Supporting Information

Design of a 'New Motif' with β-Amino Acids and α-Aminoxy Acids: Synthesis of Hybrid Peptides with 12/10-Helix**

Gangavaram V. M. Sharma,* Vennampalli Manohar, Samit K. Dutta, Velaparthi Subash and Ajit C. Kunwar*

Indian Institute of Chemical Technology, Hyderabad 500 007 (India)

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General experimental: The monomer (*R*)-β-Caa was synthesized from D-glucose and the monomer (*R*)-Ama was synthesized from L-ethyl lactate. The monomers (*S*)-β-hAla and Ama were synthesized from L-Ala and ethyl glycolate respectively. Deprotection of Boc-group was achieved with CF_3COOH (0.1 mL per 100 mg) in CH_2Cl_2 at 0 °C, while, esters were hydrolyzed with aq. 4N NaOH (4 mL/1 mmol) at 0 °C-room temperature. The synthesis of oligomers involved coupling of monomers in the requisite sequence using standard coupling reagents EDCI, HOBt and DIPEA in CH_2Cl_2. The compounds reported were purified by column chromatography over silica gel (60-120 mesh).

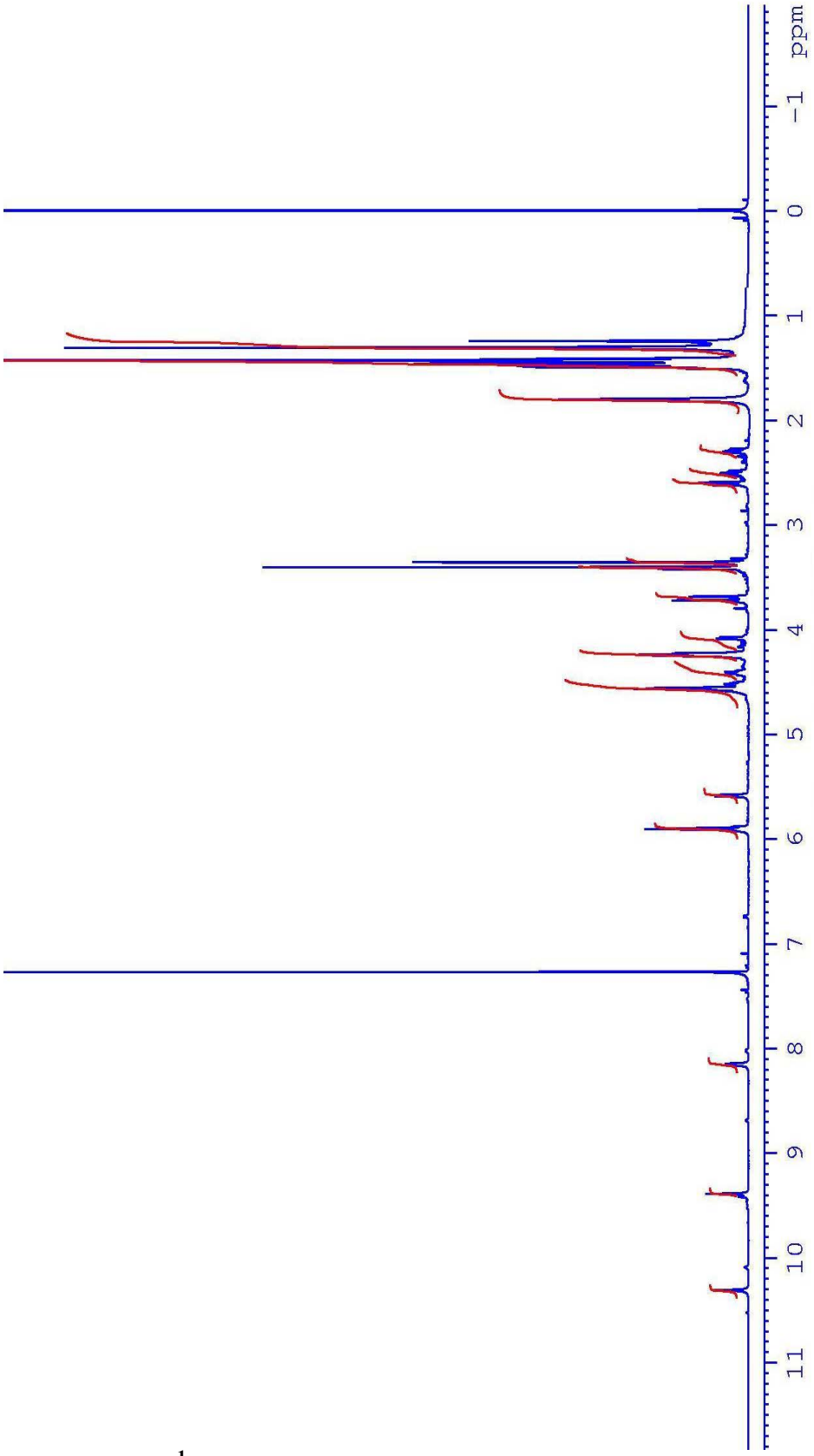
Solvents were dried over standard drying agents and freshly distilled prior to use. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. Melting points were determined in open capillaries and were not corrected. Optical rotations were measured in $CHCl_3$ solutions on a Perkin-Elmer 343 polarimeter at room temperature using a cell of 1 dm of length and λ = 598 nm. IR spectra were recorded with an FT-IR spectrometer between 400 and 4000 cm^{-1} in KBr pellets. Mass spectra were obtained under high resolution mass spectrometry (HRMS) on Q-STAR-XL (Applied Biosystems).

Synthesis of peptides 3b and 4b; 5a and 5b

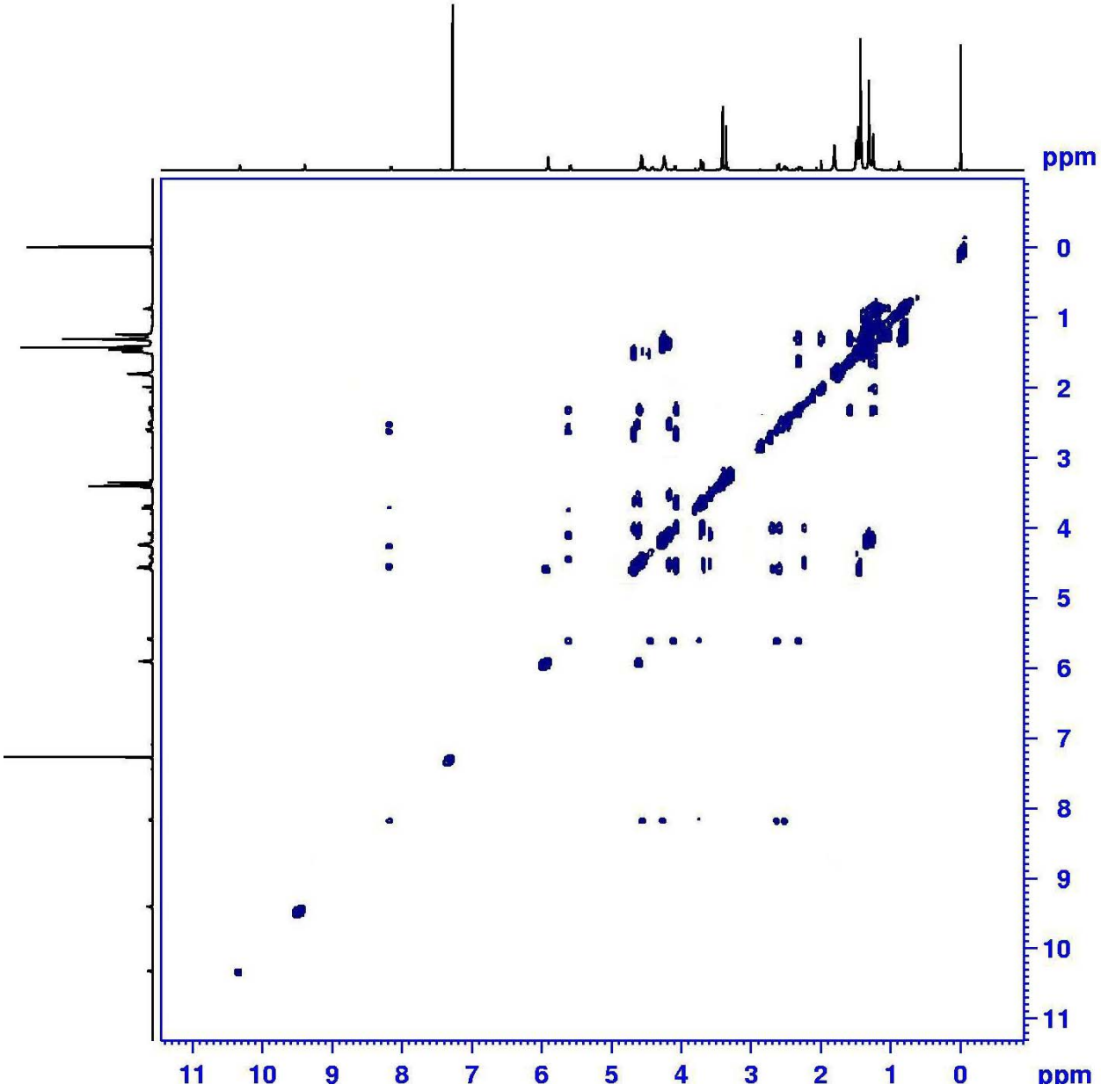
The peptides **5a** and **5b** were prepared from monomers **1**, and **2a**. Accordingly, coupling of acid **8** with the amine **2a** (prepared by the reaction of **7b** with hydrazine hydrate in CH_3OH at room temperature for 2 h) in the presence of EDCI and HOBt in CH_2Cl_2 at room temperature for 5 h furnished the dipeptide **13** in 66.29% yield, $[\alpha]_D$ = -69.54 (*c* 1.07, $CHCl_3$). Base (aq. 4N NaOH) hydrolysis of dipeptide **13** gave the acid **14**,

while **13** was converted into the corresponding amine salt **15** on exposure to CF_3COOH in CH_2Cl_2 for 2 h. The thus derived acid **14** was then coupled with amine **15** in the presence of EDCI, HOBt and DIPEA in CH_2Cl_2 for 5 h to furnish the tetrapeptide **5a** in 53.12% yield, $[\alpha]_D$ = -19.89 (*c* 1.25, $CHCl_3$). Base hydrolysis of the ester group in **5a** with NaOH in CH_3OH gave the corresponding acid **16** (90.27%), which on coupling with the dipeptide amine TFA salt **15** under the above reaction conditions afforded the hexapeptide **5b** in 35.4% yield, $[\alpha]_D$ = -1.85 (*c* 0.09, $CHCl_3$).

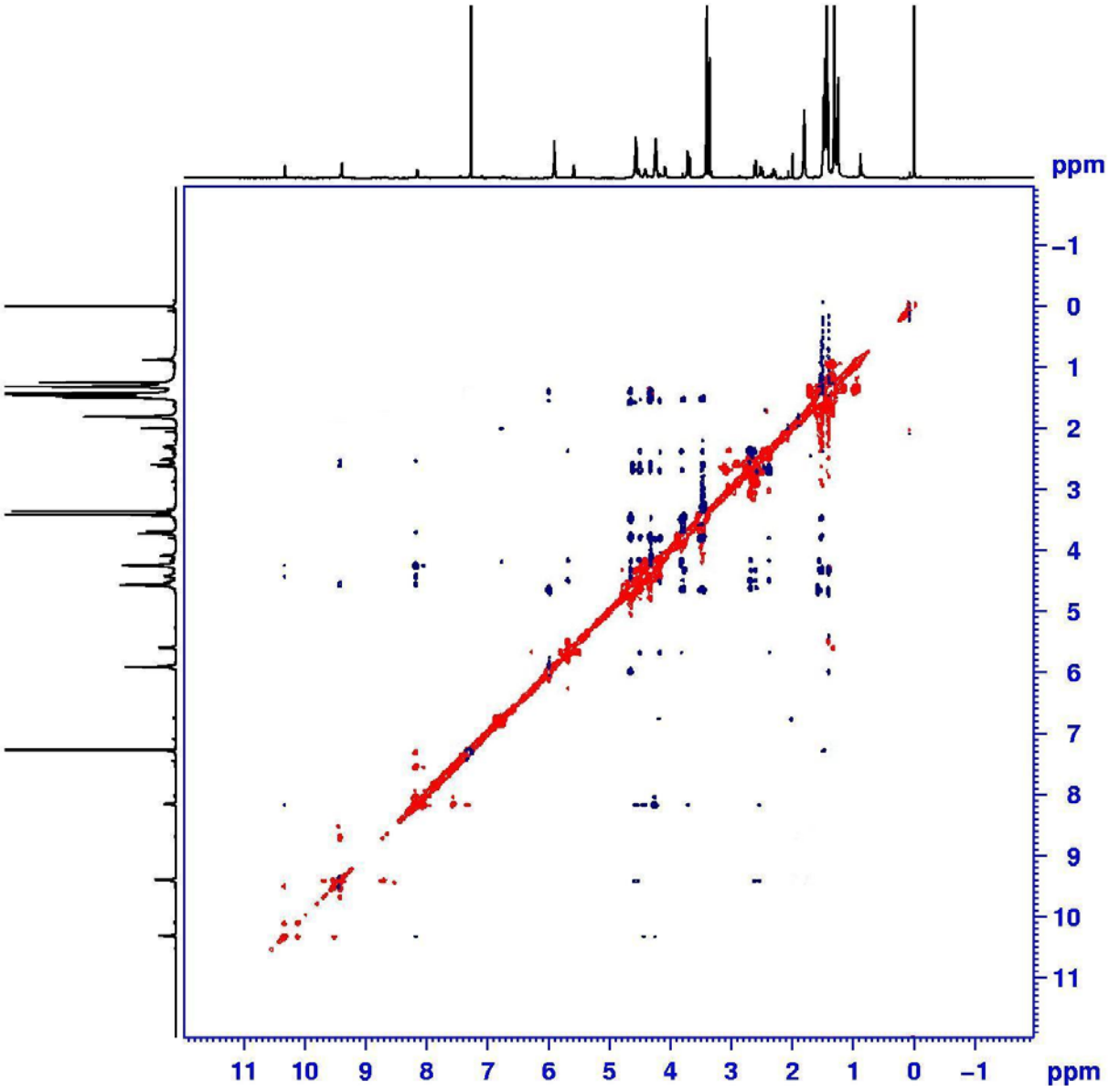
The peptides **3b** and **4b** were prepared from monomers **1a** and **2**. Accordingly, ester **1a** was subjected to hydrolysis with aq. 4N NaOH at room temperature to afford the acid **17** in 98.5% yield. Coupling of acid **17** with the amine **2** (prepared by the reaction of **7a** with hydrazine hydrate in CH_3OH at room temperature for 2 h) in the presence of EDCI and HOBt in CH_2Cl_2 at room temperature for 5 h furnished the dipeptide **18** in 58.59% yield, $[\alpha]_D$ = +38.15 (*c* 0.065, $CHCl_3$). Base (aq. 4N NaOH) hydrolysis of dipeptide **18** gave the acid **19**, while **18** was converted into the corresponding amine salt **20** on exposure to CF_3COOH in CH_2Cl_2 for 2 h. The thus derived acid **19** was then coupled with amine **20** in the presence of EDCI, HOBt and DIPEA in CH_2Cl_2 for 5 h to furnish the tetrapeptide **3b** in 48.21% yield, $[\alpha]_D$ = +246.7 (*c* 1.04, $CHCl_3$). Tetrapeptide **3b** was converted into the corresponding amine salt **21** on exposure to CF_3COOH in CH_2Cl_2 for 2 h. Coupling of acid **19** salt **21** under the above reaction conditions afforded the hexapeptide **4b** in 24.1% yield, $[\alpha]_D$ = +249.55 (*c* 0.13, $CHCl_3$).



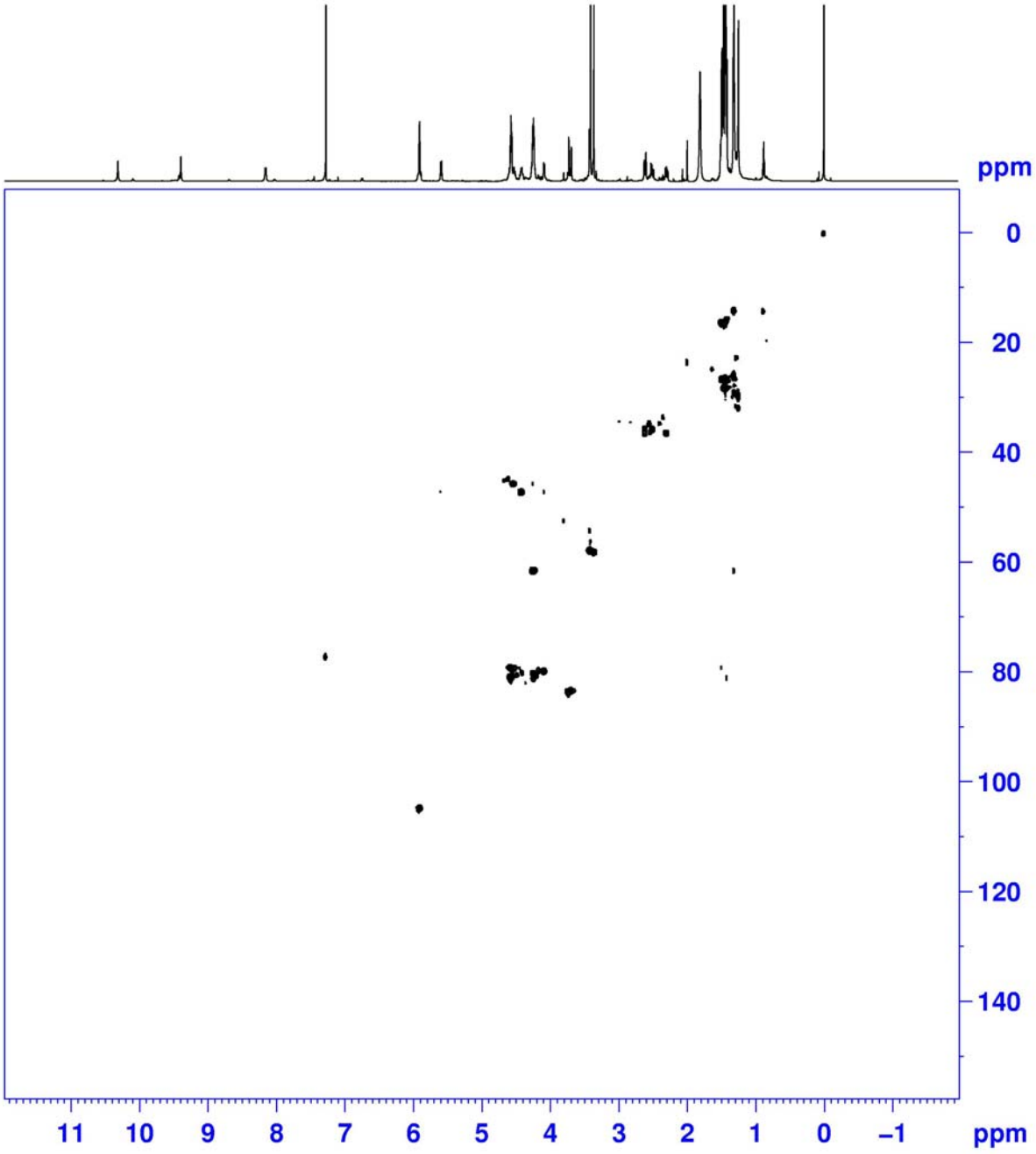
Supporting Figure 1. ^{1}H NMR spectrum of peptide 3a (600 MHz, $CDCl_3$, 278 K)



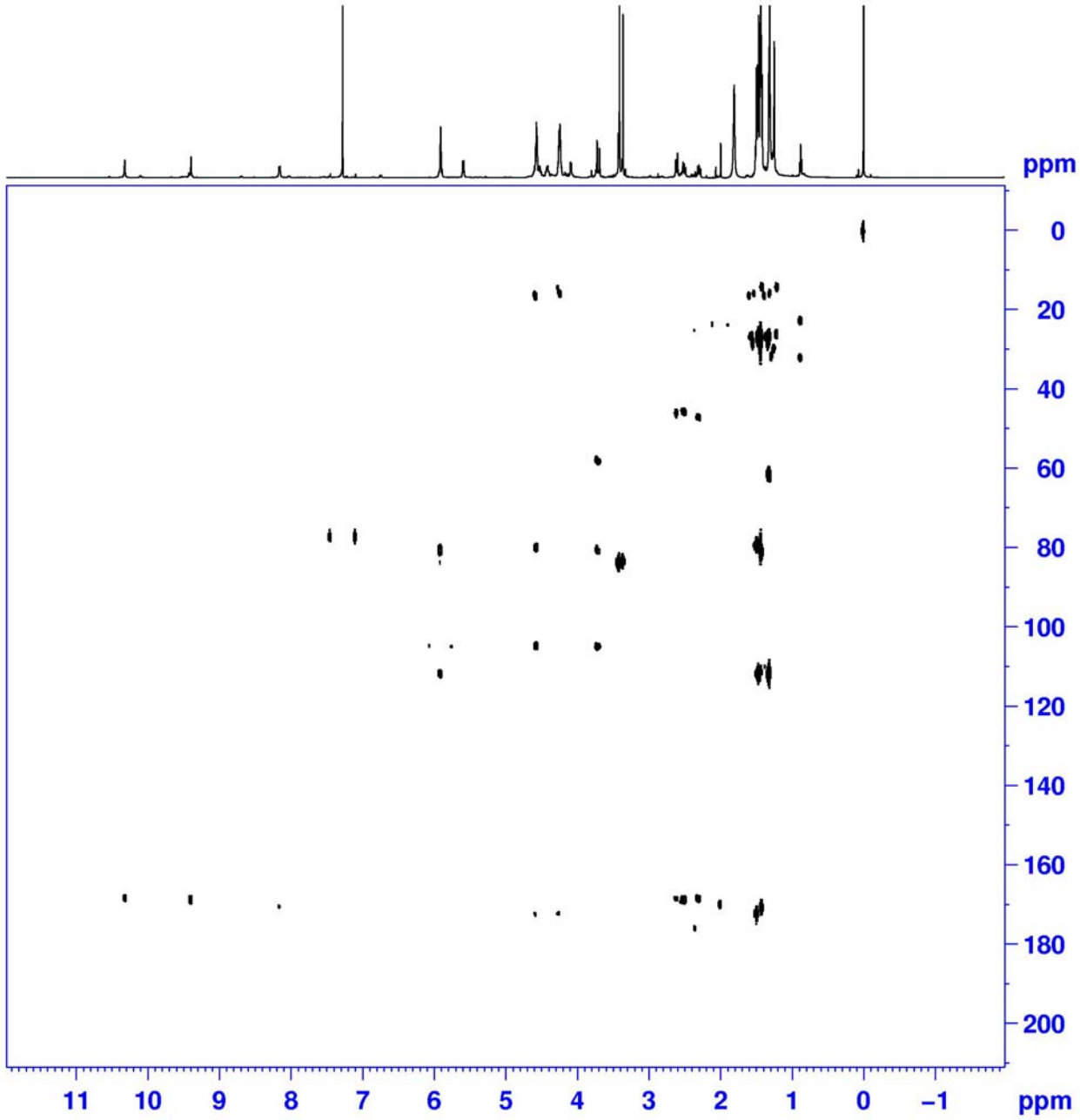
Supporting Figure 2. TOCSY spectrum of peptide 3a (600 MHz, $CDCl_3$, 278 K)



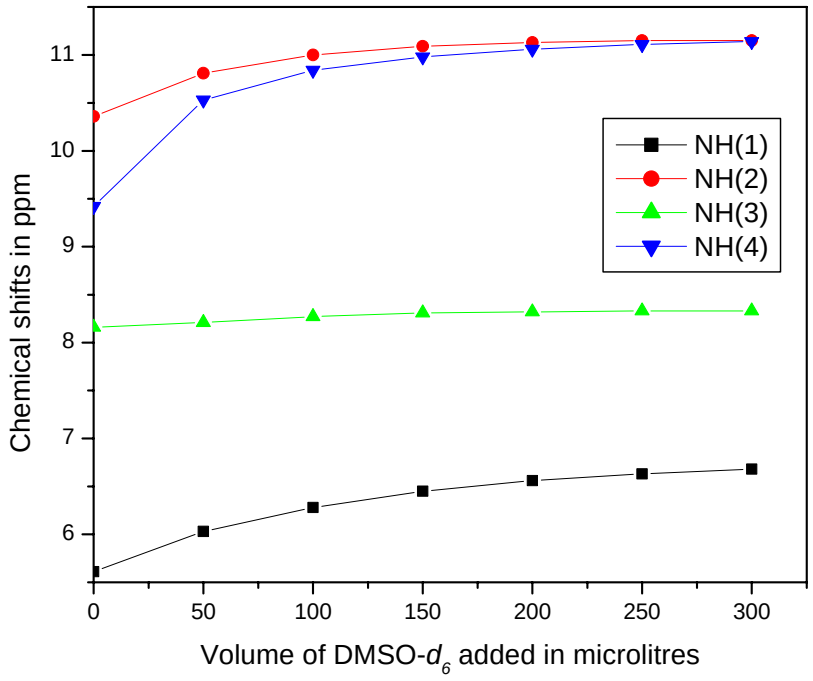
Supporting Figure 3. ROESY spectrum of peptide 3a (600 MHz, $CDCl_3$, 278 K)



Supporting Figure 4. HSQC spectrum of peptide 3a (600 MHz, $CDCl_3$, 278 K)



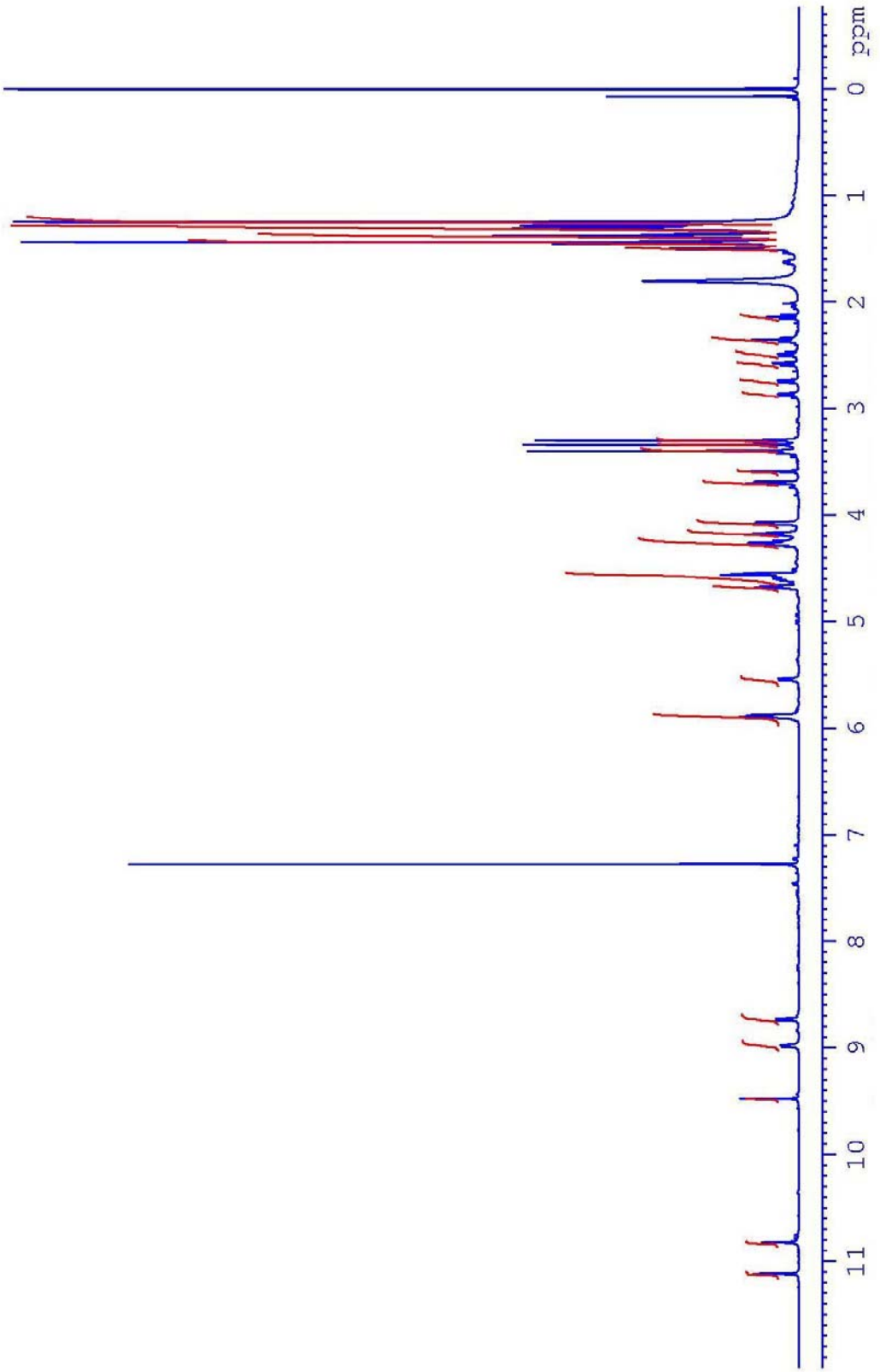
Supporting Figure 5. HMBC spectrum of peptide 3a (600 MHz, $CDCl_3$, 278 K)



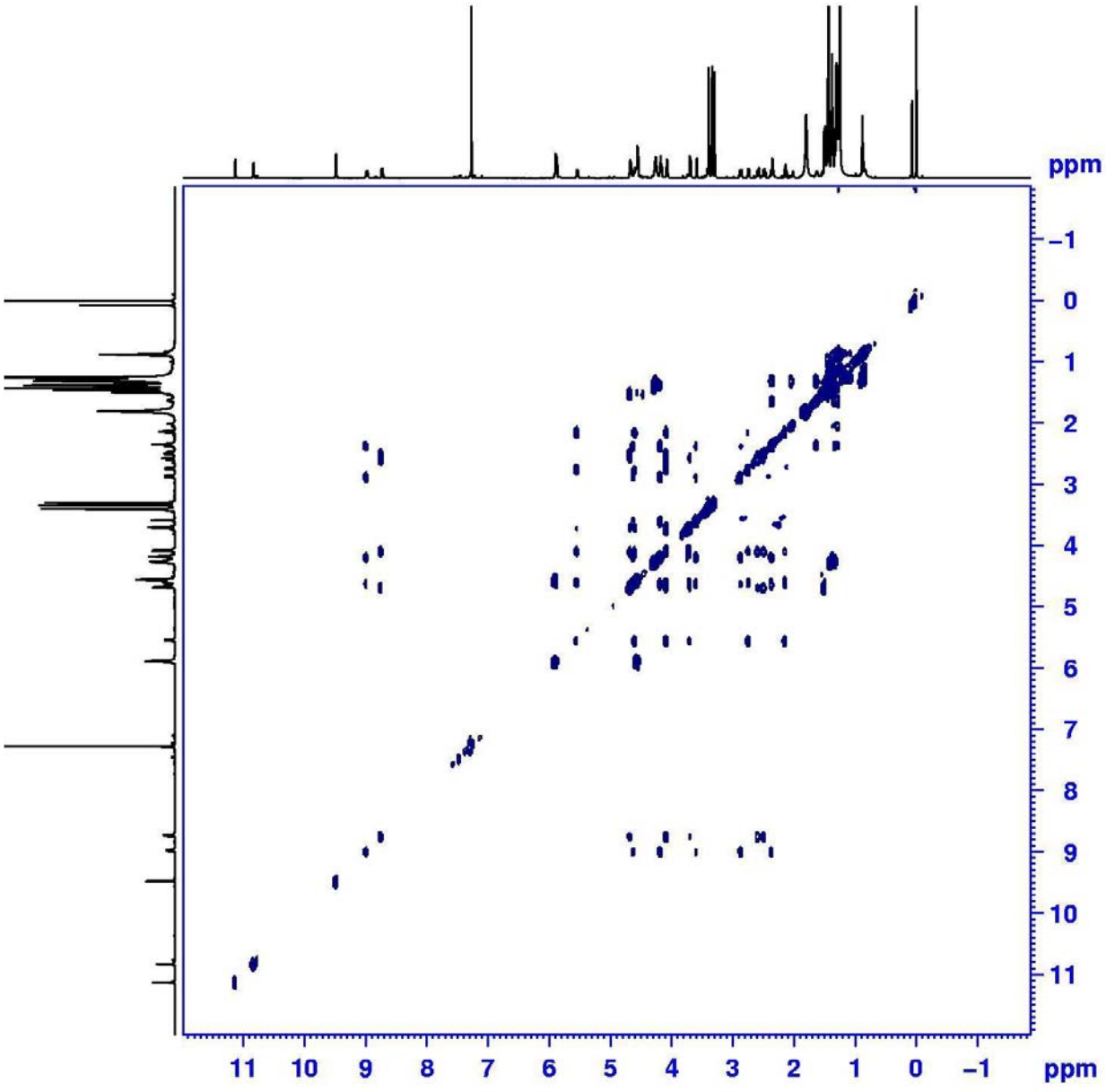
Supporting Figure 6. Solvent titration plot for peptide 3a

Residue	Atom	Residue	Atom	Lower bond (Å)	Higher bond (Å)
1	NH	1	CαH (*pro-R*)	2.52	3.08
1	CβH	2	NH	3.15	3.84
1	CβH	3	NH	2.55	3.12
1	CβH	3	CαH (*pro-R*)	2.34	2.85
2	NH	1	CαH (*pro-S*)	2.38	2.91
2	NH	2	CαH	2.96	3.61
2	NH	3	NH	2.88	3.53
3	NH	2	CαH	2.16	2.63
3	NH	3	CαH (*pro-R*)	2.61	3.20
3	CβH	4	NH	2.95	3.61
4	NH	3	CαH (*pro-S*)	2.72	3.32
4	NH	4	CαH	2.88	3.53

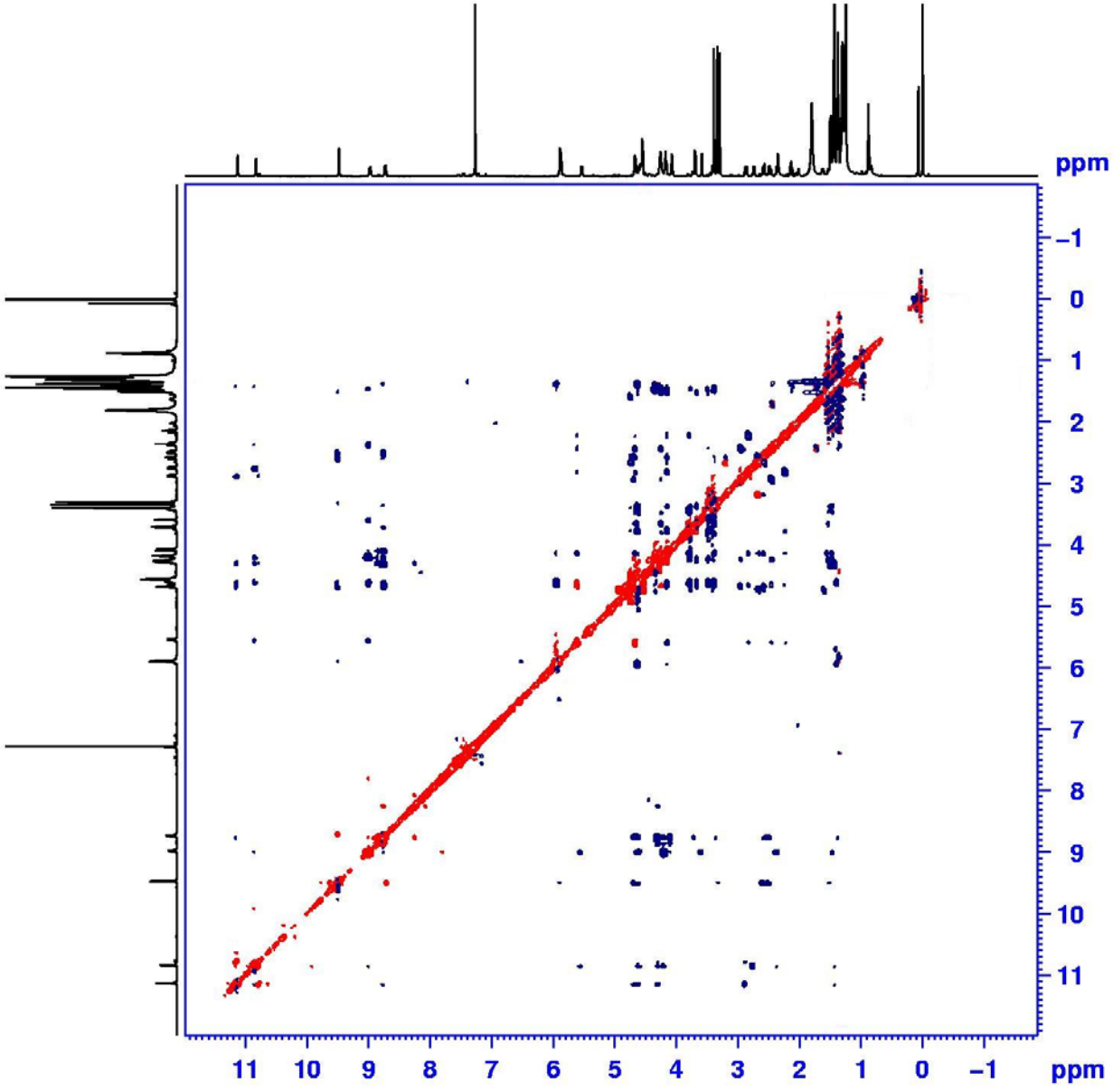
Supporting Table 1. Distance constraints used in MD calculations for peptide 3a, derived from ROESY experiment in $CDCl_3$ (600 MHz, 278 K)



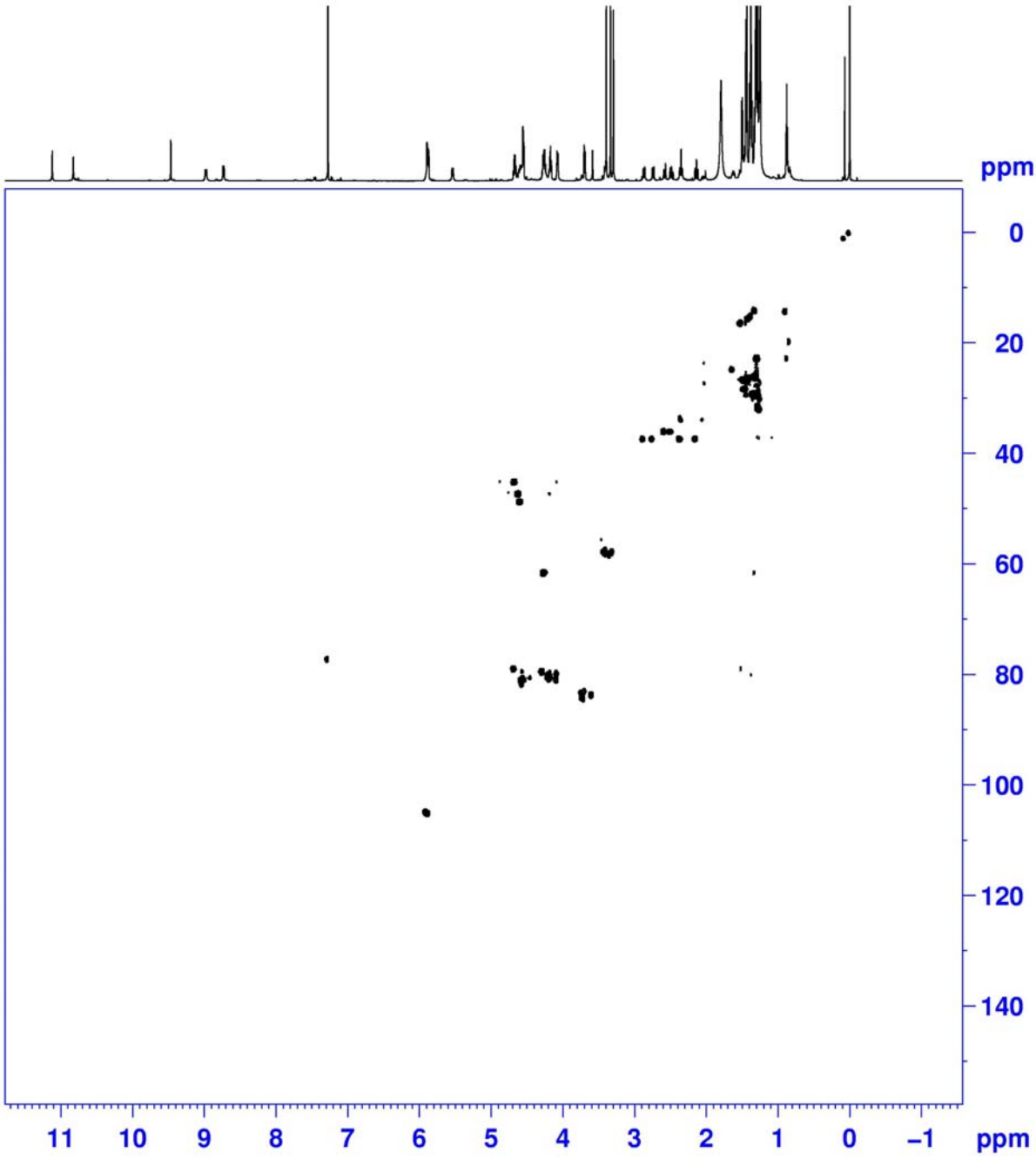
Supporting Figure 7. ^{1}H NMR spectrum of peptide 4a (600 MHz, $CDCl_3$, 278K)



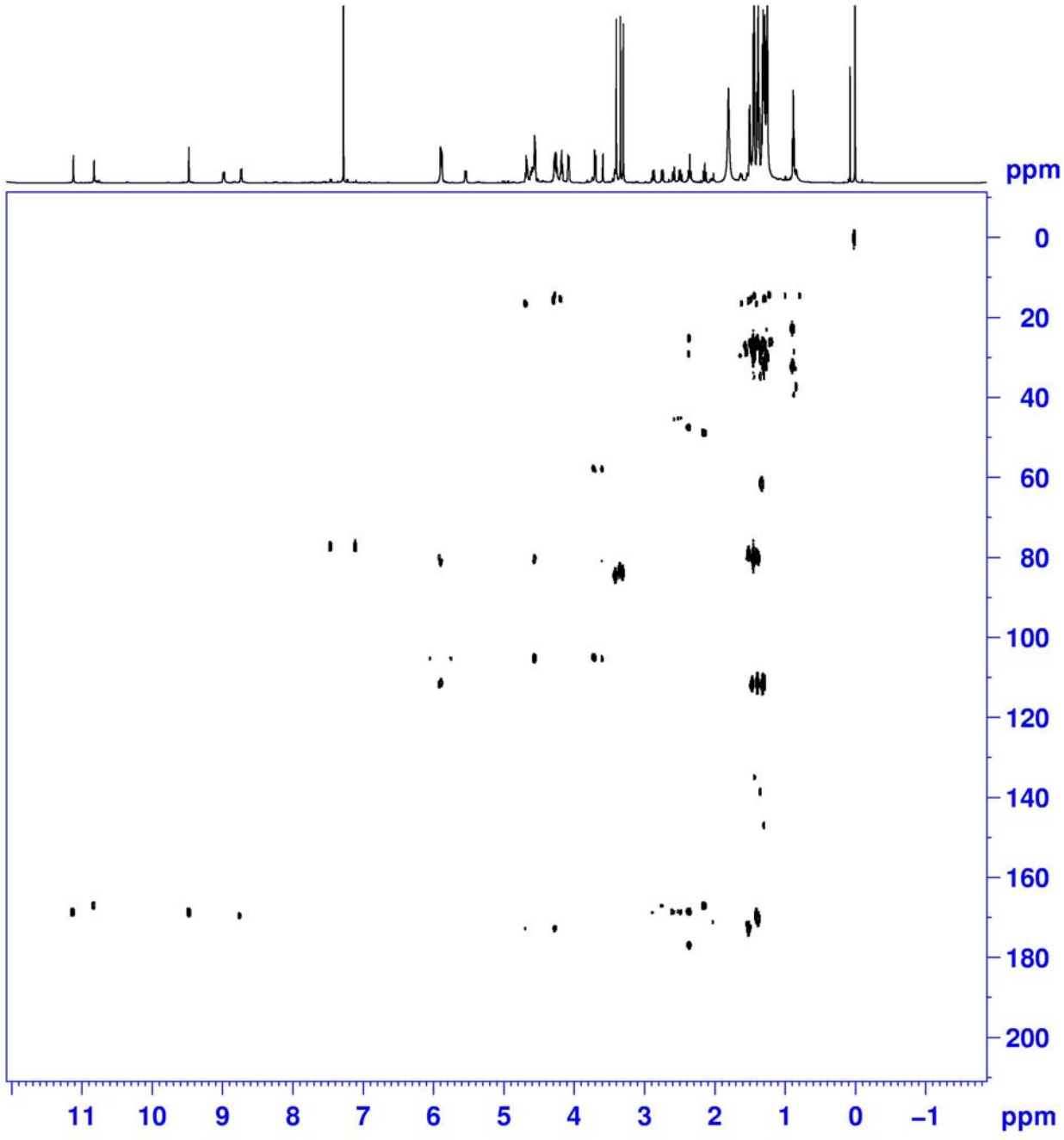
Supporting Figure 8. TOCSY spectrum of peptide 4a (600 MHz, $CDCl_3$, 278 K)



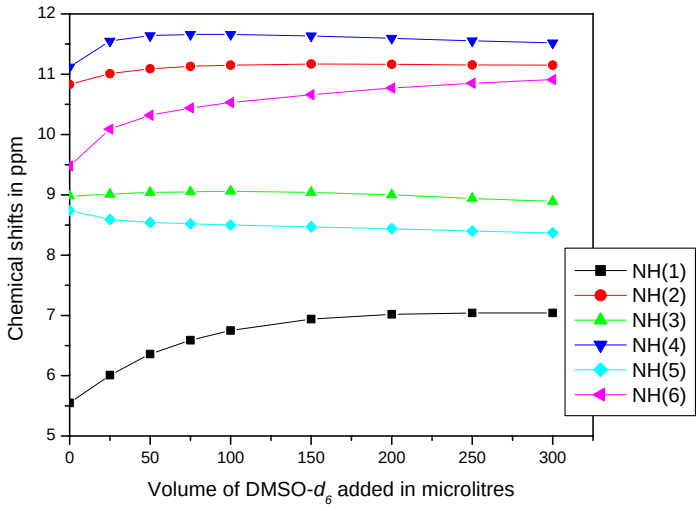
Supporting Figure 9. ROESY spectrum of peptide 4a (600 MHz, $CDCl_3$, 278 K)



Supporting Figure 10. HSQC spectrum of peptide 4a (600 MHz, $CDCl_3$, 278 K)



Supporting Figure 11. HMBC spectrum of peptide 4a (600 MHz, $CDCl_3$, 278 K)



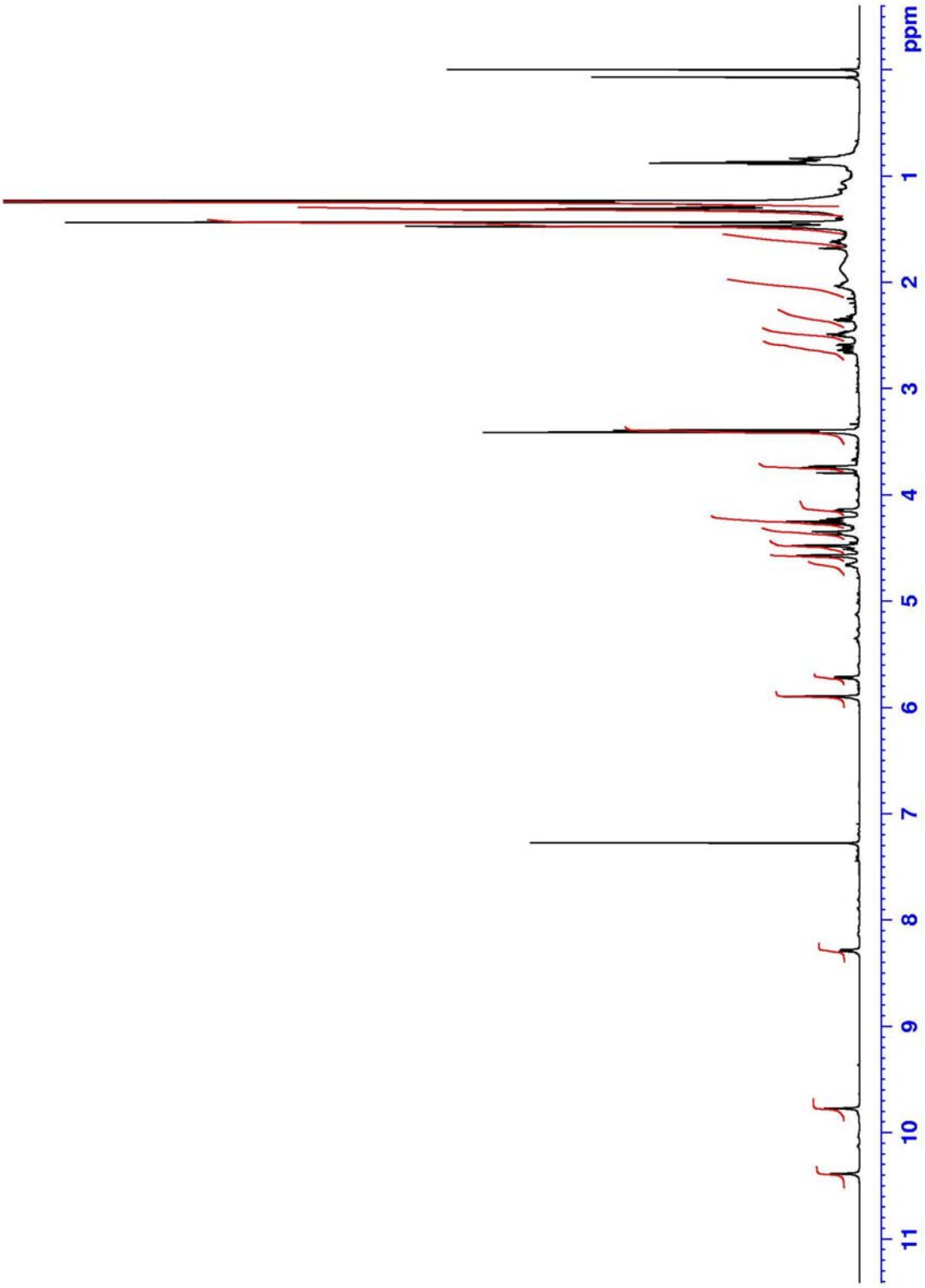
Supporting Figure 12. Solvent titration plot for peptide 4a

Residue	Atom	Residue	Atom	Lower bond (Å)	Higher bond (Å)
1	NH	1	CαH (*pro-R*)	2.45	3.00
1	CβH	2	NH	2.70	3.31
1	CβH	3	NH	2.36	2.88
1	CβH	3	CαH (*pro-R*)	2.18	2.66
2	NH	1	CαH (*pro-S*)	2.38	2.91
2	NH	2	CαH	2.82	3.44
2	NH	3	NH	3.30	4.03
2	NH	4	CαH	2.84	3.47
3	NH	2	CαH	1.90	2.32
3	NH	3	CαH (*pro-R*)	2.61	3.19
3	CβH	4	NH	2.60	3.18
3	CβH	5	NH	2.37	2.89
3	CβH	5	CαH (*pro-R*)	2.17	2.65
4	NH	3	CαH (*pro-S*)	2.27	2.77
4	NH	4	CαH	2.80	3.42
4	NH	5	NH	3.23	3.95
4	NH	6	CαH	3.86	4.72
5	NH	4	CαH	1.90	2.32
5	NH	5	CαH (*pro-R*)	2.59	3.18
5	CβH	6	NH	2.74	3.35
6	NH	5	CαH (*pro-S*)	2.34	2.86
6	NH	6	CαH	2.31	2.83

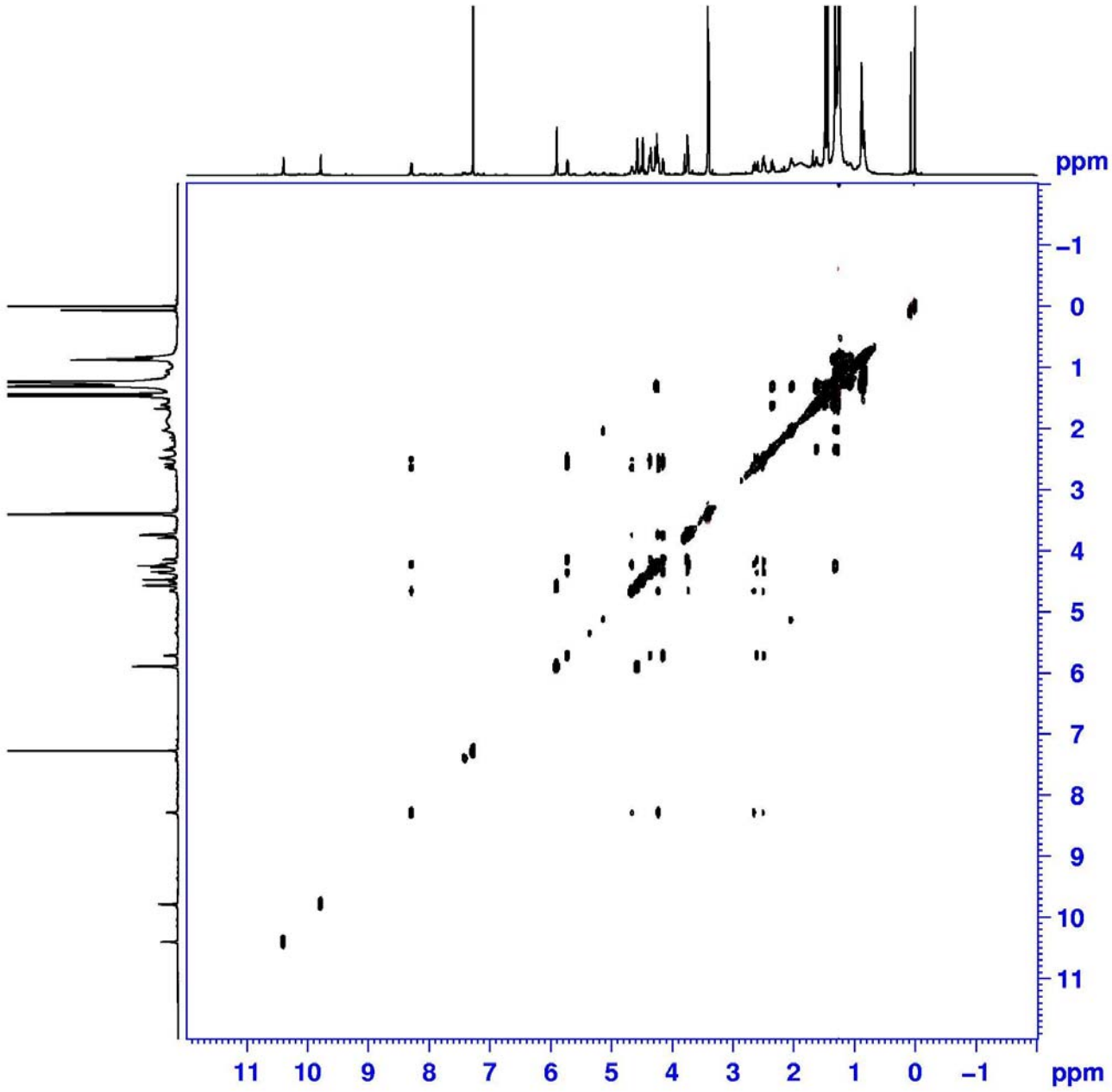
Supporting Table 2. Distance constraints used in MD calculations for peptide 4a, derived from ROESY experiment in $CDCl_3$ (600 MHz, 278 K)

Residue / Protons	Res-1	Res-2	Res-3	Res-4
NH	5.72 (d, J = 9.2)	10.39 (s)	8.29 (d, J = 9.5)	9.77 (s)
CαH	2.60 (dd, J = 3.6, 15.0)	4.27 (d, J = 15.6)	2.64 (dd, J = 3.5, 14.5)	4.46 (d, J =17.0)
Cα'H	2.47 (dd, J = 8.4, 15.0)	4.37 (d, J = 15.6)	2.48 (dd, J = 8.7, 14.5)	4.50 (d, J = 17.0)
CβH	4.35 (m)	_	4.65 (ddt, J = 3.5, 8.7, 9.5, 8.7)	_
C4H	4.15 (dd, J = 3.1, 8.0)	_	4.22 (m)	_
C3H	3.74 (d, J = 3.1)	_	3.75 (d, J = 3.0)	_
C2H	4.57 (d, J =3.8)	_	4.58 (d, J = 3.8)	_
C1H	5.89 (d, J = 3.8)	_	5.89 (d, J = 3.8)	_
Acetonides:	1.47 (3H, s), 1.32 (3H, s), 1.31 (6H, 2s)			
OMe:	3.41(s), 3.39 (s)			
Ethyl ester:	4.24 (2H, m, -CH_2), 1.30 (3H, t, J = 7.0, -CH_3)			
Boc:	1.44 (9H, s)			

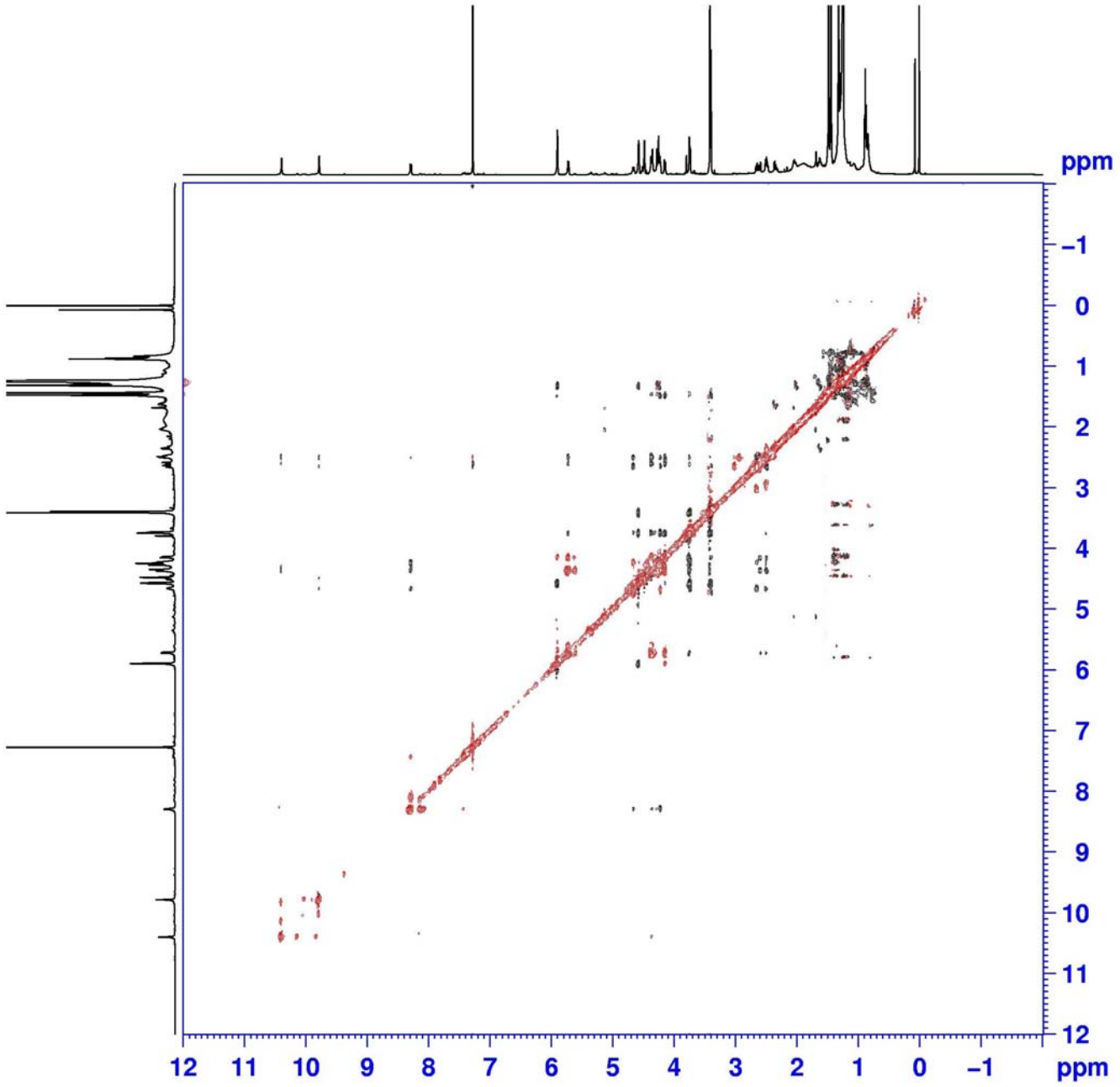
Supporting Table 3. ^{1}H NMR chemical shifts δ in ppm with multiplicity and coupling constants J in Hz (in parentheses) of 5a (600 MHz, $CDCl_3$, 278 K)



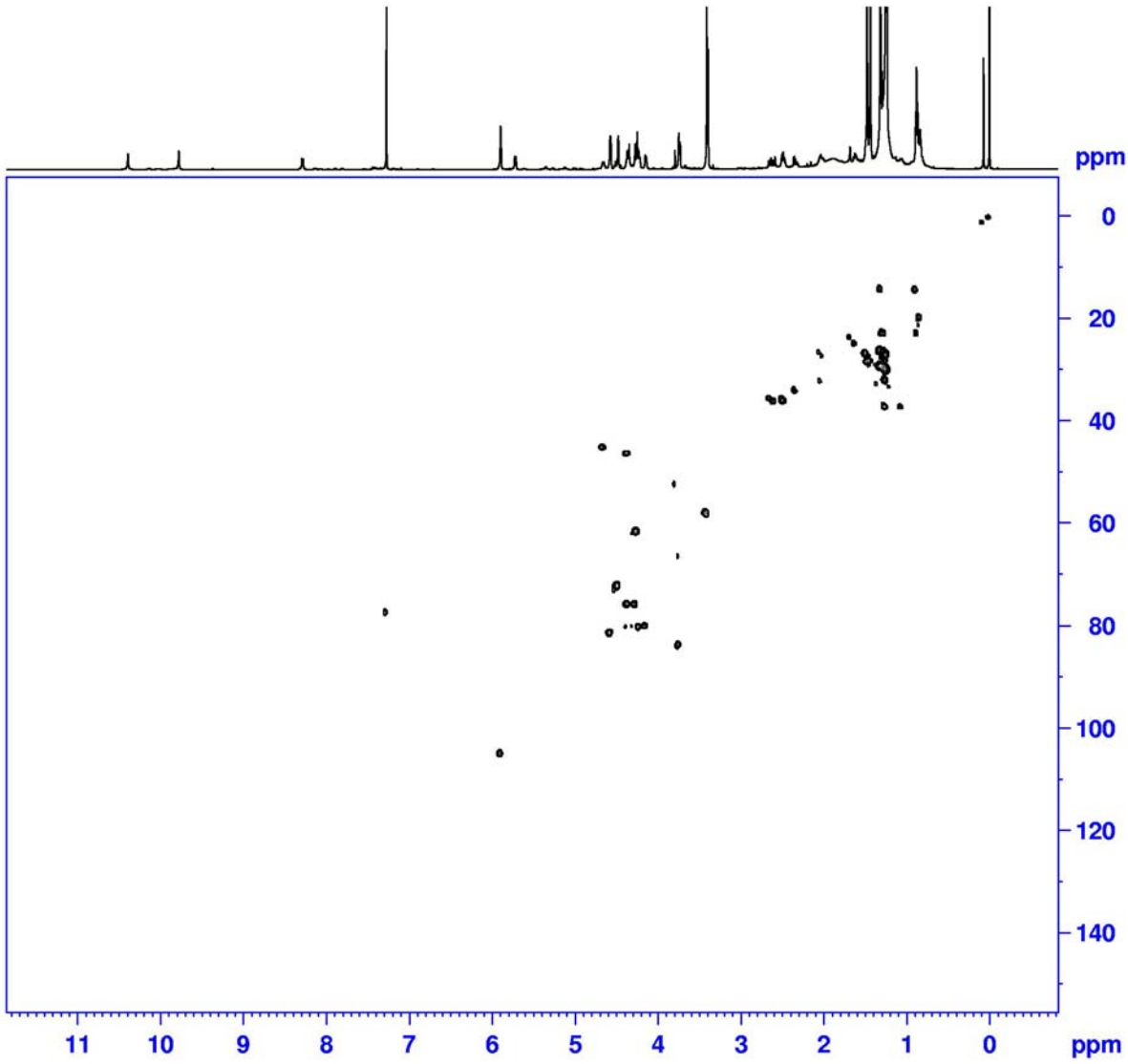
Supporting Figure 13. ^{1}H NMR spectrum of 5a (600 MHz, $CDCl_3$, 278 K)



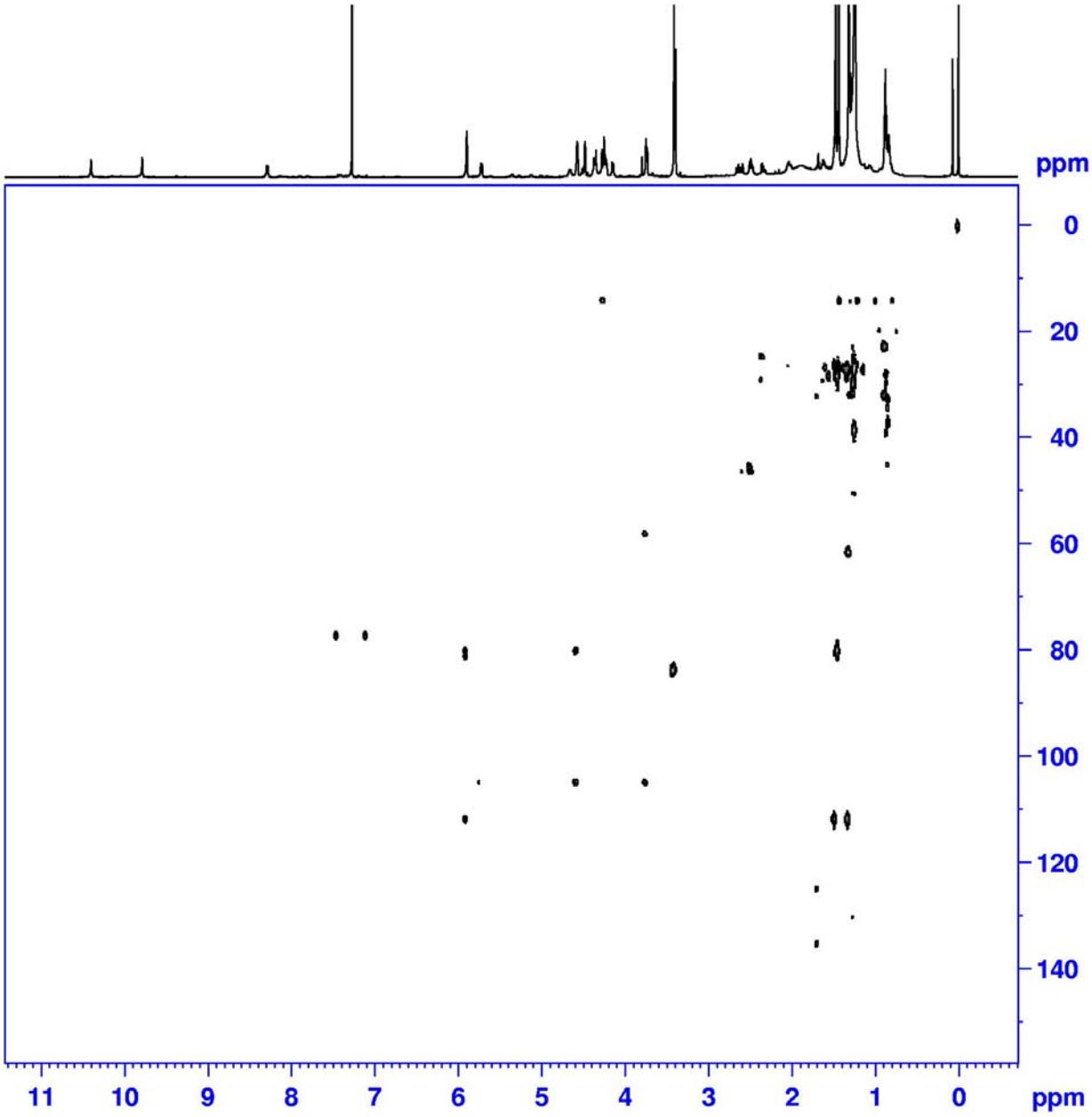
Supporting Figure 14. TOCSY spectrum of 5a (600 MHz, $CDCl_3$, 278 K)



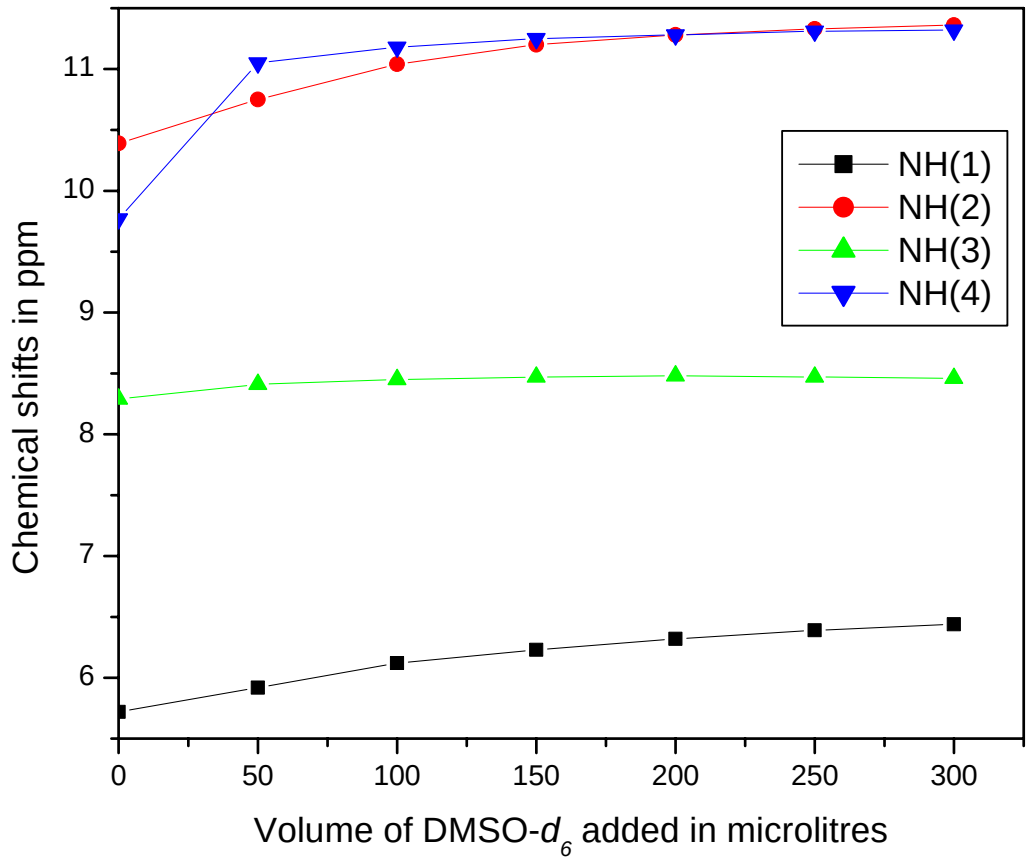
Supporting Figure 15. ROESY spectrum of 5a (600 MHz, $CDCl_3$, 278 K)



Supporting Figure 16. HSQC spectrum of 5a (600 MHz, $CDCl_3$, 278 K)



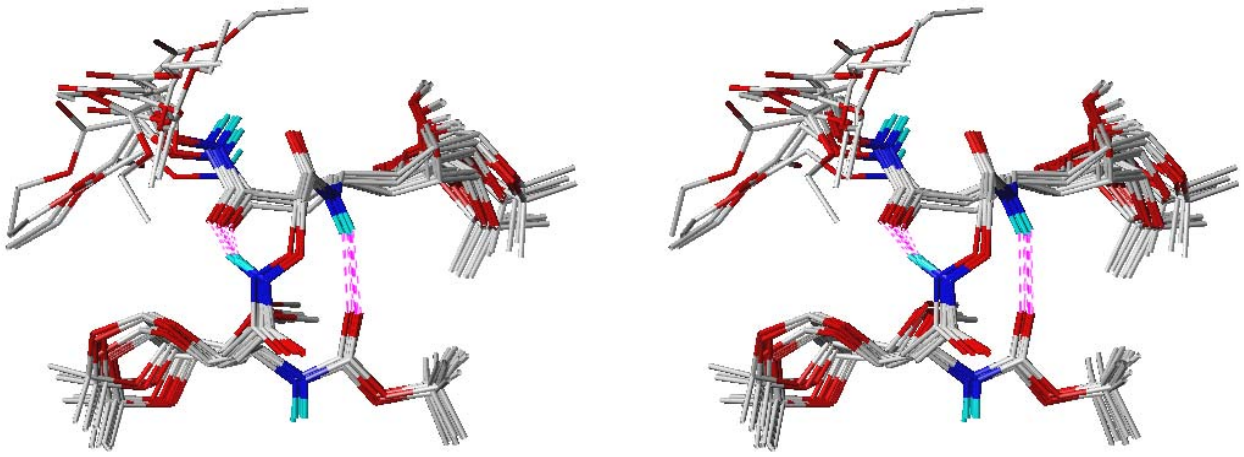
Supporting Figure 17. HMBC spectrum of peptide 5a (600 MHz, $CDCl_3$, 278 K)



Supporting Figure 18. Solvent titration plot for 5a

Residue	Atom	Residue	Atom	Lower bond (Å)	Higher bond (Å)
1	NH	1	CαH (*pro-R*)	2.70	3.30
1	CβH	2	NH	2.92	3.57
1	CβH	3	NH	2.70	3.30
2	NH	1	CαH (*pro-S*)	3.18	3.88
2	NH	2	CαH	3.28	4.01
2	NH	3	NH	3.40	4.15
3	NH	2	CαH	2.96	3.62
3	NH	3	CαH (*pro-R*)	3.13	3.82
3	CβH	4	NH	3.12	3.81
4	NH	3	CαH (*pro-S*)	2.89	3.35
4	NH	4	CαH	2.89	3.54

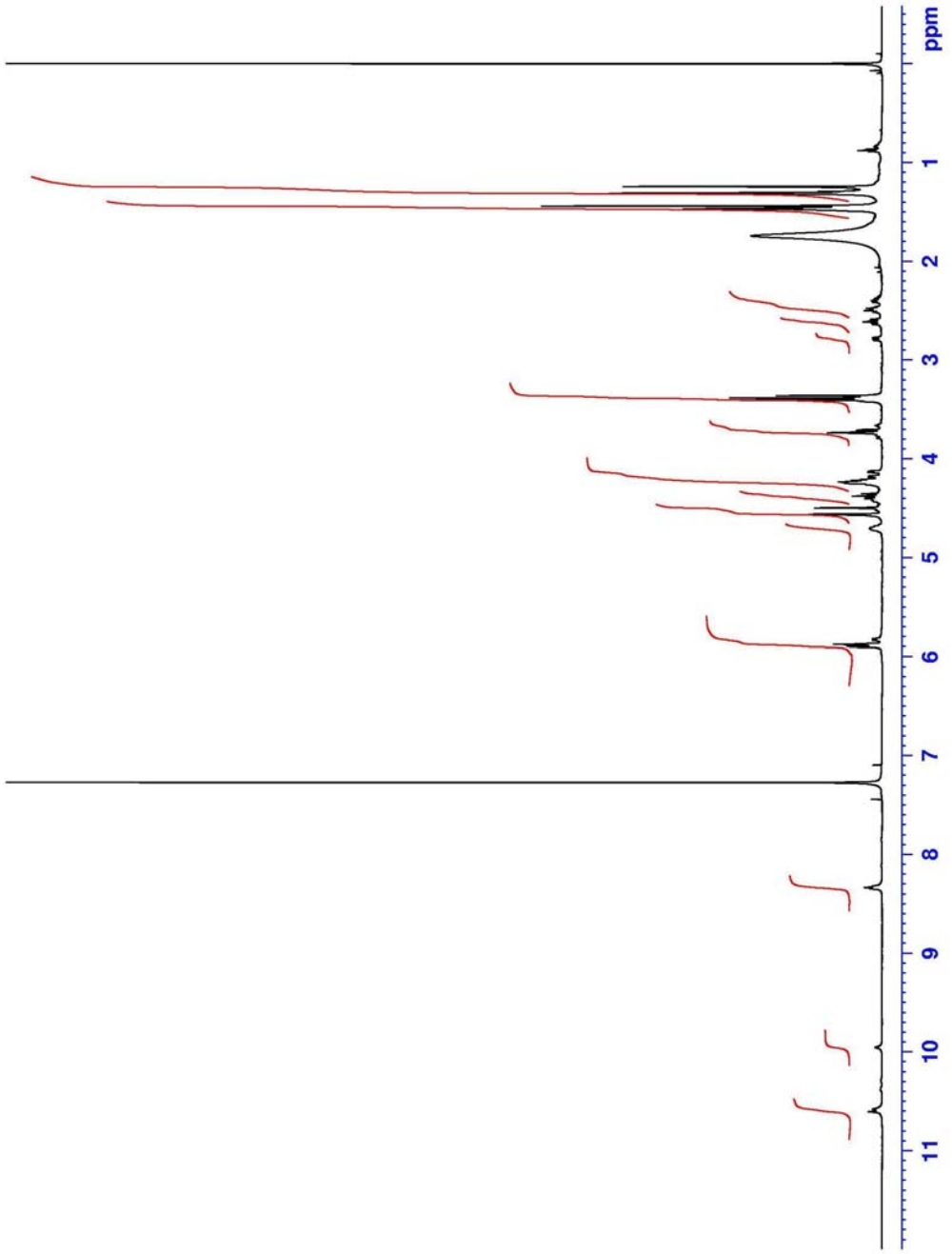
Supporting Table 4. Distance constraints used in MD calculations for 5a, derived from ROESY experiment in $CDCl_3$ (600 MHz, 278 K)



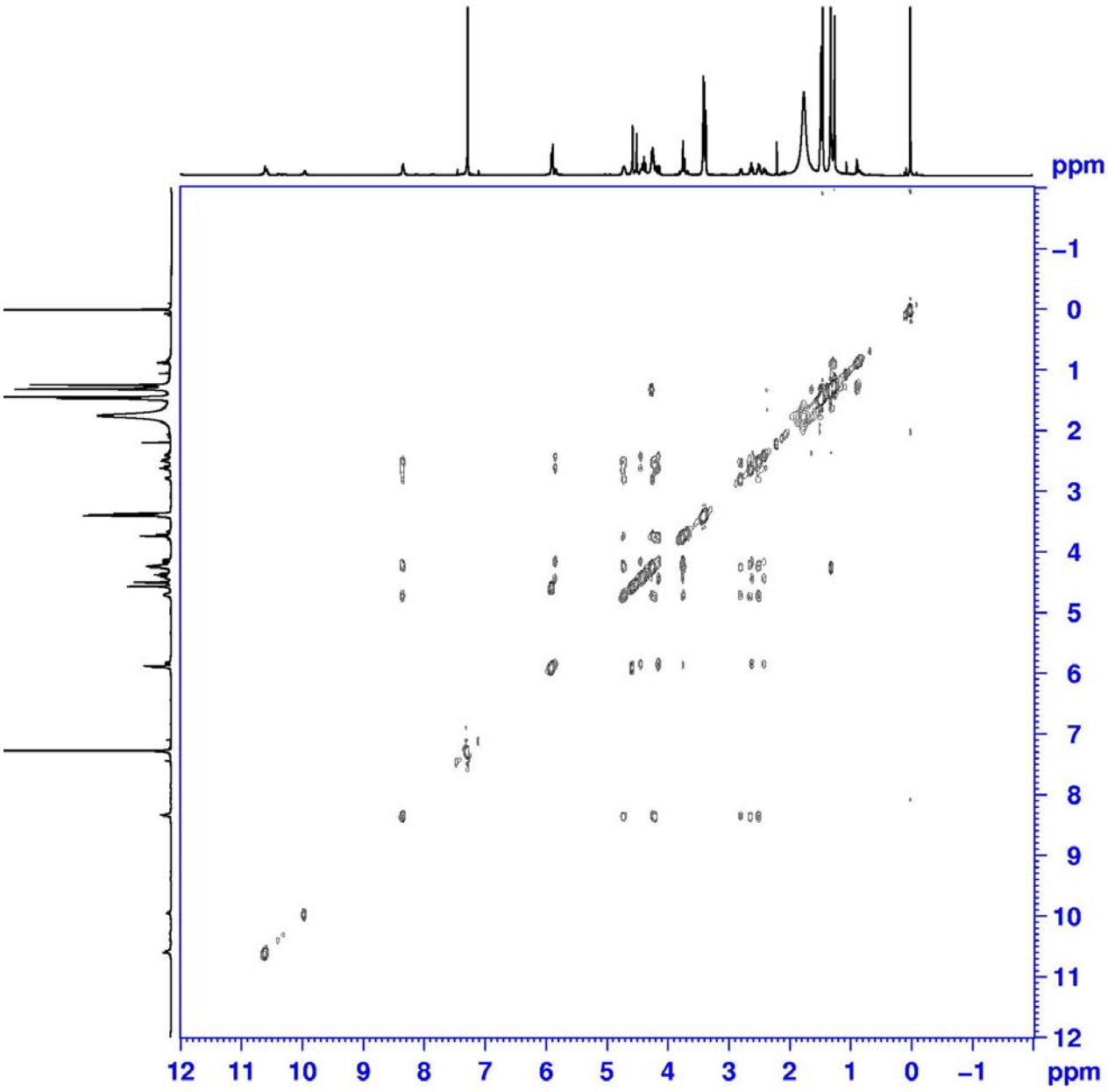
Supporting Figure 19. Stereoview of twenty superimposed structures of 5a (H-bonds are shown as dotted lines)

Residue / Protons	Res-1	Res-2	Res-3	Res-4	Res-5	Res-6
NH	5.83 (d, *J* = 9.8)	10.61 (s)	8.33 (d, *J* = 8.2)	10.58 (s)	8.35 (d, *J* = 9.0)	9.95 (s)
CαH	2.61 (dd, *J* = 3.6, 14.3)	4.38 (m)	2.79 (dd, *J* = 3.3, 14.7)	4.42 (m)	2.63 (dd, *J* = 3.6, 14.8)	4.72 (m)
Cα'H	2.40 (dd, *J* = 9.2, 14.3)	4.24 (m)	2.51 (dd, *J* = 10.0, 14.7)	4.24 (m)	2.5 (dd, *J* = 9.0, 14.8)	4.72 (m)
CβH	4.43 (m)	_	4.24 (m)	_	4.71 (m)	_
C4H	4.13 (dd, *J* = 3.1, 7.9)	_	4.32 (m)	_	4.18 (dd, *J* = 3.1, 7.7)	_
C3H	3.73 (d, *J* = 3.1)	_	3.71 (d, *J* = 3.1)	_	3.74 (d, *J* = 3.1)	_
C2H	4.56 (d, *J* = 3.9)	_	4.56 (d, *J* = 3.9)	_	4.56 (d, *J* = 3.9)	_
C1H	5.87 (d, *J* = 3.9)	_	5.80 (d, *J* = 3.9)	_	5.90 (d, *J* = 3.9)	_
Acetonides(6): 1.47 (6H, 2s), 1.46 (3H, s), 1.31 (9H, 3s). OMe: 3.40 (3H, s), 3.39 (3H, s), 3.36 (3H, s). Ethyl ester: 4.25 (2H, m, $-CH_2$), 1.31 (3H, t, *J* = 7.0, $-CH_3$). Boc: 1.99 (9H, s)						

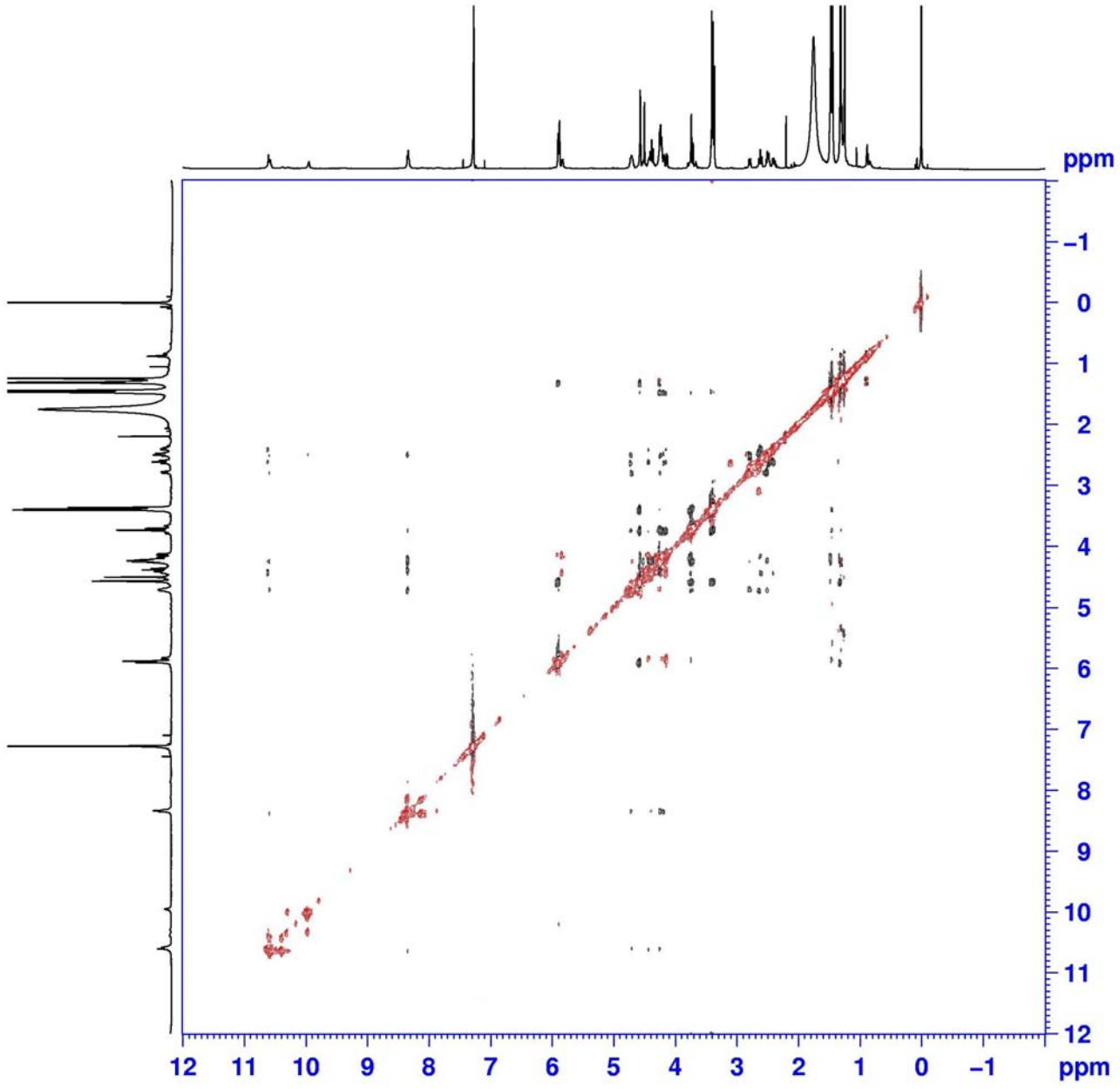
Supporting Table 5. ^{1}H NMR chemical shifts δ in ppm with multiplicity and coupling constants *J* in Hz (in parentheses) of 5b (600 MHz, $CDCl_3$, 278 K)



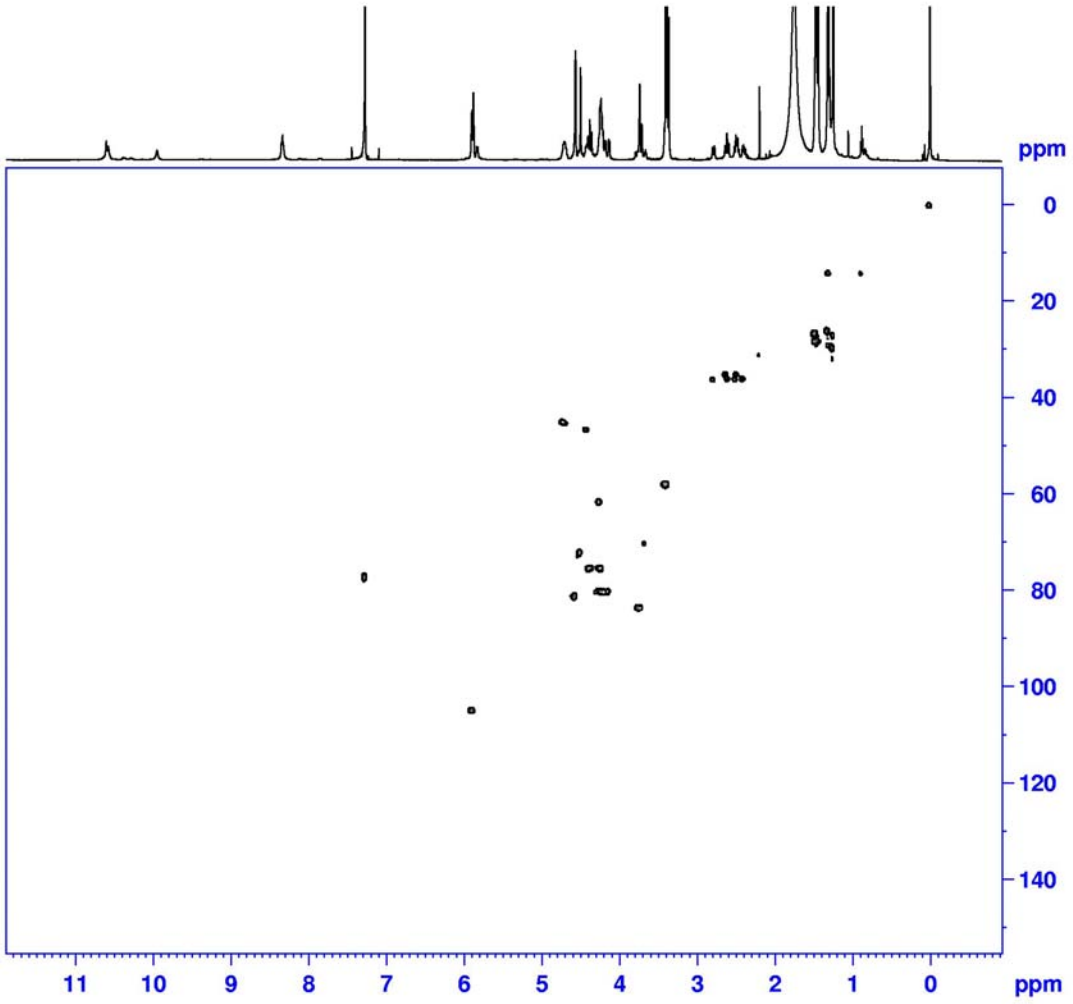
Supporting Figure 20. ^{1}H NMR spectrum of 5b (600 MHz, $CDCl_3$, 278 K)



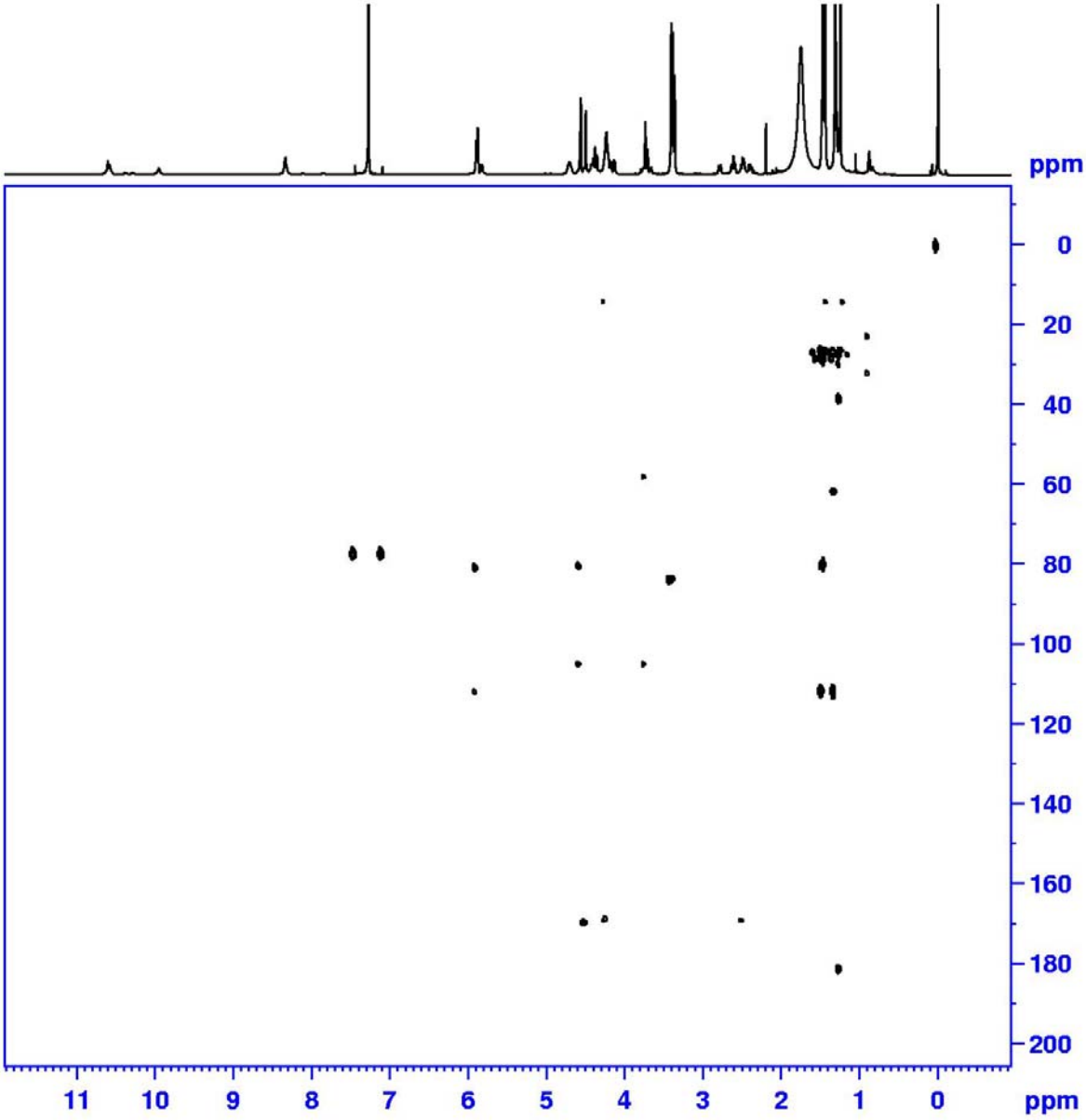
Supporting Figure 21. TOCSY spectrum of peptide 5b (600 MHz, $CDCl_3$, 278 K)



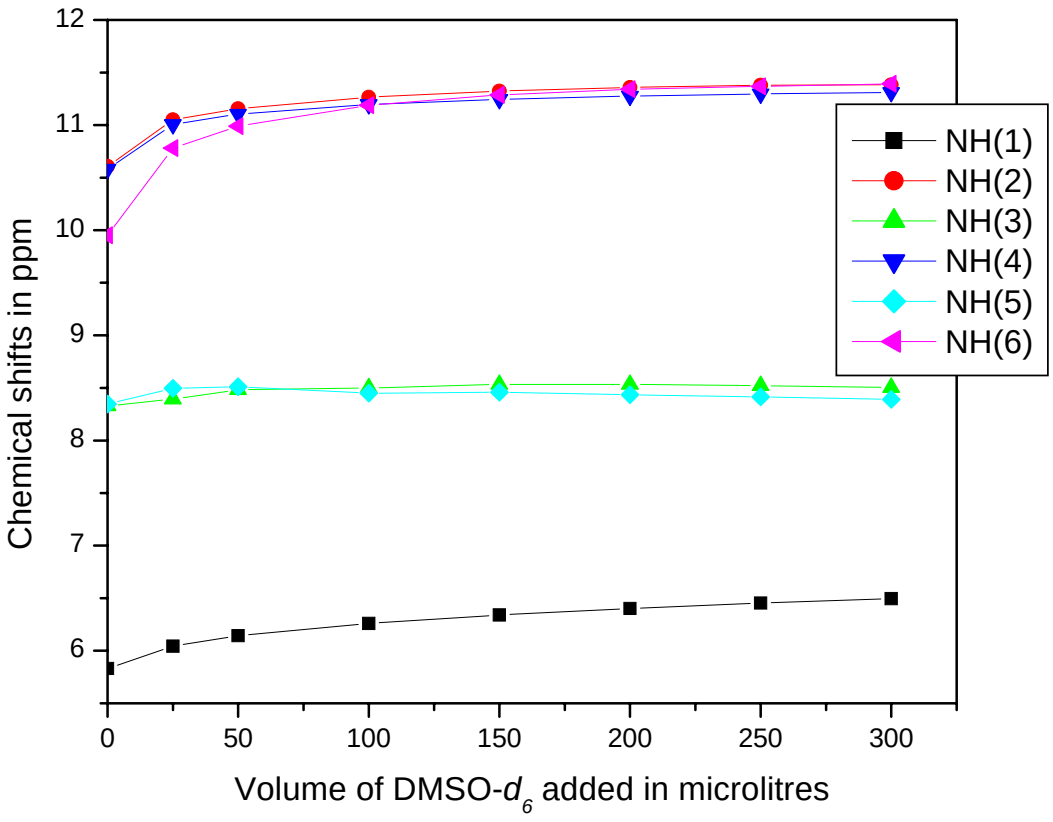
Supporting Figure 22. ROESY spectrum of peptide 5b (600 MHz, $CDCl_3$, 278 K)



Supporting Figure 23. HSQC spectrum of 5b (600 MHz, $CDCl_3$, 278 K)



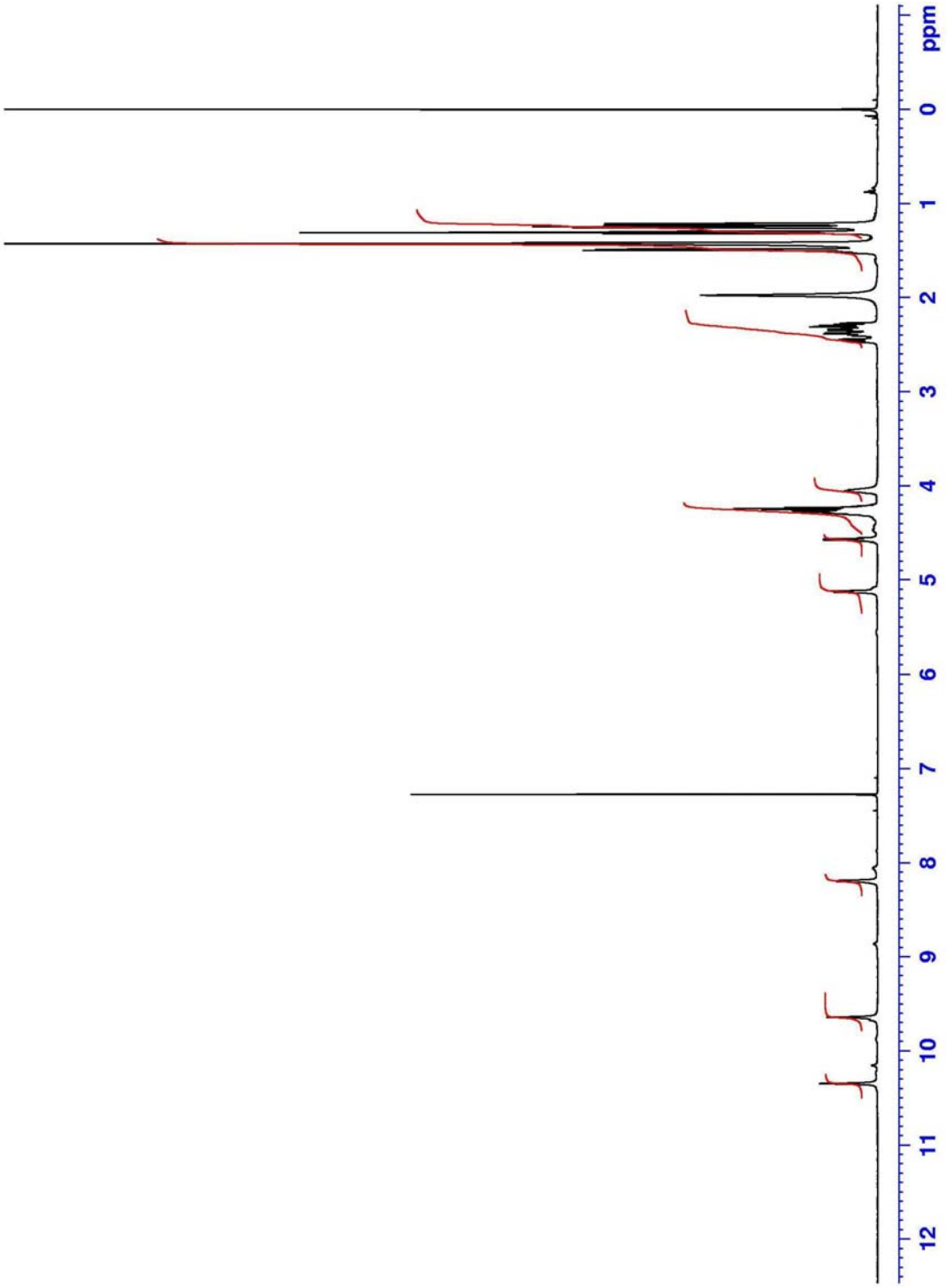
Supporting Figure 24. HMBC spectrum of peptide 5b (600 MHz, $CDCl_3$, 278 K)



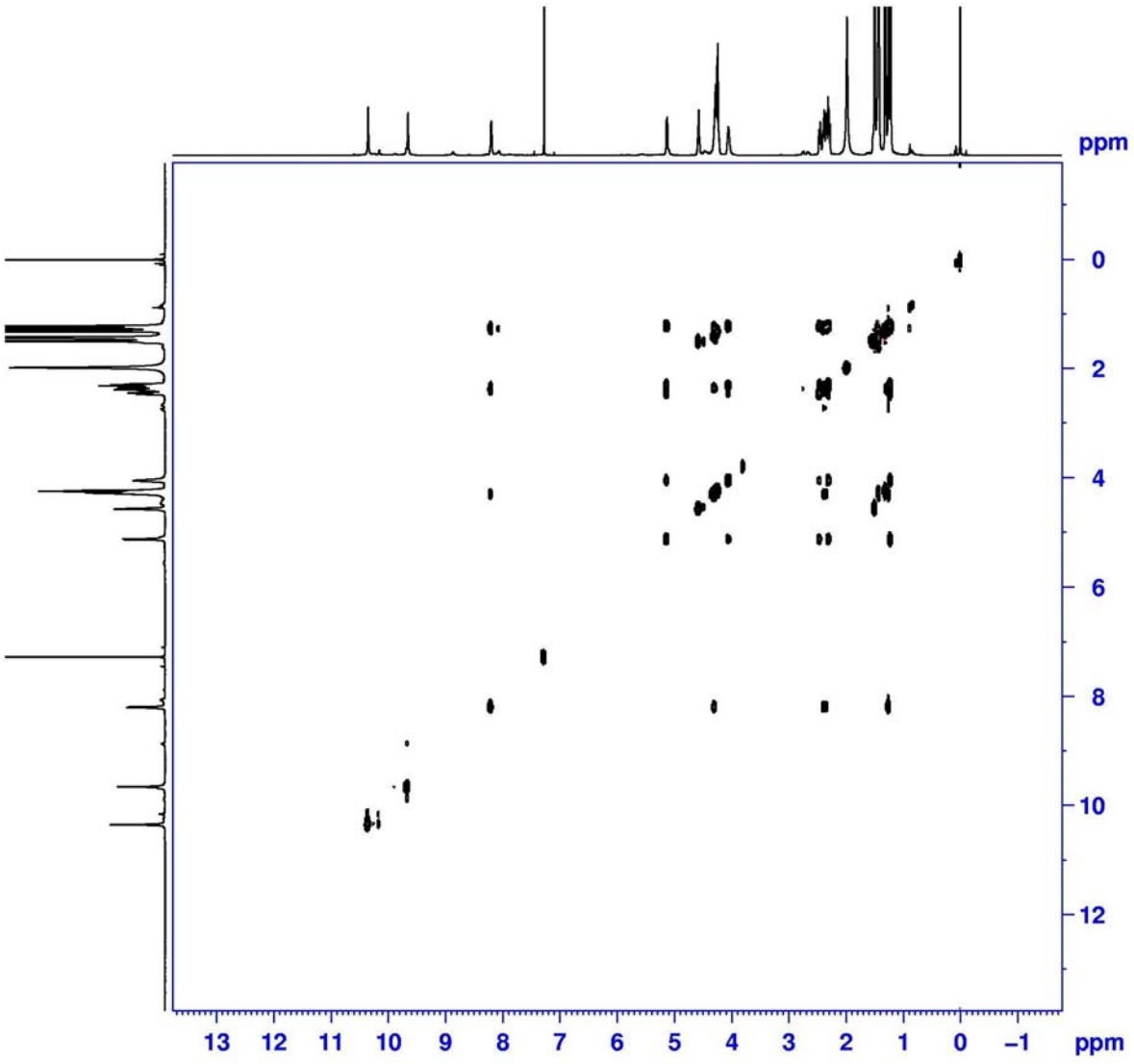
Supporting Figure 25. Solvent titration plot for peptide 5b

Supporting Table 6. ^{1}H NMR chemical shifts δ in ppm with multiplicity and coupling constants J in Hz (in parentheses) of 3b (600 MHz, $CDCl_3$, 278 K)

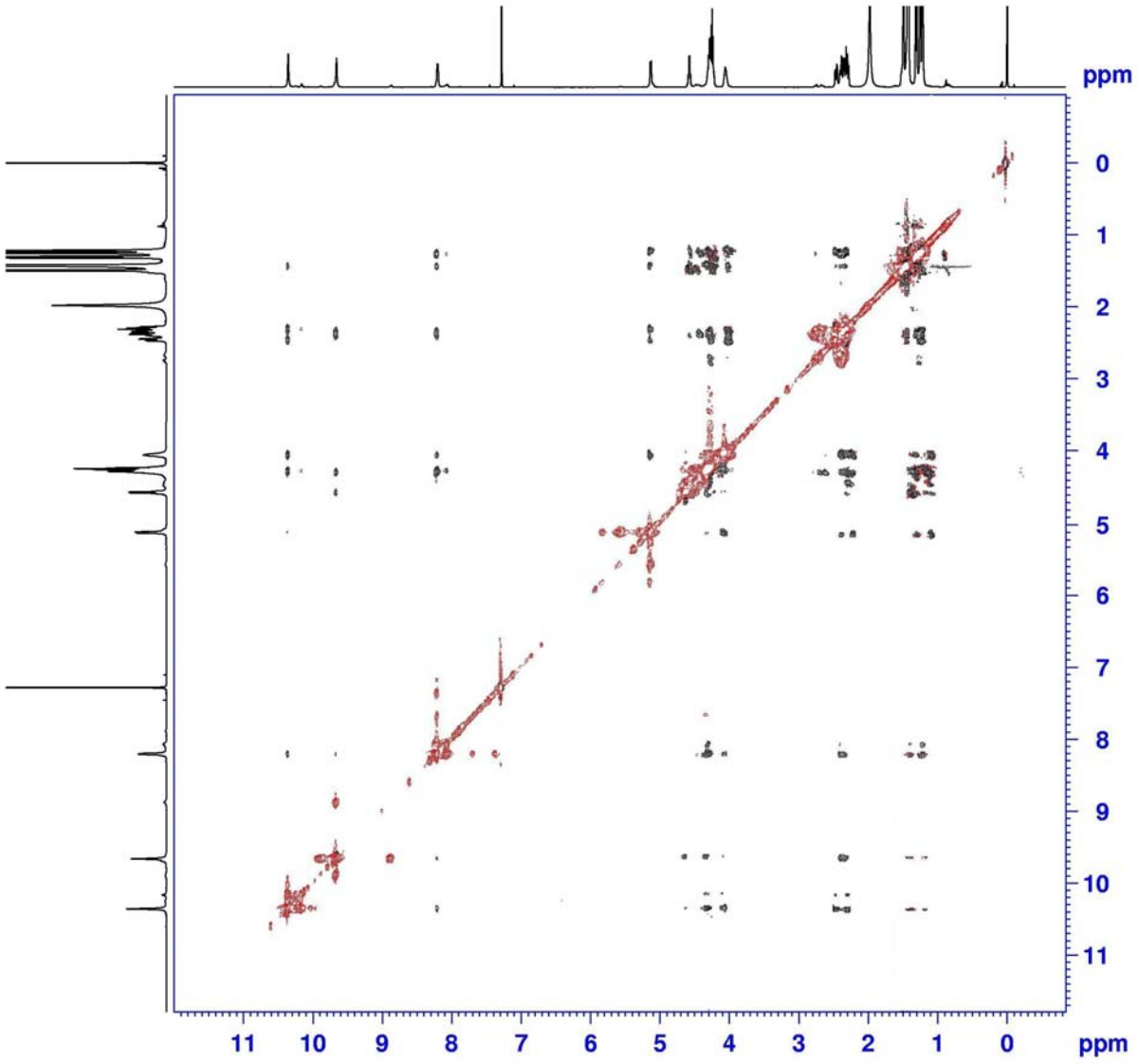
Residue / Protons	Res-1	Res-2	Res-3	Res-4
NH	5.18 (d, J = 8.8)	10.4 (s)	8.21 (d, J = 7.8)	9.72 (s)
CαH	2.46 (dd, J = 4.8, 14.5) *pro S*	4.25 (q, J = 7.1)	2.39 (dd, J = 5.0, 14.0) *pro S*	4.57 (q, J = 7.2)
Cα'H	2.29 (dd, J = 8.8, 14.5) *pro R*	_	2.34 (dd, J = 8.5, 14.0) *pro R*	_
CβH	4.05 (m)	1.42 (d, , J = 7.1)	4.24 (m)	1.49 (d, , J = 7.2)
CγH	1.22 (d, , J = 6.9)	_	1.25 (d, J = 6.9)	_
Ethyl ester: 4.25 (2H, m, -CH_2), 1.31 (3H, t, J = 7.2, -CH_3) Boc: 1.43(9H, s)				



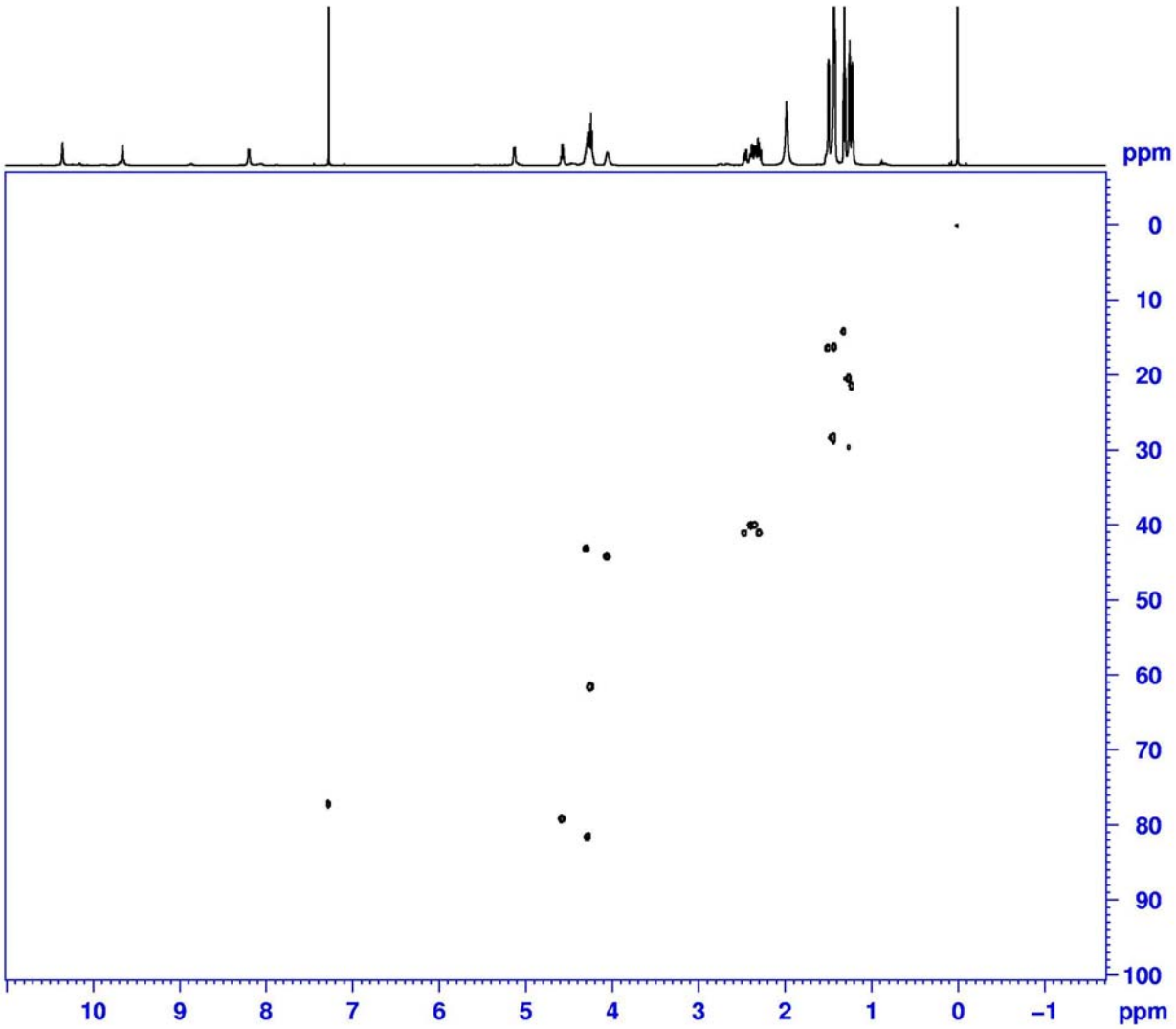
Supporting Figure 26. ^{1}H NMR spectrum of peptide 3b (600 MHz, $CDCl_3$, 278 K)



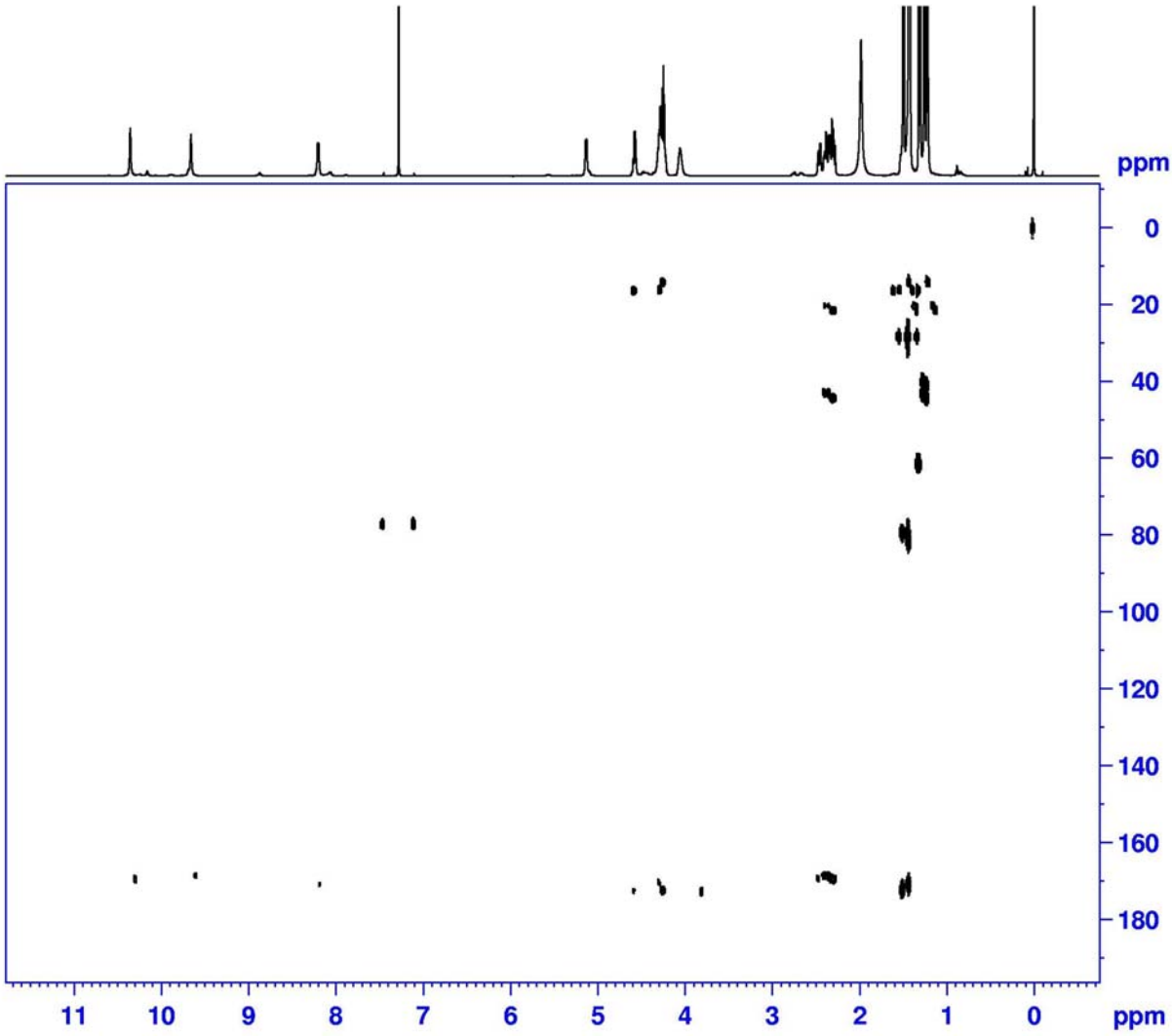
Supporting Figure 27. TOCSY spectrum of peptide 3b (600 MHz, $CDCl_3$, 278 K)



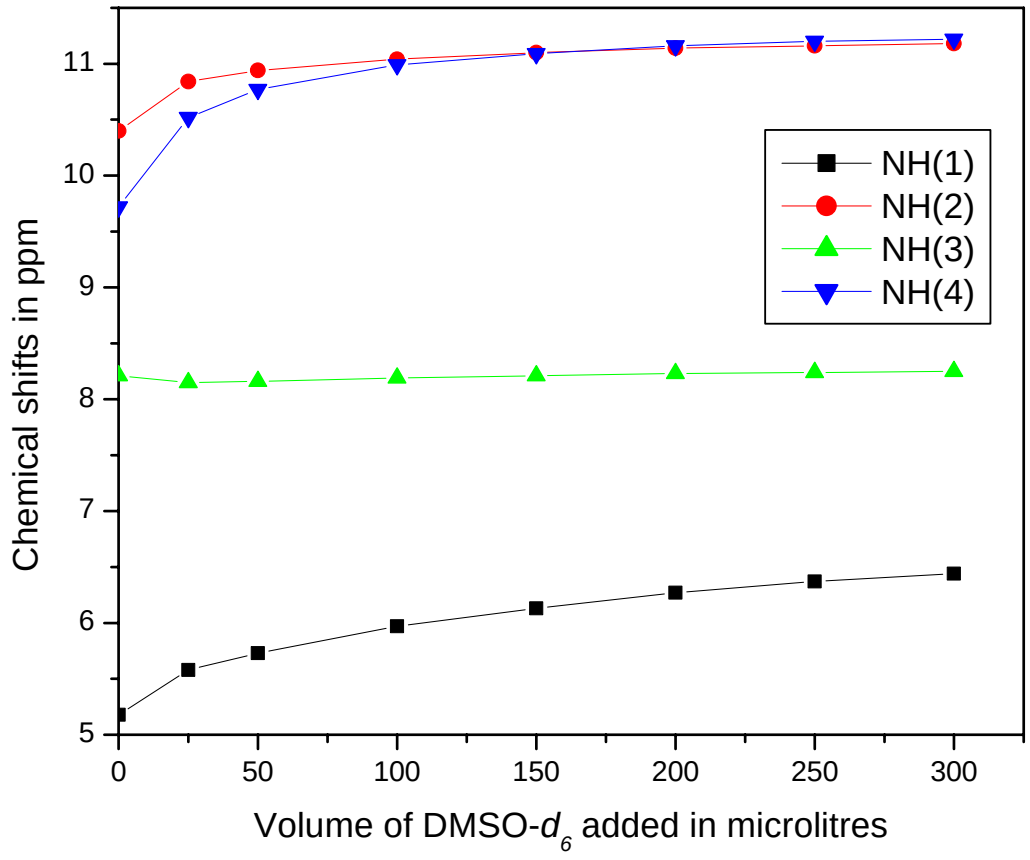
Supporting Figure 28. ROESY spectrum of peptide 3b (600 MHz, $CDCl_3$, 278 K)



Supporting Figure 29. HSQC spectrum of peptide 3b (600 MHz, $CDCl_3$, 278 K)



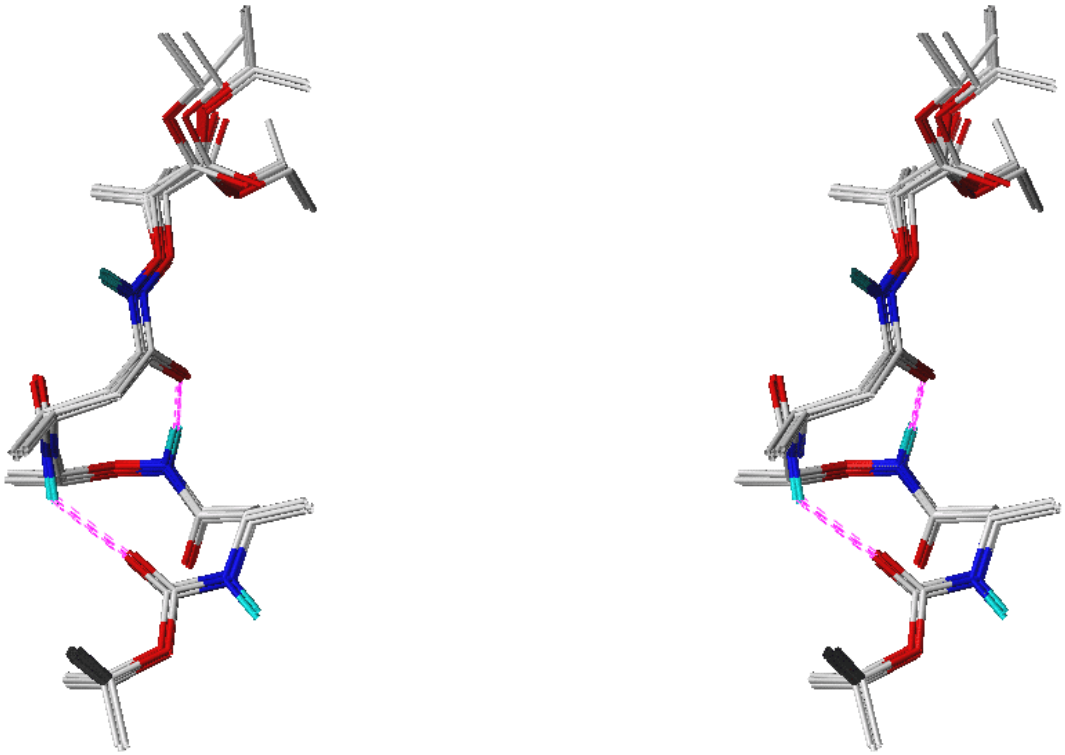
Supporting Figure 30. HMBC spectrum of peptide 3b (600 MHz, $CDCl_3$, 278 K)



Supporting Figure 31. Solvent titration plot for peptide 3b

Residue	Atom	Residue	Atom	Lower bond (Å)	Higher bond (Å)
1	NH	1	CαH (*pro-R*)	2.87	3.51
1	CβH	2	NH	3.08	3.76
1	CβH	3	NH	3.33	4.07
1	CβH	3	CαH (*pro-R*)	1.9	2.31
2	NH	1	CαH (*pro-S*)	3.13	3.83
2	NH	2	CαH	3.56	4.34
2	NH	3	NH	3.49	4.27
3	NH	3	CαH (*pro-R*)	2.97	3.63
3	CβH	4	NH	3.22	3.94
4	NH	3	CαH (*pro-S*)	3.35	3.69

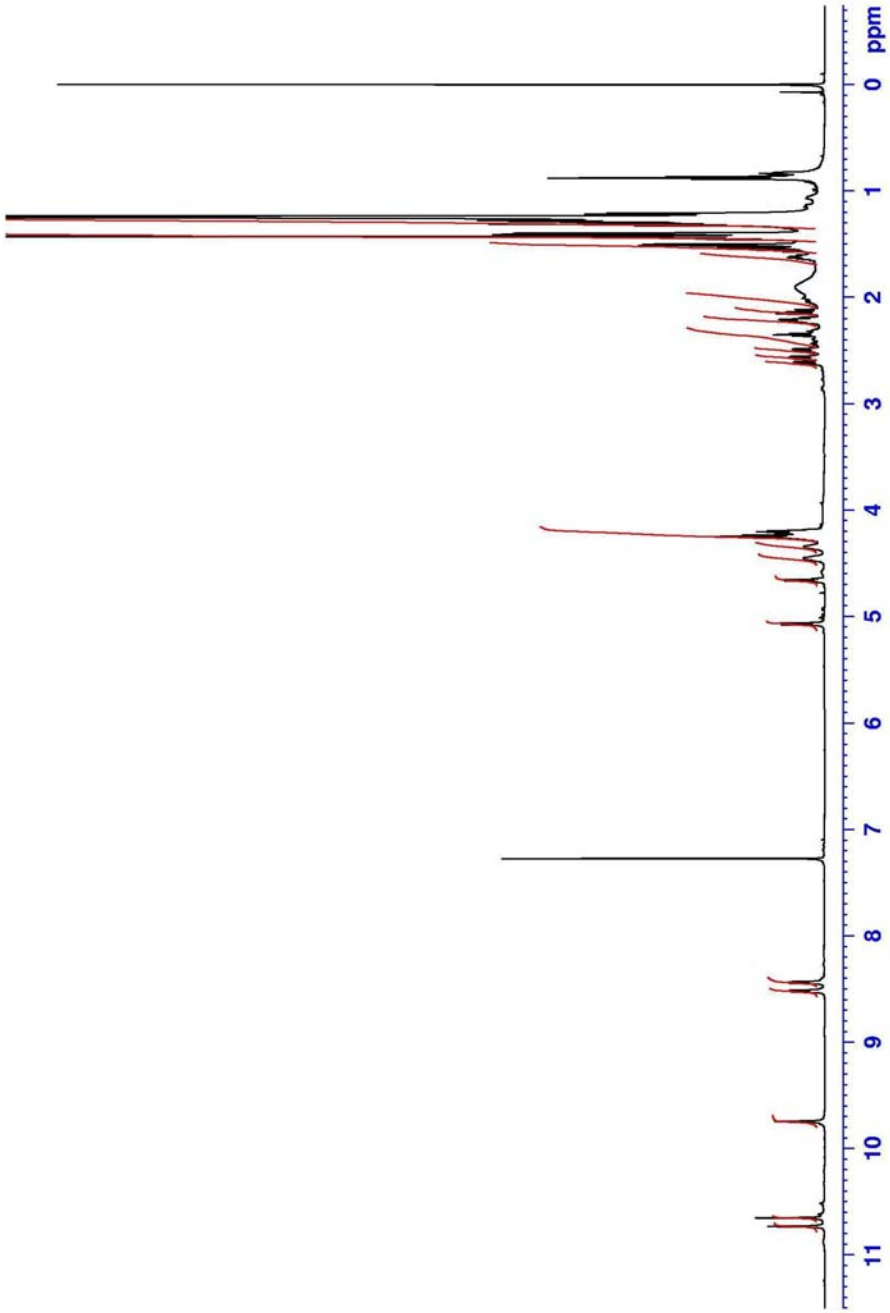
Supporting Table 7. Distance constraints used in MD calculations for peptide 3b, derived from ROESY experiment in $CDCl_3$ (600 MHz, 278 K)



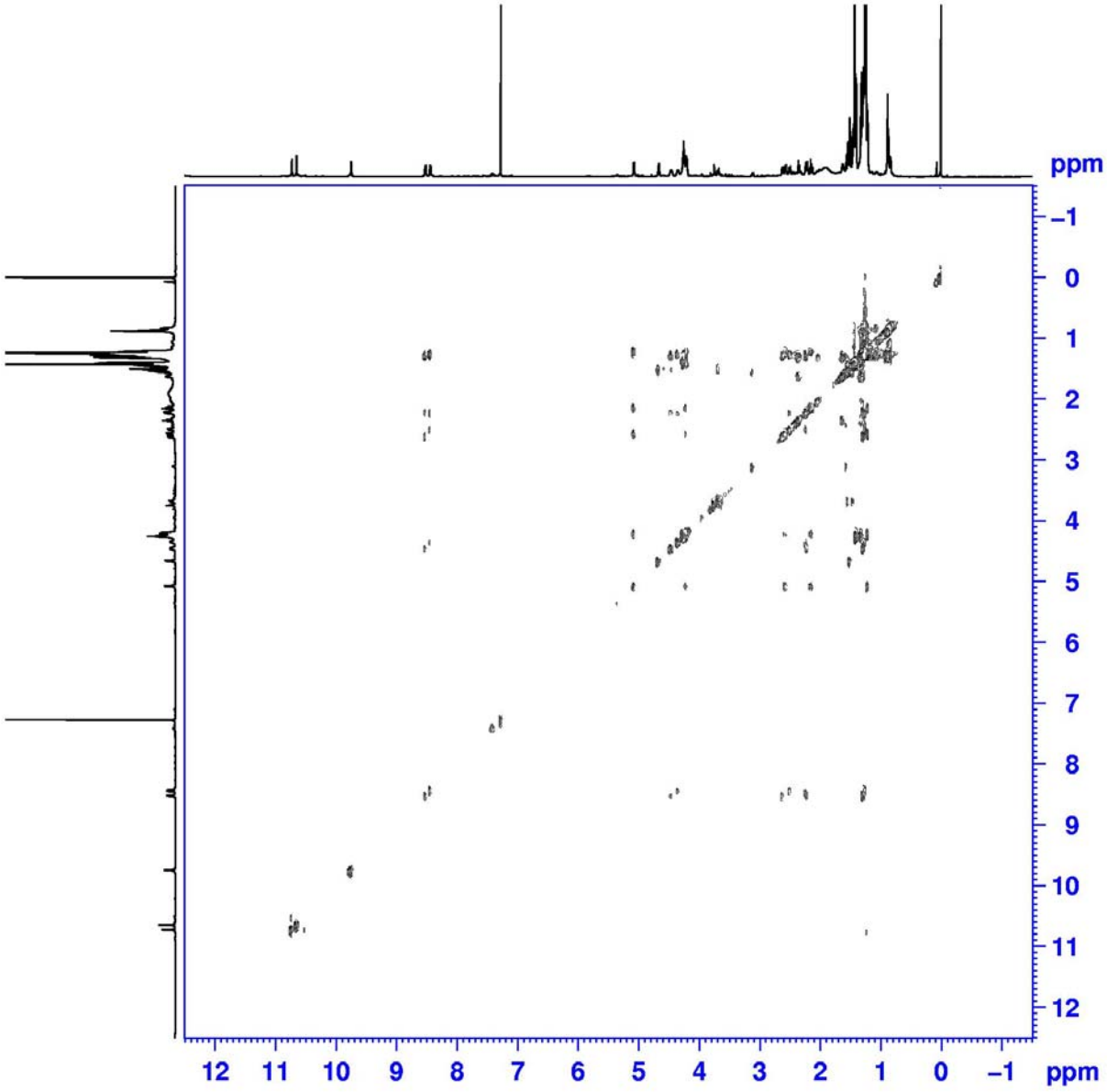
Supporting Figure 32. Stereoview of twenty superimposed structures of 3b (H-bonds are shown as dotted lines)

Residue / Protons	Res-1	Res-2	Res-3	Res-4	Res-5	Res-6
NH	5.06 (d, J = 10.1)	10.62 (s)	8.52 (d, J = 9.3)	10.72 (s)	8.44 (d, J = 8.2)	9.73 (s)
CαH	2.57 (dd, J = 3.6, 13.8)	4.21 (q, J = 7.0)	2.62 (dd, J = 3.3, 13.9)	4.24 (q, J = 7.0)	2.50 (dd, J = 3.9, 13.9)	4.66 (q, J = 7.0)
Cα'H	2.14 (dd, J = 10.8, 13.8)	_	2.21 (dd, J =9.9, 13.9)	_	2.23 (dd, J =9.3, 13.9)	_
CβH	4.21 (m)	1.40 (d, J = 7.0)	4.46 (m)	1.39 (d, J = 7.0)	4.35 (m)	1.51 (d, J = 7.0)
CγH	1.21 (d, J = 6.9)	_	1.29 (d, J = 6.8)	_	1.26 (d, J = 6.7)	_
Ethyl ester: 4.25 (2H, m, -CH_2), 1.31 (3H, t, J = 7.1, -CH_3) Boc: 1.43(9H, s)						

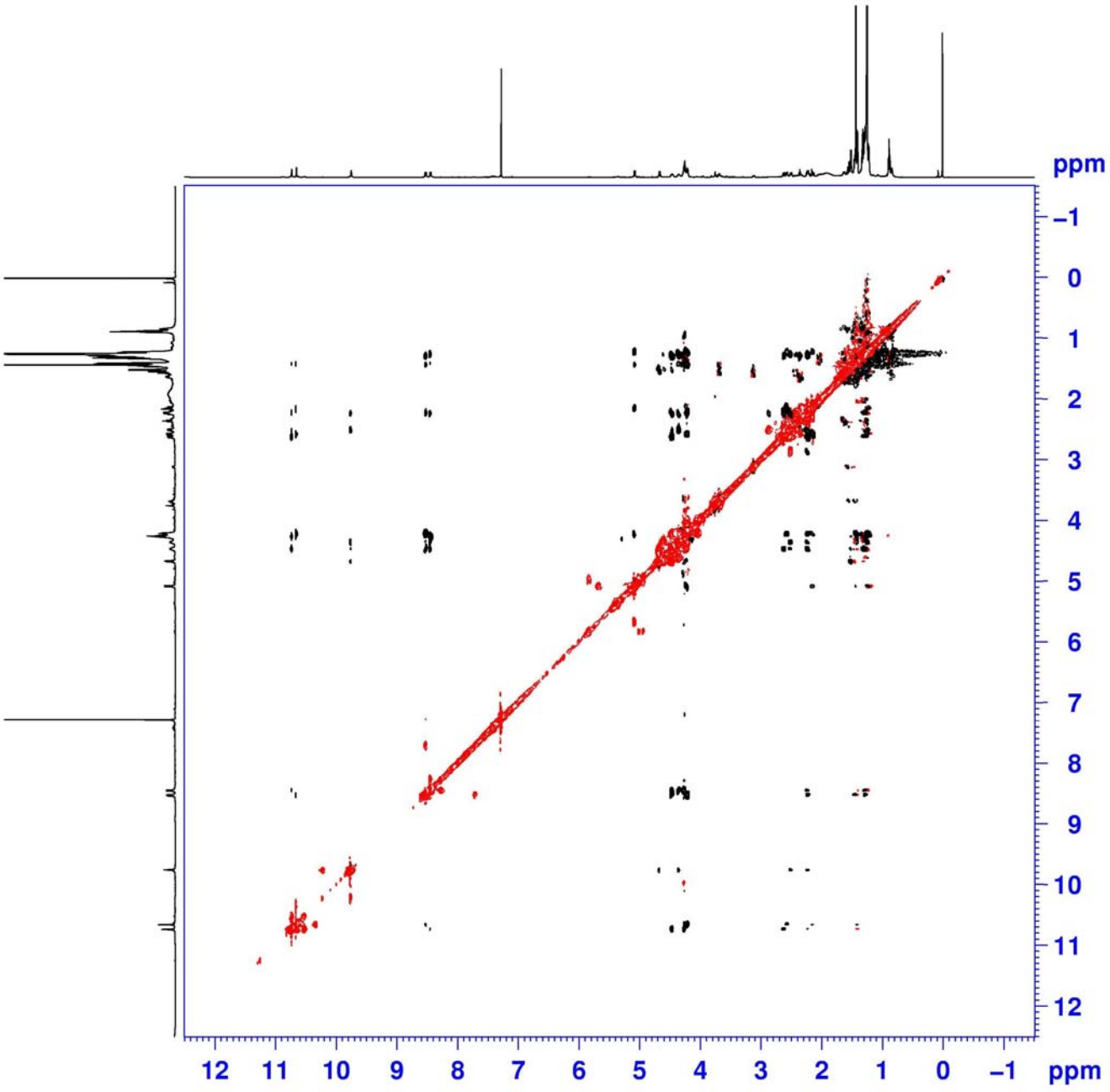
Supporting Table 8. ^{1}H NMR chemical shifts δ in ppm with multiplicity and coupling constants J in Hz (in parentheses) of 3b (600 MHz, $CDCl_3$, 278 K)



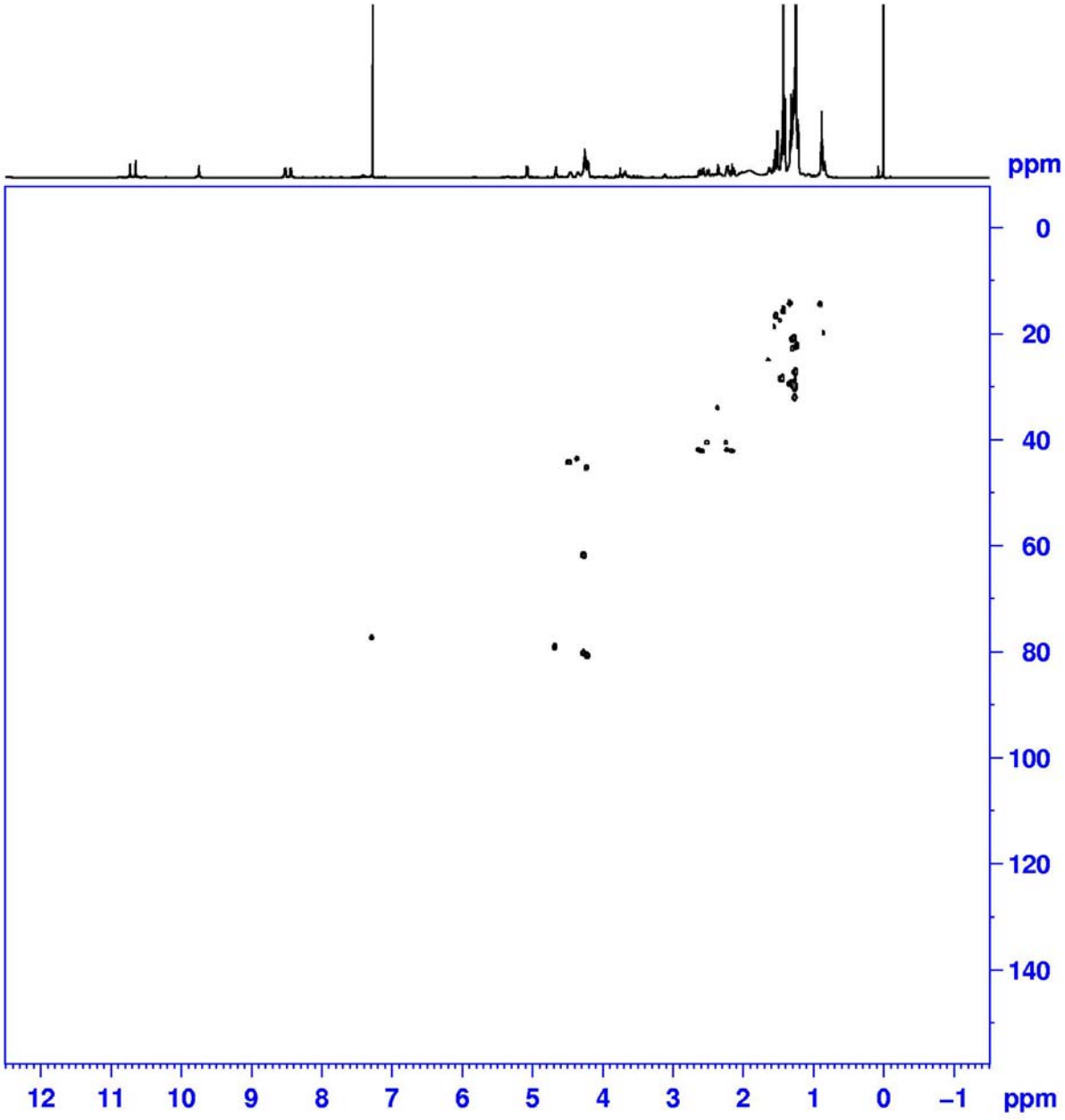
Supporting Figure 33. ^{1}H NMR spectrum of peptide 4b (600 MHz, $CDCl_3$, 278K)



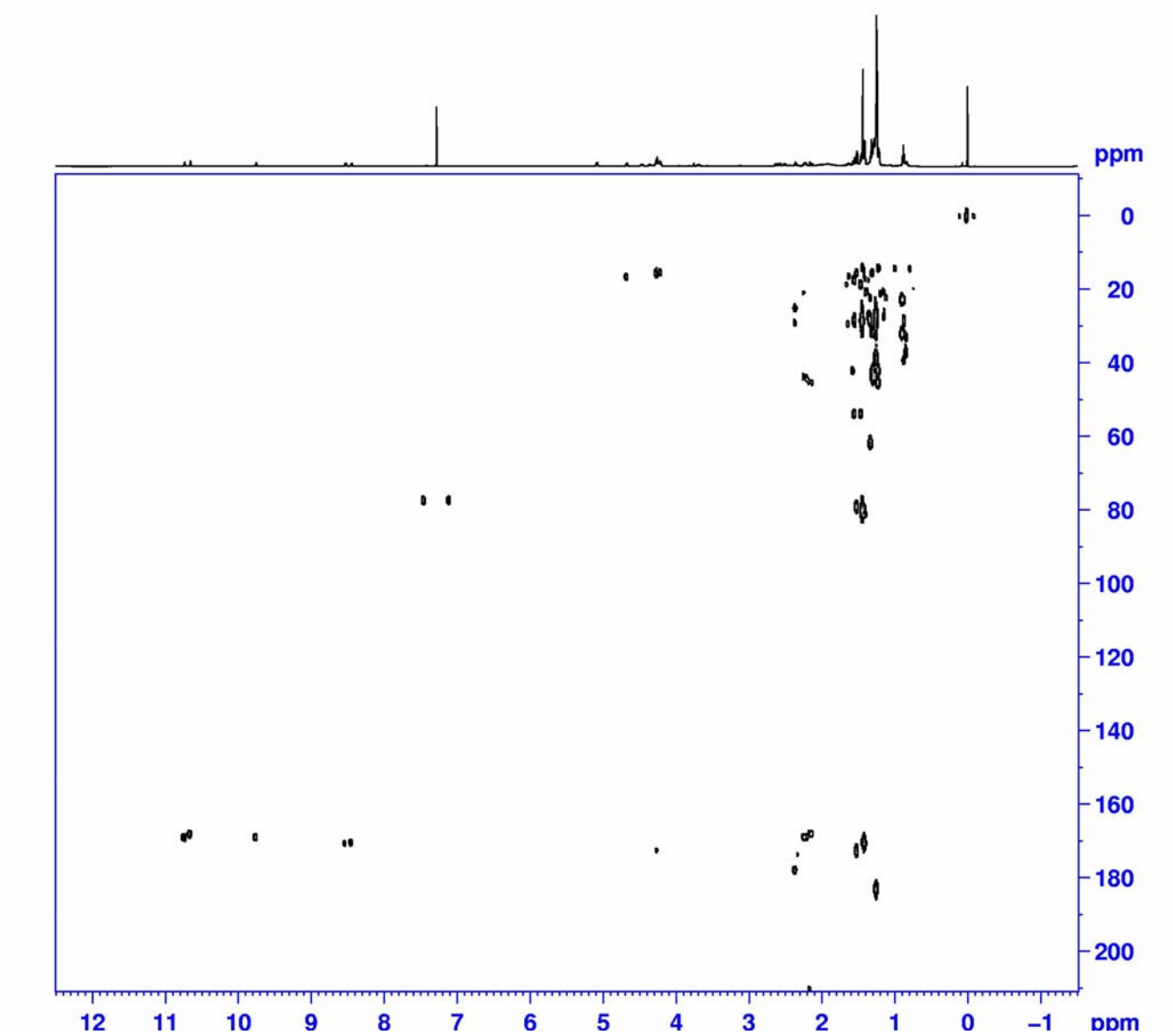
Supporting Figure 34. TOCSY spectrum of peptide 4b (600 MHz, $CDCl_3$, 278 K)



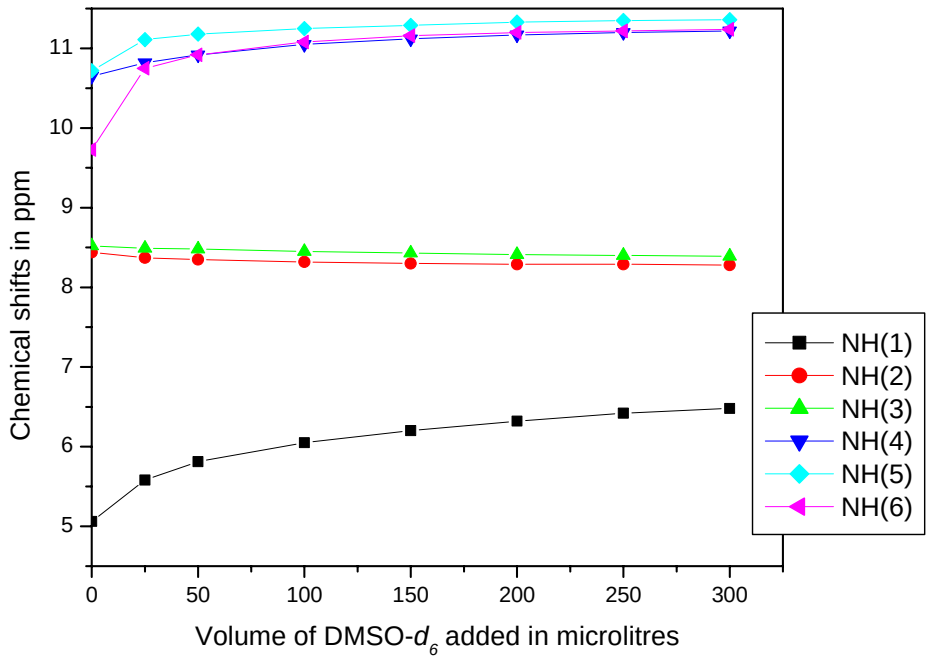
Supporting Figure 35. ROESY spectrum of peptide 4b (600 MHz, $CDCl_3$, 278 K)



Supporting Figure 36. HSQC spectrum of peptide 4b (600 MHz, $CDCl_3$, 278 K)



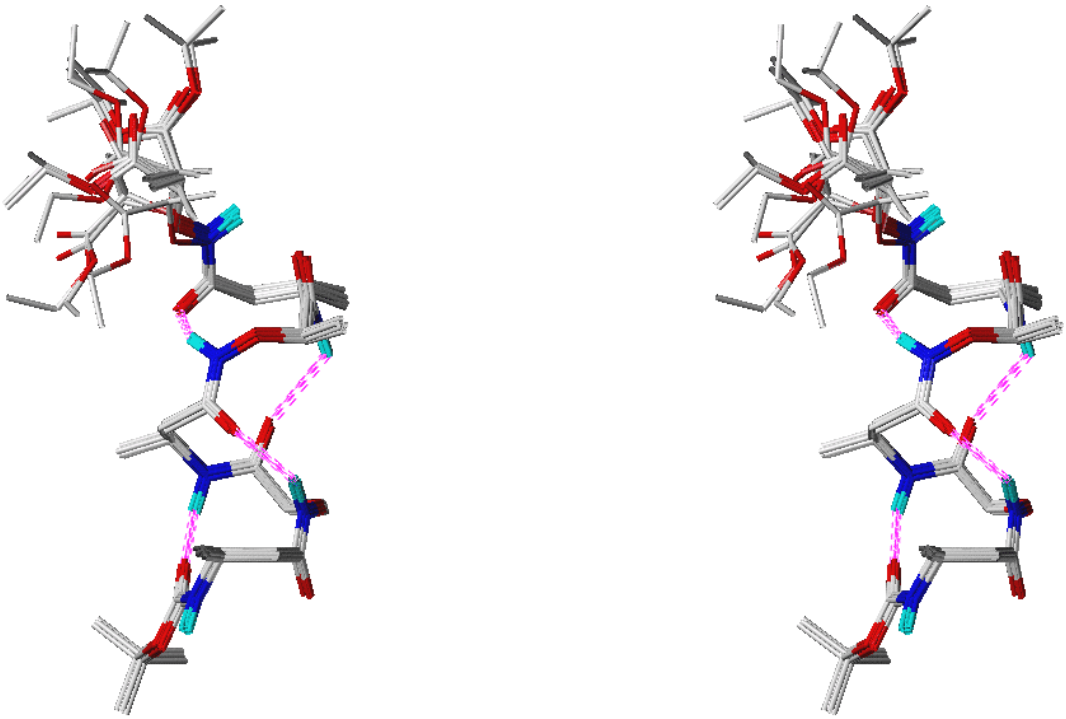
Supporting Figure 37. HMBC spectrum of peptide 4b (600 MHz, $CDCl_3$, 278 K)



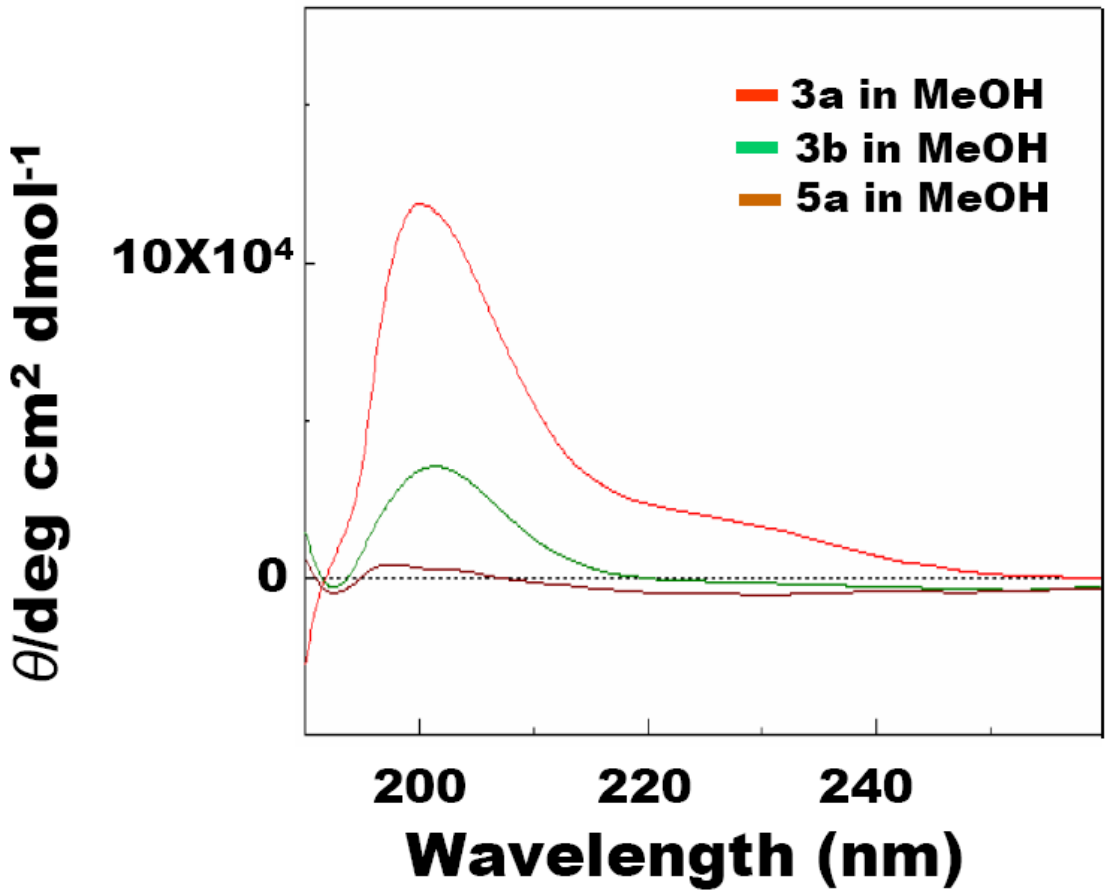
Supporting Figure 38. Solvent titration plot for peptide 4b

Residue	Atom	Residue	Atom	Lower bond (Å)	Higher bond (Å)
1	NH	1	CαH (*pro-R*)	3.21	3.92
1	CβH	2	NH	3.04	3.72
1	CβH	3	CαH (*pro-R*)	2.12	2.59
2	NH	1	CαH (*pro-S*)	2.51	3.06
2	NH	2	CαH	3.13	3.82
2	NH	3	NH	4.11	5.02
2	NH	4	CαH	3.02	3.70
3	NH	2	CαH	2.55	3.12
3	NH	3	CαH (*pro-R*)	3.06	3.75
3	CβH	4	NH	2.55	3.11
3	CβH	5	NH	3.48	4.25
3	CβH	5	CαH (*pro-R*)	2.90	3.55
4	NH	3	CαH (*pro-S*)	2.42	2.96
4	NH	5	NH	4.33	5.29
4	NH	6	CαH	4.56	5.57
5	NH	4	CαH	2.53	3.09
5	NH	5	CαH (*pro-R*)	2.90	3.54
5	CβH	6	NH	3.70	4.52
6	NH	5	CαH (*pro-S*)	3.09	3.78

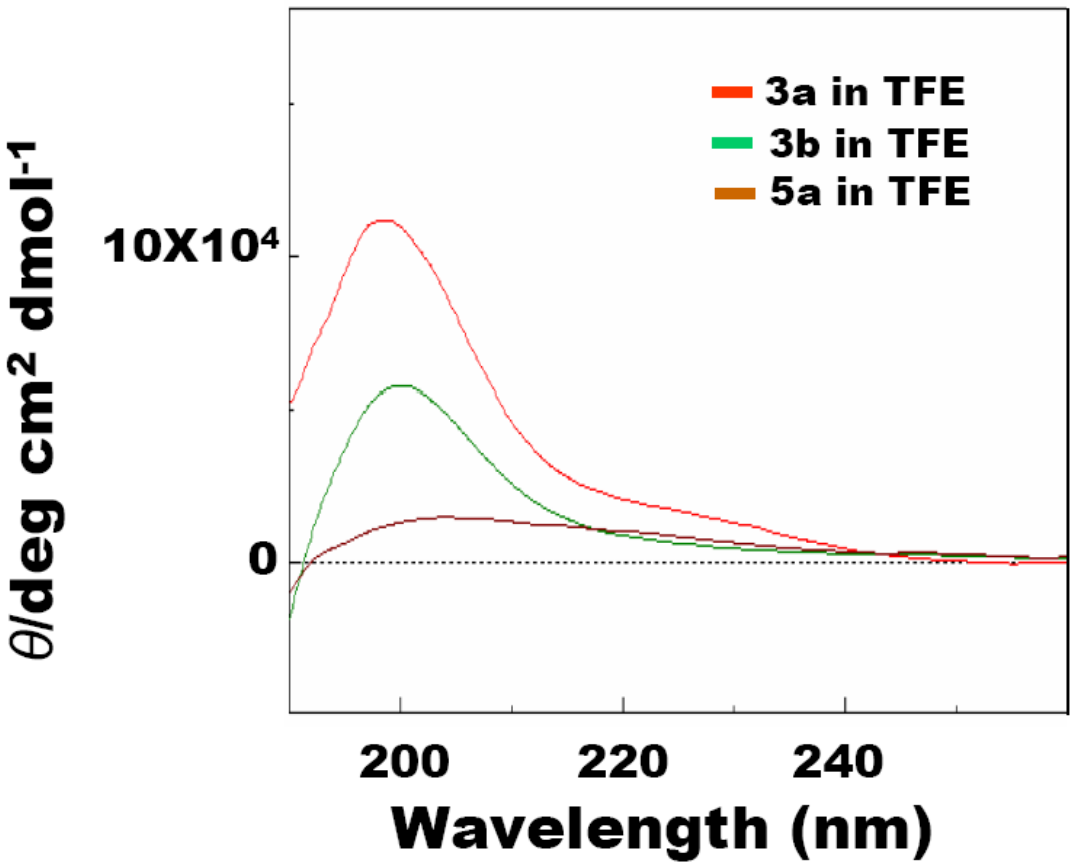
Supporting Table 9. Distance constraints used in MD calculations for peptide 4b, derived from ROESY experiment in $CDCl_3$ (600 MHz, 278 K)



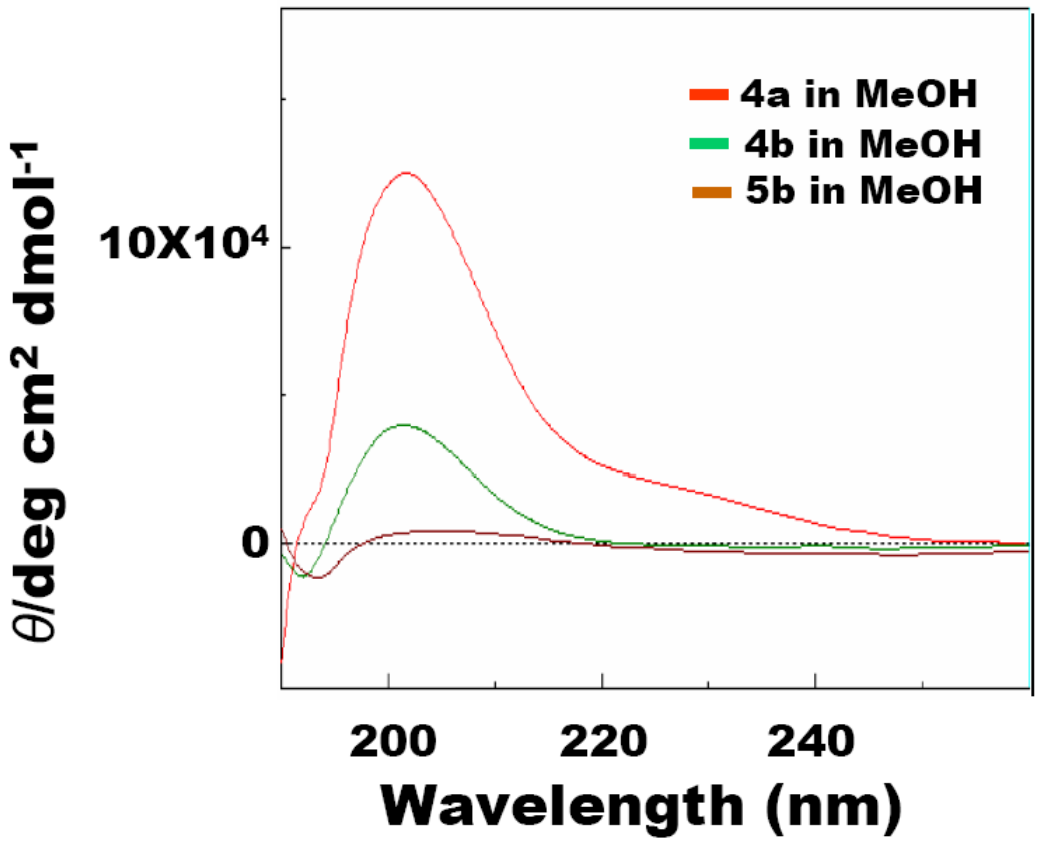
Supporting Figure 39. Stereoview of twenty superimposed structures of 4b (H-bonds are shown as dotted lines)



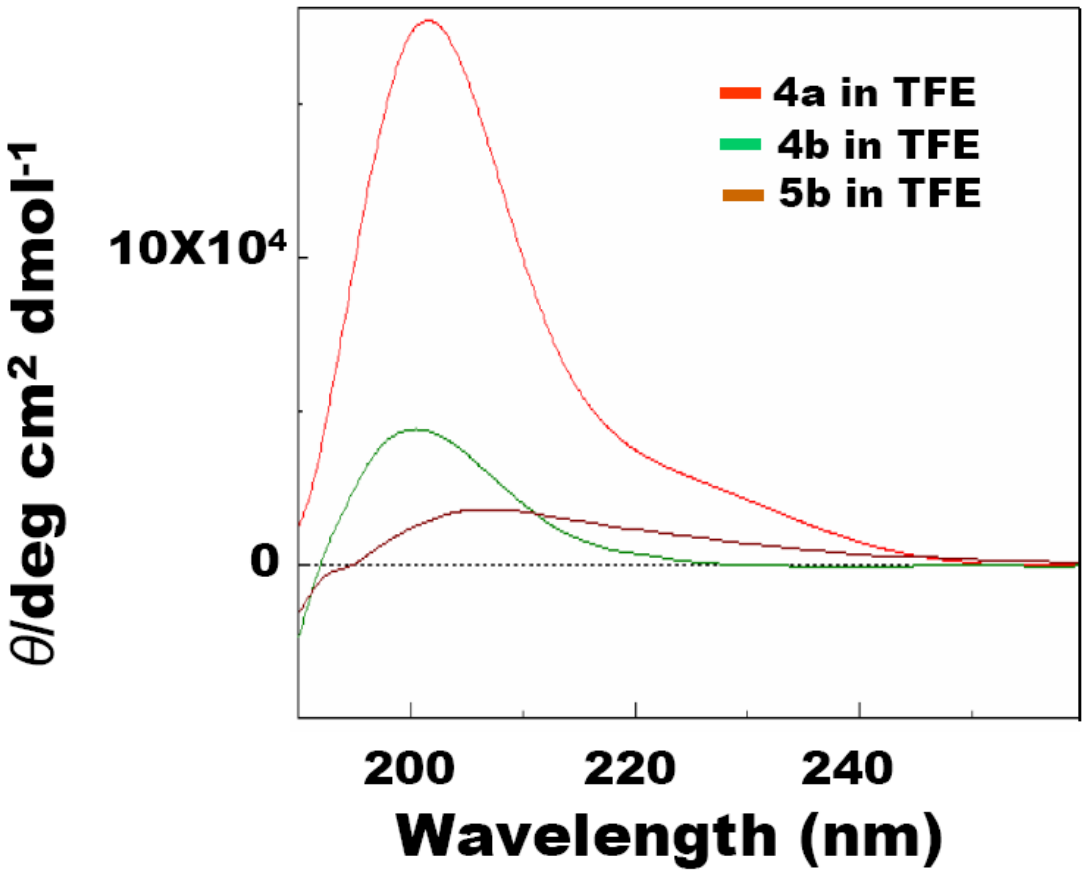
Supporting Figure 40. Circular Dichroism (CD) spectra of peptides 3a, 3b and 5a in methanol



Supporting Figure 41. Circular Dichroism (CD) spectra of peptides 3a, 3b and 5a in TFE



Supporting Figure 42. Circular Dichroism (CD) spectra of peptides 4a, 4b and 5b in methanol



Supporting Figure 43. Circular Dichroism (CD) spectra of peptides 4a, 4b and 5b in TFE