SUPPORTING INFORMATION

Structure-based design of inhibitors selective for human proteasome β2c or β2i subunits

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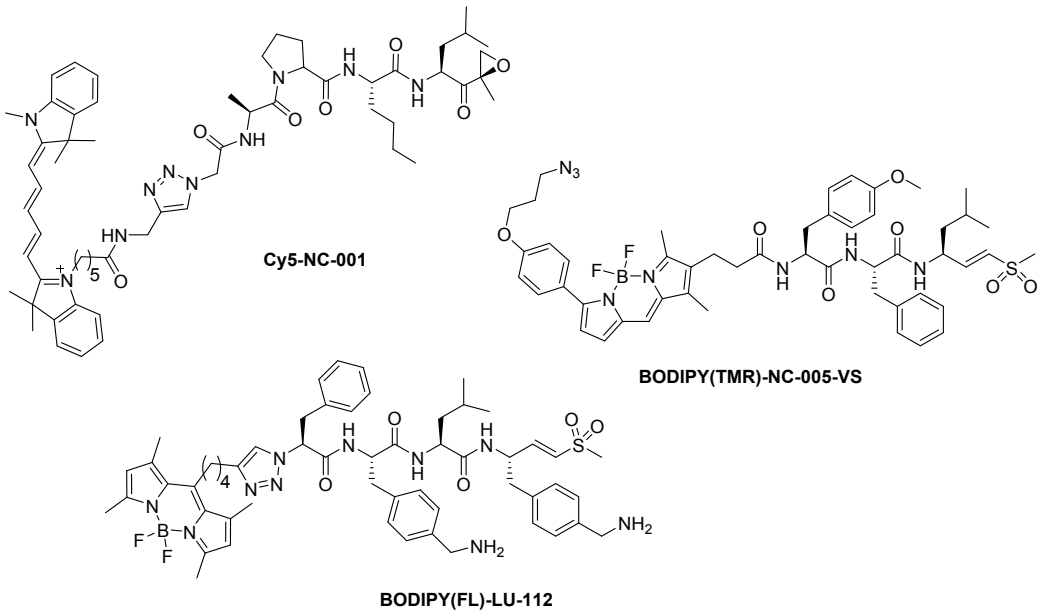


Figure S1. Structures of activity-based probes used.

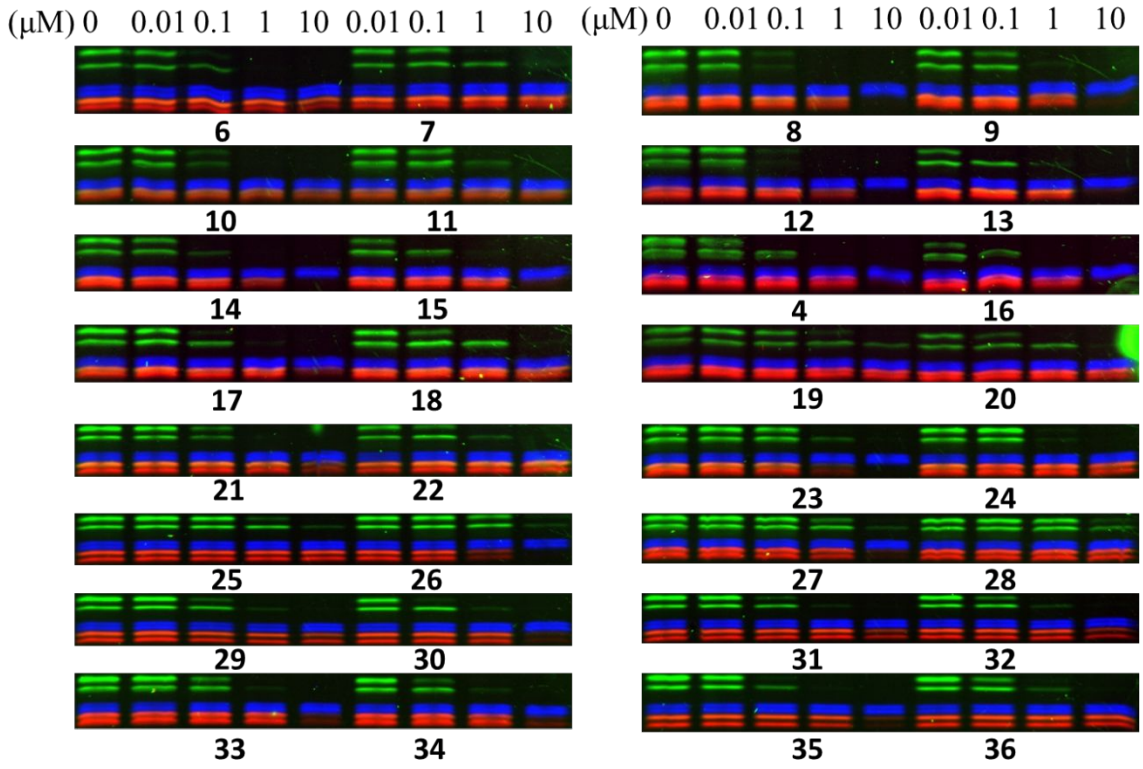


Figure S2. Inhibition profiles of compounds **4**, **6-36**, determined in Raji cell lysate.

Table S1. The apparent IC_{50} (nM) values of compounds **4**, **6-36**, determined in Raji cell lysate.

Compound	β2c	β2i	β5c	β5i	β1c	β 1i
6	23	106	>10000	>10000	>10000	>10000
7	160	6472	>10000	>10000	>10000	>10000
8	29	23	4469	>10000	>10000	>10000
9	69	346	5509	1833	>10000	>10000
10	32	47	>10000	>10000	>10000	>10000
11	72	697	>10000	>10000	>10000	>10000
12	35	22	1135	1301	>10000	>10000
13	11	514	5530	>10000	>10000	>10000
14	17	47	883	2337	>10000	>10000
15	8	197	>10000	5219	>10000	>10000
4 (LU-002c)	10	316	>10000	>10000	>10000	>10000
16	8	331	>10000	>10000	>10000	>10000
17	21	131	>10000	1834	>10000	>10000
18	26	5832	>10000	>10000	>10000	>10000
19	238	1350	>10000	>10000	>10000	>10000
20	72	>10000	>10000	>10000	>10000	>10000
21	47	61	2236	3144	>10000	>10000
22	18	537	>10000	>10000	>10000	>10000
23	206	204	460	410	>10000	>10000
24	383	322	>10000	>10000	>10000	>10000
25	281	>10000	>10000	>10000	>10000	>10000
26	2250	>10000	419	555	>10000	>10000
27	510	4076	1944	>10000	>10000	>10000

28	3333	>10000	>10000	>10000	>10000	>10000
29	35	259	>10000	>10000	>10000	>10000
30	11	280	3641	3974	>10000	>10000
31	31	202	>10000	>10000	>10000	>10000
32	43	363	>10000	>10000	>10000	>10000
33	41	174	>10000	>10000	>10000	>10000
34	17	171	1193	3222	>10000	>10000
35	16	45	1041	>10000	>10000	>10000
36	40	420	>10000	>10000	>10000	>10000

Table S2. The apparent pIC_{50} values of compounds **4**, **6-36**, determined in Raji cell lysate.

Compound	β2c	β2i	β5c	β5i	β1c	β1i
6	7.65±0.18	6.97±0.10	<5	<5	<5	<5
7	6.80±0.12	5.19±0.51	<5	<5	<5	<5
8	7.57±0.17	7.64±0.10	5.35±0.39	<5	<5	<5
9	7.16±0.09	6.46±0.45	5.25±0.77	5.74±0.58	<5	<5
10	7.50±0.14	7.32±0.10	<5	<5	<5	<5
11	7.14±0.08	6.16±0.20	<5	<5	<5	<5
12	7.46±0.33	7.66±0.15	5.95±0.24	5.89±0.03	<5	<5
13	7.94±0.12	6.29±0.62	5.26±0.73	<5	<5	<5
14	7.76±0.20	7.33±0.08	6.05±0.26	5.63±0.48	<5	<5
15	8.10±0.09	6.71±0.11	<5	5.28±0.68	<5	<5
4 (LU-002c)	7.99±0.11	6.50±0.35	<5	<5	<5	<5
16	8.10±0.09	6.48±0.44	<5	<5	<5	<5

17	7.67±0.18	6.88±0.04	<5	5.74±0.65	<5	<5
18	7.58±0.03	5.23±0.42	<5	<5	<5	<5
19	6.62±0.08	5.87±0.13	<5	<5	<5	<5
20	7.14±0.16	<5	<5	<5	<5	<5
21	7.33±0.08	7.22±0.21	5.65±0.27	5.50±0.23	<5	<5
22	7.74±0.21	6.27±0.50	<5	<5	<5	<5
23	6.69±0.19	6.69±0.25	6.34±0.18	6.39±0.25	<5	<5
24	6.42±0.43	6.49±0.34	<5	<5	<5	<5
25	6.55±0.11	<5	<5	<5	<5	<5
26	5.65±0.34	<5	6.38±0.04	6.26±0.11	<5	<5
27	6.29±0.14	5.39±0.21	5.71±0.47	<5	<5	<5
28	5.48±0.24	<5	<5	<5	<5	<5
29	7.46±0.30	6.59±0.25	<5	<5	<5	<5
30	7.97±0.03	6.55±0.18	5.44±0.36	5.40±0.15	<5	<5
31	7.51±0.18	6.70±0.09	<5	<5	<5	<5
32	7.37±0.11	6.44±0.21	<5	<5	<5	<5
33	7.39±0.05	6.76±0.13	<5	<5	<5	<5
34	7.76±0.04	6.77±0.05	5.92±0.56	5.49±0.53	<5	<5
35	7.79±0.16	7.35±0.14	5.98±0.17	<5	<5	<5
36	7.40±0.04	6.38±0.09	<5	<5	<5	<5

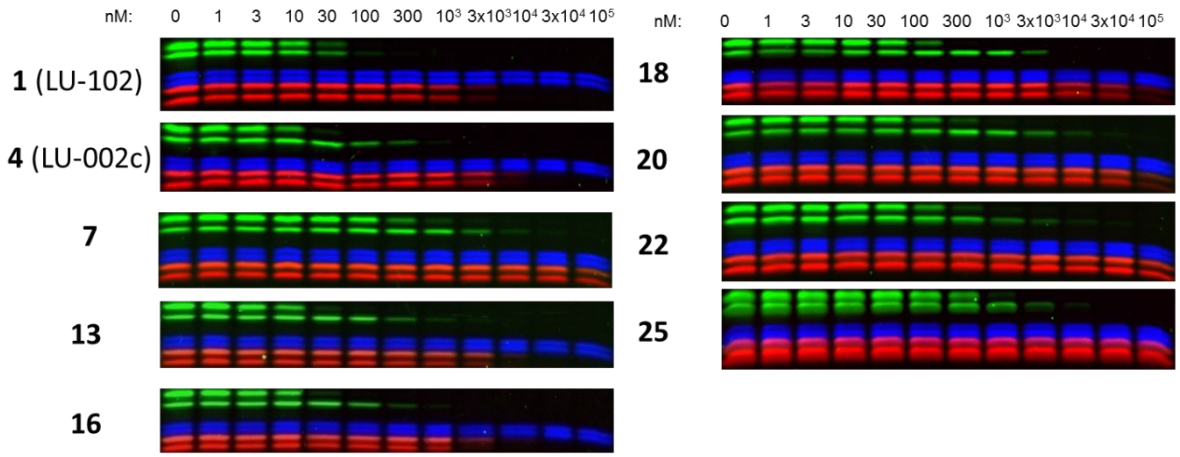


Figure S3. Inhibition profiles of compounds **1**, **4**, **7**, **13**, **16**, **18**, **20**, **22** and **25**, determined in Raji cell lysate.

Table S3. The apparent pIC_{50} values of compounds **1**, **4**, **7**, **13**, **16**, **18**, **20**, **22** and **25s**, determined in Raji cell lysate.

Compound	β2c	β2i	β5c	β5i	β1c	β 1i
1 (LU102)	7.88±0.09	7.71±0.06	5.88±0.11	5.93±0.09	<4	<4
4 (LU-002c)	8.28±0.04	6.85±0.06	5.88±0.06	5.55±0.08	<4	<4
7	6.77±0.07	5.54±0.10	<4	<4	<4	<4
13	8.23±0.08	6.65±0.15	5.85±0.07	5.67±0.07	<4	<4
16	8.16±0.07	6.97±0.08	6.13±0.14	5.68±0.10	<4	<4
18	7.34±0.05	5.61±0.13	5.07±0.13	4.90±0.15	<4	<4
20	7.11±0.04	5.39±0.15	4.34±0.23	4.24±0.18	<4	<4
22	7.19±0.05	6.38±0.06	<4	<4	<4	<4
25	6.35±0.13	5.51±0.08	<4	<4	<4	<4

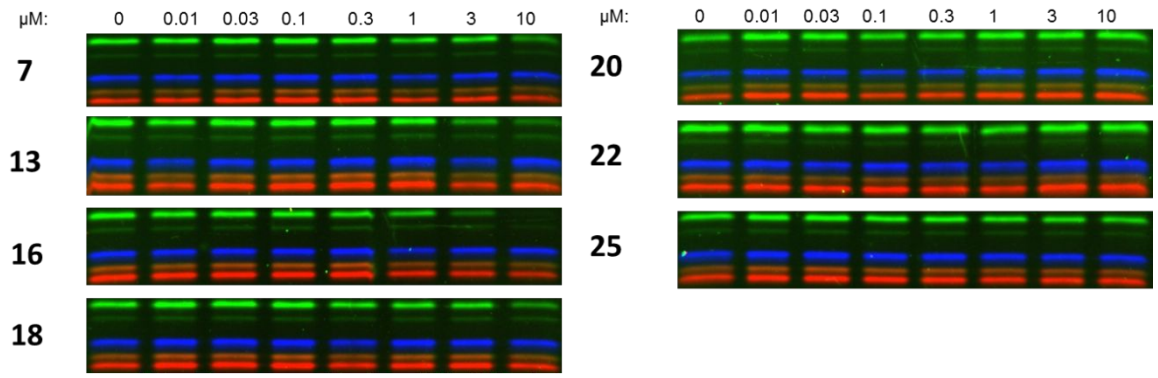


Figure S4. Inhibition profiles of compounds **1**, **4**, **7**, **13**, **16**, **18**, **20**, **22** and **25**, determined intact RPMI-8226 cells.

Table S4. The apparent pIC_{50} values of compounds **13** and **16**, determined in intact RPMI-8226 cells.

Compound	β2c	β2i	β5c	β5i	β1c	β 1i
13	5.70±0.07	<5	<5	<5	<5	<5
16	5.90±0.07	<5	<5	<5	<5	<5

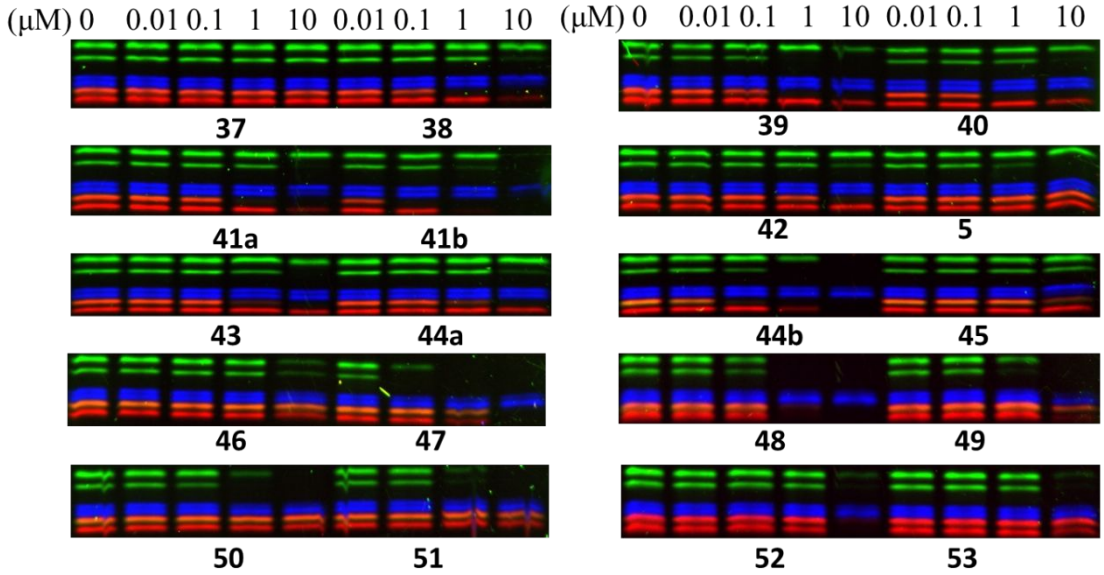


Figure S5. Inhibition profiles of compounds **5**, **37-53**, determined in Raji cell lysate.

Table S5. The apparent IC_{50} (nM) values of compounds **5, 37-53**, determined in Raji cell lysate.

compound	β2i	β2c	β5i	β5c	β1i	β1c
37	>10000	>10000	>10000	>10000	>10000	>10000
38	5530	>10000	122	>10000	>10000	>10000
39	215	>10000	126	>10000	>10000	>10000
40	8406	>10000	191	>10000	>10000	>10000
41a	4956	>10000	173	1742	2521	>10000
41b	264	6421	>10000	176	1412	>10000
42	2764	>10000	3978	>10000	>10000	>10000
5	319	>10000	>10000	>10000	>10000	>10000
43	2800	>10000	375	>10000	>10000	>10000
44a	>10000	>10000	399	>10000	>10000	>10000
44b	97	915	16	443	998	>10000
45	>10000	>10000	9678	>10000	>10000	>10000
46	4845	4242	>10000	>10000	>10000	>10000
47	13.4	38.9	>10000	>10000	>10000	>10000
48	73	97	430	145	133	>10000
49	287	850	>10000	8106	761	>10000
50	97	349	>10000	>10000	>10000	>10000
51	206	233	>10000	>10000	>10000	>10000
52	3615	2328	>10000	3735	>10000	>10000
53	3116	1160	>10000	6275	>10000	>10000

Table S6. The apparent pIC_{50} values of compounds **5**, **37-53**, determined in Raji cell lysate.

compound	β2i	β2c	β5i	β5c	β1i	β1c
37	<5	<5	<5	<5	<5	<5
38	5.23±0.28	<5	6.92±0.13	<5	<5	<5
39	6.67±0.23	<5	6.90±0.23	<5	<5	<5
40	5.08±0.8	<5	6.72±0.27	<5	<5	<5

41a	5.31±0.29	<5	6.76±0.16	5.76±0.02	5.60±0.15	<5
41b	6.58±0.12	5.19±0.62	<5	6.75±0.22	5.85±0.29	<5
42	5.56±0.32	<5	5.4±0.12	<5	<5	<5
5	6.50±0.01	<5	<5	<5	<5	<5
43	5.55±0.06	<5	6.42±0.22	<5	<5	<5
44a	<5	<5	6.40±0.04	<5	<5	<5
44b	7.01±0.10	6.04±0.06	7.81±0.18	6.35±0.09	6.00±0.25	<5
45	<5	<5	5.01±0.33	<5	<5	<5
46	5.32±0.16	5.37±0.10	<5	<5	<5	<5
47	7.87±0.14	7.41±0.09	<5	<5	<5	<5
48	7.14±0.08	7.01±0.12	6.37±0.28	6.84±0.19	6.88±0.07	<5
49	6.54±0.16	6.07±0.09	<5	5.09±0.18	6.12±0.08	<5
50	7.02±0.09	6.46±0.09	<5	<5	<5	<5
51	6.69±0.34	6.63±0.23	<5	<5	<5	<5
52	5.44±0.49	5.63±0.46	<5	5.43±0.40	<5	<5
53	5.51±0.21	5.94±0.18	<5	5.20±0.44	<5	<5

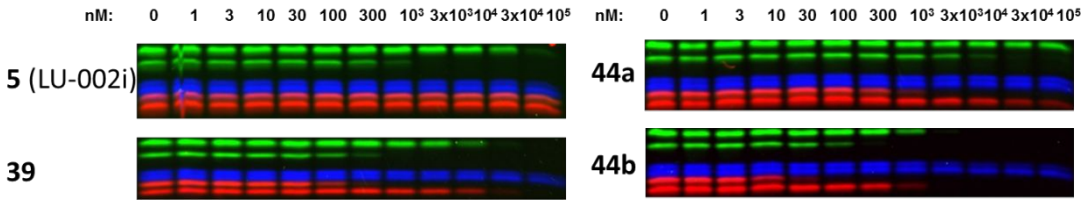


Figure S6. Inhibition profiles of compounds **5**, **39**, **44a** and **44b**, determined in Raji cell lysate.

Table S7. The apparent pIC_{50} values of compounds **5**, **39**, **44a** and **44b**, determined in Raji cell lysates.

compound	β2i	β2c	β5i	β5c	β1i	β1c
5 (LU-002i)	6.74±0.05	4.92±0.14	<4	<4	<4	<4
39	7.24±0.05	5.60±0.09	7.34±0.05	5.30±0.07	<4	<4
44a	5.48±0.10	<4	6.63±0.06	5.13±0.15	<4	<4
44b	7.30±0.06	6.23±0.04	8.23±0.06	6.63±0.09	<4	5.82±0.10

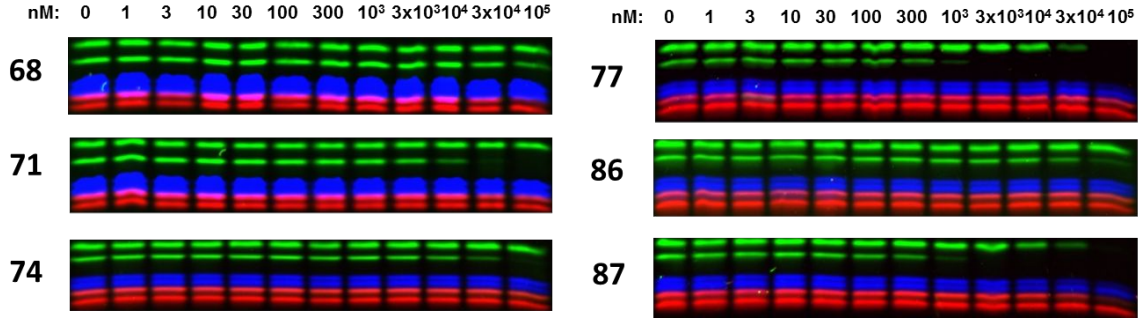


Figure S7. Inhibition profiles of compounds **68**, **71**, **74**, **77**, **86** and **87**, determined in Raji cell lysate.

Table S8. The apparent pIC_{50} values of compounds **68**, **71**, **74**, **77**, **86** and **87s**, determined in Raji cell lysates.

compound	β2i	β2c	β5i	β5c	β1i	β1c
68	<4	<4	<4	<4	<4	<4
71	5.60±0.09	<4	<4	<4	<4	<4
74	4.92±0.08	<4	<4	<4	<4	<4
77	6.42±0.05	4.56±0.08	<4	<4	<4	<4

86	4.47±0.07	<4	<4	<4	<4	<4
87	6.72±0.07	4.72±0.08	4.55±0.07	<4	<4	4.28±0.09

Table S9. The apparent IC_{50} (μM) values of compounds **5** and **87**, determined in Raji cell lysates.

compound	β2i	β2c	β5i	β5c	β1i	β1c
5 (LU-002i)	0.293	>3	>3	>3	>3	>3
87	0.319	>3	>3	>3	>3	>3

Table S10. The apparent pIC_{50} values of compounds **5** and **87**, determined in Raji cell lysates.

compound	β2i	β2c	β5i	β5c	β1i	β1c
5	6.53±0.04	<5.52	<5.52	<5.52	<5.52	<5.52
87	6.50±0.06	<5.52	<5.52	<5.52	<5.52	<5.52

Table S11. The apparent IC_{50} (μM) values of compounds **5** and **87**, determined intact RPMI-8226 cells.

compound	β2i	β2c	β5i	β5c	β1i	β1c
39	0.124	>10	0.183	>10	>10	>10
87	0.159	>10	>10	>10	>10	>10

Table S12. The apparent pIC_{50} values of compounds **5** and **87**, determined intact RPMI-8226 cells.

compound	β2i	β2c	β5i	β5c	β1i	β1c
39	6.91±0.12	<5	6.74±0.11	<5	<5	<5
87	6.80±0.14	<5	<5	<5	<5	<5

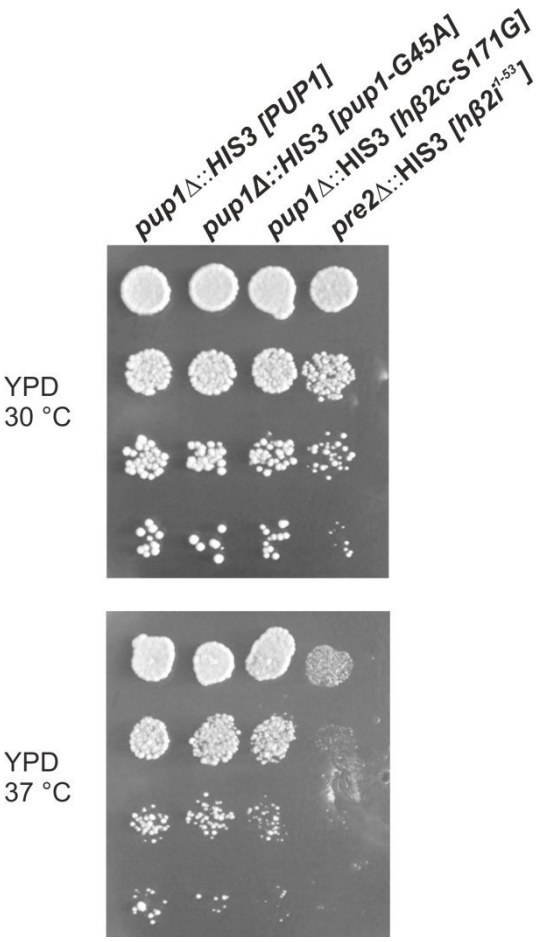


Figure S8: Growth tests by serial dilution of WT and mutant yeast strains. Serial dilutions of cells were spotted on YPD plates and incubated for 3 days either at 30 °C or 37 °C.

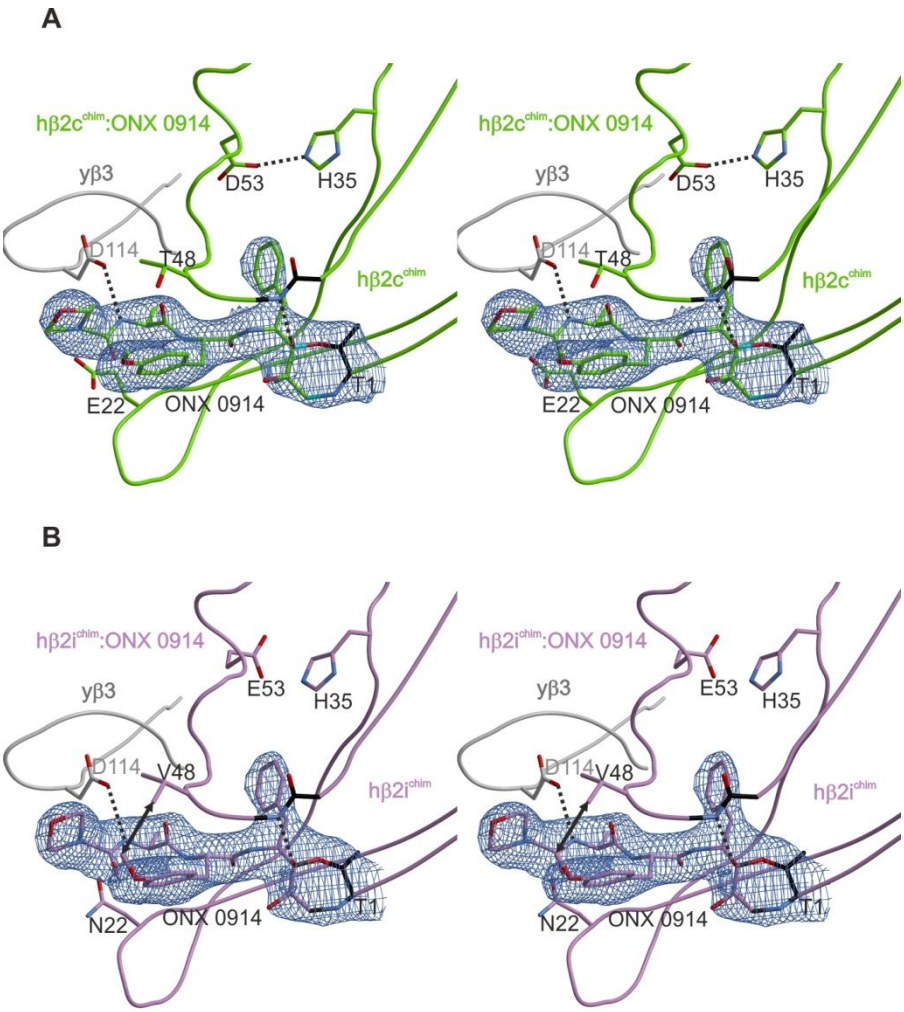
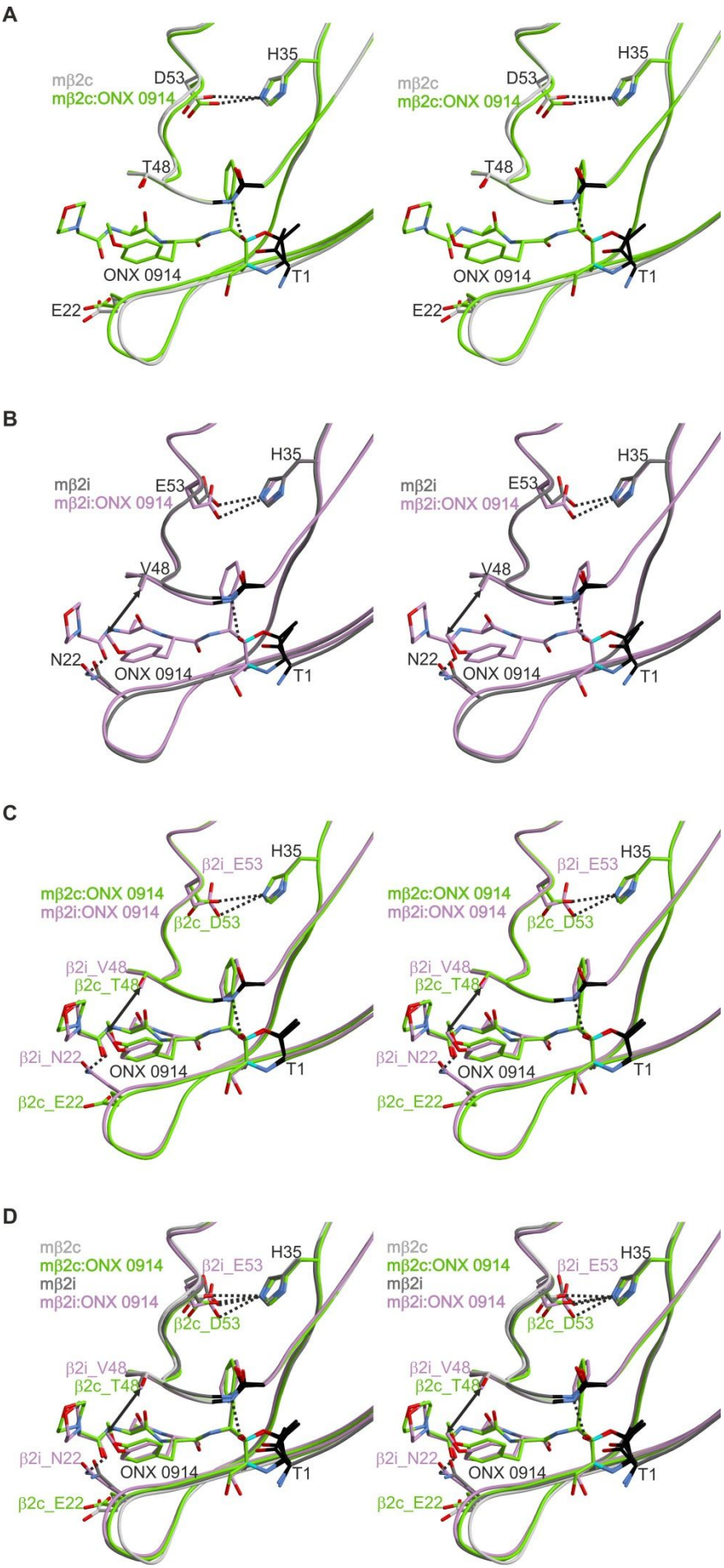


Figure S9. Stereo representations of human-yeast chimeric β2 active sites in complex with ONX 0914. $2F_O$-F_C electron density maps for the ligand bound to β2c (green) and β2i (purple) chimeric subunits respectively are shown as blue meshes contoured to 1σ. Hydrogen bonds are depicted as black dashed lines, while hydrophobic contacts are highlighted by double arrows. PDB IDs: 6HTC (hβ2c chimera:ONX 0914), 6HV4 (hβ2i chimera:ONX 0914).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D53
T48
ONX 0914
T1
E22
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H35
E53
V48
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T1
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β2c_T48
β2i_N22
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T1
β2c_E22
D
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H35
β2i_E53
β2c_D53
β2i_V48
β2c_T48
β2i_N22
ONX 0914
T1
β2c_E22

Figure S10. Structural superpositions of (A) the mouse β2c active site in its apo and ONX 0914 bound state; (B) the mouse β2i active site in its apo and ONX 0914 bound state; (C) the mouse β2c and β2i active sites bound to ONX 0914; (D) mouse β2c and β2i active sites in their ligand bound and ligand-free states shown in stereo. Color coding is according to Figure S1. Hydrogen bonds are depicted as black dashed lines, while hydrophobic contacts are highlighted by double arrows. PDB IDs: 3UNE (mouse cCP), 3UNH (mouse iCP), 3UNB (mouse cCP:ONX 0914), 3UNF (mouse iCP:ONX 0914).

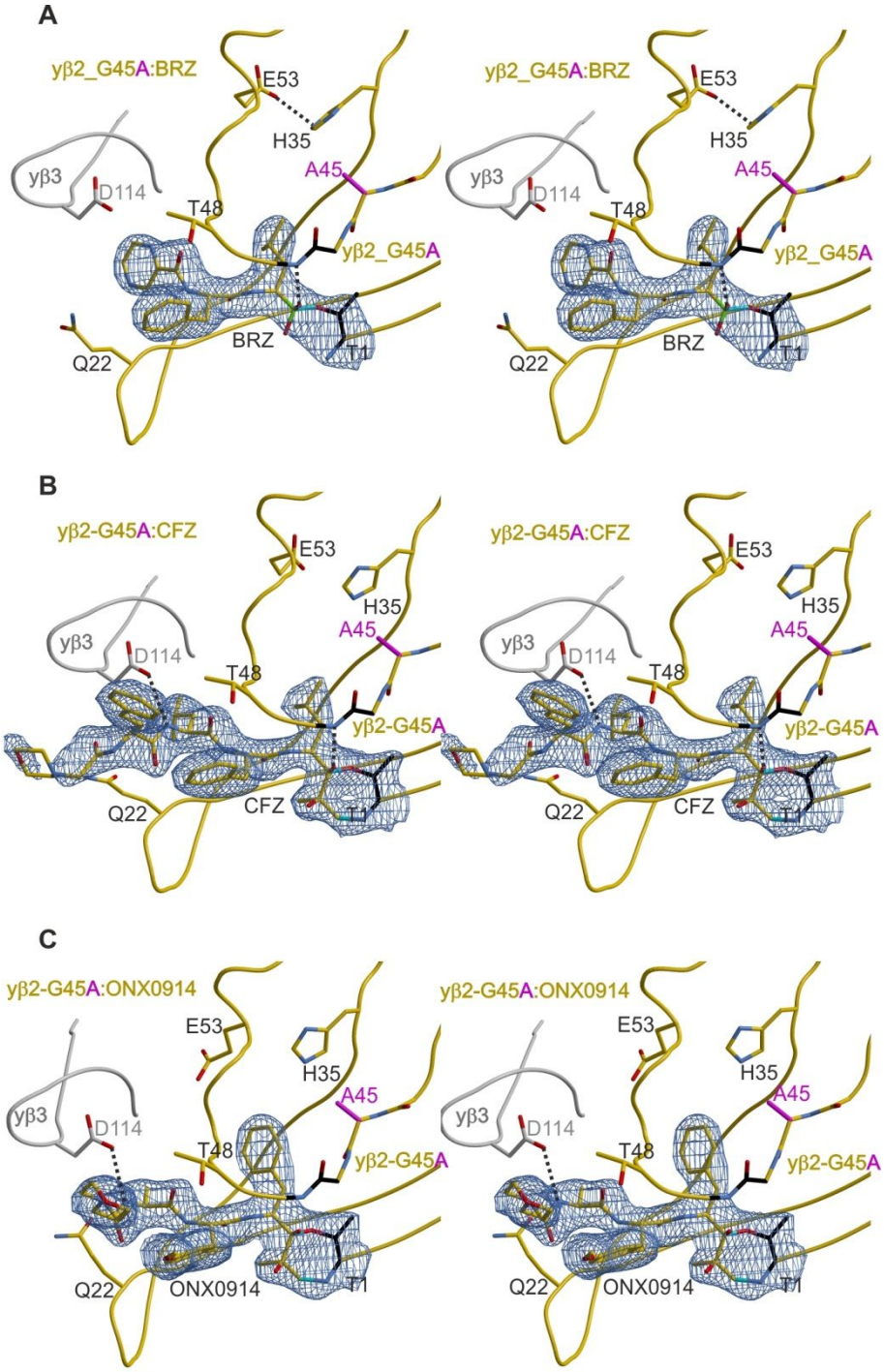
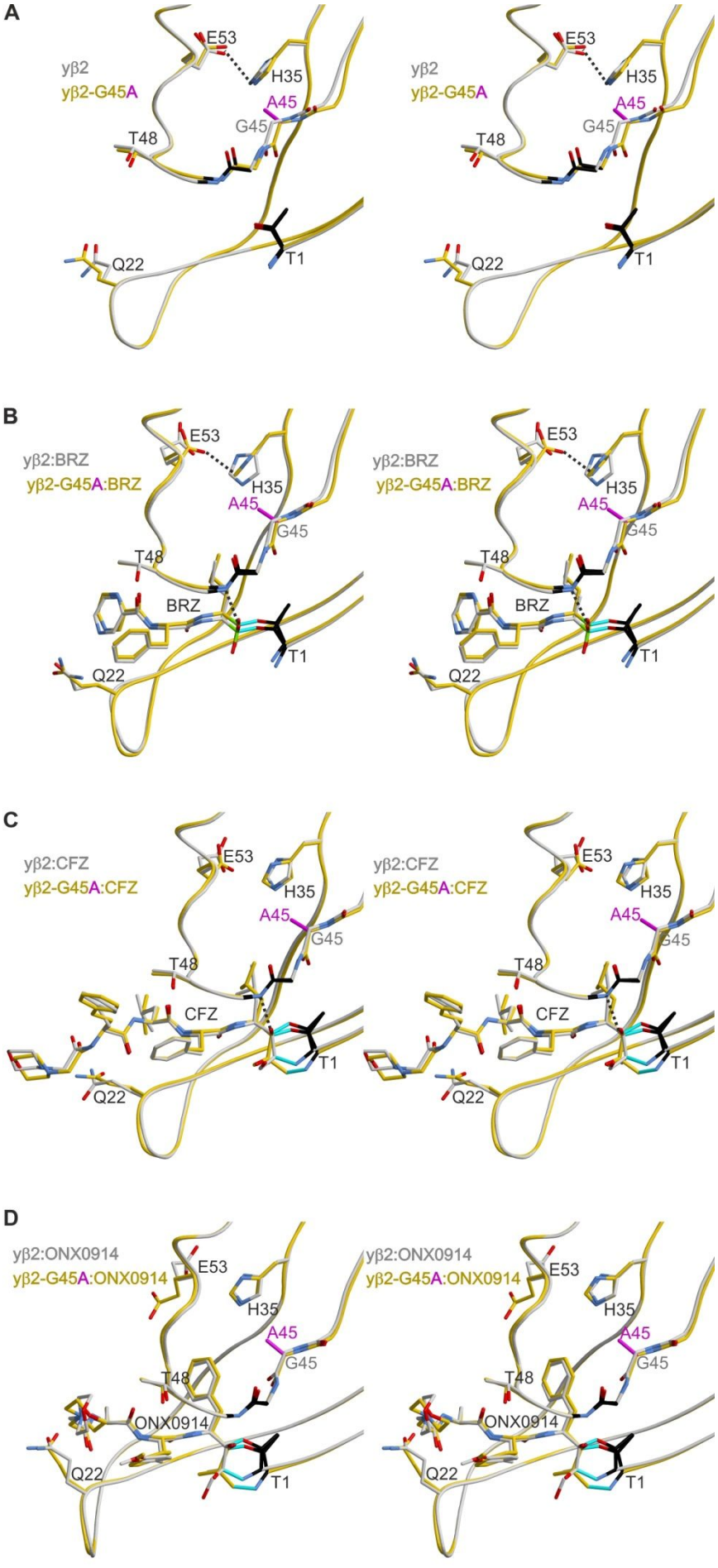


Figure S11. Stereo representations of the yβ2-G45A mutant active site in complex with the proteasome inhibitors bortezomib (BRZ, A), carfilzomib (CFZ, B) and ONX 0914 (C). $2F_O$-F_C electron density maps (blue meshes, contoured to 1σ) are displayed for the ligands and the catalytic Thr1. The site of mutation Ala45 is highlighted in magenta. Hydrogen bonds are depicted as black dashed lines. PDB IDs: 6HWD (yCP-β2G45A:bortezomib), 6HWE (yCP-β2G45A:carfilzomib), 6HWF (yCP-β2G45A:ONX 0914).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T48
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H35
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Q22
T1

Figure S12. Structural superpositions of (A) the WT (PDB ID 5CZ4[1]) and G45A-mutant yβ2 active sites in their apo state; (B) the WT (PDB ID 4QVL[2]) and G45A-mutant yβ2 active sites in complex with bortezomib (BRZ); (C) the WT (PDB ID 4QW4[2]) and G45A-mutant yβ2 active sites in complex with carfilzomib (CFZ); (D) the WT (PDB ID 4QWX[2]) and G45A-mutant yβ2 active sites in complex with ONX 0914. All panels are shown in stereo. Color coding is according to Figure S4. Hydrogen bonds are depicted as black dashed lines. Ala45 does not alter the conformation of inhibitors bound to Thr1. Please note that the epoxyketone inhibitors (BRZ, CFZ) previously determined in complex with WT proteasomes have been modelled as a morpholine ring structure with Thr1, while more recent studies suggest formation of a seven-membered ring at the active site[3]. PDB IDs: 5CZ4 (yCP), 6HWC (yCP-β2G45A), 4QVL (yCP:bortezomib), 6HWD (yCP-β2G45A:bortezomib), 4QW4 (yCP:carfilzomib), 6HWE (yCP-β2G45A:carfilzomib), 4QWX (yCP:ONX 0914), 6HWF (yCP-β2G45A:ONX 0914).

.

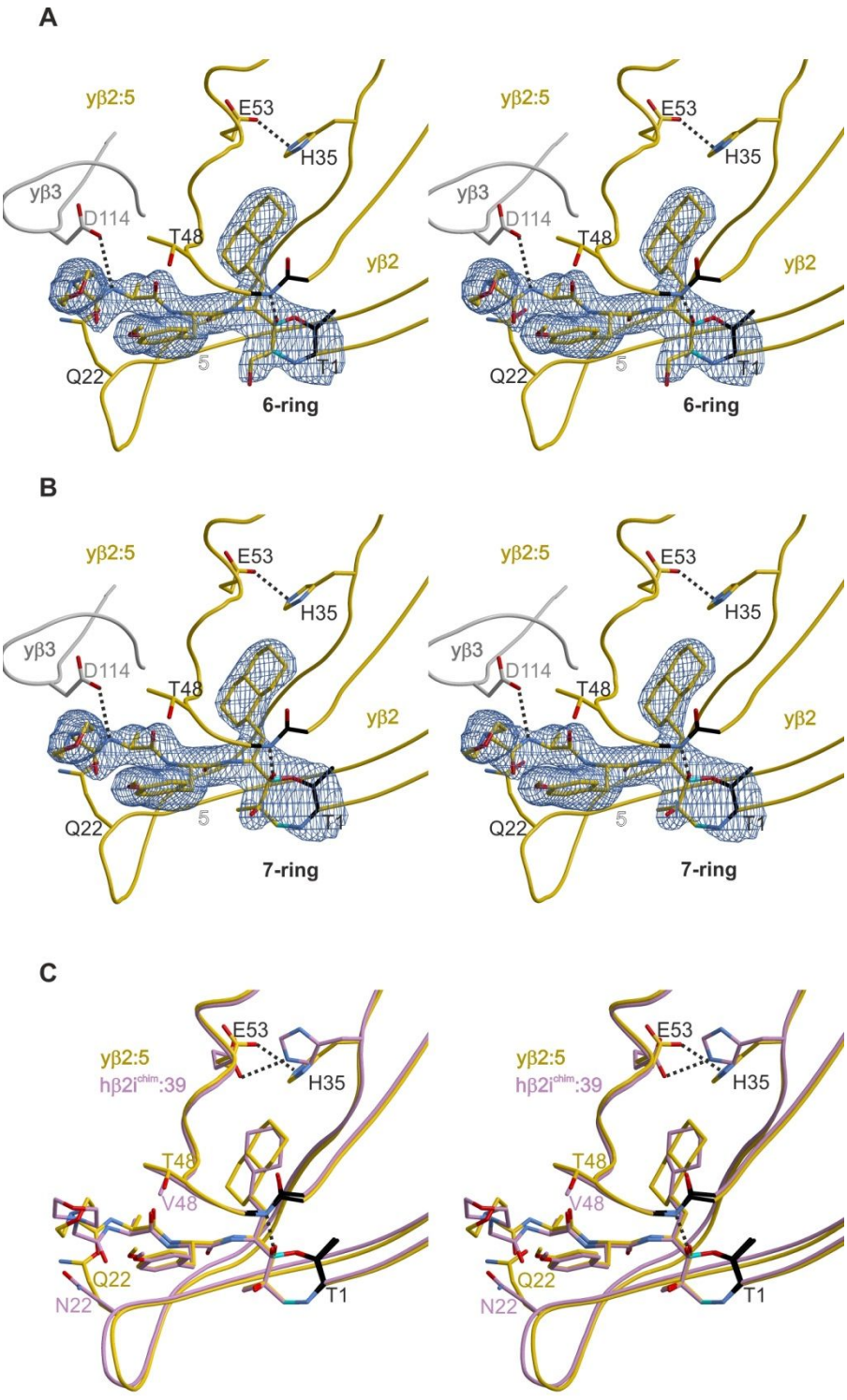


Figure S13: Stereo representations of the WT yβ2 active site in complex with compound **5**. The covalent adduct of the active site Thr1 and the ligand is modelled as (A) six-membered morpholine ring and (B) seven-membered ring structure. The $2F_O$-F_C electron density maps (blue meshes, contoured to 1σ), displayed for the ligands and the catalytic Thr1, indicate that in this case the morpholine ring system fits

the experimental data better. (C) Superposition of the WT yβ2 active site in complex with the first-in-class β2i-inhibitor **5** and the human-yeast chimeric β2i subunit bound to the second-most selective inhibitor for β2i, compound **39**. Hydrogen bonds are depicted as black dashed lines. PDB IDs: 6HVY (yCP:**5**), 6HVV (hβ2i chimera:**39**).

Table S13. X-ray data collection and refinement statistics.

	hβ2c chimera	***hβ2c chimera: ONX 0914***	***hβ2c chimera:4***	***hβ2c chimera:7***
Crystal parameters				
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Cell constants	a = 135.7 Å	a = 135.6 Å	a = 134.3 Å	a = 133.9 Å
	b = 300.6 Å	b = 300.8 Å	b = 299.9 Å	b = 300.4 Å
	c = 145.1 Å	c = 144.6 Å	c = 144.2 Å	c = 144.0 Å
	β = 113.1 °	β = 112.9°	β = 112.7°	β = 112.8°
CPs / AU[a]	1	1	1	1
Data collection				
Beam line	ID23, ESRF	X06SA, SLS	X06SA, SLS	X06SA, SLS
Wavelength (Å)	1.0	1.0	1.0	1.0
Resolution range (Å)[b]	50–2.7 (2.8–2.7)	50-2.8 (2.9-2.8)	50-3.0 (3.1-3.0)	50-3.0 (3.1-3.0)
No. observations	886780	787101	646229	618990
No. unique reflections[c]	288098	256275	206485	199569
Completeness (%)[b]	98.7 (99.7)	98.0 (98.5)	98.5 (99.5)	95.5 (97.5)
R_{merge} (%)[b, d]	9.0 (52.5)	9.6 (52.2)	8.2 (56.2)	8.3 (58.9)
I/σ (I)[b]	10.0 (2.4)	8.4 (2.0)	11.9 (3.0)	13.2 (2.8)
Refinement (REFMAC5)				
Resolution range (Å)	15-2.7	15-2.8	15-3.0	15-3.0
No. refl. working set	272120	241898	194640	189590
No. refl. test set	14332	12731	10245	9979
No. non hydrogen	49888	49695	49459	49350
No. of ligand atoms	-	252	172	164
Solvent (H_2O, ions, MES)	944	499	343	242
R_{work}/R_{free} (%)[e]	19.3 / 22.0	18.0 / 21.8	17.4 / 20.1	17.7 / 20.6
r.m.s.d. bond (Å) / angle (°)[f]	0.007 / 1.2	0.007 / 1.2	0.007 / 1.2	0.007 / 1.2
Average B-factor (Å^2)	59.6	72.4	72.2	81.8
Ramachandran Plot (%)[g]	98.1 / 1.8 / 0.1	97.8 / 2.1 / 0.1	97.7 / 2.1 / 0.2	97.5 / 2.3 / 0.2
PDB accession code	6HTB	6HTC	6HTD	6HTP

[a] Asymmetric unit
[b] The values in parentheses for resolution range, completeness, R_{merge} and I/σ (I) correspond to the highest resolution shell
[c] Data reduction was carried out with XDS and from a single crystal. Friedel pairs were treated as identical reflections
[d] $R_{merge}(I) = \Sigma_{hkl}\Sigma_j \mid I(hkl)_j - \langle I(hkl)\rangle \mid / \Sigma_{hkl}\,\Sigma_j\, I(hkl)_j$, where $I(hkl)_j$ is the j^{th} measurement of the intensity of reflection hkl and $\langle I(hkl)\rangle$ is the average intensity
[e] $R = \Sigma_{hkl} \mid |F_{obs}| - |F_{calc}| \mid / \Sigma_{hkl} |F_{obs}|$, 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] Percentage of residues in favored / allowed / outlier region

	hβ2c chimera: 13	*hβ2c chimera: 16*	*hβ2c chimera:18*	*hβ2c chimera:20*
Crystal parameters				
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Cell constants	a = 136.4 Å	a = 135.2 Å	a = 133.9 Å	a = 134.0 Å
	b = 300.5 Å	b = 299.4 Å	b = 300.4 Å	b = 299.3 Å
	c = 144.8 Å	c = 144.8 Å	c = 144.0 Å	c = 143.5 Å
	β = 113.4°	β = 113.1°	β = 112.6°	β = 112.2°
CPs / AU[a]	1	1	1	1
Data collection				
Beam line	X06SA, SLS	X06SA, SLS	X06SA, SLS	X06SA, SLS
Wavelength (Å)	1.0	1.0	1.0	1.0
Resolution range (Å)[b]	50-2.6 (2.7-2.6)	50-2.9 (3.0-2.9)	50-3.0 (3.1-3.0)	50-3.0 (3.1-3.0)
No. observations	945971	710568	637428	635019
No. unique reflections[c]	317160	230576	205059	206139
Completeness (%)[b]	97.0 (99.3)	98.8 (99.4)	98.4 (99.4)	98.9 (99.6)
R_{merge} (%)[b, d]	7.1 (51.0)	9.8 (56.0)	9.1 (59.6)	9.1 (55.9)
I/σ (I)[b]	9.9 (2.0)	8.2 (2.0)	10.6 (2.5)	10.9 (2.0)
Refinement (REFMAC5)				
Resolution range (Å)	15-2.6	15-2.9	15-3.0	15-3.0
No. refl. working set	299769	217469	193322	194272
No. refl. test set	15777	11445	10174	10224
No. non hydrogen	49891	49735	49488	49393
No. of ligand atoms	176	180	168	160
Solvent (H_2O, ions, MES)	705	611	376	289
R_{work}/R_{free} (%)[e]	19.4 / 22.4	18.4 / 21.2	18.1 / 21.8	17.8 / 20.7
r.m.s.d. bond (Å) / angle (°)[f]	0.007 / 1.2	0.007 / 1.2	0.007 / 1.2	0.007 / 1.2
Average B-factor (Å^2)	67.8	65.6	71.9	78.2
Ramachandran Plot (%)[g]	97.8 / 2.0 / 0.2	97.8 / 2.0 / 0.2	97.6 / 2.2 / 0.2	97.6 / 2.2 / 0.2
PDB accession code	6HTR	6HUB	6HUC	6HUQ

[a] Asymmetric unit

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

[c] Data reduction was carried out with XDS and from a single crystal. Friedel pairs were treated as identical reflections

[d] $R_{merge}(I) = \Sigma_{hkl}\Sigma_j \mid I(hkl)_j - \langle I(hkl)\rangle \mid / \Sigma_{hkl}\, \Sigma_j\, I(hkl)_j$, where $I(hkl)_j$ is the j^{th} measurement of the intensity of reflection hkl and $\langle I(hkl)\rangle$ is the average intensity

[e] $R = \Sigma_{hkl} \mid |F_{obs}| - |F_{calc}| \mid / \Sigma_{hkl} |F_{obs}|$, 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] Percentage of residues in favored / allowed / outlier region

	hβ2c chimera: 29	*hβ2c chimera:39*	*hβ2i chimera*	*hβ2i chimera: ONX 0914*
Crystal parameters				
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Cell constants	a = 134.7 Å	a = 134.1 Å	a = 135.4 Å	a = 135.0 Å
	b = 299.6 Å	b = 299.9 Å	b = 301.7 Å	b = 298.8 Å
	c = 143.6 Å	c = 143.5 Å	c = 145.0 Å	c = 143.4 Å
	β = 112.4°	β = 112.7°	β = 113.1 °	β = 112.5°
CPs / AU[a]	1	1	1	1
Data collection				
Beam line	X06SA, SLS	X06SA, SLS	X06SA, SLS	X06SA, SLS
Wavelength (Å)	1.0	1.0	1.0	1.0
Resolution range (Å)[b]	50-2.8 (2.9-2.8)	50-3.1 (3.2-3.1)	50–2.7 (2.8–2.7)	50-3.0 (3.1-3.0)
No. observations	785120	576142	879669	642979
No. unique reflections[c]	255383	186168	283072	203267
Completeness (%)[b]	99.1 (99.4)	98.6 (99.3)	96.9 (98.7)	97.2 (99.0)
R_{merge} (%)[b, d]	7.9 (58.5)	9.8 (58.2)	7.7 (49.5)	9.3 (57.3)
I/σ (I)[b]	11.4 (2.0)	12.2 (2.6)	9.7 (2.5)	10.0 (3.2)
Refinement (REFMAC5)				
Resolution range (Å)	15-2.8	15-3.1	15-2.7	15-3.0
No. refl. working set	242613	175330	267382	191584
No. refl. test set	12770	9228	14073	10084
No. non hydrogen	49573	49440	49998	49736
No. of ligand atoms	176	172	-	252
Solvent (H_2O, ions, MES)	453	232	626	320
R_{work}/R_{free} (%)[e]	19.4 / 22.1	16.8 / 21.3	17.7 / 20.9	18.4 / 21.4
r.m.s.d. bond (Å) / angle (°)[f]	0.007 / 1.2	0.007 / 1.2	0.007 / 1.1	0.007 / 1.2
Average B-factor (Å^2)	77.3	77.7	62.3	74.1
Ramachandran Plot (%)[g]	97.7 / 2.1 / 0.2	97.8 / 2.1 / 0.1	98.0 / 1.9 / 0.1	97.7 / 2.2 / 0.1
PDB accession code	6HUU	6HUV	6HV3	6HV4

[a] Asymmetric unit

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

[c] Data reduction was carried out with XDS and from a single crystal. Friedel pairs were treated as identical reflections

[d] $R_{merge}(I) = \Sigma_{hkl}\Sigma_j \mid I(hkl)_j - \langle I(hkl)\rangle \mid / \Sigma_{hkl}\, \Sigma_j\, I(hkl)_j$, where $I(hkl)_j$ is the j^{th} measurement of the intensity of reflection hkl and $\langle I(hkl)\rangle$ is the average intensity

[e] $R = \Sigma_{hkl} \mid |F_{obs}| - |F_{calc}| \mid / \Sigma_{hkl} |F_{obs}|$, 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] Percentage of residues in favored / allowed / outlier region

	hβ2i chimera:4	*hβ2i chimera:7*	*hβ2i chimera: 13*	*hβ2i chimera: 16*
Crystal parameters				
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Cell constants	a = 134.7 Å	a = 134.1 Å	a = 134.9 Å	a = 135.8 Å
	b = 300.4 Å	b = 302.1 Å	b = 300.6 Å	b = 299.6 Å
	c = 144.1 Å	c = 143.2 Å	c = 144.8 Å	c = 144.6 Å
	β = 112.6°	β = 112.6°	β = 112.8°	β = 113.2°
CPs / AU[a]	1	1	1	1
Data collection				
Beam line	X06SA, SLS	X06SA, SLS	X06SA, SLS	X06SA, SLS
Wavelength (Å)	1.0	1.0	1.0	1.0
Resolution range (Å)[b]	50-3.0 (3.1-3.0)	50-3.4 (3.5-3.4)	50-2.9 (2.8-2.9)	50-2.7 (2.8-2.7)
No. observations	660230	407662	736625	873416
No. unique reflections[c]	205492	137474	229426	286280
Completeness (%)[b]	97.6 (99.3)	95.4 (96.4)	97.9 (96.5)	98.7 (99.7)
R_{merge} (%)[b, d]	8.1 (57.0)	12.7 (64.7)	9.5 (59.4)	8.9 (52.9)
I/σ (I)[b]	12.5 (3.2)	7.8 (2.0)	11.9 (2.6)	8.7 (2.1)
Refinement (REFMAC5)				
Resolution range (Å)	15-3.0	15-3.4	15-2.9	15-2.7
No. refl. working set	193694	129100	216413	270398
No. refl. test set	10194	6795	11390	14231
No. non hydrogen atoms	49771	49514	49895	50166
No. of ligand atoms	172	164	176	180
Solvent (H_2O, ions, MES)	259	10	379	646
R_{work}/R_{free} (%)[e]	17.3 / 20.4	17.4 / 22.9	18.2 / 20.8	19.1 / 21.9
r.m.s.d. bond (Å) / angle (°)[f]	0.007 / 1.2	0.007 / 1.2	0.007 / 1.2	0.007 / 1.2
Average B-factor (Å^2)	78.2	103.1	64.5	68.0
Ramachandran Plot (%)[g]	97.8 / 2.1 / 0.1	97.8 / 2.1 / 0.1	97.9 / 2.0 / 0.1	97.9 / 2.0 / 0.1
PDB accession code	6HV5	6HV7	6HVA	6HVR

[a] Asymmetric unit

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

[c] Data reduction was carried out with XDS and from a single crystal. Friedel pairs were treated as identical reflections

[d] $R_{merge}(I) = \Sigma_{hkl}\Sigma_j \mid I(hkl)_j - \langle I(hkl)\rangle \mid / \Sigma_{hkl}\, \Sigma_j\, I(hkl)_j$, where $I(hkl)_j$ is the j^{th} measurement of the intensity of reflection hkl and $\langle I(hkl)\rangle$ is the average intensity

[e] $R = \Sigma_{hkl} \mid |F_{obs}| - |F_{calc}| \mid / \Sigma_{hkl} |F_{obs}|$, 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] Percentage of residues in favored / allowed / outlier region

	hβ2i chimera:18	*hβ2i chimera:20*	*hβ2i chimera: 29*	*hβ2i chimera:39*
Crystal parameters				
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Cell constants	a = 134.1 Å	a = 135.6 Å	a = 135.3 Å	a = 136.1 Å
	b = 300.6 Å	b = 300.1 Å	b = 299.5 Å	b = 299.4 Å
	c = 143.5 Å	c = 144.5 Å	c = 143.9 Å	c = 144.5 Å
	β = 112.8°	β = 112.9°	β = 112.4°	β = 113.1°
CPs / AU[a]	1	1	1	1
Data collection				
Beam line	X06SA, SLS	X06SA, SLS	X06SA, SLS	X06SA, SLS
Wavelength (Å)	1.0	1.0	1.0	1.0
Resolution range (Å)[b]	50-3.1 (3.2-3.1)	50-2.9 (3.0-2.9)	50-2.9 (3.0-2.9)	50-2.7 (2.8-2.7)
No. observations	569816	717608	699266	828589
No. unique reflections[c]	184642	229119	227714	283962
Completeness (%)[b]	97.6 (99.3)	97.7 (96.6)	97.5 (98.8)	97.8 (98.9)
R_{merge} (%)[b, d]	9.3 (52.3)	8.3 (47.8)	8.2 (52.8)	7.4 (59.6)
I/σ (I)[b]	10.6 (2.7)	10.5 (2.4)	10.2 (2.5)	11.4 (2.1)
Refinement (REFMAC5)				
Resolution range (Å)	15-3.1	15-2.9	15-2.9	15-2.7
No. refl. working set	173892	216112	214796	268224
No. refl. test set	9153	11374	11305	14118
No. non hydrogen atoms	49747	49844	49892	50097
No. of ligand atoms	168	160	176	172
Solvent (H_2O, ions, MES)	239	344	376	585
R_{work}/R_{free} (%)[e]	17.6 / 20.5	17.9 / 20.6	19.0 / 22.0	18.4 / 21.9
r.m.s.d. bond (Å) / angle (°)[f]	0.007 / 1.2	0.007 / 1.2	0.007 / 1.2	0.007 / 1.2
Average B-factor (Å^2)	71.4	67.4	75.0	63.8
Ramachandran Plot (%)[g]	97.7 / 2.2 / 0.2	97.9 / 2.0 / 0.1	97.9 / 2.0 / 0.1	97.8 / 2.1 / 0.1
PDB accession code	6HVS	6HVT	6HVU	6HVV

[a] Asymmetric unit

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

[c] Data reduction was carried out with XDS and from a single crystal. Friedel pairs were treated as identical reflections

[d] $R_{merge}(I) = \Sigma_{hkl}\Sigma_j \mid I(hkl)_j - \langle I(hkl)\rangle \mid / \Sigma_{hkl}\,\Sigma_j\, I(hkl)_j$, where $I(hkl)_j$ is the j^{th} measurement of the intensity of reflection hkl and $\langle I(hkl)\rangle$ is the average intensity

[e] $R = \Sigma_{hkl} \mid |F_{obs}| - |F_{calc}| \mid / \Sigma_{hkl} |F_{obs}|$, 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] Percentage of residues in favored / allowed / outlier region

	hβ2i chimera:43	*yCP:4*	*yCP:5 7- and 6-membered ring*	*yCP:7*
Crystal parameters				
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Cell constants	a = 134.2 Å	a = 136.8 Å	a = 136.6 Å	a = 137.3 Å
	b = 299.9 Å	b = 300.1 Å	b = 301.8 Å	b = 299.7 Å
	c = 143.2 Å	c = 145.7 Å	c = 145.6 Å	c = 145.4 Å
	β = 112.5°	β = 113.1°	β = 113.1°	β = 113.4°
CPs / AU[a]	1	1	1	1
Data collection				
Beam line	X06SA, SLS	X06SA, SLS	X06SA, SLS	X06SA, SLS
Wavelength (Å)	1.0	1.0	1.0	1.0
Resolution range (Å)[b]	50-3.0 (3.1-3.0)	50-2.8 (2.9-2.8)	50-2.7 (2.8-2.7)	50-2.8 (2.9-2.8)
No. observations	639472	902685	885917	814744
No. unique reflections[c]	204830	256585	290007	253749
Completeness (%)[b]	98.2 (99.2)	97.0 (94.0)	97.9 (98.6)	96.1 (98.6)
R_{merge} (%)[b, d]	9.1 (59.2)	6.3 (42.9)	7.4 (55.2)	7.4 (54.0)
I/σ (I)[b]	11.8 (2.2)	16.6 (3.9)	12.5 (2.4)	12.0 (2.6)
Refinement (REFMAC5)				
Resolution range (Å)	15-3.0	15-2.8	15-2.7	15-2.8
No. refl. working set	193054	243755	273927	239545
No. refl. test set	10161	12830	14418	12608
No. non hydrogen atoms	49804	49813	50046	49856
No. of ligand atoms	184	172	92	164
Solvent (H_2O, ions, MES)	280	337	578	388
R_{work}/R_{free} (%)[e]	16.5 / 20.2	18.7 / 20.6	18.1 / 21.8	17.4 / 20.6
r.m.s.d. bond (Å) / angle (°)[f]	0.007 / 1.2	0.004 / 0.9	0.006 / 1.1	0.007 / 1.1
Average B-factor (Å^2)	75.1	63.5	61.4	68.0
Ramachandran Plot (%)[g]	97.6 / 2.3 / 0.1	97.3 / 2.5 / 0.2	97.9 / 1.9 / 0.2	97.6 / 2.2 / 0.2
PDB accession code	6HVW	6HVX	6HVY	6HW0

[a] Asymmetric unit

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

[c] Data reduction was carried out with XDS and from a single crystal. Friedel pairs were treated as identical reflections

[d] $R_{merge}(I) = \Sigma_{hkl}\Sigma_j \mid I(hkl)_j - \langle I(hkl)\rangle \mid / \Sigma_{hkl}\,\Sigma_j\, I(hkl)_j$, where $I(hkl)_j$ is the j^{th} measurement of the intensity of reflection hkl and $\langle I(hkl)\rangle$ is the average intensity

[e] $R = \Sigma_{hkl} \mid |F_{obs}| - |F_{calc}| \mid / \Sigma_{hkl} |F_{obs}|$, 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] Percentage of residues in favored / allowed / outlier region

	yCP:13	*yCP:16*	*yCP:18*	*yCP:20*
Crystal parameters				
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Cell constants	a = 135.5 Å	a = 137.0 Å	a = 138.4 Å	a = 137.0 Å
	b = 299.3 Å	b = 299.3 Å	b = 299.5 Å	b = 299.9 Å
	c = 145.4 Å	c = 145.6 Å	c = 147.3 Å	c = 145.5 Å
	β = 113.0°	β = 113.0°	β = 113.2°	β = 113.2°
CPs / AU[a]	1	1	1	1
Data collection				
Beam line	ID30B, ESRF	X06SA, SLS	ID30B, ESRF	X06SA, SLS
Wavelength (Å)	1.0	1.0	1.0	1.0
Resolution range (Å)[b]	50-2.6 (2.7-2.6)	50-2.9 (3.0-2.9)	50-2.9 (3.0-2.9)	50-2.7 (2.8-2.7)
No. observations	990364	731924	745220	921732
No. unique reflections[c]	321242	233034	239026	296671
Completeness (%)[b]	98.5 (99.2)	98.0 (99.5)	98.3 (99.6)	98.7 (99.7)
R_{merge} (%)[b, d]	6.6 (57.2)	8.5 (53.5)	6.4 (55.1)	7.1 (49.2)
I/σ (I)[b]	12.3 (2.7)	11.3 (2.7)	13.8 (2.8)	11.4 (2.1)
Refinement (REFMAC5)				
Resolution range (Å)	15-2.6	15-2.9	15-2.9	15-2.7
No. refl. working set	303621	219799	225482	274527
No. refl. test set	15980	11568	11868	1449
No. non hydrogen atoms	50186	49798	49715	49868
No. of ligand atoms	176	180	168	160
Solvent (H_2O, ions, MES)	700	314	243	404
R_{work}/R_{free} (%)[e]	19.1 / 21.5	17.3 / 21.0	18.0 / 21.1	17.5 / 20.6
r.m.s.d. bond (Å) / angle (°)[f]	0.006 / 1.1	0.007 / 1.1	0.007 / 1.1	0.007 / 1.2
Average B-factor (Å^2)	69.0	72.6	87.6	66.9
Ramachandran Plot (%)[g]	97.6 / 2.2 / 0.2	97.6 / 2.2 / 0.2	97.5 / 2.3 / 0.2	97.7 / 2.1 / 0.2
PDB accession code	6HW3	6HW4	6HW5	6HW6

[a] Asymmetric unit

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

[c] Data reduction was carried out with XDS and from a single crystal. Friedel pairs were treated as identical reflections

[d] $R_{merge}(I) = \Sigma_{hkl}\Sigma_j \mid I(hkl)_j - \langle I(hkl)\rangle \mid / \Sigma_{hkl}\, \Sigma_j\, I(hkl)_j$, where $I(hkl)_j$ is the j^{th} measurement of the intensity of reflection hkl and $\langle I(hkl)\rangle$ is the average intensity

[e] $R = \Sigma_{hkl} \mid |F_{obs}| - |F_{calc}| \mid / \Sigma_{hkl} |F_{obs}|$, 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] Percentage of residues in favored / allowed / outlier region

	yCP:29	*yCP:39*	*yCP:41b*	*yCP:43*
Crystal parameters				
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Cell constants	a = 136.3 Å	a = 137.2 Å	a = 136.9 Å	a = 136.5 Å
	b = 299.4 Å	b = 299.7 Å	b = 299.9 Å	b = 300.4 Å
	c = 145.0 Å	c = 145.5 Å	c = 145.4 Å	c = 146.3 Å
	β = 112.7°	β = 113.1°	β = 113.1°	β = 113.6°
CPs / AU[a]	1	1	1	1
Data collection				
Beam line	X06SA, SLS	X06SA, SLS	X06SA, SLS	X06SA, SLS
Wavelength (Å)	1.0	1.0	1.0	1.0
Resolution range (Å)[b]	50-2.7 (2.8-2.7)	50-2.8 (2.9-2.8)	50-2.8 (2.9-2.8)	50-2.8 (2.9-2.8)
No. observations	995443	789628	793875	873523
No. unique reflections[c]	290015	255698	257255	260396
Completeness (%)[b]	99.0 (99.3)	96.7 (94.8)	97.5 (97.3)	98.4 (98.1)
R_{merge} (%)[b, d]	7.7 (54.1)	7.7 (50.6)	7.4 (57.9)	8.0 (50.1)
I/σ (I)[b]	10.9 (2.0)	10.6 (1.7)	12.8 (2.5)	12.7 (2.6)
Refinement (REFMAC5)				
Resolution range (Å)	15-2.7	15-2.8	15-2.8	15-2.8
No. refl. working set	275514	241316	242842	245757
No. refl. test set	14501	12701	12781	12934
No. non hydrogen atoms	49784	49764	49834	49763
No. of ligand atoms	176	172	172	92
Solvent (H_2O, ions, MES)	304	285	358	367
R_{work}/R_{free} (%)[e]	20.2 / 22.5	17.0 / 20.6	17.4 / 20.5	18.5 / 21.6
r.m.s.d. bond (Å) / angle (°)[f]	0.004 / 0.9	0.006 / 1.1	0.006 / 1.1	0.006 / 1.1
Average B-factor (Å^2)	77.4	72.9	65.5	64.0
Ramachandran Plot (%)[g]	97.5 / 2.2 / 0.3	97.6 / 2.2 / 0.2	97.5 / 2.2 / 0.3	97.6 / 2.2 / 0.2
PDB accession code	6HW7	6HW8	6HW9	6HWA

[a] Asymmetric unit

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

[c] Data reduction was carried out with XDS and from a single crystal. Friedel pairs were treated as identical reflections

[d] $R_{merge}(I) = \Sigma_{hkl}\Sigma_j \mid I(hkl)_j - \langle I(hkl)\rangle \mid / \Sigma_{hkl}\, \Sigma_j\, I(hkl)_j$, where $I(hkl)_j$ is the j^{th} measurement of the intensity of reflection hkl and $\langle I(hkl)\rangle$ is the average intensity

[e] $R = \Sigma_{hkl} \mid |F_{obs}| - |F_{calc}| \mid / \Sigma_{hkl} |F_{obs}|$, 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] Percentage of residues in favored / allowed / outlier region

	yCP:44b	*yCP-β2G45A*	*yCP-β2G45A: bortezomib*	*yCP-β2G45A: carfilzomib*
Crystal parameters				
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Cell constants	a = 136.6 Å	a = 135.4 Å	a = 135.5 Å	a = 136.8 Å
	b = 299.9 Å	b = 301.2 Å	b = 300.1 Å	b = 300.2 Å
	c = 145.6 Å	c = 144.6 Å	c = 144.9 Å	c = 145.5 Å
	β = 113.2°	β = 113.0 °	β = 113.1 °	β = 113.3 °
CPs / AU[a]	1	1	1	1
Data collection				
Beam line	X06SA, SLS	X06SA, SLS	X06SA, SLS	X06SA, SLS
Wavelength (Å)	1.0	1.0	1.0	1.0
Resolution range (Å)[b]	50-2.6 (2.7-2.6)	50-2.8 (2.9-2.8)	50-2.8 (2.9-2.8)	50-2.3 (2.4-2.3)
No. observations	976104	766765	772253	1356610
No. unique reflections[c]	321591	250653	255734	467751
Completeness (%)[b]	97.6 (98.8)	96.0 (98.6)	98.1 (98.9)	98.4 (99.1)
R_{merge} (%)[b, d]	7.0 (55.0)	9.1 (49.3)	8.0 (46.4)	5.3 (54.8)
I/σ (I)[b]	11.3 (2.4)	9.5 (2.5)	11.0 (2.9)	15.2 (2.3)
Refinement (REFMAC5)				
Resolution range (Å)	15-2.6	15-2.8	15-2.8	15-2.3
No. refl. working set	303954	236637	241378	442835
No. refl. test set	15998	12455	12704	23307
No. non hydrogen atoms	50242	50127	50223	52020
No. of ligand atoms	192	-	168	312
Solvent (H_2O, ions, MES)	746	734	677	2278
R_{work}/R_{free} (%)[e]	18.9 / 22.1	19.5 / 22.4	18.6 / 21.1	20.4 / 23.1
r.m.s.d. bond (Å) / angle (°)[f]	0.006 / 1.1	0.007 / 1.1	0.007 / 1.1	0.007 / 1.2
Average B-factor (Å^2)	62.9	63.2	64.8	56.4
Ramachandran Plot (%)[g]	97.7 / 2.1 / 0.2	98.0 / 1.9 / 0.1	97.9 / 2.0 / 0.1	98.0 / 1.9 / 0.1
PDB accession code	6HWB	6HWC	6HWD	6HWE

[a] Asymmetric unit

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

[c] Data reduction was carried out with XDS and from a single crystal. Friedel pairs were treated as identical reflections

[d] $R_{merge}(I) = \Sigma_{hkl}\Sigma_j \mid I(hkl)_j - \langle I(hkl)\rangle \mid / \Sigma_{hkl}\, \Sigma_j\, I(hkl)_j$, where $I(hkl)_j$ is the j^{th} measurement of the intensity of reflection hkl and $\langle I(hkl)\rangle$ is the average intensity

[e] $R = \Sigma_{hkl} \mid |F_{obs}| - |F_{calc}| \mid / \Sigma_{hkl} |F_{obs}|$, 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] Percentage of residues in favored / allowed / outlier region

	yCP-β2G45A: ONX 0914
Crystal parameters	
Space group	$P2_1$
Cell constants	a = 136.6 Å
	b = 299.7 Å
	c = 145.1 Å
	β = 113.4 °
CPs / AU[a]	1
Data collection	
Beam line	X06SA, SLS
Wavelength (Å)	1.0
Resolution range (Å)[b]	50-2.5 (2.6-2.5)
No. observations	1105580
No. unique reflections[c]	359000
Completeness (%)[b]	97.5 (99.1)
R_{merge} (%)[b, d]	6.6 (59.0)
I/σ (I)[b]	12.0 (2.4)
Refinement (REFMAC5)	
Resolution range (Å)	15-2.5
No. refl. working set	339515
No. refl. test set	17869
No. non hydrogen	50768
No. of ligand atoms	252
Solvent (H_2O, ions, MES)	1086
R_{work}/R_{free} (%)[e]	18.9 / 21.6
r.m.s.d. bond (Å) / angle (°)[f]	0.007 / 1.3
Average B-factor (Å^2)	58.2
Ramachandran Plot (%)[g]	97.6 / 2.2 / 0.2
PDB accession code	6HWF

[a] Asymmetric unit

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

[c] Data reduction was carried out with XDS and from a single crystal. Friedel pairs were treated as identical reflections

[d] $R_{merge}(I) = \Sigma_{hkl}\Sigma_j \mid I(hkl)_j - \langle I(hkl)\rangle \mid / \Sigma_{hkl}\, \Sigma_j\, I(hkl)_j$, where $I(hkl)_j$ is the j^{th} measurement of the intensity of reflection hkl and $\langle I(hkl)\rangle$ is the average intensity

[e] $R = \Sigma_{hkl} \mid |F_{obs}| - |F_{calc}| \mid / \Sigma_{hkl} |F_{obs}|$, 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] Percentage of residues in favored / allowed / outlier region

Table S14: Subunits targeted by β2c and β2i inhibitors in crystal soaking experiments.

	wt yβ1	***wt yβ2***	***wt yβ5***	***β2c***	***β2i***
ONX 0914	+	+	+	+	+
4	-	+	+	+	+
5	-	+	-	-	-
7	-	+	+	+	+
13	-	+	+	+	+
16	-	+	+	+	+
18	-	+	+	+	+
20	-	+	+	+	+
29	-	+	+	+	+
39	-	+	+	+	+
41b	-	+	+	n.d.	n.d.
43	-	-	+	-	+
44b	-	+	+	n.d.	n.d.

Table S15. Oligonucleotides used in this study.

Oligonucleotide	**Sequence 5' – 3'**
PSMB-for	CCT GAT TGT AGA AAA TAG AAT TGA GTG AGC
PSMB-rev	GAT TTA CTA TAC TAA AAT ATA CTT AAG TTC TAT GTT TTA C
PUP1-prom-rev	GCT CAC TCA ATT CTA TTT TCT ACA ATC AGG
PUP1-ter-for	GTA AAA CAT AGA ACT TAA GTA TAT TTT AGT ATA GTA AAT C
PUP1-Age-rev	GGT ACC GGT GGA AGT TGC CTT AGG
pBS-uni	TTG TAA AAC GAC GGC CAG TG
pBS-rev	GAA ACA GCT ATG ACC ATG ATT ACG
PSMB7-S171G-for	CTT GGG TCC GGT GGG AAC ATT GAT TTG TG
PSMB7-S171G-rev	CAA ATC AAT GTT CCC ACC GGA CCC AAG G
beta2i-129-for	GGG ATC TGG TTC TCT AGC GGC AAT GGC TGT G

beta2i-129-rev	CCG CTA GAG AAC CAG ATC CCA AGG CTG TAA ATG
beta2i-1-93-for	CAT TAT TCA GAT ACC AAG GTC ATA TTG GTG C
beta2i-1-93-rev	CCT TGG TAT CTG AAT AAT GTT TGC CGT AG
beta2i-1-52-for	CTG ATG CTG AGG CAG TTA CGC AGT TGA TC
beta2i-1-52-rev	GCG TAA CTG CCT CAG CAT CAG CGG CTA CG
y93-rev	CAT GAC CTT GGT ACT TAA ATA GGT GCT GC
2i93-for	TTT AAG TAC CAA GGT CAT GTT GGC GCT TC

Synthesis and characterization of compounds.

General procedures

All reagents were of commercial grade and used as received unless indicate otherwise. Dried solvents were stored over 4 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. 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 $KMnO_4$ (20 g/L) and K_2CO_3 (10 g/L) in water, 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 CD_3OD or $CDCl_3$ as internal standard. Coupling constants are given in Hz and peak assignments are based on 2D ^1H COSY and ^{13}C HSQC NMR experiments. All presented ^{13}C APT spectra are proton decoupled. LC-MS 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, MeCN and 1.0% TFA in H_2O (0.1% TFA end concentration). Methods used are: 15 min (0→0.5 min: 10% MeCN; 0.5→10.5 min: 10% → 90% MeCN; 10.5→12.5 min: 90% MeCN; 12.5→15 min: 90% → 10% MeCN) or 12.5 min (0→0.5 min: 10% MeCN; 0.5→8.5 min: 10% → 90% MeCN; 8.5→10.5 min: 90% MeCN; 10.5→12.5 min: 90% → 10% MeCN). HRMS was recorded on a

LTQ Orbitrap (ThermoFinnigan). For reverse phase HPLC purification, an automated Gilson HPLC system equipped with a C18 semiprep column (Phenomenex Gemini C18, 5µm 250×10 mm) and a GX281 fraction collector. H-Phe(4-CH_2NH_2)VS[4], Mop-Ala-Tyr(Me)-$NHNH_2$[5], N_3Phe-Phe(4-CH_2NHBoc)-Leu-$NHNH_2$[4] were synthesized according to literature procedures.

General procedure A

Free amine (1.0 eq.) and free acid (1.2 eq.) were dissolved in DCM, followed by addition of HCTU (1.2 eq.) and DiPEA (3.5 eq.). After stirring overnight, the reaction mixture was concentrated *in vacuo* and re-dissolved in EtOAc, washed with 1M HCl (2×), sat. aq. $NaHCO_3$ (3×) and brine (in case of morpholino acetic acid coupling, no 1M HCl washing). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel flash column chromatography yielded the target compound.

General procedure B

The appropriate Boc-protected C-terminally modified leucine derivative was dissolved in TFA and stirred for 20 min. Co-evaporation with toluene (3x) afforded the TFA-salt, which was used without further purification.

General procedure C

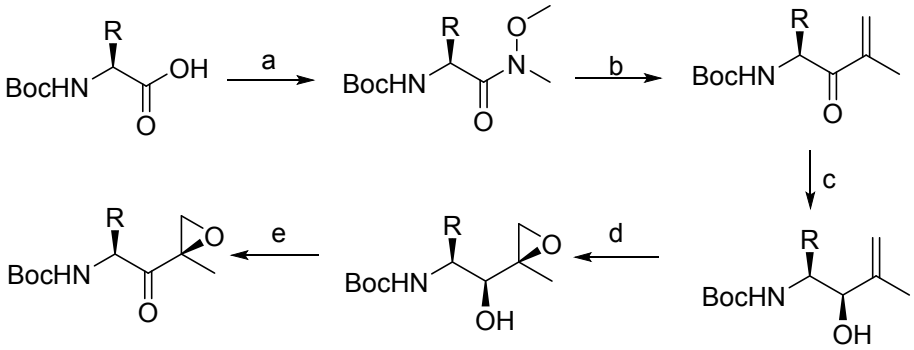
The starting material was dissolved in MeOH, follow by the addition of hydrazine monohydrate (30 eq.). The reaction mixture was stirred overnight at room temperature and then refluxed for 2h. The reaction mixture was concentrated *in vacuo* and co-evaporated with toluene (3x) to give the product in a quantitative yield. The product was directly used in next step without any further purification.

General procedure D

The hydrazide was dissolved in 1:1 DMF:DCM (v/v) and cooled to -30 ºC. *t*BuONO (1.1 eq.) and HCl (4M solution in 1,4-dioxane, 2.8 eq.) were added, and the mixture was stirred for 3 h at -30 ºC after which TLC analysis (10% MeOH/DCM, v/v) showed complete consumption of the starting material.

The epoxyketone amine or vinyl sulfone amine was added to the reaction mixture as a solution in DMF with 5.0 eq. of DiPEA and this mixture was allowed to warm up to room temperature slowly overnight. The mixture was diluted with EtOAc and washed with H_2O (2x) and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*.

Standard procedures of amino acid epoxyketone synthesis



Scheme S1. Reagents and conditions: (a) NH(Me)OMe·HCl, HCTU, DiPEA, DCM; (b) 2-bromopropene, *t*BuLi, Et_2O, –78 °C; (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C; (d) *t*BuOOH, $VO(acac)_2$, DCM, 0 °C; (e) Dess-Martin periodinane, DCM.

General procedure E: Boc-AA-N(OMe)Me. Boc-AA-OH (1.0 eq.) and *N*,*O*-dimethylhydroxylamine (2.0 eq.) are dissolved, followed by the addition of HCTU (1.2 equiv) and DiPEA (3.5 equiv). After stirring overnight, the reaction mixture was concentrated *in vacuo* and re-dissolved in EtOAc, washed with 1M HCl (2×), sat. aq. $NaHCO_3$ (3×) and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel flash column chromatography yielded the target compound.

General procedure F: Boc-AA-C(CH_3)=CH_2. A solution of 2-bromopropene (3.0 eq.) in dry Et_2O was cooled down to -78 °C under argon atmosphere and stirred for 15 min before adding tBuLi (4.5 eq.). The reaction mixture was stirred for 15 min. The Weinreb amide was coevaporated with toluene and dissolved in dried Et_2O. This solution was added dropwise to the reaction mixture during 30 min. The

resulting reaction mixture was allowed to warm up to rt and quenched after 2 h with sat. aq. NH_4Cl. The water layer was extracted with EtOAc (3×) and the combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography yielded the product.

General procedure G: Boc-AA-OH-C(CH_3)=CH_2. The product obtained from last step was dissolved in methanol, followed by addition of $CeCl_3 \cdot 7H_2O$ (1.5 eq.). After the solution turned clear, it was cooled down to 0 °C and $NaBH_4$ (1.4 eq.) was added portion-wise. After 5 min TLC analysis indicated complete conversion and the reaction mixture was quenched with glacial AcOH. The mixture was concentrated, coevaporated with toluene, dissolved in EtOAc, washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography yielded the title compound.

General procedure H: Boc-AA-EK. The alcohol was coevaporated with toluene, dissolved in DCM and cooled down to 0 °C. After addition of $VO(acac)_2$ (0.05 eq.) the solution turned light blue-green and subsequent addition of tBuOOH (3.0 eq.) resulted in a dark brown-purple reaction mixture. After stirring for 1 h the reaction mixture was removed from the ice bath. After 15 min, the reaction mixture was concentrated *in vacuo*, dissolved in EtOAc and washed with a 1 : 1 mixture of sat. aq. $NaHCO_3$ and H_2O. The aqueous layer was extracted with EtOAc (3×) and the combined organics were washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude intermediate. Dess–Martin periodinane (1.5 eq.) was dissolved in DCM and cooled down to 0 °C. The intermediate was coevaporated with toluene, dissolved in DCM and added to the Dess–Martin periodinane solution. After 1.5 h the reaction mixture was removed from the ice bath. After TLC analysis indicated full conversion of the intermediate and the reaction was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with DCM. The combined organics were washed with H_2O (3×) and brine, dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography yielded the title compound.

Tert-butyl (S)-(1-cyclohexyl-2-(methoxy(methyl)amino)-2-oxoethyl)carbamate (**98**). This compound was prepared according to general procedure E on a 2.0 mmol scale. Purification by silica gel flash

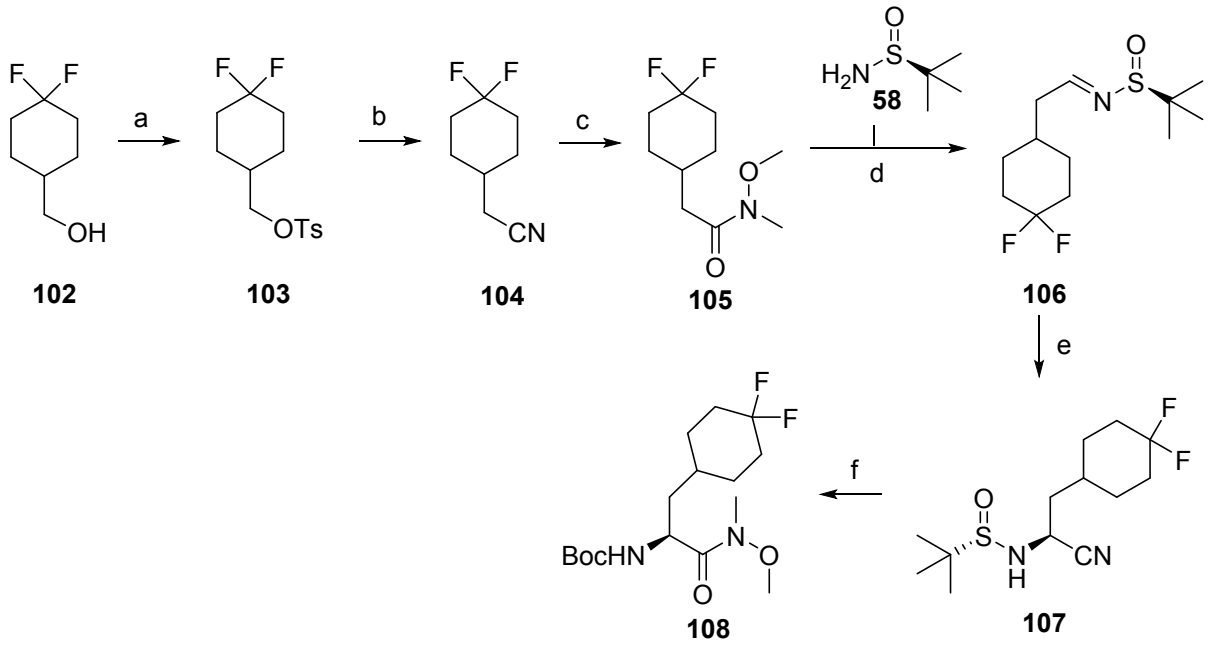
column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (570 mg, 1.9 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (d, J = 9.8 Hz, 1H), 4.59 (t, J = 8.1 Hz, 1H), 3.78 (s, 3H), 3.21 (s, 3H), 1.87-1.51 (m, 6H), 1.43 (s, 9H), 1.32-0.95 (m, 5H). ^{13}C NMR (100 MHz, CDCl3) δ 172.55, 155.41, 78.79, 61.18, 54.12, 40.69, 31.42, 29.26, 28.00, 27.93, 25.83, 25.75, 25.65. HRMS calculated for $C_{15}H_{28}N_2O_4$ 301.21218 $[M+H]^+$; found 301.21222.

Tert-butyl (S)-(1-cyclohexyl-3-methyl-2-oxobut-3-en-1-yl)carbamate (**99**). This compound was prepared according to general procedure F on a 1.9 mmol scale. Purification by silica gel flash column chromatography (1% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (365 mg, 1.3 mmol, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08 (s, 1H), 5.89 (d, J = 1.9 Hz, 1H), 5.29 (d, J = 9.2 Hz, 1H), 4.93-4.90 (m, 1H), 1.98-1.82 (m, 3H), 1.84-1.53 (m, 5H), 1.43 (s, 9H), 1.35-0.80 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.53, 155.75, 143.18, 126.33, 79.42, 58.20, 41.92, 30.28, 28.36, 27.63, 26.23, 26.05, 26.02, 17.69. HRMS calculated for $C_{16}H_{27}NO_3$ 282.20637 $[M+H]^+$; found 282.20640.

Tert-butyl ((1S,2R)-1-cyclohexyl-2-hydroxy-3-methylbut-3-en-1-yl)carbamate (**100**). This compound was prepared according to general procedure G on a 1.3 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (354 mg, 1.2 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (s, 1H), 4.92 (s, 1H), 4.57 (d, J = 10.1 Hz, 1H), 4.09 (d, J = 6.6 Hz, 1H), 3.67-3.61 (m, 1H), 2.51 (s, 1H), 1.90-1.54 (m, 9H), 1.42 (s, 9H), 1.30-0.87 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.38, 145.74, 112.95, 79.23, 76.68, 56.84, 37.78, 31.23, 28.44, 27.32, 26.43, 26.27, 18.33. HRMS calculated for $C_{16}H_{29}NO_3$ 284.22202 $[M+H]^+$; found 284.22204.

Boc-Chg-EK (**101**). This compound was prepared according to general procedure H on a 1.2 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (119 mg, 0.40 mmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (d, J = 9.4 Hz, 1H), 4.25-4.21 (m, 1H), 3.27 (d, J = 5.0 Hz, 1H), 2.87 (d, J = 5.0 Hz, 1H), 1.75-1.54 (m, 5H), 1.51 (s, 3H), 1.41 (s, 9H), 1.29-0.90 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.07, 155.70,

79.65, 59.32, 56.61, 51.79, 40.30, 30.05, 28.36, 27.88, 26.20, 26.06, 26.04, 16.41. HRMS calculated for $C_{16}H_{27}NO_4$ 298.20128 $[M+H]^+$; found 298.20133. $[\alpha]_D20$ +122 (C=1.0, $CHCl_3$).



Scheme S2. Reagents and conditions: (a) TsCl/TEA/DCM; (b) NaCN/DMF; (c) i) KOH/ethylene glycol; ii) N,O-dimethylhydroxylamine hydrochloride, HCTU/DiPEA/DCM; (d) i) $LiAlH_4/Et_2O$; ii) 58/$CuSO_4$/DCM; (e) Et_2AlCN/i-PrOH/THF; (f) i) 6M HCl, reflux; ii) Boc_2O/TEA/THF/H_2O; iii) N,O-dimethylhydroxylamine hydrochloride, HCTU/DiPEA/DCM.

(4,4-difluorocyclohexyl)methyl 4-methylbenzenesulfonate (**103**). (4,4-difluorocyclohexyl)methanol 102 (3.0 g, 20.0 mmol) was dissolved in anhydrous DCM, followed by the addition of TsCl (7.6 g, 40 mmol, 2.0 eq.) and TEA (5.6 mL, 40 mmol, 2.0 eq.). After stirring at r.t. for 48 h, the reaction mixture was concentrated *in vacuo*. The residue was re-dissolved in EtOAc and washed with sat. aq. $NaHCO_3$ (2×) and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (5.6 g, 18.4 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 3.86 (d, J = 6.0 Hz, 2H), 2.43 (s, 3H), 2.07-1.99 (m, 2H), 1.89-1.53 (m, 5H), 1.31-1.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.89, 132.56, 129.84, 127.66, 125.37, 122.99, 120.58, 73.47, 35.11, 32.80, 32.57, 32.32, 25.02, 24.93, 21.39.

2-(4,4-difluorocyclohexyl)acetonitrile (**104**). Compound **103** (5.6 g, 18.4 mmol) was dissolved in DMF, followed by the addition of NaCN (1.8 g, 36.8 mmol, 2 eq.). After refluxing overnight, the reaction mixture was diluted with EtOAc, washed with H_2O (2×), sat. aq. $NaHCO_3$ (2×) and brine, dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (2.7 g, 17.0 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (d, J = 6.7 Hz, 2H), 2.19-2.01 (m, 2H), 1.98-1.64 (m, 5H), 1.52-1.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.04, 122.66, 120.25, 118.19, 32.98, 32.75, 32.72, 32.64, 32.63, 32.49, 27.98, 23.04.

2-(4,4-difluorocyclohexyl)-N-methoxy-N-methylacetamide (**105**). Compound **104** (2.7 g, 17.0 mmol) was dissolved in ethylene glycol, followed by addition of KOH (7.6 mL, 136 mmol, 1 g/mL solution, 8.0 eq.). The reaction was stirred at 170 °C overnight. The reaction mixture was poured in to H_2O and the pH was adjusted to 2-3 with conc. HCl. The mixture was extracted with EtOAc (3×) and the combined organic layer was washed by H_2O (3×), brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude intermediate was directly coupled with N,O-dimethylhydroxylamine hydrochloride (1.2 eq.) according to general procedure E on a 17.0 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (3.6 g, 16.1 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.19 (s, 3H), 2.37 (d, J = 7.0 Hz, 2H), 2.16-1.66 (m, 7H), 1.38-1.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.19, 125.89, 123.51, 121.10, 61.26, 37.61, 33.67, 33.42, 33.20, 32.33, 32.06, 28.97. HRMS calculated for $C_{10}H_{17}F_2NO_2$ 222.13001 $[M+H]^+$; found 222.13002.

(S,E)-N-(2-(4,4-difluorocyclohexyl)ethylidene)-2-methylpropane-2-sulfinamide (**106**). Compound **105** (3.6 g, 16.1 mmol) was dissolved in Et_2O and the reaction solution was cooled to 0 °C. $LiAlH_4$ (20.9 mL, 20.9 mmol, 1 M solution in Et_2O, 1.3 eq.) was slowly added and the reaction was stirred at 0 ºC for 2 h. The reaction was quenched with 0.1 M HCl and the suspension solution was filtrated. The filtrate was concentrated *in vacuo* and co-evaporated with toluene (3×). The obtained aldehyde intermediate was dissolved in anhydrous DCM, followed by the addition of (S)-2-methylpropane-2-sulfinamide 58

(2.9 g, 24.2 mmol, 1.5 eq.) and anhydrous $CuSO_4$ (10.3 g, 64.4 mmol, 4.0 eq.). After stirring at r.t. for 48 h, the suspension solution was filtrated through Celite and concentrated *in vacuo*. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 25% EtOAc/pentane) yielded the title compound (3.3 g, 12.4 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (t, J = 4.9 Hz, 1H), 2.51-2.48 (m, 2H), 2.15-2.01 (m, 2H), 2.01-1.58 (m, 5H), 1.46-1.32 (m, 2H), 8.81 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.03, 125.35, 122.94, 120.56, 56.48, 41.75, 33.42, 33.17, 33.12, 32.91, 28.82, 28.69, 22.22. HRMS calculated for $C^{12}H^{21}F^2NOS$ 266.13847 $[M+H]^+$; found 266.13837.

(S)-N-((S)-1-cyano-2-(4,4-difluorocyclohexyl)ethyl)-2-methylpropane-2-sulfinamide (**107**). Compound **106** (3.3 g, 12.4 mmol) was dissolved in anhydrous THF and the solution was cooled to -78 °C. Et_2AlCN (18.6 mL, 18.6 mmol, 1M solution in toluene, 1.5 eq.) was added to anhydrous THF, followed by the addition of i-PrOH (2.8 mL, 37.2 mmol, 3.0 eq.). After stirring at r.t. for 15 min, this solution was slowly added to a cooled solution of compound **106** in anhydrous THF. The reaction was stirred at r.t. until TLC-MS analysis showed the complete conversion of the starting material. The reaction mixture was cooled to -78 ºC again and sat. aq. $NaHCO_3$ (16 mL) was added. The reaction mixture was allowed to warm up to r.t. and the suspension solution was filtrated. The filtrate was concentrated in vacuo and purification by silica gel flash column chromatography (5% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (3.3 g, 11.3 mmol, 91%) as a single diastereoisomer (de > 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (d, J = 9.1 Hz, 1H), 4.22-4.15 (m, 1H), 2.14-2.00 (m, 2H), 1.89-1.80 (m, 5H), 1.70-1.62 (m, 2H), 1.37-1.29 (m, 2H), 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.49, 123.08, 120.70, 119.66, 57.06, 44.59, 40.23, 33.04, 31.85, 28.19, 22.46. HRMS calculated for $C_{13}H_{22}F_2N_2OS$ 293.14937 $[M+H]^+$; found 293.14936.

(S)-tert-butyl3-(4,4-difluorocyclohexyl)-1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (**108**). Compound **107** (3.3 g, 11.3 mmol) was dissolved in 6M HCl and refluxed for 48 h. The mixture was co-evaporated with toluene (3×) to give the unprotected amino acid as the HCl salt. Subsequently, the amino acid was re-dissolved in THF/H_2O (1:1, v/v), followed by the addition of Boc_2O (5.1 g, 23.4 mmol, 1.5 eq.) and TEA (8.7 mL, 62.4 mmol, 4 eq.). After stirring overnight, the mixture was

concentrated in vacuo and re-dissolved in EtOAc. The organic layer was washed with H_2O, brine, dried over $MgSO_4$ and concentrated in vacuo.Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane with 0.1% acetic acid) yielded the crude Boc protected amino acid. The crude intermediate was directly used in peptide coupling according to general procedure E. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (1.5 g, 4.3 mmol, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (d, J = 9.6 Hz, 1H), 4.84-4.66 (m, 1H), 3.78 (s, 3H), 3.20 (s, 3H), 2.13-1.94 (m, 3H), 1.80-1.51 (m, 5H), 1.44 (s, 9H), 1.36-1.18 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.29, 155.68, 125.90, 123.52, 121.11, 79.57, 61.57, 48.48, 38.94, 33.67, 33.48, 33.25, 33.00, 32.16, 29.68, 29.59, 28.29, 27.86, 27.77. HRMS calculated for $C_{16}H_{28}F_2N_2O_4$ 351.20899 $[M+H]^+$; found 351.20898.

(S)-Tert-butyl 1-(4,4-difluorocyclohexyl)-4-methyl-3-oxopent-4-en-2-ylcarbamate (**109**). This compound was prepared according to general procedure F on a 0.68 mmol scale. Purification by silica gel flash column chromatography (1% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (157 mg, 0.47 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (s, 1H), 5.91 (d, J = 1.8 Hz, 1H), 5.30 (d, J = 8.9 Hz, 1H), 5.23-5.02 (m, 1H), 2.18-1.97 (m, 3H), 1.90 (s, 3H), 1.75-1.56 (m, 4H), 1.44 (s, 9H), 1.39-1.22 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.99, 155.65, 142.15, 126.41, 125.88, 123.50, 121.10, 79.80, 52.09, 40.36, 33.80, 33.55, 33.38, 33.15, 32.53, 29.86, 29.76, 28.35, 28.12, 28.02, 17.84. HRMS calculated for $C_{17}H_{27}F_2NO_3$ 332.20318 $[M+H]^+$; found 332.20319.

Tert-butyl(2S,3R)-1-(4,4-difluorocyclohexyl)-3-hydroxy-4-methylpent-4-en-2- ylcarbamate (**110**). This compound was prepared according to general procedure G on a 0.47 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (133 mg, 0.40 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (s, 1H), 4.95-4.94 (m, 1H), 4.92-4.83 (m, 1H), 4.18-4.05 (m, 1H), 3.94-3.76 (m, 1H), 2.66 (s, 1H), 2.13-1.93 (m, 3H), 1.75 (d, J = 6.3 Hz, 3H), 1.70-1.61 (m, 2H), 1.50-1.35 (m, 11H), 1.35-1.25 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.08, 144.83, 126.19, 123.81, 121.41, 112.01, 111.47, 79.56, 77.68, 50.19, 34.21, 33.95, 33.69, 33.44,

33.20, 32.38, 30.25, 30.15, 28.46, 27.98, 27.89, 19.43. HRMS calculated for $C_{17}H_{29}F_2NO_3$ 334.21883 $[M+H]^+$; found 334.21889.

Boc-Cha(4,4-2F)-EK (**111**). This compound was prepared according to general procedure H on a 0.40 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (40 mg, 0.12 mmol, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (d, J = 9.2 Hz, 1H), 4.36-4.31 (m, 1H), 3.26 (d, J = 4.9 Hz, 1H), 2.90 (d, J = 4.9 Hz, 1H), 2.19-1.89 (m, 3H), 1.80-1.59 (m, 4H), 1.55 (s, 3H), 1.42 (s, 9H), 1.37-1.13 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.26, 155.74, 125.96, 123.56, 121.18, 80.12, 59.06, 52.46, 51.00, 37.74, 33.77, 33.51, 33.29, 33.03, 32.65, 29.85, 29.76, 28.41, 27.85, 27.76, 16.83. HRMS calculated for $C_{17}H_{27}F_2NO_4$ 348.19809 $[M+H]^+$; found 348.19812. $[\alpha]_D20$ +80 (C 0.5, $CHCl_3$).

Tert-butyl (S)-(4-cyclohexyl-1-(methoxy(methyl)amino)-1-oxobutan-2-yl)carbamate (**112**). Boc-HomoCha-OH was prepared according to literature procedures6, followed by the peptide coupling according to general procedure E on a 2.1 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (588 mg, 1.8 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (d, J = 9.2 Hz, 1H), 4.66-4.61 (m, 1H), 3.78 (s, 3H), 3.20 (s, 3H), 1.79-1.69 (m, 6H), 1.43 (s, 9H), 1.30-1.08 (m, 7H), 0.99-0.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.14, 155.34, 78.92, 61.25, 50.32, 37.08, 33.13, 32.71, 32.61, 29.81, 29.36, 28.08, 26.34, 26.04, 26.02. HRMS calculated for $C_{17}H_{32}N_2O_4$ 329.24348 $[M+H]^+$; found 329.24346.

Tert-butyl (S)-(1-cyclohexyl-5-methyl-4-oxohex-5-en-3-yl)carbamate (**113**). This compound was prepared according to general procedure F on a 0.91 mmol scale. Purification by silica gel flash column chromatography (1% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (224 mg, 0.72 mmol, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (s, 1H), 5.88 (d, J = 1.8 Hz, 1H), 5.36 (d, J = 8.4 Hz, 1H), 5.02-4.98 (m, 1H), 1.90 (s, 3H), 1.84-1.77 (m, 1H), 1.69-1.60 (m, 5H), 1.50-1.47 (m, 10H), 1.25-1.07 (m, 7H), 0.90-0.80 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.07, 155.43, 142.36, 125.92, 79.42,

54.30, 37.44, 33.29, 33.05, 32.65, 31.25, 28.34, 26.57, 26.26, 26.24, 17.79. HRMS calculated for $C_{18}H_{31}NO_3$ 310.23767 $[M+H]^+$; found 310.23775.

Tert-butyl ((3S,4R)-1-cyclohexyl-4-hydroxy-5-methylhex-5-en-3-yl)carbamate (**114**). This compound was prepared according to general procedure G on a 0.72 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (208 mg, 0.67 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (s, 1H), 4.93 (s, 1H), 4.83-4.73 (m, 1H), 4.16-4.04 (m, 1H), 3.73-3.67 (m, 1H), 2.77 (s, 1H), 1.75-1.60 (m, 8H), 1.53-1.42 (m, 10H), 1.33-1.08 (m, 7H), 0.93-0.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.36, 145.12, 111.79, 111.50, 79.36, 77.72, 53.39, 37.71, 33.98, 33.65, 33.21, 28.48, 26.74, 26.45, 26.40, 25.78, 19.50. HRMS calculated for $C_{18}H_{33}NO_3$ 312.25332 $[M+H]^+$; found 312.25336.

Boc-HomoCha-EK (**115**). This compound was prepared according to general procedure H on a 0.67 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (52 mg, 0.16 mmol, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (d, J = 8.0 Hz, 1H), 4.28-4.22 (m, 1H), 3.25 (d, J = 5.0 Hz, 1H), 2.88 (d, J = 5.0 Hz, 1H), 1.81-1.56 (m, 6H), 1.52 (s, 3H), 1.43 (s, 9H), 1.38-1.06 (m, 7H), 0.96-0.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.40, 155.67, 79.81, 59.13, 53.17, 52.33, 37.45, 33.49, 33.15, 33.02, 29.01, 28.43, 26.69, 26.39, 26.35, 16.82. HRMS calculated for $C_{18}H_{31}NO_4$ 326.23258 $[M+H]^+$; found 326.23271. [α]D20 +106 (C 1.0, CHCl3).

Boc-Cha(4-CF_3)-OH (116). Boc-Phe(4-CF_3)-OH (1.0 g, 3.0 mmol) was dissolved in MeOH, followed by the addition of Rh on activated alumina (5 wt.%, 300 mg). The mixture was placed under H_2 (4 bar, Parr apparatus) for 48 h. The mixture was filtrated through Celite and concentrated *in vacuo* to give the title product in a quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.09 (s, 1H), 6.78 (d, J = 7.8 Hz, 0.4 H), 5.32 (d, J = 8.6 Hz, 0.5 H), 4.47-3.97 (m, 1H), 2.10-0.91 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.55, 177.12, 177.03, 157.21, 155.85, 132.12, 131.87, 129.35, 129.12, 126.57, 126.35, 123.80, 123.57, 81.94, 80.11, 52.92, 51.87, 40.60, 40.33, 39.65, 35.27, 33.39, 33.16, 31.61, 30.63, 29.39, 29.18,

28.99, 28.76, 28.19, 28.08, 27.36, 27.26, 24.79, 24.66, 20.67, 20.42. HRMS calculated for $C_{15}H_{24}F_3NO_4$ 340.17302 $[M+H]^+$; found 340.17316.

Tert-butyl (S)-(1-(methoxy(methyl)amino)-1-oxo-3-(4-(trifluoromethyl)cyclohexyl)propan-2-yl)carbamate (**117**). This compound was prepared according to general procedure E on a 3.0 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33-5.28 (m, 1H), 4.72-4.67 (m, 1H), 3.79 (s, 3H), 3.22-3.20 (m, 3H), 2.13-0.86 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.34, 155.67, 155.56, 132.03, 131.82, 129.26, 129.05, 126.49, 126.29, 123.71, 79.31, 77.36, 61.43, 48.73, 48.10, 41.87, 41.61, 40.70, 40.44, 39.94, 35.13, 33.26, 32.00, 31.92, 30.38, 29.45, 29.04, 28.17, 26.78, 24.78, 24.62, 20.57, 20.11. HRMS calculated for $C_{17}H_{29}F_3N_2O_4$ 383.21522 $[M+H]^+$; found 383.21544.

Tert-butyl (S)-(4-methyl-3-oxo-1-(4-(trifluoromethyl)cyclohexyl)pent-4-en-2-yl)carbamate (**118**). This compound was prepared according to general procedure F on a 3.0 mmol scale. Purification by silica gel flash column chromatography (1% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (795 mg, 2.2 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (s, 1H), 5.99-5.80 (m, 1H), 5.43-5.39 (m, 1H), 5.27-4.95 (m, 1H), 2.25-1.10 (m, 24H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.11, 201.03, 155.57, 142.23, 142.16, 132.08, 129.30, 129.06, 126.53, 126.06, 79.46, 52.27, 51.76, 41.90, 41.63, 41.03, 40.45, 40.19, 36.62, 33.55, 32.12, 30.58, 29.57, 29.44, 28.19, 27.14, 24.86, 24.69, 20.83, 20.62, 17.69. HRMS calculated for $C_{18}H_{28}F_3NO_3$ 364.20940 $[M+H]^+$; found 364.20946.

Tert-butyl ((2S,3R)-3-hydroxy-4-methyl-1-(4-(trifluoromethyl)cyclohexyl)pent-4-en-2-yl)carbamate (**119**). This compound was prepared according to general procedure G on a 2.2 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09-4.85 (m, 3H), 4.19-4.03 (m, 1H), 3.81-3.76 (m, 1H), 3.24 (s, 1H), 1.78-1.13 (m, 24H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.74, 156.16, 144.89, 144.47, 132.23, 129.45, 129.23, 126.68, 126.45, 111.75, 111.42, 79.39, 77.77, 77.66, 50.70,

49.95, 40.70, 40.44, 35.19, 32.60, 30.59, 30.04, 29.52, 28.37, 28.28, 26.89, 25.07, 24.83, 20.94, 20.48, 19.35. HRMS calculated for $C_{18}H_{30}F_3NO_3$ 366.22505 $[M+H]^+$; found 366.22509.

Boc-Cha(4-CF_3)-EK (**120**). This compound was prepared according to general procedure H on a 2.2 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (191 mg, 0.50 mmol, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (t, J = 9.3 Hz, 1H), 4.41-4.19 (m, 1H), 3.28 (d, J = 4.9 Hz, 1H), 2.91 (d, J = 4.9 Hz, 1H), 2.12-1.78 (m, 4H), 1.71-1.66 (m, 3H), 1.59-1.49 (m, 7H), 1.41 (s, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.39, 209.35, 155.76, 155.70, 132.19, 131.97, 129.41, 129.20, 126.64, 126.43, 123.87, 79.91, 59.07, 52.44, 51.19, 50.66, 41.98, 41.72, 40.80, 40.53, 38.62, 33.72, 32.26, 30.31, 29.69, 28.34, 26.72, 24.95, 24.71, 20.83, 20.32, 16.75. HRMS calculated for $C_{18}H_{28}F_3NO_4$ 380.20432 $[M+H]^+$; found 380.20444. $[\alpha]_D20$ + 82 (C 1.0, $CHCl_3$).

Tert-butyl (S)-(1-(methoxy(methyl)amino)-3-(4-methylcyclohexyl)-1-oxopropan-2-yl)carbamate (**121**). Boc-Cha(4-Me)-OH was prepared according to the literature procedure[6], followed by peptide coupling according to general procedure E on a 3.1 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (1.0 g, 3.0 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25-5.21 (m, 1H), 4.89-4.53 (m, 1H), 3.79-3.75 (m, 3H), 3.21-3.19 (m, 3H), 2.10-1.13 (m, 20H), 0.97-0.83 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.76, 155.55, 155.48, 79.07, 61.38, 48.62, 48.24, 40.27, 36.88, 35.04, 34.83, 33.80, 33.66, 32.53, 32.03, 31.93, 31.05, 30.62, 30.23, 30.10, 29.75, 29.49, 28.18, 27.31, 22.47, 20.25, 14.02. HRMS calculated for $C_{17}H_{32}N_2O_4$ 329.24348 $[M+H]^+$; found 329.24354.

Tert-butyl (S)-(4-methyl-1-(4-methylcyclohexyl)-3-oxopent-4-en-2-yl)carbamate (**122**). This compound was prepared according to general procedure F on a 3.0 mmol scale. Purification by silica gel flash column chromatography (1% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (703 mg, 2.3 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (s, 1H), 5.82-5.65 (m, 1H), 5.24-5.20 (m, 1H), 5.00-4.91 (m, 1H), 1.76-1.75 (m, 3H), 1.68-.96 (m, 20H), 0.74 (dd, J = 13.0, 6.7 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.33, 155.45, 155.41, 142.21, 142.17, 125.75, 79.19, 52.21,

51.93, 41.37, 38.22, 35.06, 34.85, 33.95, 33.89, 32.55, 32.26, 31.49, 30.67, 30.50, 29.93, 29.71, 28.20, 27.49, 22.49, 20.10, 17.72. HRMS calculated for $C_{18}H_{31}NO_3$ 310.23767 $[M+H]^+$; found 310.23774.

Tert-butyl ((2S,3R)-3-hydroxy-4-methyl-1-(4-methylcyclohexyl)pent-4-en-2-yl)carbamate (**123**). This compound was prepared according to general procedure G on a 2.3 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15-4.79 (m, 2H), 4.15-4.06 (m, 1H), 3.92-3.80 (m, 1H), 2.10-0.64 (m, 27H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.07, 144.85, 144.38, 111.66, 111.07, 79.06, 77.64, 77.57, 60.39, 50.50, 50.11, 35.33, 35.03, 34.34, 33.76, 32.72, 31.50, 30.95, 30.53, 29.98, 29.52, 28.33, 27.19, 22.62, 20.09, 19.40, 14.08. HRMS calculated for $C_{18}H_{33}NO_3$ 312.25332 $[M+H]^+$; found 312.25341.

Boc-Cha(4-CH_3)-EK (**124**). This compound was prepared according to general procedure H on a 2.3 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (209 mg, 0.64 mmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03-4.83 (m, 1H), 4.37-4.27 (m, 1H), 3.30-3.29 (m, 1H), 2.90-2.88 (m, 1H), 1.95-0.70 (m, 27H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.65, 155.74, 155.70, 79.73, 59.09, 59.06, 52.43, 52.39, 51.22, 50.95, 38.93, 35.81, 35.24, 34.96, 34.22, 34.11, 32.68, 32.03, 31.72, 30.86, 30.39, 30.22, 30.05, 28.48, 28.38, 27.22, 22.67, 20.34. HRMS calculated for $C_{18}H_{31}NO_4$ 326.23258 [M+H]+; found 326.23272. $[\alpha]_D20$ +103 (C 1.0, $CHCl_3$).

Tert-butyl (S)-(1-(methoxy(methyl)amino)-3-(4-methoxycyclohexyl)-1-oxopropan-2-yl)carbamate (**125**). Boc-Cha(4-OMe)-OH was prepared according to the literature procedures[10] followed by peptide coupling according to general procedure E on a 2.0 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (449 mg, 1.3 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31-5.08 (m, 1H), 4.74 (s, 1H), 3.78 (s, 3H), 3.39 (s, 1H), 3.33-3.29 (m, 3H), 3.19 (s, 3H), 2.09-1.55 (m, 5H), 1.49-1.24 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.76, 173.68, 155.54, 155.48, 79.26, 79.12, 75.26, 61.35, 55.34, 48.35, 48.25, 39.60, 39.21, 33.32,

32.64, 31.95, 31.67, 31.53, 31.33, 28.75, 28.60, 28.17, 27.84, 25.82. HRMS calculated for $C_{17}H_{32}N_2O_5$ 345.23840 $[M+H]^+$; found 345.23842.

Tert-butyl (S)-(1-(4-methoxycyclohexyl)-4-methyl-3-oxopent-4-en-2-yl)carbamate (**126**). This compound was prepared according to general procedure F on a 1.3 mmol scale. Purification by silica gel flash column chromatography (1% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (217 mg, 0.67 mmol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 1H), 5.88 (d, J = 1.8 Hz, 1H), 5.27 (d, J = 8.9 Hz, 1H), 5.13-5.03 (m, 1H), 3.42-3.37 (m, 1H), 3.29 (s, 3H), 1.93-1.79 (m, 5H), 1.53-1.24 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.41, 155.57, 142.13, 126.01, 79.43, 75.23, 55.52, 52.04, 40.74, 33.10, 29.65, 28.94, 28.82, 28.30, 27.98, 26.11, 17.81. HRMS calculated for $C_{18}H_{31}NO_4$ 326.23258 $[M+H]^+$; found 326.23279.

Tert-butyl ((2S,3R)-3-hydroxy-1-(4-methoxycyclohexyl)-4-methylpent-4-en-2-yl)carbamate (**127**). This compound was prepared according to general procedure G on a 0.67 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (s, 1H), 4.94-4.86 (m, 2H), 4.14-4.11 (m, 1H), 3.88-3.83 (m, 1H), 3.40-3.38 (m, 1H), 3.28 (s, 3H), 1.90-1.77 (m, 2H), 1.63-1.55 (m, 1H), 1.50-1.26 (m, 17H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.10, 144.90, 111.18, 79.24, 77.64, 75.71, 55.54, 50.20, 34.48, 32.85, 29.14, 28.74, 28.44, 28.36, 26.04, 19.51. HRMS calculated for $C_{18}H_{33}NO_4$ 328.24824 $[M+H]^+$; found 328.24846.

Boc-Cha(4-OMe)-EK (**128**). This compound was prepared according to general procedure H on a 0.67 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (56 mg, 0.16 mmol, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (d, J = 8.9 Hz, 1H), 4.36-4.26 (m, 1H), 3.43-3.36 (m, 1H), 3.30-3.29 (m, 3H), 3.27 (d, J = 5.0 Hz, 1H), 2.88 (d, J = 5.1 Hz, 1H), 1.94-1.79 (m, 2H), 1.68-1.55 (m, 2H), 1.46-1.23 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.55, 155.63, 79.72, 58.94, 55.50, 52.29, 50.92, 37.99, 33.24, 29.67, 29.16, 28.43,

28.30, 28.06, 25.87, 16.76. HRMS calculated for $C_{18}H_{31}NO_5$ 342.22750 $[M+H]^+$; found 342.22755. $[\alpha]_D20$ +89 (C=1.0, $CHCl_3$).

Tert-butyl (S)-3-(decahydronaphthalen-2-yl)-1-(methoxy(methyl) amino)-1-oxopropan-2-ylcarbamate (**129**). Boc-2-DecAla-OH was prepared according to the literature procedure[6], followed by peptide coupling according to general procedure E on a 1.5 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (442 mg, 1.2 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (d, J = 9.4 Hz, 1H), 4.75 (d, J = 9.4 Hz, 1H), 3.79 (s, 3H), 3.20 (s, 3H), 1.87-0.85 (m, 28H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.81, 155.51, 79.13, 77.36, 61.42, 48.21, 40.63, 40.47, 35.88, 35.60, 34.72, 33.16, 32.02, 31.96, 31.52, 29.53, 28.20, 26.86, 26.53, 25.60, 20.79. HRMS calculated for $C_{20}H_{36}N_2O_4$ 369.27478 $[M+H]^+$; found 369.27489.

Tert-butyl ((2S)-1-(decahydronaphthalen-2-yl)-4-methyl-3-oxopent-4-en-2-yl)carbamate (**130**). This compound was prepared according to general procedure F on a 1.2 mmol scale. Purification by silica gel flash column chromatography (1% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (297 mg, 0.85 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (d, J = 7.7 Hz, 1H), 5.85-5.78 (m, 1H), 5.20-5.16 (m, 1H), 5.11-5.04 (m, 1H), 1.86 (s, 3H), 1.68-1.17 (m, 28H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.59, 155.53, 142.30, 125.98, 79.46, 52.04, 41.95, 41.69, 36.03, 35.80, 35.70, 35.10, 33.39, 32.34, 32.32, 32.16, 31.85, 28.43, 28.34, 27.01, 27.00, 26.90, 25.76, 25.74, 20.95, 20.91, 17.88. HRMS calculated for $C_{21}H_{35}NO_3$ 350.26897 $[M+H]^+$; found 350.26910.

Tert-butyl ((2S,3R)-1-(decahydronaphthalen-2-yl)-3-hydroxy-4-methylpent-4-en-2-yl)carbamate (**131**). This compound was prepared according to general procedure G on a 0.85 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (287 mg, 0.82 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (s, 1H), 4.95-4.78 (m, 2H), 4.14-4.11 (m, 1H), 3.88 (d, J = 8.9 Hz, 1H), 2.98 (s, 1H), 1.80-1.07 (m, 31H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.12, 144.96, 111.27, 111.18, 79.25, 77.80, 77.71, 50.36, 50.27, 36.17, 35.88, 34.93, 34.84,

33.76, 32.48, 32.42, 32.26, 28.80, 28.43, 28.36, 27.06, 26.73, 25.80, 25.76, 20.97, 19.56. HRMS calculated for $C_{21}H_{37}NO_3$ 352.28462 $[M+H]^+$; found 352.28476.

Boc-2-DecAla-EK (**132**). This compound was prepared according to general procedure H on a 0.82 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (76 mg, 0.21 mmol, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88-4.85 (m, 1H), 4.38-4.32 (m, 1H), 3.32-3.26 (m, 1H), 2.93-2.86 (m, 1H), 1.74-1.12 (m, 31H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.79, 209.71, 155.72, 79.81, 59.18, 59.11, 52.47, 50.92, 39.29, 39.09, 36.13, 35.87, 35.83, 35.80, 35.27, 35.21, 33.52, 32.41, 32.14, 31.43, 29.79, 28.61, 28.42, 27.12, 27.08, 26.56, 25.84, 25.80, 21.01, 16.91. HRMS calculated for $C_{12}H_{30}N_2O_4$ 366.26389 $[M+H]^+$; found 366.26393. $[\alpha]_D$20 + 90 (C 1.0, $CHCl_3$).

Tert-butyl (S)-(3-([1,1'-bi(cyclohexan)]-4-yl)-1-(methoxy(methyl)amino)-1-oxopropan-2-yl) carbamate (**133**). Boc-BiCha-OH was prepared according to the literature procedure[6], followed by peptide coupling according to general procedure E on a 1.8 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (627 mg, 1.6 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10-5.06 (m, 1H), 4.63-4.58 (m, 1H), 3.72-3.67 (m, 3H), 3.13-3.12 (m, 3H), 1.80-0.66 (m, 32H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.81, 155.64, 79.22, 61.49, 48.85, 43.20, 41.77, 40.50, 40.42, 36.21, 34.19, 34.14, 32.45, 32.04, 30.72, 30.69, 30.45, 30.39, 30.17, 29.79, 29.59, 28.28, 28.17, 26.78, 26.76, 26.69, 26.67, 25.52, 25.10. HRMS calculated for $C_{22}H_{40}N_2O_4$ 397.30608 $[M+H]^+$; found 397.30569.

Tert-butyl (S)-(1-([1,1'-bi(cyclohexan)]-4-yl)-4-methyl-3-oxopent-4-en-2-yl)carbamate (**134**). This compound was prepared according to general procedure F on a 1.6 mmol scale. Purification by silica gel flash column chromatography (1% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (491 mg, 1.3 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (s, 1H), 5.97-5.79 (m, 1H), 5.31-5.26 (m, 1H), 5.13-5.03 (m, 1H), 1.91-1.89 (m, 3H), 1.75-0.81 (m, 32H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.41, 155.51, 142.31, 142.23, 125.81, 79.31, 52.40, 52.04, 43.19, 41.60, 41.51, 40.27, 37.49,

34.51, 34.25, 32.65, 31.06, 30.61, 30.47, 30.43, 30.19, 29.80, 29.61, 28.33, 28.27, 26.79, 26.77, 26.69, 26.67, 25.58, 25.39, 17.80. HRMS calculated for $C_{23}H_{39}NO_3$ 378.30027 $[M+H]^+$; found 378.30036.

Tert-butyl ((2S,3R)-1-([1,1'-bi(cyclohexan)]-4-yl)-3-hydroxy-4-methylpent-4-en-2-yl)carbamate (**135**). This compound was prepared according to general procedure G on a 1.3 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (488 mg, 1.29 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07-5.03 (m, 1H), 5.00-4.86 (m, 2H), 4.17-4.09 (m, 1H), 3.94-3.59 (m, 1H), 1.80-0.77 (m, 36H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.15, 144.95, 144.86, 111.72, 111.15, 79.16, 77.74, 77.68, 60.43, 50.81, 43.41, 43.30, 41.64, 40.12, 34.67, 31.54, 31.11, 31.05, 30.54, 30.51, 30.26, 30.23, 30.00, 29.73, 28.39, 28.32, 27.96, 26.84, 26.74, 25.82, 25.37, 19.48. HRMS calculated for $C_{23}H_{41}NO_3$ 380.31592 $[M+H]^+$; found 380.31602.

Boc-BiCha-EK (**136**). This compound was prepared according to general procedure H on a 1.29 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (228 mg, 0.58 mmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92-4.89 (m, 1H), 4.40-4.18 (m, 1H), 3.30 (d, J = 4.9 Hz, 1H), 2.89 (d, J = 4.9 Hz, 1H), 1.89-0.82 (m, 35H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.63, 155.75, 79.71, 59.11, 59.05, 52.45, 52.38, 51.31, 50.98, 43.32, 41.75, 40.32, 38.95, 35.09, 34.72, 34.39, 32.35, 31.32, 30.87, 30.81, 30.63, 30.59, 30.32, 30.29, 29.90, 29.75, 29.64, 28.38, 27.88, 26.91, 26.83, 26.81, 26.78, 25.75, 25.26, 16.84. HRMS calculated for $C_{23}H_{39}NO_4$ 394.29519 $[M+H]^+$; found 394.29511. $[\alpha]_D$20 +83 (C 1.0, $CHCl_3$).

Tert-butyl(S)-3-(bicyclo[2.2.1]heptan-2-yl)-1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (**137**). Boc-NorAla-OH was prepared according to the literature procedure[6], followed by peptide coupling according to general procedure E on a 1.0 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (254 mg, 0.78 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17-5.09 (m, 1H), 4.75-4.54 (m, 1H), 3.79 (s, 3H), 3.20 (s, 3H), 2.27-1.98 (m, 2H), 1.98-1.65 (m, 2H), 1.58-1.41 (m, 13H), 1.38-1.23 (m, 3H), 1.23-1.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.57, 155.55, 79.38, 61.60, 61.60, 50.28, 50.09, 49.64, 49.00,

41.89, 40.74, 40.57, 40.04, 39.84, 39.58, 38.55, 38.44, 38.32, 37.16, 37.09, 36.32, 35.56, 35.51, 35.22, 32.13, 30.10, 29.95, 28.38, 22.74, 22.05. HRMS calculated for $C_{17}H_{30}N_2O_4$ 327.22783 $[M+H]^+$; found 327.22794.

Tert-butyl (S)-1-(bicyclo[2.2.1]heptan-2-yl)-4-methyl-3-oxopent-4-en-2-ylcarbamate (**138**). This compound was prepared according to general procedure F on a 0.78 mmol scale. Purification by silica gel flash column chromatography (1% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (183 mg, 0.60 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (d, J = 6.9 Hz, 1H), 5.88 (d, J = 5.7 Hz, 1H), 5.27-5.19 (m, 1H), 5.11-4.82 (m, 1H), 2.25-1.97 (m, 2H), 1.94-1.65 (m, 5H), 1.52-1.38 (m, 13H), 1.34-1.02 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.64, 155.49, 142.61, 126.15, 79.54, 53.73, 53.66, 53.24, 52.70, 41.89, 41.37, 41.05, 40.84, 40.74, 40.03, 40.00, 39.88, 38.72, 38.60, 38.53, 38.34, 37.26, 37.19, 37.15, 37.01, 36.80, 36.73, 36.58, 35.57, 35.29, 30.23, 30.08, 30.03, 28.67, 28.58, 28.42, 22.71, 22.51, 17.92. HRMS calculated for $C_{18}H_{29}NO_3$ 308.22202 $[M+H]^+$; found 308.22215.

Tert-butyl(2S,3R)-1-(bicyclo[2.2.1]heptan-2-yl)-3-hydroxy-4-methylpent-4-en-2-ylcarbamate (**139**). This compound was prepared according to general procedure G on a 0.60 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (170 mg, 0.55 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10-4.86 (m, 2H), 4.77-4.70 (m, 1H), 4.22-3.97 (m, 1H), 3.74-3.62 (m, 1H), 2.80-2.45 (m, 1H), 2.23-1.95 (m, 2H), 1.95-1.56 (m, 4H), 1.56-0.84 (m, 19H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.29, 145.08, 111.93, 111.43, 79.41, 78.08, 52.70, 52.52, 52.14, 42.31, 40.99, 40.24, 39.91, 39.39, 38.81, 37.29, 37.18, 36.82, 36.72, 36.61, 35.62, 35.16, 31.56, 30.73, 30.32, 30.16, 28.52, 22.93, 22.23, 19.57. HRMS calculated for $C_{18}H_{31}NO_3$ 310.23767 $[M+H]^+$; found 310.23777.

Boc-NorAla-EK (**140**). This compound was prepared according to general procedure H on a 0.55 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (48 mg, 0.15 mmol, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02-4.69 (m, 1H), 4.39-4.12 (m, 1H), 3.28 (d, J = 4.8 Hz, 1H), 2.91-2.86 (m, 1H), 2.35-2.03 (m, 2H),

1.83-0.94 (m, 23H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.64, 155.57, 79.72, 59.07, 52.53, 52.39, 51.24, 41.98, 40.82, 40.08, 39.83, 39.32, 38.63, 38.43, 37.27, 37.18, 37.08, 36.73, 36.60, 35.44, 35.21, 34.38, 30.13, 30.03, 29.83, 29.70, 28.58, 28.33, 22.73, 22.03, 16.79. HRMS calculated for $C_{18}H_{29}NO_4$ 324.21693 $[M+H]^+$; found 324.21705. $[\alpha]_D$20 +81 (C 0.3, $CHCl_3$).

(S)-(1,2,3,4-tetrahydronaphthalen-1-yl)methanol (**55i**). (S)-1,2,3,4-Tetrahydronaphthalene-1-carboxylic acid **54** (2.0 g, 11.4 mmol) was dissolved in anhydrous Et_2O and the reaction solution was cooled to 0 °C. $LiAlH_4$ (14.8 mL, 14.8 mmol, 1M solution in Et_2O, 1.3 eq.) was slowly added and the reaction was stirred at 0 °C for 2 h. The reaction was quenched with 0.1 M HCl and the mixture was filtrated. The filtrate was concentrated in vacuo and purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) gave the title compound in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-6.85 (m, 4H), 3.77-3.50 (m, 3H), 2.91-2.85 (m, 1H), 2.78-2.57 (m, 2H), 2.01-1.57 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.64, 136.70, 128.99, 128.72, 125.77, 125.36, 66.51, 60.38, 40.08, 29.51, 24.70, 19.31. HRMS calculated for $C_{11}H_{14}O$ 163.11174 $[M+H]^+$; found 163.11164.

(S)-(1,2,3,4-tetrahydronaphthalen-1-yl)methyl-4-methylbenzenesulfonate (**55ii**). Compound **55i** (1.85 g, 11.4 mmol) was dissolved in anhydrous DCM, followed by the addition of TsCl (4.3 g, 22.8 mmol, 2.0 eq.) and TEA (3.2 mL, 22.8 mmol, 2.0 eq.). After stirring at r.t. for 48 h, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc and washed with sat. aq. $NaHCO_3$ (2×) and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (3.5 g, 11.1 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 7.09-6.89 (m, 4H), 4.15-4.12 (m, 1H), 4.00 (t, J = 9.7 Hz, 1H), 3.09-3.03 (m, 1H), 2.71-2.48 (m, 2H), 2.34 (s, 3H), 1.91-1.48 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.43, 137.44, 133.87, 132.64, 129.56, 129.07, 128.51, 127.42, 126.32, 125.46, 72.79, 36.79, 28.89, 24.20, 21.14, 18.43.

(R)-2-(1,2,3,4-tetrahydronaphthalen-1-yl)acetonitrile (**55**). Compound **55ii** (3.5 g, 11.1 mmol) was dissolved in DMF, followed by the addition of NaCN (1.1 g, 22.2 mmol, 2 eq.). After refluxing overnight, the reaction mixture was diluted with EtOAc, washed with H_2O (2×), sat. aq. $NaHCO_3$ (2×) and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (1.8 g, 10.5 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-6.97 (m, 4H), 3.06-3.00 (m, 1H), 2.77-2.59 (m, 2H), 2.57-2.35 (m, 2H), 1.99-1.61 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.62, 136.23, 129.00, 127.57, 126.28, 125.58, 118.55, 34.09, 28.86, 27.67, 23.99, 19.06. HRMS calculated for $C_{12}H_{13}N$ 172.11208 $[M+H]^+$; found 172.11197.

(R)-N-methoxy-N-methyl-2-(1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (**56**). Compound **55** (1.8 g, 10.5 mmol) was dissolved in ethylene glycol, followed by the addition of KOH (4.7 mL, 84 mmol, 1 g/mL solution, 8.0 eq.). The reaction was stirred at 170 ºC overnight. The reaction mixture was poured in H_2O and the pH was adjusted to 2-3 with conc. HCl. The mixture was extracted with EtOAc (3×) and the combined organic layer was washed by H_2O (3×), brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude intermediate was directly coupled with N,O-dimethylhydroxylamine hydrochloride (1.2 eq.) according to general procedure B on a 10.5 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (1.2 g, 5.1 mmol, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.01 (m, 4H), 3.59 (s, 3H), 3.48-3.42 (m, 1H), 3.20 (s, 3H), 2.85-2.66 (m, 4H), 2.00-1.64 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.62, 139.98, 137.09, 129.15, 128.46, 125.80, 125.72, 61.15, 39.34, 33.85, 33.85, 29.58, 28.05, 19.48. HRMS calculated for $C_{14}H_{19}NO_2$ 234.14886 $[M+H]^+$; found 234.14874.

(S)-2-methyl-N-((E)-2-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)ethylidene)propane-2-sulfinamide (**59**). Compound **56** (1.2 g, 5.1 mmol) was dissolved in Et_2O and the reaction solution was cooled to 0 °C. $LiAlH_4$ (6.6 mL, 6.6 mmol, 1 M solution in Et_2O, 1.3 eq.) was slowly added and the reaction was stirred at 0 °C for 2 h. The reaction was quenched with 0.1 M HCl and the suspension was filtrated. The filtrate was concentrated *in vacuo* and co-evaporated with toluene (3×). The obtained aldehyde intermediate **57**

was dissolved in anhydrous DCM, followed by the addition of (S)-2-methylpropane-2-sulfinamide **58** (0.92 g, 7.7 mmol, 1.5 eq.) and anhydrous $CuSO_4$ (3.3 g, 20.4 mmol, 4.0 eq.). After stirring at r.t. for 48 h, the suspension solution was filtrated through Celite and concentrated *in vacuo*. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 25% EtOAc/pentane) yielded the title compound (1.2 g, 4.3 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (t, J = 4.8 Hz, 1H), 7.22-6.96 (m, 4H), 3.34-3.28 (m, 1H), 2.96-2.65 (m, 4H), 1.98-1.61 (m, 4H), 1.18 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.64, 138.95, 137.11, 129.24, 128.14, 125.94, 125.82, 56.64, 43.17, 34.97, 29.46, 28.11, 22.33, 19.76. HRMS calculated for $C_{16}H_{23}NOS$ 278.15731 $[M+H]^+$; found 278.15723.

(S)-N-((S)-1-cyano-2-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl)-2-methylpropane-2-sulfinamide (**60**). Compound **59** (1.2 g, 4.3 mmol) was dissolved in anhydrous THF and the solution was cooled to -78 °C. Et_2AlCN (6.5 mL, 6.5 mmol, 1M solution in toluene, 1.5 eq.) was added to anhydrous THF, followed by the addition of i-PrOH (1.0 mL, 12.9 mmol, 3.0 eq.). After stirring at r.t. for 15 min, this solution was slowly added to a cooled solution of compound **130** in anhydrous THF. The reaction was stirred at r.t. until TLC-MS analysis showed complete conversion of the starting material. The reaction mixture was cooled to -78 °C again and sat. aq. $NaHCO_3$ (5.5 mL) was added. The reaction mixture was allowed to warm up to r.t. and the suspension solution was filtrated. The filtrate was concentrated *in vacuo* and purification by silica gel flash column chromatography (5% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound(1.1 g, 3.6 mmol, 84%) as a single diastereoisomer (de > 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-6.92 (m, 4H), 4.48 (d, J = 8.5 Hz, 1H), 4.31-4.25 (m, 1H), 3.13-3.07 (m, 1H), 2.85-2.67 (m, 2H), 2.30-2.23 (m, 1H), 2.16-2.01 (m, 1H), 1.99-1.59 (m, 4H), 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.57, 136.89, 129.43, 128.35, 126.23, 125.86, 119.47, 57.06, 44.91, 41.94, 34.11, 29.09, 27.26, 22.54, 19.21. HRMS calculated for $C_{17}H_{24}N_2OS$ 305.16821 $[M+H]^+$; found 305.16827.

Boc-1-(R)-TetraNal-OH (**61**). Compound **60** (1.1 g, 3.6 mmol) was dissolved in 6M HCl and refluxed for 48 h. The mixture was co-evaporated with toluene (3×) to give the unprotected amino acid as the HCl salt. Subsequently, the amino acid was dissolved in THF/H2O (1:1, v/v), followed by the addition

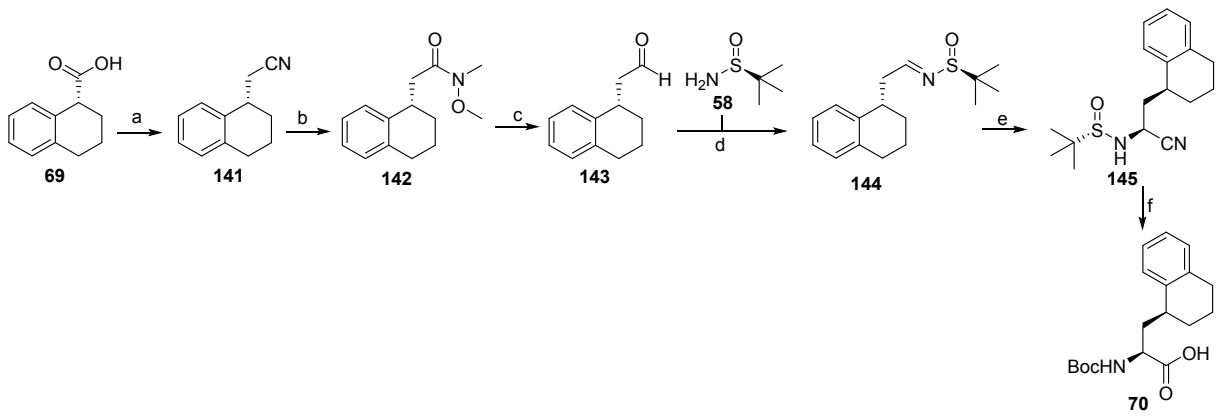
of Boc_2O (1.2 g, 5.4 mmol, 1.5 eq.) and TEA (2.0 mL, 14.4 mmol, 4 eq.). After stirring overnight, the mixture was concentrated *in vacuo* and the residue dissolved in EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane with 0.1% acetic acid) yielded the title compound (670 mg, 2.1 mmol, 58 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.46 (s, 1H), 7.16-7.01 (m, 4H), 5.08 (d, J = 8.4 Hz, 1H), 4.46-4.24 (m, 1H), 3.12-2.88 (m, 1H), 2.88-2.61 (m, 2H), 2.24-2.17 (m, 1H), 2.04-1.68 (m, 5H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.91, 177.20, 155.55, 155.51, 139.90, 137.07, 129.35, 128.77, 126.01, 125.86, 114.20, 52.36, 40.01, 34.36, 29.81, 29.45, 28.42, 19.43. HRMS calculated for $C_{18}H_{25}NO_4$ 320.18563 $[M+H]^+$; found 320.18567.

Tert-butyl ((S)-1-(methoxy(methyl)amino)-1-oxo-3-((R)-1,2,3,4-tetrahydronaphthalen-1-yl) propan-2-yl)carbamate (**62**). This compound was prepared according to general procedure E on a 1.3 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (355 mg, 1.0 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 7.5 Hz, 1H), 7.17-7.00 (m, 3H), 5.24 (d, J = 9.6 Hz, 1H), 4.95-4.80 (m, 1H), 3.57 (s, 3H), 3.16 (s, 3H), 2.94-2.67 (m, 3H), 2.09-1.62 (m, 6H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.62, 155.57, 140.20, 136.63, 129.17, 129.11, 125.82, 125.56, 79.58, 61.49, 49.20, 34.33, 32.13, 29.09, 28.82, 28.40, 19.11. HRMS calculated for $C_{20}H_{30}N_2O_4$ 363.22783 $[M+H]^+$; found 363.22791.

Tert-butyl ((S)-4-methyl-3-oxo-1-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)pent-4-en-2-yl) carbamate (**63**). This compound was prepared according to general procedure F on a 1.0 mmol scale. Purification by silica gel flash column chromatography (1% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (267 mg, 0.78 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.26 (m, 1H), 7.21-6.98 (m, 3H), 5.81 (s, 1H), 5.78-5.74 (m, 1H), 5.35 (d, J = 8.8 Hz, 1H), 5.22-5.16 (m, 1H), 2.92-2.86 (m, 1H), 2.85-2.62 (m, 2H), 2.16-1.97 (m, 1H), 1.97-1.59 (m, 8H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.41, 155.47, 142.26, 140.07, 136.58, 129.29, 129.07, 126.59, 126.00, 125.79, 79.73, 52.64, 41.72, 34.18, 29.09, 28.76, 28.41, 19.06, 17.83. HRMS calculated for $C_{21}H_{29}NO_3$ 344.22202 [M+H]+; found 344.22205.

Tert-butyl ((2S,3R)-3-hydroxy-4-methyl-1-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)pent-4-en-2-yl)-carbamate (**64**). This compound was prepared according to general procedure G on a 0.78 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (158 mg, 0.46 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-6.97 (m, 4H), 5.02 (s, 1H), 4.98-4.77 (m, 2H), 4.14 (s, 1H), 4.02-3.94 (m, 1H), 2.93-2.80 (m, 1H), 2.80-2.68 (m, 2H), 2.61-2.51 (m, 1H), 1.95-1.67 (m, 6H), 1.62 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.14, 144.95, 140.71, 136.70, 129.28, 128.86, 125.80, 125.63, 111.57, 79.54, 77.84, 51.68, 36.11, 34.98, 29.26, 29.09, 28.51, 19.37. HRMS calculated for $C_{21}H_{31}NO_3$ 346.23767 $[M+H]^+$; found 346.23772.

Boc-1-(R)-TetraNal-EK (**65**). This compound was prepared according to general procedure H on a 0.46 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (53 mg, 0.15 mmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.02 (m, 4H), 4.96 (d, J = 9.0 Hz, 1H), 4.49-4.44 (m, 1H), 3.28 (d, J = 5.0 Hz, 1H), 2.99-2.89 (m, 1H), 2.85 (d, J = 5.0 Hz, 1H), 2.81-2.65 (m, 2H), 2.11-1.69 (m, 6H), 1.50 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.84, 155.50, 140.00, 136.97, 129.31, 128.83, 126.05, 125.88, 79.99, 59.12, 52.34, 51.92, 39.38, 35.16, 29.41, 28.60, 28.44, 19.49, 16.76. HRMS calculated for $C_{21}H_{29}NO_4$ 360.21693 $[M+H]^+$; found 360.21690. $[\alpha]_D$20 + 78(C 1.0, $CHCl_3$).



Scheme S3. Synthesis of compound **70**. Reagents and conditions: (a) i) $LiAlH_4/Et_2O$; ii)TsCl/TEA/DCM; iii) NaCN/DMF; (b) i) KOH/ethylene glycol; ii) N,O-dimethylhydroxylamine hydrochloride, HCTU/DiPEA/DCM; (c) $LiAlH_4/Et_2O$; d) **58**/$CuSO_4$/DCM; (e) Et_2AlCN/i-PrOH/THF; (f) i) 6 M HCl, reflux; ii) Boc_2O/TEA/THF/H2O.

(R)-(1,2,3,4-tetrahydronaphthalen-1-yl)methanol (**141i**). This compound was obtained using the same procedures as described above for the preparation of compound **55i** on a 11.4 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (1.8 g, 11.1 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.09 (m, 1H), 7.09-6.94 (m, 3H), 3.72-3.68 (m, 1H), 3.67-3.57 (m, 2H), 2.91-2.85 (m, 1H), 2.68 (t, J = 5.6 Hz, 2H), 2.00-1.57 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.66, 136.71, 129.00, 128.73, 125.78, 125.37, 66.52, 40.09, 29.52, 24.71, 19.31. HRMS calculated for $C_{11}H_{14}O$ 163.11174 $[M+H]^+$; found 163.11152.

(R)-(1,2,3,4-tetrahydronaphthalen-1-yl)methyl 4-methylbenzenesulfonate (**141ii**). This compound was obtained using the same procedures as described above for the preparation of compound **55ii** on a 11.1 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (3.2 g, 10.1 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.67 (m, 2H), 7.27 (d, J = 8.1 Hz, 2H), 7.10-6.91 (m, 4H), 4.17-4.13 (m, 1H), 4.01 (t, J = 9.7 Hz, 1H), 3.12-3.05 (m, 1H), 2.72-2.58 (m, 2H), 2.37 (s, 3H), 1.90-1.49 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.59, 137.63, 133.99, 132.70, 129.68, 129.21, 128.69, 127.58, 126.46, 125.58, 72.94, 36.92, 29.03, 24.30, 21.34, 18.52.

(S)-2-(1,2,3,4-tetrahydronaphthalen-1-yl)acetonitrile (**141**). This compound was obtained using the same procedures as described above for the preparation of compound **55** on a 10.1 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (1.7 g, 9.9 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-6.94 (m, 4H), 3.08-3.02 (m, 1H), 2.77-2.61 (m, 2H), 2.61-2.36 (m, 2H), 2.02-1.64 (m, 4H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 136.70, 136.30, 129.08, 127.63, 126.36, 125.66, 118.59, 34.19, 28.93, 27.75, 24.09, 19.13. HRMS calculated for $C_{12}H_{13}N$ 172.11208 $[M+H]^+$; found 172.11194.

(S)-N-methoxy-N-methyl-2-(1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (**142**). This compound was obtained using the same procedures as described above for the preparation of compound **56** on a 9.9 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (0.7 g, 3.0 mmol, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-6.93 (m, 4H), 3.54 (s, 3H), 3.50-3.33 (m, 1H), 3.16 (s, 3H), 2.79-2.61 (m, 4H), 1.97-1.62 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.07, 139.64, 136.68, 128.83, 128.11, 125.49, 125.41, 60.79, 39.07, 33.57, 29.28, 27.83, 19.24. HRMS calculated for $C_{14}H_{19}NO_2$ 234.14886 $[M+H]^+$; found 234.14883.

(S)-2-methyl-N-((E)-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)ethylidene)propane-2-sulfinamide (**144**). This compound was obtained using the same procedures as described above for the preparation of compound **59** on a 3.0 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 25% EtOAc/pentane) yielded the title compound (584 mg, 2.1 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.11 (m, 1H), 7.22-6.94 (m, 4H), 3.30-3.24 (m, 1H), 2.93-2.61 (m, 4H), 1.98-1.58 (m, 4H), 1.17 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.64, 138.64, 136.93, 129.16, 128.04, 125.88, 125.68, 56.43, 42.99, 34.99, 29.32, 28.13, 22.22, 19.68. HRMS calculated for $C_{16}H_{23}NOS$ 278.15731 $[M+H]^+$; found 278.15724.

(S)-N-((S)-1-cyano-2-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl)-2-methylpropane-2-sulfinamide (**145**). This compound was obtained using the same procedures as described above for the preparation of compound 60 on a 2.1 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (506 mg, 1.7 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.02 (m, 4H), 4.30 (d, J = 8.9 Hz, 1H), 4.24-4.18 (m, 1H), 3.10-3.04 (m, 1H), 2.88-2.62 (m, 2H), 2.33-2.26 (m, 1H), 2.13-2.05 (m, 1H), 1.97-1.63 (m, 4H), 1.26 (s, 9H). 13C NMR (100 MHz, CDCl3) δ 138.56, 137.04, 129.51, 128.51, 126.35, 125.97, 119.89, 57.27, 45.25, 42.03,

33.58, 29.19, 27.08, 22.65, 19.13. HRMS calculated for $C_{17}H_{24}N_2OS$ 305.16821 $[M+H]^+$; found 305.16828.

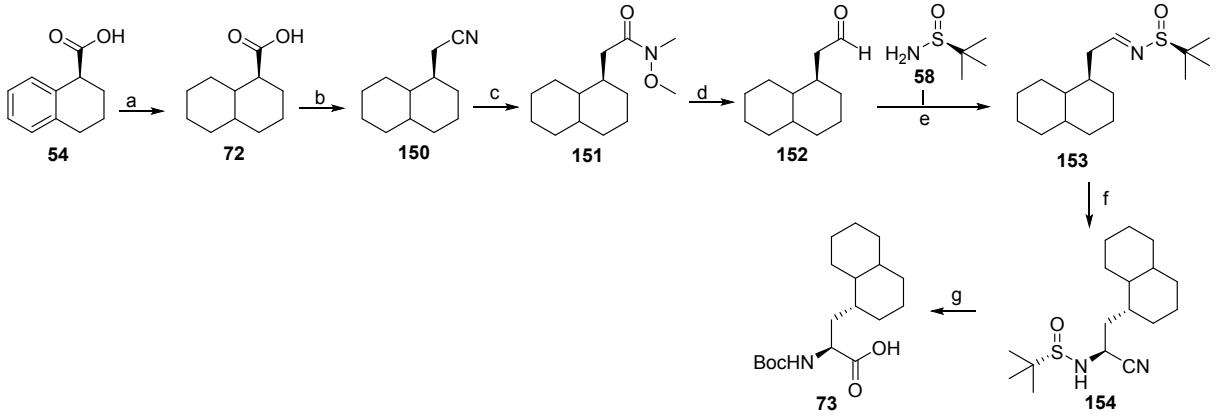
Tert-butyl ((S)-1-(methoxy(methyl)amino)-1-oxo-3-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)propan-2-yl)carbamate (**146**). Compound **70** was obtained using the same procedures as described above for the preparation of compound **61** on a 1.7 mmol scale. The crude product was directly coupled with N,O-dimethylhydroxylamine according to general procedure E. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (430 mg, 1.2 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-6.97 (m, 4H), 5.54 (d, J = 9.6 Hz, 1H), 4.83 (t, J = 10.0 Hz, 1H), 3.78 (s, 3H), 3.16 (s, 3H), 3.00-2.85 (m, 1H), 2.77-2.69 (m, 2H), 2.05-1.67 (m, 6H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.49, 155.92, 140.23, 136.94, 128.94, 128.49, 125.56, 125.49, 79.36, 61.48, 48.85, 39.79, 33.67, 32.08, 29.56, 28.25, 26.24, 19.19. HRMS calculated for $C_{20}H_{30}N_2O_4$ 363.22783 $[M+H]^+$; found 363.22782.

Tert-butyl ((S)-4-methyl-3-oxo-1-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)pent-4-en-2-yl)carbamate (**147**). This compound was prepared according to general procedure F on a 1.2 mmol scale. Purification by silica gel flash column chromatography (1% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (320 mg, 0.93 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13-6.96 (m, 4H), 6.08 (s, 1H), 5.87 (d, J = 1.8 Hz, 1H), 5.47 (d, J = 9.0 Hz, 1H), 5.25-5.19 (m, 1H), 3.07-2.92 (m, 1H), 2.81-2.67 (m, 2H), 2.09-2.01 (m, 1H), 1.99-1.59 (m, 8H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.12, 155.89, 142.21, 140.20, 137.13, 129.17, 128.58, 126.00, 125.77, 79.73, 52.45, 41.44, 34.11, 29.73, 28.37, 26.58, 19.53, 17.89. HRMS calculated for $C_{21}H_{29}NO_3$ 344.22202 $[M+H]^+$; found 344.22206.

Tert-butyl ((2S,3R)-3-hydroxy-4-methyl-1-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)pent-4-en-2-yl) carbamate (**148**). This compound was prepared according to general procedure G on a 0.93 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (221 mg, 0.64 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-6.95 (m, 4H), 5.07 (d, J = 9.5 Hz, 1H), 5.00 (s, 1H), 4.91-4.89 (m, 1H), 4.25-4.04 (m, 1H), 4.04-3.83 (m, 1H),

2.92-2.59 (m, 4H), 1.99-1.56 (m, 9H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.27, 144.80, 141.23, 137.27, 129.10, 128.68, 125.67, 125.50, 112.40, 111.39, 79.51, 77.81, 50.44, 35.43, 33.75, 29.82, 28.49, 26.77, 19.53, 19.49. HRMS calculated for $C_{21}H_{31}NO_3$ 346.23767 $[M+H]^+$; found 346.23773.

Boc-1-(S)-TetraNal-EK (**149**). This compound was prepared according to general procedure H on a 0.64 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (50 mg, 0.14 mmol, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-6.93 (m, 4H), 4.99 (d, J = 9.2 Hz, 1H), 4.41-4.35 (m, 1H), 3.21 (d, J = 5.0 Hz, 1H), 2.90-2.82 (m, 2H), 2.75-2.55 (m, 2H), 2.03-1.61 (m, 6H), 1.40 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.23, 156.01, 140.19, 137.48, 129.39, 128.73, 125.95, 125.83, 80.09, 59.17, 52.59, 51.41, 38.79, 34.16, 29.72, 28.45, 26.02, 19.13, 16.87. HRMS calculated for $C_{21}H_{29}NO_4$ 360.21693 $[M+H]^+$; found 360.21695. $[\alpha]_D20$ +116 (C 1.0, $CHCl_3$).



Scheme S4. Synthesis of compound **73**. Reagents and conditions: (a) PtO_2/AcOH, 4 bar H_2; (b) i) $LiAlH_4/Et_2O$; ii) TsCl/TEA/DCM; iii) NaCN/DMF; (c) i) KOH/ethylene glycol; ii) N,O-dimethylhydroxylamine hydrochloride, HCTU/DiPEA/DCM; (d) $LiAlH_4/Et_2O$; (e) **58**/$CuSO_4$/DCM; (f) Et_2AlCN/i-PrOH/THF; (g) i) 6 M HCl, reflux; ii) Boc_2O/TEA/THF/H_2O.

(1S)-decahydronaphthalene-1-carboxylic acid (**72**). (S)-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid **54** (2 g, 11.4 mmol) was dissolved in AcOH, followed by the addition of PtO_2 (130 mg). The mixture was placed under H_2 (4 bar, Parr apparatus) for 48 h. The mixture was filtrated through Celite

and concentrated *in vacuo* to give the title product in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.12 (s, 1H), 2.50-2.45 (m, 1H), 2.18-2.12 (m, 1H), 1.85-1.16 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.96, 47.44, 38.58, 36.79, 32.33, 26.51, 25.48, 24.88, 21.85, 21.48, 20.80. HRMS calculated for $C_{11}H_{18}O_2$ 183.13796 $[M+H]^+$; found 183.13792.

((1S)-decahydronaphthalen-1-yl)methanol (150i). This compound was obtained using the same procedures as described above for the preparation of compound 55i on a 11.4 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (1.1 g, 6.5 mmol, 57%). 1H NMR (400 MHz, CDCl3) δ 3.51-3.36 (m, 2H), 3.14 (s, 1H), 1.86-0.97 (m, 17H). 13C NMR (100 MHz, CDCl3) δ 65.50, 44.18, 37.54, 37.10, 32.61, 26.71, 26.40, 25.81, 23.82, 21.27, 20.05. HRMS calculated for C11H20O 169.15869 [M+H]+; found 169.15840.

((1S)-decahydronaphthalen-1-yl)methyl 4-methylbenzenesulfonate (**150ii**). This compound was obtained using the same procedures as described above for the preparation of compound **55i** on a 6.5 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (2.0 g, 6.2 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.72 (m, 2H), 7.34 (d, J = 8.2 Hz, 2H), 3.92-3.76 (m, 2H), 2.44 (s, 3H), 1.85-0.94 (m, 17H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.61, 133.01, 129.75, 127.77, 73.05, 40.76, 36.96, 36.56, 32.28, 26.37, 25.88, 25.26, 23.17, 21.55, 20.99, 19.73. HRMS calculated for $C_{18}H_{26}O_3S$ 323.16754 $[M+H]^+$; found 323.16807.

2-((1R)-decahydronaphthalen-1-yl)acetonitrile (**150**). This compound was obtained using the same procedures as described above for the preparation of compound **55** on a 6.2 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (1.0 g, 5.6 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44-0.31 (m, 19H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.07, 39.27, 38.67, 36.89, 32.06, 26.50, 26.23, 25.97, 24.66, 21.47, 20.85, 19.34. HRMS calculated for $C_{12}H_{19}N$ 178.15903 $[M+H]^+$; found 178.15893.

2-((1R)-decahydronaphthalen-1-yl)-N-methoxy-N-methylacetamide (**151**). This compound was obtained using the same procedures as described above for the preparation of compound 56 on a 5.6 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (1.3 g, 5.4 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.18 (s, 3H), 2.35-2.24 (m, 2H), 2.07-1.98 (m, 1H), 1.79-1.06 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.17, 61.03, 40.28, 38.03, 37.27, 35.87, 32.42, 26.95, 26.67, 26.45, 25.10, 21.16, 20.16. HRMS calculated for $C_{14}H_{25}NO_2$ 240.19581 $[M+H]^+$; found 240.19588.

(S)-N-((E)-2-((1R)-decahydronaphthalen-1-yl)ethylidene)-2-methylpropane-2-sulfinamide (**153**). This compound was obtained using the same procedures as described above for the preparation of compound **59** on a 5.4 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 25% EtOAc/pentane) yielded the title compound (1.4 g, 4.9 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, J = 6.0, 4.7 Hz, 1H), 2.54-2.23 (m, 2H), 1.97-1.88 (m, 1H), 1.81-1.03 (m, 25H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.82, 56.47, 40.60, 40.03, 39.37, 37.35, 32.50, 27.20, 26.62, 26.55, 25.20, 22.39, 21.16, 19.76. HRMS calculated for $C_{16}H_{29}NOS$ 284.20426 $[M+H]^+$; found 284.20438.

(S)-N-((S)-1-cyano-2-((1R)-decahydronaphthalen-1-yl)ethyl)-2-methylpropane-2-sulfinamide (**154**). This compound was obtained using the same procedures as described above for the preparation of compound **131** on a 4.9 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (914 mg, 3.0 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (d, J = 9.0 Hz, 1H), 4.16-4.09 (m, 1H), 1.89-1.04 (m, 28H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.87, 56.87, 44.74, 39.30, 38.65, 37.42, 37.09, 32.35, 26.51, 26.44, 26.27, 25.10, 22.43, 21.03, 19.78. HRMS calculated for $C_{17}H_{30}N_2OS$ 311.21516 $[M+H]^+$; found 311.21511.

Tert-butyl ((S)-3-((1R)-decahydronaphthalen-1-yl)-1-(methoxy(methyl)amino)-1-oxopropan-2-yl)-carbamate (**155**). This compound was obtained using the same procedures as described above for the preparation of compound **146** on a 3.0 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (728 mg, 2.0

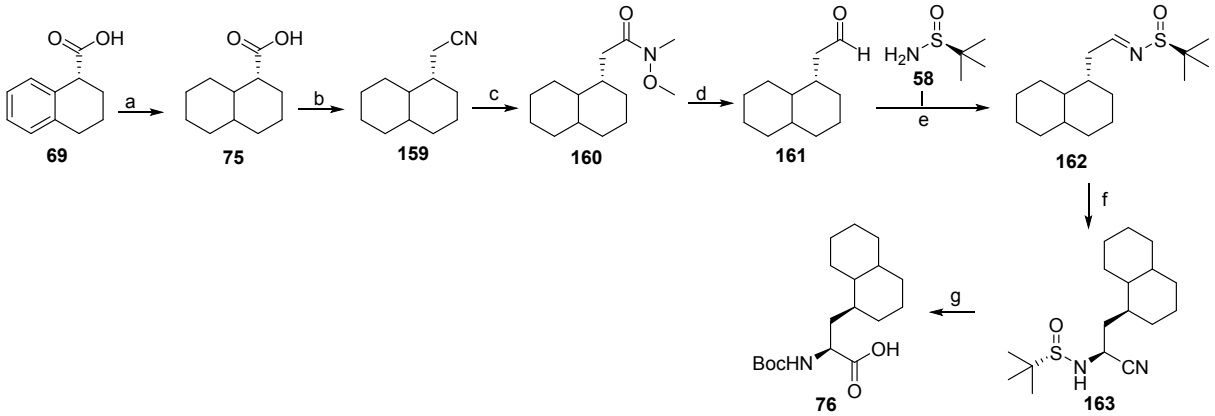
mmol, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (d, J = 9.6 Hz, 1H), 4.70-4.58 (m, 1H), 3.77 (s, 3H), 3.18 (s, 3H), 1.79-1.08 (m, 28H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.95, 155.70, 79.39, 61.58, 60.36, 48.37, 38.35, 37.70, 37.29, 36.08, 32.54, 28.33, 28.22, 27.87, 26.74, 25.39, 21.38, 19.39. HRMS calculated for $C_{20}H_{36}N_2O_4$ 369.27478 $[M+H]^+$; found 369.27527.

Tert-butyl ((S)-1-((1R)-decahydronaphthalen-1-yl)-4-methyl-3-oxopent-4-en-2-yl)carbamate (**156**). This compound was prepared according to general procedure F on a 2.0 mmol scale. Purification by silica gel flash column chromatography (1% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (244 mg, 0.7 mmol, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 1H), 5.87 (d, J = 1.8 Hz, 1H), 5.19 (d, J = 8.8 Hz, 1H), 5.07-5.01 (m, 1H), 1.80-1.49 (m, 11H), 1.44 (s, 11H), 1.31-1.20 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.04, 155.54, 142.73, 125.77, 79.53, 38.86, 38.20, 37.42, 37.25, 32.54, 28.36, 27.89, 26.80, 26.73, 25.33, 21.37, 20.00, 17.96. HRMS calculated for $C_{21}H_{35}NO_3$ 350.26897 $[M+H]^+$; found 350.26907. $[\alpha]_D$20 +53 (C 1.0, $CHCl_3$).

Tert-butyl ((2S,3R)-1-((1R)-decahydronaphthalen-1-yl)-3-hydroxy-4-methylpent-4-en-2-yl)carbamate (**157**). This compound was prepared according to general procedure G on a 0.7 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) gave the title compound in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (s, 1H), 4.94 (d, J = 1.6 Hz, 1H), 4.83 (d, J = 9.2 Hz, 1H), 4.18-4.08 (m, 1H), 3.84-3.73 (m, 1H), 2.89 (s, 1H), 1.76-1.71 (m, 7H), 1.64-1.36 (m, 20H), 1.28-1.21 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.17, 145.03, 111.36, 79.30, 77.93, 60.49, 50.24, 38.13, 32.64, 31.42, 28.44, 28.39, 26.95, 26.75, 25.57, 21.46, 19.65. HRMS calculated for $C_{21}H_{37}NO_3$ 352.28462 $[M+H]^+$; found 352.28466.

Boc-1-(R)-DecAla-EK (**158**). This compound was prepared according to general procedure H on a 0.7 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (46 mg, 0.13 mmol, 19%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (d, J = 8.8 Hz, 1H), 4.32-4.26 (m, 1H), 3.31 (d, J = 5.0 Hz, 1H), 2.89 (d, J = 5.0 Hz, 1H), 1.81-1.63 (m, 5H), 1.62-1.48 (m, 9H), 1.42 (s, 11H), 1.31-1.18 (m, 6H). 13C NMR (100 MHz, $CDCl_3$) δ 210.13,

155.83, 79.88, 59.26, 52.41, 50.69, 38.11, 37.42, 34.88, 32.68, 28.43, 28.13, 26.89, 26.79, 25.48, 21.45, 19.32, 16.88. HRMS calculated for $C_{21}H_{35}NO_4$ 366.26389 $[M+H]^+$; found 366.26391. $[\alpha]_D$20 +67 (C 0.3, $CHCl_3$).



Scheme S5. Synthesis of compound **76s**. Reagents and conditions: (a) PtO_2/AcOH, 4 bar H_2; (b) i) $LiAlH_4/Et_2O$; ii) TsCl/TEA/DCM; iii) NaCN/DMF; (c) i) KOH/ethylene glycol; ii) N,O-dimethylhydroxylamine hydrochloride, HCTU/DiPEA/DCM; (d) $LiAlH_4/Et_2O$; (e) **58**/$CuSO_4$/DCM; (f) Et_2AlCN/i-PrOH/THF; (g) i) 6 M HCl, reflux; ii) Boc_2O/TEA/THF/H_2O.

(1R)-decahydronaphthalene-1-carboxylic acid (**158**). This compound was obtained using the same procedures as described above for the preparation of compound **72** on a 11.4 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52-2.46 (m, 1H), 2.18-2.11 (m, 1H), 1.85-1.17 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.08, 47.57, 38.76, 36.90, 32.45, 26.62, 25.60, 25.00, 21.99, 21.66, 20.93. HRMS calculated for $C_{11}H_{18}O_2$ 183.13796 $[M+H]^+$; found 183.13790.

((1R)-decahydronaphthalen-1-yl)methanol (**159i**). This compound was obtained using the same procedures as described above for the preparation of compound **55i** on a 11.4 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (1.2 g, 7.1 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51-3.37 (m, 2H), 2.90 (s, 1H), 1.83-0.97 (m, 17H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.59, 44.23, 37.56, 37.12, 32.63, 26.73, 26.42, 25.83, 23.84, 21.29, 20.09. HRMS calculated for $C_{11}H_{20}O$ 169.15869 $[M+H]^+$; found 169.15878.

((1R)-decahydronaphthalen-1-yl)methyl 4-methylbenzenesulfonate (**159ii**). This compound was obtained using the same procedures as described above for the preparation of compound **55ii** on a 7.1 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (2.1 g, 6.5 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 3.90-3.75 (m, 2H), 2.43 (s, 3H), 1.84-0.93 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.52, 132.92, 129.67, 127.66, 72.92, 40.67, 36.87, 36.47, 32.19, 26.28, 25.79, 25.17, 23.06, 21.42, 20.90, 19.62. HRMS calculated for $C_{18}H_{26}O_3S$ 323.16754 $[M+H]^+$; found 323.16734.

2-((1S)-decahydronaphthalen-1-yl)acetonitrile (**159**). This compound was obtained using the same procedures as described above for the preparation of compound **55** on a 6.5 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (1.1 g, 6.2 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (d, J = 7.7 Hz, 2H), 1.89-1.07 (m, 17H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.28, 39.39, 38.80, 37.01, 32.18, 26.65, 26.34, 26.09, 24.78, 21.64, 20.97, 19.48. HRMS calculated for $C_{12}H_{19}N$ 178.15903 $[M+H]^+$; found 178.15897.

2-((1S)-decahydronaphthalen-1-yl)-N-methoxy-N-methylacetamide (**160**). This compound was obtained using the same procedures as described above for the preparation of compound **56** on a 6.2 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (1.4 g, 5.8 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.18 (s, 3H), 2.33-2.24 (m, 2H), 2.07-1.98 (m, 1H), 1.79-1.07 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.12, 61.03, 40.28, 38.03, 37.27, 35.86, 32.42, 26.95, 26.67, 26.45, 25.10, 21.16, 20.16. HRMS calculated for $C_{14}H_{25}NO_2$ 240.19581 $[M+H]^+$; found 240.19582.

(S)-N-((E)-2-((1S)-decahydronaphthalen-1-yl)ethylidene)-2-methylpropane-2-sulfinamide (**162**). This compound was obtained using the same procedures as described above for the preparation of compound **59** on a 5.8 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 25% EtOAc/pentane) yielded the title compound (1.5 g, 5.3 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.05 (t, J = 5.2 Hz, 1H), 2.52-2.31 (m, 2H), 1.94-1.86 (m, 1H), 1.79-1.07 (m, 25H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.65, 56.43, 40.13, 39.34, 37.35, 32.49, 27.15, 26.65, 26.51, 25.16, 22.34, 21.17, 19.84. HRMS calculated for $C_{16}H_{29}NOS$ 284.20426 $[M+H]^+$; found 284.20437.

(S)-N-((S)-1-cyano-2-((1S)-decahydronaphthalen-1-yl)ethyl)-2-methylpropane-2-sulfinamide (**163**). This compound was obtained using the same procedures as described above for the preparation of compound **60** on a 5.3 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (1.0 g, 3.2 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (d, J = 8.7 Hz, 1H), 4.17-4.07 (m, 1H), 1.90-1.04 (m, 28H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.86, 56.92, 44.32, 39.20, 38.58, 37.39, 37.12, 32.32, 26.55, 26.35, 26.26, 25.17, 22.47, 21.05, 19.70. HRMS calculated for $C_{17}H_{30}N_2OS$ 311.21516 $[M+H]^+$; found 311.21509.

Tert-butyl ((S)-3-((1S)-decahydronaphthalen-1-yl)-1-(methoxy(methyl)amino)-1-oxopropan-2-yl)-carbamate (**164**). This compound was obtained using the same procedures as described above for the preparation of compound **146** on a 3.2 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (934 mg, 2.5 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (d, J = 9.5 Hz, 1H), 4.71-4.66 (m, 1H), 3.77 (s, 3H), 3.19 (s, 3H), 1.80-1.08 (m, 28H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.11, 155.82, 79.37, 61.55, 48.76, 41.83, 37.82, 37.77, 37.61, 32.57, 28.34, 28.24, 26.85, 26.62, 25.81, 25.44, 21.29, 20.24. HRMS calculated for $C_{20}H_{36}N_2O_4$ 369.27478 $[M+H]^+$; found 369.27509.

Tert-butyl ((S)-1-((1S)-decahydronaphthalen-1-yl)-4-methyl-3-oxopent-4-en-2-yl)carbamate (**165**). This compound was prepared according to general procedure F on a 2.5 mmol scale. Purification by silica gel flash column chromatography (1% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (639 mg, 1.8 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 1H), 5.87 (d, J = 1.8 Hz, 1H), 5.30 (d, J = 9.1 Hz, 1H), 5.15-5.04 (m, 1H), 1.90 (s, 3H), 1.83-1.00 (m, 28H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.45, 155.58, 142.09, 125.93, 79.25, 52.18, 41.71, 38.82, 38.00, 37.55, 32.47, 28.22, 26.74,

26.53, 25.88, 25.31, 21.19, 20.14, 17.74. HRMS calculated for $C_{21}H_{35}NO_3$ 350.26897 $[M+H]^+$; found 350.26903. $[\alpha]_D20$ +75 (C 1.0, $CHCl_3$).

Tert-butyl ((2S,3R)-1-((1S,4aS,8aS)-decahydronaphthalen-1-yl)-3-hydroxy-4-methylpent-4-en-2-yl)-carbamate (**166**). This compound was prepared according to general procedure G on a 1.4 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) gave the title compound in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (s, 1H), 4.91 (s, 1H), 4.86 (d, J = 8.0 Hz, 1H), 4.17-4.08 (m, 1H), 3.84-3.78 (m, 1H), 3.01 (s, 1H), 1.77-1.73 (m, 5H), 1.65-1.08 (m, 26H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.25, 144.96, 111.20, 79.24, 77.81, 50.72, 42.33, 37.90, 37.81, 32.80, 32.66, 28.42, 26.96, 26.74, 25.90, 25.55, 21.39, 20.37, 19.51. HRMS calculated for $C_{21}H_{37}NO_3$ 352.28462 $[M+H]^+$; found 352.28465.

Boc-1-(S)-DecAla-EK (**167**). This compound was prepared according to general procedure H on a 1.4 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (17 mg, 47 μmol, 3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (d, J = 8.9 Hz, 1H), 4.30-4.25 (m, 1H), 3.28 (d, J = 5.0 Hz, 1H), 2.88 (d, J = 5.1 Hz, 1H), 1.81-1.54 (m, 9H), 1.51 (s, 4H), 1.42 (s, 9H), 1.30-1.17 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.85, 155.88, 79.91, 59.11, 52.52, 51.33, 42.19, 38.32, 37.76, 36.52, 32.67, 29.84, 28.45, 26.94, 26.63, 25.80, 25.50, 21.39, 20.38, 16.92. HRMS calculated for $C_{21}H_{35}NO_4$ 366.26389 $[M+H]^+$; found 366.26393. [α]D20 +66 (C 0.3, $CHCl_3$).

cis-cis-Decahydro-1-naphthoic acid (**79ab**). The title compound was prepared according to the literature procedure[7] on a 11.6 mmol scale in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.68 (s, 1H), 2.51-2.46 (m, 1H), 2.23-2.07 (m, 1H), 1.86-1.17 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.20, 47.55, 38.72, 36.87, 32.42, 26.59, 25.57, 24.97, 21.95, 21.61, 20.90. HRMS calculated for $C_{11}H_{18}O_2$ 183.13796 $[M+H]^+$; found 183.13790.

(1-decahydronaphthalen-1-yl)methanol (**80i**). This compound was obtained using the same procedures as described above for the preparation of compound **55i** on a 11.6 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (1.8 g, 10.7 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 1H), 3.48-3.34 (m, 2H), 1.89-0.94 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.18, 44.02, 37.44, 37.04, 32.52, 26.62, 26.32, 25.73, 23.73, 21.18, 19.93.

(1-decahydronaphthalen-1-yl)methyl 4-methylbenzenesulfonate (**80ii**). This compound was obtained using the same procedures as described above for the preparation of compound **55ii** on a 10.7 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (3.3 g, 10.2 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.72 (m, 2H), 7.39-7.30 (m, 2H), 3.92-3.69 (m, 2H), 2.44 (s, 3H), 1.84-0.91 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.59, 132.98, 129.73, 127.74, 73.02, 40.74, 36.94, 36.54, 32.26, 26.35, 25.86, 25.24, 23.14, 21.52, 20.97, 19.71. HRMS calculated for $C_{18}H_{26}O_3S$ 323.16754 $[M+H]^+$; found 323.16743.

2-((1)-decahydronaphthalen-1-yl)acetonitrile (**80**). This compound was obtained using the same procedures as described above for the preparation of compound **55** on a 10.2 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (1.5 g, 8.5 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46-0.39 (m, 19H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.12, 39.30, 38.70, 36.92, 32.09, 26.54, 26.26, 26.00, 24.70, 21.51, 20.89, 19.38. HRMS calculated for $C_{12}H_{19}N$ 178.15903 $[M+H]^+$; found 178.15895.

2-(1-decahydronaphthalen-1-yl)-N-methoxy-N-methylacetamide (**81**). This compound was obtained using the same procedures as described above for the preparation of compound **56** on a 8.5 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (1.8 g, 7.5 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.17 (s, 3H), 2.36-2.27 (m, 2H), 2.07-1.97 (m, 1H), 1.77-1.06 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.05,

60.87, 40.15, 37.89, 37.16, 32.30, 26.82, 26.55, 26.33, 24.98, 21.03, 20.03. HRMS calculated for $C_{14}H_{25}NO_2$ 240.19581 $[M+H]^+$; found 240.19578.

(S)-N-((E)-2-(1-decahydronaphthalen-1-yl)ethylidene)-2-methylpropane-2-sulfinamide (**83**). This compound was obtained using the same procedures as described above for the preparation of compound **59** on a 7.5 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 25% EtOAc/pentane) yielded the title compound (1.8 g, 6.4 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.03 (m, 1H), 2.53-2.31 (m, 2H), 1.96-1.86 (m, 1H), 1.79-1.07 (m, 25H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.78, 169.68, 56.46, 40.57, 40.50, 40.16, 40.00, 39.36, 37.38, 37.32, 32.51, 32.48, 27.18, 26.67, 26.60, 26.53, 25.18, 22.37, 21.19, 21.14, 19.87, 19.74. HRMS calculated for $C_{16}H_{29}NOS$ 284.20426 $[M+H]^+$; found 284.20440.

(S)-N-((S)-1-cyano-2-(1-decahydronaphthalen-1-yl)ethyl)-2-methylpropane-2-sulfinamide (**84**). This compound was obtained using the same procedures as described above for the preparation of compound **60** on a 6.4 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (1.5 g, 4.8 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63-4.59 (m, 1H), 4.16-4.09 (m, 1H), 1.88-1.04 (m, 28H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.87, 119.85, 56.88, 44.76, 44.28, 39.30, 39.20, 38.65, 38.57, 37.42, 37.39, 37.11, 37.09, 32.35, 32.30, 26.54, 26.51, 26.44, 26.33, 26.27, 26.24, 25.16, 25.10, 22.46, 22.44, 21.03, 19.78, 19.68. HRMS calculated for $C_{17}H_{30}N_2OS$ 311.21516 $[M+H]^+$; found 311.21511.

Tert-butyl ((S)-3-(1-decahydronaphthalen-1-yl)-1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate (**168**). This compound was obtained using the same procedures as described above for the preparation of compound **146** on a 4.8 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (1.1 g, 3.0 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (d, J = 9.3 Hz, 1H), 4.99 (s, 0.5H), 4.67 (s, 0.5H), 3.78 (s, 3H), 3.20 (s, 3H), 1.81-1.09 (m, 28H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.75, 155.54, 79.01, 77.36, 61.36, 60.10, 48.53, 48.14, 41.56, 37.58, 37.43, 37.36, 37.06, 35.70, 32.33, 28.10, 28.03, 27.64, 26.62,

26.52, 26.38, 25.56, 25.18, 21.15, 21.05, 20.75, 19.99, 19.15. HRMS calculated for $C_{20}H_{36}N_2O_4$ 369.27478 $[M+H]^+$; found 369.27525.

Tert-butyl ((S)-1-(1-decahydronaphthalen-1-yl)-4-methyl-3-oxopent-4-en-2-yl)carbamate (**85a** and **85b**). These compounds were prepared according to general procedure F on a 3.0 mmol scale. Purification by HPLC (73% MeCN-H_2O) yielded the two diasteroisomers as two separate fraction. (**85a**: 81 mg, 0.23 mmol, 8%; **85b**: 170 mg, 0.49 mmol, 16%). **85a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (s, 1H), 5.87 (s, 1H), 5.14 (d, J = 8.9 Hz, 1H), 5.06-5.01 (m, 1H), 1.90 (s, 3H), 1.79-1.07 (m, 28H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.17, 155.62, 142.80, 125.87, 79.68, 52.09, 38.97, 38.28, 37.50, 37.36, 32.61, 28.43, 27.96, 26.87, 25.40, 21.44, 20.07, 18.03. HRMS calculated for $C_{21}H_{35}NO_3$ 350.26897 $[M+H]^+$; found 350.26913. $[\alpha]_D20$ +53 (C 1, $CHCl_3$). **85b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (s, 1H), 5.87 (s, 1H), 5.16-4.97 (m, 2H), 1.90 (s, 3H), 1.84-0.98 (m, 28H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.88, 155.83, 142.33, 126.28, 79.76, 52.47, 41.96, 39.17, 38.25, 37.77, 32.70, 28.48, 26.97, 26.75, 26.15, 25.52, 21.42, 20.37, 17.99. HRMS calculated for $C_{21}H_{35}NO_3$ 350.26897 $[M+H]^+$; found 350.26904. $[\alpha]_D20$ +69 (C 1, $CHCl_3$).

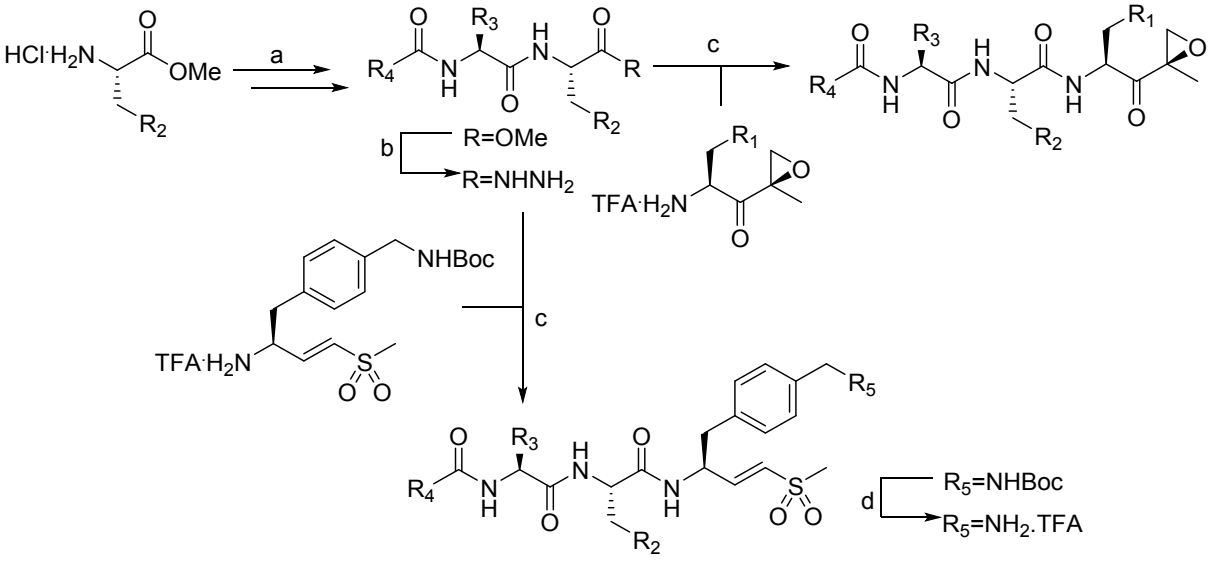
Tert-butyl ((2S,3R)-1-((1R,4aS,8aS)-decahydronaphthalen-1-yl)-3-hydroxy-4-methylpent-4-en-2-yl)-carbamate (**169**). This compound was prepared according to general procedure G on a 0.23 mmol scale startimng from compound **85a**. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) gave the title compound in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (s, 1H), 4.95 (s, 1H), 4.74 (d, J = 8.9 Hz, 1H), 4.18-4.08 (m, 1H), 3.86-3.76 (m, 1H), 2.56 (s, 1H), 1.76-1.69 (m, 7H), 1.63-1.57 (m, 2H), 1.55-1.36 (m, 18H), 1.29-1.23 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.25, 145.07, 111.45, 79.42, 78.04, 50.46, 38.18, 37.93, 37.53, 32.69, 31.55, 29.79, 28.49, 28.41, 28.41, 26.99, 26.80, 25.62, 21.50, 19.70. HRMS calculated for $C_{21}H_{37}NO_3$ 352.28462 $[M+H]^+$; found 352.28472.

Tert-butyl ((2S,3R)-1-((1S,4aR,8aR)-decahydronaphthalen-1-yl)-3-hydroxy-4-methylpent-4-en-2-yl)-carbamate (**170**). This compound was prepared according to general procedure G on a 0.49 mmol scale

with compound **85b**. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) gave the title compound in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (s, 1H), 4.92 (s, 1H), 4.83 (d, J = 9.2 Hz, 1H), 4.18-4.12 (m, 1H), 3.84-3.79 (m, 1H), 2.76 (s, 1H), 1.76-1.69 (m, 5H), 1.64-1.61 (m, 2H), 1.54-1.35 (m, 18H), 1.30-1.21 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.27, 144.99, 111.23, 79.28, 77.85, 60.50, 50.76, 42.34, 37.82, 32.85, 32.68, 28.44, 26.98, 26.75, 25.93, 25.57, 21.41, 20.39, 19.53, 14.22. HRMS calculated for $C_{21}H_{37}NO_3$ 352.28462 $[M+H]^+$; found 352.28465.

Boc-1-cis-cis-DecAla-EK (**171**). This compound was prepared according to general procedure H on a 0.23 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (19 mg, 52 μmol, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (d, J = 8.7 Hz, 1H), 4.32-4.26 (m, 1H), 3.31 (d, J = 5.0 Hz, 1H), 2.89 (d, J = 5.0 Hz, 1H), 1.81-1.49 (m, 15H), 1.42 (s, 12H), 1.25-1.16 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.15, 155.84, 79.92, 59.28, 52.43, 50.73, 38.24, 38.16, 37.45, 34.93, 32.71, 29.84, 28.45, 28.15, 26.91, 26.82, 25.51, 21.47, 19.35, 16.90. HRMS calculated for $C_{21}H_{35}NO_4$ 366.26389 $[M+H]^+$; found 366.26401. [α]D20 +68 (C 0.3, $CHCl_3$).

Boc-1-cis-cis-DecAla-EK (**172**). This compound was prepared according to general procedure H on a 0.49 mmol scale. Purification by silica gel flash column chromatography (2% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (49 mg, 0.13 mmol, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (d, J = 8.9 Hz, 1H), 4.30-4.25 (m, 1H), 3.28 (d, J = 5.0 Hz, 1H), 2.88 (d, J = 5.1 Hz, 1H), 1.81-1.48 (m, 15H), 1.42 (s, 12H), 1.28-1.22 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.80, 155.86, 79.86, 59.08, 52.49, 51.31, 42.16, 38.31, 37.75, 36.50, 32.66, 29.81, 28.43, 26.92, 26.62, 25.79, 25.48, 21.37, 20.36, 16.89. HRMS calculated for $C_{21}H_{35}NO_4$ 366.26389 $[M+H]^+$; found 366.26391. [α]D20 + 95 (C 0.3, $CHCl_3$).



Scheme S6. General scheme for the synthesis of peptide-epoxyketones/vinyl sulfone. Reagents and conditions: (a). Sequential peptide coupling and Boc removal. Peptide coupling: HCTU, DiPEA, Boc-AA-OH, DCM. Boc-removal: TFA; (b) $NH_2NH_2.H_2O$, MeOH; (c) i) tBuONO, HCl, DMF, DCM, -30oC; ii) amine, DiPEA, -30 $^oC \rightarrow$ RT; (d) TFA.

Boc-Leu-Leu-OMe (**173**). This compound was prepared according to general procedure A on a 3.0 mmol scale using Boc-Leu-OH and H-Leu-OMe as starting materials. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 10% EtOAc/pentane) yielded the title compound (1.0 g, 2.8 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (d, J = 8.3 Hz, 1H), 4.94 (d, J = 8.2 Hz, 1H), 4.64-4.58 (m, 1H), 4.17-4.05 (m, 1H), 3.73 (s, 3H), 1.68-1.44 (m, 15H), 1.00-0.81 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.29, 172.37, 155.83, 80.15, 53.02, 52.38, 52.38, 50.69, 41.59, 40.93, 28.38, 24.76, 22.96, 22.24, 21.91. HRMS calculated for $C_{18}H_{34}N_2O_5$ 359.25405 $[M+H]^+$; found 359.25405.

Benz-Leu-Leu-OMe (**174**). Compound **173** (125 mg, 0.35 mmol) was deprotected using the general procedure B, followed by the peptide coupling with benzoic acid using general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (110 mg, 0.30 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.74 (m, 2H), 7.55-7.46 (m, 1H), 7.44-7.40 (m, 2H), 6.82-6.78 (m, 2H), 4.81-4.76 (m, 1H), 4.60-4.55 (m, 1H), 3.74 (s, 3H), 1.84-1.46 (m, 6H), 0.98 (d, J = 6.0 Hz, 6H), 0.87-0.85 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.22, 172.13,

167.48, 133.93, 131.91, 128.71, 127.19, 52.42, 52.02, 50.97, 41.46, 41.31, 24.96, 24.90, 23.04, 22.84, 22.47, 21.91. HRMS calculated for $C_{20}H_{30}N_2O_4$ 363.22783 $[M+H]^+$; found 363.22795.

Benz-Leu-Leu-$NHNH_2$ (**175**). The title compound was prepared according to the general C on a 0.35 mmol scale using staring material **174** in quantitative yield.

Pyra-Leu-Leu-OMe (**176**). Compound **173** (90 mg, 0.25 mmol) was deprotected using the general procedure B, followed by the peptide coupling with benzoic acid using general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (87 mg, 0.24 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.79 (s, 1H), 8.57 (s, 1H), 8.22 (d, J = 7.8 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 4.79-4.73 (m, 1H), 4.63-4.58 (m, 1H), 3.75 (s, 3H), 1.82-1.52 (m, 6H), 1.03-0.75 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.28, 171.44, 147.68, 144.52, 144.11, 142.90, 52.45, 51.72, 50.95, 41.46, 24.90, 24.87, 23.03, 22.77, 22.21, 21.99. HRMS calculated for $C_{18}H_{28}N_4O_4$ 365.21833 $[M+H]^+$; found 365.21834.

Pyra-Leu-Leu-$NHNH_2$ (**177**). The title compound was prepared according to the general C on a 0.24 mmol scale using staring material **176** in quantitative yield.

Phnico-Leu-Leu-OMe (**178**). Compound 173 (89 mg, 0.25 mmol) was deprotected using the general procedure B, followed by the peptide coupling with 6-phenylnicotinic acid using general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (94 mg, 0.21 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.09-7.94 (m, 2H), 7.94-7.63 (m, 2H), 7.48-7.28 (m, 4H), 4.90 (s, 1H), 4.58 (s, 1H), 3.73 (s, 3H), 1.78-1.52 (m, 6H), 0.97-0.80 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.21, 159.94, 148.78, 138.31, 136.07, 129.80, 128.90, 127.53, 127.30, 119.94, 52.33, 51.04, 41.19, 41.00, 24.97, 24.88, 22.97, 22.75, 22.28, 21.88. HRMS calculated for $C_{25}H_{33}N_3O_4$ 440.25438 $[M+H]^+$; found 440.25398.

Phnico-Leu-Leu-$NHNH_2$ (**179**). The title compound was prepared according to the general C on a 0.21 mmol scale using staring material 178 in quantitative yield.

Dibenz-Leu-Leu-OMe (**180**). Compound **173** (107 mg, 0.30 mmol) was deprotected using the general procedure B, followed by the peptide coupling with 2,4-dichlorobenzoic acid using general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (122 mg, 0.28 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (t, J = 1.5 Hz, 1H), 7.32 (d, J = 1.4 Hz, 2H), 6.90 (d, J = 8.3 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 4.80-4.74 (m, 1H), 4.61-4.55 (m, 1H), 3.74 (s, 3H), 1.84-1.45 (m, 6H), 1.03-0.84 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.10, 171.36, 165.17, 135.89, 133.24, 131.53, 129.99, 129.16, 52.44, 52.36, 50.95, 41.29, 41.27, 24.88, 24.86, 22.98, 22.87, 22.39, 21.92. HRMS calculated for $C_{20}H_{28}Cl_2N_2O_4$ 431.14989 $[M+H]^+$; found 431.14969.

Dibenz-Leu-Leu-$NHNH_2$ (**181**). The title compound was prepared according to the general C on a 0.28 mmol scaleusing staring material 180 in quantitative yield.

Morph-Leu-Leu-OMe (**182**). Compound **173** (101 mg, 0.28 mmol) was deprotected using the general procedure B, followed by the peptide coupling with 2-morpholinoacetic acid using general procedure A. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (100 mg, 0.26 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 6.70-6.52 (m, 1H), 4.58-4.50 (m, 2H), 3.73 (s, 7H), 3.17-2.91 (m, 2H), 2.53 (s, 4H), 1.65-1.52 (m, 6H), 0.97-0.90 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.24, 66.99, 53.91, 52.42, 51.14, 50.86, 41.33, 40.90, 24.94, 24.93, 23.02, 22.90, 22.24, 21.92. HRMS calculated for $C_{19}H_{35}N_3O_5$ 386.26495 $[M+H]^+$; found 386.26544.

Morph-Leu-Leu-$NHNH_2$ (**183**). The title compound was prepared according to the general procedure C on a 0.26 mmol scale using staring material **182** in quantitative yield.

Methia-Leu-Leu-OMe (**184**). Compound **173** (100 mg, 0.28 mmol) was deprotected using the general procedure B, followed by the peptide coupling with 2-methylthiazole-5-carboxylic acidusing general procedure A. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (97 mg, 0.25 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.15 (d, J = 7.8 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H), 4.69 (d, J = 7.5 Hz, 1H), 4.60-4.55 (m, 1H), 3.74 (s, 3H), 2.73 (s, 3H), 1.81-1.48 (m, 6H), 0.97-0.68 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.21, 131.04, 128.93, 52.42, 52.17, 51.02, 41.36, 41.22, 24.91, 22.95, 22.82, 22.27, 21.93. HRMS calculated for $C_{18}H_{29}N_3O_4S$ 384.19515 $[M+H]^+$; found 384.19561.

Methia-Leu-Leu-$NHNH_2$ (**185**). The title compound was prepared according to the general procedure C on a 0.25 mmol scale using staring material **184** in quantitative yield.

Boc-Phe-Leu-Leu-OMe (**186**). Compound **173** (100 mg, 0.28 mmol) was deprotected using the general procedure B, followed by the peptide coupling with Boc-Phe-OH using general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (131 mg, 0.26 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.13 (m, 5H), 6.91 (d, J = 8.0 Hz, 1H), 6.86-6.70 (m, 1H), 5.29 (d, J = 8.0 Hz, 1H), 4.61-4.39 (m, 3H), 3.72 (s, 3H), 3.10-2.98 (m, 2H), 1.72-1.41 (m, 6H), 1.38 (s, 9H), 0.96-0.82 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.20, 171.57, 155.60, 136.62, 129.40, 128.64, 126.95, 80.21, 55.64, 52.31, 51.74, 50.80, 41.17, 38.09, 28.31, 24.86, 24.56, 22.86, 22.30, 21.97. HRMS calculated for $C_{27}H_{43}N_3O_6$ 507.32246 $[M+H]^+$; found 507.32211.

N_3Acetyl-Phe-Leu-Leu-OMe (**187**). Compound **186** (131 mg, 0.26 mmol) was deprotected using the general procedure B and the de-protected intermediate was dissolved in DMF, followed by the addition of DiPEA (136 µl, 0.78 mmol, 3.0 eq.) and chloroacetic anhydride (55 mg, 0.32 mmol, 1.2 eq.). The reaction was stirred at r.t. and upon the complete conversion of the deprotected intermediate, sodium azide (25 mg, 0.39 mmol, 1.5 eq.) was added. After stirring at r.t. overnight, the reaction solution was diluted with EtOAc. The organic layer was washed with H_2O (2×), 1M HCl (1×), sat. aq. $NaHCO_3$ (2×)

and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 35% EtOAc/pentane) yielded the title compound (97 mg, 0.20 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.49 (m, 2H), 7.39 (d, J = 7.6 Hz, 1H), 7.25-7.21 (s, 3H), 7.16-7.07 (m, 2H), 5.01 (d, J = 8.2 Hz, 1H), 4.70-4.50 (m, 2H), 3.85 (s, 2H), 3.73 (s, 3H), 3.10-2.91 (m, 2H), 1.78-1.40 (m, 6H), 0.95-0.86 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.16, 136.18, 129.37, 128.65, 127.13, 54.12, 52.36, 52.08, 51.85, 51.07, 41.79, 40.93, 38.97, 25.04, 24.74, 22.95, 22.90, 22.42, 22.08. HRMS calculated for $C_{24}H_{36}N_6O_5$ 489.28199 $[M+H]^+$; found 489.28172.

N_3Acetyl-Phe-Leu-Leu-$NHNH_2$ (**188**). The title compound was prepared according to the general C on a 0.20 mmol scale using starting material **187** in quantitative yield.

Fmoc-Leu-Ser(tBu)-OMe (**189**). This compound was prepared according to general procedure A on a 0.5 mmol scale using Fmoc-Leu-OH and H-Ser(tBu)-OMe as starting materials. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (229 mg, 0.44 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 7.5 Hz, 2H), 7.59-7.56 (m, 2H), 7.39-7.34 (m, 2H), 7.33-7.21 (m, 2H), 6.89 (d, J = 8.0 Hz, 1H), 5.73 (d, J = 8.5 Hz, 1H), 4.74 (d, J = 8.1 Hz, 1H), 4.41-4.29 (m, 3H), 4.20-4.17 (m, 1H), 3.81-3.78 (m, 1H), 3.71 (s, 3H), 3.55-3.52 (m, 1H), 1.81-1.48 (m, 3H), 1.09 (s, 9H), 0.97-0.93 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.76, 156.08, 143.87, 141.21, 127.65, 127.03, 125.13, 125.10, 119.93, 119.91, 73.44, 66.97, 61.77, 53.30, 52.78, 52.35, 47.08, 41.91, 27.21, 24.58, 22.96, 22.04. HRMS calculated for $C_{29}H_{38}N_2O_6$ 511.28026 $[M+H]^+$; found 511.27996.

H-Leu-Ser(tBu)-OMe (**190**). (complicated NMR due to rotamers) Compound **189** (229 mg, 0.44 mmol) was dissolved in Et_2NH and MeCN (1:1, v/v) and stirred at r.t. The reaction progress was monitored by TLC-MS analysis and upon the complete conversion of the starting material, the reaction solution was concentrated *in vacuo*. Purification by silica gel flash column chromatography (20% EtOAc/pentane → 50% EtOAc/pentane, and then 10% MeOH/ EtOAc) yielded the title compound (106 mg, 0.37 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$/MeOD) δ 4.04-4.02 (m, 1H), 3.97-3.82 (m, 1H), 3.78-3.70 (m, 3H),

3.61-3.57 (m, 1H), 3.46 (s, 1H), 1.96-1.57 (m, 3H), 1.20-1.17 (d, J = 10.4 Hz, 9H), 1.01-0.91 (m, 6H). 13C NMR (100 MHz, $CDCl_3$/MeOD) δ 176.08, 170.91, 169.56, 167.02, 73.70, 73.49, 62.52, 61.62, 55.78, 53.08, 52.52, 52.09, 44.36, 43.64, 26.91, 26.81, 24.42, 23.62, 22.83, 22.71, 21.23, 20.71. HRMS calculated for $C_{14}H_{28}N_2O_4$ 289.21218 $[M+H]^+$; found 289.21216.

N_3Phe-Leu-Ser(tBu)-OMe (**191**). This compound was prepared according to general procedure A on a 0.22 mmol scale through coupling 190 and (S)-2-azido-3-phenylpropanoic acid. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (42 mg, 0.09 mmol, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.17 (m, 5H), 6.72 (d, J = 8.5 Hz, 1H), 6.58 (d, J = 8.3 Hz, 1H), 4.68-4.65 (m, 1H), 4.25-4.22 (m, 1H), 3.84-3.81 (m, 1H), 3.74 (s, 3H), 3.56-3.53 (m, 1H), 3.35-3.30 (m, 1H), 3.09-3.04 (m, 1H), 1.64-1.32 (m, 3H), 1.14 (s, 9H), 0.91-0.89 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.38, 170.72, 168.26, 136.01, 129.69, 128.76, 127.37, 73.71, 65.52, 61.78, 52.96, 52.57, 51.56, 41.63, 38.49, 29.83, 27.40, 24.56, 22.98, 22.22. HRMS calculated for $C_{23}H_{35}N_5O_5$ 462.27110 $[M+H]^+$; found 462.27079.

N_3Phe-Leu-Ser(tBu)-$NHNH_2$ (**192**). Compound **191** (42 mg, 0.09 mmol) was dissolved in MeOH, followed by the addition of hydrazine monohydrate (132 µl, 2.7mmol, 30 eq.). The reaction mixture was refluxed until TLC-MS analysis showed complete conversion of the starting material. The reaction mixture was concentrated *in vacuo* and co-evaporated with toluene (3x) to give the product in a quantitative yield. The product was directly used in next step without any further purification.

Boc-Leu-Leu(4-F)-OMe (**193**). Boc-Leu(4-F)-OH[8] (125 mg, 0.5 mmol) was dissolved in MeOH and cooled to 0 ºC, followed by the addition of $SOCl_2$ (109 µl, 1.5mmol, 3.0 eq.). After stirring at r.t. overnight, the reaction mixture was concentrated *in vacuo* and co-evaporated with toluene (3x) to give the H-Leu(4-F)-OMe hydrochloride salt which was directly coupled with Boc-Leu-OH according to general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (139 mg, 0.37 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 5.09 (d, J = 8.6 Hz, 1H), 4.70-4.65 (m, 1H), 4.17 (d, J = 7.6 Hz, 1H), 3.73 (s,

3H), 2.27-1.95 (m, 2H), 1.66-1.63 (m, 1H), 1.44-1.42 (m, 12H), 1.37 (d, J = 6.3 Hz, 3H), 0.95-0.92 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.36, 155.63, 95.74, 94.09, 79.92, 52.95, 52.44, 49.50, 42.45, 42.23, 41.10, 28.32, 27.21, 26.79, 26.54, 24.69, 22.91, 22.14. HRMS calculated for $C_{18}H_{33}FN_2O_5$ 377.24463 $[M+H]^+$; found 377.24456.

N_3Phe-Leu-Leu(4-F)-OMe (**194**). Compound **193** (139 mg, 0.37 mmol) was deprotected using the general procedure B, followed by the peptide coupling with (S)-2-azido-3- phenylpropanoic acid using general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 25% EtOAc/pentane) yielded the title compound (118 mg, 0.26 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.20 (m, 6H), 6.82-6.80 (m, 1H), 6.70 (d, J = 8.5 Hz, 1H), 4.69-4.64 (m, 1H), 4.50-4.44 (m, 1H), 4.26-4.22 (m, 1H), 3.73 (s, 3H), 3.32-3.28 (m, 1H), 3.07-3.01 (m, 1H), 2.22-1.99 (m, 2H), 1.65-1.57 (m, 1H), 1.42 (d, J = 4.2 Hz, 3H), 1.36 (d, J = 4.1 Hz, 3H), 0.89-0.86 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.23, 171.22, 168.71, 135.98, 129.60, 128.69, 127.29, 96.03, 94.38, 65.46, 52.60, 51.33, 49.69, 42.16, 41.95, 40.64, 38.36, 27.59, 27.34, 26.37, 26.13, 24.49, 22.94, 22.13. HRMS calculated for $C_{22}H_{32}FN_5O_4$ 450.25111 $[M+H]^+$; found 450.25091.

N_3Phe-Leu-Leu(4-F)-$NHNH_2$ (**195**). The title compound was prepared according to the general C on a 0.26 mmol scale using staring material **59** in quantitative yield.

Boc-Leu-Ser(Me)-OMe (**196**). Boc-Ser(Me)-OH (219 mg, 1.0 mmol) was dissolved in MeOH and cooled to 0 ºC, followed by the addition of $SOCl_2$ (218 µl, 3.0 mmol, 3.0 eq.). After stirring at r.t. overnight, the reaction mixture was concentrated *in vacuo* and co-evaporated with toluene (3x) to give the H-Ser(Me)-OMe hydrochloride salt. The obtained building block was directly coupled with Boc-Leu-OH according to general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (175 mg, 0.51 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, J = 8.3 Hz, 1H), 5.12 (d, J = 8.5 Hz, 1H), 4.74-4.70 (m, 1H), 4.25-4.19 (m, 1H), 3.85-3.82 (m, 1H), 3.76 (s, 3H), 3.60-3.57 (m, 1H), 3.34 (s, 3H), 1.78-1.60 (m, 2H), 1.55-1.48 (m, 1H), 1.45 (s, 9H), 0.96-0.92 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.71, 170.54, 155.61,

79.92, 72.11, 59.31, 53.00, 52.57, 41.58, 28.34, 24.71, 23.02, 22.01. HRMS calculated for $C_{16}H_{30}N_2O_6$ 347.21766 $[M+H]^+$; found 347.21775.

N_3Phe-Leu-Ser(Me)-OMe (**197**). Compound **196** (175 mg, 0.51 mmol) was deprotected using the general procedure B, followed by peptide coupling with (S)-2-azido-3-phenylpropanoic acid using general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (250 mg, 0.45 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.20 (m, 5H), 7.09 (d, J = 8.3 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 4.73-4.69 (m, 1H), 4.65-4.59 (m, 1H), 4.25-4.22 (m, 1H), 3.84-3.80 (m, 1H), 3.75 (s, 3H), 3.57-3.54 (m, 1H), 3.33-3.28 (m, 4H), 3.08-3.02 (m, 1H), 1.66-1.38 (m, 3H), 0.91-0.88 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.70, 170.42, 168.44, 136.06, 129.54, 128.60, 127.19, 72.06, 65.24, 59.27, 52.54, 51.44, 41.66, 38.27, 24.49, 22.90, 22.11. HRMS calculated for $C_{20}H_{29}N_5O_5$ 420.22415 $[M+H]^+$; found 420.22390.

N_3Phe-Leu-Ser(Me)-$NHNH_2$ (**198**). The title compound was prepared according to the general C on a 0.45 mmolscale using staring material **197** in quantitative yield.

Fmoc-Leu-Thr(tBu)-OMe (**199**). This compound was prepared according to general procedure A on a 0.5 mmol scale using Fmoc-Leu-OH and H-Thr(tBu)-OMe as starting materials. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (255 mg, 0.49 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.5 Hz, 2H), 7.62-7.55 (m, 2H), 7.40-7.36 (m, 2H), 7.31-7.27 (m, 2H), 6.62 (d, J = 8.4 Hz, 1H), 5.66-5.46 (m, 1H), 4.52 (d, J = 9.1 Hz, 1H), 4.42-4.33 (m, 3H), 4.22 (d, J = 6.8 Hz, 2H), 3.69 (s, 3H), 1.81-1.48 (m, 3H), 1.16-1.09 (m, 12H), 0.99-0.90 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.01, 156.05, 143.95, 143.75, 141.26, 127.68, 127.07, 125.15, 74.17, 67.29, 67.00, 57.79, 53.46, 52.22, 47.14, 42.05, 28.29, 24.61, 22.94, 22.16, 20.92. HRMS calculated for $C_{30}H_{40}N_3O_6$ 525.29591 $[M+H]^+$; found 525.29567.

H-Leu-Thr(tBu)-OMe (**200**). This compound was obtained using the same procedures as described above for the preparation of compound **190** on a 0.49 mmol scale. Purification by silica gel flash column

chromatography (20% EtOAc/pentane → 50% EtOAc/pentane, and then 10% MeOH/EtOAc) yielded the title compound (134 mg, 0.44mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 9.6 Hz, 1H), 4.51-4.48 (m, 1H), 4.27-4.21 (m, 1H), 3.71 (s, 3H), 3.57-3.39 (m, 1H), 1.82-1.62 (m, 4H), 1.44-1.38 (m, 1H), 1.13 (s, 9H), 0.98-0.92 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.36, 171.51, 74.03, 67.51, 57.53, 53.73, 52.17, 44.27, 28.39, 24.90, 23.48, 21.43, 20.94. HRMS calculated for $C_{15}H_{30}N_2O_4$ 303.22783 $[M+H]^+$; found 303.22803.

N_3Phe-Leu-Thr(tBu)-OMe (**201**). This compound was prepared according to general procedure A on a 0.17 mmol scale though coupling **200** and (S)-2-azido-3-phenylpropanoic acid. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (72 mg, 0.15 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 6.78 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 9.1 Hz, 1H), 4.53-4.43 (m, 2H), 4.27-4.20 (m, 2H), 3.71 (s, 3H), 3.35-3.31 (m, 1H), 3.09-3.04 (m, 1H), 1.55-1.45 (m, 3H), 1.17 (d, J = 6.2 Hz, 3H), 1.12 (s, 9H), 0.91 (d, J = 6.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.01, 170.98, 168.22, 167.77, 136.02, 129.63, 128.70, 127.29, 74.30, 67.27, 66.27, 65.97, 65.42, 64.40, 57.90, 52.31, 51.67, 41.68, 38.44, 28.38, 24.52, 22.89, 22.24, 21.08. HRMS calculated for $C_{24}H_{37}N_5O_5$ 476.28675 $[M+H]^+$; found 476.28641.

N_3Phe-Leu-Thr(tBu)-$NHNH_2$ (**202**). Compound **201** (72 mg, 0.15 mmol) was dissolved in MeOH, followed by the addition of hydrazine monohydrate (220 µl, 4.5 mmol, 30 eq.). The reaction solution was refluxed until TLC-MS analysis showed the complete conversion of the starting material. The reaction mixture was concentrated in vacuo and co-evaporated with toluene (3x) to give the product in a quantitative yield. The product was directly used in next step without any further purification.

Boc-Leu-Ala(CF_3)-OMe (**203**). Boc-Ala(CF_3)-OH[9] (80 mg, 0.31 mmol) was dissolved in MeOH and cooled to 0 ºC, followed by the addition of $SOCl_2$ (68 µl, 0.93 mmol, 3.0 eq.). After stirring at r.t. overnight, the reaction mixture was concentrated *in vacuo* and co-evaporated with toluene (3x) to give the H-Ala(CF_3)-OMe hydrochloride salt which was directly coupled with Boc-Leu-OH according to general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane →

20% EtOAc/pentane) yielded the title compound (105 mg, 0.27 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 5.04-4.97 (m, 1H), 4.82-4.75 (m, 1H), 4.18 (s, 1H), 3.78-3.77 (m, 3H), 2.91-2.57 (m, 2H), 1.75-1.60 (m, 2H), 1.52-1.41 (m, 10H), 1.00-0.89 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.16, 155.84, 127.07, 124.31, 53.07, 47.38, 40.80, 40.63, 35.63, 35.34, 35.06, 34.78, 28.32, 24.78, 22.96, 21.98. HRMS calculated for $C_{16}H_{27}F_3N_2O_5$ 385.19448 $[M+H]^+$; found 385.19466.

N_3Phe-Leu-Ala(CF_3)-OMe (**204**). Compound **203** (105 mg, 0.27 mmol) was deprotected using the general procedure B, followed by the peptide coupling with (S)-2-azido-3-phenylpropanoic acid using general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (119 mg, 0.26 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (m, 6H), 6.79-6.72 (m, 1H), 4.80-4.73 (m, 1H), 4.59-4.48 (m, 1H), 4.28-4.25 (m, 1H), 3.78-3.76 (m, 3H), 3.33-3.28 (m, 1H), 3.08-3.02 (m, 1H), 2.88-2.56 (m, 2H), 1.64-1.34 (m, 3H), 0.91-0.85 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.67, 171.44, 170.05, 169.98, 168.97, 135.96, 129.63, 128.74, 127.36, 65.31, 53.17, 51.36, 47.41, 40.64, 40.42, 38.30, 35.59, 35.32, 35.02, 34.74, 24.55, 22.92, 22.13. HRMS calculated for $C_{20}H_{26}F_3N_5O_4$ 458.20097 $[M+H]^+$; found 458.20065.

N_3Phe-Leu-Ala(CF_3)-$NHNH_2$ (**205**). The title compound was prepared according to the general C on a 0.26 mmol scale using staring material **204s** in quantitative yield.

Boc-Leu-Gly-OMe (**206**). Boc-Gly-OH (350 mg, 2.0 mmol) was dissolved in MeOH and cooled to 0 ºC, followed by the addition of $SOCl_2$ (0.42 mL, 6.0 mmol, 3.0 eq.). After stirring at r.t. overnight, the reaction mixture was concentrated *in vacuo* and co-evaporated with toluene (3x) to give the H-Gly-OMe hydrochloride salt which was directly coupled with Boc-Leu-OH according to general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (302 mg, 1.96 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 5.26 (d, J = 8.5 Hz, 1H), 4.24 (s, J = 7.2, 5.4 Hz, 1H), 4.18-3.89 (m, 2H), 3.74 (s, 3H), 1.80-1.62 (m, 2H), 1.53 (dd, J = 9.4, 5.9 Hz, 1H), 1.44 (s, 9H), 1.26 (s, 1H), 1.07- 0.75 (m, 6H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 173.29, 170.23, 155.83, 79.95, 77.45, 77.13, 76.82, 52.25, 41.35, 41.09, 29.69, 28.31, 24.69, 22.97, 21.93. HRMS calculated for $C_{14}H_{26}N_2O_5$ 303.19145 $[M+H]^+$; found 303.19147.

N_3Phe-Leu-Gly-OMe (**207**). Compound **206** (297 mg, 0.98 mmol) was deprotected using the general procedure B, followed by the peptide coupling with (S)-2-azido-3- phenylpropanoic acid using general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (255 mg, 0.67 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.10 (m, 7H), 4.50 (dd, J = 8.7, 5.8 Hz, 1H), 4.25 (dd, J = 7.8, 4.2 Hz, 1H), 4.01 (t, J = 5.5 Hz, 2H), 3.74 (s, 3H), 3.31 (dd, J = 14.1, 4.2 Hz, 1H), 3.06 (dd, J = 14.1, 7.8 Hz, 1H), 1.62 (ddd, J = 13.6, 8.2, 5.7 Hz, 1H), 1.53-1.33 (m, 3H), 1.26 (s, 2H), 0.88 (dd, J = 8.4, 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.89, 170.12, 168.87, 135.96, 129.62, 128.75, 127.35, 77.48, 77.16, 76.84, 65.26, 52.50, 51.48, 41.25, 40.86, 38.34, 29.80, 24.58, 22.96, 22.16. HRMS calculated for $C_{18}H_{25}N_5O_4$ 376.19793 $[M+H]^+$; found 376.19788.

N_3Phe-Leu-Gly-$NHNH_2$ (**208**). The title compound was prepared according to the general procedure C on a 0.67 mmol scale using staring material **207** in quantitative yield.

Boc-Leu-Ala-OMe (**209**). This compound was prepared according to general procedure A on a 0.5 mmol scale. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (123.6 mg, 0.39 mmol, 78%). The analytical data was the same as reported in the literature.[11]

Pyra-Leu-Ala-OMe (**210**). Compound **209** (79 mg, 0.25 mmol) was deprotected using the general procedure B, followed by the peptide coupling with pyrazine-2-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 30% EtOAc/pentane) yielded the title compound (74 mg, 0.23 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (d, J = 1.5 Hz, 1H), 8.77 (d, J = 2.5 Hz, 1H), 8.56-8.55 (m, 1H), 8.26 (d, J = 8.7 Hz, 1H), 7.04 (d, J = 7.4 Hz, 1H), 4.81-4.75 (m, 1H), 4.61-4.54 (m, 1H), 3.76 (s, 3H), 1.89-1.65 (m, 3H), 1.39 (d, J = 4.0 Hz 3H), 0.99-

0.96 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.22, 171.36, 163.13, 147.53, 144.45, 144.14, 142.86, 52.57, 51.79, 48.21, 41.54, 24.88, 22.98, 22.14, 18.17. HRMS calculated for $C_{15}H_{22}N_4O_4$ 323.17138 $[M+H]^+$; found 323.17134.

Pyra-Leu-Ala-$NHNH_2$ (**211**). The title compound was prepared according to the general procedure C on a 0.23 mmol scale using staring material **210** in quantitative yield.

Methia-Leu-Ser(Me)-OMe (**212**). Compound **196** (295mg, 0.85mmol) was deprotected using the general procedure B, followed by the peptide coupling with 2-methylthiazole-5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (20% EtOAc/pentane → 65% EtOAc/pentane) yielded the title compound (136 mg, 0.37mmol, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H),4.77-4.71 (m, 2H), 3.85 (dd, J = 9.5, 3.1 Hz, 1H), 3.77 (s, 3H), 3.58 (dd, J = 9.5, 3.3 Hz, 1H), 3.32 (s, 3H), 2.71 (s, 3H), 1.81-1.66 (m, 3H), 0.95-0.93 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.57, 170.63, 170.50, 160.55, 143.36, 133.87, 71.95, 59.37, 52.75, 52.70, 52.16, 41.51, 24.87, 23.00, 22.03. HRMS calculated for $C_{16}H_{25}N_3O_5S$ 372.15877 $[M+H]^+$; found 372.15873.

Methia-Leu-Ser(Me)-$NHNH_2$ (**213**). The title compound was prepared according to the general C on a 0.37 mmol scale using staring material **212** in quantitative yield.

Boc-Chg-Leu-OMe (**214**). Boc-Chg-OH was coupled with H-Leu-OMe according to general procedure A on a 0.78 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (256 mg, 0.67 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 7.9 Hz, 1H), 5.43 (d, J = 9.2 Hz, 1H), 4.61-4.55 (m, 1H), 4.04-4.00 (m, 1H), 3.72 (s, 3H), 1.83-1.56 (m, 9H), 1.44 (s, 10H), 1.33-1.01 (m, 5H), 0.93-0.91 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.01, 171.77, 155.79, 79.37, 59.18, 51.98, 50.68, 40.98, 40.25, 29.36, 28.47, 28.24, 26.12, 25.86, 24.67, 22.65, 21.82. HRMS calculated for $C_{20}H_{36}N_2O5$ 385.26970 $[M+H]^+$; found 385.26996.

Methia-Chg-Leu-OMe (**215**). Compound **214** (256 mg, 0.67 mmol) was deprotected using the general procedure B, followed by the peptide coupling with 2-methylthiazole-5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (233 mg, 0.57 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.07-7.96 (m, 2H), 4.69-4.65 (m, 1H), 4.57-4.35 (m, 1H), 3.74 (s, 3H), 2.72 (s, 3H), 2.03-1.48 (m, 9H), 1.32-0.90 (m, 5H), 0.82-0.79 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.92, 171.98, 170.22, 160.66, 143.80, 133.91, 58.51, 51.96, 51.21, 40.41, 39.88, 29.49, 29.12, 26.16, 25.81, 24.77, 22.66, 21.66, 19.52. HRMS calculated for $C_{20}H_{31}N_3O_4S$ 410.21080 $[M+H]^+$; found 410.21024.

Methia-Chg-Leu-$NHNH_2$ (**216**). The title compound was prepared according to the general procedure C on a 0.57 mmol scale using staring material **215** in quantitative yield.

Boc-Cha-Leu-OMe (**217**). Boc-Cha-OH was coupled with H-Leu-OMe according to general procedure A on a 1.0 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (380 mg, 0.95 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, J = 8.1 Hz, 1H), 5.14 (d, J = 8.6 Hz, 1H), 4.63-4.57 (m, 1H), 4.23-4.17 (m, 1H), 3.72 (s, 3H), 1.79-1.53 (m, 9H), 1.44 (s, 9H), 1.30-1.09 (m, 4H), 0.99-0.81 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.15, 172.55, 155.74, 79.83, 52.29, 52.17, 50.63, 41.37, 39.70, 33.98, 33.56, 32.82, 28.29, 26.43, 26.23, 26.10, 24.71, 22.83, 21.85. HRMS calculated for $C_{21}H_{38}N_2O_5$ 399.28535 $[M+H]^+$; found 399.28477.

Methia-Cha-Leu-OMe (**218**). Compound **217** (279 mg, 0.70 mmol) was deprotected using the general procedure B, followed by the peptide coupling with 2-methylthiazole-5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (245 mg, 0.58 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 7.9 Hz, 1H), 8.20 (s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 4.87-4.81 (m, 1H), 4.57-4.52 (m, 1H), 3.73 (s, 3H), 2.71 (s, 3H), 1.72-1.54 (m, 10H), 1.49-1.34 (m, 1H), 1.21-1.07 (m, 3H), 0.95-0.74 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.13, 172.96, 170.08, 160.71, 144.02, 133.81, 51.94, 51.75, 50.90,

40.64, 39.29, 33.96, 33.29, 32.58, 26.32, 26.02, 25.95, 24.68, 22.61, 21.72, 19.43. HRMS calculated for $C_{21}H_{33}N_3O_4S$ 424.22645 $[M+H]^+$; found 424.22580.

Methia-Cha-Leu-$NHNH_2$ (**219**). The title compound was prepared according to the general procedure C on a 0.58 mmol scale using staring material **218** in quantitative yield.

Boc-HomoCha-Leu-OMe (**220**). Boc-HomoCha-OH was prepared according to the literature procedure,[6] followed by peptide coupling with H-Leu-OMe according to general procedure A on a 1.2 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (446 mg, 1.1 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 7.9 Hz, 1H), 5.59 (d, J = 8.4 Hz, 1H), 4.60-4.55 (m, 1H), 4.23-4.11 (m, 1H), 3.71 (s, 3H), 1.90-1.51 (m, 10H), 1.44 (s, 9H), 1.35-1.03 (m, 7H), 1.03-0.74 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.95, 172.39, 155.60, 79.30, 54.37, 51.85, 50.53, 40.82, 37.36, 33.11, 33.00, 32.81, 29.97, 28.14, 26.42, 26.10, 24.54, 22.61, 21.66. HRMS calculated for $C_{22}H_{40}N_2O_5$ 413.30100 $[M+H]^+$; found 413.30059.

Methia-HomoCha-Leu-OMe (**221**). Compound **220** (239 mg, 0.58 mmol) was deprotected using the general procedure B, followed by the peptide coupling with 2-methylthiazole-5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (198 mg, 0.45 mmol, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.91-7.90 (m, 1H), 7.76-7.56 (m, 1H), 4.80-4.76 (m, 1H), 4.57-4.53 (m, 1H), 3.73 (s, 3H), 2.71 (s, 3H), 1.92-1.45 (m, 10H), 1.39-0.98 (m, 6H), 0.87-0.80 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.93, 172.38, 170.26, 160.63, 143.77, 133.78, 53.88, 52.09, 50.98, 40.76, 37.46, 33.23, 33.07, 30.08, 26.52, 26.20, 24.77, 22.66, 21.76, 19.48. HRMS calculated for $C_{22}H_{35}N_3O_4S$ 438.24210 $[M+H]^+$; found 438.24170.

Methia-HomoCha-Leu-NHNH2 (**222**). The title compound was prepared according to the general C on a 0.45 mmol scale using staring material **221** in quantitative yield.

Boc-Cha(4-Me)-Leu-OMe (**223**). Boc-Cha(4-Me)-OH was prepared according to the literature procedure[6] followed by peptide coupling with H-Leu-OMe according to general procedure A on a 1.2 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (445 mg, 1.1 mmol, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18-7.15 (m, 1H), 5.49-5.45 (m, 1H), 4.62-4.57 (m, 1H), 4.31-4.17 (m, 1H), 3.72 (s, 3H), 1.73-1.54 (m, 5H), 1.44 (s, 10H), 0.95-0.82 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.91, 172.61, 155.63, 79.39, 67.61, 51.87, 50.50, 40.95, 39.62, 36.44, 34.96, 34.85, 33.59, 32.46, 30.55, 30.39, 28.88, 28.12, 24.53, 22.62, 22.46, 21.67. HRMS calculated for $C_{22}H_{40}N_2O_5$ 413.30100 $[M+H]^+$; found 413.30064.

Methia-Cha(4-Me)-Leu-OMe (**224**). Compound **223** (288 mg, 0.7 mmol) was deprotected using the general procedure B, followed by peptide coupling with 2-methylthiazole-5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (273 mg, 0.62 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 2.9 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.56-7.48 (m, 1H), 4.85-4.65 (m, 1H), 4.58-4.53 (m, 1H), 3.73 (d, J = 1.1 Hz, 3H), 2.71 (s, 3H), 1.88-1.03 (m, 14H), 0.89-0.76 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.07, 173.04, 172.87, 172.85, 170.32, 170.30, 160.79, 160.75, 143.90, 133.83, 77.48, 77.16, 76.84, 52.15, 51.85, 50.99, 40.92, 40.88, 39.51, 36.46, 35.04, 34.96, 33.89, 33.42, 32.69, 32.60, 31.55, 30.66, 30.51, 30.03, 29.04, 28.17, 24.81, 22.71, 22.63, 21.84, 20.22, 19.56. HRMS calculated for $C_{22}H_{35}N_3O_4S$ 438.24210 $[M+H]^+$; found 438.24175.

Methia-Cha(4-Me)-Leu-$NHNH_2$ (**225**). The title compound was prepared according to the general C on a 0.62 mmol scale using staring material **224** in quantitative yield.

Boc-Cha(4-OMe)-Leu-OMe (**226**). Boc-Cha(4-OMe)-OH was prepared according to the literature procedure[6] followed by peptide coupling with H-Leu-OMe according to general procedure A on a 0.9 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (365 mg, 0.85 mmol, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ

6.83 (d, J = 8.0 Hz, 1H), 5.23 (d, J = 8.7 Hz, 1H), 4.61-4.57 (m, 1H), 4.20-4.17 (m, 1H), 3.72 (s, 3H), 3.41-3.38 (m, 1H), 3.34-3.28 (m, 3H), 1.90-1.61 (m, 5H), 1.59-1.48 (m, 3H), 1.44 (s, 11H), 1.36-1.23 (m, 4H), 0.95-0.90 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.04, 172.43, 155.73, 79.76, 79.39, 75.16, 55.54, 55.41, 52.11, 50.61, 41.25, 38.81, 33.38, 32.95, 28.93, 28.78, 28.25, 27.33, 26.74, 24.67, 22.78, 21.79. HRMS calculated for $C_{22}H_{40}N_2O_6$ 429.29591 $[M+H]^+$; found 429.29573.

Methia-Cha(4-OMe)-Leu-OMe (**227**). Compound **226** (184 mg, 0.43 mmol) was deprotected using the general procedure B, followed by peptide coupling with 2-methylthiazole-5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (137 mg, 0.30 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.92-7.88 (m, 1H), 7.48-7.43 (m, 1H), 4.81-4.76 (m, 1H), 4.57-4.52 (m, 1H), 3.73 (s, 3H), 3.46-3.14 (m, 4H), 2.71 (s, 3H), 2.12-0.97 (m, 14H), 0.89-0.76 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.98, 172.94, 172.75, 172.63, 170.46, 160.76, 143.79, 133.78, 133.69, 79.38, 75.21, 55.59, 55.49, 52.23, 52.20, 51.90, 51.72, 51.00, 40.91, 38.75, 33.48, 33.00, 30.68, 28.84, 28.79, 27.36, 26.61, 24.79, 22.70, 21.83, 19.53. HRMS calculated for $C_{22}H_{35}N_3O_5S$ 454.23702 $[M+H]^+$; found 454.23677.

Methia-Cha(4-OMe)-Leu-$NHNH_2$ (**228**). The title compound was prepared according to general C on a 0.30 mmol scale using staring material **227** in quantitative yield.

Boc-1-DecAla-Leu-OMe (**229**). Boc-1-DecAla-OH was prepared according to the literature procedure[6] followed by peptide coupling with H-Leu-OMe according to general procedure A on a 0.5 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (202 mg, 0.45 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 1H), 5.10-5.00 (m, 1H), 4.71-4.47 (m, 1H), 4.21-3.99 (m, 1H), 3.72 (s, 3H), 1.96-0.61 (m, 38H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.28, 173.15, 172.93, 155.80, 79.89, 77.36, 52.22, 50.65, 47.68, 43.14, 43.01, 41.50, 37.77, 37.56, 37.41, 34.50, 34.30, 32.63, 30.23, 28.30, 26.85, 26.78, 26.70, 26.60, 26.44, 26.02,

25.95, 25.45, 24.73, 22.83, 21.93, 21.30, 20.06. HRMS calculated for $C_{25}H_{44}N_2O_5$ 453.33230 $[M+H]^+$; found 453.33210.

Methia-1-DecAla-Leu-OMe (**230**). Compound **229** (103 mg, 0.23 mmol) was deprotected using the general procedure B, followed by peptide coupling with 2-methylthiazole- 5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (55 mg, 0.12 mmol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22-8.04 (m, 1H), 7.47-7.31 (m, 1H), 7.25-6.93 (m, 1H), 4.78-4.48 (m, 2H), 3.74 (s, 3H), 2.72 (s, 3H), 1.96-0.54 (m, 28H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.19, 173.02, 172.96, 172.89, 172.49, 171.97, 170.59, 160.88, 160.78, 160.71, 160.41, 143.68, 133.79, 133.75, 125.97, 120.65, 109.43, 52.56, 52.34, 52.00, 51.67, 51.03, 47.90, 47.75, 43.11, 41.32, 41.23, 40.81, 39.70, 39.41, 38.87, 37.93, 37.86, 37.52, 37.44, 36.70, 36.16, 35.86, 34.93, 34.53, 34.29, 33.26, 32.60, 32.33, 30.28, 27.33, 26.91, 26.72, 26.62, 26.45, 25.95, 25.44, 24.87, 22.77, 21.96, 21.33, 20.08, 19.94, 19.63. HRMS calculated for $C_{25}H_{39}N_3O_4S$ 478.27340 $[M+H]^+$; found 478.27332.

Methia-1-DecAla-Leu-$NHNH_2$ (**231**). The title compound was prepared according to the general procedure C on a 0.12 mmol scale using staring material **230** in quantitative yield.

Boc-2-DecAla-Leu-OMe (**232**). Boc-2-DecAla-OH was prepared according to the literature procedure[6] followed by peptide coupling with H-Leu-OMe according to general procedure A on a 0.5 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (158 mg, 0.35 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82-6.76 (m, 1H), 5.17 (d, J = 8.3 Hz, 1H), 4.63-4.57 (m, 1H), 4.22-4.15 (m, 1H), 3.72 (s, 3H), 1.74-1.16 (m, 31H), 0.92 (d, J = 5.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.15, 172.55, 155.74, 79.82, 60.37, 52.37, 52.15, 50.63, 41.37, 39.81, 35.93, 35.79, 35.73, 34.72, 33.79, 32.92, 32.34, 32.22, 32.12, 28.28, 27.00, 26.64, 26.58, 25.70, 24.71, 22.82, 21.86, 20.89. HRMS calculated for $C_{25}H_{44}N_2O_5$ 453.33230 $[M+H]^+$; found 453.33200.

Methia-2-DecAla-Leu-OMe (**233**). Compound **232** (158 mg, 0.35 mmol) was deprotected using the general procedure B, followed by peptide coupling with 2-methylthiazole- 5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (155 mg, 0.32 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-8.15 (m, 1H), 7.99-7.94 (m, 1H), 7.56-7.50 (m, 1H), 4.82-4.75 (m, 1H), 4.58-4.53 (m, 1H), 3.73-3.72 (m, 3H), 2.71-2.70 (m, 3H), 1.80-1.09 (m, 21H), 0.91-0.82 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.06, 172.88, 170.28, 160.74, 143.90, 133.84, 52.16, 51.86, 50.98, 40.93, 39.84, 35.86, 35.70, 35.65, 34.84, 32.91, 32.28, 32.15, 32.10, 27.77, 27.16, 26.99, 26.57, 25.70, 24.79, 22.69, 21.85, 20.91, 19.53. HRMS calculated for $C_{25}H_{39}N_3O_4S$ 478.27340 $[M+H]^+$; found 478.27318.

Methia-2-DecAla-Leu-$NHNH_2$ (**234**). The title compound was prepared according to the general procedure C on a 0.32 mmol scale using staring material **233** in quantitative yield.

Boc-BiCha-Leu-OMe (**235**). Boc-BiCha-OH was prepared according to the literature procedure[6] followed by peptide coupling with H-Leu-OMe according to general procedure A on a 0.5 mmol scale. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (198 mg, 0.41 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (t, J = 7.5 Hz, 1H), 5.08 (d, J = 8.5 Hz, 1H), 4.63-4.57 (m, 1H), 4.16-4.08 (m, 1H), 3.72 (s, 3H), 1.93-0.78 (m, 41H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.18, 173.16, 172.51, 155.80, 79.95, 52.87, 52.23, 50.67, 43.32, 41.60, 41.45, 40.18, 34.32, 31.03, 30.58, 30.27, 29.90, 29.81, 29.69, 28.98, 28.32, 26.88, 26.79, 26.77, 25.66, 25.47, 24.75, 22.87, 21.89. HRMS calculated for $C_{27}H_{48}N_2O_5$ 481.36360 $[M+H]^+$; found 481.36345.

Methia-BiCha-Leu-OMe (**236**). Compound **235** (101 mg, 0.21 mmol) was deprotected using the general procedure B, followed by the peptide coupling with 2-methylthiazole-5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (65 mg, 0.13 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.11 (m, 1H), 7.51-7.48 (m, 1H), 7.23-7.17 (m, 1H), 4.77-4.68 (m, 1H), 4.59-4.53 (m, 1H), 3.74-

3.73 (m, 3H), 2.71 (s, 3H), 1.96-0.68 (m, 32H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.09, 173.06, 172.53, 172.49, 170.47, 170.45, 160.76, 160.72, 133.76, 52.30, 52.21, 51.80, 51.05, 43.31, 41.65, 41.09, 40.32, 39.74, 35.91, 34.47, 33.80, 33.13, 31.12, 30.59, 30.31, 30.29, 29.88, 29.77, 29.70, 29.08, 26.91, 26.81, 25.59, 25.45, 24.88, 22.78, 21.93, 19.65. HRMS calculated for $C_{27}H_{43}N_3O_4S$ 506.30470 $[M+H]^+$; found 506.30469.

Methia-BiCha-Leu-$NHNH_2$ (**237**). The title compound was prepared according to the general procedure C on a 0.13 mmol scale using staring material **236** in quantitative yield.

Boc-Leu-Cha-OMe (**238**). This compound was obtained using the same procedures as described above for the preparation of compound **203** on a 1.5 mmol scale using Boc-Cha-OH and Boc-Leu-OH as starting materials. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (435 mg, 1.1 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8.0 Hz, 1H), 5.40 (d, J = 8.6 Hz, 1H), 4.64-4.58 (m, 1H), 4.25-4.19 (m, 1H), 3.71 (s, 3H), 1.83-1.59 (m, 8H), 1.44 (s, 11H), 1.29-1.07 (m, 4H), 0.99-0.79 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.15, 172.52, 155.60, 79.48, 77.36, 52.75, 51.94, 49.89, 41.10, 39.57, 33.82, 33.27, 32.29, 28.19, 26.22, 25.97, 25.81, 24.48, 22.67, 22.08. HRMS calculated for $C_{21}H_{38}N_2O_5$ 399.28535 $[M+H]^+$; found 399.28479.

Methia-Leu-Cha-OMe (**239**). Compound **238** (200 mg, 0.50 mmol) was deprotected using the general procedure B, followed by peptide coupling with 2-methylthiazole-5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (207 mg, 0.49 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.41 (d, J = 7.7 Hz, 1H), 4.78-4.72 (m, 1H), 4.60-4.55 (m, 1H), 3.73 (s, 3H), 2.71 (s, 3H), 1.79-1.47 (m, 10H), 1.33-1.26 (m, 1H), 1.18-1.09 (m, 3H), 0.91-0.87 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.21, 172.44, 170.33, 160.68, 143.69, 133.82, 52.17, 50.37, 40.92, 39.39, 33.98, 33.21, 32.46, 26.29, 25.98, 25.86, 24.77, 22.80, 22.07, 19.47. HRMS calculated for $C_{21}H_{33}N_3O_4S$ 424.22645 $[M+H]^+$; found 424.22604.

Methia-Leu-Cha-$NHNH_2$ (**240**). The title compound was prepared according to the general procedure C on a 0.49 mmol scale using staring material **239** in quantitative yield.

Boc-Leu-HomoCha-OMe (**241**). This compound was obtained using the same procedures as described above for the preparation of compound **203** on a 1.2 mmol scale using Boc-HomoCha-OH and Boc-Leu-OH as starting materials. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (413 mg, 1.0 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, J = 7.8 Hz, 1H), 5.23 (d, J = 8.5 Hz, 1H), 4.56-4.51 (m, 1H), 4.22-4.16 (m, 1H), 3.73 (s, 3H), 1.89-1.81 (m, 1H), 1.73-1.61 (m, 8H), 1.44 (s, 11H), 1.29-1.09 (m, 7H), 0.95-0.92 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.78, 172.47, 155.68, 79.75, 52.93, 52.31, 52.14, 41.16, 37.27, 33.16, 33.03, 32.62, 29.64, 28.29, 26.52, 26.22, 24.63, 22.83, 22.10. HRMS calculated for $C_{22}H_{40}N_2O_5$ 413.30100 $[M+H]^+$; found 413.30056.

Methia-Leu-HomoCha-OMe (**242**). Compound **241** (207 mg, 0.5 mmol) was deprotected using the general procedure B, followed by the peptide coupling with 2-methylthiazole-5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (210 mg, 0.48 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 4.77-4.72 (m, 1H), 4.53-4.48 (m, 1H), 3.74 (s, 3H), 2.71 (s, 3H), 1.94-1.50 (m, 10H), 1.30-1.04 (m, 6H), 1.04-0.65 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.79, 172.41, 170.43, 160.69, 143.64, 133.85, 52.71, 52.24, 52.18, 41.05, 37.27, 33.10, 33.01, 32.81, 29.48, 26.52, 26.23, 24.81, 22.85, 22.10, 19.52. HRMS calculated for $C_{22}H_{35}N_3O_4S$ 438.24210 $[M+H]^+$; found 438.24181.

Methia-Leu-HomoCha-$NHNH_2$ (**243**). The title compound was prepared according to the general procedure C on a 0.48 mmol scale using staring material **106** in quantitative yield.

Boc-Leu-Cha(4-Me)-OMe (**244**). This compound was obtained using the same procedures as described above for the preparation of compound **203** on a 2.0 mmol scale using Boc-Cha(4-Me)-OH and Boc-Leu-OH as starting materials. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (410 mg, 1.0 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, J = 8.6 Hz, 1H), 5.47 (d, J = 8.7 Hz, 1H), 4.64-4.55 (m, 1H), 4.26-4.16 (m, 1H), 3.72-3.71 (m, 3H), 1.88-1.52 (m, 7H), 1.44 (s, 13H), 1.27-1.20 (m, 2H), 1.00-0.79 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.12, 172.65, 155.62, 79.44, 77.36, 52.73, 51.91, 50.26, 41.03, 34.87, 34.70, 33.64, 33.19, 32.41, 32.26, 31.05, 30.43, 30.21, 29.99, 29.06, 28.16, 27.56, 24.46, 22.64, 22.43, 22.06, 20.12. HRMS calculated for $C_{22}H_{40}N_2O_5$ 413.30100 $[M+H]^+$; found 413.30065.

Methia-Leu-Cha(4-Me)-OMe (**245**). Compound **244** (206 mg, 0.5 mmol) was deprotected using the general procedure B, followed by peptide coupling with 2-methylthiazole-5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (160 mg, 0.37 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.13 (m, 1H), 7.61-7.54 (m, 1H), 7.28-7.22 (m, 1H), 4.81-4.63 (m, 1H), 4.63-4.38 (m, 1H), 3.74-3.73 (m, 3H), 2.73-2.71 (m, 3H), 1.98-1.09 (m, 14H), 0.94-0.79 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.28, 173.25, 172.44, 172.30, 170.47, 170.45, 160.70, 143.67, 133.81, 133.80, 52.26, 52.17, 50.76, 50.50, 41.06, 40.95, 39.52, 36.39, 34.92, 34.80, 33.87, 33.23, 32.52, 32.48, 31.38, 30.57, 30.36, 30.07, 29.12, 27.71, 24.82, 22.87, 22.56, 22.15, 20.24, 19.56. HRMS calculated for $C_{22}H_{35}N_3O_4S$ 438.24210 $[M+H]^+$; found 438.24182.

Methia-Leu-Cha(4-Me)-$NHNH_2$ (**246**). The title compound was prepared according to the general procedure C on a 0.37 mmol scale using staring material **245** in quantitative yield.

Boc-Leu-Cha(4-OMe)-OMe (**247**). This compound was obtained using the same procedures as described above for the preparation of compound **203** on a 0.85 mmol scale using Boc-Cha(4-OMe)-OH and Boc-Leu-OH as starting materials. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (284 mg, 0.66 mmol, 78%). ^{1}H

NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 8.3 Hz, 1H), 5.34 (d, J = 8.3 Hz, 1H), 4.64-4.59 (m, 1H), 4.21-4.17 (m, 1H), 3.72-3.71 (m, 3H), 3.40-3.37 (m, 1H), 3.33-3.28 (m, 3H), 1.89-1.24 (m, 23H), 0.95-0.92 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.10, 172.94, 172.51, 155.60, 79.55, 79.20, 75.05, 55.40, 55.32, 52.81, 52.02, 49.91, 41.04, 38.71, 33.31, 32.66, 31.41, 31.22, 31.11, 30.22, 28.76, 28.45, 28.19, 27.30, 26.10, 24.50, 22.71, 22.04. HRMS calculated for $C_{22}H_{40}N_2O_6$ 429.29591 $[M+H]^+$; found 429.29568.

Methia-Leu-Cha(4-OMe)-OMe (**248**). Compound **247** (142 mg, 0.33 mmol) was deprotected using the general procedure B, followed by peptide coupling with 2-methylthiazole-5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (108 mg, 0.24 mmol, 73%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.61-7.57 (m, 1H), 7.27 (d, J = 8.0 Hz, 1H), 4.74-4.69 (m, 1H), 4.64-4.46 (m, 1H), 3.73 (s, 3H), 3.37-3.15 (m, 4H), 2.72 (s, 3H), 1.83-1.03 (m, 14H), 0.94-0.88 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.20, 173.01, 172.41, 172.35, 170.59, 170.51, 160.74, 160.69, 143.56, 133.83, 133.77, 79.27, 75.17, 55.53, 55.48, 52.27, 52.16, 50.61, 50.39, 40.99, 40.91, 38.86, 38.52, 33.51, 32.84, 31.44, 31.29, 31.04, 30.51, 29.68, 28.79, 28.54, 27.36, 26.22, 24.80, 22.85, 22.10, 19.53. HRMS calculated for $C_{22}H_{35}N_3O_5S$ 454.23702 $[M+H]^+$; found 454.23684.

Methia-Leu-Cha(4-OMe)-$NHNH_2$ (**249**). The title compound was prepared according to the general procedure C on a 0.24 mmol scale using staring material **248** in quantitative yield.

Boc-Leu-1-DecAla-OMe (**250**). This compound was obtained using the same procedures as described above for the preparation of compound **203** on a 0.8 mmol scale using Boc-1-DecAla-OH and Boc-Leu-OH as starting materials. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (236 mg, 0.52 mmol, 65%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.92-6.51 (m, 1H), 5.14-5.11 (m, 1H), 4.69-4.47 (m, 1H), 4.16 (s, 1H), 3.78-3.63 (m, 3H), 1.82-0.78 (m, 36H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.58, 173.34, 172.51, 155.66, 79.81, 52.92, 52.17, 52.16, 52.10, 50.26, 49.88, 47.60, 42.97, 41.32, 41.22, 40.71, 34.44, 34.23, 34.15, 33.15, 32.54, 32.51,

30.18, 30.07, 28.29, 27.44, 26.78, 26.74, 26.68, 26.61, 26.48, 26.37, 26.24, 25.96, 25.81, 25.36, 24.63, 21.25, 19.95, 19.61. HRMS calculated for $C_{25}H_{44}N_2O_5$ 453.33230 $[M+H]^+$; found 453.33179.

Methia-Leu-1-DecAla-OMe (**251**). Compound **250** (122 mg, 0.27 mmol) was deprotected using the general procedure B, followed by peptide coupling with 2-methylthiazole-5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (109 mg, 0.23 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.13 (m, 1H), 7.46-7.32 (m, 1H), 7.19-6.95 (m, 1H), 4.78-4.42 (m, 2H), 3.81-3.59 (m, 3H), 2.72 (s, 3H), 2.03- 0.47 (m, 28H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.54, 173.33, 173.28, 173.01, 172.23, 172.19, 172.08, 171.94, 170.61, 160.68, 160.64, 133.78, 52.30, 52.10, 50.63, 50.18, 47.55, 42.92, 41.16, 41.03, 40.73, 40.70, 39.41, 38.86, 38.68, 37.86, 37.69, 37.46, 37.24, 36.83, 35.62, 34.43, 34.21, 32.55, 31.89, 29.98, 26.77, 26.51, 26.33, 26.25, 25.95, 25.79, 25.34, 24.83, 22.87, 22.20, 21.26, 19.98, 19.67, 19.57. HRMS calculated for $C_{25}H_{39}N_3O_4S$ 478.27340 $[M+H]^+$; found 478.27332.

Methia-Leu-1-DecAla-$NHNH_2$ (**252**). The title compound was prepared according to the general procedure C on a 0.2 mmol scale using staring material **251** in quantitative yield.

Boc-Leu-2-DecAla-OMe (**253**). This compound was obtained using the same procedures as described above for the preparation of compound **203** on a 0.70 mmol scale using Boc-2-DecAla-OH and Boc-Leu-OH as starting materials. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (211 mg, 0.47 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86-6.78 (m, 1H), 5.28-5.06 (m, 1H), 4.66-4.60 (m, 1H), 4.20-4.15 (m, 1H), 3.71 (s, 3H), 1.87-1.08 (m, 30H), 0.95-0.88 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.29, 172.48, 155.68, 79.75, 52.88, 52.11, 50.01, 41.17, 40.08, 35.80, 35.62, 34.70, 32.72, 32.26, 32.11, 31.98, 31.78, 28.27, 27.80, 26.95, 26.83, 26.59, 26.51, 25.67, 25.64, 24.60, 22.80, 22.15, 20.85. HRMS calculated for $C_{25}H_{44}N_2O_5$ 453.33230 $[M+H]^+$; found 453.33201.

Methia-Leu-2-DecAla-OMe (**254**). Compound **253** (211 mg, 0.47 mmol) was deprotected using the general procedure B, followed by peptide coupling with 2-methylthiazole-5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (219 mg, 0.46 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 1.9 Hz, 1H), 7.79-7.68 (m, 1H), 7.42-7.34 (m, 1H), 4.78-4.70 (m, 1H), 4.63-4.56 (m, 1H), 3.74-3.70 (m, 3H), 2.71 (s, 3H), 1.87-0.53 (m, 28H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.21, 172.45, 170.48, 160.66, 143.59, 133.85, 52.17, 50.43, 50.39, 40.89, 40.86, 40.75, 39.72, 39.69, 35.93, 35.57, 34.14, 32.57, 32.23, 32.04, 31.94, 31.88, 27.64, 26.93, 26.58, 25.62, 22.82, 22.09, 20.84, 19.47. HRMS calculated for $C_{25}H_{39}N_3O_4S$ 478.27340 $[M+H]^+$; found 478.27323.

Methia-Leu-2-DecAla-Phe(4-CH_2NH_2)-VS (**255**). The title compound was prepared according to the general PROCEDUREC on a 0.46 mmol scale using staring material **118** IN quantitative yield.

Boc-Leu-BiCha-OMe (**256**). This compound was obtained using the same procedures as described above for the preparation of compound **203** on a 0.8 mmol scale using Boc-BiCha-OH and Boc-Leu-OH as starting materials. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (300 mg, 0.62 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73-6.68 (m, 1H), 5.09 (d, J = 8.1 Hz, 1H), 4.64-4.55 (m, 1H), 4.22-4.04 (m, 1H), 3.72-3.71 (m, 3H), 1.94-0.66 (m, 41H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.31, 172.46, 155.74, 79.91, 52.96, 52.23, 50.51, 50.16, 43.29, 41.70, 41.07, 40.40, 36.04, 34.35, 33.71, 32.76, 30.54, 30.25, 30.07, 29.73, 29.59, 28.51, 28.33, 26.86, 26.76, 25.51, 25.28, 24.69, 22.87, 22.20. HRMS calculated for $C_{27}H_{48}N_2O_5$ 481.36360 $[M+H]^+$; found 481.36346.

Methia-Leu-BiCha-OMe (**257**). Compound **256** (154 mg, 0.32 mmol) was deprotected using the general procedure B, followed by peptide coupling with 2-methylthiazole-5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (140 mg, 0.28 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.11 (m, 1H), 7.48-7.41 (m, 1H), 7.18-7.10 (m, 1H), 4.75-4.70 (m, 1H), 4.61-4.52 (m, 1H), 3.74-

3.73 (m, 3H), 2.71 (s, 3H), 1.97-0.65 (m, 32H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.29, 173.26, 172.38, 172.19, 170.46, 160.70, 160.68, 143.66, 133.78, 133.74, 52.32, 52.16, 50.86, 50.50, 43.24, 41.62, 41.13, 40.90, 40.32, 39.58, 35.72, 34.38, 33.59, 32.76, 30.95, 30.54, 30.24, 29.97, 29.66, 29.54, 28.42, 26.88, 26.76, 25.50, 25.27, 24.84, 22.90, 22.19, 19.61. HRMS calculated for $C_{27}H_{43}N_3O_4S$ 506.30470 $[M+H]^+$; found 506.30462.

Methia-Leu-BiCha-$NHNH_2$ (**258**) The title compound was prepared according to the general procedure C on a 0.28 mmol scale using staring material **257** in quantitative yield.

Boc-Cha-Cha-OMe (**259**). This compound was obtained using the same procedures as described above for the preparation of compound **203** on a 1.5 mmol scale using Boc-Cha-OH as starting material. Purification by silica gel flash column chromatography (5% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (438 mg, 1.0 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, J = 7.9 Hz, 1H), 5.30 (d, J = 8.4 Hz, 1H), 4.64-4.58 (m, 1H), 4.25-4.19 (m, 1H), 3.72 (s, 3H), 1.86-0.75 (m, 35H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.15, 172.52, 155.60, 79.56, 77.36, 60.26, 52.17, 51.99, 49.91, 39.79, 33.84, 33.40, 33.31, 32.73, 32.33, 28.21, 26.33, 26.26, 26.11, 26.00, 25.84. HRMS calculated for $C_{24}H_{42}N_2O_5$ 439.31665 $[M+H]^+$; found 439.31656.

Methia-Cha-Cha-OMe (**260**). Compound **259** (438 mg, 1.0 mmol) was deprotected using the general procedure B, followed by the peptide coupling with 2-methylthiazole-5-carboxylic acid using general procedure A. Purification by silica gel flash column chromatography (10% EtOAc/pentane → 50% EtOAc/pentane) yielded the title compound (439 mg, 0.95 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 4.83-4.77 (m, 1H), 4.59-4.54 (m, 1H), 3.73 (s, 3H), 2.71 (s, 3H), 1.73-1.08 (m, 22H), 0.92-0.76 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.01, 172.65, 170.12, 160.58, 143.74, 133.81, 77.36, 51.95, 51.55, 50.27, 39.24, 33.90, 33.84, 33.27, 33.00, 32.58, 32.40, 26.26, 26.21, 26.00, 25.90, 25.87, 25.76, 19.37. HRMS calculated for $C_{24}H_{37}N_3O_4S$ 464.25775 $[M+H]^+$; found 464.25755.

Methia-Cha-Cha-$NHNH_2$ (**261**). The title compound was prepared according to the general procedure C on a 0.95 mmol scale using staring material **260** in quantitative yield.

Benz-Leu-Leu-Phe(4-aminomethyl)-VS TFA salt (**6**). This compound was prepared according to the general procedure D on a 50 µmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (30%-40% MeCN-H_2O) yielded the title compound (7.3 mg, 10.4 µmol, 21%). ^{1}H NMR (600 MHz, MeOD) δ 7.93-7.82 (m, 2H), 7.62-7.54 (m, 1H), 7.52-7.49 (m, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.35-7.27 (m, 2H), 6.86-6.82 (m, 1H), 6.64-6.61 (m, 1H), 4.59-4.57 (m, 1H), 4.38-4.34 (m, 1H), 4.09 (s, 2H), 3.09-2.91 (m, 5H), 1.83-1.47 (m, 6H), 1.09-0.85 (m, 12H). ^{13}C NMR (150 MHz, MeOD) δ 175.17, 174.28, 170.80, 146.61, 139.63, 135.10, 133.05, 132.92, 131.88, 131.23, 130.18, 129.62, 128.63, 54.60, 54.56, 53.59, 53.55, 53.50, 53.46, 52.47, 52.38, 44.07, 42.77, 41.64, 41.60, 41.36, 40.31, 40.28, 26.19, 25.96, 23.46, 23.38, 22.06, 21.76. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 15.0 min): Rt (min): 6.12 (ESI-MS (m/z): 585.13, ($M+H^+$)). HRMS calculated for $C_{31}H_{44}N_4O_5S$ 585.31052 $[M+H]^+$; found 585.31048.

Pyra-Leu-Leu-Phe(4-aminomethyl)-VS TFA salt (**7**). This compound was prepared according to the general procedure D on a 50 µmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (30%-35% MeCN-H_2O) yielded the title compound (3.5 mg, 5.0 µmol, 10%). ^{1}H NMR (600 MHz, MeOD) δ 9.26 (d, J = 1.5 Hz, 1H), 8.84 (d, J = 2.5 Hz, 1H), 8.75-8.74 (m, 1H), 7.43-7.37 (m, 2H), 7.37-7.30 (m, 2H), 6.86-6.82 (m, 1H), 6.67-6.56 (m, 1H), 4.66-4.59 (m, 1H), 4.39-4.35 (m, 1H), 4.12 (s, 2H), 3.08-2.98 (m, 2H), 2.97 (s, 3H), 1.86-1.46 (m, 6H), 1.05-0.85 (m, 12H). ^{13}C NMR (150 MHz, MeOD) δ 174.59, 174.26, 165.66, 148.85, 146.57, 145.85, 144.86, 139.60, 132.96, 131.89, 131.26, 130.22, 54.04, 53.49, 52.39, 44.09, 42.76, 41.93, 41.54, 40.30, 26.16, 25.95, 23.40, 22.01, 21.74. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 15.0 min): Rt (min): 5.48 (ESI-MS (m/z): 587.20, (M+H+)). HRMS calculated for $C_{29}H_{42}N_6O_5$ S 587.30102 [M+H]+; found 587.30099.

Phnico-Leu-Leu-Phe(4-aminomethyl)-VS TFA salt (**8**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (30%-45% MeCN-H_2O) yielded the title compound (3.3 mg, 4.3 μmol, 9%). ^{1}H NMR (600 MHz, MeOD) δ 9.13-9.09 (m, 1H), 8.37-8.34 (m, 1H), 8.09-8.04 (m, 2H), 8.03-8.01 (m, 1H), 7.60-7.46 (m, 3H), 7.43-7.27 (m, 4H), 6.85-6.82 (m, 1H), 6.64-6.61 (m, 1H), 4.62-4.58 (m, 1H), 4.40-4.36 (m, 1H), 4.10 (s, 2H), 3.08-2.90 (m, 5H), 1.90-1.49 (m, 6H), 1.08-0.87 (m, 12H). ^{13}C NMR (150 MHz, MeOD) δ 175.02, 174.32, 168.52, 161.32, 149.75, 146.56, 139.62, 139.32, 138.00, 132.95, 131.92, 131.26, 131.10, 130.21, 130.03, 129.44, 128.39, 121.71, 54.66, 53.56, 52.51, 52.42, 44.08, 42.77, 41.53, 41.38, 40.32, 26.18, 26.00, 23.47, 23.38, 22.07, 21.75. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 15.0 min): Rt (min): 6.31 (ESI-MS (m/z): 662.20, (M+H+)). HRMS calculated for $C_{36}H_{47}N_5O_5S$ 662.33707 $[M+H]^+$; found 662.33712.

Dibenz-Leu-Leu-Phe(4-aminomethyl)-VS TFA salt (**9**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (30%-40% MeCN-H_2O) yielded the title compound (4.3 mg, 5.6 μmol, 11%). ^{1}H NMR (600 MHz, MeOD) δ 7.55-7.43 (m, 3H), 7.42-7.26 (m, 4H), 6.86-6.81 (m, 1H), 6.63-6.60 (m, 1H), 4.57-4.53 (m, 1H), 4.41-4.39 (m, 1H), 4.13-4.06 (m, 2H), 3.11-2.88 (m, 5H), 1.84-1.46 (m, 6H), 1.05-0.90 (m, 12H). ^{13}C NMR (150 MHz, MeOD) δ 174.30, 174.11, 168.71, 146.68, 146.56, 139.62, 138.58, 134.07, 132.91, 132.88, 132.51, 132.30, 131.86, 131.24, 130.45, 130.17, 129.94, 128.79, 127.04, 54.67, 54.30, 53.30, 52.38, 44.07, 42.77, 42.17, 41.34, 40.27, 26.02, 25.92, 23.48, 23.43, 21.93, 21.82. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 15.0 min): Rt (min): 6.58 (ESI-MS (m/z): 653.13, (M+H+)). HRMS calculated for $C_{31}H_{42}Cl_2N_4O_5S$ 653.23257 $[M+H]^+$; found 653.23287.

Morph-Leu-Leu-Phe(4-aminomethyl)-VS TFA salt (**10**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (25%-35% MeCN-H_2O) yielded the title compound (5.0 mg, 6.9 μmol, 14%). ^{1}H NMR (600 MHz, MeOD) δ 7.45-7.38 (m, 2H), 7.37-7.31 (m, 2H), 6.83-6.77

(m, 1H), 6.58-6.51 (m, 1H), 4.82-4.79 (m, 1H), 4.45-4.41 (m, 1H), 4.39-4.32 (m, 1H), 4.11 (s, 2H), 4.03-3.86 (m, 6H), 3.11-2.91 (m, 5H), 1.76-1.41 (m, 6H), 1.10-0.83 (m, 12H). ^{13}C NMR (150 MHz, MeOD) δ 174.47, 174.31, 146.47, 139.59, 133.04, 131.93, 131.29, 130.25, 65.01, 58.61, 54.03, 53.63, 53.46, 52.60, 44.05, 42.75, 41.96, 41.85, 40.23, 25.96, 25.87, 23.45, 23.38, 21.89, 21.82. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 15.0 min): Rt (min): 4.28 (ESI-MS (m/z): 608.27, (M+H+)). HRMS calculated for $C_{30}H_{49}N_5O_6S$ 608.34763 $[M+H]^+$; found 608.34759.

Methia-Leu-Leu-Phe(4-aminomethyl)-VS TFA salt (**11**). This compound was prepared according to the general procedure D on a 70 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (25%-40% MeCN-H_2O) yielded the title compound (8.8 mg, 12.2 μmol, 17%). ^{1}H NMR (600 MHz, MeOD) δ 8.27 (s, 1H), 7.40 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 6.83-6.80 (m, 1H), 6.62-6.59 (m, 1H), 4.52-4.50 (m, 1H), 4.35-4.32 (m, 1H), 4.11 (s, 2H), 3.02-3.01 (m, 2H), 2.96 (s, 3H), 2.75 (s, 3H), 1.83-1.47 (m, 6H), 1.07-0.86 (m, 12H). ^{13}C NMR (150 MHz, MeOD) δ 174.90, 174.28, 173.09, 163.19, 146.52, 144.56, 139.63, 135.33, 132.96, 131.90, 131.27, 130.21, 54.50, 53.59, 52.43, 44.07, 42.77, 41.42, 41.26, 40.33, 26.10, 25.97, 23.44, 23.34, 22.02, 21.71, 19.13. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 15.0 min): Rt (min): 5.51 (ESI-MS (m/z): 606.13, (M+H+)). HRMS calculated for $C_{29}H_{43}N_5O_5S_2$ 606.27784 $[M+H]^+$; found 606.27799.

N3Acetyl-Phe-Leu-Leu-Phe(4-aminomethyl)-VS TFA salt (**12**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (30%-40% MeCN-H_2O) yielded the title compound (7.3 mg, 10.4 μmol, 21%). ^{1}H NMR (600 MHz, MeOD) δ 7.43-7.35 (m, 4H), 7.33-7.22 (m, 5H), 6.85-6.82 (m, 1H), 6.66-6.63 (m, 1H), 4.60-4.57 (m, 1H), 4.31-4.29 (m, 2H), 4.09 (s, 2H), 3.91 (d, J = 2.6 Hz, 2H), 3.19-3.15 (m, 1H), 3.08-2.96 (m, 3H), 2.95 (s, 3H), 1.71-1.46 (m, 6H), 1.00-0.86 (m, 12H). ^{13}C NMR (150 MHz, MeOD) δ 174.85, 174.32, 174.01, 170.95, 146.44, 139.72, 137.86, 132.92, 131.81, 131.35, 130.30, 130.19, 129.63, 128.04, 57.07, 54.14, 53.81, 52.72, 52.43, 44.07, 42.77, 41.45, 41.10, 40.40, 38.30, 26.00, 25.82, 23.50, 23.39, 21.78, 21.76. LC-MS (linear gradient 10 → 90%

MeCN/H_2O, 0.1% TFA, 15.0 min): Rt (min): 6.44 (ESI-MS (m/z): 711.27, (M+H+)). HRMS calculated for $C_{35}H_{50}N_8O_6S$ 711.36468 $[M+H]^+$; found 711.36500.

N3Phe-Leu-Ser-Phe(4-CH2NH2)-VS TFA salt (**13**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (30%-40% MeCN-H_2O) yielded the title compound (2.8 mg, 3.8 μmol, 8%). ^1H NMR (600 MHz, MeOD) δ 7.46-7.23 (m, 9H), 6.85-6.81 (m, 1H), 6.76-6.73 (m, 1H), 4.39-4.27 (m, 2H), 4.20-4.17 (m, 1H), 4.11 (s, 2H), 3.84-3.81 (m, 1H), 3.76-3.73 (m, 1H), 3.25-3.22 (m, 1H), 3.07-2.98 (m, 3H), 2.95 (s, 3H), 1.69-1.52 (m, 3H), 1.02-0.88 (m, 6H). ^{13}C NMR (150 MHz, MeOD) δ 174.33, 172.23, 171.81, 146.65, 139.69, 137.84, 133.00, 131.84, 131.26, 130.42, 130.24, 129.65, 128.10, 65.38, 62.75, 56.70, 53.80, 52.56, 44.09, 42.77, 41.38, 40.25, 38.72, 25.82, 23.46, 21.84. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 15.0 min): Rt (min): 6.27 (ESI-MS (m/z): 628.20, ($M+H^+$)). HRMS calculated for $C_{30}H_{41}N_7O_6S$ 628.29118 $[M+H]^+$; found 628.29123.

N3Phe-Leu-Leu(4-F)-Phe(4-CH_2NH_2)-VS TFA salt (**14**). This compound was prepared according to the general procedure D on a 100 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (40%-45% MeCN-H_2O) yielded the title compound (22.1 mg, 28.1 μmol, 28%). ^1H NMR (400 MHz, MeOD) δ 7.45-7.23 (m, 10H), 6.84-6.79 (m, 1H), 6.65-6.61 (m, 1H), 4.90-4.77 (m, 1H), 4.55-4.50 (m, 1H), 4.36-4.32 (m, 1H), 4.22-4.19 (m, 1H), 4.12 (s, 2H), 3.26-3.21 (m, 1H), 3.06-2.96 (m, 3H), 2.95 (s, 3H), 2.24-1.88 (m, 2H), 1.64-1.55 (m, 3H), 1.44-1.33 (m, 6H), 0.99-0.92 (m, 6H). ^{13}C NMR (100 MHz, MeOD) δ 174.03, 173.42, 172.16, 146.45, 146.43, 139.58, 137.81, 133.01, 131.87, 131.25, 130.42, 130.26, 129.66, 129.27, 128.62, 128.11, 96.77, 95.12, 65.48, 53.85, 53.82, 52.58, 52.49, 51.87, 44.05, 43.02, 42.81, 42.76, 41.13, 40.24, 38.65, 27.48, 27.24, 27.14, 26.90, 25.76, 23.42, 21.87. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 15.0 min): Rt (min): 6.95 (ESI-MS (m/z): 672.20, ($M+H^+$)). HRMS calculated for $C_{33}H_{46}FN_7O_5S$ 672.33379 $[M+H]^+$; found 672.33384.

N_3Phe-Leu-Ser(Me)-Phe(4-CH_2NH_2)-VS TFA salt (**15**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (40%-45% MeCN-H_2O) yielded the title compound (10.6 mg, 14.0 μmol, 28%). ^{1}H NMR (400 MHz, MeOD) δ 8.31 (t, J = 8.4 Hz, 2H), 7.99 (d, J = 8.0 Hz, 1H), 7.46-7.21 (m, 9H), 6.86-6.81 (m, 1H), 6.71-6.67 (m, 1H), 4.47-4.31 (m, 2H), 4.20-4.16 (m, 1H), 4.11 (s, 2H), 3.69-3.65 (m, 1H), 3.59-3.55 (m, 1H), 3.38 (s, 3H), 3.25-3.20 (m, 1H), 3.10-2.98 (m, 3H), 2.96 (s, 3H), 1.68-1.45 (m, 3H), 0.98-0.89 (m, 6H). ^{13}C NMR (100 MHz, MeOD) δ 174.40, 172.24, 172.16, 171.64, 146.83, 139.70, 137.82, 132.99, 131.80, 131.20, 130.41, 130.23, 129.65, 128.10, 72.76, 65.40, 65.36, 59.42, 54.90, 54.80, 53.78, 53.68, 52.67, 52.58, 44.06, 42.86, 41.35, 40.08, 38.73, 25.80, 23.46, 21.85. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 5.82 (ESI-MS (m/z): 642.27, ($M+H^+$)). HRMS calculated for $C_{31}H_{43}N_7O_6S$ 642.30683[$M+H]^+$; found 642.30685.

N_3Phe-Leu-Thr-Phe(4-CH_2NH_2)-VS TFA salt (**16**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (30%-40% MeCN-H2O) yielded the title compound (6.9 mg, 9.1 μmol, 18%). ^{1}H NMR (600 MHz, MeOD) δ 7.43-7.24 (m, 11H), 6.87-6.83 (m, 1H), 6.73-6.70 (m, 1H), 4.94-4.91 (m, 1H), 4.43-4.36 (m, 1H), 4.25 (d, J = 3.6 Hz, 1H), 4.24-4.16 (m, 2H), 4.11 (s, 3H), 3.26-3.23 (m, 1H), 3.10-2.96 (m, 4H), 2.96 (s, 3H), 1.69-1.56 (m, 3H), 1.17 (d, J = 6.4 Hz, 3H), 0.98-0.88 (m, 6H). ^{13}C NMR (150 MHz, MeOD) δ 174.57, 172.36, 171.64, 146.70, 139.65, 137.87, 132.99, 131.85, 131.25, 130.40, 130.22, 129.65, 128.10, 68.34, 65.40, 59.84, 54.05, 52.48, 44.09, 42.78, 41.31, 40.28, 38.76, 25.86, 23.44, 21.82, 20.24. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 15.0 min): Rt (min): 6.43 (ESI-MS (m/z): 642.27, ($M+H^+$)). HRMS calculated for $C_{31}H_{43}N_7O_6S$ 642.30683 [$M+H]^+$; found 642.30687.

N_3Phe-Leu-Ala(CF_3)-Phe(4-CH_2NH_2)-VS TFA salt (**17**). This compound was prepared according to the general procedure D on a 91 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (40%-45% MeCN-H2O) yielded the title compound (24.3 mg, 30.6 μmol, 34%). ^{1}H NMR (400 MHz, MeOD) δ 7.46-7.22 (m, 10H), 6.98-6.94 (m, 1H), 6.86-6.76

(m, 1H), 6.66-6.58 (m, 1H), 4.69-4.54 (m, 1H), 4.32-4.03 (m, 4H), 3.27-3.17 (m, 1H), 3.14-2.61 (m, 8H), 1.72-1.48 (m, 3H), 1.01-0.89 (td, J = 14.5, 5.9 Hz, 6H). ^{13}C NMR (100 MHz, MeOD) δ 174.78, 174.41, 172.71, 172.30, 170.85, 146.62, 146.12, 139.73, 139.48, 137.82, 133.05, 132.99, 131.99, 131.88, 131.37, 131.28, 130.40, 130.33, 130.28, 130.17, 129.64, 128.09, 65.34, 64.73, 54.91, 54.02, 53.16, 53.07, 52.88, 44.04, 42.84, 42.74, 41.13, 40.98, 40.37, 38.72, 38.66, 35.32, 35.03, 35.00, 25.73, 25.54, 23.37, 22.91, 22.54, 21.88. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 15.0 min): Rt (min): 7.07 (ESI-MS (m/z): 680.13, ($M+H^+$)). HRMS calculated for $C_{31}H_{40}F_3N_7O_5S$ 680.28365 $[M+H]^+$; found 680.28362.

N_3Phe-Leu-Gly-Phe(4-CH_2NH_2)-VS TFA salt (**18**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (40%-50% MeCN-H_2O) yielded the title compound (9.6 mg, 16.0 μmol, 32%). ^{1}H NMR (400 MHz, MeOD) δ 7.56-7.13 (m, 9H), 6.88 (dd, J = 15.2, 4.9 Hz, 1H), 6.73 (dd, J = 15.2, 1.5 Hz, 1H), 4.25 (dd, J = 9.0, 5.7 Hz, 1H), 4.12 (dd, J = 8.9, 4.8 Hz, 1H), 4.07 (s, 2H), 3.97 (d, J = 16.9 Hz, 1H), 3.63 (d, J = 16.9 Hz, 1H), 3.22 (dd, J = 14.1, 4.8 Hz, 1H), 3.09-2.93 (m, 6H), 1.66-1.56 (m, 3H), 1.00-0.81 (m, 6H). ^{13}C NMR (101 MHz, MeOD) δ 175.01, 172.43, 171.13, 162.70, 162.34, 146.69, 139.76, 137.82, 132.98, 131.78, 131.31, 130.39, 130.23, 129.65, 128.10, 65.01, 54.30, 52.61, 44.04, 43.52, 42.78, 41.11, 40.37, 38.66, 25.78, 23.25, 22.14. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 15.0 min): Rt (min): 5.84 (ESI-MS (m/z): 598.00, ($M+H^+$)). HRMS calculated for $C_{29}H_{39}N_7O_5S$ 598.28061 $[M+H]^+$; found 598.28052.

Pyra-Leu-Ala-Phe(4-CH_2NH_2)-VS TFA salt (**19**). This compound was prepared according to the general procedure D on a 70 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (40%-45% MeCN-H_2O) yielded the title compound (12.1 mg, 18.4 μmol, 26%). ^{1}H NMR (400 MHz, MeOD) δ 9.24 (d, J = 1.5 Hz, 1H), 8.82 (d, J = 2.5 Hz, 1H), 8.72 (dd, J = 2.5, 1.5 Hz, 1H), 7.38 (d, J = 8.2 Hz, 2H), 7.36-7.31 (m, 2H), 6.83 (dd, J = 15.2, 4.9 Hz, 1H), 6.63 (dd, J= 15.2, 1.6 Hz, 1H), 4.85-4.80 (m, 1H), 4.63-4.59 (m, 1H), 4.30-4.24 (m, 1H), 4.09 (s, 2H), 3.07-2.99 (m, 2H), 2.95 (s, 3H), 1.84-1.70 (m, 3H), 1.32 (d, J = 7.2 Hz, 3H), 1.02-0.96 (m, 6H). ^{13}C NMR

(100 MHz, MeOD) δ 173.10, 164.24, 147.45, 145.24, 144.41, 143.43, 138.21, 131.59, 130.38, 129.85, 128.81, 52.47, 50.96, 49.52, 42.65, 41.35, 40.47, 38.85, 24.72, 22.06, 20.55, 16.41. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 4.39 (ESI-MS (m/z): 545.13, ($M+H^+$)). HRMS calculated for $C_{26}H_{36}N_6O_5S$ 546.25407 $[M+H]^+$; found 546.25373.

Methia-Leu-Ser(Me)-Phe(4-CH_2NH_2)-VS TFA salt (**20**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (40%-45% MeCN-H_2O) yielded the title compound (10.6 mg, 14.0 μmol, 28%). ^{1}H NMR (600 MHz, MeOD) δ 8.27 (s, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.37-7.34 (m, 2H), 6.83 (dd, J = 15.1, 4.4 Hz, 1H), 6.69 (dd, J = 15.2, 1.8 Hz, 1H), 4.53 (dd, J = 9.9, 5.0 Hz, 1H), 4.46 (t, J = 5.5 Hz, 1H), 4.11 (s, 2H), 3.69 (dd, J = 9.6, 5.4 Hz, 1H), 3.59 (dd, J = 9.6, 5.6 Hz, 1H), 3.35 (s, 3H), 3.09-2.98 (m, 2H), 2.96 (s, 3H), 2.75 (s, 3H), 1.84-1.66 (m, 3H), 1.02 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H). ^{13}C NMR (150 MHz, MeOD) δ 174.79, 173.15, 171.57, 163.17, 146.74, 144.56, 139.67, 135.22, 132.97, 131.83, 131.21, 130.21, 72.60, 59.35, 54.89, 54.37, 52.60, 44.06, 42.85, 41.17, 40.09, 26.08, 23.39, 21.91, 19.13. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 4.59 (ESI-MS (m/z) 594.13 ($M+H^+$)). HRMS calculated for $C_{27}H_{39}N_5O_6S_2$ 594.24145 [M+H]+; found 594.24120.

Methia-Chg-Leu-Phe(4-CH_2NH_2)-VS (**21**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (35%-40% MeCN-H_2O) yielded the title compound (11.2 mg, 15.0 μmol, 30%). ^{1}H NMR (600 MHz, MeOD) δ 8.40-8.16 (m, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.82-6.78 (m, 1H), 6.61-6.59 (m, 1H), 4.86-4.81 (m, 1H), 4.38-4.36 (m, 1H), 4.30-4.21 (m, 1H), 4.10 (s, 2H), 3.06-2.97 (m, 2H), 2.95 (s, 3H), 2.74 (s, 3H), 1.92-1.59 (m, 8H), 1.37-1.10 (m, 6H), 0.95-0.90 (m, 6H). ^{13}C NMR (150 MHz, MeOD) δ 174.30, 174.22, 173.73, 173.65, 173.04, 163.12, 146.41, 144.46, 139.52, 135.40, 133.01, 131.93, 131.26, 130.24, 61.26, 53.62, 53.53, 52.57, 52.48, 44.02, 42.76, 41.40, 41.36, 40.66, 40.42, 40.39, 30.89, 30.77, 30.69, 27.24, 27.06, 25.90, 23.46, 21.66,

19.12. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 5.34 (ESI-MS (m/z): 632.20, ($M+H^+$)). HRMS calculated for $C_{31}H_{45}N_5O_5S_2$ 632.29349 $[M+H]^+$; found 632.29352.

Methia-Cha-Leu-Phe(4-CH_2NH_2)-VS TFA salt (**22**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (40%-45% MeCN-H_2O) yielded the title compound (12.3 mg, 16.2 μmol, 32%). ^1H NMR (400 MHz, MeOD) δ 8.28 (s, 1H), 7.48-7.19 (m, 4H), 6.85-6.79 (m, 1H), 6.63-6.59 (m, 1H), 4.87-4.81 (m, 1H), 4.54-4.50 (m, 1H), 4.35-4.31 (m, 1H), 4.10 (s, 2H), 3.07-2.98 (m, 2H), 2.96 (s, 3H), 2.75 (s, 3H), 1.85-0.84 (m, 22H). ^{13}C NMR (100 MHz, MeOD) δ 175.03, 174.26, 173.11, 163.18, 146.53, 144.56, 139.59, 135.34, 132.97, 131.87, 131.25, 130.22, 53.90, 53.60, 52.43, 44.05, 42.77, 41.28, 40.35, 39.90, 35.52, 34.71, 33.56, 27.54, 27.35, 27.25, 25.95, 23.47, 21.68, 19.13. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 5.71 (ESI-MS (m/z): 646.27, ($M+H^+$)). HRMS calculated for $C_{32}H_{47}N_5O_5S_2$ 646.30914 $[M+H]^+$; found 646.30902.

Methia-HomoCha-Leu-Phe(4-CH_2NH_2)-VS TFA salt (**23**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (40%-50% MeCN-H_2O) yielded the title compound (15.9 mg, 20.6 μmol, 41%). ^1H NMR (600 MHz, MeOD) δ 8.29 (s, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.35-7.31 (m, 2H), 6.83-6.80 (m, 1H), 6.63-6.60 (m, 1H), 4.36-4.33 (m, 2H), 4.10 (s, 2H), 3.02 (d, J = 7.6 Hz, 2H), 2.96 (s, 3H), 2.74 (s, 3H), 1.95-1.60 (m, 10H), 1.56-1.51 (m, 1H), 1.38-1.23 (m, 6H), 0.97-0.89 (m, 8H). ^{13}C NMR (150 MHz, MeOD) δ 174.71, 174.26, 173.05, 163.31, 146.47, 144.62, 139.58, 135.33, 132.98, 131.91, 131.24, 130.22, 56.81, 53.62, 52.44, 44.04, 42.79, 41.16, 40.39, 38.77, 34.73, 34.47, 34.36, 29.99, 27.70, 27.40, 25.95, 23.48, 21.66, 19.13. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 6.01 (ESI-MS (m/z): 660.27, ($M+H^+$)). HRMS calculated for $C_{33}H_{49}N_5O_5S_2$ 660.32479 $[M+H]^+$; found 660.32481.

Methia-Cha(4-Me)-Leu-Phe(4-CH_2NH_2)-VS TFA salt (**24**). This compound was prepared according to the general procedure D on a 80 μmol scale, followed by the removal of the Boc protecting group using

the general procedure B. Purification by HPLC (42%-47% MeCN-H_2O) yielded the title compound (18.5 mg, 10.4 μmol, 24%). ^{1}H NMR (600 MHz, MeOD) δ 8.27 (d, J = 1.2 Hz, 1H), 7.40 (d, J = 7.9 Hz, 2H), 7.36-7.30 (m, 2H), 6.84-6.80 (m, 1H), 6.63-6.59 (m, 1H), 4.54-4.48 (m, 1H), 4.35-4.32 (m, 1H), 4.10 (s, 2H), 3.02-3.00 (m, 2H), 2.96 (s, 3H), 2.74 (s, 3H), 1.92-1.30 (m, 14H), 0.99-0.84 (m, 10H). ^{13}C NMR (150 MHz, MeOD) δ 175.00, 174.27, 173.08, 163.20, 146.52, 144.59, 139.58, 135.32, 132.97, 131.89, 131.24, 130.21, 54.32, 54.06, 53.62, 52.42, 44.05, 42.79, 41.31, 40.34, 39.84, 36.28, 36.18, 35.32, 34.63, 33.95, 33.54, 31.83, 31.64, 30.18, 28.77, 25.94, 23.45, 23.01, 21.70, 19.13. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 5.99 (ESI-MS (m/z): 660.27, ($M+H^+$)). HRMS calculated for $C_{33}H_{49}N_5O_5S_2$ 660.32479 $[M+H]^+$; found 660.32493.

Methia-Cha(4-OMe)-Leu-Phe(4-CH_2NH_2)-VS TFA salt (**25**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (30%-40% MeCN-H_2O) yielded the title compound (13.4 mg, 17.0 μmol, 34%). ^{1}H NMR (400 MHz, MeOD) δ 8.27 (s, 1H), 7.45-7.24 (m, 4H), 6.84-6.79 (m, 1H), 6.62-6.58 (m, 1H), 4.86-4.81 (m, 1H), 4.53-4.49 (m, 1H), 4.34-4.30 (m, 1H), 4.10 (s, 2H), 3.45 (t, J = 3.6 Hz, 1H), 3.02-2.97 (m, 2H), 2.95 (s, 3H), 2.74 (s, 3H), 1.98-1.25 (m, 14H), 0.95-0.87 (m, 6H). ^{13}C NMR (100 MHz, MeOD) δ 174.95, 174.27, 173.11, 163.16, 146.55, 144.55, 139.60, 135.34, 132.97, 131.86, 131.25, 130.22, 76.75, 55.83, 53.92, 53.61, 52.42, 44.05, 42.77, 41.30, 40.32, 39.14, 34.47, 29.90, 29.77, 28.53, 27.41, 25.95, 23.46, 21.69, 19.13. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 5.20 (ESI-MS (m/z): 676.33, ($M+H^+$)). HRMS calculated for $C_{33}H_{49}N_5O_6S_2$ 676.31970 $[M+H]^+$; found 676.31980.

Methia-1-DecAla-Leu-Phe(4-CH_2NH_2)-VS TFA salt (**26**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (40%-50% MeCN-H_2O) yielded the title compound (11.1 mg, 13.6 μmol, 27%). ^{1}H NMR (600 MHz, MeOD) δ 8.29-8.25 (m, 1H), 7.40 (d, J = 7.8 Hz, 2H), 7.34-7.30 (m, 2H), 6.86-6.77 (m, 1H), 6.66-6.58 (m, 1H), 4.86-4.81 (m, 1H), 4.49-4.39 (m, 1H), 4.39-4.26 (m, 1H), 4.10 (d, J = 2.5 Hz, 2H), 3.95-3.85 (m, 1H), 3.68 (s, 1H), 3.27-3.21 (m, 1H), 3.02-2.96

(m, 5H), 2.75-2.74 (m, 3H), 1.84-1.20 (m, 22H), 0.96-0.88 (m, 6H). ^{13}C NMR (150 MHz, MeOD) δ 175.04, 174.69, 174.26, 174.12, 173.14, 163.27, 163.22, 146.50, 146.34, 144.67, 144.63, 144.57, 139.58, 132.99, 131.94, 131.87, 131.25, 130.23, 68.13, 64.91, 54.21, 53.60, 52.45, 44.64, 44.55, 44.04, 42.76, 41.73, 41.21, 41.14, 40.70, 40.38, 39.41, 39.10, 39.01, 38.97, 36.77, 36.27, 33.72, 30.89, 28.42, 27.97, 27.81, 26.57, 25.97, 23.49, 22.34, 21.68, 21.15, 20.77, 19.14. LC-MS (linear gradient 10 → 90% MeCN/H2O, 0.1% TFA, 12.5 min): Rt (min): 6.49 (ESI-MS (m/z): 700.27, ($M+H^+$)). HRMS calculated for $C_{36}H_{53}N_5O_5S_2$ 700.35609 $[M+H]^+$; found 700.35626.

Methia-2-DecAla-Leu-Phe(4-CH_2NH_2)-VS TFA salt (**27**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (40%-50% MeCN-H_2O) yielded the title compound (14.8 mg, 18.2 μmol, 36%). ^{1}H NMR (600 MHz, MeOD) δ 8.31-8.22 (m, 1H), 7.40 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 6.83-6.80 (m, 1H), 6.62-6.59 (m, 1H), 4.57-4.50 (m, 1H), 4.35-4.32 (m, 1H), 4.10 (s, 2H), 3.05-2.96 (m, 5H), 2.74 (s, 3H), 1.82-1.20 (m, 22H), 0.95 (d, J = 6.2 Hz, 3H), 0.91 (d, J = 6.3 Hz, 3H). ^{13}C NMR (150 MHz, MeOD) δ 175.09, 175.03, 174.29, 173.08, 163.17, 146.52, 144.58, 139.58, 135.34, 132.97, 131.90, 131.25, 130.22, 53.97, 53.90, 53.62, 52.43, 44.06, 42.79, 41.31, 40.36, 40.07, 37.53, 37.37, 37.33, 37.24, 37.22, 36.31, 36.28, 34.00, 33.55, 33.49, 33.35, 33.29, 32.97, 30.89, 29.00, 28.13, 27.95, 26.85, 25.96, 23.46, 21.98, 21.72, 19.13. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 6.55 (ESI-MS (m/z): 700.33, ($M+H^+$)). HRMS calculated for $C_{36}H_{53}N_5O_5S_2$ 700.35609 $[M+H]^+$; found 700.35633.

Methia-BiCha-Leu-Phe(4-CH_2NH_2)-VS TFA salt (**28**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (45%-55% MeCN-H_2O) yielded the title compound (7.7 mg, 9.2 μmol, 18%). ^{1}H NMR (600 MHz, MeOD) δ 8.26 (s, 1H), 7.44-7.37 (m, 2H), 7.34-7.32 (m, 2H), 6.83-6.79 (m, 1H), 6.62-6.59 (m, 1H), 4.91-4.76 (m, 1H), 4.53-4.46 (m, 1H), 4.35-4.31 (m, 1H), 4.10 (s, 2H), 3.02-3.00 (m, 2H), 2.96 (s, 3H), 2.75 (s, 3H), 1.94-1.44 (m, 18H), 1.3-1.14 (m, 6H), 0.96-0.90 (m, 8H). ^{13}C NMR (150 MHz, MeOD) δ 175.12, 175.04, 174.35, 174.27, 173.10, 163.20, 163.16,

146.46, 144.56, 139.59, 135.36, 132.98, 131.88, 131.27, 130.23, 126.12, 54.43, 54.39, 54.07, 54.04, 53.72, 53.68, 53.63, 53.59, 52.55, 52.53, 52.46, 52.43, 44.69, 44.04, 42.76, 41.27, 40.37, 39.86, 36.16, 35.81, 34.92, 33.87, 32.56, 31.72, 31.41, 30.96, 30.89, 29.49, 27.94, 27.86, 26.74, 26.53, 25.97, 23.48, 21.68, 19.13. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 7.08 (ESI-MS (m/z): 728.27, ($M+H^+$)). HRMS calculated for $C_{38}H_{57}N_5O_5S_2$ 728.38739 $[M+H]^+$; found 728.38763.

Methia-Leu-Cha-Phe(4-CH_2NH_2)-VS TFA salt (**29**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (38%-43% MeCN-H_2O) yielded the title compound (11.0 mg, 14.5 μmol, 29%). ^1H NMR (400 MHz, MeOD) δ 8.28 (s, 1H), 7.48-7.25 (m, 4H), 6.85-6.79 (m, 1H), 6.62-6.58 (m, 1H), 4.89-4.78 (m, 1H), 4.52-4.50 (m, 1H), 4.38-4.35 (m, 1H), 4.10 (s, 2H), 3.07-2.98 (m, 2H), 2.96 (s, 3H), 2.75 (s, 3H), 1.83-0.79 (m, 22H). ^{13}C NMR (100 MHz, MeOD) δ 174.77, 174.37, 173.11, 163.13, 146.56, 144.54, 139.61, 135.36, 132.96, 131.85, 131.25, 130.22, 54.44, 52.80, 52.40, 44.06, 42.79, 41.12, 40.30, 40.02, 35.40, 34.85, 33.14, 27.51, 27.40, 27.19, 26.07, 23.27, 22.17, 19.13. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 5.59 (ESI-MS (m/z): 646.27, ($M+H^+$)). HRMS calculated for $C_{32}H_{47}N_5O_5S_2$ 646.30914 $[M+H]^+$; found 646.30930.

Methia-Leu-HomoCha-Phe(4-CH_2NH_2)-VS TFA salt (**30**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (40%-50% MeCN-H_2O) yielded the title compound (13.0 mg, 16.8 μmol, 34%). ^1H NMR (400 MHz, MeOD) δ 8.27 (s, 1H), 7.50-7.17 (m, 4H), 6.85-6.80 (m, 1H), 6.62-6.58 (m, 1H), 4.87-4.83 (m, 1H), 4.56-4.52 (m, 1H), 4.23-4.19 (m, 1H), 4.10 (s, 2H), 3.09-2.88 (m, 5H), 2.75 (s, 3H), 1.89-1.53 (m, 10H), 1.40-0.76 (m, 14H). ^{13}C NMR (100 MHz, MeOD) δ 174.77, 173.84, 173.11, 163.08, 146.61, 144.52, 139.59, 135.35, 132.97, 131.88, 131.25, 130.23, 55.31, 54.29, 52.41, 44.06, 42.80, 41.13, 40.26, 38.53, 34.52, 34.48, 34.20, 30.17, 27.68, 27.38, 27.35, 26.07, 23.35, 22.03, 19.13. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min):

5.99 (ESI-MS (m/z): 600.27, ($M+H^+$)). HRMS calculated for $C_{33}H_{49}N_5O_5S_2$ 660.32479 $[M+H]^+$; found 660.32494.

Methia-Leu-Cha(4-Me)-Phe(4-CH_2NH_2)-VS TFA salt (31). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (42%-47% MeCN-H_2O) yielded the title compound (15.4 mg, 19.9 μmol, 40%). ^1H NMR (600 MHz, MeOD) δ 8.28-8.27 (m, 1H), 7.43-7.26 (m, 4H), 6.85-6.81 (m, 1H), 6.63-6.59 (m, 1H), 4.54-4.50 (m, 1H), 4.39-4.31 (m, 1H), 4.11 (s, 2H), 3.08-2.84 (m, 5H), 2.75 (s, 3H), 1.82-1.23 (m, 15H), 1.04-0.97 (m, 6H), 0.94 (d, J = 6.9 Hz, 2H), 0.86 (d, J = 6.5 Hz, 1H). ^{13}C NMR (150 MHz, MeOD) δ 174.85, 174.73, 174.38, 174.35, 173.10, 163.18, 163.11, 146.58, 144.58, 139.62, 135.33, 132.96, 131.89, 131.25, 130.22, 54.51, 54.38, 53.29, 52.92, 52.39, 44.06, 42.82, 41.14, 41.00, 40.29, 39.92, 36.29, 36.08, 35.16, 34.76, 33.88, 33.11, 33.01, 31.91, 31.62, 31.12, 30.90, 30.25, 28.29, 26.08, 26.06, 23.29, 23.27, 22.99, 22.19, 22.12, 19.13. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 5.95 (ESI-MS (m/z): 660.27, ($M+H^+$)). HRMS calculated for $C_{33}H_{49}N_5O_5S_2$ 660.32479 $[M+H]^+$; found 660.32476.

Methia-Leu-Cha(4-OMe)-Phe(4-CH_2NH_2)-VS TFA salt (**32**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (30%-40% MeCN-H_2O) yielded the title compound (10.4 mg, 13.2 μmol, 26%). ^1H NMR (600 MHz, MeOD) δ 8.27 (s, 1H), 7.42-7.30 (m, 4H), 6.84-6.80 (m, 1H), 6.61-6.59 (m, 1H), 4.53-4.51 (m, 1H), 4.38-4.33 (m, 1H), 4.11 (s, 2H), 3.43-3.37 (m, 1H), 3.30 (s, 3H), 3.05-2.98 (m, 2H), 2.96 (s, 3H), 2.75 (s, 3H), 1.89-1.65 (m, 6H), 1.60-1.58 (m, 2H), 1.50-1.42 (m, 3H), 1.37-1.28 (m, 3H), 1.04-0.97 (m, 6H). ^{13}C NMR (150 MHz, MeOD) δ 174.85, 174.77, 174.29, 173.10, 163.09, 146.55, 144.53, 139.64, 135.37, 132.96, 131.89, 131.27, 130.21, 76.73, 55.82, 54.41, 54.37, 52.97, 52.88, 52.52, 52.43, 44.08, 42.79, 41.14, 40.27, 39.38, 34.35, 30.90, 29.95, 29.71, 28.69, 26.98, 26.09, 23.30, 22.12, 19.13. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 5.17 (ESI-MS (m/z): 676.20, ($M+H^+$)). HRMS calculated for $C_{33}H_{49}N_5O_6S_2$ 676.31970 $[M+H]^+$; found 676.31964.

Methia-Leu-1-DecAla-Phe(4-CH_2NH_2)-VS TFA salt (**33**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (40%-50% MeCN-H_2O) yielded the title compound (9.9 mg, 12.2 μmol, 24%). ^{1}H NMR (600 MHz, MeOD) δ 8.31-8.24 (m, 1H), 7.41-7.39 (m, 2H), 7.36-7.32 (tm, 2H), 6.87-6.78 (m, 1H), 6.63-6.54 (m, 1H), 4.87-4.83 (m, 1H), 4.58-4.47 (m, 1H), 4.42-4.23 (m, 1H), 4.10 (s, 2H), 3.94-3.84 (m, 1H), 3.68 (s, 1H), 3.28-3.19 (m, 1H), 3.06-2.90 (m, 5H), 2.80-2.69 (m, 3H), 1.84-1.48 (m, 11H), 1.44-1.15 (m, 9H), 1.07-0.91 (m, 8H). ^{13}C NMR (150 MHz, MeOD) δ 174.82, 174.71, 174.67, 174.41, 174.36, 173.15, 163.21, 163.11, 146.61, 146.55, 146.51, 144.53, 139.64, 139.61, 139.56, 135.42, 132.96, 131.95, 131.82, 131.27, 131.23, 130.22, 126.12, 68.13, 64.90, 54.83, 54.61, 54.34, 54.30, 53.12, 52.56, 52.42, 44.63, 44.41, 44.06, 42.79, 42.43, 41.03, 40.75, 40.29, 39.80, 39.58, 39.10, 39.06, 38.78, 37.22, 35.62, 35.44, 33.72, 32.52, 27.90, 27.71, 27.50, 26.98, 26.93, 26.52, 26.06, 26.03, 23.29, 23.23, 22.26, 22.18, 19.14. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 6.26 (ESI-MS (m/z): 700.33, ($M+H^+$)). HRMS calculated for $C_{36}H_{53}N_5O_5S_2$ 700.35609 $[M+H]^+$; found 700.35632.

Methia-Leu-2-DecAla-Phe(4-CH_2NH_2)-VS TFA salt (**34**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (40%-50% MeCN-H_2O) yielded the title compound (16.5 mg, 20.3 μmol, 41%). ^{1}H NMR (600 MHz, MeOD) δ 8.29-8.23 (m, 1H), 7.40 (d, J = 8.1 Hz, 2H), 7.36-7.30 (m, 2H), 6.84-6.81 (m, 1H), 6.62-6.58 (n, 1H), 4.57-4.48 (m, 1H), 4.40-4.36 (m, 1H), 4.10 (s, 2H), 3.07-2.94 (m, 5H), 2.74 (s, 3H), 1.82-1.07 (m, 22H), 1.05-0.97 (m, 6H). ^{13}C NMR (150 MHz, MeOD) δ 174.73, 174.44, 174.36, 173.11, 163.10, 146.60, 144.56, 139.61, 135.38, 132.96, 131.84, 131.25, 130.22, 54.43, 54.41, 54.27, 52.91, 52.78, 52.39, 44.07, 42.81, 41.08, 40.32, 40.19, 40.07, 37.52, 37.46, 37.24, 37.20, 36.28, 36.13, 34.09, 33.55, 33.47, 33.37, 33.23, 32.42, 30.90, 29.17, 28.10, 27.57, 26.83, 26.07, 23.28, 22.18, 21.99, 19.13. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 6.38 (ESI-MS (m/z): 700.33, ($M+H^+$)). HRMS calculated for $C_{36}H_{53}N_5O_5S_2$ 700.35609 $[M+H]^+$; found 700.35629.

Methia-Leu-BiCha-Phe(4-CH_2NH_2)-VS TFA salt (**35**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (45%-50% MeCN-H_2O) yielded the title compound (12.0 mg, 14.3 μmol, 29%). ^{1}H NMR (600 MHz, MeOD) δ 8.35-8.24 (m, 1H), 7.48-7.25 (m, 4H), 6.83-6.79 (m, 1H), 6.62-6.59 (m, 1H), 4.91-4.76 (m, 1H), 4.53-4.46 (m, 1H), 4.35-4.31 (m, 1H), 4.10 (s, 2H), 3.02-3.00 (m, 2H), 2.96 (s, 3H), 2.75 (s, 3H), 1.96-1.44 (m, 18H), 1.28-1.06 (m, 6H), 0.96-0.90 (m, 8H). ^{13}C NMR (150 MHz, MeOD) δ 175.12, 175.04, 175.02, 174.35, 174.27, 173.10, 163.20, 146.48, 144.56, 139.59, 135.36, 132.98, 131.88, 131.27, 130.23, 126.12, 54.43, 54.39, 54.07, 54.04, 53.72, 53.68, 53.63, 53.59, 52.55, 52.53, 52.46, 52.43, 44.72, 44.69, 44.04, 42.76, 41.27, 41.24, 40.37, 39.86, 36.16, 35.81, 34.92, 33.87, 32.56, 31.72, 31.41, 30.96, 30.89, 29.49, 27.94, 27.86, 27.84, 26.74, 26.53, 25.97, 23.48, 21.68, 19.13. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 6.90 (ESI-MS (m/z): 728.40, ($M+H^+$)). HRMS calculated for $C_{38}H_{57}N_5O_5S_2$ 728.38739 $[M+H]^+$; found 728.38769.

Methia-Cha-Cha-Phe(4-CH_2NH_2)-VS TFA salt (**36**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (42%-47% MeCN-H_2O) yielded the title compound (6.5 mg, 9.2 μmol, 18%). ^{1}H NMR (600 MHz, MeOD) δ 8.26 (s, 1H), 7.38 (d, J = 8.1 Hz, 2H), 7.33-7.27 (m, 2H), 6.79 (dd, J = 15.2, 5.2 Hz, 1H), 6.58 (dd, J = 15.2, 1.5 Hz, 1H), 4.85-4.80 (m, 1H), 4.52-4.49 (m, 1H), 4.37-4.33 (m, 1H), 4.08 (s, 2H), 3.02-2.96 (m, 2H), 2.94 (s, 3H), 2.73 (s, 3H), 2.66 (s, 1H), 1.93-0.77 (m, 27H). ^{13}C NMR (150 MHz, MeOD) δ 174.97, 174.89, 174.43, 174.35, 173.14, 163.13, 146.55, 144.55, 139.60, 135.38, 132.98, 131.85, 131.26, 130.23, 53.82, 52.89, 52.86, 52.80, 52.77, 52.51, 52.42, 44.05, 42.78, 40.35, 40.01, 39.97, 39.81, 35.48, 35.39, 34.88, 34.65, 33.68, 33.12, 27.55, 27.52, 27.42, 27.35, 27.25, 27.21, 19.14. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 6.12 (ESI-MS (m/z): 686.33, ($M+H^+$)). HRMS calculated for $C_{35}H_{51}N_5O_5S_2$ 686.34044 $[M+H]^+$; found 686.34011.

Morph-Ala-Try(Me)-Chg-EK TFA salt (**37**). The corresponding warhead (Boc-Chg-EK) was de-protected according to general procedure B, follow by azide coupling using the general procedure D on a 50 μmol scale. Purification by HPLC (30%-45% MeCN-H_2O) yielded the title compound (11.5 mg, 16.8 μmol, 34%). ^{1}H NMR (600 MHz, MeOD) δ 7.10 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 4.59-4.57 (m, 1H), 4.45-4.37 (m, 2H), 3.77 (s, 3H), 3.74-3.69 (m, 4H), 3.15 (d, J = 5.0 Hz, 1H), 3.09-2.79 (m, 5H), 2.50 (t, J = 4.5 Hz, 4H), 1.80-1.63 (m, 5H), 1.51-1.46 (m, 1H), 1.44 (s, 3H), 1.33 (d, J = 7.1 Hz, 3H), 1.28-1.15 (m, 4H), 1.03-0.96 (m, 1H). ^{13}C NMR (150 MHz, MeOD) δ 210.17, 174.25, 172.96, 172.02, 159.96, 131.39, 129.81, 114.77, 67.85, 62.39, 60.09, 55.83, 55.61, 54.71, 52.22, 49.66, 41.62, 38.06, 30.89, 29.65, 27.18, 27.14, 27.03, 18.62, 16.21. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 5.53 (ESI-MS (m/z): 573.33, ($M+H^+$)). HRMS calculated for $C_{30}H_{44}N_4O_7$ 573.32828 $[M+H]^+$; found 573.32812.

Morp-Ala-Tyr(Me)-Cha(4,4-2F)-EK TFA salt (**38**). The corresponding warhead (Boc-Cha(4,4-2F)-EK) was deprotected according to general procedure B, follow by azide coupling using the general procedure D on a 50 μmol scale. Purification by HPLC (30%-45% MeCN-H_2O) yielded the title compound (11.4 mg, 15.5 μmol, 31%). ^{1}H NMR (400 MHz, MeOD) δ 7.19-7.11 (m, 2H), 6.87-6.76 (m, 2H), 4.62-4.50 (m, 2H), 4.37 (q, J = 7.1 Hz, 1H), 4.03-3.85 (m, 6H), 3.78 (s, 3H), 3.19 (d, J = 5.0 Hz, 1H), 3.06-3.01 (m, 1H), 2.96 (d, J = 5.0 Hz, 1H), 2.88-2.82 (m, 1H), 2.07-1.50 (m, 8H), 1.48 (s, 3H), 1.43-1.18 (m, 6H). ^{13}C NMR (100 MHz, MeOD) δ 208.90, 174.22, 173.38, 165.06, 159.99, 131.38, 129.91, 126.99, 124.60, 122.22, 114.80, 64.87, 59.93, 58.38, 55.84, 55.64, 53.92, 52.94, 50.66, 50.50, 38.05, 37.38, 34.60, 34.35, 34.12, 33.87, 33.65, 30.75, 30.65, 28.80, 28.71, 18.07, 16.78. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 5.72 (ESI-MS (m/z): 623.00, ($M+H^+$)). HRMS calculated for $C_{31}H_{44}F_2N_4O_7$ 623.32508 [M+H]+; found 623.32499.

Morp-Ala-Tyr(Me)-HomoCha-EK TFA salt (**39**). The corresponding warhead (Boc-HomoCha-EK) was deprotected according to general procedure B, follow by azide coupling using the general procedure D on a 50 μmol scale. Purification by HPLC (30%-45% MeCN-H_2O) yielded the title compound (12.3 mg, 17.2 μmol, 34%). ^{1}H NMR (600 MHz, MeOD) δ 7.25-7.01 (m, 2H), 6.91-6.67 (m, 2H), 4.60-4.57 (m,

1H), 4.48-4.28 (m, 2H), 3.77 (s, 3H), 3.71-3.70 (m, 4H), 3.21 (d, J = 4.9 Hz, 1H), 3.09-2.88 (m, 4H), 2.84-2.79 (m, 1H), 2.56-2.37 (m, 4H), 1.83-1.63 (m, 6H), 1.52-1.39 (m, 4H), 1.38-1.16 (m, 9H), 0.97-0.83 (m, 2H). ^{13}C NMR (150 MHz, MeOD) δ 209.19, 174.20, 173.30, 171.99, 159.94, 131.41, 130.02, 114.75, 67.85, 62.40, 60.01, 55.75, 55.60, 54.71, 53.06, 52.92, 49.65, 38.48, 38.15, 34.61, 34.02, 29.11, 27.72, 27.44, 27.38, 18.65, 16.84. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 6.23 (ESI-MS (m/z): 601.33, ($M+H^+$)). HRMS calculated for $C_{32}H_{48}N_4O_7$ 601.35958 $[M+H]^+$; found 601.35945.

Morp-Ala-Tyr(Me)-Cha(4-CF_3)-EK TFA salt (**40**). The corresponding warhead (Boc-Cha(4-CF_3)- EK) was deprotected according to general procedure B, follow by azide coupling using the general procedure D on a 50 μmol scale. Purification by HPLC (30%-45% MeCN-H_2O) yielded the title compound (15.0 mg, 19.5 μmol, 39%). ^{1}H NMR (400 MHz, MeOD) δ 7.18-7.08 (m, 2H), 6.85-6.77 (m, 2H), 4.62-4.54 (m, 1H), 4.50-4.47 (m, 1H), 4.38-4.32 (m, 1H), 3.96-3.86 (m, 6H), 3.76 (s, 3H), 3.19-3.16 (m, 1H), 3.09-2.77 (m, 3H), 2.13 (s, 1H), 2.01-1.17 (m, 18H). ^{13}C NMR (100 MHz, MeOD) δ 209.05, 174.16, 173.34, 165.13, 159.99, 131.42, 129.96, 114.80, 64.90, 60.06, 58.44, 55.66, 53.94, 53.04, 51.07, 50.52, 41.80, 38.13, 34.96, 33.72, 33.07, 31.19, 30.80, 30.53, 27.43, 21.63, 21.11, 18.05, 16.84. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 6.18 (ESI-MS (m/z): 655.20, ($M+H^+$)). HRMS calculated for $C_{32}H_{45}F_3N_4O_7$ 655.33131 $[M+H]^+$; found 655.33133.

Morp-Ala-Tyr(Me)-Cha(4-Me)-EK TFA salt (**41a** and **41b**). The corresponding warhead (Boc-Cha(4-Me)-EK) was deprotected according to general procedure B, followed by azide coupling using the general procedure D on a 100 μmol scale. Purification by HPLC (35%-40% MeCN-H_2O) yielded the title compounds (**41a**: 12.7 mg, 17.8 μmol, 18% and **41b**: 7.5 mg, 10.5 μmol, 11%). **41a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.1 Hz, 1H), 7.15-7.06 (m, 2H), 6.84-6.71 (m, 3H), 6.29 (d, J = 7.8 Hz, 1H), 4.60-4.35 (m, 3H), 3.77 (s, 3H), 3.71 (t, J = 4.6 Hz, 4H), 3.26 (d, J = 5.0 Hz, 1H), 3.05-2.84 (m, 5H), 2.49 (s, 4H), 1.80-1.74 (m, 1H), 1.62-1.09 (m, 17H), 0.90 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.23, 171.96, 170.77, 158.66, 130.51, 128.35, 114.06, 66.93, 61.63, 59.19, 55.32, 54.42, 53.82, 52.54, 50.10, 48.55, 36.83, 35.48, 31.71, 30.79, 30.34, 30.26, 29.97, 27.26, 20.42, 17.78, 16.83.

LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 6.18 (ESI-MS (m/z): 601.27, ($M+H^+$)). HRMS calculated for $C_{32}H_{48}N_4O_7$ 601.35958 $[M+H]^+$; found 601.35938. **41b**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.17-7.07 (m, 2H), 6.86-6.77 (m, 2H), 6.73 (d, J = 7.5 Hz, 1H), 6.24 (d, J = 7.8 Hz, 1H), 4.58-4.34 (m, 3H), 3.78 (s, 3H), 3.73 (t, J = 4.7 Hz, 4H), 3.26 (d, J = 4.0 Hz, 1H), 3.10-2.85 (m, 5H), 2.52 (s, 4H), 1.84-1.44 (m, 9H), 1.37 (d, J = 7.1 Hz, 3H), 1.31-1.06 (m, 4H), 0.89-0.83 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.26, 171.94, 170.72, 158.68, 130.53, 114.10, 66.86, 61.56, 59.17, 55.33, 54.41, 53.79, 52.52, 49.88, 48.63, 38.67, 36.83, 35.24, 34.99, 34.29, 33.97, 32.65, 32.00, 22.75, 17.71, 16.85. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 6.26 (ESI-MS (m/z): 601.27, ($M+H^+$)). HRMS calculated for $C_{32}H_{48}N_4O_7$ 601.35958 $[M+H]^+$; found 601.35944.

Morp-Ala-Tyr(Me)-Cha(4-OMe)-EK TFA salt (**42**). The corresponding warhead (Boc-Cha(4- OMe)-EK) was deprotected according to general procedure B, follow by azide coupling using the general procedure D on a 80 μmol scale. Purification by HPLC (30%-40% MeCN-H_2O) yielded the title compound (15.3 mg, 20.9 μmol, 26%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 8.5 Hz, 2H), 6.82-6.78 (m, 3H), 6.29 (d, J = 7.9 Hz, 1H), 4.58-4.53 (m, 2H), 4.47-4.40 (m, 1H), 3.77 (s, 3H), 3.71 (t, J = 4.6 Hz, 4H), 3.40-3.37 (m, 1H), 3.29 (s, 3H), 3.23 (d, J = 5.0 Hz, 1H), 3.05-2.85 (m, 5H), 2.49 (s, 4H), 1.89-1.79 (m, 2H), 1.65-1.59 (m, 2H), 1.54-1.50 (m, 4H), 1.45-1.24 (m, 9H), 1.20-1.13 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.22, 171.96, 170.71, 158.66, 130.49, 128.33, 114.06, 75.24, 66.93, 61.63, 59.10, 55.67, 55.31, 54.49, 53.81, 52.45, 49.83, 48.52, 37.84, 36.91, 33.35, 29.20, 28.51, 28.00, 25.96, 17.78, 16.81. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 5.23 (ESI-MS (m/z): 617.33, ($M+H^+$)). HRMS calculated for $C_{32}H_{48}N_4O_8$ 617.35449 $[M+H]^+$; found 617.35438.

Morp-Ala-Tyr(Me)-2-DecAla-EK TFA salt (**43**). The corresponding warhead (Boc-2-DecAla-EK) was deprotected according to general procedure B, followed by azide coupling using the general procedure D on a 70 μmol scale. Purification by HPLC (45%-50% MeCN-H_2O) yielded the title compound (21.2 mg, 28.1 μmol, 40%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.12 (d, J = 8.4 Hz, 2H), 6.84-6.71

(m, 3H), 6.26 (d, J = 8.0 Hz, 1H), 4.56-4.53 (m, 2H), 4.45-4.39 (m, 1H), 3.77 (s, 3H), 3.71 (t, J = 4.6 Hz, 4H), 3.25-3.25 (m, 1H), 3.06-2.83 (m, 5H), 2.50 (s, 4H), 1.72-0.99 (m, 25H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.28, 171.96, 170.70, 158.67, 130.52, 128.37, 114.08, 66.91, 61.62, 59.23, 59.17, 55.31, 54.45, 54.41, 53.81, 49.79, 48.56, 38.94, 38.86, 36.89, 36.85, 36.13, 35.87, 35.76, 35.73, 35.29, 35.17, 33.41, 32.42, 32.38, 32.14, 31.39, 28.46, 27.09, 27.05, 26.46, 25.81, 25.75, 21.00, 17.79, 16.85. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 6.81 (ESI-MS (m/z): 641.33, ($M+H^+$)). HRMS calculated for $C_{35}H_{52}N_4O_7$ 641.39088 $[M+H]^+$; found 641.39069.

Morp-Ala-Tyr(Me)-BiCha-EK TFA salt (**44a** and **44b**). The corresponding warhead (Boc-BiCha-EK) was deprotected according to general procedure B, followed by azide coupling using the general procedure D on a 87 µmol scale. Purification by HPLC (55%-65% MeCN-H_2O) yielded the title compounds (**44a**: 17.7 mg, 22.6 µmol, 26% and **44b**: 5.9 mg, 7.5 µmol, 8.6%). **44a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.15-7.07 (m, 2H), 6.84-6.70 (m, 3H), 6.30 (d, J = 7.8 Hz, 1H), 4.61-4.34 (m, 3H), 3.77 (s, 3H), 3.71 (t, J = 4.6 Hz, 4H), 3.27 (d, J = 5.0 Hz, 1H), 3.05-2.85 (m, 5H), 2.49 (s, 4H), 1.84-1.60 (m, 6H), 1.54-1.25 (m, 15H), 1.22-1.05 (m, 6H), 0.91-0.82 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.13, 171.84, 170.68, 158.55, 130.40, 128.24, 113.95, 66.82, 61.52, 59.11, 55.21, 54.30, 53.71, 52.46, 50.07, 48.45, 41.65, 40.24, 36.72, 34.69, 31.19, 30.68, 30.51, 27.77, 26.74, 25.60, 25.13, 17.69, 16.72. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 7.37 (ESI-MS (m/z): 669.33, ($M+H^+$)). HRMS calculated for $C_{37}H_{56}N_4O_7$ 669.42218 $[M+H]^+$; found 669.42216. **44b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.17-7.09 (m, 2H), 6.87-6.74 (m, 3H), 6.24 (d, J = 7.5 Hz, 1H), 4.58-4.50 (m, 2H), 4.44-4.37 (m, 1H), 3.77-3.74 (m, 7H), 3.25 (d, J = 5.0 Hz, 1H), 3.14-2.80 (m, 5H), 2.55 (s, 4H), 1.72-1.62 (m, 8H), 1.50 (s, 4H), 1.37 (d, J = 7.1 Hz, 3H), 1.24-0.79 (m, 14H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.28, 171.92, 170.73, 158.69, 130.54, 128.36, 114.10, 59.17, 55.33, 54.41, 53.74, 52.52, 49.92, 43.35, 43.29, 38.69, 36.85, 34.80, 34.25, 32.32, 30.36, 30.32, 29.88, 29.68, 26.96, 17.69, 16.86. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 7.47 (ESI-MS (m/z): 669.40, ($M+H_+$)). HRMS calculated for $C_{37}H_{56}N_4O_7$ 669.42218 $[M+H]^+$; found 669.42209.

Morp-Ala-Tyr(Me)-NorAla-EK TFA salt (**45**). The corresponding warhead (Boc-NorAla-EK) was deprotected according to general procedure B, followed by azide coupling using the general procedure D on a 50 µmol scale. Purification by HPLC (30%-45% MeCN-H_2O) yielded the title compound (6.6 mg, 9.3 µmol, 19%). ^{1}H NMR (600 MHz, MeOD) δ 7.17-7.08 (m, 2H), 6.87-6.78 (m, 2H), 4.65 (s, 1H), 4.62-4.50 (m, 1H), 4.50-4.34 (m, 2H), 3.77 (s, 3H), 3.74-3.70 (m, 4H), 3.23-3.21 (m, 1H), 3.10-3.01 (m, 2H), 3.01-2.91 (m, 2H), 2.84-2.80 (m, 1H), 2.52-2.47 (m, 4H), 2.26-2.01 (m, 2H), 1.99-1.63 (m, 2H), 1.58-1.28 (m, 12H), 1.28-1.06 (m, 3H). ^{13}C NMR (150 MHz, MeOD) δ 209.15, 174.19, 173.27, 172.04, 159.94, 131.41, 130.00, 114.75, 67.86, 62.40, 60.01, 54.70, 53.01, 52.90, 52.32, 52.25, 51.15, 49.69, 49.64, 43.25, 42.03, 41.21, 40.99, 40.75, 40.19, 39.97, 39.64, 38.63, 38.43, 38.36, 38.05, 38.03, 37.84, 37.72, 37.12, 36.22, 35.96, 35.20, 34.40, 31.02, 30.78, 29.70, 29.57, 23.61, 22.95, 18.65, 16.89. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 5.96 (ESI-MS (m/z): 599.40, ($M+H^+$)). HRMS calculated for $C_{32}H_{46}N_4O_7$ 599.34393 $[M+H]^+$; found 599.34371.

N_3Phe-Phe(4-CH_2NH_2)-Leu-Chg-EK (**46**). This compound was prepared according to the general procedure A on a 50 µmol scale, followed by the removal of the Boc protecting group using the general procedure D. Purification by HPLC (40%-50% MeCN-H_2O) yielded the title compound (7.8 mg, 10.0 µmol, 20%). 1H NMR (850 MHz, MeOD) δ 8.28 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 8.1 Hz, 2H), 7.33-7.28 (m, 4H), 7.27-7.23 (m, 3H), 4.75-4.62 (m, 1H), 4.47-4.43 (m, 2H), 4.09 (s, 2H), 4.05-4.01 (m, 1H), 3.28 (d, J = 5.2 Hz, 1H), 3.18-3.11 (m, 2H), 2.93 (d, J = 5.2 Hz, 1H), 2.92-2.84 (m, 2H), 1.82-1.77 (m, 3H), 1.74-1.64 (m, 3H), 1.57-1.51 (m, 3H), 1.47 (s, 3H), 1.34-1.21 (m, 4H), 1.11-1.06 (m, 1H), 0.98-0.97 (m, 3H), 0.94-0.93 (m, 3H). 13C NMR (213 MHz, MeOD) δ 210.58, 174.46, 172.65, 171.36, 139.48, 137.85, 132.86, 131.27, 130.35, 130.02, 129.63, 128.09, 65.45, 60.51, 56.77, 55.26, 52.93, 52.37, 44.06, 41.88, 41.47, 38.85, 38.75, 30.97, 29.82, 27.28, 27.16, 27.13, 25.82, 23.39, 22.11, 16.45. LC-MS (linear gradient 10 → 90% MeCN/H2O, 0.1% TFA, 12.5 min): Rt (min): 6.73 (ESI-MS (m/z): 660.33, (M+H+)). HRMS calculated for C36H49N7O5 660.38679 [M+H]+; found 660.38700.

N_3Phe-Phe(4-CH_2NH_2)-Leu-HomoCha-EK (**47**). This compound was prepared according to the general procedure A on a 50 µmol scale, followed by the removal of the Boc protecting group using the general

procedure D. Purification by HPLC (45%-55% MeCN-H_2O) yielded the title compound (8.1 mg, 10.1 μmol, 20%). ^{1}H NMR (850 MHz, MeOD) δ 7.38-7.36 (m, 2H), 7.33-7.28 (m, 4H), 7.27-7.18 (m, 3H), 4.73-4.67 (m, 1H), 4.47-4.38 (m, 2H), 4.09 (s, 2H), 4.04-4.00 (m, 1H), 3.27-3.25 (m, 1H), 3.19-3.09 (m, 2H), 2.96 (d, J = 5.2 Hz, 1H), 2.92-2.83 (m, 2H), 1.86-1.80 (m, 2H), 1.76-1.65 (m, 5H), 1.60-1.54 (m, 2H), 1.50-1.45 (m, 4H), 1.39-1.33 (m, 1H), 1.29-1.15 (m, 5H), 1.02-0.88 (m, 8H). ^{13}C NMR (213 MHz, MeOD) δ 209.37, 174.62, 172.65, 171.39, 139.54, 137.86, 132.84, 131.26, 130.35, 130.02, 129.63, 128.09, 65.43, 60.24, 55.33, 53.71, 53.03, 52.83, 44.06, 41.99, 38.85, 38.57, 34.81, 34.63, 34.04, 28.83, 27.71, 27.45, 27.38, 25.79, 23.42, 22.11, 16.99. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 7.25 (ESI-MS (m/z): 688.33, ($M+H^+$)). HRMS calculated for $C_{38}H_{53}N_7O_5$ 688.41809[$M+H]^+$; found 688.41829.

N_3Phe-Phe(4-CH_2NH_2)-Leu-Cha(4-Me)-EK (**48**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (45%-55% MeCN-H_2O) yielded the title compound (8.7 mg, 10.8 μmol, 22%). ^{1}H NMR (850 MHz, MeOD) δ 7.39-7.19 (m, 9H), 4.72-4.66 (m, 1H), 4.58-4.51 (m, 1H), 4.46-4.43 (m, 1H), 4.08 (s, 2H), 4.05-3.98 (m, 1H), 3.27-3.26 (m, 1H), 3.20-3.08 (m, 2H), 2.97-2.95 (m, 1H), 2.91-2.80 (m, 2H), 1.90-1.84 (m, 1H), 1.75-1.64 (m, 3H), 1.64-1.23 (m, 14H), 1.01-0.93 (m, 8H), 0.88-0.87 (m, 1H). ^{13}C NMR (213 MHz, MeOD) δ 209.61, 174.69, 174.58, 172.66, 172.65, 171.60, 171.39, 139.56, 137.86, 132.84, 131.25, 131.20, 130.34, 130.32, 130.03, 130.01, 129.63, 129.61, 128.08, 65.45, 60.25, 60.18, 55.41, 55.33, 53.12, 53.08, 52.86, 51.73, 51.43, 44.06, 42.03, 41.98, 38.85, 38.77, 38.54, 36.37, 36.15, 35.46, 35.08, 33.94, 32.93, 31.35, 31.13, 28.00, 25.79, 23.43, 23.04, 22.11, 17.08. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 7.17 (ESI-MS (m/z): 688.40, ($M+H^+$)). HRMS calculated for $C_{38}H_{53}N_7O_5$ 688.41809 [$M+H]^+$; found 688.41844.

N_3Phe-Phe(4-CH_2NH_2)-Leu-Cha(4-OMe)-EK (**49**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (40%-50% MeCN-H_2O) yielded the title compound (8.6 mg, 10.5 μmol, 21%). ^{1}H NMR (850 MHz, MeOD) δ 7.39-7.18 (m, 9H), 4.71-4.67 (m, 1H), 4.57-4.55

(m, 1H), 4.45-4.42 (m, 1H), 4.09 (s, 2H), 4.04-4.00 (m, 1H), 3.44-3.42 (m, 1H), 3.32 (s, 3H), 3.27 (d, J = 5.2 Hz, 1H), 3.19-3.15 (m, 1H), 3.13-3.10 (m, 1H), 2.96 (d, J = 5.2 Hz, 1H), 2.91-2.83 (m, 2H), 1.87 (t, J = 14.0 Hz, 2H), 1.74-1.42 (m, 12H), 1.40-1.28 (m, 3H), 1.02-0.94 (m, 6H). ^{13}C NMR (213 MHz, MeOD) δ 209.57, 174.64, 174.63, 172.66, 172.64, 171.60, 171.38, 139.65, 139.56, 137.86, 137.74, 136.11, 135.86, 132.85, 131.25, 131.20, 130.35, 130.32, 130.04, 130.02, 129.63, 129.61, 128.09, 76.96, 65.46, 65.39, 60.21, 55.80, 55.42, 55.33, 53.09, 52.91, 51.39, 44.05, 44.02, 42.02, 41.99, 39.05, 38.86, 38.75, 38.48, 29.87, 29.60, 29.05, 26.77, 26.39, 25.79, 23.43, 22.11, 17.07. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 6.43 (ESI-MS (m/z): 704.33, ($M+H^+$)). HRMS calculated for $C_{38}H_{53}N_7O_6$ 704.41301 $[M+H]^+$; found 704.41334.

N_3Phe-Phe(4-CH_2NH_2)-Leu-1-DecAla-EK (**50**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (55%-70% MeCN-H_2O) yielded the title compound (4.1 mg, 4.9 μmol, 10%). ^{1}H NMR (850 MHz, MeOD) δ 7.39-7.23 (m, 9H), 4.71-4.69 (m, 1H), 4.67-4.61 (m, 1H), 4.56-4.51 (m, 1H), 4.47-4.43 (m, 1H), 4.09 (s, 2H), 4.03-4.00 (m, 2H), 3.27-3.24 (m, 1H), 3.20-3.16 (m, 1H), 3.12-3.10 (m, 1H), 2.97-2.94 (m, 1H), 2.91-2.88 (m, 1H), 2.86-2.82 (m, 1H), 1.81-1.17 (m, 25H), 1.01-0.99 (m, 3H), 0.96-0.94 (m, 3H). ^{13}C NMR (213 MHz, MeOD) δ 210.03, 209.68, 174.75, 174.63, 172.64, 171.39, 162.70, 162.53, 139.62, 137.88, 132.85, 131.25, 130.34, 130.03, 129.63, 128.09, 65.45, 60.16, 55.35, 53.09, 52.89, 51.69, 51.03, 49.37, 44.45, 44.07, 43.20, 42.02, 41.98, 39.86, 39.49, 39.13, 36.11, 35.69, 35.50, 34.63, 33.74, 32.47, 31.11, 28.01, 27.90, 27.73, 27.55, 27.04, 25.81, 23.42, 22.33, 22.15, 21.25, 17.06. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 7.65 (ESI-MS (m/z): 728.33, ($M+H^+$)). HRMS calculated for $C_{41}H_{57}N_7O_5$ 728.44939 $[M+H]^+$; found 728.44986.

N_3Phe-Phe(4-CH_2NH_2)-Leu-2-DecAla-EK (**51**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (55%-70% MeCN-H_2O) yielded the title compound (7.6 mg, 9.0 μmol, 18%). ^{1}H NMR (850 MHz, MeOD) δ 7.41-7.18 (m, 9H), 4.73-4.67 (m, 1H), 4.62-4.54 (m, 1H),

4.47-4.40 (m, 1H), 4.09 (s, 2H), 4.04-4.01 (m, 1H), 3.29-3.08 (m, 3H), 2.98-2.81 (m, 3H), 1.83-1.03 (m, 25H), 1.03-0.89 (m, 6H). ^{13}C NMR (213 MHz, MeOD) δ 209.69, 209.64, 174.57, 172.70, 172.65, 171.40, 162.65, 162.48, 139.62, 139.58, 137.87, 132.85, 131.25, 131.19, 130.34, 130.33, 130.03, 130.02, 129.63, 129.61, 128.08, 65.44, 65.39, 60.24, 60.20, 55.43, 55.36, 55.34, 53.11, 53.10, 52.88, 51.39, 51.30, 44.06, 44.03, 41.98, 40.40, 39.06, 38.86, 38.82, 38.79, 38.69, 37.51, 37.30, 37.26, 37.21, 36.48, 36.45, 34.45, 33.63, 33.48, 33.44, 33.26, 32.32, 29.47, 28.15, 27.39, 26.86, 25.80, 23.41, 23.40, 22.17, 22.14, 22.01, 21.98, 17.10. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 7.68 (ESI-MS (m/z): 728.33, ($M+H^+$)). HRMS calculated for $C_{41}H_{57}N_7O_5$ 728.44939 $[M+H]^+$; found 728.44991.

N_3Phe-Phe(4-CH_2NH_2)-Leu-BiCha-EK (**52**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (60%-70% MeCN-H_2O) yielded the title compound (3.1 mg, 3.6 μmol, 7%). ^{1}H NMR (600 MHz, MeOD) δ 7.41-7.15 (m, 9H), 4.71-4.67 (m, 1H), 4.52-4.49 (m, 1H), 4.46-4.43 (m, 1H), 4.07 (s, 2H), 4.04-4.00 (m, 1H), 3.28-3.25 (m, 1H), 3.19-3.10 (m, 2H), 2.98-2.95 (m, 1H), 2.93-2.79 (m, 2H), 1.95-1.89 (m, 1H), 1.82-1.33 (m, 20H), 1.31-1.09 (m, 6H), 1.02-0.91 (m, 8H). ^{13}C NMR (150 MHz, MeOD) δ 209.62, 174.71, 172.66, 171.41, 139.47, 137.86, 133.18, 131.27, 131.25, 130.35, 130.33, 129.97, 129.64, 128.10, 65.46, 60.30, 60.19, 55.34, 53.17, 52.86, 51.44, 49.57, 48.57, 44.73, 44.17, 42.02, 41.93, 38.86, 38.77, 31.91, 31.66, 31.64, 31.41, 28.63, 27.95, 27.88, 26.56, 26.08, 25.80, 23.44, 22.12, 17.11. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 8.24 (ESI-MS (m/z): 756.33, ($M+H^+$)). HRMS calculated for $C_{43}H_{61}N_7O_5$ 756.48069 $[M+H]^+$; found 756.48145.

N_3Phe-Phe(4-CH_2NH_2)-Leu-NorAla-EK (**53**). This compound was prepared according to the general procedure D on a 50 μmol scale, followed by the removal of the Boc protecting group using the general procedure B. Purification by HPLC (40%-50% MeCN-H_2O) yielded the title compound (3.9 mg, 4.9 μmol, 10%). ^{1}H NMR (850 MHz, MeOD) δ 7.41-7.17 (m, 9H), 4.74-4.64 (m, 2H), 4.47-4.38 (m, 2H), 4.09 (s, 2H), 4.03-3.99 (m, 1H), 3.28-3.25 (m, 1H), 3.19-3.15 (m, 1H), 3.12-3.10 (m, 1H), 2.98-2.94 (m,

1H), 2.91-2.82 (m, 2H), 2.26-2.12 (m, 3H), 1.85-1.46 (m, 12H), 1.42-1.23 (m, 4H), 1.03-0.90 (m, 6H). ^{13}C NMR (213 MHz, MeOD) δ 209.66, 209.34, 174.60, 174.52, 172.66, 171.39, 139.69, 139.59, 137.86, 137.74, 132.84, 131.26, 131.21, 130.34, 130.32, 130.02, 129.63, 128.09, 65.44, 60.33, 60.26, 55.34, 55.30, 53.12, 53.01, 52.95, 52.87, 51.73, 44.07, 43.31, 42.11, 42.02, 41.98, 41.15, 41.02, 40.79, 40.14, 40.08, 39.67, 38.85, 38.80, 38.50, 38.46, 38.23, 38.08, 38.06, 37.97, 37.83, 37.80, 37.06, 36.22, 35.98, 34.05, 31.04, 30.99, 30.95, 30.82, 29.73, 29.60, 25.80, 23.64, 23.41, 22.98, 22.12, 17.06. LC-MS (linear gradient 10 → 90% MeCN/H_2O, 0.1% TFA, 12.5 min): Rt (min): 6.98 (ESI-MS (m/z): 686.27, ($M+H^+$)). HRMS calculated for $C_{38}H_{51}N_7O_5$ 686.40244 $[M+H]^+$; found 686.40278.

Boc-Tyr(O-$C_2H_4N_3$)-OMe (**90**). Boc-Tyr-OMe **88** (442 mg, 1.5 mmol) was dissolved in anhydrous DMF, followed by the addition of compound **89** (433 mg, 1.8 mmol, 1.2 eq.) and K_2CO_3 (830 mg, 6 mmol, 4.0 eq.). The reaction mixture was stirred for 48h at 80 °C when TLC analysis showed formation of the product. The reaction mixture was concentrated *in vacuo* and redissovled in EtOAc and washed with H_2O (3x) and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel column chromatography (4% EtOAc/pentane → 20% EtOAc/pentane) yielded the title compound (437 mg, 1.2 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 8.1 Hz, 2H), 6.84 (d, J = 7.8 Hz, 2H), 5.19 (d, J = 7.3 Hz, 1H), 4.52 (d, J = 6.7 Hz, 1H), 4.16-4.00 (m, 2H), 3.69 (s, 3H), 3.53 (d, J = 4.3 Hz, 2H), 3.16-2.86 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.18, 171.52, 157.10, 154.96, 130.18, 130.09, 128.64, 128.48, 114.42, 79.56, 77.48, 77.16, 76.84, 66.77, 63.93, 63.50, 61.10, 60.15, 54.43, 53.22, 51.95, 49.91, 49.35, 37.69, 37.16, 29.45, 28.08. HRMS calculated for $C_{17}H_{24}N_4O_5$ 365.18195 $[M+H]^+$; found 365.18204.

Boc-Ala-Tyr(O-C2H4N3)-OMe (**91**). Boc protecting group of Compound **90** (302 mg, 0.83 mmol) was removed according to general procedure B, followed by the peptide coupling with Boc-Ala-OH according to general procdure A. Purification by flush column chromatography (5% EtOAc/pentane → 50% EtOAc/pentane) yielded the titled compound (336 mg, 0.77 mmol, 93%). 1H NMR (400 MHz, CDCl3) δ 7.04 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 6.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 2H), 5.45 (d, J = 6.3 Hz, 1H), 4.79 (d, J = 6.5 Hz, 1H), 4.22 (s, 1H), 4.09 (t, J = 4.8 Hz, 2H), 3.68 (s, 3H), 3.55 (d, J = 4.8 Hz,

2H), 3.06 (td, J = 15.9, 14.9, 5.9 Hz, 2H), 1.43 (s, 9H), 1.37-1.22 (m, 4H). 13C NMR (100 MHz, CDCl3) δ 172.47, 171.68, 157.12, 155.24, 130.23, 128.45, 114.41, 79.65, 77.48, 77.16, 76.84, 66.74, 53.27, 52.11, 49.97, 36.83, 29.49, 28.15, 18.25. HRMS calculated for C20H29N5O6 436.21906 [M+H]+; found 436.21908.

Morp-Ala-Tyr(O-$C_2H_4N_3$)-OMe (**92**). The Boc protecting group in compound **91** (336 mg, 0.77 mmol) was removed according to general procedure B, followed by peptide coupling with 2-morpholinoacetic acid according to general procedure A. Purification by silica gel column chromatography (0% MeOH/DCM → 3% MeOH/DCM) yielded the title compound (116 mg, 0.25 mmol, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.2 Hz, 1H), 7.12-6.99 (m, 2H), 6.92 (d, J = 7.8 Hz, 1H), 6.88-6.74 (m, 2H), 4.86-4.71 (m, 1H), 4.56 (p, J = 7.1 Hz, 1H), 4.10 (q, J = 5.0 Hz, 2H), 3.72 (s, 3H), 3.72-3.65 (m, 4H), 3.58 (q, J = 4.6 Hz, 2H), 3.10 (dd, J = 13.9, 5.6 Hz, 1H), 3.04-2.97 (m, 2H), 2.97-2.86 (m, 1H), 2.49 (t, J = 4.6 Hz, 4H), 1.37 (d, J = 7.0 Hz, 3H), 1.21 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.88, 171.80, 171.77, 169.84, 169.81, 157.30, 157.25, 130.37, 130.32, 128.58, 128.52, 114.55, 77.48, 77.16, 76.84, 66.93, 66.90, 66.87, 61.74, 61.70, 53.71, 53.49, 52.37, 50.12, 48.05, 36.96, 36.80, 29.65, 18.36. HRMS calculated for $C_{21}H_{30}N_6O_6$ 463.22966 $[M+H]^+$; found 463.22974.

Morph-Ala-Tyr(O-$C_2H_4N_3$)-N_2H_4 (**93**). Compound **92** (116 mg, 0.25 mmol) was dissolved in MeOH, followed by addition of hydrazine monohydrate (0.36 ml, 7.5 mmol, 30 eq.). The reaction mixture was stirred overnight at room temperature and then refluxed at 70 °C until TLC analysis showed complete conversion of the starting material. The reaction mixture was concentrated in vacuo and then co-evaporated with toluene (3x) which yielded the title compound in quantitative yield and used without further purification.

Morp-Ala-Tyr(O-$C_2H_4N_3$)-1-DecAla-EK (**95**). H-1-DecAla-EK (**94**) was prepared according to literature procedure,[10] and subjected to azide coupling to **93** using the general procedure D on a 66 μmol scale. Purification by flash column chromatography (0% MeOH/DCM → 3% MeOH/DCM) yielded the title compound (30 mg, 37 μmol, 56%). ^{1}H NMR (600 MHz, MeOD) δ 7.23 (d, J = 8.6 Hz, 2H), 6.92

(d, J = 8.6 Hz, 2H), 4.74-4.63 (m, 1H), 4.63-4.53 (m, 1H), 4.44 (q, J = 7.1 Hz, 1H), 4.21 (t, J = 4.8 Hz, 3H), 4.11-3.84 (m, 7H), 3.66 (dd, J = 5.6, 3.8 Hz, 2H), 3.25 (dd, J = 24.5, 5.1 Hz, 2H), 3.12 (dd, J = 14.0, 5.9 Hz, 1H), 3.05-2.96 (m, 1H), 2.91 (ddd, J = 13.5, 8.4, 5.0 Hz, 1H), 2.74 (s, 1H), 2.14-1.81 (m, 3H), 1.77 (dq, J = 19.5, 7.5, 5.4 Hz, 3H), 1.70-1.56 (m, 7H), 1.56-1.51 (m, 5H), 1.51-1.43 (m, 3H), 1.41 (dd, J = 7.2, 3.1 Hz, 4H), 1.38-1.20 (m, 5H), 1.11-0.96 (m, 1H). ^{13}C NMR (150 MHz, MeOD) δ 209.48, 174.14, 173.36, 173.30, 158.74, 131.57, 130.65, 115.54, 68.43, 64.94, 60.10, 59.93, 58.49, 55.59, 53.96, 52.93, 52.81, 51.38, 50.99, 50.49, 49.43, 49.28, 49.14, 49.00, 48.86, 48.72, 48.58, 44.46, 43.09, 40.39, 39.50, 39.12, 38.26, 36.48, 34.85, 33.85, 33.73, 31.14, 27.99, 27.93, 27.69, 26.75, 26.54, 22.32, 21.22, 18.13, 16.88.

List of abbreviations

BODIPY, boron-dipyrromethene, (4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene); DiPEA, N,N-diisopropylethylamine; ek, epoxyketone; EtOAc, ethyl acetate; pent, pentane; DCM, dichloromethane; HCTU, 2-(6-chloro-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; Phg, phenylglycine; 1-Nal, 1-naphthylalanine; 2-Nal, 2-naphthylalanine; BiPhe, biphenylalanine; Chg, cyclohexylglycine; Cha, cyclohexylalanine; HomoCha, homocyclohexylalanien; 1-DecAla, 1-decahydronaphthalenylalanine; 2-DecAla, 2-decahydronaphthalenylalanine; BiCha, bicyclohexylalanine; NorAla, norbornanealanine; Ala(ada), adamantanealanine; Ala(tBu), t-butylalanine; Pyra, pyrazine-2-carboxyl; Phnico, 6-phenylnicotinyl; Dibenz, 2,5-dichlorobenzyl; Morph, 2-morpholinoacetyl; Methia, 2-methylthiazol-5-carboxyl.

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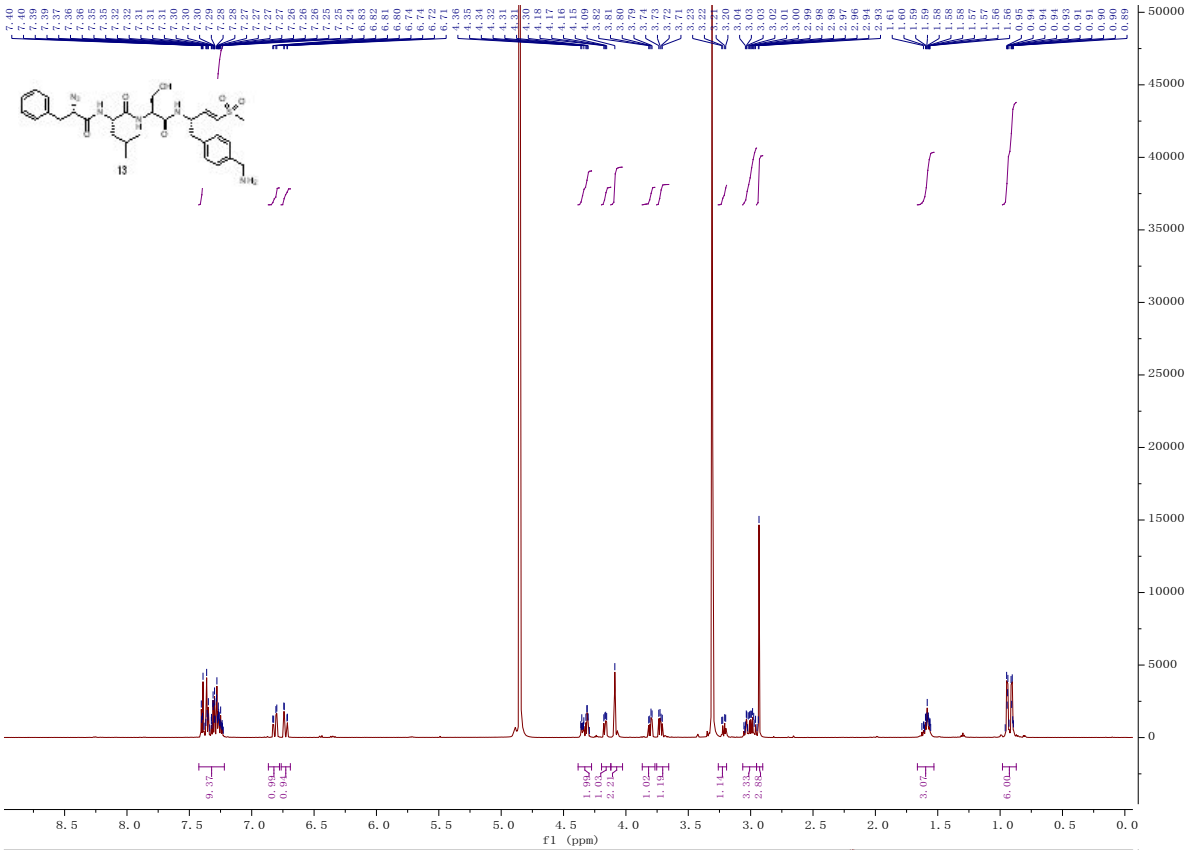
NMR-spectra of compounds **13**, **39**, **68**, **71**, **74**, **77**, **86**, and **87s**.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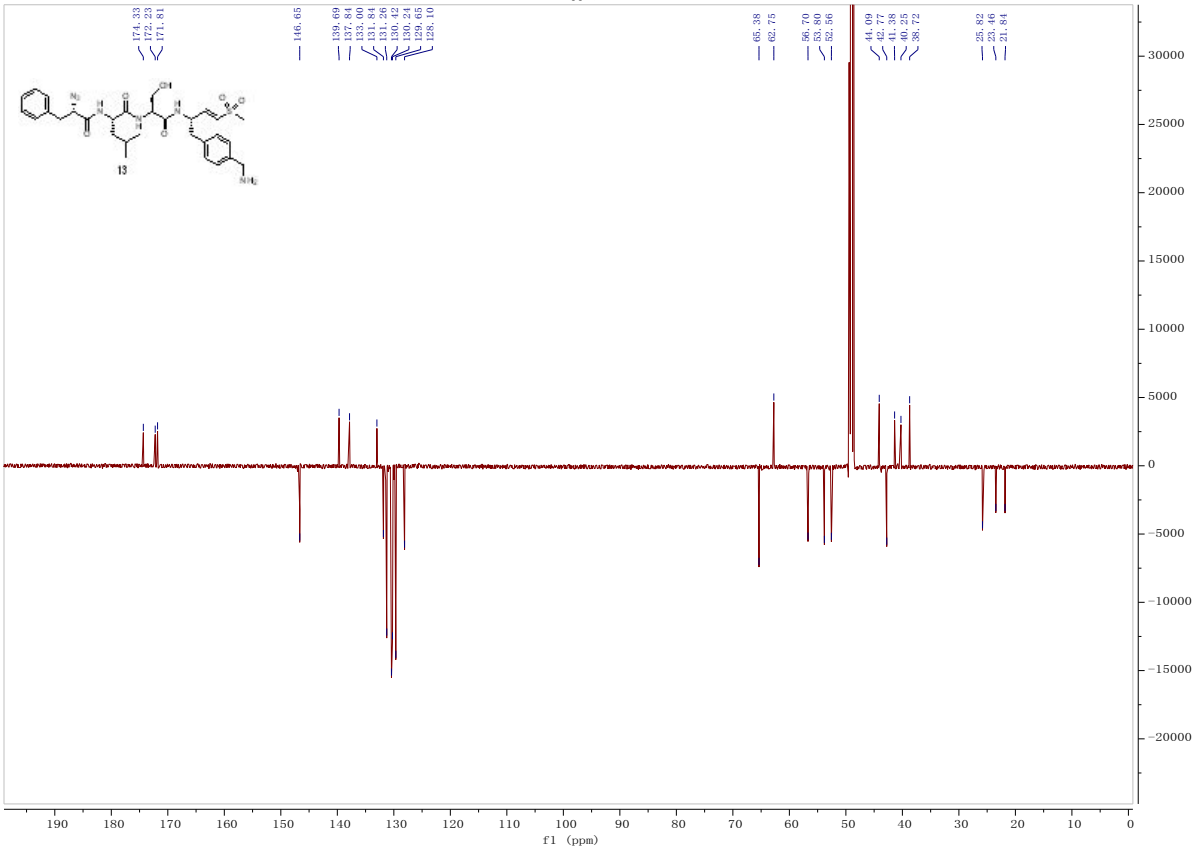
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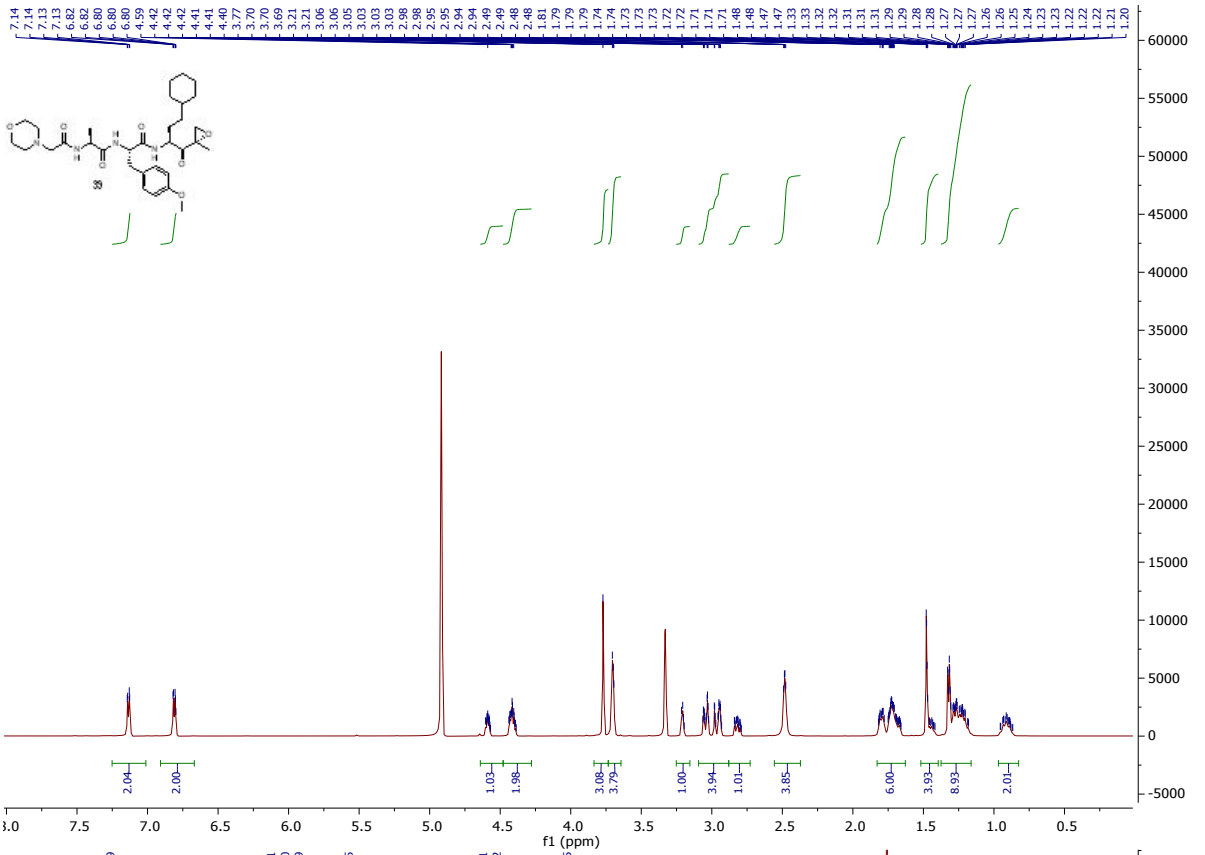

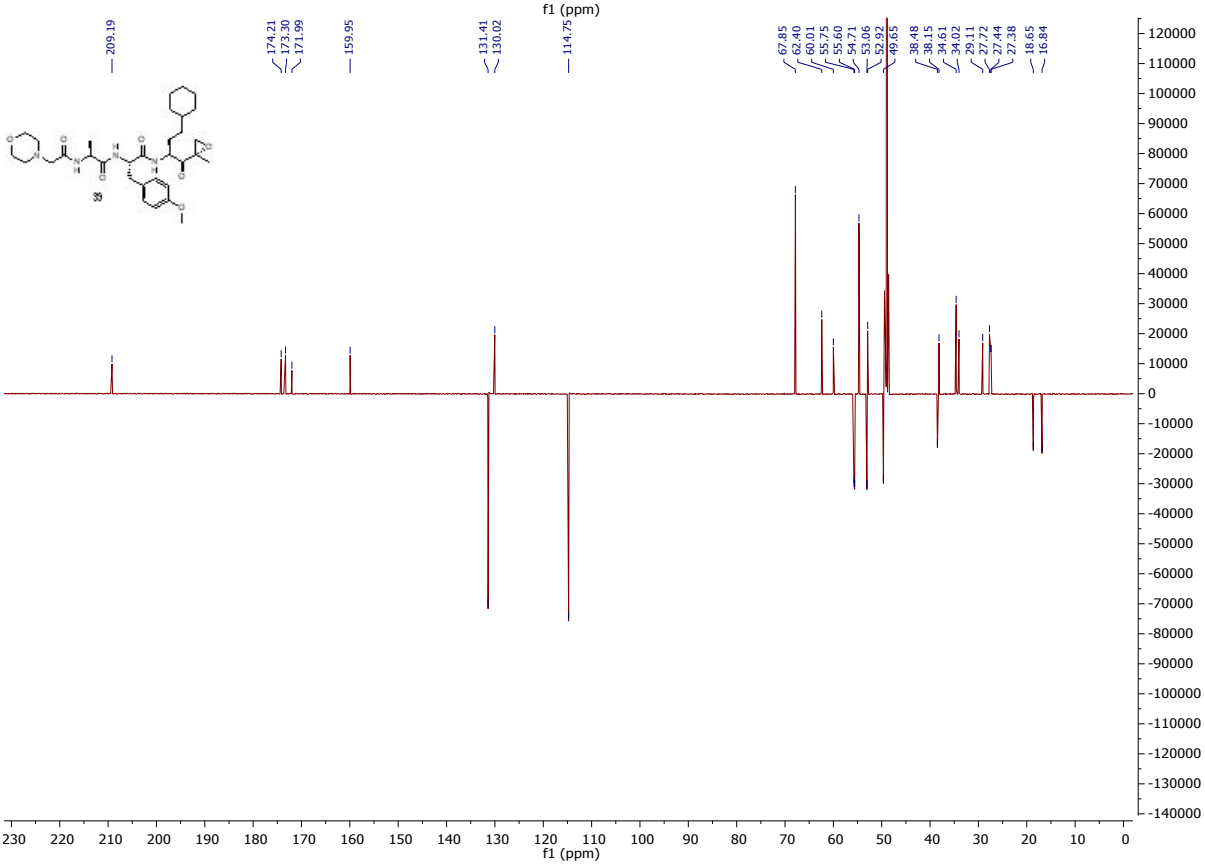

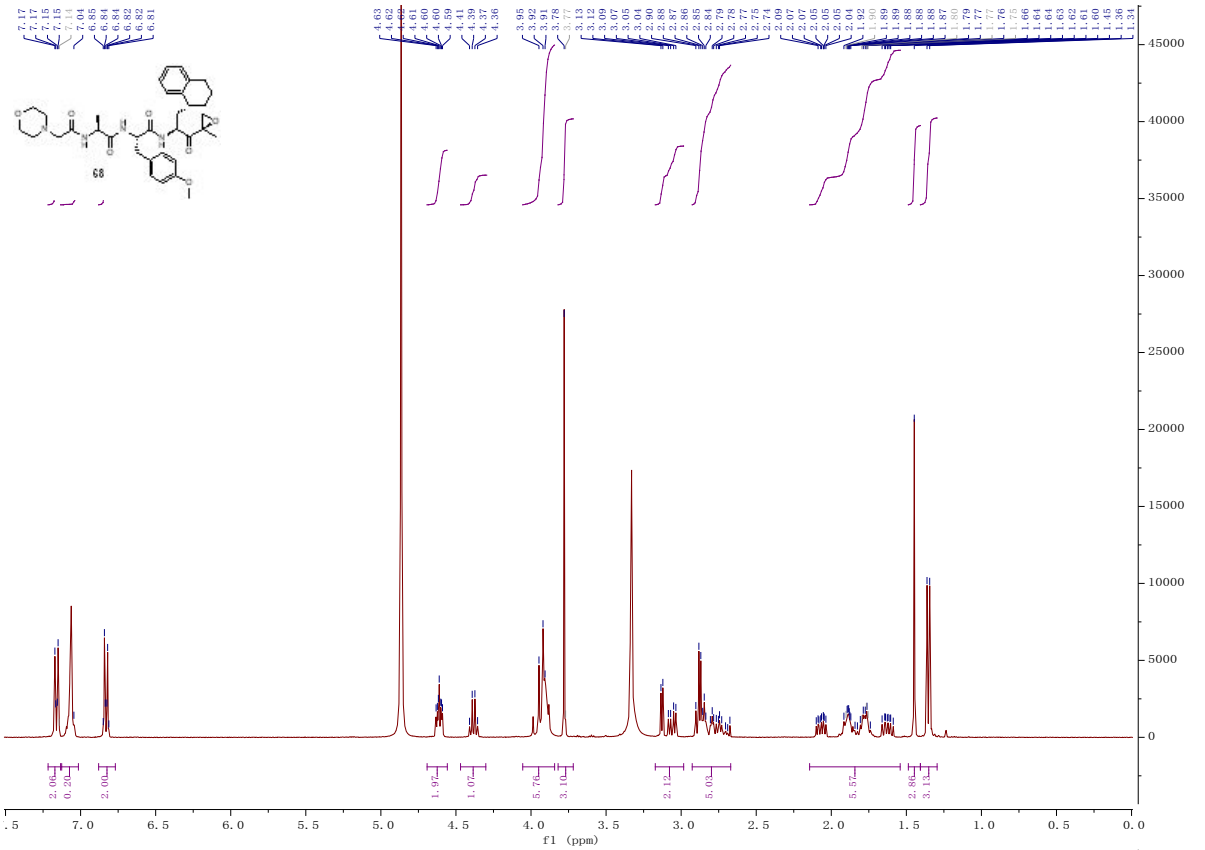
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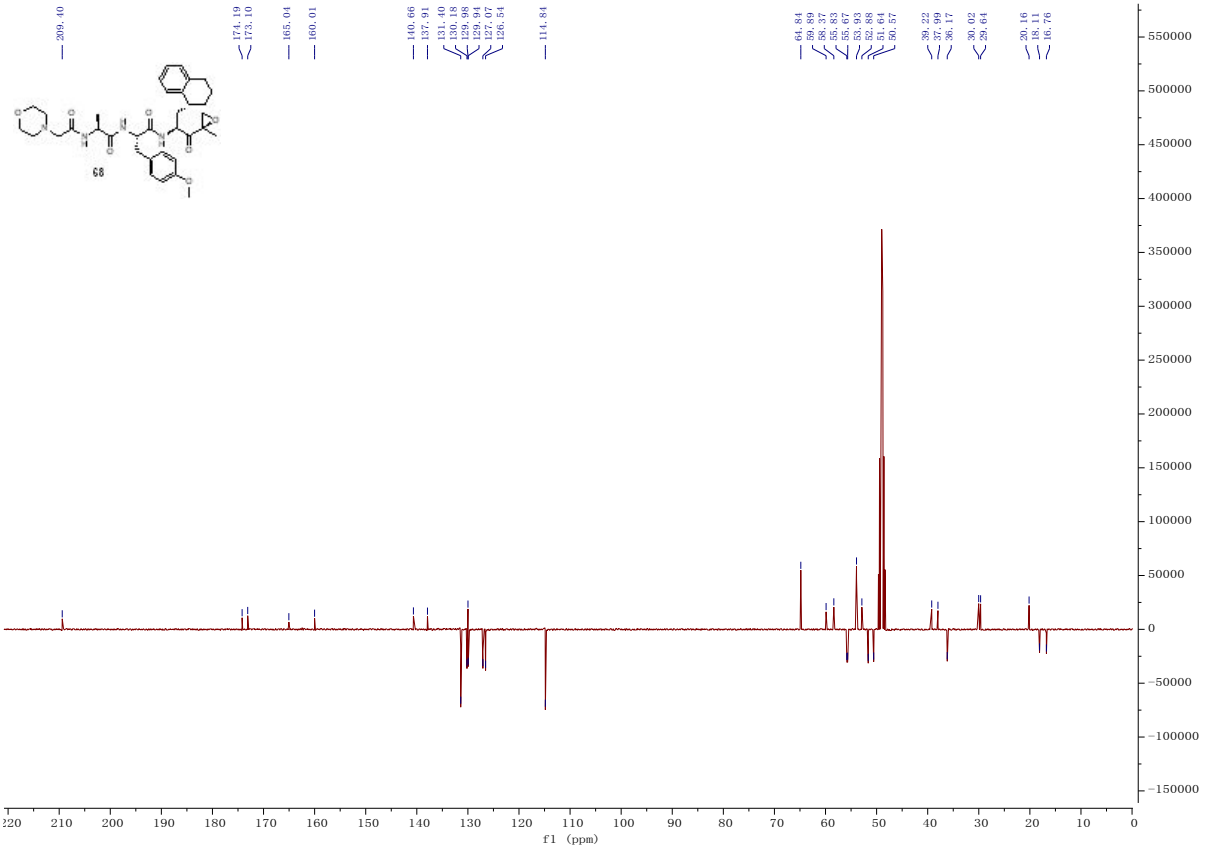
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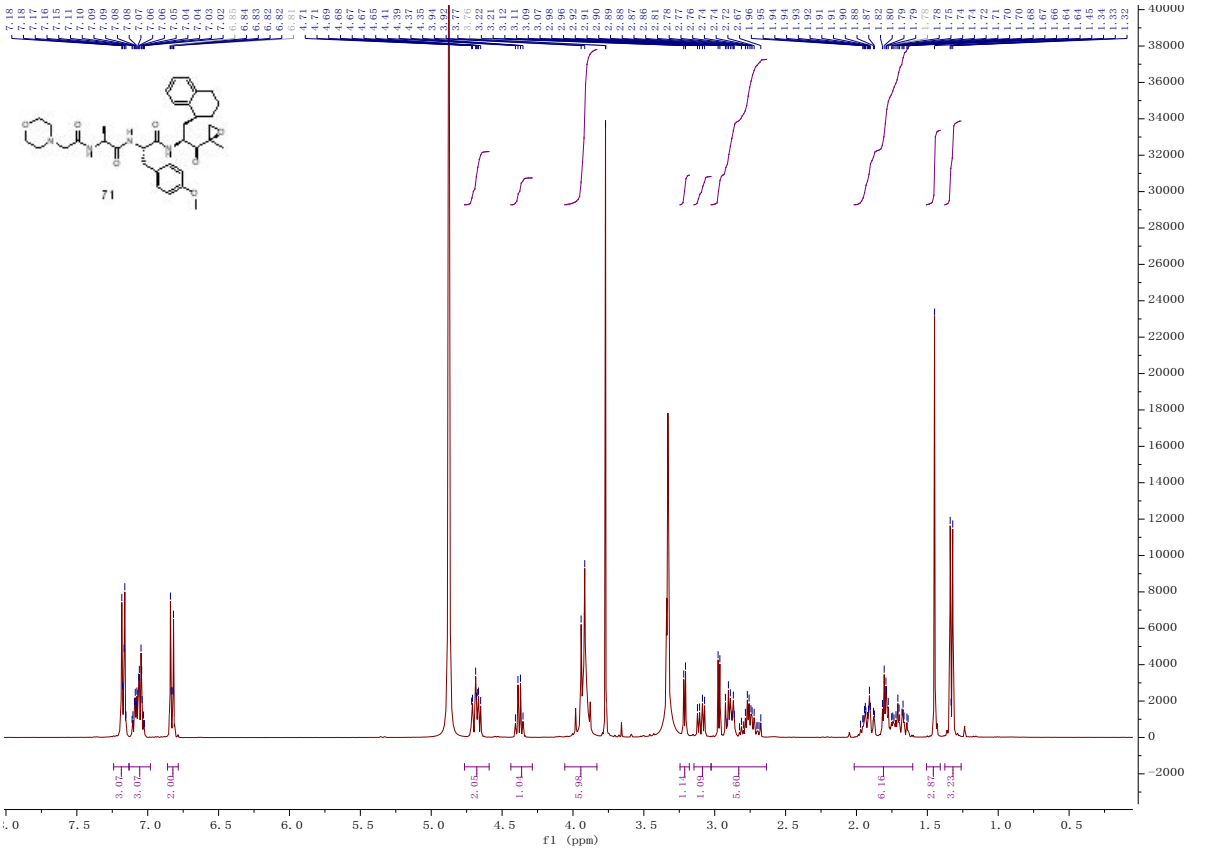
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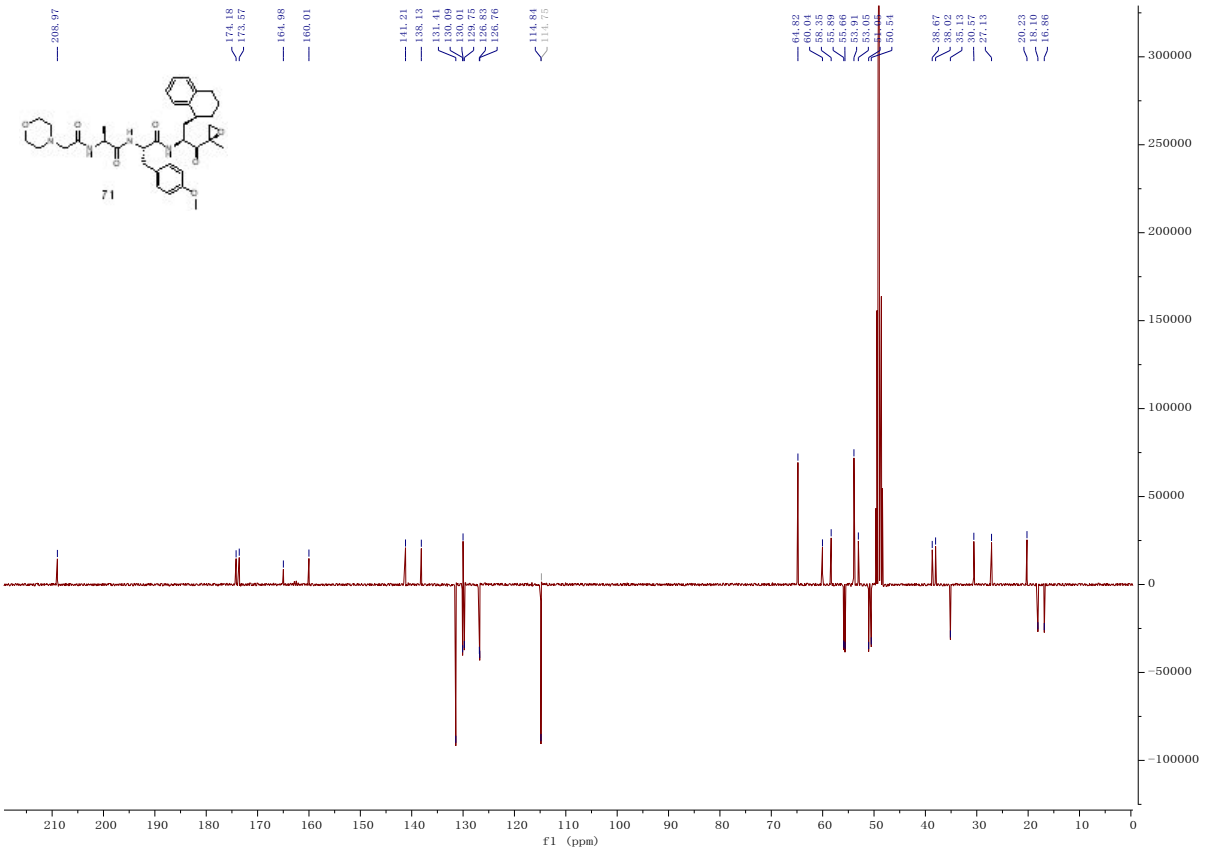
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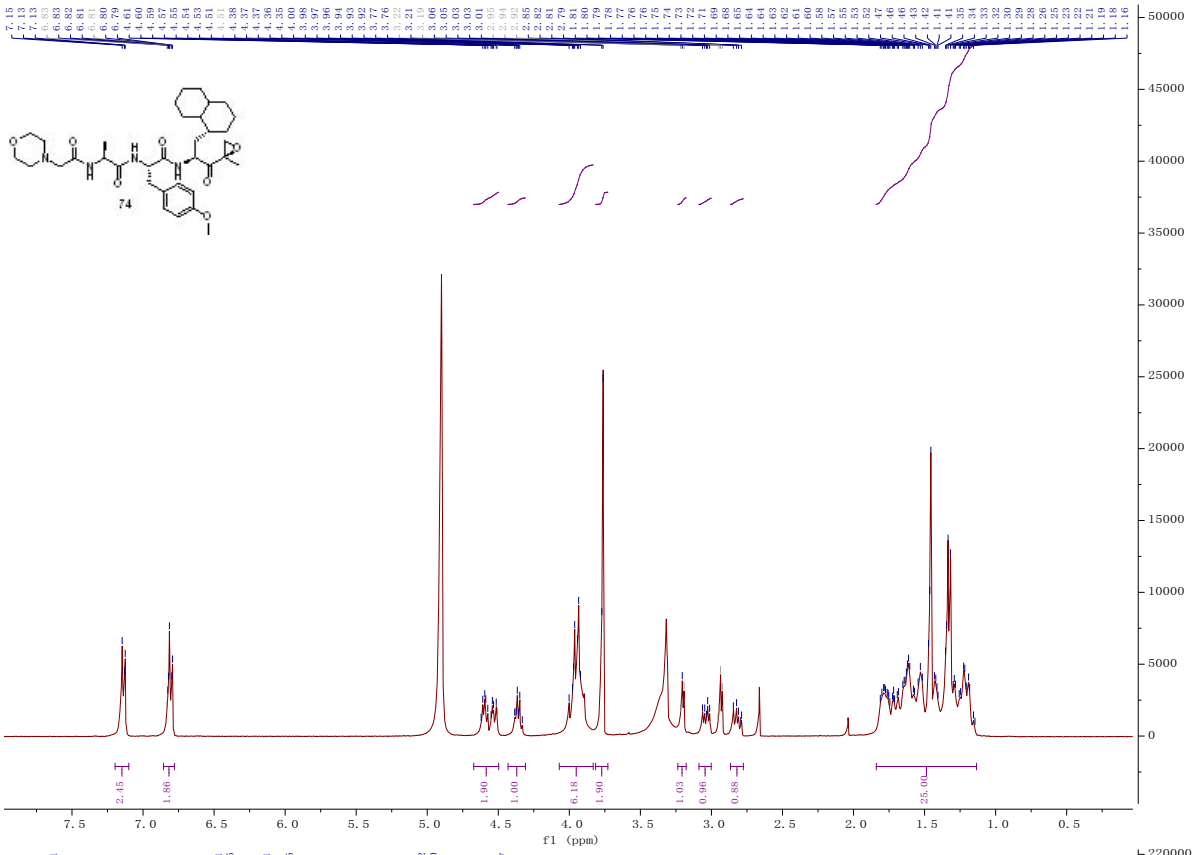
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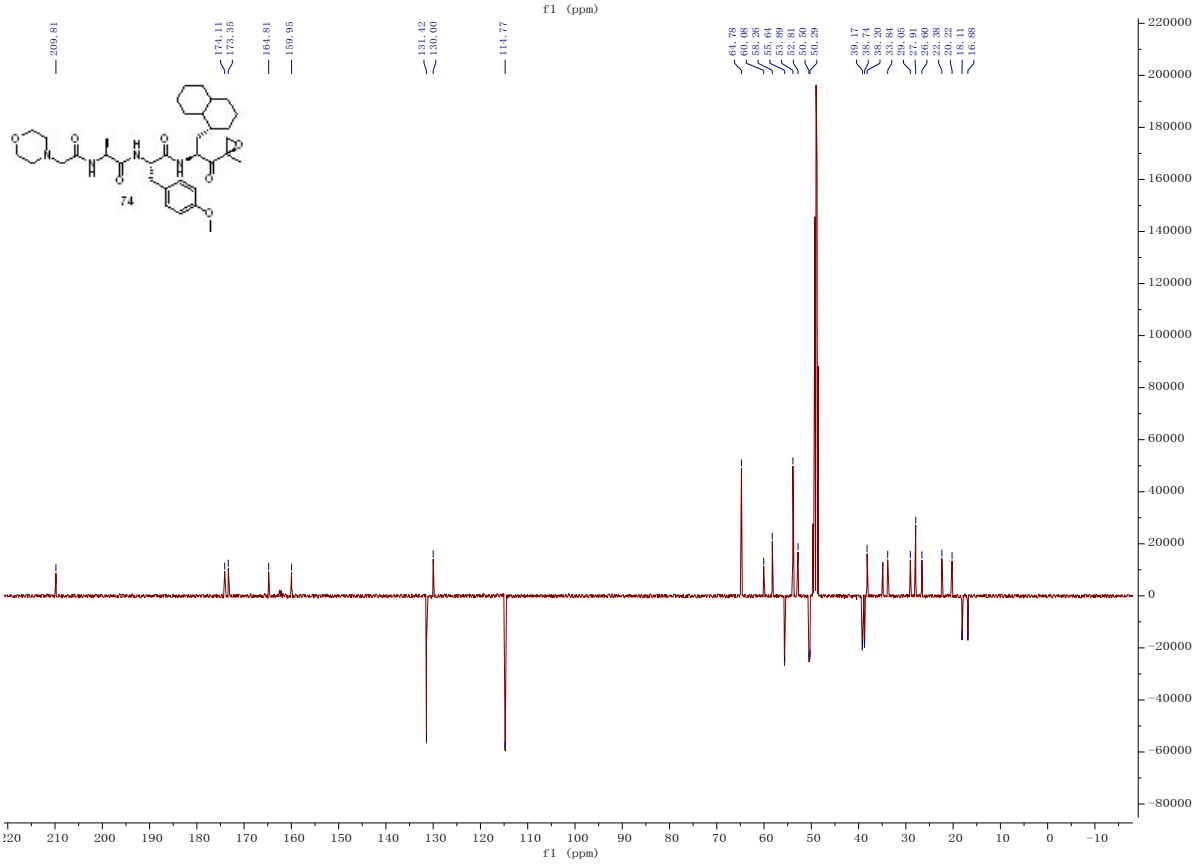
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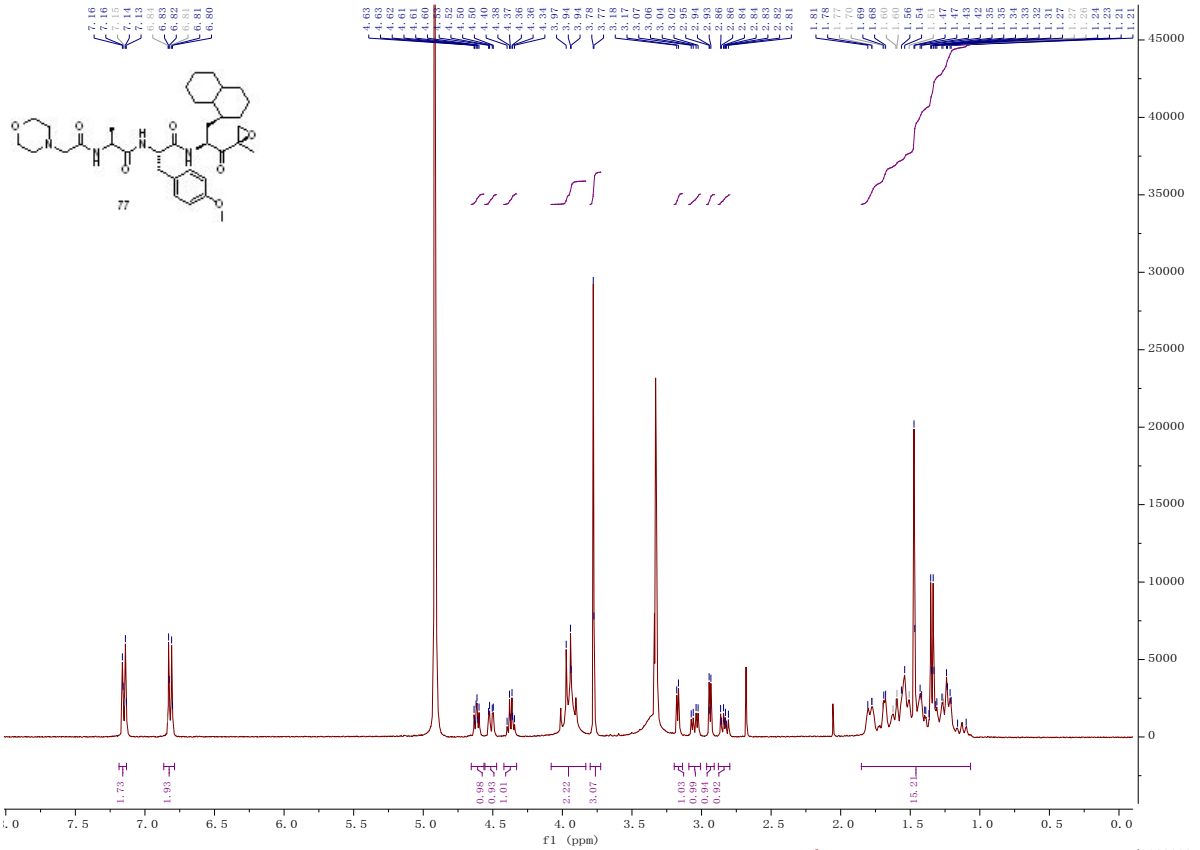
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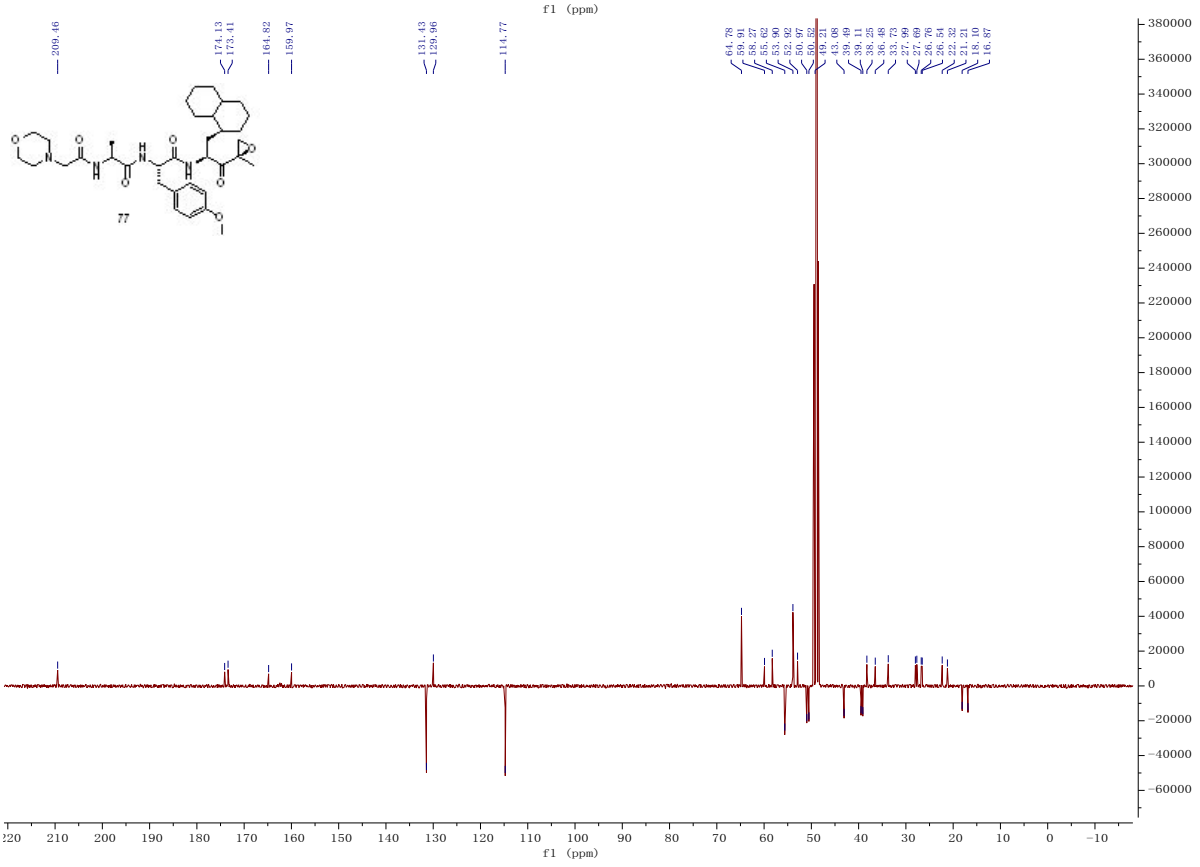
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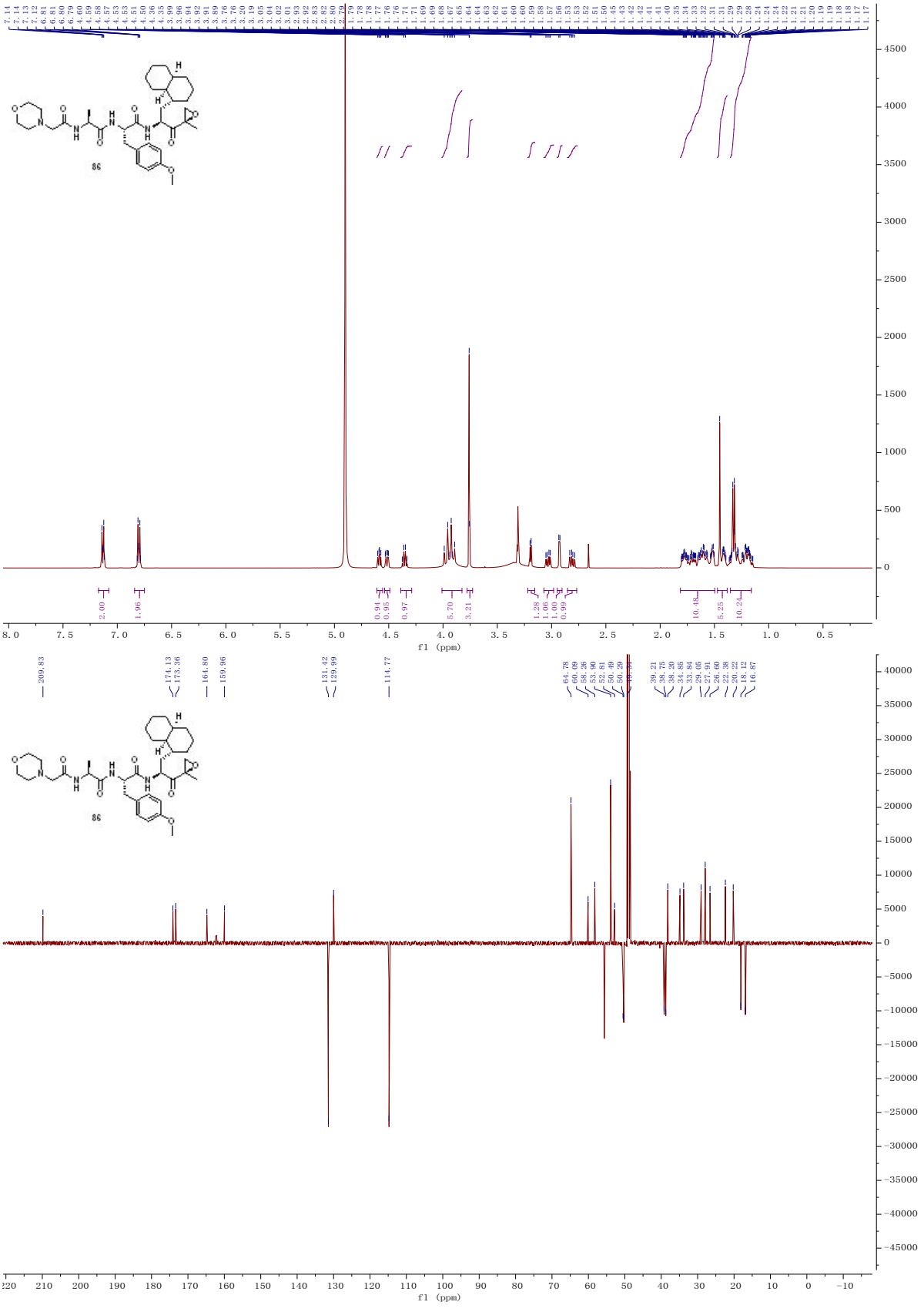

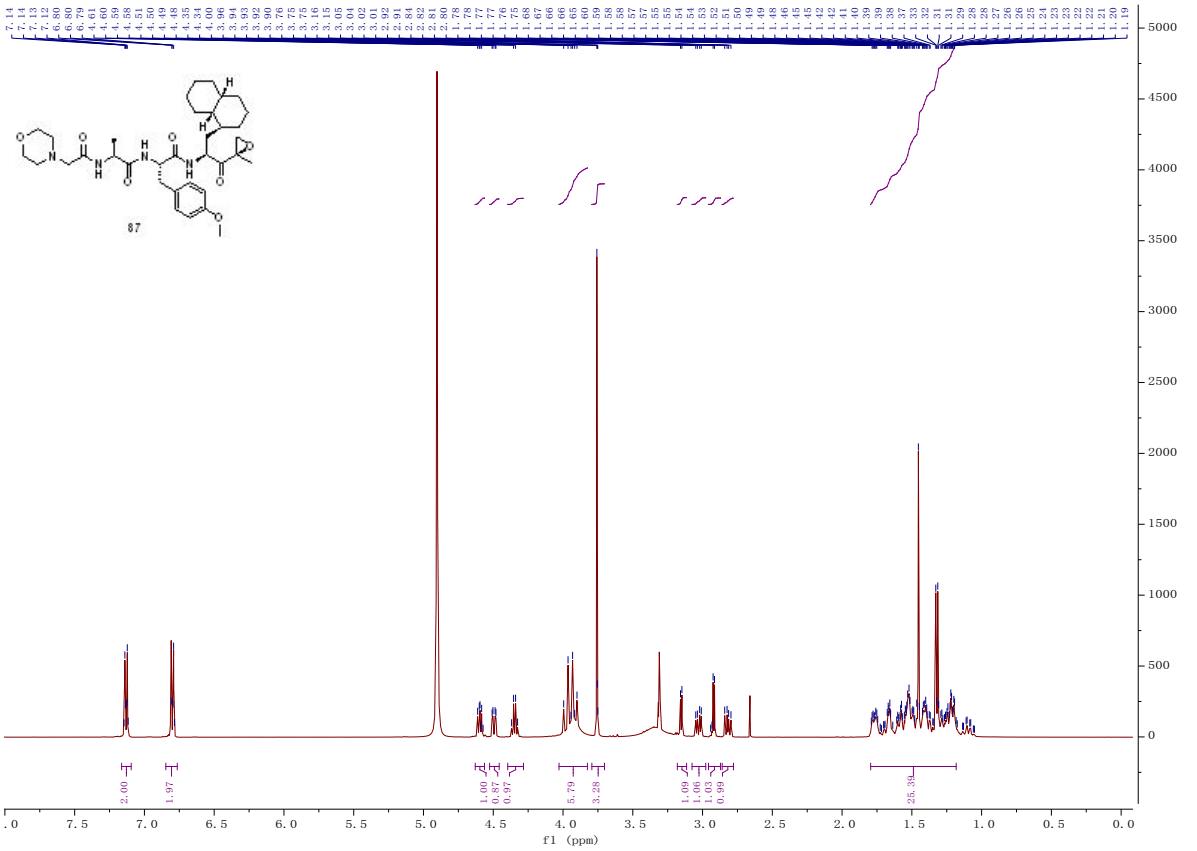
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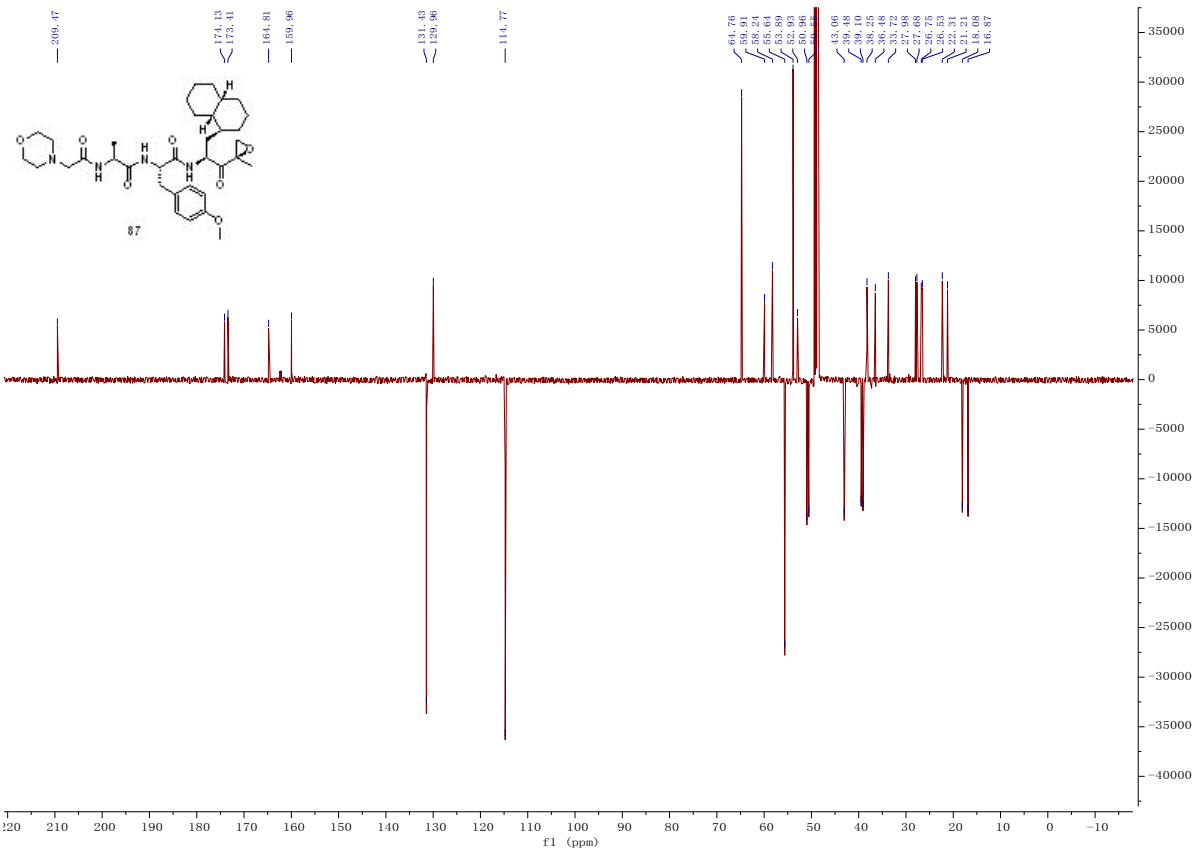
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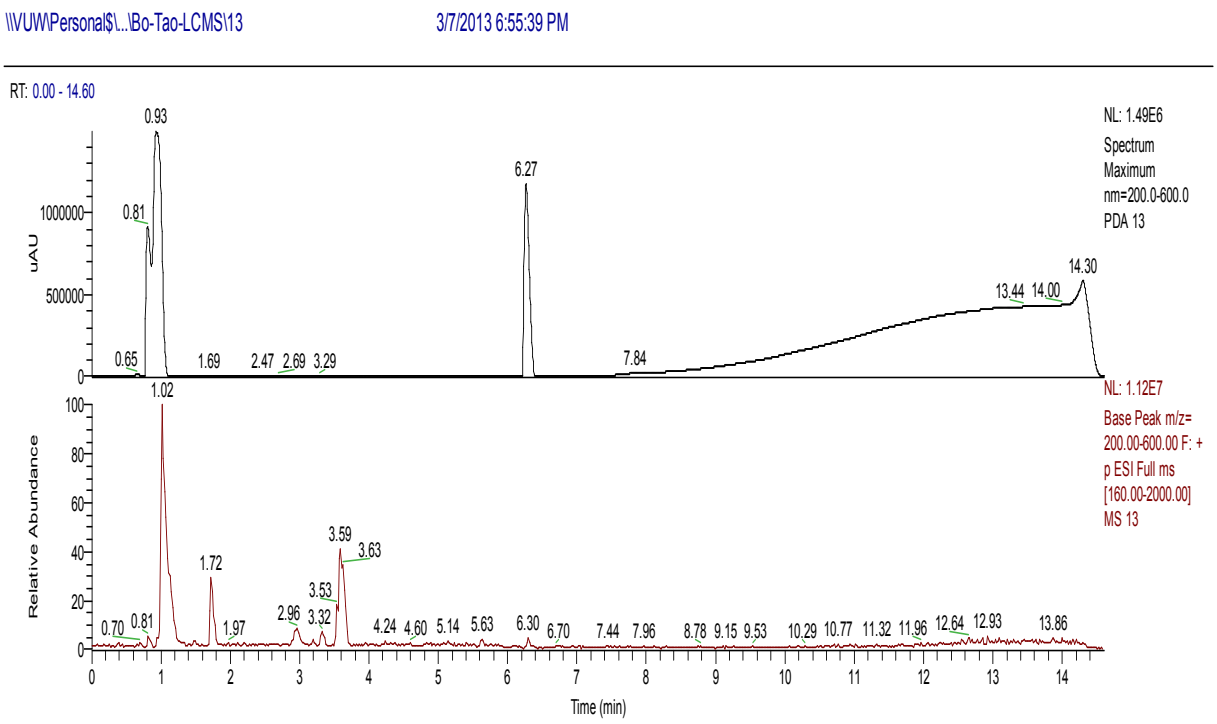
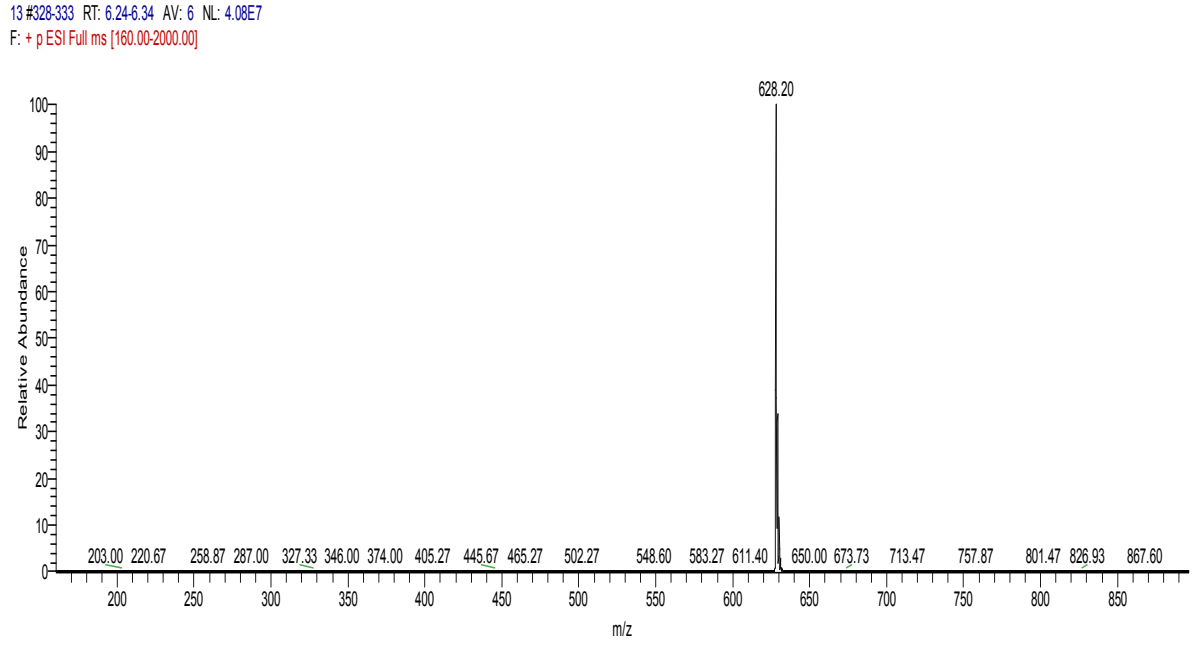
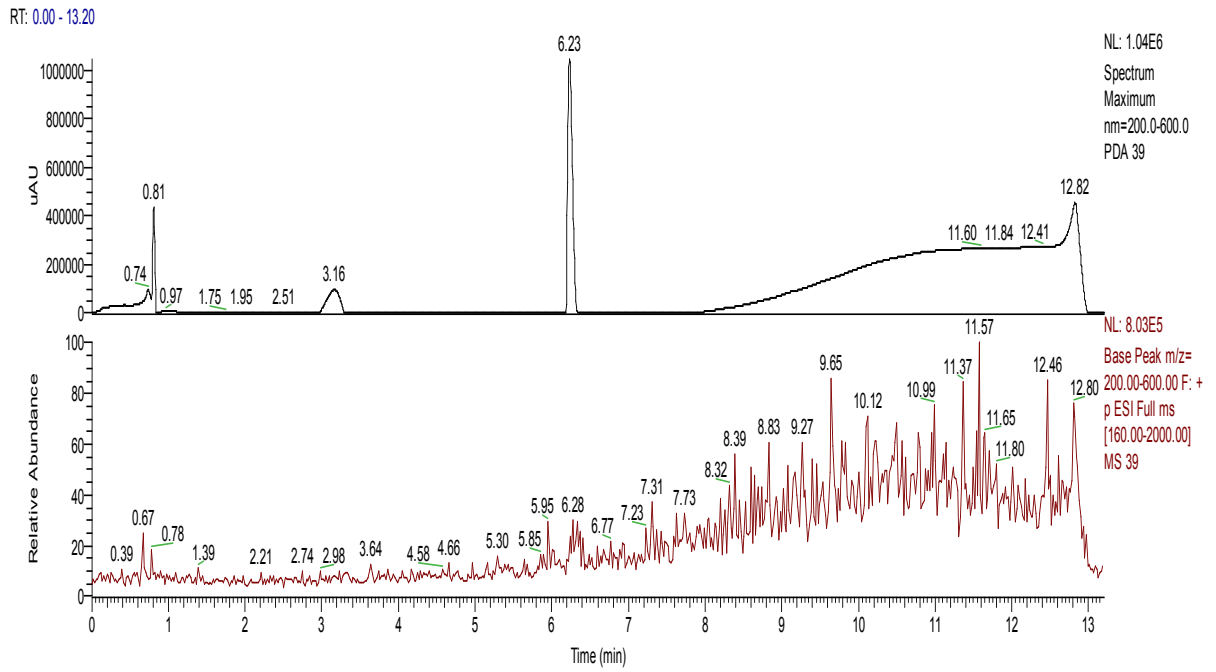
LC-MS-spectra of compounds 13, 39, 68, 71, 74, 77, 86, 87.



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3.16
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11.65
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8.83
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7.31
7.73
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6.77
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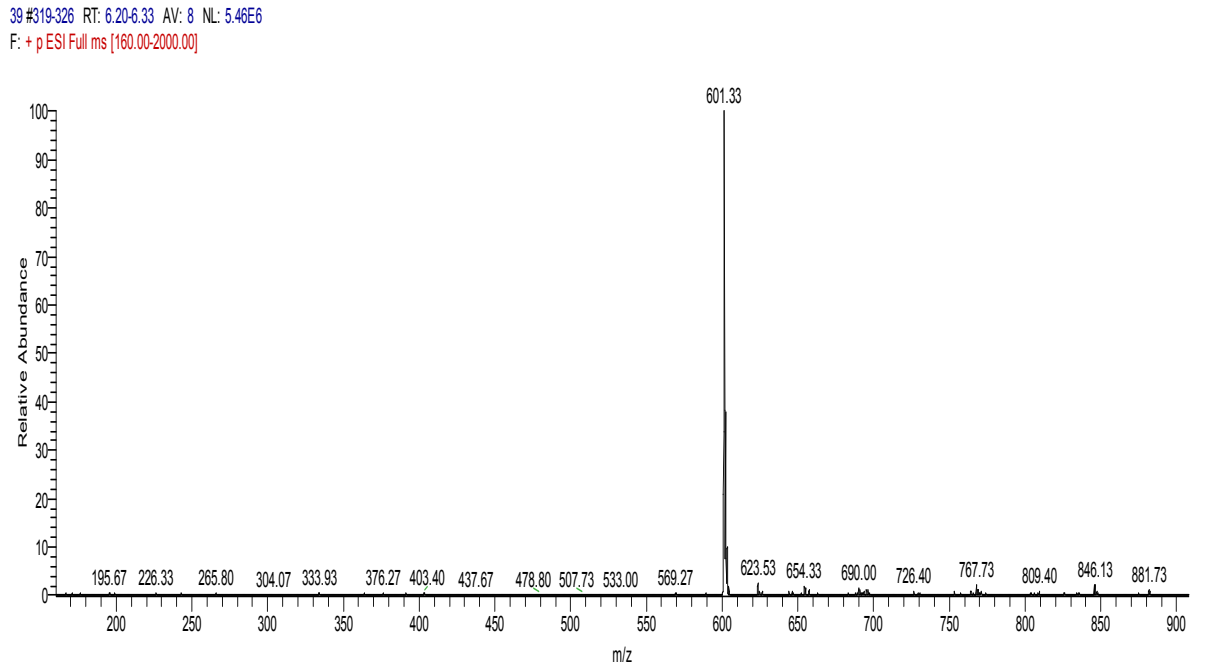
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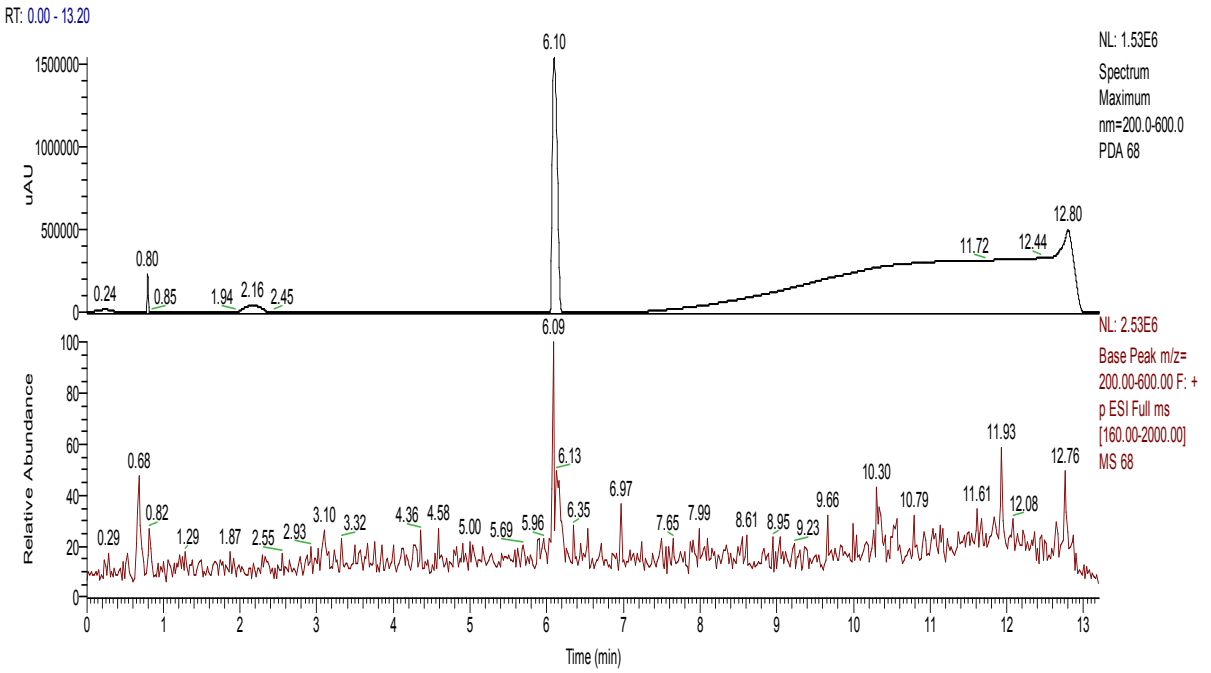
m/z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200.00-600.00 F: +
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6.35
6.97
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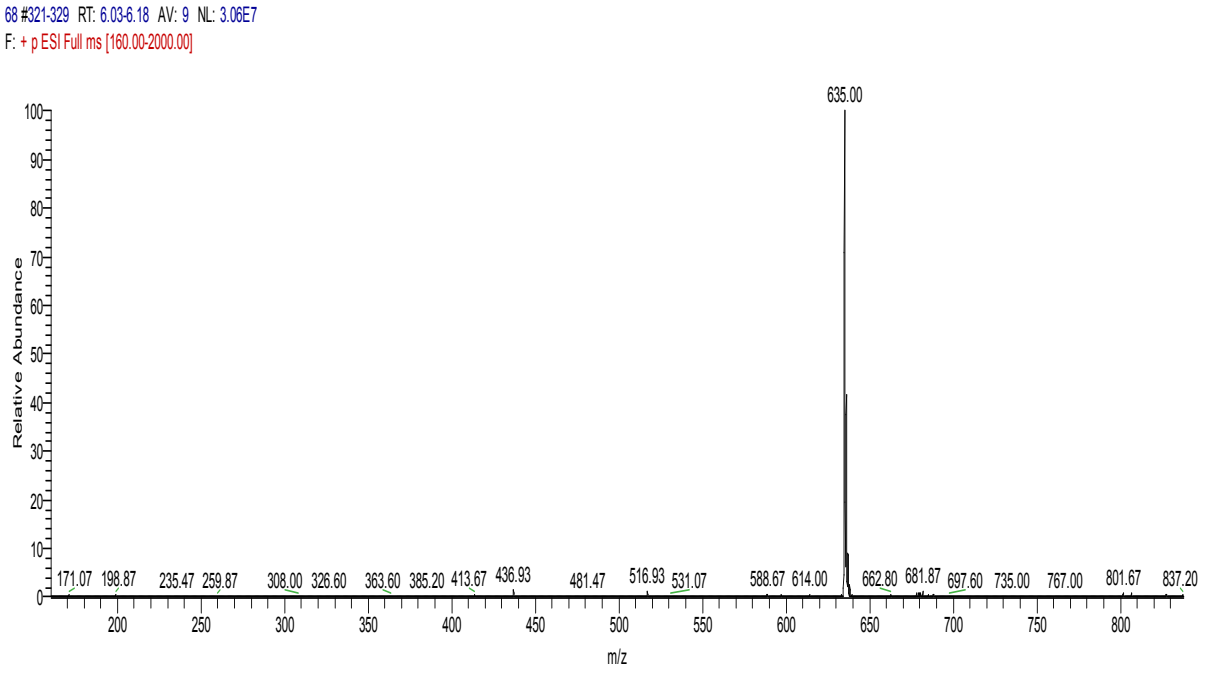
Time (min)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m/z

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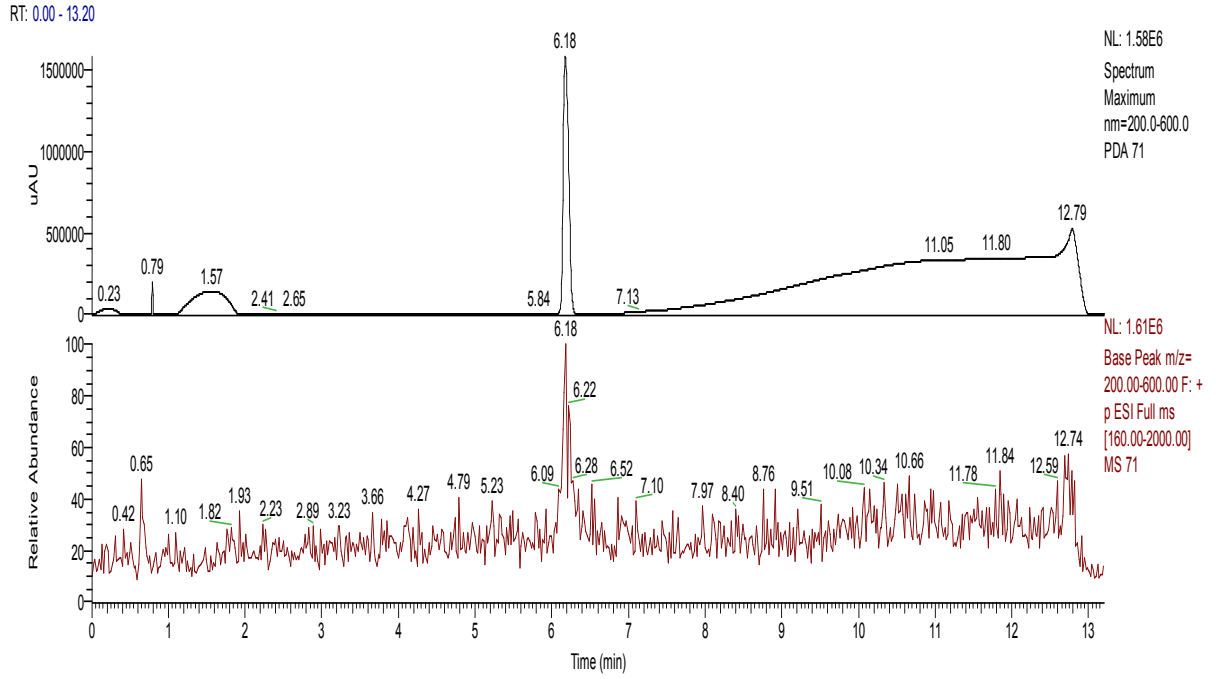

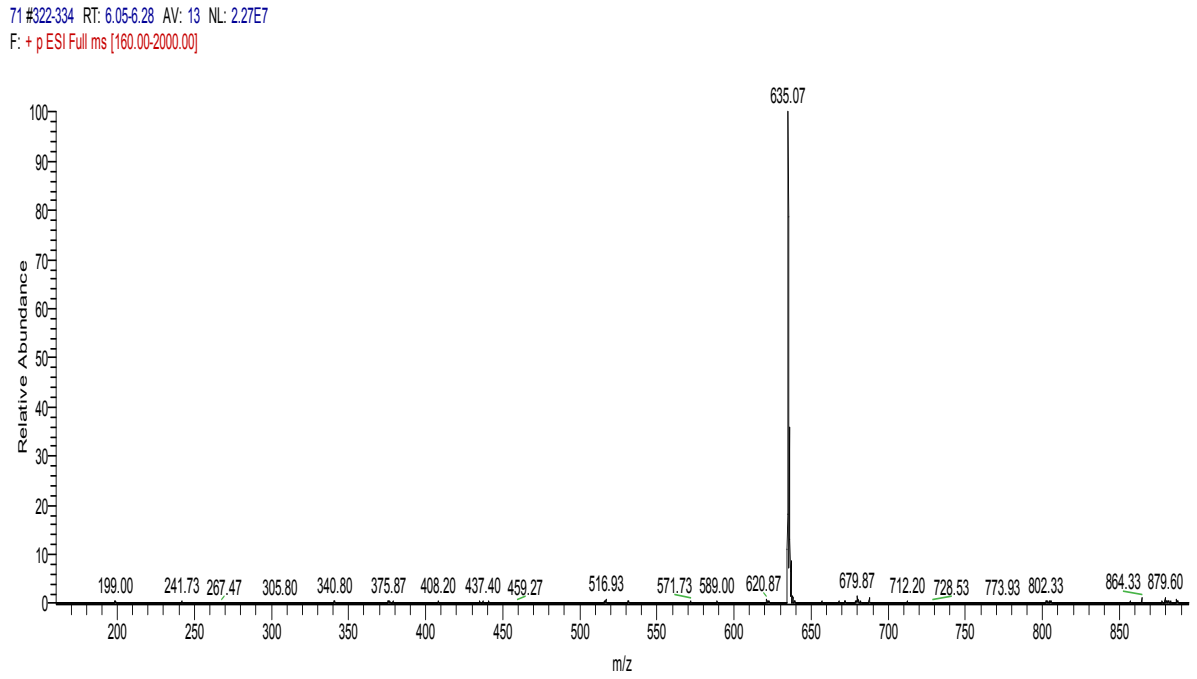

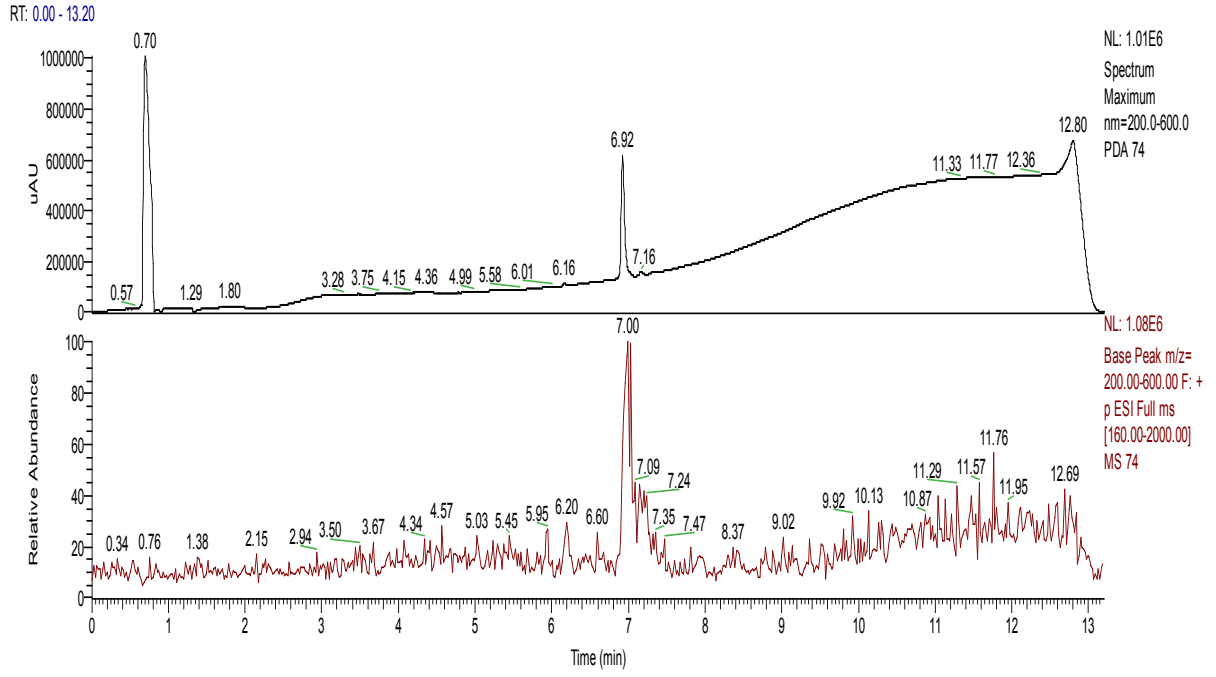

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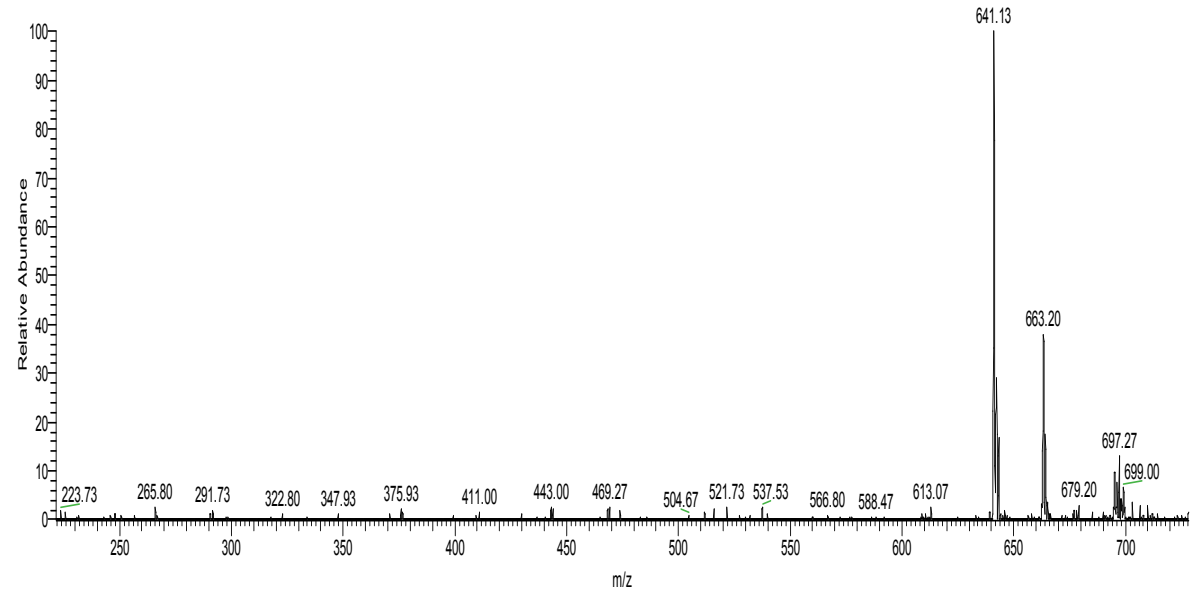

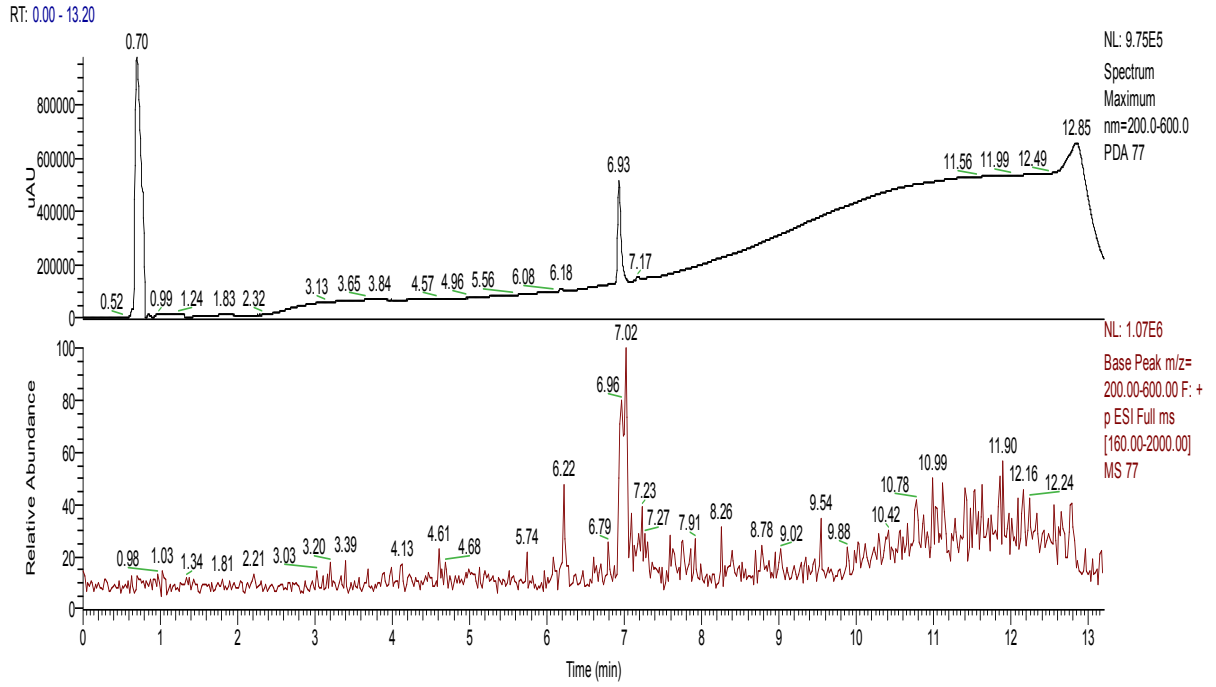
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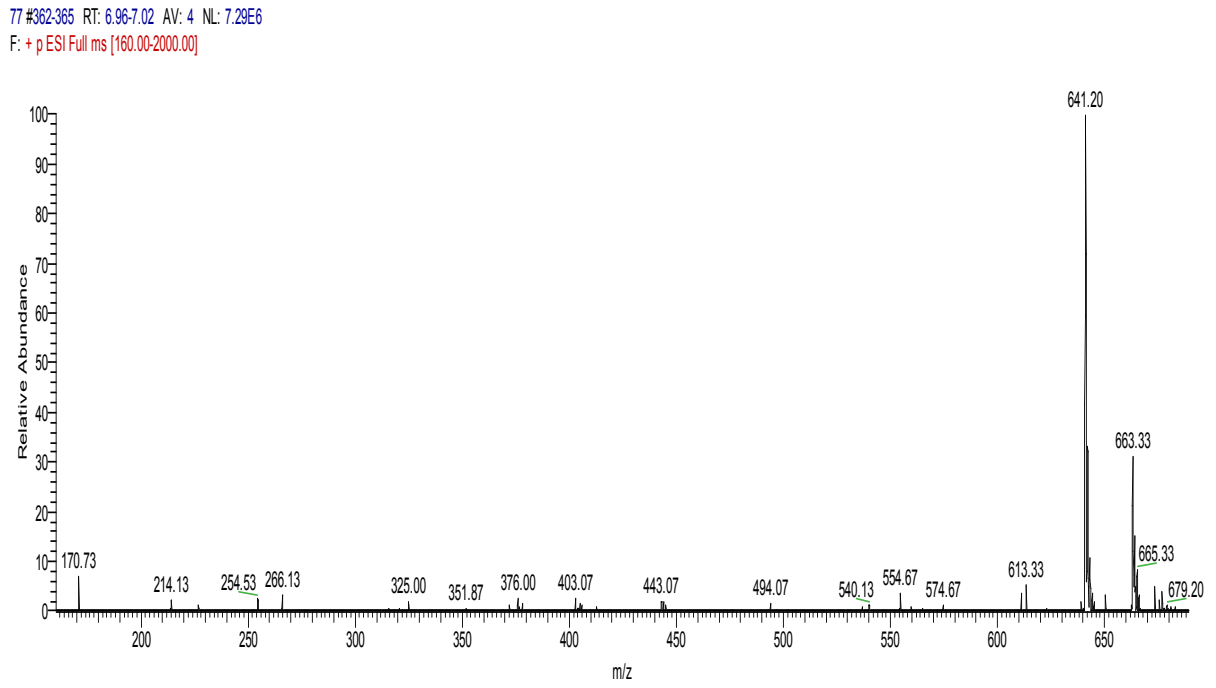
MS 77
Relative Abundance
Time (min)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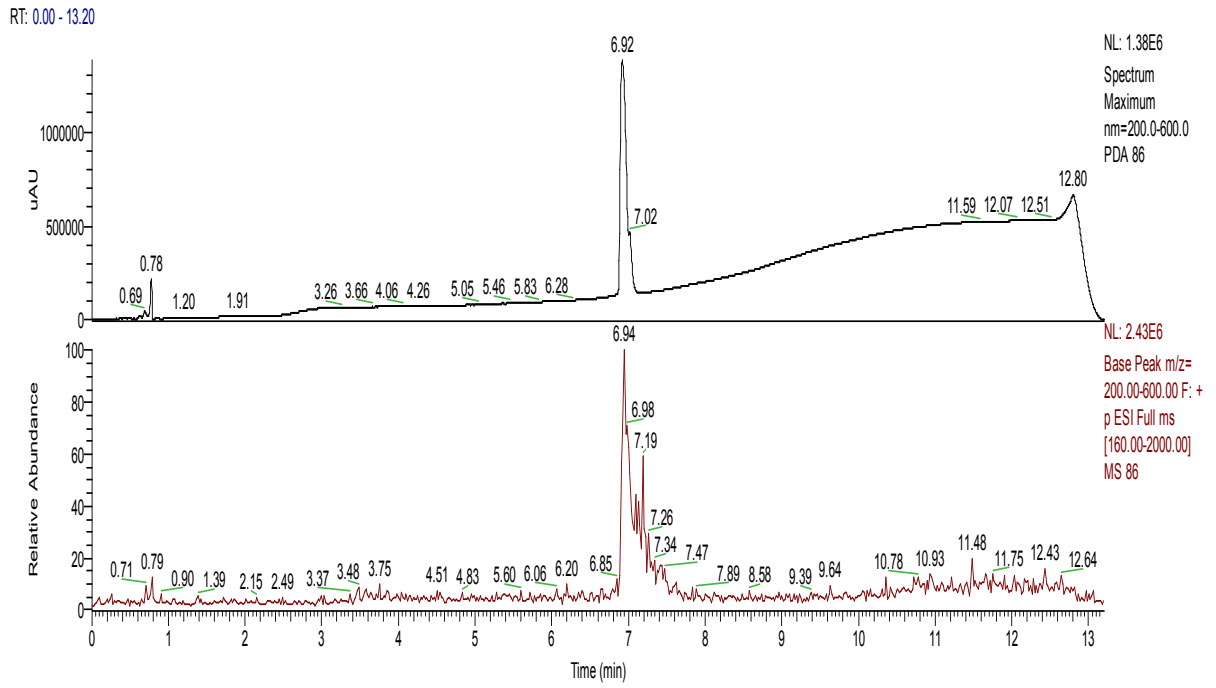
Relative Abundance
m/z



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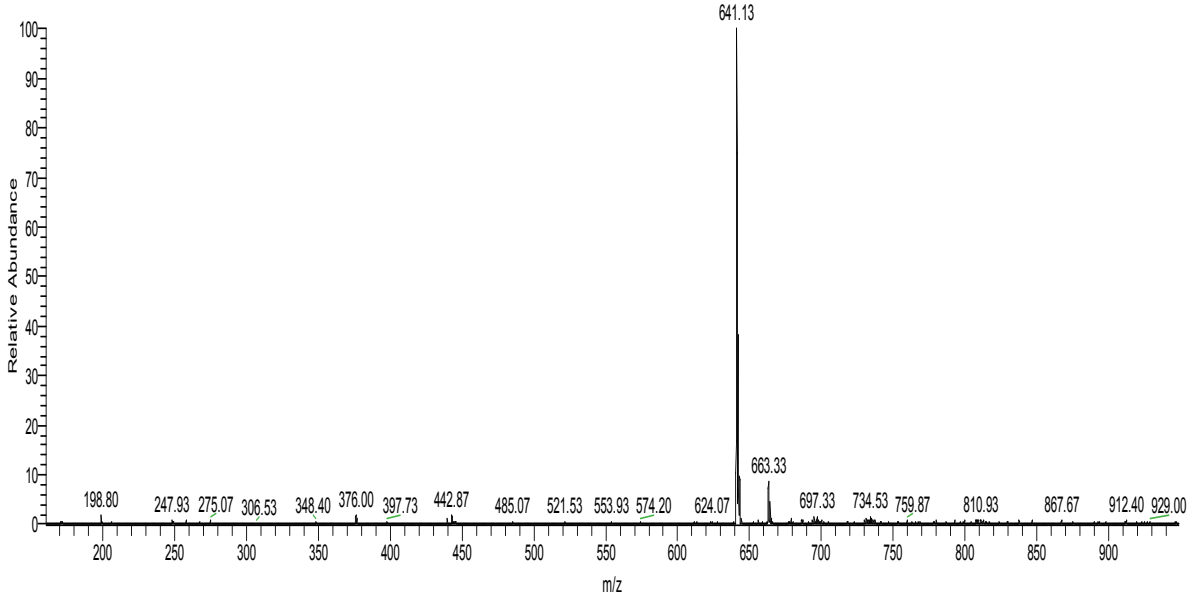

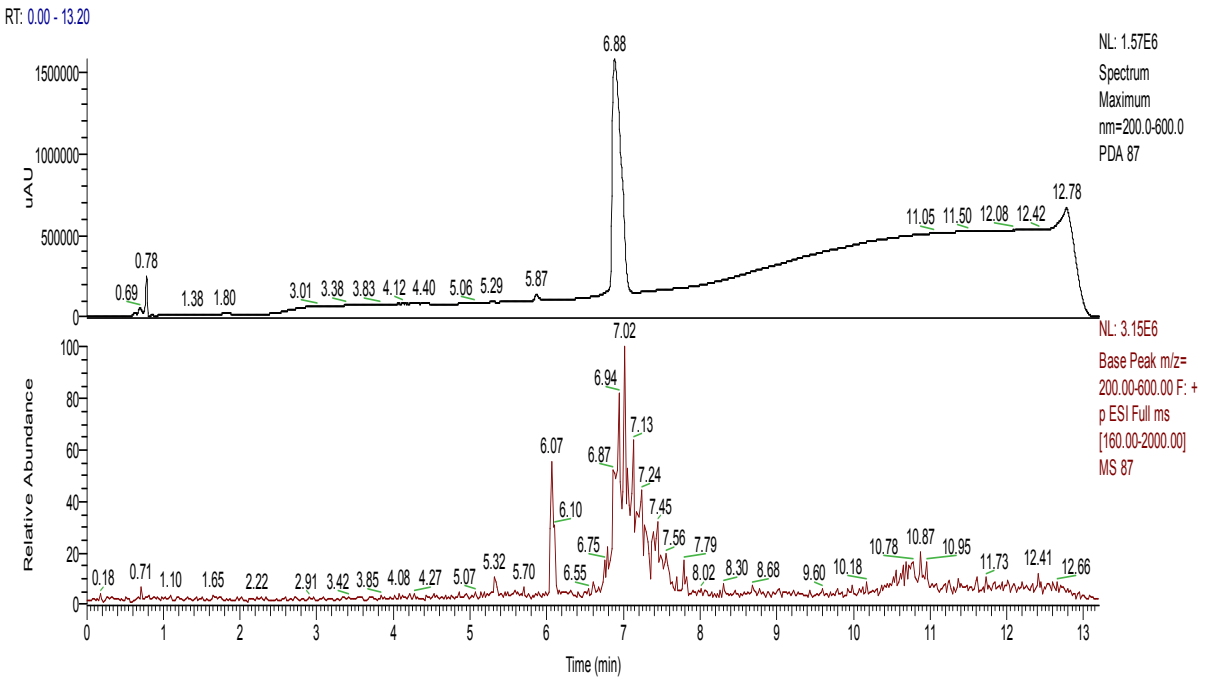
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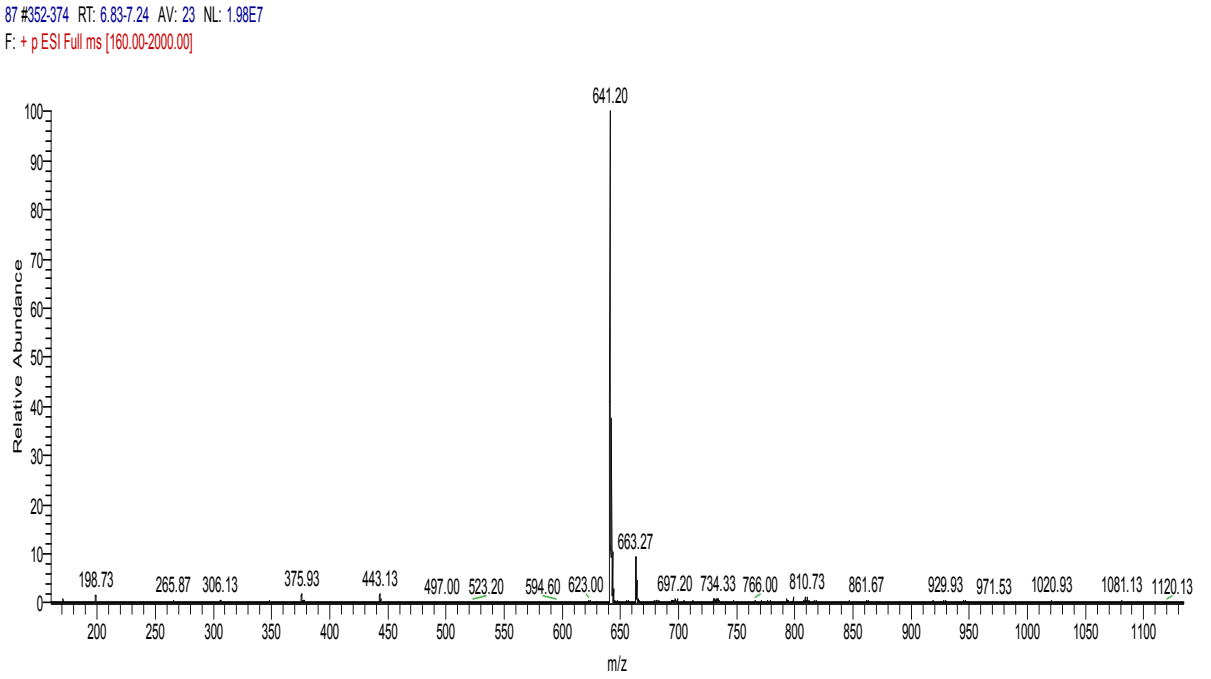
NL: 3.15E6
Base Peak m/z=
200.00-600.00 F: +
p ESI Full ms
[160.00-2000.00]
MS 87
Relative Abundance
Time (min)


87 #352-374 RT: 6.83-7.24 AV: 23 NL: 1.98E7
F: + p ESI Full ms [160.00-2000.00]
Relative Abundance
m/z