Electronic Supplementary Material (ESI) for RSC Advances.

Dimerized Fusion Inhibitor Peptides Targeting the HR1-HR2 Interaction of SARS-CoV-2

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I. General methods for synthesis and characterization of compounds

I-I. General methods

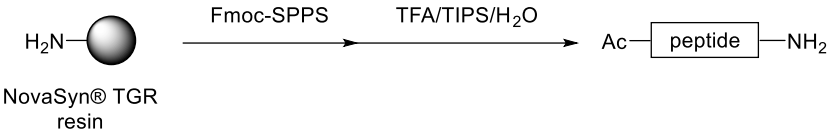
All reagents and solvents are purchased from Sigma-Aldrich, Novabiochem, Tokyo Chemical Industry Co., Ltd. (TCI), FUJIFILM Wako Pure Chemical Corporation, KANTO CHEMICAL CO., INC., NACALAI TESQUE, INC., WATANABE CHEMICAL INDUSTRIES, LTD., KOKUSAN CHEMICAL Co.,Ltd. without further purification unless otherwise noted. For analytical reverse phase HPLC (RP-HPLC), a Cosmosil $5C_{18}$-ARII column (4.6 x 250 mm, Nacalai Tesque, Inc., Kyoto, Japan) was employed with a linear gradient of MeCN containing 0.1% (v/v) trifluoroacetic acid (TFA) (Solvent B) in H_2O containing 0.1% (v/v) TFA (Solvent A) at a flow rate of 1.0 cm^3min^{-1} on a PU-2089 plus (JASCO Corporation, Ltd., Tokyo, Japan), and eluting products were detected by UV at 220 nm using JASCO UV-2075 plus. Preparative RP-HPLC was performed using a Cosmosil $5C_{18}$-ARII column (20 × 250 mm, Nacalai Tesque, Inc., Japan) on a JASCO PU-2086 plus, PU-2087 plus, and PU-4086-Binary (JASCO Corporation, Ltd.) in a linear gradient of MeCN containing 0.1% TFA (Solvent B) in H_2O containing 0.1% (v/v) TFA (Solvent A) at a flow rate of 10 cm^3min^{-1}, and eluting products were detected by UV at 220 nm using JASCO UV-2075 plus and UV-4075. Semi-preparative RP-HPLC is performed using a Cosmosil $5C_{18}$-AR II column (10 x 250 mm, Nacalai Tesque, Inc.) on a JASCO PU-2089 plus (JASCO Corporation, Ltd., Tokyo, Japan) in a suitable gradient mode of MeCN in H_2O containing 0.1% (v/v) TFA at a flow rate of 3 cm^3min^{-1}, and eluting products were detected by UV at 220 nm using JASCO UV-2075 plus. Low- resolution mass (ESI-TOF MS) spectra were recorded on a Bruker Daltonics micrOTOF focus (Bruker, MA, USA) in the positive detection mode.

I-II. General Fmoc-based solid phase peptide synthesis

Peptides were synthesized using NovaSyn® TGR resin (0.25 mmol/g, 0.05, 0.1 or 0.2 mmol scales) and 2-chlorotrityl chloride resin (0.2 mmol/g, 0.05, 0.1 or 0.2 mmol scales). 9-Fluorenylmethyloxycarbonyl (Fmoc)-based solid-phase peptide syntheses (SPPS) were manually and automatically performed (PurePrepChorus, Gyros Protein Technologies, AZ, USA). The following side chain protected amino acids were used: Boc for Lys, Pbf for Arg, O^{t}Bu for Asp and Glu, Trt for Asn, Cys and Gln, ^{t}Bu for Ser, Thr, and Tyr. In the manual peptide synthesis procedures, each cycle of SPPS involves (i) 20 min shaking for Fmoc removal (20% piperidine/DMF) and (ii) 120 min to overnight coupling (Fmoc-amino acid (Fmoc-AA-OH) (3 or 5 equiv.), 1-hydroxybenzotriazole monohydrate (HOBt·H_2O) (3 or 5 equiv.) and

N,*N'*-diisopropylcarbodiimide (DIPCI) (3 or 5 equiv.) in DMF). Coupling was monitored by the Kaiser ninhydrin test. The coupling step was repeated (double coupling) using a mixture of Fmoc amino acid (5 equiv.), HOBt·H_2O (5 equiv.), DIPCI (5 equiv.) in DMF, if needed. In the automated peptide synthesis procedure (0.1 mmol scale) using NovaSyn® TGR resin, each cycle of SPPS involves (i) 2 min shaking for Fmoc removal (20% piperidine/DMF (6 mL) twice at 50 °C) and (ii) 5 min shaking for coupling (Fmoc-AA-OH (5 equiv), Oxyma Pure (5.5 equiv), and DIPCI (5 equiv.) in DMF (6 mL) at 90 °C). In the automated peptide synthesis procedure (0.1 mmol scale) using 2-chlorotrityl chloride resin, each cycle of SPPS involves (i) 7 min shaking for Fmoc removal (20% piperidine/DMF (6 mL) twice at room temperature) and (ii) 2 h shaking for coupling (Fmoc-AA-OH (5 equiv), Oxyma Pure (5.5 equiv), and DIPCI (5 equiv.) in DMF (6 mL) at room temperature). The elongated peptide resins were treated with Ac_2O (20 equiv.), pyridine (20 equiv.) in DMF for 45 min for acetylation. The protected R_8 peptide resin was treated with chloroacetic acid (40 equiv.) and DIPCI (40 equiv.) in DMF (10 mL) for 1 h for chloroacetylation as reported previously.[S1] After construction of protected peptides on the resins, the resins were extensively washed (DMF, dichloromethane (DCM), and Et_2O) and then dried *in vacuo*. The protected peptide was cleaved from the resin with the deprotection of all the protecting groups on their side chain functional groups by treatment with a mixture of TFA/triisopropylsilane (TIPS)/H_2O = 95:2.5:2.5 (v/v) or TFA/triisopropylsilane (TIPS)/H_2O/ethanedithiol (EDT) = 95/2.5/2.5/7.5 (v/v) at room temperature for 2 h. The reaction mixture was filtered, and the resin was washed with TFA (3 times). The filtrate was removed by nitrogen gas flow, and the residue was precipitated by the addition of cold Et_2O. After centrifugation, the supernatant was removed. The precipitate was washed with cold Et_2O (3 times). The obtained crude peptide was purified by preparative and semi-preparative RP-HPLC. The purified peptide was identified by ESI-TOF MS and analytical RP-HPLC, and was lyophilized to obtain as a white powder.

I-III. Synthesis of monomer peptides 1a – 8a.



1a Ac–**ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE**–NH_2

2a Ac–**ISGINASVVNIQEEIKKLNEEAKKLNESLIDLQE**–NH_2

3a Ac–**ISGINASVVNIQEEIKRLNEVAKKLNESLIDLQE**–NH_2

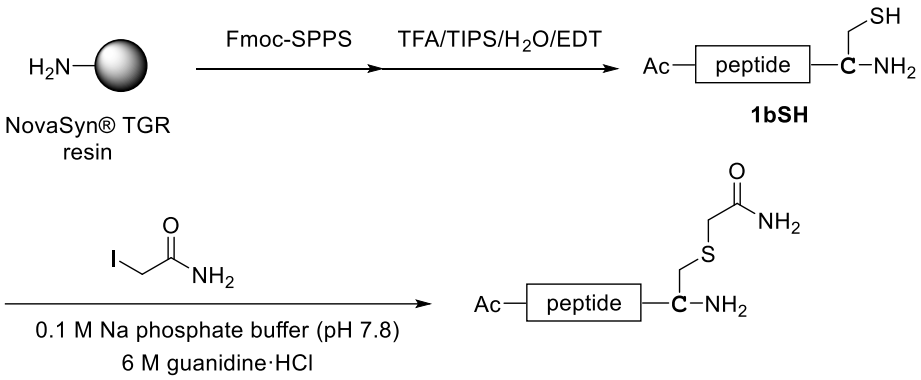
4a Ac–**ISGINASVVNIQKEIERLNKVAKELNKSLIDLQE**–NH_2

5a Ac–**ISGINASVVEIQKEIERLNKVAKNLNESLIDLQE**–NH_2

6a Ac–**ISGINASVVEIQKEIERLNKVAKELNKSLIDLQE**–NH_2

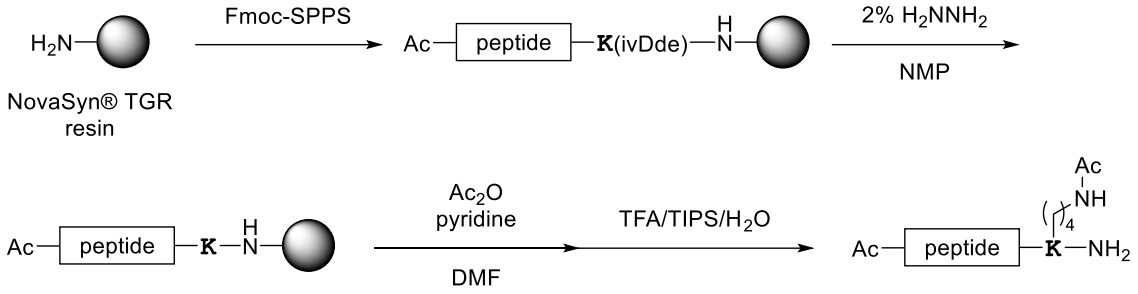
7a Ac–**ISGINASVVNIQKEIERLNKVAKELNESLIDLQE**–NH_2

The peptides **1a** – **7a** were synthesized following the general Fmoc-SPPS procedures mentioned in the section **I-II**.



1b Ac–**ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE–RERERE–GC**(CH_2CONH_2)–NH_2

The peptide **1b** was synthesized using gereral Fmoc-SPPS procedures mentioned in the section **I-II** followed by acetamide capping. In brief, the purified **1bSH** (12.4 mg, 2.25 µmol) was treated with iodoacetamide (4.2 mg, 22.5 µmol) in 0.1 M Na phosphate buffer (pH 7.8, 6 M guanidine·HCl, 2.25 mL, peptide concentration: 1.0 mM) at room temperature for 3 h. The mixture was purified using preparative RP-HPLC to obtain **1b**.



8a Ac–**SLDQINVTFLDLEYEMKKLEEAIKKLEESYIDLKEL–GSGK**(Ac)–NH_2

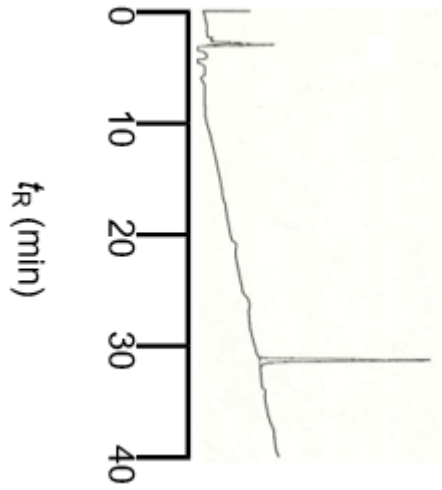
The peptide **8a** was synthesized using gereral Fmoc-SPPS procedures mentioned in the section **I-II** followed by selective deprotection of ivDde group on lysine ε-amino group and its acetyl capping. In brief, the constructed resin was treated with 2% H_2NNH_2 in *N*-methylpyrrolidone (NMP, v/v) at room temperature for 3 h and overnight (twice). The resin was then treated with Ac_2O (10 equiv.), pyridine (10 equiv.) in DMF for 60 min for acetylation. The resulting resin was treated with the TFA cocktail followed by preparative RP-HPLC purification to obtain **8a**.

Table S1. HPLC, mass and yield data of monomer peptides.

Peptide	Analytical HPLC[a]		Preparative HPLC[b]	*m/z*		Yield[d] (%)
	[c]t_R (min)	Gradient (%)	Gradient (%)	Calcd	Found	
1a	31.3	20 to 60	37 to 47	1247.4 $[M+3H]^{3+}$	1274.9	9.6
1bSH	29.6	5 to 60	35 to 50	1210.1 $[M+3H]^{3+}$	1210.4	5.7
1b	29.5	5 to 60	35 to 50	1224.6 $[M+3H]^{3+}$	1225.1	24
2a	35.0	5 to 60	30 to 55	1284.4 $[M+3H]^{3+}$	1284.8	8.5
3a	31.2	20 to 60	38 to 48	1283.7 $[M+3H]^{3+}$	1284.7	9.2
4a	21.2	20 to 80	40 to 50	1283.4 $[M+3H]^{3+}$	1283.9	2.6
5a	21.2	20 to 80	40 to 55	1283.7 $[M+3H]^{3+}$	1284.2	2.6
6a	31.0	20 to 60	38 to 48	1288.4 $[M+3H]^{3+}$	1288.9	9.0
7a	32.5	20 to 60	38 to 48	1283.7 $[M+3H]^{3+}$	1284.1	10.2
8a	34.0	20 to 60	35 to 50	1183.9 $[M+3H]^{3+}$	1187.1	5.3

0 1% TFA in H_2O (v/v, solvent A) and 0.1% TFA in MeCN (v/v, solvent B) was used for HPLC elution over 40 min.
[a]Cosmosil $5C_{18}$-AR-II analytical column was employed with a linear gradient of solvent B in solvent A over 40 min.
[b]Cosmosil $5C_{18}$-AR-II preparative column was employed with a linear gradient of solvent B in solvent A over 40 min.
[c]Retention time. [d]from NovaSyn® TGR resin.

1a

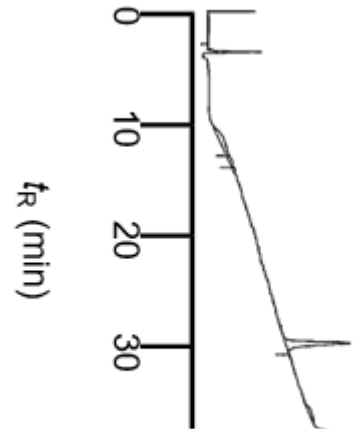


Sequence:

Ac-**ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE**-NH_2

Retention time: 31.3 min

1bSH

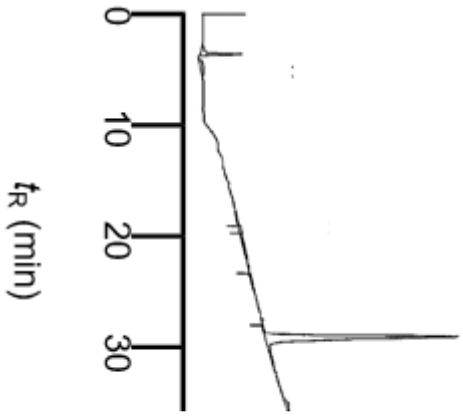


Sequence:

Ac-**ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE-RERERE-GC**-NH_2

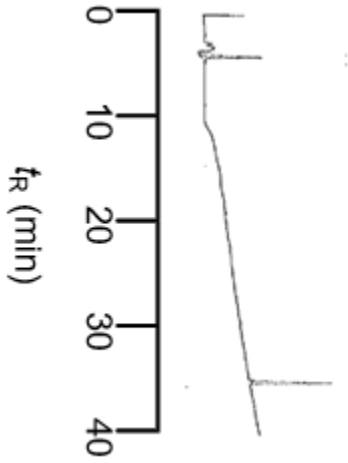
Retention time: 29.6 min

1b



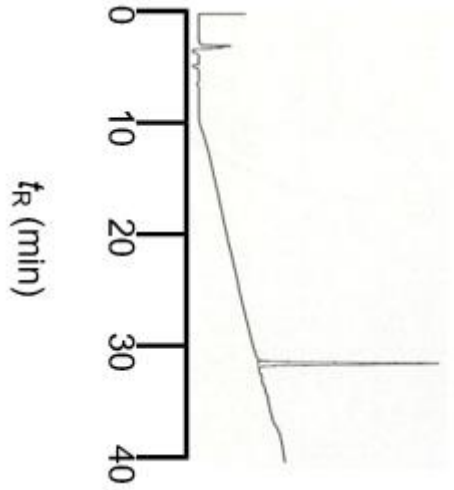
Sequence:
Ac-**ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE-RERERE-GC**(CH_2CONH_2)-NH_2
Retention time: 29.5 min

2a



Sequence:
Ac-**ISGINASVVNIQEEIKKLNEEAKKLNESLIDLQE**-NH_2
Retention time: 35.0 min

3a

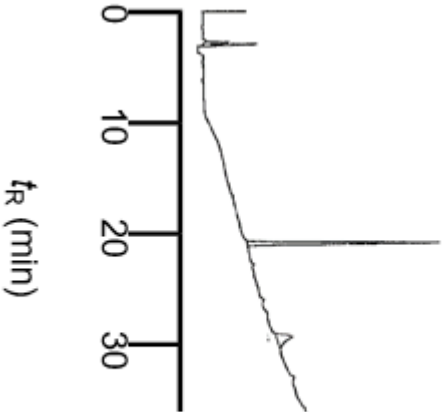


Sequence:

Ac-**ISGINASVVNIQEEIKRLNEVAKKLNESLIDLQE**-NH_2

Retention time: 31.2 min

4a

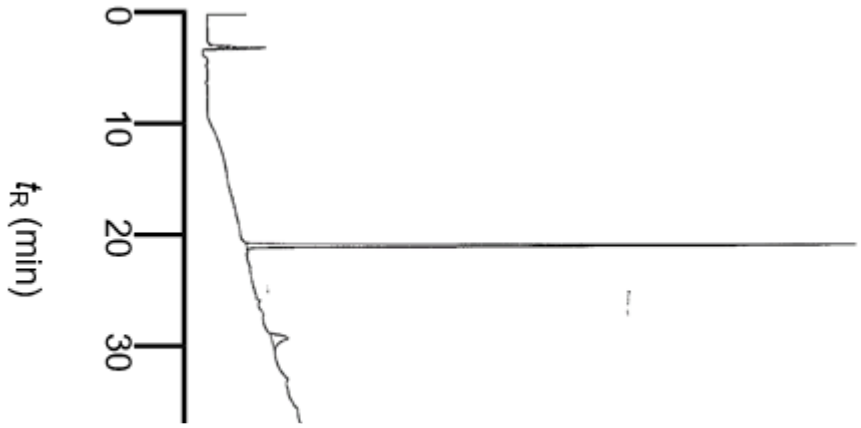


Sequence:

Ac-**ISGINASVVNIQKEIERLNKVAKELNKSLIDLQE**-NH_2

Retention time: 21.1 min

5a

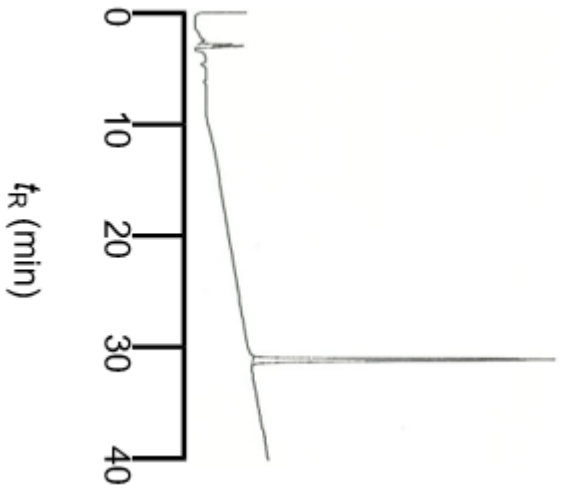


Sequence:

Ac-**ISGINASVVEIQKEIERLNKVAKNLNESLIDLQE**-NH_2

Retention time: 21.1 min

6a

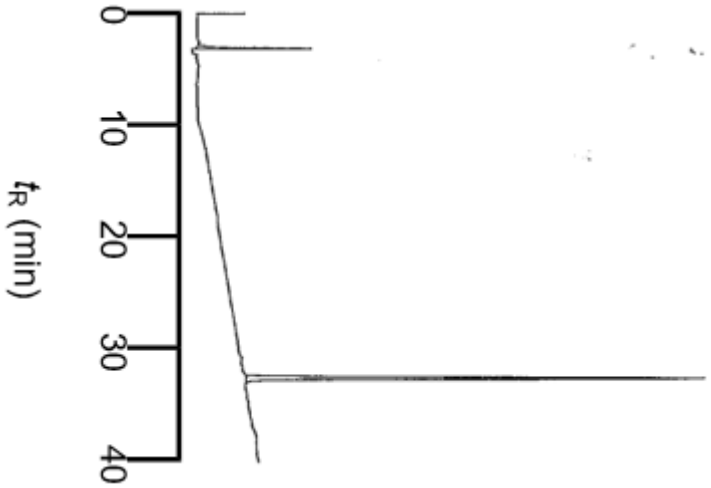


Sequence:

Ac-**ISGINASVVEIQKEIERLNKVAKELNKSLIDLQE**-NH_2

Retention time: 31.0 min

7a

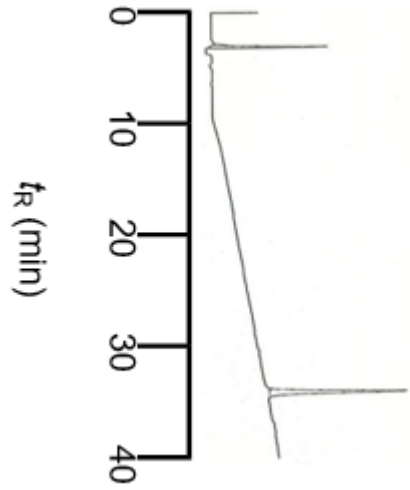


Sequence:

Ac-**ISGINASVVNIQKEIERLNKVAKELNESLIDLQE**-NH_2

Retention time: 32.5 min

8a



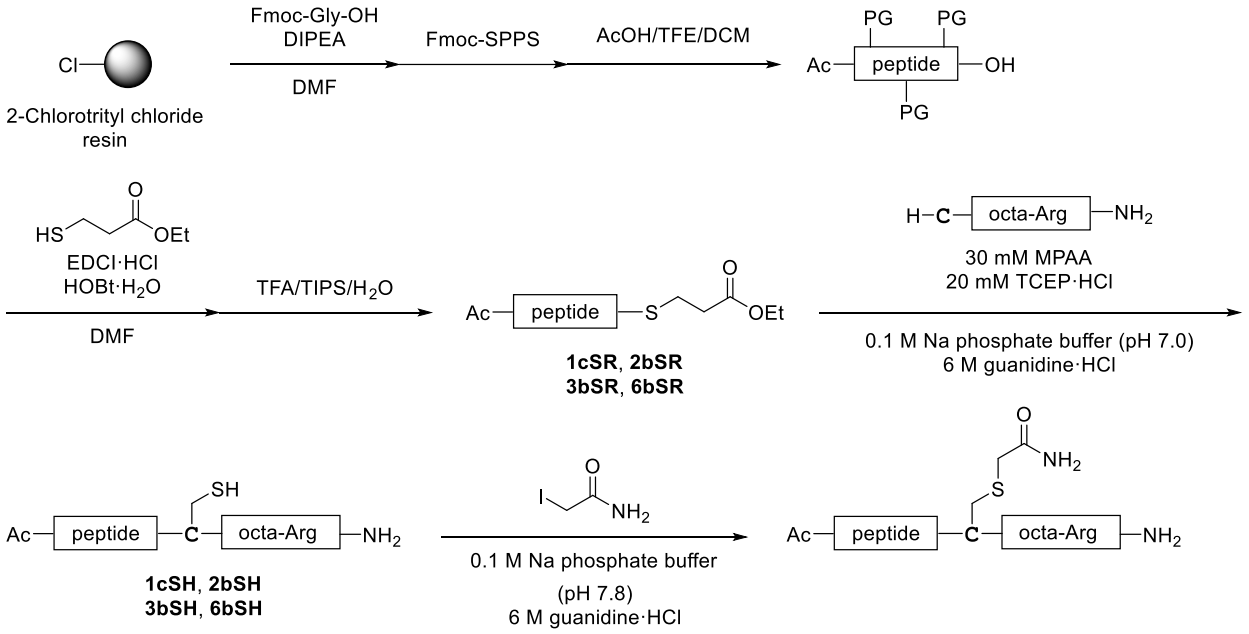
Sequence:

Ac-**SLDQINVTFLDLEYEMKKLEEAIKKLEESYIDLKEL-GSGK**(Ac)-NH_2

Retention time: 34.0 min

Figure S1. HPLC charts of purified HR2 monomer peptides.

I-IV. Synthesis of octa-arginine-conjugated peptides 1c – 7b.



1c Ac–**ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE**–**GGGSGGG**–**C**(CH_2CONH_2)–**R**$_8$–NH_2

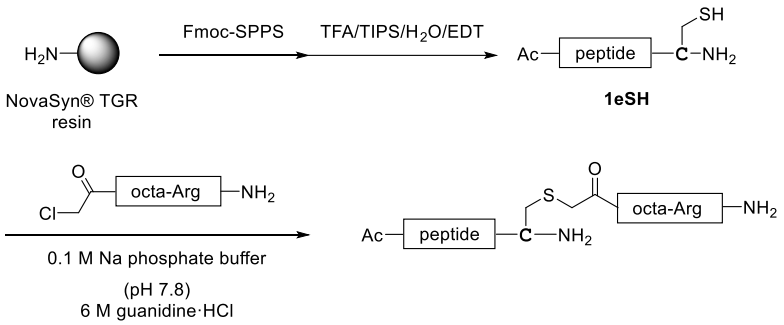
2b Ac–**ISGINASVVNIQEEIKKLNEEAKKLNESLIDLQE**–**GGGSGGG**–**C**(CH_2CONH_2)–**R**$_8$–NH_2

3b Ac–**ISGINASVVNIQEEIKRLNEVAKKLNESLIDLQE**–**GGGSGGG**–**C**(CH_2CONH_2)–**R**$_8$–NH_2

6b Ac–**ISGINASVVEIQKEIERLNKVAKELNKSLIDLQE**–**GGGSGGG**–**C**(CH_2CONH_2)–**R**$_8$–NH_2

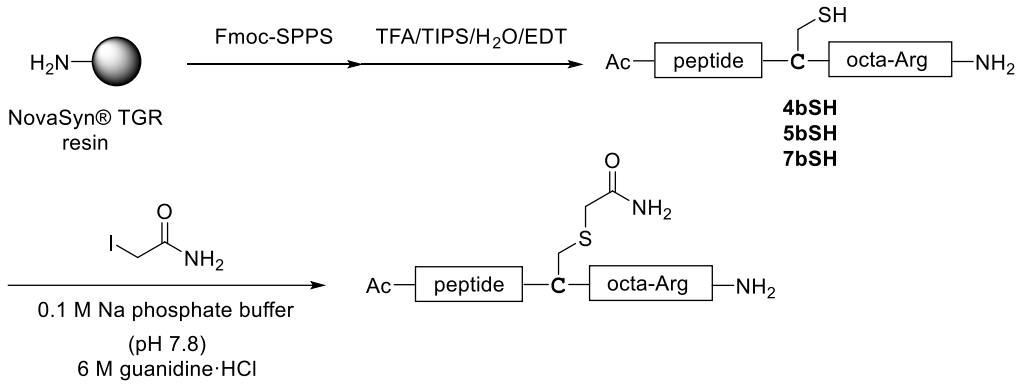
The peptides **1c**, **2b**, **3b**, and **6b** were synthesized using gereral Fmoc-SPPS procedures mentioned in the section **I-II** followed by cleavage of protected peptides, thioesterification, native chemical ligation (NCL), and acetamide capping. In brief, the constructed peptide on 2-chlorotrityl chloride resin was cleaved from resin with AcOH/trifluoroethanol (TFE)/DCM = 1:1:3 as a protected peptide with C-terminal carboxylic acid. The crude peptide was subsequently coupled with ethyl 3-mercaptopropionate (20 equiv.) using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI·HCl, 10 equiv.) and HOBt·H_2O (10 equiv.) in DMF at room temperature overnight. The volatile was removed *in vacuo* and the residue was treated with TFA/TIPS/H_2O = 95:2.5:2.5 (v/v) for global deprotection followed by RP-HPLC purification. The obtained peptide thioester was treated with H-**C**-**R**$_8$-NH_2 in 0.1 M Na phosphate buffer (pH 7.8, 6 M guanidine·HCl, peptide concentration: 1.0 mM) in the presence of 30 mM 4-mercaptophenylacetic acid (MPAA) and 20 mM tris(2-carboxyethyl)phosphine hydrochloride (TCEP·HCl) at room temperature overnight. The reaction mixture was then purified using preparative RP-HPLC to obtain the NCL product. The generated thiol of the peptide was capped by treatment of iodoacetamide (20 equiv.) in 0.1 M Na

phosphate buffer (pH 7.8, 6 M guanidine·HCl, peptide concentration: 1.0 mM) at room temperature for 1 h. The mixture was purified using preparative RP-HPLC to obtain desired peptide.



1e Ac–**GC**(Acm)**GG–ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE–RERERE–GC**(CH_2CO–**R_8**–NH_2)–NH_2

The peptides **1e** was synthesized using gereral Fmoc-SPPS procedures mentioned in the section **I-II** followed by conjugation of chloroacetylated octa-arginine peptide. In brief, the purified peptide **1eSH** (11.7 mg, 2.00 mmol) was treated with chloroacetyl-**R_8**-NH_2 (22.6 mg, 10.0 µmol) in 0.1 M Na phosphate buffer (pH 7.8, 6 M guanidine·HCl, peptide concentration: 1.0 mM) at room temperature overnight. The mixture was purified using preparative RP-HPLC to obtain desired peptide.



4b Ac–**ISGINASVVNIQKEIERLNKVAKELNKSLIDLQE–GGGSGGG–C**(CH_2CONH_2)–**R_8**–NH_2

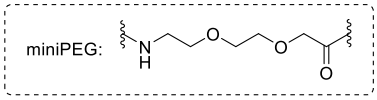
5b Ac–**ISGINASVVEIQKEIERLNKVAKNLNESLIDLQE–GGGSGGG–C**(CH_2CONH_2)–**R_8**–NH_2

7b Ac–**ISGINASVVNIQKEIERLNKVAKELNESLIDLQE–GGGSGGG–C**(CH_2CONH_2)–**R_8**–NH_2

The peptides **4b**, **5b**, and **7b** were synthesized using gereral Fmoc-SPPS procedures mentioned in the section **I-II** followed by acetamide capping. In brief, the purified thiol peptide was treated with iodoacetamide (20 equiv.) in 0.1 M Na phosphate buffer (pH 7.8, 6 M guanidine·HCl, peptide concentration: 1.0 mM) at room

temperature for 1 h. The mixture was purified using preparative RP-HPLC to obtain desired peptide.

1d Ac–**ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE–GSG**–(miniPEG)$_2$–**R$_8$**–NH_2



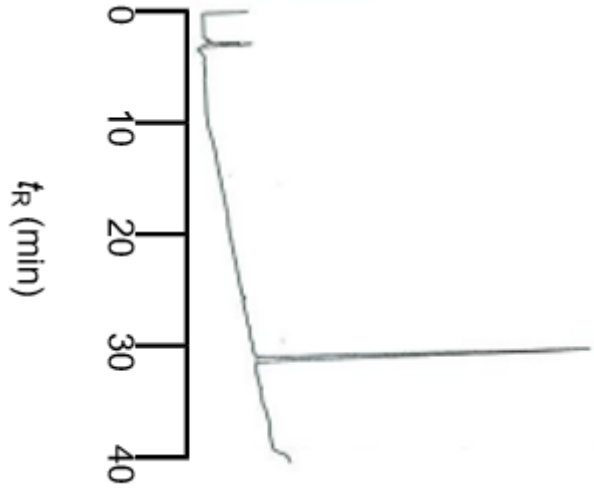
The peptide **1d** was synthesized using gereral Fmoc-SPPS procedures mentioned in the section **I-II** followed by purification using preparative RP-HPLC to obtain desired peptide.

Table S2. HPLC, mass and yield data of intermediate peptide thioesters.

Peptide	Analytical HPLC[a]		Preparative HPLC[b]	*m/z*		Yield[d] (%)
	[c]t_R (min)	Gradient (%)	Gradient (%)	Calcd	Found	
1cSR	32.4	20 to 60	38 to 48	1456.4 $[M+3H]^{3+}$	1456.8	8.1
2bSR	35.7	5 to 60	33 to 43	1466.4 $[M+3H]^{3+}$	1466.9	7.4
3bSR	31.8	20 to 60	38 to 48	1466.1 $[M+3H]^{3+}$	1466.4	7.1
6bSR	32.0	20 to 60	35 to 55	1476.7 $[M+3H]^{3+}$	1476.2	6.7

0 1% TFA in H_2O (v/v, solvent A) and 0.1% TFA in MeCN (v/v, solvent B) was used for HPLC elution over 40 min.
[a]Cosmosil 5C_{18}-AR-II analytical column was employed with a linear gradient of solvent B in solvent A over 40 min.
[b]Cosmosil 5C_{18}-AR-II preparative column was employed with a linear gradient of solvent B in solvent A over 40 min.
[c]Retention time. [d]from 2-chlorotrityl chloride resin.

1cSR

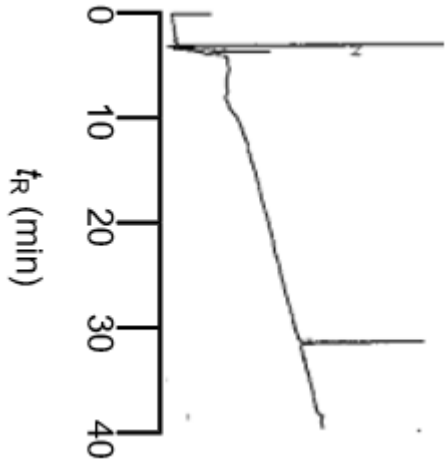


Sequence:

Ac-**ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE-GGGSGGG**-S$(CH_2)_2CO_2Et$

Retention time: 32.4

2bSR

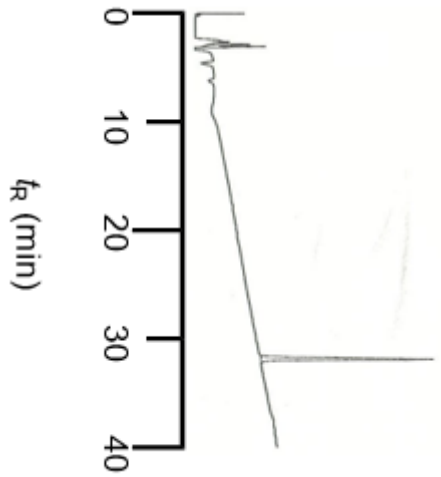


Sequence:

Ac-**ISGINASVVNIQEEIKKLNEEAKKLNESLIDLQE-GGGSGGG**-S$(CH_2)_2CO_2Et$

Retention time: 35.7 min

3bSR

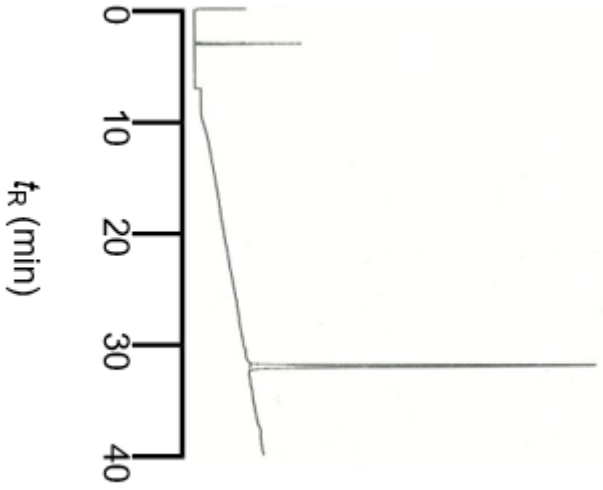


Sequence:

Ac-**ISGINASVVNIQEEIKRLNEVAKKLNESLIDLQE-GGGSGGG**-S$(CH_2)_2CO_2Et$

Retention time: 31.8 min

6bSR



Sequence:

Ac-**ISGINASVVEIQKEIERLNKVAKELNKSLIDLQE-GGGSGGG**-S$(CH_2)_2CO_2Et$

Retention time: 32.0

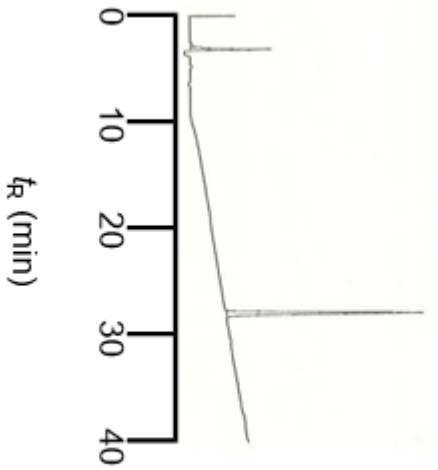
Figure S2. HPLC charts of purified intermediate peptide thioesters.

Table S3. HPLC, mass and yield data of intermediates for octa-arginine conjugated peptides.

Peptide	Analytical HPLC[a]		Preparative HPLC[b]	*m/z*		Yield[d] (%)
	[c]t_R (min)	Gradient (%)	Gradient (%)	Calcd	Found	
1cSH	27.9	20 to 60	38 to 48	1401.5 $[M+4H]^{4+}$	1401.8	26.2
1eSH	28.9	5 to 60	35 to 45	1296.4 $[M+4H]^{4+}$	1296.5	3.2[e]
2bSH	32.1	5 to 60	25 to 45	1409.3 $[M+4H]^{4+}$	1409.4	25.5
3bSH	27.4	20 to 60	35 to 55	1408.5 $[M+4H]^{4+}$	1408.9	30.2
4bSH	27.3	20 to 60	30 to 47	1408.3 $[M+4H]^{4+}$	1408.0	ND[f]
5bSH	28.0	20 to 60	30 to 47	1408.5 $[M+4H]^{4+}$	1408.9	ND
6bSH	275	20 to 60	35 to 45	1412.0 $[M+4H]^{4+}$	1412.5	29.3
7bSH	28.0	20 to 60	30 to 47	1408.5 $[M+4H]^{4+}$	1408.9	ND

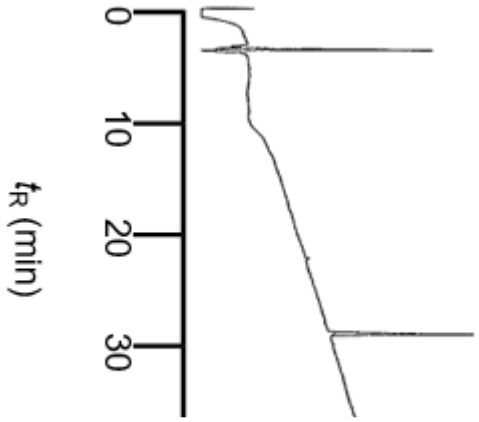
0 1% TFA in H_2O (v/v, solvent A) and 0.1% TFA in MeCN (v/v, solvent B) was used for HPLC elution over 40 min.
[a]Cosmosil $5C_{18}$-AR-II analytical column was employed with a linear gradient of solvent B in solvent A over 40 min.
[b]Cosmosil $5C_{18}$-AR-II preparative column was employed with a linear gradient of solvent B in solvent A over 40 min.
[c]Retention time. [d]from NCL. [e]from NovaSyn® TGR resin.
[f]ND: not determined. The intermediate was used in next step without purification

1cSH



Sequence:
Ac-**ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE**-**GGGSGGG**-**C**-**R**$_8$-NH_2
Retention time: 27.9

1eSH

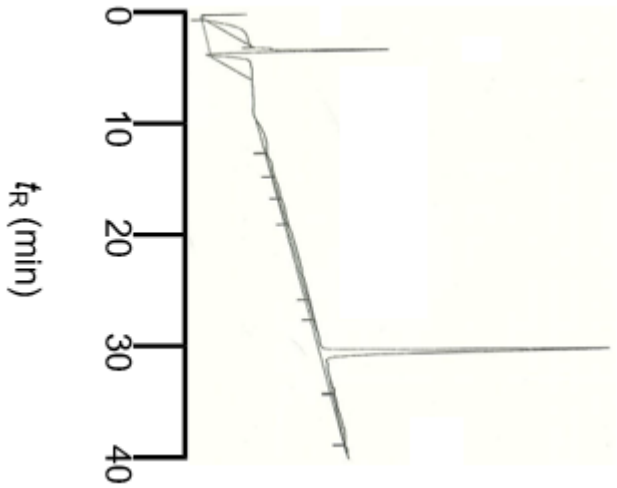


Sequence:

Ac-**GC**(Acm)**GG-ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE-RERERE-GC**-NH_2

Retention time: 28.9

2bSH

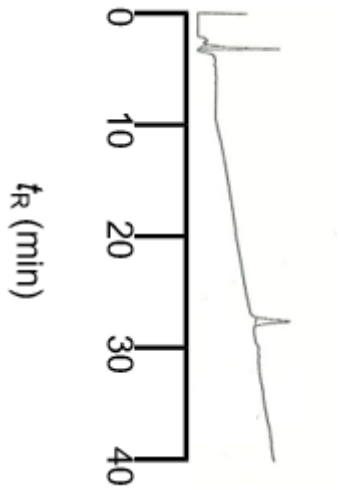


Sequence:

Ac-**ISGINASVVNIQEEIKKLNEEAKKLNESLIDLQE-GGGSGGG-C-R_8**-NH_2

Retention time: 32.1 min

3bSH

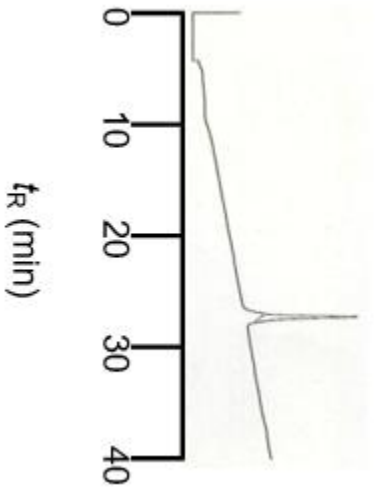


Sequence:

Ac-**ISGINASVVNIQEEIKRLNEVAKKLNESLIDLQE**-**GGGSGGG**-**C**-**R**$_8$-NH_2

Retention time: 27.4 min

4bSH

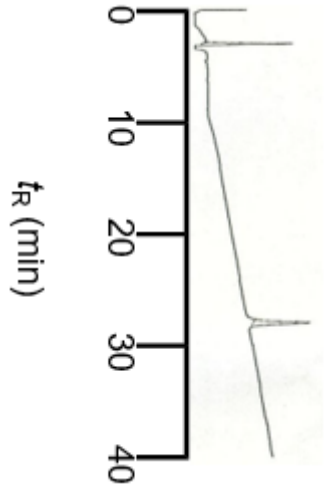


Sequence:

Ac-**ISGINASVVNIQKEIERLNKVAKELNKSLIDLQE**-**GGGSGGG**-**C**-**R**$_8$-NH_2

Retention time: 27.3 min

5bSH

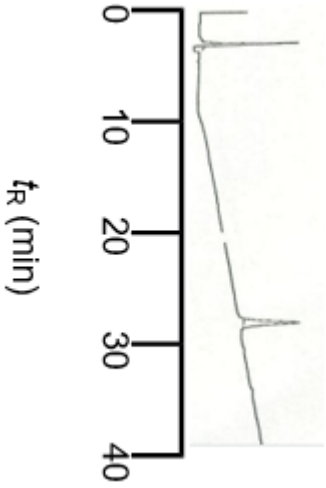


Sequence:

Ac-**ISGINASVVEIQKEIERLNKVAKNLNESLIDLQE**-GGGSGGG-C-R_8-NH_2

Retention time: 28.0 min

6bSH

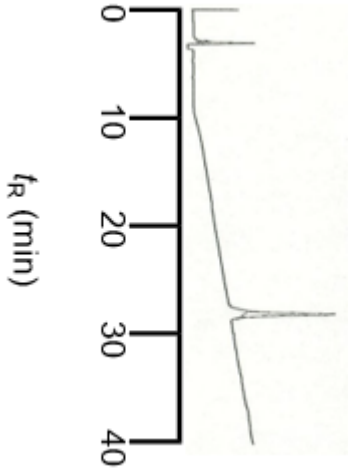


Sequence:

Ac-**ISGINASVVEIQKEIERLNKVAKELNKSLIDLQE**-GGGSGGG-C-R_8-NH_2

Retention time: 27.5

7bSH



Sequence:

Ac-**ISGINASVVNIQKEIERLNKVAKELNESLIDLQE**-**GGGSGGG**-**C**-**R**$_8$-NH_2

Retention time: 28.0 min

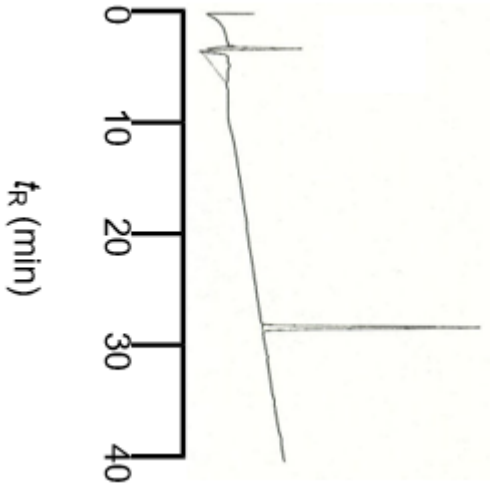
Figure S3. HPLC charts of purified intermediates for octa-arginine conjugated peptides.

Table S4. HPLC, mass and yield data of octa-arginine conjugated peptides.

Peptide	Analytical HPLC[a]		Preparative HPLC[b]	*m/z*		Yield (%)
	[c]t_R (min)	Gradient (%)	Gradient (%)	Calcd	Found	
1c	28.0	20 to 60	38 to 48	1415.8 $[M+4H]^{4+}$	1416.0	33.2
1d	28.2	20 to 60	30 to 45	1391.0 $[M+4H]^{4+}$	1391.5	9.2[d]
1e	27.8	5 to 60	35 to 45	1298.7 $[M+5H]^{5+}$	1298.7	14.9
2b	33.3	20 to 60	38 to 48	1423.8 $[M+4H]^{4+}$	1423.7	25.0
3b	27.6	20 to 60	35 to 55	1422.8 $[M+4H]^{4+}$	1423.0	34.0
4b	27.0	20 to 60	30 to 47	1422.5 $[M+4H]^{4+}$	1422.9	3.6[d]
5b	28.0	20 to 60	30 to 47	1422.8 $[M+4H]^{4+}$	1423.3	3.2[d]
6b	27.0	20 to 60	35 to 45	1426.3 $[M+4H]^{4+}$	1426.7	35.0
7b	28.1	20 to 60	30 to 47	1422.8 $[M+4H]^{4+}$	1423.0	3.1[d]

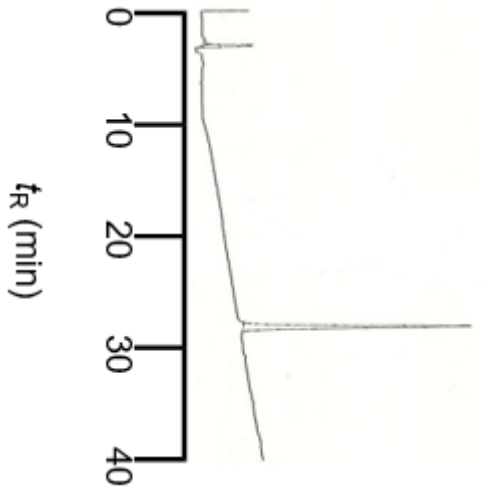
0 1% TFA in H_2O (v/v, solvent A) and 0.1% TFA in MeCN (v/v, solvent B) was used for HPLC elution over 40 min.
[a]Cosmosil $5C_{18}$-AR-II analytical column was employed with a linear gradient of solvent B in solvent A over 40 min.
[b]Cosmosil $5C_{18}$-AR-II preparative column was employed with a linear gradient of solvent B in solvent A over 40 min.
[c]Retention time. [d]2 steps from NovaSyn® TGR resin bound peptides.

1c



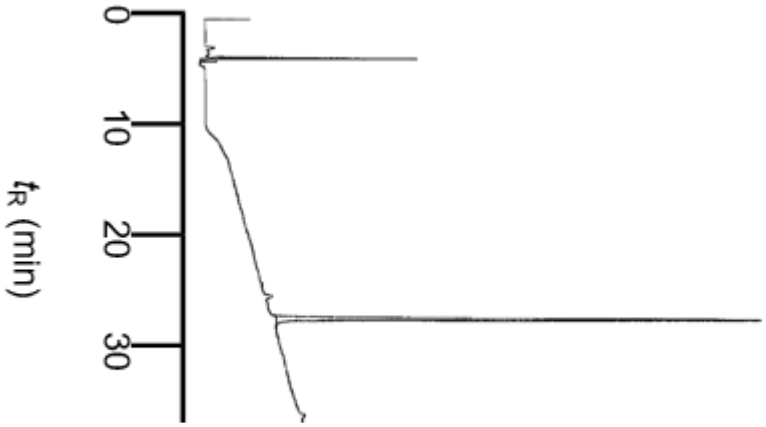
Sequence:
Ac-**ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE**-**GGGSGGG**-**C**(CH_2CONH_2)-**R**$_8$-NH_2
Retention time: 28.1 min

1d



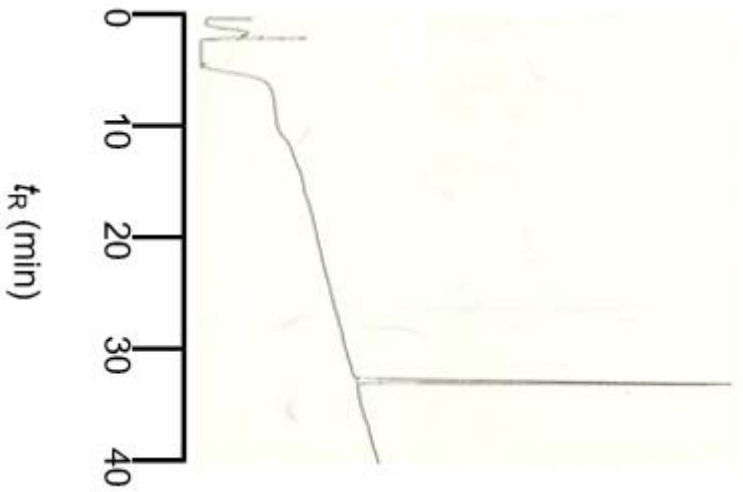
Sequence:
Ac-**ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE**-(miniPEG)$_2$-**R**$_8$-NH_2
Retention time: 28.2 min

1e



Sequence:
Ac-**GC**(Acm)**GG-ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE-RERERE-**
-GC(CH_2CO-**R**$_8$-NH_2)-NH_2
Retention time: 27.8

2b

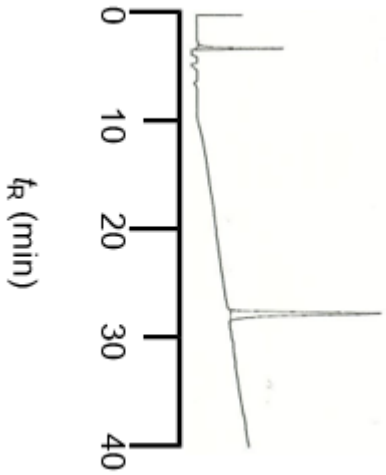


Sequence:

Ac-**ISGINASVVNIQEEIKKLNEEAKKLNESLIDLQE-GGGSGGG-C**(CH_2CONH_2)-**R**$_8$-NH_2

Retention time: 33.3 min

3b

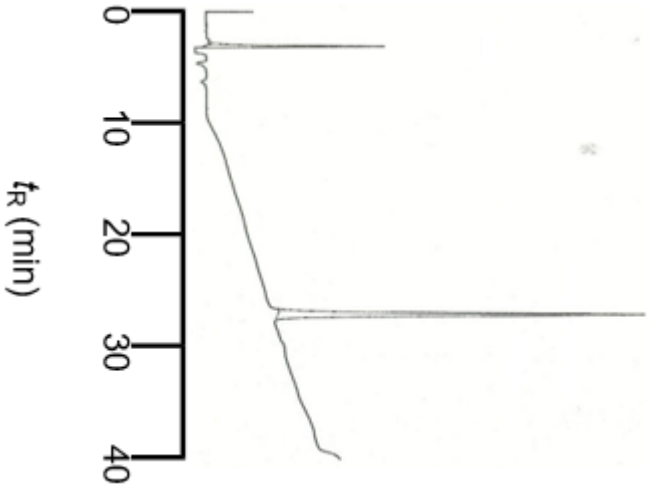


Sequence:

Ac-**ISGINASVVNIQEEIKRLNEVAKKLNESLIDLQE-GGGSGGG-C**(CH_2CONH_2)-**R**$_8$-NH_2

Retention time: 27.6 min

4b

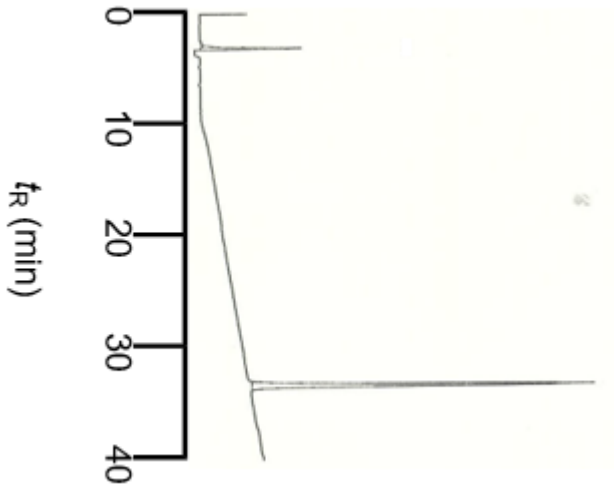


Sequence:

Ac-**ISGINASVVNIQKEIERLNKVAKELNKSLIDLQE-GGGSGGG-C**(CH_2CONH_2)-**R**$_8$-NH_2

Retention time: 27.0 min

5b

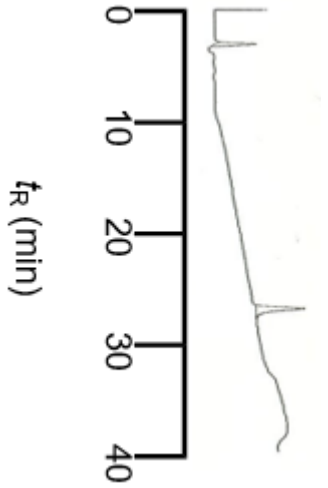


Sequence:

Ac-**ISGINASVVEIQKEIERLNKVAKNLNESLIDLQE-GGGSGGG-C**(CH_2CONH_2)-**R**$_8$-NH_2

Retention time: 28.0 min

6b

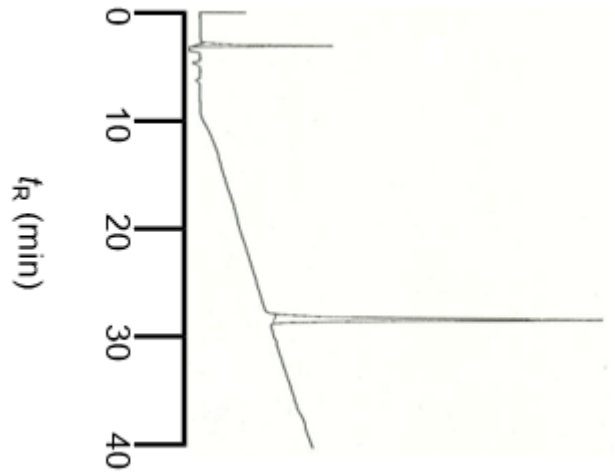


Sequence:

Ac-**ISGINASVVEIQKEIERLNKVAKELNKSLIDLQE-GGGSGGG-C**(CH_2CONH_2)-**R**$_8$-NH_2

Retention time: 27.0

7b



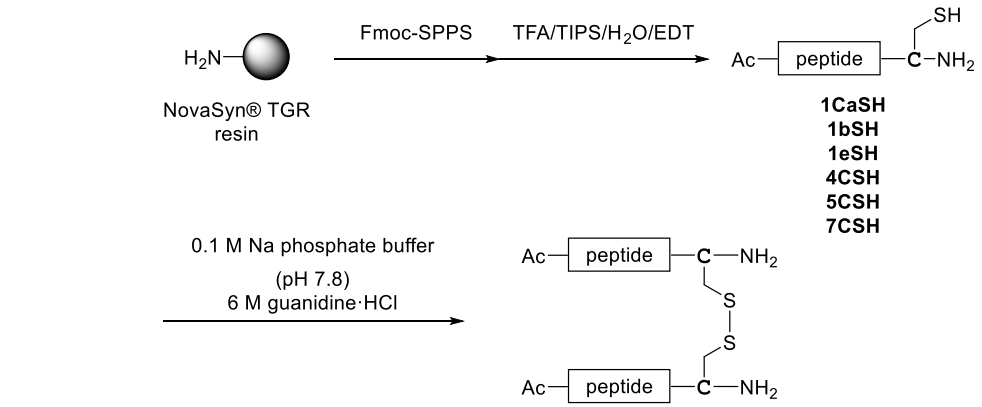
Sequence:

Ac-**ISGINASVVNIQKEIERLNKVAKELNESLIDLQE-GGGSGGG-C**(CH_2CONH_2)-**R**$_8$-NH_2

Retention time: 28.1 min

Figure S4. HPLC charts of purified octa-arginine conjugated peptides.

I-V. Synthesis of *C*-terminal dimers 1Ca – 8C.



1Ca Ac–ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE–GGGSGGG–C(S–)–NH_2)$_2$

1Cb Ac–ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE–RERERE–GC(S–)–NH_2)$_2$

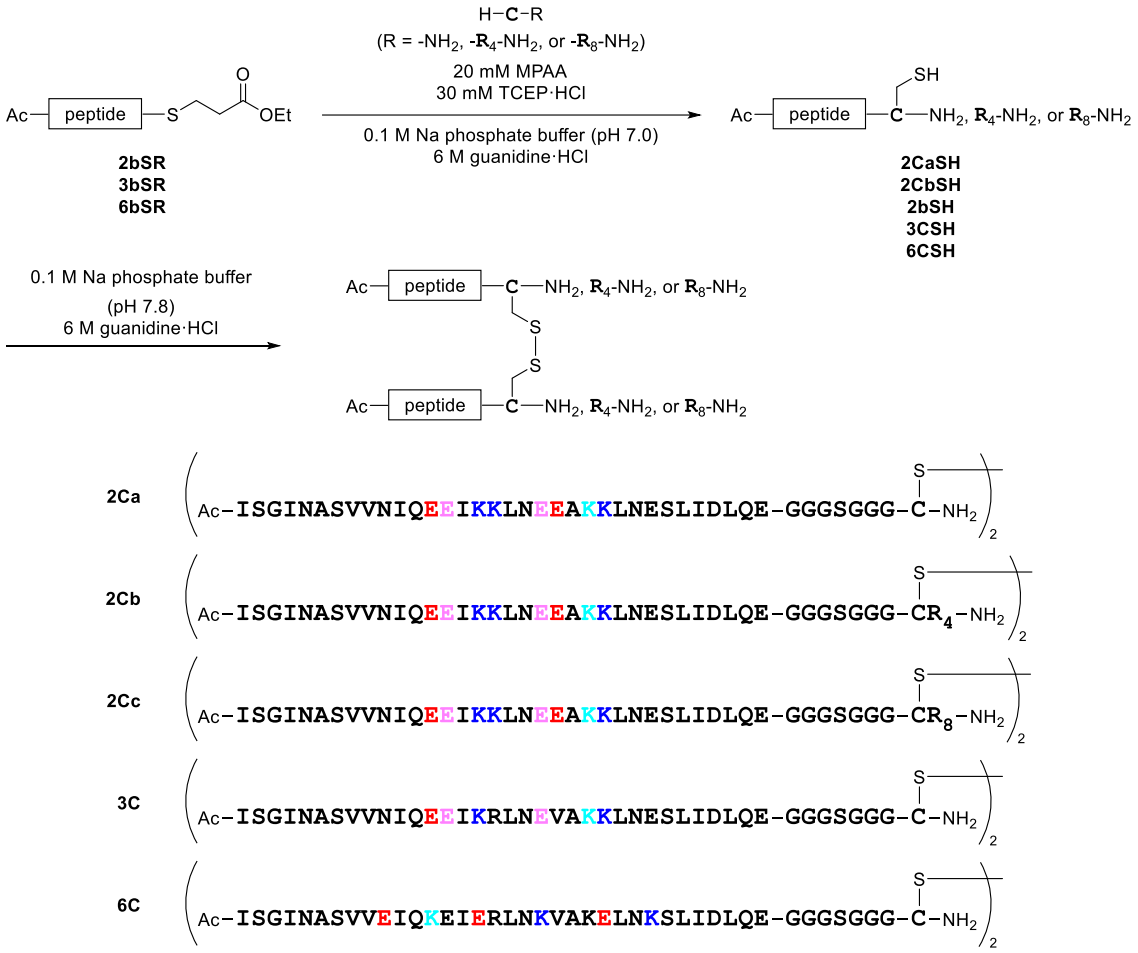
1Cc Ac–GC(Acm)GG–ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE–RERERE–GC(S–)–NH_2)$_2$

4C Ac–ISGINASVVNIQKEIERLNKVAKELNKSLIDLQE–GGGSGGG–C(S–)–NH_2)$_2$

5C Ac–ISGINASVVEIQKEIERLNKVAKNLNESLIDLQE–GGGSGGG–C(S–)–NH_2)$_2$

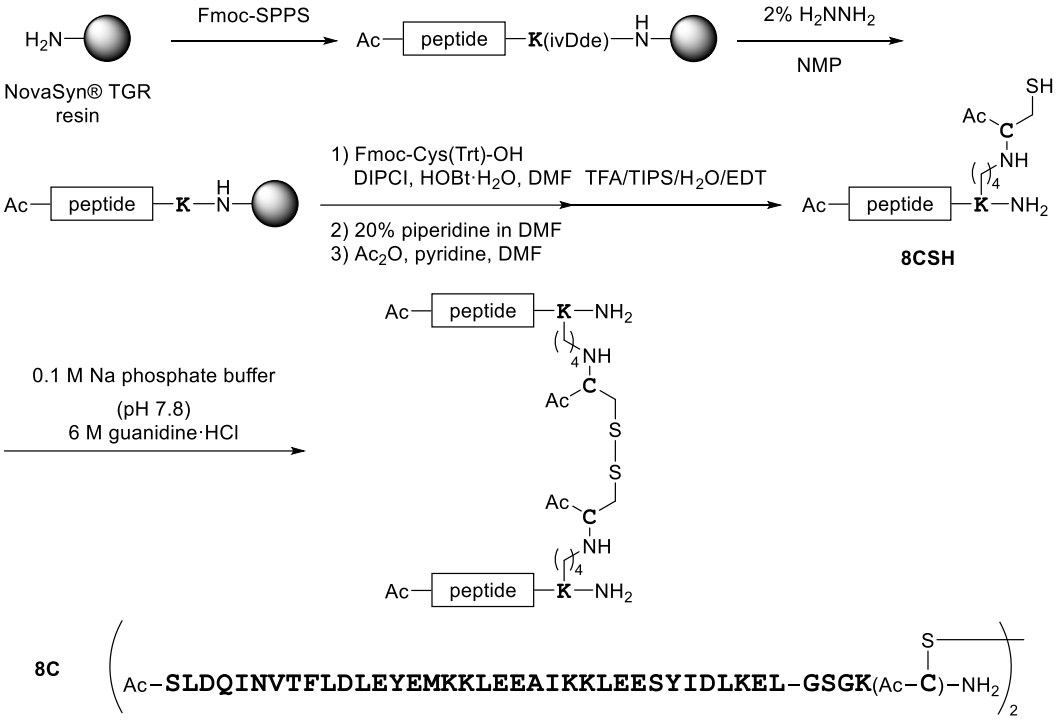
7C Ac–ISGINASVVNIQKEIERLNKVAKELNESLIDLQE–GGGSGGG–C(S–)–NH_2)$_2$

The peptides **1Ca**, **1Cb**, **1Cc**, **4C**, **5C**, and **7C** were synthesized using gereral Fmoc-SPPS procedures mentioned in the section **I-II** followed by disulfide bond formation *via* air oxidation. In brief, the purified thiol peptide was incubated in 0.1 M Na phosphate buffer (pH 7.8, 6 M guanidine·HCl, peptide concentration: 1.0 mM) at 37 °C for 72 h. The mixture was purified using preparative RP-HPLC to obtain desired peptide.



The peptides **2Ca**, **2Cb**, **2Cc**, **3C**, and **6C** were synthesized using gereral Fmoc-SPPS procedures mentioned in the section **I-II** followed by cleavage of protected peptides, thioesterification, native chemical ligation (NCL) as shown in the section **I-IV**, and disulfide bond formation *via* air oxidation. In brief, the constructed peptide on 2-chlorotrityl chloride resin was cleaved from resin with AcOH/TFE/DCM = 1:1:3 as a protected peptide with C-terminal carboxylic acid. The crude peptide was subsequently coupled with ethyl 3-mercaptopropionate (20 equiv.) using EDCI·HCl (10 equiv.) and HOBt·H_2O (10 equiv.) in DMF at room temperature overnight. The volatile was removed *in vacuo* and the residue was treated with TFA/TIPS/H_2O = 95:2.5:2.5 (v/v) for global deprotection followed by RP-HPLC purification. The obtained peptide thioester was treated with H-**C**-NH_2, H-**C**-**R**$_4$-NH_2, or H-**C**-**R**$_8$-NH_2 in 0.1 M Na phosphate buffer (pH 7.8, 6 M guanidine·HCl, each peptide concentration: 1 mM) in the presence of 30 mM MPAA and 20 mM TCEP·HCl at room temperature overnight. The reaction mixture was then purified using preparative RP-HPLC to obtain the NCL product. The generated thiol peptide was incubated in 0.1 M Na phosphate buffer (pH

7.8, 6 M guanidine·HCl, peptide concentration: 1.0 mM) at 37 °C for 72 h. The mixture was purified using preparative RP-HPLC to obtain desired peptide.



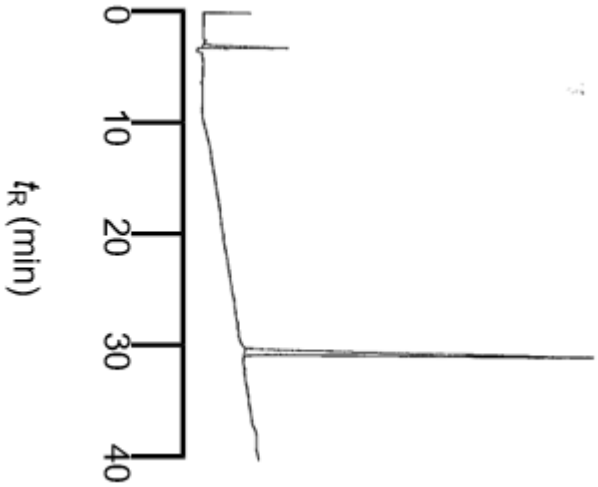
The peptide **8C** was synthesized using gereral Fmoc-SPPS procedures mentioned in the section **I-II** followed by selective deprotection of ivDde group on lysine ε-amino group, its coupling with Fmoc-Cys(Trt)-OH, acetyl capping, and disulfide bond formation *via* air oxidation. In brief, the constructed resin was treated with 2% H_2NNH_2 in NMP (v/v) at room temperature for 3 h and overnight (twice). The resin was then coupled with Fmoc-Cys(Trt)-OH (5 equiv.) using DIPCI (5 equiv.) and HOBt·H_2O (5 equiv.) in DMF. After Fmoc removal by 20% piperidine/DMF (v/v), the resin was treated with Ac_2O (10 equiv.), pyridine (10 equiv.) in DMF for 60 min for acetylation. The resulting resin was treated with the TFA cocktail followed by preparative RP-HPLC purification to obtain **8CSH**. The obtained **8CSH** (21.1 mg, 3.81 mmol) was incubated in 0.1 M Na phosphate buffer (pH 7.8, 6 M guanidine·HCl, 3.81 mL, peptide concentration: 1.0 mM) at 37 °C for 72 h. The mixture was purified using preparative RP-HPLC to obtain the desired peptide **8C**.

Table S5. HPLC, mass and yield data of intermediate peptides for *C*-terminal dimers.

Peptide	Analytical HPLC[a]		Preparative HPLC[b]	*m/z*		Yield[d] (%)
	[c]t_R (min)	Gradient (%)	Gradient (%)	Calcd	Found	
1CaSH	30.3	20 to 60	38 to 48	1452.1 $[M+3H]^{3+}$	1452.1	8.0
2CaSH	34.9	5 to 60	25 to 45	1462.1 $[M+4H]^{4+}$	1462.3	20.2[e]
2CbSH	33.7	5 to 60	25 to 45	1252.9 $[M+4H]^{4+}$	1253.0	23.3[e]
3CSH	30.1	20 to 60	42 to 50	1461.1 $[M+3H]^{3+}$	1461.6	20.2[e]
4CSH	29.6	20 to 60	38 to 48	1461.2 $[M+3H]^{3+}$	1461.1	8.7
5CSH	30.5	20 to 60	38 to 48	1461.1 $[M+3H]^{3+}$	1461.5	9.0
6CSH	33.3	20 to 60	38 to 48	1466.1 $[M+3H]^{3+}$	1466.3	28.6[e]
7CSH	30.7	20 to 60	38 to 48	1461.0 $[M+3H]^{3+}$	1461.5	8.3
8CSH	23.5	20 to 80	35 to 50	1212.6 $[M+4H]^{4+}$	1212.8	4.3

0 1% TFA in H2O (v/v, solvent A) and 0.1% TFA in MeCN (v/v, solvent B) was used for HPLC elution over 40 min.
[a]Cosmosil $5C_{18}$-AR-II analytical column was employed with a linear gradient of solvent B in solvent A over 40 min.
[b]Cosmosil $5C_{18}$-AR-II preparative column was employed with a linear gradient of solvent B in solvent A over 40 min.
[c]Retention time. [d]from NovaSyn® TGR resin. [e]from NCL.

1CaSH

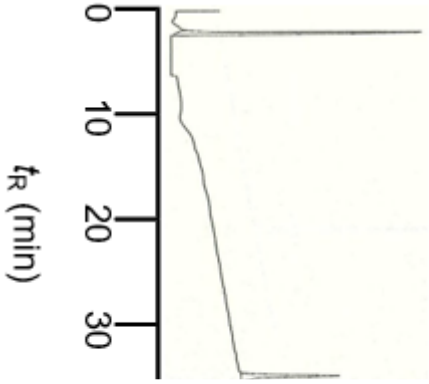


Sequence:

Ac-**ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE**-**GGGSGGG**-**C**-NH_2

Retention time: 30.3 min

2CaSH

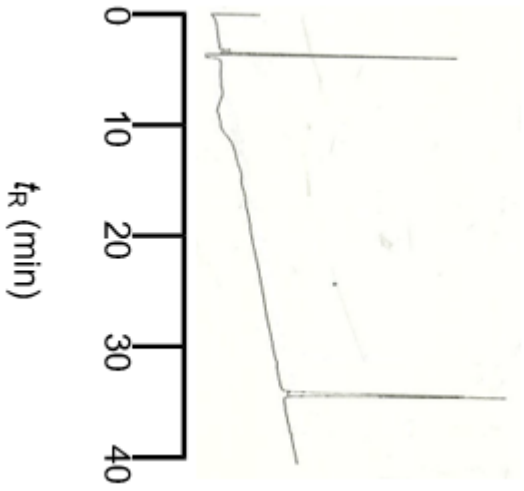


Sequence:

Ac-**ISGINASVVNIQEEIKKLNEEAKKLNESLIDLQE-GGGSGGG-C**-NH_2

Retention time: 34.9 min

2CbSH

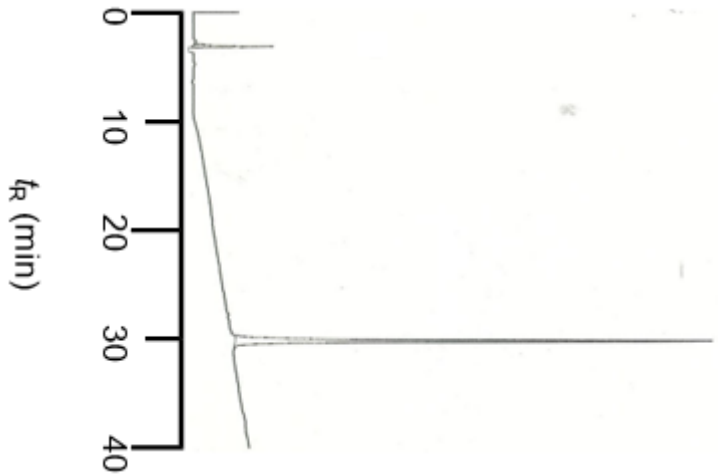


Sequence:

Ac-**ISGINASVVNIQEEIKKLNEEAKKLNESLIDLQE-GGGSGGG-C-R**$_4$-NH_2

Retention time: 33.7 min

3CSH

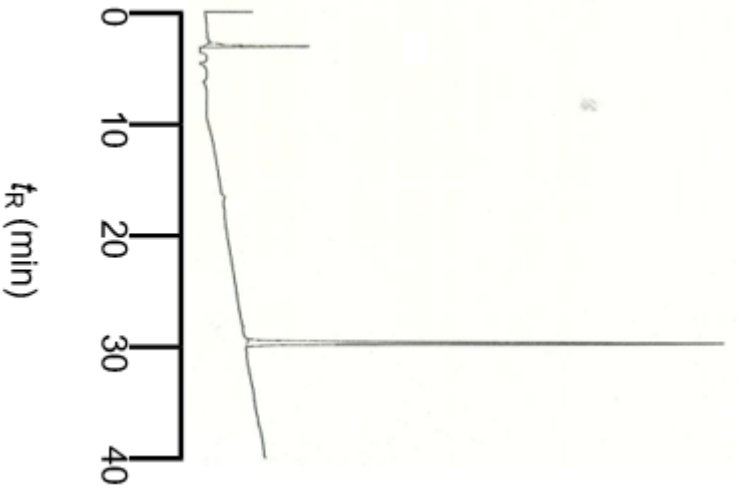


Sequence:

Ac-**ISGINASVVNIQEEIKRLNEVAKKLNESLIDLQE-GGGSGGG-C**-NH_2

Retention time: 30.1 min

4CSH

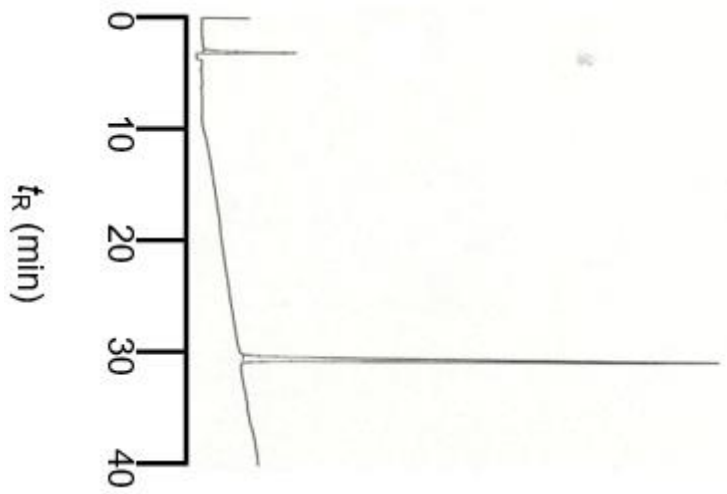


Sequence:

Ac-**ISGINASVVNIQKEIERLNKVAKELNKSLIDLQE-GGGSGGG-C**-NH_2

Retention time: 29.6 min

5CSH

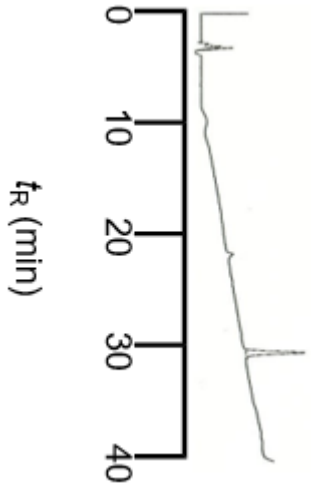


Sequence:

Ac-**ISGINASVVEIQKEIERLNKVAKNLNESLIDLQE-GGGSGGG-C**-NH_2

Retention time: 30.5 min

6CSH

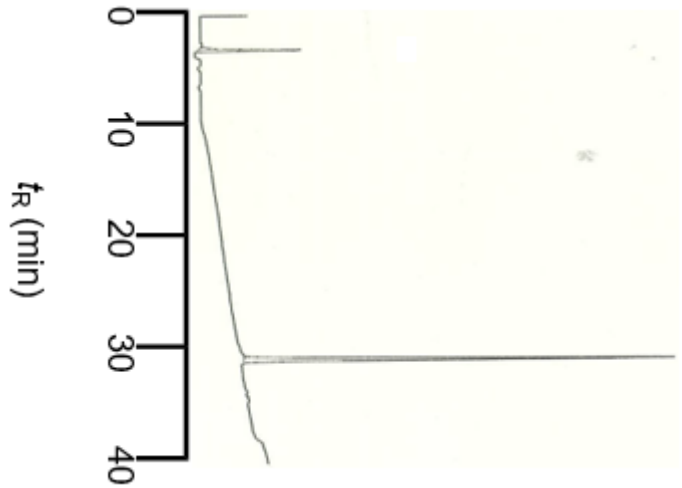


Sequence:

Ac-**ISGINASVVEIQKEIERLNKVAKELNKSLIDLQE-GGGSGGG-C**-NH_2

Retention time: 33.3 min

7CSH

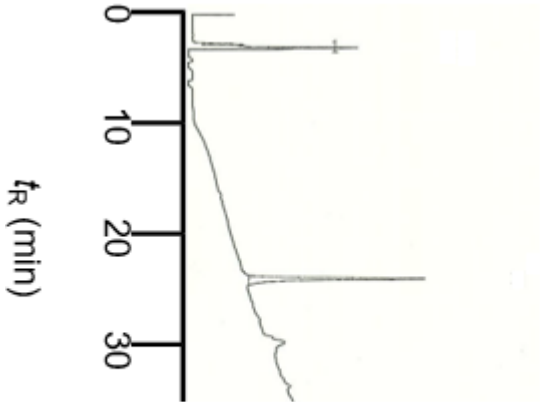


Sequence:

Ac-**ISGINASVVNIQKEIERLNKVAKELNESLIDLQE-GGGSGGG-C**-NH_2

Retention time: 30.7 min

8CSH



Sequence:

Ac-**SLDQINVTFLDLEYEMKKLEEAIKKLEESYIDLKEL-GSGK**(Ac-**C**)-NH_2

Retention time: 23.5 min

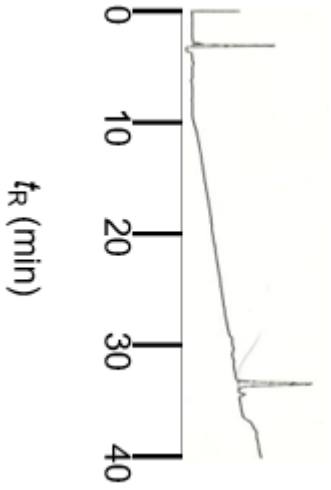
Figure S5. HPLC charts of purified intermediate peptides for *C*-terminal dimers.

Table S6. HPLC, mass and yield data of *C*-terminal dimers.

Peptide	Analytical HPLC[a]		Preparative HPLC[b]	*m/z*		Yield (%)
	[c]t_R (min)	Gradient (%)	Gradient (%)	Calcd	Found	
1Ca	33.4	20 to 60	38 to 48	2177.4 $[M+4H]^{4+}$	2177.4	10.8
1Cb	30.8	5 to 60	35 to 50	1934.4 $[M+5H]^{5+}$	1935.6	6.1
1Cc	30.1	5 to 60	35 to 50	1037.2 $[M+10H]^{10+}$	1037.4	6.6
2Ca	30.5	20 to 60	38 to 48	2192.4 $[M+4H]^{4+}$	2192.6	23.4
2Cb	33.2	5 to 60	25 to 45	1253.0 $[M+4H]^{4+}$	1253.1	21.2
2Cc	34.4	5 to 60	25 to 45	2816.8 $[M+4H]^{4+}$	2816.9	20.1
3C	33.3	20 to 60	38 to 48	2191.1 $[M+4H]^{4+}$	2191.2	18.6
4C	32.1	20 to 60	38 to 48	2190.7 $[M+4H]^{4+}$	2191.0	25.0
5C	33.2	20 to 60	38 to 48	2191.1 $[M+4H]^{4+}$	2191.5	18.6
6C	33.7	20 to 60	38 to 48	2198.2 $[M+4H]^{4+}$	2198.5	22.5
7C	33.8	20 to 60	38 to 48	2191.1 $[M+4H]^{4+}$	2191.3	31.5
8C	23.9	20 to 80	35 to 50	1940.0 $[M+5H]^{5+}$	1939.4	15.9

0 1% TFA in H_2O (v/v, solvent A) and 0.1% TFA in MeCN (v/v, solvent B) was used for HPLC elution over 40 min.
[a]Cosmosil $5C_{18}$-AR-II analytical column was employed with a linear gradient of solvent B in solvent A over 40 min.
[b]Cosmosil $5C_{18}$-AR-II preparative column was employed with a linear gradient of solvent B in solvent A over 40 min.
[c]Retention time.

1Ca

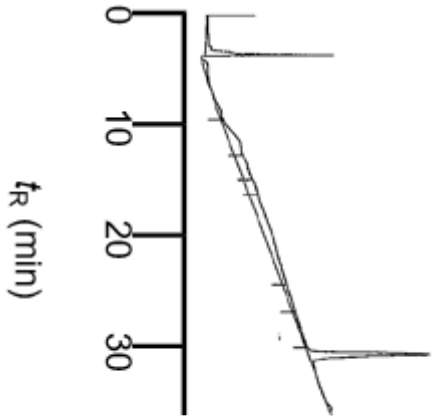


Sequence:

(Ac-**ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE-GGGSGGG-C**-NH_2)$_2$ with S———S disulfide bridge

Retention time: 33.4 min

1Cb

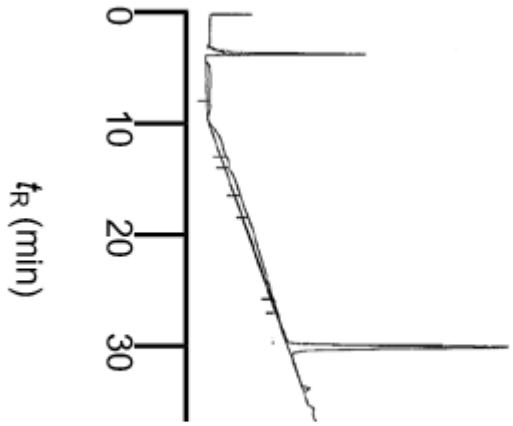


Sequence:

(Ac-**ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE-RERERE-GC**-NH_2)$_2$
(S———S)

Retention time: 30.8 min

1Cc

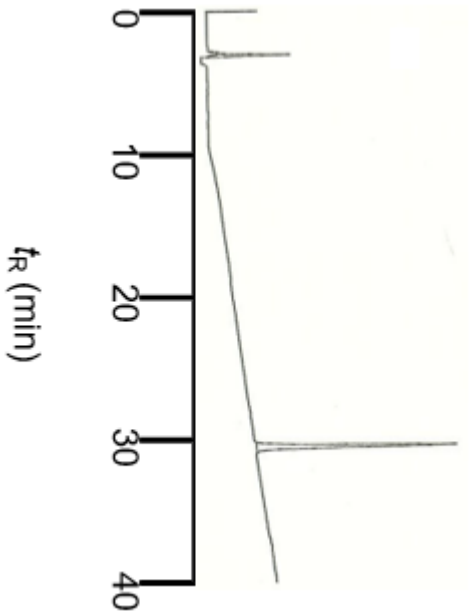


Sequence:

(Ac-**GC**(Acm)**GG-ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE-RERERE-GC**-NH_2)$_2$
(S———S)

Retention time: 30.1 min

2Ca

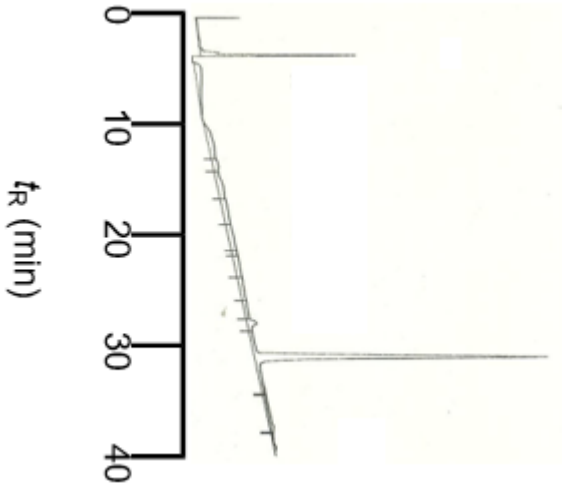


Sequence:

(Ac-**ISGINASVVNIQEEIKKLNEEAKKLNESLIDLQE-GGGSGGG-C**-NH_2)$_2$

Retention time: 30.5 min

2Cb

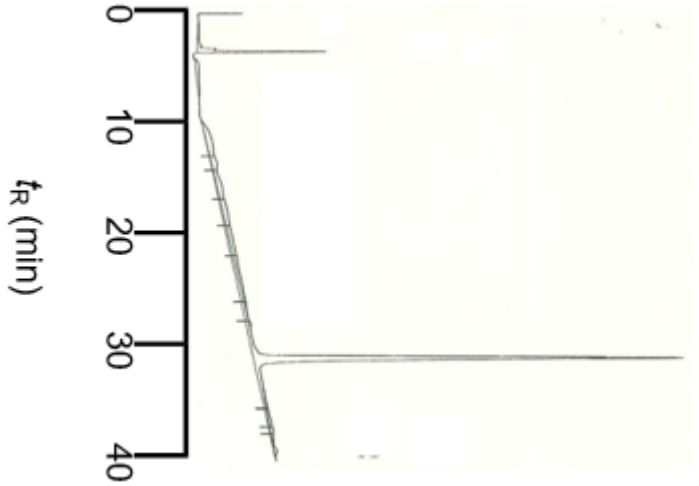


Sequence:

(Ac-**ISGINASVVNIQEEIKKLNEEAKKLNESLIDLQE-GGGSGGG-C-R**$_4$-NH_2)$_2$

Retention time: 33.2 min

2Cc



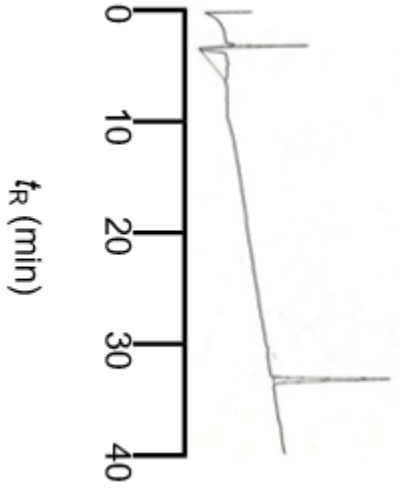
Sequence:

(Ac-**ISGINASVVNIQEEIKKLNEEAKKLNESLIDLQE-GGGSGGG-C**-R_8-NH_2)$_2$

S———

Retention time: 34.4 min

3C



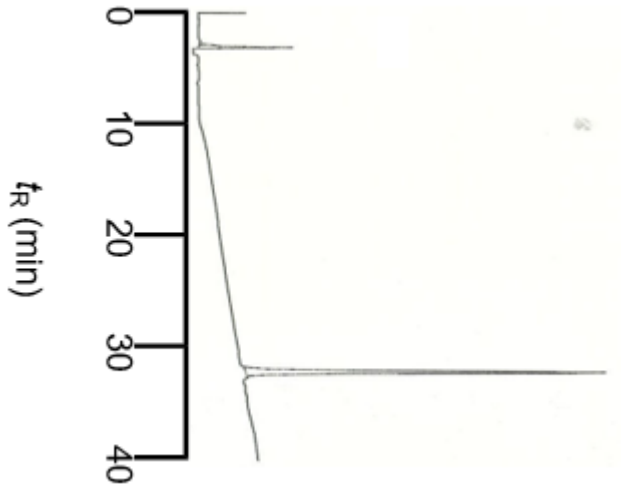
Sequence:

(Ac-**ISGINASVVNIQEEIKRLNEVAKKLNESLIDLQE-GGGSGGG-C**-NH_2)$_2$

S———

Retention time: 33.3 min

4C



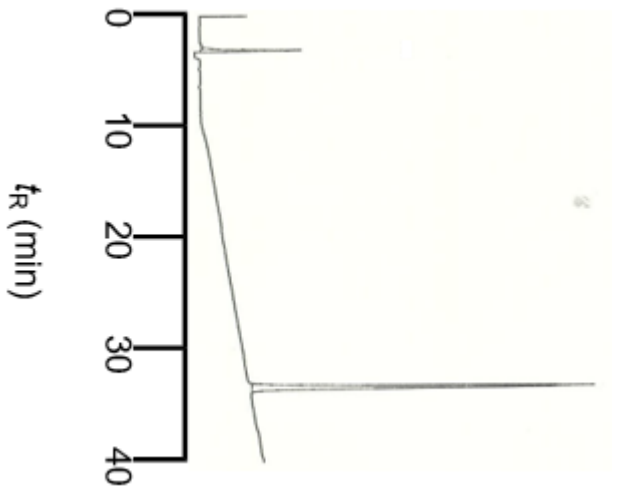
Sequence:

(Ac-**ISGINASVVNIQKEIERLNKVAKELNKSLIDLQE-GGGSGGG-C**-NH_2)$_2$

S——

Retention time: 32.1 min

5C



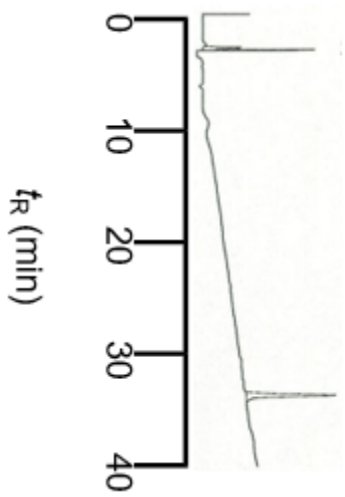
Sequence:

(Ac-**ISGINASVVEIQKEIERLNKVAKNLNESLIDLQE-GGGSGGG-C**-NH_2)$_2$

S——

Retention time: 33.2 min

6C

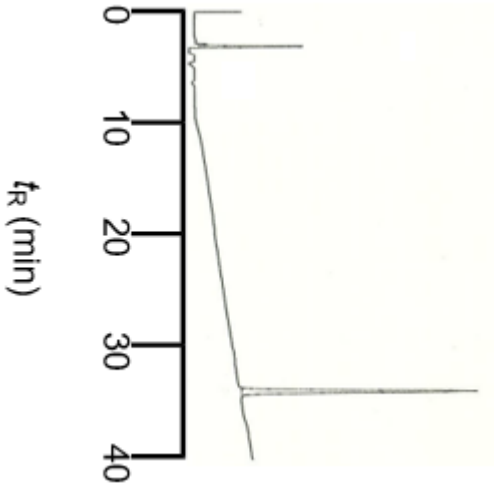


Sequence:

(Ac-**ISGINASVVEIQKEIERLNKVAKELNKSLIDLQE-GGGSGGG-C**-NH_2)$_2$ (S—S)

Retention time: 33.7 min

7C

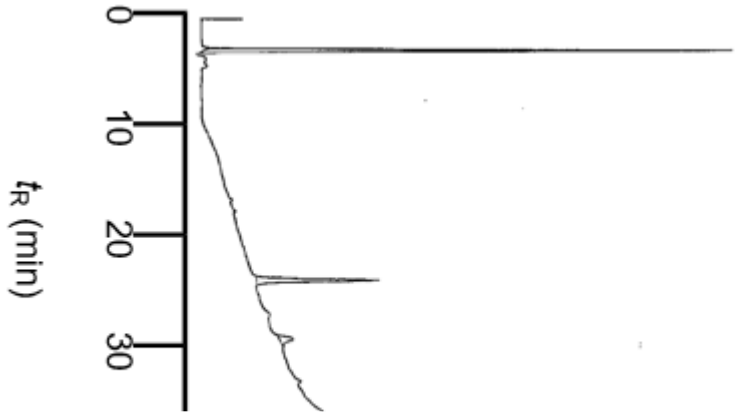


Sequence:

(Ac-**ISGINASVVNIQKEIERLNKVAKELNESLIDLQE-GGGSGGG-C**-NH_2)$_2$ (S—S)

Retention time: 33.8 min

8C



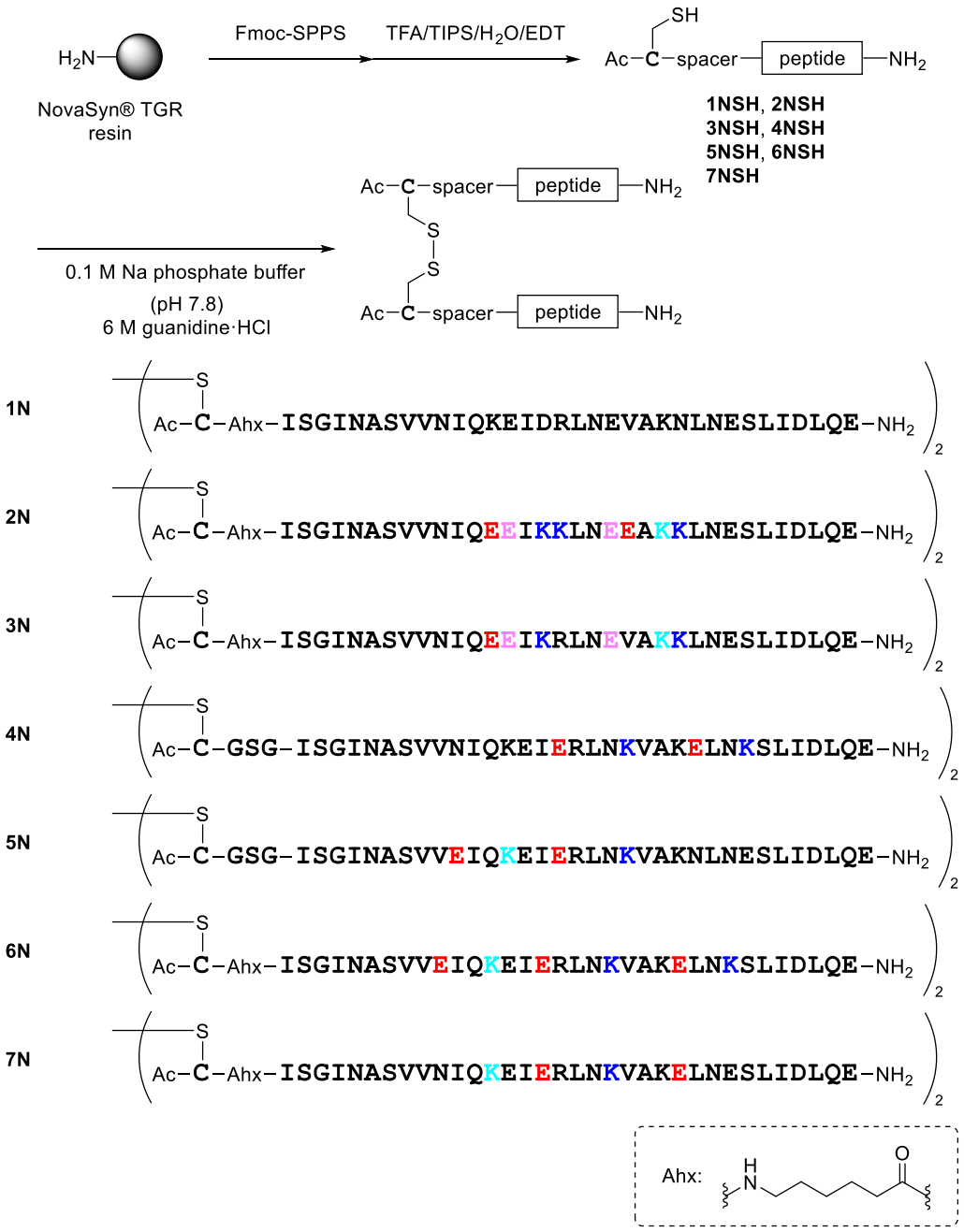
Sequence:

(Ac-**SLDQINVTFLDLEYEMKKLEEAIKKLEESYIDLKEL-GSGK**(Ac-**C**)-NH_2)$_2$

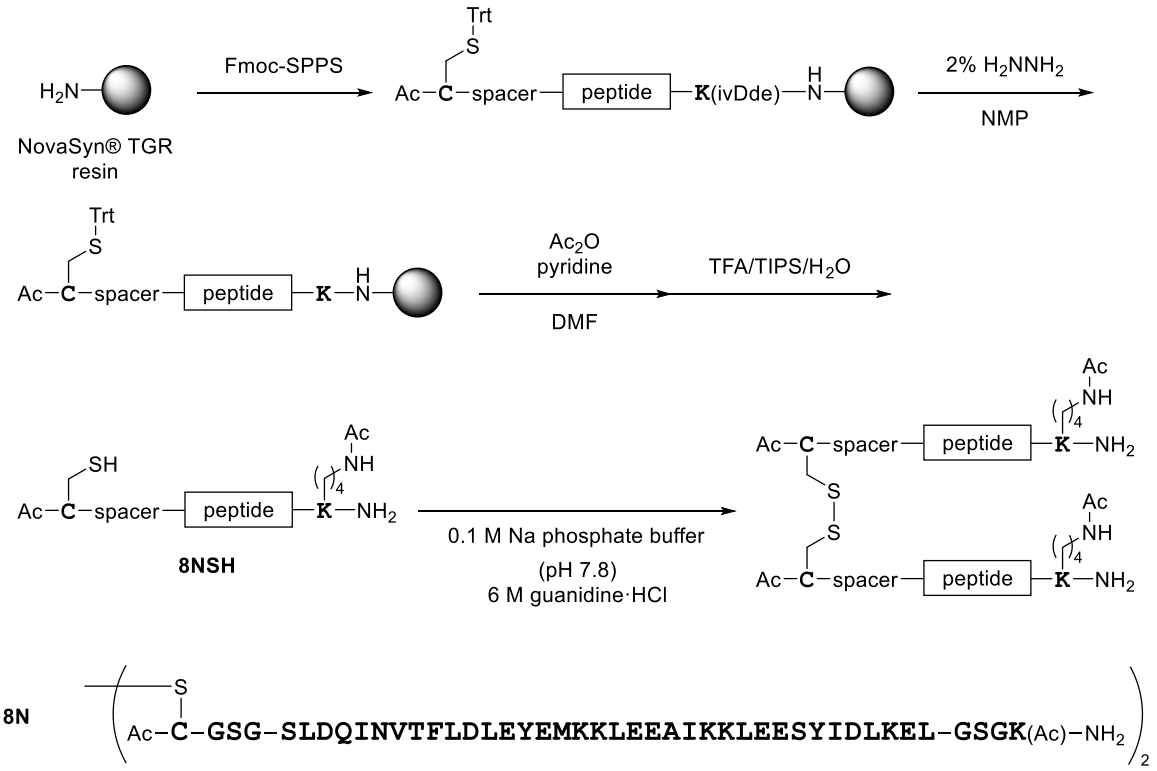
Retention time: 23.5 min

Figure S6. HPLC charts of purified *C*-terminal dimers.

I-VI. Synthesis of *N*-terminal dimers 1N – 8N.



The peptides **1N**, **2N**, **3N**, **4N**, **5N**, **6N**, and **7N** were synthesized using gereral Fmoc-SPPS procedures mentioned in the section **I-II** followed by disulfide bond formation *via* air oxidation. In brief, the purified thiol peptide was incubated in 0.1 M Na phosphate buffer (pH 7.8, 6 M guanidine·HCl, peptide concentration: 1.0 mM) at 37 °C for 72 h. The mixture was purified using preparative RP-HPLC to obtain desired peptide.



8N $\left(\text{Ac–C–GSG–SLDQINVTFLDLEYEMKKLEEAIKKLEESYIDLKEL–GSGK(Ac)–NH}_2\right)_2$

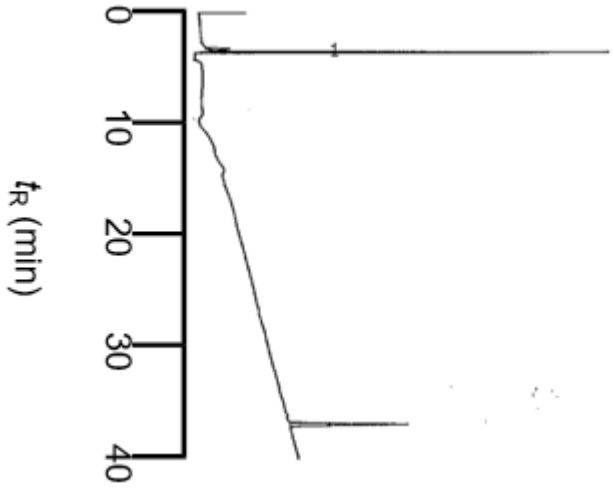
The peptide **8N** was synthesized using gereral Fmoc-SPPS procedures mentioned in the section **I-II** followed by selective deprotection of ivDde group on lysine ε-amino group, its acetyl capping, and disulfide bond formation *via* air oxidation. In brief, the constructed resin was treated with 2% H_2NNH_2 in NMP (v/v) at room temperature for 3 h and overnight (twice). The resin was then treated with Ac_2O (20 equiv.), pyridine (20 equiv.) in DMF for 60 min for acetylation. The resulting resin was treated with the TFA cocktail followed by preparative RP-HPLC purification to obtain **8NSH**. The obtained **8NSH** was incubated in 0.1 M Na phosphate buffer (pH 7.8, 6 M guanidine·HCl, peptide concentration: 1.0 mM) at 37 °C for 72 h. The mixture was purified using preparative RP-HPLC to obtain desired peptide.

Table S7. HPLC, mass and yield data of intermediate peptides for *N*-terminal dimers.

Peptide	Analytical HPLC[a]		Preparative HPLC[b]	*m/z*		Yield (%)
	[c]t_R (min)	Gradient (%)	Gradient (%)	Calcd	Found	
1NSH	36.8	5 to 60	35 to 50	1346.7 $[M+3H]^{3+}$	1346.9	11.2
2NSH	32.3	5 to 60	30 to 55	1356.4 $[M+3H]^{3+}$	1357.0	12.3
3NSH	36.7	5 to 60	30 to 55	1355.7 $[M+3H]^{3+}$	1356.2	8.8
4NSH	20.4	20 to 80	40 to 50	1384.8 $[M+3H]^{3+}$	1385.3	8.9
5NSH	20.5	20 to 80	40 to 55	1385.1 $[M+3H]^{3+}$	1385.6	8.9
6NSH	31.4	20 to 60	38 to 48	1360.4 $[M+3H]^{3+}$	1360.9	11.0
7NSH	32.2	20 to 60	38 to 48	1355.7 $[M+3H]^{3+}$	1356.0	10.3
8NSH	23.0	20 to80	40 to 50	1262.9 $[M+3H]^{3+}$	1263.3	4.3

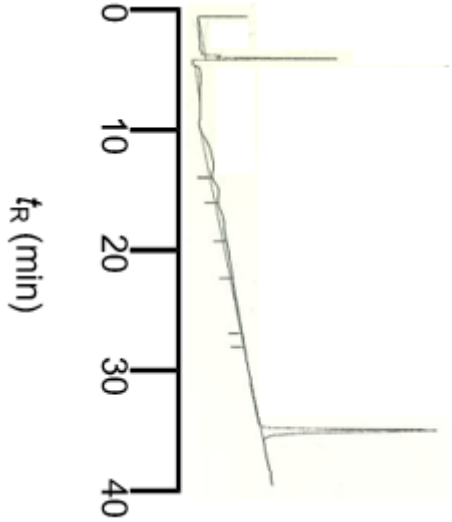
0 1% TFA in H_2O (v/v, solvent A) and 0.1% TFA in MeCN (v/v, solvent B) was used for HPLC elution over 40 min.
[a]Cosmosil $5C_{18}$-AR-II analytical column was employed with a linear gradient of solvent B in solvent A over 40 min.
[b]Cosmosil $5C_{18}$-AR-II preparative column was employed with a linear gradient of solvent B in solvent A over 40 min.
[c]Retention time.

1NSH



Sequence:
Ac-**C**-Ahx-**ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE**-NH_2
Retention time: 36.8 min

2NSH

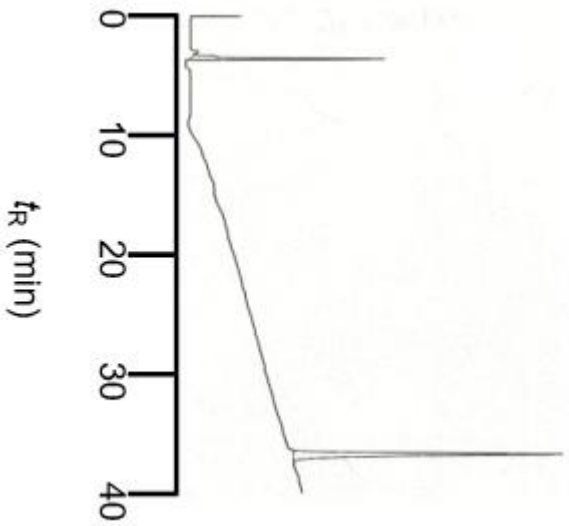


Sequence:

Ac-**C**-Ahx-**ISGINASVVNIQEEIKKLNEEAKKLNESLIDLQE**-NH_2

Retention time: 32.3 min

3NSH

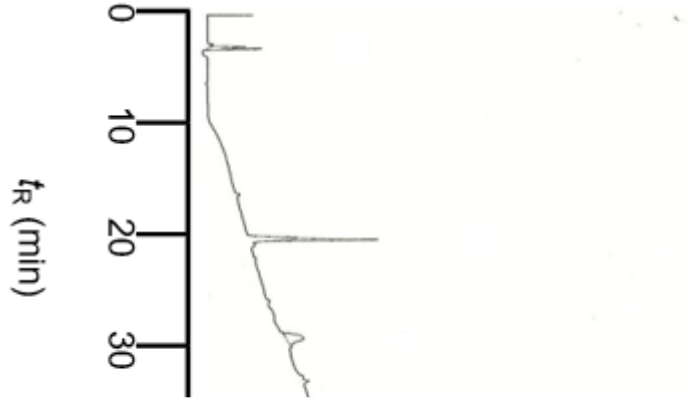


Sequence:

Ac-**C**-Ahx-**ISGINASVVNIQEEIKRLNEVAKKLNESLIDLQE**-NH_2

Retention time: 36.7 min

4NSH

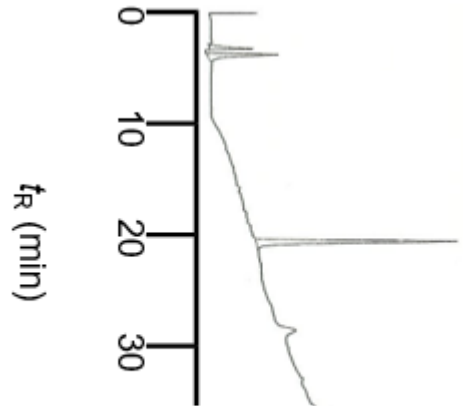


Sequence:

Ac-**C-GSG-ISGINASVVNIQKEIERLNKVAKELNKSLIDLQE**-NH_2

Retention time: 20.4 min

5NSH

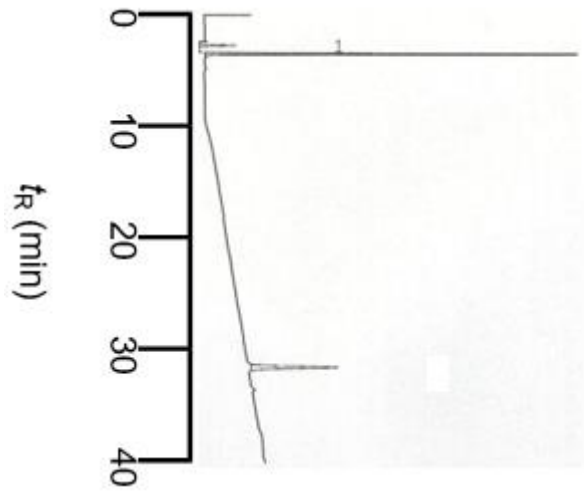


Sequence:

Ac-**C-GSG-ISGINASVVEIQKEIERLNKVAKNLNESLIDLQE**-NH_2

Retention time: 20.6 min

6NSH

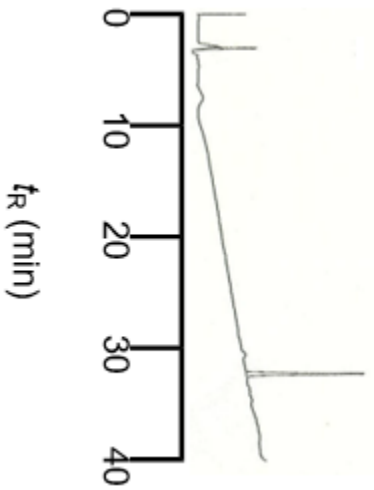


Sequence:

Ac-**C**-Ahx-**ISGINASVVEIQKEIERLNKVAKELNKSLIDLQE**-NH_2

Retention time: 31.4 min

7NSH

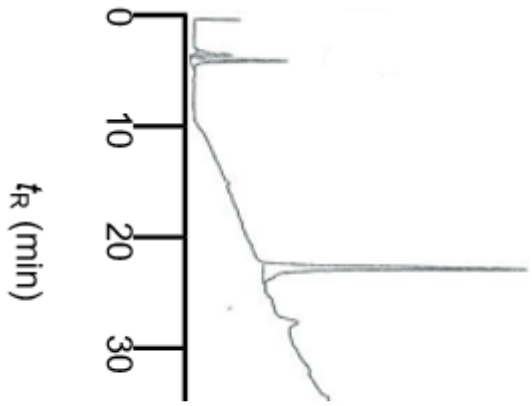


Sequence:

Ac-**C**-Ahx-**ISGINASVVNIQKEIERLNKVAKELNESLIDLQE**-NH_2

Retention time: 32.2 min

8NSH



Sequence:

Ac-**C-GSG-SLDQINVTFLDLEYEMKKLEEAIKKLEESYIDLKEL-GSGK**(Ac)-NH_2

Retention time: 23.0 min

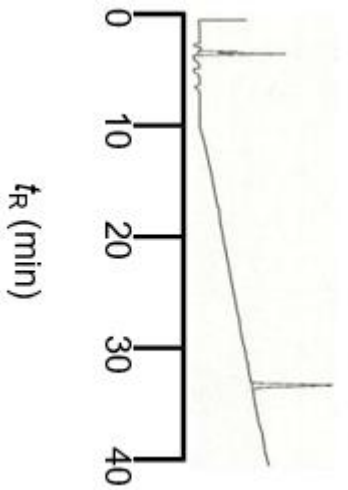
Figure S7. HPLC charts of purified intermediate peptides for *N*-terminal dimers.

Table S8. HPLC, mass and yield data of *N*-terminal dimers.

Peptide	Analytical HPLC[a]		Preparative HPLC[b]	*m/z*		Yield (%)
	[c]t_R (min)	Gradient (%)	Gradient (%)	Calcd	Found	
1N	32.8	20 to 60	38 to 48	2018.8 $[M+4H]^{4+}$	2019.4	20.2
2N	36.5	5 to 60	35 to 50	2034.4 $[M+4H]^{4+}$	2034.5	22.1
3N	38.2	5 to 60	35 to 50	2032.9 $[M+4H]^{4+}$	2033.4	20.1
4N	20.9	20 to 80	40 to 55	1039.0 $[M+8H]^{8+}$	1038.9	12.1
5N	21.4	20 to 80	40 to 55	1039.1 $[M+8H]^{8+}$	1039.1	12.4
6N	33.3	20 to 60	33 to 55	2039.9 $[M+4H]^{4+}$	2040.4	20.0
7N	33.8	20 to 60	38 to 48	2032.9 $[M+4H]^{4+}$	2033.2	20.4
8N	23.2	20 to 80	40 to 50	2019.8 $[M+5H]^{5+}$	2020.2	16.0

0 1% TFA in H_2O (v/v, solvent A) and 0.1% TFA in MeCN (v/v, solvent B) was used for HPLC elution over 40 min.
[a]Cosmosil $5C_{18}$-AR-II analytical column was employed with a linear gradient of solvent B in solvent A over 40 min.
[b]Cosmosil $5C_{18}$-AR-II preparative column was employed with a linear gradient of solvent B in solvent A over 40 min.
[c]Retention time.

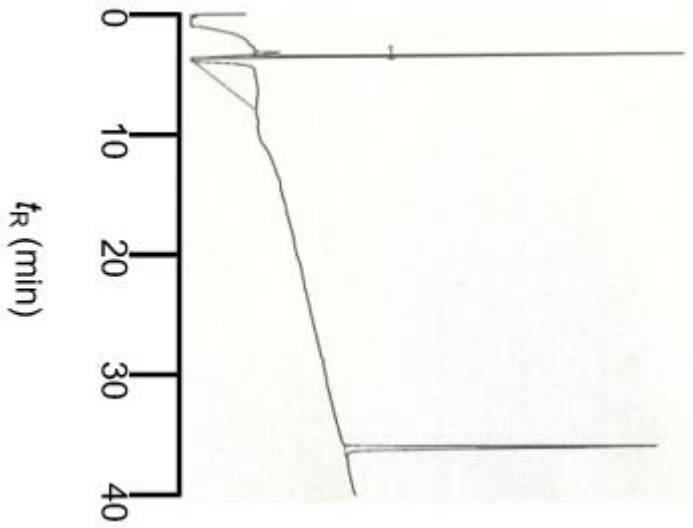
1N



Sequence:

Retention time: 32.8 min

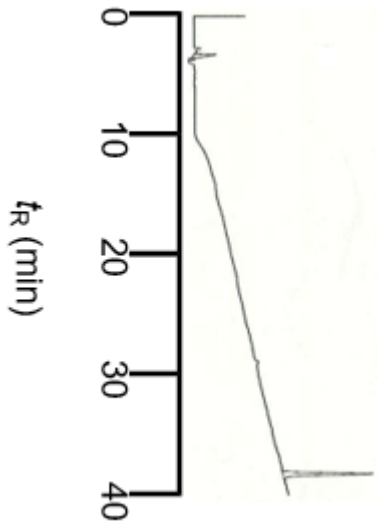
2N



Sequence:

Retention time: 36.5 min

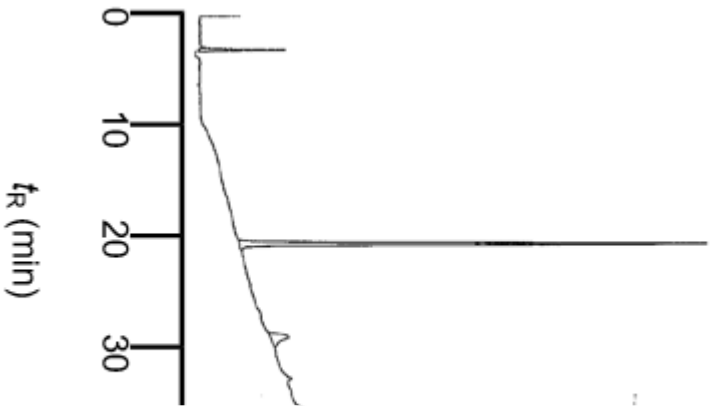
3N



Sequence:

Retention time: 38.2 min

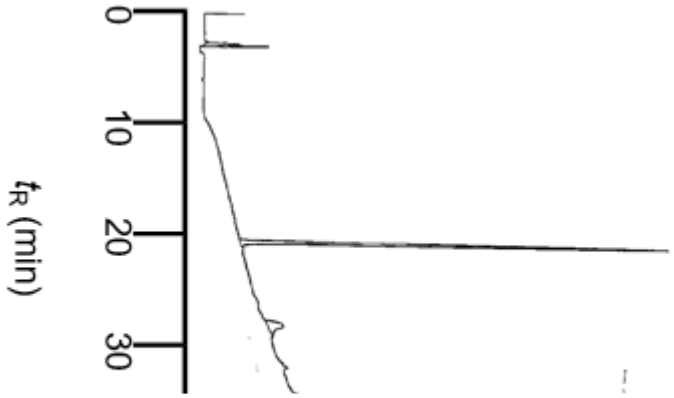
4N



Sequence:

Retention time: 20.9 min

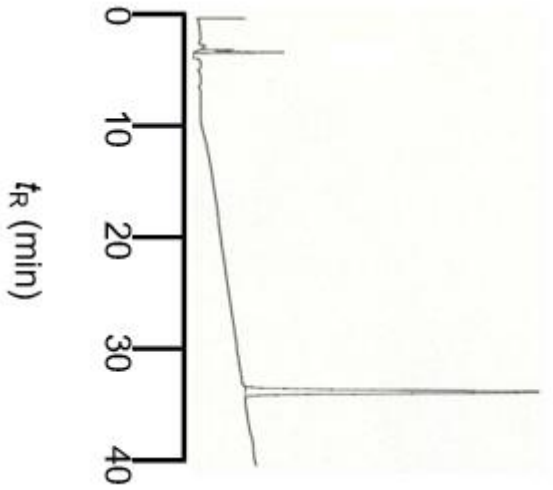
5N



Sequence:

Retention time: 20.9 min

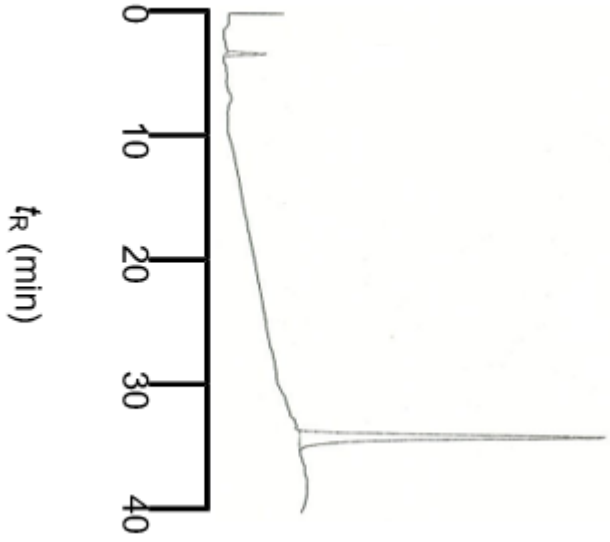
6N



Sequence:

Retention time: 33.3 min

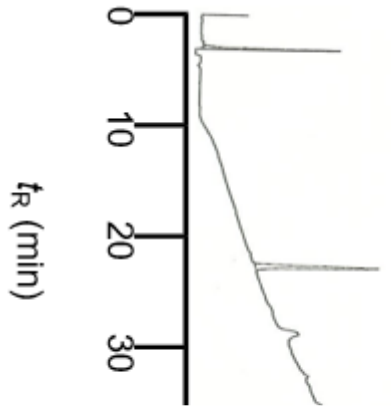
7N



Sequence:

Retention time: 33.8 min

8N



Sequence:

(Ac-**C**-**GSG-SLDQINVTFLDLEYEMKKLEEAIKKLEESYIDLKEL-GSGK**(Ac)-NH_2)$_2$

Retention time: 23.2 min

Figure S8. HPLC charts of purified *N*-terminal dimers.

II. Biological evaluation of the sinthesized peptides.

II-I. Figure S9. Results from plaque reduction assay of experiments 1 to 7.

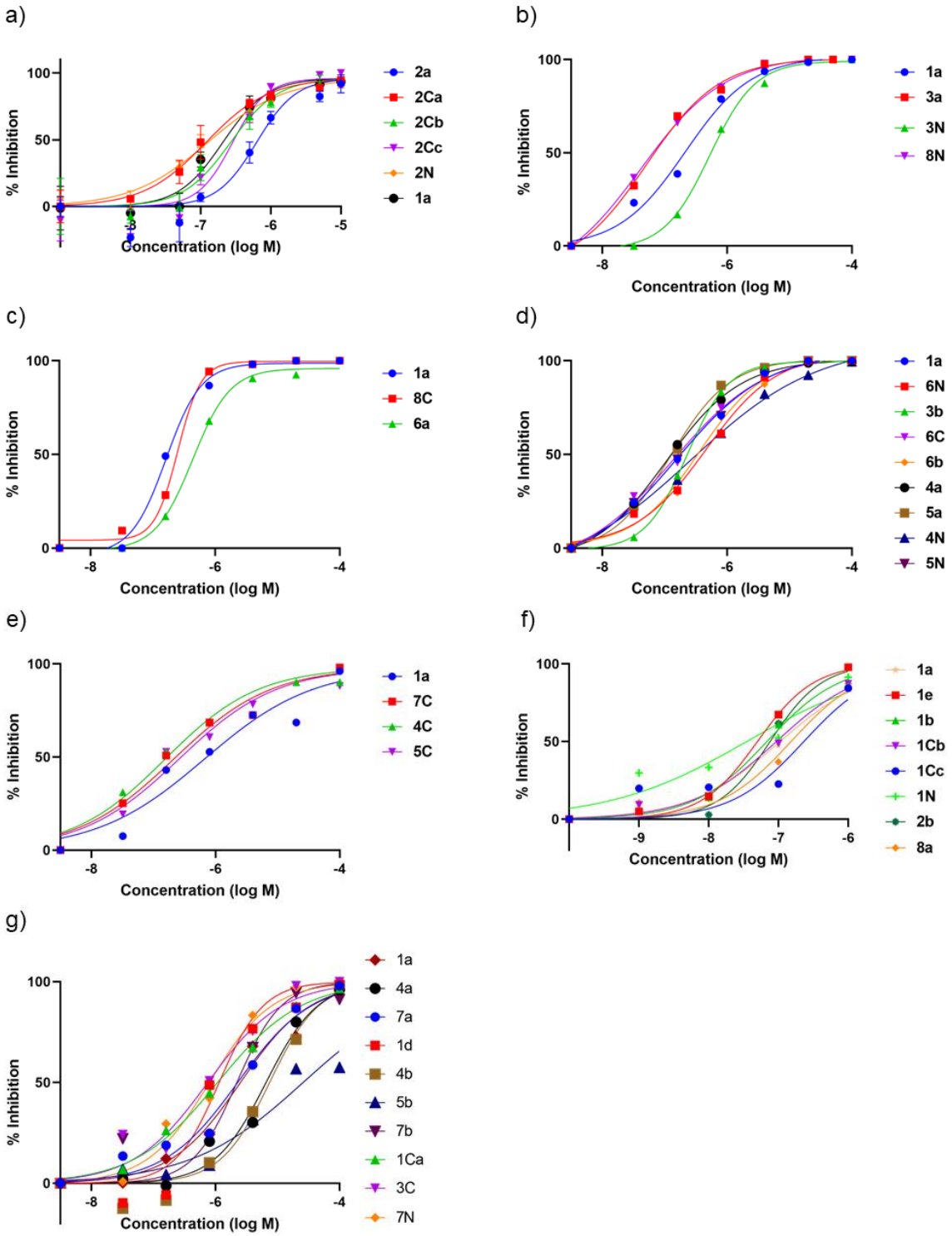


Figure S9. Results from plaque reduction assays of experiments (a) 1 to (g) 7. The X axis represents inhibitor concentration (log M) and the Y axis represents %inhibition

based on the plaque number of DMSO control. Data points represent average ± SEM from three independent experiments or single experiment and fit using non-linear regression in GraphPad Prism 9.

II-II. Figure S10. Results from plaque reduction assays in Table 5.

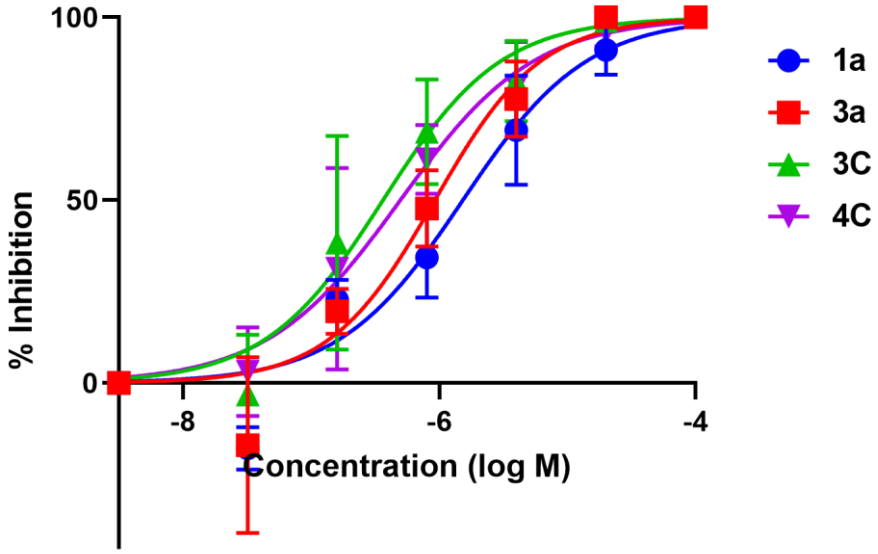


Figure S10. Results from plaque reduction assays in Table 5. The X axis represents inhibitor concentration (log M) and the Y axis represents %inhibition based on the plaque number of DMSO control. Data points represent average ± SEM from three independent experiments and fit using non-linear regression in GraphPad Prism 9.

III. Reference for Supplementary Information.

S1. T. Narumi, M. Komoriya, C. Hashimoto, H. Wu, W. Nomura, S. Suzuki, T. Tanaka, J. Chiba, N. Yamamoto, T. Murakami and H. Tamamura, *Bioorg. Med. Chem.*, 2012, **20**, 1468–1474.