Supporting Information

Helix Formation in Preorganized β/γ-Peptide Foldamers: Hydrogen-Bond Analogy to the α-Helix without α-Amino Acid Residues

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I. Materials and Instrumentation

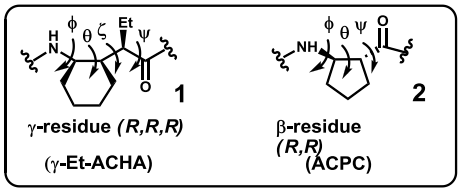
Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker AC-300 (300 MHz) spectrometers. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), or quartet (q). All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AC-300 (75 MHz) spectrometer. Mass spectra (MS) were obtained using an electrospray ionization (ESI) mass spectrometer. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Perkin-Elmer 241 digital polarimeter and are reported as follows: $[\alpha]^{rt}_D$ (*c* in g per 100 mL solvent). Flasks were oven-dried overnight and cooled under a stream of nitrogen. All reagents were purchased from Aldrich Chemical Company. Flash chromatography was performed using silica gel 60 Å (32-63 mesh) from Sorbent Technologies. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm E. Merck pre-coated silica gel 60 (particle size 0.040–0.063 mm). Visualization was performed using a UV lamp or potassium permanganate stain.

II. Peptide Synthesis and Purification

Peptides **3, 4** and **5** were synthesized by conventional solution phase methods using a fragment condensation strategy. The *tert*-butyloxycarbonyl group (Boc) was used for N-terminal protection, and the C-terminal was protected as a benzy ester (OBn). Deprotection at the N-terminus was performed using 4N HCl in dioxane, and hydrogenation was done to remove the C-terminal protecting groups.

Boc-protected amino acids, *N, N*-Diisopropylethylamine (DIEA), and coupling reagents (*N*,*N*-dimethylamino) propyl-3-ethylcarbodiimide hydrochloride (EDCI) and 1-Hydroxybenzotriazole (HOBt) were purchased from Sigma-Aldrich and Chem-Impex.

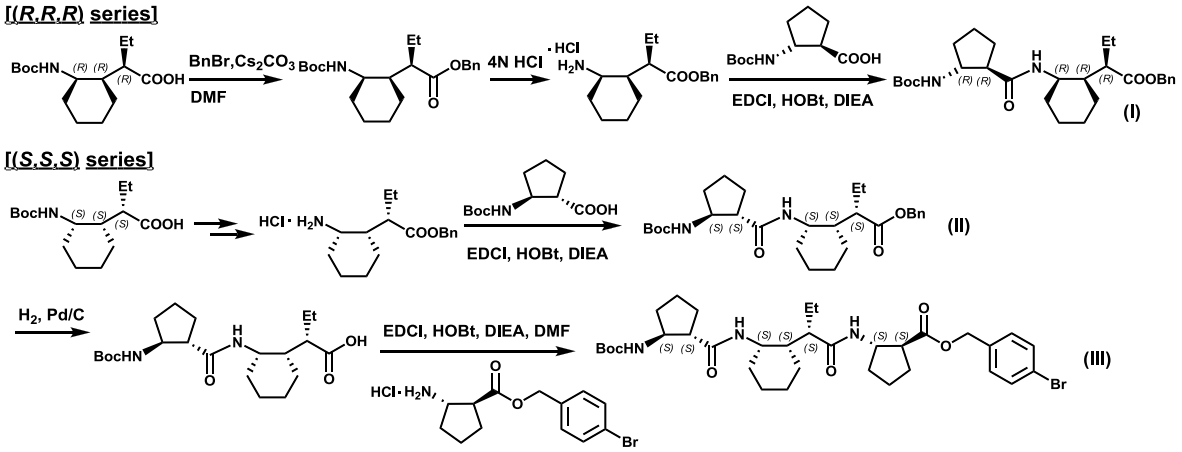
X-ray quality crystals of **3** and **4** were grown from a chloroform/diethyl ether mixture and by evaporation of a $CHCl_3$/heptane mixture, respectively.



Cyclic γ amino acid residue **1** (*R*, *R*, *R*) and β amino acid residue **2** (*R*, *R*) which was synthesized by using published protocols.[S1,S2] **γ-(Et)ACHA** stands for cyclic gamma amino acid.

[S1] Guo, L.; Chi, Y.; Almeida, A. M.; Guzei, I. A.; Parker, B. K.; Gellman, S. H. *J. Am. Chem. Soc.* **2009**, *131*, 16018.
[S2] LePlae, P. R.; Umezawa, N.; Lee, H.-S.; Gellman, S. H. *J. Org. Chem.* **2001**, 66, 5629.

Preparation of dipeptide fragments I, II and tripeptide fragments III



Scheme S1 Preparation of dipeptide fragments I, II and tripeptide fragments III

Dipeptide (I) (*R,R,R series*): (*R,R*)-Boc-ACPC-OH (250 mg, 1.09 mmol) was added directly to a solution of (*R,R,R*)-HCl·NH_2-γ-(Et) ACHA-OBn (340 mg, 1.09 mmol), EDCI (250 mg, 1.3 mmol) and *N,N*-Diisopropylethylamine (380 µL, 2.18 mmol) in CH_2Cl_2 (10 mL). The resulting solution was stirred for 24-36 hrs at room temperature. The reaction mixture was diluted with excess amount of EtOAc, washed with 1M $NaHSO_4$, aqueous saturated $NaHCO_3$ and brine. The organic layer was collected and dried over Na_2SO_4, filtered and concentrated to give the desired dipeptide I, which was purified via column chromatography to yield 450 mg (85% yield) peptide (*R,R,R,R,R*)-Boc-ACPC-γ-(Et)ACHA-OBn as white foam. TLC R_f = 0.56 (EtOAc/hexanes, v/v, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 6.4 Hz, 1H), 7.36-7.27 (m, 5H), 5.22, 4.96 (AB, J_{AB} = 12.5 Hz, 2H), 4.66 (d, *J* = 5.7 Hz, 1H), 4.17 (m, 1H), 3.90 (m,1H), 2.65 (m, 1H), 2.44 (td, *J* = 10.2, 3.9 Hz, 1H), 2.10 (m, 1H), 1.88-1.21 (m, 25H), 0.84 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR: (75.4 MHz, CDCl3) delta 175.88, 172.81, 156.58, 136.59, 128.59, 128.11, 80.11, 66.38, 57.28, 53.43, 49.90, 46.85, 42.23, 33.54, 31.61, 28.58, 27.28, 26.13, 24.88, 24.29, 23.48, 20.63, 11.82; HRMS *m/z* (ESI): calcd. for: $C_{28}H_{42}N_2O_5Na$ $[M+Na]^+$ 487.3167, found 487.3166

Tetrapeptide 3 (*R,R,R series*): (*R,R,R,R,R*)-Boc-ACPC-γ-(Et)ACHA-OH (120 mg, 0.3 mmol) was added directly to a solution of (*R,R,R,R,R*)-HCl·NH_2-ACPC-γ-(Et)ACHA-OBn (128 mg, 0.3 mmol), EDCI (70 mg, 0.37 mmol), HOBt (50 mg, 0.37 mmol), and *N,N* Diisopropylethylamine (64 µL, 0.37 mmol) in DMF (3 mL). The resulting solution was stirred for two days at room temperature. The reaction mixture was diluted with excess amount of EtOAc, washed with 1M $NaHSO_4$, aqueous saturated $NaHCO_3$ and brine. The organic layer was collected and dried over $MgSO_4$, filtered and concentrated to give the desired tetrapeptide, which was purified via column chromatography to yield 185 mg (80% yield) peptide (*R,R,R,R,R,R,R,R,R,R*)-Boc-ACPC-γ-(Et)ACHA-ACPC-γ-(Et)ACHA-OBn as white solid. TLC R_f = 0.23 (EtOAc/hexanes, v/v, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.6 Hz, 1H), 7.44-7.21 (m, 6H), 6.14 (d, *J* = 9.5 Hz, 1H), 5.28, 4.98 (AB, J_{AB} = 12.5 Hz, 2H), 4.77 (d, *J* =

6.0 Hz, 1H), 4.37 (m, 1H), 4.28-4.01 (m,3H), 2.75 (ddd, *J* = 8.8, 6.0, 3.1 Hz, 1H), 2.57 (td, *J* = 10.4, 4.0 Hz, 1H), 2.42 (ddd, *J* = 8.2, 6.6, 4.8 Hz, 1H), 2.17-2.01 (m, 2H), 1.95-1.20 (m, 42H), 0.93-0.75 (m, 6H); 13C NMR: (75.4 MHz, cdcl3) delta 176.35, 174.51, 174.45, 174.26, 156.22, 136.84, 128.49, 128.45, 127.77, 101.43, 80.19, 66.16, 56.46, 56.03, 54.70, 52.29, 50.10, 49.25, 46.80, 46.56, 42.22, 34.55, 32.12, 31.95, 31.74, 31.14, 29.90, 28.58, 27.99, 26.41, 25.89, 25.68, 24.14, 23.82, 23.22, 22.89, 22.80, 20.53, 11.99, 11.67; HRMS *m/z* (ESI): calcd. for:$C_{44}H_{69}N_4O_7$ $[M+H]^+$ 765.5161, found 765.5170

Hexamer 5 (*R,R,R series***):** (*R,R,R,R,R*)-Boc-ACPC-γ-(Et)ACHA-OH (83 mg, 0.206 mmol) was added directly to a solution of (*R,R,R,R,R,R,R,R,R,R*)- $HCl{\cdot}NH_2$-ACPC-γ-(Et)ACHA-ACPC-γ-(Et)ACHA-OBn (145 mg, 0.206 mmol), EDCI (48 mg, 0.25 mmol), HOBt (34 mg, 0.25 mmol), and *N*,*N* Diisopropylethylamine (44 µL, 0.25 mmol) in DMF (2 mL). The resulting solution was stirred for two days at room temperature. The reaction mixture was diluted with excess amount of EtOAc, washed with 1M $NaHSO_4$, aqueous saturated $NaHCO_3$ and brine. The organic layer was collected and dried over $MgSO_4$, filtered and concentrated to give the desired **hexamer 5**, which was purified via column chromatography to yield 161 mg (75% yield) peptide Boc-ACPC-γ-(Et)ACHA-ACPC-γ-(Et)ACHA-ACPC-γ-(Et)ACHA-OBn as white solid. TLC R_f = 0.12 (EtOAc/hexanes, v/v, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.2 Hz, 2H), 7.61 (m, 2H), 7.48-7.20 (m, 5H), 5.92 (d, *J* = 9.4 Hz, 1H), 5.30, 5.02 (AB, J_{AB} = 12.7 Hz, 2H), 4.79 (d, *J* = 7.2 Hz, 1H), 4.50 (m, 1H), 4.40 (m, 1H), 4.24 (m, 3H), 4.07(m, 1H), 2.83(m, 1H), 2.68 (td, *J* = 10.1, 3.9 Hz, 1H), 2.51(m, 1H), 2.38(m, 1H), 2.15-1.20 (m, 62H), 0.96-0.80 (m, 9H); 13C NMR: (125.7 MHz, CDCl3) delta 179.17, 177.44, 177.27, 176.93, 176.53, 175.99, 158.76, 139.63, 130.95, 130.82, 130.03, 83.03, 68.52, 58.72, 58.17, 57.07, 56.77, 54.71, 54.68, 52.86, 52.89, 51.29, 49.16, 48.84, 44.72, 44.32, 43.65, 37.66, 37.40, 37.35, 34.98, 34.56, 33.64, 33.61, 31.03, 30.56, 29.01, 28.96, 28.86, 28.24, 28.15, 27.16, 26.07, 26.00, 25.97, 25.57, 25.52, 25.35, 23.24, 23.12, 22.87, 14.59, 14.05, 13.96, 2.64; HRMS *m/z* (ESI): calcd. for: $C_{60}H_{94}N_6O_9Na$ $[M+Na]^+$ 1065.6975, found 1065.6969

Tripeptide (III) (*S,S,S series***):** (*S,S,S,S,S*)-Boc-ACPC-γ-(Et)ACHA-OH (214 mg, 0.54 mmol) was added directly to a solution of (*S,S*)-$HCl{\cdot}NH_2$- ACPC-OBn(*p*-Br) (181 mg, 0.54 mmol), EDCI (125 mg, 0.65 mmol), HOBt (88 mg, 0.65 mmol), and DIEA (188 µL, 1.08 mmol) in DMF (5 mL). The resulting solution was stirred for two days at room temperature. The reaction mixture was diluted with excess amount of EtOAc, washed with 1M $NaHSO_4$, aqueous saturated $NaHCO_3$ and brine. The organic layer was collected and dried over $MgSO_4$, filtered and concentrated to give the desired peptide, which was purified via column chromatography to yield peptide Boc-ACPC-γ-(Et)ACHA-ACPC-OBn(*p*-Br) as white foam (310 mg, 85% yield). TLC R_f = 0.32 (EtOAc/hexanes, v/v, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 6.8 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.48 (d, *J* = 9.0 Hz, 1H), 5.12, 5.06 (AB, J_{AB} = 12.8 Hz, 2H), 4.77 (d, *J* = 5.3 Hz, 1H), 4.46 (m, 1H), 4.13 (m, 1H), 4.01 (m, 1H), 2.99 (m, 1H), 2.52 (m, 1H), 2.15-0.70 (m, 36H); ^{13}C NMR: (75.4 MHz, $CDCl_3$) delta 175.78, 175.10, 174.54, 156.32, 135.96, 131.67, 130.01, 121.90, 80.21, 65.56, 57.08, 54.83, 54.47, 50.49, 50.05, 46.86, 42.70, 34.29, 32.99,

31.13, 30.09, 29.77, 28.58, 25.99, 25.63, 24.08, 22.36, 20.31, 12.32; HRMS *m/z* (ESI): calcd. for $C_{34}H_{51}BrN_3O_6$ $[M+H]^+$ 676.2956, found 676.2954

Pentapeptide 4 (*S,S,S series*): (*S,S,S,S,S*)-Boc-ACPC-γ-(Et)ACHA-OH (200 mg, 0.51 mmol) was added directly to a solution of $HCl{\cdot}NH_2$-ACPC-γ-(Et)ACHA-ACPC-OBn(*p*-Br) (310 mg, 0.51 mmol), EDCI (108 mg, 0.56 mmol), HOBt (76 mg, 0.56 mmol), and *N,N*-Diisopropylethylamine (175 µL, 1.00 mmol) in DMF (5 mL). The resulting solution was stirred for two days at room temperature. The reaction mixture was diluted with excess amount of EtOAc, washed with 1M $NaHSO_4$, aqueous saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to give the desired amide, which was purified via column chromatography to yield 361 mg (75% yield) peptide Boc-(D)Ala-(Et)ACHA-OBn as white foam. TLC R_f = 0.18 (EtOAc/hexanes, v/v, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 6.0 Hz, 1H), 7.57 (d, *J* = 9.6 Hz, 1H), 7.50 (d, *J* = 9.3 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 5.88 (d, *J* = 9.9 Hz, 1H), 5.14, 5.10 (AB, J_{AB} = 13 Hz, 2H), 4.77 (d, *J* = 7.2 Hz, 1H), 4.44 (m, 2H), 4.21 (m, 2H), 4.08 (m, 1H), 3.21 (m, 1H), 2.53 (m, 1H), 2.37 (m, 1H), 2.12 (m, 2H), 2.02-1.16 (m, 49H), 0.94-0.82 (m, 6H); ^{13}C NMR: (125.7 MHz, CDCl3) delta 176.61, 175.27, 174.93, 174.48, 173.51, 156.29, 136.41, 131.57, 129.95, 121.62, 80.53, 65.30, 56.24, 54.82, 54.71, 54.65, 52.35, 50.90, 50.47, 50.23, 46.37, 42.08, 41.22, 35.44, 34.97, 32.55, 32.09, 31.34, 31.31, 30.79, 30.40, 28.60, 26.65, 26.50, 25.86, 25.81, 24.68, 24.59, 23.66, 23.51, 23.05, 20.77, 20.69, 12.32, 12.27, 11.65; HRMS *m/z* (ESI): calcd. for: $C_{50}H_{76}BrN_5O_8Na$ $[M+Na]^+$ 976.4770, found 976.4772

III. Crystal structure of tetramer 3

The crystal structure of tetramer **3** contains two molecules in the asymmetric unit; (**Figure S1**) the two conformations are very similar. Each independent molecule forms one 13-atom H-bonded ring, involving the NH group of the second ACPC residue and the carbonyl of the N-terminal Boc group. The other possible 13-atom ring H-bond does not form in either case [N--O distance~ 4.9Å]; instead, each molecule contains an 8-atom ring H-bond involving the carbonyl of the first γ-residue and the NH group of second γ-residue. The urethane NH (N-terminus) and NH group of first γ-residue are intermolecularly H-bonded to the carbonyls of an ACPC residue (**Figure S1**).

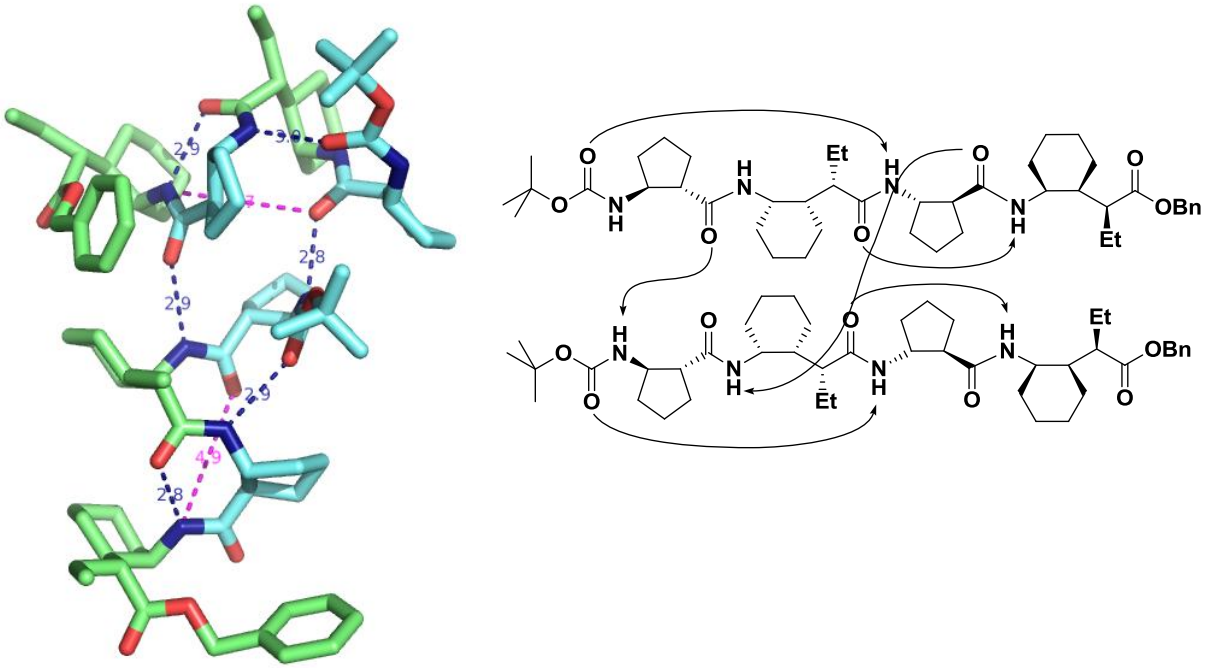


Figure S1 Structure of tetramer **3** (arrows indicate H-bonds in the crystal structures of **3**)

IV. Torsion Angles for γ-residues

Table S1 compares backbone torsion angles for the β- and γ-residues in tetramer **3** including both independent molecules and pentamer **4** with analogous values from the computational work of Hofmann et al.[2], from the NMR analysis of flexible β/γ-peptides in organic solvent by Sharma, Kunwar et al.[3], and from the crystal structures of short hybrid peptides of Balaram et al.[4-5]

The preorganized γ-residues in tetrame **3** including both independent molecules display g^-,g^- local conformations about the C_α-C_β (ζ) and C_β-C_γ (θ) bonds, and ψ near -120°. A wider distribution is observed for the torsion angle ϕ, with a clustering observed near ±140°. The γ-residues in **4** display g^+,g^+ local conformations about the C_α-C_β (ζ) and C_β-C_γ (θ) bonds, and ψ

and ϕ near -120°. These values are consistent with the predictions for the 13-helical conformation from Hofmann et al.[S3]

Table S1. Backbone Torsion Angles (deg)[a] from β/γ Peptides

Peptides	residues	ϕ	θ	ζ	ψ
β/γ-pentamer **4**	β	-107.7	93.3		-128.3
(*S,S,S* series)	γ	-134.7	60.1	59.8	-121.0
	β	-133.6	113.5		-85.7
	γ	-147.3	57.9	46.5	-129.8
	β	-167.9	141.4		-155.0
β/γ-Tetramer **3**	β	88.4	-100.7		136.4
(*R,R,R* series)	γ	140.5	-59.7	-61.2	116.0
Molecule(1)	β	96.3	-102.1		27.1
	γ	144.7	-55.1	-45.1	127.8
β/γ-Tetramer **3**	β	86.2	-100.6		133.8
(*R,R,R* series)	γ	142.3	-58.7	-62.6	116.3
Molecule (2)	β	90.3	-108.8		45
	γ	166.6	-58.0	-56.7	105.8
computational	β	69.3	-101.0		141.9
survey by Hofmann [S3]	γ	130.1	-60.7	-62.8	129.6
	β	97.4	-91.9		113.8
	γ	123.1	-58.8	-62.4	134.4
	β	94.0	-93.2		112.6
	γ	129.9	-61.4	-61.9	128.0
	β	95.7	-90.2		119.2
	γ	116.7	-60.7	-61.6	136.1
β/γ tetrapeptide	β	120	60		0
by Sharma [S4]	γ	120	-60	60	-120
hybrid undecapeptide	β	-103	78		-107
by Balaram [S5]	γ	-121	63	57	-121
hybrid tripeptide	β	-109.7	81.0		-120.4
by Balaram [S6]	γ	-114.4	63.0	67.5	-123.0

[S3] Baldauf, C.; Gunther, R.; Hofmann, H. J. *J. Org. Chem.* **2006**, *71*, 1200

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[S5] Karle, I. L.; Pramanik, A.; Banerjee, A.; Bhattacharjya, S.; Balaram, P. *J. Am. Chem. Soc.* **1997**, *119*, 9087

[S6] Vasudev, P. G.; Ananda, K.; Chatterjee, S.; Aravinda, S.; Shamala, N.; Balaram, P. *J. Am. Chem. Soc.* **2007**, *129*, 4039

V. Helix Parameters for β/γ-peptide

Calculation of helix parameters

Parameters for the 13-helix of β/γ pentapeptide **4** and α-helix for α-peptides were calculated by previous reported methods (Table S2). [S7,S8] For β, γ-residues, mid-point of Cα and Cβ of β-residues and Cβ of γ-residues were used as imaginary Cαs for the calculations. Helical parameters of β/γ 13-helix are analogous to α-helix.

Table S2. Helical Parameters

backbone	helix type	H-bond	res/turn *n*	rise/turn *p* (Å)	rise/res *d* (Å)	radius *r* (Å)
α-peptides	α-helix[6]	i,i+4	3.7	5.4	1.5	2.3
β/γ-peptides	13-helix	i,i+3	2.6	5.4	2.1	2.5

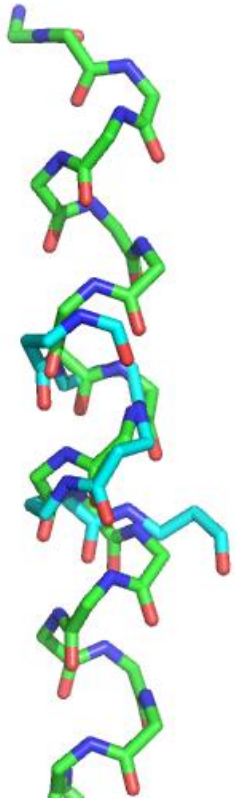


Figure S2 Overlay of two backbone conformations for β/γ pentapeptide **4** and α-helix

Figure S2 shows the superposition of β/γ pentapeptide **4** and α-helix of α-peptides backbone structures with an RMSD of 0.989Å.

[S7] Barlow, D. J; Thorton, J. M. *J. Mol. Biol.* **1988**, *5*, 601.

[S8] (a) Sugeta, H.; Miyazawa, T. *Biopolymers* **1967**, *5*, 673. (b) Kahn, P. C. *Comput. Chem.* **1989**, *13*, 185.

VI. Crystallographic Experimental Section

Data Collection for TETRAMER 3 (gellman119)

A colorless crystal with approximate dimensions 0.42 x 0.08 x 0.07 mm^3 was selected under oil under ambient conditions and attached to the tip of a MiTeGen MicroMount©. The crystal was mounted in a stream of cold nitrogen at 100(1) K and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed on a Bruker SMART APEXII diffractometer with Cu K_α (λ = 1.54178 Å) radiation and the diffractometer to crystal distance of 4.03 cm.

The initial cell constants were obtained from three series of scans at different starting angles. Each series consisted of 41 frames collected at intervals of 0.6º in a 25º range about with the exposure time of 20 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program. The final cell constants were calculated from a set of 9831 strong reflections from the actual data collection.
The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a resolution of 0.83 Å. A total of 133008 data were harvested by collecting 16 sets of frames with 0.8º scans in with an exposure time 30-80 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [3.1]

Structure Solution and Refinement

The systematic absences in the diffraction data were consistent for the space groups $P2_12_12_1$ that yielded chemically reasonable and computationally stable results of refinement [3.2, 3.3].
A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic 3

displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients.

The unit cell contains two symmetry independent molecules of the foldamer, two partially occupied molecules of solvated $CHCl_3$, and two or three unidentified solvent molecules, *vide infra*.

Atoms C8 is disordered over two positions with the major component being occupied 72.9(5)% of the time. Atoms C8a is disordered over two positions with the major component being occupied 69.9(6)% of the time. Atoms C19 and C20 are equally disordered over two positions.

There are two partially occupied molecules of chloroform in the unit cell, the occupancy factors are 50 and 72%. Restraints and constraints were used in the refinement of partially occupied moieties.

There were partially occupied solvate molecules also present in the asymmetric unit. A significant amount of time was invested in identifying and refining the disordered molecules. Bond length restraints and constraints were applied to model the molecules (as chloroform, heptane, and ethyl acetate) but the resulting isotropic displacement coefficients suggested the molecules were mobile. In addition, the refinement was computationally unstable. Option SQUEEZE of program PLATON [3.4] was used to correct the diffraction data for diffuse scattering effects and to identify the solvate molecule. PLATON calculated the upper limit of volume that can be occupied by these solvents to be 1288 $Å_3$, or 12.4 % of the unit cell volume. The program calculated 312 electrons in the unit cell for the diffuse species. It is likely that all three crystallization solvents chloroform, heptane, and ethyl acetate are present in small ratios and are disordered over several positions. Please note that all derived results in the following tables are based on the known contents. No data are given for the diffusely scattering species. The final least-squares refinement of 1083 parameters against 9780 data resulted in residuals R (based on F^2 for $I \geq 2\sigma$) and wR (based on F^2 for all data) of 0.0586 and 0.1399, respectively. The final difference Fourier map was featureless.

The molecular diagrams are drawn with 30% probability ellipsoids.

References

[3.1] Bruker-AXS. (2007) APEX2, SADABS, and SAINT Software Reference Manuals. Bruker-AXS, Madison, Wisconsin, USA.

[3.2] Sheldrick, G. M. (2008) SHELXL. *Acta Cryst.* **A64**, 112-122.

[3.3] Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. "OLEX2: a complete structure solution, refinement and analysis program". *J. Appl. Cryst.* (2009) **42**, *339-341*.

[3.4] A.L. Spek (1990) Acta Cryst. A46, C34.

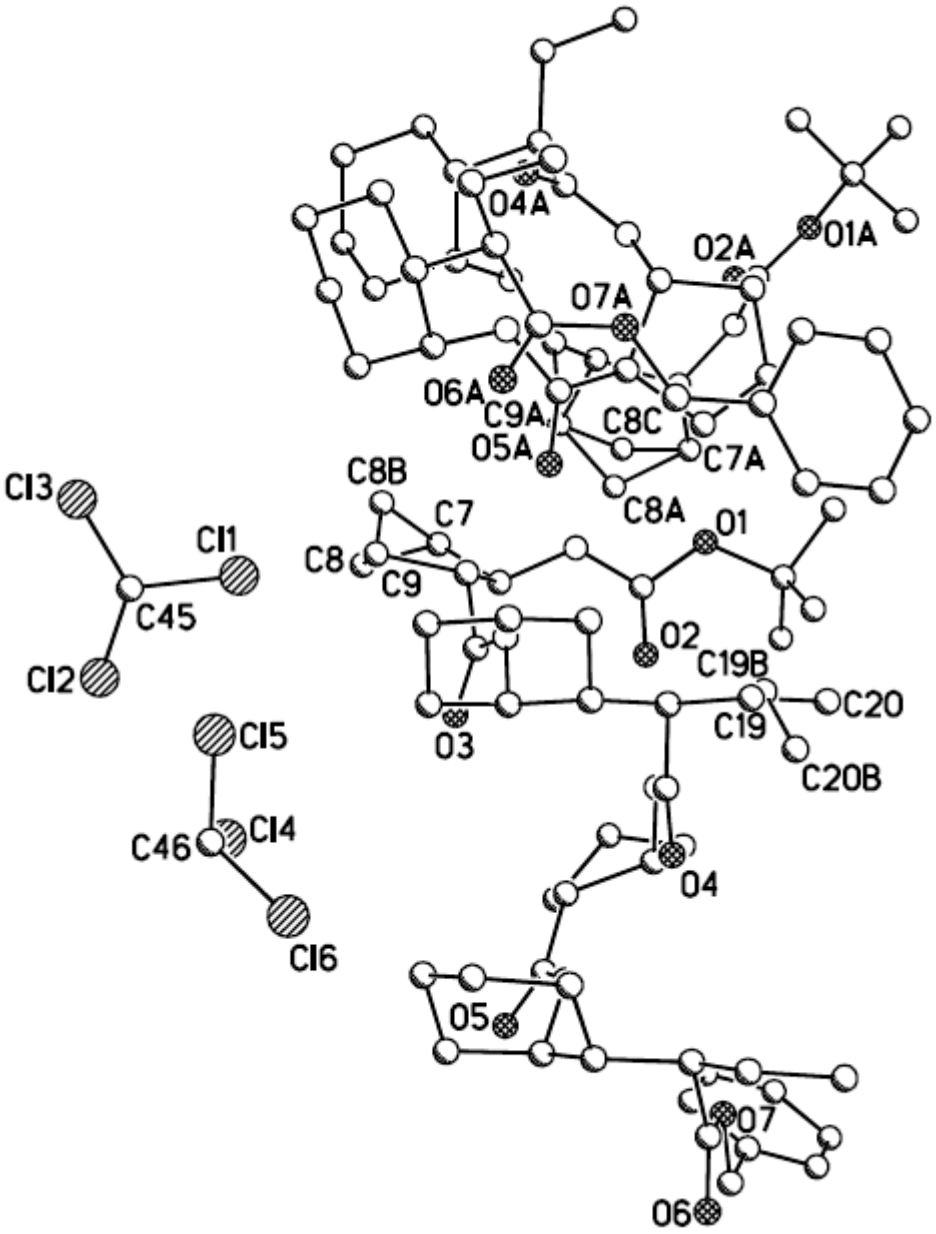


Figure S3. The content of the asymmetric unit. All H atoms are omitted.

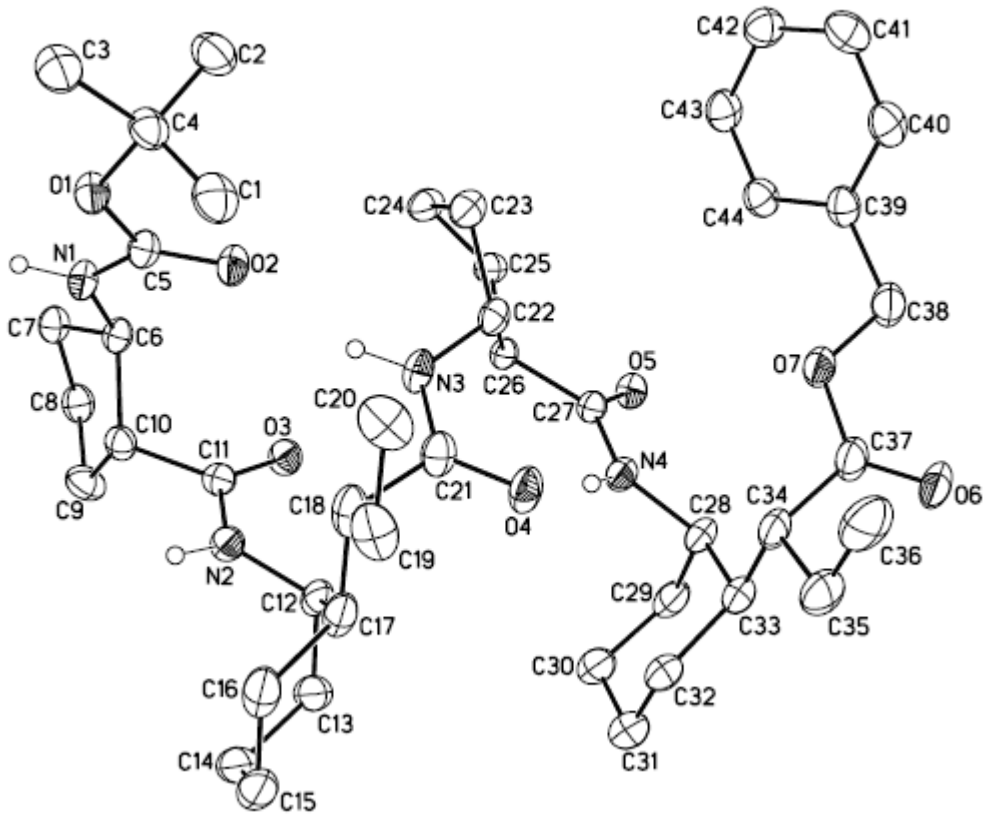


Figure S4. The first foldamer molecule. All H atoms attached to C atoms are omitted.

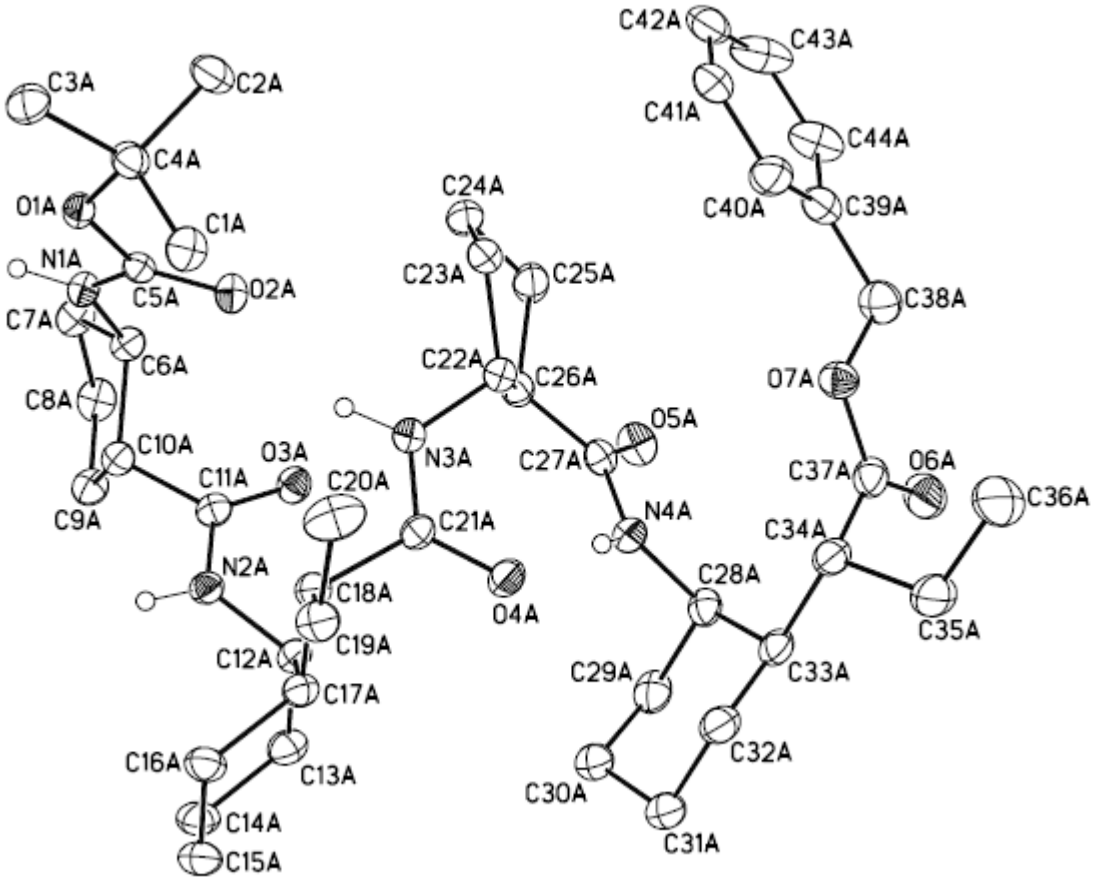


Figure S5. The second foldamer molecule. All H atoms attached to C atoms are omitted.

Table 1. Crystal data and structure refinement for gellman119.

Identification code	gellman119	
Empirical formula	C_{44} H_{68} N_4 O_7 x 0.61 $CHCl_3$ x unidentified solvent	
Formula weight	837.84	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 16.5029(4) Å	α= 90°.
	b = 20.8999(5) Å	β= 90°.
	c = 30.0805(7) Å	γ = 90°.
Volume	10375.0(4) $Å^3$	
Z	8	
Density (calculated)	1.073 Mg/m^3	
Absorption coefficient	1.411 mm^{-1}	
F(000)	3611	
Crystal size	0.42 x 0.08 x 0.07 mm^3	
Theta range for data collection	2.57 to 69.62°.	
Index ranges	-20<=h<=19, -25<=k<=25, -35<=l<=36	
Reflections collected	133008	
Independent reflections	19287 [R(int) = 0.0521]	
Completeness to theta = 67.00°	99.7 %	
Absorption correction	Empirical with SADABS	
Max. and min. transmission	0.9089 and 0.5914	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	19287 / 50 / 1083	
Goodness-of-fit on F^2	0.978	
Final R indices [I>2sigma(I)]	R1 = 0.0511, wR2 = 0.1353	
R indices (all data)	R1 = 0.0630, wR2 = 0.1436	
Absolute structure parameter	0.033(17)	
Largest diff. peak and hole	0.688 and -0.261 $e.Å^{-3}$	

Table S3. Hydrogen bonds for TETRAMER gellman119 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(3A)	0.88	1.97	2.795(3)	155.5
N(2)-H(2)...O(5A)	0.88	2.05	2.917(3)	169.2
N(3)-H(3)...O(2)	0.88	2.06	2.917(3)	163.7
N(4)-H(4)...O(4)	0.88	1.93	2.806(3)	174.2
N(3A)-H(3AD)...O(2A)	0.88	2.13	2.959(3)	157.6
N(4A)-H(4A)...O(4A)	0.88	2.04	2.900(3)	166.8
N(1A)-H(1AD)...O(3)#1	0.88	2.02	2.847(3)	155.2
N(2A)-H(2AD)...O(5)#1	0.88	2.07	2.902(3)	157.7

Symmetry transformations used to generate equivalent atoms:
#1 -x+2,y+1/2,-z+1/2

Data Collection of PENTAMER 4(gellman130)

A colorless crystal with approximate dimensions 0.19 x 0.19 x 0.05 mm^3 was selected under oil under ambient conditions and attached to the tip of a MiTeGen MicroMount©. The crystal was mounted in a stream of cold nitrogen at 100(1) K and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed on a Bruker SMART APEXII diffractometer with Cu K_α (λ = 1.54178 Å) radiation and the diffractometer to crystal distance of 4.03 cm.

The initial cell constants were obtained from three series of scans at different starting angles. Each series consisted of 50 frames collected at intervals of 0.5º in a 25º range about with the exposure time of 30 seconds per frame. The reflections were successfully indexed by an automated indexing routine built in the APEXII program. The final cell constants were calculated from a set of 9895 strong reflections from the actual data collection.
The data were collected by using the full sphere data collection routine to survey the reciprocal space to the extent of a full sphere to a resolution of 0.82 Å. A total of 64171 data were harvested by collecting 16 sets of frames with 0.8º scans in with an exposure time 35-70 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [4.1]

Structure Solution and Refinement

The systematic absences in the diffraction data were uniquely consistent for the space group $P2_12_12_1$ that yielded chemically reasonable and computationally stable results of refinement [4.2-4.4].

A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic 3

displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. Atoms Br1 and C45-C50 are disordered over two positions with a minor component contribution of 6.95(18) % and were refined with restraints and constraints. All chiral centers have the absolute configuration of S. There are three intramolecular and two intermolecular hydrogen bonding interactions present.

The final least-squares refinement of 581 parameters against 8952 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0576 and 0.1695, respectively. The final difference Fourier map was featureless.

The molecular diagram is drawn with 50% probability ellipsoids.

References

[4.1] Bruker-AXS. (2007) APEX2, SADABS, and SAINT Software Reference Manuals. Bruker-AXS, Madison, Wisconsin, USA.

[4.2] Sheldrick, G. M. (2008) SHELXL. *Acta Cryst.* **A64**, 112-122.

[4.3] Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. "OLEX2: a complete structure solution, refinement and analysis program". *J. Appl. Cryst*. (2009) **42**, *339-341*.

[4.4] Guzei, I.A. (2006-2008). Internal laboratory computer programs "Inserter", "FCF_filter", "Modicifer".

[4.5] Pennington, W.T. (1999) *J. Appl. Cryst.* **32**(5), 1028-1029.

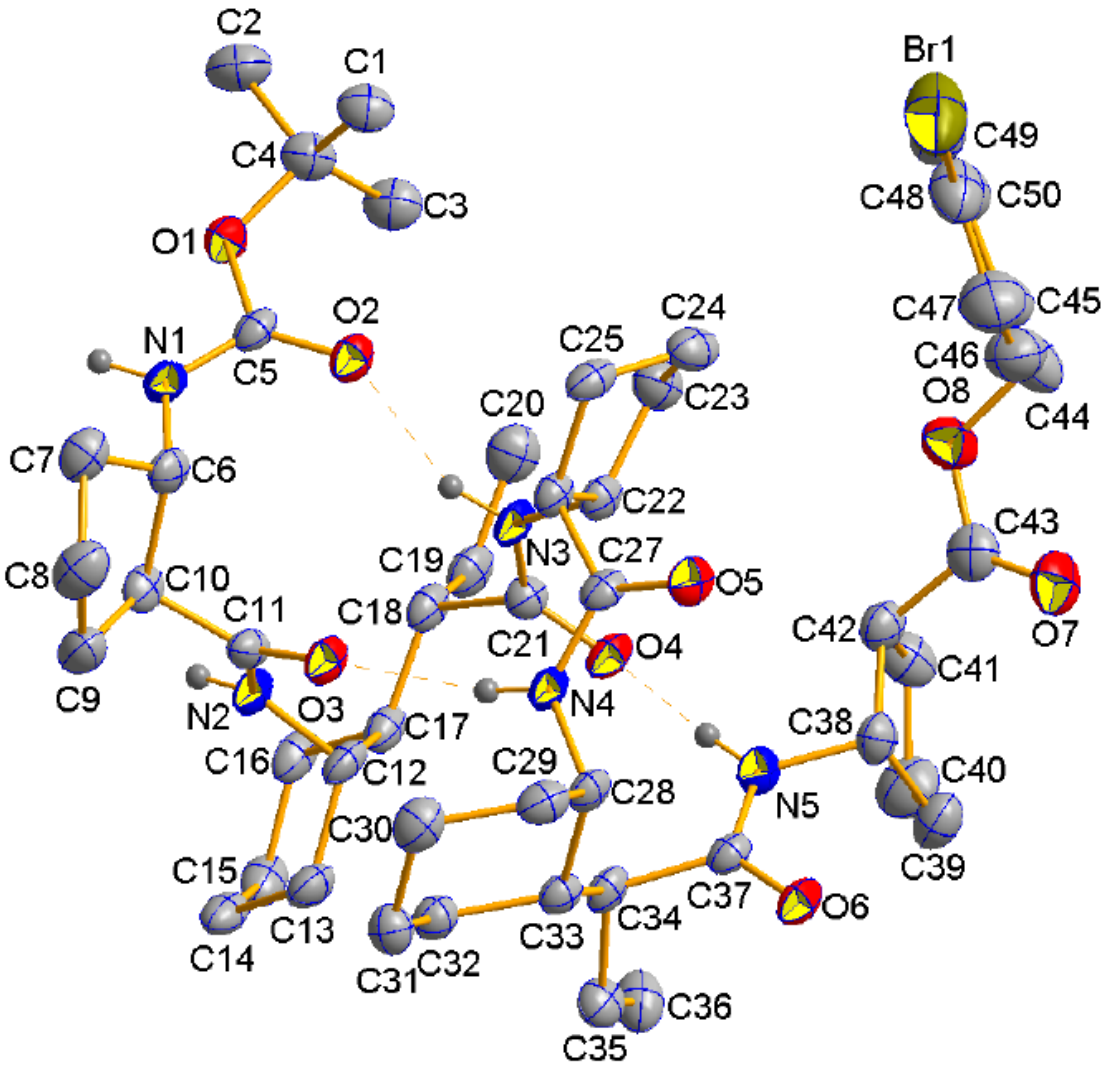


Figure S6. A molecular drawing of gellman130 [4.5]. All hydrogen atoms attached to carbon atoms were omitted for clarity. Only one position of the disordered atoms is shown. Hydrogen bonds are shown with dashed lines.

Table S4. Crystal data and structure refinement for gellman130

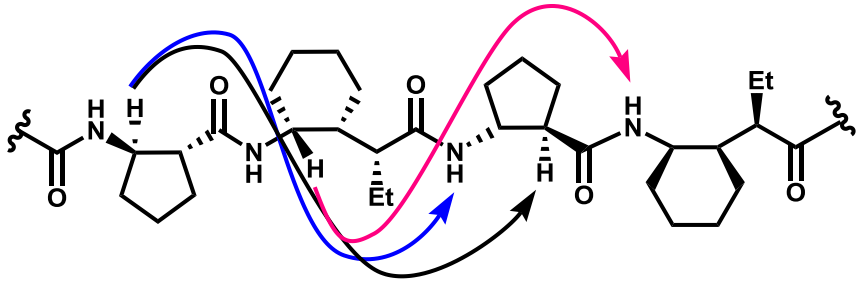
Identification code	gellman130	
Empirical formula	$C_{50}H_{76}BrN_5O_8$	
Formula weight	955.07	
Temperature	100(1) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 10.9331(2) Å	α= 90°.
	b = 18.5573(3) Å	β= 90°.
	c = 24.7143(4) Å	γ = 90°.
Volume	5014.25(15) $Å^3$	
Z	4	
Density (calculated)	1.265 Mg/m^3	
Absorption coefficient	1.567 mm^{-1}	
F(000)	2040	
Crystal size	0.19 x 0.19 x 0.05 mm^3	
Theta range for data collection	2.98 to 67.64°.	
Index ranges	-11<=h<=12, -21<=k<=22, -29<=l<=29	
Reflections collected	64171	
Independent reflections	8952 [R(int) = 0.0860]	
Completeness to theta = 67.00°	99.6 %	
Absorption correction	Analytical with SADABS	
Max. and min. transmission	0.9258 and 0.7550	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8952 / 18 / 581	
Goodness-of-fit on F^2	0.951	
Final R indices [I>2sigma(I)]	R1 = 0.0576, wR2 = 0.1434	
R indices (all data)	R1 = 0.0915, wR2 = 0.1695	
Absolute structure parameter (Flack x)	-0.03(2)	
Absolute structure parameter (Hooft y)	0.024(9)	
Largest diff. peak and hole	0.460 and -0.672 $e.Å^{-3}$	

Table S5. Hydrogen bonds for gellman130 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(6)#1	0.88	1.96	2.826(5)	165.9
N(2)-H(2)...O(5)#1	0.88	2.14	2.994(4)	162.0
N(3)-H(3)...O(2)	0.88	2.13	2.923(5)	149.9
N(4)-H(4)...O(3)	0.88	2.07	2.918(4)	161.9
N(5)-H(5)...O(4)	0.88	2.02	2.885(4)	168.8

Symmetry transformations used to generate equivalent atoms:
#1 -x+2,y-1/2,-z+3/2

VII. Two-dimensional NMR analysis

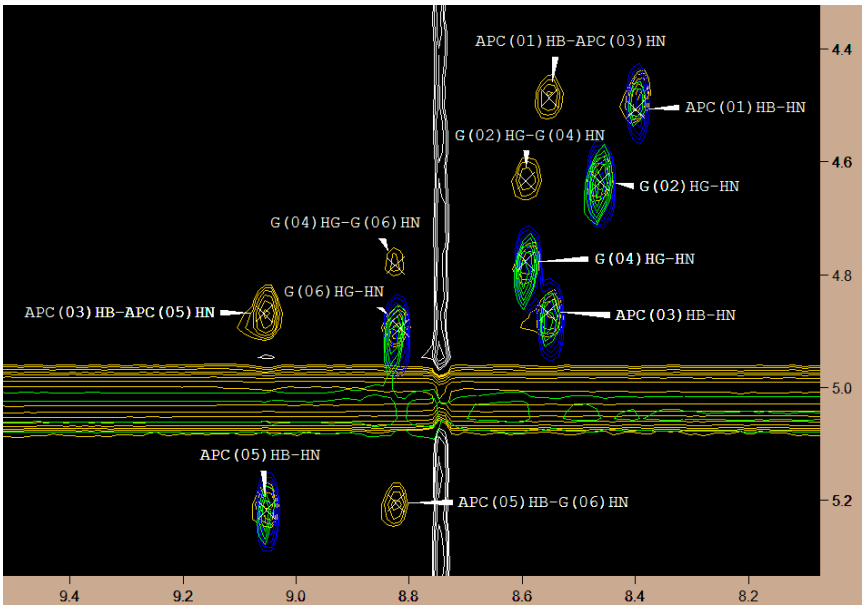


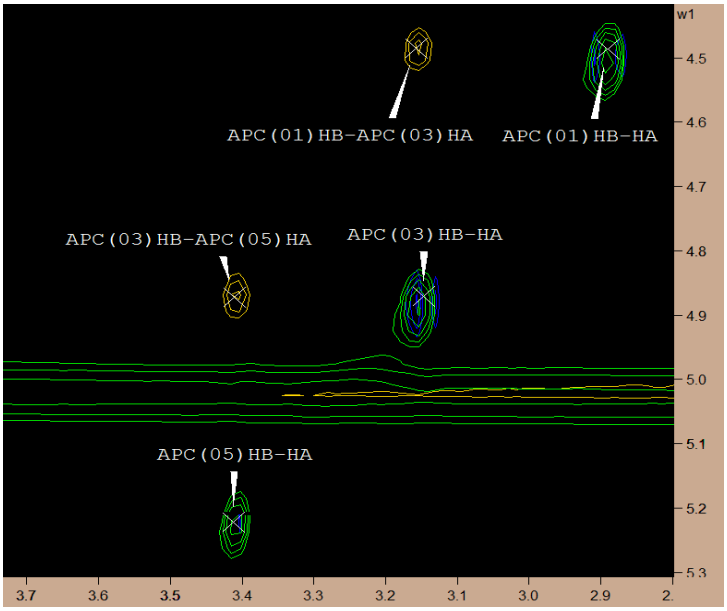
Gamma stands for cyclic gamma amino acid residue (*R*, *R*, *R*) which was synthesized by *n*-butanal and (*S*)-**A** in this section.

Figure S7. Characteristic NOEs patterns observed for the 1:1 α/γ-peptide hexamer 5 in pyridine-d6

NMR Chemical Shift Data (ppm)

βγβγβγ, 2 mM, 20 °C		Backbone atoms			Side-chain
residue	**NH**	**α**	**β**	**γ**	**Unassigned**
Boc					
APC	8.298	2.874	4.485		2.137,1.982,1.877, 1.708, 1.568
Gamma	8.464	2.38	2.07	4.476	1.861,1.695,1.573,1.272
APC	8.551	3.144	4.87		2.305,2.148,1.945,1.759,1.557
Gamma	8.593	2.38	2.204	4.778	1.973,1.830,1.560, 1.295
APC	9.053	3.384	5.211		2.12,1.993,1.886,1.538
Gamma	8.825	2.373	2.16	4.916	2.057,1.898,1.556,1.309
Bn		CH_2= 5.424, 5.590			o= 7.704 m= 7.389 p= 7.262





Gold = ROESY
Green = TOCSY
Blue = COSY

Figure S8 Partial ROESY Spectrum of Hexamer in pyridine-d6 at 293K

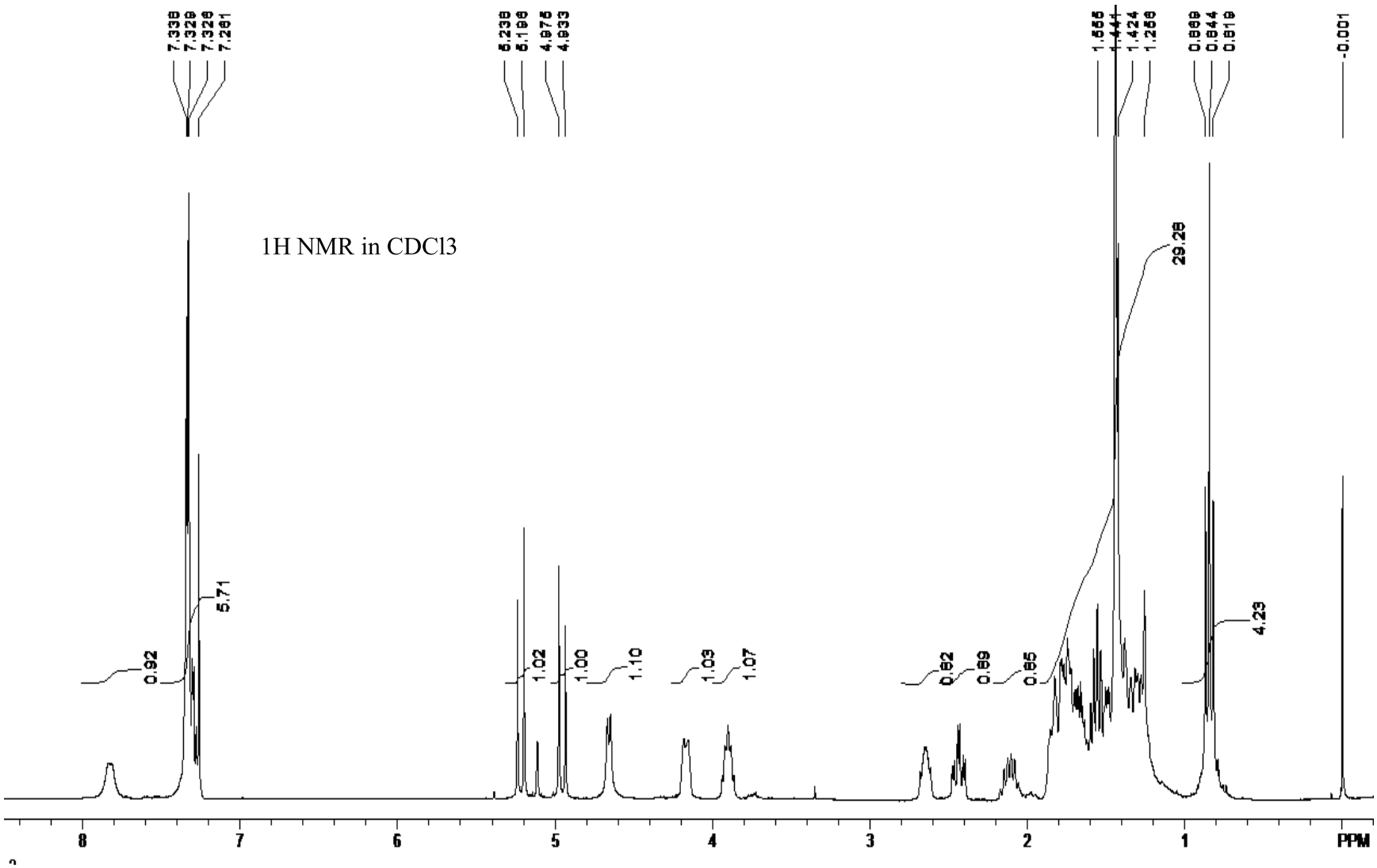
NMR Acquisitions:

NMR samples were prepared by dissolving the peptide in pyridine-d6. Samples were prepared with total volumes of approximately 600 μL for 5 mm NMR tubes. Samples were referenced to tetramethylsilane. The NMR samples were stable in solution for weeks showing no apparent precipitation of peptide or decrease in NMR signal strength over the entire period of study. In all cases sharp lines were observed in 1D spectra suggesting that the peptides were not aggregated in solution. NMR experiments were performed on Varian INOVA 600 MHz spectrometers at 20º C using a Varian 3 mm $^{1}H/^{13}C/^{15}N$ with 3 axis PFG. The reported temperatures are presumed to be accurate to ≈ 1 K.

gCosy,Tocsy, Roesy;

Standard Varian pulse sequences were used, and data were processed using Varian VNMR 6.1 software and analyzed with the sparky[1] program. Spectral windows of 8000 Hz were used. Shifted sine bell window functions were generally applied before Fourier transformation. For all samples gCOSY spectra were obtained in absolute mode with gradient echo coherence selection; TOCSY[2] and ROESY[2,4] spectra were acquired in the sensitive mode with hypercomplex phase cycling (States-Haberkorn method). All experiments were performed by collecting 2048 points in f2 and 300-600 points in f1. TOCSY experiments employed a standard MLEV-17 spin lock sequence with a spin lock field of 7-8 KHz and mixing time of 80 ms. ROESY experiments used spin-locking fields of ~3 kHz's and mixing times of 250 ms. The ^{1}H chemical shift assignment of the peptides was achieved by the sequential assignment procedures[5] .

(1) Goddard, D. T.; Kneller, D. G. *SPARKY 3*, University of California, San Francisco.
(2) Bax, A.; davies, D. G.; *J. Mag. Res*, **1985**; *65*, 355.
(3) Jeener, J. M.; Bachmann, P.; Ernst, R. R.; *J. Chem. Phy.* **1979**, *29*, 1012-1014.
(4) Bothner-By A. A.; Stephens R. L.; Lee, J.; Warren, C. D.; Jeanloz, R. W.; *J. Am. Chem. Soc.* **1984**; *106*, 811-813.
(5) Wuthrich, K.; *NMR of Proteins and Nucleic Acids;* Wiley-Interscience: New York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0.819
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29.26
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4.23
0.92
1.02
1.00
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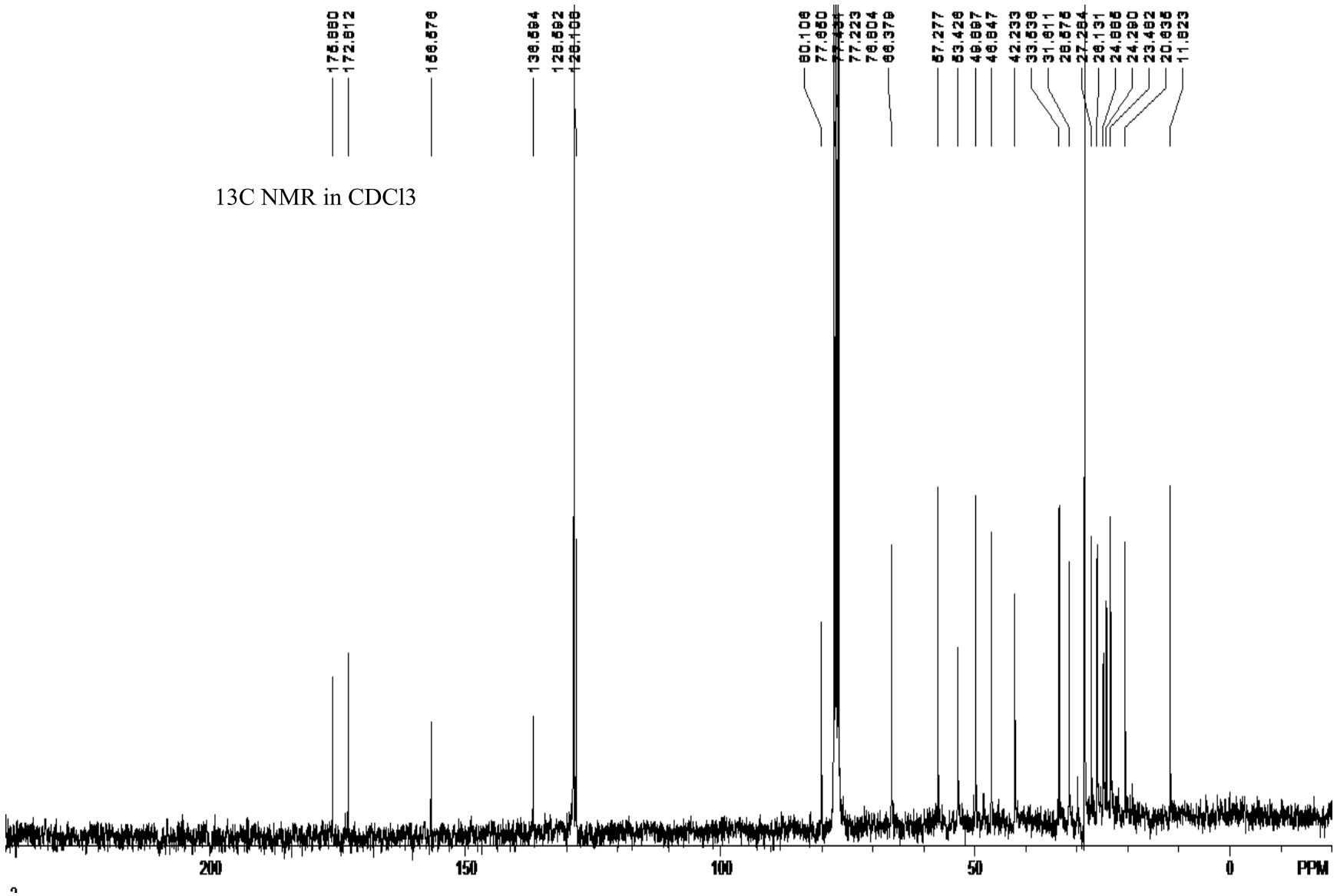
7
6
5
4
3
2
1
PPM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28.575
27.284
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150
100
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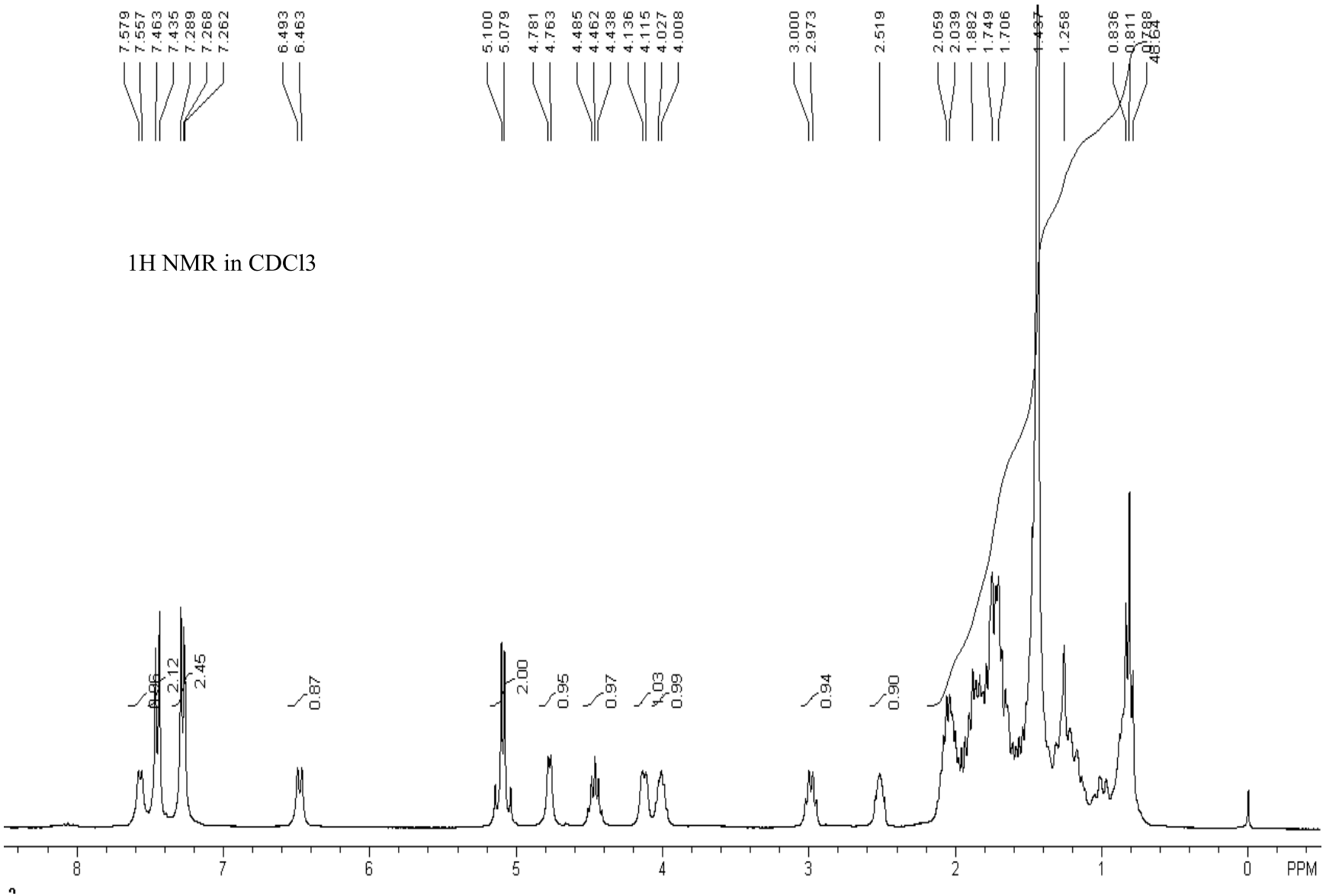
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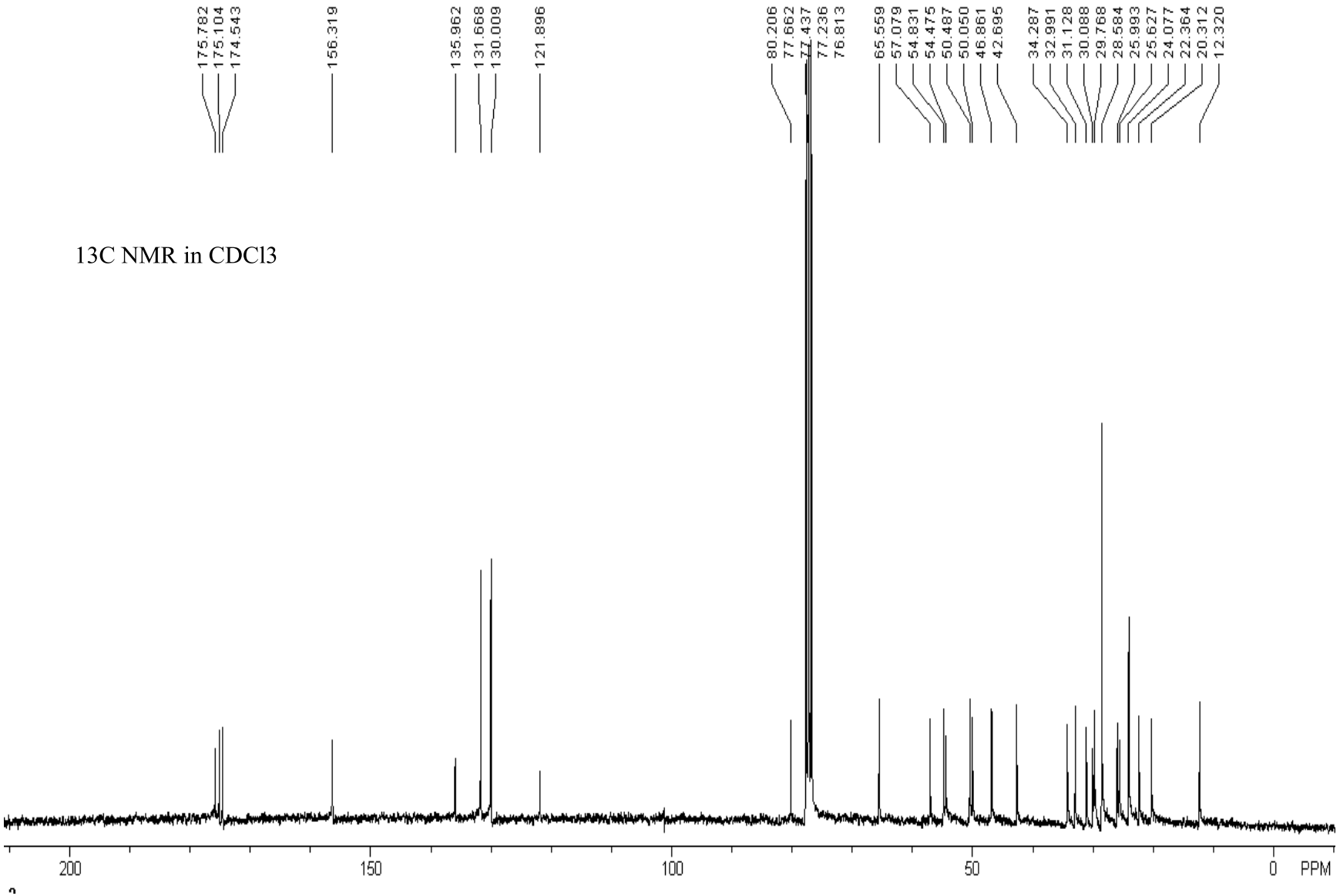

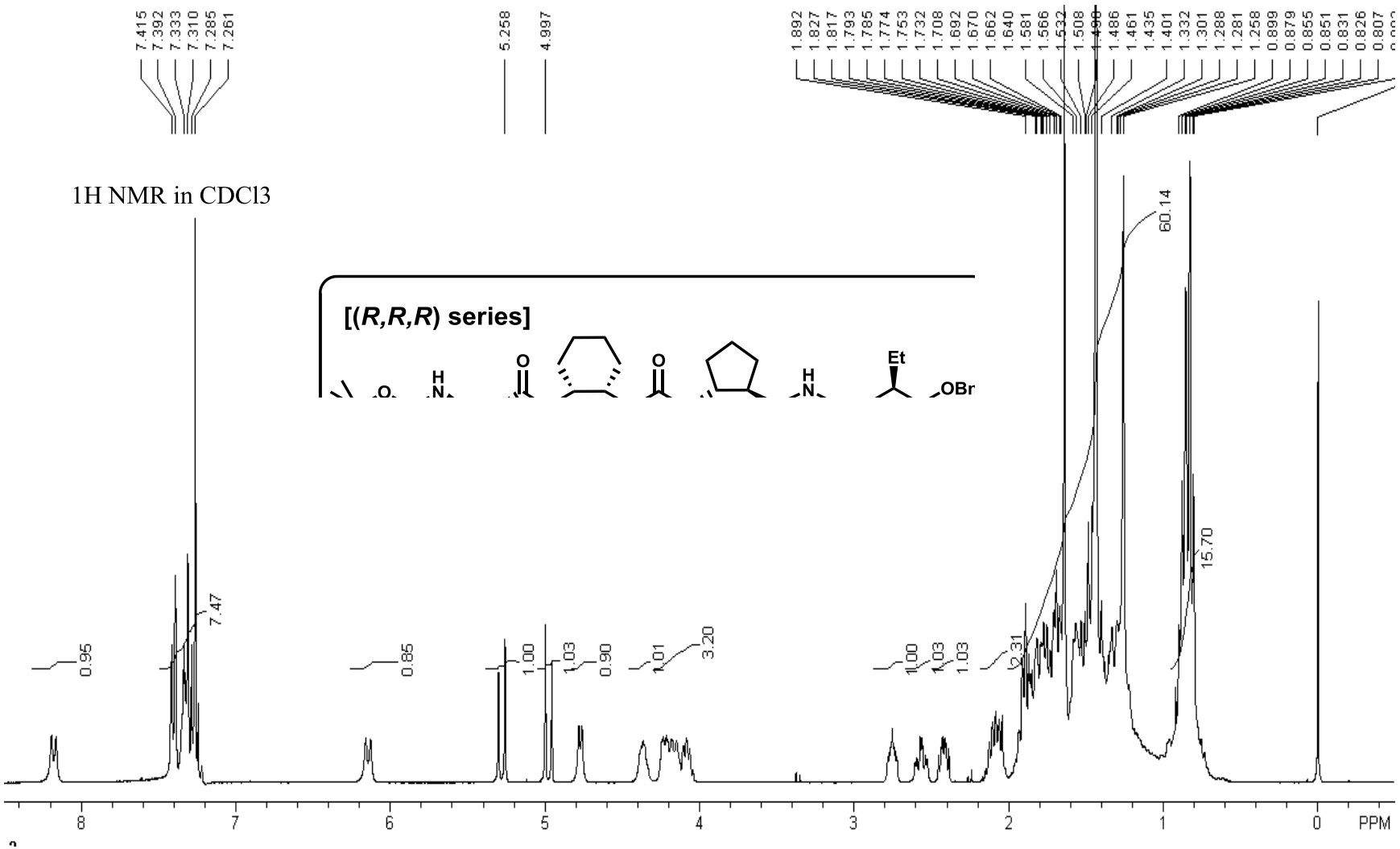
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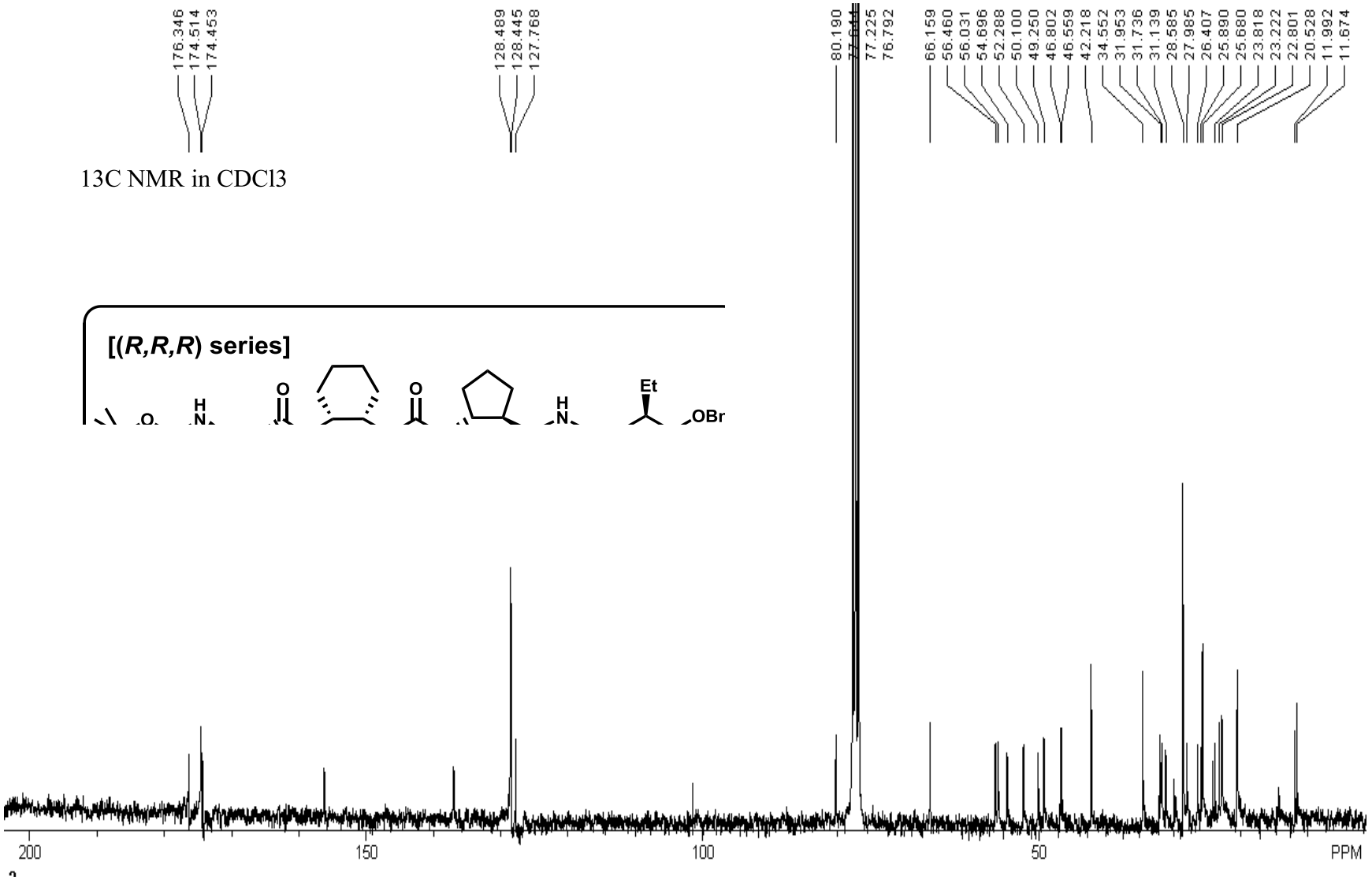

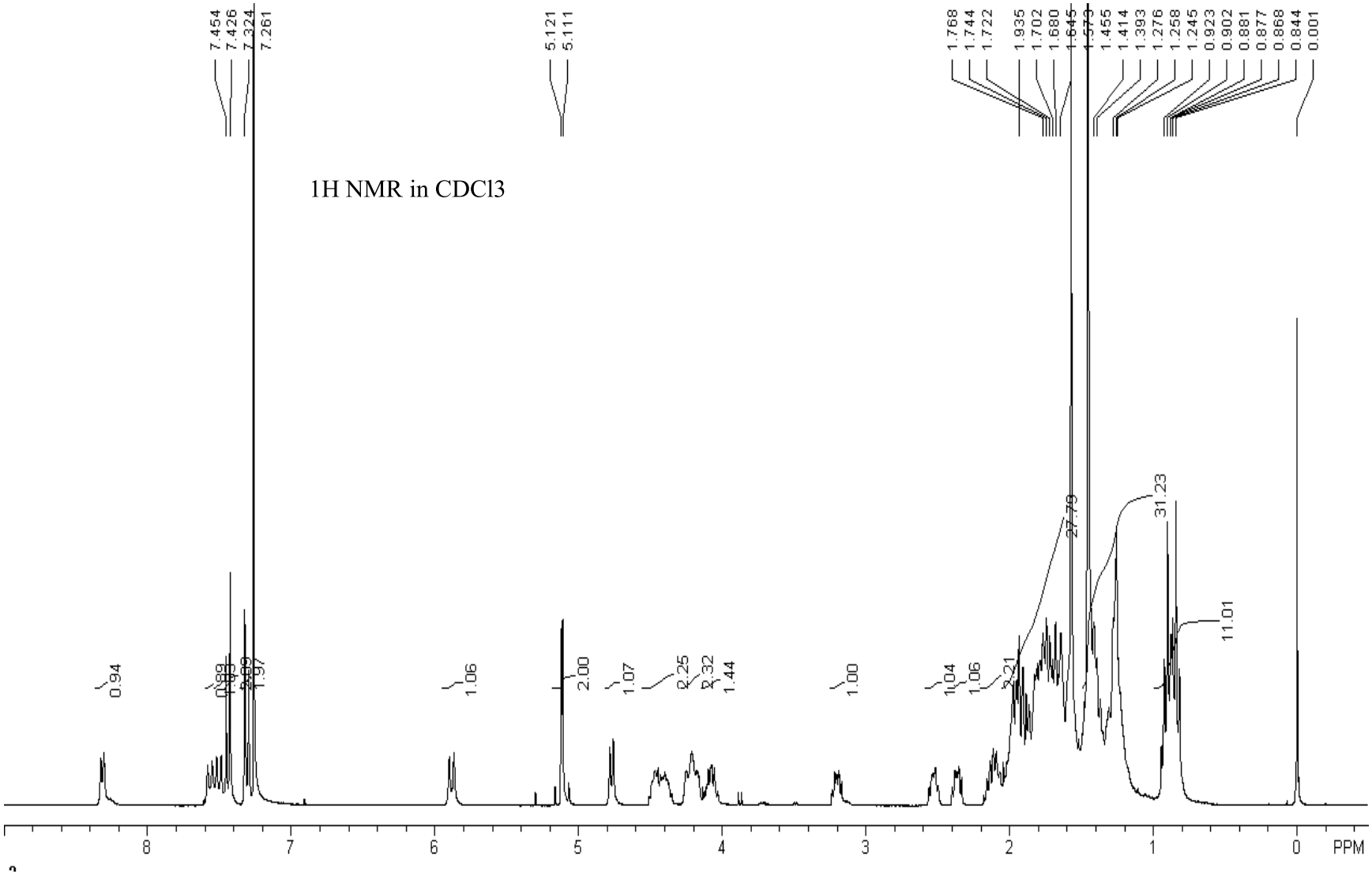
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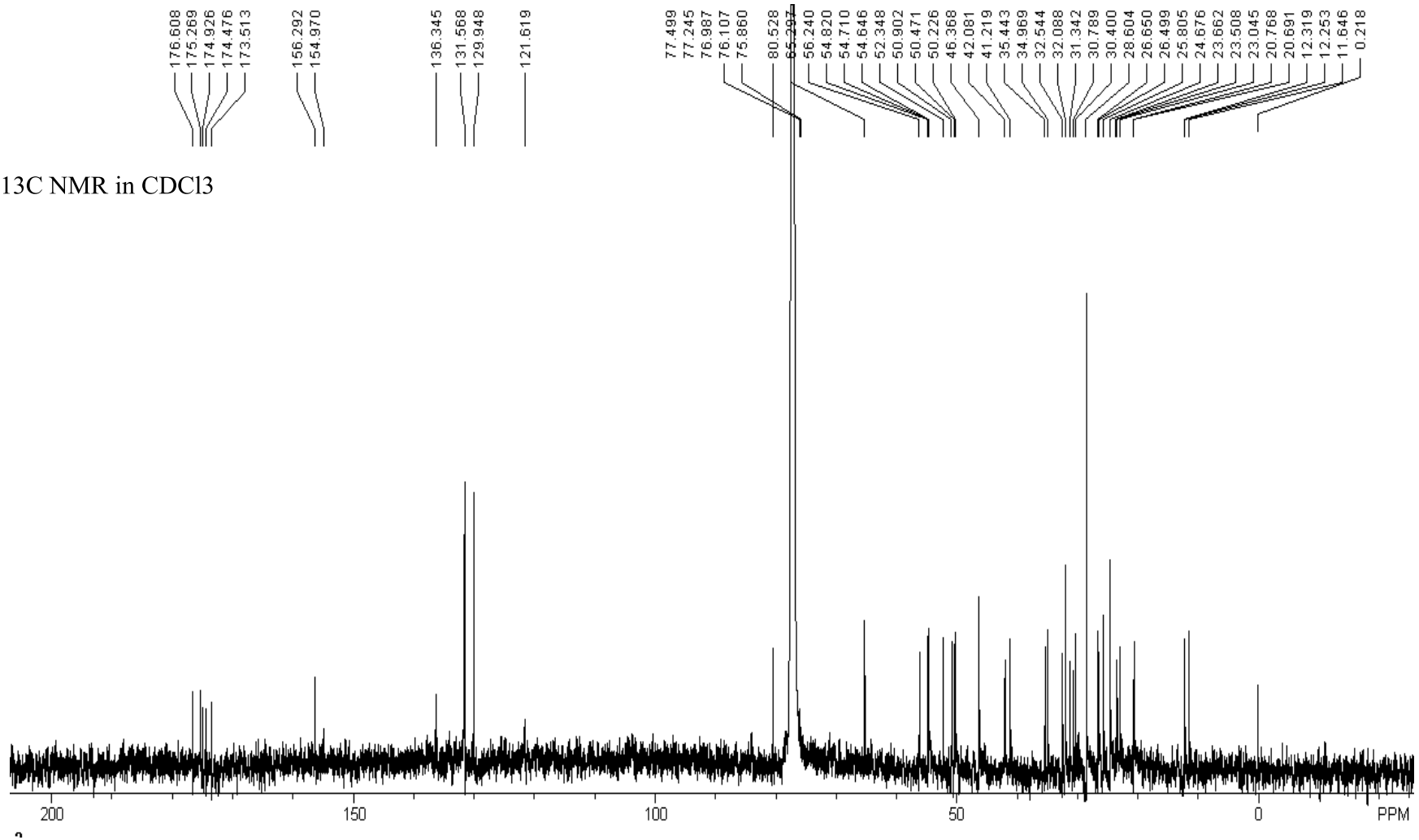
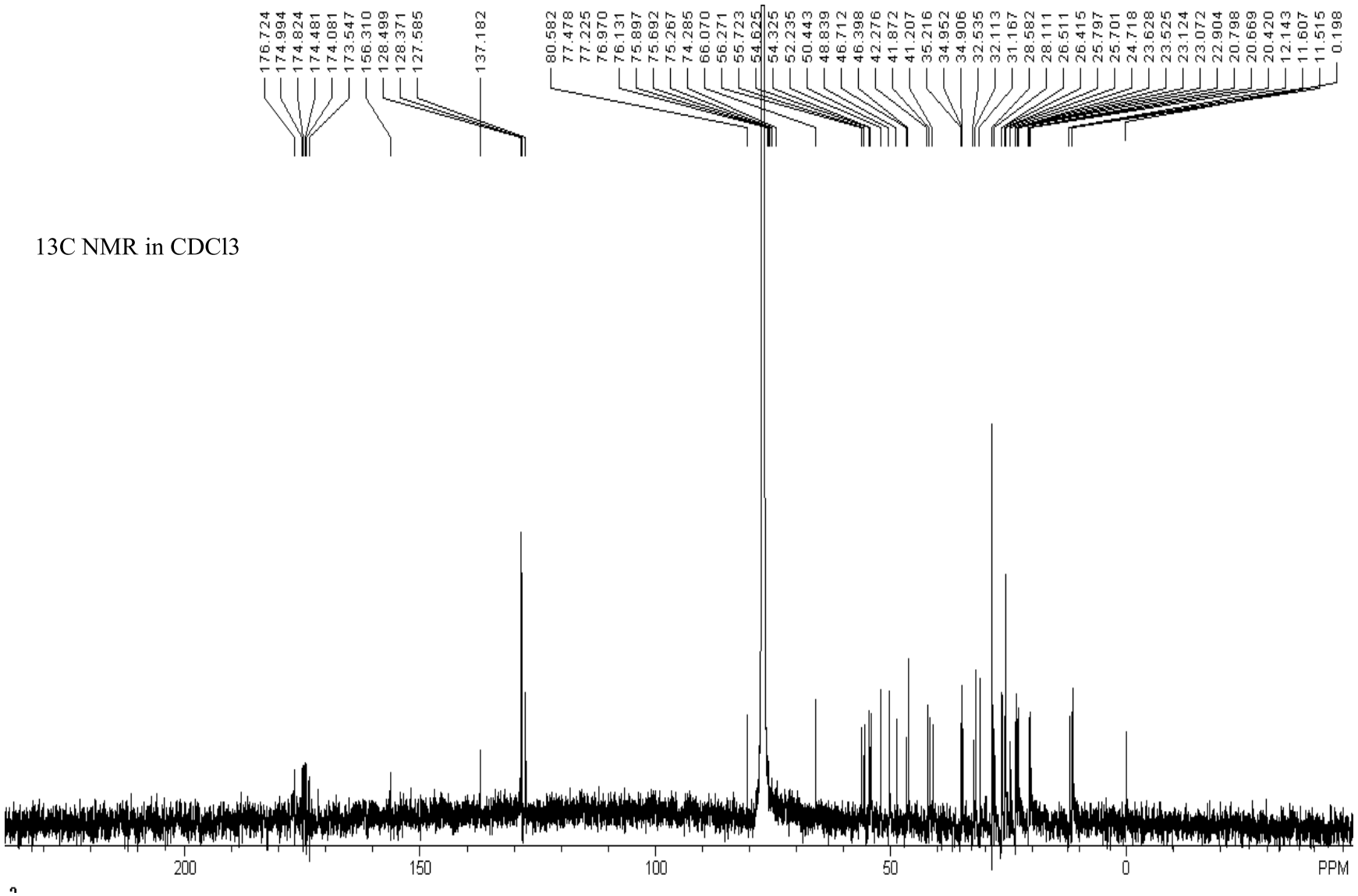
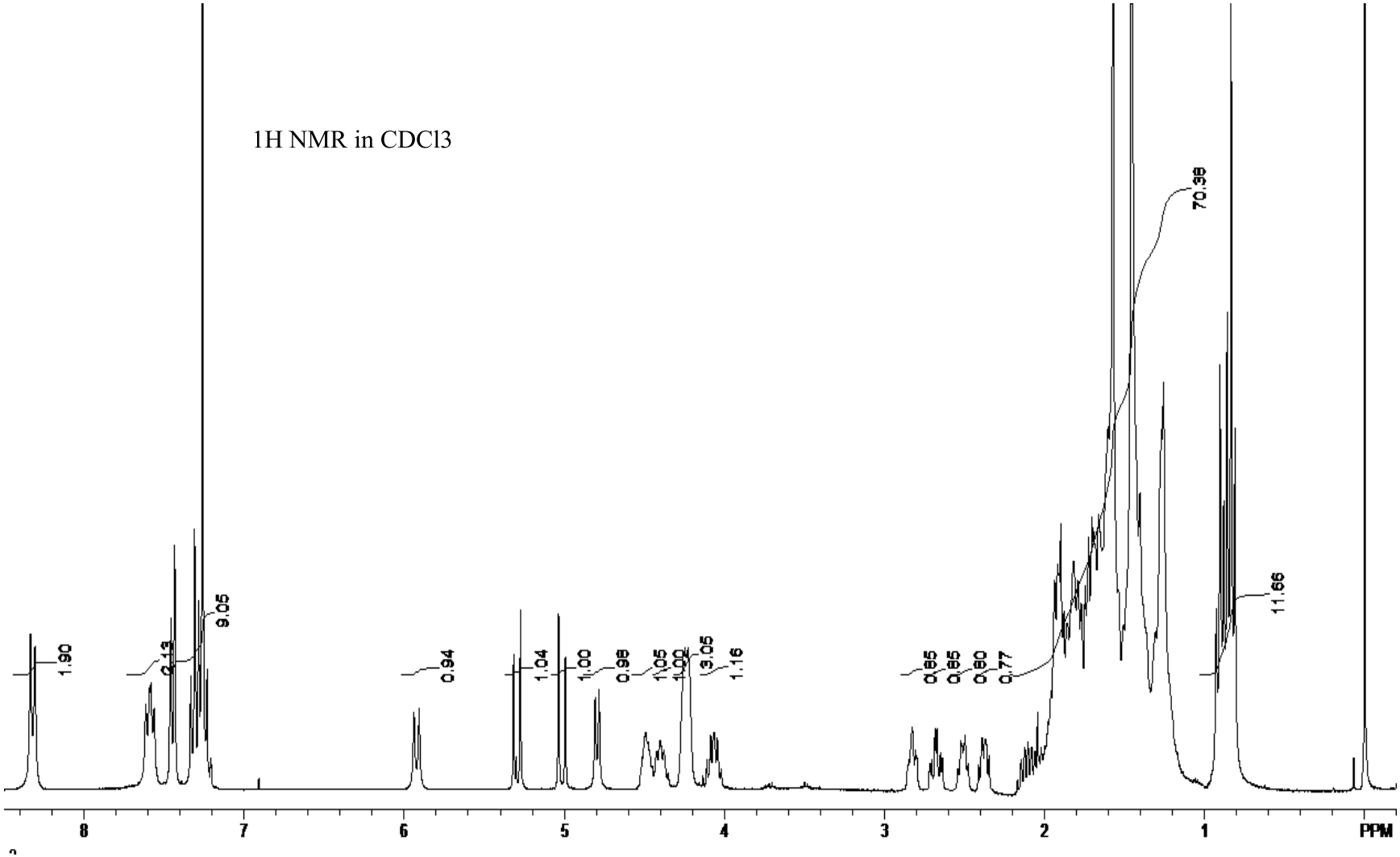


13C NMR in CDCl3

13C NMR in CDCl3

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70.36
11.66
8
7
6
5
4
3
2
1
PPM