Supporting Information

Enhancing Molecular Diversity in Peptoid Oligomers Using Amino Acid Synthons

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Contents

1. Summaraized MS Characterization Data

Table S1. Calculated and observed electrospray ionization mass spectrometry data for synthesized peptoid oligomers **1-16**. Data was obtained using a Waters AutoPurification HPLC/MS system.

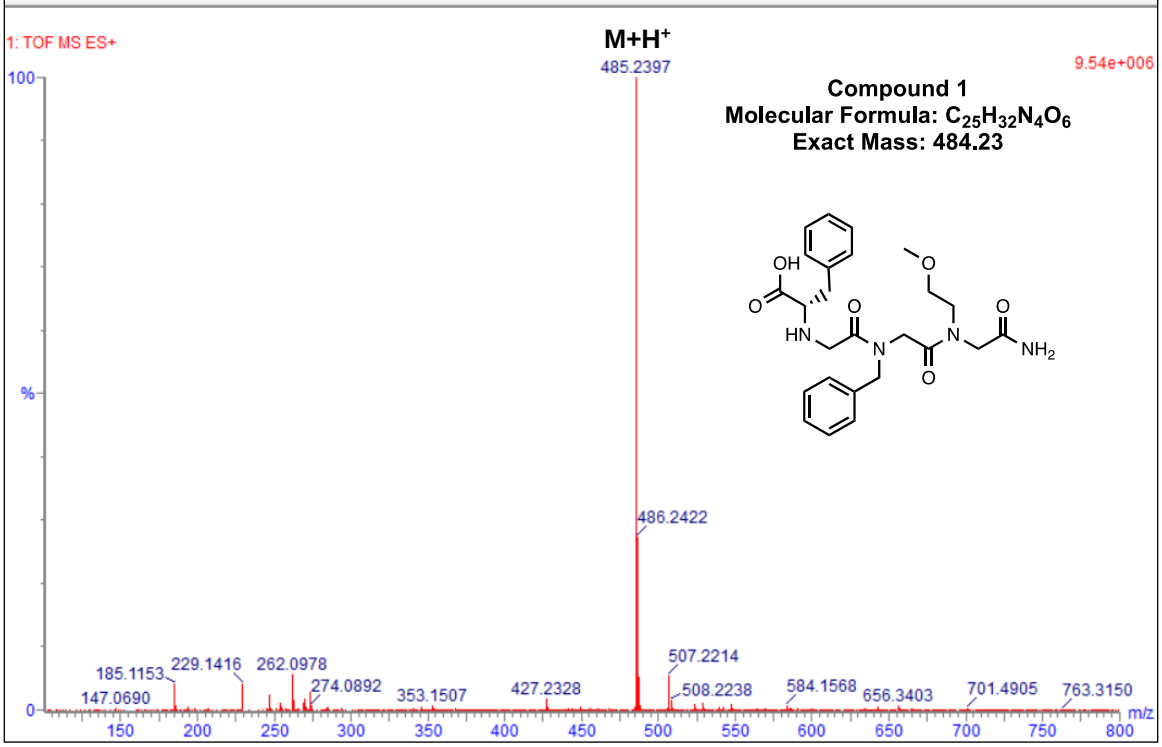
Peptoid	Molecular Formula	Calculated *m*/*z*	Observed *m*/*z*
1	$C_{25}H_{32}N_4O_6$	[*M* + H^+]: 485.24	[*M* + H^+]: 485.4
2	$C_{29}H_{39}N_5O_6$	[*M* + H^+]: 554.30	[*M* + H^+]: 554.5
3	$C_{41}H_{61}N_7O_9$	[*M* + H^+]: 796.46	[*M* + H^+]: 796.8
4	$C_{29}H_{40}N_4O_6$	[*M* + H^+]: 541.30	[*M* + H^+]: 541.5
5	$C_{41}H_{62}N_6O_9$	[*M* + H^+]: 783.47	[*M* + H^+]: 783.7
6	$C_{31}H_{42}N_4O_5S$	[*M* + H^+]: 583.30	[*M* + H^+]: 583.6
7	$C_{68}H_{89}N_{11}O_{11}$	[*M* + H^+]: 1236.68	[*M* + H^+]: 1237.0 [*M* + $2H^+$]/2: 619.4
8	$C_{58}H_{78}N_{14}O_{14}$	[*M* + H^+]: 1195.59	[*M* + H^+]: 1195.9 [*M* + $2H^+$]/2: 598.6
9	$C_{66}H_{91}IN_{12}O_{11}$	[*M* + H^+]: 1355.61	[*M* + H^+]: 1356.1 [*M* + $2H^+$]/2: 678.7
10	$C_{63}H_{85}BrF_3N_{11}O_{14}S$	[*M* + H^+]: 1388.52	[*M* + H^+]: 1390.7 [*M* + $2H^+$]/2: 695.9
11	$C_{67}H_{88}N_{12}O_{11}$	[*M* + H^+]: 1237.68	[*M* + H^+]: 1238.1 [*M* + $2H^+$]/2: 619.7
12	$C_{61}H_{87}F_3N_{10}O_{12}$	[*M* + H^+]: 1209.66	[*M* + H^+]: 1209.1 [*M* + $2H^+$]/2: 605.6
13	$C_{72}H_{91}N_{11}O_{14}S$	[*M* + H^+]: 1366.66	[*M* + H^+]: 1367.0 [*M* + $2H^+$]/2: 684.1
14	$C_{68}H_{100}N_{10}O_{11}S$	[*M* + H^+]: 1265.74	[*M* + H^+]: 1266.2 [*M* + $2H^+$]/2: 633.7
15	$C_{52}H_{85}N_9O_{12}S$	[*M* + H^+]: 1060.61	[*M* + H^+]: 1061.0 [*M* + $2H^+$]/2: 531.2
16	$C_{62}H_{95}N_9O_{13}S_2$	[*M* + H^+]: 1238.66	[*M* + H^+]: 1239.1 [*M* + $2H^+$]/2: 620.1

High-resolution Mass Spectrometry (HRMS) of Peptoids 1, 4, and 5

HRMS spectra were obtained for compounds 1,4, and 5 using a Waters G3 QTof MS system (ZORBAX StableBond 300, C_{18}, 4.6 x 50 mm).

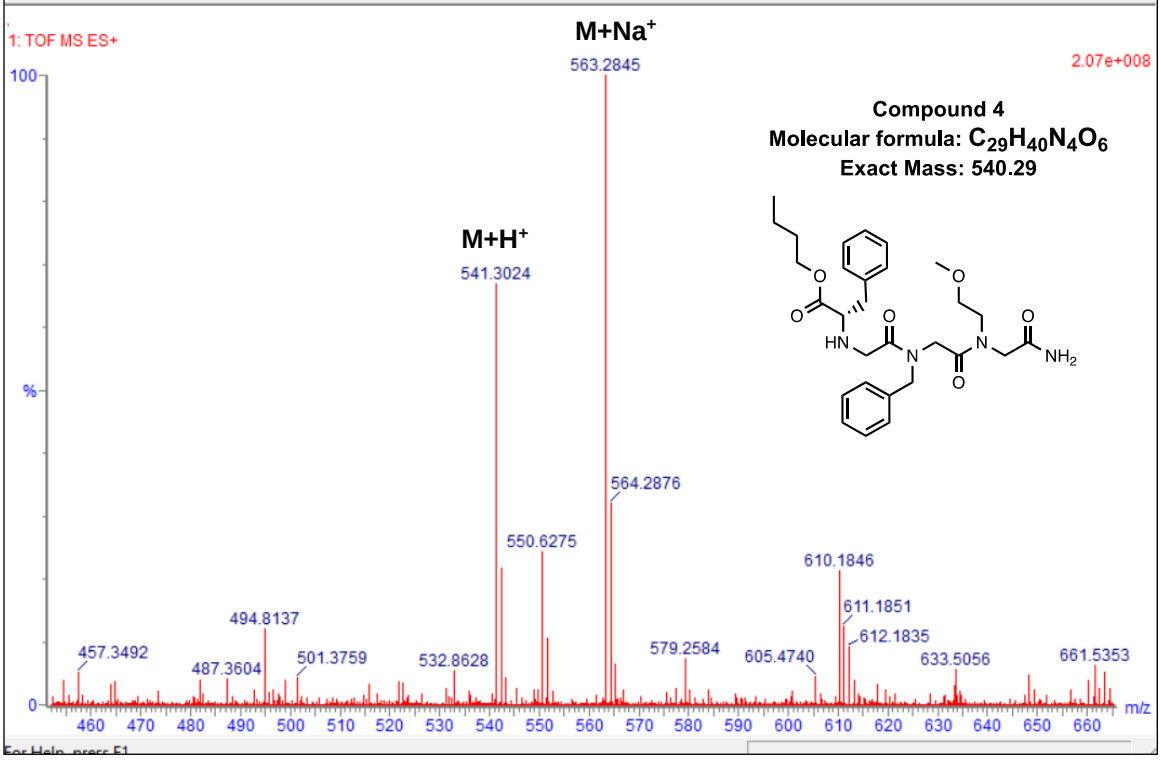
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
2091 formula(e) evaluated with 11 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT Norm	Fit Conf %	C	H	N	O
485.2397	485.2387	1.0	2.1	6.5	C24 H37 O10	334.7	0.272	76.18	24	37		10
	485.2400	-0.3	-0.6	11.5	C25 H33 N4 O6	336.0	1.588	20.43	25	33	4	6
	485.2387	1.0	2.1	17.5	C22 H25 N14	338.5	4.077	1.70	22	25	14	
	485.2373	2.4	4.9	12.5	C21 H29 N10 O4	338.6	4.211	1.48	21	29	10	4
	485.2413	-1.6	-3.3	16.5	C26 H29 N8 O2	340.6	6.180	0.21	26	29	8	2
	485.2419	-2.2	-4.5	-1.5	C13 H37 N6 O13	345.0	10.533	0.00	13	37	6	13
	485.2392	0.5	1.0	-0.5	C9 H33 N12 O11	345.5	11.039	0.00	9	33	12	11
	485.2405	-0.8	-1.6	4.5	C10 H29 N16 O7	345.5	11.062	0.00	10	29	16	7



Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
2797 formula(e) evaluated with 12 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT Norm	Fit Conf %	C	H	N	O
541.3024	541.3026	-0.2	-0.4	11.5	C29 H41 N4 O6	1420.2	0.218	80.40	29	41	4	6
	541.3013	1.1	2.0	6.5	C28 H45 O10	1421.9	1.899	14.97	28	45		10
	541.3013	1.1	2.0	17.5	C26 H33 N14	1423.4	3.424	3.26	26	33	14	
	541.2999	2.5	4.6	12.5	C25 H37 N10 O4	1424.7	4.679	0.93	25	37	10	4
	541.3039	-1.5	-2.8	16.5	C30 H37 N8 O2	1425.5	5.437	0.44	30	37	8	2
	541.3031	-0.7	-1.3	4.5	C14 H37 N16 O7	1430.1	10.064	0.00	14	37	16	7
	541.3045	-2.1	-3.9	-1.5	C17 H45 N6 O13	1430.2	10.220	0.00	17	45	6	13
	541.3018	0.6	1.1	-0.5	C13 H41 N12 O11	1430.5	10.472	0.00	13	41	12	11



Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

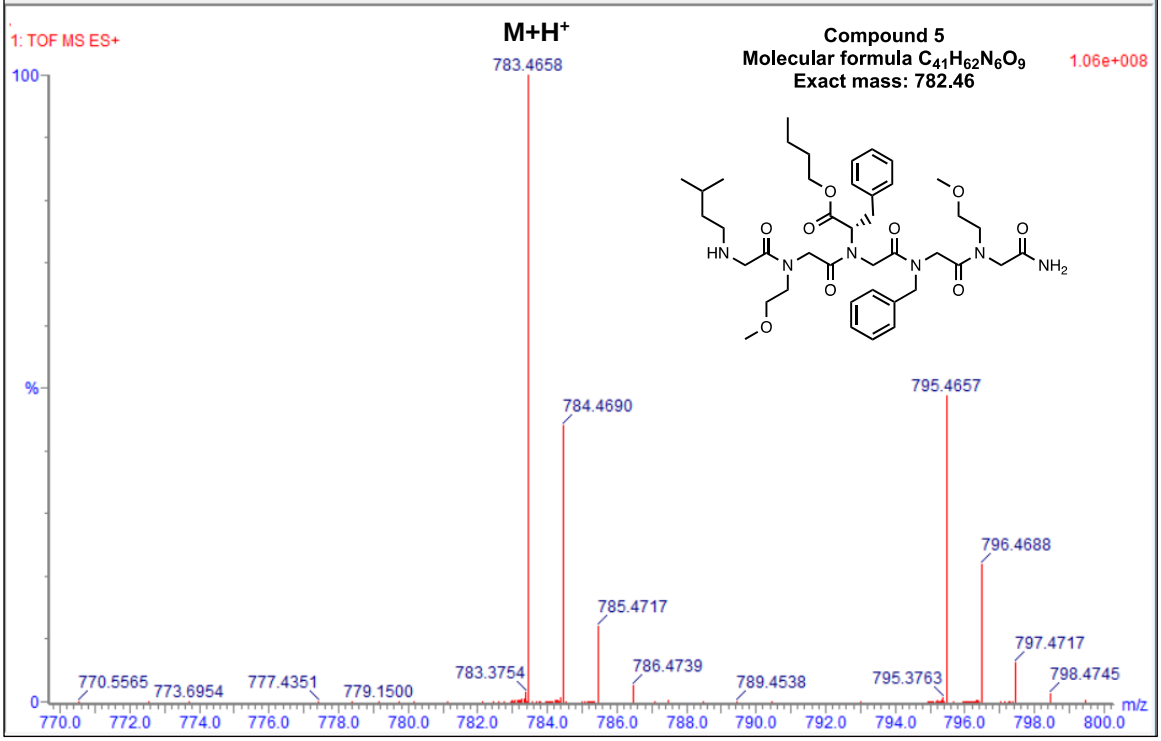
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

7598 formula(e) evaluated with 30 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT Norm	Fit Conf %	C	H	N	O
783.4658	783.4643	1.5	1.9	8.5	C40 H67 N2 O13	531.7	0.177	83.76	40	67	2	13
	783.4630	2.8	3.6	14.5	C37 H59 N12 O7	534.1	2.610	7.36	37	59	12	7
	783.4657	0.1	0.1	13.5	C41 H63 N6 O9	534.3	2.757	6.35	41	63	6	9
	783.4643	1.5	1.9	19.5	C38 H55 N16 O3	535.7	4.178	1.53	38	55	16	3
	783.4670	-1.2	-1.5	18.5	C42 H59 N10 O5	536.4	4.951	0.71	42	59	10	5
	783.4683	-2.5	-3.2	12.5	C45 H67 O11	538.8	7.353	0.06	45	67		11
	783.4683	-2.5	-3.2	23.5	C43 H55 N14 O	538.9	7.361	0.06	43	55	14	1
	783.4675	-1.7	-2.2	0.5	C29 H67 N8 O16	539.1	7.606	0.05	29	67	8	16



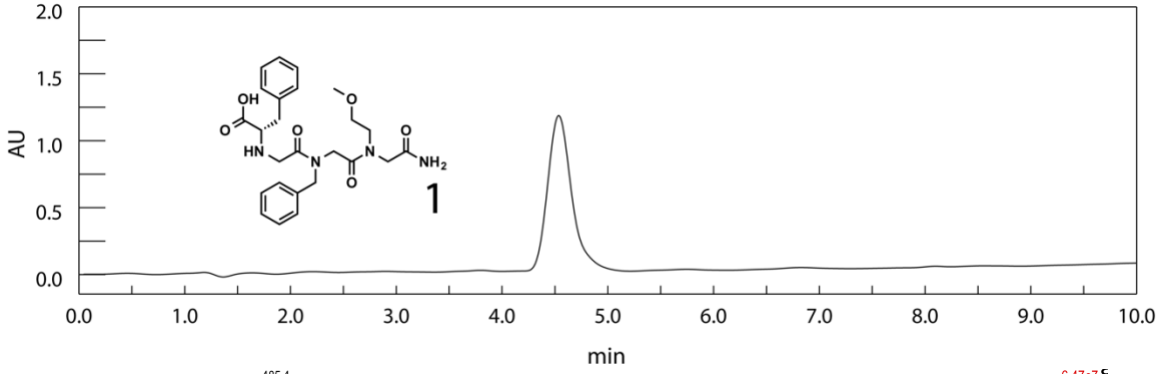
2. Analytical RP-HPLC Spectra and HPLC/MS Spectra

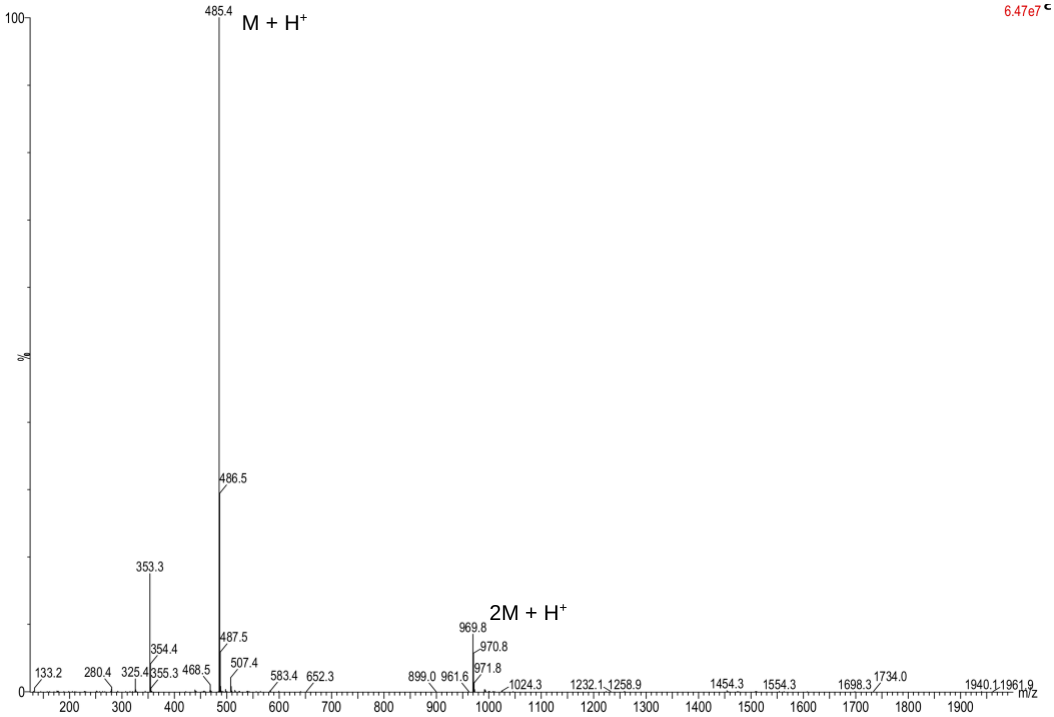
Analytical RP-HPLC and ESI-MS data for peptoids **1-16**. ESI-MS spectra were obtained using a Waters AutoPurification HPLC/MS system with a semi-preparative C_{18} column. Analytical HPLC spectra were obtained from a linear gradient of 5-95% ACN/H_2O (0.1% TFA) over 10 min using a C_{18} column (Waters XBridge BEH300 4.6x50 mm) with a flow rate of 0.7 mL/min at UV detection 220 nm. For compound 5, an Agilent HPLC 1260 Infinity with an Eclipse Plus C_{18} column (3.5 uM, 4.6 x 100 mm) was used in place of the Waters instrument.

The overall purified percent yield values were calculated by dividing the mass of isolated pure product by the theoretical mass determined from the reaction scale using 100 mg of resin with 0.2 mmol/g loading. The average yields per number of steps was determined using the overall purified yield and the number of reaction steps required for each oligomer synthesis, including the initial resin deprotection step and the final resin cleavage step.

1:

Amine submonomer 1: 2-Methoxyethylamine
Amine submonomer 2: Benzylamine
Amine submonomer 3: L-Phenylalanine
Theoretical yield: 9.69 mg
Crude Mass: 9.3 mg Crude Yield: 96%
Pure Mass: 7.3 mg Overall Purified Yield: 75%
Average Yield over 8 Steps: 97%
Calculated *m/z* [$M + H^+$]: 485.24





2:

Amine submonomer 1: 2-Methoxyethylamine

Amine submonomer 2: Benzylamine

Amine submonomer 3: L-Phenylalanine

Amino acid side chain coupling partner: Morpholine

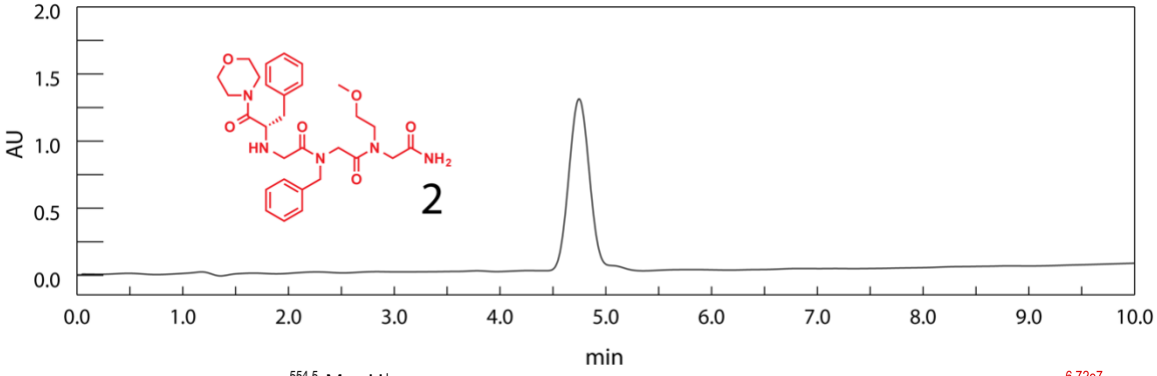
Theoretical Yield: 11.07 mg

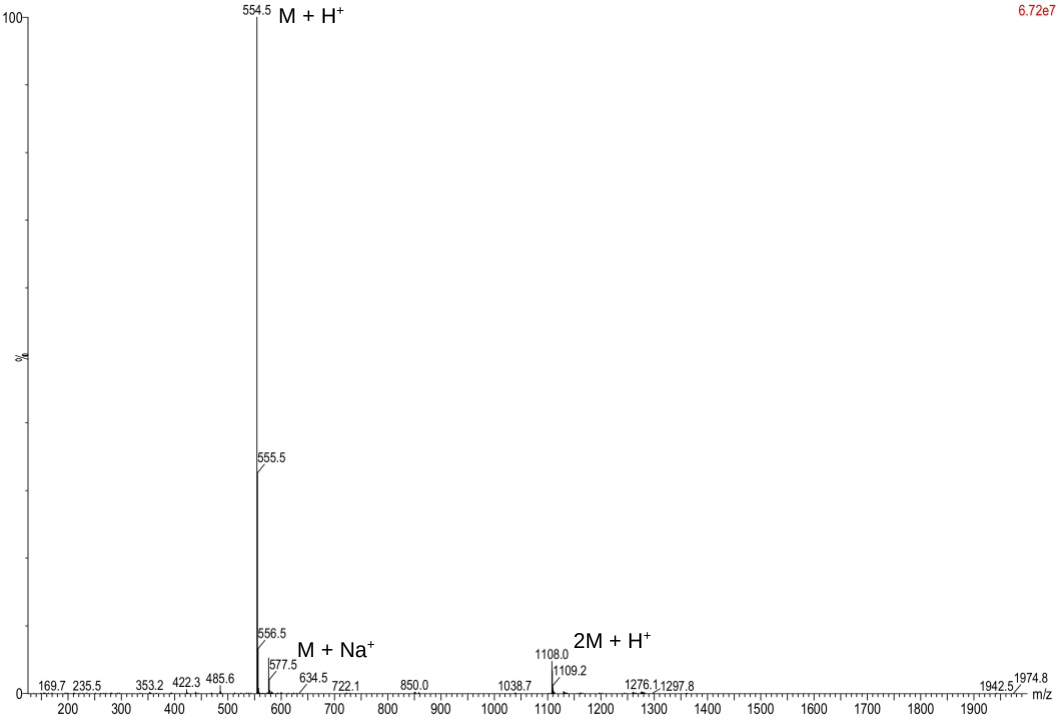
Crude Mass: 11.0 mg — Crude Yield: 99%

Pure Mass: 7.6 mg — Overall Purified Yield: 69%

Average Yield Over 9 Steps: 96%

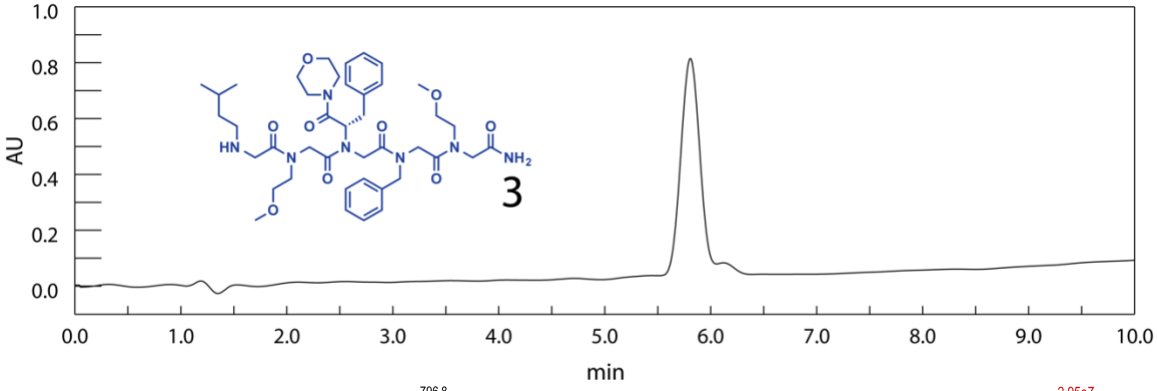
Calculated *m/z* [$M + H^+$]: 554.30

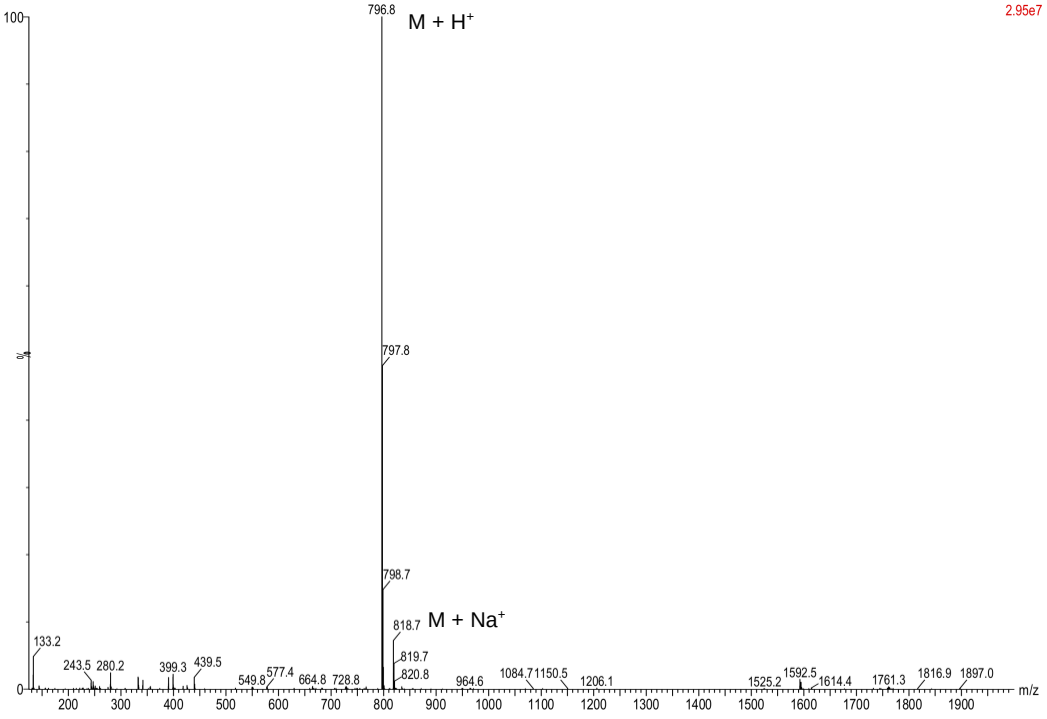




3:

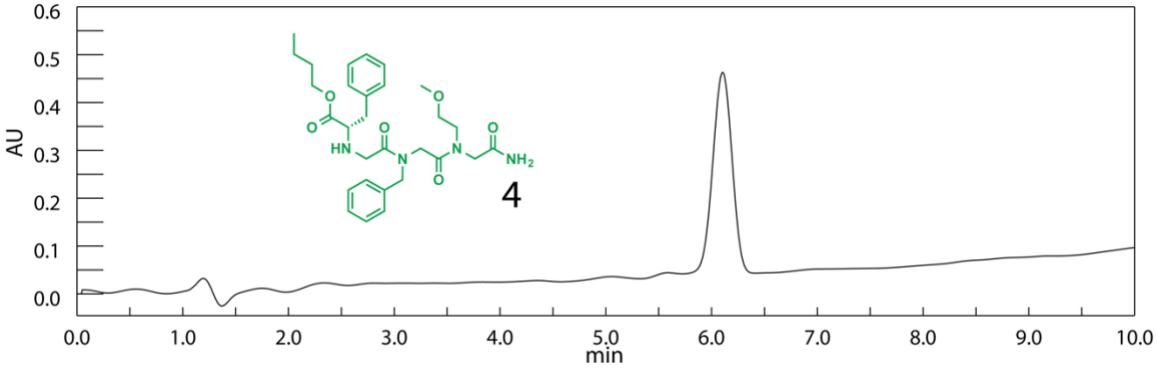
Amine submonomer 1: 2-Methoxyethylamine
Amine submonomer 2: Benzylamine
Amine submonomer 3: L-Phenylalanine
    Amino acid side chain coupling partner: Morpholine
Amine submonomer 4: 2-Methoxyethylamine
Amine submonomer 5: Isopentylamine
Theoretical Yield: 15.92 mg
Crude Mass: 14.1 mg Crude Yield: 89%
Pure Mass: 7.0 mg Overall Purified Yield: 44%
Average Yield Over 13 Steps: 94%
Calculated *m/z* [$M + H^+$]: 796.46

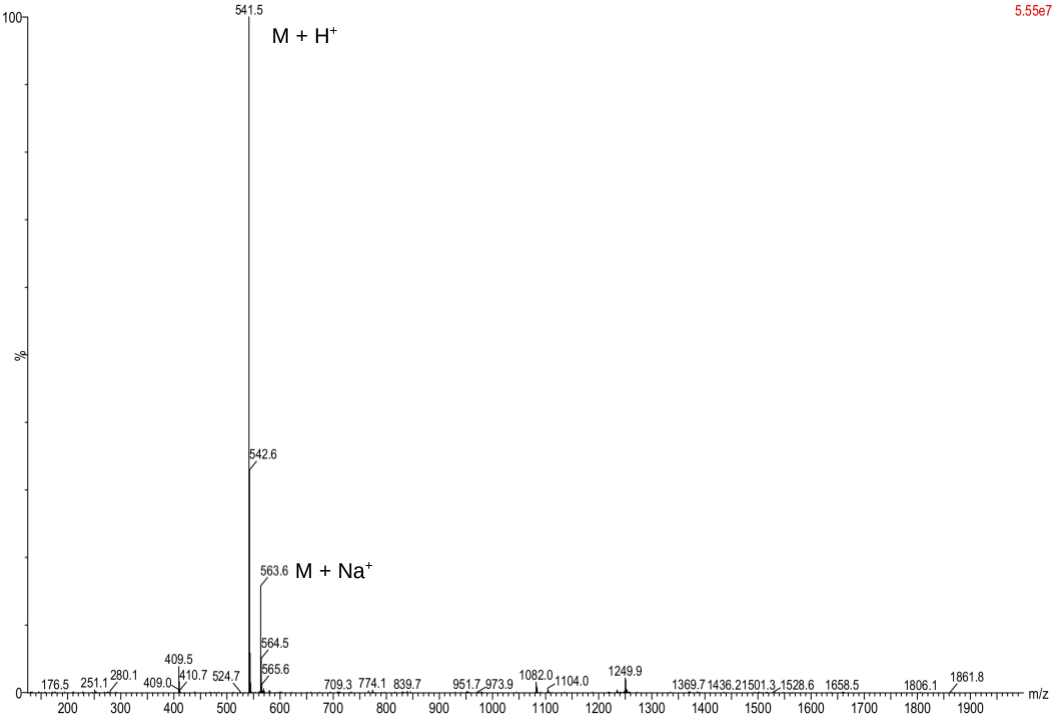




4:

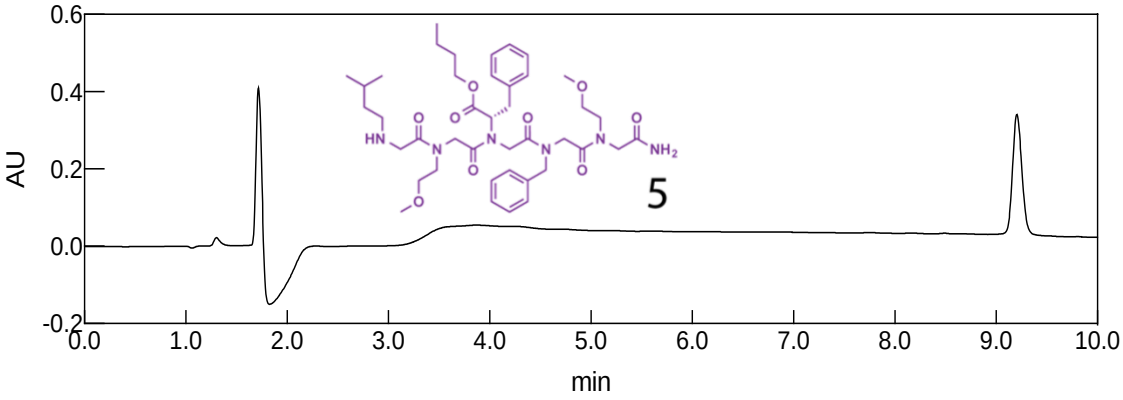
Amine submonomer 1: 2-Methoxyethylamine
Amine submonomer 2: Benzylamine
Amine submonomer 3: L-Phenylalanine
Amino acid side chain coupling partner: 1-Butanol
Theoretical Yield: 10.81 mg
Crude Mass: 10.3 mg Crude Yield: 95%
Pure Mass: 5.1 mg Overall Purified Yield: 47%
Average Yield Over 9 Steps: 92%
Calculated *m/z* [$M + H^+$]: 541.30

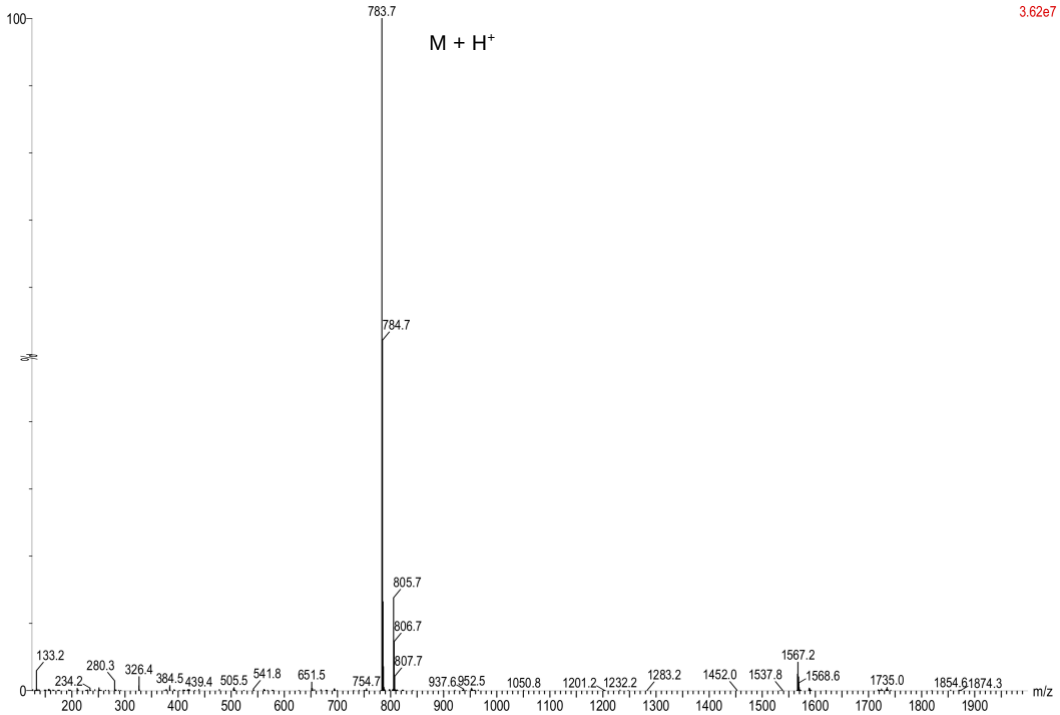




5:

Amine submonomer 1: 2-Methoxyethylamine
Amine submonomer 2: Benzylamine
Amine submonomer 3: L-Phenylalanine
Amino acid side chain coupling partner: 1-Butanol
Amine submonomer 4: 2-Methoxyethylamine
Amine submonomer 5: Isopentylamine
Theoretical Yield: 15.65 mg
Crude Mass: 15.5 mg Crude Yield: 99%
Pure Mass: 6.9 mg Overall Purified Yield: 44%
Average Yield Over 13 Steps: 94%
Calculated *m/z* [*M* + H^+]: 783.47





6:

Amine submonomer 1: 2-Methoxyethylamine

Amine submonomer 2: Benzylamine

Amine submonomer 3: L-Phenylalanine

Amino acid side chain coupling partner: Cyclohexanethiol

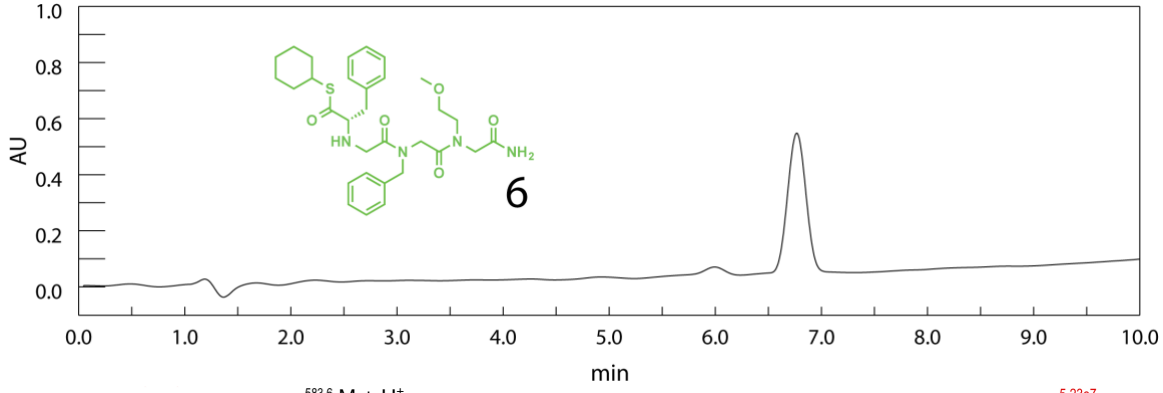
Theoretical Yield: 11.65 mg

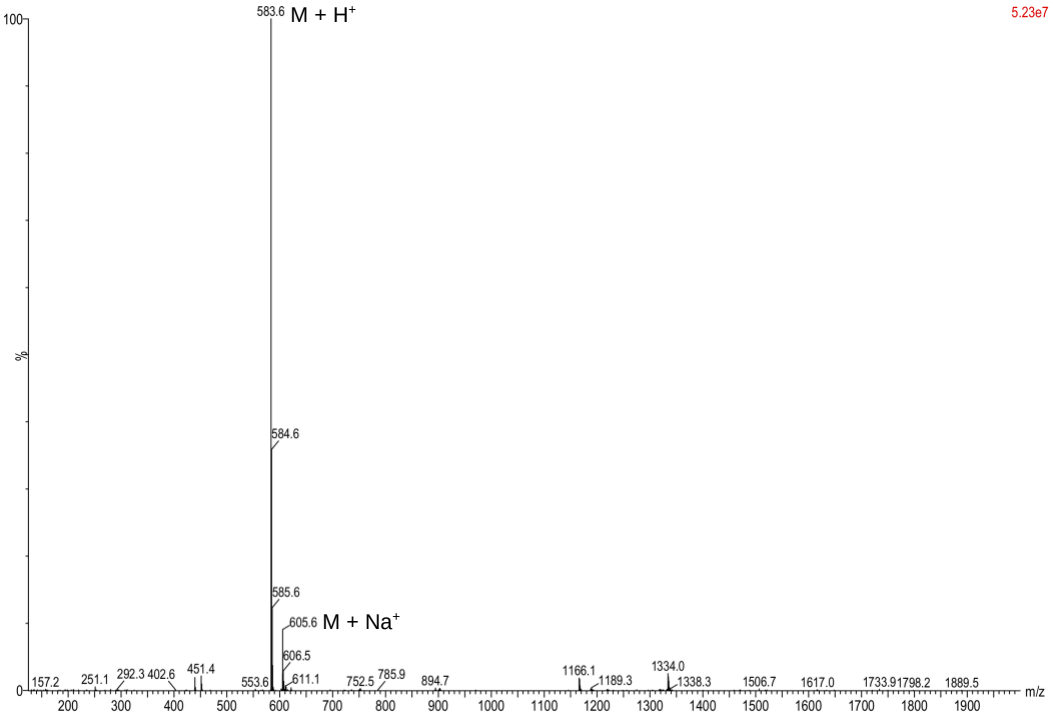
Crude Mass: 11.2 mg — Crude Yield: 96%

Pure Mass: 5.5 mg — Overall Purified Yield: 47%

Average Yield Over 9 Steps: 92%

Calculated *m/z* [$M + H^+$]: 583.30





7:

Amine submonomer 1: L-Alanine

Amino acid side chain coupling partner: 2-Methoxyethylamine

Amine submonomer 2: (*S*)-1-Phenylethylamine

Amine submonomer 3: L-Phenylalanine

Amino acid side chain coupling partner: Benzylamine

Amine submonomer 4: L-Leucine

Amino acid side chain coupling partner: Isopropylamine

Amine submonomer 5: (*S*)-1-Phenylethylamine

Amine submonomer 6: L-Alanine

Amino acid side chain coupling partner: Aniline

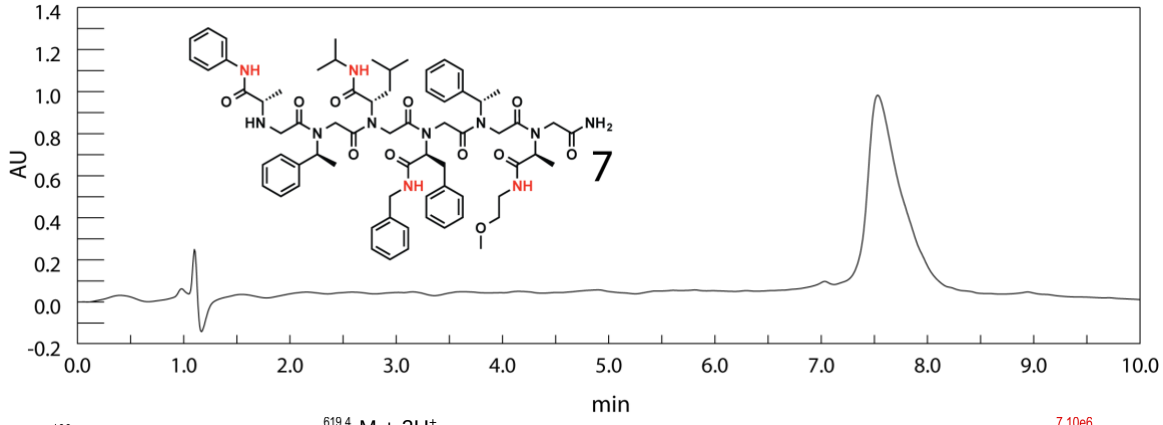
Theoretical Yield: 24.7 mg

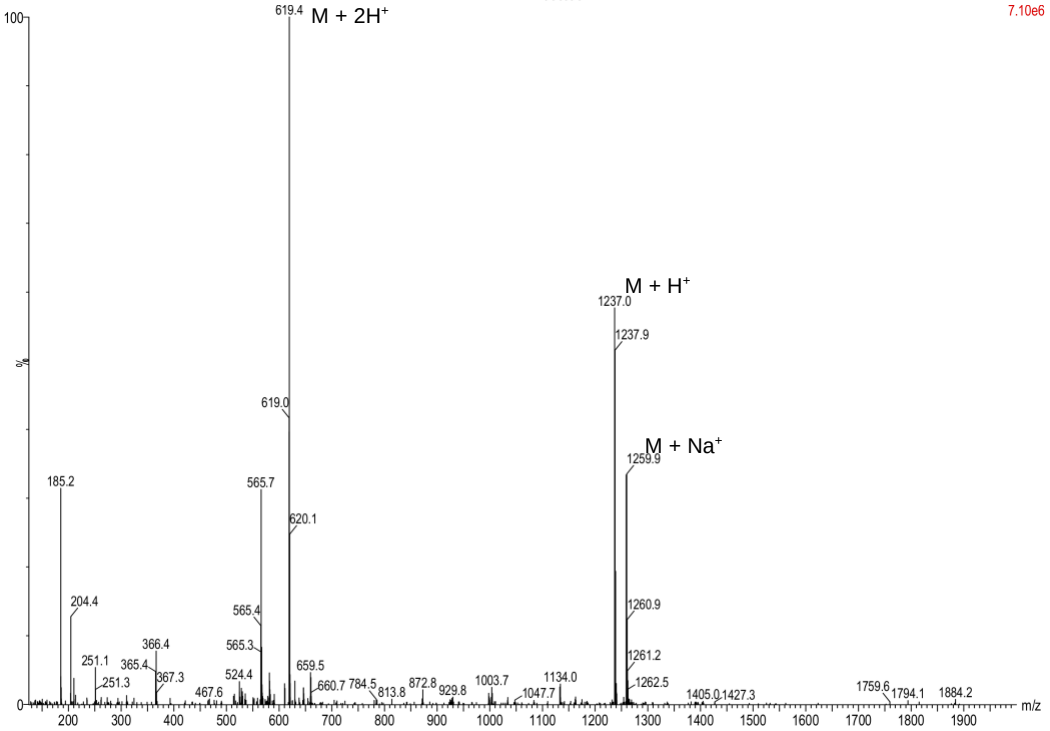
Crude Mass: 6.2 mg Crude Yield: 25%

Pure Mass: 1.2 mg Overall Purified Yield: 5%

Average Yield Over 18 Steps: 85%

Calculated *m/z* [*M* + H^+]: 1236.68





8:

Amine submonomer 1: L-Phenylalanine

Amino acid side chain coupling partner: Propargylamine

Amine submonomer 2: Aniline

Amine submonomer 3: L-Glutamine

Amino acid side chain coupling partner: β-Alanine *tert*-butyl ester

Amine submonomer 4: L-Serine

Amino acid side chain coupling partner: (*S*)-1-Phenylethylamine

Amine submonomer 5: *N*-Boc-ethylenediamine

Amine submonomer 6: L-Proline

Amino acid side chain coupling partner: *N*-Boc-ethylenediamine

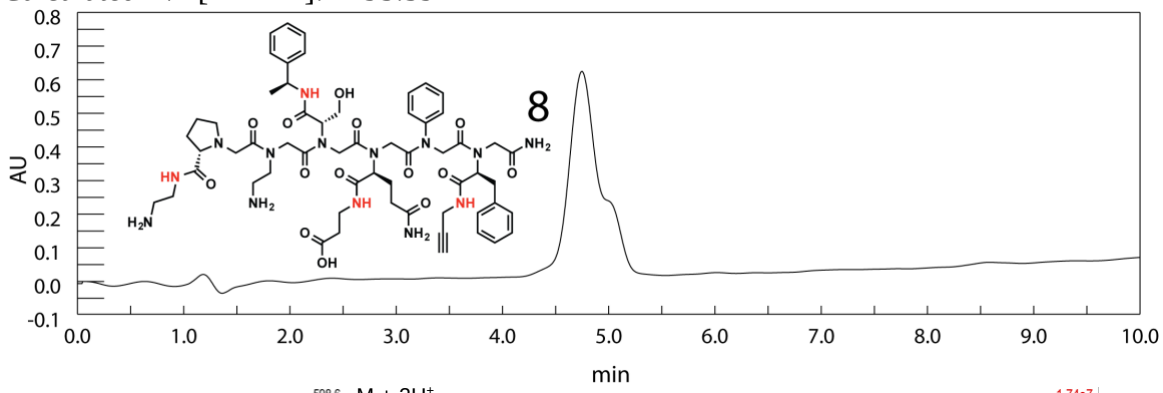
Theoretical Yield: 23.9 mg

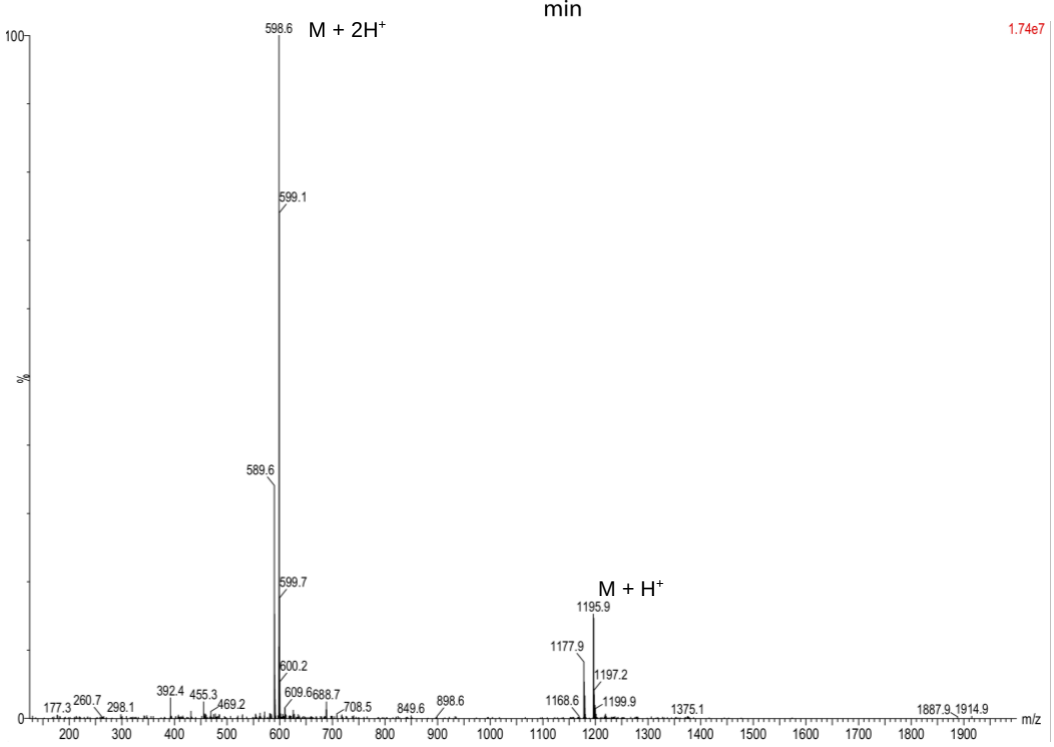
Crude Mass: 15.0 mg Crude Yield: 63%

Pure Mass: 2.3 mg Overall Purified Yield: 10%

Average Yield Over 18 Steps: 88%

Calculated *m/z* [*M* + H^+]: 1195.59





9:

Amine submonomer 1: Glycine

Amino acid side chain coupling partner: Isopentylamine

Amine submonomer 2: (*S*)-1-Phenylethylamine

Amine submonomer 3: L-Isoleucine

Amino acid side chain coupling partner: *N*-Boc-ethylenediamine

Amine submonomer 4: L-Phenylalanine

Amino acid side chain coupling partner: Cyclopropylmethanamine

Amine submonomer 5: 2-Methoxyethylamine

Amine submonomer 6: D-Phenylalanine

Amino acid side chain coupling partner: 4-Iodoaniline

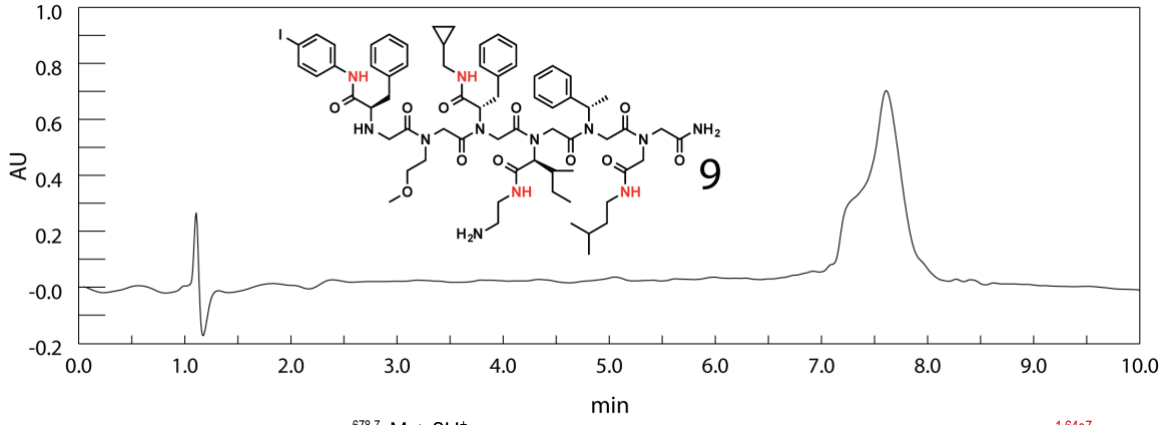
Theoretical Yield: 27.1 mg

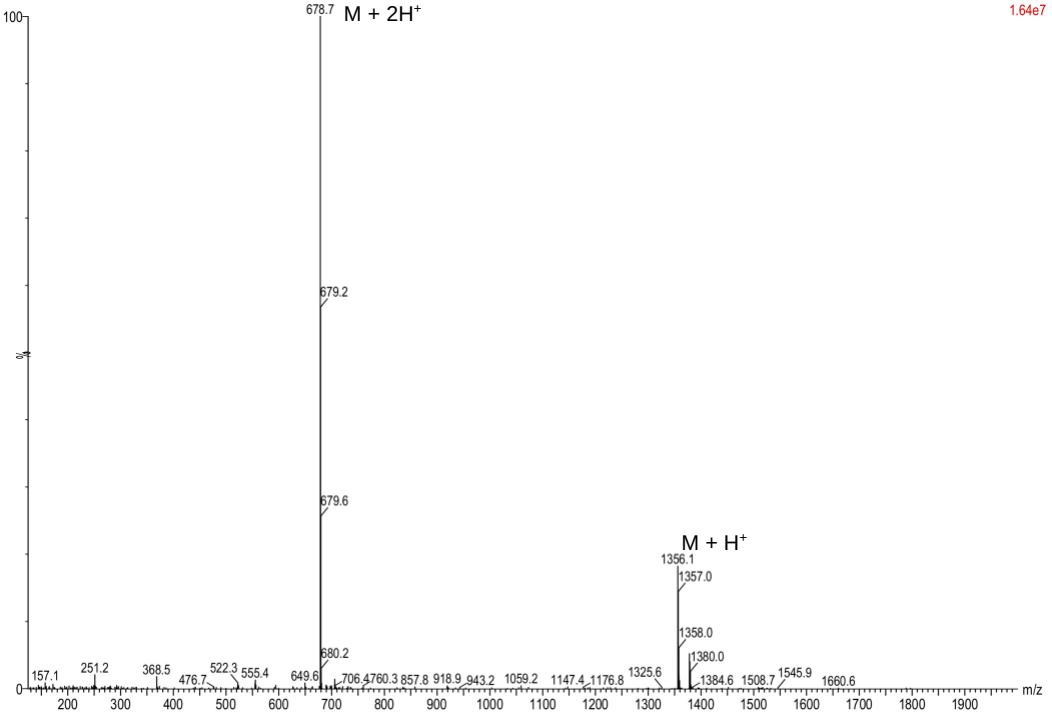
Crude Mass: 5.7 mg | Crude Yield: 21%

Pure Mass: 1.9 mg | Overall Purified Yield: 7%

Average Yield Over 18 Steps: 86%

Calculated *m/z* [*M* + H^+]: 1355.61





10:

Amine submonomer 1: L-Alanine

Amino acid side chain coupling partner: Isopropylamine

Amine submonomer 2: 2-Methoxyethylamine

Amine submonomer 3: L-Phenylalanine

Amino acid side chain coupling partner: 4-(Trifluoromethoxy)benzylamine

Amine submonomer 4: L-Valine

Amino acid side chain coupling partner: Furfurylamine

Amine submonomer 5: 2-Methoxyethylamine

Amine submonomer 6: L-Methionine

Amino acid side chain coupling partner: 3-Bromobenzylamine

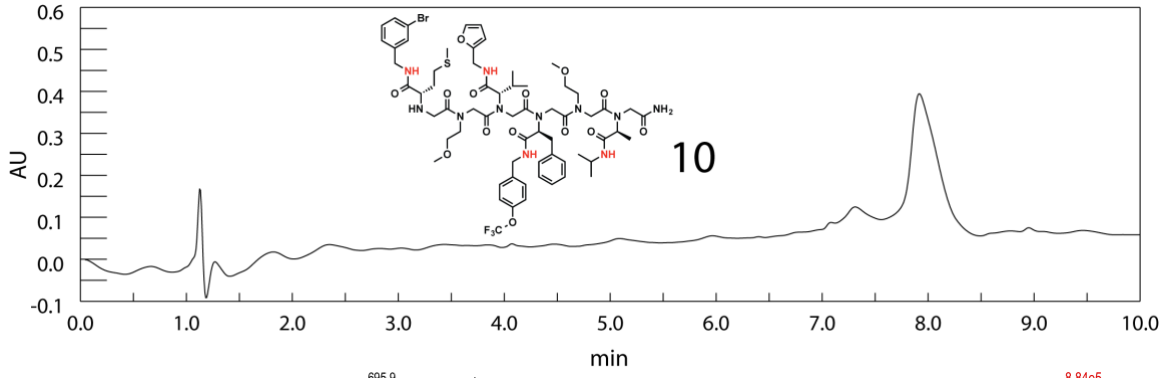
Theoretical Yield: 27.7 mg

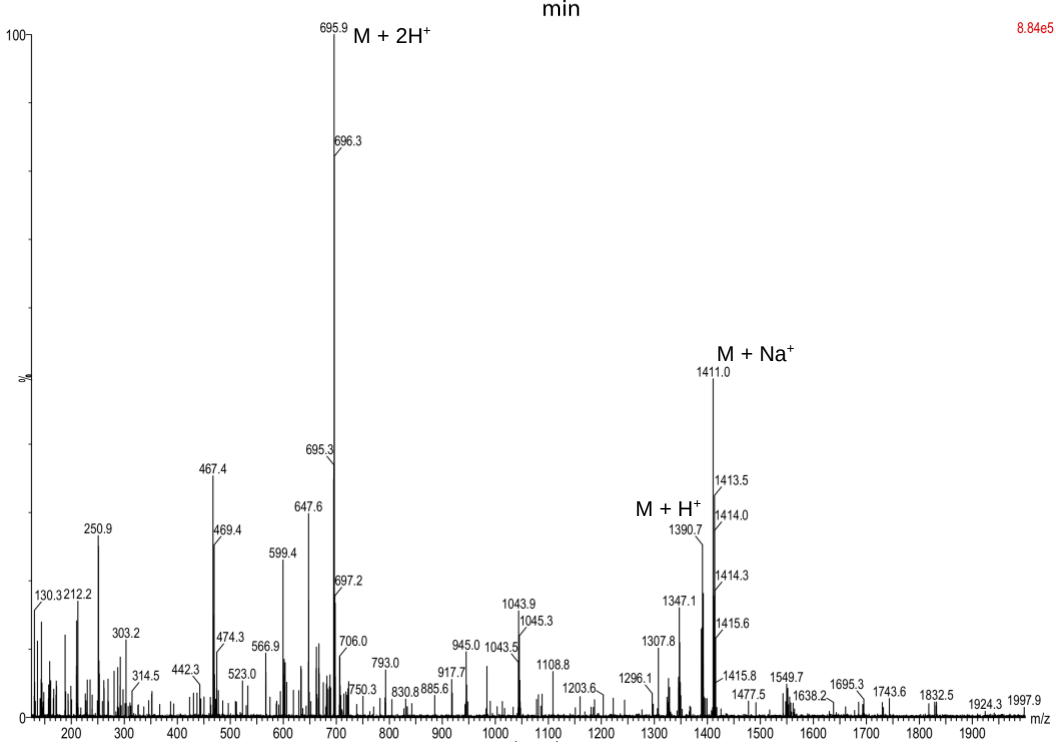
Crude Mass: 2.8 mg | Crude Yield: 10%

Pure Mass: 0.4 mg | Overall Purified Yield: 2%

Average Yield Over 18 Steps: 80%

Calculated *m/z* [*M* + H^+]: 1388.52





11:

Amine submonomer 1: L-Leucine

Amino acid side chain coupling partner: 2,2-Diphenylethylamine

Amine submonomer 2: Benzylamine

Amine submonomer 3: β-Alanine

Amino acid side chain coupling partner: *N*-Boc-ethylenediamine

Amine submonomer 4: β-Alanine

Amino acid side chain coupling partner: 4-Methylbenzylamine

Amine submonomer 5: Benzylamine

Amine submonomer 6: L-Alanine

Amino acid side chain coupling partner: O-*tert*-Butyl-dimethylsilyl-ethanolamine

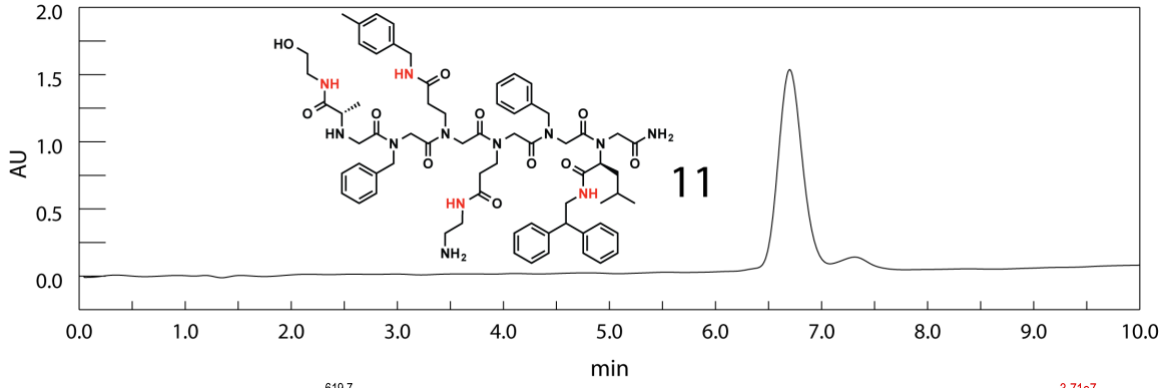
Theoretical Yield: 24.7 mg

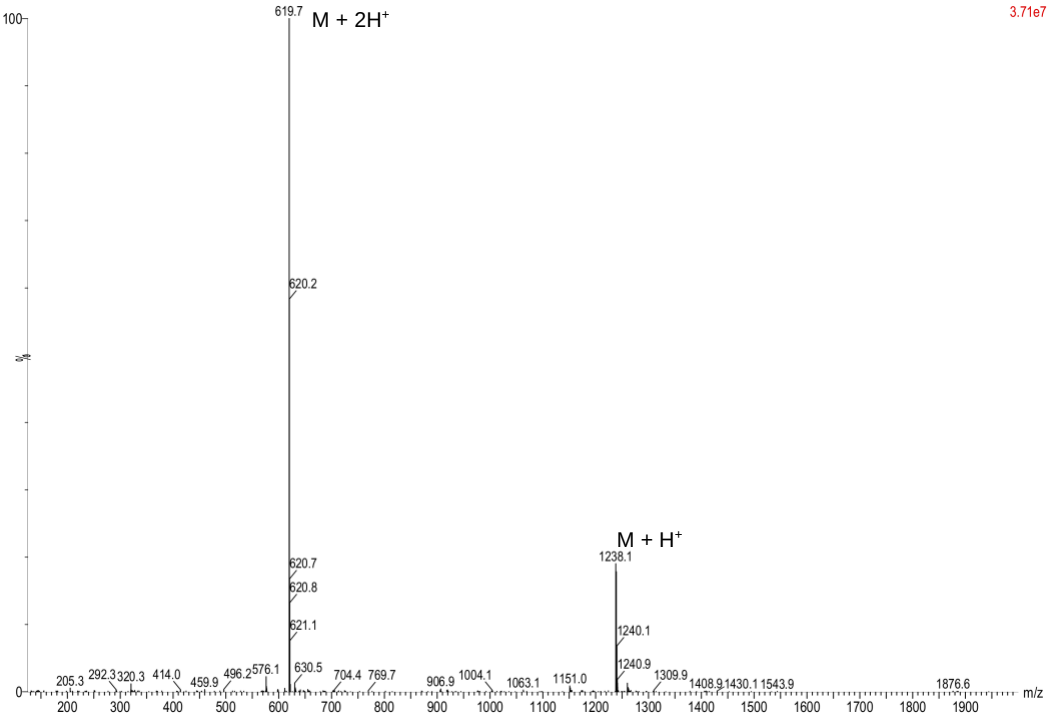
Crude Mass: 5.1 mg | Crude Yield: 21%

Pure Mass: 2.4 mg | Overall Purified Yield: 10%

Average Yield Over 18 Steps: 88%

Calculated *m/z* [$M + H^+$]: 1237.68





12:

Amine submonomer 1: L-Alanine

Amino acid side chain coupling partner: *N*-Boc-ethylenediamine

Amine submonomer 2: Isopentylamine

Amine submonomer 3: L-Leucine

Amino acid side chain coupling partner: Benzyl alcohol

Amine submonomer 4: L-Alanine

Amino acid side chain coupling partner: Benzylamine

Amine submonomer 5: Isopentylamine

Amine submonomer 6: L-Phenylalanine

Amino acid side chain coupling partner: Trifluoroethanol

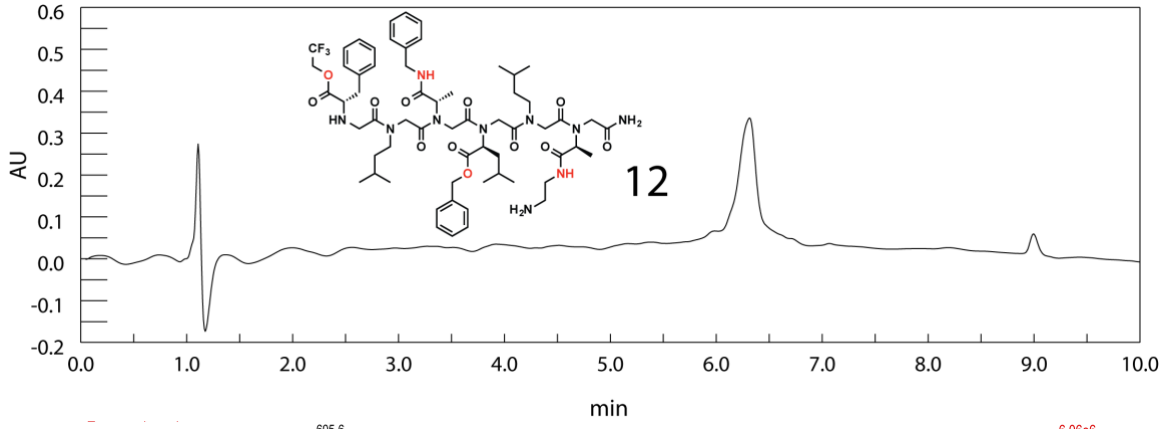
Theoretical Yield: 24.1 mg

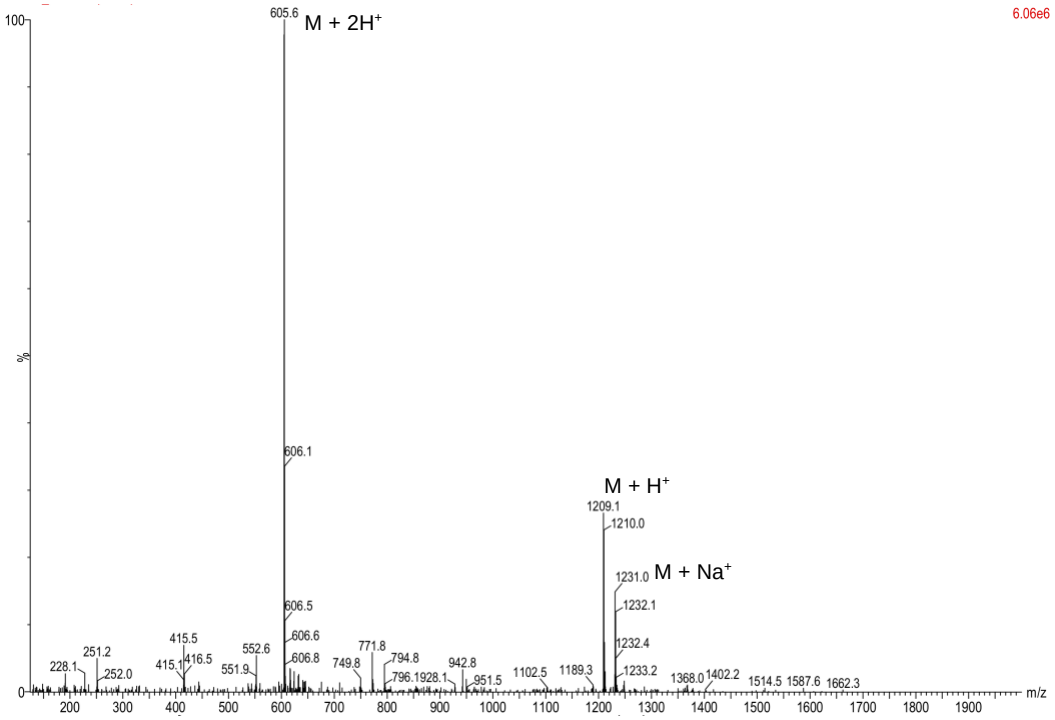
Crude Mass: 5.8 mg Crude Yield: 24%

Pure Mass: 0.6 mg Overall Purified Yield: 3%

Average Yield Over 18 Steps: 82%

Calculated *m/z* [*M* + H^+]: 1209.66





13:

Amine submonomer 1: L-Phenylalanine

Amino acid side chain coupling partner: (*S*)-1-Phenylethylamine

Amine submonomer 2: 2-Methoxyethylamine

Amine submonomer 3: L-Phenylalanine

Amino acid side chain coupling partner: 2-Methoxyethylamine

Amine submonomer 4: L-Phenylalanine

Amino acid side chain coupling partner: *N*-Boc-ethylenediamine

Amine submonomer 5: 2-Methoxyethylamine

Amine submonomer 6: L-Phenylalanine

Amino acid side chain coupling partner: Furfurylthiol

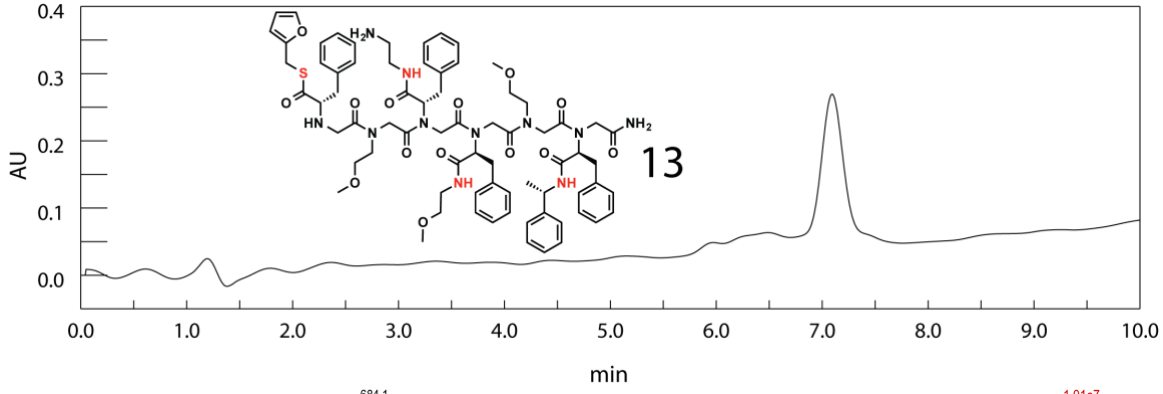
Theoretical Yield: 27.3 mg

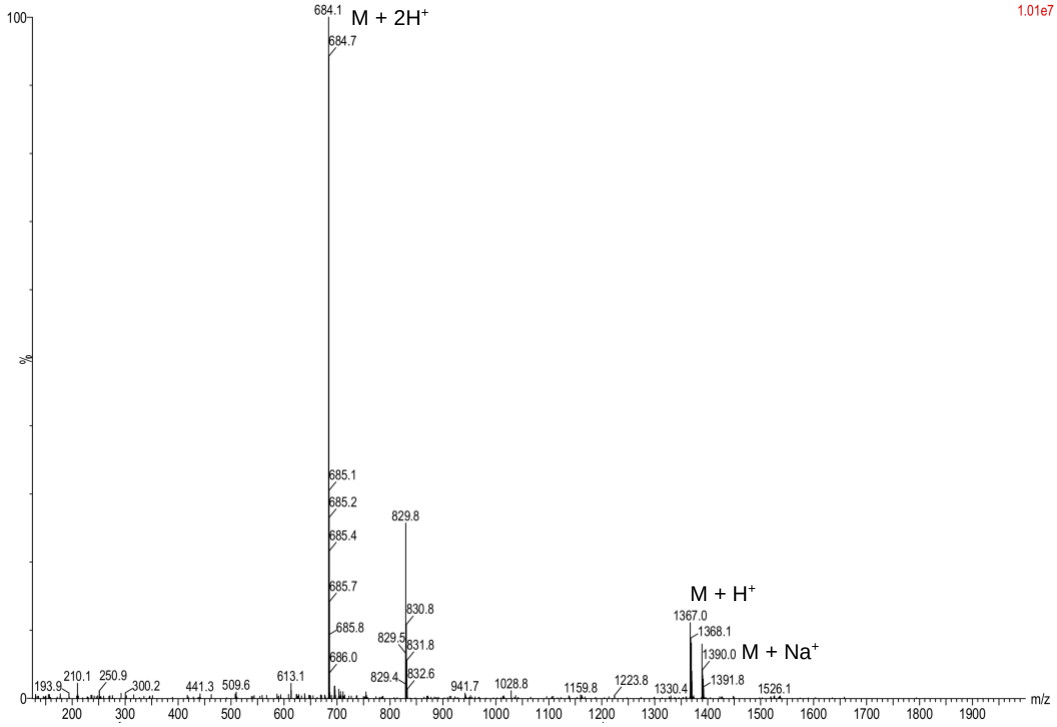
Crude Mass: 4.4 mg Crude Yield: 16%

Pure Mass: 0.6 mg Overall Purified Yield: 2%

Average Yield Over 18 Steps: 80%

Calculated *m/z* [*M* + H^+]: 1366.66





14:

Amine submonomer 1: L-Alanine

Amino acid side chain coupling partner: (*S*)-1-Methoxy-2-propylamine

Amine submonomer 2: Benzylamine

Amine submonomer 3: L-Leucine

Amino acid side chain coupling partner: (*S*)-1-Cyclohexylethylamine

Amine submonomer 4: L-Alanine

Amino acid side chain coupling partner: Isopropylamine

Amine submonomer 5: Benzylamine

Amine submonomer 6: L-Phenylalanine

Amino acid side chain coupling partner: Cyclohexanethiol

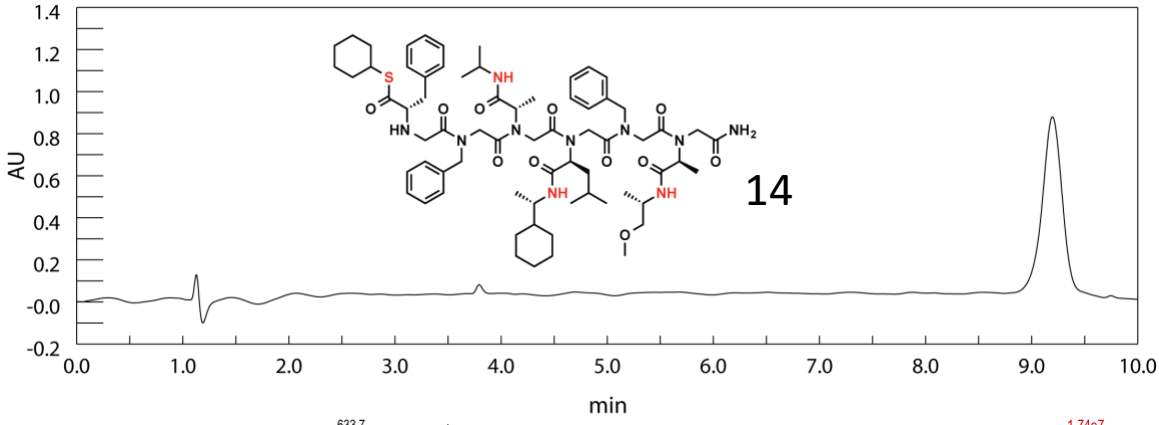
Theoretical Yield: 25.3 mg

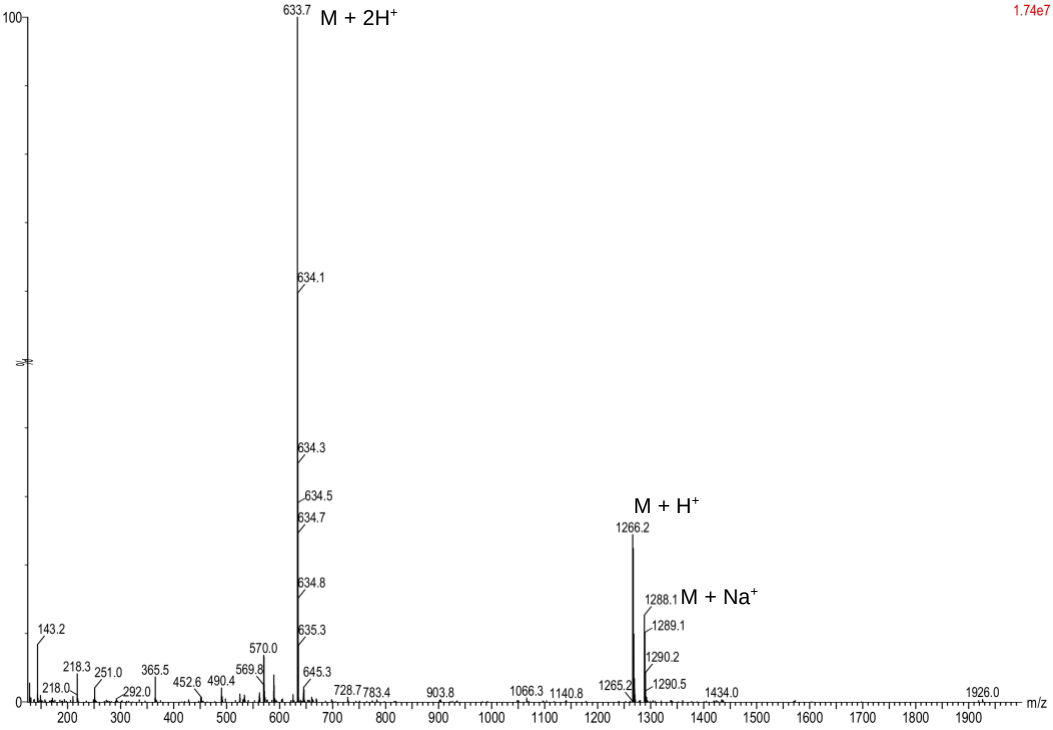
Crude Mass: 5.7 mg Crude Yield: 23%

Pure Mass: 1.2 mg Overall Purified Yield: 5%

Average Yield Over 18 Steps: 85%

Calculated *m/z* [*M* + H^+]: 1265.74





15:

Amine submonomer 1: L-Alanine

Amino acid side chain coupling partner: 4-Methoxyphenethylamine

Amine submonomer 2: 1-Propylamine

Amine submonomer 3: L-Alanine

Amino acid side chain coupling partner: Piperidine

Amine submonomer 4: L-Alanine

Amino acid side chain coupling partner: 1-Butanol

Amine submonomer 5: 1-Propylamine

Amine submonomer 6: L-Alanine

Amino acid side chain coupling partner: 1-Butanethiol

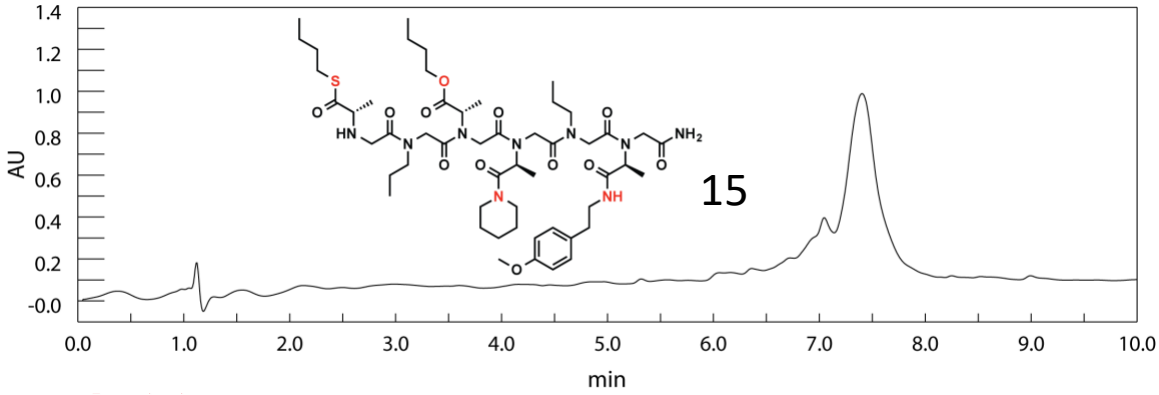
Theoretical Yield: 21.2 mg

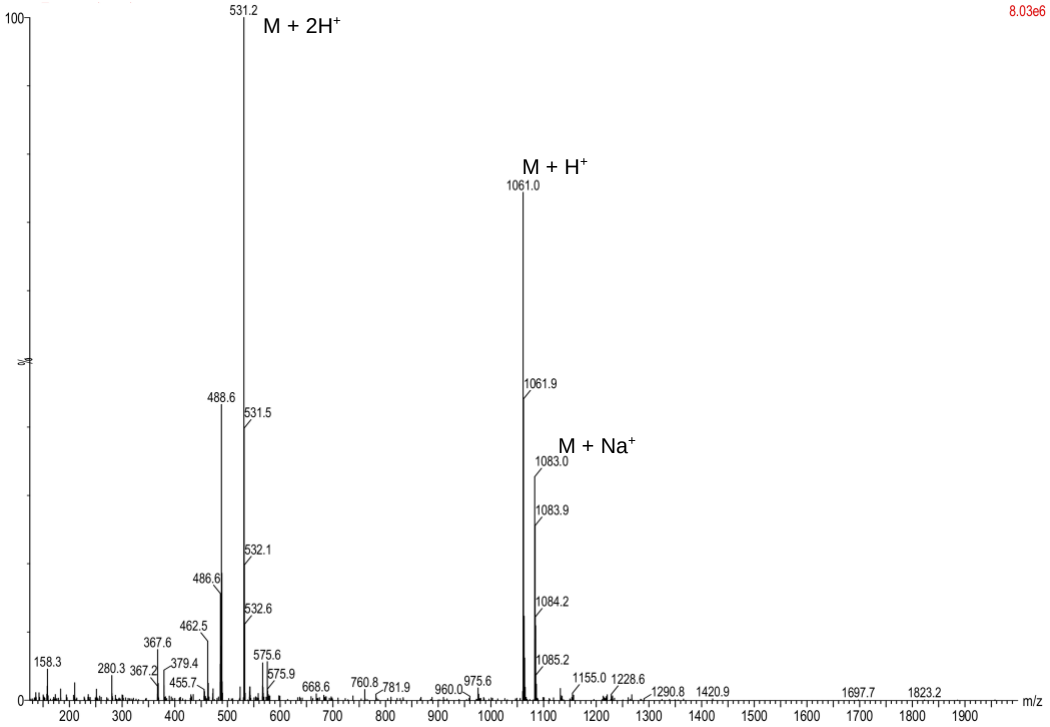
Crude Mass: 4.2 mg Crude Yield: 20%

Pure Mass: 1.0 mg Overall Purified Yield: 5%

Average Yield Over 18 Steps: 85%

Calculated *m/z* [$M + H^+$]: 1060.61





16:

Amine submonomer 1: L-Isoleucine

Amino acid side chain coupling partner: Morpholine

Amine submonomer 2: Benzylamine

Amine submonomer 3: L-Phenylalanine

Amino acid side chain coupling partner: 1-Butanol

Amine submonomer 4: L-Methionine

Amino acid side chain coupling partner: Piperidine

Amine submonomer 5: 2-Methoxyethylamine

Amine submonomer 6: Sarcosine

Amino acid side chain coupling partner: 1-Butanethiol

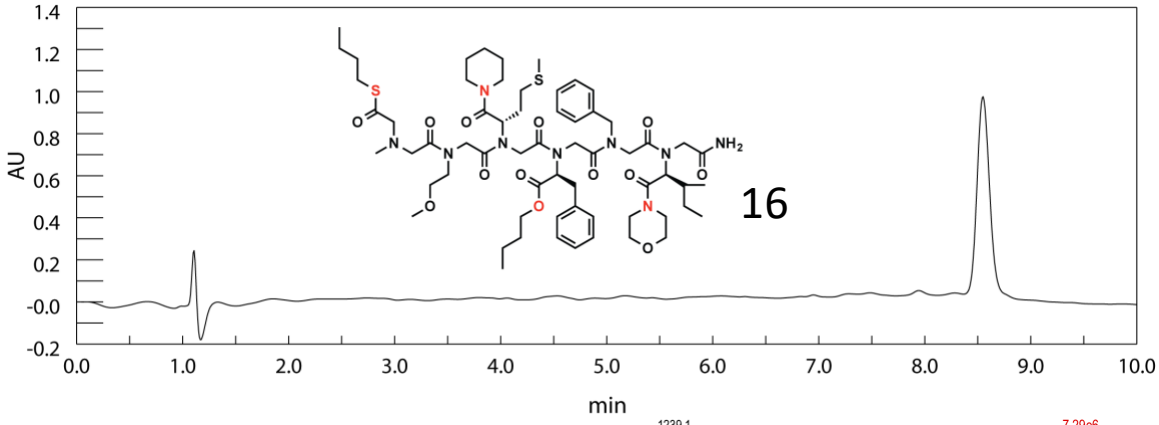
Theoretical Yield: 24.7 mg

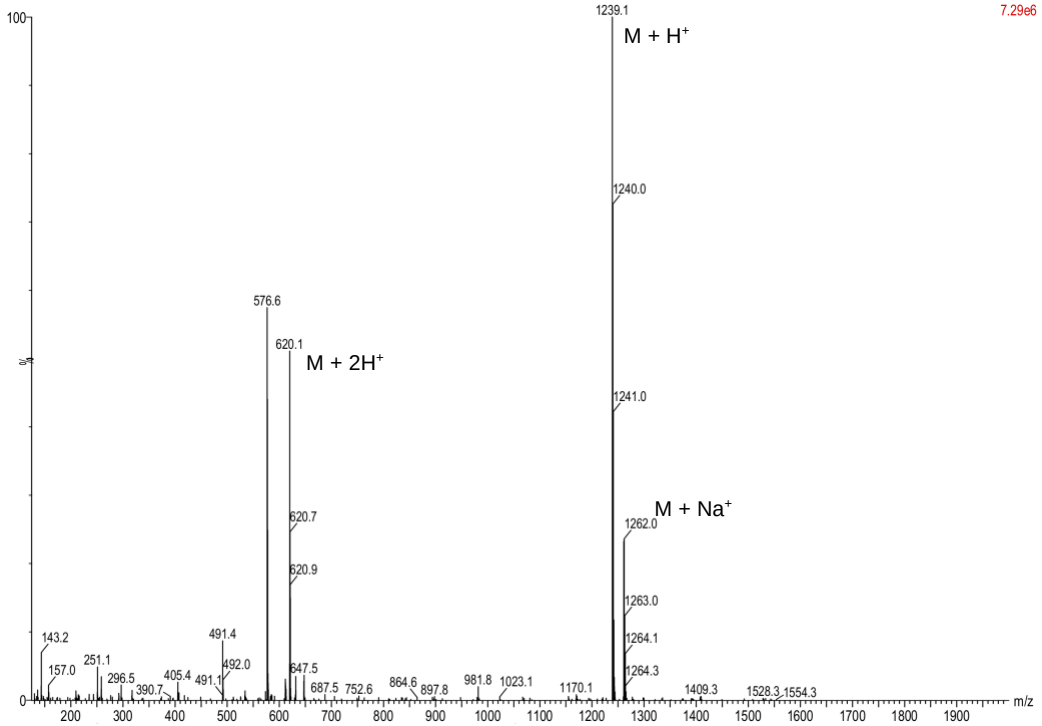
Crude Mass: 4.4 mg | Crude Yield: 18%

Pure Mass: 1.4 mg | Overall Purified Yield: 6%

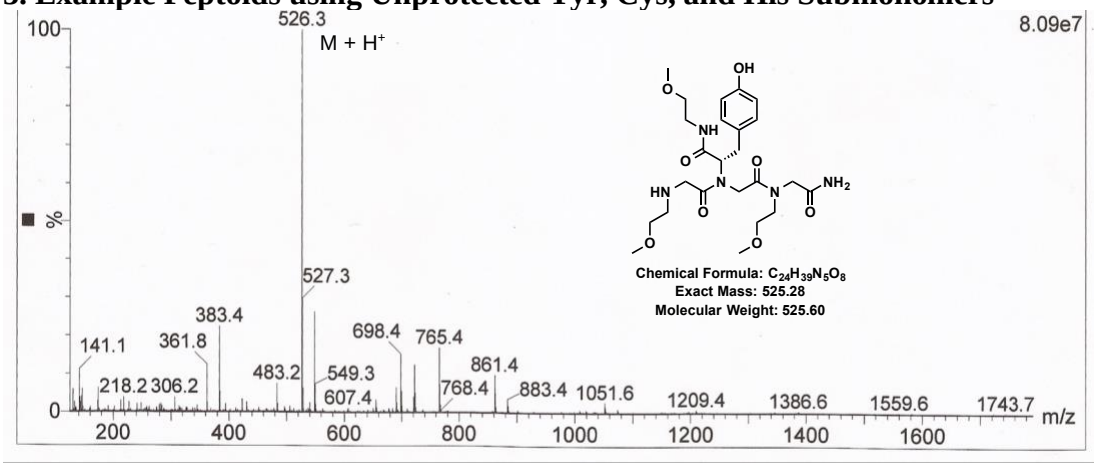
Average Yield Over 18 Steps: 86%

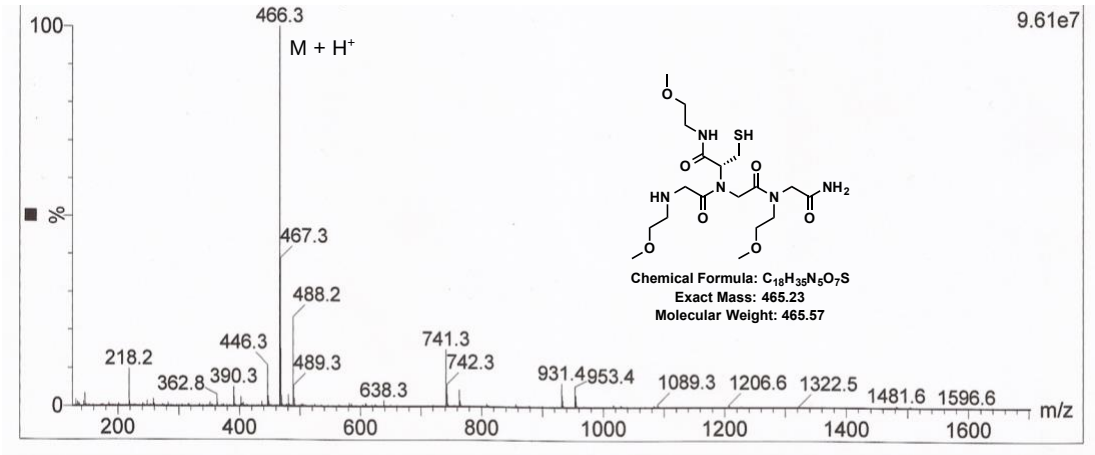
Calculated *m/z* [*M* + H^+]: 1238.66

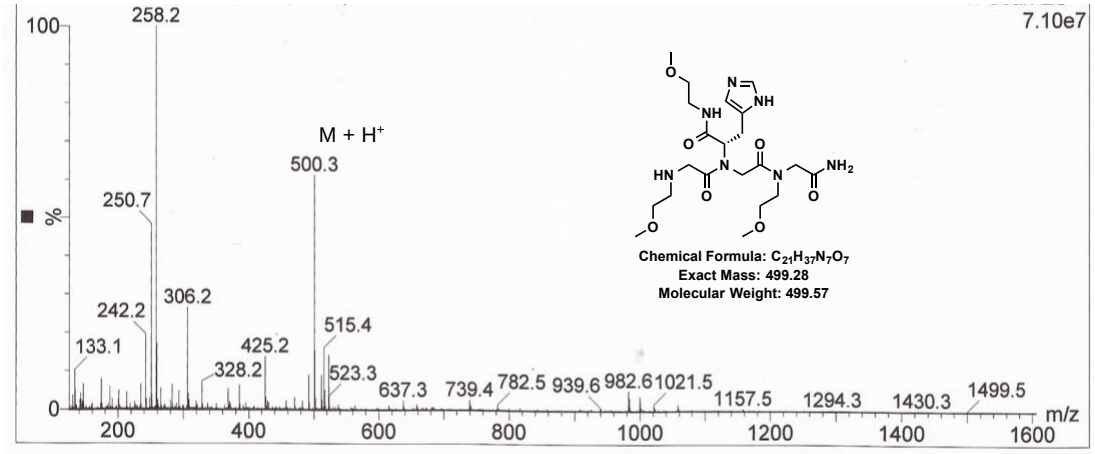




3. Example Peptoids using Unprotected Tyr, Cys, and His Submonomers

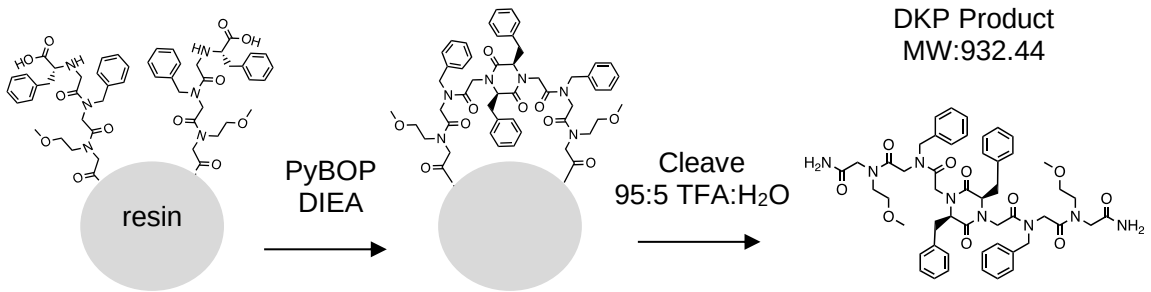


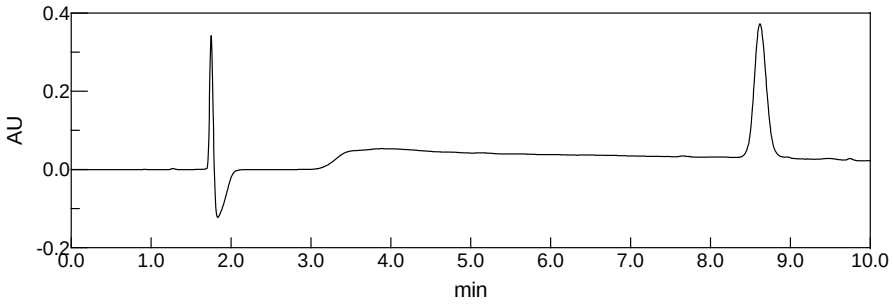


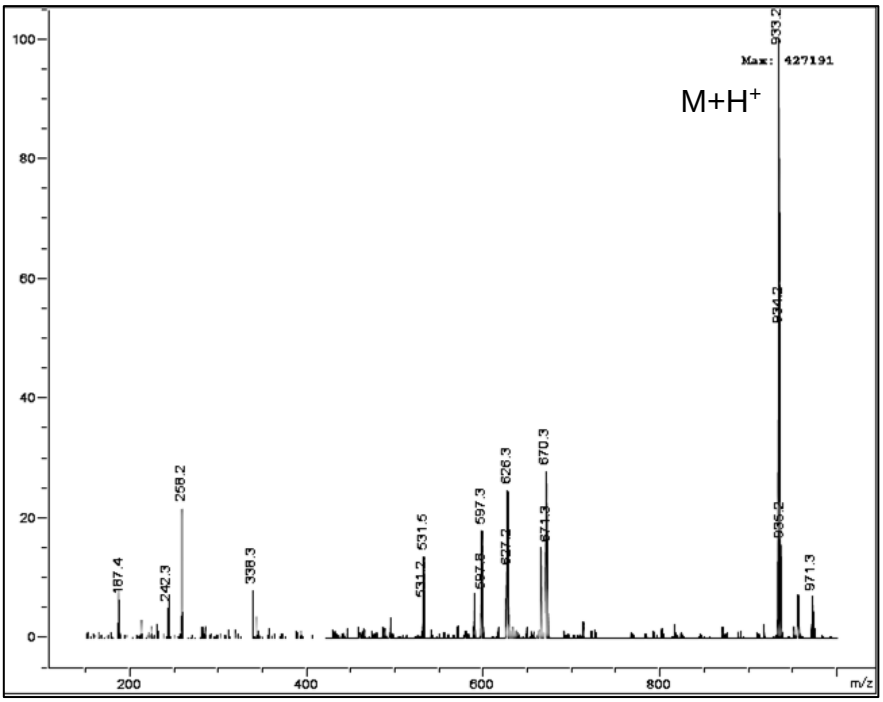


4. Intermolecular, On-Resin DKP Formation

Figure S1. Proposed formation of diketopiperazines during the activation of a carboxylic acid peptoid side chain. An example of a putative DKP product formed between two L-phenylalanine carboxylic acid termini is shown. The side product was isolated by preparative HPLC and observed by LCMS. The extent of DKP formation appears to increase when the nucleophilicity of the desired synthon decreases. Notably this DKP formation results in termination of chain elongation.







5. Circular Dichroism of Compounds 1, 4 and 5.

All CD experiments were conducted using a Jasco J-1500 circular dichroism spectrometer.

The sign for the ellipticity of compound 5 is opposite of that for compounds 1 and 4, which we attribute to a distinct conformational influence resulting from the presence of this monomer at non-terminal residues. Variations in circular dichroism may also arise due to partial racemization of the side chains under basic conditions. The influence of stereochemistry on conformation will be the subject of additional study.

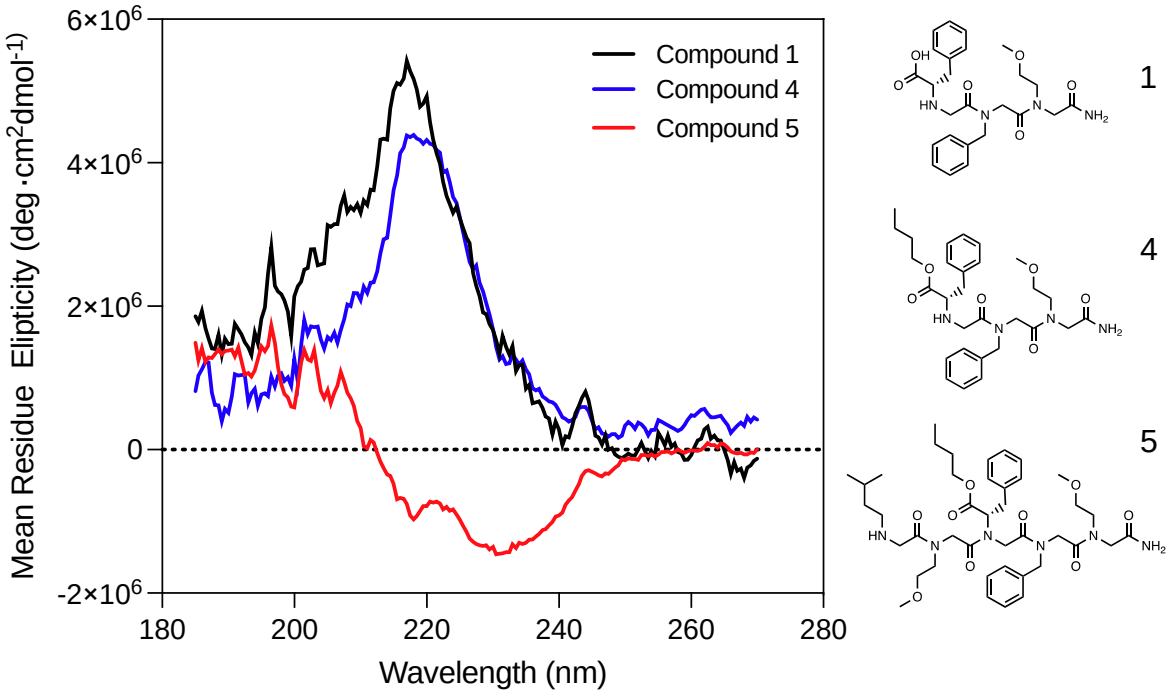


Figure S2. Circular Dichroism (CD) spectra of peptoids 1,4, and 5. Samples were prepared at 0.625 mM (~0.3-0.5 mg/mL) peptoid in acetonitrile and filtered (0.2 micron). 5 accumulations per sample were obtained at room temperature in a quartz cuvette (1mm pathlength). Solvent baseline was subtracted from the spectra and no smoothing functions were applied.