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2-Oxoamides based on dipeptides as selective calcium-independent phospholipase A_2 inhibitors

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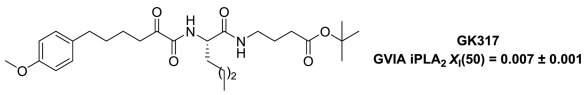
Abstract

Calcium-independent phospholipase A_2 (GVIA iPLA$_2$) has recently attracted interest as a medicinal target. The number of known GVIA iPLA$_2$ inhibitors is limited to a handful of synthetic compounds (bromoenol lactone and polyfluoroketones). To expand the chemical diversity, a variety of 2-oxoamides based on dipeptides and ether dipeptides were synthesized and studied for their in vitro inhibitory activity on human GVIA iPLA$_2$ and their selectivity over the other major intracellular GIVA cPLA$_2$ and the secreted GV sPLA$_2$. Structure-activity relationship studies revealed the first 2-oxoamide derivative (GK317), which presents potent inhibition of GVIA iPLA$_2$ (X_I(50) value of 0.007) and at the same time significant selectivity over GIVA cPLA$_2$ and GV sPLA$_2$.

Graphical Abstract



Keywords

Dipeptides; Inhibitors; Oxoamides; Phospholipase A_2; Pseudodipeptides

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1. Introduction

Phospholipases A_2 (PLA_2s) are a superfamily of enzymes characterized by their ability to hydrolyze the ester bond at the *sn*-2 position of glycerophospholipids.[1] Historically, much attention has been paid to two types of PLA_2s: the cytosolic enzymes ($cPLA_2$)[2] and the secreted enzymes ($sPLA_2$).[3] More recently in comparison to them, another group of enzymes, the Ca^{2+}-independent phospholipases A_2, designated as GVI $iPLA_2$s, has attracted growing interest and attention.[4–6] The $iPLA_2$s are intracellular enzymes that do not require Ca^{2+} either for their activity or for translocation to membranes. The GVIA $iPLA_2$ is the most widely described of the $iPLA_2$s and expression of its activity was described in P388D1 macrophage-like cells in 1994.[7] In contrast to $cPLA_2$, which exhibits a marked preference for hydrolysis of arachidonic acid from the *sn*-2 position, this enzyme does not demonstrate this substrate specificity. It is a 85 kDa protein (752 amino acids) with a serine lipase consensus sequence (GTSGT) for an Asp Ser dyad catalytic mechanism for its catalytic domain which is preceded by eight N-terminal ankyrin (Ank) repeats.[8,9]

As summarized in a recent review,[4] increased or decreased expression of $iPLA_2$s may affect the metabolic state, CNS function, cardiovascular performance and cell survival and therefore, dysregulation of $iPLA_2$s may play a critical role in the development of many diseases. Due to the involvement of PLA_2s in chronic inflammatory conditions, a variety of synthetic inhibitors have been developed.[1,10–12] Bromoenol lactone (**1**, BEL, Figure 1) is the first selective GVIA $iPLA_2$ inhibitor reported in literature.[13] It is an irreversible and covalent inhibitor and its (*R*)-and (*S*)-enantiomers present different inhibitory properties.[14] Although BEL has been widely used to inhibit $iPLA_2$ in cellular systems and in vivo, it has to keep in mind that it is able to inhibit other enzymes, like magnesium-dependent phosphatidate phosphohydrolase-1.[15] Fluoroketones FKGK11 (**2**),[16] FKGK18 (**3**)[17] and GK187 (**4**)[18] (Figure 1) constitute a very important class of selective and potent GVIA $iPLA_2$ inhibitors. These inhibitors have been used to study the role of the enzyme ex vivo and in vivo and in particular in autoimmune diseases.[19–22] FKGK11 showed strong reduction in the clinical severity and progression of experimental autoimmune encephalomyelitis.[19] Administration of FKGK18 to non-obese diabetic (NOD) mice significantly reduced diabetes incidence in association with reduced insulitis, improved glucose homeostasis, and β-cell preservation.[21] Computational studies as well as deuterium exchange mass spectrometry, shed light on the binding mode of fluoroketone inhibitors in the active site of GVIA $iPLA_2$ and the role that membranes play in the binding and hydrolysis of the phospholipid substrates.[23,24]

The aim of this work was to develop new potent and selective inhibitors of GVIA $iPLA_2$. Based on our observation that some of the 2-oxoamides we have developed as inhibitors of GIVA $cPLA_2$ presented some GVIA $iPLA_2$ inhibition, we synthesized several new 2-oxoamides based on dipeptides and pseudodipeptides and we studied their in vitro inhibitory activity on human GVIA $iPLA_2$ as well as their selectivity over GIVA $cPLA_2$ and GV $sPLA_2$.

2. Results and discussion

2.1. Design of inhibitors

Both GIVA cPLA$_2$ and GVIA iPLA$_2$ share the same catalytic mechanism utilizing serine for their catalytic action. We have developed a novel class of 2-oxoamides as inhibitors of GIVA cPLA$_2$.[25–31] 2-Oxoamides were initially designed to target the active site serine of GIVA cPLA$_2$. However, it became clear that some 2-oxoamides could also inhibit GVIA iPLA$_2$. Long chain 2-oxoamides based on γ- or δ-amino acids containing a free carboxyl group were found to be selective inhibitors of GIVA cPLA$_2$.[26,28,30,32] However, the corresponding esters inhibit both GIVA cPLA$_2$ and GVIA iPLA$_2$.[28] In particular, we have observed that some 2-oxoamides based on dipeptides or ether dipeptide analogues presented a slight preference to inhibit GVIA iPLA$_2$.[31]

To develop 2-oxoamides as selective GVIA iPLA$_2$ inhibitors, we designed compounds, where the 2-oxoamide functionality, that ensures the interaction with the active site serine, was accompanied by an aromatic group at a medium distance from the activated carbonyl and a dipeptide or a pseudodipeptide unit (Figure 2). We have shown by extended structure-activity relationship studies on polyfluoroketone derivatives that the optimum distance between the activated carbonyl and the aromatic group corresponds to four carbon atoms.[16,17] In addition, the favorable aromatic groups were either a phenyl ring, alone or with a para-methoxy substitution, or a naphthalene ring.[17,18] We envisaged that the presence of a small peptide unit could create favorable interactions with the amino acid residues of the enzyme. Our previous studies have shown that polar groups create unfavorable interactions with the residues of the GVIA iPLA$_2$ active site. Thus, we employed mainly non-polar amino acids in combination with an ester C-terminal group. The amino component of the inhibitor was initially designed to be the dipeptide Nle-Gly.

2.2. Synthesis of inhibitors

2-Hydroxy acids **8a** and **8b** were synthesized as described earlier[33] and the synthesis of **8c** is depicted in Scheme 1. The key-intermediate was the cyanohydrin **6**, which was converted to carboxylic acid under hydrolytic conditions.

The synthesis of 2-oxoamides **12a–f** based on the dipeptide Nle-Gly started by the coupling of carbobenzoxy-L-norleucine (**9**) with *tert*-butyl glycinate (Scheme 2).

After hydrogenation and coupling with 2-hydroxy acids **8a–c**, oxidation of 2-hydroxy amides **11a–c** gave the target 2-oxoamides **12a–c**. The corresponding acids **13a,b** were prepared by treatment with trifluoroacetic acid. Derivatives **12d–f** containing beta-alanine, gamma-aminobutyric acid or 5-aminovaleric acid instead of glycine were synthesized by similar procedures (Scheme 2). In addition, the ethyl ester derivative **16** was synthesized in a similar manner (Scheme 3).

The pseudodipeptides **17a,b** were used as starting materials for the synthesis of the 2-oxoamide ether analogs **19a–d** (Scheme 4), after removal of the N-protecting group and coupling with 2-hydroxy acids **8a–c**.

2-Oxoamides **25a–g** based on a variety of dipeptide *tert*-butyl esters were synthesized as shown in Scheme 5. The synthesis of additional analogs required for the structure-activity relationship studies is depicted in Schemes 6 and 7.

2.3. In vitro inhibition of GIVA cPLA$_2$, GVIA iPLA$_2$ and GV sPLA$_2$

All synthesized inhibitors were tested for inhibition of human GVIA iPLA$_2$, GIVA cPLA$_2$, and GV sPLA$_2$ using previously described mixed micelle-based assays.[26,28.30] The inhibition results are presented in Tables 1 and 2, either as percent inhibition or as $X_I(50)$ values. At first, the percent of inhibition for each PLA$_2$ enzyme at 0.091 mole fraction of each inhibitor was determined. Then, the $X_I(50)$ values were measured for compounds that displayed greater than 95% inhibition. The $X_I(50)$ is the mole fraction of the inhibitor in the total substrate interface required to inhibit the enzyme by 50%.

Initially, we studied the role of the dipeptide or dipeptide analog using as aromatic rings phenyl, p-methoxy-phenyl and naphthyl (Table 1). First of all, it is obvious that a free carboxyl group led to totally inactive compounds for GVIA iPLA$_2$ (**13a**, **13b**, **20d**). Thus, an ester group (ethyl or *tert*-butyl) was employed for the other derivatives. Comparing compounds **12a** with **19b** and **19d** with **12c**, it seems that the dipeptide unit gave better inhibitory results for GVIA iPLA$_2$ than the ether pseudodipeptide, irrespectively of which aromatic group was used. Comparing compounds **16** with **12b** and **19a** with **19d**, *tert*-butyl ester provided better results than the ethyl ester. From the results summarized in Table 1, compound **12c** stands out as for the inhibition of GVIA iPLA$_2$. It inhibited GVIA iPLA$_2$ with an $X_I(50)$ value of 0.012, while it presented only weak inhibition of GIVA cPLA$_2$ and GV sPLA$_2$. Thus, further modifications were accomplished on compound **12c**, which is based on the dipeptide Nle-Gly-OBu^t.

The results of the in vitro potency and selectivity for analogs of **12c** are summarized in Table 2. Replacement of the *tert*-butyl group of **12c** by the benzyl one (compound **31a**) reduced the inhibitory potency (from $X_I(50)$ 0.012 to $X_I(50)$ 0.026). Increase or decrease of the peptide size destroyed the activity. The 2-oxoamides based on either a single amino acid derivative, Nle-OBu^t (compound **29**), Nle-NH$_2$ (compound **27**), or a tripeptide, Nle-Gly-Gly-OBu^t (compound **33**), presented weak activity on GIVA iPLA$_2$. Replacement of Nle by other amino acids containing small aliphatic chains, such as Leu, Ile, and Val (compounds **22a–c**) was examined. Only Leu analog (**22a**) produced an interesting activity, however half potency ($X_I(50)$ 0.024) in comparison with the Nle derivative **12c**. Then, Gly was replaced by L- and D-Ala (compounds **22c** and **22d**), but again a decrease of the activity was observed. The replacement of L-Nle by D-Nle (compound **22f**) also decreased the activity. The next step was the elongation of the carbon chain of Gly keeping Nle as the first amino acid of the dipeptide.

Thus, analogs of **12c** containing beta-alanine (compound **12d**), or GABA (compound **12e**) or aminovaleric acid (compound **12f**) were tested. It was gratifying that compound **12e** (GK317) exhibited higher activity ($X_I(50)$ 0.007) in comparison to **12c**. Finally, the *tert*-butyl ester of **12e** was replaced by a benzyl one (compound **31b**) and Nle of **12e** by Leu

(compound **22g**). However, both derivatives presented reduced inhibitory activity of GVIA iPLA$_2$ in comparison to **12e**.

Taken together, we have identified a 2-oxoamide based on Nle-GABA-OBu^t, compound **12e** (GK317), which presents potent inhibition of GVIA iPLA$_2$ (X_I(50) value of 0.007). This compound was found to present weak inhibitory activity over the other major intracellular GIVA cPLA$_2$ (52.6% at 0.091 mole fraction) and the secreted GV sPLA$_2$ (44.8% at 0.091 mole fraction). The length of the chain of the C-terminal amino acid seems critical, because either increase or decrease results in reduction of the inhibitory activity on GVIA iPLA$_2$. Two commercially available inhibitors of GVIA iPLA$_2$ and GIVA cPLA$_2$ have been included in Table 2 for comparison purposes. FKGK11 selectively inhibits GVIA iPLA$_2$ [X_I(50) 0.014][17], while AACOCF$_3$ inhibits both GVIA iPLA$_2$ [X_I(50) 0.028][13] and GIVA cPLA$_2$ [X_I(50) 0.036][1].

Phospholipases A$_2$ are water-soluble enzymes acting on water-insoluble substrates that exist in aggregated form in aqueous solution. Mixed micelles and the surface dilution kinetics model were successfully used by our laboratory for assaying the enzymatic activity of these enzymes and conducting inhibitory response curves for small molecule inhibitors. As part of surface-dilution considerations, the enzyme may undergo surface binding to membranes, whereby the enzyme either associates nonspecifically with the surface of the lipid aggregate or associates specifically with a phospholipid in the aggregate's surface. Thus, a two dimensional unit such as mole fraction is more relevant for expressing the inhibitory activity of PLA$_2$ inhibitors since they will first incorporate in the aggregated substrate in order to access the enzyme active site and compete with phospholipid substrate. With this caveat, we hereby provide the effective concentrations translated to solution for the most potent iPLA$_2$ inhibitors of this series and the reference inhibitors: compound **12c** IC$_{50}$ 6.6 μM, compound **31a** IC$_{50}$ 14 μM, compound **22a** IC$_{50}$ 13 μM, compound **12e** IC$_{50}$ 3.8 μM, FKGK11 IC$_{50}$ 0.77 μM, AACOCF$_3$ IC$_{50}$ 15 μM.

3. Conclusion

In conclusion, a variety of 2-oxoamides based on dipeptides and ether dipeptides were synthesized. Structure-activity relationship studies revealed the first iPLA$_2$ selective 2-oxoamide, compound **12e** (GK317), which presents around 13 times more potent inhibition of GVIA iPLA$_2$ than of GIVA cPLA$_2$. This inhibitor has the same order of magnitude of GVIA iPLA$_2$ inhibition with our previously described fluoroketone inhibitor FKGK11 (X_I(50) 0.0014). Importantly, FKGK11 has been studied in vivo in various animal models and significant effects have been reported for its action in animal models of autoimmune diseases. Thus, we propose that the new oxoamide inhibitor GK317 may be a useful tool for studies in cells and in vivo and may serve as a lead for the development of more potent and selective oxoamide inhibitors of GVIA iPLA$_2$. The dipeptidic component of the inhibitor seems that contributes to the selectivity for GVIA iPLA$_2$.

4. Experimental section

4.1. General procedures

Merck Silica Gel 60 (70–230 or 230–400 mesh) was used for the chromatographic purification of products and Silica Gel 60 254 aluminum plates for the thin-layer chromatography (TLC). UV light and/or phosphomolybdic acid and/or ninhydrin in EtOH was employed for visualizing spots. A Büchi 530 apparatus was used to estimate melting points and they were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury at 200 MHz and 50 MHz respectively. Samples were diluted in $CDCl_3$. Chemical shifts are given in ppm, and coupling constants (*J*) in Hz. Peak multiplicities are typified as: s, singlet, d, doublet, dd, doublet of douplets, t, triplet, q, quartet and m, multiplet. Electron spray ionization (ESI) mass spectra were recorded on a Finnigan Surveyor MSQ Plus spectrometer. Specific rotations of the compounds were measured at 25 °C on a Perkin-Elmer 343 polarimeter using a 10 cm cell. Dichloromethane was dried by standard procedures and stored over molecular sieves. No further purification of other solvents and chemicals needed as they were reagent grade. HRMS spectra were recorded on a Bruker Maxis Impact QTOF Spectrometer.

Compounds **8a**, **8b** have been described elsewhere and their analytical data are in accordance with literature.[33]

4.2. Chemistry

4.2.1. 2-Hydroxy-6-(4-methoxyphenyl)hexanenitrile (6)—To a stirred solution of alcohol **5** (1.0 mmol) in toluene and EtOAc (1:1, 6.0 mL), H_2O (0.5 mL) and NaBr (0.11 g, 1.1 mmol) were added. The mixture was cooled at −5 °C and under vigorous stirring AcNH-Tempo (0.21 mg, 0.01 mmol) was added, followed by the addition of an aqueous solution of NaOCl 0.5 M (2.2 mL, 1.1 mmol) and $NaHCO_3$ (0.24 g, 3.0 mmol) within 1 h. The aqueous layer was separated and washed with EtOAc (20 mL). The combined organic layers were washed consecutively with 5% aqueous citric acid (10 mL) containing KI (0.04 g), 10% aqueous $Na_2S_2O_3$ (10 mL), and brine and dried over Na_2SO_4. The solvents were evaporated under reduced pressure and the residue was used directly to the next reaction.

To a solution of the resulting aldehyde (1.0 mmol) in CH_2Cl_2 (1.3 mL) an aqueous solution of $NaHSO_3$ (0.25 mL, 6 M) was added and a white solid was formed. The mixture was stirred for 30 min at room temperature, the organic solvent was evaporated under reduced pressure, water (1.0 mL) was added and the mixture was cooled at 0 °C. Under vigorous stirring an aqueous solution of KCN 6 M (0.25 mL, 15.0 mmol) was added dropwise. The reaction mixture was stirred for 18 h at room temperature. Then, the aqueous layer was washed with CH_2Cl_2 (10 mL) and the organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using EtOAc/petroleum ether (bp 40–60 °C) 2:8 as eluent. Yield 67%; Yellowish oil; ^{1}H NMR ($CDCl_3$): δ 7.11 (d, *J*= 8.2 Hz, 2H, arom), 6.85 (d, *J*= 8.6 Hz, 2H, arom), 4.43 (q, *J*= 6.6 Hz, 1H, CH), 3.80 (s, 3H, OCH_3), 3.58 (d, *J*= 6.6 Hz, 1H, OH), 2.60 (t, *J*= 7.0 Hz, 2H, $PhCH_2$), 1.95–1.80 (m, 2H, CH_2), 1.75–1.45 (m, 4H, $2xCH_2$); ^{13}C NMR ($CDCl_3$): δ 157.5, 134.0, 129.2, 120.0, 113.7, 61.0, 55.2, 34.8, 34.5, 30.8, 24.0; MS

(ESI) *m/z* (%): 237 ([M+NH_4]$^+$, 100); Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.01; H, 7.94; N, 6.33.

4.2.2. Methyl 2-hydroxy-6-(4-methoxyphenyl)hexanoate (7)

A solution of cyanhydrin **6** (1.0 mmol) in dry HCl/CH_3OH 6 M (0.33 mL) was stirred for 18 h at room temperature. The organic solvent was evaporated under reduced pressure and H_2O was added (1 mL) as well as K_2CO_3 for neutralizing pH. The aqueous layer was washed with EtOAc (3×15 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using EtOAc/petroleum ether (bp 40–60 °C) 2:8 as eluent. Yield 70%; Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.09 (d, *J*= 8.4 Hz, 1H, arom), 6.83 (d, *J*= 8.8 Hz, 1H, arom), 4.19 (q, *J*= 5.2 Hz, 1H, CH), 3.79 (s, 3H, $PhOCH_3$), 3.77 (s, 3H, $COOCH_3$), 2.77 (d, *J*= 5.6 Hz, 1H, OH), 2.57 (t, *J* = 7.2 Hz, 2H, $PhCH_2$), 1.90–1.40 (m, 6H, 3xCH_2); ^{13}C NMR ($CDCl_3$): δ 175.7, 157.6, 134.4, 129.2, 113.6, 70.3, 55.2, 52.5, 34.8, 34.2, 31.4, 24.4; MS (ESI) *m/z* (%): 270 ([M+NH_4]$^+$, 100); Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.42; H, 8.05.

4.2.3. 2-Hydroxy-6-(4-methoxyphenyl)hexanoic acid (8c)—To a stirred solution of a methyl ester **7** (1.0 mmol) in methanol (10 mL), 1 M NaOH (1.5 mmol) was added and the mixture was left overnight at room temperature. After the completion of the reaction, methanol was evaporated under reduced pressure, water (10 mL) was added and the mixture was acidified with 1 M HCl to pH 1. The aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. Yield 96%; White solid; mp 94–96°C; ^{1}H NMR ($CDCl_3$): δ 7.10 (d, *J*= 8.4 Hz, 2H, arom), 6.83 (d, *J*= 8.8 Hz, 2H, arom), 4.35–4.20 (m, 1H, CH), 3.79 (s, 3H, OCH_3), 5.65–2.50 (m, 2H, C*H*$_2$CH), 2.00 – 1.40 (m, 7H, 3xCH_2, OH);); ^{13}C NMR ($CDCl_3$): δ 179.8, 157.6, 134.4, 129.2, 113.7, 70.1, 55.2, 34.7, 33.9, 31.3, 24.4; MS (ESI) *m/z* (%): 237 ([M−H]$^-$, 100); Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.32; H, 7.78.

4.2.4. Coupling method

To a stirred solution of the amino component (1.0 mmol) in CH_2Cl_2 (10.0 mL) cooled at 0 °C, Et_3N (0.3 mL, 2.2 mmol) and subsequently 1-(3-dimethyl-aminopropyl)-3-ethyl carbodiimide hydrochloride (WSCI.HCl) (0.21 g, 1.1 mmol) and 1-hydroxybenzotriazole (HOBt) (0.14 g, 1.0 mmol) were added. The acid component (1.0 mmol) was added and the reaction mixture was stirred for 1 h at 0 °C and then overnight at room temperature. After the completion of the reaction, the solvent was evaporated under reduced pressure and EtOAc (20 mL) was added. The organic layer was washed consecutively with brine, 5% citric acid, brine, 5% $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated under reduced pressure. Purification by column chromatography eluting with the appropriate mixture of EtOAc/petroleum ether (bp 40–60 °C) afforded the product.

4.2.4.1 *tert*-Butyl (*S*)-(2-(((benzyloxy)carbonyl)amino)hexanoyl)glycinate (10a)—Yield 62%; Yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.39–7.28 (m, 5H, arom), 6.70 (br s, 1H, NHCO), 5.47 (d, *J*= 7.4 Hz, 1H, OCONH), 5.09 (s, 2H, $PhCH_2$), 4.20–4.03 (m, 1H, CH),

3.97–3.92 (m, 2H, CH_2), 1.80–1.50 (m, 2H, CHC*H*$_2$), 1.44 [s, 9H, $C(CH_3)_3$], 1.35–1.22 (m, 4H, 2xCH_2), 0.88 (t, *J*= 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 172.3, 169.8, 156.2, 136.3, 128.6, 128.1, 128.0, 81.2, 66.9, 56.8, 41.3, 34.9, 31.9, 28.3, 25.7, 22.4, 13.9; MS (ESI) *m/z* (%): 377 ([M−H]$^-$, 100); Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.12; H, 8.13; N, 7.35.

4.2.4.2 (*S*)-*tert*-Butyl 3-(2(((benzyloxy)carbonyl)amino) hexanamido)propanoate (10b)—Yield 46%; Yellow oil; $[\alpha]_D^{20}$ −7.2 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.41–7.28 (m, 5H, arom), 6.65–6.45 (m, 1H, NHCO), 5.39 (d, *J*= 7.4 Hz, 1H, OCONH), 5.10 (s, 2H, $PhCH_2$), 4.20–4.00 (m, 1H, CH), 3.57–3.38 (m, 2H, NHC*H*$_2$), 2.43 (t, *J*= 6.0 Hz, 2H, CH_2COOBu^t), 1.80–1.50 (m, 2H, CHC*H*$_2$), 1.45 [s, 9H, $C(CH_3)_3$], 1.35–1.22 (m, 4H, 2xCH_2), 0.88 (t, *J*= 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 171.7, 171.6, 156.0, 136.2, 128.5, 128.1, 128.0, 81.1, 66.9, 55.0, 35.0, 34.9, 32.6, 28.1, 27.4, 22.4, 13.9; MS (ESI) *m/z* (%): 391 ([M−H]$^-$, 100); Anal. Calcd for $C_{21}H_{32}N_2O_5$: C, 64.26; H, 8.22; N, 7.14. Found: C, 64.08; H, 8.44; N, 7.01.

4.2.4.3 (*S*)-*tert*-Butyl 4-(2-(((benzyloxy)carbonyl)amino)hexanamido)butanoate (10c)—Yield 70%; Pink-brown solid; mp 57–59 °C; $[\alpha]_D^{20}$ −2.9 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.35–7.28 (m, 5H, arom), 6.75 (br s, 1H, NHCO), 5.69 (d, *J*= 8.4 Hz, 1H, OCONH), 5.07 (s, 2H, $PhCH_2$), 4.20–4.10 (m, 1H, CH), 3.32–3.15 (m, 2H, NHC*H*$_2$), 2.23 (t, *J*= 7.2 Hz, 2H, CH_2COOBu^t), 1.83–1.55 (m, 4H, $CH_2CH_2COOBu^t$, CHC*H*$_2$), 1.41 [s, 9H, $C(CH_3)_3$], 1.35–1.24 (m, 4H, 2xCH_2), 0.85 (t, *J*= 6.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 172.9, 172.2, 156.4, 136.5, 128.7, 128.3, 128.2, 80.8, 67.1, 55.3, 39.1, 33.0, 32.9, 28.3, 27.8, 24.8, 22.6, 14.1; MS (ESI) *m/z* (%): 405 ([M−H]$^-$, 100); Anal. Calcd for $C_{22}H_{34}N_2O_5$: C, 65.00; H, 8.43; N, 6.89. Found: C, 64.87; H, 8.56; N, 6.78.

4.2.4.4. (*S*)-*tert*-Butyl 5-(2-(benzyloxycarbonylamino)hexanamido)pentanoate (10d)—Yield 60%; Yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.44-7.15 (m, 5H, arom), 6.66-6.41 (m, 1H, NHCO), 5.61 (d, *J* = 8.2 Hz, 1H, OCONH), 5.05 (s, 2H, CH_2), 4.24-3.95 (m, 1H, CH), 3.34-3.00 (m, 2H, CH_2), 2.32-2.03 (m, 2H, CH_2), 1.90-1.11 [m, 19H, 5×CH_2, $C(CH_3)_3$], 0.95-0.71 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 172.8, 171.8, 156.1, 136.1, 128.4, 128.0, 127.9, 80.2, 66.8, 55.0, 38.9, 34.8, 32.5, 28.7, 28.0, 27.5, 23.7, 22.3, 13.8; MS (ESI) *m/z* (%): 419 ([M−H]$^-$, 100); Anal. Calcd for $C_{23}H_{36}N_2O_5$: C, 65.69; H, 8.63; N, 6.66. Found: C, 65.43; H, 8.79; N, 6.54.

4.2.4.5. *tert*-Butyl 2-((2*S*)-2-(2-hydroxy-6-phenylhexanamido)hexanamido)acetate (mixture of diastereomers) (11a)— Yield 66%; Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.53–7.03 (m, 6H, arom, NH), 6.95–6.78 (m, 1H, NH), 4.58–4.41 (m, 1H, CH), 4.19-4.06 (m, 1H, CH), 4.02–3.76 (m, 2H, CH_2), 3.48 (br s, 1H, OH), 2.61 (t, *J* = 7.2 Hz, 2H, $PhCH_2$), 1.99–1.19 [m, 21H, 6xCH_2, $C(CH_3)_3$], 0.89 (t, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 174.4, 174.1, 171.9, 171.6, 168.8, 168.6, 142.4, 128.3, 128.2, 125.7, 82.5, 82.0, 71.9, 52.6, 52.8, 42.0, 35.8, 35.7, 34.5, 34.7, 31.8, 31.9, 31.2, 28.0, 27.6, 24.7, 24.6, 22.3, 22.4, 13.9; MS (ESI) *m/z* (%): 435 ([M+H]$^+$, 75); Anal Calcd for $C_{24}H_{38}N_2O_5$: C, 66.33; H, 8.81; N, 6.45. Found: C, 66.09; H, 8.92; N, 6.32.

4.2.4.6. *tert*-Butyl 2-((2*S*)-2-(2-hydroxy-6-(naphthalen-2-yl)hexanamido)hexanamido)acetate (mixture of diastereomers) (11b)—Yield 47%; Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.80–7.23 (m, 8H, arom, NH), 7.15–6.99 (m, 1H, NH), 4.63–4.40 (m, 1H, CH), 4.23-4.06 (m, 1H, CH), 4.02–3.75 (m, 2H, CH_2NH), 2.76 (t, *J*= 7.6 Hz, 2H, $PhCH_2$), 2.02–1.18 [m, 21H, 6xCH_2, $C(CH_3)_3$], 0.88 (t, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 174.5, 174.8, 172.0, 172.3, 168.7, 168.6, 139.9, 133.5, 131.8, 127.7, 127.5, 127.3, 127.2, 126.2, 125.8, 125.0, 82.3, 72.0, 71.9, 52.7, 52.5, 41.9, 35.8, 34.6, 32.0, 31.1, 27.9, 27.5, 24.7, 22.3, 22.2, 13.9; MS (ESI) *m/z* (%): 485 ($[M+H]^+$, 100); Anal Calcd for $C_{28}H_{40}N_2O_5$: C, 69.39; H, 8.32; N, 5.78. Found: C, 69.24; H, 8.44; N, 5.60.

4.2.4.7. *tert*-Butyl 2-((2*S*)-2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)hexanamido)acetate (mixture of diastereomers) (11c)—Yield 81%; Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.26–7.13 (m, 1H, NH), 7.07 (d, *J*= 8.4 Hz, 2H, arom), 6.95–6.85 (m, 1H, NH), 6.81 (d, *J*= 8.6 Hz, 2H, arom), 4.57–4.41 (m, 1H, CH), 4.19–4.05 (m, 1H, CH), 4.00–3.93 (m, 1H, OH), 3.89 (d, *J*= 5.2 Hz, 2H, CH_2COOBu^t), 3.78 (s, 3H, CH_3O), 2.55 (t, *J*= 7.6 Hz, 2H, $PhCH_2$), 1.95–1.49 (m, 6H, 3xCH_2), 1.46 [s, 9H, $C(CH_3)_3$], 1.39–1.21 (m, 6H, 3xCH_2), 0.89 (t, *J*= 6.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 174.6, 174.3, 172.2, 171.9, 168.7, 168.6, 157.6, 134.5, 129.2, 113.6, 82.4, 72.1, 55.2, 52.7, 52.6, 42.0, 34.7, 34.6, 32.0, 31.4, 28.0, 27.6, 24.7, 22.3, 13.9; MS (ESI) *m/z* (%): 463 ($[M-H]^-$, 100); Anal Calcd for $C_{25}H_{40}N_2O_6$: C, 64.63; H, 8.68; N, 6.03. Found: C, 64.45; H, 8.79; N, 5.91.

4.2.4.8. *tert*-Butyl 3-((2*S*)-2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)hexanamido)propanoate (mixture of diastereomers) (11d)—Yield 57%; Yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.21–7.12 (m, 1H, NH), 7.07 (d, *J*= 8.6 Hz, 2H, arom), 6.81 (d, *J*= 8.6 Hz, 2H, arom), 4.45–4.28 (m, 1H, CH), 4.17–4.04 (m, 1H, CH), 3.78 (s, 3H, CH_3O), 3.52–3.35 (m, 2H, NHC*H*$_2$), 2.55 (t, *J*= 7.4 Hz, 2H, $PhCH_2$), 2.43 (t, *J*= 6.4 Hz, 2H, CH_2COOBu^t), 1.91–1.48 (m, 6H, 3xCH_2), 1.45 [s, 9H, $C(CH_3)_3$], 1.36–1.16 (m, 6H, 3xCH_2), 0.88 (t, *J*= 6.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 174.3, 174.1, 171.7, 171.5, 157.6, 134.5, 129.2, 113.6, 81.3, 71.9, 55.2, 52.7, 35.1, 34.8, 34.5, 32.3, 31.4, 29.7, 28.1, 27.5, 24.7, 22.3, 13.9; MS (ESI) *m/z* (%): 477 ($[M-H]^-$, 100); Anal Calcd for $C_{26}H_{42}N_2O_6$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.01; H, 8.98; N, 5.72.

4.2.4.9. *tert*-Butyl 4-((2*S*)-2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)hexanamido)butanoate (mixture of diastereomers) (11e)—Yield 37%; Yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.26–7.16 (m, 1H, NH), 7.07 (d, *J*= 8.2 Hz, 2H, arom), 6.99–6.87 (m, 1H, NH), 6.81 (d, *J*= 8.4 Hz, 2H, arom), 4.49–4.29 (m, 1H, CH), 4.17–4.03 (m, 1H, CH), 3.78 (s, 3H, CH_3O), 3.36–3.11 (m, 2H, NHC*H*$_2$), 2.55 (t, *J*= 7.6 Hz, 2H, $PhCH_2$), 2.25 (t, *J*= 7.2 Hz, 2H, CH_2COOBu^t), 1.90–1.47 (m, 8H, 4xCH_2), 1.43 [s, 9H, $C(CH_3)_3$], 1.35–1.18 (m, 6H, 3xCH_2), 0.88 (t, *J*= 6.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 174.6, 174.3, 173.0, 172.7, 172.0, 171.7, 157.6, 134.4, 129.2, 113.6, 80.7, 71.9, 55.2, 52.9, 39.0, 34.8, 32.9, 32.1, 31.5, 29.7, 28.0, 27.7, 25.9, 24.7, 22.4, 13.9; MS (ESI) *m/z* (%): 493 ($[M+H]^+$, 100); Anal Calcd for $C_{27}H_{44}N_2O_6$: C, 65.83; H, 9.00; N, 5.69. Found: C, 65.68; H, 9.22; N, 5.56.

4.2.4.10. *tert*-Butyl 5-((2*S*)-2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)hexanamido)pentanoate (mixture of diastereomers) (11f)—Yield 37%; Yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.70-7.29 (m, 2H, 2×NHCO), 7.06 (d, *J* = 8.2 Hz, 2H, arom), 6.79 (d, *J* = 8.2 Hz, 2H, arom), 4.49-4.27 (m, 1H, CH), 4.19-3.98 (m, 1H, CH), 3.76 (s, 3H, CH_3O), 3.31-3.01 (m, 2H, NH*CH*$_2$), 2.63-2.37 (m, 2H, $PhCH_2$), 2.29-2.06 (m, 2H, CH_2), 1.93-1.71 (m, 2H, CH_2), 1.70-1.06 [m, 23H, $C(CH_3)_3$, 7×CH_2], 0.87 (t, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 174.9, 173.2, 172.0, 157.5, 134.5, 129.1, 113.6, 80.4, 71.9, 55.1, 52.6, 39.0, 34.8, 34.5, 31.8, 31.4, 28.6, 28.0, 27.6, 24.7, 22.3, 21.9, 13.8; MS (ESI) *m/z* (%): 507 ([M+H]$^+$, 100); Anal Calcd for $C_{28}H_{46}N_2O_6$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.04; H, 9.34; N, 5.42.

4.2.4.11. Ethyl 2-((2*S*)-2-(2-hydroxy-6-(naphthalen-2-yl)hexanamido)hexanamido)acetate (mixture of diastereomers) (15)—Yield 42%; Whitish oil; ^{1}H NMR ($CDCl_3$): δ 7.83–6.77 (m, 9H, 2xNH, arom), 4.57–4.34 (m, 1H, CH), 4.26–4.06 (m, 3H, $COOCH_2$, CH), 3.97 (d, *J* = 5.0 Hz, 2H, NHC*H*$_2$), 2.78 (t, *J* = 7.4 Hz, 2H, $PhCH_2$), 2.02–1.41 (m, 8H, 4xCH_2), 1.39–1.17 (m, 7H, 2xCH_2, CH_3), 0.89 (t, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (CDCl): δ 174.9, 172.3, 169.7, 139.9, 133.5, 131.8, 127.7, 127.5, 127.3, 127.2, 126.2, 125.8, 125.0, 72.0, 61.5, 41.2, 35.8, 34.4, 33.7, 31.0, 27.5, 24.7, 22.3, 14.0, 13.9; MS (ESI) *m/z* (%): 457 ([M+H]$^+$, 100); Anal Calcd for $C_{26}H_{36}N_2O_5$: C, 68.40; H, 7.95; N, 6.14. Found: C, 68.29; H, 8.06; N, 6.01.

4.2.4.12. Ethyl 2-(((2*S*)-2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)hexyl)oxy)acetate (mixture of diastereomers) (18a)—Yield 19%; Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.09 (d, *J*= 8.4Hz, 2H, arom), 6.91 (d, *J*= 8.6 Hz, 1H, NH), 6.82 (d, *J*= 8.0 Hz, 2H, arom), 4.20 (q, *J*= 6.6 Hz, 2H, OC*H*$_2$$CH_3$), 4.15–3.95 (m, 4H, 2xCH, OCH_2CO), 3.78 (s, 3H, CH_3O), 3.65 (dd, J_1= 9.2 Hz, J_2= 3.4 Hz, 1H, C*H*HO), 3.46 (dd, J_1= 10.4 Hz, J_2= 3.4 Hz, CH*H*O), 2.56 (t, *J*= 7.2 Hz, 2H, $PhCH_2$), 1.82–1.75 (br s, 1H, OH), 1.70–1.48 (m, 6H, 3xCH_2), 1.21 (t, 3H, OCH_2C*H*$_3$), 1.48–1.10 (m, 6H, 3xCH_2); ^{13}C NMR ($CDCl_3$): δ 173.6, 170.9, 157.6, 134.5, 129.2, 113.6, 73.1, 71.7, 68.1, 61.0, 55.2, 49.0, 34.9, 34.8, 31.5, 31.1, 30.3, 29.7, 28.2, 24.5, 22.5, 14.1, 14.0; MS (ESI) *m/z* (%): 424 ([M+H]$^+$, 100); Anal Calcd for $C_{23}H_{37}NO_6$: C, 65.22; H, 8.81; N, 3.31. Found: C, 65.02; H, 8.99; N, 3.23.

4.2.4.13. *tert*-Butyl 2-(((2*S*)-2-(2-hydroxy-6-phenylhexanamido)hexyl)oxy)acetate (mixture of diastereomers) (18b)—Yield 53%; Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.37–6.76 (m, 6H, NH, arom), 4.15–3.78 (m, 4H, OCH_2CO, 2xCH), 3.61 (dd, J_1 = 9.4 Hz, J_2 = 3.6 Hz, 1H, CHC*H*HO), 3.41 (dd, J_1 = 9.4 Hz, J_2 = 3.4 Hz, 1H, CHCH*H*O), 2.60 (t, *J* = 7.2 Hz, 2H, $PhCH_2$), 1.98–1.04 (m, 21H, 6xCH_2, $C(CH_3)_3$), 0.87 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 174.1, 170.2, 142.5, 128.3, 128.2, 125.5, 82.8, 73.1, 72.0, 68.4, 48.7, 35.8, 34.6, 31.3, 30.9, 28.2, 28.0, 24.7, 22.5, 14.0; MS (ESI) *m/z* (%): 422 ([M+H]$^+$, 100); Anal Calcd for $C_{24}H_{39}NO_5$: C, 68.38; H, 9.32; N, 3.32. Found: C, 68.15; H, 9.47; N, 3.28.

4.2.4.14 *tert*-Butyl 2-(((2*S*)-2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)hexyl)oxy)acetate (mixture of diastereomers)

(18c)—Yield 67%; Yellowish oil; ^{1}H NMR ($CDCl_3$): δ 7.15–7.04 (m, 1H, NH), 7.06 (d, *J*= 8.6 Hz, 2H, arom), 6.79 (d, *J*= 8.6 Hz, 2H, arom), 4.20–3.95 (m, 2H, 2xCH), 3.93 (s, 2H, OCH_2CO), 3.76 (s, 3H, CH_3O), 3.60 (dd, J_1= 9.6 Hz, J_2= 3.6 Hz, 1H, CHC*H*HO), 3.50 (dd, J_1= 10.8 Hz, J_2= 4.0 Hz, 1H, CHCH*H*O), 2.54 (t, *J*= 7.2 Hz, 2H, $PhCH_2$), 2.44 (br s, 1H, OH), 1.95–1.50 (m, 6H, 3xCH_2), 1.45 [s, 9H, $C(CH_3)_3$], 1.40–1.20 (m, 6H, 3xCH_2), 0.88 (t, *J*= 6.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 174.1, 173.9, 170.1, 170.0, 157.4, 134.6, 134.5, 129.1, 125.4, 113.5, 82.1, 82.0, 73.0, 72.0, 71.6, 68.5, 68.3, 55.1, 48.8, 48.5, 34.8, 34.5, 30.1, 29.6, 31.5, 30.9, 29.5, 28.1, 28.0, 24.6, 24.4, 22.4, 13.9; MS (ESI) *m/z* (%): 452 ([M+H]$^+$, 100); Anal Calcd for $C_{25}H_{41}NO_6$: C, 66.49; H, 9.15; N, 3.10. Found: C, 66.21; H, 9.31; N, 3.02.

4.2.4.15 *tert*-Butyl 2-((2*S*)-2-(2-hydroxy-6-(naphthalen-2-yl)hexanamido)hexyl)oxy)acetate (mixture of diastereomers) (18d)—Yield 69%; Yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.91–7.18 (m, 7H, arom), 7.01 (brs, 1H, NH), 4.23–3.77 (m, 4H, 2xCH, CH_2COO), 3.70–3.32 (m, 2H, CH_2O), 2.79 (t, *J*= 6.6 Hz, 2H, $PhCH_2$), 2.01–1.04 [m, 21H, 6xCH_2, $C(CH_3)_3$], 0.89 (t, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 179.6, 170.4, 140.0, 133.6, 131.9, 127.8, 127.7, 127.6, 127.4, 126.3, 125.8, 125.0, 82.1, 73.1, 72.1, 68.3, 49.1, 48.9, 35.9, 31.1, 31.0, 28.2, 28.0, 24.7, 24.6, 22.5, 14.0; MS (ESI) *m/z* (%): 472 ([M+H]$^+$, 100); Anal Calcd for $C_{28}H_{41}NO_5$: C, 71.31; H, 8.76; N, 2.97. Found: C, 71.12; H, 8.84; N, 2.93.

4.2.4.16. (*S*)-*tert*-Butyl 2-(2-(((benzyloxy)carbonyl)amino)-4-methylpentanamido)acetate (23a)—Yield 80%; Yellowish oil; $[\alpha]_D^{20}$ −16.1 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.32–7.18 (m, 5H, arom), 7.13 (t, *J*=5.0 Hz, 1H, NHCO), 5.97 (d, *J*= 8.6 Hz, 1H, OCONH), 5.01 (q, *J*= 8.4 Hz, 2H, $PhCH_2$), 4.39–4.22 (m, 1H, CH), 3.82 (dd, J_1= 2.6Hz, J_2= 5.2 Hz, 2H, CH_2COOBu^t), 1.70–1.47 (m, 3H, $CHCH_2$), 0.86 (d, *J*= 5.8 Hz, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 172.7, 168.7, 156.2, 136.0, 128.2, 127.8, 127.7, 81.8, 66.6, 41.6, 41.2, 27.7, 24.3, 22.8, 21.5; MS (ESI) *m/z* (%): 379 ([M+H]$^+$, 100); Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.29; H, 8.17; N, 7.32.

4.2.4.17. *tert*-Butyl 2-((2*S*,3*R*)-2-(((benzyloxy)carbonyl)amino)-3-methylpentanamido)acetate (23b)—Yield 78%; White solid; mp 133–135 °C; $[\alpha]_D^{20}$ −2.5 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.41–7.23 (m, 5H, arom), 6.76 (t, *J*= 4.6 Hz, 1H, NHCO), 5.65 (d, *J*= 9.0 Hz, 1H, OCONH), 5.16–4.98 (m, 2H, $PhCH_2$), 4.19–4.08 (m, 1H, CH), 3.91 (dd, J_1= 5.0 Hz, J_2= 8.6 Hz, 2H, CH_2COOBu^t), 1.97–1.76 (m, 1H, CH), 1.45 [s, 9H, $C(CH_3)_3$], 1.30–0.99 (m, 2H, CH_2), 0.95–0.79 (m, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 171.4, 168.6, 156.3, 136.1, 128.4, 128.0, 127.9, 82.2, 66.9, 59.5, 41.9, 37.3, 27.9, 24.6, 15.4, 11.3; MS (ESI) *m/z* (%): 379 ([M+H]$^+$, 100); Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.29; H, 8.12; N, 7.31.

4.2.4.18. (*S*)-*tert*-Butyl 2-(2-(((benzyloxy)carbonyl)amino)-3-methylbutanamido)acetate (23c)—Yield 57%; White solid; mp 145–148 °C; $[\alpha]_D^{20}$ −5.3 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.44–7.20 (m, 5H, arom), 6.82 (br s, 1H, NHCO), 5.69 (d, *J*= 9.0 Hz, 1H, OCONH), 5.17–5.00 (m, 2H, $PhCH_2$), 4.19–4.05 (m, 1H, CH), 3.91 (dd, J_1= 5.4 Hz, J_2= 13.2 Hz, 2H, CH_2COOBu^t), 2.21–2.03 (m, 1H, CH), 1.45 [s,

9H, $C(CH_3)_3$], 0.97 (d, *J*= 6.8 Hz, 3H, CH_3), 0.93 (d, *J*= 6.8 Hz, 3H, CH_3); $_{13}$C NMR ($CDCl_3$): δ 171.4, 169.6, 156.4, 136.1, 128.4, 128.0, 127.9, 82.2, 66.9, 60.1, 41.8, 31.0, 27.9, 19.2, 17.7; MS (ESI) *m/z* (%): 365 ($[M+H]^+$, 100); Anal. Calcd for $C_{19}H_{28}N_2O_5$: C, 62.62; H, 7.74; N, 7.69. Found: C, 62.44; H, 7.81; N, 7.59.

4.2.4.19. (*S*)-*tert*-Butyl 2-((*S*)-2-(((benzyloxy)carbonyl)amino)hexanamido)propanoate (23d)—Yield 72%; White solid; mp 91–93 °C; ^{1}H NMR ($CDCl_3$): δ 7.42–7.28 (m, 5H, arom), 6.50 (d, *J*= 7.2 Hz, 1H, NHCO), 5.36 (d, *J*= 7.8 Hz, 1H, OCONH), 5.12 (s, 2H, $PhCH_2$), 4.55–4.35 (m, 1H, $CHCOOBu^t$), 4.25–4.06 (m, 1H, CH), 1.95–1.22 [m, 18H, 3xCH_2, $C(CH_3)_3$, $CHCH_3$], 0.89 (t, *J*= 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 171.8, 171.1, 156.4, 136.01, 128.5, 128.1, 128.0, 82.1, 66.9, 54.9, 48.6, 32.6, 27.9, 27.4, 22.4, 18.5, 13.9; MS (ESI) *m/z* (%): 393 ($[M+H]^+$, 80); Anal. Calcd for $C_{21}H_{32}N_2O_5$: C, 64.26; H, 8.22; N, 7.14. Found: C, 64.01; H, 8.37; N, 7.06.

4.2.4.20. (*R*)-*tert*-Butyl 2-((*S*)-2-(((benzyloxy)carbonyl)amino)hexanamido)propanoate (23e)—Yield 36%; White solid; mp 80–82 °C; ^{1}H NMR ($CDCl_3$): δ 7.40–7.22 (m, 5H, arom), 6.76 (d, *J*= 5.2 Hz, 1H, NHCO), 5.56 (d, *J*= 6.6 Hz, 1H, OCONH), 5.09 (s, 2H, $PhCH_2$), 4.53–4.34 (m, 1H, $CHCOOBu^t$), 4.30–4.09 (m, 1H, CH), 1.95–1.52 (m, 2H, CH_2), 1.44 [s, 9H, $C(CH_3)_3$], 1.32–1.20 (m, 4H, 2xCH_2), 0.86 (t, *J*= 6.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 171.9, 171.1, 156.1, 136.1, 128.4, 128.0, 127.9, 82.0, 66.8, 54.8, 48.5, 32.4, 27.8, 27.4, 22.3, 18.4, 13.8; MS (ESI) *m/z* (%): 393 ($[M+H]^+$, 75); Anal. Calcd for $C_{21}H_{32}N_2O_5$: C, 64.26; H, 8.22; N, 7.14. Found: C, 64.03; H, 8.39; N, 7.05.

4.2.4.21. (*R*)-*tert*-Butyl 2-(2-(((benzyloxy)carbonyl)amino)hexanamido) acetate (23f)—Yield 66%; White solid; mp 84–85 °C; $[\alpha]_D^{20}$ 9.2 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 5H, arom), 6.75 (br s, 1H, NHCO), 5.60 (d, *J*= 8.2 Hz, 1H, OCONH), 5.17–5.00 (m, 2H, $PhCH_2$), 4.30–4.13 (m, 1H, CH), 3.89 (d, *J*= 5.0 Hz, 2H, CH_2COOBu^t), 1.93–1.47 (m, 2H, $CHCH_2$), 1.44 [s, 9H, $C(CH_3)_3$], 1.35–1.17 (m, 4H, 2xCH_2), 0.86 (t, *J*= 6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 172.0, 168.7, 156.1, 136.1, 128.4, 128.1, 128.0, 82.2, 66.9, 54.8, 41.8, 32.4, 27.9, 27.5, 22.3, 13.8; MS (ESI) *m/z* (%): 379 ($[M+H]^+$, 78); Anal calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.32; H, 8.05; N, 7.30.

4.2.4.22. (*S*)-*tert*-Butyl 4-(2-(benzyloxycarbonylamino)-4-methylpentanamido)butanoate (23g)—Yield 60%; Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.34-7.18 (m, 5H, arom), 6.66-6.41 (t, *J* = 4.6 Hz, 1H, NHCO), 5.83 (d, *J* = 8.4 Hz, 1H, OCONH), 5.13-4.88 (m, 2H, PhCH2), 4.26-4.05 (m, 1H, CH), 3.33-3.00 (m, 2H, CH_2), 2.17 (t, *J* = 7.2 Hz, 2H, CH_2), 1.81-1.37 [m, 14H, $C(CH_3)_3$, 2×CH_2, CH), 0.85 (d, *J* = 6.8 Hz, 6H, 2×CH_3); ^{13}C NMR ($CDCl_3$): δ 172.5, 169.0, 156.2, 136.1, 128.3, 128.2, 127.9, 80.3, 66.7, 53.4, 41.4, 38.7, 32.6, 27.9, 24.5, 22.7, 21.8; MS (ESI) *m/z* (%): 407 ($[M+H]^+$, 85); Anal calcd for $C_{22}H_{34}N_2O_5$: C, 65.00; H, 8.43; N, 6.89. Found: C, C, 64.75; H, 8.61; N, 6.78.

4.2.4.23. *tert*-Butyl 2-((2*S*)-2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)-4-methylpentanamido)acetate (mixture of diastereomers) (24a)—Yield 66%;

Yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.33 (d, *J*= 8.8 Hz, 1H, NHCO), 7.18 (t, *J*= 5.2 Hz, 1H, NHCO), 7.06 (d, *J*= 8.6 Hz, 2H, arom), 6.80 (d, *J*= 8.4 Hz, 2H, arom), 4.64–4.49 (m, 1H, CH), 4.16–4.05 (m, 1H, CH), 3.87 (t, *J*= 4.8 Hz, 2H, CH_2COOBu^t), 3.77 (s, 3H, CH_3O), 2.77 (br s, 1H, OH), 2.53 (t, *J*= 7.6 Hz, 2H, $PhCH_2$), 1.98–1.35 (m, 9H, 4xCH_2, CH), 1.44 [s, 9H, $C(CH_3)_3$], 0.91 (t, *J*= 5.6 Hz, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 174.8, 174.6, 172.7, 172.4, 168.8, 168.6, 157.4, 134.4, 129.1, 113.5, 82.3, 55.1, 51.1, 41.9, 40.9, 34.8, 31.5, 27.9, 24.6, 22.9, 21.8; MS (ESI) *m/z* (%): 465 ($[M+H]^+$, 100); Anal Calcd for $C_{25}H_{40}N_2O_6$: C, 64.63; H, 8.68; N, 6.03. Found: C, 64.49; H, 8.79; N, 5.95.

4.2.4.24. *tert*-Butyl 2-((2*S*,3*R*)-2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)-3-methylpentanamido)acetate (mixture of diastereomers) (24b)—

Yield 90%; Yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.43 (dd, J_1=3.4 Hz, J_2= 9.2 Hz, 1H, NHCO), 7.19 (t, *J*= 5.0 Hz, 1H, NHCO), 7.06 (d, *J*= 8.6 Hz, 2H, arom), 6.79 (d, *J*= 8.2 Hz, 2H, arom), 4.67 (br s, ½H, OH), 4.47–4.35 (m, 1H, CH), 4.27 (br s, ½H, OH), 4.17–4.07 (m, 1H, CH), 4.05–3.80 (m, *J*= 4.8 Hz, 2H, CH_2COOBu^t), 3.76 (s, 3H, CH_3O), 2.53 (t, *J*= 7.4 Hz, 2H, $PhCH_2$), 1.98–1.46 (m, 6H, 3xCH_2), 1.44 [s, 9H, $C(CH_3)_3$], 1.28–1.01 (m, 2H, CH_2), 0.98–0.79 (m, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 174.7, 174.5, 171.8, 171.5, 168.5, 157.4, 134.5, 129.1, 113.5, 82.2, 72.0, 57.2, 55.1, 41.9, 36.9, 34.8, 34.6, 31.5, 27.9, 24.6, 15.4, 15.3, 11.1; MS (ESI) *m/z* (%): 465 ($[M+H]^+$, 100); Anal Calcd for $C_{25}H_{40}N_2O_6$: C, 64.63; H, 8.68; N, 6.03. Found: C, 64.47; H, 8.81; N, 5.92.

4.2.4.25. *tert*-Butyl 2-((2*S*)-2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)-3-methylbutanamido)acetate (mixture of diastereomers) (24c)—

Yield 68%; Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.52–7.28 (m, 2H, 2xNHCO), 7.05 (d, *J*= 8.6 Hz, 2H, arom), 6.79 (d, *J*= 8.4 Hz, 2H, arom), 4.45–4.32 (m, 1H, CH), 4.17–4.06 (m, 1H, CH), 4.06–3.78 (m, 2H, CH_2COOBu^t), 3.76 (s, 3H, CH_3O), 2.84 (br s, 1H, OH), 2.52 (t, *J*= 7.0 Hz, 2H, $PhCH_2$), 1.96–1.26 (m, 6H, 3xCH_2), 1.44 [s, 9H, $C(CH_3)_3$], 1.04–0.80 (m, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 174.8, 174.7, 171.8, 171.6, 168.5, 157.4, 134.5, 129.1, 113.5, 82.1, 71.8, 57.9, 57.7, 55.1, 41.9, 34.8, 31.5, 30.9, 27.9, 24.6, 19.2, 18.1; MS (ESI) *m/z* (%): 451 ($[M+H]^+$, 100); Anal Calcd for $C_{24}H_{38}N_2O_6$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.79; H, 8.72; N, 6.09.

4.2.4.26. (2*S*)-*tert*-Butyl 2-((2*S*)-2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)hexanamido)propanoate (mixture of diastereomers) (24d)—

Yield 68%; Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.18 (d, *J*= 8.4 Hz, 1H, NHCO), 7.06 (d, *J*= 8.6 Hz, 2H, arom), 6.85–6.70 [(m, 3H, 2xarom, NHCO)], 4.49–4.29 (m, 2H, 2xCH), 4.16–4.04 (m, 1H, CH), 3.83 (br s, 1H, OH), 3.76 (s, 3H, CH_3O), 2.53 (t, *J*= 7.6 Hz, 2H, $PhCH_2$), 1.90–1.48 (m, 6H, 3xCH_2), 1.44 [s, 9H, $C(CH_3)_3$], 1.39–1.19 (m, 6H, 3xCH_2), 1.33 [d, *J*= 7.2 Hz, 3H, $CH(CH_3)$], 0.87 (t, *J*= 7.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 174.0, 171.7, 171.1, 157.6, 134.4, 129.2, 113.6, 82.1, 71.9, 55.2, 52.8, 48.7, 34.8, 32.3, 31.5, 27.9, 27.5, 24.6, 22.4, 18.4, 13.9; MS (ESI) *m/z* (%): 479 ($[M+H]^+$, 100); Anal Calcd for $C_{26}H_{42}N_2O_6$: C, 65.25; H, 8.85; N, 5.85. Found: C, 65.01; H, 8.99; N, 5.72.

4.2.4.27. (2*R*)-*tert*-Butyl 2-((2*S*)-2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)hexanamido)propanoate (mixture of

diastereomers) (24e)—Yield 38%; Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.09 (d, *J*= 8.6 Hz, 2H, arom), 7.03–6.88 (m, 1H, NHCO), 6.82 (d, *J*= 8.8 Hz, 2H, arom), 6.63 (t, *J*= 6.8 Hz, 1H, NHCO), 4.52–4.33 (m, 2H, 2xCH), 4.26–4.19 (m, 1H, CH), 3.79 (s, 3H, CH_3O), 3.20 (br s, ½H, OH), 2.83 (br s, ½H, OH), 2.56 (t, *J*= 7.6 Hz, 2H, $PhCH_2$), 1.98–1.52 (m, 6H, $3xCH_2$), 1.46 [s, 9H, $C(CH_3)_3$], 1.40–1.25 (m, 6H, $3xCH_2$), 1.37 [d, *J*= 7.2 Hz, 3H, $CH(CH_3)$], 0.89 (t, *J*= 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 174.5, 174.1, 172.1, 171.8, 171.3, 171.0, 157.5, 134.5, 129.2, 113.6, 82.3, 82.2, 72.1, 71.9, 55.2, 52.7, 52.4, 48.7, 34.8, 34.4, 31.9, 31.5, 27.9, 26.0, 24.7, 22.3, 18.4, 18.3, 13.9; MS (ESI) *m/z* (%): 479 ($[M+H]^+$, 100); Anal Calcd for $C_{26}H_{42}N_2O_6$: C, 65.25; H, 8.85; N, 5.85. Found: C, 65.02; H, 8.99; N, 5.74.

4.2.4.28. *tert*-Butyl 2-((2*R*)-2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)hexanamido)acetate (mixture of diastereomers) (24f)—

Yield 79%; Yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.38 (d, *J*= 8.4 Hz, 1H, NHCO), 7.25–7.12 (m, 1H, NHCO), 7.06 (d, *J*= 8.4 Hz, 2H, arom), 6.79 (d, *J*= 8.4 Hz, 2H, arom), 4.60–4.45 (m, 1H, CH), 4.14–4.06 (m, 1H, CH), 3.94–3.80 (m, 2H, CH_2COOBu^t), 3.76 (s, 3H, CH_3O), 2.53 (t, *J*= 7.0 Hz, 2H, $PhCH_2$), 1.90–1.48 (m, 6H, $3xCH_2$), 1.44 [s, 9H, $C(CH_3)_3$], 1.36–1.21 (m, 6H, $3xCH_2$), 0.95–0.77 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 174.8, 174.5, 172.4, 172.1, 168.7, 168.6, 157.4, 134.4, 129.1, 113.5, 82.2, 71.8, 55.1, 52.6, 41.9, 34.8, 32.1, 31.5, 27.9, 27.6, 24.6, 22.3, 13.9; MS (ESI) *m/z* (%): 465 ($[M+H]^+$, 100); Anal Calcd for $C_{25}H_{40}N_2O_6$: C, 64.63; H, 8.68; N, 6.03. Found: C, 64.42; H, 8.76; N, 5.96.

4.2.4.29. *tert*-Butyl 4-((2S)-2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)-4-methylpentanamido)butanoate (mixture of diastereomers) (24g)—

Yield 71%; Yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.18 (d, *J*= 8.4 Hz, 1H, NHCO), 7.12-6.92 (m, 3H, NHCO, arom), 6.80 (d, *J* = 7.8 Hz, 2H, arom), 4.53-4.33 (m, 1H, CH), 4.17-4.01 (m, 1H, CH), 3.77 (s, 3H, CH_3), 3.32-3.09 (m, 2H, CH_2), 2.54 (t, *J*= 7.2 Hz, 2H, CH_2), 2.24 (t, *J*= 7.0 Hz, 2H, CH_2), 1.97-1.31 [m, 20H, $5\times CH_2$, CH, $C(CH_3)_3$], 0.97-0.86 (m, 6H, $2\times CH_3$); ^{13}C NMR ($CDCl_3$): δ 174.7, 173.0, 172.1, 157.5, 134.5, 129.2, 113.6, 80.7, 72.1, 55.2, 52.6, 41.0, 38.9, 34.3, 34.8, 32.9, 31.5, 28.0, 24.7, 22.9, 22.1; MS (ESI) *m/z* (%): 493 ($[M+H]^+$, 100); Anal Calcd for $C_{27}H_{44}N_2O_6$: C, 65.83; H, 9.00; N, 5.69. Found: C, 65.62; H, 9.14; N, 5.56.

4.2.4.30. *N*-((*S*)-1-amino-1-oxohexan-2-yl)-2-hydroxy-6-(4-methoxyphenyl)hexanamide (mixture of diastereomers) (26)—

Yield 52%; Yellow syrup; ^{1}H NMR ($CDCl_3$): δ 7.26–7.16 (m, 1H, NH), 7.07 (d, *J*= 8.6 Hz, 2H, arom), 6.81 (d, *J*= 8.8 Hz, 2H, arom), 6.76 (br s, ½H, NH_2), 6.54 (br s, ½H, NH_2), 6.19 (br s, ½H, NH_2), 5.91 (br s, ½H, NH_2), 4.47–4.28 (m, 1H, CH), 4.17–4.03 (m, 1H, CH), 3.78 (s, 3H, CH_3O), 2.55 (t, *J*= 7.0 Hz, 2H, $PhCH_2$), 1.94–1.20 (m, 13H, $6xCH_2$, OH), 0.89 (t, *J*= 6.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 175.2, 174.4, 157.6, 134.5, 129.2, 113.7, 72.0, 55.2, 52.6, 34.9, 33.9, 31.7, 31.5, 29.8, 27.6, 24.7, 22.3, 13.9; MS (ESI) *m/z* (%): 351 ($[M+H]^+$, 100); Anal Calcd for $C_{19}H_{30}N_2O_4$: C, 65.12; H, 8.63; N, 7.99. Found: C, 64.97; H, 8.79; N, 7.94.

4.2.4.31. (2*S*)-*tert*-Butyl 2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)hexanoate (mixture of diastereomers) (28)—

Yield 46%; Yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.08 (d, *J*= 8.8 Hz, 2H, arom), 6.98 (d, *J*= 8.2 Hz,

1H, NH), 6.82 (d, *J*= 8.6 Hz, 2H, arom), 4.57–4.40 (m, 1H, CH), 4.18–4.07 (m, 1H, CH), 3.79 (s, 3H, CH_3O), 3.09 (br s, ½H, OH), 2.90 (br s, ½H, OH), 2.56 (t, *J*= 7.2 Hz, 2H, $PhCH_2$), 1.93–1.53 (m, 6H, 3xCH_2), 1.47 [s, 9H, $C(CH_3)_3$], 1.41–1.16 (m, 6H, 3xCH_2), 0.90 (t, *J*= 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ (173.5, 171.8), 157.6, 134.5, 129.2, 113.7, 82.1, 72.0, 55.2, 52.3, 34.8, 34.7, 32.2, 31.4, 28.0, 27.1, 24.6, 22.3, 13.9; MS (ESI) *m/z* (%): 408 ($[M+H]^+$, 100); Anal Calcd for $C_{23}H_{37}NO_5$: C, 67.78; H, 9.15; N, 3.44. Found: C, 67.61; H, 9.39; N, 3.35.

4.2.4.32. Benzyl 2-((2*S*)-2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)hexanamido)acetate (mixture of diastereomers) (30a)—

Yield 40%; White oil; ^{1}H NMR ($CDCl_3$): δ 7.42–7.28 (m, 5H, arom), 7.21–7.02 [(m, 3H, NH, 2xarom), 7.01–6.87 (m, 1H, NH), 6.81 (d, *J*= 8.2 Hz, 2H, arom), 5.15 (s, 2H, OCH_2Ph), 4.56–4.36 (m, 1H, CH), 4.19–3.95 (m, 3H, CH, $NHCH_2$), 3.77 (s, 3H, CH_3O), 3.55 (br s, ½H, OH), 3.15 (br s, ½H, OH), 2.55 (t, *J*= 7.6 Hz, 2H, $PhCH_2$), 2.06–1.14 (m, 12H, 6xCH_2), 0.89 (t, *J*= 5.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 174.6, 174.3, 172.3, 172.0, 169.4, 157.6, 135.0, 134.4, 129.2, 128.6, 128.5, 128.4, 113.6, 71.9, 67.2, 55.2, 52.7, 41.3, 34.8, 31.8, 31.4, 29.7, 27.6, 24.6, 22.4, 13.9; MS (ESI) *m/z* (%): 497 ($[M-H]^-$, 100); Anal Calcd for $C_{28}H_{38}N_2O_6$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.21; H, 7.84; N, 5.52.

4.2.4.33. *tert*-Butyl 2-(2-((2*S*)-2-(2-hydroxy-6-(4-methoxyphenyl)hexanamido)hexanamido)acetamido)acetate (mixture of diastereomers) (32)—

Yield 46%; Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.61–7.40 (m, 2H, 2xNHCO), 7.20 (t, *J*= 5.2 Hz, 1H, NHCO), 7.07 (d, *J*= 8.4 Hz, 2H, arom), 6.81 (d, *J*= 8.8 Hz, 2H, arom), 4.51–4.31 (m, 1H, CH), 4.13–3.83 (m, 5H, CH, 2xNHC*H*$_2$], 3.78 (s, 3H, CH_3O), 3.16–3.01 (m, 1H, OH), 2.55 (t, *J*= 7.6 Hz, 2H, $PhCH_2$), 1.98–1.48 (m, 6H, 3xCH_2), 1.45 [s, 9H, $C(CH_3)_3$], 1.38–1.20 (m, 6H, 3xCH_2), 0.89 (t, *J*= 6.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 175.8, 175.2, 172.5, 169.4, 169.2, 157.5, 134.4, 129.2, 113.6, 82.7, 82.5, 72.0, 70.4, 55.2, 53.6, 42.9, 41.9, 34.8, 34.4, 31.4, 28.8, 28.0, 24.9, 22.6, 22.3, 13.9; MS (ESI) *m/z* (%): 520 ($[M-H]^-$, 100); Anal Calcd for $C_{27}H_{43}N_3O_7$: C, 62.17; H, 8.31; N, 8.06. Found: C, 61.90; H, 8.45; N, 7.96.

4.2.5 Oxidation of 2-hydroxyamides

To a stirred solution of 2-hydroxyamide (1.0 mmol) in dry CH_2Cl_2 (10 mL), Dess–Martin periodinane was added (0.64 g, 1.5 mmol) and the mixture was stirred for 1 h at room temperature. The organic phase was washed with 5% $NaHCO_3$, dried over Na_2SO_4 and the organic solvent was evaporated under reduced pressure. The residue was purified by column chromatography with the appropriate mixture of solvents as eluent.

4.2.5.1. (*S*)-*tert*-Butyl 2-(2-(2-oxo-6-phenylhexanamido)hexanamido)acetate (12a)—

Yield 80%; Colorless oil; $[\alpha]_D^{20}$ −17.2 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.40 (d, *J* = 8.6Hz, 1H, COCON*H*), 7.34-7.09 (m, 5H, arom), 6.39 (t, *J* = 4.8 Hz, 1H, NH), 4.46–4.29 (m, 1H, CH), 3.92 (dd, J_1= 1.8Hz, J_2 = 5.2Hz, 2H, NHC*H*$_2$), 2.95 (t, *J* = 6.6 Hz, 2H, $COCOCH_2$), 2.62 (t, *J* = 7.0 Hz, 2H, CH_2Ph), 2.03–1.58 (m, 6H, 3xCH_2), 1.45 [s, 9H, $C(CH_3)_3$], 1.40–1.22 (m, 4H, 2xCH_2), 0.88 (t, *J*= 6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.1, 170.5, 168.5, 160.0, 142.0, 128.4, 128.3, 125.8, 82.6, 53.2, 42.0, 36.6, 35.6, 32.0,

30.8, 28.0, 27.5, 22.7, 22.3, 13.8; MS (ESI) *m/z* (%): 450 ([M+NH_4]$^+$, 100); Anal. Calcd for $C_{24}H_{36}N_2O_5$: C, 66.64; H, 8.39; N, 6.48. Found: C, 66.51; H, 8.52; N, 6.39.

4.2.5.2. (*S*)-*tert*-Butyl 2-(2-(6-(naphthalen-2-yl)-2-oxohexanamido)hexanamido)acetate (12b)—Yield 99%; Colorless oil; $[\alpha]_D^{20}$ −16.0 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.88–7.21 (m, 8H, 7xarom, NH), 6.61 (br s, 1H, NH), 4.53–4.33 (m, 1H, CH), 4.02–3.82 (m, 2H, CH_2COO), 2.97 (t, *J* = 6.6 Hz, 2H, $PhCH_2$), 2.79 (t, *J* = 7.0 Hz, 2H, CH_2COCO), 2.12–1.56 (m, 6H, 3xCH_2), 1.45 [s, 9H, $C(CH_3)_3$], 1.37–1.16 (m, 4H, 2xCH_2), 0.89 (t, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.0, 170.7, 168.5, 160.0, 139.5, 133.5, 131.9, 127.8, 127.5, 127.3, 127.2, 126.3, 125.8, 125.0, 82.4, 53.1, 41.9, 36.6, 35.7, 32.0, 30.5, 27.9, 27.5, 22.6, 22.3, 13.8; MS (ESI) *m/z* (%): 483 ([M+H]$^+$, 45); Anal. Calcd for $C_{28}H_{38}N_2O_5$: C, 69.68; H, 7.94; N, 5.80. Found: C, 69.45; H, 8.03; N, 5.66.

4.2.5.3. (*S*)-*tert*-Butyl 2-(2-(6-(4-methoxyphenyl)-2-oxohexanamido)hexanamido)acetate (12c)—Yield 72%; Colorless oil; $[\alpha]_D^{20}$ −16.6 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.49 (d, *J* = 8.6 Hz, 1H, NH), 7.08 (d, *J* = 8.6 Hz, 2H, arom), 6.81 (d, *J* = 8.8 Hz, 2H, arom), 6.60 (t, *J* = 5.0 Hz, 1H, NH), 4.48–4.34 (m, 1H, CH), 3.91 (dd, J_1 = 2.2 Hz, J_2 = 5.2 Hz, 2H, $NHCH_2$), 3.78 (s, 3H, CH_3O), 2.93 (t, *J* = 6.4 Hz, 2H, $PhCH_2$), 2.57 (t, *J* = 7.0 Hz, 2H, CH_2COCO), 1.99–1.75 (m, 2H, CH_2), 1.69–1.55 (m, 4H, 2xCH_2), 1.46 [s, 9H, $C(CH_3)_3$], 1.40–1.27 (m, 4H, 2xCH_2), 0.88 (t, *J* = 7.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.0, 170.7, 168.6, 160.0, 157.6, 134.1, 129.2, 113.6, 82.5, 55.2, 53.1, 42.0, 36.6, 34.6, 32.0, 31.0, 27.9, 27.5, 22.6, 22.3, 13.8; MS (ESI) *m/z* (%): 461 ([M−H]$^-$, 100); HRMS (ESI) calcd for $C_{25}H_{37}N_2O_6^-$ [M−H]$^-$: 461.2657. Found: 461.2654; Anal. Calcd for $C_{25}H_{38}N_2O_6$: C, 64.91; H, 8.28; N, 6.06. Found: C, 64.79; H, 8.43; N, 5.94.

4.2.5.4. (*S*)-*tert*-Butyl 3-(2-(6-(4-methoxyphenyl)-2-oxohexanamido)hexanamido)propanoate (12d)—Yield 78%; Yellowish oil; $[\alpha]_D^{20}$ −8.6 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.45 (d, *J* = 8.6 Hz, 1H, NH), 7.09 (d, *J* = 8.6 Hz, 2H, arom), 6.82 (d, *J* = 8.6 Hz, 2H, arom), 6.53 (br t, 1H, NH), 4.33–4.20 (m, 1H, CH), 3.78 (s, 3H, CH_3O), 3.55–3.37 (m, 2H, NHC*H*$_2$), 2.93 (t, *J* = 6.8 Hz, 2H, $PhCH_2$), 2.57 (t, *J* = 6.8 Hz, 2H, CH_2COCO), 2.44 (t, *J* = 6.2 Hz, 2H, CH_2COOBu^t), 1.96–1.69 (m, 2H, CH_2), 1.69–1.54 (m, 4H, 2xCH_2), 1.44 [s, 9H, $C(CH_3)_3$], 1.37–1.22 (m, 4H, 2xCH_2), 0.88 (t, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.1, 171.8, 170.4, 159.9, 157.7, 134.1, 129.2, 113.7, 81.3, 55.2, 53.3, 36.6, 35.1, 34.6, 32.2, 31.0, 29.7, 28.0, 27.5, 22.6, 22.3, 13.8; MS (ESI) *m/z* (%): 475 ([M−H]$^-$, 100); HRMS (ESI) calcd for $C_{26}H_{39}N_2O_6^-$ [M−H]$^-$: 475.2814. Found 475.2820; Anal. Calcd for $C_{26}H_{40}N_2O_6$: C, 65.52; H, 8.46; N, 5.88. Found: C, 65.37; H, 8.61; N, 5.79.

4.2.5.5. (*S*)-*tert*-Butyl 4-(2-(6-(4-methoxyphenyl)-2-oxohexanamido)hexanamido)butanoate (12e)—Yield 70%; Yellow solid; mp 50–52 °C; $[\alpha]_D^{20}$ −9.3 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.42 (d, *J* = 8.2 Hz, 1H, NH), 7.09 (d, *J* = 8.8 Hz, 2H, arom), 6.82 (d, *J* = 8.6 Hz, 2H, arom), 6.39 (br t, 1H, N*H*CH_2), 4.36–4.17 (m, 1H, CH), 3.78 (s, 3H, CH_3O), 3.36–3.17 (m, 2H, NHC*H*$_2$), 3.00–2.83 (m, 2H, $PhCH_2$), 2.64–2.50 (m, 2H, CH_2COCO), 2.27 (t, *J* = 7.2 Hz, 2H, CH_2COOBu^t), 1.89–1.68 (m, 4H,

2xCH_2), 1.68–1.56 (m, 4H, 2xCH_2), 1.44 [s, 9H, $C(CH_3)_3$], 1.38–1.20 (m, 4H, 2xCH_2), 0.89 (t, *J*= 6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.1, 172.8, 170.5, 159.9, 157.7, 134.1, 129.2, 113.7, 80.8, 55.2, 53.4, 39.2, 36.6, 34.6, 33.0, 32.1, 31.0, 28.0, 27.6, 24.4, 22.6, 22.3, 13.8; MS (ESI) *m/z* (%): 489 ([M−H]$^-$, 100); HRMS (ESI) calcd for $C_{27}H_{41}N_2O_6^-$ [M−H]$^-$: 489.2970. Found 489.2970; Anal. Calcd for $C_{27}H_{42}N_2O_6$: C, 66.10; H, 8.63; N, 5.71. Found: C, 65.92; H, 8.87; N, 5.57.

4.2.5.6. (*S*)-*tert*-Butyl 5-(2-(6-(4-methoxyphenyl)-2-oxohexanamido)hexanamido)pentanoate (12f)—Yield 65%; White solid; ^{1}H NMR ($CDCl_3$): δ 7.49 (d, *J* = 8.4 Hz, 1H, NH), 7.08 (d, *J* = 8.4 Hz, 2H, arom), 6.81 (d, *J* = 8.4 Hz, 2H, arom), 6.36 (t, *J* = 5.6 Hz, 1H, NH), 4.39-4.20 (m, 1H, CH), 3.77 (s, 3H, CH_3O), 3.37-3.11 (m, 2H, CH_2), 3.00-2.77 (m, 2H, CH_2), 2.65-2.43 (m, 2H, CH_2), 2.23 (t, *J* = 6.6 Hz, 2H, CH_2), 1.95-1.48 (m, 10H, 5×CH_2), 1.43 [s, 9H, $C(CH_3)_3$], 1.36-1.18 (m, 4H, 2×CH_2), 0.88 (t, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.0, 172.9, 170.5, 159.9, 157.6, 134.0, 129.2, 113.6, 80.3, 55.2, 53.3, 39.0, 36.6, 34.7, 34.6, 32.1, 30.9, 28.6, 28.0, 27.5, 22.6, 22.3, 21.9, 13.8; HRMS (ESI) calcd for $C_{28}H_{44}N_2NaO_6^+$ [M + Na]$^+$: 527.3092. Found: 527.3096; Anal. Calcd for $C_{28}H_{44}N_2O_6$: C, 66.64; H, 8.79; N, 5.55. Found: C, 66.41; H, 8.99; N, 5.41.

4.2.5.7. (*S*)-Ethyl 2-(2-(6-(naphthalen-2-yl)-2-oxohexanamido)hexanamido)acetate (16)—Yield 80%; Yellowish oil; $[\alpha]_D^{20}$ −21.4 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.85–7.28 (m, 8H, NH, arom), 6.67 (t, *J* =5.0 Hz, 1H, NH), 4.52–4.34 (m, 1H, NHC*H*), 4.20 (q, *J* = 7.2 Hz, 2H, OCH_2), 4.02 (dd, J_1 = 2.6 Hz, J_2 = 5.0 Hz, 2H, NHCH_2), 2.97 (t, *J* = 6.8 Hz, 2H, CH_2COCO), 2.80 (t, *J* = 6.6 Hz, 2H, CH_2Ph), 2.06–1.59 (m, 6H, 3xCH_2) 1.45–1.18 (m, 7H, 2xCH_2, CH_3), 0.89 (t, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.0, 170.9, 169.5, 160.0, 139.4, 133.5, 131.9, 127.8, 127.5, 127.3, 127.2, 126.3, 125.8, 125.0, 61.6, 53.1, 41.3, 36.6, 35.7, 31.9, 30.6, 27.5, 22.6, 22.3, 14.0, 13.8; MS (ESI) *m/z* (%): 455 ([M+H]$^+$, 100); Anal. Calcd for $C_{26}H_{34}N_2O_5$: C, 68.70; H, 7.54; N, 6.16. Found: C, 68.54; H, 7.68; N, 6.02.

4.2.5.8. (*S*)-Ethyl 2-((2-(6-(4-methoxyphenyl)-2-oxohexanamido)hexyl)oxy)acetate (19a)—Yield 61%; Yellow oil; $[\alpha]_D^{20}$ −4.9 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.32 (d, *J*= 9.0 Hz, 1H, NH), 7.09 (d, *J*= 8.6 Hz, 2H, arom), 6.82 (d, *J*= 8.6 Hz, 2H, arom), 4.22 (q, *J*= 7.2 Hz, 2H, OCH_2CH_3), 4.07 (s, 2H, OCH_2CO), 4.05–3.90 (m, 1H, CH), 3.79 (s, 3H, CH_3O), 3.65 (dd, J_1= 9.4 Hz, J_2= 4.2 Hz, 1H, CHC*H*HO), 3.53 (dd, J_1= 9.4 Hz, J_2= 3.8 Hz, 1H, CHCH*H*O), 2.95 (t, *J*= 6.8 Hz, 2H, $PhCH_2$), 2.58 (t, *J*= 6.8 Hz, 2H, CH_2COCO), 1.70–1.55 (m, 6H, 3xCH_2), 1.35–1.20 (m, 7H, 2xCH_2, OCH_2CH_3), 0.89 (t, *J*= 6.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 199.0, 170.4, 159.9, 134.1, 129.2, 113.6, 72.5, 68.2, 61.0, 55.2, 49.4, 36.6, 34.6, 31.0, 30.9, 28.0, 22.7, 22.5, 14.2, 13.9; MS (ESI) *m/z* (%): 422 ([M+H]$^+$, 100); HRMS (ESI) calcd for $C_{23}H_{34}NO_6^-$ [M−H]$^-$: 420.2392. Found 420.2389; Anal. Calcd for $C_{23}H_{35}NO_6$: C, 65.54; H, 8.37; N, 3.32. Found: C, 65.39; H, 8.49; N, 3.27.

4.2.5.9. (*S*)-*tert*-Butyl 2-((2-(2-oxo-6-phenylhexanamido)hexyl)oxy)acetate (19b)—Yield 95%; Colorless oil; $[\alpha]_D^{20}$ −10.2 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.44–7.02

(m, 6H, NH, arom), 4.05–3.85 (m, 3H, OCH_2COO, CH), 3.61 (dd, J_1 = 9.4 Hz, J_2 = 4.2 Hz, 1H, C*H*HO), 3.49 (dd, J_1 = 9.4 Hz, J_2 = 4.0 Hz, 1H, CH*H*O), 2.94 (t, J = 6.6 Hz, 2H, CH_2COCO), 2.62 (t, J = 6.8 Hz, 2H, CH_2Ph), 1.77–1.53 (m, 6H, 3xCH_2), 1.45 [s, 9H $C(CH_3)_3$], 1.36–1.14 (m, 4H, 2xCH_2), 0.87 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.9, 169.5, 159.9, 142.1, 128.3, 128.3, 125.7, 81.8, 72.4, 68.8, 49.4, 36.6, 35.6, 31.0, 30.8, 28.1, 22.8, 22.5, 13.9; MS (ESI) *m/z* (%): 420 ($[M+H]^+$, 40); Anal. Calcd for $C_{24}H_{37}NO_5$: C, 68.71; H, 8.89; N, 3.34. Found: C, 68.45; H, 9.05; N, 3.21.

4.2.5.10. (*S*)-*tert*-Butyl 2-((2-(6-(4-methoxyphenyl)-2-oxohexanamido)hexyl)oxy)acetate (19c)—Yield 86%; Yellow oil; $[\alpha]_D^{20}$ −7.0 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.29 (d, *J*= 9.2 Hz, 1H, NH), 7.09 (d, *J*= 8.8 Hz, 2H, arom), 6.81 (d, *J*= 8.6 Hz, 2H, arom), 4.05–3.97 (m, 1H, CH), 3.95 (s, 2H, OCH_2CO), 3.78 (s, 3H, CH_3O), 3.63 (dd, J_1= 9.4 Hz, J_2= 4.2 Hz, 1H, CHC*H*HO), 3.50 (dd, J_1= 9.4 Hz, J_2= 3.8 Hz, 1H, CHCH*H*O), 2.94 (t, *J*= 6.4 Hz, 2H, $PhCH_2$), 2.57 (t, *J*= 7.0 Hz, 2H, CH_2COCO), 1.75–1.55 (m, 6H, 3xCH_2), 1.47 [s, 9H, $C(CH_3)_3$], 1.40–1.20 (m, 4H, 2xCH_2), 0.88 (t, *J*= 6.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.9, 169.4, 159.9, 157.6, 134.1, 129.2, 113.6, 81.7, 72.4, 68.7, 55.2, 49.4, 36.6, 34.6, 31.0, 30.9, 28.0, 22.6, 22.4, 13.9; MS (ESI) *m/z* (%): 448 ($[M-H]^-$, 100); HRMS (ESI) calcd for $C_{25}H_{38}NO_6^-$ $[M-H]^-$: 448.2705. Found 448.2699; Anal. Calcd for $C_{25}H_{39}NO_6$: C, 66.79; H, 8.74; N, 3.12. Found: C, 66.55; H, 8.87; N, 3.09.

4.2.5.11. (*S*)-*tert*-Butyl 2-((2-(6-(naphthalen-2-yl)-2-oxohexanamido)hexyl)oxy)acetate (19d)—Yield 84%; Yellowish oil; $[\alpha]_D^{20}$ −7.2 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.88–7.19 (m, 8H, NH, arom), 4.10–3.84 (m, 3H, CH, CH_2COO), 3.64 (dd, J_1 = 4.0 Hz, J_2 = 9.4 Hz, 1H, C*H*HO), 3.52 (dd, J_1 = 3.8 Hz, J_2 = 9.4 Hz, 1H, CH*H*O), 2.99 (t, *J* = 6.6 Hz, 2H, CH_2COCO), 2.82 (t, *J* = 6.6 Hz, 2H, $PhCH_2$), 1.89–1.53 (m, 6H, 3xCH_2), 1.47 [s, 9H, $C(CH_3)_3$], 1.37–1.15 (m, 4H, 2xCH_2), 0.89 (t, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.9, 169.5, 159.9, 139.5, 133.5, 131.9, 127.8, 127.5, 127.4, 127.3, 126.3, 125.8, 125.0, 81.8, 72.4, 68.7, 49.4, 36.6, 35.7, 31.0, 30.6, 28.0, 22.7, 22.4, 13.9; MS (ESI) *m/z* (%): 470 ($[M+H]^+$, 33); Anal. Calcd for $C_{28}H_{39}NO_5$: C, 71.61; H, 8.37; N, 2.98. Found: C, 71.39; H, 8.61; N, 2.85.

4.2.5.12. (*S*)-*tert*-Butyl 2-(2-(6-(4-methoxyphenyl)-2-oxohexanamido)-4-methylpentanamido)acetate (25a)—Yield 82%; Colorless oil; $[\alpha]_D^{20}$ −21.4 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.51 (d, *J*= 8.0 Hz, 1H, NH), 7.07 (d, *J*= 8.8 Hz, 2H, arom), 6.80 (d, *J*= 8.6 Hz, 2H, arom), 6.78–6.67 (m, 1H, NH), 4.57–4.44 (m, 1H, CH), 3.90 (dd, J_1= 2.4 Hz, J_2= 5.2 Hz, 2H, $NHCH_2$), 3.76 (s, 3H, CH_3O), 2.92 (t, *J*= 6.4 Hz, 2H, $PhCH_2$), 2.55 (t, *J*= 7.0 Hz, 2H, CH_2COCO), 1.74–1.55 (m, 6H, 3xCH_2), 1.44 [s, 9H, $C(CH_3)_3$], 0.93 (d, *J*= 4.2 Hz, 3H, CH_3), 0.90 (d, *J*= 4.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.1,171.2, 168.5, 160.0, 157.5, 133.9, 129.0, 113.5, 82.1, 55.0, 51.3, 41.8, 40.9, 36.5, 34.5, 30.8, 27.8, 24.5, 22.8, 22.4, 21.6; MS (ESI) *m/z* (%): 461 ($[M-H]^-$, 100); HRMS (ESI) calcd for $C_{25}H_{37}N_2O_6^-$ $[M-H]^-$: 461.2657. Found 461.2658; Anal. Calcd for $C_{25}H_{38}N_2O_6$: C, 64.91; H, 8.28; N, 6.06. Found: C, 64.73; H, 8.50; N, 5.93.

4.2.5.13. *tert*-Butyl 2-((2*S*,3*R*)-2-(6-(4-methoxyphenyl)-2-oxohexanamido)-3-methylpentanamido)acetate (25b)—Yield 69%; Colorless oil; $[\alpha]_D^{20}$ −17.0 (c 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.56 (d, *J*= 9.0 Hz, 1H, NH), 7.07 (d, *J*= 8.2 Hz, 2H, arom), 6.80 (d, *J*= 8.4 Hz, 2H, arom), 6.77–6.67 (m, 1H, NH), 4.38–4.27 (m, 1H, CH), 3.92 (dd, J_1= 5.2 Hz, J_2= 14.4 Hz, 2H, $NHCH_2$), 3.76 (s, 3H, CH_3O), 2.92 (t, *J*= 6.4 Hz, 2H, $PhCH_2$), 2.55 (t, *J*= 6.6 Hz, 2H, CH_2COCO), 2.04–1.85 (m, 1H, CH), 1.65–1.53 (m, 4H, 2xCH_2), 1.44 [s, 9H, $C(CH_3)_3$], 1.32–1.03 (m, 2H, CH_2), 0.99–0.81 (m, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 197.9, 170.3, 168.4, 159.9, 157.5, 133.9, 129.0, 113.5, 82.1, 57.5, 55.0, 41.8, 37.1, 36.5, 34.5, 30.8, 27.8, 24.7, 22.4, 15.2, 11.0; MS (ESI) *m/z* (%): 461 ([M−H]$^-$, 100); HRMS (ESI) calcd for $C_{25}H_{37}N_2O_6^-$ [M−H]$^-$: 461.2657. Found 461.2662; Anal. Calcd for $C_{25}H_{38}N_2O_6$: C, 64.91; H, 8.28; N, 6.06. Found: C, 64.79; H, 8.39; N, 6.01.

4.2.5.14. (*S*)-*tert*-Butyl 2-(2-(6-(4-methoxyphenyl)-2-oxohexanamido)-3-methylbutanamido)acetate (25c)—Yield 80%; Colorless oil; $[\alpha]_D^{20}$ −13.1 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.60 (d, *J*= 9.2 Hz, 1H, NH), 7.06 (d, *J*= 8.6 Hz, 2H, arom), 6.97–6.85 (m, 1H, NH), 6.79 (d, *J*= 8.6 Hz, 2H, arom), 4.32 (dd, J_1= 7.0 Hz, J_2=9.0 Hz, 1H, CHCO), 3.92 (dd, J_1= 5.4 Hz, J_2= 18.8 Hz, 2H, NHCH_2), 3.76 (s, 3H, CH_3O), 2.92 (t, *J*= 5.0 Hz, 2H, $PhCH_2$), 2.55 (t, *J*= 6.8 Hz, 2H, CH_2COCO), 2.29–2.08 (m, 1H, CH), 1.68–1.54 (m, 4H, 2xCH_2), 1.44 [s, 9H, $C(CH_3)_3$], 1.03–0.87 (m, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 197.9, 170.2, 168.5, 160.0, 157.5, 133.9, 129.1, 113.5, 82.2, 58.3, 55.0, 41.8, 36.5, 34.5, 31.1, 30.9, 27.8, 22.4, 19.1, 18.0; MS (ESI) *m/z* (%): 447 ([M−H]$^-$, 100); HRMS (ESI) calcd for $C_{24}H_{35}N_2O_6^-$ [M−H]$^-$: 447.2501. Found 447.2509; Anal. Calcd for $C_{24}H_{36}N_2O_6$: C, 64.26; H, 8.09; N, 6.25. Found: C, 64.02; H, 8.03; N, 6.09.

4.2.5.15. (*S*)-*tert*-Butyl 2-((*S*)-2-(6-(4-methoxyphenyl)-2-oxohexanamido)hexanamido)propanoate (25d)—Yield 94%; Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.47 (d, *J*= 8.6 Hz, 1H, NH), 7.08 (d, *J*= 8.6 Hz, 2H, arom), 6.82 (d, *J*= 8.6 Hz, 2H, arom), 6.51 (d, *J*= 7.4 Hz, 1H, NH), 4.53–4.30 (m, 2H, 2xCH), 3.78 (s, 3H, CH_3O), 2.93 (t, *J*= 7.0 Hz, 2H, $PhCH_2$), 2.57 (t, *J*= 7.0 Hz, 2H, CH_2COCO), 1.97–1.72 (m, 2H, CH_2), 1.68–1.56 (m, 4H, 2xCH_2), 1.46 [s, 9H, $C(CH_3)_3$], 1.36 (d, *J*= 7.2 Hz, 3H, CH_3), 1.34–1.21 (m, 4H, 2xCH_2), 0.88 (t, *J*= 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.1, 171.7, 170.0, 159.9, 157.7, 134.1, 129.2, 113.7, 82.2, 55.2, 53.2, 48.7, 36.6, 34.6, 32.1, 31.0, 27.9, 27.5, 22.6, 22.3, 18.5, 13.8; MS (ESI) *m/z* (%): 475 ([M−H]$^-$, 100); HRMS (ESI) calcd for $C_{26}H_{39}N_2O_6^-$ [M−H]$^-$: 475.2814. Found 475.2819; Anal. Calcd for $C_{26}H_{40}N_2O_6$: C, 65.52; H, 8.46; N, 5.88. Found: C, 65.27; H, 8.62; N, 5.73.

4.2.5.16. (*R*)-*tert*-Butyl 2-((*S*)-2-(6-(4-methoxyphenyl)-2-oxohexanamido)hexanamido)propanoate (25e)—Yield 85%; Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.42 (d, *J*= 8.4 Hz, 1H, NH), 7.08 (d, *J*= 8.4 Hz, 2H, arom), 6.80 (d, *J*= 8.6 Hz, 2H, arom), 6.49 (d, *J*= 6.8 Hz, 1H, NH), 4.54–4.23 (m, 2H, 2xCH), 3.77 (s, 3H, CH_3O), 2.93 (t, *J*= 6.6 Hz, 2H, $PhCH_2$), 2.56 (t, *J*= 6.8 Hz, 2H, CH_2COCO), 1.98–1.53 (m, 6H, 3xCH_2), 1.44 [s, 9H, $C(CH_3)_3$], 1.37 (d, *J*= 7.0 Hz, 3H, CH_3), 1.33–1.19 (m, 4H, 2xCH_2), 0.87 (t, *J*= 7.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.1, 171.8,169.8, 159.9, 157.6, 134.1, 128.2, 113.7, 82.3, 55.2, 53.1, 48.7, 36.6, 34.6, 32.1, 31.0, 27.9, 27.5, 22.6, 22.3, 18.5, 13.9; MS (ESI) *m/z* (%): 475 ([M−H]$^-$, 100); HRMS (ESI) calcd for $C_{26}H_{39}N_2O_6^-$ [M−H]$^-$:

475.2814. Found 475.2820; Anal. Calcd for $C_{26}H_{40}N_2O_6$: C, 65.52; H, 8.46; N, 5.88. Found: C, 65.33; H, 8.69; N, 5.73.

4.2.5.17. (*R*)-*tert*-Butyl 2-(2-(6-(4-methoxyphenyl)-2-oxohexanamido)hexanamido)acetate (25f)—Yield 84%; Colorless oil; $[\alpha]_D^{20}$ 16.0 (c 0.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.54 (d, *J*= 8.4 Hz, 1H, NH), 7.05 (d, *J*= 8.4 Hz, 2H, arom), 6.79 (d, *J*= 8.4 Hz, 2H, arom), 6.75–6.66 (m, 1H, NH), 4.53–4.30 (m, 1H, CH), 3.90 (dd, J_1= 1.6 Hz, J_2= 5.0 Hz, 2H, NHCH_2), 3.75 (s, 3H, CH_3O), 2.91 (t, *J*= 6.4 Hz, 2H, $PhCH_2$), 2.54 (t, *J*= 6.8 Hz, 2H, CH_2COCO), 1.94–1.51 (m, 6H, 3xCH_2), 1.43 [s, 9H, $C(CH_3)_3$], 1.32–1.19 (m, 4H, 2xCH_2), 0.85 (t, *J*= 6.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.0, 170.7, 168.5, 159.9, 157.6, 134.0, 129.1, 113.6, 82.3, 55.1, 53.0, 41.9, 36.5, 34.5, 32.0, 30.9, 27.9, 27.5, 22.5, 22.2, 13.8; MS (ESI) *m/z* (%): 461 ($[M-H]^-$, 100); HRMS (ESI) calcd for $C_{25}H_{37}N_2O_6^-$ $[M-H]^-$: 461.2657. Found 461.2660; Anal. Calcd for $C_{25}H_{38}N_2O_6$: C, 64.91; H, 8.28; N, 6.06. Found: C, 64.73; H, 8.46; N, 6.01.

4.2.5.18. (*S*)-*tert*-Butyl 4-(2-(6-(4-methoxyphenyl)-2-oxohexanamido)-4-methylpentanamido)butanoate (25g)—Yield 79%; White solid; ^{1}H NMR ($CDCl_3$): δ 7.58 (d, *J*= 8.4 Hz, 1H, NH), 7.06 (d, *J*= 8.4 Hz, 2H, arom), 6.80 (d, *J*= 8.4 Hz, 2H, arom), 6.36 (t, *J*= 5.6 Hz, 1H, NH), 4.50–4.42 (m, 1H, CH), 3.90 (m, 2H, CH_2), 3.72 (s, 3H, CH_3O), 2.92 (t, *J*= 6.5 Hz, 2H, $PhCH_2$), 2.54 (t, *J*= 6.7 Hz, 2H, CH_2), 1.99–1.31 [m, 20H, 5xCH_2, CH, $C(CH_3)_3$], 0.98–0.85 (m, 6H, 2xCH_3); ^{13}C NMR ($CDCl_3$): δ 198.1, 170.5, 168.5, 159.8, 157.5, 134.5, 129.2, 113.6, 82.2, 55.1, 53.4, 41.7, 38.9, 36.6, 34.3, 32.7, 31.0, 27.9, 27.5, 24.7, 22.9, 22.1; HRMS (ESI) calcd for $C_{27}H_{42}N_2NaO_6^+$ $[M+Na]^+$: 513.2935. Found: 513.2949; Anal. Calcd for $C_{27}H_{42}N_2O_6$: C, 66.10; H, 8.63; N, 5.71. Found: C, 65.89; H, 8.78; N, 5.64.

4.2.5.19. (*S*)-*N*-(1-Amino-1-oxohexan-2-yl)-6-(4-methoxyphenyl)-2-oxohexanamide (27)—Yield 71%; Yellow oil; $[\alpha]_D^{20}$ −16.6 (c 0.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.44 (d, *J*= 7.8 Hz, 1H, NH), 7.09 (d, *J*= 8.6 Hz, 2H, arom), 6.82 (d, *J*= 8.6 Hz, 2H, arom), 6.09, 5.71 (2xbr s, 2H, NH_2), 4.46–4.31 (m, 1H, CH), 3.79 (s, 3H, CH_3O), 2.93 (t, *J*= 6.4 Hz, 2H, $PhCH_2$), 2.58 (t, *J*= 6.8 Hz, 2H, CH_2COCO), 1.99–1.76 (m, 2H, CH_2), 1.70–1.57 (m, 4H, 2xCH_2), 1.39–1.30 (m, 4H, 2xCH_2), 0.89 (t, *J*= 7.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.1, 172.8, 160.0, 157.7, 134.0, 129.2, 113.7, 55.2, 52.8, 36.6, 34.6, 31.8, 31.0, 27.5, 22.6, 22.3, 13.8; MS (ESI) *m/z* (%): 347 ($[M-H]^-$, 100); HRMS (ESI) calcd for $C_{19}H_{27}N_2O_4^-$ $[M-H]^-$: 347.1976. Found 347.1976; Anal. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04. Found: C, 65.23; H, 8.27; N, 7.93.

4.2.5.20. (*S*)-*tert*-Butyl 2-(6-(4-methoxyphenyl)-2-oxohexanamido)hexanoate (29)—Yield 88%; Yellow oil; $[\alpha]_D^{20}$ −8.7 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.38 (d, *J*= 8.2 Hz, 1H, NH), 7.09 (d, *J*= 8.6 Hz, 2H, arom), 6.83 (d, *J*= 8.8 Hz, 2H, arom), 4.53–4.34 (m, 1H, CH), 3.79 (s, 3H, CH_3O), 2.94 (t, *J*= 7.0 Hz, 2H, $PhCH_2$), 2.58 (t, *J*= 6.8 Hz, 2H, CH_2COCO), 1.95–1.72 (m, 1H, CHCH*H*), 1.72–1.55 (m, 5H, 2xCH_2, CHC*H*H), 1.48 [s, 9H, $C(CH_3)_3$], 1.39–1.19 (m, 4H, 2xCH_2), 0.90 (t, *J*= 6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.4, 170.6, 159.6, 157.7, 134.1, 129.2, 113.7, 82.3, 55.2, 52.7, 36.5, 34.6, 32.1, 31.0, 28.0, 27.1, 22.7, 22.3, 13.8; MS (ESI) *m/z* (%): 404 ($[M-H]^-$, 100); HRMS (ESI) calcd for

$C_{23}H_{34}NO_5^-$ [M−H]$^-$: 404.2442. Found 404.2442; Anal. Calcd for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70; N, 3.45. Found: C, 67.94; H, 8.88; N, 3.31.

4.2.5.21. (*S*)-Benzyl 2-(2-(6-(4-methoxyphenyl)-2-oxohexanamido)hexanamido)acetate (31a)—Yield 75%; Yellowish solid; mp 69–73 °C; $[\alpha]_D^{20}$ −17.5 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.48–7.28 (m, 6H, NH, arom), 7.08 (d, *J*= 8.4 Hz, 2H, arom), 6.82 (d, *J*= 8.6 Hz, 2H, arom), 6.52 (t, *J*= 5.2 Hz, 1H, N*H*CH_2), 5.17 (s, 2H, OCH_2Ph), 4.47–4.27 (m, 1H, CH), 4.08 (d, *J*= 5.2 Hz, 2H, NHC*H*$_2$), 3.78 (s, 3H, CH_3O), 2.92 (t, *J*= 6.6 Hz, 2H, $PhCH_2$), 2.57 (t, *J*= 7.0 Hz, 2H, CH_2COCO), 2.01–1.77 (m, 1H, CHC*H*H), 1.77–1.54 (m, 5H, 2xCH_2, CHCH*H*), 1.38–1.20 (m, 4H, 2xCH_2), 0.88 (t, *J*= 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.0, 170.8, 169.3, 160.0, 157.7, 134.9, 134.1, 129.2, 113.7, 67.3, 55.2, 53.1, 41.3, 36.6, 34.6, 31.8, 31.0, 27.5, 22.6, 22.3, 13.8; MS (ESI) *m/z* (%): 495 ([M−H]$^-$, 100); HRMS (ESI) calcd for $C_{28}H_{35}N_2O_6^-$ [M−H]$^-$: 495.2501. Found 495.2497; Anal. Calcd for $C_{28}H_{36}N_2O_6$: C, 67.72; H, 7.31; N, 5.64. Found: C, 67.52; H, 7.47; N, 5.52.

4.2.5.22. Benzyl (S)-4-(2-(6-(4-methoxyphenyl)-2-oxohexanamido)hexanamido)butanoate (31b)—Yield 70%; Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.48–7.20 (m, 6H, NH, arom), 7.08 (d, *J*= 8.4 Hz, 2H, arom), 6.80 (d, *J*= 8.4 Hz, 2H, arom), 6.50 (t, *J*= 5.3 Hz, 1H, NH), 5.10 (s, 2H, OCH_2Ph), 4.40–4.25 (m, 1H, CH), 3.98 (d, *J*= 5.3 Hz, 2H, CH_2), 3.77 (s, 3H, CH_3O), 2.92 (t, *J*= 6.6 Hz, 2H, $PhCH_2$), 2.56 (t, *J*= 6.9 Hz, 2H, CH_2), 2.01–1.20 (m, 14H, 7xCH_2), 0.89 (t, *J*= 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.0, 170.7, 169.0, 159.9, 157.6, 134.8, 134.1, 129.2, 128.2, 127.6, 126.2, 113.7, 67.2, 55.3, 53.2, 41.3, 36.6, 34.6, 32.1, 31.0, 29.8, 27.5, 23.4, 22.6, 22.3, 13.8; MS (ESI) *m/z* (%): 523 ([M−H]$^-$, 100); HRMS (ESI) calcd for $C_{30}H_{40}N_2O_6^-$ [M−H]$^-$: 523.2814. Found 523.2811; Anal. Calcd for $C_{30}H_{40}N_2O_6$: C, 68.81; H, 7.51; N, 5.35. Found: C, 68.62; H, 7.72; N, 5.22.

4.2.5.23. (*S*)-*tert*-Butyl 2-(2-(2-(6-(4-methoxyphenyl)-2-oxohexanamido)hexanamido)acetamido)acetate (33)—Yield 72%; Brown syrup; $[\alpha]_D^{20}$ −10.8 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.53 (d, *J*= 8.0 Hz, 1H, NH), 7.17 (br s, 1H, NH), 7.08 (d, *J*= 8.4 Hz, 2H, arom), 6.90 (br s, 1H, NH), 6.81 (d, *J*= 8.2 Hz, 2H, arom), 4.40–4.20 (m, 1H, CH), 4.04–3.97 (m, 2H, NHC*H*$_2$CO), 3.94 (d, *J*= 5.2 Hz, 2H, NHC*H*$_2$CO), 3.78 (s, 3H, CH_3O), 2.99–2.83 (m, 2H, $PhCH_2$), 2.61–2.50 (m, 2H, CH_2COCO), 1.97–1.52 (m, 4H, 2xCH_2), 1.44 [s, 9H, $C(CH_3)_3$], 1.36–1.28 (m, 4H, 2xCH_2), 0.88 (t, *J*= 6.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 197.9, 171.3, 168.9, 168.8, 160.3, 157.6, 134.0, 129.2, 113.6, 82.5, 55.2, 53.6, 41.9, 36.6, 34.6, 31.7, 31.0, 29.7, 27.6, 27.9, 22.5, 22.3, 13.8; MS (ESI) *m/z* (%): 518 ([M−H]$^-$, 100); HRMS (ESI) calcd for $C_{27}H_{40}N_3O_7^-$ [M−H]$^-$: 518.2872. Found 518.2869; Anal. Calcd for $C_{27}H_{41}N_3O_7$: C, 62.41; H, 7.95; N, 8.09. Found: C, 62.24; H, 8.07; N, 8.00.

4.2.6. Cleavage of *tert*-butyl protecting group

A solution of the *tert*-butyl ester derivative (1.0 mmol) in 50% TFA/CH_2Cl_2 (0.5 M) was stirred for 1–3 h at room temperature. After the completion of the reaction, the organic

solvent was evaporated under reduced pressure and the residue was purified by recrystallization using diethyl ether/petroleum ether (bp 40–60 °C).

4.2.6.1. (*S*)-2-(2-(2-Oxo-6-phenylhexanamido)hexanamido)acetic acid (13a)— Yield 88%; Colorless oil; $[\alpha]_D^{20}$ −14.2 (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.52 (br s, 1H, OH), 7.78 (d, *J* = 8.8 Hz, 1H, NH), 7.47–7.06 (m, 6H, 5x arom, NH), 4.70–4.45 (m, 1H, CH), 4.15–3.90 (m, 2H, C*H*$_2$COOH), 2.92 (t, *J* = 6.4 Hz, 2H, $COCOCH_2$), 2.62 (t, *J* = 6.6 Hz, 2H, $PhCH_2$), 2.05–1.50 (m, 6H, 3xCH_2), 1.48–1.12 (m, 4H, 2xCH_2), 0.88 (t, *J* = 6.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 197.8, 172.4, 171.8, 160.2, 141.9, 128.29, 128.27, 125.7, 53.0, 41.3, 36.6, 35.5, 31.9, 30.7, 27.5, 22.6, 22.2, 13.8; MS (ESI) *m/z* (%): 375 ($[M-H]^-$, 100); Anal. Calcd for $C_{28}H_{28}N_2O_5$: C, 63.81; H, 7.50; N, 7.44. Found: C, 63.64; H, 7.69; N, 7.35.

4.2.6.2. (*S*)-2-(2-(6-(Naphthalen-2-yl)-2-oxohexanamido)hexanamido) acetic acid (13b)—Yield 98%; Yellowish syrup; $[\alpha]_D^{20}$ −10.9 (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.77–7.22 (m, 8H, arom, NH), 7.01 (br s, 1H, NH), 4.65–4.40 (m, 1H, CH), 4.02 (br s, 2H, CH_2COO), 2.93 (t, *J* = 6.6 Hz, 2H, CH_2COCO), 2.78 (t, *J* = 6.6 Hz, 2H, $PhCH_2$), 1.98–1.49 (m, 6H, 3xCH_2), 1.39–1.02 (m, 4H, 2xCH_2), 0.87 (t, *J* = 5.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 197.8, 172.6, 171.8, 160.2, 139.4, 133.5, 131.8, 127.8, 127.5, 127.3, 127.1, 126.3, 125.8, 125.0, 53.0, 36.6, 35.6, 31.9, 30.5, 30.4, 27.5, 22.6, 22.2, 13.8; MS (ESI) *m/z* (%): 425 ($[M-H]^-$, 100); Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.59; H, 7.09; N, 6.57. Found: C, 67.24; H, 7.23; N, 6.44.

4.2.6.3. (*S*)-2-((2-(6-(4-Methoxyphenyl)-2-oxohexanamido)hexyl)oxy)acetic acid (20d)—Yield 93%; Brown solid; mp 52–55 °C; $[\alpha]_D^{20}$ −10.9 (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.63 (br s, 1H, NH), 7.12 (d, *J*= 8.4 Hz, 2H, arom), 6.82 (d, *J*= 8.6 Hz, 2H, arom), 4.21–3.91 (m, 3H, CH, OC*H*$_2$COOH), 3.75 (s, 3H, CH_3O), 3.70–3.50 (m, 2H, CH_2O), 2.97–2.81 (m, 2H, $PhCH_2$), 2.65–2.48 (m, 2H, CH_2COCO), 1.74–1.48 (m, 6H, 3xCH_2), 1.40–1.20 (m, 4H, 2xCH_2), 0.93–0.80 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 198.9, 160.1, 157.6, 134.1, 129.2, 113.6, 55.2, 49.5, 36.6, 34.6, 30.9, 30.7, 29.6, 28.0, 22.6, 22.4, 13.9; MS (ESI) *m/z* (%): 392 ($[M-H]^-$, 100); HRMS (ESI) calcd for $C_{21}H_{30}NO_6^-$ $[M-H]^-$: 392.2079. Found 392.2084; Anal. Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 63.92; H, 8.09; N, 3.45.

4.3 *In vitro* PLA_2 activity assays

The activities of human GVIA $iPLA_2$, GIV $cPLA_2$ and GV $sPLA_2$ were determine using a group-specific mixed micelle modified Dole assay.[26,28,30] The substrate was prepared using slightly different conditions for each enzyme to achieve optimum activity: (i) GIVA $cPLA_2$ mixed micelle substrate consisted of 400 μM Triton X-100, 95.3 μM PAPC, 1.7 μM arachidonyl-1-^{14}C PAPC, and 3 μM PIP_2 in a buffer containing 100 mM HEPES pH 7.5, 90 μM $CaCl_2$, 2 mM DTT, and 0.1 mg/ml BSA; (ii) GVIA $iPLA_2$ mixed micelle substrate consisted of 400 μM Triton X-100, 98.3 μM PAPC, and 1.7 μM arachidonyl-1-^{14}C PAPC in a buffer containing 100 mM HEPES pH 7.5, 2 mM ATP, and 4 mM DTT; and (iii) GV $sPLA_2$ mixed micelles substrate consisted of 400 μM Triton X-100, 98.3 μM PAPC, and 1.7 μM arachidonyl-1-^{14}C PAPC in a buffer containing 50 mM Tris-HCl pH 8.0, and 5 mM

$CaCl_2$. The compounds were initially screened at 0.091 mole fraction (5 μL of 5 mM inhibitor in DMSO) in substrate (495 uL). $X_I(50)$ was determined for compounds exhibiting greater than 95% inhibition. Inhibition curves were generated using GraphPad Prism 5.0 and the non-linear regression by plotting percentage of inhibition vs log (mole fraction) to calculate the reported $X_I(50)$ and its associated error.

Acknowledgments

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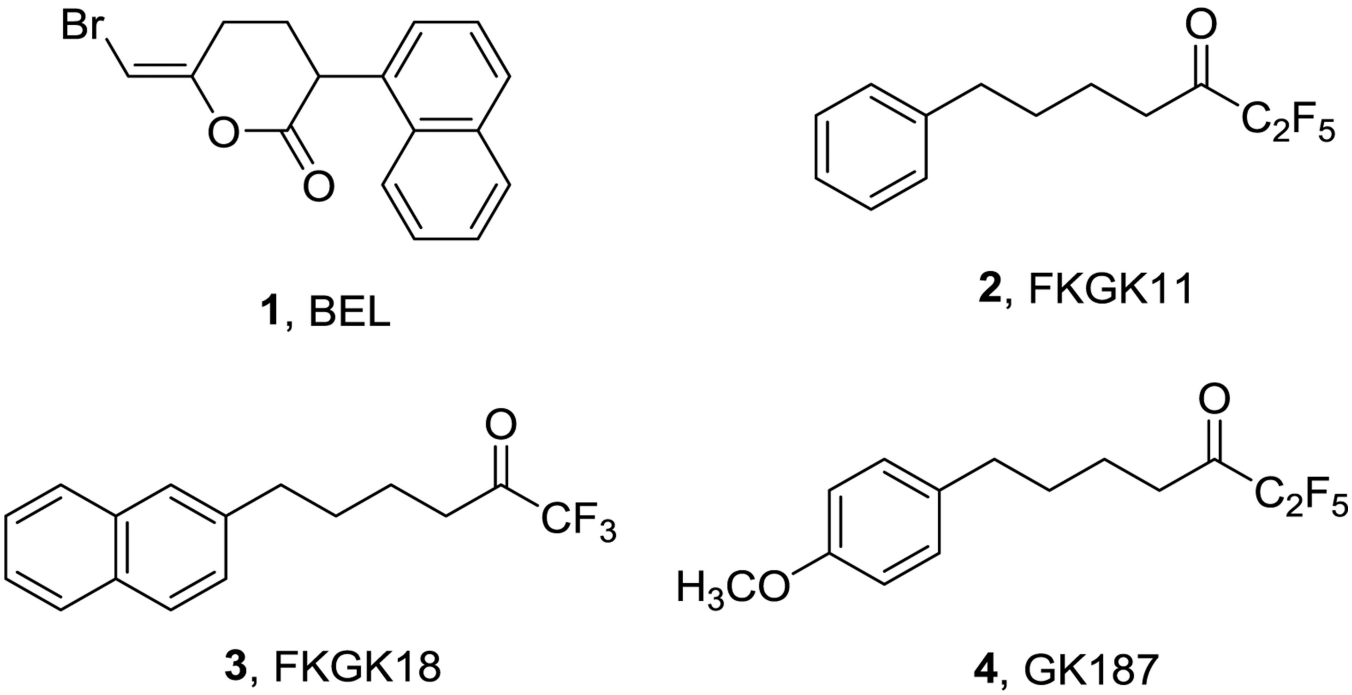


Figure 1.
Structures of known GVIA iPLA$_2$ inhibitors.

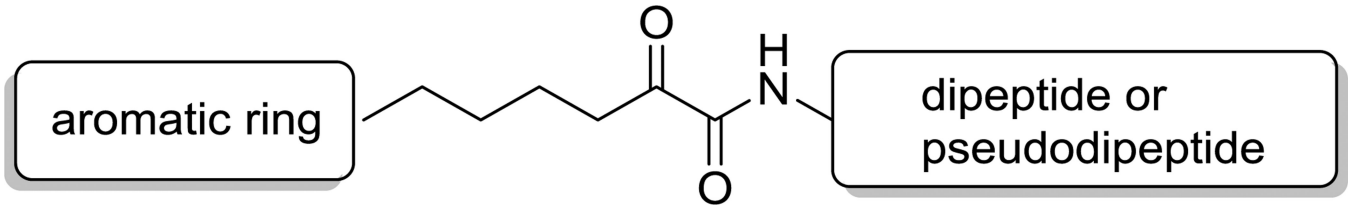
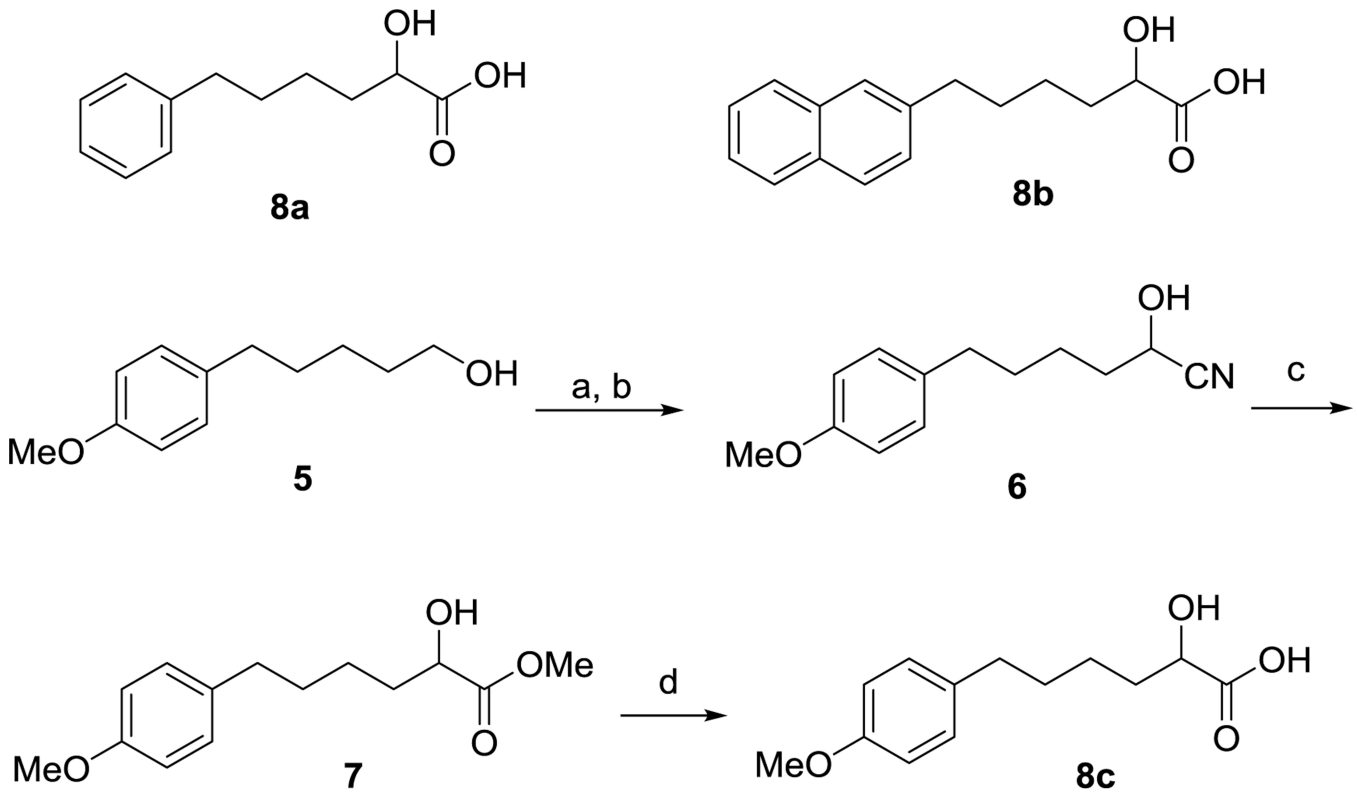
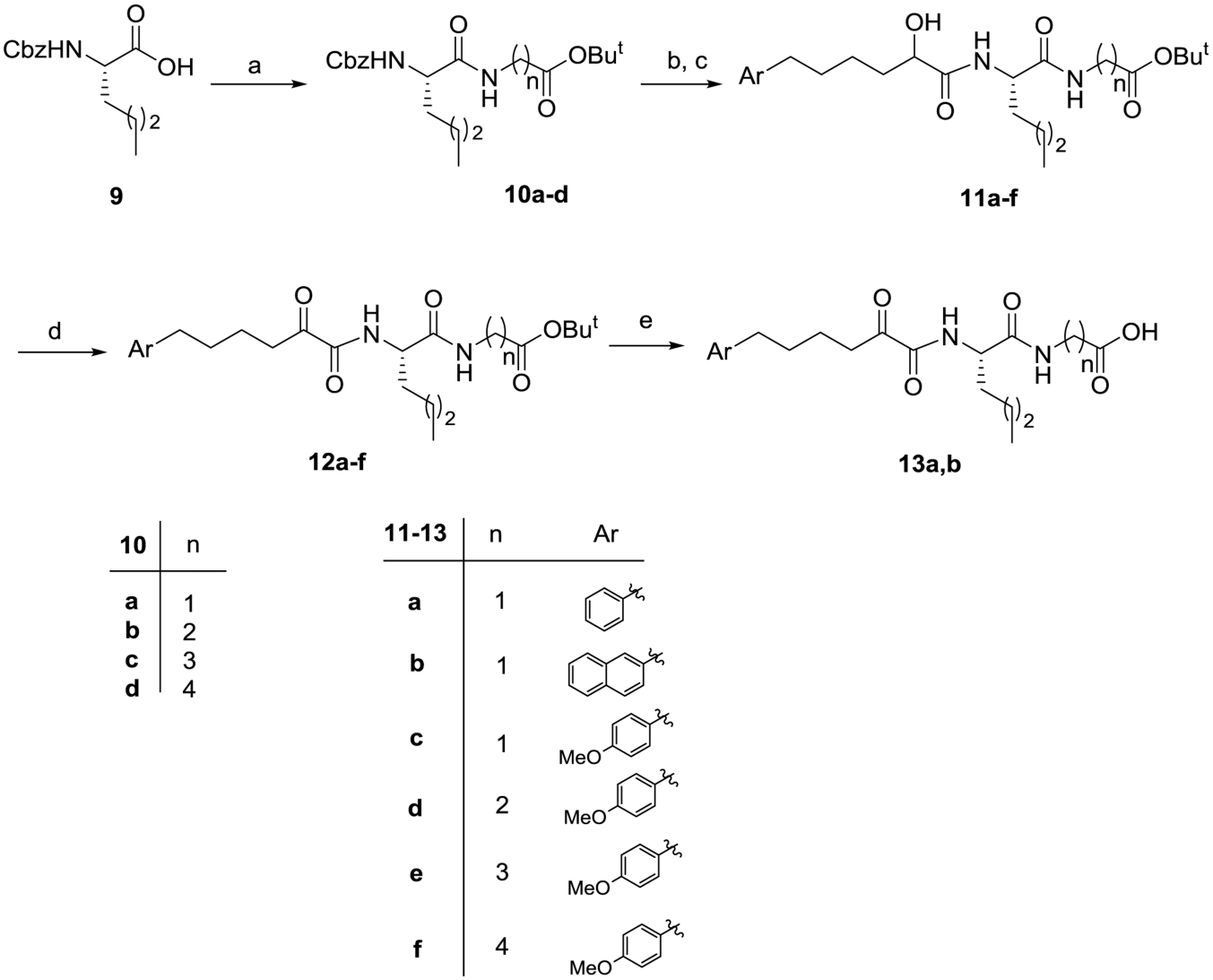


Figure 2.
Design of 2-oxoamides based on dipeptides.



Scheme 1.

Reagents and conditions: (a) NaBr, NaOCl, H_2O, $NaHCO_3$, toluene, AcNH-Tempo, AcOEt; (b) (i) $NaHSO_3$, CH_2Cl_2 (ii) KCN, H_2O; (c) 3N HCl/CH_3OH; (d) NaOH 1N, CH_3OH.

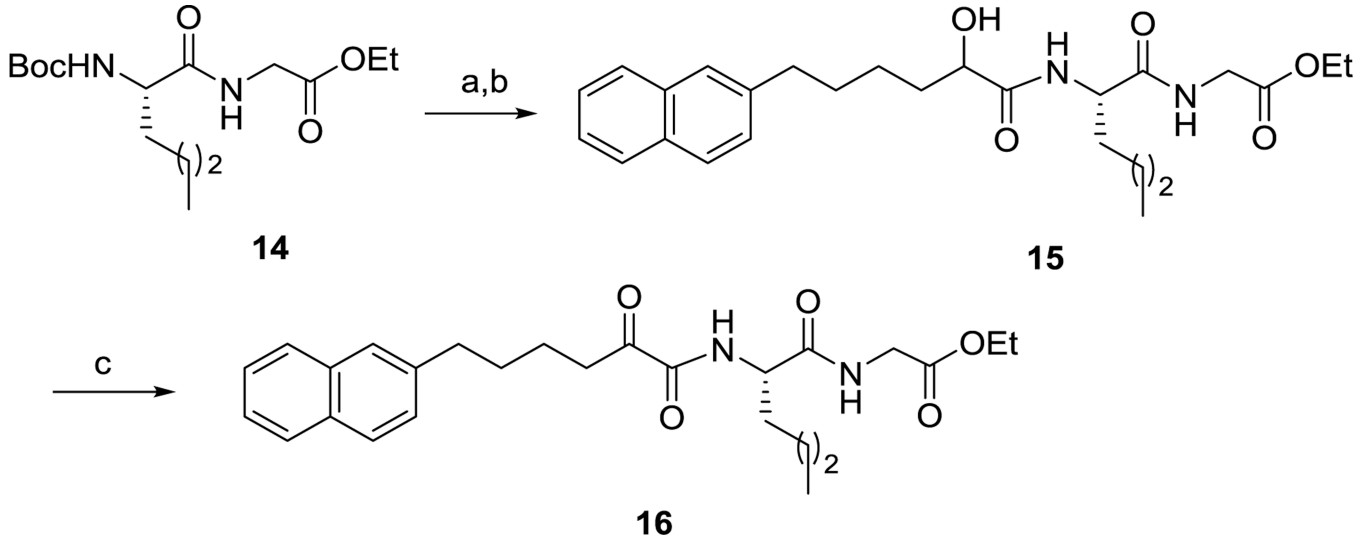


10	n
a	1
b	2
c	3
d	4

11-13	n	Ar
a	1	
b	1	
c	1	MeO
d	2	MeO
e	3	MeO
f	4	MeO

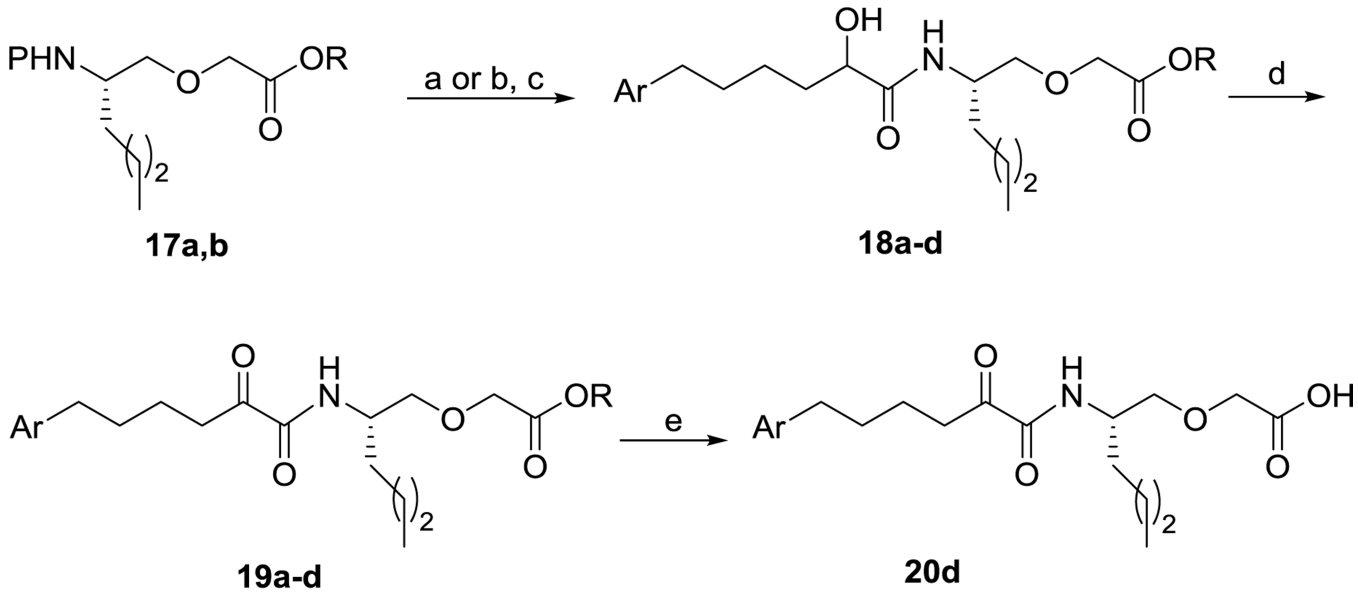
Scheme 2.

Reagents and conditions: (a) $HCl.H_2N(CH_2)_nCOOC(CH_3)_3$, WSCI.HCl, HOBt, Et_3N, CH_2Cl_2,; (b) H_2, 10% Pd/C, THF; (c) **8a–c**, WSCI.HCl, HOBt, Et_3N, CH_2Cl_2; (d) Dess-Martin periodinane, CH_2Cl_2; (e) 50% TFA/CH_2Cl_2.

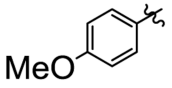
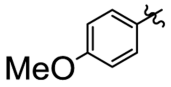
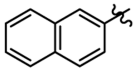


Scheme 3.

Reagents and conditions: (a) HCl/ Et_2O; (b) **8b**, WSCI.HCl, HOBt, Et_3N, CH_2Cl_2; (c) Dess-Martin periodinane.

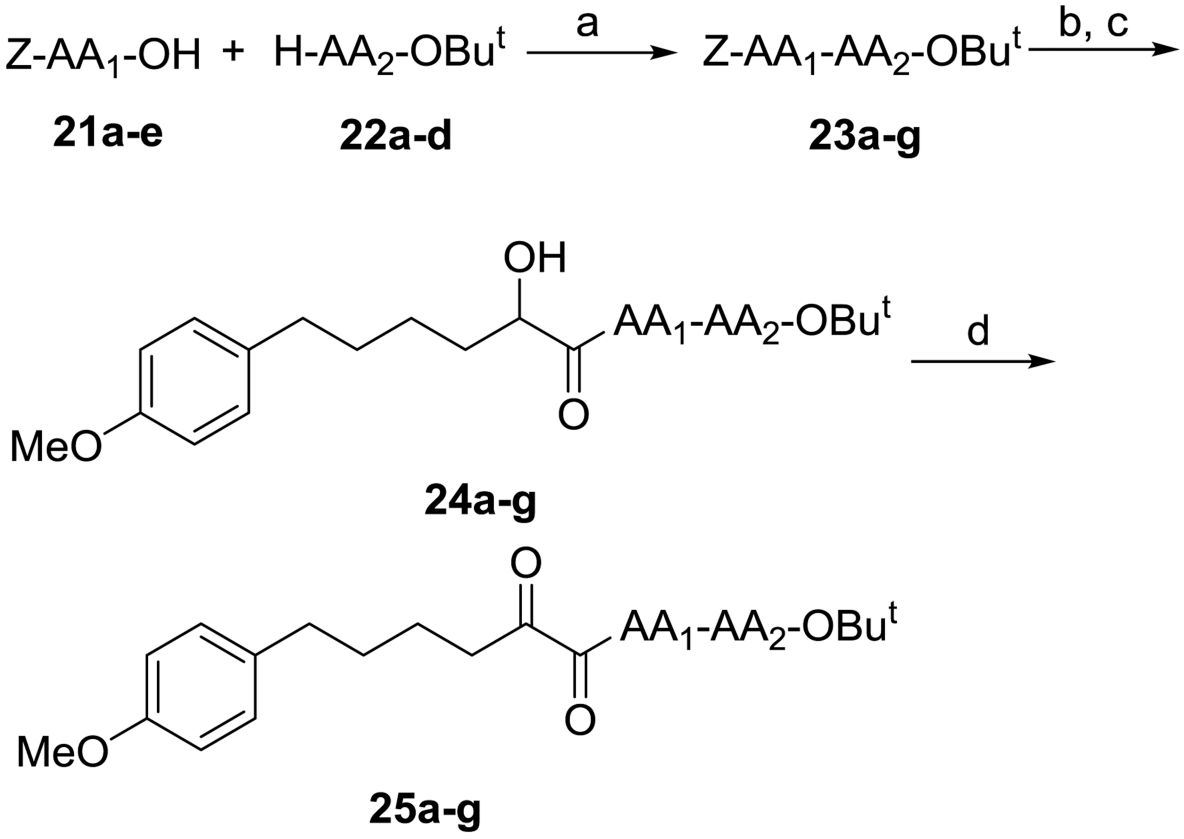


17	P	R
a	Boc	Et
b	Cbz	Bu^t

18-20	R	Ar
a	Et	
b	Bu^t	
c	Bu^t	
d	Bu^t	

Scheme 4.

Reagents and conditions: (a) TFA/CH_2Cl_2; (b) H_2, 10% Pd/C, THF; (c) **8a–c**, WSCI.HCl, HOBt, Et_3N, CH_2Cl_2; (d) Dess-Martin periodinane, CH_2Cl_2; (e) 50% TFA/CH_2Cl_2.



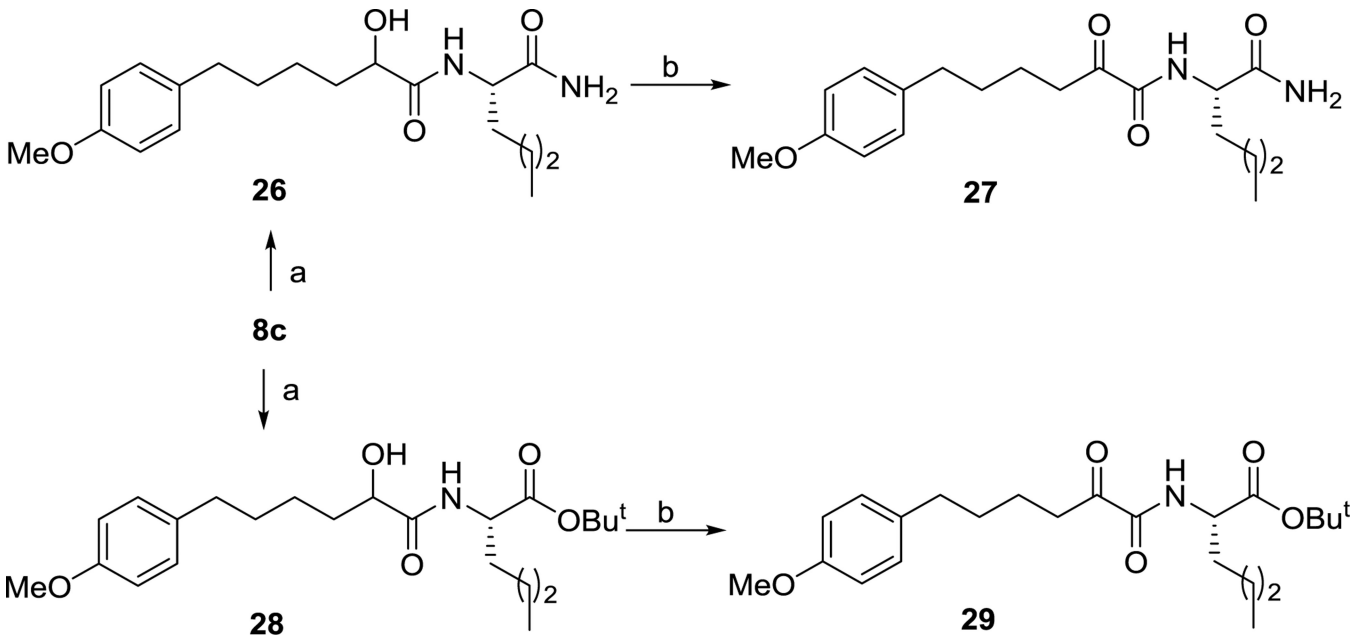
21	AA_1
a	L-Leu
b	L-Ile
c	L-Val
d	L-Nle
e	D-Nle

22	AA_2
a	Gly
b	L-Ala
c	D-Ala
d	GABA

23-25	AA_1	AA_2
a	L-Leu	Gly
b	L-Ile	Gly
c	L-Val	Gly
d	L-Nle	L-Ala
e	L-Nle	D-Ala
f	D-Nle	Gly
g	L-Leu	GABA

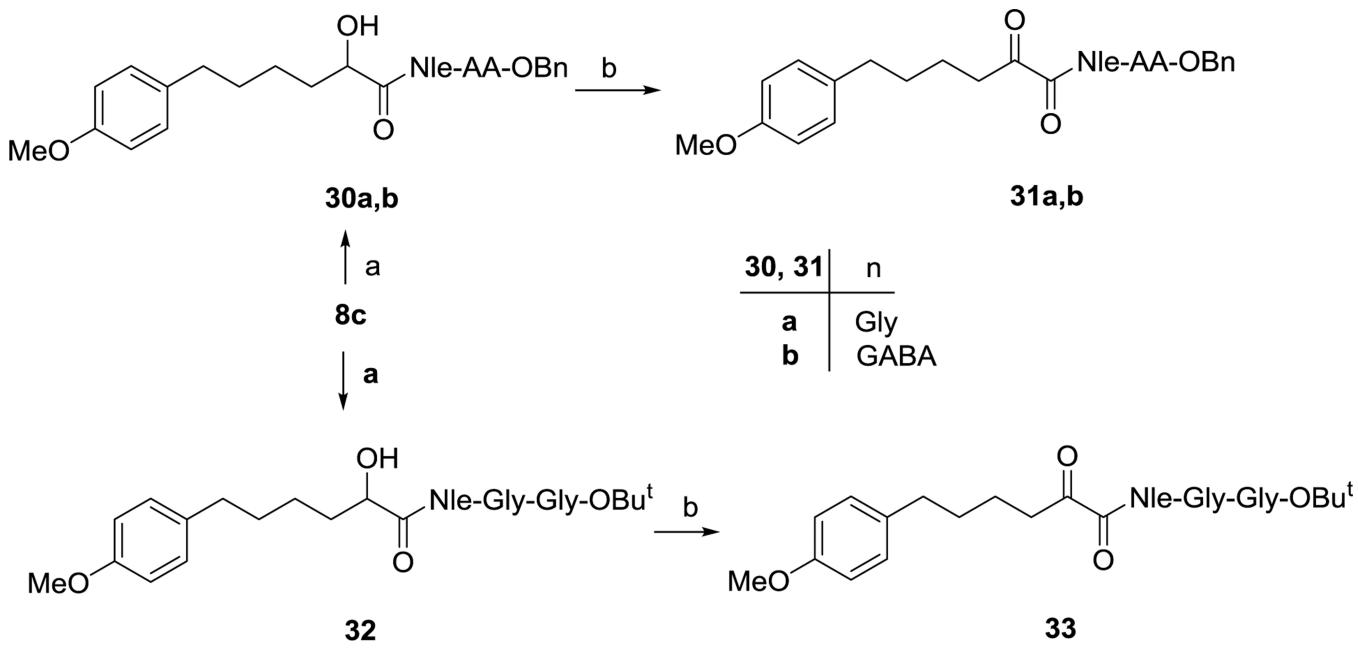
Scheme 5.

Reagents and conditions: (a) WSCI.HCl, HOBt, Et_3N, CH_2Cl_2; (b) H_2, 10% Pd/C, THF; (c) **8c**, WSCI.HCl, HOBt, Et_3N, CH_2Cl_2; (d) Dess-Martin periodinane, CH_2Cl_2.



Scheme 6.

Reagents and conditions: (a) Nle-NH_2 (for **26**) or Nle-OBu^t (for **28**), WSCI.HCl, HOBt, Et_3N, CH_2Cl_2; (b) Dess-Martin periodinane, CH_2Cl_2.

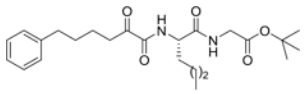
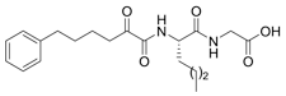
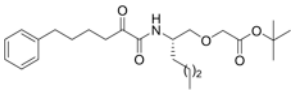
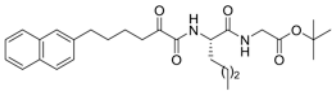
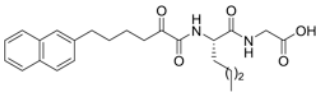
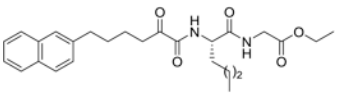
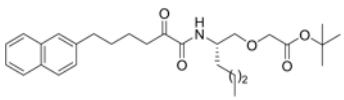
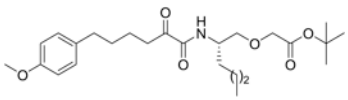
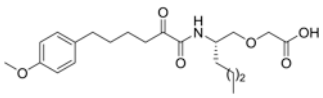
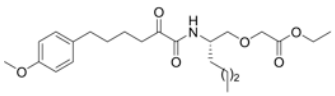
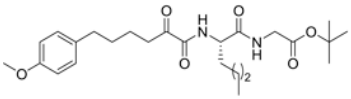


Scheme 7.

Reagents and conditions: (a) Nle-AA-OBn (for **30a,b**) or Nle-Gly-Gly-OBu^t (for **32**), WSCI.HCl, HOBt, Et_3N, CH_2Cl_2; (b) Dess-Martin periodinane, CH_2Cl_2.

Table 1

2-Oxoamides based on the dipeptide Nle-Gly and its ether analog containing various aromatic rings.[a]

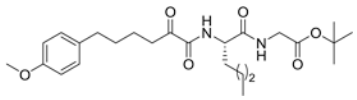
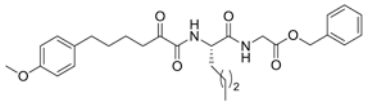
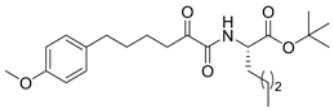
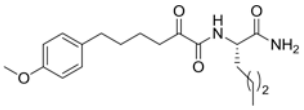
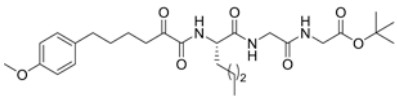
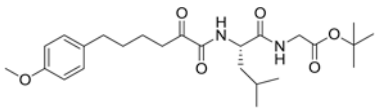
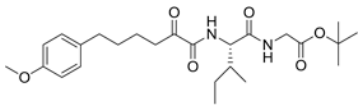
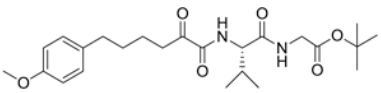
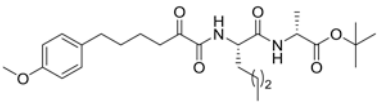
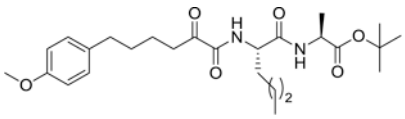
Number	Structure	% Inhbition		
		GVIA $iPLA_2$	GIVA $cPLA_2$	GV $sPLA_2$
12a		91.1 ± 0.6	46.9 ± 3.8	43.4 ± 5.5
13a		N.D.	N.D.	N.D.
19b		76.0 ± 3.5	82.3 ± 1.4	57.5 ± 4.6
12b		89.1 ± 1.0	57.5 ± 4.3	44.8 ± 5.7
13b		N.D.	43.1 ± 5.1	N.D.
16		77.1 ± 1.1	70.5 ± 3.8	54.4 ± 4.6
19c		88.4 ± 2.1	85.5 ± 1.0	63.9 ± 4.3
19d		93.6	-	-
20d		N.D.	-	-
19a		75.2	-	-
12c		>95 $X_I(50)$ 0.012 ± 0.002	40.2 ± 2.5	45.3 ± 3.3

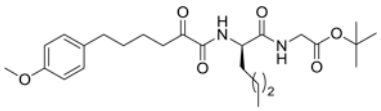
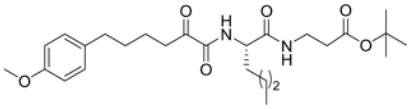
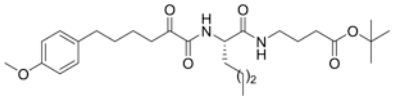
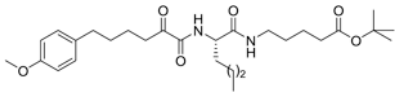
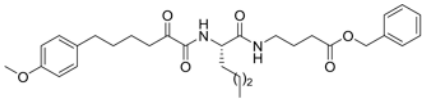
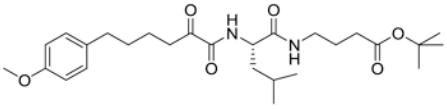
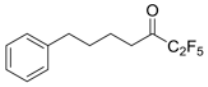
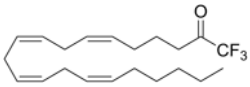
[a]Average percent inhibition and standard error (n = 3) are reported for each compound at 0.091 mol fraction. $X_I(50)$ values were determined for inhibitors with greater than 95% inhibition.

N.D. signifies compounds with less than 25% inhibition (or no detectable inhibition).

Table 2

2-Oxoamide analogs of inhibitor **12c**.[a]

Number	Structure	% Inhbition		
		GVIA iPLA$_2$	GIVA cPLA$_2$	GV sPLA$_2$
12c		>95 X_I(50) 0.012 ± 0.002	40.2 ± 2.5	45.3 ± 3.3
31a		>95 X_I(50) 0.026 ± 0.008	52.3 ± 1.2	N.D.
29		60.0 ± 3.0	85.7 ± 1.0	60.6 ± 3.2
27		66.2 ± 4.0	29.3 ± 2.6	31.1 ± 3.1
33		66.5 ± 2.5	27.1 ± 3.6	N.D.
22a		>95 X_I(50) 0.024 ± 0.06	51.6 ± 4.2	40.8 ± 5.2
22b		81.8 ± 4.6	57.3 ± 3.3	48.2 ± 9.3
22c		85.7 ± 1.7	35.4 ± 4.4	47.1 ± 4.0
22d		87.1 ± 1.0	73.4 ± 1.3	49.9 ± 0.8
22c		87.5 ± 1.9	57.4 ± 3.1	46.6 ± 6.6

Number	Structure	% Inhbition		
		GVIA iPLA$_2$	GIVA cPLA$_2$	GV sPLA$_2$
22f		>95 X_I(50) 0.04 ± 0.04	68.0 ± 0.4	39.3 ± 4.6
12d		83.1 ± 1.4	37.8 ± 2.3	32.5 ± 6.2
12e GK317		>95 X_I(50) 0.007 ± 0.001	52.6 ± 2.5	44.8 ± 4.5
12f		90.1 ± 2.5	64.5 ± 5.8	56.3 ± 4.5
31b		78.3 ± 9.3	47.9 ± 8.6	27.7 ± 4.8
22g		92.8 ± 1.0	58.0 ± 3.7	N.D.
FKGK11		X_I(50) 0.014[17]	N.D.[17]	28[17]
AACOCF$_3$		X_I(50) 0.028[13]	X_I(50) 0.036[13]	-

[a]Average percent inhibition and standard error (n = 3) are reported for each compound at 0.091 mol fraction. X_I(50) values were determined for inhibitors with greater than 95% inhibition.

N.D. signifies compounds with less than 25% inhibition (or no detectable inhibition).