Supplementary Material

Conformation and Dynamics of a Cyclic Disulfide-Bridged Peptide: Effects of Temperature and Solvent

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Peptide Synthesis.

Cyclo(Boc-Cys-Pro-Gly-Cys-OMe) (1): The linear tetrapeptide Boc-Cys(Trt)-Pro-Gly-Cys(Acm)-OMe (**6**) (1.61 g, 2 mmol) was dissolved in chloroform p.a. (400 mL). Whilst fast stirring, a solution of iodine (1.52 g, 6 mmol) dissolved in methanol (60 mL) was added dropwise to the stirred solution. The reaction mixture was stirred for 90 minutes at room temperature. Afterwards the reaction mixture was quenched with $Na_2S_2O_3$ (0.1 M) to destroy excess iodine. Chloroform was removed in vacuo and the residue washed with chloroform (150 mL, four times). The collected organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated to give yellow crystalline compound. The raw product was purified using column chromatography. Elution with DCM/EtOAc (9:1) and ethyl acetate afforded colorless powder (0.4 g, 40.8%). M.p. 120°C. ^{1}H NMR (400 MHz, (d_6)DMSO): δ = 8.67 (br. t, Gly NH), 7.57 (d, J = 6.3 Hz, Cys(4) NH), 7.37 (d, J = 7.9 Hz, Cys(1) NH), 4.43 - 4.40 (m, Cys(1) αCH), 4.30 - 4.26 (m, Cys(4) αCH, Pro αCH), 3.74, 3.59 (2 x dd, J = 17.6, 6.6 Hz, 17.5, 8.5, Gly αCH_2), 3.69 - 3.63, 3.50 - 3.46 (m, Pro δCH_2), 3.64 (s, OCH_3), 3.36 - 3.29, 3.07 (m, Cys(4) βCH_2), 3.36 - 3.29, 2.85 (m, Cys(1) βCH_2), 2.11 - 2.03, 1.91 - 1.82 (m, Pro $\gamma,\beta CH_2$), 1.39 (s, Boc CH_3) ppm. ^{13}C NMR (101 MHz, (d_6)DMSO): δ = 171.89 (Pro CO), 170.11 (OMe CO), 169.14 (Cys(1) CO), 168.86 (Gly CO), 154.76 (Boc CO), 78.85 (Boc Cq), 60.80 (Pro αCH), 53.04 (Cys(4) αCH), 52.24 (OCH_3), 52.11 (Cys(1) αCH), 46.82, 42.15 (Gly αCH_2), 37.01 (Cys(1) βCH_2), 34.98 (Cys(4) βCH_2), 28.46 (Pro βCH_2), 28.05, 24.68 (Pro γCH_2) ppm. ^{1}H NMR (400 MHz, CD_3CN): δ = 7.51 (d, J = 6.6 Hz, Cys(4) NH), 7.24 (br., Gly NH), 5.84 (br., Cys(1) NH), 4.59 (dd, J = 17.5, 5.8 Hz, Cys(1) αCH), 4.43-4.41 (m, Cys(4) αCH), 4.29 (dd, J = 8.0, 5.4 Hz, 1H, Pro αCH), 3.73 - 3.67 (m, Gly αCH_2), 3.70-3.64 (m, Pro δCH_2), 3.36, 3.07 (m, Cys(4) βCH_2, Cys(1) βCH_2), 2.20 - 1.89 (m, Pro $\beta,\delta CH_2$,), 1.42 (s, Boc CH_3) ppm. ^{13}C NMR (101 MHz, CD_3CN): δ = 172.88 (Pro CO), 171.48 (OMe CO), 171.06 (Cys(1) CO), 170.32 (Gly CO), 155.86 (Boc CO), 80.61 (Boc Cq), 62.65 (Pro αCH), 55.47 (Cys(4) αCH), 53.15 (OCH_3), 53.03 (Cys(1) αCH), 48.52 (Pro δCH_2), 43.27 (Gly αCH_2), 39.46 (Cys(1) βCH_2), 37.13 (Cys(4) βCH_2), 29.63 (Pro βCH_2), 28.55 (Boc CH_3), 26.01 (Pro γCH_2) ppm. IR: $\tilde{\upsilon}$ = 3323, 2978, 1763, 1641, 1537, 1434, 1366, 1305, 1211, 1169, 1046, 1022, 917, 860, 785 cm^{-1}. FAB-MS *m/z*: 512.9 (11) $[M + Na]^+$, 490.9 (3) $[M + H]^+$, 390.9 (4) $[M - Boc + H]^+$, 57 (100). $C_{19}H_{30}N_4O_7S_2$ (490.60): calcd. C 46.52, H 6.16, N 11.42, S 13.07; found C 46.67, H 6.06, N 10.66, S 11.7.

Boc-Cys(Trt)-Pro-Gly-Cys(Acm)-OMe (6): Boc-Cys(Trt)-OH (6.06 g, 0.013 mol) was dissolved in DMF (25 mL) and cooled to -18 °C. Whilst stirring, DCCI (3.39 g, 0.016 mol) and HOBt (2.22 g, 0.016 mol) were dissolved in DMF (60 mL) and added one after another to the solution. The reaction mixture was stirred for 30 minutes at -20 °C. A cooled solution of deprotected compound H-Pro-Gly-Cys(Acm)-OMe*CF_3COOH (6.06 g, 0.013 mol) and NMM (5.95 mL, 0.054 mol) dissolved in 90 mL DMF was added at once to the reaction mixture. Afterwards the reaction mixture was stirred for two hours at -20 °C and stirred for additional 20 hours at 20°C. The reaction mixture was allowed to stand for one hour and precipitated dicyclohexylurea was filtered off. The solvent was evaporated, the residue was dissolved in ethyl acetate/5% $KHCO_3$ and additional dicyclohexylurea was filtered off. The filtrate was washed with 5% $KHCO_3$ (90 mL, four times), 5% $KHSO_4$ (90 mL, three times) and brine (90 mL). The collected organic layers were dried over Na_2SO_4 and the solvent was evaporated. As raw product yellow foam was obtained which was purified using column chromatography. Elution with DCM/Et_2O (1:1), DCM/EtOAc (2:3) and ethyl acetate afforded pure colorless foam (6.19 g, 60.6%). M.p. 100°C. ^{1}H NMR (400 MHz, (d_6)DMSO): δ = 8.48 (t, J = 6.1 Hz, Acm NH), 8.17 (d, J = 7.7 Hz, Cys(4) NH), 8.08 (t, J = 5.9 Hz, Gly NH), 7.40-7.20 (m, ArH), 7.09 (d, J = 8.6 Hz, Cys(1) NH), 4.49 (m, Cys(4) αCH), 4.22 (qd, J = 13.5, 6.4 Hz, Acm CH_2, Pro αCH), 4.43 (m, Cys(1) αCH), 3.63 (s, OCH_3), 3.27 - 3.23, 2.84 (m, dd, J = 13.7, 8.0 Hz, Gly αCH_2), 2.98 (2 x dd, J = 13.8, 5.9 Hz, J = 13.7, 8.0 Hz, Cys(4) βCH_2), 2.55 - 2.49, 2.32 (m, dd, J = 12.6, 4.6 Hz, Cys(1) βCH_2), 1.99 - 1.91, 1.79 - 1.71 (m, Pro βCH_2), 1.85 (s, Acm CH_3), 1.80 - 1.71 (m, Pro γCH_2), 1.36 (s, Boc CH_3) ppm. ^{13}C NMR (101 MHz, (d_6)DMSO): δ = 171.54 (Cys CO), 170.98 (Acm CO), 169.51 (Cys CO), 168.87 (Gly CO), 168.70 (Pro CO), 155.16 (Boc CO), 144.41 (Ar C), 129.24 (Ar C), 128.05 (Ar C), 126.77 (Ar C), 78.26 (Boc Cq), 66.48 (Trt Cq), 59.68 (Pro αCH), 52.27 (Cys(4) αCH), 52.20 (Cys(1) αCH), 52.06 (OCH_3), 46.44 (Pro δCH_2), 41.62 (Gly αCH_2), 40.57 (Acm CH_2), 32.71 (Cys(1) βCH_2), 31.80 (Cys(4) βCH_2), 28.98 (Pro βCH_2), 28.17 (Boc CH_3), 24.38 (Pro γCH_2), 22.58 (Acm CH_3) ppm. IR: $\tilde{\upsilon}$ = 3304, 3057, 2975, 1742, 1658, 1658, 1522, 1443, 1367, 1166, 1043, 922, 853, 744, 701, 675, 618 cm^{-1}. FAB-MS *m/z*: 828.2 (6) [M + Na]$^+$, 706.2 (0.1) [M - Boc + H]$^+$), 243.1 (100) [Trt + H]$^+$. $C_{41}H_{51}N_5O_8S_2$ (805.6): calcd. C 61.10, H 60.38, N 8.69, S 7.96; found C 8.23, H 60.87, N 8.23, S 7.64.

H-Cys(Acm)-OH*HCl: Boc-Cys(Acm)-OH*HCl (9.36 g, 0.032 mol) was dissolved in hydrochloric acid (1.2 N, 30 mL)/acetic acid (30 mL) and the reaction mixture was stirred for 20 minutes at 20°C. The solvent was evaporated to give colorless oil. After treatment with dry ether a colorless powder could be obtained. Therefore 100 mL of dry ether was added to the compound and the flask was placed in an ultrasonic bath for one hour. The precipitated colorless solid was extracted and dried under high vacuum conditions (13.85 g, 94.6%). The hygroscopic compound should be kept under argon atmosphere. ^{1}H NMR (400 MHz, (d_6)DMSO): δ = 8.76 (t, J = 6.3 Hz, Acm NH), 4.35 – 4.15 (m, Acm CH_2, Cys αCH), 3.74 (s, OCH_3), 3.58 (s, NH_3^+), 3.18-3.03 (Cys βCH_2), 1.85 (s, Acm CH_3) ppm. ^{13}C NMR (101 MHz, (d_6)DMSO): δ = 169.67 (Cys CO), 168.60 (Acm CO), 52.15 (Cys αCH), 40.63 (Acm CH_2), 30.28 (Cys βCH_2), 22.63 (Acm CH_3) ppm. FAB-MS *m/z*: 193.1 (100) $[M - HCl + H]^+$).

H-Cys(Acm)-OMe*HCl: Methanol (30 mL) was placed in a double-walled reaction flask and cooled to -15°C. Thionyl chloride (5.2 mL, 0.073 mol) was added dropwise to the stirred methanol. Thereby the temperature should not increase beyond -5°C. H-Cys(Acm)-OH*HCl was added to the reaction mixture at once and stirred for 30 minutes at -5°C and then for five hours at 50°C. After removal of the solvent, the crude was carefully coevaporated (five times) using methanol to give white foam (13.76 g, 93%). Due to the hygroscopic nature of the compound it should be kept under inert atmosphere. M.p. 130 - 132°C. ^{1}H NMR (400 MHz, (d_6)DMSO): δ = 8.82 (br., Acm NH, NH_3^+), 4.33 - 4.18 (m, Acm CH_2, Cys αCH), 3.74 (s, OCH_3), 3.61 (br., NH_3^+), 3.41 - 3.25 (Cys βCH_2), 1.85 (s, Acm CH_3) ppm. ^{13}C NMR (101 MHz, (d_6)DMSO): δ = 169.67 (Cys CO), 168.60 (Acm CO), 52.94 (OCH_3), 52.15 (Cys αCH), 40.63 (Acm CH_2), 30.28 (Cys βCH_2), 22.63 (Acm CH_3) ppm. FAB-MS *m/z*: 207.1 (100) $[M - HCl + H]^+$).

Gly-OMe*HCl: Glycine (22.52 g, 0.30 mol) was dissolved in methanol (300 mL) and cooled to 0°C. Thionyl chloride (23.6 mL, 0.32 mol) was added dropwise to the stirred solution. After complete addition of thionyl chloride the reaction mixture was stirred for four hours at 55°C and afterwards overnight at room temperature. The solvent was removed and the white solid was coevaporated using methanol to remove excess of thionyl chloride. After storage in a desiccator over KOH under dynamic vacuum of a membrane pump white crystalline needles could be obtained (37.65 g, 99%). M.p. 184°C. ^{1}H NMR (400 MHz, (d_6)DMSO): δ = 8.61 (s, NH_3^+), 3.75 (s, αCH_2), 3.72 (s, OCH_3) ppm. ^{13}C NMR (101 MHz, (d_6)DMSO): δ = 168.00 (CO), 52.51 (OCH_3), 39.49 (Gly αCH_2) ppm. IR: $\tilde{\upsilon}$ = 2969, 2658, 2585, 1764, 1590, 1526, 1439, 1258, 1137, 1056, 956, 878, 676 cm^{-1}. FAB-MS *m/z*: 89.0

(100) $[M - HCl + H]^+$. $C_3H_8NO_2Cl$ (124.54): calcd. C 28.67, H 6.37, N 11.15; found C 28.58, H 5.7, N 11.15.

Boc-Pro-Gly-OMe: According to the procedure published by Jung et al.[26] the dipeptide was synthesized and varied slightly to give higher yields by using a double-walled flask coupled to an external cryostat which allows temperature control. Boc-Pro-OH (18.3 g, 0.085 mol) was stirred in a mixture of DCM/DMF (1:1) and the solution was cooled to -20 °C. NMM (0.34 mL, 0.085 mol) and IBCF (11.02 mL, 0.085 mol) were added dropwise using a syringe. After ten minutes a cooled suspension of Gly-OMe*HCl (10.67 g, 0.085 mol) and NMM (9.34 mL, 0.085 mol) in DCM/DMF (1:1) was added to the reaction mixture at once at -15 °C. The suspension was stirred for one hour at -15°C and afterwards for 90 minutes at -5 °C. The reaction mixture was raised to 20°C and the reaction was stopped by adding 5% $KHCO_3$ (5 mL). The solvent was removed carefully in vacuo to give a yellow solid. The residue was dissolved in ethyl acetate/5% $KHSO_4$ (200 mL) and washed with 5% $KHSO_4$ (40 mL, four times), 5% $KHCO_3$ (40 mL, two times) and brine (20 mL). The organic layer was dried and the solvent was removed. The obtained colorless oil solidified after a few minutes and was crystallized from pentane/ethyl acetate (1:1) to yield a colorless crystalline compound (21.09 g, 86.7%). M.p. 78 °C. ^{1}H NMR (400 MHz, (d_6)DMSO): 8.22 (br., NH), 4.13 - 4.07 (m, Pro αCH), 3.88 - 3.76 (o, Gly αCH_2), 3.61 (s, OCH_3), 3.40 - 3.30, 3.30 - 3.25 (m, Pro δCH_2), 2.13 - 2.03, 1.80 - 1.73 (m, Pro $\gamma,\beta CH_2$), 1.33 (s, Boc CH_3) ppm. ^{13}C NMR (101 MHz, (d_6)DMSO): δ = 173.05 (Gly CO), 170.21 (Pro CO), 153.40 (Boc CO), 79.00 (Boc Cq), 60.00 (Pro αCH), 51.63 (OCH_3), 46.43 (Pro δCH_2), 40.54 (Gly αCH_2), 30.96 (Pro βC), 27.99 (Boc CH_3), 23.09 (Pro γCH_2) ppm. IR: $\tilde{\upsilon}$ = 3304, 1755, 1660, 1534, 1416, 1261, 1611, 978, 627 cm^{-1}. FAB-MS *m/z*: 309.1 (35) $[M + Na]^+$, 287.1 (57) $[M + H]^+$, 231.1 (41) [M - t-butyl + H]$^+$, 213.1 [M - t-butyloxy +H]$^+$, 187.1 (100) [M - Boc + H]$^+$. $C_{13}H_{22}N_2O_5$ (286.33): calcd. C 54.53, H 7.74, N 9.78; found C 54.41, H 7.37, N 9.68.

Boc-Pro-Gly-OH: Boc-Pro-Gly-OMe (20.8 g, 0.0726 mol) was dissolved in methanol (200 mL) and stirred at 38°C. Sodium hydroxide (2N, 104.5 mL) was added dropwise to the solution and the reaction mixture was stirred for two hours at 38°C and afterwards for 30 minutes at 20°C. The basic solution was neutralized using hydrochloric acid (1 N). After evaporation of methanol the pH value of the solution was adjust to three to yield a colorless crystalline compound. The colorless needles were sucked off and washed with small portions of distilled water (16.8 g, 85%). M.p. 170 °C. ^{1}H NMR (400 MHz, (d_6)DMSO): δ = 12.50 (bs, COOH), 8.07 (br., NH), 4.13 - 4.07 (m, Pro αCH), 3.72 (qd, J = 17.4, 5.9 Hz, Gly αCH_2), 3.39 – 3.34, 3.30 - 3.23 (m, Pro δCH_2), 2.09, 1.80 (b, Pro γ,β CH_2), 1.32 (s, CH_3) ppm. ^{13}C

NMR (101 MHz, (d_6)DMSO): δ = 172.74 (Gly CO), 171.14 (Pro CO), 153.39 (Boc CO), 78.56 (Boc Cq), 59.72 (Pro αCH), 46.50 (Pro δCH_2), 40.65 (Gly αCH_2), 30.97 (Pro βCH_2), 28.00 (Boc CH_3), 23.11 (Pro γCH_2) ppm. IR: $\tilde{\upsilon}$ = 3327, 2971, 1772, 1663, 1558, 1418, 1257, 1165, 1126, 983, 758, 672 cm^{-1}. FAB-MS *m/z* = 295.1 (100) $[M + Na]^+$, 273.1 (31) $[M + H]^+$, 217.0 (15) $[M$ - t-butyl $+ H]^+$, 195.0 (28) $[M$ - Boc $+ Na]^+$, 173.1 (43) $[M$ - Boc $+ H]^+$. $C_{12}H_{20}N_2O_5$ (272.30): calcd. C 52.93, H 7.40, N 10.28; found C 52.29, N 10.18, H 7.15.

Boc-Pro-Gly-Cys(Acm)-OMe: Boc-Pro-Gly-OH (6.25 g, 0.023 mol) and DCCI (5.22 g, 0.0253 mol) were dissolved in DMF (40 mL) and stirred at -2°C. A suspension of H-Cys(Acm)-OMe*HCl (5.58 mL, 0.023 mol) and triethylamine (3.5 mL, 0.025 mol) in DMF (15 mL) was added at one to the reaction mixture and stirred at -2°C. After two hours the suspension was further stirred overnight at 20 °C. Precipitated dicyclohexylurea was filtered off and the solvent was evaporated. The residue was dissolved in chloroform (40 mL) and washed with HCl (0.1 N, 20 mL, two times), $NaHCO_3$ (0.5 N, 20 mL, four times) and brine (40 mL). The organic layer was dried over anhydrous Na_2SO_4 and removed in vacuo. The crude compound was purified by column chromatography. Elution with DCM/Et_2O (7:3 and 1:1) and ethyl acetate afforded pure colorless tripeptide (6.18 g, 58.4%). M.p. 85°C. ^1H NMR (400 MHz, (d_6)DMSO): δ = 8.47 (br. s, Acm NH), 8.26 (dd, J = 64.7, 7.5 Hz, Cys NH), 8.06 (br., Gly NH), 4.57 - 4.50 (m, Cys αCH), 4.27 - 4.16 (m, Acm CH_2), 4.13 - 4.07 (m, Pro αCH), 3.85 - 3.68 (m, Gly αCH_2), 3.64 (s, OCH_3), 3.39 - 3.24 (m, Pro δCH_2), 2.90 (ddd, J = 21.9, 13.8, 6.9 Cys βCH_2), 1.84 (s, Acm CH_3), 2.13 - 2.02, 186 - 1.69 (m, Pro $\beta,\gamma CH_2$),1.35 (s, Boc CH_3) ppm. ^{13}C NMR (101 MHz, (d_6)DMSO): δ = 172.98 (Gly CO), 172.63 (Pro CO), 171.22 (Acm CO), 169.66 (Cys CO), 153.57 (Boc CO), 78.73 (Boc Cq), 59.92 (Pro αCH), 52.44 (Cys αCH), 52.92 (OCH_3), 46.68 (Pro δCH_2), 41.76 (Gly αCH_2), 40.74 (Acm CH_2), 31.99 (Cys βCH_2), 31.17 (Pro βCH_2), 28.23 (Boc CH_3), 23.28 (Pro γCH_2), 22.72 (Acm CH_3) ppm. IR: $\tilde{\upsilon}$ = 3302, 2976, 1748, 1658, 1529, 1409, 1366, 1254, 1164, 1127, 1091, 854, 773 cm^{-1}. FAB-MS *m/z*: 483.2 (44) $[M + Na]^+$, 461.2 (15) $[M + H]^+$, 361.1 (31) $[M$ - Boc $+ H]^+$. $C_{19}H_{32}N_4O_7S$ (460.55): calcd. C 49.53, H 6.99, N 12.16, S 6.96; found C 48.88, H 7.05, N 11.84, S 6.24.

Standard procedure for removing Boc protecting groups: A solution of Boc protected peptide (0.014 mol) was dissolved in TFA (0.77 mol) and stirred for 100 minutes. The solvent was removed in vacuo and the obtained oil was coevaporated with hexane (five times). Subsequently dry ether was added and then placed in a supersonic bath. Due to the hygroscopic nature of the deprotected peptide it can be useful to repeat the steps of

evaporation to remove excess acid and precipitation of the compound using anhydrous ether. The deprotected peptide was obtained as a colorless powder (92 - 94%).

Crystal structure details

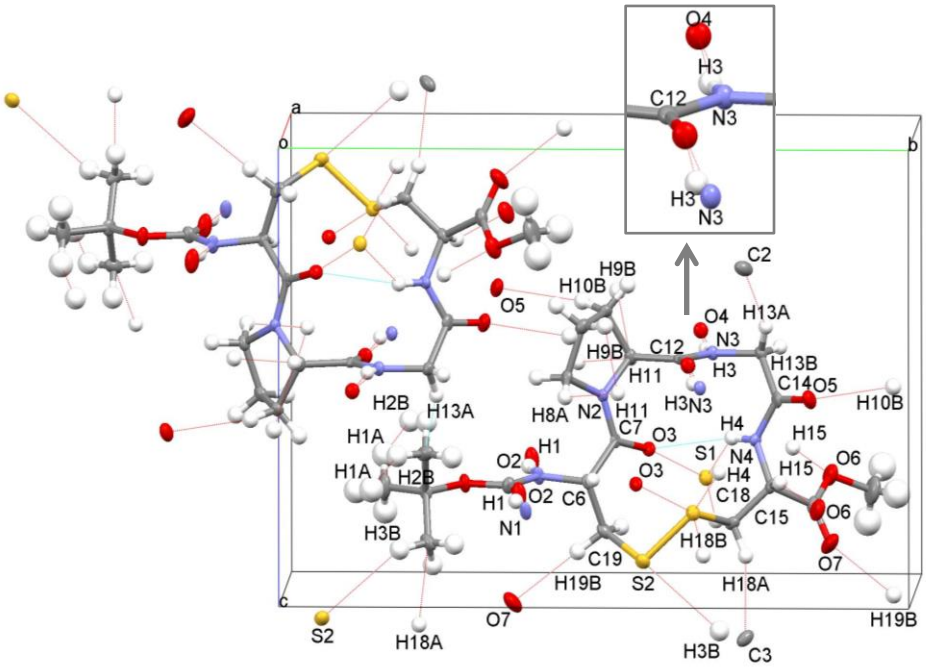


Figure S1. Crystal packing of **1** showing the van der Waals interactions (red) and hydrogen bonding (blue). The $NH_{Gly}\cdots O{=}C_{Pro}$ interaction between the amide proton of glycine (H3) and the carbonyl oxygen atom of the proline residue of the neighbor peptide molecule (O4) is highlighted (see arrow).

Table S1. Crystal data and refinement details for **1**

empirical formula	$C_{19}H_{30}N_4O_7S_2$
M_r (g mol^{-1})	490.59
λ (Å)	0.71073
crystal size (mm^3)	0.39 × 0.06 × 0.03
crystal system	monoclinic
space group	$P2_1$
T (K)	106(2)
a (Å)	5.04229(17)
b (Å)	18.3451(5)
c (Å)	12.8083(4)

β (°)	97.227(3)
V (Å^3)	1175.37(7)
Z	2
ρ_{calc} (g cm^{-3})	1.386
μ (mm^{-1})	0.273
θ range (°)	3.21 - 25.49
data collected / unique	31657 / 4344
R_{int}	0.0821
observed data ($I > 2\sigma(I)$)	3700
Goodness-of-fit on F^2	1.027
refined parameters	294
R_1 [$I > 2\sigma(I)$]	0.0372
wR_2 (all data)	0.0709
residuals (e Å^{-3})	0.231 / -0.203

Table S2. Dihedral angles of the peptide backbone of **1**

			Type I β-turns[1]	Type II β-turns[1]	Type III β-turns[1]
Dihedral angles [°]					
C5-N1-C6-C7	ϕ_{Cys1}	-140.1(2)			
N1-C6-C7-N2	ψ_{Cys1}	52.2(3)			
C6-C7-N2-C11	ω_{Cys1}	176.9(2)			
C7-N2-C11-C12	ϕ_{Pro2}	-62.2(3)	-60	-60	-60
N2-C11-C12-N3	ψ_{Pro2}	135.6(2)	-30	120	-30
C11-C12-N3-C13	ω_{Pro2}	178.4(3)			
C12-N3-C13-C14	ϕ_{Gly3}	60.4(3)	-90	80	-60
N3-C13-C14-N4	ψ_{Gly3}	29.4(4)	0	0	-30
C13-C14-N4-C15	ω_{Gly3}	174.1(1)			
C14-N4-C15-C16	ϕ_{Cys4}	-78.8(3)			
N1-C6-C19-S2	χ^1_{Cys1}	- 135.5(2)			
C6-C19-S2-S1	χ^2_{Cys1}	-52.9(2)			
N4-C15-C18-S1	χ^1_{Cys4}	-75.6(2)			
C15-C18-S1-S2	χ^2_{Cys4}	174.94(16)			
C19-S2-S1-C18	χ_{ss}	-85.26(13)			
N2-C11-C10-C9	χ^1_{Pro2}	28.1(3)			

C11-C10-C9-C8	χ^2_{Pro2}	-38.5(3)
C10-C9-C8-N2	χ^3_{Pro2}	33.4(3)
C9-C8-N2-C11	χ^4_{Pro2}	-16.7(3)
C8-N2-C11-C10	θ_{Pro2}	-6.9(3)

[1]*Venkatachalam, C. M. Biopolymers* ***1968****, 6, 1425.*

Table S3. Peptides vs. identification number

Peptide	ID
cyclo(Boc-Cys-Pro-Gly-Cys-OMe)	**1**
cyclo(Boc-Cys-Pro-Aib-Cys-OMe)	**2**
cyclo(Boc-Cys-Pro-Aib-Cys-NHMe)	**3**
cyclo(Ac-Cys-Pro-Ser-Cys-NHMe)	**4**
cyclo(Ac-Cys-Pro-Val-Cys-NHMe)	**5**
Boc-Cys(Trt)-Pro-Gly-Cys(Acm)-OMe	**6**
Boc-Cys(Trt)-Pro-Aib-Cys(Acm)-OMe	**7**

Computational details

Table S4. Populations of conformers at 300 K in gas phase, water and acetonitrile (MD simulations of 500 ps, time step 1 fs)

300 K (Population in %)			
Conformer	Gas	Water	Acetonitrile
A	66.2	26.6	17.4
B	33.1	73.4	78.7
C	0.2	1.95	3.8
D	0.5	0.01	0.02

Table S5. Selected hydrogen bond distances (500 ps, time step 1 fs)

300 K			
Average value	Gas	Water	Acetonitrile
C=Ocys-HNcys	3.13±0.32	2.79±0.31	2.70±0.31
C=Ocys-HNgly	2.23±0.30	2.95±0.37	2.87±0.37
C=Opro-HNcys	3.27±0.32	3.14±0.33	3.27±0.33

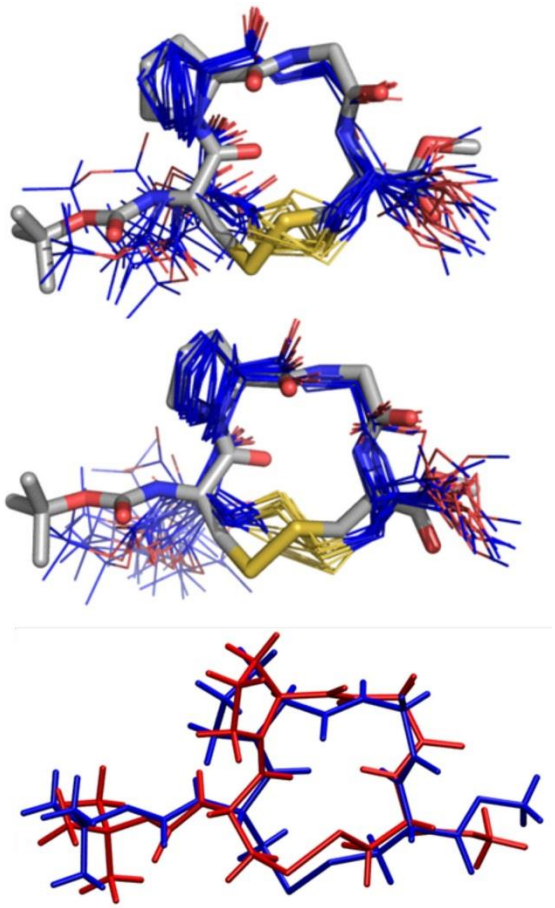


Figure S2. NMR ensemble vs. x-ray structure of **1** (top: DMSO(d_6), middle: CD_3CN) and overlay between the average simulated structure of the peptide in acetonitrile (with NMR restrains, red) and the peptide crystal structure (bottom).

Table S6. Experimental distance restraints vs. MD values: For two-atoms distance restraints the distances averaged over all the simulation are provided. For distance restraints involving more than two atoms the values for r for which g(r) features a maximum are given. All distances are in Å. Groups with an * contain more than one atom (Figure S3)

Group 1	Group 2	NMR	MD
H from t-butil*	2HA	6.52 - 4.72	5.22; 6.38; 7.12
H from t-butil*	2HB1	6.46 - 4.66	6.48; 7.42
H from t-butil*	2HN	6.20 - 4.40	4.28; 5.54
2HN	2HA	4.79 - 2.99	2.84 ± 0.10
2HN	2HB1	4.61 - 2.81	3.16 ± 0.24
2HN	2HB2	5.60 - 3.80	3.87 ± 0.61
2HN	3HD*	5.66 - 3.86	3.44; 4.34
2HA	2HB1	4.20 - 2.40	3.03 ± 0.06
2HA	2HB2	3.88 - 2.08	2.53 ± 0.12
2HA	3HD*	3.23 - 1.43	2.26
2HB1	2HB2	2.83 - 1.03	1.73 ± 0.06
2HB2	3HD*	3.85 - 2.05	4.74
3HA	3HB1	3.59 - 1.79	2.73 ± 0.09
3HA	3HB2	4.10 - 2.30	2.30 ± 0.11
3HA	3HG*	3.51 - 1.71	3.92
3HA	4HN	3.70 - 1.90	2.23 ± 0.18
3HA	4HA2	4.36 - 2.56	4.25 ± 0.15
3HA	5HN	5.76 - 3.96	3.96 ± 0.27
3HB1	3HG*	3.04 - 1.24	2.38; 2.70
3HB1	4HN	5.74 - 3.94	4.07 ± 0.25
3HB2	3HG*	2.76 - 0.96	2.40; 3.02
3HB2	4HN	5.67 - 3.87	4.32 ± 0.21
3HD*	3HB1	3.81 - 2.01	4.02
3HD*	3HB2	4.26 - 2.46	2.98; 3.88
3HD*	3HG*	3.50 - 1.70	2.32; 2.76; 2.98
3HG*	4HN	5.35 - 3.55	5.05; 5.83
4HN	4HA1	3.99 - 2.19	2.96 ± 0.06
4HN	4HA2	4.06 - 2.26	2.33 ± 0.12
4HN	5HN	4.09 - 2.29	2.51 ± 0.26
4HA1	4HA2	3.38 - 1.58	1.74 ± 0.06
4HA1	5HN	5.09 - 3.29	3.19 ± 0.20
4HA2	5HN	5.30 - 3.50	3.32 ± 0.16
4HA2	5HB2	4.11 - 2.31	5.86 ± 0.29
4HN	5HA	4.88 - 3.08	5.08 ± 0.19
5HN	5HB1	3.75 - 1.95	3.46 ± 0.13
5HN	5HB2	5.19 - 3.39	2.79 ± 0.30
5HA	5HB1	3.70 - 1.90	2.43 ± 0.15
5HA	5HB2	4.84 - 3.04	3.05 ± 0.09
5HB1	5HB2	2.84 - 1.04	1.73 ± 0.06

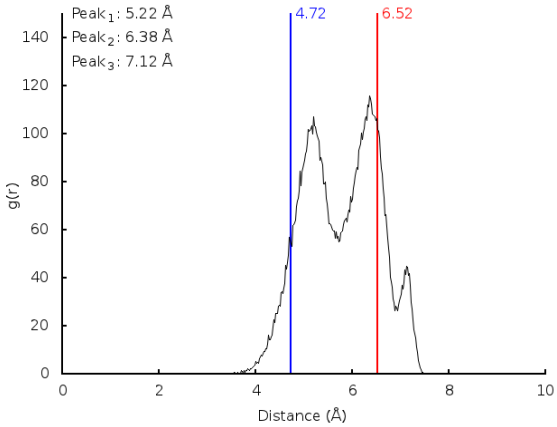
There are three distance restraints involving the tert-butyl moiety in the C-terminal group. The pair distribution function g(r) vs. distance of the tert-butyl hydrogen and 2HA shows three peaks (Figure S3, A). Two of these peaks are within the experimental range, while the smaller one is found to be 0.6 Å beyond the upper experimental range. The behavior of the restraints related to 2HB1 shows a quite symmetric distribution of g(r) around the upper extreme of the NMR range (Figure S3, B) with the highest r peak at 6.48 Å being just 0.02 Å larger than the 6.46 Å experimental limit. In the case of the restraints with 2HN (Figure S3, C) almost all g(r) values are within the experimental range. The value for r in the outside peak is 4.28 Å which is 0.12 Å below the lower limit of 4.40 Å.

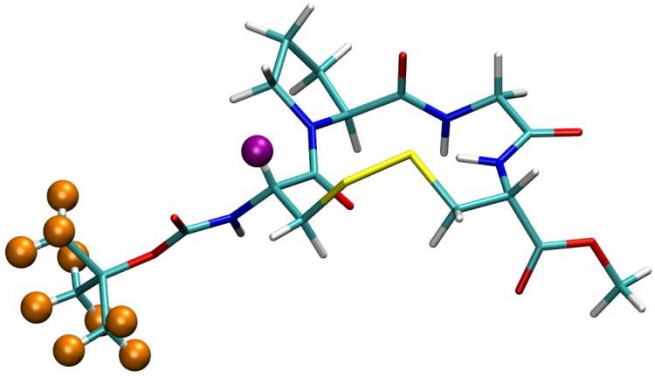
The MD average distances for 3HA-3HB2 and 3HA-5HN (Figure S3, N and R) are equal to the lower value of their respective NMR range. These distance values oscillate around the lower value of the experimental range during the entire simulation. In the case of 2HN-2HA, 3HB2-3HG*, 3HD*-3HB1, 4HA1-5HN, 4HA2-5HN and 4HN-5HA (Figure S3, D, U, W, AE, AF and AH) the difference between the average distance (or the r values of the peaks in g(r)) and the experimental extreme values is lower than 0.30 Å. So, the average distance does not fall within the experimental range but still there is a good agreement between the simulated and the experimental NMR structures. In the case of 2HN-2HB2 the difference between the average distance and the lower value of the NMR range is just 0.07 Å but the time behavior of the distance (Figure S3) shows two possible states. During the first half of the MD simulation the distance values are within the experimental range while at the end the two atoms get closer and the distance fall below the NMR range. The average distance value for the second half of the dynamics is 3.44 Å which is 0.36 Å smaller than the lower value in the experimental range (Table S6).

Larger differences between experiment and theory (0.4 to 0.9 Å) are found for 2HN-3HD*, 2HB2-3HD*, 3HA-3HG*, 4HN-3HG*, and 5HN-5HB2 (Figure S3, G, L, O, Z and AJ). Finally the restraint between 4HA2-5HB2 is badly reproduced (Figure S3, AG). The difference between the average value and the upper limit of the NMR range is 1.75 Å. However, the MD simulations show in general a good agreement with the NMR results. Of the 39 distance restraints only 6 show deviations from the experimental range bigger than 0.4 Å.

Figure S3. Interatomic distance vs. time or pair distribution function for the groups defined in Table S6

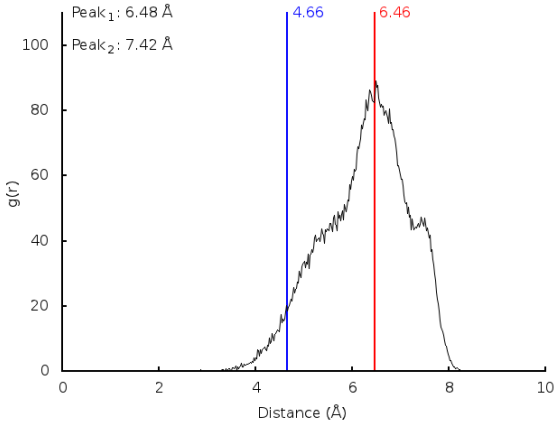
A

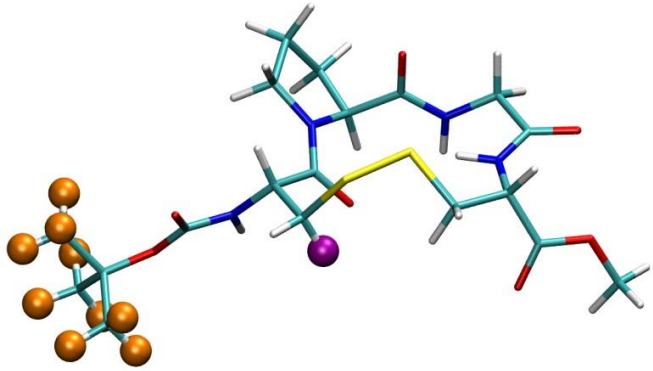




H from t-butil*-2HA

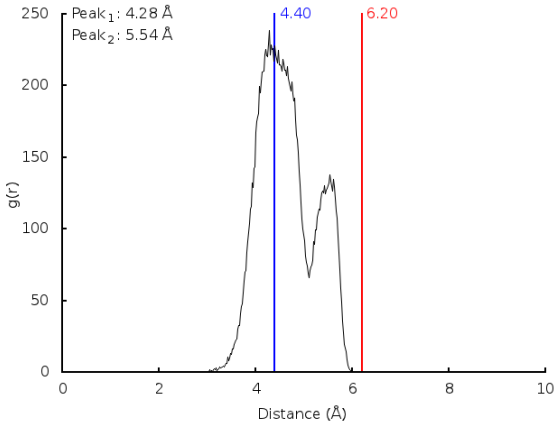
B

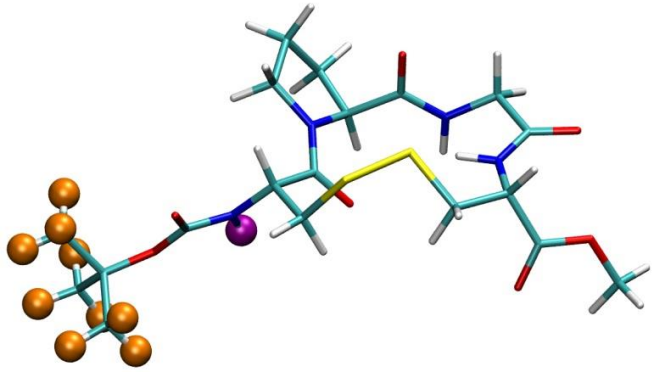




H from t-butil*-2HB1

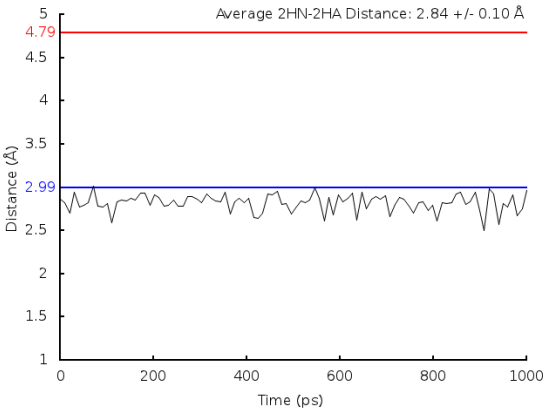
C

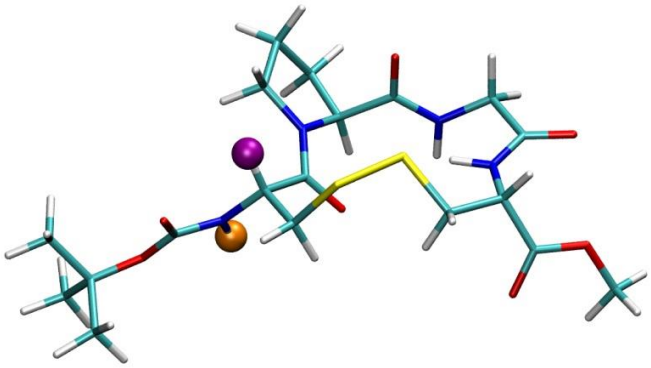




H from t-butil*-2HN

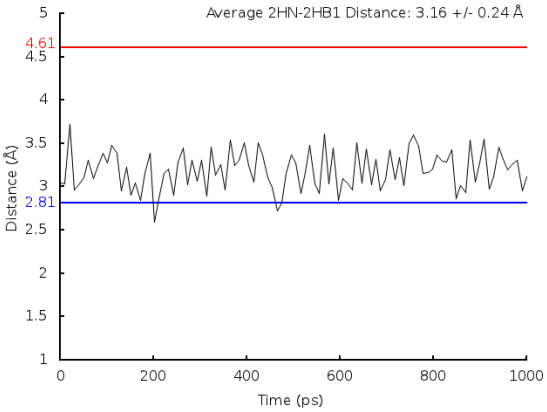
D

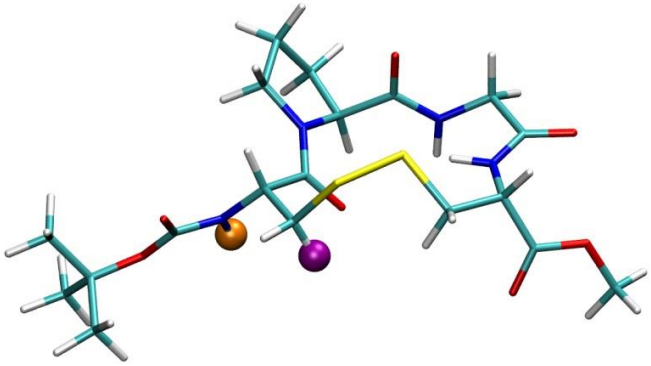




2HN-2HA

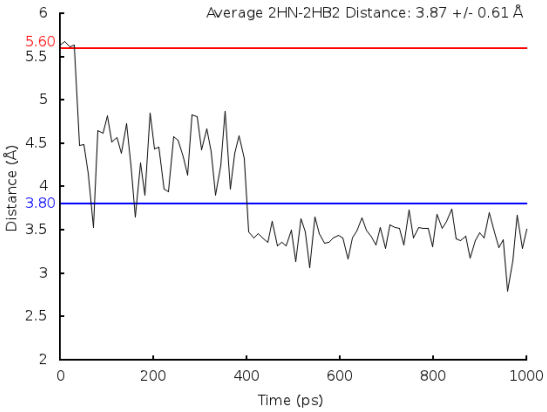
E

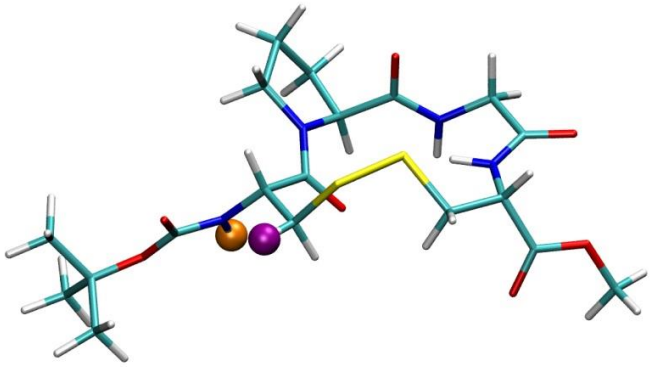




2HN-2HB1

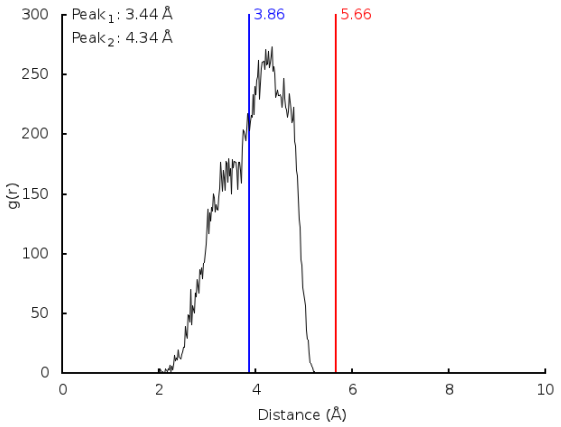
F

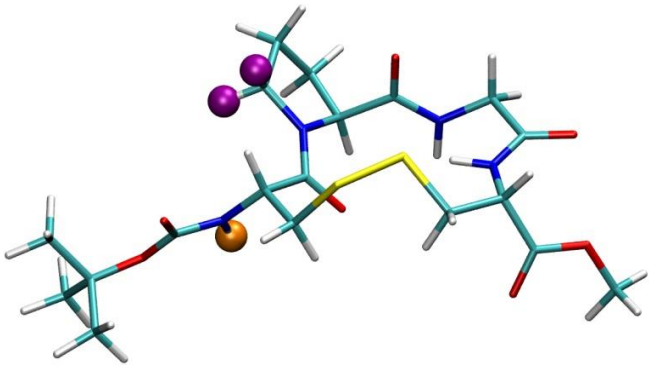




2HN-2HB2

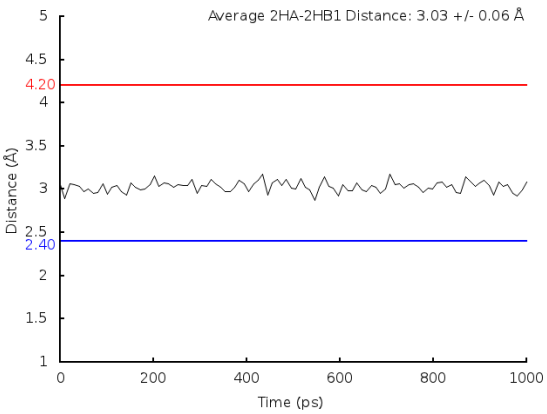
G

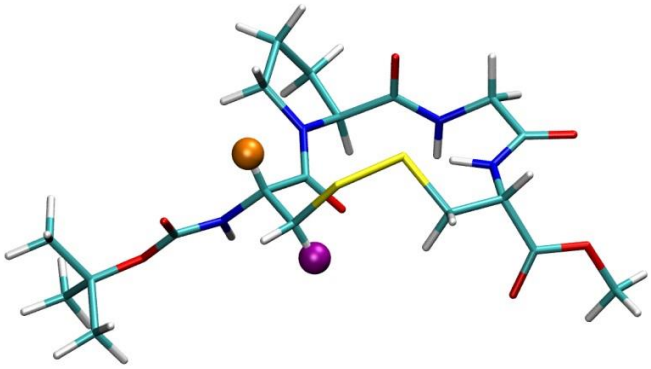




2HN-(3HD*)

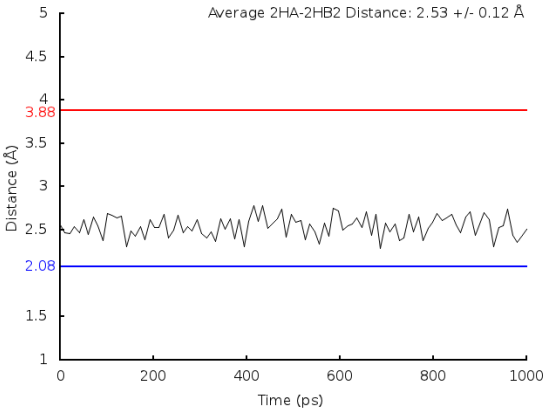
H

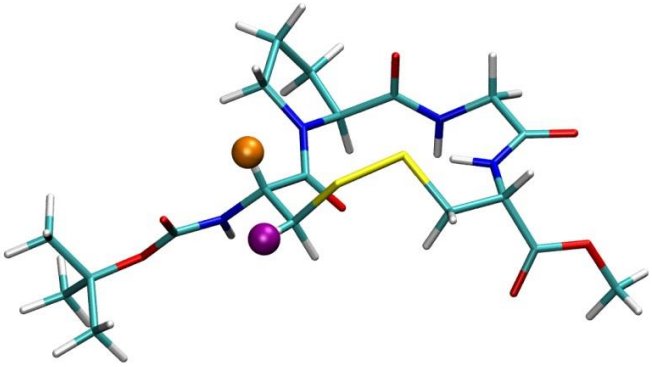




2HA-2HB1

I





2HA-2HB2

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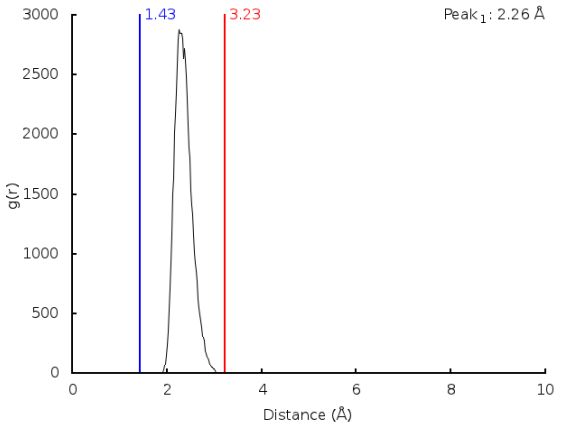
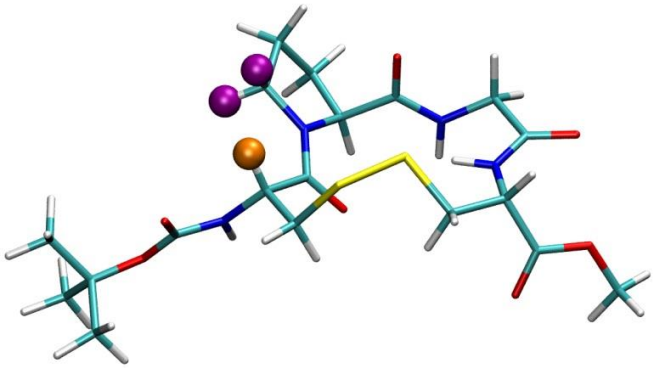
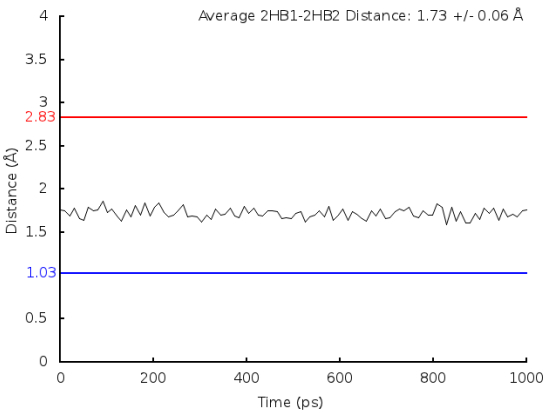
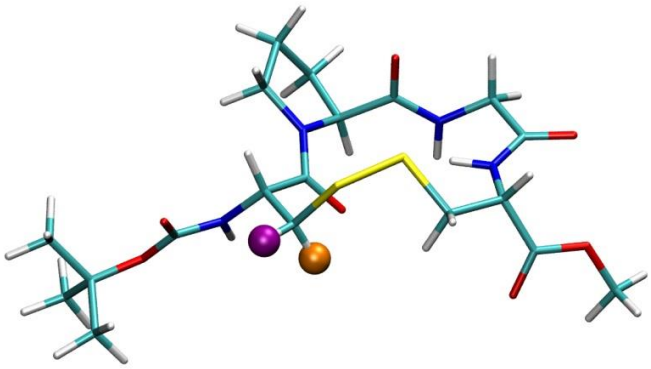




2HA-(3HD*)

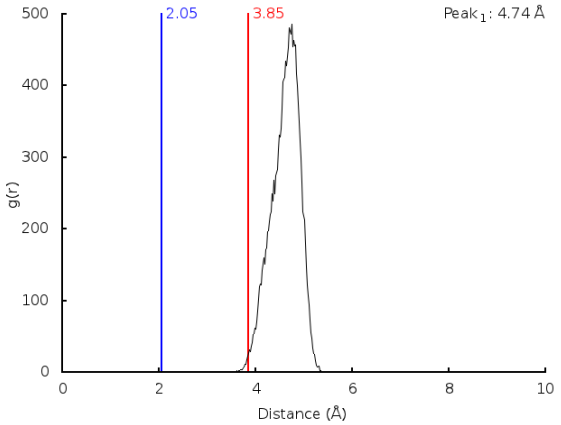
K

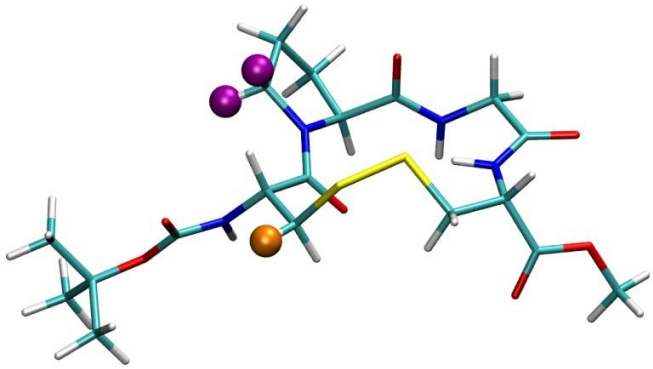




2HB1-2HB2

L





2HB2-(3HD*)

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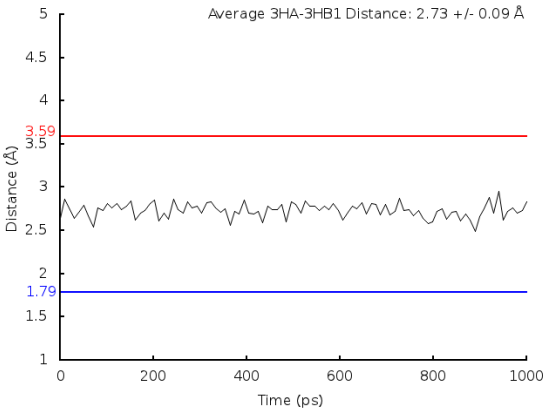
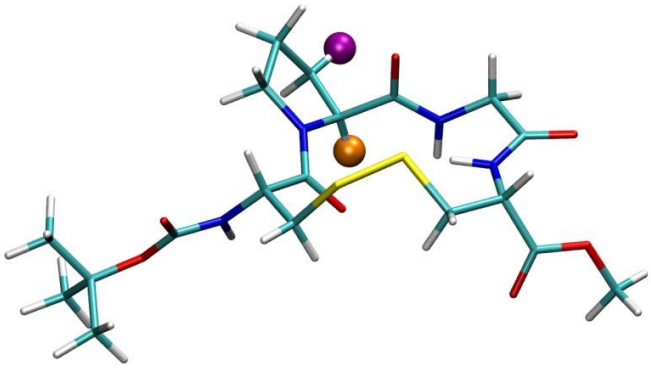
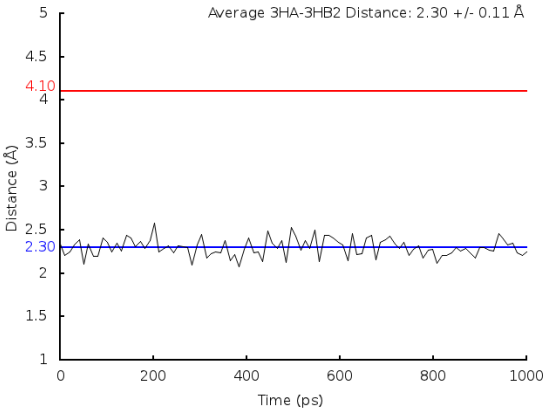
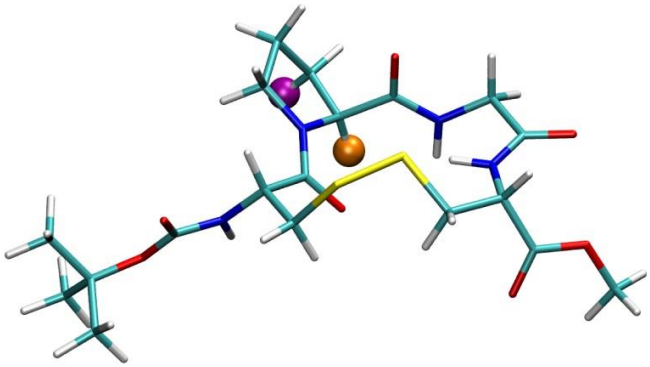




3HA-3HB1

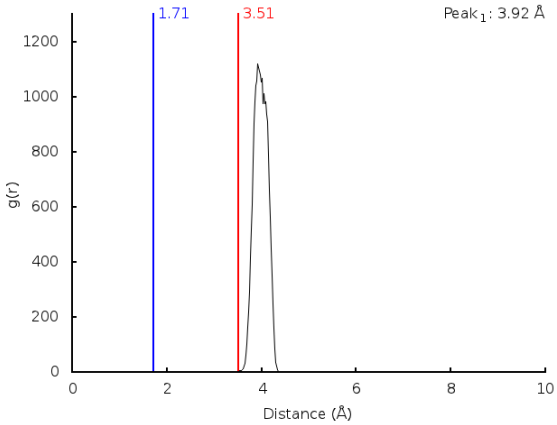
N

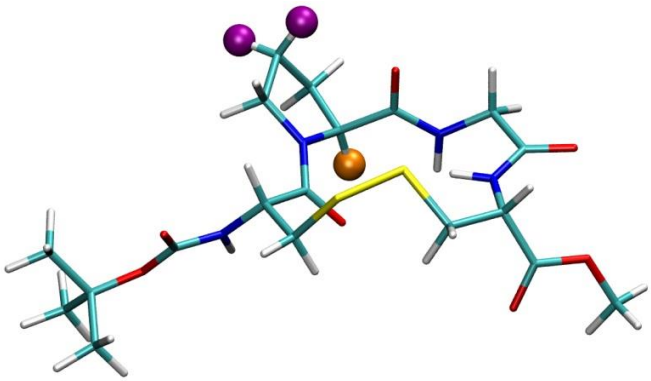




3HA-3HB2

O





3HA-(3HG*)

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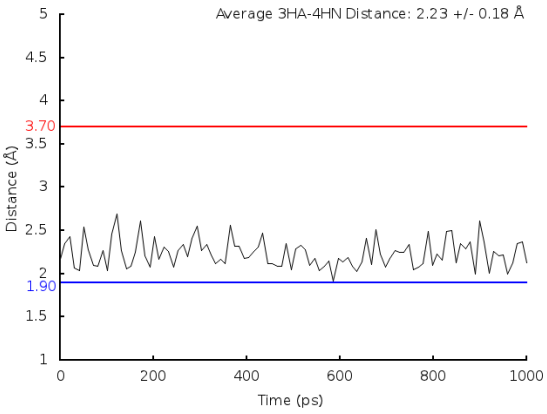
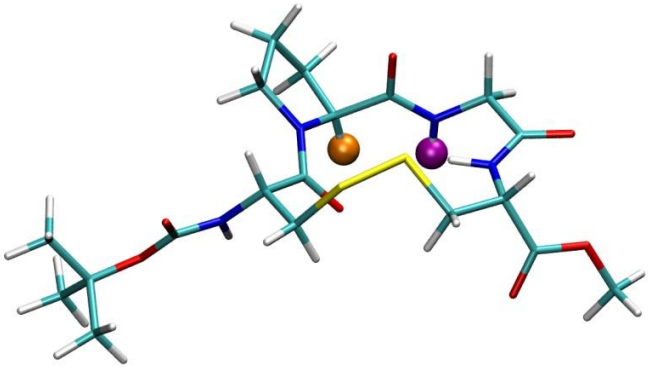
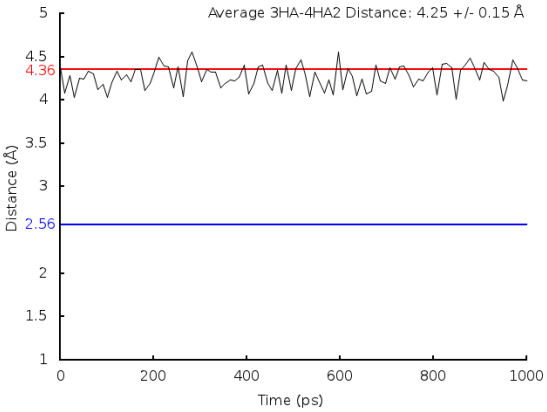
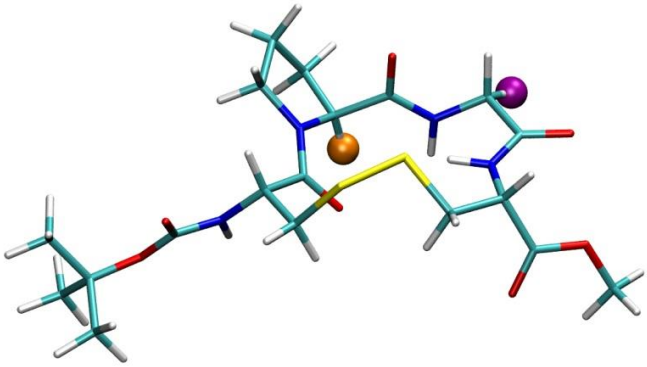




3HA-4HN

Q





3HA-4HA2

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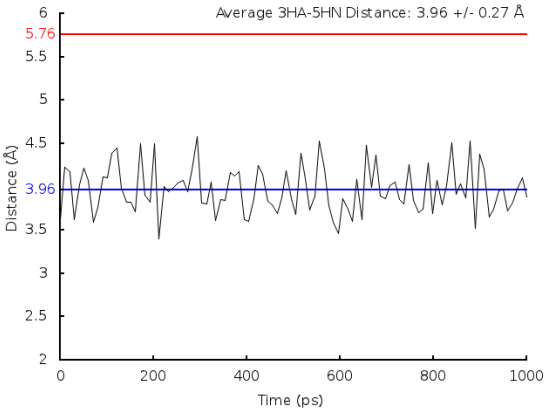

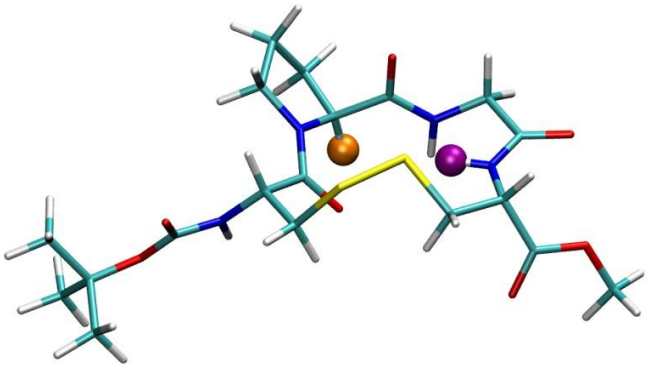

3HA-5HN

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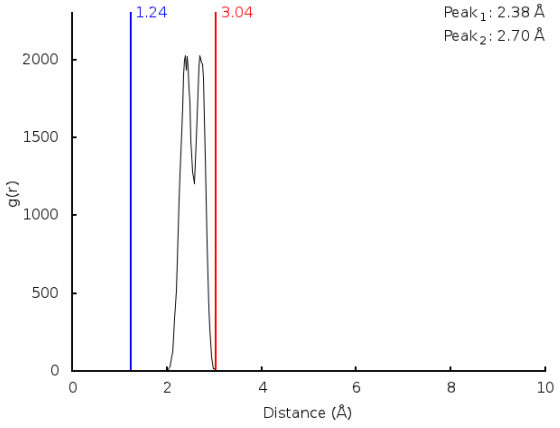

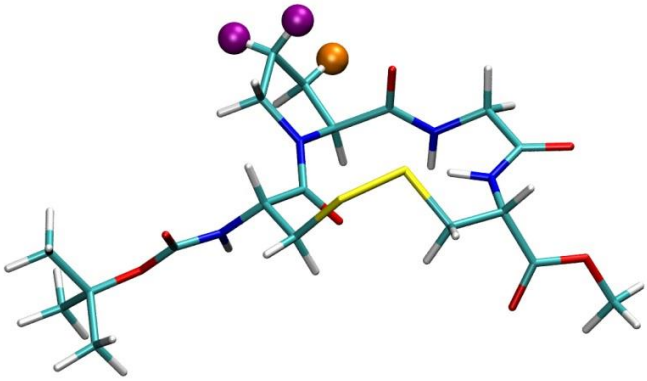

3HB1-(3HG*)

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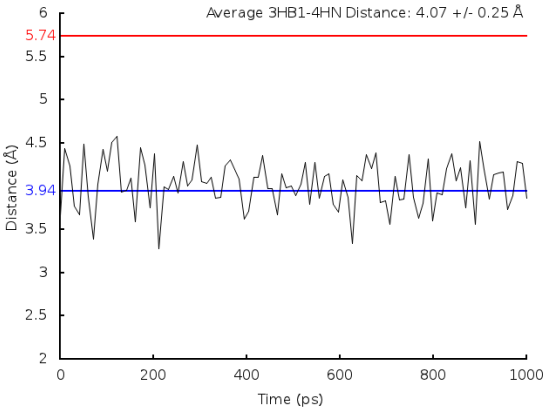

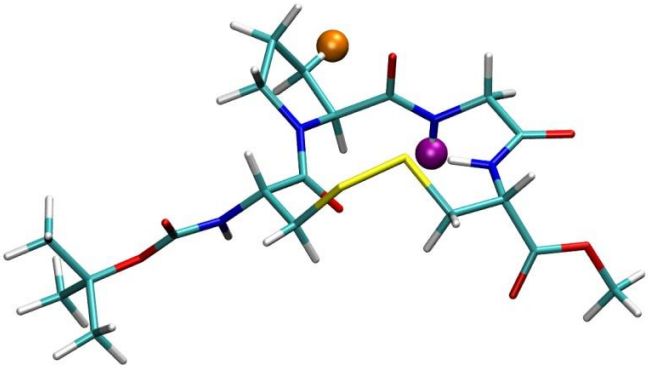

3HB1-4HN

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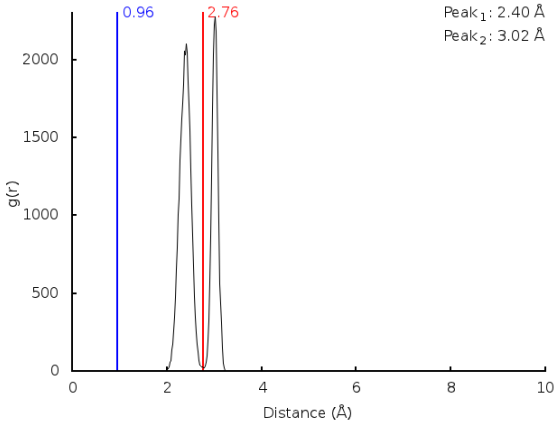

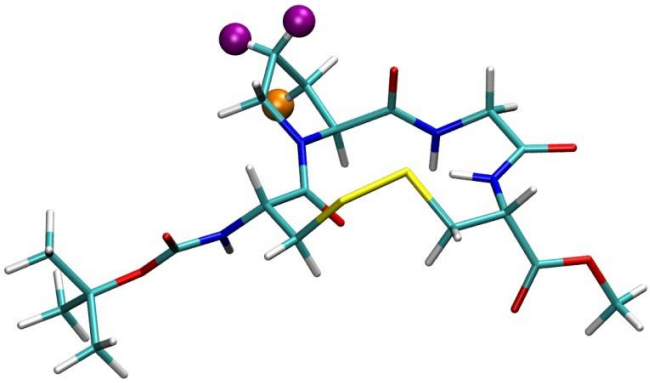

3HB2-(3HG*)

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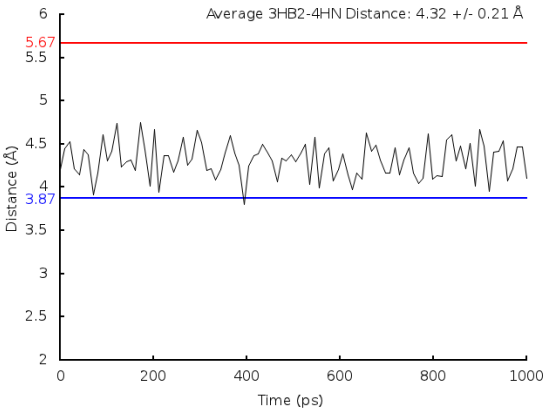

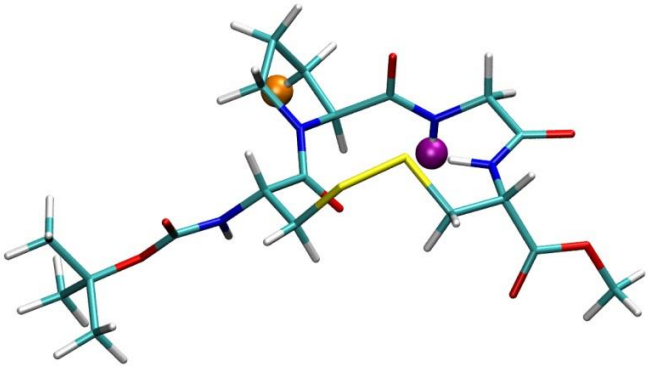

3HB2-4HN

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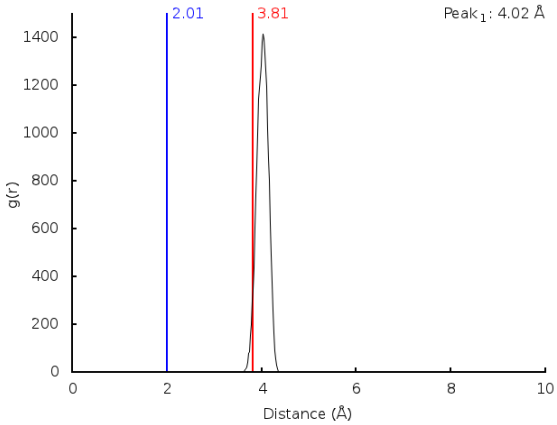
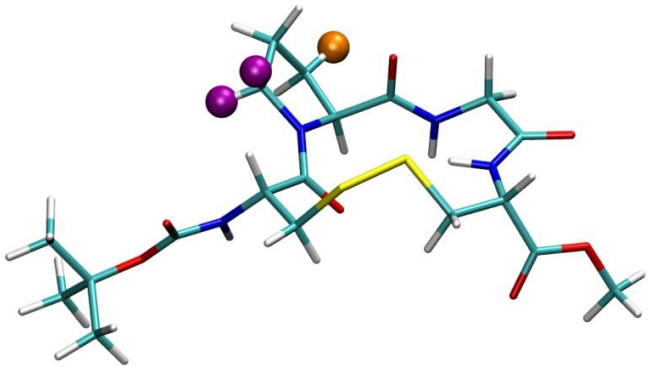
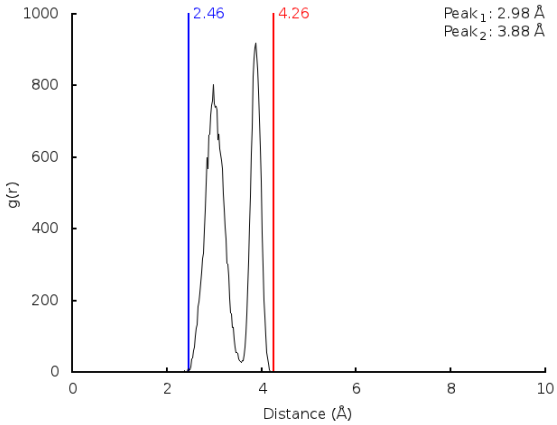
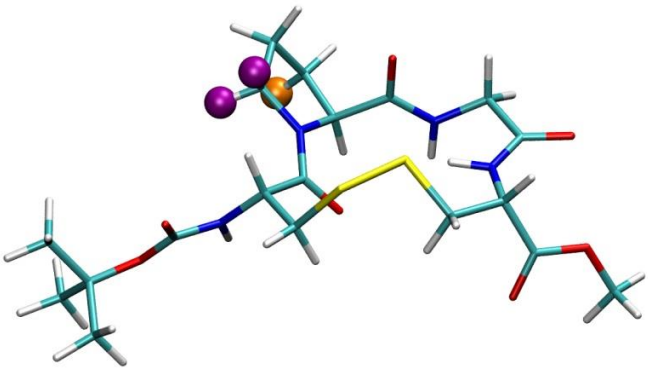




3HB1-(3HD*)

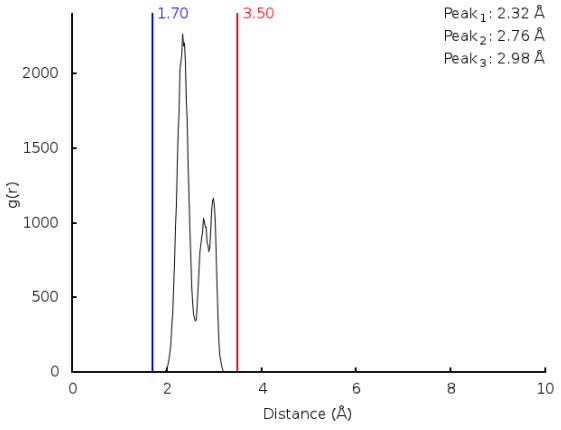
X

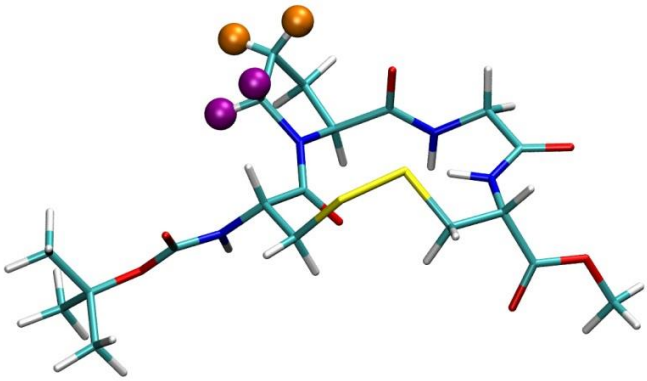




3HB2-(3HD*)

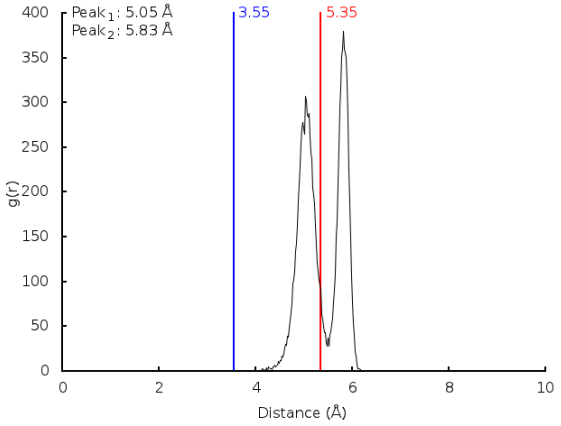
Y

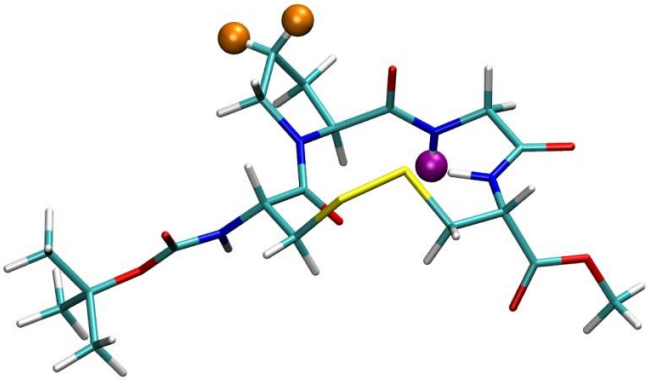




(3HG*)-(3HD*)

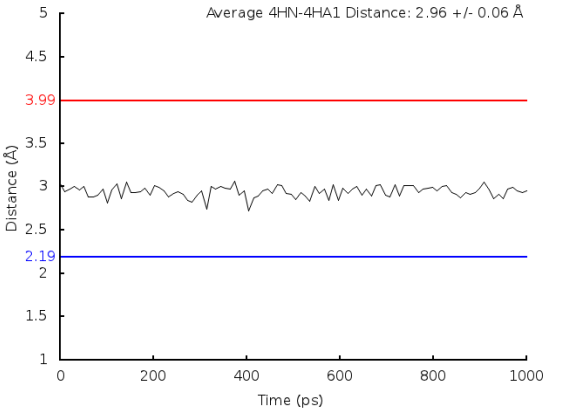
Z

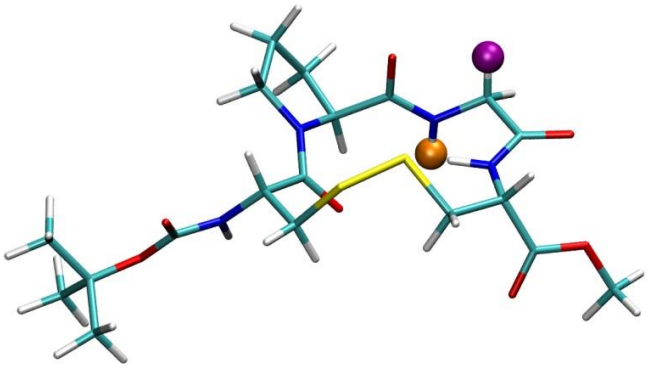




4HN-(3HG*)

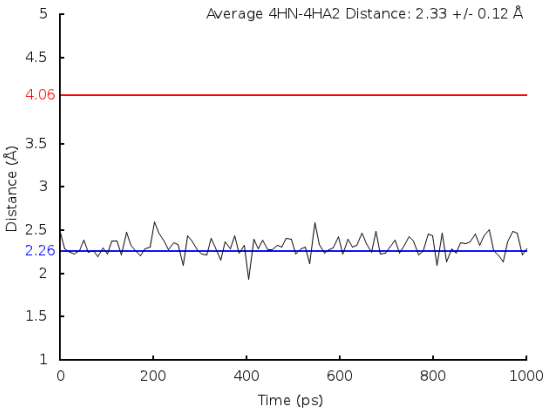
AA

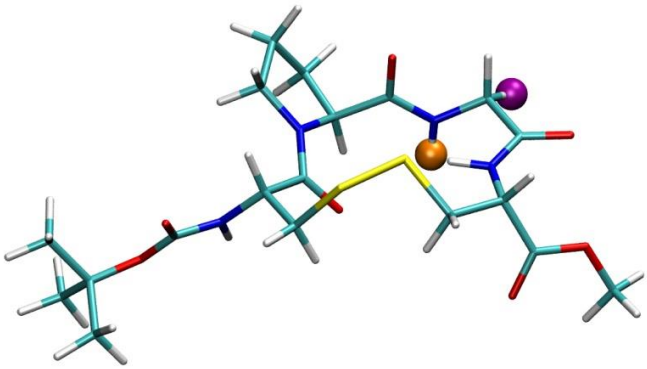




4HN-4HA1

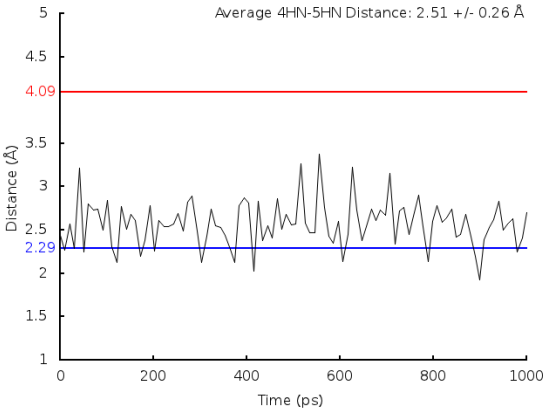
AB

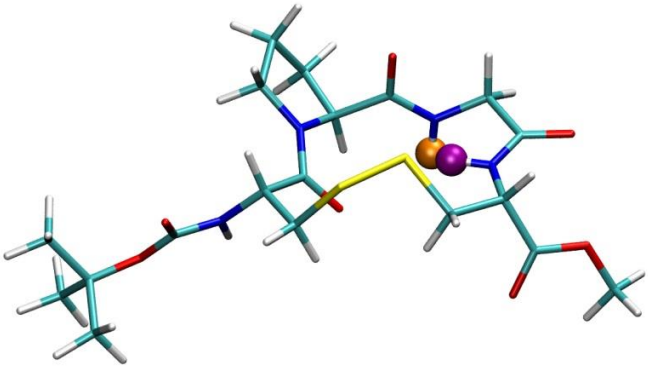




4HN-4HA2

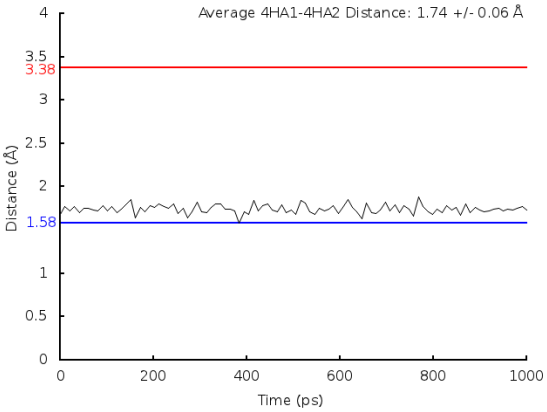
AC

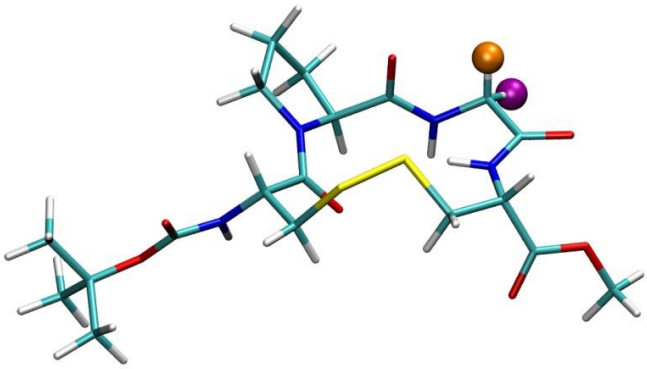




4HN-5HN

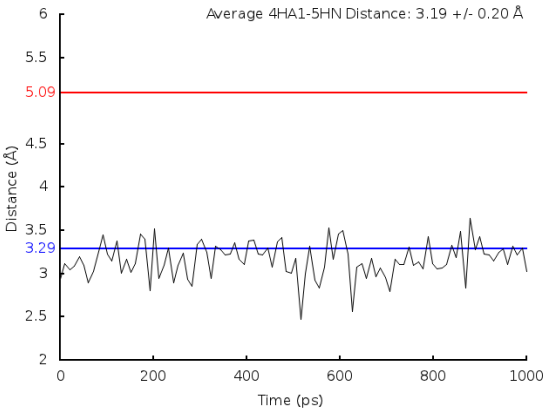
AD

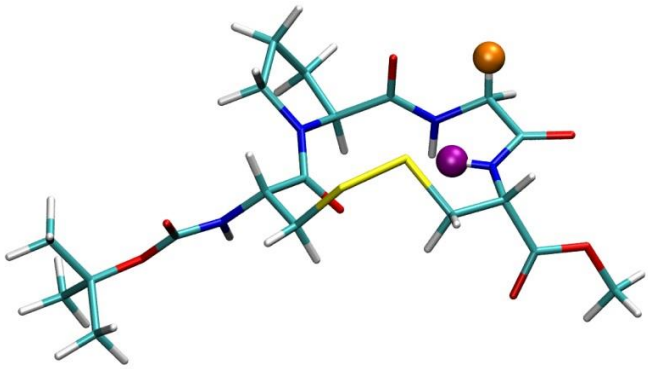




4HA1-4HA2

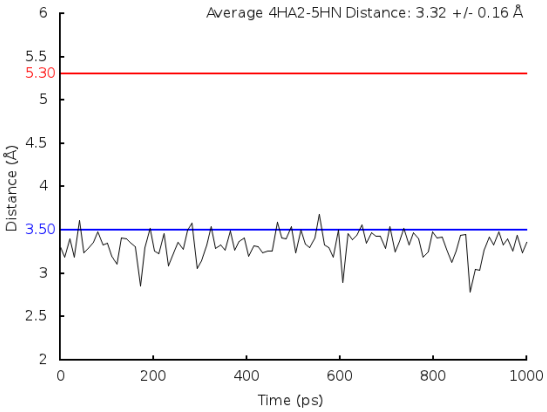
AE

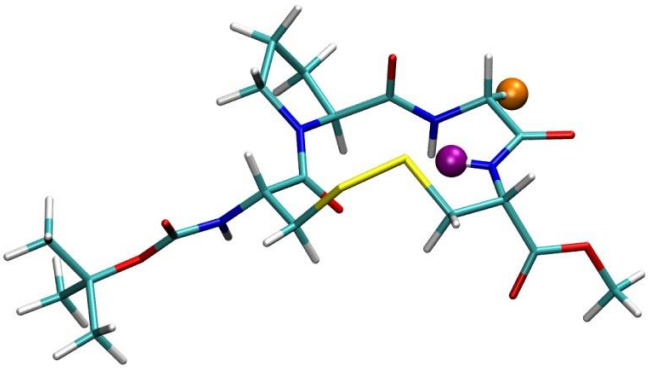




4HA1-5HN

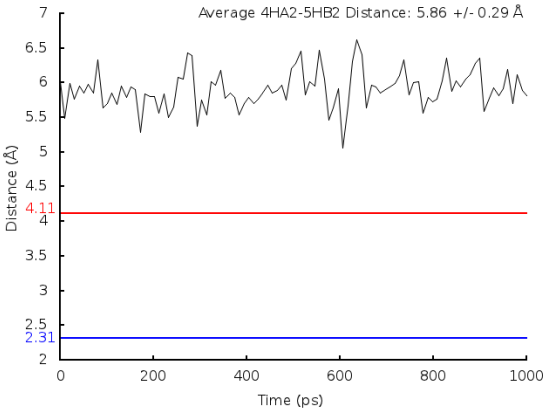
AF

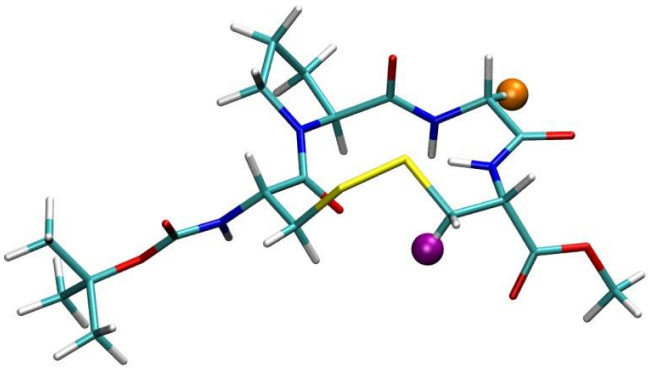




4HA2-5HN

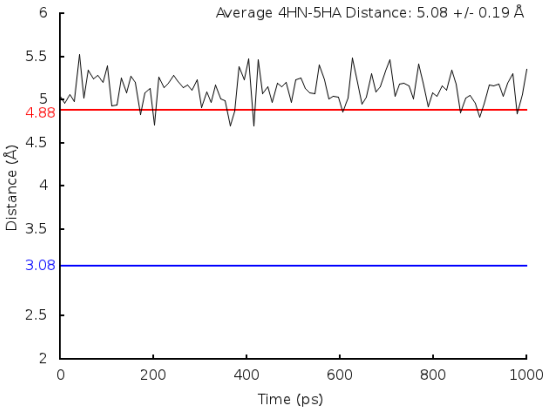
AG

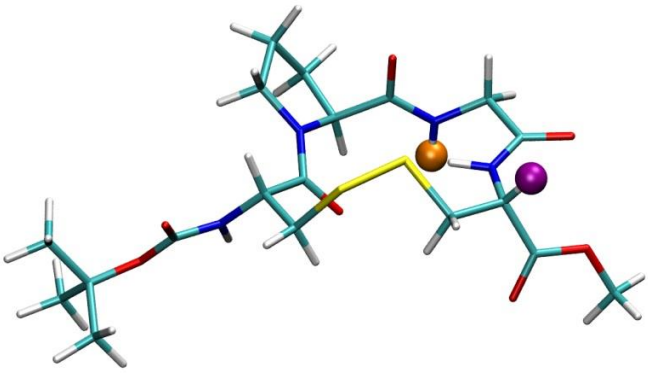




4HA2-5HB2

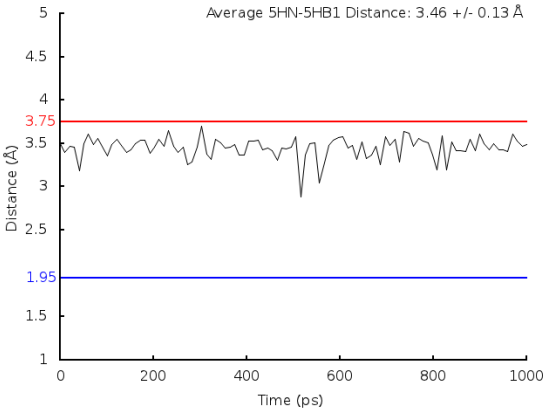
AH

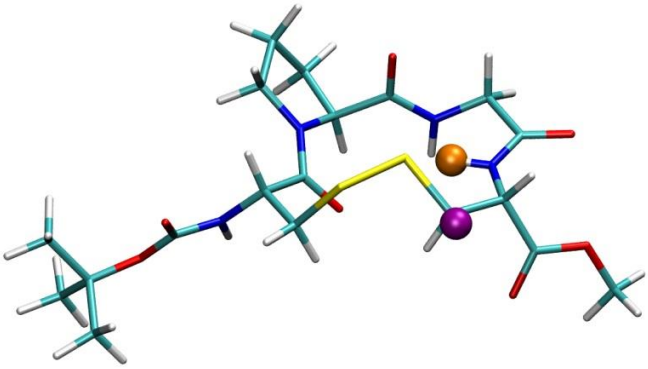




4HN-5HA

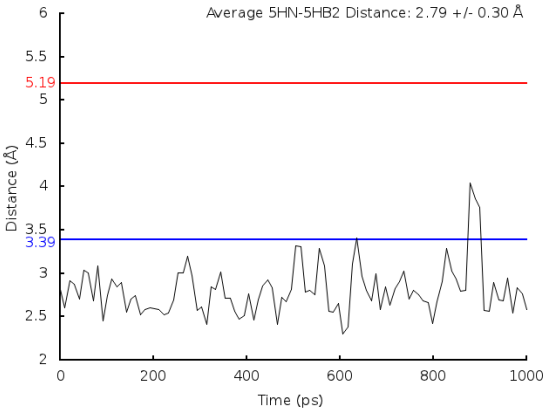
AI

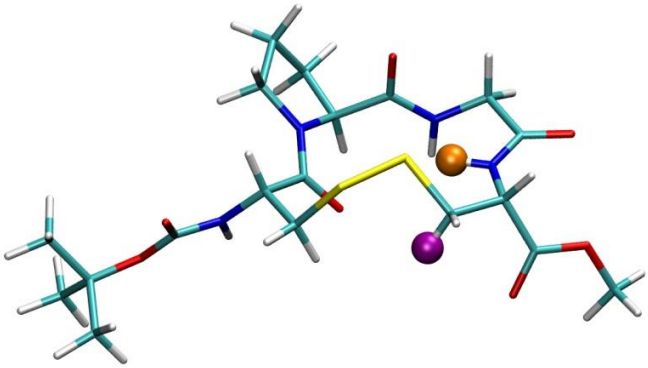




5HN-5HB1

AJ





5HN-5HB2

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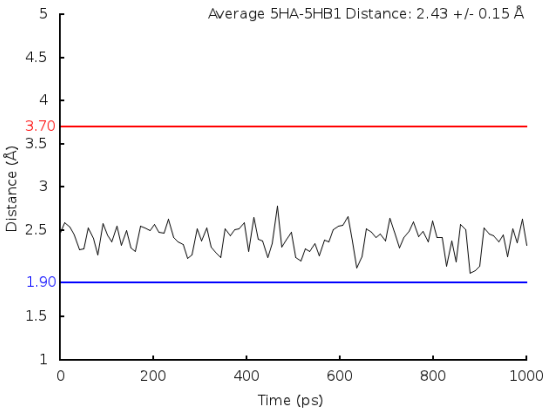
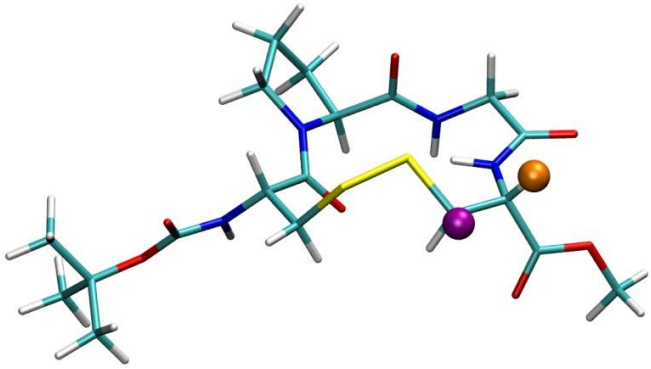
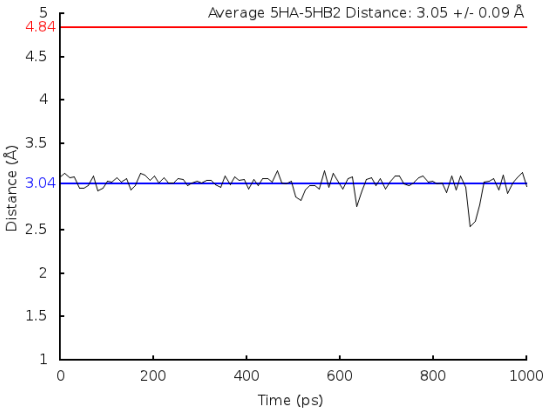
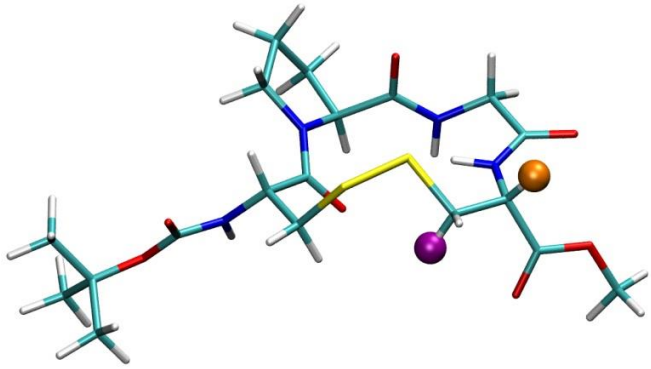




5HA-5HB1

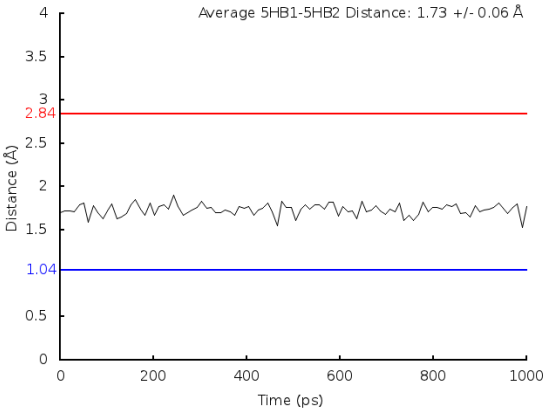
AL

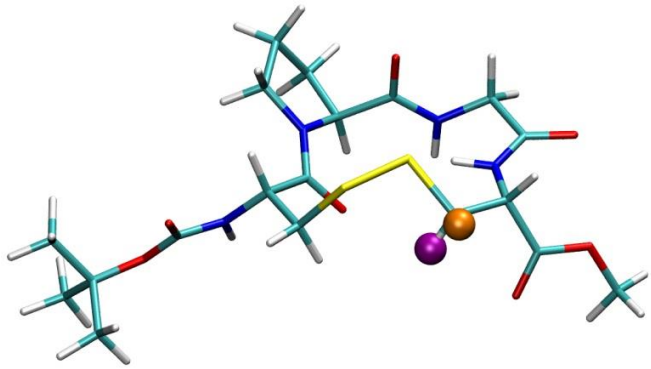




5HA-5HB2

AM





5HB1-5HB2

Table S7. Structural statistics of **1** in DMSO(d_6) as well as CD_3CN

1	DMSO(d_6)	CD_3CN
	Number of distance restraints	
All	43	39
Intraresidue, $\|i-j\| = 0$	24	23
Sequential, $\|i-j\| = 1$	15	15
Short-range, $\|i-j\| \leq 1$	39	38
Medium-range, $1 < \|i-j\| < 5$	4	1
Long-range, $\|i-j\| \geq 5$	0	0
	Energy (kcal/mol)	
E_{total}	9.51	9.84
E_{vdw}	1.88	1.16
E_{NOE}	0.82	1.74
E_{bonds}	0.38	0.45
E_{angles}	5.85	5.80
	RMSD (Å)	
Backbone average	0.20 ± 0.10	0.25 ± 0.20
Heavy atom average	0.48 ± 0.21	0.52 ± 0.11
Backbone average MD		0.37 ± 0.14
Heavy atom average MD		0.51 ± 0.20
	Number of restraints violations	
NOE > 0.5 Å	0	0
Dihedral angle > 5°	0	0

Table S8. Structural statistics of the NMR ensemble (20 energy lowest structures) considering hydrogen restraints

	1 in DMSO(d_6) (i+3)[a]	**1** in CD_3CN (i+3)[a]	**1** in DMSO(d_6) (i+2)[b]	**1** in CD_3CN (i+2)[b]
Energy (kcal/mol)				
E_{total}	6.15	12.63	8.07	8.70
E_{vdw}	0.47	2.10	1.70	0.93
E_{NOE}	0.89	1.60	1.30	1.65
E_{bonds}	0.20	0.66	0.30	0.41
E_{angles}	4.10	7.53	4.87	5.71
RMSD (Å)				
Backbone average	0.11 ± 0.14	0.21 ± 0.09	0.33 ± 0.11	0.24 ± 0.14
Heavy atom average	0.30 ± 0.25	0.41 ± 0.18	0.65 ± 0.22	0.49 ± 0.25

[a] hydrogen bond restraint between Cys(1) C=O and Cys(4) NH ($N^{\cdots}O$ = 3 Å, $N^{\cdots}H$ = 2 Å);
[b] hydrogen bond restraint between Cys(1) C=O and Cys(4) NH ($N^{\cdots}O$ = 3 Å, $N^{\cdots}H$ = 2 Å).

FTIR spectra.

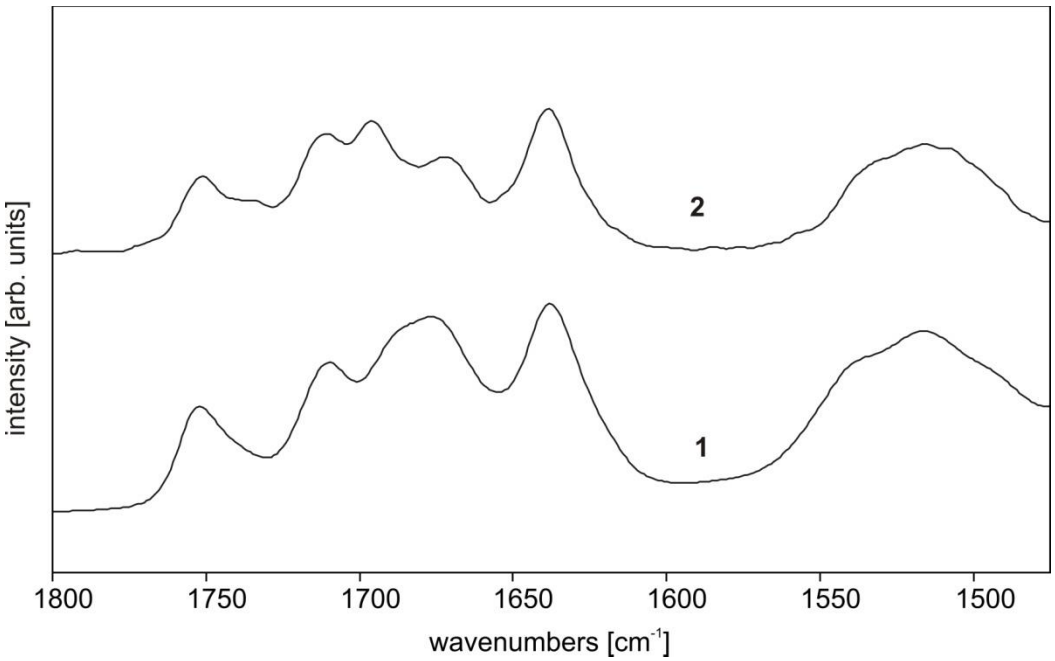


Figure S4. Static FTIR spectra of **1** and **2** in CH_3CN, resolution is 4 cm^{-1}, ~20 °C

Cartesian coordinates of relevant stationary points

acn-I

C	7.16860200	-1.72470800	0.44776200
H	6.89932900	-2.47645000	1.19266100
H	8.25640400	-1.71058300	0.35112500
H	6.72995900	-1.99195600	-0.51110600
C	7.32469100	0.01868900	2.24101000
H	8.40846300	0.08396800	2.13112000
H	7.09159100	-0.73884900	2.99090400
H	6.94670500	0.98264800	2.58534000
C	6.96876500	0.73300000	-0.13391300
H	6.55989900	1.68719600	0.20645700
H	6.53287900	0.47327400	-1.09635900
H	8.04861300	0.84643500	-0.25184300
C	6.69655000	-0.34959900	0.90410500
O	5.26376100	-0.38988600	1.22384900
O	4.60464300	-0.93731700	-0.89434600
C	4.36129100	-0.68402000	0.27149400
N	3.10521000	-0.63853600	0.79568100
H	3.01408300	-0.42949900	1.77668400
C	1.92999100	-0.92572900	-0.00698900
H	2.26688400	-0.95651400	-1.04511900
C	1.31822700	-2.27826900	0.36574600
H	0.61242100	-2.16400700	1.18762400
H	2.12552000	-2.94385400	0.67674600
S	0.54423500	-3.20583300	-1.00510000
C	0.93396200	0.22745800	0.18239300
O	-0.16028000	0.05423300	0.73138600
N	1.33581900	1.44441700	-0.21321200
C	0.45263400	2.59044600	0.00341000
H	0.18467500	2.65576700	1.05967200
C	1.30027200	3.78131500	-0.47773700
H	0.67973200	4.58912700	-0.86460000
H	1.88842200	4.16499800	0.35924400
C	2.21494700	3.16189600	-1.54094000
H	3.10414000	3.76105300	-1.73591200
H	1.65857100	3.02114500	-2.46667800
C	2.56436400	1.80122500	-0.93818600
H	2.81205300	1.05114300	-1.68751600
H	3.39970900	1.88304200	-0.23615400
C	-0.80577000	2.44621100	-0.85242800
O	-0.72945500	2.21010200	-2.05127000
N	-1.97404500	2.64029700	-0.19963900
H	-1.99299900	2.69835300	0.81000800
C	-3.23965600	2.47671700	-0.87361100
H	-3.10544200	2.72645500	-1.92684000
H	-3.98306000	3.14458200	-0.44328200
C	-3.80404100	1.06221300	-0.83261600
O	-4.97250800	0.84832900	-1.15209800
N	-2.95734300	0.07601900	-0.48629700
H	-2.03385000	0.27674300	-0.11858600
C	-3.38817400	-1.29179300	-0.59188100
H	-3.82824200	-1.46348900	-1.57752000
C	-2.20304100	-2.23163300	-0.36412400
H	-2.53580800	-3.26771700	-0.39271100
H	-1.73982700	-2.00397700	0.59716200
S	-0.95931400	-1.96690100	-1.68098100
C	-4.46722400	-1.62355400	0.43337700
O	-5.16112700	-2.69877300	0.04341100
C	-6.19590100	-3.12341000	0.94429200
H	-5.76810500	-3.36600300	1.91565500
H	-6.63929700	-4.00018500	0.48341500
H	-6.93271200	-2.32983100	1.05611600
O	-4.65505700	-1.04104200	1.47376000
C	-5.94774400	1.61165900	2.07539000
C	-4.60028300	2.14860800	2.24889600

N	-3.54114200	2.59419700	2.36671900
H	-6.08947200	1.36219500	1.02253100
H	-6.67706500	2.35613500	2.39220400
H	-6.04698100	0.70213400	2.66386600

acn-II

C	6.89465800	-1.73964600	0.24040000
H	6.61975300	-2.72218700	0.62954300
H	7.97695200	-1.62458000	0.33210400
H	6.61883500	-1.67675300	-0.80995300
C	6.62744400	-0.73397900	2.51947400
H	7.70152400	-0.56231200	2.60677800
H	6.39390000	-1.72095400	2.92167300
H	6.10073800	0.01953800	3.10714900
C	6.48190100	0.74661000	0.50443700
H	5.91915400	1.48807600	1.07580900
H	6.20824700	0.81380100	-0.54638600
H	7.54603900	0.96883200	0.60902000
C	6.21335900	-0.64831300	1.05701300
O	4.76691300	-0.89470800	1.12043500
O	4.43171100	-0.70708000	-1.13014600
C	4.02406700	-0.89881000	0.00204200
N	2.72293300	-1.16315800	0.31347400
H	2.47071700	-1.18068500	1.28952100
C	1.66577000	-1.09931800	-0.68459800
H	2.14918200	-0.92896000	-1.64387500
C	0.90407600	-2.41919000	-0.71407900
H	0.30631800	-2.53047500	0.19134200
H	1.63064000	-3.23287900	-0.75519800
S	-0.12969800	-2.68496000	-2.19432000
C	0.79011300	0.08533000	-0.25684100
O	-0.01906800	-0.05676100	0.67539900
N	1.06546500	1.27465100	-0.79718800
C	0.53503400	2.49917300	-0.19408900
H	0.66507100	2.44665800	0.88857400
C	1.38550300	3.59613100	-0.85221700
H	0.86152800	4.55086100	-0.88741500
H	2.30565100	3.72367200	-0.27737500
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H	2.56222400	3.48592900	-2.70459000
H	0.82154500	3.16607400	-2.88768500
C	1.90319900	1.53307800	-1.98576400
H	1.56303300	0.92348800	-2.82279900
H	2.94681800	1.29695300	-1.76885500
C	-0.94387000	2.66820900	-0.53646500
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C	-6.49701200	-2.69362900	0.93386800
H	-7.00951900	-1.92009700	1.50239000
H	-5.97598400	-3.36502000	1.61430600
H	-7.19154500	-3.23823200	0.30251800
O	-4.47725000	-1.23205400	1.80599400

C	-1.63054100	-0.52997900	3.40836000
C	-1.32592400	0.89708600	3.42671100
N	-1.08474000	2.02706000	3.42559100
H	-1.57979800	-0.92862500	4.42071700
H	-2.63016300	-0.68099800	2.99698500
H	-0.89913500	-1.02133000	2.76739000

III

C	6.20251200	1.44532100	-0.01230600
H	5.71963800	2.23359400	-0.59389800
H	7.27139000	1.66361100	0.04114200
H	5.79152800	1.43395100	0.99482700
C	6.60383700	0.12241200	-2.10126400
H	6.42212800	-0.82783800	-2.60566400
H	7.68046500	0.28954500	-2.03910000
H	6.15526400	0.92396000	-2.69026600
C	6.58539900	-1.05580600	0.10951900
H	6.37006800	-2.00336000	-0.38867200
H	6.17309400	-1.07468700	1.11607600
H	7.66957400	-0.93754800	0.17014900
C	6.00798600	0.09913000	-0.70030900
O	4.58362700	-0.13213600	-0.96227000
O	3.97068900	-0.11881800	1.23937100
C	3.70830900	-0.22142800	0.05287100
N	2.45680500	-0.46402900	-0.42329600
H	2.27524400	-0.35223400	-1.40976300
C	1.31985100	-0.42456600	0.47991600
H	1.60921400	-0.91491700	1.40715200
C	0.92513700	1.03108000	0.75598800
H	0.51293000	1.48277700	-0.14397900
H	1.83362500	1.56339100	1.04941100
S	-0.16945600	1.29628600	2.19406400
C	0.21982500	-1.17499900	-0.27036900
O	-0.06559100	-0.80377100	-1.41921700
N	-0.34846200	-2.24468100	0.29377600
C	-1.29060100	-3.06789000	-0.47808900
H	-0.83313300	-3.31780000	-1.43725300
C	-1.49703800	-4.28905600	0.42562500
H	-2.47804400	-4.73615500	0.27787400
H	-0.72666700	-5.03179100	0.20551900
C	-1.31209700	-3.72136400	1.83738800
H	-1.08962600	-4.48694600	2.57992900
H	-2.21419000	-3.18290200	2.12732200
C	-0.15584200	-2.73584800	1.66992400
H	-0.20256400	-1.91455100	2.38414700
H	0.81463800	-3.23316300	1.75413200
C	-2.61813500	-2.33210200	-0.72671600
O	-3.51945300	-2.32350600	0.10028800
N	-2.73222700	-1.74432200	-1.94395600
H	-1.87321200	-1.57768900	-2.44791000
C	-3.92156500	-0.98385800	-2.25873100
H	-4.80535900	-1.56437600	-2.00278400
H	-3.93542600	-0.77306500	-3.32837300
C	-4.05640700	0.33557300	-1.50305400
O	-5.16067800	0.81296600	-1.28049500
N	-2.90164000	0.94764100	-1.14278100
H	-2.01003600	0.48291000	-1.26823600
C	-2.96688200	2.07084600	-0.24471000
H	-3.86964600	2.63808300	-0.48731000
C	-3.10609700	1.62221800	1.21977800
H	-4.07976100	1.13799600	1.32365300
H	-3.05014000	2.46798400	1.90315900
S	-1.94097800	0.31968900	1.73942000
C	-1.78677100	2.99329700	-0.45810700
O	-1.88898100	4.07890600	0.31415800
C	-0.77720800	4.98748000	0.24421700
H	0.12678300	4.48232600	0.58197100
H	-1.03284000	5.80730200	0.90755500

H	-0.64518600	5.33547700	-0.77830100
O	-0.87454200	2.79456200	-1.22607100

IV

C	-6.73250400	-1.60483600	-0.15928300
H	-6.52062500	-2.65886000	-0.35015700
H	-7.80875600	-1.44747300	-0.25775500
H	-6.42847400	-1.35284200	0.85437100
C	-6.45815900	-1.09124200	-2.59596000
H	-5.90710200	-0.49840400	-3.32769400
H	-7.52419200	-0.88639100	-2.70661200
H	-6.27954000	-2.14904900	-2.79425000
C	-6.19891600	0.75278300	-0.91986800
H	-5.89533700	1.01295800	0.09183400
H	-7.25312500	1.00592000	-1.05183800
H	-5.61453800	1.33377900	-1.63669100
C	-6.01279500	-0.73651800	-1.18402600
O	-4.58211100	-1.06838600	-1.20816900
O	-4.19591300	-0.45522500	0.95619300
C	-3.82305200	-0.90585600	-0.11372300
N	-2.55399600	-1.34194200	-0.36068800
H	-2.30422500	-1.51437500	-1.32291700
C	-1.48009800	-1.11419500	0.59561300
H	-1.95135700	-0.90730600	1.55317300
C	-0.62327300	-2.37134200	0.69136900
H	-0.01299000	-2.48078200	-0.20643700
H	-1.28738300	-3.23416500	0.76860900
S	0.41573100	-2.47935500	2.18339900
C	-0.71146200	0.09724300	0.05080300
O	-0.03523200	-0.03208800	-0.98291900
N	-0.94694000	1.28835000	0.61117500
C	-0.63250500	2.52227700	-0.11925000
H	-0.98559200	2.41400400	-1.14699100
C	-1.40694200	3.58885200	0.66578400
H	-0.93784000	4.56793700	0.58595100
H	-2.42559100	3.64684100	0.27545300
C	-1.41027100	3.04695100	2.09950600
H	-2.19960700	3.48016700	2.71290800
H	-0.44287000	3.24431200	2.55904000
C	-1.60546200	1.54143500	1.90991200
H	-1.11825800	0.96027300	2.69309900
H	-2.66050300	1.26664400	1.85185500
C	0.87045700	2.82168900	-0.12666000
O	1.44116300	3.28807900	0.84771200
N	1.49530300	2.57551400	-1.30685200
H	1.00884700	1.99251700	-1.97110000
C	2.92913300	2.73215700	-1.41542100
H	3.22893900	3.63828900	-0.89170700
H	3.20828400	2.82694900	-2.46444200
C	3.74644800	1.59454900	-0.81780700
O	4.96084400	1.69099600	-0.70281600
N	3.06623700	0.49259300	-0.43262000
H	2.08210700	0.37908900	-0.64448600
C	3.80816300	-0.60464500	0.12621500
H	4.45509000	-0.23946500	0.92634100
C	2.84687500	-1.67059200	0.64769400
H	3.40068000	-2.49654100	1.09067700
H	2.23239400	-2.03427900	-0.17814500
S	1.75180400	-0.92625400	1.91306000
C	4.70407200	-1.24836600	-0.93060100
O	5.74530500	-1.86046800	-0.35711200
C	6.64622800	-2.50908400	-1.27044500
H	6.12023700	-3.28637700	-1.82227000
H	7.43101300	-2.93224500	-0.65168700
H	7.04922300	-1.77619400	-1.96653300
O	4.47852800	-1.25470400	-2.11478600