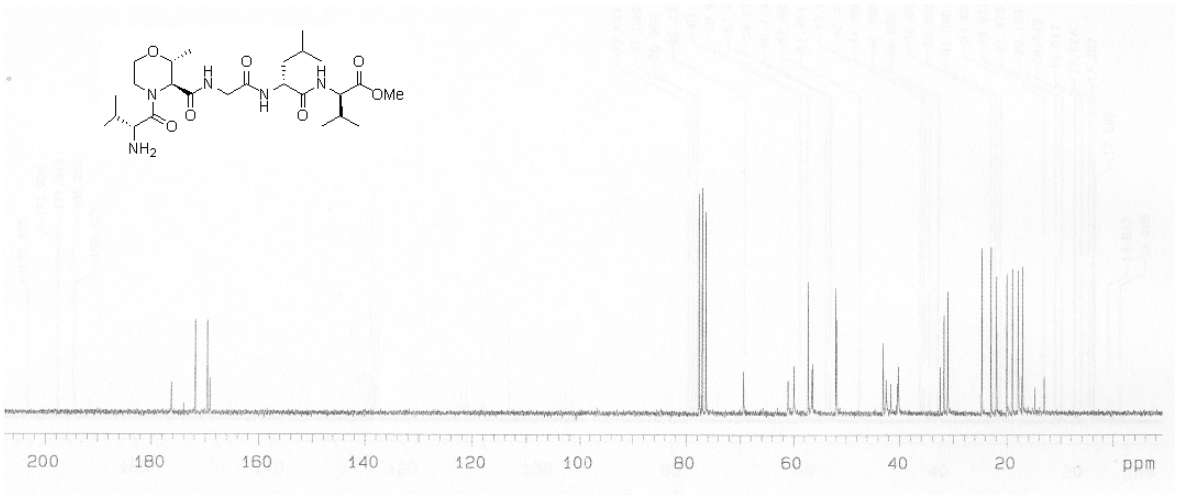
Compound 9c





Compound 10a





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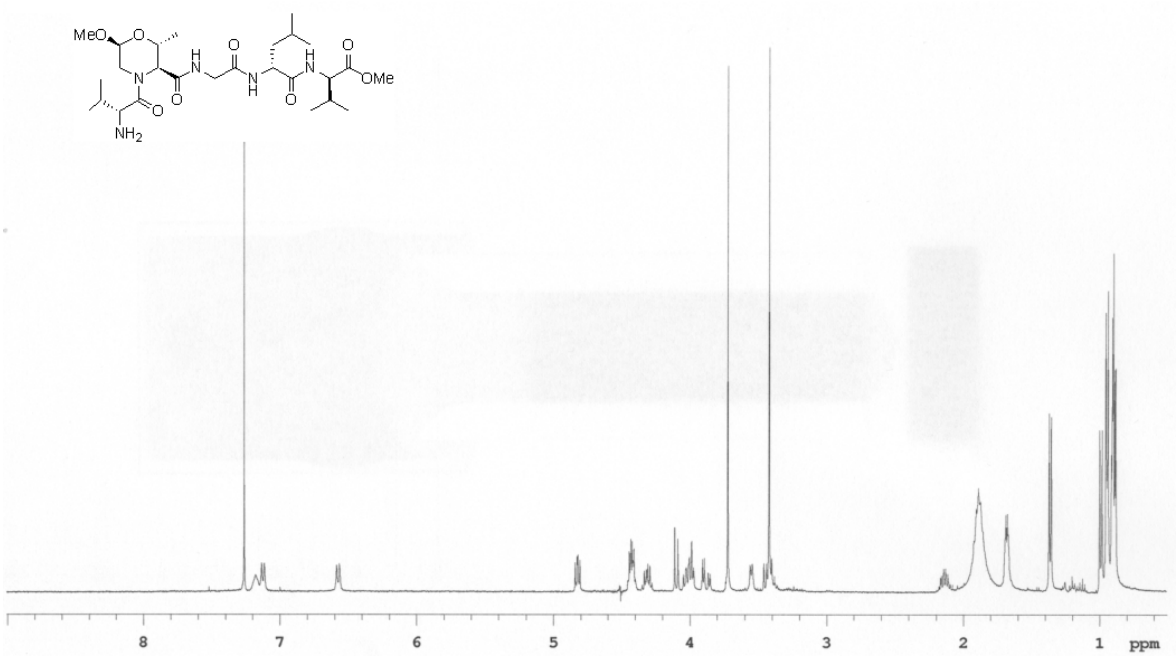
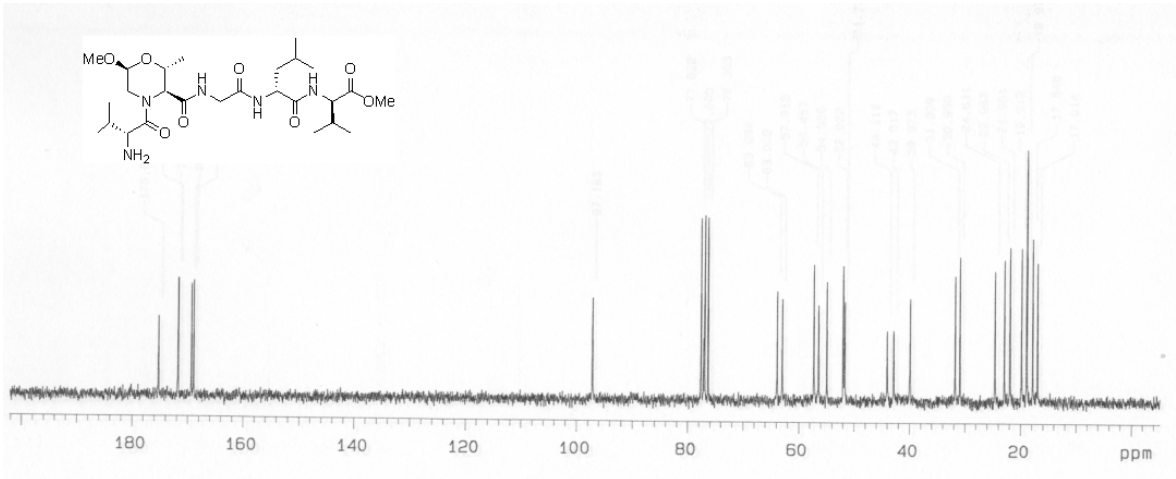
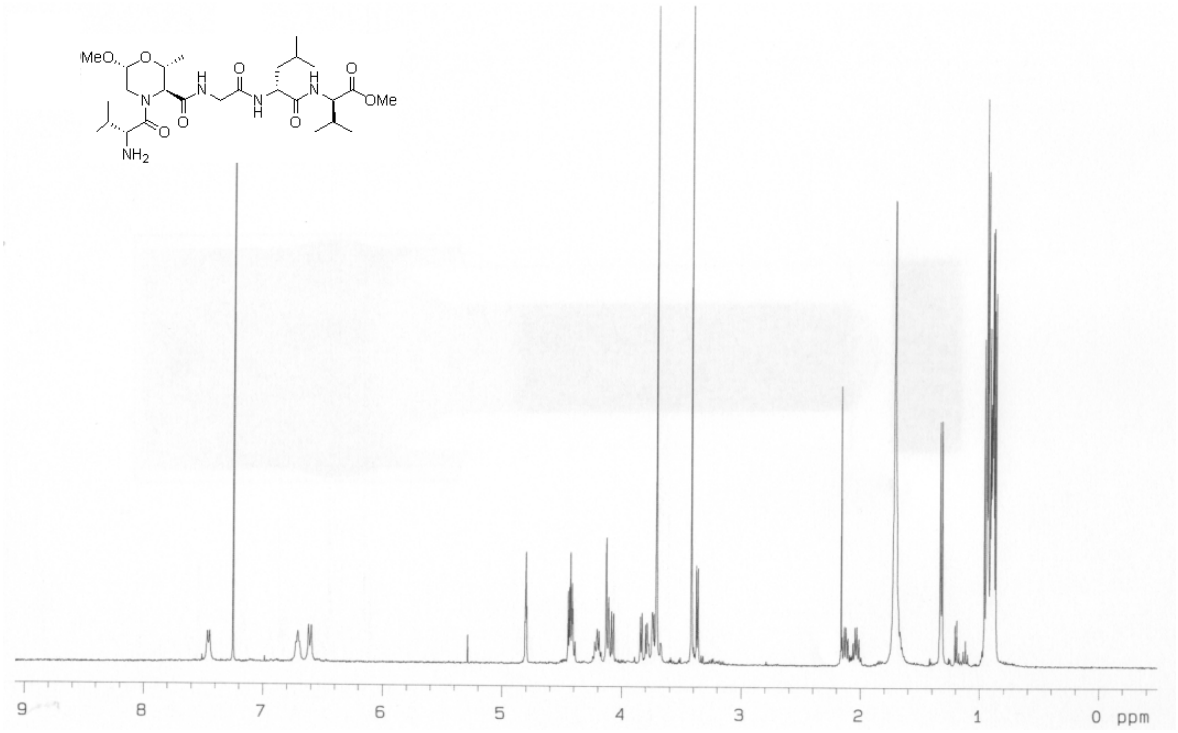
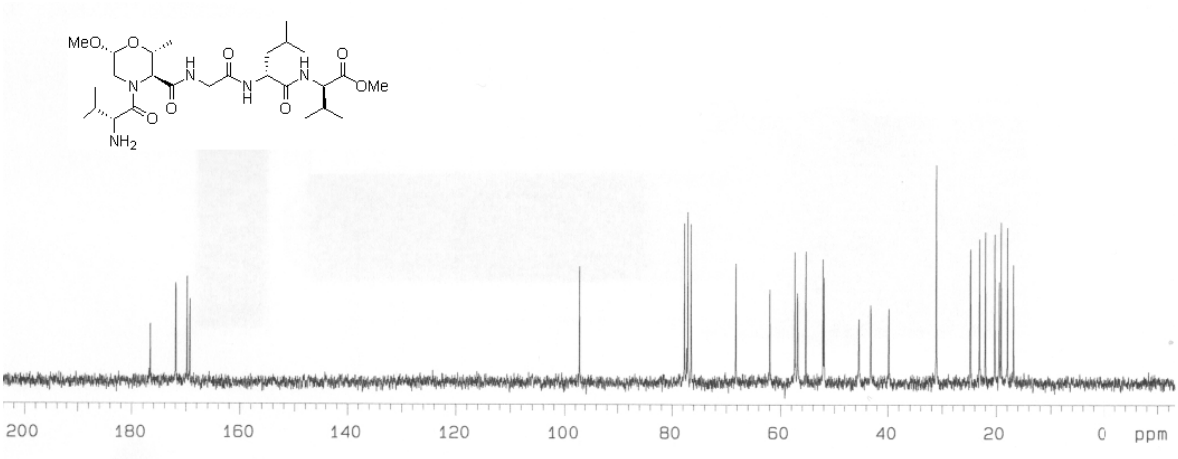


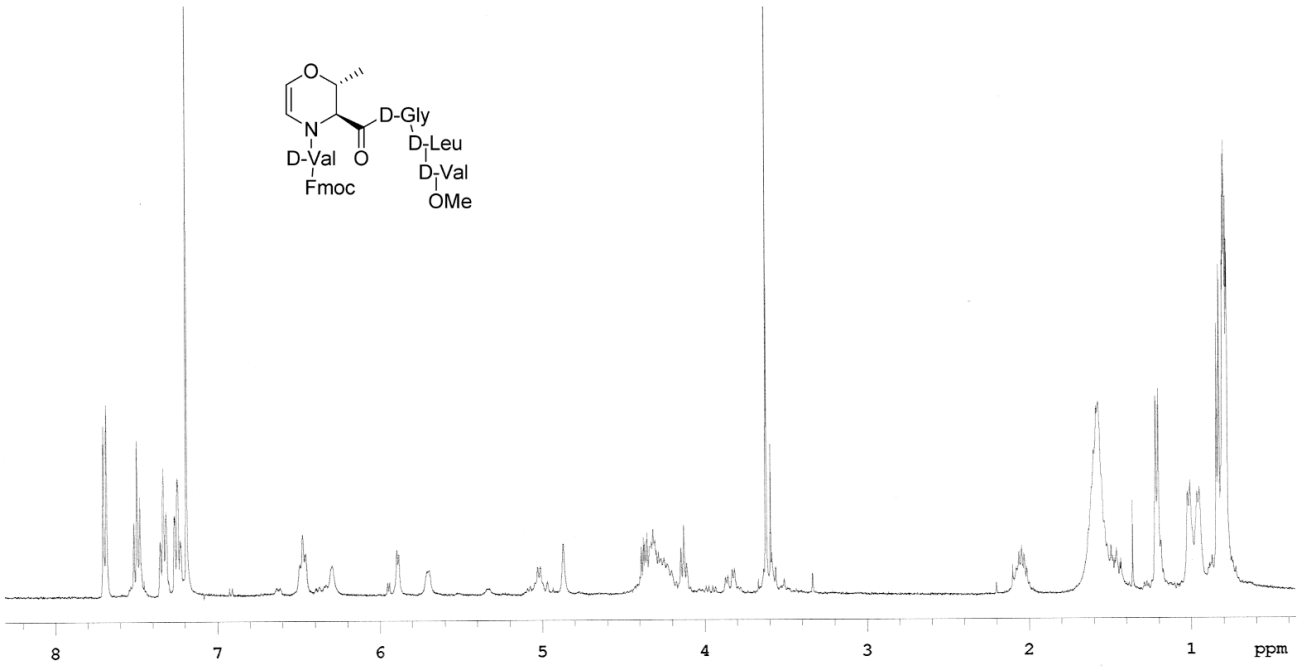


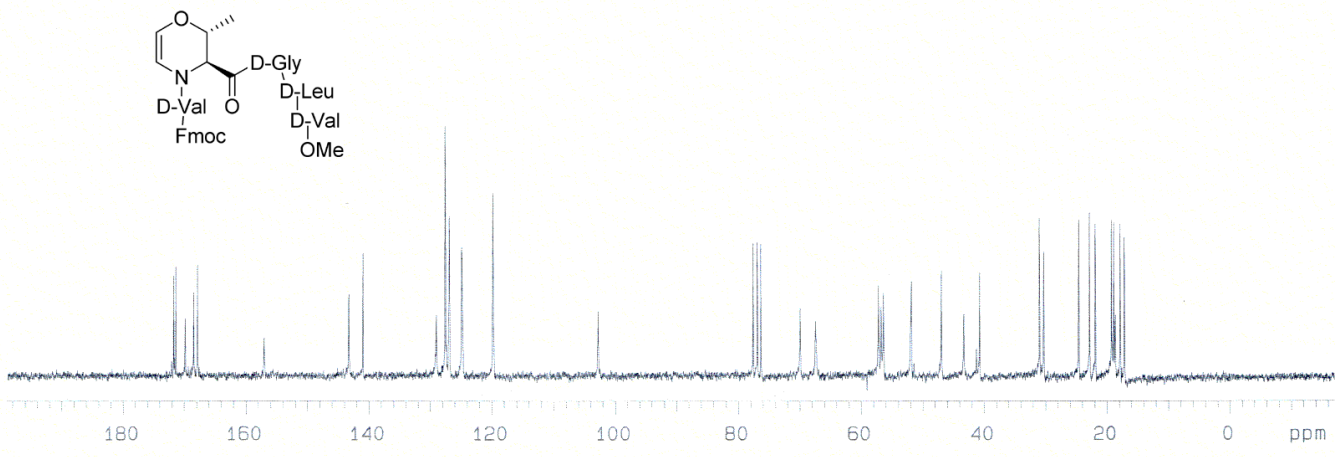
Compound 10c





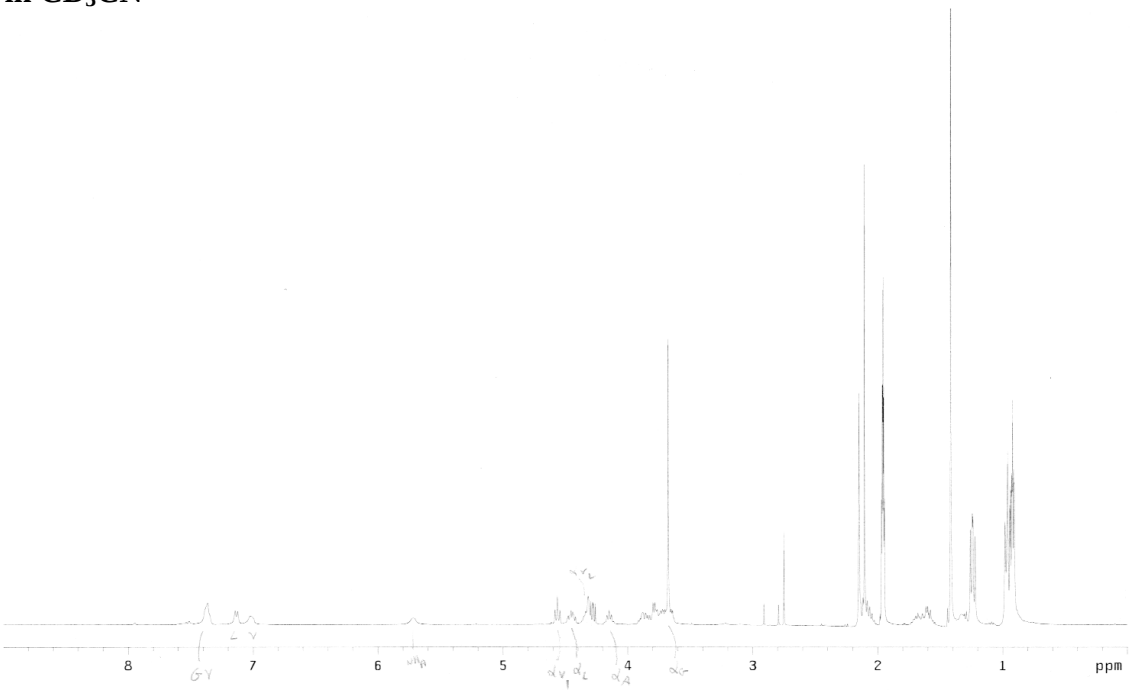
Compound 11



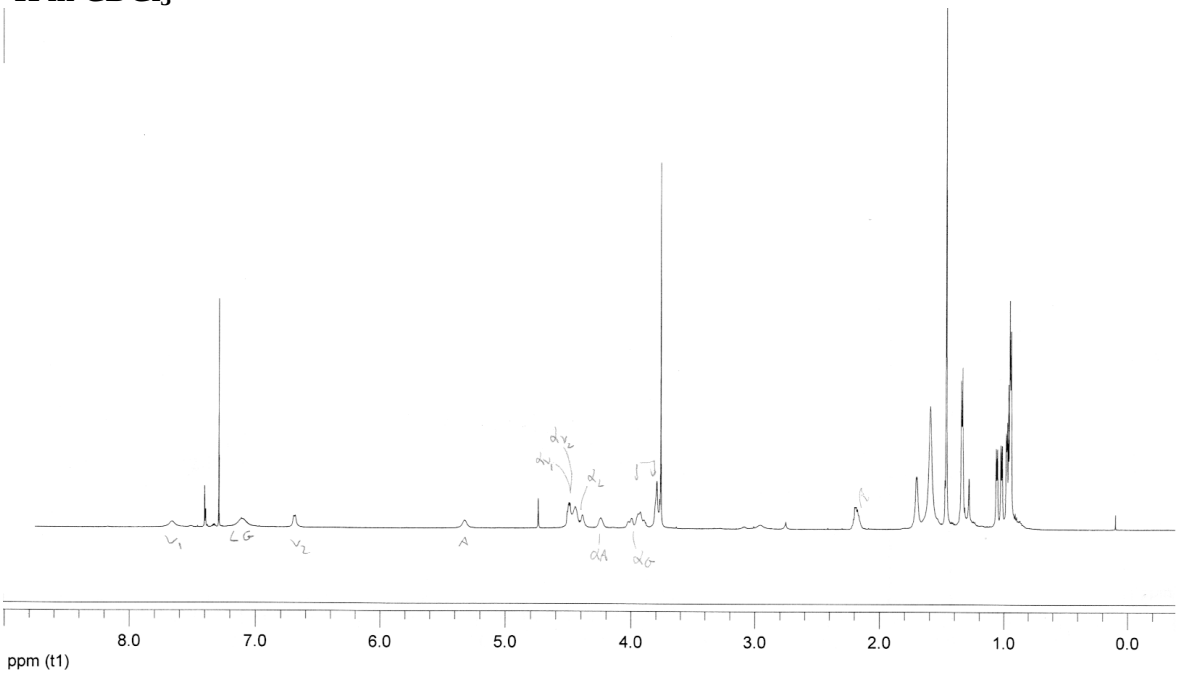


Compound I

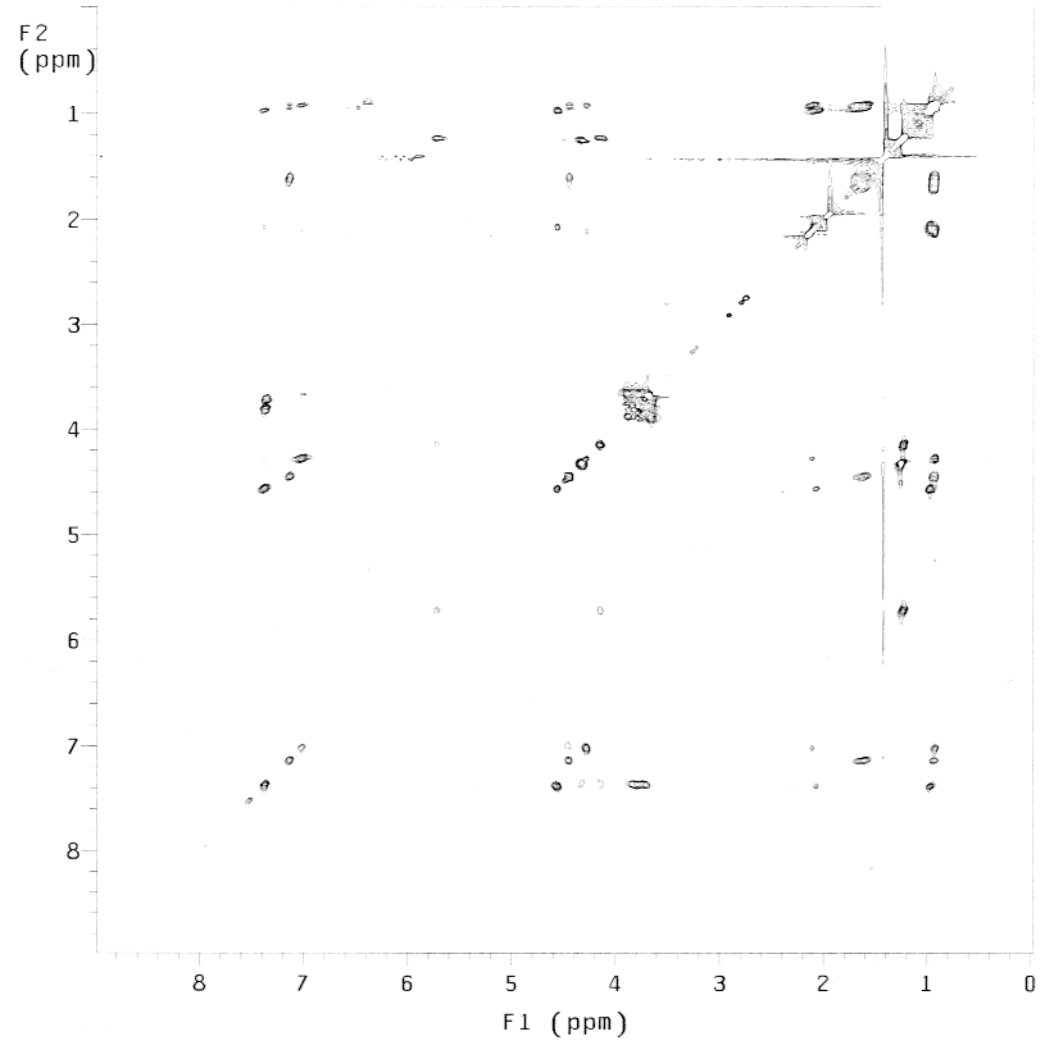
^{1}H in CD_3CN



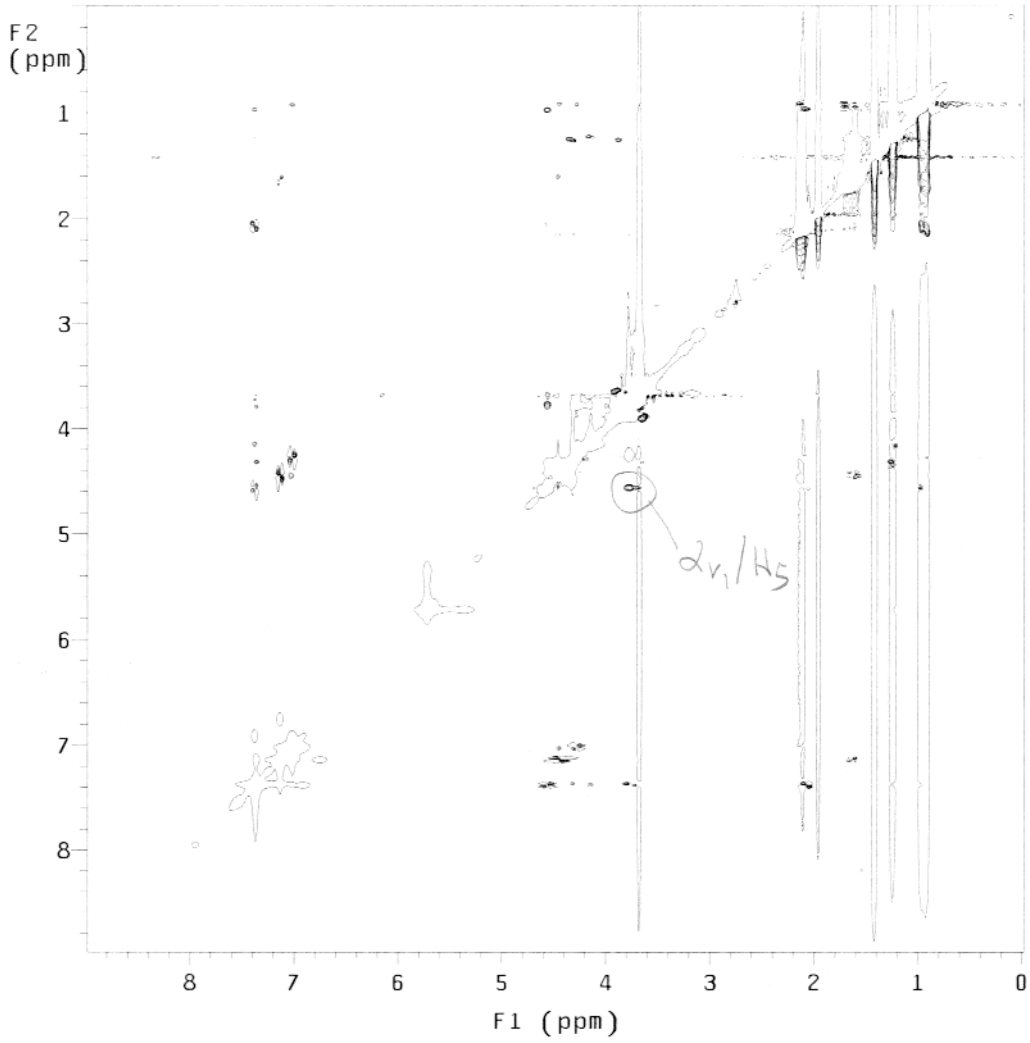
^{1}H in $CDCl_3$



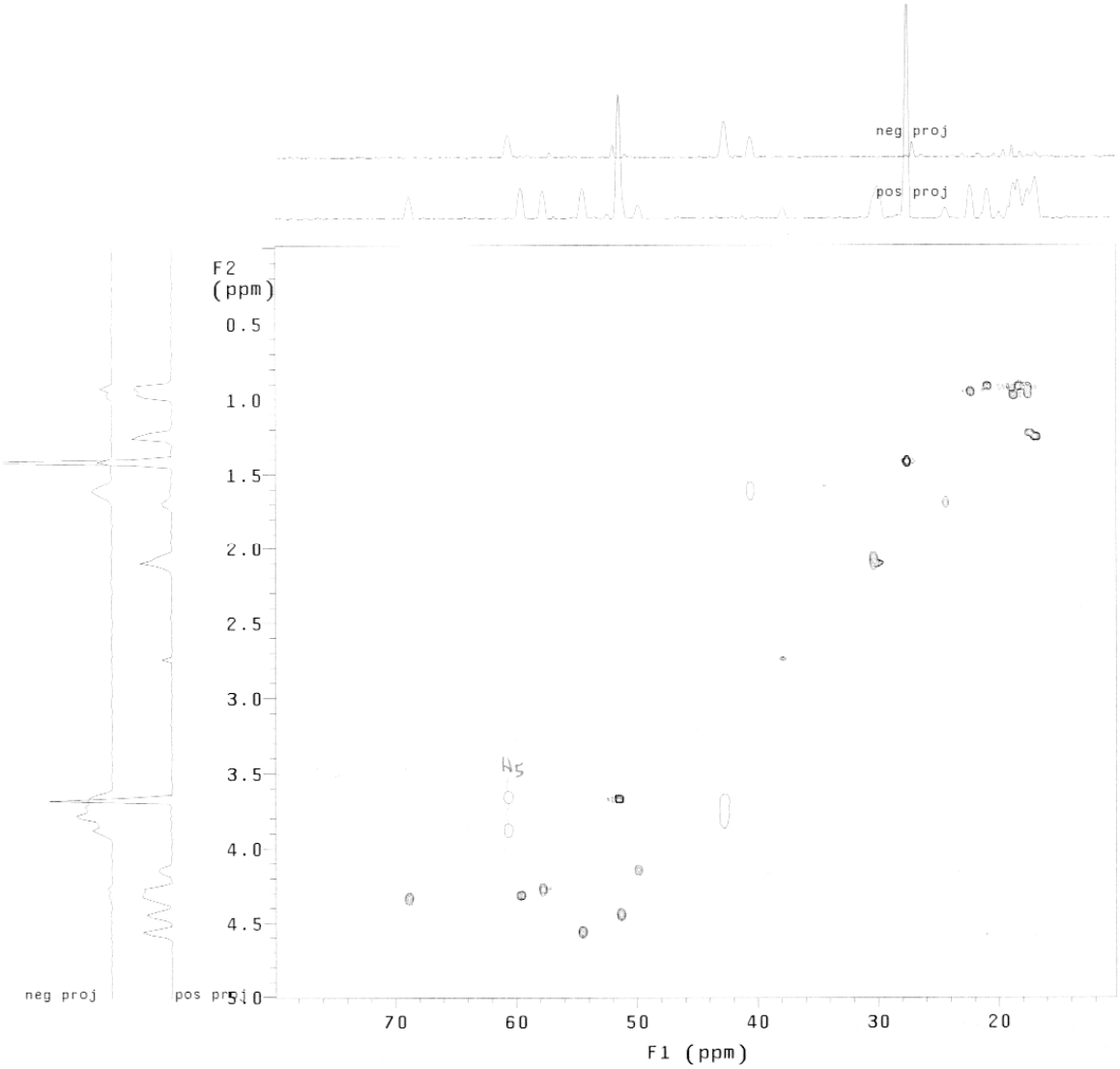
TOCSY



ROESY

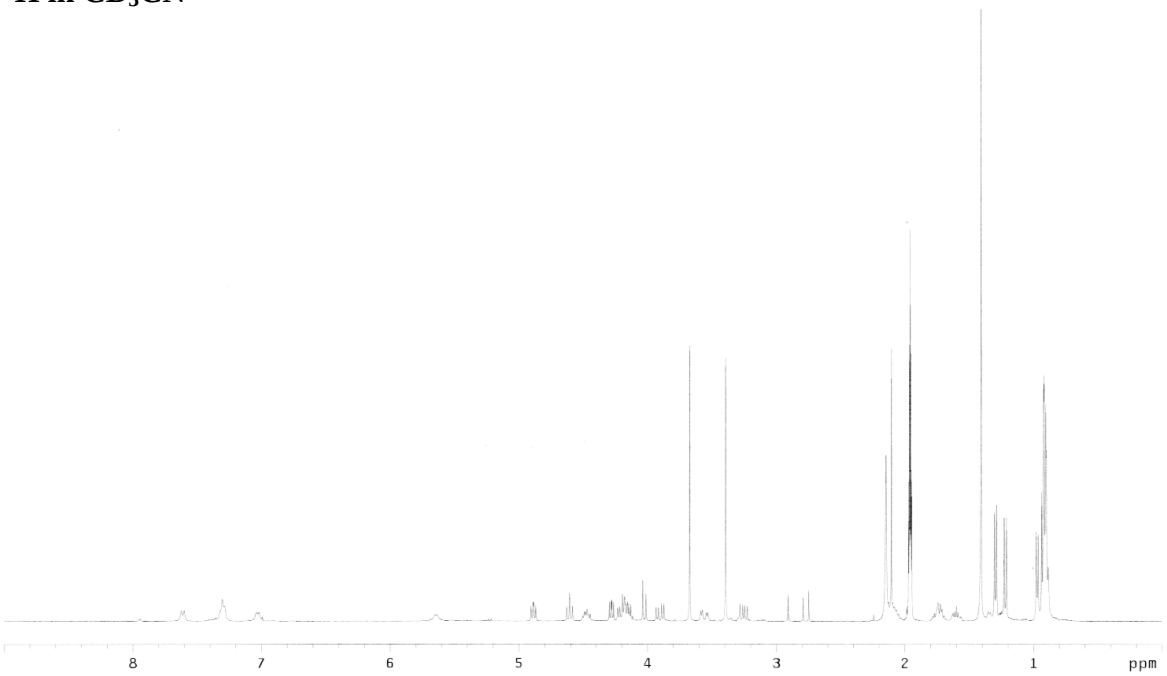


gHSQC

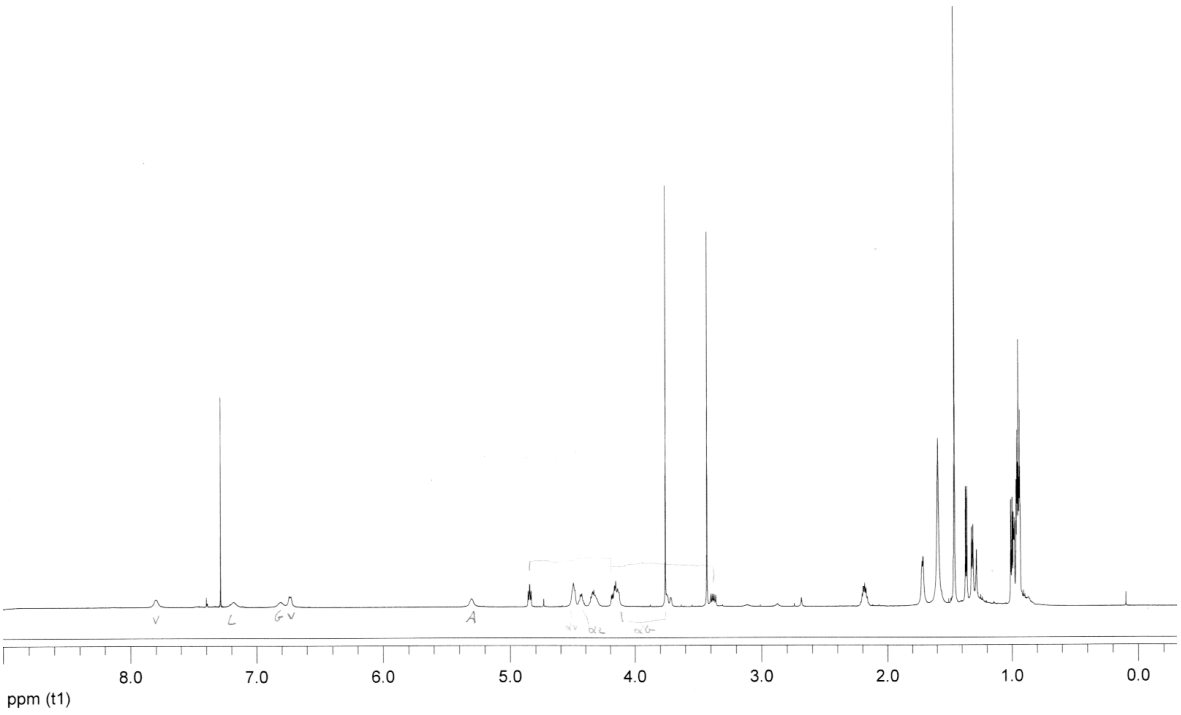


Compound II

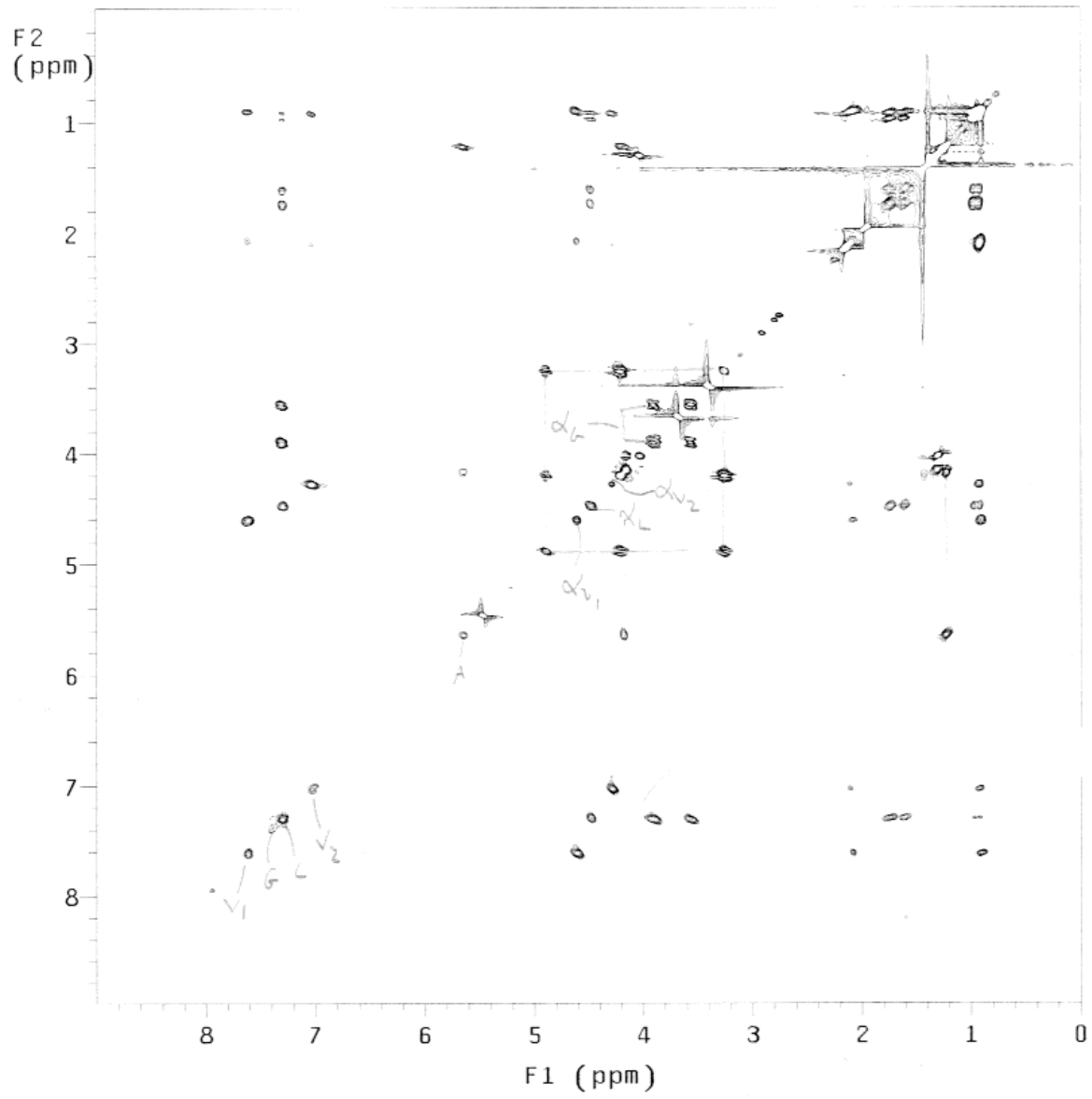
^1H in CD_3CN



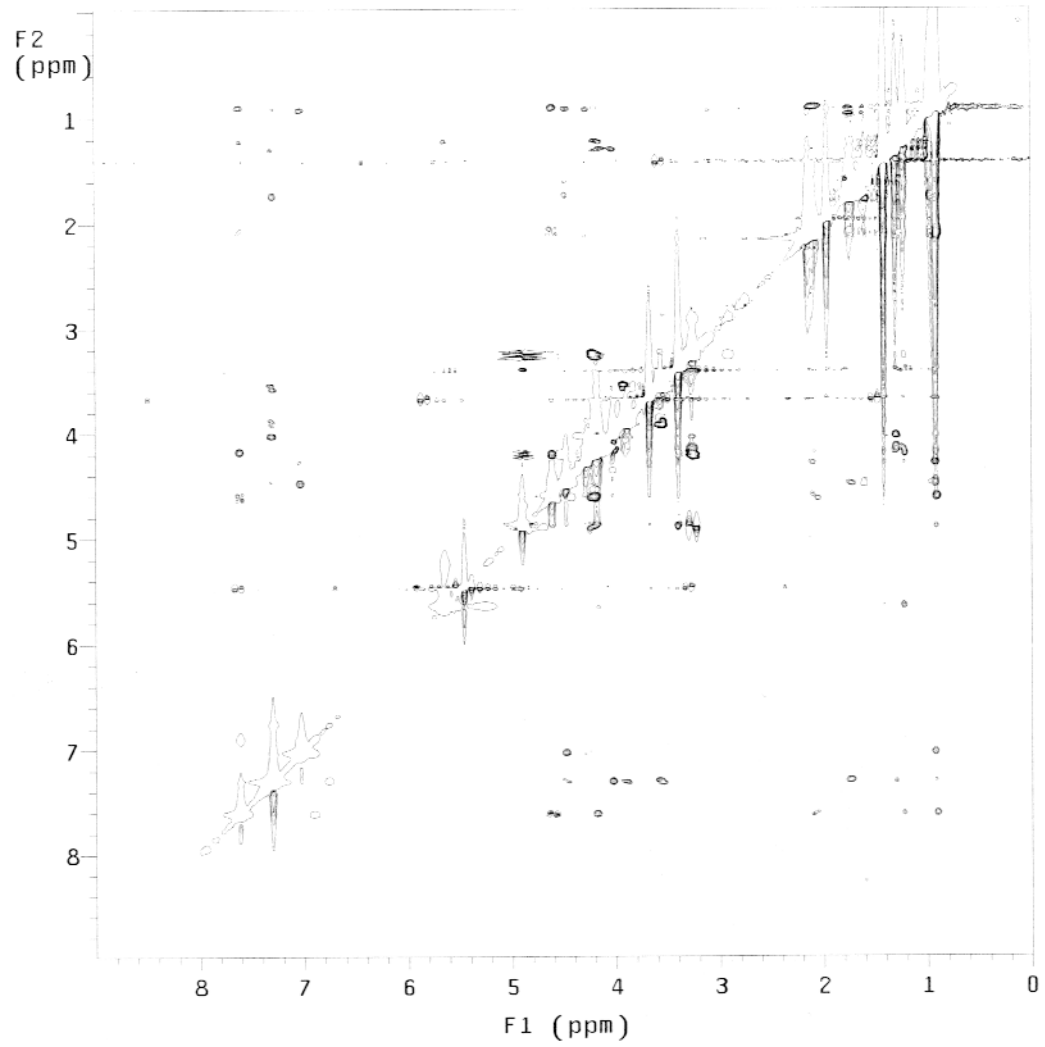
^1H in $CDCl_3$



TOCSY



ROESY



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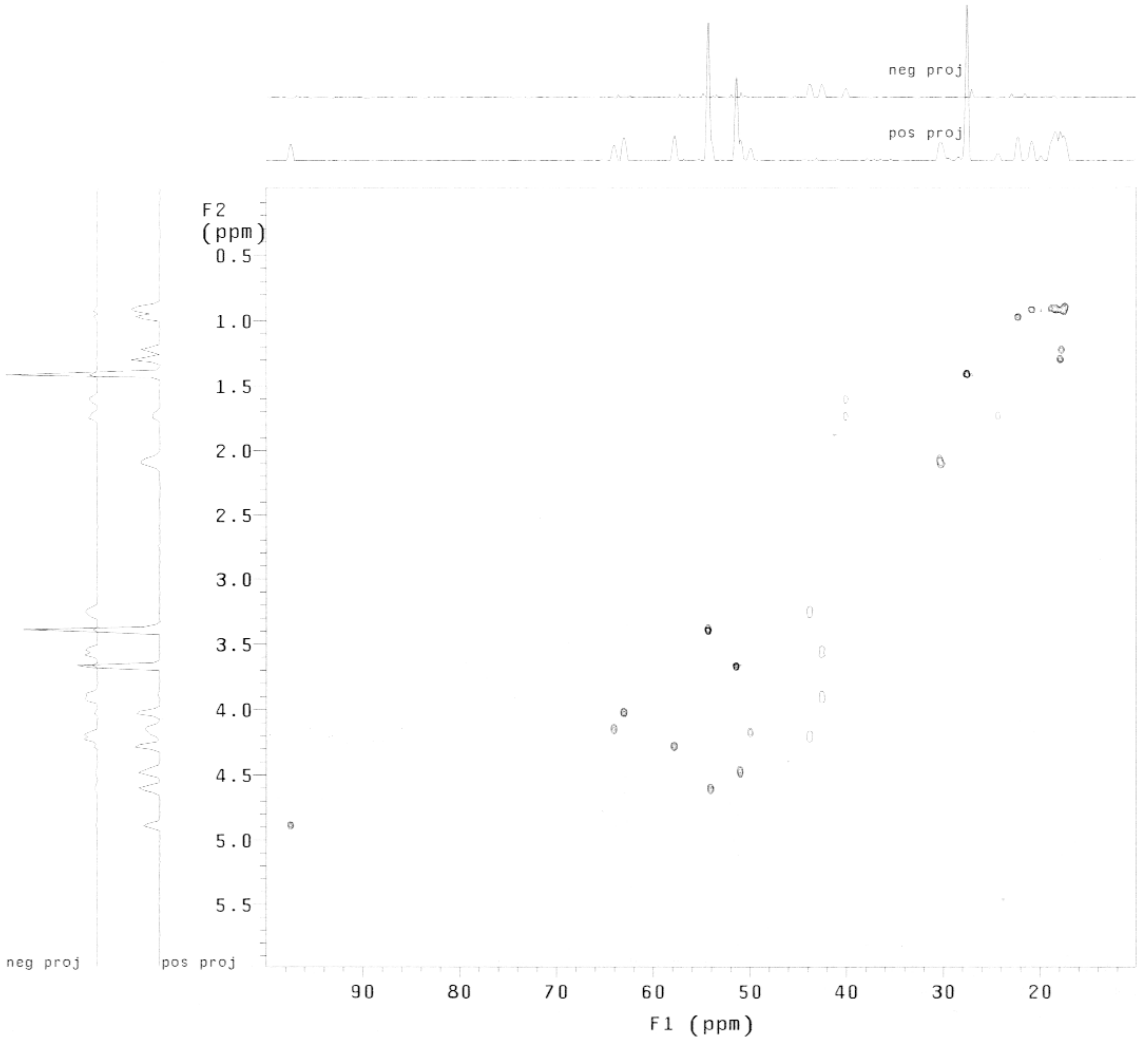
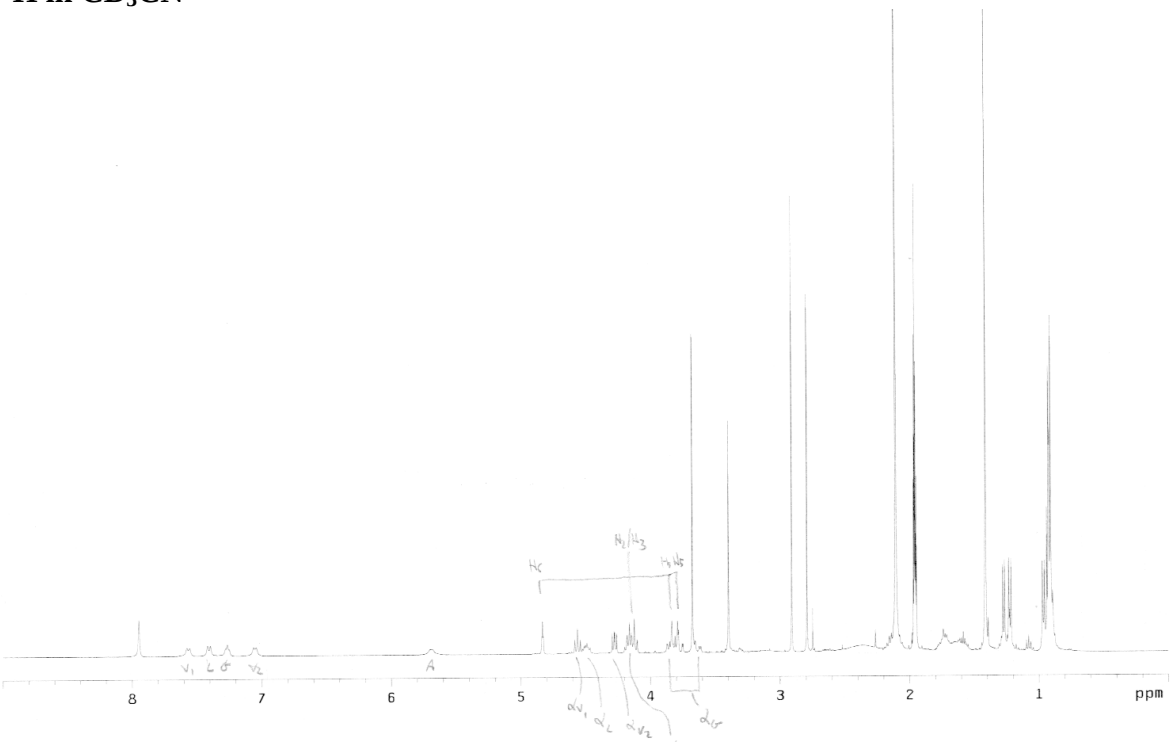
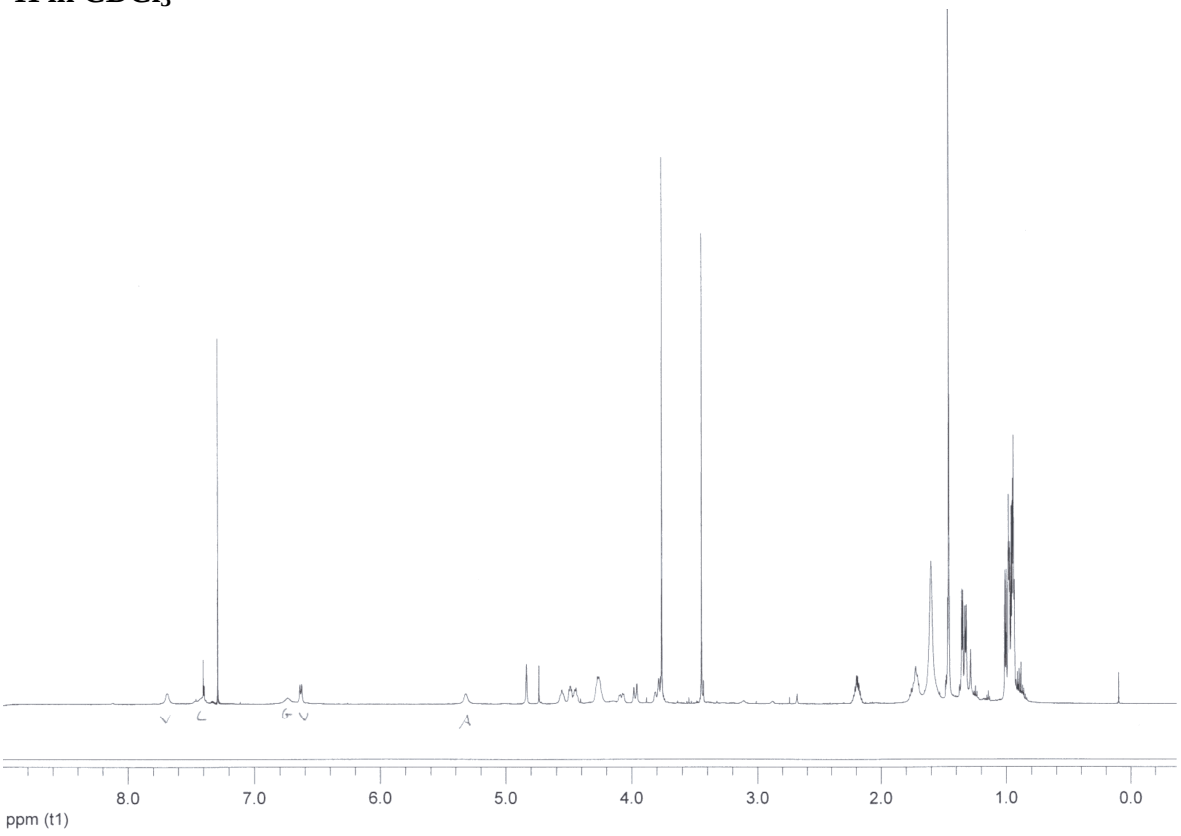


Compound III

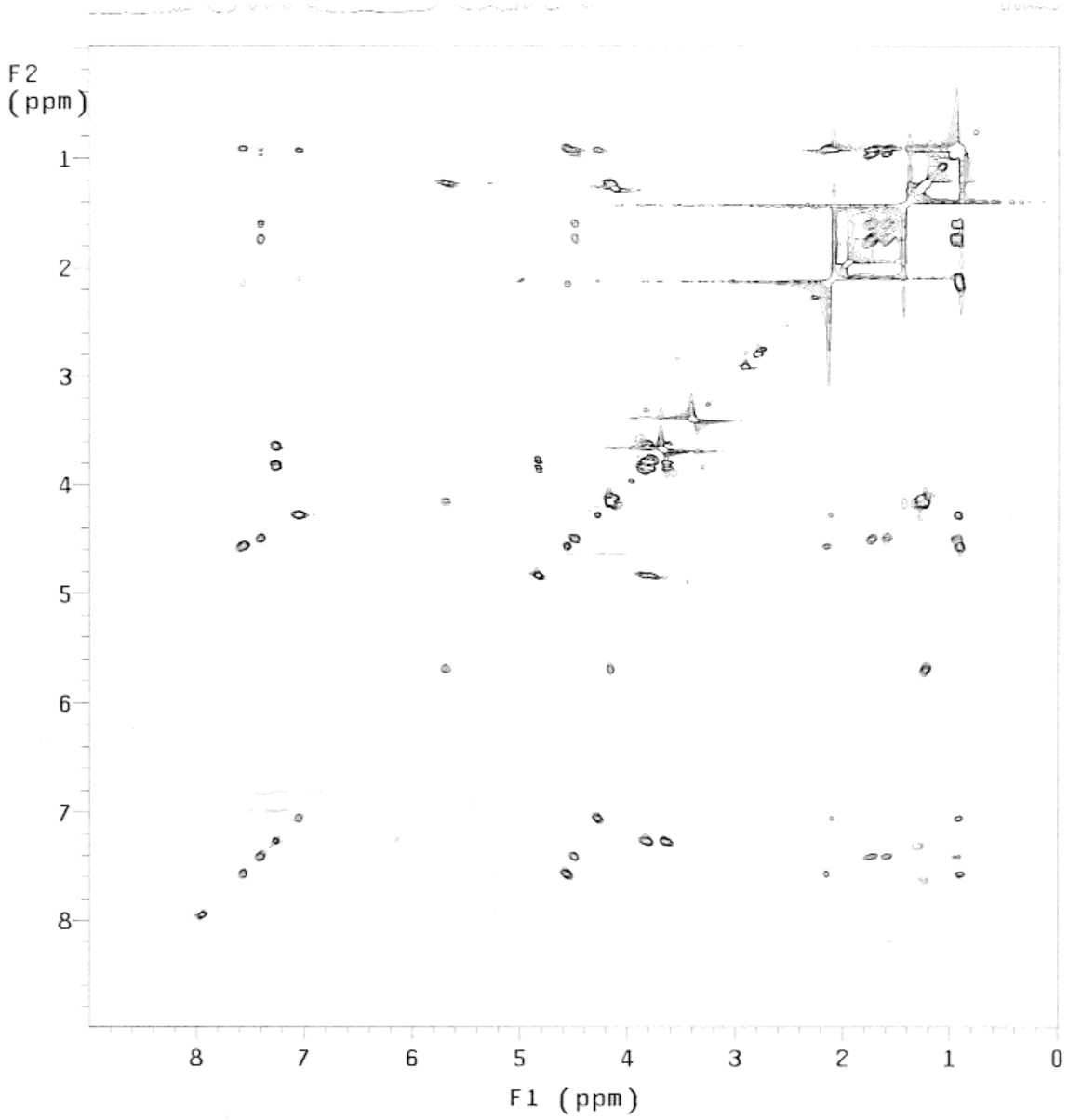
^{1}H in CD_3CN



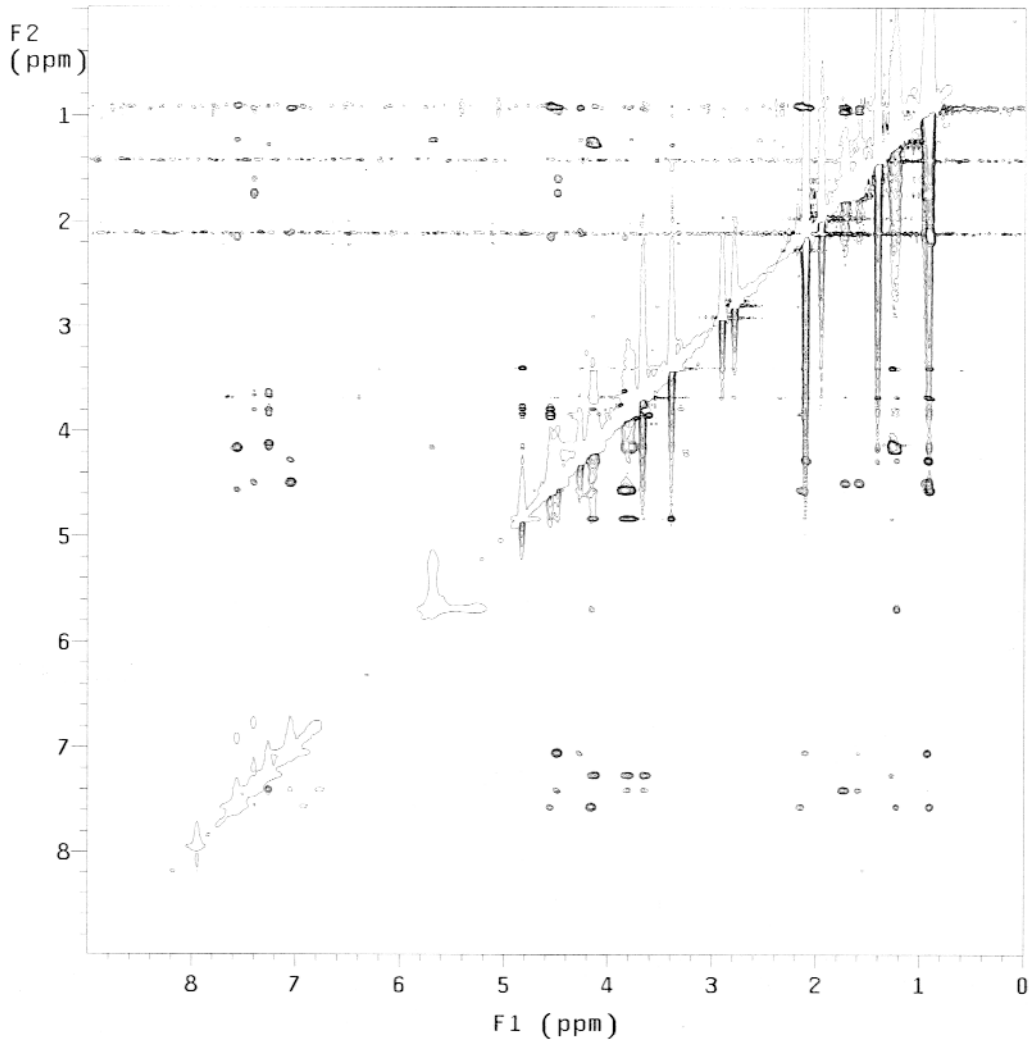
^{1}H in $CDCl_3$



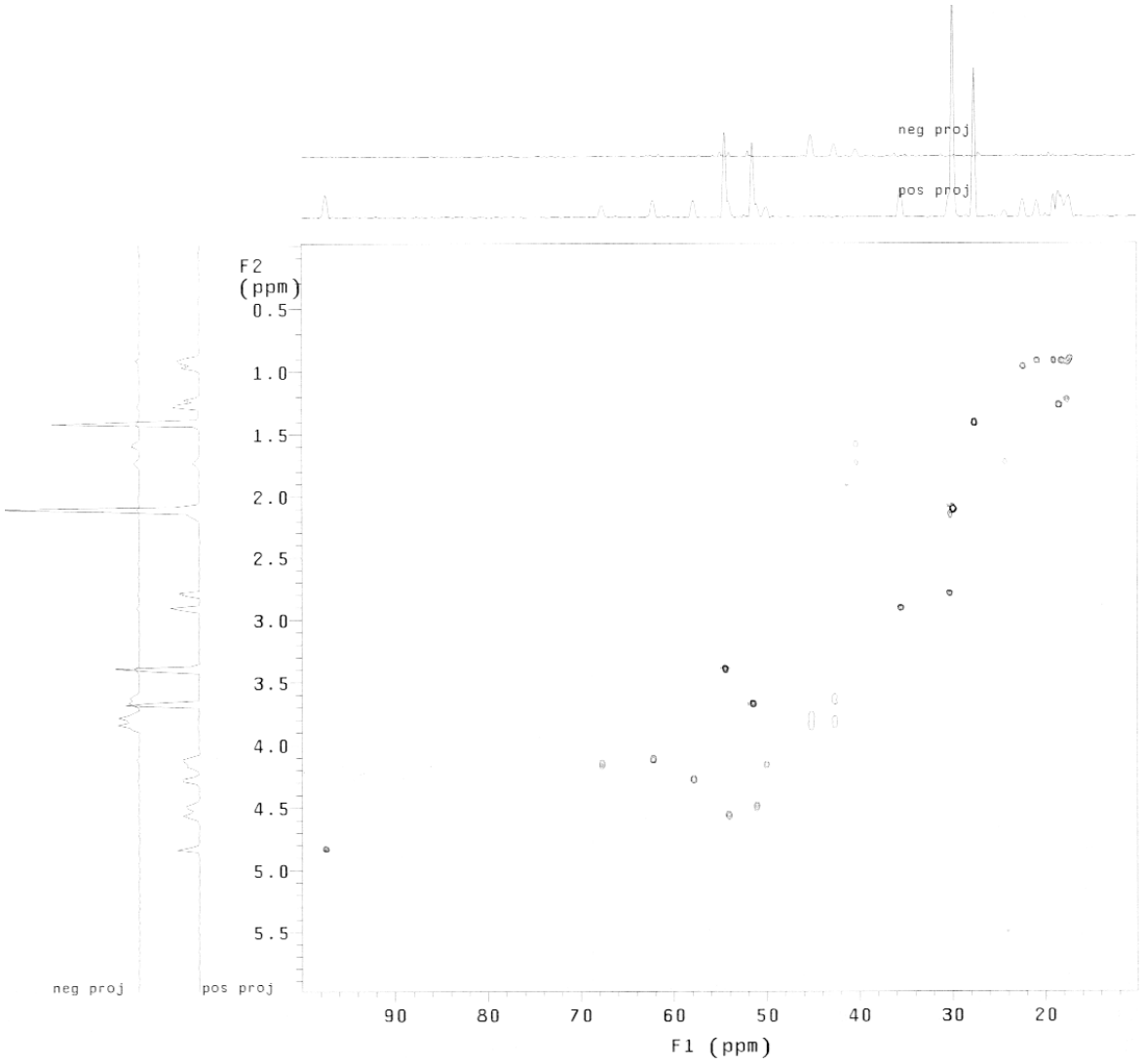
TOCSY



ROESY

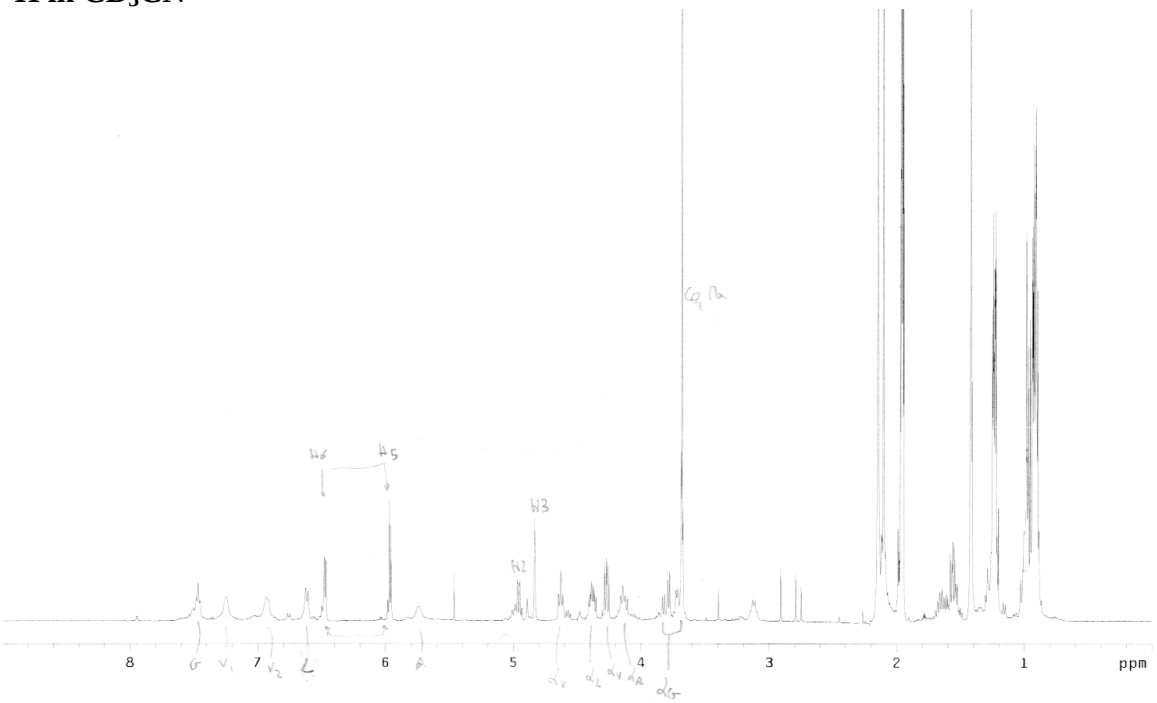


gHSQC

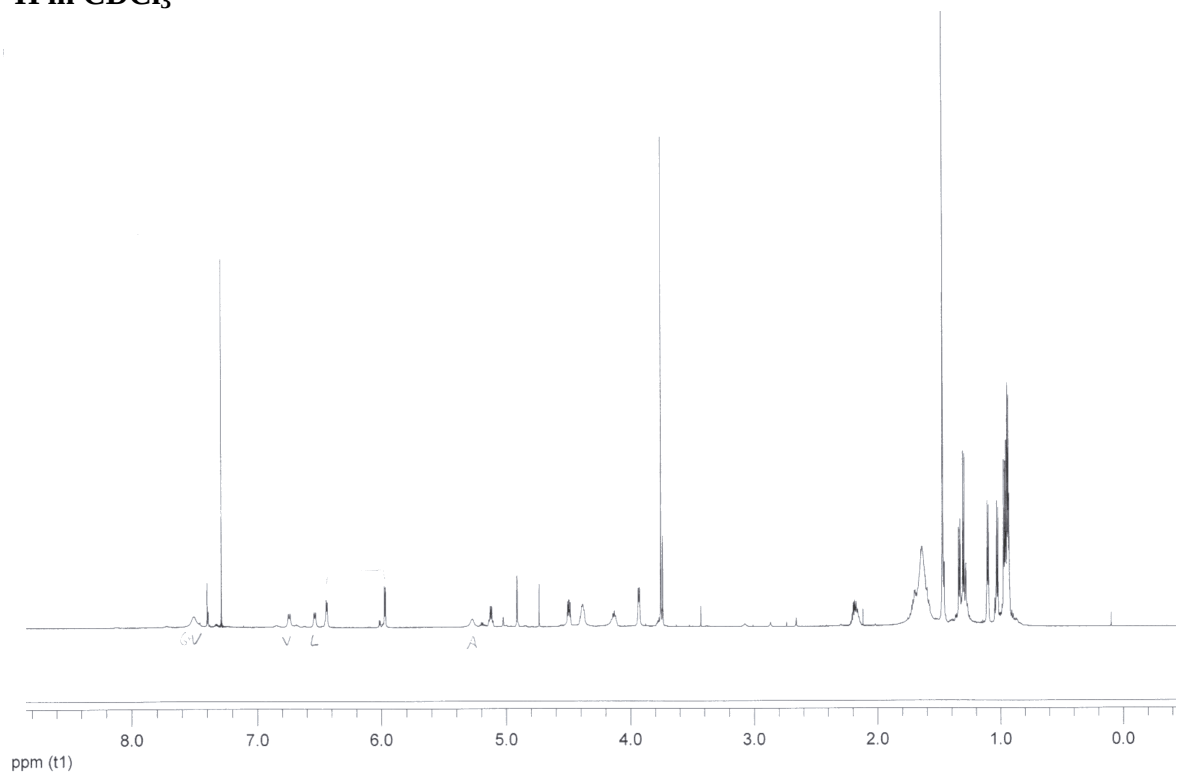


Compound IV

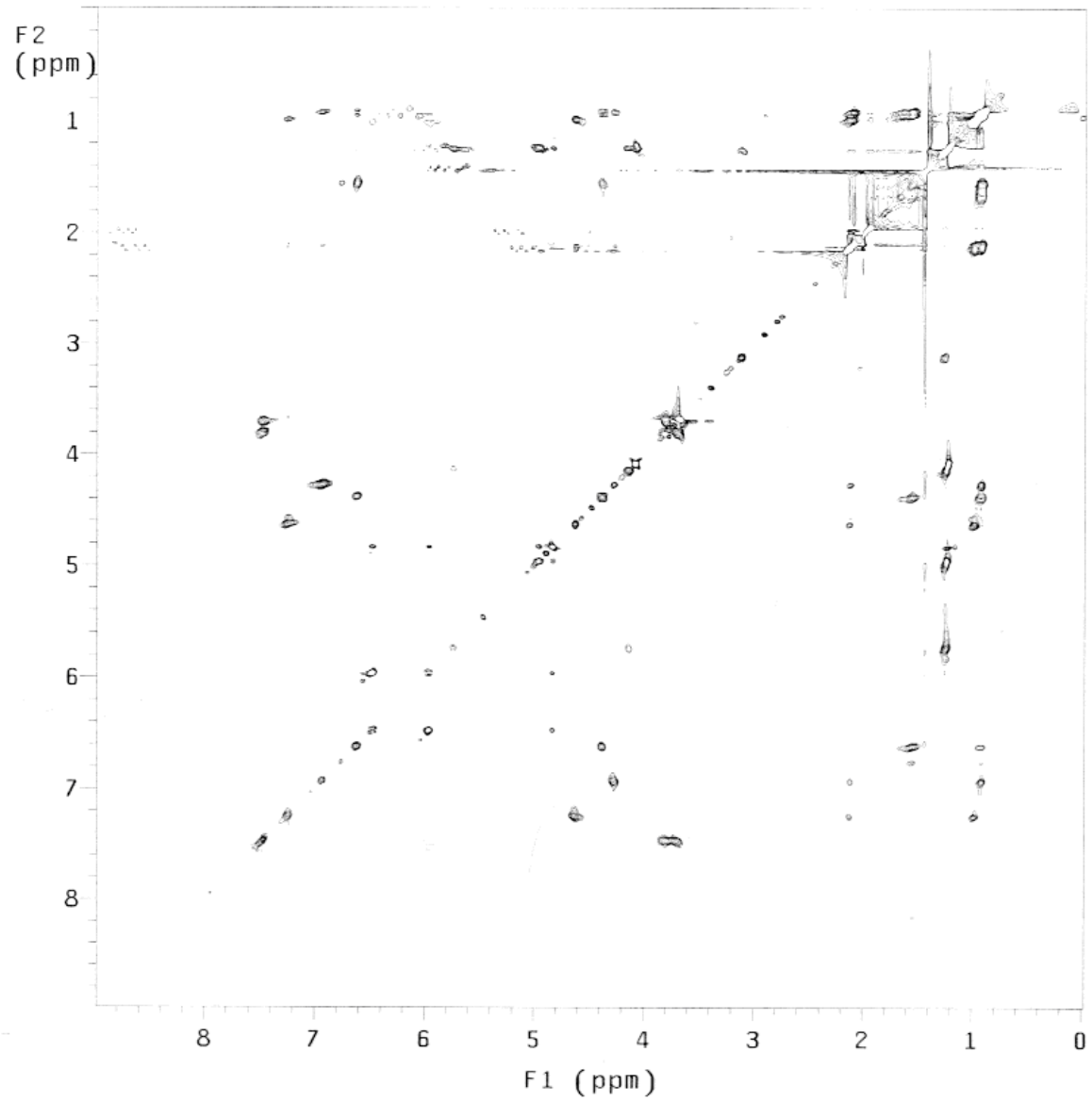
^{1}H in CD_3CN



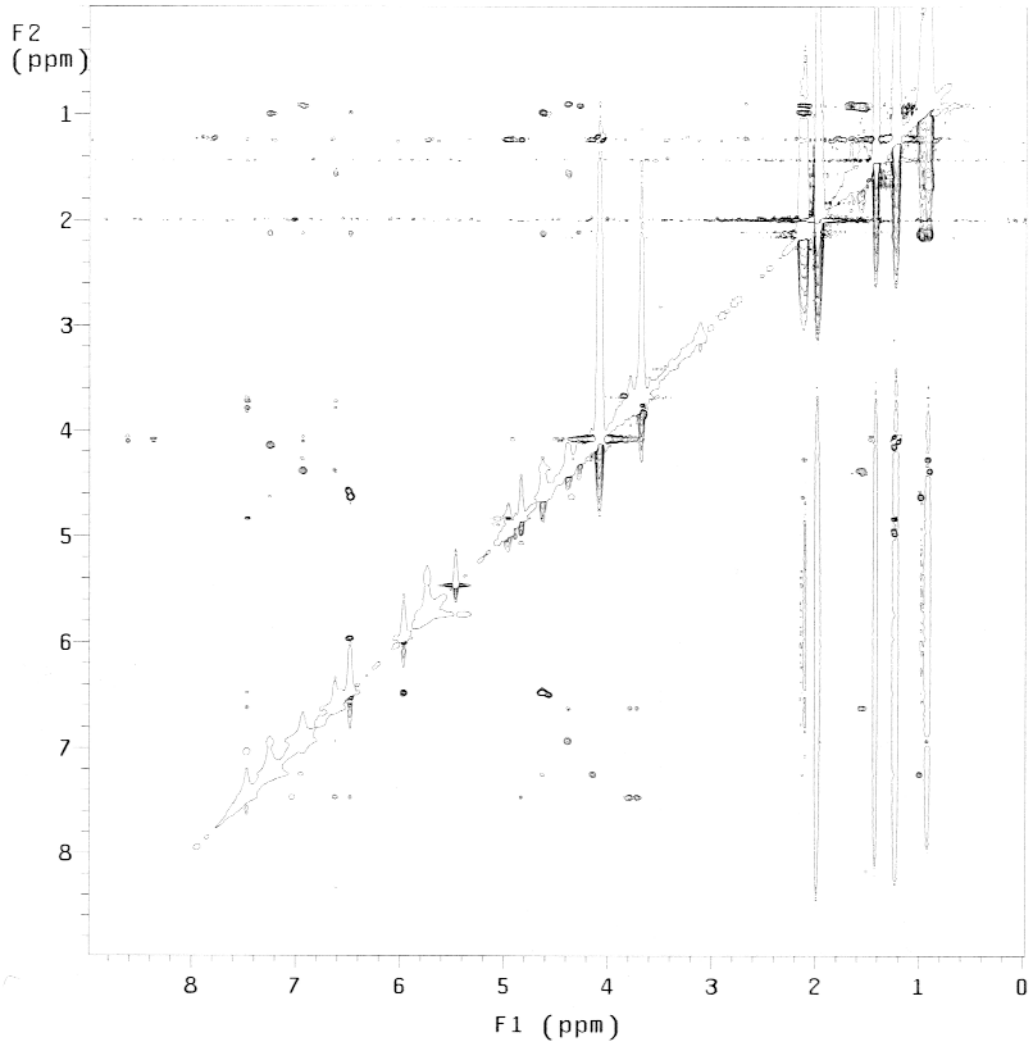
^{1}H in $CDCl_3$



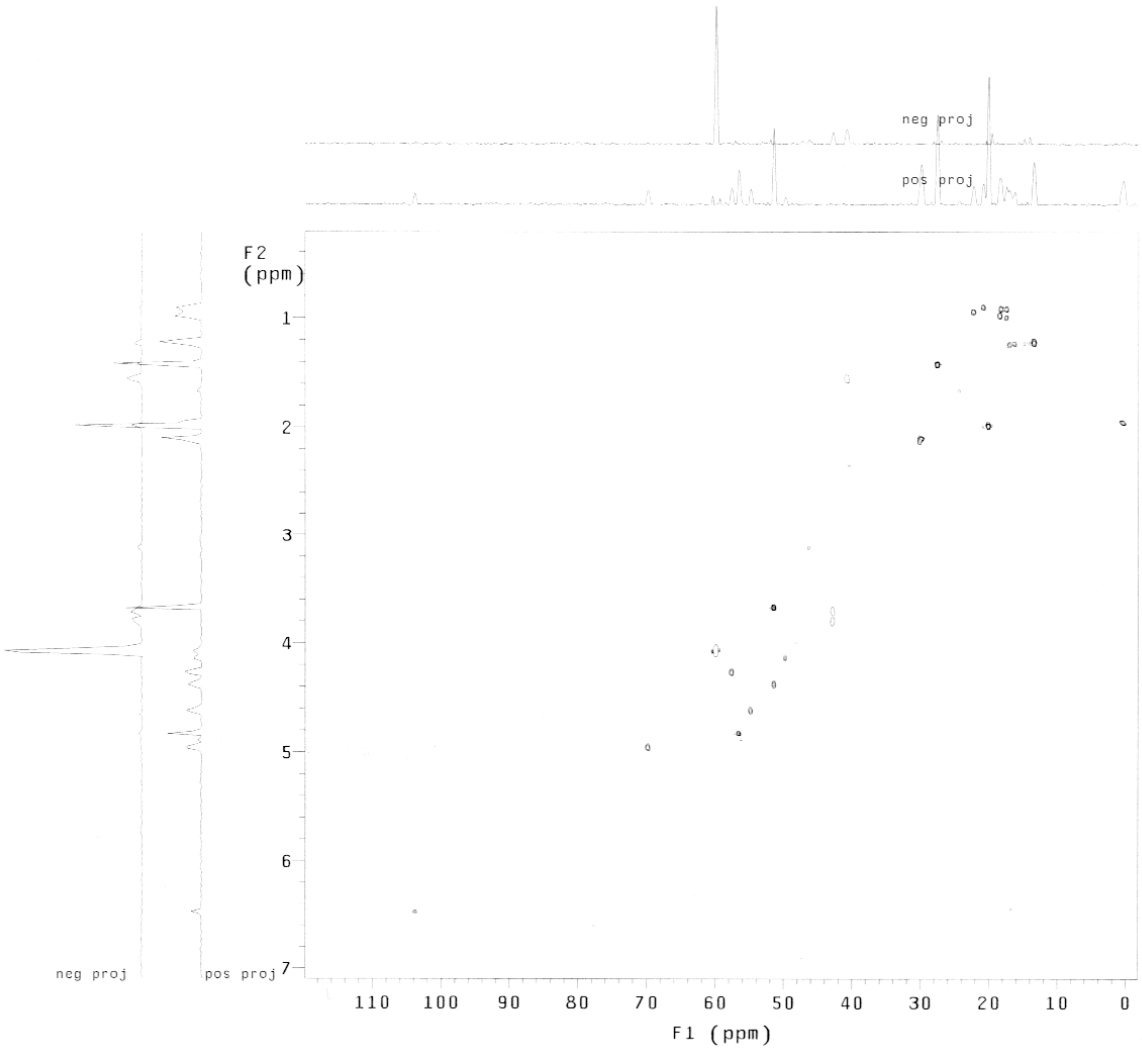
TOCSY



ROESY



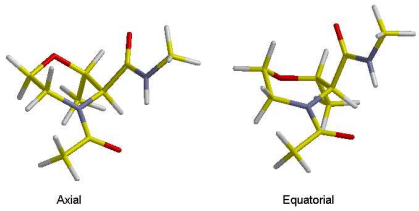
gHSQC


neg proj
pos proj
F2
(ppm)
1
2
3
4
5
6
7
neg proj
pos proj
110
100
90
80
70
60
50
40
30
20
10
0
F1 (ppm)

Computational data

Ab initio single point calculations of the electronic properties of the most abundant minimum energy conformer at the 6-31G*/HF level of quantum chemical theory. The axial structure is referred to the conformation having the substituents at C-2 and C-3 in axial orientation (1 a.u. = 627.5 kcal/mol).

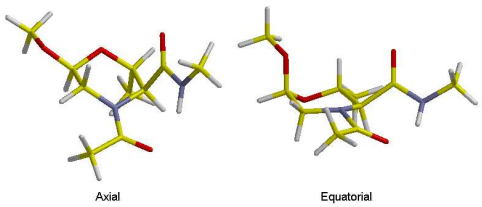
4-Acetyl-2-Me-Mor-3-methylamide (scaffold I)



Axial
Run type: Single point energy
Model: RHF/3-21G(*)
Number of shells: 74
46 S shells
28 SP shells
Number of basis functions: 158
Number of electrons: 108
Number of heavy atoms: 14
Number of hydrogens: 16
Use of molecular symmetry disabled
Molecular charge: 0
Spin multiplicity: 1
Memory model: direct 9.8 Mb
Point Group = C1 Order = 1 Nsymop = 1
This system has 84 degrees of freedom
E(HF) = -679.8130698 a.u.

Equatorial
Run type: Single point energy
Model: RHF/3-21G(*)
Number of shells: 74
46 S shells
28 SP shells
Number of basis functions: 158
Number of electrons: 108
Number of heavy atoms: 14
Number of hydrogens: 16
Use of molecular symmetry disabled
Molecular charge: 0
Spin multiplicity: 1
Memory model: direct 9.8 Mb
Point Group = C1 Order = 1 Nsymop = 1
This system has 84 degrees of freedom
E(HF) = -679.8147176 a.u.

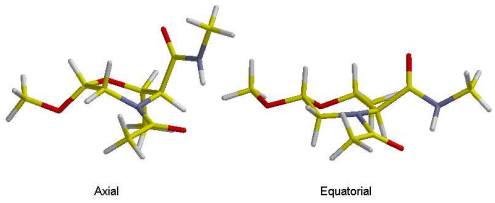
4-Acetyl-2-Me-(6*S*)-OMe-Mor-3-methylamide (scaffold II)



Axial
Run type: Single point energy
Model: RHF/3-21G(*)
Number of shells: 84
52 S shells
32 SP shells
Number of basis functions: 180
Number of electrons: 124
Number of heavy atoms: 16
Number of hydrogens: 18
Use of molecular symmetry disabled
Molecular charge: 0
Spin multiplicity: 1
Memory model: direct 11.8 Mb
Point Group = C1 Order = 1 Nsymop = 1
This system has 96 degrees of freedom
E(HF) = -793.0866731 a.u.

Equatorial
Run type: Single point energy
Model: RHF/3-21G(*)
Number of shells: 84
52 S shells
32 SP shells
Number of basis functions: 180
Number of electrons: 124
Number of heavy atoms: 16
Number of hydrogens: 18
Use of molecular symmetry disabled
Molecular charge: 0
Spin multiplicity: 1
Memory model: direct 11.8 Mb
Point Group = C1 Order = 1 Nsymop = 1
This system has 96 degrees of freedom
E(HF) = -793.0767991 a.u.

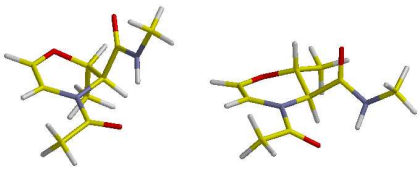
4-Acetyl-2-Me-(6*R*)-OMe-Mor-3-methylamide (scaffold III)



Axial
Run type: Single point energy
Model: RHF/3-21G(*)
Number of shells: 84
52 S shells
32 SP shells
Number of basis functions: 180
Number of electrons: 124
Number of heavy atoms: 16
Number of hydrogens: 18
Use of molecular symmetry disabled
Molecular charge: 0
Spin multiplicity: 1
Memory model: direct 11.8 Mb
Point Group = C1 Order = 1 Nsymop = 1
This system has 96 degrees of freedom
E(HF) = -793.0667033 a.u.

Equatorial
Run type: Single point energy
Model: RHF/3-21G(*)
Number of shells: 84
52 S shells
32 SP shells
Number of basis functions: 180
Number of electrons: 124
Number of heavy atoms: 16
Number of hydrogens: 18
Use of molecular symmetry disabled
Molecular charge: 0
Spin multiplicity: 1
Memory model: direct 11.8 Mb
Point Group = C1 Order = 1 Nsymop = 1
This system has 96 degrees of freedom
E(HF) = -793.0771600 a.u.

4-Acetyl-2-Me-3,4-dihydro-2*H*-[1,4]oxazine-3-methylamide (scaffold IV)



Axial Equatorial

Axial

Run type: Single point energy
Model: RHF/3-21G(*)
Number of shells: 70
42 S shells
28 SP shells
Number of basis functions: 154
Number of electrons: 106
Number of heavy atoms: 14
Number of hydrogens: 14
Use of molecular symmetry disabled
Molecular charge: 0
Spin multiplicity: 1
Memory model: direct 9.5 Mb
Point Group = C1 Order = 1 Nsymop = 1
This system has 78 degrees of freedom
E(HF) = -678.6528640 a.u.

Equatorial

Run type: Single point energy
Model: RHF/3-21G(*)
Number of shells: 70
42 S shells
28 SP shells
Number of basis functions: 154
Number of electrons: 106
Number of heavy atoms: 14
Number of hydrogens: 14
Use of molecular symmetry disabled
Molecular charge: 0
Spin multiplicity: 1
Memory model: direct 9.5 Mb
Point Group = C1 Order = 1 Nsymop = 1
This system has 78 degrees of freedom
E(HF) = -678.6417848 a.u.