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Journal

Bioorganic & Medicinal Chemistry, 24(19)

ISSN

0968-0896

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Publication Date

2016-10-01

DOI

10.1016/j.bmc.2016.07.057

Peer reviewed

HHS Public Access

Author manuscript

Bioorg Med Chem. Author manuscript; available in PMC 2017 October 01.

Published in final edited form as:

Bioorg Med Chem. 2016 October 1; 24(19): 4544–4554. doi:10.1016/j.bmc.2016.07.057.

2-Oxoamide inhibitors of cytosolic group IVA phospholipase A_2 with reduced lipophilicity

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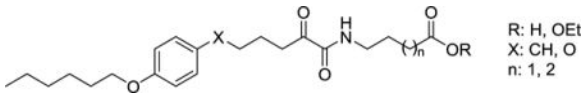
Abstract

Cytosolic GIVA phospholipase A_2 (GIVA $cPLA_2$) initiates the eicosanoid pathway of inflammation and thus inhibitors of this enzyme constitute novel potential agents for the treatment of inflammatory diseases. Traditionally, GIVA $cPLA_2$ inhibitors have suffered systemically from high lipophilicity. We have developed a variety of long chain 2-oxoamides as inhibitors of GIVA PLA_2. Among them, AX048 was found to produce a potent analgesic effect. We have now reduced the lipophilicity of AX048 by replacing the long aliphatic chain with a chain containing an ether linked aromatic ring with in vitro inhibitory activities similar to AX048.

Graphical abstract



Keywords

GIVA $cPLA_2$; Inhibitors; Lipophilicity; 2-Oxoamides; Phospholipase A_2

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1. Introduction

Cytosolic Group IVA phospholipase A_2 (GIVA $cPLA_2$) is an enzyme which plays a central role in inflammatory diseases.[1, 2] It catalyzes the hydrolysis of the ester bond at the *sn*-2 position of glycerophospholipids releasing free fatty acids, including arachidonic acid, and lysophospholipids. Arachidonic acid initiates the cascade of bioactive eicosanoids, while lysophospholipids may be converted to other bioactive lipids such as platelet activating factor (PAF) or lyso-phosphatidic acid (LPA). Therefore, inhibitors of PLA_2 may regulate the production of a large number of inflammatory mediators and their discovery has attracted widespread interest in finding new medicinal agents for the treatment of inflammatory diseases.

A great variety of synthetic GIVA $cPLA_2$ inhibitors have been reported in the literature and they have been summarized in recent review articles.[2–4] The first inhibitor of GIVA $cPLA_2$ reported was the arachidonoyl trifluoromethyl ketone (**1**, Fig 1).[5] Wyeth has reported a series of indole-based inhibitors.[6–10]

Among them, ecopladib[7] (**2**, Fig 1) showed oral efficacy in inflammation models and advanced to phase I clinical trials, while giripladib (**3**, Fig 1) showed oral efficacy in vivo and was advanced into a phase II clinical trial for osteoarthritis. However, the trials were terminated because of standard gastrointestinal issues. Another important class of inhibitors, pyrrolidine-based compounds, was developed by Shionogi. Pyrrophenone (**4**, Fig 1) is a potent inhibitor, which strongly inhibited arachidonic acid release, prostaglandin E_2, as well as thromboxane B_2 and leukotriene B_4 formation in human whole blood.[11, 12] The structurally related inhibitor, pyrroxyphene[13] (**5**, Fig 1) displayed anti-arthritic and anti-bone destructive action in a murine arthritis model.[14] A great number of 1,3-disubstituted propan-2-ones have been synthesized and tested, for example compound **6**.[15–22] We have developed various long chain 2-oxoamides as inhibitors of GIVA PLA_2.[23–27] One of them, namely AX048 (**7**, Fig 1),[28] was found to be systemically bioavailable producing a potent analgesic effect. In vivo, intrathecal (30 μg) and systemic (0.2–3 mg/kg i.p.) administration of AX048 blocked carrageenan hyperalgesia and after systemic delivery in a model of spinally mediated hyperalgesia induced by substance P.

Usually, GIVA $cPLA_2$ inhibitors suffer from high lipophilicity, which has as a consequence poor aqueous solubility and poor bioavailability. In the past, efforts to lower the lipophilicity of GVIA $cPLA_2$ inhibitors have been accomplished.[22, 29–31] As an example, Lehr and coworkers developed 1,3-disubstituted propan-2-ones with reduced lipophilicity.[22] The aim of the present work is to develop 2-oxoamides with reduced lipophilicity focusing on the inhibitor AX048 which demonstrates analgesic effect.[28] In an effort to identify more “drug-like” inhibitors, several new 2-oxoamides were designed and synthesized and their in vitro activities are presented here.

2. Results and discussion

2.1. Design of inhibitors with reduced lipophilicity

The mechanistic details of GIVA cPLA$_2$ abstraction of its phospholipid substrate from the lipid-water interface at the membrane surface have recently been described.[32, 33] Synthetic lipophilic inhibitors of this enzyme are likely to partition into membranes prior to interacting with the enzyme and good inhibitors have all possessed substantial lipophilicity. When the lipophilicity of an inhibitor decreases, the inhibitory potency may decrease, but bioavailability may increase.

Our goal in this study was to design inhibitors which retained the potency of AX48, but with reduced lipophilicity.

The lipophilicity of the inhibitors is measured by the ClogP value. In Figure 1, the ClogP values of several common GIVA cPLA$_2$ inhibitors, calculated by ChemOffice Ultra 11.00. are presented. It is quite clear that these inhibitors present a common drawback: high lipophilicity. The ClogP values for these inhibitors range from 6.55 to 10.75.

Inhibitors with such high values are not expected to present favorable ADME properties according to Lipinski's rule of five.[34] The main lipophilic part of the oxoamide inhibitor AX048 is the long aliphatic chain. To decrease the lipophilicity, we envisaged the replacement of it by chains incorporating an aromatic ring along with one or two ether oxygens. These ether oxygens can be placed either near or at remote distance from the activated carbonyl, which interacts with the active site serine. Another option is the introduction of polar functionalities such as a sulfonamide or carboxylic group, at the end of the hydrophobic chain which may reduce the lipophilicity.

The compounds shown in Figure 2 were designed specifically to reduce lipophilicity without compromising inhibitory potency.

2.2. Synthesis of inhibitors

For the synthesis of the designed 2-oxoamides, a variety of 2-hydroxy acids were synthesized as shown in Schemes 1 and 2. First, the known esters **8**[35] and **9**[36], and esters **12** and **14**, synthesized as depicted in Scheme 1, were reduced to alcohols **15a–d**. Amino alcohol **18**, protected by the tosyl group, was prepared by the reduction of acid **16** using the mixed anhydride/NaBH$_4$ method[37] (Scheme 1). Alcohols **15a–d** and **18** were oxidized to aldehydes and subsequently converted to cyanohydrins **19a–e** (Scheme 2). 2-Hydroxy acids **21a–e** were obtained by conversion to hydroxyamides and hydrolysis under basic conditions.

Ethyl γ-amino butyrate (**22**) and ethyl 5-aminopentanoate (**23**) were coupled with 2-hydroxy acids **21a–e** and the products either oxidized to 2-oxoamides **25a–c** containing an ester group, or first hydrolyzed and subsequently oxidized to 2-oxoamides **27a–d** containing a free carboxyl group (Scheme 3). 2-Oxoamide derivative **28**, containing a terminal free carboxyl group, was obtained by oxidative conversion of the phenyl group of compound **24e**

to carboxyl using $NaIO_4$-$RuCl_3$.[38, 39] At the same time, the hydroxyamide functionality was also oxidized to an oxoamide (Scheme 3).

Compound **21d** was also coupled with *tert*-butyl 4-aminobutanoate (**30**). Oxidation of compound **31**, followed by treatment with trifluoroacetic acid afforded the target compound **33** (Scheme 4).

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 GIVA cPLA$_2$, GVIA iPLA$_2$ and GV sPLA$_2$ using previously described mixed micelle-based assays.[24–26] The inhibition results are presented in Table 1, 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 85% inhibition. The $X_I(50)$ is the mole fraction of the inhibitor in the total substrate interface required to inhibit the enzyme by 50%. The ClogP values of all synthesized inhibitors are also summarized in Table 1.

Initially, the long aliphatic chain of AX048 was replaced by chains containing an aromatic group along with an ether group. Analog **25b** exhibited very weak inhibitory activity on GIVA cPLA$_2$, but considerable activity on GVIA iPLA$_2$. However, analog **25a** inhibited both the intracellular enzymes GIVA cPLA$_2$ and GVIA iPLA$_2$ with $X_I(50)$ values of 0.020 and 0.013, respectively. In the case of 2-oxoamides containing an ester group, the position of the O atom influences the activity toward GVIA cPLA$_2$. When the oxygen is at the δ-position from the activated carbonyl group, inhibitor **25b** only weakly inhibits cPLA$_2$, while when it is on the other side of the aromatic group with a greater distance from the activated carbonyl, good inhibition is observed. The 2-oxoamides **27b** and **27a**, that contain a free carboxyl group, selectively inhibited GIVA cPLA$_2$ without affecting GVIA iPLA$_2$ activity. This is in agreement with our previous observations that 2-oxoamides containing a free carboxyl group selectively inhibit GIVA cPLA$_2$.[25, 26, 40] The inhibitor containing the O atom nearer to the activated carbonyl presented less inhibitory potency than the one containing the O atom on the other side of the ring. Inhibitor **25a** not only possesses lower lipophilicity (ClogP 6.30) than that of AX048 (ClogP 7.61), but also exhibits the same inhibition of both GIVA cPLA$_2$ and GVIA iPLA$_2$ as AX048. In addition, the corresponding analog **27a** presented even better potency toward GIVA cPLA$_2$ ($X_I(50)$ values of 0.016) with a significantly lower lipophilicity (ClogP 5.32).

Compound **32**, containing two ether oxygens, did not present any significant inhibition of GIVA cPLA$_2$. However, increasing the distance between the oxoamide functionality and the free carboxyl by one carbon atom led to increase of the inhibitory potency on GIVA cPLA$_2$. Compound **27d** presents a $X_I(50)$ value of 0.013 for GIVA cPLA$_2$ and at the same time reduced lipophilicity (ClogP 4.82). Thus, compounds **27a** and **27d** clearly presented higher inhibitory potency on GIVA cPLA$_2$ in comparison to AX048 and its corresponding acid AX006[28] and considerably lower lipophilicity. In addition, both of them are more potent inhibitors of GIVA cPLA$_2$ than the widely known and commercially available inhibitor AATFMK ($X_I(50)$ value of 0.036).[21]

In another approach to reduce the lipophilicity, a sulfonamide group was introduced at the end of the long chain. Both the ethyl ester **25c** and the free acid **27c** presented lower lipophilicity (ClogP 5.69 and 4.71, respectively) than AX048. However, the *in vitro* activities were dramatically decreased. Only **25c** presented a weak inhibition of GIVA cPLA$_2$. Additionally, a carboxylic acid group was introduced at the end of the long chain, but this substitution resulted in a sizable reduction in the lipophilicity (ClogP 4.61). Unfortunately, this compound was inactive toward both GIVA cPLA$_2$ and GVIA iPLA$_2$. Thus, although the introduction of the sulfonamide or the carboxyl functionalities led to compounds with reduced lipophilicities (**25c**, **27c**, **28**), these compounds displayed a dramatic loss in the inhibitory activity.

3. Conclusion

Lipophilicity is a very important parameter in the case of GIVA cPLA$_2$ inhibitors because this enzyme exhibits its catalytic action at the lipid-water interface. Thus, a potential PLA$_2$ inhibitor has to possess substantial lipophilicity, which usually leads to unfavorable ADME properties. Efforts to reduce the lipophilicity are usually accompanied by reduced inhibitory activity. We achieved a reduction in the lipophilicity of the *in vivo* active 2-oxoamide inhibitor AX048 by replacing the long aliphatic chain with a chain containing an aromatic ring along with one or two ether oxygens. These new derivatives (**25a**, **27a** and **27d**) possess *in vitro* inhibitory activities against GIVA cPLA$_2$ and GVIA iPLA$_2$ similar to AX048. Thus, we achieved a reduction in the lipophilicity without compromising inhibitory potency.

4. Experimental section

4.1. General

Melting points were determined on a Buchi 530 apparatus and are uncorrected. NMR spectra were recorded on a Varian Mercury spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz respectively in $CDCl_3$ or as specified. Chemical shifts are given in ppm, and peak multiplicities are described as follows: s, singlet, d, doublet, t, triplet and m, multiplet. Electron spray ionization (ESI) mass spectra were recorded on a Finnigan, Surveyor MSQ Plus spectrometer. TLC plates (Silica Gel 60 F254) and Silica Gel 60 (70–230 or 230–400 mesh) for column chromatography were purchased from Merck. Spots were visualized with UV light and/or phosphomolybdic acid and/or ninhydrin, both in EtOH. Dichloromethane was dried by standard procedures and stored over molecular sieves. All other solvents and chemicals were reagent grade and used without further purification.

The synthesis of compounds **8**,[35] **9**[36] has been described previously.

4.2. Chemistry

4.2.1. (*E*)-Methyl 12-phenyldodec-11-enoate (11)—To a stirred solution of $Br^-P^+Ph_3(CH_2)_9COOCH_3$ (579 mg, 1.1 mmol) in dry THF (4 mL) under N_2 atmosphere, NaH (53 mg, 2.2 mmol) was added, followed by a solution of benzaldehyde (106 mg, 1.0 mmol) in dry THF (0.3 mL). The reaction mixture was stirred under N_2 atmosphere overnight at room temperature. The organic solvent was evaporated under reduced pressure, and H_2O (5 mL) was added dropwise. The product was extracted with Et_2O (3 × 5 mL), and

the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using petroleum ether (bp 40–60 °C)/EtOAc 95:5 as eluent. Yield 76%; white oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.34–7.14 (m, 5H, Ph), 6.38 (d, 1H, Ph*CH*=CH, J = 11.8 Hz), 5.70–5.57 (dt, 1H, PhCH=*CH*, J_1 = 11.8 Hz, J_2 = 7.0 Hz), 3.63 (s, 3H, OCH_3), 2.35–2.20 (m, 4H, CH_2CO, CH_2), 1.75–1.55 (m, 2H, CH_2), 1.40–1.35 (m, 2H, CH_2), 1.34–1.10 (m, 10H, 5 × CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.2, 137.7, 133.1, 128.7, 128.0, 126.3, 125.8, 51.3, 34.0, 33.0, 29.9, 29.3, 29.2, 29.1, 29.0, 28.5, 24.9. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.01; H, 9.92.

4.2.2. Methyl 12-phenyldodecanoate (12)—To a solution of **11** (288 mg, 1.0 mmol) in EtOH (5 mL) (through which N_2 had been passed for 5 min), 10% Pd/C catalyst (11 mg) was added. The reaction mixture was stirred under H_2 atmosphere overnight at room temperature. The catalyst was removed by filtration through a pad of Celite, and the organic solvent was evaporated under reduced pressure. The residue was purified by column chromatography using petroleum ether (bp 40–60 °C)/EtOAc as eluent. Yield 81%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–7.20 (m, 5H, Ph), 3.74 (s, 3H, OCH_3), 2.69 (t, 2H, $PhCH_2$, J = 7.2 Hz), 2.38 (t, 2H, CH_2CO, J = 7.4 Hz), 1.78–1.60 (m, 4H, 2 × CH_2), 1.42–1.15 (m, 14H, 7 × CH_2) ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.0, 142.7, 128.2, 128.1, 125.4, 51.2, 35.9, 34.0, 31.4, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 24.8. Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.22; H, 10.58.

4.2.3. Ethyl 4-(4-(hexyloxy)phenoxy)butanoate (14)—To a stirred solution of **13** (194 mg, 1.0 mmol) in acetone (8 mL), K_2CO_3 (414 mg, 3 mmol) and ethyl 4-bromobutyrate (0.2 mL, 1.5 mmol) were added and the reaction mixture was refluxed overnight. The organic solvent was evaporated under reduced pressure and the residue was treated with H_2O to remove potassium carbonate and extracted with CH_2Cl_2 (3 × 5 mL). The organic solvent was evaporated under reduced pressure and the residue was purified by column chromatography using petroleum ether (bp 40–60 °C)/EtOAc 8/2 as eluent. Yield 100%; colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.90–6.70 (m, 4H, arom), 4.09 (q, 2H, OCH_2CH_3, J = 6.0 Hz), 3.90 (t, 2H, OCH_2, J = 6.0 Hz), 3.84 (t, 2H, OCH_2, J = 6.0 Hz), 3.42 (t, 2H, CH_2COO, J = 6.0 Hz), 2.60–2.30 (m, 4H, 2 × CH_2), 2.20–1.90 (m, 4H, 2 × CH_2), 1.71 (quintet, 2H, CH_2, J = 6.0 Hz), 1.22 (t, 3H, OCH_2CH_3, J = 6.0 Hz), 0.86 (t, 3H, CH_3, J = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.1, 153.2, 152.7, 115.1, 68.4, 67.1, 60.2, 32.3, 30.7, 29.2, 27.6, 25.6, 24.6, 14.1, 13.9. Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.98; H, 9.30.

4.2.4. General method for the reduction of esters to alcohols—To a stirred solution of the ester **8, 9** or **12** (1.0 mmol) in dry Et_2O (10 mL), a solution of 1.0 M DIBALH in hexane (2.5 mL, 2.5 mmol) was added dropwise under N_2 atmosphere at room temperature. The mixture was stirred for 2 h after the addition was complete, and then H_2O (5 mL) was added dropwise. The entire mixture was stirred for 30 more min, and then filtered through a pad of Celite. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography using petroleum ether (bp 40–60 °C)/ EtOAc as eluent.

4.2.4.1. 5-(4-(Hexyloxy)phenyl)pentan-1-ol (15a): Yield 72%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.29 (d, 2H, arom, J = 8.8 Hz), 7.03 (d, 2H, arom, J = 8.8 Hz), 4.15 (t, 2H, CH_2OPh, J = 6.6 Hz), 3.84 (t, 2H, CH_2OH, J = 6.2 Hz), 2.78 (t, 2H, PhCH_2, J = 7.4 Hz), 2.43 (bs, 1H, OH), 2.05–1.95 (m, 2H, CH_2), 1.88–1.45 (m, 12H, 6 × CH_2), 1.13 (t, 3H, CH_3, J= 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.2, 134.4, 129.1, 114.3, 68.0, 62.8, 34.9, 32.6, 31.6, 31.4, 29.3, 25.7, 25.3, 22.6, 14.0. Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.06; H, 10.85.

4.2.4.2. 4-(4-Octylphenoxy)butan-1-ol (15b): Yield 84%; white solid; mp 42–44 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.09 (d, 2H, arom, J = 8.8 Hz), 6.82 (d, 2H, arom, J = 8.8 Hz), 3.99 (t, 2H, CH_2OPh, J = 5.8 Hz), 3.73 (t, 2H, CH_2OH, J = 5.8 Hz), 2.55 (t, 2H, PhCH_2, J = 7.4 Hz), 2.38 (bs, 1H, OH), 1.98–1.20 (m, 16H, 8 × CH_2), 0.89 (t, 3H, CH_3, J= 6.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.8, 135.2, 129.2, 114.3, 67.7, 62.6, 35.0, 31.9, 31.7, 29.5, 29.4, 29.2, 25.9, 22.6, 14.1. Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.36; H, 10.98.

4.2.4.3. 12-Phenyldodecan-1-ol (15c): Yield 99%; white solid; mp 42–44 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–7.21 (m, 5H, Ph), 3.71 (t, 2H, CH_2OH, J = 6.6 Hz), 2.68 (t, 2H, PhCH_2, J= 7.4 Hz), 2.56 (bs, 1H, OH), 1.70–1.58 (m, 4H, 2 × CH_2), 1.45–1.24 (m, 16H, 8 × CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 142.9, 128.4, 128.2, 125.5, 63.1, 36.0, 32.8, 31.5, 29.6, 29.5, 29.4, 29.3, 25.7. Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.16; H, 11.79.

4.2.5. 4-(4-(Hexyloxy)phenoxy)butan-1-ol (15d)—To a stirred solution of the ester **14** (308 mg, 1.0 mmol) in dry THF (3.3 mL) a solution of 1.0 M $LiAlH_4$ in THF (1.1 mL, 1.1 mmol) was added dropwise under N_2 atmosphere and the mixture was refluxed for 4 h. After cooling to room temperature, HCl 1N (4.4 mL, 4.4 mmol) was added dropwise and the mixture was stirred for 1 h. The solvent was evaporated under reduced pressure and AcOEt and H_2O were added. The aqueous layer was separated and washed with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using petroleum ether (bp 40–60 °C)/EtOAc 6/4 as eluent. Yield 65%; white solid; mp 49–51 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.80–6.60 (m, 4H, arom), 3.79 (t,, 2H, OCH_2, J = 6.0 Hz), 3.75 (t, 2H, OCH_2, J = 6.0 Hz), 3.54 (t, 2H, CH_2OH, J = 6.0 Hz), 3.06 (bs, 1H, OH), 1.80–1.40 (m, 6H, 3 × CH_2), 1.40–1.10 (m, 6H, 3 × CH_2), 0.78 (t, 3H, CH_3, J = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 152.9, 152.6, 115.0, 68.2, 68.0, 61.8, 31.3, 29.0, 25.6, 25.4, 22.3, 20.6, 13.8. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.02; H, 9.98.

4.2.6. 11-(4-Methylphenylsulfonamido)undecanoic acid (17)—To a solution of 11-amino-undecanoic acid (**16**) (201 mg, 1.0 mmol) in dry THF (1 mL), N-methylmorpholine was added (0.1 mL, 1.0 mmol) followed by a solution of tosyl chloride (191 mg, 1.0 mmol) in dry THF (1 mL), dropwise over 15 minutes. The reaction mixture was then stirred for 3 h. The organic solvent was evaporated under reduced pressure, H_2O (5 mL) was added, and the pH was adjusted to 2 with 6N HCl. The product was extracted with $CHCl_3$ (3 × 5 mL), and

the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using $CHCl_3$/MeOH 95:5 as eluent. Yield 30%; white solid; mp 78–80°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.60 (br s, 1H, COOH), 7.70 (d, 2H, arom, J = 8.0 Hz), 7.25 (d, 2H, arom, J = 8.0 Hz), 5.08 (br s, 1H, NH), 2.94–2.63 (m, 2H, NHCH_2), 2.37 (s, 3H, CH_3), 2.29 (t, 2H, CH_2COOH, J= 7.4 Hz), 1.62–0.95 (m, 16H, 8 × CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.3, 143.2, 136.8, 129.6, 127.0, 43.1, 33.9, 29.3, 29.2, 29.1, 29.0, 28.9, 26.4, 24.6, 21.4. Anal. Calcd for $C_{18}H_{29}NO_4S$: C, 60.82; H, 8.22; N, 3.94. Found: C, 60.72; H, 8.39; N, 3.84.

4.2.7. *N*-(11-Hydroxyundecyl)-4-methylbenzenesulfonamide (18)—To a stirred solution of **17** (355 mg,1.0 mmol) in dry THF (5 mL) at −10 °C, NMM (0.11 mL, 1.0 mmol) was added, followed by ClCOOEt (0.096 mL, 1.0 mmol). After 10 min, $NaBH_4$ (0.11 g, 3.0 mmol) was added in one portion. MeOH (10 mL) was then added dropwise to the mixture over a period of 10 min at 0 °C. The solution was stirred for an additional 10 min and the organic solvents were evaporated under reduced pressure. The residue was neutralized with 1M aqueous $KHSO_4$ and the product was extracted with EtOAc (3 × 10 mL). The organic phase was washed with 1M aqueous $KHSO_4$ (5 mL), H_2O (10 mL), 5% aqueous $NaHCO_3$ (5 mL), and H_2O (10 mL), dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography using $CHCl_3$/MeOH 95:5 as eluent. Yield 45%; white solid; mp 63–65°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.72 (d, 2H, arom, J = 8.0 Hz), 7.22 (d, 2H, arom, J = 8.0 Hz), 4.68 (t, 1H, NH, J = 6.4 Hz), 3.60 (t, 2H, CH_2OH, J= 6.6 Hz), 2.98–2.80 (m, 2H, NHCH_2), 2.61 (bs, 1H, OH), 2.40 (s, 3H, CH_3), 1.62–1.10 (m, 18H, 9 × CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 143.2, 137.8, 129.6, 127.0, 63.0, 43.1, 32.7, 29.5, 29.3, 29.0, 26.4, 25.6, 21.5. Anal. Calcd for $C_{18}H_{31}NO_3S$: C, 63.31; H, 9.15; N, 4.10. Found: C, 63.21; H, 9.22; N, 4.01.

4.2.8. General method for the synthesis of cyanohydrins 19a–e—To a solution of the alcohol **15a–d** or **18** (1.0 mmol) in a mixture of toluene (3 mL) and EtOAc (3 mL), a solution of NaBr (0.11 g, 1.1 mmol) in water (0.5 mL) was added followed by AcNH-TEMPO (2.2 mg, 0.01 mmol). To the resulting biphasic system, which was cooled at 0 °C, an aqueous solution of 0.35 M NaOCl (3.1 mL, 1.1 mmol) containing $NaHCO_3$ (0.25 g, 3 mmol) was added dropwise under vigorous stirring, at 0 °C over a period of 1 h. After the mixture had been stirred for a further 15 min at 0 °C, EtOAc (10 mL) and H_2O (10 mL) were added. The aqueous layer was separated and washed with EtOAc (2 × 10 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 without any further purification.

To a stirred solution of the aldehyde (1 mmol) in CH_2Cl_2 (1.25 mL), a solution of $NaHSO_3$ (156 mg, 1.5 mmol) in water (0.25 mL) was added and the mixture was vigorously stirred for 30 min at room temperature. The organic solvent was evaporated under reduced pressure, water was added and the mixture was cooled at 0 °C. Then, a solution of KCN (98 mg, 1.5 mmol) in water (0.25 mL) was added dropwise over a period of 3.5 h and the mixture was left under stirring overnight at room temperature. The aqueous suspension was extracted

with CH_2Cl_2 (2 × 5 mL). The combined organic layers were 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 petroleum ether (bp 40–60 °C)/EtOAc as eluent.

4.2.8.1 6-(4-(Hexyloxy)phenyl)-2-hydroxyhexanenitrile (19a): Yield 80%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.09 (d, 2H, arom, J = 8.8 Hz), 6.84 (d, 2H, arom, J = 8.8 Hz), 4.44 (t, 1H, C*H*OH, J = 7.0 Hz), 3.95 (t, 2H, C*H*$_2$OPh, J= 6.6 Hz), 2.85 (bs, 1H, OH), 2.59 (t, 2H, PhCH_2, J = 7.0 Hz), 1.92–1.74 (m, 4H, 2 × CH_2), 1.71–1.43 (m, 6H, 3 × CH_2), 1.40–1.31 (m, 4H, 2 × CH_2), 0.92 (t, 3H, CH_3, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.3, 133.8, 129.2, 119.9, 114.5, 68.1, 61.2, 35.0, 34.6, 31.6, 30.9, 29.2, 25.7, 24.1, 22.6, 14.0. Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.58; H, 9.56; N, 4.73.

4.2.8.2. 2-Hydroxy-5-(4-octylphenoxy)pentanenitrile (19b): Yield 96%; white solid; mp 50–52 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.11 (d, 2H, arom, J = 8.4 Hz), 6.83 (d, 2H, arom, J = 8.4 Hz), 4.61 (br s, 1H, C*H*OH), 4.12–3.95 (m, 2H, PhOC*H*$_2$), 3.46 (br s, 1H, OH), 2.55 (t, 2H, C*H*$_2$Ph, J= 7.6 Hz), 2.15–1.95 (m, 4H, 2 × CH_2), 1.65–1.50 (m, 2H, CH_2), 1.38–1.19 (m, 10H, 5 × CH_2), 0.90 (t, 3H, CH_3, J = 6.2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.2, 135.8, 129.3, 119.8, 114.3, 67.2, 61.0, 35.0, 32.6, 31.8, 31.7, 29.4, 29.2, 24.7, 22.7, 14.1. Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63; N, 4.62. Found: C, 75.11; H, 9.78; N, 4.54.

4.2.8.3. 2-Hydroxy-13-phenyltridecanenitrile (19c): Yield 90%; white solid; mp 36–38 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.21 (m, 5H, Ph), 4.52 (t, 1H, C*H*OH, J= 7.0 Hz), 2.89 (br s, 1H, OH), 2.68 (t, 2H, PhCH_2, J= 7.4 Hz), 1.96–1.85 (m, 2H, CH_2), 1.78–1.60 (m, 2H, CH_2), 1.60–1.45 (m, 2H, CH_2), 1.45–1.10 (m, 14H, 7 × CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 142.9, 128.4, 128.2, 125.5, 120.0, 61.3, 35.9, 35.1, 29.5, 29.4, 29.3, 29.2, 28.9, 24.5. Anal. Calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.17; N, 4.87. Found: C, 79.28; H, 10.28; N, 4.75.

4.2.8.4. 5-(4-(Hexyloxy)phenoxy)-2-hydroxypentanenitrile (19d): Yield 45%; colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.90–6.70 (m, 4H, arom), 4.55 (t, 1H, C*H*OH, J = 6.0 Hz), 3.94 (t, 2H, OCH_2, J = 6.0 Hz), 3.89 (t, 2H, OCH_2, J = 6.0 Hz), 2.10–1.90 (m, 4H, 2 × CH_2), 1.74 (quintet, 2H, CH_2, J = 6.0 Hz), 1.60–1.20 (m, 6H, 3 × CH_2), 0.89 (t, 3H, CH_3, J = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.4, 152.3, 119.9, 115.4, 68.6, 67.7, 60.8, 32.3, 31.5, 29.2, 25.6, 24.6, 22.5, 14.0. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.90; H, 8.85; N, 4.92.

4.2.8.5. N-(11-Cyano-11-hydroxyundecyl)-4-methylbenzenesulfonamide (19e): Yield 73%; white solid; mp 77–79 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.72 (d, 2H, arom, J = 8.4 Hz), 7.28 (d, 2H, arom, J = 8.4 Hz), 4.73 (t, 1H, NH, J= 5.8 Hz), 4.45 (t, 1H, C*H*OH, J= 6.6 Hz), 2.88 (q, 2H, NHC*H*$_2$, J= 6.6 Hz), 2.40 (s, 3H, CH_3), 1.85–1.70 (m, 2H, CH_2), 1.68–1.05 (m, 16H, 8 × CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 143.4, 136.8, 129.7, 127.0, 120.2, 61.2, 43.1, 35.1, 29.4, 29.1, 29.0, 28.8, 28.7, 26.3, 24.4, 21.5. Anal. Calcd for $C_{19}H_{30}N_2O_3S$: C, 62.26; H, 8.25; N, 7.64. Found: C, 62.19; H, 8.34; N, 7.57.

4.2.9. General method for the synthesis of 2-hydroxy-amides 20a–e—A solution of 2-hydroxy-nitrile **19a–e** (1.0 mmol) in conc. HCl (2.5 mL) was stirred overnight at room

temperature. Then, water was added and the aqueous solution was extracted with $CHCl_3$ (3 × 15 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The organic solvent was evaporated under reduced pressure and the resulting 2-hydroxy-amide was precipitated using Et_2O.

4.2.9.1. 6-(4-(Hexyloxy)phenyl)-2-hydroxyhexanamide (20a): Yield 80%; white solid; mp 131–133 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.07 (d, 2H, arom, J = 8.4 Hz), 6.82 (d, 2H, arom, J = 8.4 Hz), 6.32 (br s, 1H, NH), 5.52 (br s, 1H, NH), 4.18–4.05 (m, 1H, C*H*OH), 3.93 (t, 2H, C*H*$_2$OPh, J= 6.6 Hz), 2.57 (t, 2H, CH_2, J= 7.4 Hz), 2.40 (bs, 1H, OH), 2.25–1.98 (m, 2H, CH_2), 1.93–1.10 (m, 12H, 6 × CH_2), 0.91 (t, 3H, CH_3, J= 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.2, 157.3, 133.9, 129.1, 114.6, 74.9, 68.0, 35.8, 35.0, 31.4, 30.8, 29.3, 25.6, 24.4, 22.6, 14.0. Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.26; H, 9.62; N, 4.47.

4.2.9.2. 2-Hydroxy-5-(4-octylphenoxy)pentanamide (20b): Yield 67%; white solid; mp 130–132 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.05 (d, 2H, arom, J = 8.4 Hz), 6.80 (d, 2H, arom, J = 8.4 Hz), 6.31 (br, 1H, NH), 5.63 (br, 1H, NH), 4.15–4.05 (m, 1H, C*H*OH), 3.97 (t, 2H, PhOC*H*$_2$, J= 5.8 Hz), 2.52 (t, 2H, C*H*$_2$Ph, J= 7.2 Hz), 2.38 (bs, 1H, OH), 2.04–1.77 (m, 4H, 2 × CH_2), 1.78–1.65 (m, 1H, C*H*H), 1.60–1.45 (m, 3H, 1 × CH_2, CH*H*), 1.38–1.02 (m, 8H, 4 × CH_2), 0.89 (t, 3H, CH_3, J= 6.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.1, 156.4, 135.6, 129.2, 114.3, 75.0, 67.5, 35.8, 35.0, 32.0, 31.7, 31.4, 29.4, 29.3, 24.8, 22.0, 14.1. Anal. Calcd for $C_{19}H_{31}NO_3$: C, 70.99; H, 9.72; N, 4.36. Found: C, 70.87; H, 9.81; N, 4.28.

4.2.9.3. 2-Hydroxy-13-phenyltridecanamide (20c): Yield 73%; white solid; mp 117–119 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.27–7.17 (m, 5H, Ph), 6.33 (br s, 1H, NH), 5.52 (br s, 1H, NH), 4.20–4.02 (m, 1H, C*H*OH), 2.61 (t, 2H, PhCH_2, J= 7.4 Hz), 2.46 (br s, 1H, OH), 1.95–1.78 (m, 1H, C*H*H), 1.75–1.50 (m, 3H, CH*H*, CH_2), 1.48–1.02 (m, 16H, 8 × CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.1, 142.9, 128.4, 128.3, 125.5, 75.0, 36.0, 34.8, 31.4, 29.5, 29.4, 29.2, 29.1, 28.0. Anal. Calcd for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.59. Found: C, 74.63; H, 10.35; N, 4.48.

4.2.9.4. 5-(4-(Hexyloxy)phenoxy)-2-hydroxypentanamide (20d): Yield 65%; white solid; mp 146–148 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.90–6.70 (m, 4H, arom), 6.58 (bs, 1H, NH), 5.48 (bs, 1H, NH), 4.30–4.10 (m, 1H, C*H*OH), 3.98 (t, 2H, OCH_2, J = 6.0 Hz), 3.89 (t, 2H, OCH_2, J = 6.0 Hz), 2.10–1.50 (m, 6H, 3 × CH_2), 1.50–1.20 (m, 6H, 3 × CH_2), 0.89 (t, 3H, CH_3, J = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.6, 153.2, 152.6, 115.3, 71.1, 68.6, 68.3, 31.4, 31.1, 29.1, 25.5, 25.0, 22.4, 13.8. Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 65.79; H, 8.99; N, 4.68.

4.2.9.5. 2-Hydroxy-12-(4-methylphenylsulfonamido)dodecanamide (20e): Yield 50%; white solid; mp 101–103 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75 (d, 2H, arom, J = 8.4 Hz), 7.30 (d, 2H, arom, J = 8.4 Hz), 6.47 (m, 1H, N*H*H), 5.81 (m, 1H, CONH*H*), 4.93 (m, 1H, SO_2NH), 4.32–4.05 (m, 1H, C*H*OH), 3.00–2.82 (m, 2H, NHC*H*$_2$), 2.49 (bs, 1H, OH), 2.43 (s, 3H, CH_3), 2.00–1.58 (m, 4H, 2 × CH_2), 1.55–1.05 (m, 14H, 7 × CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.2, 143.3, 136.7, 129.8, 127.0, 74.9, 43.1, 35.5, 29.5, 29.4, 29.2, 29.1,

28.0, 26.2, 24.3, 21.4. Anal. Calcd for $C_{19}H_{32}N_2O_4S$: C, 59.35; H, 8.39; N, 7.29;. Found: C, 59.27; H, 8.44; N, 7.21.

4.2.10. General method for the synthesis of 2-hydroxy-acids 21a–e—To a solution of 2-hydroxy-amide **20a–e** (1.0 mmol) in a mixture of EtOH/water (2:1, 10 mL), KOH (0.56 g, 10.0 mmol) was added and the reaction mixture was refluxed for 4 h. After cooling, EtOH was removed under reduced pressure, water was added and the aqueous solution was acidified with conc. H_2SO_4 until pH 1, followed by extraction with Et_2O (3 × 5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The organic solvent was evaporated under reduced pressure and the residue was purified by recrystallization using $CHCl_3$/petroleum ether (bp 40–60 °C).

4.2.10.1. 6-(4-(Hexyloxy)phenyl)-2-hydroxyhexanoic acid (21a): Yield 96%; white solid; mp 94–96 °C; 1H NMR (200 MHz, $CDCl_3$): δ 7.08 (d, 2H, arom, J = 8.4 Hz), 6.83 (d, 2H, arom, J = 8.4 Hz), 4.91 (bs, 1H, OH), 4.28 (dd, 1H, C*H*OH, J_1 = 7.2 Hz, J_2 = 4.0 Hz), 3.94 (t, 2H, CH_2OPh, J = 6.6 Hz), 2.58 (t, 2H, PhCH_2, J = 7.4 Hz), 1.98–1.25 (m, 14H, 7 × CH_2), 0.92 (t, 3H, CH_3, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.8, 157.2, 134.2, 129.2, 114.4, 70.2, 68.1, 34.8, 34.0, 31.6, 31.3, 29.3, 25.7, 24.4, 22.6, 14.0. Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.01; H, 9.26.

4.2.10.2. 2-Hydroxy-5-(4-octylphenoxy)pentanoic acid (21b): Yield 92%; white solid; mp 102–104 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.10 (d, 2H, arom, J = 8.0 Hz), 6.82 (d, 2H, arom, J = 8.4 Hz), 4.48 (bs, 1H, OH), 4.36 (t, 1H, C*H*OH, J = 6.6 Hz), 4.00 (t, 2H, PhOCH_2, J = 5.6 Hz), 2.55 (t, 2H, CH_2Ph, J = 7.4 Hz), 2.14–1.86 (m, 4H, 2 × CH_2), 1.71–1.58 (m, 2H, CH_2), 1.38–1.15 (m, 10H, 5 × CH_2), 0.90 (t, 3H, CH_3, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.0, 156.6, 135.4, 129.2, 114.3, 70.0, 67.5, 35.0, 31.9, 31.7, 31.0, 29.5, 29.3, 24.9, 22.6, 14.1. Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.69; H, 9.45.

4.2.10.3. 2-Hydroxy-13-phenyltridecanoic acid (21c): Yield 98%; white solid; mp 62–64 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.93–7.21 (m, 5H, Ph), 5.80 (br s, 1H, OH), 4.35 (dd, 1H, C*H*OH, J_1 = 7.2 Hz, J_2 = 4.0 Hz), 2.68 (t, 2H, PhCH_2, J= 7.4 Hz), 1.95–1.79 (m, 2H, CH_2CHOH), 1.79–1.55 (m, 2H, CH_2), 1.50–1.15 (m, 16H, 8 × CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.7, 142.9, 128.4, 128.2, 125.5, 70.3, 36.0, 34.2, 31.5, 29.5, 29.4, 29.3, 29.2, 24.7. Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.39; H, 9.93.

4.2.10.4. 5-(4-(Hexyloxy)phenoxy)-2-hydroxypentanoic acid (21d): Yield 100%; white solid; mp 102–104 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.90–6.60 (m, 4H, arom), 4.92 (bs, 1H, OH), 4.30–4.00 (m, 1H, C*H*OH), 3.85 (t, 2H, OCH_2, J = 6.0 Hz), 3.80 (t, 2H, OCH_2, J = 6.0 Hz), 2.00–1.50 (m, 6H, 3 × CH_2), 1.50–1.10 (m, 6H, 3 × CH_2), 0.80 (t, 3H, CH_3, J = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.8, 153.1, 152.7, 115.2, 69.8, 68.5, 68.0, 31.4, 30.6, 29.1, 25.5, 24.8, 22.4, 13.8. Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.52; H, 8.66.

4.2.10.5. 2-Hydroxy-12-(4-methylphenylsulfonamido)dodecanoic acid (21e): Yield 82%;white solid; mp 83–85 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.70 (d, 2H, arom, J = 8.0 Hz), 7.25 (d, 2H, arom, J = 8.0 Hz), 5.15 (br s, 2H, NH, OH), 4.21 (dd, 1H, C*H*OH, J_1 = 6.6

Hz, J_2 = 5.2 Hz), 2.90–2.78 (m, 2H, NHCH_2), 2.37 (s, 3H, CH_3), 1.80–1.53 (m, 2H, CH_2), 1.44–1.35 (m, 4H, 2 × CH_2),1.30–1.15 (m, 12H, 6 × CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 178.7, 143.3, 136.7, 129.6, 127.0, 70.2, 43.1, 34.0, 29.5, 29.3, 29.2, 29.0, 28.9, 26.3, 24.5, 21.4. Anal. Calcd for $C_{19}H_{31}NO_5S$: C, 59.19; H, 8.10; N, 3.63. Found: C, 59.06; H, 8.21; N, 3.48.

4.2.11 General method for the coupling of 2-hydroxy-acids—To a stirred solution of the 2-hydroxy-acid **21a-e** (1.0 mmol) and the amine (1.0 mmol) in CH_2Cl_2 (10 mL), Et_3N (0.3 mL, 2.2 mmol in case of hydrochloride salt of the amine or 0.15 mL, 1.1 mmol in case of free amine) and subsequently 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (WSCI) (0.21 g, 1.1 mmol) and 1-hydroxybenzotriazole (HOBt) (0.14 g, 1.0 mmol) were added at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and overnight at room temperature. The solvent was evaporated under reduced pressure and EtOAc (20 mL) was added. The organic layer was washed consecutively with brine, 1 N HCl, brine, 5% $NaHCO_3$, and brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography using CH_2Cl_2/MeOH 99:1 as eluent.

4.2.11.1. Ethyl 4-(6-(4-(hexyloxy)phenyl)-2-hydroxyhexanamido)butanoate (24a): Yield 70%; white solid; mp 71–73 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.05 (d, 2H, arom, J = 8.8 Hz), 6.86 (t, 1H, NHCO, J = 8.7 Hz), 6.79 (d, 2H, arom, J = 8.8 Hz), 4.12 (q, 2H, OCH_2CH$_3$, J = 7.2 Hz), 4.04–4.01 (m, 1H, CHOH), 3.91 (t, 2H, CH_2OPh, J = 6.6 Hz), 3.50 (br s, 1H, OH), 3.29 (q, 2H, NHCH_2, J = 6.6 Hz), 2.54 (t, 2H, PhCH_2, J = 7.4 Hz), 2.33 (t, 2H, CH_2COOEt, J = 7.4 Hz), 1.89–1.51 (m, 8H,, 4 × CH_2), 1.50–1.26 (m, 8H, 4 × CH_2), 1.25 (t, 3H, CH_3, J = 7.2 Hz), 0.90 (t, 3H, CH_3, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.3, 173.2, 157.1, 134.2, 129.1, 114.3, 71.9, 67.9, 60.5, 38.4, 34.8, 34.6, 31.6, 31.5, 31.3, 29.2, 25.6, 24.6, 24.5, 22.6, 14.1, 13.9. Anal. Calcd for $C_{24}H_{39}NO_5$: C, 68.38; H, 9.32; N, 3.32. Found: C, 68.26; H, 9.41; N, 3.25.

4.2.11.2. Ethyl 4-(2-hydroxy-5-(4-octylphenoxy)pentanamido)butanoate (24b): Yield 81%; white solid; mp 78–80 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.07 (d, 2H, arom, J = 8.6 Hz), 6.98 (t, 1H, NHCO, J = 5.8 Hz), 6.80 (d, 2H, arom, J = 8.6 Hz), 4.18–4.06 (m, 3H, CHOH, OCH_2CH$_3$), 3.96 (t, 2H, PhOCH_2, J = 6.0 Hz), 3.52 (bs, 1H, OH), 3.30 (q, 2H, CONHCH_2, J = 7.0 Hz), 2.52 (t, 2H, CH_2Ph, J = 7.4 Hz), 2.34 (t, 2H, CH_2COOEt, J = 7.4 Hz), 2.18–1.72 (m, 6H, 3 × CH_2), 1.65–1.47 (m, 2H, CH_2), 1.38–1.17 (m, 13H, 5 × CH_2, CH_3), 0.87 (t, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.0, 173.2, 156.4, 135.4, 129.2, 114.2, 71.7, 67.9, 60.5, 38.4, 34.9, 31.8, 31.6, 31.5, 29.4, 29.2, 25.1, 24.7, 22.6, 14.1, 14.0. Anal. Calcd for $C_{25}H_{41}NO_5$: C, 68.93; H, 9.49; N, 3.22. Found: C, 68.85; H, 9.56; N, 3.15.

4.2.11.3. Ethyl 4-(2-hydroxy-12-(4-methylphenylsulfonamido)dodecanamido)butanoate (24c): Yield 59%; white solid; mp 57–59 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.69 (d, 2H, arom, J = 8.0 Hz), 7.25 (d, 2H, arom, J = 8.6 Hz), 6.74 (m, 1H, NHCO), 4.70 (m, 1H, SO_2NH), 4.13–4.03 (m, 3H, CHOH, CH_2CH$_3$), 3.42 (bs, 1H, OH), 3.27 (q, 2H, CONHCH_2, J = 7.0 Hz), 2.90–2.78 (m, 2H, SO_2NHCH_2), 2.37 (s, 3H, CH_3Ph), 2.30 (t, 2H, CH_2COOEt, J = 7.4 Hz), 1.87–1.63 (m, 3H, CH_2, CHH), 1.59–1.42 (m, 1H, CHH), 1.40–1.02 (m, 19H, 8 × CH_2, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.2, 173.4, 143.2, 137.0, 129.6, 127.0, 72.0,

60.6, 43.2, 38.5, 34.8, 31.7, 29.4, 29.1, 28.8, 26.3, 24.8, 24.6, 21.5, 14.1. Anal. Calcd for $C_{25}H_{42}N_2O_6S$: C, 60.21; H, 8.49; N, 5.62. Found: C, 60.13; H, 8.57; N, 5.71.

4.2.11.4. Ethyl 5-(5-(4-(hexyloxy)phenoxy)-2-hydroxypentanamido)pentanoate (24d): Yield 58%; white solid; mp 89–91 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.90–6.80 (m, 4H, arom), 6.75 (t, 1H, NH, J = 6.0 Hz), 4.30–4.10 (m, 1H, C*H*OH), 4.11 (q, 2H, OC*H*$_2$CH$_3$, J = 6.0 Hz), 3.96 (t, 2H, OCH_2, J = 6.0 Hz), 3.88 (t, 2H, OCH_2, J = 6.0 Hz), 3.28 (q, 2H, NHC*H*$_2$, J = 6.0 Hz), 2.31 (t, 2H, CH_2COO, J = 6.0 Hz), 2.20–1.50 (m, 10H, 5 × CH_2), 1.50–1.30 (m, 6H, 3 × CH_2), 1.23 (t, 3H, CH_3, J = 6.0 Hz), 0.89 (t, 3H, CH_3, J = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.5, 170.5, 153.7, 152.2, 115.5, 115.4, 71.9, 68.8, 68.6, 60.4, 38.6, 33.7, 32.2, 31.6, 29.3, 29.0, 25.7, 25.3, 22.6, 22.1, 14.2, 14.0. Anal. Calcd for $C_{24}H_{39}NO_6$: C, 65.88; H, 8.98; N, 3.20. Found: C, 65.62; H, 9.11; N, 3.32.

4.2.11.5. Ethyl 4-(2-hydroxy-13-phenyltridecanamido)butanoate (24e): Yield 87%; white solid; mp 67–69 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–7.20 (m, 5H, Ph), 6.86 (t, 1H, NHCO, J = 5.8 Hz), 4.27–4.05 (m, 3H, C*H*OH, OC*H*$_2$CH$_3$), 3.40 (q, 2H, NHC*H*$_2$, J = 6.6 Hz), 3.22 (d, 1H, OH, J = 4.8 Hz), 2.68 (t, 2H, PhC*H*$_2$, J = 7.2 Hz), 2.43 (t, 2H, C*H*$_2$COOEt, J = 7.2 Hz), 2.00–1.81 (m, 4H, $NHCH_2CH_2$, CH_2CHOH), 1.78–1.58 (m, 4H, 2 × CH_2), 1.,56–1.15 (m, 17H, 7× CH_2, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.2, 173.3, 142.9, 128.3, 128.1, 125.5, 72.1, 60.6, 38.4, 35.9, 34.9, 31.7, 31.5, 29.5, 29.4, 29.3, 29.2, 25.0, 24.6, 14.1. Anal. Calcd for $C_{25}H_{41}NO_4$: C, 71.56; H, 9.85; N, 3.34. Found: C, 71.44; H, 9.97; N, 3.26.

4.2.11.6. *tert*-Butyl 4-(5-(4-(hexyloxy)phenoxy)-2-hydroxypentanamido)butanoate (30): Yield 72%; yellowish low mp solid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.01 (t, 1H, NH, J = 6.0 Hz), 6.90–6.60 (m, 4H, arom), 4.34 (br s, 1H, OH), 4.20–4.00 (m, 1H, C*H*OH), 3.89 (t, 2H, OCH_2, J = 6.0 Hz), 3.84 (t, 2H, OCH_2, J = 6.0 Hz), 3.25 (q, 2H, NHC*H*$_2$, J = 6.0 Hz), 2.22 (t, 2H, CH_2COO, J = 6.0 Hz), 2.10–1.60 (m, 8H, 4 × CH_2), 1.40 (s, 9H, ($C(CH_3)_3$)), 1.30–1.10 (m, 6H, 3 × CH_2), 0.86 (t, 3H, CH_3, J = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.1, 172.6, 153.3, 152.4, 115.3, 115.2, 80.5, 71.6, 68.5, 38.3, 32.7, 31.7, 31.5, 29.2, 27.9, 25.6, 25.1, 24.7, 22.5, 13.9. Anal. Calcd for $C_{25}H_{41}NO_6$: C, 66.49; H, 9.15; N, 3.10. Found: C, 66.28; H, 9.33; N, 3.24.

4.2.12 General method for the saponification—To a stirred solution of the 2-hydroxyamide ester **24a–d** (1.0 mmol) in a mixture of dioxane/H_2O (9:1, 10 mL) 1 N NaOH (1.1 mL, 1.1 mmol) was added, and the mixture was stirred for 12 h at room temperature. The organic solvent was evaporated under reduced pressure, and H_2O (5 mL) was added. The aqueous layer was washed with EtOAc, acidified with 1 N HCl, and extracted with EtOAc (3 × 6 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography using $CHCl_3$/MeOH 9:1 as eluent or recrystallized from MeOH/Et_2O.

4.2.12.1. 4-(6-(4-(Hexyloxy)phenyl)-2-hydroxyhexanamido)butanoic acid (26a): Yield 86%; white solid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.18–7.10 (m, 1H, NHCO), 7.05 (d, 2H, arom, J = 8.4 Hz), 6.80 (d, 2H, arom, J = 8.4 Hz), 4.18–4.05 (m, 1H, C*H*OH), 3.92 (t, 2H, C*H*$_2$OPh, J = 6.2Hz), 3.47 (bs, 1H, OH), 3.42–3.17 (m, 2H, CONHC*H*$_2$), 2.54 (t, 2H,

PhC*H*$_2$, *J* = 7.4 Hz), 2.36 (t, 2H, C*H*$_2$COOH, *J* = 6.6 Hz), 1.85–1.20 (m, 16H, 8 × CH_2), 0.91 (t, 3H, CH_3, *J* = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 177.2, 175.4, 157.2, 134.3, 129.2, 114.3, 72.0, 68.0, 38.4, 34.8, 34.4, 31.6, 31.3, 29.3, 25.7, 24.7, 24.5, 22.6, 14.0. Anal. Calcd for $C_{22}H_{35}NO_5$: C, 67.15; H, 8.96; N, 3.56. Found: C, 67.01; H, 9.10; N, 3.47.

4.2.12.2. 4-(2-Hydroxy-5-(4-octylphenoxy)pentanamido)butanoic acid (26b): Yield 97%; white solid; mp 111–113 °C; 1H NMR (200 MHz, $CDCl_3$): δ 7.21–7.12 (m, 1H, NHCO), 7.08 (d, 2H, arom, *J* = 8.4 Hz), 6.84 (d, 2H, arom, *J* = 8.4 Hz), 4.11 (dd, 1H, C*H*OH, J_1 = 3.4 Hz, J_2 = 7.4 Hz), 4.00 (t, 2H, PhOC*H*$_2$, *J* = 5.8 Hz), 3.56 (bs, 1H, OH), 3.32 (m, 2H, NHC*H*$_2$, *J* = 7.0 Hz), 2.56 (t, 2H, C*H*$_2$Ph, *J* = 7.4 Hz), 2.37 (t, 2H, C*H*$_2$COOH, *J* = 7.4 Hz), 2.02–1.75 (m, 6H, 3 × CH_2), 1.65–1.45 (m, 2H, CH_2), 1.42–1.21 (m, 10H, 5 × CH_2), 0.93 (t, 3H, CH_3, *J* = 6.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 177.2, 176.9, 158.5, 136.0, 130.2, 115.4, 72.6, 68.8, 39.3, 36.0, 33.0, 32.9, 32.4, 32.2, 30.6, 30.4, 30.3, 26.2, 25.9, 23.7, 14.4. Anal. Calcd for $C_{23}H_{37}NO_5$: C, 67.78; H, 9.15; N, 3.44. Found: C, 67.65; H, 9.26; N, 3.36.

4.2.12.3. 4-(2-Hydroxy-12-(4-methylphenylsulfonamido)dodecanamido)butanoic acid (26c): Yield 92%; white solid; mp 58–60 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.77 (d, 2H, arom, *J* = 8.0 Hz), 7.41 (d, 2H, arom, *J* = 8.0 Hz), 6.98 (bs, 1H, NHCO), 4.70 (bs, 1H, SO_2NH), 4.04 (dd, 1H, C*H*OH, J_1 = 4.0 Hz, J_2 = 7.0 Hz), 3.81 (bs, 1H, OH), 3.31 (t, 2H, CONHC*H*$_2$, *J* = 7.0 Hz), 2.86 (t, 2H, SO_2NHC*H*$_2$, *J* = 7.0 Hz), 2.47 (s, 3H, CH_3), 2.38 (t, 2H, C*H*$_2$COOH, *J* = 7.4 Hz), 1.92–1.74 (m, 4H, 2 × CH_2), 1.71–1.57 (m, 2H, $SO_2NHCH_2CH_2$), 1.45–1.15 (m, 14H, 7 × CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 177.5, 176.9, 144.5, 139.0, 130.7, 128.0, 72.8, 44.0, 39.3, 35.7, 32.1, 30.5, 30.2, 27.6, 26.0, 25.9, 21.5. Anal. Calcd for $C_{23}H_{38}N_2O_6S$: C, 58.70; H, 8.14; N, 5.95. Found: C, 58.63; H, 8.27; N, 5.84.

4.2.12.4. 5-(5-(4-(Hexyloxy)phenoxy)-2-hydroxypentanamido)pentanoic acid (26d): Yield 100%; white solid; mp 68–70 °C; ^{1}H NMR (200 MHz, $CDCl_3$ + drops of CD_3OD): δ 7.03 (t, 1H, NH, *J* = 6.0 Hz), 6.90–6.60 (m, 4H, arom), 4.20–4.00 (m, 1H, C*H*OH), 3.92 (t, 2H, OCH_2, *J* = 6.0 Hz), 3.87 (t, 2H, OCH_2, *J* = 6.0 Hz), 3.25 (q, 2H, NHC*H*$_2$, *J* = 6.0 Hz), 2.31 (t, 2H, C*H*$_2$COOH, *J* = 6.0 Hz), 2.10–1.50 (m, 10H, 5 × CH_2), 1.50–1.10 (m, 6H, 3 × CH_2), 0.87 (t, 3H, CH_3, *J* = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$ + drops of CD_3OD): δ 176.5, 174.5, 153.4, 152.5, 115.4, 115.3, 71.6, 68.6, 38.4, 33.3, 33.0, 31.5, 29.3, 28.7, 25.7, 25.2, 22.6, 21.8, 14.0. Anal. Calcd for $C_{22}H_{35}NO_6$: C, 64.52; H, 8.61; N, 3.42. Found: C, 64.29; H, 8.83; N, 3.55.

4.2.13 General method for the oxidation of 2-hydroxyamides—To a solution of the 2-hydroxyamides **24a–c**, **26a–d** or **30** (1 mmol) in dry CH_2Cl_2 (10 mL) Dess-Martin periodinane (0.64 g, 1.5 mmol) was added and the mixture was stirred for 1 h at room temperature. The organic solvent was evaporated under reduce pressure and Et_2O (30 mL) was added. The organic phase was washed with saturated aqueous $NaHCO_3$ (20 mL) containing $Na_2S_2O_3$ (1.5 g, 9.5 mmol), H_2O (20 mL), dried over Na_2SO_4, and the organic solvent was evaporated under reduced pressure. The residue was purified by column chromatography using petroleum ether (bp 40–60 °C)/EtOAc as eluent. In the case of **26a–**

d, after reaction completion the organic solvent was evaporated and the residue was purified by column chromatography.

4.2.13.1. Ethyl 4-(6-(4-(hexyloxy)phenyl)-2-oxohexanamido)butanoate (25a): Yield 88%; white solid; mp 56–58 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–70.35 (m, 1H, NHCOCO), 7.29 (d, 2H, arom, J = 8.4 Hz), 7.03 (d, 2H, arom, J = 8.4 Hz), 4.36 (q, 2H, OCH_2CH_3, J = 7.4 Hz), 4.14 (t, 2H, CH_2OPh, J = 6.6Hz), 3.57 (q, 2H, $NHCH_2$, J = 7.0 Hz), 3.16 (t, 2H, CH_2, J = 6.6 Hz), 2.79 (t, 2H, $PhCH_2$, J = 8.0 Hz), 2.59 (t, 2H, CH_2COOEt, J = 7.4 Hz), 2.18–1.19 (m, 4H, 2 × CH_2), 1.87–1.74 (m, 4H, 2 × CH_2), 1.70–1.53 (m, 6H, 3 × CH_2), 1.48 (t, 3H, CH_3, J = 7.4 Hz), 1.13 (t, 3H, CH_3, J = 6.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 198.9, 172.9, 160.2, 157.2, 133.8, 129.1, 114.3, 67.9, 60.5, 38.6, 36.5, 34.6, 31.5, 30.9, 29.2, 25.7, 24.3, 22.6, 22.5, 14.1, 14.0. Anal. Calcd for $C_{24}H_{37}NO_5$: C, 68.71; H, 8.89; N, 3.34. Found: C, 68.64; H, 8.97; N, 3.45.

4.2.13.2. Ethyl 4-(5-(4-octylphenoxy)-2-oxopentanamido)butanoate (25b): Yield 60%; white solid; mp 49–51°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.22–7.15 (br s 1H, NHCOCO), 7.06 (d, 2H, arom, J = 8.8 Hz), 6.77 (d, 2H, arom, J = 8.4 Hz), 4.14 (q, 2H, OCH_2CH_3, J = 7.4 Hz), 3.97 (t, 2H, CH_2OPh, J = 6.2 Hz), 3.34 (q, 2H, $NHCH_2$, J = 6.6Hz), 3.12 (t, 2H, CH_2COCO, J = 7.0 Hz), 2.53 (t, 2H, CH_2Ph, J = 7.4 Hz), 2.36 (t, 2H, CH_2COOEt, J = 7.2 Hz), 2.15–2.05 (m, 2H, CH_2), 1.98–1.79 (m, 2H, CH_2), 1.65–1.48 (m, 2H, CH_2), 1.29–1.15 (m, 13H, 5 × CH_2, CH_3), 0.88 (t, 3H, CH_3, J = 6.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 198.5, 172.9, 160.2, 156.6, 135.1, 129.1, 114.2, 66.5, 60.5, 38.7, 35.0, 33.5, 31.8, 31.7, 31.5, 29.4, 29.2, 24.3, 23.3, 22.6, 14.1, 14.0. Anal. Calcd for $C_{25}H_{39}NO_5$: C, 69.25; H, 9.07; N, 3.23. Found: C, 69.11; H, 9.20; N, 3.17.

4.2.13.3. Ethyl 4-(12-(4-methylphenylsulfonamido)-2-oxododecanamido)butanoate (25c): Yield 73%; white solid; mp 105–107°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74 (d, 2H, arom, J = 8.0 Hz), 7.29 (d, 2H, arom, J = 8.4 Hz), 7.21–7.12 (m, 1H, COCONH), 4.74 (t, 1H, SO_2NH, J = 5.8 Hz), 4.12 (q, 2H, CH_2CH_3, J = 6.6 Hz), 3.34 (q, 2H, $CONHCH_2$, J = 6.6 Hz), 2.95–2.82 (m, 4H, SO_2NHCH_2, CH_2COCO), 2.41 (S, 3H, CH_3Ph), 2.34 (t, 2H, CH_2, J = 7.2 Hz), 1.94–1.80 (m, 2H, CH_2), 1.62–1.50 (m, 2H, CH_2), 1.50–1.35 (m, 2H, CH_2), 1.35–1.10 (m, 15H, 6 × CH_2, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 199.2, 172.9, 160.3, 143.2, 137.0, 129.6, 127.0, 60.5, 43.1, 38.6, 36.6, 31.5, 29.4, 29.2, 29.1, 28.9, 26.4, 24.3, 23.0, 21.4, 14.1. Anal. Calcd for $C_{25}H_{40}N_2O_6S$: C, 60.46; H, 8.12; N, 5.64. Found: C, 60.32; H, 8.26; N, 5.52.

4.2.13.4. 4-(6-(4-(Hexyloxy)phenyl)-2-oxohexanamido)butanoic acid (27a): Yield 44%; white solid; mp 73–75 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.21–7.14 (m, 1H, NHCOCO), 7.07 (d, 2H, arom, J = 8.4 Hz), 6.81 (d, 2H, arom, J = 8.4 Hz), 3.93 (t, 2H, CH_2OPh, J = 6.6 Hz), 3.38 (q, 2H, $CONHCH_2$, J = 6.6 Hz), 2.94 (t, 2H, CH_2COCO, J = 6.6 Hz), 2.57 (t, 2H, $PhCH_2$, J = 6.6 Hz), 2.42 (t, 2H, CH_2COOH,, J = 7.4 Hz), 1.94–1.83 (m, 2H, CH_2), 1.80–1.70 (m, 2H, CH_2), 1.63–1.43 (m, 4H, 2 × CH_2), 1.43–1.10 (m, 6H, 3 × CH_2), 0.91 (t, 3H, CH_3, J = 6.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 198.9, 178.0, 160.4, 157.3, 133.9, 129.2, 114.4, 68.0, 38.6, 36.6, 34.6, 31.6, 31.1, 31.0, 29.3, 25.7, 24.2, 22.7, 22.6, 14.0. Anal. Calcd for $C_{22}H_{33}NO_5$: C, 67.49; H, 8.50; N, 3.58. Found: C, 67.35; H, 8.62; N, 3.44.

4.2.13.5. 4-(5-(4-Octylphenoxy)-2-oxopentanamido)butanoic acid (27b): Yield 60%; white solid; mp 49–51 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.32–7.20 (m, 1H, NHCOCO), 7.16 (d, 2H, arom, J = 8.4 Hz), 6.87 (d, 2H, arom, J = 8.4 Hz), 4.07 (t, 2H, PhOCH_2, J = 7.5 Hz), 3.47 (q, 2H, NHCH_2, J = 6.6 Hz), 3.22 (t, 2H, CH_2COCO, J = 7.0 Hz), 2.62 (t, 2H, PhCH_2, J = 7.4 Hz), 2.51 (t, 2H, CH_2COOH, J = 7.0 Hz), 2.25–2.08 (m, 2H, CH_2), 2.08–1.90 (m, 2H, CH_2), 1.75–1.58 (m, 2H, CH_2), 1.45–1.23 (m, 10 H, 5 × CH_2), 0.98 (t, 3H, CH_3, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 198.5, 178.1, 160.3, 156.6, 135.3, 129.2, 114.2, 66.6, 38.6, 35.0, 33.6, 31.9, 31.7, 31.2, 29.5, 29.3, 24.2, 23.4, 22.6, 14.1. Anal. Calcd for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70; N, 3.45. Found: C, 68.03; H, 8.85; N, 3.27.

4.2.13.6. 4-(12-(4-Methylphenylsulfonamido)-2-oxododecanamido)butanoic acid (27c): Yield 55%; white solid; mp 98–100 °C; ^{1}H NMR (200 MHz, CD_3OD): δ 7.46 (d, 2H, arom, J = 8.2 Hz), 7.11 (d, 2H, arom, J = 8.2 Hz), 3.12–2.95 (m, 2H, CONHCH_2), 2.61–2.52 (m, 4H, SO_2NHCH_2, CH_2COCO), 2.16 (s, 3H, CH_3), 2.07 (t, 2H, CH_2COOH, J = 7.2 Hz), 1.60–1.43 (m, 2H, C$H_2$$CH_2$COOH), 1.38–1.22 (m, 2H, SO_2NHCH_2CH_2), 1.20–0.80 (m, 14H, 7 × CH_2); ^{13}C NMR (50 MHz, aceton-d6): δ 199.4, 174.0, 161.4, 143.2, 137.0, 130.0, 127.4, 43.5, 38.7, 36.9, 31.1, 30.6, 30.2, 29.8, 29.7, 29.5, 28.3, 26.8, 24.9, 23.5, 21.0. Anal. Calcd for $C_{23}H_{36}N_2O_6S$: C, 58.95; H, 7.74; N, 5.98. Found: C, 58.87; H, 7.82; N, 5.87.

4.2.13.7. 5-(5-(4-(Hexyloxy)phenoxy)-2-oxopentanamido)pentanoic acid (27d): Yield 76%; white solid; mp 91–93 °C; ^{1}H NMR (200 MHz, DMSO): δ 8.61 (t, 1H, NH, J = 6.0 Hz), 7.00–6.60 (m, 4H, arom), 3.88 (t, 2H, OCH_2, J = 6.0 Hz), 3.86 (t, 2H, OCH_2, J = 6.0 Hz), 3.09 (q, 2H, NHCH_2, J = 6.0 Hz), 2.94 (t, 2H, CH_2COCO, J = 6.0 Hz), 2.20 (t, 2H, CH_2COOH, J = 6.0 Hz), 1.92 (quintet, 2H, CH_2, J = 6.0 Hz), 1.65 (quintet, 2H, CH_2, J = 6.0 Hz), 1.50–1.40 (m, 4H, 2 × CH_2), 1.40–1.20 (m, 6H, 3 × CH_2), 0.86 (t, 3H, CH_3, J = 6.0 Hz); ^{13}C NMR (50 MHz, DMSO): δ 198.9, 176.5, 161.2, 152.8, 152.4, 115.4, 67.9, 67.1, 40.6, 33.7, 33.4, 31.1, 28.9, 28.3, 25.3, 23.1, 22.2, 22.0, 14.1. Anal. Calcd for $C_{22}H_{33}NO_6$: C, 64.84; H, 8.16; N, 3.44. Found: C, 64.56; H, 8.35; N, 3.51.

4.2.13.8. *tert*-Butyl 4-(5-(4-(hexyloxy)phenoxy)-2-oxopentanamido)butanoate (31): Yield 84%; yellowish solid; mp 55–57 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20 (t, 1H, NH, J = 6.0 Hz), 7.00–6.60 (m, 4H, arom), 3.89 (t, 2H, OCH_2, J = 6.0 Hz), 3.84 (t, 2H, OCH_2, J = 6.0 Hz), 3.28 (q, 2H, NHCH_2, J = 6.0 Hz), 3.07 (t, 2H, CH_2COCO, J = 6.0 Hz), 2.23 (t, 2H, CH_2COO, J = 6.0 Hz), 2.03 (quintet, 2H, CH_2, J = 6.0 Hz), 1.88 (quintet, 2H, CH_2, J = 6.0 Hz), 1.79 (quintet, 2H, CH_2, J = 6.0 Hz), 1.70–1.60 (m, 2H, CH_2), 1.40 (s, 9H, ($C(CH_3)_3$)), 1.30–1.10 (m, 4H, 2 × CH_2), 0.86 (t, 3H, CH_3, J = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 198.4, 172.1, 160.1, 153.2, 152.5, 115.2, 80.4, 68.4, 67.0, 38.6, 33.5, 32.6, 31.4, 29.2, 27.9, 25.6, 24.3, 23.3, 22.5, 13.9. Anal. Calcd for $C_{25}H_{39}NO_6$: C, 66.79; H, 8.74; N, 3.12. Found: C, 66.60; H, 8.86; N, 3.22.

4.2.14. 14-(4-Ethoxy-4-oxobutylamino)-13,14-dioxotetradecanoic acid (28)—To a solution of **24e** (1.0 mmol) in a mixture of CCl_4/MeCN/H_2O (1:1:2, 30 ml), $NaIO_4$ (6.2 g, 29.0 mmol) and $RuCl_3.6H_2O$ (12 mg, 0.045 mmol) were added and the mixture was stirred overnight at room temperature. Dichloromethane (30 ml) was added and, after stirring for 10 min, the organic layer was separated, dried over Na_2SO_4 and concentrated under reduced

pressure. The residue was purified by column chromatography using petroleum ether (bp 40–60 °C)/EtOAc 1:1 as eluent. Yield 25%; white solid; mp 77–79 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.18–7.08 (m, 1H, NHCOCO), 4.20–4.09 (q, 2H, OHCH_2CH$_3$, J = 6.8 Hz), 3.35 (q, 2H, NHCH_2, J = 6.8 Hz), 2.91 (t, 2H, CH_2COCO, J = 7.2 Hz), 2.39–2.31 (m, 4H, CH_2COOEt, CH_2COOH), 2.00–1.80 (m, 2H, NHCH$_2$CH_2), 1.75–1.50 (m, 4H, 2 × CH_2), 1.40–1.10 (m, 17H, 7 × CH_2, CH_3); ^{13}C; NMR (50 MHz, $CDCl_3$): δ 199.2, 179.1, 173.0, 160.3, 60.6, 38.7, 36.7, 33.9, 31.6, 29.7, 29.4, 29.3, 29.2, 29.1, 29.0, 24.6, 24.4, 23.1, 14.2. Anal. Calcd for $C_{20}H_{35}NO_6$: C, 62.31; H, 9.15; N, 3.63. Found: C, 62.25; H, 9.23; N, 3.57.

4.2.15. 4-(5-(4-(Hexyloxy)phenoxy)-2-oxopentanamido)butanoic acid (32)—A solution of the *tert*-butyl ester derivative **31** (450 mg, 1 mmol) in 50% TFA/CH_2Cl_2 (2 mL) was stirred for 1 h at room temperature. The organic solvent was evaporated under reduced pressure and the residue was purified by recrystallization [EtOAc/petroleum ether (bp 40–60 °C)]. Yield 76%; white solid; mp 109–111 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.16 (t, 1H, NH, J = 6.0 Hz), 7.00–6.60 (m, 4H, arom), 3.93 (t, 2H, OCH_2, J = 6.0 Hz), 3.88 (t, 2H, OCH_2, J = 6.0 Hz), 3.36 (q, 2H, NHCH_2, J = 6.0 Hz), 3.10 (t, 2H, CH_2COCO, J = 6.0 Hz), 2.40 (t, 2H, CH_2COOH, J = 6.0 Hz), 2.08 (quintet, 2H, CH_2, J = 6.0 Hz), 1.88 (quintet, 2H, CH_2, J = 6.0 Hz), 1.73 (quintet, 2H, CH_2, J = 6.0 Hz), 1.50–1.00 (m, 6H, 3 × CH_2), 0.89 (t, 3H, CH_3, J = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 198.5, 178.0, 160.3, 153.4, 152.6, 115.4, 68.6, 67.2, 38.6, 33.6, 31.6, 31.1, 29.3, 25.7, 24.2, 23.4, 22.6, 14.0. Anal. Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 63.91; H, 8.10; N, 3.70.

4.3. In vitro PLA_2 assays

All synthesized inhibitors were tested for inhibition of human GIVA $cPLA_2$, GVIA $iPLA_2$ and GV $sPLA_2$ using previously described mixed micelle-based assays.[24–26] The buffer and substrate conditions were optimized for each enzyme assay as follows: (i) GIVA $cPLA_2$ substrate mixed-micelles were composed of 400 μM Triton X-100, 97 μM PAPC, 1.8 μM ^{14}C-labeled PAPC, and 3 μM PIP_2 in 100 mM HEPES buffer, pH 7.5, with 90 μM $CaCl_2$, 2 mM DTT, and 0.1 mg/ml BSA; (ii) GVIA $iPLA_2$ substrate mixed-micelles were composed of 400 μM Triton X-100, 98.3 μM PAPC, and 1.7 μM ^{14}C-labeled PAPC in buffer containing 100 mM HEPES, pH 7.5, 2 mM ATP, and 4 mM DTT; (iii) GV $sPLA_2$ substrate mixed-micelles were composed of 400 μM Triton X-100, 98.3 μM PAPC, and 1.7 μM ^{14}C-labeled PAPC in buffer containing 50 mM Tris, pH 8.0, and 5 mM $CaCl_2$.

Initial screening of compounds at 0.091 mole fraction inhibitor in mixed-micelles was carried out. Compounds displaying 25% or less inhibition of the assays were considered to have no inhibitory affect (designated N.D.). We report average percent inhibition for compounds displaying less than 85% enzyme inhibition. If the percent inhibition was greater than 85%, we determined its $X_I(50)$ by plotting percent inhibition versus inhibitor mole fraction. Inhibition curves were modeled in Graphpad Prism 5.0 using nonlinear regression targeted at symmetrical sigmoidal curves based on plots of % inhibition versus log(inhibitor concentration), to calculate the reported $X_I(50)$ and associated error values.

Acknowledgments

This research has been co-financed by the European Union (European Regional Development Fund-ERDF) and Greek national funds through the Operational Program “Competitiveness and Entrepreneurship” of the National Strategic Reference Framework (NSRF) - Research Funding Program: “Phospholipases A_2 inhibitors: Developing a drug pipeline for the treatment of inflammatory neurological disorders” (G.K.) and in part by NIH grant RO1 20,501-40 (E.A.D.).

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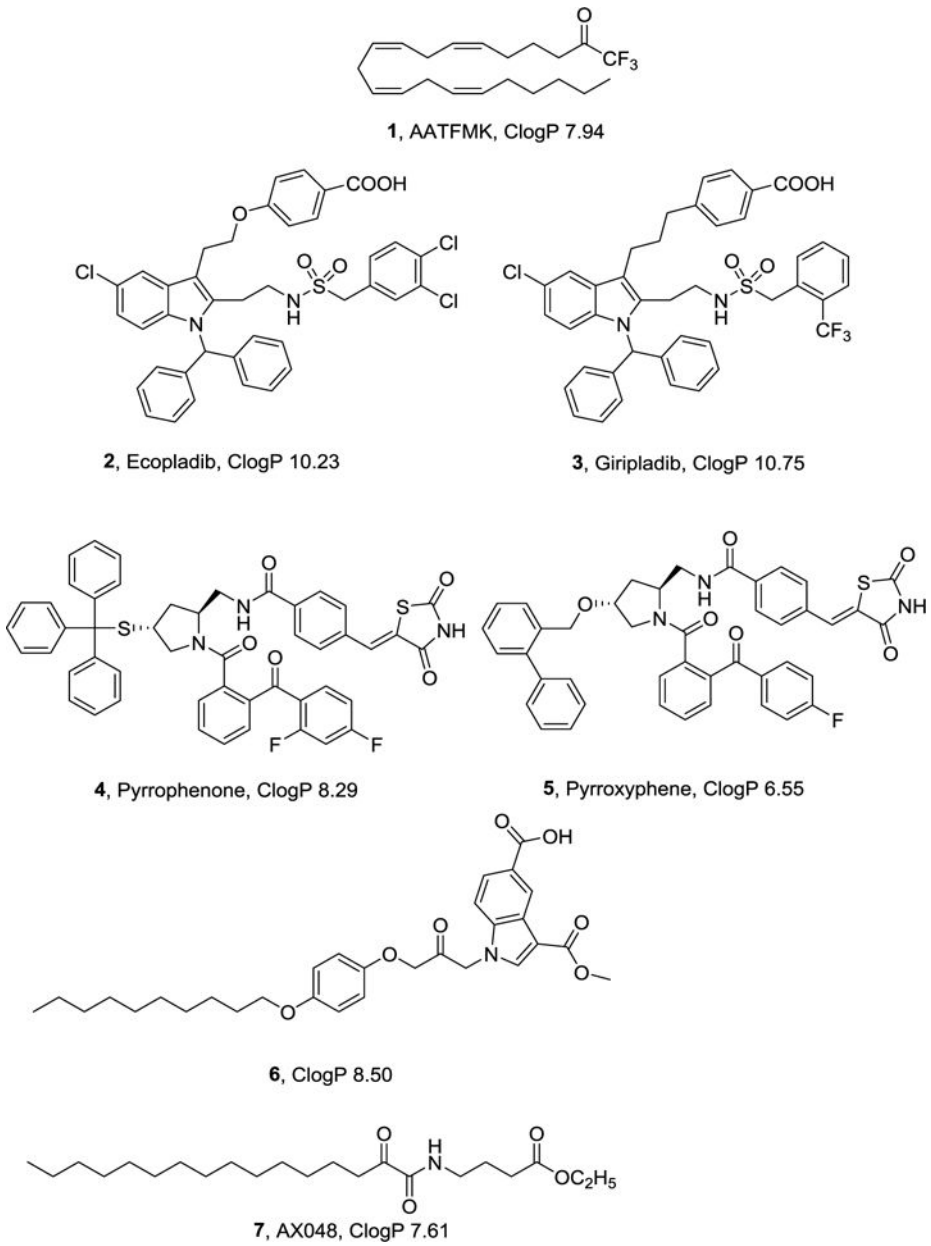


Figure 1.
ClogP values for GIVA cPLA$_2$ inhibitors.

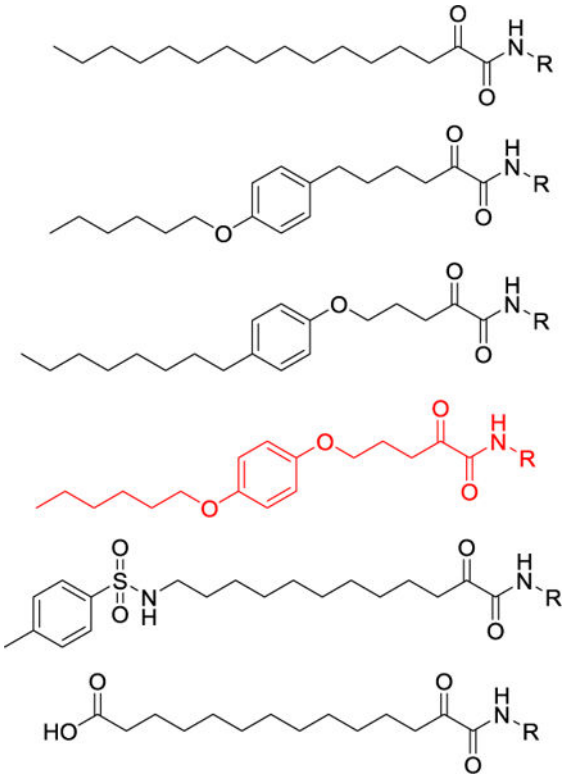
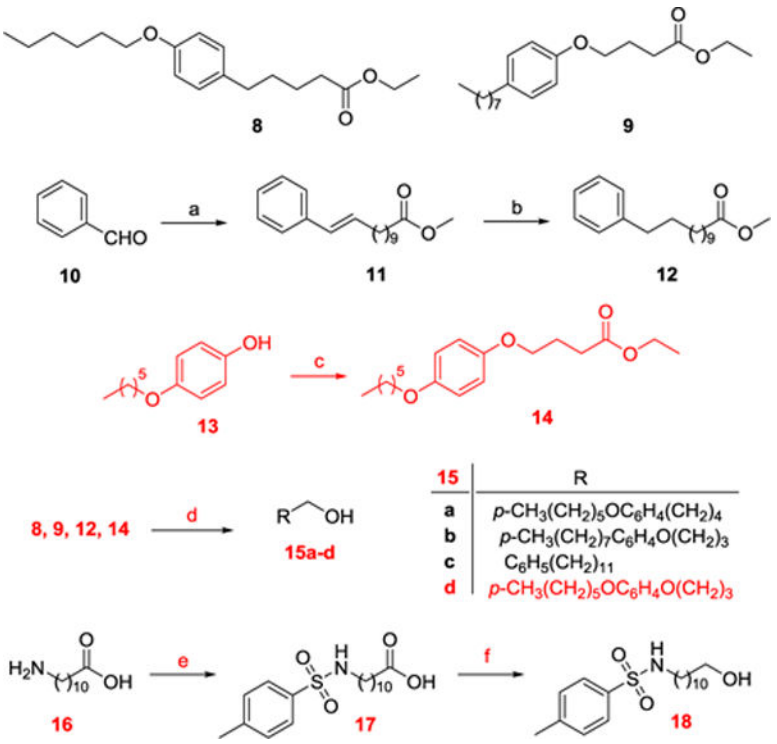
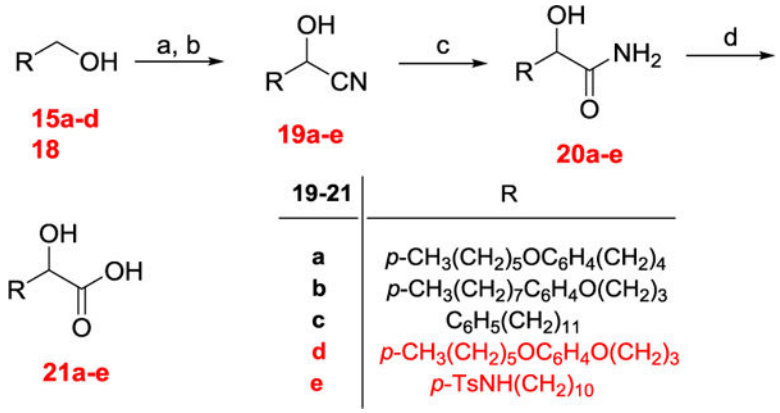


Figure 2.
Replacements of the long aliphatic chain of 2-oxoamides designed in this work.



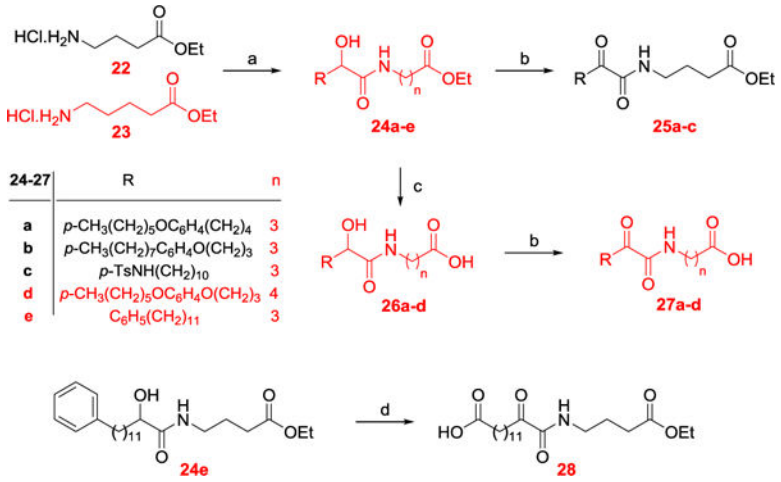
Scheme 1.

Reagents and conditions: (a) $Br^{-}P^{+}Ph_3(CH_2)_9COOCH_3$, NaH, THF, reflux; (b) H_2, 10% Pd/C, EtOH; (c) K_2CO_3, ethyl 4-bromobutyrate, acetone, reflux; (d) DIBALH, Et_2O or $LiAlH_4$, THF, reflux; (e) TsCl, NMM, THF; (f) i. NMM, $ClCO_2Et$, THF; ii. $NaBH_4$, MeOH.



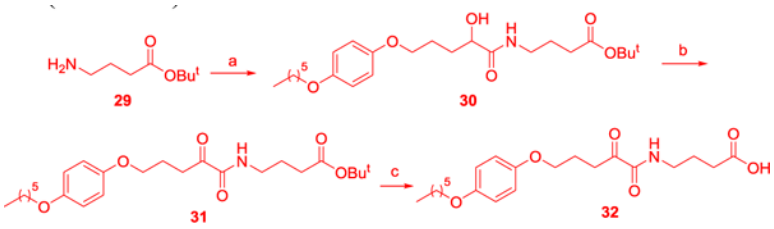
Scheme 2.

Reagents and conditions: (a) NaOCl, TEMPO, NaBr, $NaHCO_3$, EtOAc/$PhCH_3$/H_2O 3:3:0.5, −5 °C; (b) i. $NaHSO_3$, CH_2Cl_2, H_2O; ii. KCN, H_2O; (c) cone. HCl; (d) KOH, EtOH/H_2O.



Scheme 3.

Reagents and conditions: (a) **21a–e**, Et_3N, WSCI, HOBt, CH_2Cl_2; (b) Dess-Martin periodinane, CH_2Cl_2; (c) NaOH 1N, dioxane/H_2O 9:1; (d) $NaIO_4$, $RuCl_3.H_2O$, CH_3CN/CCl_4/H_2O 1:1:2.

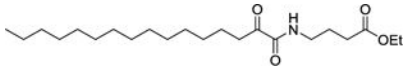
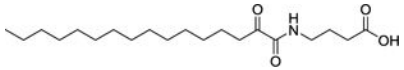
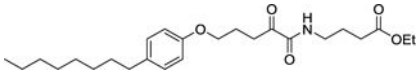
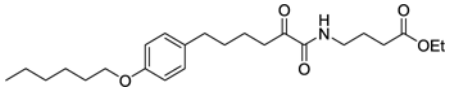
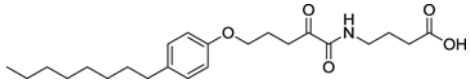
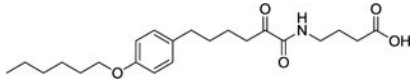
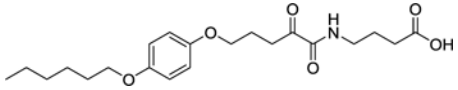
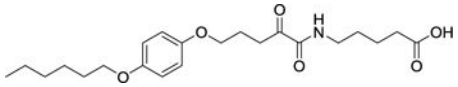
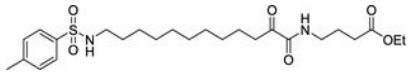


Scheme 4.

Reagents and conditions: (a) **21d**, Et_3N, WSCI, HOBt, CH_2Cl_2; (b) Dess-Martin periodinane, CH_2Cl_2; (c) 50% TFA/CH_2Cl_2.

Table 1

Inhibition of PLA_2 by 2-oxoamides[a]

Number	Structure	ClogP[b]	GIVA cPLA$_2$		GVIA iPLA$_2$		GV sPLA$_2$
			% Inhibition	X_I(50)	% Inhibition	X_I(50)	% Inhibition
AX048[28]		7.61		0.022 ± 0.009		0.027 ± 0.009	
AX006[28]		6.63		0.024 ± 0.015	N.D.		
25b		7.39	49.3 ±2.0		94.7 ±0.5	0.014± 0.003	40.6 ±5.9
25a		6.30	>85	0.020 ± 0.006	95.1 ±0.6	0.013 ± 0.003	33.8 ±6.0
27b		6.41	>85	0.023 ± 0.005	N.D.		N.D.
27a		5.32	>85	0.016 ± 0.004	N.D.		N.D.
32		4.94	63.6 ±2.6		81.1 ±1.0		N.D.
27d		4.82	88.0 ±0.9	0.013 ± 0.002	82.5 ±1.4		N.D.
25c		5.69	59.3 ±3.1		N.D.		N.D.

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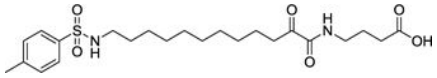
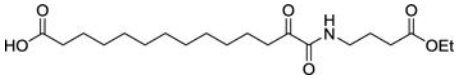
Number	Structure	ClogP[b]	GIVA cPLA$_2$		GVIA iPLA$_2$		GV sPLA$_2$
			% Inhibition	X_I(50)	% Inhibition	X_I(50)	% Inhibition
27c		4.71	N.D.		N.D.		N.D.
28		4.61	N.D.		N.D.		N.D.

[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 85% inhibition. N.D. signifies compounds with less than 25% inhibition (or no detectable inhibition).

[b] Calculated by ChemOffice Ultra 11.00.