SUPPORTING INFORMATION

Structure-based design of either β1i or β5i specific inhibitors of human immunoproteasomes

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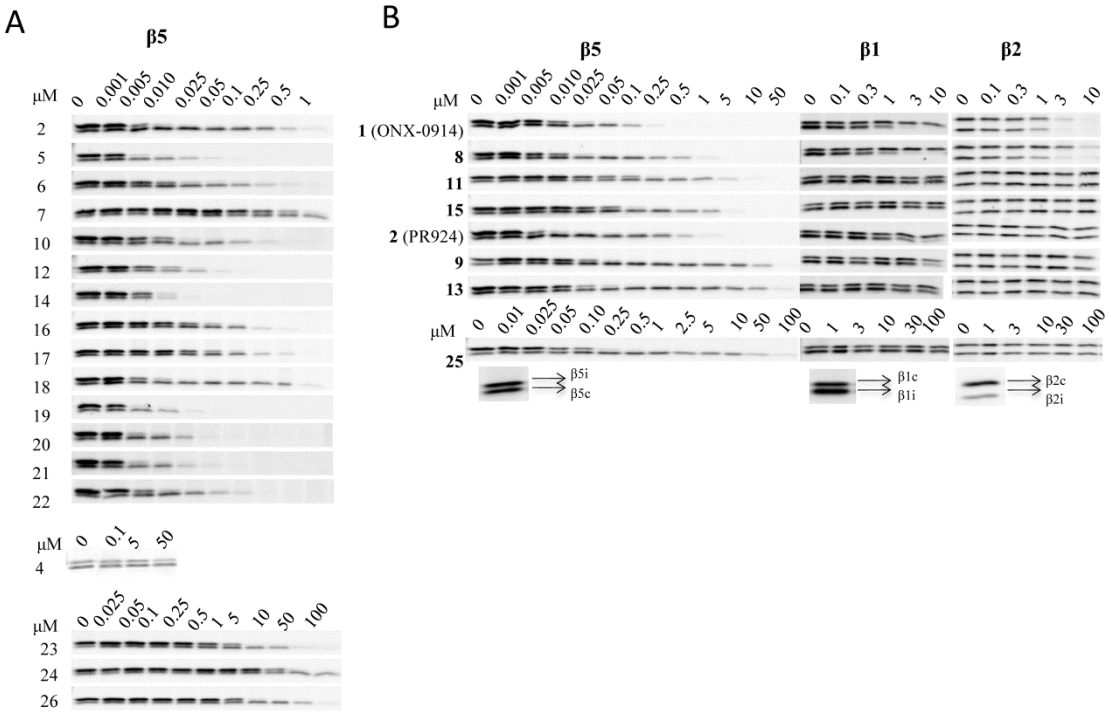


Figure S1. Assays of compounds 1-26 in Raji cell lysate. Occupancy of active site in Raji cell lysates were probed with BODIPY-MeTyr-Phe-Leu-vs (BODIPY-NC005, β5) , BODIPY-epoxomicin (pan-reactive, used for β2) or BODIPY-FL-Ala-Pro-Nle-Leu-EK (BODIPY-NC001,β1) (A) β5 inhibition of least potent/selective compounds. (B) β5, β1 and β2 inhibition profiles of most selective and potent β5i inhibitors, compared to literature compounds **1** and **2**.

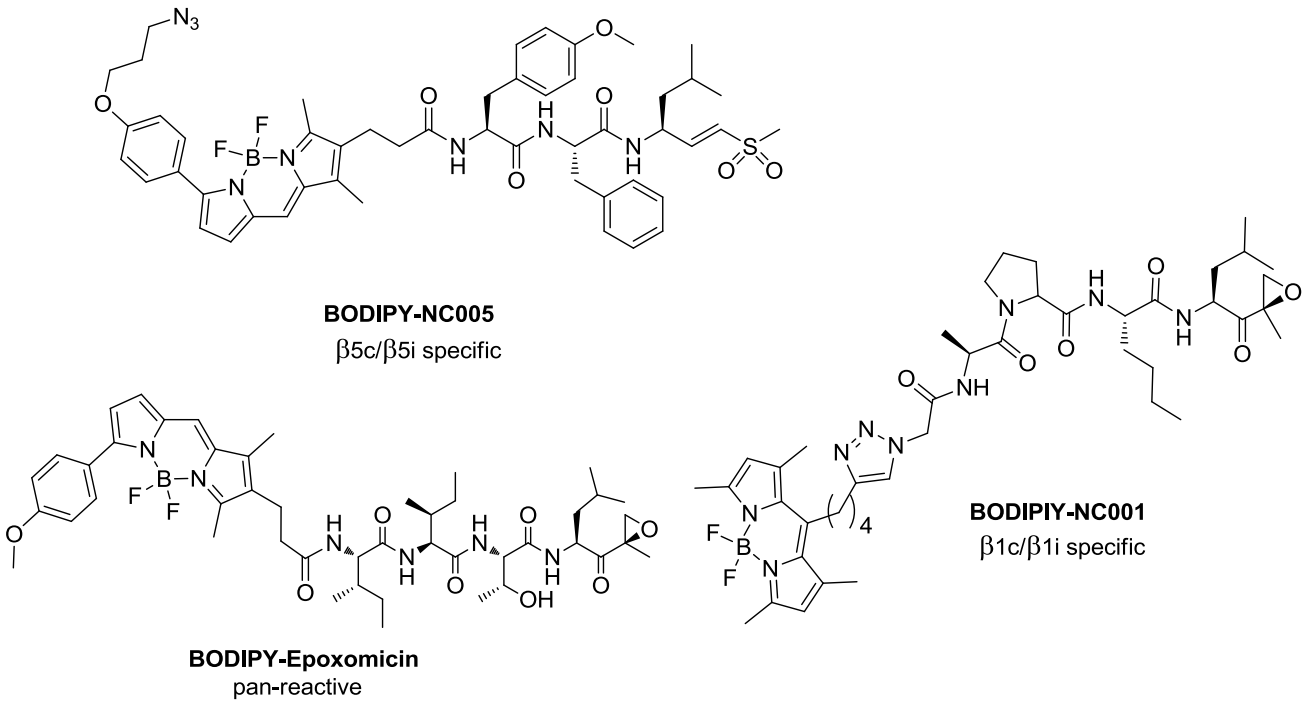


Figure S2. Structures of activity based probes.

Table S1: Apparent pIC50 values of β5i selective inhibitors, determined in Raji cell lysates

	Apparent pIC_{50}					
Compound	**β5i**	**β5c**	**β1i**	**β1c**	**β2i**	**β2c**
1, ONX-0914	8.24 ± 0.02	7.27 ± 0.04	6.33 ± 0.06	<4.0	6.23 ± 0.06	5.95 ± 0.06
4	<4.3	<4.3	n.d.	n.d.	n.d.	n.d.
5	8.71 ± 0.05	7.71 ± 0.06	n.d.	n.d.	n.d.	n.d.
6	8.23 ± 0.04	6.98 ± 0.03	n.d.	n.d.	n.d.	n.d.
7	6.61 ± 0.14	5.74 ± 0.24	n.d.	n.d.	n.d.	n.d.
8, LU-005i	8.18 ± 0.04	6.54 ± 0.07	6.52 ± 0.03	<4.0	6.39 ± 0.04	5.61± 0.07
2, PR-924	8.61 ± 0.03	6.64 ± 0.07	5.74 ± 0.05	<4.0	<4.0	<4.0
9, LU-015i	8.08 ± 0.02	5.34 ± 0.06	5.15 ± 0.07	<4.0	<4.0	<4.0
10	8.30 ± 0.03	7.10 ± 0.04	n.d.	n.d.	n.d.	n.d.
11, LU-025i	7.45 ± 0.02	5.73 ± 0.07	<4.0	<4.0	<4.0	<4.0
12	8.52 ± 0.03	7.84 ± 0.03	n.d.	n.d.	n.d.	n.d.
13, LU-035i	7.96 ± 0.03	4.90 ± 0.09	<4.0	<4.0	<4.0	<4.0
14	8.30 ± 0.02	8.22 ± 0.05	n.d.	n.d.	n.d.	n.d.
15, LU-045i	7.50 ± 0.03	6.08 ± 0.06	<4.0	<4.0	<4.0	<4.0
16	7.89 ± 0.02	6.98 ± 0.05	n.d.	n.d.	n.d.	n.d.
17	7.86 ± 0.02	6.94 ± 0.05	n.d.	n.d.	n.d.	n.d.
18	8.53 ± 0.03	6.81 ± 0.12	n.d.	n.d.	n.d.	n.d.
19	8.84 ± 0.07	7.77 ± 0.18	n.d.	n.d.	n.d.	n.d.
20	8.68 ± 0.02	7.87 ± 0.03	n.d.	n.d.	n.d.	n.d.
21	8.93 ± 0.01	8.00 ± 0.02	n.d.	n.d.	n.d.	n.d.
22	8.49 ± 0.04	7.37 ± 0.06	n.d.	n.d.	n.d.	n.d.
23	6.41 ± 0.04	4.84 ± 0.14	n.d.	n.d.	n.d.	n.d.
24	5.24 ± 0.07	<4.0	n.d.	n.d.	n.d.	n.d.
25, LU-055i	7.27 ± 0.06	4.61 ± 0.08	<5.0	<5.0	<5.0	<5.0
26	6.20 ± 0.04	4.21 ± 0.10	n.d.	n.d.	n.d.	n.d.

n.d. : not determined

Table S2: Apparent pIC50 values of inhibitors, determined in intact RPMI-8226 cells

	Apparent pIC_{50}					
Compound	**β5i**	**β5c**	**β1i**	**β1c**	**β2i**	**β2c**
1, ONX-0914	7.74 ± 0.03	6.74 ± 0.03	6.47 ± 0.03	<5.3	6.23 ± 0.06	5.95 ± 0.06
8	7.36 ± 0.03	5.37 ± 0.05	6.42 ± 0.04	<5.3	6.05 ± 0.04	5.31 ± 0.08
11	6.99 ± 0.02	5.36 ± 0.07	5.14 ± 0.06	<5.0	<5.0	<5.0
15	7.23 ± 0.04	5.53 ± 0.08	5.21 ± 0.06	<5.0	<5.0	<5.0
2, PR-924	7.61 ± 0.04	<4.0	5.46 ± 0.15	<4.0	<4.0	<4.0
9	6.65 ± 0.04	<4.0	4.97 ± 0.09	<4.0	<4.0	<4.0
13	6.43 ± 0.05	<4.0	<4.0	<4.0	<4.0	<4.0
25	6.41 ± 0.24	<4.0	<4.0	<4.0	<4.0	<4.0
3	<5.0	<5.0	6.86 ± 0.08	6.43 ± 0.10	<5.0	<5.0
37	4.18 ± 0.04	4.21 ± 0.06	6.89 ± 0.04	4.34 ± 0.12	<4.0	<4.0

n.d. : not determined

Table S3: Apparent pIC50 values of proline analogues of NC001, determined in Raji cell lysate

Compound	**β1c**	**β1i**	**β5(i)**	**β2(i)**
3, NC-001	7.06 ± 0.08	7.36 ± 0.06	n.d.	n.d.
27	6.08 ± 0.14	6.76 ± 0.06	n.d.	n.d.
28	6.64 ± 0.07	7.17 ± 0.07	n.d.	n.d.
29	7.25 ± 0.01	7.07 ± 0.31	n.d.	n.d.
30	6.64 ± 0.22	7.19 ± 0.16	n.d.	n.d.
31	6.37 ± 0.37	6.70 ± 0.27	n.d.	n.d.
32	7.20 ± 0.17	7.72 ± 0.27	n.d.	n.d.
33	6.55 ± 0.21	7.29 ±0.09	n.d.	n.d.
34	6.23 ± 0.06	7.18 ± 0.03	5.37 ± 0.07	<4.0
35	5.47 ± 0.09	7.06 ± 0.07	4.54 ± 0.05	<4.3
36	5.32 ± 0.08	7.38 ± 0.04	5.52 ± 0.05	<4.0
37, LU-001i	4.62 ± 0.08	7.02 ± 0.02	4.70 ± 0.06	<4.0
38	4.84 ± 0.06	6.98 ± 0.03	6.01 ± 0.06 (5.51 ± 0.08)	4.60 ± 0.04 (4.75 ± 0.05)

n.d. : not determined

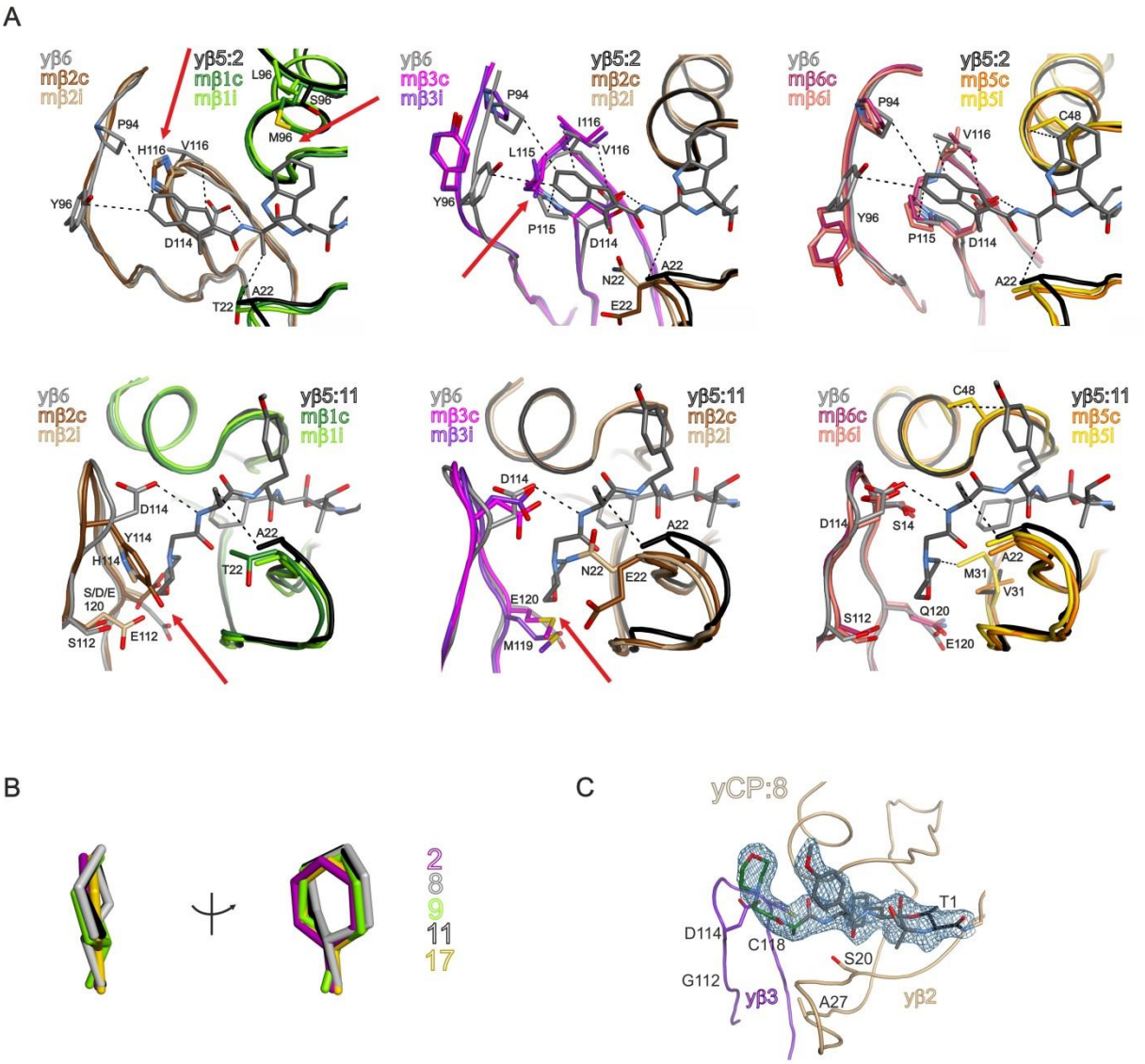


Figure S3. Structural characterization of yCP:ligand complexes.
(A) Superpositions of the yβ5/6 substrate binding channel in complex with **2** and **11** onto the mβ1/2 (left panel), mβ2/3 (middle) and mβ5/6 (right) active sites of the murine cCP and iCP provide structural insights into the β5i selectivity of **2** and **11** (as well as **9** and **17)**. Steric clashes with surrounding amino acids (red arrows) prevent/impair binding to the mβ1 and mβ2 subunits. Hydrophobic interactions and hydrogen bonds are marked by black dotted lines.
(B) Structural superpositions of the indicated ligands reveal that the P1 cyclohexyl and phenyl groups bound to the S1 pocket of the yβ5 active site perfectly match to each other.
(C) Compound **8** is also bound to the yβ2/3 substrate binding channel. The $2F_O$-F_C electron density map (blue) for the ligand is contoured at 1 σ. The inhibitor and Thr1 have been omitted for phasing. The P3 site and the N-cap of the inhibitor are marked in green.

Table S4. X-Ray data collection and refinement statistics.

	yCP:2	yCP:8	yCP:9	yCP:11	yCP:17
Crystal parameter					
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Cell dimensions	a=136 Å	a=137 Å	a=135 Å	a=136 Å	a=136 Å
	b=299 Å	b=300 Å	b=299 Å	b=300 Å	b=300 Å
	c=145 Å	c=145 Å	c=145 Å	c=146 Å	c=147 Å
	β=113°	β=113°	β=113°	β=113°	β=113°
Molecules per AU[a]	1	1	1	1	1
Data collection					
Beam line	SLS, PX06SA	SLS, PX06SA	SLS, PX06SA	SLS, PX06SA	SLS, PX06SA
Wavelength (Å)	1.0	1.0	1.0	1.0	1.0
Resolution range (Å)[b]	20-2.8	20-2.4	20-2.8	20-2.8	20-2.9
	(2.9-2.8)	(2.5-2.4)	(2.9-2.8)	(2.9-2.8)	(3.0-2.9)
No. observations[c]	722203	1259620	661838	757040	589615
No. unique reflections[c]	247440	409646	241410	254162	227749
Completeness (%)[b]	94.7 (96.7)	98.3 (99.1)	93.1 (97.5)	96.2 (97.1)	95.4 (97.4)
R_{merge} (%)[b,d]	8.6 (50.2)	5.2 (44.3)	11.0 (48.7)	7.8 (49.1)	8.5 (45.1)
I/σ (I)[b]	10.3 (2.6)	13.6 (2.8)	7.3 (2.1)	11.7 (2.3)	8.5 (1.9)
Refinement (*REFMAC5*)					
Resolution range (Å)	15-2.8	15-2.4	15-2.8	15-2.8	15-2.9
No. refl. working set	235067	389163	229339	241453	216361
No. refl. test set	12372	20483	12071	12709	11388
No. non hydrogen	49995	50340	49673	49610	49633
Solvent (water, Mg^{2+}, MES)	599	868	277	222	245
Inhibitor (non-hydrogen)	92	168	92	84	84
R_{work}/ R_{free} (%)[e]	17.6 / 20.2	19.9 / 21.5	22.3 / 24.8	17.9 / 19.9	18.4 / 20.9
R.m.s.d. bond / angles (Å)/(°)[f]	0.004 / 1.00	0.005 / 1.12	0.005 / 1.01	0.005 / 1.10	0.005 / 1.12
Average B-factor ($Å^2$)	62.1	59.9	54.6	61.1	73.8
Ramachandran Plot (%) [g]	97.4 / 2.3 / 0.4	97.0 / 2.6 / 0.4	96.7 / 2.9 / 0.4	96.8 / 2.7 / 0.5	95.9 / 3.4 / 0.7
PDB accession code	4QLT	4QLQ	4QLU	4QLS	4QLV

[a] Asymmetric unit

[b] The values in parentheses of resolution range, completeness, R_{merge} and I/σ (I) correspond to the last resolution shell

[c] Data reduction has been carried out with XDS and from 1 crystal. [1] Friedel pairs were treated as identical reflections

[d] $R_{merge}(I) = \Sigma_{hkl}\Sigma_j | [I(hkl)j - I(hkl)] |/[\Sigma_{hkl} Ihkl$, where I(hkl)j is the measurement of the intensity of reflection hkl and <I(hkl)> is the average intensity

[e] $R = \Sigma_{hkl} | |F_{obs}| - |F_{calc}| |/\Sigma_{hkl} |Fobs|$, where R_{free} is calculated without a sigma cut off for a randomly chosen 5% of reflections, which were not used for structure refinement, and R_{work} is calculated for the remaining reflections

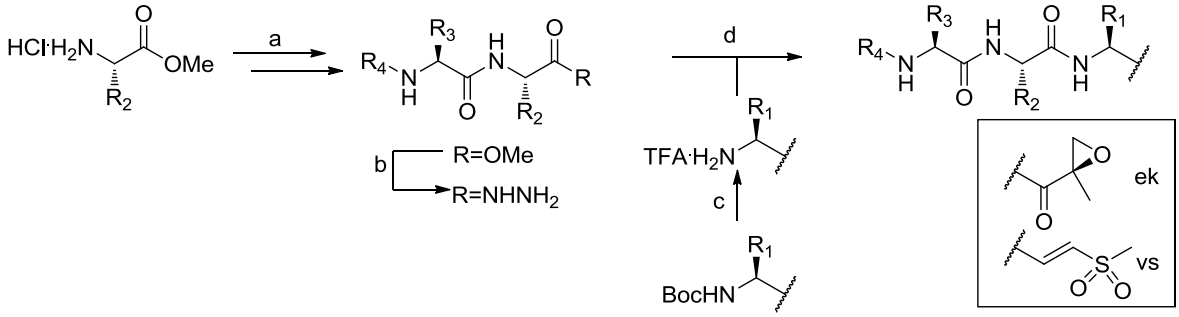
[f] Deviations from ideal bond lengths/angles

[g] Number of residues in favored region / allowed region / outlier region

Synthesis and characterization of compounds.

General procedures

Acetonitrile (ACN), dichloromethane (DCM), N,N-dimethylformamide (DMF), methanol (MeOH),diisopropylethylamine (DiPEA) and trifluoroacetic acid (TFA) were of peptide synthesis grade, purchased at Biosolve, and used as received. All general chemicals (Fluka, Acros, Merck, Aldrich, Sigma, Iris Biotech) were used as received. Traces of water were removed from reagents used in reactions that require anhydrous conditions by co-evaporation with toluene. Solvents that were used in reactions were stored over 4 Å molecular sieves, except methanol and acetonitrile which were stored over 3 Å molecular sieves. Column chromatography was performed on Screening Devices b.v. Silica Gel, with a particle size of 40-63 μm and pore diameter of 60 Å. The eluents toluene, ethyl acetate and petroleum ether (40-60 °C boiling range) were distilled prior to use. TLC analysis was conducted on Merck aluminium sheets (Silica gel 60 F254). Compounds were visualized by UV absorption (254 nm), by spraying with a solution of $(NH_4)6Mo_7O_{24}\cdot 4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)4\cdot 2H_2O$ (10 g/L) in 10% sulphuric acid, a solution of $KMnO_4$ (20 g/L) and K_2CO_3 (10 g/L) in water, or ninhydrin (0.75 g/L) and acetic acid (12.5 mL/L) in ethanol, where appropriate, followed by charring at ca. 150 ºC. ^1H and ^{13}C-NMR spectra were recorded on a Bruker AV-400 (400 MHz) or AV-600 (600 MHz) spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane, CD_3OD or $CDCl_3$ as internal standard. High resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile 50/50 (v/v) and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution R = 60,000 at m/z 400 (mass range m/z = 150-2,000) and dioctylpthalate (m/z = 391.28428) as a "lock mass". The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan). Optical rotations were recorded on a Propol automatic polarimeter. LCMS analysis was performed on a Finnigan Surveyor HPLC system with a Gemini C18 50 × 4.60 mm column (detection at 200-600 nm), coupled to a Finnigan LCQ Advantage Max mass spectrometer with ESI. The applied buffers were H_2O, ACN and 1.0% aq. TFA. HPLC purification was performed on a Gilson HPLC system coupled to a Phenomenex Gemini 5μm 250×10 mm column and a GX281 fraction collector. Boc-Adamantyl-Ala-OH[2], Boc-Leu-EK, Boc-Phe-EK and Boc-Phe-VS[3] were synthesized according to literature procedures.



Scheme S1. General synthetic route towards peptide-epoxyketones and peptide vinylsulfones. Reagent and conditions: (a). Sequential peptide coupling/Boc or Fmoc removal. Peptide coupling: HCTU, DiPEA, Boc-AA-OH/Fmoc-AA-OH, DCM. Boc-removal: TFA/DCM. Fmoc-removal: THF, DBU, EtSH; (b) $NH_2NH_2\cdot H_2O$, MeOH; (c) TFA; (d) i) tBuONO, HCl, DMF, DCM, -30°C; ii) amine (warhead), DiPEA, -30°C → RT.

Synthesis of warheads

Standard procedures amino acid epoxyketone synthesis

A. Boc-AA-N(OMe)Me

To a solution of Boc-AA-OH (1 equiv) in DCM are added HCTU (1.2 equiv), N,O,-dimethylhydroxylamine (2 equiv) and DiPEA (3.5 equiv). After completion of the reaction (1 h to overnight), the solvent is removed. The residue is dissolved in EtOAc and washed with 1M HCl (2x), sat aq $NaHCO_3$ (2x), brine and dried over Na_2SO_4, filtered and concentrated. The crude product is purified by column chromatography (EtOAc /pent).

B. Boc-AA-C(CH_3)=CH_2

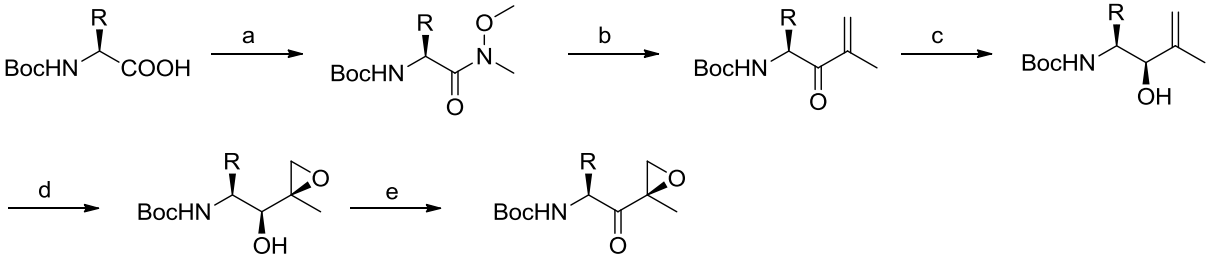
To a solution of 2-bromopropene (3 equiv) in Et_2O at -78^{o}C is added tBuLi (4.5 equiv, from 1.7 M in pent) in 10 in. After stirring for 15 min. at -78^{o}C, the weinreb amide (1 equiv) in Et_2O is added slowly in 10 min. The reaction mixtures is stirred for 2-4 h, while warming up to max. -40^{o}C. After TLC analysis revealed completion of the reaction, the reaction is quenched by the addition of sat. NH_4Cl and warmed to RT. The mixture is transferred to a seperatory funnel and the water layer is extracted with EtOAc (3X). The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by column chromatography (EtOAc /pent mixtures).

C. Boc-AA-OH-C(CH_3)=CH_2

To a solution of alkene **B** (1 equiv) in MeOH is added $CeCl_3{\cdot}7H_2O$ (1.6 equiv) and the mixture is stirred at RT. After the solution became clear, the mixture is cooled to 0^{o}C and $NaBH_4$ (1.3 equiv) is added in portion in 10 min. After TLC analysis showed completion of the reaction (about 30 min), the reaction is quenched by the addition of AcOH. The mixture is stirred for 15 min. followed by the addition of toluene and removal of the solvent. The residue is redissolved in a H_2O/ EtOAc mixture, which is then transferred to a seperatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc (2X). The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified (if necessary) by column chromatography (EtOAc /pent mixtures) .

D. Boc-AA-EK

To a solution of alcohol **C** in DCM at 0^{o}C is added $VO(acac)_2$ (0.1 equiv) followed by the addition of tBuOOH (5.5 M in decane, 3 equiv). The reaction mixture is stirred at 0^{o}C for 2-3 h. after which TLC analysis showed completion of the reaction. The reaction mixture is concentrated, redissolved in EtOAc and washed with 0.5 sat. $NaHCO_3$ (2x), H_2O and brine. The organic layer is dried over Na_2SO_4, filtered and concentrated. The crude product is added as a solution in DCM to a solution of Dess-Martin-Periodane (1.5-3 equiv) in DCM at 0^{o}C. After TLC analysis revealed completion of the reaction, the reaction was quenched by the addition of sat. $NaHCO_3$. The mixture was transferred to a seperatory funnel and the layers were separated. The aqueous layer was extracted with DCM (1x) and the combined organics were washed with sat. $NaHCO_3$ (1x) and brine and dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (EtOAc /pent mixtures).



Scheme S2. Epoxyketone warhead synthesis. Reagents and conditions: (a) NH(Me)OMe·HCl, HCTU, DiPEA, DCM; (b) 2-bromopropene, tBuLi, Et_2O, –78 °C; (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C; (d) tBuOOH, $VO(Acac)_2$, DCM, 0 °C; (e) Dess-Martin periodinane, DCM. R= cycohexyl (compounds 38-41), adamantly (compounds 42-45), 2-naphtyl (compounds 46-49), 1-naphtyl (compounds 50-53), biphenyl (compounds 54-57)

(S)-tert-butyl(3-cyclohexyl-1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate (39)
This compound was synthesized according to the general procedure **A** described above on a 3.7 mmol scale and was isolated after column chromatography (10→30% EtOAc:pent) in a quantitative yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 5.03 (d, *J* = 9.3 Hz, 1H), 4.75 – 4.59 (m, 1H), 3.70 (s, 3H), 3.11 (s, 3H), 1.83 (d, *J* = 12.6 Hz, 1H), 1.71 – 1.47 (m, 4H), 1.46 – 1.24 (m, 12H), 1.23 – 0.96 (m, 3H), 0.85 (dt, *J* = 30.7, 11.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.93, 155.63, 79.35, 61.55, 48.27, 40.43, 34.01, 33.93, 32.15, 32.08, 28.31, 26.45, 26.24, 26.02. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 9.13 (ESI-MS (m/z): 314.80 ($M+H^+$)). HRMS: calcd. for $C_{16}H_{30}N_2O_4$ 315.22783 $[M+2H]^{2+}$; found 315.22781. $[\alpha]_D^{21}$ = -20 (C=1, $CHCl_3$)

(S)-tert-butyl (1-cyclohexyl-4-methyl-3-oxopent-4-en-2-yl)carbamate (40)
This compound was synthesized according to the general procedure **B** described above on a 3.7 mmol scale and was isolated after column chromatography (10→30% EtOAc:pent) (842 mg, 2.85 mmol, 77%). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.00 (s, 1H), 5.79 (s, 1H), 5.15 (d, *J* = 8.6 Hz, 1H), 5.02 (dd, *J* = 12.4, 6.1 Hz, 1H), 1.91 (d, *J* = 12.0 Hz, 1H), 1.81 (s, 3H), 1.70 – 1.40 (m, 5H), 1.35 (s, 9H), 1.26 – 0.96 (m, 5H), 0.95 – 0.65 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.59, 155.53, 142.21, 126.01, 79.43, 51.91, 41.62, 34.21, 34.06, 32.36, 28.30, 26.40, 26.26, 26.06, 17.84.

tert-butyl((S)-3-cyclohexyl-1-((R)-2-methyloxiran-2-yl)-1-oxopropan-2-yl)carbamate (41)
This compound was synthesized according to the general procedure **C** described above on a 11.5 mmol scale and the crude (quant) was used directly in used in procedure **D** and was isolated after column chromatography (10→30% EtOAc:pent) (210 mg, 0.68 mmol, 49%). ^{1}H NMR (400 MHz, Chloroform-d) δ 4.83 (d, *J* = 8.6 Hz, 1H), 4.38 – 4.22 (m, 1H), 3.26 (d, *J* = 4.9 Hz, 1H), 2.86 (d, *J* = 5.0 Hz, 1H), 1.84 (d, *J* = 12.7 Hz, 1H), 1.74 – 1.52 (m, 5H), 1.49 (s, 3H), 1.39 (s, 9H), 1.27 – 1.03 (m, 5H), 1.03 – 0.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.76, 155.73, 79.81, 59.12, 52.47, 50.86, 38.92, 34.36, 34.19, 32.01, 28.40, 26.48, 26.36, 26.04, 16.90. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 10.06 (ESI-MS (m/z): 311.60 ($M+H^+$)). HRMS: calcd. for $C_{17}H_{29}NO_4$ 312.21693 $[M+H]^+$; found 312.21689. $[\alpha]_D^{21}$ = 113.2 (C=0.5, $CHCl_3$)

tert-butyl((R)-3-((3R,5R,7R)-adamantan-1-yl)-1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate (42)

This compound was synthesized according to the general procedure B described above on a 1.55 mmol scale and was isolated after column chromatography (0→20% EtOAc:pent) (552 mg, 97%). ^{1}H NMR (400 MHz, Chloroform-d) δ 4.96 (d, J = 9.5 Hz, 1H), 4.77 (t, J = 8.4 Hz, 1H), 3.76 (s, 3H), 3.15 (s, 3H), 1.97 – 1.86 (m, 3H), 1.71 – 1.56 (m, 6H), 1.56 – 1.46 (m, 6H), 1.39 (s, 9H), 1.29 – 1.18 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.56, 155.25, 79.48, 61.64, 47.04, 46.74, 42.57, 42.48, 37.02, 36.97, 32.69, 32.34, 28.75, 28.71, 28.47.

tert-butyl((R)-1-((3R,5R,7R)-adamantan-1-yl)-4-methyl-3-oxopent-4-en-2-yl)carbamate (43)

This compound was synthesized according to the general procedure B described above on a 1 mmol scale and was isolated after column chromatography (0→20% EtOAc:pent) (239 mg, 69%). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.06 (s, 1H), 5.81 (s, 1H), 5.11 (t, J = 8.5 Hz, 1H), 4.99 (d, J = 9.1 Hz, 1H), 1.91 (s, 3H), 1.85 (s, 3H), 1.69 – 1.46 (m, 13H), 1.38 (s, 9H), 1.10 (dd, J = 14.7, 9.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.68, 154.96, 142.05, 125.76, 79.42, 49.88, 47.12, 42.46, 36.75, 32.94, 28.52, 28.27, 17.90.

tert-butyl((2R,3S)-1-((3R,5R,7R)-adamantan-1-yl)-3-hydroxy-4-methylpent-4-en-2-yl)carbamate (44)

This compound was synthesized according to the general procedure **C** described above on a 0.69 mmol scale and the crude (quant) was used directly in the next step. ^{1}H NMR (400 MHz, Chloroform-d) δ 5.02 (s, 1H), 4.93 (s, 1H), 4.71 (d, *J* = 8.4 Hz, 1H), 4.09 (s, 1H), 3.85 (dd, *J* = 17.4, 8.6 Hz, 1H), 2.43 (bs, 1H), 1.91 (s, 3H), 1.74 (s, 3H), 1.71 – 1.56 (m, 6H), 1.55 – 1.36 (m, 14H), 1.30 – 1.20 (m, 2H), 0.98 (dd, *J* = 14.7, 10.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.61, 145.07, 111.36, 79.43, 79.04, 48.50, 42.77, 42.68, 42.49, 37.09, 31.90, 28.77, 28.60, 28.50, 19.67.

tert-butyl((R)-3-((3R,5R,7R)-adamantan-1-yl)-1-((R)-2-methyloxiran-2-yl)-1-oxopropan-2-yl)carbamate (45)

This compound was synthesized according to the general procedure **D** described above on a 0.69 mmol scale and was isolated after column chromatography (0→20% EtOAc:pent) (88 mg, 0.24 mmol, 33%). ^{1}H NMR (400 MHz, Chloroform-d) δ 4.75 (d, J = 8.6 Hz, 1H), 4.37 (t, J = 8.4 Hz, 1H), 3.31 (d, J = 5.0 Hz, 1H), 2.87 (d, J = 5.0 Hz, 1H), 1.95 (s, 3H), 1.73 – 1.53 (m, 12H), 1.51 (s, 3H), 1.40 (s, 9H), 1.35 (d, J = 1.9 Hz, 1H), 0.96 (dd, J = 14.5, 9.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.42, 155.35, 79.85, 58.96, 52.49, 49.02, 45.18, 42.68, 36.98, 33.03, 28.78, 28.50, 17.12. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 11.03 (ESI-MS (m/z): 363.80 HRMS: calcd. for $C_{21}H_{33}NO_4$ 364.24824 $[M+H]^+$; found 364.24832. $[\alpha]_D^{21}$ = 99.2 (C=0.5, $CHCl_3$)

tert-butyl(R)-(1-(methoxy(methyl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamate (46)

This compound was synthesized according to the general procedure **A** described above on a 1.0 mmol scale and was isolated after column chromatography (10→50% EtOAc:pent) in a quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.79-7.77(m, 3H), 7.61(s, 1H), 7.46-7.39 (m, 2H), 7.32 (d, *J*=8 MHz, 1H), 5.27(d, *J*=8 MHz, 1H), 5.05(m, 1H), 3.64(s, 3H), 3.25-3.20(m, 1H), 3.15(s, 3H), 3.06-3.00(m, 1H), 1.35(s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 172.33, 155.26, 134.18, 133.47, 132.40, 128.10, 127.99, 127.67, 127.61, 126.00, 125.55, 79.63, 61.62, 51.50, 38.99, 32.12, 28.32. LC-MS (linear gradient 10 → 90% MeCN, 0.1%

TFA, 15 min): R_t (min): 8.79 (ESI-MS (m/z): 358.73 ($M+H^+$)). HRMS: cald. for $C_{20}H_{26}N_2O_4$, 359.19666 $[M+H]^{1+}$; found 359.19653. $[\alpha]_D^{21}$ = + 19.8 (C=1, $CHCl_3$)

tert-butyl(R)-(4-methyl-1-(naphthalen-2-yl)-3-oxopent-4-en-2-yl)carbamate (47)
This compound was synthesized according to the general procedure **B** described above on a 1.0 mmol scale and was isolated after column chromatography (10→30% EtOAc:pent) (251 mg, 0.74 mmol, 74%). ^{1}H NMR(400 MHz, $CDCl_3$): δ ppm 7.73-7.71(m, 3H), 7.50(s, 1H), 7.44-7.39 (m, 2H), 7.21 (d, *J*=8.4 MHz, 1H), 6.02(s, 1H), 5.79(s, 1H), 5.37-5.35(m, 2H), 3.28-3.24(m, 1H), 3.08-3.04(m, 1H), 1.83(s, 3H), 1.38(s, 9H).^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 200.12, 155.12, 142.45, 133.74, 133.39, 132.38, 128.14, 128.04, 127.65, 126.69, 126.06, 125.62, 79.69, 54.95, 39.91, 29.73, 28.33, 17.76.

tert-butyl((2R,3S)-3-hydroxy-4-methyl-1-(naphthalen-2-yl)pent-4-en-2-yl)carbamate (48)
This compound was synthesized according to the general procedure **C** described above on a 0.74 mmol scale and and was isolated after column chromatography (1→10% EtOAc:pent) (126 mg, 0.37 mmol, 50%).^{1}H NMR(400 MHz, $CDCl_3$): δ ppm 7.78-7.76(m, 3H), 7.60(s, 1H), 7.44-7.39 (m, 2H), 7.32 (d, *J*=1.2 MHz, 1H), 5.1(s, 1H), 4.90(s, 1H), 4.86(d, *J*=8.4 MHz, 1H), 4.21(s, 1H), 4.10(d, *J*=7.2 MHz, 1H), 3.08-3.01(m, 2H)1, 2.89(t, *J*=10 MHz, *J*=13.2 MHz, 1H), 1.82 (s, 3H), 1.35(s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 155.90, 144.85, 136.13, 133.54, 132.20, 127.89, 127.62, 127.53, 125.91, 125.31, 112.36, 79.47, 53.75, 34.55, 28.26, 19.16.

tert-butyl((R)-1-((R)-2-methyloxiran-2-yl)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamate (49)
This compound was synthesized according to the general procedure **D** described above on a 0.37 mmol scale and was isolated after column chromatography (10→30% EtOAc:pent) (75 mg, 0.21 mmol, 57%). ^{1}H NMR(400 MHz, $CDCl_3$): δ ppm 7.82-7.76(m, 3H), 7.58(s, 1H), 7.47-7.40(m, 2H), 7.30(d, *J*=1.6 MHz, 1H), 5.03(d, *J*=8 MHz, 1H), 4.69(m, 1H), 3.32-3.29(m, 1H), 3.27(d, *J*=4.8 MHz, 1H), 2.90(d, *J*=4.8 MHz, 1H), 2.88-2.82(m, 1H), 1.50(s, 3H), 1.33(s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 208.43, 155.33, 133.59, 133.45, 132.50, 128.31, 128.11, 127.76, 127.62, 127.49, 126.22, 125.78, 79.94, 59.35, 53.78, 52.55, 37.62, 28.30, 16.72. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 9.70 (ESI-MS (m/z): 355.67 ($M+H^+$)). HRMS: cald. for $C_{21}H_{25}NO_4$, 356.18557 $[M+H]^+$; found 356.18563. $[\alpha]_D^{21}$ = 146.4 (C=1, $CHCl_3$)

tert-butyl(R)-(1-(methoxy(methyl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate (50)
This compound was synthesized according to the general procedure **A** described above on a 1.0 mmol scale and was isolated after column chromatography (10→50% EtOAc:pent) in a quantitative yield. ^{1}H NMR(400 MHz, $CDCl_3$): δ ppm 8.20 (d. *J*=8Hz, 1H), 7.79 (d, *J*= 8Hz, 1H), 7.69 (d, *J*=8Hz, 1H), 7.52-7.29(m, 4H), 5.58 (d, *J* = 9.0 Hz, 2H), 5.15-5.10 (m, 1H), 3.59-3.34 (m, 5H), 3.03 (s, 3H), 1.35 (s, 9H) ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 172.09, 154.95, 133.48, 132.68, 132.14, 128.60, 128.45, 128.18, 127.44, 127.30, 125.80, 125.25, 124.99, 123.33, 123.04, 79.02, 77.36, 61.02, 50.77, 35.75, 31.66, 28.05. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 8.56 (ESI-MS (m/z): 360.1 ($M+H^+$)). HRMS: cald. for $C_{20}H_{26}N_2O_4$, 359.19663 $[M]^+$; found 359.19653. $[\alpha]_D^{21}$ = 8.4 (C=1, $CHCl_3$)

tert-butyl (R)-(4-methyl-1-(naphthalen-1-yl)-3-oxopent-4-en-2-yl)carbamate (51)

This compound was synthesized according to the general procedure **B** described above on a 1.0 mmol scale and was isolated after column chromatography (10→30% EtOAc:pent) (200 mg, 0.59 mmol, 59%). ^{1}H NMR(400 MHz, $CDCl_3$): δ ppm 8.12(d, *J*=8.4 MHz, 1H), 7.81(d, *J*=8 MHz, 1H), 7.70(d, *J*=8.4 MHz, 1H), 7.54-7.50(m, 1H), 7.46(t, *J*=7.2 MHz, *J*=7.2 MHz, 1H), 7.32(t, *J*=7.6 MHz, *J*=7.6 MHz, 1H), 7.17(d, *J*=7.2 MHz, 1H), 5.64(s, 1H), 5.48-5.43(m, 3H), 3.54(m, 1H), 3.38-3.33(m, 1H),1.68(s, 3H), 1.4(s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 200.92, 155.09, 142.78, 133.83, 132.66, 132.23, 129.05, 128.78, 128.15, 127.70, 126.55, 126.37, 125.66, 125.21, 123.69, 123.18, 79.66, 53.95, 37.42, 28.36, 17.41.

tert-butyl((2R,3S)-3-hydroxy-4-methyl-1-(naphthalen-1-yl)pent-4-en-2-yl)carbamate (52)

This compound was synthesized according to the general procedure **C** described above on a 0.59 mmol scale and and was isolated after column chromatography (1→10% EtOAc:pent) (119 mg, 0.35 mmol, 60%). ^{1}H NMR(400 MHz, $CDCl_3$): δ ppm 8.01(d, *J*=8.0 MHz, 1H), 7.85(d, *J*=7.6 MHz, 1H), 7.34(d, *J*=8.0 MHz, 1H), 7.52-7.44(m, 2H), 7.40(t, *J*=7.2 MHz, *J*=8.0 MHz, 1H), 7.33(d, *J*=6.8 MHz, 1H), 5.21(s, 1H), 5.08(s, 1H), 4.76(d, *J*=8.8 MHz, 1H), 4.34(s, 1H), 4.04-4.02(m, 1H), 3.44(d, *J*=14.0 MHz, 1H), 3.17(t, *J*=10.8 MHz, *J*=13.2 MHz, 1H), 2.94(s, 1H), 1.87(s, 3H), 1.28(s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 155.92, 144.97, 134.94, 133.97, 132.51, 128.87, 128.09, 127.34, 127.13, 125.99, 125.51, 123.64, 112.94, 112.47, 79.45, 77.66, 53.92, 30.92, 29.80, 28.31, 27.55, 19.47.

tert-butyl((2R)-1-hydroxy-1-((R)-2-methyloxiran-2-yl)-3-(naphthalen-1-yl)propan-2-yl)carbamate (53)

This compound was synthesized according to the general procedure **D** described above on a 1.38 mmol scale and was isolated after column chromatography (10→30% EtOAc:pent) (117 mg, 0.33 mmol, 93%). ^{1}H NMR(400 MHz, $CDCl_3$): δ ppm 8.28(d, *J*=8.4 MHz, 1H), 7.86(d, *J*=8 MHz, 1H), 7.78(d, *J*=8.4 MHz, 1H), 7.60-7.56(m, 1H), 7.52-7.48(m, 1H), 7.41(t, *J*=7.2 MHz, *J*=8 MHz, 1H), 7.27(d, *J*=7.6 MHz, 1H), 4.98(d, *J*=7.6 MHz, 1H), 4.74-4.69(m,1H), 3.66(dd, *J*=4.8 MHz, *J*=4.8 MHz, 1H), 3.34(d, *J*=4.8 MHz, 1H), 3.03-2.97(m, 1H), 2.91(d, *J*=4.8 MHz, 1H), 1.48(s, 3H), 1.30(s, 9H).^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 208.95, 208.90, 155.24, 133.99, 132.27, 128.91, 128.83, 128.53, 128.11, 127.80, 127.69, 126.56, 125.93, 125.58, 125.31, 125.15, 123.87, 123.74, 123.62, 79.91, 59.44, 53.91, 52.98, 52.62, 52.37, 51.59, 37.19, 35.17, 29.81, 28.44, 28.32, 27.66, 16.61. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 9.71 (ESI-MS (m/z): 355.53 (M^+)). HRMS: cald. for $C_{21}H_{25}NO_4$ 356.18563 $[M+H]^+$; found 356.18556.

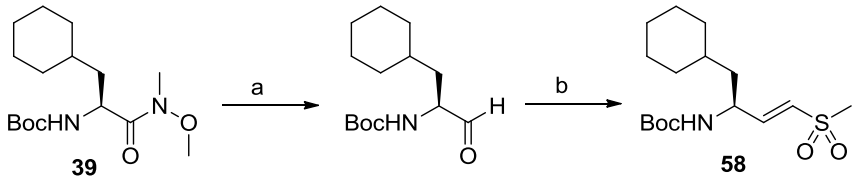
tert-butyl(R)-(3-([1,1'-biphenyl]-4-yl)-1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate (54)

This compound was synthesized according to the general procedure **A** described above on a 2 mmol scale and was isolated after column chromatography (10→50% EtOAc:pent) in a quantitative yield. ^{1}H NMR(400 MHz, $CDCl_3$): δ ppm 7.56(t, *J*=1.2 MHz, *J*=7.2 MHz, 2H), 7.54(d, *J*=8.4 MHz, 2H), 7.49(t, *J*=7.6 MHz, *J*=7.6 MHz, 2H), 7.31-7.23(m, 3), 5.36(d, *J*=8.8 MHz, 1H), 5.00-4.98(m, 1H),3.65(s, 3H), 3.16(s, 3H), 3.13-3.08(dd, *J*=6 MHz, *J*=5.6 MHz, 2H), 2.93-2.88(m, 1H), 1.39(s, 9H).^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 172.14, 155.15, 140.76, 139.45, 135.67, 129.82, 128.65, 127.07, 126.91, 126.87, 79.42, 61.45, 51.43, 38.23, 31.96, 28.23. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 9.37 (ESI-MS (m/z): 385.73 ($M+H^+$)). HRMS: cald. for $C_{22}H_{28}N_2O_4$ 358.21218 $[M+H]^+$; found 385.21255. $[\alpha]_D^{21}$ = +10 (C=1, $CHCl_3$)

tert-butyl (R)-(1-([1,1'-biphenyl]-4-yl)-4-methyl-3-oxopent-4-en-2-yl)carbamate (55)
This compound was synthesized according to the general procedure **B** described above on a 2.0 mmol scale and was isolated after column chromatography (10→30% EtOAc:pent) (679 mg, 1.86 mmol, 93%). ^{1}H NMR(400 MHz, $CDCl_3$): δ ppm ppm 7.56-7.54(m, 2H), 7.49(d, *J*=8 MHz, 2H), 7.42(t, *J*=7.2 MHz, *J*=7.2 MHz, 2H), 7.32(t, *J*=7.2 MHz, *J*=7.2 MHz, 1H), 7.14(d, *J*=8 MHz, 2H), 6.05(s, 1H), 5.86(s, 1H), 5.38-5.30(m, 2), 3.18-3.13(m, 1H), 2.97-2.92(m, 1H), 1.87(s, 3H), 1.41(s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 200.02, 155.11, 142.41, 140.78, 139.70, 135.25, 130.10, 129.93, 129.90, 128.76, 127.22, 127.07, 126.99, 126.68, 79.70, 54.96, 39.39, 29.74, 28.36, 17.80.

tert-butyl((2R,3S)-1-([1,1'-biphenyl]-4-yl)-3-hydroxy-4-methylpent-4-en-2-yl)carbamate (56)
This compound was synthesized according to the general procedure **C** described above on a 1.86 mmol scale and and was isolated after column chromatography (1→10% EtOAc:pent) (444 mg, 1.21 mmol, 65%). ^{1}H NMR(400 MHz, $CDCl_3$): δ ppm 7.57-7.55(m, 2H), 7.51(d, *J*=8.0 MHz, 2H), 7.44-7.40(m, 2H), 7.34-7.32(m, 1H), 7.27-7.24(m, 2H), 5.10(s, 1H), 5.00(s, 1H), 4.78(d, *J*=8.8 MHz, 1H), 4.21(s, 1H), 4.04(s, 1H), 2.95(dd, *J*=4.0 MHz, *J*=3.6 MHz, 1H), 2.77-2.71(m, 1H), 2.66(s, 1H), 1.83(s, 3H), 1.34(s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 144.89, 141.15, 139.24, 137.71, 129.96, 128.84, 127.17, 127.15, 127.09, 112.41, 79.59, 77.26, 53.86, 34.13, 28.39, 19.21.

tert-butyl((R)-3-([1,1'-biphenyl]-4-yl)-1-((R)-2-methyloxiran-2-yl)-1-oxopropan-2-yl)carbamate (57)
This compound was synthesized according to the general procedure **D** described above on a 1.21 mmol scale and was isolated after column chromatography (10→30% EtOAc:pent) (194 mg, 0.51 mmol, 42%). ^{1}H NMR(400 MHz, $CDCl_3$): δ ppm 7.59-7.52(m, 5H), 7.45-7.41(m, 2H), 7.35-7.31(m, 1H), 7.24(d, *J*=8.0 MHz, 1H), 5.00(d, *J*=8 MHz, 1H), 4.64-4.59(m, 1H), 3.31(d, *J*=4.8 MHz, 1H), 3.18(d, *J*=4.4 MHz, *J*=4.8 MHz, 1H), 2.93(d, *J*=6.2 MHz, 1H), 2.79-2.74(m, 1H), 1.53(s, 3H), 1.37(s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 208.41, 155.36, 140.85, 139.98, 135.06, 129.95, 128.87, 127.36, 127.34, 127.13, 80.02, 59.32, 53.78, 52.06, 37.14, 28.38, 16.77. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 10.22 (ESI-MS (m/z): 381.40 (M^+)). HRMS: cald. for $C_{23}H_{27}NO_4$ 382.20125 $[M+H]^+$; found 382.20128. $[\alpha]_D^{21}$ = +115.6 (C=1, $CHCl_3$)



Scheme S3. Synthesis of Boc-Cha-VS (58). Reagents and conditions: (a) $LiAlH_4$, Et_2O; (b) Diethyl((methylsulfonyl)methyl) phosphonate, NaH, THF, 0^{o}C, 72% (over two steps).

(S,E)-tert-butyl (1-cyclohexyl-4-(methylsulfonyl)but-3-en-2-yl)carbamate (58)
Weinreb amide **38** (0.80 g, 2.60 mmol) was dissolved in Et_2O (25 mL), put under an argon atmosphere and cooled to 0 °C. $LiAlH_4$ (1.5 equiv, 3,9 mmol, 3.9 mL of a 1 M solution in THF) was added slowly and the mixture was stirred at 0°C for 0.5 h after which TLC analysis indicated complete conversion of the starting compound. 1 M aq. HCl was slowly added and the layers were separated. The organic layer was extracted with 1 M HCl and brine, dried over Na_2SO_4 and concentrated. Diethyl((methylsulfonyl)methyl) phosphonate (1.5 equiv, 3.90 mmol, 0.90 g) was dissolved in THF (25 mL) and cooled to 0 °C under an argon atmosphere. NaH (1.5 equiv, 3.90 mmol, 156 mg, 60% w/w in mineral oil) was slowly added and the mixture was stirred at 0 ºC for 30 min. Next, the freshly obtained aldehyde (in THF (5 mL)) was slowly added and the mixture was stirred for 1.5 h while slowly warming it to RT. After this time TLC analysis indicated complete conversion of the aldehyde. EtOAc was added and the mixture was extracted with 1 M aq. HCl (2×) and brine, dried over Na_2SO_4 and concentrated. Column chromatography (10→30% EA:pent) yielded the title compound (617 mg, 1.86 mmol, 72%, contains 16% *Z*-isomer, based on NMR). ^{1}H NMR (Peaks reported for *E*-isomer) (400 MHz, Chloroform-d) δ 6.78 (dd, *J* = 15.1, 5.0 Hz, 1H), 6.45 (dd, *J* = 15.1, 1.5 Hz, 1H), 4.68 (d, *J* = 7.7 Hz, 1H), 4.40 (s, 1H), 2.89 (s, 3H), 1.75 (d, *J* = 12.8 Hz, 1H), 1.71 – 1.50 (m, 4H), 1.39 (m, 11H), 1.15 (m, 4H), 1.02 – 0.71 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.13, 149.30, 148.83, 128.93, 80.01, 48.80, 43.79, 42.92, 41.97, 34.07, 33.96, 33.87, 33.52, 32.61, 28.43, 28.38, 28.35, 26.40, 26.36, 26.27, 26.17, 26.02. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 7.94 (ESI-MS (m/z): 331.80 ($M+H^+$)). HRMS: calcd. for $C_{16}H_{29}NO_4S$ 332.18901 $[M+H]^+$; found 332.18912. $[\alpha]_D^{21}$ = -9.2 (C=1, $CHCl_3$)

Synthesis of peptide hydrazides

MorphAc-Ala-Tyr(OMe)-OMe (60b)
Boc-Ala-OH (208 mg, 1.1 mmol, 1.1 equiv) was dissolved in DCM. HCTU (496 mg, 1.2 mmol, 1.2 equiv), HCl.H-Tyr(OMe)-OMe (231 mg, 1 mmol, 1 equiv) and DiPEA (0.61 mL, 3.5 mmol, 3.5 equiv) were added and the mixture was stirred for 2 h before being concentrated. The residue was dissolved in EtOAc, washed with 1M HCl (2x), sat aq NaHCO3 (2x), brine and dried over Na_2SO_4, filtered and concentrated. Column chromatography (10→40% EtOAc:pent) yielded Boc-Ala-Tyr(OMe)-OMe (365 mg, 0.96 mmol, 96%.). Boc-Ala-Tyr(OMe)-OMe (365 mg, 0.54 mmol, 1 equiv) was dissolved in TFA and stirred for 30 min, followed by coevaporation with tol (3x) providing TFA·H-Ala-Tyr(OMe)-OMe **60a**. Morpholino acetic acid·TFA (310 mg, 1.2 mmol, 1.2 equiv) was dissolved in DCM. HCTU (496 mg, 1.2 mmol, 1.2 equiv), HCl.H-Ala-Tyr(OMe)-OMe (365 mg, 0.96 mmol, 1 equiv) and DiPEA (0.78 mL, 4.5 mmol, 4.5 equiv) were added and the mixture was stirred overnight before being concentrated. The residue was dissolved in EtOAc and washed with sat aq $NaHCO_3$ (2x), brine and dried over Na_2SO_4, filtered and concentrated. Column chromatography (1→3% MeOH:DCM) yielded the title compound in a quantitative yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.53 (d, *J* = 7.9 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.71 (d, *J* = 7.7 Hz, 1H), 4.74 (q, *J* = 6.8 Hz, 1H), 4.49 (p, *J* = 7.1 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.69 – 3.64 (m, 4H), 3.12 – 2.87 (m, 4H), 2.52 – 2.40 (m, 4H), 1.34 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.89, 171.85, 169.91, 158.68, 130.29, 127.73, 114.01, 66.96, 61.77, 55.23, 53.80, 53.53, 52.46, 48.16, 36.89, 18.27.

MorphAc-Ala-Tyr(OMe)-$NHNH_2$ (61)
Methyl ester **60b** (390 mg, 0.96 mmol, 1 equiv) was dissolved in MeOH (10 mL). Hydrazine hydrate (1500 µl, 29 mmol, 30 equiv) was added and the mixture was stirred for 3 h before

being co-evaporated with tol (3x). The residue was used without further purification. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.07 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 4.46 (t, *J* = 7.3 Hz, 1H), 4.39 (d, *J* = 7.0 Hz, 1H), 3.73 (s, 3H), 3.71 – 3.65 (m, 4H), 3.06 – 2.77 (m, 4H), 2.50 – 2.42 (m, 4H), 1.29 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 173.82, 172.46, 171.73, 159.73, 131.41, 129.71, 115.00, 68.02, 62.55, 56.16, 54.85, 54.77, 38.43, 19.26.

Fmoc-D-Ala-Trp(Boc)-OMe (62)
H-Trp(Boc)-OMe (486 mg, 1.53 mmol, 1 equiv) was dissolved in DCM. HCTU (759 mg, 1.8 mmol, 1.2 equiv), Fmoc-D-Ala-OH (684 mg, 1.8 mmol, 1.2 equiv) and DiPEA (0.93 mL, 5.4 mmol, 3.5 equiv) were added and the mixture was stirred for 1.5 h before being concentrated. The residue was dissolved in EtOAc and washed with 1M HCl (2x), sat aq NaHCO3 (2x), brine and dried over Na_2SO_4, filtered and concentrated. Column chromatography (20→80% EtOAc:pent) yielded the title compound in a quantitative yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.10 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 6.9 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.44 – 7.34 (m, 3H), 7.31 – 7.25 (m, 3H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 5.68 (d, *J* = 7.4 Hz, 1H), 4.99 – 4.89 (m, 1H), 4.41 – 4.28 (m, 3H), 4.21 – 4.14 (m, 1H), 3.65 (s, 3H), 3.32 – 3.09 (m, 2H), 1.65 (s, 9H), 1.36 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.16, 171.86, 155.90, 149.50, 143.87, 143.74, 141.27, 141.25, 135.27, 130.33, 127.70, 127.05, 125.11, 124.60, 124.23, 122.61, 119.96, 118.72, 115.32, 114.79, 83.71, 67.08, 60.44, 52.51, 52.46, 50.38, 47.04, 28.18, 27.39, 19.02, 14.23.

H-D-Ala-Trp(Boc)-OMe (63)
To a solution of Fmoc-D-Ala-Trp(Boc)-OMe **62** (1.19 g, 1.53 mmol, 1 equiv) in THF (15 mL) were added DBU (67 µL, 0.46 mmol, 0.3 equiv) and ethanethiol (11 mL, 15.3 mmol, 10 equiv). After 45 min. the reaction mixture was concentrated and co-evaporated with toluene. Column chromatography (50→100% EtOAc:pent →10% MeOH in EtOAc) yielded the title compound (575 mg, 1.38 mmol, 90%) ^{1}H NMR (400 MHz, Chloroform-d) δ 8.10 (s, 1H), 7.53 (d, *J* = 9.1 Hz, 1H), 7.43 (s, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.25 (t, *J* = 6.6 Hz, 1H), 4.84 (s, 1H), 3.73 (s, 3H), 3.49 – 3.13 (m, 3H), 1.68 (s, 9H), 1.24 (d, *J* = 5.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.17, 171.94, 130.07, 124.33, 123.68, 122.32, 118.41, 115.09, 114.93, 83.68, 55.14, 52.08, 52.05, 49.80, 49.55, 27.65, 26.78, 20.26. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 6.58 (ESI-MS (m/z): 389.93 ($M+H^+$)).

3MeIndAc-D-Ala-Trp-OMe (64)
H-D-Ala-H-Trp(Boc)-OMe **63** (155.6 mg, 0.4 mmol, 1 equiv) was dissolved in DCM. HCTU (198 mg, 0.48 mmol, 1.2 equiv), 3-methylindene-2-carboxylic acid (84 mg, 0.48 mmol, 1.2 equiv) and DiPEA (0.24 mL, 1.4 mmol, 3.5 equiv) were added and the mixture was stirred overnight before being concentrated. The residue was dissolved in EtOAc and washed with 1M HCl (2x), sat aq NaHCO3 (2x), brine and dried over Na_2SO_4, filtered and concentrated. Column chromatography (20→60% EtOAc:pent) yielded the title compound (198 mg, 0.36 mmol, 90%). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.16 – 8.03 (m, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.37 – 7.23 (m, 4H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.60 (d, *J* = 7.3 Hz, 1H), 4.93 (q, *J* = 6.5 Hz, 1H), 4.75 (p, *J* = 6.9 Hz, 1H), 3.66 (s, 3H), 3.54 (s, 2H), 3.36 – 3.16 (m, 2H), 2.47 (s, 3H), 1.64 (s, 9H), 1.42 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.53, 171.86, 165.75, 147.51, 145.53, 142.22, 131.84, 130.34, 127.25, 126.74, 124.62, 124.27, 123.85, 122.64, 120.79, 118.75, 115.34, 114.97, 83.72, 52.63, 52.57, 48.63, 38.32, 28.23, 27.33, 18.97, 12.31. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 10.51 (ESI-MS (m/z): 545.93 ($M+H^+$)).

3MeIndAc-D-Ala-Trp(Boc)-$NHNH_2$ (65)

Methyl ester **64** (165 mg, 0.30 mmol, 1 equiv) was dissolved in MeOH (4 mL). Hydrazine hydrate (523 µl, 10.5 mmol, 35 equiv) was added and the mixture was stirred for 3 h before being co-evaporated with tol (3x). The residue was used without further purification (isolated as mixture of + and - Boc. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.61 – 7.49 (m, 1H), 7.49 – 7.38 (m, 3H), 7.28 (dq, *J* = 26.3, 11.2, 9.3 Hz, 3H), 7.07 – 6.92 (m, 2H), 4.73 – 4.59 (m, 1H), 4.59 – 4.48 (m, 1H), 4.45 – 4.33 (m, 1H), 3.65 – 3.41 (m, 1H), 3.27 – 3.14 (m, 1H), 2.45 (d, *J* = 7.5 Hz, 2H), 1.42 (s, 6H (partially –Boc)), 1.30 – 1.15 (m, 3H). LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 6.16 (ESI-MS (m/z): 445.93 ($M+H^+$ -Boc) and 7.76 (ESI-MS (m/z): 546.00 ($M+H^+$ +Boc).

Boc-D-Ala-Tyr(OMe)-OMe (66)

Boc-D-Ala-OH (208 mg, 1.1 mmol, 1.1 equiv) was dissolved in DCM. HCTU (455 mg, 1.1 mmol, 1.1 equiv), HCl.H-Tyr(OMe)-OMe (231 mg, 1 mmol, 1 equiv) and DiPEA (0.61 mL, 3.5 mmol, 3.5 equiv) were added and the mixture was stirred for 2 h before being concentrated. The residue was dissolved in EtOAc, washed with 1M HCl (2x), sat aq NaHCO3 (2x), brine and dried over Na_2SO_4, filtered and concentrated. Column chromatography (0→30% EtOAc:pent) yielded the title compound (349 mg, 0.92 mmol, 92%.). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.99 (d, *J* = 8.6 Hz, 2H), 6.87 – 6.71 (m, 3H), 5.17 (d, *J* = 7.5 Hz, 1H), 4.85 – 4.70 (m, 1H), 4.29 – 4.11 (m, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.01 (qd, *J* = 14.0, 5.9 Hz, 2H), 1.40 (s, 9H), 1.26 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.42, 171.97, 158.66, 155.45, 130.29, 127.74, 113.98, 79.98, 55.18, 53.27, 52.33, 49.94, 37.04, 28.34, 18.56.

MorphAc-D-Ala-Tyr(OMe)-OMe (67)

Boc-D-Ala-Tyr(OMe)-OMe **66** (221 mg, 0.54 mmol, 1 equiv) was dissolved in TFA and stirred for 30 min, followed by coevaporation with tol (3x). Morpholino acetic acid·TFA (154 mg, 0.59 mmol, 1.1 equiv) was dissolved in DCM. HCTU (245 mg, 0.59 mmol, 1.1 equiv), HCl.H-D-Ala-Tyr(OMe)-OMe (221 mg, 0.54 mmol, 1 equiv) and DiPEA (0.42 mL, 2.4 mmol, 4.5 equiv) were added and the mixture was stirred overnight before being concentrated. The residue was dissolved in EtOAc and washed with 1M HCl (2x), sat aq NaHCO3 (2x), brine and dried over Na_2SO_4, filtered and concentrated. Column chromatography (1→3% MeOH:DCM) yielded the title compound (160 mg, 0.39 mmol, 79%.). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.01 (dd, *J* = 14.1, 8.4 Hz, 3H), 6.76 (d, *J* = 8.6 Hz, 2H), 4.73 (q, *J* = 7.3 Hz, 1H), 4.53 (p, *J* = 7.0 Hz, 1H), 3.71 (s, 3H), 3.65 (d, *J* = 4.8 Hz, 7H), 3.09 – 2.85 (m, 4H), 2.51 – 2.36 (m, *J* = 4.3 Hz, 4H), 1.24 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.82, 171.80, 169.78, 158.58, 130.25, 127.79, 113.85, 66.86, 61.74, 55.15, 53.69, 53.25, 52.28, 48.00, 36.92, 18.65.

MorphAc-D-Ala-Tyr(OMe)-$NHNH_2$ (68)

Methyl ester **67** (160 mg, 0.39 mmol, 1 equiv) was dissolved in MeOH (4 mL). Hydrazine hydrate (567 µl, 11.7 mmol, 30 equiv) was added and the mixture was stirred for 3 h before being co-evaporated with tol (3x). The residue was used without further purification. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 4.54 (dd, *J* = 9.4, 5.5 Hz, 1H), 4.30 (q, *J* = 7.0 Hz, 1H), 3.74 (s, 3H), 3.70 (t, *J* = 4.6 Hz, 4H), 3.12 (dd, *J* = 14.0, 5.5 Hz, 1H), 2.98 (d, *J* = 3.6 Hz, 2H), 2.79 (dd, *J* = 14.0, 9.4 Hz, 1H), 2.56 – 2.39 (m, *J* = 4.3 Hz, 4H), 1.13 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 173.59, 171.81, 171.34, 159.17, 130.68, 129.29, 114.37, 67.38, 61.89, 55.51, 54.14, 53.98, 37.50, 18.50. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 3.14 (ESI-MS (m/z): 408.13 ($M+H^+$)).

3MeIndAc-D-Ala-Tyr(OMe)-OMe (69)
Boc-D-Ala-Tyr(OMe)-OMe **66** was dissolved in TFA and stirred for 30 min, followed by coevaporation with tol (3x). 3-methylindene-2-carboxylic acid (97 mg, 0.55 mmol, 1.1 equiv) was dissolved in DCM. HCTU (227 mg, 0.55 mmol, 1.1 equiv), HCl.H-D-Ala-Tyr(OMe)-OMe (205 mg, 0.50 mmol, 1 equiv) and DiPEA (0.30 mL, 1.75 mmol, 3.5 equiv) were added and the mixture was stirred overnight before being concentrated. The residue was dissolved in EtOAc and washed with 1M HCl (2x), sat aq NaHCO3 (2x), brine and dried over Na_2SO_4, filtered and concentrated. Column chromatography (10→80% EtOAc:pent) yielded the title compound (159 mg, 0.36 mmol, 73%.). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.39 (d, *J* = 7.2 Hz, 2H), 7.31 (q, *J* = 7.1 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 6.66 (d, *J* = 7.0 Hz, 1H), 4.81 (q, *J* = 7.6 Hz, 1H), 4.67 (p, *J* = 6.9 Hz, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 3.51 (s, 2H), 3.13 (dd, *J* = 14.0, 5.3 Hz, 1H), 3.00 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.42 (s, 3H), 1.35 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.75, 172.32, 165.93, 158.66, 147.94, 145.41, 142.22, 131.49, 130.27, 127.85, 127.30, 126.72, 123.81, 120.77, 113.93, 55.11, 53.49, 52.48, 48.85, 38.17, 36.79, 18.57, 12.23.

3MeIndAc-D-Ala-Tyr(OMe)-NHNH$_2$ (70)
Methyl ester **69** (159 mg, 0.36 mmol, 1 equiv) was dissolved in MeOH (4 mL). Hydrazine hydrate (523 µl, 10.8 mmol, 30 equiv) was added and the mixture was stirred for 3 h before being co-evaporated with tol (3x). The residue was used without further purification. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.47 – 7.25 (m, 4H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.72 (d, *J* = 8.6 Hz, 2H), 4.61 – 4.52 (m, 1H), 4.41 (q, *J* = 7.1 Hz, 1H), 3.60 (d, *J* = 14.3 Hz, 5H), 3.11 (dd, *J* = 14.0, 5.4 Hz, 1H), 2.86 (dd, *J* = 14.0, 8.9 Hz, 1H), 2.46 (s, 3H), 1.25 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 174.39, 171.92, 167.55, 159.10, 149.04, 145.83, 142.99, 131.82, 130.62, 129.01, 127.89, 127.22, 124.29, 121.26, 114.31, 55.36, 53.85, 49.98, 38.48, 37.28, 17.86, 12.45. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 5.88 (ESI-MS (m/z): 437.00 ($M+H^+$)).

MorphAc-D-Ala-Trp(Boc)-OMe (71)
H-D-Ala-H-Trp(Boc)-OMe **63** (167 mg, 0.43 mmol, 1 equiv) was dissolved in DCM. HCTU (198 mg, 0.48 mmol, 1.1 equiv), Morpholino acetic acid (124 mg, 0.48 mmol, 1.1 equiv) and DiPEA (0.24 mL, 1.4 mmol, 3.3 equiv) were added and the mixture was stirred overnight before being concentrated. The residue was dissolved in EtOAc and washed with 1M HCl (2x), sat aq NaHCO3 (2x), brine and dried over Na_2SO_4, filtered and concentrated. Column chromatography (1→3% MeOH:DCM) yielded the title compound in a quantitative yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.08 (d, *J* = 6.9 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.38 (s, 1H), 7.27 (t, *J* = 7.0 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 4.85 (q, *J* = 6.0 Hz, 1H), 4.54 (p, *J* = 7.0 Hz, 1H), 3.72 – 3.62 (m, 7H), 3.20 (qd, *J* = 14.8, 5.9 Hz, 2H), 2.98 – 2.85 (m, 2H), 2.49 – 2.37 (m, *J* = 4.5 Hz, 4H), 1.63 (s, 9H), 1.29 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.92, 171.80, 169.86, 149.51, 130.30, 124.61, 124.26, 122.62, 118.76, 115.31, 114.84, 83.73, 66.93, 61.74, 53.73, 53.37, 52.51, 52.34, 48.11, 28.22, 27.32, 18.52. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 6.68 (ESI-MS (m/z): 517.07 ($M+H^+$)).

MorphAc-D-Ala-Trp(Boc)-NHNH$_2$ (72)
Methyl ester **71** (234 mg, 0.43 mmol, 1 equiv) was dissolved in MeOH (6 mL). Hydrazine hydrate (640 µl, 12.9 mmol, 30 equiv) was added and the mixture was stirred for 3 h before being co-evaporated with tol (3x). The residue was used without further purification (isolated as mixture of + and - Boc. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.55 (d, *J* = 8.7 Hz, 1H), 7.32

(d, *J* = 8.1 Hz, 1H), 7.09 (t, *J* = 7.1 Hz, 1H), 7.07 – 6.97 (m, 2H), 4.67 – 4.55 (m, 2H), 4.31 (q, *J* = 7.0 Hz, 1H), 3.67 (hept, *J* = 6.9, 5.9 Hz, 4H), 3.26 (dd, *J* = 14.7, 6.1 Hz, 1H), 3.13 (dd, *J* = 14.7, 7.6 Hz, 1H), 2.91 (d, *J* = 4.6 Hz, 2H), 2.51 – 2.34 (m, 4H), 1.42 (s, 5H (Boc, partially removed)), 1.15 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 173.36, 172.21, 171.28, 137.02, 127.87, 123.96, 122.07, 119.47, 118.62, 111.90, 109.76, 67.27, 61.81, 54.16, 54.03, 53.31, 49.14, 28.53, 28.29, 18.26. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 3.56 (ESI-MS (m/z): 417.07 ($M+H^+$)).

3MeIndAc-Ala-Tyr(OMe)-OMe (73)

TFA·H-Ala-Tyr(OMe)-OMe **60a** (79 mg, 0.21 mmol, 1 equiv) was dissolved in DCM. HCTU (101 mg, 0.25 mmol, 1.2 equiv), 3-methylindene-2-carboxylic acid (43 mg, 0.25 mmol, 1.2 equiv) and DiPEA (0.13 mL, 0.74 mmol, 3.5 equiv) were added and the mixture was stirred overnight before being concentrated. The residue was dissolved in EtOAc and washed with 1M HCl (2x), sat aq NaHCO3 (2x), brine and dried over Na_2SO_4, filtered and concentrated. Column chromatography (10→50% EtOAc:pent) yielded the title compound (66 mg, 0.15 mmol, 75%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.45 (t, *J* = 7.9 Hz, 2H), 7.34 (p, *J* = 7.0 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 7.9 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 2H), 6.36 (d, *J* = 7.4 Hz, 1H), 4.81 (q, *J* = 7.1 Hz, 1H), 4.69 (p, *J* = 7.0 Hz, 1H), 3.73 (s, 3H), 3.57 (s, 3H), 3.54 (s, 2H), 3.11 (dd, *J* = 14.1, 5.4 Hz, 1H), 2.99 (dd, *J* = 14.1, 7.0 Hz, 1H), 2.52 (s, 3H), 1.43 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.28, 171.92, 165.81, 158.69, 148.13, 145.59, 142.17, 131.53, 130.25, 127.74, 127.42, 126.88, 123.91, 120.89, 113.96, 55.05, 53.57, 52.47, 48.49, 38.27, 37.02, 18.27, 12.39. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 8.42 (ESI-MS (m/z): 437.00 ($M+H^+$)).

3MeIndAc-Ala-Tyr(OMe)-$NHNH_2$ (74)

Methyl ester **73** (66 mg, 0.15 mmol, 1 equiv) was dissolved in MeOH (1.5 mL) and $CHCl_3$ (0.5 mL). Hydrazine hydrate (218 µl, 4.5 mmol, 30 equiv) was added and the mixture was stirred for 3 h before being co-evaporated with tol (3x). The residue was used without further purification. No NMR-analysis was performed due to poor solubility of the product in MeOD and $CDCl_3$ and mixtures thereof. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 6.14 (ESI-MS (m/z): 437.00 ($M+H^+$)).

Fmoc-Hyp(tBu)-Nle-OMe (75)

Fmoc-Hyp(tBu)-OH (1.47 g, 3.6 mmol, 1.2 equiv) and HCTU (1.49 mg, 3.6 mmol, 1.2 equiv) were dissolved in DCM (30 mL). After addition of DiPEA (1.8 mL, 10.5 mmol, 3.5 equiv) the reaction mixture was stirred for approximately 15 min until it became a clear solution. H-NLe-OMe HCl (545 mg, 3 mmol, 1 equiv) was added and the reaction mixture was stirred for 30 min temperature before being concentrated. The residue was dissolved in EtOAc (50mL) and washed with 1M HCl (2x), sat. aq. $NaHCO_3$ (2x) and brine (1x). The organic layer was dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (30→60% EtOAc: Pent) yielded the title compound (1.75 g, 3.00 mmol, 100%). Complex NMR due to a presence of rotamers. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.72 (d, *J* = 7.4 Hz, 2H), 7.63 – 7.48 (m, 2H), 7.36 (t, *J* = 7.3 Hz, 2H), 7.32 – 7.22 (m, 2H), 7.17 (d, *J* = 7.5 Hz, 0.7H), 6.46 (d, *J* = 7.7 Hz, 0.3H), 4.62 – 4.08 (m, 6H), 3.69 (s, 3H), 3.54 (s, 1H), 3.44 – 3.20 (m, 1H), 2.48 – 2.34 (m, 0.8H), 2.19 (s, 0.8H), 2.06 – 1.88 (m, 1H), 1.86 – 1.72 (m, 0.8H), 1.65 (dd, *J* = 14.3, 7.2 Hz, 0.6H), 1.33 – 1.07 (m, 13H), 0.79 (q, *J* = 9.2, 7.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.64, 171.83, 171.18, 155.81, 154.77, 144.00, 143.76, 143.67, 141.16, 127.61, 126.92, 73.94, 69.56, 68.43, 67.79, 60.25, 59.45, 58.88, 54.03, 53.04, 52.36, 52.11, 51.76, 47.00, 39.02, 36.09, 32.02, 31.70, 28.20, 27.30, 22.11, 13.75.

H-Hyp(tBu)-Nle-OMe (76)
Fmoc-Hyp(tBu)-Nle-OMe **75** (1745 mg, 3.00 mmol, 1 equiv) was dissolved in THF (30 mL). After addition of ethanethiol (2.22 mL, 30 mmol, 10 equiv) and DBU (45 µL, 0.3 mmol, 0.1 equiv), the reaction mixture was stirred for 1 h. The reaction mixture was then concentrated and co-evaporated with toluene (3x). Purification by column chromatography (10→100% EtOAc: Pent) yielded the title compound (540 mg, 1.72 mmol, 57%, not completely pure). The product was used without further purification.

Fmoc-Ala-Hyp(tBu)-Nle-OMe (77)
Fmoc-Ala-OH (274 mg, 0.88 mmol, 1.2 equiv) and HCTU (364 mg, 0.88 mmol, 1.2 equiv) were dissolved in DCM (3 mL). After addition of DiPEA (0.45 mL, 2.56 mmol, 3.5 equiv) the reaction mixture was stirred for 15 min until it became a clear solution. Crude Hyp(tBu)-Nle-OMe **76** (250 mg, 0.73 mmol, 1 equiv) was added and the reaction mixture was stirred for 30 min. The reaction mixture was then concentrated and the residue dissolved in EtOAc (50 mL) before being washed with 1M HCl (2x), sat. aq. $NaHCO_3$ (2x) and brine (1x). The organic layer was dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (30→50% EtOAc: Pent) yielded the title compound (211 mg, 0.348 mmol, 48%, not completely pure), which was used without further purification.

H-Ala-Hyp(tBu)-Nle-OMe (78)
Fmoc-Ala-Hyp(tBu)-Nle-OMe **77** (639 mg, 1.05 mmol, 1 equiv) was dissolved in THF (11 mL). After addition of ethanethiol (0.78 mL, 10.5 mmol, 10 equiv) and DBU (32 µL, 0.21 mmol, 0.2 equiv) the reaction mixture was stirred for 1h. the reaction mixture was concentrated and co-evaporated with toluene (3x). Purification by column chromatography (4:6:0→9:0:1 EtOAc: Pent: MeOH) yielded the title compound (247 mg, 0.64 mmol, 61%), which was directly used in the next step.

N_3Gly-Ala-Hyp(tBu)-Nle-OMe (79)
Ala-Hyp(tBu)-Nle-OMe (247 mg, 0.64 mmol, 1 equiv) was dissolved in DMF (7 mL) before adding $(ClAc)_2O$ (131 mg, 0.77 mmol, 1.2 equiv) and DiPEA (0.45 mL, 2.56 mmol, 4 equiv). The reaction mixture was stirred for 1h before NaN_3 (166 mg, 2.56 mmol, 4 equiv) was added. The reaction mixture was then stirred overnight followed by addition of EtOAc (50 mL). The mixture was washed with 1M HCl (2x), sat. aq. $NaHCO_3$ (2x) and brine (1x). The organic layer was dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (0→3% MeOH: DCM) yielded the title compound (114 mg, 0.29, 46%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.29 (d, *J* = 3.7 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 4.65 – 4.51 (m, 2H), 4.51 – 4.22 (m, 2H), 3.91 (s, 2H), 3.73 – 3.51 (m, 4H), 3.49 – 3.22 (m, 1H), 2.48 – 2.18 (m, 1H), 1.87 (m, 1H), 1.80 – 1.65 (m, 1H), 1.65 – 1.47 (m, 1H), 1.36 – 0.94 (m, 16H), 0.81 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.70, 171.68, 170.48, 166.06, 74.14, 69.82, 58.56, 53.53, 52.28, 52.25, 52.20, 46.51, 35.49, 31.74, 28.13, 27.28, 22.11, 18.01, 13.77. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 6.62 (ESI-MS (m/z): 469.07 ($M+H^+$)).

N_3Gly-Ala-Hyp(tBu)-Nle-$NHNH_2$ (80)
Azido-Ac-Ala-Hyp(tBu)-Nle-OMe **79** was dissolved in MeOH (3 mL). After addition of hydrazine (0.42 mL, 8.7 mmol, 30 equiv) the reaction mixture was stirred for approximately 2 hours at room temperature. The reaction mixture was concentrated before being co-evaporated with MeOH (2x). This yielded the title compound in a quantitative yield. ^{1}H NMR (400 MHz, Methanol-d4) δ 4.66 (q, *J* = 6.9 Hz, 1H), 4.56 (t, *J* = 7.1 Hz, 1H), 4.52 – 4.41 (m, 1H), 4.24 (dd, *J* = 8.4, 5.9 Hz, 1H), 3.90 (d, *J* = 9.7 Hz, 2H), 3.82 (dd, *J* = 10.3, 5.6 Hz, 1H),

3.70 – 3.19 (m, 2H), 2.21 – 2.00 (m, 2H), 1.86 – 1.57 (m, 2H), 1.51 – 1.06 (m, 16H), 0.93 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 173.99, 173.45, 173.22, 169.59, 75.42, 71.34, 71.14, 69.27, 60.39, 55.46, 54.95, 53.59, 52.51, 49.66, 49.45, 49.23, 49.02, 48.81, 48.60, 48.42, 48.38, 48.12, 38.29, 32.82, 28.99, 28.55, 23.37, 17.09, 14.30. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 4.77 (ESI-MS (m/z): 469.13 ($M+H^+$)).

Boc-Thz-Nle-OMe (81)

Boc-Thz-OH (843 mg, 3.6 mmol, 1.2 equiv) and HCTU (1.50 g, 3.6 mmol, 1.2 equiv) were dissolved in DCM (30 mL). After addition of DiPEA (1.8 mL, 10.5 mmol, 3.5 equiv) the reaction mixture was stirred for approximately 15 min until it became a clear solution. H-NLe-OMe HCl (543 mg, 3 mmol, 1 equiv) was added and the reaction mixture was stirred for 30 min before being concentrated. The residue was dissolved in EtOAc (50 mL) and washed with 1M HCl (2x), sat. aq. $NaHCO_3$ (2x) and brine (1x). The organic layer was dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (10→50% EtOAc:pent) yielded the title compound (989 mg, 2.74 mmol, 91%). 1H NMR (400 MHz, Chloroform-d) δ 7.11 (bs, 1H), 6.62 (bs, 1H), 4.92 – 4.46 (m, 3H), 4.46 – 4.15 (m, 1H), 3.71 (s, 3H), 3.54 – 2.95 (m, 2H), 1.96 – 1.73 (m, 1H), 1.73 – 1.55 (m, 1H), 1.47 (s, 9H), 1.36 – 1.09 (m, 4H), 0.99 – 0.69 (m, 3H). 13C NMR (101 MHz, CDCl3) δ 172.63, 169.94, 80.04, 52.43, 52.41, 52.23, 32.28, 28.30, 28.25, 27.31, 27.27, 22.34, 22.31, 13.97, 13.95.

Boc-Ala-Thz-Nle-OMe (82)

Boc-Thz-Nle-OMe **81** (989 mg, 2.74 mmol) was dissolved in 10 mL TFA. After 30 min the reaction mixture was concentrated before being co-evaporated with toluene (3x). Boc-Ala-OH (607 mg, 3.2 mmol, 1.2 equiv), HCTU (1.36 g, 3.29 mmol, 1.2 equiv) and DiPEA (1.7 mL, 9.59 mmol, 3.5 equiv) were dissolved in DCM (14 mL) and stirred at room temperature for 15 min until the reaction mixture became clear. The crude TFA salt was then dissolved in DCM (14 mL) and added to the reaction mixture. The reaction mixture was stirred for approximately 30 min before being concentrated. The residue was dissolved in EtOAc (50 mL) and washed with 1M HCl (2x), sat. aq. $NaHCO_3$ (2x) and brine (1x). The organic layer was dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (40→60% EtOAc: Pent) yielded the title compound (747 mg, 1.73 mmol, 63%). Complex NMR due to a presence of rotamers. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.03 (d, *J* = 6.3 Hz, 0.3H), 7.50 (d, *J* = 7.9 Hz, 0.2H), 6.97 (d, *J* = 5.9 Hz, 0.5H), 5.36 (d, *J* = 6.6 Hz, 0.6H), 5.16 (m, 0.4H), 5.01 (m, 0.5H), 4.81 (d, *J* = 9.3 Hz, 0.6H), 4.74 – 4.62 (m, 0.4H), 4.61 – 4.35 (m, 2.5H), 4.35 – 4.20 (m, 0.6H), 4.16 (dd, *J* = 7.4, 4.2 Hz, 0.3H), 3.94 (d, *J* = 9.9 Hz, 0.2H), 3.78 – 3.57 (m, 3H), 3.52 – 3.29 (m, 1H), 3.21 – 2.98 (m, 1H), 2.02 – 1.70 (m, 1H), 1.70 – 1.50 (m, 1H), 1.50 – 1.04 (m, 16H), 0.84 (d, *J* = 5.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.70, 170.67, 168.89, 80.04, 66.01, 62.89, 62.21, 53.65, 53.24, 52.50, 52.44, 52.40, 52.22, 52.06, 49.38, 49.19, 48.05, 35.37, 34.55, 32.16, 31.95, 31.81, 30.28, 28.39, 28.17, 27.48, 27.21, 22.27, 18.82, 16.54, 13.93.

Azido-Ac-Ala-Thz-Nle-OMe (3) (83)

Boc-Ala-Thz-Nle-OMe **82** (349 mg, 0.81 mmol) was dissolved in 1:1 TFA:DCM (10 mL). After 30 min the reaction mixture was concentrated before being co-evaporated with toluene (3x). The crude TFA salt was dissolved in DMF (8 mL) before adding $(ClAc)_2O$ (164 mg, 0.97 mmol, 1.2 equiv) and DiPEA (0.56 mL, 3.24 mmol, 4 equiv). The reaction mixture was stirred for 1 h before NaN_3 (210 mg, 3.24 mmol, 4 equiv) was added. After stirring overnight. EtOAc (50mL) was added to the reaction mixture before being washed with 1M HCl (2x), sat. aq. $NaHCO_3$ (2x) and brine (1x). The organic layer was dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (80→100% EtOAc:Tol) yielded the

title compound (213 mg, 0.51 mmol, 64%). Complex NMR due to a presence of rotamers. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.85 (d, *J* = 7.4 Hz, 0.2H), 7.30 (d, *J* = 9.1 Hz, 0.8H), 7.14 (d, 0.3H), 7.00 (d, *J* = 7.6 Hz, 0.7H), 4.97 – 4.30 (m, 5H), 3.91+3.84 (2xs, 2H), 3.68+3.62 (2xs, 3H), 3.37 (dd, *J* = 11.7, 4.1 Hz, 1H), 3.18 (dd, *J* = 11.6, 7.3 Hz, 1H), 1.92 – 1.71 (m, 1H), 1.71 – 1.51 (m, 1H), 1.48 – 1.04 (m, 7H), 0.84 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.73, 171.27, 168.83, 166.44, 62.83, 62.29, 53.14, 52.43, 52.37, 52.29, 52.21, 51.73, 49.51, 49.31, 48.61, 46.89, 34.79, 32.19, 31.85, 30.47, 29.62, 28.03, 27.17, 22.19, 21.99, 18.27, 16.62, 13.83.

N_3Gly-Ala-Thz-Nle-NHNH$_2$ (84)

Azido-Ac-Ala-Thz-Nle-OMe **83** (213 mg, 0.51 mmol) was dissolved in MeOH (5 mL). After addition of hydrazine hydrate (0.75 mL, 15.4 mmol, 30 equiv) the reaction mixture was stirred for 2 h. The reaction mixture was then concentrated before being co-evaporated with MeOH (3x). This yielded the title compound in a quantitative yield. Complex NMR due to a presence of rotamers. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.72 – 7.44 (m, 2H), 7.37 (d, *J* = 8.1 Hz, 1H), 5.15 – 4.22 (m, 5H), 3.92 (s, 2H), 3.84 – 3.40 (m, 3H), 3.40 – 3.05 (m, 2H), 1.84 – 1.47 (m, 2H), 1.47 – 1.05 (m, 7H), 0.82 (t, *J* = 6.5 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 172.02, 171.48, 169.47, 169.21, 166.87, 62.93, 62.72, 53.22, 52.19, 52.12, 51.80, 49.71, 49.16, 48.17, 47.08, 34.96, 32.66, 32.40, 31.46, 30.31, 29.66, 27.93, 27.58, 22.30, 21.18, 17.98, 17.37, 13.93. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 4.11 (ESI-MS (m/z): 415.00 ($M+H^+$)).

Boc-Aze-Nle-OMe (85)

To a suspension of Boc-Aze-OH (201.4 mg, 1.0 mmol, 1 equiv) in DCM (10 mL), HCTU (495.6 mg, 1.2 mmol, 1.2 equiv) and DiPEA (0.57 mL, 3.5 mmol) were added. After a few minutes, H-Nle-OMe HCl (220 mg, 1.2 mmol) was added. After stirring for 1 hour, the reaction mixture was concentrated and the residue was dissolved in EtOAc (25 mL), washed with 1 M HCl (2x), sat. $NaHCO_3$ (3x) and brine (1x), dried over $MgSO_4$ and concentrated. Purification by column chromatography (30→60% EtOAc:pent) yielded the title compound (270 mg, 0.82 mmol, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75-4.48 (m, 2H), 3.95-3.75 (m, 2H), 3.75 (s, 3H, OCH_3), 2.52-2.35 (m, 2H), 1.88-1.70 (m, 2H), 1.65-1.22 (m, 4H), 1.48 (s, 9H), 0.91 (m, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.46, 171.28, 80.87, 62.01, 52.12, 51.94, 47.01, 31.93, 29.59, 28.12, 27.29, 22.20, 13.20.

Boc-Ala-Aze-Nle-OMe (86)

Boc-Aze-Nle-OMe **85** (270 mg, 0.82 mmol, 1 equiv) was dissolved in TFA (4.5 mL) and after stirring for 40 min, the reaction mixture was concentrated and the residue was co-evaporated with toluene (3x). Next, Boc-Ala-OH (187 mg, 1.0 mmol, 1.2 equiv), HCTU (409 mg, 1.0 mmol, 1 equiv) and DiPEA (0.48 mL, 2.9 mmol) in DCM (5 mL) was stirred for 2 min, followed by the addition of the TFA salt in DCM (10). After stirring overnight, the reaction mixture was concentrated and the residue was dissolved in EtOAc (25 mL) and washed with 1 M HCl (2x), $NaHCO_3$ (3x) and brine (1x), dried over $MgSO_4$ and concentrated. Purification by column chromatography (50→100% EtOAc:pent) yielded the title compound (280 mg, 0.7 mmol, 85%). Complex NMR due to a 7:1 ratio of rotamers. Peaks of major rotamer are reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.5 Hz, 1H), 5.24 (d, 7.5 Hz), 4.94 (q, *J* = 6.3 Hz, 1H), 4.48 (q, *J* = 7.5 Hz, 1H), 4.26 (m, 2H), 4.08 (m, 1H), 3.71 (s, 3H), 2.76-2.69 (m, 1H), 2.51-2.42 (m, 1H), 1.82-1.61 (m, 2H), 1.41 (s, 9H), 1.24 (m, 7H), 0.87 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.89, 172.44, 170.10, 155.10, 79.77, 61.79, 52.34, 52.22, 48.82, 45.50, 31.60, 28.27, 27.29, 22.14, 18.41, 18.34, 13.84.

N_3Gly-Ala-Aze-Nle-OMe (87)
Boc-Ala-Aze-Nle-OMe **86** (256 mg, 0.64 mmol, 1 equiv) was dissolved in TFA. After stirring for 30 min, the mixture was evaporated and co-evaporated with toluene (3x). The obtained TFA-salt was dissolved in DMF (6 mL) and $(ClOAc)_2O$ (348 mg, 2.0 mmol, 1.2 equiv) and DiPEA (1.18 mL, 6.8 mmol, 4 equiv) were added. After 1.5 h, NaN_3 (0.27 g, 4.1 mmol) was added and the resulting mixture was stirred overnight. The reaction mixture was diluted with EtOAc, washed with 1M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. Purification by column chromatography (1→3% MeOH:DCM) yielded the title compound (144 mg, 0.38 mmol, 59%). Complex NMR due to a 7.5:1 ratio of rotamers. Peaks of major rotamer are reported. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.91 (d, J = 7.7 Hz, 1H), 7.26 (d, J = 7.3 Hz, 1H), 4.95 (dd, J = 9.3, 6.3 Hz, 1H), 4.58 – 4.49 (m, 2H), 4.35 (q, J = 8.8 Hz, 1H), 4.19 – 4.08 (m, 1H), 3.98 (s, 2H), 3.74 (s, 3H), 2.80 – 2.69 (m, 1H), 2.57 – 2.43 (m, 1H), 1.83 (dq, J = 14.2, 5.5, 4.8 Hz, 1H), 1.76 – 1.59 (m, 1H), 1.41 – 1.19 (m, 7H), 0.89 (q, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.83, 172.45, 169.77, 166.48, 61.80, 52.29, 52.25, 52.18, 49.00, 44.39, 31.63, 27.24, 22.12, 18.46, 17.99, 13.82. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 5.44 (ESI-MS (m/z): 383.07 ($M+H^+$)).

N_3Gly-Ala-Aze-Nle-$NHNH_2$ (88)
Methyl ester **87** (144 mg, 0.38 mmol, 1 equiv) was dissolved in MeOH (4 mL) before adding hydrazine hydrate (582 µL, 11.4 mmol, 30 equiv). After stirring for 4 h at RT, TLC analysis showed complete conversion. The reaction mixture was concentrated and co-evaporated with toluene to give the title compound in a quantitative yield. No NMR-analysis was performed due to poor solubility of the product in MeOD and $CDCl_3$ and mixtures thereof. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 3.67 (ESI-MS (m/z): 383.07 ($M+H^+$)).

Boc-Ala-Pip-Nle-OMe (89)
To a solution of Boc-Pip-OH (720 mg, 3.6 mmol, 1.2 equiv) in DCM (35 mL), HCTU (1.50 g, 3.6 mmol, 1.2 equiv) and DiPEA (1.9 mL, 10.5 mmol, 3.5 eq) were added. Then H-Nle-OMe HCl (0.554g, 3 mmol, 1 equiv) was added. The mixture was stirred for 3 h before being concentrated. The residue was dissolved in EtOAc, washed with 1M HCl (2x), sat aq NaHCO3 (2x), brine and dried over Na_2SO_4, filtered and concentrated. Column chromatography (50→80% EtOAc:pent) yielded Boc-Pip-Nle-OMe (1.09 g, 2.79 mmol, 93%), which was dissolved in TFA and stirred for 30 min. The mixture was concentrated and co-evaporated with toluene (3x), providing a solid which was directly used in the next step. Boc-Ala-OH (385 mg, 2.0 mmol, 1.2 equiv) was dissolved in DCM (20 mL). HCTU (843 mg, 2.0 mmol, 1.2 equiv), TFA·H-Pip-Nle-OMe (631 mg, 1.7 mmol, 1 equiv) and DiPEA (1.0 mL, 6.0 mmol, 3.5 equiv) were added and the mixture was stirred for 2 h before being concentrated. The residue was dissolved in EtOAc, washed with 1M HCl (2x), sat aq NaHCO3 (2x), brine and dried over Na_2SO_4, filtered and concentrated. Column chromatography (50→80% EtOAc:pent) yielded the title compound in a quantitative yield. Complex NMR due to a 2:1 ratio of rotamers. 1H NMR (400 MHz, Chloroform-d) δ 7.88 (d, J = 7.5 Hz, 0.3H), 6.47 (d, J = 7.5 Hz, 0.7H), 5.55 (d, J = 7.8 Hz, 0.7H), 5.26 (d, J = 6.2 Hz, 0.4H), 5.17 (d, J = 4.8 Hz, 0.7H), 4.65 (q, J = 6.9 Hz, 0.6H), 4.55 (d, J = 13.5 Hz, 0.4H), 4.51 – 4.39 (m, 1.4H), 4.34 (ddd, J = 9.3, 7.7, 5.5 Hz, 0.4H), 3.75 (d, J = 12.8 Hz, 0.6H), 3.67 (s, 2H), 3.63 (s, 1H), 3.13 (t, J = 12.2 Hz, 0.6H), 2.44 (q, J = 12.9 Hz, 0.8H), 2.16 (d, J = 13.6 Hz, 0.6H), 1.88 – 1.40 (m, 6H), 1.38 (s, 6H), 1.33 (s, 3H), 1.28 – 1.12 (m, 7H), 0.85 – 0.77 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.93, 172.74, 172.15, 170.37, 169.83, 156.28, 155.03, 80.19, 79.58, 52.13, 46.50, 43.65, 39.92, 31.96, 30.44, 27.40, 26.36, 25.59, 25.33, 24.82, 22.21, 22.11, 20.67, 20.21.

N_3Gly-Ala-Pip-Nle-OMe (90)

1:1 DCM/TFA (10 mL) was added to **89** (726 mg, 1.7 mmol, 1 equiv) and after 30 min, the reaction mixture was concentrated and co-evaporated with toluene to give the deprotected peptide, which was dissolved in DMF (14 mL). $(ClAc)_2O$ (348 mg, 2.0 mmol, 1.2 equiv) and DiPEA (1.18 mL, 6.8 mmol, 4 equiv) were added. After 1.5 h, NaN_3 (0.27 g, 4.1 mmol) was added and the resulting mixture was stirred overnight. The reaction mixture was diluted with EtOAc, washed with 1M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. Purification by column chromatography (1→3% MeOH:DCM) yielded the title compound (631 mg, 1.53 mmol, 90%). Complex NMR due to a 3.5:1 ratio of rotamers. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.57 (d, *J* = 7.6 Hz, 0.2H), 7.40 (d, *J* = 7.3 Hz, 0.8H), 7.04 (d, *J* = 5.8 Hz, 0.2H), 6.42 (d, *J* = 7.6 Hz, 0.8H), 5.21 (d, *J* = 4.7 Hz, 0.7H), 4.96 (p, *J* = 6.9 Hz, 0.7H), 4.70 (p, *J* = 6.7 Hz, 0.7H), 4.57 (d, *J* = 13.4 Hz, 0.7H), 4.50 (m, 1H), 4.47 – 4.36 (m, 0.3H), 3.96 (d, *J* = 5.2 Hz, 1.3H), 3.77 (d, *J* = 13.2 Hz, 0.8H), 3.72 (s, 2.3 H), 3.69 (s, 0.7H), 3.28 – 3.18 (m, 0.8H), 2.54 (t, *J* = 13.3 Hz, 0.5H), 2.21 (d, *J* = 13.7 Hz, 0.8H), 1.88 – 1.40 (m, 8H), 1.35 (d, *J* = 6.9 Hz, 3H), 1.33 – 1.14 (m, 4H), 0.85 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.87, 172.07, 170.16, 169.49, 165.96, 52.69, 52.30, 52.14, 43.78, 40.26, 32.12, 30.77, 28.26, 27.48, 26.64, 25.83, 25.38, 24.87, 22.32, 22.17, 20.72, 20.22. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 6.36 (ESI-MS (m/z): 410.93 ($M+H^+$)).

N_3Gly-Ala-Pip-Nle-$NHNH_2$ (91)

Methyl ester **90** (631 mg, 1.53 mmol, 1 equiv) was dissolved in MeOH (15 mL) before adding hydrazine hydrate (2.2 mL, 45.9 mmol, 30 equiv). After stirring for 4 h at RT, TLC analysis showed complete conversion. The reaction mixture was concentrated and co-evaporated with toluene to give the title compound in a quantitative yield. No NMR-analysis was performed due to poor solubility of the product in MeOD and $CDCl_3$ and mixtures thereof. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 4.35 (ESI-MS (m/z): 411.00 ($M+H^+$)).

Boc-(4S)FPro-Nle-OMe (92)

HBTU (0.455 g, 1.2 mmol, 1.2 equiv) was added to a suspension of *N*-Boc-cis-4-fluoro-L-proline (0.233 g, 1.0 mmol, 1 equiv) in DCM (5 mL). The resulting reaction mixture was stirred for 5 min before subsequent addition of DiPEA (0.6 mL, 3.5 mmol, 3.5 equiv) and H-NLe-OMe HCl (1.2 mmol, 1.2 equiv). The reaction mixture was stirred for 1 h and then washed with 1M HCl, sat. aq. $NaHCO_3$, H_2O and brine, dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (1:1 EA:pent) gave the title compound as needle-like crystals in a quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.17 (s, 1H), 4.83 (d, J = 48.2 Hz, 1H), 4.26 (s, 1H), 4.08 (s, 1H), 3.68 – 3.23 (m, 5H), 2.69 – 1.96 (m, 2H), 1.68 (s, 1H), 1.52 (s, 1H), 1.38 (s, 9H), 1.17 (m, 4H), 0.80 (t, J = 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.47, 92.45, 90.73, 81.37, 59.89, 53.94, 52.11, 37.47, 32.15, 28.07, 26.80, 22.15, 13.71; LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 7.60 (ESI-MS (m/z): 360.93 ($M+H^+$)).

Boc-Ala-(4S)-FPro-Nle-OMe (93)

TFA (6 mL) was added to **92** (0.68 g, 1.9 mmol) and stirred for half an hour before the reaction mixture was concentrated and co-evaporated with toluene (3x). HBTU (0.87 g, 2.3 mmol, 1.2 equiv) was added to a solution of Boc-Ala-OH (0.43 g, 2.3 mmol, 1.2 equiv) in DCM (5 mL) and the resulting reaction mixture was stirred for 5 min before addition of DiPEA (1.3 mL, 7.6 mmol, 3.5 equiv) and a solution of the deprotected peptide in DCM (4

mL). The resulting yellow suspension was stirred for 3 days and was diluted with EtOAc, washed with 1M HCl, sat. aq. $NaHCO_3$, H_2O and brine, dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (4:2 EA:pent) yielded the title compound (755 mg, 1.8 mmol, 93%). Complex NMR due to rotamers. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.10 (d, *J* = 8.0 Hz, 0.4 H), 7.01 (d, *J* = 7.5 Hz, 0.6 H), 5.53 – 5.03 (m, 2H), 4.80 (d, *J* = 9.8 Hz, 0.6 H), 4.63 – 4.21 (m, 2.4 H), 4.06 – 3.76 (m, 2H), 3.72 (s, 2H), 3.66 (s, 1H), 3.04 – 2.82 (m, 1H), 2.41 – 2.07 (m, 1H), 1.98 – 1.71 (m, 1H), 1.71 – 1.52 (m, 1H), 1.52 – 1.33 (m, 10H), 1.34 – 1.08 (m, 6H), 0.85 (q, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.97, 172.82, 172.74, 172.64, 170.58, 169.52, 155.94, 155.26, 93.15, 91.37, 91.19, 89.44, 80.24, 79.93, 59.30, 59.15, 54.12, 53.88, 52.61, 52.32, 52.22, 52.08, 48.66, 47.83, 38.61, 38.35, 38.14, 34.32, 34.11, 31.94, 30.14, 29.68, 28.37, 28.32, 28.22, 27.77, 26.81, 22.24, 22.00, 18.57, 16.58, 13.83. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 7.28 (ESI-MS (m/z): 431.93 ($M+H^+$)).

N_3Gly-Ala-(4S)-FPro-Nle-OMe (94)

TFA (6 mL) was added to **93** (1.75 mmol, 1 equiv). After 30 min, the reaction mixture was concentrated and co-evaporated with toluene to give the deprotected peptide, which was dissolved in DMF (18 mL). $(ClOAc)_2O$ (0.36 g, 2.1 mmol) and DiPEA (0.9 mL, 5.3 mmol) were added and the reaction mixture turned deep red. After 1.5 h NaN_3 (0.34 g, 5.2 mmol) was added and the resulting mixture was stirred overnight. The reaction mixture was diluted with EtOAc, washed with 1M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. Purification by column chromatography (9:1 EA:pent → 1:9 MeOH:EA) yielded the title compound (425 mg, 1.0 mmol, 59%).%). LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 6.00 (ESI-MS (m/z): 415.00 ($M+H^+$)). Complex NMR due to rotamers. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.77 (d, *J* = 7.9 Hz, 0.3 H), 7.14 (d, *J* = 6.9 Hz, 0.7 H), 6.93 (d, *J* = 7.4 Hz, 0.7 H), 6.73 (d, *J* = 4.6 Hz, 0.3 H), 5.32 (m, 1H), 4.86 – 4.65 (m, 1H), 4.67 – 4.33 (m, 2H), 4.15 – 3.85 (m, 4H), 3.76 (s, 2H), 3.71 (s, 1H), 2.93 – 2.75 (m, 1H), 2.42 – 2.04 (m, 1H), 1.95 – 1.60 (m, 2H), 1.55 (d, *J* = 6.9 Hz, 2H), 1.42 (d, *J* = 6.9 Hz, 1H), 1.37 – 1.07 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H).

N_3Gly-Ala-(4S)-FPro-Nle-$NHNH_2$ (95)

Methyl ester **94** (1.0 mmol, 1 equiv) was dissolved in MeOH (10 mL) before adding hydrazine hydrate (1.0 mL, 21 mmol, 21 equiv). After stirring for 4 h at rt TLC analysis showed incomplete conversion and the reaction mixture was refluxed for 45 min to achieve full consumption of the starting material. The reaction mixture was concentrated and co-evaporated with toluene to give the title compound in a quantitative yield. No NMR-analysis was performed due to poor solubility of the product in MeOD and $CDCl_3$ and mixtures thereof. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 4.49 (ESI-MS (m/z): 415.07 ($M+H^+$)).

Boc-(4R)FPro-Nle-OMe (96)

HBTU (0.455 g, 1.2 mmol, 1.2 equiv) was added to a suspension of *N*-Boc-cis-4-fluoro-L-proline (0.233 g, 1.0 mmol, 1 equiv) in DCM (5 mL). The resulting reaction mixture was stirred for 5 min before subsequent addition of DiPEA (0.6 mL, 3.5 mmol, 3.5 equiv) and H-NLe-OMe HCl (1.2 mmol, 1.2 equiv). The reaction mixture was stirred for 1 h and then washed with 1M HCl, sat. aq. $NaHCO_3$, H_2O and brine, dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (1:1 EA:pent) gave the title compound as a yellow oil (288 mg, 0.80 mmol, 80%). LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 7.60 (ESI-MS (m/z): 360.93 ($M+H^+$)). Complex NMR due to rotamers. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.33 (d, *J* = 6.3 Hz, 0.6H), 6.50 (s, 0.4H), 5.16 (d, *J* = 53.0

Hz, 1H), 4.57 – 4.20 (m, 2H), 4.15 – 3.74 (m, 1H), 3.69 (s, 3H), 3.56 – 3.26 (m, 1H), 2.72 – 2.18 (m, 2H), 1.85 – 1.72 (m, 1H), 1.72 – 1.53 (m, 1H), 1.43 (s, 9H), 1.23 (d, *J* = 17.3 Hz, 4H), 0.83 (t, *J* = 5.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.72, 170.71, 92.88, 91.13, 80.99, 59.42, 58.06, 53.54, 53.31, 52.50, 52.31, 52.05, 37.81, 34.68, 34.47, 32.38, 31.96, 29.73, 28.31, 27.35, 22.31, 13.87.

Boc-Ala-(4R)-FPro-Nle-OMe (97)

TFA (6 mL) was added to **96** (0.52 g, 1.43 mmol) and stirred for half an hour before the reaction mixture was concentrated and co-evaporated with toluene (3x). HBTU (0.645 g, 1.7 mmol, 1.2 equiv) was added to a solution of Boc-Ala-OH (0.325 g, 1.7 mmol, 1.2 equiv) in DCM (5 mL) and the resulting reaction mixture was stirred for 5 min before addition of DiPEA (1.0 mL, 5.7 mmol, 4 equiv) and a solution of the deprotected peptide in DCM (4 mL). The resulting yellow suspension was stirred for 3 days and was diluted with EtOAc, washed with 1M HCl, sat. aq. $NaHCO_3$, H_2O and brine, dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (50→60% EA:pent) yielded the title compound (592 mg, 1.40 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (s, 1H), 5.53 (d, J = 6.8 Hz, 1H), 5.33 (d, J = 52.6 Hz, 1H), 4.77 (t, J = 7.8 Hz, 1H), 4.51 (m, 2H), 4.21 – 4.03 (m, 1H), 3.74 (s, 3H), 3.71 – 3.54 (m, 1H), 2.46 (m, 2H), 1.90 – 1.56 (m, 2H), 1.44 (s, 9H), 1.31 (m, 7H), 0.88 (t, J = 5.6 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3): δ 172.76, 169.94, 155.06, 92.68, 90.89, 79.82, 58.25, 53.60, 53.37, 52.55, 52.39, 47.93, 34.22, 33.99, 31.90, 28.39, 27.36, 22.26, 18.68, 13.91; LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 7.15 (ESI-MS (m/z): 431.93 ($M+H^+$)).

N_3Gly-Ala-(4R)-FPro-Nle-OMe (98)

TFA (4.6 mL) was added to **97** (592 mg, 1.40 mmol, 1 equiv) and after 30 min, the reaction mixture was concentrated and co-evaporated with toluene to give the deprotected peptide, which was dissolved in DMF (14 mL). $(ClOAc)_2O$ (0.28 g, 1.60 mmol, 1.1 equiv) and DiPEA (0.9 mL, 5.3 mmol, 3.8 equiv) were added and the reaction mixture turned deep red. After 1.5 h NaN_3 (0.27 g, 4.1 mmol) was added and the resulting mixture was stirred overnight. The reaction mixture was diluted with EtOAc, washed with 1M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. Purification by column chromatography (1:1 EA:pent) yielded the title compound (383 mg, 0.92 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 7.7 Hz, 1H), 5.33 (d, J = 52.6 Hz, 1H), 4.76 (dt, J = 12.3, 7.5 Hz, 2H), 4.57 – 4.46 (m, 1H), 4.17 – 3.59 (m, 7H), 2.53 (ddt, J = 46.6, 17.0, 6.2 Hz, 2H), 1.84 (ddd, J = 13.5, 10.2, 6.1 Hz, 1H), 1.70 (ddd, J = 13.6, 8.7, 4.7 Hz, 1H), 1.39 – 1.25 (m, 7H), 0.89 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.76, 171.65, 169.87, 166.13, 92.70, 90.91, 58.36, 53.73, 53.50, 52.55, 52.47, 52.39, 46.90, 34.54, 34.32, 31.88, 27.38, 22.26, 18.14, 13.90; LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 5.82 (ESI-MS (m/z): 415.00 ($M+H^+$)).

N_3Gly-Ala-(4R)-FPro-Nle-$NHNH_2$ (99)

Methyl ester **98** (383 mg, 0.92 mmol, 1 equiv) was dissolved in MeOH (9.2 mL) before adding hydrazine hydrate (0.9 mL, 18.4 mmol, 20 equiv). After stirring for 4 h at RT, TLC analysis showed incomplete conversion and the reaction mixture was refluxed for 45 min to achieve full consumption of the starting material. The reaction mixture was concentrated and co-evaporated with toluene to give the title compound in a quantitative yield. No NMR-analysis was performed due to poor solubility of the product in MeOD and $CDCl_3$ and mixtures thereof. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 4.20 (ESI-MS (m/z): 415.07 ($M+H^+$)).

Boc-4,4-F_2Pro-Nle-OMe (100)
Boc-4,4-F_2Pro-OH (301 mg, 1.2 mmol, 1.2 equiv) and HCTU (496 mg, 1.2 mmol, 1.2 equiv) were dissolved in DCM (10 mL). After addition of DiPEA (0.6 mL, 3.5 mmol, 3.5 equiv) the reaction mixture was stirred for approximately 15 min until it became a clear solution. H-NLe-OMe HCl (182 mg, 1.0 mmol, 1 equiv) was added and the reaction mixture was stirred for 30 min before being concentrated. The residue dissolved in EtOAc (50 mL) and washed with 1M HCl (2x), sat. aq. $NaHCO_3$ (2x) and brine (1x). The organic layer was, dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (10→30% EtoAc:pent) yielded the title compound (352 mg, 0.93 mmol, 93%). ^{1}H NMR (400 MHz, Chloroform-d) δ 4.57 (bs, 2H), 4.03 – 3.57 (m, 2H), 3.75 (s, 3H), 3.04 – 2.45 (m, 2H), 1.85 (m, 1H), 1.68 (m, 1H), 1.49 (s, 9H), 1.29 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.64, 53.59, 52.42, 32.11, 28.25, 27.23, 22.34, 13.89.

Boc-Ala-4,4-F_2Pro-Nle-OMe (101)
Boc-4,4-F_2Pro-Nle-OMe (302 mg, 0.80 mmol, 1 equiv) **100** was dissolved in 1:1 TFA: DCM (10 mL). After 30 min the reaction mixture was concentrated before being co-evaporated with toluene (3x). Boc-Ala-OH (182 mg, 0.96 mmol, 1.2 equiv), HCTU (397 mg, 0.96 mmol, 1.2 equiv) and DiPEA (0.5 mL, 2.8 mmol, 3.5 equiv) were dissolved in DCM (8 mL) and stirred for 15 min until the reaction mixture became a clear solution. The crude TFA salt was then dissolved in DCM (4 mL) and added to the reaction mixture. The reaction mixture was stirred overnight at room temperature and under argon atmosphere before being concentrated. The residue was dissolved in EtOAc (50mL) and washed with 1M HCl (2x), sat. aq. $NaHCO_3$ (2x) and brine (1x). The organic layer was dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (30→50% EtOAc:pent) yielded the title compound (167 mg, 0.37 mmol, 46%). Complex NMR due to a presence of rotamers. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.21 (d, *J* = 8.1 Hz, 0.3H), 7.13 (d, *J* = 7.3 Hz, 0.7H), 5.38 (d, *J* = 7.6 Hz, 0.7H), 5.21 (bs, 0.3H), 4.79 (dd, *J* = 9.2, 5.3 Hz, 0.7H), 4.60 – 3.72 (m, 3.3H), 3.65 (2xs, 3H), 3.36 – 2.11 (m, 2H), 1.98 – 1.50 (m, 2H), 1.43 – 1.13 (m, 16H), 0.82 (t, *J* = 6.8 Hz, 3H).

Azido-Ac-Ala-4,4-F_2Pro-Nle-OMe (102)
Boc-Ala-4,4-F_2Pro-Nle-OMe (167 mg, 0.37 mmol, 1 equiv) **101** was dissolved in 1:1 TFA: DCM (10 mL). After 30 min the reaction mixture was concentrated before being co-evaporated with toluene (3x). The crude TFA salt was dissolved in DMF (4 mL) before adding $(ClAc)O_2$ (76 mg, 0.45 mmol, 1.2 equiv) and DiPEA (0.26 mL, 1.49 mmol, 4 equiv). The reaction mixture was stirred for one hour at room temperature and under argon atmosphere before NaN_3 (97 mg, 1.49 mmol, 4 equiv) was added. The reaction mixture was then stirred overnight at room temperature and under argon atmosphere. EtOAc (50 mL) was then added to the reaction mixture before being washed with 1M HCl (2x), sat. aq. $NaHCO_3$ (2x) and brine (1x).The organic layer was dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (0→3% MeOH:DCM) yielded the title compound (117 mg, 0.27 mmol, 73%). Complex NMR due to a presence of rotamers. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.01 (d, *J* = 8.0 Hz, 0.2H), 7.18 (d, *J* = 7.1 Hz, 0.8H), 7.06 (d, *J* = 7.4 Hz, 0.8H), 6.97 (s, 0.2H), 4.76 (dd, *J* = 9.1, 5.7 Hz, 1H), 4.64 (p, *J* = 6.9 Hz, 1H), 4.58 – 4.37 (m, 1H), 4.15 (td, *J* = 12.1, 7.1 Hz, 1H), 3.94 (s, 2H), 3.91 – 3.75 (m, 1H), 3.67 (d, *J* = 22.4 Hz, 3H), 3.01 – 2.43 (m, 2H), 1.79 (m, 1H), 1.63 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.24 (dd, *J* = 18.0, 6.8 Hz, 4H), 0.83 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.83, 172.70, 172.10, 171.42, 169.35, 168.64, 167.67, 166.45, 128.72, 126.24, 123.75, 59.02, 57.86, 53.99, 53.68, 53.34, 53.00, 52.55, 52.44, 52.37, 52.26, 51.79, 47.37, 46.70, 35.99, 35.74, 35.49, 31.88, 30.38, 27.97, 27.21, 22.22, 21.96, 17.87, 16.76, 13.84.

Azido-Ac-Ala-4,4- F_2Pro-Nle-$NHNH_2$ (103)
Azido-Ac-Ala-4,4-F_2-Nle-OMe (117 mg, 0.27 mmol) **102** was dissolved in MeOH (3 mL). After addition of hydrazine hydrate (0.41 mL, 8.31 mmol, 30 equiv) the reaction mixture was stirred for 2 h. The reaction mixture was then concentrated before being co-evaporated with MeOH (3x). This yielded the title compound in a quantitative yield. Complex NMR due to a presence of rotamers. ^{1}H NMR (400 MHz, Methanol-d4) δ 4.69-4.63 (m, 1H), 4.54 (q, *J* = 7.0 Hz, 1H), 4.42 – 4.14 (m, 2H), 4.14 – 3.92 (m, 1H), 3.88-3.82 (m, 2H), 2.89 – 2.57 (m, 1H), 2.56 – 2.26 (m, 1H), 1.85 – 1.49 (m, 2H), 1.30 (m, 7H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 173.60, 173.24, 171.93, 169.90, 130.30, 127.83, 125.37, 60.02, 59.22, 54.99, 54.66, 54.34, 53.57, 52.42, 52.12, 48.36, 48.06, 38.18, 37.94, 37.69, 32.97, 32.37, 29.12, 28.84, 23.33, 23.20, 17.23, 16.75, 14.23. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 4.24 (ESI-MS (m/z): 433.00 ($M+H^+$)).

Synthesis of final compounds via azide couplings.

General procedure for azide couplings.
Compounds **4-37** were prepared via azide coupling of properly protected tripeptide hydrazide and properly deprotected vinyl sulfone amines and epoxyketone amines. The appropriate hydrazide was dissolved in 1:1 DMF:DCM (v/v) and cooled to -30 °C. *t*BuONO (1.1 equiv) and HCl (4M solution in 1,4-dioxane, 2.8 equiv) were added, and the mixture was stirred for 3h at -30 °C after which TLC analysis (10% MeOH/DCM, v/v) showed complete consumption of the starting material. The epoxyketone or vinyl sulfone as a free amine was added to the reaction mixture as a solution in DMF. DiPEA (5 equiv) was added to the reaction mixture, and this mixture was allowed to warm to RT slowly overnight. The mixture was diluted with EtOAc and extracted with H_2O (3×). The organic layer was dried over $MgSO_4$ and purified by flash column chromatography (1-5% MeOH in DCM) and HPLC-purification (if necessary).

MorphAc-Ala-Tyr(OMe)-Ala(Ada)-EK (4)
This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (2→4% MeOH in DCM) provided the title compound (21.62 mg, 68%) as a white powder after lyophilisation. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.43 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 8.6 Hz, 2H), 6.92 – 6.66 (m, 3H), 6.14 (d, J = 7.5 Hz, 1H), 4.58 – 4.47 (m, 2H), 4.41 (p, J = 7.3 Hz, 1H), 3.76 (s, 3H), 3.68 (t, J = 4.6 Hz, 4H), 3.32 (d, J = 5.0 Hz, 1H), 3.00 – 2.91 (m, 3H), 2.89 – 2.83 (m, 2H), 2.44 (q, J = 4.2 Hz, 4H), 1.91 (s, 3H), 1.70 – 1.53 (m, 6H), 1.50 (s, 3H), 1.44 – 1.40 (m, 5H), 1.39 – 1.28 (m, 5H), 1.01 – 0.93 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.78, 172.02, 170.31, 170.23, 158.67, 130.54, 128.54, 114.08, 67.03, 61.72, 59.06, 55.33, 54.29, 53.86, 52.54, 48.32, 47.92, 44.66, 42.44, 36.83, 36.62, 32.91, 28.62, 17.66, 17.07. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 6.52 (ESI-MS (m/z): 639.6 ($M+H^+$)) HRMS: calcd. for $C_{35}H_{50}N_4O_7$ 639.37523 $[M+2H]^{2+}$; found 639.37524

MorphAc-Ala-Tyr(OMe)-BiPhe-EK (5)
This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (2→4% MeOH in DCM) provided the title compound (21.18 mg, 64.5%) as a white powder after lyophilisation. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.59 – 7.51 (m, 2H), 7.51 – 7.38 (m, 5H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.09 (dd, *J* = 8.4, 3.2 Hz, 4H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.68 (d, *J* = 7.5 Hz, 1H), 6.36 (d, *J* = 7.3 Hz, 1H), 4.77 (td, *J* = 7.9, 4.7 Hz, 1H), 4.50 (t, *J* = 7.1 Hz, 1H), 4.34 (t, *J* = 7.2 Hz, 1H), 3.73 (s, 3H), 3.67 (t, *J* = 4.5 Hz, 4H), 3.29 (d, *J* = 4.9 Hz, 1H), 3.12 (dd, *J* = 14.1, 4.6 Hz, 1H), 2.98 –

2.78 (m, 5H), 2.73 (dd, *J* = 14.1, 8.3 Hz, 1H), 2.44 – 2.38 (m, 4H), 1.51 (s, 3H), 1.26 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.02, 171.96, 170.52, 170.30, 158.69, 140.66, 140.05, 134.76, 130.52, 129.76, 128.89, 128.33, 127.44, 127.32, 127.09, 114.11, 67.02, 61.68, 59.36, 55.30, 54.32, 53.82, 52.75, 52.65, 48.39, 36.79, 36.65, 17.69, 16.69. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 7.05 (ESI-MS (m/z): 657.13 ($M+H^+$)). HRMS: calcd. for $C_{37}H_{44}N_4O_7$ 657.32828 $[M+H]^+$; found 657.32831

MorphAc-Ala-Tyr(OMe)-2-Nal-EK (6)
Compound XX was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (2→4% MeOH in DCM) followed by purification by HPLC (20-70% MeCN, 0.1 % TFA, 10 min gradient) provided the title compound (13.75 mg, 43.5%) as a white powder after lyophilisation. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.82 – 7.70 (m, 3H), 7.49 – 7.34 (m, 4H), 7.18 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 6.61 (d, *J* = 7.5 Hz, 1H), 6.33 (d, *J* = 7.2 Hz, 1H), 4.88 – 4.78 (m, 1H), 4.46 (q, *J* = 7.0 Hz, 1H), 4.31 – 4.22 (m, 1H), 3.74 (s, 3H), 3.67 (t, *J* = 4.5 Hz, 4H), 3.34 – 3.20 (m, 2H), 2.96 – 2.75 (m, 6H), 2.45 – 2.37 (m, 4H), 1.50 (s, 3H), 1.15 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.03, 171.89, 170.48, 170.25, 158.68, 133.43, 133.21, 132.53, 130.53, 128.39, 128.34, 128.01, 127.80, 127.63, 127.25, 126.36, 125.95, 114.10, 67.01, 61.67, 59.42, 55.33, 54.31, 53.81, 52.74, 52.67, 48.38, 37.26, 36.82, 17.59, 16.69. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 6.60 (ESI-MS (m/z): 631.20 ($M+H^+$)). HRMS: calcd. for $C_{35}H_{42}N_4O_7$ 631.31263 $[M+H]^+$; found 631.31262

MorphAc-Ala-Tyr(OMe)-1-Nal-EK (7)
This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (2→4% MeOH in DCM) followed by purification by HPLC (20-70% MeCN, 0.1 % TFA, 10 min gradient) provided the title compound (9.51 mg, 30.1%) as a white powder after lyophilisation. ^{1}H NMR (400 MHz, Chloroform-d) ^{1}H NMR (400 MHz, Chloroform-d) δ 8.17 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.60 – 7.46 (m, 2H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.30 (dd, *J* = 8.1, 7.1 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 6.7 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.54 (d, *J* = 7.3 Hz, 1H), 6.09 (d, *J* = 6.6 Hz, 1H), 4.83 (ddd, *J* = 9.8, 6.6, 4.7 Hz, 1H), 4.42 – 4.26 (m, 2H), 3.79 (s, 3H), 3.72 – 3.57 (m, 5H), 3.33 (d, *J* = 4.9 Hz, 1H), 2.97 – 2.78 (m, 6H), 2.43 (s, 4H), 1.51 (s, 3H), 1.24 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.37, 171.79, 170.29, 158.76, 134.01, 132.02, 131.85, 130.64, 129.03, 128.53, 128.32, 127.53, 126.71, 126.10, 125.25, 123.65, 114.14, 67.04, 61.71, 59.54, 55.39, 54.36, 53.84, 52.79, 52.08, 48.33, 37.10, 34.63, 17.80, 16.61. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 6.56 (ESI-MS (m/z): 631.13 ($M+H^+$)). HRMS: calcd. for $C_{35}H_{42}N_4O_7$ 631.31263 $[M+H]^+$; found 631.31262

3MeIndAc-D-Ala-Trp-BiPhe-EK (10)
This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→2% MeOH in DCM) provided the title compound (33.13 mg, 95.3%) as a white powder after lyophilisation. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.11 (s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.46 – 7.28 (m, 9H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 7.0 Hz, 1H), 7.10 – 6.99 (m, 3H), 6.89 (d, *J* = 2.2 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 7.5 Hz, 1H), 6.46 (d, *J* = 6.5 Hz, 1H), 4.80 – 4.67 (m, 2H), 4.42 (p, *J* = 6.9 Hz, 1H), 3.52 (dd, *J* = 7.3, 2.1 Hz, 2H), 3.35 – 3.22 (m, 2H), 3.13 – 2.98 (m, 2H), 2.84 (d, *J* = 4.9 Hz, 1H), 2.67 (dd, *J* = 13.8, 8.9 Hz, 1H), 2.48 (t, *J* = 2.1 Hz, 3H), 1.43 (s, 3H), 1.34 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.18, 172.58, 171.09, 166.32, 148.29, 145.55, 142.29, 140.51, 139.56, 136.11, 135.39, 131.49,

129.87, 129.03, 127.54, 127.48, 127.44, 127.11, 126.96, 126.86, 123.93, 123.56, 122.28, 120.95, 119.81, 118.72, 111.34, 110.02, 59.36, 53.56, 53.24, 52.64, 49.58, 38.33, 36.38, 27.47, 18.10, 16.65, 12.51. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 10.61 (ESI-MS (m/z): 695.07 ($M+H^+$)). HRMS: calcd. for $C_{43}H_{42}N_4O_5$ 695.32280 $[M+H]^+$; found 695.32275

3MeIndAc-Ala-Tyr(OMe)-Cha-EK (12)

This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→2% MeOH in DCM) provided the title compound (21.22 mg, 68.9%) as a white powder after lyophilisation. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.53 – 7.43 (m, 2H), 7.42 – 7.31 (m, 2H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 8.6 Hz, 2H), 6.44 (d, *J* = 7.9 Hz, 1H), 6.12 (d, *J* = 7.0 Hz, 1H), 4.68 – 4.53 (m, 3H), 3.56 – 3.48 (m, 2H), 3.47 (s, 3H), 3.28 (d, *J* = 5.0 Hz, 1H), 3.00 (d, *J* = 6.8 Hz, 2H), 2.88 (d, *J* = 5.0 Hz, 1H), 2.52 (t, *J* = 2.2 Hz, 3H), 1.84 – 1.53 (m, 5H), 1.50 (s, 3H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.30 – 1.03 (m, 6H), 0.97 – 0.77 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.32, 172.43, 170.89, 166.11, 158.63, 148.85, 145.56, 142.10, 131.03, 130.34, 128.32, 127.64, 127.03, 123.97, 121.04, 113.93, 59.18, 54.97, 54.38, 52.53, 49.72, 48.74, 38.68, 38.21, 36.74, 34.46, 34.02, 32.05, 26.45, 26.33, 26.08, 17.84, 16.85, 12.50. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 10.34 (ESI-MS (m/z): 616.13 ($M+H^+$)). HRMS: calcd. for $C_{36}H_{45}N_3O_6$ 616.32811 $[M+H]^+$; found 616.32813

3MeIndAc -Ala-Tyr(OMe)-Phe-EK (14)

This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→2% MeOH in DCM) provided the title compound (15.31 mg, 50.2%) as a white powder after lyophilisation. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.53 – 7.42 (m, 2H), 7.42 – 7.30 (m, 2H), 7.24 (d, *J* = 7.3 Hz, 3H), 7.08 – 6.99 (m, 4H), 6.82 (d, *J* = 7.7 Hz, 1H), 6.62 (d, *J* = 8.6 Hz, 2H), 6.45 (d, *J* = 7.5 Hz, 1H), 6.08 (d, *J* = 7.1 Hz, 1H), 4.84 – 4.74 (m, 1H), 4.59 – 4.47 (m, 2H), 3.53 – 3.45 (m, 5H), 3.29 (d, *J* = 4.9 Hz, 1H), 3.09 (dd, *J* = 14.0, 5.0 Hz, 1H), 2.91 (dd, *J* = 13.0, 5.9 Hz, 3H), 2.71 (dd, *J* = 13.9, 8.2 Hz, 1H), 2.53 (t, *J* = 2.2 Hz, 3H), 1.48 (s, 3H), 1.36 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.21, 172.44, 170.60, 166.09, 158.64, 148.82, 145.58, 142.12, 135.77, 131.08, 130.34, 129.39, 128.65, 128.34, 128.06, 127.63, 127.22, 127.02, 123.97, 121.04, 120.46, 113.97, 59.34, 55.02, 54.34, 52.68, 52.60, 48.63, 38.21, 37.27, 36.75, 17.78, 16.63, 12.50. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 9.57 (ESI-MS (m/z): 610.13 ($M+H^+$)). HRMS: calcd. for $C_{36}H_{39}N_3O_6$ 610.29116 $[M+H]^+$; found 610.29114

MorphAc-D-Ala-Trp-Phe-EK (16)

This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→3% MeOH in DCM) provided the title compound (19.43 mg, 65.9%) as a white powder after lyophilisation.^{1}H NMR (400 MHz, Chloroform-d) δ 8.15 (s, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 6.2 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.23 – 7.05 (m, 5H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.88 (d, *J* = 6.4 Hz, 2H), 6.68 (d, *J* = 7.8 Hz, 1H), 6.42 (d, *J* = 7.5 Hz, 1H), 4.66 (p, *J* = 7.6 Hz, 2H), 4.30 (p, *J* = 7.0 Hz, 1H), 3.78 – 3.60 (m, 4H), 3.30 (dd, *J* = 14.7, 5.2 Hz, 1H), 3.22 (d, *J* = 4.9 Hz, 1H), 3.05 (dd, *J* = 14.6, 7.3 Hz, 1H), 2.97 – 2.89 (m, 3H), 2.84 (d, *J* = 4.9 Hz, 1H), 2.61 (dd, *J* = 13.8, 8.4 Hz, 1H), 2.56 – 2.38 (m, 4H), 1.42 (s, 3H), 1.31 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.22, 171.83, 170.77, 136.18, 136.12, 129.43, 128.60, 127.46, 126.93, 123.57, 122.43, 119.94, 118.86, 111.41, 110.03, 67.03, 61.67, 59.25, 53.82, 53.66, 52.93, 52.59, 48.87, 36.97, 27.70, 17.63, 16.57. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min):

6.25 (ESI-MS (m/z): 590.13 ($M+H^+$)). HRMS: calcd. for $C_{32}H_{39}N_5O_6$ 590.29731 $[M+H]^+$; found 590.29730

MorphAc-D-Ala-Tyr(OMe)-Phe-EK (17)

This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→3% MeOH in DCM) provided the title compound (21.60 mg, 74.4%) as a white powder after lyophilisation. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.55 (d, *J* = 6.2 Hz, 1H), 7.23 (d, *J* = 6.8 Hz, 3H), 7.07 (d, *J* = 8.6 Hz, 2H), 7.01 (dd, *J* = 7.3, 1.8 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.43 (d, *J* = 7.5 Hz, 1H), 4.72 (td, *J* = 7.9, 4.9 Hz, 1H), 4.52 (q, *J* = 6.7 Hz, 1H), 4.33 (p, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 3.74 – 3.67 (m, 4H), 3.27 (d, *J* = 5.0 Hz, 1H), 3.03 (dd, *J* = 13.9, 4.8 Hz, 1H), 2.97 (s, 2H), 2.93 (dd, *J* = 6.4, 4.7 Hz, 2H), 2.89 (d, *J* = 5.0 Hz, 1H), 2.71 (dd, *J* = 13.9, 8.2 Hz, 1H), 2.59 – 2.40 (m, 4H), 1.44 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.24, 171.83, 170.41, 158.78, 135.91, 130.50, 129.41, 128.65, 128.21, 127.17, 114.19, 67.05, 61.69, 59.28, 55.37, 54.28, 53.85, 52.83, 52.54, 48.74, 37.14, 37.04, 17.66, 16.56. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 6.17 (ESI-MS (m/z): 581.20 ($M+H^+$)) HRMS: calcd. for $C_{31}H_{40}N_4O_7$ 581.29698 $[M+H]^+$; found 581.29694

3MeIndAc-D-Ala-Tyr(OMe)-Phe-EK (18)

This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→2% MeOH in DCM) provided the title compound (23.89 mg, 78.3%) as a white powder after lyophilisation. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.46 (t, *J* = 6.3 Hz, 2H), 7.40 – 7.27 (m, 2H), 7.12 (dt, *J* = 26.3, 7.8 Hz, 5H), 6.99 (d, *J* = 6.9 Hz, 2H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 8.6 Hz, 2H), 6.60 (d, *J* = 7.5 Hz, 1H), 6.43 (d, *J* = 6.9 Hz, 1H), 4.72 (td, *J* = 8.0, 5.0 Hz, 1H), 4.62 – 4.48 (m, 2H), 3.70 (s, 3H), 3.60 – 3.54 (m, 2H), 3.24 (d, *J* = 4.9 Hz, 1H), 3.04 – 2.93 (m, 3H), 2.85 (d, *J* = 4.9 Hz, 1H), 2.68 (dd, *J* = 13.8, 8.3 Hz, 1H), 2.53 (t, *J* = 2.1 Hz, 3H), 1.40 (s, 3H), 1.32 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.31, 172.54, 170.61, 166.15, 158.72, 148.43, 145.59, 142.27, 135.82, 131.45, 130.50, 129.34, 128.52, 128.31, 127.49, 127.09, 126.91, 123.94, 120.97, 114.10, 59.30, 55.27, 54.37, 52.86, 52.53, 49.05, 38.31, 37.19, 36.87, 18.33, 16.53, 12.52. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 9.62 (ESI-MS (m/z): 610.07 ($M+H^+$)). HRMS: calcd. for $C_{36}H_{39}N_3O_6$ 610.29116 $[M+H]^+$; found 610.29114

3MeIndAc-Ala-Tyr(OMe)-BiPhe-EK (19)

This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→2% MeOH in DCM) provided the title compound (18.21 mg, 53.1%) as a white powder after lyophilisation. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.58 – 7.28 (m, 11H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 8.6 Hz, 2H), 6.55 (d, *J* = 7.5 Hz, 1H), 6.08 (d, *J* = 7.0 Hz, 1H), 4.81 (td, *J* = 8.1, 4.8 Hz, 1H), 4.60 – 4.49 (m, 2H), 3.55 – 3.37 (m, 5H), 3.32 (d, *J* = 4.9 Hz, 1H), 3.14 (dd, *J* = 14.0, 4.7 Hz, 1H), 2.95 (d, *J* = 6.9 Hz, 2H), 2.92 (d, *J* = 4.9 Hz, 1H), 2.76 (dd, *J* = 14.0, 8.4 Hz, 1H), 2.51 (t, *J* = 2.2 Hz, 3H), 1.51 (s, 3H), 1.34 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.01, 172.33, 170.61, 165.99, 158.52, 148.66, 145.44, 141.99, 140.57, 139.90, 134.77, 130.96, 130.22, 129.67, 128.75, 128.19, 127.93, 127.49, 127.27, 127.18, 126.97, 126.89, 123.84, 120.91, 120.34, 113.85, 59.25, 54.86, 54.18, 52.61, 52.52, 48.57, 38.08, 36.65, 36.59, 17.65, 16.56, 12.37. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 10.56 (ESI-MS (m/z): 686.13 ($M+H^+$)). HRMS: calcd. for $C_{42}H_{43}N_3O_6$ 686.32246 $[M+H]^+$; found 686.32245

MorphAc-D-Ala-Trp-BiPhe-EK (20)
This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→3% MeOH in DCM) provided the title compound (21.86 mg, 63.7%) as a white powder after lyophilisation. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.97 (s, 1H), 7.67 – 7.32 (m, 9H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.10 (t, *J* = 7.1 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 1.7 Hz, 1H), 6.64 (d, *J* = 7.9 Hz, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 4.79 – 4.63 (m, 2H), 4.28 (p, *J* = 7.0 Hz, 1H), 3.78 – 3.62 (m, 4H), 3.35 (dd, *J* = 14.7, 4.7 Hz, 1H), 3.29 (d, *J* = 4.9 Hz, 1H), 3.08 – 2.95 (m, 2H), 2.92 (s, 2H), 2.88 (d, *J* = 4.9 Hz, 1H), 2.68 (dd, *J* = 13.8, 8.7 Hz, 1H), 2.56 – 2.39 (m, 4H), 1.46 (s, 3H), 1.32 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.14, 174.77, 171.84, 170.82, 140.51, 139.50, 136.07, 135.40, 129.90, 129.10, 127.62, 127.51, 127.15, 126.99, 123.48, 122.39, 119.91, 118.82, 111.33, 109.86, 67.03, 61.61, 59.29, 53.79, 53.55, 52.99, 52.64, 49.01, 36.41, 27.48, 17.38, 16.63. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 7.33 (ESI-MS (m/z): 666.20 ($M+H^+$)). HRMS: calcd. for $C_{42}H_{43}N_3O_6$ 666.32861 $[M+H]^+$; found 666.32861

MorphAc-D-Ala-Tyr(OMe)-BiPhe-EK (21)
This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→3% MeOH in DCM) provided the title compound (25.08 mg, 746.3.4%) as a white powder after lyophilisation.^{1}H NMR (400 MHz, Chloroform-d) δ 7.60 – 7.38 (m, 7H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 4H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 7.5 Hz, 1H), 4.77 (td, *J* = 7.9, 4.6 Hz, 1H), 4.56 (q, *J* = 6.6 Hz, 1H), 4.33 (p, *J* = 7.0 Hz, 1H), 3.71 (s, 3H), 3.68 (d, *J* = 4.7 Hz, 4H), 3.29 (d, *J* = 4.9 Hz, 1H), 3.07 (dd, *J* = 13.9, 4.5 Hz, 1H), 3.03 – 2.86 (m, 5H), 2.78 (dd, *J* = 13.9, 8.2 Hz, 1H), 2.53 – 2.36 (m, 4H), 1.47 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.13, 171.85, 170.48, 158.80, 140.65, 139.93, 135.00, 130.53, 129.83, 128.92, 128.18, 127.45, 127.30, 127.09, 114.19, 67.03, 61.61, 59.30, 55.30, 54.24, 53.79, 52.87, 52.59, 48.76, 37.02, 36.65, 17.53, 16.61. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 7.26 (ESI-MS (m/z): 657.27 ($M+H^+$)). HRMS: calcd. for $C_{37}H_{44}N_4O_7$ 657.32828 $[M+H]^+$; found 657.32831

3MeIndAc-D-Ala-Tyr(OMe)-BiPhe-EK (22)
This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→3% MeOH in DCM) provided the title compound (26.38 mg, 79.2%) as a white powder after lyophilisation.^{1}H NMR (400 MHz, Chloroform-d) δ 7.54 – 7.49 (m, 2H), 7.47 – 7.27 (m, 9H), 7.08 (dd, *J* = 8.2, 5.8 Hz, 4H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.73 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 7.5 Hz, 1H), 6.36 (d, *J* = 6.9 Hz, 1H), 4.76 (td, *J* = 8.1, 4.7 Hz, 1H), 4.66 – 4.45 (m, 2H), 3.64 (s, 3H), 3.56 – 3.49 (m, 2H), 3.28 (d, *J* = 4.9 Hz, 1H), 3.10 – 2.90 (m, 3H), 2.90 – 2.86 (m, 1H), 2.72 (dd, *J* = 13.9, 8.5 Hz, 1H), 2.50 (t, *J* = 2.1 Hz, 3H), 1.43 (s, 3H), 1.33 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.17, 172.52, 170.72, 166.19, 158.74, 148.56, 145.55, 142.22, 140.61, 139.89, 134.99, 131.34, 130.51, 129.82, 128.88, 128.28, 127.50, 127.40, 127.22, 127.03, 126.90, 123.94, 120.99, 114.10, 59.34, 55.21, 54.30, 52.93, 52.58, 49.17, 38.27, 36.85, 36.66, 18.29, 16.60, 12.51. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 10.67 (ESI-MS (m/z): 686.13 ($M+H^+$)). HRMS: calcd. for $C_{42}H_{43}N_3O_6$ 686.32246 $[M+H]^+$; found 686.32251

MorphAc-Ala-Tyr(OMe)-Phe-VS (23)
This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→3% MeOH in DCM) provided the title compound (13.08 mg, 43.5%) as a white powder after lyophilisation. Isolated with 19% *cis* isomer. Peaks reported correspond to *trans* isomer. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.47 (s, 1H), 7.35 – 7.20 (m, 5H), 7.16 – 7.10 (m, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.85 – 6.75 (m, 2H), 6.57 (dd, *J* = 24.5, 6.5 Hz, 1H), 6.18 (dd, *J* = 15.1, 1.7 Hz, 1H), 4.98 (p, *J* = 7.1 Hz, 1H), 4.56 – 4.41 (m, 1H), 4.27 – 4.11 (m, 1H), 3.77 (s, 3H), 3.72 (t, *J* = 4.5 Hz, 4H), 3.08 – 2.75 (m, 9H), 2.47 (d, *J* = 32.6 Hz, 4H), 1.31 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.09, 170.45, 158.72, 146.23, 136.09, 130.37, 130.11, 129.48, 129.34, 128.82, 128.76, 128.07, 127.25, 114.35, 114.22, 66.88, 61.50, 55.36, 54.82, 53.86, 50.45, 49.44, 42.75, 39.81, 36.34, 17.27. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 4.98 (ESI-MS (m/z): 601.27 ($M+H^+$)). HRMS: calcd. for $C_{30}H_{46}N_4O_7S$ 601.26905 $[M+H]^+$; found 601.26904

MorphAc-Ala-Tyr(OMe)-Cha-VS (24)
This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→3% MeOH in DCM) provided the title compound (15.27 mg, 50.3%) as a white powder after lyophilisation. Isolated with 13% *cis* isomer. Peaks reported correspond to *trans* isomer. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.48 (d, *J* = 6.2 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.72 (dd, *J* = 15.1, 4.5 Hz, 1H), 6.63 (d, *J* = 7.5 Hz, 1H), 6.45 (d, *J* = 8.3 Hz, 1H), 6.18 (dd, *J* = 15.1, 1.7 Hz, 1H), 4.72 (p, *J* = 7.4 Hz, 1H), 4.55 (q, *J* = 7.4 Hz, 1H), 4.28 (p, *J* = 7.0 Hz, 1H), 3.79 (s, 3H), 3.72 (t, *J* = 4.5 Hz, 4H), 3.15 (dd, *J* = 14.0, 6.1 Hz, 1H), 3.04 – 2.94 (m, 2H), 2.89 (s, 3H), 2.83 (d, *J* = 16.7 Hz, 1H), 2.48 (dq, *J* = 11.7, 7.1 Hz, 4H), 1.83 – 1.51 (m, 5H), 1.45 – 1.33 (m, 5H), 1.29 – 1.04 (m, 4H), 1.04 – 0.76 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.14, 170.45, 158.78, 147.69, 130.48, 129.15, 128.14, 114.39, 66.95, 61.56, 55.35, 54.87, 53.89, 49.47, 47.41, 42.80, 41.30, 36.33, 34.05, 33.63, 32.46, 26.46, 26.31, 26.15, 17.45. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 5.44 (ESI-MS (m/z): 607.33 ($M+H^+$)). HRMS: calcd. for $C_{30}H_{46}N_4O_7S$ 607.31600 $[M+H]^+$; found 607.31604

3MeIndAc-Ala-Tyr(OMe)-Phe-VS (26)
This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→3% MeOH in DCM) provided the title compound (9.98 mg, 30.9%) as a white powder after lyophilisation. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.52 (s, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.40 – 7.28 (m, 3H), 7.22 – 7.03 (m, 3H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.63 – 6.59 (m, 1H), 6.57 (d, *J* = 4.6 Hz, 1H), 6.41 (d, *J* = 6.1 Hz, 1H), 6.05 (dd, *J* = 15.1, 1.4 Hz, 1H), 4.79 (tt, *J* = 10.1, 5.1 Hz, 1H), 4.68 (p, *J* = 7.0 Hz, 1H), 4.35 (q, *J* = 6.7 Hz, 1H), 3.58 – 3.34 (m, 3H), 3.24 (dd, *J* = 14.4, 7.7 Hz, 1H), 2.72 (s, 3H), 2.44 (t, *J* = 2.1 Hz, 3H), 1.67 – 1.50 (m, 5H), 1.46 (d, *J* = 7.0 Hz, 3H), 1.33 – 1.23 (m, 3H), 1.21 – 1.04 (m, 3H), 0.95 – 0.68 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.02, 171.07, 166.62, 148.87, 147.57, 145.39, 142.22, 136.36, 130.91, 129.07, 127.68, 127.42, 126.96, 123.97, 123.69, 122.53, 121.04, 120.06, 118.58, 111.81, 109.99, 54.48, 50.03, 47.37, 42.68, 40.96, 38.33, 33.99, 33.35, 32.65, 27.51, 26.41, 26.17, 26.10, 17.80, 12.60. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 8.34 (ESI-MS (m/z): 645.20 ($M+H^+$)). HRMS: calcd. for $C_{36}H_{44}N_4O_5S$ 645.31052 $[M+H]^+$; found 645.31055

N_3Gly-Ala-Hyp-Nle-Leu-EK (27)
This compound was obtained by the general protocol for azide coupling on a 64 µmol scale. Purification by column chromatography (0→1.5% MeOH in DCM) provided the product (7.6

mg, 12.5 µmol, 20%), which was next deprotected in 1:1 DCM:TFA (2 mL). After stirring for 30 min, the mixture was evaporated and co-evaporated with toluene (3x). Purification by HPLC (C18, linear gradient 20 → 70% MeCN: MeOH, 0.1% TFA) yielded the title compound (2.55 mg, 4.63 µmol, 7%). Complex NMR due to a 9:1 ratio of rotamers. Peaks of major rotamer are reported. ^{1}H NMR (600 MHz, Chloroform-d) δ 7.13 (dd, *J* = 18.5, 7.3 Hz, 2H), 6.40 (d, *J* = 8.0 Hz, 1H), 4.73 – 4.69 (m, 1H), 4.66 (t, *J* = 7.8 Hz, 1H), 4.59 (dt, *J* = 9.9, 5.5 Hz, 2H), 4.28 (q, *J* = 7.8 Hz, 1H), 3.99 (s, 2H), 3.85 (d, *J* = 11.1 Hz, 1H), 3.63 (dd, *J* = 11.1, 4.0 Hz, 1H), 3.29 (d, *J* = 5.0 Hz, 1H), 2.89 (d, *J* = 5.0 Hz, 1H), 2.44 – 2.36 (m, 1H), 2.18 – 2.10 (m, 1H), 1.86 – 1.76 (m, 1H), 1.66 – 1.60 (m, 1H), 1.54 (ddd, *J* = 13.2, 9.7, 3.2 Hz, 1H), 1.51 (s, 3H), 1.38 (d, *J* = 6.9 Hz, 3H), 1.35 – 1.22 (m, 7H), 0.93 (dd, *J* = 6.5, 4.5 Hz, 6H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.56, 172.29, 171.71, 170.78, 166.79, 70.46, 59.21, 58.89, 55.47, 53.77, 52.59, 52.55, 50.50, 47.06, 40.21, 36.41, 31.79, 27.66, 25.34, 23.49, 22.47, 21.42, 17.97, 16.88, 14.03. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 6.10 (ESI-MS (m/z): 552.20 ($M+H^+$)). HRMS: calcd. for $C_{25}H_{41}N_7O_7$ 552.31402 $[M+H]^+$; found 552.31403

N_3Gly-Ala-Thz-Nle-Leu-EK (28)

This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (0→2% MeOH in DCM) provided the title compound (10.4 mg, 18.7 µmol, 37 as a white powder after lyophilisation. Complex NMR due to a 2:1 ratio of rotamers. ^{1}H NMR (600 MHz, Chloroform-d) δ 7.38 (m, 0.3H) 7.09 (d, *J* = 13.0 Hz, 0.7H), 7.01 – 6.70 (m, 1.4H), 6.27 (d, *J* = 6.8 Hz, 0.6H), 5.07 – 4.12 (m, 7H), 4.07 – 3.87 (m, 2H), 3.75 – 2.70 (m, 3H), 2.09 – 1.03 (m, 15H), 1.00 – 0.66 (m, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 209.62, 208.41, 171.90, 171.61, 171.52, 171.40, 171.27, 168.95, 168.65, 168.54, 166.34, 68.33, 63.48, 63.08, 62.63, 59.20, 56.06, 53.55, 52.68, 52.56, 52.36, 50.62, 49.93, 49.61, 49.44, 49.11, 47.10, 40.75, 40.28, 35.09, 32.22, 31.34, 29.83, 27.45, 25.35, 23.49, 22.47, 22.22, 21.47, 18.54, 16.87, 13.99.

LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 7.12 (ESI-MS (m/z): 554.13 ($M+H^+$)). HRMS: calcd. for $C_{24}H_{39}N_7O_6S$ 554.27553$[M+H]^+$; found 554.27545

N_3Gly-Ala-Aze-Nle-Leu-EK (29)

This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→2% MeOH in DCM) provided the title compound (14.4 mg, 55%) as a white powder after lyophilisation. Complex NMR due to a 5:1 ratio of rotamers. Peaks of major rotamer are reported. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.83 (d, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 6.8 Hz, 1H), 6.42 (d, *J* = 8.0 Hz, 1H), 4.91 (dd, *J* = 9.3, 6.4 Hz, 1H), 4.62 – 4.48 (m, 2H), 4.32 (ddd, *J* = 12.6, 5.0, 2.8 Hz, 2H), 4.16 – 4.07 (m, 1H), 3.98 (d, *J* = 3.2 Hz, 2H), 3.31 (d, *J* = 5.0 Hz, 1H), 2.87 (d, *J* = 5.0 Hz, 1H), 2.80 – 2.66 (m, 1H), 2.57 – 2.40 (m, 1H), 1.93 – 1.71 (m, 1H), 1.68 – 1.50 (m, 3H), 1.49 (s, 3H), 1.39 – 1.17 (m, 8H), 0.92 (dd, *J* = 6.4, 3.5 Hz, 6H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.61, 174.09, 171.51, 170.25, 166.41, 62.12, 59.20, 53.58, 52.58, 50.43, 49.15, 44.70, 40.21, 31.67, 27.66, 25.36, 23.46, 22.44, 21.46, 18.68, 18.28, 16.86, 14.05. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 6.64 (ESI-MS (m/z): 522.20 ($M+H^+$)). HRMS: calcd. for $C_{26}H_{43}N_7O_6$ 522.30346 $[M+H]^+$; found 522.30341

N_3Gly-Ala-Pip-Nle-Leu-EK (30)

This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→2% MeOH in DCM) provided the title compound (18.6 mg, 67%) as a white powder after lyophilisation. Complex NMR due to a 1.5:1 ratio of rotamers. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.44 (d, J = 8.2 Hz, 0.4H), 7.38

(d, J = 7.3 Hz, 0.6H), 7.06 (d, J = 6.0 Hz, 0.4H), 6.84 (d, J = 8.7 Hz, 0.4H), 6.45 (d, J = 7.7 Hz, 0.6H), 6.28 (d, J = 7.9 Hz, 0.6H), 5.18 (d, J = 4.3 Hz, 0.6H), 4.96 (p, J = 6.9 Hz, 0.6H), 4.83 (p, J = 6.9 Hz, 0.4H), 4.67 – 4.48 (m, 2H), 4.38 – 4.25 (m, 1H), 3.98 (d, J = 5.4 Hz, 1.2H), 3.95 – 3.91 (m, 0.8H), 3.78 (d, J = 13.5 Hz, 0.6H), 3.28 (d, J = 5.0 Hz, 1H), 3.25 – 3.16 (m, 0.6H), 2.88 (d, J = 5.0 Hz, 0.6H), 2.85 (d, J = 4.9 Hz, 0.4H), 2.62 – 2.55 (m, 0.4H), 2.50 (dd, m, 0.4H), 2.22 – 2.14 (m, 0.6H), 1.86 – 1.06 (m, 20H), 0.95 – 0.83 (m, 9H). ^{13}C NMR (101 MHz, CDCl3) δ 208.71, 208.68, 172.48, 172.40, 171.74, 171.59, 170.62, 169.25, 168.65, 166.25, 59.46, 59.26, 57.11, 55.76, 53.37, 52.99, 52.83, 52.69, 52.44, 50.84, 49.97, 46.44, 45.87, 44.06, 40.82, 40.56, 40.41, 32.51, 31.66, 28.60, 27.86, 26.85, 25.98, 25.66, 25.59, 25.51, 25.14, 23.79, 23.72, 22.73, 22.53, 21.64, 21.06, 20.53, 18.74, 17.29, 17.13, 17.04, 14.26. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 7.34 (ESI-MS (m/z): 550.07 ($M+H^+$)). HRMS: calcd. for $C_{26}H_{43}N_7O_6$ 550.33476 $[M+H]^+$; found 550.33472

N_3Gly-Ala-(4S)-FPro-Nle-Leu-EK (31)

This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (2→3% MeOH in DCM) followed by purification by HPLC (30-70% MeCN, 0.1 % TFA, 10 min gradient) provided the title compound (2.51 mg, 9%) as a white powder after lyophilisation. Complex NMR due to a 3:2 ratio of rotamers. ^{1}H NMR (600 MHz, Chloroform-d) δ 7.36 (d, *J* = 7.0 Hz, 0.4H), 7.05 (d, *J* = 7.2 Hz, 0.6H) 6.85 (d, *J* = 9.0 Hz, 0.4 H), 6.81 (d, *J* = 5.5 Hz, 0.4H), 6.73 (d, *J* = 7.7 Hz, 0.6H), 6.29 (d, *J* = 7.9 Hz, 0.6H), 5.43 – 5.24 (m, 1H), 4.79 – 4.64 (m, 1.6H), 4.60 – 4.54 (m, 1H), 4.48 (d, *J* = 9.4 Hz, 0.4H), 4.39 – 4.30 (m, 0.6H), 4.20 (m, 0.4H), 4.04 – 3.80 (m, 4H), 3.30 (d, *J* = 5.0 Hz, 0.6H), 3.27 (d, *J* = 4.9 Hz, 0.4H), 2.94 (t, *J* = 15.5 Hz, 0.4H), 2.88 (d, *J* = 5.0 Hz, 0.6H), 2.85 (d, *J* = 4.9 Hz, 0.4H), 2.83 – 2.74 (m, 0.6H), 2.40 – 2.16 (m, 1H), 1.90 – 1.16 (m, 15H), 1.10 (ddd, *J* = 14.0, 10.3, 4.5 Hz, 0.4H), 0.99 – 0.89 (m, 6H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 209.58, 208.31, 172.97, 172.12, 171.95, 171.54, 170.09, 169.60, 168.52, 166.44, 92.20 (d, *J* = 179.4 Hz), 90.36 (d, *J* = 176.2 Hz),, 59.61, 59.49, 59.26, 58.89, 55.87, 54.38 (d, *J* = 24.0 Hz), 54.19 (d, *J* = 24.1 Hz), 53.21, 52.61, 52.57, 52.48, 52.36, 50.49, 49.26, 48.68, 46.93, 40.84, 40.14, 38.80 (d, *J* = 21.3 Hz), 34.60 (d, *J* = 21.4 Hz), 32.05, 31.23, 30.47, 27.99, 27.26, 25.32, 25.25, 23.59, 23.51, 22.46, 22.17, 21.57, 21.43, 18.40, 16.90, 16.70, 16.61, 14.00, 13.95 LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 7.78 (ESI-MS (m/z): 554.20 ($M+H^+$)). HRMS: calcd. for $C_{25}H_{41}FN_7O_6$ $[M+H]^+$; 554.30969, found 554.30969.

N_3Gly-Ala-(4R)-FPro-Nle-Leu-EK (32)

This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (1→2% MeOH in DCM) followed by purification by HPLC (30-70% MeCN, 0.1 % TFA, 10 min gradient) provided the title compound (2.95 mg, 11%) as a white powder after lyophilisation. Complex NMR due to a 95:5 ratio of rotamers. Peaks of major rotamer are reported. ^{1}H NMR (600 MHz, Chloroform-d) δ 7.21 (d, *J* = 6.9 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.23 (d, *J* = 8.0 Hz, 1H), 5.32 (d, *J* = 52.5 Hz, 1H), 4.76 (p, *J* = 6.9 Hz, 1H), 4.70 (t, *J* = 8.0 Hz, 1H), 4.62 – 4.56 (m, 1H), 4.30 (q, *J* = 7.7 Hz, 1H), 4.09 – 3.93 (m, 3H), 3.65 (ddd, *J* = 34.0, 12.3, 3.1 Hz, 1H), 3.29 (d, *J* = 4.9 Hz, 1H), 2.90 (d, *J* = 5.0 Hz, 1H), 2.65 – 2.49 (m, 1H), 2.43 (ddd, *J* = 22.6, 14.8, 8.2 Hz, 1H), 1.81 (dq, *J* = 13.3, 7.3, 6.6 Hz, 1H), 1.67 – 1.59 (m, 2H), 1.55 (ddd, *J* = 13.0, 9.7, 3.1 Hz, 1H), 1.51 (s, 3H), 1.48 – 1.42 (m, 1H), 1.36 (d, *J* = 6.9 Hz, 3H), 1.34 – 1.21 (m, 4H), 0.94 (t, *J* = 6.7 Hz, 6H), 0.89 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.52, 171.99, 171.42, 169.92, 166.11, 91.74 (d, *J* = 180.5), 59.21, 58.63, 53.80, 53.69 (d, *J* = 16 Hz), 52.70, 52.59, 50.51, 47.05, 40.31, 34.25 (d, *J* = 21.7 Hz), 31.97, 27.61, 25.37, 23.50, 22.48, 21.45, 18.33, 16.88, 14.04. LC-MS

(linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min): R_t (min): 7.65 (ESI-MS (m/z): 554.20 ($M+H^+$)). HRMS: calcd. for $C_{25}H_{41}FN_7O_6$ $[M+H]^+$; 554.30969, found 554.30969.

N_3Gly-Ala-4,4-F_2Pro-Nle-Leu-EK (33)

This compound was obtained by the general protocol for azide coupling on a 69 µmol scale. Purification by column chromatography (0→1.5% MeOH in DCM) provided the title compound (16.9 mg, 18.7 µmol, 24%) as a white powder after lyophilisation. Complex NMR due to a 3:1 ratio of rotamers. ^{1}H NMR (600 MHz, Chloroform-d) δ 7.56 (d, *J* = 7.2 Hz, 0.3H), 7.12 (d, *J* = 7.2 Hz, 0.7H), 7.03 (d, *J* = 7.7 Hz, 0.7H), 7.00 – 6.95 (m, 0.3H), 6.76 (d, *J* = 8.8 Hz, 0.3H), 6.36 (d, *J* = 8.0 Hz, 0.7H), 4.77 (dd, *J* = 9.2, 5.7 Hz, 0.8H), 4.72 – 4.63 (m, 1H), 4.59 (ddd, *J* = 10.8, 8.2, 3.0 Hz, 0.7H), 4.35 (q, *J* = 7.7 Hz, 1.5H), 4.29 – 4.05 (m, 1H), 4.00 (d, *J* = 4.9 Hz, 1.4H), 3.98 – 3.81 (m, 1.3H), 3.76 (m, 0.3H), 3.29 (d, *J* = 5.0 Hz, 0.7H), 3.26 (d, *J* = 4.4 Hz, 0.3H), 2.90 (d, *J* = 5.0 Hz, 0.7H), 2.88 – 2.77 (m, 1H), 2.71 (m, 0.3H), 2.58 (m, 1H), 1.92 – 1.16 (m, 15H), 0.97 – 0.82 (m, 9H). ^{13}C NMR (151 MHz, $CDCl_3$, peaks of major rotamer) δ ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.55, 172.20, 171.37, 168.73, 166.41, 126.20 (t, *J* = 249.2 Hz), 59.21, 58.10, 53.76 (t, *J* = 23.0 Hz), 53.60, 52.55, 50.56, 46.84, 40.17, 39.73, 39.56, 35.77 (t, *J* = 24.2 Hz) 32.22, 27.42, 25.32, 23.46, 22.45, 21.38, 18.03, 16.86, 14.00. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 7.25 (ESI-MS (m/z): 572.20 ($M+H^+$)). HRMS: calcd. for $C_{25}H_{39}F_2N_7O_6$ 572.30326 $[M+H]^+$; found 572.30323

N_3Gly-Ala-Pro-Nle-PheEK (34)

This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (0→2% MeOH in DCM) provided the title compound (12.14 mg, 43%) as a white powder after lyophilisation. Complex NMR due to a 5:1 ratio of rotamers. Peaks of major rotamer are reported. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.32 – 7.20 (m, 3H), 7.17 – 7.12 (m, 3H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.52 (d, *J* = 7.5 Hz, 1H), 4.81 (td, *J* = 7.9, 5.1 Hz, 1H), 4.74 (p, *J* = 7.0 Hz, 1H), 4.49 (dd, *J* = 8.1, 2.8 Hz, 1H), 4.23 (td, *J* = 7.9, 5.6 Hz, 1H), 3.97 (d, *J* = 4.7 Hz, 2H), 3.70 – 3.49 (m, 2H), 3.31 (d, *J* = 4.9 Hz, 1H), 3.13 (dd, *J* = 14.0, 5.0 Hz, 1H), 2.90 (d, *J* = 4.9 Hz, 1H), 2.79 (dd, *J* = 14.0, 8.1 Hz, 1H), 2.26 (ddd, *J* = 12.8, 6.6, 3.3 Hz, 1H), 2.17 – 2.06 (m, 1H), 2.01 (ddq, *J* = 16.4, 7.2, 4.4, 3.9 Hz, 1H), 1.89 (ddd, *J* = 18.2, 12.4, 7.8 Hz, 1H), 1.73 (dq, *J* = 13.4, 7.3 Hz, 2H), 1.48 (s, 3H), 1.36 (d, *J* = 6.9 Hz, 3H), 1.32 – 1.11 (m, 6H), 0.92 – 0.77 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.56, 171.32 171.40, 170.81, 166.18, 135.79, 129.85, 129.45, 128.69, 128.54, 127.23, 60.01, 59.39, 53.34, 52.67, 52.65, 47.47, 46.80, 37.20, 31.58, 27.56, 27.26, 25.29, 22.44, 18.39, 16.68, 13.99. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 6.76 (ESI-MS (m/z): 570.13 ($M+H^+$)). HRMS: calcd. for $C_{28}H_{39}N_7O_6$ 570.30346 $[M+H]^+$; found 570.30347

N_3Gly-Ala-Pro-Nle-ChaEK (35)

This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (0→2% MeOH in DCM) provided the title compound (11.35 mg, 39%) as a white powder after lyophilisation. Complex NMR due to a 5:1 ratio of rotamers. Peaks of major rotamer are reported. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.16 (d, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 6.35 (d, *J* = 7.9 Hz, 1H), 4.76 (p, *J* = 7.0 Hz, 1H), 4.57 (dd, *J* = 8.1, 2.4 Hz, 2H), 4.29 (td, *J* = 7.8, 5.8 Hz, 1H), 3.97 (d, *J* = 5.0 Hz, 2H), 3.69 – 3.51 (m, 2H), 3.30 (d, *J* = 5.0 Hz, 1H), 2.87 (d, *J* = 5.0 Hz, 1H), 2.32 (ddd, *J* = 12.5, 6.7, 3.3 Hz, 1H), 2.18 – 1.87 (m, 3H), 1.84 – 1.53 (m, 10H), 1.50 (s, 3H), 1.38 (d, *J* = 6.9 Hz, 3H), 1.34 – 1.07 (m, 9H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, all peaks reported) δ 208.63, 172.28, 171.59, 170.83, 166.18, 60.08, 59.23, 53.43, 52.67, 52.61,

49.82, 47.48, 46.82, 38.64, 34.54, 34.11, 32.04, 31.81, 27.60, 27.40, 26.47, 26.36, 26.08, 25.31, 22.50, 18.42, 16.89, 14.04. LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 7.50 (ESI-MS (m/z): 576.27 ($M+H^+$)). HRMS: calcd. for $C_{28}H_{45}N_7O_6$ 576.35041 $[M+H]^+$; found 576.35040

N_3Gly-Ala-4,4-F_2Pro-Nle-PheEK (36)

This compound was obtained by the general protocol for azide coupling on a 50 µmol scale. Purification by column chromatography (0→2% MeOH in DCM) provided the title compound (15.20 mg, 50%) as a white powder after lyophilisation. Complex NMR due to a 2:1 ratio of rotamers. Peaks of major rotamer are reported. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.33 – 7.20 (m, 3H), 7.16 – 7.11 (m, 3H), 6.89 (d, *J* = 7.7 Hz, 1H), 6.36 (d, *J* = 7.4 Hz, 1H), 4.81 (td, *J* = 7.8, 5.0 Hz, 1H), 4.72 – 4.62 (m, 2H), 4.28 – 4.21 (m, 1H), 4.14 (td, *J* = 12.3, 7.7 Hz, 1H), 3.99 (d, *J* = 3.7 Hz, 2H), 3.93 – 3.75 (m, 1H), 3.30 (d, *J* = 4.9 Hz, 1H), 3.14 (dd, *J* = 14.1, 5.0 Hz, 1H), 2.91 (d, *J* = 4.9 Hz, 1H), 2.78 (dt, *J* = 14.0, 7.0 Hz, 2H), 2.53 – 2.44 (m, 1H), 1.85 – 1.66 (m, 2H), 1.50 (s, 3H), 1.36 (d, *J* = 6.9 Hz, 3H), 1.23 (ddt, *J* = 26.4, 15.1, 5.0 Hz, 4H), 0.85 (td, *J* = 7.0, 3.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.45, 172.27, 171.05, 168.58, 166.35, 135.61, 129.92, 129.42, 128.76, 128.59, 127.34, 127.08, 126.18, 59.43, 58.00, 56.06, 53.70 (t, *J* = 31 Hz), 53.51, 52.79, 52.57, 52.14, 46.81, 37.10, 35.46 (t, *J* = 23 Hz), 31.87, 27.37, 22.43, 18.06, 16.71, 13.99.

LC-MS (linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min): R_t (min): 7.24 (ESI-MS (m/z): 606.20 ($M+H^+$)). HRMS: calcd. for $C_{28}H_{37}F_2N_7O_6$ 606.28461 $[M+H]^+$; found 606.28467

List of abbreviations

biphe, biphenylalanine; BODIPY, boron-dipyrromethene, (4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene); DiPEA, N,N-diisopropylethylamine; ek, epoxyketone; EA, ethyl acetate; pent, pentane; HBTU, 2-(1H-benzotriazole-1-yl)-1,1,3,3- tetramethyluronium hexafluorophosphate; HCTU, 2-(6-chloro-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; ek, epoxyketone; Cha, cyclohexylalanine; 1-Nap, 1-naphtylalanine; 2-Nap, 2-naphtylalanine; vs, methyl vinyl sulfone.

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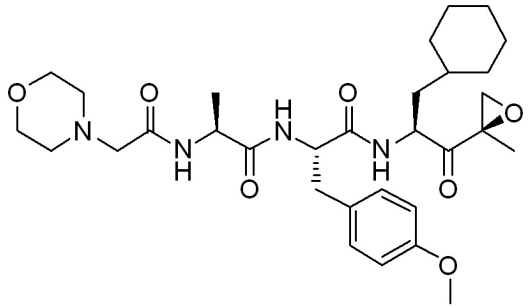
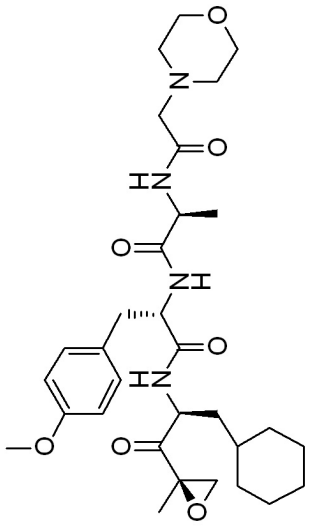
8 ^{1}H NMR (400 MHz, Chloroform-d)



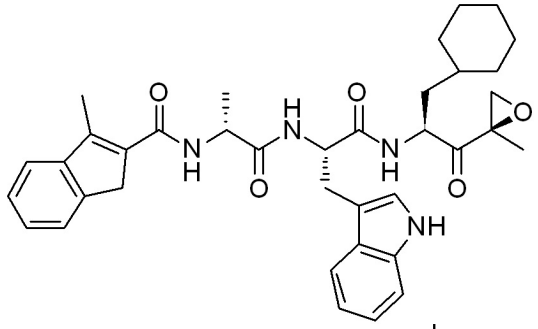
8 ^{13}C NMR (101 MHz, Chloroform-d)

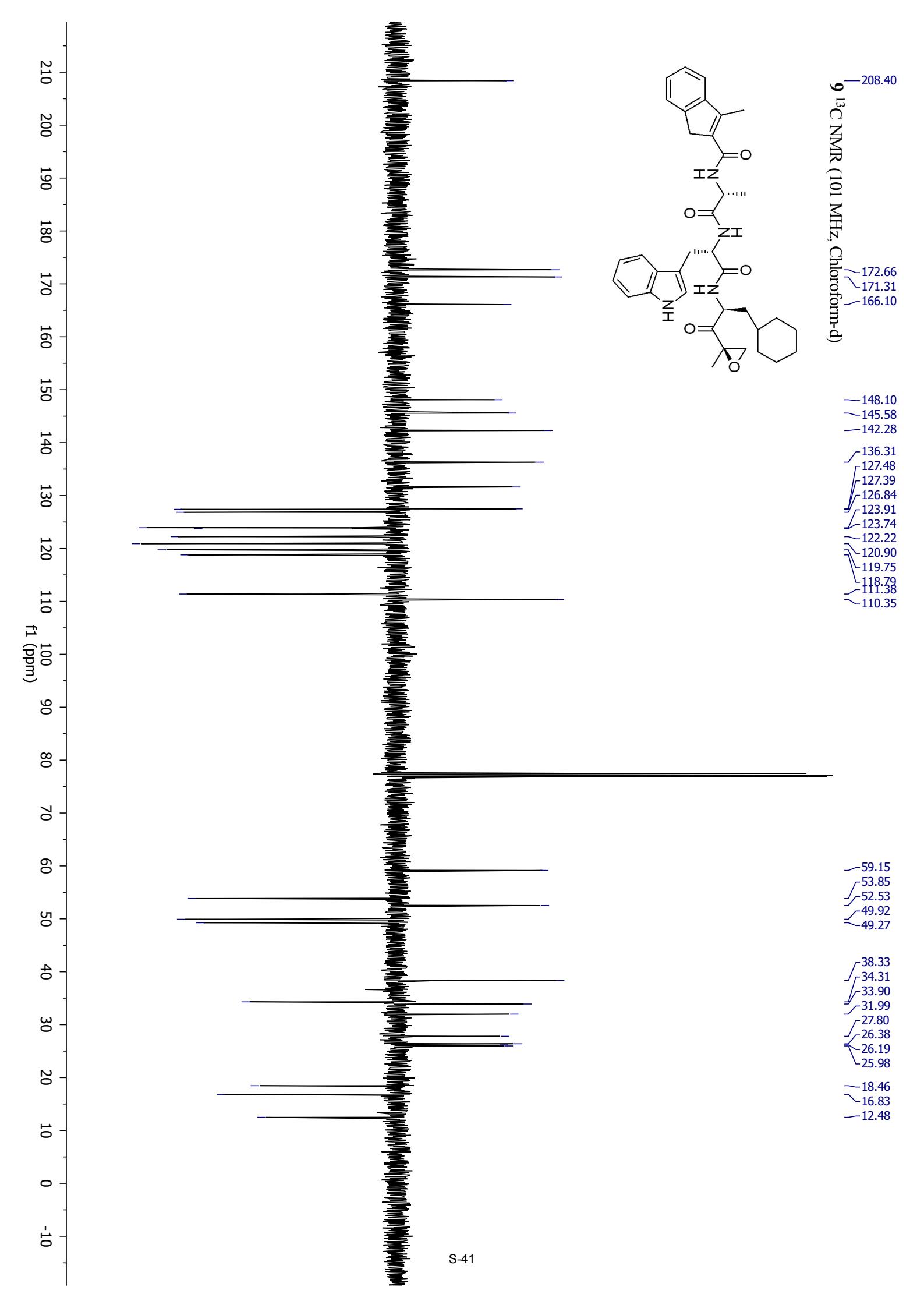


208.24
171.99
170.71
170.30
158.66
130.50
128.35
114.07
67.03
61.72
59.15
55.31
54.39
53.86
52.51
49.74
48.43
38.63
36.81
34.42
34.02
31.98
26.42
26.33
26.05
17.84
16.83

f1 (ppm)

9 ^{1}H NMR (400 MHz, Chloroform-d)




9 13C NMR (101 MHz, Chloroform-d)
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171.31
166.10
148.10
145.58
142.28
136.31
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127.39
126.84
123.91
123.74
122.22
120.90
119.75
118.79
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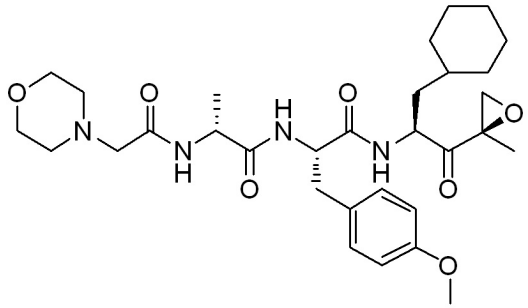
59.15
53.85
52.53
49.92
49.27
38.33
34.31
33.90
31.99
27.80
26.38
26.19
25.98
18.46
16.83
12.48
f1 (ppm)

11 ^{1}H NMR (400 MHz, Chloroform-d)



7.57 7.55 7.26 7.12 7.10 6.82 6.80 6.59 6.57 6.37 6.35

4.62 4.61 4.59 4.57 4.55 4.55 4.53 4.51 4.50 4.36 4.34 4.33 3.77 3.73 3.72 3.71 3.28 3.26 3.03 3.02 3.00 2.87 2.86 2.55 2.54 2.52 2.51 2.50 1.73 1.70 1.68 1.63 1.57 1.54 1.48 1.45 1.32 1.30 1.24 1.20 1.17 1.14 1.12 0.91 0.88 0.85

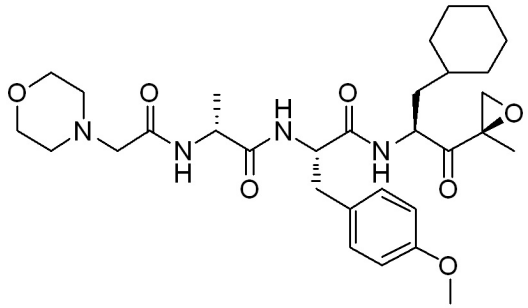
S-42

0.86 1.98 1.97 0.94 0.91 1.99 0.97 3.33 3.81 0.97 3.98 1.01 3.83 5.54 3.33 3.09 5.35 2.01

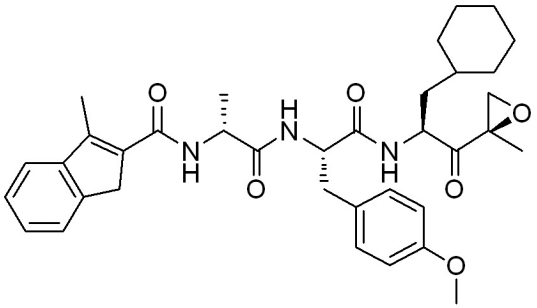
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

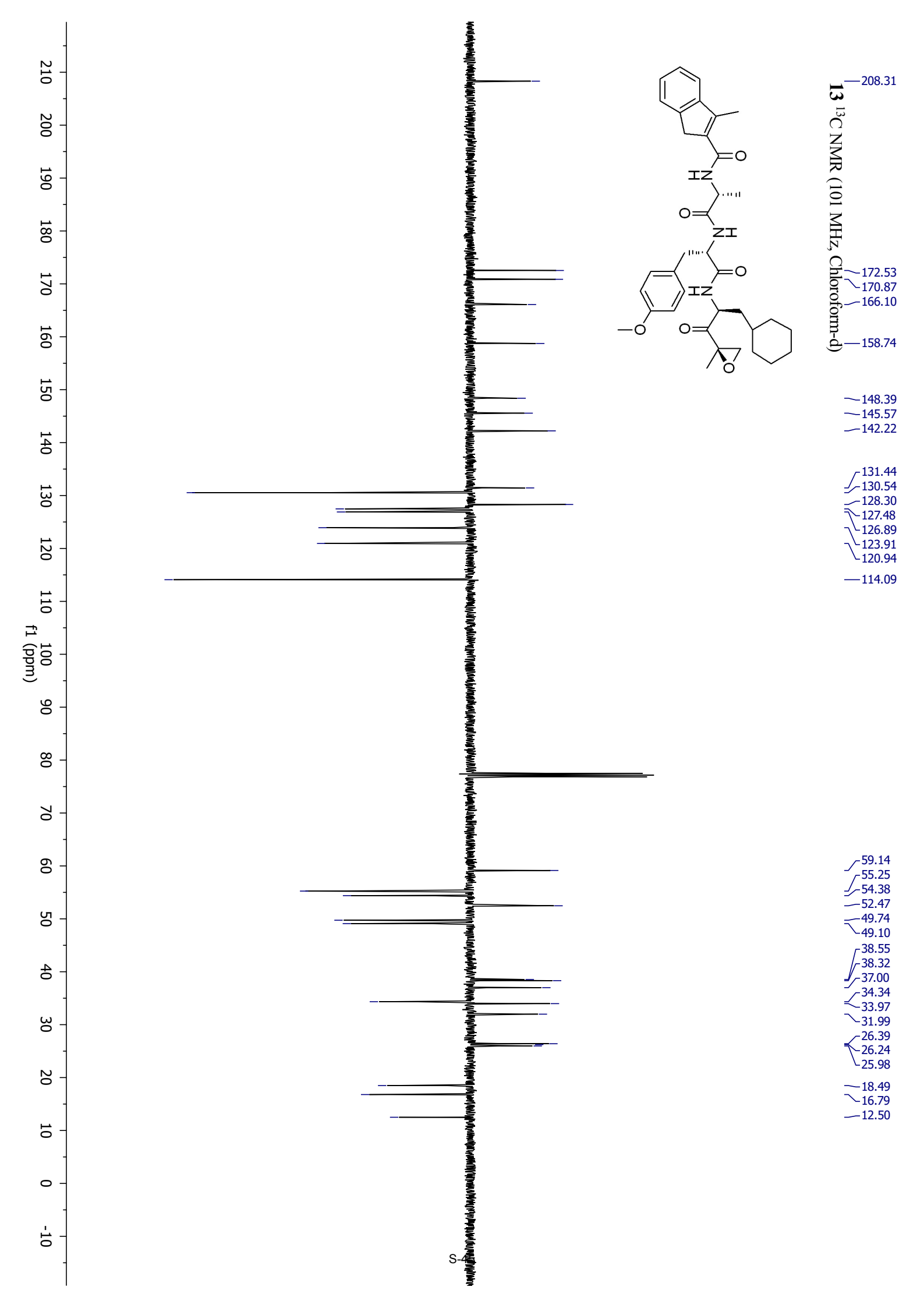
f1 (ppm)

11 ^{13}C NMR (101 MHz, Chloroform-d)



13 ^{1}H NMR (400 MHz, Chloroform-d)




13 13C NMR (101 MHz, Chloroform-d)
208.31
172.53
170.87
166.10
158.74
148.39
145.57
142.22
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130.54
128.30
127.48
126.89
123.91
120.94
114.09
59.14
55.25
54.38
52.47
49.74
49.10
38.55
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34.34
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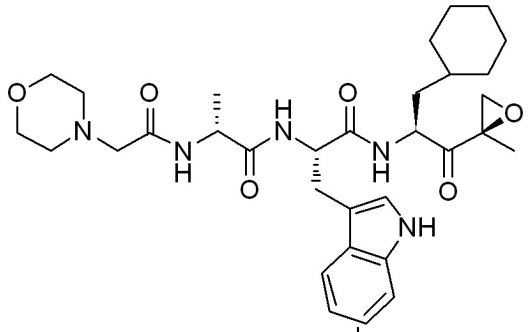
31.99
26.39
26.24
25.98
18.49
16.79
12.50
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

15 ^{1}H NMR (400 MHz, Chloroform-d)



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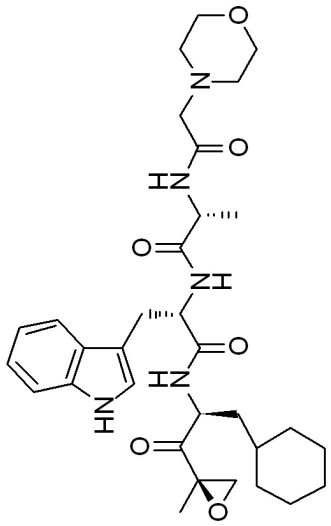
S-46

0.89 1.04 0.85 1.06 3.06 0.96 0.87 1.02 1.03 1.01 4.02 1.02 2.03 1.81 1.01 3.81 4.13 5.29 3.12 5.43 2.18

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

f1 (ppm)

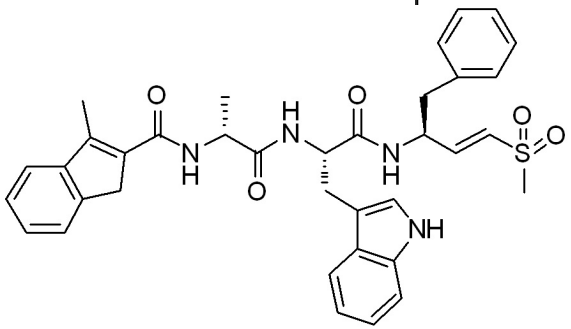
15 ^{13}C NMR (101 MHz, Chloroform-d)



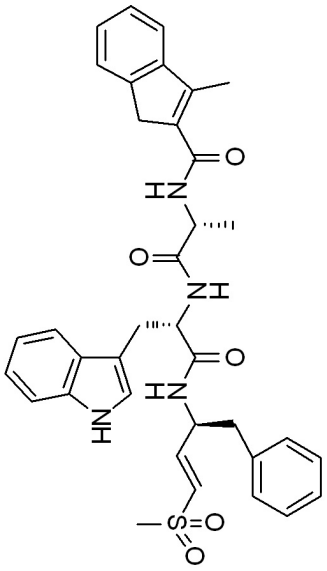
208.33
171.87
171.00
136.31
127.49
123.61
122.40
119.91
118.87
111.42
110.35
67.02
61.74
59.09
53.85
53.80
52.52
49.74
48.85
38.51
34.23
33.94
31.99
27.96
26.41
26.23
26.01
18.02
16.81

f1 (ppm)

25 ^{1}H NMR (400 MHz, Chloroform-d)



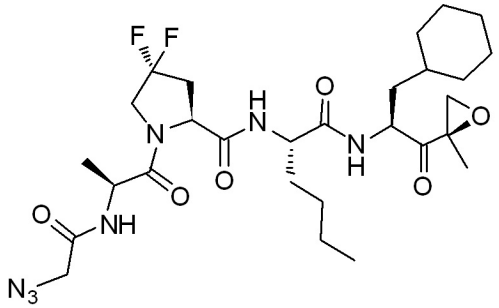
25 ^{13}C NMR (101 MHz, Chloroform-d)



173.04
171.06
166.84
148.99
146.31
145.34
142.25
129.36
128.75
127.76
126.99
126.94
124.03
122.50
121.09
119.97
111.70
109.63
54.34
50.90
50.30
43.75
42.65
39.50
38.36
26.96
17.43
12.71

f1 (ppm)

37 ^{1}H NMR (400 MHz, Chloroform-d)



7.26 7.09 7.07 6.96 6.94 6.14 6.12 4.80 4.78 4.77 4.76 4.69 4.67 4.65 4.61 4.60 4.59 4.58 4.57 4.56 4.33 4.31 4.31 4.14 4.01 4.00 3.97 3.95 3.28 3.27 2.89 2.88 2.85 2.84 1.81 1.80 1.80 1.79 1.78 1.73 1.72 1.70 1.68 1.64 1.63 1.63 1.61 1.60 1.59 1.58 1.57 1.51 1.49 1.49 1.48 1.47 1.45 1.40 1.38 1.34 1.33 1.32 1.31 1.30 1.29 1.29 1.28 1.27 1.26 1.25 1.24 1.23 1.22 1.21 1.20 1.19 1.17 1.14 0.98 0.97 0.95 0.94 0.93 0.91 0.90 0.88 0.86

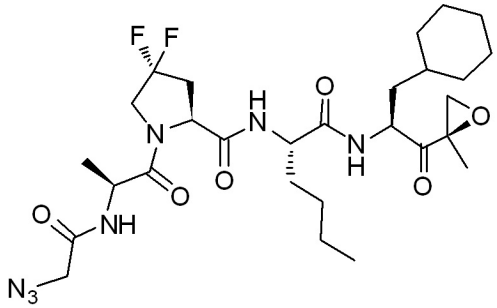
S-50

1.00 1.02 1.09 1.11 1.39 1.80 1.13 1.83 2.23 1.29 1.19 1.68 1.19 14.25 3.83 3.46 13.83 5.41

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

f1 (ppm)

37 ^{13}C NMR (151 MHz, Chloroform-d)



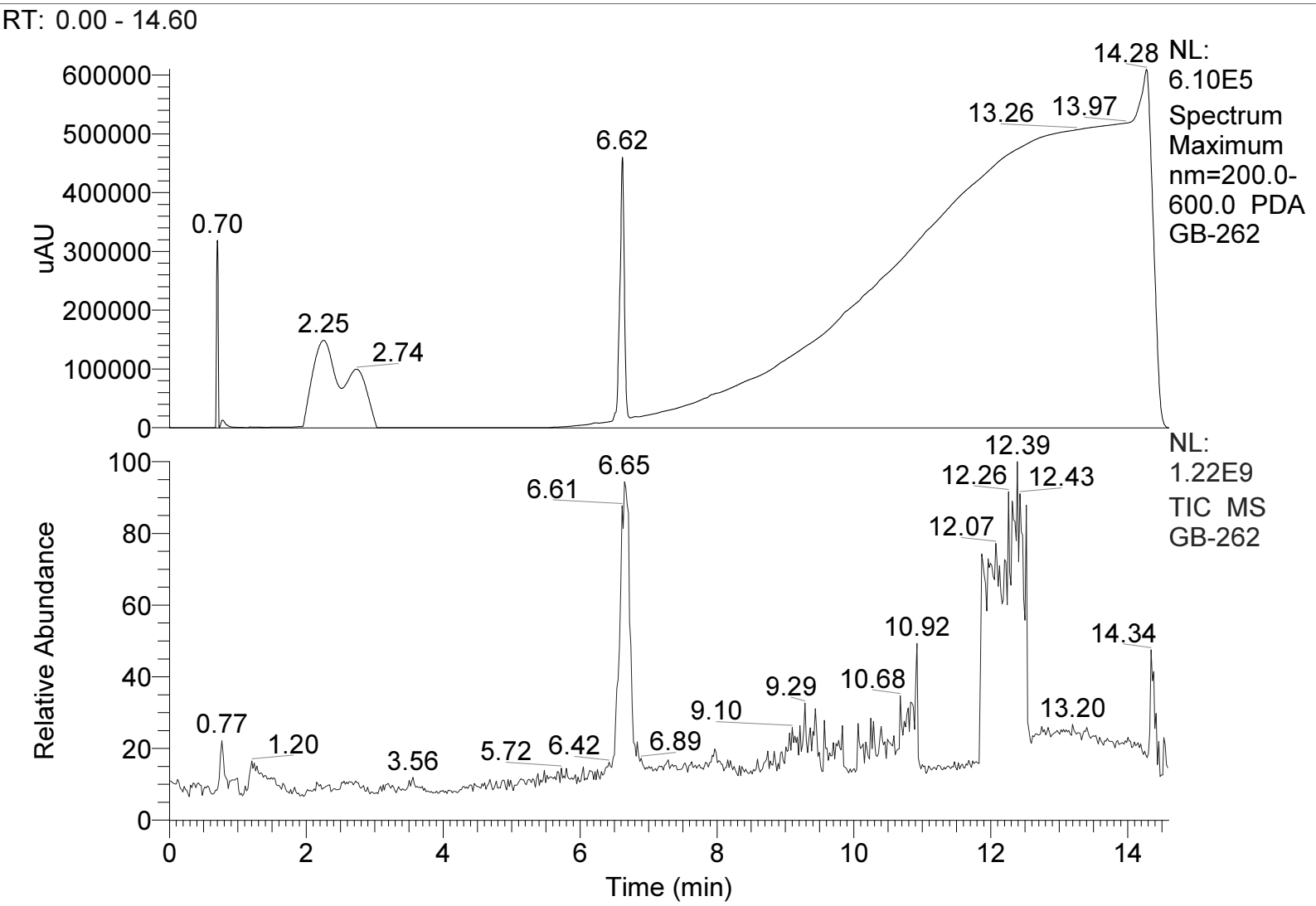
209.85 208.58 172.22 171.73 171.56 171.28 168.78 168.67 168.58 166.34 127.84 126.18 124.53 59.24 59.07 59.03 58.91 58.06 56.08 53.94 53.73 53.57 53.51 52.59 52.54 52.50 52.17 49.95 48.70 47.79 46.82 38.58 35.78 35.62 35.45 34.48 34.23 34.09 32.21 32.02 31.97 31.32 28.05 27.37 26.45 26.42 26.31 26.03 22.47 22.23 18.08 16.89 16.69 16.65 14.03 13.97

S-51

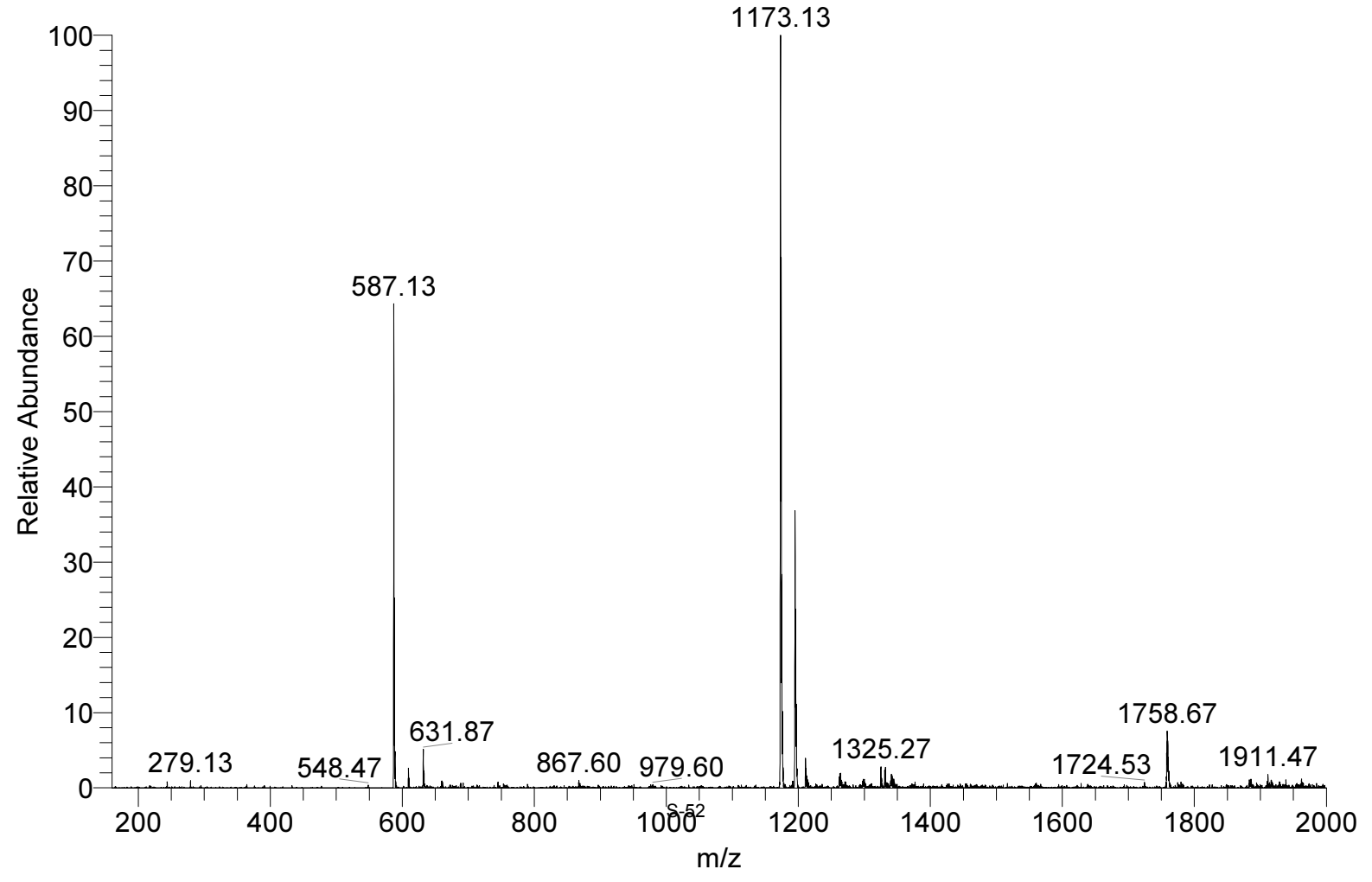
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40

f1 (ppm)

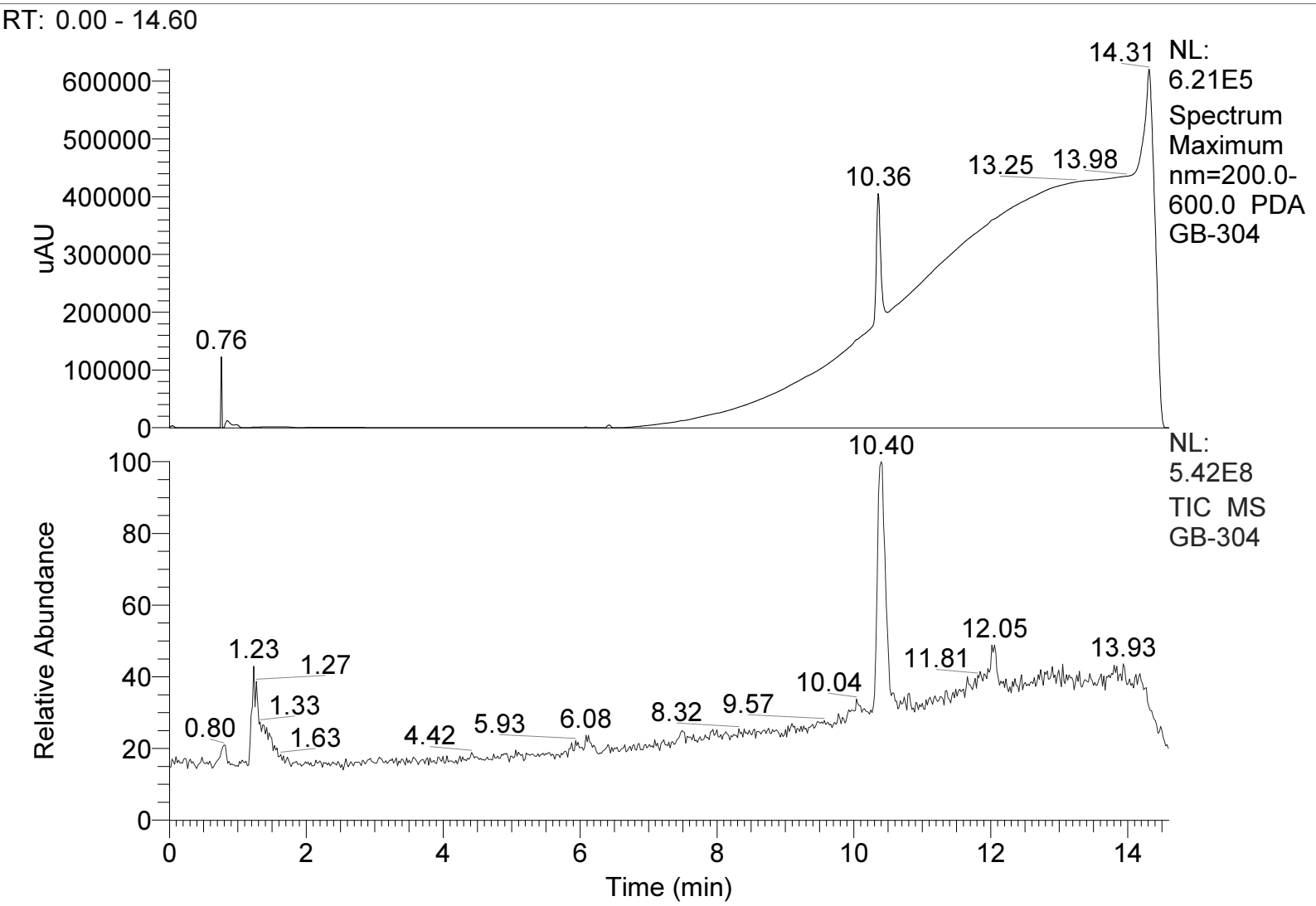
(8) linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min



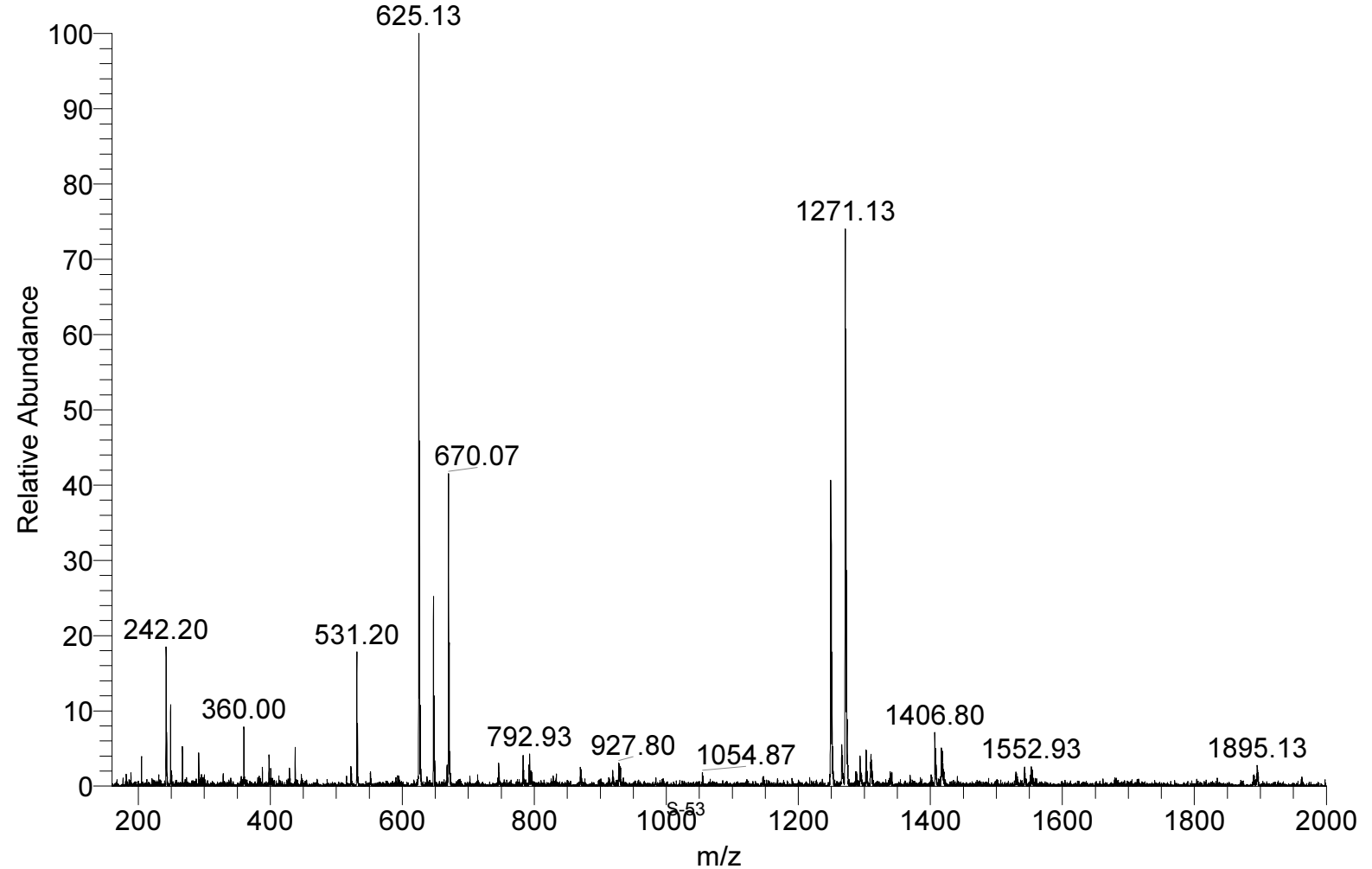
GB-262 #345-356 RT: 6.54-6.74 AV: 12 NL: 1.60E7
T: + p ESI Full ms [160.00-2000.00]



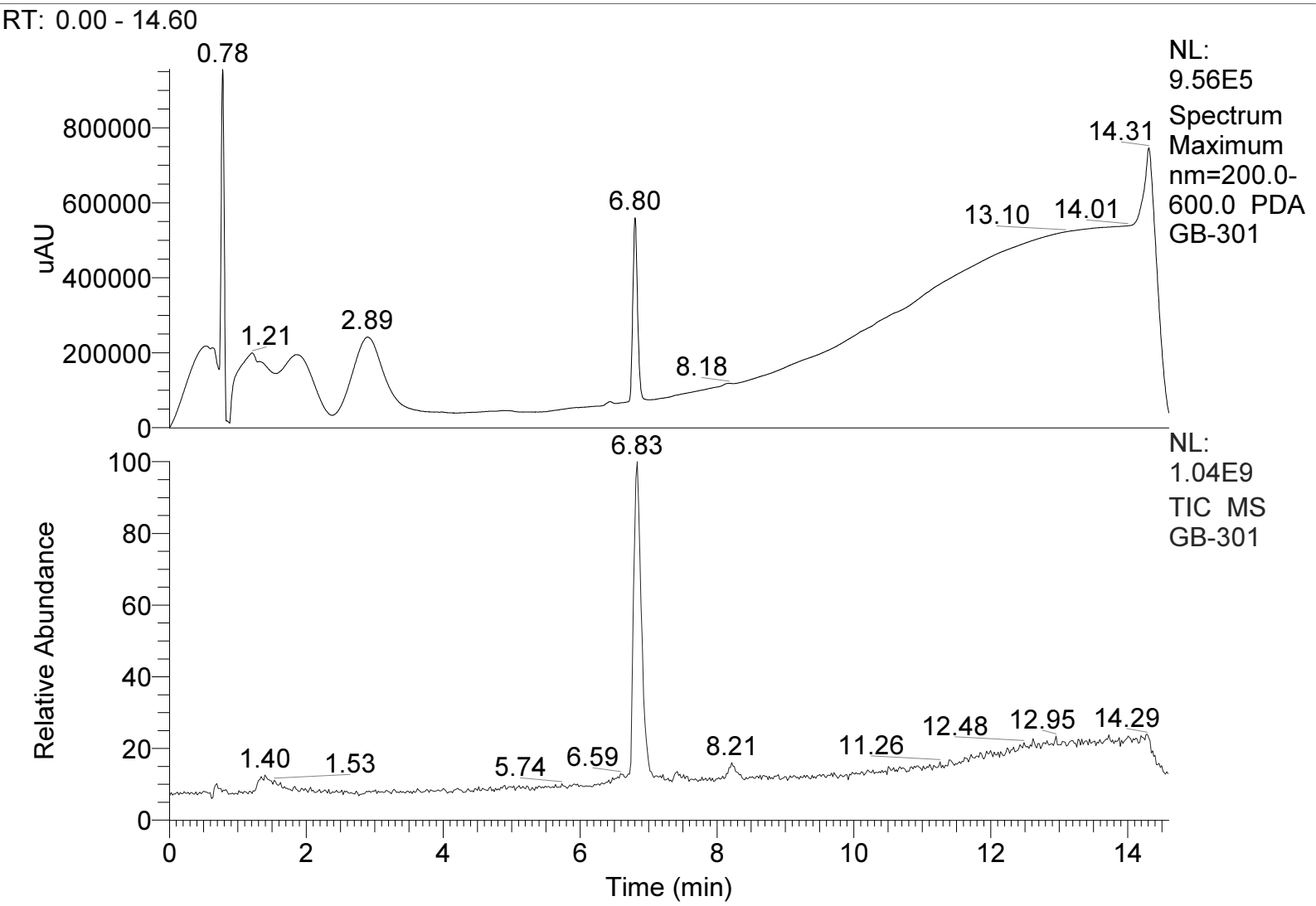
(9) linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min

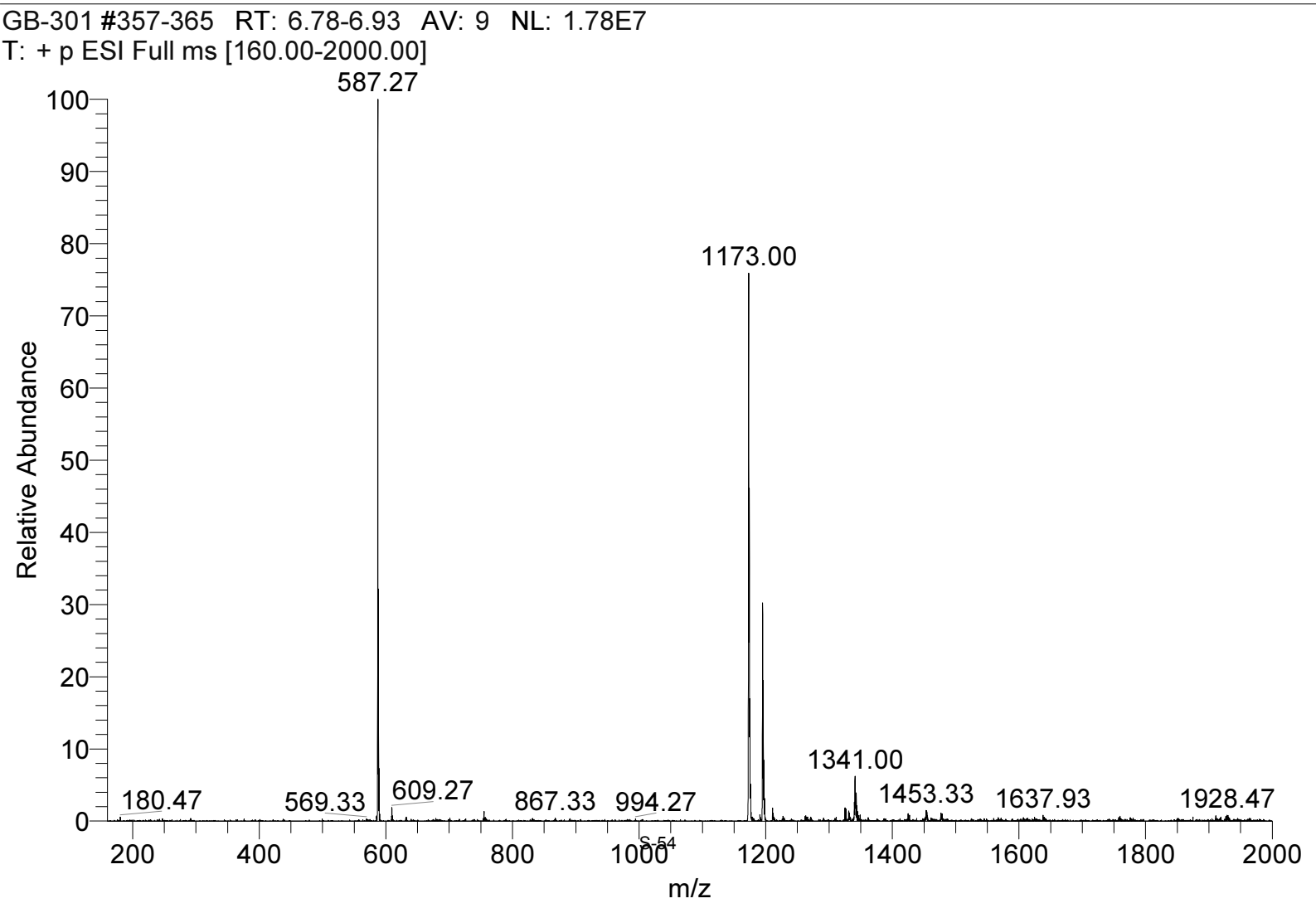


GB-304 #544-559 RT: 10.28-10.57 AV: 16 NL: 3.04E6
T: + p ESI Full ms [160.00-2000.00]

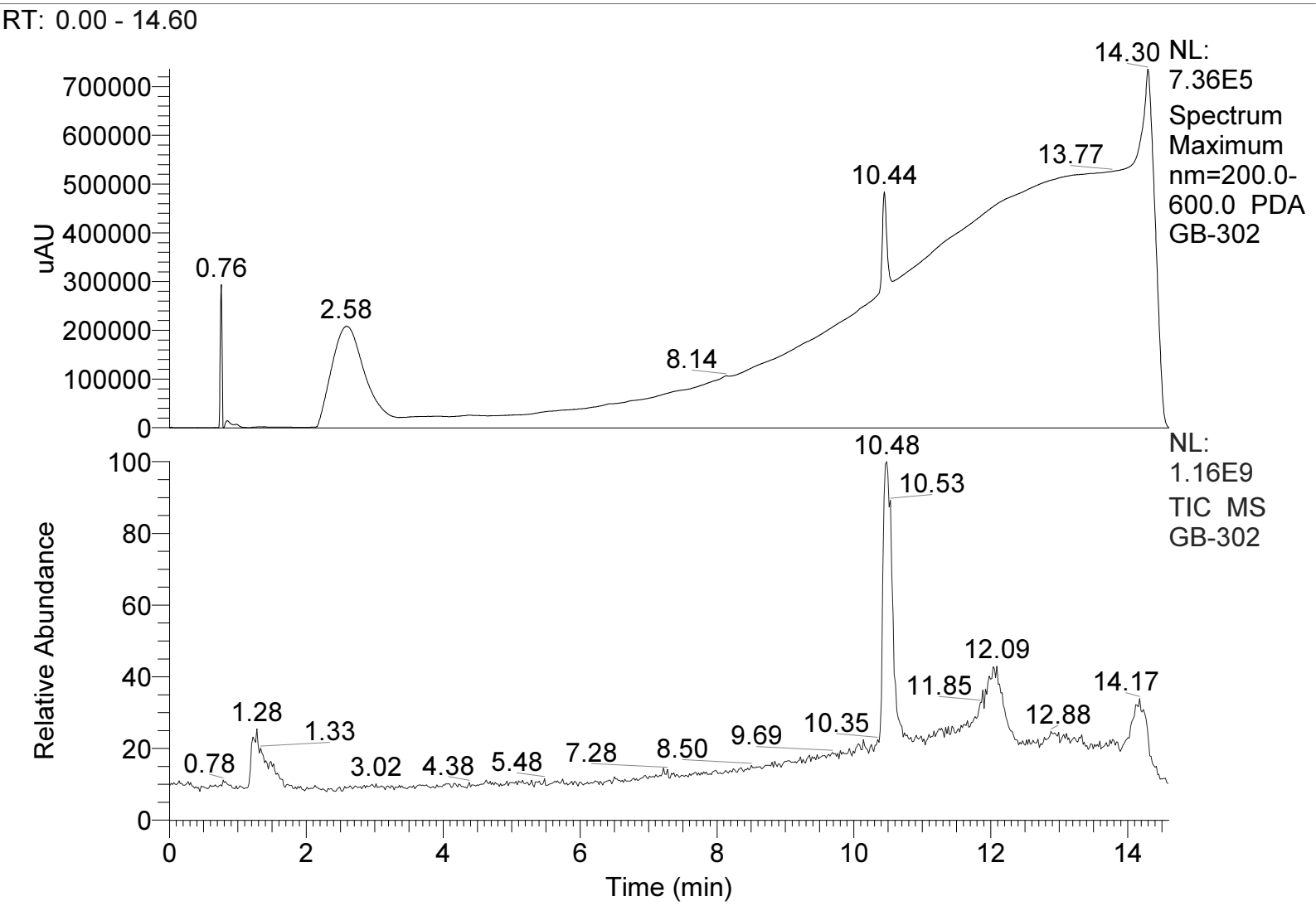


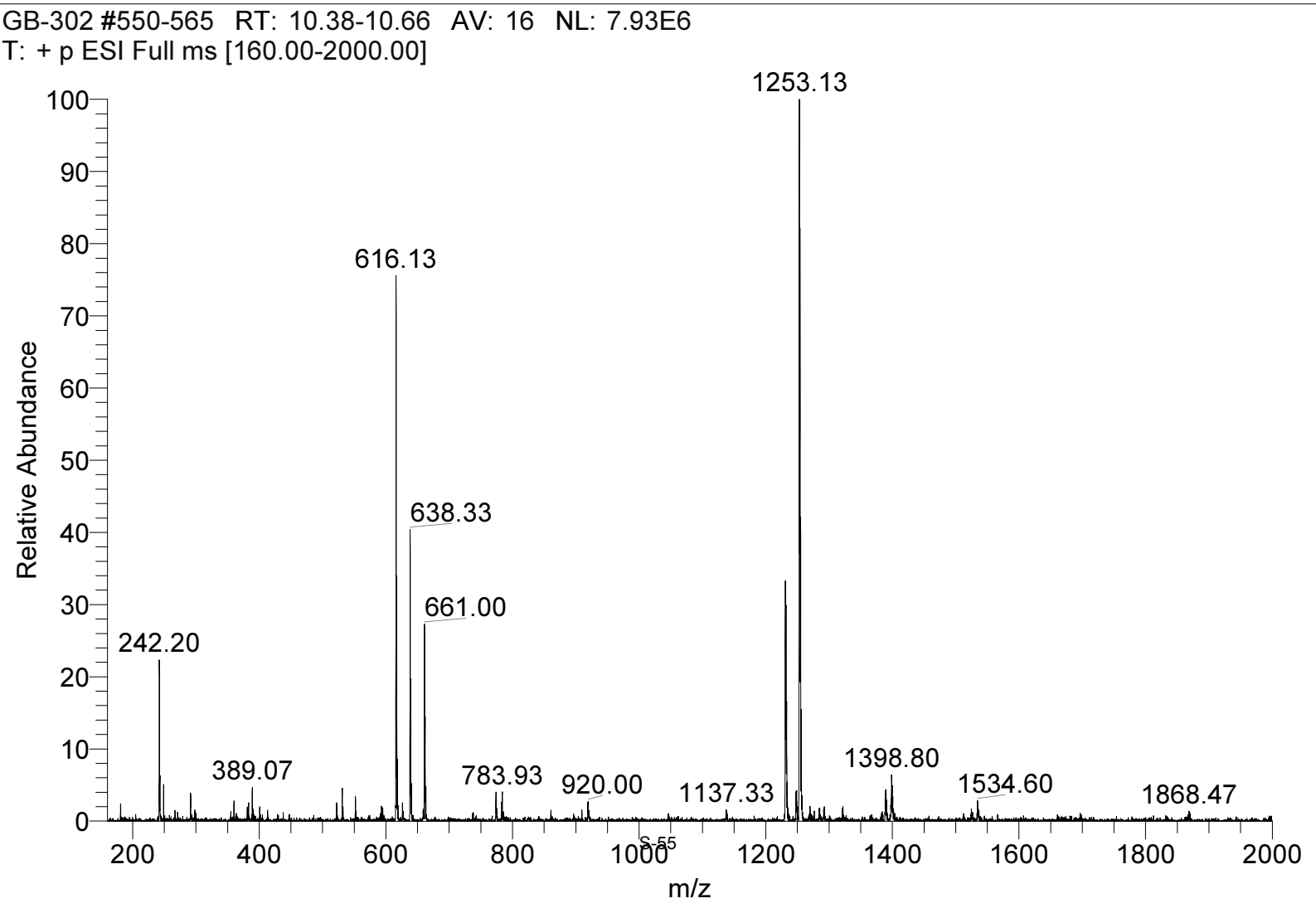
(11) linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min



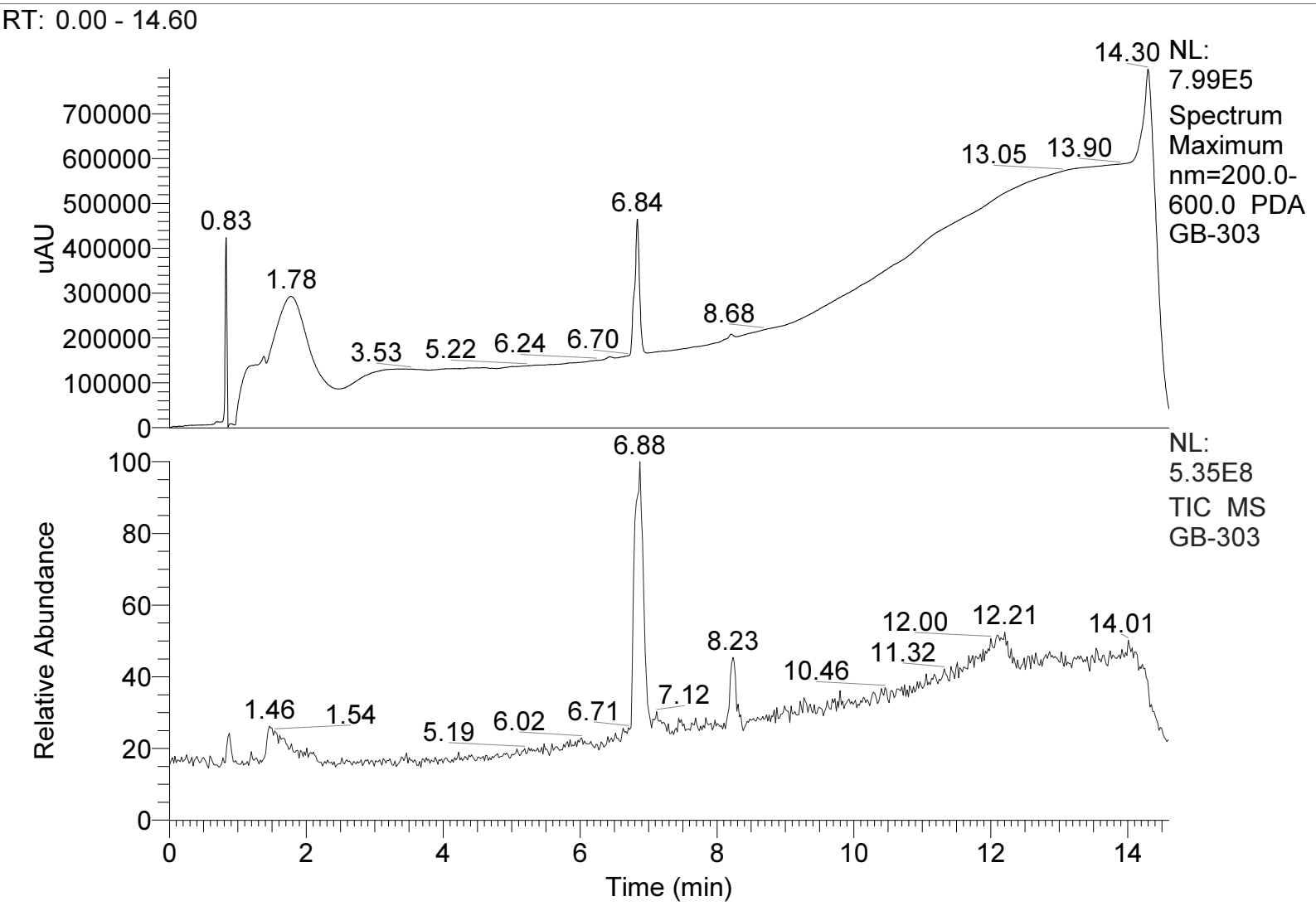


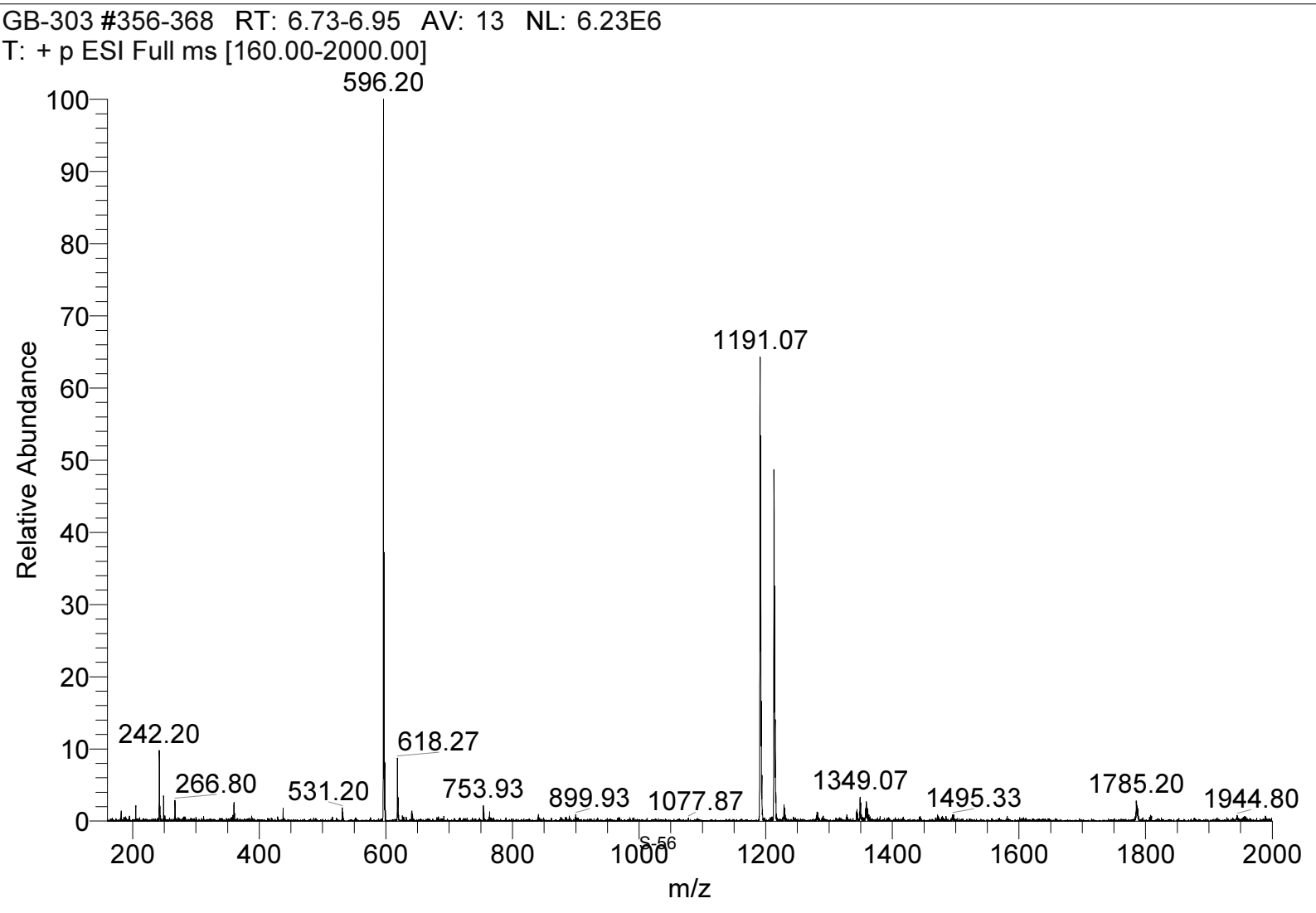
(13) linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min



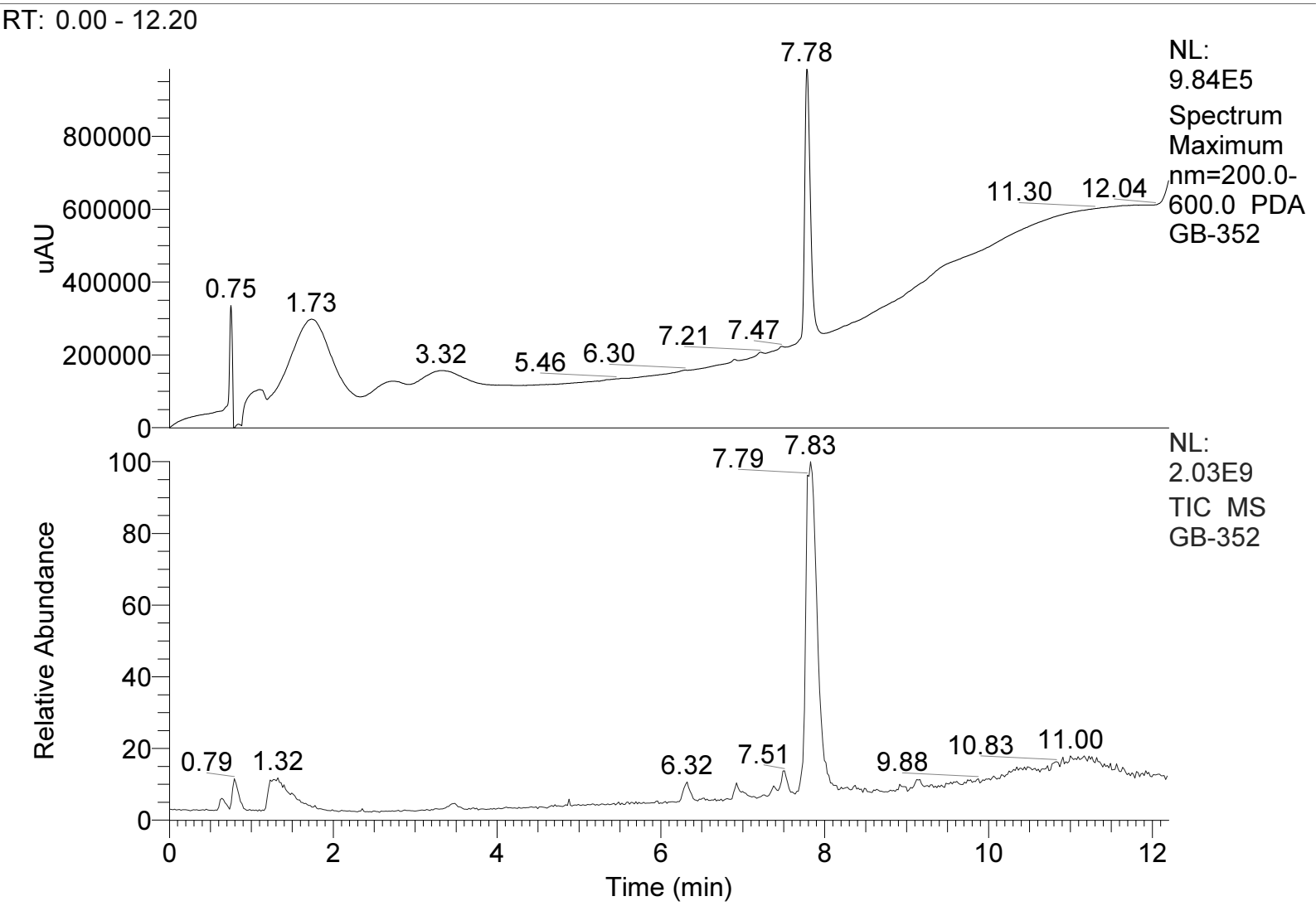


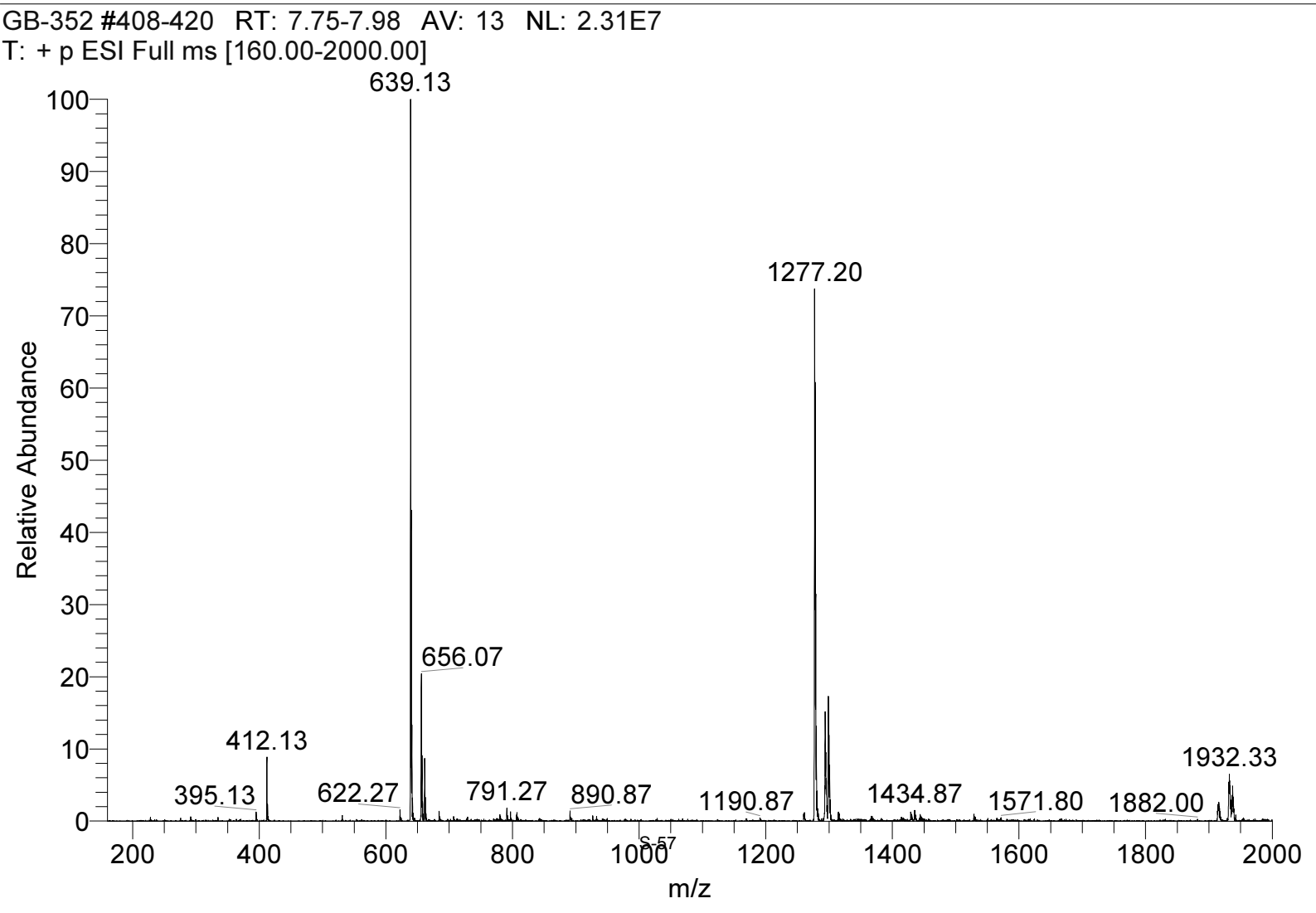
(15) linear gradient 10 → 90% MeCN, 0.1% TFA, 15 min





(25) linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min





(37) linear gradient 10 → 90% MeCN, 0.1% TFA, 12.5 min