Synthesis of Highly Structured and Receptor-Selective Tetradecapeptidic Analogs of Somatostatin:

Fine-tuning the non-covalent interactions among their aromatic residues

Pablo Martín-Gago

Synthesis of Highly Structured and Receptor-Selective Tetradecapeptidic Analogs of Somatostatin: Fine-tuning the non-covalent interactions among their aromatic residues.

Supplementary Mateterial

Pablo Martín-Gago

Facultad de Química

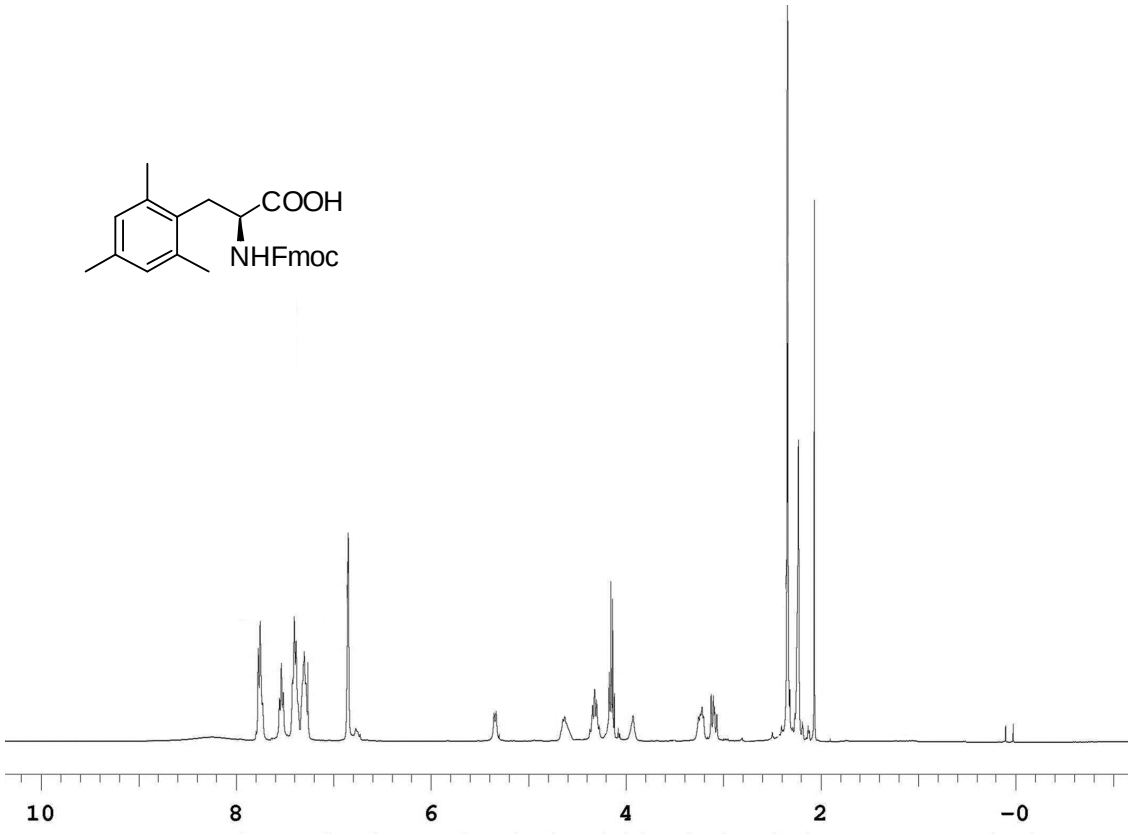
Departamento de Química Orgánica

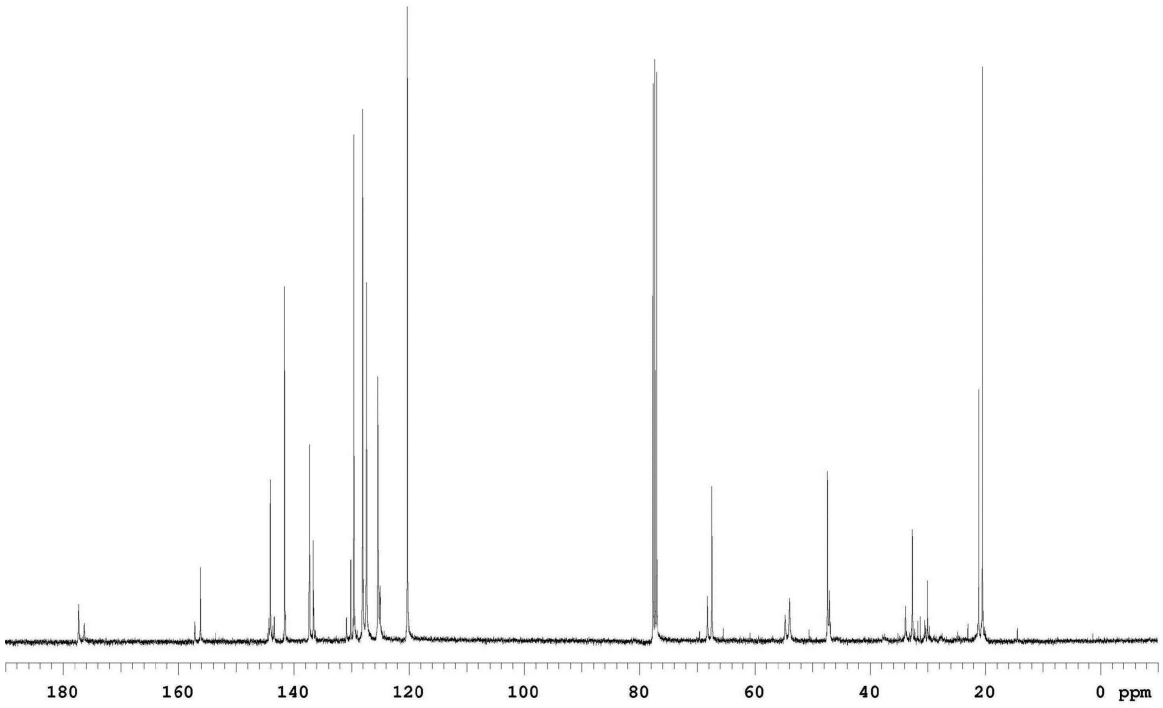
Programa de doctorado: Química Orgánica Bienio 2010-2012

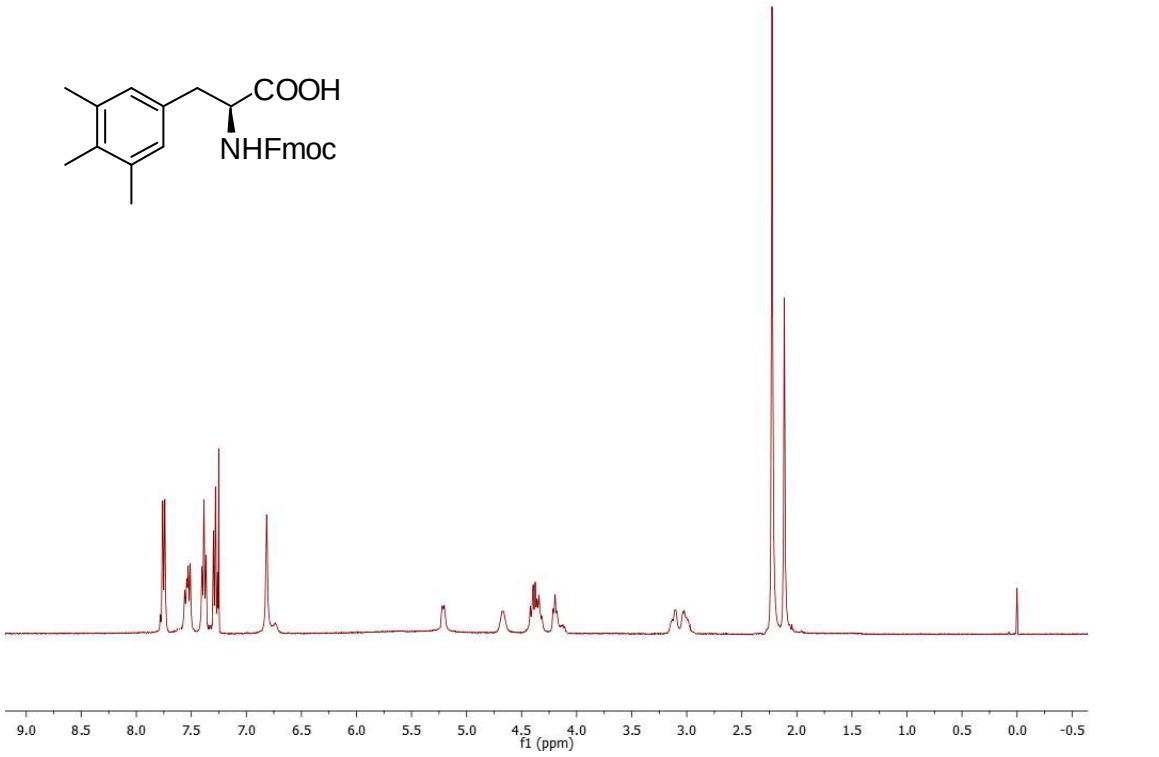
Director de tesis: Antoni Riera Escalé

Part I

Spectra of the final products:



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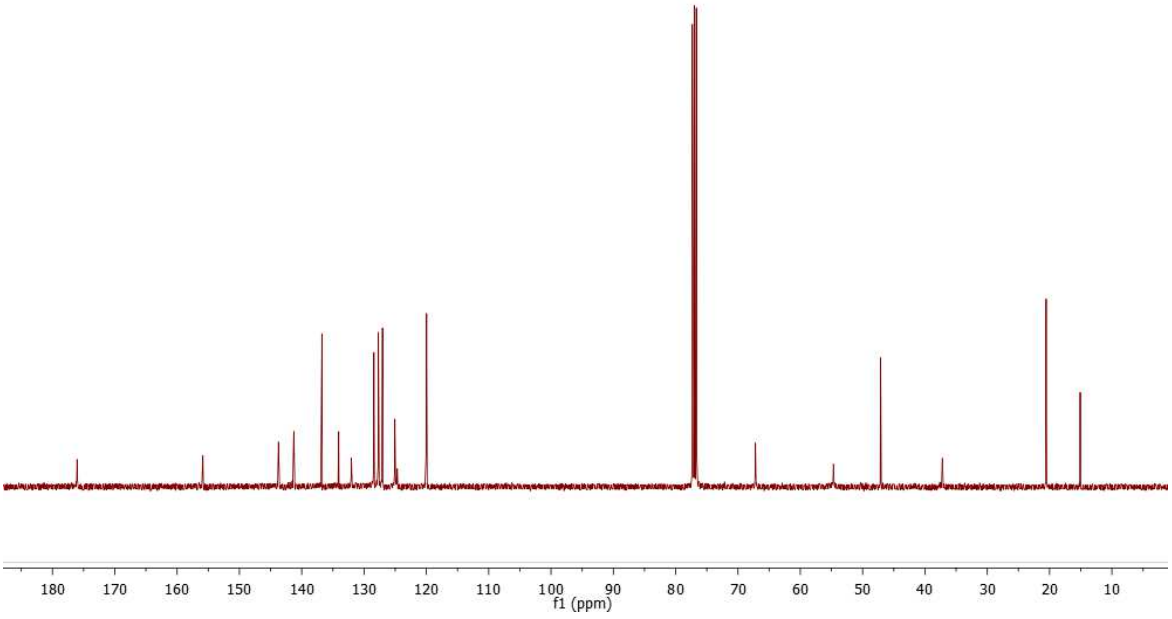
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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170
160
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60
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30
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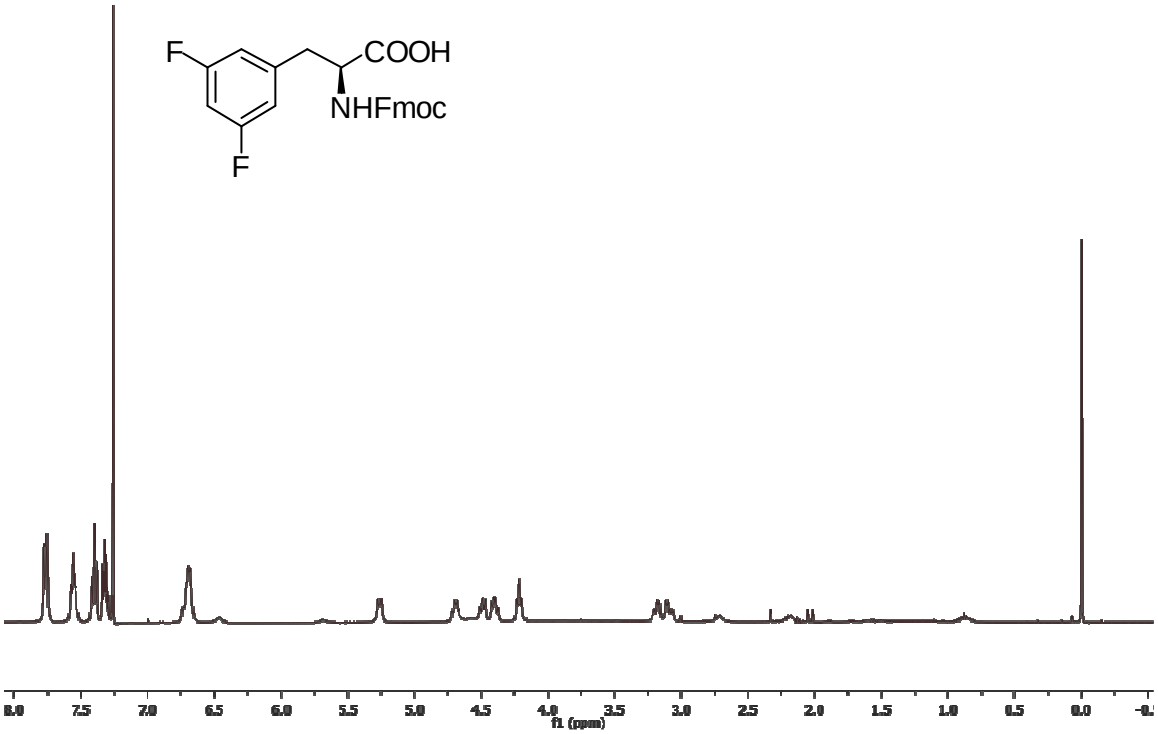
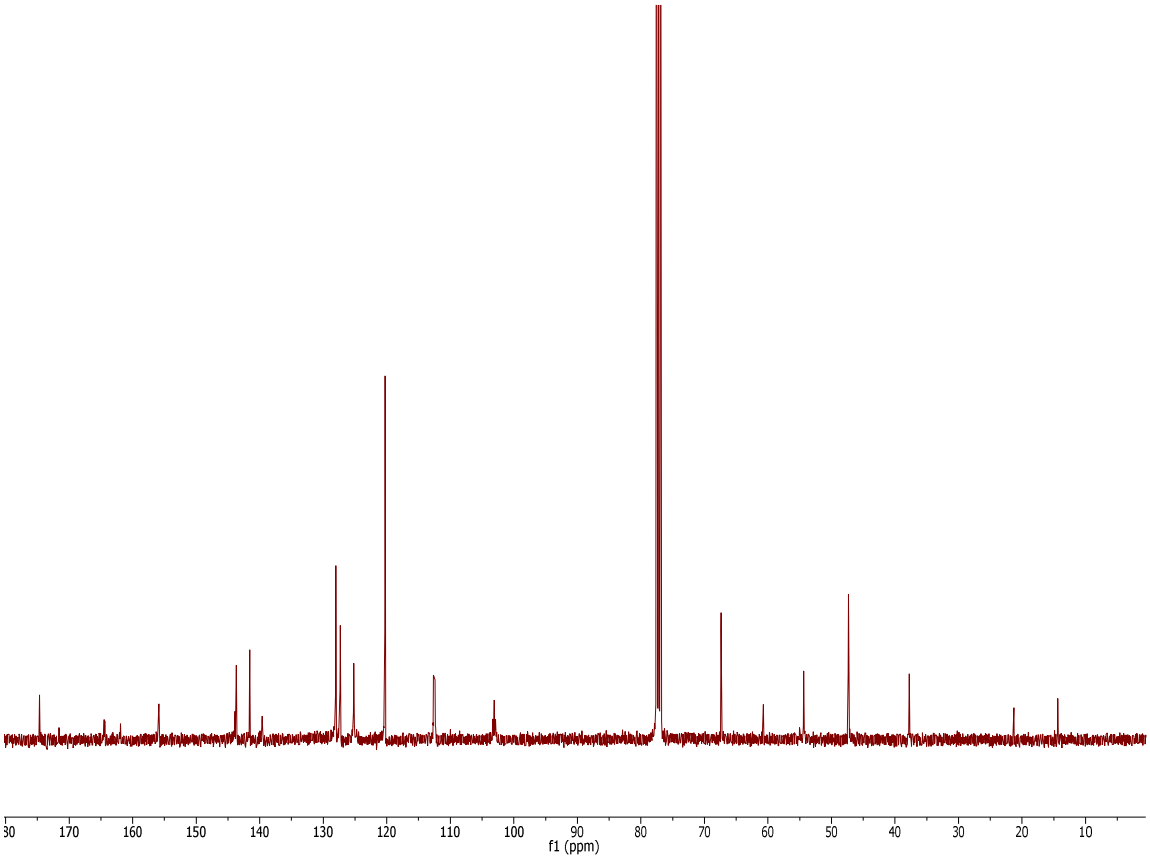
10
f1 (ppm)


F
COOH
NHFmoc
F
f1 (ppm)

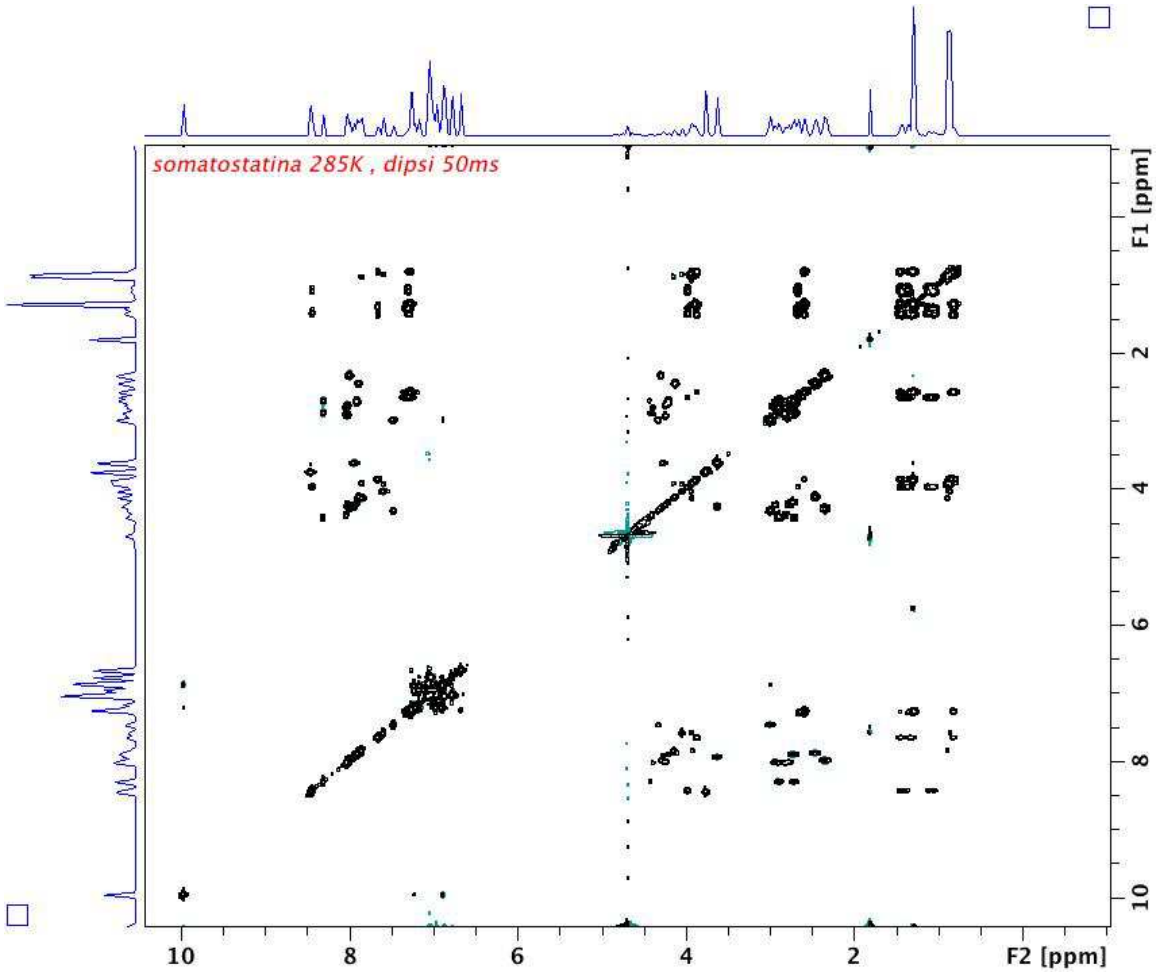

f1 (ppm)

Part II

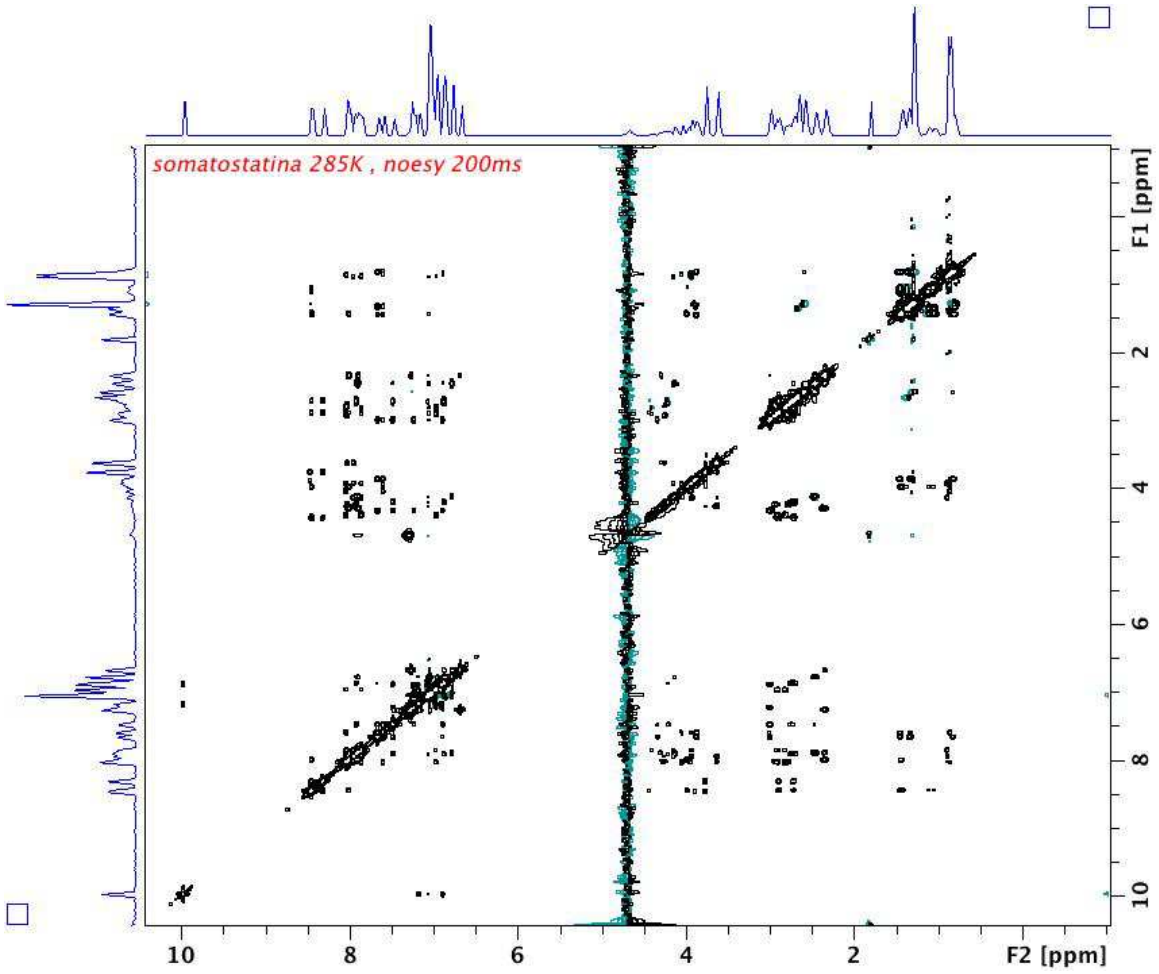
Full characterization of SRIF analogs (in order of appearance):

Control Compounds:

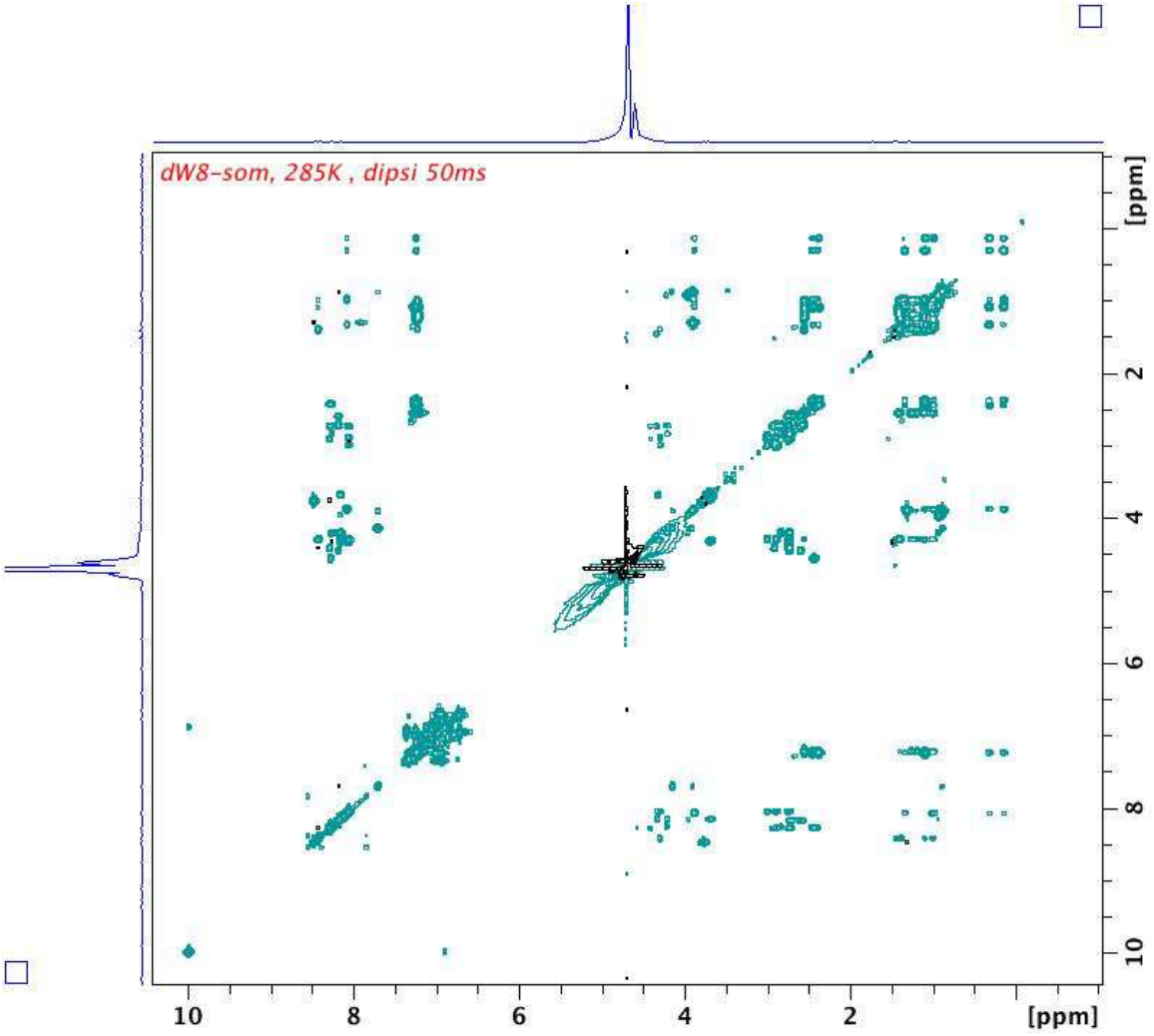
SRIF, TOCSY 50 ms



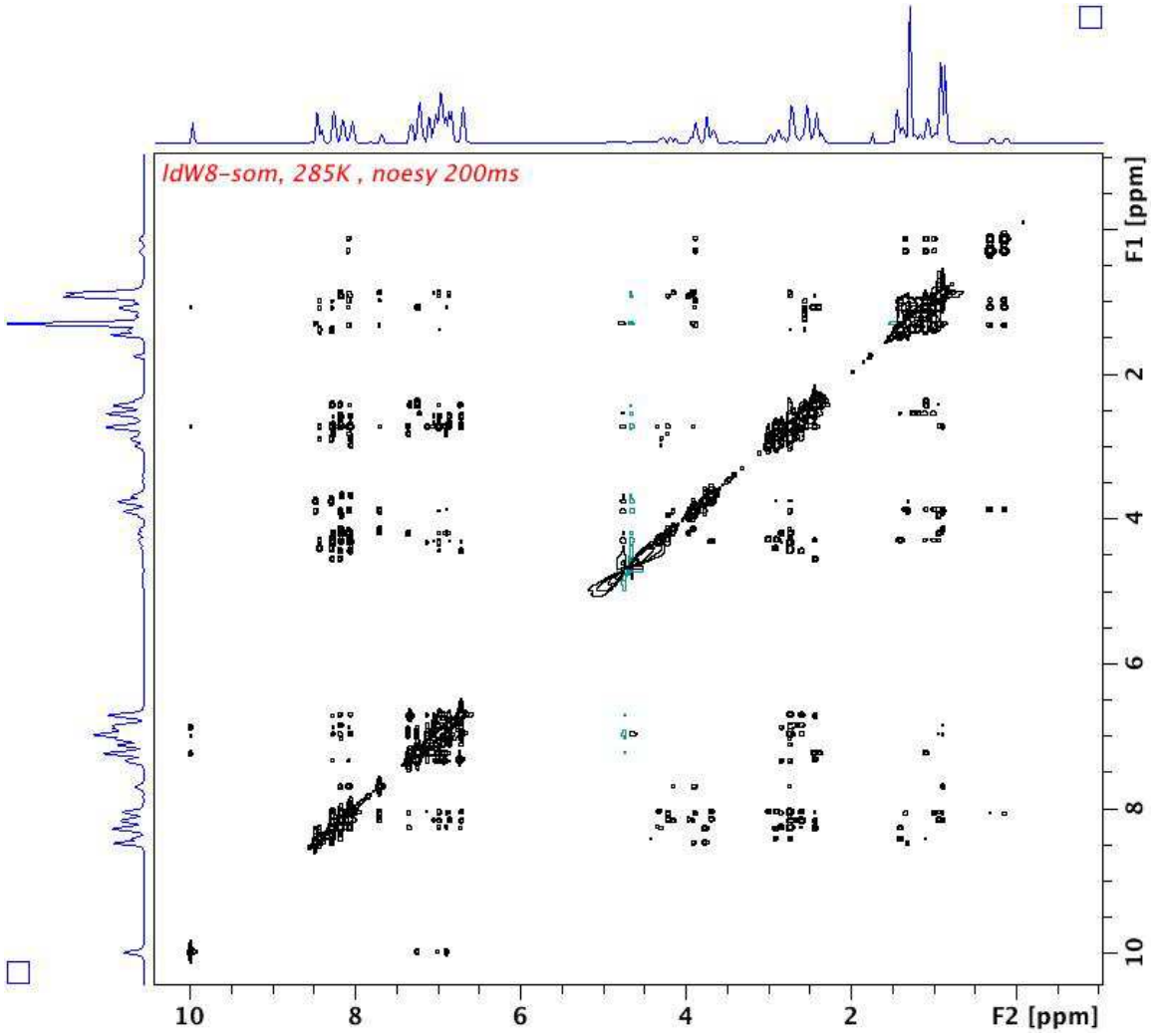
SRIF, NOESY 200 ms



[D-Trp8]-SRIF, TOCSY 50 ms



[D-Trp8]-SRIF, NOESY 200 ms



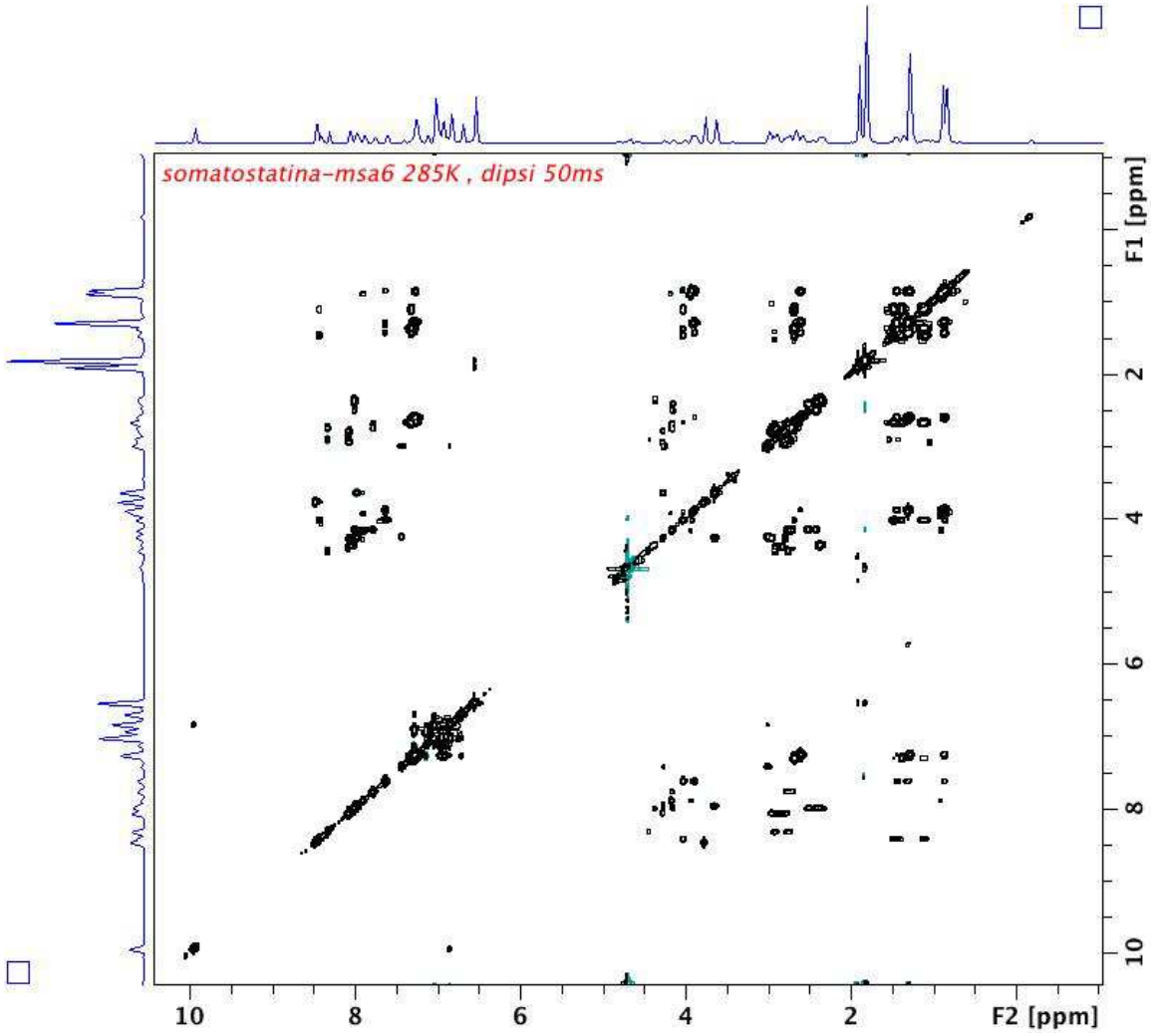
Analogs containing the Msa amino acid:

[L-Msa6]-SRIF, 45: Somatostatin analog **45** was synthesized following the general procedure from 0.136g of 2-Cl-Trt resin (1.60 mmol/g) and using Fmoc-L-Msa-OH, affording 0.20 g in 60% yield (95% purity after purification). HPLC: t_R = 14.3 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for $C_{79}H_{110}N_{18}O_{19}S_2$: 1678.8; found, 1680.2.

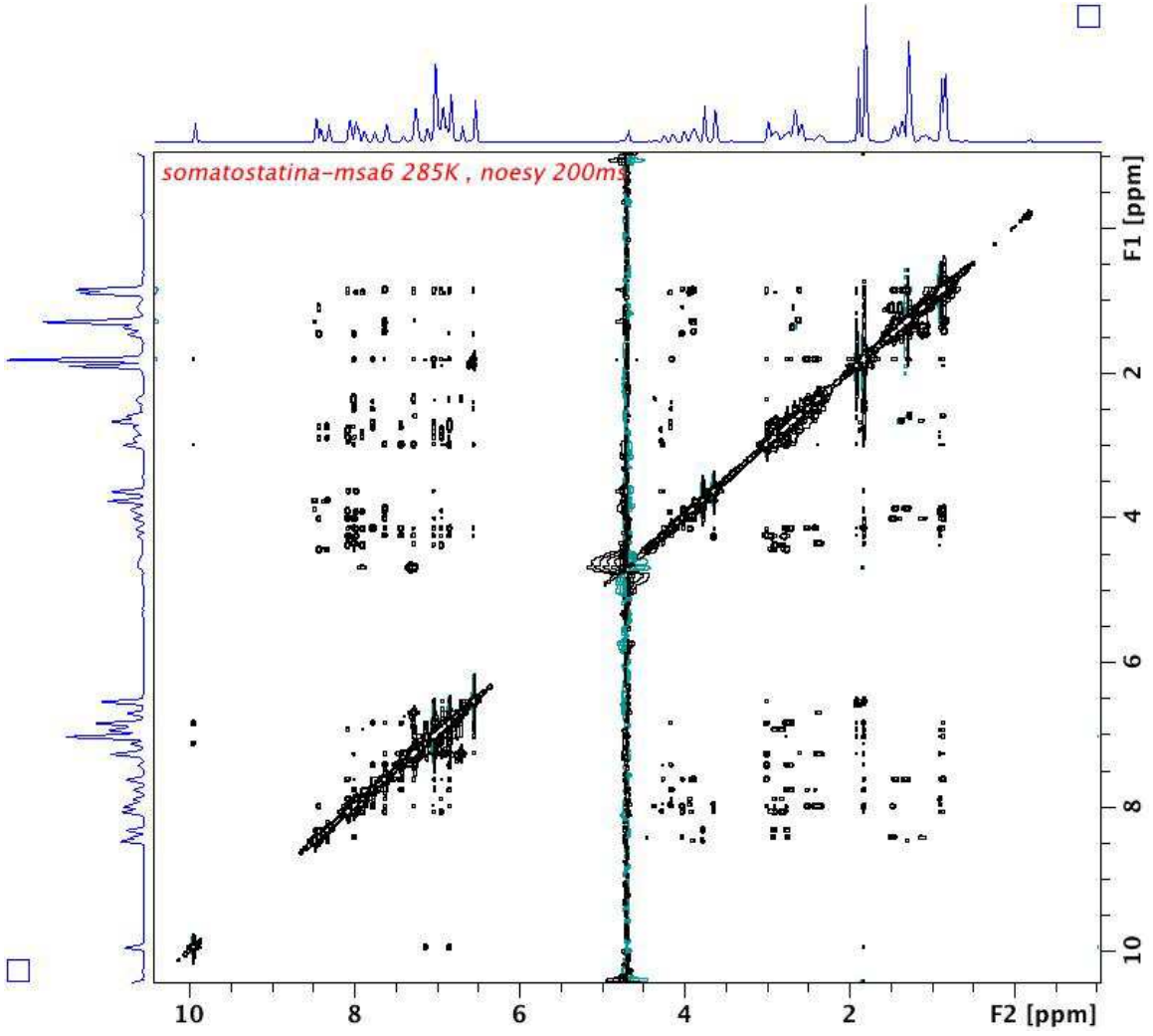
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.90	H^α 3.89	H^β 1.29		
2 Gly	H^N 8.47	H^α 3.77			
3 Cys	H^N 8.32	H^α 4.44	H^β 2.81		
4 Lys	H^N 8.42	H^α 4.02	H^β 1.47	H^γ 1.10	H^δ 1.37
				H^ε 2.68	H^Z 7.30
5 Asn	H^N 7.99	H^α 4.36	H^β 2.36	H^δ 6.98	
6 Msa	H^N 7.99	H^α 4.15	H^β 2.45	H^E 6.54	H^F 1.1
					H^H 1.90
7 Phe	H^N 7.78	H^α 4.15	H^β 2.72	H^D 6.84	H^E 7.03
8 Trp	H^N 7.42	H^α 4.25	H^β 2.99	H^{D1} 7.00	H^{E3} 7.27
		H^{H2} 6.99	H^{E1} 9.94	H^{Z3} 6.90	H^{Z2} 7.13
9 Lys	H^N 7.62	H^α 3.87	H^β 1.37	H^γ 0.85	H^δ 1.27
			H^ε 2.60		H^Z 7.26
10 Thr	H^N 7.62	H^α 4.01	H^β 3.91	H^γ 0.85	
11 Phe	H^N 8.07	H^α 4.38	H^β 2.86	H^D 6.99	H^E 7.03
12 Thr	H^N 7.89	H^α 4.16	H^β 3.92	H^γ 0.88	
13 Ser	H^N 7.96	H^α 4.26	H^β 3.64		
14 Cys	H^N 8.06	H^α 4.27	H^β 2.86		

TOCSY 50 ms



NOESY 200 ms



Structural Statistics for the 25 Lowest Energy Structures of [L-Msa6]-SRIF

Restraints used for the calculation ‹SA›[a]	
Intraresidual	0
Sequential (|i-j| =1)	56
Medium range(1 < |i-j| ≤ 4)	18
Long range (|i-j| > 4)	18
Unambiguous	All
Ambiguous	0
All	92
Restraint per residue ratio	6.6
Dihedral angle restrictions	24
RSMD (Å) from experimental[b]	0.02548 ± 0.00117
NOE:	$0.01224 \pm 4.5 \times 10^{-3}$
Bonds (Å)	1.755± 0.0147
Angles (°)	
Coordinate Precision (Å)[c]	0.61
All Atoms	
CNS potential energy (kcal mol^{-1})	28.31 ± 39.86
Total energy[d]	-388.1 ± 28.5
Electrostatic	34.28 ± 10.15
Van der Waals	35.53 ± 2.61
Bonds	199.2 ± 32.9
Angles	

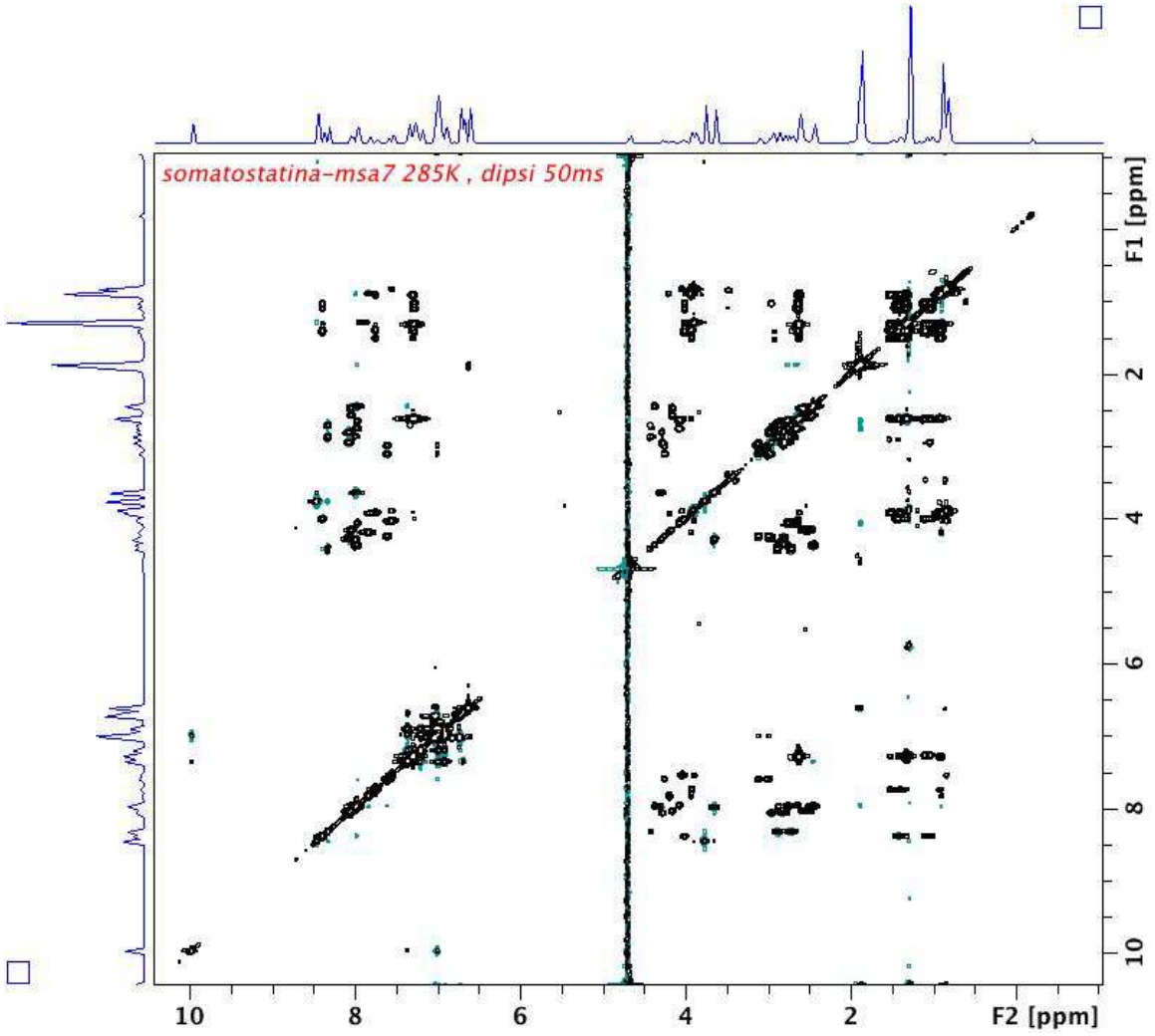
[a] ‹SA› refers to the ensemble of the 25 structures with the lowest energy.
[b] R.m.s deviation between the ensemble of structures <SA> and the lowest energy structure.
[c] No distance restraint in any of the structures included in the ensemble was violated by more than 0.3 Å.
[d] $E_{L\text{-}J}$ is the Lennard-Jones van der Waals energy calculated using the CHARMM-PARMALLH6 parameters. $E_{L\text{-}J}$ was not included in the target function during the structure calculation.

[**L-Msa7]-SRIF, 46:** Somatostatin analog **46** was synthesized following the general procedure from 0.136 g of 2-Cl-Trt resin (1.60 mmol/g) and using Fmoc-L-Msa-OH, affording 0.24 g in 22% yield and 73.8% of purity (97% purity after purification). HPLC: t_R = 14.8 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for $C_{79}H_{110}N_{18}O_{19}S_2$: 1678.8; found, 1679.8.

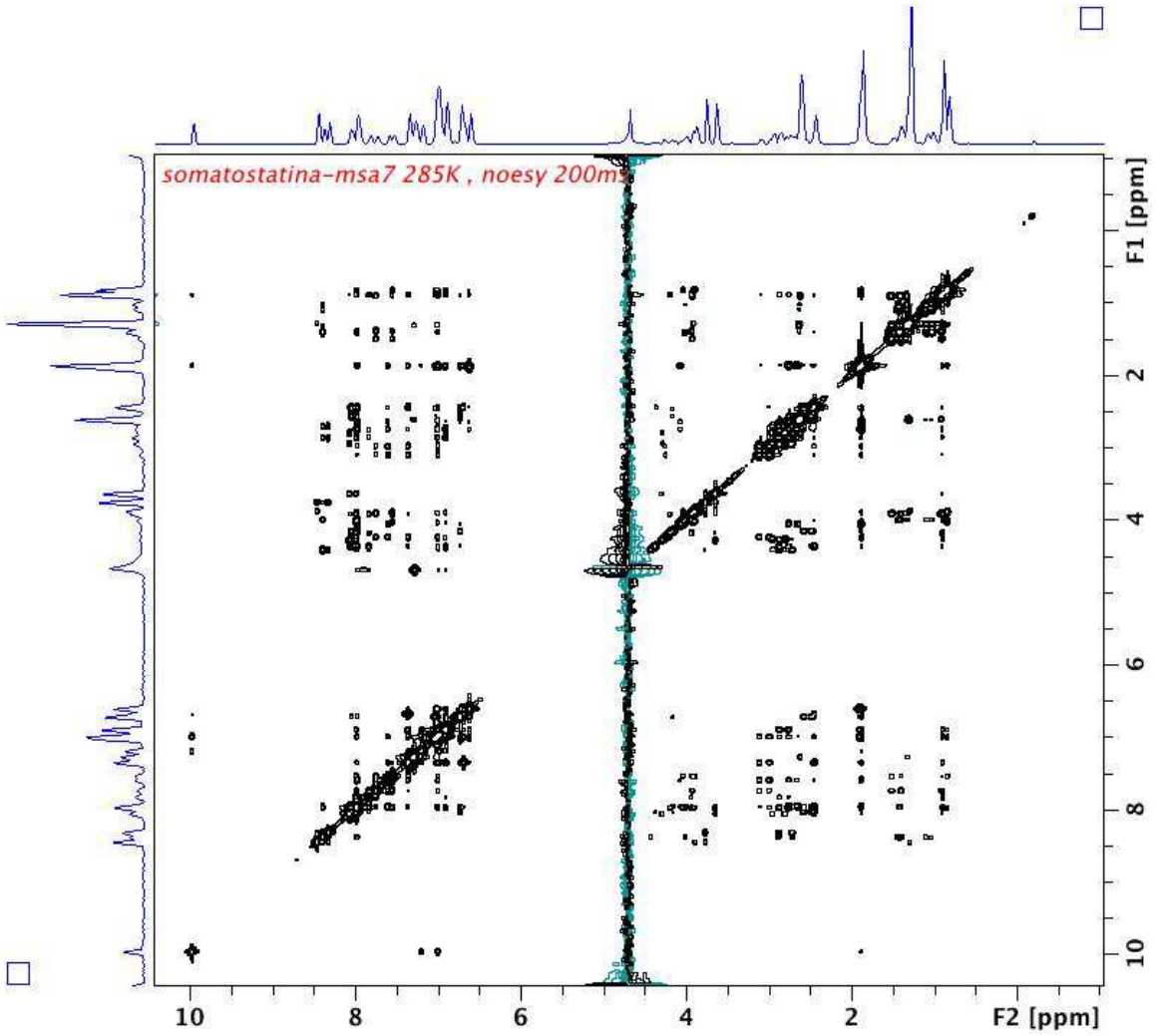
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.89	H^α 3.88	H^β 1.29		
2 Gly	H^N 8.45	H^α 3.76			
3 Cys	H^N 8.32	H^α 4.41	H^β 2.79		
4 Lys	H^N 8.38	H^α 4.49	H^β 1.40	H^γ 1.04	H^δ 1.31
				H^ε 2.62	H^Z 7.27
5 Asn	H^N 8.24	H^α 4.36	H^β 2.44	H^δ 7.07	
6 Phe	H^N 8.04	H^α 4.93	H^β 2.52	H^D 6.72	H^E 7.02
7 Msa	H^N 7.96	H^α 4.05	H^β 2.75	H^E 6.61	H^F 1.87
					H^H 1.90
8 Trp	H^N 7.59	H^α 4.24	H^β 3.01	H^{D1} 7.00	H^{E3} 7.35
		H^{H2} 6.99	H^{E1} 9.96	H^{Z3} 6.90	H^{Z2} 7.19
9 Lys	H^N 7.74	H^α 3.91	H^β 1.44	$H^{\gamma 1}$ 0.90	H^δ 1.06
			H^ε 2.40		H^Z 7.28
10 Thr	H^N 7.54	H^α 4.08	H^β 3.85	H^γ 0.83	
11 Phe	H^N 7.98	H^α 4.37	H^β 2.80	H^D 6.90	H^E 7.00
12 Thr	H^N 7.82	H^α 4.18	H^β 3.92	H^γ 0.89	
13 Ser	H^N 7.98	H^α 4.29	H^β 3.64		
14 Cys	H^N 8.06	H^α 4.27	H^β 2.89		

TOCSY 50 ms



NOESY 200 ms



Structural Statistics for the 25 Lowest Energy Structures of [L-Msa7]-SRIF

Restraints used for the calculation ‹SA›[a]	
Intraresidual	0
Sequential (|i-j| =1)	65
Medium range(1 < |i-j| ≤ 4)	14
Long range (|i-j| > 4)	14
Unambiguous	All
Ambiguous	0
All	93
Restraint per residue ratio	6.6
RSMD (Å) from experimental[b]	
NOE:	0.1585 ± 0.0679
Bonds (Å)	$0.011 \pm 3.0 \times 10^{-3}$
Angles (º)	1.58± 0.02
Coordinate Precision (Å)[c]	
All Atoms	0.63
CNS potential energy (kcal mol^{-1})	
Total energy[d]	213.7 ± 17.6
Electrostatic	-409.6 ± 19.7
Van der Waals	12.2 ± 7.5
Bonds	28.91 ± 17.49
Angles	151.6 ± 42.7

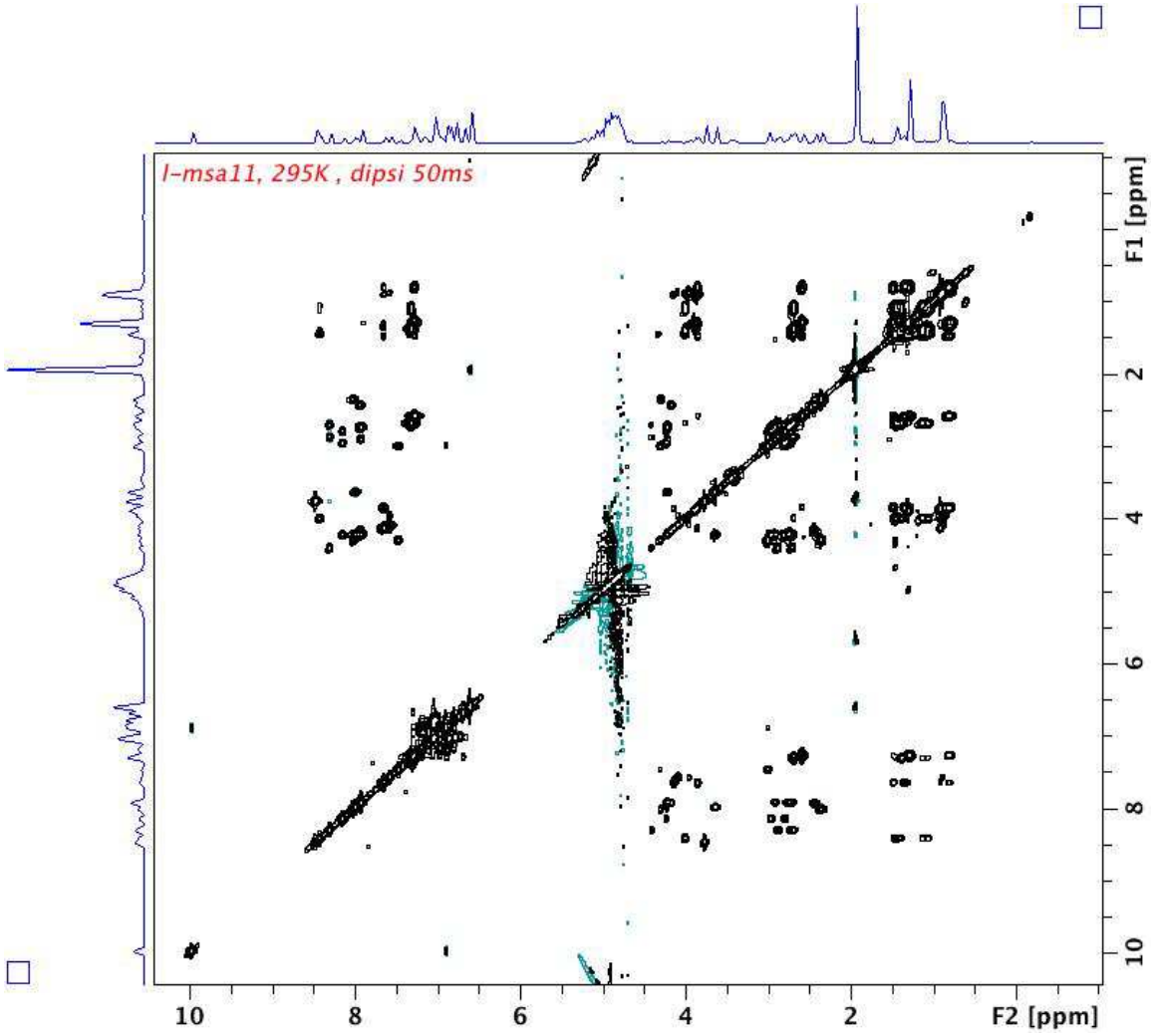
[a] ‹SA› refers to the ensemble of the 25 structures with the lowest energy.
[b] R.m.s deviation between the ensemble of structures <SA> and the lowest energy structure.
[c] No distance restraint in any of the structures included in the ensemble was violated by more than 0.3 Å.
[d] E_{L-J} is the Lennard-Jones van der Waals energy calculated using the CHARMM-PARMALLH6 parameters. E_{L-J} was not included in the target function during the structure calculation.

[**L-Msa11]-SRIF, 47:** Somatostatin analog **47** was synthesized following the general procedure from 0.136 g of 2-Cl-Trt resin (1.60 mmol/g) and using Fmoc-L-Msa-OH, affording 0.28 g in 44% yield (99% purity after purification). HPLC: t_R = 14.1 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for $C_{79}H_{110}N_{18}O_{19}S_2$: 1678.8; found, 1680.0.

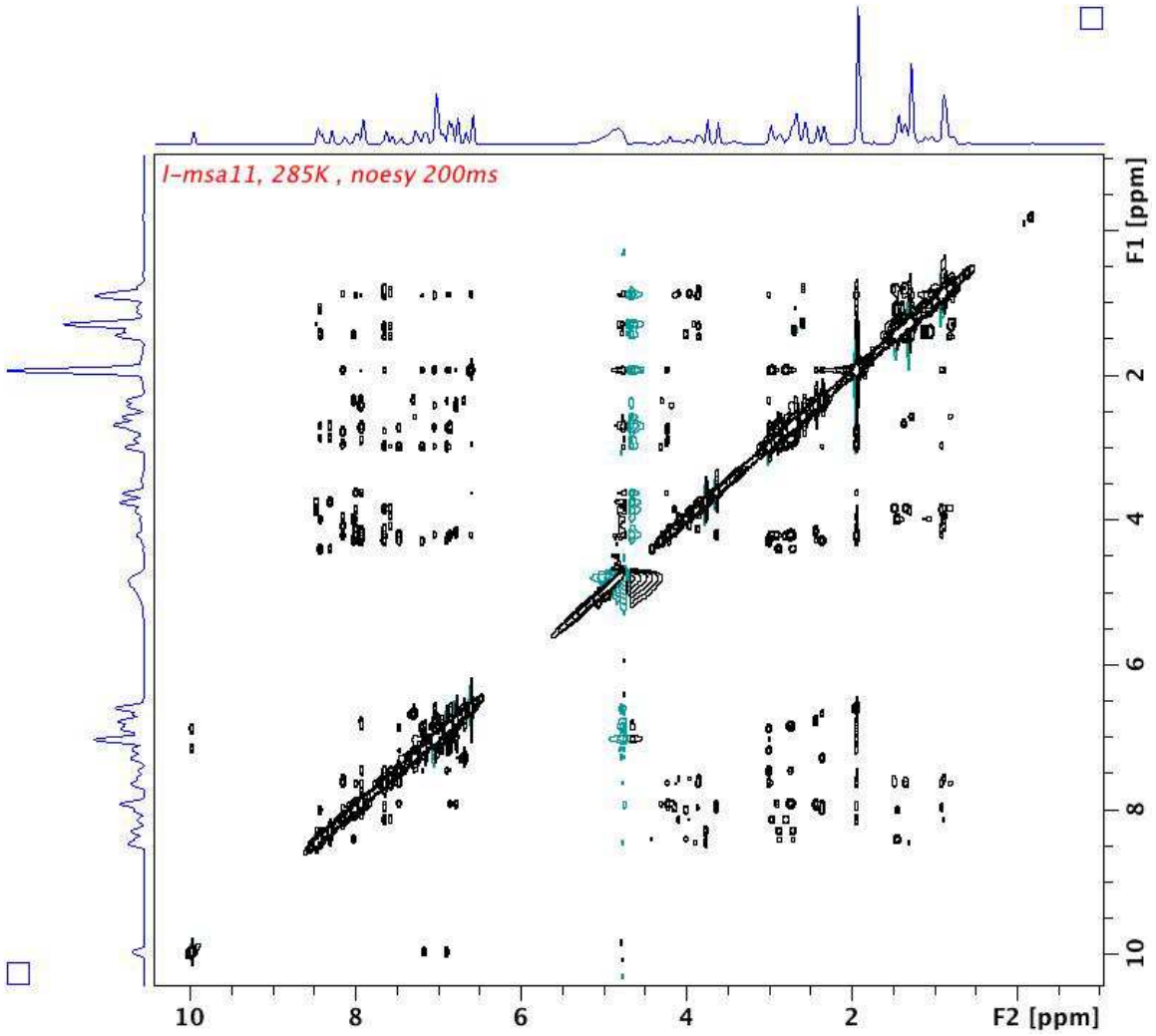
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.89	H^α 3.88	H^β 1.29		
2 Gly	H^N 8.47	H^α 3.75			
3 Cys	H^N 8.30	H^α 4.96	H^β 2.79		
4 Lys	H^N 8.41	H^α 4.00	H^β 1.40	H^γ 1.10	H^δ 1.37
				H^ε 2.68	H^Z 7.30
5 Asn	H^N 8.01	H^α 4.29	H^β 2.35	H^δ 6.99	
6 Phe	H^N 7.93	H^α 4.17	H^β 2.42	H^D 6.78	H^E 7.03
7 Phe	H^N 7.92	H^α 4.20	H^β 2.73	H^E 6.85	H^E 7.03
8 Trp	H^N 7.50	H^α 4.30	H^β 2.99	H^{D1} 6.89	H^{E3} 7.19
		H^{H2} 6.89	H^{E1} 9.97	H^{Z3} 6.96	H^{Z2} 7.17
9 Lys	H^N 7.65	H^α 3.85	H^β 1.41	H^γ 0.80	H^δ 1.28
			H^ε 2.58		H^Z 7.27
10 Thr	H^N 7.57	H^α 4.08	H^β 3.85	H^γ 0.88	
11 Msa	H^N 8.14	H^α 4.22	H^β 2.87	H^E 6.59	H^F 1.93
					H^H 1.95
12 Thr	H^N 7.64	H^α 4.08	H^β 3.95	H^γ 0.88	
13 Ser	H^N 7.98	H^α 4.21	H^β 3.63		
14 Cys	H^N 7.92	H^α 4.17	H^β 2.75		

TOCSY 50 ms



NOESY 200 ms



Structural Statistics for the 25 Lowest Energy Structures of [L-Msa11]-SRIF

Restraints used for the calculation ‹SA›[a]	
Intraresidual	0
Sequential (|i-j| =1)	40
Medium range(1 < |i-j| ≤ 4)	7
Long range (|i-j| > 4)	14
Unambiguous	All
Ambiguous	0
All	61
Restraint per residue ratio	4.4
Dihedral angle restrictions	23
RSMD (Å) from experimental[b]	
NOE:	0.02529 ± 0.00096
Bonds (Å)	$0.0009908 \pm 5.4 \times 10^{-4}$
Angles (°)	1.418± 0.027
Coordinate Precision (Å)[c]	
All Atoms	0.56
CNS potential energy (kcal mol^{-1})	
Total energy[d]	-39.62 ± 15.01
Electrostatic	-418.1 ± 13.7
Van der Waals	2.062 ± 9.09
Bonds	23.33 ± 2.66
Angles	129.2 ± 4.9

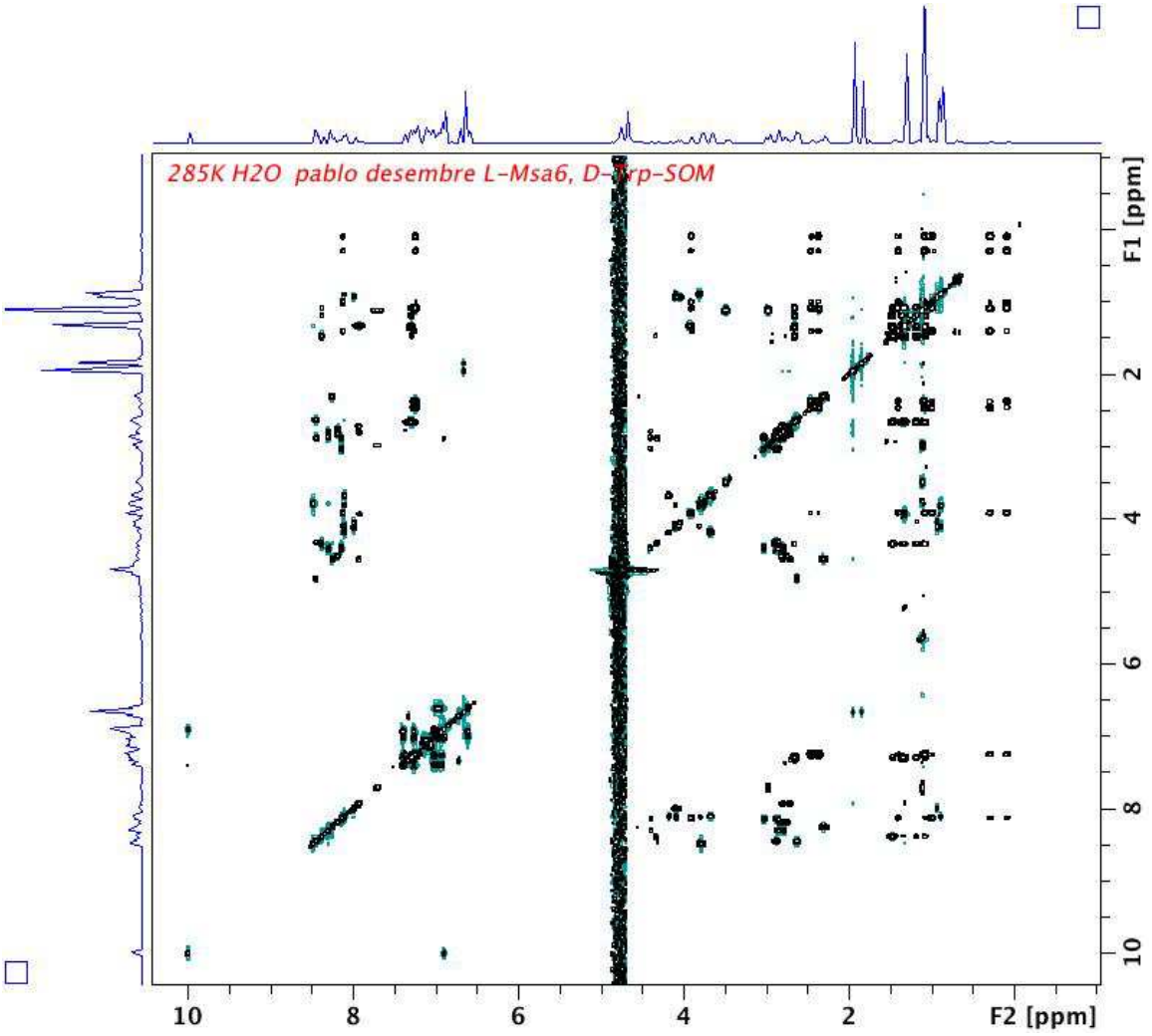
[a] ‹SA› refers to the ensemble of the 25 structures with the lowest energy.
[b] R.m.s deviation between the ensemble of structures <SA> and the lowest energy structure.
[c] No distance restraint in any of the structures included in the ensemble was violated by more than 0.3 Å.
[d] E_{L-J} is the Lennard-Jones van der Waals energy calculated using the CHARMM-PARMALLH6 parameters. E_{L-J} was not included in the target function during the structure calculation.

[L-Msa6_D-Trp8]-SRIF, 48: Somatostatin analog **48** was synthesized following the general procedure from 2.0 g of 2-Cl-Trt resin (1.60 mmol/g) and using Fmoc-L-Msa-OH, affording 1.93 g in 45% yield and 90% of purity (99% after purification). HPLC: t_R = 13.4 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for $C_{79}H_{110}N_{18}O_{19}S_2$: 1678.8; found, 1680.4.

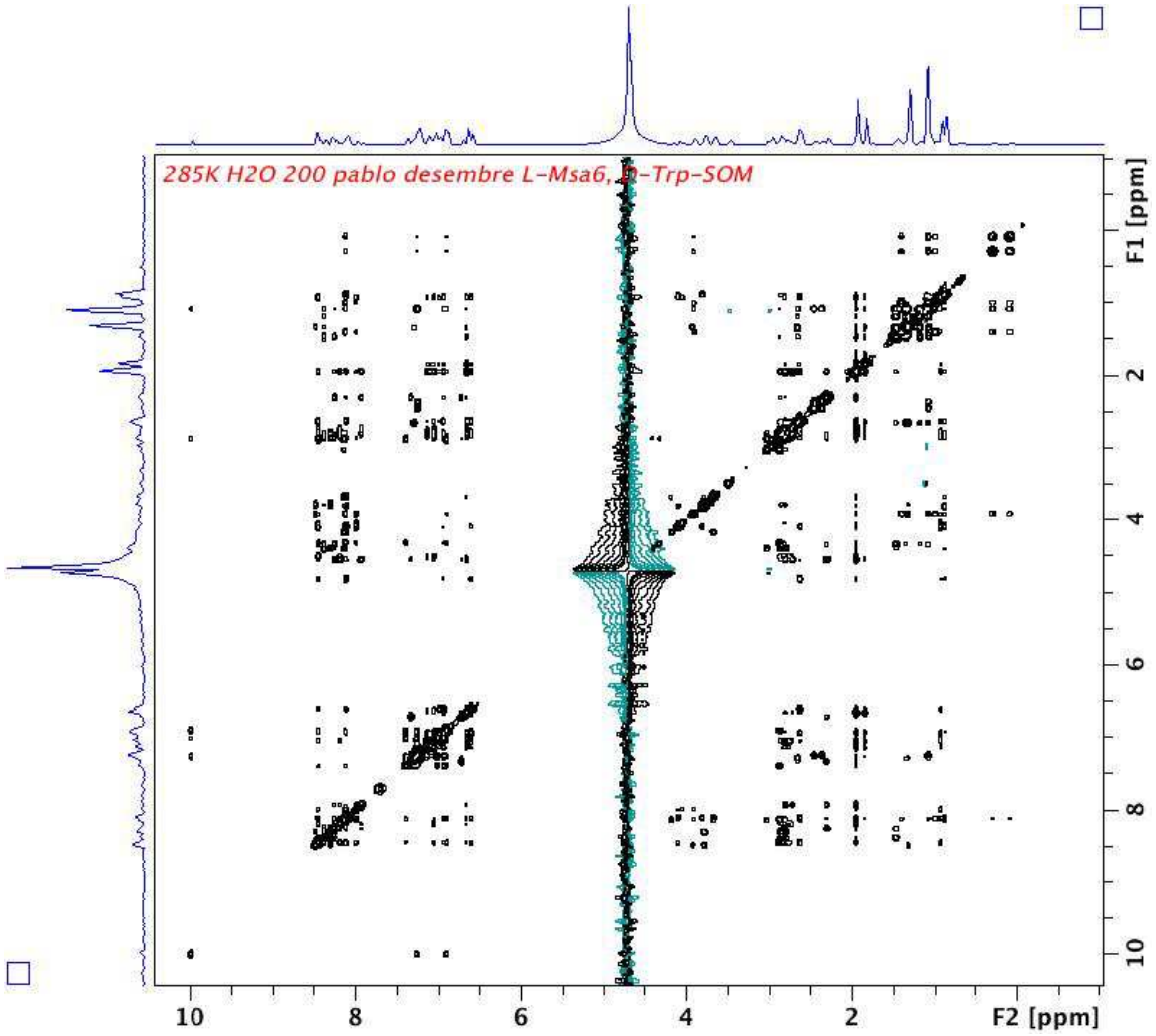
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.91	H^α 3.90	H^β 1.31		
2 Gly	H^N 8.47	H^α 3.77			
3 Cys	H^N 8.29	H^α 4.38	H^β 3.59		
4 Lys	H^N 8.37	H^α 4.32	H^β 1.45	H^γ 1.12	H^δ 1.30
				H^ε 2.64	H^Z 7.28
5 Asn	H^N 8.24	H^α 4.53	H^β 2.36	H^δ 7.02	
6 Msa	H^N 7.92	H^α 4.53	H^β 2.73	H^E 6.65	H^F 1.93
					H^H 1.83
7 Phe	H^N 8.18	H^α 4.49	H^β 2.77	H^D 7.04	H^E 7.13
					H^Z 7.08
8 D-Trp	H^N 8.43	H^α 4.30	H^β 2.84	H^{D1} 6.88	H^{E3} 7.38
		H^{H2} 7.01	H^{E1} 9.99	H^{Z3} 6.91	H^{Z2} 6.88
9 Lys	H^N 8.11	H^α 3.89	H^β 1.18	$H^{\gamma1}$ 0.56	H^δ 1.06
			H^ε 2.40	$H^{\gamma2}$ 0.07	H^Z 7.24
10 Thr	H^N 7.98	H^α 4.08	H^β 4.03	H^γ 0.91	
11 Phe	H^N 8.44	H^α 4.80	H^β 2.61	H^D 6.60	H^E 6.93
					H^Z 6.98
12 Thr	H^N 8.10	H^α 4.08	H^β 3.79	H^γ 0.87	
13 Ser	H^N 8.09	H^α 4.16	H^β 3.66		
14 Cys	H^N 8.13	H^α 4.38	H^β 2.93		

TOCSY 50 ms



NOESY 200 ms


285K H2O 200 pablo desembre L-Msa6,D-Trp-SOM
F1 [ppm]
F2 [ppm]
10
8
6
4
2

Structural Statistics for the 25 Lowest Energy Structures of [L-Msa6,D-Trp8]-SRIF

Restraints used for the calculation ‹SA›[a]	
Intraresidual	0
Sequential (|i-j| =1)	92
Medium range(1 < |i-j| ≤ 4)	26
Long range (|i-j| > 4)	19
Unambiguous	All
Ambiguous	0
All	137
Restraint per residue ratio	9.8
RSMD (Å) from experimental[b]	
NOE:	$0.03650 \pm 5.3 \times 10^{-4}$
Bonds (Å)	$0.01874 \pm 4.4 \times 10^{-4}$
Angles (°)	2.00 ± 0.02
Coordinate Precision (Å)[c]	
All Atoms	0.39
CNS potential energy (kcal mol^{-1})	
Total energy[d]	314.8 ± 11.0
Electrostatic	-400.6 ± 20.9
Van der Waals	133.6 ± 11.3
Bonds	82.54 ± 3.85
Angles	255.4 ± 6.2

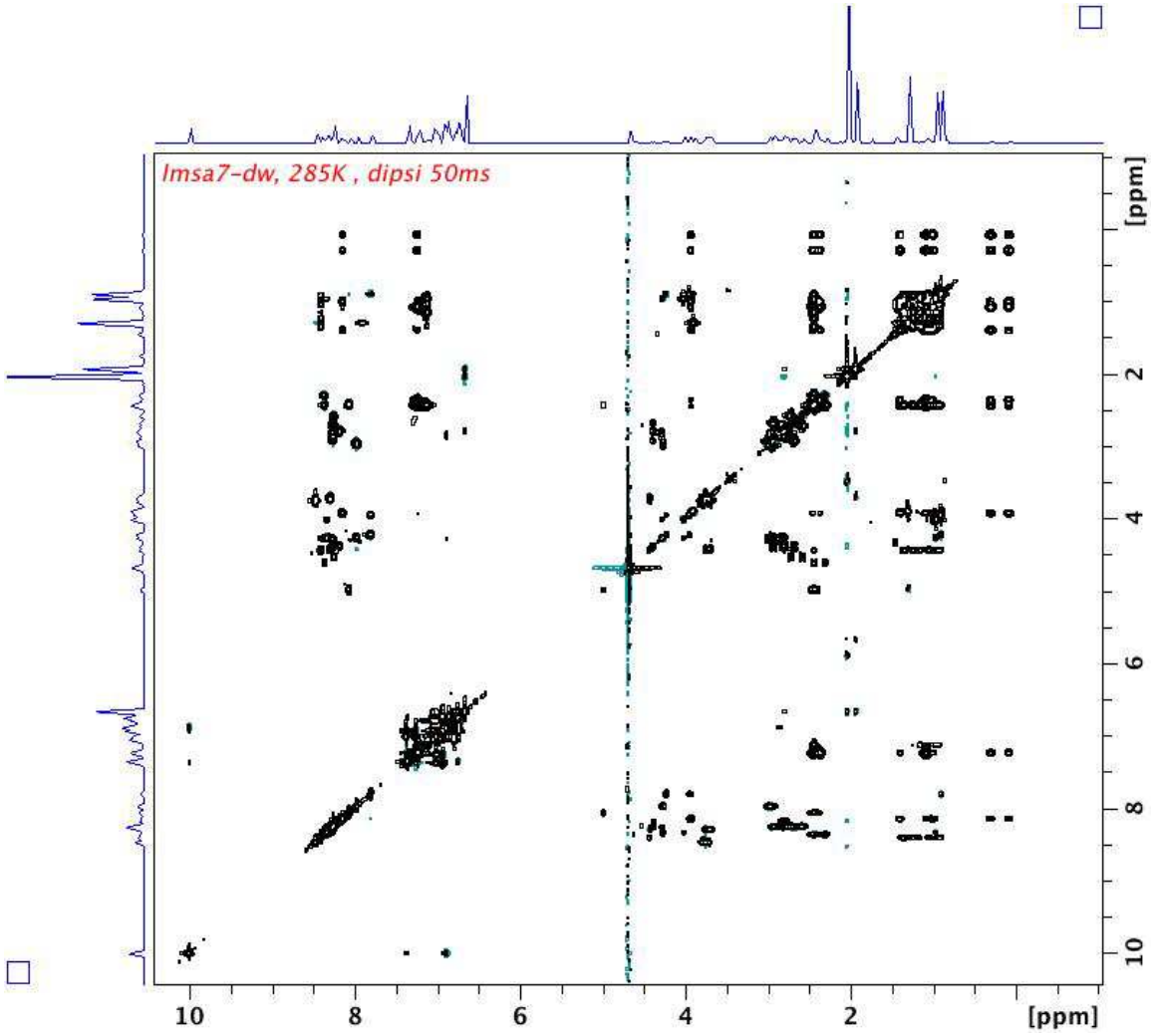
[a] ‹SA› refers to the ensemble of the 25 structures with the lowest energy.
[b] R.m.s deviation between the ensemble of structures <SA> and the lowest energy structure.
[c] No distance restraint in any of the structures included in the ensemble was violated by more than 0.3 Å.
[d] E_{L-J} is the Lennard-Jones van der Waals energy calculated using the CHARMM-PARMALLH6 parameters. E_{L-J} was not included in the target function during the structure calculation.

[L-Msa7_D-Trp8]-SRIF, 49: Somatostatin analog **49** was synthesized following the general procedure from 2 g of 2-Cl-Trt resin (1.60 mmol/g) and using Fmoc-L-Msa-OH, affording 2.15 g in 48% yield and 88% of purity (98% after purification). HPLC: t_R = 13.4 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for $C_{79}H_{110}N_{18}O_{19}S_2$: 1678.8; found, 1680.4.

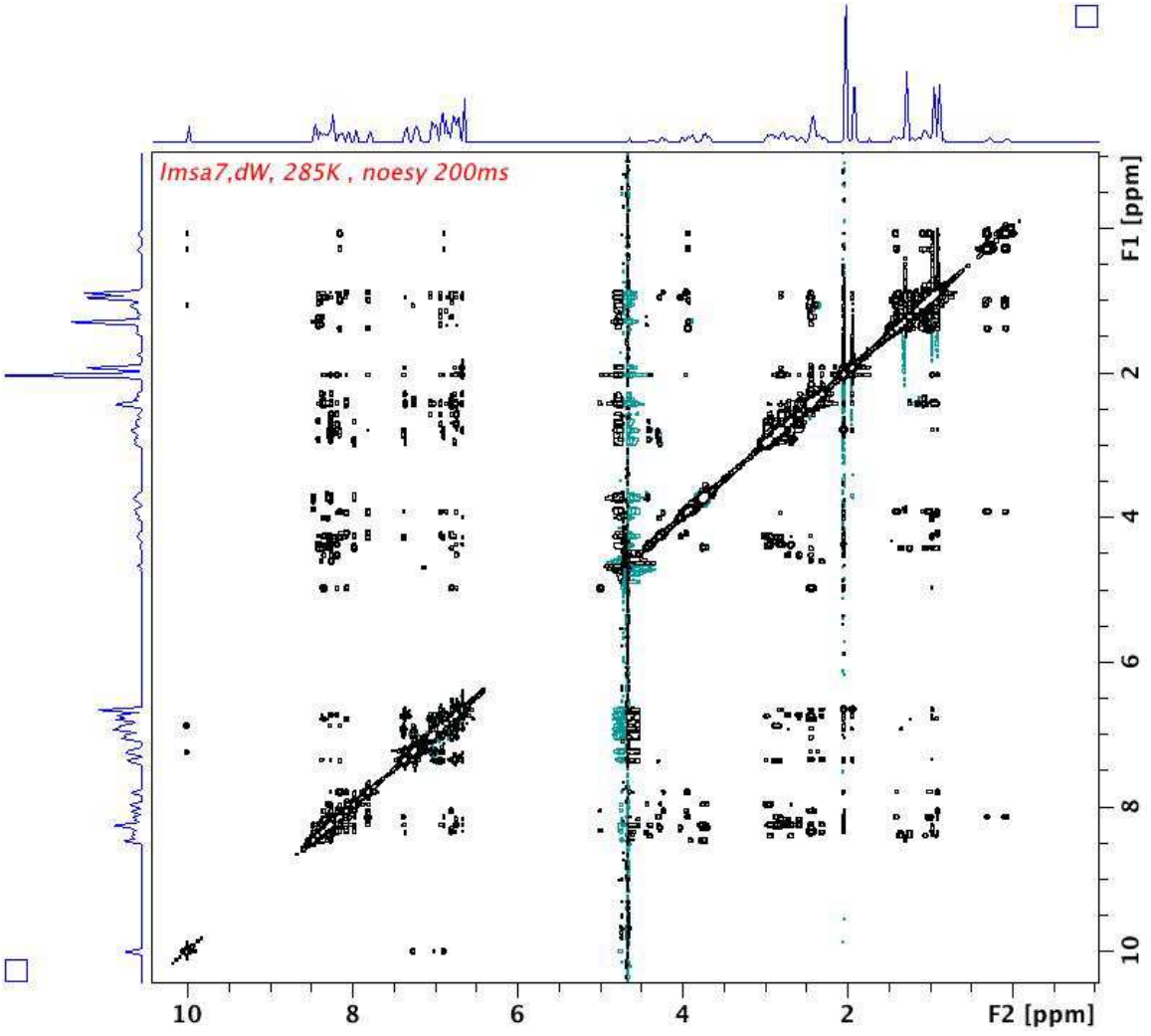
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.91	H^α 3.89	H^β 1.29		
2 Gly	H^N 8.47	H^α 3.75			
3 Cys	H^N 8.26	H^α 4.39	H^β 2.81		
4 Lys	H^N 8.41	H^α 4.43	H^β 1.29	H^γ 0.98	H^δ 1.15
				H^ε 2.43	H^Z 7.13
5 Asn	H^N 8.36	H^α 4.61	H^β 2.36	H^δ 7.03	
6 Phe	H^N 8.26	H^α 4.53	H^β 2.64	H^D 6.73	H^E 6.93
7 Msa	H^N 8.18	H^α 4.38	H^β 2.79	H^E 6.66	H^F 2.03
					H^H 1.93
8 D-Trp	H^N 8.26	H^α 4.28	H^β 2.84	H^{D1} 6.88	H^{E3} 7.37
		H^{H2} 7.01	H^{E1} 10.00	H^{Z3} 6.93	H^{Z2} 7.26
9 Lys	H^N 8.14	H^α 3.76	H^β 1.19	$H^{\gamma 1}$ 1.19	H^δ 1.39
			H^ε 2.55	$H^{\gamma 2}$ 0.08	H^Z 7.23
10 Thr	H^N 7.80	H^α 4.22	H^β 3.95	H^γ 0.90	
11 Phe	H^N 8.07	H^α 4.99	H^β 2.41	H^D 6.78	H^E 7.06
					H^Z 7.00
12 Thr	H^N 8.34	H^α 4.26	H^β 4.01	H^γ 0.96	
13 Ser	H^N 8.29	H^α 4.42	H^β 3.72		
14 Cys	H^N 7.97	H^α 4.27	H^β 2.96		

TOCSY 50 ms



NOESY 200 ms



Structural Statistics for the 25 Lowest Energy Structures of [L-Msa7,D-Trp8]-SRIF

Restraints used for the calculation ‹SA›[a]	
Intraresidual	0
Sequential (|i-j| =1)	109
Medium range(1 < |i-j| ≤ 4)	51
Long range (|i-j| > 4)	53
Unambiguous	All
Ambiguous	0
All	213
Restraint per residue ratio	15.2
RSMD (Å) from experimental[b]	
NOE:	$0.02835 \pm 2.6 \times 10^{-3}$
Bonds (Å)	$0.01994 \pm 1.2 \times 10^{-3}$
Angles (º)	2.211 ± 0.045
Coordinate Precision (Å)[c]	
All Atoms	0.31
CNS potential energy (kcal mol^{-1})	
Total energy[d]	459.8 ± 36.1
Electrostatic	-363.8 ± 34.7
Van der Waals	131.7 ± 10.4
Bonds	93.81 ± 11.49
Angles	312.2 ± 12.6

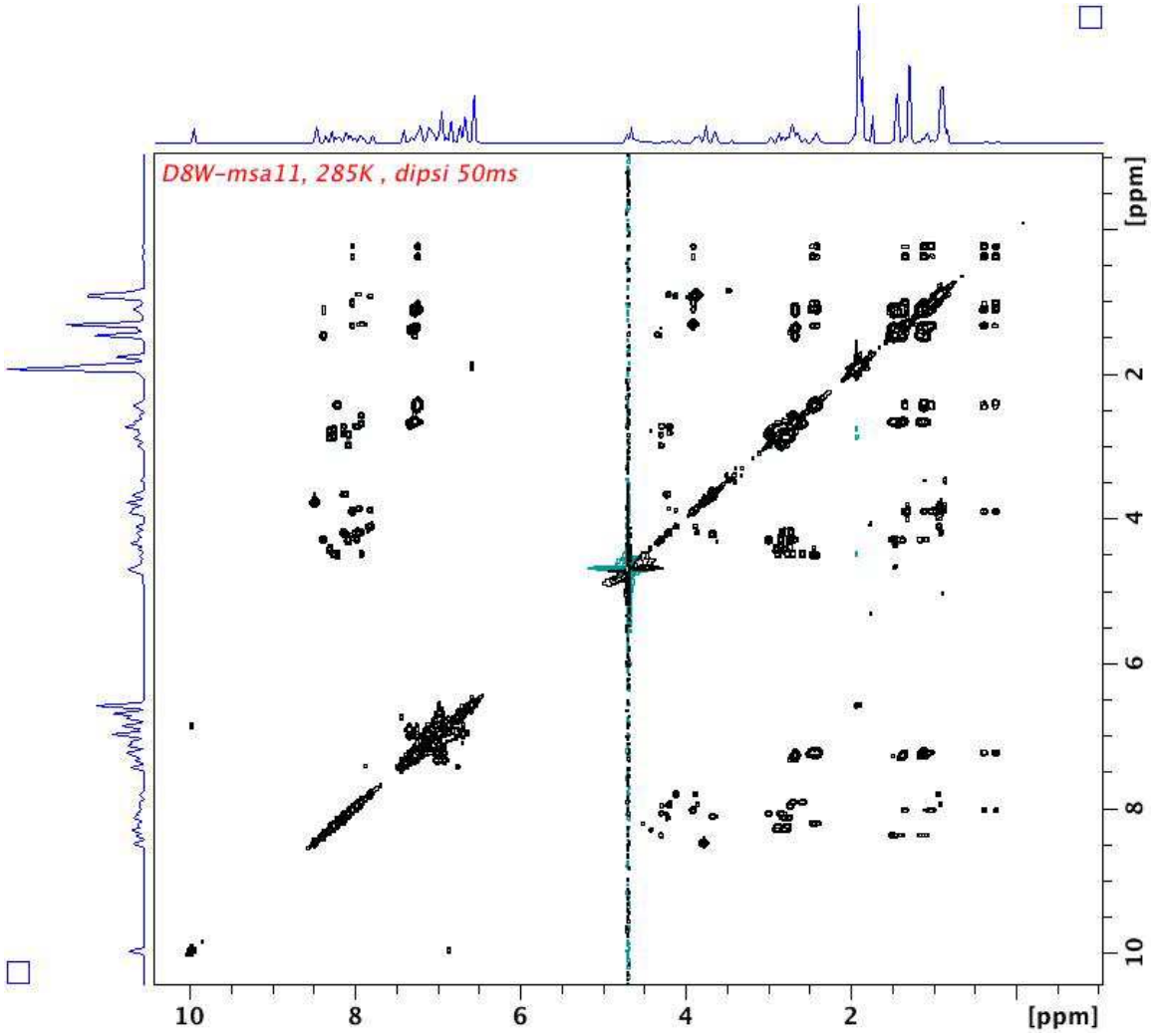
[a] ‹SA› refers to the ensemble of the 25 structures with the lowest energy.
[b] R.m.s deviation between the ensemble of structures <SA> and the lowest energy structure.
[c] No distance restraint in any of the structures included in the ensemble was violated by more than 0.3 Å.
[d] E_{L-J} is the Lennard-Jones van der Waals energy calculated using the CHARMM-PARMALLH6 parameters. E_{L-J} was not included in the target function during the structure calculation.

[L-Msa11_D-Trp8]-SRIF, 50: Somatostatin analog **50** was synthesized following the general procedure from 2 g of 2-Cl-Trt resin (1.60 mmol/g) and using Fmoc-L-Msa-OH, affording 1.59 g in 35% yield and 88% of purity (98% after purification). HPLC: t_R = 12.8 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for $C_{79}H_{110}N_{18}O_{19}S_2$: 1678.8; found, 1680.6.

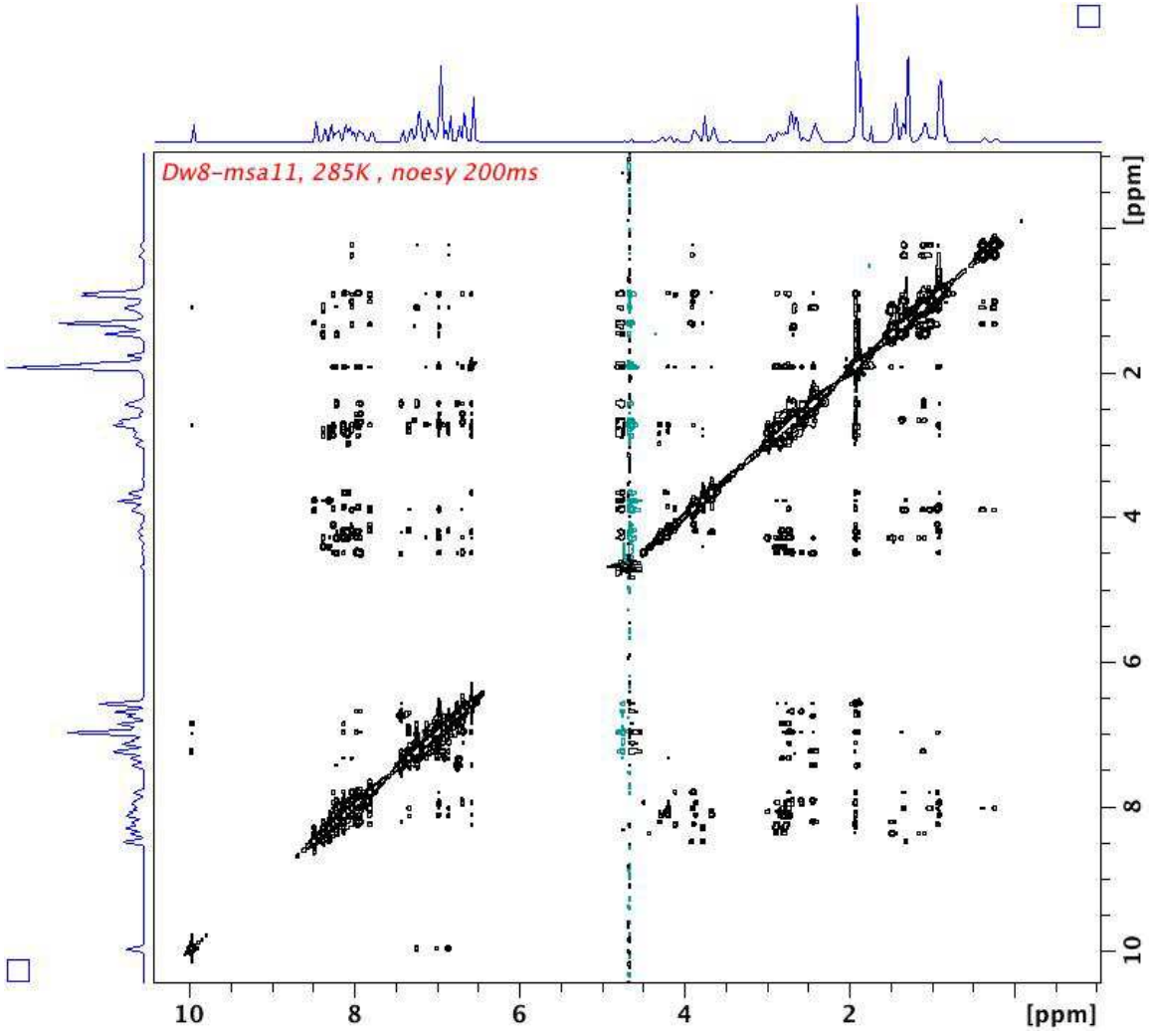
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.90	H^α 3.90	H^β 1.30		
2 Gly	H^N 8.48	H^α 3.77			
3 Cys	H^N 8.30	H^α 4.41	H^β 2.83		
4 Lys	H^N 8.10	H^α 4.29	H^β 1.45	H^γ 1.11	H^δ 1.357
				H^ε 2.66	H^Z 7.27
5 Asn	H^N 8.21	H^α 4.50	H^β 2.43	H^δ 7.09	
6 Phe	H^N 7.92	H^α 4.48	H^β 2.63	H^D 6.68	H^E 6.97
7 Phe	H^N 7.97	H^α 4.28	H^β 2.72	H^D 6.97	H^E 7.12
					H^Z 7.08
8 D-Trp	H^N 8.13	H^α 4.181	H^β 2.76	H^{D1} 6.85	H^{E3} 7.33
		H^{H2} 7.05	H^{E1} 9.97	H^{Z3} 6.91	H^{Z2} 7.24
9 Lys	H^N 8.02	H^α 4.35	H^β 1.17	$H^{\gamma1}$ 0.37	H^δ 1.10
			H^ε 2.42	$H^{\gamma2}$ 0.23	H^Z 7.23
10 Thr	H^N 7.81	H^α 4.07	H^β 3.88	H^γ 0.92	
11 Msa	H^N 8.25	H^α 4.48	H^β 2.81	H^E 6.57	H^F 1.91
					H^Z 1.87
12 Thr	H^N 7.95	H^α 4.19	H^β 3.85	H^γ 0.90	
13 Ser	H^N 8.12	H^α 4.21	H^β 3.66		
14 Cys	H^N 8.07	H^α 4.28	H^β 2.90		

TOCSY 50 ms



NOESY 200 ms



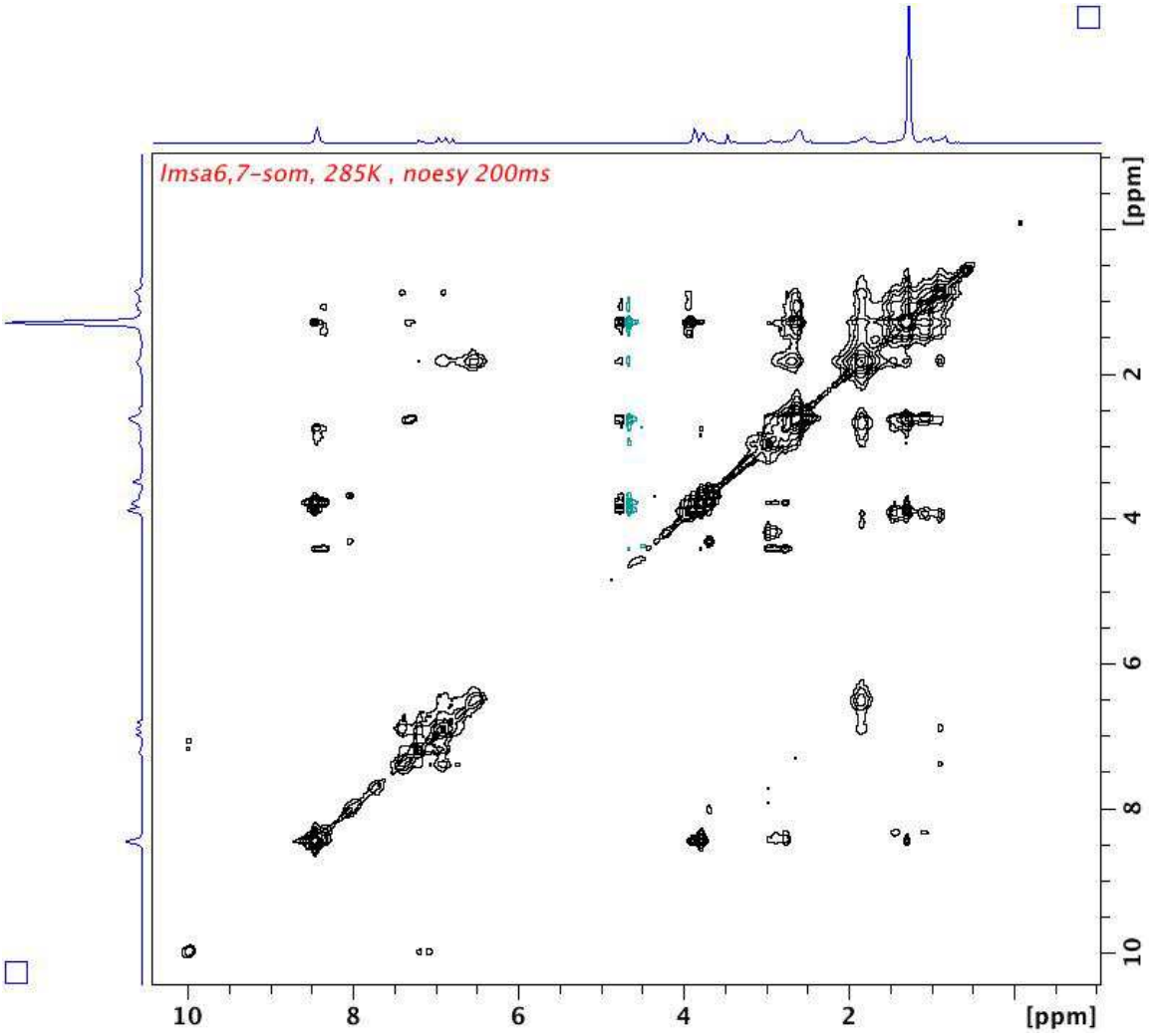
Structural Statistics for the 25 Lowest Energy Structures of [L-Msa11,D-Trp8]-SRIF

Restraints used for the calculation ‹SA›[a]	
Intraresidual	0
Sequential (|i-j| =1)	99
Medium range(1 < |i-j| ≤ 4)	47
Long range (|i-j| > 4)	42
Unambiguous	All
Ambiguous	0
All	188
Restraint per residue ratio	13.4
RSMD (Å) from experimental[b]	
NOE:	$0.007165 \pm 2.0 \times 10^{-3}$
Bonds (Å)	$0.006702 \pm 1.1 \times 10^{-3}$
Angles (º)	1.341 ± 0.049
Coordinate Precision (Å)[c]	
All Atoms	0.42
CNS potential energy (kcal mol^{-1})	
Total energy[d]	-168.7 ± 41.6
Electrostatic	-451.5 ± 47.0
Van der Waals	37.05 ± 19.71
Bonds	10.86 ± 3.67
Angles	114.9 ± 8.5

[a] ‹SA› refers to the ensemble of the 25 structures with the lowest energy.
[b] R.m.s deviation between the ensemble of structures <SA> and the lowest energy structure.
[c] No distance restraint in any of the structures included in the ensemble was violated by more than 0.3 Å.
[d] E_{L-J} is the Lennard-Jones van der Waals energy calculated using the CHARMM-PARMALLH6 parameters. E_{L-J} was not included in the target function during the structure calculation.

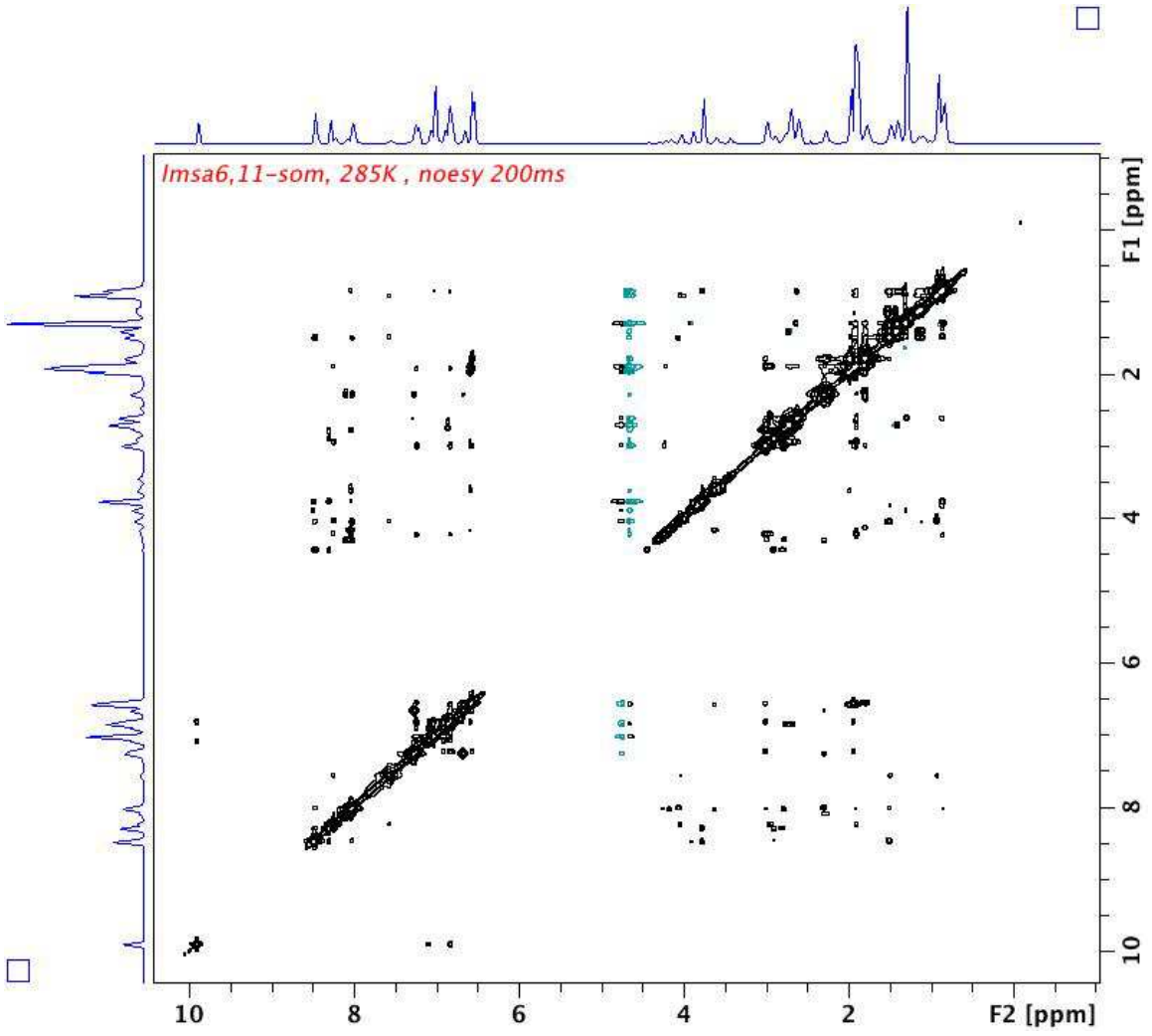
[**L-Msa6,7]-SRIF, 51**: Somatostatin analog **51** was synthesized following the general procedure from 0.10 g of 2-Cl-Trt resin (1.60 mmol/g) and using Fmoc-L-Msa-OH, affording 0.12 g of **10** in 20% yield (98% purity after purification). HPLC: t_R = 16.5 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ =220 nm]. HRMS: calcd. for $C_{82}H_{116}N_{18}O_{19}S_2$: 1721.1; found, 1721.0.

NOESY 200 ms



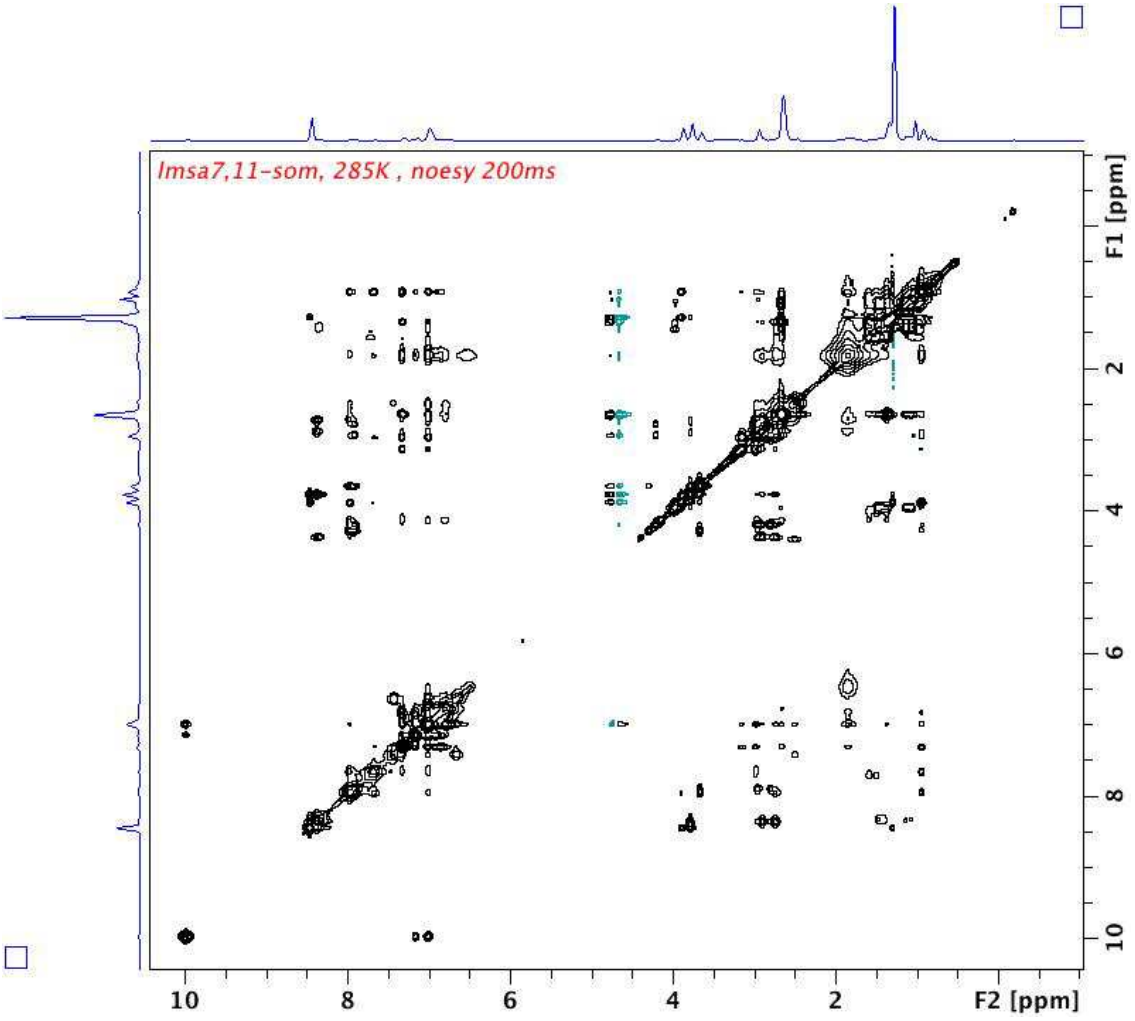
[**L-Msa6,11]-SRIF, 52:** Somatostatin analog **52** was synthesized following the general procedure from 0.136 g of 2-Cl-Trt resin (1.60 mmol/g) and using Fmoc-L-Msa-OH, affording 0.28 g in 44% yield (99% purity after purification). HPLC: t_R = 15.4 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for $C_{82}H_{116}N_{18}O_{19}S_2$: 1721.1; found, 1720.8.

NOESY 200 ms



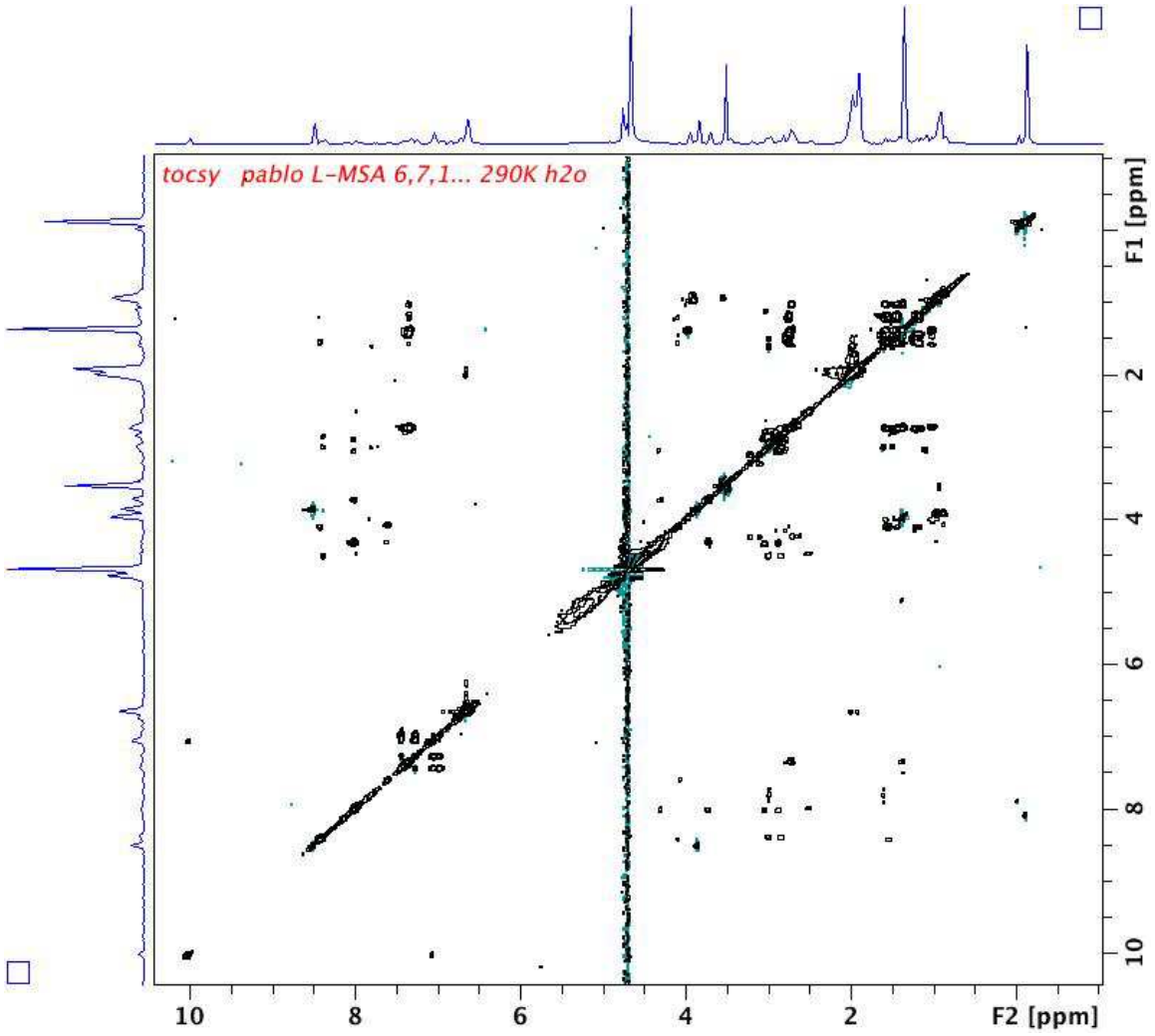
[**L-Msa7,11]-SRIF, 53:** Somatostatin analog **53** was synthesized following the general procedure from 0.10 g of 2-Cl-Trt resin (1.60 mmol/g) and using Fmoc-L-Msa-OH, affording 0.13 g in 44% yield (99% purity after purification). HPLC: t_R = 16.4 [Gradient 25-60%B in 20min, flux: 1 mL.min^{-1}, λ =220 nm]. HRMS: calcd. for $C_{82}H_{116}N_{18}O_{19}S_2$: 1721.1; found, 1721.0.

NOESY 200 ms

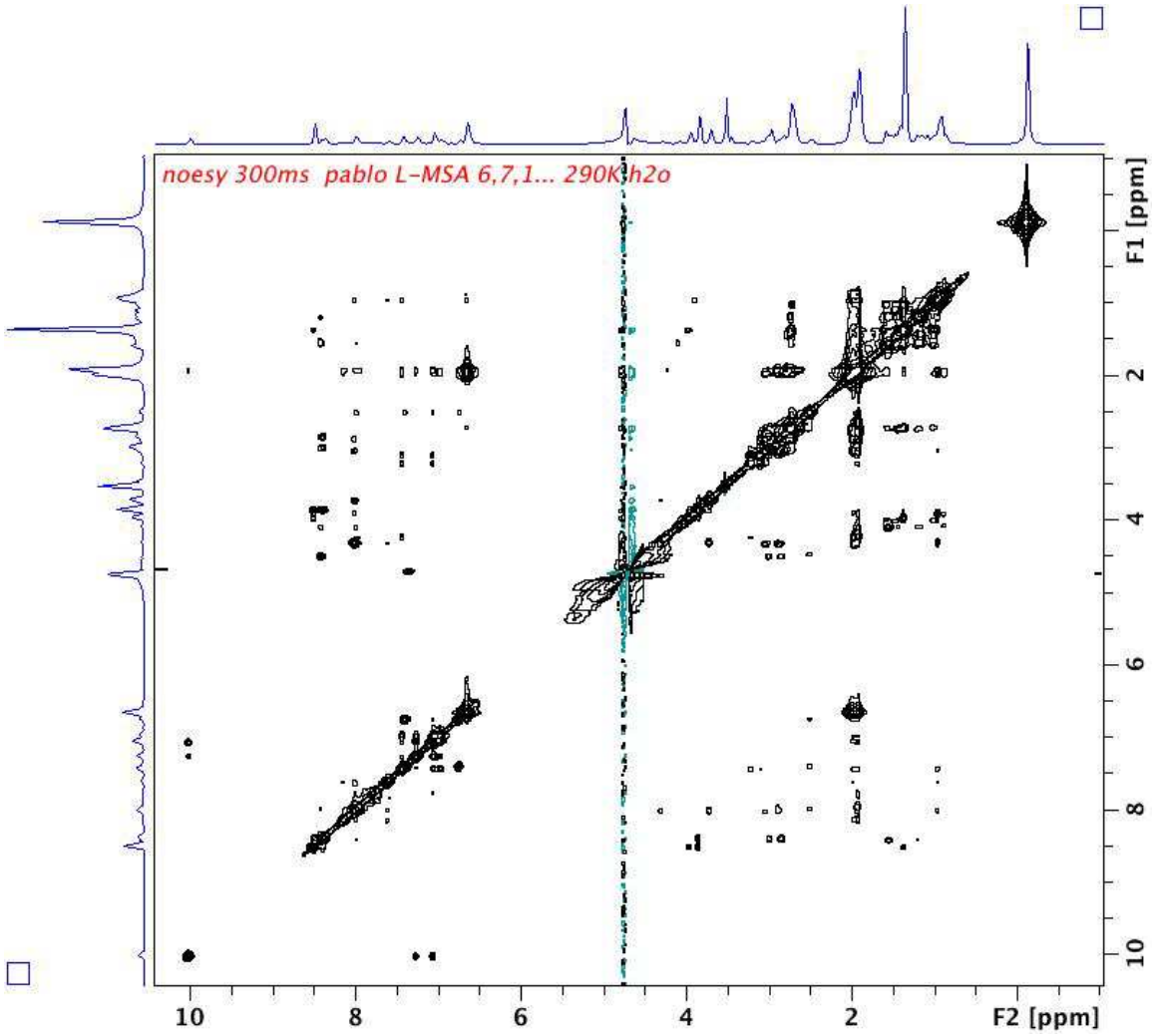


[**L-Msa6,7,11]-SRIF, 54:** Somatostatin analog was synthesized following the general procedure from 0.10 g of 2-Cl-Trt resin (1.60 mmol/g) and using Fmoc-L-Msa-OH, affording 0.10 g in 44% yield (95% purity after purification). HPLC: t_R = 18.4 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for $C_{85}H_{122}N_{18}O_{19}S_2$: 1762.9; found, 1763.2.

TOCSY 50 ms



NOESY 200 ms



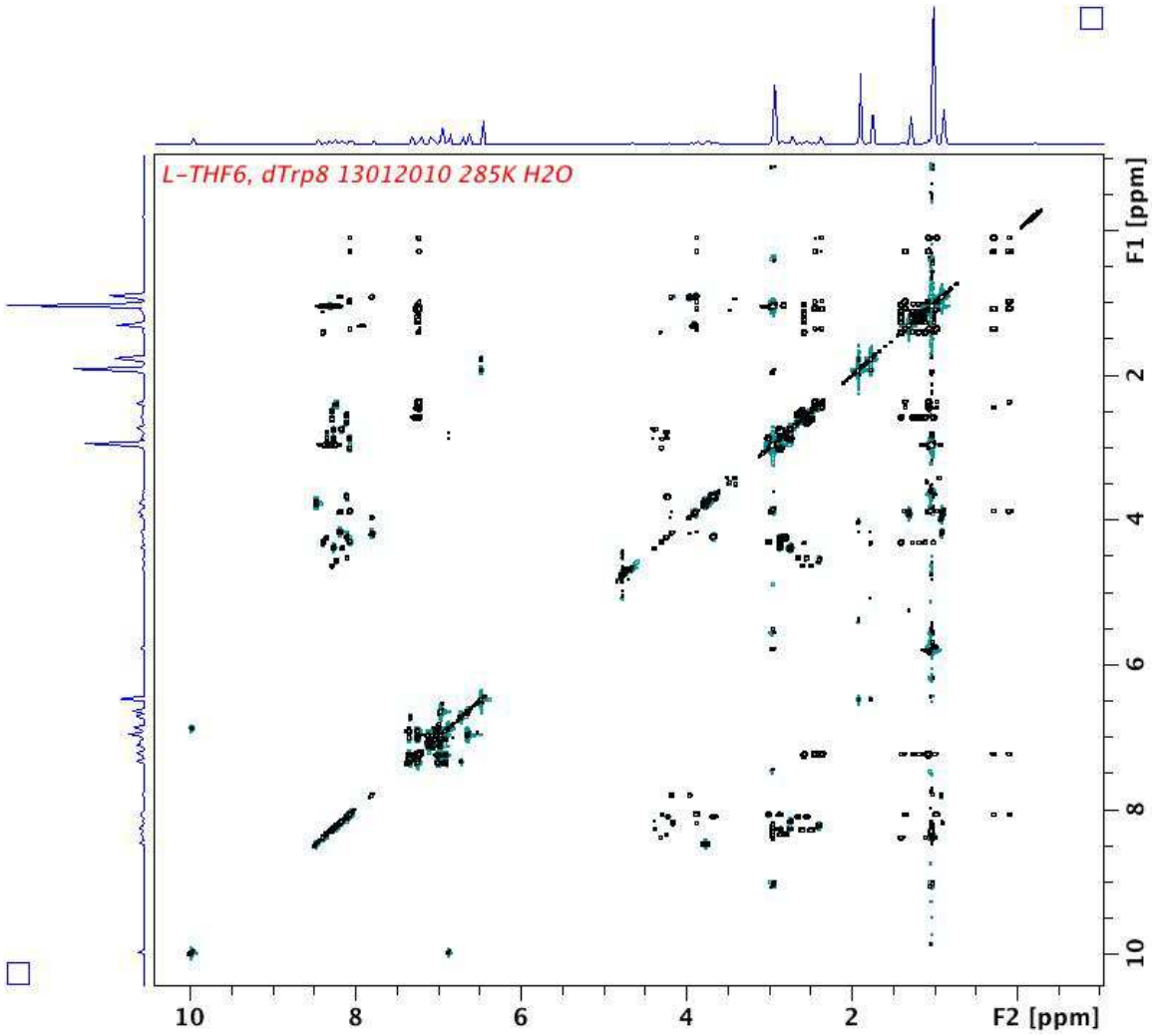
Analogs containing the Tmp amino acid:

[L-Tmp6_D-Trp8]-SRIF, 55: Somatostatin analog **55** was synthesized following the general procedure from 0.20 g of 2-Cl-Trt resin (0.8 mmol/g) and using Fmoc-L-Tmp-OH, affording 0.18 g in 63% yield (98% purity after purification). HPLC: t_R = 14.2 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd for $C_{79}H_{110}N_{18}O_{19}S_2$: 1678.7636; found, 1678.7638.

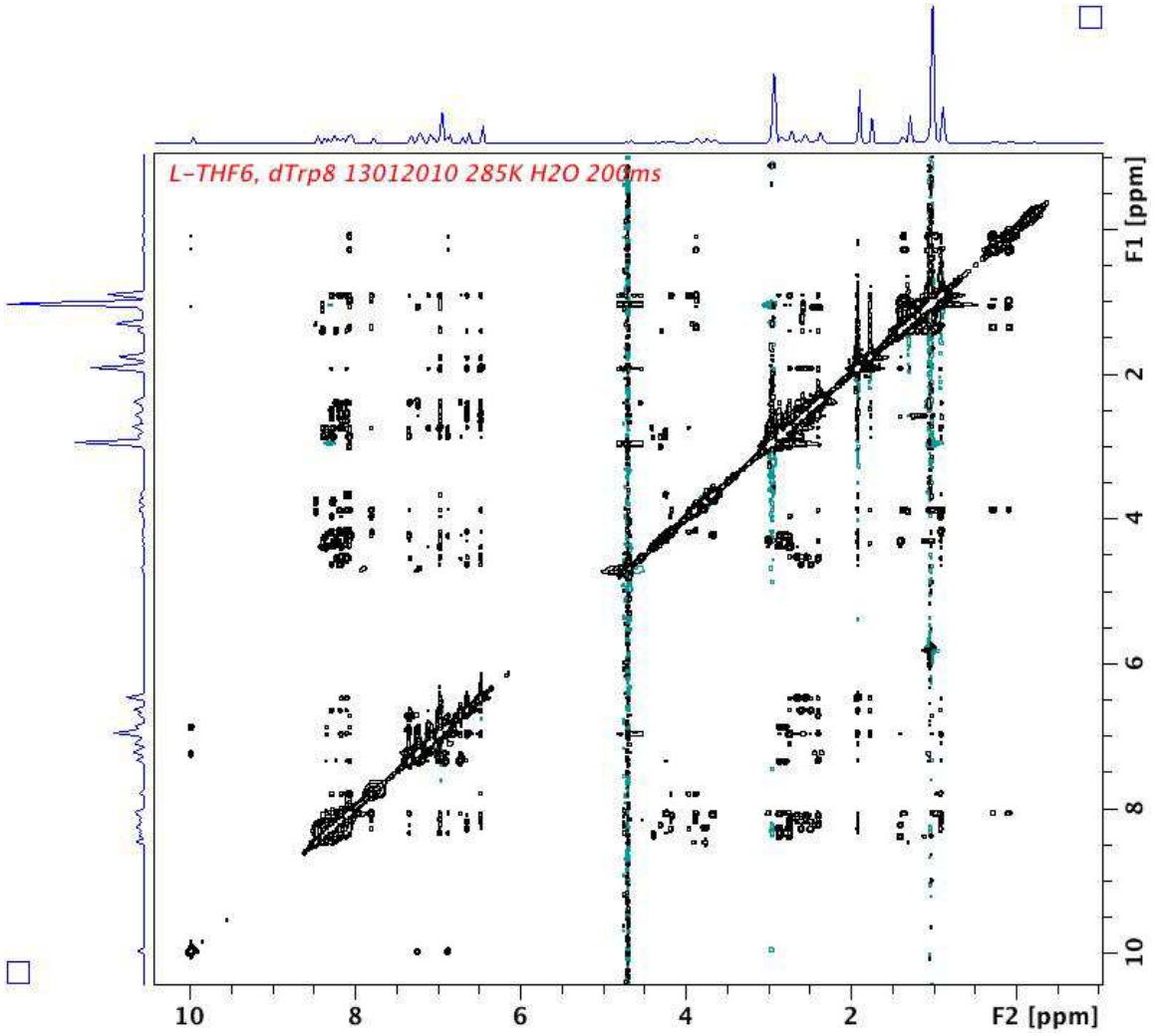
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.88	H^α 3.89	H^β 1.29		
2 Gly	H^N 8.46	H^α 3.75			
3 Cys	H^N 8.26	H^α 4.37	H^β 2.79		
4 Lys	H^N 8.38	H^α 4.29	H^β 1.38	H^γ 1.49	H^δ 1.21
				H^ε 2.56	H^Z 7.23
5 Asn	H^N 8.22	H^α 4.53	H^β 2.38	$H^{\delta21}$ 7.33	$H^{\delta22}$ 5.08
6 Tmp	H^N 8.09	H^α 4.51	H^β 2.58	H^D 6.47	H^F 1.90
					H^H 1.76
7 Phe	H^N 8.15	H^α 4.37	H^β 2.72	H^δ 7.10	H^E 7.10
					H^Z 7.06
8 D-Trp	H^N 8.33	H^α 4.22	H^β 2.80	H^{D1} 6.86	H^{E3} 7.34
		H^{H2} 6.99	H^{E1} 9.97	H^{Z3} 6.90	H^{Z2} 7.23
9 Lys	H^N 8.06	H^α 3.86	H^β 1.15	$H^{\gamma1}$ 0.26	H^δ 1.05
			H^ε 2.39	$H^{\gamma2}$ 0.07	H^Z 7.22
10 Thr	H^N 7.79	H^α 4.16	H^β 3.95	H^γ 0.89	
11 Phe	H^N 8.27	H^α 4.61	H^β 2.53	H^D 6.63	H^E 6.96
12 Thr	H^N 8.17	H^α 4.15	H^β 3.86	H^γ 0.89	
13 Ser	H^N 8.09	H^α 4.22	H^β 3.65		
14 Cys	H^N 8.06	H^α 4.29	H^β 2.92		

TOCSY 50 ms



NOESY 200 ms



Structural Statistics for the 25 Lowest Energy Structures of [L-Tmp6_D-Trp8]-SRIF

Restraints used for the calculation ‹SA›[a]	
Intraresidual	0
Sequential (|i-j| =1)	66
Medium range(1 < |i-j| ≤ 4)	17
Long range (|i-j| > 4)	21
Unambiguous	All
Ambiguous	0
All	104
Dihedral angle restrictions	20
Restraint per residue ratio	18.8
RSMD (Å) from experimental[b]	
NOE:	0.01886 ± 0.00061
Bonds (Å)	0.01238 ± 0.00110
Angles (°)	1.58 ± 0.04
Coordinate Precision (Å)[c]	0.74
All Atoms	
CNS potential energy (kcal mol^{-1})	
Total energy[d]	-49.44 +/- 12.17
Electrostatic	-409.6 +/- 14.3
Van der Waals	12.76 +/- 8.21
Bonds	36.58 +/- 5.962
Angles	161.4 +/- 7.8

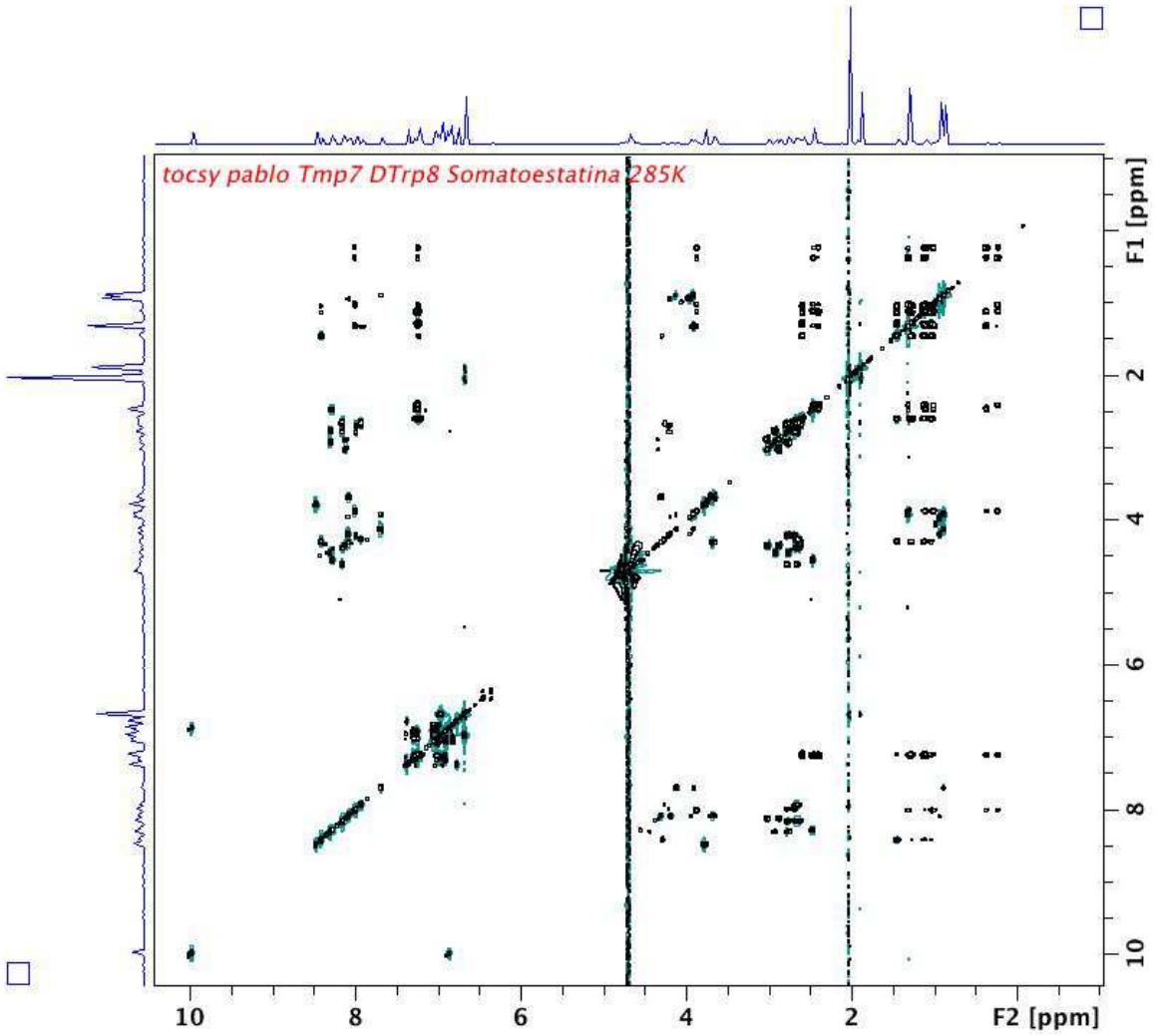
[a] ‹SA› refers to the ensemble of the 25 structures with the lowest energy.
[b] R.m.s deviation between the ensemble of structures <SA> and the lowest energy structure.
[c] No distance restraint in any of the structures included in the ensemble was violated by more than 0.3 Å.
[d] E_{L-J} is the Lennard-Jones van der Waals energy calculated using the CHARMM-PARMALLH6 parameters. E_{L-J} was not included in the target function during the structure calculation.

[L-Tmp7_D-Trp8]-SRIF,: Somatostatin analog **56** was synthesized following the general procedure from 0.20 g of 2-Cl-Trt resin (0.8 mmol/g) and using Fmoc-L-Tmp-OH, affording 0.16 g in 59% yield (99% purity after purification). HPLC: t_R = 13.8 [Gradient 25-60%B in 20min, flux: 1 mL.min^{-1}, λ =220 nm]. HRMS: calcd. for $C_{79}H_{110}N_{18}O_{19}S_2$: 1678.7636; found, 1678.7656.

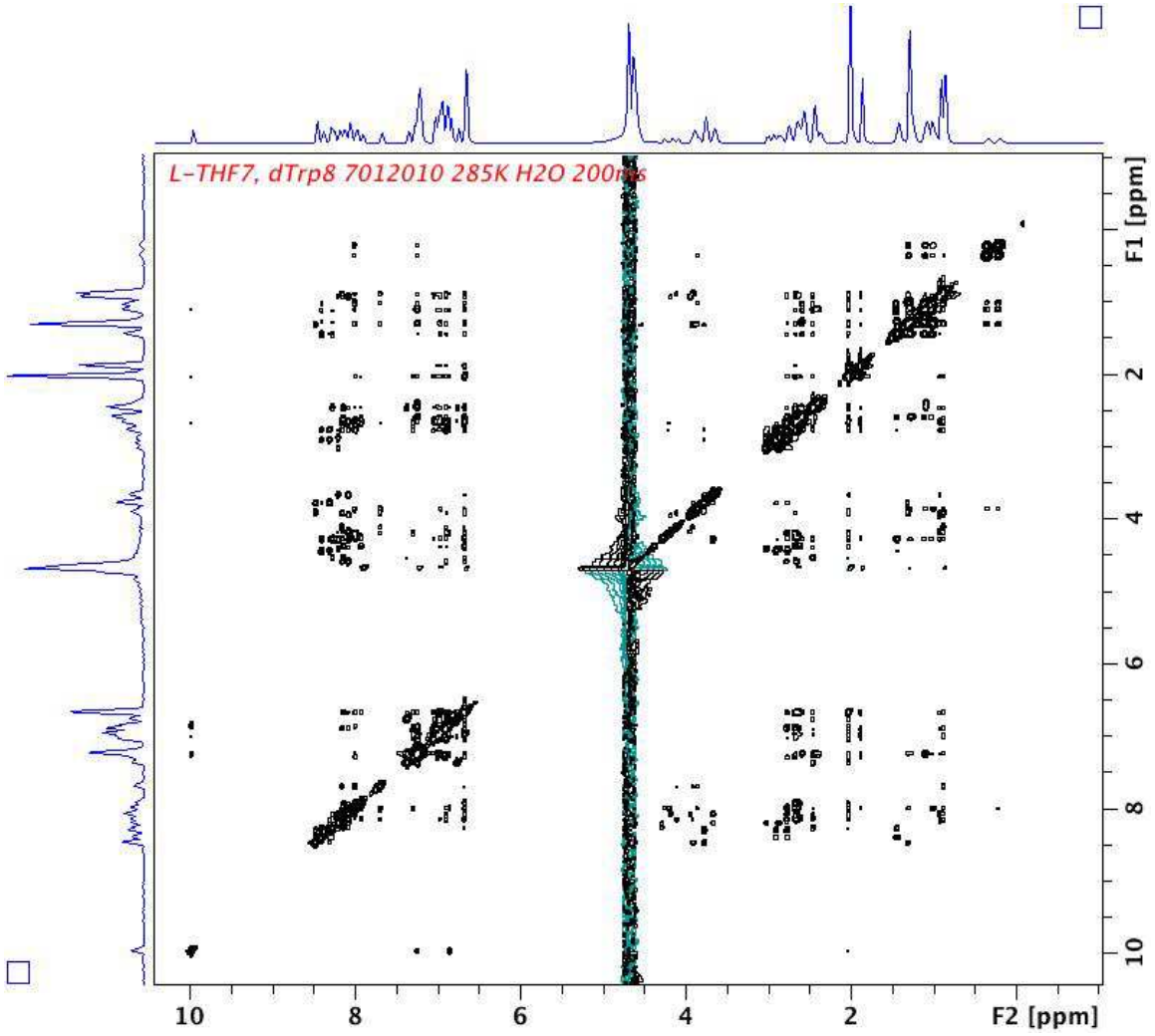
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.91	H^α 3.89	H^β 1.30		
2 Gly	H^N 8.47	H^α 3.77			
3 Cys	H^N 8.29	H^α 4.43	H^β 2.83		
4 Lys	H^N 8.41	H^α 4.43	H^β 1.43	H^γ 1.06	H^δ 1.26
				H^ε 2.57	H^Z 7.23
5 Asn	H^N 8.27	H^α 4.53	H^β 2.45	H^δ 7.06	
6 Phe	H^N 8.15	H^α 4.37	H^β 2.64	H^D 6.67	H^E 6.96
7 Tmp	H^N 7.92	H^α 4.25	H^β 2.65	H^D 6.67	H^F 2.02
					H^H 1.88
8 D-Trp	H^N 7.99	H^α 4.19	H^β 2.72	H^{D1} 6.85	H^{E3} 7.29
		H^{H2} 6.99	H^{E1} 9.97	H^{Z3} 6.90	H^{Z2} 7.24
9 Lys	H^N 8.00	H^α 3.86	H^β 1.14	$H^{\gamma2}$ 0.34	H^δ 1.09
			H^ε 2.40	$H^{\gamma3}$ 0.20	H^Z 7.23
10 Thr	H^N 7.69	H^α 4.11	H^β 3.90	H^γ 0.87	
11 Phe	H^N 8.15	H^α 4.59	H^β 2.70	H^D 6.89	H^E 7.04
12 Thr	H^N 8.08	H^α 4.17	H^β 3.94	H^γ 0.92	
13 Ser	H^N 8.07	H^α 4.29	H^β 3.66		
14 Cys	H^N 8.12	H^α 4.35	H^β 2.94		

TOCSY 50 ms


tocsy pablo Tmp7 DTrp8 Somatoestatina 285K
F1 [ppm]
F2 [ppm]
10
8
6
4
2

NOESY 200 ms



Structural Statistics for the 25 Lowest Energy Structures of [L-Tmp7_D-Trp8]-SRIF

Restraints used for the calculation ‹SA›[a]	
Intraresidual	0
Sequential (|i-j| =1)	57
Medium range(1 < |i-j| ≤ 4)	20
Long range (|i-j| > 4)	13
Unambiguous	All
Ambiguous	0
All	90
Dihedral angle restrictions	20
Restraint per residue ratio	7.9
RSMD (Å) from experimental[b]	
NOE:	0.1585 ± 0.0679
Bonds (Å)	0.00409 +/- 0.0003
Angles (°)	1.083 +/- 0.01695
Coordinate Precision (Å)[c]	0.42
All Atoms	
CNS potential energy (kcal mol^{-1})	
Total energy[d]	-318.3 +/- 11.4
Electrostatic	-435.6 +/- 13
Van der Waals	-38.48 +/- 3.75
Bonds	3.994 +/- 0.596
Angles	75.43 +/- 2.36

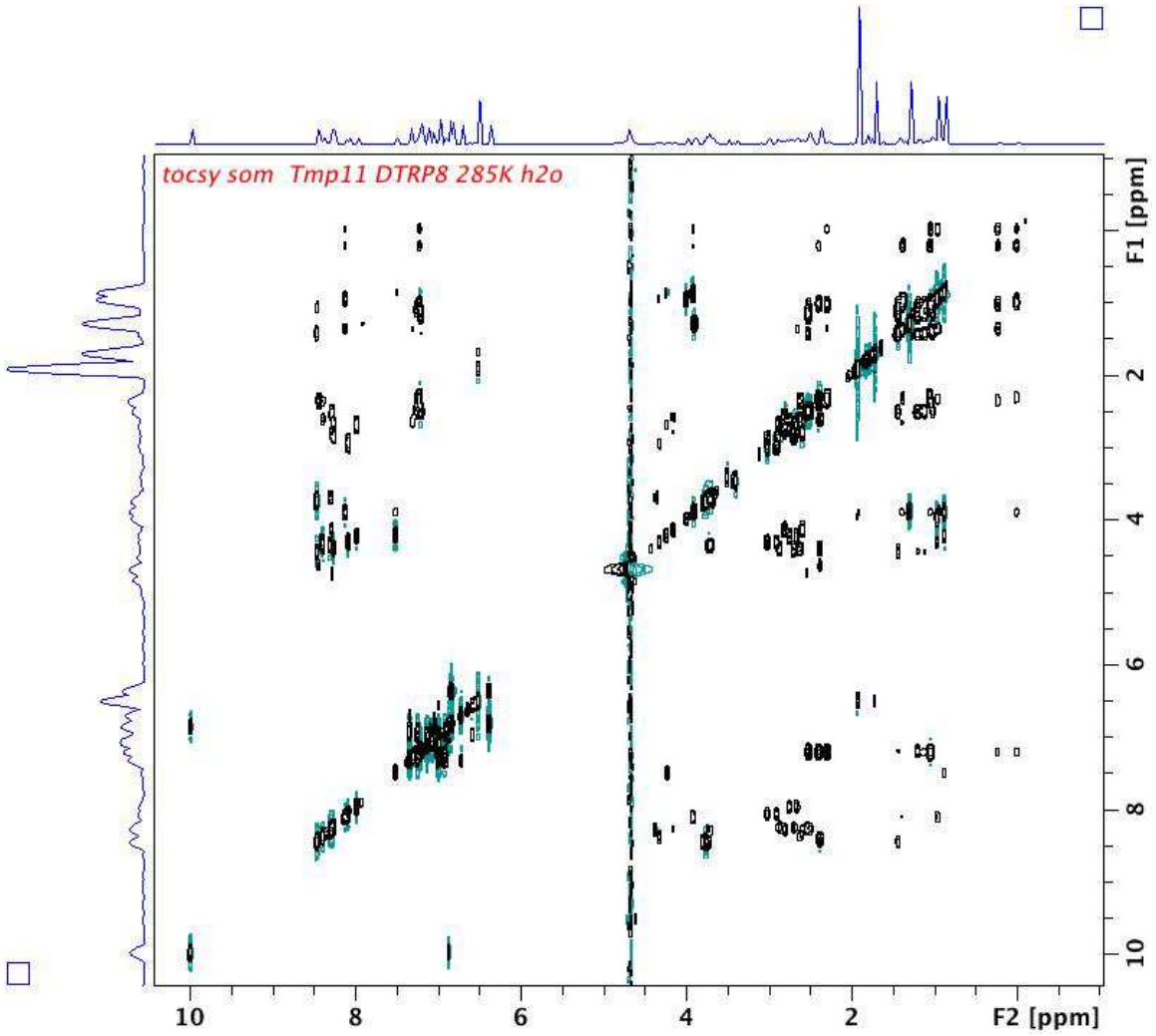
[a] ‹SA› refers to the ensemble of the 25 structures with the lowest energy.
[b] R.m.s deviation between the ensemble of structures <SA> and the lowest energy structure.
[c] No distance restraint in any of the structures included in the ensemble was violated by more than 0.3 Å.
[d] E_{L-J} is the Lennard-Jones van der Waals energy calculated using the CHARMM-PARMALLH6 parameters. E_{L-J} was not included in the target function during the structure calculation.

[L-Tmp11_D-Trp8]-SRIF, 57: Somatostatin analog **57** was synthesized following the general procedure from 0.20 g of 2-Cl-Trt resin (0.8 mmol/g) and using Fmoc-L-Tmp-OH, affording 0.15 g in 42% yield (99% purity after purification). HPLC: t_R = 14.3 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for $C_{79}H_{110}N_{18}O_{19}S_2$: 1678.7636; found, 1678.7644.

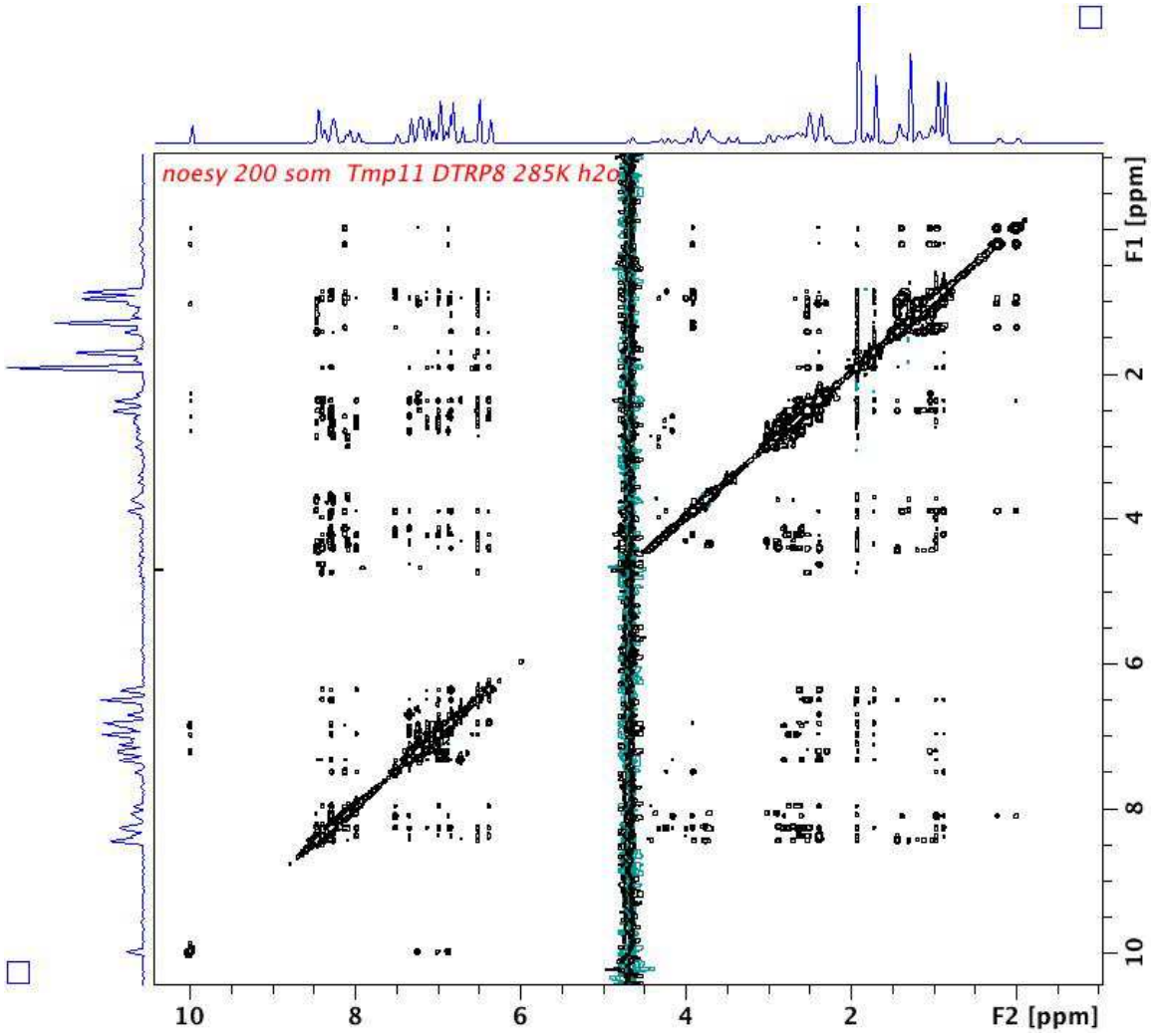
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala		H^{α} 3.88	H^{β} 1.28		
2 Gly	H^{N} 8.46	H^{α} 3.74			
3 Cys	H^{N} 8.25	H^{α} 4.40	H^{β} 2.77		
4 Lys	H^{N} 8.46	H^{α} 4.44	H^{β} 1.42	H^{γ} 1.11 H^{ε} 2.55	H^{Z} 7.20
5 Asn	H^{N} 8.43	H^{α} 4.63	H^{β} 2.36	$H^{\delta 21}$ 7.33	$H^{\delta 22}$ 6.71
6 Phe	H^{N} 8.38	H^{α} 4.41	H^{β} 2.49	H^{D} 6.37	H^{E} 6.83
7 Phe	H^{N} 7.97	H^{α} 4.22	H^{β} 2.69	H^{D} 6.98	H^{E} 7.12 H^{Z} 7.06
8 D-Trp	H^{N} 8.26	H^{α} 4.14 H^{H2} 6.99	H^{β} 2.72 H^{E1} 9.98	H^{D1} 6.86 H^{Z3} 6.90	H^{E3} 7.33 H^{Z2} 7.23
9 Lys	H^{N} 8.12	H^{α} 3.90	H^{β} 0.94 H^{ε} 2.28	$H^{\gamma 2}$ 0.49 $H^{\gamma 3}$ 0.16	H^{Z} 7.21
10 Thr	H^{N} 7.50	H^{α} 4.22	H^{β} 3.90	H^{γ} 0.86	
11 Tmp	H^{N} 8.27	H^{α} 4.75	H^{β} 2.51	H^{D} 6.50	H^{F} 1.91 H^{H} 1.70
12 Thr	H^{N} 8.39	H^{α} 4.31	H^{β} 3.98	H^{γ} 0.95	
13 Ser	H^{N} 8.29	H^{α} 4.35	H^{β} 3.69		
14 Cys	H^{N} 8.08	H^{α} 4.31	H^{β} 2.91		

TOCSY 50 ms



NOESY 200 ms



Structural Statistics for the 25 Lowest Energy Structures of [L-Tmp11_D-Trp8]-SRIF

Restraints used for the calculation ‹SA›[a]	
Intraresidual	0
Sequential (|i-j| =1)	63
Medium range(1 < |i-j| ≤ 4)	9
Long range (|i-j| > 4)	19
Unambiguous	All
Ambiguous	0
All	91
Dihedral angle restrictions	18
Restraint per residue ratio	7.8
RSMD (Å) from experimental[b]	
NOE:	0.00696 +/- 0.0017
Bonds (Å)	0.00515 +/- 0.00069
Angles (°)	1.117 +/- 0.020
Coordinate Precision (Å)[c]	0.58
All Atoms	
CNS potential energy (kcal mol^{-1})	
Total energy[d]	-282.7 +/- 10.66
Van der Waals	-37.99 +/- 4.964
Electrostatic	-417.9 +/- 8.767
Bonds	6.401 +/- 1.744
Angles	80.22 +/- 3.025

[a] ‹SA› refers to the ensemble of the 25 structures with the lowest energy.
[b] R.m.s deviation between the ensemble of structures <SA> and the lowest energy structure.
[c] No distance restraint in any of the structures included in the ensemble was violated by more than 0.3 Å.
[d] $E_{L\text{-}J}$ is the Lennard-Jones van der Waals energy calculated using the CHARMM-PARMALLH6 parameters. $E_{L\text{-}J}$ was not included in the target function during the structure calculation.

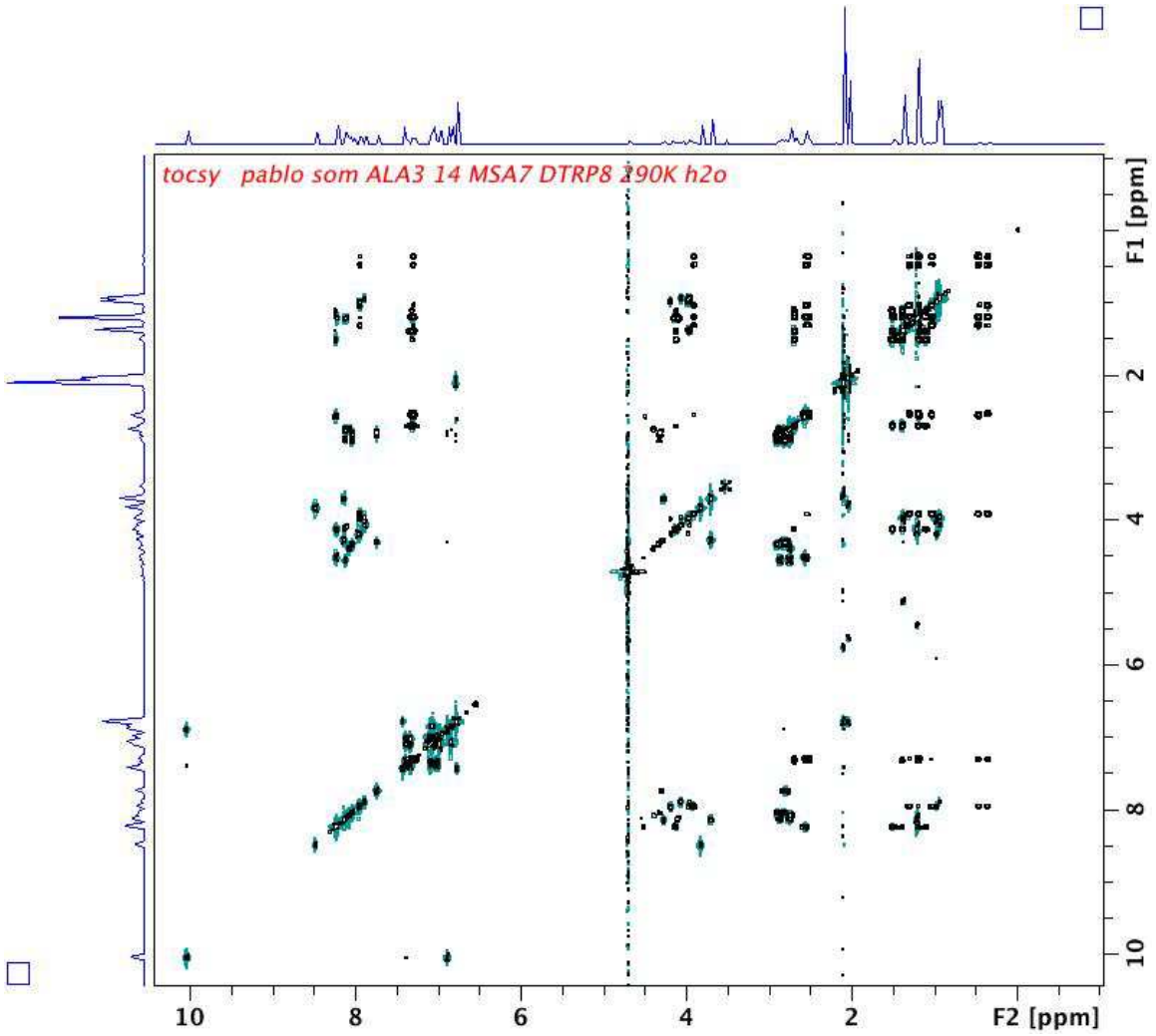
Linear Derivatives:

[Ala(3,14)_L-Msa7_D-Trp8]-SRIF, 58: Somatostatin analog **58** was synthesized following the general procedure from 0.10 g of 2-Cl-Trt resin (0.8 mmol/g) and using Fmoc-L-Msa-OH, affording 0.12 g in 86% yield (99% purity after purification). HPLC: t_R = 10.7 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd for $C_{79}H_{112}N_{18}O_{19}$: 1616.8351; found, 1616.8337.

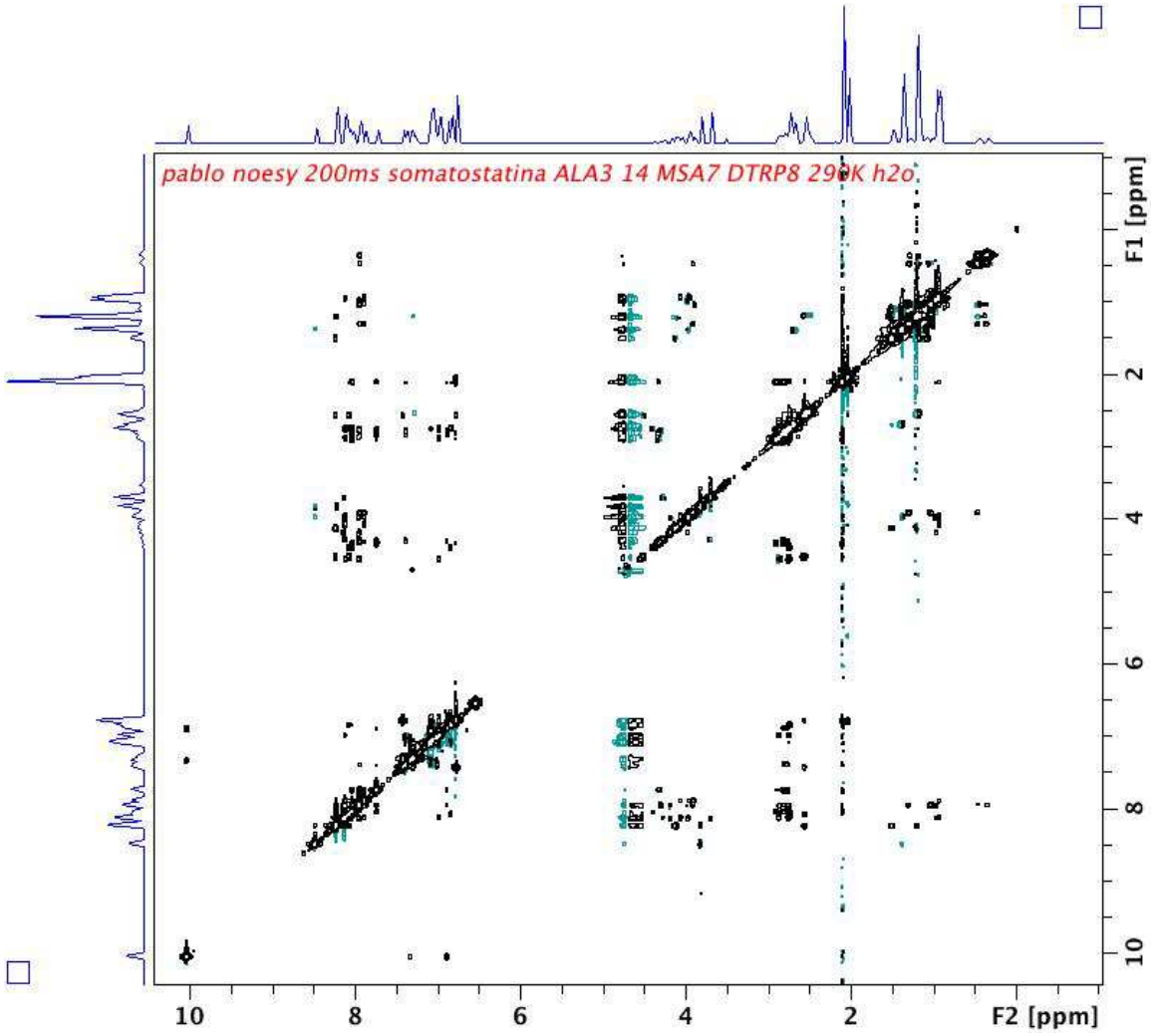
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala		H^{α} 3.95	H^{β} 1.36		
2 Gly	H^{N} 8.47	H^{α} 3.80			
3 Ala	H^{N} 8.21	H^{α} 4.13	H^{β} 1.19		
4 Lys	H^{N} 8.22	H^{α} 4.11	H^{β} 1.26	H^{δ} 1.37	H^{ε} 2.68
					H^{Z2} 7.30
5 Asn	H^{N} 8.22	H^{α} 4.50	H^{β} 2.55	$H^{\delta21}$ 7.42	$H^{\delta22}$ 6.76
6 Phe	H^{N} 8.07	H^{α} 4.38	H^{β} 2.73	H^{D} 6.83	H^{E} 7.07
7 Msa	H^{N} 8.03	H^{α} 4.32	H^{β} 2.84	H^{F} 2.09	H^{E} 6.77
					H^{H} 2.02
8 D-Trp	H^{N} 7.73	H^{α} 4.29	H^{β} 2.79	H^{D1} 6.88	H^{E3} 7.38
		H^{H2} 7.08	H^{E1} 10.03	H^{Z3} 7.00	H^{Z2} 7.32
9 Lys	H^{N} 7.94	H^{α} 3.90	H^{β} 1.15	H^{γ} 0.42	H^{ε} 2.52
				H^{δ} 1.18	H^{Z2} 7.28
10 Thr	H^{N} 7.88	H^{α} 4.05	H^{β} 3.95	H^{γ} 0.92	
11 Phe	H^{N} 8.11	H^{α} 4.54	H^{β} 2.79	H^{D} 6.97	H^{E} 7.09
12 Thr	H^{N} 7.94	H^{α} 4.17	H^{β} 3.97	H^{γ} 0.96	
13 Ser	H^{N} 8.13	H^{α} 4.26	H^{β} 3.68		
14 Ala	H^{N} 8.10	H^{α} 4.08	H^{β} 1.20		

TOCSY 50 ms


tocsy pablo som ALA3 14 MSA7 DTRP8 290K h2o
F1 [ppm]
F2 [ppm]
10
8
6
4
2

NOESY 200 ms

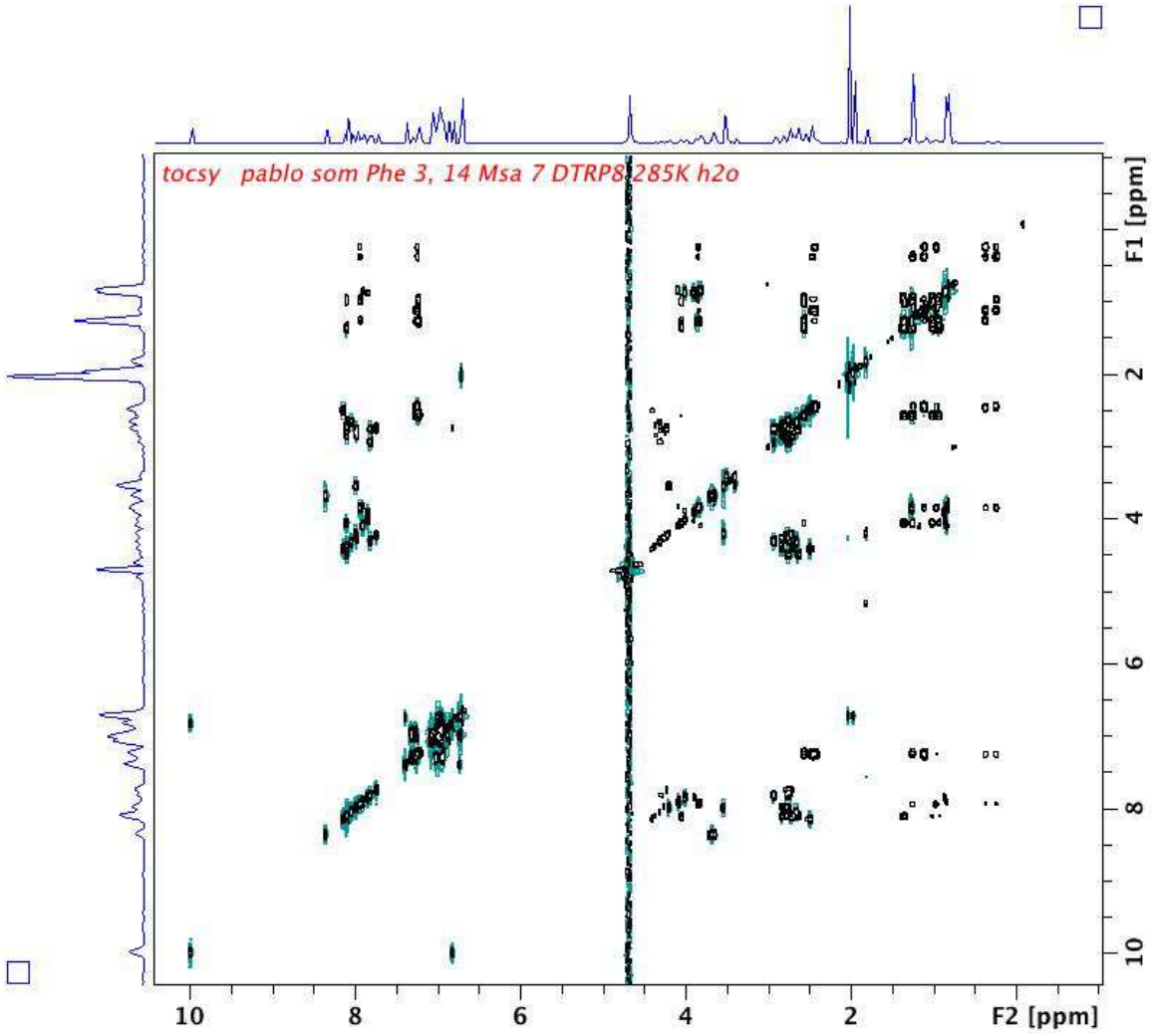

pablo noesy 200ms somatostatina ALA3 14 MSA7 DTRP8 29
K h2o
F1 [ppm]
F2 [ppm]
10
8
6
4
2

[Phe(3,14)_L-Msa7_D-Trp8]-SRIF, 59: Somatostatin analog **59** was synthesized following the general procedure from 0.10 g of 2-Cl-Trt resin (0.8 mmol/g) and using Fmoc-L-Msa-OH, affording 0.14 g in 81% yield (99% purity after purification). HPLC: t_R = 12.2 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd for $C_{91}H_{120}N_{18}O_{19}$: 1768.8977; found, 1768.8969.

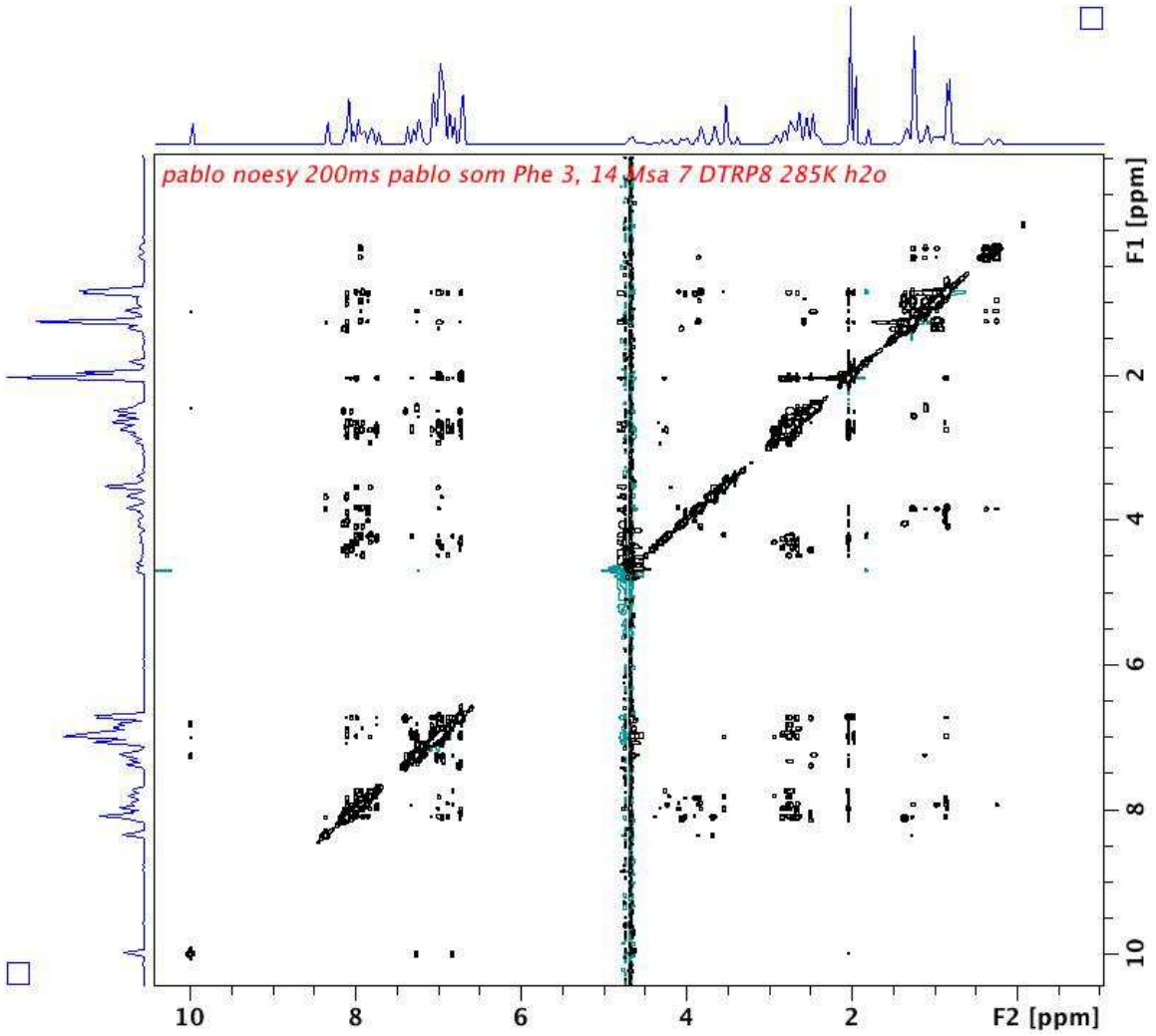
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala		H^{α} 3.83	H^{β} 1.25		
2 Gly	H^{N} 8.35	H^{α} 3.66			
3 Phe	H^{N} 8.09	H^{α} 4.36	H^{β} 2.75	H^{D} 6.95	H^{E} 7.07
4 Lys	H^{N} 8.10	H^{α} 4.09	H^{β} 1.34	H^{γ} 0.94	H^{ε} 2.55
					H^{Z2} 7.22
5 Asn	H^{N} 8.13	H^{α} 4.49	H^{β} 2.47	$H^{\delta 21}$ 7.38	$H^{\delta 22}$ 6.72
6 Phe	H^{N} 8.04	H^{α} 4.39	H^{β} 2.64	H^{D} 6.72	H^{E} 6.98
7 Msa	H^{N} 7.97	H^{α} 4.29	H^{β} 2.76	H^{F} 2.02	H^{E} 6.71
					H^{H} 1.95
8 D-Trp	H^{N} 7.73	H^{α} 4.27	H^{β} 2.73	H^{D1} 6.81	H^{E3} 7.31
		H^{H2} 7.00	H^{E1} 9.98	H^{Z3} 6.93	H^{Z2} 7.25
9 Lys	H^{N} 7.93	H^{α} 3.88	H^{β} 1.09	H^{γ} 0.29	H^{ε} 2.42
				H^{δ} 1.09	H^{Z2} 7.23
10 Thr	H^{N} 7.84	H^{α} 3.99	H^{β} 3.89	H^{γ} 0.85	
11 Phe	H^{N} 8.08	H^{α} 4.57	H^{β} 2.68	H^{D} 6.87	H^{E} 6.99
12 Thr	H^{N} 7.90	H^{α} 4.17	H^{β} 3.81	H^{γ} 0.81	
13 Ser	H^{N} 7.98	H^{α} 4.28	H^{β} 3.52		
14 Phe	H^{N} 8.81	H^{α} 4.29	H^{β} 2.82	H^{D} 6.98	H^{E} 7.07

TOCSY 50 ms


tocsy pablo som Phe 3, 14 Msa 7 DTRP8 285K h2o
F1 [ppm]
F2 [ppm]
10
8
6
4
2

NOESY 200 ms


pablo noesy 200ms pablo som Phe 3, 14 Msa 7 DTRP8 285K h2o
F1 [ppm]
F2 [ppm]
10
8
6
4
2

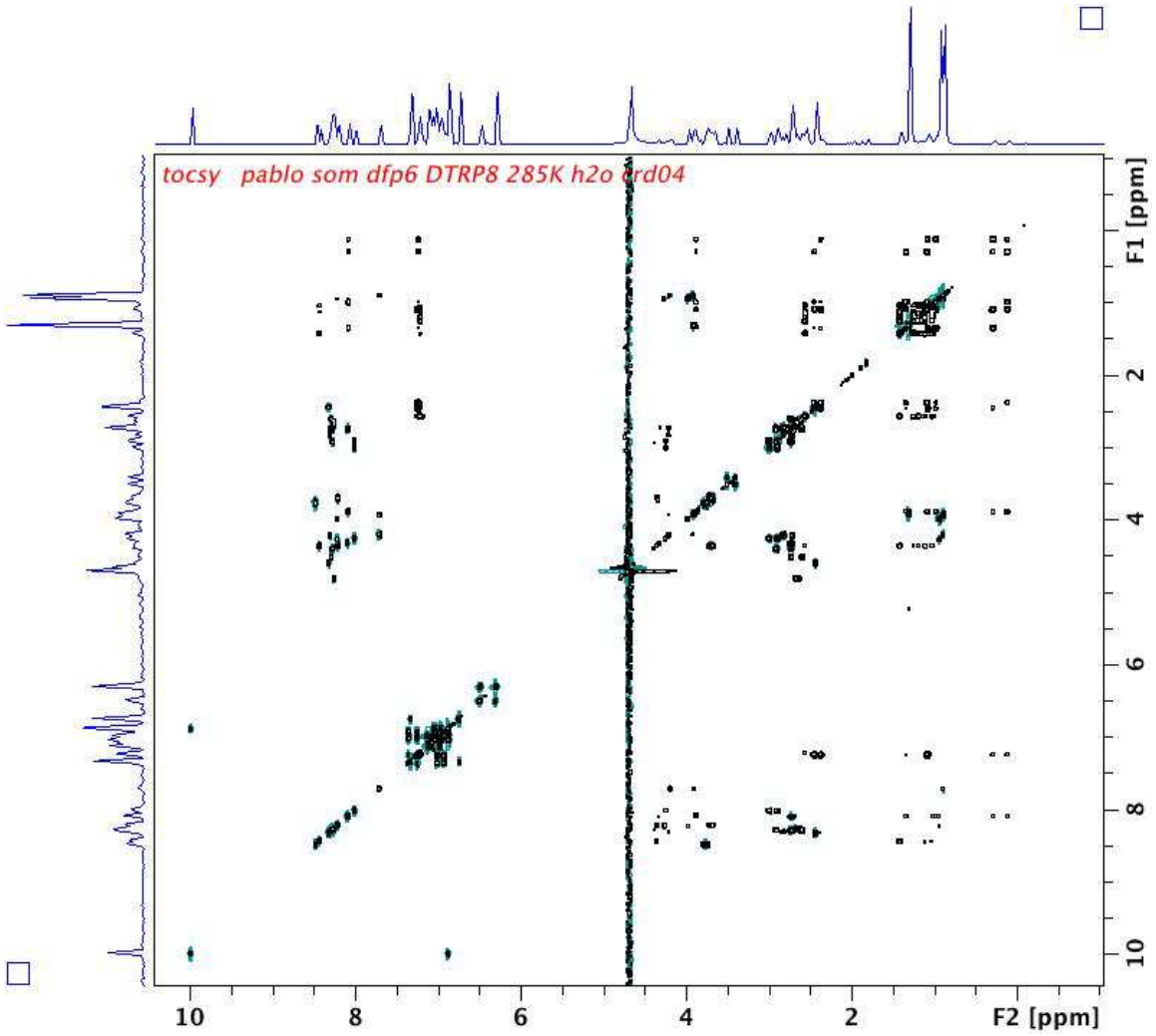
Analogs containing the Dfp amino acid:

[L-Dfp6_D-Trp8]-SRIF, 60: Somatostatin analog **60** was synthesized following the general procedure from 0.20 g of 2-Cl-Trt resin (0.8 mmol/g) and using Fmoc-L-Dfp-OH, affording 0.08 g in 43% yield (99% purity after purification). HPLC: t_R = 16.5 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for $C_{76}H_{102}F_2N_{18}O_{19}S_2$: 1672.6978; found, 1672.6981.

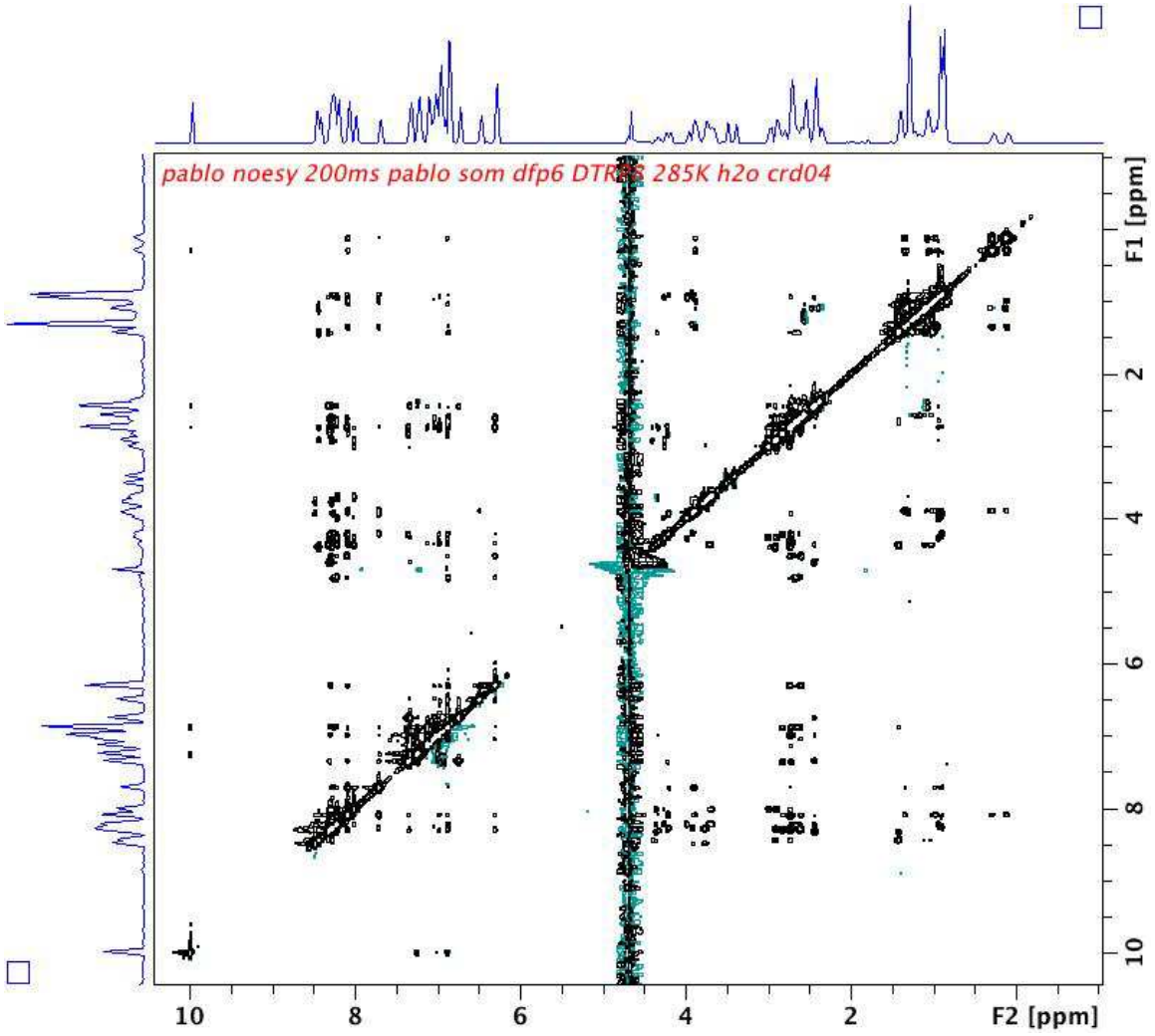
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.90	H^α 3.89	H^β 1.29		
2 Gly	H^N 8.47	H^α 3.75			
3 Cys	H^N 8.27	H^α 4.38	H^β 2.81		
4 Lys	H^N 8.43	H^α 4.34	H^β 1.21	H^γ 1.05	H^ε 2.54
5 Asn	H^N 8.31	H^α 4.58	H^β 2.42	$H^{\delta21}$ 7.33	$H^{\delta22}$ 6.73
6 Dfp	H^N 8.28	H^α 4.49	H^β 2.65	H^D 6.29	H^Z 6.48
7 Phe	H^N 8.08	H^α 4.30	H^β 2.71	H^D 6.97	H^E 7.11
8 D-Trp	H^N 8.29	H^α 4.19	H^β 2.76	H^{D1} 6.87	H^{E3} 7.35
		H^{H2} 7.00	H^{E1} 9.13	H^{Z3} 6.92	H^{Z2} 7.24
9 Lys	H^N 8.08	H^α 3.87	H^β 1.14	$H^{\gamma2}$ 0.28	H^E 2.38
				$H^{\gamma3}$ 0.10	
10 Thr	H^N 7.70	H^α 4.18	H^β 3.91	H^γ 0.88	
11 Phe	H^N 8.25	H^α 4.79	H^β 2.65	H^D 6.86	H^E 7.03
					H^Z 6.97
12 Thr	H^N 8.21	H^α 4.25	H^β 3.97	H^γ 0.92	
13 Ser	H^N 8.20	H^α 4.34	H^β 3.68		
14 Cys	H^N 8.00	H^α 4.23	H^β 2.93		

TOCSY 50 ms


tocsy pablo som dfp6 DTRP8 285K h2o crd04
F1 [ppm]
F2 [ppm]
10
8
6
4
2

NOESY 200 ms


pablo noesy 200ms pablo som dfp6 DTR25 285K h2o crd04
F1 [ppm]
F2 [ppm]
10
8
6
4
2

Structural Statistics for the 25 Lowest Energy Structures of [L-Dfp6_D-Trp8]-SRIF

Restraints used for the calculation ‹SA›[a]	
Intraresidual	0
Sequential (|i-j| =1)	48
Medium range(1 < |i-j| ≤ 4)	27
Long range (|i-j| > 4)	28
Unambiguous	All
Ambiguous	0
All	99
Dihedral angle restrictions	22
Restraint per residue ratio	8.6
RSMD (Å) from experimental[b]	
NOE:	0.01067 +/- 0.0007425
Bonds (Å)	0.005913 +/- 0.0003035
Angles (°)	0.6805 +/- 0.02805
Coordinate Precision (Å)[c]	0.62
All Atoms	
CNS potential energy (kcal mol^{-1})	
Total energy[d]	-357.2 +/- 8.1
Van der Waals	-38.62 +/- 4.65
Electrostatic	-447.1 +/- 10.2
Bonds	7.991 +/- 0.822
Angles	28.54 +/- 2.35

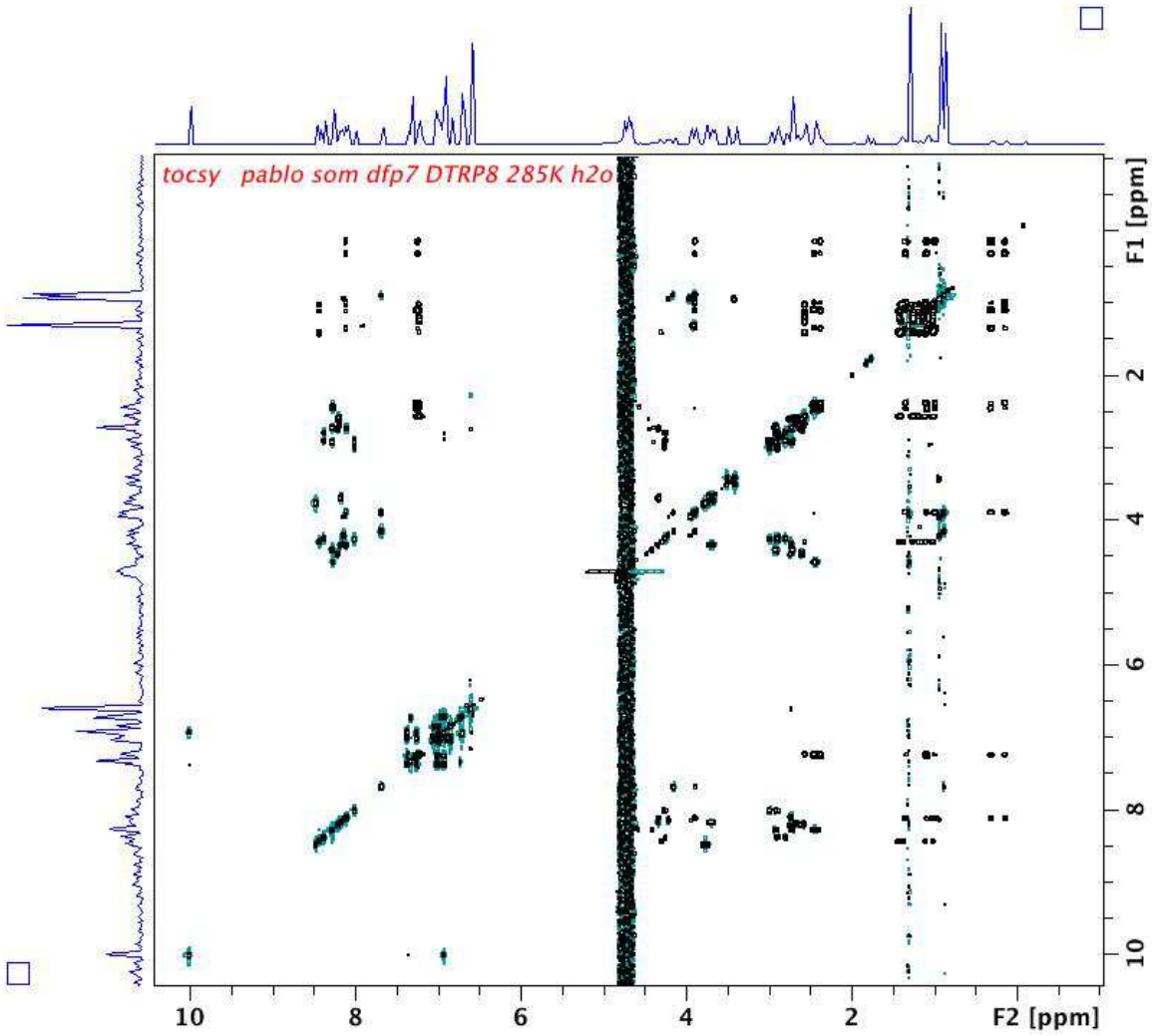
[a] ‹SA› refers to the ensemble of the 25 structures with the lowest energy.
[b] R.m.s deviation between the ensemble of structures <SA> and the lowest energy structure.
[c] No distance restraint in any of the structures included in the ensemble was violated by more than 0.3 Å.
[d] $E_{L\text{-}J}$ is the Lennard-Jones van der Waals energy calculated using the CHARMM-PARMALLH6 parameters. $E_{L\text{-}J}$ was not included in the target function during the structure calculation.

[L-Dfp7_D-Trp8]-SRIF, 61: Somatostatin analog **61** was synthesized following the general procedure from 0.20 g of 2-Cl-Trt resin (0.8 mmol/g) and using Fmoc-L-Dfp-OH, affording 0.11 g in 53% yield (99% purity after purification). HPLC: t_R = 15.6 [Gradient 25-60%B in 20min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd for $C_{76}H_{102}F_2N_{18}O_{19}S_2$: 1672.6978; found, 1672.6964.

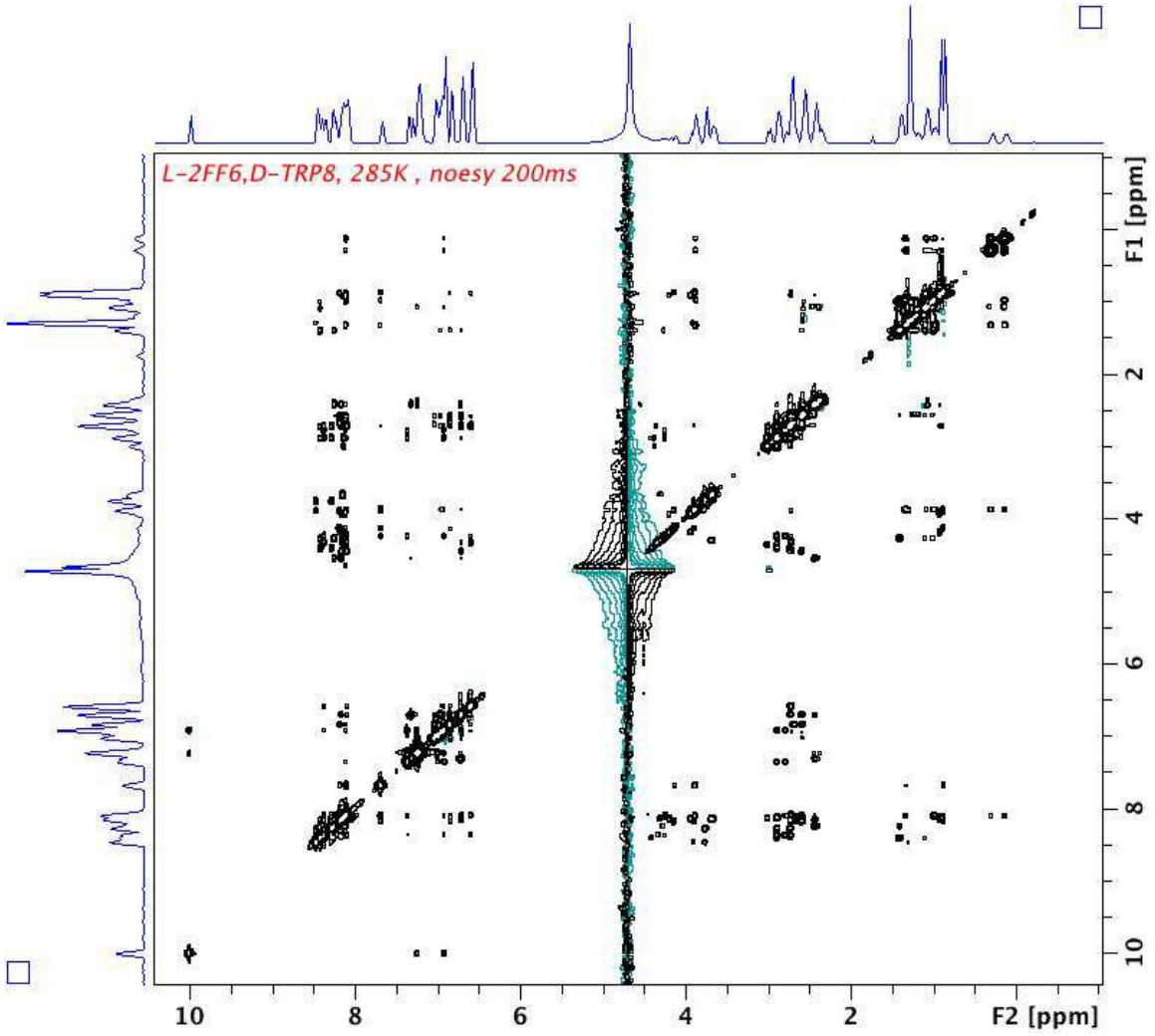
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.91	H^α 3.89	H^β 1.30		
2 Gly	H^N 8.47	H^α 3.75			
3 Cys	H^N 8.28	H^α 4.41	H^β 2.81		
4 Lys	H^N 8.41	H^α 4.27	H^β 1.21	H^γ 1.05	H^ε 2.56
					H^{Z2} 7.23
5 Asn	H^N 8.25	H^α 4.19	H^β 2.42	$H^{\delta21}$ 7.32	$H^{\delta22}$ 6.71
6 Phe	H^N 8.16	H^α 4.45	H^β 2.65	H^D 6.71	H^E 6.96
7 Dfp	H^N 8.09	H^α 4.33	H^β 2.71	H^D 6.59	
8 D-Trp	H^N 8.37	H^α 4.24	H^β 2.83	H^{D1} 6.92	H^{E3} 7.25
		H^{H2} 6.92	H^{E1} 10.00	H^{Z3} 7.00	H^{Z2} 7.36
9 Lys	H^N 8.10	H^α 3.87	H^β 1.13	$H^{\gamma2}$ 0.29	H^E 2.40
				$H^{\gamma3}$ 0.13	
10 Thr	H^N 7.68	H^α 4.13	H^β 3.89	H^γ 0.87	
11 Phe	H^N 8.19	H^α 4.66	H^β 2.63	H^D 6.84	H^E 7.03
12 Thr	H^N 8.11	H^α 4.19	H^β 3.93	H^γ 0.92	
13 Ser	H^N 8.15	H^α 4.31	H^β 3.67		
14 Cys	H^N 8.13	H^α 4.36	H^β 2.94		

TOCSY 50 ms



NOESY 200 ms



Structural Statistics for the 25 Lowest Energy Structures of [L-Dfp7_D-Trp8]-SRIF

Restraints used for the calculation ‹SA›[a]	
Intraresidual	0
Sequential (|i-j| =1)	63
Medium range(1 < |i-j| ≤ 4)	22
Long range (|i-j| > 4)	10
Unambiguous	All
Ambiguous	0
All	95
Dihedral angle restrictions	19
Restraint per residue ratio	8.1
RSMD (Å) from experimental[b]	
NOE:	0.02691 +/- 0.002473
Bonds (Å)	0.01357 +/- 0.0008174
Angles (°)	1.176 +/- 0.03831
Coordinate Precision (Å)[c]	0.68
All Atoms	
CNS potential energy (kcal mol^{-1})	
Total energy[d]	-195.3 +/- 14.12
Van der Waals	-13.57 +/- 7.295
Electrostatic	-441.3 +/- 15.76
Bonds	42.16 +/- 5.115
Angles	85.18 +/- 5.597

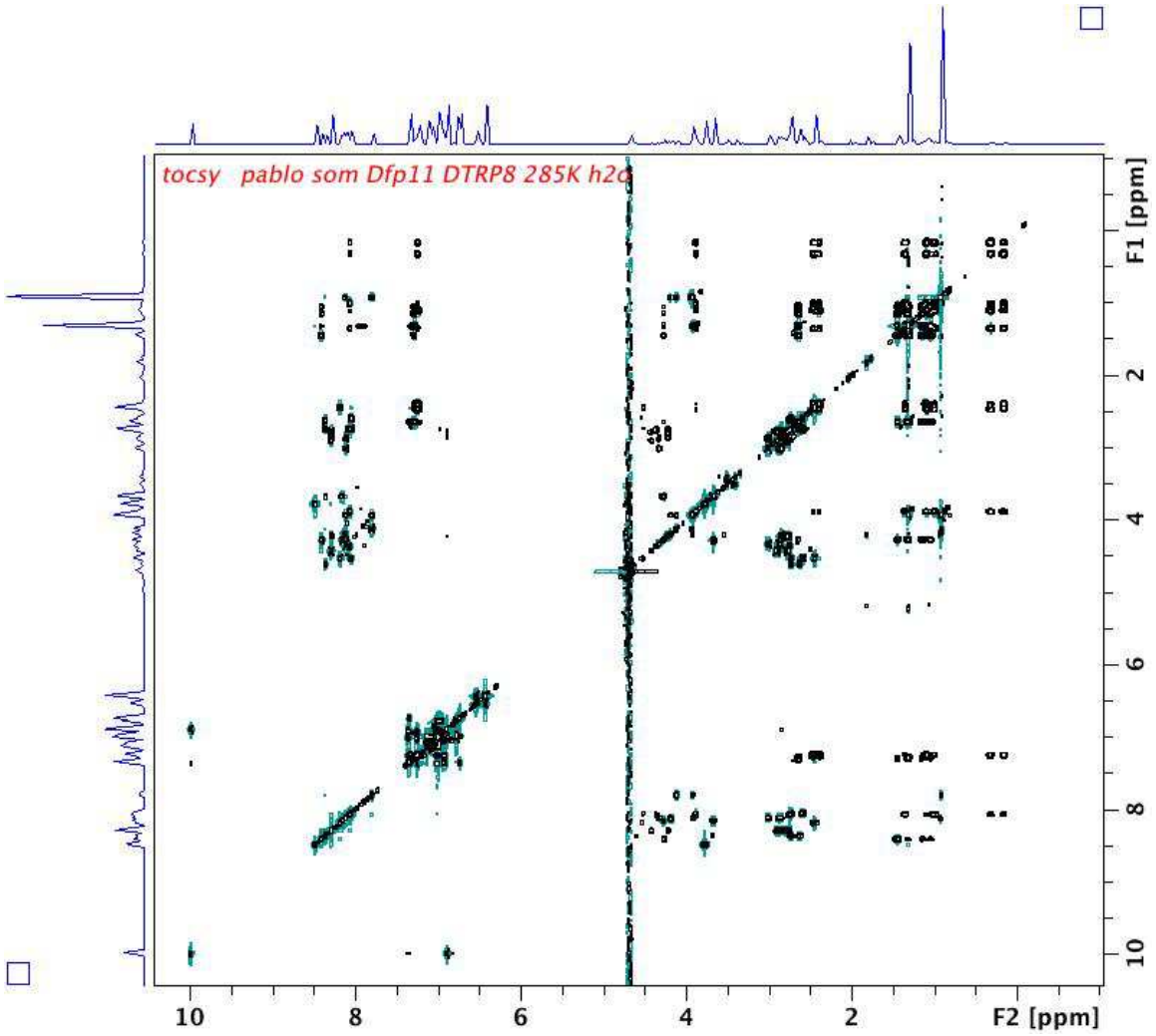
[a] ‹SA› refers to the ensemble of the 25 structures with the lowest energy.
[b] R.m.s deviation between the ensemble of structures <SA> and the lowest energy structure.
[c] No distance restraint in any of the structures included in the ensemble was violated by more than 0.3 Å.
[d] E_{L-J} is the Lennard-Jones van der Waals energy calculated using the CHARMM-PARMALLH6 parameters. E_{L-J} was not included in the target function during the structure calculation.

[L-Dfp11_D-Trp8]-SRIF, 62: Somatostatin analog **62** was synthesized following the general procedure from 0.20 g of 2-Cl-Trt resin (0.8 mmol/g) and using Fmoc-L-Dfp-OH, affording 0.14 g in 67% yield (99% purity after purification). HPLC: t_R = 17.2 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for $C_{76}H_{102}F_2N_{18}O_{19}S_2$: 1672.6978; found, 1672.6894.

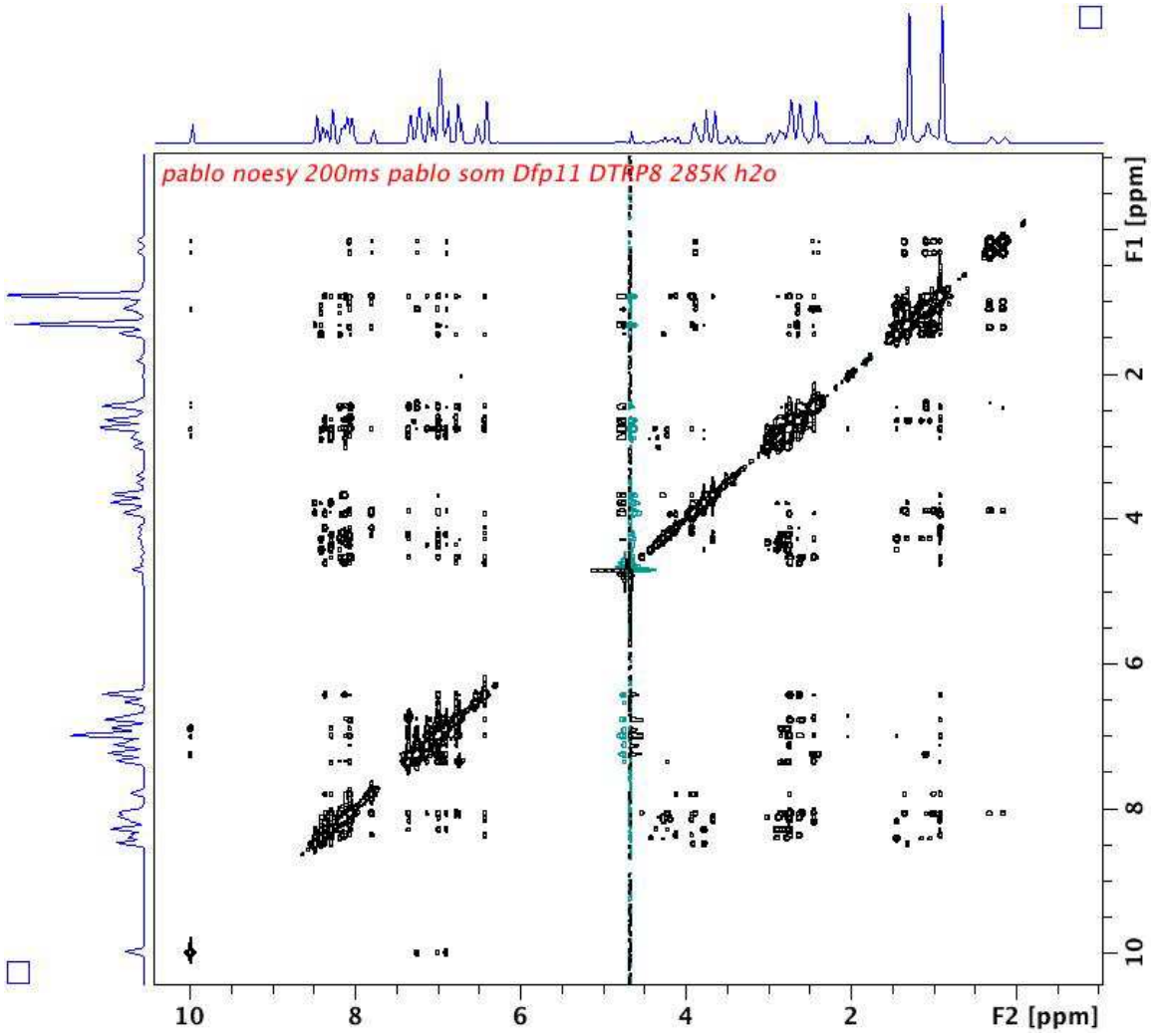
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.91	H^α 3.89	H^β 1.30		
2 Gly	H^N 8.48	H^α 3.76			
3 Cys	H^N 8.28	H^α 4.41	H^β 2.82		
4 Lys	H^N 8.40	H^α 4.25	H^β 1.43	H^γ 1.08	H^ε 2.62 H^{Z2} 7.27
5 Asn	H^N 8.17	H^α 4.51	H^β 2.43	$H^{\delta21}$ 7.33	$H^{\delta22}$ 6.73
6 Phe	H^N 8.04	H^α 4.51	H^β 2.64	H^D 6.76	H^E 6.99 H^Z 6.95
7 Phe	H^N 8.06	H^α 4.34	H^β 2.73	H^D 6.98	H^E 7.12 H^Z 7.07
8 D-Trp	H^N 8.28	H^α 4.20	H^β 2.78	H^{D1} 6.88	H^{E3} 7.35
		H^{H2} 6.99	H^{E1} 9.98	H^{Z3} 6.91	H^{Z2} 7.24
9 Lys	H^N 8.06	H^α 3.87	H^β 1.65	$H^{\gamma2}$ 0.30 $H^{\gamma3}$ 0.14	H^E 2.41
10 Thr	H^N 7.79	H^α 4.10	H^β 3.91	H^γ 0.90	
11 Dfp	H^N 8.35	H^α 4.59	H^β 2.68	H^D 6.42	H^Z 6.53
12 Thr	H^N 8.11	H^α 4.17	H^β 3.91	H^γ 0.90	
13 Ser	H^N 8.15	H^α 4.14	H^β 3.65		
14 Cys	H^N 8.11	H^α 4.31	H^β 2.92		

TOCSY 50 ms



NOESY 200 ms


pablo noesy 200ms pablo som Dfp11 DTRP8 285K h2o
F1 [ppm]
F2 [ppm]
10
8
6
4
2

Structural Statistics for the 25 Lowest Energy Structures of [L-Dfp11_D-Trp8]-SRIF

Restraints used for the calculation ‹SA›[a]	
Intraresidual	0
Sequential (|i-j| =1)	72
Medium range(1 < |i-j| ≤ 4)	13
Long range (|i-j| > 4)	21
Unambiguous	All
Ambiguous	0
All	106
Dihedral angle restrictions	10
Restraint per residue ratio	8.3
RSMD (Å) from experimental[b]	
NOE:	0.0226 +/- 0.001326
Bonds (Å)	0.01415 +/- 0.001073
Angles (°)	1.72 +/- 0.07001
Coordinate Precision (Å)[c]	0.49
All Atoms	
CNS potential energy (kcal mol^{-1})	
Total energy[d]	4.57 +/- 17.83
Van der Waals	5.861 +/- 8.52
Electrostatic	-407.4 +/- 11.8
Bonds	45.91 +/- 6.96
Angles	182.4 +/- 14.9

[a] ‹SA› refers to the ensemble of the 25 structures with the lowest energy.
[b] R.m.s deviation between the ensemble of structures <SA> and the lowest energy structure.
[c] No distance restraint in any of the structures included in the ensemble was violated by more than 0.3 Å.
[d] E_{L-J} is the Lennard-Jones van der Waals energy calculated using the CHARMM-PARMALLH6 parameters. E_{L-J} was not included in the target function during the structure calculation.

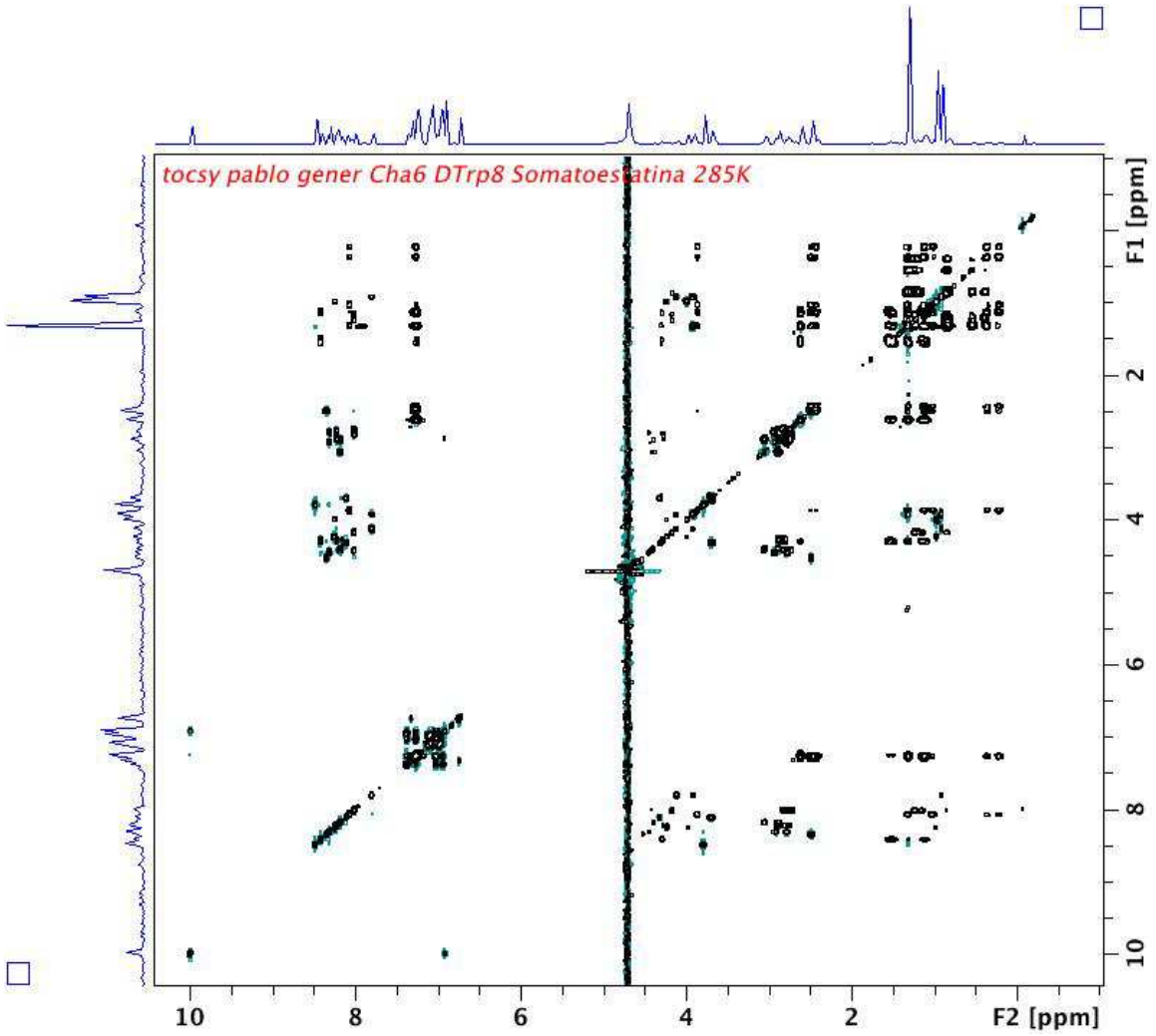
Analogs containing the Cha amino acid:

[L-Cha6_D-Trp8]-SRIF, 63: Somatostatin analog **63** was synthesized following the general procedure from 0.4 g of 2-Cl-Trt resin (0.8 mmol/g) and using Fmoc-L-Cha-OH, affording 0.38 g in 66% yield (99% purity after purification). HPLC: t_R = 12.3 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for $C_{76}H_{110}N_{18}O_{19}S_2$: 1642.7631; found, 1642.7630.

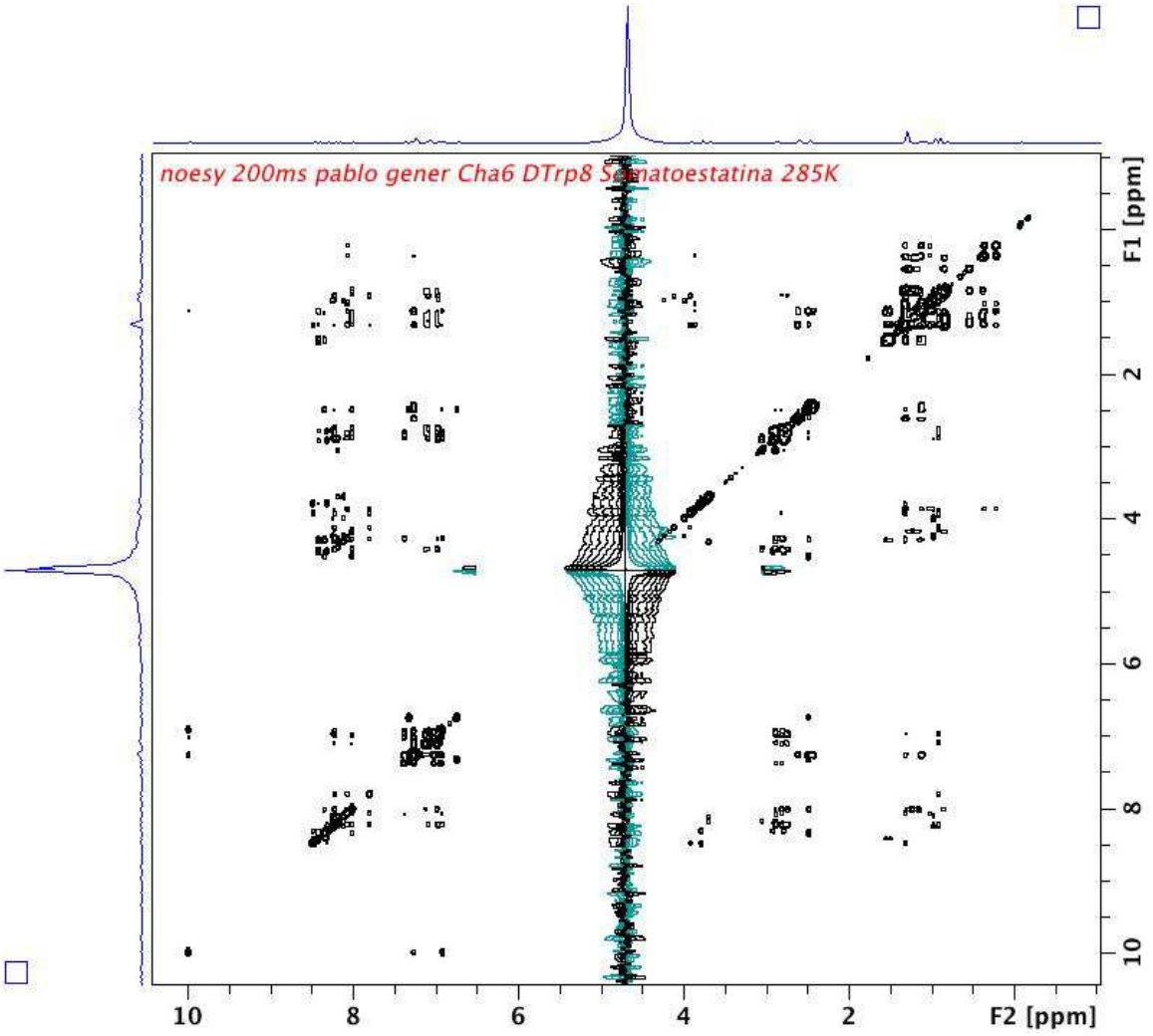
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.91	H^α 3.90	H^β 1.30		
2 Gly	H^N 8.47	H^α 3.77			
3 Cys	H^N 8.30	H^α 4.43	H^β 2.83		
4 Lys	H^N 8.41	H^α 4.27	H^β 1.50	H^γ 1.11	H^δ 1.30
5 Asn	H^N 8.33	H^α 4.50	H^β 2.47	$H^{\delta21}$ 7.31	$H^{\delta22}$ 6.73
6 Cha	H^N 7.97	H^α 4.40	H^β 2.76		
7 Phe	H^N 8.21	H^α 4.22	H^β 2.71	H^D 6.88	H^E 7.11
8 D-Trp	H^N 8.21	H^α 4.26	H^β 2.83	H^{D1} 6.90	H^{E3} 7.37
		H^{H2} 7.00	H^{E1} 9.98	H^{Z3} 6.92	H^{Z2} 7.25
9 Lys	H^N 8.06	H^α 3.85	H^β 1.02	H^γ 0.34	H^δ 1.10
10 Thr	H^N 7.79	H^α 4.10	H^β 3.90	H^γ 0.90	
11 Phe	H^N 8.30	H^α 4.42	H^β 2.93	H^D 7.13	
12 Thr	H^N 8.24	H^α 4.22	H^β 3.97	H^γ 0.96	
13 Ser	H^N 8.10	H^α 4.30	H^β 3.68		
14 Cys	H^N 8.17	H^α 4.38	H^β 2.91		

TOCSY 50 ms


tocsy pablo gener Cha6 DTrp8 Somatoestatina 285K
F1 [ppm]
F2 [ppm]
10
8
6
4
2

NOESY 200 ms

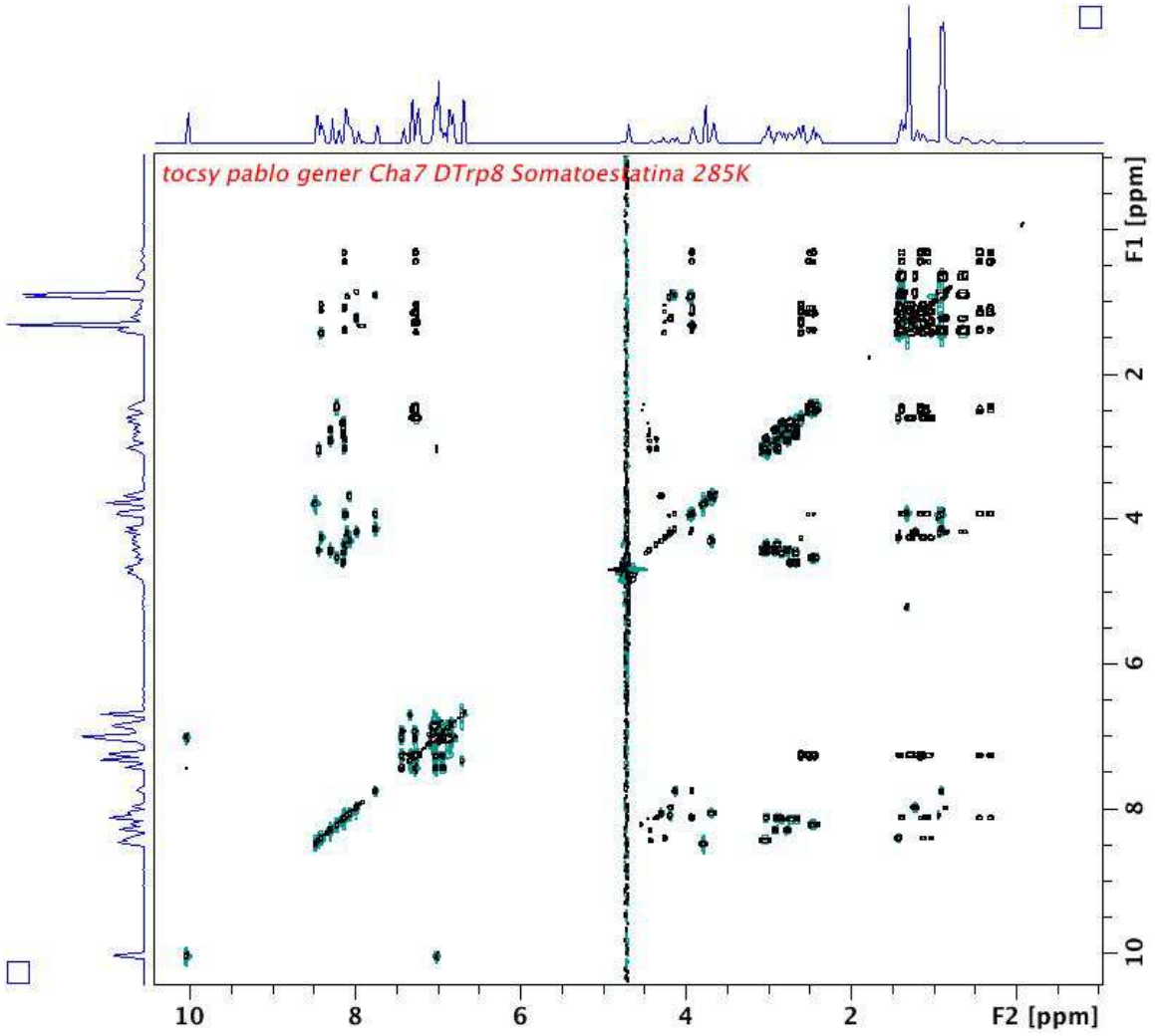

noesy 200ms pablo gener Cha6 DTrp8 Somatoestatina 285K
F1 [ppm]
F2 [ppm]
10
8
6
4
2

[L-Cha7_D-Trp8]-SRIF, 64: Somatostatin analog **64** was synthesized following the general procedure from 0.4 g of 2-Cl-Trt resin (0.8 mmol/g) and using Fmoc-L-Cha-OH, affording 0.34 g in 59% yield (98% purity after purification). HPLC: t_R = 16.4 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for $C_{76}H_{110}N_{18}O_{19}S_2$: 1642.7631; found, 1642.7632.

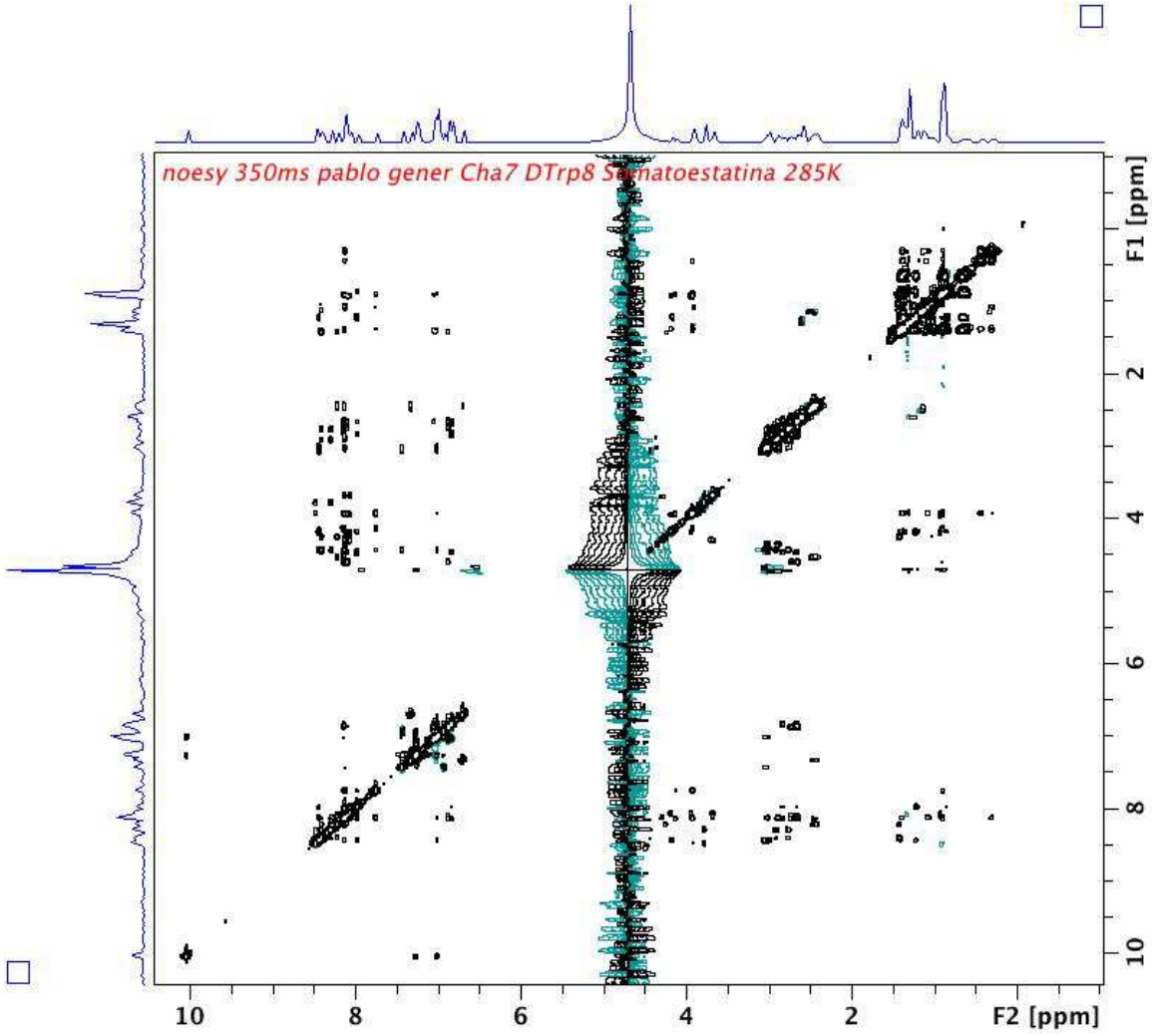
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.91	H^α 3.90	H^β 1.30		
2 Gly	H^N 8.48	H^α 3.42			
3 Cys	H^N 8.29	H^α 4.40	H^β 2.83		
4 Lys	H^N 8.40	H^α 3.24	H^β 1.41	H^γ 1.07	
5 Asn	H^N 8.21	H^α 4.51	H^β 2.44	$H^{\delta21}$ 7.33	$H^{\delta22}$ 6.70
6 Phe	H^N 8.13	H^α 4.45	H^β 2.73	H^D 6.83	H^E 7.03
7 Cha	H^N 7.97	H^α 4.16	H^β 2.99		
8 D-Trp	H^N 8.43	H^α 4.42	H^β 3.01	H^{D1} 7.00	H^{E3} 7.43
		H^{H2} 7.01	H^{E1} 10.03	H^{Z3} 6.92	H^{Z2} 7.27
9 Lys	H^N 8.12	H^α 3.91	H^β 1.20	$H^{\gamma2}$ 0.41	H^δ 1.12
				$H^{\gamma3}$ 0.29	
10 Thr	H^N 7.75	H^α 4.11	H^β 3.91	H^γ 0.89	
11 Phe	H^N 8.14	H^α 4.58	H^β 2.69	H^D 6.87	H^E 7.05
12 Thr	H^N 8.09	H^α 4.17	H^β 3.93	H^γ 0.91	
13 Ser	H^N 8.06	H^α 4.28	H^β 3.67		
14 Cys	H^N 8.12	H^α 4.34	H^β 2.95		

TOCSY 50 ms


tocsy pablo gener Cha7 DTrp8 Somatoestatina 285K
F1 [ppm]
F2 [ppm]
10
8
6
4
2

NOESY 200 ms

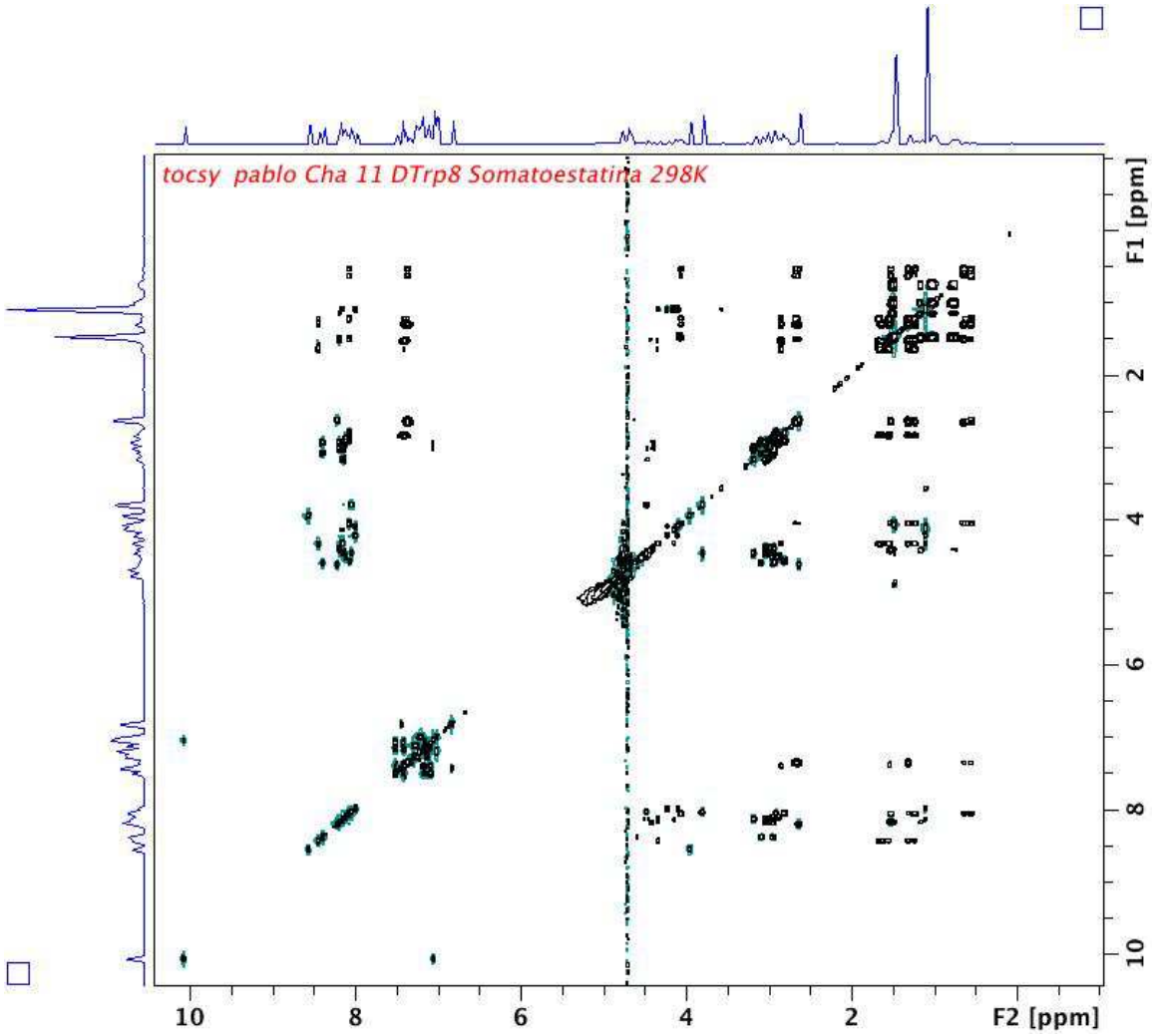

noesy 350ms pablo gener Cha7 DTrp8 Somatoestatina 285K
F1 [ppm]
F2 [ppm]
10
8
6
4
2

[L-Cha11_D-Trp8]-SRIF, 65: Somatostatin analog **65** was synthesized following the general procedure from 0.4 g of 2-Cl-Trt resin (0.8 mmol/g) and using Fmoc-L-Cha-OH, affording 0.35 g in 61% yield (98% purity after purification). HPLC: t_R = 16.3 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for $C_{76}H_{110}N_{18}O_{19}S_2$: 1642.7631; found, 1642.7632.

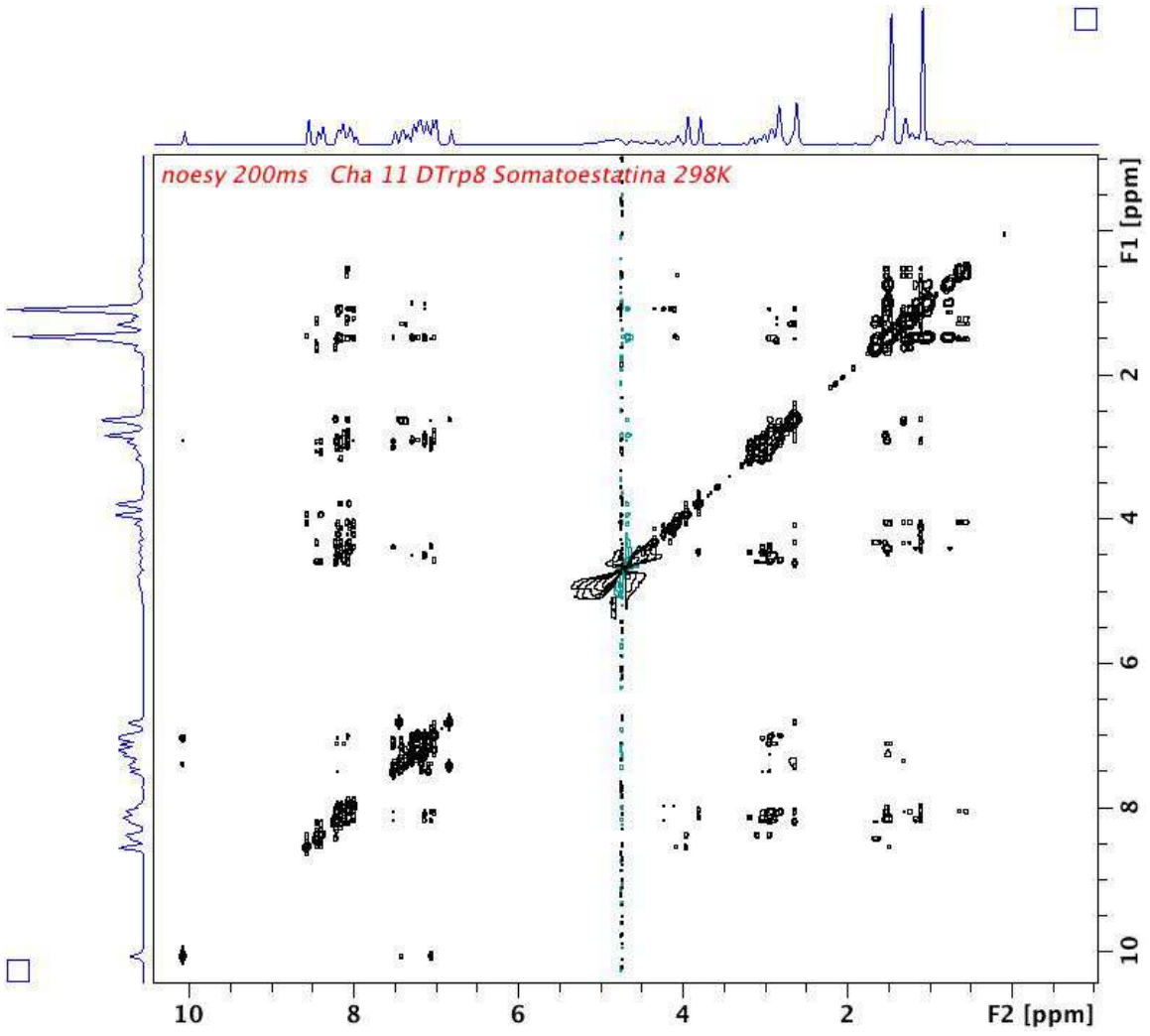
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala		H^{α} 4.06	H^{β} 1.46		
2 Gly	H^{N} 8.56	H^{α} 3.94			
3 Cys	H^{N} 8.39	H^{α} 4.59	H^{β} 2.96		
4 Lys	H^{N} 8.44	H^{α} 4.33	H^{β} 1.63	H^{γ} 1.26	H^{δ} 1.52 H^{ε} 2.83
5 Asn	H^{N} 8.21	H^{α} 4.62	H^{β} 2.62	$H^{\delta21}$ 7.44	$H^{\delta22}$ 6.83
6 Phe	H^{N} 8.06	H^{α} 4.57	H^{β} 2.84	H^{D} 7.01	H^{E} 7.21
7 Phe	H^{N} 8.11	H^{α} 4.51	H^{β} 2.90	H^{D} 7.12	H^{E} 7.28
8 D-Trp	H^{N} 8.19	H^{α} 4.39 H^{H2} 7.16	H^{β} 2.98 H^{E1} 10.07	H^{D1} 7.05 H^{Z3} 7.08	H^{E3} 7.51 H^{Z2} 7.41
9 Lys	H^{N} 8.06	H^{α} 4.05	H^{β} 1.38	H^{γ} 0.58	H^{δ} 1.60 H^{ε} 2.64
10 Thr	H^{N} 7.50	H^{α} 4.21	H^{β} 4.08	H^{γ} 1.09	
11 Cha	H^{N} 8.18	H^{α} 4.41	H^{β} 2.82		
12 Thr	H^{N} 7.57	H^{α} 4.32	H^{β} 4.14	H^{γ} 1.09	
13 Ser	H^{N} 7.51	H^{α} 4.46	H^{β} 3.79		
14 Cys	H^{N} 8.14	H^{α} 4.46	H^{β} 3.11		

TOCSY 50 ms



NOESY 200 ms

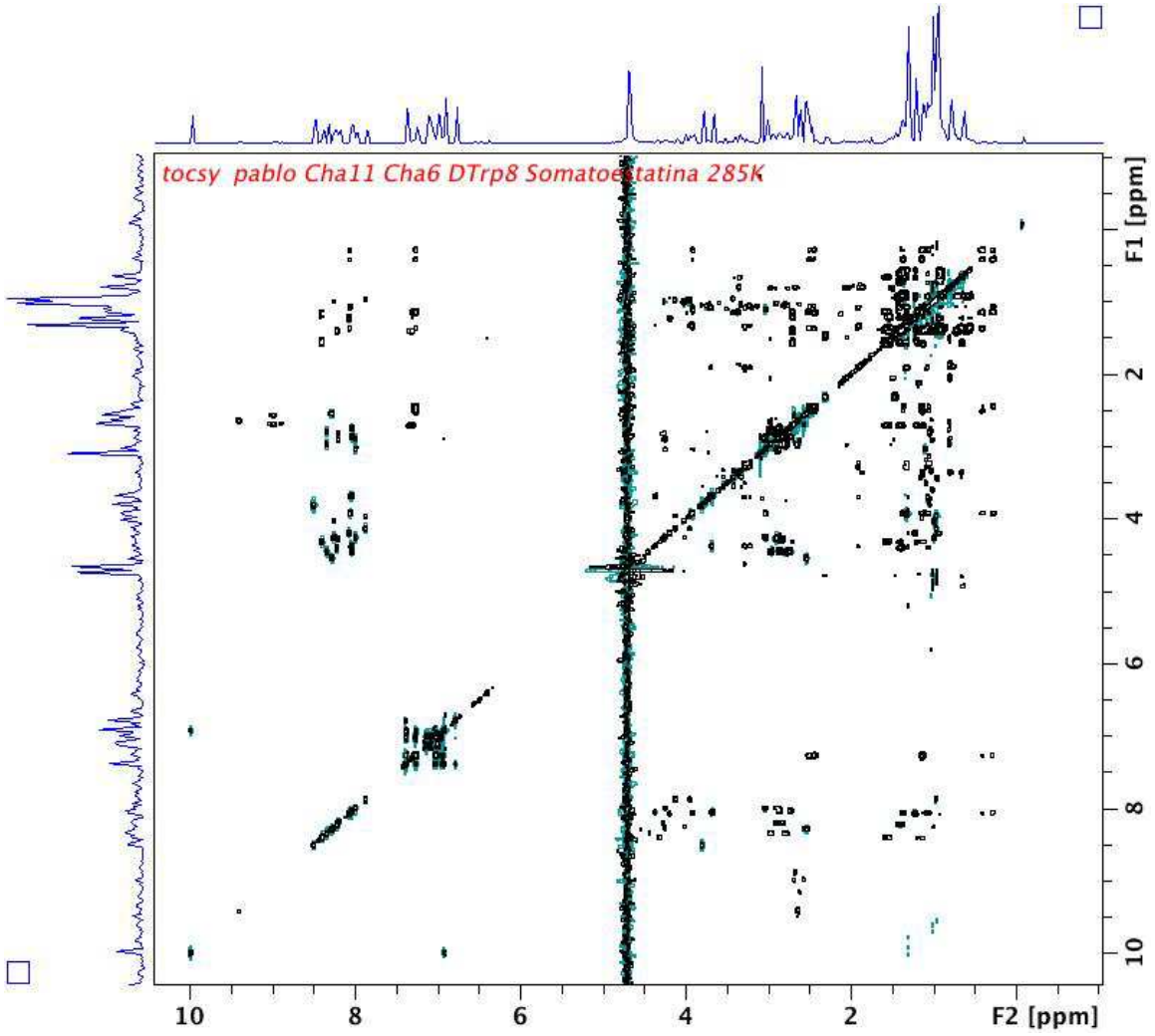

noesy 200ms Cha 11 DTrp8 Somatoestatina 298K
F1 [ppm]
F2 [ppm]
10
8
6
4
2

[L-Cha6,11_D-Trp8]-SRIF, 66: Somatostatin analog **66** was synthesized following the general procedure from 0.2 g of 2-Cl-Trt resin (0.8 mmol/g) and using Fmoc-L-Cha-OH, affording 0.11 g in 48% yield (98% purity after purification). HPLC: t_R = 17.6 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for $C_{76}H_{116}N_{18}O_{19}S_2$: 1648.8100; found, 1648.8114.

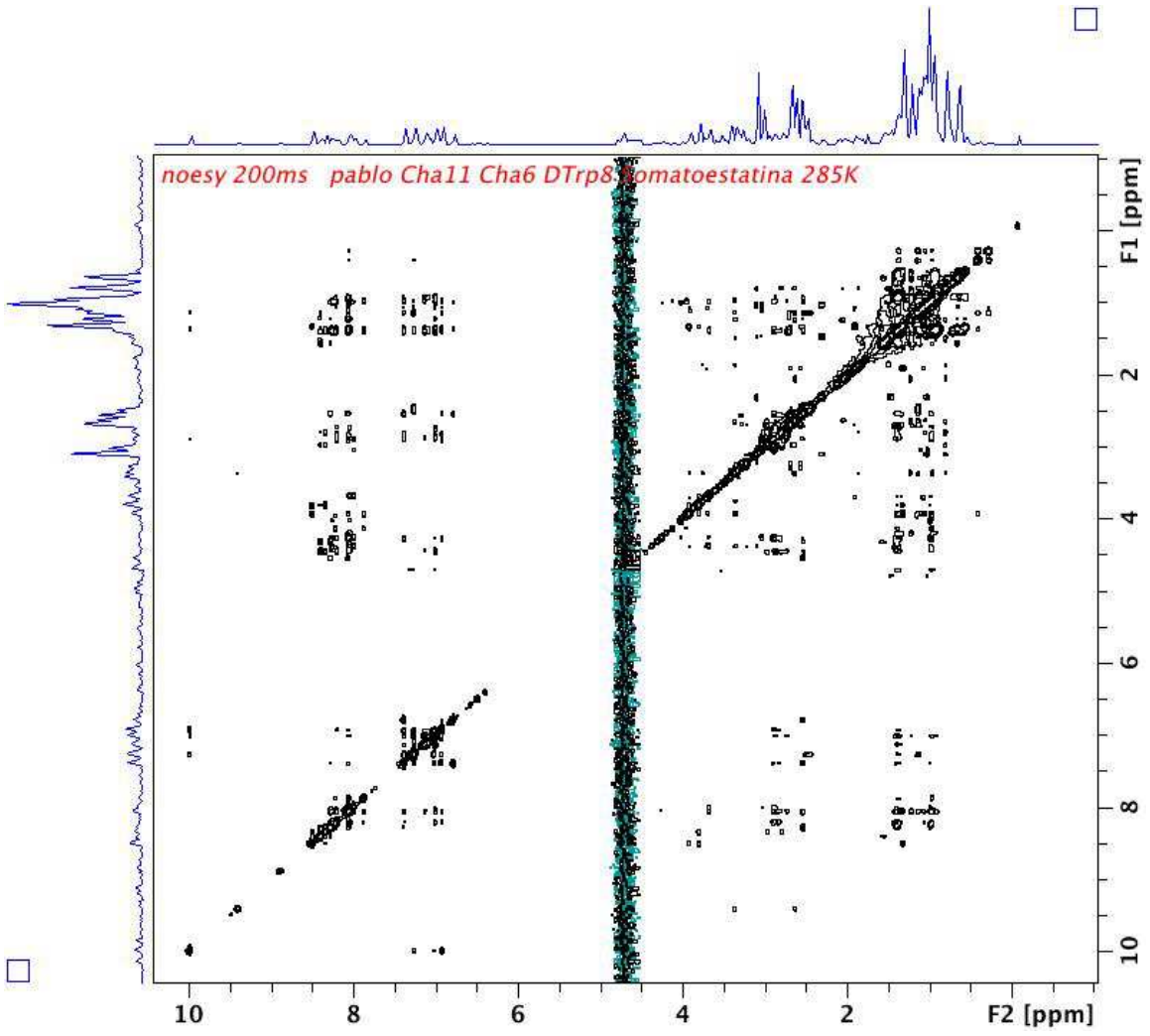
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala		H^{α} 3.91	H^{β} 1.30		
2 Gly	H^{N} 8.50	H^{α} 3.79			
3 Cys	H^{N} 8.33	H^{α} 4.43	H^{β} 2.86		
4 Lys	H^{N} 8.39	H^{α} 4.30	H^{β} 1.36	H^{γ} 1.11	
5 Asn	H^{N} 8.27	H^{α} 4.52	H^{β} 2.52	$H^{\delta 21}$ 7.30	$H^{\delta 22}$ 6.90
6 Cha	H^{N} 8.06	H^{α} 4.18	H^{β} 3.20		
7 Phe	H^{N} 8.04	H^{α} 4.42	H^{β} 2.78	H^{D} 7.00	H^{E} 7.12
8 D-Trp	H^{N} 8.19	H^{α} 4.26	H^{β} 2.84	H^{D1} 6.91	H^{E3} 7.38
		H^{H2} 6.92	H^{E1} 9.98	H^{Z3} 7.00	H^{Z2} 7.26
9 Lys	H^{N} 8.05	H^{α} 3.91	H^{β} 1.19	$H^{\gamma 2}$ 0.39	$H^{\gamma 3}$ 0.26
10 Thr	H^{N} 7.87	H^{α} 4.11	H^{β} 3.94	H^{γ} 0.95	
11 Cha	H^{N} 8.21	H^{α} 4.38	H^{β} 3.11		
12 Thr	H^{N} 8.25	H^{α} 4.24	H^{β} 4.01	H^{γ} 0.97	
13 Ser	H^{N} 8.04	H^{α} 4.35	H^{β} 3.66		
14 Cys	H^{N} 7.99	H^{α} 4.23	H^{β} 2.91		

TOCSY 50 ms


tocsy pablo Cha11 Cha6 DTrp8 Somatostatina 285K
F1 [ppm]
F2 [ppm]
10
8
6
4
2

NOESY 200 ms


noesy 200ms pablo Cha11 Cha6 DTrp8 somatoestatina 285K
F1 [ppm]
F2 [ppm]
10
8
6
4
2

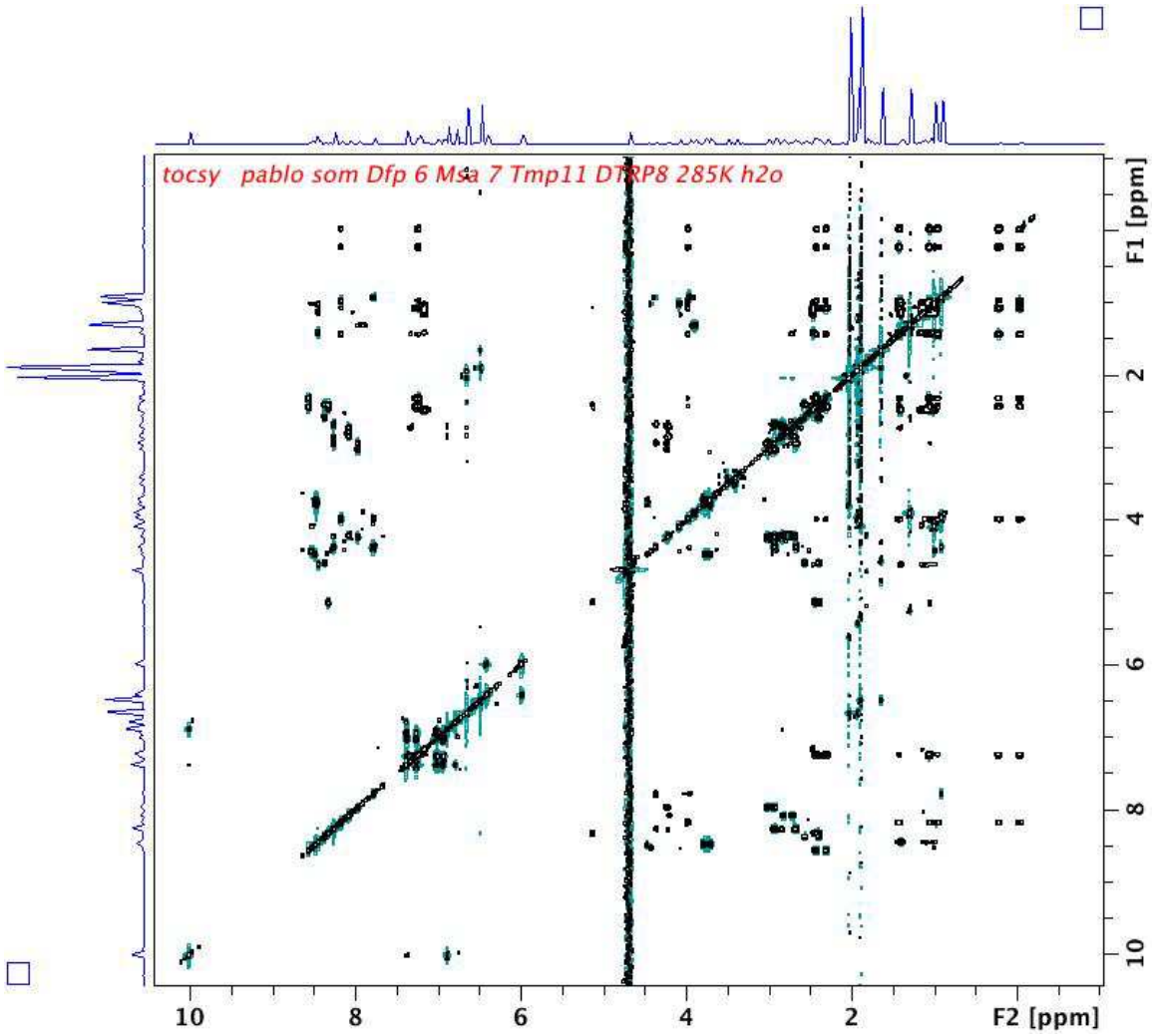
Highly modified analogs:

[L-Dfp6_L-Msa7_L-Tmp11_D-Trp8]-SRIF, 67: Somatostatin analog **67** was synthesized following the general procedure from 0.05 g of 2-Cl-Trt resin (0.8 mmol/g) and using Fmoc-L-Tmp-OH, Fmoc-L-Dfp_OH and Fmoc-L-Msa-OH, affording 0.06 g in 73% yield (99% purity after purification). HPLC: t_R = 17.4 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ =220 nm]. HRMS: calcd. for 1756.7917; found, 1756.7923.

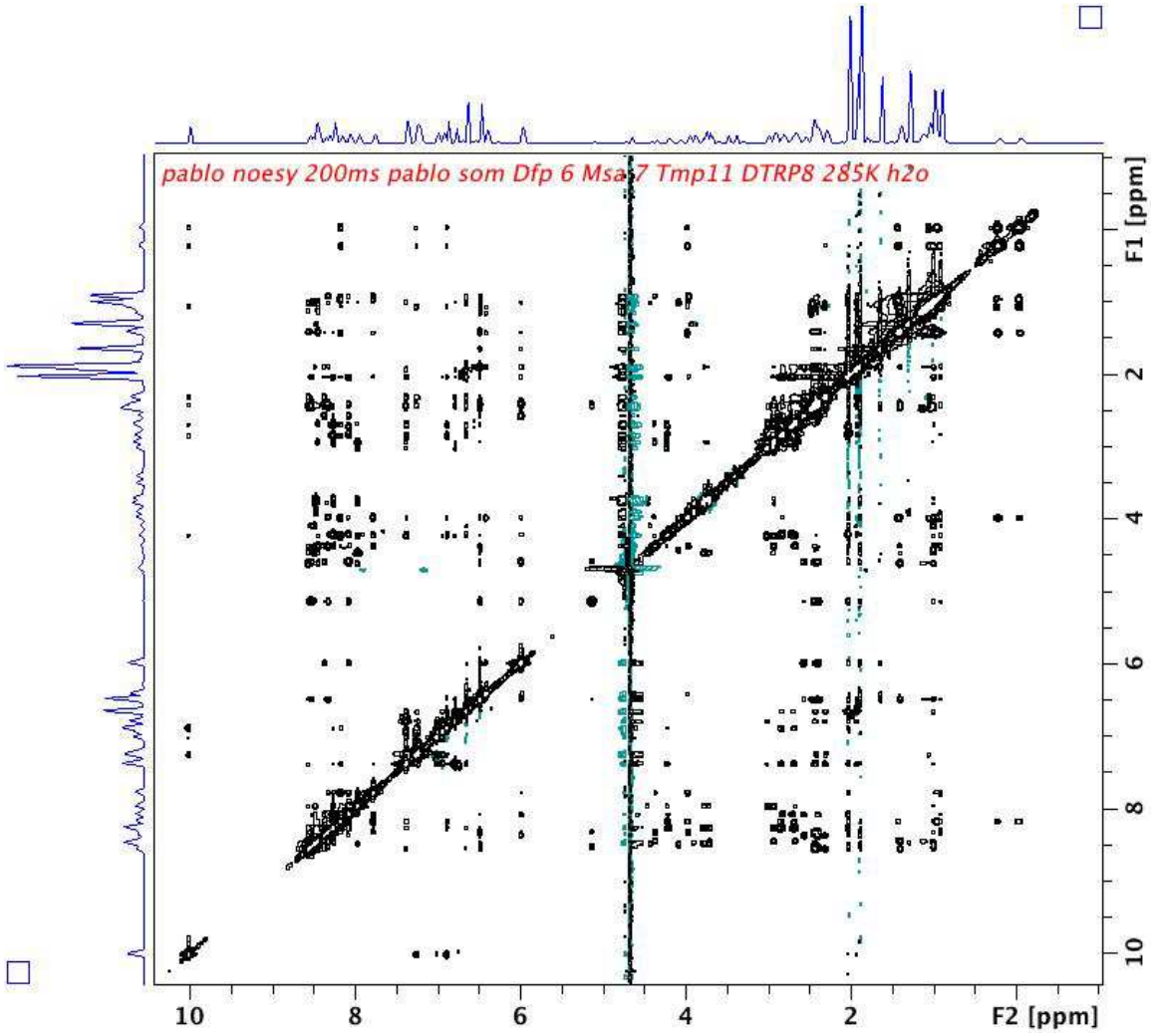
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.90	H^α 3.89	H^β 1.28		
2 Gly	H^N 8.46	H^α 3.72			
3 Cys	H^N 8.25	H^α 4.35	H^β 2.81		
4 Lys	H^N 8.44	H^α 4.59	H^β 1.39	H^δ 1.05	H^ε 2.45
					H^{Z2} 7.16
5 Asn	H^N 8.55		H^β 2.34	$H^{\delta21}$ 7.34	$H^{\delta22}$ 6.78
6 Dfp	H^N 8.36	H^α 4.57	H^β 2.46	H^D 6.01	H^Z 6.41
7 Msa	H^N 8.07	H^α 4.19	H^β 2.76	H^F 2.02	H^E 6.65
					H^H 1.92
8 D-Trp	H^N 8.26	H^α 4.20	H^β 2.75	H^{D1} 6.88	H^{E3} 7.37
		H^{H2} 7.01	H^{E1} 10.01	H^{Z3} 6.93	H^{Z2} 7.25
9 Lys	H^N 8.17	H^α 3.97	H^β 1.17	H^γ 0.08	H^ε 2.34
				H^δ 1.18	H^{Z2} 7.23
10 Thr	H^N 7.77	H^α 4.41	H^β 4.07	H^γ 0.90	
11 Tmp	H^N 8.31	H^α 5.12	H^β 2.40	H^D 6.48	H^F 2.02
					H^H 1.63
12 Thr	H^N 8.52	H^α 4.41	H^β 4.07	H^γ 0.99	
13 Ser	H^N 8.47	H^α 4.45	H^β 3.73		
14 Cys	H^N 7.96	H^α 4.22	H^β 2.97		

TOCSY 50 ms


tocsy pablo som Dfp 6 Msa 7 Tmp11 DTRP8 285K h2o
F1 [ppm]
F2 [ppm]
10
8
6
4
2

NOESY 200 ms


pablo noesy 200ms pablo som Dfp 6 Msa 7 Tmp11 DTRP8 285K h2o
F1 [ppm]
F2 [ppm]
10
8
6
4
2

Structural Statistics for the 25 Lowest Energy Structures of [L-Dfp6_Msa7_Tmp11_D-Trp8]-SRIF

Restraints used for the calculation ‹SA›[a]	
Intraresidual	0
Sequential (|i-j| =1)	58
Medium range(1 < |i-j| ≤ 4)	18
Long range (|i-j| > 4)	20
Unambiguous	All
Ambiguous	0
All	96
Dihedral angle restrictions	20
Restraint per residue ratio	8.3
RSMD (Å) from experimental[b]	
NOE:	0.01151 +/- 0.001102
Bonds (Å)	0.005705 +/- 0.0003366
Angles (°)	1.464 +/- 0.01335
Coordinate Precision (Å)[c]	0.32
All Atoms	
CNS potential energy (kcal mol^{-1})	
Total energy[d]	-206.2 +/- 16.0
Van der Waals	-24.42 +/- 7.72
Electrostatic	-425.7 +/- 17.2
Bonds	8.034 +/- 0.954
Angles	143.6 +/- 2.6

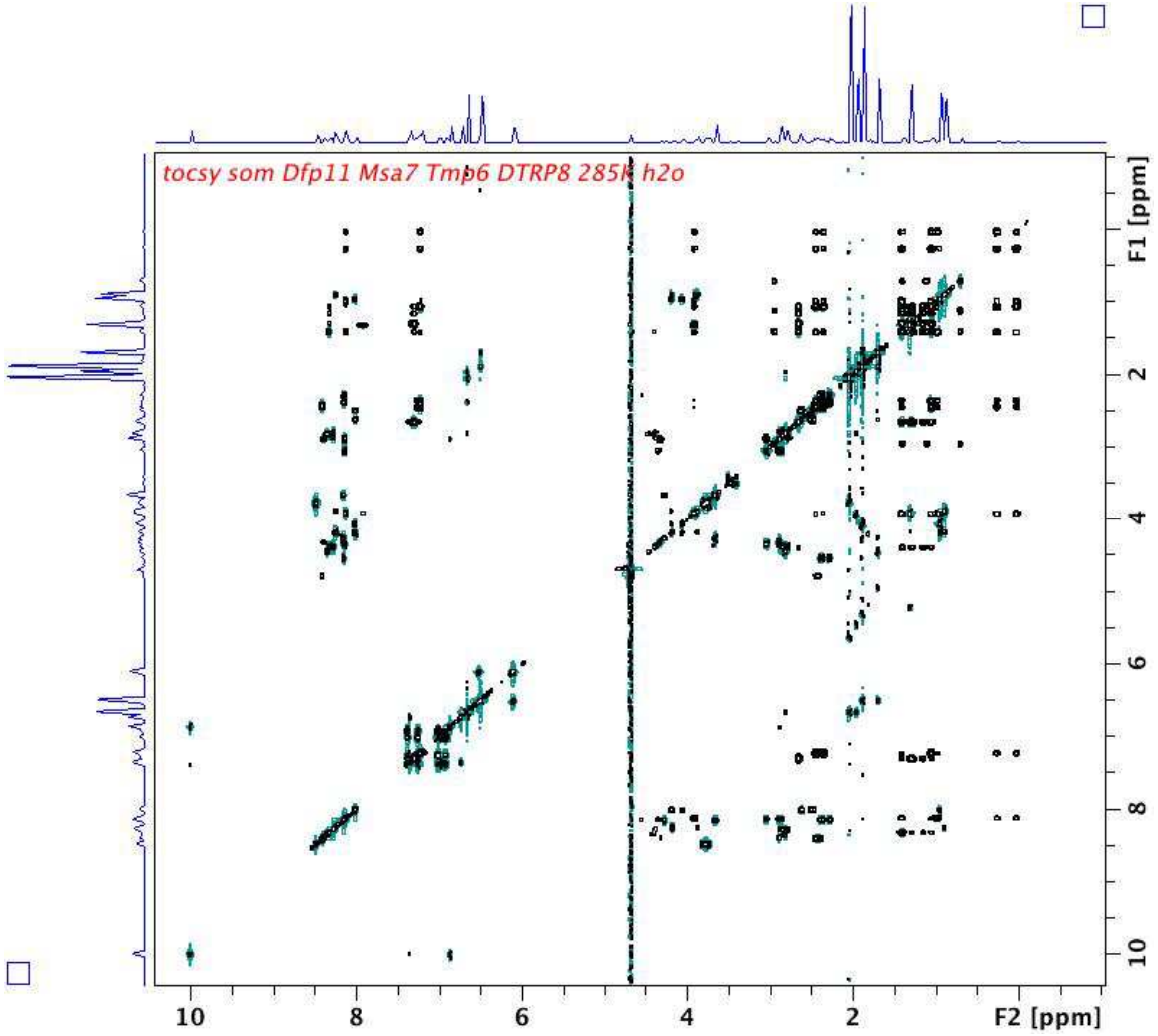
[a] ‹SA› refers to the ensemble of the 25 structures with the lowest energy.
[b] R.m.s deviation between the ensemble of structures <SA> and the lowest energy structure.
[c] No distance restraint in any of the structures included in the ensemble was violated by more than 0.3 Å.
[d] E_{L-J} is the Lennard-Jones van der Waals energy calculated using the CHARMM-PARMALLH6 parameters. E_{L-J} was not included in the target function during the structure calculation.

[L-Tmp6_L-Msa7_L-Dfp11_D-Trp8]-SRIF, 68: Somatostatin analog **68** was synthesized following the general procedure from 0.05 g of 2-Cl-Trt resin (0.8 mmol/g) and using Fmoc-L-Tmp-OH, Fmoc-L-Dfp_OH and Fmoc-L-Msa-OH, affording 0.03 g of **68** in 42% yield (99% purity after purification). HPLC: t_R = 17.9 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for 1756.7917; found, 1756.7929.

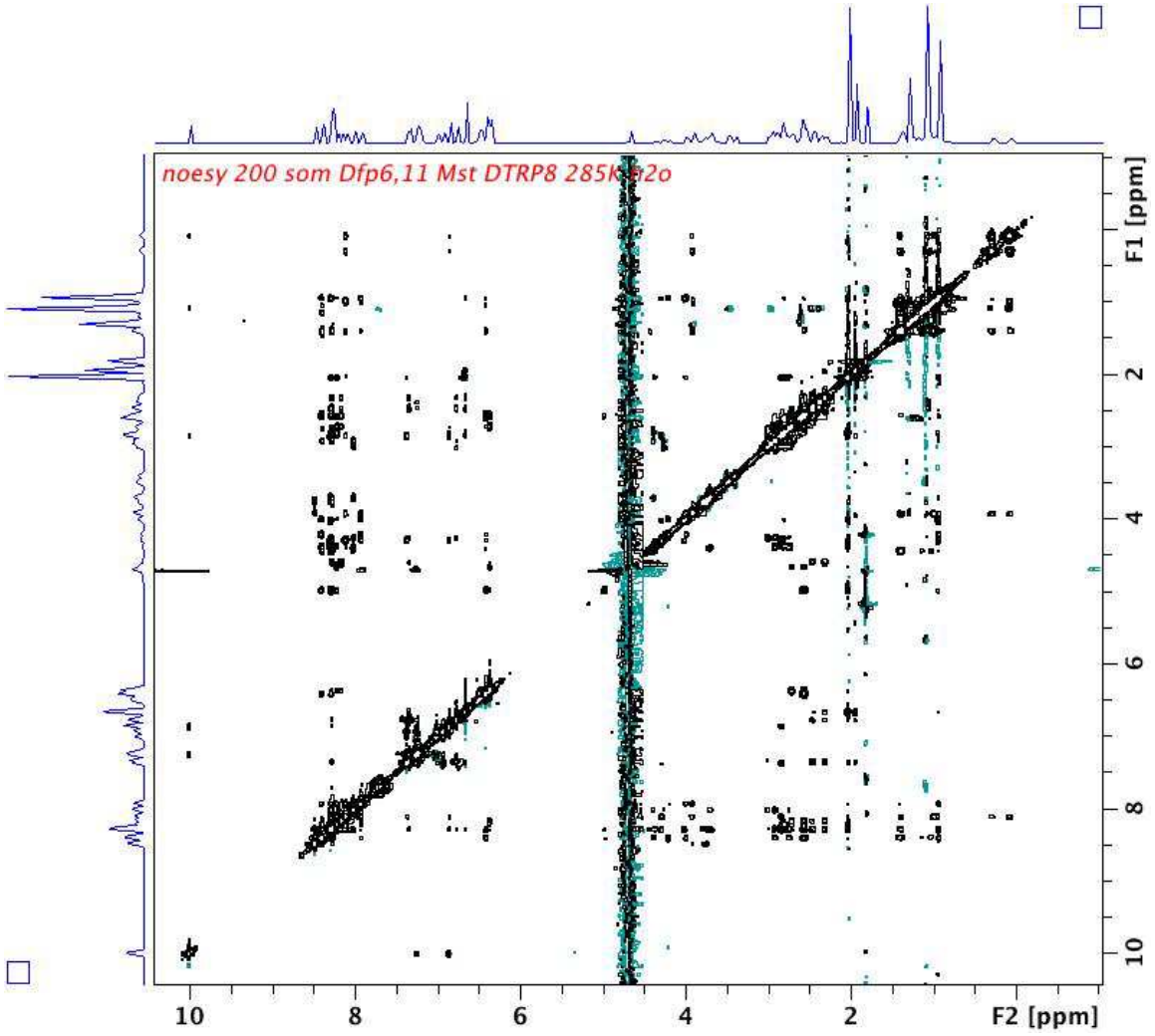
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.91	H^α 3.89	H^β 1.29		
2 Gly	H^N 8.48	H^α 3.75			
3 Cys	H^N 8.27	H^α 4.37	H^β 2.81		
4 Lys	H^N 8.31	H^α 4.37	H^β 1.38	H^δ 1.07 H^δ 1.27	H^ε 2.63
5 Asn	H^N 8.14	H^α 4.52	H^β 2.31	$H^{\delta 21}$ 7.35	$H^{\delta 22}$ 6.73
6 Tmp	H^N 8.00		H^β 2.53	H^D 6.49	H^F 1.87 H^H 1.68
7 Msa	H^N 8.34	H^α 4.44	H^β 2.80	H^F 2.03	H^F 1.87 H^H 1.94
8 D-Trp	H^N 8.38	H^α 4.30	H^β 2.87	H^{D1} 6.86	H^{E3} 7.37
		H^{H2} 7.00	H^{E1} 9.99	H^{Z3} 6.91	H^{Z2} 7.25
9 Lys	H^N 8.12	H^α 3.90	H^β 1.08	H^γ 0.13 H^δ 1.03	H^ε 2.42
10 Thr	H^N 8.01	H^α 4.17	H^β 4.05	H^γ 0.94	
11 Dfp	H^N 8.40	H^α 4.77	H^β 2.40	H^D 6.10	H^Z 6.52
12 Thr	H^N 8.24	H^α 4.16	H^β 3.87	H^γ 0.88	
13 Ser	H^N 8.14	H^α 4.25	H^β 3.65		
14 Cys	H^N 8.13	H^α 4.34	H^β 2.93		

TOCSY 50 ms



NOESY 200 ms



Structural Statistics for the 25 Lowest Energy Structures of [L-Tmp6_Msa7_Dfp11_D-Trp8]-SRIF

Restraints used for the calculation ‹SA›[a]	
Intraresidual	0
Sequential (|i-j| =1)	64
Medium range(1 < |i-j| ≤ 4)	14
Long range (|i-j| > 4)	26
Unambiguous	All
Ambiguous	0
All	104
Dihedral angle restrictions	22
Restraint per residue ratio	9.0
RSMD (Å) from experimental[b]	
NOE:	0.005728 +/- 0.0007341
Bonds (Å)	0.004458 +/- 0.0003346
Angles (º)	1.381 +/- 0.0224
Coordinate Precision (Å)[c]	0.34
All Atoms	
CNS potential energy (kcal mol^{-1})	
Total energy[d]	-275.2 +/- 9.1
Van der Waals	-46.53 +/- 3.85
Electrostatic	-439.6 +/- 12.0
Bonds	4.915 +/- 0.744
Angles	127.9 +/- 4.1

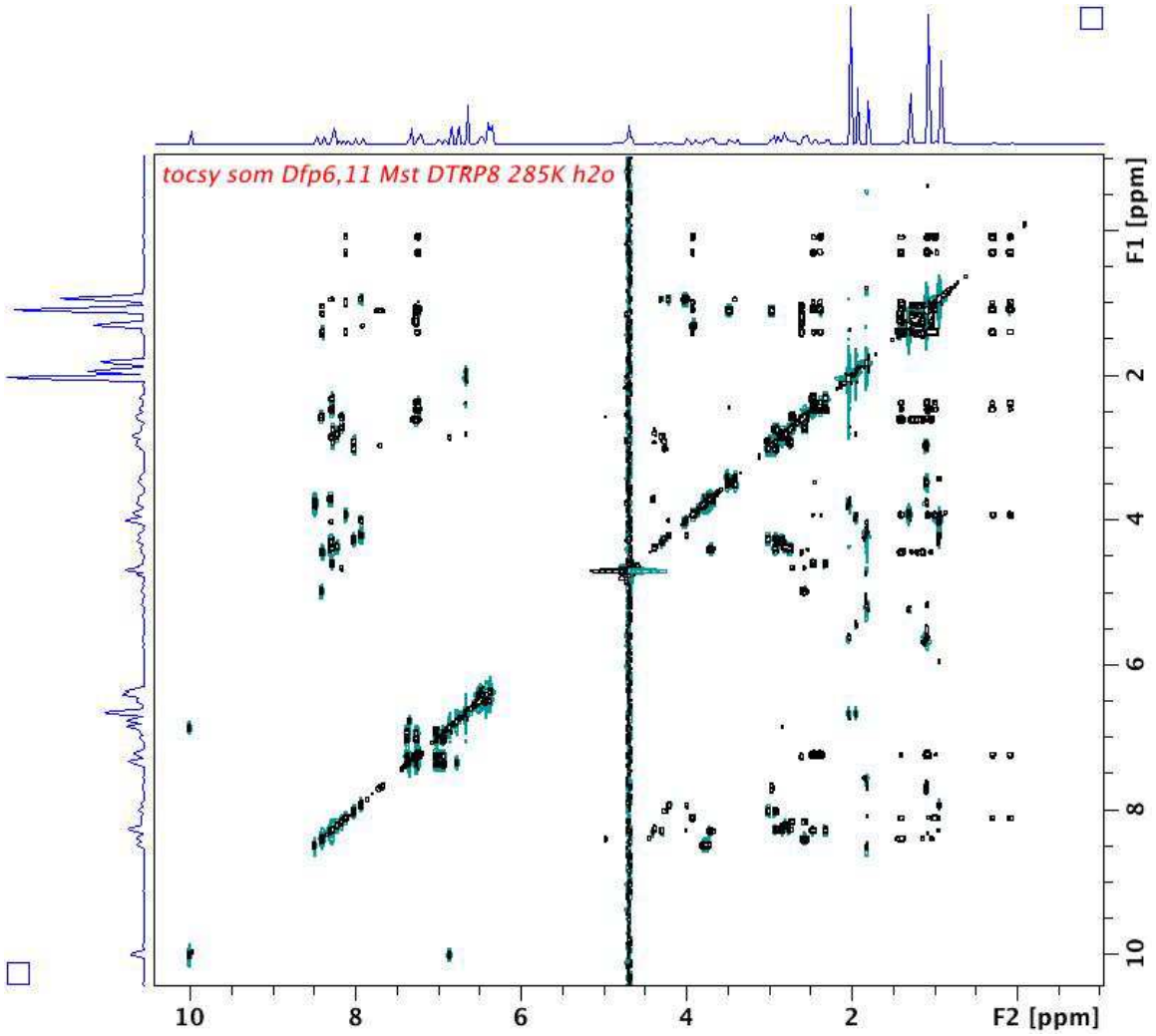
[a] ‹SA› refers to the ensemble of the 25 structures with the lowest energy.
[b] R.m.s deviation between the ensemble of structures <SA> and the lowest energy structure.
[c] No distance restraint in any of the structures included in the ensemble was violated by more than 0.3 Å.
[d] E_{L-J} is the Lennard-Jones van der Waals energy calculated using the CHARMM-PARMALLH6 parameters. E_{L-J} was not included in the target function during the structure calculation.

[L-Dfp6,11_L-Msa7_D-Trp8]-SRIF, 69: Somatostatin analog **69** was synthesized following the general procedure from 0.05 g of 2-Cl-Trt resin (0.8 mmol/g) and using Fmoc-L-Dfp-OH and Fmoc-L-Msa-OH, affording 0.05 g in 61% yield (99% purity after purification). HPLC: t_R = 16.1 [Gradient 25-60% B in 20 min, flux: 1 mL.min^{-1}, λ=220 nm]. HRMS: calcd. for 1756.7917; found, 1756.7923.

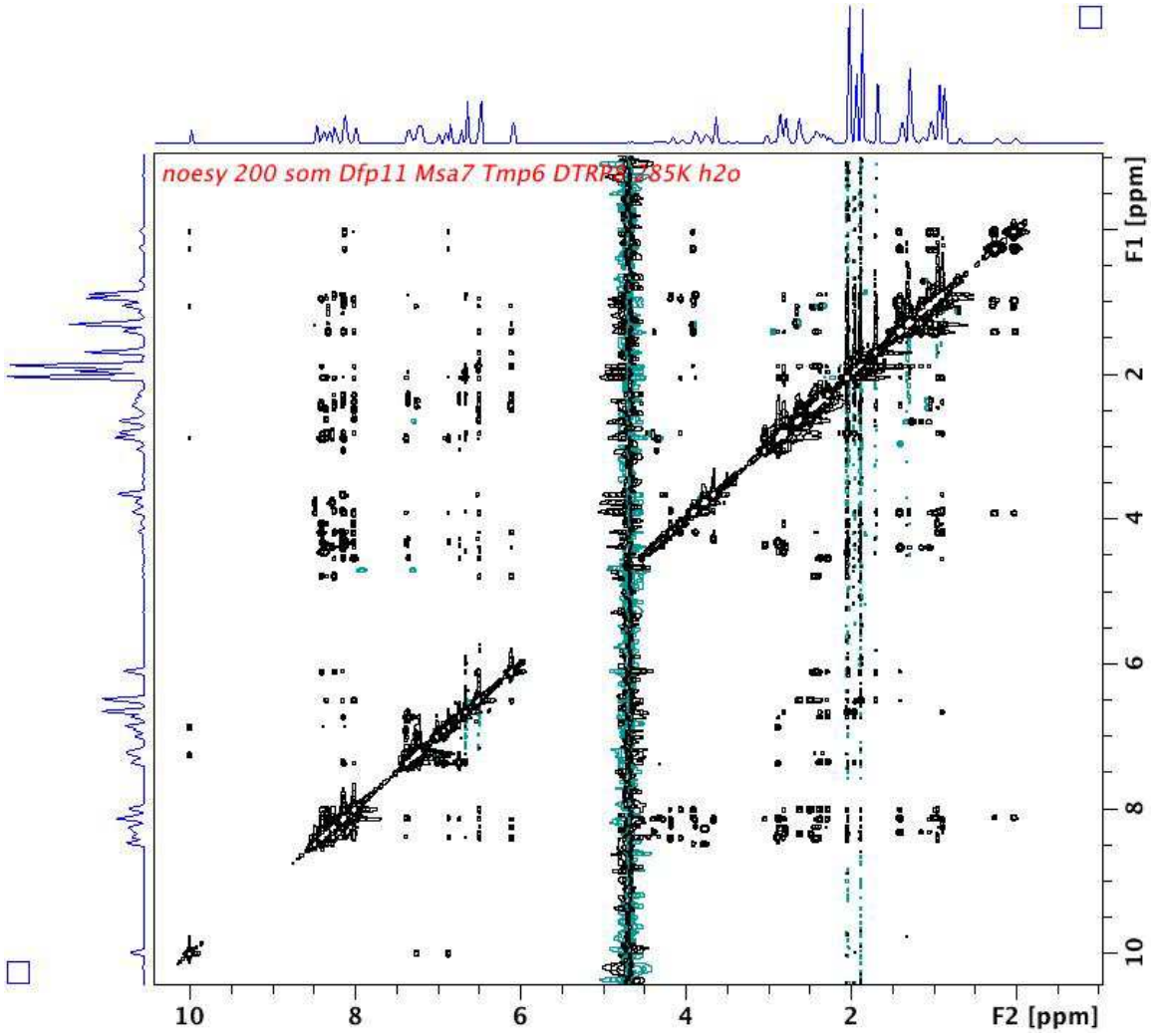
NMR: Data from ^{1}H NMR, TOCSY, NOESY (D_2O, 600 MHz)

Residue	Chemical shift (ppm)				
1 Ala	H^N 7.91	H^α 3.89	H^β 1.29		
2 Gly	H^N 8.48	H^α 3.75			
3 Cys	H^N 8.26	H^α 4.37	H^β 2.81		
4 Lys	H^N 8.37	H^α 4.42	H^β 1.38	H^δ 1.26	H^ε 2.59
				H^γ 1.08	H^{Z2} 7.26
5 Asn	H^N 8.28	H^α 4.58	H^β 2.38	$H^{\delta21}$ 7.34	$H^{\delta22}$ 6.76
6 Dfp	H^N 7.61	H^α 5.66	H^β 2.62	H^D 6.36	
7 Msa	H^N 8.21	H^α 4.35	H^β 3.73	H^E 6.66	H^F 2.02
8 D-Trp	H^N 8.32	H^α 4.27	H^β 2.83	H^{D1} 6.85	H^{E3} 7.25
		H^{H2} 6.93	H^{E1} 10.03	H^{Z3} 7.00	H^{Z2} 7.37
9 Lys	H^N 8.11	H^α 3.91	H^β 1.16	H^γ 0.17	H^ε 2.40
				H^δ 1.21	H^{Z2} 7.23
10 Thr	H^N 7.93	H^α 4.19	H^β 3.99	H^γ 0.93	
11 Dfp	H^N 8.40	H^α 4.62	H^β 2.55	H^D 6.46	H^Z 6.51
12 Thr	H^N 8.28	H^α 4.19	H^β 4.00	H^γ 0.93	
13 Ser	H^N 8.29	H^α 4.38	H^β 3.67		
14 Cys	H^N 8.01	H^α 4.24	H^β 2.95		

TOCSY 50 ms



NOESY 200 ms


noesy 200 som Dfp11 Msa7 Tmp6 DTRP2 285K h2o
F1 [ppm]
F2 [ppm]
10
8
6
4
2

Structural Statistics for the 25 Lowest Energy Structures of [L-Dfp6,11_Msa7_D-Trp8]-SRIF

Restraints used for the calculation ‹SA›[a]	
Intraresidual	0
Sequential (|i-j| =1)	53
Medium range(1 < |i-j| ≤ 4)	28
Long range (|i-j| > 4)	11
Unambiguous	All
Ambiguous	0
All	92
Dihedral angle restrictions	22
Restraint per residue ratio	8.1
RSMD (Å) from experimental[b]	
NOE:	0.005899 +/- 0.001354
Bonds (Å)	0.005061 +/- 0.0003145
Angles (°)	1.104 +/- 0.01969
Coordinate Precision (Å)[c]	0.34
All Atoms	
CNS potential energy (kcal mol^{-1})	
Total energy[d]	-308.4 +/- 9.2
Van der Waals	-29.22 +/- 5.00
Electrostatic	-452.8 +/- 9.6
Bonds	6.093 +/- 0.758
Angles	78.41 +/- 2.817

[a] ‹SA› refers to the ensemble of the 25 structures with the lowest energy.
[b] R.m.s deviation between the ensemble of structures <SA> and the lowest energy structure.
[c] No distance restraint in any of the structures included in the ensemble was violated by more than 0.3 Å.
[d] E_{L-J} is the Lennard-Jones van der Waals energy calculated using the CHARMM-PARMALLH6 parameters. E_{L-J} was not included in the target function during the structure calculation.