Supplementary Materials to:

Triazolopeptides inhibiting the interaction between Neuropilin-1 and Vascular Endothelial Growth Factor-165

by

Bartlomiej Fedorczyk*, Piotr F.J. Lipinski, Anna K. Puszko, Dagmara Tymecka, Beata Wilenska, Wioleta Dudka, Gerard Y. Perret, Rafal Wieczorek and Aleksandra Misicka*

***Corresponding authors:** Aleksandra Misicka, misicka@chem.uw.edu.pl, Bartlomiej Fedorczyk, bfedorczyk@chem.uw.edu.pl

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SM-SYN. Synthetic data

Compound 1

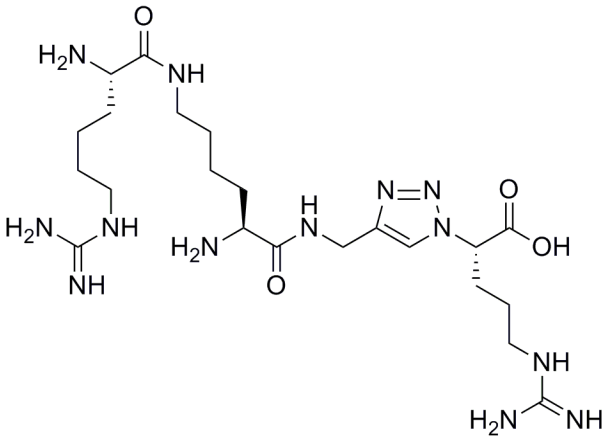
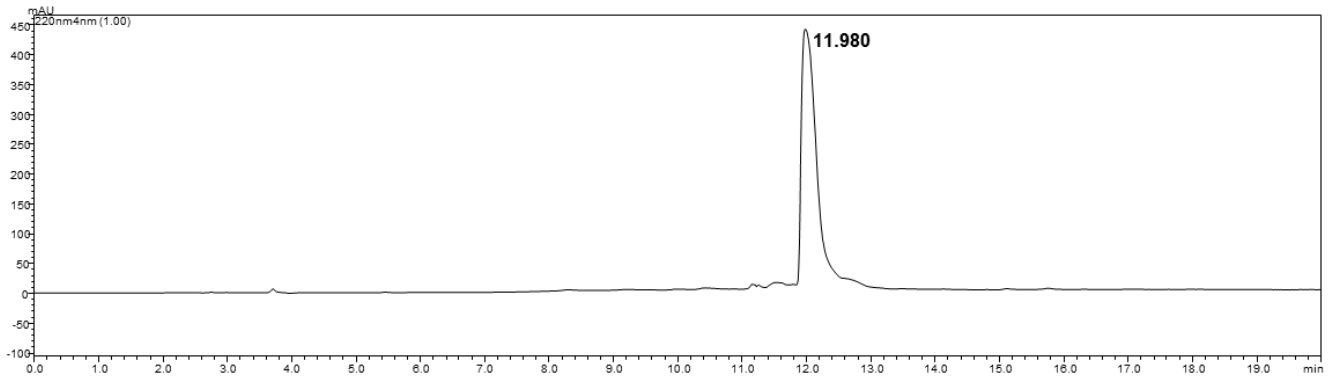
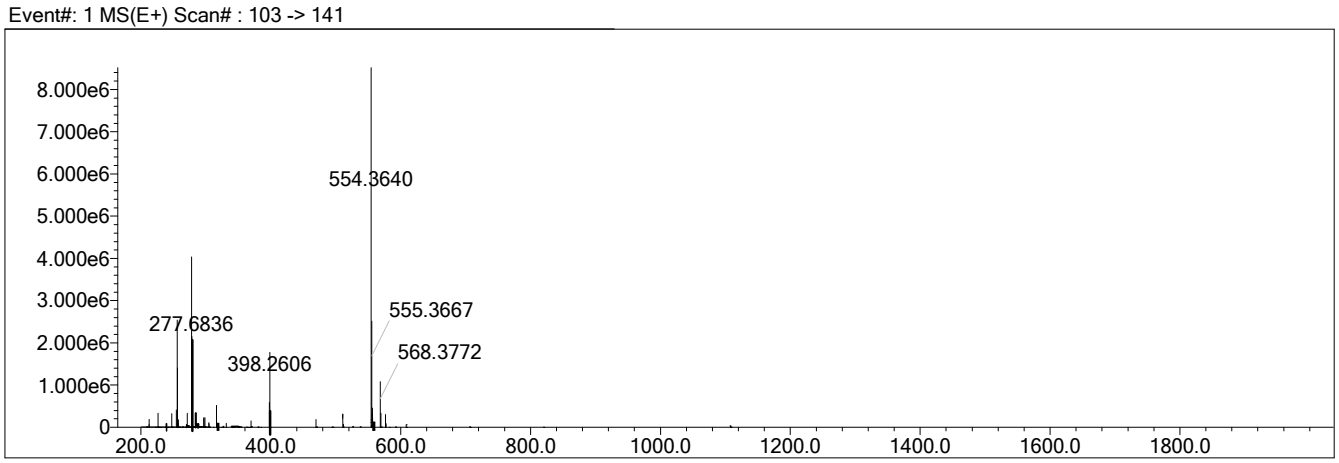


Figure SM-SYN-1a. Structure of compound **1** Lys(Har)-GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	99.80	C22 H43 N13 O4	[M+H]+	554.3640	554.3634	0.6	1.08	100.00	8.0

Figure SM-SYN-1b. HPLC chromatogram of compound 1 at 220 nm and MS spectrum

Compound 2

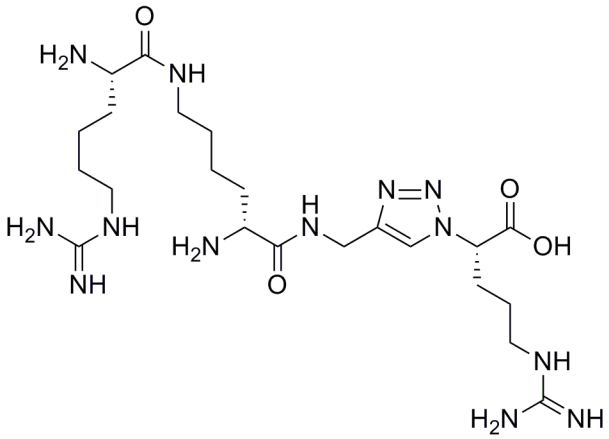
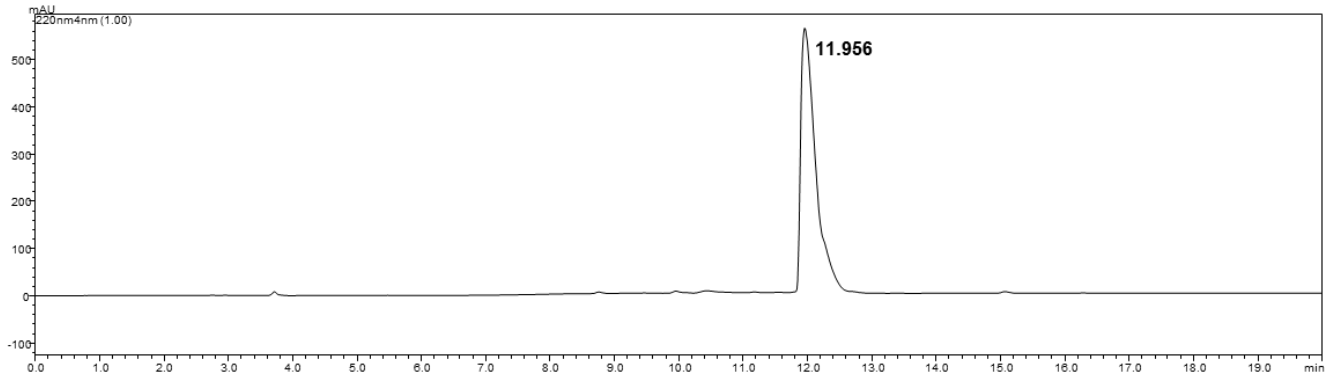
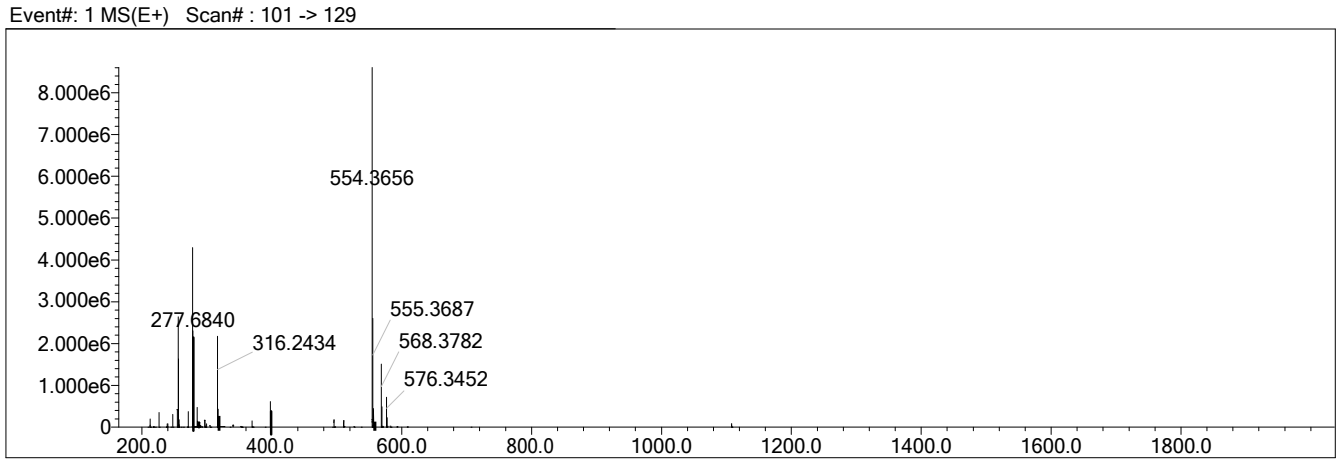


Figure SM-SYN-2a. Structure of compound **2** D-Lys(Har)-GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
4	92.58	C22 H43 N13 O4	[M+H]+	554.3656	554.3634	2.2	3.97	100.00	8.0

Figure SM-SYN-2b. HPLC chromatogram of compound **2** at 220 nm and MS spectrum

Compound 3

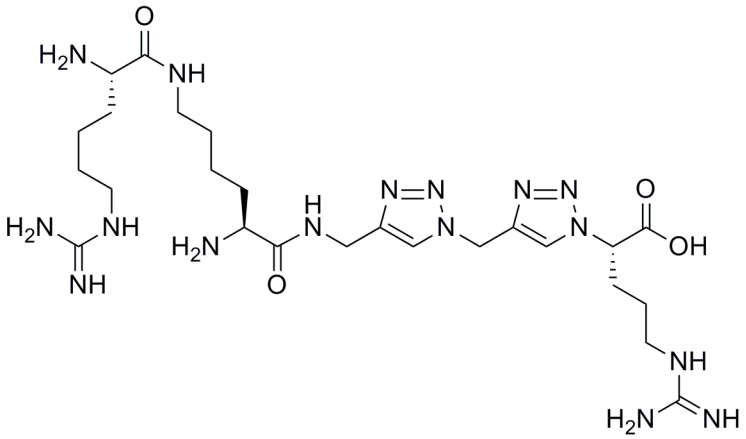
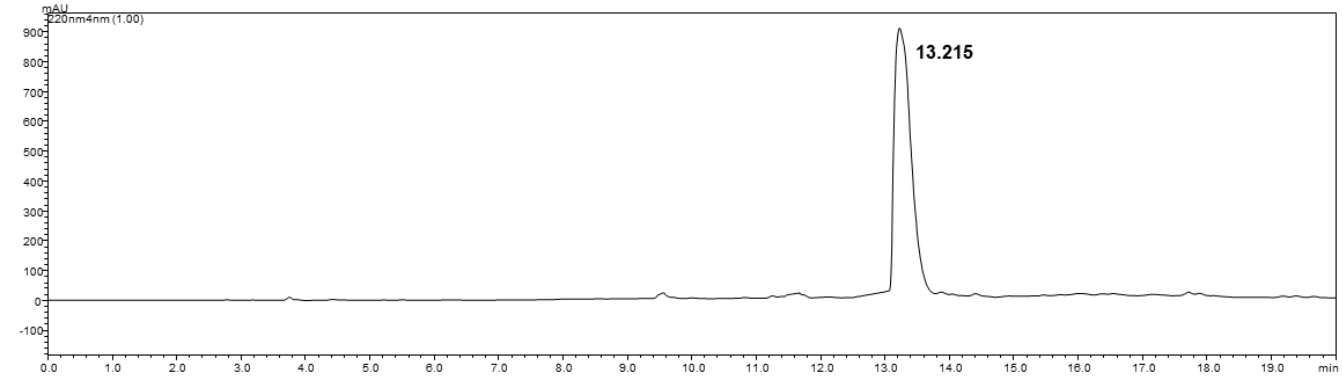


Figure SM-SYN-3a. Structure of compound **3** Lys(Har)-GlyΨ[Trl]GlyΨ[Trl]Arg.



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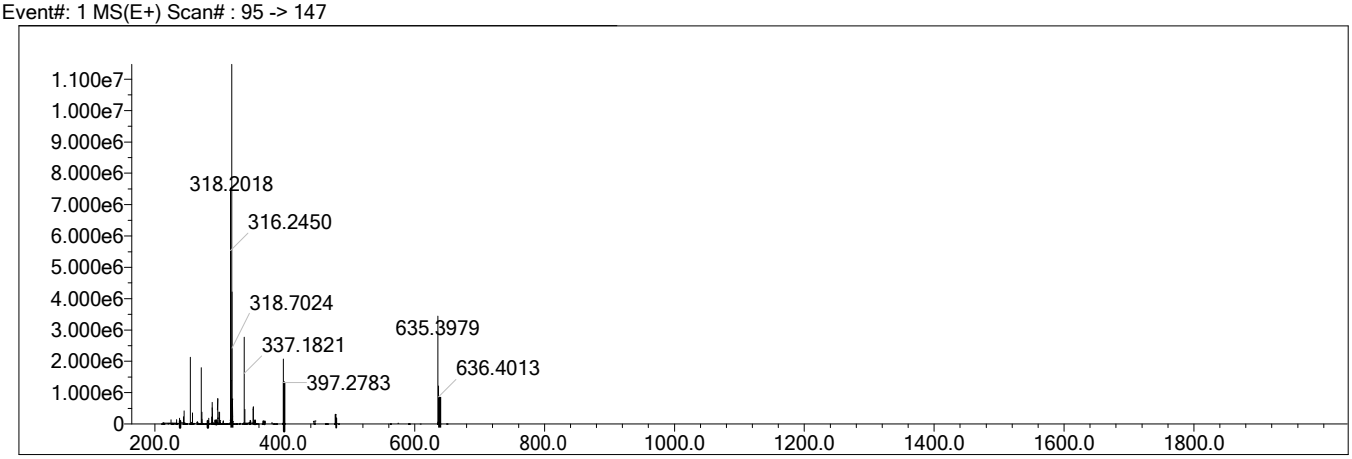


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
4	95.42	C25 H46 N16 O4	[M+H]+	635.3979	635.3961	1.8	2.83	100.00	11.0

Figure SM-SYN-3b. HPLC chromatogram of compound **3** at 220 nm and MS spectrum

Compound 4

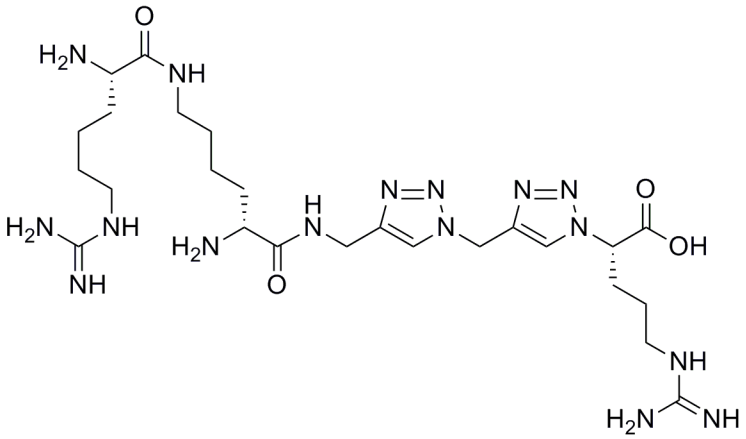
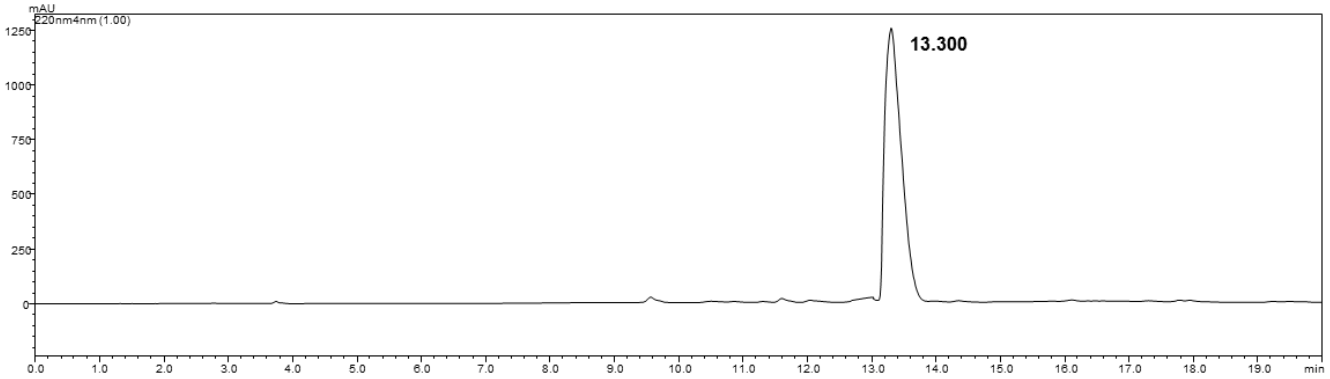
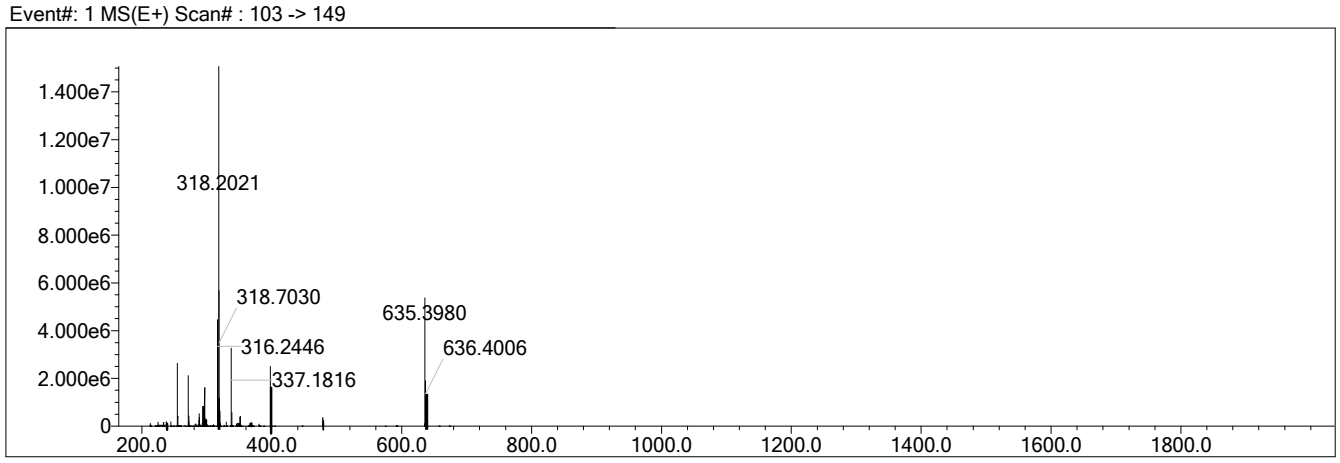


Figure SM-SYN-4a. Structure of compound **4** D-Lys(Har)-GlyΨ[Trl]GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
4	95.03	C25 H46 N16 O4	[M+H]+	635.3980	635.3961	1.9	2.99	100.00	11.0

Figure SM-SYN-4b. HPLC chromatogram of compound **4** at 220 nm and MS spectrum

Compound 5

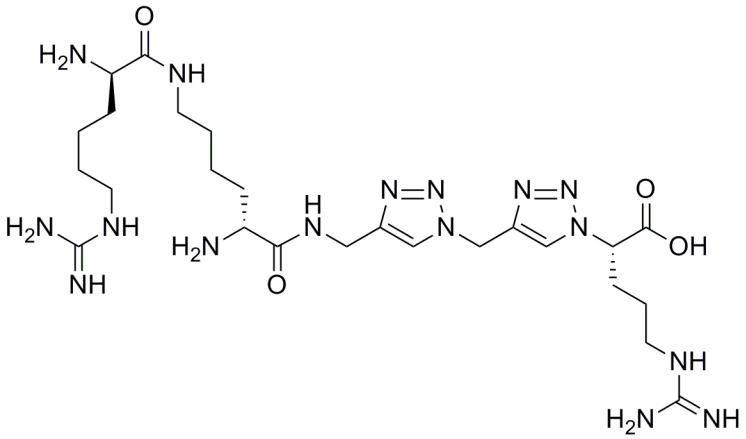
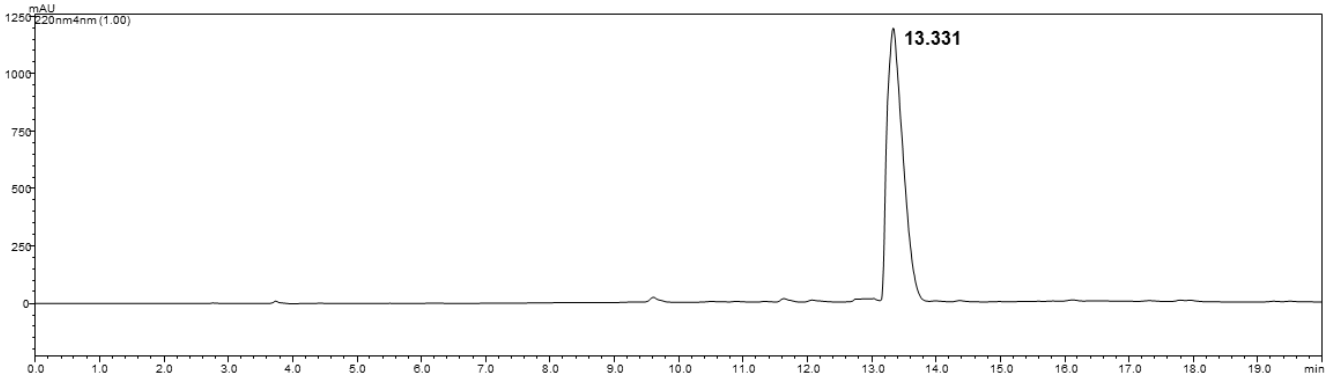
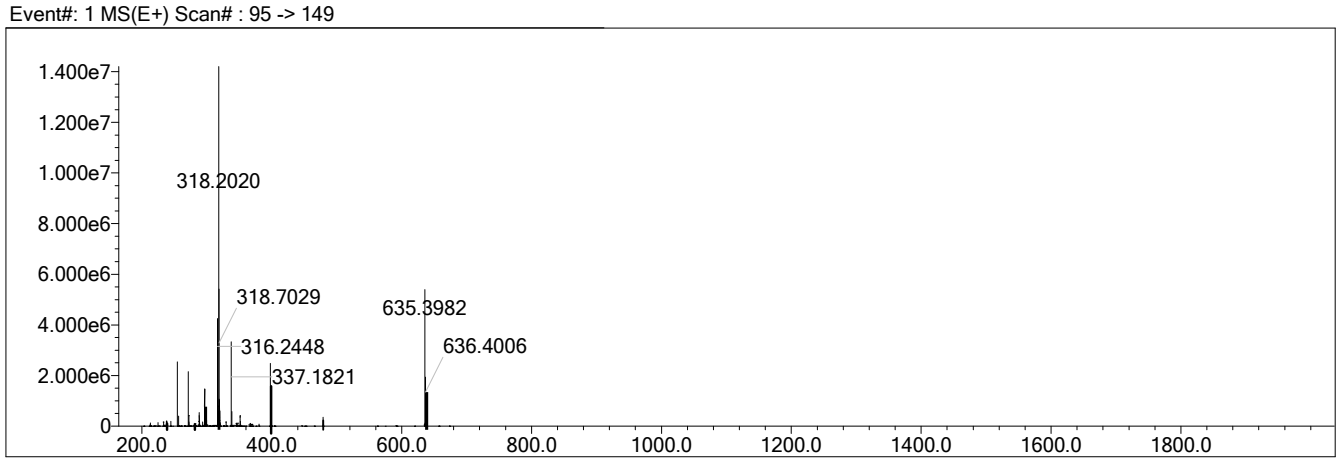


Figure SM-SYN-5a. Structure of compound **5** D-Lys(D-Har)-GlyΨ[Trl]GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
4	94.22	C25 H46 N16 O4	[M+H]+	635.3982	635.3961	2.1	3.31	100.00	11.0

Figure SM-SYN-5b. HPLC chromatogram of compound **5** at 220 nm and MS spectrum

Compound 6

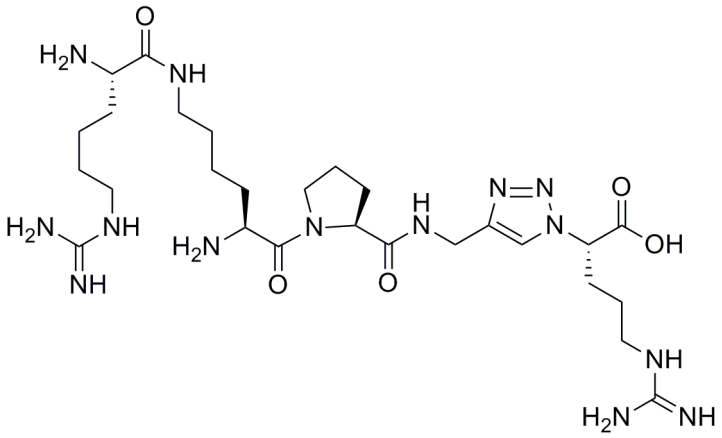
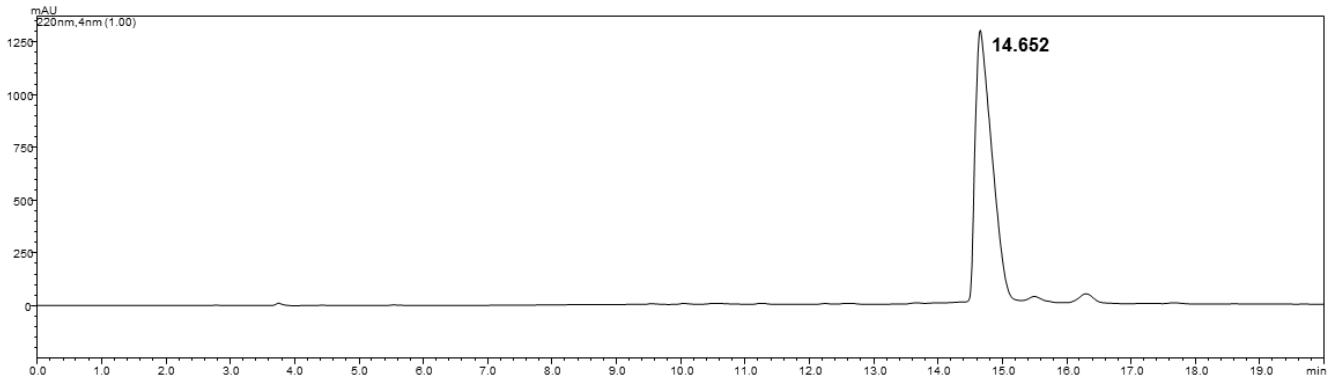
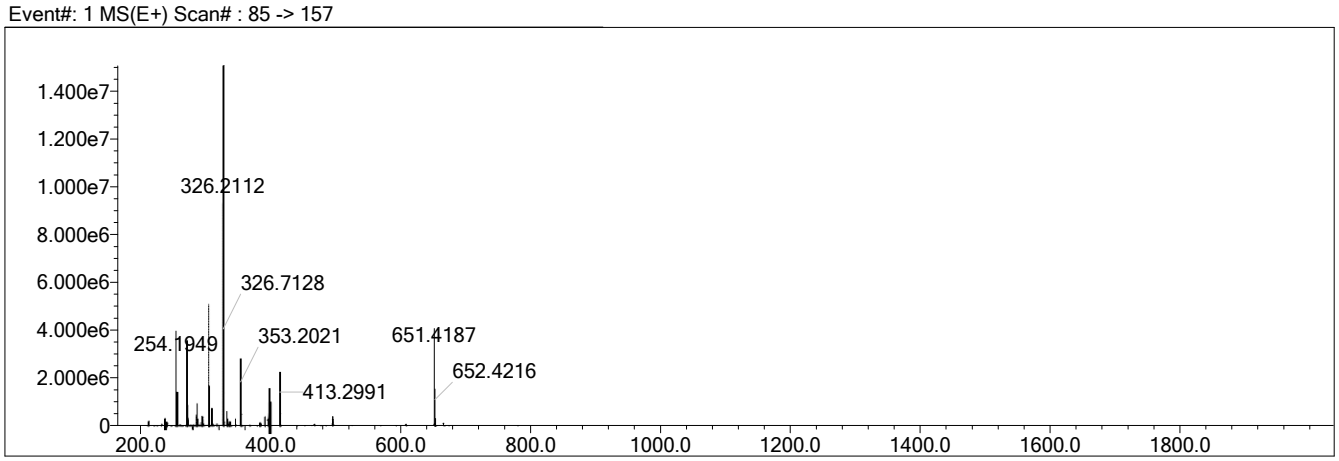


Figure SM-SYN-6a. Structure of compound **6** Lys(Har)-Pro-GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
4	92.53	C27 H50 N14 O5	[M+H]+	651.4187	651.4161	2.6	3.99	100.00	10.0

Figure SM-SYN-6b. HPLC chromatogram of compound **6** at 220 nm and MS spectrum

Compound 7

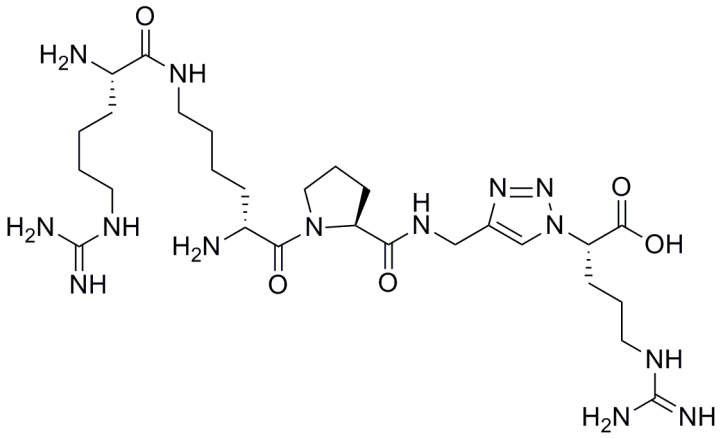
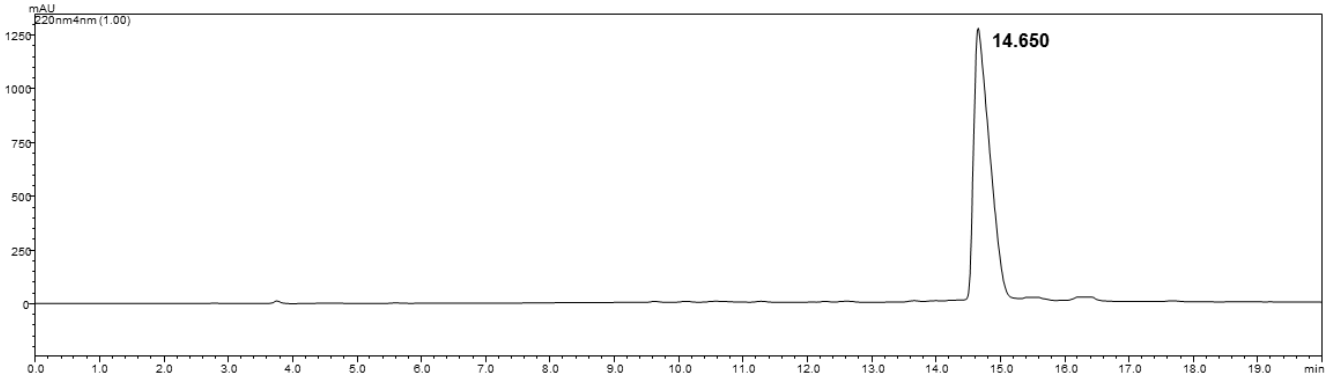
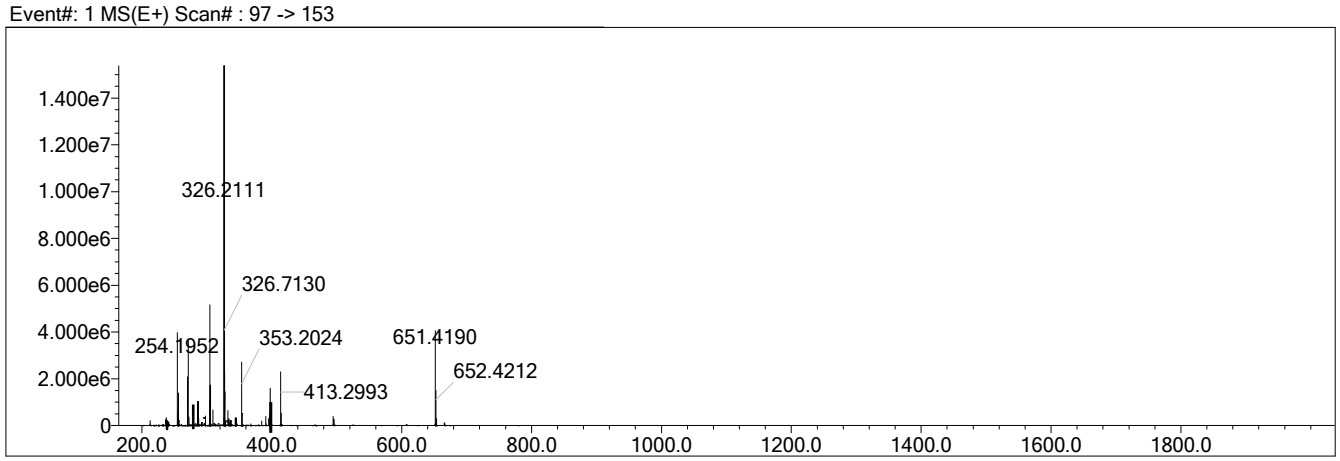


Figure SM-SYN-7a. Structure of compound **7** D-Lys(Har)-Pro-GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
4	91.38	C27 H50 N14 O5	[M+H]+	651.4190	651.4161	2.9	4.45	100.00	10.0

Figure SM-SYN-7b. HPLC chromatogram of compound **7** at 220 nm and MS spectrum

Compound 8

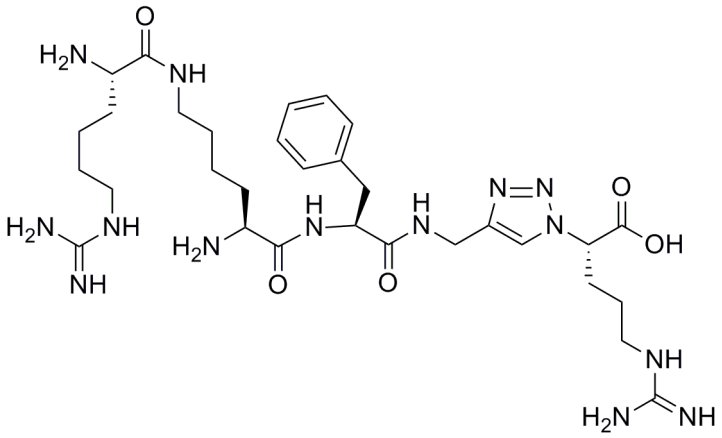
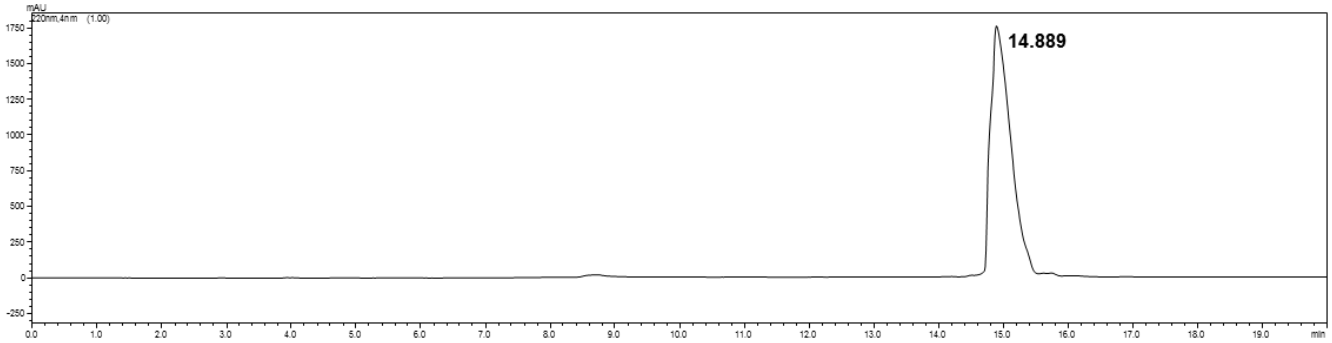
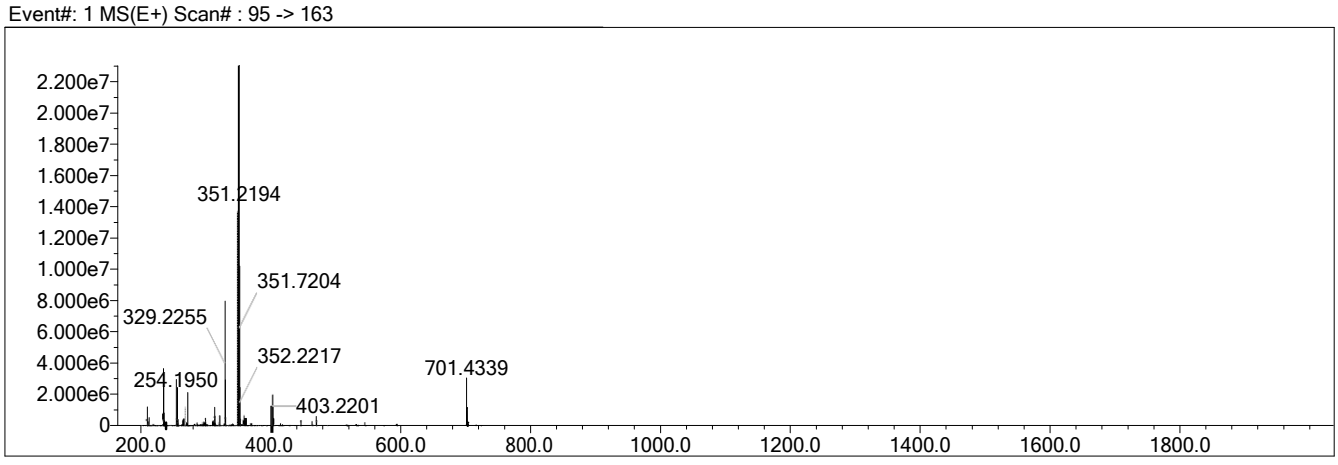


Figure SM-SYN-8a. Structure of compound **8** Lys(Har)-Phe-GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	95.03	C31 H52 N14 O5	[M+H]+	701.4339	701.4318	2.1	2.99	100.00	13.0

Figure SM-SYN-8b. HPLC chromatogram of compound **8** at 220 nm and MS spectrum

Compound 9

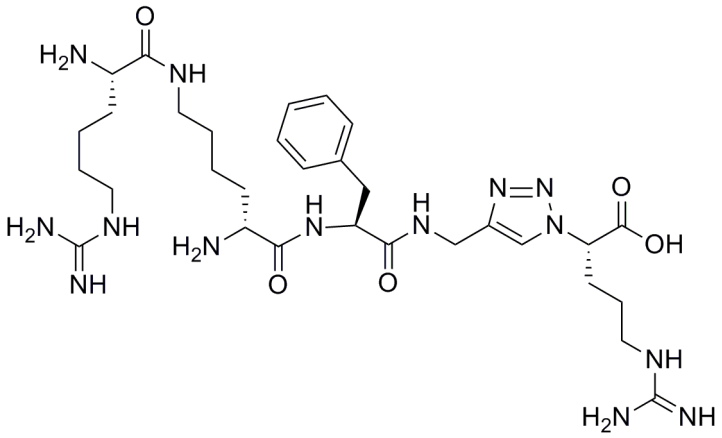
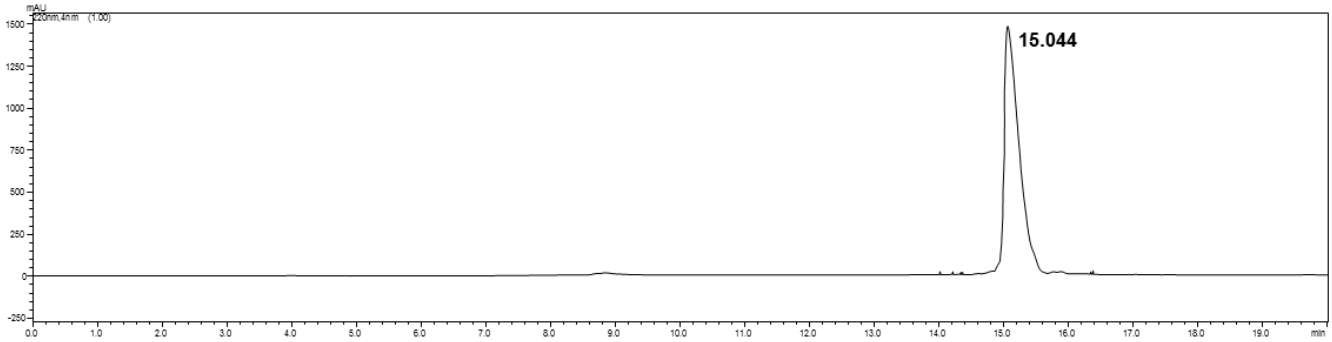
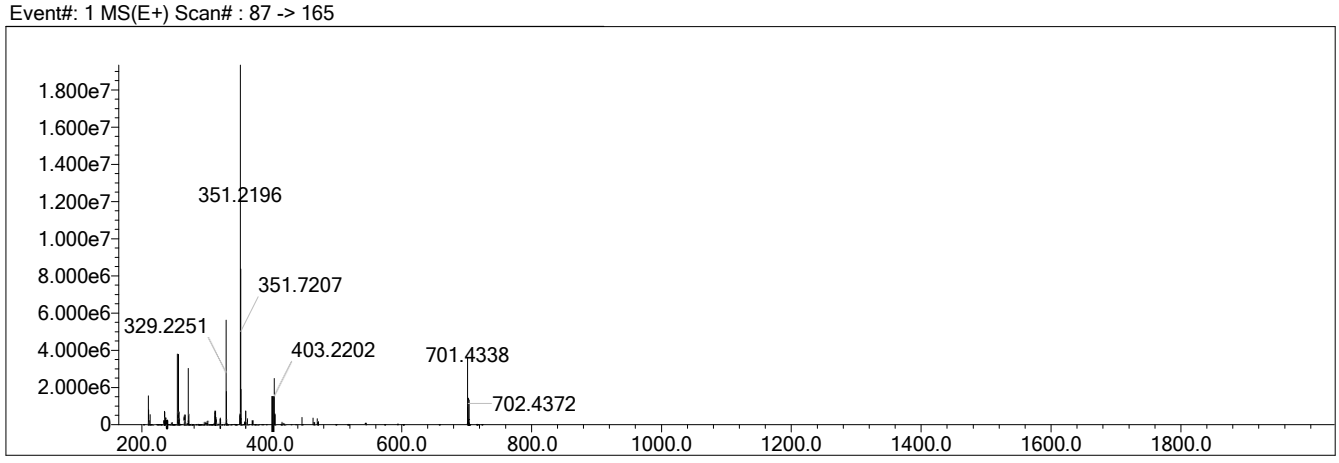


Figure SM-SYN-9a. Structure of compound **9** D-Lys(Har)-Phe-GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
2	94.20	C31 H52 N14 O5	[M+H]+	701.4338	701.4318	2.0	2.85	98.77	13.0

Figure SM-SYN-9b. HPLC chromatogram of compound **9** at 220 nm and MS spectrum

Compound 10

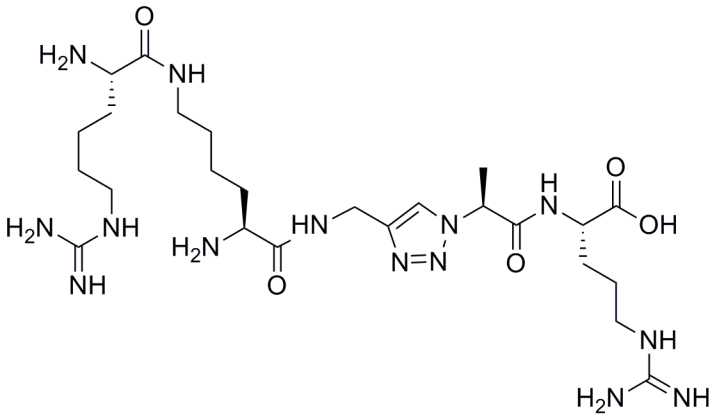
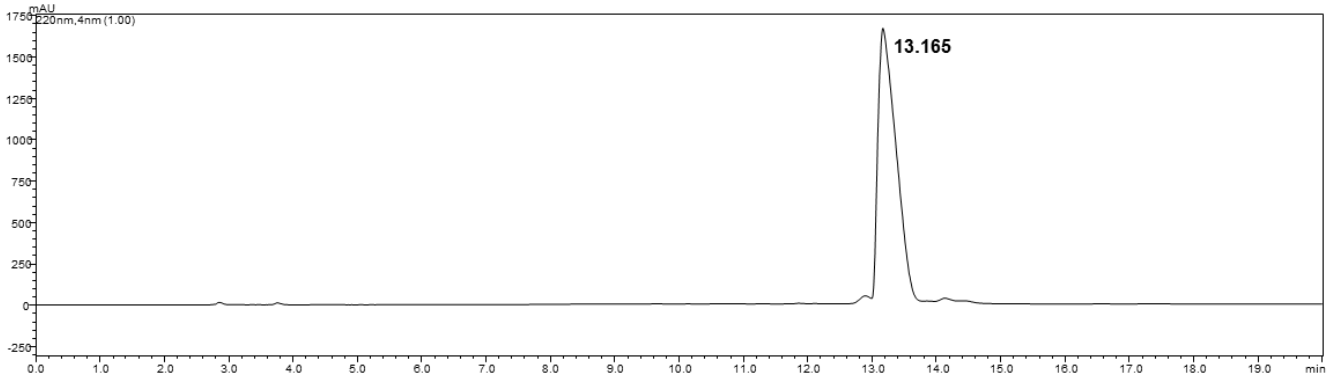
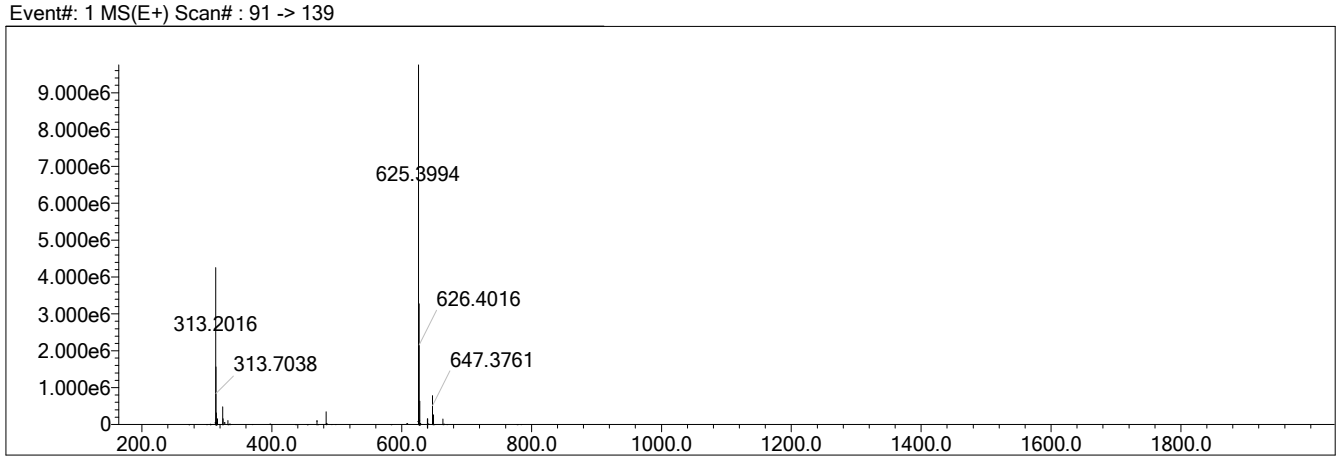


Figure SM-SYN-10a. Structure of compound **10** Lys(Har)-GlyΨ[Trl]Ala-Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
2	98.10	C25 H48 N14 O5	[M+H]+	625.3994	625.4005	-1.1	-1.76	100.00	9.0

Figure SM-SYN-10b. HPLC chromatogram of compound **10** at 220 nm and MS spectrum

Compound 11

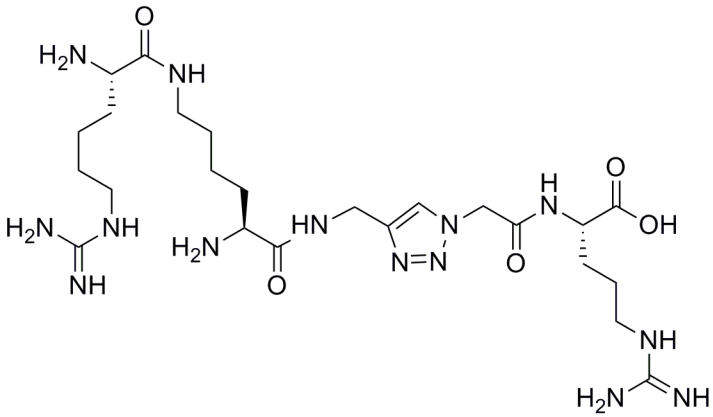
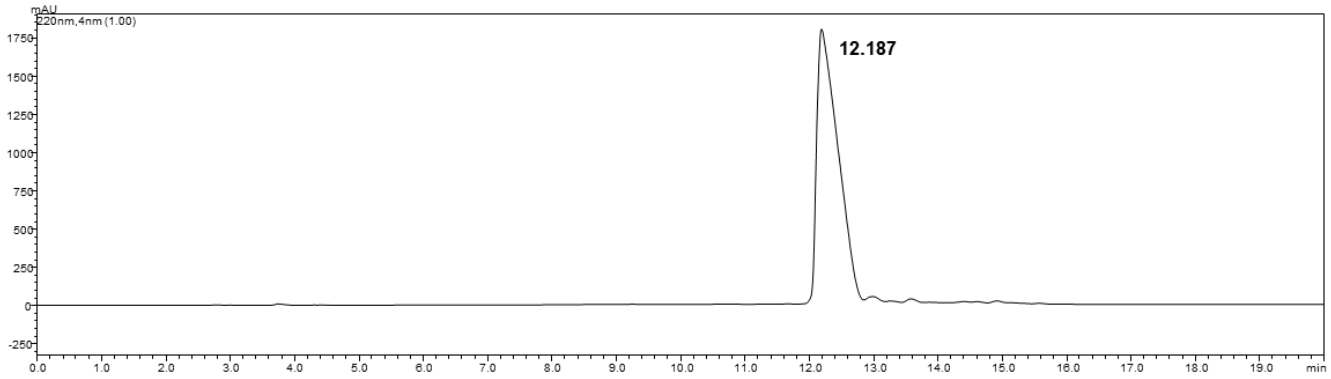
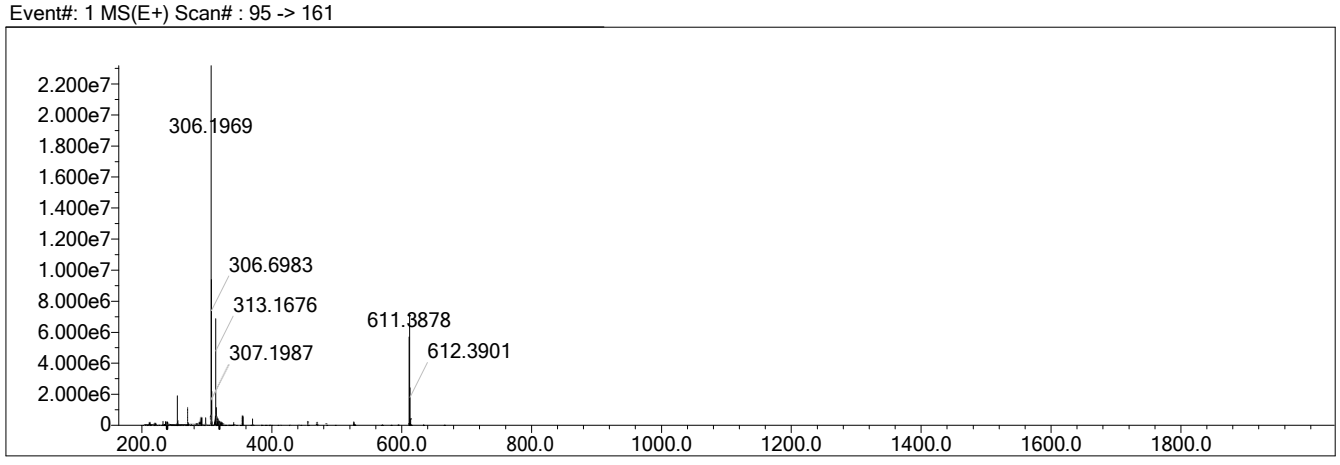


Figure SM-SYN-11a. Structure of compound **11** Lys(Har)-GlyΨ[Trl]Gly-Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
4	90.22	C24 H46 N14 O5	[M+H]+	611.3878	611.3848	3.0	4.91	100.00	9.0

Figure SM-SYN-11b. HPLC chromatogram of compound **11** at 220 nm and MS spectrum

Compound 12

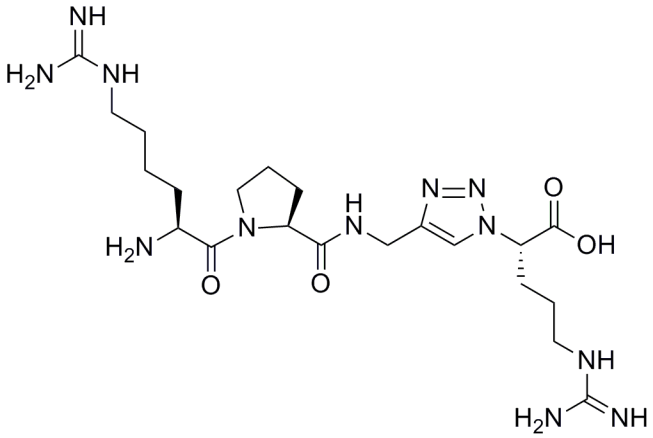
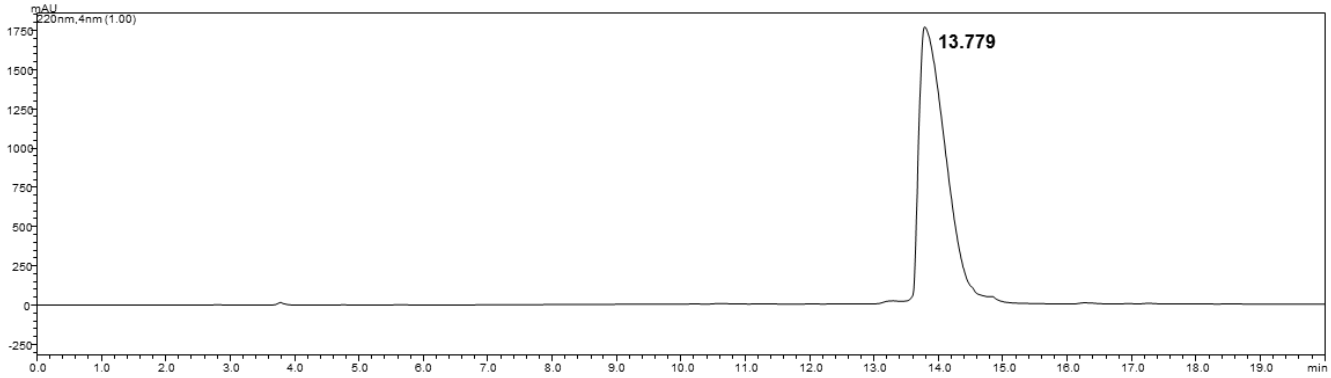
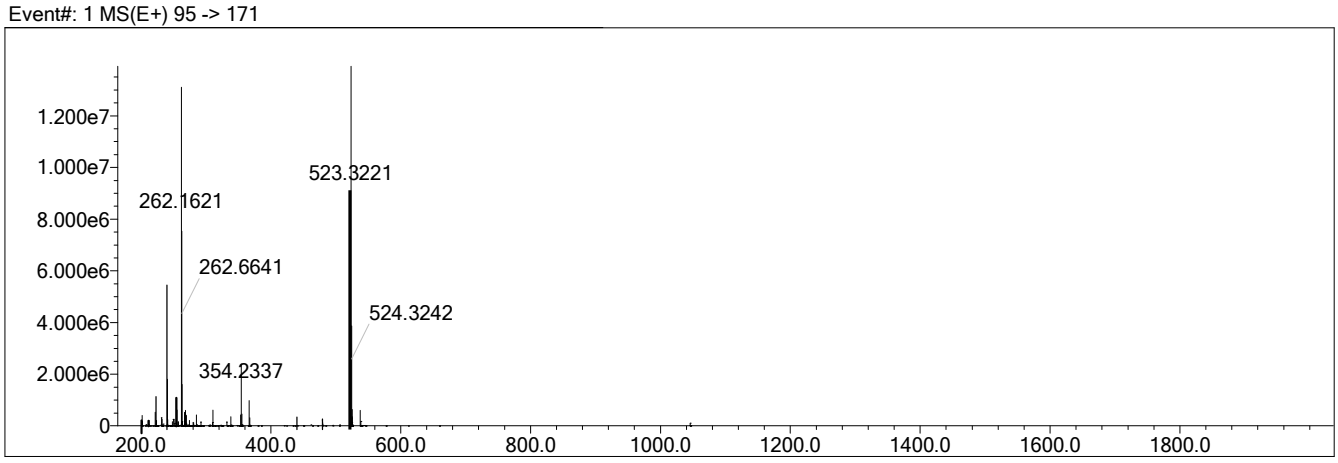


Figure SM-SYN-12a. Structure of compound **12** Har-Pro-GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	98.20	C21 H38 N12 O4	[M+H]+	523.3221	523.3212	0.9	1.72	100.00	9.0

Figure SM-SYN-12b. HPLC chromatogram of compound **12** at 220 nm and MS spectrum

Compound 13

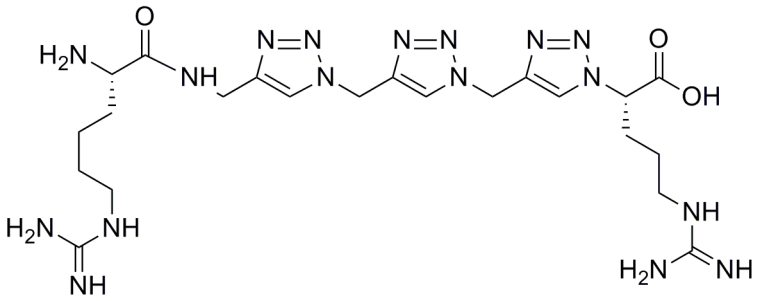
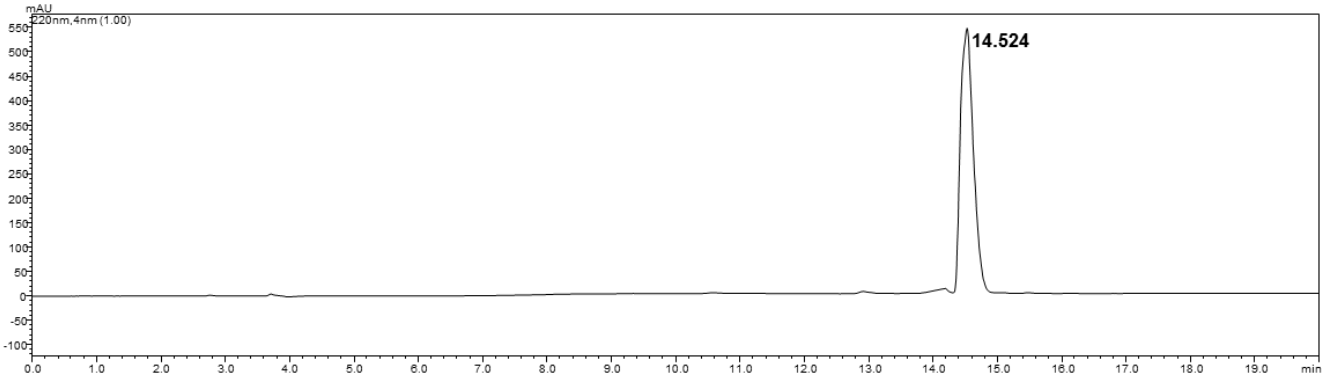
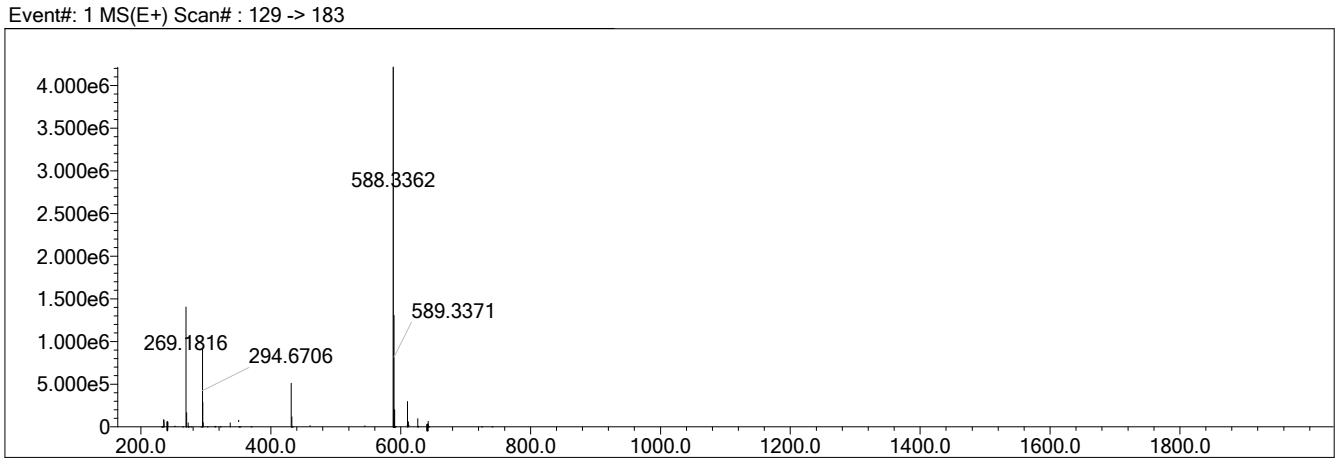


Figure SM-SYN-13a. Structure of compound **13** Har-GlyΨ[Trl]GlyΨ[Trl]GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
3	89.50	C22 H37 N17 O3	[M+H]+	588.3362	588.3338	2.4	4.08	96.97	13.0

Figure SM-SYN-13b. HPLC chromatogram of compound **13** at 220 nm and MS spectrum

Compound 14

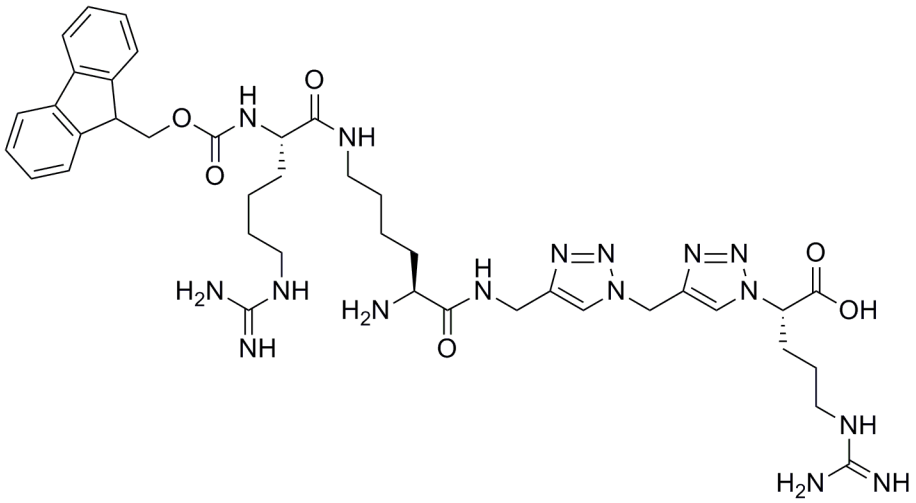
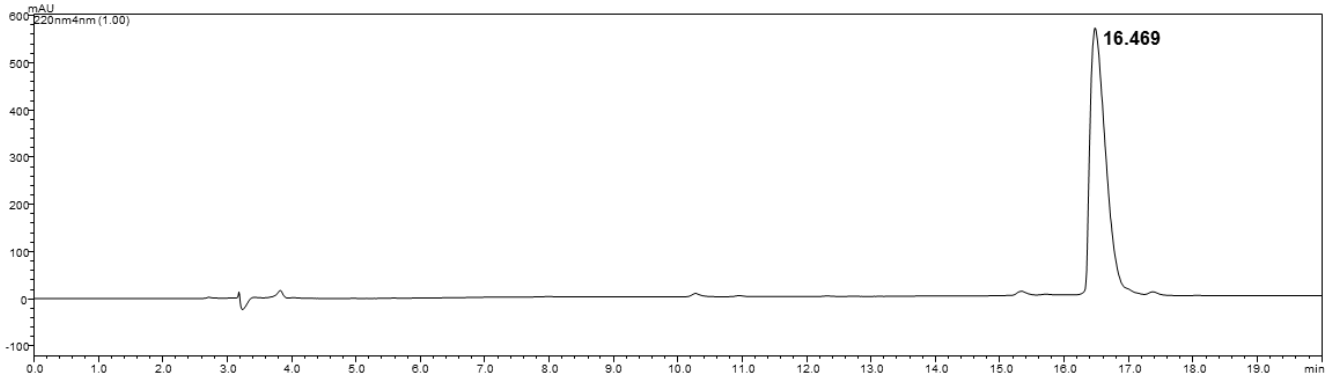
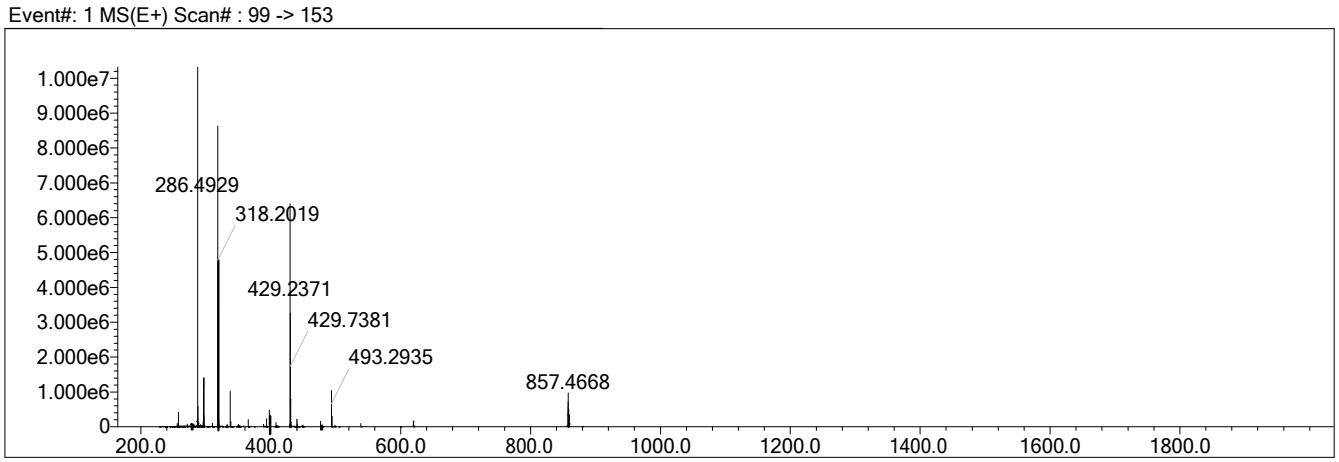


Figure SM-SYN-14a. Structure of compound **14** Lys(Fmoc-Har)-GlyΨ[Trl]GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
4	79.55	C40 H56 N16 O6	[M+2H]2+	429.2371	429.2357	1.4	3.26	84.31	21.0

Figure SM-SYN-14b. HPLC chromatogram of compound **14** at 220 nm and MS spectrum

Compound 15

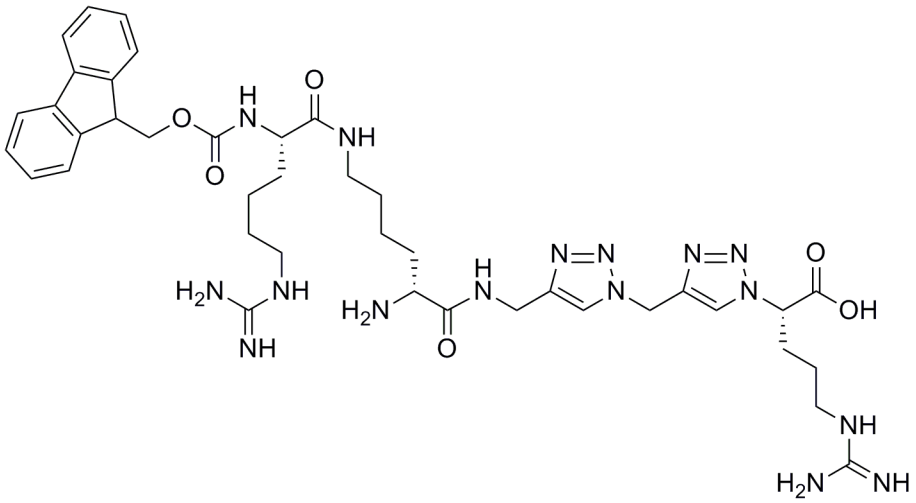
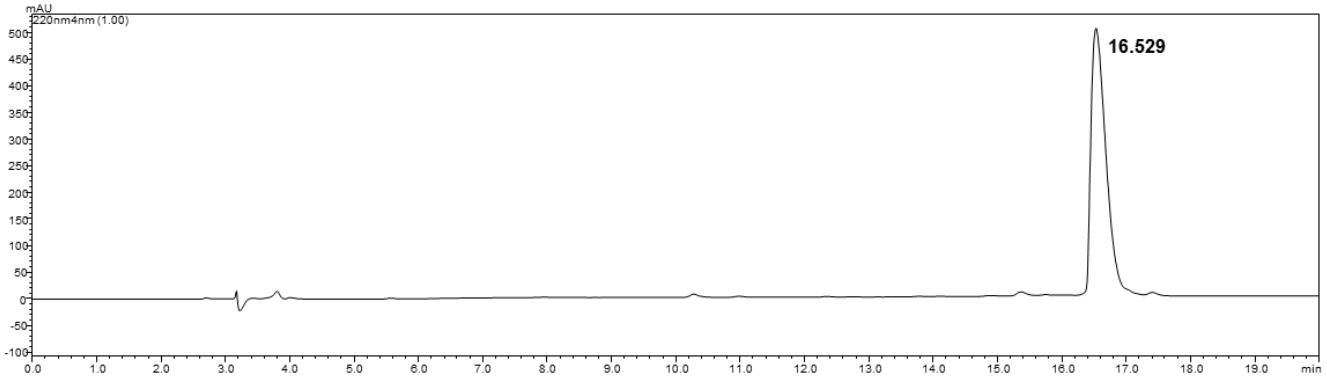
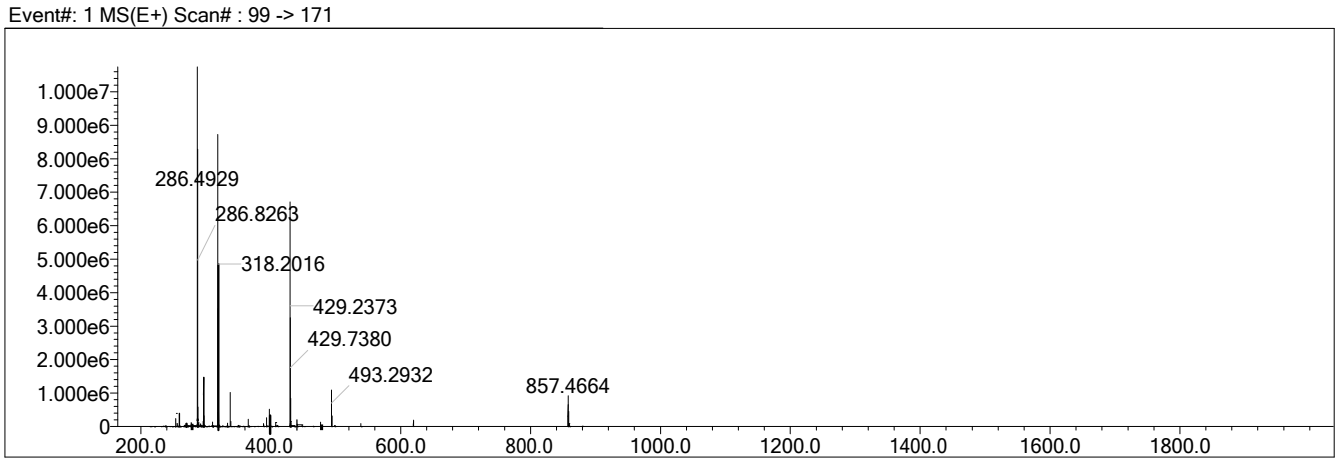


Figure SM-SYN-15a. Structure of compound **15** D-Lys(Fmoc-Har)-GlyΨ[Trl]GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
4	76.97	C40 H56 N16 O6	[M+2H]2+	429.2373	429.2357	1.6	3.73	82.61	21.0

Figure SM-SYN-15b. HPLC chromatogram of compound **15** at 220 nm and MS spectrum

Compound 16

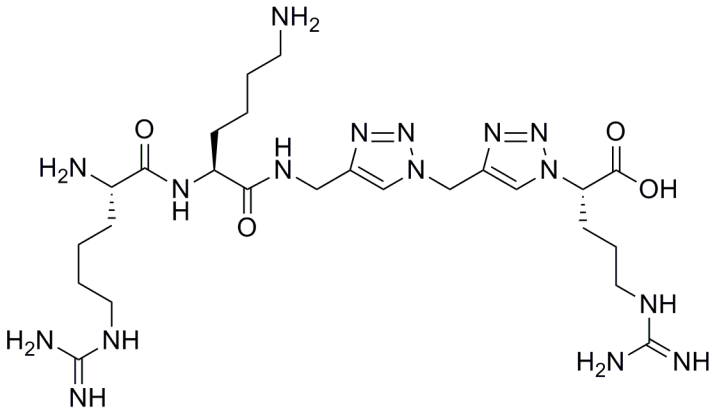
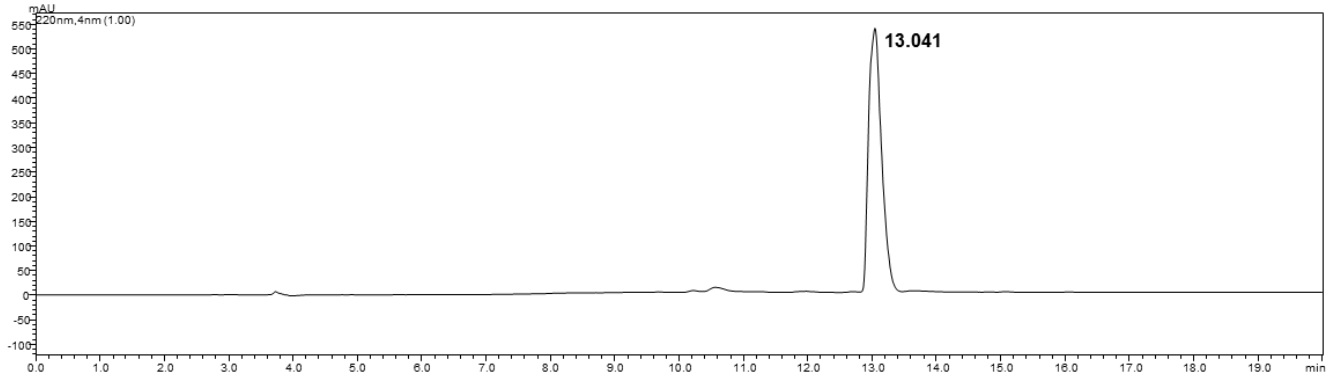
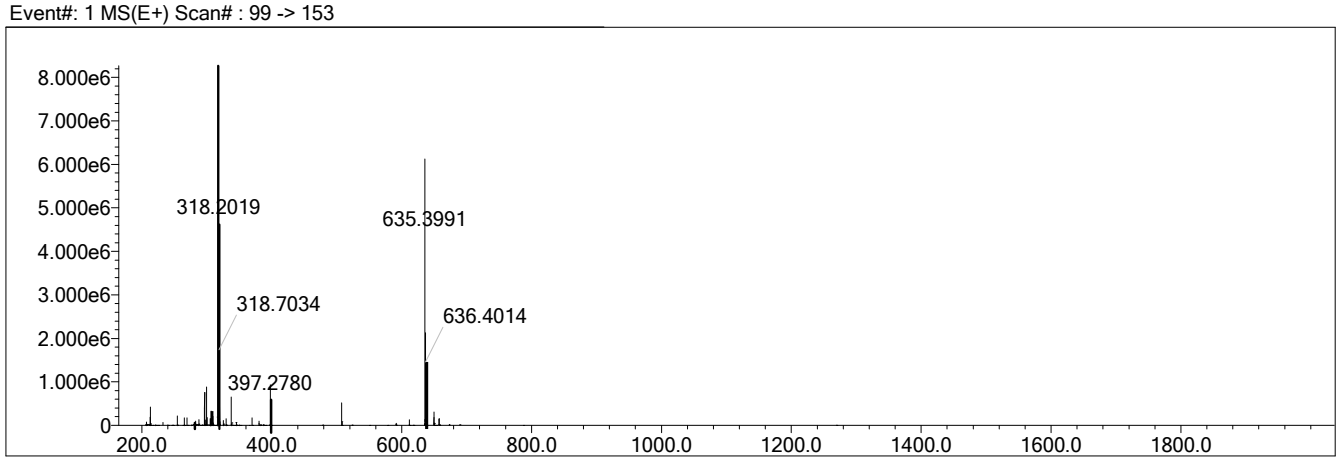


Figure SM-SYN-16a. Structure of compound **16** Har-Lys-GlyΨ[Trl]GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
4	90.70	C25 H46 N16 O4	[M+H]+	635.3991	635.3961	3.0	4.72	100.00	11.0

Figure SM-SYN-16b. HPLC chromatogram of compound **16** at 220 nm and MS spectrum

Compound 17

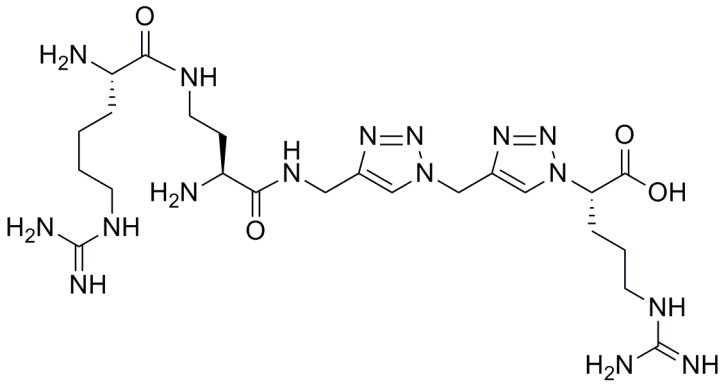
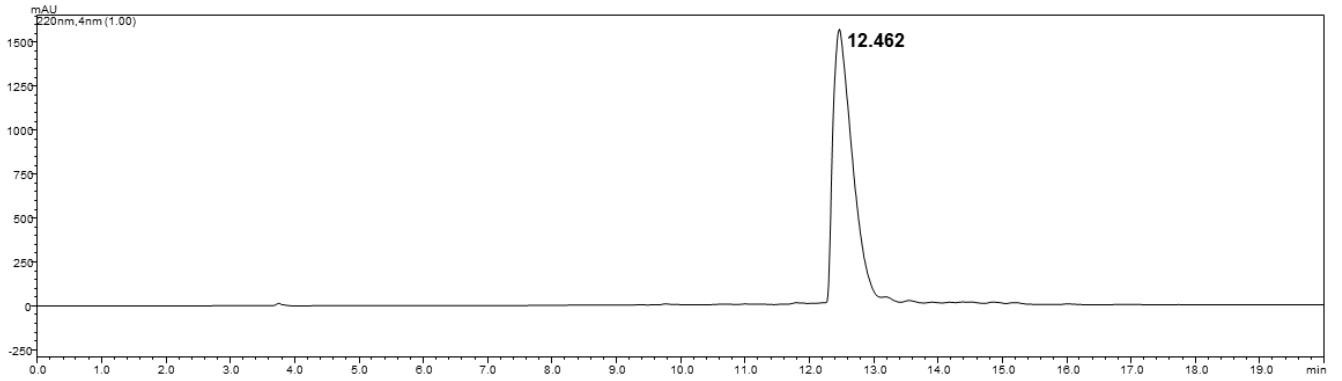
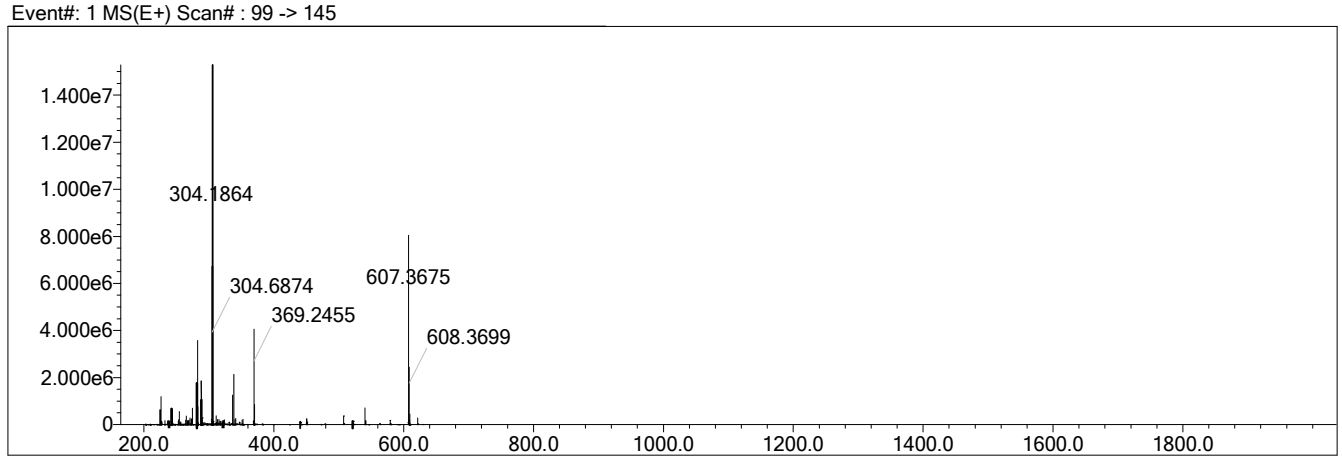


Figure SM-SYN-17a. Structure of compound **17** Dab(Har)-GlyΨ[Trl]GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
5	82.68	C23 H42 N16 O4	[M+H]+	607.3675	607.3648	2.7	4.45	90.49	11.0

Figure SM-SYN-17b. HPLC chromatogram of compound **17** at 220 nm and MS spectrum

Compound 18

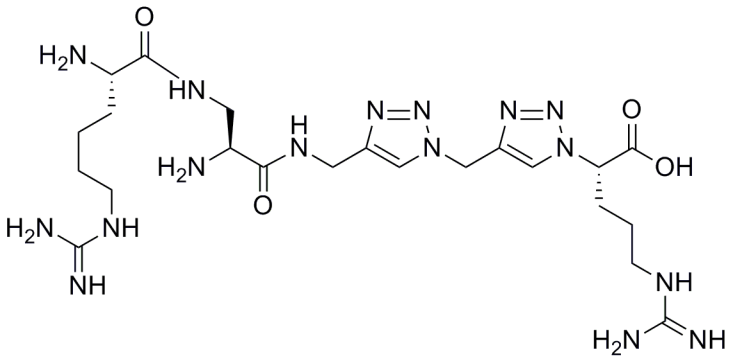
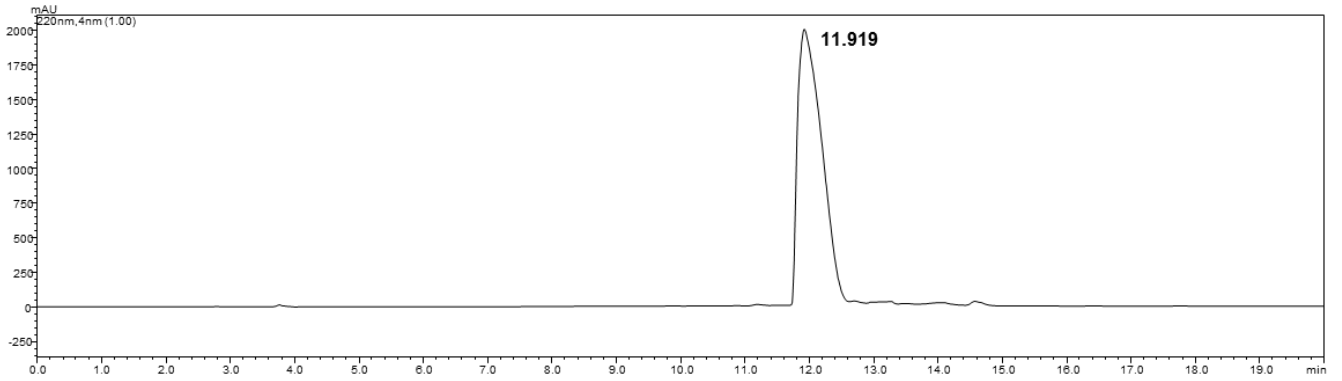
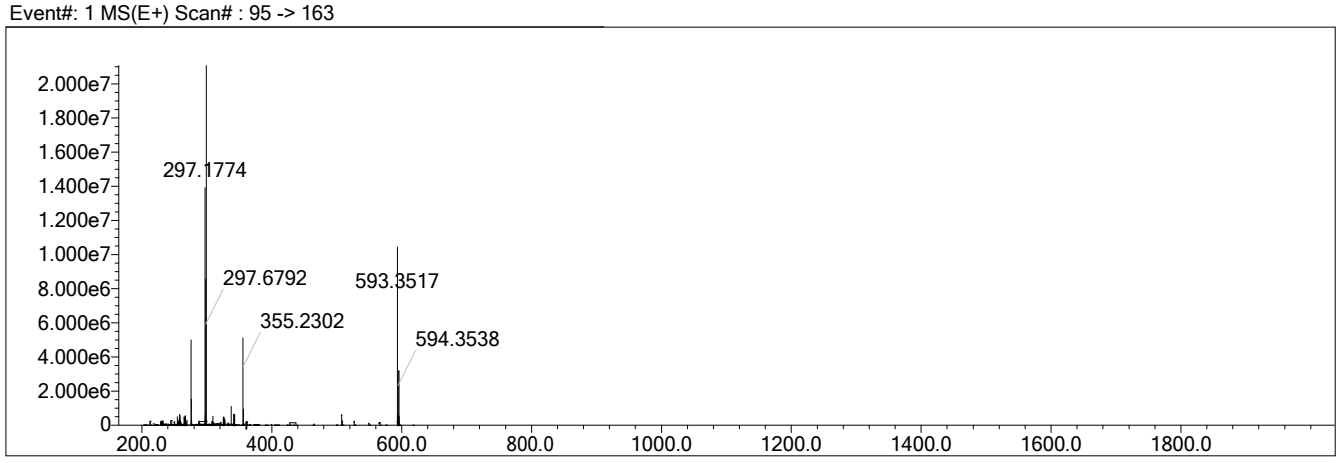


Figure SM-SYN-18a. Structure of compound **18** Dap(Har)-GlyΨ[Trl]GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
4	91.55	C22 H40 N16 O4	[M+H]+	593.3517	593.3491	2.6	4.38	100.00	11.0

Figure SM-SYN-18b. HPLC chromatogram of compound **18** at 220 nm and MS spectrum

Compound 19

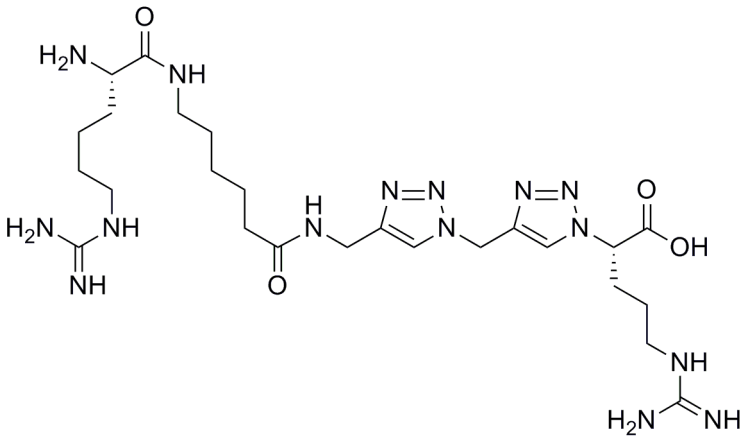
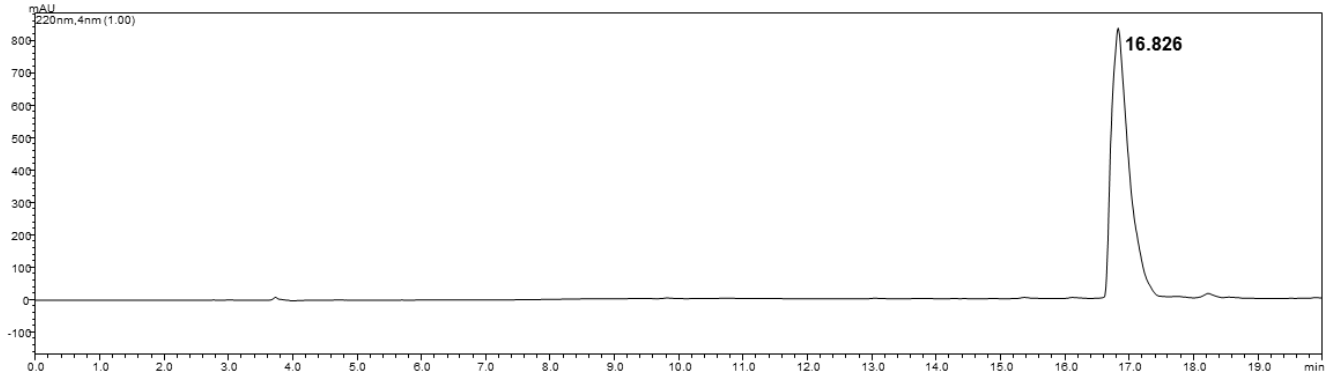
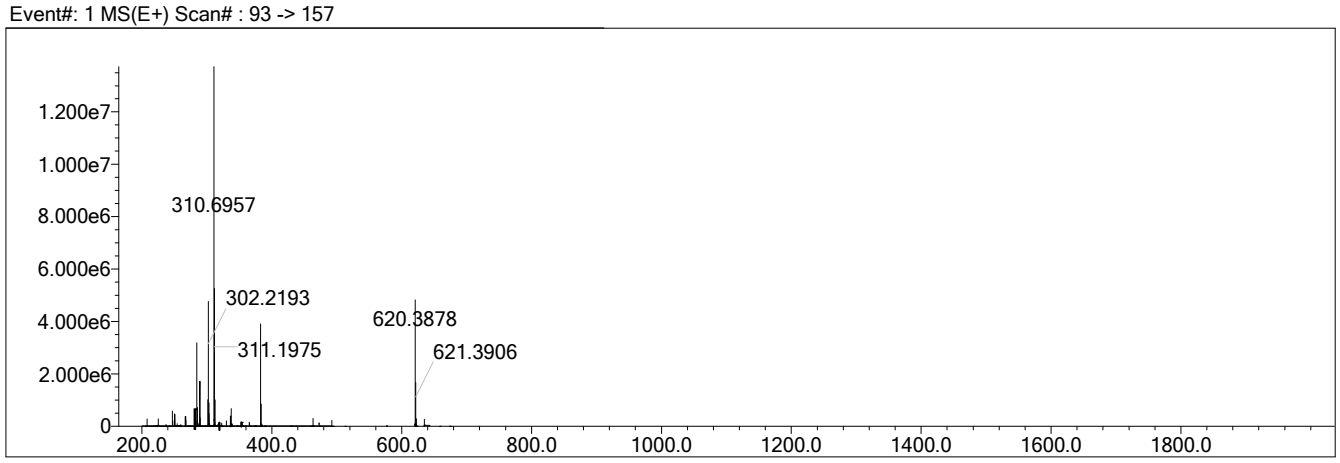


Figure SM-SYN-19a. Structure of compound **19** Har-6Ahx-GlyΨ[Trl]GlyΨ[Trl]]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
5	89.70	C25 H45 N15 O4	[M+H]+	620.3878	620.3852	2.6	4.19	97.47	11.0

Figure SM-SYN-19b. HPLC chromatogram of compound **19** at 220 nm and MS spectrum

Compound 20

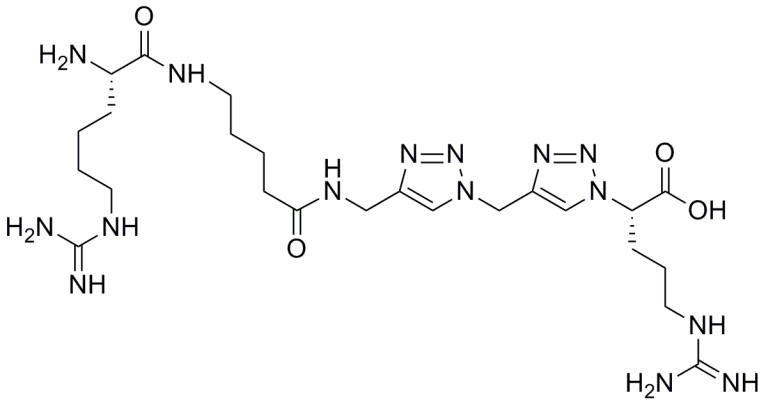
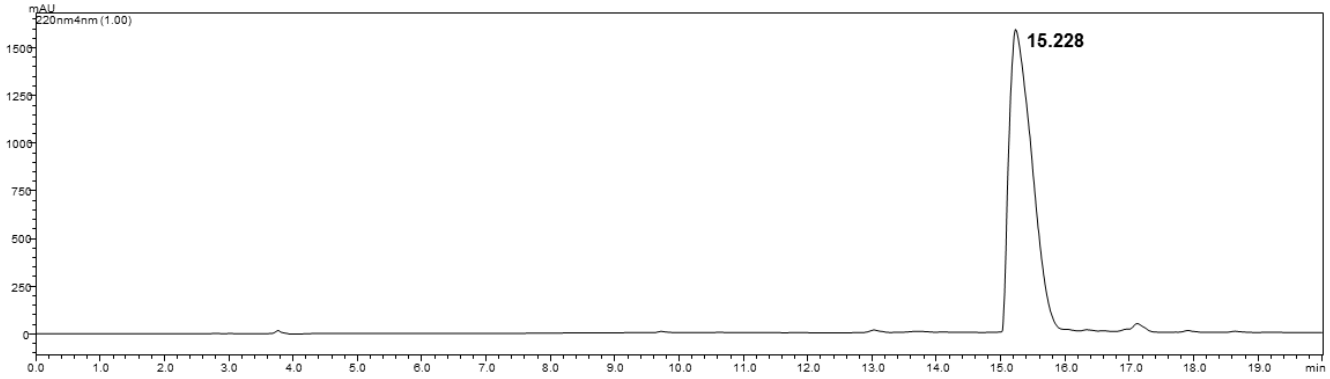
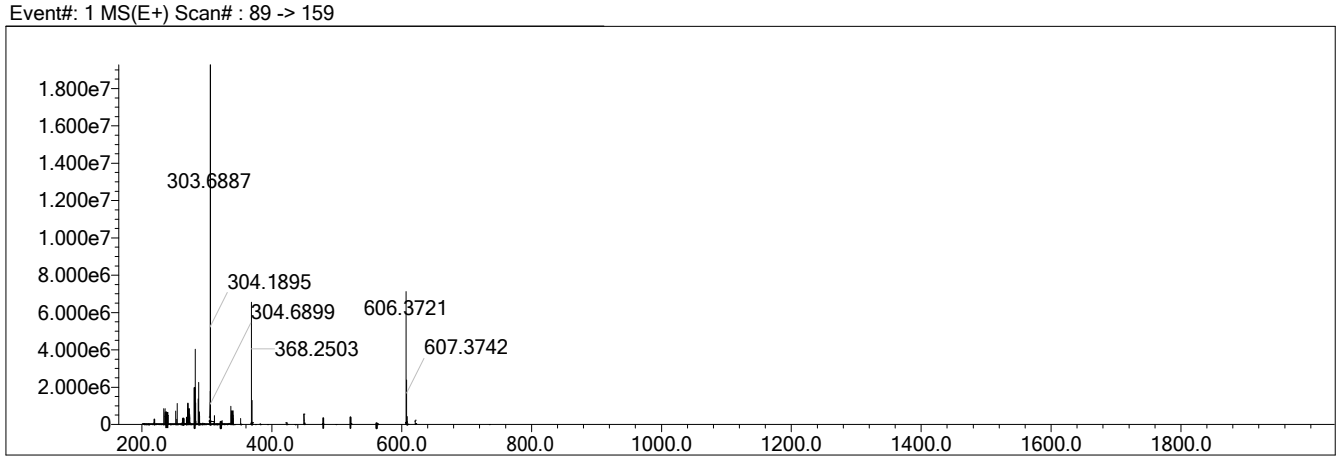


Figure SM-SYN-20a. Structure of compound **20** Har-5Ava-GlyΨ[Trl]GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
4	91.78	C24 H43 N15 O4	[M+H]+	606.3721	606.3695	2.6	4.29	100.00	11.0

Figure SM-SYN-20b. HPLC chromatogram of compound **20** at 220 nm and MS spectrum

Compound 21

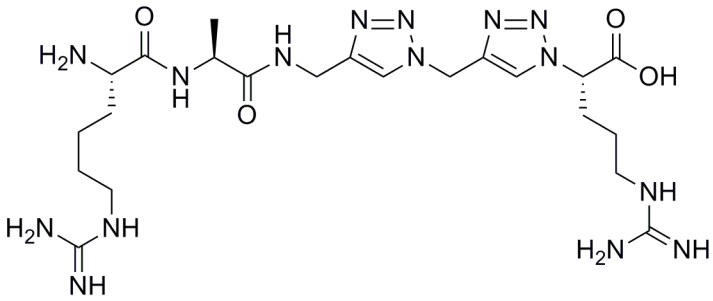
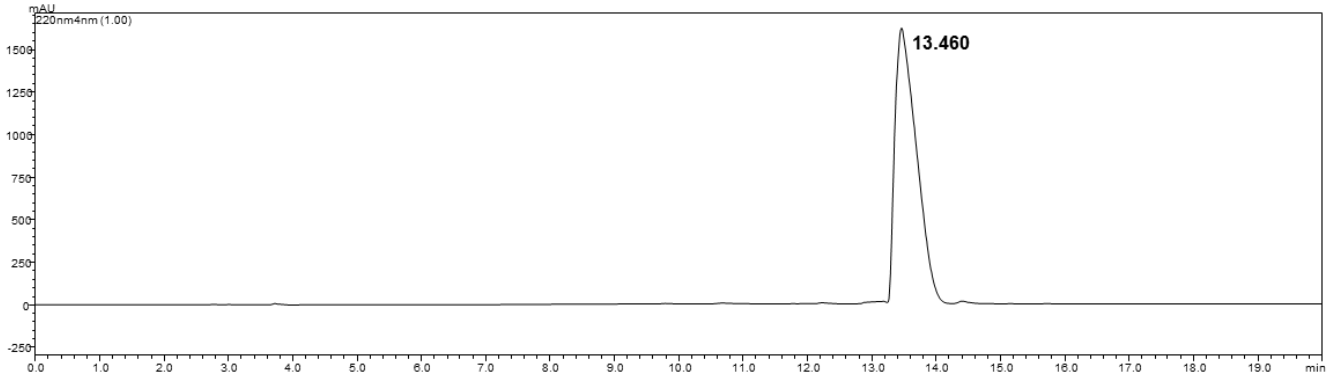
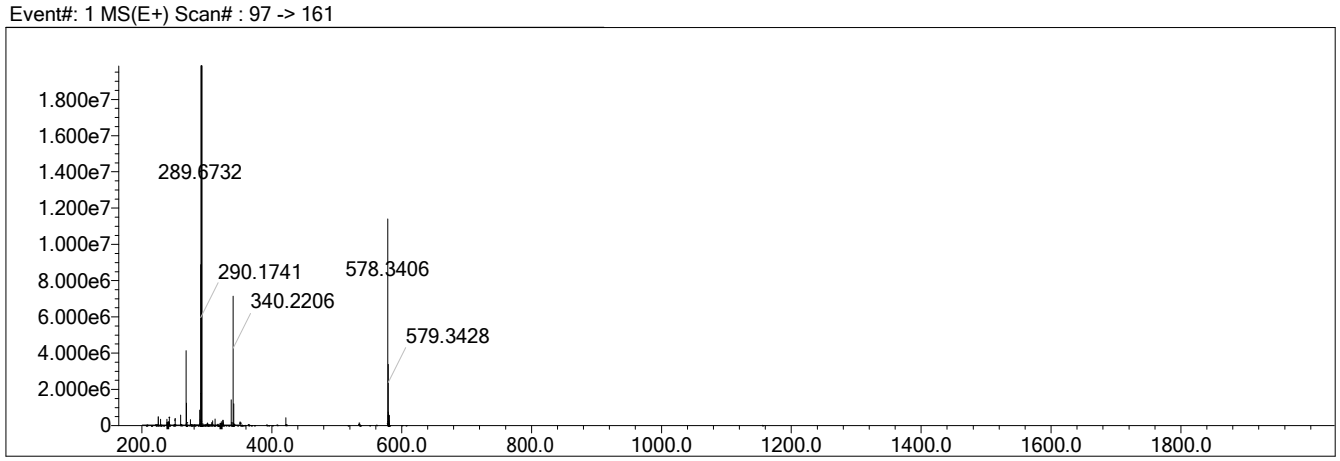


Figure SM-SYN-21a. Structure of compound **21** Har-Ala-GlyΨ[Trl]GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
4	92.13	C22 H39 N15 O4	[M+H]+	578.3406	578.3382	2.4	4.15	100.00	11.0

Figure SM-SYN-21b. HPLC chromatogram of compound **21** at 220 nm and MS spectrum

Compound 22

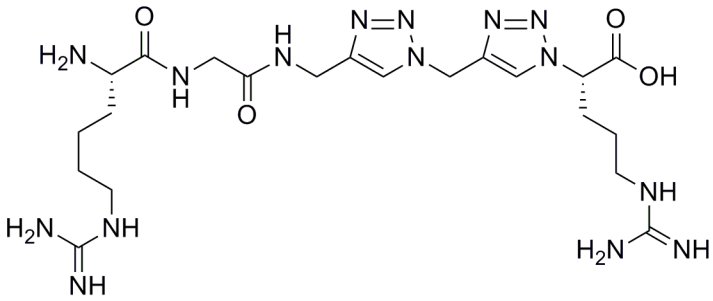
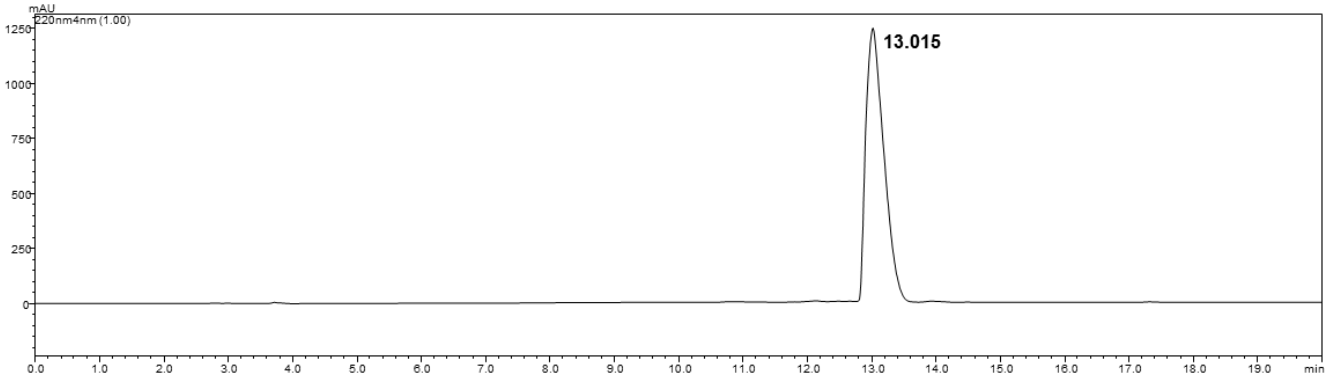
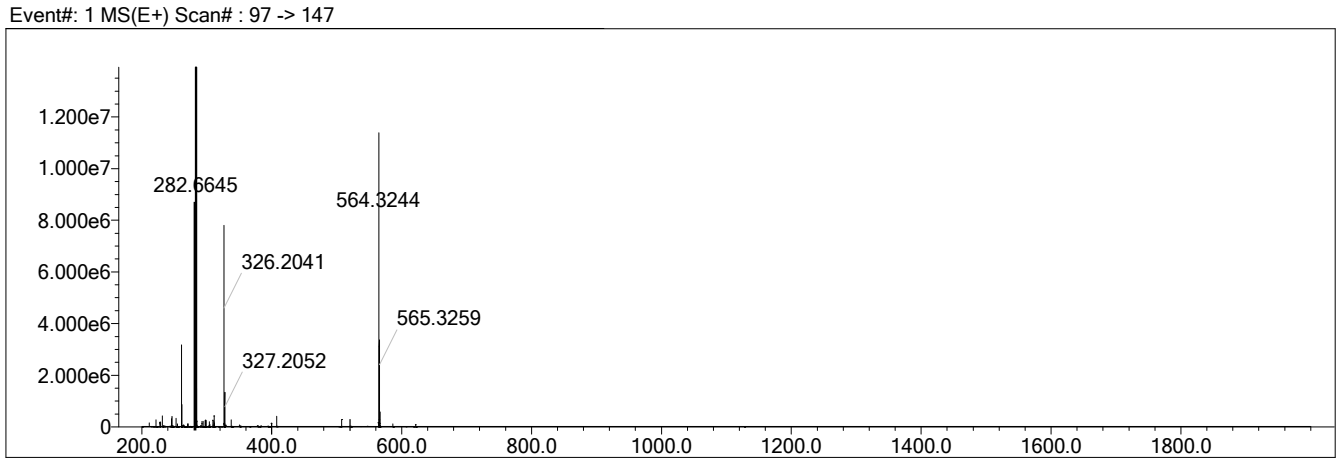


Figure SM-SYN-22a. Structure of compound **22** Har-Gly-GlyΨ[Trl]GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
4	94.53	C21 H37 N15 O4	[M+H]+	564.3244	564.3226	1.8	3.19	100.00	11.0

Figure SM-SYN-22b. HPLC chromatogram of compound **22** at 220 nm and MS spectrum

Compound 23

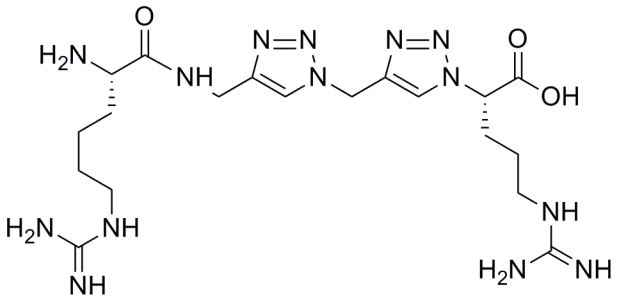
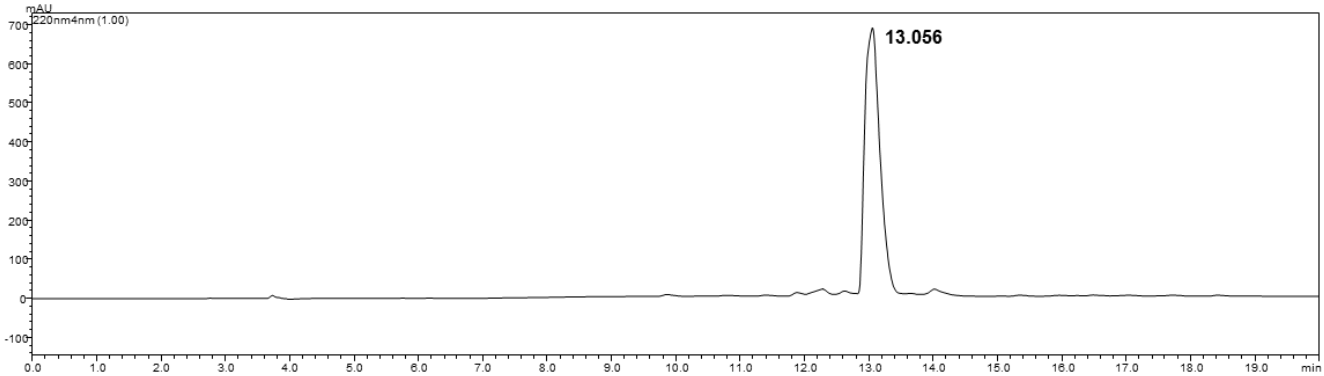
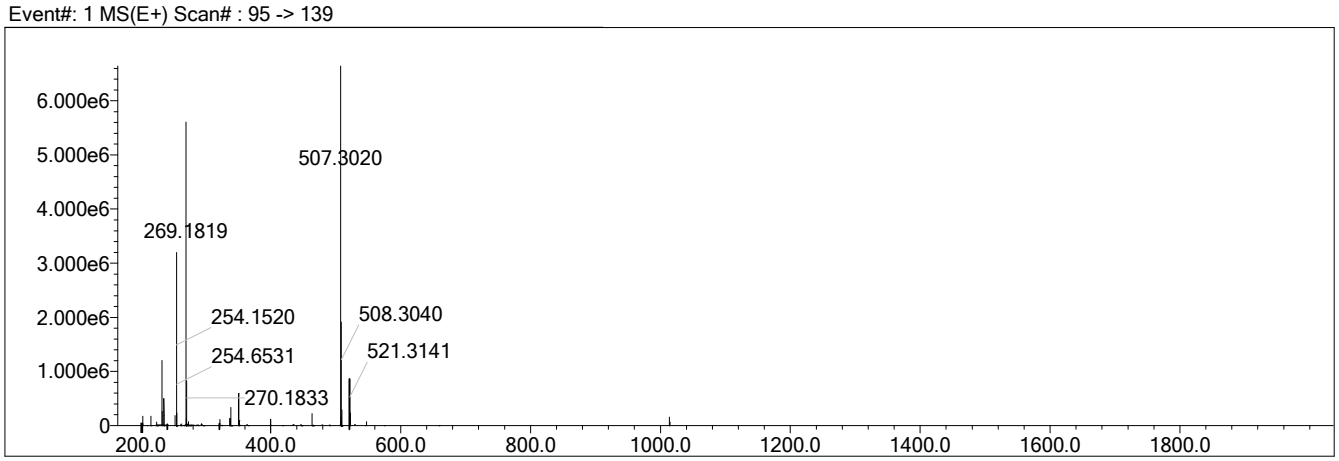


Figure SM-SYN-23a. Structure of compound **23** Har-GlyΨ[Trl]GlyΨ[Trl]Arg.





Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
2	98.08	C19 H34 N14 O3	[M+H]+	507.3020	507.3011	0.9	1.77	100.00	10.0

Figure SM-SYN-23b. HPLC chromatogram of compound **23** at 220 nm and MS spectrum

Compound (24)

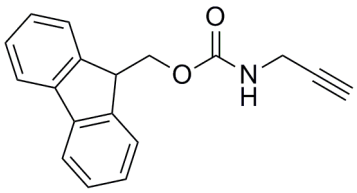


Figure SM-SYN-24a. Structure of compound **24** Fmoc-propargylamine

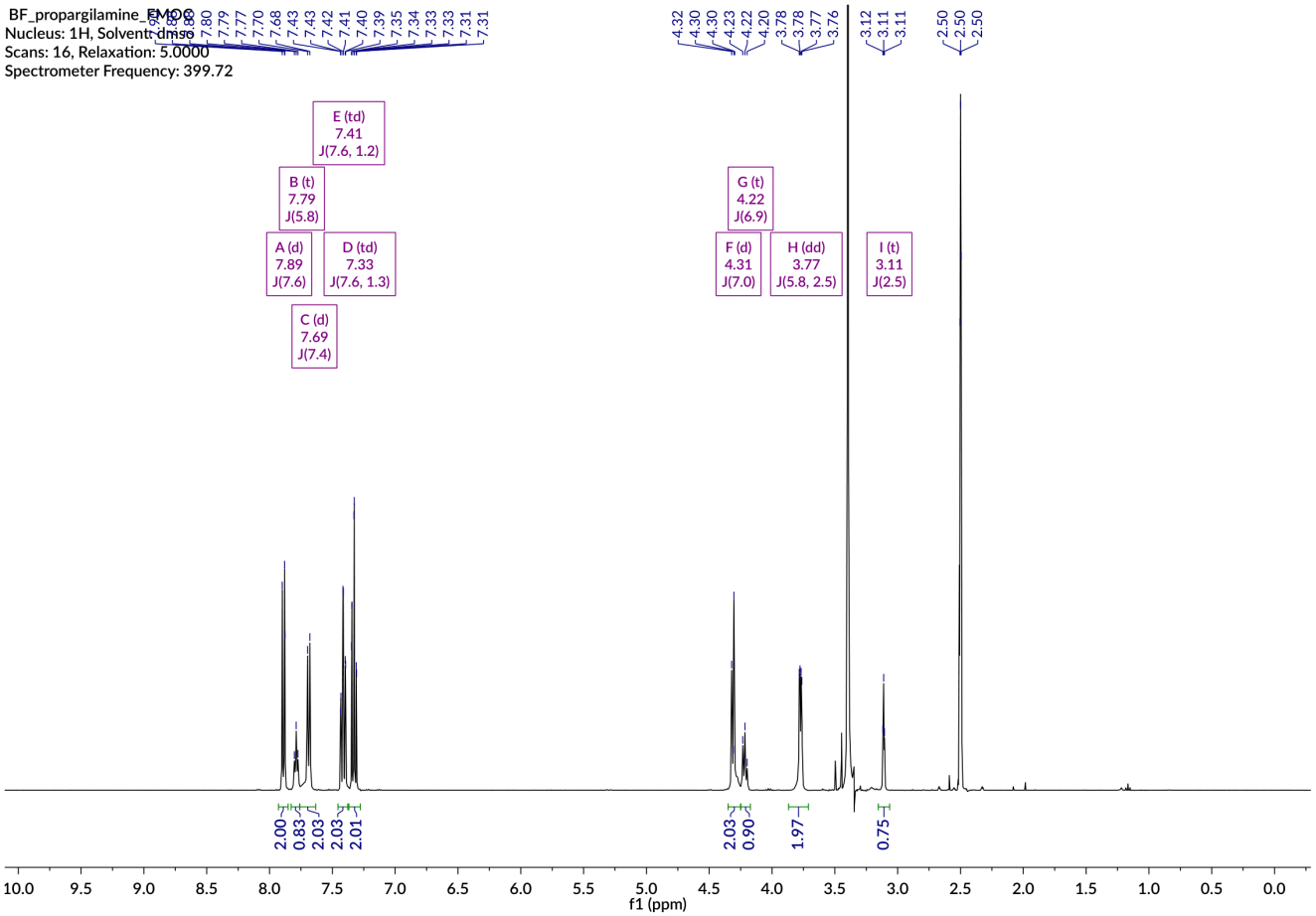


Figure SM-SYN-24b. ^{1}H NMR spectrum of compound **24** Fmoc-propargylamine

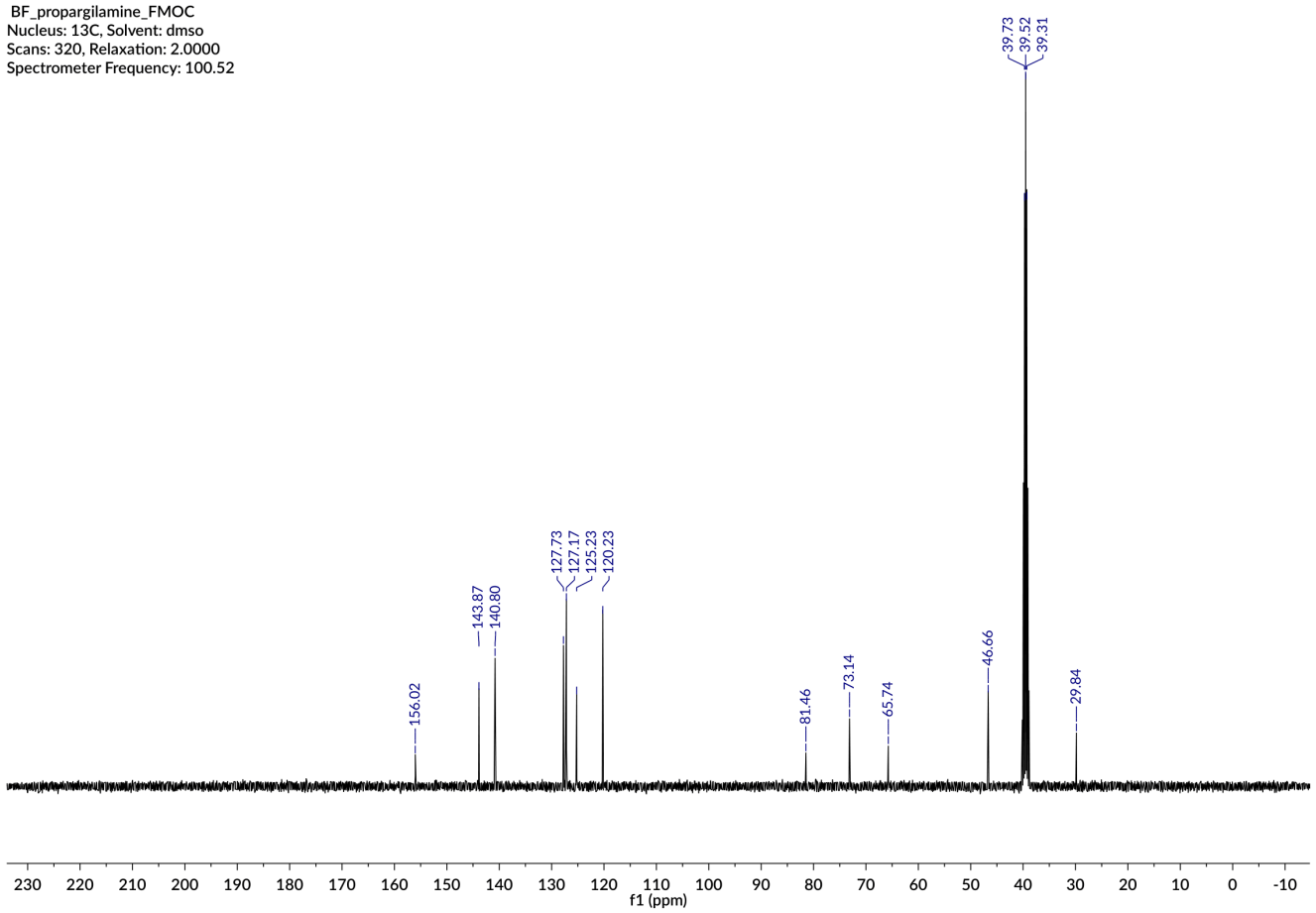


Figure SM-SYN-24c. ^{13}C NMR spectrum of compound **24** Fmoc-propargylamine

SM-INH. Inhibitory activity

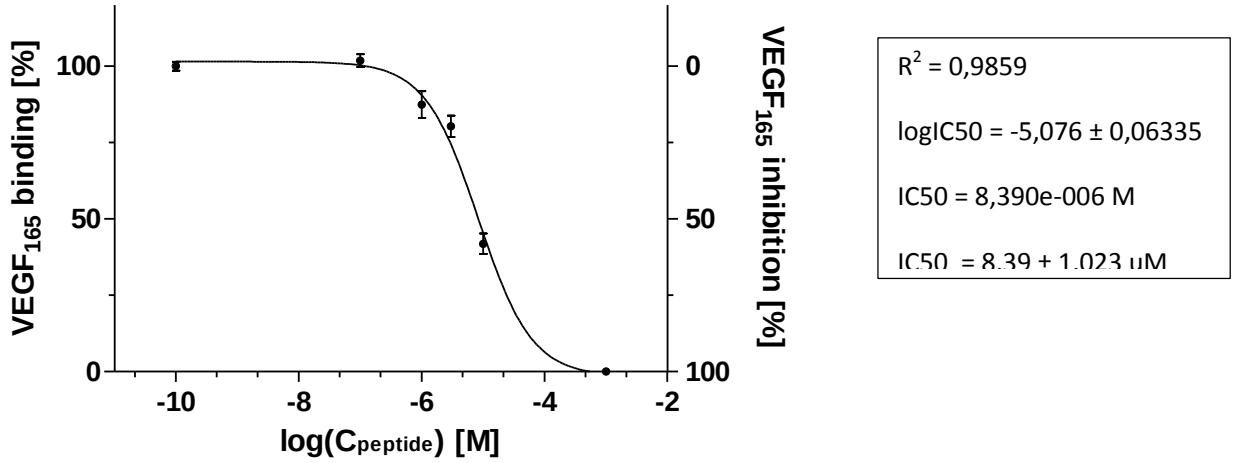


Figure SM-INH-1. Dose-response curve for compound **3** Lys(Har)-GlyΨ[Trl]GlyΨ[Trl]Arg

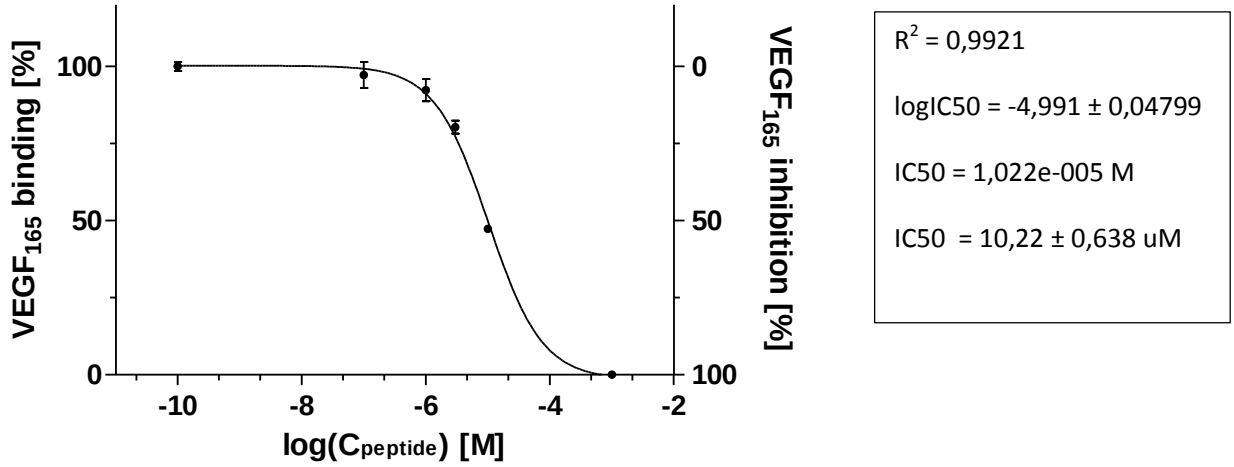


Figure SM-INH-2. Dose-response curve for compound **4** D-Lys(Har)-GlyΨ[Trl]GlyΨ[Trl]Arg

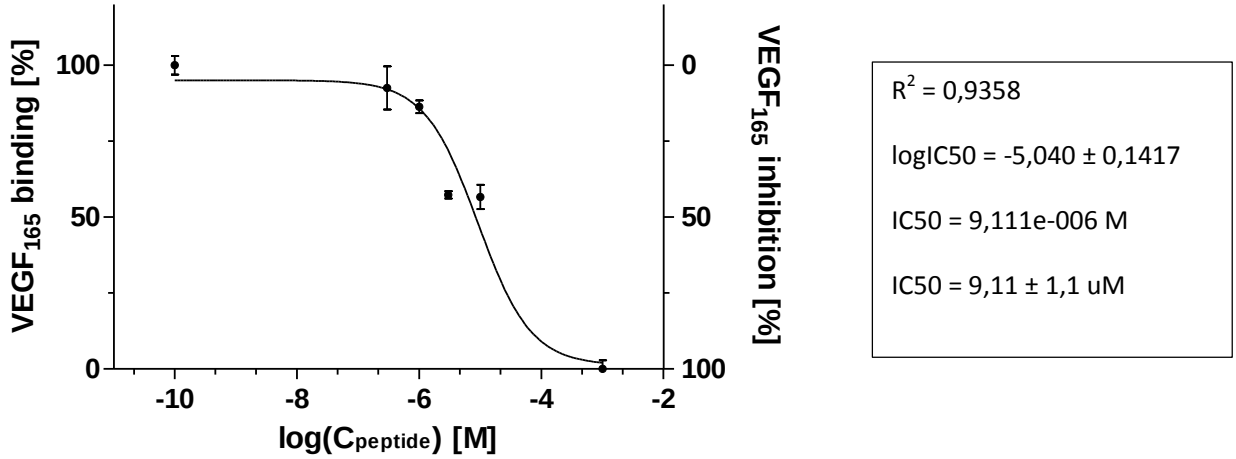


Figure SM-INH-3. Dose-response curve for compound **5** D-Lys(D-Har)-GlyΨ[Trl]GlyΨ[Trl]Arg.

SM-COR. Correlational analysis

Table SM-COR-1. Variable matrix for correlation analysis. Variable symbols explained in Table SM-COR-2.

	sequence	% activity at 10 μM	dis_{N-C}	$dis_{N-C,\ norm}$	$1Trl_{C-N}$	$2Trl_{C-N}$	$3Trl_{C-N}$	am_{1N}	am_{2N}	bb	L_{BR}	L_{2N}
1	H-Lys(hArg)-GlyΨ[Trl]Arg-OH	28.1	25	0.44	1	0	0	1	1	0	1	1
2	H-D-Lys(hArg)-GlyΨ[Trl]Arg-OH	33.1	25	0.44	1	0	0	1	1	0	1	0
3	H-Lys(hArg)-GlyΨ[Trl]GlyΨ[Trl]Arg-OH	58.1	30	1.00	1	1	0	1	1	0	1	1
4	H-D-Lys(hArg)-GlyΨ[Trl]GlyΨ[Trl]Arg-OH	52.6	30	1.00	1	1	0	1	1	0	1	0
5	H-D-Lys(D-hArg)-GlyΨ[Trl]GlyΨ[Trl]Arg-OH	48.5	30	1.00	1	1	0	1	1	0	0	0
6	H-Lys(hArg)-Pro-GlyΨ[Trl]Arg-OH	18.3	28	0.78	1	0	0	1	1	0	1	1
7	H-D-Lys(hArg)-Pro-GlyΨ[Trl]Arg-OH	38.4	28	0.78	1	0	0	1	1	0	1	0
8	H-Lys(hArg)-Phe-GlyΨ[Trl]Arg-OH	30.9	28	0.78	1	0	0	1	1	0	1	1
9	H-D-Lys(hArg)-Phe-GlyΨ[Trl]Arg-OH	37.9	28	0.78	1	0	0	1	1	0	1	0
10	H-Lys(hArg)-GlyΨ[Trl]Ala-Arg-OH	43.3	28	0.78	0	1	0	1	1	0	1	1
11	H-Lys(hArg)-GlyΨ[Trl]Gly-Arg-OH	30.6	28	0.78	0	1	0	1	1	0	1	1
12	H-hArg-Pro-GlyΨ[Trl]Arg-OH	9.2	21	0.00	1	0	0	1	0	1	1	1
13	H-hArg-GlyΨ[Trl]GlyΨ[Trl]GlyΨ[Trl]Arg-OH	34.7	28	0.78	1	1	1	1	0	1	1	1
14	H-Lys(Fmocα-hArg)-GlyΨ[Trl]GlyΨ[Trl]Arg-OH	57.7	30	1.00	1	1	0	0	1	0	1	1
15	H-D-Lys(Fmocα-hArg)-GlyΨ[Trl]GlyΨ[Trl]Arg-OH	43.7	30	1.00	1	1	0	0	1	0	1	0
16	H-hArg-Lys-GlyΨ[Trl]GlyΨ[Trl]Arg-OH	36.5	26	0.56	1	1	0	1	0	1	1	1
17	H-Dab(hArg)-GlyΨ[Trl]GlyΨ[Trl]Arg-OH	41.3	28	0.78	1	1	0	1	1	0	1	1
18	H-Dap(hArg)-GlyΨ[Trl]GlyΨ[Trl]Arg-OH	25.3	27	0.67	1	1	0	1	1	0	1	1
19	H-hArg-6Ahx-GlyΨ[Trl]GlyΨ[Trl]]Arg-OH	30.5	30	1.00	1	1	0	1	0	1	1	0.5
20	H-hArg-5Ava-GlyΨ[Trl]GlyΨ[Trl]Arg-OH	29.7	29	0.89	1	1	0	1	0	1	1	0.5
21	H-hArg-Ala-GlyΨ[Trl]GlyΨ[Trl]]Arg-OH	27.8	26	0.56	1	1	0	1	0	1	1	1
22	H-hArg-Gly-GlyΨ[Trl]GlyΨ[Trl]Arg-OH	35.7	26	0.56	1	1	0	1	0	1	1	0.5
23	H-hArg-GlyΨ[Trl]GlyΨ[Trl]Arg-OH	20	23	0.22	1	1	0	1	0	1	1	1

Table SM-COR-2. Explanation of variables symbols.

$dis_{N\text{-}C}$	topological distance between guanidines at N to C direction
$1Trl_{C\text{-}N}$	triazole unit instead of the 1st amide/peptide bond C to N direction
$2Trl_{C\text{-}N}$	triazole unit instead of the 2nd amide/peptide bond C to N direction
$3Trl_{C\text{-}N}$	triazole unit instead of the 3rd amide/peptide bond C to N direction
am_{1N}	free amine present by the 1st amide/peptide bond (going from the N-terminus or from the residue attached to the N-terminal side chain)
am_{2N}	free amine present by the 2nd amide/peptide bond (going from the N-terminus or from the residue attached to the N-terminal side chain)
bb	backbone (1) or sidechain (0) coupling at N-terminus
L_{1N}	L-amino acid at the residue attached to the N-terminal side chain
L_{2N}	L-amino acid at the N-terminal residue; 0.5 value means achiral AA

Listing SM-COR-1. Equations of the models developed by correlational analysis.

1. $act = 3.7 * dis_{N\text{-}C} - 67.3$, $R^2 = 0.54$, n = 23 (MODEL 1)
2. $act = 8.6\ (\pm 5.0) + 20.9\ (\pm 8.6) * dis_{N\text{-}C,\ norm} + 8.7\ (\pm 4.5) * am_{2N} + 8.6\ (\pm 4.6) * 2Trl_{C\text{-}N}$, $R^2 = 0.63$, n = 23. (MODEL 2)
3. $act = -\ 34.7\ (\pm 27.2) + 2.0\ (\pm 1.1) * dis_{N\text{-}C} + 6.2\ (\pm 6.9) * 1Trl_{C\text{-}N} + 10.0\ (\pm 5.3) * 2Trl_{C\text{-}N} + 2.0\ (\pm 9.0) * 3Trl_{C\text{-}N} - 3.6\ (\pm 6.8) * am_{1N} + 10.5\ (\pm 5.5) * am_{2N}$, $R^2 = 0.66$, n = 23.
4. $act = -\ 41.8\ (\pm 23.0) + 2.0\ (\pm 1.0) * dis_{N\text{-}C} + 7.0\ (\pm 6.4) * 1Trl_{C\text{-}N} + 10.6\ (\pm 4.9) * 2Trl_{C\text{-}N} + 10.8\ (\pm 4.9) * am_{2N}$, $R^2 = 0.66$, n = 23.
5. $act = -\ 25.9\ (\pm 26.0) + 1.9\ (\pm 1.0) * dis_{N\text{-}C} + 10.3\ (\pm 4.8) * 2Trl_{C\text{-}N} + 9.1\ (\pm 4.5) * am_{2N} - 4.9\ (\pm 4.2) * L_{2N}$, $R^2 = 0.66$, n = 23.

SM-SIM. Simulations

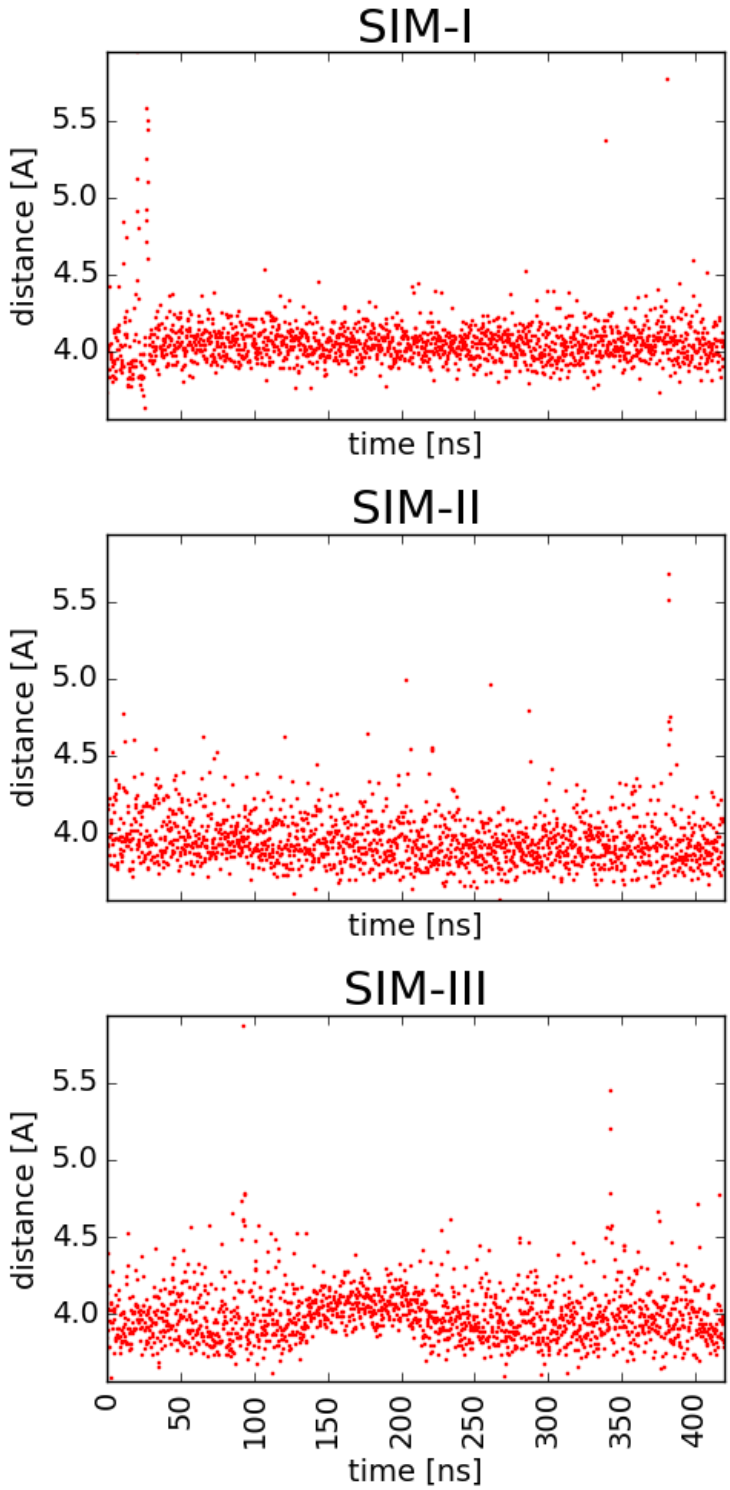


Figure SM-SIM-1. Time evolution of distance between Cγ atom of Asp320 and Cζ of Arg residue in compound 3. Data come from simulations SIM-I, SIM-II, SIM-III.

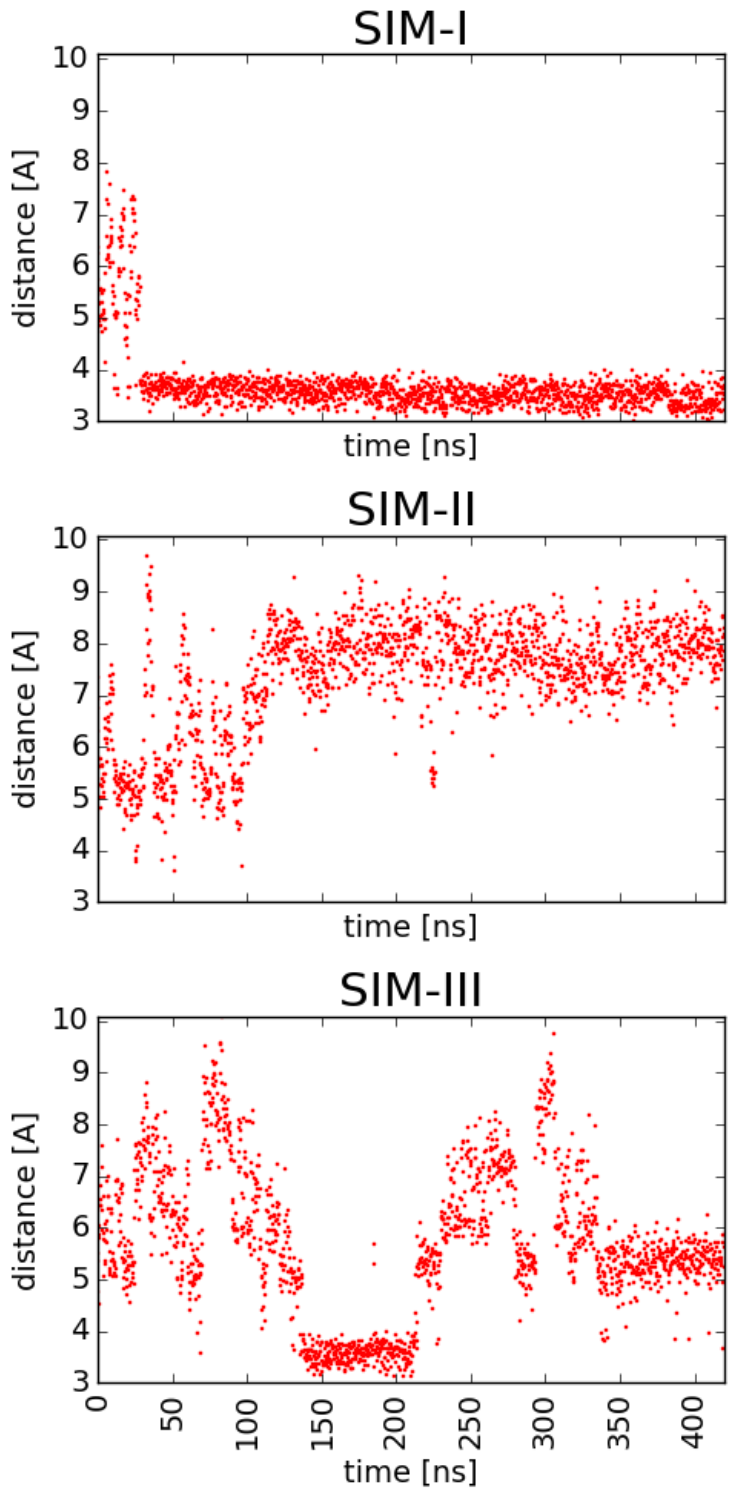


Figure SM-SIM-2. Time evolution of distance between Oγ atom of Ser346 and C of Arg residue in compound 3. Data come from simulations SIM-I, SIM-II, SIM-III.

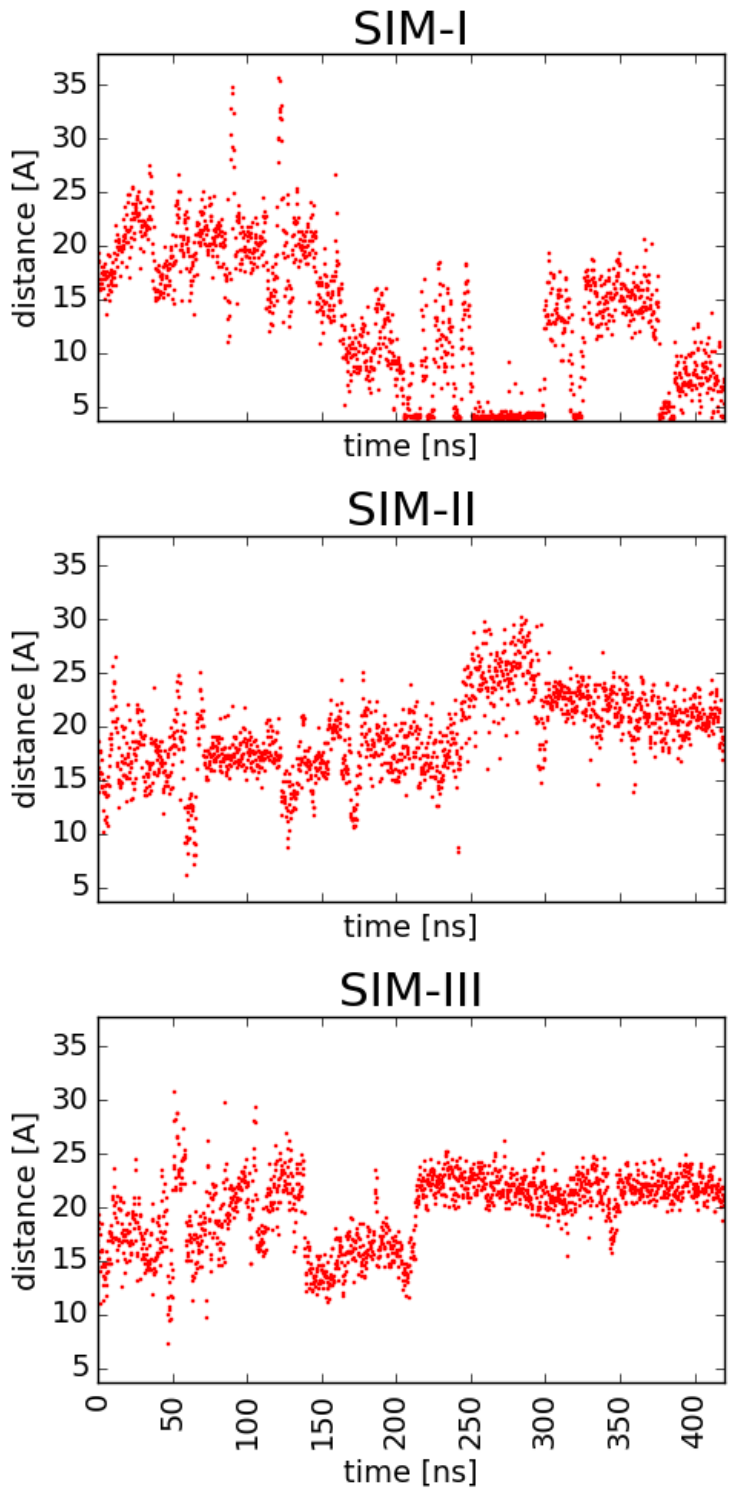


Figure SM-SIM-3. Time evolution of distance between Cδ atom of Glu319 and Cζ of Har residue in compound 3. Data come from simulations SIM-I, SIM-II, SIM-III.

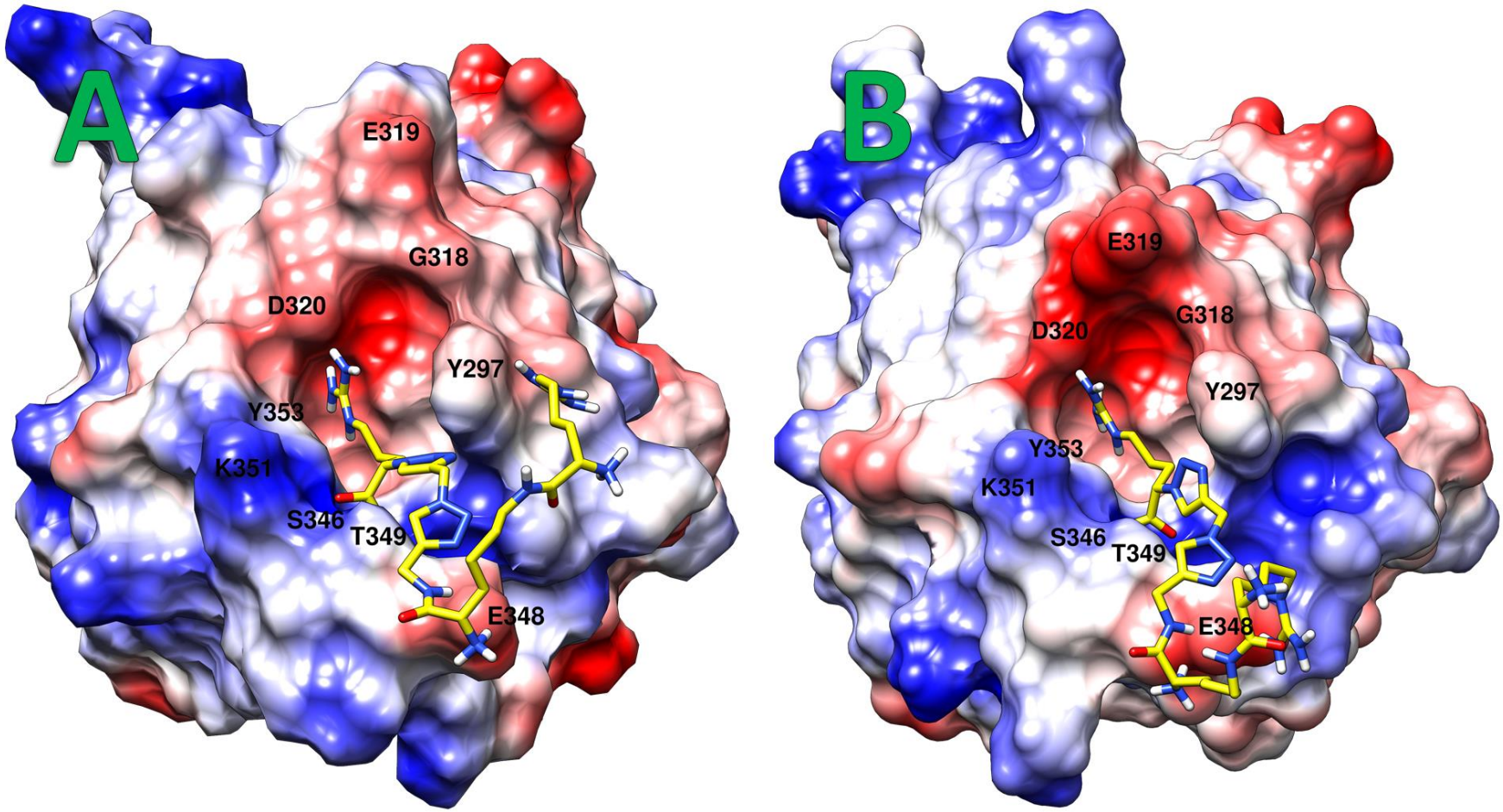


Figure SM-SIM-4. Representative snapshots out of the trajectories presented according to the convention given in the main paper. **A.** SIM-I, t = 50.0 ns **B.** SIM-I, t = 100.0 ns. *continued*

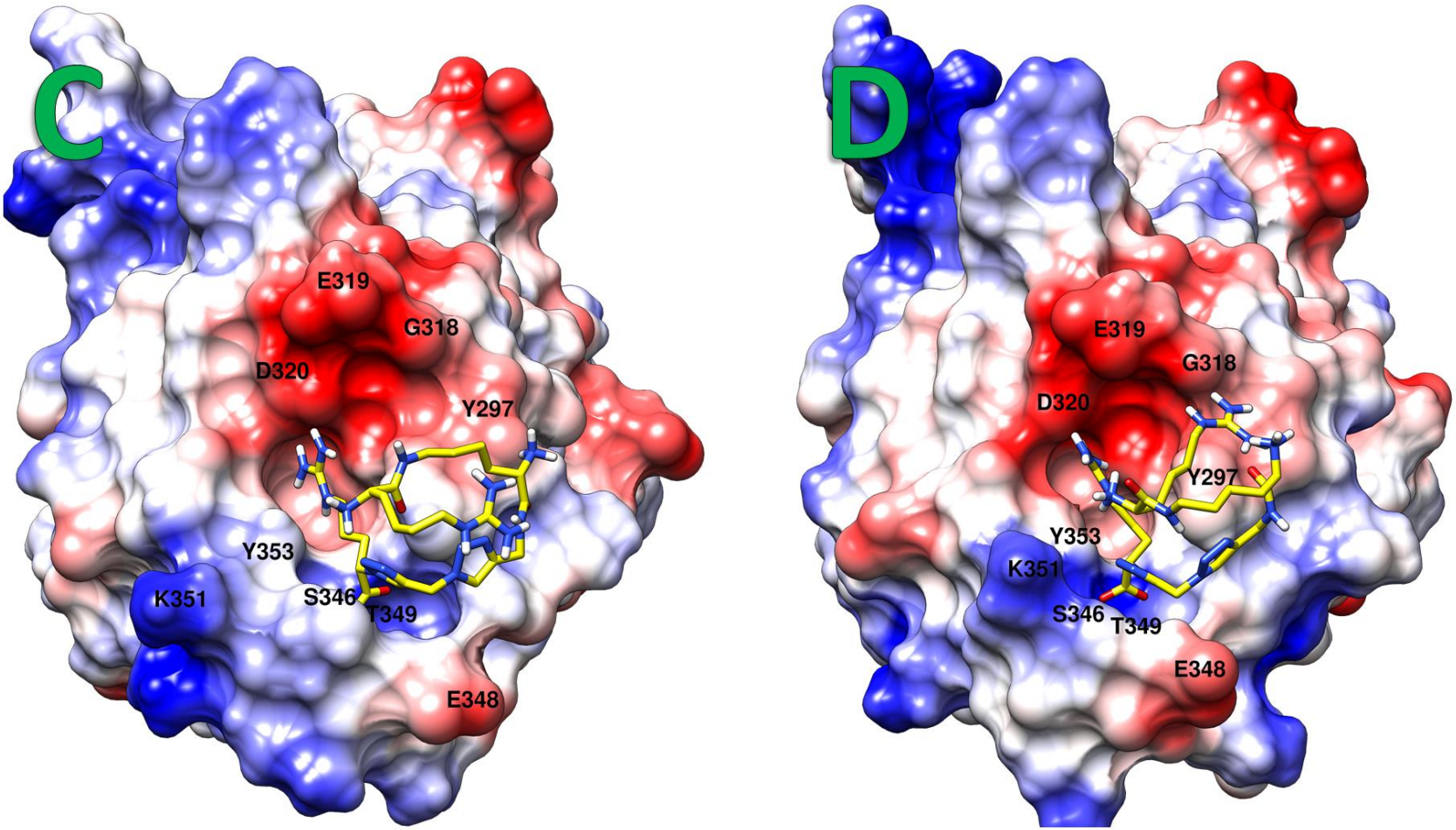


Figure SM-SIM-4. *Continuation* Representative snapshots out of the trajectories presented according to the convention given in the main paper. **C.** SIM-I, t = 150.0 ns **D.** SIM-I, t = 350.0 ns. *continued*

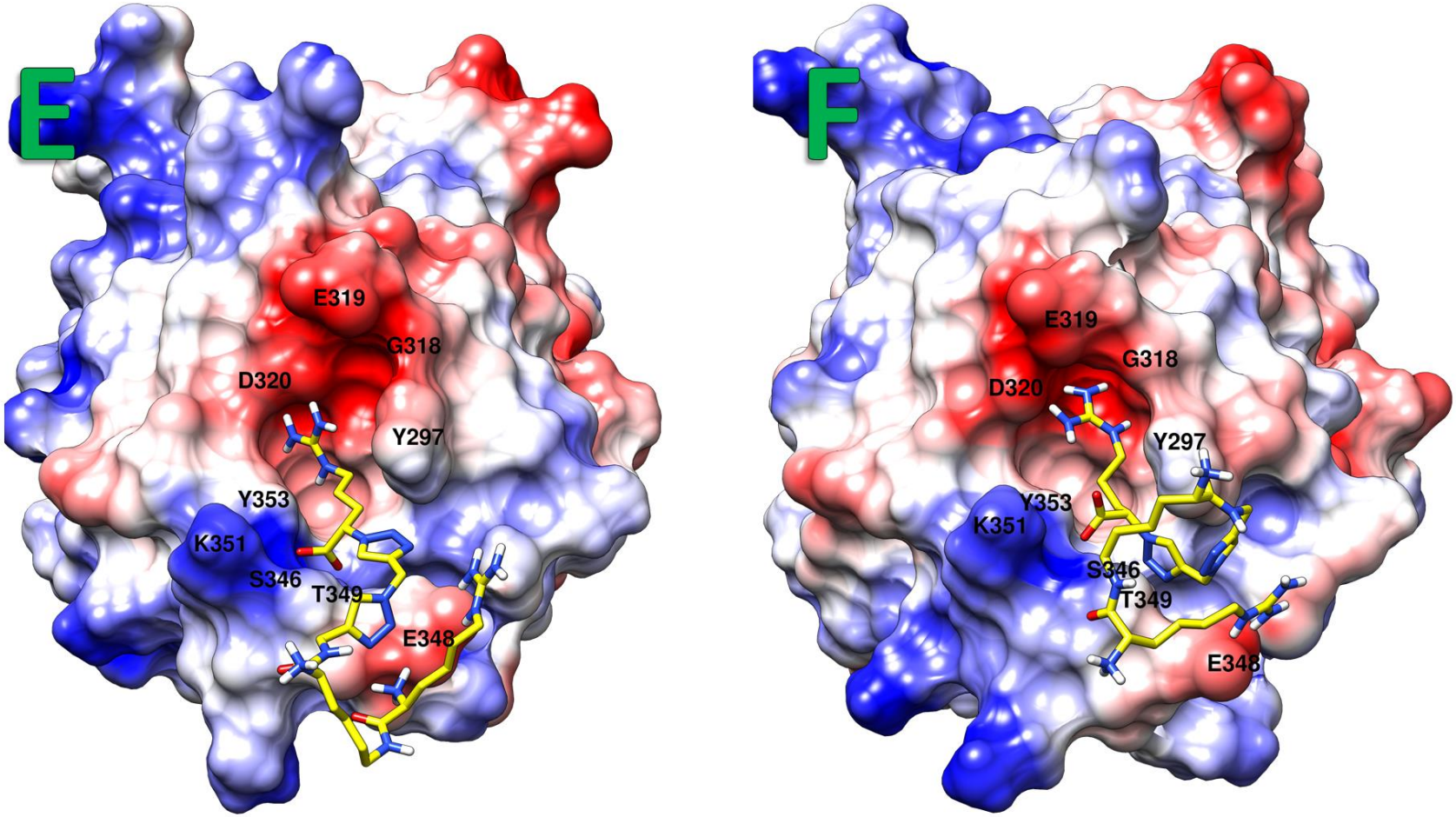


Figure SM-SIM-4. *Continuation* Representative snapshots out of the trajectories presented according to the convention given in the main paper. **E.** SIM-I, t = 400.0 ns **F.** SIM-II, t = 100.0 ns. *continued*

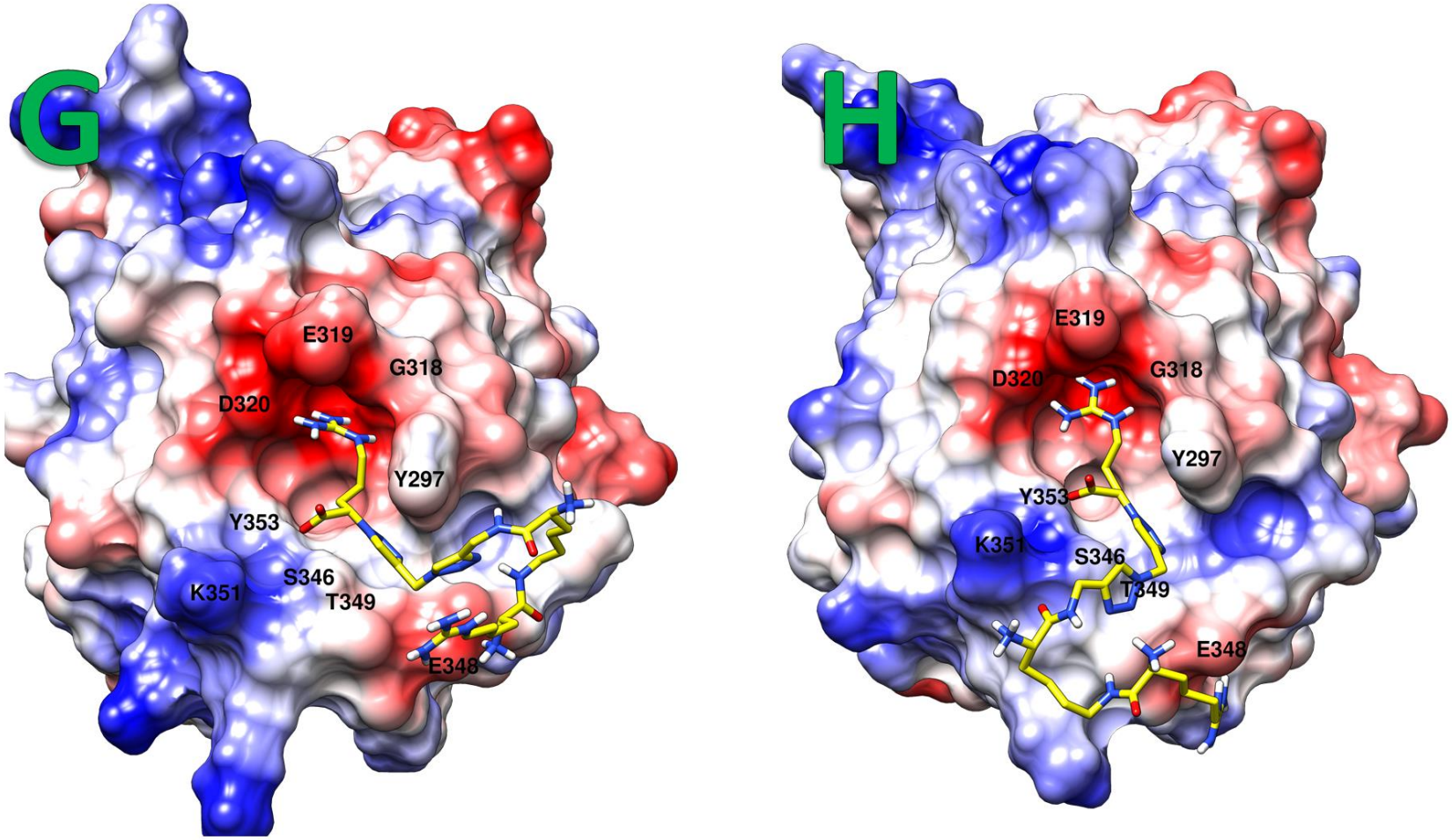


Figure SM-SIM-4. *Continuation* Representative snapshots out of the trajectories presented according to the convention given in the main paper. **G.** SIM-II, t = 200.0 ns **H.** SIM-II, t = 350.0 ns. *continued*

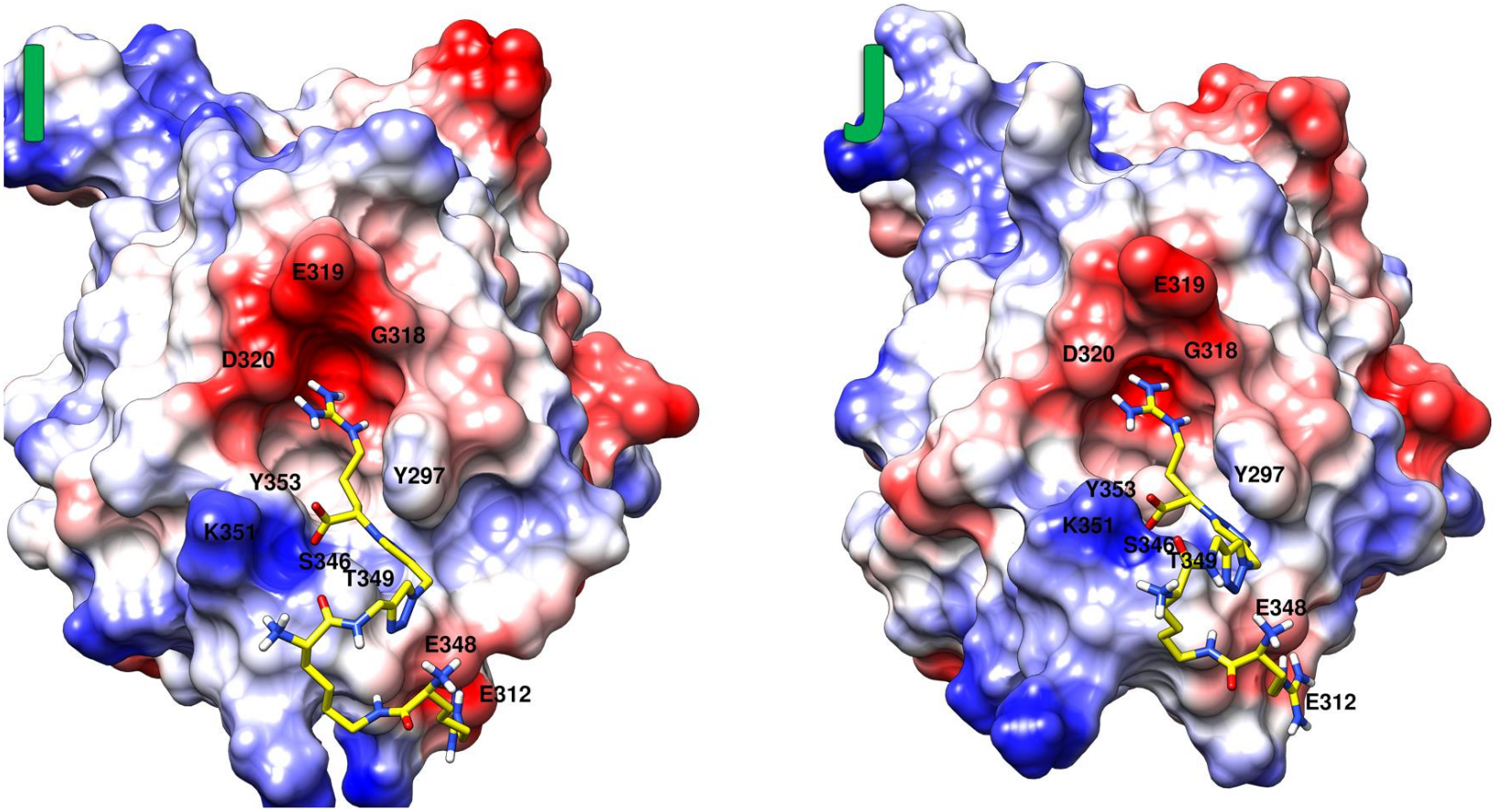


Figure SM-SIM-4. *Continuation* Representative snapshots out of the trajectories presented according to the convention given in the main paper. **I.** SIM-III, t = 250.0 ns **J.** SIM-III, t = 400.0 ns.

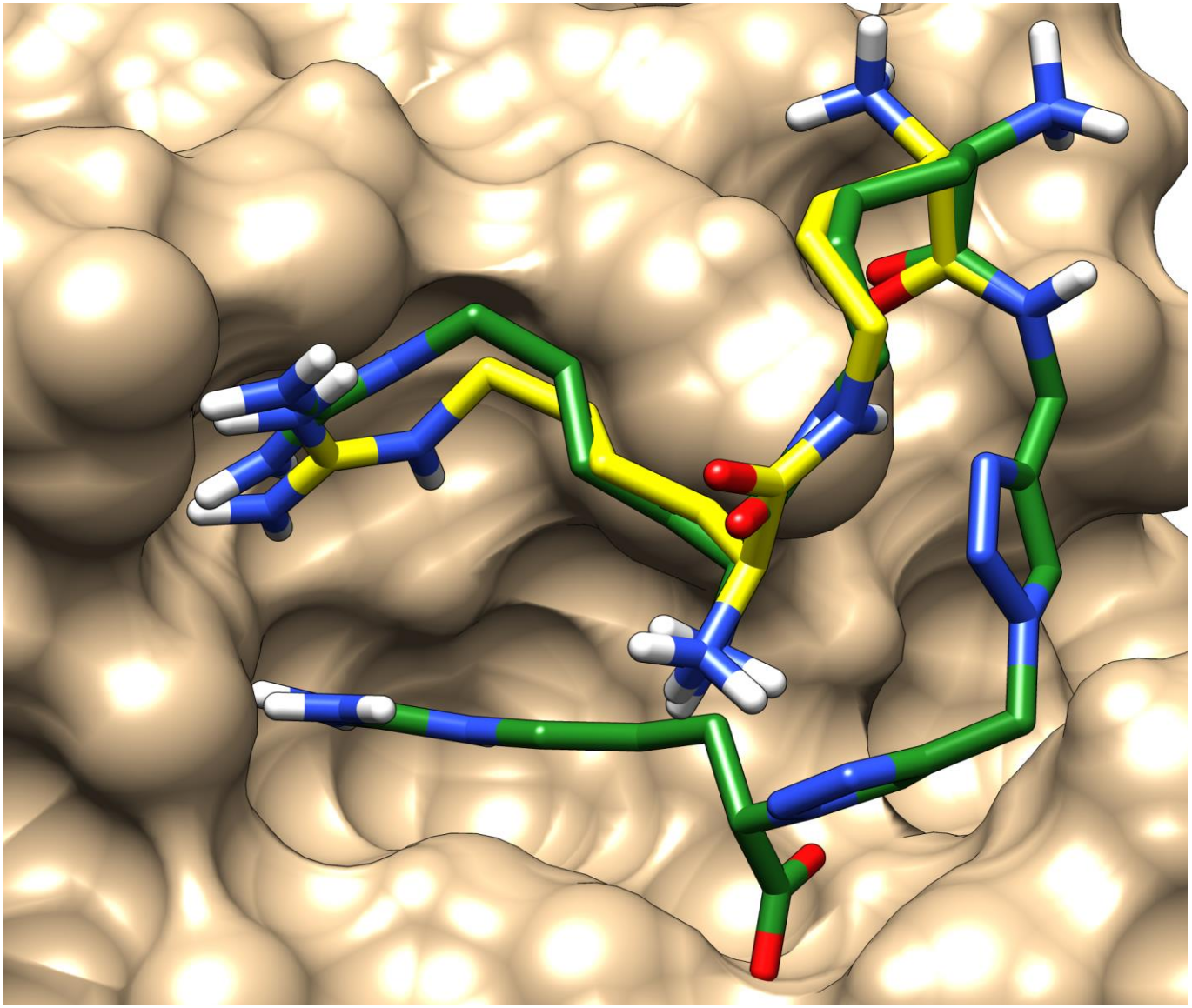


Figure SM-SIM-5. Complex of compound **3** (yellow) with NRP-1 as found in SIM-I, a representative snapshot of the binding mode discussed in the main text. In forest green given is a copy of molecule 3 but with inverted stereochemistry at Cα of Lys residue and optimized geometry of the Lys(Har) fragment (restraints of protein atoms and the remaining part of compound **3**). As it can be seen, the inversion of stereochemistry does not require major readjustment of the Lys(Har) fragment and allows for retaining of the key contacts.

Table SM-SIM-1. Persistency of the interactions between compound **3** and Neuropilin-1 as found in molecular dynamics simulations.

	SIM-I	**SIM-IA**	**SIM-IB**	**SIM-IC**	**SIM-II**	**SIM-III**
C-terminal Arg guanidine with Asp320	99%	100%	100 %	100%	100%	100%
C-terminal Arg carboxylate with Ser346	93%	100%	100%	100%	7%	26%
C-terminal Arg carboxylate with Thr349	96%	75%	98%	99%	20%	67%
Har guanidine with Glu319	19%	27%	50%	42%	0%	0%
hydrogen of the amide bond joining Har and Lys with the phenolic function of Tyr297	28%	30%	48%	45%	8%	2%
$2Trl_{C\text{-}N}$ (C5H) with Glu348	24%	16%	36%	47%	1%	0%

SM-RES. Proteolytic resistance

Compound 3

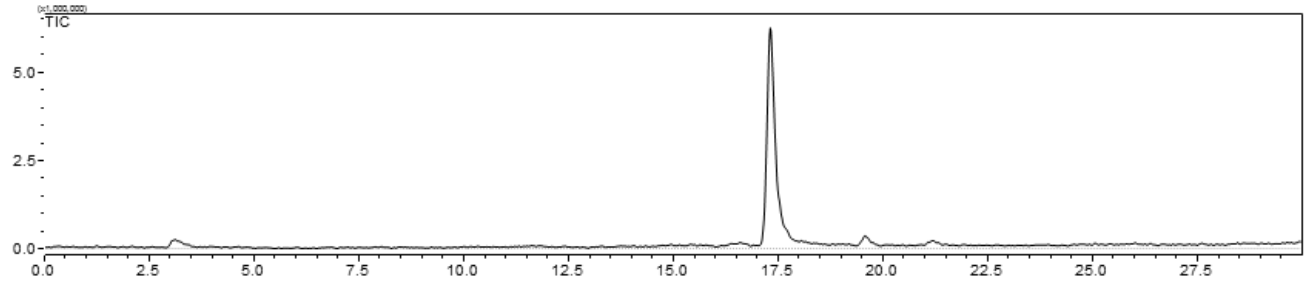


Figure SM-STA-1. TIC chromatogram for the blank compound **3**.

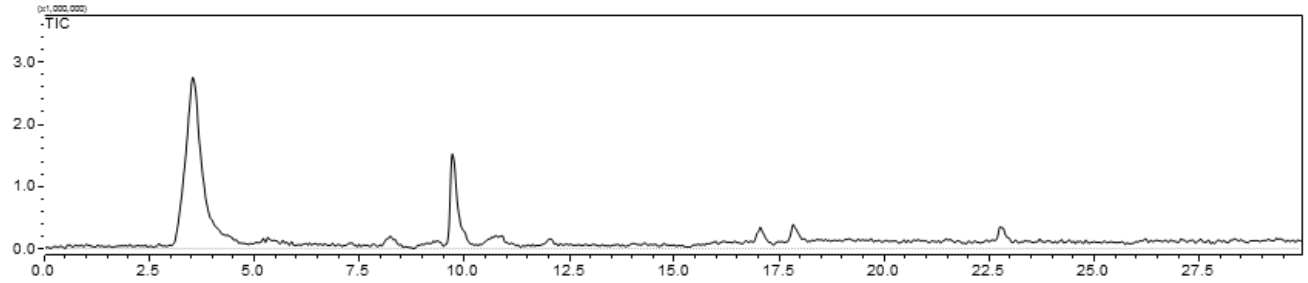


Figure SM-STA-2. TIC chromatogram for the blank human plasma.

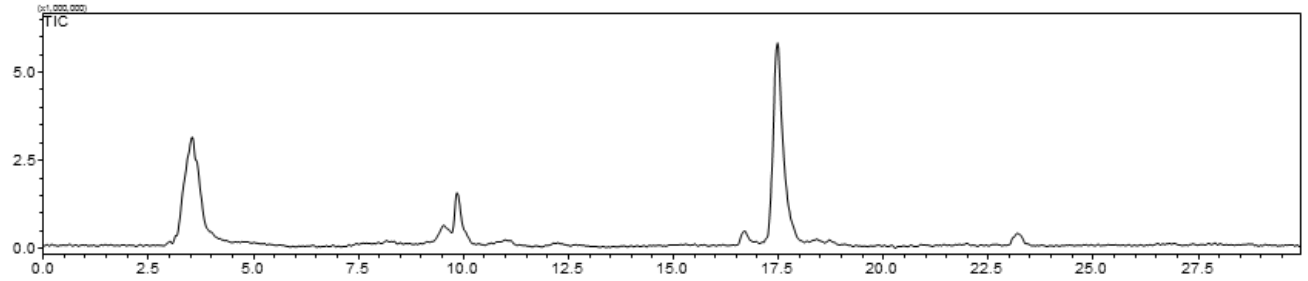


Figure SM-STA-3. TIC chromatogram for the compound **3** at starting point (0 h).

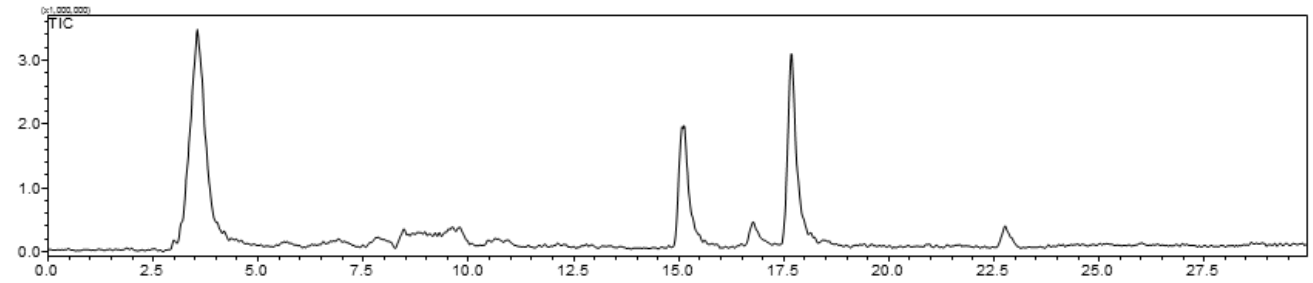


Figure SM-STA-4. TIC chromatogram for the compound **3** at ending point (48 h).

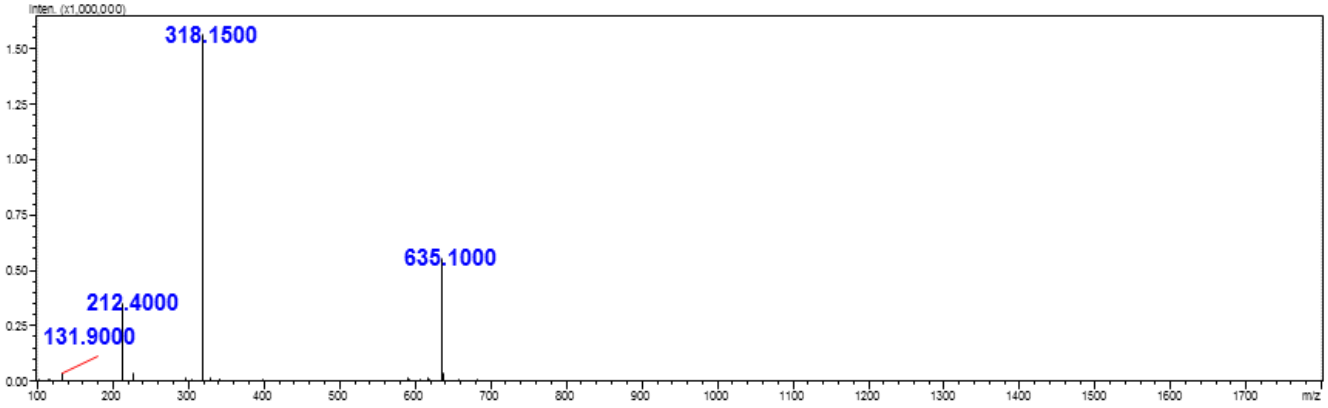


Figure SM-STA-5. Mass spectrum for the compound **3** (RT c.a. 17.5 min).

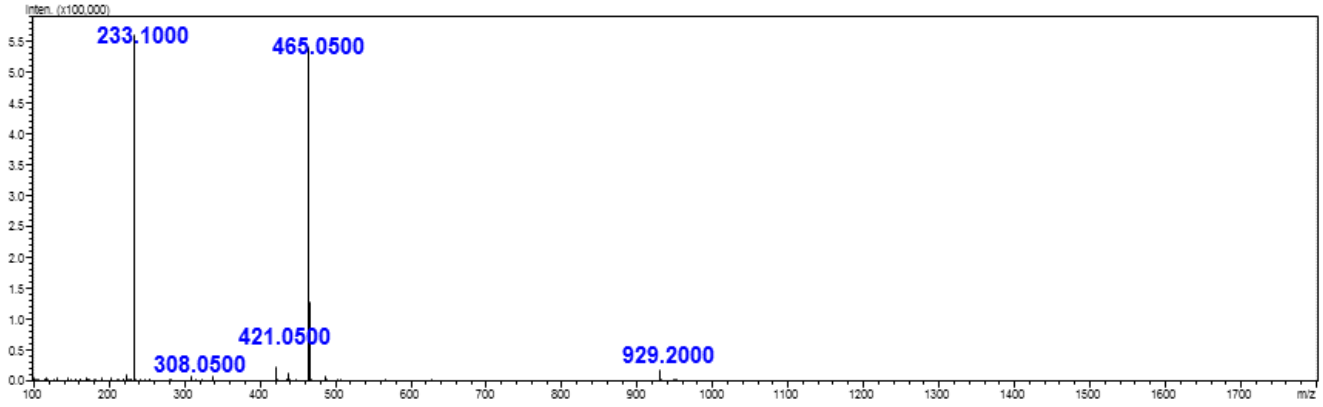


Figure SM-STA-6. Mass spectrum for metabolite (RT c.a. 15 min).

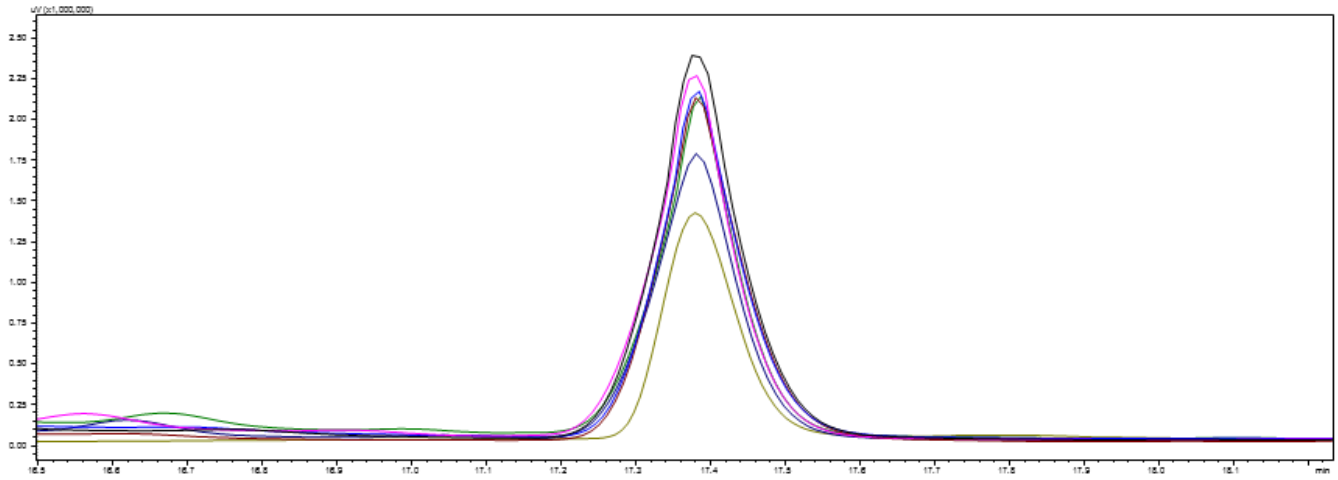


Figure SM-STA-7. Overlap of chromatograms at 210 nm for the compound **3** at all timepoints.

Table SM-STA-1. Data sheet for figure 8 in main text taken from peak integration for compound **3**.

time [h]	Area 1st repet.	Area 2nd repet.	Area 3rd repet.	Area average (AV)	Standard deviation (SD)	AV/SD	Relative
0	18215057	18610127	18966987	18597390	307106	1.7%	100.0%
8		17025853	16948717	16987285	38568	0.2%	91.3%
16		16487412	16990000	16738706	251294	1.5%	90.0%
24	15387650	16649994	16850114	16295919	647419	4.0%	87.6%
32		15197203	15216682	15206943	9740	0.1%	81.8%
40	13337943	13648096	13983715	13656585	263704	1.9%	73.4%
48	12668865	14197196		13433031	764166	5.7%	72.2%

Compound 4

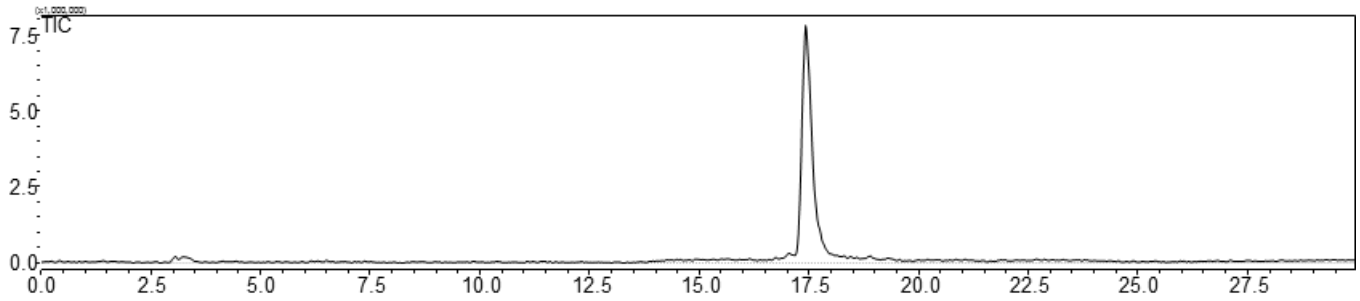


Figure SM-STA-8. TIC chromatogram for the blank compound **4**.

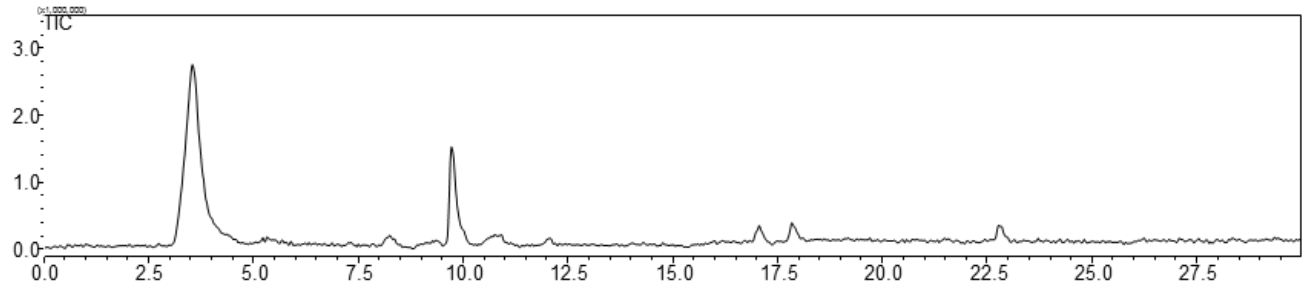


Figure SM-STA-9. TIC chromatogram for the blank human plasma.

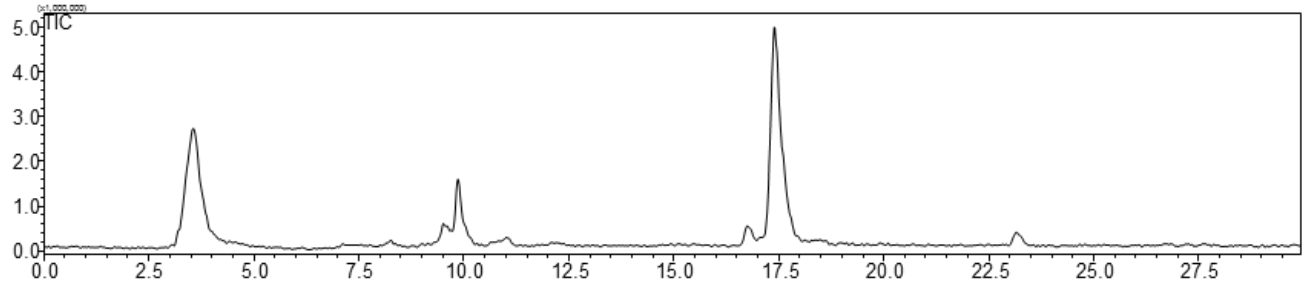


Figure SM-STA-10. TIC chromatogram for the compound **4** at starting point (0 h).

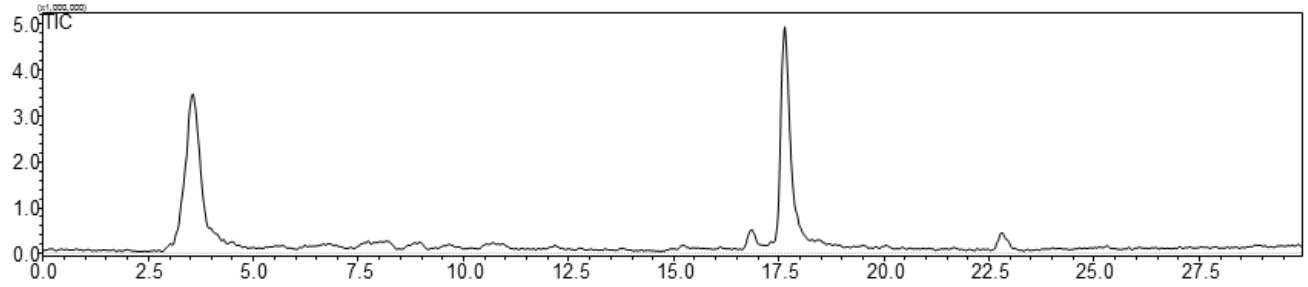


Figure SM-STA-11. TIC chromatogram for the compound **4** at ending point (48 h).

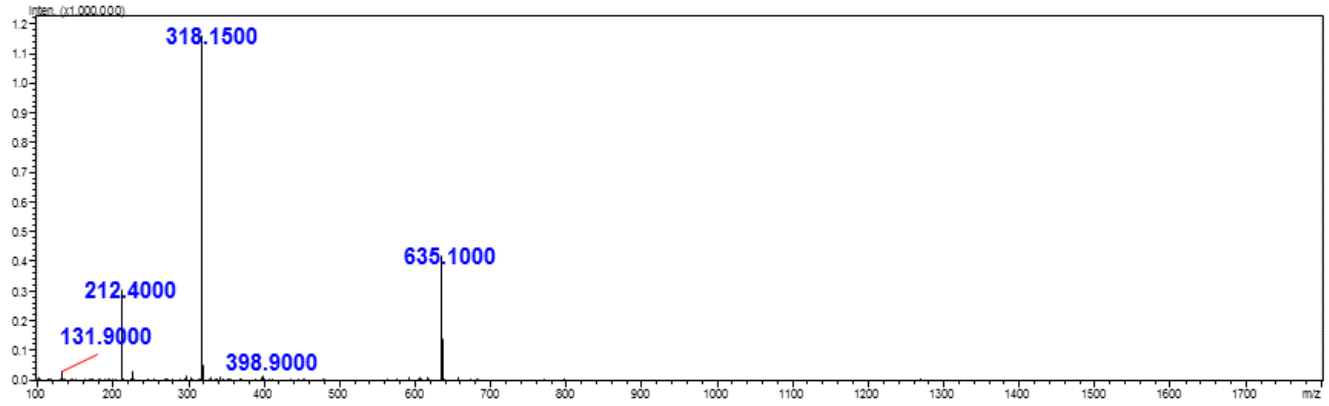


Figure SM-STA-12. Mass spectrum for the compound **4** (RT c.a. 17.5 min).

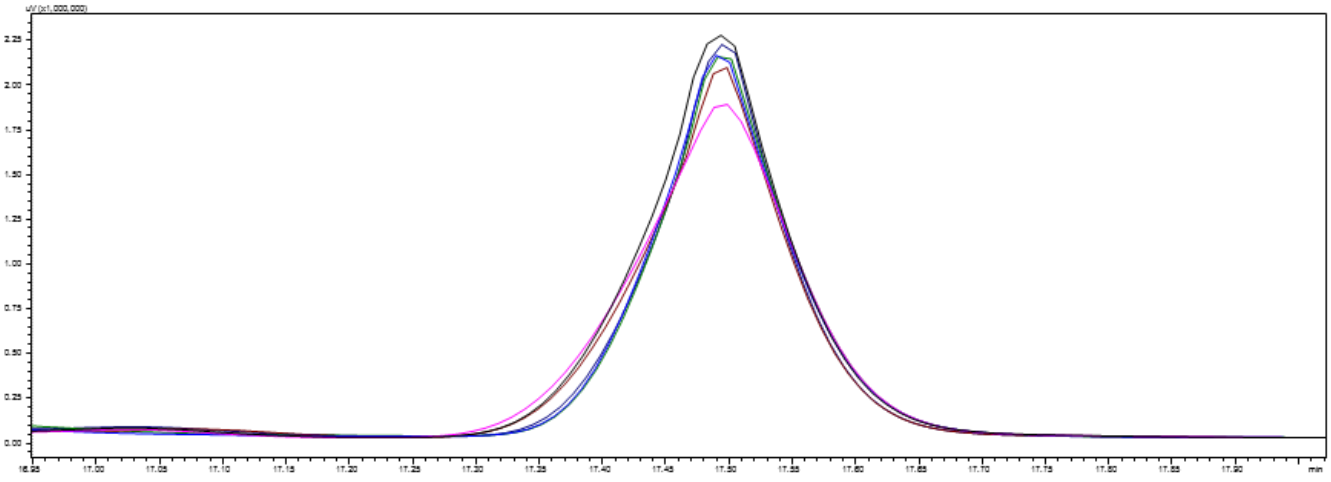


Figure SM-STA-13. Overlap of chromatograms at 210 nm for the compound **4** at all timepoints.

Table SM-STA-2. Data sheet for figure 8. in main text taken from peak integration for compound **4**.

time [h]	Area 1st repet.	Area 2nd repet.	Area 3rd repet.	Area average (AV)	Standard deviation (SD)	AV/SD	Relative
0	17745877	17829358	17962532	17845922	89221	0.5%	100.0%
8	17199190	17944581	18094145	17745972	391425	2.2%	99.4%
16	16969384	17225800	17049665	17081616	107092	0.6%	95.7%
24	16265501	17031240	out	16648371	382870	2.3%	93.3%
32	16380385	16589325	16886092	16618601	207489	1.2%	93.1%
40	16189564	16614762	17010034	16604787	335030	2.0%	93.0%
48	16223374	16328206	16609676	16387085	163110	1.0%	91.8%

SM-SUR. Preliminary cell survival test

Compound 4

Table SM-CYT-1. Data sheet for figure 9. in main text accessed by Muse Cell Analyser (all values in %).

	24h	48h	24h	48h	24h	48h
Concentration [µM]	**1st repetition**		**2nd repetition**		**3rd repetition**	
k 1	99.10	99.60	99.60	99.95	99.96	out
k 2	99.00	99.30	98.80	99.96	99.95	99.50
k 3	98.90	99.70	99.70	out	100.00	98.70
0.1	99.40	99.40	99.80	99.97	99.98	98.80
0.1	99.60	99.50	99.60	99.99	99.99	99.30
0.1	98.90	99.70	99.70	99.96	99.99	99.70
1	99.30	99.60	99.70	99.97	100.00	99.40
1	98.90	99.40	99.50	99.70	99.99	99.60
1	99.00	98.90	99.40	99.83	out	98.60
10	99.00	99.40	99.90	99.96	99.96	98.80
10	99.00	99.50	99.50	99.94	99.94	99.20
10	99.10	99.50	99.50	99.96	99.96	99.70
50	98.70	99.70	99.90	99.95	99.98	98.80
50	98.80	99.70	98.80	99.96	99.98	99.70
50	98.40	99.30	99.30	99.97	99.98	99.00
100	98.60	99.20	99.40	99.96	99.98	99.10
100	98.90	99.50	99.70	99.95	100.00	99.40
100	99.60	99.50	99.60	99.97	99.97	99.30