Supporting Information

Pyrrolidine Ring Puckering and Prolyl Amide Bond Configurations of 2-methyl-allo-hydroxyproline-based dipeptides

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Experimental procedure

Synthesis of compound 1a and 1b

The detail synthesis of lactones **1a** and **1b** was given in our earlier report.[1]

Lactone **1a**;$[\alpha]_D^{21}$ -18.8º (c = 0.13, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.84 (s, 3H), 2.11 (m, 2H), 3.60-3.70 (dd, 2H, *J*=31, 11 Hz), 4.94 (bs, 1H), 5.09-5.19 (m, 2H), 7.32-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 46.1, 53.2, 64.5, 67.5, 75.1, 128.1, 128.2, 128.6, 135.9, 155.3, 172.3; FTIR (neat) υ = 3399, 3019, 1644, 1215 cm^{-1}; HRMS (ESI-TOF) calculated for $[C_{14}H_{15}NO_4+H]^+$ 262.1074, found 262.1075.

Lactone **1b;** $[\alpha]_D^{21}$ +40.7º (c = 0.15, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.84 (s, 3H), 2.10-2.13 (m, 2H), 3.60-3.71 (dd, 2H, *J*=31, 11 Hz), 4.94 (bs, 1H), 5.09-5.16 (m, 2H), 7.30-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 46.1, 53.2, 64.5, 67.5, 75.1, 128.1, 128.2, 128.6, 135.9, 155.3, 172.3; FTIR (neat) υ = 3399, 3019, 1644, 1215 cm^{-1}; HRMS (ESI-TOF) calculated for $[C_{14}H_{15}NO_4+H]^+$ 262.1074, found 262.1075.

Synthesis of compounds 2a and 2b

A mixture of L-Ala-NMe (0.15 mmol) and bicyclic lactone **1a** or **1b** (0.1 mmol) in dry pyridine (500 µL) was stirred at 60 ºC for 5 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with 10 mL of ethyl acetate and washed with 1N HCl (3 X 10 mL) followed by brine wash. The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated to give the residue which was purified by silica gel column chromatography using methanol-chloroform (2:98) as eluent to give compounds **2a** (21 mg, 58 %) and **2b** (24 mg, 66 %) respectively as a colourless oil.

Compound 2a: (For complete NMR data see Table-2); HRMS (ESI-TOF) calculated for $[C_{18}H_{25}N_3O_5+H]^+$ 364.1867, found 364.1853.

Compound 2b: (For complete NMR data see Table-3): HRMS (ESI-TOF) calculated for $[C_{18}H_{25}N_3O_5+H]^+$ 364.1867, found 364.1851.

Synthesis of compound 3

To a solution of compound **2b** (31 mg, 0.08 mmol) in methanol (2 mL) was added 10% Pd/C (4 mg) and the reaction mixture was subjected to hydrogenation at 10 psi for 1 h. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to obtain amine as

gummy residue. The resultant amino alcohol (16 mg) was dissolved in acetic anhydride (1 mL) and stirred at room temperature until complete consumption of starting material. The excess acetic anhydride was removed by evaporation under vacuum. The crude product showed two spots on TLC due to the formation of some amount of O-acetyl product which was selectively hydrolyzed using potassium carbonate in methanol (1 mL) at room temperature for 30 min. The volatiles were removed under vacuum and the crude product was purified by column chromatography using methanol-chloroform (5:95) as eluent to get the desired N-acetyl-L-Allo-Hyp-L-Ala-NMe amide **3** (yield, 14 mg, 64 %) as a colourless oil.

(For complete NMR data see Table-4); HRMS (ESI-TOF) calculated for $[C_{12}H_{21}N_3O_4+H]^+$ 272.1605, found 272.1616.

Synthesis of compound 4a and 4b

To a solution of bicyclic lactone **1a** or **1b** (261 mg, 1 mmol) in toluene (2 mL) was added methylamine hydrochloride (110 mg, 1.5 mmol) followed by addition of sodium bicarbonate (126 mg, 1.5 mmol) in water (500 µL) and the biphasic medium was stirred at 60 ºC for 12 h.[2] After completion, the reaction mixture was diluted with ethyl acetate (20 mL), washed with 10% aq. potassium bisulfate (2 X 10 mL) and brine. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to give the crude product which was purified by column chromatography using methanol-chloroform (3:97) as eluent to get compounds **4a** (230 mg, 79%) and **4b** (249 mg, 85 %) was obtained as colorless oil.

Compound **4a**; (For complete NMR data see Table-5); HRMS (ESI-TOF) calculated for $[C_{15}H_{20}N_2O_2+H]^+$ 293.1496, found 293.1495.

Compound **4b**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (s., 3 H), 1.92 (dd, *J = 14.2, 4.6* Hz, 1 H), 2.64 (dd, *J = 14.0, 1.4* Hz, 1 H), 2.84 (d, *J = 4.5* Hz, 3 H), 3.55 (dd, *J = 11.7, 3.8* Hz, 1 H), 3.73 (dd, *J = 11.7, 1.4* Hz, 1 H), 4.22 - 4.32 (m, 1 H) 4.88 (d, *J = 8.1* Hz, 1 H), 5.07-5.21 (m, 2 H), 7.07 (bs, 1H), 7.29 - 7.39 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.2, 26.8, 46.4, 57.7, 65.9, 67.2, 68.8, 127.7, 128.1, 128.6, 136.3, 155.2, 175.7; HRMS (ESI-TOF) calculated for $[C_{15}H_{20}N_2O_2+H]^+$ 293.1496, found 293.1498.

Synthesis of compound 5a

To a mixture of compound **4a** (106 mg, 0.36 mmol) and 3,4-dihydro-2*H*-pyran (100 µL, 1.08 mmol) in ethyl acetate (1 mL) was added anhydrous pyridinium *p*-toluenesulfonate (90 mg, 0.36

mmol) at room temperature and the reaction mixture was stirred for 12 h. After completion of the reaction, volatiles were removed under vacuum and the crude product obtained was directly purified by column chromatography using ethyl acetate-hexane (1:10) as eluent. The compound **5a** (98 mg, 72%) was obtained as colourless oil and as a mixture of diastereomers as indicated by NMR spectroscopy.

^{1}H NMR (400 MHz, $CDCl_3$) δ, 1.45 - 1.59 (m, 5 H), 1.63 - 1.72 (m, 3 H), 1.72 - 1.84 (m, 1 H), 2.04 - 2.26 (m, 1 H), 2.31 - 2.44 (m, 1 H), 2.58 (d, *J = 1.7* Hz, 1 H), 3.49 - 3.65 (m, 2 H), 2.70 (d, *J = 3.4* Hz, 2 H), 3.77 - 3.96 (m, 2 H), 4.28 - 4.42 (m, 1 H), 4.60 - 4.69 (m, 1 H), 5.02 - 5.17 (m, 2 H), 7.28 - 7.42 (m, 5 H); ^{13} C NMR (100 MHz, $CDCl_3$) δ, 19.0, 19.2 , 19.3, 22.6, 23.0, 23.0, 24.1, 25.3, 29.7, 30.6, 44.2, 45.2, 45.5, 46.6, 52.1, 52.4, 53.4, 53.9, 62.2, 62.4, 62.4, 62.6, 64.0, 64.5, 64.6, 65.0, 66.6, 66.7, 67.0, 67.1, 71.6, 71.8, 72.3, 72.4, 97.5, 97.6, 97.9, 127.7, 127.7 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.4, 136.1, 136.4, 136.8, 136.9, 154.1, 154.2, 154.4, 154.5, 174.0, 174.2, 174.4; HRMS (ESI-TOF) calculated for $[C_{20}H_{28}N_2O_5+H]^+$ 377.2071, found 377.2058.

Synthesis of compound 5b

A mixture of compound **4b** (249 mg, 0.85 mmol), DIEA (900 µL, 5.2 mmol) and DMAP (32 mg, 0.26 mmol) in dry DCM (5 mL) was treated dropwise with methoxymethyl chloride (275 µL, 3.5 mmol). The reaction mixture was allowed to stir for 24 h at room temperature. After completion of reaction, volatiles were removed under vacuum and the crude product obtained was directly purified by column chromatography using ethyl acetate-hexane (1:10) as eluent to get compound **5b** (215 mg, 75 %) as colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63 (s., 3 H), 1.91 (dd, *J = 14.2, 4.6* Hz, 1 H), 2.64 (dd, *J = 14.0, 1.4* Hz, 1 H), 2.84 (d, *J = 4.59* Hz, 3 H), 3.11 (s, 3H), 3.55 (dd, *J = 11.7, 3.8* Hz, 1 H), 3.73 (dd, *J = 11.7, 1.4* Hz, 1 H), 4.22 - 4.32 (m, 1 H) 4.88 (d, *J = 8.1* Hz, H), 5.07-5.21 (m, 2 H), 7.07 (bs, 1H), 7.29 - 7.39 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, 23.1, 29.7, 43.5, 53.7, 55.7, 65.7, 67.7, 72.4, 95.0, 128.0, 128.3, 128.5, 135.9, 156.0, 175.2; HRMS (ESI-TOF) calculated for $[C_{17}H_{24}N_2O_5+H]^+$ 337.1758, found 337.1752.

Synthesis of compound 6a

A solution of compound **6a** (0.24 mmol) in methanol (5 mL) was treated with 10% Pd/C (10 mg) and the reaction mixture was subjected to hydrogenation at 10 psi for 1 h. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to obtain amine as

gummy residue. The resultant amino amide in acetonitrile (5 mL) was added cbz-L-alanine (60 mg, 0.26 mmol) and triethylamine (70 µL, 0.51 mmol) followed by addition of HBTU (100 mg, 0.26 mmol). The reaction mixture was stirred for 24 h at room temperature and evaporated to a residue which was partitioned between ethyl acetate (10 mL) and brine (10 mL). The aqueous phase extracted with ethyl acetate (3 x 10 mL) and the combined organic phase was washed with 10% aqueous sodium bicarbonate, dried and evaporated to a residue that was purified by colunm chromatography using methanol-chloroform (3:97) as eluent to get the compound **6a** (53 mg, 50%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ, 0.74- 0.97 (m, 6 H), 1.32 - 1.44 (m, 3 H), 1.44 - 1.68 (m, 11 H), 1.71 (br. s., 3 H), 2.53 (s, 2H), 2.55 (s, 1H), 3.46 - 3.65 (m, 2 H), 3.70 - 3.97 (m, 3 H), 4.06 - 4.22 (m, 1 H), 4.40 - 4.63 (m, 2 H), 4.64 - 4.74 (m, 1 H), 4.77 (d, *J =3.6* Hz, 1 H), 5.06 - 5.22 (m, 2 H), 7.30 - 7.47 (m, 5 H); HRMS (ESI-TOF) calculated for $[C_{23}H_{33}N_3O_6+H]^+$ 448.2446, found 448.2422.

Synthesis of compound 6b

Compound **6b** was synthesied by following the same procedure discribed for compound **6a** using lactone **5b** as starting matarial. Yield (65 mg, 67%) as colourless oil.

(For complete NMR data see Table-6); HRMS (ESI-TOF) calculated for $[C_{20}H_{29}N_3O_6+H]^+$ 408.2129, found 408.2137.

Synthesis of compound 7a

To a stirred solution of compound **6a** (35 mg, 0.078 mmol) in methanol (100 µL) was added acetyl chloride (0.1 µL, 0.0016 mmol) at room temperature. The reaction mixture was stirred for 20 min at rt and then quenched upon addition of triethylamine (50 µL). The volatiles were removed by evaporation under vacuum and the residue was purified by silica gel column chromatography using methanol-chloroform (5:95) as eluent to provide compound **7a** (20 mg, 71 %) as colourless oil.

(For complete NMR data see Table-8); HRMS (ESI-TOF) calculated for $[C_{18}H_{25}N_3O_5+H]^+$ 364.1867, found 364.1861.

Synthesis of compound 7b

To a solution of compound **6b** (14 mg, 0.034 mmol) in methanol (400 µL) was added Dowex 50X strong acidic resin (28 mg, 0.068 mmol) and the mixture was stirred at 60 ºC for 6 h. The mixture

was then filtered resin was washed with methanol (1mL X 2) and the combined filtrate was evaporated to a residue which was purified by silica gel column chromatography using methanol-chloroform (5:95) as eluent to provide compound **7b** (10 mg, 81 %) as colourless oil.
(For complete NMR data see Table-9); HRMS (ESI-TOF) calculated for $[C_{18}H_{25}N_3O_5+H]^+$ 364.1867, found 364.1862.

Synthesis of compound 9

To a solution of *trans* L-4-hydroxyproline (2.0 gm, 15.26 mmol) in methanol (15 mL) was added thionyl chloride (1.2 mL,) drop-wise over a period of 5 min at 0 ºC. The reaction mixture was slowly warmed to room temperature over a period of 1 h and then stirred at 65 ºC for 12 h. After completion of the reaction, the volatiles were removed by evaporation under vacuum and the residue obtained was suspended in DCM (35 mL). To this suspension was added TEA (5.2 mL) followed by slow addition of Boc_2O () at 0 ºC and the reaction was stirred at room temperature for 1 h. After completion of the reaction as indicated by TLC, 10 % aqueous citric acid solution (35 mL) was added and the aqueous layer was further extracted with DCM (2 X 35 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated to a residue which was purified by silica gel column chromatography using ethyl acetate-hexane (2:8) as eluent.
To a solution of *trans* L-Na-Boc-4-hydroxyproline methyl ester (1.7 g, 6.94 mmol) in THF (50 mL) was added *p*-nitrobenzoic acid (4.64 g, 27.27 mmol) and triphenyl phosphine (7.14 g, 27.27 mmol). The reaction mixture was cooled to 0 0C and diethyl azodicarboxylate (DEAD, 4.4 mL, 27.27 mmol) was slowly added over 10 min. After being stirred at rt for 18 h, the reaction mixture was concentrated to give a thick yellow oil which was crystallized in a small amount of diethyl ether overnight and filtered. The filtrate was concentrated and purified by silica gel column chromatography using ethyl acetate-hexane (2:8) as eluent to give the PNBA ester as gummy solid (2.2 g, 85 %).

Synthesis of compound 10

To the stirred solution of compound **9** (1.14 g, mmol) in a mixture of THF-methanol (3:1, 40 mL) was added LiOH (3 eq.) dissolved in water (10 mL) and the reaction mixture was stirred at room temperature for 2 h. After completion of reaction as indicated by TLC, the solvent was removed under reduced pressure and the resulting residue was acidified with citric acid up to *p*H-3. This mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum to give the crude

product which was purified column chromatography using methanol-choroform (0.5:9.5) as eluent. The compound **10** (0.66 g, 90 %) was obtained as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ, 1.46 (s, 3 H), 1.42 (s, 4 H), 2.08 (dd, *J = 13.9, 7.5* Hz, 1 H), 2.32 (dddd, *J = 18.8, 14.1, 9.7, 4.5* Hz, 1 H), 3.46 - 3.58 (m, 1 H), 3.60 - 3.74 (m, 1 H), 3.78 (d, *J =5.3* Hz, 2 H), 4.25 - 4.42 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, 38.5, 52.5, 55.3, 70.2, 80.5, 153.7, 165.3; HRMS (ESI-TOF) calculated for $[C_{10}H_{17}NO_5+H]^+$ 232.1179, found 232.1183.

Synthesis of compound 11

To a stirring solution of compound **10** (100 mg, 0.43 mmol) and L-alanine N-methylamide (53 mg, 0.52 mmol) in acetonitrile (3 mL) was added triethylamine (120 µL, 0.86 mmol) followed by addition of HBTU (200 mg, 0.52 mmol).). After being stirred for 24 h at room temperature, the reaction mixture was evaporated to a residue which was partitioned between ethyl acetate (20 mL) and brine (20 mL). The aqueous phase was further extracted with ethyl acetate (3 x 20 mL) and the combined organic phase was washed with 10% aqueous citric acid, dried and evaporated to residue that was purified by column chromatography using methanol-chloroform (5:95) as eluent to get compound **11** (95 mg, 50%) as gummy solid.

(For complete NMR data see Table-10); HRMS (ESI-TOF) calculated for $[C_{10}H_{17}NO_5+H]^+$ 316.1867, found 316.1872.

Synthesis of compound 12

To a stirring solution of compound **10** (100.0 mg, 0.43 mmol) and methylamine (53 mg, 0.52 mmol 1M solution in THF) in acetonitrile (3 mL) was added triethylamine (120 µL, 0.86 mmol) followed by addition of HBTU (200 mg, 0.52 mmol).). After being stirred for 24 h at room temperature, the reaction mixture was evaporated to a residue which was partitioned between ethyl acetate (20 mL) and brine (20 mL). The aqueous phase was further extracted with ethyl acetate (3 x 20 mL) and the combined organic phase was washed with 10% aqueous citric acid, dried and evaporated to a residue that was purified by column chromatography using methanol-chloroform (5:95) as eluent to get compound **12** (80 mg, 76 %) as colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 9 H), 2.08 - 2.23 (m, 1 H), 2.33 (d, *J = 14.0* Hz, 1 H), 2.85 (d, *J = 4.5* Hz, 3 H), 3.41 - 3.58 (m, 2 H), 4.30 - 4.43 (m, 2 H), 5.40 (d, *J = 8.8* Hz, 1 H), 6.97 - 7.11 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ, 26.5, 28.4, 35.8, 53.4, 57.1, 59.6, 70.7, 80.7, 155.6, 173.9; HRMS (ESI-TOF) calculated for $[C_{10}H_{17}NO_5+H]^+$ 245.1496, found 245.1498.

Synthesis of compound 13

The compound **12** (33 mg, 0.15 mmol) was treated with 50% trifluoroacetic acid in dichloromethane (2 mL) at 0ºC and the reaction mixture was warmed up to room temperature for 2 h. The reaction mixture was evaporated to residue which was triturated with cold diethyl ether (2 mL). The diethyl ether was removed and the residue was suspended in acetonitrile (2 mL). To the stirred suspension was added cbz-L-alanine (41 mg, 0.18 mmol) and triethylamine (120 µL, 0.86 mmol) followed by addition of HBTU (200 mg, 0.52 mmol). After being stirred for 24 h at room temperature, the reaction mixture was evaporated to a residue which was partitioned between ethyl acetate (20 mL) and brine (20 mL). The aqueous phase was further extracted with ethyl acetate (3 x 20 mL) and the combined organic phase was washed with 10% aqueous citric acid, dried and evaporated to a residue that was purified by column chromatography using methanol-chloroform (5:95) as eluent to get compound **13** (37 mg, 90%) as colourless oil.

(For complete NMR data see Table-11); HRMS (ESI-TOF) calculated for $[C_{17}H_{23}N_3O_5+H]^+$ 350.1710, found 350.1713.

NMR Studies:

NMR spectra were acquired on 300, 500 and 700 MHz spectrometers at room temperature or else as mentioned, of 5-10 mM concentration of peptides in appropriate solvents with TMS as an internal standard or the solvent signals as secondary standard and the chemical shifts (*δ)* are shown in ppm scales. Multiplicities of NMR signals are designated as s (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *br* (broad), *td* (triplet of a doublet), *dt* (doublet of a triplet) and *m* (multiplet, for unresolved lines). ^{13}C spectra were recorded at 125 and 175 MHz with complete proton decoupling. The proton resonance assignments were carried out using ^{1}H-^{1}H Two-dimensional Correlation spectroscopy (COSY) and total correlation spectroscopy (TOCSY)[2]. The TOCSY experiments were performed with mixing time of 0.08s, and spin-locking field of 10 kHz. Spatial correlations were obtained by performing two-dimensional ROESY experiments. ROESY experiments were performed by using a mixing time of 200 ms, which was selected after acquiring series of ROESY spectra at different mixing times *i.e*., 100 ms, 150mS, 200ms, 250ms and 300 ms. The measured volumes of some of the rOes vs variable mixing times were plotted. Homonuclear two-dimensional experiments were carried out in the phase sensitive mode. The spectra were acquired with 1024x256 or 2048x192 free induction decays (FID) containing 8-16 transients with relaxation delay 1-2 s, and the spectra were processed with Gaussian apodization in both the dimensions. Heteronuclear two-dimensional ^{1}H-^{13}C spectra *i.e*., HSQC and HMBC were collected using standard pulse sequences.[3] The spectra were acquired with 1024x256 FID containing 8-16

transients with the spectral width of 8 ppm in F2 dimension and 200 ppm in F1 dimension. Variable temperature (VT) studies were carried out with temperature intervals of 10°K from 303°K - 343°K. Deviations in the chemical shift positions per degree Kelvin was calculated and reported as $\Delta\delta/\Delta T$ (ppb/°K).

Table 1: Important rOe's with chemical shifts (δ in ppm) for all the studied peptides.

Compound No.	**Important rOe's with chemical shift**
2a	**PC$_{\alpha}$Me** (1.70)↔ PC$_{\beta}$H$_{(pro\text{-}R)}$ (2.07)strong, PC$_{\beta}$H$_{(pro\text{-}S)}$ (2.49)medium & PC$_{\delta}$H$_{(pro\text{-}S)}$ (3.57)weak **PC$_{\gamma}$H** (4.33)↔ PC$_{\beta}$H$_{(pro\text{-}R)}$ (2.07)/ PC$_{\beta}$H$_{(pro\text{-}S)}$ (2.49)strong & PC$_{\delta}$H$_{(pro\text{-}S)}$ (3.57)/ PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.91)strong **PC$_{\delta}$H$_{(pro\text{-}S)}$** (3.57)↔ PC$_{\beta}$H$_{(pro\text{-}R)}$ (2.07)strong
2b	**PC$_{\alpha}$Me** (1.56)↔ PC$_{\beta}$H$_{(pro\text{-}S)}$ (2.01)strong, PC$_{\beta}$H$_{(pro\text{-}R)}$ (2.37)medium, PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.49)strong & PC$_{\gamma}$H (4.40)weak **PC$_{\gamma}$H** (4.40)↔ PC$_{\beta}$H$_{(pro\text{-}S)}$ (2.01)/ PC$_{\beta}$H$_{(pro\text{-}R)}$ (2.36)strong & PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.49)/ PC$_{\delta}$H$_{(pro\text{-}S)}$ (3.87)strong P**C$_{\delta}$H$_{(pro\text{-}R)}$** (3.49)↔ PC$_{\beta}$H$_{(pro\text{-}S)}$ (2.01)strong **PC$_{\delta}$H$_{(pro\text{-}S)}$** (3.87)↔ Ph-CH$_2$(5.13)Medium
3	**PC$_{\alpha}$Me** (1.56)↔ PC$_{\beta}$H$_{(pro\text{-}S)}$ (2.00)strong, PC$_{\beta}$H$_{(pro\text{-}R)}$ (2.36)medium & PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.60)medium **PC$_{\gamma}$H** (4.44)↔ PC$_{\beta}$H$_{(pro\text{-}S)}$ (2.00)/ PC$_{\beta}$H$_{(pro\text{-}R)}$ (2.36)strong & PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.60)/ PC$_{\delta}$H$_{(pro\text{-}S)}$ (3.75)strong **PC$_{\delta}$H$_{(pro\text{-}R)}$** (3.60)↔ PC$_{\beta}$H$_{(pro\text{-}S)}$ (2.00)strong **Ac-CH$_3$**(2.10)↔ PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.60)/ PC$_{\delta}$H$_{(pro\text{-}S)}$ (3.75)strong
6b	**PC$_{\alpha}$Me** (1.65)↔ PC$_{\beta}$H$_{(pro\text{-}S)}$ (1.91)strong, PC$_{\beta}$H$_{(pro\text{-}R)}$ (2.84)medium, PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.90)weak & PC$_{\gamma}$H (4.32)weak **PC$_{\gamma}$H** (4.32)↔ PC$_{\beta}$H$_{(pro\text{-}S)}$ (1.91)/ PC$_{\beta}$H$_{(pro\text{-}R)}$ (2.84)strong, PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.90)/ PC$_{\delta}$H$_{(pro\text{-}S)}$ (3.69)strong & PC$_{\alpha}$Me (1.65) weak **PC$_{\delta}$H$_{(pro\text{-}R)}$** (3.90)↔ PC$_{\beta}$H$_{(pro\text{-}S)}$ (2.91)medium **AC$_{\beta}$H** (1.41)↔ PC$_{\delta}$H$_{(pro\text{-}S)}$ (3.69)strong & PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.90)weak **AC$_{\alpha}$H** (4.49)↔ PC$_{\delta}$H$_{(pro\text{-}S)}$ (3.69)strong & PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.90)strong
7a	**PC$_{\alpha}$Me** (1.41)↔ PC$_{\beta}$H$_{(pro\text{-}R/S)}$ (1.94)strong, PC$_{\delta}$H$_{(pro\text{-}S)}$ (3.71)weak & PC$_{\gamma}$H (4.27)medium **PC$_{\gamma}$H** (4.27)↔ PC$_{\beta}$H$_{(pro\text{-}R/S)}$ (1.94)strong, PC$_{\delta}$H$_{(pro\text{-}S)}$ (3.71)strong & PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.55)medium **NMe$_{NH}$**(7.11) ↔ PC$_{\alpha}$Me (1.41)strong, PC$_{\beta}$H$_{(pro\text{-}R/S)}$ (1.94)medium, PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.55)medium, Ph-CH$_2$(5.05)weak & P-OH(5.27)weak **AC$_{\beta}$H** (1.15)↔ PC$_{\delta}$H$_{(pro\text{-}S)}$ (3.71)strong & PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.55)weak **AC$_{\alpha}$H** (4.23)↔ PC$_{\delta}$H$_{(pro\text{-}S)}$ (3.71)strong & PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.55)strong
7b	**PC$_{\alpha}$Me** (1.65)↔ PC$_{\beta}$H$_{(pro\text{-}S)}$ (1.95)strong, PC$_{\beta}$H$_{(pro\text{-}R)}$ (2.45)medium, PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.68)medium **PC$_{\gamma}$H** (4.33)↔ PC$_{\beta}$H$_{(pro\text{-}S)}$ (1.95)/ PC$_{\beta}$H$_{(pro\text{-}R)}$ (2.45)strong, PC$_{\delta}$H$_{(pro\text{-}R)}$ (3.68)strong & PC$_{\delta}$H$_{(pro\text{-}S)}$ (3.75)strong

	PCδH$_{(pro\text{-}R)}$ (3.68)↔ PCβH$_{(pro\text{-}S)}$ (1.95)medium **ACβH** (1.37)↔ PCδH$_{(pro\text{-}S)}$ (3.75)strong & PCδH$_{(pro\text{-}R)}$ (3.68)medium **ACαH** (4.41)↔ PCδH$_{(pro\text{-}S)}$ (3.75)strong & PCδH$_{(pro\text{-}R)}$ (3.68)strong
11	**Boc-CH$_3$**(1.48)↔ PCδH$_{(pro\text{-}R)}$ (3.45)medium & PCδH$_{(pro\text{-}S)}$ (3.55)medium
13	**PαH**(4.63)↔ PCβH$_{(pro\text{-}R)}$ (2.16)strong & PCβH$_{(pro\text{-}S)}$ (2.31)strong **PCγH** (4.50)↔ PCβH$_{(pro\text{-}R)}$ (2.16)strong, PCβH$_{(pro\text{-}S)}$ (2.31)strong, PCδH$_{(pro\text{-}S)}$ (3.65)strong & PCδH$_{(pro\text{-}R)}$ (3.81)strong **P-OH**(5.71)↔ PCβH$_{(pro\text{-}S)}$ (2.31)weak & PCδH$_{(pro\text{-}S)}$ (3.65)weak **ACβH** (1.39)↔ PH$\delta_{pro\text{-}S}$(3.65)strong **ACαH** (4.44)↔ PCδH$_{(pro\text{-}S)}$ (3.65)strong & PCδH$_{(pro\text{-}R)}$ (3.81)strong

ROE build-up rate:

For identifying the suitable mixing time, ROESY spectra at different mixing times i.e., 100ms, 150ms, 200ms, 250ms and 300 ms were acquired on a 700 MHz NMR spectrometer. The fids with different mixing time were processed by using NMR pipe software. Volumes were measured along with peak intensity by summation of the intensity in a defined area around the center of the peak. Four peaks were selected and a graph was plotted between peak intensity vs mixing times and is given below in the figure A.

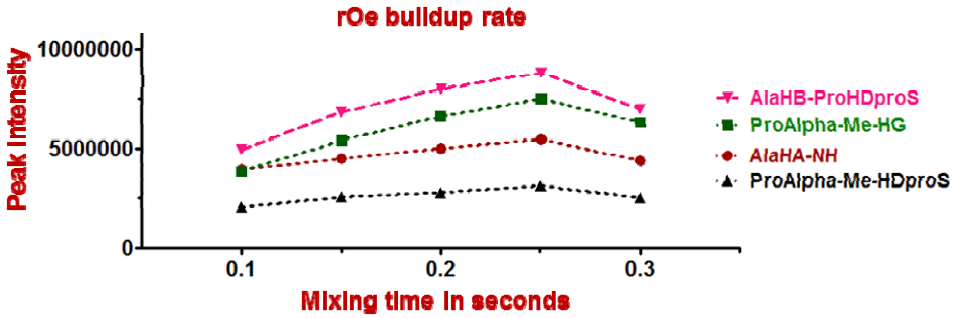


Figure A: rOe build-up cure

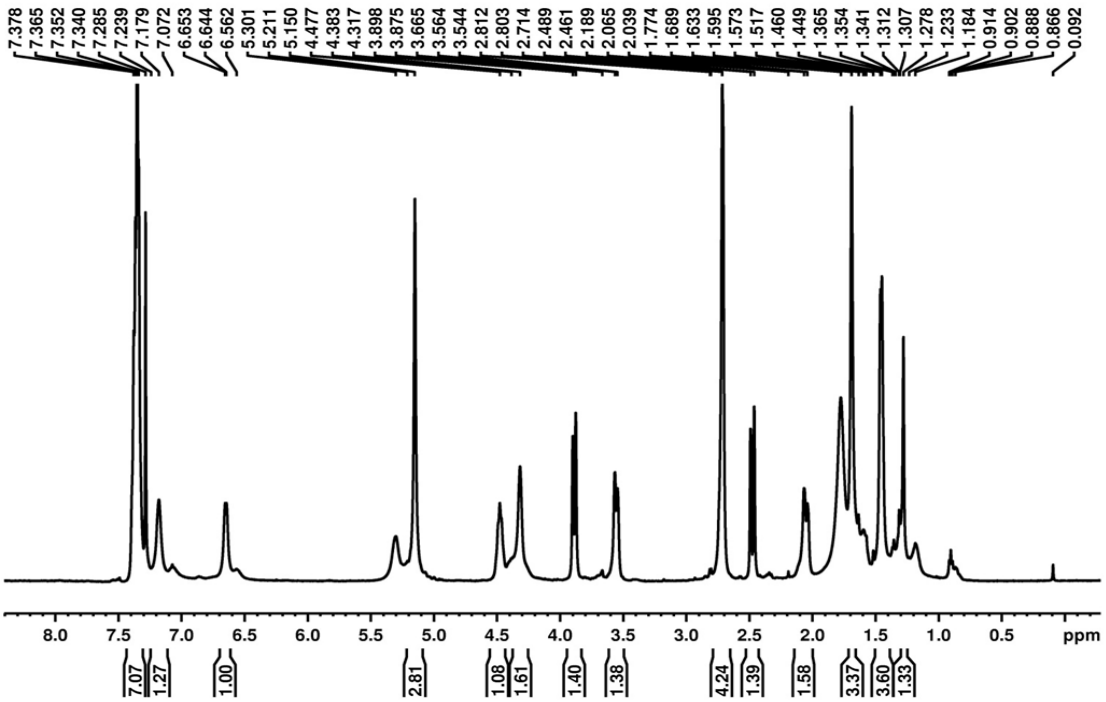


Figure 1: ^{1}H NMR spectrum of peptide **2a** (500MHz, $CDCl_3$, 300 K)

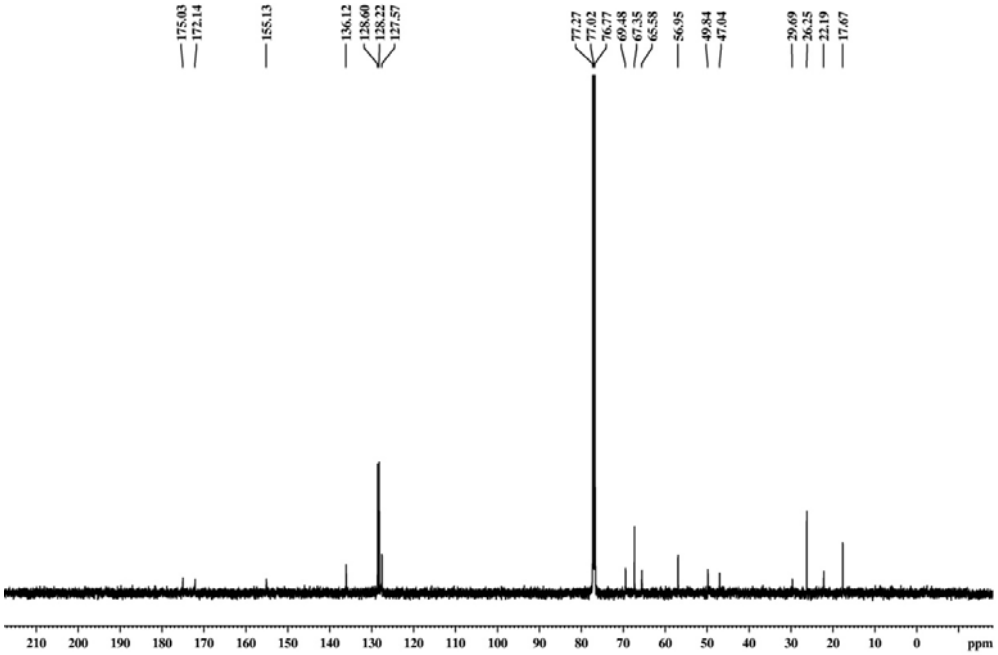


Figure 2: ^{13}C NMR spectrum of peptide **2a** (500MHz, $CDCl_3$, 300 K)

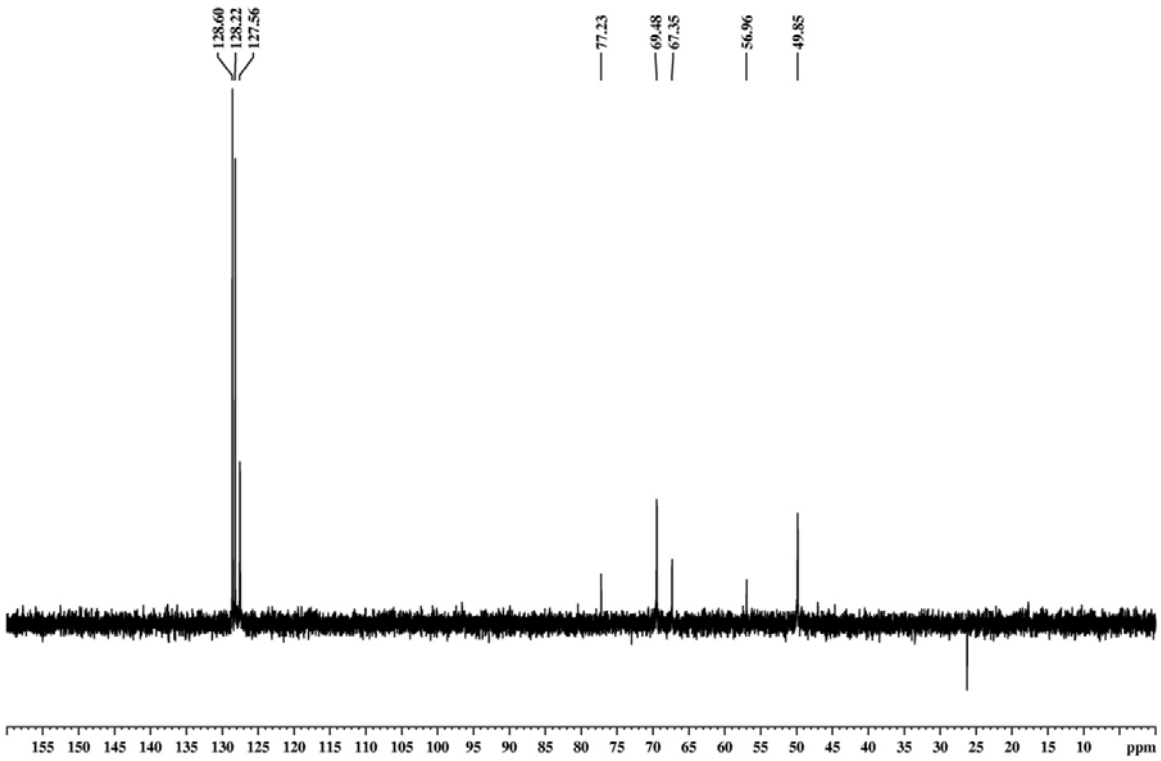


Figure 3: ^{13}C-Dept 90 NMR spectrum of peptide **2a** (500MHz, $CDCl_3$, 300 K)

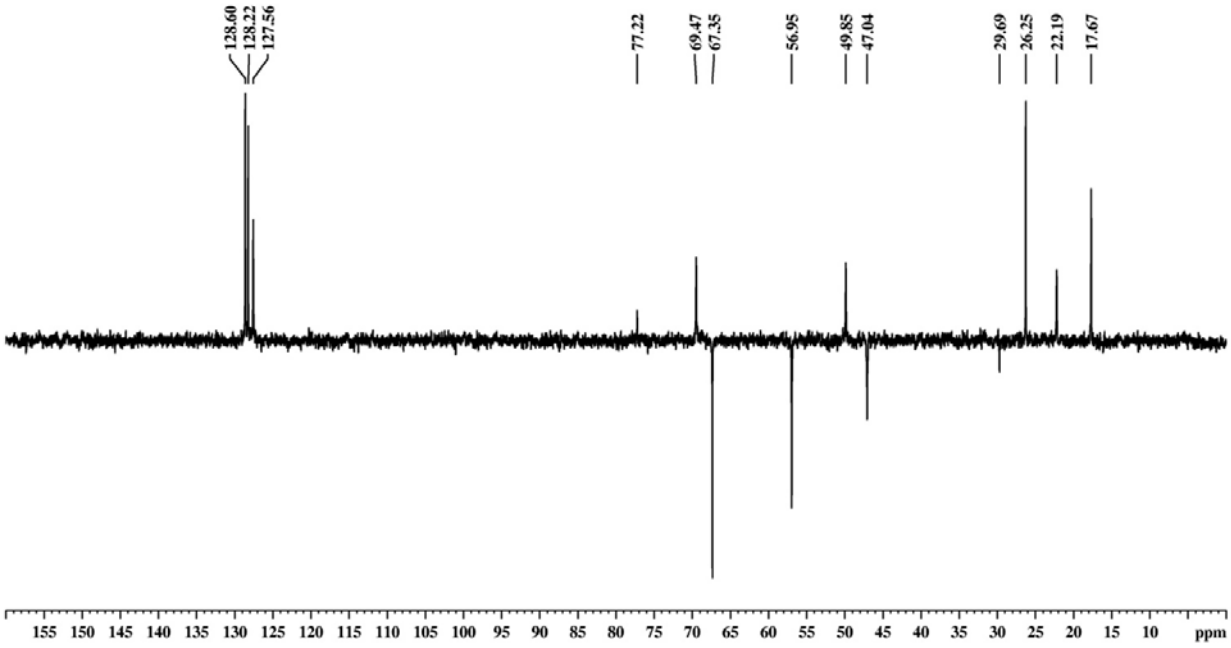


Figure 4: ^{13}C-Dept 135 NMR spectrum of peptide **2a** (500MHz, $CDCl_3$, 300 K)

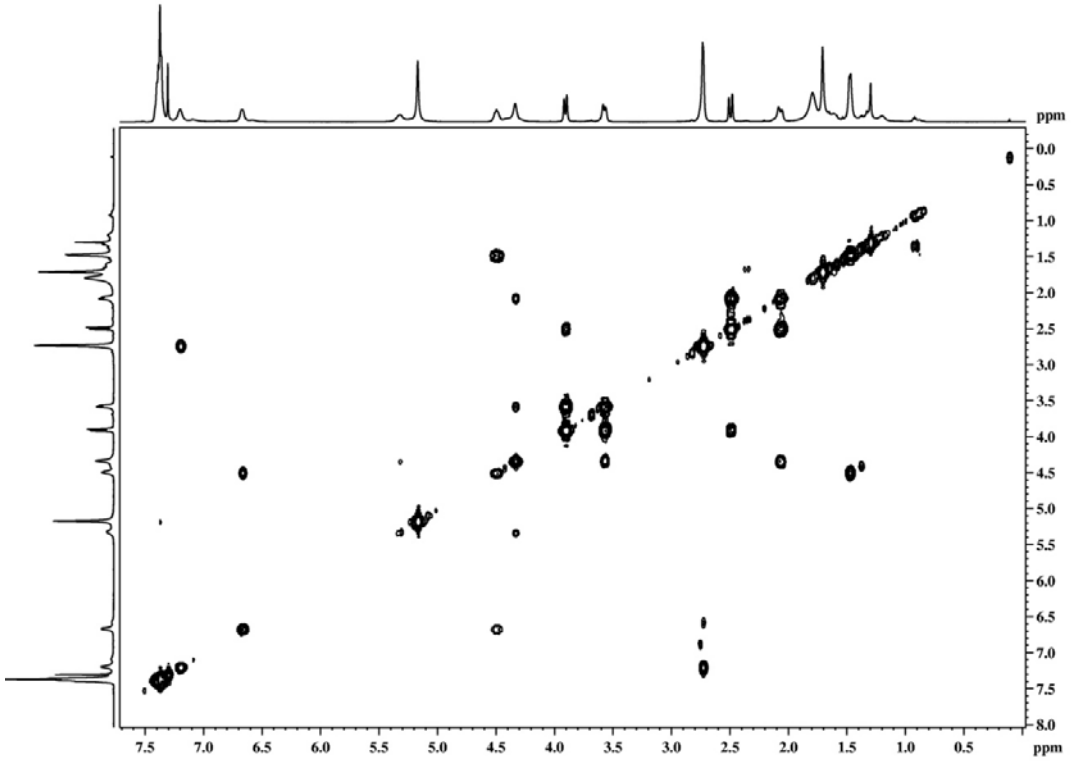


Figure 5: 2D-COSY NMR spectrum of peptide **2a** (500MHz, $CDCl_3$, 300 K)

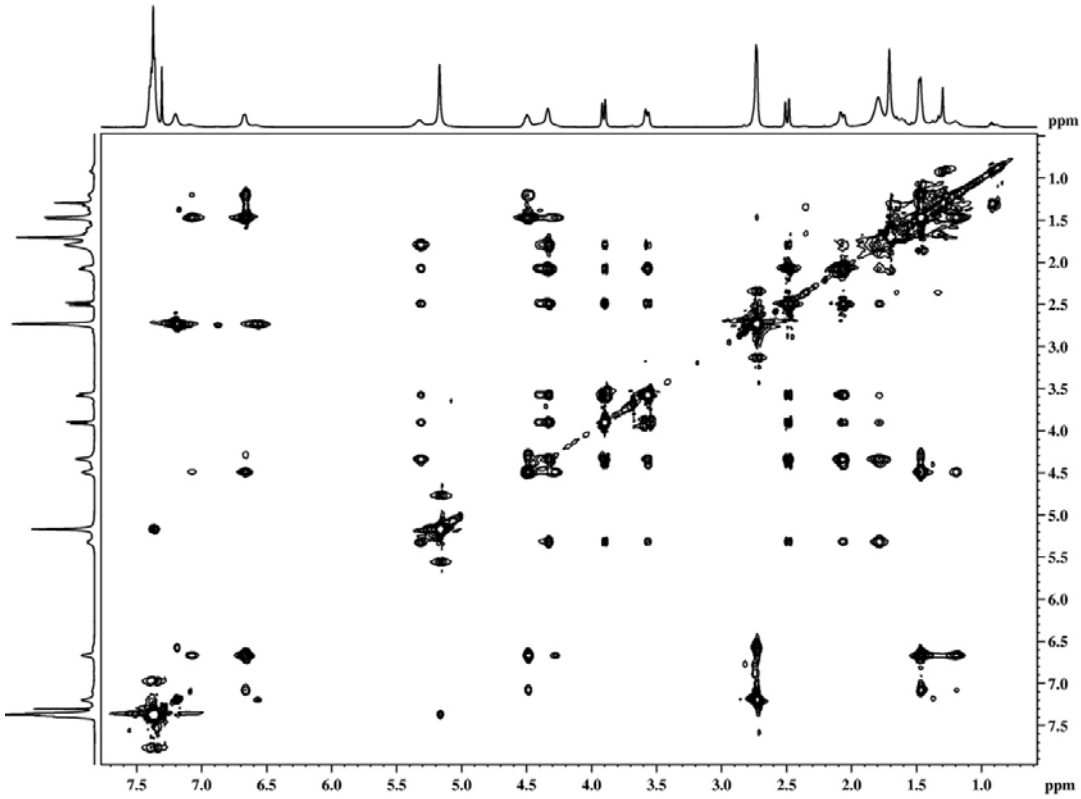


Figure 6: 2D-TOCSY NMR spectrum of peptide **2a** (500MHz, $CDCl_3$, 300 K)

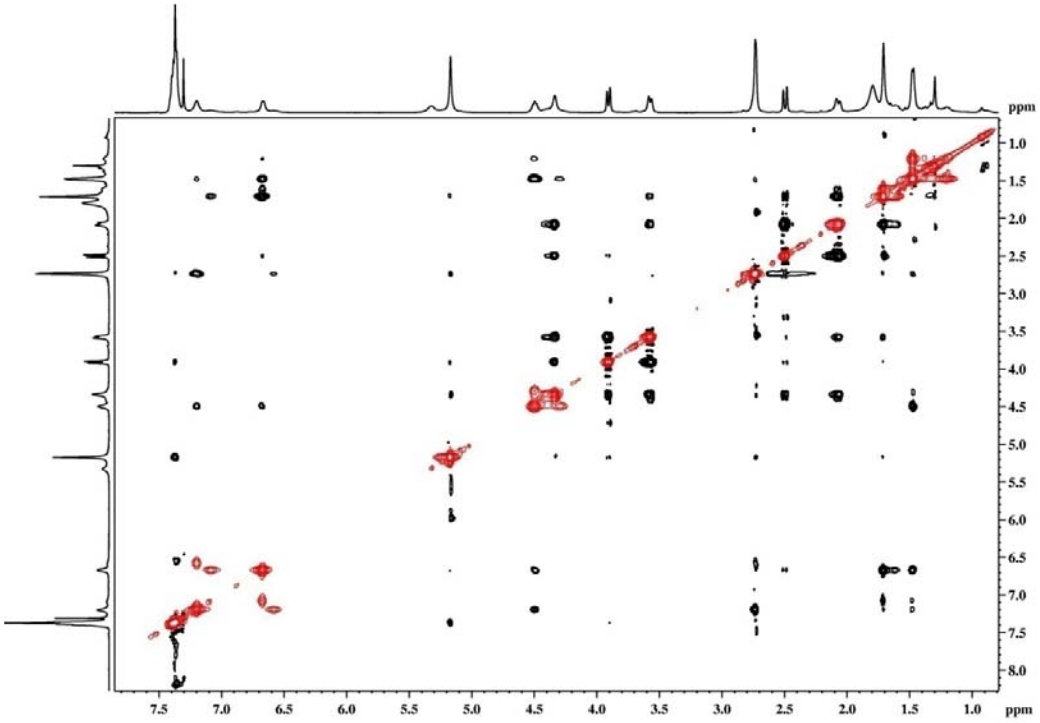


Figure 7: 2D-ROESY NMR spectrum of peptide **2a** (500MHz, $CDCl_3$ 300 K)

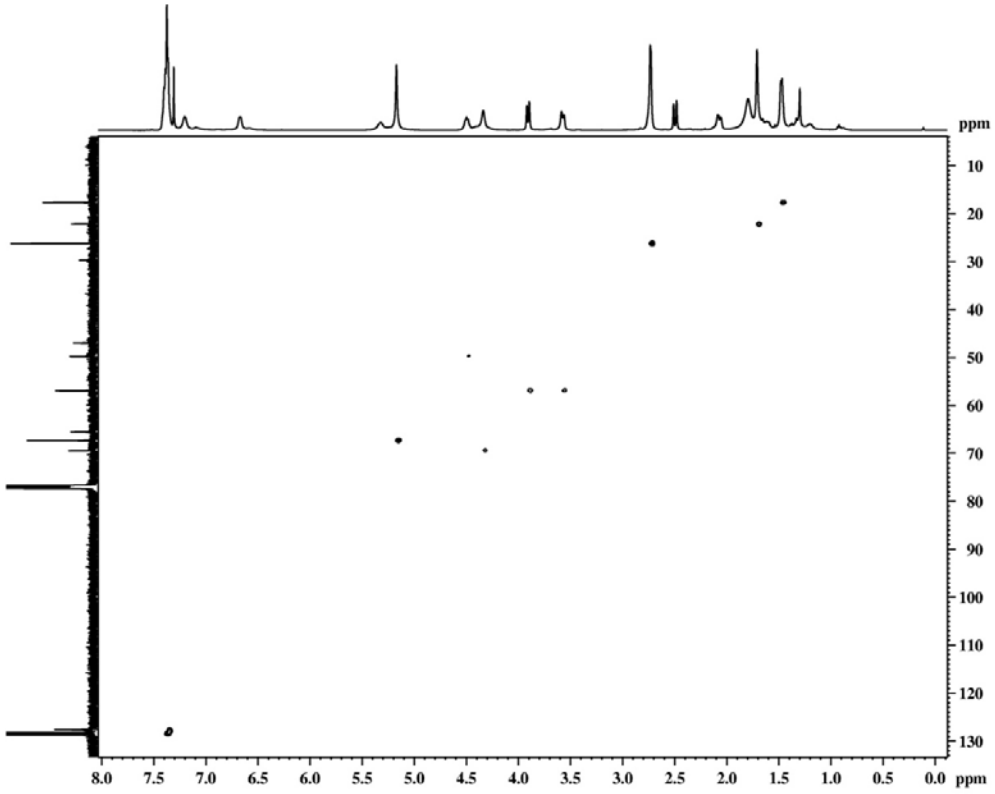


Figure 8: 2D-HSQC NMR spectrum of peptide **2a** (500MHz, $CDCl_3$, 300 K)

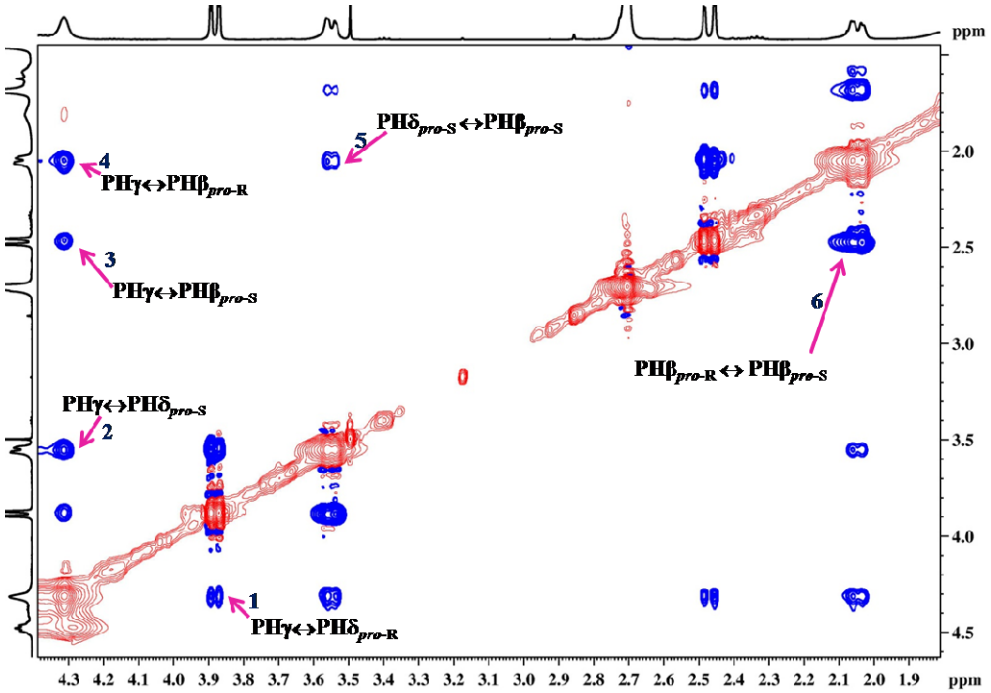


Figure 9: 2D-ROESY expansion spectrum of peptide **2a** (500MHz, $CDCl_3$, 300 K)

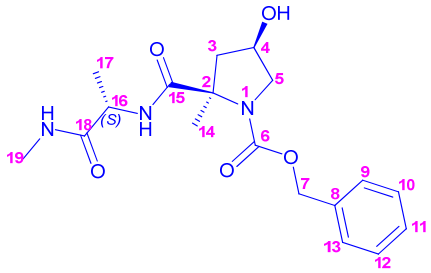


Table 2: ^{1}H chemical shifts (δ in ppm) and coupling constants (J in Hz) for peptide **2a** (500 MHz, $CDCl_3$, 300 K)

Residue/ Protons	**NMe**	**Pro**	**Ala**
NH	7.18, (*br*)	-	6.65 (*d*, $^3J_{NH\text{-}C\alpha H}$ = 7.0)
CαH	-	-	4.46 (*m*)
CβH$_{(pro\text{-}S)}$/ CβH$_{(pro\text{-}R)}$	-	2.07 (*dd*, $^3J_{C\gamma H\text{-}C\beta H}$ = 4.4, 14.2)/ 2.49 (*dd*, $^3J_{C\gamma H\text{-}C\beta H}$ = 2.4, 14.2)	1.45, (*d*, $^3J_{C\alpha H\text{-}C\beta H}$ = 6.9)
CγH	-	4.33 (*m*)	
CδH$_{(pro\text{-}S)}$/ CδH$_{(pro\text{-}R)}$	-	3.57,(*dd*, $^3J_{C\delta H\text{-}C\gamma H}$ = 2.3,12.0) /3.91,(*dd*, $^3J_{C\delta H\text{-}C\gamma H}$ = 2.8,12.0)	
Others :- Pro-OH = 5.34 (*br*), N-Me = 2.73, (*d* $^3J_{CNH\text{-}CMe\text{-}H}$ = 4.0), Pro-CαMe = 1.68, (*s*), Ph-CH_2(2H) = 5.17,(*s*), Ph-H(5H) = 7.42-7.33, (*m*)			
Carbons: 2C=65.6, 3C=47.1, 4C=69.5, 5C=57.0, 6C=155.1, 7C=67.4, 8C=136.1, 9C=128.6, 10C=128.2, 11C=127.6, 14C=22.2, 15C=175.1, 16C=50.0, 17C=17.7, 18C=172.1, 19C=26.3			

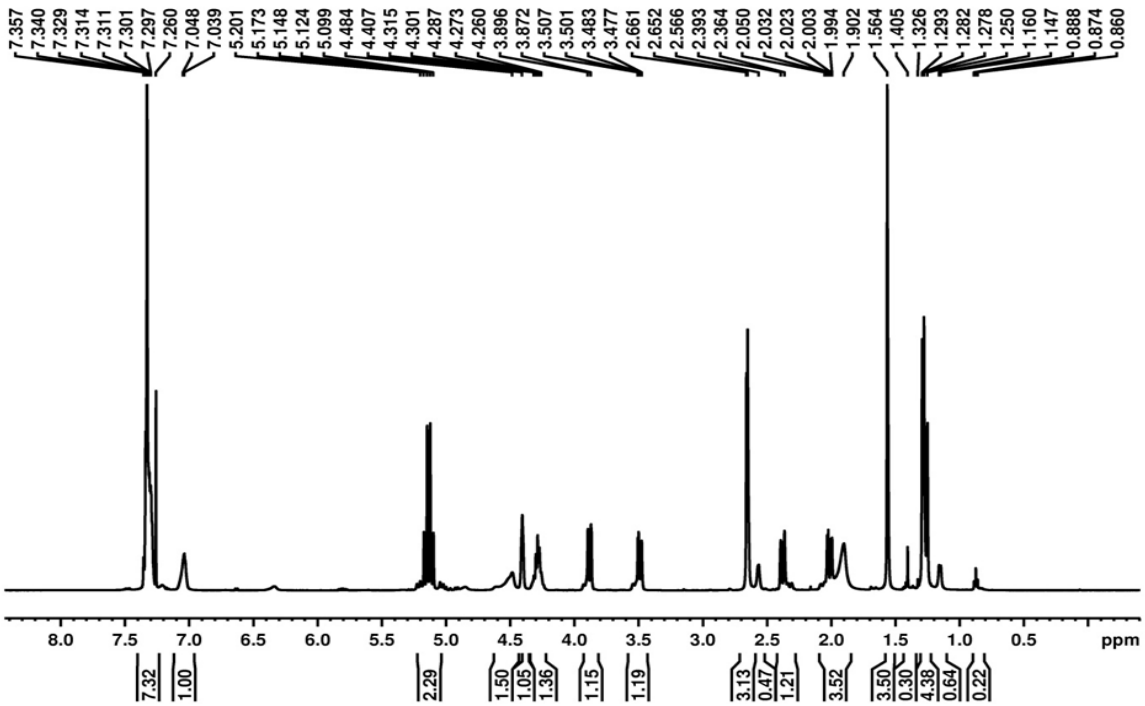


Figure 10: ^{1}H NMR spectrum of peptide **2b** (500MHz, $CDCl_3$, 300 K)

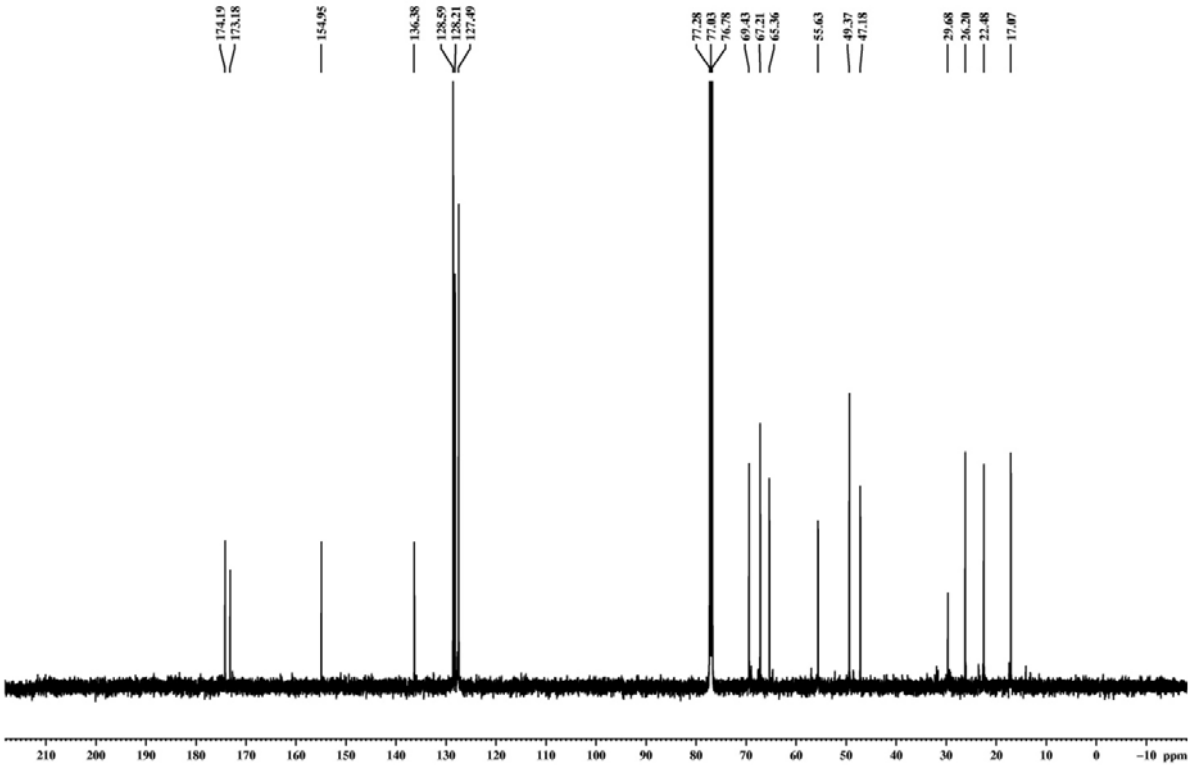


Figure 11: ^{13}C NMR spectrum of peptide **2b** (500MHz, $CDCl_3$, 300 K)

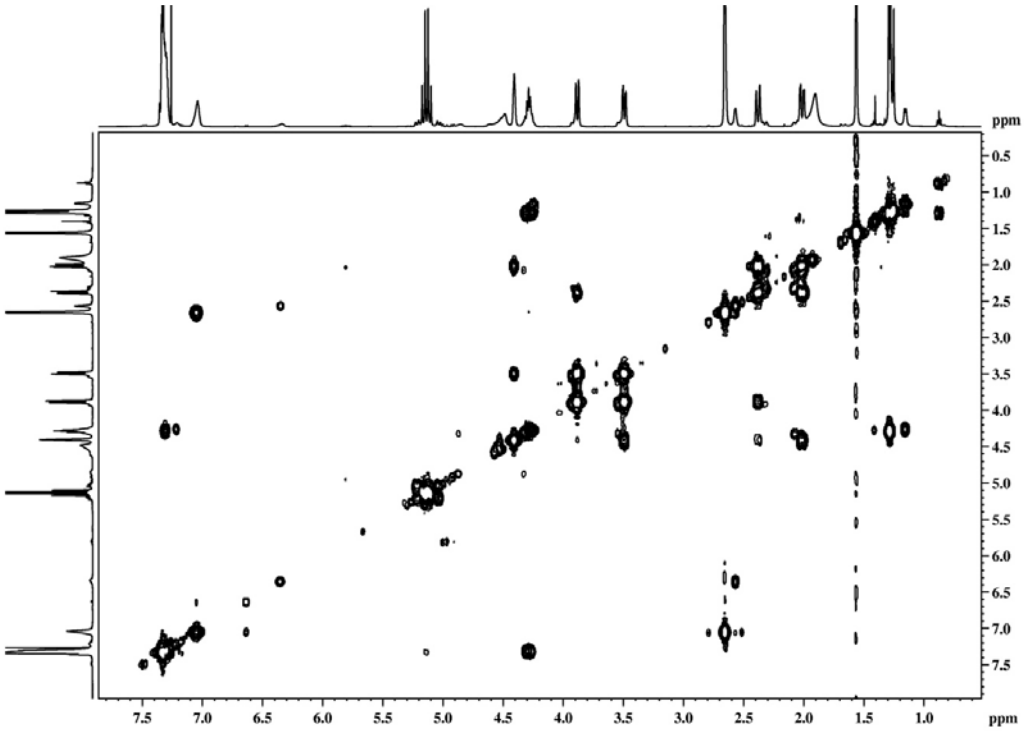


Figure 12: 2D-COSY NMR spectrum of peptide **2b** (500MHz, $CDCl_3$, 300 K)

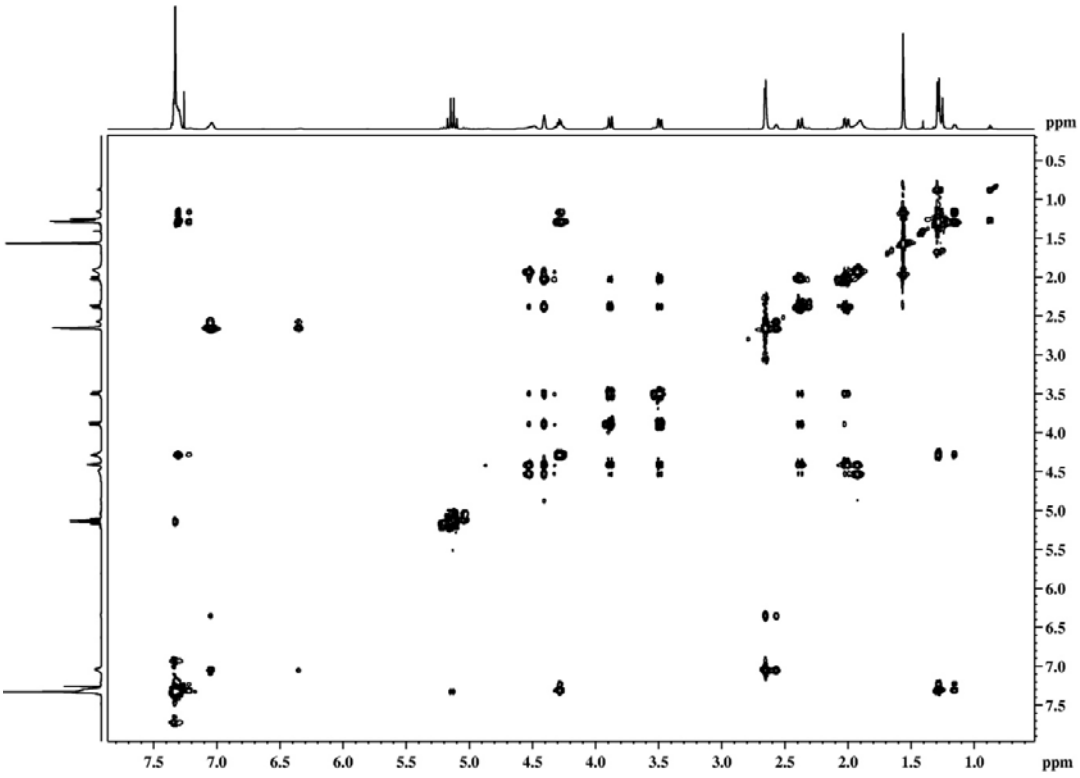


Figure 13: 2D-TOCSY NMR spectrum of peptide **2b** (500MHz, $CDCl_3$ 300 K)

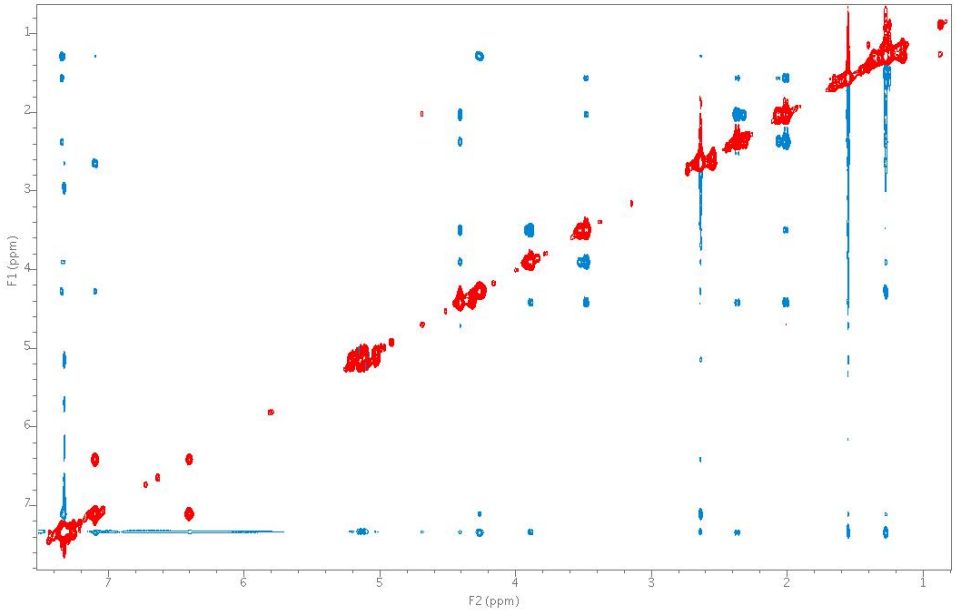


Figure 14: 2D-ROESY NMR spectrum of peptide **2b** (700MHz, DMSO-d_6)

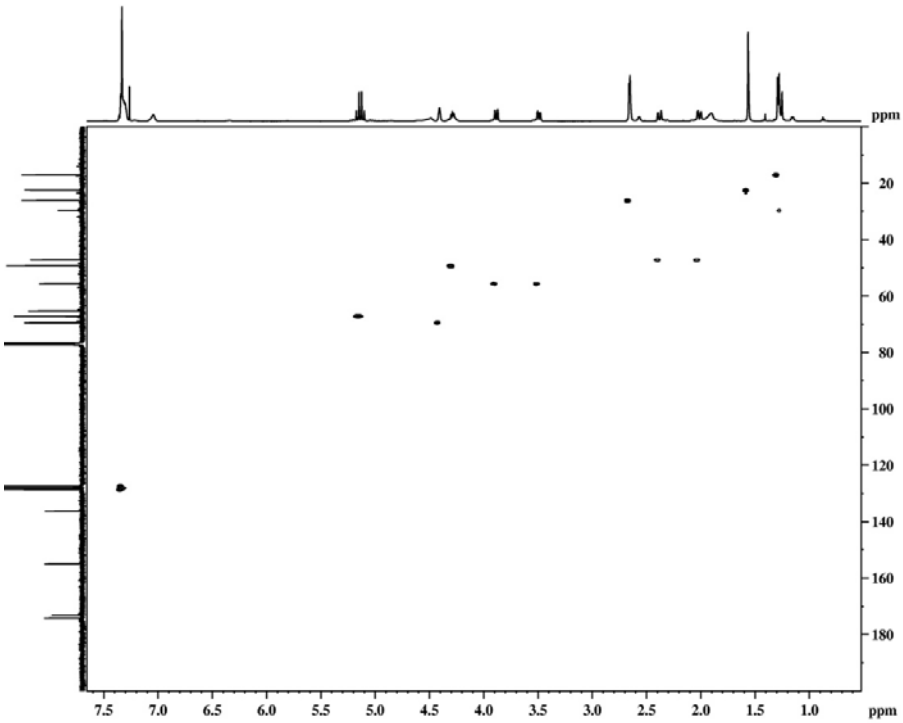


Figure 15: 2D-HSQC NMR spectrum of peptide **2b** (500MHz, $CDCl_3$, 300 K)

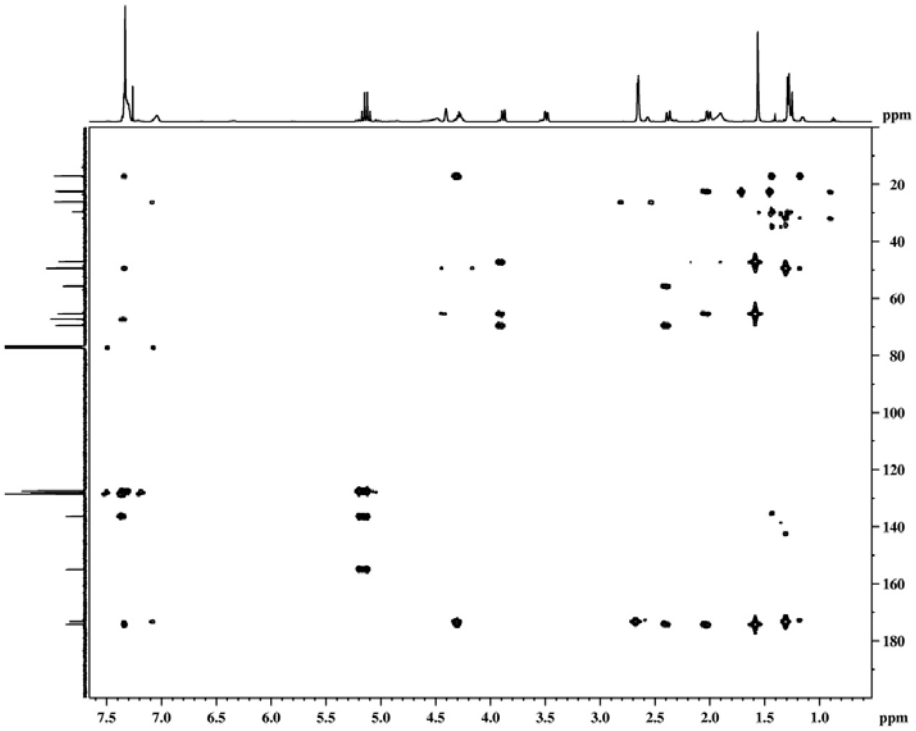


Figure 16: 2D-HMBC NMR spectrum of peptide **2b** (500MHz, $CDCl_3$, 300 K)

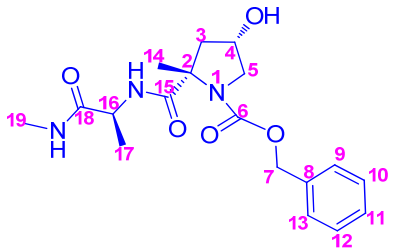


Table 3: ^{1}H chemical shifts (δ in ppm) and coupling constants (J in Hz) for peptide **2b** (500 MHz, $CDCl_3$, 300K)

Residue/ Protons	**NMe**	**pro**	**Ala**
NH	7.08, (*br*)	-	7.30, (*br*)
CαH	-	-	4.27,(*m*)
CβH$_{(pro\text{-}S)}$/ CβH$_{(pro\text{-}R)}$	-	2.01(*dd*, $^3J_{C\gamma H\text{-}C\beta H}$ = 4.3, 15.0)/ 2.37(*dd*, $^3J_{C\gamma H\text{-}C\beta H}$ = 2.4, 15.0)	1.28, (*d*, $^3J_{C\alpha H\text{-}C\beta H}$ = 6.9)
CγH/	-	4.40(*m*)	
CδH$_{(pro\text{-}R)}$/ CδH$_{(pro\text{-}S)}$	-	3.49,(*dd*, $^3J_{C\delta H\text{-}C\gamma H}$= 3.0, 12.1) /3.87,(*dd*, $^3J_{C\delta H\text{-}C\gamma H}$ = 1.7, 12.1)	
Others : Pro-OH= 4.50 (*br*), N-Me = 2.67 (*d*,$^3J_{CNH\text{-}CMe\text{-}H}$ = 4.7), Pro-Me = 1.56, (*s*), Ph-CH_2(2H) = 5.13,(*m*) Ph-H(5H) = 7.34-7.27, (*m*),			
Carbons: 2C=65.3, 3C=47.1, 4C=69.4, 5C=55.6, 6C=154.9, 7C=67.2, 8C=136.3, 9C =128.5, 10C=127.4, 11C=128.2, 12C=127.4, 13C=128.5, 14C=22.4, 15C=174.2, 16C=49.3, 17C=17.0, 18C=173.2, 19C=26.1 ** $\Delta\delta/\Delta T$ (ppb) of **NMe-HN = 4.6**			

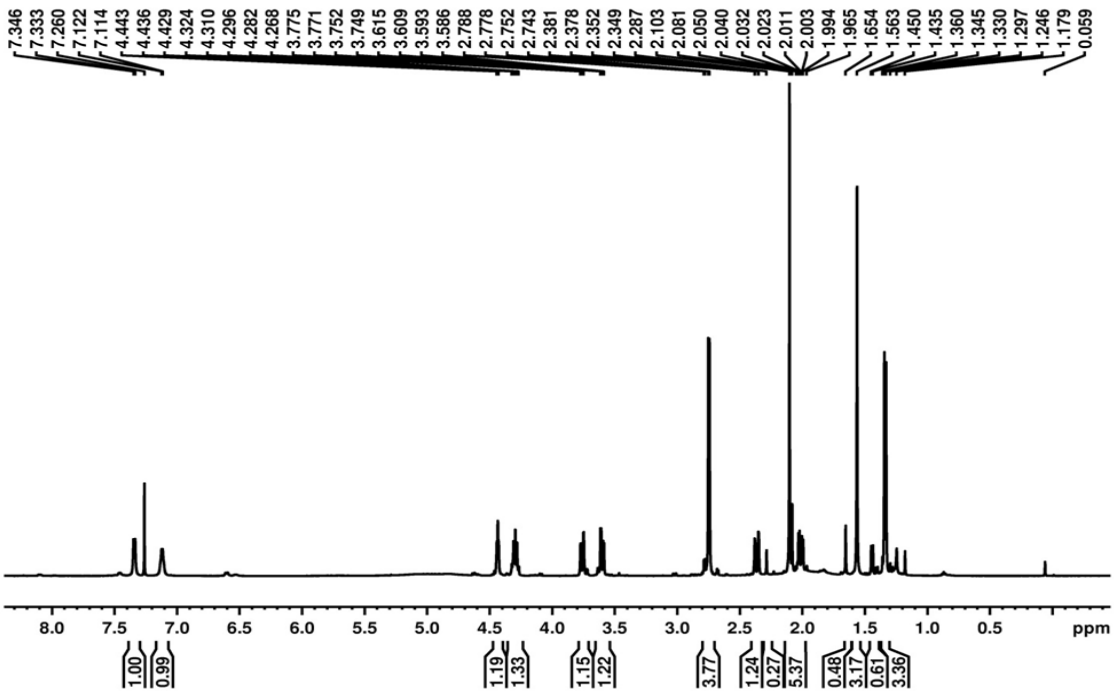


Figure 17: ^{1}H NMR spectrum of peptide **3** (500MHz, $CDCl_3$, 300 K)

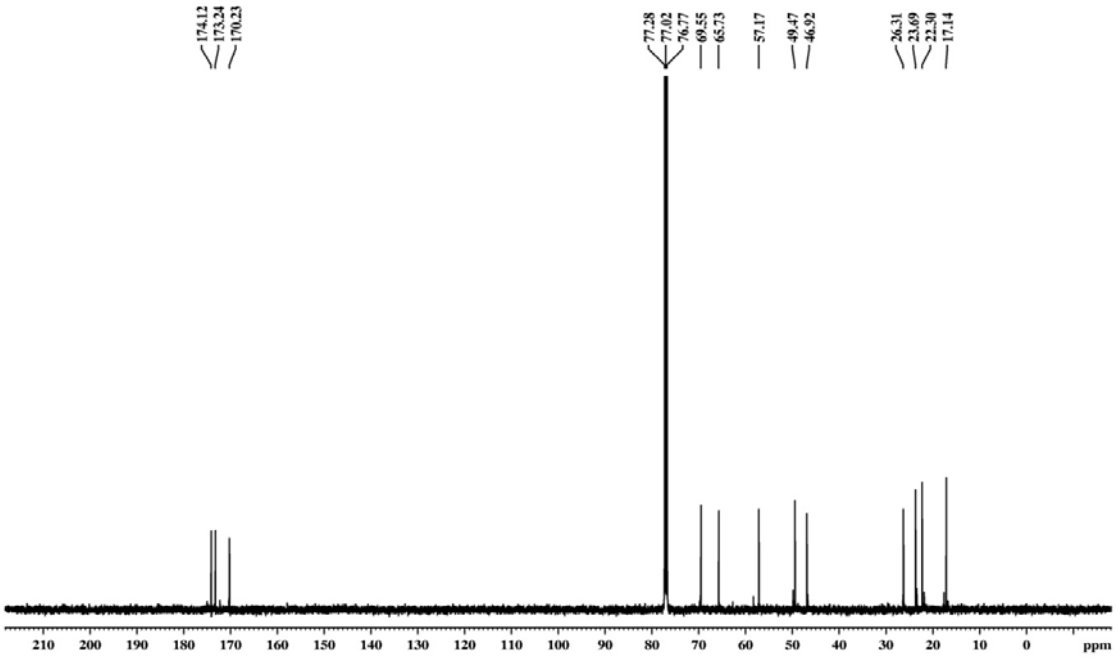


Figure 18: ^{13}C NMR spectrum of peptide **3** (500MHz, $CDCl_3$, 300K)

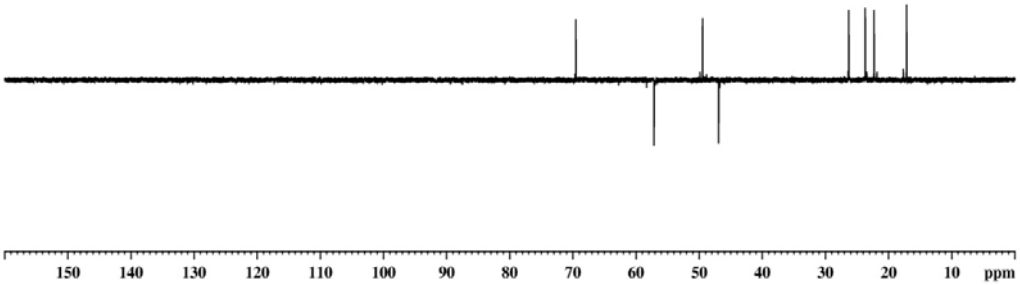


Figure 19: ^{13}C Dept 135 NMR spectrum of peptide **3** (500MHz, $CDCl_3$, 300 K)

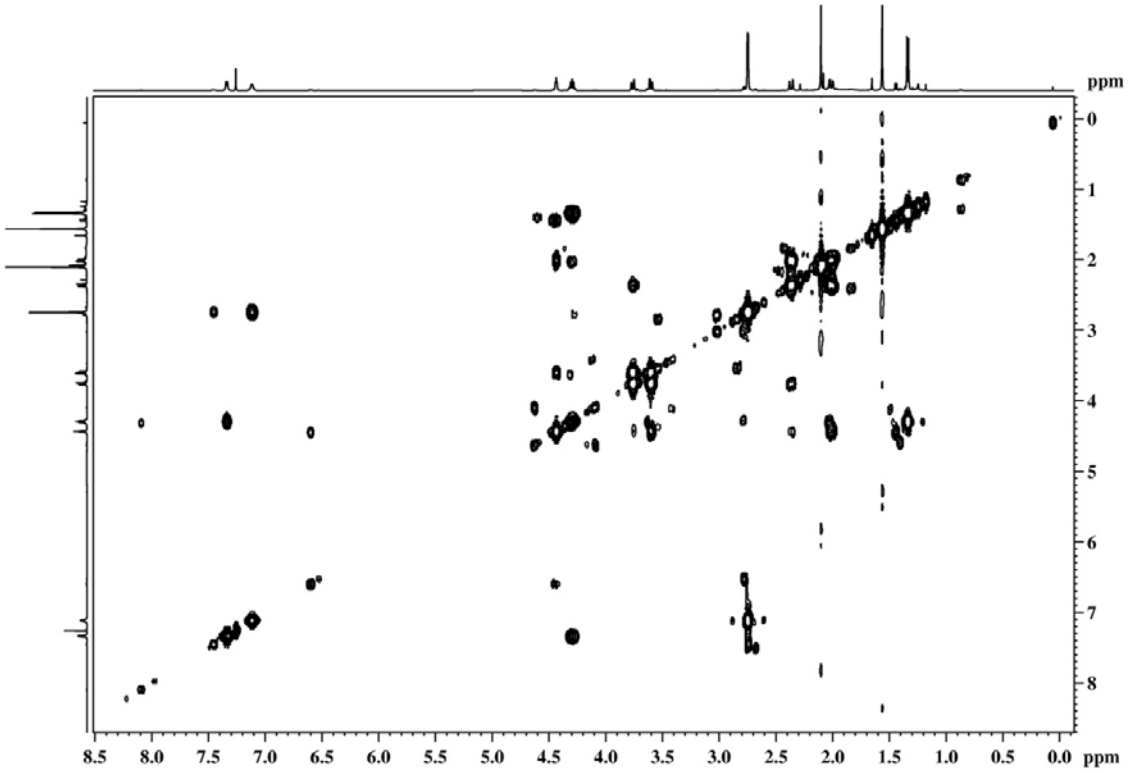


Figure 20: 2D-COSY NMR spectrum of peptide **3** (500MHz, $CDCl_3$, 300 K)

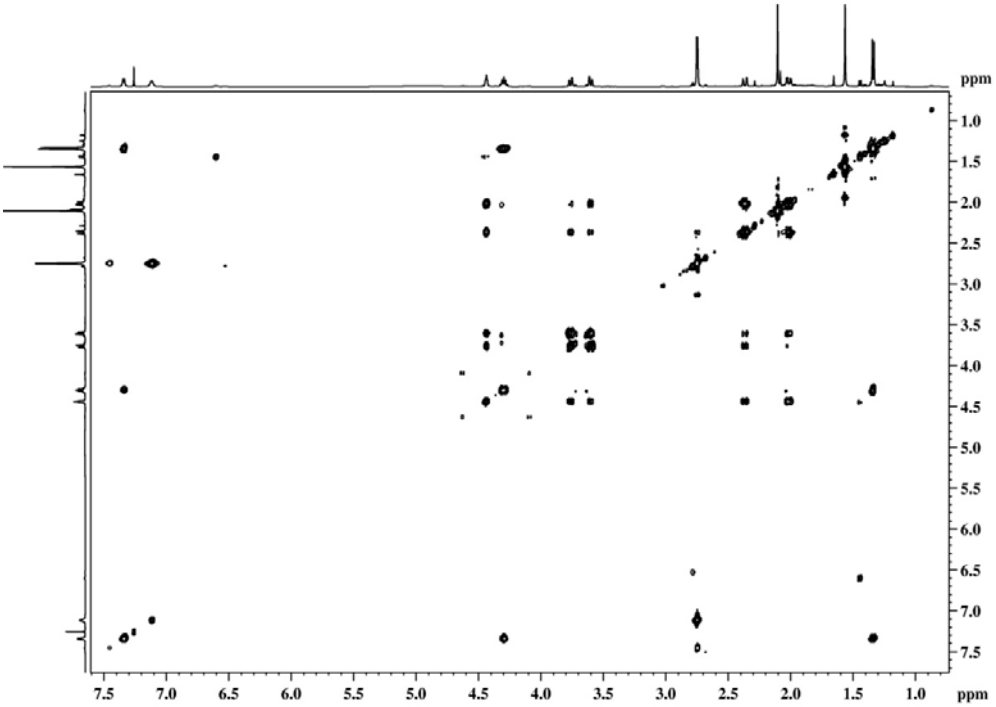


Figure 21: 2D-TOCSY NMR spectrum of peptide **3** (500MHz, $CDCl_3$, 300 K)

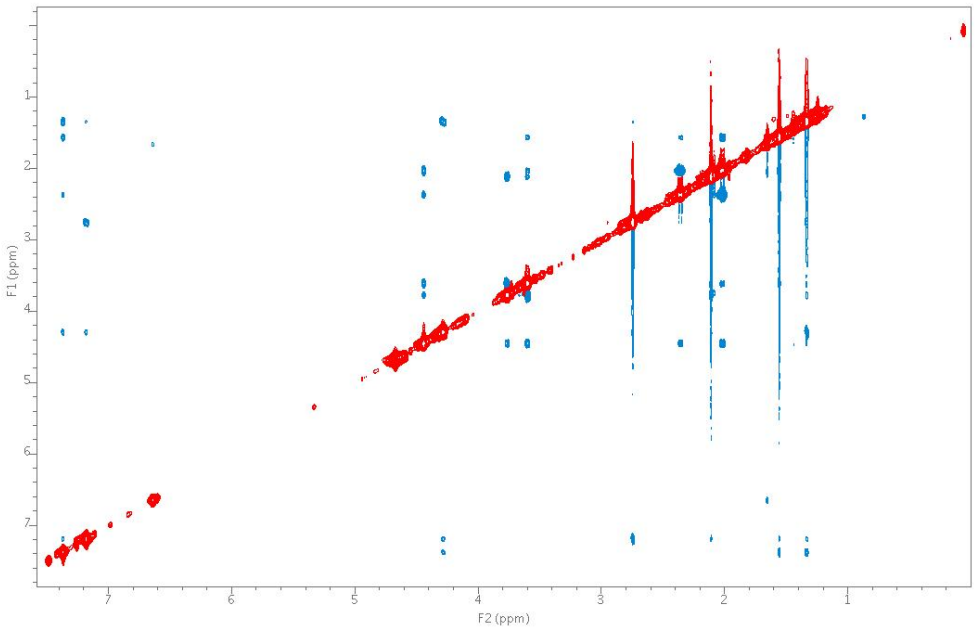


Figure 22: 2D-ROESY NMR spectrum of peptide **3** (700MHz, $CDCl_3$)

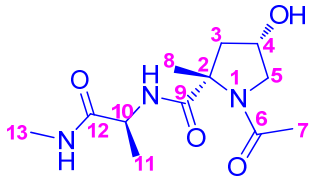


Table 4: ^{1}H chemical shifts (δ in ppm) and coupling constants (J in Hz) for peptide **3** (500 MHz, $CDCl_3$, 300K)

Residue/ Protons	**NMe**	**pro**	**Ala**
NH	7.11(*br*)	-	7.34 (*d*, $^{3}J_{NH\text{-}C\alpha H}$ = 6.5)
$C_{\alpha}H$	-	-	4.30 (*t*, $^{3}J_{NH\text{-}C\alpha H}$ = 3.8)
$C_{\beta}H_{(pro\text{-}S)}$/ $C_{\beta}H_{(pro\text{-}R)}$	-	2.00 (*dd*, $^{3}J_{C\gamma H\text{-}C\beta H}$ = 4.5, 14.5)/ 2.36 (*dd*, $^{3}J_{C\gamma H\text{-}C\beta H}$ = 1.9, 14.5)	1.34, (*d*, $^{3}J_{C\alpha H\text{-}C\beta H}$ = 7.2)
$C_{\gamma}H$/	-	4.44,(*m*)	
$C_{\delta}H$/ $C_{\delta'}H$	-	3.60,(*dd*, $^{3}J_{C\delta H\text{-}C\gamma H}$ = 3.5,11.2) /3.75,(*dd*, $^{3}J_{C\delta H\text{-}C\gamma H}$ = 1.9,11.2)	
Others : Pro-OH (*br*), N-Me = 2.72, ($^{3}J_{CNH\text{-}CMe\text{-}H}$ = 4.6), pro-Me = 1.56, (*s*), Ac-CH_3 = 2.10 (*s*)			
Carbons: 2C=65.7, 3C=46.9, 4C=69.5, 5C=57.1, 6C=170.2, 7C=23.6, 8C=22.3, 9C=174.1, 10C=49.5, 11C=17.1, 12C=173.2, 13C=26.3 ** $\Delta\delta/\Delta T$ (ppb) of **NMe-HN** = 4.50 and **Ala-HN** = 3.43			

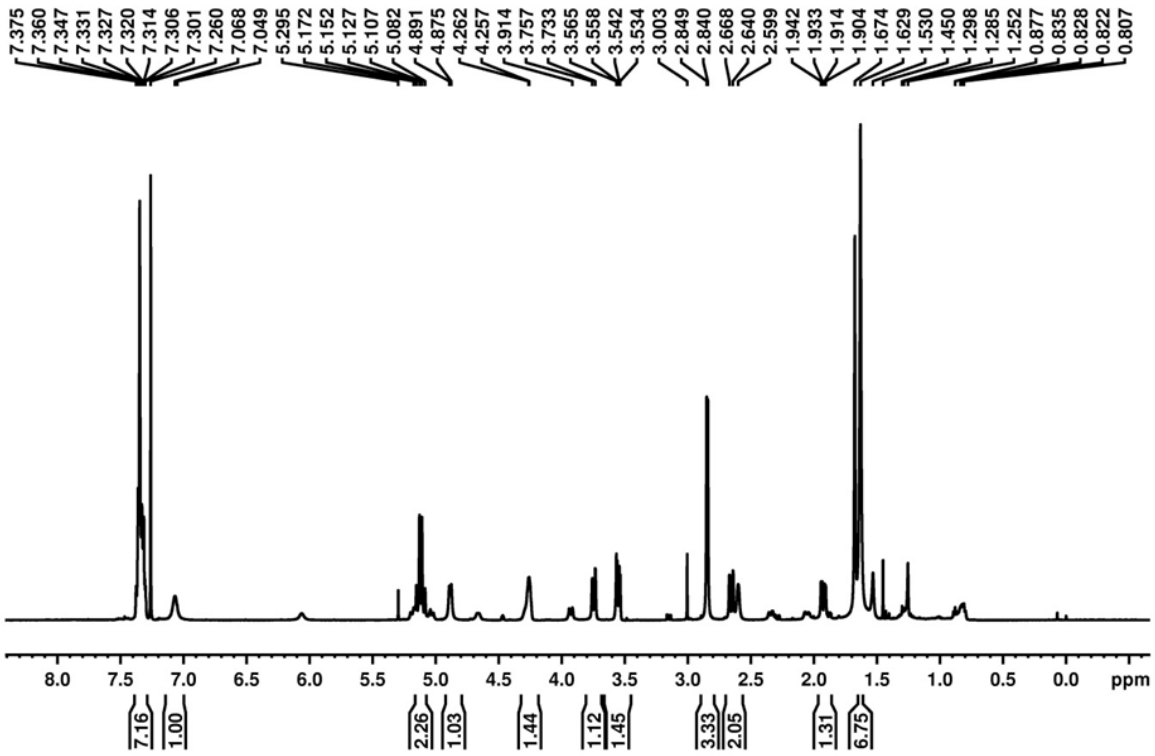


Figure 23: ^{1}H NMR spectrum of peptide **4a** (500MHz, $CDCl_3$, 300 K)

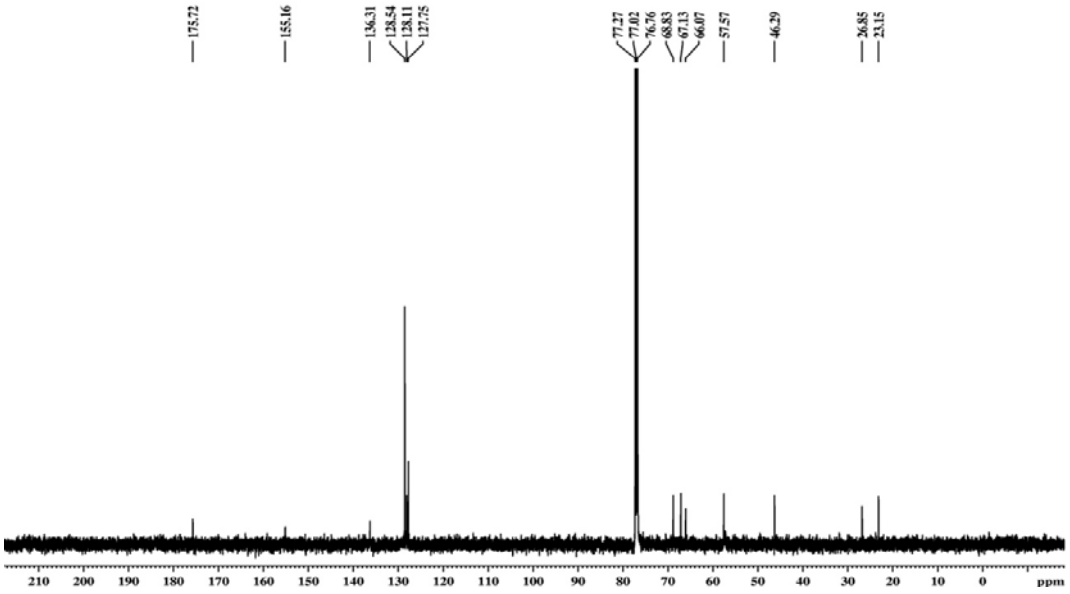


Figure 24: ^{13}C NMR spectrum of peptide **4a** (500MHz, $CDCl_3$, 300 K)

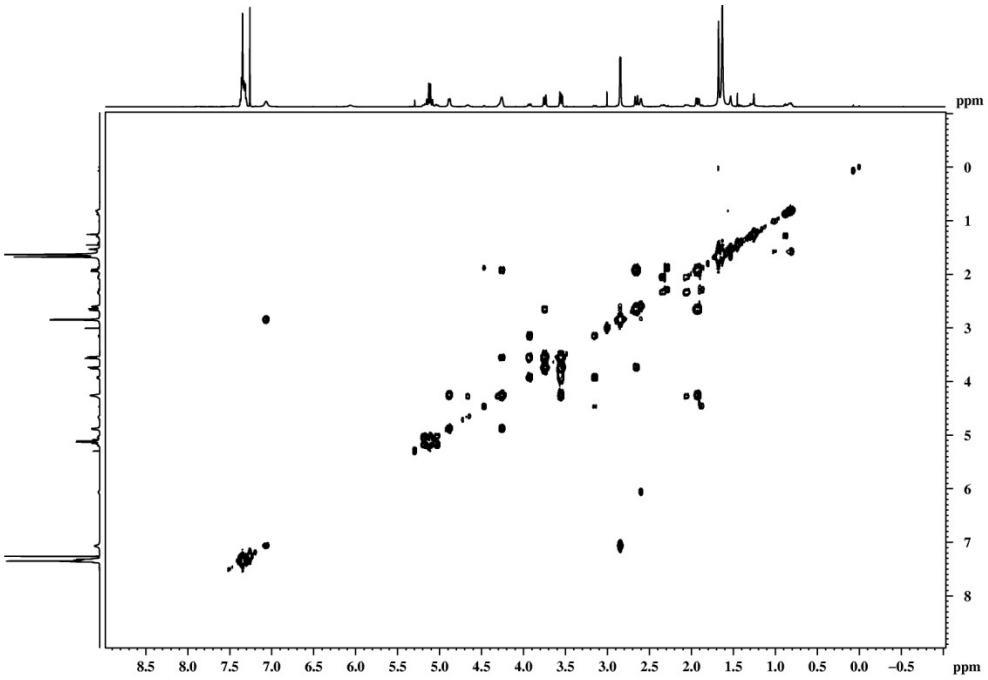


Figure 25: 2D-COSY NMR spectrum of peptide **4a** (500MHz, $CDCl_3$, 300 K)

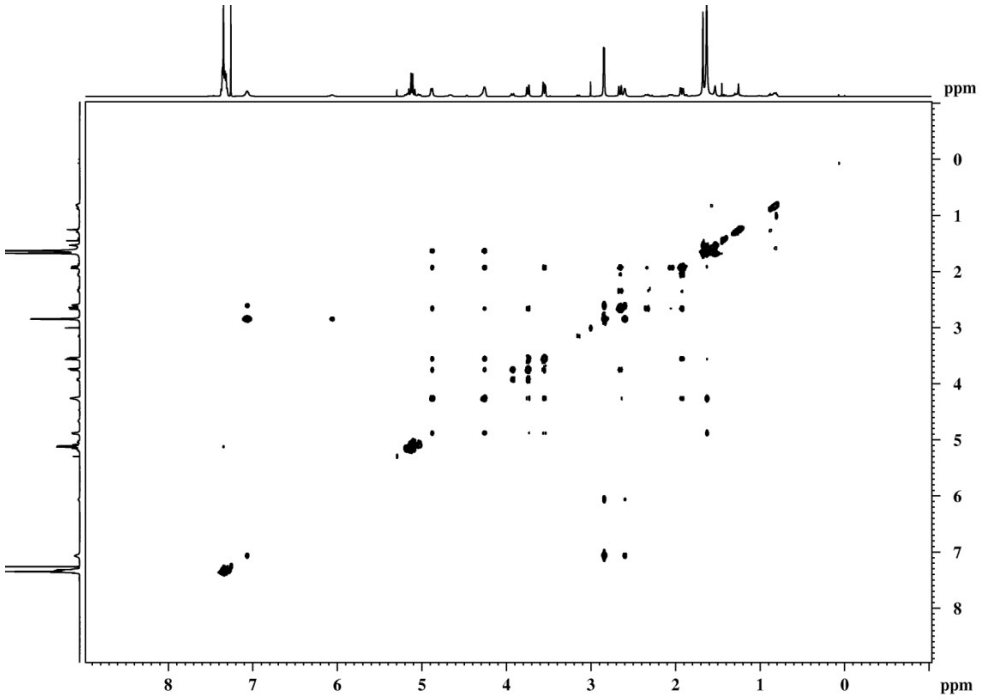


Figure 26: 2D-TOCSY NMR spectrum of peptide **4a** (500MHz, $CDCl_3$, 300 K)

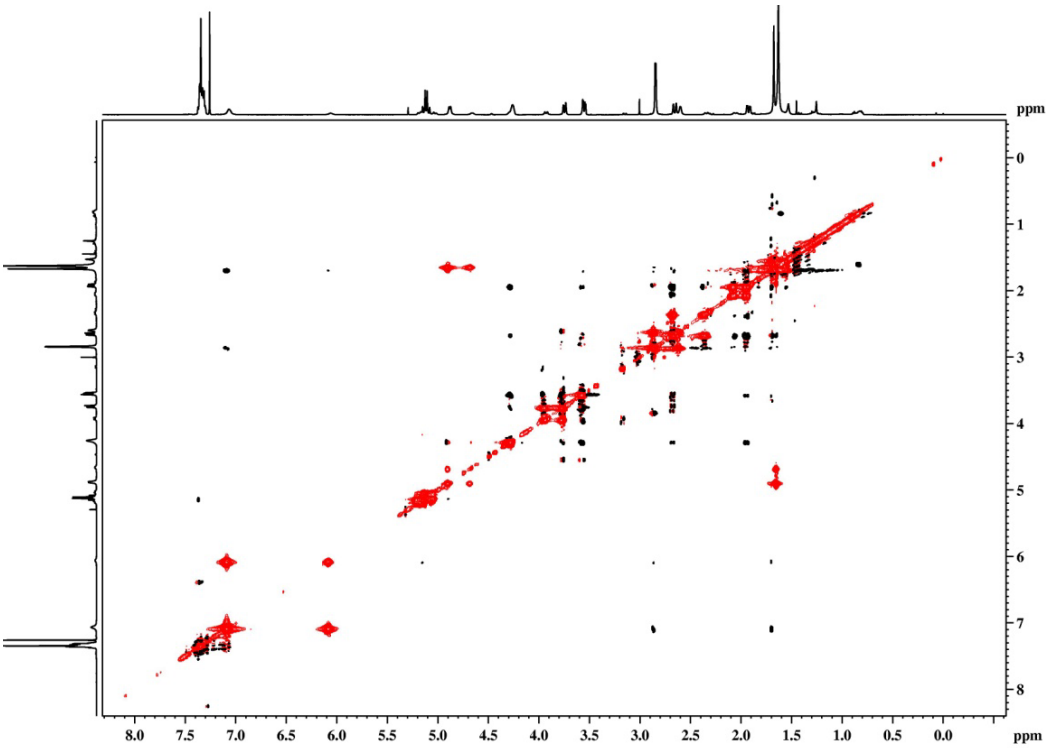


Figure 27: 2D-ROESY NMR spectrum of peptide **4a** (500MHz, $CDCl_3$, 300 K)

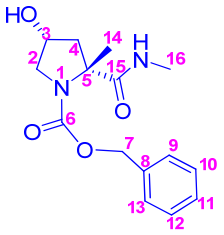


Table 5: ^{1}H chemical shifts (δ in ppm) and coupling constants (J in Hz) for peptide **4a** (500 MHz, $CDCl_3$, 300 K)

Residue/ Protons	**N-Me NH**	**Pro**
NH	7.07 (br)	-
C$_\alpha$H	-	-
C$_\beta$H/ C$_\beta$H	-	1.91,(*dd*, $^3J_{C\alpha H\text{-}C\beta H}$ = 4.2, 14.0)/ 2.37,(*dd*, $^3J_{C\alpha H\text{-}C\beta H}$ = 1.4, 14.0)
C$_\gamma$H/ C$_{\gamma'}$H	-	4.25,(m)
C$_\delta$H/ C$_{\delta'}$H	-	3.55,(*dd*, $^3J_{C\delta H\text{-}C\beta H}$= 3.3,12.0) /3.73,(*dd*, $^3J_{C\delta' H\text{-}C\beta H}$ = 1.5,12.0)
Others : Pro-OH= 4.88, N-Me = 2.83 (*d*,$^3J_{CNH\text{-}CMe\text{-}H}$ = 4.8), Pro-Me = 1.63 (s), Ph-CH2(2H) = 5.11,(m) Ph-H(5H) = 7.38-7.29, (m),		
Carbons: 2C=57.6, 3C=68.8, 4C=46.3, 5C=66.1, 6C=155.2, 7C=67.1, 8C=136.3, 9C=128.5, 10C=127.7, 11C=128.1, 12C=127.7, 13C=128.5, 14C=23.1, 15C=175.7,		

16C=26.8.
** Δδ/ΔT (ppb) of **NMe-HN** = 5.50

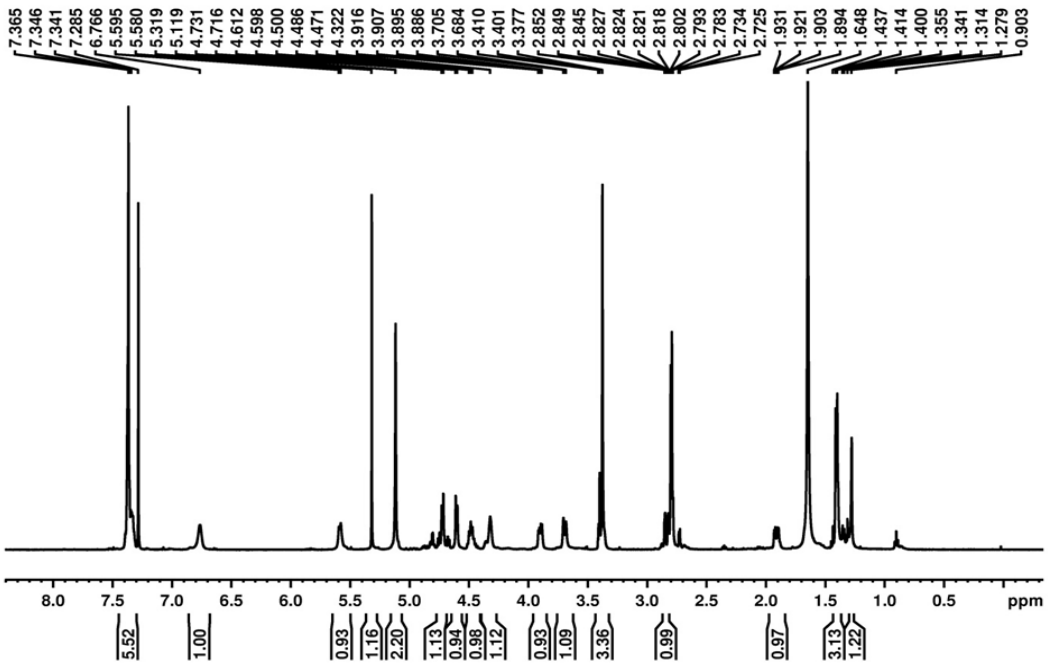


Figure 28: ^{1}H NMR spectrum of peptide **6b** (500MHz, $CDCl_3$, 300 K)

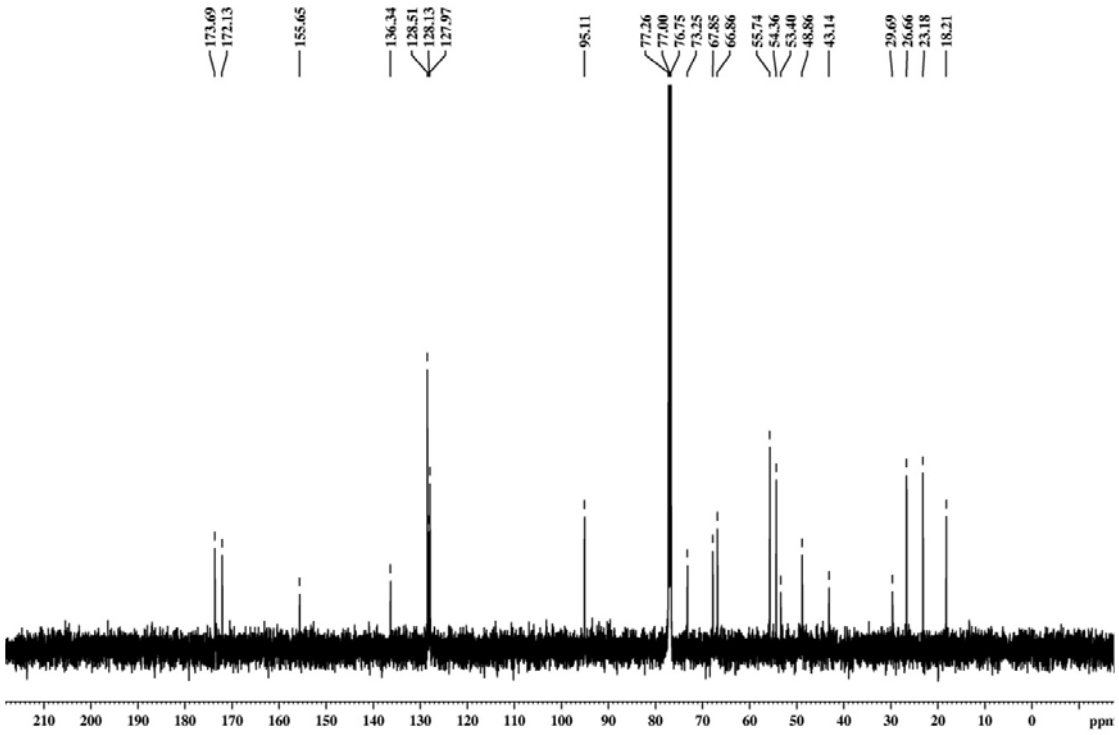


Figure 29: ^{13}C NMR spectrum of peptide **6b** (500MHz, $CDCl_3$, 300 K)

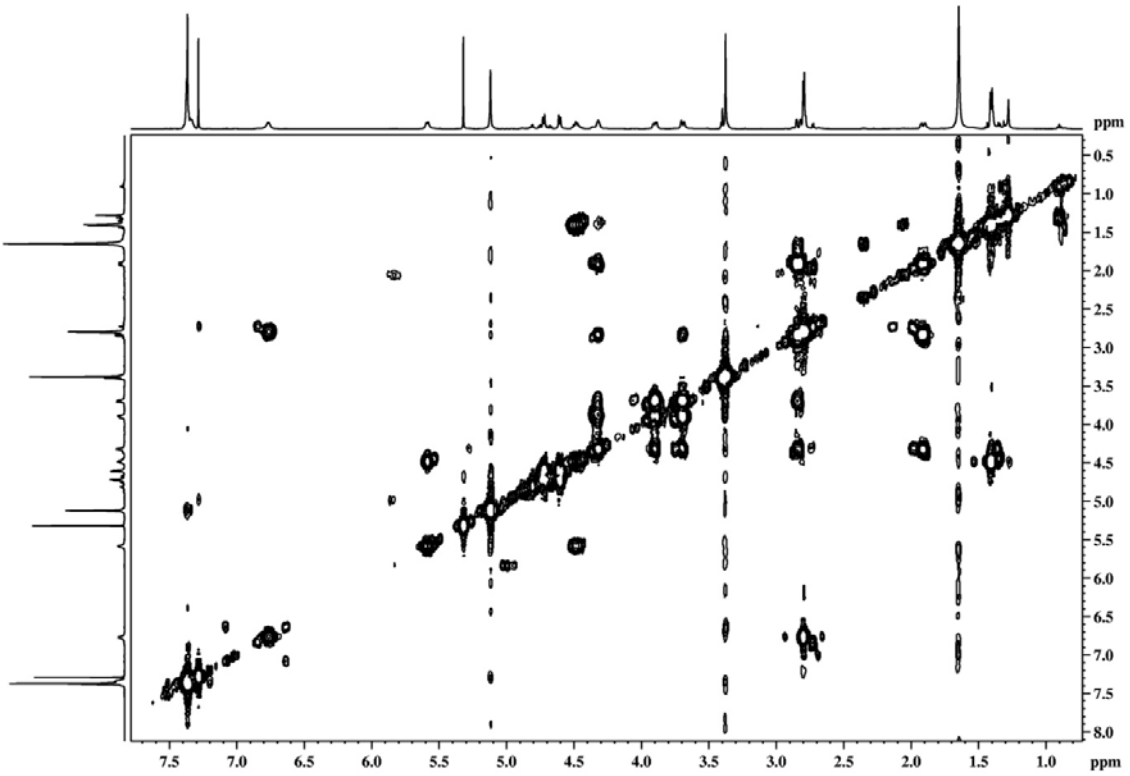


Figure 30: 2D-COSY NMR spectrum of peptide **6b** (500MHz, $CDCl_3$, 300 K)

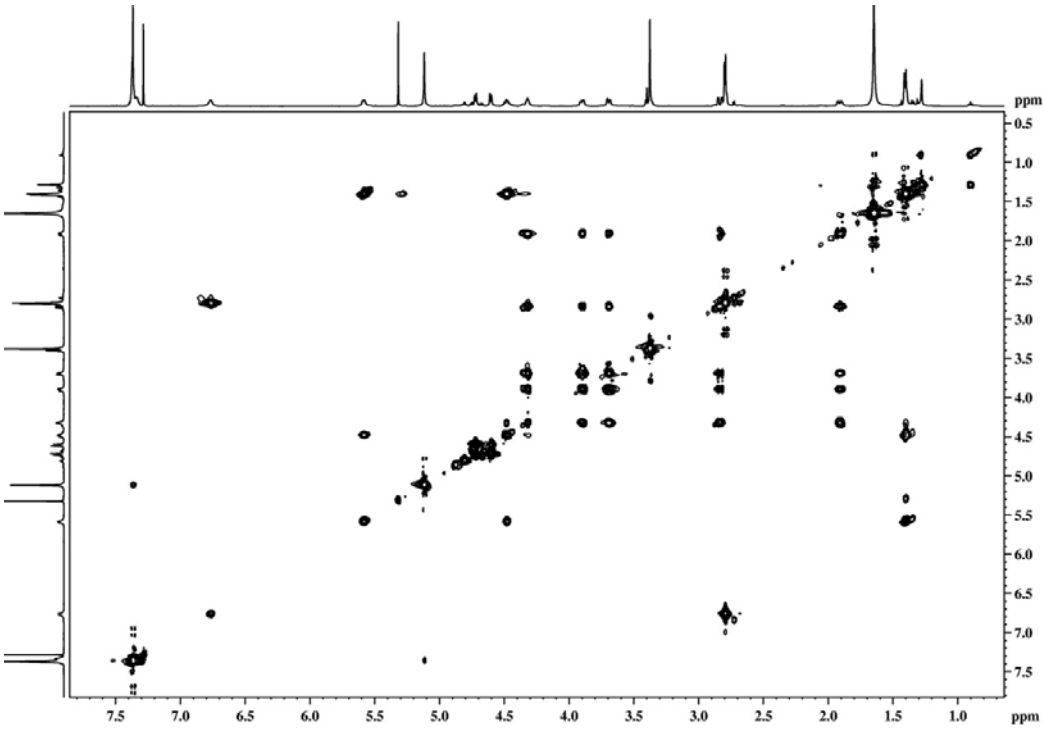


Figure 31: 2D-TOCSY NMR spectrum of peptide **6b** (500MHz, $CDCl_3$, 300 K)

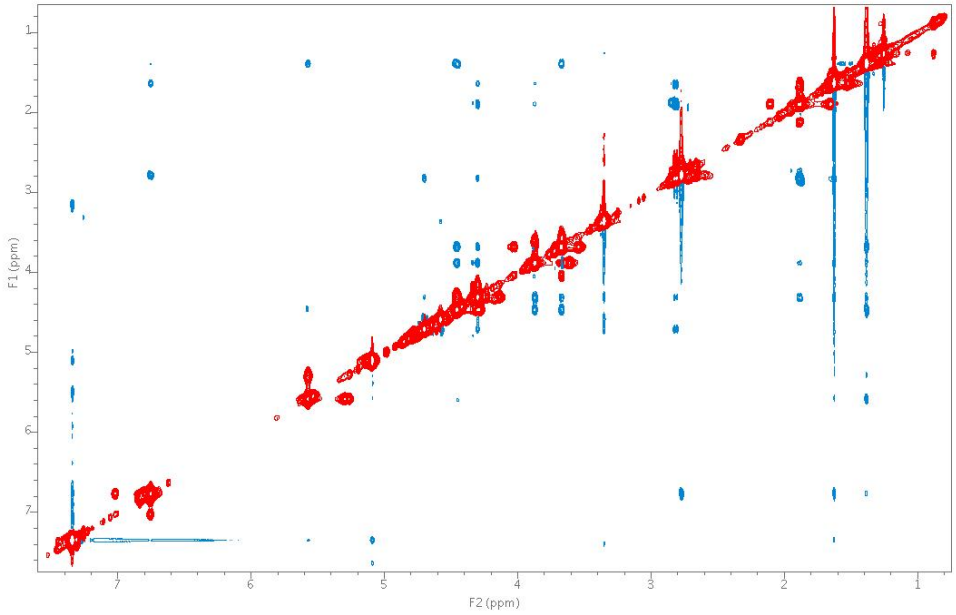


Figure 32: 2D-ROESY NMR spectrum of peptide **6b** (700MHz, $CDCl_3$)

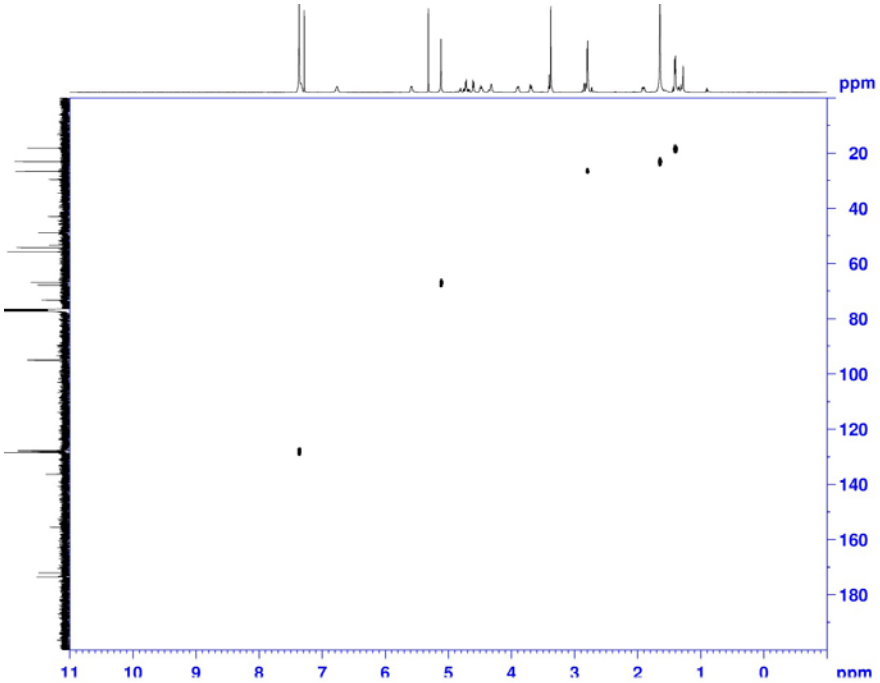


Figure 33: 2D-HSQC NMR spectrum of peptide **6b** (500MHz, $CDCl_3$ 300 K)

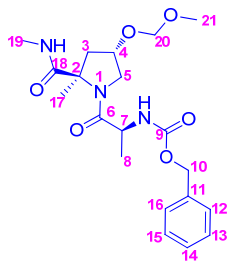
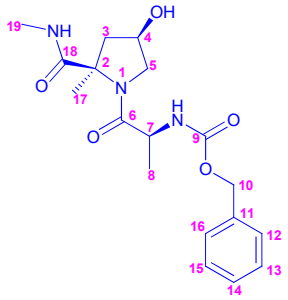


Table 6: ^{1}H chemical shifts (δ in ppm) and coupling constants (J in Hz) for peptide **6b** (500 MHz, $CDCl_3$, 300K)

Residue/ Protons	**N-Me NH**	**pro**	**Ala**
NH	6.77, (*br*)	-	5.59, (*d*, $^{3}J_{NH\text{-}C\alpha H}$ = 7.6)
C$_\alpha$H	-	-	4.46,(*m*)
C$_\beta$H$_{(pro\text{-}S)}$/ C$_\beta$H$_{(pro\text{-}R)}$	-	1.91, (*dd*, $^{3}J_{C\gamma H\text{-}C\beta H}$ = 5.0, 14.0)/ 2.84, (*dd*, $^{3}J_{C\gamma H\text{-}C\beta H}$ = 1.6, 14.0)	1.40, (*d*, $^{3}J_{C\alpha H\text{-}C\beta H}$ = 6.6)
C$_\gamma$H/	-	4.32,(*m*)	
C$_\delta$H$_{(pro\text{-}S)}$/ C$_\delta$H$_{(pro\text{-}R)}$	-	3.69,(*dd*, $^{3}J_{C\delta H\text{-}C\gamma H}$ = 2.6,11.0) /3.90,(*dd*, $^{3}J_{C\delta H\text{-}C\gamma H}$ = 4.6,11.0)	
Others : N-Me = 2.79 (*d*,$^{3}J_{CNH\text{-}CMe\text{-}H}$ = 4.7), Pro-CαMe = 1.65 (*s*), Ph-CH_2(2H) = 5.12 (*s*), Ph-H(5H) = 7.40-7.32 (*m*), MOM-CH_3(3H) = 3.37 (*s*), MOM-CH_2 (1H) = 4.59 (*d, J*=7.0) & (1H) = 4.71(*d, J*=7.0)			
Carbons: 2C=66.8, 3C=48.8, 4C=73.2, 5C=54.3 6C=173.6, 7C=53.3, 8C=18.2, 9C=172.1, 10C=67.8, 11C=136.3, 12C=128.5, 13C=128.1, 14C=127.9, 15C=128.1, 16C=128.5, 17C=23.2, 18C=155.6, 19C=26.6, 20C=95.1, 21C= 55.7 **$\Delta\delta/\Delta T$ (ppb) of **NMe-HN** = 5.01 and **Ala-HN** = 7.72			



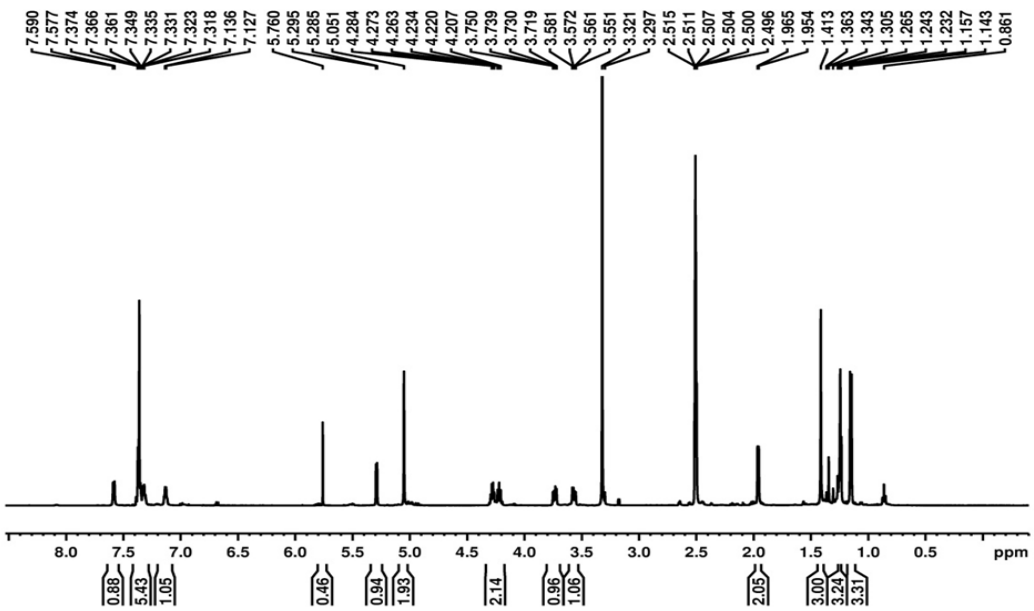


Figure 34: ^{1}H NMR spectrum of peptide **7a** (300 MHz, DMSO-d_6, 300 K)

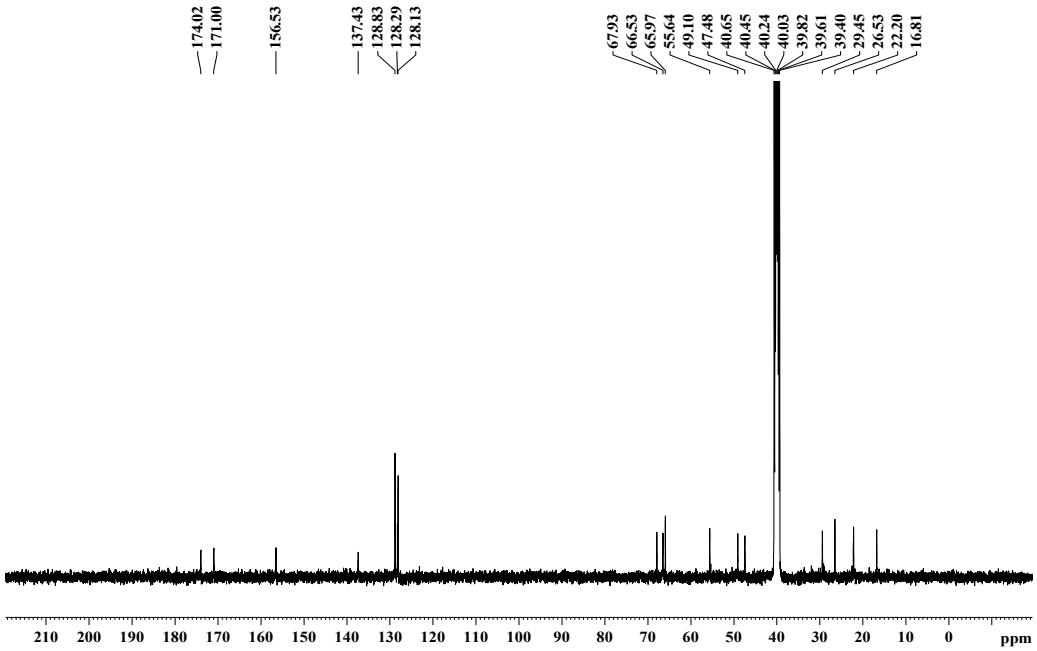


Figure 35**:** ^{13}C NMR spectrum of peptide **7a** (50 MHz, DMSO-d_6, 300 K)

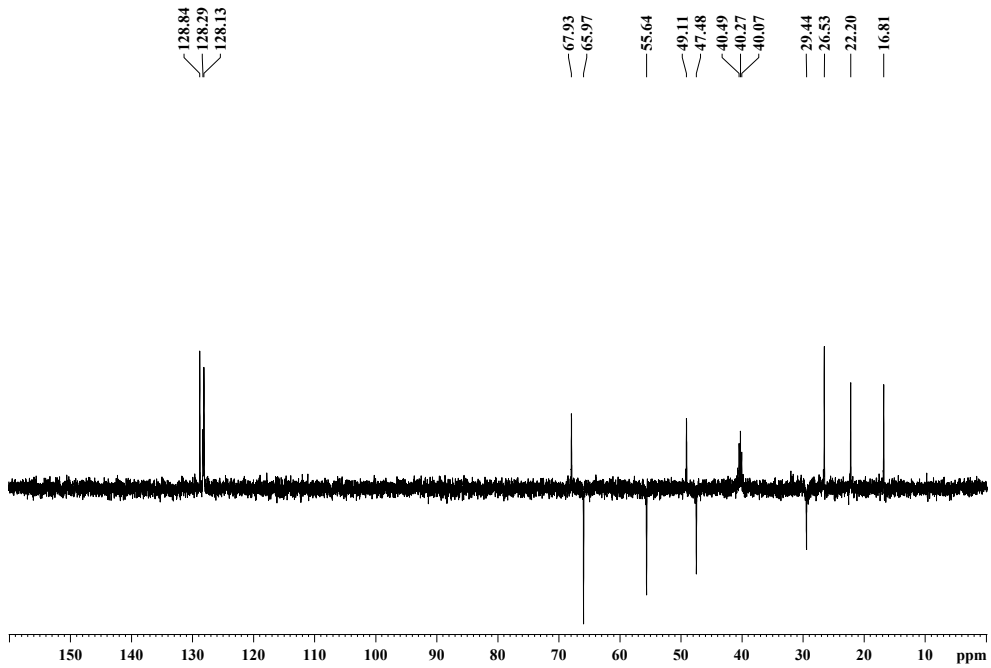


Figure 36: ^{13}C DEPT 135 NMR spectrum of peptide**7a** (50 MHz, DMSO-d_6, 300 K)

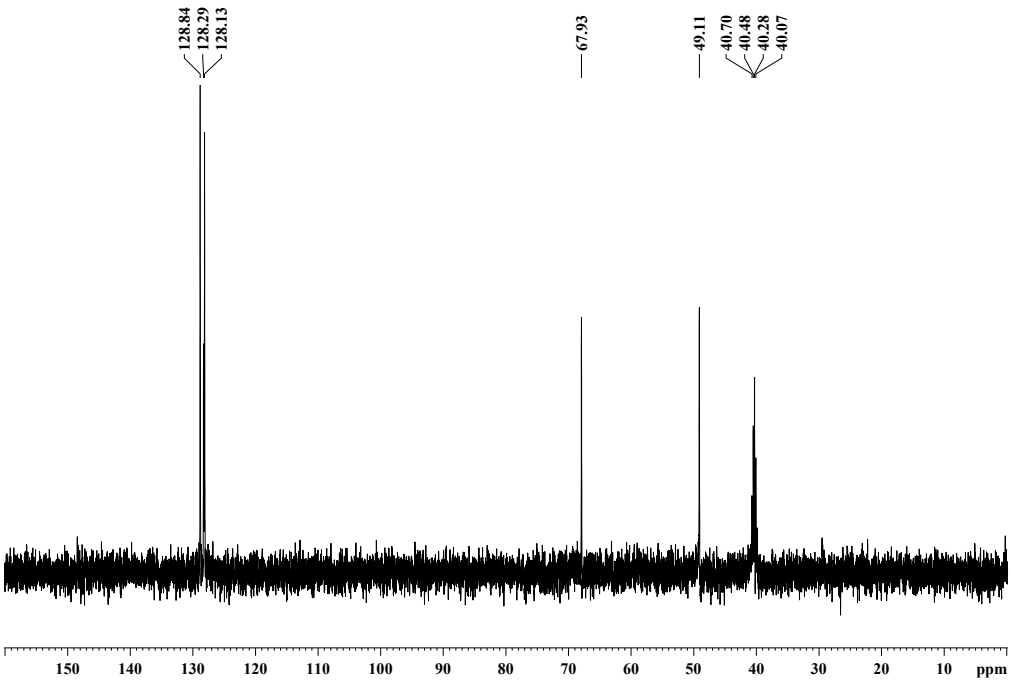


Figure 37: ^{13}C-Dept90 NMR spectrum of peptide **7a** (125 MHz, DMSO-d_6, 300 K)

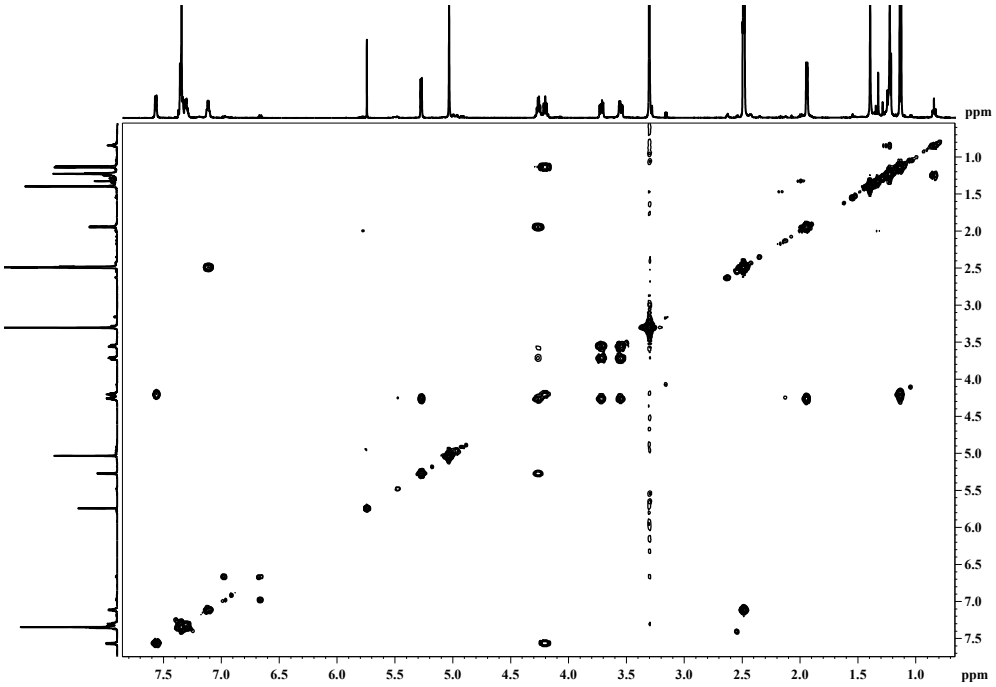


Figure 38: 2D-COSY spectrum of peptide **7a** (500 MHz, DMSO-d_6, 300 K)

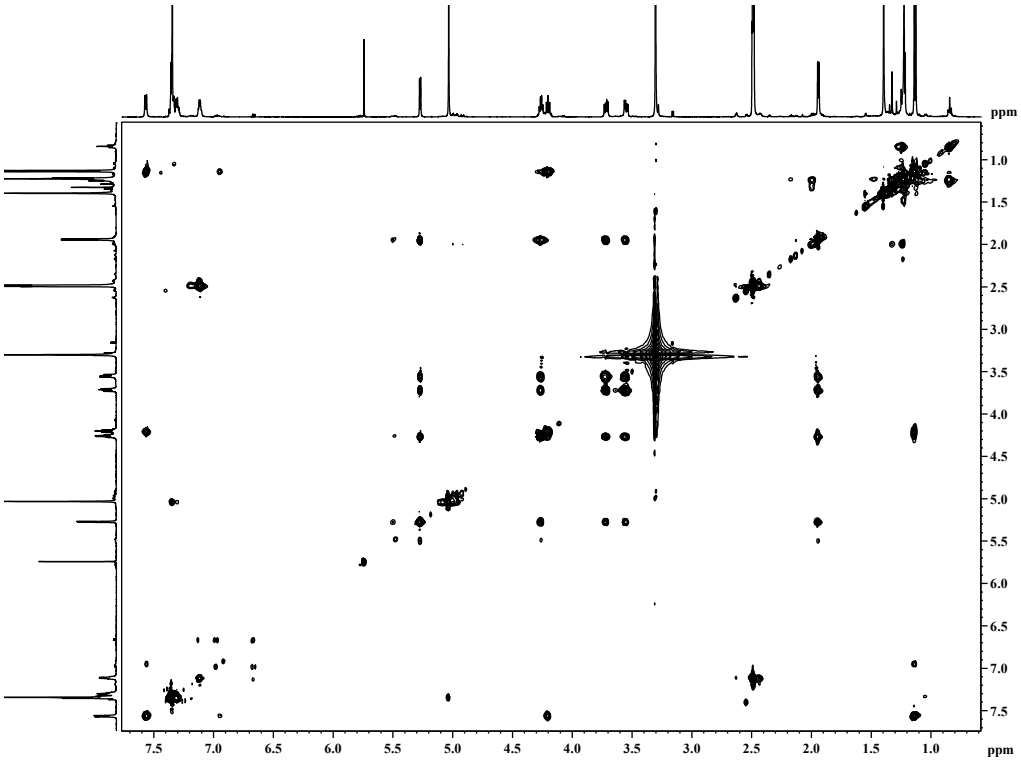


Figure 39: 2D-TOCSY spectrum of peptide **7a** (500 MHz, DMSO-d_6, 300 K)

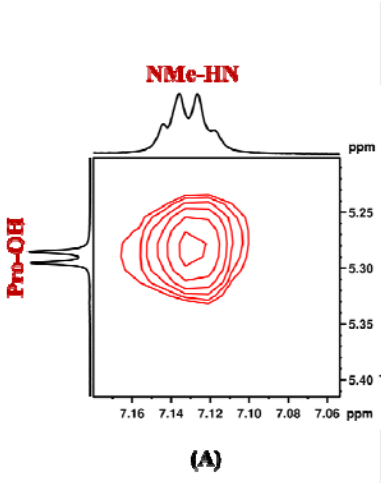


Figure 40: **A)** Expansion of rOe between N-Me-NH and Pro-OH.

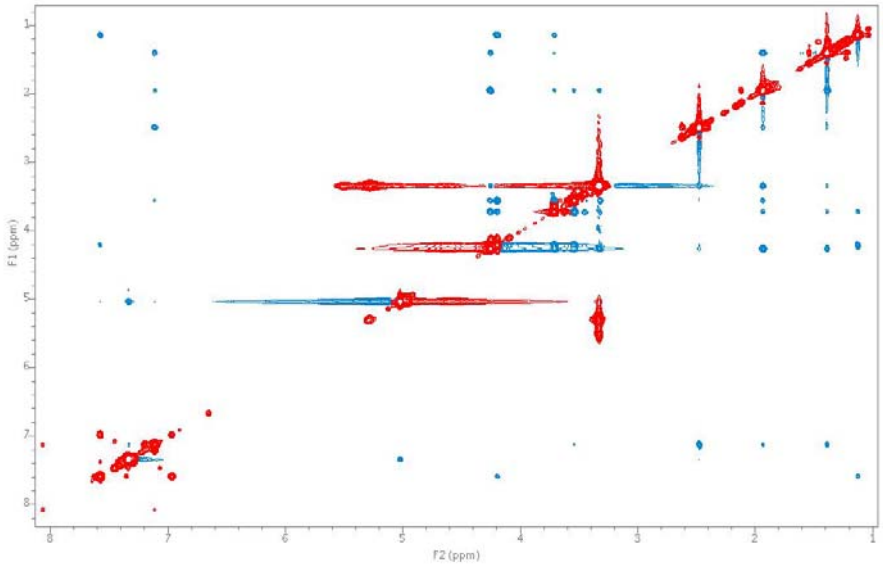


Figure 41: 2D-ROESY spectrum of peptide **7a** (700 MHz, DMSO-d_6)

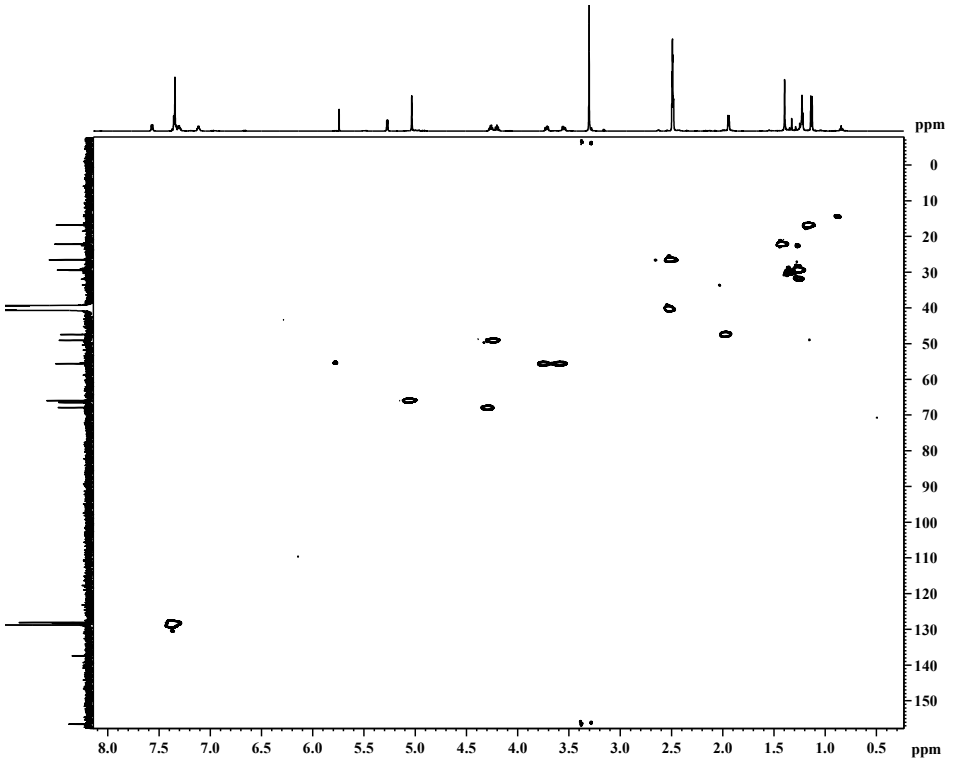


Figure 42: 2D-HSQC spectrum of peptide **7a** (500 MHz, DMSO-d_6, 300 K)

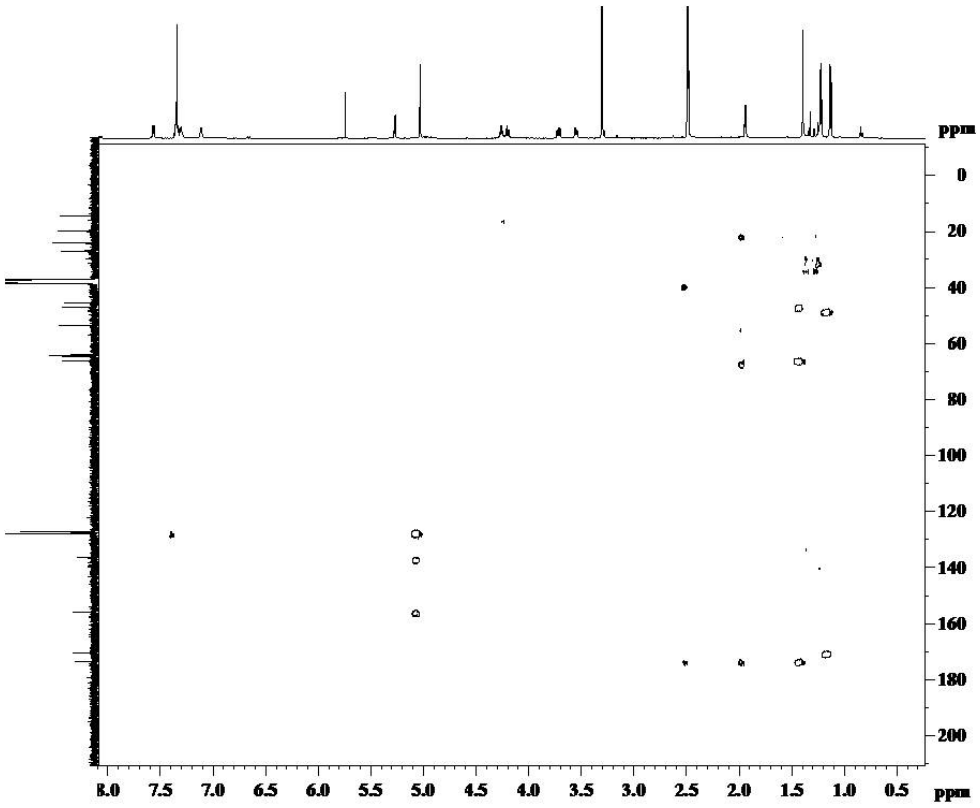


Figure 43: 2D-HMBC spectrum of peptide **7a** (500 MHz, DMSO-d_6, 300 K)

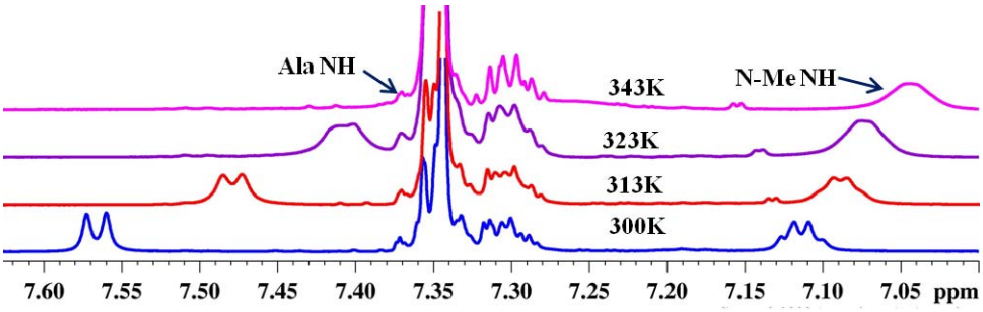


Figure 44: [1]H stacked spectra of peptide **7a** from 300K to 343K (500 MHz, DMSO-d_6)

Table7: Variable temperature study of peptide **7a** in DMSO-d_6 (500 MHz)

Temperature	**Ala NH** (Chemical shift in ppm)	**N-Me NH**
300	7.56	7.11
313	7.47	7.09
323	7.40	7.07
343	7.36	7.04
Δδ/ΔT (ppb)	**4.65**	**1.62**

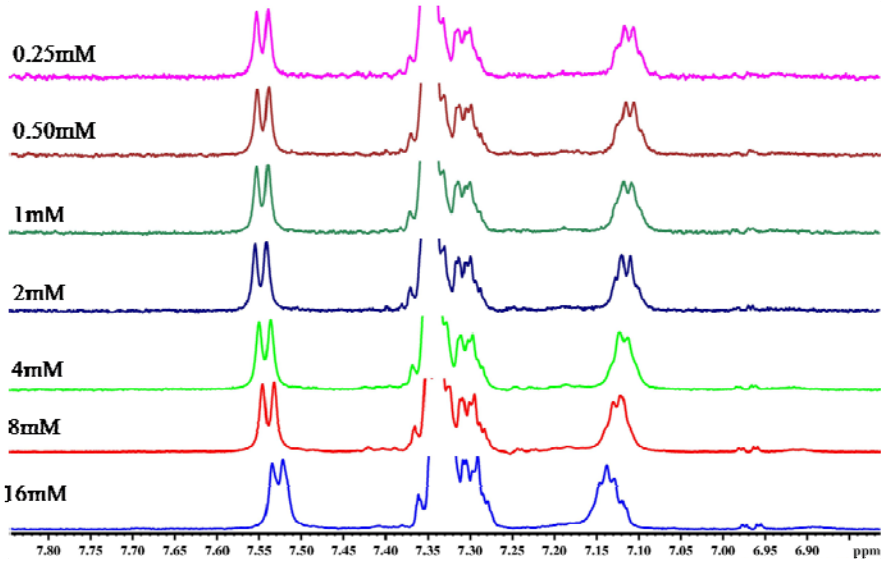


Figure 45: Aggregation spectrum of peptide **7a** (500 MHz, DMSO-d_6, 300 K)

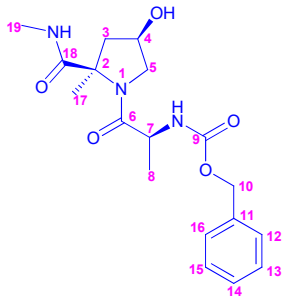


Table 8: ^{1}H chemical shifts (δ in ppm) and coupling constants (J in Hz) for peptide **7a** (500 MHz, DMSO-d_6, 300K)

Residue/ Protons	**N-Me NH**	**Pro**	**Ala**
NH	7.11 (q, $^{3}J_{CNH\text{-}CMe\text{-}H}$ = 4.5)	-	7.56 (d, $^{3}J_{NH\text{-}C\alpha H}$ = 6.4)
C$_\alpha$H	-	-	4.23 (m)
C$_\beta$H/ C$_{\beta'}$H	-	1.94,(d, $^{3}J_{C\gamma H\text{-}C\beta H}$ = 5.4)	1.15 (d, $^{3}J_{C\alpha H\text{-}C\beta H}$ = 6.3)
C$_\gamma$H/ C$_{\gamma'}$H	-	4.27,(m)	
C$_\delta$H$_{(pro\text{-}R)}$ / C$_\delta$H$_{(pro\text{-}R)}$	-	3.55 (dd, $^{3}J_{C\delta H\text{-}C\gamma H}$ = 10.3,15.8)/ 3.71 (dd, $^{3}J_{C\delta H\text{-}C\gamma H}$ = 10.3,15.8)	
Others :-Pro-OH = 5.27(d, $^{3}J_{C\gamma H\text{-}CH}$ = 5.0), N-Me = 2.50, (d $^{3}J_{CNH\text{-}CMe\text{-}H}$ = 4.5), Pro-αMe = 1.41(s), Ph-CH$_2$(2H) = 5.05(s), Ph-H(5H) = 7.28-7.37, (m)			
Carbons: 2C=66.5, 3C=47.5, 4C=67.9, 5C=55.6, 6C=174.0, 7C=49.1, 8C=16.8, 9C=156.5, 10C =65.9, 11C=137.4, 12C=128.8, 13C=128.1, 14C=128.2, 15C=128.1, 16C=128.8, 17C=22.2, 18C=171.0, 19C=26.5			

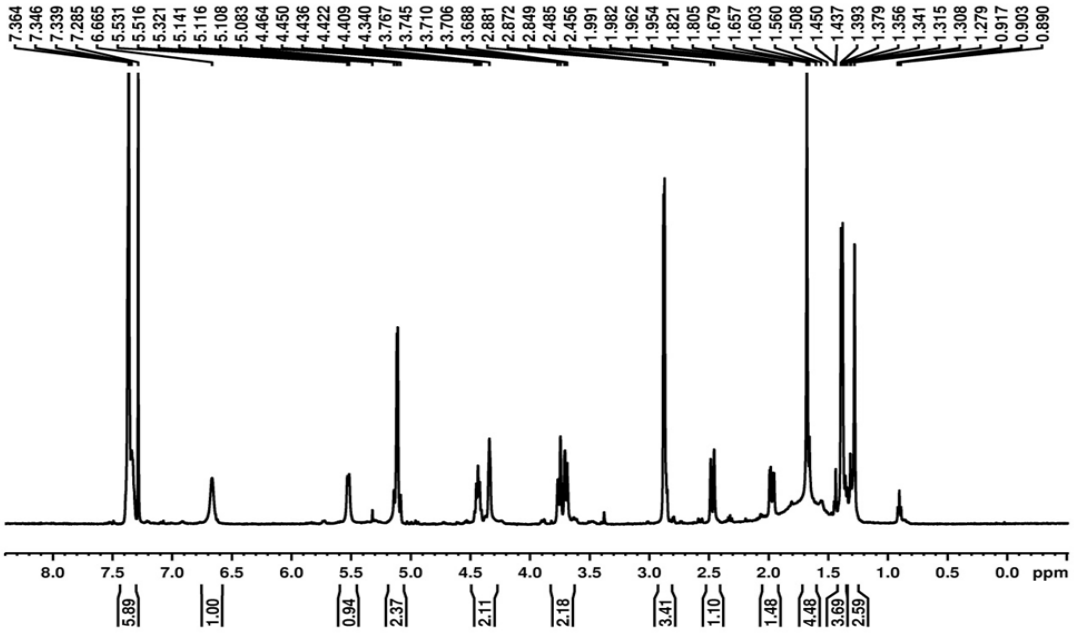


Figure 46: ^{1}H NMR spectrum of peptide **7b** (500MHz, $CDCl_3$ 300 K)

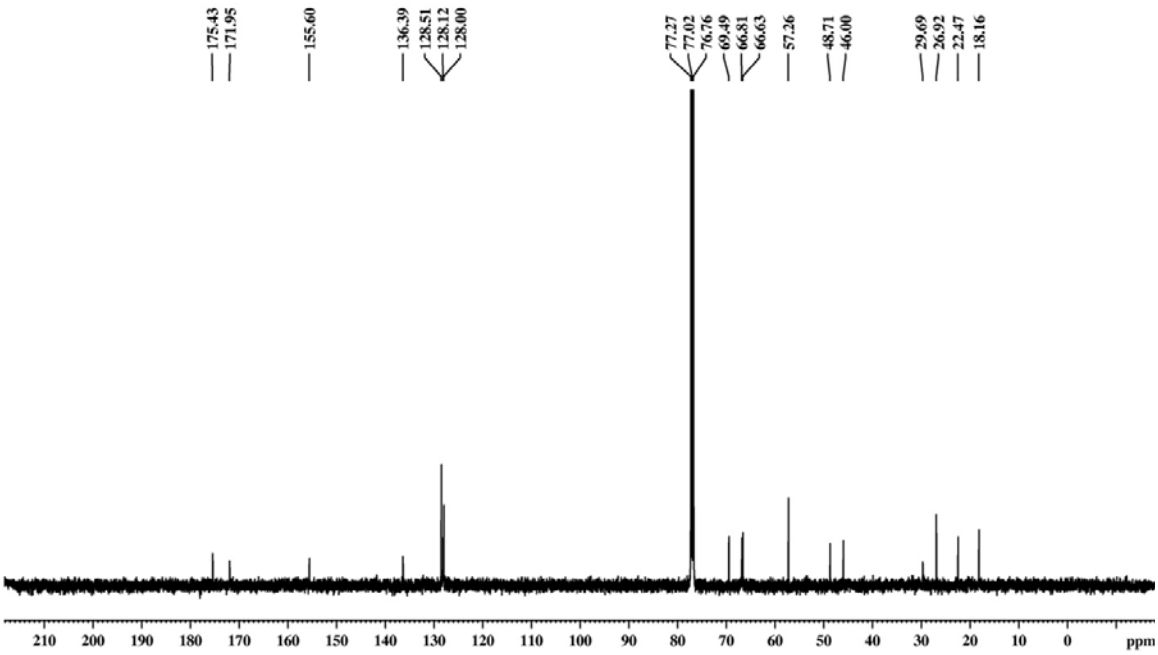


Figure 47: ^{13}C NMR spectrum of peptide **7b** (500MHz, $CDCl_3$ 300 K)

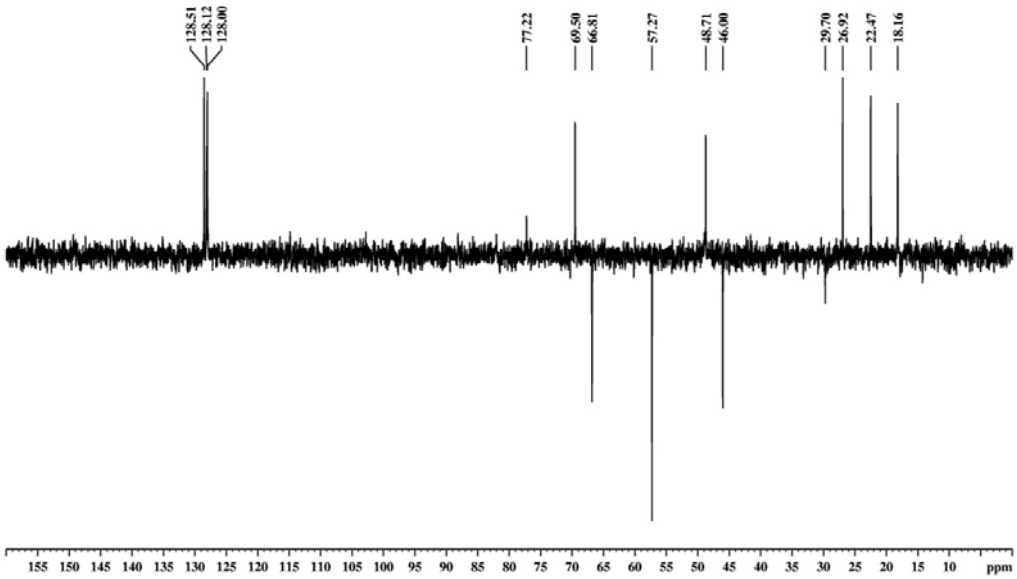


Figure 48: ^{13}CDept 135 NMR spectrum of peptide **7b** (500MHz, $CDCl_3$ 300 K)

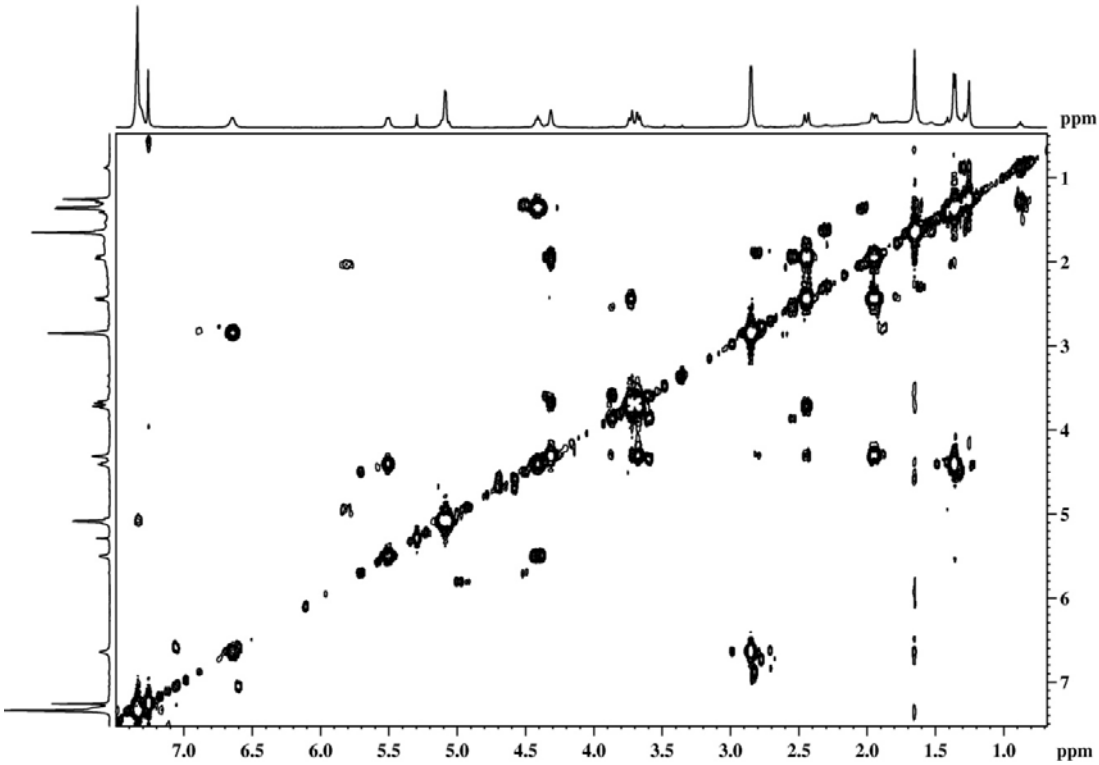


Figure 49: 2D-COSY NMR spectrum of peptide **7b** (500MHz, $CDCl_3$ 300 K)

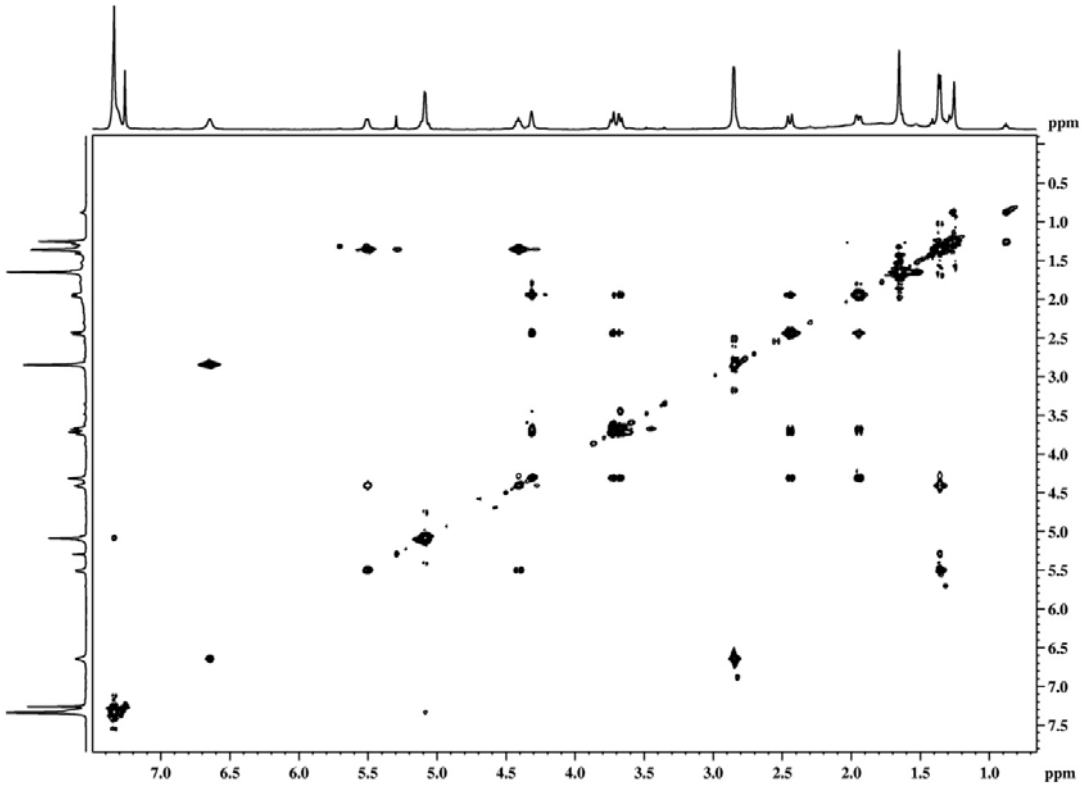


Figure 50: 2D-TOCSY NMR spectrum of peptide **7b** (500MHz, $CDCl_3$ 300 K)

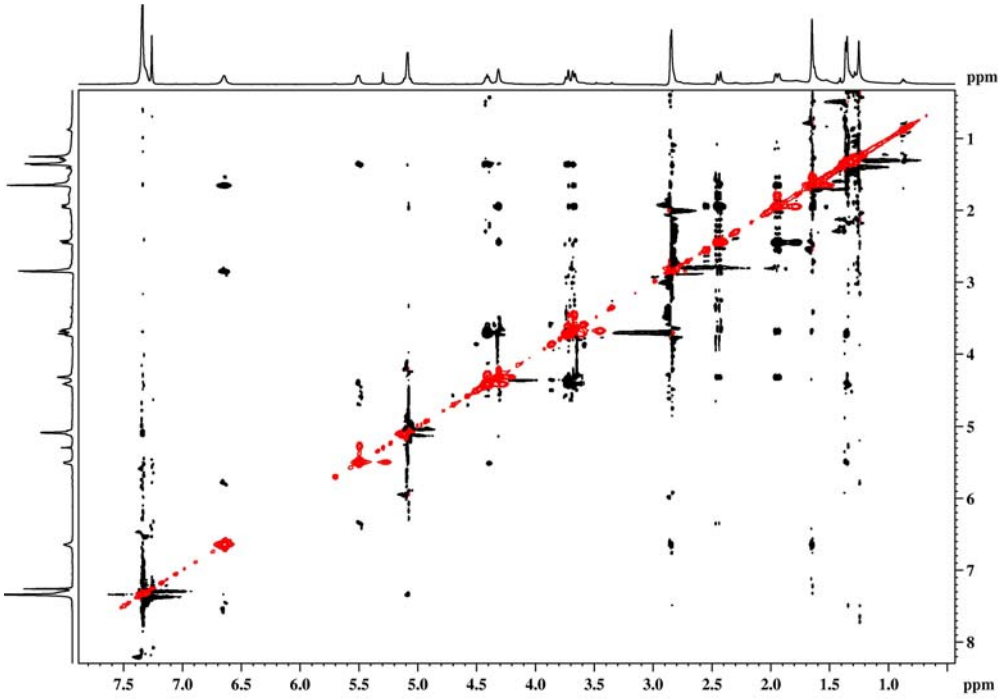


Figure 51: 2D-ROESY NMR spectrum of peptide **7b** (500MHz, $CDCl_3$ 300 K)

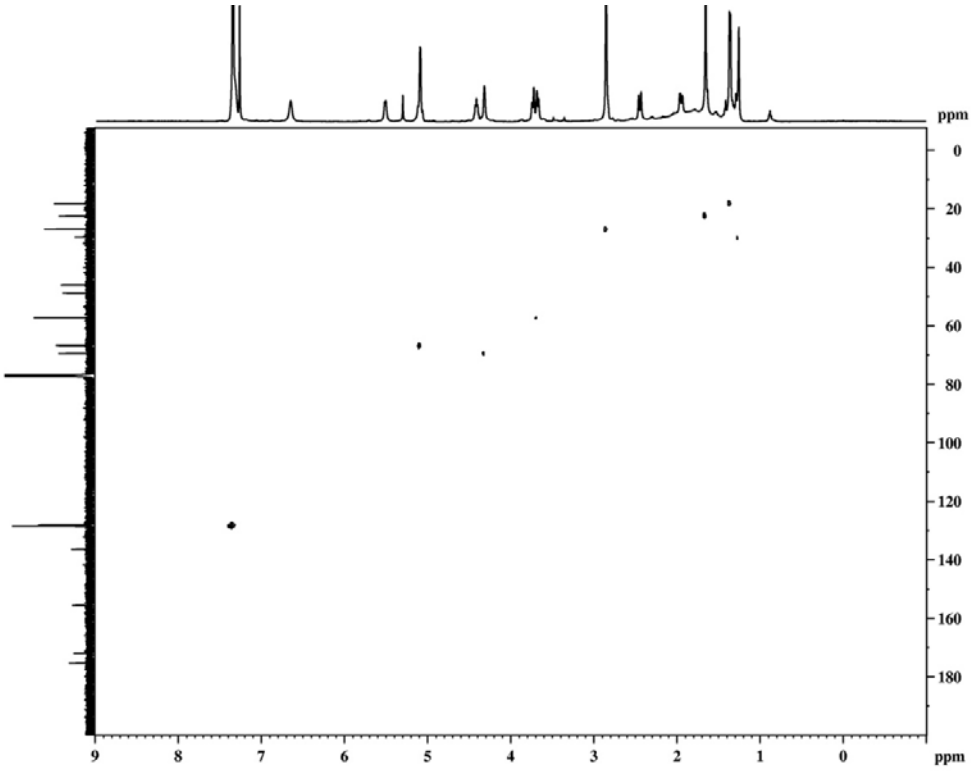


Figure 52: 2D-HSQC NMR spectrum of peptide **7b** (500MHz, $CDCl_3$ 300 K)

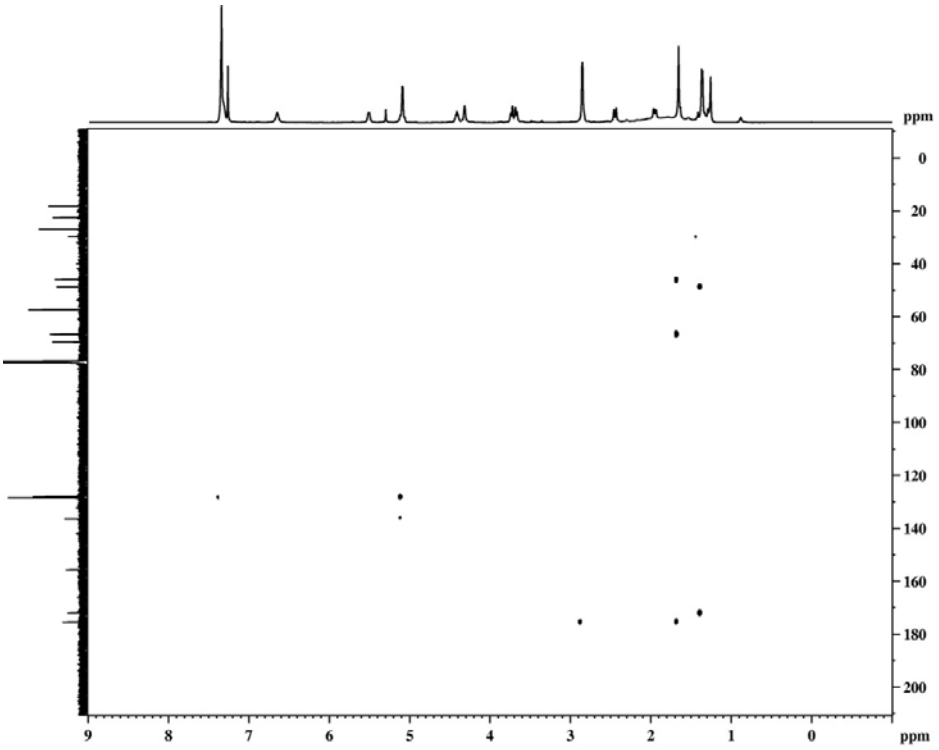


Figure 53: 2D-HMBC NMR spectrum of peptide **7b** (500MHz, $CDCl_3$ 300 K)

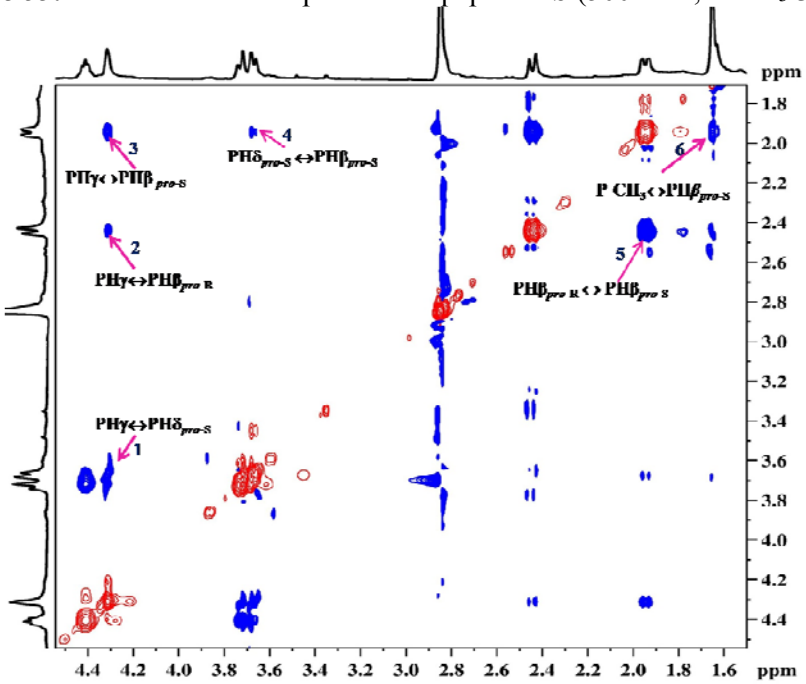


Figure 54: 2D-ROESY expansion spectrum of peptide **7b** (500MHz, $CDCl_3$ 300 K)

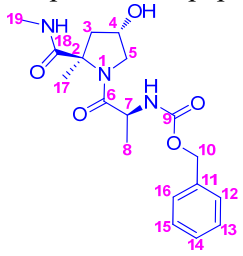


Table 9: ^{1}H chemical shifts (δ in ppm) and coupling constants (J in Hz) for peptide **7b** (500 MHz, $CDCl_3$, 300 K)

Residue/ Protons	**NH (N-Me)**	**pro**	**Ala**
NH	6.67 (*br*)	-	5.52 (*d*, $^{3}J_{NH\text{-}C\alpha H}$ = 7.0)
$C_{\alpha}H$	-	-	4.41 (*m*)
$C_{\beta}H_{(pro\text{-}S)}$ /$C_{\beta}H_{(pro\text{-}R)}$	-	1.95 (*dd*, $^{3}J_{C\gamma H\text{-}C\beta H}$ = 4.5, 14.5)/ 2.45 (*dd*, $^{3}J_{C\gamma H\text{-}C\beta H}$ = 1.9, 14.5)	1.37 (*d*, $^{3}J_{C\alpha H\text{-}C\beta H}$ = 7.2)
$C_{\gamma}H$/	-	4.33 (*t* = 3.5)	
$C_{\delta}H_{(pro\text{-}R)}$ / $C_{\delta}H_{(pro\text{-}S)}$	-	3.68 (*dd*, $^{3}J_{C\delta H\text{-}C\gamma H}$ = 3.2,12.2) /3.75 (*dd*, $^{3}J_{C\delta H\text{-}C\gamma H}$ = 1.8,12.2)	
Others: Pro-OH = 4.53(br), N-Me = 2.87, (*d* $^{3}J_{CNH\text{-}CMe\text{-}H}$ = 4.6), pro-αMe = 1.65 (*s*), Ph-CH_2(2H) = 5.07 (*dd J*=16.0, 13.0), Ph-H(5H) = 7.38-7.30 (*m*),			
Carbons:2C=66.6, 3C=46.0, 4C=69.4, 5C=57.2, 6C=175.4, 7C=48.7, 8C=18.1, 9C=155.6, 10C=66.8, 11C=136.3, 12C=128.5, 13C=128.1, 14C=128.0, 17C=22.4, 18C=171.9, 19C=26.9 ** $\Delta\delta/\Delta T$ (ppb) of **NMe-HN = 4.01 and Ala-HN = 7.75**			

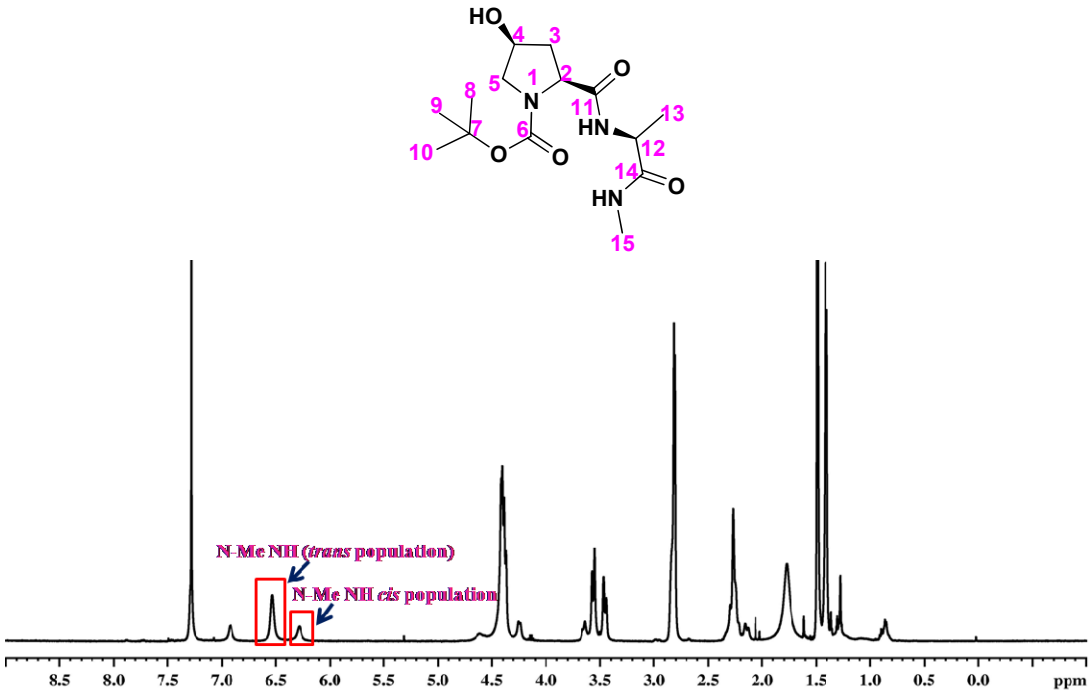


Figure 55: ^{1}H NMR spectrum of peptide **11** showing both *cis* and *trans* population in 1:0.25 ratio (500MHz, $CDCl_3$, 300 K)

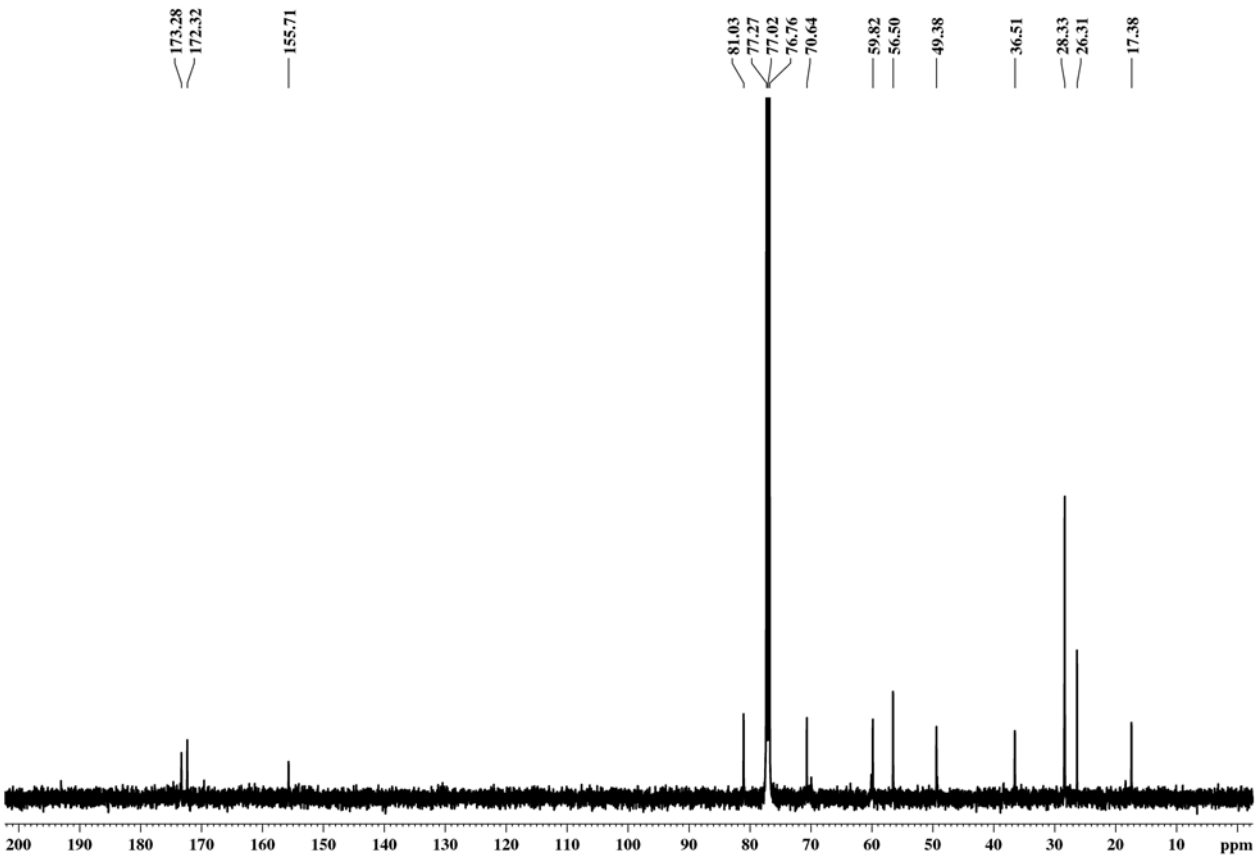


Figure 56: ^{13}C NMR spectrum of peptide **11** (500MHz, $CDCl_3$ 300 K)

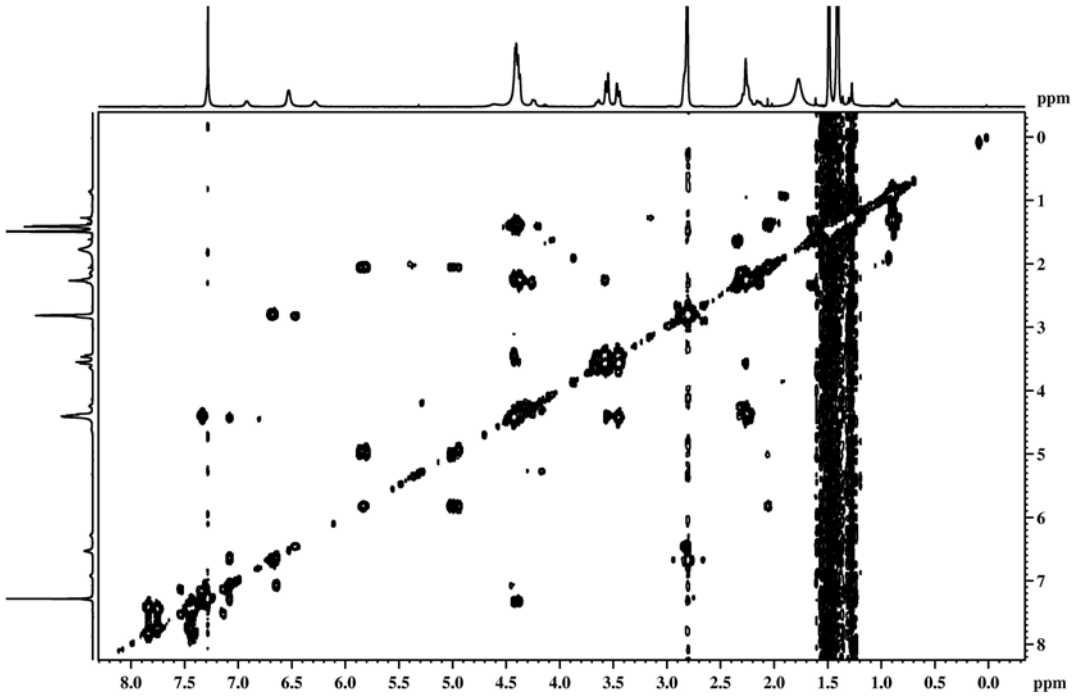


Figure 57: 2D-COSY NMR spectrum of peptide **11** (500MHz, $CDCl_3$, 300 K)

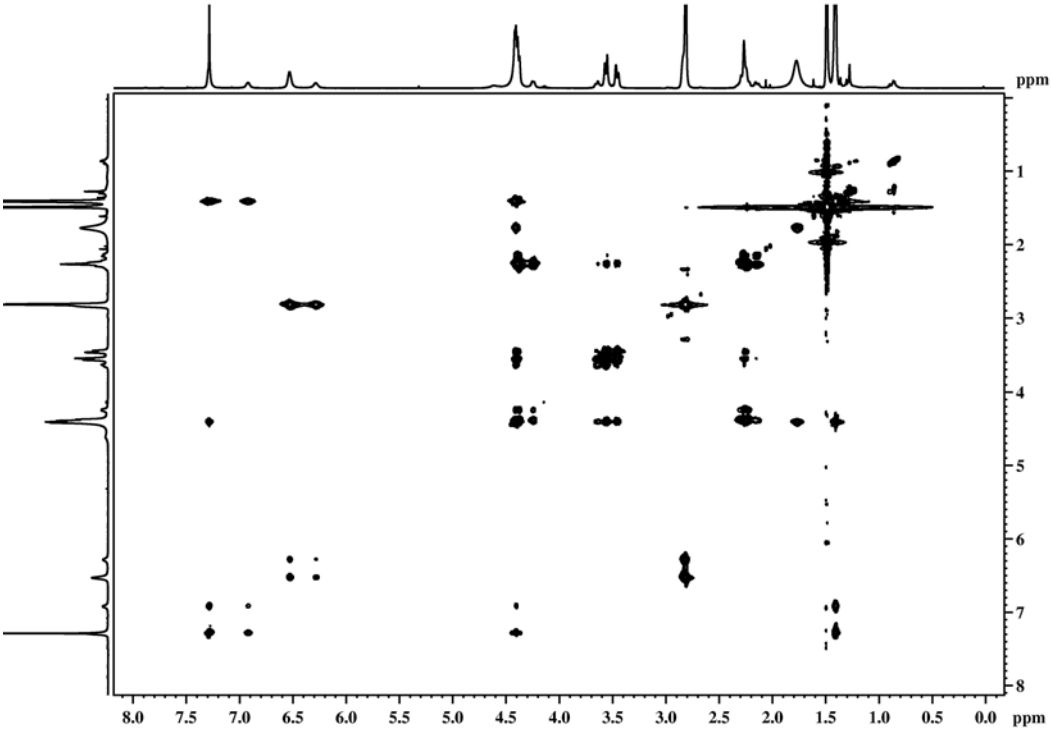


Figure 58: 2D-TOCSY NMR spectrum of peptide **11** (500MHz, $CDCl_3$, 300 K)

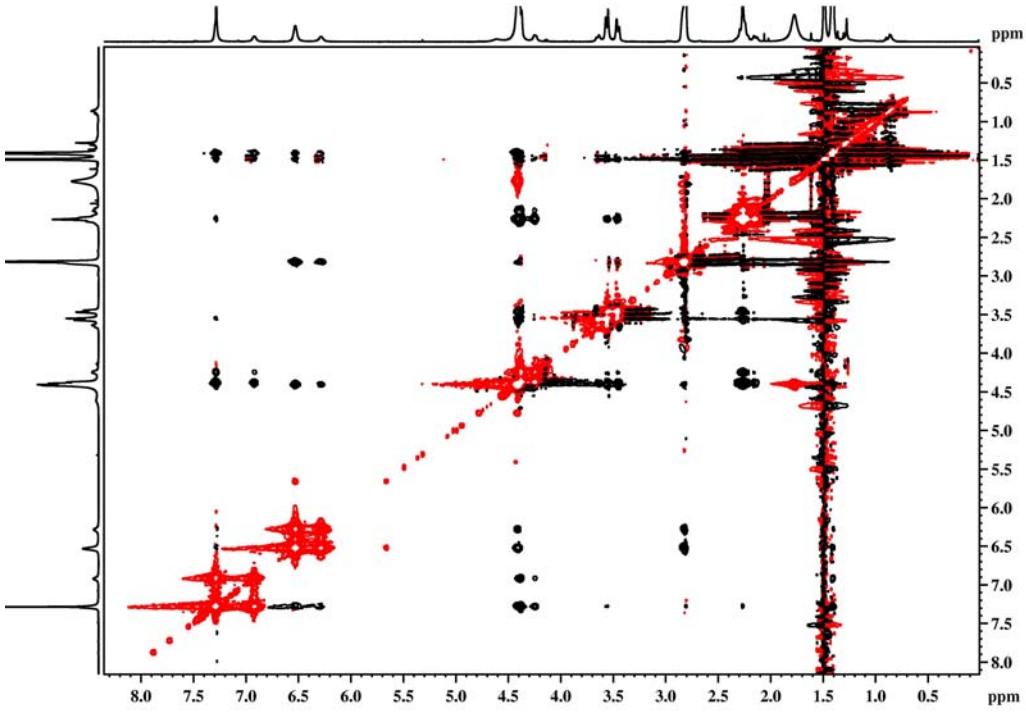


Figure 59: 2D-ROESY NMR spectrum of peptide **11** (500MHz, $CDCl_3$, 300 K)

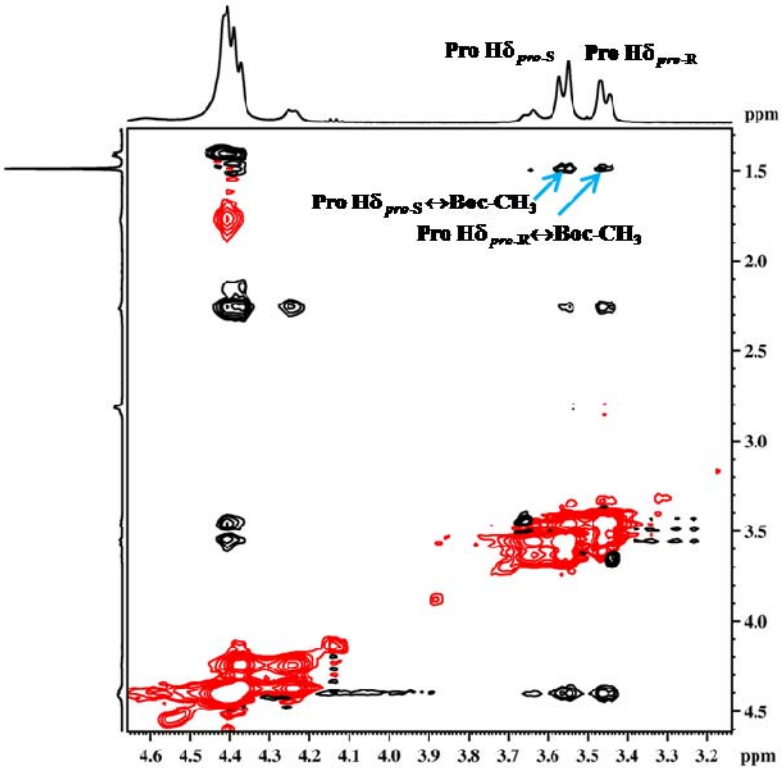


Figure 60: 2D-ROESY expansion of the major population of peptide **11** showing rOe between Pro$C_\delta H_{(pro\text{-}R)}$↔Boc-$CH_3$, Pro$C_\delta H_{(pro\text{-}S)}$ ↔ Boc-CH_3 confirmed that prolyl amide bond exist in *trans* conformation for major population (500MHz, $CDCl_3$,300 K)

Table 10: ^1H chemical shifts (δ in ppm) and coupling constants (J in Hz) for peptide **11** *trans* population (500 MHz, $CDCl_3$, 300 K)

Residue/ Protons	**NH1 (N-Me)**	**Pro**	**Ala**
NH	6.28 (*br*)	-	7.28 (*br*)
$C_\alpha H$	-	4.37(*m*)	4.46 (*m*)
$C_\beta H$/ $C_\beta H$	-	2.25 (*m*)	1.40 (*d*, $^3J_{C\alpha H\text{-}C\beta H}$ = 6.9)
$C_\gamma H$/	-	4.38 (*m*)	
$C_\delta H$/ $C_\delta H$	-	3.45 (*dd*,$^3J_{C\delta Pro\text{-}R\text{-}C\gamma H}$ 1.9,12.5)/ /3.55 (*dd*, $^3J_{C\delta Pro\text{-}S\text{-}C\gamma H}$ 3.1,1.9)	
Others :- N-Me = 2.82 (*d*,$^3J_{CNH\text{-}CMe\text{-}H}$ = 4.4), Boc$(CH_3)_3$(9H) = 1.48 (*s*)			
Carbons:2C=56.5, 3C=36.5, 4C=70.6, 5C=59.8, 6C=155.7, 7C=81.0, 8C/9C/10C=28.3, 11C=173.3, 12C=49.4, 13C=17.4, 14C=172.3, 15C=26.3			

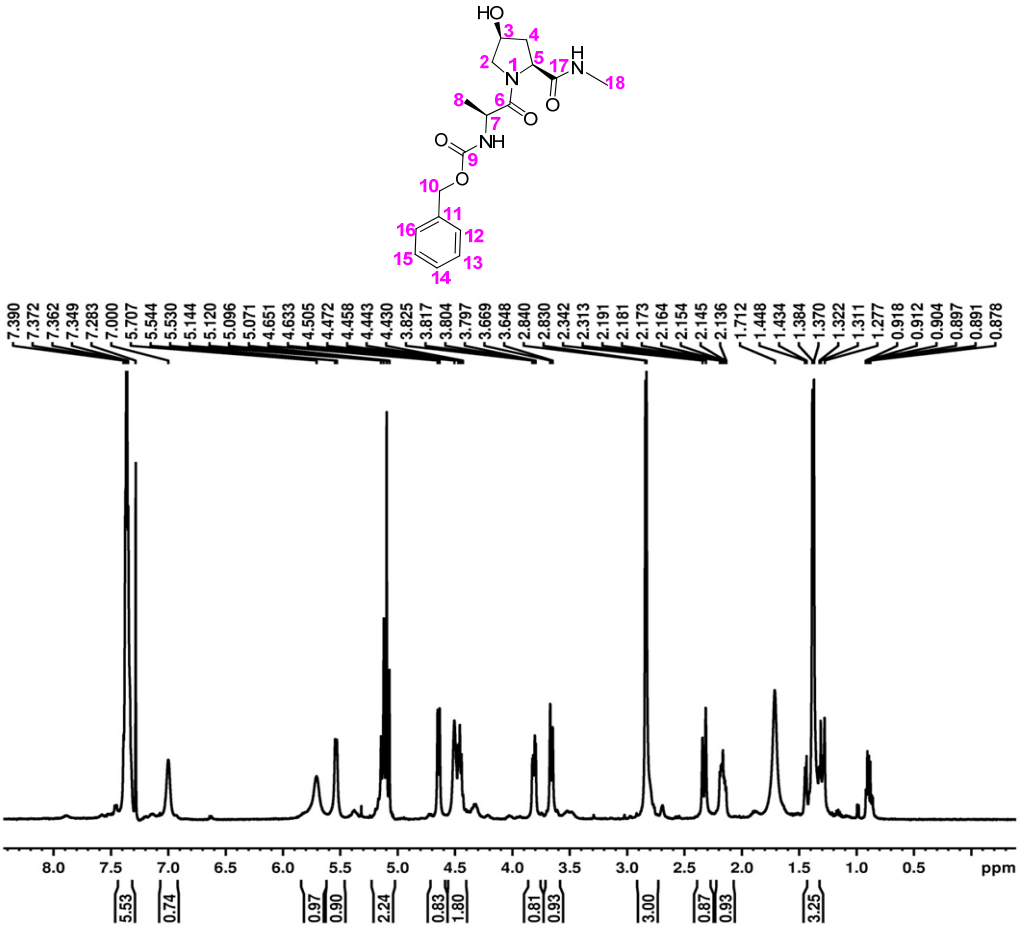


Figure 61: ^{1}H NMR spectrum of peptide **13** (500MHz, $CDCl_3$ 300 K)

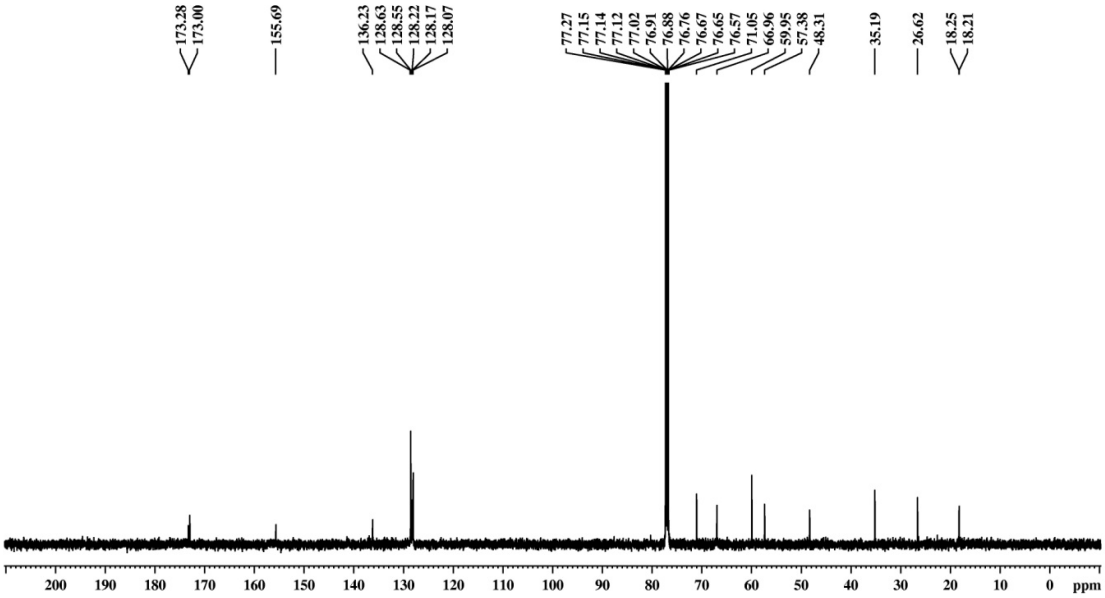


Figure 62: ^{13}C NMR spectrum of peptide **13** (500MHz, $CDCl_3$ 300 K)

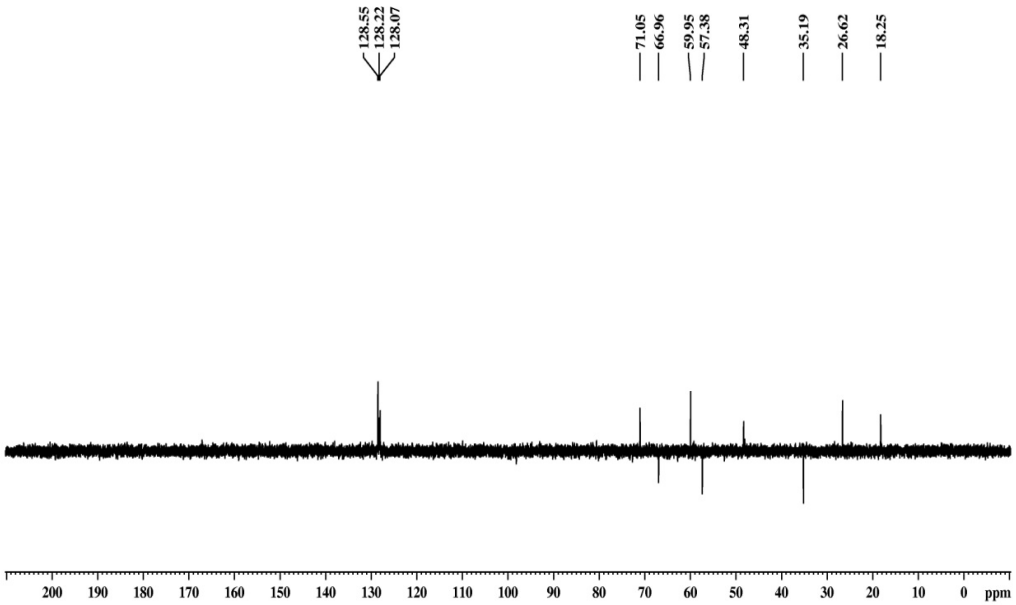


Figure 63: ^{13}C Dept-135 NMR spectrum of peptide **13** (500MHz, $CDCl_3$ 300 K)

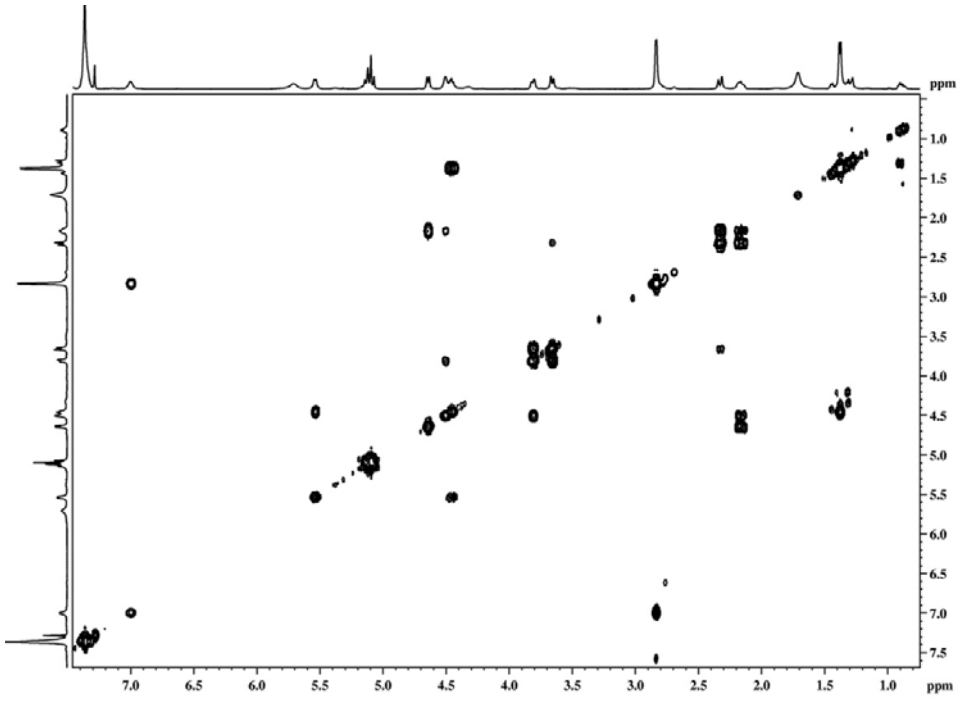


Figure 64: 2D-COSY NMR spectrum of peptide **13** (500MHz, $CDCl_3$ 300 K)

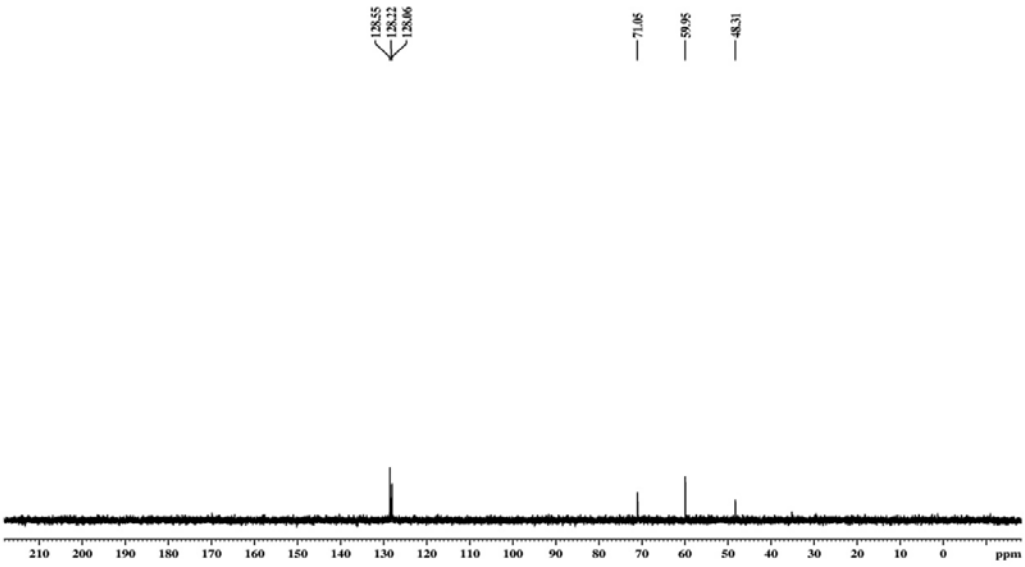


Figure 65: ^{13}C Dept-90 NMR spectrum of peptide **13** (500MHz, $CDCl_3$ 300 K)

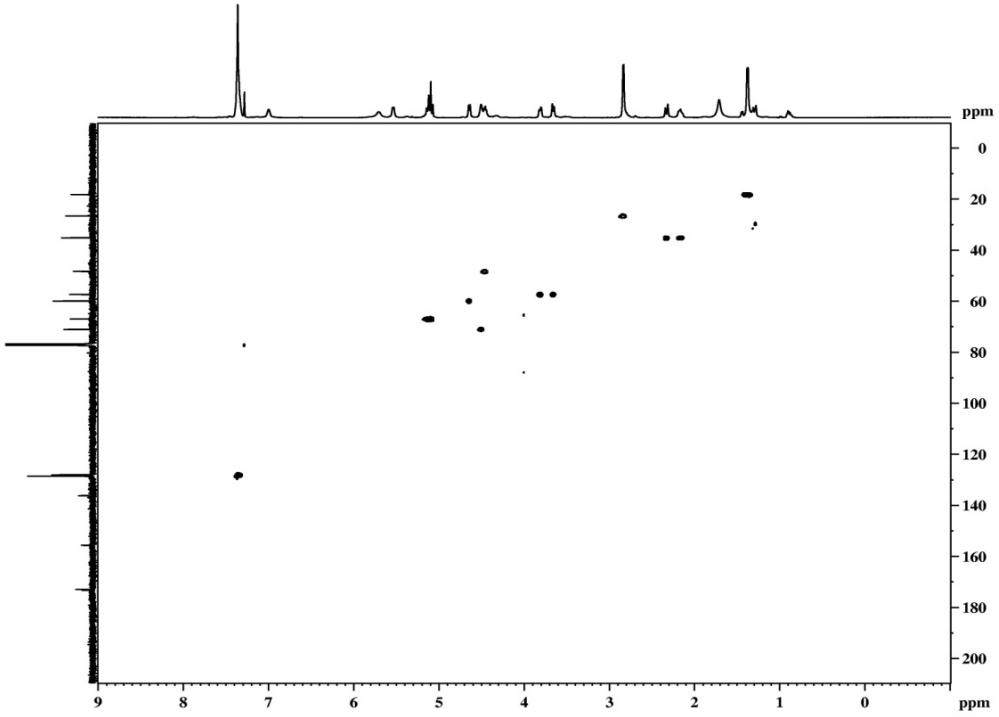


Figure 66: 2D-HSQC NMR spectrum of peptide **13** (500MHz, $CDCl_3$ 300 K)

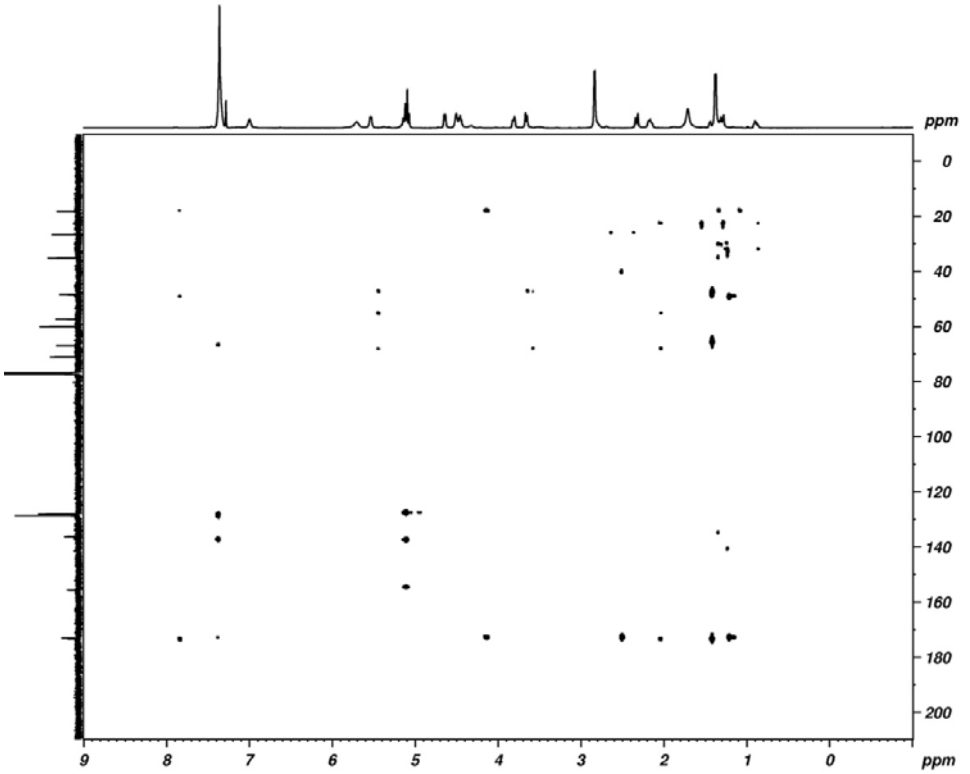


Figure 67: 2D-HMBC NMR spectrum of peptide **13** (500MHz, $CDCl_3$ 300 K)

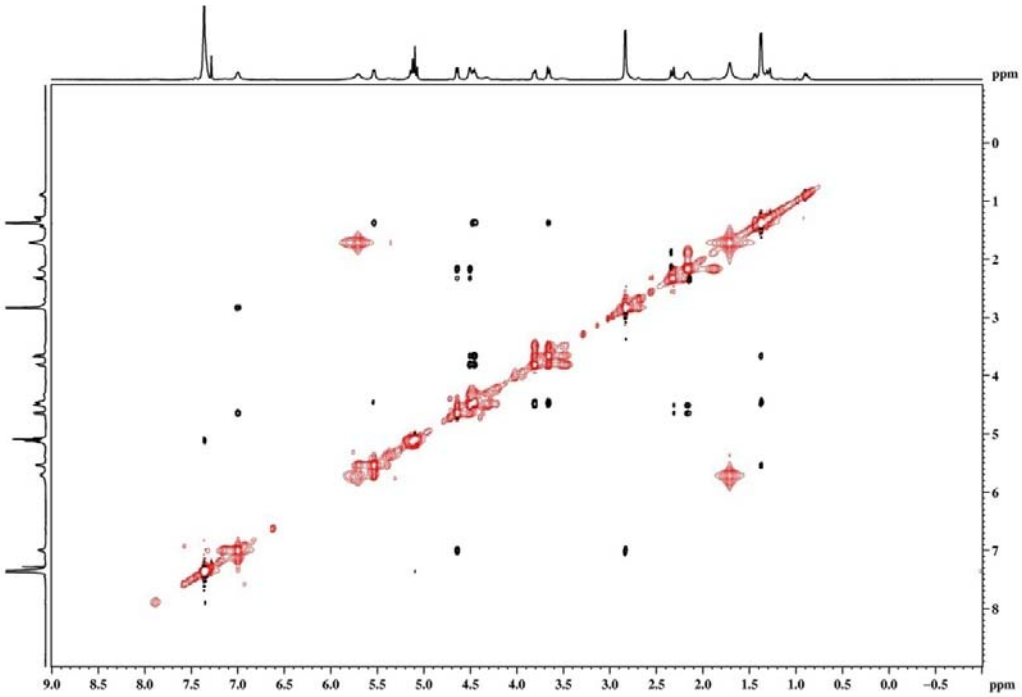


Figure 68: 2D-ROESY NMR spectrum of peptide **13** (500MHz, $CDCl_3$ 300 K)

Table 11: ^{1}H chemical shifts (δ in ppm) and coupling constants (J in Hz) for peptide **13** *trans* population (500 MHz, $CDCl_3$, 300 K)

Residue/ Protons	**NH1 (N-Me)**	**pro**	**Ala NH**
NH	7.00 (*br*)	-	5.54
CαH	-	4.63(*m*)	4.44(*m*)
CβH/ CβH	-	2.16,(*dd*, $^{3}J_{C\alpha H\text{-}C\beta H}$ = 4.6, 14.0)/ 2.31,(*dd*, $^{3}J_{C\alpha H\text{-}C\beta H}$ = 1.0, 14.0)	1.39 (*d*, $^{3}J_{C\alpha H\text{-}C\beta H}$ = 6.8)
CγH	-	4.50,*(m*)	
CδH/ CδH	-	3.65 (*br d,*12.0)/ /3.81 (*dd*, $^{3}J_{C\delta H\text{-}C\beta H}$ = 3.3,12.0)	
Others :-Pro-OH= 5.71, N-Me = 2.82 (*d*,$^{3}J_{CNH\text{-}CMe\text{-}H}$ = 4.8), Ph-CH_2(2H) = 5.10 (*m*) Ph-H(5H) = 7.41-7.27 (*m*)			
Carbons: 2C=59.9, 3C=35.2, 4C=71.1, 5C=57.4, 6C=173.3, 7C=48.3, 8C=18.2, 9C=155.7, 10C=66.9, 11C=136.2, 12C=128.5, 13C=128.2, 14C=128.1, 15C=128.2, 16C=128.5, 17C=173.0, 18C=26.3 ** $\Delta\delta/\Delta T$ (ppb) of **NMe-HN =** 5.10 and **Ala- HN =** 4.8			

Molecular Dynamics Study:

Energy minimization and restrained molecular dynamic simulations (MD) were performed on Discovery studio 3.0 version, using CHARMm[4] force field with default parameters throughout the simulation. Distance restraints used in the simulated molecular dynamics were calculated from the volume integrals of the cross peaks in the ROESY spectra, which were acquired with 200ms mixing time. Further, Offset corrections were performed for these rOe volumes,[5], using the following equation:

$$rOe_{eff} = (rOe_{exp} / \sin\Theta_1 . \sin\Theta_2)$$

Where, rOe_{eff} is the offset corrected rOe volumes, rOe_{exp} is the experimental volumes; Θ_1, Θ_2 are the angles between the spins' precession axis and the x,y plane.

These rOe_{eff} volumes were converted into distances by using two-spin approximation with a reference distance of 1.80 Å for the geminal protons, using the equation

$$r_2 = [r_1^{6} * \eta_1/\eta_2]^{1/6}$$

Where, r_2 = distance of the two nuclei to be measured, r_1 is the distance of two germinal protons, η_1 is the reference rOe effective volume, η_2 is the effective volume of the two nuclei.
A Force constant of 10 Kcal/Å 5 Kcal/Å were used for distance and torsionalrestraints. Minimizations were done initially with steepest descent algorithm followed by conjugate gradient methods for maximum 1000 iterations or RMS Deviation of 0.001 Kcal /mol, whichever was earlier. CDCl3 or DMSO was used explicitly, during the entire simulations. The molecules were initially equilibrated for 5 pS and then subjected to 5nS production run. Starting from 50 K, they were heated to 300 K in five steps increasing the temperature 50 K at each step. 20 structures were stored from the production run and are again energy minimized with the above-mentioned protocol. The structures were overlapped and the ensemble was presented in the figures (include figure numbers)

Table 12: Distance constraints used in the MD calculation for compound **2b** derived from ROESY experiment in $CDCl_3$ (700 MHz)

Sl.No.	Residue	ROE_{exp}	ROE_{eff}	Experimental distances, r (A^0)	Calculated distances (A^0) from MD
1	$AC_{\alpha}H$ - A_{NH}	5.26E+06	5.86E+06	2.89	2.60
2	$AC_{\alpha}H$ - NMe_{HN}	3.96E+06	4.34E+06	3.04	3.08
3	$AC_{\beta}H$ - $AC_{\alpha}H$	2.45E+07	2.73E+07	2.24	2.22
4	$AC_{\beta}H$ - A_{NH}	1.40E+07	1.73E+07	2.41	2.81
5	$AC_{\beta}H$ - NMe_{HN}	2.39E+06	2.91E+06	3.25	3.42
6	$PC_{\alpha}Me$ - $PC_{\beta}H_{(pro\text{-}R)}$	1.33E+07	1.52E+07	2.46	2.49
7	$PC_{\alpha}Me$ - $PC_{\delta}H_{(pro\text{-}R)}$	6.96E+06	7.98E+06	2.74	3.01
8	$PC_{\alpha}Me$ - $PC_{\gamma}H$	1.82E+06	1.99E+06	3.46	3.68
9	$PC_{\beta}H_{(pro\text{-}R)}$ - $AC_{\alpha}H$	1.57E+06	1.65E+06	3.57	3.81
10	$PC_{\beta}H_{(pro\text{-}R)}$ - $AC_{\beta}H$	2.23E+06	2.60E+06	3.31	3.46
11	$PC_{\beta}H_{(pro\text{-}R)}$ - A_{NH}	3.85E+06	4.49E+06	3.02	2.89
12	$PC_{\beta}H_{(pro\text{-}R)}$ - $PC_{\gamma}H$	7.38E+06	7.74E+06	2.76	2.88
13	$PC_{\beta}H_{(pro\text{-}S)}$ - A_{NH}	1.69E+06	2.00E+06	3.45	3.52
14	$PC_{\beta}H_{(pro\text{-}S)}$ - $PC_{\alpha}Me$	2.37E+07	2.76E+07	2.23	2.29
15	$PC_{\beta}H_{(pro\text{-}S)}$ - $PC_{\delta}H_{(pro\text{-}R)}$	7.61E+06	8.18E+06	2.73	2.95
16	$PC_{\beta}H_{(pro\text{-}S)}$ - $PC_{\gamma}H$	1.66E+07	1.77E+07	2.40	2.34
17	$PC_{\delta}H_{(pro\text{-}R)}$- $PC_{\gamma}H$	1.67E+07	1.69E+07	2.42	2.59
18	$PC_{\delta}H_{(pro\text{-}S)}$- A_{HN}	4.74E+06	5.29E+06	2.94	3.18
19	$PC_{\delta}H_{(pro\text{-}S)}$- $PC_{\delta}H_{(pro\text{-}R)}$	**9.91E+07**	**1.00E+08**	**1.80**	**1.78**
20	$PC_{\delta}H_{(pro\text{-}S)}$- $PC_{\gamma}H$	8.40E+06	8.43E+06	2.72	2.61

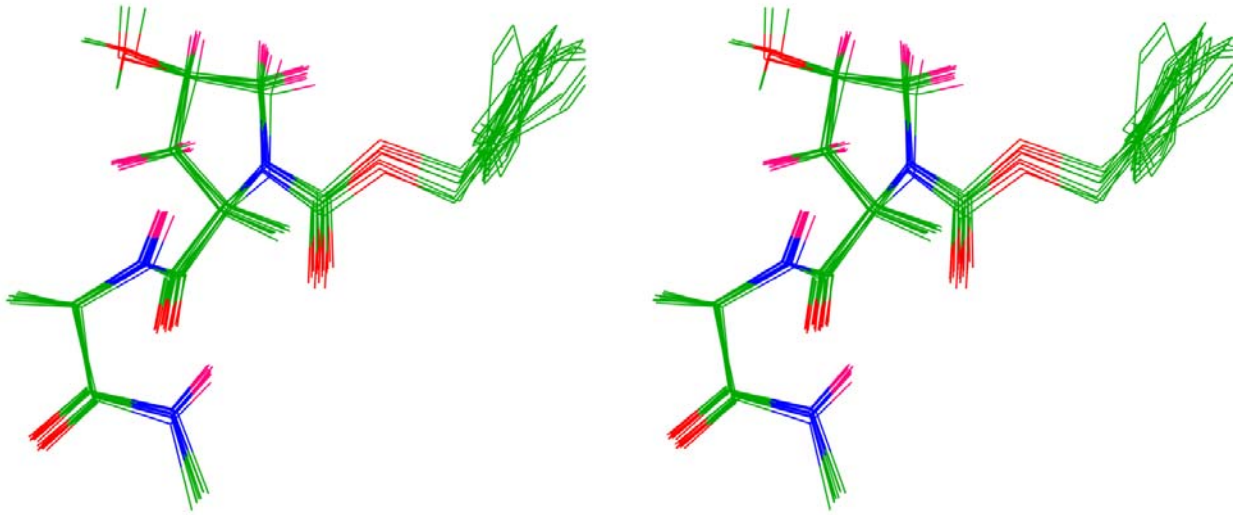


Figure 69: 15 superimposed least energy conformations of compound **2b.**

Table 13: Distance constraints used in the MD calculation for compound **3** derived from ROESY experiment in $CDCl_3$ (700 MHz)

Sl.No.	Residue	ROE_{exp}	ROE_{eff}	Experimental distances, r (A^0)	Calculated distances (A^0) from MD
1	$AC_{\alpha}H$ - A_{NH}	2.82E+06	3.18E+06	2.74	2.84
2	$AC_{\alpha}H$ - NMe_{HN}	2.37E+06	2.64E+06	2.83	3.05
3	$AC_{\beta}H$ - A_{NH}	6.80E+06	8.60E+06	2.32	2.35
4	$AC_{\beta}H$ - NMe	1.55E+06	1.80E+06	3.01	3.34
5	$AC_{\beta}H$ - NMe_{HN}	1.32E+06	1.65E+06	3.06	2.84
6	$AC_{\beta}H$ - $PC_{\beta}H_{(pro\text{-}R)}$	2.72E+06	3.22E+06	2.74	2.87
7	$PC_{\alpha}Me$ - A_{NH}	3.99E+06	4.97E+06	2.56	2.65
8	$PC_{\alpha}Me$ - $PC_{\beta}H_{(pro\text{-}R)}$	4.72E+06	5.50E+06	2.50	2.85
9	$PC_{\alpha}Me$ - $PC_{\beta}H_{(pro\text{-}S)}$	1.40E+07	1.66E+07	2.08	2.38
10	$PC_{\alpha}Me$ - $PC_{\delta}H_{(pro\text{-}R)}$	3.38E+06	3.77E+06	2.67	2.65
11	$PC_{\alpha}Me$ - $PC_{\delta}H_{(pro\text{-}S)}$	4.31E+05	4.79E+05	3.76	3.65
12	$PC_{\alpha}Me$ - $PC_{\gamma}H$	1.09E+06	1.21E+06	3.22	3.13
13	$PC_{\beta}H_{(pro\text{-}R)}$ - A_{NH}	2.07E+06	2.46E+06	2.86	2.92
14	$PC_{\beta}H_{(pro\text{-}R)}$ - $PC_{\delta}H_{(pro\text{-}R)}$	8.51E+05	9.04E+05	3.38	3.46
15	$PC_{\beta}H_{(pro\text{-}R)}$ - $PC_{\gamma}H$	4.74E+06	5.00E+06	2.54	2.67
16	$PC_{\beta}H_{(pro\text{-}S)}$ - $PC_{\delta}H_{(pro\text{-}R)}$	4.28E+06	4.63E+06	2.57	2.52
17	$PC_{\beta}H_{(pro\text{-}S)}$ - $PC_{\delta}H_{(pro\text{-}S)}$	3.27E+06	3.53E+06	2.69	2.81
18	$PC_{\beta}H_{(pro\text{-}S)}$ - $PC_{\gamma}H$	1.02E+07	1.10E+07	2.23	2.15
19	$PC_{\delta}H_{(pro\text{-}S)}$- $PC_{\delta}H_{(pro\text{-}R)}$	**3.92E+07**	**3.97E+07**	**1.80**	**1.78**
20	$PC_{\delta}H_{(pro\text{-}R)}$- $PC_{\gamma}H$	9.70E+06	9.79E+06	2.27	2.32
21	$PC_{\delta}H_{(pro\text{-}S)}$- $PC_{\gamma}H$	4.47E+06	4.50E+06	2.59	2.68

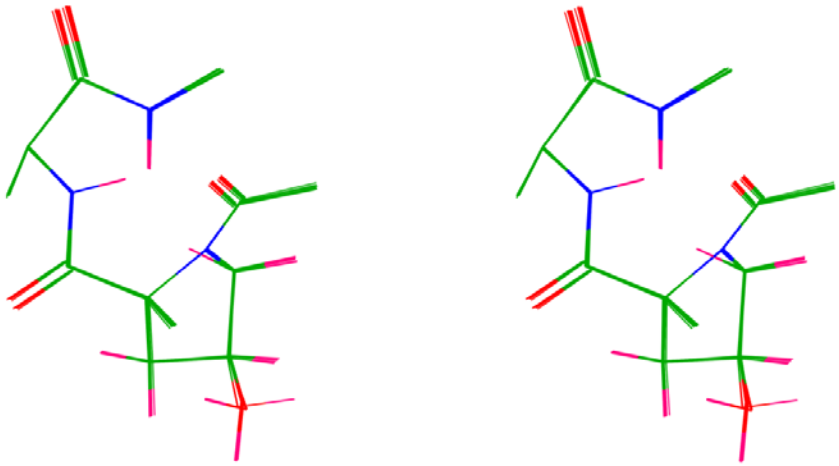


Figure 70: 15 superimposed least energy conformations of compound **3**

Table 14: Distance constraints used in the MD calculations for compound **6b** derived from ROESY experiment in $CDCl_3$ (700 MHz)

Sl.No.	Residue	ROE_{exp}	ROE_{eff}	Experimental distances, r (A^0)	Calculated distances (A^0) from MD
1	$AC_{\alpha}H$ - A_{HN}	1.32E+06	1.35E+06	3.12	2.98
2	$AC_{\beta}H$ - A_{HN}	3.04E+06	3.38E+06	2.66	2.62
3	$AC_{\beta}H$ - NMe_{HN}	9.24E+05	1.08E+06	3.24	3.38
4	$AC_{\beta}H$ - $PC_{\delta}H_{(pro\text{-}R)}$	5.49E+05	6.01E+05	3.57	3.75
5	$AC_{\beta}H$ - $PC_{\delta}H_{(pro\text{-}S)}$	4.67E+06	5.12E+06	2.50	3.13
6	$PC_{\alpha}Me$ - NMe_{HN}	3.50E+06	4.03E+06	2.60	2.85
7	$PC_{\alpha}Me$ - $PC_{\delta}H_{(pro\text{-}R)}$	1.28E+06	1.38E+06	3.11	3.18
8	$PC_{\alpha}Me$ - $PC_{\gamma}H$	1.62E+06	1.75E+06	2.99	3.13
9	$PC_{\beta}H_{(pro\text{-}R)}$ - $PC_{\beta}H_{(pro\text{-}S)}$	**3.36E+07**	**3.66E+07**	**1.80**	**1.78**
10	$PC_{\beta}H_{(pro\text{-}R)}$ - $PC_{\delta}H_{(pro\text{-}S)}$	1.59E+06	1.64E+06	3.02	3.20
11	$PC_{\beta}H_{(pro\text{-}R)}$- $PC_{\gamma}H$	1.82E+06	1.87E+06	2.97	2.76
12	$PC_{\beta}H_{(pro\text{-}R)}$- $PC_{\delta}H_{(pro\text{-}R)}$	1.96E+06	2.09E+06	2.90	3.05
13	$PC_{\beta}H_{(pro\text{-}S)}$- $PC_{\gamma}H$	4.09E+06	4.36E+06	2.57	2.61
14	$PC_{\delta}H_{(pro\text{-}R)}$ - $PC_{\gamma}H$	5.56E+06	5.58E+06	2.46	2.73
15	$PC_{\delta}H_{(pro\text{-}S)}$ - $PC_{\gamma}H$	2.34E+06	2.35E+06	2.85	2.69
16	$PC_{\gamma}H$ - MOM_{Me}	1.04E+06	1.05E+06	3.25	2.98

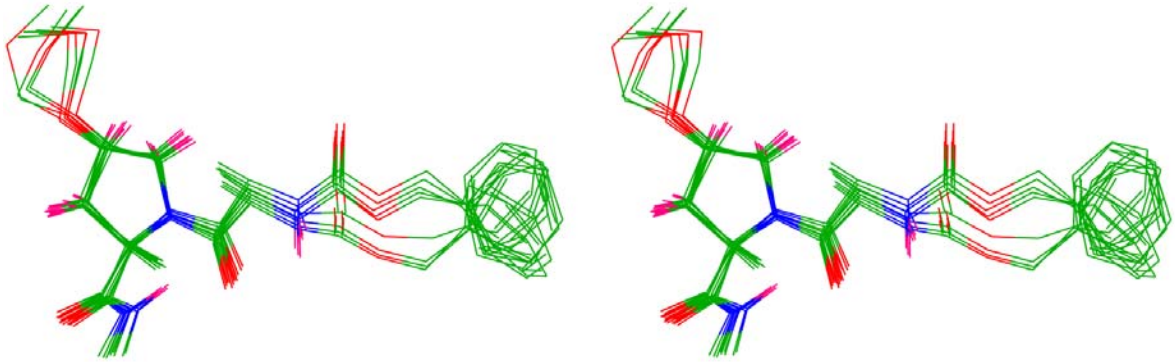


Figure 71: 15 superimposed least energy conformations of compound **6b.**

Table 15: Distance constraints used in the MD calculation for compound **7a** derived from ROESY experiment in DMSO-d_6 (700 MHz)

Sl.No.	Residue	ROE_{exp}	ROE_{eff}	Experimental distances, r (A^0)	Calculated distances (A^0) from MD
1	$AC_{\alpha}H$ - A_{HN}	3.95E+06	4.48E+06	2.56	2.68
2	$AC_{\alpha}H$ - NMe_{HN}	7.02E+05	7.75E+05	3.43	3.57
3	$AC_{\beta}H$ - $PC_{\delta}H_{(pro\text{-}R)}$	1.24E+06	1.40E+06	3.10	3.27
4	$AC_{\beta}H$ - $PC_{\delta}H_{(pro\text{-}S)}$	4.45E+06	5.03E+06	2.51	2.72
5	NMe_{Me} - NMe_{HN}	8.53E+06	9.71E+06	2.25	2.17
6	$PC_{\alpha}Me$ - $PC_{\beta}H$	1.45E+07	1.70E+07	2.05	2.15
7	$PC_{\alpha}Me$ - $PC_{\gamma}H$	4.31E+06	4.78E+06	2.53	2.68
8	$PC_{\beta}H$- $PC_{\delta}H_{(pro\text{-}R)}$	3.40E+06	3.65E+06	2.65	2.81
9	$PC_{\beta}H$- $PC_{\delta}H_{(pro\text{-}S)}$	2.75E+06	2.95E+06	2.74	2.91
10	$PC_{\beta}H$- $PC_{\gamma}H$	1.41E+07	1.52E+07	2.09	2.11
11	$PC_{\delta}H_{(pro\text{-}R)}$ - $AC_{\alpha}H$	1.50E+07	1.53E+07	2.09	1.96
12	$PC_{\delta}H_{(pro\text{-}R)}$ –A_{NH}	8.08E+05	9.14E+05	3.33	3.56
13	$PC_{\delta}H_{(pro\text{-}R)}$-NMeHN	2.13E+06	2.34E+06	2.85	2.98
14	$PC_{\delta}H_{(pro\text{-}R)}$- $PC_{\alpha}Me$	5.12E+05	5.67E+05	3.61	3.72
15	$PC_{\delta}H_{(pro\text{-}R)}$- $PC_{\beta}H$	2.99E+06	3.21E+06	2.70	2.83
16	$PC_{\delta}H_{(pro\text{-}R)}$- $PC_{\gamma}H$	5.66E+06	5.76E+06	2.45	2.61
17	$PC_{\delta}H_{(pro\text{-}S)}$ - $PC_{\alpha}Me$	1.16E+07	1.18E+07	2.18	2.25
18	$PC_{\delta}H_{(pro\text{-}S)}$ - $AC_{\beta}H$	2.91E+06	3.29E+06	2.70	2.86
19	$PC_{\delta}H_{(pro\text{-}S)}$ - $PC_{\alpha}Me$	1.51E+06	1.67E+06	3.02	3.13
20	$PC_{\delta}H_{(pro\text{-}S)}$ - $PC_{\beta}H$	2.69E+06	2.88E+06	2.75	2.89
21	$PC_{\delta}H_{(pro\text{-}S)}$ - $PC_{\delta}H_{(pro\text{-}R)}$	**3.64E+07**	**3.68E+07**	**1.80**	**1.78**
22	$PC_{\delta}H_{(pro\text{-}S)}$ - $PC_{\gamma}H$	1.26E+07	1.28E+07	2.15	2.26

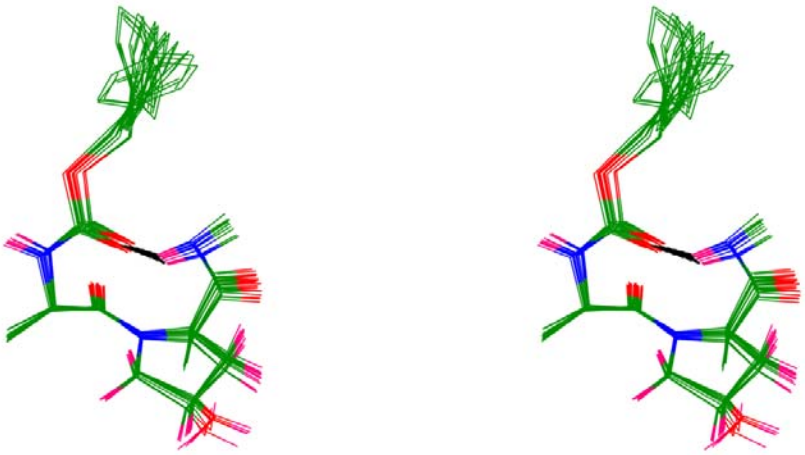


Figure 72: 15 superimposed least energy conformations of **7a**

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