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Supplementary Information

Cyclodipeptides from Metagenomic Library of a Japanese Marine Sponge

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Comparative data of cyclodipeptide 1-7 production in clone pDC113 and negative control (NC, strain EPI300 carrying pCC1FOS fosmid vector)

The respective 2 plates of pDC113 and NC were cultured in the same conditions (30 °C, **3d**) and subjected to the same extraction and separation procedures and finally using same volume of MeOH to dissolve the LH-20 cyclodipeptides fraction before injection (both 5 μL) to RP-HPLC-DAD. HPLC analysis was performed on ODS column (Cosmosil $5C_{18}$ PAQ waters, 4.6 × 250 mm) with a mixture of H_2O and MeCN, both containing 0.05% TFA: 0-20 min, 5-35% MeCN; 20-45 min, 35-100% MeCN; and 45-55 min, 100% MeCN, 0.8 mL min^{-1}. DAD profiles were measured with a Shimadzu HPLC System: LC-20AD and SPD-20A Prominence Diode Array Detector.

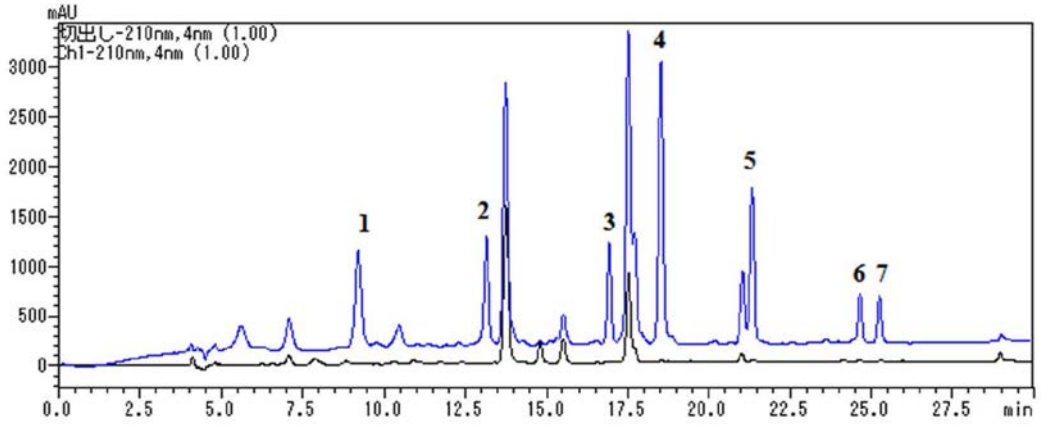

Figure S1. RP-HPLC-DAD profile of LH-20 fraction of pDC113 and NC. Blue line indicates profile of pDC113; black line indicates profile of negative control.

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^{1}H, ^{13}C chemical shifts, and ^{1}H-^{1}H COSY data of cyclodipeptides 1-7 and 9

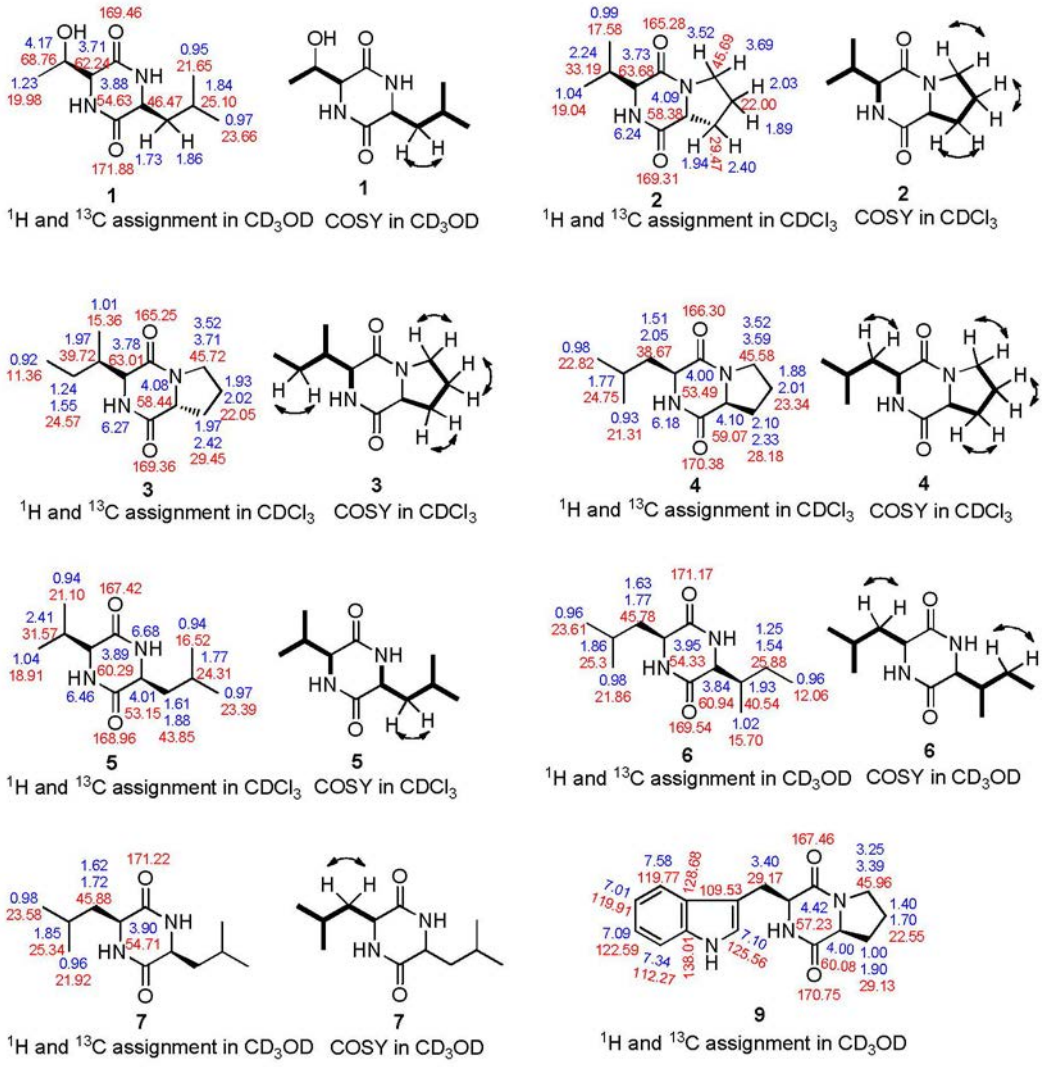

Figure S2. Chemical shifts and COSY of cyclodipeptides **1**-**7** and **9**. ^{1}H NMR (500 MHz) chemical shifts (blue), ^{13}C NMR (125 MHz) chemical shifts (red) and ^{1}H-^{1}H COSY (bold line and arrows) are shown.

^{1}H, ^{13}C chemical shifts, and ^{1}H-^{1}H COSY data of cyclodipeptides 8, 10 and 11

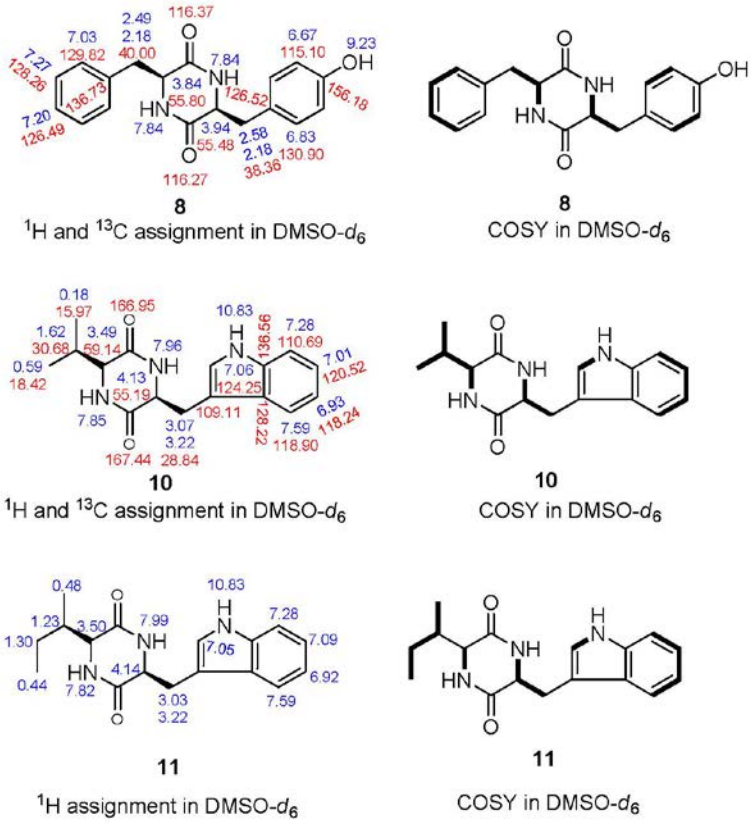

Figure S3. Chemical shifts and COSY of cyclodipeptides **8**, **10** and **11**. ^{1}H NMR (500 MHz) chemical shifts (blue), ^{13}C NMR (125 MHz) chemical shifts (red), and main ^{1}H-^{1}H COSY (bold line) correlations are shown. ^{13}C NMR of **10** were inferred from its HMQC and some of HMBC data.

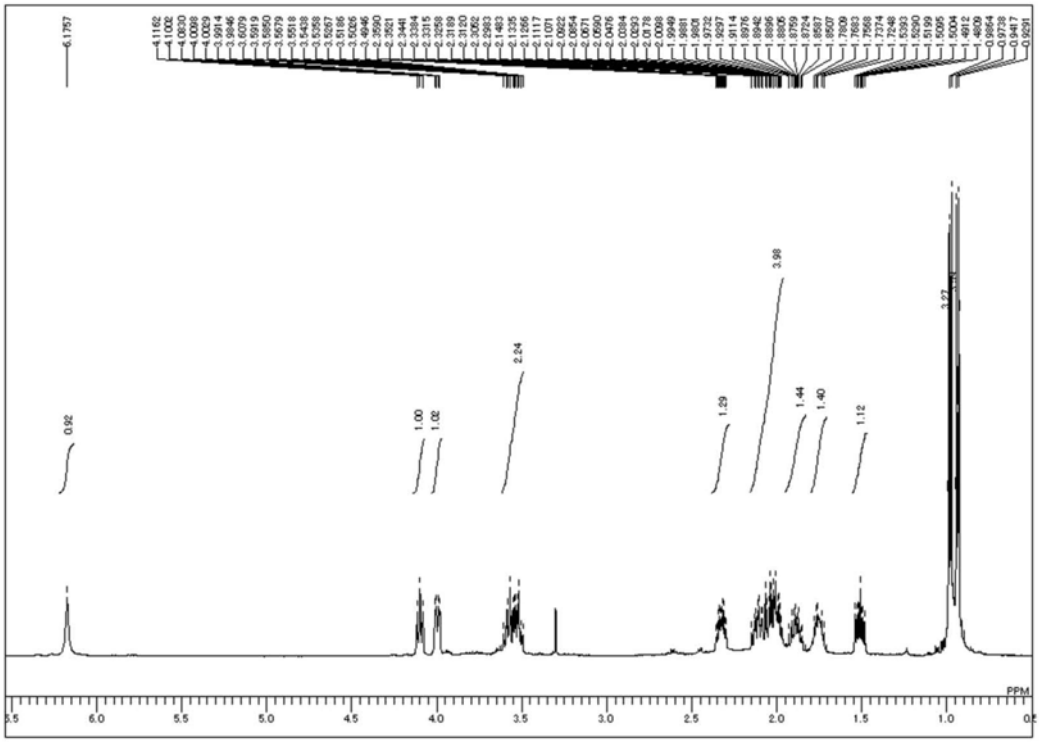

Figure S4. ^{1}H NMR spectrum of Cyclo(L-Leu-L-Pro) (**4**) (500 MHz, $CDCl_3$).

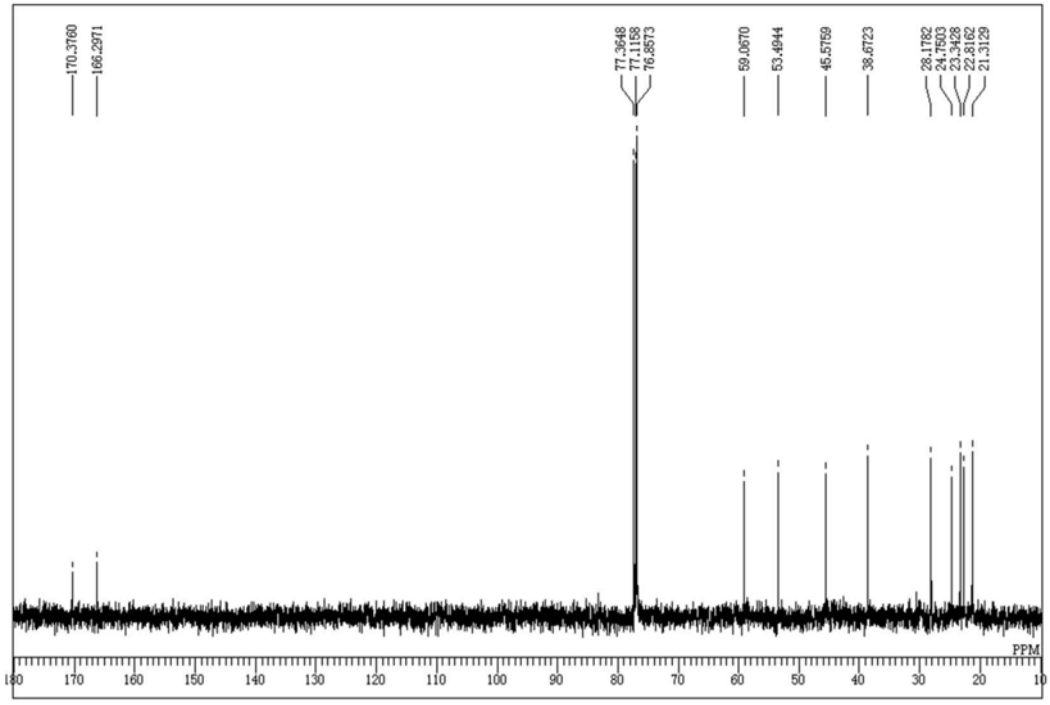

Figure S5. ^{13}C NMR spectrum of Cyclo(L-Leu-L-Pro) (**4**) (125 MHz, $CDCl_3$).

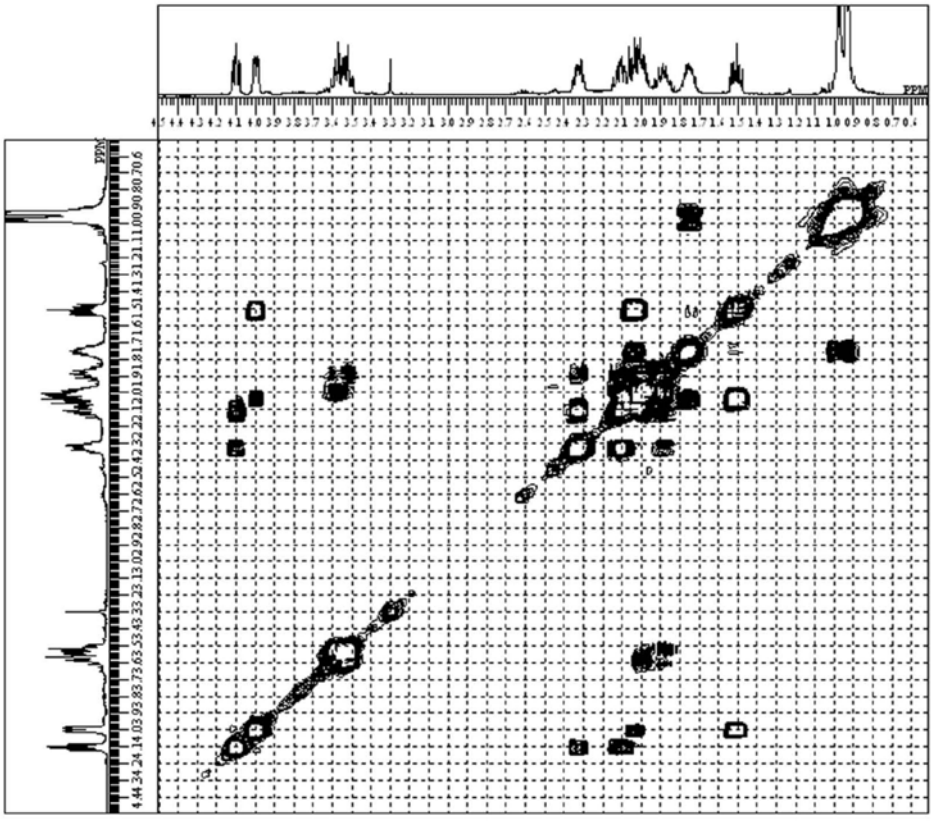

Figure S6. ^{1}H-^{1}H COSY spectrum of Cyclo(L-Leu-L-Pro) (**4**).

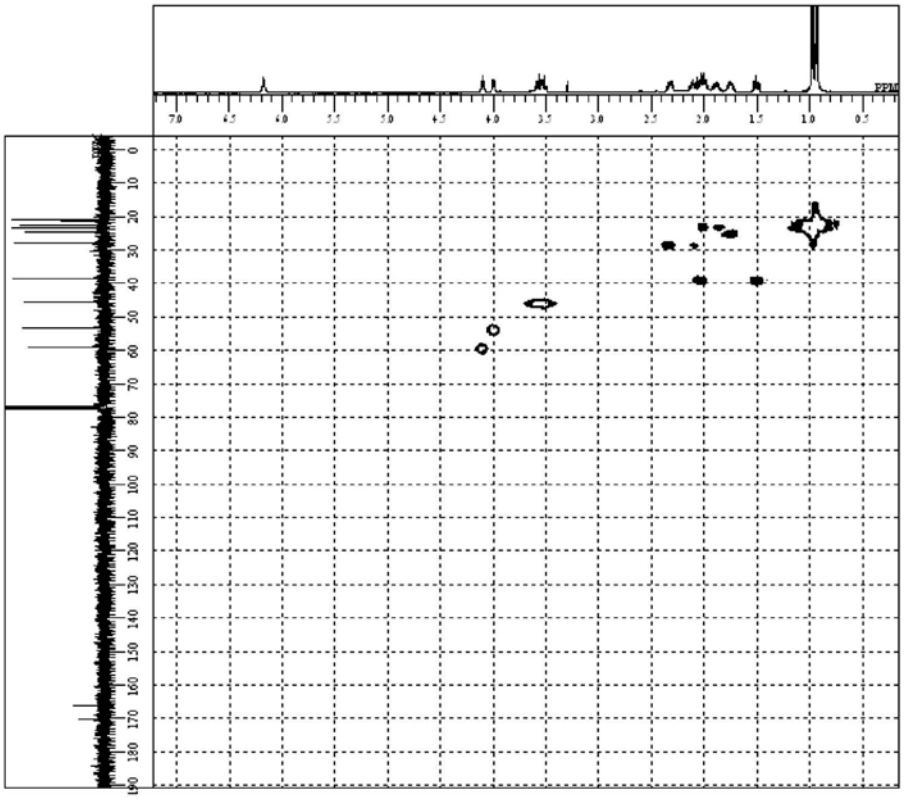

Figure S7. HMQC spectrum of Cyclo(L-Leu-L-Pro) (**4**).

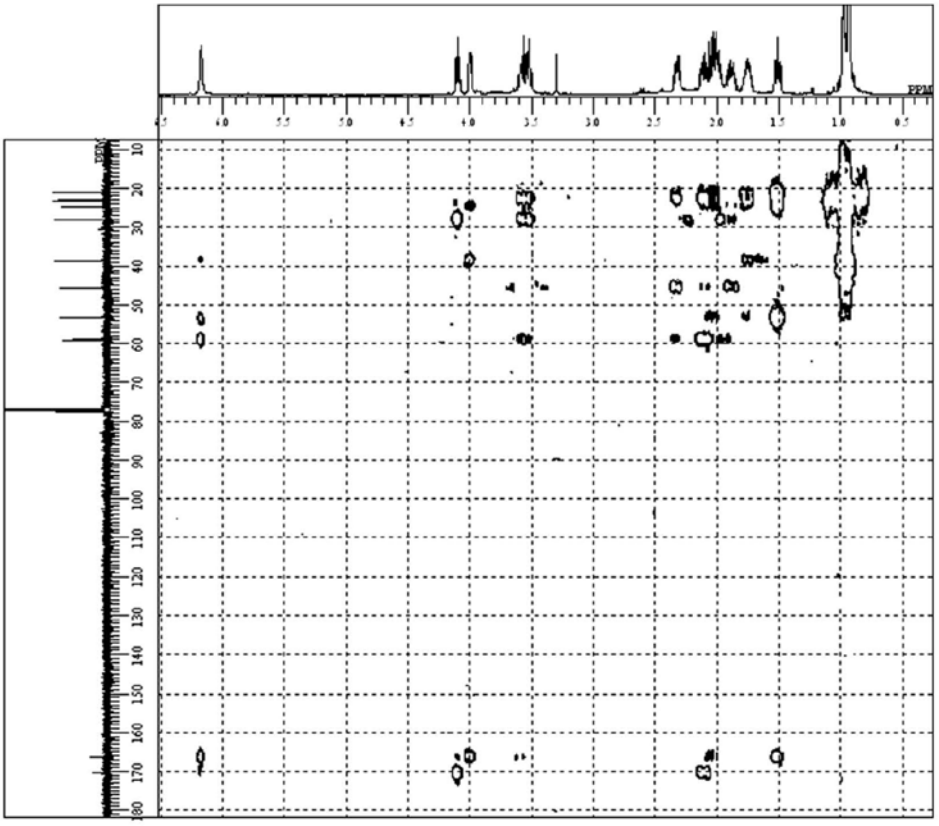

Figure S8. HMBC spectrum of Cyclo(L-Leu-L-Pro) (**4**).

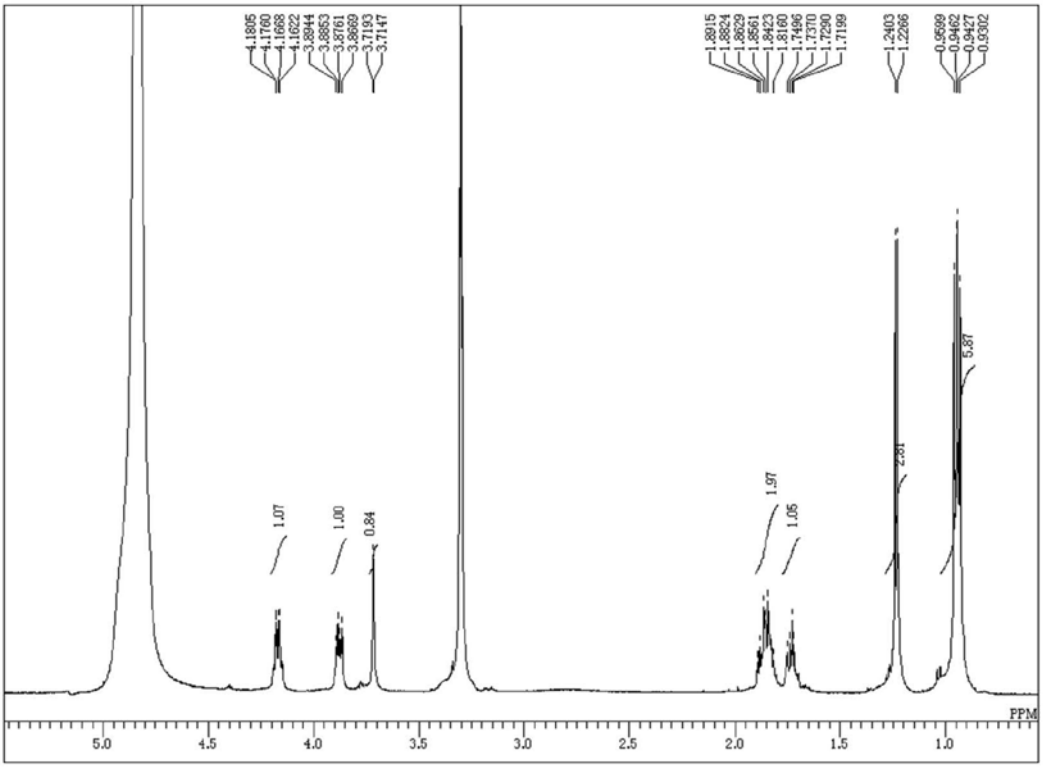

Figure S9. [1]H NMR of Cyclo(L-Thr-L-Leu) (**1**) (500 MHz, CD_3OD).

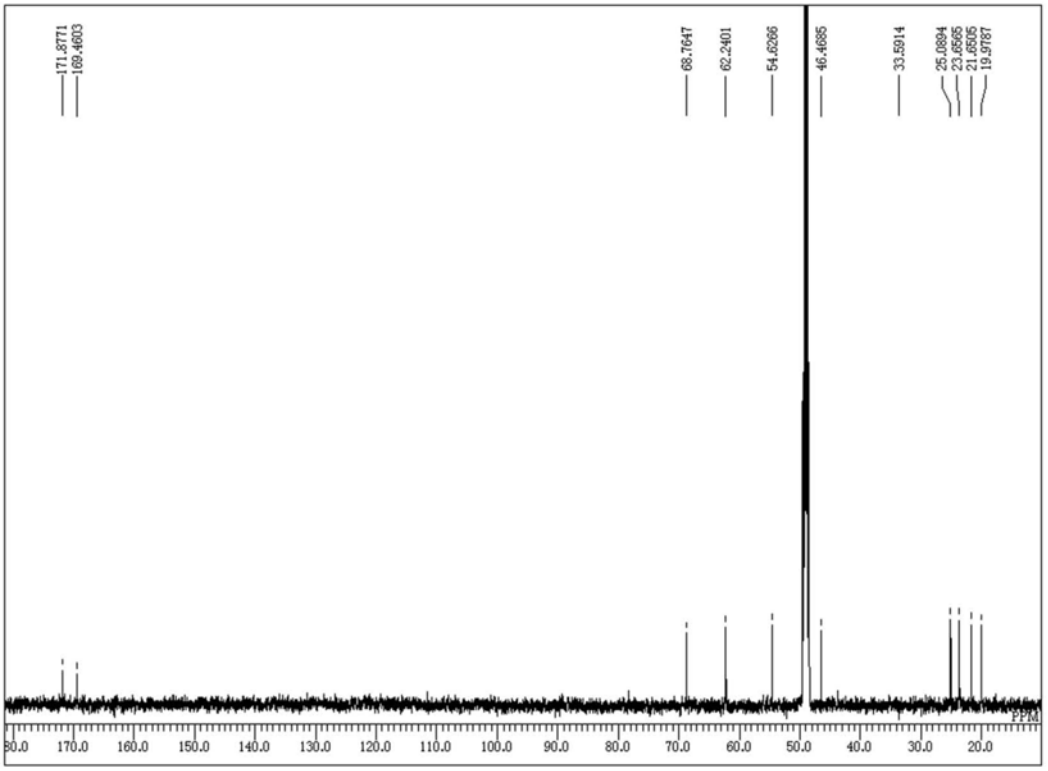

Figure S10. [13]C NMR of Cyclo(L-Thr-L-Leu) (**1**) (125 MHz, CD_3OD).

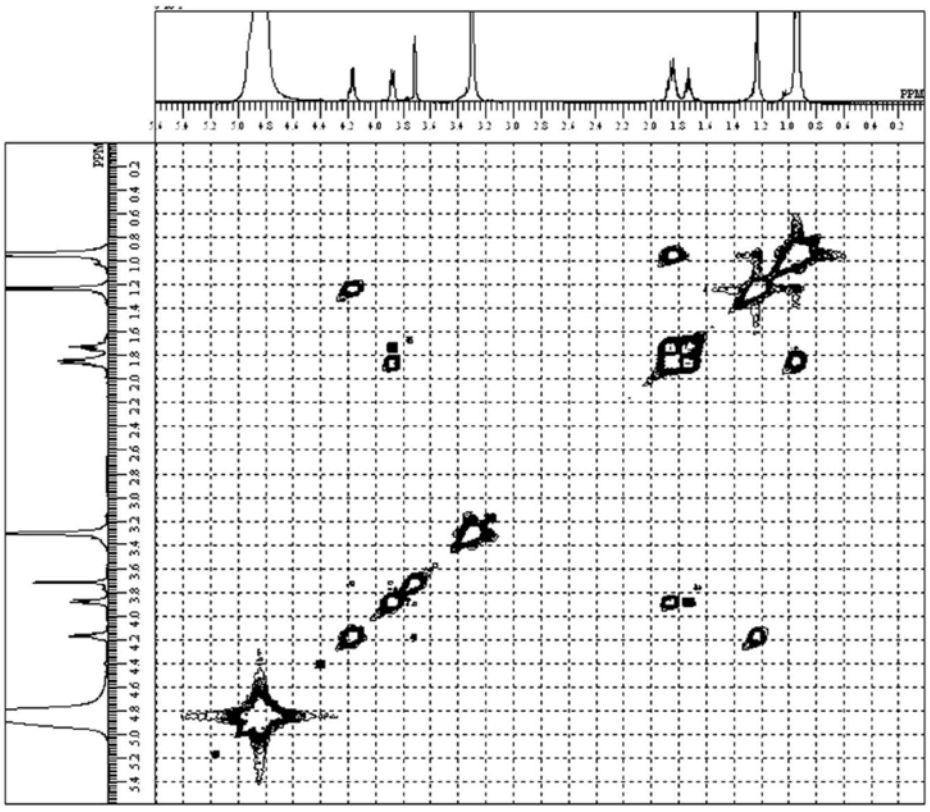

Figure S11. ^{1}H-^{1}H COSY of Cyclo(L-Thr-L-Leu) (**1**).

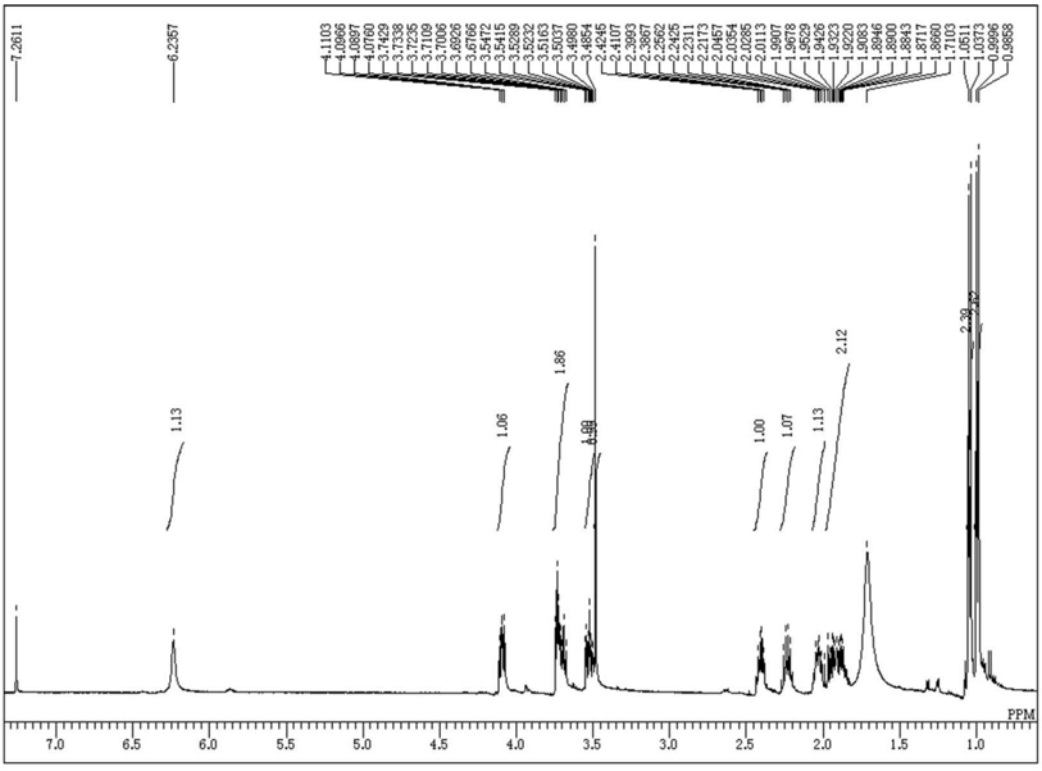

Figure S12. ^{1}H NMR of Cyclo(L-Val-D-Pro) (**2**) (500 MHz, $CDCl_3$).

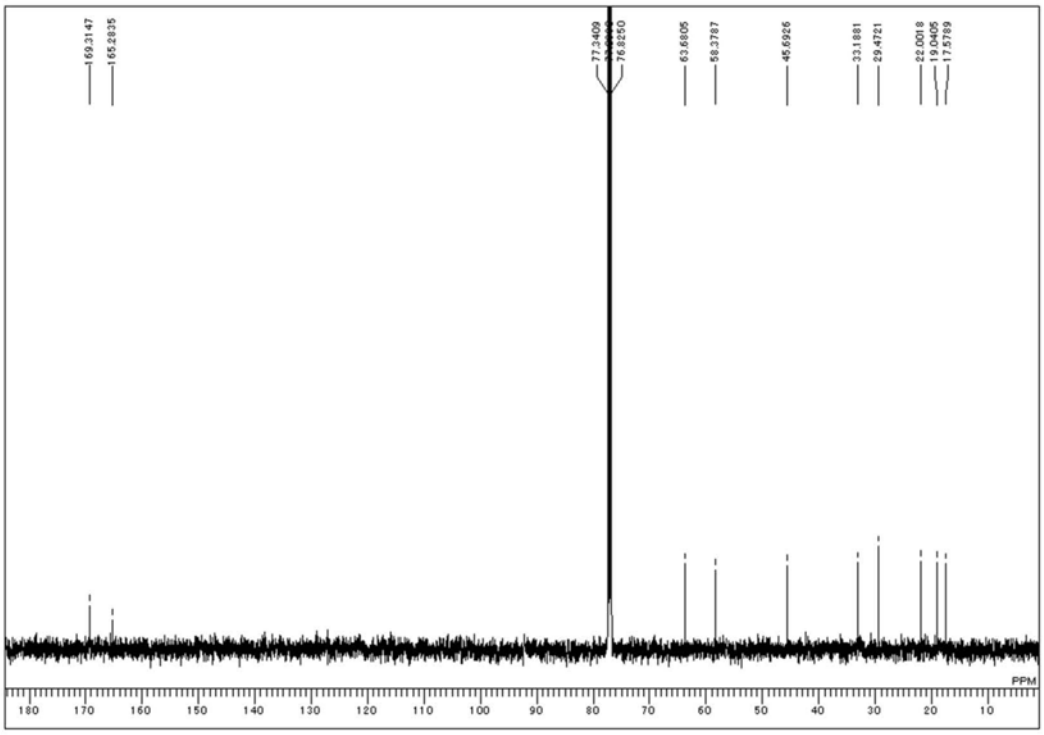

Figure S13. ^{13}C NMR of Cyclo(L-Val-D-Pro) (**2**) (125 MHz, $CDCl_3$).

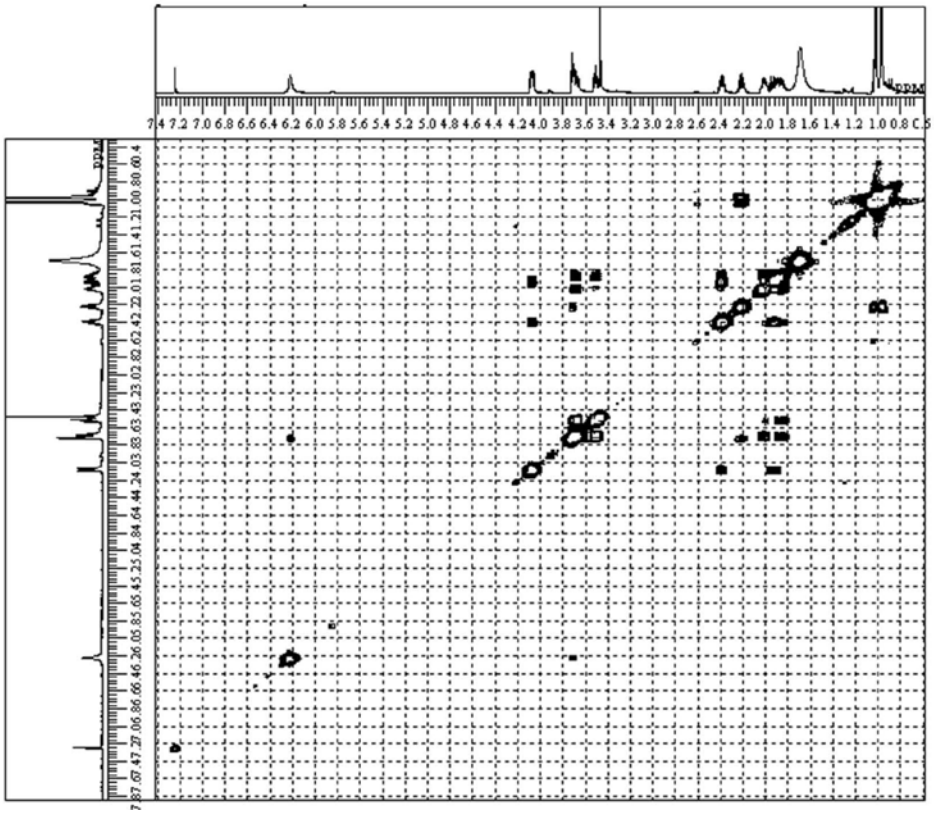

Figure S14. ^{1}H-^{1}H COSY of Cyclo(L-Val-D-Pro) (**2**).

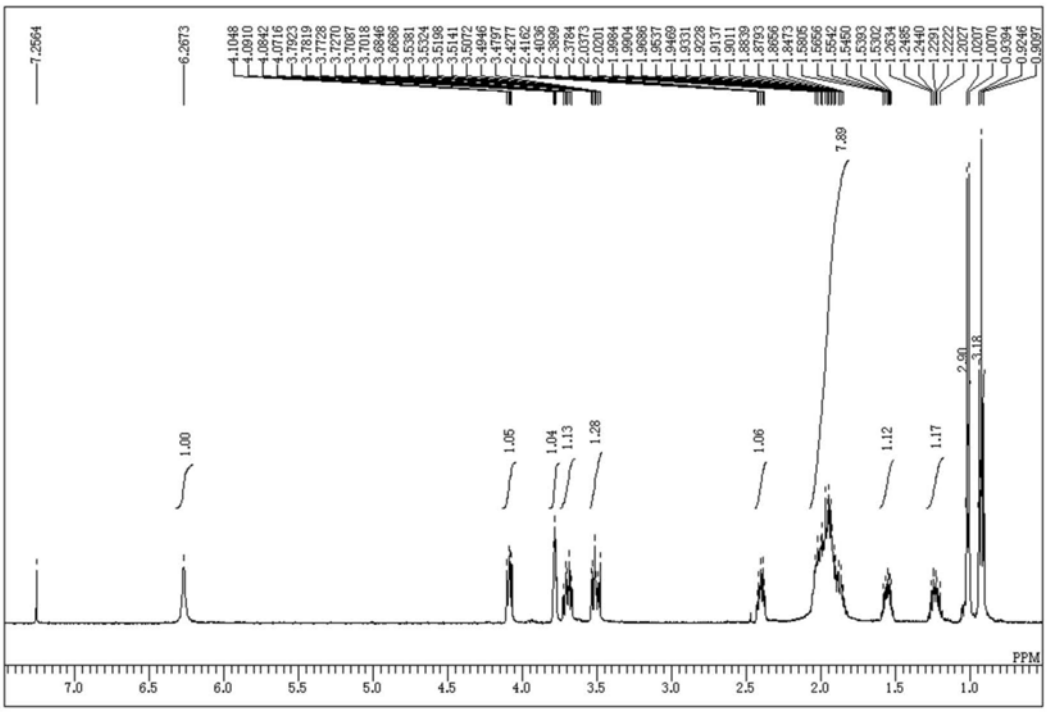

Figure S15. ^{1}H NMR of Cyclo(L-Ile-D-Pro) (**3**) (500 MHz, $CDCl_3$).

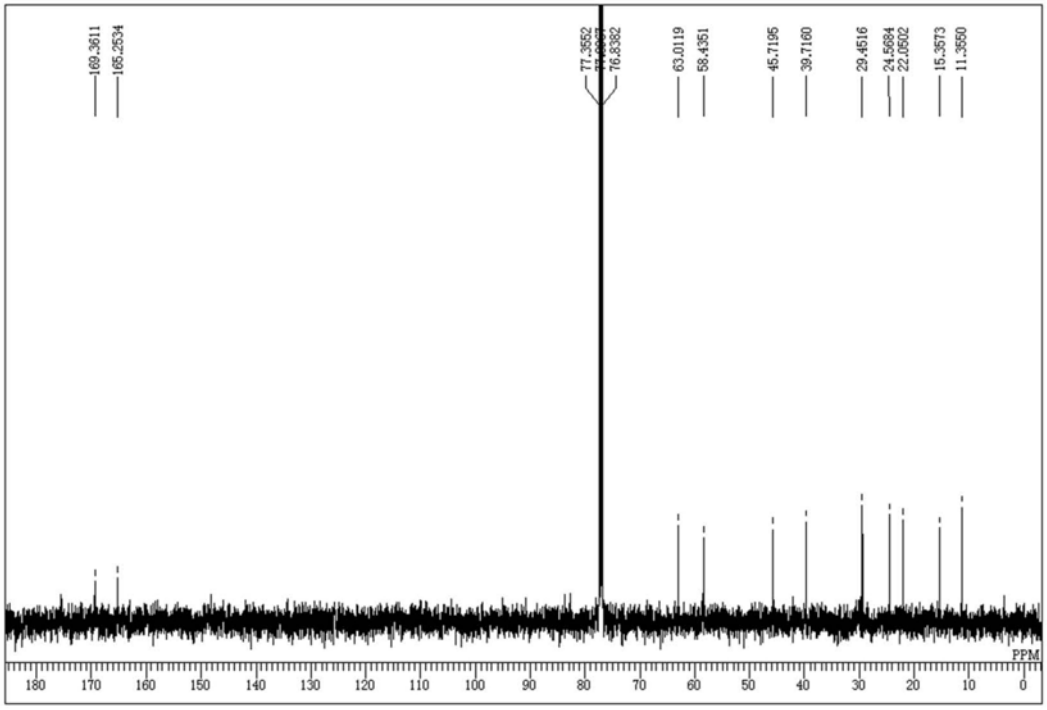

Figure S16. ^{13}C NMR of Cyclo(L-Ile-D-Pro) (**3**) (125 MHz, $CDCl_3$).

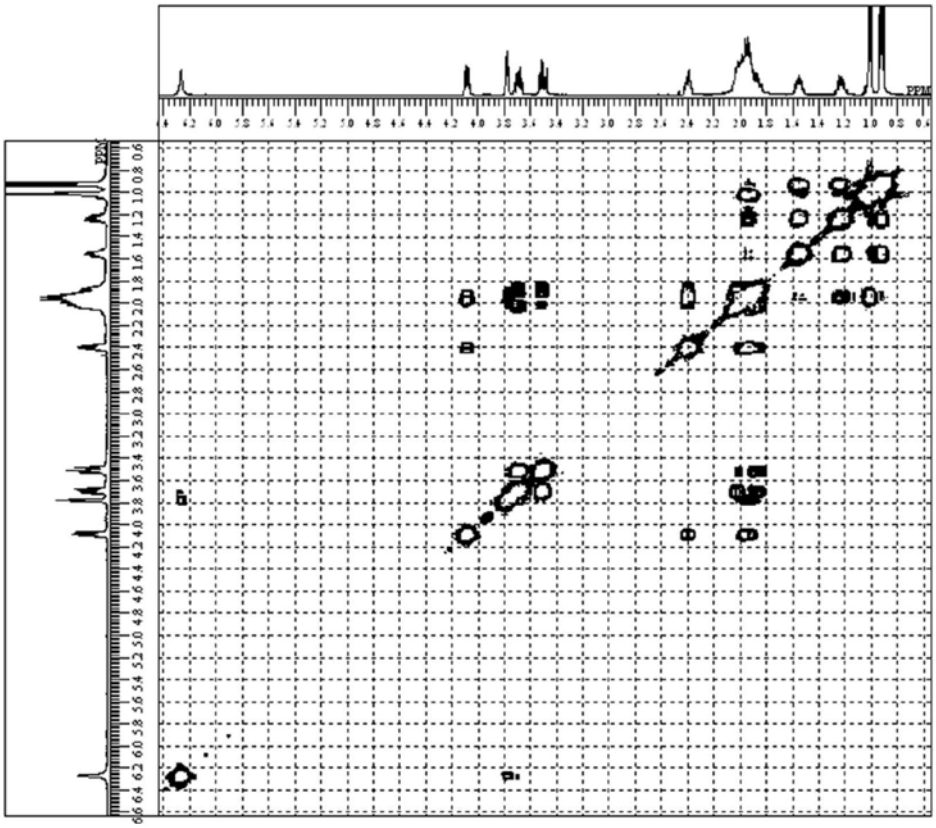

Figure S17. ^{1}H-^{1}H COSY of Cyclo(L-Ile-D-Pro) (**3**).

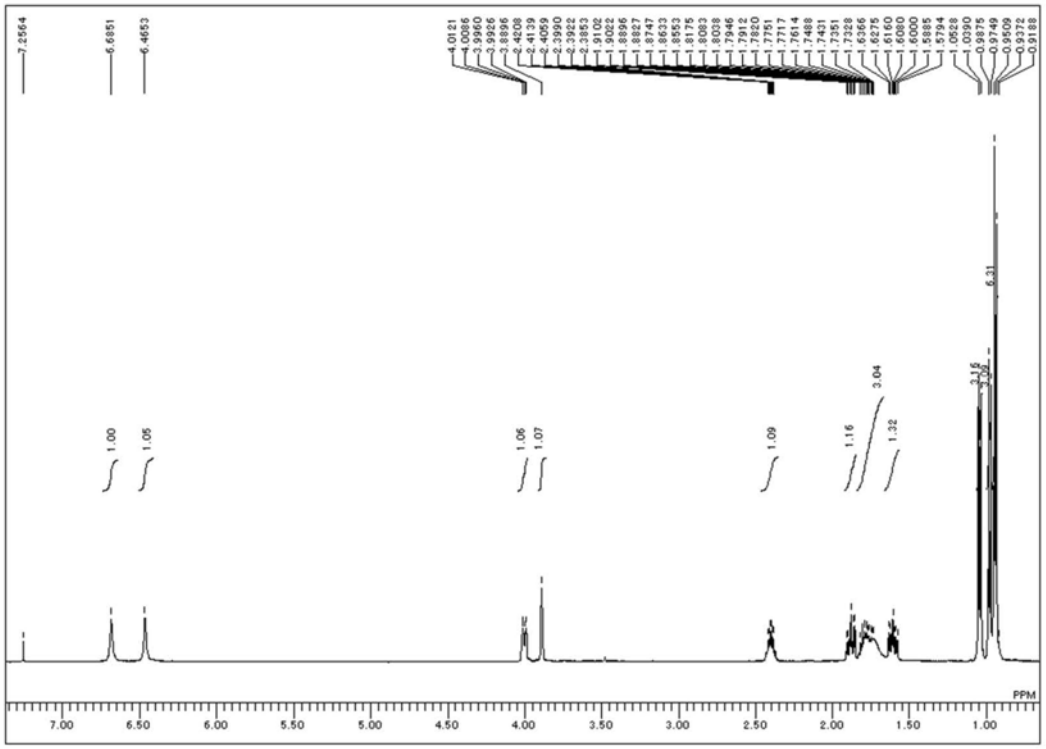

Figure S18. ^{1}H NMR of Cyclo(L-Val-L-Leu) (**5**) (500 MHz, $CDCl_3$).

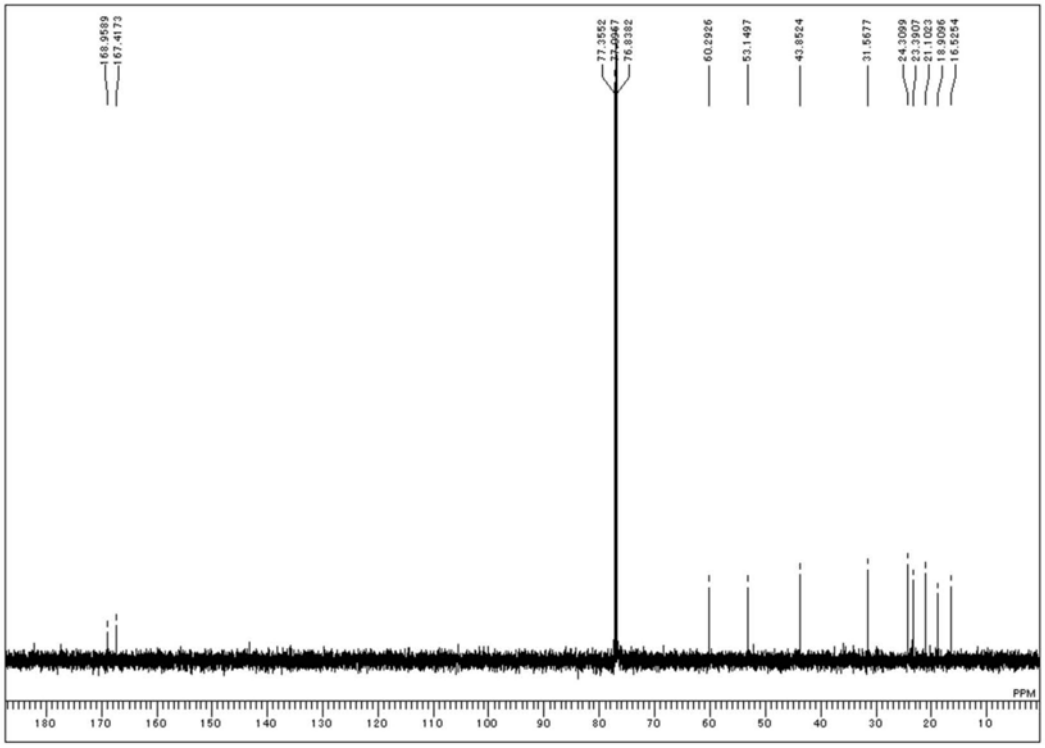

Figure S19. ^{13}C NMR of Cyclo(L-Val-L-Leu) (**5**) (125 MHz, $CDCl_3$).

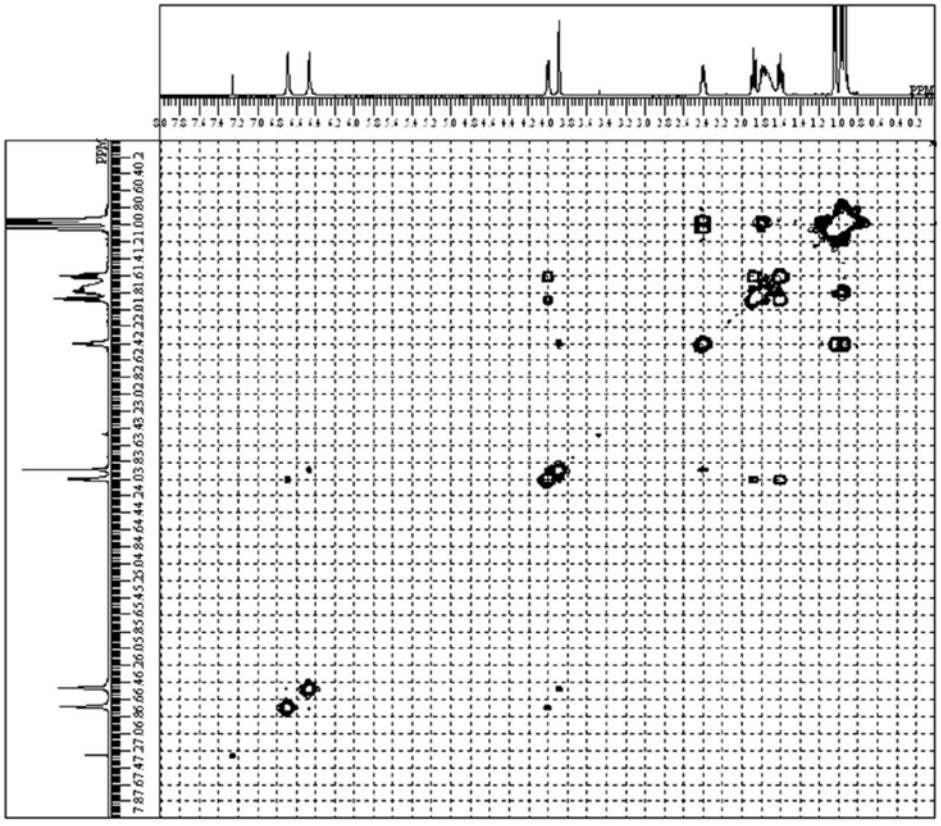

Figure S20. ^{1}H-^{1}H COSY of Cyclo(L-Val-L-Leu) (**5**).

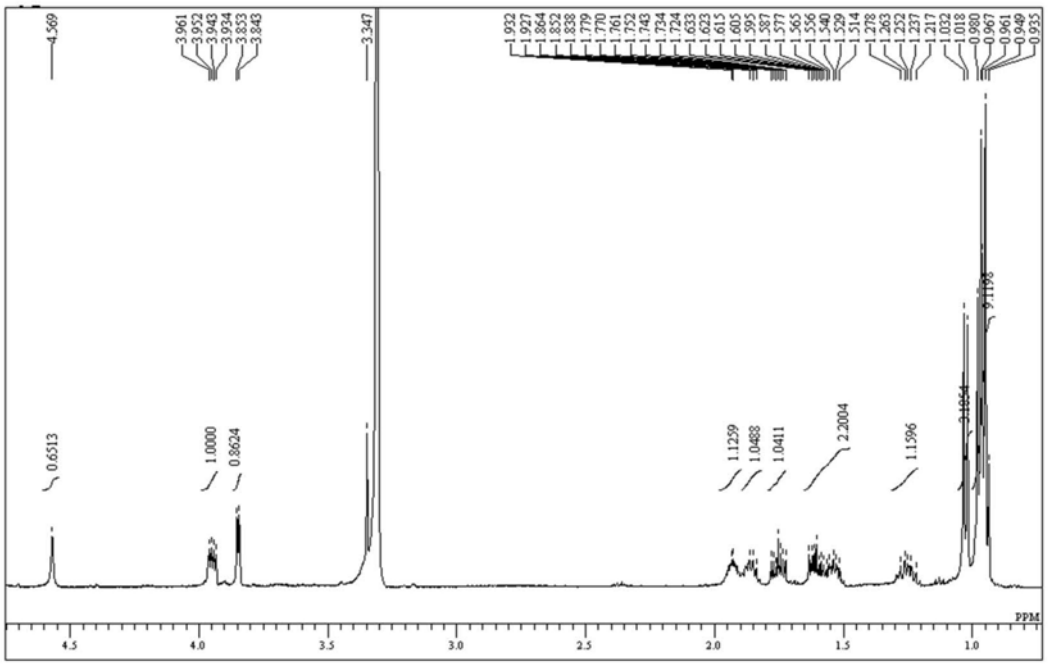

Figure S21. ^{1}H NMR of Cyclo(L-Leu-L-Ile) (**6**) (500 MHz, CD_3OD).

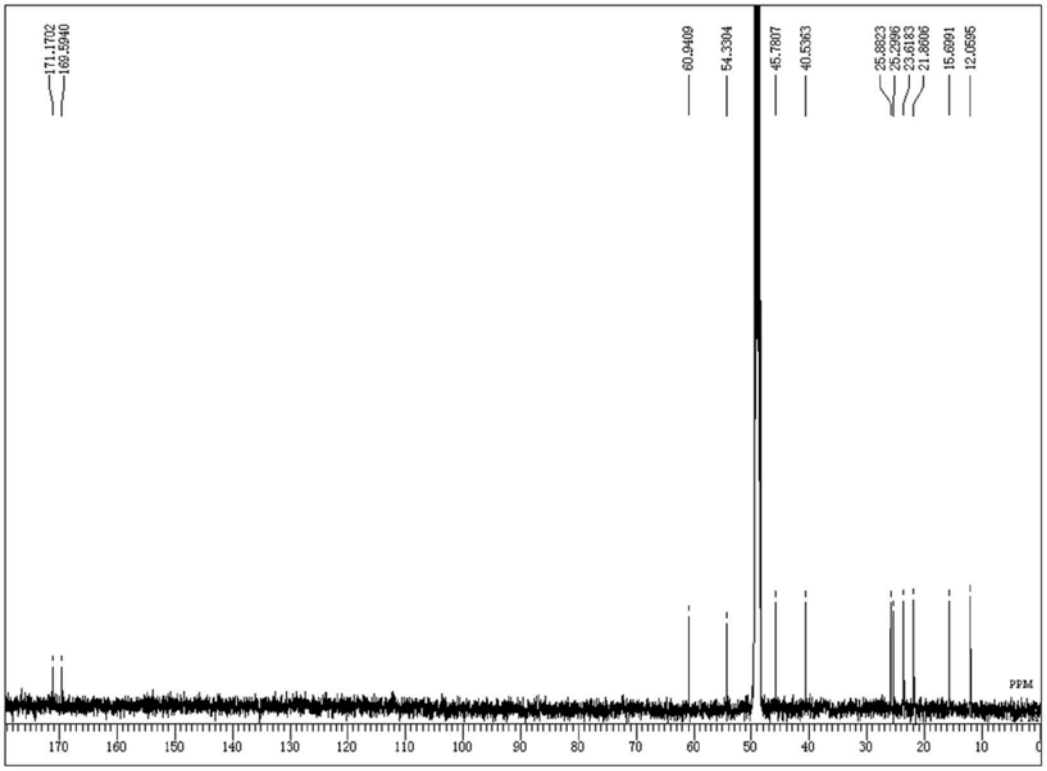

Figure S22. ^{13}C NMR of Cyclo(L-Leu-L-Ile) (**6**) (125 MHz, CD_3OD).

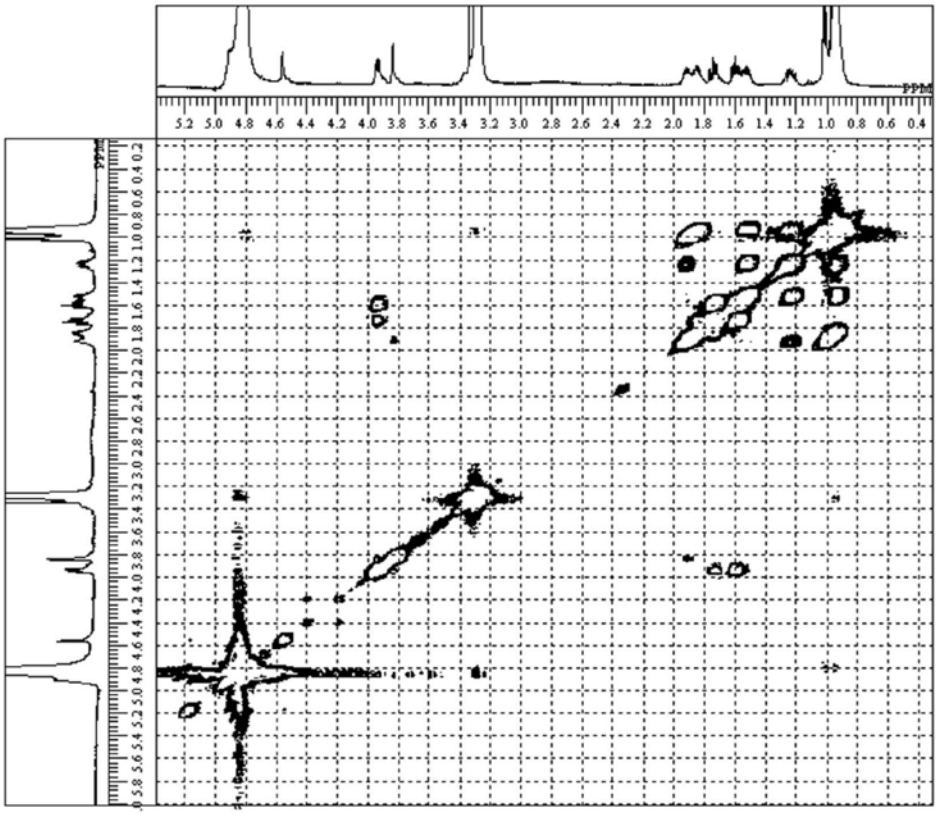

Figure S23. ^{1}H-^{1}H COSY of Cyclo(L-Leu-L-Ile) (**6**).

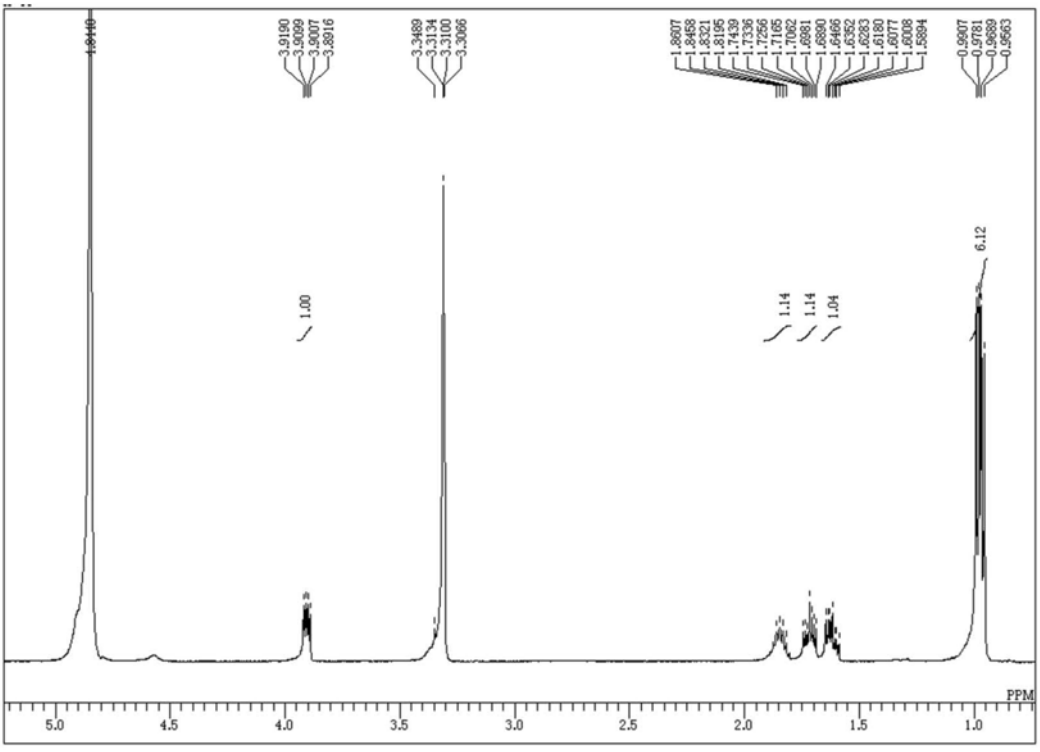

Figure S24. ^{1}H NMR of Cyclo(L-Leu-L-Leu) (**7**) (500 MHz, CD_3OD).

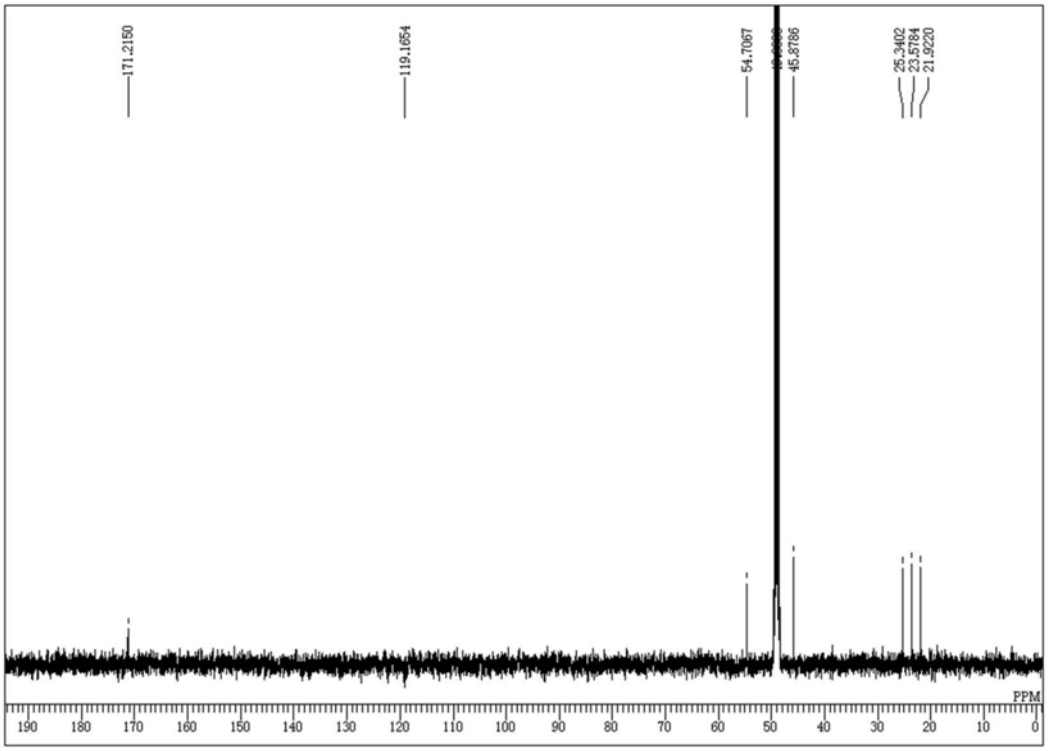

Figure S25. ^{13}C NMR of Cyclo(L-Leu-L-Leu) (**7**) (125 MHz, CD_3OD).

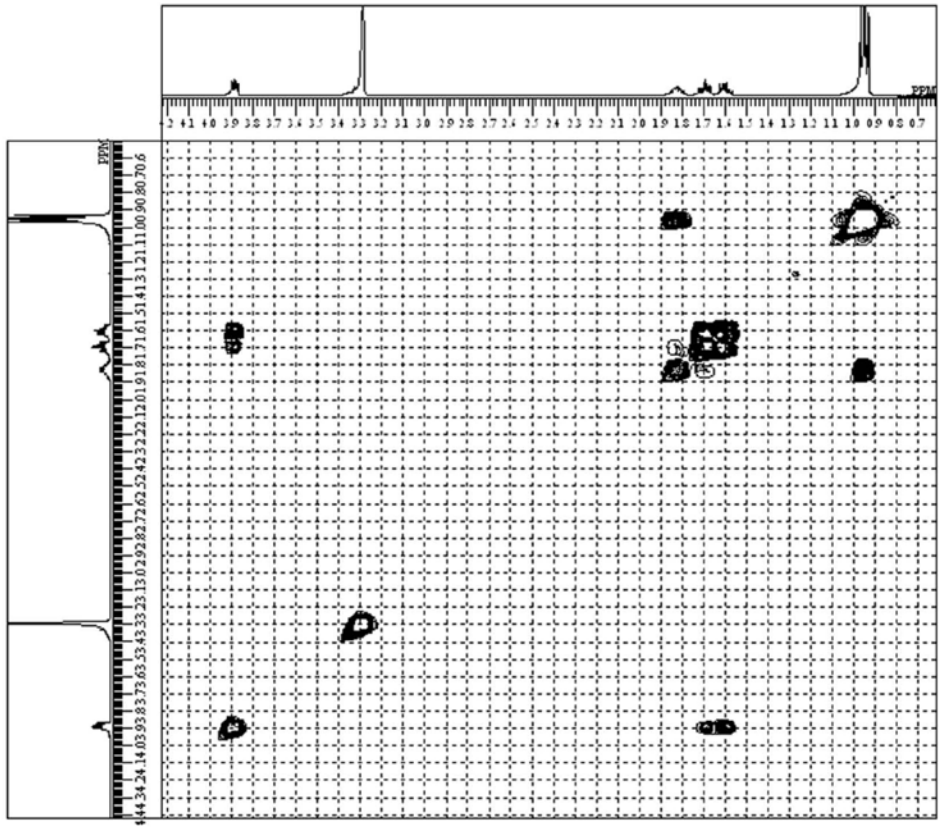

Figure S26. ^{1}H-^{1}HCOSY of Cyclo(L-Leu-L-Leu) (**7**).

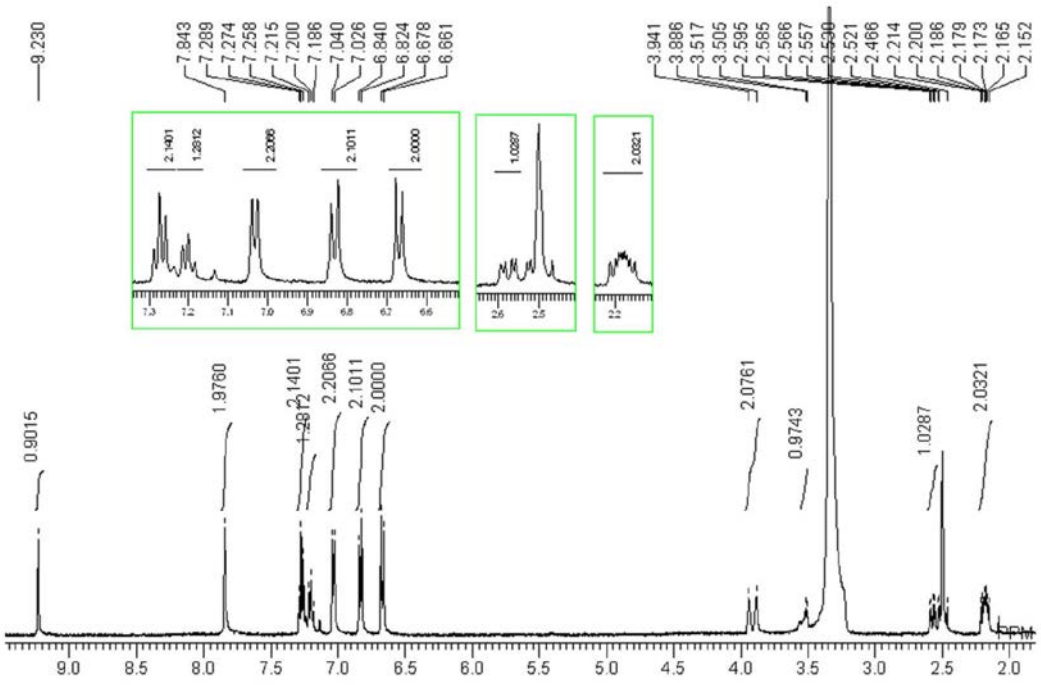

Figure S27. [1]H NMR of Cyclo(L-Phe-L-Tyr) (**8**) (500 MHz, DMSO).

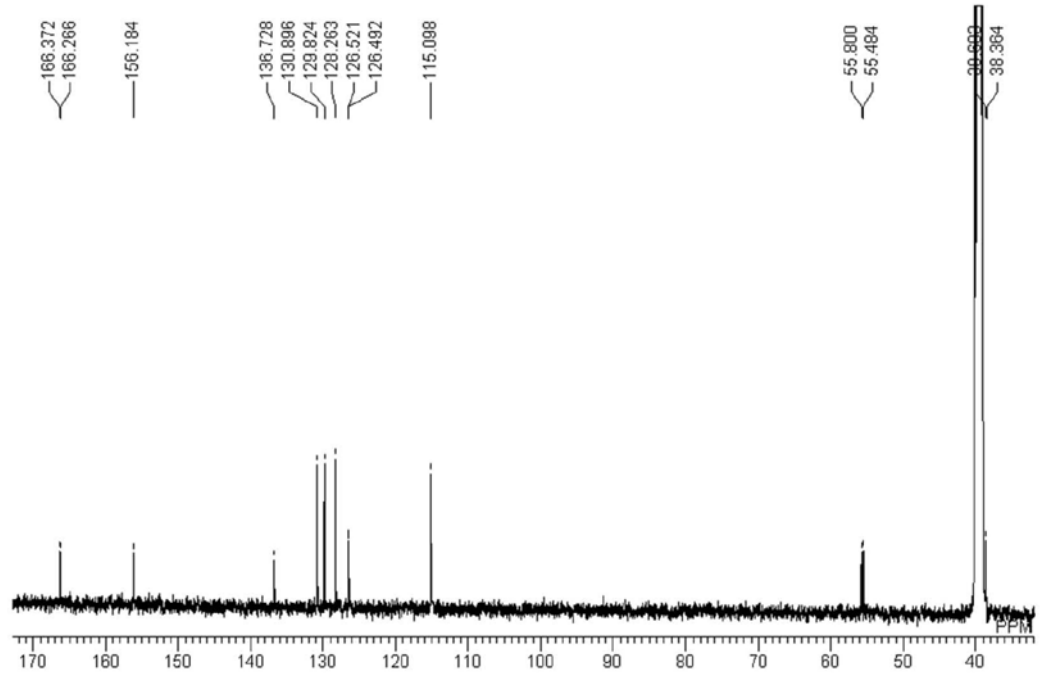

Figure S28. [13]C NMR of Cyclo(L-Phe-L-Tyr) (**8**) (125 MHz, DMSO).

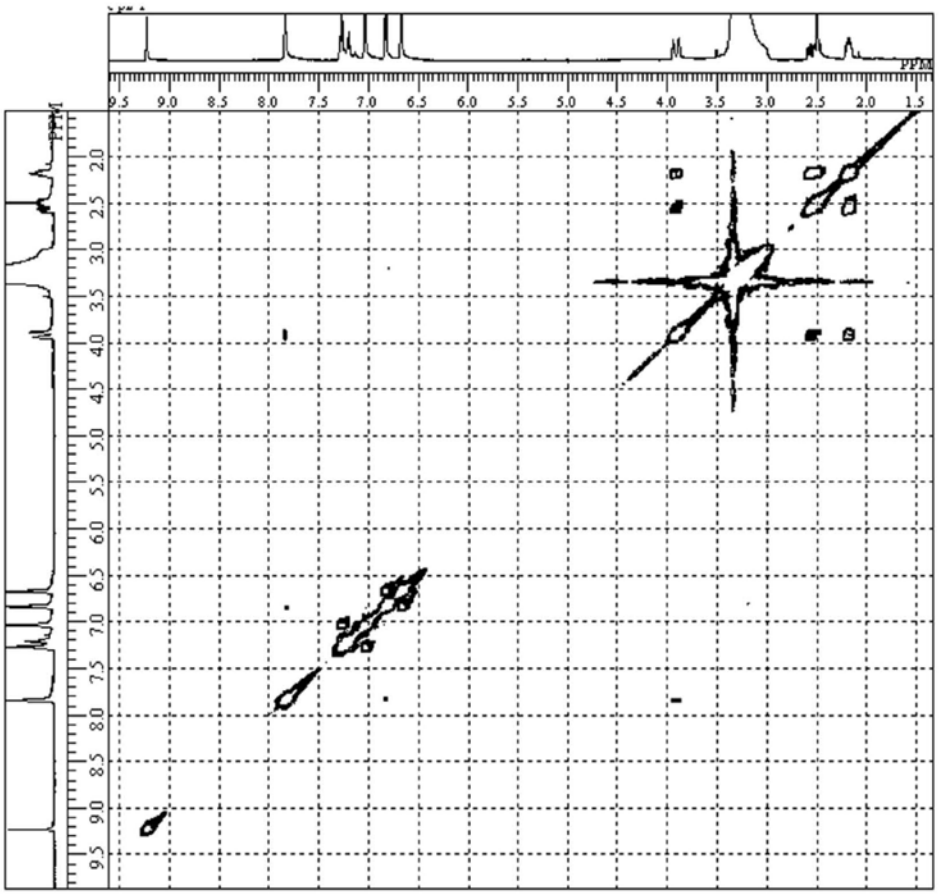

Figure S29. ^{1}H-^{1}H COSY of Cyclo(L-Phe-L-Tyr) (**8**).

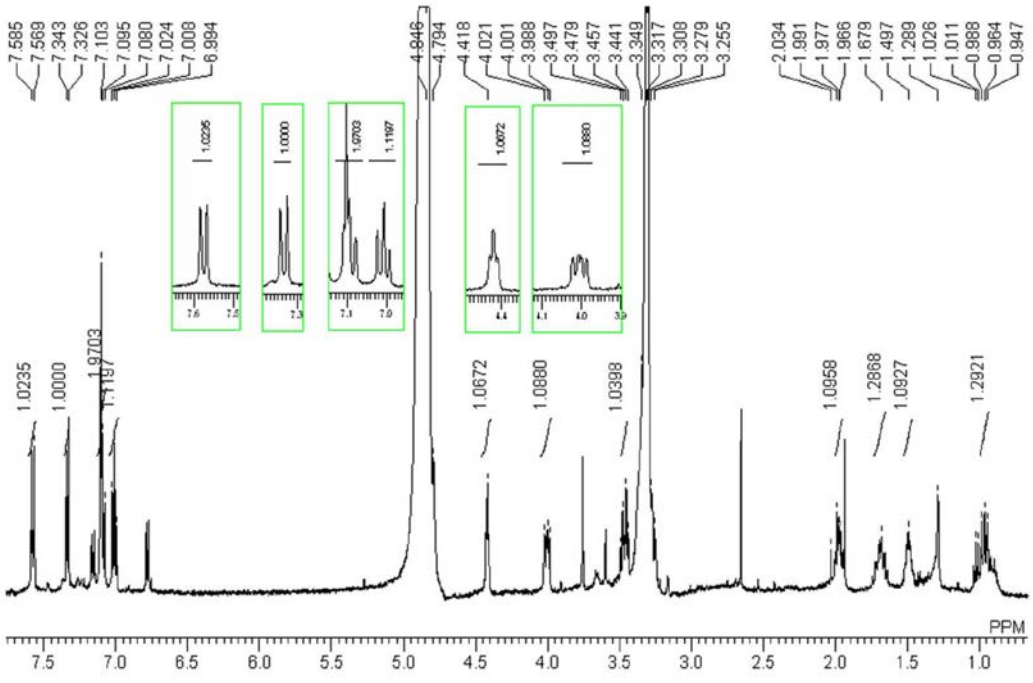

Figure S30. ^{1}H NMR of Cyclo(L-Trp-L-Pro) (**9**) (500 MHz, CD_3OD).

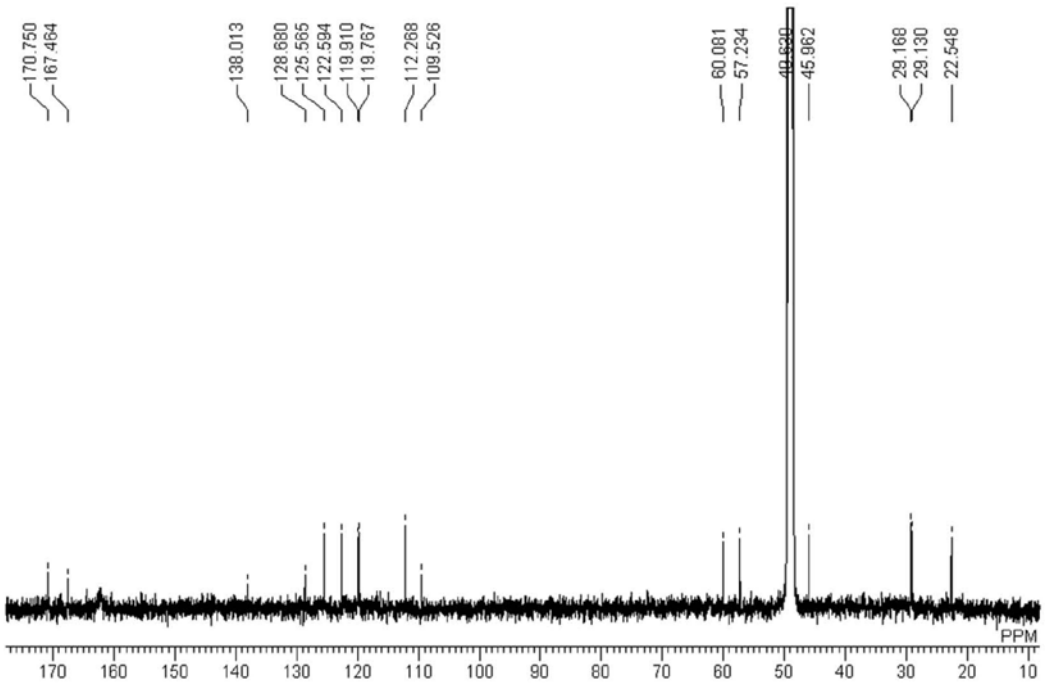

Figure S31. ^{13}C NMR of Cyclo(L-Trp-L-Pro) (**9**) (125 MHz, CD_3OD).

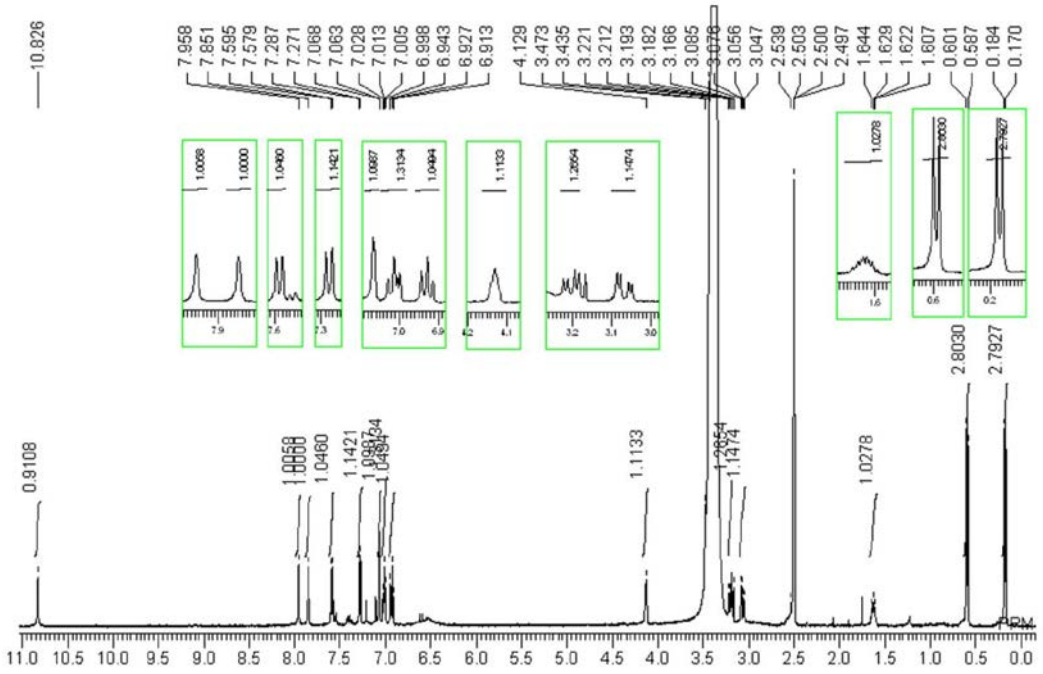

Figure S32. ^{1}H NMR of Cyclo(L-Val-L-Trp) (**10**) (500 MHz, DMSO).

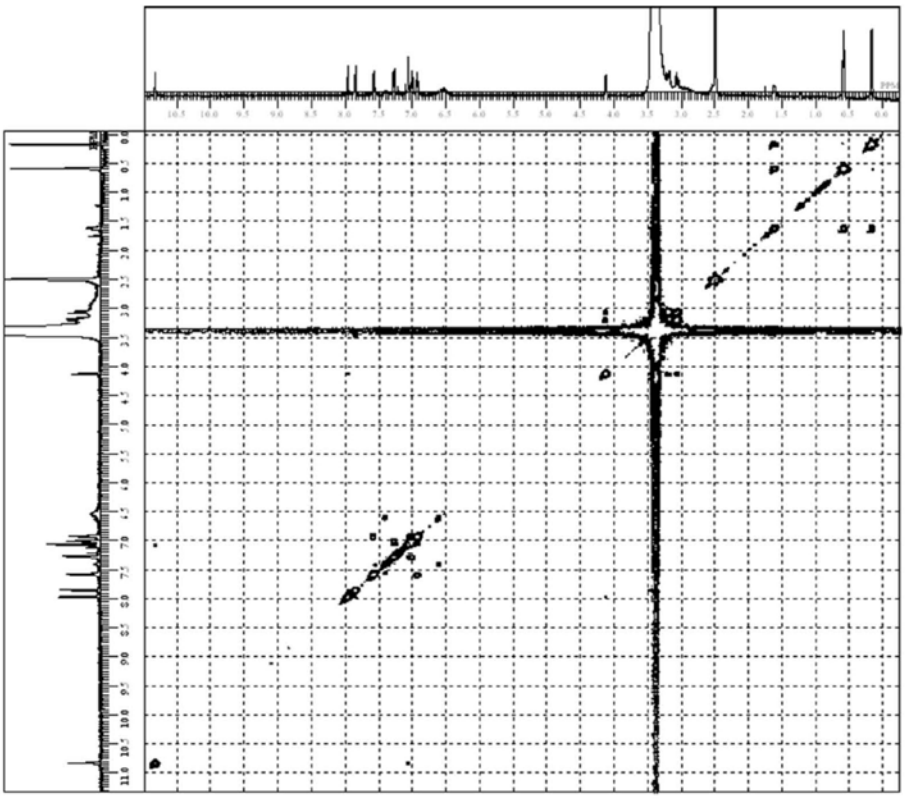

Figure S33. ^{1}H-^{1}H COSY of Cyclo(L-Val-L-Trp) (**10**).

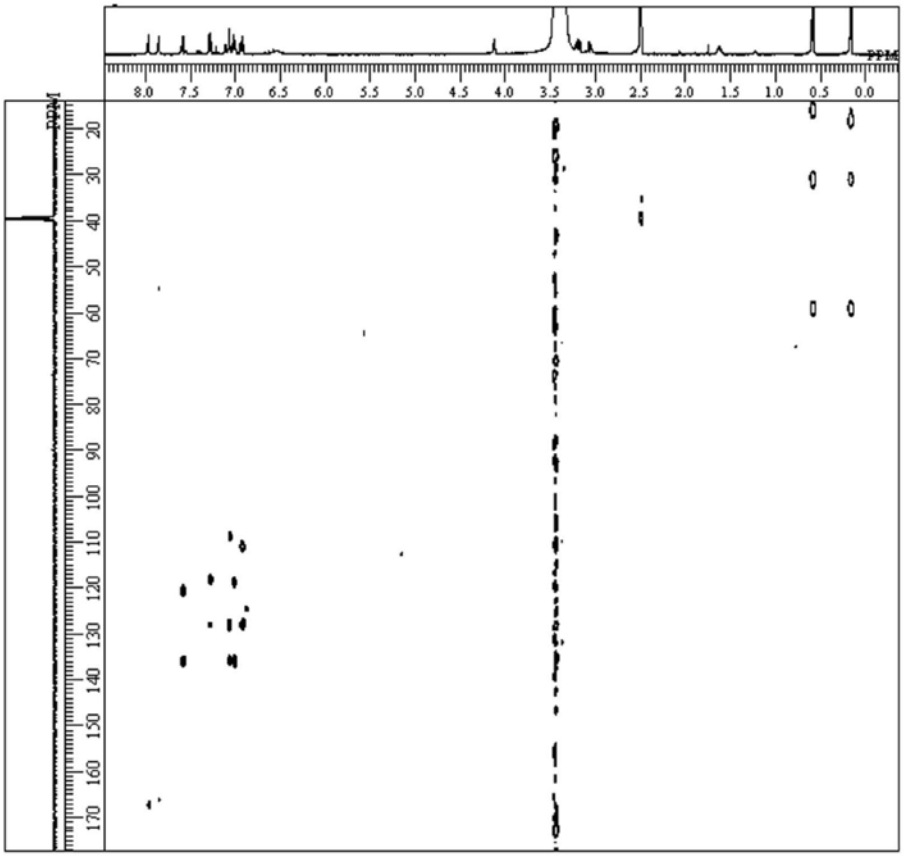

Figure S34. Some easily detected HMBC of Cyclo(L-Val-L-Trp) (**10**).

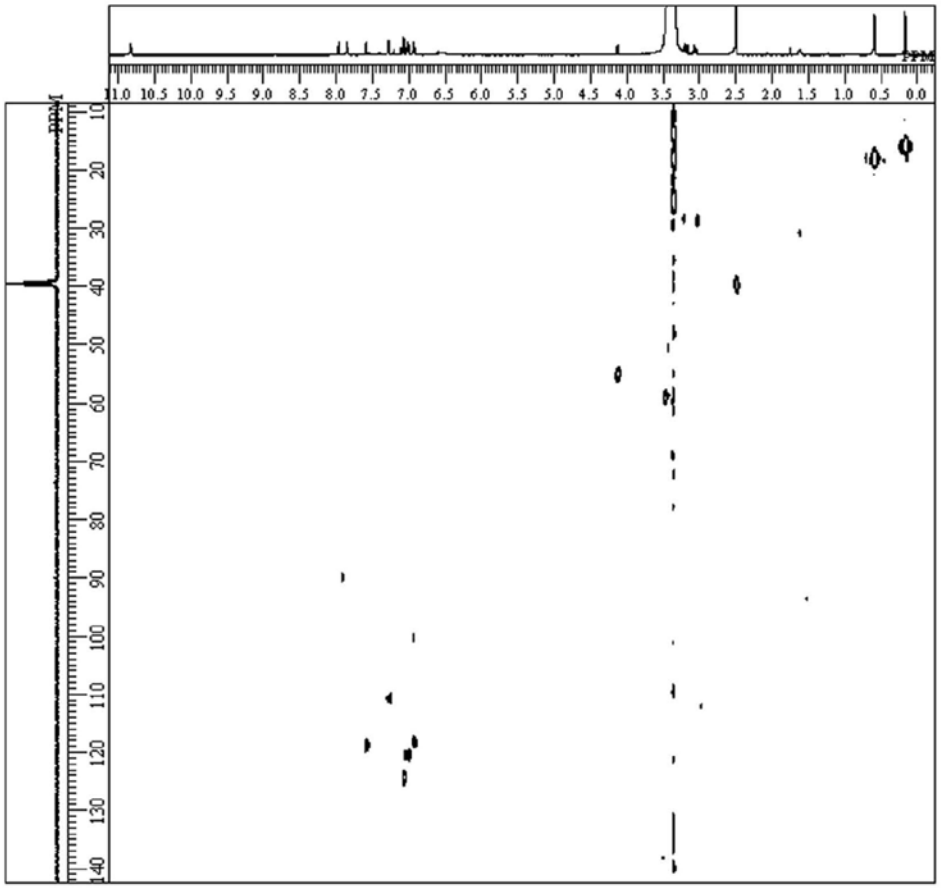

Figure S35. HMQC of Cyclo(L-Val-L-Trp) (**10**).

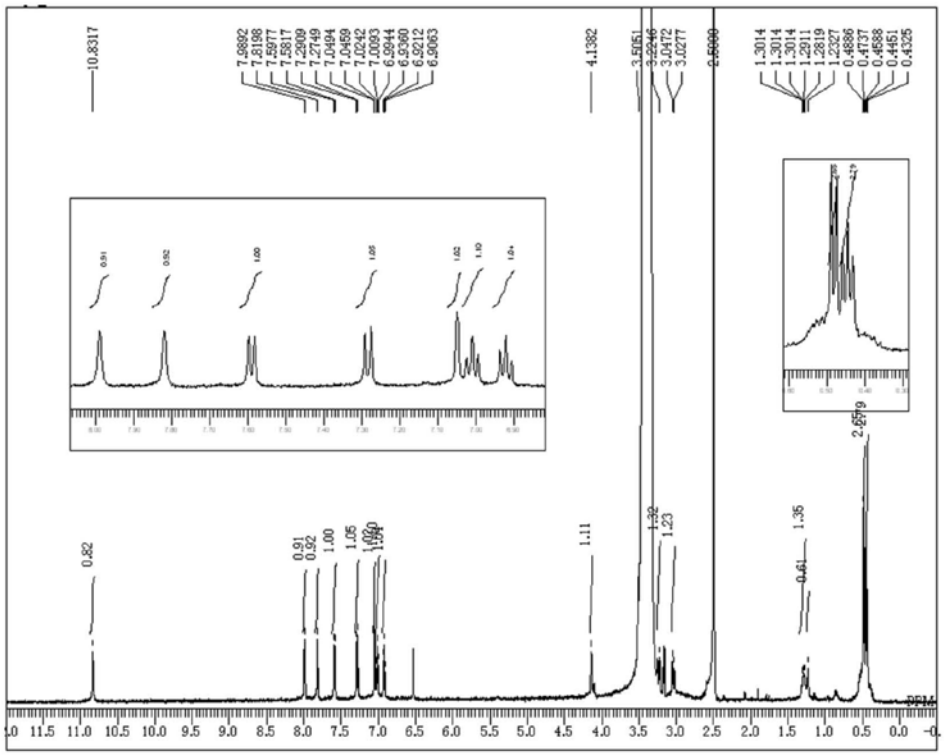

Figure S36. ^{1}H NMR of Cyclo(L-Ile-L-Trp) (**11**) (500 MHz, DMSO).

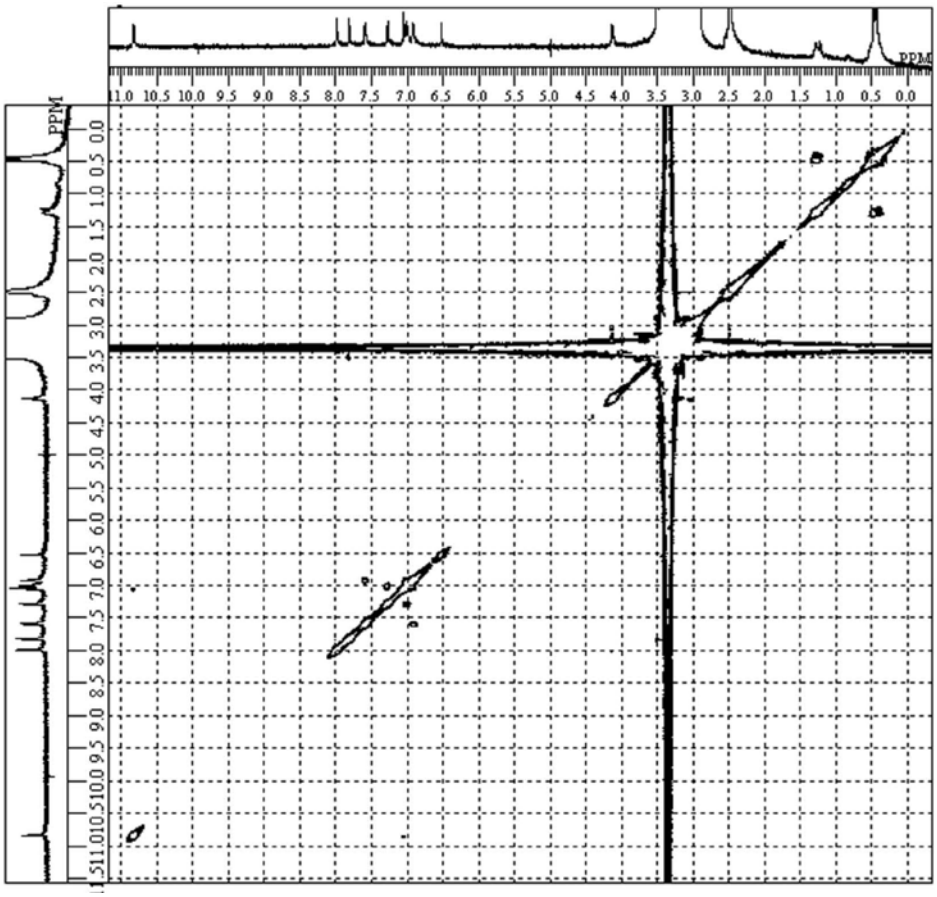

Figure S37. ^{1}H-^{1}H COSY of Cyclo(L-Ile-L-Trp) (**11**).

LC-MS data of cyclodipeptides 8-11

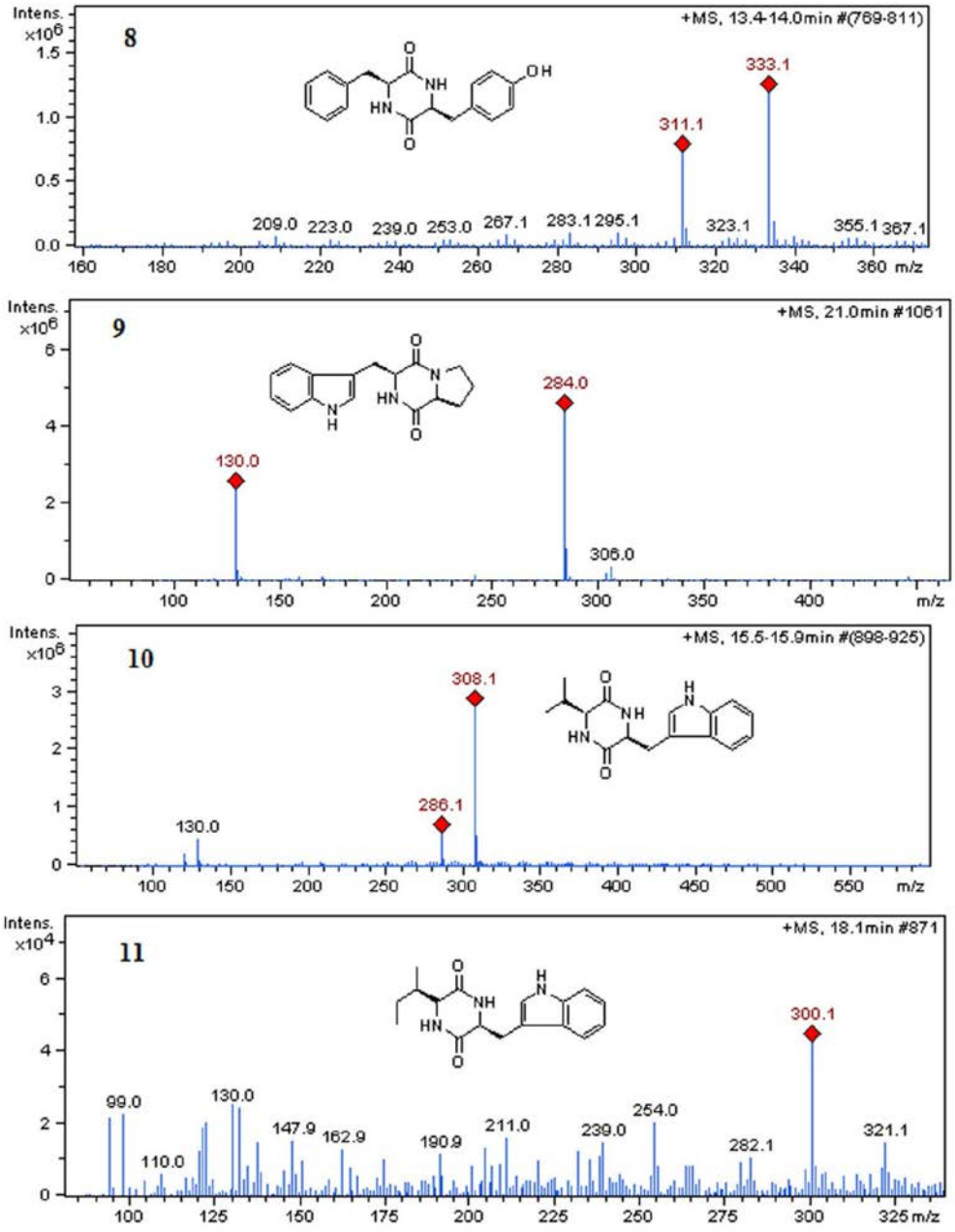

Figure S38. LC-MS data of cyclodipeptides **8-11**.

Liquid chromatography-mass spectrometry (LC-MS, Agilent 1100 series-Bruker Esquire 4000) analysis was performed on ODS column (TSK-Gel ODS-80Ts, 4.6 × 150 mm) with a mixture of H_2O and MeCN, both containing 0.1% acetic acid: 30-100% MeCN 30 min; 100% MeCN 10 min, 0.2 mL min^{-1}. Detected wavelength: 280 nm. Positive ESI.