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Research paper

Discovery of highly potent renin inhibitors potentially interacting with the S3′ subsite of renin

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ABSTRACT

To exploit the S3′ subsite of renin active site for renin inhibitor design, 42 aliskiren derivatives with modified P2′ portion were designed, synthesized and biologically evaluated. Some highly potent renin inhibitors (IC_{50} < 3 nM) were identified, among which compounds **38** (IC_{50} = 0.9 nM) and **39** (IC_{50} = 0.7 nM) were over 2.5-fold more potent than aliskiren (IC_{50} = 2.3 nM). SAR analysis indicated that incorporation of polar hydrophilic moieties into the P2′ portion of renin inhibitors generally enhanced the potency. Consistently with this, molecular modeling study revealed that the triazole part of **39** could provide additional interactions to the S3′ subsite of renin active site. Moreover, *in vivo* evaluation in the double transgenic mouse hypertension model demonstrated that **39** produced greater reduction of the mean arterial blood pressure than ariskiren at the doses of 17.0 and 34.0 μmol/kg, respectively. Taken together, the S3′ subsite of renin active site merits further consideration for renin inhibitor design.

1. Introduction

The renin-angiotensin-aldosterone system (RAAS) plays major roles in the regulation of blood pressure [1]. In the RAAS, angiotensinogen as the only known endogenous substrate of renin can be cleaved under the catalysis of renin to release angiotensin I (Ang I), which is in turn converted to angiotensin II (Ang II) by the angiotensin converting enzyme (ACE). Being a potent vaso-active peptide, Ang II not only causes the blood vessel constriction by acting on angiotensin receptor type 1 (AT_1), but also stimulates the aldosterone production from adrenal cortex and subsequently induces the kidney tubules to increase the reabsorption of sodium and water, thus resulting in increased plasma volume and blood pressure. Blocking the cleavage of angiotensinogen has been proposed as a promising approach to the treatment of hypertension since it is a rate-limiting step at the upstream of RAAS [2]. Renin inhibitors, which can interrupt the interactions between renin and angiotensinogen, are particularly attractive owing to renin's extremely high specificity for angiotensinogen [3–5]. Tremendous research efforts have been exerted to find orally active renin inhibitors [6–11] and some drug candidates have entered into clinical trials (Fig. 1). However, to date, only aliskiren (**1**) was approved by the U.S. FDA.

The catalytic site of renin was defined to comprise 4 parts: the non-prime subsites S1–S4, the non-substrate cavity S3sp, the flap β-hairpin loop, and the prime subsites S1′–S3′ [12]. A large number of renin inhibitors were designed to interact with the former 3 parts [13–18]. Nevertheless, increasing evidences emerged to imply the importance of the prime subsites [6,7,9,19–24]. For example, the crystallography study revealed that the prime subsite S2′ had key interactions with the P2′ portion of aliskren. However, the prime subsite S3′ was neglected and thus remains to be explored. In the previous study, we identified a highly potent aliskiren derivative (**4**) bearing a terminal 1*H*-1,2,3-triazole that might reach the prime subsite S3′ [25]. To investigate the compatibility of S3′ subsite, we carried out further structural modifications based on **4**. Thus, various substituents were incorporated into the triazole ring of **4** or used to replace the P2′ portion of ariskiren, giving rise to aliskiren derivatives **5**-**46** (Fig. 2). The *in vitro* and *in vivo* studies

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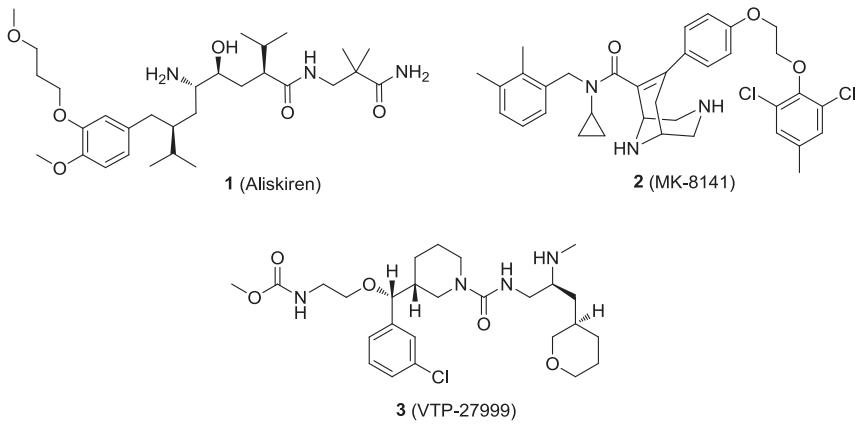


Fig. 1. Chemical structures of representative renin inhibitors.

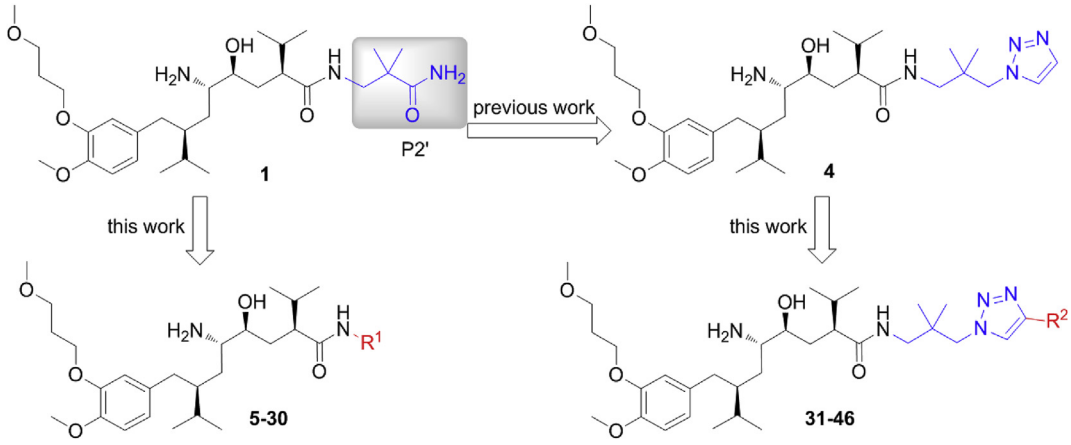


Fig. 2. Structural modification of the P2′ segment of aliskiren.

showed that some compounds were highly potent renin inhibitors that probably interacted with the renin S3′ subsite. Herein, we report the details of this work.

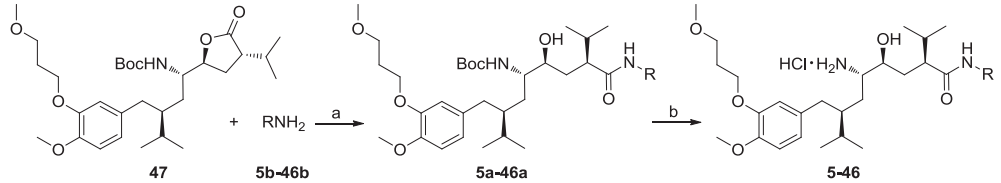
2. Result and discussion

2.1. Chemistry

Compounds **5-46** were synthesized according to the reaction sequence depicted in Scheme 1 [26,27]. Lactone **47** [28] was amidated with various amines **5b-46b** (Supporting Information) in the presence of 2-hydroxypyridine to afford the corresponding amides **5a-46a**, which were treated with 4 *N* HCl/dioxane to give target compounds **5-46** as hydrochloride salts.

2.2. In vitro evaluation for renin inhibitory activity and SAR analysis

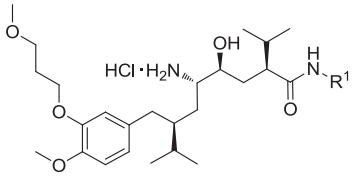
Compounds **5-46** were evaluated for their inhibitory activity against human renin, with using **1** and **4** as the positive controls. As shown in Tables 1 and 2, all the designed compounds showed considerable renin inhibitory activity ($IC_{50} \leq 34$ nM). In particular, some highly potent renin inhibitors ($IC_{50} < 3$ nM) were identified, among which compounds **38** ($IC_{50} = 0.9$ nM) and **39** ($IC_{50} = 0.7$ nM) exhibited the best potency. In comparison with triazole **4** ($IC_{50} = 2.0$ nM), pyridines **5** ($IC_{50} = 2.2$ nM), **6** ($IC_{50} = 1.5$ nM) and **26** ($IC_{50} = 2.6$ nM) maintained high inhibitory potency, while most of the phenyl derivatives had decreased potency. For instance, compound **7** (IC_{50} = 34.0 nM) was 17-fold less potent than **4**.

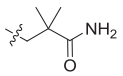
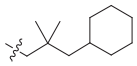
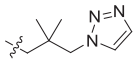
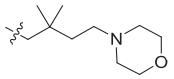
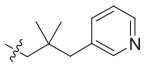
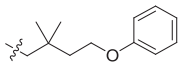
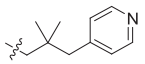
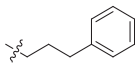
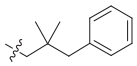
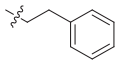
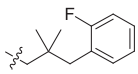
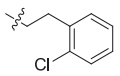
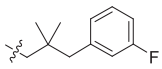
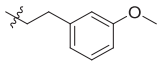
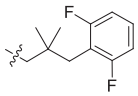
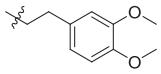
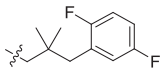
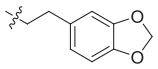
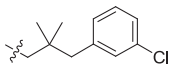
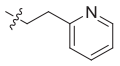
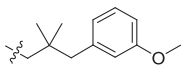
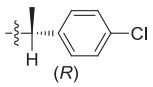
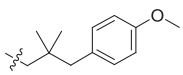
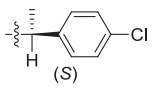
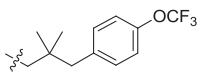
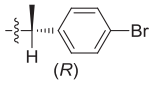
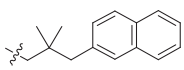
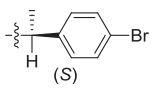


Reagents and conditions: a) Et_3N, 2-hydroxypyridine, 100 °C; b) 4 N HCl/dioxane, 0 °C.

Scheme 1. Synthesis of compounds **5-46**.

Table 1
In vitro renin inhibitory activity of compounds **5-30**.



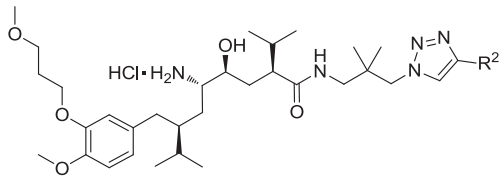
Cpd	R^1	IC_{50} (nM)	Cpd	R^1	IC_{50} (nM)
1		2.3	**17**		15.5
4		2.0	**18**		1.8
5		2.2	**19**		8.5
6		1.5	**20**		12.1
7		34.0	**21**		11.5
8		9.2	**22**		27.7
9		9.8	**23**		7.2
10		16.1	**24**		4.4
11		12.4	**25**		11.0
12		9.8	**26**		2.6
13		12.3	**27**		30.0
14		10.2	**28**		15.2
15		13.4	**29**		33.7
16		11.2	**30**		20.9

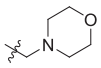
Interestingly, removal of the geminal dimethyl groups (*e.g.* **20**) or incorporation of fluorine, chloride, oxygen and nitrogen-contained functions (*e.g.* **8**, **13** and **15**) could recover the inhibitory potency to some extent, indicating that the renin S3′ subsite might tend to accommodate hydrophilic polar moieties. This trend was reflected particularly among triazoles **31-46** (Table 2). For example, compounds **37-40** and **45-46** (IC_{50} = 0.7–1.5 nM) all exhibited higher potency than **4**. In addition, substituent configuration (*e.g.* **28** *vs* **27**, **30** *vs* **29**) and size (*e.g.* **33** *vs* **34**) had substantial effects on the renin inhibitory potency.

2.3. Molecular dynamics modeling

Notably, triazoles **4** and **39** bear flexible long chains. Molecular dynamics modeling [29] was performed to predict the possible binding modes of **4** and **39** in human renin (Fig. 3A and B). For the

Table 2
In vitro renin inhibitory activity of compounds **31-46**.



Cpd	R^2	IC_{50} (nM)	Cpd	R^2	IC_{50} (nM)
4	H	2.0	**38**		0.9
31		1.6	**39**		0.7
32		7.0	**40**		1.1
33		5.8	**41**		5.2
34		17.1	**42**		1.9
35		5.0	**43**		2.1
36		13.1	**44**		2.7
37		1.5	**45**		1.0
			46		1.1

convenience of comparison (Fig. 3C), the predicted binding conformation of **39** was aligned to the crystal structure of **1** bound to human renin (PDB code: 2V0Z). As illustrated in Fig. 3, the P1–P3 portions of **1**, **4,** and **39** were closely overlapped, which all made hydrogen bonding interactions with Tyr14, Gly217, Asp32, Asp215 and Gly34. However, unlike **1**, both **4** and **39** could extend toward the S3′ subsite, resulting in more interactions with renin. For example, the triazole N_3 atom of both **4** and **39** formed hydrogen bond with the hydroxyl group of Thr295. Moreover, the hydroxyethyl group on the triazole ring of **39** made additional hydrogen bonding interactions with the carboxylate of Pro293, indicating why **39** was more potent than **4**.

2.4. Inhibitory selectivity for human renin over human cathepsins D and E

Triazole **39** was selected to test its inhibitory selectivity for human renin over other two aspartyl proteases, human cathepsins D and E. As shown in Fig. 4, the inhibitory activity of **39** against both cathepsins D and E was rather weak, indicating that **39** was highly selective for human renin.

2.5. In vivo antihypertensive evaluation

Double transgenic hypertensive mice (dTGM) harboring both human angiotensinogen and renin genes [30] were used for *in vivo* antihypertensive evaluation of compound **39**, with using aliskiren **1** as the positive control. As demonstrated in Fig. 5A, oral administration of **39** to dTGMs induced robust reduction of the mean arterial blood pressure (MAP) in a dose-dependent manner. The antihypertensive effect could be sustained over 14 h and the maximum MAP reduction was reached up to 40–50 mmHg. At the dose of 8.5 μmol/kg, the antihypertensive effect of **39** was comparable to that of **1** (Fig. 5B), while at the doses of 17.0 and 34.0 μmol/kg, **39** exhibited much better hypotensive effect than **1** (Fig. 5C and D).

3. Conclusion

Some highly potent renin inhibitors have been discovered by structural modification of aliskiren derivative **4**. Among them, compounds **38-40** and **45-46** (IC_{50} = 0.7–1.1 nM) were found to be 2–3 fold more potent than ariskiren (IC_{50} = 2.3 nM). In the dTGM hypertensive model, the selected compound **39** displayed comparable or better *in vivo* antihypertensive effect than aliskiren. Molecular modeling study suggested that compounds **4** and **39** might make additional interactions with the S3′ subsite of renin active site, thus highlighting its importance for further design of renin inhibitors.

4. Experimental section

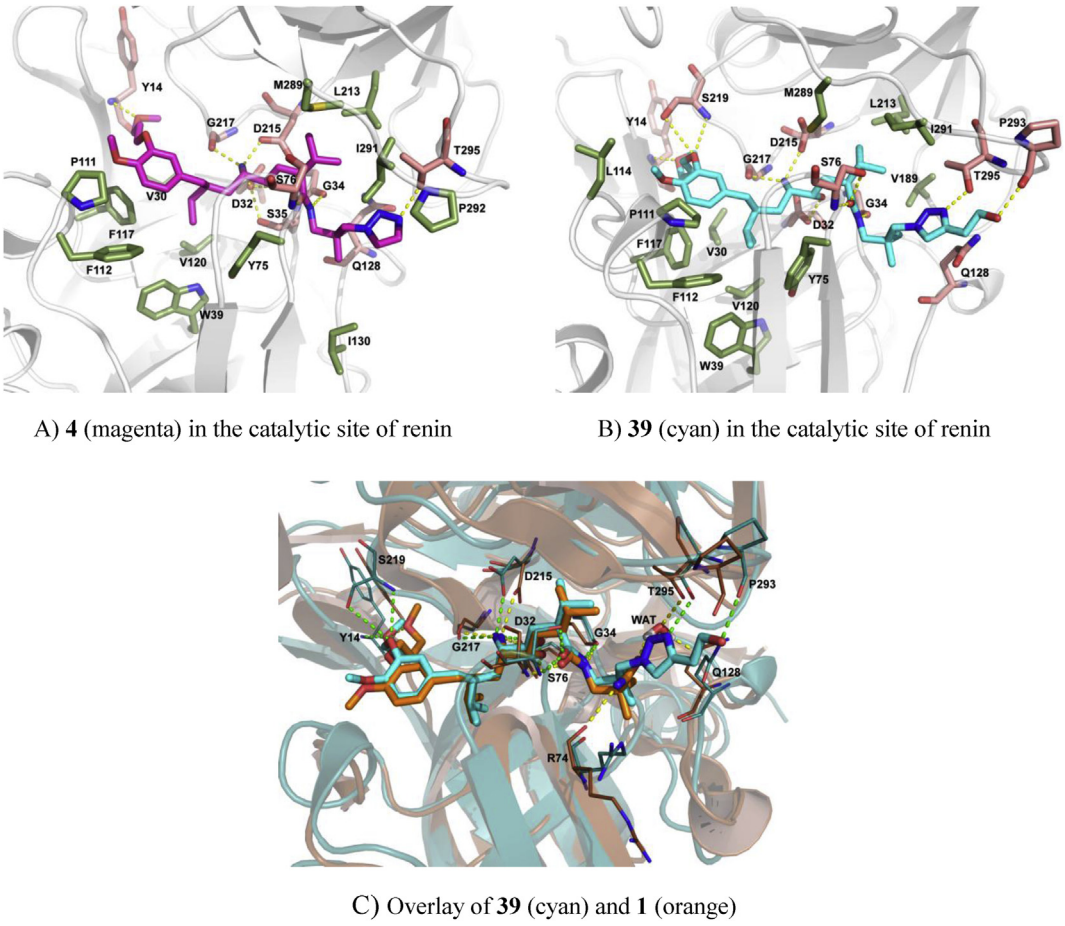
4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded at 300/500 and 75/125 MHz respectively on an ACF * 300Q Bruker or ACF * 500Q Bruker spectrometer with Me_4Si as the internal reference. Low-resolution and high-resolution mass spectra (LRMS and HRMS) were given with electron impact mode. The mass analyzer type used for the HRMS measurements was TOF. Reactions were monitored by TLC on silica gel 60 F254 plates (Qingdao Ocean Chemical Company, China). Column chromatography was carried out on silica gel (200–300 mesh, Qingdao Ocean Chemical Company, China). Optical rotation data were recorded on Jasco p-1020 Polarimeter. The purity of final compounds was determined by HPLC in Agilent 1100 system or SHIMADZU LC-20AT with Diamonsil C18 column 5 μm 250 × 4.6 nm. Unless specially noted, 95% aqueous acetonitrile containing 0.1% trifluoroacetic acid was used as the HPLC eluent. The flow rate, oven temperature and UV detection wavelength were set to 0.5 mL/min, 25 °C and 215 nm, respectively.

4.2. Synthesis of compounds ***5a-46a***

4.2.1. *tert-Butyl (3S,5S,6S,8S)-8-(2,2-dimethyl-3-(naphthalen-2-yl) propylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy) benzyl)-2,9-dimethyldecan-5-ylcarbamate (**16a**)*

Compound **47** (92 mg, 0.17 mmol) was dissolved in Et_3N (2 mL). To the solution was added 2-hydroxypyridine (17 mg, 0.17 mmol) and **16b** (145 mg, 0.68 mmol). After stirred at 100 °C for 18 h, the mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate (5 mL) and acidified with 1 N HCl solution. The organic layer was collected and the aqueous layer was extracted with ethyl acetate (10 mL × 3). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 6/1) to afford **16a** as a solid (79 mg, 62%). [α]25 D-25.0 (*c* 0.20, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80–0.83 (m, 6 H), 0.89–0.95 (m, 12 H), 1.17–1.25 (m, 2 H), 1.43 (s, 9 H), 1.56–1.65 (m, 5 H), 1.80–1.87 (m, 1 H), 1.97–1.99 (m, 1 H), 2.04–2.10 (m, 2 H), 2.35–2.39 (m, 1 H), 2.58–2.62 (m, 1 H), 2.71 (s, 2 H), 3.11–3.14 (m, 1 H), 3.28–3.32 (m, 1 H), 3.34 (s, 3 H), 3.41–3.52 (m, 2 H), 3.56 (t, 2 H, *J* = 5 Hz), 3.81 (s, 3 H), 4.10 (t, 2 H, *J* = 5 Hz), 4.63 (d, 1 H, *J* = 10 Hz), 5.67 (s, 1 H), 6.67–6.76 (m, 3 H), 7.26–7.29 (m, 1 H), 7.41–7.47 (m, 2 H), 7.59 (s, 1 H), 7.75–7.82 (m, 3

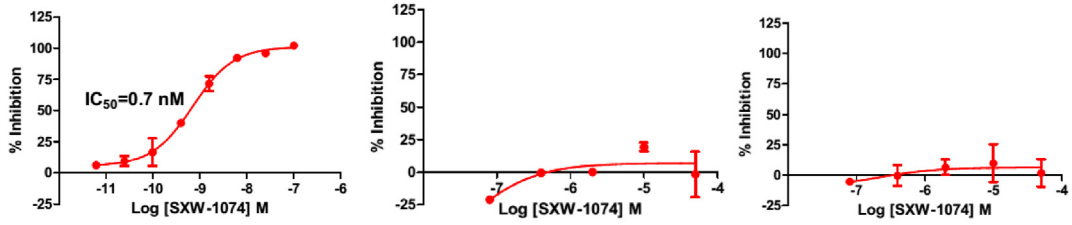


A) **4** (magenta) in the catalytic site of renin

B) **39** (cyan) in the catalytic site of renin

C) Overlay of **39** (cyan) and **1** (orange)

Fig. 3. Modelling predicted binding modes of **4** and **39** in the catalytic site of human renin. The inhibitors and the interacting amino acid residues are displayed in a stick model (colored by atom: oxygen atom in red and nitrogen atom in blue). The amino acid residues forming hydrogen bonds (showed as dashed yellow lines) with the inhibitors are shown in pink and those interacting with the inhibitors via hydrophobic contacts are shown in green. Graphs were generated using the PyMOL software. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



A) B) C)

Fig. 4. Inhibitory activity of **39** against: A) human renin; B) Cathepsin D; C) Cathepsin E.

H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 20.3, 21.3, 25.1, 25.2, 28.1, 28.3, 29.7, 32.6, 34.5, 35.9, 37.4, 42.3, 46.7, 49.3, 51.6, 54.1, 56.0, 58.5, 66.0, 69.4, 71.3, 79.1, 111.7, 114.6, 121.3, 125.3, 125.9, 127.3, 128.7, 129.0, 132.0, 133.3, 134.3, 135.8, 147.6, 148.2, 156.7, 176.2. ESI-MS *m/z* 749.5 $[M+H]^+$. HRMS calcd for $C_{45}H_{69}N_2O_7$ $[M+H]^+$ *m/z* 749.5105, found 749.5113.

*4.2.2. tert-Butyl (3S,5S,6S,8S)-8-(2,2-dimethyl-3-(pyridin-3-yl) propylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy) benzyl)-2,9-dimethyldecan-5-yl-carbamate (**5a**)*

Following a similar procedure for the preparation of **16a**, **5a** was prepared starting from **47** (150 mg, 0.28 mmol) and **5b** (450 mg, 2.74 mmol). Solid (128 mg, 66%). [α]25 D-26.3 (*c* 0.30, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78–0.84 (m, 6 H), 0.88–0.94 (m, 12 H), 1.16–1.25 (m, 2 H), 1.43 (s, 9 H), 1.55–1.64 (m, 5 H), 1.86–1.99 (m, 1 H), 2.06–2.08 (m, 3 H), 2.35–2.38 (m, 1 H), 2.54 (s, 2 H), 2.57–2.58 (m, 1 H), 3.02–3.06 (m, 1 H), 3.24–3.28 (m, 1 H), 3.34 (s, 3 H), 3.40–3.51 (m, 2 H), 3.56 (t, 2 H, J = 6.0 Hz), 3.81 (s, 3 H), 4.09 (t, 2 H, J = 6.5 Hz), 4.67 (d, 1 H, J = 8.5 Hz), 5.84 (s, 1 H), 6.67–6.75 (m, 3 H), 7.20–7.23 (m, 1 H), 7.49 (d, 1 H, J = 7.5 Hz), 8.40 (s, 1 H), 8.46 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 20.3, 21.2, 24.6, 24.8, 28.2, 28.3, 29.6, 29.7, 32.4, 34.6, 35.5, 37.4, 42.3, 43.2, 49.1, 51.4, 54.1, 56.0, 58.6, 66.0, 69.4, 71.4, 79.2, 111.7, 114.5, 121.3, 123.0, 128.7, 133.7, 134.2, 137.8, 147.5, 147.6, 148.2, 151.1, 176.2. ESI-MS *m/z* 700.5

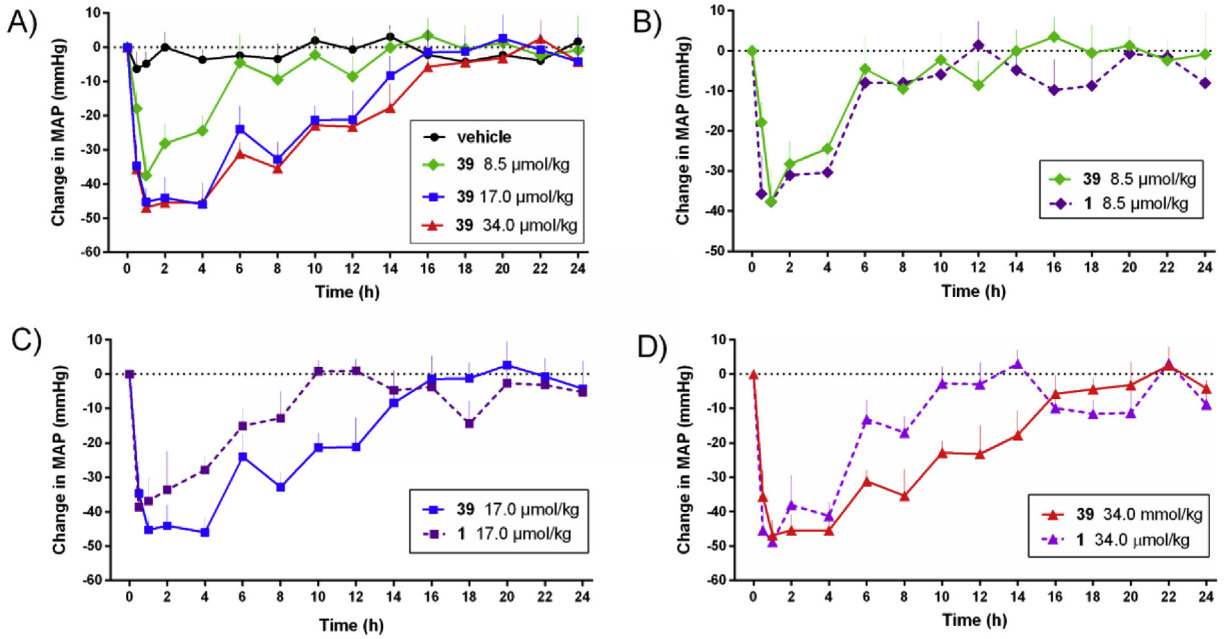


Fig. 5. Effect of **1** and **39** on MAP in dTGMs.

$[M+H]^+$. HRMS calcd for $C_{40}H_{66}N_3O_7$ $[M+H]^+$ *m/z* 700.4901, found 700.4903.

*4.2.3. tert-Butyl (3S,5S,6S,8S)-8-(2,2-dimethyl-3-(pyridin-4-yl) propylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy) benzyl)-2,9-dimethyldecan-5-ylcarbamate (**6a**)*

Following a similar procedure for the preparation of **16a**, **6a** was prepared starting from **47** (150 mg, 0.28 mmol) and **6b** (450 mg, 2.74 mmol). Solid (108 mg, 55%). [α]25 D-12.0 (*c* 0.40, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 0.79–0.84 (m, 6 H), 0.88–0.97 (m, 12 H), 1.18–1.26 (m, 2 H), 1.44 (s, 9 H), 1.55–1.73 (m, 5 H), 1.89–1.93 (m, 1 H), 2.07–2.09 (m, 3 H), 2.37–2.41 (m, 1 H), 2.53 (s, 2 H), 2.57–2.60 (m, 1 H), 3.04–3.08 (m, 1 H), 3.25–3.29 (m, 1 H), 3.35 (s, 3 H), 3.39–3.52 (m, 2 H), 3.57 (t, 2 H, *J* = 6.5 Hz), 3.82 (s, 3 H), 4.10 (t, 2 H, *J* = 6.0 Hz), 4.64 (d, 1 H, *J* = 9.0 Hz), 5.85 (s, 1 H), 6.67–6.76 (m, 3 H), 7.09 (d, 2 H, *J* = 4.5 Hz), 8.50 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 20.3, 21.2, 24.7, 24.8, 28.2, 28.3, 29.6, 29.8, 32.4, 34.7, 35.6, 37.4, 42.3, 45.5, 49.2, 51.4, 54.1, 56.0, 58.6, 66.0, 69.4, 71.4, 79.2, 111.7, 114.5, 121.3, 125.8, 134.2, 147.4, 147.6, 148.2, 149.2, 156.8, 176.2. ESI-MS *m/z* 700.5 $[M+H]^+$. HRMS calcd for $C_{40}H_{66}N_3O_7$ $[M+H]^+$ *m/z* 700.4901, found 700.4900.

*4.2.4. tert-Butyl (3S,5S,6S,8S)-8-(2,2-dimethyl-3-phenylpropylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**7a**)*

Following a similar procedure for the preparation of **16a**, **7a** was prepared starting from **47** (120 mg, 0.22 mmol) and **7b** (160 mg, 0.88 mmol). Solid (103 mg, 67%). [α]25 D-14.1 (*c* 0.11, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$) δ 0.80–0.83 (m, 6 H), 0.90–0.93 (m, 12 H), 1.18–1.26 (m, 2 H), 1.44 (s, 9 H), 1.57–1.64 (m, 4 H), 1.86–1.99 (m, 3 H), 2.04–2.12 (m, 2 H), 2.34–2.41 (m, 1 H), 2.55–2.62 (m, 3 H), 3.05–3.11 (m, 1 H), 3.21–3.28 (m, 1 H), 3.35 (s, 3 H), 3.42–3.50 (m, 2 H), 3.57 (t, 2 H, *J* = 6 Hz), 3.82 (s, 3 H), 4.10 (t, 2 H, *J* = 6 Hz), 4.65 (d, 1 H, *J* = 6 Hz), 5.68 (s, 1 H), 6.67–6.77 (m, 3 H), 7.13–7.30 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 20.3, 21.3, 25.0, 25.1, 25.2, 28.0, 28.3, 29.6, 32.5, 34.5, 35.6, 37.4, 42.2, 46.6, 49.2, 51.6, 54.0, 56.0, 58.5, 66.0, 69.4, 71.2, 79.1, 111.7, 114.5, 121.3, 126.2, 128.0, 130.3, 134.2, 138.2, 147.6, 148.2, 156.6, 176.2. ESI-MS *m/z* 699.1 $[M+H]^+$. HRMS calcd for $C_{41}H_{67}N_2O_7$ $[M+H]^+$ *m/z* 699.4948, found 699.4951.

*4.2.5. tert-Butyl (3S,5S,6S,8S)-8-(3-(2-fluorophenyl)-2,2-dimethylpropylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**8a**)*

Following a similar procedure described for preparation of **16a**, **8a** was prepared starting from **47** (100 mg, 0.18 mmol) and **8b** (200 mg, 1.10 mmol). Solid (82 mg, 61%). [α]25 D-19.3 (*c* 0.3, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 0.75–0.88 (m, 6 H), 0.92–1.00 (m, 12 H), 1.20–1.32 (m, 2 H), 1.47 (s, 9 H), 1.55–1.65 (m, 2 H), 1.65–1.75 (m, 3 H), 1.90–2.00 (m, 1 H), 2.08–2.15 (m, 3 H), 2.37–2.45 (m, 1 H), 2.58–2.65 (m, 3 H), 3.08–3.15 (m, 1 H), 3.17–3.25 (m, 1 H), 3.37 (s, 3 H), 3.40–3.50 (m, 1 H), 3.55–3.63 (m, 3 H), 3.84 (s, 3 H), 4.13 (t, 2 H, *J* = 6.3 Hz), 4.68 (d, 1 H, *J* = 8.7 Hz), 5.85–6.00 (m, 1 H), 6.70–6.75 (m, 1 H), 6.75–6.82 (m, 2 H), 7.02–7.12 (m, 2 H), 7.15–7.25 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 20.4, 21.3, 25.0, 25.1, 28.1, 28.4, 29.6, 32.6, 34.5, 36.1, 37.4, 38.5, 42.4, 48.7, 51.7, 54.0, 56.0, 58.6, 66.0, 69.5, 71.2, 79.1, 111.8, 114.6, 115.1, 121.3, 123.7, 125.1, 128.1, 132.9, 134.3, 147.6, 148.3, 156.7, 160.5, 176.4. ESI-MS *m/z* 717.5 $[M+H]^+$. HRMS calcd for $C_{41}H_{66}N_2FO_7$ $[M+H]^+$ *m/z* 717.4854, found 717.4856.

*4.2.6. tert-Butyl (3S,5S,6S,8S)-8-(3-(3-fluorophenyl)-2,2-dimethylpropylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**9a**)*

Following a similar procedure for the preparation of **16a**, **9a** was prepared starting from **47** (150 mg, 0.28 mmol) and **9b** (203 mg, 1.12 mmol). Solid (113 mg, 56%). [α]25 D-13.5 (*c* 0.42, CH_3OH). ^1H NMR (500 MHz, $CDCl_3$) δ 0.82–0.83 (m, 6 H), 0.89–0.98 (m, 12 H), 1.18–1.27 (m, 1 H), 1.44 (s, 9 H), 1.56–1.71 (m, 5 H), 1.87–1.91 (m, 2 H), 2.04–2.10 (m, 3 H), 2.36–2.41 (m, 1 H), 2.54 (s, 2 H), 2.57–2.61 (m, 1 H), 3.05–3.09 (m, 1 H), 3.22–3.26 (m, 1 H), 3.35 (s, 3 H), 3.38–3.52 (m, 2 H), 3.57 (t, 2 H, *J* = 5 Hz), 3.82 (s, 3 H), 4.10 (t, 2 H, *J* = 5 Hz), 4.63 (d, 1 H, *J* = 10 Hz), 5.73 (s, 1 H), 6.68–6.92 (m, 6 H), 7.21–7.24 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 20.3, 21.3, 24.9, 25.0, 28.2, 28.3, 29.6, 32.5, 34.6, 35.6, 37.4, 42.3, 46.1, 49.2, 51.6, 54.1, 56.0, 58.6, 66.0, 69.4, 71.3, 79.2, 111.8, 113.0, 114.6, 117.1, 121.3, 126.1, 126.1, 129.2, 129.3, 134.3, 140.7, 147.6, 148.3, 156.7, 161.6, 176.2. ESI-

MS *m/z* 717.5 $[M+H]^+$. HRMS calcd for $C_{41}H_{66}N_2O_7F$ $[M+H]^+$ *m/z* 717.4854, found 717.4862.

*4.2.7. tert-Butyl (3S,5S,6S,8S)-8-(3-(2,6-difluorophenyl)-2,2-dimethylpropylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**10a**)*

Following a similar procedure for the preparation of **16a**, **10a** was prepared starting from **47** (100 mg, 0.18 mmol) and **10b** (151 mg, 0.76 mmol). White solid (60 mg, 43%). [α]25 D-12.5 (*c* 0.47, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$) δ 0.85–1.00 (m, 18 H), 1.20–1.30 (m, 2 H), 1.44 (s, 9 H), 1.55–1.70 (m, 4 H), 1.85–1.95 (m, 1 H), 2.00–2.20 (m, 4 H), 2.30–2.45 (m, 1 H), 2.55–2.65 (m, 3 H), 3.05–3.25 (m, 3 H), 3.34 (s, 3 H), 3.37–3.45 (m, 1 H), 3.57 (t, 2 H, $J = 6.0$ Hz), 3.82 (s, 3 H), 4.05–4.15 (m, 2 H), 4.66 (d, 1 H, $J = 8.1$ Hz), 6.15–6.40 (m, 1 H), 6.65–6.90 (m, 5 H), 7.10–7.15 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 20.4, 21.2, 24.9, 28.1, 28.3, 29.6, 31.8, 32.5, 34.4, 36.8, 37.4, 42.3, 48.8, 51.4, 56.0, 58.5, 66.0, 69.5, 71.1, 80.2, 110.9, 111.2, 111.7, 114.6, 121.2, 127.9, 134.4, 147.5, 148.2, 160.2, 163.5, 174.8. ESI-MS *m/z* 757.5 $[M+Na]^+$. HRMS calcd for $C_{41}H_{64}N_2F_2O_7Na$ $[M+Na]^+$ *m/z* 757.4579, found 757.4581.

*4.2.8. tert-butyl (3S,5S,6S,8S)-8-(3-(2,5-difluorophenyl)-2,2-dimethylpropylcarbamoyl)-6-hydroxy-3-(4- methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**11a**)*

Following a similar procedure for the preparation of **16a**, **11a** was prepared starting from **47** (100 mg, 0.19 mmol) and **11b** (223 mg, 1.12 mmol). White solid (117 mg, 85%). [α]25 D-20.3 (*c* 0.11, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.78–0.85 (m, 6 H), 0.89 (s, 6 H), 0.93–1.00 (m, 6 H), 1.15–1.25 (m, 1 H), 1.46 (s, 9 H), 1.47–1.52 (m, 1 H), 1.53–1.65 (m, 4 H), 1.68–1.75 (m, 1 H), 1.75–1.82 (m, 1 H), 1.98–2.03 (m, 2 H), 2.25–2.35 (m, 2 H), 2.58–2.63 (m, 2 H), 2.65–2.73 (m, 1 H), 3.10–3.15 (m, 2 H), 3.34 (s, 3 H), 3.38–3.45 (m, 1 H), 3.57 (t, 2 H, $J = 6.3$ Hz), 3.79 (s, 3 H), 4.05 (t, 2 H, $J = 6.3$ Hz), 5.98 (d, 2 H, $J = 9.8$ Hz), 6.68–6.75 (m, 1 H), 6.75–6.85 (m, 2 H), 6.92–7.10 (m, 3 H), 7.70–7.78 (m, 1 H). ^{13}C NMR (125 MHz, CD_3OD) δ 17.0, 20.8, 21.0, 21.5, 25.1, 25.2, 28.9, 29.0, 29.0, 30.7, 32.0, 32.8, 35.2, 37.5, 38.2, 39.4, 43.7, 50.5, 51.8, 55.0, 56.7, 58.9, 67.3, 70.5, 73.3, 79.9, 113.5, 115.3, 116.2, 117.1, 119.9, 123.0, 128.9, 136.2, 149.1, 149.8, 158.6, 158.7, 160.6, 178.4. ESI-MS *m/z* 735.5 $[M+H]^+$. HRMS calcd for $C_{41}H_{65}N_2F_2O_7$ $[M+H]^+$ *m/z* 735.4760, found 735.4762.

*4.2.9. tert-Butyl (3S,5S,6S,8S)-8-(3-(3-chlorophenyl)-2,2-dimethylpropylcarbamoyl)-6-hydroxy-3-(4-methoxy -3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**12a**)*

Following a similar procedure for the preparation of **16a**, **12a** was prepared starting from **47** (134 mg, 0.25 mmol) and **12b** (248 mg, 1.25 mmol). Solid (106 mg, 58%). [α]25 D-23.5 (*c* 0.2, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 0.80–0.83 (m, 6 H), 0.88–0.95 (m, 12 H), 1.18–1.26 (m, 2 H), 1.43 (s, 9 H), 1.60–1.68 (m, 5 H), 1.86–1.99 (m, 1 H), 2.03–2.12 (m, 3 H), 2.34–2.41 (m, 1 H), 2.51–2.62 (m, 3 H), 3.01–3.08 (m, 1 H), 3.21–3.27 (m, 1 H), 3.34 (s, 3 H), 3.42–3.50 (m, 2 H), 3.54 (t, 2 H, $J = 6.3$ Hz), 3.81 (s, 3 H), 4.09 (t, 2 H, $J = 6.3$ Hz), 4.63 (d, 1 H, $J = 9.3$ Hz), 5.75 (s, 1 H), 6.66–6.76 (m, 3 H), 7.02–7.21 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 19.9, 20.8, 24.3, 24.4, 27.7, 27.8, 31.9, 34.1, 35.1, 36.9, 41.8, 45.5, 48.6, 51.0, 53.6, 58.1, 65.5, 69.0, 70.8, 78.7, 111.2, 114.0, 120.8, 125.9, 128.1, 128.7, 129.8, 133.2, 133.7, 139.8, 147.1, 147.7, 156.3, 175.7. ESI-MS *m/z* 733.5 $[M+H]^+$. HRMS calcd for $C_{41}H_{66}N_2O_7Cl$ $[M+H]^+$ *m/z* 733.4559, found 733.4562.

*4.2.10. tert-Butyl (3S,5S,6S,8S)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-(3-(3-methoxyphenyl-2,2-dimethylpropylcarbamoyl)-2,9-dimethyldecan-5-ylcarbamate (**13a**)*

Following a similar procedure for the preparation of **16a**, **13a** was prepared starting from **47** (150 mg, 0.28 mmol) and **13b** (640 mg, 3.31 mmol). Solid (148 mg, 73%). [α]25 D-13.0 (*c* 0.12, CH_3OH). ^1H NMR (500 MHz, $CDCl_3$) δ 0.80–0.83 (m, 6 H), 0.89–0.95 (m, 12 H), 1.18–1.26 (m, 2 H), 1.44 (s, 9 H), 1.57–1.67 (m, 5 H), 1.86–2.09 (m, 4 H), 2.36–2.40 (m, 1 H), 2.49 (s, 2 H), 2.59–2.61 (m, 1 H), 3.05–3.09 (m, 1 H), 3.23–3.26 (m, 1 H), 3.35 (s, 3 H), 3.42–3.52 (m, 2 H), 3.57 (t, 2 H, $J = 5$ Hz), 3.79 (s, 3 H), 3.82 (s, 3 H), 4.10 (t, 2 H, $J = 5$ Hz), 4.65 (d, 1 H, $J = 10$ Hz), 5.62 (s, 1 H), 6.70–6.76 (m, 6 H), 7.18–7.21 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.7, 20.3, 21.2, 24.9, 25.1, 25.2, 28.0, 28.3, 29.6, 32.5, 34.5, 35.6, 37.3, 42.2, 46.6, 49.1, 51.6, 54.0, 55.1, 56.0, 58.5, 65.9, 69.4, 71.2, 79.1, 111.1, 111.6, 114.5, 116.4, 121.3, 122.8, 128.9, 134.2, 139.9, 147.5, 148.2, 156.7, 159.2, 176.1. ESI-MS *m/z* 729.5 $[M+H]^+$. HRMS calcd for $C_{42}H_{69}N_2O_8$ $[M+H]^+$ *m/z* 729.5054, found 729.5056.

*4.2.11. tert-Butyl (3S,5S,6S,8S)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-(3-(4-methoxyphenyl)-2,2-dimethylpropylcarbamoyl)-2,9-dimethyldecan-5-ylcarbamate (**14a**)*

Following a similar procedure for the preparation of **16a**, **14a** was prepared starting from **47** (150 mg, 0.28 mmol) and **14b** (320 mg, 1.66 mmol). Solid (133 mg, 65%). [α]25 D-21.0 (*c* 0.2, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 0.80–0.83 (m, 6 H), 0.89–0.95 (m, 12 H), 1.19–1.28 (m, 2 H), 1.45 (s, 9 H), 1.58–1.68 (m, 4 H), 1.85–1.89 (m, 2 H), 2.00–2.12 (m, 3 H), 2.37–2.41 (m, 1 H), 2.49 (s, 2 H), 2.60–2.63 (m, 1 H), 3.05–3.09 (m, 1 H), 3.22–3.26 (m, 1 H), 3.36 (s, 3 H), 3.43–3.53 (m, 2 H), 3.58 (t, 2 H, $J = 6.5$ Hz), 3.80 (s, 3 H), 3.83 (s, 3 H), 4.11 (m, 2 H), 4.66 (d, 1 H, $J = 9.0$ Hz), 5.67 (s, 1 H), 6.69–6.84 (m, 5 H), 7.05 (d, 2 H, $J = 8.5$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 20.3, 21.2, 24.9, 25.0, 28.1, 28.3, 29.6, 32.5, 34.5, 35.4, 37.3, 42.2, 45.7, 49.1, 51.6, 54.0, 55.1, 56.0, 58.5, 60.2, 66.0, 69.4, 71.1, 79.0, 111.7, 113.4, 114.5, 121.3, 130.2, 131.2, 134.2, 147.5, 148.2, 156.7, 158.1, 176.1. ESI-MS *m/z* 729.5 $[M+H]^+$. HRMS calcd for $C_{42}H_{69}N_2O_8$ $[M+H]^+$ *m/z* 729.5054, found 729.5056.

*4.2.12. tert-Butyl (3S,5S,6S,8S)-8-(2,2-dimethyl-3-(4-(trifluoromethoxy)phenyl)propylcarbamoyl)-6-hydroxy-3 -(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**15a**)*

Following a similar procedure for the preparation of **16a**, **15a** was prepared starting from **47** (100 mg, 0.18 mmol) and **15b** (187 mg, 0.76 mmol). Solid (61 mg, 41%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.80–1.00 (m, 18 H), 1.15–1.30 (m, 2 H), 1.43 (s, 9 H), 1.50–1.70 (m, 4 H), 1.80–1.90 (m, 1 H), 2.00–2.10 (m, 3 H), 2.35–2.40 (m, 1 H), 2.50–2.60 (m, 4 H), 3.00–3.25 (m, 3 H), 3.34 (s, 3 H), 3.45–3.50 (m, 1 H), 3.56 (t, 2 H, $J = 6.3$ Hz), 3.81 (s, 3 H), 4.09 (t, 2 H, $J = 6.3$ Hz), 4.64 (d, 1 H, $J = 7.2$ Hz), 5.80–6.10 (m, 1 H), 6.60–6.80 (m, 3 H), 7.05–7.20 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 20.3, 21.2, 24.5, 24.6, 24.8, 24.9, 28.3, 29.6, 32.4, 34.6, 35.5, 37.4, 42.3, 45.4, 45.5, 49.2, 51.4, 54.1, 56.0, 58.6, 66.0, 69.4, 71.3, 79.3, 111.6, 114.5, 120.4, 121.3, 131.4, 131.6, 134.1, 136.9, 147.5, 147.7, 148.3, 156.9, 176.4. ESI-MS *m/z* 805.5 $[M+Na]^+$. HRMS calcd for $C_{42}H_{65}N_2O_8F_3Na$ $[M+Na]^+$ *m/z* 805.4591, found 805.4593.

*4.2.13. tert-Butyl (3S,5S,6S,8S)-8-(3-cyclohexyl-2,2-dimethylpropylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3 -methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**17a**)*

Following a similar procedure for the preparation of **16a**, **17a** was prepared starting from **47** (102 mg, 0.19 mmol) and **17b** (600 mg, 3.55 mmol). Solid (98 mg, 74%). [α]25 D-25.6 (*c* 0.30, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 0.81–0.83 (m, 6 H), 0.85–0.95 (m, 12 H), 1.09–1.12 (m, 3 H), 1.13–1.35 (m, 6 H), 1.44 (s, 9 H), 1.55–1.70 (m, 11 H), 1.85–1.93 (m, 1 H), 2.04–2.12 (m, 2 H), 2.33–2.42 (m, 1 H), 2.55–2.65 (m, 1 H), 2.95–3.10 (m, 1 H), 3.10–3.25 (m, 1 H), 3.34 (s, 3 H), 3.40–3.45 (m, 1 H), 3.50–3.60 (m, 3 H), 3.82 (s, 3 H), 4.10 (t, 2 H, $J = 6.2$ Hz), 4.64 (d, 1 H, $J = 8.5$ Hz), 5.70–5.73 (m, 1 H), 6.67–6.76 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$)

δ 16.7, 20.4, 21.3, 25.5, 25.6, 26.2, 26.5, 28.0, 28.4, 29.6, 29.7, 32.7, 33.6, 34.6, 34.8, 36.0, 37.5, 42.3, 47.7, 49.8, 51.8, 54.0, 56.1, 58.6, 66.0, 69.5, 71.2, 79.1, 111.7, 114.6, 121.3, 134.3, 147.5, 148.3, 156.7, 176.4. ESI-MS *m/z* 727.5 $[M+Na]^+$. HRMS calcd for $C_{41}H_{72}N_2O_7Na$ $[M+Na]^+$ *m/z* 727.5237, found 727.5239.

4.2.14. tert-Butyl (3S,5S,6S,8S)-8-(2,2-dimethyl-4-morpholinobutylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**18a**)

Following a similar procedure for the preparation of **16a**, **18a** was prepared starting from **47** (100 mg, 0.18 mmol) and **18b** (190 mg, 1.10 mmol). Solid (73 mg, 55%). [α]25 D-14.00 (*c* 0.2, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 0.78–0.83 (m, 6 H), 0.90–1.00 (m, 12 H), 1.15–1.30 (m, 2 H), 1.44 (s, 9 H), 1.47–1.52 (m, 2 H), 1.55–1.69 (m, 4 H), 1.70–1.76 (m, 1 H), 1.90–1.95 (m, 1 H), 2.05–2.12 (m, 3 H), 2.33–2.40 (m, 1 H), 2.43–2.53 (m, 2 H), 2.54–2.70 (m, 5 H), 3.07–3.13 (m, 2 H), 3.34 (s, 3 H), 3.42–3.50 (m, 1 H), 3.57–3.60 (m, 3 H), 3.73–3.80 (m, 4 H), 3.82 (s, 3 H), 4.10 (t, 2 H, $J = 6.3$ Hz), 4.60 (d, 1 H, $J = 9.3$ Hz), 6.65–6.73 (m, 1 H), 6.75–6.83 (m, 2 H), 6.95–7.05 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.7, 20.4, 21.5, 25.8, 26.0, 28.0, 28.4, 29.5, 29.7, 32.7, 34.1, 34.4, 35.5, 37.4, 42.3, 48.0, 51.7, 53.5, 54.0, 54.4, 56.1, 58.6, 66.0, 66.3, 69.5, 70.9, 111.8, 114.7, 121.4, 134.5, 147.9, 148.3, 156.7, 176.3. ESI-MS *m/z* 722.5 $[M+H]^+$. HRMS calcd for $C_{40}H_{72}N_3O_8$ $[M+H]^+$ *m/z* 722.5319, found 722.5322.

4.2.15. tert-Butyl (3S,5S,6S,8S)-8-(2,2-dimethyl-4-phenoxybutylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**19a**)

Following a similar procedure for the preparation of **16a**, **19a** was prepared starting from **47** (100 mg, 0.18 mmol) and **19b** (217 mg, 1.12 mmol). Solid (107 mg, 78%). [α]25 D-16.0 (*c* 0.1, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 0.80–0.85 (m, 6 H), 0.92–0.98 (m, 6 H), 1.00–1.05 (m, 6 H), 1.10–1.40 (m, 2 H), 1.47 (s, 9 H), 1.53–1.70 (m, 4 H), 1.70–1.75 (m, 1 H), 1.76–1.80 (m, 2 H), 1.90–1.97 (m, 1 H), 2.03–2.07 (m, 1 H), 2.08–2.15 (m, 2 H), 2.37–2.43 (m, 1 H), 2.60–2.67 (m, 1 H), 3.15–3.22 (m, 1 H), 3.25–3.30 (m, 1 H), 3.38 (s, 3 H), 3.43–3.50 (m, 1 H), 3.54–3.57 (m, 1 H), 3.59 (t, 2 H, $J = 6.3$ Hz), 3.85 (s, 3 H), 4.08 (t, 2 H, $J = 6.1$ Hz), 4.13 (t, 2 H, $J = 6.3$ Hz), 4.66 (d, 1 H, $J = 8.5$ Hz), 6.10–6.17 (m, 1 H), 6.68–6.75 (m, 1 H), 6.75–6.83 (m, 2 H), 6.90–6.95 (m, 2 H), 6.96–7.02 (m, 1 H), 7.28–7.35 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 20.4, 21.4, 25.9, 26.0, 28.1, 28.4, 29.5, 29.6, 32.7, 34.0, 34.5, 37.4, 38.6, 42.3, 48.5, 51.9, 54.1, 56.0, 58.6, 64.6, 66.0, 69.5, 71.1, 79.0, 111.7, 114.4, 114.6, 121.0, 121.3, 129.5, 134.4, 147.6, 148.2, 156.7, 158.4, 176.2. ESI-MS *m/z* 729.5 $[M+H]^+$. HRMS calcd for $C_{42}H_{69}N_2O_8$ $[M+H]^+$ *m/z* 729.5054, found 729.5057.

4.2.16. tert-Butyl (3S,5S,6S,8S)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyl-8-(3-phenylpropylcarbamoyl)decan-5-ylcarbamate (**20a**)

Following a similar procedure for the preparation of **16a**, **20a** was prepared starting from **47** (80 mg, 0.15 mmol) and **20b** (203 mg, 1.5 mmol). Solid was obtained (66 mg, 66%). [α]25 D-10.00 (*c* 0.30, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 0.75–0.85 (m, 6 H), 0.85–1.00 (m, 6 H), 1.10–1.28 (m, 2 H), 1.44 (s, 9 H), 1.50–1.70 (m, 5 H), 1.80–1.90 (m, 3 H), 1.95–2.02 (m, 1 H), 2.05–2.15 (m, 2 H), 2.33–2.42 (m, 1 H), 2.55–2.70 (m, 3 H), 3.15–3.28 (m, 1 H), 3.35 (s, 3 H), 3.37–3.52 (m, 3 H), 3.57 (t, 2 H, $J = 6.2$ Hz), 3.82 (s, 3 H), 4.10 (t, 2 H, $J = 6.2$ Hz), 4.64 (d, 1 H, $J = 9$ Hz), 5.70–5.85 (m, 1 H), 6.65–6.73 (m, 1 H), 6.74–6.85 (m, 2 H), 7.15–7.35 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 20.4, 20.5, 21.1, 28.2, 28.4, 29.6, 29.7, 31.2, 32.6, 33.4, 34.6, 37.4, 39.1, 42.2, 51.4, 54.0, 56.1, 58.6, 66.0, 69.5, 71.2, 79.2, 111.7, 114.6, 121.4, 126.0, 128.3, 128.5, 134.3, 141.4, 147.6, 148.3, 156.7, 176.1. ESI-MS *m/z* 693.4 $[M+Na]^+$. HRMS calcd for $C_{39}H_{62}N_2O_7Na$ $[M+Na]^+$ *m/z* 693.4455, found 693.4458.

4.2.17. tert-Butyl (3S,5S,6S,8S)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyl-8- (phenethylcarbamoyl) decan-5-ylcarbamate (**21a**)

Following a similar procedure for the preparation of **16a**, **21a** was prepared starting from **47** (80 mg, 0.15 mmol) and **21b** (182 mg, 1.5 mmol). Solid (61 mg, 62%). [α]25 D-15.00 (*c* 0.2, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 0.82–0.89 (m, 12 H), 1.12–1.25 (m, 2 H), 1.44 (s, 9 H), 1.50–1.70 (m, 5 H), 1.82–1.93 (m, 2 H), 2.04–2.12 (m, 2 H), 2.34–2.42 (m, 1 H), 2.59–2.65 (m, 1 H), 2.74–2.92 (m, 2 H), 3.34 (s, 3 H), 3.35–3.45 (m, 2 H), 3.57 (m, 4 H), 3.82 (s, 3 H), 4.10 (t, 2 H, $J = 6.4$ Hz), 4.60 (d, 1 H, $J = 9$ Hz), 5.70–5.73 (m, 1 H), 6.67–6.80 (m, 3 H), 7.20–7.33 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 20.3, 20.4, 21.2, 28.0, 28.4, 29.6, 29.7, 32.6, 34.4, 35.6, 37.4, 40.2, 42.2, 51.3, 53.9, 56.0, 58.6, 66.0, 69.5, 71.2, 79.1, 111.7, 114.6, 121.4, 126.5, 128.6, 128.7, 134.3, 138.9, 147.6, 148.3, 156.7, 176.1. ESI-MS *m/z* 657.4 $[M+H]^+$. HRMS calcd for $C_{38}H_{61}N_2O_7$ $[M+H]^+$ *m/z* 657.4479, found 657.4483.

4.2.18. tert-Butyl (3S,5S,6S,8S)-8-(2-chlorophenethylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**22a**)

Following a similar procedure for the preparation of **16a**, **22a** was prepared starting from **47** (80 mg, 0.15 mmol) and **22b** (234 mg, 1.5 mmol). Solid (52 mg, 51%). [α]25 D-16.00 (*c* 0.3, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 0.78–0.92 (m, 12 H), 1.10–1.25 (m, 2 H), 1.45 (s, 9 H), 1.50–1.55 (m, 1 H), 1.56–1.70 (m, 4 H), 1.80–2.00 (m, 2 H), 2.03–2.13 (m, 2 H), 2.30–2.45 (m, 1 H), 2.55–2.65 (m, 1 H), 2.90–3.05 (m, 2 H), 3.34 (s, 3 H), 3.38–3.50 (m, 2 H), 3.52–3.63 (m, 4 H), 3.82 (s, 3 H), 4.10 (t, 2 H, $J = 6.3$ Hz), 4.64 (d, 1 H, $J = 8.9$ Hz), 5.70–5.90 (m, 1 H), 6.65–6.80 (m, 3 H), 7.15–7.40 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 20.3, 20.4, 21.2, 28.1, 28.4, 29.6, 32.6, 33.3, 34.4, 37.4, 38.9, 42.3, 51.3, 53.9, 56.0, 58.6, 66.0, 69.5, 71.1, 79.1, 111.6, 114.5, 121.4, 127.0, 128.0, 129.6, 130.9, 134.1, 134.3, 136.4, 147.5, 148.2, 156.6, 176.2. ESI-MS *m/z* 713.4 $[M+Na]^+$. HRMS calcd for $C_{38}H_{59}N_2O_7ClNa$ $[M+Na]^+$ *m/z* 713.3909, found 713.3911.

4.2.19. tert-Butyl (3S,5S,6S,8S)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-(3-methoxyphenethylcarbamoyl)-2,9-dimethyldecan-5-ylcarbamate (**23a**)

Following a similar procedure for the preparation of **16a**, **23a** was prepared starting from **47** (80 mg, 0.15 mmol) and **23b** (227 mg, 1.5 mmol). Solid (45 mg, 44%). [α]25 D-21.1 (*c* 0.09, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$) δ 0.75–0.90 (m, 12 H), 1.10–1.22 (m, 2 H), 1.44 (s, 9 H), 1.47–1.55 (m, 2 H), 1.55–1.70 (m, 3 H), 1.80–1.95 (m, 2 H), 2.03–2.11 (m, 2 H), 2.33–2.43 (m, 1 H), 2.55–2.65 (m, 1 H), 2.72–2.90 (m, 2 H), 3.34 (s, 3 H), 3.36–3.45 (m, 2 H), 3.50–3.65 (m, 4 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 4.10 (t, 2 H, $J = 6.2$ Hz), 4.62 (d, 1 H, $J = 8.6$ Hz), 5.65–5.75 (m, 1 H), 6.65–6.85 (m, 6 H), 7.18–7.30 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 20.4, 20.5, 21.2, 28.1, 28.4, 29.7, 29.8, 32.6, 34.4, 35.7, 37.4, 40.2, 42.3, 51.2, 53.9, 55.2, 56.1, 58.6, 66.0, 69.5, 71.2, 79.1, 109.6, 111.7, 111.9, 114.6, 121.1, 121.4, 129.6, 134.3, 140.4, 147.4, 148.1, 156.6, 159.8, 175.9. ESI-MS *m/z* 687.5 $[M+H]^+$. HRMS calcd for $C_{39}H_{63}N_2O_8$ $[M+H]^+$ *m/z* 687.4584, found 687.4590.

4.2.20. tert-Butyl (3S,5S,6S,8S)-8-(3,4-dimethoxyphenethylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**24a**)

Following a similar procedure for the preparation of **16a**, **24a** was prepared starting from **47** (80 mg, 0.15 mmol) and **24b** (272 mg, 1.5 mmol). Solid (83 mg, 77%). [α]25 D-20.3 (*c* 0.11, CH_3OH). ^1H NMR (500 MHz, $CDCl_3$) δ 0.78–0.90 (m, 12 H), 1.15–1.22 (m, 1 H), 1.44 (s, 9 H), 1.53–1.70 (m, 6 H), 1.80–1.90 (m, 1 H), 1.91–2.00 (m, 1 H), 2.04–2.11 (m, 2 H), 2.35–2.42 (m, 1 H), 2.57–2.65 (m, 1 H), 2.70–2.83 (m, 2 H), 3.34 (s, 3 H), 3.37–3.50 (m,

4 H), 3.56 (t, 2 H, $J = 6.0$ Hz), 3.81 (s, 3 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 4.09 (t, 2 H, $J = 6.5$ Hz), 4.63 (d, 1 H, $J = 8.5$ Hz), 5.65–5.80 (m, 1 H), 6.67–6.85 (m, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 20.3, 21.2, 28.2, 28.4, 29.7, 29.8, 32.6, 34.5, 35.4, 37.4, 40.5, 42.3, 51.3, 54.1, 55.9, 56.0, 56.1, 58.6, 60.3, 66.1, 69.5, 71.2, 79.1, 111.5, 111.8, 112.0, 114.7, 120.7, 121.3, 131.3, 134.3, 147.6, 147.9, 148.3, 149.2, 156.7, 175.9. ESI-MS *m/z* 717.5 $[M+H]^+$. HRMS calcd for $C_{40}H_{65}N_2O_9$ $[M+H]^+$ *m/z* 717.4690, found 717.4696.

4.2.21. tert-Butyl (3S,5S,6S,8S)-8-(2-(benzo[d][1,3]dioxol-5-yl) ethylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy) benzyl)-2,9-dimethyldecan-5-ylcarbamate (**25a**)

Following a similar procedure for the preparation of **16a**, **25a** was prepared starting from **47** (80 mg, 0.15 mmol) and **25b** (248 mg, 1.5 mmol). Solid (83 mg, 79%). [α]25 D-16.00 (*c* 0.2, CH_2Cl_2) ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78–0.92 (m, 12 H), 1.10–1.27 (m, 2 H), 1.44 (s, 9 H), 1.53–1.58 (m, 2 H), 1.60–1.70 (m, 3 H), 1.80–2.00 (m, 2 H), 2.03–2.13 (m, 2 H), 2.30–2.45 (m, 1 H), 2.55–2.65 (m, 1 H), 2.66–2.80 (m, 2 H), 3.34 (s, 3 H), 3.38–3.50 (m, 4 H), 3.56 (t, 2 H, $J = 6.3$ Hz), 3.82 (s, 3 H), 4.10 (t, 2 H, $J = 6.3$ Hz), 4.64 (d, 1 H, $J = 8.7$ Hz), 5.67–5.75 (m, 1 H), 5.92 (s, 2 H), 6.60–6.80 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 20.3, 20.4, 21.2, 28.1, 28.4, 29.6, 29.7, 32.6, 34.5, 35.4, 37.4, 40.5, 42.3, 51.3, 54.0, 56.0, 58.6, 66.0, 69.5, 71.1, 79.1, 100.9, 108.3, 109.0, 111.7, 114.5, 121.3, 121.6, 132.5, 134.3, 146.2, 147.6, 147.8, 148.2, 156.7, 176.1. ESI-MS *m/z* 723.4 $[M+Na]^+$. HRMS calcd for $C_{39}H_{60}N_2O_9Na$ $[M+Na]^+$ *m/z* 723.4197, found 723.4200.

4.2.22. tert-Butyl (3S,5S,6S,8S)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyl-8-(2-(pyridin-2-yl) ethylcarbamoyl)decan-5-ylcarbamate (**26a**)

Following a similar procedure for the preparation of **16a**, **26a** was prepared starting from **47** (80 mg, 0.15 mmol) and **26b** (184 mg, 1.5 mmol). Solid (65 mg, 66%). [α]25 D+18.50 (*c* 0.2, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72–0.92 (m, 12 H), 1.07–1.30 (m, 3 H), 1.45 (s, 9 H), 1.53–1.75 (m, 5 H), 1.82–1.92 (m, 1 H), 1.95–2.02 (m, 1 H), 2.03–2.13 (m, 2 H), 2.27–2.36 (m, 1 H), 2.63–2.68 (m, 1 H), 2.90–2.98 (m, 2 H), 3.35 (s, 3 H), 3.50–3.62 (m, 4 H), 3.81 (s, 3 H), 3.93–4.03 (m, 1 H), 4.08 (t, 2 H, $J = 6$ Hz), 4.77 (d, 1 H, $J = 9.3$ Hz), 6.37–6.47 (m, 1 H), 6.60–6.72 (m, 2 H), 6.73–6.80 (m, 1 H), 7.15–7.25 (m, 2 H), 7.62–7.72 (m, 1 H), 8.45 (d, 1 H, $J = 3.6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 20.2, 20.4, 21.3, 27.5, 28.4, 29.6, 29.8, 33.0, 34.6, 37.2, 37.6, 38.9, 42.1, 51.5, 53.2, 56.0, 58.6, 65.9, 69.5, 70.3, 78.7, 111.5, 114.5, 121.3, 121.8, 123.8, 134.5, 137.3, 147.4, 148.1, 148.7, 156.5, 159.7, 176.0. ESI-MS *m/z* 680.4 $[M+Na]^+$. HRMS calcd for $C_{37}H_{59}N_3O_7Na$ $[M+Na]^+$ *m/z* 680.4251, found 680.4253.

4.2.23. tert-Butyl (3S,5S,6S,8S)-8-((R)-1-(4-chlorophenyl) ethylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy) benzyl)-2,9-dimethyldecan-5-ylcarbamate (**27a**)

Following a similar procedure for the preparation of **16a**, **27a** was prepared starting from **47** (100 mg, 0.18 mmol) and **27b** (290 mg, 1.86 mmol). Solid (76 mg, 57%). [α]25 D-5.50 (*c* 0.2, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77–0.83 (m, 6 H), 0.90–1.08 (m, 6 H), 1.00–1.10 (m, 1 H), 1.44 (s, 9 H), 1.44–1.47 (m, 3 H), 1.50–1.70 (m, 6 H), 1.82–1.90 (m, 1 H), 2.00–2.10 (m, 3 H), 2.32–2.40 (m, 1 H), 2.50–2.60 (m, 1 H), 3.17–3.30 (m, 2 H), 3.34 (s, 3 H), 3.56 (t, 2 H, $J = 6.5$ Hz), 3.82 (s, 3 H), 4.08 (t, 2 H, $J = 6.0$ Hz), 4.52 (d, 1 H, $J = 9$ Hz), 5.05–5.15 (m, 1 H), 6.00–6.10 (m, 1 H), 6.60–6.75 (m, 3 H), 7.25–7.35 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 20.3, 20.4, 21.1, 21.7, 28.4, 29.6, 29.9, 32.3, 35.0, 37.5, 42.3, 48.0, 51.0, 54.2, 56.1, 58.6, 66.1, 69.5, 71.4, 79.4, 111.9, 114.6, 121.4, 127.7, 128.7, 133.0, 134.2, 142.1, 147.7, 148.3, 156.8, 175.2. ESI-MS *m/z* 713.4 $[M+Na]^+$. HRMS calcd for $C_{38}H_{59}N_2O_7ClNa$ $[M+Na]^+$ *m/z* 713.3909, found 713.3911.

4.2.24. tert-Butyl (3S,5S,6S,8S)-8-((S)-1-(4-chlorophenyl) ethylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy) benzyl)-2,9-dimethyldecan-5-ylcarbamate (**28a**)

Following a similar procedure for the preparation of **16a**, **28a** was prepared starting from **47** (100 mg, 0.18 mmol) and **28b** (290 mg, 1.86 mmol). Solid (68 mg, 51%). [α]25 D-45.50 (*c* 0.2, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.90 (m, 12 H), 1.10–1.30 (m, 2 H), 1.45 (s, 9 H), 1.45–1.50 (m, 3 H), 1.53–1.70 (m, 5 H), 1.80–1.90 (m, 1 H), 2.04–2.11 (m, 3 H), 2.35–2.43 (m, 1 H), 2.55–2.62 (m, 1 H), 3.34 (s, 3H), 3.36–-3.50 (m, 2 H), 3.57 (t, 2 H, $J = 6$ Hz), 3.82 (s, 3 H), 4.10 (t, 2 H, $J = 6.3$ Hz), 4.64 (d, 1 H, $J = 8.4$ Hz), 5.04–5.15 (m, 1 H), 6.00–6.15 (m, 1 H), 6.63–6.80 (m, 3 H), 7.20–7.35 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 20.4, 21.1, 21.7, 28.2, 28.4, 29.6, 30.0, 32.5, 34.7, 37.4, 42.3, 48.1, 51.0, 54.1, 56.1, 58.6, 66.1, 69.5, 71.3, 79.3, 111.8, 114.6, 121.3, 127.6, 128.7, 133.0, 134.2, 141.9, 147.6, 148.3, 156.7, 175.3. ESI-MS *m/z* 713.4 $[M+Na]^+$. HRMS calcd for $C_{38}H_{59}N_2O_7ClNa$ $[M+Na]^+$ *m/z* 713.3909, found 713.3910.

4.2.25. tert-Butyl (3S,5S,6S,8S)-8-((R)-1-(4-bromophenyl) ethylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy) benzyl)-2,9-dimethyldecan-5-ylcarbamate (**29a**)

Following a similar procedure described for the preparation of **16a**, **29a** was prepared starting from **47** (100 mg, 0.18 mmol) and **29b** (373 mg, 1.86 mmol). Solid (82 mg, 58%). [α]25 D+6.50 (*c* 0.2, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75–0.95 (m, 12 H), 1.20–1.30 (m, 1 H), 1.43 (s, 9 H), 1.44–1.47 (m, 3 H), 1.50–1.70 (m, 5 H), 1.75–1.90 (m, 2 H), 2.00–2.12 (m, 3 H), 2.32–2.42 (m, 1 H), 2.46–2.60 (m, 1 H), 3.15–3.25 (m, 1 H), 3.34 (s, 3 H), 3.36–3.45 (m, 1 H), 3.56 (t, 2 H, $J = 6.0$ Hz), 3.82 (s, 3 H), 4.06 (t, 2 H, $J = 5.4$ Hz), 4.52 (d, 1 H, $J = 6.3$ Hz), 5.05–5.15 (m, 1 H), 6.00–6.15 (m, 1 H), 6.60–6.75 (m, 3 H), 7.20–7.30 (m, 2 H), 7.40–7.50 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 20.3, 20.4, 21.1, 21.7, 28.4, 29.6, 29.9, 32.3, 35.0, 37.6, 42.3, 48.1, 51.0, 54.2, 56.0, 58.6, 66.0, 69.5, 71.4, 79.3, 111.7, 114.5, 120.9, 121.2, 128.0, 131.6, 134.2, 142.7, 147.6, 148.2, 156.8, 175.1. ESI-MS *m/z* 757.3 $[M+Na]^+$. HRMS calcd for $C_{38}H_{59}N_2O_7BrNa$ $[M+Na]^+$ *m/z* 757.3403, found 757.3406.

4.2.26. tert-Butyl (3S,5S,6S,8S)-8-((S)-1-(4-bromophenyl) ethylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy) benzyl)-2,9-dimethyldecan-5-ylcarbamate (**30a**)

Following a similar procedure for the preparation of **16a**, **30a** was prepared starting from **47** (100 mg, 0.18 mmol) and **30b** (373 mg, 1.86 mmol). Solid (72 mg, 51%). [α]25 D-43.00 (*c* 0.2, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80–0.90 (m, 12 H), 1.15–1.30 (m, 2 H), 1.44 (s, 9 H), 1.44–1.47 (m, 4 H), 1.55–1.70 (m, 5 H), 1.80–1.90 (m, 1 H), 2.00–2.10 (m, 3 H), 2.35–2.40 (m, 1 H), 2.52–2.60 (m, 1 H), 3.34 (s, 3 H), 3.35–3.50 (m, 2 H), 3.56 (t, 2 H, $J = 6.0$ Hz), 3.82 (s, 3 H), 4.10 (t, 2 H, $J = 6.0$ Hz), 4.63 (d, 1 H, $J = 8.0$ Hz), 5.05–5.15 (m, 1 H), 5.95–6.10 (m, 1 H), 6.60–6.80 (m, 3 H), 7.15–7.25 (m, 2 H), 7.40–7.50 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.0, 20.3, 21.1, 21.6, 28.3, 28.4, 29.7, 30.1, 32.5, 34.7, 37.4, 42.4, 48.2, 51.0, 54.1, 56.1, 58.6, 66.1, 69.5, 71.4, 79.3, 111.9, 114.7, 121.1, 121.4, 128.0, 131.7, 134.3, 142.5, 147.7, 148.3, 156.8, 175.2. ESI-MS *m/z* 757.3 $[M+Na]^+$. HRMS calcd for $C_{38}H_{59}N_2O_7BrNa$ $[M+Na]^+$ *m/z* 757.3403, found 757.3405.

4.2.27. tert-Butyl (3S,5S,6S,8S)-8-(3-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**31a**)

Following a similar procedure for the preparation of **16a**, **31a** was prepared starting from **47** (150 mg, 0.28 mmol) and **31b** (450 mg, 2.31 mmol). Solid (121 mg, 59%). [α]25 D-11.00 (*c* 0.4, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81–0.87 (m, 6 H), 0.86–0.97

(m, 16 H), 1.14–1.28 (m, 2 H), 1.45 (s, 9 H), 1.57–1.71 (m, 4 H), 1.92–1.97 (m, 3 H), 2.05–2.12 (m, 3 H), 2.34–2.38 (m, 1 H), 2.63–2.67 (m, 1 H), 2.95–2.99 (m, 1 H), 3.11–3.15 (m, 1 H), 3.35 (s, 3 H), 3.47–3.53 (m, 2 H), 3.58 (t, 2 H, J = 6.5 Hz), 3.83 (s, 3 H), 4.06–4.14 (m, 4 H), 4.74 (d, 1 H, J = 9.5 Hz), 6.48 (s, 1 H), 6.69–6.79 (m, 3 H), 7.34 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.5, 7.7, 7.8, 16.6, 20.3, 20.4, 21.3, 23.8, 24.1, 27.9, 28.4, 29.5, 29.6, 32.7, 34.3, 36.9, 37.3, 42.2, 46.1, 51.4, 53.8, 56.0, 57.5, 58.5, 66.0, 69.4, 71.0, 78.9, 111.7, 114.6, 121.3, 121.5, 134.4, 147.5, 148.2, 149.9, 156.6, 176.7. ESI-MS m/z 730.5 $[M+H]^+$. HRMS calcd for $C_{40}H_{68}N_5O_7$ $[M+H]^+$ m/z 730.5119, found 730.5121.

*4.2.28. tert-Butyl (3S,5S,6S,8S)-8-(3-(4-tert-butyl-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**32a**)*

Following a similar procedure for the preparation of **16a**, **32a** was prepared starting from **47** (150 mg, 0.28 mmol) and **32b** (118 mg, 0.56 mmol). Solid (67 mg, 32%). [α]25 D-2.15 (c 0.27, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.83 (m, 6 H), 0.94–0.98 (m, 12 H), 1.16–1.26 (m, 1H), 1.35 (s, 10 H), 1.44 (s, 9 H), 1.57–1.74 (m, 5 H), 1.93–1.95 (m, 1 H), 2.03–2.12 (m, 3 H), 2.33–2.37 (m, 1 H), 2.64–2.68 (m, 1 H), 2.95–2.99 (m, 1 H), 3.11–3.15 (m, 1 H), 3.35 (s, 3 H), 3.48–3.52 (m, 2 H), 3.57 (t, 2 H, J = 3.8 Hz), 3.82 (s, 3 H), 4.08–4.15 (m, 4 H), 4.78 (d, 1 H, J = 5.7 Hz), 6.54 (s, 1 H), 6.69–6.79 (m, 3 H), 7.29 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 20.3, 20.5, 21.4, 23.8, 24.3, 27.9, 28.4, 29.5, 29.7, 30.4, 30.7, 32.8, 34.3, 36.9, 37.4, 42.2, 46.2, 51.6, 53.8, 56.1, 57.5, 58.6, 66.0, 69.5, 70.9, 78.9, 111.8, 114.7, 120.3, 121.4, 134.4, 147.6, 148.3, 156.6, 157.5, 176.8. ESI-MS m/z 746.5 $[M+H]^+$. HRMS calcd for $C_{41}H_{72}N_5O_7$ $[M+H]^+$ m/z 746.5432, found 746.5436.

*4.2.29. tert-Butyl (3S,5S,6S,8S)-8-(3-(4-butyl-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**33a**)*

Following a similar procedure for the preparation of **16a**, **33a** was prepared starting from **47** (150 mg, 0.28 mmol) and **33b** (610 mg, 2.9 mmol). Solid (110 mg, 53%). [α]25 D-18.00 (c 0.2, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.82 (m, 6 H), 0.91–0.96 (m, 15 H), 1.14–1.22 (m, 2 H), 1.34–1.44 (m, 11 H), 1.57–1.68 (m, 7 H), 1.92–2.12 (m, 4 H), 2.31–2.38 (m, 1 H), 2.64–2.74 (m, 3 H), 2.92–2.99 (m, 1 H), 3.10–3.15 (m, 1 H), 3.35 (s, 3 H), 3.50–3.59 (m, 4 H), 3.82 (s, 3 H), 4.08–4.12 (m, 4 H), 4.76 (d, 1 H, J = 9.3 Hz), 6.55 (s, 1 H), 6.68–6.79 (m, 3 H), 7.36 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 16.6, 20.3, 20.4, 21.3, 22.2, 23.8, 24.1, 25.2, 27.9, 28.4, 29.6, 31.4, 32.7, 34.3, 36.9, 37.4, 42.2, 46.2, 51.5, 53.8, 56.1, 57.5, 58.6, 66.0, 69.5, 71.0, 78.9, 111.7, 114.6, 121.3, 122.3, 134.4, 147.5, 148.2, 148.3, 156.6, 176.8. ESI-MS m/z 746.5 $[M+H]^+$. HRMS calcd for $C_{41}H_{72}N_5O_7$ $[M+H]^+$ m/z 746.5432, found 746.5435.

*4.2.30. tert-Butyl (3S,5S,6S,8S)-8-(3-(4-hexyl-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**34a**)*

Following a similar procedure for the preparation of **16a**, **34a** was prepared starting from **47** (150 mg, 0.28 mmol) and **34b** (267 mg, 1.12 mmol). Solid (117 mg, 54%). [α]25 D-15.0 (c 0.11, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, 6 H, J = 6.0 Hz), 0.87–1.00 (m, 16 H), 1.11–1.21 (m, 2 H), 1.31–1.35 (m, 4 H), 1.44 (s, 9 H), 1.57–1.67 (m, 8 H), 1.91–1.94 (m, 1 H), 2.05–2.13 (m, 3 H), 2.30–2.37 (m, 1 H), 2.62–2.72 (m, 3 H), 2.92–2.99 (m, 1 H), 3.10–3.17 (m, 1 H), 3.34 (s, 3 H), 3.50–3.59 (m, 4 H), 3.82 (s, 3 H), 4.08–4.15 (m, 4 H), 4.76 (d, 1 H, J = 9.2 Hz), 6.56 (s, 1 H), 6.67–6.78 (m, 3 H), 7.36 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 16.6, 20.3, 20.4, 21.3, 22.3, 23.8, 24.1, 25.5, 27.8, 28.4, 28.8, 29.1, 29.6, 31.4, 32.7, 34.3, 36.9, 37.3, 42.2, 46.2, 51.4, 53.8, 56.0, 57.5, 58.6, 66.0, 69.5, 71.0, 78.8, 104.4, 111.7, 114.6, 121.3, 122.3, 134.4, 147.5, 148.2, 156.6, 176.8. ESI-MS m/z 774.6 $[M+H]^+$. HRMS calcd for $C_{43}H_{76}N_5O_7$ $[M+H]^+$ m/z 774.5745, found 774.5751.

*4.2.31. tert-Butyl (3S,5S,6S,8S)-8-(2,2-dimethyl-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**35a**)*

Following a similar procedure for the preparation of **16a**, **35a** was prepared starting from **47** (150 mg, 0.28 mmol) and **35b** (193 mg, 0.84 mmol). Solid (98 mg, 46%). [α]25 D-11.69 (c 0.32, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.82 (m, 6 H), 0.95–1.01 (m, 12 H), 1.17–1.26 (m, 2 H), 1.44 (s, 9 H), 1.56–1.73 (m, 5 H), 1.93–1.94 (m, 1 H), 2.06–2.10 (m, 2 H), 2.17–2.19 (m, 1 H), 2.34–2.39 (m, 1 H), 2.60–2.64 (m, 1 H), 3.02–3.06 (m, 1 H), 3.17–3.21 (m, 1 H), 3.34 (s, 3 H), 3.48 (s, 2 H), 3.56 (t, 2 H, J = 3.7 Hz), 3.81 (s, 3 H), 4.10 (t, 2 H, J = 3.6 Hz), 4.18–4.22 (m, 2 H), 4.73 (d, 1 H, J = 5.6 Hz), 6.50 (s, 1 H), 6.68–6.78 (m, 3 H), 7.32–7.44 (m, 3 H), 7.83–7.85 (m, 2 H), 7.94 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 20.3, 21.3, 23.8, 28.0, 28.4, 29.6, 32.7, 34.4, 37.0, 37.4, 42.3, 46.2, 51.4, 53.9, 56.1, 57.7, 58.6, 66.1, 69.5, 71.2, 79.0, 111.8, 114.7, 121.3, 125.7, 128.3, 128.8, 130.1, 134.4, 147.5, 148.3, 156.7, 176.8. ESI-MS m/z 766.5 $[M+H]^+$. HRMS calcd for $C_{43}H_{68}N_5O_7$ $[M+H]^+$ m/z 766.5119, found 766.5125.

*4.2.32. tert-Butyl (3S,5S,6S,8S)-8-(2,2-dimethyl-3-(4-p-tolyl-1H-1,2,3-triazol-1-yl)propylcarbamoyl)-6- hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**36a**)*

Following a similar procedure for the preparation of **16a**, **36a** was prepared starting from **47** (150 mg, 0.28 mmol) and **36b** (138 mg, 0.84 mmol). Solid (88 mg, 40%). [α]25 D-7.00 (c 0.30, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.82 (m, 6 H), 0.94–1.00 (m, 12 H), 1.18–1.25 (m, 2 H), 1.44 (s, 9 H), 1.56–1.72 (m, 5 H), 1.92–1.93 (m, 1 H), 2.02–2.09 (m, 2 H), 2.15–2.18 (m, 1 H), 2.37 (s, 4 H), 2.60–2.63 (m, 1 H), 3.00–3.04 (m, 1 H), 3.15–3.19 (m, 1 H), 3.33 (s, 3 H), 3.45–3.48 (m, 1 H), 3.53–3.57 (m, 3 H), 3.80 (s, 3 H), 4.08–4.10 (m, 2 H), 4.16–4.23 (m, 2 H), 4.71 (d, 1 H, J = 5.4 Hz), 6.48 (s, 1 H), 6.67–6.77 (m, 3 H), 7.22–7.23 (m, 2 H), 7.70–7.72 (m, 2 H), 7.83 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 20.3, 21.2, 21.3, 23.8, 24.1, 28.0, 28.4, 29.6, 32.6, 34.3, 37.0, 37.3, 42.2, 46.2, 51.5, 53.9, 56.0, 57.6, 58.5, 66.0, 69.4, 71.1, 79.0, 111.8, 114.7, 120.8, 121.3, 125.6, 127.4, 129.5, 124.4, 138.1, 147.6, 147.7, 148.2, 156.6, 176.7. ESI-MS m/z 780.5 $[M+H]^+$. HRMS calcd for $C_{44}H_{70}N_5O_7$ $[M+H]^+$ m/z 780.5275, found 780.5283.

*4.2.33. tert-Butyl (3S,5S,6S,8S)-8-(2,2-dimethyl-3-(4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)propylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**37a**)*

Following a similar procedure for the preparation of **16a**, **38a** was prepared starting from **47** (150 mg, 0.28 mmol) and **37b** (410 mg, 1.78 mmol). Solid (162 mg, 76%). [α]25 D-21.00 (c 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–0.83 (m, 6 H), 0.95–1.03 (m, 12 H), 1.23–1.28 (m, 2 H), 1.44 (s, 9 H), 1.56–1.74 (m, 4 H), 1.92–1.95 (m, 1 H), 2.04–2.10 (m, 3 H), 2.18–2.20 (m, 1 H), 2.32–2.39 (m, 1 H), 2.62–2.68 (m, 1 H), 3.01–3.08 (m, 1 H), 3.14–3.21 (m, 1 H), 3.34 (s, 3 H), 3.47–3.53 (m, 2 H), 3.57 (t, 2 H, J = 6.3 Hz), 3.82 (s, 3 H), 4.10 (m, 2 H), 4.25 (s, 2 H), 4.80 (d, 1 H, J = 9.6 Hz), 6.45–6.55 (m, 1 H), 6.68–6.78 (m, 3 H), 7.23–6.27 (m, 1 H), 7.77–7.82 (m, 1 H), 8.15–8.17 (m, 1 H), 8.24 (s, 1 H), 8.58 (d, 1 H, J = 4.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 20.3, 21.2, 23.7, 24.1, 27.9, 28.3, 29.6, 29.7, 32.6, 34.3, 37.0, 37.3, 42.2, 46.2, 51.4, 53.9, 56.0, 57.8, 58.5, 66.0, 69.4, 71.2, 79.0, 111.7, 114.6, 120.2, 121.3, 122.9, 123.6, 134.3, 134.6, 136.9, 147.5, 148.1, 148.2, 149.3, 156.6, 176.7. ESI-MS m/z 767.5 $[M+H]^+$. HRMS calcd for $C_{42}H_{67}N_6O_7$ $[M+H]^+$ m/z 767.5071, found 767.5077.

*4.2.34. tert-Butyl (3S,5S,6S,8S)-6-hydroxy-8-(3-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropylcarbamoyl)-3-(4-methoxy-3-(3-methoxypropoxy) benzyl)-2,9-dimethyldecan-5-ylcarbamate (**38a**)*

Following a similar procedure for the preparation of **16a**, **38a** was prepared starting from **47** (150 mg, 0.28 mmol) and **38b** (205 mg, 0.84 mmol). Solid (88 mg, 40%). [α]25 D-21.00 (*c* 0.30, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (s, 6 H), 0.91–0.95 (m, 12 H), 1.19–1.24 (m, 2 H), 1.42 (s, 9 H), 1.51–1.64 (m, 5 H), 1.83–1.87 (m, 1 H), 2.04–2.10 (m, 3 H), 2.33–2.37 (m, 1 H), 2.58–2.62 (m, 1 H), 2.89 (s, 1 H), 2.98–3.02 (m, 1 H), 3.12–3.16 (m, 1 H), 3.33 (s, 3 H), 3.39–3.44 (m, 2 H), 3.56 (t, 2 H, $J = 3.7$ Hz), 3.80 (s, 3 H), 4.08–4.10 (m, 2 H), 4.17–4.20 (m, 2 H), 4.76 (s, 3 H), 6.41 (s, 1 H), 6.67–6.75 (m, 3 H), 7.65 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 20.3, 21.2, 23.9, 28.0, 28.4, 29.6, 29.9, 32.1, 34.2, 36.8, 37.4, 42.3, 46.4, 51.2, 53.9, 56.1, 56.3, 58.0, 58.6, 66.1, 69.5, 71.3, 79.2, 111.8, 114.7, 121.3, 123.5, 134.4, 147.6, 147.9, 148.3, 156.7, 176.6. ESI-MS *m/z* 720.5 $[M+H]^+$. HRMS calcd for $C_{38}H_{66}N_5O_8$ $[M+H]^+$ *m/z* 720.4911, found 720.4917.

*4.2.35. tert-Butyl (3S,5S,6S,8S)-6-hydroxy-8-(3-(4-(2-hydroxyethyl)-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropylcarbamoyl)-3-(4-methoxy-3-(3-methoxypropoxy) benzyl)-2,9-dimethyldecan-5-ylcarbamate (**39a**)*

Following a similar procedure for the preparation of **16a**, **39a** was prepared starting from **47** (121 mg, 0.22 mmol) and **39b** (179 mg, 0.90 mmol). Solid (128 mg, 62%). [α]25 D-17.7 (*c* 0.18, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$) δ 0.79–0.80 (m, 6 H), 0.92–0.95 (m, 12 H), 1.11–1.24 (m, 1 H), 1.43 (s, 9 H), 1.53–1.64 (m, 6 H), 1.87–1.92 (m, 1 H), 2.02–2.11 (m, 3 H), 2.31–2.38 (m, 1 H), 2.58–2.64 (m, 2 H), 2.90–2.98 (m, 2 H), 3.00–3.04 (m, 1 H), 3.11–3.18 (m, 1 H), 3.33 (s, 3 H), 3.47–3.53 (m, 2 H), 3.56 (t, 2 H, $J = 6.3$ Hz), 3.81 (s, 3 H), 3.92 (t, 2 H, $J = 5.7$ Hz), 4.07–4.14 (m, 4 H), 4.73 (d, 1 H, $J = 9.3$ Hz), 6.43 (s, 1 H), 6.66–6.76 (m, 3 H), 7.52 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 19.8, 20.8, 23.3, 23.5, 27.4, 27.9, 28.1, 29.1, 29.2, 31.9, 33.8, 36.4, 36.8, 41.8, 45.8, 50.8, 53.3, 55.5, 57.2, 58.1, 60.9, 65.5, 68.9, 70.7, 78.5, 111.2, 114.1, 120.8, 123.0, 133.8, 144.9, 147.0, 147.7, 156.2, 176.2. ESI-MS *m/z* 734.5 $[M+H]^+$. HRMS calcd for $C_{39}H_{68}N_5O_8$ $[M+H]^+$ *m/z* 734.5068, found 734.5074.

*4.2.36. tert-Butyl (3S,5S,6S,8S)-6-hydroxy-8-(3-(4-(1-hydroxyethyl)-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropylcarbamoyl)-3-(4-methoxy-3-(3-methoxypropoxy) benzyl)-2,9-dimethyldecan-5-ylcarbamate (**40a**)*

Following a similar procedure for the preparation of **16a**, **40a** was prepared starting from **47** (150 mg, 0.28 mmol) and **40b** (222 mg, 0.84 mmol). Solid (91 mg, 44%). [α]25 D-8.00 (*c* 0.28, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (s, 6 H), 0.93–0.98 (m, 12 H), 1.12–1.26 (m, 2 H), 1.44 (s, 9 H), 1.55–1.66 (m, 9 H), 1.86–1.88 (m, 1 H), 2.05–2.12 (m, 3 H), 2.34–2.38 (m, 1 H), 2.60–2.64 (m, 1 H), 2.99–3.07 (m, 1 H), 3.11–3.20 (m, 1 H), 3.35 (s, 3 H), 3.40–3.48 (m, 2 H), 3.57 (t, 2 H, $J = 3.7$ Hz), 3.82 (s, 3 H), 4.08–4.19 (m, 4 H), 4.74–4.79 (m, 1 H), 5.07 (t, 1 H, $J = 3.6$ Hz), 6.39 (s, 1 H), 6.68–6.77 (m, 3 H), 7.58 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 20.3, 21.2, 23.3, 23.8, 27.9, 28.4, 29.6, 29.9, 32.4, 34.4, 36.8, 37.3, 42.3, 46.3, 51.3, 53.9, 56.0, 57.9, 58.6, 62.9, 66.0, 69.4, 71.3, 79.1, 111.8, 114.7, 121.4, 121.9, 134.4, 147.6, 148.2, 152.4, 156.6, 176.5. ESI-MS *m/z* 734.5 $[M+H]^+$. HRMS calcd for $C_{39}H_{68}N_5O_8$ $[M+H]^+$ *m/z* 734.5068, found 734.5071.

*4.2.37. tert-Butyl (3S,5S,6S,8S)-6-hydroxy-8-(3-(4-(1-hydroxycyclopentyl)-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropylcarbamoyl)-3-(4-methoxy-3-(3-methoxypropoxy) benzyl)-2,9-dimethyldecan-5-ylcarbamate (**41a**)*

Following a similar procedure for the preparation of **16a**, **41a** was prepared starting from **47** (150 mg, 0.28 mmol) and **41b** (266 mg, 1.12 mmol). Solid (131 mg, 64%). [α]23 D-11.50 (*c* 0.36, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$) δ 0.80–0.81 (m, 6 H), 0.92–0.97 (m, 12 H), 1.18–1.26 (m, 2 H), 1.43 (s, 9 H), 1.53–1.64 (m, 4 H), 1.82–1.92 (m, 3 H), 1.98–2.11 (m, 9 H), 2.31–2.39 (m, 2 H), 2.61–2.67 (m, 1 H), 3.04–3.18 (m, 2 H), 3.34 (s, 3 H), 3.48 (s, 2 H), 3.57 (t, 3 H, $J = 6.2$ Hz), 3.82 (s, 3 H), 4.07–4.15 (m, 4 H), 4.79 (d, 1 H, $J = 8.6$ Hz), 6.36 (s, 1 H), 6.67–6.77 (m, 3 H), 7.55 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 20.3, 20.4, 21.2, 23.6, 23.9, 24.1, 27.8, 28.4, 29.6, 32.4, 3*41*4.3, 36.8, 37.3, 41.2, 41.3, 42.3, 46.3, 51.4, 53.8, 56.0, 57.9, 58.5, 65.9, 69.4, 71.2, 78.8, 111.7, 114.6, 121.3, 121.7, 134.3, 147.5, 148.2, 154.4, 156.6, 176.6. ESI-MS *m/z* 774.5 $[M+H]^+$. HRMS calcd for $C_{42}H_{72}N_5O_8$ $[M+H]^+$ *m/z* 774.5381, found 774.5390.

*4.2.38. tert-Butyl (3S,5S,6S,8S)-8-(3-(4-((dimethylamino)methyl)-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**42a**)*

Following a similar procedure for the preparation of **16a**, **42a** was prepared starting from **47** (150 mg, 0.28 mmol) and **42b** (237 mg, 1.12 mmol). Solid (124 mg, 59%). [α]25 D-11.11 (*c* 0.54, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$) δ 0.84–0.86 (m, 6 H), 0.99–1.02 (m, 12 H), 1.23–1.31 (m, 1 H), 1.49 (s, 9 H), 1.59–1.76 (m, 5 H), 1.93–2.20 (m, 4 H), 2.37 (s, 6 H), 2.67–2.73 (m, 1 H), 2.90–3.06 (m, 1 H), 3.16–3.23 (m, 1 H), 3.40 (s, 3 H), 3.55–3.64 (m, 6 H), 3.72 (s, 2 H), 3.87 (s, 3 H), 4.15 (t, 2 H, $J = 6.0$ Hz), 4.21–4.24 (m, 2 H), 4.87 (d, 1 H, $J = 9.2$ Hz), 6.61 (s, 1 H), 6.73–6.83 (m, 3 H), 7.73 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 20.3, 20.4, 21.2, 23.8, 24.0, 27.8, 28.4, 29.6, 29.7, 32.5, 34.3, 36.9, 37.3, 42.2, 44.8, 46.1, 51.3, 53.3, 53.8, 54.0, 56.0, 57.6, 58.5, 65.9, 69.4, 71.1, 79.0, 111.7, 114.5, 121.3, 124.6, 134.3, 144.1, 147.5, 148.2, 156.6, 176.7. ESI-MS *m/z* 747.5 $[M+H]^+$. HRMS calcd for $C_{40}H_{71}N_6O_7$ $[M+H]^+$ *m/z* 747.5384, found 747.5390.

*4.2.39. tert-Butyl (3S,5S,6S,8S)-8-(3-(4-((diethylamino)methyl)-1H-1,2,3-triazol-1-yl)-2,2- dimethylpropylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**43a**)*

Following a similar procedure for the preparation of **16a**, **43a** was prepared starting from **47** (150 mg, 0.28 mmol) and **43b** (250 mg, 1.04 mmol). Solid (120 mg, 56%). ^1H NMR (500 MHz, $CDCl_3$) δ 0.80–0.83 (m, 6 H), 0.94–0.97 (m, 12 H), 1.18–1.26 (m, 9 H), 1.44 (s, 9 H), 1.57–1.75 (m, 5 H), 1.90–1.94 (m, 1 H), 2.05–2.10 (m, 2 H), 2.10–2.14 (m, 1 H), 2.33–2.37 (m, 1 H), 2.64–2.73 (m, 4 H), 2.94–2.98 (m, 1 H), 3.11–3.15 (m, 1 H), 3.35 (s, 3 H), 3.50–3.56 (m, 2 H), 3.57 (t, 2 H, $J = 6.5$ Hz), 3.82 (s, 3 H), 3.95 (s, 2 H), 4.10 (t, 2 H, $J = 6.0$ Hz), 4.17 (m, 2 H), 4.71 (d, 1 H, $J = 9.0$ Hz), 6.47 (s, 1 H), 6.68–6.78 (m, 3 H), 7.84 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.2, 13.6, 16.6, 19.1, 20.4, 21.3, 23.8, 24.1, 27.9, 28.4, 29.6, 29.7, 30.5, 32.7, 34.3, 37.0, 37.3, 42.2, 46.1, 46.7, 47.4, 51.4, 53.8, 56.0, 57.6, 58.5, 65.5, 66.0, 69.5, 71.0, 78.9, 111.7, 114.7, 121.3, 125.0, 128.8, 130.8, 134.4, 147.7, 148.2, 156.7, 176.7. ESI-MS *m/z* 775.6 $[M+H]^+$. HRMS calcd for $C_{42}H_{75}N_6O_7$ $[M+H]^+$ *m/z* 775.5697, found 775.5702.

*4.2.40. tert-Butyl (3S,5S,6S,8S)-8-(3-(4-((diisopropylamino) methyl)-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**44a**)*

Following a similar procedure for the preparation of **16a**, **44a** was prepared starting from **47** (150 mg, 0.28 mmol) and **44b** (300 mg, 1.12 mmol). Solid was obtained (121 mg, 54%). [α]25 D-10.73 (*c* 0.41, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$) δ 0.84–0.86 (m, 6 H), 0.99–1.09 (m, 24 H), 1.16–1.31 (m, 2 H), 1.50 (s, 9 H), 1.62–1.74 (m, 5 H), 1.95–1.99 (m, 1 H), 2.09–2.24 (m, 3 H), 2.35–2.43 (m, 1 H), 2.69–2.75 (m, 1 H), 2.94–3.22 (m, 4 H), 3.40 (s, 3 H), 3.54–3.64 (m, 4 H), 3.81 (s, 2 H), 3.87 (s, 3 H), 4.13–4.19 (m, 5 H), 4.85 (d, 1 H, $J = 9.3$ Hz), 6.73–6.84 (m, 3 H), 7.50 (s, 1 H). ^{13}C NMR (75 MHz,

$CDCl_3$) δ 16.5, 20.3, 20.4, 20.7, 21.3, 23.7, 24.1, 27.7, 28.4, 29.4, 29.6, 32.7, 34.3, 36.9, 37.3, 40.9, 42.2, 46.1, 51.4, 53.7, 56.0, 57.6, 58.5, 65.9, 69.4, 71.0, 78.8, 111.6, 114.6, 121.3, 123.8, 134.4, 147.5, 148.2, 150.7, 156.6, 176.7. ESI-MS *m/z* 803.6 $[M+H]^+$. HRMS calcd for $C_{44}H_{79}N_6O_7$ $[M+H]^+$ *m/z* 803.6010, found 803.6016.

*4.2.41. tert-Butyl (3S,5S,6S,8S)-8-(2,2-dimethyl-3-(4-(piperidin-1-ylmethyl)-1H-1,2,3-triazol-1-yl) propylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**45a**)*

Following a similar procedure for the preparation of **16a**, **45a** was prepared starting from **47** (150 mg, 0.28 mmol) and **45b** (400 mg, 1.6 mmol). Solid (113 mg, 52%). [α]25 D-20.0 (*c* 0.1, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 0.78–0.81 (m, 6 H), 0.93–0.96 (m, 12 H), 1.17–1.24 (m, 1 H), 1.43 (s, 9 H), 1.43–1.45 (m, 4 H), 1.60–1.62 (m, 8 H), 1.89–1.91 (m, 1 H), 2.05–2.07 (m, 2 H), 2.18–2.20 (m, 1 H), 2.31–2.35 (m, 1 H), 2.40–2.60 (m, 3 H), 2.64–2.66 (m, 1 H), 2.95–2.99 (m, 1 H), 3.13–3.17 (m, 1 H), 3.33 (s, 3 H), 3.50–3.57 (m, 3 H), 3.56 (t, 2 H, *J* = 6.5 Hz), 3.70 (s, 2 H), 3.81 (s, 3 H), 4.09 (t, 2 H, *J* = 6.0 Hz), 4.16 (m, 2 H), 4.72 (d, 1 H, *J* = 9.0 Hz), 5.52 (s, 1 H), 6.67–6.77 (m, 3 H), 7.70 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.9, 16.6, 20.3, 20.4, 21.2, 23.8, 24.1, 25.4, 27.8, 28.4, 29.6, 29.7, 32.6, 34.5, 36.9, 37.3, 42.2, 46.2, 51.2, 52.9, 53.6, 53.7, 54.0, 56.0, 57.6, 58.5, 63.3, 66.0, 69.4, 70.5, 71.0, 78.8, 111.7, 114.6, 121.3, 124.8, 134.4, 147.5, 148.2, 156.0, 176.7. ESI-MS *m/z* 787.6 $[M+H]^+$. HRMS calcd for $C_{43}H_{75}N_6O_7$ $[M+H]^+$ *m/z* 787.5697, found 787.5701.

*4.2.42. tert-Butyl (3S,5S,6S,8S)-8-(2,2-dimethyl-3-(4-(morpholinomethyl)-1H-1,2,3-triazol-1-yl) propylcarbamoyl)-6-hydroxy-3-(4-methoxy-3-(3-methoxypropoxy)benzyl)-2,9-dimethyldecan-5-ylcarbamate (**46a**)*

Following a similar procedure for the preparation of **16a**, **46a** was prepared starting from **47** (150 mg, 0.28 mmol) and **46b** (284 mg, 1.12 mmol). Solid (80 mg, 36%). [α]23 D-4.71 (*c* 0.42, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$) δ 0.80–0.82 (m, 6 H), 0.94–0.97 (m, 12 H), 1.18–1.26 (m, 2 H), 1.45 (s, 9 H), 1.56–1.68 (m, 5 H), 1.88–1.96 (m, 1 H), 2.04–2.12 (m, 3 H), 2.32–2.40 (m, 1 H), 2.51 (t, 4 H, *J* = 4.0 Hz), 2.61–2.67 (m, 1 H), 2.90–3.01 (m, 1 H), 3.11–3.18 (m, 1 H), 3.34 (s, 3 H), 3.48–3.59 (m, 4 H), 3.68–3.72 (m, 6 H), 3.82 (s, 3 H), 4.10 (t, 2 H, *J* = 6.3 Hz), 4.15 (s, 2 H), 4.73 (d, 1 H, *J* = 9.3 Hz), 6.49 (s, 1 H), 6.67–6.77 (m, 3 H), 7.61 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 20.3, 21.2, 23.8, 24.1, 27.9, 28.4, 29.6, 32.5, 34.3, 36.9, 37.3, 42.2, 46.1, 51.4, 53.3, 53.5, 53.8, 56.0, 57.5, 58.6, 65.9, 66.7, 69.4, 71.1, 79.0, 111.7, 114.5, 121.3, 124.3, 134.3, 143.8, 147.5, 148.2, 156.6, 176.7. ESI-MS *m/z* 789.5 $[M+H]^+$. HRMS calcd for $C_{42}H_{73}N_6O_8$ $[M+H]^+$ *m/z* 789.5490, found 789.5492.

*4.3. Synthesis of compounds **5-46***

*4.3.1. (2S,4S,5S,7S)-5-Amino-N-(2,2-dimethyl-3-(naphthalen-2-yl) propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**16**)*

Compound **16a** (35 mg, 0.047 mmol) was added to 4 N HCl/dioxane (2.0 mL, 8.0 mmol) at −4 °C under N_2. After stirred for 2 h, the solution was concentrated in vacuo to give **16** as a solid (30 mg, 98%). Purity = 97.8% (HPLC eluent: 75% aqueous acetonitrile containing 0.1% trifluoroacetic acid). [α]25 D-15.0 (*c* 0.20, CH_2Cl_2). ^1H NMR (300 MHz, CD_3OD) δ 0.87–0.93 (m, 12 H), 0.96–1.00 (m, 6 H), 1.44–1.53 (m, 3 H), 1.71–1.79 (m, 4 H), 1.98–2.00 (m, 2 H), 2.36–2.39 (m, 2 H), 2.44–2.73 (m, 4 H), 3.05–3.10 (m, 1 H), 3.16–3.23 (m, 1 H), 3.28–3.30 (m, 1 H), 3.32 (s, 3 H), 3.56 (t, 2 H, *J* = 6 Hz), 3.77 (s, 3 H), 4.04 (t, 2 H, *J* = 6 Hz), 6.71–6.84 (m, 3 H), 7.30–7.33 (m, 1 H), 7.40–7.45 (m, 2 H), 7.62 (s, 1 H), 7.73–7.81 (m, 3 H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.4, 19.2, 20.5, 21.4, 25.5, 25.6, 30.6, 32.1, 32.8, 35.0, 37.1, 38.1, 42.8, 47.4, 50.6, 51.2, 56.6, 56.8, 58.9, 67.3, 69.9, 70.4, 113.6, 116.1, 122.9, 126.3, 126.9, 128.2, 129.9, 130.3, 133.6, 134.7, 137.3, 149.4, 149.9, 177.7. ESI-MS *m/z* 649.5 $[M+H]^+$. HRMS calcd for $C_{40}H_{61}N_2O_5$ $[M+H]^+$ *m/z* 649.4580, found 649.4583.

*4.3.2. (2S,4S,5S,7S)-5-Amino-N-(2,2-dimethyl-3-(pyridin-3-yl) propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**5**)*

Following a similar procedure for the preparation of **16**, **5** was prepared starting from **5a** (56 mg, 0.08 mmol). Solid (49 mg, 99%). [α]25 D-9.0 (*c* 0.20, CH_2Cl_2). ^1H NMR (300 MHz, CD_3OD) δ 0.91–1.00 (m, 18 H), 1.28–1.29 (m, 1 H), 1.45–1.65 (m, 3 H), 1.66–1.90 (m, 4 H), 2.01–2.03 (m, 2 H), 2.42–2.50 (m, 2 H), 2.59–2.63 (m, 1 H), 2.70–2.75 (m, 1 H), 2.83 (s, 2 H), 3.06–3.09 (m, 1 H), 3.20–3.23 (m, 1 H), 3.35 (s, 3 H), 3.59 (t, 2 H, *J* = 6 Hz), 3.80 (s, 3 H), 4.07 (t, 2 H, *J* = 6.3 Hz), 6.75–6.88 (m, 3 H), 7.95–8.10 (m, 1 H), 8.50–8.60 (m, 1 H), 8.74 (s, 1 H), 8.84 (s, 1 H). ^{13}C NMR (75 MHz, CD_3OD) δ 18.3, 19.3, 20.5, 21.4, 25.2, 30.7, 32.1, 32.8, 35.0, 37.7, 38.2, 42.8, 46.7, 50.3, 51.1, 56.7, 56.9, 58.8, 67.4, 68.1, 69.9, 70.4, 113.8, 116.3, 122.9, 127.9, 134.8, 140.8, 140.9, 143.6, 149.5, 149.9, 178.0, 178.1. ESI-MS *m/z* 600.4 $[M+H]^+$. HRMS calcd for $C_{35}H_{58}N_3O_5$ $[M+H]^+$ *m/z* 600.4376, found 600.4380.

*4.3.3. (2S,4S,5S,7S)-5-Amino-N-(2,2-dimethyl-3-(pyridin-4-yl) propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**6**)*

Following a similar procedure for the preparation of **16**, **6** was prepared starting from **6a** (70 mg, 0.10 mmol). Solid (60 mg, 99%). [α]25 D-20.0 (*c* 0.20, CH_2Cl_2). ^1H NMR (300 MHz, CD_3OD) δ 0.92–1.07 (m, 18 H), 1.41–1.45 (m, 1 H), 1.50–1.58 (m, 2 H), 1.72–1.90 (m, 4 H), 2.01–2.03 (m, 2 H), 2.45–2.50 (m, 2 H), 2.58–2.63 (m, 1 H), 2.70–2.75 (m, 1 H), 2.90 (s, 2 H), 3.09–3.12 (m, 1 H), 3.23–3.26 (m, 1 H), 3.34 (s, 3 H), 3.58 (t, 2 H, *J* = 6.3 Hz), 3.80 (s, 3 H), 4.07 (t, 2 H, *J* = 6.3 Hz), 6.76–6.88 (m, 3 H), 7.90–8.15 (m, 3 H), 8.73 (d, 2 H, *J* = 5.1 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ 18.2, 18.3, 19.4, 20.5, 21.4, 25.0, 25.1, 30.7, 32.1, 32.8, 35.0, 37.0, 38.2, 42.8, 43.2, 51.1, 56.7, 56.9, 58.9, 67.4, 69.9, 70.4, 113.8, 116.3, 122.9, 134.8, 140.8, 140.9, 143.6, 149.5, 149.9, 178.1. ESI-MS *m/z* 600.4 $[M+H]^+$. HRMS calcd for $C_{35}H_{58}N_3O_5$ $[M+H]^+$ *m/z* 600.4376, found 600.4378.

*4.3.4. (2S,4S,5S,7S)-5-Amino-N-(2,2-dimethyl-3-phenylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**7**)*

Following a similar procedure for the preparation of **16**, **7** was prepared starting from **7a** (30 mg, 0.043 mmol). Solid (26 mg, 98%). Purity = 95.2% (HPLC eluent: 90% aqueous acetonitrile containing 0.1% trifluoroacetic acid). [α]25 D-10.0 (*c* 0.2, CH_2Cl_2). ^1H NMR (500 MHz, CD_3OD) δ 0.82–0.89 (m, 12 H), 0.95–0.97 (d, 6 H, *J* = 10 Hz), 1.23–1.36 (m, 3 H), 1.42–1.49 (m, 1 H), 1.65–1.68 (m, 1 H), 1.75–1.81 (m, 3 H), 1.98–2.03 (m, 2 H), 2.26–2.29 (m, 1 H), 2.44–2.50 (m, 2 H), 2.55 (s, 2 H), 3.02–3.07 (m, 1 H), 3.15–3.17 (m, 1 H), 3.25–3.27 (m, 1 H), 3.33 (s, 3 H), 3.57 (t, 2 H, *J* = 5 Hz), 3.78 (s, 3 H), 4.05 (t, 2 H, *J* = 5 Hz), 6.72–6.83 (m, 3 H), 7.13–7.25 (m, 5 H). ^{13}C NMR (125 MHz, CD_3OD) δ 16.5, 18.6, 19.3, 20.1, 23.9, 24.0, 29.0, 29.2, 30.6, 34.0, 35.3, 37.0, 41.8, 45.8, 49.2, 50.4, 54.1, 55.3, 57.4, 65.9, 69.0, 72.2, 112.2, 114.8, 121.4, 125.7, 127.2, 130.2, 134.3, 138.3, 147.8, 148.3, 176.7. ESI-MS *m/z* 599.3 $[M+H]^+$. HRMS calcd for $C_{36}H_{59}N_2O_5$ $[M+H]^+$ *m/z* 599.4424, found 599.4426.

4.3.5. (2S,4S,5S,7S)-5-Amino-N-(3-(2-fluorophenyl)-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**8**)

Following a similar procedure for the preparation of **16**, **8** was prepared starting from **8a** (60 mg, 0.084 mmol). Solid (51 mg, 98%). Purity = 97.5%. [α]25 D-12.0 (*c* 0.23, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.85–1.00 (m, 18 H), 1.40–1.46 (m, 1 H), 1.48–1.55 (m, 1 H), 1.55–1.60 (m, 1 H), 1.70–1.80 (m, 3 H), 1.80–1.85 (m, 1 H), 1.98–2.05 (m, 2 H), 2.30–2.37 (m, 1 H), 2.40–2.50 (m, 1 H), 2.58–2.65 (m, 3 H), 2.67–2.75 (m, 1 H), 3.00–3.05 (m, 1 H), 3.20–3.28 (m, 1 H), 3.29–3.32 (m, 1 H), 3.34 (s, 3 H), 3.58 (t, 2 H, *J* = 6.2 Hz), 3.80 (s, 3 H), 4.07 (t, 2 H, *J* = 6.4 Hz), 6.73–6.78 (m, 1 H), 6.78–6.83 (m, 1 H), 6.83–6.87 (m, 1 H), 7.00–7.10 (m, 2 H), 7.18–7.25 (m, 2 H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.5, 19.2, 20.5, 21.4, 25.2, 30.7, 30.8, 32.2, 32.9, 35.0, 37.5, 38.1, 39.6, 42.9, 50.6, 51.3, 56.7, 56.9, 58.9, 67.4, 70.0, 70.4, 113.7, 116.0, 116.2, 122.9, 124.8, 126.5, 129.3, 134.2, 134.9, 149.5, 150.0, 162.0, 163.9, 177.7. ESI-MS *m/z* 617.5 $[M+H]^+$. HRMS calcd for $C_{36}H_{58}N_2FO_5$ $[M+H]^+$ *m/z* 617.4330, found 617.4332.

4.3.6. (2S,4S,5S,7S)-5-Amino-N-(3-(3-fluorophenyl)-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**9**)

Following a similar procedure for the preparation of **16**, **9** was prepared starting from **9a** (35 mg, 0.049 mmol). Solid (30.4 mg, 95%). Purity = 98.9%. [α]25 D-16.0 (*c* 0.2, CH_2Cl_2). ^1H NMR (300 MHz, CD_3OD) δ 0.88–0.92 (m, 12 H), 0.98–1.00 (m, 6 H), 1.39–1.46 (m, 3 H), 1.54–1.82 (m, 4 H), 1.99–2.06 (m, 2 H), 2.36–2.48 (m, 2 H), 2.58–2.70 (m, 4 H), 3.00–3.04 (m, 1 H), 3.18–3.23 (m, 1 H), 3.30–3.31 (m, 1 H), 3.34 (s, 3 H), 3.58 (t, 2 H, *J* = 6 Hz), 3.80 (s, 3 H), 4.07 (t, 2 H, *J* = 6 Hz), 6.74–6.99 (m, 6 H), 7.23–7.31 (m, 1 H). ^{13}C NMR (75 MHz, CD_3OD) δ 18.3, 19.2, 20.5, 21.4, 25.3, 25.4, 30.6, 30.7, 32.1, 32.8, 34.9, 36.7, 38.1, 42.8, 46.8, 50.5, 51.2, 56.6, 56.8, 58.8, 67.3, 70.0, 70.3, 113.7, 114.0, 116.0, 118.0, 122.8, 127.5, 130.3, 134.8, 142.5, 149.4, 149.9, 162.3, 177.7. ESI-MS *m/z* 617.4 $[M+H]^+$. HRMS calcd for $C_{36}H_{58}N_2O_5F$ $[M+H]^+$ *m/z* 617.4330, found 617.4332.

4.3.7. (2S,4S,5S,7S)-5-Amino-N-(3-(2,6-difluorophenyl)-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4- methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**10**)

Following a similar procedure for the preparation of **16**, **10** was prepared starting from **10a** (20 mg, 27.2 mmol). Solid (16.6 mg, 96%). Purity = 95.6% (HPLC eluent: 90% aqueous acetonitrile containing 0.1% trifluoroacetic acid). [α]25 D-8.4 (*c* 0.53, CH_3OH). ^1H NMR (300 MHz, CD_3OD) δ 0.85–1.00 (m, 18 H), 1.35–1.45 (m, 1 H), 1.50–1.60 (m, 2 H), 1.70–1.85 (m, 4 H), 1.95–2.05 (m, 2 H), 2.30–2.50 (m, 2 H), 2.60–2.70 (m, 4 H), 2.95–3.15 (m, 2 H), 3.25–3.30 (m, 1 H), 3.31 (s, 3 H), 3.58 (t, 2 H, *J* = 6 Hz), 3.80 (s, 3 H), 4.07 (t, 2 H, *J* = 6.3 Hz), 6.73–6.90 (m, 5 H), 7.18–7.35 (m, 1 H). ^{13}C NMR (75 MHz, CD_3OD) δ 18.5, 19.2, 20.5, 21.4, 24.8, 25.2, 30.7, 32.1, 32.8, 33.2, 35.0, 38.0, 38.1, 42.8, 50.7, 51.3, 56.7, 56.8, 58.9, 67.4, 69.9, 70.4, 111.9, 113.7, 116.2, 122.9, 129.5, 134.8, 149.5, 149.9, 161.5, 164.8, 177.7. ESI-MS *m/z* 635.4 $[M+H]^+$. HRMS calcd for $C_{36}H_{57}N_2O_5F_2$ $[M+H]^+$ *m/z* 635.4236, found 635.4241.

4.3.8. (2S,4S,5S,7S)-5-Amino-N-(3-(2,5-difluorophenyl)-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**11**)

Following a similar procedure for the preparation of **16**, **11** was prepared starting from **11a** (21 mg, 28.6 mmol). Solid (16.5 mg, 95%). Purity = 98.5%. [α]25 D-7.4 (*c* 0.46, CH_3OH). ^1H NMR (300 MHz, CD_3OD) δ 0.78–1.00 (m, 18 H), 1.40–1.50 (m, 2 H), 1.50–1.60 (m, 2 H), 1.65–1.85 (m, 4 H), 1.95–2.05 (m, 2 H), 2.35–2.40 (m, 1 H), 2.40–2.50 (m, 1 H), 2.55–2.65 (m, 3 H), 2.65–2.75 (m, 1 H), 2.98–3.08 (m, 1 H), 3.18–3.30 (m, 1 H), 3.34 (s, 3 H), 3.58 (t, 2 H, *J* = 5.9 Hz), 3.79 (s, 3 H), 4.06 (t, 2 H, *J* = 5.5 Hz), 6.65–6.90 (m, 3 H), 6.93–7.10 (m, 3 H). ^{13}C NMR (75 MHz, CD_3OD) δ 18.3, 19.1, 20.4, 20.6, 21.3, 25.1, 28.7, 28.8, 30.5, 30.6, 32.0, 32.8, 34.9, 37.3, 38.0, 39.4, 42.7, 50.3, 51.1, 56.6, 56.7, 58.8, 67.2, 69.9, 70.3, 73.1, 113.5, 115.3, 116.0, 117.0, 119.8, 122.8, 128.3, 134.7, 149.3, 149.8, 157.1, 161.2, 177.7. ESI-MS *m/z* 635.4 $[M+H]^+$. HRMS calcd for $C_{36}H_{57}N_2F_2O_5$ $[M+H]^+$ *m/z* 635.4236, found 635.4241.

4.3.9. (2S,4S,5S,7S)-5-Amino-N-(3-(3-chlorophenyl)-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**12**)

Following a similar procedure for the preparation of **16**, **12** was prepared starting from **12a** (47 mg, 0.064 mmol). Solid (32 mg, 98%). Purity = 98.0%. [α]25 D-14.0 (*c* 0.20, CH_2Cl_2). ^1H NMR (300 MHz, CD_3OD) δ 0.85–0.99 (m, 18 H), 1.39–1.54 (m, 3 H), 1.72–1.86 (m, 4 H), 2.00–2.04 (m, 2 H), 2.36–2.48 (m, 2 H), 2.56–2.71 (m, 4 H), 2.99–3.04 (m, 1 H), 3.17–3.22 (m, 1 H), 3.30–3.33 (m, 1 H), 3.34 (s, 3 H), 3.58 (t, 2 H, *J* = 6 Hz), 3.79 (s, 3 H), 4.06 (t, 2 H, *J* = 6 Hz), 6.73–6.87 (m, 3 H), 7.09–7.27 (m, 4 H). ^{13}C NMR (75 MHz, CD_3OD) δ 18.4, 19.2, 20.5, 21.4, 25.3, 25.3, 30.6, 32.1, 32.8, 34.9, 36.7, 38.1, 42.8, 46.7, 50.5, 51.1, 56.6, 56.8, 58.9, 67.3, 69.9, 70.3, 113.6, 116.0, 122.8, 127.2, 130.1, 130.3, 131.4, 134.6, 134.7, 142.0, 149.4, 149.9, 177.7. ESI-MS *m/z* 633.5 $[M+H]^+$. HRMS calcd for $C_{36}H_{58}N_2O_5Cl$ $[M+H]^+$ *m/z* 633.4034, found 633.4035.

4.3.10. (2S,4S,5S,7S)-5-Amino-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-N-(3-(3-methoxyphenyl)-2,2-dimethylpropyl)-8-methylnonanamide, hydrochloride salt (**13**)

Following a similar procedure for the preparation of **16**, **13** was prepared starting from **13a** (53 mg, 0.073 mmol). Solid (46 mg, 98%). Purity = 93.5%. [α]25 D-13.8 (*c* 0.4, CH_2Cl_2). ^1H NMR (500 MHz, CD_3OD) δ 0.83–0.99 (m, 18 H), 1.25–1.50 (m, 5 H), 1.65–1.83 (m, 4 H), 2.01–2.03 (m, 2 H), 2.32–2.36 (m, 1 H), 2.42–2.46 (m, 1 H), 2.53–2.62 (m, 3 H), 2.70–2.71 (m, 1 H), 3.00–3.02 (m, 1 H), 3.34 (s, 3 H), 3.58 (t, 2 H, *J* = 5 Hz), 3.77 (s, 3 H), 3.80 (s, 3 H), 4.06 (t, 2 H, *J* = 5 Hz), 6.72–6.87 (m, 6 H), 7.15–7.18 (m, 1 H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.0, 19.8, 20.7, 21.5, 25.5, 25.6, 30.4, 30.6, 32.0, 34.5, 35.2, 36.7, 38.3, 43.1, 47.3, 50.6, 51.6, 55.5, 55.9, 56.6, 58.8, 67.2, 70.4, 72.5, 112.2, 113.5, 116.1, 117.6, 122.8, 124.1, 129.7, 135.3, 141.2, 149.2, 149.8, 160.7, 178.0. ESI-MS *m/z* 629.5 $[M+H]^+$. HRMS calcd for $C_{37}H_{61}N_2O_6$ $[M+H]^+$ *m/z* 629.4530, found 629.4532.

4.3.11. (2S,4S,5S,7S)-5-Amino-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-N-(3-(4-methoxyphenyl)-2,2-dimethylpropyl)-8-methylnonanamide, hydrochloride salt (**14**)

Following a similar procedure for the preparation of **16**, **14** was prepared starting from **14a** (46 mg, 0.063 mmol). Solid (40 mg, 99%). Purity = 96.2%. [α]25 D-21.0 (*c* 0.2, CH_2Cl_2). ^1H NMR (500 MHz, CD_3OD) δ 0.83–0.99 (m, 18H), 1.43–1.49 (m, 1 H), 1.54–1.57 (m, 2 H), 1.72–1.75 (m, 3 H), 1.80–1.83 (m, 1 H), 2.01–2.03 (m, 2 H), 2.32–2.36 (m, 1 H), 2.43–2.50 (m, 3 H), 2.58–2.62 (m, 1 H), 2.70–2.71 (m, 1 H), 2.98–3.02 (m, 1 H), 3.17–3.21 (m, 1 H), 3.28–3.31 (m, 1 H), 3.34 (s, 3 H), 3.58 (t, 2 H, *J* = 6.0 Hz), 3.76 (s, 3 H), 3.79 (s, 3 H), 4.06 (t, 2 H, *J* = 6.5 Hz), 6.74–6.87 (m, 5 H), 7.06–7.07 (m, 2 H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.4, 19.2, 20.5, 21.4, 25.3, 25.4, 30.6, 32.1, 32.8, 35.0, 36.7, 38.1, 42.8, 46.4, 50.5, 50.6, 51.2, 51.3, 55.6, 56.7, 56.8, 58.9, 67.3, 69.9, 70.4, 113.7, 114.3, 116.1, 122.9, 131.6, 132.5, 134.8, 149.4, 149.9, 159.6, 177.7. ESI-MS *m/z* 629.5 $[M+H]^+$.

HRMS calcd for $C_{37}H_{61}N_2O_6$ $[M+H]^+$ *m/z* 629.4530, found 629.4533.

*4.3.12. (2S,4S,5S,7S)-5-Amino-N-(2,2-dimethyl-3-(4-(trifluoromethoxy)phenyl)propyl)-4-hydroxy-2-isopropyl -7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**15**)*

Following a similar procedure for the preparation of **16**, **15** was prepared starting from **15a** (20 mg, 25.5 mmol). Solid (16.3 mg, 93%). Purity = 95.6% (HPLC eluent: 60% aqueous acetonitrile containing 0.1% trifluoroacetic acid). [α]25 D-4.0 (*c* 0.68, CH_3OH). ^1H NMR (300 MHz, CD_3OD) δ 0.80–1.00 (m, 18 H), 1.43–1.55 (m, 3 H), 1.65–1.85 (m, 4 H), 1.95–2.05 (m, 2 H), 2.30–2.50 (m, 2 H), 2.55–2.70 (m, 4 H), 2.95–3.25 (m, 3 H), 3.33 (s, 3 H), 3.58 (t, 2 H, *J* = 6.0 Hz), 3.79 (s, 3 H), 4.06 (t, 2 H, *J* = 5.7 Hz), 6.70–6.90 (m, 3 H), 7.10–7.30 (m, 4 H). ^{13}C NMR (75 MHz, CD_3OD) δ 18.3, 19.3, 20.5, 21.4, 25.0, 25.3, 25.4, 30.7, 32.1, 32.8, 35.0, 36.7, 38.1, 42.8, 46.4, 50.6, 51.2, 56.7, 56.8, 58.9, 67.3, 70.0, 70.4, 113.6, 116.1, 121.4, 122.9, 133.1, 133.2, 134.8, 139.0, 148.9, 149.4, 149.9, 177.8. ESI-MS *m/z* 683.4 $[M+H]^+$. HRMS calcd for $C_{37}H_{58}N_2O_6F_3$ $[M+H]^+$ *m/z* 683.4247, found 683.4252.

*4.3.13. (2S,4S,5S,7S)-5-Amino-N-(3-cyclohexyl-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**17**)*

Following a similar procedure for the preparation of **16**, **17** was prepared starting from **17a** (21 mg, 29.8 mmol). Solid (17.2 mg, 96%). Purity = 99.0%. [α]25 D-7.1 (*c* 0.43, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.87–1.05 (m, 18 H), 1.14–1.17 (m, 2 H), 1.25–1.47 (m, 6 H), 1.50–1.85 (m, 12 H), 2.00–2.05 (m, 2 H), 2.27–2.33 (m, 1 H), 2.44–2.48 (m, 1 H), 2.58–2.65 (m, 1 H), 2.67–2.75 (m, 1 H), 2.85–2.90 (m, 1 H), 3.17–3.22 (m, 1 H), 3.25–3.31 (m, 1 H), 3.35 (s, 3 H), 3.59 (t, 2 H, *J* = 6.2 Hz), 3.80 (s, 3 H), 4.07 (t, 2 H, *J* = 6.3 Hz), 6.74–6.88 (m, 3 H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.4, 19.2, 20.5, 21.4, 25.9, 26.0, 27.3, 27.6, 30.7, 32.1, 32.9, 34.9, 35.0, 36.3, 37.1, 38.1, 42.9, 51.1, 51.2, 51.3, 56.7, 56.8, 58.9, 67.4, 70.0, 70.4, 113.8, 116.2, 122.9, 134.8, 149.5, 150.0, 177.6. ESI-MS *m/z* 605.5 $[M+H]^+$. HRMS calcd for $C_{36}H_{65}N_2O_5$ $[M+H]^+$ *m/z* 605.4893, found 605.4898.

*4.3.14. (2S,4S,5S,7S)-5-Amino-N-(2,2-dimethyl-4-morpholinobutyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3 -methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**18**)*

Following a similar procedure for the preparation of **16**, **18** was prepared starting from **18a** (20 mg, 27.7 mmol). Solid (16.5 mg, 96%). Purity = 95.3%. [α]25 D-3.1 (*c* 0.29, CH_3OH). ^1H NMR (300 MHz, CD_3OD) δ 0.80–1.10 (m, 18 H), 1.20–1.50 (m, 3 H), 1.50–1.65 (m, 2 H), 1.65–1.90 (m, 6 H), 1.95–2.05 (m, 2 H), 2.29–2.55 (m, 2 H), 2.56–2.75 (m, 2 H), 3.00–3.08 (m, 1 H), 3.10–3.20 (m, 3 H), 3.20–3.30 (m, 2 H), 3.35 (s, 4 H), 3.43–3.55 (m, 2 H), 3.59 (t, 2 H, *J* = 6.2 Hz), 3.81 (s, 3 H), 3.83–3.90 (m, 1 H), 4.00–4.05 (m, 1 H), 4.08 (t, 2 H, *J* = 6.3 Hz), 6.75–6.90 (m, 3 H). ^{13}C NMR (75 MHz, CD_3OD) δ 18.4, 19.4, 20.6, 21.5, 25.4, 25.5, 30.7, 30.9, 32.1, 32.9, 33.8, 35.1, 35.4, 38.2, 42.9, 51.2, 53.2, 53.3, 54.9, 56.7, 57.0, 58.9, 65.1, 67.4, 69.9, 70.4, 113.7, 116.2, 123.0, 134.9, 149.5, 150.0, 178.1. ESI-MS *m/z* 622.5 $[M+H]^+$. HRMS calcd for $C_{35}H_{64}N_3O_6$ $[M+H]^+$ *m/z* 622.4795, found 622.4801.

*4.3.15. (2S,4S,5S,7S)-5-Amino-N-(2,2-dimethyl-4-phenoxybutyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**19**)*

Following a similar procedure for the preparation of **16**, **19** was prepared starting from **19a** (30 mg, 0.041 mmol). Solid (26.2 mg, 96%). Purity = 94.2%. [α]25 D-8.6 (*c* 0.1, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.90–1.11 (m, 18 H), 1.38–1.45 (m, 2 H), 1.50–1.58 (m, 2 H), 1.70–1.77 (m, 5 H), 1.78–1.85 (m, 1 H), 1.98–2.05 (m, 2 H), 2.27–2.35 (m, 1 H), 2.40–2.47 (m, 1 H), 2.58–2.65 (m, 1 H), 2.65–2.73 (m, 1 H), 3.01–3.07 (m, 1 H), 3.23–3.27 (m, 1 H), 3.34 (s, 3 H), 3.58 (t, 2 H, *J* = 6.2 Hz), 3.79 (s, 3 H), 4.03–4.10 (m, 4 H), 6.74–6.80 (m, 1 H), 6.81–6.83 (m, 1 H), 6.84–6.88 (m, 1 H), 6.89–6.93 (m, 3 H), 7.20–7.27 (m, 2 H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.5, 19.3, 20.5, 21.4, 26.1, 26.2, 28.8, 30.7, 30.8, 32.2, 32.9, 34.9, 35.2, 38.1, 39.8, 42.9, 50.3, 50.4, 51.3, 51.4, 56.7, 56.9, 58.9, 65.8, 67.4, 70.0, 70.4, 113.7, 115.6, 116.2, 121.7, 123.0, 130.5, 134.9, 149.5, 150.0, 160.3, 177.6. ESI-MS *m/z* 629.5 $[M+H]^+$. HRMS calcd for $C_{37}H_{61}N_2O_6$ $[M+H]^+$ *m/z* 629.4530, found 629.4537.

*4.3.16. (2S,4S,5S,7S)-5-Amino-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methyl-N-(3-phenylpropyl)nonanamide, hydrochloride salt (**20**)*

Following a similar procedure for the preparation of **16**, **20** was prepared starting from **20a** (60 mg, 0.09 mmol). Solid (50 mg, 94%). Purity = 94.4%. [α]25 D-7.1 (*c* 0.42, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.88–0.92 (m, 6 H), 0.94–0.97 (m, 6 H), 1.41–1.44 (m, 1 H), 1.52–1.58 (m, 2 H), 1.70–1.85 (m, 6 H), 1.97–2.02 (m, 2 H), 2.18–2.26 (m, 1 H), 2.42–2.46 (m, 1 H), 2.57–2.74 (m, 4 H), 3.13–3.18 (m, 1 H), 3.24–3.32 (m, 2 H), 3.33 (s, 3 H), 3.57 (t, 2 H, *J* = 6.1 Hz), 3.79 (s, 3 H), 4.06 (t, 2 H, *J* = 6.2 Hz), 6.74–6.76 (m, 1 H), 6.78–6.90 (m, 2 H), 7.13–7.26 (m, 5 H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.5, 19.2, 20.6, 21.3, 30.7, 32.0, 32.5, 32.8, 34.3, 35.1, 38.1, 40.1, 42.9, 51.4, 56.7, 56.8, 58.9, 67.4, 69.9, 70.4, 113.8, 116.2, 122.9, 126.9, 129.4, 134.8, 142.9, 149.5, 149.9, 177.3. ESI-MS *m/z* 571.4 $[M+H]^+$. HRMS calcd for $C_{34}H_{55}N_2O_5$ $[M+H]^+$ *m/z* 571.4111, found 571.4116.

*4.3.17. (2S,4S,5S,7S)-5-Amino-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methyl-N-phenethylnonanamide, hydrochloride salt (**21**)*

Following a similar procedure for the preparation of **16**, **21** was prepared starting from **21a** (23 mg, 35.0 mmol). Solid (16.0 mg, 94%). Purity = 97.6%. [α]25 D-8.1 (*c* 0.33, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.85–0.97 (m, 12H), 1.27–1.30 (m, 1H), 1.35–1.44 (m, 1H), 1.50–1.60 (m, 2H), 1.70–1.80 (m, 3H), 2.00–2.03 (m, 2H), 2.17–2.21 (m, 1H), 2.42–2.48 (m, 1H), 2.61–2.65 (m, 1H), 2.70–2.75 (m, 1H), 2.79–2.82 (m, 2H), 3.28–3.32 (m, 2H), 3.33 (s, 3H), 3.50–3.55 (m, 1H), 3.57 (t, 2H, *J* = 6.2 Hz), 3.78 (s, 3H), 4.05 (t, 2H, *J* = 6.3 Hz), 6.74–6.78 (m, 1H), 6.82–6.86 (m, 2H), 7.17–7.29 (m, 5H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.5, 19.2, 20.6, 21.2, 28.8, 30.7, 32.0, 32.8, 35.0, 36.8, 38.1, 42.0, 42.3, 51.3, 56.7, 56.8, 58.9, 67.4, 69.8, 70.4, 113.7, 116.3, 123.0, 127.4, 129.5, 129.8, 134.9, 140.4, 149.5, 150.0, 177.2. ESI-MS *m/z* 557.4 $[M+H]^+$. HRMS calcd for $C_{33}H_{53}N_2O_5$ $[M+H]^+$ *m/z* 557.3954, found 557.3961.

*4.3.18. (2S,4S,5S,7S)-5-Amino-N-(2-chlorophenethyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**22**)*

Following a similar procedure for the preparation of **16**, **22** was prepared starting from **22a** (19 mg, 24.0 mmol). Solid (15.3 mg, 94%). Purity = 99.4%. [α]25 D-9.5 (*c* 0.40, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.80–0.95 (m, 12 H), 1.25–1.35 (m, 1 H), 1.45–1.50 (m, 1 H), 1.50–1.60 (m, 2 H), 1.70–1.80 (m, 4 H), 1.95–2.05 (m, 2 H), 2.15–2.25 (m, 1 H), 2.40–2.50 (m, 1 H), 2.60–2.67 (m, 1 H), 2.68–2.75 (m, 1 H), 2.96 (t, 2 H, *J* = 7.5 Hz), 3.32–3.38 (m, 4 H), 3.53–3.60 (m, 3 H), 3.78 (s, 3 H), 4.05 (t, 2 H, *J* = 6.2 Hz), 6.74–6.78 (m, 1 H), 6.80–6.87 (m, 2 H), 7.15–7.25 (m, 2 H), 7.28–7.38 (m, 2 H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.5, 19.2, 20.5, 21.3, 28.7, 28.9, 30.7, 30.8, 32.0, 32.8, 34.5, 34.9, 38.1, 40.2, 42.9, 51.2, 56.7, 56.9, 58.9, 67.5, 69.8, 70.4, 113.7, 116.2, 122.9, 128.2, 129.3, 130.5, 132.1, 134.8, 135.1, 137.9, 149.5, 150.0, 177.4. ESI-MS *m/z* 591.4 $[M+H]^+$. HRMS calcd for $C_{33}H_{52}N_2O_5Cl$ $[M+H]^+$ *m/z* 591.3565, found 591.3569.

*4.3.19. (2S,4S,5S,7S)-5-Amino-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-N-(3-methoxyphenethyl)-8-methylnonanamide, hydrochloride salt (**23**)*

Following a similar procedure for the preparation of **16**, **23** was prepared starting from **23a** (40 mg, 0.058 mmol). Solid (35 mg, 97%). Purity = 95.9% (HPLC eluent: 60% aqueous containing 0.1% trifluoroacetic acid). [α]25 D-11.5 (*c* 0.15, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.85–1.00 (m, 12 H), 1.38–1.46 (m, 1 H), 1.50–1.60 (m, 2 H), 1.67–1.80 (m, 4 H), 1.95–2.05 (m, 2 H), 2.15–2.22 (m, 1 H), 2.42–2.50 (m, 1 H), 2.58–2.65 (m, 1 H), 2.67–2.75 (m, 1 H), 2.76–2.81 (m, 2 H), 3.28–3.30 (m, 1 H), 3.32–3.37 (m, 4 H), 3.47–3.55 (m, 1 H), 3.57 (t, 2 H, J = 6.2 Hz), 3.77 (s, 3 H), 3.78 (s, 3 H), 4.05 (t, 2 H, J = 6.3 Hz), 6.73–6.78 (m, 2 H), 6.78–6.83 (m, 3 H), 6.83–6.87 (m, 1 H), 7.18 (m, 1 H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.5, 19.2, 20.5, 21.2, 30.7, 32.0, 32.8, 35.0, 36.8, 38.1, 41.9, 42.9, 51.2, 55.6, 56.7, 56.8, 58.9, 67.4, 69.8, 70.4, 112.8, 113.7, 115.5, 116.2, 122.0, 122.9, 130.5, 134.8, 141.9, 149.4, 149.9, 161.3, 177.3. ESI-MS *m/z* 587.4 $[M+H]^+$. HRMS calcd for $C_{34}H_{55}N_2O_6$ $[M+H]^+$ *m/z* 587.4060, found 587.4065.

*4.3.20. (2S,4S,5S,7S)-5-Amino-N-(3,4-dimethoxyphenethyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**24**)*

Following a similar procedure for the preparation of **16**, **24** was prepared starting from **24a** (20 mg, 27.9 mmol). Solid (16.7 mg, 97%). Purity = 96.8%. [α]25 D-16.8 (*c* 0.36, CH_3OH). ^1H NMR (300 MHz, CD_3OD) δ 0.80–1.00 (m, 12 H), 1.35–1.60 (m, 3 H), 1.65–1.82 (m, 4 H), 1.95–2.05 (m, 2 H), 2.15–2.25 (m, 1 H), 2.40–2.50 (m, 1 H), 2.58–2.80 (m, 4 H), 3.24–3.32 (m, 2 H), 3.34 (s, 3 H), 3.45–3.53 (m, 1 H), 3.57 (t, 2 H, J = 6.3 Hz), 3.78 (s, 3 H), 3.79 (s, 3 H), 3.82 (s, 3 H), 4.05 (t, 2 H, J = 6.3 Hz), 6.73–6.80 (m, 2 H), 6.80–6.90 (m, 4 H). ^{13}C NMR (75 MHz, CD_3OD) δ 18.5, 19.3, 20.6, 21.3, 30.7, 32.0, 32.8, 35.0, 36.4, 38.2, 42.1, 42.9, 51.3, 56.6, 56.7, 56.9, 58.9, 67.3, 69.8, 70.4, 113.4, 113.6, 114.0, 116.1, 122.2, 122.9, 133.4, 134.8, 149.2, 149.4, 149.9, 150.5, 177.3. ESI-MS *m/z* 617.4 $[M+H]^+$. HRMS calcd for $C_{35}H_{57}N_2O_7$ $[M+H]^+$ *m/z* 617.4166, found 617.4171.

*4.3.21. (2S,4S,5S,7S)-5-Amino-N-(2-(benzo[d][1,3]dioxol-5-yl) ethyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**25**)*

Following a similar procedure for the preparation of **16**, **25** was prepared starting from **25a** (19 mg, 0.027 mmol). Solid (15.3 mg, 94%). Purity = 93.5%. [α]25 D-11.0 (*c* 0.29, CH_3OH). ^1H NMR (300 MHz, CD_3OD) δ 0.80–1.02 (m, 12 H), 1.35–1.45 (m, 1 H), 1.50–1.60 (m, 2 H), 1.65–1.80 (m, 4 H), 1.97–2.05 (m, 2 H), 2.12–2.22 (m, 1 H), 2.40–2.50 (m, 1 H), 2.58–2.66 (m, 1 H), 2.67–2.75 (m, 3 H), 3.22–2.30 (m, 2 H), 3.34 (s, 3 H), 3.43–2.50 (m, 1 H), 3.57 (t, 2 H, J = 6.0 Hz), 3.79 (s, 3 H), 4.05 (t, 2 H, J = 6.3 Hz), 5.88 (s, 2 H), 6.63–6.80 (m, 4 H), 6.80–6.88 (m, 2 H). ^{13}C NMR (75 MHz, CD_3OD) δ 18.5, 19.3, 20.6, 21.2, 30.7, 32.0, 32.8, 35.0, 36.5, 38.1, 42.2, 42.9, 51.3, 56.6, 56.8, 58.9, 67.3, 69.8, 70.4, 102.1, 109.1, 110.0, 113.6, 116.1, 122.7, 122.9, 134.2, 134.8, 147.6, 149.1, 149.4, 149.9, 177.3. ESI-MS *m/z* 601.4 $[M+H]^+$. HRMS calcd for $C_{34}H_{53}N_2O_7$ $[M+H]^+$ *m/z* 601.3853, found 601.3859.

*4.3.22. (2S,4S,5S,7S)-5-Amino-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methyl-N-(2-(pyridin-2-yl)ethyl)nonanamide, hydrochloride salt (**26**)*

Following a similar procedure for the preparation of **16**, **26** was prepared starting from **26a** (60 mg, 0.091 mmol). Solid (53 mg, 98%). Purity = 99.3%. [α]25 D-4.5 (*c* 0.40, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.80–0.90 (m, 6 H), 0.90–1.00 (m, 6 H), 1.28–1.32 (m, 1 H), 1.35–1.42 (m, 1 H), 1.45–1.65 (m, 3 H), 1.65–1.85 (m, 4 H), 1.97–2.05 (m, 2 H), 2.22–2.30 (m, 1 H), 2.42–2.52 (m, 1 H), 2.58–2.66 (m, 1 H), 2.67–2.75 (m, 1 H), 3.25–2.28 (m, 1H), 3.34 (s, 3 H), 3.58 (t, 2 H, J = 6.0 Hz), 3.60–3.65 (m, 1 H), 3.70–3.76 (m, 1 H), 3.79 (s, 3 H), 4.07 (t, 2 H, J = 6.0 Hz), 6.75–6.90 (m, 3 H), 7.90–8.05 (m, 2 H), 8.53 (t, 1 H, J = 5 Hz), 8.76 (d, 1 H, J = 5 Hz). ^{13}C NMR (125 MHz, CD_3OD) δ 18.4, 19.4, 20.4, 21.2, 30.7, 30.8, 32.0, 32.8, 34.7, 35.0, 38.2, 39.1, 42.9, 50.8, 56.7, 57.0, 58.9, 67.4, 69.8, 70.4, 113.7, 116.2, 123.0, 126.5, 129.2, 134.8, 142.8, 147.8, 149.4, 150.0, 156.2, 177.8. ESI-MS *m/z* 558.4 $[M+H]^+$. HRMS calcd for $C_{32}H_{52}N_3O_5$ $[M+H]^+$ *m/z* 558.3907, found 558.3911.

*4.3.23. (2S,4S,5S,7S)-5-Amino-N-((R)-1-(4-chlorophenyl)ethyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**27**)*

Following a similar procedure for the preparation of **16**, **27** was prepared starting from **27a** (20 mg, 28.9 mmol). Solid (16.0 mg, 94%). Purity = 97.3%. [α]25 D+18.5 (*c* 0.46, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.80–1.00 (m, 12 H), 1.25–1.35 (m, 1 H), 1.35–1.50 (m, 5 H), 1.60–1.70 (m, 3 H), 1.70–1.80 (m, 1 H), 1.97–2.05 (m, 2 H), 2.27–2.40 (m, 2 H), 2.50–2.65 (m, 2 H), 3.10–3.20 (m, 1 H), 3.33 (s, 3 H), 3.57 (t, 2 H, J = 5.5 Hz), 3.79 (s, 3 H), 4.05 (t, 2 H, J = 5.5 Hz), 4.95–5.05 (m, 1 H), 6.60–6.68 (m, 1 H), 6.75–6.85 (m, 2 H), 7.25–7.40 (m, 4 H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.2, 19.4, 20.7, 21.2, 22.7, 30.7, 30.8, 32.1, 33.1, 35.4, 38.3, 42.8, 50.9, 51.0, 56.7, 56.8, 58.9, 67.4, 70.0, 70.4, 113.7, 116.1, 122.8, 129.0, 129.6, 133.5, 134.8, 144.5, 149.4, 150.0, 176.5. ESI-MS *m/z* 591.4 $[M+H]^+$. HRMS calcd for $C_{33}H_{52}N_2O_5Cl$ $[M+H]^+$ *m/z* 591.3565, found 591.3568.

*4.3.24. (2S,4S,5S,7S)-5-Amino-N-((S)-1-(4-chlorophenyl)ethyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**28**)*

Following a similar procedure described for the preparation of **16**, **28** was prepared starting from **28a** (23 mg, 33.3 mmol). Solid (18.7 mg, 95%). Purity = 96.5%. [α]25 D-34.7 (*c* 0.38, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.75–1.00 (m, 12 H), 1.25–1.35 (m, 1 H), 1.43 (d, 3 H, J = 6.0 Hz), 1.50–1.59 (m, 2 H), 1.65–1.80 (m, 4 H), 1.95–2.05 (m, 2 H), 2.22–2.31 (m, 1 H), 2.40–2.50 (m, 1 H), 2.60–2.75 (m, 2 H), 3.25–3.30 (m, 1 H), 3.33 (s, 3 H), 3.58 (t, 2 H, J = 5.5 Hz), 3.80 (s, 3H), 4.07 (t, 2H, J = 5.0 Hz), 4.95–5.05 (m, 1H), 6.75–6.90 (m, 3H), 7.25–7.35 (m, 4H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.5, 19.3, 20.5, 21.3, 22.3, 30.7, 30.8, 32.2, 32.8, 34.9, 38.1, 42.9, 51.0, 56.8, 56.9, 58.9, 67.5, 69.9, 70.4, 113.8, 116.3, 123.0, 129.1, 129.4, 133.7, 134.8, 144.0, 149.5, 149.9, 176.6. ESI-MS *m/z* 591.4 $[M+H]^+$. HRMS calcd for $C_{33}H_{52}N_2O_5Cl$ $[M+H]^+$ *m/z* 591.3565, found 591.3569.

*4.3.25. (2S,4S,5S,7S)-5-Amino-N-((R)-1-(4-bromophenyl)ethyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**29**)*

Following a similar procedure for the preparation of **16**, **29** was prepared starting from **29a** (20 mg, 27.2 mmol). Solid (16.8 mg, 97%). Purity = 93.6%. [α]25 D+13.5 (*c* 0.36, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.80–1.00 (m, 12H), 1.40–1.46 (m, 6H), 1.60–1.70 (m, 3H), 1.75–1.82 (m, 1H), 1.97–2.05 (m, 2H), 2.27–2.40 (m, 2H), 2.50–2.65 (m, 2H), 3.13–3.17 (m, 1H), 3.34 (s, 3H), 3.58 (t, 2H, J = 6.0 Hz), 3.79 (s, 3H), 4.05 (t, 2H, J = 6.0 Hz), 4.95–5.05 (m, 1H), 6.60–6.68 (m, 1H), 6.75–6.85 (m, 2H), 7.25–7.32 (m, 2H), 7.42–7.48 (m, 2H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.3, 19.4, 20.6, 21.2, 22.6, 22.7, 28.8, 30.7, 30.8, 32.1, 33.2, 35.4, 38.2, 42.8, 49.8, 49.9, 51.0, 51.1, 56.7, 56.8, 58.9, 67.4, 70.0, 70.4, 113.8, 116.2, 121.6, 122.9, 129.3, 132.6, 134.7, 144.9, 149.5, 149.9, 176.5. ESI-MS *m/z* 635.3 $[M+H]^+$. HRMS calcd for $C_{33}H_{52}N_2O_5Br$ $[M+H]^+$ *m/z* 635.3060, found 635.3067.

*4.3.26. (2S,4S,5S,7S)-5-Amino-N-((S)-1-(4-bromophenyl)ethyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**30**)*

Following a similar procedure for the preparation of **16**, **30** was prepared starting from **30a** (21 mg, 28.6 mmol). Solid (17.6 mg, 97%). Purity = 98.4%. [α]25 D-31.4 (*c* 0.40, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.80–1.00 (m, 12H), 1.25–1.35 (m, 1H), 1.40–1.45 (m, 3H), 1.50–1.60 (m, 2H), 1.60–1.80 (m, 4H), 1.95–2.05 (m, 2H), 2.20–2.30 (m, 1H), 2.40–2.50 (m, 1H), 2.60–2.80 (m, 2H), 3.25–3.30 (m, 1H), 3.33 (s, 3H), 3.57 (t, 2H, *J* = 5.5 Hz), 3.79 (s, 3H), 4.07 (t, 2H, *J* = 5.5 Hz), 4.95–5.05 (m, 1H), 6.60–6.68 (m, 1H), 6.75–6.90 (m, 2H), 7.25–7.30 (m, 2H), 7.40–7.50 (m, 2H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.5, 19.3, 20.5, 21.3, 22.3, 30.6, 30.7, 32.2, 32.8, 34.9, 38.1, 42.9, 50.9, 56.7, 56.8, 58.9, 67.5, 69.9, 70.4, 113.8, 116.3, 121.7, 123.0, 129.4, 132.5, 134.8, 144.6, 149.5, 150.0, 176.5. ESI-MS *m/z* 635.3 $[M+H]^+$. HRMS calcd for $C_{33}H_{52}N_2O_5Br$ $[M+H]^+$ *m/z* 635.3060, found 635.3068.

*4.3.27. (2S,4S,5S,7S)-5-Amino-N-(3-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**31**)*

Following a similar procedure for the preparation of **16**, **31** was prepared starting from **31a** (56 mg, 0.077 mmol). Solid (49 mg, 99%). Purity = 98.6%. [α]25 D-15.5 (*c* 0.2, CH_2Cl_2). ^1H NMR (300 MHz, CD_3OD) δ 0.80–1.00 (m, 20H), 1.05–1.10 (m, 2H), 1.41–1.65 (m, 4H), 1.73–1.85 (m, 4H), 1.95–2.05 (m, 3H), 2.33–2.36 (m, 1H), 2.41–2.47 (m, 1H), 2.60–2.64 (m, 1H), 2.69–2.70 (m, 1H), 3.07–3.10 (m, 1H), 3.14–3.16 (m, 1H), 3.34 (s, 3H), 3.58 (t, 2H, *J* = 6.0 Hz), 3.80 (s, 3H), 4.07 (t, 2H, *J* = 6.3 Hz), 4.18–4.25 (m, 2H), 6.75–6.88 (m, 3H), 7.82 (s, 1H). ^{13}C NMR (125 MHz, CD_3OD) δ 6.4, 8.6, 18.4, 19.3, 20.5, 22.3, 23.8, 23.9, 30.7, 30.7, 32.1, 32.8, 34.9, 37.8, 38.1, 42.8, 43.4, 48.0, 51.1, 56.7, 56.9, 58.8, 60.2, 67.4, 68.1, 69.9, 70.4, 83.6, 87.7, 113.8, 116.2, 122.9, 125.5, 125.5, 134.8, 149.4, 150.1, 178.0. ESI-MS *m/z* 630.5 $[M+H]^+$. HRMS calcd for $C_{35}H_{60}N_5O_5$ $[M+H]^+$ *m/z* 630.4594, found 630.4597.

*4.3.28. (2S,4S,5S,7S)-5-Amino-N-(3-(4-tert-butyl-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropyl)-4-hydroxy-2- isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**32**)*

Following a similar procedure for the preparation of **16**, **32** was prepared starting from **32a** (59 mg, 0.079 mmol). Solid (53 mg, 98%). Purity = 96.0%. [α]25 D-4.81 (*c* 0.47, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.90–0.92 (m, 6H), 0.98 (s, 12H), 1.42 (s, 10H), 1.54–1.59 (m, 2H), 1.72–1.85 (m, 4H), 2.02 (t, 2H, *J* = 5.7 Hz), 2.40–2.49 (m, 2H), 2.59–2.63 (m, 1H), 2.72 (s, 1H), 3.14–3.23 (dd, 2H, *J* = 13.7 Hz, *J* = 10.6 Hz), 3.30–3.32 (m, 1H), 3.34 (s, 3H), 3.59 (t, 2H, *J* = 5.9 Hz), 3.80 (s, 3H), 4.07 (t, 2H, *J* = 5.9 Hz), 4.39 (s, 2H), 6.76–6.88 (m, 3H), 8.39 (s, 1H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.4, 19.4, 20.5, 21.4, 23.8, 23.9, 30.2, 30.7, 30.8, 32.2, 32.8, 34.9, 37.9, 38.2, 42.8, 48.0, 51.1, 56.7, 56.9, 58.9, 60.6, 67.4, 69.9, 70.4, 113.7, 116.2, 122.9, 125.9, 134.8, 149.5, 149.9, 156.1, 178.2. ESI-MS *m/z* 646.5 $[M+H]^+$. HRMS calcd for $C_{36}H_{64}N_5O_5$ $[M+H]^+$ *m/z* 646.4907, found 646.4913.

*4.3.29. (2S,4S,5S,7S)-5-Amino-N-(3-(4-butyl-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**33**)*

Following a similar procedure for the preparation of **16**, **33** was prepared starting from **33a** (50 mg, 0.067 mmol). Solid (43 mg, 98%). Purity = 98.4%. [α]25 D-6.2 (*c* 0.60, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.91–0.99 (m, 21H), 1.41–1.47 (m, 3H), 1.50–1.60 (m, 2H), 1.71–1.77 (m, 5H), 1.84–1.85 (m, 1H), 2.02–2.04 (m, 2H), 2.39–2.41 (m, 1H), 2.46–2.50 (m, 1H), 2.60–2.64 (m, 1H), 2.71–2.73 (m, 1H), 2.80 (t, 2H, *J* = 6 Hz), 3.13–3.22 (m, 2H), 3.30–3.33 (m, 1H), 3.35 (s, 3H), 3.59 (t, 2H, *J* = 6 Hz), 3.81 (s, 3H), 4.08 (t, 2H, *J* = 6 Hz), 4.30–4.38 (m, 2H), 6.76–6.89 (m, 3H), 8.22 (s, 1H). ^{13}C NMR (125 MHz, CD_3OD) δ 14.0, 18.4, 19.3, 20.5, 21.3, 23.1, 23.8, 30.7, 30.7, 32.1, 34.9, 37.9, 38.1, 42.8, 48.0, 51.1, 56.7, 56.9, 58.9, 60.1, 67.4, 69.9, 70.4, 113.7, 116.2, 122.9, 126.9, 134.7, 147.5, 149.4, 149.9, 178.0. ESI-MS *m/z* 646.5 $[M+H]^+$. HRMS calcd for $C_{36}H_{64}N_5O_5$ $[M+H]^+$ *m/z* 646.4907, found 646.4910.

*4.3.30. (2S,4S,5S,7S)-5-Amino-N-(3-(4-hexyl-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropyl)-4-hydroxy-2- isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**34**)*

Following a similar procedure for the preparation of **16**, **34** was prepared starting from starting with **34a** (50 mg, 0.065 mmol). Solid (43 mg, 98%). Purity = 98.8%. [α]25 D-13.00 (*c* 0.2, CH_2Cl_2). ^1H NMR (500 MHz, CD_3OD) δ 0.83–0.99 (m, 20H), 1.25–1.33 (m, 9H), 1.44–1.49 (m, 1H), 1.65–1.68 (m, 3H), 1.73–1.78 (m, 3H), 2.00–2.03 (m, 2H), 2.29–2.33 (m, 1H), 2.42–2.50 (m, 3H), 2.69 (t, 2H, *J* = 5 Hz), 3.02–3.18 (m, 2H), 3.30–3.33 (m, 1H), 3.34 (s, 3H), 3.58 (t, 2H, *J* = 5 Hz), 3.79 (s, 3H), 4.06 (t, 2H, *J* = 5 Hz), 4.20–4.23 (m, 2H), 6.72–6.84 (m, 3H), 7.84 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 12.9, 16.5, 18.6, 19.3, 20.0, 22.1, 22.5, 22.6, 24.8, 28.4, 29.1, 29.2, 30.7, 31.2, 33.8, 34.2, 36.5, 37.1, 41.8, 46.6, 50.4, 54.1, 55.3, 57.3, 57.4, 65.9, 69.0, 72.7, 112.1, 114.7, 121.4, 123.2, 134.4, 147.5, 147.7, 148.3, 177.0. ESI-MS *m/z* 674.5 $[M+H]^+$. HRMS calcd for $C_{38}H_{68}N_5O_5$ $[M+H]^+$ *m/z* 674.5220, found 674.5223.

*4.3.31. (2S,4S,5S,7S)-5-Amino-N-(2,2-dimethyl-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propyl)-4-hydroxy-2- isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**35**)*

Following a similar procedure for the preparation of **16**, **35** was prepared starting from **35a** (62 mg, 0.081 mmol). Solid (56 mg, 98%). Purity = 95.1%. [α]25 D-7.67 (*c* 0.49, CH_3OH). ^1H NMR (300 MHz, CD_3OD) δ 0.87–0.90 (m, 6H), 0.98–1.00 (m, 12H), 1.28–1.55 (m, 4H), 1.73–1.85 (m, 4H), 1.98–2.02 (m, 2H), 2.39–2.49 (m, 2H), 2.56–2.61 (m, 1H), 2.71 (s, 1H), 3.12 (s, 2H), 3.33 (s, 3H), 3.57 (t, 2H, *J* = 6.1 Hz), 3.78 (s, 3H), 4.05 (t, 2H, *J* = 6.2 Hz), 4.37 (s, 2H), 6.73–6.86 (m, 3H), 7.38–7.48 (m, 3H), 7.83–7.86 (m, 2H), 8.59 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 18.4, 19.3, 20.5, 21.4, 23.9, 24.1, 30.6, 30.7, 32.2, 32.8, 35.0, 37.9, 38.2, 42.8, 48.1, 51.2, 56.7, 56.9, 58.9, 59.5, 67.3, 70.0, 70.3, 113.6, 116.1, 122.9, 124.5, 126.9, 129.8, 130.1, 130.7, 134.7, 148.0, 149.4, 149.9, 178.1. ESI-MS *m/z* 666.5 $[M+H]^+$. HRMS calcd for $C_{38}H_{60}N_5O_5$ $[M+H]^+$ *m/z* 666.4594, found 666.4600.

*4.3.32. (2S,4S,5S,7S)-5-Amino-N-(2,2-dimethyl-3-(4-p-tolyl-1H-1,2,3-triazol-1-yl)propyl)-4-hydroxy-2- isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**36**)*

Following a similar procedure for the preparation of **16**, **36** was prepared starting from **36a** (63 mg, 0.081 mmol). Solid (52 mg, 90%). Purity = 95.8% (HPLC eluent: 60% aqueous acetonitrile containing 0.1% trifluoroacetic acid). [α]25 D-11.86 (*c* 0.28, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 0.86 (t, 6H, *J* = 6.5 Hz), 0.97–0.99 (m, 12H), 1.27–1.49 (m, 4H), 1.65–1.85 (m, 4H), 1.97–2.03 (m, 2H), 2.36 (s, 4H), 2.44–2.59 (m, 3H), 3.17–3.18 (m, 2H), 3.33 (s, 3H), 3.56 (t, 2H, *J* = 6.3 Hz), 3.78 (s, 3H), 4.05 (t, 2H, *J* = 6.3 Hz), 4.30 (s, 2H), 6.72–6.84 (m, 3H), 7.23–7.25 (m, 2H), 7.70–7.72 (m, 2H), 8.39 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 18.2, 19.7, 20.6, 21.3, 21.4, 23.9, 24.1, 30.7, 32.2, 35.1, 37.9, 38.3, 43.1, 48.1, 51.5, 56.2, 56.7, 58.9, 59.0, 67.3, 68.1, 70.4, 72.1, 113.7, 116.2, 122.9, 123.4, 126.6, 128.8, 130.6, 135.3, 139.4, 148.6, 149.3, 149.8, 178.3. ESI-MS *m/z* 680.5 $[M+H]^+$.

HRMS calcd for $C_{39}H_{62}N_5O_5$ $[M+H]^+$ *m/z* 680.4751, found 680.4756.

*4.3.33. (2S,4S,5S,7S)-5-Amino-N-(2,2-dimethyl-3-(4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**37**)*

Following a similar procedure for the preparation of **16**, **37** was prepared starting from **37a** (50 mg, 0.065 mmol). Solid (43 mg, 99%). Purity = 97.5%. [α]25 D-2.00 (*c* 0.2, CH_2Cl_2). ^{1}H NMR (500 MHz, CD_3OD) δ 0.89–0.91 (m, 6H), 0.99–1.02 (m, 12H), 1.44–1.49 (m, 1H), 1.51–1.60 (m, 2H), 1.70–1.74 (m, 3H), 1.78–1.87 (m, 1H), 1.99–2.03 (m, 2H), 2.42–2.50 (m, 2H), 2.57–2.61 (m, 1H), 2.74–2.75 (m, 1H), 3.19–3.22 (m, 2H), 3.34 (s, 3H), 3.37–3.40 (m, 1H), 3.58 (t, 2H, *J* = 6.5 Hz), 3.79 (s, 3H), 4.06 (t, 2H, *J* = 6.0 Hz), 4.45 (s, 2H), 6.72–6.90 (m, 3H), 7.91 (t, 1H, *J* = 6.0 Hz), 8.45–8.46 (m, 1H), 8.56 (t, 1H, *J* = 7.0 Hz), 8.75–8.76 (m, 1H), 9.10 (s, 1H). ^{13}C NMR (125 MHz, CD_3OD) δ 18.3, 19.4, 20.5, 21.3, 23.9, 23.9, 30.6, 32.2, 32.8, 35.0, 38.0, 38.2, 42.8, 48.1, 48.2, 51.1, 56.7, 56.9, 58.8, 59.5, 67.3, 68.1, 69.9, 70.3, 113.7, 116.1, 122.9, 125.2, 126.6, 128.9, 134.7, 140.6, 143.3, 145.4, 147.7, 149.4, 149.9, 178.1. ESI-MS *m/z* 667.5 $[M+H]^+$. HRMS calcd for $C_{37}H_{59}N_6O_5$ $[M+H]^+$ *m/z* 667.4547, found 667.4550.

*4.3.34. (2S,4S,5S,7S)-5-Amino-4-hydroxy-N-(3-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropyl)-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**38**)*

Following a similar procedure for the preparation of **16**, **38** was prepared starting from **38a** (70 mg, 0.097 mmol). Solid (63 mg, 99%). Purity = 98.2%. [α]25 D-10.80 (*c* 0.40, CH_3OH). ^{1}H NMR (300 MHz, CD_3OD) δ 0.90–0.92 (m, 6H), 0.97 (s, 12H), 1.29–1.54 (m, 5H), 1.72–1.86 (m, 4H), 1.98–2.02 (m, 2H), 2.39–2.51 (m, 2H), 2.58–2.72 (m, 2H), 3.11–3.23 (dd, 2H, *J* = 13.9 Hz, *J* = 8.2 Hz), 3.34 (s, 3H), 3.59 (t, 2H, *J* = 6.2 Hz), 3.80 (s, 3H), 4.07 (t, 2H, *J* = 6.3 Hz), 4.40 (s, 2H), 4.47 (s, 2H), 6.76–6.88 (m, 3H), 8.38 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 18.3, 19.4, 20.5, 21.4, 23.8, 23.9, 30.7, 30.8, 32.2, 32.8, 34.9, 37.9, 38.2, 42.8, 48.0, 51.0, 55.5, 56.7, 56.9, 58.9, 60.3, 67.4, 69.9, 70.4, 113.7, 116.1, 122.9, 127.2, 134.8, 149.3, 149.4, 149.9, 171.2. ESI-MS *m/z* 620.4 $[M+H]^+$. HRMS calcd for $C_{33}H_{58}N_5O_6$ $[M+H]^+$ *m/z* 620.4387, found 620.4392.

*4.3.35. (2S,4S,5S,7S)-5-Amino-4-hydroxy-N-(3-(4-(2-hydroxyethyl)-1H-1,2,3-triazol-1-yl)-2,2- dimethylpropyl)-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**39**)*

Following a similar procedure for the preparation of **16**, **39** was prepared starting from **39a** (45 mg, 0.062 mmol). Solid (39 mg, 99%). Purity = 99.5%. [α]25 D-5.8 (*c* 0.15, CH_3OH). ^{1}H NMR (500 MHz, CD_3OD) δ 0.76–0.90 (m, 18H), 1.18–1.23 (m, 1H), 1.28–1.50 (m, 3H), 1.60–1.80 (m, 4H), 1.86–1.96 (m, 2H), 2.28–2.40 (m, 2H), 2.48–2.55 (m, 1H), 2.58–2.65 (m, 1H), 2.82–2.92 (m, 2H), 3.00–3.12 (m, 2H), 3.20–3.22 (m, 2H), 3.23 (s, 3H), 3.58 (t, 2H, *J* = 6.5 Hz), 3.70 (s, 3H), 4.06 (t, 2H, *J* = 6.0 Hz), 4.20–4.35 (m, 2H), 6.63–6.70 (m, 1H), 6.72–6.80 (m, 2H), 8.24 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 16.0, 18.1, 18.8, 19.5, 22.0, 22.1, 27.9, 28.6, 28.7, 30.2, 33.5, 41.3, 46.1, 49.8, 53.7, 54.7, 56.9, 60.2, 65.3, 68.5, 72.1, 111.6, 114.1, 120.9, 123.6, 133.9, 143.9, 147.2, 147.8, 176.5. ESI-MS *m/z* 634.5 $[M+H]^+$. HRMS calcd for $C_{34}H_{60}N_5O_6$ $[M+H]^+$ *m/z* 634.4544, found 634.4546.

*4.3.36. (2S,4S,5S,7S)-5-Amino-4-hydroxy-N-(3-(4-(1-hydroxyethyl)-1H-1,2,3-triazol-1-yl)-2,2- dimethylpropyl)-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**40**)*

Following a similar procedure for the preparation of **16**, **40** was prepared starting from **40a** (42 mg, 0.057 mmol). Solid (28 mg, 73%). Purity = 97.9%. [α]25 D-7.13 (*c* 0.30, CH_3OH). ^{1}H NMR (300 MHz, CD_3OD) δ 0.90–0.92 (m, 6H), 0.97 (s, 12H), 1.28–1.57 (m, 7H), 1.72–1.80 (m, 4H), 2.02 (t, 2H, *J* = 5.4 Hz), 2.43–2.51 (m, 2H), 2.60–2.70 (m, 2H), 3.12–3.24 (m, 2 H), 3.34 (s, 3H), 3.58 (t, 2H, *J* = 5.7 Hz), 3.84 (s, 3H), 4.07 (t, 2H, *J* = 5.6 Hz), 4.43 (s, 2H), 5.09 (s, 1H), 6.76–6.88 (m, 3H), 8.49 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 16.9, 17.9, 19.1, 19.9, 22.4, 22.5, 29.2, 29.3, 30.8, 31.4, 33.5, 36.5, 36.7, 41.3, 46.5, 49.6, 55.3, 55.4, 57.5, 59.4, 61.0, 65.9, 68.5, 68.9, 112.2, 114.7, 121.5, 125.4, 133.4, 147.9, 148.5, 149.7, 176.7. ESI-MS *m/z* 634.5 $[M+H]^+$. HRMS calcd for $C_{34}H_{60}N_5O_6$ $[M+H]^+$ *m/z* 634.4544, found 634.4549.

*4.3.37. (2S,4S,5S,7S)-5-Amino-4-hydroxy-N-(3-(4-(1-hydroxycyclopentyl)-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropyl)-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**41**)*

Following a similar procedure for the preparation of **16**, **41** was prepared starting from **41a** (50 mg, 0.065 mmol). Solid (42 mg, 96%). Purity = 98.3%. [α]25 D-9.67 (*c* 0.30, CH_3OH). ^{1}H NMR (300 MHz, CD_3OD) δ 0.84–0.88 (m, 6H), 0.94–1.00 (m, 12H), 1.21–1.50 (m, 4H), 1.67–1.81 (m, 6H), 1.96–2.09 (m, 8H), 2.28–2.50 (m, 4H), 3.14–3.16 (m, 2H), 3.35 (s, 3H), 3.59 (t, 2H, *J* = 6.2 Hz), 3.80 (s, 3H), 4.08 (t, 2H, *J* = 6.2 Hz), 4.25 (s, 2H), 6.73–6.86 (m, 3H), 7.93 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 17.9, 20.1, 20.8, 21.5, 23.9, 24.0, 24.5, 30.5, 30.7, 32.2, 35.2, 35.6, 37.9, 38.5, 41.9, 43.2, 48.0, 51.8, 55.5, 56.7, 58.8, 67.2, 70.4, 74.2, 79.5, 113.5, 116.0, 122.8, 124.0, 135.8, 149.1, 149.7, 155.4, 178.5. ESI-MS *m/z* 674.5 $[M+H]^+$. HRMS calcd for $C_{37}H_{64}N_5O_6$ $[M+H]^+$ *m/z* 674.4857, found 674.4862.

*4.3.38. (2S,4S,5S,7S)-5-Amino-N-(3-(4-((dimethylamino)methyl)-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**42**)*

Following a similar procedure for the preparation of **16**, **42** was prepared starting from **42a** (54 mg, 0.072 mmol). Solid (50 mg, 99%). Purity = 98.1%. [α]25 D-13.06 (*c* 0.34, CH_3OH). ^{1}H NMR (300 MHz, CD_3OD) δ 0.85 (t, 6H, *J* = 6.2 Hz), 0.91–0.99 (m, 12H), 1.21–1.36 (m, 5H), 1.64–1.84 (m, 4H), 1.97–2.06 (m, 2H), 2.26 (s, 7H), 2.39–2.51 (m, 3H), 3.08–3.20 (m, 3H), 3.34 (s, 3H), 3.58 (t, 2H, *J* = 6.2 Hz), 3.79 (s, 3H), 4.06 (t, 2H, *J* = 6.3 Hz), 4.27 (s, 2H), 6.72–6.85 (m, 3H), 8.01 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 16.5, 18.7, 19.3, 20.0, 22.4, 22.5, 29.0, 29.2, 30.7, 33.7, 34.2, 36.5, 37.1, 41.8, 43.4, 46.6, 50.4, 52.8, 54.0, 55.2, 57.5, 65.8, 68.9, 72.3, 112.0, 114.6, 121.4, 125.4, 134.4, 142.8, 147.7, 148.3, 177.1. ESI-MS *m/z* 647.5 $[M+H]^+$. HRMS calcd for $C_{35}H_{63}N_6O_5$ $[M+H]^+$ *m/z* 647.4860, found 647.4865.

*4.3.39. (2S,4S,5S,7S)-5-Amino-N-(3-(4-((diethylamino)methyl)-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**43**)*

Following a similar procedure for the preparation of **16**, **43** was prepared starting from **43a** (30 mg, 0.038 mmol). Solid (26 mg, 99%). Purity = 99.4%. [α]25 D-5.0 (*c* 0.2, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3OD) δ 0.87–0.99 (m, 18H), 1.25–1.28 (m, 1H), 1.39–1.40 (m, 8H), 1.49–1.55 (m, 3H), 1.72–1.80 (m, 4H), 2.00–2.04 (m, 2H), 2.38–2.43 (m, 2H), 2.58–2.65 (m, 1H), 2.70–2.75 (m, 1H), 3.11–3.24 (m, 4H), 3.34 (s, 3H), 3.58 (t, 2H, *J* = 6.0 Hz), 3.80 (s, 3H), 4.07 (t, 2H, *J* = 6.6 Hz), 4.25–4.40 (m, 2H), 4.45–4.55 (m, 2H), 6.75–6.89 (m, 3H), 8.41 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 9.5, 18.4, 19.3, 20.5, 21.4, 23.9, 24.0, 30.7, 30.8, 32.1, 32.9, 34.9, 37.9, 38.1, 42.8, 46.9, 51.0, 56.7, 56.9, 58.9, 59.3, 67.4, 69.9, 70.4, 113.8, 116.3, 122.9, 129.7, 134.8, 137.2, 149.5, 149.9, 178.0. ESI-MS *m/z* 673.5 $[M-H]^-$. HRMS calcd for $C_{37}H_{65}N_6O_5$ $[M-H]^-$ *m/z* 673.5016, found 673.5018.

*4.3.40. (2S,4S,5S,7S)-5-Amino-N-(3-(4-((diisopropylamino) methyl)-1H-1,2,3-triazol-1-yl)-2,2- dimethylpropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**44**)*

Following a similar procedure for the preparation of **16**, **44** was prepared starting from **44a** (57 mg, 0.071 mmol). Solid was obtained (50 mg, 95%). Purity = 96.7%. [α]25 D-9.94 (*c* 0.31, CH_3OH). ^1H NMR (300 MHz, CD_3OD) δ 0.90–0.99 (m, 18H), 1.45–1.55 (m, 16H), 1.72–1.80 (m, 4H), 2.00–2.04 (m, 2H), 2.41–2.51 (m, 2H), 2.58–2.63 (m, 1H), 2.70 (s, 1H), 3.10–3.23 (m, 2H), 3.35 (s, 3H), 3.59 (t, 2H, *J* = 6.2 Hz), 3.79 (s, 3H), 3.84–3.86 (m, 2H), 4.08 (t, 2H, *J* = 6.2 Hz), 4.34 (s, 2H), 4.53 (s, 2H), 6.76–6.89 (m, 3H), 8.39 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 16.4, 16.9, 17.6, 17.9, 19.1, 19.9, 22.5, 22.6, 29.2, 29.3, 30.7, 32.4, 33.6, 36.5, 36.7, 41.3, 46.6, 49.7, 55.2, 55.3, 55.4, 57.4, 57.7, 65.9, 68.5, 68.9, 112.2, 114.6, 121.5, 127.4, 133.3, 137.9, 148.0, 148.5, 176.6. ESI-MS *m/z* 703.5 $[M+H]^+$. HRMS calcd for $C_{39}H_{71}N_6O_5$ $[M+H]^+$ *m/z* 703.5486, found 703.5492.

*4.3.41. (2S,4S,5S,7S)-5-Amino-N-(2,2-dimethyl-3-(4-(piperidin-1-ylmethyl)-1H-1,2,3-triazol-1-yl)propyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**45**)*

Following a similar procedure for the preparation of **16**, **45** was prepared starting from **45a** (56 mg, 0.072 mmol). Solid (49 mg, 99%). Purity = 95.4%. [α]25 D-14.0 (*c* 0.2, CH_2Cl_2). ^1H NMR (500 MHz, CD_3OD) δ 0.82–0.88 (m, 18H), 1.25–1.27 (m, 1H), 1.32–1.37 (m, 2H), 1.46–1.50 (m, 3H), 1.64–1.73 (m, 5H), 1.85–1.93 (m, 4H), 2.31–2.39 (m, 2H), 2.51–2.63 (m, 2H), 2.93–3.11 (m, 4H), 3.25 (s, 3H), 3.35–3.45 (m, 3H), 3.49 (m, 2H), 3.71 (s, 3H), 3.98 (m, 2H), 4.20–4.30 (m, 2H), 4.30–4.40 (m, 2H), 6.67–6.79 (m, 3H), 8.30 (s, 1H). ^{13}C NMR (125 MHz, CD_3OD) δ 7.9, 18.4, 19.3, 20.5, 21.4, 22.6, 24.0, 24.1, 24.2, 30.6, 30.7, 32.1, 32.8, 35.0, 37.9, 38.1, 42.7, 48.2, 51.1, 52.2, 53.8, 54.3, 56.7, 56.8, 58.9, 59.4, 67.4, 69.5, 70.4, 113.7, 116.2, 122.9, 130.0, 134.7, 137.3, 149.4, 149.9, 178.1. ESI-MS *m/z* 685.5 $[M-H]^-$. HRMS calcd for $C_{38}H_{65}N_6O_5$ $[M-H]^-$ *m/z* 685.5016, found 685.5018.

*4.3.42. (2S,4S,5S,7S)-5-Amino-N-(2,2-dimethyl-3-(4-(morpholinomethyl)-1H-1,2,3-triazol-1-yl)propyl)-4- hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide, hydrochloride salt (**46**)*

Following a similar procedure for the preparation of **16**, **46** was prepared starting from **46a** (70 mg, 0.089 mmol). Solid (63 mg, 98%). Purity = 99.1%. [α]23 D-3.35 (*c* 0.62, CH_3OH). ^1H NMR (300 MHz, CD_3OD) δ 0.93 (t, 6H, *J* = 6.2 Hz), 1.00–1.04 (m, 12H), 1.36–1.57 (m, 4H), 1.74–1.86 (m, 4H), 2.06–2.10 (m, 3H), 2.25–2.75 (m, 8H), 3.16–3.27 (m, 3H), 3.41 (s, 3H), 3.65 (t, 2H, *J* = 6.1 Hz), 3.74 (s, 4H), 3.87 (s, 3H), 4.14 (t, 2H, *J* = 6.1 Hz), 4.34 (s, 2H), 6.79–6.89 (m, 3H), 8.10 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 17.9, 20.1, 20.8, 21.5, 23.9, 24.0, 30.5, 30.7, 32.2, 35.2, 35.7, 38.0, 38.5, 43.3, 48.0, 51.8, 53.9, 54.2, 55.5, 56.7, 58.9, 67.3, 67.6, 70.4, 74.3, 84.5, 113.5, 116.1, 122.8, 126.9, 135.9, 144.0, 149.7, 178.5. ESI-MS *m/z* 689.5 $[M+H]^+$. HRMS calcd for $C_{37}H_{65}N_6O_6$ $[M+H]^+$ *m/z* 689.4966, found 689.4972.

4.4. In vitro assay

The inhibitory activity of test compounds against the human recombinant rennin was measured by using the Sensolyte® 520 Renin Assay Kits. Into microplate wells were added 3 μL of the test compound solutions (100 nM, 20 nM, 4 nM, 0.8 nM and 0.16 nM) and 10 μL of the human recombinant rennin solution. At the same time, the following controls were set up: 1) inhibitor controls containing 3 μL of the Ac-HPFV-(Sta)-LF-NH_2 solution (10 μM) and 10 μL of the human recombinant rennin solution; 2) vehicle controls containing 3 μL of vehicle and 10 μL of the human recombinant rennin solution; 3) positive controls containing 3 μL of the assay buffer and 10 μL of the human recombinant rennin solution; 4) substrate controls containing 13 μL of the assay buffer. The plate was incubated for 30 min at 37 °C. Meanwhile, the rennin substrate solution (20 μM) was pre-incubated at 37 °C. Into each well was added 17 μL of the pre-incubated rennin substrate solution to initiate the enzymatic reaction. The plate was gently shaked for no more than 30 s to mix the reagents completely and incubated for 15 min at 37 °C. The fluorescence intensity for each well was measured at Ex/Em = 490 nm/520 nm and expressed in relative fluorescence units (RFU) with the fluorescence intensity of substrate controls as the background. The IC_{50} values were determined by using non-linear regression analysis.

In similar fashions, the inhibitory activity of **39** against the human rennin (Anaspec, catalog 72040), cathepsin D (Enzo, catalog SE199-0025) and cathepsin E (R&D, catalog 1294-AS-010) was assayed.

4.5. In vivo evaluation

Male and female hypertensive dTGMs (19–26 g, >20 weeks) carrying both human angiotensinogen (hAOGEN) and human renin (hREN) genes were randomly divided into two groups: group of compound **1** (n = 7) and group of compounds **39** (n = 7). The mean arterial pressure (MAP) of animals was measured using a programmable sphygmomanometer BP-98A (Softron, Tokyo, Japan) by the tail-cuff method. Baseline values were recorded for 24 h prior to administration of vehicle (physiological saline). Following vehicle oral administration, mice MAP values were monitored for 24 h. After a rest of two days, mice were then administrated orally by gavages with **1** or **39** at doses of 8.5, 17.0 and 34.0 μmol/kg, respectively, and animals were also monitored for a further 24 h post-dose. The experimental interval of each dose is two days. The MAP values are reported as changes from the corresponding time-matched baseline values per hour.

4.6. Molecular dynamic modeling

The conformational search was performed in MOE software (version 2012.10, Chemical Computing Group Inc., Montreal, QC, Canada) under the MMFF94x force field. Aliskiren in the complex structure (PDB code: 2V0Z) was modified to **4** and **39**, and protonated at pH 7.0. The stochastic method was used to explore conformation space to find reasonable conformations. With restraint on the renin protein and the P_3–P_1' portions of the inhibitors, only the P_2'–P_3' portions were submitted to stochastic conformational search. To obtain conformations with lowest energy, further conformational search was performed by the LowModeMD method. Rejection limit and iteration limit were set to 100 and 10,000 with maximum energy minimization iteration at 500, respectively. The conformation with the lowest energy for each compound was chosen for further studies.

The complex structures were refined via molecular dynamic simulation in Amber software (version 9). The force field parameters of ligands derived from GAFF force field with BCC charges were obtained by Antechamber module. The AMBER FF03 force field parameters were applied. Each complex model was soaked into a periodic box of TIP3P water with a margin of 10 Å for each dimension and then Na^+ ion was added to neutralize the whole systems. During simulation, Partical Mesh Ewald (PME) with 10 Å cutoff was employed in the computation of electrostatic interactions. The Langevin thermostat with a collision frequency of 2 ps^{-1} and isotropic position scaling barostat with a pressure relaxation time of 2 ps were used. The SHAKE algorithm was used to constrain all covalent bonds connecting hydrogen atoms.

The systems were firstly minimized by 500 steps via the steepest descent method and 500 steps via the conjugate gradient method with 5 kcal/mol·Å2 restraint on the complexes. Similar 1000-step minimization was performed without restraint on the complexes. Then, the models with restraint were heated from 0 K to 300 K within 50 ps and maintained at 300 K for 50 ps by the NVT method. The systems were further equipoised over 500 ps without any restraint by the NPT method and finally run a 5 ns simulation at a constant temperature of 300 K and under a constant pressure of 1 atm. The snapshots with the lowest RMSD to the average structures in MD were retrieved from the simulation trajectories. The complexes after MD simulation were further subjected to a round of energy minimization in MOE, and then taken as the final models.

To validate the computational method, the renin-aliskiren complex structure (PDB code: 2V0Z) was refined by MD simulation. The final model gave a RMSD 1.4 Å to the alpha-carbon of protein and the interactions between the ligand and the protein kept well during the MD simulations, indicating that the MD simulation could help to refine the modeling structure for the designed inhibitors.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.08.060.

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