Supporting Information for:

Stereoselective recognition of the Ac-Glu-Tyr-OH dipeptide by pseudopeptidic cages

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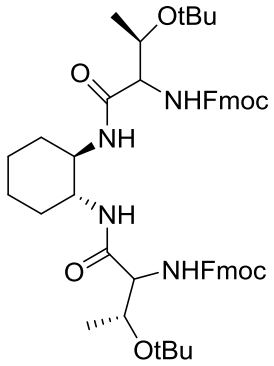
1. Synthesis and Characterization of receptor CyThr

$(Fmoc)_2$-1b



Fmoc-Thr(*t*Bu)-OH (3.73 g, 9.40 mmol) was dissolved in dry DMF (10 ml) and dry DCM (10 ml). 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronoium hexafluorphosphate (HATU, 3.41 g, 8.97 mmol) and *N*,*N*-Diisopropylethylamine (DIPEA, 6.0 ml, 34.2 mmol) were added over the solution. The reaction mixture was cooled to 0 °C. A solution of the dihydrochloride salt of (*R,R*)-1,2-diaminocyclohexane (800 mg, 4.27 mmol) in dry DMF (10 ml) was added over the mixture. The solution was allowed to warm to room temperature for 16 hours, after which complete conversion of starting material was observed by TLC. The mixture was diluted with water and extracted with AcOEt (3 x 50 ml). Combined organic fractions were washed with aqueous LiCl (5% w/w), dried over $MgSO_4$ and concentrated to dryness. The residue was purified by flash chromatography using hexane: AcOEt as eluent (from 20% to 50% AcOEt) to give 3.10 g of **$(Fmoc)_2$-1b** (83% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 4H), 7.60 (dd, *J* = 7.7, 3.9 Hz, 4H), 7.38 (td, *J* = 7.3, 2.9 Hz, 4H), 7.28 (t, *J* = 7.5 Hz, 4H), 7.22 (d, *J* = 5.5 Hz, 2H), 6.03 (d, *J* = 5.3 Hz, 2H), 4.40-4.31 (m, 4H), 4.23 (t, *J* = 7.3 Hz, 2H), 4.15 (dd, *J* = 6.4, 3.9 Hz, 2H), 4.09 (t, *J* = 4.6 Hz, 2H), 3.68 (s, 2H), 2.09 (d, *J* = 12.7 Hz, 2H), 1.76 (d, *J* = 8.1 Hz, 2H), 1.39-1.34 (m, 2H), 1.28 (s, 18H), 1.02 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 156.0, 144.1, 143.9, 141.4, 127.8, 127.1, 125.3, 120.1, 75.5, 67.1, 66.5, 58.5, 53.6, 47.3, 32.2, 28.2, 24.5, 17.1.

HRMS (ESI-TOF) *m/z* [**$(Fmoc)_2$-1b** + H]$^+$ Calcd for $C_{52}H_{65}N_4O_8$ 873.4802, found 873.4832.

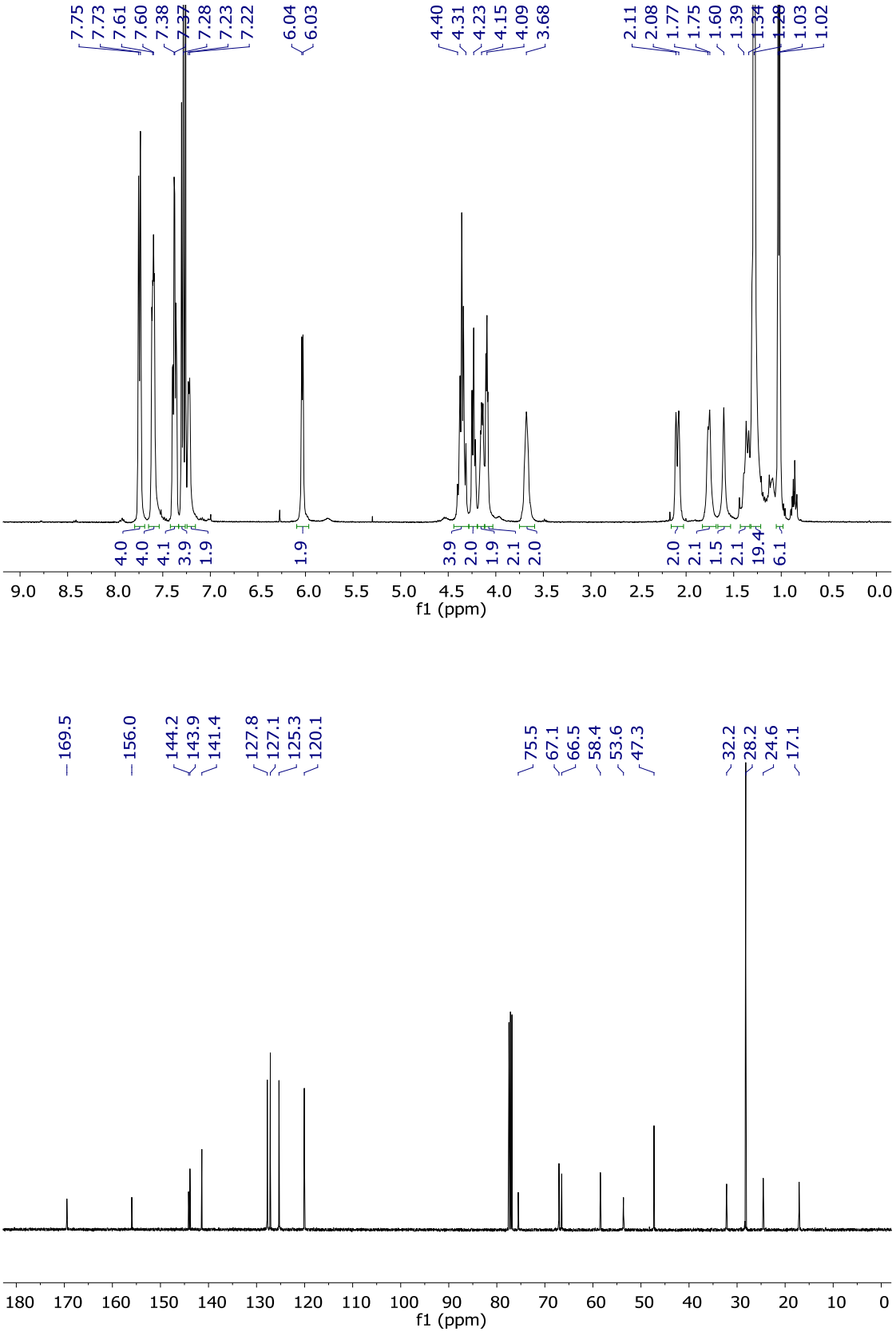


Figure S1. ^{1}H-NMR (CD_3OD, 400 MHz) and ^{13}C-NMR (CD_3OD, 101 MHz) spectra of **$(Fmoc)_2$-1b**.

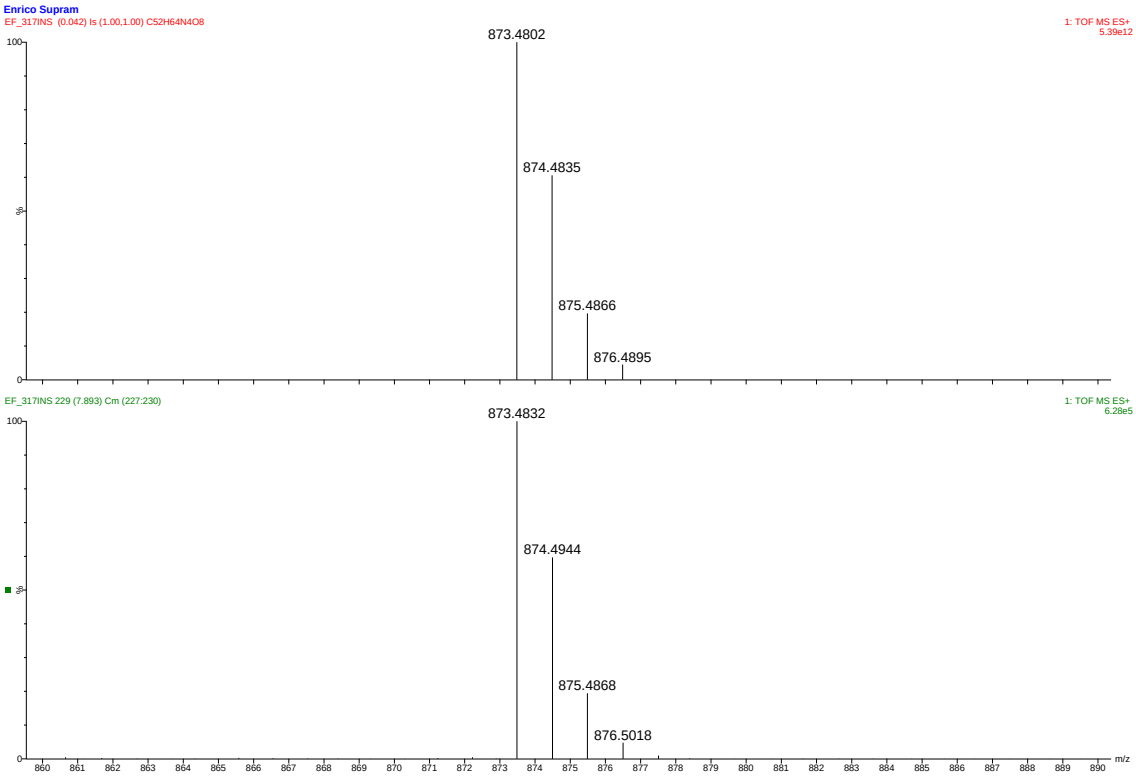
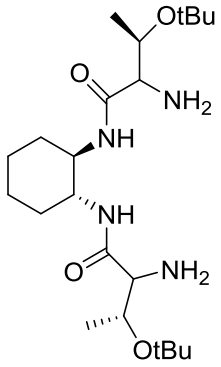


Figure S2. HRMS (ESI+) experimental spectrum of **$(Fmoc)_2$-1b** (bottom) and simulated spectrum for $C_{52}H_{65}N_4O_8$ (top).

1b



(Fmoc)$_2$-1b (3.06 g, 3.51 mmol) was dissolved in 10 mL of 20% Piperidine in DMF. After several minutes the product precipitated as a white solid but the mixture was allowed to react for 6h until complete conversion of starting material was observed by TLC. Excess diethyl ether was added over the reaction mixture and the product was filtered off and washed with additional diethyl ether. **1b** was obtained as a white solid (1.13 g, 75% yield).

^{1}H NMR (400 MHz, CD_3OD) δ 3.81 (qd, *J* = 6.2, 4.7 Hz, 2H), 3.65-3.60 (m, 2H), 3.13 (d, *J* = 4.8 Hz, 2H), 1.99-1.94 (m, 2H), 1.79-1.74 (m, 2H), 1.38-1.31 (m, 4H), 1.22 (s, 18H), 1.09 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (101 MHz, CD_3OD) δ 175.1, 75.4, 70.4, 61.0, 54.4, 33.1, 28.8, 25.7, 19.3.

HRMS (ESI-TOF) *m/z* [**1b** + H]$^+$ Calcd for $C_{22}H_{45}N_4O_4$ 429.3441, found 429.3503.

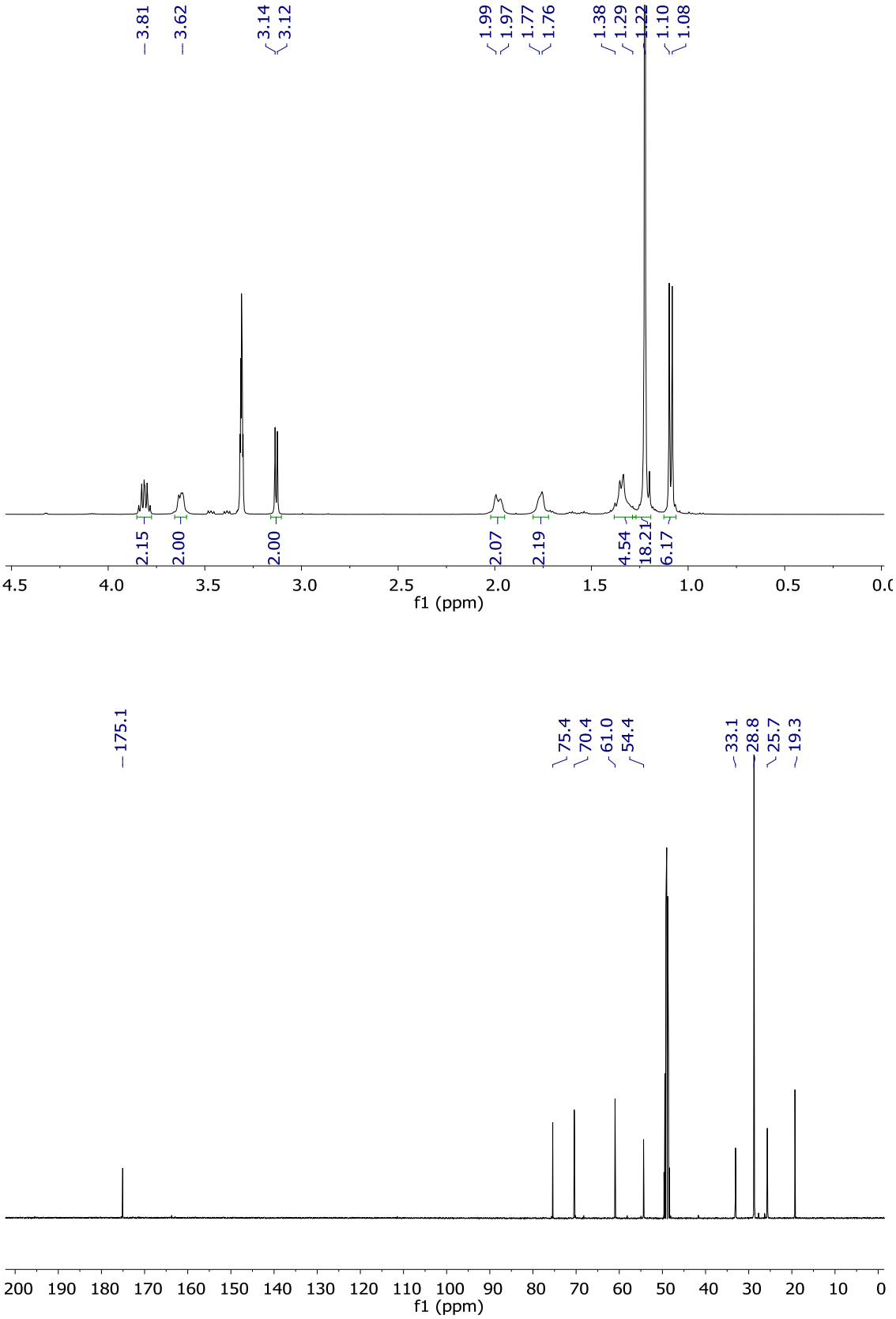


Figure S3. ^{1}H-NMR (CD_3OD, 400 MHz) and ^{13}C-NMR (CD_3OD, 101 MHz) spectra of **1b.**

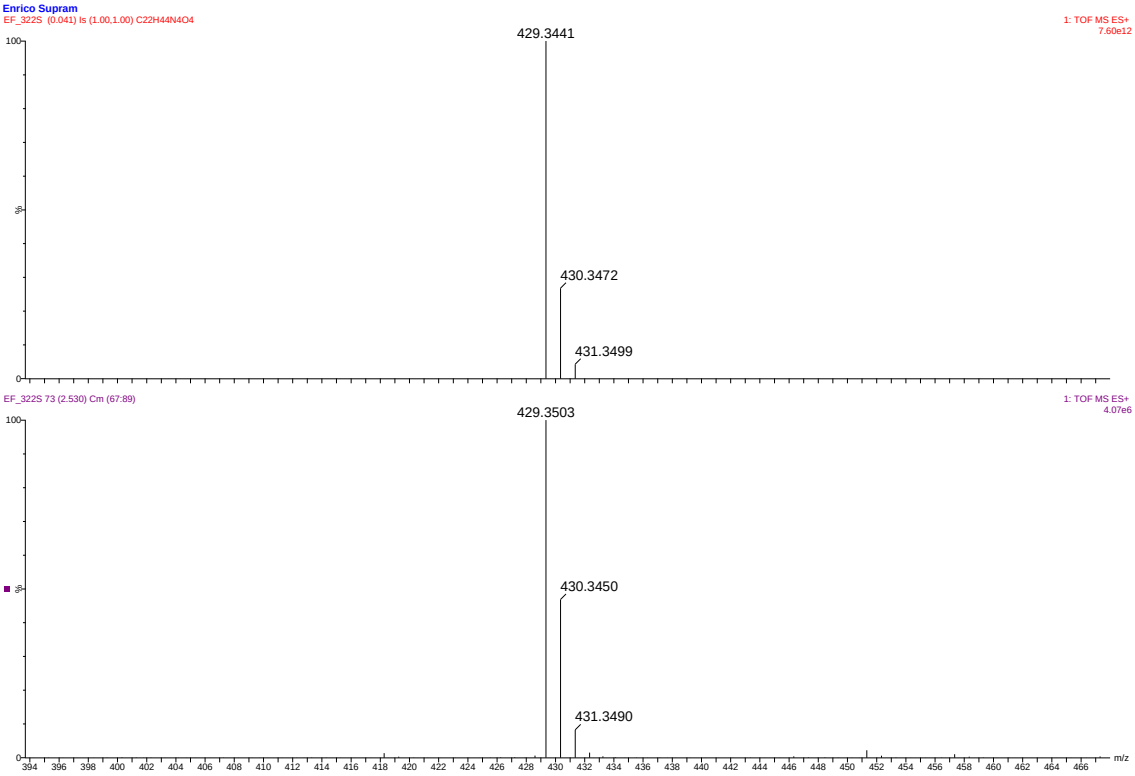
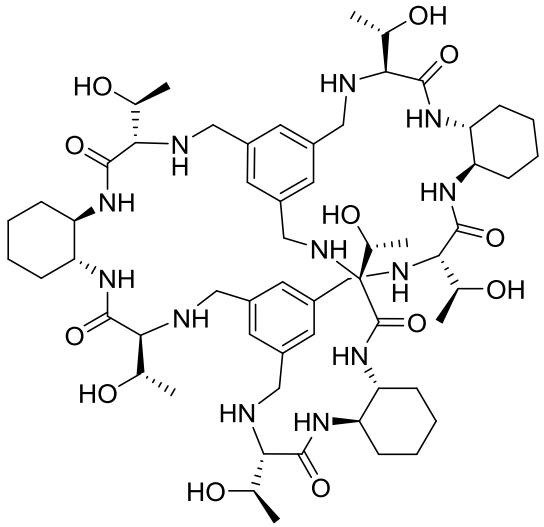


Figure S4. HRMS (ESI+) experimental spectrum of **1b** (bottom) and simulated spectrum for $C_{22}H_{45}N_4O_4$ (top).

Cy_Thr free amine



A solution of benzene-1,3,5-tricarbaldehyde (116 mg, 0.72 mmol) in CH_3OH (25 ml) was added over a solution of **1b** (461 mg, 1.07 mmol) in CH_3OH (10 ml). The mixture was stirred at room temperature during 20 hours. Then, $NaBH_4$ (163 mg, 4.32 mmol) was carefully added and the mixture was allowed to react for 16 hours. The mixture was concentrated to half volume and concentrated HCl (*ca.* 2 ml) was added. After 2 hours the mixture was evaporated to dryness. The residue obtained was dissolved in water and basified with 1N NaOH, and the product was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated at reduced pressure. The product was purified using reversed-phase flash chromatography (eluant: 1% to 20% MeCN in water; 0.1% TFA in both solvents). The TFA salt was transformed into the free-base amine using an ion-exchange resin, affording **CyThr** as a white solid (233 mg, 55% yield).

^{1}H NMR (400 MHz, CD_3OD) δ 6.94 (s, 6H), 3.97 , 3.94 3.94 (p, *J* = 6.3 Hz, 6H), 3.82-3.80 (m, 6H), 3.65 (d, *J* = 12.9 Hz, 6H), 3.42 (d, *J* = 12.9 Hz, 6H), 3.04 (d, *J* = 6.3 Hz, 6H), 2.11-2.09 (m, 6H), 1.84- 1.72 (m, 6H), 1.40-1.32 (m, 12H), 1.23 (d, *J* = 6.3 Hz, 24H).

^{13}C NMR (101 MHz, CD_3OD) δ 174.4, 140.2, 127.4, 69.4, 69.2, 54.0, 53.5, 33.5, 25.8, 20.2.

HRMS (ESI-TOF) *m/z* [**CyThr** + H]$^+$ Calcd for $C_{60}H_{97}N_{12}O_{12}$ 1177.7349, found 1177.7354; [**CyThr** + Na]$^+$ Calcd for ($C_{60}H_{96}N_{12}O_{12}Na$) 1199.7168, found 1199.7227.

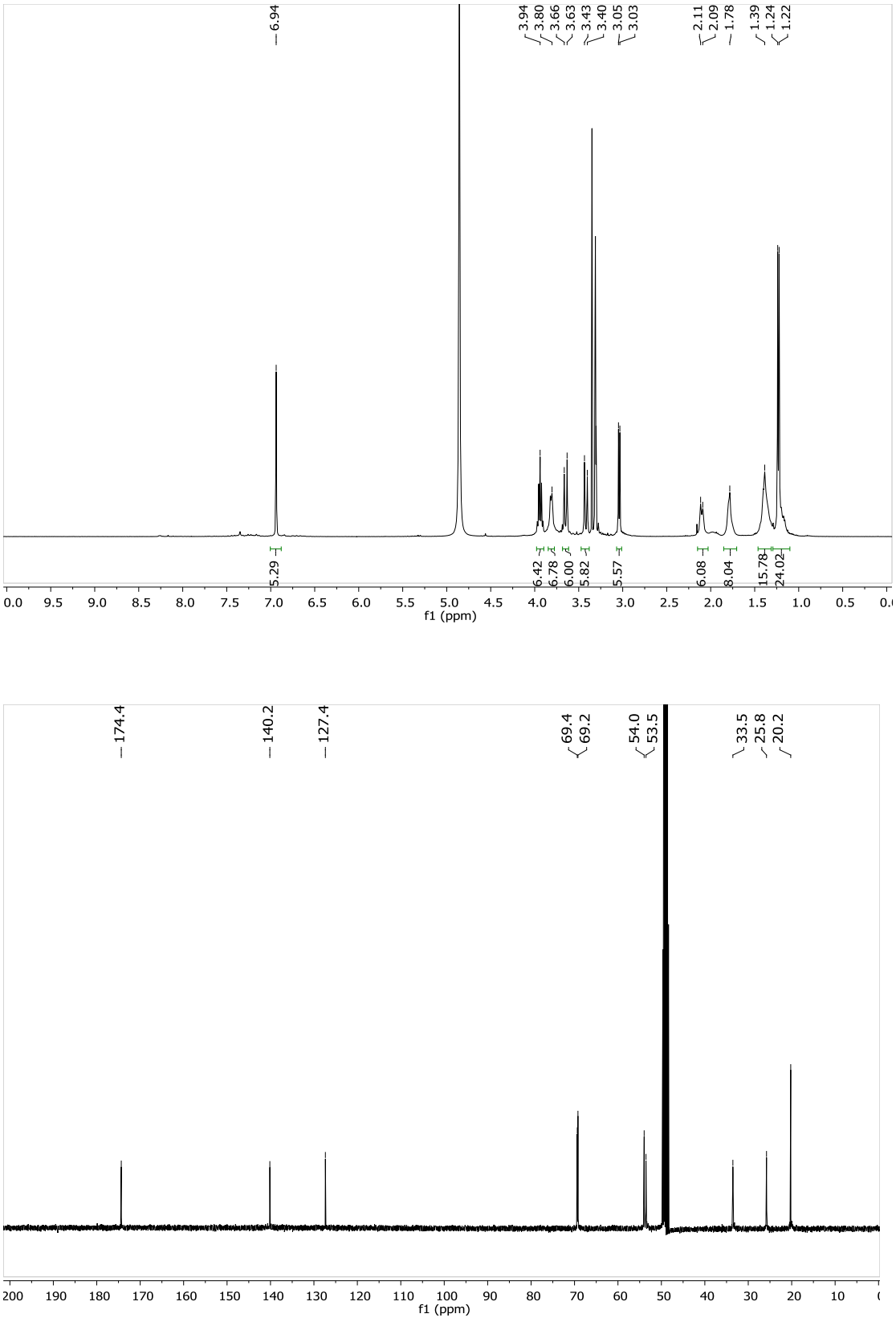


Figure S5. ^{1}H-NMR (CD_3OD, 400 MHz) and ^{13}C-NMR (CD_3OD, 101 MHz) spectra of **CyThr**.

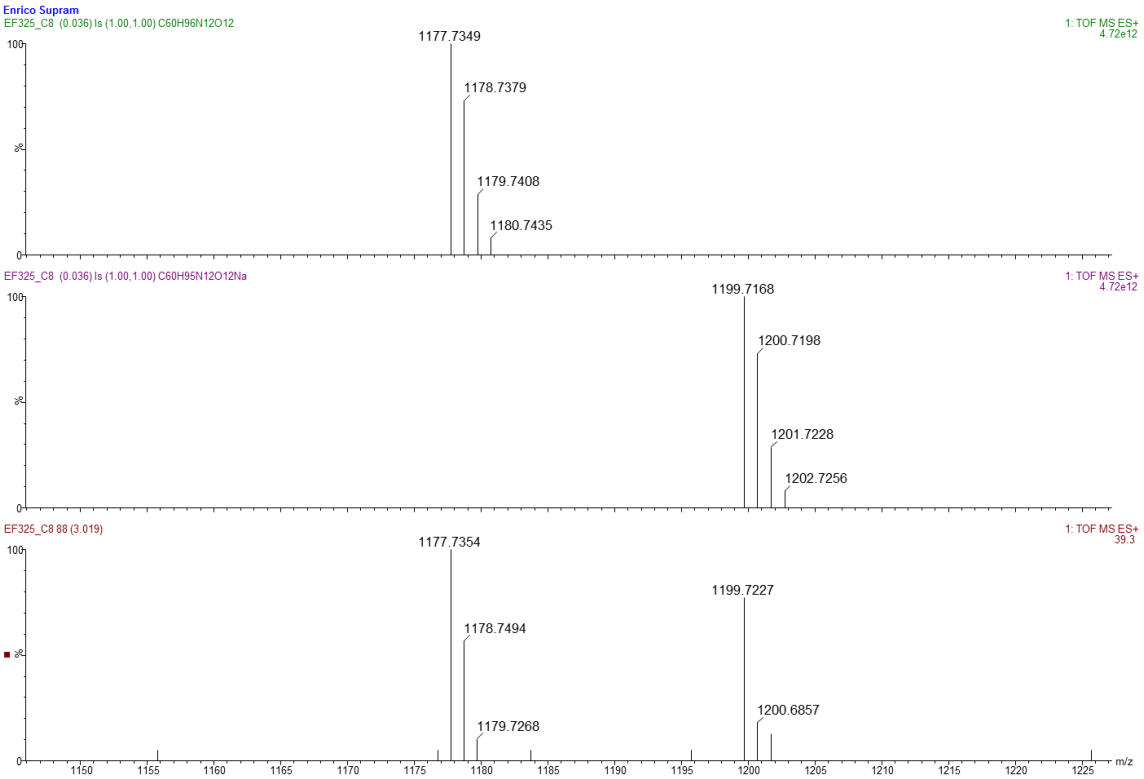


Figure S6. HRMS (ESI+) experimental spectrum of **CyThr** (bottom); simulated spectrum for $C_{60}H_{97}N_{12}O_{12}$ (top), simulated spectrum for $C_{60}H_{96}N_{12}O_{12}Na$ (middle).

2. Synthesis and Characterization of dipeptides

L-L AcEYOH, d_3 L-L AcEYOH, D-D AcEYOH, D-L AcEYOH and L-D AcEYOH were prepared by standard Fmoc Solid Phase Peptide Synthesis on a Wang resin.

General procedure for the synthesis of Ac-EY-OH dipeptides:

Wang resin (2.5 g, 100-200 mesh particle size, extent of labeling: 1.1 mmol/g loading, 2.75 mmol) was suspended in 1 : 1 DCM : DMF mixture (40 ml). In a separate flask, Fmoc-Tyr(*t*Bu)-OH (11 mmol) was dissolved in 15 ml of dry DMF, to which solution Hydroxybenzotriazole (HOBt, 1.68 g, 11 mmol) was added. This solution was added to the resin suspension, followed by DMAP (50 mg, 0.40 mmol). After 10 minutes *N,N'*-Diisopropylcarbodiimide (DIC, 1.70 ml, 11 mmol) was added, and the reaction mixture shaken during 4 hours. The resin was filtered, washed with DCM and DMF (*ca.* 150 ml total volume) and dried. It was suspended in 1 : 4 piperidine : DMF and shaken during 10 minutes. Resin was filtered and the treatment repeated. It was filtered again and washed with DMF, *i*PrOH and DCM. Presence of primary amine was assessed by reacting a small amount of resin with 2,4,6-trinitrobenzensulfonic acid (TNBS) in presence of DIPEA (red color). Resin was suspended in 1 : 1 DCM : DMF mixture (50 ml). In a separate flask, Fmoc-Glu(*t*Bu)-OH (2.05 g, 6.87 mmol), HATU (2.61 g, 6.87 mmol) and DIPEA (2.40 ml, 13.7 mmol) were dissolved in 20 ml of dry DMF, and this solution was added to the resin suspension. The reaction mixture was shaken during 16 hours. It was filtered and washed with DMF and DCM (*ca.* 150 ml total volume) and dried. It was suspended in 1 : 4 piperidine : DMF and shaken during 10 minutes. Resin was filtered and the treatment repeated. It was filtered again and washed with DMF, *i*PrOH and DCM. Presence of primary amine was assessed by reacting a small amount of resin with 2,4,6-trinitrobenzensulfonic acid (TNBS) in presence of DIPEA (red color). Resin was suspended in DCM (40 ml); acetyl anhydride (1.30 ml, 13.7 mmol) and DIPEA (2.60 ml, 15 mmol) were added to the resin suspension, and the reaction mixture shaken during 4 hours. The resin was filtered, washed with plenty of DCM and dried. It was suspended in 50 : 50 : 1 TFA : DCM : TES mixture (80 ml). It was stirred at room temperature during 2 hours. The resin was filtered and washed with plenty of DCM. The filtrate was concentrated. The residue was washed several times with hexane and diethyl ether until a pale yellow solid was obtained. The crude Ac-EY-OH dipeptide was purified by reversed-phase column chromatography (mobile phase: 1% to 20% MeCN in water). Pure Ac-EY-OH dipeptides were obtained as white solids¸ overall typical yield was *ca.* 35%.

Ac-L-Glu-L-Tyr-OH

^{1}H NMR (400 MHz, CD_3OD) δ 7.03 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 2H), 4.58 (dd, *J* = 8.1, 5.1 Hz, 1H), 4.39 (dd, *J* = 8.6, 5.7 Hz, 1H), 3.10 (dd, *J* = 14.0, 5.1 Hz, 1H), 2.91 (dd, *J* = 14.0, 8.1 Hz, 1H), 2.36 (t, *J* = 7.7 Hz, 2H), 2.11 – 1.97 (m, 1H), 1.95 (s, 3H), 1.87 (dt, *J* = 13.9, 8.1 Hz, 1H).

^{13}C NMR (101 MHz, CD_3OD) δ 176.5, 174.5, 173.4, 173.3, 131.4, 128.8, 116.2, 55.2, 53.8, 37.4, 31.1, 28.2, 22.4.

HRMS (ESI-TOF) *m/z* [2 **Ac-L-Glu-L-Tyr-OH** + H]$^+$ Calcd for $C_{32}H_{41}N_4O_{14}$ 705.2619, found 705.2695; [**Ac-L-Glu-L-Tyr-OH** + H]$^+$ Calcd for $C_{16}H_{21}N_2O_7$ 353.1349, found 353.1316.

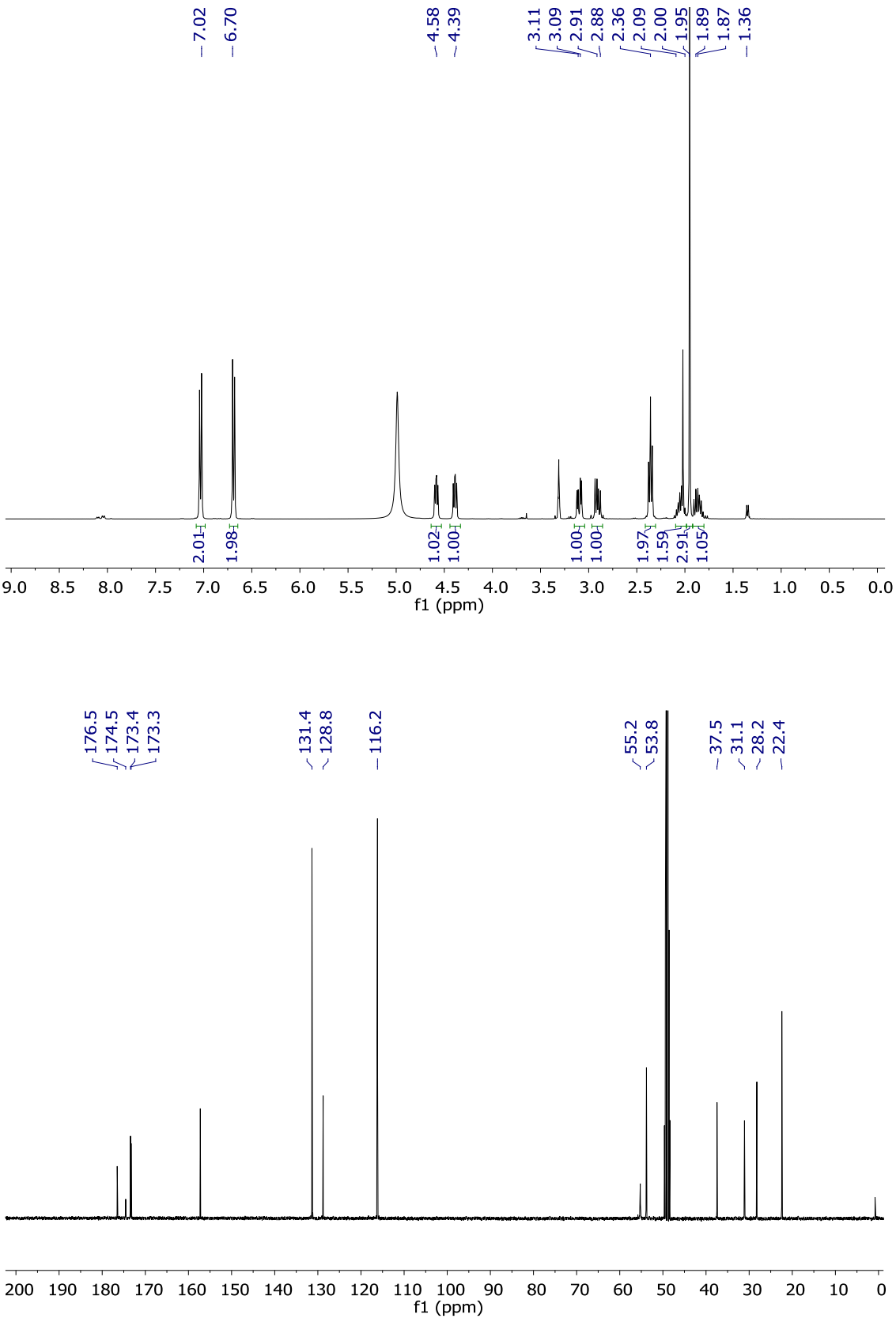


Figure S7. ^{1}H-NMR (CD_3OD, 400 MHz) and ^{13}C-NMR (CD_3OD, 101 MHz) spectra of **Ac-L-Glu-L-Tyr-OH**.

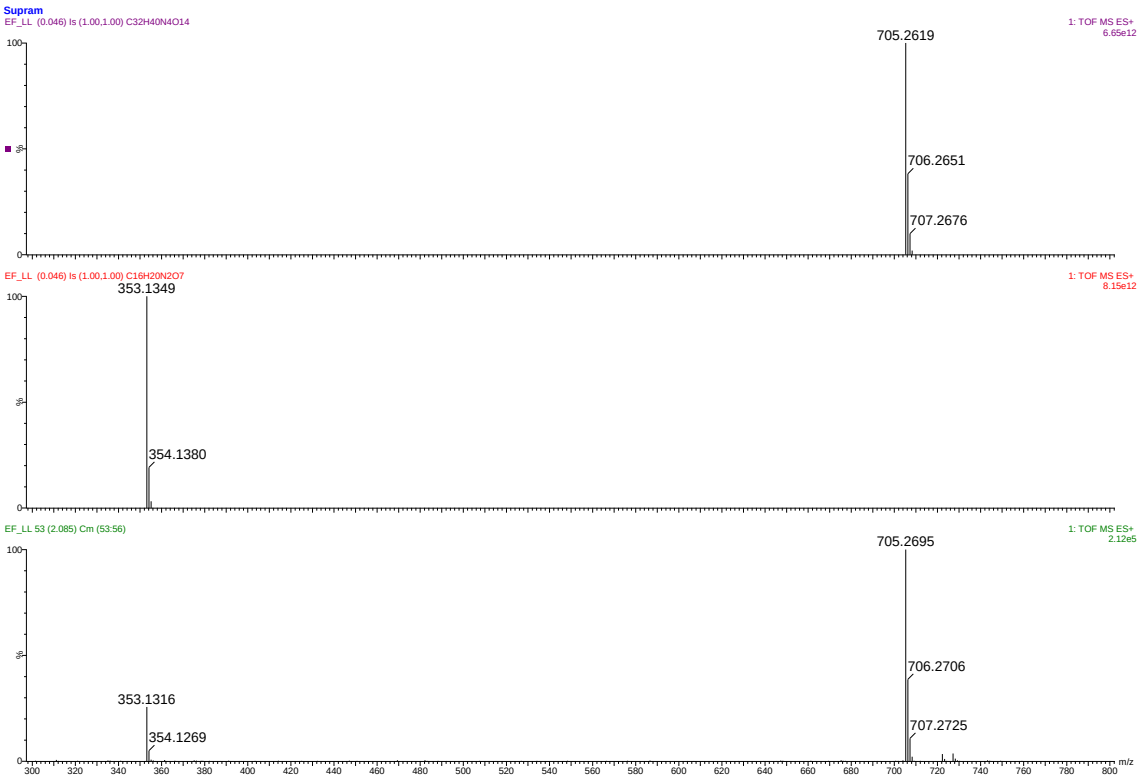


Figure S8. HRMS (ESI+) spectrum of **Ac-L-Glu-L-Tyr-OH** (bottom); simulated spectrum for [2 **Ac-L-Glu-L-Tyr-OH** + H]$^+$ (top); simulated spectrum for [**Ac-L-Glu-L-Tyr-OH** + H]$^+$ (middle).

Ac-D-Glu-D-Tyr-OH

^{1}H NMR (400 MHz, CD_3OD) δ 7.03 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 4.58 (dd, *J* = 8.0, 5.2 Hz, 1H), 4.39 (dd, *J* = 8.5, 5.8 Hz, 1H), 3.10 (dd, *J* = 14.0, 5.1 Hz, 1H), 2.91 (dd, *J* = 14.0, 8.1 Hz, 1H), 2.36 (t, *J* = 7.7 Hz, 2H), 2.11 – 1.97 (m, 1H), 1.95 (s, 3H), 1.87 (dt, *J* = 14.2, 8.0 Hz, 1H).

^{13}C NMR (101 MHz, CD_3OD) δ 176.5, 174.6, 173.4, 173.3, 157.3, 131.4, 128.8, 116.2, 55.2, 53.8, 37.5, 31.1, 28.2, 22.4.

HRMS (ESI-TOF) *m/z* [2 **Ac-D-Glu-D-Tyr-OH** + H]$^+$ Calcd for $C_{32}H_{41}N_4O_{14}$ 705.2619, found 705.2692; [**Ac-D-Glu-D-Tyr-OH** + H]$^+$ Calcd for $C_{16}H_{21}N_2O_7$ 353.1349, found 353.1324.

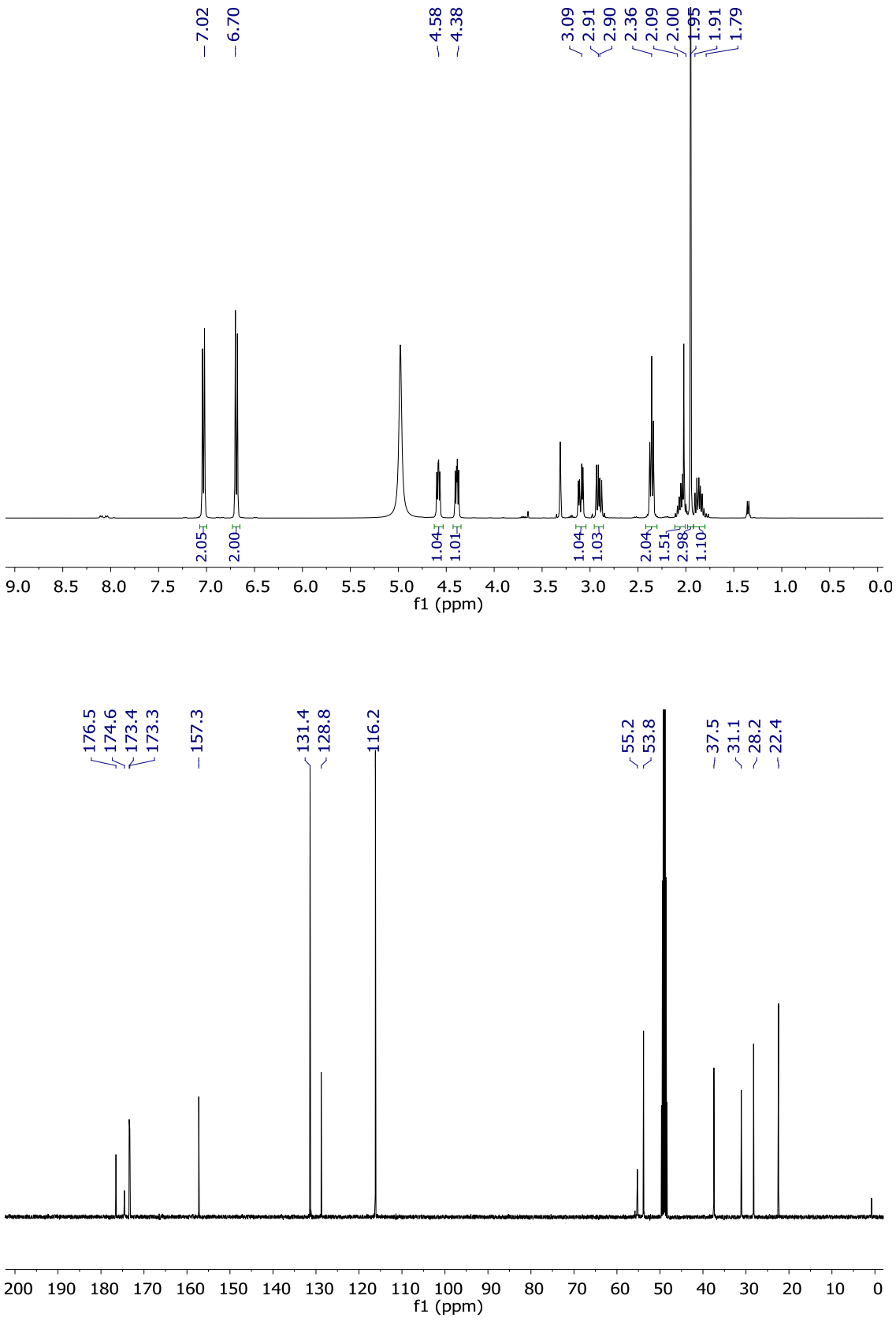


Figure S9. ^{1}H-NMR (CD_3OD, 400 MHz) and ^{13}C-NMR (CD_3OD, 101 MHz) spectra of **Ac-D-Glu-D-Tyr-OH**.

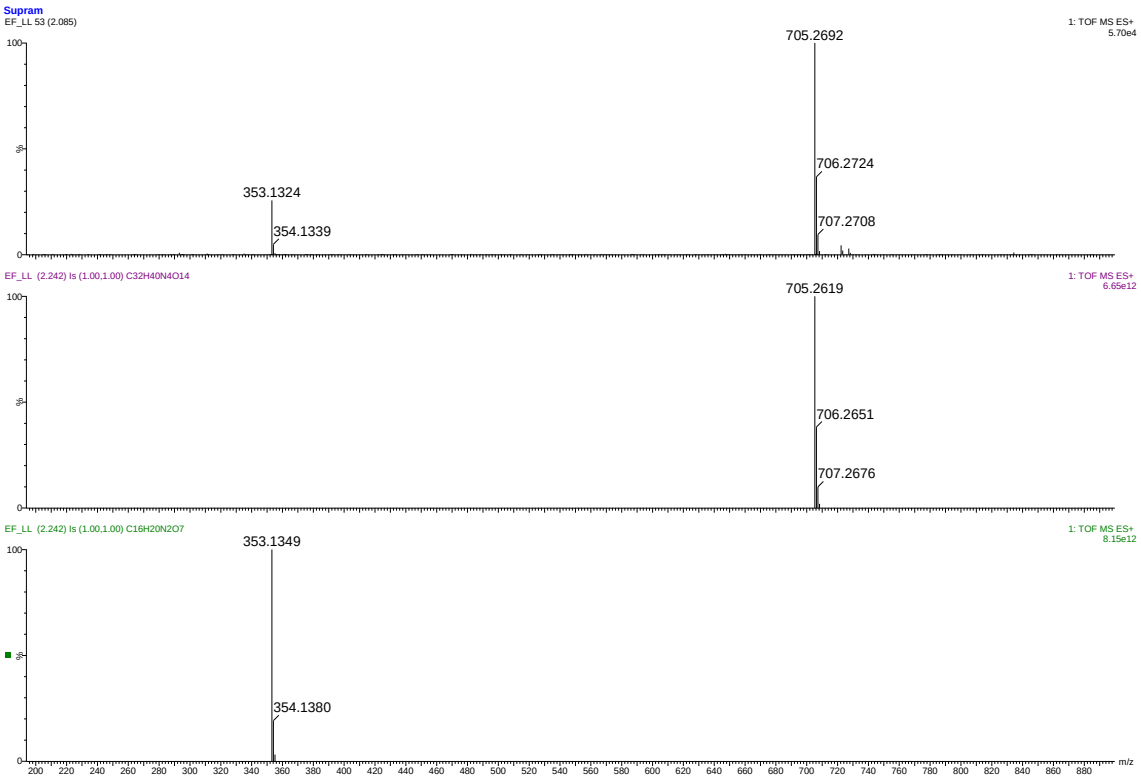


Figure S10. HRMS (ESI+) spectrum of **Ac-D-Glu-D-Tyr-OH** (top); simulated spectrum for [2 **Ac-D-Glu-D-Tyr-OH** + H]$^+$ (middle); simulated spectrum for [**Ac-D-Glu-D-Tyr-OH** + H]$^+$ (bottom).

***d_3*- Ac-L-Glu-L-Tyr-OH**

^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (d, *J* = 7.9 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 4.59 (dd, *J* = 8.1, 5.2 Hz, 1H), 4.39 (dd, *J* = 8.5, 5.8 Hz, 1H), 3.10 (dd, *J* = 14.0, 5.1 Hz, 1H), 2.90 (dd, *J* = 14.0, 8.1 Hz, 1H), 2.36 (t, *J* = 7.7 Hz, 2H), 2.11 – 1.97 (m, 1H), 1.86 (dt, *J* = 15.7, 7.7 Hz, 1H).

^{13}C NMR (101 MHz, CD_3OD) δ 176.5, 174.5, 173.5, 173.3, 157.3, 131.4, 128.8, 116.2, 55.2, 53.8, 37.5, 31.1, 28.2.

HRMS (ESI-TOF) *m/z* [2 ***d_3*- Ac-L-Glu-L-Tyr-OH** + H]$^+$ Calcd for $C_{32}H_{35}D_6N_4O_{14}$ 711.3089, found 711.3042; [***d_3*- Ac-L-Glu-L-Tyr-OH** + H]$^+$ Calcd for $C_{16}H_{17}D_3N_2O_7$ 356.1584, found 356.1523.

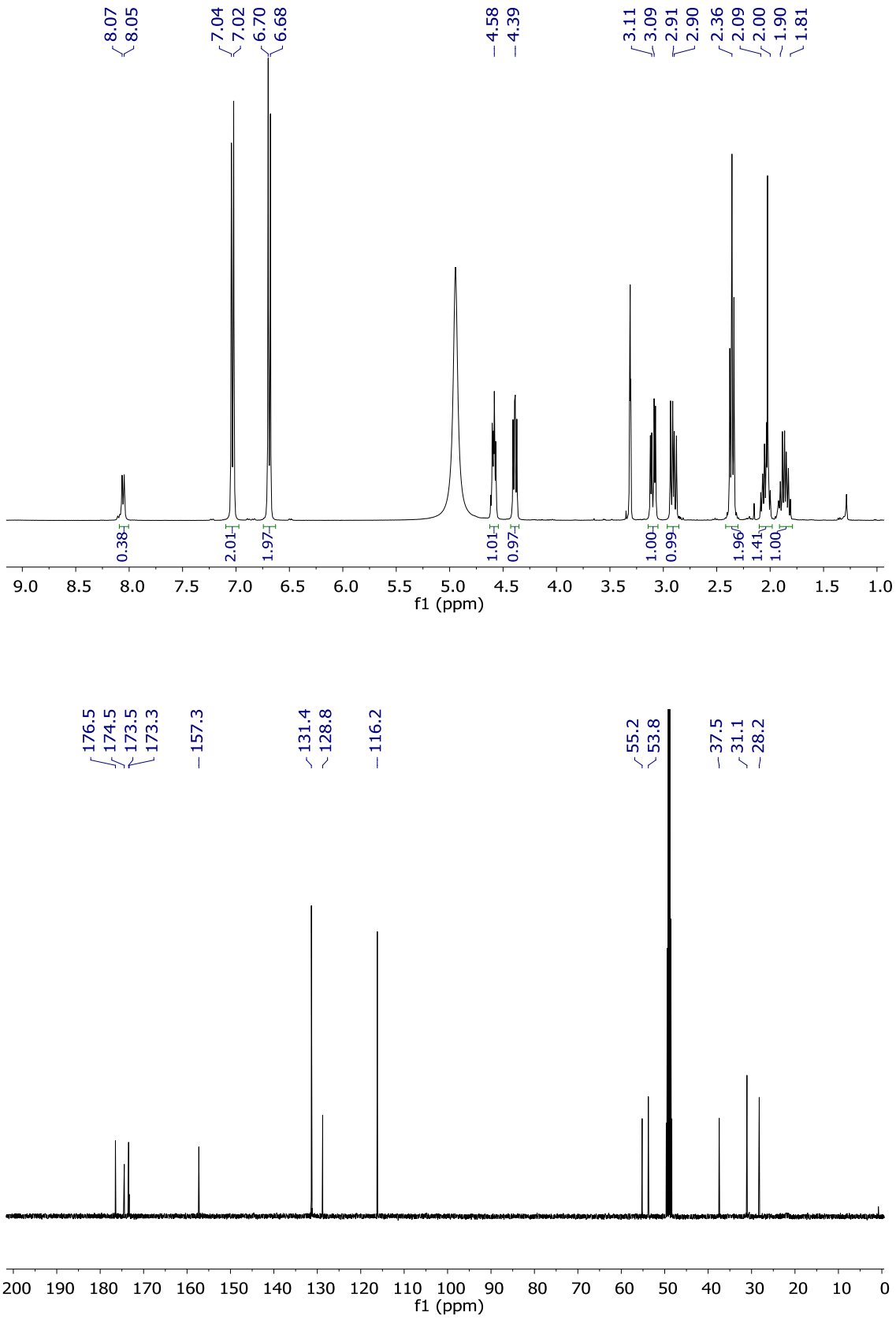


Figure S11. ^{1}H-NMR (CD_3OD, 400 MHz) and ^{13}C-NMR (CD_3OD, 101 MHz) spectra of ***d*$_3$- Ac-L-Glu-L-Tyr-OH**.

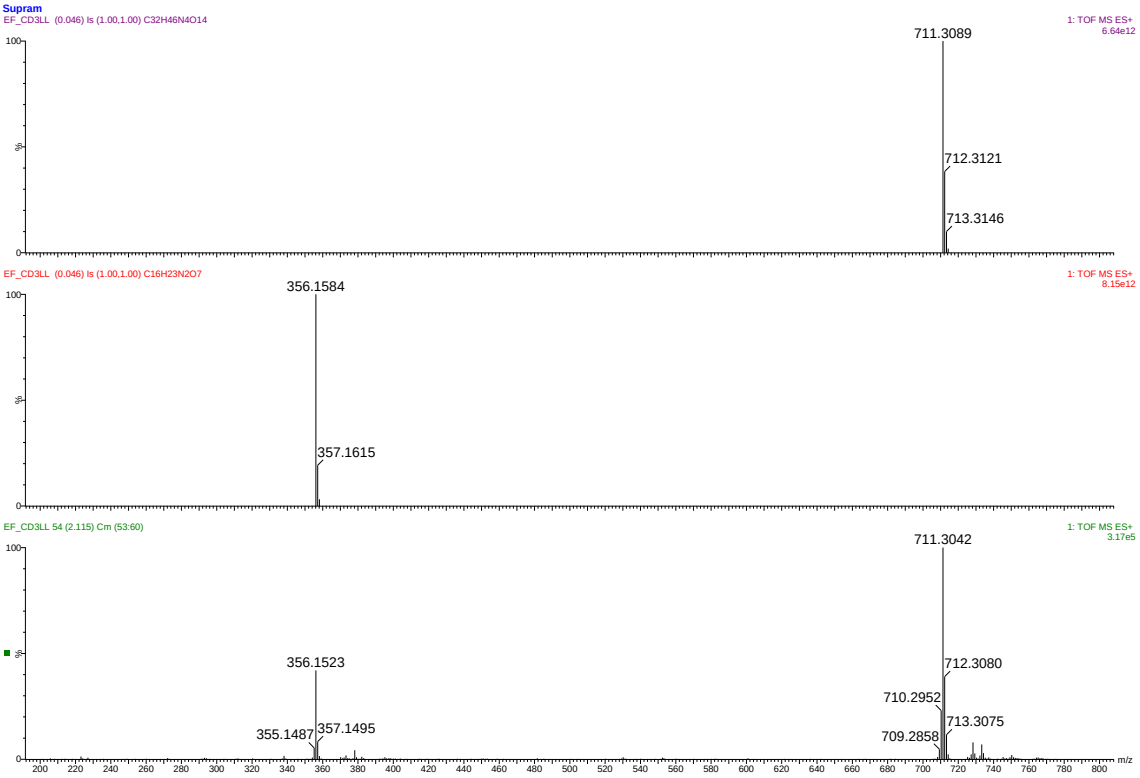


Figure S12. HRMS (ESI+) spectrum of ***d*$_3$- Ac-L-Glu-L-Tyr-OH** (bottom); simulated spectrum for [2 ***d*$_3$- Ac-L-Glu-L-Tyr-OH** + H]$^+$ (top); simulated spectrum for [***d*$_3$- Ac-L-Glu-L-Tyr-OH** + H]$^+$ (middle).

Ac-D-Glu-L-Tyr-OH

^{1}H NMR (400 MHz, CD_3OD) δ 7.02 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 4.60 (dd, *J* = 8.6, 4.9 Hz, 1H), 4.39 (dd, *J* = 8.6, 5.3 Hz, 1H), 3.11 (dd, *J* = 14.0, 4.9 Hz, 1H), 2.90 (dd, *J* = 14.0, 8.7 Hz, 1H), 2.29-2.0 (m, 2H), 2.01-1.91 (m, 1H), 1.96 (s, 3H), 1.80-1.71 (m, 1H).

^{13}C NMR (101 MHz, CD_3OD) δ 176.5, 174.5, 173.3, 157.4, 131.3, 128.8, 116.3, 55.1, 53.9, 37.6, 30.9, 28.5, 22.5.

HRMS (ESI-TOF) *m/z* [2 **Ac-D-Glu-L-Tyr-OH** + H]$^+$ Calcd for $C_{32}H_{41}N_4O_{14}$ 705.2619, found 705.2647; [**Ac-D-Glu-L-Tyr-OH** + H]$^+$ Calcd for $C_{16}H_{21}N_2O_7$ 353.1349, found 353.1317.

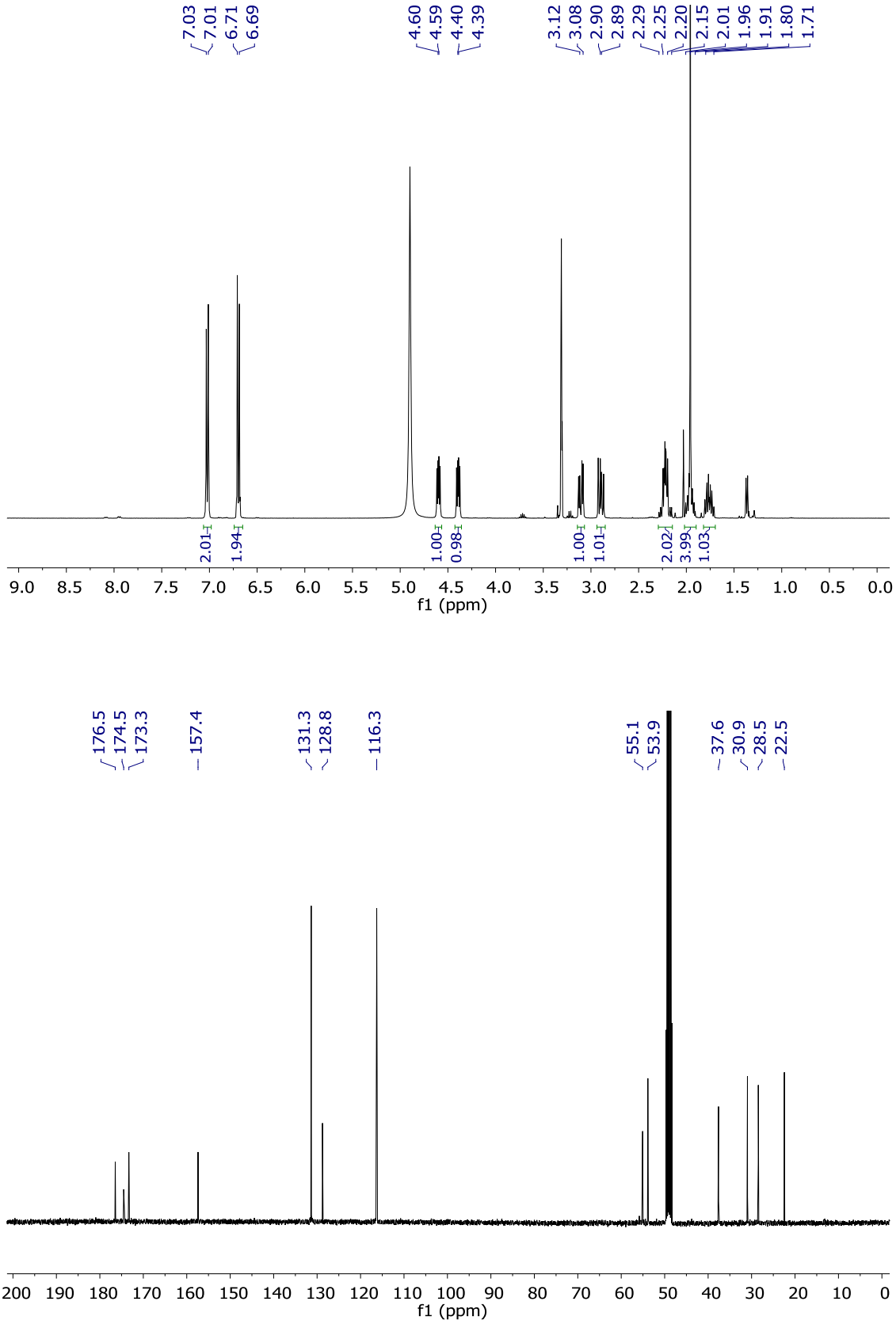


Figure S13. ^{1}H-NMR (CD_3OD, 400 MHz) and ^{13}C-NMR (CD_3OD, 101 MHz) spectra of **Ac-D-Glu-L-Tyr-OH**.

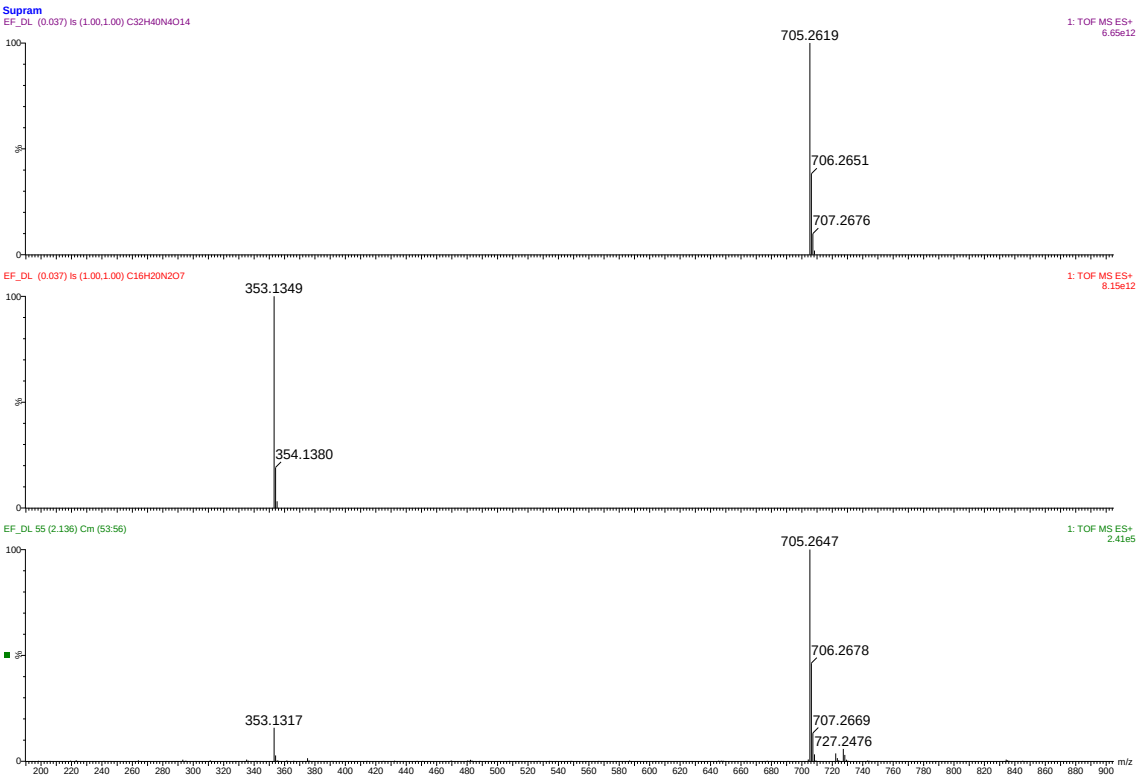


Figure S14. HRMS (ESI+) spectrum of **Ac-D-Glu-L-Tyr-OH** (bottom); simulated spectrum for [2 **Ac-D-Glu-L-Tyr-OH** + H]$^+$ (top); simulated spectrum for [**Ac-D-Glu-L-Tyr-OH** + H]$^+$ (middle).

Ac-L-Glu-D-Tyr-OH

^{1}H NMR (400 MHz, CD_3OD) δ 7.02 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 4.59 (dd, *J* = 8.6, 4.9 Hz, 1H), 4.38 (dd, *J* = 8.5, 5.3 Hz, 1H), 3.11 (dd, *J* = 14.0, 4.8 Hz, 1H), 2.90 (dd, *J* = 14.0, 8.7 Hz, 1H), 2.29-2.0 (m, 2H), 2.00-1.92 (m, 1H), 1.96 (s, 3H), 1.81-1.71 (m, 1H).

^{13}C NMR (101 MHz, CD_3OD) δ 176.5, 174.6, 173.3, 157.4, 131.4, 128.8, 116.3, 55.1, 53.9, 37.6, 31.0, 28.4, 22.5.

HRMS (ESI-TOF) *m/z* [2 **Ac-L-Glu-D-Tyr-OH** + H]$^+$ Calcd for $C_{32}H_{41}N_4O_{14}$ 705.2619, found 705.2645; [**Ac-L-Glu-D-Tyr-OH** + H]$^+$ Calcd for $C_{16}H_{21}N_2O_7$ 353.1349, found 353.1316.

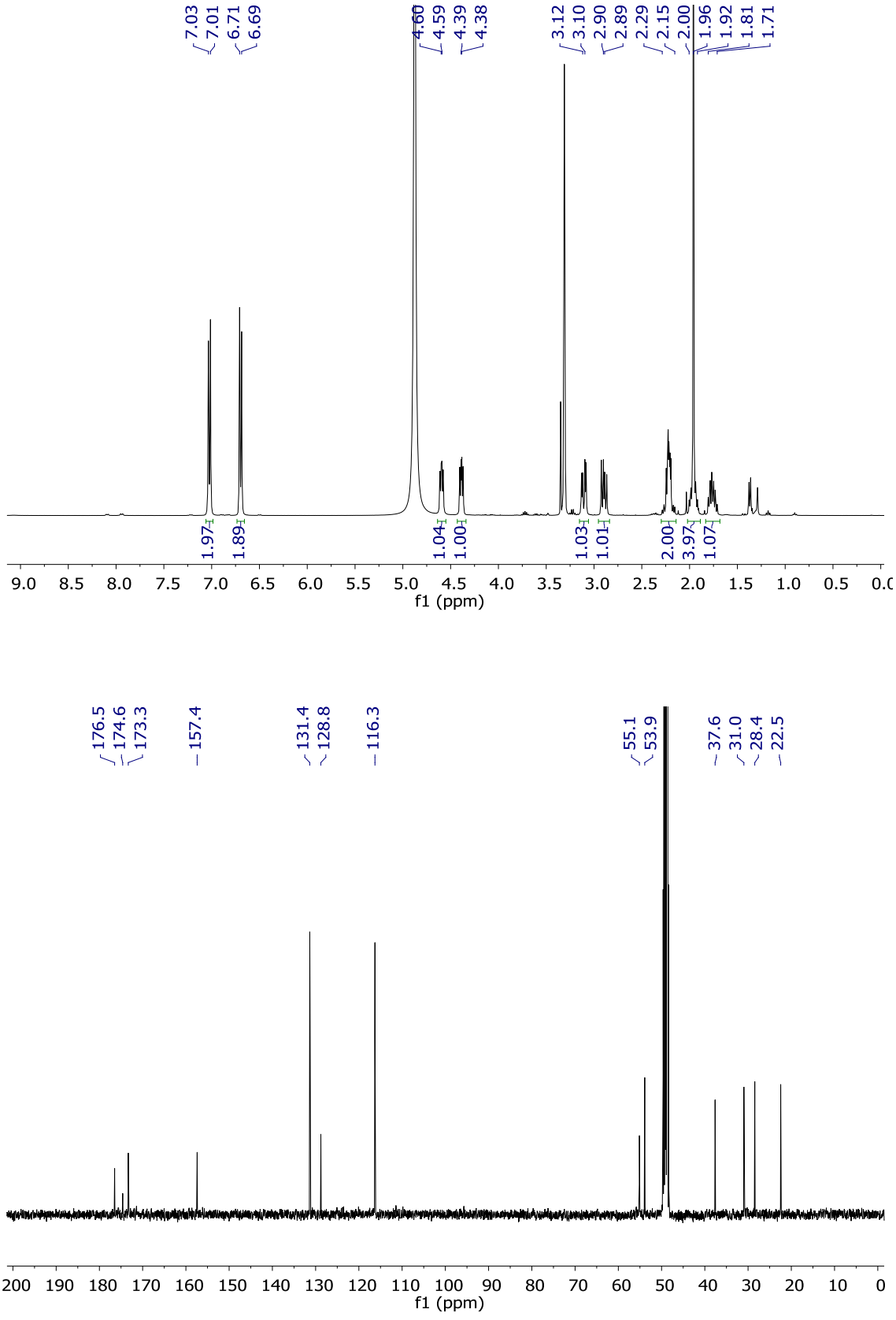


Figure S15. ^{1}H-NMR (CD_3OD, 400 MHz) and ^{13}C-NMR (CD_3OD, 101 MHz) spectra of **Ac-L-Glu-D-Tyr-OH**.

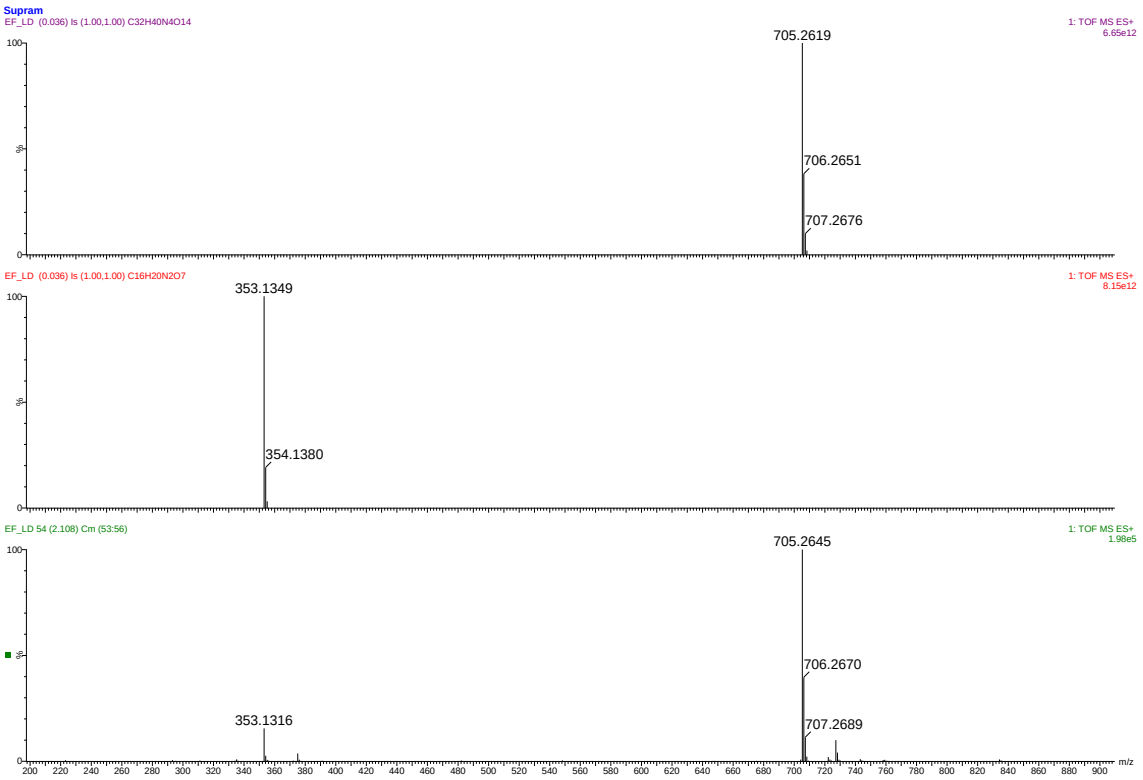


Figure S16. HRMS (ESI+) spectrum of **Ac-L-Glu-D-Tyr-OH** (bottom); simulated spectrum for [2 **Ac-L-Glu-D-Tyr-OH** + H]$^+$ (top); simulated spectrum for [**Ac-L-Glu-D-Tyr-OH** + H]$^+$ (middle).

3. NMR titrations

^{1}H NMR titration procedure

The titrations were performed with the cage receptors as free amines. Stock solutions of the cages were prepared by weighting the corresponding amount of the receptor and reaching a final concentration around 1 mM in the chosen solvents mixture (a) 2 : 1 CD_3CN : H_2O; b) 1 : 1 CD_3CN : H_2O; c) 6.4 : 1 CD_3CN : H_2O).

Stock solutions of the titrant containing 20-45 mM dipeptide were prepared by dissolving the dipeptides in the stock solution of the corresponding cage, thus maintaining the concentration of the cage constant during the titration experiment. The stock solution of the cage was introduced in a NMR tube and the ^{1}H NMR spectrum (500 MHz, 298 K) was acquired using the water excitation sculpting (DPFGSE) sequence from the CHEMPACK library of Agilent VnmrJ32 software. Then volumes of the stock solution of the titrant were added and the ^{1}H NMR spectrum recorded after each addition.

Different signals shifted upon addition of the dipeptides, and their shifts were fitted to a 1 : 1 receptor : substrate model using HypNmr 2008 version 4.0.71 software.[1] Following we show, for every titration experiment, the data set introduced (experimental) and obtained (fit) during the fitting process, the output value (logK) for the formation of every supramolecular complex, the plot of the experimental (symbols) and the fitted (lines) values of the chemical shifts, and the plot of the simulated species distribution obtained with HySS2009 software[2] and selected ^{1}H NMR spectra of representative titration points.

[1] For further details concerning the way the program works see: C. Frassineti, S. Ghelli, P. Gans, A. Sabatini, M.S. Moruzzi and A. Vacca, *Analytical Biochemistry* **1995**, *231*, 374-382; C. Frassineti, L. Alderighi, P. Gans, A. Sabatini, A.Vacca, S. Ghelli, *Anal. Bioanal. Chem*. **2003**, *376*, 1041-1052.

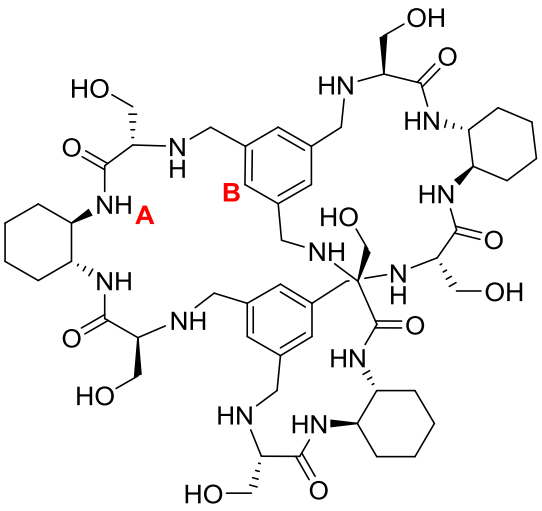
[2] L. Alderighi , P. Gans, A. Ienco , D. Peters, A. Sabatini and A. Vacca, *Coordination Chemistry Reviews* **1999**, *184*, 311-318).

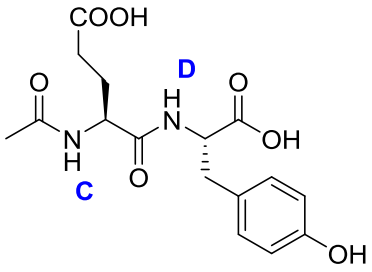
Data for the NMR titration CySer vs. Ac-L-Glu-L-Tyr-OH

Solvent: 1 : 1 CD_3CN : H_2O

Results of the HypNMR2008 fitting:

Log K = 2.84 (4); K = 692





Data Set:

[**CySer**]	[AcEYOH]	A	A fit	B	B fit	C	C fit	D	D fit
0.00102	0	8.133	8.1324	6.712	6.7237				
0.00102	0.00014	8.142	8.1427	6.737	6.7418				
0.00102	0.000414	8.16	8.1607	6.779	6.7739	7.831	7.8013	7.351	7.333
0.00102	0.00068	8.176	8.176	6.809	6.801	7.803	7.7914	7.36	7.3529
0.00102	0.000941	8.189	8.189	6.833	6.8241	7.781	7.7823	7.37	7.3711
0.00102	0.00132	8.207	8.205	6.86	6.8525	7.759	7.7703	7.387	7.3951
0.00102	0.00192	8.226	8.2246	6.89	6.8874	7.736	7.7541	7.415	7.4274
0.00102	0.00259	8.241	8.2406	6.915	6.9158	7.722	7.7395	7.446	7.4565
0.00102	0.00361	8.256	8.2573	6.939	6.9455	7.708	7.7228	7.482	7.4898
0.00102	0.00503	8.269	8.2719	6.962	6.9714	7.697	7.7068	7.519	7.5218
0.00102	0.00716	8.283	8.2845	6.982	6.9938	7.689	7.6917	7.554	7.552
0.00102	0.00967	8.293	8.293			7.684	7.6809	7.577	7.5736
0.00102	0.0121	8.296	8.298	7.015	7.0178	7.681	7.6741	7.59	7.5872
0.00102	0.016	8.301	8.3031	7.024	7.0268	7.678	7.6671	7.599	7.6012
0.00102	0.0211	8.314	8.307	7.052	7.0337	7.675	7.6615	7.624	7.6124

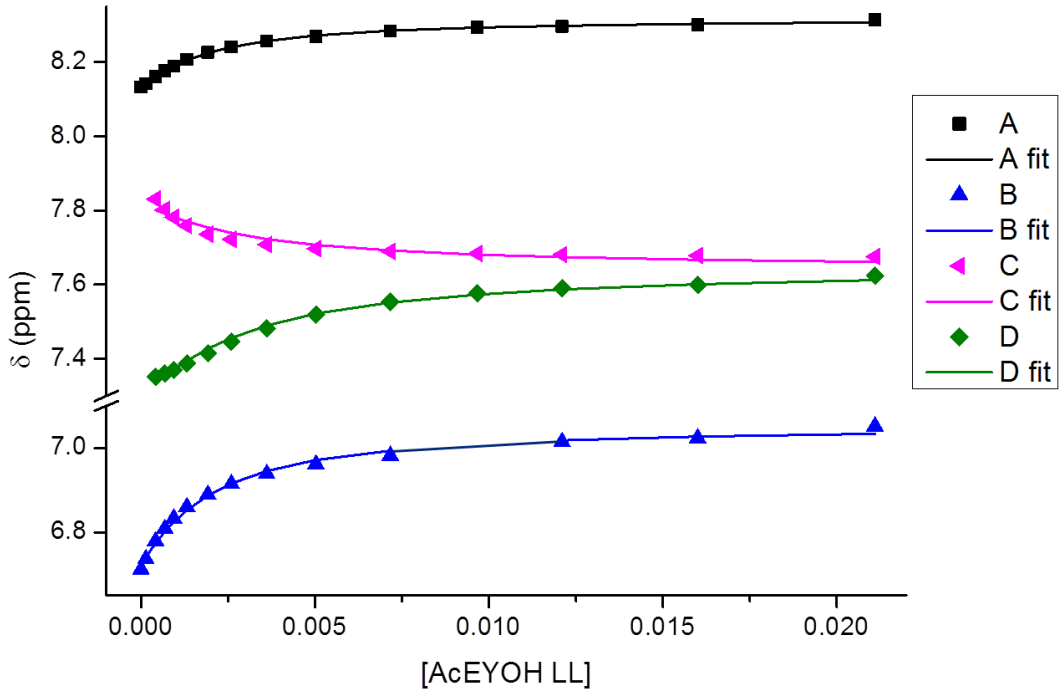


Figure S17. Plot of the experimental (symbols) and fitting (lines) data.

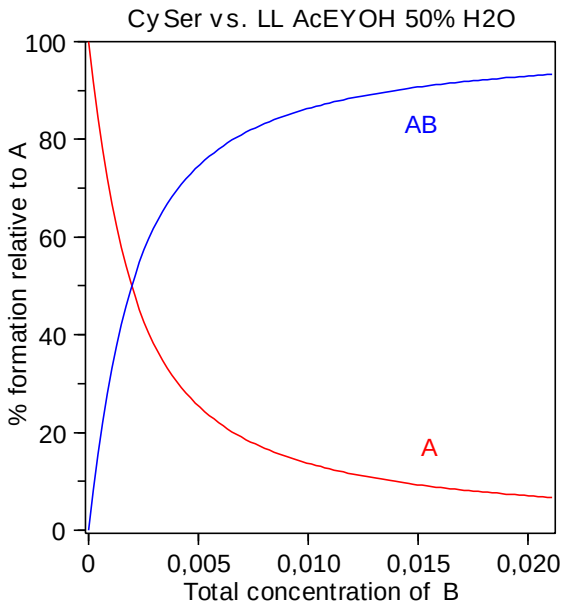


Figure S18. Species distribution as a function of the concentration of the dipeptide.

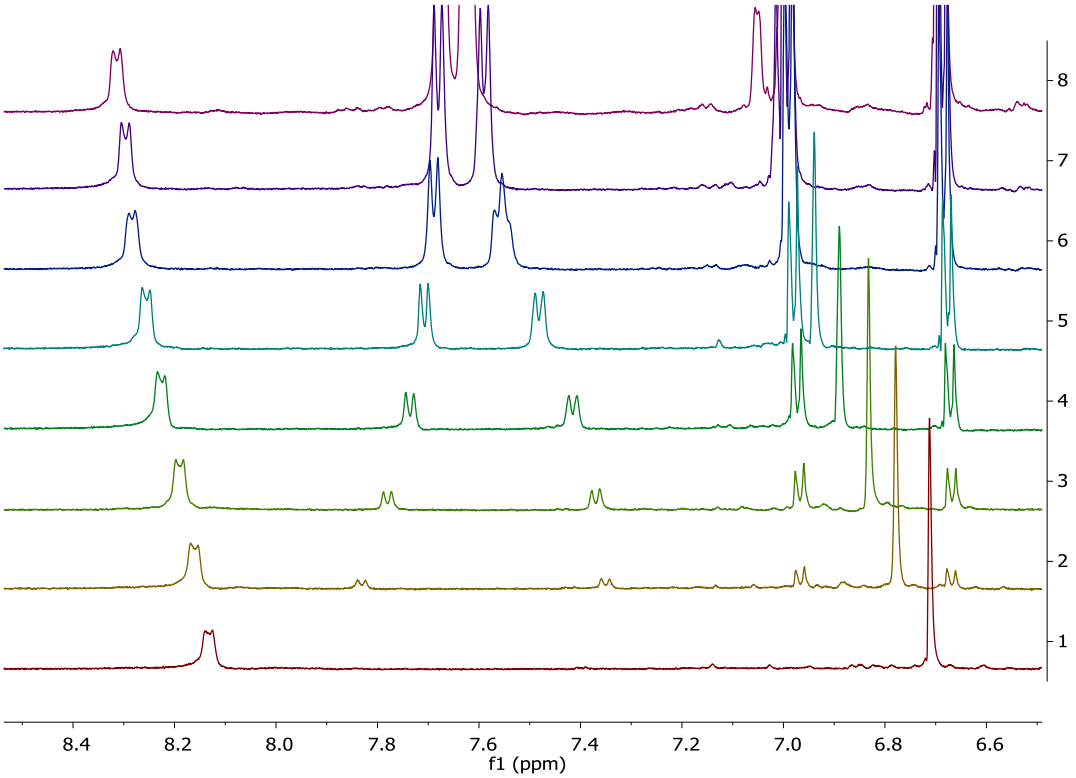


Figure S19. Selected stacked spectra (8.5-6.5 ppm range) of the **CySer** *vs.* Ac-L-Glu-L-Tyr-OH titration in 1:1 $CD_3CN:H_2O$; [**CySer**]= 1.14 mM, [Ac-L-Glu-L-Tyr-OH]=0 mM, 0. 404 mM, 0.918 mM, 1.87 mM, 3.53 mM, 9.44 mM, 21.3 mM (from bottom to top).

Data for the NMR titration CySer vs. Ac-L-Glu-L-Tyr-EYOH

Solvent: 6.4 : 1 CD_3CN : H_2O

Results of the HypNMR2008 fitting:

Log K = 2.85 (4); K = 708

Data Set:

[**CySer**]	[AcEYOH]	A	A fit	B	B fit	C	C fit	D	D fit
0.00104	0	8.019	8.0181	6.892	6.899				
0.00104	0.000139	8.037	8.0345	6.907	6.9105				
0.00104	0.000412	8.066	8.0638	6.934	6.9308	7.553	7.5267	7.296	7.2944
0.00104	0.000677	8.089	8.0885	6.956	6.948	7.527	7.5157	7.301	7.303
0.00104	0.000936	8.109	8.1095	6.969	6.9626	7.509	7.5057	7.307	7.3109
0.00104	0.00131	8.135	8.1351	6.987	6.9805	7.483	7.4924	7.319	7.3213
0.00104	0.00191	8.164	8.1669	7.004	7.0026	7.457	7.4743	7.335	7.3356
0.00104	0.00258	8.191	8.1927	7.019	7.0205	7.44	7.458	7.353	7.3484
0.00104	0.0036	8.214	8.2194	7.032	7.0391	7.421	7.4393	7.368	7.3631
0.00104	0.00501	8.236	8.2423	7.044	7.0551	7.408	7.4215	7.382	7.377
0.00104	0.00712	8.258	8.2621	7.056	7.0689				
0.00104	0.00963	8.274	8.2753	7.069	7.0781	7.396	7.3928	7.396	7.3996
0.00104	0.0121	8.285	8.2833	7.081	7.0837	7.392	7.3852	7.406	7.4055
0.00104	0.0161	8.299	8.2913	7.097	7.0892	7.389	7.3773	7.41	7.4117
0.00104	0.0212	8.304	8.2972	7.115	7.0933	7.385	7.3712	7.414	7.4165

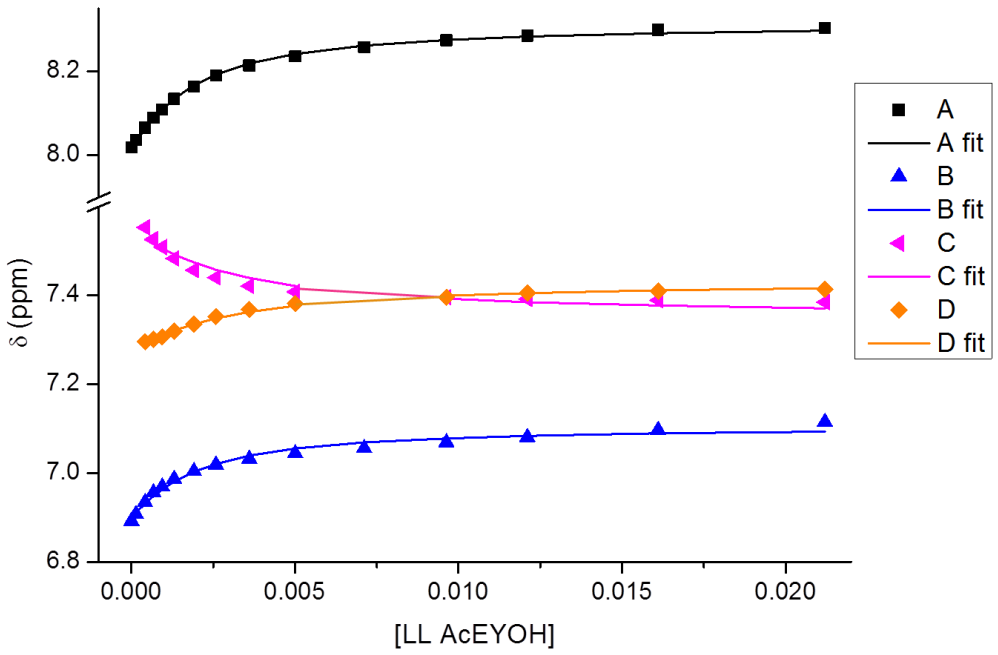


Figure S20. Plot of the experimental (symbols) and fitting (lines) data.

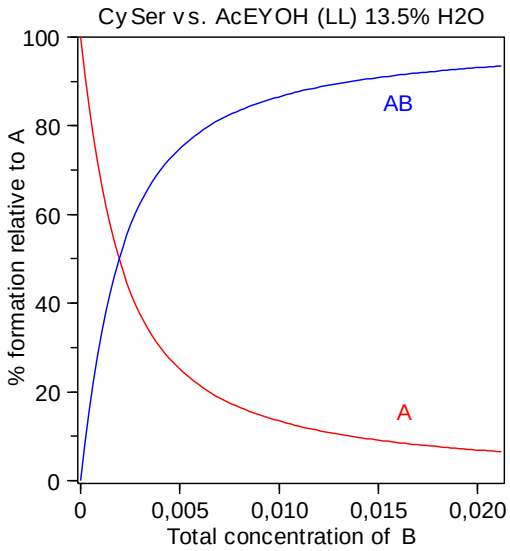


Figure S21. Species distribution as a function of the concentration of the dipeptide.

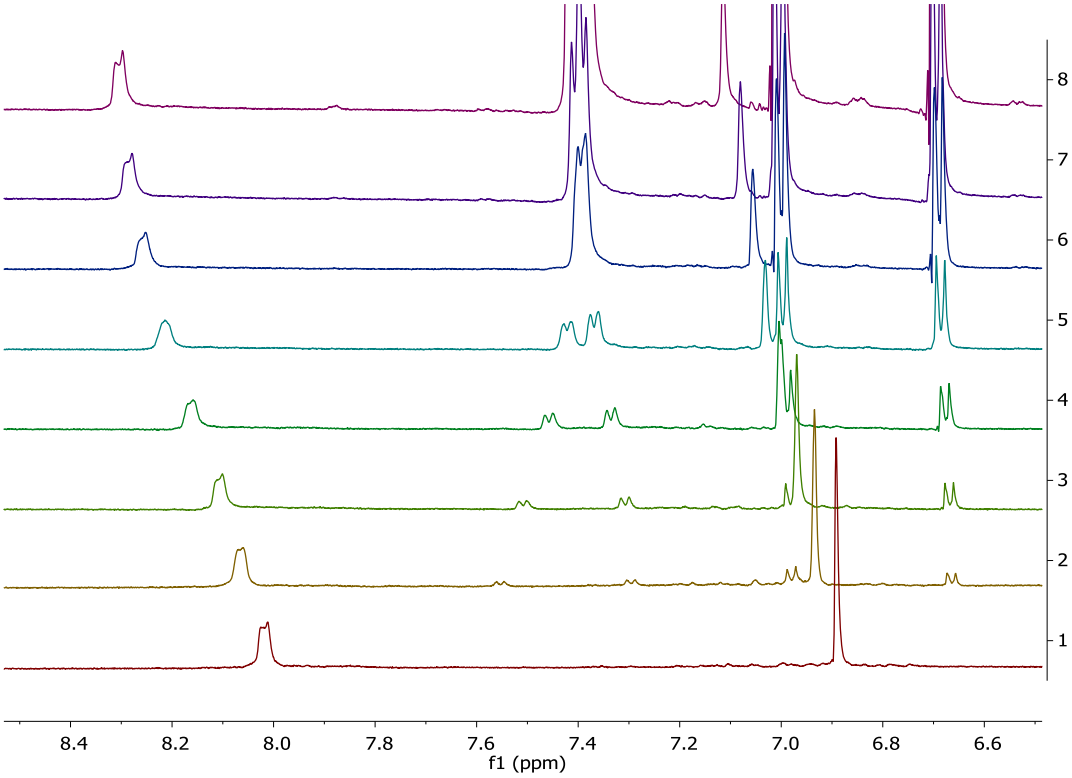


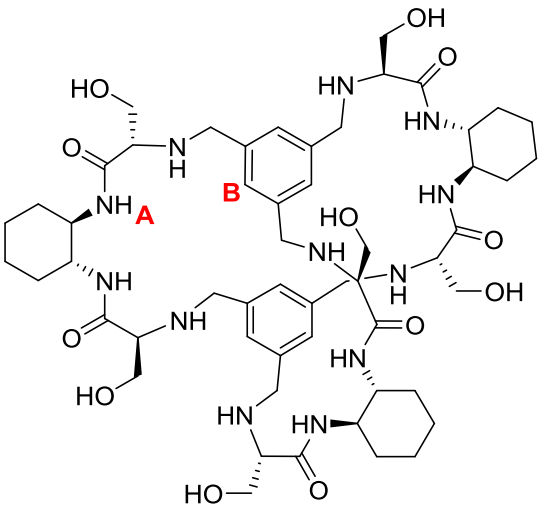
Figure S22. Selected stacked spectra (8.5-6.5 ppm range) of the **CySer** *vs.* Ac-L-Glu-L-Tyr-OH titration in 6.4:1 $CD_3CN:H_2O$; [**CySer**]= 1.14 mM, [Ac-L-Glu-L-Tyr-OH]=0 mM, 0. 404 mM, 0.918 mM, 1.87 mM, 3.53 mM, 9.44 mM, 21.3 mM (from bottom to top).

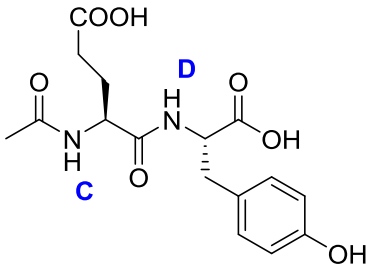
Data for the NMR titration CySer vs. Ac-L-Glu-L-Tyr-OH

Solvent: 2 : 1 CD_3CN : H_2O

Results of the HypNMR2008 fitting:

Log K = 2.80 (3); K = 631





Data Set:

[**CySer**]	[AcEYOH-LL]	A	A fit	B	B fit	C	C fit	D	D fit
0.00114	0	8.109	8.1058	6.748	6.7563				
0.00114	0.000136	8.12	8.1159	6.77	6.7709				
0.00114	0.000404	8.133	8.1341	6.802	6.7974	7.782	7.7473	7.343	7.3346
0.00114	0.000664	8.15	8.1497	6.828	6.8201	7.755	7.7361	7.349	7.3478
0.00114	0.000918	8.165	8.1632	6.849	6.8398	7.732	7.7259	7.355	7.3599
0.00114	0.00129	8.182	8.1803	6.87	6.8646	7.709	7.712	7.365	7.3764
0.00114	0.00187	8.204	8.2015	6.898	6.8955	7.682	7.6931	7.383	7.3987
0.00114	0.00253	8.222	8.2196	6.921	6.9219	7.664	7.6753	7.406	7.4198
0.00114	0.00353	8.24	8.239	6.945	6.9501	7.644	7.6544	7.436	7.4446
0.00114	0.00491	8.254	8.2562	6.965	6.9751	7.63	7.634	7.462	7.4688
0.00114	0.00699	8.27	8.2714	6.988	6.9974	7.617	7.614	7.491	7.4925
0.00114	0.00944	8.279	8.2818	7.004	7.0124	7.606	7.5995	7.51	7.5097
0.00114	0.0119	8.287	8.2882			7.6	7.5899	7.523	7.521
0.00114	0.0161	8.295	8.2949	7.034	7.0315	7.592	7.5796	7.539	7.5333
0.00114	0.0213	8.304	8.2996	7.056	7.0384	7.584	7.572	7.553	7.5423
0.00125	0	8.106	8.1058	6.747	6.7563				
0.00125	0.000137	8.114	8.1156	6.765	6.7705				
0.00125	0.000406	8.129	8.1333	6.798	6.7962	7.784	7.7594	7.343	7.3202
0.00125	0.000668	8.146	8.1486	6.824	6.8186	7.754	7.7483	7.347	7.3334
0.00125	0.000923	8.16	8.162	6.846	6.838	7.732	7.7379	7.352	7.3456
0.00125	0.00129	8.178	8.1786	6.868	6.8623	7.707	7.7241	7.361	7.3621

0.00125	0.00188	8.199	8.2002	6.895	6.8937	7.683	7.7043	7.378	7.3854
0.00125	0.00254	8.221	8.2184	6.922	6.9202	7.662	7.6858	7.403	7.4074
0.00125	0.00354	8.237	8.238	6.941	6.9487	7.644	7.6637	7.425	7.4336
0.00125	0.00494	8.252	8.2557	6.962	6.9744	7.627	7.6416	7.454	7.4598
0.00125	0.00702	8.267	8.2711	6.983	6.9969	7.61	7.6202	7.485	7.4852
0.00125	0.00949	8.28	8.2816			7.604	7.6043	7.507	7.504
0.00125	0.0119	8.287	8.288	7.018	7.0215	7.597	7.5941	7.518	7.516
0.00125	0.0159	8.297	8.2945	7.035	7.031	7.59	7.5833	7.534	7.5289
0.00125	0.0211	8.305	8.2994	7.056	7.0381	7.584	7.5748	7.548	7.539

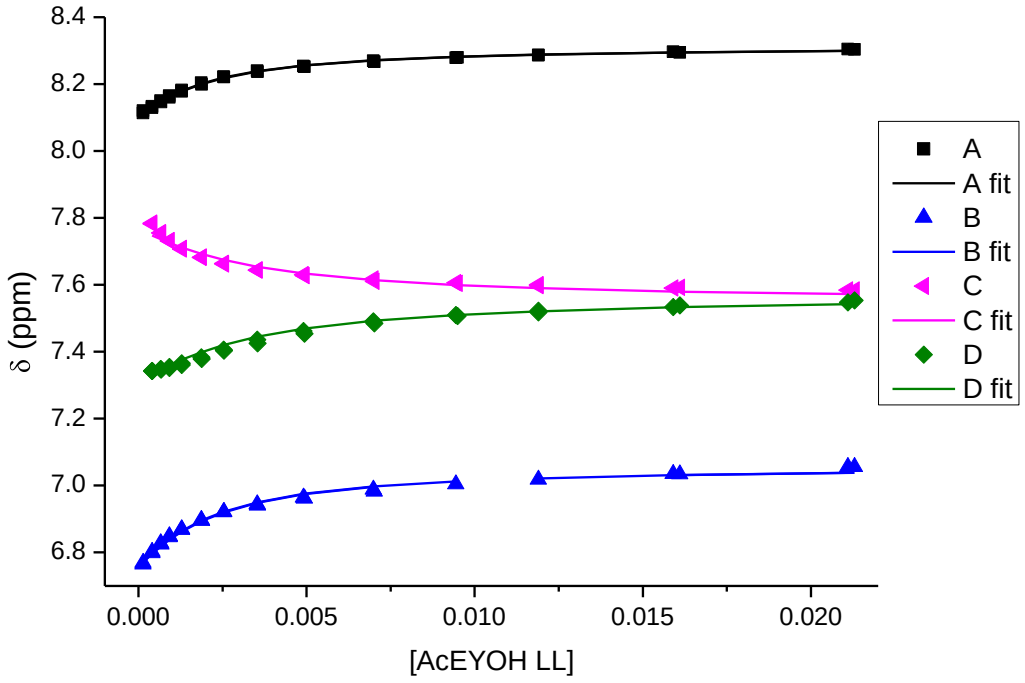


Figure S23. Plot of the experimental (symbols) and fitting (lines) data.

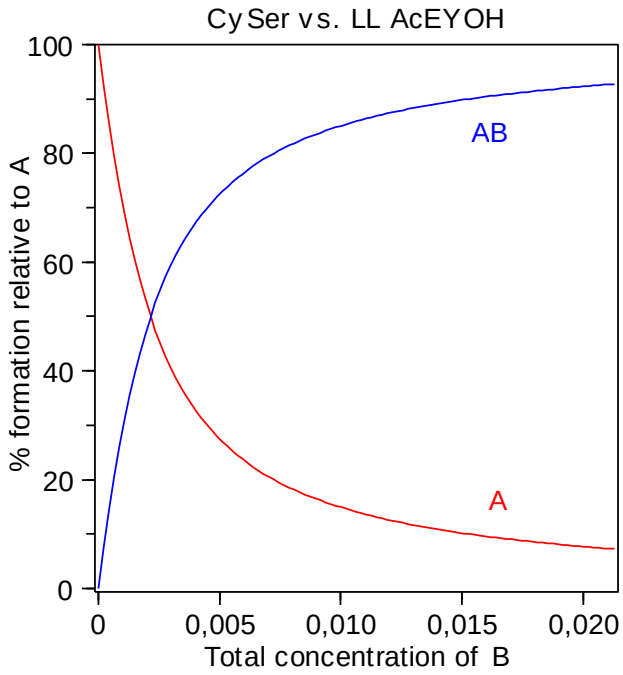


Figure S24. Species distribution as a function of the concentration of the dipeptide.

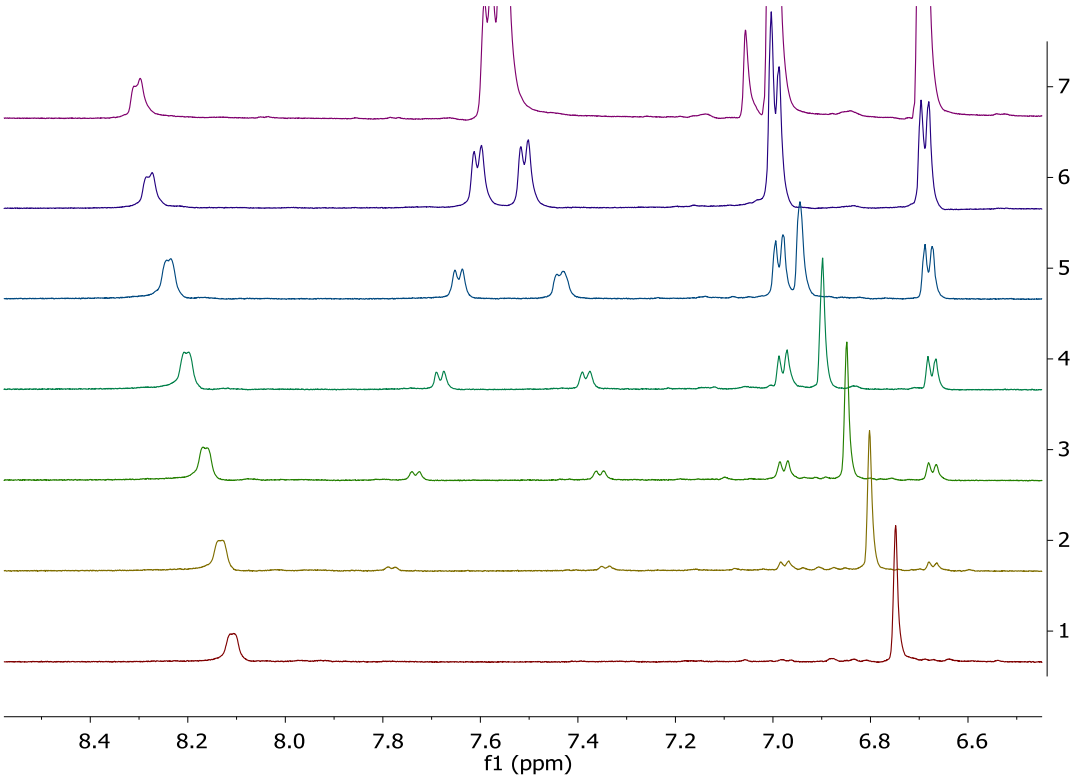


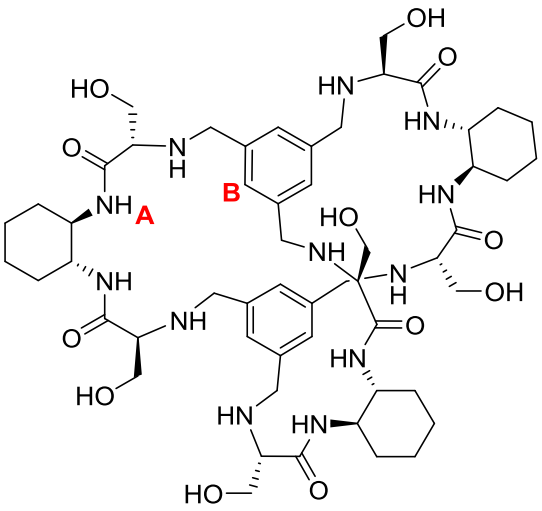
Figure S25. Selected stacked spectra (8.5-6.5 ppm range) of the **CySer** *vs.* Ac-L-Glu-L-Tyr-OH titration in 2:1 $CD_3CN:H_2O$; [**CySer**]= 1.14 mM, [Ac-L-Glu-L-Tyr-OH]=0 mM, 0. 404 mM, 0.918 mM, 1.87 mM, 3.53 mM, 9.44 mM, 21.3 mM (from bottom to top).

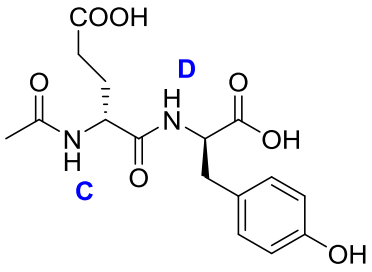
Data for the NMR titration CySer vs. Ac-D-Glu-D-Tyr-OH

Solvent: 2 : 1 CD_3CN : H_2O

Results of the HypNMR2008 fitting:

Log K = 2.66 (3); K = 457





Data Set:

[**CySer**]	[**AcEYOH-DD**]	A	A fit	B	B fit	C	C fit	D	D fit
0.00109	0	8.105	8.0948	6.75	6.7511				
0.00109	0.000132	8.11	8.1028	6.763	6.7614				
0.00109	0.000392	8.12	8.1174	6.786	6.7802	7.796	7.7727	7.354	7.3568
0.00109	0.000645	8.133	8.1302	6.805	6.7967	7.777	7.7648	7.363	7.3629
0.00109	0.000892	8.142	8.1414	6.823	6.8111	7.761	7.7575	7.367	7.3685
0.00109	0.00125	8.147	8.1557	6.843	6.8296	7.743	7.7477	7.374	7.376
0.00109	0.00182	8.176	8.1746	6.867	6.8539	7.724	7.7341	7.382	7.3865
0.00109	0.00246	8.194	8.1913	6.886	6.8754	7.708	7.7213	7.391	7.3964
0.00109	0.00342	8.21	8.2101	6.907	6.8996	7.693	7.7059	7.402	7.4083
0.00109	0.00477	8.227	8.2281	6.927	6.9229	7.68	7.6898	7.416	7.4206
0.00109	0.00678	8.244	8.2451	6.944	6.9447	7.669	7.6737	7.432	7.433
0.00109	0.00917	8.257	8.2573	6.963	6.9605	7.661	7.6613	7.445	7.4426
0.00109	0.01158	8.269	8.2652	6.981	6.9707	7.655	7.653	7.455	7.449
0.00109	0.01551	8.28	8.2734	6.985	6.9812	7.653	7.644	7.463	7.4559
0.00109	0.02061	8.291	8.2797			7.65	7.6369	7.473	7.4614
0.00125	0	8.103	8.0948	6.742	6.7511				
0.00125	0.000134	8.107	8.1026	6.753	6.7611				
0.00125	0.000398	8.115	8.1168	6.772	6.7795	7.803	7.7888	7.352	7.3444
0.00125	0.000655	8.125	8.1294	6.791	6.7956	7.788	7.7806	7.36	7.3507
0.00125	0.000905	8.134	8.1404	6.806	6.8099	7.774	7.773	7.364	7.3565
0.00125	0.00127	8.146	8.1547	6.824	6.8283	7.756	7.7627	7.368	7.3645
0.00125	0.00184	8.164	8.1734	6.845	6.8523	7.739	7.7484	7.375	7.3755
0.00125	0.00249	8.182	8.1903	6.87	6.8741	7.721	7.7345	7.382	7.3862

0.00125	0.00348	8.201	8.2096	6.891	6.899	7.706	7.7173	7.392	7.3994
0.00125	0.00484	8.221	8.2278	6.915	6.9224	7.689	7.6997	7.406	7.413
0.00125	0.00688	8.244	8.245	6.937	6.9446	7.683	7.6817	7.425	7.4269
0.00125	0.00931	8.257	8.2574	6.952	6.9605	7.669	7.6677	7.433	7.4376
0.00125	0.0117	8.263	8.2652	6.96	6.9706	7.667	7.6585	7.441	7.4448
0.00125	0.0157	8.281	8.2735			7.659	7.6483	7.455	7.4526

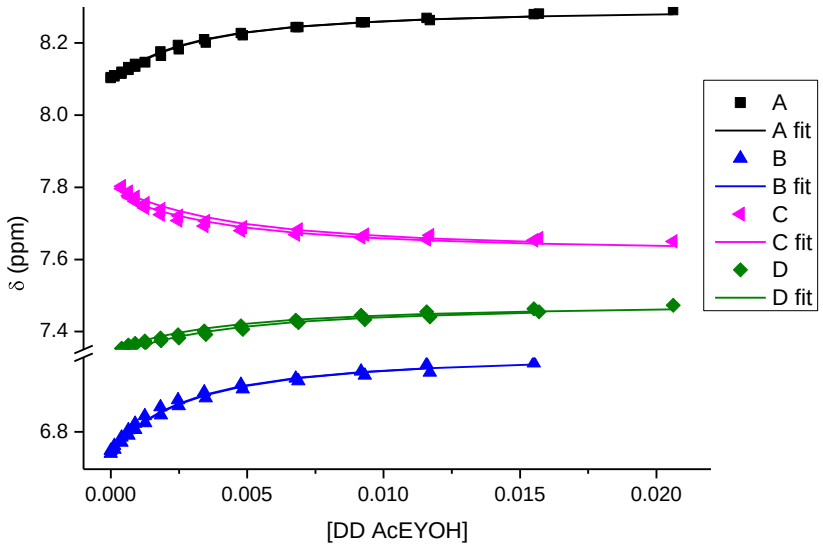


Figure S26. Plot of the experimental (symbols) and fitting (lines) data.

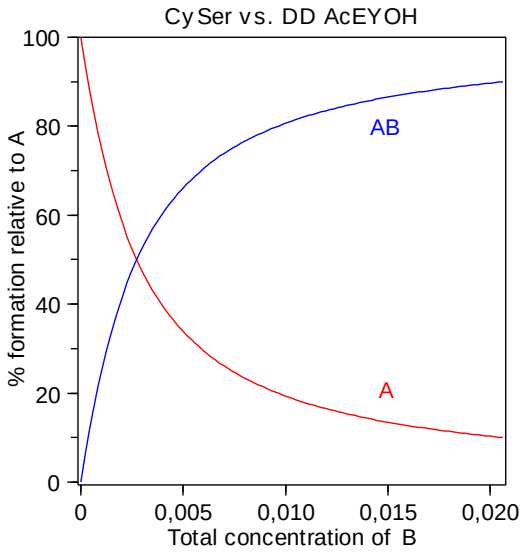


Figure S27. Species distribution as a function of the concentration of the dipeptide.

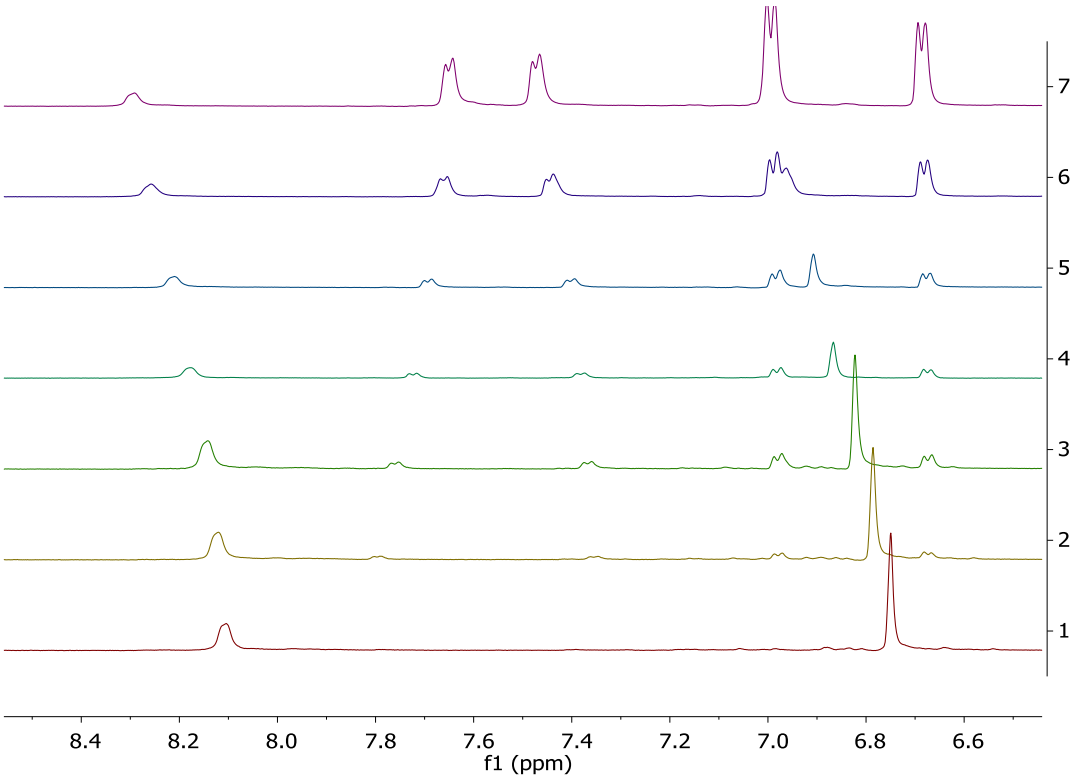


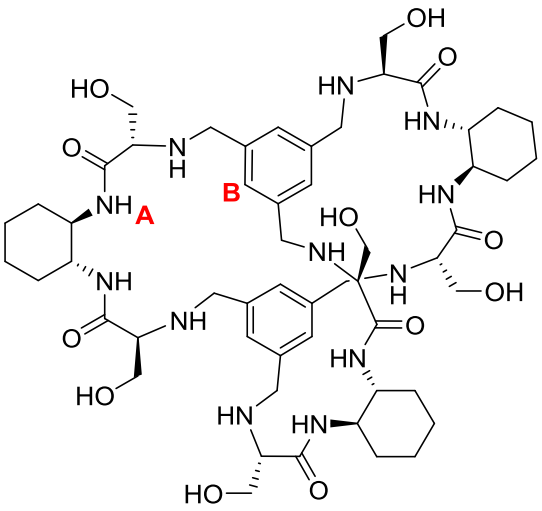
Figure S28. Selected stacked spectra (8.5-6.5 ppm range) of the **CySer** *vs.* Ac-D-Glu-D-Tyr-OH titration in 2:1 $CD_3CN:H_2O$; [**CySer**]= 1.1 mM, [Ac-D-Glu-D-Tyr-OH]=0 mM, 0.392 mM, 0.892 mM, 1.82 mM, 3.42 mM, 9.17 mM, 20.6 mM (from bottom to top).

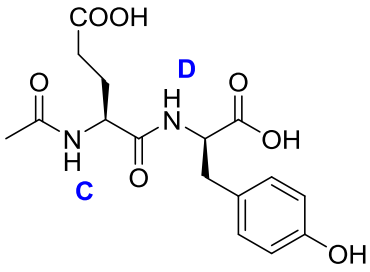
Data for the NMR titration CySer vs. Ac-L-Glu-D-Tyr-OH

Solvent: 2 : 1 CD_3CN : H_2O

Results of the HypNMR2008 fitting:

Log K = 2.65 (4); K = 447





Data Set:

[**CySer**]	[AcEYOH LD]	A	A fit	B	B fit	C	C fit	D	D fit
0.00114	0	8.109	8.1042	6.753	6.7614				
0.00114	0.000136	8.116	8.1124	6.768	6.7722				
0.00114	0.000404	8.131	8.1273	6.794	6.7917	7.878	7.8559	7.325	7.3077
0.00114	0.000664	8.144	8.1404	6.817	6.8088	7.855	7.8447	7.327	7.3175
0.00114	0.000918	8.155	8.1518	6.835	6.8238	7.838	7.8343	7.33	7.3265
0.00114	0.00129	8.17	8.1667	6.853	6.8431	7.818	7.8203	7.334	7.3387
0.00114	0.00187	8.188	8.1858	6.879	6.8682	7.792	7.8011	7.345	7.3554
0.00114	0.00253	8.204	8.203	6.896	6.8906	7.771	7.7826	7.355	7.3714
0.00114	0.00353	8.224	8.2224	6.92	6.916	7.748	7.7603	7.378	7.3908
0.00114	0.00491	8.244	8.2407	6.942	6.94	7.728	7.7375	7.403	7.4106
0.00114	0.00699	8.26	8.2581	6.965	6.9628	7.707	7.7143	7.43	7.4308
0.00114	0.00944	8.271	8.2705			7.698	7.6966	7.448	7.4461
0.00114	0.0119	8.281	8.2786			7.694	7.6847	7.462	7.4565
0.00114	0.0158	8.298	8.2867			7.68	7.6722	7.484	7.4673
0.00114	0.0208	8.305	8.2929			7.674	7.6622	7.491	7.476
0.00119	0	8.109	8.1042	6.752	6.7614				
0.00119	0.000136	8.112	8.1123	6.765	6.772				
0.00119	0.000402	8.126	8.127	6.79	6.7912	7.877	7.8631	7.321	7.3014
0.00119	0.000661	8.136	8.1398	6.809	6.808	7.858	7.8518	7.323	7.3113
0.00119	0.000914	8.145	8.1512	6.823	6.8229	7.84	7.8414	7.325	7.3203
0.00119	0.00128	8.16	8.1657	6.844	6.8419	7.824	7.8274	7.331	7.3325

0.00119	0.00186	8.178	8.1849	6.868	6.867	7.8	7.8078	7.339	7.3495
0.00119	0.00252	8.194	8.2022	6.887	6.8896	7.776	7.7888	7.349	7.366
0.00119	0.00351	8.212	8.2216	6.908	6.915	7.756	7.766	7.367	7.3858
0.00119	0.00489	8.236	8.2401	6.934	6.9393	7.731	7.7424	7.399	7.4064
0.00119	0.00695	8.249	8.2576	6.951	6.9622	7.713	7.7184	7.416	7.4272
0.00119	0.0094	8.266	8.2702	6.975	6.9786	7.695	7.6999	7.444	7.4433
0.00119	0.0118	8.273	8.2782			7.692	7.6876	7.452	7.4539
0.00119	0.0158	8.285	8.2866			7.682	7.6742	7.471	7.4656
0.00119	0.0209	8.295	8.293			7.674	7.6637	7.484	7.4747

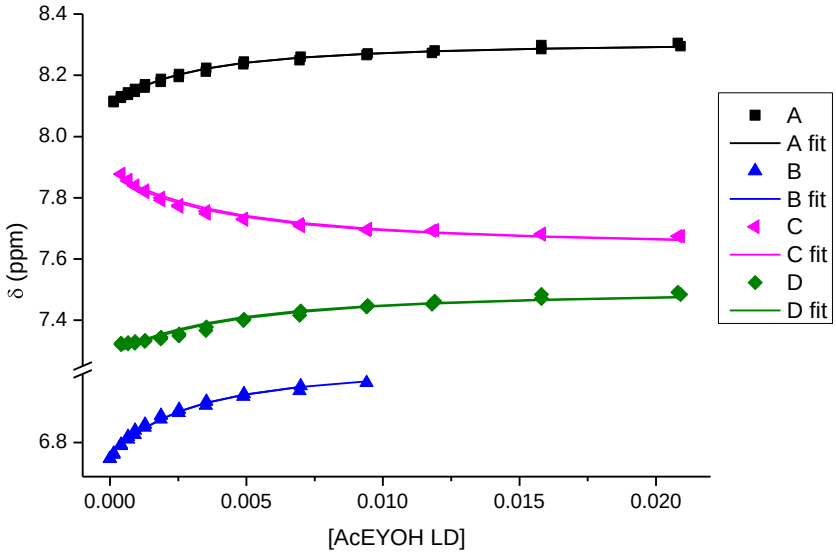


Figure S29. Plot of the experimental (symbols) and fitting (lines) data.

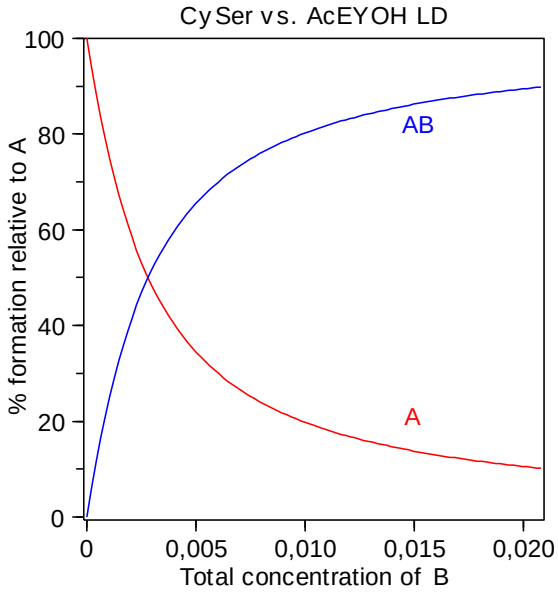


Figure S30. Species distribution as a function of the concentration of the dipeptide.

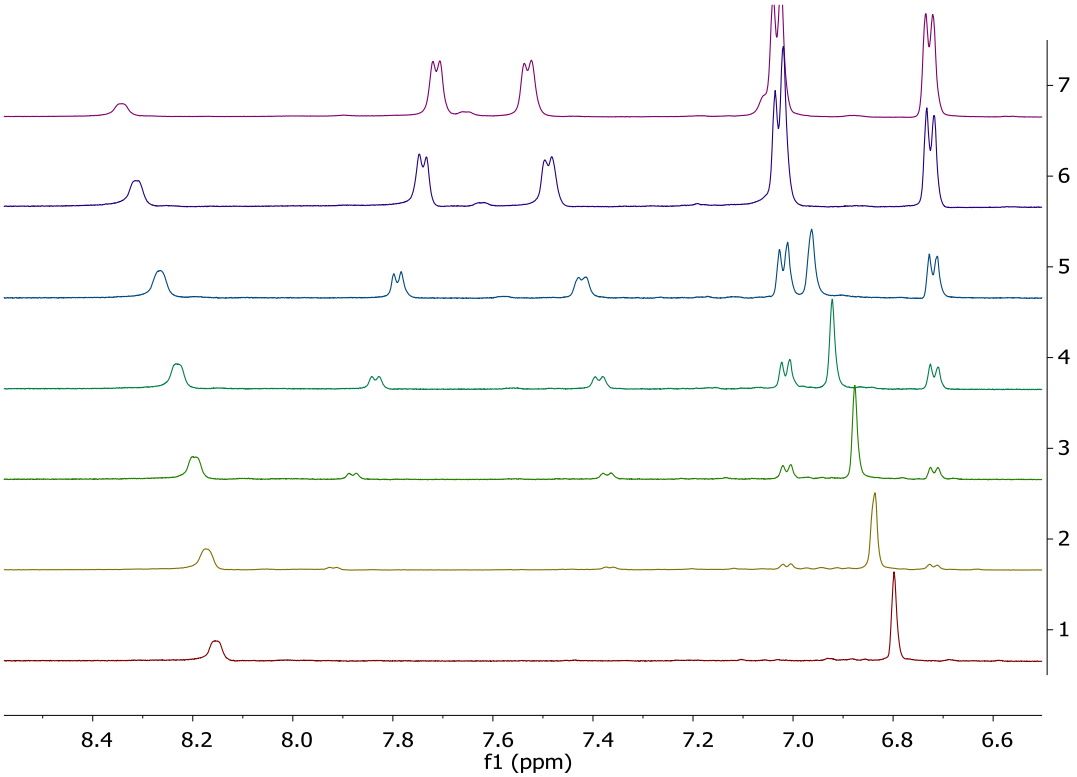


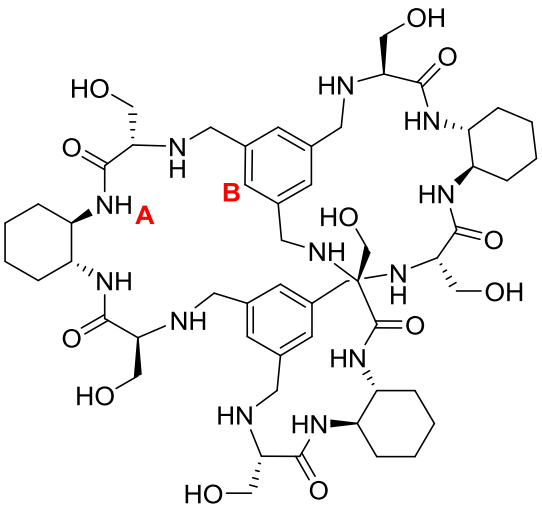
Figure S31. Selected stacked spectra (8.5-6.5 ppm range) of the **CySer** *vs.* Ac-L-Glu-D-Tyr-OH titration in 2:1 $CD_3CN:H_2O$; [**CySer**]= 1.14 mM, [Ac-L-Glu-D-Tyr-OH]=0 mM, 0. 404 mM, 0.914 mM, 1.87 mM, 3.53 mM, 9.44 mM, 20.8 mM (from bottom to top).

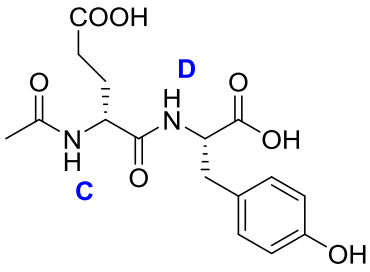
Data for the NMR titration CySer vs. Ac-D-Glu-L-Tyr-OH

Solvent: 2 : 1 CD_3CN : H_2O

Results of the HypNMR2008 fitting:

Log K = 2.45 (2); K = 282





Data Set:

[**CySer**]	[AcEYOH DL]	A	A fit	B	B fit	C	C fit	D	D fit
0.00114	0	8.113	8.1054	6.756	6.7624				
0.00114	0.000136	8.116	8.1108	6.764	6.7696				
0.00114	0.000402	8.122	8.1206	6.782	6.7829	7.902	7.9018	7.337	7.333
0.00114	0.000661	8.13	8.1293	6.797	6.7948	7.894	7.8929	7.344	7.3396
0.00114	0.000914	8.137	8.1372	6.809	6.8055	7.884	7.885	7.348	7.3456
0.00114	0.00128	8.149	8.1476	6.828	6.8195	7.875	7.8745	7.355	7.3535
0.00114	0.00186	8.163	8.1618	6.849	6.8387	7.858	7.8601	7.362	7.3642
0.00114	0.00252	8.176	8.1753	6.867	6.857	7.843	7.8465	7.369	7.3745
0.00114	0.00351	8.193	8.1914	6.888	6.8787	7.825	7.8302	7.38	7.3867
0.00114	0.00489	8.207	8.2081	6.906	6.9013	7.807	7.8134	7.393	7.3993
0.00114	0.00695	8.23	8.2251	6.932	6.9243	7.796	7.7962	7.414	7.4122
0.00114	0.0094	8.24	8.2384	6.943	6.9423	7.78	7.7828	7.424	7.4223
0.00114	0.0119	8.251	8.2475	6.954	6.9547	7.771	7.7736	7.433	7.4292
0.00114	0.016	8.262	8.2574			7.763	7.7636	7.446	7.4367
0.00114	0.0213	8.273	8.2652			7.758	7.7557	7.457	7.4427
0.00119	0	8.105	8.1054	6.752	6.7624				
0.00119	0.000134	8.112	8.1106	6.763	6.7695				
0.00119	0.000398	8.12	8.1203	6.779	6.7825	7.902	7.9021	7.34	7.3327
0.00119	0.000655	8.129	8.1289	6.794	6.7942	7.896	7.8933	7.346	7.3393
0.00119	0.000905	8.132	8.1367	6.806	6.8047	7.889	7.8855	7.351	7.3452
0.00119	0.00127	8.144	8.147	6.822	6.8187	7.877	7.8751	7.355	7.353

0.00119	0.00184	8.158	8.161	6.84	6.8377	7.862	7.8609	7.359	7.3637
0.00119	0.00249	8.168	8.1744	6.859	6.8557	7.849	7.8474	7.367	7.3738
0.00119	0.00348	8.186	8.1907	6.879	6.8777	7.831	7.831	7.376	7.3861
0.00119	0.00484	8.199	8.2073	6.895	6.9002	7.813	7.8142	7.385	7.3987
0.00119	0.00688	8.219	8.2244	6.918	6.9234	7.797	7.7969	7.402	7.4117
0.00119	0.00931	8.232	8.2378	6.934	6.9415	7.784	7.7834	7.415	7.4219
0.00119	0.0117	8.243	8.2468	6.945	6.9537	7.777	7.7743	7.425	7.4287
0.00119	0.0158	8.254	8.2569	6.96	6.9674	7.767	7.7641	7.438	7.4364
0.00119	0.0209	8.271	8.2647			7.761	7.7562	7.452	7.4423

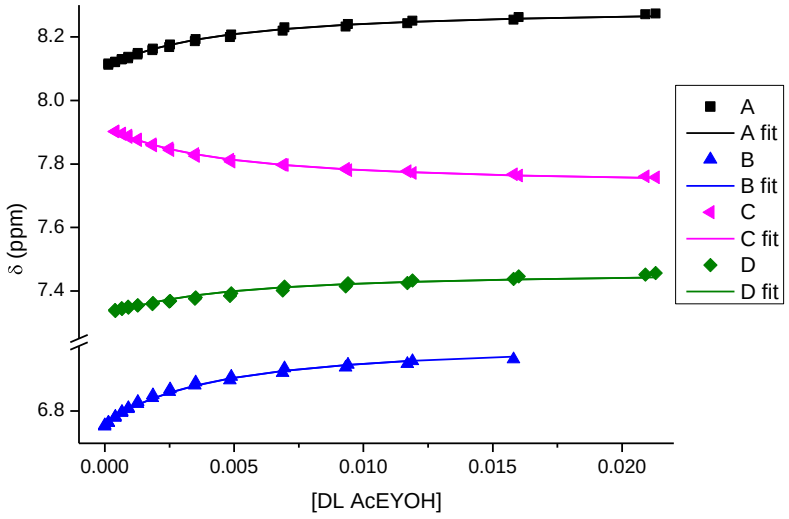


Figure S32. Plot of the experimental (symbols) and fitting (lines) data.

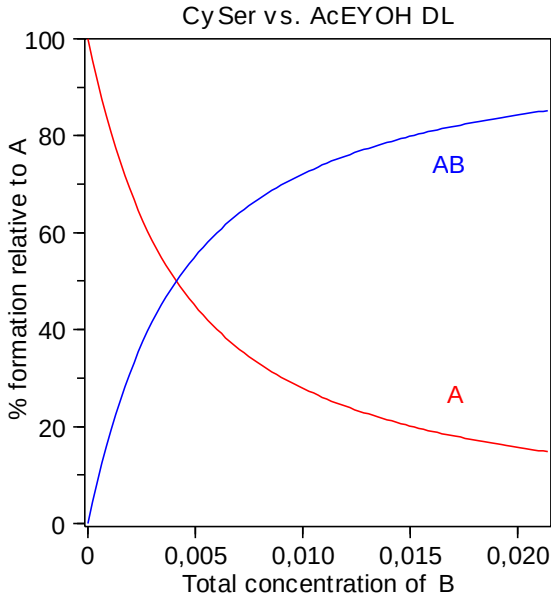


Figure S33. Species distribution as a function of the concentration of the dipeptide.

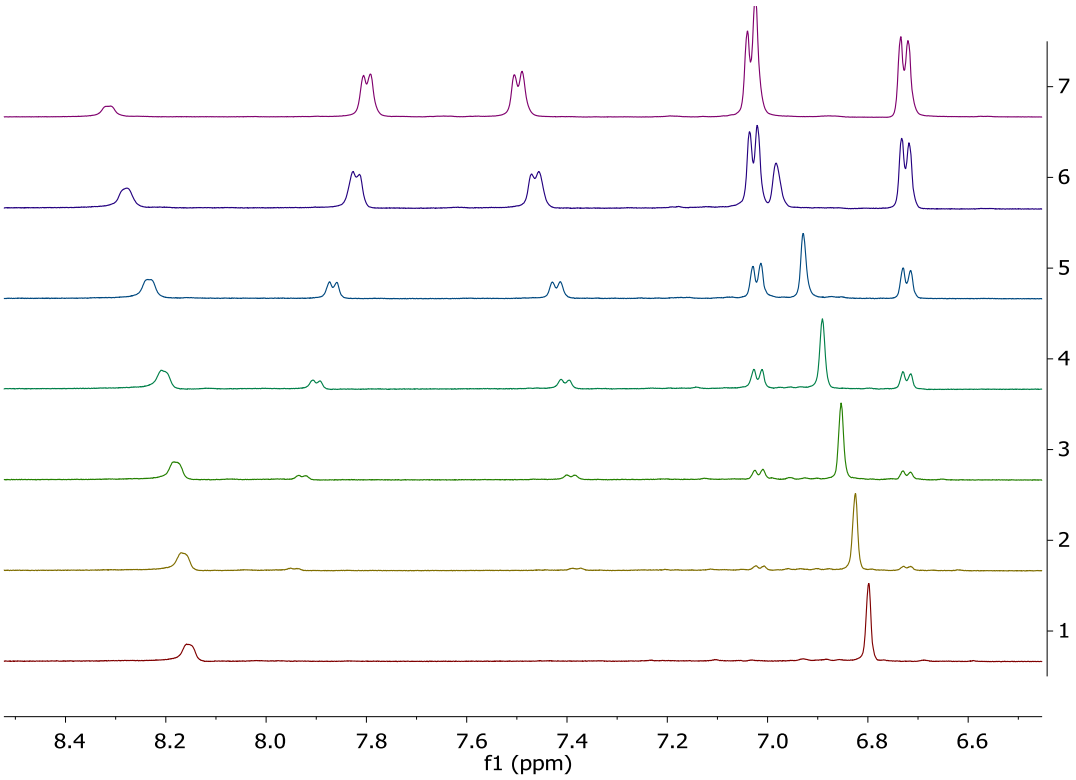


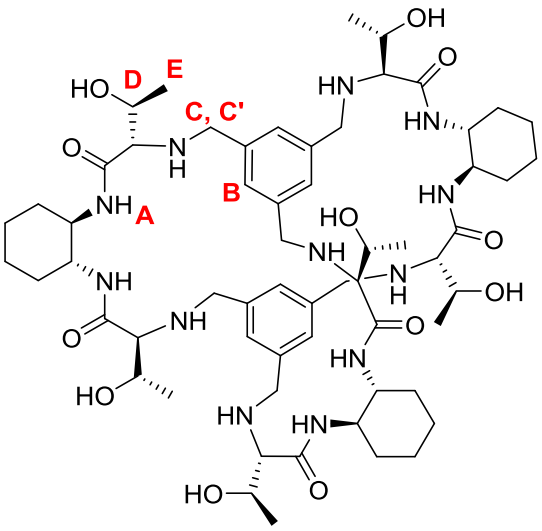
Figure S34. Selected stacked spectra (8.5-6.5 ppm range) of the **CySer** *vs.* Ac-D-Glu-L-Tyr-OH titration in 2:1 $CD_3CN:H_2O$; [**CySer**]= 1.14 mM, [Ac-D-Glu-L-Tyr-OH]=0 mM, 0. 402 mM, 0.914 mM, 1.86 mM, 3.51 mM, 9.4 mM, 21.3 mM (from bottom to top).

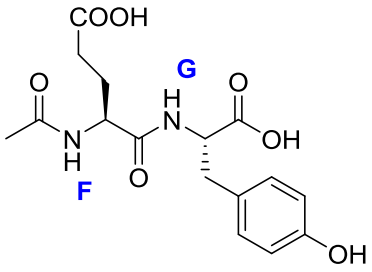
Data for the NMR titration CyThr vs. Ac-L-Glu-L-Tyr-OH

Solvent: 2 : 1 CD_3CN : H_2O

Results of the HypNMR2008 fitting:

Log K = 2.74 (2); K = 550





Data Set:

[**CyThr**]	[AcEYOHLL]	A	A fit	B	B fit	C	C fit	C'	C' fit
0.0011	0	8.154	8.1621	6.691	6.6918	3.382	3.3883	3.181	3.1858
0.0011	0.000132	8.172	8.1771	6.705	6.7053	3.393	3.3966	3.2	3.2029
0.0011	0.000392	8.203	8.2042	6.731	6.7297	3.413	3.4116	3.235	3.2338
0.0011	0.000645	8.23	8.2278	6.752	6.7509	3.428	3.4247	3.263	3.2606
0.0011	0.000892	8.254	8.2483	6.771	6.7694	3.44	3.436	3.287	3.2839
0.0011	0.00125	8.28	8.2742	6.794	6.7927	3.454	3.4504	3.316	3.3134
0.0011	0.00182	8.313	8.3076	6.822	6.8229	3.471	3.4689	3.353	3.3515
0.0011	0.00246	8.342	8.3365	6.848	6.8489	3.487	3.4849	3.386	3.3843
0.0011	0.00342	8.371	8.3678	6.875	6.8771	3.502	3.5022	3.42	3.4201
0.0011	0.00477	8.395	8.3971	6.899	6.9035	3.515	3.5184	3.452	3.4533
0.0011	0.00678	8.417	8.4235	6.922	6.9273	3.53	3.5331	3.48	3.4835
0.0011	0.00917	8.438	8.442	6.945	6.944				
0.0011	0.0116	8.452	8.4538	6.963	6.9546				
0.0011	0.0155	8.464	8.4656						
0.0011	0.0206	8.477	8.4746						
[**CyThr**]	[AcEYOHLL]	D	D fit	E	E fit	F	F fit	G	G fit
0.0011	0	3.002	3.0028	1.068	1.0699				
0.0011	0.000132	3.024	3.0251	1.073	1.0738				
0.0011	0.000392	3.067	3.0656	1.081	1.0807	7.801	7.7655	7.335	7.3203
0.0011	0.000645	3.102	3.1007	1.088	1.0867	7.769	7.7531	7.34	7.3342

0.0011	0.000892	3.133	3.1312	1.093	1.0919	7.743	7.7417	7.348	7.3469
0.0011	0.00125	3.171	3.1698	1.1	1.0985	7.715	7.7264	7.358	7.3639
0.0011	0.00182	3.22	3.2197	1.108	1.107	7.685	7.7052	7.377	7.3876
0.0011	0.00246	3.263	3.2627	1.115	1.1144	7.663	7.6854	7.401	7.4097
0.0011	0.00342	3.307	3.3094	1.122	1.1224	7.642	7.6619	7.43	7.4358
0.0011	0.00477	3.348	3.353	1.128	1.1298	7.623	7.6381	7.459	7.4624
0.0011	0.00678	3.383	3.3924	1.134	1.1366	7.61	7.6147	7.486	7.4885
0.0011	0.00917	3.421	3.42	1.139	1.1413	7.599	7.5971	7.509	7.5081
0.0011	0.0116	3.449	3.4376	1.144	1.1443	7.593	7.5853	7.526	7.5212
0.0011	0.0155			1.149	1.1473	7.586	7.5731	7.542	7.5348
0.0011	0.0206			1.152	1.1496	7.582	7.5635	7.548	7.5456

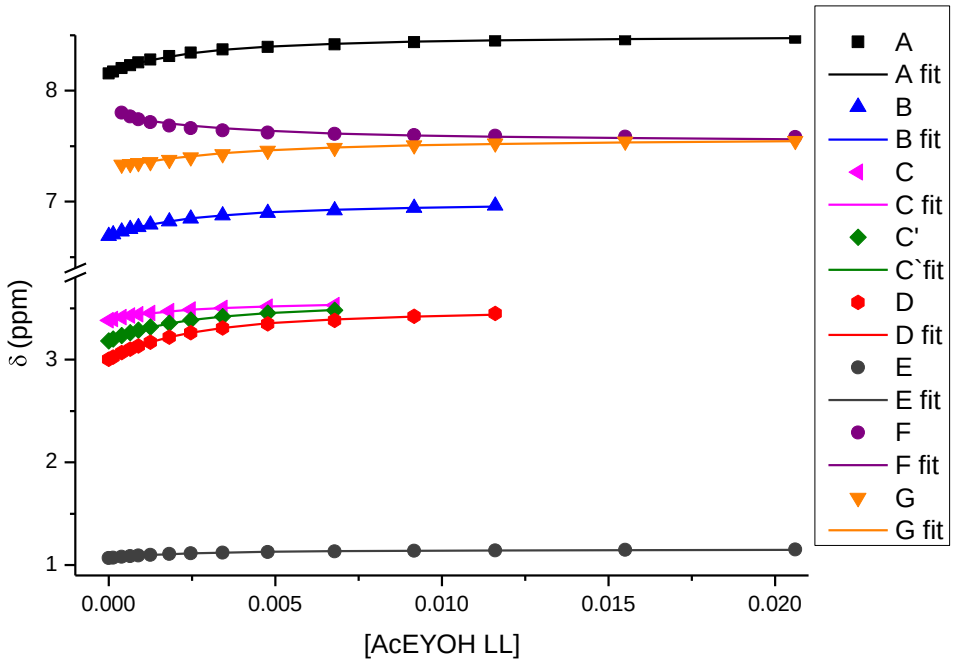


Figure S35. Plot of the experimental (symbols) and fitting (lines) data.

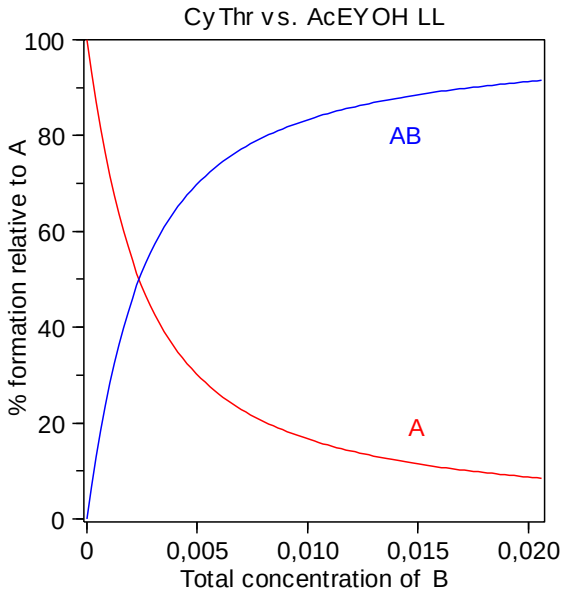


Figure S36. Species distribution as a function of the concentration of the dipeptide.

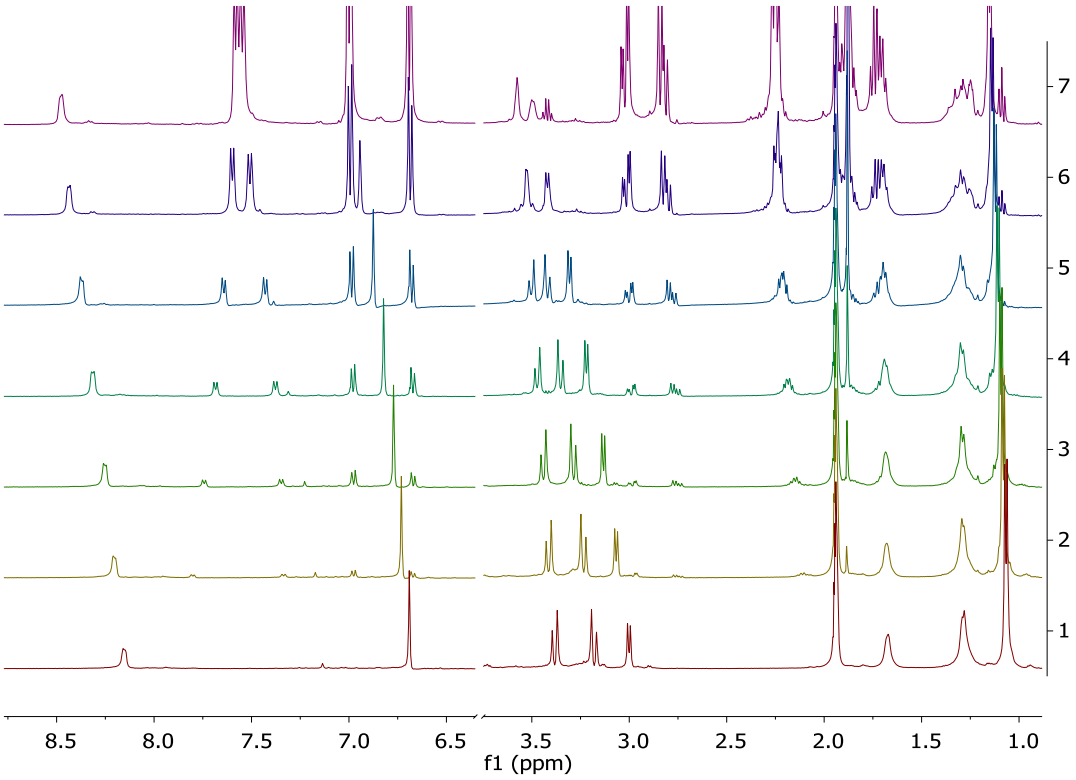


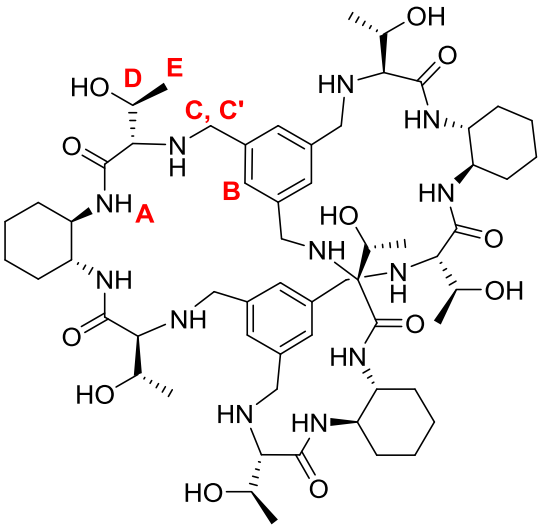
Figure S37. Selected stacked spectra (8.6-6.4 and 3.7-0.8 ppm ranges) of the **CyThr** *vs.* Ac-L-Glu-L-Tyr-OH titration in 2:1 $CD_3CN:H_2O$; [**CyThr**]= 1.1 mM, [Ac-L-Glu-L-Tyr-OH]=0 mM, 0.392 mM, 0.892 mM, 1.82 mM, 3.42 mM, 9.17 mM, 20.6 mM (from bottom to top).

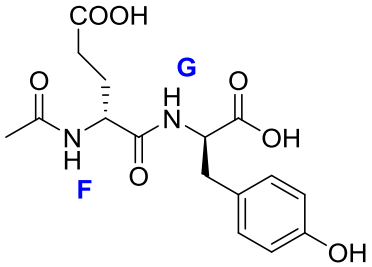
Data of the NMR titration CyThr vs. Ac-D-Glu-D-Tyr-OH

Solvent: 2 : 1 CD_3CN : H_2O

Results of the HypNMR2008 fitting:

Log K = 2.66 (2); K = 457





Data Set:

[**CyThr**]	[AcEYOHDD]	A	A fit	B	B fit	C	C fit	C'	C' fit
0.0011	0	8.151	8.1652	6.69	6.6985	3.382	3.3913	3.18	3.1922
0.0011	0.000132	8.165	8.1768	6.7	6.7084	3.39	3.3978	3.193	3.205
0.0011	0.000392	8.208	8.1979	6.734	6.7264	3.415	3.4096	3.238	3.2282
0.0011	0.000645	8.224	8.2163	6.75	6.7421	3.427	3.42	3.259	3.2486
0.0011	0.000892	8.242	8.2325	6.764	6.756	3.436	3.4291	3.277	3.2665
0.0011	0.00125	8.26	8.2532	6.779	6.7737	3.446	3.4408	3.297	3.2895
0.0011	0.00182	8.287	8.2805	6.799	6.7971	3.459	3.4561	3.323	3.3197
0.0011	0.00246	8.304	8.3047	6.816	6.8178	3.47	3.4697	3.345	3.3465
0.0011	0.00342	8.329	8.3319	6.835	6.841	3.482	3.485	3.37	3.3765
0.0011	0.00477	8.353	8.3581	6.857	6.8634	3.496	3.4998	3.398	3.4055
0.0011	0.00678	8.378	8.3827	6.879	6.8845	3.509	3.5136	3.427	3.4327
0.0011	0.00917	8.395	8.4005	6.893	6.8997	3.518	3.5236	3.442	3.4524
0.0011	0.0116	8.404	8.412	6.903	6.9096	3.525	3.5301	3.457	3.4652
0.0011	0.0155	8.425	8.4238	6.922	6.9196	3.538	3.5367	3.481	3.4782
0.0011	0.0206	8.444	8.4329	6.944	6.9274	3.552	3.5418	3.508	3.4883
[**CyThr**]	[AcEYOHDD]	D	D fit	E	E fit	F	F fit	G	G fit
0.0011	0	3.001	3.0121	1.068	1.0721	x	0	x	0
0.0011	0.000132	3.017	3.0289	1.071	1.075	x	7.7864	x	7.339
0.0011	0.000392	3.071	3.0595	1.082	1.0802	7.803	7.7773	7.35	7.3466
0.0011	0.000645	3.098	3.0862	1.087	1.0848	7.779	7.769	7.357	7.3535
0.0011	0.000892	3.121	3.1098	1.092	1.0888	7.763	7.7614	7.362	7.3598

0.0011	0.00125	3.147	3.1398	1.096	1.094	7.745	7.7512	7.368	7.3682
0.0011	0.00182	3.181	3.1796	1.103	1.1007	7.724	7.7369	7.378	7.3801
0.0011	0.00246	3.21	3.2147	1.108	1.1068	7.708	7.7233	7.387	7.3913
0.0011	0.00342	3.246	3.2542	1.113	1.1135	7.691	7.7071	7.399	7.4047
0.0011	0.00477	3.282	3.2923	1.119	1.12	7.679	7.6902	7.416	7.4187
0.0011	0.00678	3.322	3.328	1.125	1.1261	7.668	7.6732	7.432	7.4328
0.0011	0.00917	3.342	3.3538	1.129	1.1306	7.661	7.6601	7.443	7.4436
0.0011	0.0116	3.362	3.3706	1.131	1.1334	7.656	7.6512	7.449	7.451
0.0011	0.0155	3.393	3.3877	1.136	1.1363	7.652	7.6418	7.461	7.4588
0.0011	0.0206	3.425	3.4009	1.141	1.1386	7.648	7.6343	7.472	7.465

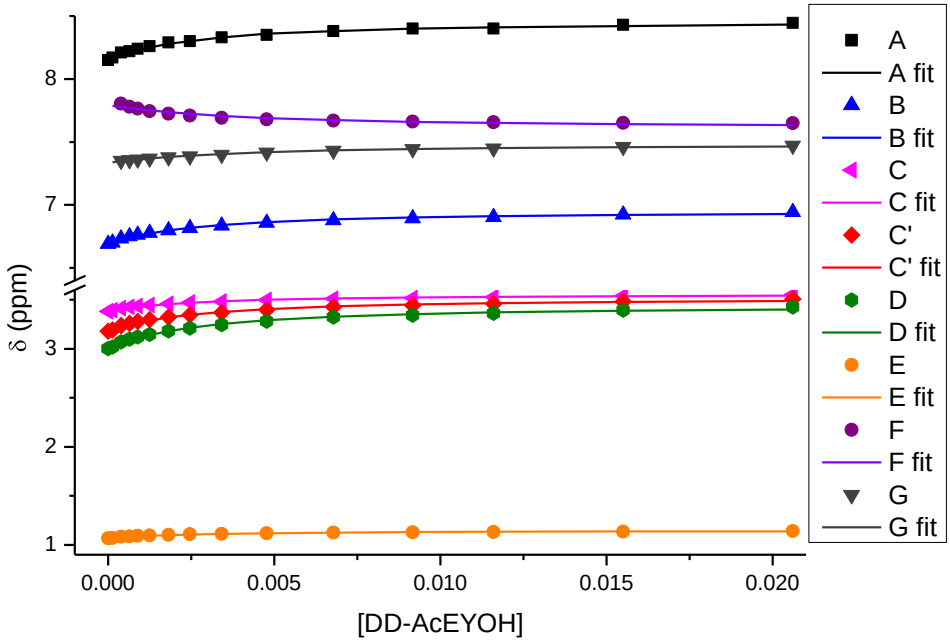


Figure S38. Plot of the experimental (symbols) and fitting (lines) data.

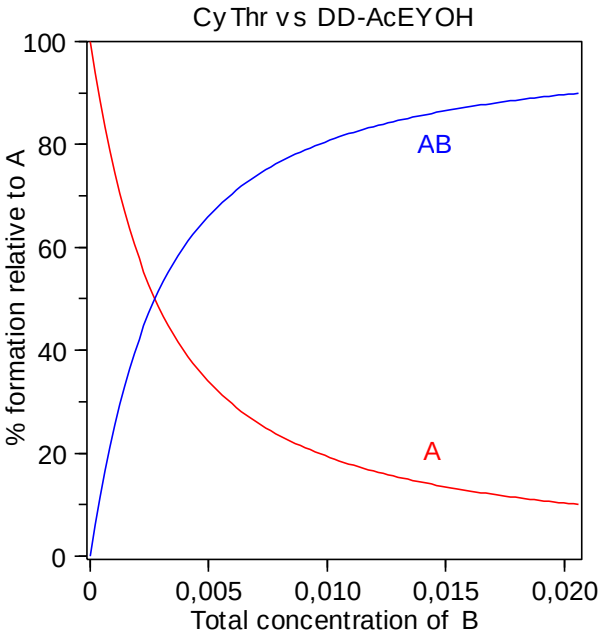


Figure S39. Species distribution as a function of the concentration of the dipeptide.

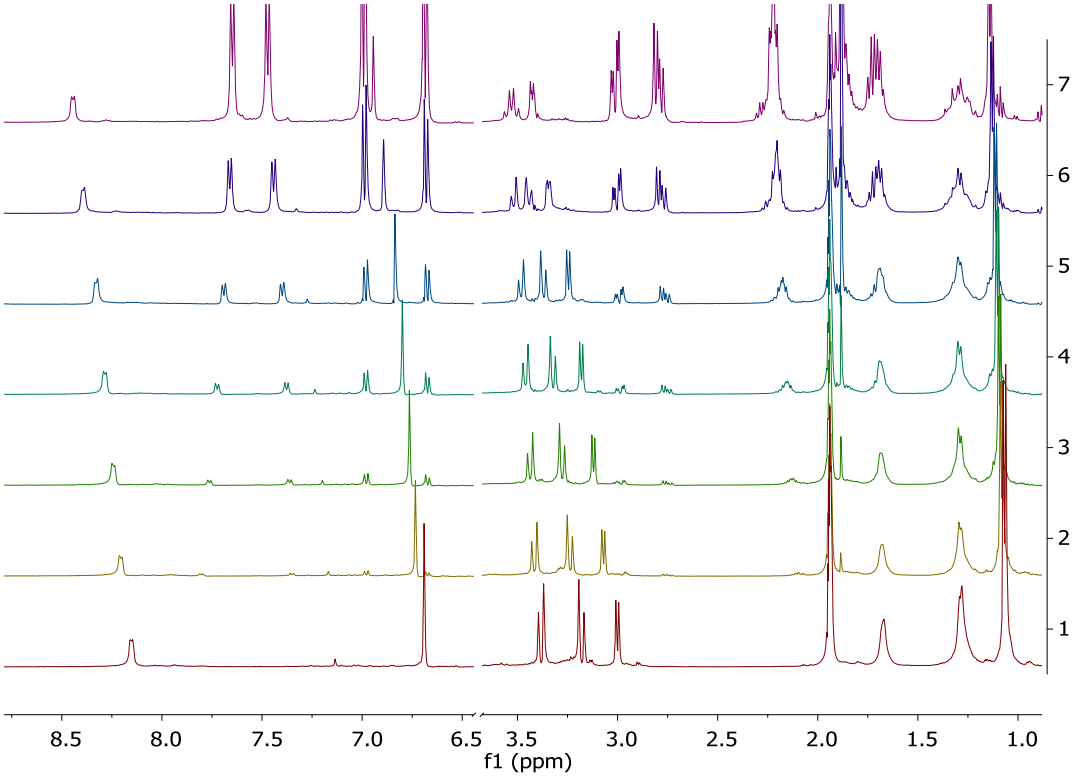


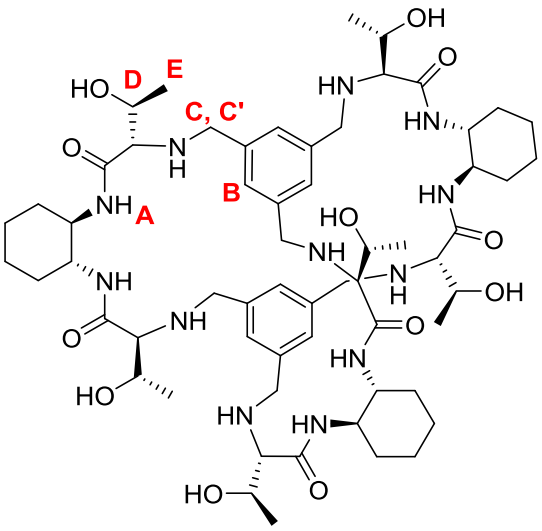
Figure S40. Selected stacked spectra (8.7-6.5 and 3.7-0.8 ppm ranges) of the **CyThr** *vs.* Ac-D-Glu-D-Tyr-OH titration in 2:1 $CD_3CN:H_2O$; [**CyThr**]= 1.1 mM, [Ac-D-Glu-D-Tyr-OH]=0 mM, 0.392 mM, 0.892 mM, 1.82 mM, 3.42 mM, 9.17 mM, 20.6 mM (from bottom to top).

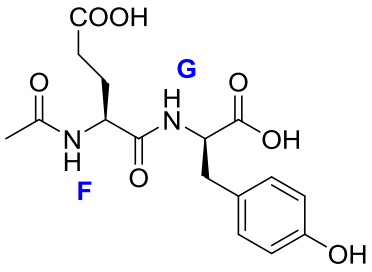
Data for the NMR titration CyThr vs. Ac-L-Glu-D-Tyr-OH

Solvent: 2 : 1 CD_3CN : H_2O

Results of the HypNMR2008 fitting:

log K = 2.53 (2); K = 339





Data Set:

[**CyThr**]	[AcEYOH LD]	A	A fit	B	B fit	C	C fit	C’	C’ fit
0.0011	0	8.154	8.1592	6.69	6.6922	3.382	3.3881	3.181	3.1856
0.0011	0.000132	8.165	8.1698	6.699	6.7012	3.389	3.3939	3.192	3.1971
0.0011	0.000392	8.187	8.1891	6.718	6.7177	3.404	3.4046	3.218	3.2183
0.0011	0.000645	8.209	8.2063	6.736	6.7323	3.417	3.414	3.241	3.2372
0.0011	0.000892	8.227	8.2216	6.75	6.7453	3.427	3.4225	3.26	3.254
0.0011	0.00125	8.246	8.2415	6.765	6.7623	3.438	3.4335	3.28	3.2758
0.0011	0.00182	8.27	8.2685	6.785	6.7853	3.451	3.4484	3.307	3.3055
0.0011	0.00246	8.297	8.2933	6.806	6.8065	3.465	3.462	3.334	3.3327
0.0011	0.00342	8.325	8.3223	6.829	6.8312	3.479	3.478	3.363	3.3645
0.0011	0.00477	8.351	8.3518	6.852	6.8563	3.493	3.4943	3.394	3.3968
0.0011	0.00678	8.377	8.3809	6.877	6.8811	3.508	3.5103	3.425	3.4288
0.0011	0.00917	8.401	8.403	6.896	6.8999	3.519	3.5225	3.45	3.453
0.0011	0.0116	8.412	8.4178	6.909	6.9126	3.529	3.5307	3.469	3.4693
0.0011	0.0155	8.432	8.4333	6.927	6.9258	3.541	3.5392	3.491	3.4863
0.0011	0.0206	8.451	8.4456	6.947	6.9363				
[**CyThr**]	[AcEYOH LD]	D	D fit	E	E fit	F	F fit	G	G fit
0.0011	0	3.002	3.0026	1.07	1.0705				
0.0011	0.000132	3.016	3.018	1.07	1.0731				
0.0011	0.000392	3.047	3.0462	1.077	1.0779	7.899	7.8766	7.321	7.3045
0.0011	0.000645	3.075	3.0712	1.083	1.0821	7.877	7.8649	7.324	7.3133
0.0011	0.000892	3.099	3.0935	1.088	1.0859	7.858	7.8543	7.326	7.3214
0.0011	0.00125	3.125	3.1225	1.092	1.0909	7.837	7.84	7.33	7.3323

0.0011	0.00182	3.161	3.1619	1.098	1.0976	7.808	7.8197	7.335	7.3476
0.0011	0.00246	3.197	3.1981	1.105	1.1037	7.785	7.8002	7.349	7.3623
0.0011	0.00342	3.236	3.2403	1.112	1.1109	7.761	7.7762	7.368	7.3805
0.0011	0.00477	3.278	3.2833	1.119	1.1182	7.735	7.7505	7.391	7.4
0.0011	0.00678	3.318	3.3258	1.125	1.1255	7.716	7.7235	7.417	7.4204
0.0011	0.00917	3.352	3.3579	1.129	1.1309	7.7	7.702	7.437	7.4367
0.0011	0.0116	3.376	3.3796	1.134	1.1346	7.692	7.6869	7.451	7.4481
0.0011	0.0155	3.405	3.4022	1.138	1.1385	7.682	7.6707	7.467	7.4604
0.0011	0.0206	3.436	3.4201	1.142	1.1415	7.673	7.6574	7.482	7.4704

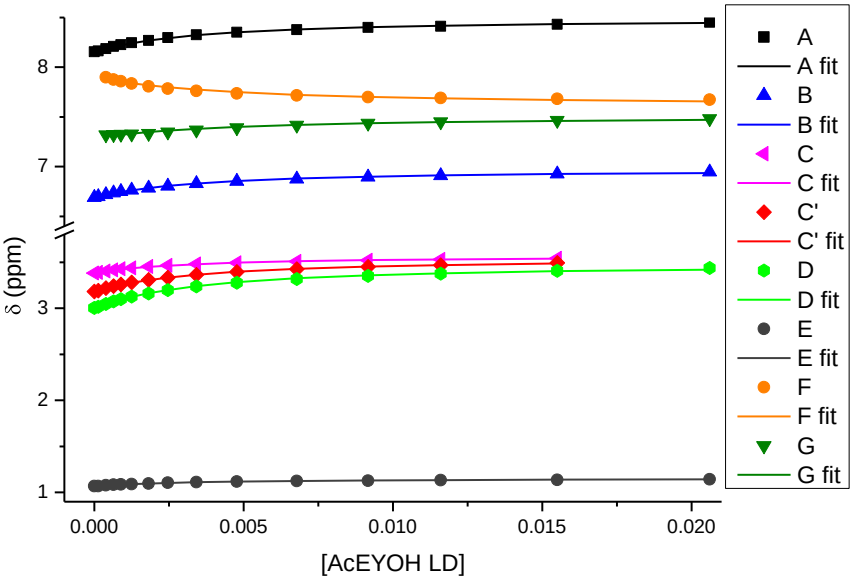


Figure S41. Plot of the experimental (symbols) and fitting (lines) data.

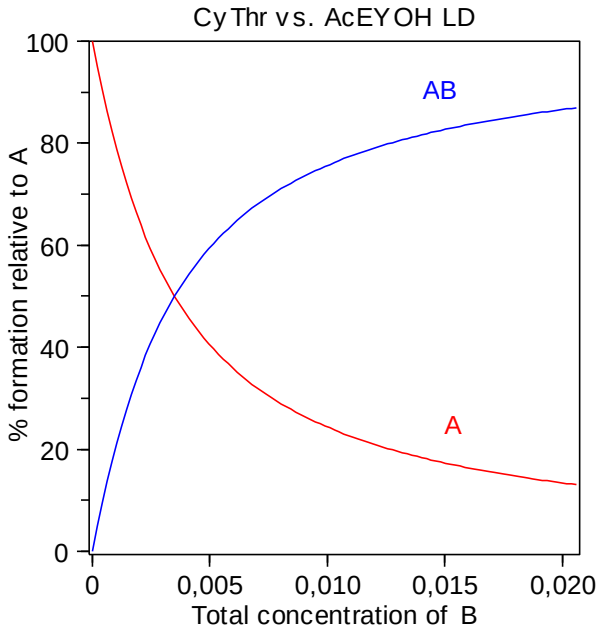


Figure S42. Species distribution as a function of the concentration of the dipeptide.

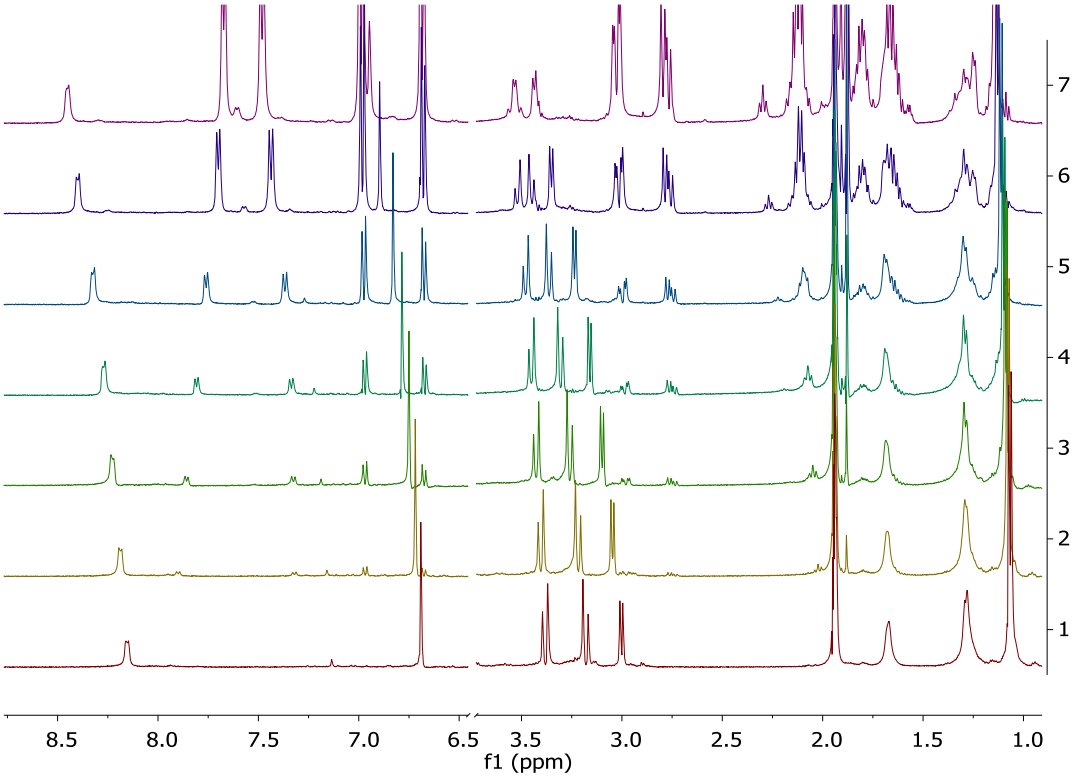


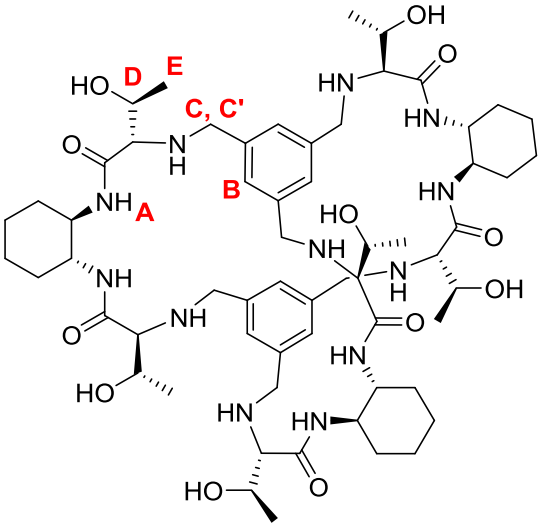
Figure S43. Selected stacked spectra (8.7-6.5 and 3.7-0.9 ppm ranges) of the **CyThr** *vs.* Ac-L-Glu-D-Tyr-OH titration in 2:1 $CD_3CN:H_2O$; [**CyThr**]= 1.1 mM, [Ac-L-Glu-D-Tyr-OH]=0 mM, 0.392 mM, 0.892 mM, 1.82 mM, 3.42 mM, 9.17 mM, 20.6 mM (from bottom to top).

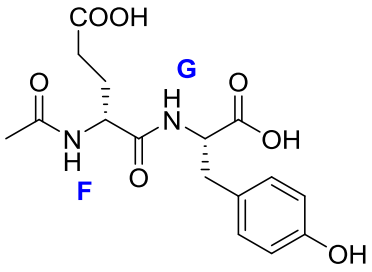
Data of the NMR titration CyThr vs. Ac-D-Glu-L-Tyr-OH

Solvent: 2 : 1 CD_3CN : H_2O

Results of the HypNMR2008 fitting:

Log K = 2.30 (2); K = 200





Data Set:

[**CyThr**]	[AcEYOH DL]	A	A fit	B	B fit	C	C fit	C'	C' fit
0.0011	0	8.155	8.1671	6.692	6.7012	3.383	3.3933	3.182	3.1955
0.0011	0.000132	8.169	8.1731	6.703	6.7062	3.392	3.3966	3.197	3.2021
0.0011	0.000392	8.186	8.1842	6.718	6.7155	3.404	3.4027	3.218	3.2144
0.0011	0.000645	8.2	8.1944	6.728	6.7239	3.411	3.4083	3.231	3.2256
0.0011	0.000892	8.209	8.2037	6.737	6.7316	3.418	3.4134	3.243	3.2358
0.0011	0.00125	8.221	8.2161	6.746	6.7419	3.424	3.4202	3.255	3.2496
0.0011	0.00182	8.237	8.2338	6.759	6.7566	3.434	3.4299	3.274	3.269
0.0011	0.00246	8.253	8.251	6.772	6.7709	3.442	3.4393	3.29	3.288
0.0011	0.00342	8.274	8.2726	6.789	6.7888	3.454	3.4511	3.312	3.3117
0.0011	0.00477	8.298	8.2964	6.807	6.8086	3.465	3.4641	3.336	3.338
0.0011	0.00678	8.319	8.3223	6.825	6.8301	3.476	3.4783	3.36	3.3665
0.0011	0.00917	8.335	8.3439	6.845	6.848	3.487	3.4901	3.387	3.3902
0.0011	0.0116	8.355	8.3595	6.856	6.8609	3.494	3.4986	3.4	3.4074
0.0011	0.0155	8.373	8.3768	6.873	6.8753	3.506	3.5081	3.425	3.4265
0.0011	0.0206	8.402	8.3914	6.897	6.8874	3.52	3.5161	3.453	3.4426
[**CyThr**]	[AcEYOH DL]	D	D fit	E	E fit	F	F fit	G	G fit
0.0011	0	3.005	3.0177	1.07	1.0729				
0.0011	0.000132	3.021	3.0262	1.072	1.0744				
0.0011	0.000392	3.046	3.0421	1.077	1.0772	7.907	7.9011	7.332	7.3304
0.0011	0.000645	3.066	3.0566	1.08	1.0798	7.896	7.8952	7.336	7.335
0.0011	0.000892	3.077	3.0699	1.084	1.0821	7.89	7.8897	7.342	7.3393
0.0011	0.00125	3.093	3.0877	1.087	1.0853	7.881	7.8822	7.347	7.3452

0.0011	0.00182	3.116	3.1129	1.092	1.0897	7.87	7.8713	7.355	7.3537
0.0011	0.00246	3.138	3.1375	1.095	1.0941	7.859	7.8606	7.361	7.3622
0.0011	0.00342	3.167	3.1682	1.101	1.0995	7.845	7.8467	7.371	7.3731
0.0011	0.00477	3.199	3.2022	1.106	1.1055	7.828	7.8308	7.381	7.3855
0.0011	0.00678	3.232	3.2392	1.111	1.1121	7.81	7.813	7.394	7.3995
0.0011	0.00917	3.264	3.27	1.116	1.1175	7.796	7.7977	7.408	7.4115
0.0011	0.0116	3.285	3.2922	1.12	1.1215	7.786	7.7863	7.418	7.4205
0.0011	0.0155	3.313	3.3169	1.125	1.1259	7.776	7.7733	7.432	7.4306
0.0011	0.0206	3.355	3.3378	1.131	1.1296	7.766	7.7621	7.449	7.4394

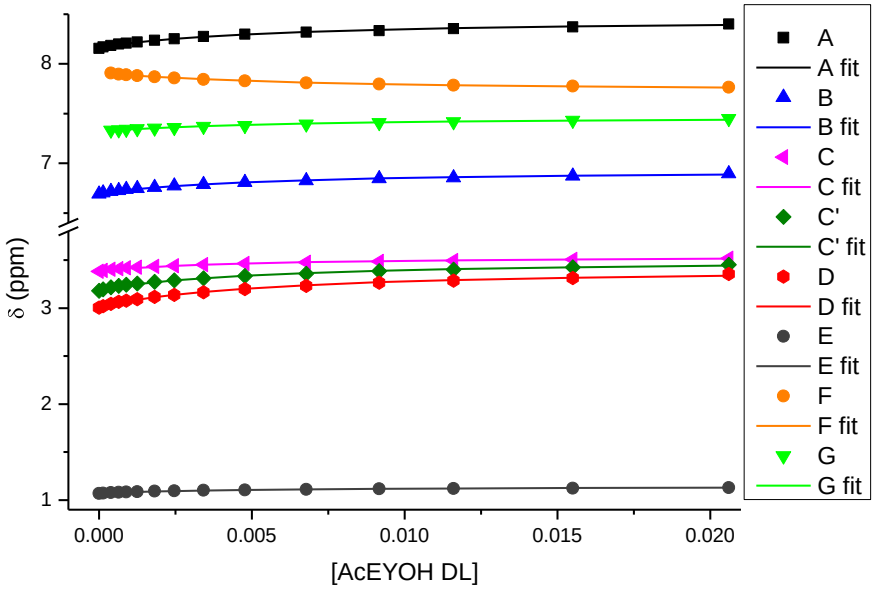


Figure S44. Plot of the experimental (symbols) and fitting (lines) data.

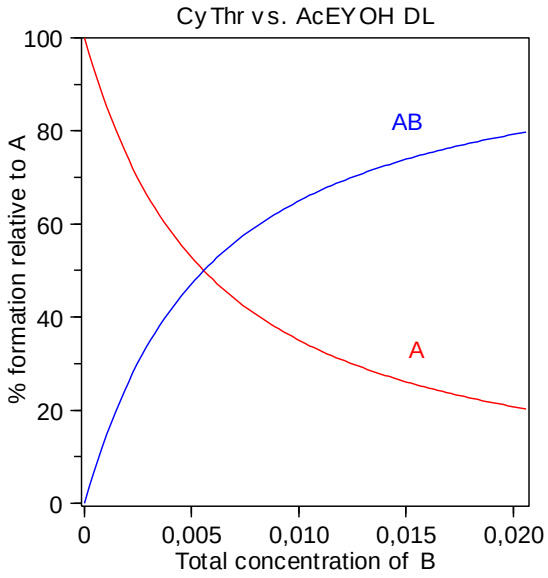


Figure S45. Species distribution as a function of the concentration of the dipeptide.

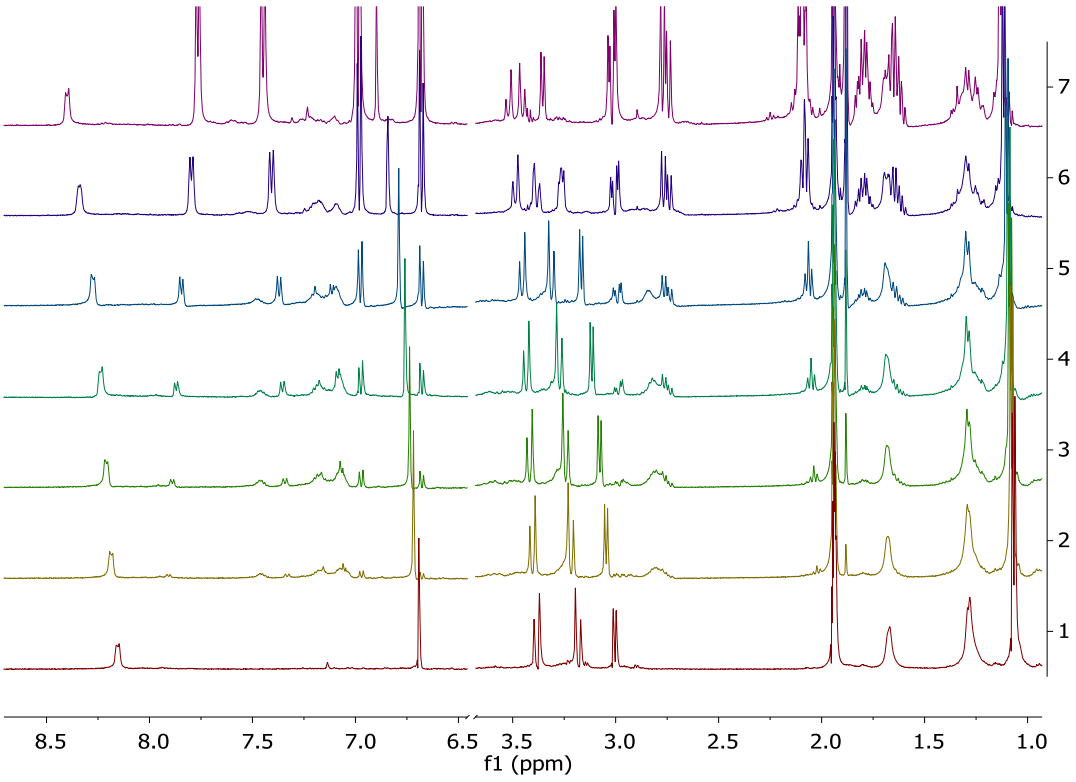


Figure S46. Selected stacked spectra (8.7-6.5 and 3.7-0.9 ppm ranges) of the **CyThr** *vs.* Ac-D-Glu-L-Tyr-OH titration in 2:1 $CD_3CN:H_2O$; [**CyThr**]= 1.1 mM, [Ac-D-Glu-L-Tyr-OH]=0 mM, 0.392 mM, 0.892 mM, 1.82 mM, 3.42 mM, 9.17 mM, 20.6 mM (from bottom to top).

4. ESI-MS studies and CID experiments with **CySer** and **CyThr**

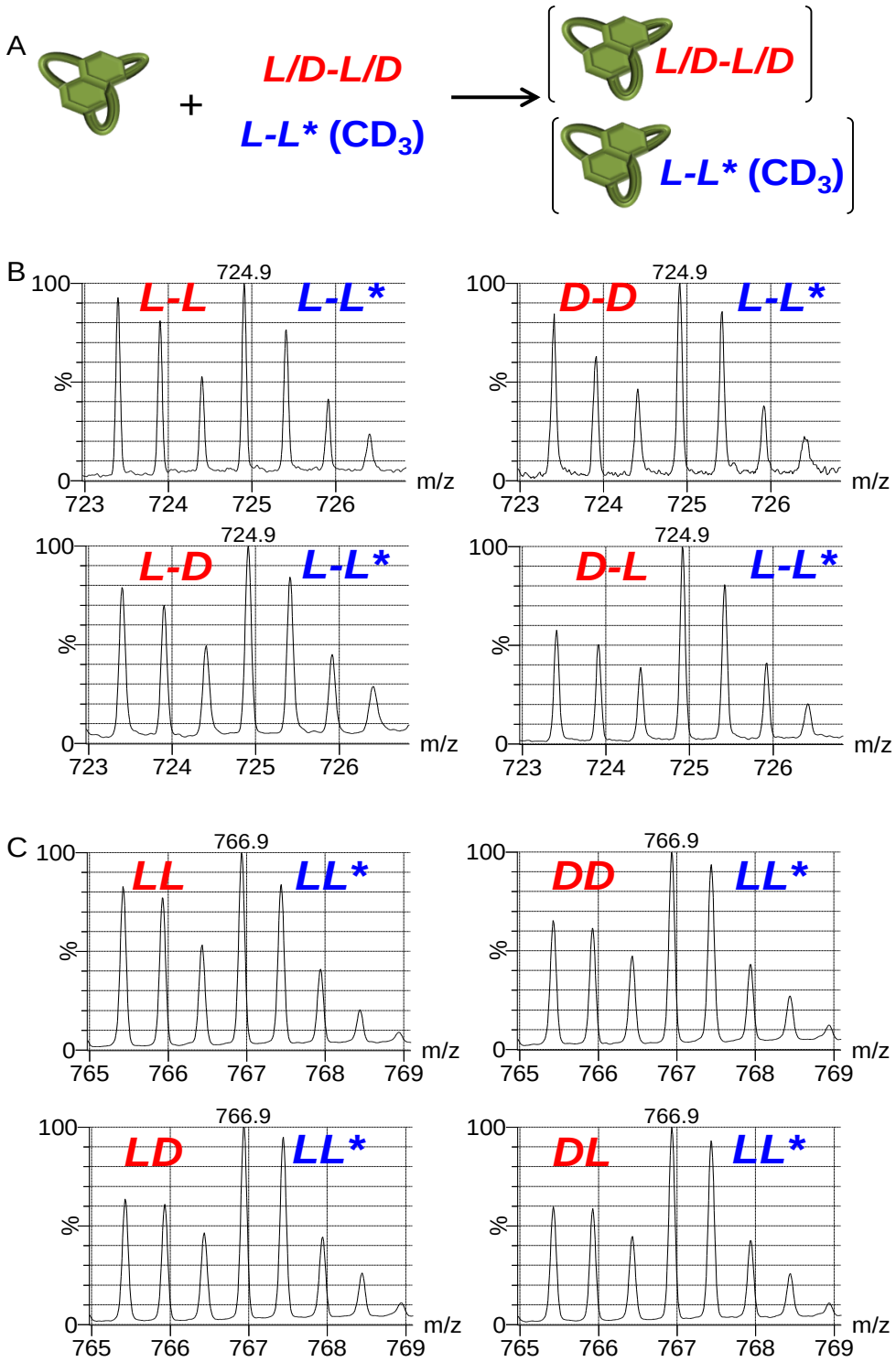


Figure S47. A) Schematic representation of the enantiomer-labelled method for the ESI-MS study of the stereoselective recognition of dipeptides (charges are omitted for simplicity). (B, C) Portion of the ESI mass spectra obtained from a mixture of **CySer** (or **CyThr**), each Ac-Glu-Tyr-OH dipeptide and d^3-Ac-L-Glu-L-Tyr-OH; the peaks labelled in red and blue correspond to the [Cage + Ac-Glu-Tyr-OH +2H]$^{2+}$ and [Cage + d^3-Ac-Glu-Tyr-OH +2H]$^{2+}$ supramolecular complexes, respectively.

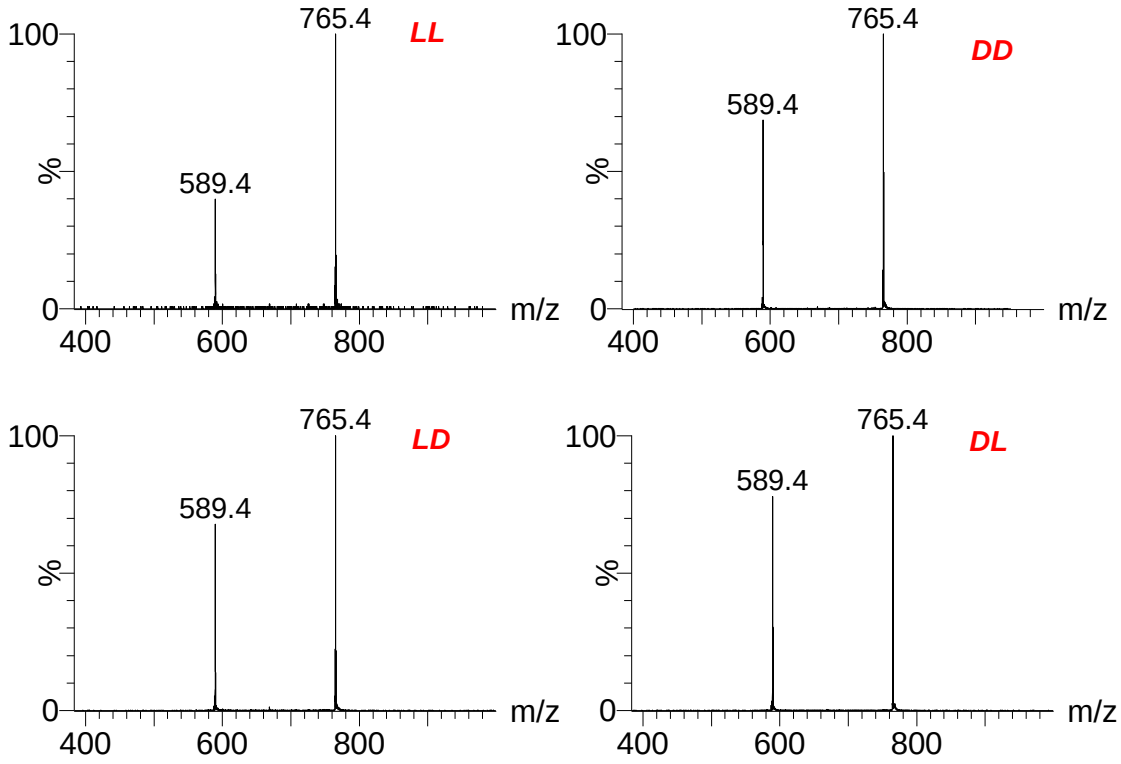


Figure S48. CID mass spectra of mass-selected adducts [**CyThr** + Ac-Glu-Tyr-OH +2H]$^{2+}$ at $CE_{Elaboratory}$ = 5 eV for the corresponding complexes formed by the **CyThr** host and the different stereoisomers of the dipeptide.

5. Molecular Modelling

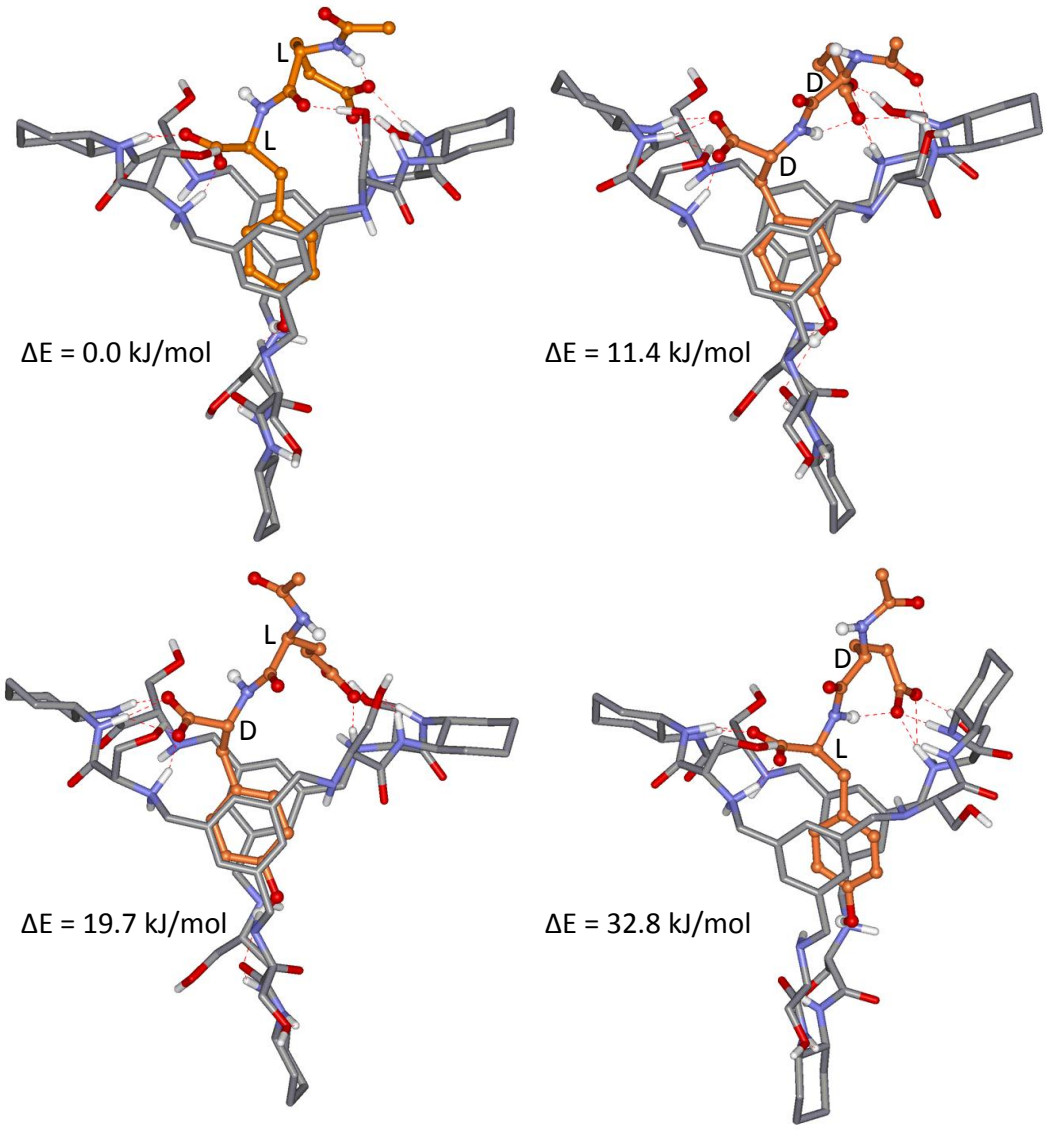


Fig. S49. Molecular mechanics structures for the four diastereomeric complexes formed between the **CySer** cage and the corresponding D/L-D/L dipeptides. Non-polar hydrogen atoms have been omitted for clarity and the dipeptide substrates are represented with orange C-atoms. The possible H-bonds are drawn in red dashed lines and the calculated relative MMFF energies are also included. The inclusion of the Tyr residue seems to be more efficient for the dipeptides having L-Tyr configuration, as suggested by the shorter averaged distances (in Å) between the corresponding stacked closest C atoms of the Tyr residue and the two aromatic rings of the host: 3.93 (LL), 4.02 (DD), 4.01 (LD) and 3.96 (DL). On the other hand, the possible total number of H-bonds was also monitored for the corresponding supramolecular complexes rendering: 14 (LL), 14 (DD), 13 (LD) and 12 (DL).

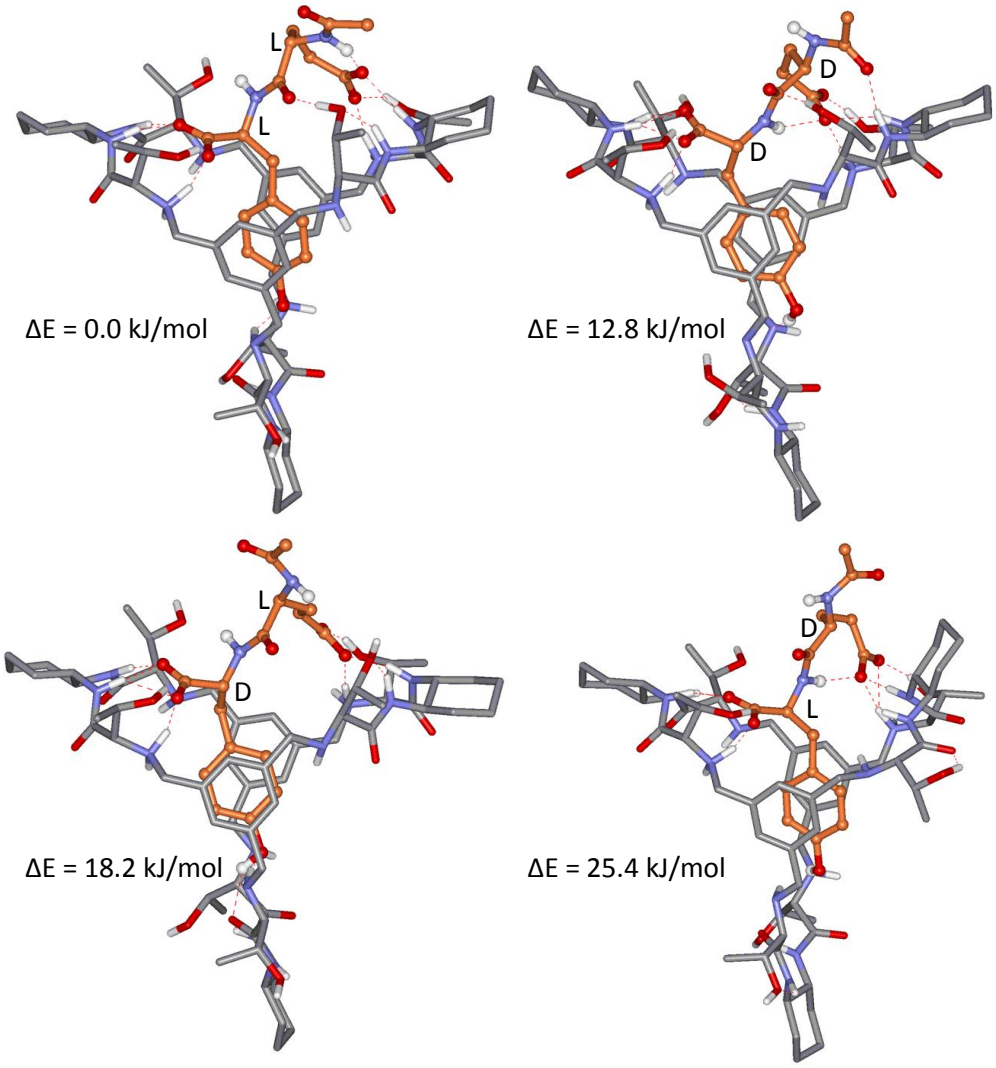


Figure S50. Molecular mechanics structures for the four diastereomeric complexes formed between the **CyThr** cage and the corresponding D/L-D/L dipeptides. Non-polar hydrogen atoms have been omitted for clarity and the dipeptide substrates are represented with orange C-atoms. The possible H-bonds are drawn in red dashed lines and the calculated relative MMFF energies are also included.