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Synthesis of 2-oxoamides based on sulfonamide analogues of γ -amino acids and their activity on phospholipase A₂

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Abstract

A variety of lipophilic 2-oxoamides containing sulfonamide analogues of γ -amino acids as well as acyl sulfonamides of γ -aminobutyric acid were synthesized. Their ability to inhibit intracellular GIVA cPLA₂ and GVIA iPLA₂ as well as secreted GV sPLA₂ was evaluated. The sulfonamide group seems a bioisosteric group suitable to replace the carboxyl group in 2-oxoamide inhibitors of GVIA cPLA₂.

Keywords

acyl sulfonamides; inhibitors; 2-oxoamides; phospholipase A₂; sulfonamides

Introduction

The phospholipase A₂ (PLA₂) superfamily of enzymes consists of a broad range of enzymes defined by their ability to catalyze the hydrolysis of the ester bond at the *sn*-2 position of phospholipids, yielding free fatty acids, including arachidonic acid, and lysophospholipids. 1–4 Historically, a broad classification divides the PLA₂ classes into three types: secretory (sPLA₂), cytosolic Ca²⁺-dependent (cPLA₂) and cytosolic Ca²⁺-independent (iPLA₂). PLA₂ enzymes have been systematically classified into 15 groups and subgroups on the basis of their nucleotide and amino acid sequence. 1–3,4 Among the various phospholipases, the Group IVA cPLA₂ (GIVA cPLA₂) is a particularly attractive target for drug development, since it is the rate-limiting provider of arachidonic acid and lysophospholipids that can be converted into prostaglandins, leukotrienes and PAF, respectively. 5 The role of the other intracellular PLA₂, calcium-independent PLA₂ (GVIA iPLA₂), in the inflammatory process is still unclear, and it appears to be the primary PLA₂ for basal metabolic functions within the cell. 6,7 Both intracellular enzymes share the same catalytic mechanism utilizing a serine residue as the nucleophile. The other major class of PLA₂ enzymes includes the small, secreted sPLA₂s and is characterized by a catalytic His/Asp dyad and catalytic Ca²⁺. 1,3,4,8 A well-studied, simple example of this class is the human Group V secreted phospholipase

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A₂ (GV sPLA₂).^{9,10} In many cases the activity of GV sPLA₂ is dependent on or linked to the activity of GIVA cPLA₂.^{1,11,12}

A great variety of compounds have been studied for their activity against GIVA cPLA₂ and the synthetic inhibitors of GIVA cPLA₂ have been summarized in a recent review.¹³ Within the last five years, we have been developing a novel class of GIVA cPLA₂ inhibitors that are based on the 2-oxoamide reactive functionality.¹⁴⁻²⁰ Lipophilic 2-oxoamides based on γ -aminobutyric acid (compound **1a**, Figure 1) or the non-natural amino acid γ -norleucine (compound **1b**, Figure 1) are potent inhibitors of GIVA cPLA₂ presenting *in vivo* anti-inflammatory and analgesic activity.^{14,15} AX048 (compound **1c**, Figure 1), the ethyl ester derivative of compound **1a**, is the first systemically bioavailable compound with a significant affinity for GIVA cPLA₂, which produces potent anti-hyperalgesia.¹⁷ We also synthesized 2-oxoamides based on long chain β -amino acids, however such derivatives were found inactive.¹⁶ On the contrary, 2-oxoamide AX109 based on the non-natural amino acid δ -norleucine (compound **1d**, Figure 1) exhibit slightly higher inhibitory activity than the corresponding analogue based on γ -norleucine.¹⁹

The aim of this work was to synthesize lipophilic 2-oxoamides containing sulfonamide groups bioisosteric to the carboxyl group and to evaluate their activity on three human PLA₂ isoforms.

Results and Discussion

We have previously shown that 2-oxoamides based on γ - or δ -amino acids containing a free carboxyl group are selective inhibitors of GIVA cPLA₂, affecting the activity of neither GVIA iPLA₂ nor GV sPLA₂.^{15,19} Ethyl ester AX048 inhibits *in vitro* not only GIVA cPLA₂, but also calcium-independent GVIA iPLA₂, which is the main other intracellular PLA₂ isoform.¹⁷ In addition, methyl esters of 2-oxoamides may inhibit *in vitro* both GIVA cPLA₂ and GVIA iPLA₂.¹⁸ Bioisosterism represents an interesting approach used in medicinal chemistry for the rational modification of lead compounds into agents exhibiting improved properties.²¹ Non-classical bioisosteres for the carboxyl group may involve replacement of either only the hydroxyl portion or both the hydroxyl and carbonyl group of this functional group. We designed the replacement of the hydroxyl group of the carboxylic acid by a sulfonamide group, resulting in the formation of acyl sulfonamide (Figure 1). In addition, we decided to replace the entire carboxyl functional group by a sulfonamide group. As known, the pK_a values for sulfonamides are similar to that of an aryl carboxylic acid.²¹ Numerous examples in literature report such replacements leading to compounds with improved biological activities.²²⁻²⁵ Furthermore, we and others have recently demonstrated that the conversion of the proline carboxyl group to acyl sulfonamides is successful for the preparation of improved organocatalysts.^{26,27}

For the synthesis of 2-oxoamides containing a sulfonamide group, two different synthetic routes were studied using 1,3-propanediamine and 1,4-butanediamine as starting materials. Monotosylation of diamines **2a,b** led to derivatives **3a,b**, which were coupled with 2-hydroxy-hexadecanoic acid using *N*-ethyl-*N'*-dimethylaminopropylcarbodiimide (WSCl)²⁸ as a coupling agent in the presence of *N*-hydroxybenzotriazole (HOBt) to afford 2-hydroxyamides **4a,b** (Figure 2). However, this route led to low yields and impure products for monomesylated derivatives. Thus, monoacylated derivatives **6a,b** were prepared by coupling of diamines **2a,b** with 2-hydroxyhexadecanoic acid using the WSCI/HOBt method (Figure 3). Then, the amino group of **6a,b** was mesylated by treatment with methanesulfonyl chloride to give compounds **7a,b**. Oxidation of compounds **4a,b** and **7a,b** to 2-oxoamides **5a,b** and **8a,b** was carried out by the Dess-Martin periodinane or the PDC reagent (Figure 2 and 3).

2-Oxoamides **14a,b** containing a short linear side chain were synthesized from Boc-norleucinol (**9**), which was prepared by reduction of Boc-norleucine^{29,30} as depicted in Figure 4. As we have previously shown, *N*-protected amino aldehydes are useful intermediates for the synthesis of γ -amino acids and other non-natural amino acids.^{31,32} Thus, Boc-norleucinol (**9**) was oxidized to aldehyde by the NaOCl/AcNH-TEMPO method and reacted with (triphenyl phosphoranylidene)acetonitrile to produce unsaturated nitrile **10**. After hydrogenation of the double bond, the nitrile group was reduced to amino group by NiCl₂·6H₂O/NaBH₄³³ and immediately reacted with methane or toluenesulfonyl chloride. Removal of the Boc group, coupling with 2-hydroxyhexadecanoic acid and oxidation produced 2-oxoamides **14a,b**.

The synthesis of acyl sulfonamides based on γ -aminobutyric acid is presented in Figure 5. Boc- γ -aminobutyric acid (**15**) was coupled with methane or toluene sulfonamides by the DCC/DMAP method.²⁶ By procedures similar to those described above, derivatives **18a,b** were prepared. The acidic hydrogen of the sulfonamide group of compound **17b** was replaced by a methyl group by treatment with methyl iodide in the presence of Na₂CO₃. Then, oxidation of compound **19** led to compound **20**.

Compounds **5a,b**, **8a,b**, **14a,b**, **18a,b** and **20** were tested for their ability to inhibit human GIVA cPLA₂ in a GIVA cPLA₂-specific assay, which uses mixed micelles of substrate 1-palmitoyl-2-arachidonyl phosphatidylcholine, phosphatidylinositol 4,5-bisphosphate and detergent Triton X-100 (97: 3: 400 μ M), as previously described.¹⁵ In addition, their activity against GVIA iPLA₂ and the secreted PLA₂ isoform GV sPLA₂ was determined. The *in vitro* assay systems for GVIA iPLA₂ and GV sPLA₂ have been previously described.^{18,19} The compounds synthesized in this work were initially tested at a 0.091 mole fraction. When the inhibitory potency was higher than 80%, X_I(50) values were determined. The X_I(50) is the mole fraction of inhibitor in the total substrate interface required to inhibit the enzyme by 50%. The results are summarized in Table 1.

Among the 2-oxoamides based on monomesylated or monotosylated 1,3-propanediamine and 1,4-butanediamine (compounds **5a,b** and **8a,b**, Table 1), only compound **5a** showed moderate inhibition of intracellular GIVA cPLA₂ and GVIA iPLA₂. However, when a short linear side chain corresponding to the norleucine side chain was introduced at the neighboring carbon atom near the 2-oxoamide functionality, both sulfonamide derivatives **14a** and **14b** presented significant inhibition of GIVA cPLA₂. In addition, compound **14a** exhibited moderate inhibition of GVIA iPLA₂. Acyl sulfonamide derivatives **18a** and **18b** are very weak inhibitors of GIVA cPLA₂. On the contrary, derivative **20** significantly inhibited GIVA cPLA₂. Among the compounds studied in this work only four derivatives (**14a**, **14b**, **18a** and **20**) presented some weak inhibition of GV sPLA₂.

From the above results, it seems that sulfonamides containing a short linear side chain (**14a** and **14b**) are good inhibitors of GIVA cPLA₂ [X_I(50) values 0.029 and 0.033, respectively]. None of the acyl sulfonamides **18a** and **18b** considerably inhibited GIVA cPLA₂ and GVIA iPLA₂. Surprisingly, derivative **20** lacking an acidic hydrogen preferentially inhibited GIVA cPLA₂ [X_I(50) 0.033]. The three derivatives **14a**, **14b** and **20** inhibited GIVA cPLA₂ at a level comparable to the lead compounds AX006 and AX048 [X_I(50) values 0.024 and 0.031 respectively].¹⁷ Furthermore, their potency is comparable to that of the reference inhibitor of GIVA cPLA₂ arachidonyl trifluoromethyl ketone [X_I(50) 0.036].¹⁴ In addition, compounds **14b** and **20** preferentially inhibit GIVA cPLA₂, in comparison to GVIA iPLA₂. We have recently reported that 2-oxoamide derivatives containing a tetrazole or a phosphonate group in replacement of the carboxyl group presented very weak activity on GIVA cPLA₂.²⁰ On the contrary, in the present study we demonstrate that 2-oxoamides **14a**, **14b** and **20** containing sulfonamide groups efficiently inhibit GIVA cPLA₂.

We have proposed a model for the binding of 2-oxoamide inhibitors containing a free carboxyl group to GIVA cPLA₂.¹⁵ According to that model the carboxyl group of the inhibitor interacts with the polar binding site (Arg 200) in a manner similar to that of the phosphate group of the substrate phospholipid. It should be noticed that compound **20** lacks an acidic hydrogen able to interact through electrostatic interactions. Thus, it seems that an alternative interaction of the acyl sulfonamide group with the active site of GIVA cPLA₂ is possible. The oxygen atoms or the nitrogen atom of the sulfonamide group may act as hydrogen bond acceptors.

In conclusion, we synthesized a variety of lipophilic 2-oxoamides containing a sulfonamide or an acyl sulfonamide group. Three of them inhibited GIVA cPLA₂ at a level similar to that of the lead compounds AX006 and AX048. Thus, the bioisosteric sulfonamide group seems a group suitable to replace the carboxyl group in lipophilic 2-oxoamides inhibitors of GIVA cPLA₂.

Materials and Methods

Melting points are uncorrected. Specific rotations were measured on a Perkin Elmer 841 polarimeter using a 10 cm cell. NMR spectra were recorded on a 200-MHz spectrometer. TLC plates (silica gel 60 F₂₅₄) and silica gel 60 (70-230 or 230-400 mesh) for column chromatography were purchased from Merck. Visualization of spots was effected with UV light and/or phosphomolybdic acid and/or ninhydrin, both in EtOH stain. THF was dried by standard procedures and stored over molecular sieves. All other solvents and chemicals were reagent grade and used without further purification. Fast atom bombardment (FAB) mass spectra were recorded using a VG analytical ZAB-SE instrument.

General Procedure for the Reaction of Diamines with Toluenesulfonyl Chloride

A solution of TsCl (0.15 g, 0.8 mmol) in dry THF (0.76 mL) was added drop-wise to a stirred solution of diamine **2a,b** (1 mmol) and NMM (0.11 mL, 1 mmol) in THF (1 mL) over a period of 30 min. The volatile components were removed under reduced pressure and the residue was partitioned between 5% NaHCO₃ (5 mL) and CH₂Cl₂ (5 mL). The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (2 × 5 mL). Combined CH₂Cl₂ solutions were dried (Na₂SO₄) and concentrated to afford an oil that was extracted with 1 N HCl (5 mL) and precipitated material was filtered off. The filtrate was extracted with Et₂O (2 × 3 mL) and was then basified (pH 11) by the addition of NH₃ (25%) and extracted with CH₂Cl₂ (2 × 10 mL). The CH₂Cl₂ extracts were combined, dried over Na₂SO₄ and evaporated under reduced pressure.

N-(3-Aminopropyl)-4-methylbenzenesulfonamide (3a)—Yield 35%; white solid; mp 112-114 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.73 (2H, d, *J* = 6.6 Hz, Ph), 7.28 (2H, d, *J* = 7.6 Hz, Ph), 3.05 (2H, t, *J* = 5.4 Hz, CH₂NH), 2.77 (2H, t, *J* = 5.2 Hz, H₂NCH₂), 2.41 (3H, s, C₆H₄CH₃), 1.62-1.45 (2H, m, H₂NCH₂CH₂). ¹³C NMR (50 MHz, CDCl₃): δ 143.2, 136.9, 129.9, 127.3, 43.0, 40.9, 31.1, 21.8. Anal. calcd for C₁₀H₁₆N₂O₂S: C, 52.61; H, 7.06; N, 12.27. Found: C, 52.45; H, 7.23; N, 12.41.

N-(4-Aminobutyl)-4-methylbenzenesulfonamide (3b)—Yield 38%; yellow oil; used without any purification in the next step.

General Procedure for the Coupling Reaction of Diamines with 2-Hydroxyhexadecanoic Acid

To a stirred solution of 2-hydroxy hexadecanoic acid (0.27g, 1 mmol) and the diamine (1 mmol) in CH₂Cl₂ (5 mL), Et₃N (0.15 mL, 1.1 mmol) and subsequently WSCI (0.21 g, 1.1

mmol) and HOBt (0.15 g, 1 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 the residue was used in the next step without any purification.

A solution of MsCl (0.08 mL, 1 mmol), in dry THF (1 mL) was added drop-wise to a stirred solution of the amine (1 mmol) and NMM (0.11 mL, 1 mmol) in THF (0.76 mL) over a period of 30 min. The organic solvent was evaporated under reduced pressure and the residue was dissolved in AcOEt. The organic layer was washed consecutively with brine, 10% aqueous KHSO₄, brine, dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography.

2-Hydroxy-N-(3-(methylsulfonamido)propyl)hexadecanamide (7a)—Yield 38%; white solid; mp 134-137 °C. ¹H NMR (200 MHz, DMSO-d₆): δ 7.74 (1H, t, *J* = 5.4 Hz, NH), 6.94 (1H, t, *J* = 5.4 Hz, NH), 5.40 (1H, d, *J* = 4.8 Hz, OH), 3.82-3.75 (1H, m, CHOH), 3.31-3.06 (2H, m, CH₂NHCO), 2.91-2.88 (2H, m, CH₂NHSO₂), 2.88 (3H, s, CH₃SO₂), 1.62-1.45 (4H, m, 2 × CH₂), 1.29-1.18 (24H, m, 12 × CH₂), 0.85 (3H, t, *J* = 6.8 Hz, CH₃). ¹³C NMR (50 MHz, DMSO-d₆): δ 175.2, 71.4, 36.1, 34.8, 31.9, 29.3, 25.1, 22.7, 14.6. Anal. calcd for C₂₀H₄₂N₂O₄S: C, 59.08; H, 10.41; N, 6.89. Found: C, 58.87; H, 10.63; N, 6.98.

2-Hydroxy-N-(4-(methylsulfonamido)butyl)hexadecanamide (7b)—Yield 36%; white solid; mp 139 °C. ¹H NMR (200 MHz, DMSO-d₆): δ 7.74 (1H, t, *J* = 5.4 Hz, NH), 6.94 (1H, t, *J* = 5.4 Hz, NH), 5.42 (1H, d, *J* = 4.8 Hz, OH), 3.80-3.76 (1H, m, CHOH), 3.30-3.05 (2H, m, CH₂NHCO), 2.90-2.89 (2H, m, CH₂NHSO₂), 2.88 (3H, s, CH₃SO₂), 1.62-1.45 (6H, m, 3 × CH₂), 1.30-1.15 (24H, m, 12 × CH₂), 0.85 (3H, t, *J* = 6.8 Hz, CH₃). ¹³C NMR (50 MHz, DMSO-d₆): δ 175.1, 71.3, 36.1, 34.7, 31.9, 29.6, 29.3, 25.1, 22.7, 14.6. Anal. calcd for C₂₁H₄₄N₂O₄S: C, 59.96; H, 10.54; N, 6.66. Found: C, 59.80; H, 10.78; N, 6.78.

(S,E)-tert-Butyl 1-cyanohept-1-en-3-ylcarbamate (10)—To a solution of compound **9** (0.22g, 1 mmol) in a mixture of toluene-EtOAc (6 mL), a solution of NaBr (0.11 g, 1.1 mmol) in water (0.5 mL) was added, followed by TEMPO (0.21 mg, 0.01 mmol). To the resulting biphasic system, which was cooled at -5 °C, an aqueous solution of 0.35 M NaOCl (2.2 mL, 1.1 mmol) containing NaHCO₃ (0.24 g, 3 mmol) was added drop-wise while stirring vigorously at -5 °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 H₂O (5 mL) were added. The aqueous layer was separated and washed with EtOAc (10 mL). The combined organic layers were washed consecutively with 5% aqueous citric acid (10 mL) containing KI (0.18 g), 10% aqueous Na₂S₂O₃ (10 mL), and brine, dried over Na₂SO₄ and evaporated under reduced pressure. The residue was used immediately in the next step without any purification.

To the solution of (*S*)-tert-butyl 1-oxohexan-2-ylcarbamate (0.22g, 1 mmol) in dry THF (10 mL), NCCH=P(C₆H₅)₃ (0.33 g, 1.1 mmol) was added and the reaction mixture was refluxed for 1 h. The organic solvent was evaporated under reduced pressure and the residue was purified by column chromatography [EtOAc-petroleum ether (bp 40-60 °C) 3:7]. Yield 74%; white solid; mp 50-53 °C; [α]_D -11.8 (c 1.0 CHCl₃). ¹H NMR (200 MHz, CDCl₃): δ 6.63 (1H, dd, *J* = 5.4 Hz, *J* = 16.4 Hz, CH=CHCN), 5.48 (1H, d, *J* = 16.4 Hz, CH=CHCN), 4.52 (1H, d, *J* = 6.6 Hz, CONH), 4.25-4.05 (1H, m, CHNH), 1.52-1.45 [11H, m, C(CH₃)₃, CH₂CH], 1.45-1.10 (4H, m, 2 × CH₂), 0.91 (3H, t, *J* = 6.0 Hz, CH₃). ¹³C NMR (50 MHz, CDCl₃): δ 155.2, 154.9, 117.1, 99.4, 79.5, 52.1, 33.7, 28.2, 27.6, 22.2, 13.8. Anal. calcd for C₁₃H₂₂N₂O₂: C, 65.51; H, 9.30; N, 11.75. Found: C, 65.43; H, 9.54; N, 11.81.

(S)-tert-Butyl 1-cyanoheptan-3-ylcarbamate (11)—To a solution of the unsaturated nitrile **10** (0.24g, 1 mmol) in MeOH (10 mL) (through which N₂ had been passed for 5 min), 10% Pd/C catalyst was added. The reaction mixture was stirred under H₂ 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 [EtOAc-petroleum ether (bp 40-60 °C) 3:7]. Yield 84%; white solid; mp 38-40 °C; [α]_D +0.7 (c 1.0 CHCl₃). ¹H NMR (200 MHz, CDCl₃): δ 4.42 (1H, d, *J* = 8.8 Hz, OCONH), 3.62-3.48 (1H, m, NHCH), 2.38 (2H, t, *J* = 7.6 Hz, CH₂CN), 1.94-1.58 (2H, m, CH₂CH₂CN), 1.41-1.28 [11H, m, C(CH₃)₃, CH₂CH], 1.28-1.18 (4H, m, 2 × CH₂), 0.87 (3H, t, *J* = 6.0 Hz, CH₃). ¹³C NMR (50 MHz, CDCl₃): δ 155.7, 119.7, 79.4, 50.0, 34.8, 31.6, 28.2, 27.9, 22.3, 14.1, 13.9. Anal. calcd for C₁₃H₂₄N₂O₂: C, 64.97; H, 10.07; N, 11.66. Found: C, 64.75; H, 10.22; N, 11.48.

General Procedure for the Synthesis of Compounds 12a,b—To a stirred solution of nitrile **11** (0.24g, 1 mmol) in MeOH (8 mL) was added nickel chloride hexahydrate (1.19 g, 5 mmol) at 0 °C, followed by sodium borohydride (0.30 g, 8 mmol) in small portions. After stirring for 30 min at room temperature, water was added and the mixture neutralized with 0.5 M H₂SO₄ and the organic solvent was removed under reduced pressure. The aqueous phase was extracted with ethyl acetate (5 × 15 mL). After drying (Na₂SO₄) the solvent was evaporated to dryness and the amine was used directly for the reaction with sulfonyl chlorides as described above.

(S)-tert-Butyl 1-(methylsulfonamido)octan-4-ylcarbamate (12a)—Yield 40%; white solid; mp 75-77 °C; [α]_D -5.0 (c 1.0 CHCl₃). ¹H NMR (200 MHz, CDCl₃): δ 5.17-5.13 (1H, m, NH), 4.39 (1H, d, *J* = 8.8 Hz, NH), 3.60-3.35 (1H, m, CHNH), 3.10-3.02 (2H, m, CH₂NHSO₂), 2.92 (3H, s, SO₂CH₃), 1.62-1.52 (2H, m, CH₂CH₂NHSO₂), 1.47-1.27 [17H, m, C(CH₃)₃, 4 × CH₂], 0.86 (3H, t, *J* = 6.5 Hz, CH₃). ¹³C NMR (50 MHz, CDCl₃): δ 155.8, 78.9, 50.0, 43.0, 39.9, 35.3, 32.6, 28.3, 27.9, 26.3, 22.4, 13.9. Anal. calcd for C₁₄H₃₀N₂O₄S: C, 52.15; H, 9.38; N, 8.69. Found: C, 52.00; H, 9.49; N, 8.63.

(S)-tert-Butyl 1-(4-methylphenylsulfonamido)octan-4-ylcarbamate (12b)—Yield 38%; white solid; mp 88-90 °C; [α]_D -2.7 (c 1.0 CHCl₃). ¹H NMR (200 MHz, CDCl₃): δ 7.70 (2H, d, *J* = 8.0 Hz, Ph), 7.25 (2H, d, *J* = 8.0 Hz, Ph), 5.05-4.98 (1H, m, NH), 4.22 (1H, d, *J* = 9.2 Hz, NH), 3.48-3.23 (1H, m, CHNH), 2.98-2.76 (2H, m, CH₂NHSO₂), 2.38 (3H, s, PhCH₃), 1.43-1.10 [19H, m, 5 × CH₂, C(CH₃)₃], 0.82 (3H, t, *J* = 6.2 Hz, CH₃CH₂). ¹³C NMR (50 MHz, CDCl₃): δ 155.9, 143.2, 137.0, 129.6, 127.0, 79.1, 50.1, 43.0, 35.2, 32.7, 28.3, 25.8, 22.5, 21.5, 14.0. Anal. calcd for C₂₀H₃₄N₂O₄S: C, 60.27; H, 8.60; N, 7.03. Found: C, 60.02; H, 8.82; N, 6.95.

General Procedure for the Coupling of Boc- γ -Aminobutyric Acid with Sulfonamides—To a solution of compound **15** (0.20g, 1 mmol) in CH₂Cl₂ (20 mL) MsCl or TsCl (1 mmol) was added followed by DCC (0.21 g, 1 mmol) and 4-dimethylaminopyridine (0.12 g, 1 mmol). The mixture was stirred for 24 h and the dicyclohexylurea was removed by filtration through a pad of Celite. The organic solvent was evaporated under reduced pressure and the residue was purified by column chromatography [CHCl₃-MeOH 9:1].

tert-Butyl 4-(methylsulfonamido)-4-oxobutylcarbamate (16a)—Yield 64%; white solid; mp 105-107 °C. ¹H NMR (200 MHz, CDCl₃): δ 4.98 (1H, t, *J* = 5.6 Hz, NH), 3.26 (3H, s, SO₂CH₃), 3.20-3.05 (2H, m, NHCH₂), 2.38 (2H, t, *J* = 7.2 Hz, CH₂CO), 1.85-1.62 (2H, m, CH₂CH₂CO), 1.42 [9H, s, (CH₃)₃]. ¹³C NMR (50 MHz, CDCl₃): δ 172.9, 156.8,

79.8, 41.2, 39.2, 33.4, 28.3, 22.4. Anal. calcd for $C_{10}H_{20}N_2O_5S$: C, 42.84; H, 7.19; N, 9.99. Found: C, 42.65; H, 7.36; N, 10.05.

tert-Butyl 4-(4-methylphenylsulfonamido)-4-oxobutylcarbamate (16b)—Yield 68%; white solid; mp 144–146 °C. 1H NMR (200 MHz, $CDCl_3$): δ 7.87 (2H, d, $J = 8.4$ Hz, Ph), 7.25 (2H, d, $J = 8.0$ Hz, Ph), 4.93 (1H, t, $J = 5.6$ Hz, NH), 3.12–2.95 (2H, m, $NHCH_2$), 2.36 (3H, s, $PhCH_3$), 2.26 (2H, t, $J = 6.6$ Hz, CH_2CO), 1.78–1.58 (2H, m, CH_2CH_2CO), 1.36 [9H, s, $C(CH_3)_3$]. ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.4, 156.7, 144.7, 135.7, 129.4, 128.1, 79.5, 39.1, 33.2, 28.2, 25.2, 21.5. Anal. calcd for $C_{16}H_{24}N_2O_5S$: C, 53.91; H, 6.79; N, 7.86. Found: C, 53.82; H, 6.87; N, 7.83.

General Procedure for the Removal of Boc Group—*N*-Boc-protected compound (1 mmol) was added to a solution of 5 N HCl in MeOH (7 mL, 35 mmol). After being stirred at room temperature for 30 min, the mixture was evaporated, dry Et_2O was added, and the product was filtered and used for coupling with 2-hydroxy acid.

General Method for the Coupling of 2-Hydroxy-hexadecanoic Acids with Amines

To a stirred solution of 2-hydroxy-hexadecanoic acid (0.27 g, 1 mmol) and the diamine (1 mmol) in CH_2Cl_2 (5 mL), Et_3N (0.15 mL, 1.1 mmol) and subsequently WSCI (0.21 g, 1.1 mmol) and HOBt (0.15 g, 1 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 the residue was used immediately in the next step without any purification.

2-Hydroxy-*N*-[3-(4-methylphenylsulfonamido)propyl]hexadecanamide (4a)—Yield 52%; white solid; mp 82–85 °C. 1H NMR (200 MHz, $CDCl_3$): δ 7.68 (2H, d, $J = 7.8$ Hz, Ph), 7.25 (2H, d, $J = 7.6$ Hz, Ph), 7.05 (1H, t, $J = 5.6$ Hz, NH), 5.98 (1H, t, $J = 7.8$ Hz, NH), 4.12–3.98 (1H, m, $CHOH$), 3.75–3.59 (1H, m, $CHOH$), 3.38–3.22 (2H, m, CH_2NHCO), 3.00–2.78 (2H, m, CH_2NHSO_2), 2.38 (3H, s, $3H, C_6H_4CH_3$), 1.80–1.40 (4H, m, $2 \times CH_2$), 1.38–1.12 (24H, m, $12 \times CH_2$), 0.85 (3H, t, $J = 6.6$ Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 175.4, 143.2, 136.9, 129.6, 126.9, 72.0, 39.9, 35.6, 34.7, 31.9, 29.7, 29.6, 29.4, 29.3, 25.1, 22.6, 21.5, 14.1. Anal. calcd for $C_{26}H_{46}N_2O_4S$: C, 64.69; H, 9.61; N, 5.80. Found: C, 64.55; H, 9.68; N, 5.86.

2-Hydroxy-*N*-(4-(4-methylphenylsulfonamido)butyl)hexadecanamide (4b)—Yield 48%; white solid; mp 90–91 °C. 1H NMR (200 MHz, $CDCl_3$): δ 7.68 (2H, d, $J = 7.8$ Hz, Ph), 7.24 (2H, d, $J = 9.2$ Hz, Ph), 6.83 (1H, t, $J = 5.4$ Hz, NH), 5.43 (1H, t, $J = 7.8$ Hz, NH), 4.08–3.98 (1H, m, $CHOH$), 3.72–3.57 (1H, m, $CHOH$), 3.45–3.02 (2H, m, CH_2NHCO), 2.98–2.79 (2H, m, CH_2NHSO_2), 2.37 (3H, s, $C_6H_4CH_3$), 1.81–1.48 (6H, m, $3 \times CH_2$), 1.40–1.05 (24H, s, $12 \times CH_2$), 0.82 (3H, t, $J = 6.6$ Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 175.0, 143.7, 136.9, 130.0, 127.3, 72.4, 43.0, 38.6, 35.0, 32.2, 29.9, 29.8, 29.7, 29.6, 26.9, 25.4, 22.9, 21.8, 14.4. Anal. calcd for $C_{27}H_{48}N_2O_4S$: C, 65.28; H, 9.74; N, 5.64. Found: C, 65.37; H, 9.58; N, 5.73.

2-Hydroxy-*N*-[(*S*)-1-(methylsulfonamido)octan-4-yl]hexadecanamide (13a)—Yield 45%; white solid; mp 98–101 °C. 1H NMR (200 MHz, $CDCl_3$): δ 6.52–6.32 (1H, m, NH), 5.37–5.02 (1H, m, NH), 4.10–4.02 (1H, s, $CHOH$), 4.00–3.81 (1H, s, $CHNH$), 3.60–3.22 (1H, b, $CHOH$), 3.20–3.10 (2H, m, CH_2NHSO_2), 2.95 (3H, s, SO_2CH_3), 1.78–1.26 (36H, m, $18 \times CH_2$), 0.88 (6H, t, $J = 6.0$ Hz, $2 \times CH_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.5, 72.3, 48.7, 48.2, 43.0, 39.9, 35.0, 34.7, 32.3, 32.0, 29.7, 29.5, 28.1, 26.3, 25.1, 22.7, 22.5, 14.1, 14.0. Anal. calcd for $C_{25}H_{52}N_2O_4S$: C, 62.98; H, 10.99; N, 5.88. Found: C, 62.73; H, 11.14; N, 5.99.

2-Hydroxy-N-[(S)-1-(4-methylphenylsulfonamido)octan-4-yl]hexadecanamide (13b)—Yield 45%; white solid; ^1H NMR (200 MHz, CDCl_3): δ 7.73 (2H, d, $J = 7.6$ Hz, Ph), 7.29 (2H, d, $J = 7.8$ Hz, Ph), 6.63-6.40 (1H, m, NH), 5.74-5.51 (1H, m, NH), 4.18-4.00 (1H, m, CHOH), 3.90-3.75 (1H, m, CHNH), 3.02-2.75 (2H, m, CH_2NHSO_2), 2.42 (3H, s, PhCH_3), 1.84-1.15 (36H, m, $18 \times \text{CH}_2$), 0.87 (6H, s, $2 \times \text{CH}_3$). ^{13}C NMR (50 MHz, CDCl_3): δ 174.5, 143.3, 136.7, 129.6, 127.0, 72.1, 48.8, 48.3, 42.9, 34.9, 32.2, 31.9, 29.7, 29.3, 28.0, 25.7, 25.0, 22.6, 22.5, 21.4, 14.1, 13.9. Anal. calcd for $\text{C}_{31}\text{H}_{56}\text{N}_2\text{O}_4\text{S}$: C, 67.35; H, 10.21; N, 5.07. Found: C, 67.46; H, 10.09; N, 5.03.

2-Hydroxy-N-[4-(methylsulfonamido)-4-oxobutyl]hexadecanamide (17a)—Yield 45%; white solid; mp 94-96 °C. ^1H NMR (200 MHz, CDCl_3): δ 6.79 (1H, t, $J = 5.4$ Hz, NH), 4.07 (1H, dd, $J = 3.6$ Hz, $J = 7.8$ Hz, CHOH), 3.68 (3H, s, SO_2CH_3), 3.41-3.24 (2H, m, NHCH_2), 2.88 (1H, b, CHOH), 2.37 (2H, t, $J = 7.2$ Hz, CH_2CONH), 1.90-1.75 (3H, m, CHHCHOH , $\text{CH}_2\text{CH}_2\text{CO}$), 1.73-1.42 (1H, m, CHHCHOH), 1.38-1.10 (24H, s, $12 \times \text{CH}_2$), 0.87 (3H, t, $J = 6.4$ Hz, CH_3). ^{13}C NMR (50 MHz, CDCl_3): δ 174.2, 173.8, 72.1, 51.7, 38.4, 34.9, 31.9, 31.4, 29.7, 29.6, 29.5, 29.4, 29.3, 23.0, 24.7, 14.1. Anal. calcd for $\text{C}_{21}\text{H}_{42}\text{N}_2\text{O}_5\text{S}$: C, 58.03; H, 9.74; N, 6.45. Found: C, 57.83; H, 9.93; N, 6.41.

2-Hydroxy-N-[4-(4-methylphenylsulfonamido)-4-oxobutyl]hexadecanamide (17b)—Yield 39%; white solid; mp 78-80 °C. ^1H NMR (200 MHz, CDCl_3): δ 7.87 (2H, d, $J = 8.0$ Hz, Ph), 7.25 (2H, d, $J = 8.0$ Hz, Ph), 7.15 (1H, t, $J = 5.4$ Hz, NH), 4.17-4.08 (1H, m, CHOH), 3.58-3.32 (1H, m, CHHNHCO), 3.27-3.05 (1H, m, CHHNHCO), 2.36 (3H, s, PhCH_3), 2.24 (2H, t, $J = 6.0$ Hz, CH_2CO), 1.95-1.65 (3H, m, $\text{CH}_2\text{CH}_2\text{CO}$, CHHCHOH), 1.60-1.09 (25H, m, $12 \times \text{CH}_2$, CHHCHOH), 0.82 (3H, t, $J = 6.2$ Hz, CH_3). ^{13}C NMR (50 MHz, CDCl_3): δ 176.3, 172.3, 144.8, 135.7, 129.4, 128.3, 72.2, 38.4, 34.4, 33.9, 31.9, 29.7, 29.5, 29.3, 25.3, 24.7, 22.6, 21.6, 14.1. Anal. calcd for $\text{C}_{27}\text{H}_{46}\text{N}_2\text{O}_5\text{S}$: C, 63.50; H, 9.08; N, 5.48. Found: C, 63.24; H, 9.21; N, 5.63.

Synthesis of N-[4-(N,4-Dimethylphenylsulfonamido)-4-oxobutyl]-2-hydroxyhexadecanamide (19)—To a stirred solution of **17b** (0.51 g, 1 mmol) in dry THF (10 mL), Na_2CO_3 (0.21 g, 2 mmol) and CH_3I (0.48 mL, 7.7 mmol) were added at room temperature. The reaction mixture was stirred for 24 h at room temperature. The organic solvent was evaporated under reduced pressure and water was added. The mixture extracted with CHCl_3 (3×10 mL), the organic layers were combined, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography [CHCl_3 -MeOH 95:5].

Yield 41%; white solid; mp 60-62 °C. ^1H NMR (200 MHz, CDCl_3): δ 7.78 (2H, d, $J = 8.4$ Hz, Ph), 7.34 (2H, d, $J = 8.4$ Hz, Ph), 6.76 (1H, t, $J = 5.8$ Hz, NH), 4.05 (1H, dd, $J = 3.2$ Hz, $J = 7.2$ Hz, CHOH), 3.42-3.00 (5H, m, CONHCH_2 , NCH_3), 2.67 (2H, t, $J = 6.6$ Hz, CH_2CO), 2.44 (3H, s, PhCH_3), 1.95-1.68 (3H, m, $\text{CONHCH}_2\text{CH}_2$, CHHCHOH), 1.65-1.53 (1H, m, CHHCHOH), 1.45-1.05 (24H, m, $12 \times \text{CH}_2$), 0.88 (3H, t, $J = 7.0$ Hz, CH_3). ^{13}C NMR (50 MHz, CDCl_3): δ 174.4, 173.0, 145.1, 135.9, 129.9, 127.5, 72.1, 38.3, 34.7, 33.8, 33.1, 31.9, 29.6, 29.5, 29.4, 29.3, 25.1, 24.3, 22.6, 21.6, 14.1. Anal. calcd for $\text{C}_{28}\text{H}_{48}\text{N}_2\text{O}_5\text{S}$: C, 64.09; H, 9.22; N, 5.34. Found: C, 63.92; H, 9.34; N, 5.39.

General Procedures for the Oxidation of 2-Hydroxyamides to 2-oxoamides

Method A—A solution of 2-hydroxyamide (1 mmol) in dry CH_2Cl_2 (1 mL) was added drop-wise to a stirred solution of the Dess-Martin reagent (0.47 g, 1.1 mmol) in CH_2Cl_2 (3 mL) over a period of 2 min. After stirring for 20 min at room temperature the mixture was diluted with Et_2O (20 mL) and poured into a saturated aqueous NaHCO_3 (10 mL) containing 1.5 g of $\text{Na}_2\text{S}_2\text{O}_3$. The mixture was stirred for 5 min. Et_2O (20 mL) was added, the layers

were separated and the ether layer was washed with saturated aqueous NaHCO₃, water and dried (Na₂SO₄). The organic solvent was evaporated under reduced pressure and the residue was purified by column chromatography.

N-(3-(4-Methylphenylsulfonamido)propyl)-2-oxohexadecanamide (5a): Yield 73%; white solid; 80-81 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.75 (2H, d, *J* = 8.0 Hz, Ph), 7.30 (2H, d, *J* = 8.0 Hz, Ph), 7.20-7.08 (1H, m, NH), 5.26 (1H, t, *J* = 7.8 Hz, NH), 3.40-3.32 (2H, m, CH₂NHCO), 2.98-2.84 (4H, m, CH₂NHSO₂, CH₂COCO), 2.42 (3H, s, C₆H₄CH₃), 1.81-1.15 (26H, m, 13 × CH₂), 0.88 (3H, t, *J* = 6.6 Hz, CH₃). ¹³C NMR (50 MHz, CDCl₃): δ 198.8, 160.9, 143.4, 137.0, 129.7, 127.0, 39.8, 36.8, 35.8, 31.9, 29.7, 29.6, 29.4, 29.3, 29.1, 23.1, 22.7, 21.5, 14.1. MS(FAB): *m/z* = 481 (100%) [M + H]⁺. Anal. calcd for C₂₆H₄₄N₂O₄S: C, 64.96; H, 9.23; N, 5.83. Found: C, 65.03; H, 9.44; N, 5.78.

N-(4-(4-Methylphenylsulfonamido)butyl)-2-oxohexadecanamide (5b): Yield 78%; white solid; 100-103 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.68 (2H, d, *J* = 8.2 Hz, Ph), 7.25 (2H, d, *J* = 8.0 Hz, Ph), 6.95 (1H, t, *J* = 5.4 Hz, NH), 4.61 (1H, t, *J* = 6.6 Hz, NH), 3.21-3.12 (2H, m, CH₂NHCO), 2.95-2.70 (4H, m, CH₂NHSO₂, CH₂COCO), 2.37 (3H, s, C₆H₄CH₃), 1.72-1.06 (28H, m, 14 × CH₂), 0.82 (3H, t, *J* = 6.6 Hz, CH₃). ¹³C NMR (50 MHz, CDCl₃): δ 199.5, 160.5, 143.7, 137, 130.0, 127.3, 42.8, 38.9, 37.0, 32.1, 29.9, 29.7, 29.6, 29.3, 27.0, 26.5, 23.4, 22.9, 21.7, 14.4. Anal. calcd for C₂₇H₄₆N₂O₄S: C, 65.55; H, 9.37; N, 5.66. Found: C, 65.34; H, 9.52; N, 5.78.

(S)-N-[1-(Methylsulfonamido)octan-4-yl]-2-oxohexadecanamide (14a): Yield 79%; white solid; mp 88-91 °C. ¹H NMR (200 MHz, CDCl₃): δ 6.76 (1H, d, *J* = 9.2 Hz, NH), 4.72 (1H, t, *J* = 5.8 Hz, NH), 3.92-3.81 (1H, m, CHNH), 3.20-3.04 (2H, m, CH₂NHSO₂), 2.96 (3H, s, SO₂CH₃), 2.92 (2H, t, *J* = 7.8 Hz, CH₂COCO), 1.80-1.05 (34H, m, 17 × CH₂), 0.88 (6H, t, *J* = 6.6 Hz, 2 × CH₃). ¹³C NMR (50 MHz, CDCl₃): δ 199.5, 160.0, 49.1, 42.8, 40.1, 36.8, 34.7, 32.1, 31.9, 29.6, 29.4, 29.3, 29.0, 28.0, 26.4, 23.1, 22.7, 22.4, 14.1, 13.9. MS (FAB): *m/z* = 475 (100%) [M + H]⁺. Anal. calcd for C₂₅H₅₀N₂O₄S: C, 63.25; H, 10.62; N, 5.90. Found: C, 63.08; H, 10.77; N, 5.96.

(S)-N-[1-(4-Methylphenylsulfonamido)octan-4-yl]-2-oxohexadecanamide (14b): Yield 83%; white solid; mp 99-101 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.69 (2H, d, *J* = 7.6 Hz, Ph), 7.25 (2H, d, *J* = 8.0 Hz, Ph), 6.62 (1H, d, *J* = 10.0 Hz, NH), 4.75 (1H, t, *J* = 6.0 Hz, NH), 3.79-3.67 (1H, m, CHNH), 2.98-2.75 (4H, m, CH₂NH, CH₂COCO), 2.37 (3H, s, PhCH₃), 1.74-1.02 (34H, m, 17 × CH₂), 0.82 (6H, s, 2 × CH₃). ¹³C NMR (50 MHz, CDCl₃): δ 199.5, 160.0, 143.3, 136.9, 129.7, 127.1, 49.1, 42.9, 36.8, 34.7, 32.2, 31.9, 29.6, 29.4, 29.3, 29.1, 28.0, 25.9, 23.2, 22.7, 22.4, 21.5, 14.1, 13.9. MS (FAB): *m/z* = 551 (100%) [M + H]⁺. Anal. calcd for C₃₁H₅₄N₂O₄S: C, 67.59; H, 9.88; N, 5.09. Found: C, 67.45; H, 9.95; N, 5.14.

N-[4-(Methylsulfonamido)-4-oxobutyl]-2-oxohexadecanamide (18a): Yield 90%; white solid; mp 70-72 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.18 (1H, t, *J* = 5.8 Hz, NH), 3.64 (3H, s, SO₂CH₃), 3.69-3.25 (m, 2H, NHCH₂), 2.87 (2H, t, *J* = 7.0 Hz, CH₂COCO), 2.34 (2H, t, *J* = 7.4 Hz, CH₂CONH), 1.86 (2H, quintet, *J* = 6.8 Hz, NHCH₂CH₂), 1.61-1.50 (2H, m, CH₂CH₂COCO), 1.38-1.12 (22H, m, 11 × CH₂), 0.84 (3H, t, *J* = 6.2 Hz, CH₃). ¹³C NMR (50 MHz, CDCl₃): δ 199.1, 173.3, 160.3, 51.6, 38.6, 36.6, 31.8, 31.2, 29.5, 29.3, 29.2, 29.0, 24.3, 23.1, 22.6, 14.0. Anal. calcd for C₂₁H₄₀N₂O₅S: C, 58.30; H, 9.32; N, 6.48. Found: C, 58.18; H, 9.41; N, 6.61.

N-[4-(4-Methylphenylsulfonamido)-4-oxobutyl]-2-oxohexadecanamide (18b): Yield 96%; white solid; mp 124-126 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.86 (2H, d, *J* = 8.0 Hz, Ph), 7.31-7.20 (3H, m, Ph, NH), 3.27-3.15 (2H, m, NHCH₂), 2.83 (2H, t, *J* = 7.4 Hz,

CH₂COCO), 2.36 (3H, s, PhCH₃), 2.26 (2H, t, *J* = 6.6 Hz, CH₂CONHSO₂), 1.83-1.63 (2H, m, NHCH₂CH₂), 1.58-1.35 (2H, m, CH₂CH₂COCO), 1.35-1.05 (22H, s, 11 × CH₂), 0.80 (3H, t, *J* = 5.8 Hz, CH₃). ¹³C NMR (50 MHz, CDCl₃): δ 198.7, 171.0, 160.9, 144.9, 135.7, 129.5, 128.2, 38.3, 36.8, 33.4, 31.8, 29.6, 29.4, 29.3, 29.0, 24.4, 23.0, 22.6, 21.6, 14.1. MS (FAB): *m/z* = 509 (90%) [M + H]⁺. Anal. calcd for C₂₇H₄₄N₂O₅S: C, 63.75; H, 8.72; N, 5.51. Found: C, 63.42; H, 8.99; N, 5.63.

***N*-[4-(*N*,4-Dimethylphenylsulfonamido)-4-oxobutyl]-2-oxohexadecanamide (20):** Yield 75%; light yellow solid; mp 80-82 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.76 (2H, d, *J* = 8.4 Hz, Ph), 7.36 (2H, d, *J* = 8.2 Hz, Ph), 7.07 (1H, t, *J* = 5.8 Hz, NH), 3.41-3.18 (5H, m, NHCH₂, NCH₃), 2.89 (2H, t, *J* = 7.4 Hz, CH₂COCO), 2.73 (2H, t, *J* = 7.0 Hz, CH₂CONCH₃), 2.45 (3H, s, PhCH₃), 1.87 (2H, quintet, *J* = 6.6 Hz, NHCH₂CH₂), 1.78-1.52 (2H, m, CH₂CH₂COCO), 1.45-1.15 (22H, m, 11 × CH₂), 0.88 (3H, t, *J* = 6.2 Hz, CH₃). ¹³C NMR (50 MHz, CDCl₃): δ 199.1, 172.5, 160.3, 145.0, 136.1, 130.0, 127.3, 38.5, 36.7, 33.8, 33.0, 31.9, 29.6, 29.4, 29.3, 29.1, 24.2, 23.2, 22.7, 21.6, 14.1. Anal. calcd for C₂₈H₄₆N₂O₅S: C, 64.33; H, 8.87; N, 5.36. Found: C, 64.49; H, 8.78; N, 5.29.

Method B—To a solution of 2-hydroxyamide (1 mmol), in CH₃COOH (5 mL), PDC (1.13 g, 3 mmol) was added and the mixture was stirred for 30 min at room temperature. The mixture was then neutralized with 5% NaHCO₃ and extracted with AcOEt (3 × 10 mL). The organic layers were washed with brine and dried (Na₂SO₄). The organic solvent was evaporated under reduced pressure and the residue was purified by column chromatography.

***N*-(3-(Methylsulfonamido)propyl)-2-oxohexadecanamide (8a):** Yield 66%; white solid; mp 107-110 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.35-7.27 (1H, m, NH), 5.10 (1H, t, *J* = 6.2 Hz, NH), 3.51-3.38 (2H, m, CH₂NHCO), 3.20-3.08 (2H, m, CH₂NHSO₂), 2.97 (3H, s, SO₂CH₃), 2.94 (2H, t, *J* = 7.8 Hz, COCOCH₂), 1.85-1.70 (2H, m, CH₂), 1.68-1.43 (4H, m, 2 × CH₂), 1.40-1.05 (20H, m, 10 × CH₂), 0.88 (3H, t, *J* = 6.9 Hz, CH₃). ¹³C NMR (50 MHz, CDCl₃): δ 199.1, 161.3, 40.7, 40.1, 37.0, 36.0, 32.1, 30.4, 29.9, 29.7, 29.6, 29.3, 23.4, 23.0, 14.4. Anal. calcd for C₂₀H₄₀N₂O₄S: C, 59.37; H, 9.96; N, 6.92. Found: C, 59.14; H, 10.15; N, 6.98.

***N*-(4-(Methylsulfonamido)butyl)-2-oxohexadecanamide (8b):** Yield 62%; white solid; mp 110-113 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.15-7.00 (1H, m, NH), 4.62-4.51 (1H, m, NH), 3.42-3.30 (2H, m, CH₂NHCO), 3.20-3.14 (2H, m, CH₂NHSO₂), 2.97 (3H, s, SO₂CH₃), 2.95-2.82 (2H, m, CH₂COCO), 1.75-1.15 (28H, m, 14 × CH₂), 0.88 (3H, t, *J* = 6.6 Hz, CH₃). ¹³C NMR (50 MHz, CDCl₃): δ 199.0, 161.4, 42.7, 40.3, 38.6, 36.7, 31.9, 29.6, 29.4, 29.3, 29.0, 27.3, 26.4, 23.1, 22.7, 14.1. Anal. calcd for C₂₁H₄₂N₂O₄S: C, 60.25; H, 10.11; N, 6.69. Found: C, 60.01; H, 10.33; N, 6.74.

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Abbreviations

AcNH-TEMPO	4-acetamido-2,2,6,6-tetramethyl-1-piperidinyloxy free radical
Boc	<i>N</i> -(tert-butoxycarbonyl)
Dess-Martin reagent	1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1 <i>H</i>)-one
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
GIVA cPLA₂	Group IVA cytosolic phospholipase A ₂
GV sPLA₂	Group V secreted phospholipase A ₂
GVIA iPLA₂	Group VIA calcium-independent phospholipase A ₂
HOBt	<i>N</i> -hydroxybenzotriazole
MsCl	methanesulfonyl chloride
NMM	<i>N</i> -methylmorpholine
PAF	platelet-activating factor

PDC	pyridinium dichromate
THF	tetrahydrofuran
TsCl	<i>p</i> -toluenesulfonyl chloride
WSCl	<i>N</i> -ethyl- <i>N'</i> -dimethylaminopropylcarbodiimide

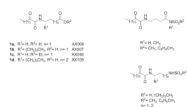
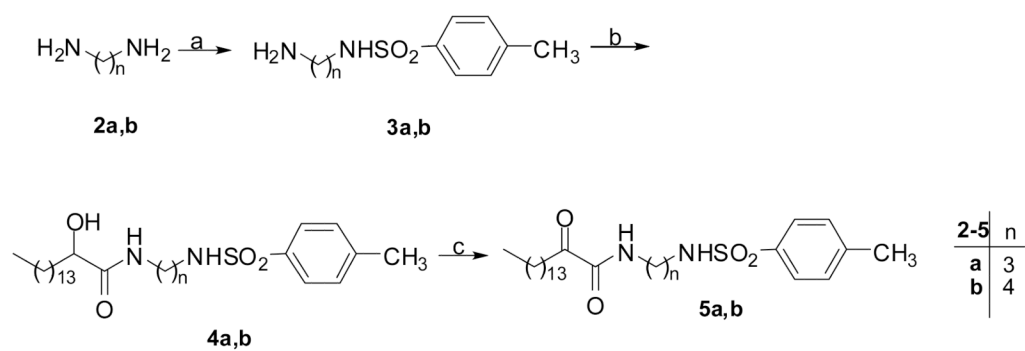


Figure 1.
Structures of known 2-oxoamide inhibitors of GIVA cPLA₂ based on γ - and δ -amino acids and inhibitors containing sulfonamide groups designed in this study.

**Figure 2.**

(a) TsCl, NMM THF; (b) $\text{CH}_3(\text{CH}_2)_{13}\text{CHOHCOOH}$, WSCI, HOBT, Et_3N , CH_2Cl_2 ; (c) Dess-Martin reagent, CH_2Cl_2 .

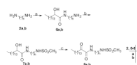


Figure 3.
(a) $\text{CH}_3(\text{CH}_2)_{13}\text{COHCOOH}$, WSCI, HOBt, Et_3N , CH_2Cl_2 ; (b) MsCl, NMM THF; (c) PDC, CH_3COOH .

**Figure 4.**

(a) NaOCl, AcNH-TEMPO, NaBr, NaHCO₃, EtOAc/PhCH₃/H₂O (3:3:0.5), -5 °C; (b) CNCH=P(C₆H₅)₃, THF, reflux; (c) H₂, 10% Pd/C, MeOH; (d) NiCl₂·6H₂O, NaBH₄, MeOH; (e) RSO₂Cl, NMM, THF; (f) 5N HCl/Et₂O; (g) CH₃(CH₂)₁₃CHOHCOOH, WSCI, HOBT, Et₃N; (h) Dess-Martin reagent, CH₂Cl₂.

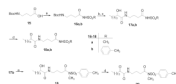


Figure 5.
 (a) RSO_2NH_2 , DCC, DMAP, CH_2Cl_2 , r.t.; (b) 5N HCl/ Et_2O ; (c) $\text{CH}_3(\text{CH}_2)_{13}\text{CHOHCOOH}$, WSCI, HOBT, Et_3N , CH_2Cl_2 ; (d) Dess-Martin reagent, CH_2Cl_2 ; (e) Na_2CO_3 , CH_3I , THF, r.t.

Table 1

In vitro inhibition of human PLA₂ by 2-oxoamides containing sulfonamide groups. Average percent inhibition and standard error (n=3) reported for each compound at 0.091 mole fraction. X_I(50) values determined for inhibitors with greater than 80% inhibition at 0.091 mole fraction. ND signifies compounds with less than 25% inhibition (or no detectable inhibition).

Compound	Structure	GIVA cPLA ₂	GVIA iPLA ₂	GV sPLA ₂
5a		X _I (50) 0.055 ± 0.006	X _I (50) 0.076 ± 0.020	ND
5b		52 ± 4	ND	ND
8a		ND	ND	ND
8b		ND	ND	ND
14a		X _I (50) 0.029 ± 0.019	X _I (50) 0.060 ± 0.037	66 ± 13
14b		X _I (50) 0.033 ± 0.018	57 ± 6	61 ± 12
18a		58 ± 2	ND	38 ± 6
18b		42 ± 8	ND	ND
20		X _I (50) 0.033 ± 0.018	53 ± 15	68 ± 9
AX006		X _I (50) 0.024 ± 0.015 ^a	ND ^a	
AX048		X _I (50) 0.031 ± 0.017 ^a	X _I (50) 0.026 ± 0.014 ^a	
AX007		X _I (50) 0.009 ± 0.004 ^b	ND ^b	

^aData taken from reference 17.

^bData taken from reference 15.