Supplemental Materials

Development of a potent inhibitor of the Plasmodium proteasome with reduced mammalian toxicity

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Supplemental Materials Table of Contents

were identified to be associated with the preferred binding of analog 18 towards the plasmodium 20S proteasome β5 subunit.

2) Supplemental Figures

a) Figure S1: Purification of the proteasome from human, both constitutive (A) and immune (B), as well as from *P. falciparum* blood stage parasites (C).

b) Figure S2: Multiple sequence alignment of the (A) β5 and (B) β6 proteins chains of the human 20S proteasome (PDB ID 4R67 chain L and M), the parasitic 20S proteasome (PDB ID 5FMG chain L and M) and the yeast 20S proteasome (PDB ID 4HRD chain K and L).

c) Figure S3-S6: ^{3}H and ^{13}C NMR spectra of analogs **18** and **19**

3) Analytical data for validation of carmaphycin B analogs

Includes chemical name, SMILES, yield data and structural validation

Supplemental Tables

Table S1: Carmaphycin B resistant strains

	GM	Lineage 1	Lineage 2	Lineage 3
average IC_{50} (μM)	24.2775	>150	52.7325	>100
SEM (n=4)	0.30		2.66	

Table S2: Sequencing Statistics for *S. cerevisiae* resistant clones

	Lineage 1 (R7c-2)	Lineage 2 (R8b-2)	Lineage 3 (R9b-2)
Total reads	30,725,372	32,374,374	25,823,710
Aligned reads	30,176,825	31,915,743	25,391,150
Percent Aligned Reads	98.2147	98.5834	98.325
Mean Coverage	210.95	221.46	179.16
Percent bases covered by 5 or more reads	99.4	99.4	99.4
Mean read length	100	100	100
Median insert size	218	224	231

Table S3: Results of whole-genome sequencing of the three resistant lines. Mutations in genes encoding ubiquitination or proteasomal proteins are bolded.

Lineage	Chr	Position	Codon Change	Gene Mutated	Gene Name	AA Change	Functional Class
Lineage 1	II	473356	Gcg/Tcg	YBR115C	LYS2	A191S	Missense
	III	1142221	Gtc/Ctc	YDR335W	MSN5	V352L	Missense
	VII	943119	gGg/gCg	YGR224W	AZR1	G105A	Missense
	VII	386978	Cgt/Ggt	YGL062W	PYC1	R595G	Missense
	VII	**261789**	**agC/agG**	**YGL131C**	**SNT2**	**S1357R**	**Missense**
	XV	177382	Att/Gtt	YOL081W	IRA2	I2105V	Missense
	XV	100169	Agg/Tgg	YOL116W	MSN1	R121W	Missense
	XV	656199	Gaa/Aaa	YOR172W	YRM1	E664K	Missense
	VI	70366	caT/caC	YFL033C	RIM15	H1354	Silent
Lineage 2	V	229448	Gtg/Atg	YER039C		V12M	Missense
	XV	539008	cTt/cCt	YOR115C	TRS33	L153P	Missense

	XVI	**732708**	**atG/atT**	**YPR103W**	**PRE2**	**M120I**	**Missense**
	XIII	380730	ctC/ctG	YMR053C	STB2	L723	Silent
Lineage 3	IV	310485					Intergenic
	IV	126219	Gtc/Ctc	YDL186W		V202L	Missense
	V	**469834**	**gCg/gAg**	**YER151C**	**UBP3**	**A864E**	**Missense**
	V	562119	ttG/ttT	YER186C		L169F	Missense
	VII	742995	gCc/gTc	YGR125W		A224V	Missense
	VIII	68009	Gac/Cac	YHL019C	APM2	D514H	Missense
	XI	102346	cCa/cGa	YKL182W	FAS1	P559R	Missense
	XI	84734	Gac/Cac	YKL189W	HYM1	D11H	Missense
	XII	447263	Ccc/Gcc	YLR153C	ACS2	P105A	Missense
	XIII	**319043**	**Agt/Cgt**	**YMR022W**	**UBC7**	**S122R**	**Missense**
	XIV	550739	Gat/Cat	YNL041C	COG6	D417H	Missense
	XIV	326862	aCa/aGa	YNL163C	RIA1	T1071R	Missense
	XV	656188	aAc/aTc	YOR172W	YRM1	N660I	Missense
	XII	627141	tcG/tcA	YLR246W	ERF2	S8	Silent
	XVI	702831	aaA/aaG	YPR081C	GRS2	K380	Silent

Table S4: Amino acid residues in the β5 binding pocket in the human 20S proteasome (PDB ID 4R67) and equivalent residue substitutions in the *Plasmodium* 20S proteasome (PDB ID 5FMG) that were identified to be associated with the preferred binding of analog 18 towards the plasmodium 20S proteasome β5 subunit.

Protein chain	Position*	Human 20S Proteasome	*P. falciparum* 20S Proteasome
β5	22	Ala	Met
	96	Ser	Cys
β6	131	Gln	Cys
	133	Asp	Ala
	136	Lys	Ser

Supplemental Figures

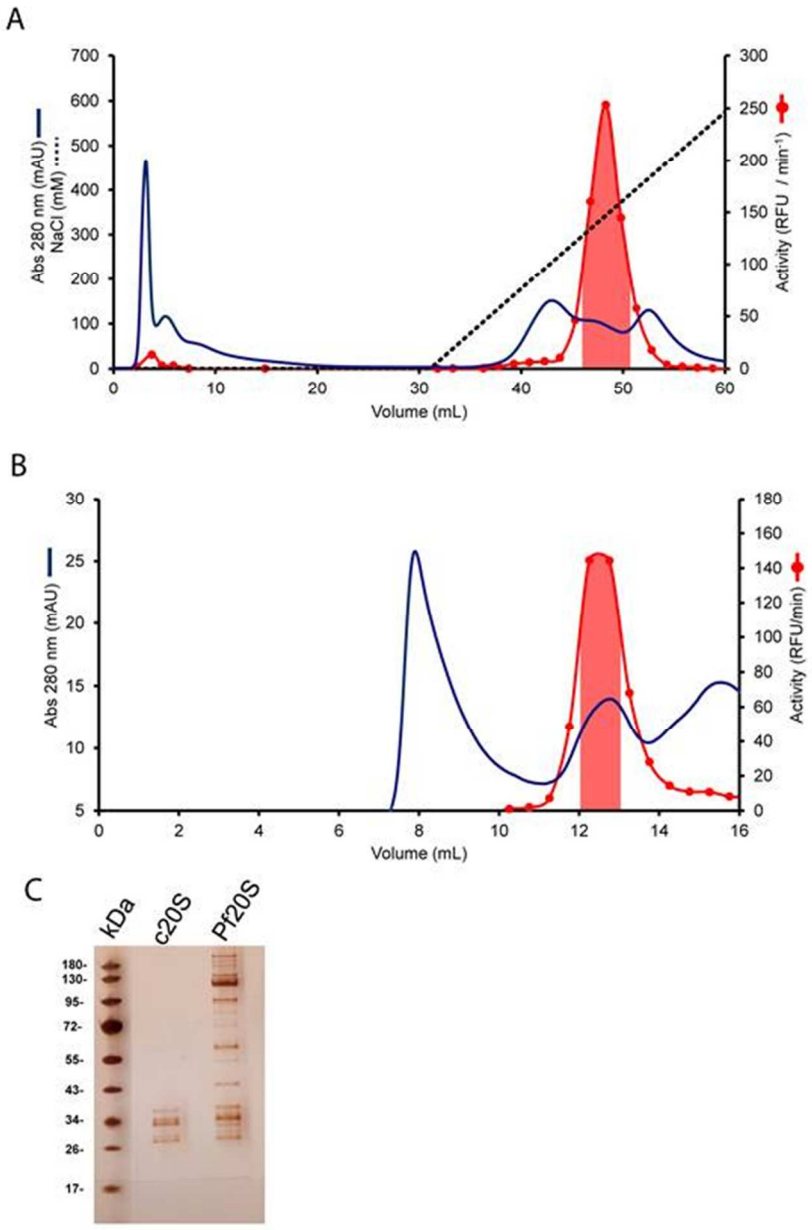

Figure S1: Enrichment of the Pf20S proteasome from *P.falciparum* lysate using A) anion exchange and B) size-exclusion chromatography. Following each chromatographic step, fractions were assayed with LLVY-AMC and the most active fractions (red shading) were pooled. C) Silver-stained SDS-PAGE gel to compare of the Pf20S alpha and beta subunits with the commercial preparation of the constitutive 20S proteasome.

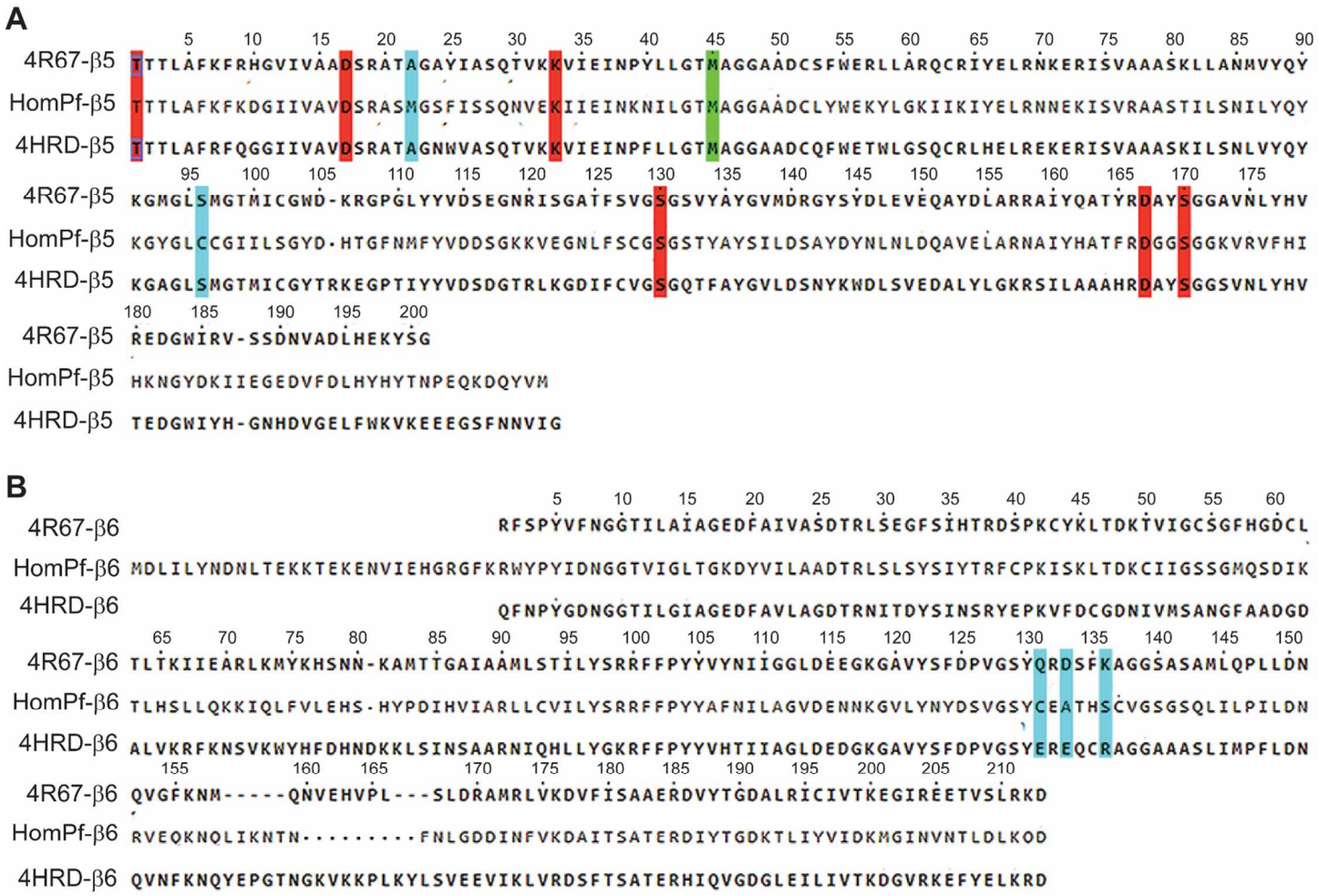

Figure S2: Multiple sequence alignment of the (A) β5 and (B) β6 proteins chains of the human 20S proteasome (PDB ID 4R67 chain L and M), the parasitic 20S proteasome (PDB ID 5FMG chain L and M) and the yeast 20S proteasome (PDB ID 4HRD chain K and L). Residue labeling is according to PDB code 4R67. The residues in red are catalytic residues and the residues in blue were identified as residue substitutions in the Pf 20S proteasome model that are associated with the preferred binding of analog **18** towards the *plasmodium* 20S proteasome β5 subunit (Table S4). The methionine residue (green) is replaced by isoleucine in the carmaphycin resistant yeast mutant strain.

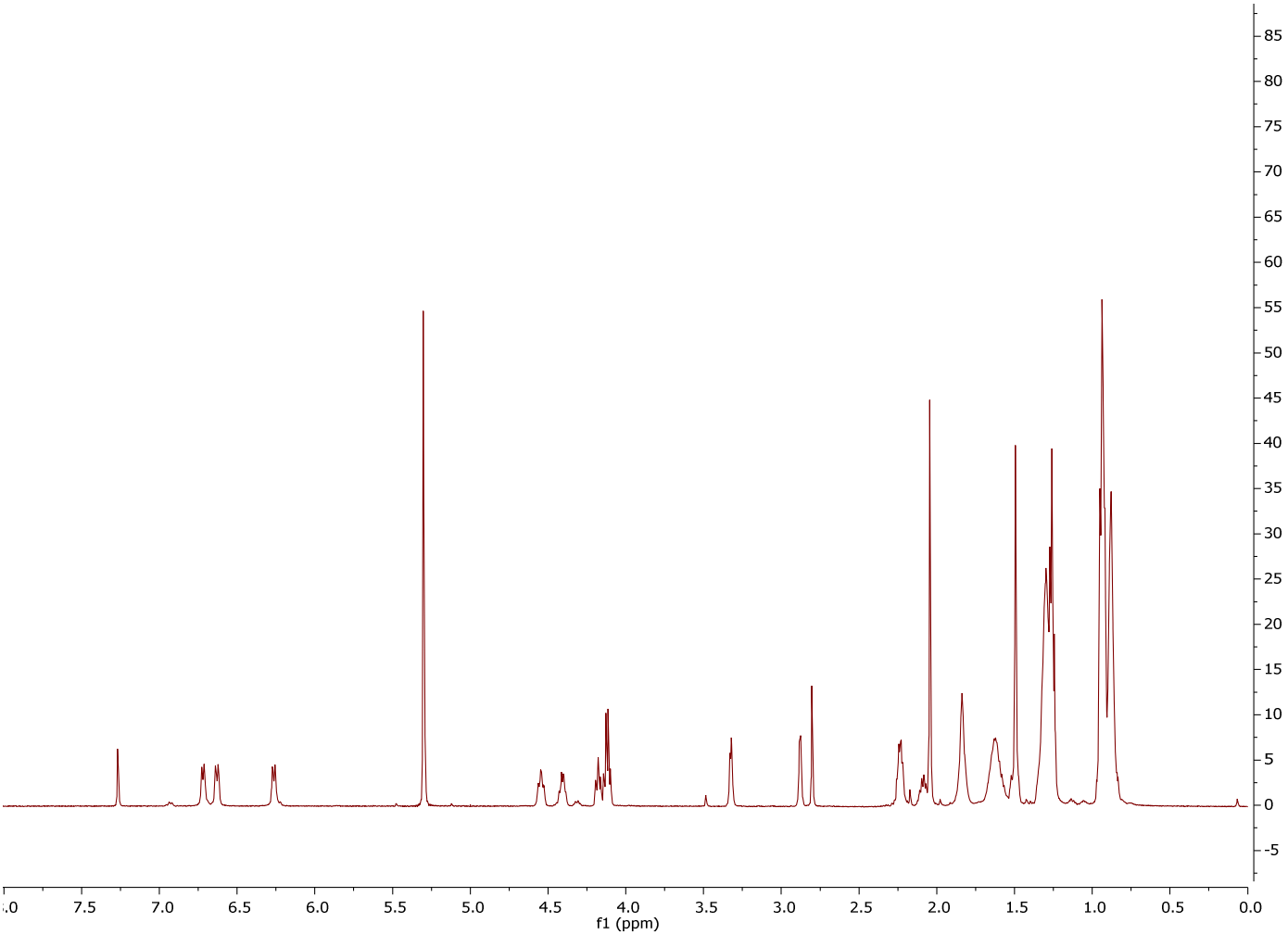

Figure S3. ^{1}H NMR spectrum of analog **18**

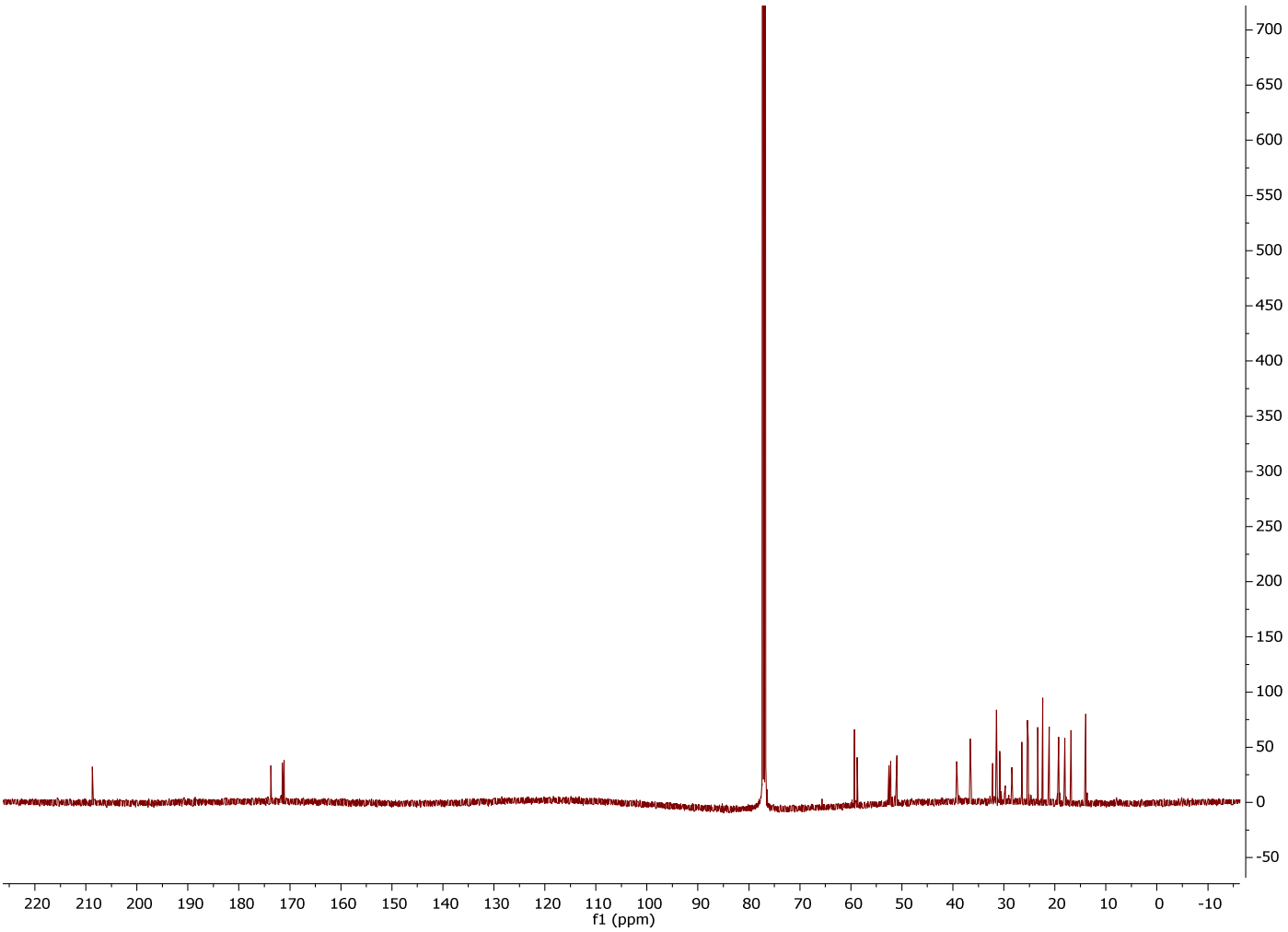

Figure S4. ^{13}C NMR spectrum of analog **18**

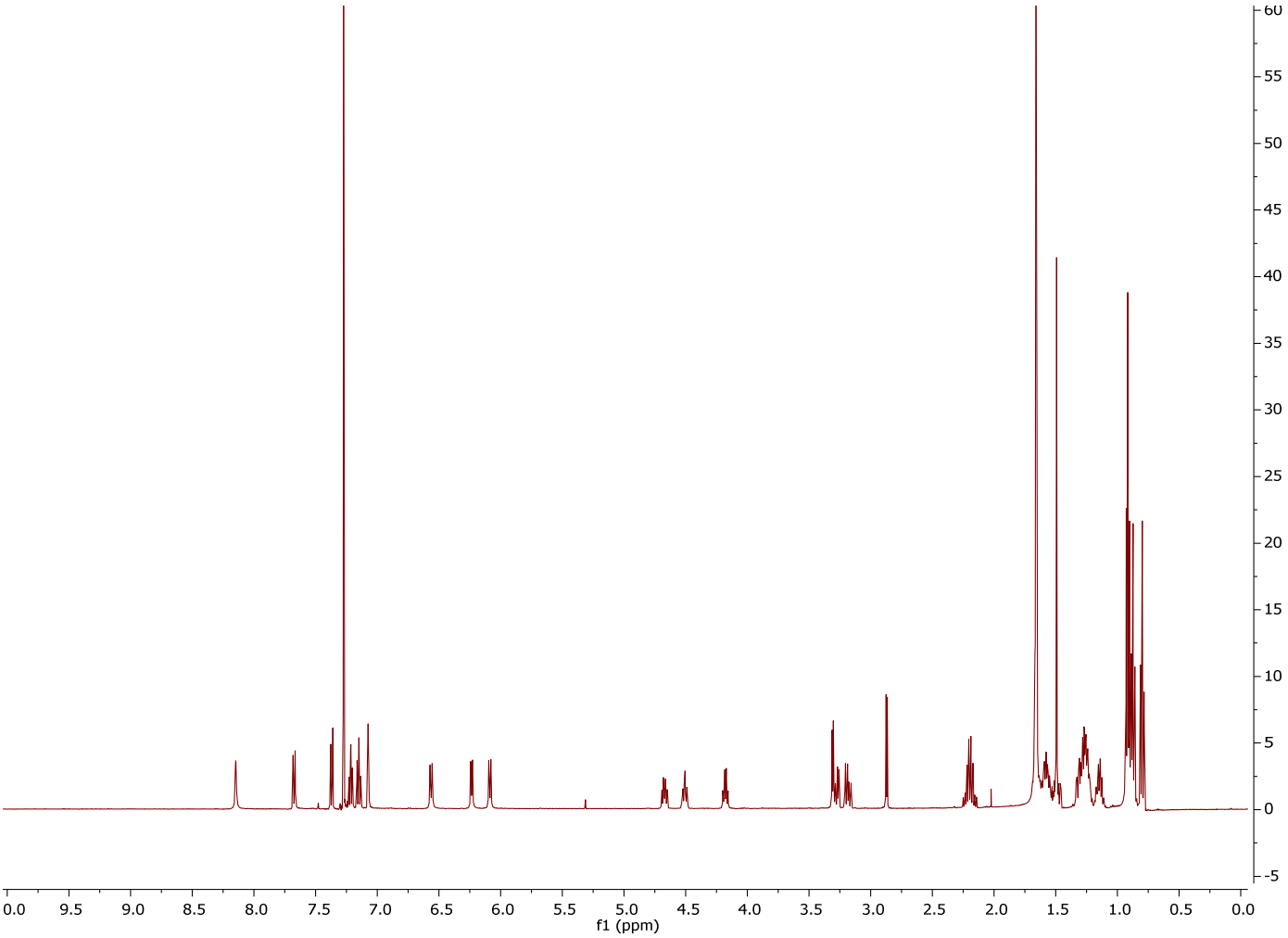

Figure S5. ^{1}H NMR spectrum of analog **19**

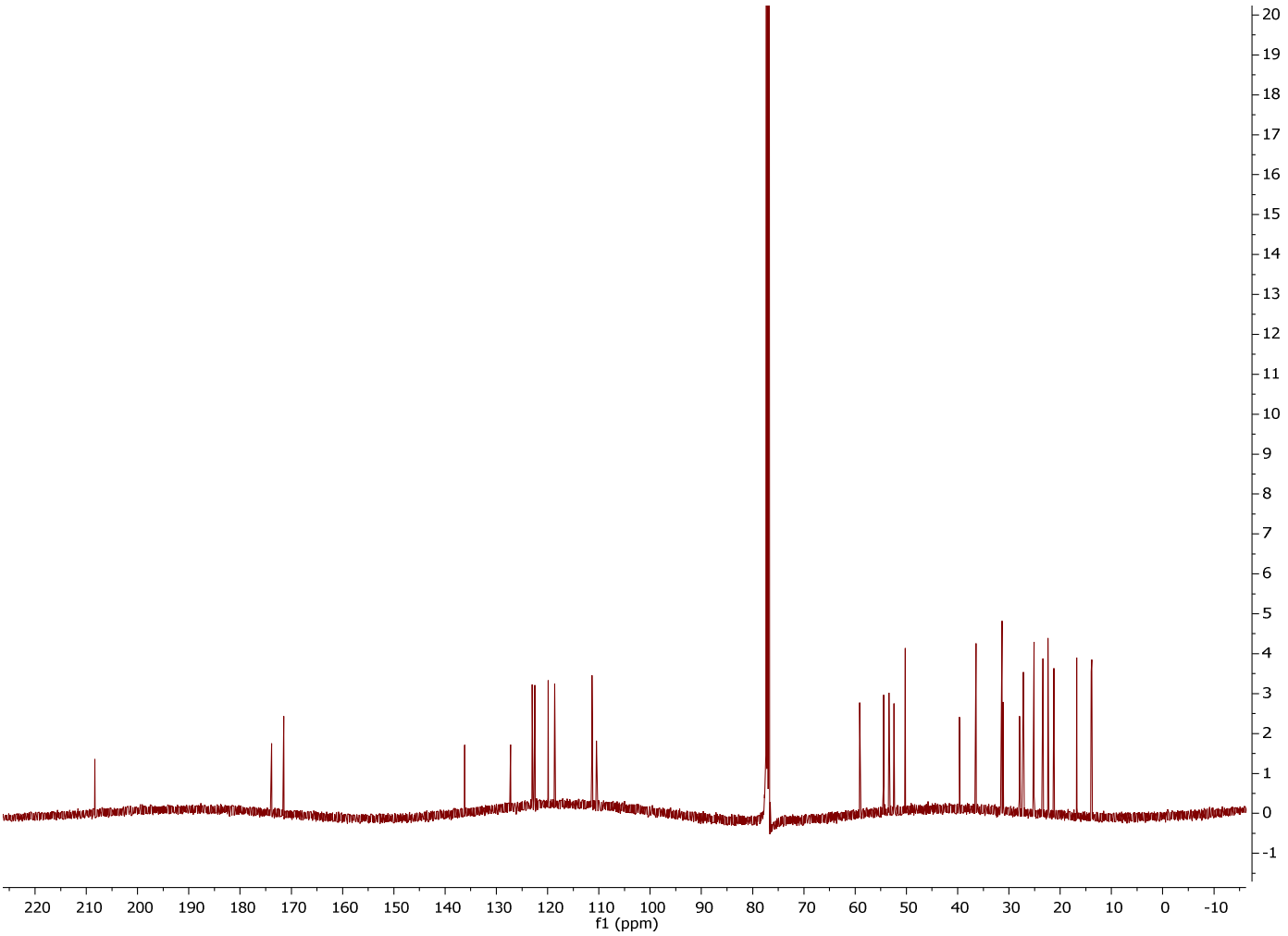

Figure S6. ^{13}C NMR spectrum of analog **19**

Analytical data for validation of carmaphycin B analogs

Analog **1**: (S)-2-((S)-2-hexanamido-3-methylbutanamido)-N-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)hexanamide.

Smile:

O=C(N[C@@H](C(C)C)C(N[C@@H](CCCC)C(N[C@@H](CC(C)C)C([C@]1(CO1)C)=O)=O)=O)CCCCC

Yield 42%; $[\alpha]^{28}_{D}$ +23 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73 (m, 2H), 6.35 (t, *J* = 6.9 Hz, 1H), 4.54 (ddd, *J* = 10.9, 8.0, 3.2 Hz, 1H), 4.40 (q, *J* = 7.5 Hz, 1H), 4.25 (t, *J* = 8.1 Hz, 1H), 3.24 (d, *J* = 5.0 Hz, 1H), 2.84 (d, *J* = 5.0 Hz, 1H), 2.26 – 2.10 (m, 2H), 1.96 (q, *J* = 6.9 Hz, 1H), 1.73 – 1.68 (m, 1H), 1.62 – 1.53 (m, 3H), 1.52 – 1.47 (m, 1H), 1.45 (d, *J* = 3.1 Hz, 3H), 1.29 – 1.13 (m, 10H), 0.87 – 0.76 (m, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.6, 173.3, 171.5, 171.3, 59.0, 58.2, 52.9, 52.4, 50.1, 39.9, 36.6, 31.9, 31.4, 31.2, 27.4, 25.4, 25.1, 23.3, 22.3, 21.1, 19.1, 18.3, 16.7, 13.9, 13.8. HRESIMS *m*/*z* $[M+Na]^+$ 481.3519 (calcd for C26H47N3O5, 481.3516).

Analog **2**: (S)-2-((S)-2-hexanamido-3-phenylpropanamido)-N-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)hexanamide.

Smile:

O=C(N[C@@H](CC1=CC=CC=C1)C(N[C@@H](CCCC)C(N[C@@H](CC(C)C)C([C@]2(CO2)C)=O)=O)=O)CCCCC

Yield 52% ; $[\alpha]^{28}_{D}$ -4 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 2H), 7.23 – 7.20 (m, 1H), 7.20 – 7.14 (m, 2H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 6.20 (d, *J* = 7.7 Hz, 1H), 4.74 (q, *J* = 6.9 Hz, 0H), 4.58 (ddd, *J* = 10.9, 7.9, 3.1 Hz, 0H), 4.37 (q, *J* = 7.1 Hz, 0H), 3.31 (d, *J* = 5.0 Hz, 1H), 3.06 (q, *J* = 6.7, 6.0 Hz, 1H), 2.89 (dd, *J* = 5.2, 1.6 Hz, 0H), 2.15 (t, *J* = 7.6 Hz, 2H), 1.71-1.78 (m, 2H), 1.66-1.68 (m, 1H), 1.52 (s, 3H), 1.50 – 1.58 (m, 4H), 1.22 – 1.32 (m, 4H), 1.15 – 1.22 (m, 4H), 0.93-0.97 (m, 6H), 0.85 (t, *J* = 7.3 Hz, 3H), 0.84 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6, 173.6, 171.7, 171.4, 136.3, 129.2, 128.6, 126.9, 59.2, 53.9, 53.2, 52.5, 50.7, 50.4, 39.7, 38.0, 36.4, 31.9, 31.3, 27.4, 25.3,

25.2, 23.4, 22.3, 22.3, 21.2, 16.8, 13.9, 13.9. HRESIMS *m*/*z* $[M+Na]^+$ 552.3406 (calcd for $C_{30}H_{47}N_3O_5Na$, 552.3413).

Analog **3**: (S)-2-((S)-2-hexanamido-3-(pyridin-4-yl)propanamido)-N-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)hexanamide.

Smile:

O=C(N[C@@H](CC1=CC=NC=C1)C(N[C@@H](CCCC)C(N[C@@H](CC(C)C)C([C@]2(CO2)C)=O)=O)=O)CCCCC

Yield 62%; $[\alpha]^{28}_D$ +6 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.6 Hz, 2H), 7.13 (d, *J* = 4.6 Hz, 2H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.24 (d, *J* = 8.0 Hz, 1H), 6.06 (d, *J* = 7.9 Hz, 1H), 4.91 – 4.73 (m, 1H), 4.67 – 4.53 (m, 1H), 4.31 (td, *J* = 7.7, 5.8 Hz, 1H), 3.29 (d, *J* = 5.0 Hz, 1H), 3.15 (dd, *J* = 14.1, 6.5 Hz, 1H), 3.00 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.92 (d, *J* = 5.1 Hz, 1H), 2.16 (t, *J* = 7.5 Hz, 2H), 1.78 (dq, *J* = 13.6, 6.6, 6.1 Hz, 1H), 1.63 – 1.54 (m, 4H), 1.53 (s, 1H), 1.35 – 1.17 (m, 8H), 0.97 (t, *J* = 6.3, 3H), 0.96 (t, *J* = 6.6, 3H), 0.88 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.4, 173.4, 171.1, 170.2, 149.9, 145.4, 124.5, 59.1, 53.3, 52.9, 52.4, 50.4, 39.9, 37.0, 36.4, 32.1, 31.2, 27.4, 25.2, 25.2, 23.3, 22.3, 22.3, 21.2, 16.7, 13.9, 13.8. HRESIMS *m*/*z* $[M+Na]^+$ 553.3367 (calcd for $C_{29}H_{46}N_4O_5Na$, 553.3366).

Analog **4**: (S)-2-((S)-3-(4-aminophenyl)-2-hexanamidopropanamido)-N-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)hexanamide.

Smile:

O=C(N[C@@H](CC1=CC=C(N)C=C1)C(N[C@@H](CCCC)C(N[C@@H](CC(C)C)C([C@]2(CO2)C)=O)=O)=O)CCCCC

Yield 50%; $[\alpha]^{28}_D$ +19 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (d, *J* = 7.8 Hz, 2H), 6.53 (d, *J* = 7.9 Hz, 2H), 6.36 (d, *J* = 7.8 Hz, 1H), 6.32 (d, *J* = 7.9 Hz, 1H), 5.93 (d, *J* = 7.3 Hz, 1H), 4.59 – 4.41 (m, 2H), 4.25 (td, *J* = 7.7, 5.7 Hz, 1H), 3.25 (d, *J* = 5.0 Hz, 1H), 2.89 (h, *J* = 7.0 Hz, 2H), 2.83 (d, *J* = 5.0 Hz, 1H), 2.08 (t, *J* = 7.6 Hz, 2H), 1.76 – 1.65 (m, 1H), 1.58 (ddt, *J* = 13.4, 6.7, 4.1 Hz, 1H), 1.50-1.45 (m, 2H), 1.47 (s, 3H), 1.28 – 1.08 (m, 11H), 0.89 (m, 6H), 0.80 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.3, 173.4, 171.3, 171.1, 145.3, 130.0,

125.8, 115.3, 59.1, 54.3, 53.2, 52.4, 50.3, 39.8, 36.9, 36.50, 31.8, 31.3, 27.3, 25.2, 23.4, 22.3, 22.3, 21.3, 16.7, 13.9, 13.9. HRESIMS *m*/*z* $[M+Na]^+$ 567.3520 (calcd for $C_{30}H_{48}N_4O_5Na$, 567.3522).

Analog **5**: tert-butyl (4-((S)-2-hexanamido-3-(((S)-1-(((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)amino)-1-oxohexan-2-yl)amino)-3-oxopropyl)phenyl)carbamate.

Smile:

O=C(N[C@@H](CC1=CC=C(NC(OC(C)(C)C)=O)C=C1)C(N[C@@H](CCCC)C(N[C@@H](CC(C)C)C([C@]2(CO2)C)=O)=O)=O)CCCCC

Yield 81%; $[\alpha]^{28}_D$ -38 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 2H), 7.15 – 7.06 (m, 2H), 6.65 (d, *J* = 7.7 Hz, 1H), 6.54 – 6.47 (m, 2H), 6.13 (d, *J* = 7.5 Hz, 1H), 4.67 (q, *J* = 7.0 Hz, 1H), 4.57 (tt, *J* = 10.5, 2.7 Hz, 1H), 3.32 (d, *J* = 5.0 Hz, 1H), 3.01 (m, 1H), 2.94-2.89 (m, 1H), 2.15 (td, *J* = 7.7, 2.1 Hz, 2H), 1.75 (m, 4H), 1.68 – 1.62 (m, 1H), 1.59 – 1.49 (m, 2H), 1.51 (s, 9H), 1.34 – 1.15 (m, 6H), 0.95 (dt, *J* = 5.6, 2.6 Hz, 6H), 0.86 (td, *J* = 7.2, 2.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.4, 173.5, 171.3, 171.0, 152.6, 137.3, 130.6, 129.7, 118.6, 80.5, 59.1, 54.1, 53.2, 52.4, 50.3, 39.8, 37.1, 36.4, 31.9, 31.3, 28.3, 27.3, 25.2, 23.3, 22.3, 22.3, 21.2, 16.7, 13.9, 13.9. HRESIMS *m*/*z* $[M+Na]^+$ 667.4050 (calcd for $C_{35}H_{56}N_4O_7Na$, 667.4047).

Analog **6**: (S)-2-((S)-2-hexanamido-3-(1H-indol-3-yl)propanamido)-N-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)hexanamide.

Smile:

O=C(N[C@@H](CC1=CNC2=C1C=CC=C2)C(N[C@@H](CCCC)C(N[C@@H](CC(C)C)C([C@]3(CO3)C)=O)=O)=O)CCCCC

Yield 48%; $[\alpha]^{28}_D$ +23 (*c* 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.09 (s, 1H), 6.42 (d, *J* = 7.9 Hz, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 6.27 (d, *J* = 7.3 Hz, 1H), 4.77 (q, *J* = 7.0 Hz, 1H), 4.56 (ddd, *J* = 10.9, 8.0, 3.3 Hz, 1H), 4.30 (td, *J* = 7.7, 5.5 Hz, 1H), 3.32 (td, *J* = 14.7, 5.4 Hz, 2H), 3.17 (dd, *J* = 14.7, 7.4 Hz, 1H), 2.90 (t, *J* = 4.7 Hz, 1H), 2.16 (t, *J* = 7.6 Hz, 2H), 1.71-1.78 (m, 2H), 1.65-1.69 (m, 1H), 1.52 (s, 3H), 1.46 – 1.58 (m, 4H), 1.19 – 1.35 (m, 4H), 1.15 – 1.22 (m, 4H), 0.90-0.98 (m, 6H), 0.85 (t, *J* = 7.3 Hz, 3H), 0.84 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR

(126 MHz, $CDCl_3$) δ 208.6, 173.5, 171.5, 171.4, 136.2, 127.4, 123.2, 122.4, 119.9, 118.7, 111.3, 110.4, 59.1, 53.7, 53.4, 52.5, 50.2, 40.4, 39.8, 36.6, 31.7, 31.4, 27.9, 27.3, 25.2, 23.4, 23.4, 22.4, 22.3, 21.3, 16.8, 13.9, 13.9. HRESIMS *m*/*z* $[M+Na]^+$ 591.3518 (calcd for $C_{32}H_{48}N_4O_5Na$, 591.3522).

Analog **7**: (S)-2-((S)-2-hexanamido-3-phenylpropanamido)-N-((S)-1-((R)-2-methyloxiran-2-yl)-1-oxo-3-phenylpropan-2-yl)hexanamide.

Smile:

O=C(N[C@@H](CC1=CC=CC=C1)C(N[C@@H](CCCC)C(N[C@@H](CC2=CC=CC=C2)C([C@]3(CO3)C)=O)=O)=O)CCCCC

Yield 28%; $[\alpha]^{28}_D$ -68 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 14.8, 7.4 Hz, 2H), 7.26 – 7.20 (m, 2H), 7.19 – 7.15 (m, 2H), 7.14 – 7.10 (m, 2H), 6.67 (d, *J* = 6.8 Hz, 1H), 6.53 (t, *J* = 6.3 Hz, 1H), 6.20 (d, *J* = 6.4 Hz, 1H), 4.80 (td, *J* = 7.8, 4.9 Hz, 1H), 4.67 (q, *J* = 7.2 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 1H), 3.33 (d, *J* = 4.9 Hz, 1H), 3.12 (dd, *J* = 13.9, 5.0 Hz, 1H), 2.99 (tt, *J* = 13.9, 7.3 Hz, 2H), 2.91 (d, *J* = 4.9 Hz, 1H), 2.79 (dd, *J* = 13.9, 8.2 Hz, 1H), 2.15 (t, *J* = 7.6 Hz, 2H), 1.81 (m, 2H), 1.67 (ddt, *J* = 16.1, 9.3, 4.3 Hz, 1H), 1.55 (td, *J* = 7.5, 5.1 Hz, 1H), 1.49 (s, 3H), 1.1-1.3 (m, 8H), 0.85 (t, *J* = 7.3 Hz, 3H), 0.84 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.6, 173.4, 171.0, 170.8, 136.4, 135.7, 129.3, 129.2, 128.7, 128.6, 127.2, 127.0, 59.3, 54.1, 53.1, 52.7, 52.5, 37.9, 37.1, 36.5, 31.8, 31.3, 27.3, 25.3, 22.4, 22.3, 16.5, 13.9, 13.9. HRESIMS *m*/*z* $[M+Na]^+$ 586.3265 (calcd for $C_{33}H_{45}N_3O_5Na$, 586.3257).

Analog **8**: (S)-2-((S)-2-hexanamido-3-(pyridin-4-yl)propanamido)-N-((S)-1-((R)-2-methyloxiran-2-yl)-1-oxo-3-phenylpropan-2-yl)hexanamide.

Smile:

O=C(N[C@@H](CC1=CC=NC=C1)C(N[C@@H](CCCC)C(N[C@@H](CC2=CC=CC=C2)C([C@]3(CO3)C)=O)=O)=O)CCCCC

Yield 48%; $[\alpha]^{28}_D$ -24 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 – 8.36 (d, *J* = 4.5 Hz, 2H), 7.25 (m, 3H), 7.13 – 7.06 (m, 2H), 6.98 (d, *J* = 4.5, Hz, 2H), 6.46 (d, *J* = 7.7 Hz, 1H), 6.24 (d, *J* = 7.4 Hz, 1H), 5.92 (d, *J* = 7.9 Hz, 1H), 4.72 (td, *J* = 7.6, 4.2 Hz, 1H), 4.60 (q, *J* = 7.3 Hz, 1H), 4.15 (td, *J* = 7.7, 5.7 Hz, 1H), 3.24 (d, *J* = 4.9 Hz, 1H), 3.09 (dd, *J* = 14.1, 4.9 Hz, 1H), 2.95 (dd, *J* = 14.1, 6.7 Hz, 1H), 2.89 (d, *J* = 7.3 Hz, 1H), 2.87 (d, *J* =

4.9 Hz, 1H), 2.71 (dd, *J* = 14.1, 8.1 Hz, 1H), 2.07 (t, *J* = 7.6 Hz, 2H), 1.61-1.57 (m, 2H), 1.50 – 1.45 (m, 2H), 1.44 (s, 3H), 1.28 – 1.06 (m, 8H), 0.80 (t, *J* = 7.1 Hz, 3H), 0.78 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.3, 173.4, 170.8, 170.2, 149.9, 145.4, 135.5, 129.3, 128.7, 127.2, 124.4, 59.3, 53.2, 53.0, 52.8, 52.6, 37.0, 36.9, 36.4, 31.8, 31.2, 27.2, 25.2, 22.3, 22.3, 16.6, 13.9, 13.8. HRESIMS *m*/*z* $[M+Na]^+$ 587.3211 (calcd for $C_{32}H_{44}N_4O_5Na$, 587.3209).

Analog **9**: (S)-2-((S)-3-(4-aminophenyl)-2-hexanamidopropanamido)-N-((S)-1-((R)-2-methyloxiran-2-yl)-1-oxo-3-phenylpropan-2-yl)hexanamide.

Smile:

O=C(N[C@@H](CC1=CC=C(N)C=C1)C(N[C@@H](CCCC)C(N[C@@H](CC2=CC=CC=C2)C([C@]3(CO3)C)=O)=O)=O)CCCCC

Yield 31%; $[\alpha]^{28}_D$ +22 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 3H), 7.11 – 7.08 (m, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 6.50 (d, *J* = 8.1 Hz, 2H), 6.30 (d, *J* = 7.5 Hz, 1H), 6.10 (d, *J* = 7.5 Hz, 1H), 5.87 (d, *J* = 7.3 Hz, 1H), 4.70 (td, *J* = 8.0, 4.9 Hz, 1H), 4.43 (q, *J* = 7.0 Hz, 1H), 4.20 – 4.08 (m, 1H), 3.27 (d, *J* = 5.0 Hz, 1H), 3.06 (dd, *J* = 14.0, 4.9 Hz, 1H), 2.92 – 2.83 (m, 2H), 2.72 (ddd, *J* = 25.3, 14.0, 7.8 Hz, 2H), 2.08 (t, *J* = 7.6 Hz, 2H), 1.62 – 1.47 (m, 3H), 1.43 (s, 3H), 1.40 – 1.29 (m, 1H), 1.19 (ddt, *J* = 19.4, 12.9, 5.8 Hz, 6H), 1.03 (q, *J* = 7.5 Hz, 2H), 0.84 – 0.79 (m, 3H), 0.76 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.5, 173.4, 171.0, 170.9, 136.3, 135.7, 129.3, 129.2, 128.7, 128.6, 127.2, 127. 3, 115.6, 59.3, 54.1, 53.1, 52.7, 52.5, 37.9, 37.1, 36.5, 31.8, 31.3, 27.3, 25.3, 22.4, 22.3, 16.6, 13.9, 13.9. HRESIMS *m*/*z* $[M+Na]^+$ 601.3375 (calcd for $C_{33}H_{46}N_4O_5Na$, 601.3366).

Analog **10**: tert-butyl (4-((S)-2-hexanamido-3-(((S)-1-(((S)-1-((R)-2-methyloxiran-2-yl)-1-oxo-3-phenylpropan-2-yl)amino)-1-oxohexan-2-yl)amino)-3-oxopropyl)phenyl)carbamate.

Smile:

O=C(N[C@@H](CC1=CC=C(NC(OC(C)(C)C)=O)C=C1)C(N[C@@H](CCCC)C(N[C@@H](CC2=CC=CC=C2)C([C@]3(CO3)C)=O)=O)=O)CCCCC

Yield 72%; $[\alpha]^{28}_{D}$ +2 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 3H), 7.23 (t, *J* = 7.2 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.68 (d, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 7.9 Hz, 1H), 6.51 (s, 1H), 6.21 (d, *J* = 7.5 Hz, 1H), 4.79 (td, *J* = 7.8, 4.9 Hz, 1H), 4.61 (q, *J* = 7.2 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 1H), 3.71 (d, *J* = 8.7 Hz, 1H), 3.33 (d, *J* = 5.0 Hz, 1H), 3.11 (dd, *J* = 13.9, 4.9 Hz, 1H), 2.99 – 2.85 (m, 3H), 2.77 (dd, *J* = 14.0, 8.3 Hz, 1H), 2.15 (t, *J* = 7.6 Hz, 2H), 1.83 (m, 2H), 1.66 (dt, *J* = 12.0, 5.5 Hz, 1H), 1.55 (td, *J* = 7.8, 5.4 Hz, 2H), 1.51 (s, 9H), 1.49 (s, 3H), 1.45 (m, 1H), 1.24 (dtd, *J* = 18.8, 14.4, 7.1 Hz, 6H), 1.11 (q, *J* = 7.8 Hz, 2H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.6, 173.4, 171.0, 171.0, 152.6, 137.3, 135.8, 130.6, 129.7, 129.3, 128.6, 127.1, 118.5, 80.5, 59.3, 54.1, 53.1, 52.7, 52.5, 37.2, 37.0, 36.4, 31.8, 31.3, 28.3, 27.2, 25.3, 22.3, 22.3, 16.5, 13.9, 13.8. HRESIMS *m*/*z* $[M+Na]^+$ 701.3896 (calcd for $C_{38}H_{54}N_4O_7Na$, 701.3890).

Analog **11**: (S)-2-((S)-2-hexanamido-3-(1H-indol-3-yl)propanamido)-N-((S)-1-((R)-2-methyloxiran-2-yl)-1-oxo-3-phenylpropan-2-yl)hexanamide.

Smile:

O=C(N[C@@H](CC1=CNC2=C1C=CC=C2)C(N[C@@H](CCCC)C(N[C@@H](CC3=CC=CC=C3)C([C@]4(CO4)C)=O)=O)=O)CCCCC

Yield 69% $[\alpha]^{28}_{D}$ +54 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 2.3 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.29 (m, 4H), 7.19 (dt, *J* = 8.3, 1.3 Hz, 1H), 7.17 – 7.08 (m, 4H), 6.88 (d, *J* = 2.5 Hz, 1H), 6.43 (d, *J* = 7.6 Hz, 1H), 6.31 (d, *J* = 7.3 Hz, 1H), 6.12 (d, *J* = 7.8 Hz, 1H), 4.74 (m, 2H), 4.23 (td, *J* = 7.7, 5.6 Hz, 1H), 3.33 (t, *J* = 5.5 Hz, 1H), 3.27 (dd, *J* = 14.5, 5.5 Hz, 1H), 3.19 – 3.01 (m, 2H), 2.95 – 2.89 (m, 1H), 2.72 – 2.63 (m, 1H), 2.23 – 2.13 (m, 2H), 1.76 (m, 2H), 1.65 – 1.57 (m, 2H), 1.51 (s, 3H), 1.37 – 1.22 (m, 4H), 1.19 – 1.12 (m, 2H), 1.05 – 0.95 (m, 2H), 0.87 (td, *J* = 7.1, 1.4 Hz, 3H), 0.78 (td, *J* = 7.4, 1.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.7, 173.4, 171.4, 171.0, 136.1, 135.9, 135.5, 129.3, 128.6, 127.1, 123.2, 122.4, 119.8, 118.8, 111.3, 110.3, 59.3, 53.7, 53.1, 52.7, 52.6, 37.1, 36.9, 36.5, 31.6, 31.3, 28.1, 27.1, 25.2, 22.3, 22.2, 16.5, 13.9, 13.8. HRESIMS *m*/*z* $[M+H]^+$ 603.3549 (calcd for C35H46N4O5H, 603.3546).

Analog **12**: N-((R)-3-(4-aminophenyl)-1-(((S)-3-(4-aminophenyl)-1-(((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)amino)-1-oxopropan-2-yl)amino)-1-oxopropan-2-yl)hexanamide .

Smile:

O=C(N[C@@H](CC1=CC=C(N)C=C1)C(N[C@@H](CC2=CC=C(N)C=C2)C(N[C@@H](CC(C)C)C([C@]3(CO3)C)=O)=O)=O)CCCCC

Yield 29%; $[\alpha]^{28}_{D}$ -16 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, CDCl3) δ 6.89 (d, *J* = 8.3 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 6.54 (d, *J* = 8.4 Hz, 2H), 6.48 (d, *J* = 8.4 Hz, 2H), 6.16 (d, *J* = 7.8 Hz, 2H), 5.77 (d, *J* = 6.8 Hz, 1H), 4.52 – 4.33 (m, 3H), 3.23 (dd, *J* = 5.0, 0.7 Hz, 1H), 2.91 (m, 2H), 2.87 – 2.79 (m, 2H), 2.70 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.00 (t, *J* = 7.7 Hz, 2H), 1.47 – 1.37 (m, 3H), 1.44 (s, 3H), 1.26 – 1.11 (m, 6H), 0.87 – 0.85 (m, 3H), 0.84 – 0.82 (m, 2H), 0.80 (d, *J* = 7.3 Hz, 3H). HRESIMS *m*/*z* $[M+Na]^+$ 616.3470 (calcd for $C_{33}H_{47}N_5O_5Na$, 616.3475).

Analog **13**: N-((R)-3-(4-aminophenyl)-1-(((S)-3-(4-aminophenyl)-1-(((S)-1-((R)-2-methyloxiran-2-yl)-1-oxo-3-phenylpropan-2-yl)amino)-1-oxopropan-2-yl)amino)-1-oxopropan-2-yl)hexanamide.

Smile:

O=C(N[C@@H](CC1=CC=C(N)C=C1)C(N[C@@H](CC2=CC=C(N)C=C2)C(N[C@@H](CC3=CC=CC=C3)C([C@]4(CO4)C)=O)=O)=O)CCCCC

Yield 19%; $[\alpha]^{28}_{D}$ +23 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, CDCl3) δ 7.19 – 7.14 (m, 4H), 7.01 – 6.98 (m, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.78 – 6.75 (m, 1H), 6.52 – 6.45 (m, 2H), 6.22 (dd, *J* = 10.4, 7.4 Hz, 1H), 5.88 (d, *J* = 7.1 Hz, 1H), 4.64 (td, *J* = 7.8, 5.0 Hz, 1H), 4.40 (q, *J* = 6.9 Hz, 1H), 4.31 (q, *J* = 7.0 Hz, 1H), 3.23 (d, *J* = 4.9 Hz, 1H), 3.05 (m, 1H), 2.91 – 2.80 (m, 2H), 2.76 (ddd, *J* = 14.1, 10.3, 6.7 Hz, 1H), 2.67 (dd, *J* = 14.1, 7.0 Hz, 1H), 2.59 (dd, *J* = 14.0, 8.5 Hz, 1H), 2.02 (t, *J* = 7.6 Hz, 2H), 1.57 – 1.28 (m, 7H), 1.28 – 1.10 (m, 4H), 0.81 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, CD_3OD) δ 207.1, 174.8, 172.1, 171.6, 161.8, 136.6, 129.6, 129.4, 128.9, 128.0, 115.4, 58.6, 54.7, 52.6, 51.5, 42.3, 36.8, 36.1, 35.4, 30.9, 25.1, 22.0, 22.0, 17.2, 15.8, 15.2, 12.9, 11.7. HRESIMS *m*/*z* $[M+Na]^+$ 650.3317 (calcd for $C_{36}H_{45}N_5O_5Na$, 650.3318).

Analog **14**: tert-butyl (4-((R)-3-(((S)-3-(4-((tert-butoxycarbonyl)amino)phenyl)-1-(((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)amino)-1-oxopropan-2-yl)amino)-2-hexanamido-3-oxopropyl)phenyl)carbamate.

Smile:

O=C(N[C@@H](CC1=CC=C(NC(OC(C)(C)C)=O)C=C1)C(N[C@@H](CC2=CC=C(NC(OC(C)(C)C)=O)C=C2)C(N[C@@H](CC(C)C)C([C@]3(CO3)C)=O)=O)=O)CCCCC

Yield 42%; $[\alpha]^{28}_{D}$ +35 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, CDCl3) δ 7.27 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.71 (s, 1H), 6.67 (s, 1H), 6.57 – 6.44 (m, 2H), 6.02 (dd, *J* = 7.5, 3.2 Hz, 1H), 4.63 – 4.57 (m, 2H), 4.53 (td, *J* = 8.0, 4.0 Hz, 1H), 3.26 (d, *J* = 5.0 Hz, 1H), 2.96 (dd, *J* = 13.6, 6.6 Hz, 2H), 2.95-2.93 (m, 2H) 2.89 (d, *J* = 4.8 Hz, 1H), 2.09 (t, *J* = 7.7 Hz, 2H), 1.87 (m, 2H), 1.58 – 1.48 (m, 18H), 1.26 (td, *J* = 8.0, 7.5, 2.4 Hz, 4H), 1.22 – 1.16 (m, 2H), 0.92 (d, *J* = 6.1 Hz, 3H), 0.91 – 0.87 (m, 3H), 0.86 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 208.1, 173.7, 170.9, 170.4, 152.8, 137.4, 137.2, 130.6, 130.5, 129.7, 129.6, 118.9, 118.8, 80.5, 59.0, 54.2, 54.1, 52.4, 50.1, 39.8, 37.0, 36.7, 36.3, 31.3, 28.3, 28.3, 25.1, 25.0, 23.3, 22.3, 21.2, 21.1, 16.6, 13.9. HRESIMS *m*/*z* $[M+Na]^+$ 816.4526 (calcd for $C_{43}H_{63}N_5O_9Na$, 816.4523).

Analog **15**: tert-butyl (4-((R)-3-(((S)-3-(4-((tert-butoxycarbonyl)amino)phenyl)-1-(((S)-1-((R)-2-methyloxiran-2-yl)-1-oxo-3-phenylpropan-2-yl)amino)-1-oxopropan-2-yl)amino)-2-hexanamido-3-oxopropyl)phenyl)carbamate.

Smile:

O=C(N[C@@H](CC1=CC=C(NC(OC(C)(C)C)=O)C=C1)C(N[C@@H](CC2=CC=C(NC(OC(C)(C)C)=O)C=C2)C(N[C@@H](CC3=CC=CC=C3)C([C@]4(CO4)C)=O)=O)=O)CCCCC

Yield 63%; $[\alpha]^{28}_{D}$ -2 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, CDCl3) δ 7.27 – 7.22 (m, 3H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.11 – 7.05 (m, 2H), 7.03 – 6.97 (m, 2H), 6.92 (dd, *J* = 8.9, 2.2 Hz, 2H), 6.64 (d, *J* = 13.8 Hz, 2H), 6.45 – 6.38 (m, 2H), 5.98 (d, *J* = 7.5 Hz, 1H), 4.73 (td, *J* = 8.0, 5.0 Hz, 1H), 4.56 (q, *J* = 7.0 Hz, 1H), 4.48 (q, *J* = 7.2 Hz, 1H), 3.27 (d, *J* = 4.9 Hz, 1H), 3.06 (dd, *J* = 14.0, 5.0 Hz, 1H), 2.99 (dd, *J* = 14.1, 6.6 Hz, 1H), 2.92 – 2.83 (m, 4H), 2.69 (dd, *J* = 13.9, 8.3 Hz, 1H), 2.10 (td, *J* = 7.6, 1.2 Hz, 2H), 1.54-1.46 (m, 2H), 1.52 (s, 18H), 1.46 (s, 3H), 1.30 – 1.25 (m, 2H), 1.24 – 1.16 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 207.1,

173.5, 170.8, 170.1, 152.7, 137.3, 137.2, 135.7, 130.6, 129.7, 129.6, 129.3, 128.5, 127.0, 118.8, 80.5, 59.2, 54.1, 54.0, 52.6, 52.5, 37.1, 36.9, 36.8, 36.4, 31.3, 28.3, 28.3, 25.2, 22.3, 16.4, 13.9. HRESIMS *m*/*z* $[M+Na]^+$ 850.4368 (calcd for $C_{46}H_{61}N_5O_9Na$, 850.4367).

Analog **16**: N-((S)-1-(((S)-3-(1H-indol-3-yl)-1-(((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)amino)-1-oxopropan-2-yl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)hexanamide.

Smile:

O=C(N[C@@H](CC1=CNC2=C1C=CC=C2)C(N[C@@H](CC3=CNC4=C3C=CC=C4)C(N[C@@H](CC(C)C)C([C@]5(CO5)C)=O)=O)=O)CCCCC

Yield 62%; $[\alpha]^{28}_D$ +63 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.14 (s, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.33 – 7.25 (m, 3H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.11 – 7.03 (m, 2H), 6.87 (d, *J* = 2.4 Hz, 1H), 6.69 (dd, *J* = 8.2, 4.4 Hz, 1H), 6.54 (t, *J* = 7.6 Hz, 1H), 6.43 (d, *J* = 8.0 Hz, 1H), 6.26 (d, *J* = 8.1 Hz, 1H), 5.83 (d, *J* = 6.6 Hz, 1H), 4.69 (ddd, *J* = 8.4, 6.2, 4.2 Hz, 1H), 4.61 (t, *J* = 5.9 Hz, 1H), 4.47 (ddd, *J* = 11.1, 8.2, 3.2 Hz, 1H), 3.54 – 3.48 (m, 1H), 3.29 (dd, *J* = 13.3, 4.5 Hz, 2H), 3.12 (dd, *J* = 14.8, 6.6 Hz, 1H), 2.85 (d, *J* = 4.9 Hz, 1H), 2.77 (dd, *J* = 14.6, 6.2 Hz, 1H), 1.73 (m, 2H), 1.59 (td, *J* = 12.2, 9.1, 4.3 Hz, 1H), 1.48 (s, 3H), 1.45 – 1.33 (m, 1H), 1.32 – 1.14 (m, 4H), 1.12 – 1.00 (m, 3H), 0.89 – 0.81 (m, 6H), 0.77 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.9, 173.6, 170.8, 170.7, 136.3, 135.9, 127.5, 127.2, 123.7, 123.3, 122.7, 122.1, 120.2, 119.4, 118.6, 118.1, 111.6, 111.3, 110.1, 109.3, 59.1, 54.2, 53.6, 52.3, 50.1, 39.3, 38.6, 35.7, 31.2, 26.9, 26.6, 24.7, 23.2, 22.3, 21.1, 16.7, 13.9. HRESIMS *m*/*z* $[M+Na]^+$ 664.3471 (calcd for $C_{37}H_{47}N_5O_5Na$, 664.3475).

Analog **17**: N-((S)-1-(((S)-3-(1H-indol-3-yl)-1-(((S)-1-((R)-2-methyloxiran-2-yl)-1-oxo-3-phenylpropan-2-yl)amino)-1-oxopropan-2-yl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)hexanamide.

Smile:

O=C(N[C@@H](CC1=CNC2=C1C=CC=C2)C(N[C@@H](CC3=CNC4=C3C=CC=C4)C(N[C@@H](CC5=CC=CC=C5)C([C@]6(CO6)C)=O)=O)=O)CCCCC

Yield 46%; $[\alpha]^{28}_{D}$ +35 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.85 – 7.81 (m, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.30 – 7.19 (m, 5H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.99 – 6.93 (m, 3H), 6.79 (d, *J* = 7.4 Hz, 1H), 6.64 (t, *J* = 7.6 Hz, 1H), 6.50 (d, *J* = 2.7 Hz, 1H), 6.44 (d, *J* = 7.7 Hz, 1H), 6.11 (d, *J* = 7.8 Hz, 1H), 5.90 (d, *J* = 6.7 Hz, 1H), 4.71 (td, *J* = 8.4, 4.4 Hz, 1H), 4.60 (dtd, *J* = 14.3, 6.9, 4.5 Hz, 2H), 3.44 (dd, *J* = 14.8, 4.6 Hz, 1H), 3.29 (d, *J* = 4.9 Hz, 1H), 3.15 (dd, *J* = 14.5, 4.4 Hz, 1H), 3.06 (dd, *J* = 14.7, 7.0 Hz, 1H), 2.96 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.86 (d, *J* = 4.9 Hz, 1H), 2.71 (dd, *J* = 14.6, 6.6 Hz, 1H), 2.54 (dd, *J* = 14.0, 8.9 Hz, 1H), 1.80 (m, 2H), 1.66 – 1.52 (m, 2H), 1.46 (s, 3H), 1.25 (dt, *J* = 15.3, 7.4 Hz, 2H), 1.19 – 1.07 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.1, 173.6, 170.9, 170.7, 136.5, 136.3, 135.7, 129.3, 128.3, 127.4, 127.1, 126.6, 123.7, 123.3, 122.6, 122.0, 120.0, 119.4, 118.7, 118.1, 111.5, 111.2, 110.1, 108.9, 59.2, 54.1, 53.7, 52.7, 52.4, 36.5, 35.8, 31.2, 27.3, 26.6, 24.9, 22.3, 16.5, 14.0. HRESIMS *m*/*z* $[M+Na]^+$ 698.3322 (calcd for $C_{40}H_{45}N_5O_5Na$, 698.3318).

Analog **18**: (S)-2-((R)-2-hexanamido-3-methylbutanamido)-N-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)hexanamide.

Smile:

O=C(CCCCC)N[C@H](C(C)C)C(N[C@@H](CCCC)C(N[C@@H](CC(C)C)C([C@]1(C)OC1)=O)=O)=O

Yield 43%; $[\alpha]^{28}_{D}$ +54 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.84 (dd, *J* = 7.9, 2.7 Hz, 1H), 6.78 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.39 (dd, *J* = 8.2, 2.6 Hz, 1H), 4.54 (ddd, *J* = 10.8, 7.6, 3.2 Hz, 1H), 4.48 – 4.39 (m, 1H), 4.22 (td, *J* = 8.0, 2.6 Hz, 1H), 3.32 (dd, *J* = 5.3, 2.5 Hz, 1H), 2.87 (dd, *J* = 5.2, 2.6 Hz, 1H), 2.23 (tt, *J* = 7.8, 2.6 Hz, 2H), 2.08 (qd, *J* = 7.0, 2.6 Hz, 1H), 2.05 – 2.00 (m, 2H), 1.87 – 1.77 (m, 1H), 1.72 – 1.55 (m, 4H), 1.53 – 1.46 (m, 3H), 1.37 – 1.19 (m, 6H), 0.93 (ddt, *J* = 9.8, 6.3, 3.1 Hz, 12H), 0.87 (tq, *J* = 6.3, 3.3, 2.7 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.2, 173.6, 171.5, 171.4, 59.0, 58.8, 52.8, 52.4, 49.9, 39.7, 36.4, 32.1, 31.4, 31.1, 27.5, 25.4, 25.1, 23.3, 22.3, 22.3, 21.1, 19.1, 18.5, 16.6, 13.9, 13.8. HRESIMS *m*/*z* $[M+Na]^+$ 504.3404 (calcd for $C_{26}H_{47}N_3O_5Na$, 504.3408).

Analog **19**: (S)-2-((R)-2-hexanamido-3-(1H-indol-3-yl)propanamido)-N-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)hexanamide.

Smile:

O=C(N[C@H](CC1=CNC2=C1C=CC=C2)C(N[C@@H](CCCC)C(N[C@@H](CC(C)C)C([C@]3(CO3)C)=O)=O)=O)CCCCC

Yield 42%; $[\alpha]^{28}_{D}$ +7 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.15 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 6.56 (d, *J* = 7.9 Hz, 1H), 6.24 (d, *J* = 7.1 Hz, 1H), 6.09 (d, *J* = 8.0 Hz, 1H), 4.67 (ddd, *J* = 8.7, 7.1, 6.0 Hz, 1H), 4.51 (ddd, *J* = 10.8, 7.9, 3.2 Hz, 1H), 4.18 (td, *J* = 8.0, 5.6 Hz, 1H), 3.35 – 3.30 (m, 1H), 3.29 – 3.24 (m, 1H), 3.18 (dd, *J* = 14.3, 8.7 Hz, 1H), 2.87 (d, *J* = 5.0 Hz, 1H), 2.26 – 2.10 (m, 2H), 1.66-1.63 (m, 1H), 1.62 – 1.54 (m, 2H), 1.53 – 1.46 (m, 4H), 1.35 – 1.21 (m, 6H), 1.15 (qd, *J* = 7.5, 1.9 Hz, 2H), 0.92 (t, *J* = 6.8 Hz, 6H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.80 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 208.3, 173.8, 171.4, 171.4, 136.1, 127.2, 122.9, 122.4, 119.9, 118.6, 111.3, 110.4, 59.1, 54.4, 53.3, 52.4, 50.2, 39.6, 36.4, 31.3, 31.1, 27.9, 27.1, 25.1, 25.1, 23.3, 22.3, 22.2, 21.2, 16.7, 13.9, 13.8. HRESIMS *m*/*z* $[M+Na]^+$ 591.3519 (calcd for $C_{32}H_{48}N_4O_5Na$, 591.3522).

Analog **20**: (S)-2-((R)-2-hexanamido-3-(pyridin-4-yl)propanamido)-N-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)hexanamide.

Smile:

O=C(N[C@H](CC1=CC=NC=C1)C(N[C@@H](CCCC)C(N[C@@H](CC(C)C)C([C@]2(CO2)C)=O)=O)=O)CCCCC

Yield 15%; $[\alpha]^{28}_{D}$ +15 (*c* 0.08, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 4.2 Hz, 2H), 7.08 (d, *J* = 4.2 Hz, 2H), 6.75 (d, *J* = 7.5 Hz, 1H), 6.23 (d, *J* = 8.2 Hz, 1H), 5.95 (d, *J* = 7.5 Hz, 1H), 4.57 (q, *J* = 7.3 Hz, 1H), 4.48 (t, *J* = 9.8 Hz, 1H), 4.25-4.15 (m, 1H), 3.21 (d, *J* = 5.2 Hz, 1H), 3.06 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.95 (dd, *J* = 13.8, 6.7 Hz, 1H), 2.82 (d, *J* = 5.0 Hz, 1H), 2.16 (t, *J* = 7.5 Hz, 2H), 1.80 (m, 1H), 1.65 – 1.50 (m, 4H), 1.52 (s, 1H), 1.42 – 1.20 (m, 8H), 0.95 (t, *J* = 6.0, 3H), 0.93 (t, *J* = 6.2, 3H), 0.86 (m, 6H). HRESIMS *m*/*z* $[M+H]^+$ 531.3549 (calcd for $C_{29}H_{47}N_4O_5$, 531.3546).