Supplementary materials

Materials

Amino acids were purchased from Iris Biotech GmbH: Fmoc-Gly-OH, Fmoc-Ala-OH, Fmoc-Pro-OH, Fmoc-Val-OH, Fmoc-Leu-OH, Fmoc-Ile-OH, Fmoc-Met-OH, Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-(Phe)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-His(Trt)-OH, Fmoc-Cys(Trt)-OH. Reagents used were purchased from Iris Biotech GmbH: OxymaPure (ethyl-2-cyano-2-(hydroxyimino)acetate), DIC (*N,N'*-diizopropylcarbodiimide), NMP (*N*-methylpirrolidone). Reagents used were purchased from VWR: DMF (dimethylformamide), DMSO (dimethly sulfoxide), MeCN (acetonitrile), piperidine, NMM (*N*-methylmorpholine).

Synthesis setup

Our system consists of JASCO HPLC modules, a PU4180 pump with RCY-4000 unit, AS4150L autosampler, UV4075 UV detector, CO4060 column oven. It is a commercially available flow peptide instrument (HPPS-4000, METALON Ltd., Hungary) consisting of a conventional Jasco LC-4000 series HPLC system, except for the PU-4180 HPLC pump, modified with an additional valve to allow recirculation and regulation of solvent flow (e.g. cleavage mixture). The ChromNAV2 software ensures a fully automated process. The autosampler injects the reagent solutions from a 2 mL sample vial placed in the sample rack. The PEEK chromatography column was used as the fixed bed reactor tube for the resin and DMF was used as the eluent.

Synthesis protocols

An NMP stock solution was prepared for each standard amino acid. All amino acids were measured into a vial with the appropriate amount of OxymaPure. The autoinjector mixed the DIC and injected the activated solution into the system. For Fmoc cleavage, 0.6 ml of 30 V/V% piperidine/DMF solution was used. 130-150 mg of TentaGel S RinkAmide (0.23 mmol/g) was added to a PEEK fixed bed column. After synthesis, the resin was washed with

DCM and dried in vacuo. The peptide was then cleaved from the resin with 5 ml of TFA solution containing 2.5% TIS and 2.5% water if the peptide contained no tryptophan, arginine, cysteine or methionine, otherwise 5 ml of TFA solution containing 250 mg phenol, 5% water, 5% thioanisole, 2.5% ethanedithiol and 1% TIS. After 3 hours the solution was filtered and the excess TFA was evaporated. Cold ether was then added to the residue. The ether-peptide suspension was centrifuged and decanted several times. After drying, the crude peptide was dissolved in water with 10% MeCN and lyophilised.

STable 1. Coupling **protocols a, b, c, d** and **e** were carried out using the following parameters at 80 °C and 50-80 bar.

protocol/parameters	**a** [e]	**b**	**c**	**d**	**e**
equiv. (aa./DIC/Oxyma)[a]	3/3/6	3/3/6	5/5/10	3/3/6	3/3/6
***c* (M)** [b]	0.11	0.22	0.22	0.11	0.22
***v* (ml/min)** [c]	0.6	0.6	0.6	0.3	0.3
t_R **(min)** [d]	1.67 (1 ml)	0.83 (0.5 ml)	1.67 (1 ml)	3.33 (1 ml)	1.67 (1 ml)
washing time [e]	2.8 min (2.2 ml)	3.6 min (2.5 ml)	2.8 min (2.2 ml)	5.7 min (2.4 ml)	7.4 min (2.9 ml)
Fmoc-deprotection time (min)	0.6 (0.6 ml)	0.6 (0.6 ml)	0.6 (0.6 ml)	0.6 (0.6 ml)	0.6 (0.6 ml)
washing time [f] **(Fmoc-cleavage)**	2.4 min (2.3 ml)	2.4 min (2.3 ml)	2.4 min (2.3 ml)	2.4 min (2.3 ml)	2.4 min (2.3 ml)
flow rate evolution	1) 0.6 ml/min {0-t-3 (min)} 2) 0.6 to 1.0 ml/min {3-t-3.5 (min)} 3) 1.0 ml/min {3.5-t-7.0 (min)} 4) 1.0 to 0.6 ml/min {7.0-t-7.5 (min)}	1) 0.6 ml/min {0-t-3 (min)} 2) 0.6 to 1.0 ml/min {3-t-3.5 (min)} 3) 1.0 ml/min {3.5-t-7.0 (min)} 4) 1.0 to 0.6 ml/min {7.0-t-7.5 (min)}	1) 0.6 ml/min {0-t-3 (min)} 2) 0.6 to 1.0 ml/min {3-t-3.5 (min)} 3) 1.0 ml/min {3.5-t-7.0 (min)} 4) 1.0 to 0.6 ml/min {7.0-t-7.5 (min)}	1) 0.3 ml/min {0-t-7.5 (min)} 2) 0.3 to 1.0 ml/min {7.5-t-8.5 (min)} 3) 1.0 ml/min {8.5-t-11.5 (min)} 4) 1.0 to 0.3 ml/min {11.5-t-12.0 (min)}	1) 0.3 ml/min {0-t-7.5 (min)} 2) 0.3 to 1.0 ml/min {7.5-t-8.5 (min)} 3) 1.0 ml/min {8.5-t-11.5 (min)} 4) 1.0 to 0.3 ml/min {11.5-t-12.0 (min)}

[a]equivalent amino acid derivative / *N,N'*-diizopropylcarbodiimide / ethyl-2-cyano-2-(hydroxyimino)acetate, [b]concentration of the amino acid solution, [c]flow rate of the reagent solution during coupling, [d]residence time of the reagents on the resin, [e]for protocols scheme and hardware setup see **Figure 1**.

Analysis

Both crude and purified products were analysed by UPLC-MS on an ACQUITY UPLC® HSS T3 1.8µm column (Waters, 100 × 2.1 mm, 100 Å) using a gradient elution consisting of 0.1% TFA in water (eluent A) and 0.1% TFA in acetonitrile (eluent B) with a gradient from 25% to 65% B over 8 min and the column temperature set at 45°C. The flow rate was set to 0.18 mL/min and the absorbance was detected at λ = 220 nm. LC-MS analysis of the compounds was performed on a Thermo Scientific Q Exactive Focus Hybrid Quadrupole-Orbitrap mass spectrometer connected directly to a Dionex 3000 UHPLC (Thermo Scientific, Bremen, Germany). The Xcalibur program (Thermo Fisher Scientific) was used for data analysis.

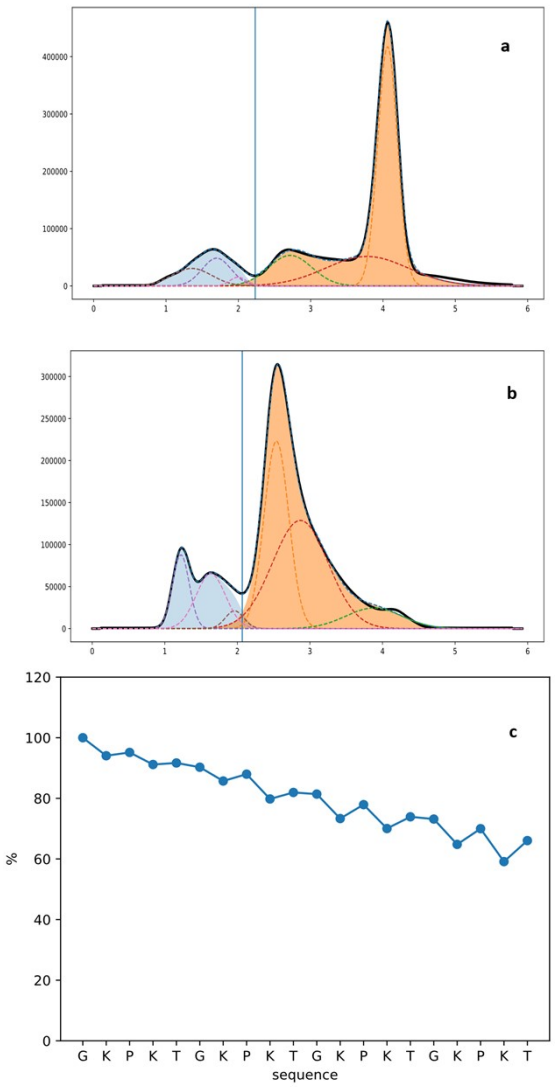
Calculation of raw yield

The weight of lyophilised starting material (m_{peptide}) was measured using an analytical balance. The theoretical yield was then divided by the actual mass of the peptide according to the following formula:

$$RawYield\ \% = \frac{m_{peptide}}{M_{peptide} \cdot l_{resin} \cdot m_{resin}} \cdot 100\% \qquad \textbf{equ. 1}$$

where M_{peptide} is the average molecular mass of the peptide, l_{resin} is the loading of the resin and m_{resin} is the mass of the resin. In the case of overall yield, the procedure is the same, but m_{peptide} is the purified product.

UV-absorption data processing and interpretation



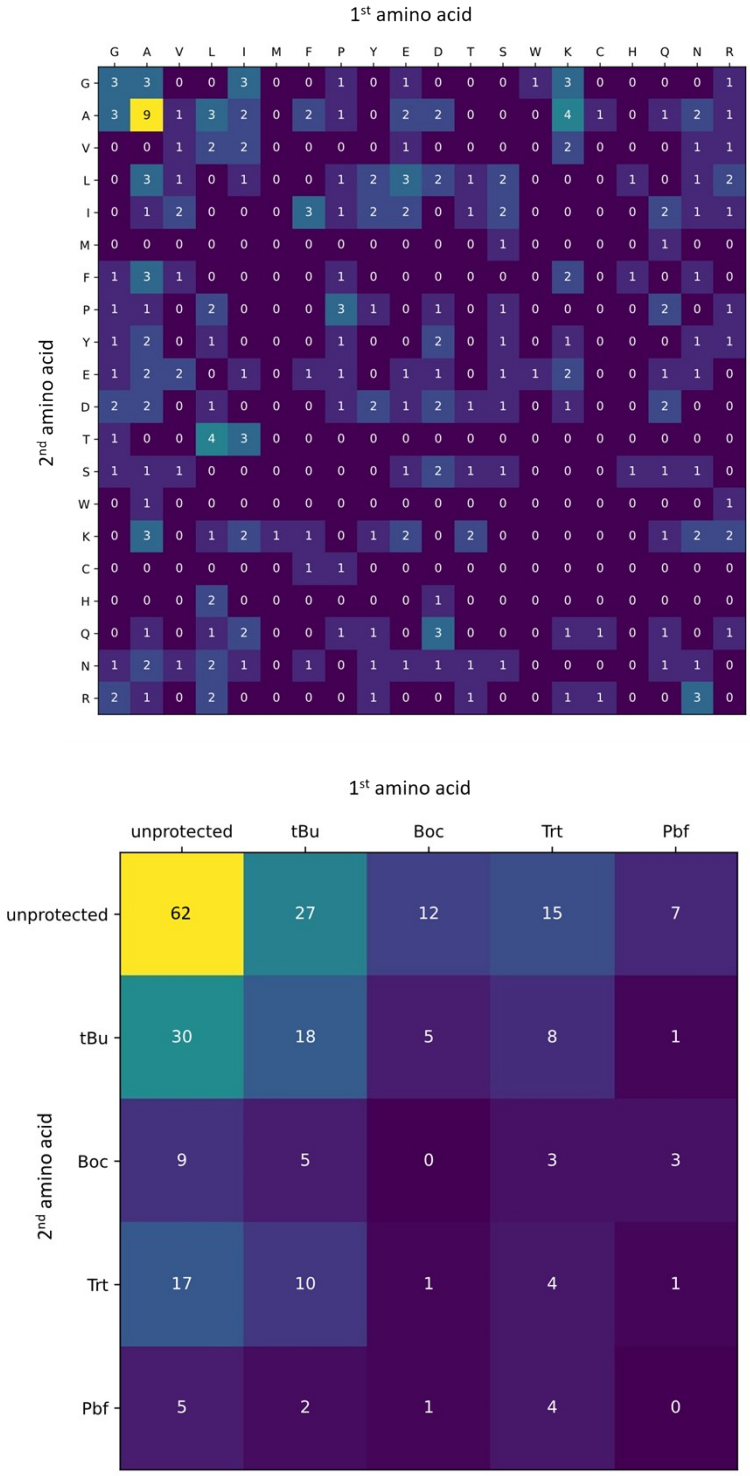
SFigure 1. a) The absorbance chromatogram (recorded at λ ~360 nm) of an SPF coupling cycle. The orange curve reflects to the absorbance variation with time of the piperidine-dibenzfulvene, the product of the Fmoc-deprotection reaction, while the blue area belongs to the amino acid coupling. The dashed lines show the individual Gaussian curves. **b)** The absorbance chromatogram (recorded at λ ~360 nm) of an SPF coupling cycle with premature Fmoc-cleavage, as the retention time of piperidine is ~4 minutes. **c)** For each cycle, the area of the Fmoc-cleavage curve is plotted as a function of the coupling cycle *i*, with respect to that of the first one (expressed in %), reported for OT(P)20= -$(GKPKT)_4$-. Note that as the total amount decreases, it is likely that some resin leakage will also occur during the repeated coupling cycles due to the rheological and mechanical properties of the PEG-based resin.

The monitored Fmoc cleavage reaction (λ ~360 nm) for residue *i* provides valuable information on how many Fmoc groups are available and thus, how many Fmoc-protected amino acids (residue *i*) were successfully coupled in the final step. The dibenzfulvene-piperidine adduct provides an opportunity to quantitatively measure the amount of Fmoc groups on the resin by obtaining the area under the cleavage chromatogram. During the synthesis, in some cases, we experienced premature Fmoc cleavage, manifested by peaks on the chromatogram where neither coupling (1-2 min) nor Fmoc cleavage (3.5 - 4.5 min) should have occurred (**SFig. 1b**).

The chromatograms prior to the measurement of the Fmoc cleavage peak were normalised by flow rate and separated by control method. For each method a variance chromatogram was calculated and fitted with several Gaussian functions (**equ. 2**), which determined the Gaussian parameters for each fit. After regression, the peaks belonging to the Fmoc cleavage were integrated. The first area under the Fmoc curve was taken as 100% and each other area was calculated relative to it. Slight deviations from the trend line were observed when several methods and different solvents were used. This can be explained by the overlapping of the acylation and Fmoc cleavage curves leading to a slightly imprecise regression.

$$f(t) = \sum_{i=1}^{n} a_i e^{-\frac{(t-b_i)_2}{c_i^2}} \qquad equ.\,2$$

Incorporated dipeptides of the foldamers currently synthesized



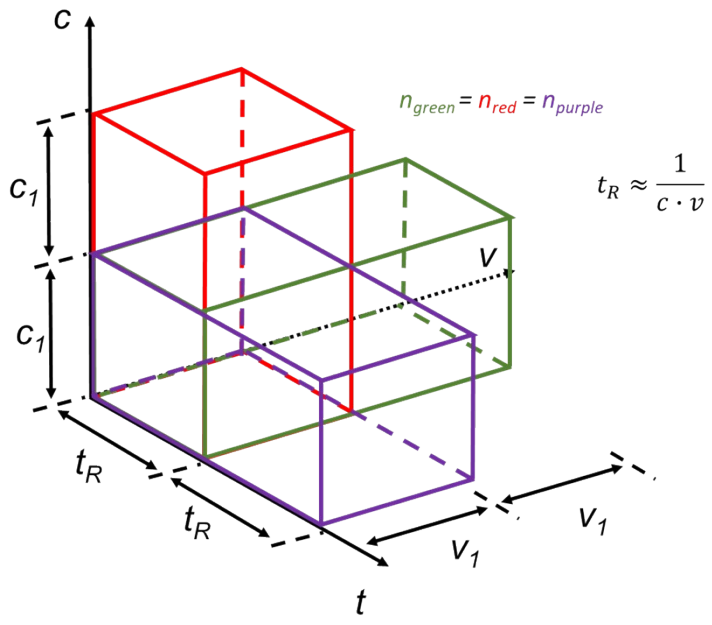
SFigure 2. The synthesised dipeptides contained in the four selected domains: BPTI, Z(Aβ3), SH3, UBI. The upper figure shows the exact dipeptides synthesised, while the lower figure groups the dipeptides comprising amino acids equipped with the same sidechain protecting groups. (The 2nd amino acids were coupled to the 1st.) These data show that each type of amino acid pair has been successfully synthesised, several more than a dozen times, with the exception of the Boc-Boc sidechain protection.

Residence Time Control (RTC)

$$n = c \cdot v \cdot t_R \qquad \textbf{equ. 3}$$

$$t_R \sim \frac{1}{c \cdot v} \qquad \textbf{equ. 4}$$

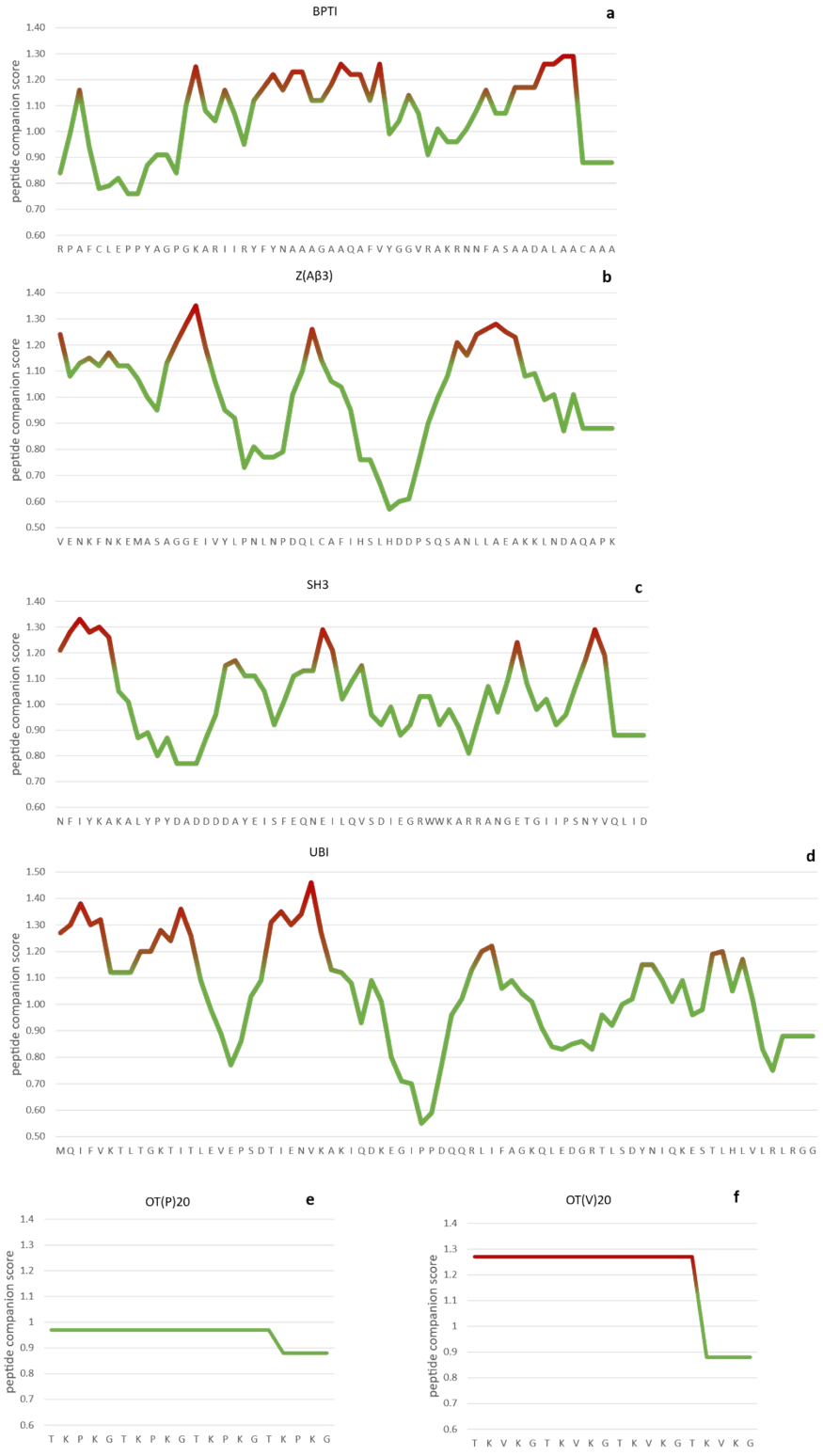
In the case of a tubular reactor, if we consider the quantity of substances n, then the relationship between concentration (c), flow rate (v) and residence time (t_R) is in accordance with **equ. 3**. Keeping the number of substances constant, n= const. and rearranging **equ. 3**, the residence time is the reciprocal function of both the concentration times and the flow rate: **equ. 4**. Reducing the flow rate increases the residence time, while increasing the concentration reduces the residence time (**SFig. 3**). Furthermore, we can change c and v simultaneously, leaving the residence time unchanged. Thus, for a coupling reaction with an ideal kinetic profile, one can increase the reagent concentration and decrease the flow rate and vice versa, leaving the residence time unchanged. When the flow rate is lower, the reagents have a longer contact time on the resin. As the acylation time becomes longer, the yield of the main product will increase accordingly, although more by-products may also be formed. It is important to note that the change in kinetic conditions may have the effect of higher rates of side reaction.



SFigure 3. To select proper flow conditions for SPF, the role of concentration (c), flow rate (v) and residence time (t_R) are set to control quantity of substances: n. (**equ. 2**). For example, swapping SPF from **protocol a** [c ~0.11 M, v = 0.6 ml/min] to **protocol e** [c ~0.2 M, v = 0.3 ml/min] is similar to that when exchanging the green to the red

cube. If the reagent concentration is doubled with respect to c_1, then a “half-residence time” gives the same quantity of substances n. (The latter change corresponds to swapping the purple cube for the red one).

Prediction of coupling difficulty with PeptideCompanion software



SFigure 4. Results from the PeptideCompanion software. Scores higher than 1.2 (red) are predicted to be difficult to synthesize by any method. **a)** peptide companion score for BPTI, **b)** peptide companion score for Z(Aβ3), **c)** peptide companion score for SH3, **d)** peptide companion score for UBI, **e)** peptide companion score for OT(P)20, **f)** peptide companion score for OT(V)20.

Synthesis of peptides and small domain proteins

STable 2. The different protocols used for the synthesis of oligotuftsins: oligomers of OT(P)5 and OT(V)5 ($M_{\text{-TKPKG-}}$ = 511.62 Da, *C* and *N*-terminus $M_{[H-NH2]}$ = 17.03 Da), where *X* is the length of the peptide and $z = X/5$, so that $M_{OT(P)20} = 4 * M_{\text{-TKPKG-}} + M_{[H-NH2]} = 4 * 511.62 + 17.03 = 2063.51$

	protocol type	**Equiv.**	**total synthesis time / OT pentapeptides**	$M_{av.}$ **of OT(P)5 and OT(V)5 pentapeptides**
OT(P)*X*	**protocol a**	3	37.5 min	*z* * 511.62 (+17.03) Da
OT(P)*X*[e]	**protocol a** for G, T **protocol e** for K, P	3	51 min	*z* * 511.62 (+17.03) Da
OT(V)*X*[e]	**protocol a** for G, T, V **protocol e** for K, P	3	46.5 min	*z* * 530.67 (+17.03) Da

STable 3. The different protocols used to optimize the SPF synthesis of BPTI[a].

RPAFCLEPPY AGPGKARIIR YFYNAAAGAA QAFVYGGVRA KRNNFASAAD ALAACAAA (58 AA)						
serial number (#)	**protocol**	**equiv. used**	**total synthesis time (h)**	**raw yield (%)[b]**	**Mw[obs c] (Da)**	**LC-MS** see SFigure
1	**a**	3	7.4	49	5978.33	20
2	**d**	3	8.6	60.5	5978.05	21
3	**b**	3	7.4	59	5978.33	22
4	**e**	3	8.6	67	5978.27	23
5	**c**	5	7.4	62.5	5978.28	24
6[d]	**e**	3	8.6	60.5	5978.18	25
7[e]	**e**	3	8.6	59.5	5977.87	26

[a] BPTI: Bovine pancreatic trypsin inhibitor[29], [b] yield was calculated according to equation 1, [c] Mw_{calc}= 5978.87 Da, [d] SPF synthesis was conducted in the solvent mixture of DMF:DMSO / 3:1. [e] SPF synthesis was conducted in the solvent mixture of DMF:MeCN / 3:1.

STable 4. The different protocols used to optimize the SPF synthesis of SH3[a].

NFIYKAKALY PYDADDDDAY EISFEQNEIL QVSDIEGRWW KARRANGETG IIPSNYVQLI D (61 AA)							
serial number (#)	**solvent**	**protocol**	**equiv. used**	**total synthesis time (h)**	**raw yield (%)[b]**	**Mw[obs c] (Da)**	**LC-MS** see SFigure
1	DMF	**protocol e for R, K, Q, N, P, E and protocol a for all other amino acids**	3	9.3	44	7128.56	28
2	DMF – DMSO 3:1				56	7128.84	29
3	DMF – MeCN 3:1				65	7128.67	30

[a] SH3: SRC Homology 3 Domain[13], [b] raw yield was calculated according to equation 1, [c] Mw^{calc}= 7128.83 Da

STable 5. The different protocols used to optimize the SPF synthesis of **Z(Aβ3)** [a].

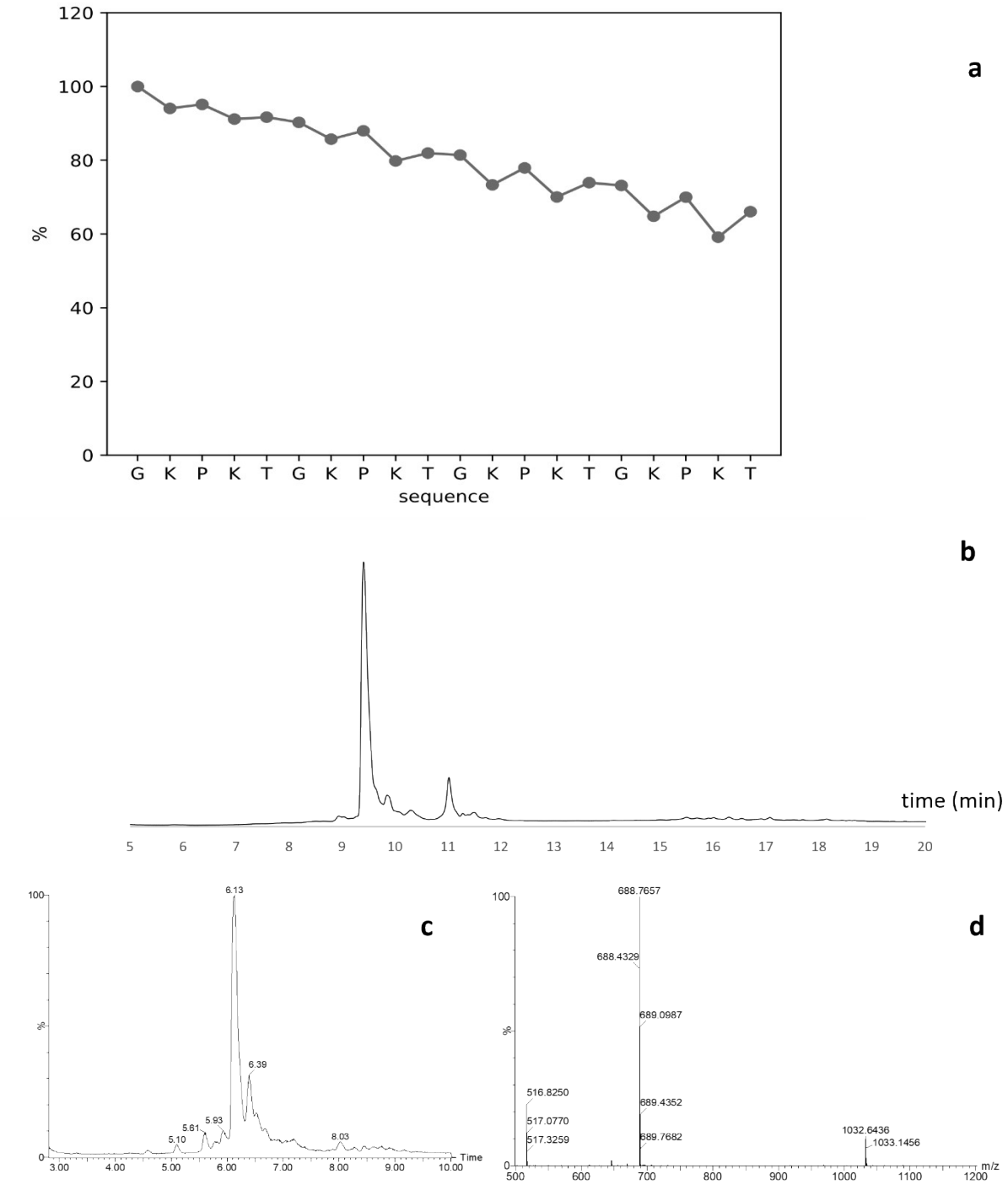
VENKFNKEMA SAGGEIVYLP NLNPDQLCAF IHSLHDDPSQ SANLLAEAKK LNDAQAPK (58 AA)							
serial number (#)	**solvent**	**protocol**	**equiv. used**	**total synthesis time (h)**	**raw yield (%)[b]**	**Mw[obs c] (Da)**	**LC-MS** see SFigure
1	DMF	**protocol e for R, K, Q, N, P, E and protocol a for all other**	3	9.0	57	6306.20	32
2	DMF – DMSO 3:1				63	6305.01	33
3	DMF – MeCN 3:1				63	6306.01	34

[a] **Z(Aβ3)**: Z amyloid binding affibody 3[28], [b] raw yield was calculated according to equation 1, [c] Mw^{calc}= 6306.10 Da

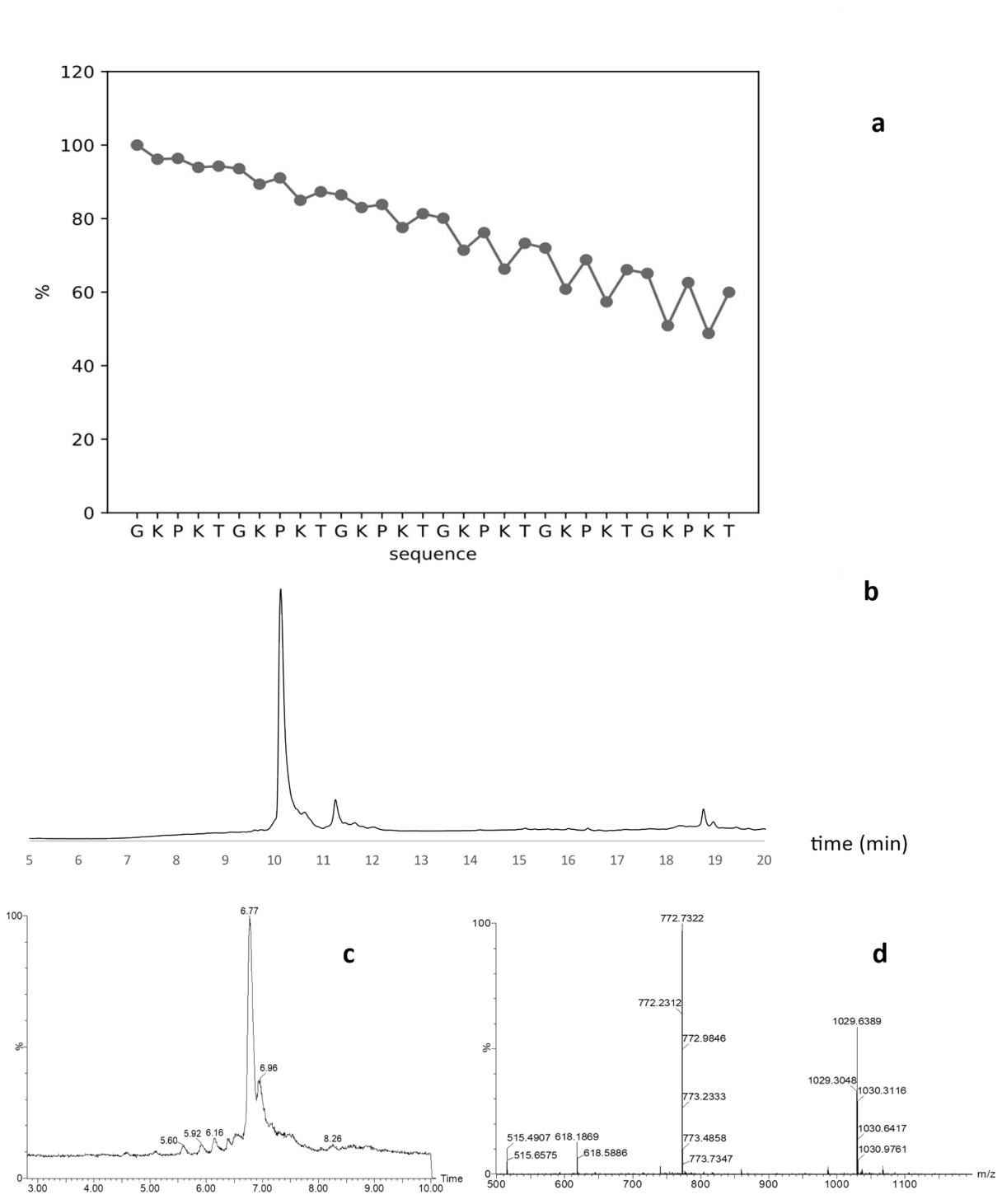
STable 6. The different protocols used to optimize the SPF synthesis of **UBI** [a].

MQIFVKTLTG KTITLEVEPS DTIENVKAKI QDKEGIPPDQ QRLIFAGKQL EDGRTLSDYN IQKESTLHLV LRLRGG (76 AA)							
serial number (#)	**solvent**	**protocol**	**equiv. used**	**total synthesis time (h)**	**raw yield (%)[b]**	**Mw[obs c] (Da)**	**LC-MS** see SFigure
1	DMF	**protocol e for R, K, Q, N, P, E and protocol a for all other**	3	11.6	51	-	36
2	DMF – DMSO 3:1				53	8431.65	37
3	DMF – MeCN 3:1				56	8431.65	38

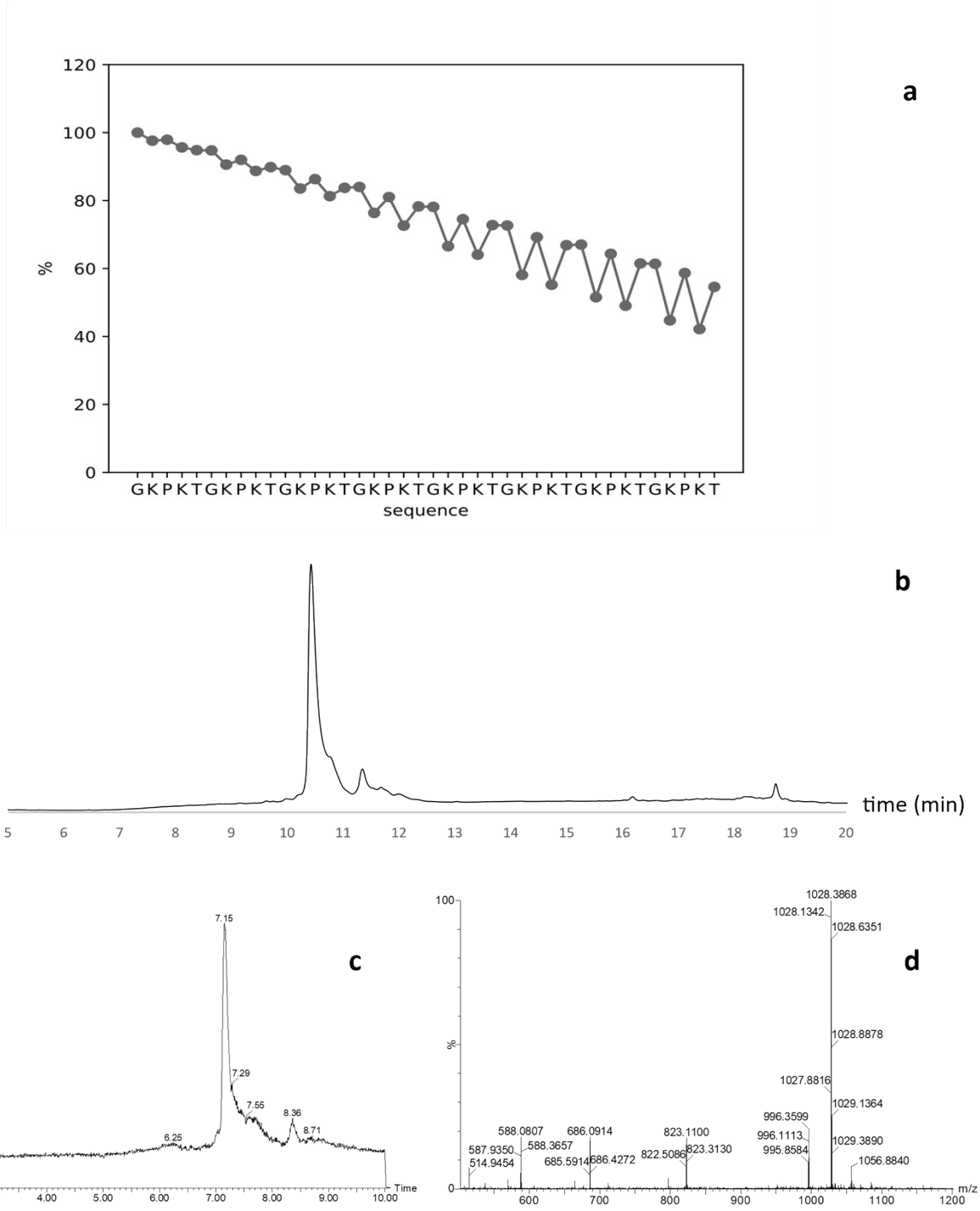
[a] **UBI**: Human Ubiquitin[30], [b] raw yield was calculated according to equation 1, [c] Mw^{calc}= 8432.64 Da



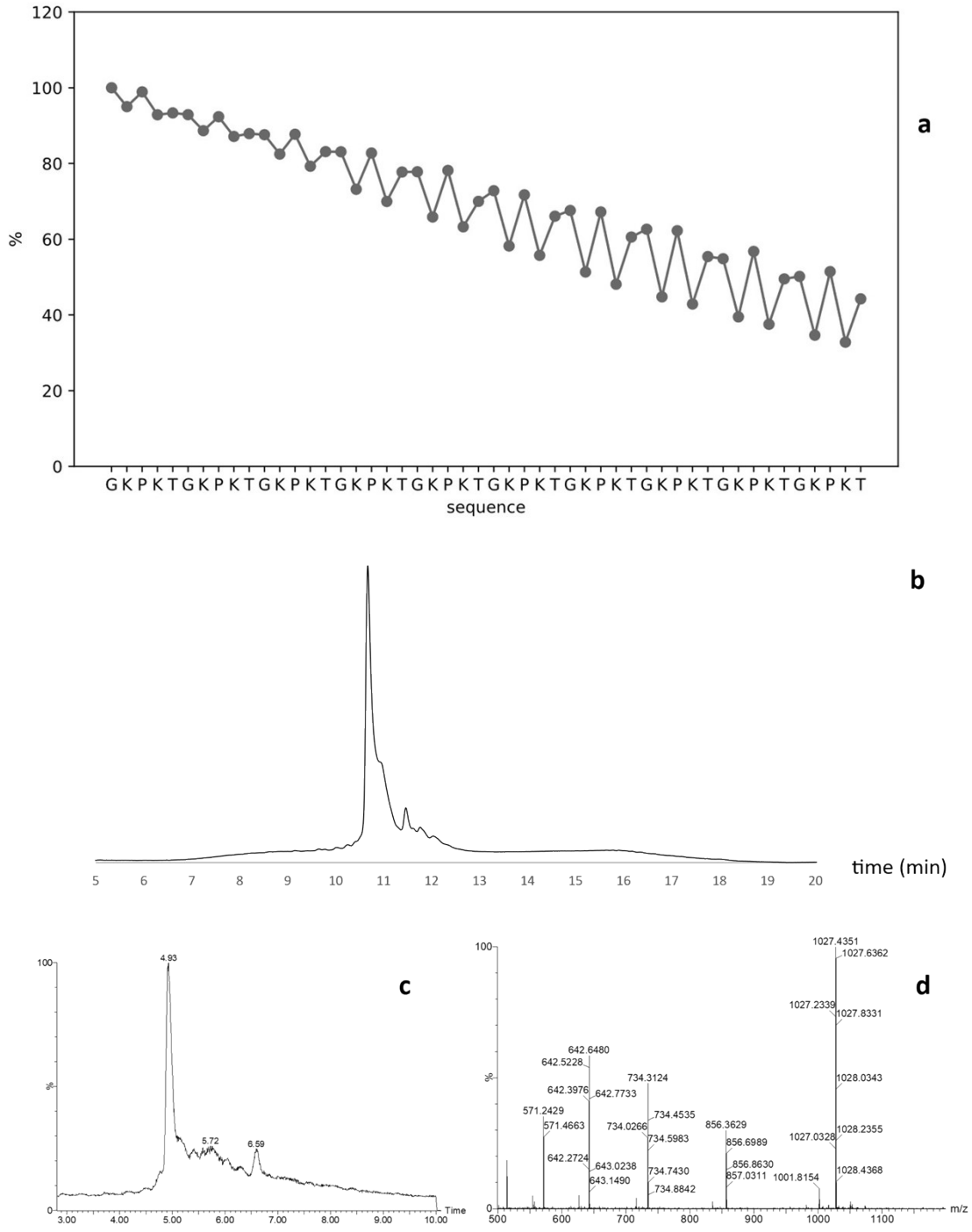
SFigure 5. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of OT(P)20. **b)** The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of OT(P)20. **c)** The LC-MS profile (total ion chromatogram) of the crude OT20, **d)** with the MS profile of the crude product (peak at 6.13 min.). Measured ions *e.g.* 688.7657: $[M + 3H]^{3+}$ and 1032.6436: $[M + 2H]^{2+}$ give Mw^{obs} = 2063.28 Da, in good agreement with its calculated counterpart Mw^{calc}= 2063.51 Da. (**STable 2)**



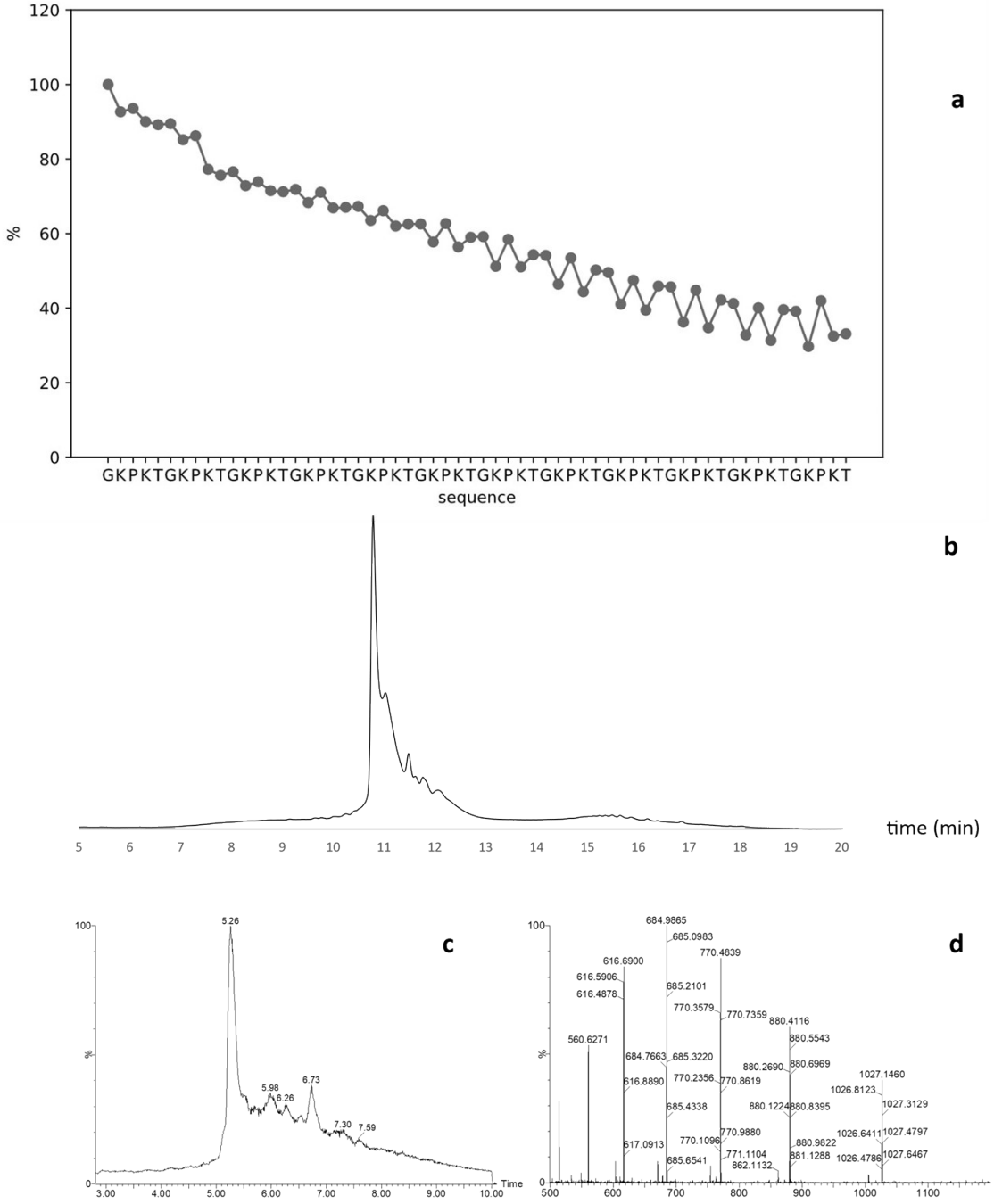
SFigure 6. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis sis of OT(P)30. **b)** The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of OT(P)30. **c)** The LC-MS profile (total ion chromatogram) of the crude OT30, **d)** with the MS profile of the crude product (peak at 6.77 min.). Measured ions *e.g.* 772.7322: $[M + 4H]^{4+}$, 1029.6389: $[M + 3H]^{3+}$ give $Mw^{obs.} = 3086.93$ Da, in good agreement with its calculated counterpart: $Mw^{calc} = 3086.75$ Da. **(STable 2)**



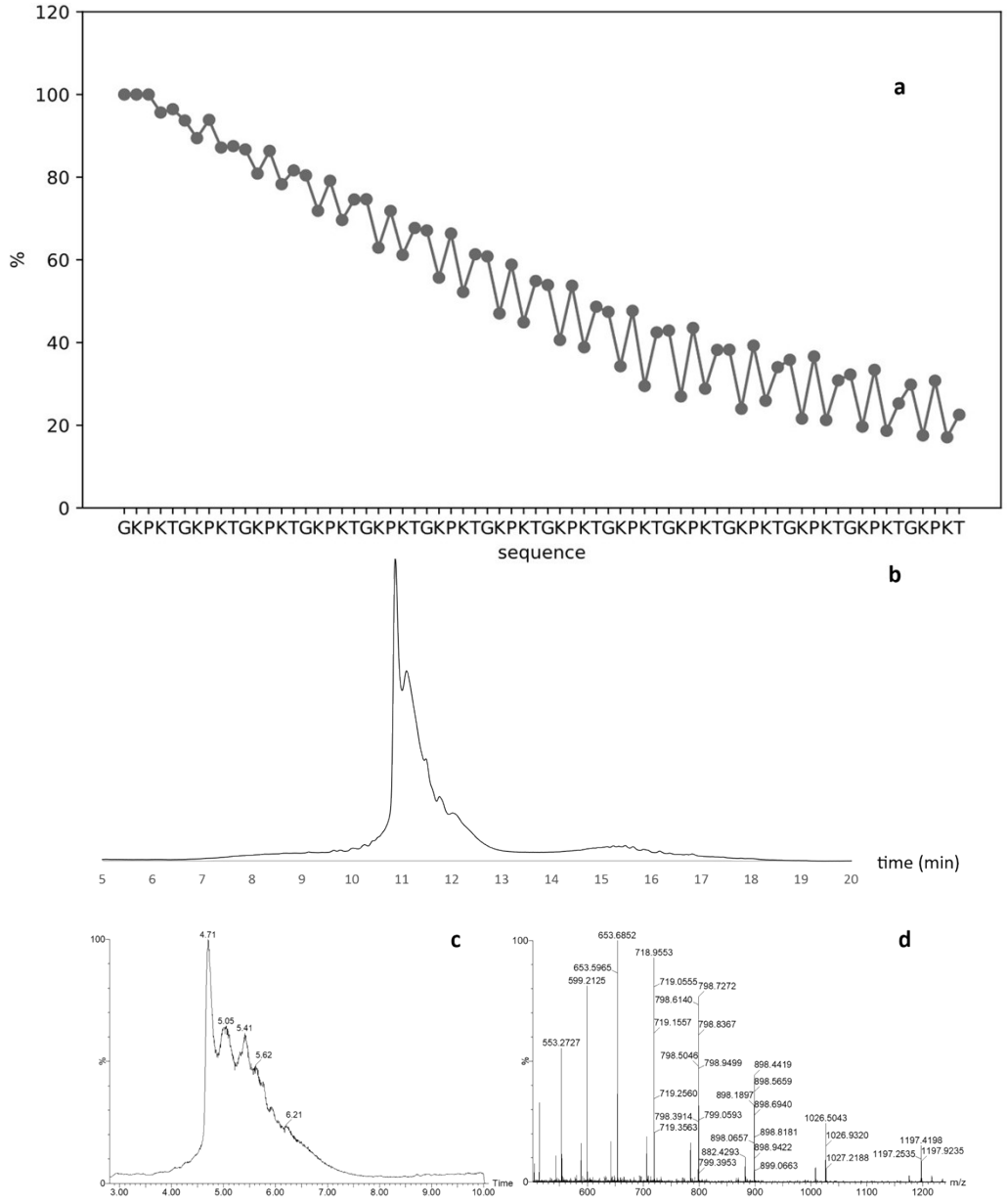
SFigure 7. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of OT(P)40. **b)** The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of OT(P)40. **c)** The LC-MS profile (total ion chromatogram) of the crude OT40, **d)** with the MS profile of the crude product (peak at 7.15 min.). Measured ions *e.g.* 1028.3868: $[M + 4H]^{4+}$, 823.1100: $[M + 5H]^{5+}$ give $Mw^{obs.}$= 4109.55 Da, in good agreement with its calculated counterpart: Mw^{calc}= 4109.99 Da. (**STable 2)**



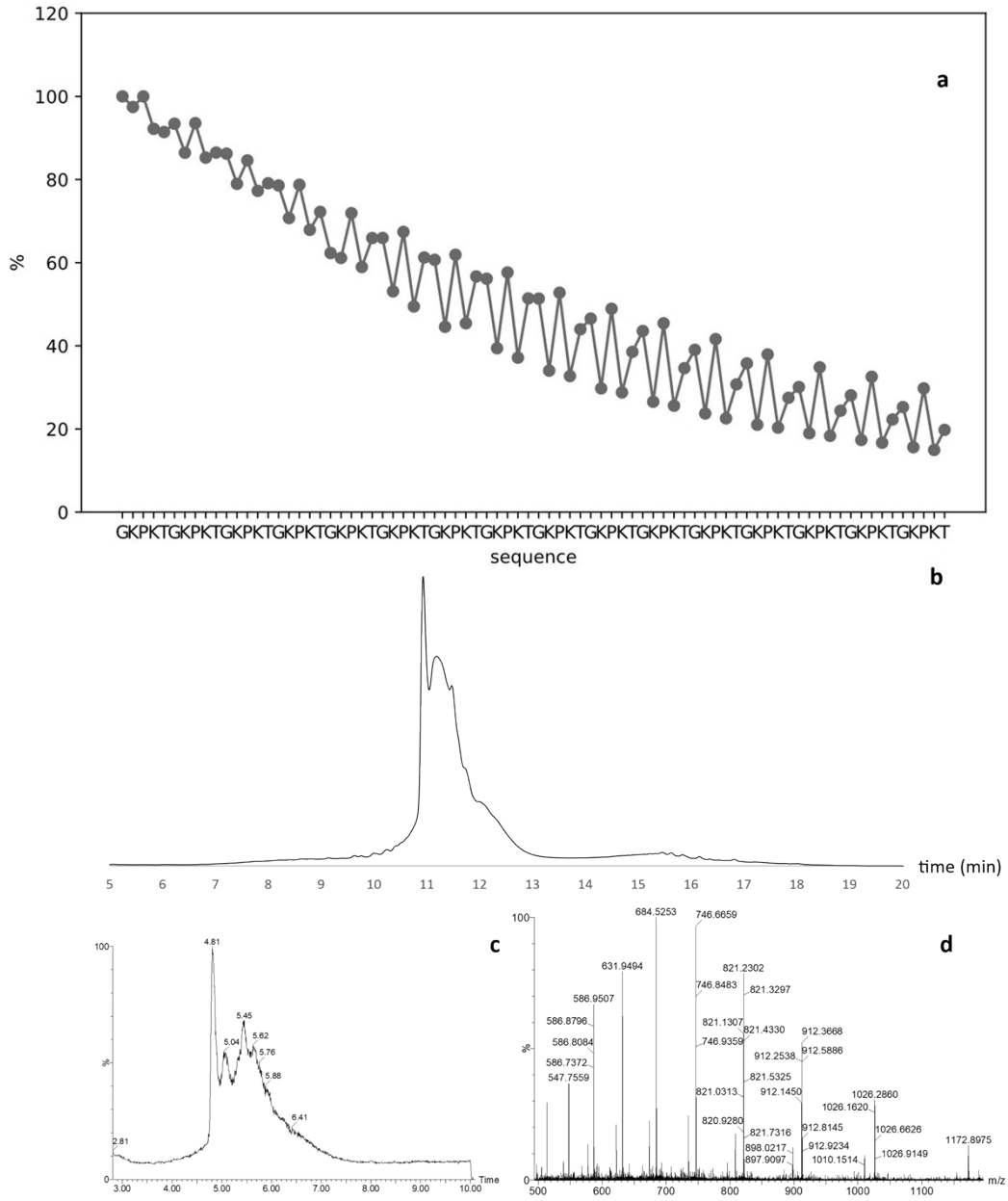
SFigure 8. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis synthesis of OT(P)50. **b)** The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of OT(P)50. **c)** The LC-MS profile (total ion chromatogram) of the crude OT(P)50, **d)** with the MS profile of the crude product (peak at 4.93 min.). Measured ions *e.g.* 734.3124: $[M + 7H]^{7+}$, 642.6480: $[M + 8H]^{8+}$ give $Mw^{obs.}$= 5133.18 Da, in good agreement with its calculated counterpart: Mw^{calc}= 5133.25 Da. (**STable 2)**



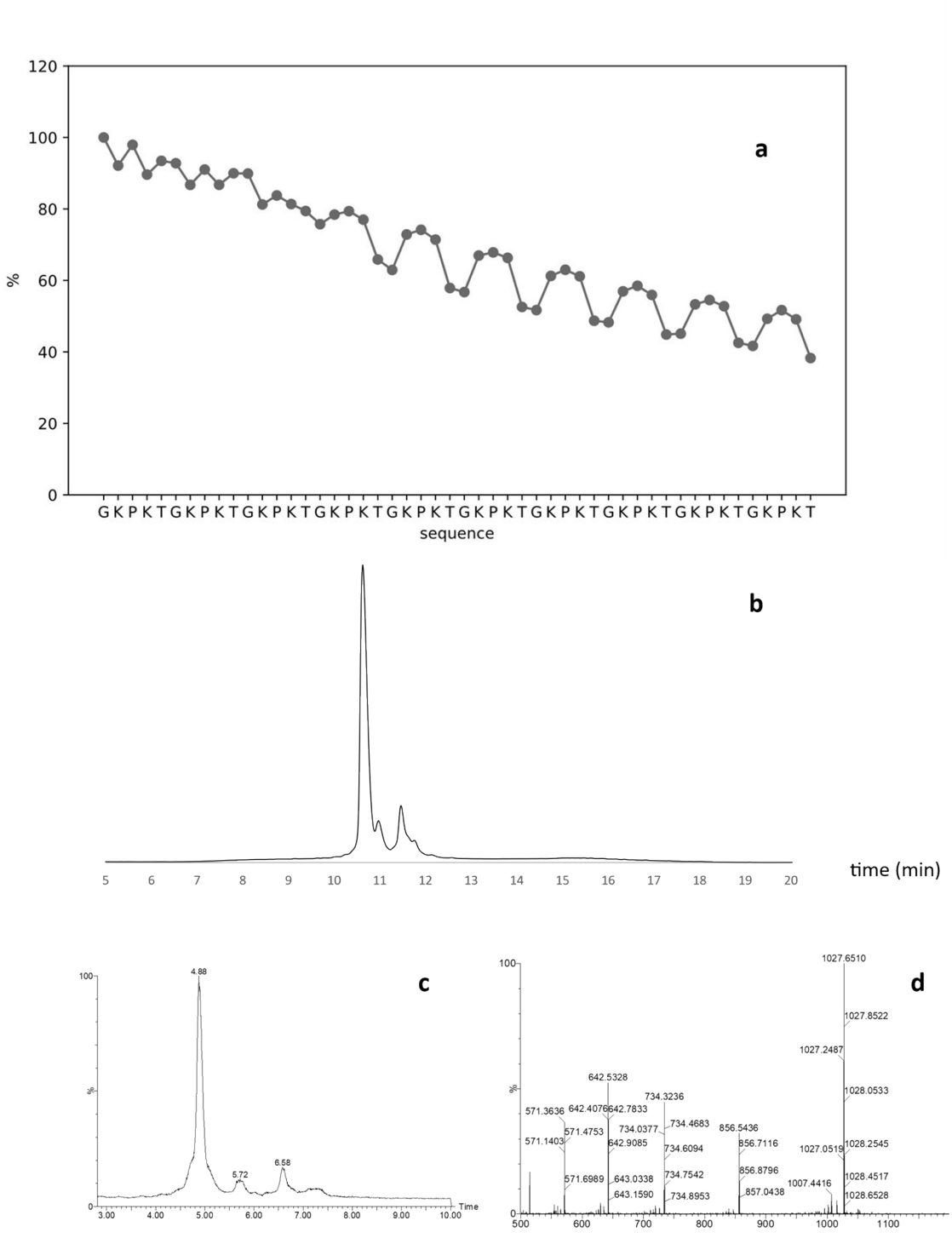
SFigure 9. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of OT(P)60. **b)** The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of OT(P)60, **c)** The LC-MS profile (total ion chromatogram) of the crude OT(P)60, **d)** with the MS profile of the crude product (peak at 5.26 min.). Measured ions *e.g.* 1027.1460: $[M + 6H]^{6+}$, 880.5543: $[M + 7H]^{7+}$ give $Mw^{obs.}$ = 6156.88 Da, in good agreement with its calculated counterpart: Mw^{calc}= 6156.47 Da. (**STable 2)**



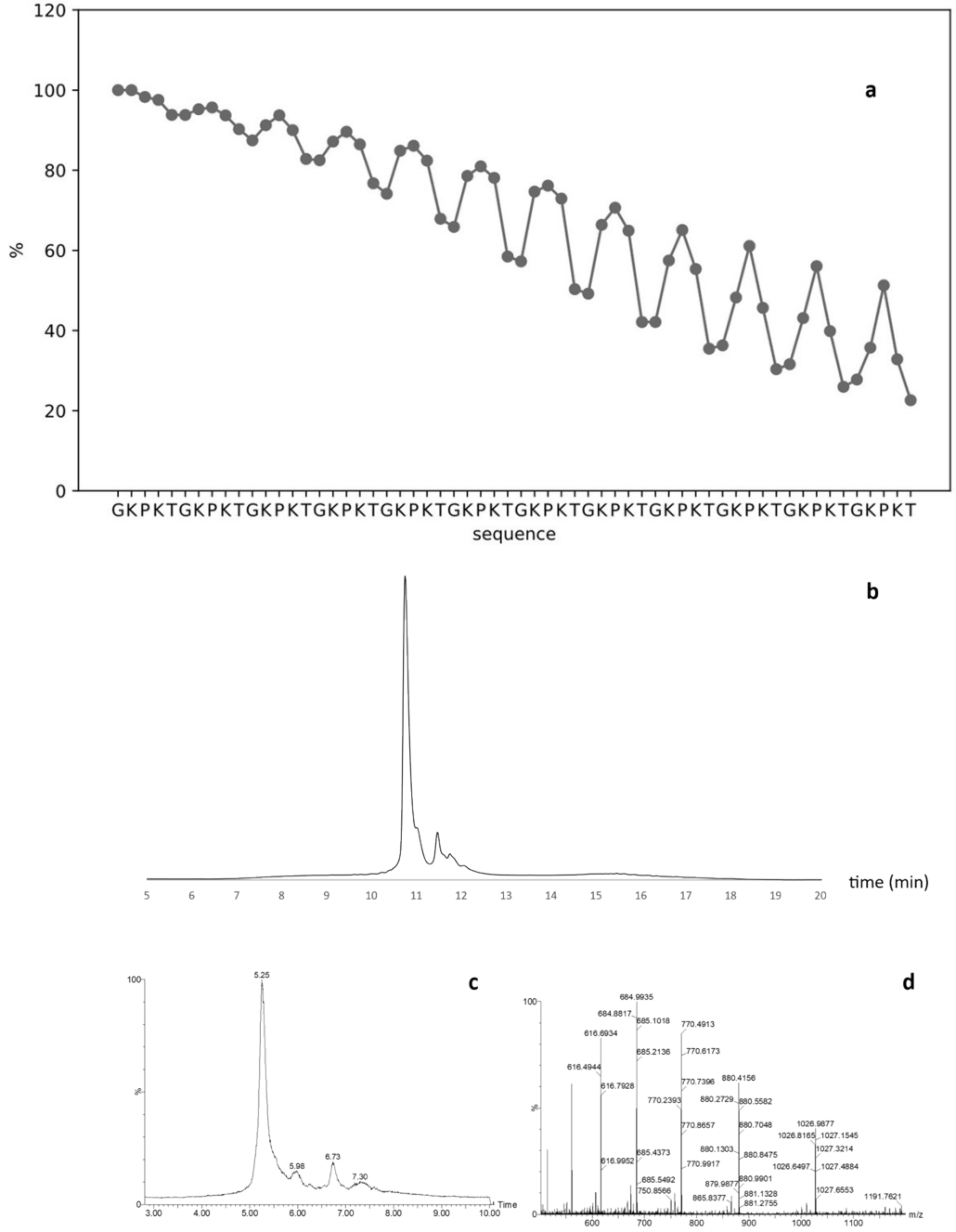
SFigure 10. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of OT(P)70, **b)** The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of OT(P)70, **c)** The LC-MS profile (total ion chromatogram) of the crude OT(P)70, **d)** with the MS profile of the crude product (peak at 4.71 min.). Measured ions *e.g.* 718.9553: $[M + 10H]^{10+}$, 653,6852: $[M + 11H]^{11+}$ give $Mw^{obs.}$= 7179.54 Da, in good agreement with its calculated counterpart: Mw^{calc}= 7179.74 Da. (**STable 2)**



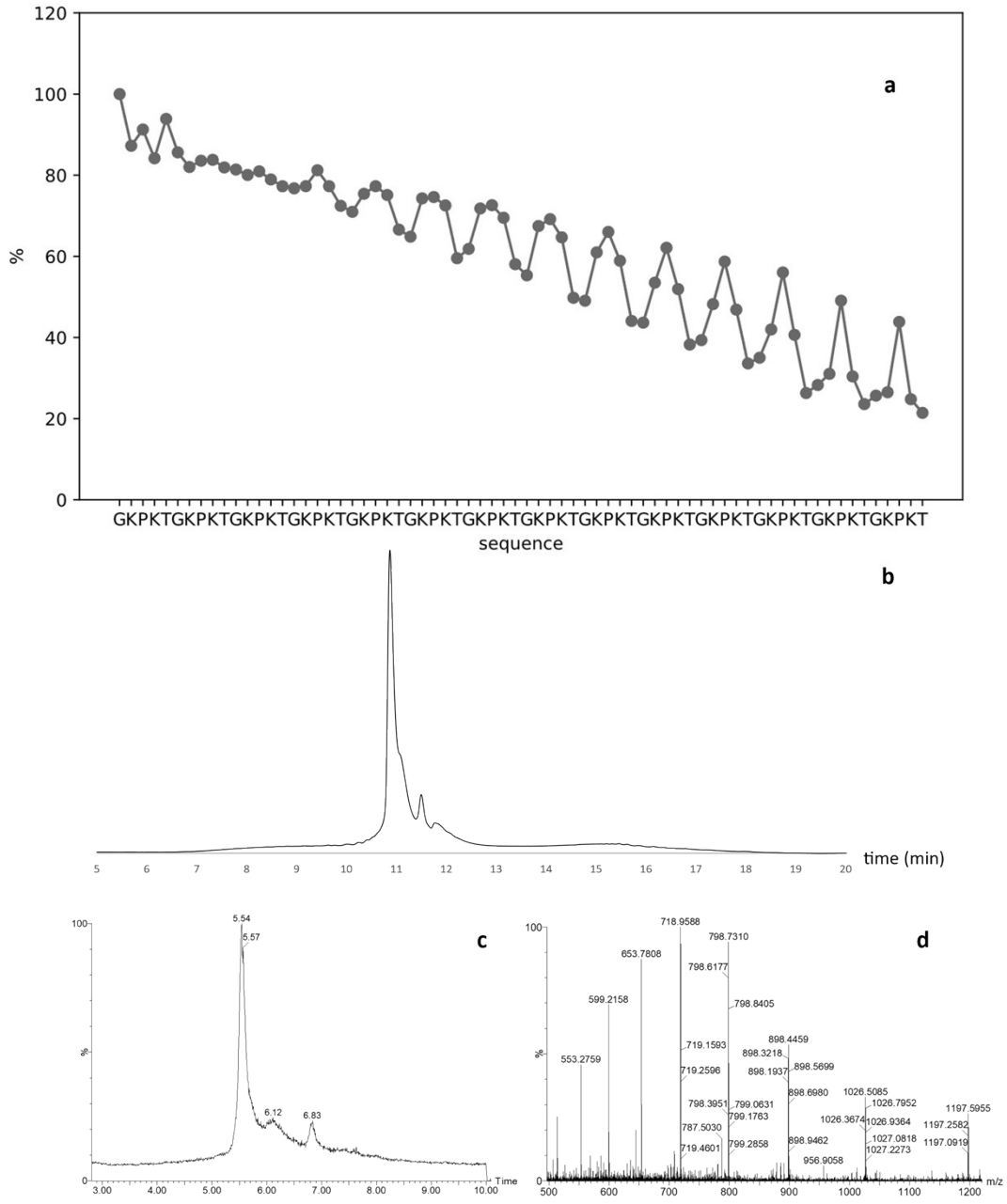
SFigure 11. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of OT(P)80. **b)** The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of OT(P)80, **c)** The LC-MS profile (total ion chromatogram) of the crude OT(P)80, **d)** with the MS profile of the crude product (peak at 4.81 min.). Measured ions *e.g.* 648.5253: $[M + 12H]^{12+}$, 746.6659: $[M + 11H]^{11+}$give $Mw^{obs.}$= 8202.30 Da, in good agreement with its calculated counterpart: Mw^{calc}= 8202.99 Da. (**STable 2)**



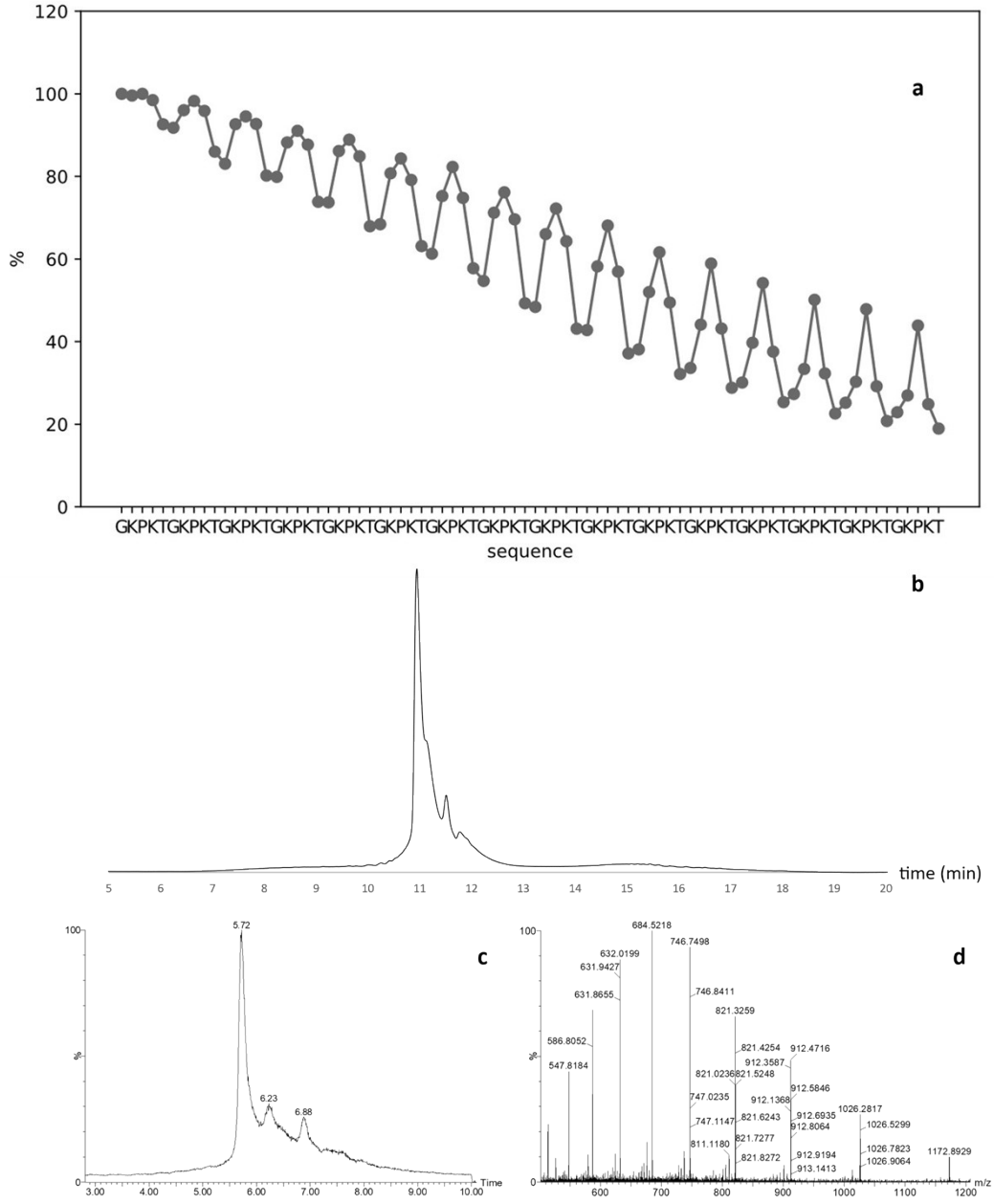
SFigure 12. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of OT(P)50[e]. **b)** The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of OT(P)50 [e] **c)** The LC-MS profile (total ion chromatogram) of the crude OT(P)50[e], **d)** with the MS profile of the crude product (peak at 4.88 min.). Measured ions *e.g.* 1027.6510: $[M + 5H]^{5+}$, 856.5436: $[M + 6H]^{6+}$ give $Mw^{obs.}$ = 5133.25 Da, in good agreement with its calculated counterpart: Mw^{calc} = 5133.26 Da. (**STable 2)**



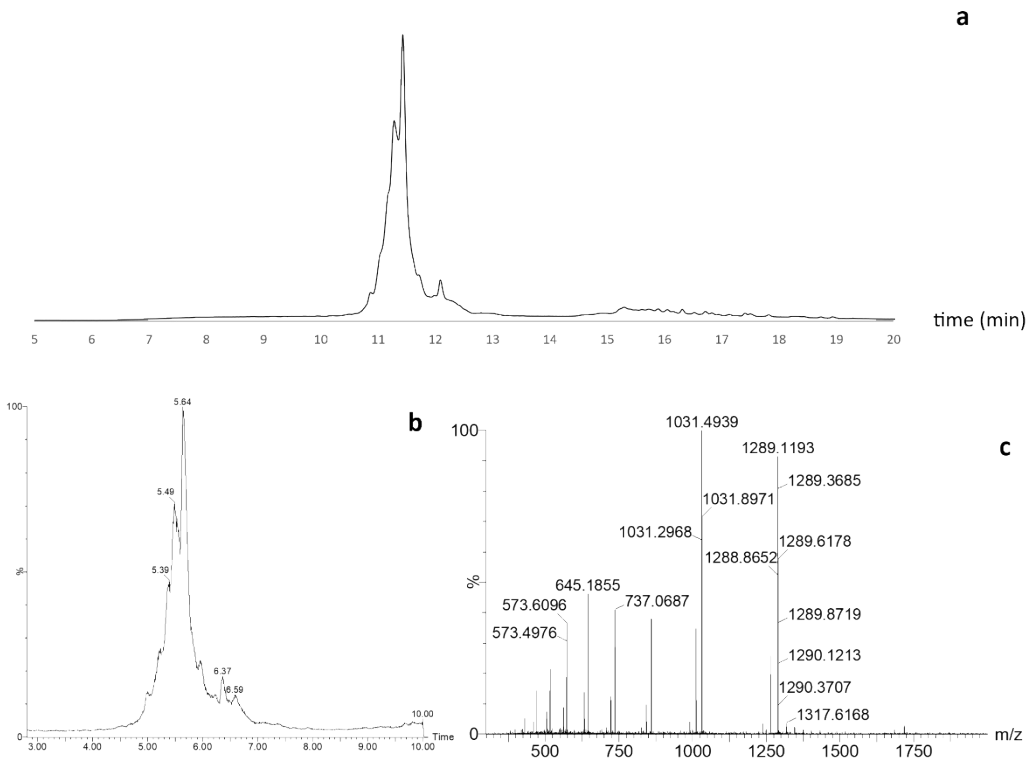
SFigure 13. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of OT(P)60[e]. **b)** The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of OT(P)60[e]. **c)** The LC-MS profile (total ion chromatogram) of the crude OT(P)60[e], **d)** with the MS profile of the crude product (peak at 5.25 min.). Measured ions *e.g.* 684.9935: $[M + 9H]^{9+}$, 770.4913: $[M + 8H]^{8+}$ give $Mw^{obs.}$= 6155.93 Da, in good agreement with its calculated counterpart: Mw^{calc}= 6156.47 Da. (**STable 2)**



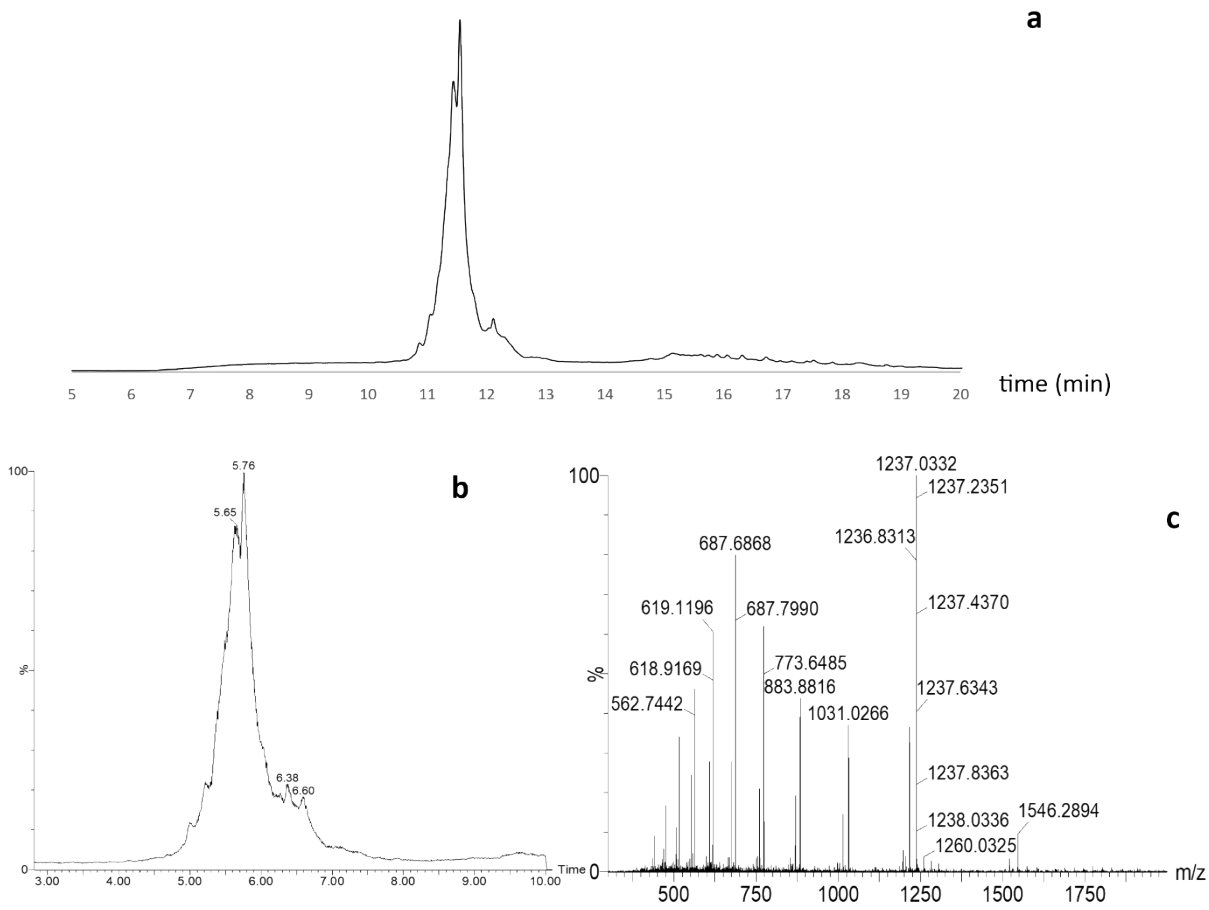
SFigure 14. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of OT(P)70^{e}. **b)** The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of OT(P)70^{e}, **c)** The LC-MS profile (total ion chromatogram) of the crude 70^{e}, **d)** with the MS profile of the crude product (peak at 5.54 min.). Measured ions *e.g.* 718.9588: $[M + 10H]^{10+}$, 798.7310: $[M + 9H]^{9+}$ give $Mw^{obs.}$= 7179.59 Da, in good agreement with its calculated counterpart: Mw^{calc}= 7179.71 Da. (**STable 2)**



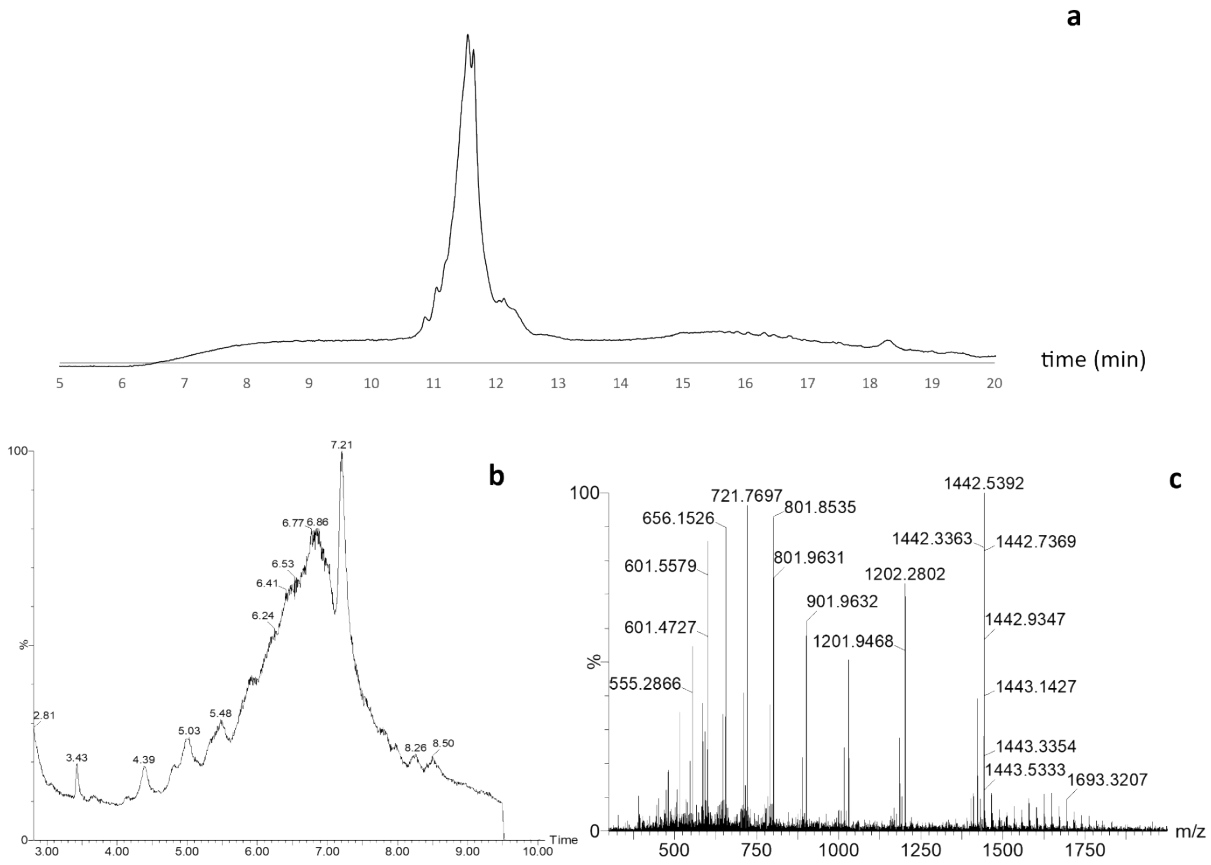
SFigure 15. a) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of OT(V)60^{e}. **b)** The LC-MS profile (total ion chromatogram) of the crude OT(V)60^{e}, **c)** with the MS profile of the crude product (peak at 5.76 min.). Measured ions *e.g.* 687.6868: $[M + 9H]^{9+}$, 1237.0332: $[M + 5H]^{5+}$ give $Mw^{obs.}$= 6180.18 Da, in good agreement with its calculated counterpart: Mw^{calc}= 6180.68 Da. (**STable 2)** of OT(P)80^{e}. **b)** The RP-HPLC chromatogram of the crude product of OT(P)80^{e}, **c)** The LC-MS profile (total ion chromatogram) of the crude OT(P)80^{e}, **d)** with the MS profile of the crude product (peak at 5.72 min.). Measured ions *e.g.* 684.5218: $[M + 12H]^{12+}$, 746.7498: $[M + 11H]^{11+}$ give $Mw^{obs.}$= 8202.26 Da, in good agreement with its calculated counterpart: Mw^{calc}= 8202.99 Da. (**STable 2)**



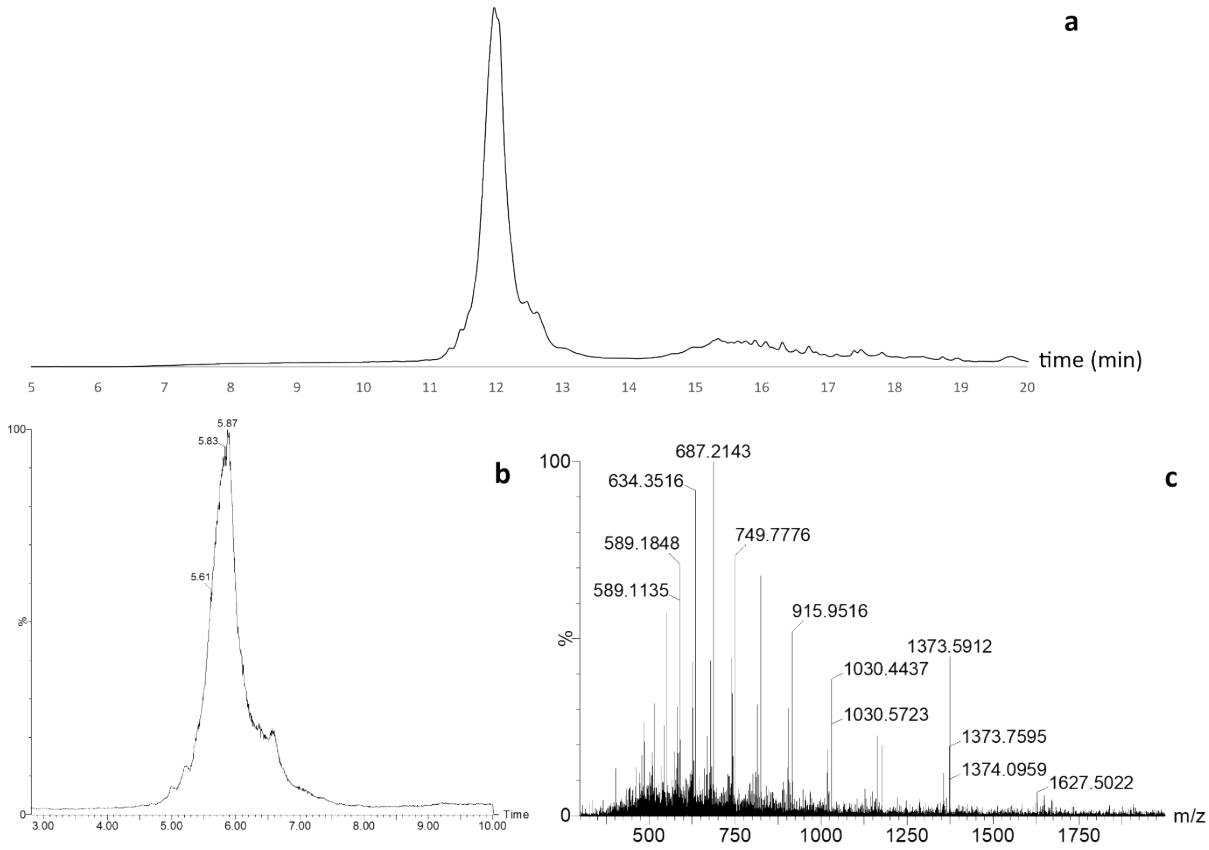
SFigure 16. a) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of OT(V)50^{e}. **b)** The LC-MS profile (total ion chromatogram) of the crude OT(V)50^{e}, **c)** with the MS profile of the crude product (peak at 5.64 min.). Measured ions *e.g.* 1031.4939: $[M + 5H]^{5+}$, 1289.1193: $[M + 4H]^{4+}$ give $Mw^{obs.}$= 5152.47 Da, in good agreement with its calculated counterpart: Mw^{calc}= 5153.41 Da. (**STable 2)**



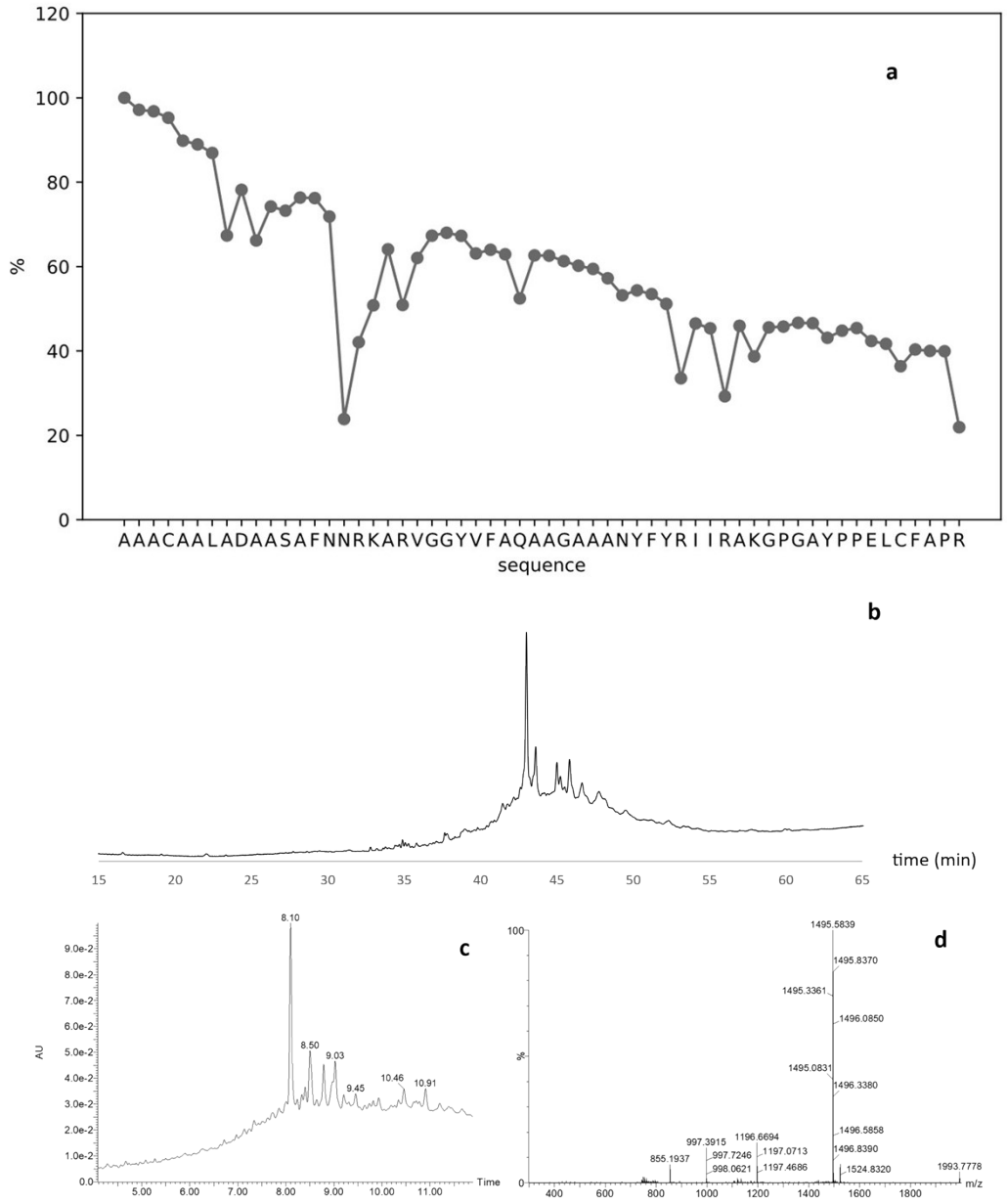
SFigure 17. a) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of OT(V)60^{e}. **b)** The LC-MS profile (total ion chromatogram) of the crude OT(V)60^{e}, **c)** with the MS profile of the crude product (peak at 5.76 min.). Measured ions *e.g.* 687.6868: $[M + 9H]^{9+}$, 1237.0332: $[M + 5H]^{5+}$ give $Mw^{obs.}$= 6180.18 Da, in good agreement with its calculated counterpart: Mw^{calc}= 6180.68 Da. (**STable 2)**



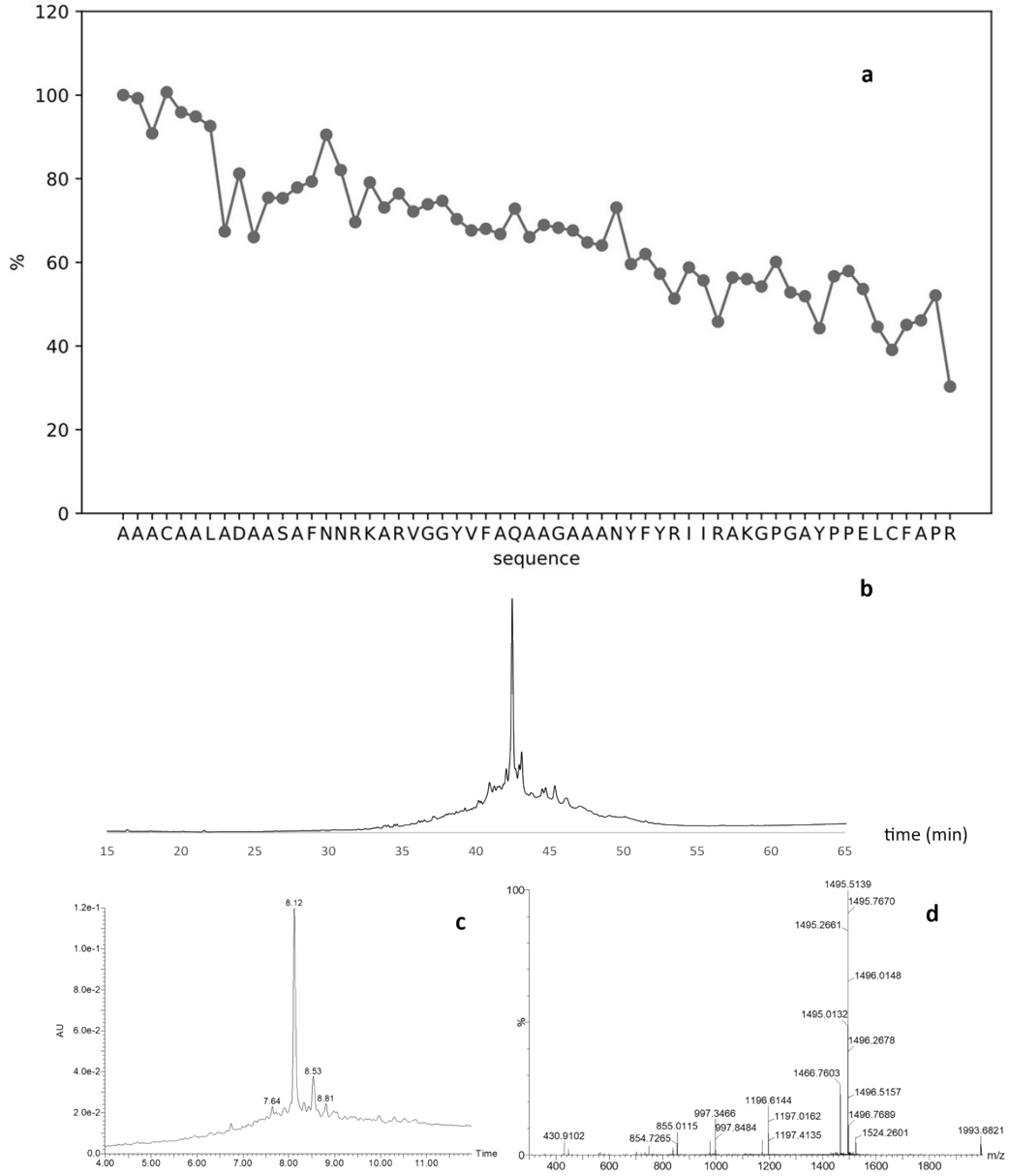
SFigure 18. a) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of OT(V)70^{e}. **b)** The LC-MS profile (total ion chromatogram) of the crude OT(V)70^{e}, **c)** with the MS profile of the crude product (peak at 7.21 min.). Measured ions *e.g.* 721.7697: $[M + 10H]^{10+}$, 801.8535: $[M + 9H]^{9+}$ give $Mw^{obs.}$ = 7207.70 Da, in good agreement with its calculated counterpart: Mw^{calc}= 7207.96 Da. (**STable 2)**



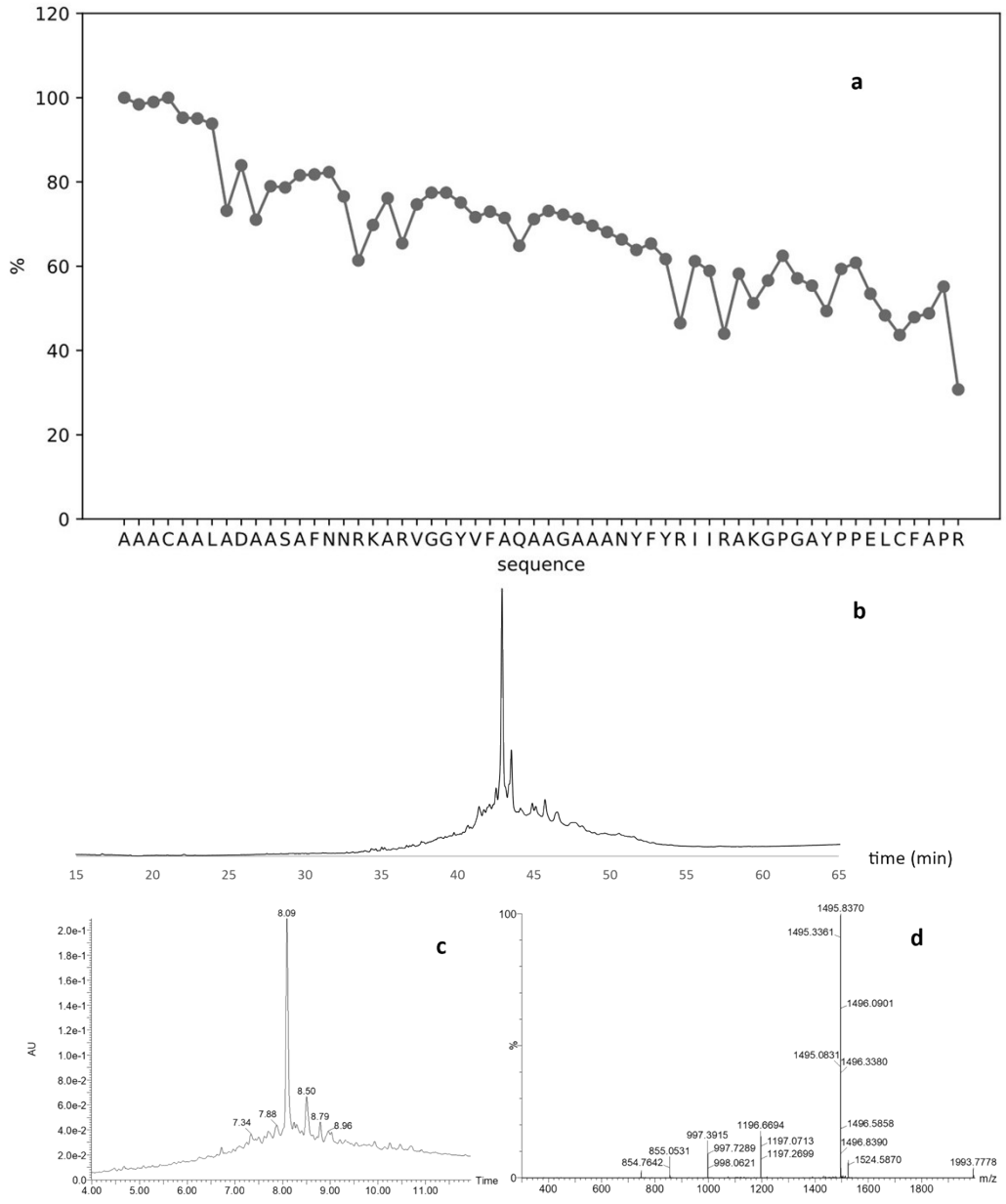
SFigure 19. a) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of OT(V)80^{e}. **b)** The LC-MS profile (total ion chromatogram) of the crude OT(V)80^{e}, **c)** with the MS profile of the crude product (peak at 5.87 min.). Measured ions *e.g.* 687.2143: $[M + 12H]^{12+}$ give $Mw^{obs.}$= 8234.57 Da, in good agreement with its calculated counterpart: Mw^{calc}= 8235.24 Da. **(STable 2)**



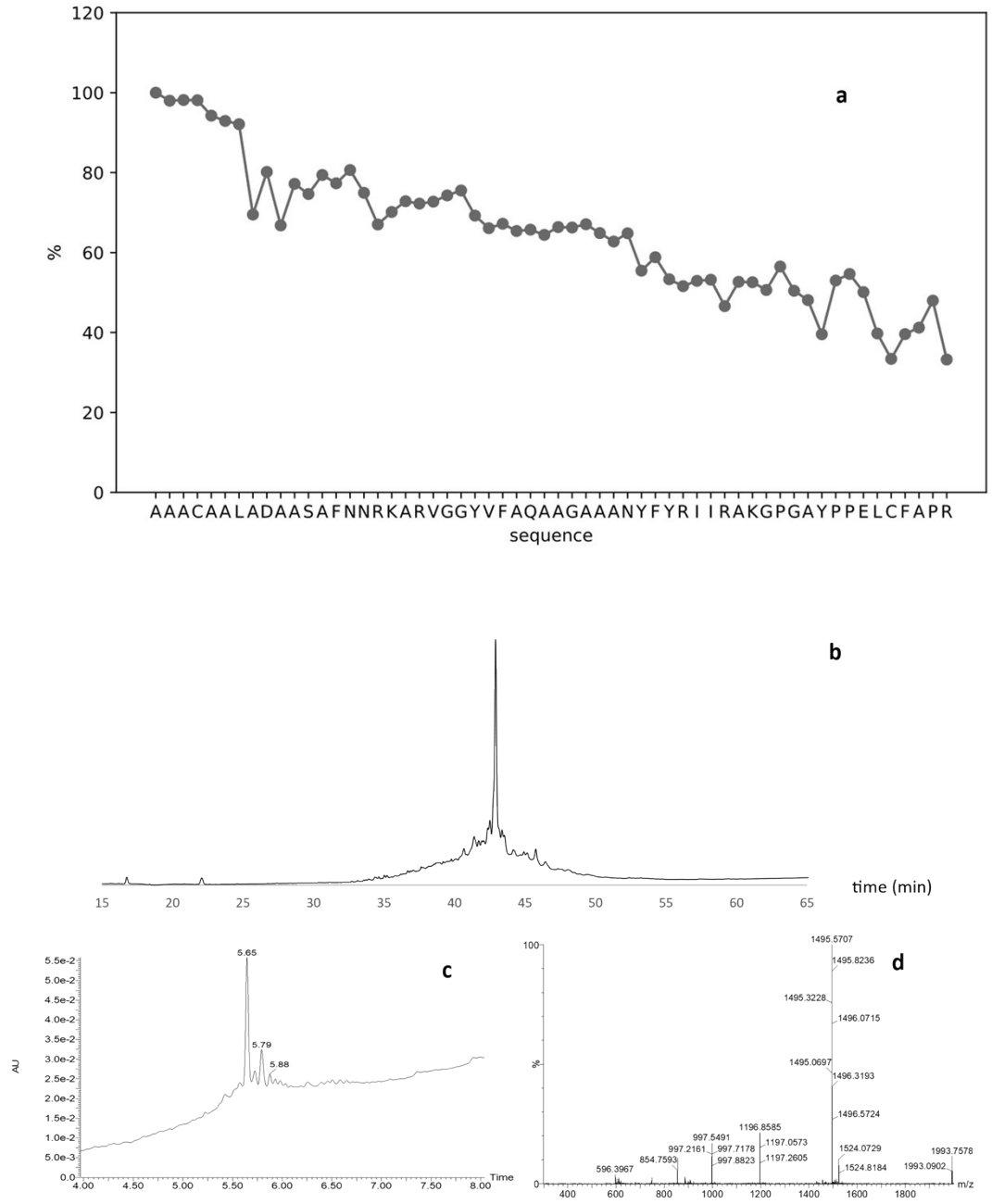
SFigure 20. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of BPTI: #1. **b**) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of BPTI: #1, **c**) The LC-MS profile of the crude BPTI: #1 with **d)** the MS profile of the crude product (peak at 8.10 min) belonging of BPTI: #1. Measured ions *e.g.*; 1196.6694: $[M + 5H]^{5+}$, 1495.5839: $[M + 4H]^{4+}$ give Mw^{obs} = 5978.33 Da, in good agreement with its calculated counterpart: Mw^{calc} = 5978.87 Da (**STable 3)**



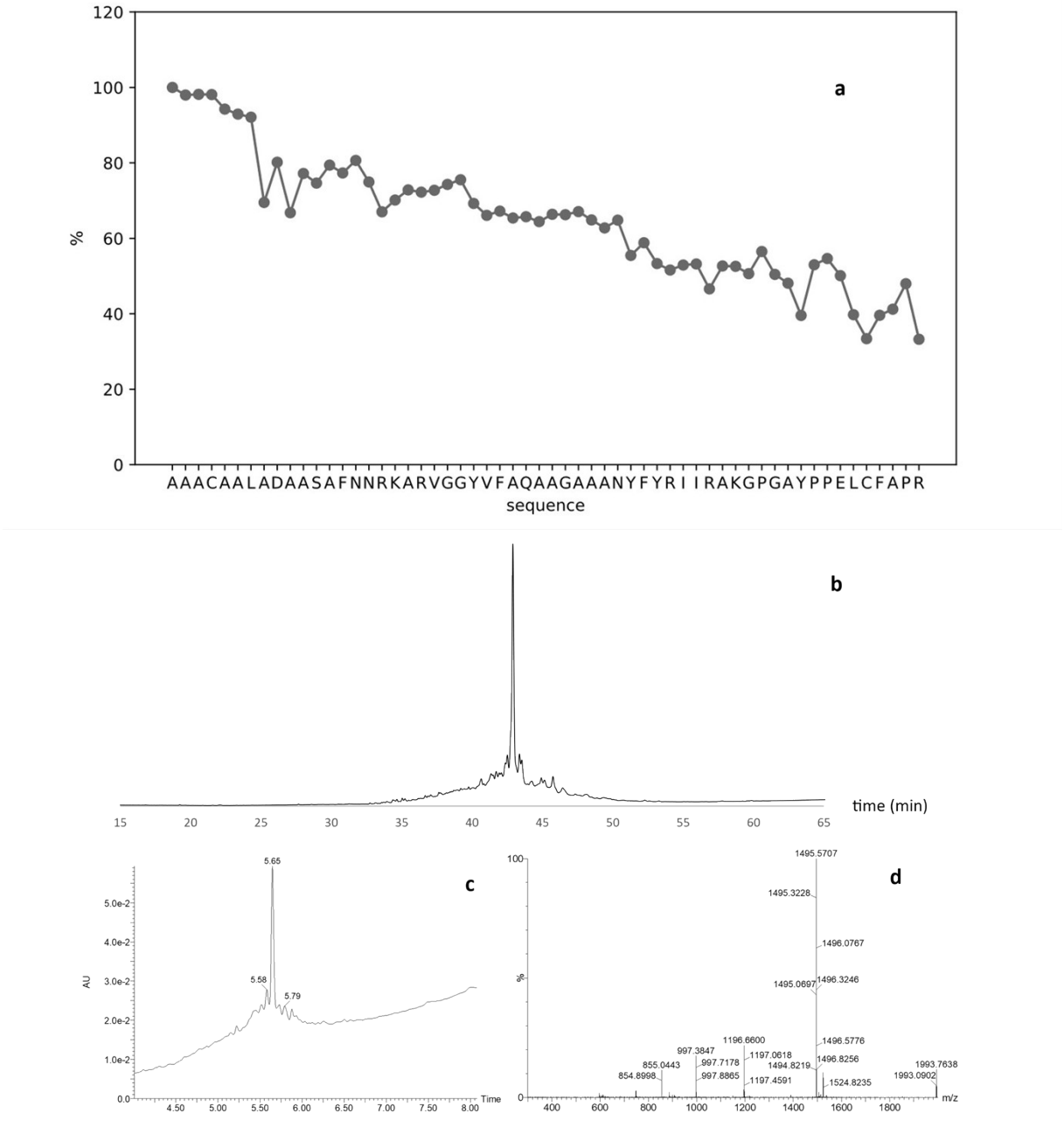
SFigure 21. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of BPTI: #2. **b**) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of BPTI: #2, **c**) The LC-MS profile of the crude BPTI: #2 with **d)** the MS profile of the crude product (peak at 8.12 min) belonging of BPTI: #2. Measured ions *e.g.*; 1196.6144: $[M + 5H]^{5+}$, 1495.5139: $[M + 4H]^{4+}$ give $Mw^{obs.}$= 5978.06 Da, in good agreement with its calculated counterpart: Mw^{calc}= 5978.87 Da (**STable 3)**



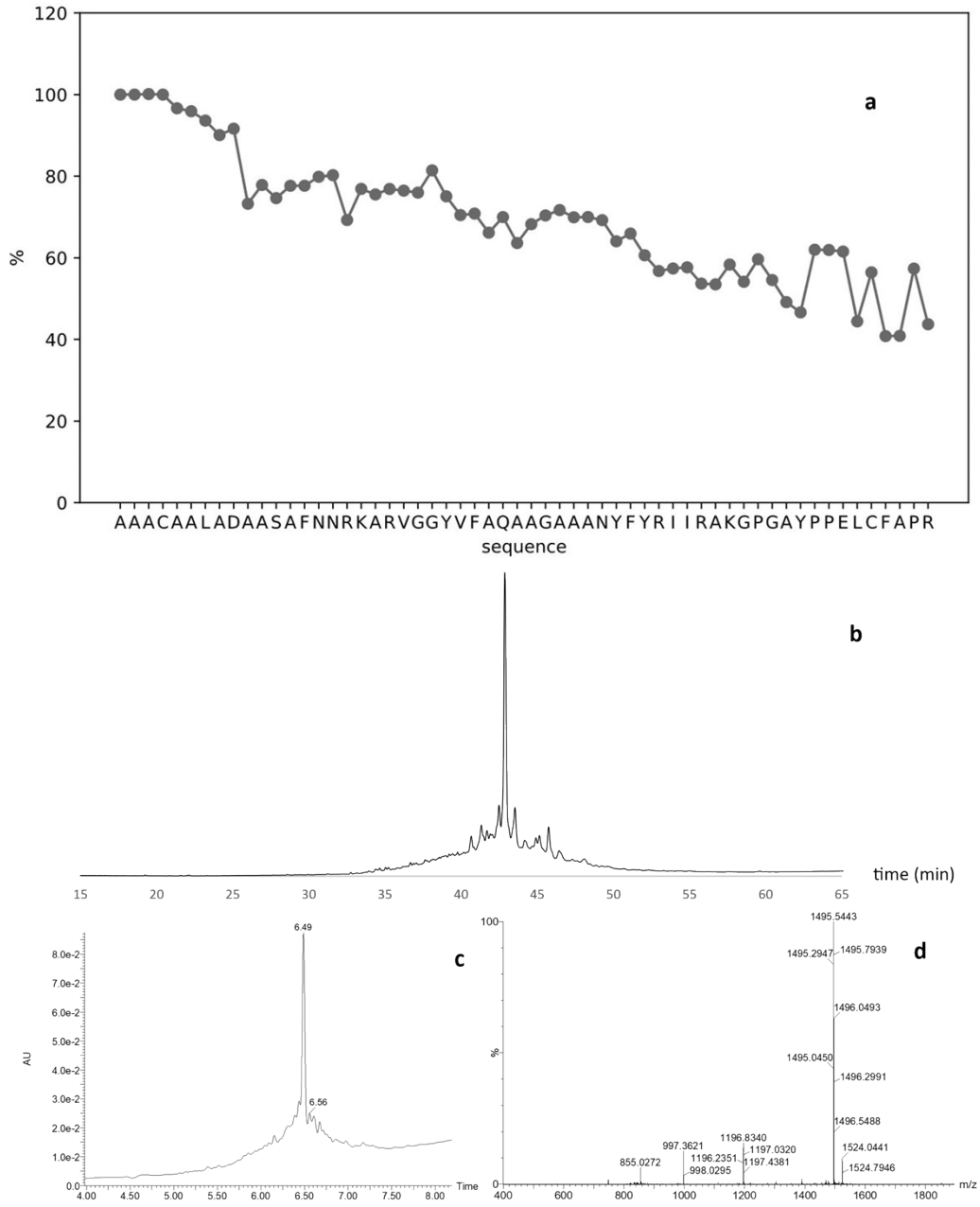
SFigure 22. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of BPTI: #3. **b**) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of BPTI: #3, **c**) The LC-MS profile of the crude BPTI: #3 with **d)** the MS profile of the crude product (peak at 8.09 min) belonging of BPTI: #3. Measured ions *e.g.*; 1196.6694: $[M + 3H]^{3+}$ give $Mw^{obs.}$= 5978.35 Da, in good agreement with its calculated counterpart: Mw^{calc}= 5978.87 Da (**STable 3)**



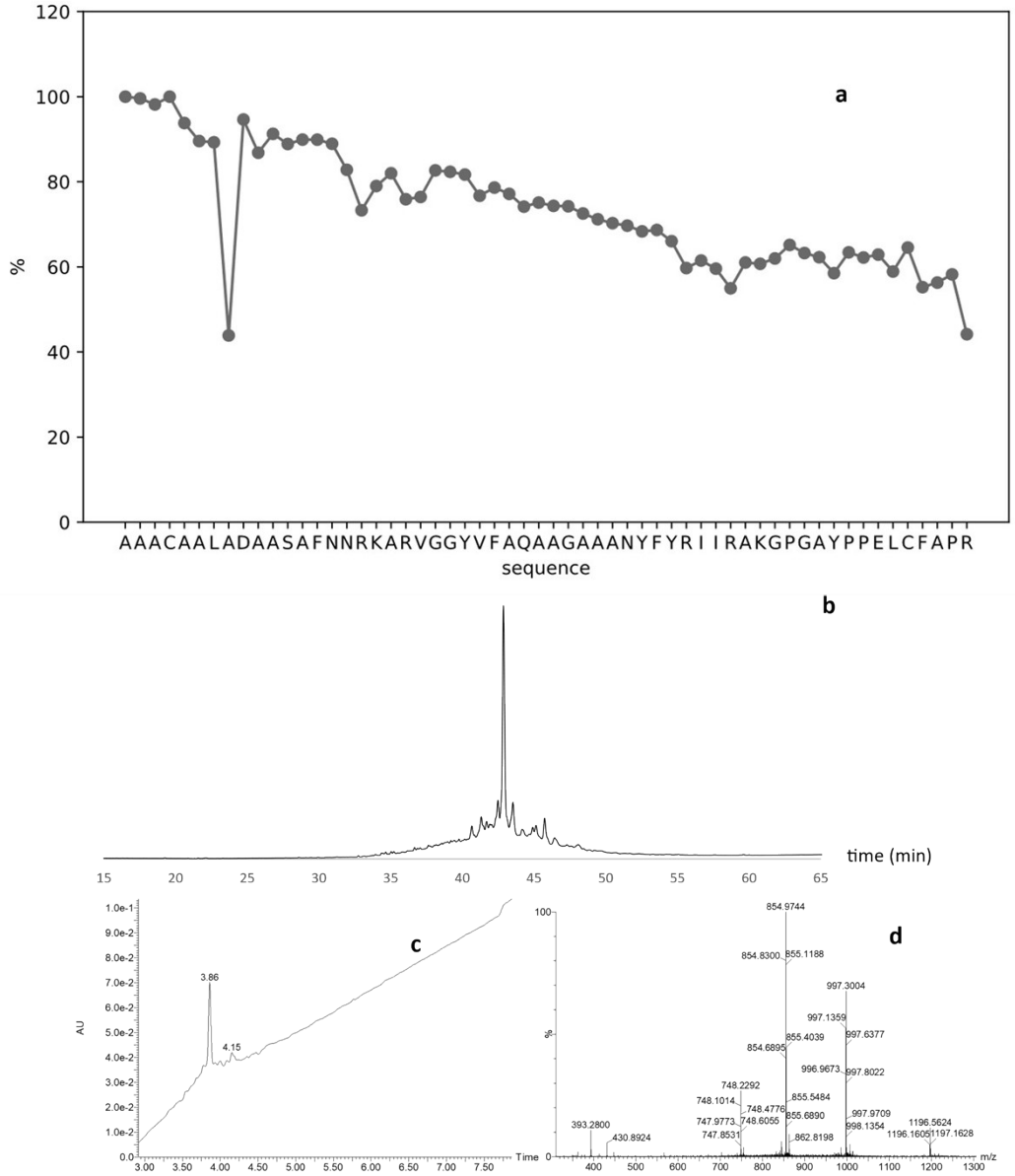
SFigure 23. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of BPTI: #4. **b**) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of BPTI: #4, **c**) The LC-MS profile of the crude BPTI: #4 with **d)** the MS profile of the crude product (peak at 5.65 min) belonging of BPTI: #4. Measured ions *e.g.* 1495.5707: $[M + 4H]^{4+}$ give $Mw^{obs.}$= 5978.28 Da, in good agreement with its calculated counterpart: Mw^{calc}= 5978.87 Da (**STable 3)**



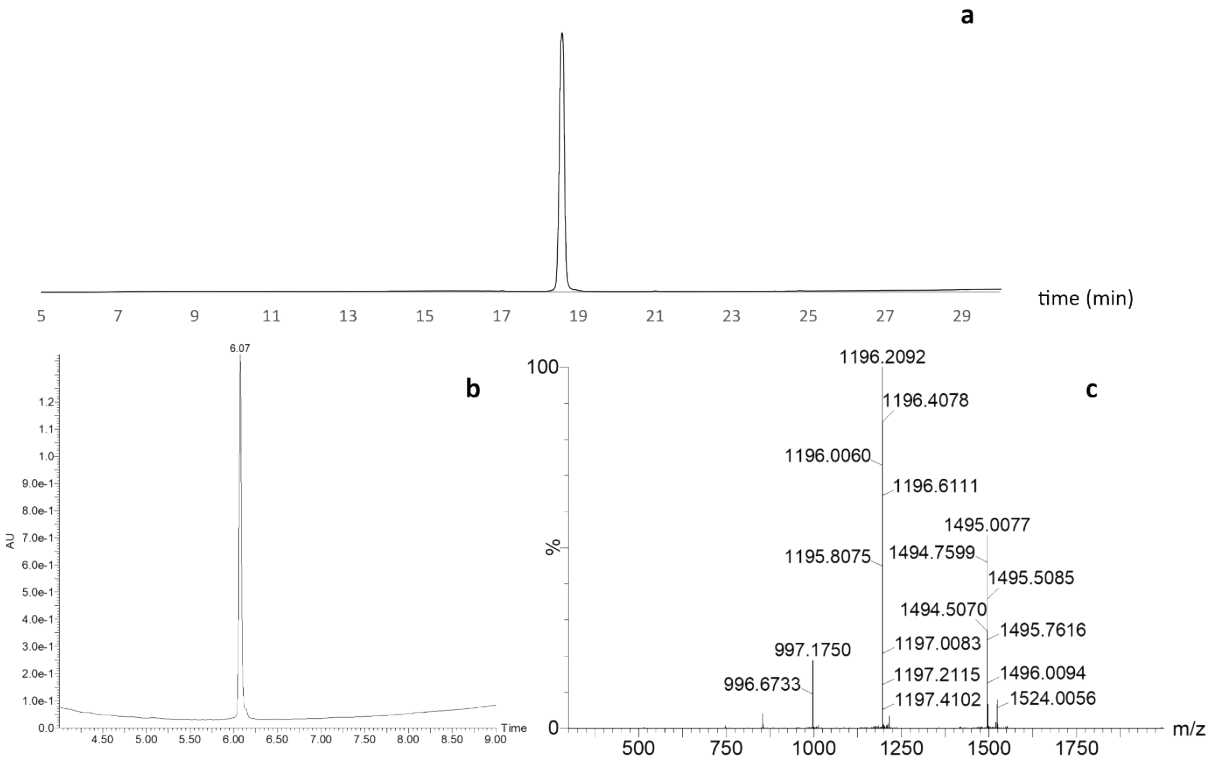
SFigure 24. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of BPTI: #5. **b**) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of BPTI: #5, **c**) The LC-MS profile of the crude BPTI: #5 with **d)** the MS profile of the crude product (peak at 5.65 min) belonging of BPTI: #5. Measured ions *e.g.*; 1196.6600: $[M + 5H]^{5+}$, 1495.5707: $[M + 4H]^{4+}$ give $Mw^{obs.}$= 5978.28 Da, in good agreement with its calculated counterpart: Mw^{calc}= 5989.87 Da (**STable 3)**



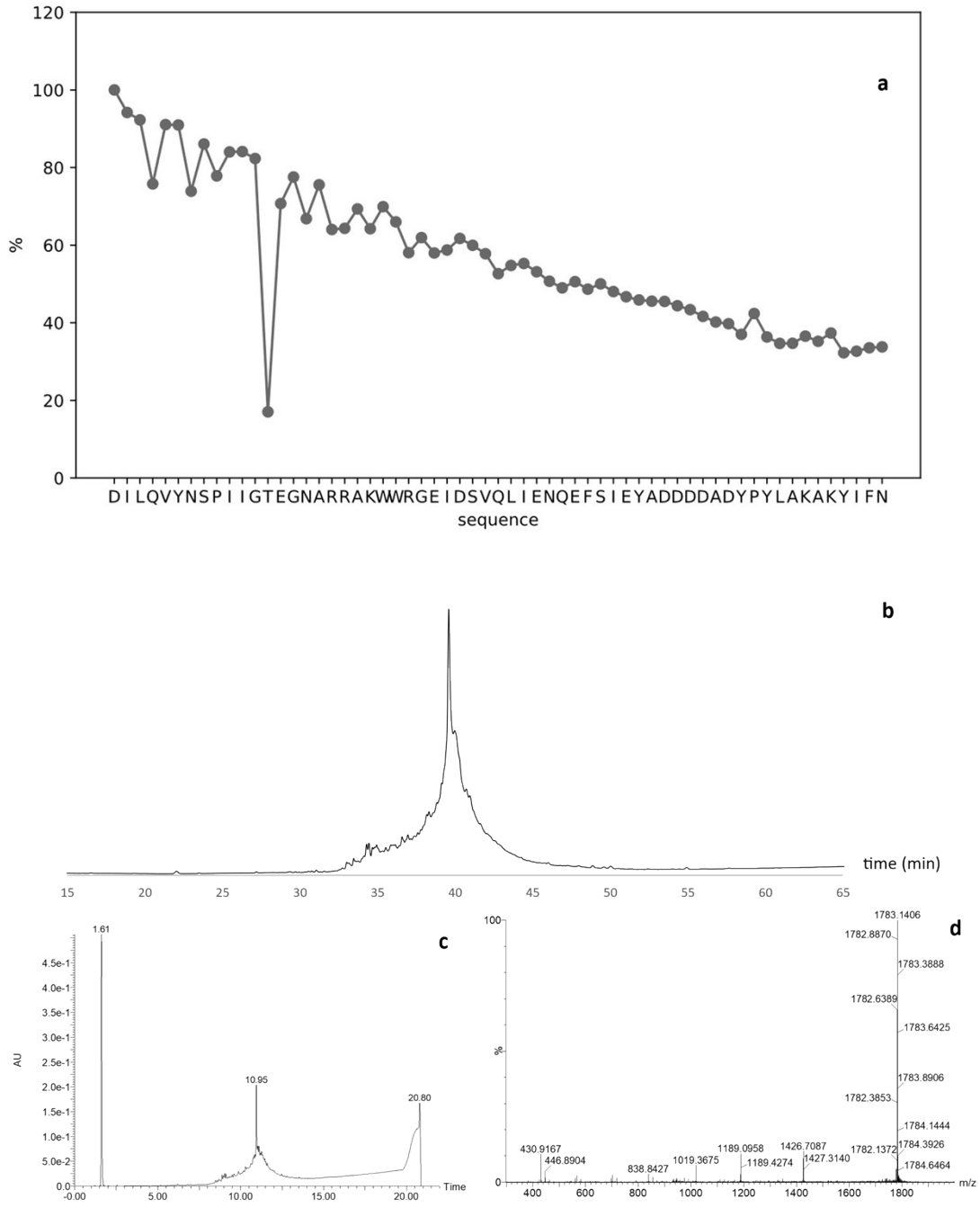
SFigure 25. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of BPTI: #6. **b**) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of BPTI: #6 , **c**) The LC-MS profile of the crude BPTI: #6 with **d)** the MS profile of the crude product (peak at 6.49 min) belonging of BPTI: #6. Measured ions *e.g.*; 1495.5443: $[M + 4H]^{4+}$ give $Mw^{obs.}$= 5978.18 Da, in good agreement with its calculated counterpart: Mw^{calc}= 5978.87 Da (**STable 3)**



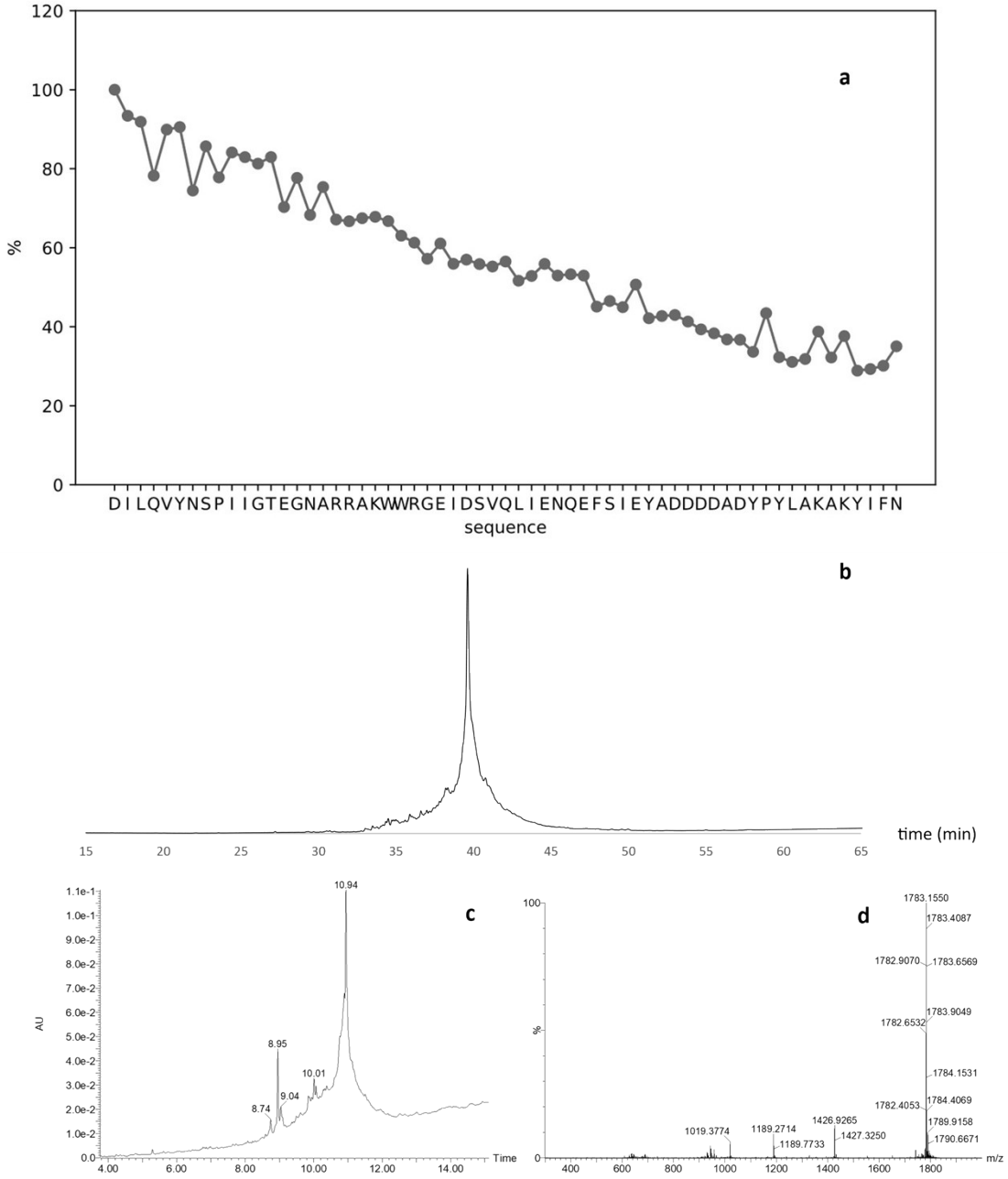
SFigure 26. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of BPTI: #7, **b**) The RP-HPLC chromatogram of the crude product of BPTI: #7, **c**) The LC-MS of the crude BPTI: #7 with **d)** the MS profile of the crude product (peak at 3.86 min) belonging of BPTI: #7. Measured ions *e.g.*; 1196.5624: $[M + 5H]^{5+}$, 997.3004: $[M + 6H]^{6+}$ give $Mw^{obs.}$= 5977.81 Da, in good agreement with its calculated counterpart: Mw^{calc}= 5978.87 Da (**STable 3)**.



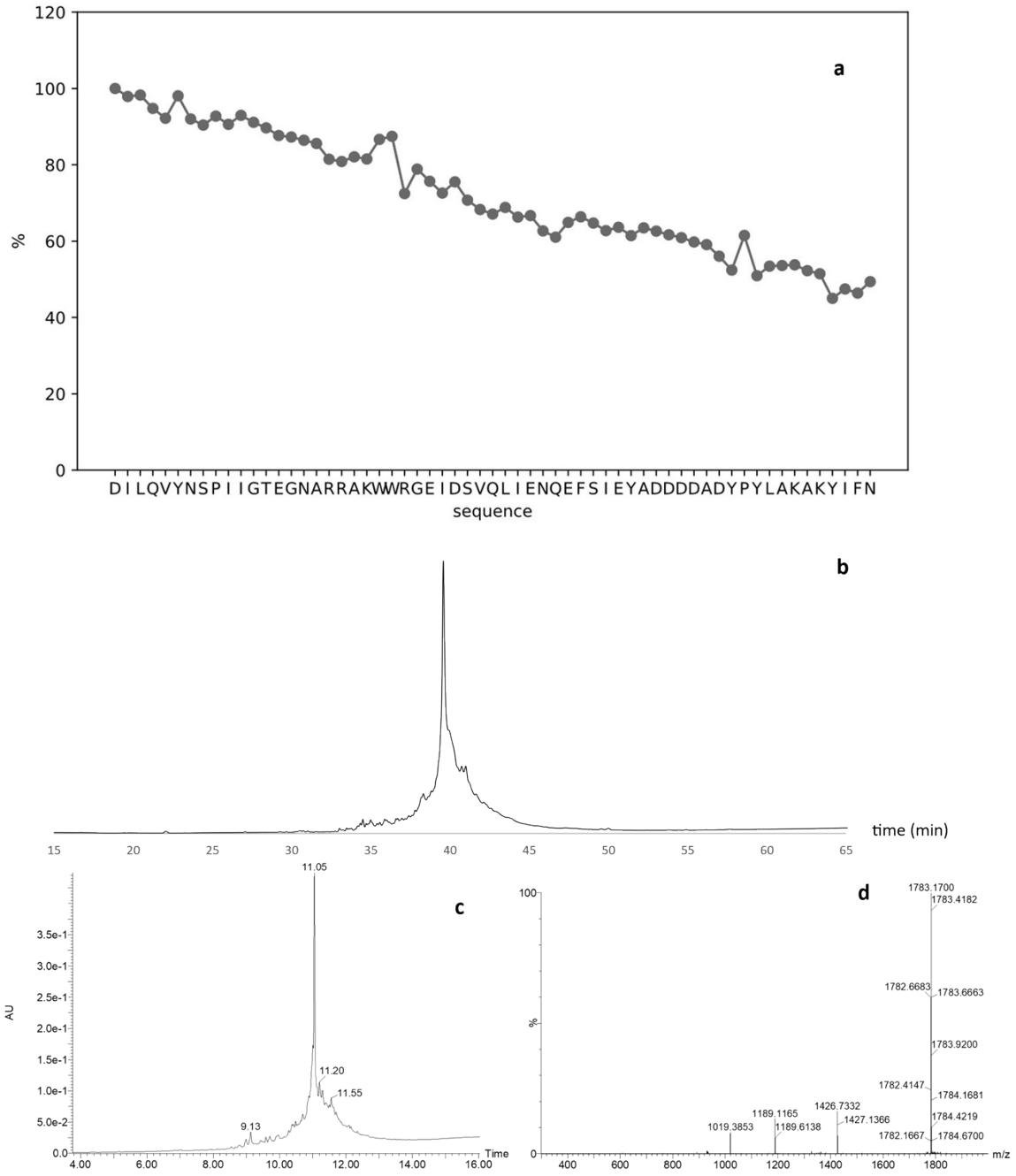
SFigure 27. a) The RP-HPLC chromatogram of the HPLC purified and cyclized BPTI. **b**) The LC-MS of the pure cyclized BPTI **c)** the MS profile of the product (peak at 6.07 min). Measured ions *e.g.*; 1196.2092: $[M + 5H]^{5+}$, 1495.0077: $[M + 4H]^{4+}$ give $Mw^{obs.}$= 5976.05 Da, in good agreement with its calculated counterpart: Mw^{calc}= 5976.86 Da.



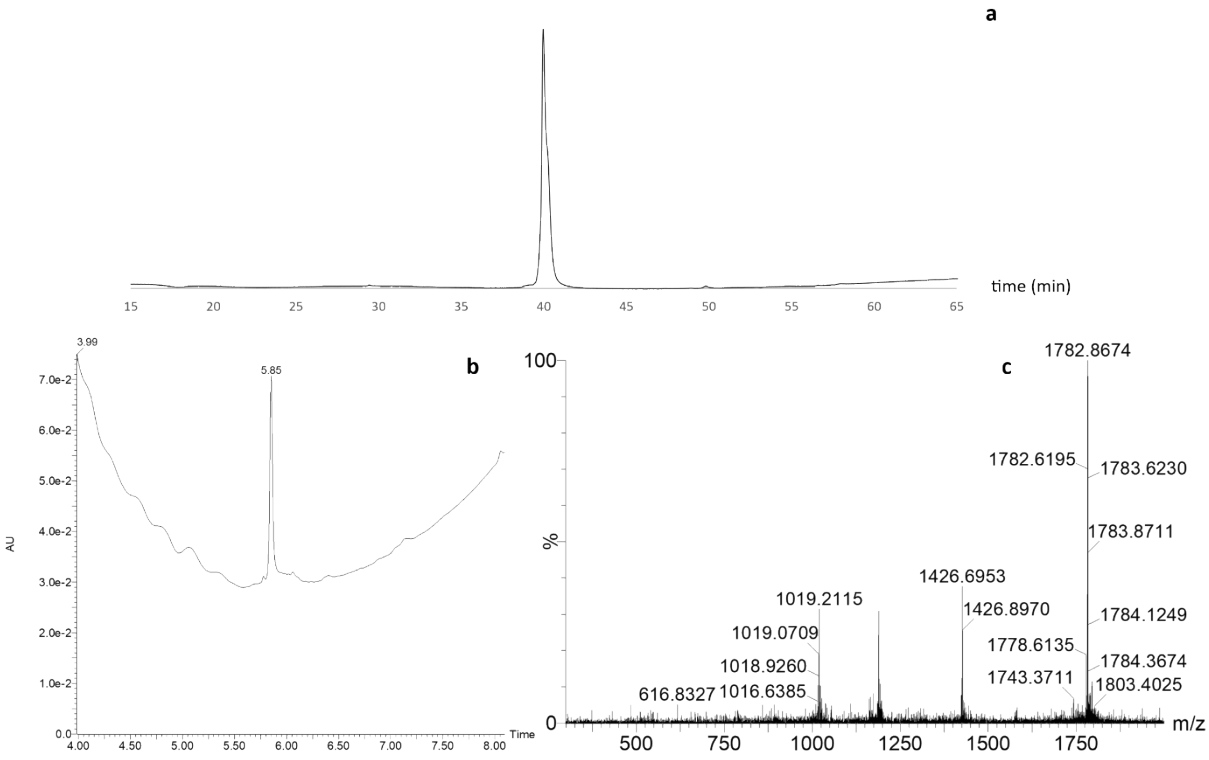
SFigure 28. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of SH3: #1. **b**) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of SH3: #1 , **c**) The LC-MS profile of the crude SH3: #1 with **d)** the MS profile of the crude product (peak at 10.95 min) belonging of SH3: #1. Measured ions *e.g.*; 1426.7087: $[M + 5H]^{5+}$ give Mw^{obs} = 7128.54 Da, in good agreement with its calculated counterpart: Mw^{calc}= 7128.84 Da (**STable 4).**



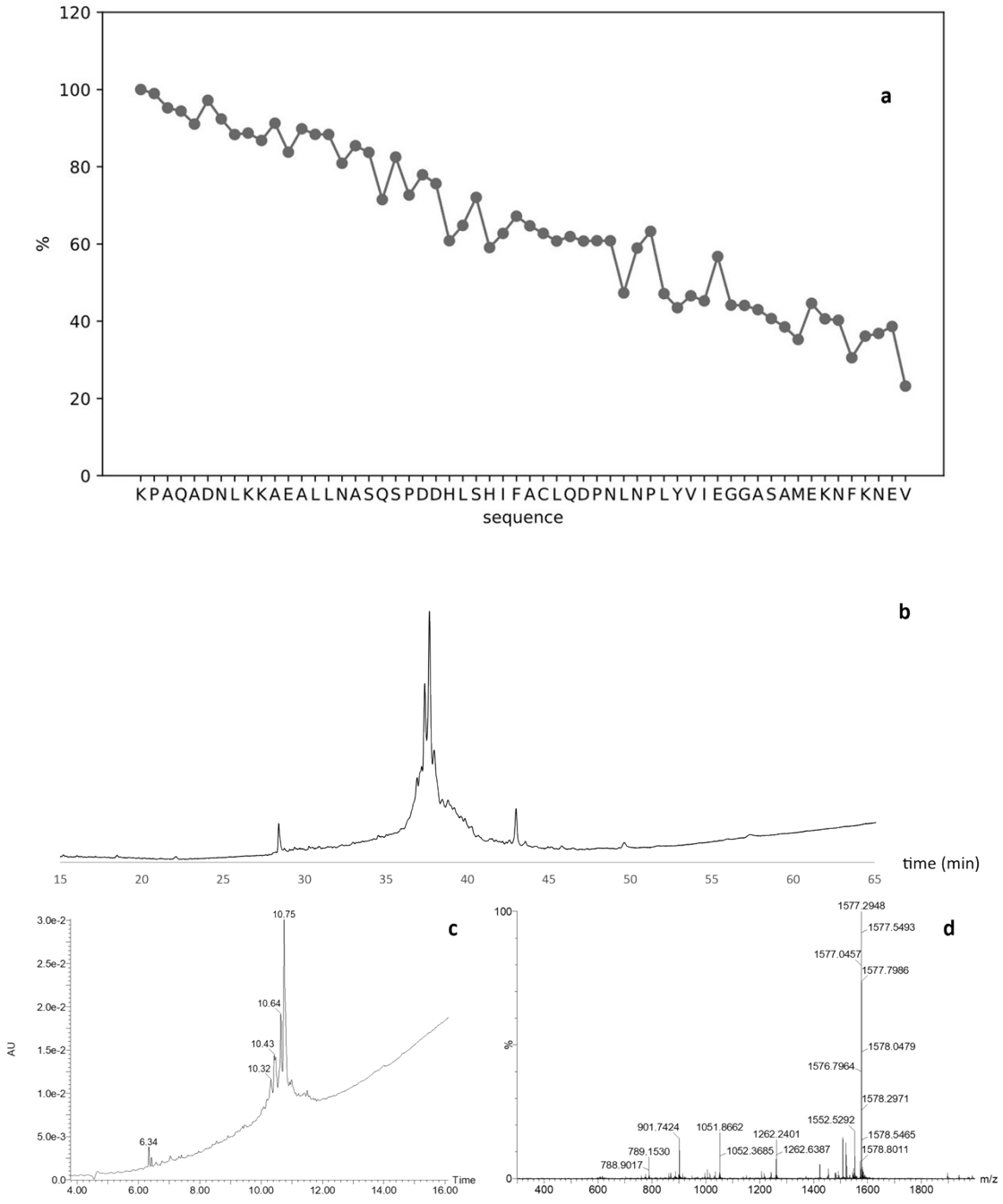
SFigure 29. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of SH3: #2. **b**) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of SH3: #2 , **c**) The LC-MS profile of the crude SH3: #2 with **d)** the MS profile of the crude product (peak at 10.94 min) belonging of SH3: #2. Measured ions *e.g.*; 1783.1550: $[M + 4H]^{4+}$ give Mw^{obs} = 7128.62 Da, in good agreement with its calculated counterpart: Mw^{calc}= 7128.84 Da (**STable 4).**



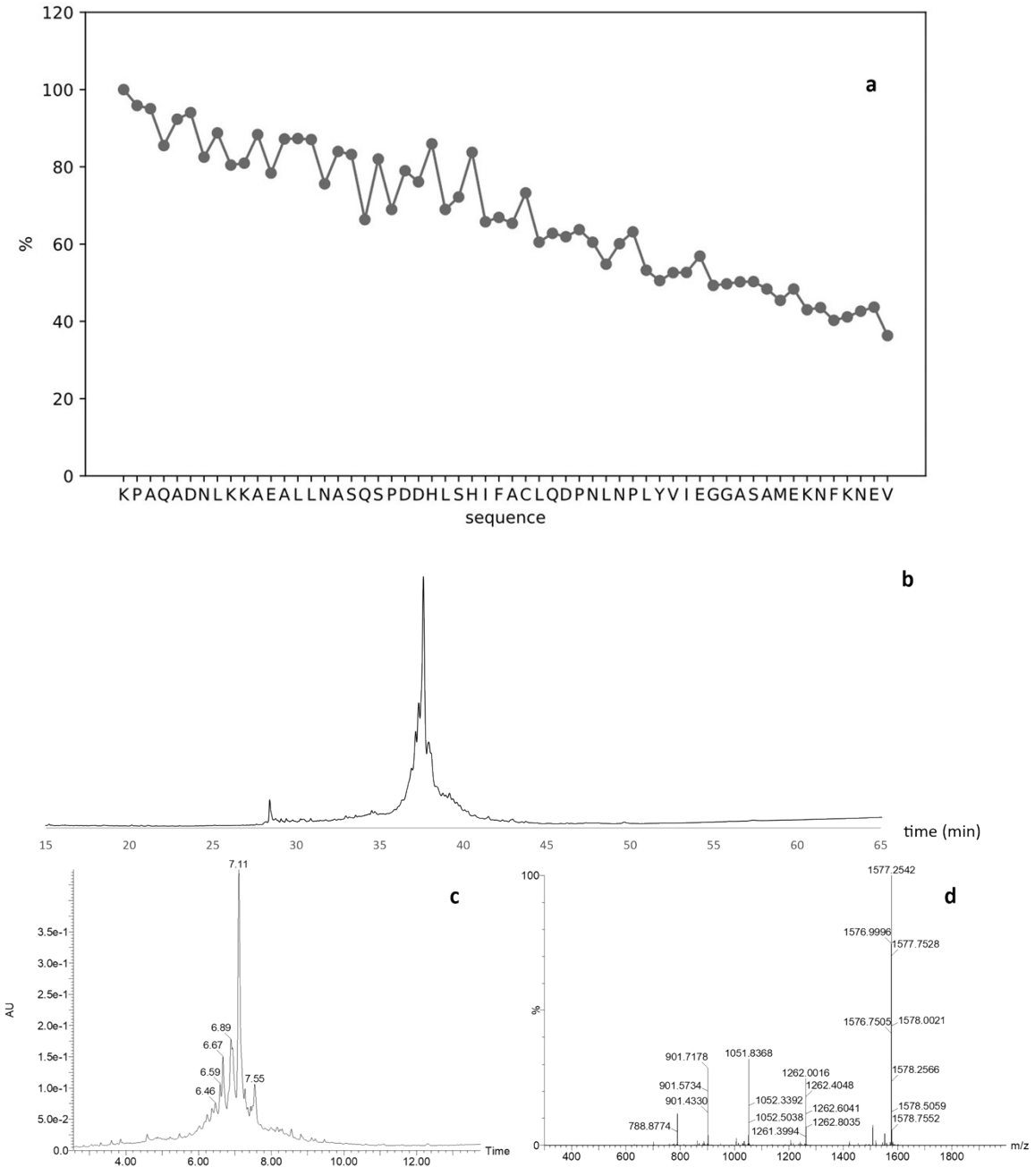
SFigure 30. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of SH3: #3. **b**) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of SH3: #3 , **c**) The LC-MS profile of the crude SH3: #3 with **d)** the MS profile of the crude product (peak at 10.95 min) belonging of SH3: #3. Measured ions *e.g.*; 1783.1700: $[M + 4H]^{4+}$ give Mw^{obs} = 7128.68 Da, in good agreement with its calculated counterpart: Mw^{calc}= 7128.84 Da (**STable 4).**



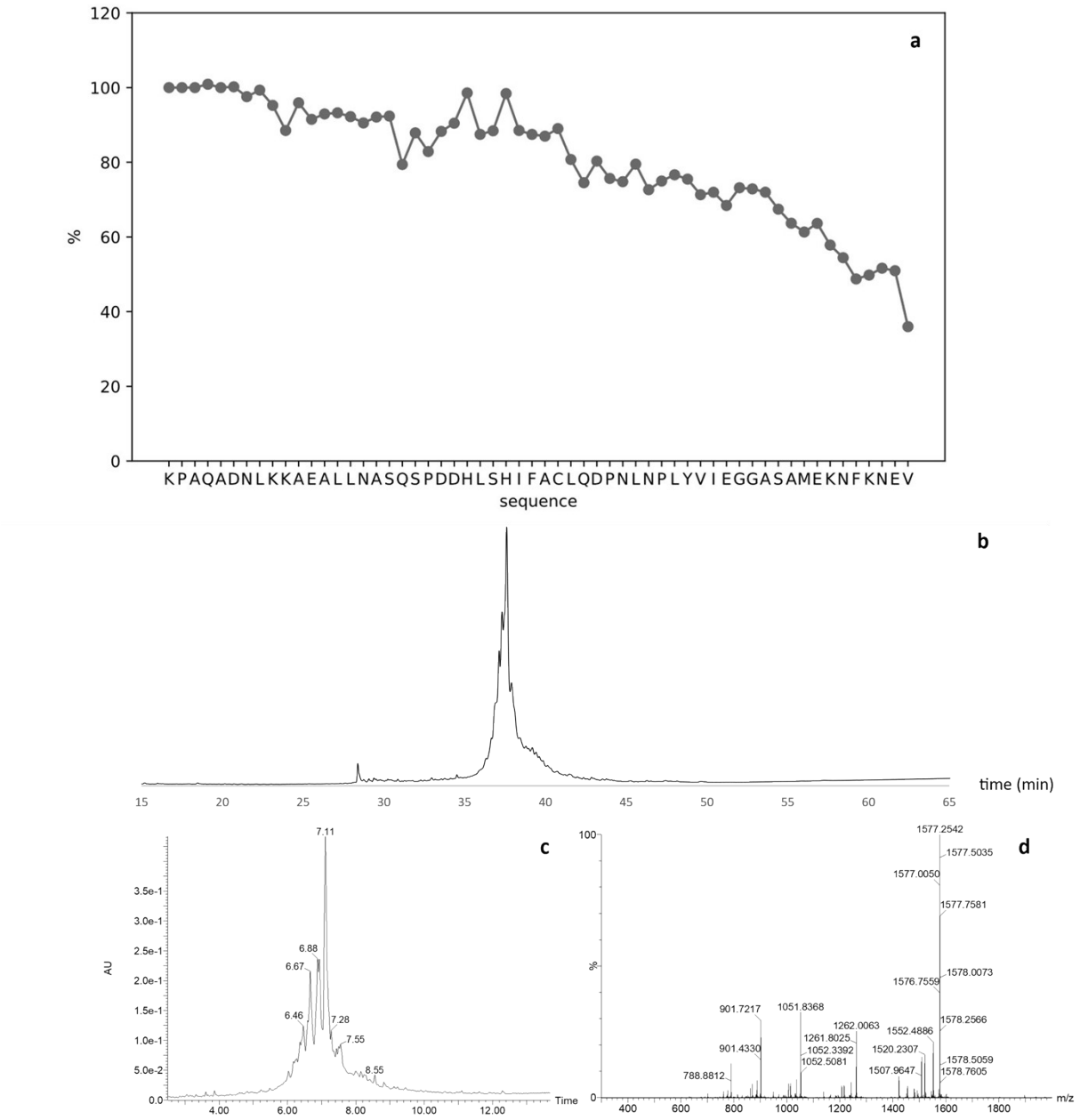
SFigure 31. a) The RP-HPLC chromatogram of the HPLC purified SH3. **b**) The LC-MS of the pure SH3 **c)** the MS profile of the product (peak at 5.85 min). Measured ions *e.g.*; 1426.6953: $[M + 5H]^{5+}$ give $Mw^{obs.}$= 7128.48 Da, in good agreement with its calculated counterpart: Mw^{calc}= 7128.84 Da.



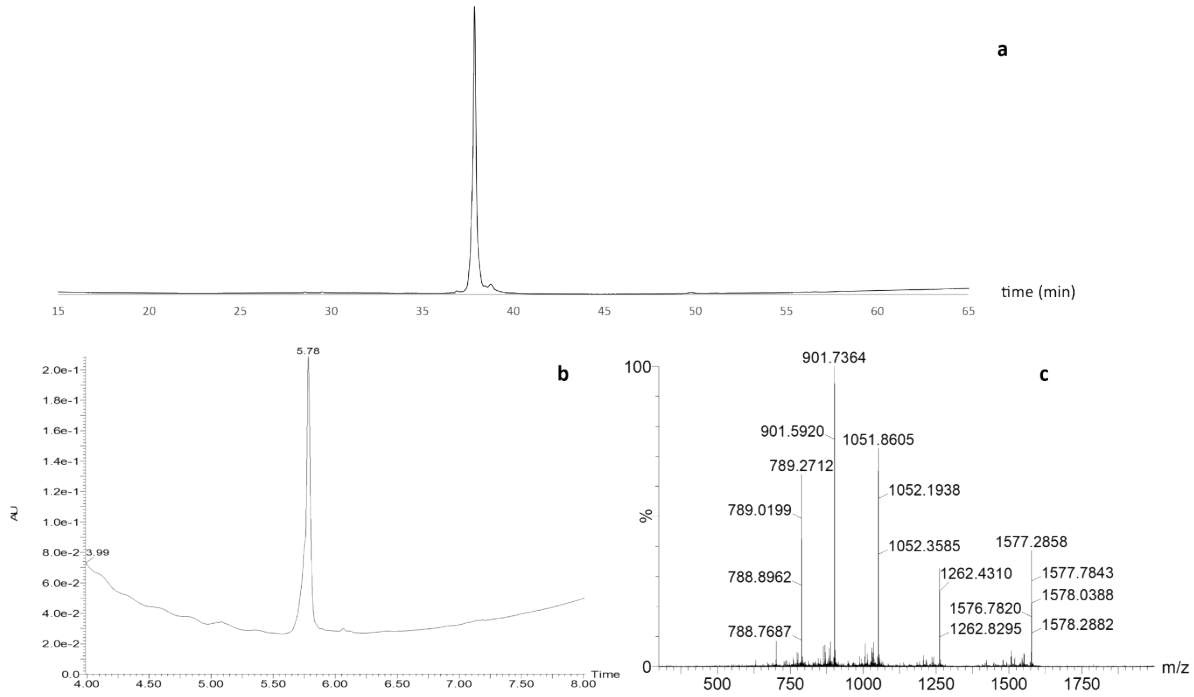
SFigure 32. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of Z(Aβ3): #1. **b**) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of Z(Aβ3): #1 , **c**) The LC-MS profile of the crude Z(Aβ3): #1 with **d)** the MS profile of the crude product (peak at 10.75 min) belonging of Z(Aβ3): #1. Measured ions *e.g.*; 1577.2948: $[M + 4H]^{4+}$ give Mw^{obs} = 6305.18 Da, in good agreement with its calculated counterpart: Mw^{calc}= 6306.10 Da (**STable 5).**



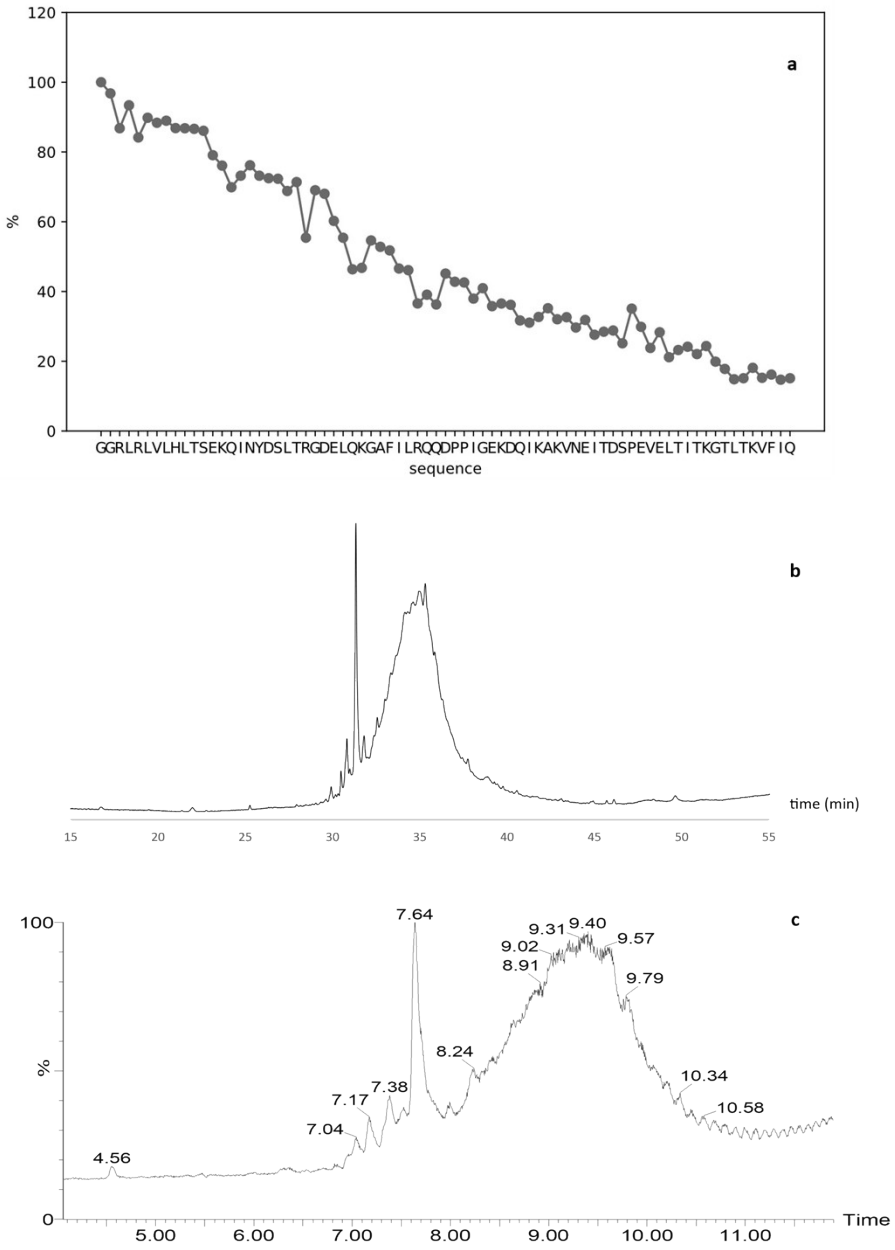
SFigure 33. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of Z(Aβ3): #2. **b**) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of Z(Aβ3): #2 , **c**) The LC-MS profile of the crude Z(Aβ3): #2 with **d)** the MS profile of the crude product (peak at 7.11 min) belonging of Z(Aβ3): #2. Measured ions *e.g.*; 1577.2948: $[M + 4H]^{4+}$ give Mw^{obs} = 6305.02 Da, in good agreement with its calculated counterpart: Mw^{calc}= 6306.10 Da (**STable 5).**



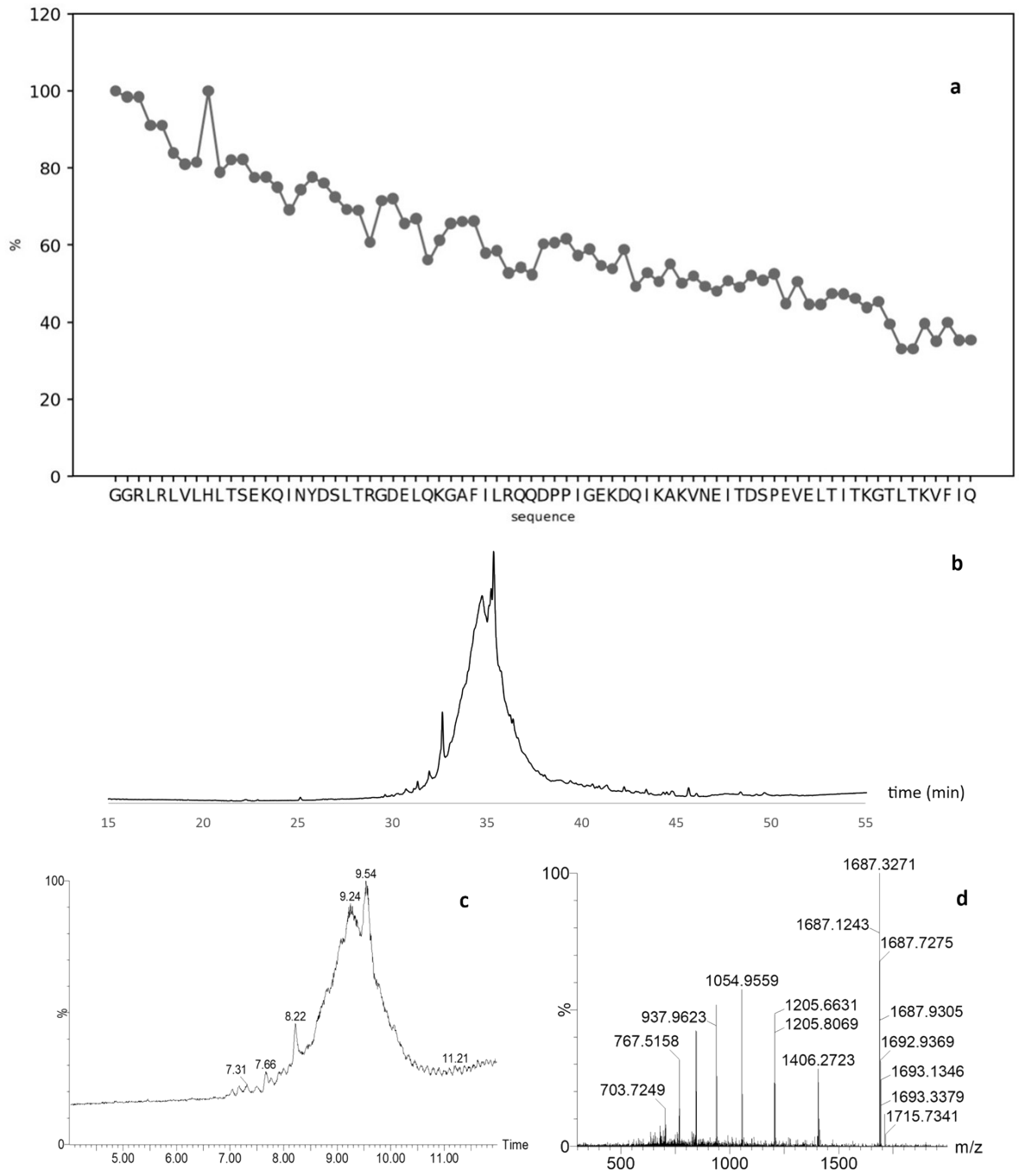
SFigure 34. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of Z(Aβ3): #3. **b**) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of Z(Aβ3): #3, **c**) The LC-MS profile of the crude Z(Aβ3): #3 with **d)** the MS profile of the crude product (peak at 7.11 min) belonging of Z(Aβ3): #3. Measured ions *e.g.*; 1577.2542: $[M + 4H]^{4+}$ give Mw^{obs} = 6305.02 Da, in good agreement with its calculated counterpart: Mw^{calc}= 6306.10 Da (**STable 5).**



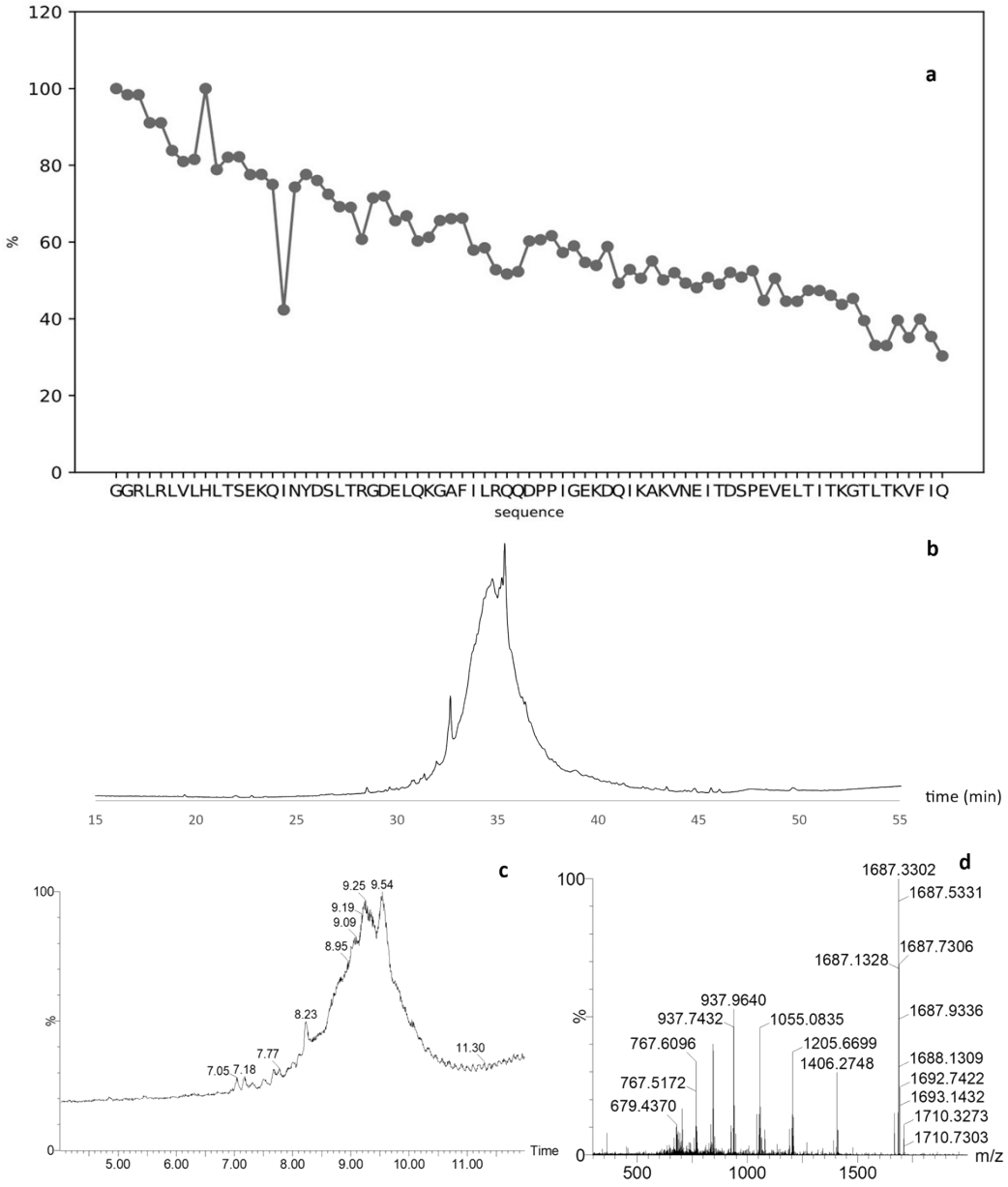
SFigure 35. a) The RP-HPLC chromatogram of the HPLC purified Z(Aβ3). **b**) The LC-MS of the pure Z(Aβ3), **c)** the MS profile of the product (peak at 5.76 min). Measured ions *e.g.*; 1426.6953: $[M + 5H]^{5+}$ give $Mw^{obs.}$= 6305.15 Da, in good agreement with its calculated counterpart: Mw^{calc}= 6306.10 Da.



SFigure 36. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of UBI: #1. **b**) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of UBI: #1, **c**) The LC-MS profile of the crude UBI: #1 (**STable 6).**



SFigure 37. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of UBI: #2. **b**) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of UBI: #2. **c**) The LC-MS profile of the crude UBI: #2 with **d)** the MS profile of the crude product (peak at 9.54 min) belonging of UBI: #2. Measured ions *e.g.*; 1054.9559: $[M + 8H]^{8+}$ give Mw^{obs} = 8431.65 Da, in good agreement with its calculated counterpart: Mw^{calc}= 8432.64 Da (**STable 6).**



SFigure 38. a) The relative area of the Fmoc cleavage peak in % during the SPF synthesis of UBI: #3. **b**) The RP-HPLC chromatogram (recorded at 220 nm) of the crude product of UBI: #3, **c**) The LC-MS profile of the crude UBI: #3 with **d)** the MS profile of the crude product (peak at 9.54 min) belonging of UBI: #3. Measured ions *e.g.*; 1687.3302: $[M + 5H]^{5+}$ give Mw^{obs} = 8431.65 Da, in good agreement with its calculated counterpart: Mw^{calc}= 8432.64 Da (**STable 4).**