Supporting Information

Efficient Activity of Magnesium/Aluminium Hydrotalcite in the Synthesis of Amides.

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1. General methods

All reactions were conducted under a dried argon stream. All the chemicals were purchased from Aldrich Chemical Co and used without further purification unless stated otherwise. Yields refer to the chromatographically and spectroscopically (^{1}H and ^{13}C) homogeneous materials, unless otherwise stated. All glassware utilized was flame-dried before use. Reactions were monitored by TLC carried out on 0.25 mm Macherey Nagel silica gel plates. Developed TLC plates were visualized under a short-wave UV lamp and by heating plates that were dipped in $Ce(SO_4)_2$. Flash column chromatography (FCC) was performed using flash silica gel (230–400) and employed a solvent polarity correlated with TLC mobility. Optical rotations were measured at 589 nm on a Perkin Elmer 343 digital polarimeter using a 100 mm cell. NMR experiments were conducted on a Varian Unity and Bruker Avance 300 MHz instruments using $CDCl_3$ (99.9% D) as the solvent, with chemical shifts (δ) referenced to internal standards residual $CHCl_3$ and $CDCl_3$,(7.26 ppm ^{1}H, 77.0 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm). Chemical shifts are in parts per million (ppm). Mass spectra were recorded on Jeol JS102 high-resolution mass spectrometer. The hydrotalcites were characterized by powder XRD with Cu-Ka radiation, using a Siemens diffractometer in the range from 4 to 70◦ (2*q*). FT-IR spectra were recorded on a Nicolet Magna 750 spectrometer, data collection was performed using DRIFT and KBr disc techniques. Specific surface areas were calculated by N_2 adsorption at 75.25K (BET method) using a Micromeritics ASAP 2000 instrument, the samples were first out-gassed at 523 K. The basic character of hydrotalcites was compared by CO_2 adsorption FT-IR experiments. The HPLC apparatus used for the analysis of **3** was an Agilent 1200 Series equipped with a Waters 2996 Photodiode Array Detector. The column was a ZORBAX Eclipse Plus C18 3.5 μm 2.1 x 100 mm (Agilent), the mobile phase flow–rate was 0.2 mL/min and the detection range was 200-600 nm. Elution solvents were A (water/formic acid 99.9/0.1, v/v) and B (Methanol) and the elution program was from 40 to 100% of B during 15 min followed by isocratic elution with 100% of B during 7 min.

2. Experimental procedures

Preparation of Al/Mg hydrotalcite[1,2]

A solution of NaOH (14.00 g) and Na_2CO_3 (9.54 g) in 70 mL of deionised water was added to a solution of $Mg(NO_3)_2 \cdot 6H_2O$ (25.64 g) and $Al(NO_3)_3 \cdot 9H_2O$ (18.75 g) in 45 mL of deionised water. The addition was made drop wise over 4 h, thus forming a white gel which is then stirred and heated to 60 °C for 18 h. The resulting gel was allowed to cool and washed with deionised water to pH = 9. The compound was dried at 110 °C for 18 h, thereby obtaining the synthesized hydrotalcite.

Preparation of calcined hydrotalcite[1,2]

The calcined hydrotalcite was obtained by heating of synthesized hydrotalcite at 500 °C in a tubular furnace under air flow for 8 h.

Preparation of rehydrated hydrotalcite[1,2]

The reconstructed layered double hydroxide was obtained by rehydration of calcined hydrotalcite. Thus, calcined hydrotalcite was immersed in methanol/water solution (v/v, 1/1) at 60 ^oC by 4 h under mechanical stirring. The solid was filtrated and dried at 110°C by one hour.

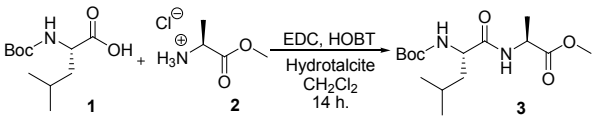
General procedure for the synthesis of amides

A solution of carboxylic acid (1 mmol), EDC (1.1 mmol), HOBT (1.1 mmol) and hydrotalcite in anhydrous CH_2Cl_2 (45 mL) was stirred at 0 °C under an argon atmosphere. Then a solution of amine (1 mmol) in anhydrous CH_2Cl_2 (5 mL) was added. The reaction mixture was stirred at for 1 h at 0 °C under argon atmosphere. After stirring for 18 h at room temperature, the reaction mixture was filtered and concentrated in vacuum. The residue was dissolved in ethyl acetate (30 ml) and washed successively with 10% citric acid solution (2 x 20 mL), 10% $NaHCO_3$ solution (2 x 25 mL), 10% K_2CO_3 solution (2 x 25 mL) and brine (2 x 25 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuum. The resulting residue was purified by flash column chromatography on silica gel.

3. Optimization conditions for the synthesis of amides

Initially, we optimized typical reaction parameters including various mole ratios of commercial hydrotalcite (HTs Aldrich®, $Mg_6Al_2(CO_3)(OH)_{16}\cdot 4H_2O$), temperature and solvents (Table S1).

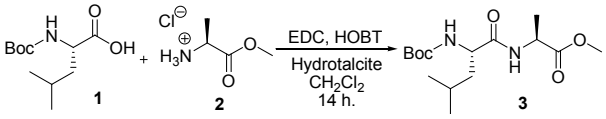
Table S1 Optimization of reaction conditions for the synthesis of peptide **3**[a]



Entry	HTs mg	Equiv. of **2**	Temp.	Solvent	Yield %[b]
1	50	1	r.t.	CH_2Cl_2	18
2	100	1	r.t.	CH_2Cl_2	30
3	125	1	r.t.	CH_2Cl_2	38
4	150	1	r.t.	CH_2Cl_2	65
5	200	1	r.t.	CH_2Cl_2	80
6	250	1	r.t.	CH_2Cl_2	95
7	300	1	r.t.	CH_2Cl_2	85
8	250	1	r.t.	$CHCl_3$	92
9	250	1	r.t.	THF	90
10	250	1	r.t.	DMF	88
11	150	1.5	r.t.	CH_2Cl_2	65
12	150	2.0	r.t.	CH_2Cl_2	70
13	150	3.0	r.t.	CH_2Cl_2	58
14	100	1	Reflux	CH_2Cl_2	26
15	150	1	Reflux	CH_2Cl_2	55

[a] Reaction conditions: *N*-Boc-Leucine **1** (1 mmol), L-Alanine methyl ester hydrochloride **2** (1 mmol), EDC (1.1 mmol), HOBT (1 mmol) CH_2Cl_2 (25 ml), r.t., 14 h. [b] Yield of isolated product after chromatographic purification.

Table S2 Catalyst screening for the synthesis of peptide **3**[a]



Entry	Hydrotalcite	mg	Yield %[b]
1	Synthesized	125	45
2	Synthesized	150	75
3	Synthesized	200	80
4	Synthesized	250	95
5	Calcined	125	70
6	Calcined	150	85
7	Calcined	200	90
8	Calcined	250	90
9	Reconstructed	125	70
10	Reconstructed	150	95
11	Reconstructed	200	95
12	Reconstructed	250	95

[a] Reaction conditions: *N*-Boc-Leucine **1** (1 mmol), L-Alanine methyl ester hydrochloride **2** (1 mmol), EDC (1.1 mmol), HOBT (1.1 mmol) CH_2Cl_2 (25 ml), r.t., 14 h. [b] Yield of isolated product after chromatographic purification.

In order to compare the efficiency of those hydrotalcites in the amide bond formation, a catalyst screening was carried out using the different concentration of hydrotalcite: synthesized, calcined and reconstructed (Table S2).

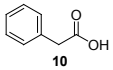
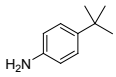
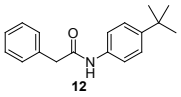
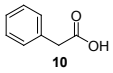
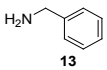
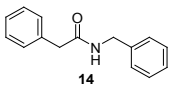
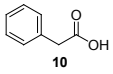
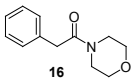
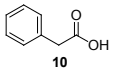
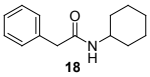
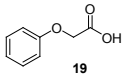
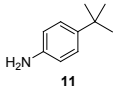
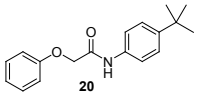
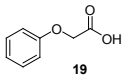
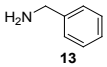
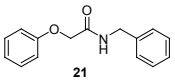
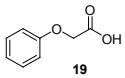
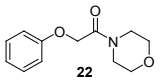
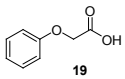
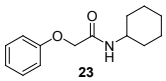
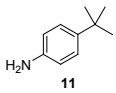
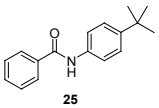
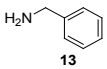
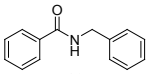
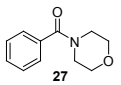
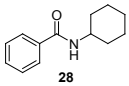
The optimized reaction conditions have prompted us to extend our studies through a variety of carboxylic acids and amines. The results are summarized in Table S3. All the reactions progressed smoothly and the isolated yields to the corresponding amides were 50-95%. Excellent yield were obtained when the reactions were carried out with primary amines in presence of reconstructed hydrotalcite (Table S3, entries 1, 2, 5 and 6). The yield is significantly minor when the reactions were performed with sterical impedes amines (Table S3, entries 3, 4, 7, 8) or benzoic acid (Table S3, entries 9-12). However, in all cases reconstructed hydrotalcite was more active than the other hydrotalcites, since a minor amount of catalyst was necessary to complete the process.

Since naturally occurring macrocycles are often found to be lactams,[3] many examples of the application of lactamization ring closing methods have been reported. In this work, we extend our study to the synthesis of lactams **30** and **32** from amino acids **29** and **31** (Table S4, entries 1 and 2), using conditions above described. In these intramolecular process, the behaviour of hydrotalcites are similar than to intermolecular reaction, excellent yields were achieved with reconstructed material.

Usually, the intramolecular amide formation from ω-amino acids is carried out used peptide coupling reagents and lactonization strategies.[4,5,6] However, in the great majority of those cases the lactamization must be performed in the presence of a base excess to set free the amine group and give place to formation of macrolactam. Thus, in this work we considerate the possibility to use a hydrotalcite to set free the amino group from its zwitterion allowing mild conditions of macrolactamization. Thus, when the ω-amino acids **33** and **35** were subjected to high dilution conditions in presence of EDC, HOBT and hydrotalcites at room temperature, the macrolactam and dimer were obtained with excellent yields. The macrolactam with 13 atoms **36** is formed with high yields (Table S4, entry 4). Whereas, when the ω-amino acids **33** is used to obtain lactam **34**, the dimer is the major product as consequence of intramolecular process (Table S4, entry 3).

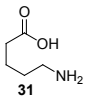
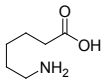
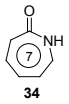
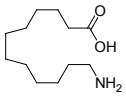
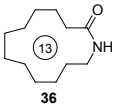
Supporting Information

Table S3 Synthesis of amides in presence of hydrotalcites[a]

Entry	Carboxylic acid	Amine	Amide	Hydrotalcite	Yield %
1	 10	 11	 12	Commercial 250 Synthesized 250 Calcined 200 Reconstructed 150	90 90 90 90
2	 10	 13	 14	Commercial 250 Synthesized 250 Calcined 200 Reconstructed 150	85 85 87 90
3	 10	 15	 16	Commercial 250 Synthesized 250 Calcined 200 Reconstructed 150	75 74 76 80
4	 10	 17	 18	Commercial 250 Synthesized 250 Calcined 200 Reconstructed 150	60 60 63 65
5	 19	 11	 20	Commercial 250 Synthesized 250 Calcined 200 Reconstructed 150	90 90 90 95
6	 19	 13	 21	Commercial 250 Synthesized 250 Calcined 200 Reconstructed 150	86 85 88 90
7	 19	 15	 22	Commercial 250 Synthesized 250 Calcined 200 Reconstructed 150	72 70 75 75
8	 19	 17	 23	Commercial 250 Synthesized 250 Calcined 200 Reconstructed 150	60 60 64 70
9	 24	 11	 25	Commercial 250 Synthesized 250 Calcined 200 Reconstructed 150	50 55 60 65
10	 24	 13	 26	Commercial 250 Synthesized 250 Calcined 200 Reconstructed 150	55 55 60 65
11	 24	 15	 27	Commercial 250 Synthesized 250 Calcined 200 Reconstructed 150	50 52 60 60
12	 24	 17	 28	Commercial 250 Synthesized 250 Calcined 200 Reconstructed 150	52 50 55 55

[a] Reaction conditions: Carboxylic acid (1 mmol), amine (1 mmol), EDC (1.1 mmol), HOBT (1.1 mmol), CH_2Cl_2 (25 ml), r.t., 14 h. [b] Yield of isolated product after chromatographic purification.

Table S4 Synthesis of lactams in presence of hydrotalcites[a,b]

Entry	Amino acid	Lactam	Hydrotalcite mg	Monomer yield %[c]	Dimer yield %[c]
1	 **29**	 **30**	Commercial 250	95	-
			Synthesized 250	95	-
			Calcined 200	95	-
			Reconstructed 150	95	-
2	 **31**	 **32**	Commercial 250	95	-
			Synthesized 250	95	-
			Calcined 200	95	-
			Reconstructed 150	95	-
3	 **33**	 **34**	Commercial 250	40	60
			Synthesized 250	35	65
			Calcined 200	42	58
			Reconstructed 150	35	65
4	 **35**	 **36**	Commercial 250	90	2
			Synthesized 250	90	2
			Calcined 200	90	2
			Reconstructed 150	90	4

[a] Reagents and conditions for the macrolactamization reaction: amino acid (1 mmol), EDC (1.1 mmol), HOBT (1.1 mmol), CH_2Cl_2 (50 mL), r.t., 18 h. [b] The amino acid was dissolved in THF (10 mL) and was slowly added using a syringe pump over the course of 18 h. [c] Yield of isolated product after chromatographic purification.

4. Characterization data

N-Boc-LeuAl-OMe ***3***.[7] Following the general procedure, the reaction was carried out starting from *N*-Boc-leucine **1** (200 mg, 0.865 mmol), L-alanine methyl ester hydrochloride **2** (120 mg, 1.470 mmol), HOBT (145 mg, 0.951 mmol), EDC (181 mg, 0.951 mmol) and commercial hydrotalcite (250 mg), to give 259 mg of a white solid (95%, mp 113-114 °C); $[\alpha]_D$ -49.2 (*c* 0.0116 in MeOH);[7] ^{1}H NMR ($CDCl_3$): δ 6.60 (1H, br s), 4.90 (1H, br s), 4.57 (1H, quintet, *J* = 7.2 Hz), 4.11 (1H, br s), 3.74 (3H, s), 1.80-1.57 (3H, m), 1.44 (9H, s), 1.40 (3H, d, *J* = 7.2 Hz), 0.95 (3H, d, *J* = 6.0 Hz), 0.94 (3H, d, *J* = 6.0 Hz). ^{13}C NMR ($CDCl_3$): δ 173.1, 172.1, 155.6, 80.1, 53.0, 52.4, 48.0, 41.3, 28.3, 24.7, 22.9, 22.0, 18.3. HRMS (FAB) calcd for $C_{15}H_{28}N_2O_5$ 316.1998, found 316.1997.

N-(4-tert-Butyl-phenyl)-2-phenyl-acetamide ***12***.[8] Following the general procedure, the reaction was carried out starting from phenylacetic acid **10** (200 mg, 1.470 mmol), 4-*tert*-butylaniline **11** (219 mg, 1.470 mmol), HOBT (247 mg, 1.617 mmol), EDC (309 mg, 1.617 mmol) and commercial hydrotalcite (250 mg), to give 353 mg of a white solid (90%). ^{1}H NMR ($CDCl_3$): δ 7.48 (1H, s), 7.39-7.25 (9H, m), 3.69 (2H, s), 1.28 (9H, s). ^{13}C NMR

($CDCl_3$): δ 169.1, 147.3, 135, 134.6, 129.3, 129, 127.4, 125.6, 119.7, 44.6, 34.3, 31.3. HRMS (FAB) calcd for $C_{18}H_{21}NO$ 267.1623, found 267.1625.

N-Benzyl-2-phenyl-acetamide ***14***.[8] Following the general procedure, the reaction was carried out starting from phenylacetic acid **10** (200 mg, 1.470 mmol), benzylamine **13** (157 mg, 1.470 mmol), HOBT (247 mg, 1.617 mmol), EDC (309 mg, 1.617 mmol) and commercial hydrotalcite (250 mg), to give 281 mg of a white solid (85%). ^{1}H NMR ($CDCl_3$): δ 7.29-7.08 (10H, m), 5.71 (1H, br s), 4.32 (2H, d, *J* = 5.7 Hz), 3.53 (2H, s).). ^{13}C NMR ($CDCl_3$): δ 171, 138.1, 134.7, 129.4, 129, 128.6, 127.5, 127.4, 127.4, 43.8, 43.6. HRMS (FAB) calcd for $C_{15}H_{15}NO$ 225.454, found 225.453.

4-Phenylacetyl-morpholine ***16***.[9] Following the general procedure, the reaction was carried out starting from phenylacetic acid **10** (200 mg, 1.470 mmol), morpholine **15** (127 mg, 1.470 mmol), HOBT (247 mg, 1.617 mmol), EDC (309 mg, 1.617 mmol) and commercial hydrotalcite (250 mg), to give 226 mg of a white solid (75%). ^{1}H NMR ($CDCl_3$): δ 7.35-7.29 (2H, m), 7.26-7.23 (3H, m), 3.73 (2H, s), 3.63-3.45 (8H, m).). ^{13}C NMR ($CDCl_3$): δ 169.6, 134.8, 128.8, 128.5, 126.9, 66.7, 66.4, 46.5, 42.1, 40.8. HRMS (FAB) calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1104.

N-Cyclohexylmethyl-2-phenyl-acetamide ***18***.[10] Following the general procedure, the reaction was carried out starting from phenylacetic acid **10** (200 mg, 1.470 mmol), cyclohexylamine **17** (157 mg, 1.470 mmol), HOBT (247 mg, 1.617 mmol), EDC (309 mg, 1.617 mmol) and commercial hydrotalcite (250 mg), to give 191 mg of a white solid (60%). ^{1}H NMR ($CDCl_3$): δ 7.27-7.22 (5H, m), 5.43 (1H, br s), 3.78-3.71 (1H, m), 3.53 (2H, s), 1.85-1.81 (2H, m), 1.63-1.58 (3H, m), 1.34-1.30 (2H, m) 1.05-0.98 (3H, m). ^{13}C NMR ($CDCl_3$): δ 170, 135.2, 129.3, 128.9, 127.2, 48.2, 43.9, 32.9, 25.5, 24.7. HRMS (FAB) calcd for $C_{14}H_{19}NO$ 217.1467, found 217.1465.

N-(4-tert-Butyl-phenyl)-2-phenoxy-acetamide ***20***.[8] Following the general procedure, the reaction was carried out starting from phenoxylacetic acid **19** (200 mg, 1.315 mmol), 4-*tert*-butylaniline **11** (196 mg, 1.315 mmol), HOBT (221 mg, 1.446 mmol), EDC (276 mg, 1.446 mmol) and commercial hydrotalcite (250 mg), to give 335 mg of a white solid (90%). ^{1}H NMR ($CDCl_3$): δ 8.25 (1H, br s), 7.53-7.50 (2H, m), 7.40-7.33 (4H, m), 7.09-6.99 (3H, m),

4.61 (2H, s), 1.33 (9H, s). ^{13}C NMR ($CDCl_3$): δ 166.1, 157, 147.8, 134.1, 129.8, 125.8, 122.3, 119.9, 114.8, 67.6, 34.3, 31.3. HRMS (FAB) calcd for $C_{18}H_{21}NO_2$ 283.1572, found 283.1571.

N-Benzyl-2-phenoxy-acetamide ***21***.[8] Following the general procedure, the reaction was carried out starting from phenoxylacetic acid **19** (200 mg, 1.315 mmol), benzylamine **13** (140 mg, 1.315 mmol), HOBT (221 mg, 1.446 mmol), EDC (276 mg, 1.446 mmol) and commercial hydrotalcite (250 mg), to give 272 mg of a white solid (86%). ^{1}H NMR ($CDCl_3$): δ 7.36-7.25 (7H, m), 7.04 (1H, t, J = 7.5 Hz), 6.90 (2H, d, J = 7.5 Hz), 4.54 (d, J = 5.7 Hz), 4.46 (2H, s). ^{13}C NMR ($CDCl_3$): δ 169, 160.7, 141.7, 129.8, 128.6, 127, 126.8, 121.1, 114.3, 67.1, 44.1. HRMS (FAB) calcd for $C_{15}H_{15}NO_2$ 241.1103, found 241.1101.

4-Phenoxyacetyl-morpholine ***22***.[8] Following the general procedure, the reaction was carried out starting from phenoxylacetic acid **19** (200 mg, 1.315 mmol), morpholine **15** (114 mg, 1.315 mmol), HOBT (221 mg, 1.446 mmol), EDC (276 mg, 1.446 mmol) and commercial hydrotalcite (250 mg), to give 177 mg of a white solid (72%). ^{1}H NMR ($CDCl_3$): δ 7.32-7.27 (2H, m), 7.02-6.93 (3H,m), 4.69 (2H, s), 3.64 (8H, m). ^{13}C NMR ($CDCl_3$): δ 166.6, 160.7, 129.8, 121.1, 114.3, 66.3, 64.9, 45.6. HRMS (FAB) calcd for $C_{12}H_{15}NO_3$ 221.1052, found 221.1052.

N-Cyclohexylmethyl-2-phenoxy-acetamide ***23***.[8] Following the general procedure, the reaction was carried out starting from phenoxylacetic acid **19** (200 mg, 1.315 mmol), cyclohexylamine **17** (130 mg, 1.315 mmol), HOBT (221 mg, 1.446 mmol), EDC (276 mg, 1.446 mmol) and commercial hydrotalcite (250 mg), to give 184 mg of a white solid (60%). ^{1}H NMR ($CDCl_3$): δ 7.34-7.29 (2H, m), 7.02 (1H, t, J = 7.5 Hz), 6.91 (2H, d, J = 7.8 Hz), 6.45 (1H, br s), 4.46 (2H, s), 3.92-3.82 (1H, m), 1.95-1.10 (10H, m). ^{13}C NMR ($CDCl_3$): δ 167.1, 157.2, 129.7, 122, 114.7, 67.4, 47.8, 32.9, 25.4, 24.7. HRMS (FAB) calcd for $C_{14}H_{19}NO_2$ 233.1416, found 233.1412.

N-(4-tert-Butyl-phenyl)-benzamide ***25***.[11] Following the general procedure, the reaction was carried out starting from benzoic acid **24** (200 mg, 1.639 mmol), 4-*tert*-butylaniline **11** (244 mg, 1.639 mmol), HOBT (257 mg, 1.802 mmol), EDC (344 mg, 1.802 mmol) and commercial hydrotalcite (250 mg), to give 207 mg of a white solid (50%). ^{1}H NMR ($CDCl_3$):

δ 7.97 (1H, br s), 7.85 (2H, dt, *J* = 6.9, 1.5 Hz), 7.57 (2H, d, *J* = 8.7 Hz), 7.53-7.50 (1H, m), 7.46 (2H, d, *J* = 7.5 Hz), 7.38 (2H, dt, *J* = 8.7, 2.1 Hz) 1.33 (9H, s). ^{13}C NMR ($CDCl_3$): δ 165.9, 147.7, 135.4, 135.2, 131.9, 128.9, 127.1, 126.0, 120.2, 34.5, 31.5. HRMS (FAB) calcd for $C_{17}H_{19}NO$ 253.1467, found 253.1467.

N-Benzyl-benzamide ***26***.[12] Following the general procedure, the reaction was carried out starting from benzoic acid **24** (200 mg, 1.639 mmol), benzylamine **13** (175 mg, 1.639 mmol), HOBT (257 mg, 1.802 mmol), EDC (344 mg, 1.802 mmol) and commercial hydrotalcite (250 mg), to give 190 mg of a white solid (55%). ^{1}H NMR ($CDCl_3$): δ 7.78 (2H, d, *J* = 7.0 Hz), 7.48 (1H, t, *J* = 7.3 Hz), 7.40 (dd, *J* = 7.6, 7.3 Hz), 7.37-7.28 (5H, m), 6.61 (1H, br s), 4.61 (2H, d, *J* = 5.8 Hz). ^{13}C NMR ($CDCl_3$): δ 167.4, 138.2, 134.4, 131.5, 128.8, 128.6, 128, 127.6, 127, 44. HRMS (FAB) calcd for $C_{14}H_{13}NO$ 211.099, found 211.098.

4-Benzoyl-morpholine ***27***.[13] Following the general procedure, the reaction was carried out starting from benzoic acid **24** (200 mg, 1.639 mmol), morpholine **15** (142 mg, 1.639 mmol), HOBT (257 mg, 1.802 mmol), EDC (344 mg, 1.802 mmol) and commercial hydrotalcite (250 mg), to give 156 mg of a white solid (50%). ^{1}H NMR ($CDCl_3$): δ 7.42-7.37 (5H, m), 3.85-3.44 (8H, m). ^{13}C NMR ($CDCl_3$): δ 170.3, 135.3, 129.7, 128.4, 127, 66.8, 46.4. HRMS (FAB) calcd for $C_{11}H_{13}NO_2$ 191.094, found 191.094.

N-Cyclohexylmethyl-benzamide ***28***.[14] Following the general procedure, the reaction was carried out starting from benzoic acid **24** (200 mg, 1.639 mmol), cyclohexylamine **17** (162 mg, 1.639 mmol), HOBT (257 mg, 1.802 mmol), EDC (344 mg, 1.802 mmol) and commercial hydrotalcite (250 mg), to give 173 mg of a white solid (52%). ^{1}H NMR ($CDCl_3$): δ 7.72 (2H, d, *J* = 7.5 Hz), 7.41 (1H, t, *J* = 7.5 Hz), 7.33 (2H, t, *J* = 7.5 Hz), 6.28 (1H, br s), 3.92-3.88 (1H, m), 2.02-1.88 (2H, m), 1.66-1.63 (2H, m), 1.62-1.57 (1H, m), 1.37-1.30 (2H, m), 1.24-1.17 (3H, m).^{13}C NMR ($CDCl_3$): δ 166.6, 134.9, 131, 128.3, 126.8, 48.6, 33, 25.4, 24.8. HRMS (FAB) calcd for $C_{13}H_{17}NO$ 203.131, found 203.133.

Pyrrolidin-2-one ***30***.[15] Following the general procedure, the reaction was carried out starting from 3-aminopropanoic acid **29** (200 mg, 2.247 mmol), HOBT (378 mg, 2.471 mmol), EDC (471 mg, 2.471 mmol) and commercial hydrotalcite (250 mg), to give 181 mg of a white solid (95%). ^{1}H NMR ($CDCl_3$): δ 6.50 (1H, br s), 3.39 (2H, t, *J* = 7.0 Hz), 2.35-2.25 (2H, m),

2.20-2.05 (2H, m). ^{13}C NMR ($CDCl_3$): δ 179.3, 42.4, 30.1, 20.9. HRMS (FAB) calcd for C_4H_7NO 85.0528, found 85.0527.

Piperidin-2-one ***32***.[16] Following the general procedure, the reaction was carried out starting from 5-aminopentanoic acid **31** (200 mg, 1.709 mmol), HOBT (287 mg, 1.879 mmol), EDC (259 mg, 1.879 mmol) and commercial hydrotalcite (250 mg), to give 160 mg of a white solid (95%). ^{1}H NMR ($CDCl_3$): δ 7.51 (1H, br s), 3.19-316 (2H, m), 2.21(2H, t, J = 6.4 Hz), 1.72-1.60 (4H, m). ^{13}C NMR ($CDCl_3$): δ 172.9, 42, 31.4, 22.1, 20.8. HRMS (FAB) calcd for C_5H_9NO 99.0684, found 99.0684.

Azepan-2-one ***34***.[17] Following the general procedure, the reaction was carried out starting from 7-aminoheptanoic acid **33** (200 mg, 1.379 mmol), HOBT (232 mg, 1.516 mmol), EDC (289 mg, 1.516 mmol) and commercial hydrotalcite (250 mg), to give 62 mg of a white solid (40%). ^{1}H NMR ($CDCl_3$): δ 7.21 (1H, br s), 3.21 (2H, q, J = 8.0 Hz), 2.45 (2H, t, J = 8.0 Hz), 1.80-1.51 (6H, m); ^{13}C NMR ($CDCl_3$): δ 179.4, 42.5, 36.5, 30.4, 29.6, 23.1. HRMS (FAB) calcd for $C_6H_{11}NO$ 113.0841, found 113.0842

1-azacyclotridecan-2-one ***36***.[18] Following the general procedure, the reaction was carried out starting from 12-aminododecanoic acid **35** (200 mg, 0.930 mmol), HOBT (156 mg, 1.023 mmol), EDC (195 mg, 1.023 mmol) and commercial hydrotalcite (250 mg), to give 164 mg of a white solid (90%). ^{1}H NMR ($CDCl_3$): δ 7.23 (1H, br s), 3.21-3.12 (2H, m), 2.14-2.09 (2H, m), 1.64-1.19 (18H, m); ^{13}C NMR ($CDCl_3$): δ 173.5, 38.9, 36.7, 28.1, 26.6, 26.2, 26.1, 25.6, 25.1, 24.8, 24.5, 23.8. HRMS (FAB) calcd for $C_{12}H_{23}NO$ 197.1780, found 197.1781

5. Synthesis of Sansalvamide A

2-Hydroxy-4-methyl-pentanoic acid ***4***.[19] To stirred solution of L-leucine (1g, 7.62 mmol) in 0.5 mol H_2SO_4 (30 mL) was added dropwise a solution of $NaNO_2$ (3 g) in water (10 mL) over a period of 3 h at 0°C, after which it was left for 24h at room temperature. Then the solution was extracted with ethyl ether (2 x 50 ml). The combined extracts were washed with brine (2 x 50 ml), dried over Na_2SO_4, filtered and concentrated in vacuum. The stick solid residue was recrystallized from hexane to give 754 mg of a white solid (75%). ^{1}H NMR ($CDCl_3$): δ 7.6 (2H, br, s), 4.23 (1H, dd, J = 7.8, 5.4 Hz), 1.89 (1H, m), 1.62 (1H, ddd J =

13.8, 6.6, 5.4 Hz), 1.57 (1H, ddd, *J* = 13.8, 7.8, 6.6 Hz), 0.95 (6H, d, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 178.5, 68.7, 43, 24.3, 23, 21.3. HRMS (FAB) calcd for $C_6H_{12}O_3$ 132.0786, found 132.0787.

O-LeuValOH ***5***.[19] *General Procedure for the formation of peptide bonds.* A solution of L-valine methyl ester hydrochloride (1.04 g, 6.24 mmol) and commercial hydrotalcite (850 mg) in anhydrous CH_2Cl_2 (40 mL) was stirred at 0°C under an argon atmosphere. Then a solution of α-hydroxy carboxylic acid **4** (680 mg, 5.2 mmol), HOBT (0.79 g, 5.2 mmol) and EDC (1.07 g, 5.2 mmol) CH_2Cl_2 (30 mL) was added and stirred for 1 h at 0°C under argon atmosphere. After stirring for 18 h at room temperature, the reaction mixture was filtered and evaporated. The residue was dissolved in ethyl acetate (50 ml) and washed successively with 10% citric acid solution (2 x 25 mL), 10% $NaHCO_3$ solution (2 x 25 mL), 10% K_2CO_3 solution (2 x 25 mL) and brine (2 x 25 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuum to give crude hydroxy ester which was used in the next reaction without further purification. To the crude product in THF (25 mL) was added a 2.5 N aqueous solution of LiOH (21.6 mL, 54 mmol) and the mixture was then stirred at room temperature for 4 h. Solid CO_2 was added to the separated THF layer and the mixture was evaporated in vacuo to leave a solid which was taken up in water (30 mL), then acidified to pH 3 with citric acid and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to give 1.081 g of a white solid (90%). ^{1}H NMR ($CDCl_3$): δ 7.27 (1H, d, *J* = 9 Hz), 6.13 (2H, s), 4.46 (1H, dd, *J* = 9, 4.8), 4.22 (1H, dd *J* = 9.3, 3.9 Hz), 2.26 (1H, m), 1.86 (1H, m), 1.59 (1H, ddd *J* = 13.8, 9.3, 6.6 Hz), 1.54 (1H, ddd *J* = 13.8, 6.6, 3.9 Hz), 0.98 (6H, d, *J* = 6.9 Hz) y 0.95 (6H, d, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 176.4, 174.7, 71, 56.8, 43.56, 30.5, 24.6, 23.4, 21.4, 19, 17.5. HRMS (FAB) calcd for $C_{11}H_{22}O_4N_1$ 232.1549, found 232.1548.

O-LeuValLeuOH ***6***.[19] Following the general procedure, the reaction was carried out starting from L-leucine methyl ester hydrochloride (654 mg, 3.6 mmol), hydroxy carboxylic acid **5** (708 mg, 3 mmol), HOBT (459 mg, 3 mmol), EDC (465 mg, 3 mmol) and commercial hydrotalcite (885 mg), to give 939 mg of a white solid (91%). ^{1}H NMR ($CDCl_3$): δ 7.38 (1H, d, *J* = 9 Hz), 7.27 (1H, d, *J* = 7.8 Hz), 4.47 (1H, ddd, *J* = 9,3, 7.8, 5.1 Hz), 4.35 (1H, dd, *J* = 9, 6 Hz), 4.09 (1H, dd, *J* = 9.9, 3.3 Hz), 2.2 (1H, m), 1.87 (1H, m), 1.73-1.42 (5H, m,), 0.95 (3H, d, *J* = 6.9 Hz), 0.94 (3H, d, *J* = 6.6 Hz), 0.94 (6H, d, *J* = 6.3 Hz), 0.93 (3H, d, *J* = 6.6

Hz), 0.9 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 176.9, 173.9, 170.7, 71.1, 56.9, 50.3, 43.4, 30.5, 24.6, 23.4, 21.4, 19, 17.5. HRMS (FAB) calcd for $C_{17}H_{33}O_5N_2$ 345.2389, found 345.2385.

O-LeuValLeuPheOH ***7***.[19] Following the general procedure, the reaction was carried out starting from L-phenylalanine methyl ester hydrochloride (719 mg, 3.33 mmol), hydroxy carboxylic acid **6** (957 mg, 2.78 mmol), HOBT (425 mg, 2.78 mmol), EDC (430 mg, 2.78 mmol) and commercial hydrotalcite (1.195 g), to give 1.197 g of a white solid (86%). ^{1}H NMR ($CDCl_3$): δ 7.42 (1H, d, J = 8.4 Hz), 7.31 (1H, d, J = 9.9 Hz), 7.29-7.16 (5H, m), 7.02 (1H, d, J = 7.5 Hz), 5.67 (2H, brs), 4.71 (1H, ddd, J = 7.5, 6.6, 5.4 Hz), 4.41 (1H, td, J = 8.4, 5.4 Hz), 4.32 (1H, dd, J = 9.3, 6 Hz), 4.09 (1H, dd, J = 9.6, 3.3 Hz), 3.19 (1H, dd, J = 14.1, 5.7 Hz), 3 (1H, dd, J = 14.1, 6.6 Hz), 2.2 (1H, m), 1.6-1.5 (5H, m), 1.8 (1H, m), 0.92 (3H, d, J = 6.6 Hz), 0.91 (6H, d, J = 6.6 Hz), 0.9 (6H, d, J = 6.3 Hz), 0.86 (3H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 175.2, 172.6, 171.4, 171.1, 136.3, 129.1, 128, 126.4, 70.4, 57.3, 53, 51.6, 43.3, 40.2, 37.1, 30.3, 24.3, 24.2, 23.2, 22.6, 21.4, 21.1, 19, 17.2. HRMS (FAB) calcd for $C_{26}H_{42}O_6N_3$ 492.3074, found 492.3078.

O-LeuValLeuPheLeuOH ***8***.[19] Following the general procedure, the reaction was carried out starting from L-leucine methyl ester hydrochloride (521 g, 2.86 mmol), hydroxy carboxylic acid **7** (1.17 g, 2.39 mmol) HOBT (365 mg, 2.39 mmol), EDC (370 mg, 2.39 mmol) and commercial hydrotalcite (1.460 g), to give 1.312 mg of a white solid (90%). ^{1}H NMR (CD_3OD): δ 8.12 (1H d, J = 8.4 Hz), 8.00 (1H, d, J = 7.8. Hz), 7.9 (1H, d, J = 8.1 Hz), 7.5 (1H, d, J = 9 Hz), 7.23-7.14 (5H, m), 4.54 (1H, td, J = 8.4, 4.8 Hz), 4.26 (ddd, 1H, J = 7.8, 6.9, 6.6 Hz), 4.26 (1H, ddd, J = 7.8, 6.9, 6.6 Hz) 4.17 (1H, dd, J = 9, 2.7 Hz), 3.85 (1H, td, J = 9, 4.2 Hz), 3.02 (1H, dd, J = 14.1, 4.8 Hz), 2.79 (1H, dd, J = 14.1, 8.7 Hz), 1.89 (1H, m), 1.73 (1H, m), 1.59 (3H, m), 1.52-1.32 (5H, m), 0.84 (6H, d, J = 6.6 Hz), 0.83 (6H, d, J = 6.6 Hz), 0.82 (3H, d, J = 6.6 Hz), 0.78 (3H, d, J = 6.6 Hz), 0.75 (3H, d, J = 6.6 Hz), 0.70 (3H, d, J = 6.6 Hz); ^{13}C NMR (CD_3OD): δ 174.4, 174.2, 171.5, 170.5, 137.6, 129.2, 128, 126.2, 69.7, 56.4, 53.2, 51.15, 50.7, 43.7, 40.9, 40.6, 37.2, 31.3, 24.2, 24.1, 24, 23.4, 22.9, 21.7, 21.5, 19.2, 17.7. HRMS (FAB) calcd for $C_{32}H_{53}O_7N_4$ 605.3914, found 605.3906.

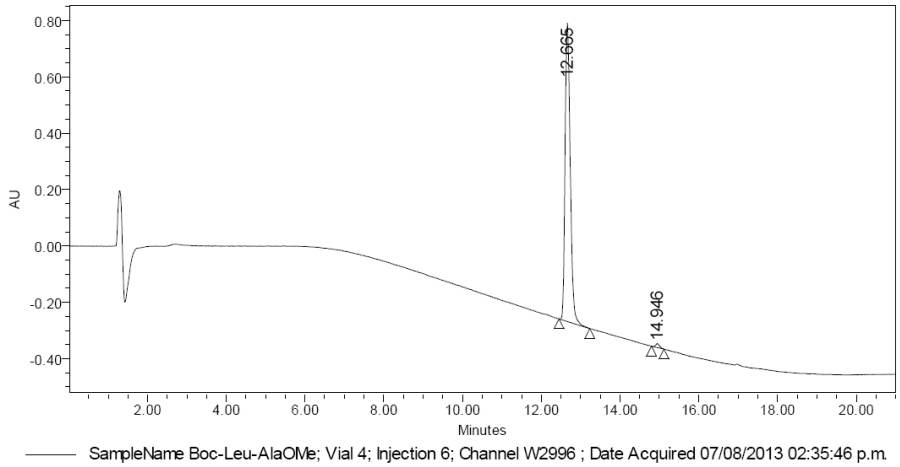
Macrolactonization of hydroxyacid ***8***.[19] A solution of HOBT (29 mg, 0.19 mmol), EDC (39 mg, 0.19 mmol) and commercial hydrotalcite (125 mg) in ethanol-free chloroform (50 mL),

was brought to reflux. Then a solution of hydroxy acid **8** (100 mg, 0.16 mmol) in 10 mL of THF was infused via syringe pump over 18 h, the reaction mixture was filtered and evaporated. It was then diluted with ethyl acetate (50 mL), washed with 10 % citric acid solution (2 x 30 mL), 10 % $NaHCO_3$ solution (2 x 30 mL), brine (2 x 30 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified through a silica gel column chromatography (25 x 2.5 cm). Elution was with hexane and then with 70 % ethyl acetate-hexane. In this way, Sansalvamide A **9** was obtained as white solid (60 mg, 65 %, m.p. 143-145 ^{o} C). ^{1}H NMR (CD_3OD): δ 7.28-7.23 (5H, m), 5.6 (1H, dd, *J* = 9, 4.8 Hz), 4.71 (1H, dd, *J* = 9.6, 5.7 Hz), 4.55 (1H, dd, *J* = 10.8, 4.8 Hz), 4.09 (1H, d, *J* = 8.4 Hz), 3.72 (1H, dd, *J* = 9, 5.1 Hz), 3.24 (1H, dd, *J* = 13.8, 4.8 Hz), 3.08 (1H, dd, *J* = 13.8, 10.8 Hz), 2.07 (1H, oct, *J* = 6.6 Hz), 1.86-1.64 (2H, m), 1.76-1.88 (2H, m), 1.72 (1H, m), 1.60-1.64 (1H, m), 1.62 (1H, m), 1.41 (1H, m), 1.38 (1H,m), δ 0.99 (6H, d, *J* = 6.6 Hz), 0.96 (6H, d, *J* = 6.6 Hz), 0.92 (3H, d, *J* = 6.6 Hz), 0.86 (3H, d, *J* = 6.6 Hz), 0.85 (3H, d, *J* = 6.6 Hz), 0.81 (3H, d, *J* = 6.6 Hz; ^{13}C NMR ($CDCl_3$): δ 174.09, 174.01, 173.6, 172.8, 171.4, 138.7, 130.2, 129.7, 128, 76.3, 60.6, 58.1, 56.4, 52.5, 41.7, 41.3, 39.6, 38, 32.1, 26.2, 26.1, 25.9, 23.5, 23.3, 23.1, 22.4, 22.1, 19.9, 18.7. HRMS (FAB) calcd for $C_{32}H_{51}O_6N_4$ 587.3809, found 587.3812. ESI MS (M+H) 587.4

6. Copy of HPLC chromatogram of 3

The sample analysed was obtained when the reaction was carried out in presence of 250 mg of hydrotalcite using CH_2Cl_2 as solvent (Table S1, entry 6).

Supporting Information



Peak Results

	Name	RT	Area	% Area	Int Type	Processed Channel Descr.
1		12.665	9643479	99.04	BB	PDA 205.0 nm
2		14.946	93380	0.96	Bb	PDA 205.0 nm

Figure S1. HPLC of **3**

7. Copy of ^{1}H and ^{13}C spectra for compounds 3-9

Supporting Information

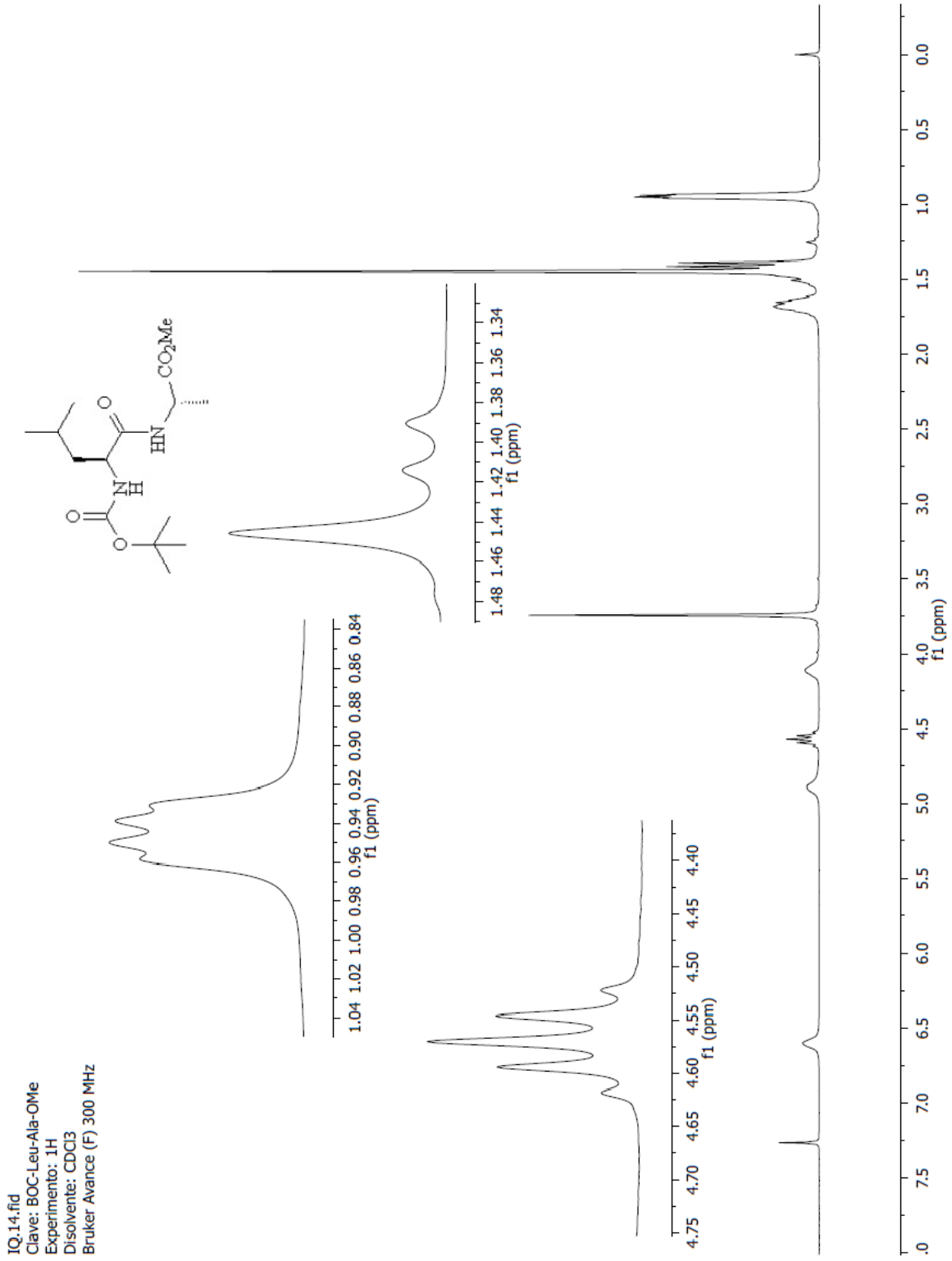


Figure S2. ^{1}H NMR of **3** in $CDCl_3$

Supporting Information

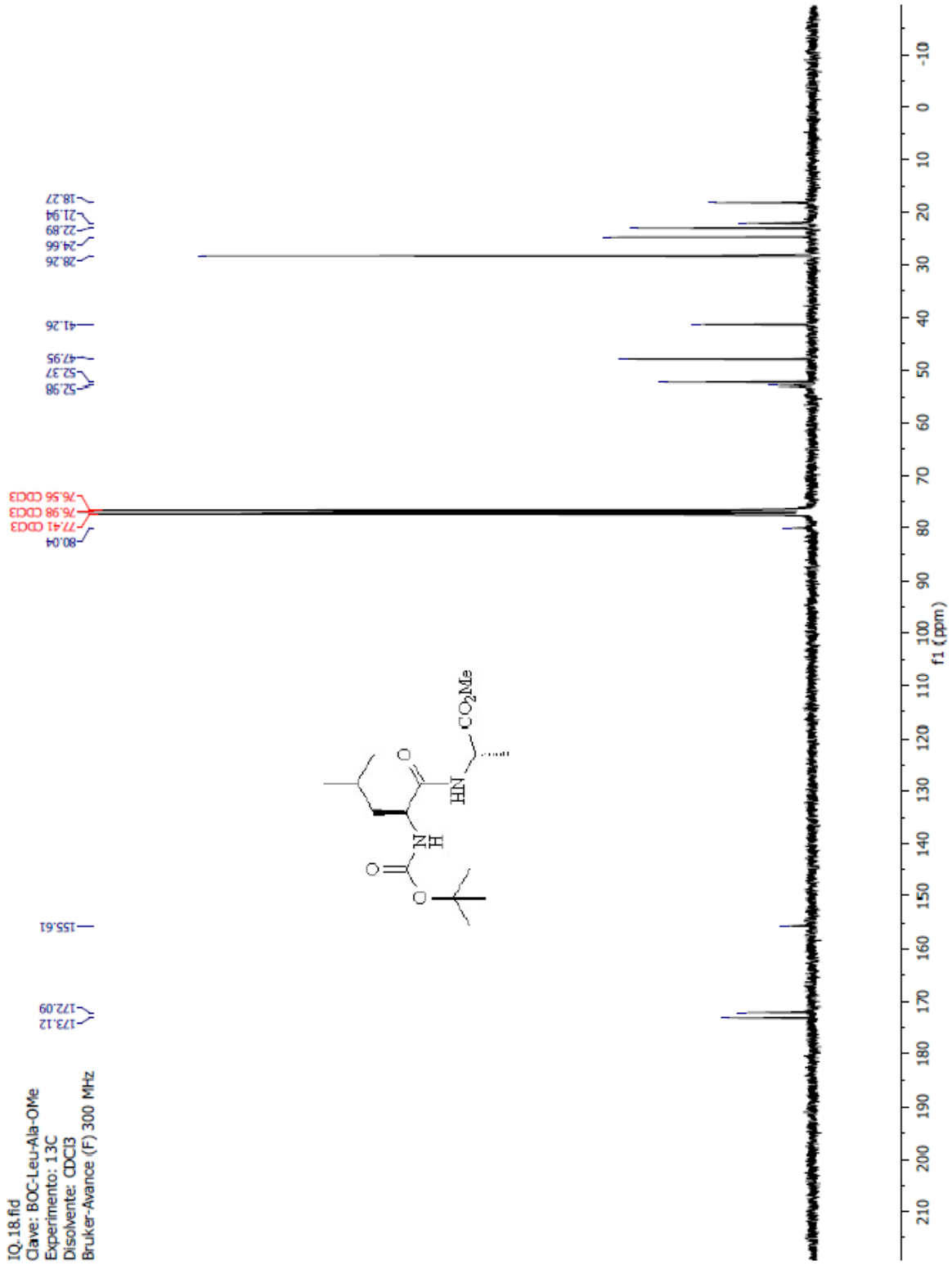


Figure S3. ^{13}C NMR of **3** in $CDCl_3$

Supporting Information

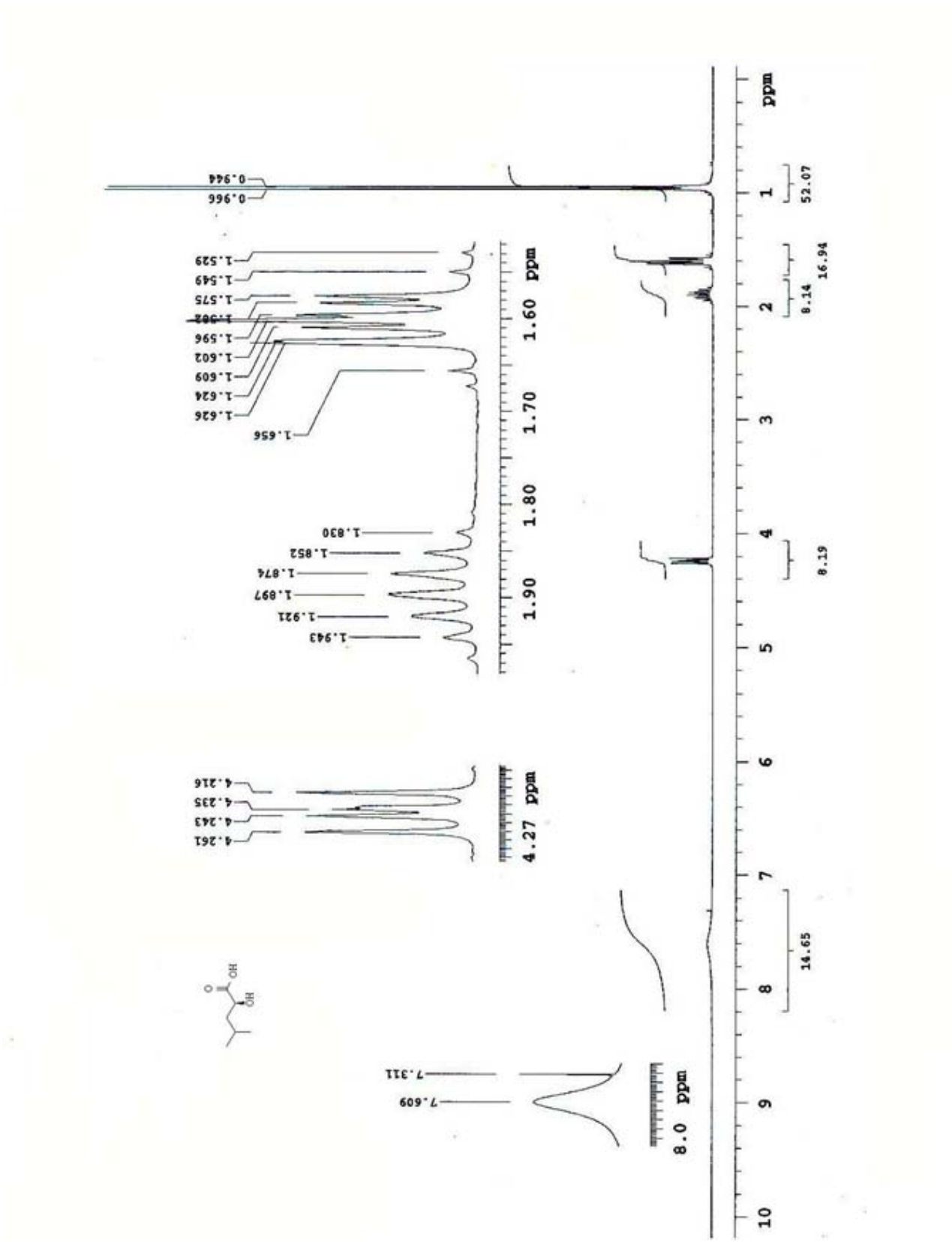


Figure S4. ^{1}H NMR of **4** in $CDCl_3$

Supporting Information

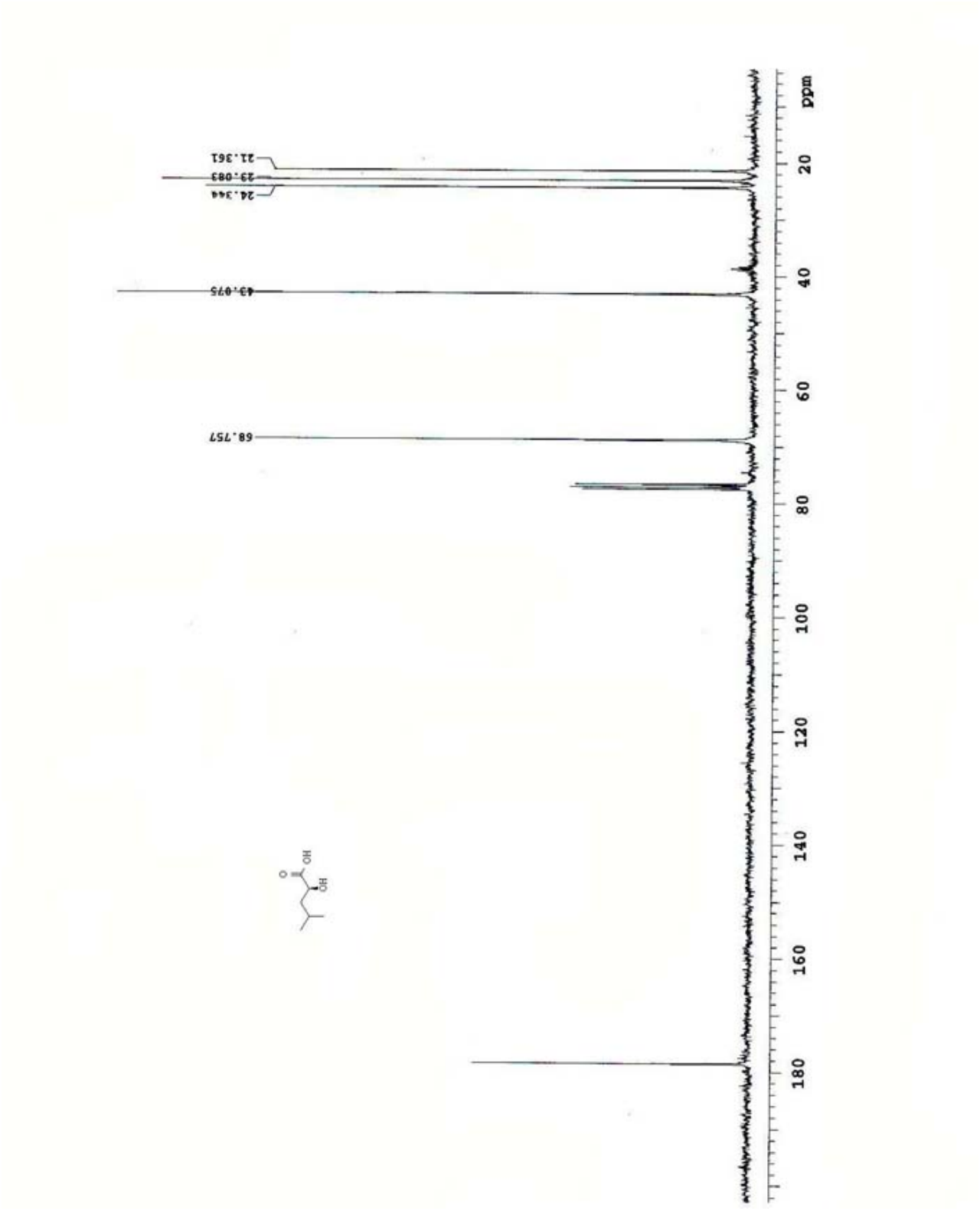


Figure S5. ^{13}C NMR of **4** in $CDCl_3$

Supporting Information

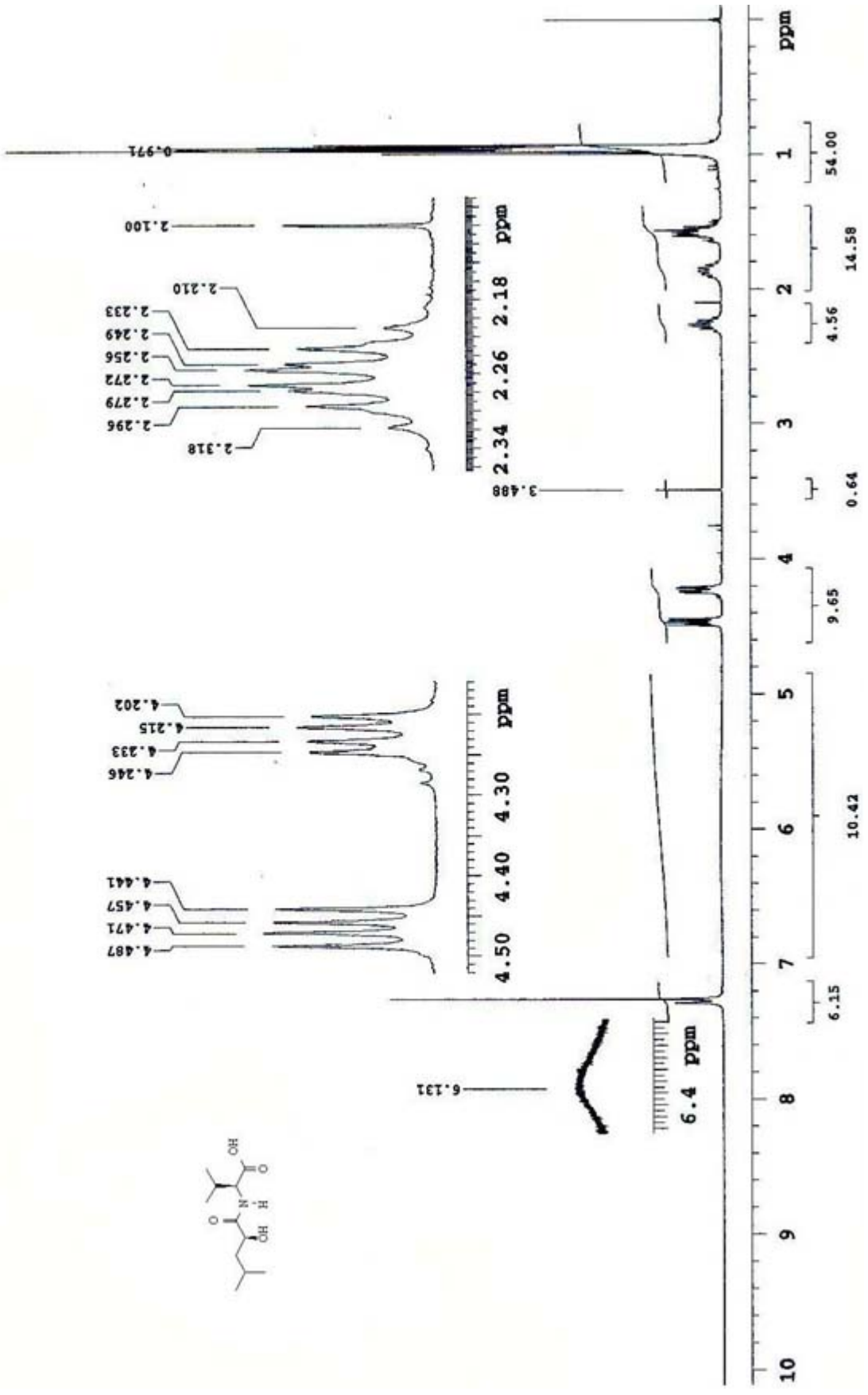


Figure S6. ^{1}H NMR of **5** in $CDCl_3$

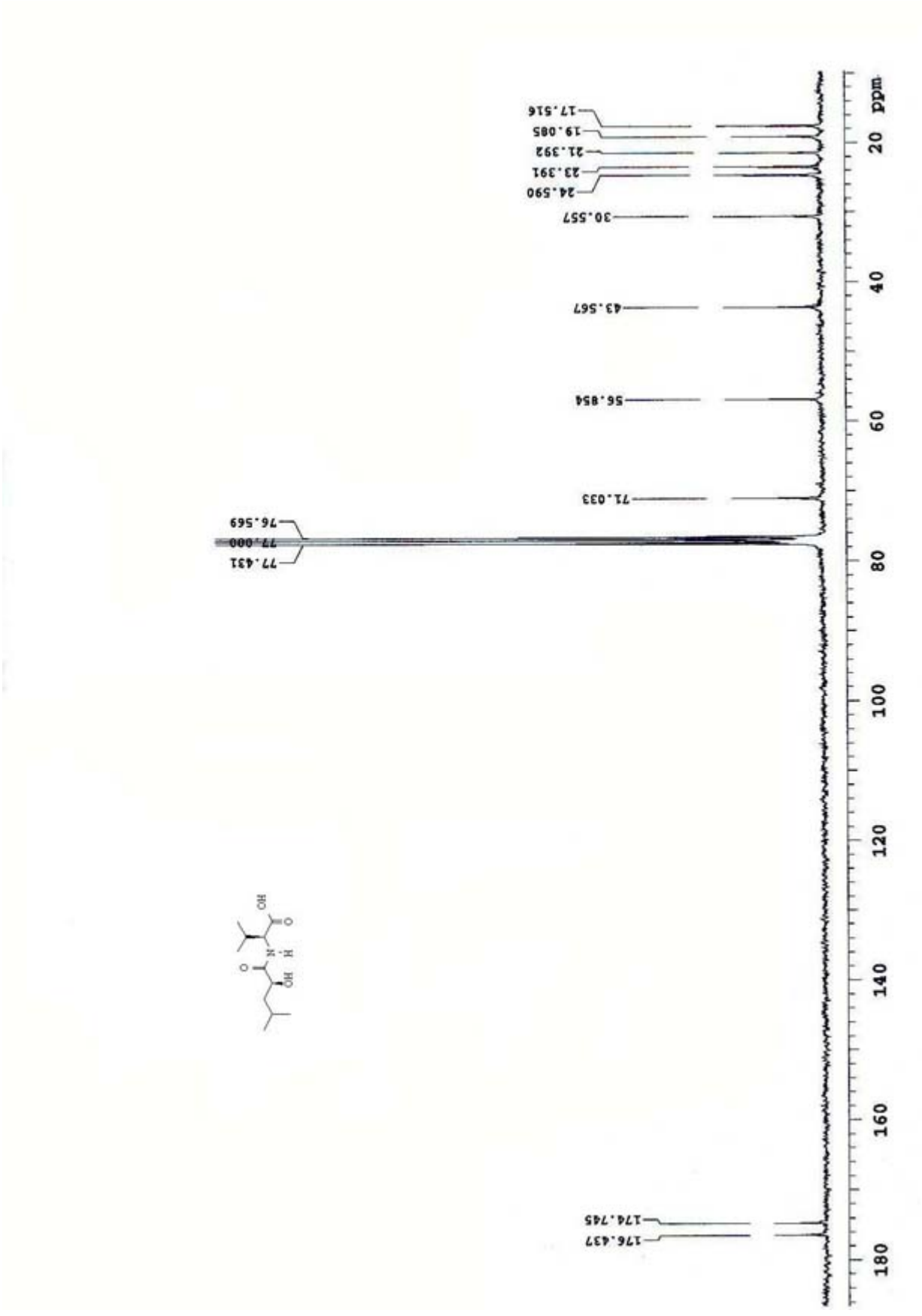


Figure S7. ^{13}C NMR of **5** in $CDCl_3$

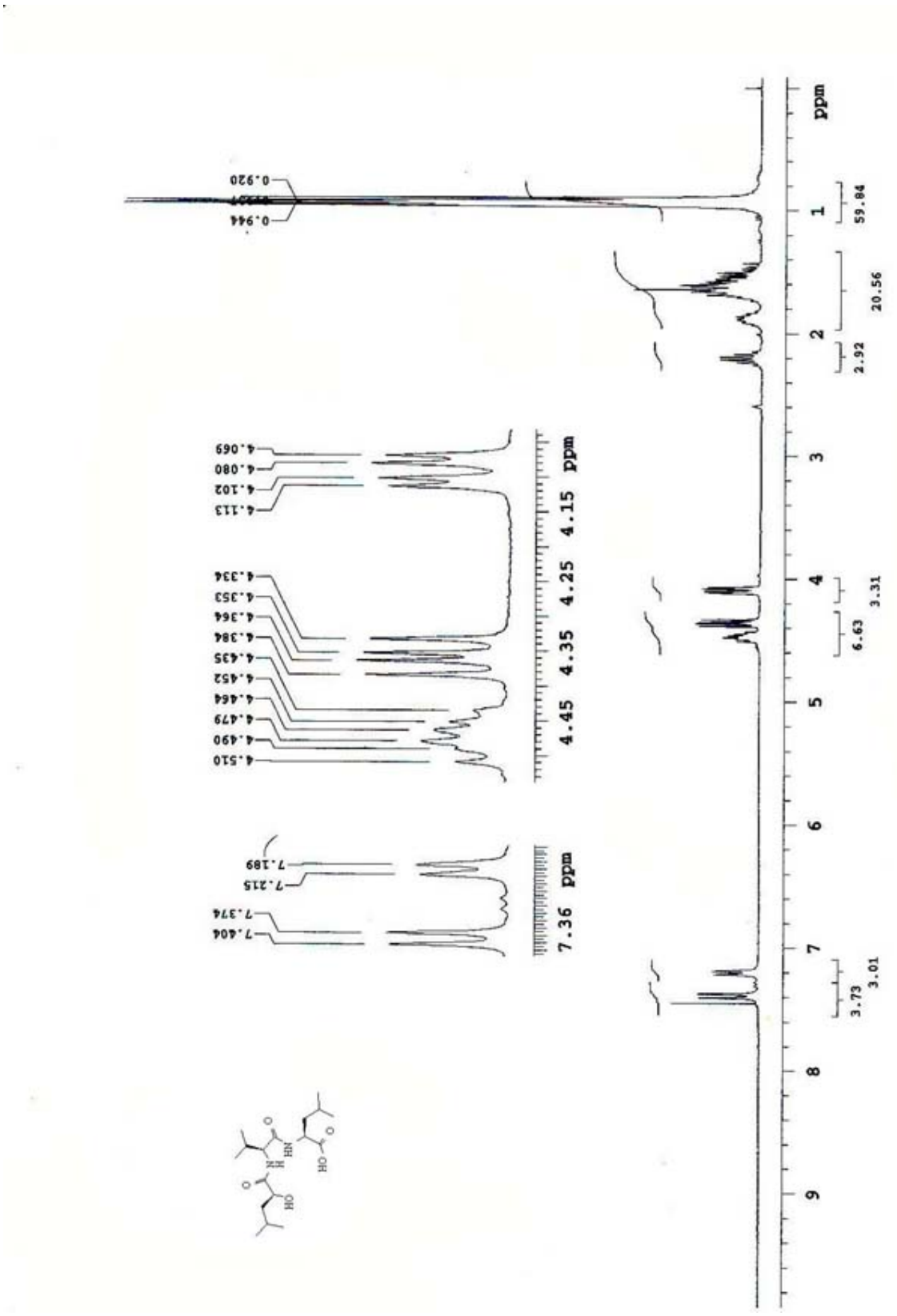


Figure S8. ^{1}H NMR of **6** in $CDCl_3$

Supporting Information

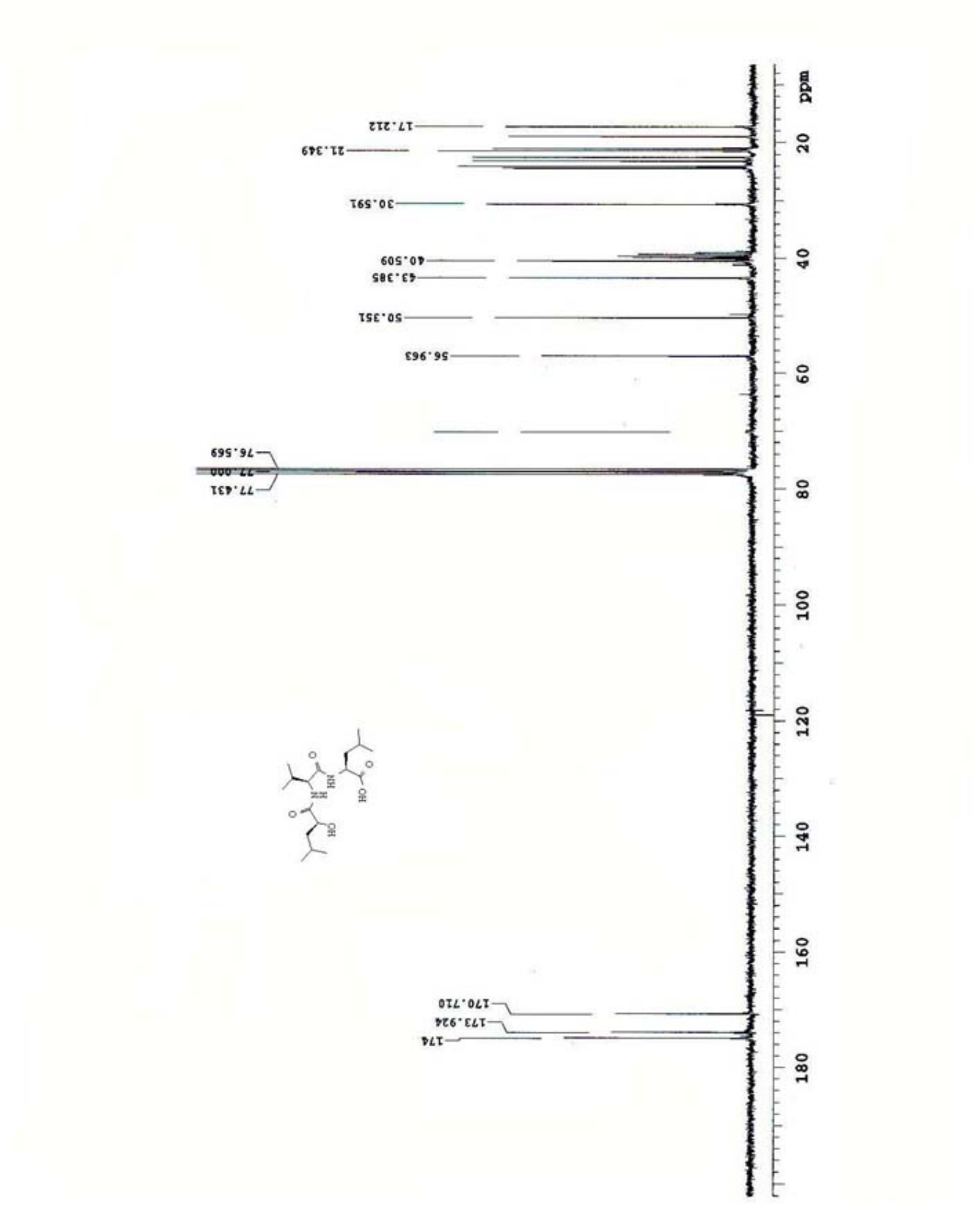


Figure S9. ^{13}C NMR of **6** in $CDCl_3$

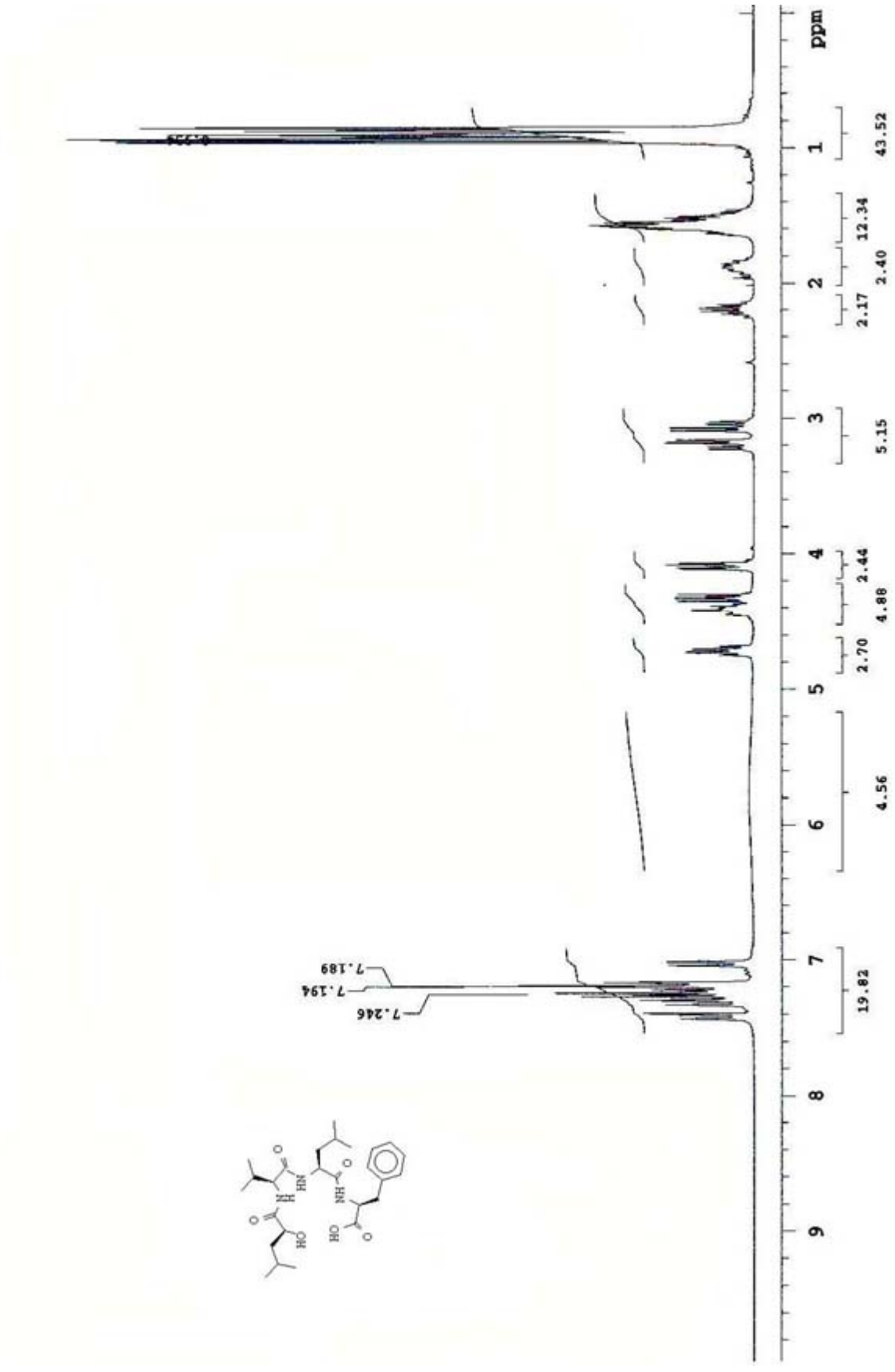


Figure S10. ^{1}H NMR of **7** in $CDCl_3$

Supporting Information

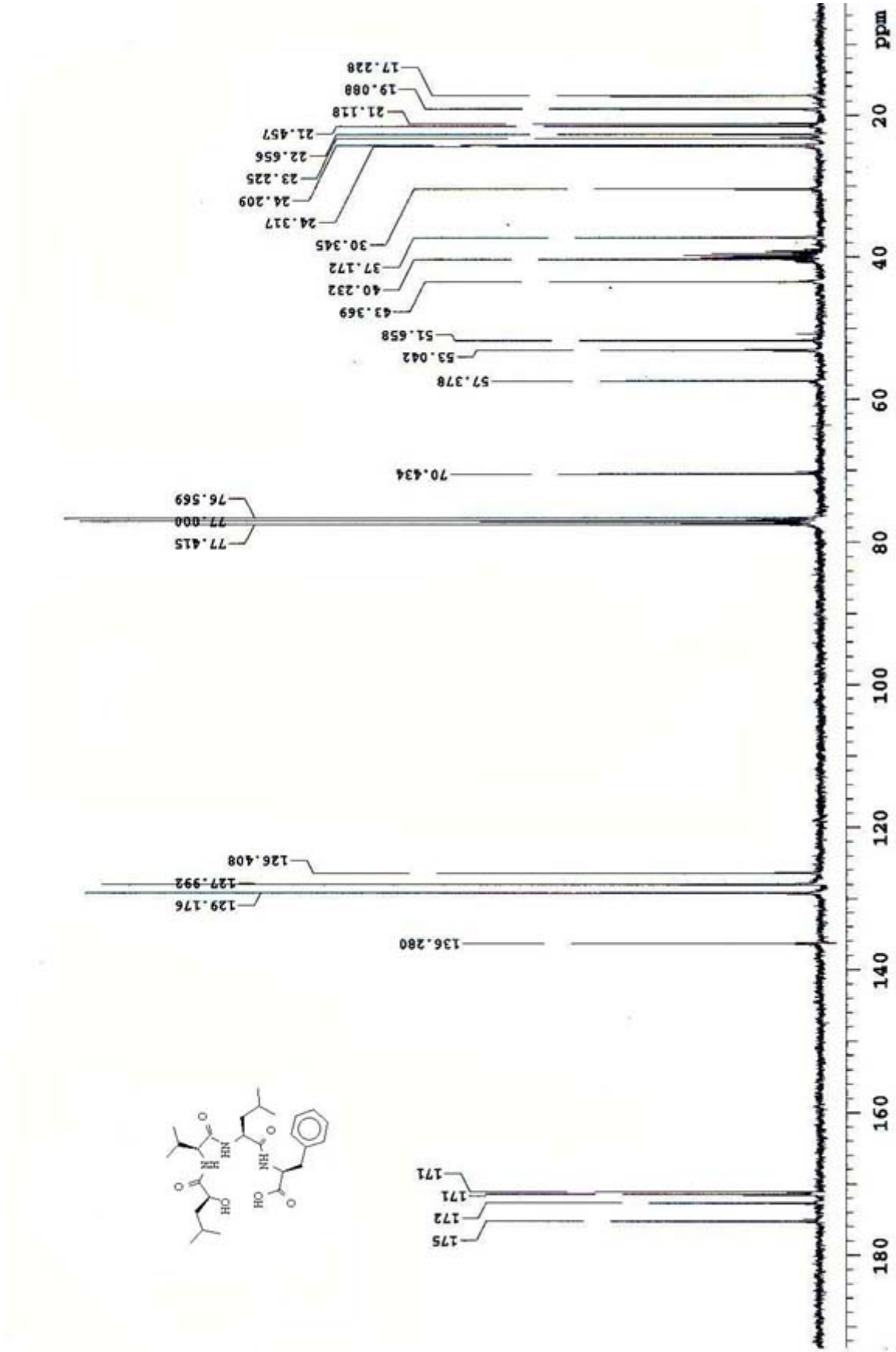


Figure S11. ^{13}C NMR of **7** in $CDCl_3$

Supporting Information

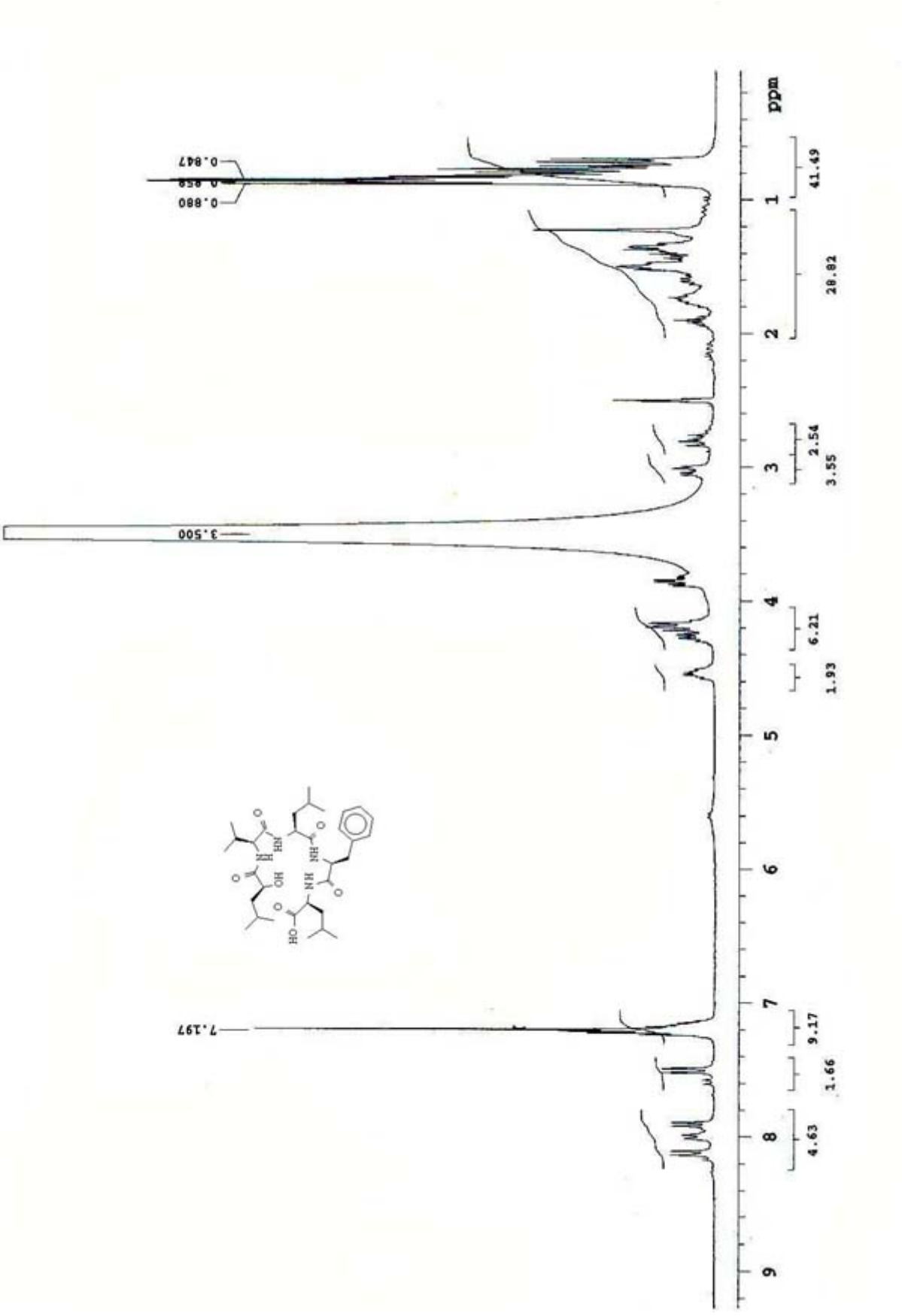


Figure S12. ^{1}H NMR of **8** in CD_3OD

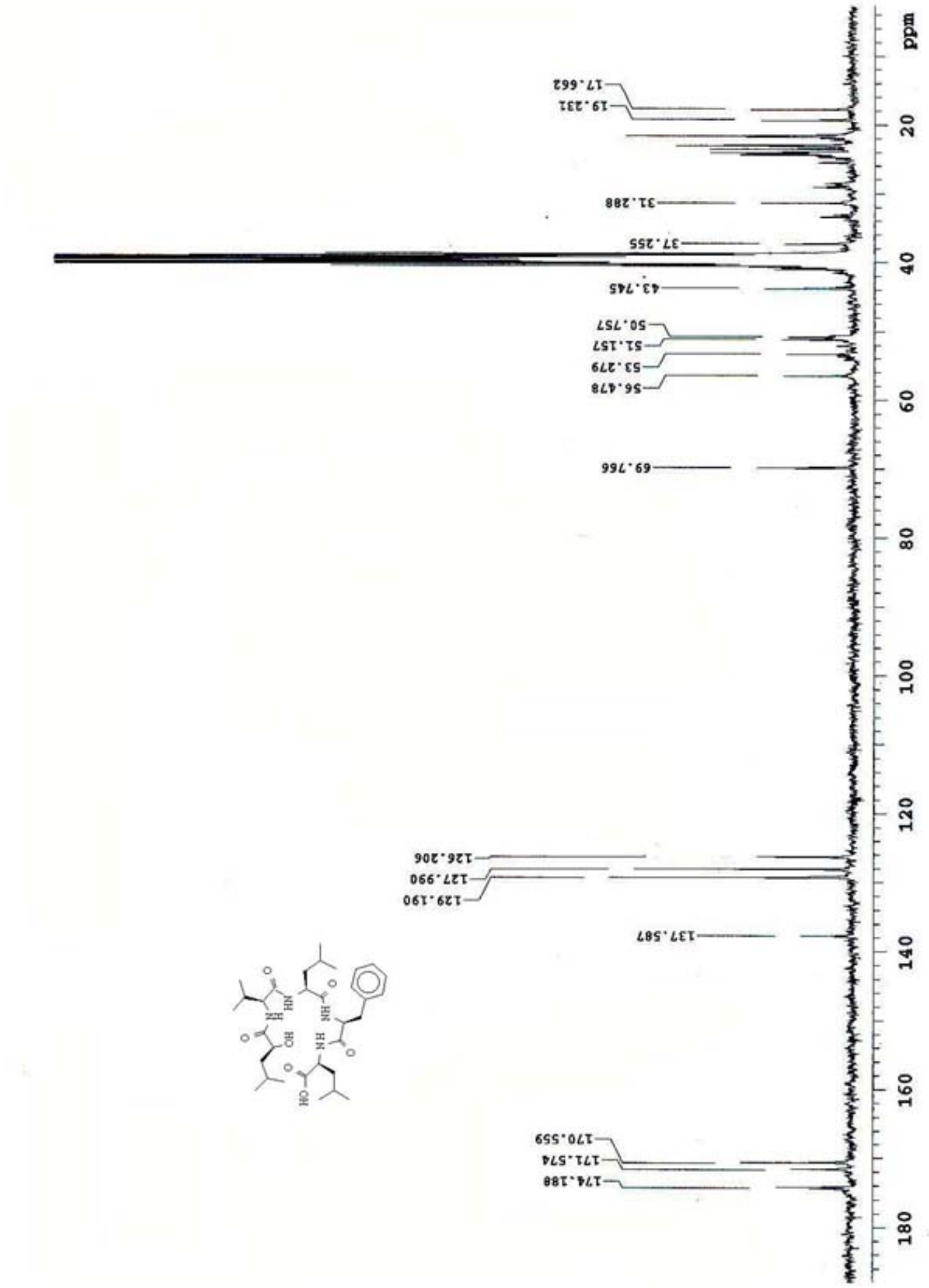


Figure S13. ^{13}C NMR of **8** in CD_3OD

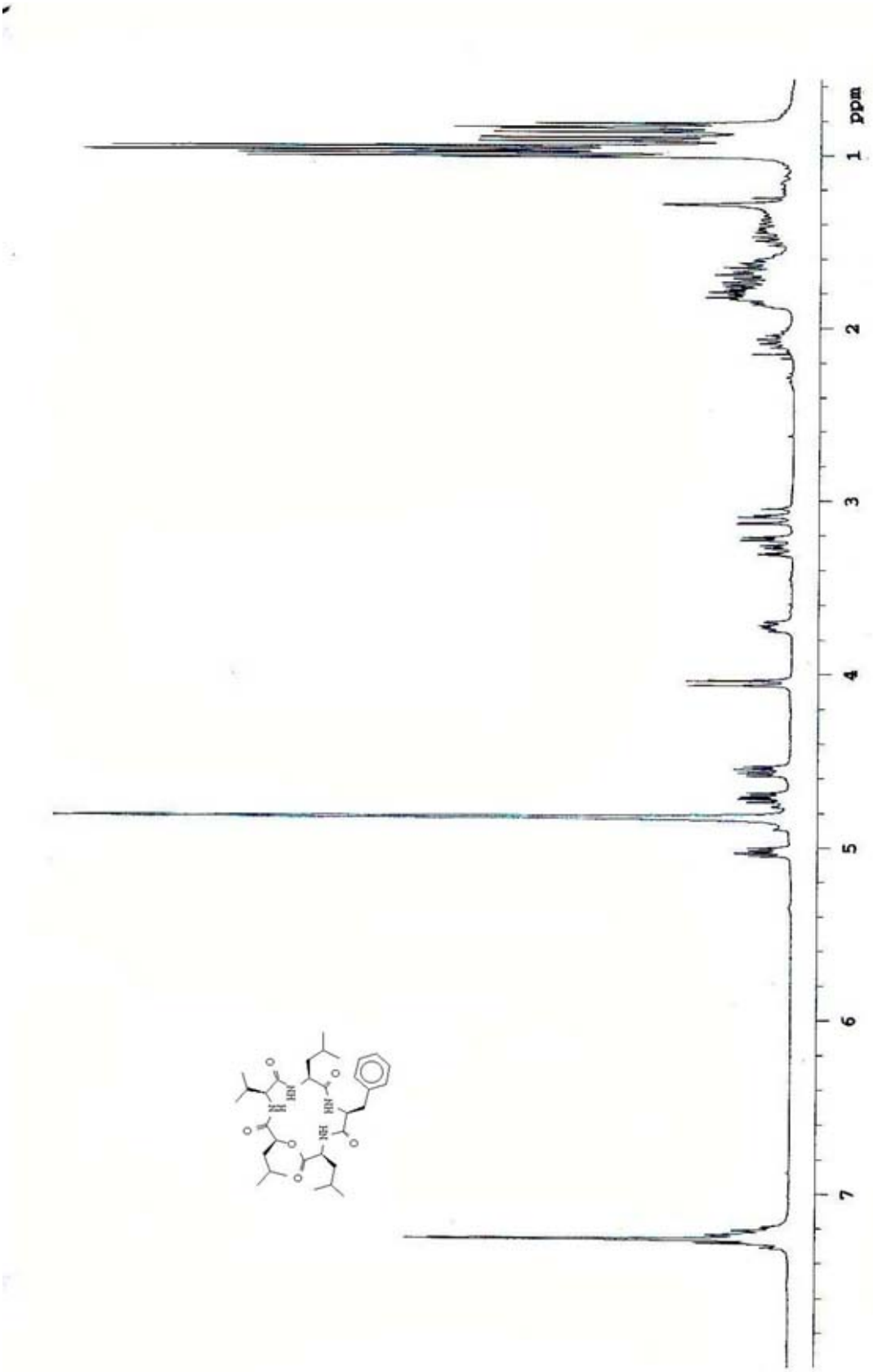


Figure S14. ^{1}H NMR of **9** in CD_3OD

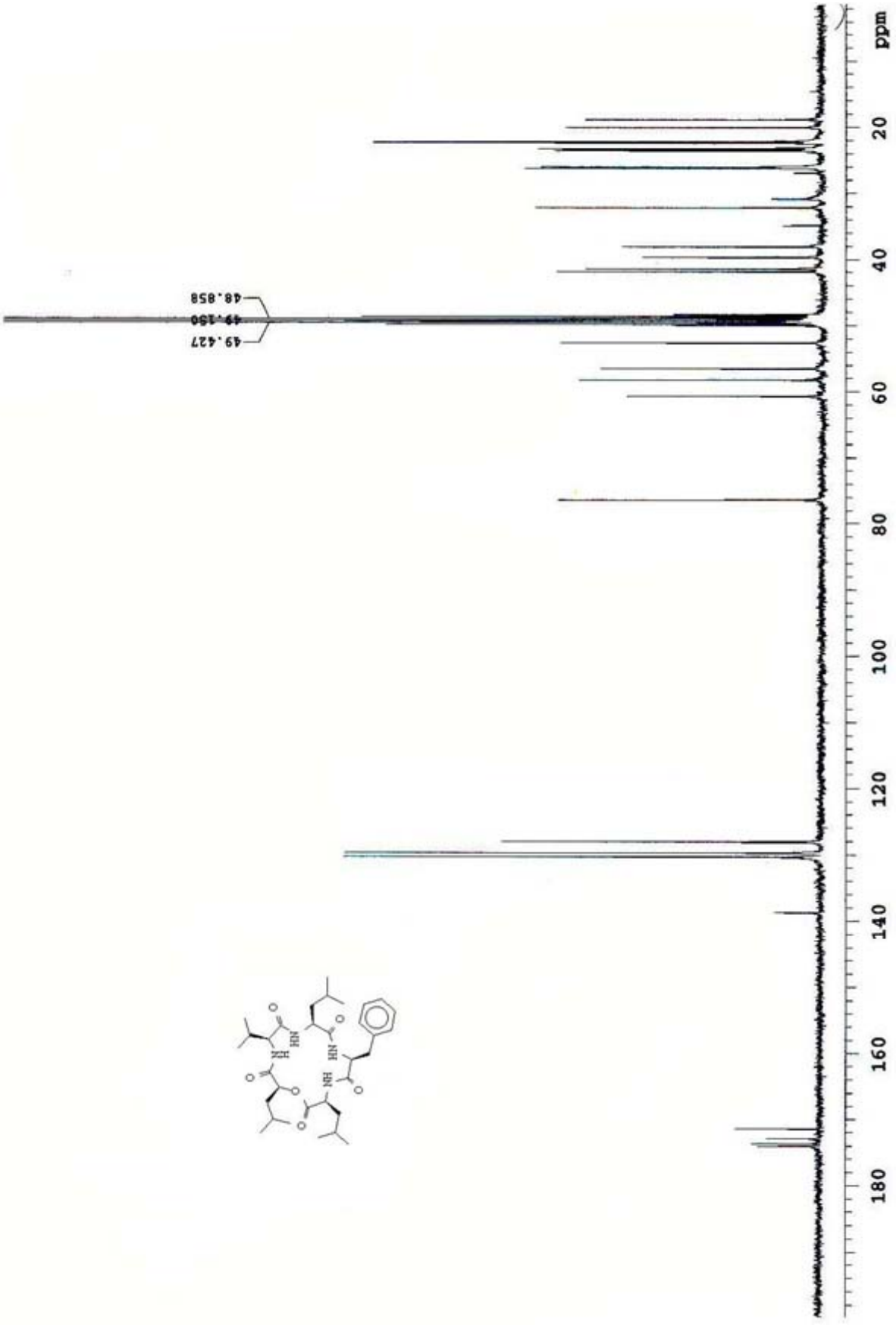


Figure S15. ^{13}C NMR of **9** in CD_3OD

8. ESI MS of Sansalvamide A

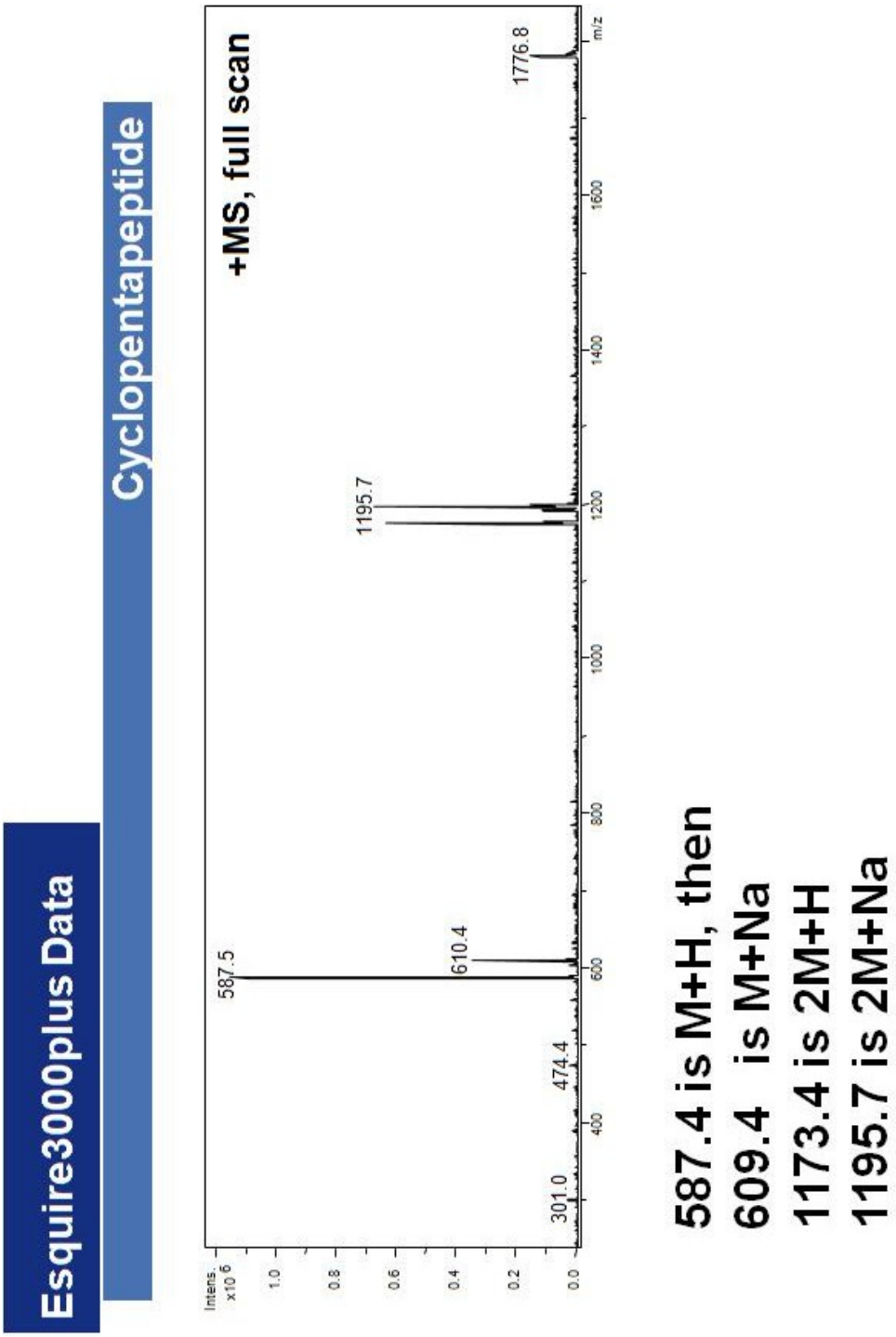


Figure S16. ESI MS of **9**

9. References

[1] N. A. Guerra-Navarro, L. N. Palacios-Grijalva, D. Angeles-Beltrán, G. E. Negrón-Silva, L. Lomas-Romero, E. González-Zamora, R. Gaviño-Ramírez, J. Navarrete-Bolaños, *Molecules*, 20011, **16**, 6561.

[2] G. Negrón, N. A. Guerra, L. Lomas, R. Gaviño, J. Cárdenas, *ARKIVOC*, 2003, **xi**, 179.

[3] A. Albrecht, Ł. Albrecht, T. Janecki, *Eur. J. Org. Chem*., 2011, 2747; H. M. A. Hassan, *Chem. Commun*., 2010, **46**, 9100.

[4] A. Parenty, X. Moreau, J. M. Campagne, *Chem. Rev*., 2006, **106**, 911.

[5] E. M. Driggers, S. P. Hale, J. Lee, N. K. Terrett, *Nat. Rev. Drug Discovery*, 2008, **7**, 608; J. Blankenstein, J. Zhu, *Eur. J. Org. Chem*., 2005, 1949.

[6] J. S. Davies, *J. Pept. Sci.*, *2003,* **9**, 471.

[7] R. Dahiya, D. Pathak, *J. Serb.Chem. Soc*., 2007, **72**, 101; C. Hashimoto, I. Muramatsu, *Bull. Chem. Soc. Jpn.*, *1989*, **62**, 1907.

[8] E. Valeur, M. Bradley, *Tetrahedron,* 2007, **63**, 8855.

[9] D. G. Pintori, M. F. Greaney, *Org. Lett*., 2011, **13**, 5713.

[10] W. K. Chan, C. M. Ho, M. K. Wong, C. M. Che, *J. Am. Chem. Soc*., 2006, **128**, 14796.

[11] K. Dooleweerdt, B. P. Fors, S. L. Buchwald, *Org. Lett*., 2010, **12**, 2350.

[12] M. A. Mohamed, K. Yamada, K. Tomioka, *Tetrahedron Lett*., 2009, **50**, 3436.

[13] T. Ohshima, T. Iwasaki, Y. Maegawa, A. Yoshiyama, K. Mashima, *J. Am. Chem. Soc*., 2008, **130**, 2944.

[14] J.-C. Hsieh, C.-H. Cheng, *Chem. Commun*., 2005, 4554.

[15] L. U. Nordstrøm, H. Vogt, R. Madsen, *J. Am. Chem. Soc.*, 2008, **130**, 17672.

[16] S. C. Ghosh, S. Muthaiah, Y. Zhang, X. Xu, S. H. Honga, *Adv. Synth. Catal*., 2009, **351**, 2643.

[17] X. C. Wang, L. Li, Z. J. Quan, H. P. Gong, H. L. Ye, X. F. Cao, *Chin. Chem. Lett*., 2009, **20**, 651.

[18] J. S. Yadav, B. V. S. Reddy, U. V. S. Reddy, K. Praneeth *Tetrahedron Lett.*, 2008, **49**, 4742.

[19] J. A. Morales-Serna, E. Sánchez, R. Velázquez, J. Bernal, E. García-Ríos, R. Gaviño, G. Negrón-Silva, J. Cárdenas, *Org. Biomol. Chem.* 2010, **8**, 4940.