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Synthesis of 2-oxoamides based on sulfonamide analogues of γ-amino acids and their activity on phospholipase A_2

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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 $cPLA_2$ and GVIA $iPLA_2$ as well as secreted GV $sPLA_2$ was evaluated. The sulfonamide group seems a bioisosteric group suitable to replace the carboxyl group in 2-oxoamide inhibitors of GVIA $cPLA_2$.

Keywords

acyl sulfonamides; inhibitors; 2-oxoamides; phospholipase A_2; sulfonamides

Introduction

The phospholipase A_2 (PLA_2) 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 PLA_2 classes into three types: secretory ($sPLA_2$), cytosolic Ca^{2+}-dependent ($cPLA_2$) and cytosolic Ca^{2+}-independent ($iPLA_2$). PLA_2 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 $cPLA_2$ (GIVA $cPLA_2$) 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 PLA_2, calcium-independent PLA_2 (GVIA $iPLA_2$), in the inflammatory process is still unclear, and it appears to be the primary PLA_2 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 PLA_2 enzymes includes the small, secreted $sPLA_2$s and is characterized by a catalytic His/Asp dyad and catalytic Ca^{2+}.[1,3,4,8] A well-studied, simple example of this class is the human Group V secreted phospholipase

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A_2 (GV $sPLA_2$).[9,10] In many cases the activity of GV $sPLA_2$ is dependent on or linked to the activity of GIVA $cPLA_2$.[1,11,12]

A great variety of compounds have been studied for their activity against GIVA $cPLA_2$ and the synthetic inhibitors of GIVA $cPLA_2$ have been summarized in a recent review.[13] Within the last five years, we have been developing a novel class of GIVA $cPLA_2$ 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 $cPLA_2$ 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 $cPLA_2$, 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 PLA_2 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 $cPLA_2$, affecting the activity of neither GVIA $iPLA_2$ nor GV $sPLA_2$.[15,19] Ethyl ester AX048 inhibits in vitro not only GIVA $cPLA_2$, but also calcium-independent GVIA $iPLA_2$, which is the main other intracellular PLA_2 isoform.[17] In addition, methyl esters of 2-oxoamides may inhibit in vitro both GIVA $cPLA_2$ and GVIA $iPLA_2$.[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 (WSCI)[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 $NiCl_2 \cdot 6H_2O/NaBH_4$[33] 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 Na_2CO_3. 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 $cPLA_2$ in a GIVA $cPLA_2$-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 μM), as previously described.[15] In addition, their activity against GVIA $iPLA_2$ and the secreted PLA_2 isoform GV $sPLA_2$ was determined. The *in vitro* assay systems for GVIA $iPLA_2$ and GV $sPLA_2$ 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-propanenediamine and 1,4-butanediamine (compounds **5a,b** and **8a,b**, Table 1), only compound **5a** showed moderate inhibition of intracellular GIVA $cPLA_2$ and GVIA $iPLA_2$. 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 $cPLA_2$. In addition, compound **14a** exhibited moderate inhibition of GVIA $iPLA_2$. Acyl sulfonamide derivatives **18a** and **18b** are very week inhibitors of GIVA $cPLA_2$. On the contrary, derivative **20** significantly inhibited GIVA $cPLA_2$. Among the compounds studied in this work only four derivatives (**14a**, **14b**, **18a** and **20**) presented some weak inhibition of GV $sPLA_2$.

From the above results, it seems that sulfonamides containing a short linear side chain (**14a** and **14b**) are good inhibitors of GIVA $cPLA_2$ [$X_I(50)$ values 0.029 and 0.033, respectively]. None of the acyl sulfonamides **18a** and **18b** considerably inhibited GIVA $cPLA_2$ and GVIA $iPLA_2$. Suprisingly, derivative **20** lacking an acidic hydrogen preferentially inhibited GIVA $cPLA_2$ [$X_I(50)$ 0.033]. The three derivatives **14a**, **14b** and **20** inhibited GIVA $cPLA_2$ 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 $cPLA_2$ arachidonyl trifluoromethyl ketone [$X_I(50)$ 0.036].[14] In addition, compounds **14b** and **20** preferentially inhibit GIVA $cPLA_2$, in comparison to GVIA $iPLA_2$. 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 $cPLA_2$.[20] On the contrary, in the present study we demonstrate that 2-oxoamides **14a**, **14b** and **20** containing sulfonamide groups efficiently inhibit GIVA $cPLA_2$.

We have proposed a model for the binding of 2-oxoamide inhibitors containing a free carboxyl group to GIVA $cPLA_2$.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 $cPLA_2$ 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 $cPLA_2$ 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 $cPLA_2$.

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 F_{254}) 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 (1mL) over a period of 30 min. The volatile components were removed under reduced pressure and the residue was partitioned between 5% $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). Combined CH_2Cl_2 solutions were dried (Na_2SO_4) 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 Et_2O (2 × 3 mL) and was then basified (pH 11) by the addition of NH_3 (25%) and extracted with CH_2Cl_2 (2 × 10 mL). The CH_2Cl_2 extracts were combined, dried over Na_2SO_4 and evaporated under reduced pressure.

***N*-(3-Aminopropyl)-4-methylbenzenesulfonamide (3a)—**Yield 35%; white solid; mp 112-114 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 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, CH_2NH), 2.77 (2H, t, *J* = 5.2 Hz, H_2NCH_2), 2.41 (3H, s, $C_6H_4CH_3$), 1.62-1.45 (2H, m, $H_2NCH_2CH_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 143.2, 136.9, 129.9, 127.3, 43.0, 40.9, 31.1, 21.8. Anal. calcd for $C_{10}H_{16}N_2O_2S$: 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 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 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 $KHSO_4$, brine, dried over Na_2SO_4, 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. ^{1}H NMR (200 MHz, DMSO-d_6): 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, C*H*OH), 3.31-3.06 (2H, m, CH_2NHCO), 2.91-2.88 (2H, m, CH_2NHSO_2), 2.88 (3H, s, CH_3SO_2), 1.62-1.45 (4H, m, 2 × CH_2), 1.29-1.18 (24H, m, 12 × CH_2), 0.85 (3H, t, *J* = 6.8 Hz, CH_3). ^{13}C NMR (50 MHz, DMSO-d_6): δ 175.2, 71.4, 36.1, 34.8, 31.9, 29.3, 25.1, 22.7, 14.6. Anal. calcd for $C_{20}H_{42}N_2O_4S$: 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. ^{1}H NMR (200 MHz, DMSO-d_6): 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, C*H*OH), 3.30-3.05 (2H, m, CH_2NHCO), 2.90-2.89 (2H, m, CH_2NHSO_2), 2.88 (3H, s, CH_3SO_2), 1.62-1.45 (6H, m, 3 × CH_2), 1.30-1.15 (24H, m, 12 × CH_2), 0.85 (3H, t, *J* = 6.8 Hz, CH_3). ^{13}C NMR (50 MHz, DMSO-d_6): δ 175.1, 71.3, 36.1, 34.7, 31.9, 29.6, 29.3, 25.1, 22.7, 14.6. Anal. calcd for $C_{21}H_{44}N_2O_4S$: 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 $NaHCO_3$ (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 H_2O (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 $Na_2S_2O_3$ (10 mL), and brine, dried over Na_2SO_4 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$(C_6H_5)_3$ (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; $[\alpha]_D$ -11.8 (*c* 1.0 $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.63 (1H, dd, *J* = 5.4 Hz, *J* = 16.4 Hz, C*H*=CHCN), 5.48 (1H, d, *J* = 16.4 Hz, CH=C*H*CN), 4.52 (1H, d, *J* = 6.6 Hz, OCONH), 4.25-4.05 (1H, m, C*H*NH), 1.52-1.45 [11H, m, $C(CH_3)_3$, CH_2CH], 1.45-1.10 (4H, m, 2 × CH_2), 0.91 (3H, t, *J* = 6.0 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_{13}H_{22}N_2O_2$: 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 N_2 had been passed for 5 min), 10% Pd/C catalyst 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 [EtOAc-petroleum ether (bp 40-60 °C) 3:7]. Yield 84%; white solid; mp 38-40 °C; $[\alpha]_D$ +0.7 (*c* 1.0 $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.42 (1H, d, *J* = 8.8 Hz, OCONH), 3.62-3.48 (1H, m, NHC*H*), 2.38 (2H, t, *J* = 7.6 Hz, CH_2CN), 1.94-1.58 (2H, m, C$H_2$$CH_2$CN), 1.41-1.28 [11H, m, $C(CH_3)_3$, CH_2CH], 1.28-1.18 (4H, m, 2 × CH_2), 0.87 (3H, t, *J* = 6.0 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_{13}H_{24}N_2O_2$: 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 H_2SO_4 and the organic solvent was removed under reduced pressure. The aqueous phase was extracted with ethyl acetate (5 × 15 mL). After drying (Na_2SO_4) 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; $[\alpha]_D$ -5.0 (*c* 1.0 $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.17-5.13 (1H, m, NH), 4.39 (1H, d, *J* = 8.8 Hz, NH), 3.60-3.35 (1H, m, C*H*NH), 3.10-3.02 (2H, m, C$H_2$$NHSO_2$), 2.92 (3H, s, SO_2CH_3), 1.62-1.52 (2H, m, C$H_2$$CH_2NHSO_2$), 1.47-1.27 [17H, m, $C(CH_3)_3$, 4 × CH_2], 0.86 (3H, t, *J* = 6.5 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_{14}H_{30}N_2O_4S$: 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; $[\alpha]_D$ -2.7 (*c* 1.0 $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): 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, C*H*NH), 2.98-2.76 (2H, m, C$H_2$$NHSO_2$), 2.38 (3H, s, $PhCH_3$), 1.43-1.10 [19H, m, 5 × CH_2, $C(CH_3)_3$], 0.82 (3H, t, *J* = 6.2 Hz, C$H_3$$CH_2$). ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_{20}H_{34}N_2O_4S$: 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 CH_2Cl_2 (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 [$CHCl_3$-MeOH 9:1].

***tert*-Butyl 4-(methylsulfonamido)-4-oxobutylcarbamate (16a)—**Yield 64%; white solid; mp 105-107 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.98 (1H, t, *J* = 5.6 Hz, NH), 3.26 (3H, s, SO_2CH_3), 3.20-3.05 (2H, m, NHCH_2), 2.38 (2H, t, *J* = 7.2 Hz, CH_2CO), 1.85-1.62 (2H, m, C$H_2$$CH_2CO$), 1.42 [9H, s, $(CH_3)_3$]. ^{13}C NMR (50 MHz, $CDCl_3$): 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. ^{1}H 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 (0.27g, 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. ^{1}H 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, C*H*OH), 3.75-3.59 (1H, m, CHO*H*), 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 × CH_2), 1.38-1.12 (24H, m, 12 × 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. ^{1}H 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, C*H*OH), 3.72-3.57 (1H, m, CHO*H*), 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 × CH_2), 1.40-1.05 (24H, s, 12 × 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. ^{1}H 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, C*H*OH), 4.00-3.81 (1H, s, C*H*NH), 3.60-3.22 (1H, b, CHO*H*), 3.20-3.10 (2H, m, CH_2NHSO$_2$), 2.95 (3H, s, SO_2CH_3), 1.78-1.26 (36H, m, 18 × CH_2), 0.88 (6H, t, *J* = 6.0 Hz, 2 × 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; ^{1}H 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, C*H*OH), 3.90-3.75 (1H, m, C*H*NH), 3.02-2.75 (2H, m, CH_2NHSO_2), 2.42 (3H, s, $PhCH_3$), 1.84-1.15 (36H, m, 18 × CH_2), 0.87 (6H, s, 2 × 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 $C_{31}H_{56}N_2O_4S$: 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. ^{1}H 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, C*H*OH), 3.68 (3H, s, SO_2CH_3), 3.41-3.24 (2H, m, $NHCH_2$), 2.88 (1H, b, CHO*H*), 2.37 (2H, t, *J* = 7.2 Hz, CH_2CONH), 1.90-1.75 (3H, m, CH*H*CHOH, CH_2CH_2CO), 1.73-1.42 (1H, m, C*H*HCHOH), 1.38-1.10 (24H, s, 12 × 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 $C_{21}H_{42}N_2O_5S$: 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. ^{1}H 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, C*H*OH), 3.58-3.32 (1H, m, C*H*HNHCO), 3.27-3.05 (1H, m, CH*H*NHCO), 2.36 (3H, s, $PhCH_3$), 2.24 (2H, t, *J* = 6.0 Hz, CH_2CO), 1.95-1.65 (3H, m, CH_2CH_2CO, C*H*HCHOH), 1.60-1.09 (25H, m, 12 × CH_2, CH*H*CHOH), 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 $C_{27}H_{46}N_2O_5S$: 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** (0.51g, 1 mmol) in dry THF (10 mL), Na_2CO_3 (0.21g, 2 mmol) and CH_3I (0.48mL, 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. ^{1}H 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, C*H*OH), 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, $CONHCH_2CH_2$, CH*H*CHOH), 1.65-1.53 (1H, m, C*H*HCHOH), 1.45-1.05 (24H, m, 12 × 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 $C_{28}H_{48}N_2O_5S$: 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 $Na_2S_2O_3$. 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 $NaHCO_3$, water and dried (Na_2SO_4). 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. ^{1}H NMR (200 MHz, $CDCl_3$): 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, CH_2NHCO), 2.98-2.84 (4H, m, CH_2NHSO_2, CH_2COCO), 2.42 (3H, s, $C_6H_4CH_3$), 1.81-1.15 (26H, m, 13 × CH_2), 0.88 (3H, t, *J* = 6.6 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_{26}H_{44}N_2O_4S$: 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. ^{1}H NMR (200 MHz, $CDCl_3$): 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, CH_2NHCO), 2.95-2.70 (4H, m, CH_2NHSO_2, CH_2COCO), 2.37 (3H, s, $C_6H_4CH_3$), 1.72-1.06 (28H, m, 14 × CH_2), 0.82 (3H, t, *J* = 6.6 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_{27}H_{46}N_2O_4S$: 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. ^{1}H NMR (200 MHz, $CDCl_3$): 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, CH_2NHSO_2), 2.96 (3H, s, SO_2CH_3), 2.92 (2H, t, *J* = 7.8 Hz, CH_2COCO), 1.80-1.05 (34H, m, 17 × CH_2), 0.88 (6H, t, *J* = 6.6 Hz, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_{25}H_{50}N_2O_4S$: 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. ^{1}H NMR (200 MHz, $CDCl_3$): 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, CH_2NH, CH_2COCO), 2.37 (3H, s, $PhCH_3$), 1.74-1.02 (34H, m, 17 × CH_2), 0.82 (6H, s, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_{31}H_{54}N_2O_4S$: 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. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.18 (1H, t, *J* = 5.8 Hz, NH), 3.64 (3H, s, SO_2CH_3), 3.69-3.25 (m, 2H, $NHCH_2$), 2.87 (2H, t, *J* = 7.0 Hz, CH_2COCO), 2.34 (2H, t, *J* = 7.4 Hz, CH_2CONH), 1.86 (2H, quintet, *J* = 6.8 Hz, $NHCH_2CH_2$), 1.61-1.50 (2H, m, CH_2CH_2COCO), 1.38-1.12 (22H, m, 11 × CH_2), 0.84 (3H, t, *J* = 6.2 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_{21}H_{40}N_2O_5S$: 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. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.86 (2H, d, *J* = 8.0 Hz, Ph), 7.31-7.20 (3H, m, Ph, NH), 3.27-3.15 (2H, m, $NHCH_2$), 2.83 (2H, t, *J* = 7.4 Hz,

CH_2COCO), 2.36 (3H, s, $PhCH_3$), 2.26 (2H, t, *J* = 6.6 Hz, $CH_2CONHSO_2$), 1.83-1.63 (2H, m, $NHCH_2CH_2$), 1.58-1.35 (2H, m, CH_2CH_2COCO), 1.35-1.05 (22H, s, 11 × CH_2), 0.80 (3H, t, *J* = 5.8 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_{27}H_{44}N_2O_5S$: 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, $CDCl_3$): 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, $NHCH_2$, NCH_3), 2.89 (2H, t, *J* = 7.4 Hz, CH_2COCO), 2.73 (2H, t, *J* = 7.0 Hz, CH_2CONCH_3), 2.45 (3H, s, $PhCH_3$), 1.87 (2H, quintet, *J* = 6.6 Hz, $NHCH_2CH_2$), 1.78-1.52 (2H, m, CH_2CH_2COCO), 1.45-1.15 (22H, m, 11 × CH_2), 0.88 (3H, t, *J* = 6.2 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_{28}H_{46}N_2O_5S$: 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 CH_3COOH (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% $NaHCO_3$ and extacted with AcOEt (3 × 10 mL). The organic layers were washed with brine and dried (Na_2SO_4). 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, $CDCl_3$): δ 7.35-7.27 (1H, m, NH), 5.10 (1H, t, *J* = 6.2 Hz, NH), 3.51-3.38 (2H, m, CH_2NHCO), 3.20-3.08 (2H, m, CH_2NHSO_2), 2.97 (3H, s, SO_2CH_3), 2.94 (2H, t, *J* = 7.8 Hz, $COCOCH_2$), 1.85-1.70 (2H, m, CH_2), 1.68-1.43 (4H, m, 2 × CH_2), 1.40-1.05 (20H, m, 10 × CH_2), 0.88 (3H, t, *J* = 6.9 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_{20}H_{40}N_2O_4S$: 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, $CDCl_3$): δ 7.15-7.00 (1H, m, NH), 4.62-4.51 (1H, m, NH), 3.42-3.30 (2H, m, CH_2NHCO), 3.20-3.14 (2H, m, CH_2NHSO_2), 2.97 (3H, s, SO_2CH_3), 2.95-2.82 (2H, m, CH_2COCO), 1.75-1.15 (28H, m, 14 × CH_2), 0.88 (3H, t, *J* = 6.6 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 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 $C_{21}H_{42}N_2O_4S$: C, 60.25; H, 10.11; N, 6.69. Found: C, 60.01; H, 10.33; N, 6.74.

Acknowledgments

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References

1. Schaloske RH, Dennis EA. The phospholipase A(2) superfamily and its group numbering system. Biochim Biophys Acta. 2006; 1761:1246–1259. [PubMed: 16973413]

2. Kudo I, Murakami M. Phospholipase A_2 enzymes. Prostaglandins Other Lipid Mediat. 2002; 68-69:3–58. [PubMed: 12432908]

3. Balsinde J, Winstead MV, Dennis EA. Phospholipase A_2 regulation of arachidonic acid mobilization. FEBS Lett. 2002; 531:2–6. [PubMed: 12401193]
4. Six DA, Dennis EA. The expanding superfamily of phospholipase A(2) enzymes: classification and characterization. Biochim Biophys Acta. 2000; 1488:1–19. [PubMed: 11080672]
5. Leslie CC. Regulation of the specific release of arachidonic acid by cytosolic phospholipase A_2. Prostaglandins Leukot Essent Fatty Acids. 2004; 70:373–376. [PubMed: 15041029]
6. Winstead MV, Balsinde J, Dennis EA. Calcium-independent phospholipase A(2): structure and function. Biochim Biophys Acta. 2000; 1488:28–39. [PubMed: 11080674]
7. Balsinde J, Balboa MA. Cellular regulation and proposed biological functions of group VIA calcium-independent phospholipase A(2) in activated cells. Cellular Signalling. 2005; 17:1052–1062. [PubMed: 15993747]
8. Berg OG, Gelb MH, Tsai MD, Jain MK. Interfacial enzymology: The secreted phospholipase A_2-paradigm. Chem Rev. 2001; 101:2613–2654. [PubMed: 11749391]
9. Balestrieri B, Arm JP. Group V $sPLA_2$: Classical and novel functions. Biochim Biophys Acta. 2006; 1761:1280–1288. [PubMed: 16945583]
10. Rosengren B, Jonsson-Rylander AC, Peilot H, Camejo G, Hurt-Camejo E. Distinctiveness of secretory phospholipase A_2 group IIA and V suggesting unique roles in atherosclerosis. Biochim Biophys Acta. 2006; 1761:1301–1308. [PubMed: 17070102]
11. Mounier CM, Ghomashchi F, Lindsay MR, James S, Singer AG, Parton RG, Gelb MH. Arachidonic acid release from mammalian cells transfected with human groups IIA and X secreted phospholipase A_2 occurs predominantly during the secretory process and with the involvement of cytosolic phospholipase A_2-α. J Biol Chem. 2004; 279:25024–25038. [PubMed: 15007070]
12. Shirai Y, Balsinde J, Dennis EA. Localization and functional interrelationships among cytosolic Group IV, secreted Group V, and Ca^{2+}-independent Group VI phospholipase A2s in P388D1 macrophages using GFP/RFP constructs. Biochim Biophys Acta. 2005; 1735:119–129. [PubMed: 15967714]
13. Magrioti V, Kokotos G. Synthetic inhibitors of Group IVA and Group VIA phospholipase A_2. Anti-Inflamm Anti-Allergy Agents Med Chem. 2006; 5:189–203.
14. Kokotos G, Kotsovolou S, Six DA, Constantinou-Kokotou V, Beltzner CC, Dennis EA. Novel 2-oxoamide inhibitors of human Group IVA phospholipase A_2. J Med Chem. 2002; 45:2891–2893. [PubMed: 12086476]
15. Kokotos G, Six DA, Loukas V, Smith T, Constantinou-Kokotou V, Hadjipavlou-Litina D, Kotsovolou S, Chiou A, Beltzner CC, Dennis EA. Inhibition of Group IVA cytosolic phospholipase A_2 by novel 2-oxoamides in vitro, in cells and in vivo. J Med Chem. 2004; 47:3615–3628. [PubMed: 15214789]
16. Constantinou-Kokotou V, Peristeraki A, Kokotos CG, Six DA, Dennis EA. Synthesis and activity of 2-oxoamides containing long chain beta-amino acids. J Pept Sci. 2005; 11:431–435. [PubMed: 15635664]
17. Yaksh TL, Kokotos G, Svensson CI, Stephens D, Kokotos CG, Fitzsimmons B, Hadjipavlou-Litina D, Hua XY, Dennis EA. Systemic and intrathecal effects of a novel series of phospholipase A_2 inhibitors on hyperalgesia and spinal prostaglandin E_2 release. J Pharmacol Exp Ther. 2006; 316:466–475. [PubMed: 16203828]
18. Stephens D, Barbayianni E, Constantinou-Kokotou V, Peristeraki A, Six DA, Cooper J, Harkewicz R, Deems RA, Dennis EA, Kokotos G. Differential inhibition of Group IVA and Group VIA phospholipases A(2) by 2-oxoamides. J Med Chem. 2006; 49:2821–2828. [PubMed: 16640343]
19. Six DA, Barbayianni E, Loukas V, Constantinou-Kokotou V, Hadjipavlou-Litina D, Stephens D, Wong AC, Magrioti V, Moutevelis-Minakakis P, Baker SF, Dennis EA, Kokotos G. Structure-activity relationship of 2-oxoamide inhibition of Group IVA cytosolic phospholipase A_2 and Group V secreted phospholipase A_2. J Med Chem. 2007; 50:4222–4235. [PubMed: 17672443]
20. Moutevelis-Minakakis P, Neokosmidi A, Filippakou M, Stephens D, Dennis EA, Kokotos G. Synthesis of lipophilic 2-oxoamides based on γ-aminobutyric and δ-aminovaleric analogues and their activity against phospholipase A_2. J Pept Sci. 2007; 13:634–641. [PubMed: 17631670]
21. Patani GA, LaVoie EJ. Bioisosterism: A Rational Approach in Drug Design. Chem Rev. 1996; 96:3147–3176. [PubMed: 11848856]

22. Schaaf TK, Hess HJ. Synthesis and biological activity of carboxyl-terminus modified prostaglandin analogues. J Med Chem. 1979; 22:1340–1346. [PubMed: 533881]
23. Johansson A, Poliakov A, Akerblom E, Wiklund K, Lindeberg G, Winiwarter S, Danielson UH, Samuelsson B, Hallberg A. Acyl sulfonamides as potent protease inhibitors of the hepatitis C virus full-length NS3 (Protease-Helicase/NTPase): A comparative study of different C-terminals. Bioorg Med Chem. 2003; 11:2551–2568. [PubMed: 12757723]
24. Liu DG, Gao Y, Voigt JH, Lee K, Nicklaus MC, Wu L, Zhang ZY, Burke TR. Acylsulfonamide-containing PTP1B inhibitors designed to mimic an enzyme-bound water of hydration. Bioorg Med Chem Lett. 2003; 13:3005–3007. [PubMed: 12941322]
25. Allegretti M, Bertini R, Cesta MC, Bizzarri C, Di Bitondo R, Di Cioccio V, Galliera E, Berdini V, Topai A, Zampella G, Russo V, Di Bello N, Nano G, Nicolini L, Locati M, Fantucci P, Florio S, Colotta F. 2-Arylpropionic CXC chemokine receptor 1 (CXCR1) ligands as novel noncometitive CXCL8 inhibitors. J Med Chem. 2005; 48:4312–4331. [PubMed: 15974585]
26. Bellis E, Vasilatou K, Kokotos G. 4-Substituted propyl sulfonamides as enantioselective organocatalysts for aldol reactions. Synthesis. 2005; 14:2407–2413.
27. Cobb AJA, Shaw DM, Longbottom DA, Gold JB, Ley SV. Organocatalysis with proline derivatives: improved catalysts for the asymmetric Mannich, nitro-Michael and aldol reactions. Org Biomol Chem. 2005; 3:84. [PubMed: 15602602]
28. Sheehan JC, Cruickshank PA, Boshart GL. A convenient synthesis of water-soluble carbodiimides. J Org Chem. 1961; 26:2525–2528.
29. Kokotos G. A convenient one-pot conversion of *N*-protected amino acids and peptides into alcohols. Synthesis. 1990:299–301.
30. Kokotos G, Noula C. Selective one-pot conversion of carboxylic acids into alcohols. J Org Chem. 1996; 61:6994–6996. [PubMed: 11667598]
31. Loukas V, Noula C, Kokotos G. Efficient protocols for the synthesis of enantiopure γ-amino acids with proteinogenic side chains. J Pept Sci. 2003; 9:312–319. [PubMed: 12803497]
32. Moutevelis-Minakakis P, Filippakou M, Sinanoglou C, Kokotos G. Synthesis of tetrazole analogs of γ- and δ–amino acids. J Pept Sci. 2006; 12:377–382. [PubMed: 16432805]
33. Constantinou-Kokotou V, Kokotos G. Synthesis of 1,3-diamines. Org Prep Proced Int. 1994; 26:599–602.

Abbreviations

AcNH-TEMPO	4-acetamido-2,2,6,6-tetramethyl-1-piperidinyloxy free radical
Boc	*N*-(tert-butoxycarbonyl)
Dess-Martin reagent	1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one
DCC	*N*,*N′*-dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
GIVA cPLA$_2$	Group IVA cytosolic phospholipase A_2
GV sPLA$_2$	Group V secreted phospholipase A_2
GVIA iPLA$_2$	Group VIA calcium-independent phospholipase A_2
HOBt	*N*-hydroxybenzotriazole
MsCl	methanesulfonyl chloride
NMM	*N*-methylmorpholine
PAF	platelet-activating factor

PDC	pyridinium dichromate
THF	tetrahydrofuran
TsCl	*p*-toluenesulfonyl chloride
WSCI	*N*-ethyl-*N′*-dimethylaminopropylcarbodiimide

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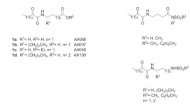


Figure 1.

Structures of known 2-oxoamide inhibitors of GIVA $cPLA_2$ based on γ- and δ-amino acids and inhibitors containing sulfonamide groups designed in this study.

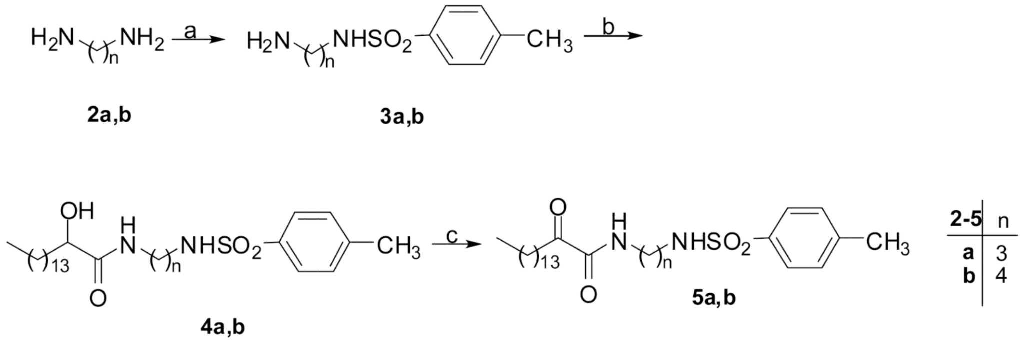


Figure 2.
(a) TsCl, NMM THF; (b) $CH_3(CH_2)_{13}CHOHCOOH$, WSCI, HOBt, Et_3N, CH_2Cl_2; (c) Dess-Martin reagent, CH_2Cl_2.

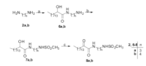


Figure 3.
(a) $CH_3(CH_2)_{13}CHOHCOOH$, WSCI, HOBt, Et_3N, CH_2Cl_2; (b) MsCl, NMM THF; (c) PDC, CH_3COOH.

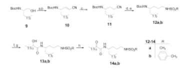


Figure 4.

(a) NaOCl, AcNH-TEMPO, NaBr, $NaHCO_3$, EtOAc/$PhCH_3$/H_2O (3:3:0.5), -5 °C; (b) CNCH=P(C_6H_5)$_3$, THF, reflux; (c) H_2, 10% Pd/C, MeOH; (d) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH; (e) RSO_2Cl, NMM, THF; (f) 5N HCl/Et_2O; (g) $CH_3(CH_2)_{13}$CHOHCOOH, WSCI, HOBt, Et_3N; (h) Dess-Martin reagent, CH_2Cl_2.

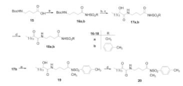
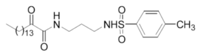
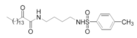
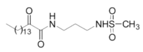
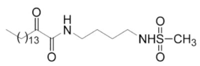
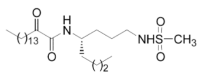
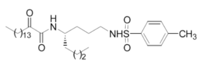
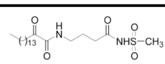
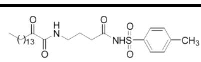
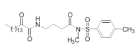
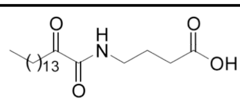
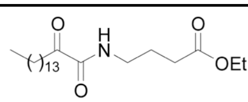
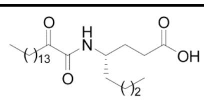


Figure 5.
(a) RSO_2NH_2, DCC, DMAP, CH_2Cl_2, r.t; (b) 5N HCl/Et_2O; (c) $CH_3(CH_2)_{13}CHOHCOOH$, WSCI, HOBt, Et_3N, CH_2Cl_2; (d) Dess-Martin reagent, CH_2Cl_2; (e) Na_2CO_3, CH_3I, THF, r.t.

Table 1

In vitro inhibition of human PLA_2 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]	

[a] Data taken from reference 17.

[b] Data taken from reference 15.