Published in final edited form as:

J Med Chem. 2009 May 28; 52(10): 3317–3327. doi:10.1021/jm900251a.

Design and Synthesis of Small Molecule Glycerol 3-Phosphate Acyltransferase Inhibitors

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Abstract

The incidence of obesity and other diseases associated with an increased triacylglycerol mass is growing rapidly, particularly in the United States. Glycerol 3-phosphate acyltransferase (GPAT) catalyzes the rate-limiting step of glycerolipid biosynthesis, the acylation of glycerol 3-phosphate with saturated long chain acyl-CoAs. In an effort to produce small molecule inhibitors of this enzyme, a series of benzoic and phosphonic acids was designed and synthesized. *In vitro* testing of this series has led to the identification of several compounds, in particular 2-(nonylsulfonamido)benzoic acid (**15g**), possessing moderate GPAT inhibitory activity in an intact mitochondrial assay.

Introduction

Obesity is currently estimated by the World Health Organization to affect at least 400 million adults worldwide. In the U.S. alone, approximately two-thirds of adults are overweight or obese.¹ Various diseases are associated with obesity, including type 2 diabetes, hypertension, cardiovascular diseases, nonalcoholic fatty liver disease, and certain types of cancer. Even though there is a growing need for anti-obesity therapeutics, there are only two drugs approved for long-term use in the U.S. Orlistat functions by blocking the absorption of fat from the diet,² and sibutramine affects the central nervous system, reducing energy intake and increasing energy use.³ Unfortunately, each of these drugs displays limited efficacy and produces undesirable side effects. Anti-obesity drugs currently in development utilize a wide variety of mechanisms, involving both central and peripheral targets. Alteration of lipid metabolism, by decreasing the *de novo* synthesis of triglycerides while increasing oxidation of stored fats, is a peripheral mechanism. This approach, based on weight loss effects observed with the compounds C75,⁴ cerulenin,⁵ and hGH₍₁₇₇₋₁₉₁₎,⁶ may be highly valuable in developing anti-obesity drugs.

The mitochondrial isoform of glycerol-3-phosphate acyltransferase-1 (mtGPAT) catalyzes the esterification of long chain acyl-CoAs with *sn*-glycerol-3-phosphate to produce lysophosphatidic acid (LPA). This reaction constitutes the first committed and rate-limiting step of glycerolipid biosynthesis.^{7, 8} The purported mechanism of this reaction is similar to that of a serine protease, with the primary hydroxyl group of glycerol-3-phosphate taking the place of serine in the catalytic triad.⁹ Next, LPA is esterified further to produce phosphatidic acid, a precursor of various lipids including triacylglycerol (TAG), the main component of animal fat. In addition to obesity, high TAG levels in the bloodstream have been linked to several diseases, notably atherosclerosis and pancreatitis.^{10,11}

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Supporting Information Available: Elemental analysis data for target compounds.

There are four known isoforms of GPAT, two microsomal isoforms located in the endoplasmic reticulum (GPAT3 and GPAT4), and two located in mitochondria (mtGPAT1 and mtGPAT2).^{12, 13} mtGPAT1 displays a strong preference for incorporating palmitoyl-CoA (16:0), thereby primarily producing saturated phospholipids, whereas the other three enzymes are not selective.^{13, 14} For recombinant mouse mtGPAT1, activity is 2-fold greater with palmitoyl-CoA than with various unsaturated chains 18 and 20 carbons in length,¹⁵ and in rat liver, kidney, and heart, mtGPAT1 incorporates palmitoyl CoA 3-10 times more effectively than other long chain saturated or unsaturated acyl-CoAs.^{14, 16-18} Of the four isoforms, only mtGPAT1 is affected by changes in diet or exercise. When excess calories are available from a high-carbohydrate diet, mtGPAT1 mRNA expression increases, resulting in greater mtGPAT1 activity.¹⁹⁻²¹ Mice that remain stationary for ten hours following a prolonged exercise regimen experience an increase in mtGPAT1 activity compared to mice that did not exercise at all, resulting in a significant overshoot of triacylglycerol (TAG) synthesis.²²

mtGPAT1-deficient mice exhibit lower hepatic TAG levels and secrete less very low density lipoprotein (VLDL) than control mice.²³ In contrast, rat hepatocytes with 2.7-fold increased mtGPAT1 activity demonstrated a significant increase in *de novo* synthesis of diacylglycerol.²⁴ Overexpression of mtGPAT1 *in vivo*, as expected from the previous result, causes the levels of accumulated TAG and diacylglycerol (DAG) in mouse liver to rise dramatically to 12-fold and 7-fold that of normal levels.²⁵ In addition to producing a certain amount of TAG dependent on the amount of active enzyme present, mtGPAT1 activity is essential for controlling the partitioning of fatty-acyl CoAs to β -oxidation or glycerolipid synthesis.

Both mtGPAT1 and carnitine palmitoyltransferase-1 (CPT-1), the enzyme that catalyzes the rate-limiting step of β -oxidation, are located on the outer mitochondrial membrane.²⁶ This suggests that there is a competition between these enzymes for fatty acyl-CoA substrates. AMP-activated protein kinase (AMPK), which inactivates acetyl-CoA carboxylase (ACC) by phosphorylation, appears to acutely regulate both of these enzymes. Inactivation of ACC by AMPK prevents the buildup of malonyl-CoA, an allosteric suppressor of CPT-1, resulting in an increase in β -oxidation.²⁷ AMPK inhibits mtGPAT1 as well, thereby decreasing the amount of TAG produced.²⁸ The relationship between these two processes has been demonstrated *in vivo*. Feeding mtGPAT1-knockout mice a high-fat, high-sugar diet to induce obesity resulted in an increase in oxidation as the long-chain acyl-CoA substrates were partitioned away from the TAG synthetic pathway toward CPT-1 and β -oxidation.²⁹ mtGPAT1 overexpression in rat hepatocytes produced an 80% reduction in fatty acid oxidation coupled to an increase in phospholipid biosynthesis.²⁴ Overexpression *in vivo* resulted in a decrease in β -oxidation as well.²⁵

The evidence suggesting that a drop in mtGPAT1 activity leads to a decrease in TAG levels as well as an increase in the amount of β -oxidation suggests that inhibition of this enzyme with a small molecule could be an effective treatment for obesity, diabetes, and other health problems associated with increased TAG synthesis. As there are no such studies of small molecule mtGPAT1 inhibitors described in the literature, we set out to design, synthesize, and test a GPAT inhibitor as a potential weight loss strategy.

Chemistry

The fundamental design of the compounds comprised structures with a negative charge at physiological pH to mimic the phosphate group of glycerol-3-phosphate and a long saturated chain to mimic the chain of palmitoyl-CoA, the substrate for which mtGPAT1 demonstrates a strong preference.¹⁴ A sulfonamide linker was chosen to represent a stable mimic of the

presumed intermediate or transition state of the acylation reaction catalyzed by GPAT (Figure 1).

The putative glycerol-3-phosphate binding pocket, as determined in GPAT isolated from squash chloroplasts, consists of several conserved positively charged amino acids, namely His-139, Lys-193, His-194, Arg-235, and Arg-237 in the squash enzyme.⁹ This conserved pocket is believed to closely interact with the phosphate of glycerol-3-phosphate, and could play an integral role in binding a carboxylate or phosphonate in an inhibitor. The conserved catalytic histidine, which is thought to deprotonate the primary hydroxyl group involved in the acylation reaction, could interact favorably with the relatively acidic sulfonamide hydrogen (Figure 1). Furthermore, the saturated chain of the alkyl sulfonamide would serve as a palmitoyl-CoA C₁₆ mimic, ideally occupying the hydrophobic palmitoyl-CoA binding site extending from the glycerol-3-phosphate binding site in the classical view of a bisubstrate analog.

The spatial relationship between the acyl-CoA and glycerol-3-phosphate in the mammalian GPAT active site is not known, however, so different linkers between the two moieties had to be examined. It was thought the most efficient way to do this would be to synthesize benzoic acids and phosphonic acids with saturated alkyl sulfonamides at each position on the aromatic ring. The distances between the sulfonamide and the carboxylate or phosphonate could also be altered by placing each group one or several methylene units from the ring. The most efficient synthetic pathway for the production of the benzoic acids was the coupling of a primary amine already present on a benzoic acid methyl ester to the alkyl sulfonyl chloride. Saponification of the ester to liberate the carboxylic acid was typically the final step in the synthetic sequence. In the case of the phosphonic acids, the phosphonates were installed through an Arbuzov reaction on a primary bromide or through aryl halide coupling reactions catalyzed by tetrakis(triphenylphosphine)palladium(0).³⁰ The protected amine already present was then deprotected, coupled to the sulfonyl chloride, and the ethyl phosphonate was deprotected to yield the phosphonic acid. The compounds produced from these several routes allowed for the determination of a preliminary SAR from the GPAT inhibition assay.

The first series of compounds was derived from the variously substituted methyl methylbenzoates (Scheme 1). The *meta*- and *para*-amines were made by following a literature protocol.³¹ Following radical bromination of the methyl group with NBS in CH₃CN, the bromide was displaced by refluxing with NaN₃ in EtOH. Under Staudinger conditions, the azide was reduced to the free amine **3**, which could then be coupled to 1-pentane- or 1-nonanesulfonyl chloride, prepared as described.³² Finally, the methyl ester **4** was converted to the carboxylate product **5** by reaction with potassium *t*-butoxide in Et₂O with water present.

The *ortho*-substituted carboxylates required a different approach than the *meta*- and *para*-compounds (Scheme 2). Indolinone **6**, formed in a reaction between the *ortho*-bromide and ammonia gas in MeOH,³³ was coupled to the alkane sulfonyl chlorides with NaH in DMF, and the resulting γ -lactam bond was readily cleaved with NaOH in THF/H₂O to produce carboxylic acids **5e** and **5f**.

The synthesis of the alkyl phosphonates **13a-f** commenced with the protection of the starting toluidines as the bis-acylated aniline **8** (Scheme 3).³⁴ Free-radical bromination with NBS in CH₃CN afforded benzyl bromide **9**, which was converted to phosphonate **10** through Arbuzov reaction with triethyl phosphite. The aniline was unmasked by exposure to a refluxing acidic solution of EtOH. Following coupling of the amine with the alkane sulfonyl

chloride to produce sulfonamide **12**, the phosphonic acid moiety was revealed by treatment with TMSBr in CH₂Cl₂ followed by methanolysis.

Compounds **15a-i** were synthesized by coupling the commercially available starting aniline with a variety of sulfonyl chlorides (Scheme 4). The resulting sulfonamides **14a-i** were then converted to the final products by hydrolysis with potassium *t*-butoxide and water in ether. Aromatic sulfonyl chlorides were used as well as the saturated C₉ chain in an attempt to mimic the CoA portion of the acyl-CoA substrate, as opposed to the alkyl chain.

Compounds **17a-f** were designed to probe the effect of linkers of different length in the aryl sulfonamide portion of the molecule. These were produced in the same manner as **15a-i**, starting with the commercially available aniline and coupling to either benzylsulfonyl chloride or phenylethylsulfonyl chloride with pyridine in methylene chloride to yield sulfonamides **16a-f** (Scheme 5). The methyl esters were then converted to the carboxylic acids **17a-f** with potassium *t*-butoxide and water in ether.

The synthesis of aryl phosphonic acids **21a-c** is shown in Scheme 6. Aryl bromide **18** underwent palladium-catalyzed aryl halide coupling with diethyl phosphite to install the phosphonate functionality.³⁰ The aniline was then deprotected by refluxing in acidic ethanol, and the free amine was coupled with commercially-available octanesulfonyl chloride to produce **20**. The final compound was then obtained by deprotecting the diethyl phosphonate with TMSBr.

Compounds **24a-c**, based on **15g**, were designed as probes to examine the effect of installing different length alkylsulfonamides on the *ortho*-substituted analogs (Scheme 7). It was believed that the compound with the saturated C₁₆-chain (**24c**) would exhibit significantly greater inhibitory activity than **15g**, as the enzyme demonstrates a marked preference for palmitoyl-CoA over other long-chain acyl-CoAs.¹⁴ Compounds **24d-f** were designed to examine the role of an electronegative group at the 4-position of the benzene ring, which could possibly mimic the electron density of the secondary alcohol on glycerol-3-phosphate. All of these compounds (**24a-f**) were produced with the same reaction sequence used to produce **15a-f** and **17a-f**.

Results and Discussion

All benzoic acids and phosphonic acids produced were then evaluated for their ability to inhibit the acylation of glycerol-3-phosphate *in vitro*. The acylation reaction between ¹⁴C-labelled glycerol-3-phosphate and palmitoyl-CoA, initiated by adding mtGPAT, was measured in the presence of varying concentrations of the inhibitor by scintillation counting.³⁵ Each reaction was performed in triplicate, and the IC₅₀ values were then calculated based on the amount of inhibitor needed to produce 50% inhibition compared to the DMSO vehicle control. Results are summarized in Tables 1-3.

Data obtained from benzoic acids **5a-f** indicate that in all cases, regardless of the position of the carboxylate with respect to the sulfonamide, the longer C₉ alkyl chain resulted in greater inhibition than the C₅ saturated chain. The most effective orientation between the acid and sulfonamide appeared to be *ortho*-substitution, as **5f** (IC₅₀ = 66.5 μM) is a better inhibitor than either **5b** (IC₅₀ = 129 μM) or **5d** (IC₅₀ = 83.5 μM). The assay data from phosphonic acids **13a-f** also indicated that the longer C₉ alkyl chain is more effective. In this series of compounds, however, there is no significant difference in activity between the different orientations of the phosphonic acid and the alkyl sulfonamide moiety. The most active compound of this class was **13d** (IC₅₀ = 62.8 μM), the *meta*-substituted phosphonic acid, though not by much over **13b** (IC₅₀ = 81.3 μM) and **13f** (IC₅₀ = 81.1 μM).

Compounds **15b**, **15c**, **15e**, **15f**, **15h**, **15i** and **17a-f** were designed to examine the possibility of an appropriately-substituted benzene ring serving as a mimic for the Coenzyme A portion of the fatty acyl-CoA natural substrate. The distance between the benzene ring and the sulfonamide sulfur does not appear to have a significant effect on the inhibitory activity of these compounds, as there is effectively no difference between one methylene and two methylene linkers. It is apparent, however, that the *ortho*-substituted compounds containing these linker methylenes (**17e-f**) are slightly more effective than the other substituted benzoic acids (**17a-d**). For the *meta*- and *para*-compounds, inhibitory activity is greater when the benzene ring is directly attached to the sulfur, although the *ortho*-compounds are all similar. The addition of a *para*-chloride on the benzene ring does lead to increases in activity for the *para*- (**15c**), *meta*- (**15f**), and *ortho*-compounds (**15i**). Compounds **15a**, **15d**, and **15g** were easily obtainable targets, which allowed for examination of the effect of the methylene linker between the benzene ring and the sulfonamide in **5a-f**. For every substitution, these compounds were the most effective GPAT inhibitors, with the *ortho*-compound (**15g**) demonstrating the greatest activity ($IC_{50} = 24.7 \mu M$). Based on these results, the long alkyl chain is likely a more effective fatty-acyl CoA recognition element for the enzyme than a simple benzene ring.

In view of the increased inhibitory activity of **15g**, two other compound series were prepared. The first, **21a-c**, probes the effectiveness of an aryl phosphonic acid in place of the benzoic acid moiety. *In vitro*, the *ortho*-substituted acid (**21c**) is less active than **15g**, and substitution of the phosphonic acid moiety does not appear to significantly affect activity (Table 3). The other compounds produced (**24a-f**) indicate the importance of chain length of the alkyl sulfonamide, as well as the effect of adding heteroatoms *para*- to the sulfonamide. It appears that the longer chain is very important to the activity of these compounds, as a C_1 -chain (**24a**) results in significantly less *in vitro* activity than the C_9 chain. Compounds **24b** and **24c** were produced to determine if the naturally-favored C_{16} chain is preferred in these compounds over other chain lengths, including the C_{14} chain. In this case, there is no observed preference for the C_{16} compound over other long chains, in contrast to that observed with the natural acyl-CoA substrates.¹⁴

Conclusions

The first preliminary structure-activity relationship of mammalian GPAT inhibition has been constructed, utilizing *in vitro* assay data from several simple sulfonamide-containing benzoic acids and phosphonic acids. It appears that a medium to long chain alkyl sulfonamide is necessary for inhibitory activity, but there is not a significant preference for the naturally-favored palmitoyl chain (C_{16}) over other shorter saturated chains. Replacement of the benzoic acid of **15g** with an aryl phosphonic acid moiety results in decreased inhibitory activity, as does the presence of chloride, fluoride, or a hydroxyl group at the 5-position of the benzene ring. The best inhibitor obtained from this study, which possesses modest inhibitory activity *in vitro*, has been evaluated in relevant biological systems, with the results to be reported in the near future.

Experimental Section

General Methods

1H and ^{13}C NMR spectra were measured on a Bruker 300 or 400 MHz NMR spectrometer. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Column chromatography was carried out on silica gel 60 (Merck, 230-400 mesh ASTM). All solvents used for reactions were distilled prior to use (Et_2O and THF over Na/benzophenone, CH_2Cl_2 and CH_3CN over CaH). High resolution mass spectra were obtained at the Mass Spectrometry Laboratory, The Johns Hopkins University, Baltimore,

MD. Elemental analyses (C, H, N) were performed by Atlantic Microlab, Norcross, GA and were within 0.4% of calculated values.

General Procedure for 4a-d

To a stirring solution of the appropriate amine **3a-c** (1.2 mmol) in CH₂Cl₂ (4 mL) at 0 °C, the sulfonyl chloride (1.3 mmol) was added dropwise, followed by Et₃N (1.3 mmol). The reaction mixture was allowed to warm to room temperature, where it was stirred for 2-3 h. Saturated NH₄Cl solution was added to quench the reaction, and the mixture was extracted with 3 × 10 mL CH₂Cl₂. The combined organic layers were dried over MgSO₄, concentrated *in vacuo*, and the products were purified by flash chromatography (20% EtOAc in hexanes).

Methyl 4-(pentylsulfonamidomethyl)benzoate 4a

¹H NMR (CDCl₃) δ 8.02 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 4.85 (br s, 1H), 4.35 (s, 2H), 3.92 (s, 3H), 2.93 (t, *J* = 8.4 Hz, 2H), 1.76 (m, 2H), 1.30 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (CDCl₃) δ 166.6, 142.1, 130.0, 129.8, 127.6, 53.4, 52.1, 46.7, 30.2, 23.2, 22.1, 13.6.

Methyl 4-(nonylsulfonamidomethyl)benzoate 4b

¹H NMR (DMSO-d₆) δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.71 (t, *J* = 6.4 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 4.22 (d, *J* = 6.4 Hz, 2H), 3.84 (s, 3H), 2.90 (t, *J* = 8.0 Hz, 2H), 1.56 (m, 2H), 1.23 (m, 12H), 0.85 (t, *J* = 6.4 Hz, 3H); ¹³C NMR (DMSO-d₆) δ 165.9, 144.2, 129.1, 128.4, 127.7, 52.0, 51.5, 45.4, 31.2, 28.6, 28.5, 28.4, 27.4, 23.0, 22.0, 13.8.

Methyl 3-(pentylsulfonamidomethyl)benzoate 4c

¹H NMR (CDCl₃) δ 8.01 (s, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 4.81 (t, *J* = 6.0 Hz, 1H), 4.35 (d, *J* = 6.0 Hz, 2H), 3.92 (s, 3H), 2.92 (t, *J* = 8.0 Hz, 2H), 1.76 (m, 2H), 1.28 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃) δ 166.6, 137.5, 132.3, 130.7, 129.1, 128.9, 128.8, 53.4, 52.2, 46.7, 30.2, 23.2, 22.1, 13.6.

Methyl 3-(nonylsulfonamidomethyl)benzoate 4d

¹H NMR (CDCl₃) δ 8.01 (s, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 4.80 (t, *J* = 6.0 Hz, 1H), 4.35 (d, *J* = 6.0 Hz, 2H), 3.92 (s, 3H), 2.93 (t, *J* = 8.0 Hz, 2H), 1.75 (m, 2H), 1.25 (m, 12H), 0.88 (t, *J* = 6.4 Hz, 3H); ¹³C NMR (CDCl₃) δ 166.6, 137.5, 132.3, 130.7, 129.1, 128.9, 128.8, 53.4, 52.2, 46.7, 31.7, 29.2, 29.1, 29.0, 28.1, 23.5, 22.6, 14.0.

General Procedure for 5a-d

To a stirring suspension of potassium *t*-butoxide (5.88 mmol) in Et₂O (15 mL) cooled to 0 °C, was added water (1.4 mmol) via syringe. The slurry was stirred for 5 min, and **4a-d** (0.67 mmol) was added. The mixture was stirred at room temperature until starting material disappeared by TLC analysis (20% EtOAc in hexanes). Ice water was added until 2 clear layers formed. The aqueous layer was separated and acidified with 1 M HCl. The product was then extracted with Et₂O (3 × 20 mL) and evaporated *in vacuo* to afford **5a-d**.

4-(Pentylsulfonamidomethyl)benzoic acid 5a

mp = 188-189 °C; ¹H NMR (MeOD) δ 8.02 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 4.31 (s, 2H), 2.95 (t, *J* = 8.1 Hz, 2H), 1.73 (m, 2H), 1.33 (m, 4H), 0.91 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (MeOD) δ 169.5, 145.0, 131.1, 131.0, 128.8, 53.6, 47.2, 31.4, 24.3, 23.2, 14.0; HRMS (FAB) calcd for C₁₃H₂₀NO₄S [M + H]⁺, 286.11131; found, 286.1111. Anal. (C₁₃H₁₉NO₄S) C, H, N.

4-(Nonylsulfonamidomethyl)benzoic acid 5b

mp = 178-180 °C; ¹H NMR (MeOD) δ 8.03 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 4.32 (s, 2H), 2.94 (t, *J* = 7.8 Hz, 2H), 1.71 (m, 2H), 1.30 (m, 12H), 0.92 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (DMSO-*d*₆) δ 167.0, 143.6, 129.5, 129.3, 127.5, 51.5, 45.4, 31.2, 28.6, 28.5, 28.4, 27.4, 23.0, 22.0, 13.9; HRMS (FAB) calcd for C₁₇H₂₈NO₄S [M + H]⁺, 342.17391; found, 342.17447. Anal. (C₁₇H₂₇NO₄S·¼(H₂O)) C, H, N.

3-(Pentylsulfonamidomethyl)benzoic acid 5c

mp = 160-161 °C; ¹H NMR (MeOD) δ 8.08 (s, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 4.31 (s, 2H), 2.92 (t, *J* = 8.1 Hz, 2H), 1.72 (m, 2H), 1.33 (m, 4H), 0.91 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (MeOD) δ 169.5, 140.2, 133.5, 132.3, 130.1, 129.8, 129.7, 53.6, 47.1, 31.4, 24.3, 23.1, 14.0; HRMS (FAB) calcd for C₁₃H₁₈NO₃S [M – OH]⁺, 268.10074; found, 268.09988. Anal. (C₁₃H₁₉NO₄S) C, H, N.

3-(Nonylsulfonamidomethyl)benzoic acid 5d

mp = 150-151 °C; ¹H NMR (MeOD) δ 8.08 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 4.31 (s, 2H), 2.91 (t, *J* = 8.0 Hz, 2H), 1.70 (m, 2H), 1.28 (m, 12H), 0.92 (t, *J* = 7.2 Hz); ¹³C NMR (MeOD) δ 169.5, 140.2, 133.5, 132.3, 130.1, 129.9, 129.7, 53.7, 47.2, 32.9, 30.4, 30.3, 30.1, 29.2, 24.6, 23.6, 14.4; HRMS (FAB) calcd for C₁₇H₂₈NO₄S [M + H]⁺, 342.17391; found, 342.17333. Anal. (C₁₇H₂₇NO₄S) C, H, N.

General Procedure for 7a-b

1.5 mmol **6** was added to DMF (8 mL), and the solution was cooled to 0 °C. NaH (1.65 mmol) was added, followed by the sulfonyl chloride (1.8 mmol), and the mixture was stirred and allowed to warm to room temperature. Reaction progress was monitored by TLC (25% MeOH in CHCl₃). When complete, saturated ammonium chloride solution was added (80 mL), the product was extracted with EtOAc (3 × 20 mL), dried over MgSO₄, and evaporated *in vacuo*. The product was purified by flash chromatography (2% MeOH in CHCl₃).

2-(Pentylsulfonyl)isoindolin-1-one 7a

¹H NMR (DMSO-*d*₆) δ 7.81 (t, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 4.94 (s, 2H), 3.60 (t, *J* = 7.8 Hz, 2H), 1.72 (m, 2H), 1.32 (m, 4H), 0.83 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃) δ 167.0, 141.2, 133.9, 129.8, 128.8, 124.9, 123.3, 53.2, 49.6, 30.0, 22.4, 21.9, 13.5.

2-(Nonylsulfonyl)isoindolin-1-one 7b

¹H NMR (DMSO-*d*₆) δ 7.82 (t, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz), 4.94 (s, 2H), 3.60 (t, *J* = 8.1 Hz, 2H), 1.71 (m, 2H), 1.36 (m, 2H), 1.21 (m, 10H), 0.83 (t, *J* = 6.3 Hz, 3H); ¹³C NMR (CDCl₃) δ 167.1, 141.2, 134.0, 130.0, 128.9, 125.1, 123.4, 53.3, 49.6, 31.7, 29.1, 29.0, 28.9, 28.0, 22.9, 22.5, 14.0.

General Procedure for 5e-f

7a-b (0.66 mmol) was dissolved in THF (3 mL), and the solution was cooled to 0 °C. 1 M NaOH (1 mL, 10 equiv) was then added, and the solution was stirred and warmed to room temperature. Reaction progress was monitored by TLC (1:1 EtOAc:hexanes). When starting material had completely reacted, saturated NaHCO₃ (30 mL) was added, and the solution was washed with EtOAc. The aqueous phase was acidified to pH 3 with 1 M HCl, and product was extracted with EtOAc, dried over MgSO₄, and evaporated *in vacuo*.

2-(Pentylsulfonamidomethyl)benzoic acid 5e

mp = 100 °C; ^1H NMR (DMSO- d_6) δ 13.0 (s, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.60 (m, 2H), 7.39 (m, 2H), 4.51 (d, J = 6.3 Hz, 2H), 2.92 (t, J = 7.8 Hz, 2H), 1.61 (m, 2H), 1.25 (m, 4H), 0.84 (t, J = 6.9 Hz, 3H); ^{13}C NMR (MeOD) δ 170.3, 140.8, 133.6, 132.3, 131.3, 130.7, 128.8, 53.6, 46.5, 31.3, 24.3, 23.1, 14.0; HRMS (FAB) calcd for $\text{C}_{13}\text{H}_{20}\text{NO}_4\text{S}$ $[\text{M} + \text{H}]^+$, 286.11131; found, 286.11103. Anal. ($\text{C}_{13}\text{H}_{19}\text{NO}_4\text{S}$) C, H, N.

2-(Nonylsulfonamidomethyl)benzoic acid 5f

mp = 79-82 °C; ^1H NMR (CDCl_3) δ 8.04 (d, J = 7.2 Hz, 1H), 7.60 (m, 2H), 7.43 (t, J = 6.8 Hz, 1H), 4.60 (s, 2H), 2.89 (t, J = 8.0 Hz, 2H), 1.66 (m, 2H), 1.28 (m, 12H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO- d_6) δ 168.3, 139.7, 132.1, 130.4, 129.8, 129.0, 127.2, 51.7, 44.1, 31.3, 28.7, 28.6, 28.5, 27.6, 23.1, 22.1, 14.0; HRMS (FAB) calcd for $\text{C}_{17}\text{H}_{28}\text{NO}_4\text{S}$ $[\text{M} + \text{H}]^+$, 342.17391; found, 342.17478. Anal. ($\text{C}_{17}\text{H}_{27}\text{NO}_4\text{S}$) C, H, N.

General Procedure for 9a-c

8a-c (31.3 mmol) was dissolved in CH_3CN (150mL) and NBS (31.3 mmol) was added. The solution was then heated to reflux with a 275 W Sunlamp. Reaction progress was monitored by TLC (30% EtOAc in hexanes). The solution was then cooled, evaporated *in vacuo*, and the mixture was purified by flash chromatography (30% EtOAc in hexanes).

N, N-(4-Bromophenyl)diacetylaniline 9a

^1H NMR (CDCl_3) δ 7.47 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 4.48 (s, 2H), 2.27 (s, 6H); ^{13}C NMR (CDCl_3) δ 172.6, 139.1, 138.4, 130.3, 128.9, 32.0, 26.7.

N, N-(3-Bromophenyl)diacetylaniline 9b

^1H NMR (CDCl_3) δ 7.44 (m, 2H), 7.20 (s, 1H), 7.08 (m, 1H), 4.48 (s, 2H), 2.28 (s, 6H); ^{13}C NMR (CDCl_3) δ 172.7, 139.7, 139.7, 130.1, 129.3, 128.6, 32.0, 26.8.

N, N-(2-Bromophenyl)diacetylaniline 9c

^1H NMR (CDCl_3) δ 7.56 (d, J = 6.8 Hz, 1H), 7.44 (m, 2H), 7.12 (d, J = 6.8 Hz, 1H), 4.32 (s, 2H), 2.36 (s, 6H); ^{13}C NMR (CDCl_3) δ 172.5, 137.9, 135.0, 131.5, 129.9, 129.5, 129.4, 28.4, 26.7.

General Procedure for 10a-c

9a-c (22.2 mmol) was dissolved in $\text{P}(\text{OEt})_3$ (25 mL, 6.6 equiv), and the solution was heated to reflux for 18 h with a reflux condenser heated to 50 °C. Reaction progress was monitored by TLC (30% EtOAc in hexanes). The reaction mixture was then cooled, and $\text{P}(\text{OEt})_3$ was removed *in vacuo*. The product was then purified by flash chromatography (2% MeOH in CHCl_3).

Diethyl N, N-4-diacetylanilinephosphonate 10a

^1H NMR (CDCl_3) δ 7.39 (dd, J = 8.4, 2.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 4.02 (m, 4H), 3.17 (d, J = 21.6 Hz, 2H), 2.25 (s, 6H), 1.22 (t, J = 6.8 Hz, 6H); ^{13}C NMR (CDCl_3) δ 172.7, 138.1 (d, J = 3.6 Hz), 132.7 (d, J = 6.5 Hz), 131.1 (d, 6.5 Hz), 128.7 (d, 3.3 Hz), 62.1 (d, 6.6 Hz), 33.4 (d, J = 137.7 Hz), 27.7, 16.2 (d, J = 5.9 Hz).

Diethyl N, N-3-diacetylanilinephosphonate 10b

^1H NMR (CDCl_3) δ 7.30 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.03 (s, 1H), 6.94 (d, J = 8.4 Hz, 1H), 3.91 (m, 4H), 3.06 (d, J = 21.6 Hz, 2H), 2.16 (s, 6H), 1.13 (t, J = 6.8 Hz, 6H); ^{13}C NMR (CDCl_3) δ 172.4, 139.1 (d, J = 3.1 Hz), 133.4 (d, J = 8.8 Hz), 129.8 (d, J =

3.6 Hz), 129.8 (d, $J = 3.7$ Hz), 129.4 (d, $J = 3.0$ Hz), 126.8 (d, $J = 3.6$ Hz), 61.8 (d, $J = 6.9$ Hz), 33.0 (d, $J = 137.4$ Hz), 26.4, 16.0 (d, $J = 5.9$ Hz).

Diethyl N, N-2-diacetylanilinephosphonate 10c

^1H NMR (CDCl_3) δ 7.60 (d, $J = 7.6$ Hz, 1H), 7.35 (m, 2H), 7.09 (d, $J = 7.6$ Hz, 1H), 4.07 (m, 4H), 2.95 (d, $J = 22.0$ Hz, 2H), 2.31 (s, 6H), 1.27 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (CDCl_3) δ 172.9, 138.3 (d, $J = 8.7$ Hz), 131.6 (d, $J = 5.1$ Hz), 130.5 (d, $J = 7.4$ Hz), 129.4 (d, $J = 2.3$ Hz), 129.1 (d, $J = 3.0$ Hz), 128.3 (d, $J = 3.0$ Hz), 62.1 (d, $J = 6.7$ Hz), 28.7 (d, $J = 140.3$ Hz), 26.9, 16.2 (d, $J = 5.8$ Hz).

General Procedure for 11a-c

Concentrated H_2SO_4 (3 mL) was added to a stirring solution of **10a-c** (9.7 mmol) in EtOH (60 mL). The solution was heated to reflux for 18 h. Reaction progress was monitored by TLC (5% MeOH in CHCl_3). The solution was diluted with water (100 mL), washed with EtOAc (30 mL), and the aqueous phase was brought to pH 9 with saturated NaHCO_3 solution. The product was extracted with EtOAc (3×30 mL), the combined organic layers were dried over MgSO_4 , and solvent was removed *in vacuo*.

Diethyl 4-aminobenzylphosphonate 11a

^1H NMR (CDCl_3) δ 6.91 (dd, $J = 8.0, 2.4$ Hz, 2H), 6.47 (d, $J = 8.0$ Hz, 2H), 3.86 (m, 4H), 3.73 (br s, 2H), 2.90 (d, $J = 21.2$ Hz, 2H), 1.10 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (CDCl_3) δ 145.3 (d, $J = 3.6$ Hz), 129.9 (d, $J = 6.5$ Hz), 119.7 (d, $J = 9.4$ Hz), 114.6 (d, $J = 2.9$ Hz), 61.5 (d, $J = 6.6$ Hz), 32.1 (d, $J = 138.1$ Hz), 15.8 (d, $J = 5.9$ Hz).

Diethyl 3-aminobenzylphosphonate 11b

^1H NMR (CDCl_3) δ 7.04 (t, $J = 8.0$ Hz, 1H), 6.64 (m, 2H), 6.53 (d, $J = 7.2$ Hz, 1H), 3.98 (m, 4H), 3.68 (br s, 2H), 3.03 (d, $J = 21.6$ Hz, 2H), 1.22 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (CDCl_3) δ 146.5 (d, $J = 2.9$ Hz), 132.3 (d, $J = 8.8$ Hz), 129.2 (d, $J = 3.0$ Hz), 119.8 (d, $J = 6.6$ Hz), 116.3 (d, $J = 6.6$ Hz), 113.6 (d, $J = 3.6$ Hz), 62.0 (d, $J = 6.6$ Hz), 33.5 (d, $J = 137.0$ Hz), 16.2 (d, $J = 5.8$ Hz).

Diethyl 2-aminobenzylphosphonate 11c

^1H NMR (CDCl_3) δ 7.03 (m, 2H), 6.73 (m, 2H), 4.30 (br s, 2H), 4.03 (m, 4H), 3.12 (d, $J = 21.2$ Hz, 2H), 1.24 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (CDCl_3) δ 145.9 (d, $J = 4.6$ Hz), 131.4 (d, $J = 6.5$ Hz), 128.1 (d, $J = 3.6$ Hz), 118.9 (d, $J = 2.9$ Hz), 117.1 (d, $J = 9.7$ Hz), 117.0 (d, $J = 3.5$ Hz), 62.3 (d, $J = 6.6$ Hz), 30.5 (d, $J = 137.9$ Hz), 16.2 (d, $J = 6.0$ Hz).

General Procedure for 12a-d

Sulfonyl chloride (4.9 mmol) was added dropwise to a solution of **11a-b** (3.3 mmol) in CH_3CN (13 mL) at 0 °C. Et_3N (3.63 mmol) was added dropwise, and the solution was stirred and allowed to warm to room temperature. Reaction progress was monitored by TLC (10% MeOH in CHCl_3). When complete (about 2 h), the reaction was quenched by adding saturated sodium bicarbonate solution. The product was extracted with EtOAc (3×10 mL), and the combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. Flash chromatography (2% MeOH in CHCl_3) afforded the product.

Diethyl 4-(pentylsulfonamido)benzylphosphonate 12a

^1H NMR (CDCl_3) δ 8.42 (br s, 1H), 7.15 (m, 4H), 4.01 (m, 4H), 3.08 (d, $J = 21.2$ Hz, 2H), 2.98 (t, $J = 8.0$ Hz, 2H), 1.76 (m, 2H), 1.28 (m, 4H), 1.25 (t, $J = 6.8$ Hz, 6H), 0.82 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 136.5 (d, $J = 3.6$ Hz), 130.5 (d, 6.6 Hz), 127.2 (d, $J = 9.7$ Hz),

120.4 (d, $J = 3.3$ Hz), 62.2 (d, $J = 6.7$ Hz), 51.1, 32.6 (d, $J = 138.1$ Hz), 30.1, 22.8, 21.9, 16.1 (d, $J = 5.8$ Hz), 13.5.

Diethyl 4-(nonylsulfonamido)benzylphosphonate 12b

^1H NMR (CDCl_3) δ 8.61 (br s, 1H), 7.12 (m, 4H), 3.99 (m, 4H), 3.06 (d, $J = 21.2$ Hz, 2H), 2.96 (t, $J = 8.0$ Hz, 2H), 1.71 (m, 2H), 1.27 (m, 12H), 1.18 (t, $J = 7.2$ Hz, 6H), 0.79 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 136.5 (d, $J = 3.0$ Hz), 130.4 (d, $J = 6.7$ Hz), 127.0 (d, $J = 9.1$ Hz), 120.2 (d, $J = 2.9$ Hz), 62.1 (d, $J = 7.0$ Hz), 51.0, 32.5 (d, $J = 137.8$ Hz), 31.5, 28.9, 28.8, 28.7, 27.9, 23.0, 22.3, 16.0 (d, $J = 5.9$ Hz), 13.7.

Diethyl 3-(pentylsulfonamido)benzylphosphonate 12c

^1H NMR (CDCl_3) δ 8.27 (br s, 1H), 7.19 (m, 3H), 7.01 (d, $J = 6.8$ Hz, 1H), 4.00 (m, 4H), 3.11 (d, $J = 21.6$ Hz, 2H), 3.02 (t, $J = 8.0$ Hz, 2H), 1.76 (m, 2H), 1.30 (m, 4H), 1.23 (t, $J = 7.2$ Hz, 6H), 0.81 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 137.8 (d, $J = 2.9$ Hz), 132.8 (d, $J = 9.2$ Hz), 129.3 (d, $J = 2.9$ Hz), 125.7 (d, $J = 6.6$ Hz), 121.2 (d, $J = 6.6$ Hz), 118.4 (d, $J = 3.5$ Hz), 62.2 (d, $J = 6.7$ Hz), 51.2, 33.3 (d, $J = 137.3$ Hz), 30.1, 22.8, 21.9, 16.1 (d, $J = 5.9$ Hz), 13.5.

Diethyl 3-(nonylsulfonamido)benzylphosphonate 12d

^1H NMR (CDCl_3) δ 8.17 (br s, 1H), 7.20 (m, 3H), 7.02 (d, $J = 7.2$ Hz, 1H), 3.99 (m, 4H), 3.12 (d, $J = 21.6$ Hz, 2H), 3.03 (t, $J = 8.0$ Hz, 2H), 1.76 (m, 2H), 1.31 (m, 12H), 1.26 (t, $J = 6.0$ Hz, 6H), 0.83 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 137.8 (d, $J = 3.6$ Hz), 132.8 (d, $J = 9.0$ Hz), 129.4 (d, $J = 2.9$ Hz), 125.7 (d, $J = 6.7$ Hz), 121.3 (d, 6.5 Hz), 118.5 (d, $J = 3.6$ Hz), 62.3 (d, 6.9 Hz), 51.3, 33.3 (d, $J = 137.4$ Hz), 31.6, 29.1, 29.0, 28.9, 28.0, 23.2, 22.4, 16.2 (d, $J = 5.9$ Hz), 13.9.

General Procedure for 12e-f

11c (1.36 mmol) was dissolved in CH_3CN (3.3 mL), then pyridine (10.8 mmol) was added. The solution was cooled to 0 °C, and sulfonyl chloride (1.63 mmol) was added slowly by syringe. The solution was allowed to warm to room temperature. Reaction progress was monitored by TLC (5% MeOH in CHCl_3). When complete, the reaction was quenched by adding saturated NaHCO_3 solution. The product was extracted with EtOAc (3 $\times$ 5 mL), washed with 1 N HCl, and the combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. The product was purified by flash chromatography (2% MeOH in CHCl_3).

Diethyl 2-(pentylsulfonamido)benzylphosphonate 12e

^1H NMR (CDCl_3) δ 8.71 (s, 1H), 7.40 (d, $J = 7.6$ Hz), 7.22 (m, 1H), 7.12 (m, 2H), 3.97 (m, 4H), 3.21 (d, $J = 21.2$ Hz, 2H), 3.11 (t, $J = 8.0$ Hz, 2H), 1.86 (m, 2H), 1.37 (m, 4H), 1.19 (t, $J = 7.2$ Hz, 6H), 0.85 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 136.2 (d, $J = 5.2$ Hz), 131.5 (d, $J = 7.2$ Hz), 128.2 (d, $J = 3.7$ Hz), 125.8 (d, $J = 2.9$ Hz), 125.5 (d, $J = 9.7$ Hz), 124.6 (d, $J = 3.5$ Hz), 62.6 (d, $J = 6.9$ Hz), 53.4, 30.9 (d, $J = 136.6$ Hz), 30.1, 23.0, 21.9, 16.0 (d, $J = 5.9$ Hz), 13.5.

Diethyl 2-(nonylsulfonamido)benzylphosphonate 12f

^1H NMR (CDCl_3) δ 8.71 (s, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.28 (m, 1H), 7.17 (m, 2H), 4.01 (m, 4H), 3.25 (d, $J = 21.2$ Hz, 2H), 3.17 (t, $J = 8.0$ Hz, 2H), 1.91 (m, 2H), 1.40 (m, 2H), 1.25 (m, 16H), 0.89 (t, $J = 7.2$ Hz); ^{13}C NMR (CDCl_3) δ 136.4 (d, $J = 5.0$ Hz), 131.7 (d, $J = 6.7$ Hz), 128.5 (d, $J = 3.7$ Hz), 126.0 (d, $J = 2.8$ Hz), 125.7 (d, $J = 10.1$ Hz), 124.9 (d, $J = 3.1$ Hz), 62.8 (d, $J = 6.7$ Hz), 53.8, 31.7, 31.2 (d, $J = 136.4$ Hz), 29.1, 29.1, 29.0, 28.2, 23.5, 22.5, 16.2 (d, $J = 5.8$ Hz), 14.0.

General Procedure for 13a-f

TMSBr (8.6 mmol) was added to a solution of **12a-f** (0.277 mmol) in CH₂Cl₂ (2 mL), and the solution was stirred at room temperature. After 24 h, the reaction was quenched by adding MeOH (3 × 1.6 mL). The solution was concentrated *in vacuo*, and dissolved in saturated NaHCO₃ solution (10 mL). This solution was washed with Et₂O (5 mL), then acidified with 1 N HCl. The product was extracted with Et₂O (3 × 5 mL), and the combined organic extracts were dried over MgSO₄ and dried *in vacuo*.

4-(Pentylsulfonamido)benzylphosphonic acid 13a

mp = 198–200 °C; ¹H NMR (MeOD) δ 7.29 (dd, *J* = 8.4, 2.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 3.10 (d, *J* = 21.6 Hz, 2H), 3.05 (t, *J* = 8.0 Hz, 2H), 1.78 (m, 2H), 1.34 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (MeOD) δ 137.9 (d, *J* = 3.7 Hz), 131.8 (d, *J* = 6.3 Hz), 130.6 (d, *J* = 9.6 Hz), 121.4 (d, *J* = 2.9 Hz), 51.8, 35.1 (d, *J* = 134.6 Hz), 31.2, 24.2, 23.1, 14.0; HRMS (FAB) calcd for C₁₂H₂₀NO₅PS [M]⁺, 321.07998; found, 321.07934. Anal. (C₁₂H₂₀NO₅PS·0.6(H₂O)) C, H, N.

4-(Nonylsulfonamido)benzylphosphonic acid 13b

mp = 201–203 °C; ¹H NMR (MeOD) δ 7.29 (dd, *J* = 8.6, 2.4 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 3.09 (d, *J* = 21.2, 2H), 3.05 (t, *J* = 8.0 Hz, 2H), 1.77 (m, 2H), 1.29 (m, 12H), 0.91 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (MeOD) δ 137.9 (d, *J* = 3.3 Hz), 131.8 (d, *J* = 6.5 Hz), 130.6 (d, *J* = 9.3 Hz), 121.4 (d, *J* = 3.0 Hz), 51.8, 35.1 (d, *J* = 134.5 Hz), 32.9, 30.3, 30.2, 30.1, 29.1, 24.5, 14.4; HRMS (FAB) calcd for C₁₆H₂₉NO₅PS [M + H]⁺, 378.15041; found, 378.14945. Anal. (C₁₆H₂₈NO₅PS) C, H, N.

3-(Pentylsulfonamido)benzylphosphonic acid 13c

mp = 127–128 °C; ¹H NMR (MeOD) δ 7.27 (t, *J* = 8.0 Hz, 1H), 7.22 (s, 1H), 7.11 (m, 2H), 3.11 (d, *J* = 21.6 Hz, 2H), 3.09 (t, *J* = 7.8 Hz, 2H), 1.78 (m, 2H), 1.38 (m, 4H), 0.91 (t, *J* = 6.4 Hz, 3H); ¹³C NMR (MeOD) δ 139.5 (d, *J* = 3.3 Hz), 136.0 (d, *J* = 9.3 Hz), 130.3 (d, *J* = 3.4 Hz), 126.8 (d, *J* = 5.9 Hz), 122.5 (d, *J* = 6.5 Hz), 119.3 (d, *J* = 3.4 Hz), 51.9, 35.8 (d, *J* = 134.2 Hz), 31.2, 24.2, 23.1, 14.0; HRMS (FAB) calcd for C₁₂H₂₁NO₅PS [M + H]⁺, 322.08781; found, 322.08830. Anal. (C₁₂H₂₀NO₅PS) C, H, N.

3-(Nonylsulfonamido)benzylphosphonic acid 13d

mp = 149–150 °C; ¹H NMR (MeOD) δ 7.27 (t, *J* = 8.0 Hz, 1H), 7.22 (s, 1H), 7.11 (m, 2H), 3.11 (d, *J* = 21.6 Hz, 2H), 3.08 (t, *J* = 7.6 Hz, 2H), 1.77 (m, 2H), 1.33 (m, 12H), 0.91 (t, *J* = 6.4 Hz, 3H); ¹³C NMR (MeOD) δ 139.5 (d, *J* = 3.0 Hz), 130.3 (d, *J* = 3.0 Hz), 126.8 (d, *J* = 6.1 Hz), 122.5, (d, *J* = 6.3 Hz), 119.3 (d, *J* = 3.5 Hz), 51.9, 35.8 (d, *J* = 134.0 Hz), 32.9, 30.3, 30.2, 30.1, 29.1, 24.5, 23.6, 14.3; HRMS (FAB) calcd for C₁₆H₂₉NO₅PS [M + H]⁺, 378.15041; found, 378.14975. Anal. (C₁₆H₂₈NO₅PS) C, H, N.

2-(Pentylsulfonamido)benzylphosphonic acid 13e

¹H NMR (DMSO-d₆) δ 9.73 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.25 (m, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 3.14 (t, *J* = 8.0 Hz, 2H), 3.10 (d, *J* = 20.8 Hz, 2H), 1.71 (m, 2H), 1.32 (m, 4H), 0.85 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (DMSO-d₆) δ 136.2 (d, *J* = 5.8 Hz), 131.6 (d, *J* = 6.4 Hz), 127.6 (d, *J* = 10.0 Hz), 127.1 (d, *J* = 3.4 Hz), 125.0 (d, *J* = 2.8 Hz), 123.7 (d, *J* = 3.0 Hz), 52.3, 32.5 (d, *J* = 130.3 Hz), 29.4, 22.7, 21.3, 13.3; HRMS (FAB) calcd for C₁₂H₂₀NO₅PS [M + H]⁺, 322.08781; found, 322.08660. Anal. (C₁₂H₂₀NO₅PS·¼(H₂O)) C, H, N.

2-(Nonylsulfonamido)benzylphosphonic acid 13f

mp = 104-106 °C; ^1H NMR (DMSO- d_6) δ 9.80 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.25 (m, 2H), 7.15 (t, J = 7.6 Hz, 1H), 3.14 (t, J = 7.6 Hz, 2H), 3.09 (d, J = 21.2 Hz, 2H), 1.68 (m, 2H), 1.35 (m, 2H), 1.22 (m, 8H), 0.85 (t, J = 6.8 Hz); ^{13}C NMR (DMSO- d_6) δ 136.3 (d, J = 5.7 Hz), 131.8 (d, J = 6.5 Hz), 127.7 (d, J = 8.7 Hz), 127.3 (d, J = 3.3 Hz), 125.2 (d, J = 2.6 Hz), 123.8 (d, J = 3.0 Hz), 52.3, 32.6 (d, J = 130.5 Hz), 31.2, 28.6, 28.5, 28.4, 27.4, 23.2, 22.0, 13.9; HRMS (FAB) calcd for $\text{C}_{16}\text{H}_{28}\text{NO}_5\text{PS}$ $[\text{M} + \text{H}]^+$, 378.15041; found, 378.15020. Anal. ($\text{C}_{16}\text{H}_{28}\text{NO}_5\text{PS}$) C, H, N.

General Procedure for 14a-i

To a stirring solution of the aniline starting material (3.3 mmol) in CH_2Cl_2 (12 mL) at 0° C was added pyridine (7.5 equiv). The sulfonyl chloride (1.2 equiv) was then added slowly via syringe. The solution was stirred and allowed to warm to room temperature. Reaction progress was monitored by TLC (20% EtOAc in hexanes). When complete, the reaction was poured into saturated NaHCO_3 solution (45 mL), extracted with CH_2Cl_2 (3×15 mL), and washed with 1 M HCl (50 mL). The combined organic phases were concentrated *in vacuo*, and recrystallization from EtOAc / hexanes afforded **14a-i**.

Methyl 4-(nonylsulfonamido)benzoate 14a

^1H NMR (DMSO- d_6) δ 10.33 (s, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 3.80 (s, 3H), 3.17 (t, J = 8.0 Hz, 2H), 1.63 (m, 2H), 1.15 (m, 12H), 0.81 (t, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO- d_6) δ 165.7, 143.1, 130.7, 123.8, 117.4, 51.8, 50.8, 31.1, 28.5, 28.5, 28.2, 27.0, 22.9, 22.0, 13.8.

Methyl 4-(phenylsulfonamido)benzoate 14b

^1H NMR (CDCl_3) δ 7.91 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 8.0 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (DMSO- d_6) δ 165.6, 142.3, 139.2, 133.2, 130.5, 129.3, 126.6, 124.4, 118.2, 51.8.

Methyl 4-(4-chlorophenylsulfonamido)benzoate 14c

^1H NMR (DMSO- d_6) δ 10.94 (s, 1H), 7.83 (m, 4H), 7.63 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (DMSO- d_6) δ 165.5, 141.9, 138.1, 138.0, 130.6, 129.5, 128.5, 124.7, 118.4, 51.8.

Methyl 3-(nonylsulfonamido)benzoate 14d

^1H NMR (DMSO- d_6) δ 10.05 (s, 1H), 7.83 (s, 1H), 7.65 (d, J = 6.8 Hz, 1H), 7.46 (m, 2H), 3.84 (s, 3H), 3.08 (t, J = 8.0 Hz, 2H), 1.63 (m, 2H), 1.63 (m, 2H), 1.15 (m, 12H), 0.81 (t, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO- d_6) δ 165.7, 138.9, 130.6, 129.7, 124.1, 123.6, 119.4, 52.1, 50.6, 31.1, 28.5, 28.5, 28.3, 27.1, 22.9, 22.0, 13.8.

Methyl 3-(phenylsulfonamido)benzoate 14e

^1H NMR (DMSO- d_6) δ 10.57 (s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.74 (s, 1H), 7.54 (m, 4H), 7.38 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (DMSO- d_6) δ 165.6, 139.2, 138.1, 133.0, 130.5, 129.6, 129.3, 126.6, 124.6, 124.4, 120.3, 52.2.

Methyl 3-(4-chlorophenylsulfonamido)benzoate 14f

^1H NMR (DMSO- d_6) δ 10.63 (s, 1H), 7.74 (m, 3H), 7.61 (m, 3H), 7.39 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (DMSO- d_6) δ 165.5, 138.0, 138.0, 137.8, 130.6, 129.8, 129.5, 128.5, 124.9, 124.6, 120.5, 52.2.

Methyl 2-(nonylsulfonamido)benzoate 14g

^1H NMR (DMSO- d_6) δ 10.15 (s, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.62 (m, 2H), 7.20 (t, J = 7.6 Hz, 1H), 3.88 (s, 3H), 3.27 (t, J = 8.0 Hz, 2H), 1.62 (m, 2H), 1.16 (m, 12H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO- d_6) δ 167.8, 139.8, 134.7, 131.0, 123.0, 118.5, 116.1, 52.6, 51.2, 31.1, 28.4, 28.2, 27.0, 22.8, 21.9, 13.8.

Methyl 2-(phenylsulfonamido)benzoate 14h

^1H NMR (CDCl_3) δ 10.67 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.4 Hz, 1H), 7.40 (m, 4H), 7.00 (t, J = 7.6 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (CDCl_3) δ 168.1, 140.0, 139.0, 134.3, 132.9, 131.0, 128.8, 126.9, 122.9, 118.9, 115.7, 52.3.

Methyl 2-(4-chlorophenylsulfonamido)benzoate 14i

^1H NMR (DMSO- d_6) δ 10.41 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.57 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (DMSO- d_6) δ 167.3, 138.3, 138.0, 137.5, 134.2, 130.9, 129.4, 128.8, 124.2, 120.5, 118.6, 52.5.

General Procedure for 15a-i

To a stirring suspension of potassium *t*-butoxide (5.88 mmol) in Et_2O (15mL) cooled to 0 °C, was added water (1.4 mmol) via syringe. The slurry was stirred for 5 min, and **14a-i** (0.67 mmol) was added. The mixture was stirred at room temperature until starting material disappeared by TLC analysis (20% EtOAc in hexanes). Ice water was added until 2 clear layers formed. The aqueous layer was separated and acidified with 1 M HCl. The product was then extracted with Et_2O (3 $\times$ 20 mL) and evaporated *in vacuo* to afford **15a-i**.

4-(Nonylsulfonamido)benzoic acid 15a

mp = 193-194 °C; ^1H NMR (MeOD) δ 7.99 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 3.17 (t, J = 8.0 Hz, 2H), 1.78 (m, 2H), 1.40 (m, 2H), 1.28 (m, 10H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (MeOD) δ 169.3, 144.3, 132.3, 126.7, 118.8, 52.4, 32.9, 30.2, 30.2, 30.0, 28.9, 24.4, 23.6, 14.3; HRMS (FAB) calcd for $\text{C}_{16}\text{H}_{25}\text{NO}_4\text{S} [\text{M}]^+$, 327.15043; found, 327.14957. Anal. ($\text{C}_{16}\text{H}_{25}\text{NO}_4\text{S} \cdot \frac{1}{4}(\text{H}_2\text{O})$) C, H, N.

4-(Phenylsulfonamido)benzoic acid 15b

mp = 186-188 °C; ^1H NMR (DMSO- d_6) δ 12.72 (br s, 1H), 10.82 (br s, 1H), 7.80 (m, 4H), 7.61 (t, J = 6.8 Hz, 1H), 7.56 (t, J = 8.0 Hz, 2H), 7.20 (t, J = 7.2 Hz, 2H); ^{13}C NMR (DMSO- d_6) δ 166.6, 141.9, 142.0, 133.2, 130.7, 129.4, 126.6, 125.6, 118.2; HRMS (FAB) calcd for $\text{C}_{13}\text{H}_{11}\text{NO}_4\text{S} [\text{M}]^+$, 277.04088; found, 277.04077. Anal. ($\text{C}_{13}\text{H}_{11}\text{NO}_4\text{S}$) C, H, N.

4-(4-Chlorophenylsulfonamido)benzoic acid 15c

mp = 254-256 °C; ^1H NMR (DMSO- d_6) δ 12.76 (br s, 1H), 10.86 (br s, 1H), 7.81 (d, J = 6.4 Hz, 4H), 7.65 (d, J = 7.2 Hz, 2H), 7.18 (d, J = 6.8 Hz, 2H); ^{13}C NMR (DMSO- d_6) δ 166.6, 141.5, 138.1, 138.0, 130.7, 129.5, 128.5, 125.9, 118.4; HRMS (FAB) calcd for $\text{C}_{13}\text{H}_{11}\text{ClNO}_4\text{S} [\text{M} + \text{H}]^+$, 312.00973; found, 312.00859. Anal. ($\text{C}_{13}\text{H}_{10}\text{ClNO}_4\text{S} \cdot \frac{1}{4}(\text{H}_2\text{O})$) C, H, N.

3-(Nonylsulfonamido)benzoic acid 15d

mp = 183-184 °C; ^1H NMR (DMSO- d_6) δ 13.03 (br s, 1H), 9.98 (s, 1H), 7.81 (s, 1H), 7.64 (m, 1H), 7.44 (m, 2H), 3.07 (t, J = 7.6 Hz, 2H), 1.65 (m, 2H), 1.21 (m, 12H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO- d_6) δ 166.8, 138.7, 131.8, 129.5, 124.3, 123.2, 119.7, 50.5,

31.1, 28.5, 28.5, 28.3, 27.1, 22.9, 22.0, 13.8; HRMS (FAB) calcd for $C_{16}H_{26}NO_4S$ [$M + H$]⁺, 328.15826; found, 328.15640. Anal. ($C_{16}H_{25}NO_4S$) C, H, N.

3-(Phenylsulfonamido)benzoic acid 15e

mp = 203–204 °C; ¹H NMR (DMSO-*d*₆) δ 13.02 (br s, 1H), 10.51 (br s, 1H), 7.75 (d, *J* = 7.2 Hz, 2H), 7.68 (s, 1H), 7.56 (m, 4H), 7.34 (m, 2H); ¹³C NMR (DMSO-*d*₆) δ 166.6, 139.2, 137.9, 133.0, 131.7, 129.4, 129.3, 126.5, 124.8, 124.0, 120.5; HRMS (FAB) calcd for $C_{13}H_{11}NO_4S$ [M]⁺, 277.04088; found, 277.04054. Anal. ($C_{13}H_{11}NO_4S \cdot \frac{1}{4}(H_2O)$) C, H, N.

3-(4-Chlorophenylsulfonamido)benzoic acid 15f

mp = 242–243 °C; ¹H NMR (MeOD) δ 7.76 (d, *J* = 8.8 Hz, 4H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.34 (m, 2H); ¹³C NMR (MeOD) δ 168.9, 140.2, 139.5, 139.0, 133.0, 130.3, 130.3, 129.8, 127.0, 126.4, 123.1; HRMS (FAB) calcd for $C_{13}H_{10}ClNO_4S$ [M]⁺, 311.00191; found, 311.00152. Anal. ($C_{13}H_{10}ClNO_4S$) C, H, N.

2-(Nonylsulfonamido)benzoic acid 15g

mp = 122–124 °C; ¹H NMR (MeOD) δ 8.11 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 3.18 (t, *J* = 8.0 Hz, 2H), 1.71 (m, 2H), 1.24 (m, 12H), 0.88 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (MeOD) δ 171.3, 142.4, 135.7, 133.1, 123.8, 118.8, 117.0, 52.3, 32.9, 30.2, 30.1, 29.9, 28.8, 24.4, 23.6, 14.4; HRMS (FAB) calcd for $C_{16}H_{25}NO_4S$ [M]⁺, 327.15043; found, 327.15044. Anal. ($C_{16}H_{25}NO_4S$) C, H, N.

2-(Phenylsulfonamido)benzoic acid 15h

mp = 213–215 °C; ¹H NMR (MeOD) δ 7.95 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.49 (m, 3H), 7.09 (t, *J* = 7.6 Hz, 1H); ¹³C NMR (DMSO-*d*₆) δ 169.7, 139.7, 138.5, 134.4, 133.5, 131.5, 129.4, 126.8, 123.3, 118.4, 116.7; HRMS (FAB) calcd for $C_{13}H_{11}NO_4S$ [M]⁺, 277.04088; found, 277.04124. Anal. ($C_{13}H_{11}NO_4S \cdot \frac{1}{4}(H_2O)$) C, H, N.

2-(4-Chlorophenylsulfonamido)benzoic acid 15i

mp = 202–203 °C; ¹H NMR (DMSO-*d*₆) δ 13.98 (br s, 1H), 11.12 (br s, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H); ¹³C NMR (MeOD) δ 171.1, 141.3, 140.6, 139.0, 135.4, 132.8, 130.3, 129.9, 124.7, 120.6, 118.3; HRMS (FAB) calcd for $C_{13}H_{10}ClNO_4S$ [M]⁺, 311.00191; found, 311.00136. Anal. ($C_{13}H_{10}ClNO_4S$) C, H, N.

General Procedure for 16a-f

To a stirring solution of the aniline starting material (3.3 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added pyridine (7.5 equiv). The sulfonyl chloride (1.2 equiv) was then added slowly via syringe. The solution was stirred and allowed to warm to room temperature. Reaction progress was monitored by TLC (20% EtOAc in hexanes). When complete, the reaction was poured into saturated $NaHCO_3$ (45 mL), extracted with CH_2Cl_2 (3 × 15 mL), and washed with 1 M HCl (50 mL). The combined organic phases were concentrated *in vacuo*, and the resulting solid was recrystallized from EtOAc / hexanes to afford **16a-f**.

Methyl 4-(phenylmethylsulfonamido)benzoate 16a

¹H NMR (DMSO-*d*₆) δ 10.37 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.33 (m, 3H), 7.24 (m, 4H), 4.58 (s, 2H), 3.82 (s, 3H); ¹³C NMR (DMSO-*d*₆) δ 165.7, 143.1, 130.9, 130.6, 129.2, 128.4, 128.3, 123.6, 117.2, 57.2, 51.8.

Methyl 4-(2-phenylethylsulfonamido)benzoate 16b

^1H NMR (CDCl_3) δ 7.97 (d, J = 7.4 Hz, 2H), 7.29 (m, 3H), 7.13 (d, J = 7.4 Hz, 2H), 7.06 (d, J = 6.8 Hz, 2H), 6.68 (s, 1H), 3.91 (s, 3H), 3.43 (t, J = 8.0 Hz, 2H), 3.14 (t, J = 8.0 Hz, 2H); ^{13}C NMR (CDCl_3) δ 166.3, 140.9, 137.1, 131.2, 129.0, 128.3, 127.1, 126.1, 118.1, 53.0, 52.1, 29.8.

Methyl 3-(phenylmethylsulfonamido)benzoate 16c

^1H NMR (DMSO-d_6) δ 10.11 (s, 1H), 7.78 (s, 1H), 7.65 (d, J = 6.8 Hz, 1H), 7.44 (m, 2H), 7.33 (m, 3H), 7.26 (m, 2H), 4.50 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.8, 138.9, 130.8, 130.6, 129.6, 129.2, 128.3, 128.2, 123.8, 123.3, 119.1, 57.1, 52.2.

Methyl 3-(2-phenylethylsulfonamido)benzoate 16d

^1H NMR (CDCl_3) δ 7.84 (d, J = 7.6 Hz, 1H), 7.79 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.26 (m, 4H), 7.14 (d, J = 7.6 Hz, 2H), 3.96 (s, 3H), 3.41 (t, J = 7.6 Hz, 2H), 3.16 (t, J = 7.6 Hz, 2H); ^{13}C NMR (CDCl_3) δ 166.4, 137.3, 137.1, 131.4, 129.7, 128.9, 128.3, 127.0, 126.0, 124.6, 121.2, 52.8, 52.4, 29.7.

Methyl 2-(phenylmethylsulfonamido)benzoate 16e

^1H NMR (CDCl_3) δ 10.34 (s, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.25 (m, 3H), 7.14 (d, J = 7.2 Hz, 2H), 7.07 (t, J = 7.6 Hz, 1H), 4.36 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (CDCl_3) δ 167.6, 140.5, 134.4, 131.0, 130.2, 128.3, 128.3, 127.8, 122.4, 117.4, 114.9, 57.7, 52.0.

Methyl 2-(2-phenylethylsulfonamido)benzoate 16f

^1H NMR (CDCl_3) δ 10.52 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.56 (t, J = 8.4 Hz, 1H), 7.25 (m, 3H), 7.11 (m, 3H), 3.95 (s, 3H), 3.45 (t, J = 8.0 Hz, 2H), 3.14 (t, J = 8.0 Hz, 2H); ^{13}C NMR (CDCl_3) δ 168.1, 140.6, 137.1, 134.7, 131.4, 128.5, 128.0, 126.7, 122.5, 117.5, 114.9, 52.9, 52.3, 29.4.

General Procedure for 17a-f

To a stirring suspension of potassium *t*-butoxide (5.88 mmol) in Et_2O (15 mL) cooled to 0 °C, was added water (1.4 mmol) via syringe. The slurry was stirred for 5 min, and **16a-f** (0.67 mmol) was added. The mixture was stirred at room temperature until starting material disappeared by TLC analysis (20% EtOAc in hexanes). Ice water was added until 2 clear layers formed. The aqueous layer was separated and acidified with 1 M HCl. The product was then extracted with Et_2O (3 $\times$ 20 mL) and evaporated *in vacuo* to afford **17a-f**.

4-(Phenylmethylsulfonamido)benzoic acid 17a

mp = 221–223 °C; ^1H NMR (DMSO-d_6) δ 12.72 (br s, 1H), 10.29 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.33 (m, 3H), 7.24 (m, 4H), 4.56 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 166.8, 142.7, 130.9, 130.8, 129.2, 128.3, 128.3, 124.8, 117.2, 57.1; HRMS (FAB) calcd for $\text{C}_{14}\text{H}_{14}\text{NO}_4\text{S}$ $[\text{M} + \text{H}]^+$, 292.06435; found, 292.06397. Anal. ($\text{C}_{14}\text{H}_{13}\text{NO}_4\text{S}$) C, H, N.

4-(2-Phenylethylsulfonamido)benzoic acid 17b

mp = 222–223 °C; ^1H NMR (DMSO-d_6) δ 12.74 (br s, 1H), 10.38 (s, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.26 (m, 2H), 7.23 (m, 2H), 7.18 (m, 3H), 3.48 (t, J = 6.4, 2H), 2.98 (t, J = 6.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 166.8, 142.4, 137.8, 130.8, 128.4, 128.3, 126.5, 125.2, 117.8, 51.9, 29.0; HRMS (FAB) calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_4\text{S}$ $[\text{M} + \text{H}]^+$, 306.08000; found, 306.07892. Anal. ($\text{C}_{15}\text{H}_{15}\text{NO}_4\text{S}$) C, H, N.

3-(Phenylmethylsulfonamido)benzoic acid 17c

mp = 205-206 °C; ^1H NMR (DMSO- d_6) δ 13.02 (br s, 1H), 10.06 (s, 1H), 7.79 (s, 1H), 7.64 (d, J = 7.2 Hz, 1H), 7.42 (m, 2H), 7.33 (m, 3H), 7.25 (m, 2H), 4.48 (s, 2H); ^{13}C NMR (DMSO- d_6) δ 166.9, 138.7, 131.8, 130.9, 129.4, 129.3, 128.3, 128.2, 124.1, 122.9, 119.4, 57.0; HRMS (FAB) calcd for $\text{C}_{14}\text{H}_{14}\text{NO}_4\text{S}$ $[\text{M} + \text{H}]^+$, 292.06435; found, 292.06448. Anal. ($\text{C}_{14}\text{H}_{13}\text{NO}_4\text{S}$) C, H, N.

3-(2-Phenylethylsulfonamido)benzoic acid 17d

mp = 199-200 °C; ^1H NMR (DMSO- d_6) δ 13.06 (s, 1H), 10.11 (s, 1H), 7.85 (s, 1H), 7.67 (d, J = 6.8 Hz, 1H), 7.48 (m, 2H), 7.24 (m, 2H), 7.17 (m, 3H), 3.38 (t, J = 8.0 Hz, 2H), 2.99 (t, J = 8.0 Hz, 2H); ^{13}C NMR (DMSO- d_6) δ 166.8, 138.5, 137.9, 131.9, 129.6, 128.4, 128.3, 126.5, 124.6, 123.8, 120.2, 51.7, 29.0; HRMS (FAB) calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_4\text{S}$ $[\text{M} + \text{H}]^+$, 306.08000; found, 306.08051. Anal. ($\text{C}_{15}\text{H}_{15}\text{NO}_4\text{S}$) C, H, N.

2-(Phenylmethylsulfonamido)benzoic acid 17e

mp = 216-219 °C; ^1H NMR (DMSO- d_6) δ 13.86 (br s, 1H), 10.68 (s, 1H), 7.99 (d, J = 7.6 Hz, 1H), 7.58 (m, 2H), 7.32 (m, 3H), 7.19 (m, 3H), 4.69 (s, 2H); ^{13}C NMR (DMSO- d_6) δ 169.6, 140.7, 134.6, 131.5, 130.7, 128.8, 128.4, 128.3, 122.4, 117.2, 115.4, 57.2; HRMS (FAB) calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_4\text{S}$ $[\text{M}]^+$, 291.05653; found, 291.05655. Anal. ($\text{C}_{14}\text{H}_{13}\text{NO}_4\text{S}$) C, H, N.

2-(2-Phenylethylsulfonamido)benzoic acid 17f

mp = 157-159 °C; ^1H NMR (DMSO- d_6) δ 13.90 (br s, 1H), 10.74 (br s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 4.4 Hz, 2H), 7.20 (m, 2H), 7.16 (m, 4H), 3.61 (t, J = 8.0 Hz, 2H), 2.98 (t, J = 8.0 Hz, 2H); ^{13}C NMR (DMSO- d_6) δ 169.7, 140.3, 137.5, 134.6, 131.6, 128.3, 128.2, 126.5, 122.6, 117.7, 115.9, 52.0, 28.9; HRMS (FAB) calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_4\text{S}$ $[\text{M} + \text{H}]^+$, 306.08000; found, 306.07886. Anal. ($\text{C}_{15}\text{H}_{15}\text{NO}_4\text{S}$) C, H, N.

General Procedure for 19a-c

The starting bromide **18** (1.96 mmol) was added to a round-bottomed flask containing diethyl phosphite (2.35 mmol), tetrakis(triphenylphosphine)palladium (0) (0.04 mmol), Et_3N (2.94 mmol), and EtOH (8 mL), and the solution was heated to reflux overnight (16 h). The solution was then diluted with 30 mL EtOAc, washed with 50 mL saturated NaHCO_3 solution, 50 mL H_2O , dried over MgSO_4 , and concentrated *in vacuo*. The product was then purified by flash chromatography (EtOAc).

Diethyl 4-acetamidophenylphosphonate 19a

Characterization data are in agreement with literature values.³⁶

Diethyl 3-acetamidophenylphosphonate 19b

^1H NMR (CDCl_3) δ 9.91 (s, 1H), 8.29 (s, 1H), 7.89 (d, J = 15.0 Hz, 1H), 7.37 (m, 2H), 4.02 (m, 4H), 2.17 (s, 3H), 1.26 (t, J = 7.2 Hz, 6H); ^{13}C NMR (CDCl_3) δ 169.3, 139.5 (d, J = 18.4 Hz), 129.2, (d, J = 16.1 Hz), 127.5 (d, J = 185 Hz), 125.7 (d, J = 8.6 Hz), 123.7 (d, J = 3.2 Hz), 122.7 (d, J = 12.1 Hz), 62.2 (d, J = 5.3 Hz), 24.0, 16.0 (d, J = 6.5 Hz).

Diethyl 2-acetamidophenylphosphonate 19c

Characterization data are in agreement with literature values.³⁷

Diethyl 4-(octylsulfonamido)phenylphosphonate 20a

^1H NMR (CDCl_3) δ 8.87 (s, 1H), 7.72 (dd, J = 13.2, 7.8 Hz, 2H), 7.37 (dd, J = 7.8, 3.6 Hz, 2H), 4.08 (m, 4H), 3.10 (t, J = 8.0 Hz, 2H), 1.79 (m, 2H), 1.29 (t, J = 7.2 Hz, 6H), 1.23 (m, 10H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3) δ 142.0 (d, J = 3 Hz), 133.2 (d, J = 10.9 Hz), 122.4 (d, J = 193 Hz), 118.1 (d, J = 15.4 Hz), 62.2 (d, J = 5.5 Hz), 51.9, 31.5, 28.8, 28.7, 28.0, 23.2, 22.4, 16.1 (d, J = 6.5 Hz), 13.8.

Diethyl 3-(octylsulfonamido)phenylphosphonate 20b

^1H NMR (CDCl_3) δ 9.53 (s, 1H), 7.89 (d, J = 15.2 Hz, 1H), 7.67 (s, 1H), 7.38 (m, 2H), 4.11 (m, 4H), 3.04 (t, J = 8.0 Hz, 2H), 1.77 (m, 2H), 1.28 (t, J = 7.2 Hz, 6H), 1.17 (m, 10H), 0.80 (t, J = 6.8 Hz, 3H); ^{13}C NMR (CDCl_3) δ 139.0 (d, J = 9.2 Hz), 129.6 (d, J = 16.2 Hz), 128.9 (d, J = 189 Hz), 125.9 (d, J = 8.3 Hz), 123.1 (d, J = 12.6 Hz), 122.2 (d, J = 3.0 Hz), 62.4 (d, J = 5.8 Hz), 51.5, 31.4, 28.7, 28.7, 28.0, 23.1, 22.3, 16.0 (d, J = 6.4 Hz), 13.8.

Diethyl 2-(octylsulfonamido)phenylphosphonate 20c

^1H NMR (CDCl_3) δ 9.94 (s, 1H), 7.73 (t, J = 8.0 Hz, 1H), 7.59 (m, 1H), 7.53 (m, 1H), 7.14 (dt, J = 7.2, 2.8 Hz, 1H), 4.09 (m, 4H), 3.14 (t, J = 8.0 Hz, 2H), 1.84 (m, 2H), 1.34 (t, J = 7.2 Hz, 6H), 1.26 (m, 10H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3) δ 142.2 (d, J = 7.4 Hz), 134.2 (d, J = 2.3 Hz), 133.1 (d, J = 5.9 Hz), 122.9 (d, J = 13.3 Hz), 118.3 (d, J = 11.5 Hz), 114.0 (d, J = 180 Hz), 62.7 (d, J = 5.2 Hz), 52.2, 31.6, 28.9, 28.8, 28.1, 23.2, 22.4, 16.1 (d, J = 6.5 Hz), 13.9.

4-(Octylsulfonamido)phenylphosphonic acid 21a

mp = 185–187 °C; ^1H NMR (MeOD) δ 7.75 (dd, J = 12.8, 8.0 Hz, 2H), 7.33 (dd, J = 8.0, 3.2 Hz, 2H), 3.15 (t, J = 8.0 Hz, 2H), 1.78 (m, 2H), 1.39 (m, 2H), 1.28 (m, 8H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (MeOD) δ 143.0 (d, J = 3.6 Hz), 133.4 (d, J = 11.0 Hz), 127.7 (d, J = 190 Hz), 119.1 (d, J = 15.2 Hz), 52.4, 32.8, 30.0, 29.9, 29.0, 24.5, 23.6, 14.3; HRMS (FAB) calcd for $\text{C}_{14}\text{H}_{25}\text{NO}_5\text{PS}$ [$\text{M} + \text{H}$] $^+$, 350.11911; found, 350.11869. Anal. ($\text{C}_{14}\text{H}_{24}\text{NO}_5\text{PS} \cdot 0.6(\text{H}_2\text{O})$) C, H, N.

3-(Octylsulfonamido)phenylphosphonic acid 21b

mp = 112–114 °C; ^1H NMR (MeOD) δ 7.72 (d, J = 14.8 Hz, 1H), 7.55 (m, 1H), 7.44 (m, 2H), 3.12 (t, J = 8.0 Hz, 2H), 1.78 (m, 2H), 1.39 (m, 2H), 1.27 (m, 8H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (MeOD) δ 139.6 (d, J = 18.2 Hz), 134.5 (d, J = 184 Hz), 130.5 (d, J = 16.1 Hz), 127.3 (d, J = 9.5 Hz), 123.8 (d, J = 3.0 Hz), 122.8 (d, J = 11.6 Hz), 52.2, 32.7, 30.0, 29.9, 29.0, 24.4, 23.5, 14.3; HRMS (FAB) calcd for $\text{C}_{14}\text{H}_{25}\text{NO}_5\text{PS}$ [$\text{M} + \text{H}$] $^+$, 350.11911; found, 350.11879. Anal. ($\text{C}_{14}\text{H}_{24}\text{NO}_5\text{PS}$) C, H, N.

2-(Octylsulfonamido)phenylphosphonic acid 21c

mp = 92–94 °C; ^1H NMR (MeOD) δ 7.70 (m, 2H), 7.54 (t, J = 8.4 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 3.18 (t, J = 7.8 Hz, 2H), 1.77 (m, 2H), 1.23 (m, 10H), 0.89 (t, J = 7.5 Hz, 3H); ^{13}C NMR (MeOD) δ 141.8 (d, J = 7.0 Hz), 134.3 (d, J = 2.7 Hz), 134.1 (d, J = 6.8 Hz), 120.4 (d, J = 178 Hz), 119.6 (d, J = 10.8 Hz), 52.6, 32.8, 29.9, 29.9, 29.0, 24.3, 23.5, 14.3; HRMS (FAB) calcd for $\text{C}_{14}\text{H}_{25}\text{NO}_5\text{PS}$ [$\text{M} + \text{H}$] $^+$, 350.11911; found, 350.11826. Anal. ($\text{C}_{14}\text{H}_{24}\text{NO}_5\text{PS}$) C, H, N.

General Procedure for 23a–f

To a stirring solution of the aniline starting material (3.3 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added pyridine (7.5 equiv). The sulfonyl chloride (1.2 equiv) was then added slowly via syringe. The solution was stirred and allowed to warm to room temperature. Reaction

progress was monitored by TLC (20% EtOAc in hexanes). When complete, the reaction was poured into saturated NaHCO₃ solution (45 mL), extracted with CH₂Cl₂ (3 × 15 mL), and washed with 1 M HCl (50 mL). The combined organic phases were concentrated *in vacuo*, and separated by flash chromatography (20 % EtOAc in hexanes) to afford **23a-f**.

Methyl 2-(methylsulfonamido)benzoate **23a**

¹H NMR (CDCl₃) δ 10.43 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.4 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 3.91 (s, 3H), 3.05 (s, 3H); ¹³C NMR (CDCl₃) δ 168.2, 140.7, 134.8, 131.4, 122.7, 117.9, 115.3, 52.4, 39.8.

Methyl 2-(tetradecylsulfonamido)benzoate **23b**

¹H NMR (CDCl₃) δ 10.42 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 8.4 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 3.91 (s, 3H), 3.12 (t, *J* = 8.0 Hz, 2H), 1.78 (m, 2H), 1.23 (m, 22H), 0.87 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃) δ 168.2, 141.0, 134.7, 131.4, 122.4, 117.6, 114.9, 52.4, 52.0, 31.8, 29.5, 29.5, 29.5, 29.4, 29.3, 29.2, 29.0, 28.8, 27.9, 23.2, 22.5, 14.0.

Methyl 2-(hexadecylsulfonamido)benzoate **23c**

¹H NMR (CDCl₃) δ 10.42 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 3.94 (s, 3H), 3.14 (t, *J* = 8.0 Hz, 2H), 1.81 (m, 2H), 1.26 (m, 26H), 0.88 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃) δ 168.3, 141.0, 134.8, 131.4, 122.4, 117.7, 115.0, 52.4, 52.1, 31.8, 29.6, 29.6, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 29.1, 28.9, 28.0, 23.3, 22.6, 14.0.

Methyl 5-chloro-2-(nonylsulfonamido)benzoate **23d**

¹H NMR (CDCl₃) δ 10.31 (br s, 1H), 8.01 (d, *J* = 2.4 Hz, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.48 (dd, *J* = 9.0, 2.4 Hz, 1H), 3.95 (s, 1H), 3.12 (t, *J* = 7.8 Hz, 2H), 1.78 (m, 2H), 1.23 (m, 12H), 0.87 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃) δ 167.3, 139.6, 134.6, 131.0, 127.8, 119.2, 116.2, 52.8, 52.3, 31.7, 29.0, 28.8, 27.9, 27.9, 23.2, 22.5, 14.0.

Methyl 5-hydroxy-2-(octylsulfonamido)benzoate **23e**

¹H NMR (CDCl₃) δ 9.91 (s, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.52 (d, *J* = 3.0 Hz, 1H), 7.07 (dd, *J* = 3.0, 9.0 Hz, 1H), 6.36 (s, 1H), 3.91 (s, 3H), 3.05 (t, *J* = 8.1 Hz, 2H), 1.76 (m, 2H), 1.22 (m, 10H), 0.86 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃) δ 168.0, 151.7, 133.3, 122.3, 120.7, 117.3, 117.0, 52.6, 51.7, 31.5, 28.8, 28.7, 27.9, 23.1, 22.4, 13.9.

Methyl 5-fluoro-2-(octylsulfonamido)benzoate **23f**

¹H NMR (CDCl₃) δ 10.15 (s, 1H), 7.75 (m, 2H), 7.25 (m, 1H), 3.95 (s, 3H), 3.09 (t, *J* = 8.0 Hz, 2H), 1.76 (m, 2H), 1.22 (m, 10H), 0.85 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (CDCl₃) δ 167.2 (d, *J* = 2.2 Hz), 157.5 (d, *J* = 242 Hz), 137.1 (d, *J* = 2.8 Hz), 122.0 (d, *J* = 22.4 Hz), 120.1 (d, *J* = 7.4 Hz), 117.4 (d, *J* = 24.3 Hz), 116.4 (d, *J* = 6.9 Hz), 52.7, 52.1, 31.5, 28.7, 28.7, 27.9, 23.2, 22.4, 13.8.

General Procedure for **24a-f**

To a stirring suspension of potassium *t*-butoxide (5.88 mmol) in Et₂O (15 mL) cooled to 0 °C was added water (1.4 mmol) via syringe. The slurry was stirred for 5 min, and **23a-f** (0.67 mmol) was added. The mixture was stirred at room temperature until starting material disappeared by TLC analysis (20% EtOAc in hexanes). Ice water was added until two clear layers formed. The aqueous layer was separated and acidified with 1 M HCl, and the product

was extracted with Et₂O (3 × 20 mL) and evaporated *in vacuo*. If necessary, the product was then recrystallized (EtOAc / hexanes) to afford pure **24a-f**.

2-(Methylsulfonamido)benzoic acid **24a**

mp = 187-189 °C; ¹H NMR (MeOD) δ 8.11 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 3.08 (s, 3H); ¹³C NMR (MeOD) δ 171.2, 142.2, 135.7, 133.0, 123.9, 119.2, 117.3, 39.9; HRMS (FAB) calcd for C₈H₉NO₄S [M]⁺, 215.02523; found, 215.02576. Anal. (C₈H₉NO₄S) C, H, N.

2-(Tetradecylsulfonamido)benzoic acid **24b**

mp = 120-122 °C; ¹H NMR (MeOD) δ 8.12 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 3.19 (t, *J* = 8.0 Hz, 2H), 1.70 (m, 2H), 1.29 (m, 22H), 0.91 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (MeOD) δ 171.4, 142.5, 135.7, 133.1, 123.8, 118.8, 117.0, 52.2, 33.0, 30.7, 30.7, 30.7, 30.6, 30.5, 30.4, 30.2, 29.9, 28.8, 24.4, 23.7, 14.4; HRMS (FAB) calcd for C₂₁H₃₅NO₄S [M]⁺, 397.22835; found, 397.22835. Anal. (C₂₁H₃₅NO₄S·¼(H₂O)) C, H, N.

2-(Hexadecylsulfonamido)benzoic acid **24c**

mp = 126-128 °C; ¹H NMR (MeOD) δ 8.12 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 3.19 (t, *J* = 7.6 Hz, 2H), 1.73 (m, 2H), 1.23 (m, 26H), 0.91 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (MeOD) δ 169.8, 140.7, 134.6, 131.6, 122.4, 117.3, 115.6, 50.9, 31.2, 29.0, 29.0, 29.0, 29.0, 29.0, 28.9, 28.8, 28.7, 28.5, 28.2, 27.0, 22.8, 22.0, 13.8; HRMS (FAB) calcd for C₂₃H₄₀NO₄S [M + H]⁺, 426.26781; found, 426.26825. Anal. (C₂₃H₃₉NO₄S) C, H, N.

5-Chloro-2-(nonylsulfonamido)benzoic acid **24d**

mp = 101-103 °C; ¹H NMR (MeOD) δ 8.05 (d, *J* = 2.8 Hz, 1H), 7.74 (d, *J* = 9.2 Hz, 1H), 7.59 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.21 (t, *J* = 8.0 Hz, 2H), 1.72 (m, 2H), 1.23 (m, 12H), 0.90 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (MeOD) δ 170.1, 141.2, 135.5, 132.4, 128.9, 120.6, 118.0, 52.5, 32.9, 30.2, 30.1, 29.9, 28.8, 24.4, 23.6, 14.4; HRMS (FAB) calcd for C₁₆H₂₄ClNO₄S [M]⁺, 361.11146; found, 361.11063. Anal. (C₁₆H₂₄ClNO₄S) C, H, N.

5-Hydroxy-2-(octylsulfonamido)benzoic acid **24e**

mp = 142-144 °C; ¹H NMR (MeOD) δ 7.56 (d, *J* = 8.8 Hz, 1H), 7.51 (d, *J* = 2.8 Hz, 1H), 7.03 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.07 (t, *J* = 8.0 Hz, 2H), 1.68 (m, 2H), 1.23 (m, 10H), 0.89 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (MeOD) δ 171.0, 154.6, 134.1, 122.8, 121.9, 119.2, 118.5, 53.1, 32.8, 29.9, 29.8, 28.8, 24.3, 23.6, 14.4. Anal. (C₁₅H₂₃NO₅S) C, H, N.

5-Fluoro-2-(octylsulfonamido)benzoic acid **24f**

mp = 141-143 °C; ¹H NMR (MeOD) δ 7.77 (m, 2H), 7.38 (m, 1H), 3.17 (t, *J* = 8.0 Hz, 2H), 1.71 (m, 2H), 1.23 (m, 10H), 0.88 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (MeOD) δ 170.2 (d, *J* = 1.8 Hz), 159.2 (d, *J* = 241 Hz), 138.6 (d, *J* = 2.7 Hz), 122.7 (d, *J* = 22.7 Hz), 121.5 (d, *J* = 7.6 Hz), 119.0 (d, *J* = 6.9 Hz), 118.8 (d, *J* = 24.1 Hz), 52.4, 32.8, 29.9, 29.9, 28.8, 24.4, 23.6, 14.3; HRMS (FAB) calcd for C₁₅H₂₂FNO₄S [M]⁺, 331.12536; found, 331.12445. Anal. (C₁₅H₂₂FNO₄S) C, H, N.

GPAT Assay

The mtGPAT assay has been reported previously.³⁵ A mitochondrial preparation of glycerol 3-phosphate acyltransferase was added to the incubation mixture containing ¹⁴C-labeled glycerol 3-phosphate, palmitoyl-CoA, and varying inhibitor concentrations to initiate the

reaction. After ten min, the reaction was terminated by adding chloroform, methanol, and 1% perchloric acid. Five min later, more chloroform and perchloric acid were added, and the upper aqueous layer was removed. After washing three times with 1% perchloric acid, the organic layer was evaporated under nitrogen, and the amount of ^{14}C present was counted to determine the extent of reaction inhibition. Data points were recorded in triplicate, and IC_{50} values were calculated based on the amount of test inhibitor necessary to produce 50% of mtGPAT activity observed in the absence of inhibitor but in the presence of DMSO vehicle control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The work was supported by the NIH 1R43DK65423 to FASgen, Inc. and donors to the Raynam Trust. Under a license agreement between FASgen, Inc. and The Johns Hopkins University, CAT is entitled to share royalty received by the University on sales of products described in this article. CAT owns FASgen, Inc. stock, which is subject to certain restrictions under university policy. The Johns Hopkins University, in accordance with its conflict of interest policies, is managing the terms of this arrangement.

Abbreviations

GPAT	glycerol 3-phosphate acyltransferase
DIO	diet-induced obese
mtGPAT	mitochondrial glycerol 3-phosphate acyltransferase
LPA	lysophosphatidic acid
TAG	triacylglycerol
VLDL	very low density lipoprotein
DAG	diacylglycerol
CPT-1	carnitine palmitoyltransferase-1
AMPK	AMP-activated protein kinase
ACC	acetyl-CoA carboxylase
FAS	fatty acid synthase

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Scheme 1.

Reaction conditions: (a) NBS, hv, CH₃CN; (b) NaN₃, EtOH, reflux; (d) C₉H₁₉SO₂Cl or C₅H₁₁SO₂Cl, pyridine, CH₂Cl₂, 0 °C to rt; (e) K⁺O⁻*t*-Bu, Et₂O, H₂O, 0 °C to rt.

Scheme 2.

Reaction conditions: (a) NH₃, MeOH, reflux; (b) NaH, RSO₂Cl, DMF, 0 °C to rt; (c) NaOH, THF/H₂O, 0 °C to rt.

Scheme 3.

Reaction conditions: (a) NBS, hv, CH₃CN; (b) P(OEt)₃, reflux; (c) H₂SO₄, EtOH, reflux; (d) C₉H₁₉SO₂Cl or C₅H₁₁SO₂Cl, pyridine, CH₃CN, 0 °C to rt; (e) TMSBr, CH₂Cl₂, rt.

Scheme 4.

Reaction conditions: (a) RSO₂Cl, pyridine, CH₂Cl₂, 0 °C to rt; (b) K⁺O⁻-*t*-Bu, Et₂O, H₂O, 0 °C to rt.

Scheme 5.

Reaction conditions: (a) RSO_2Cl , pyridine, CH_2Cl_2 , 0°C to rt; (b) $\text{K}^+\text{O}^-t\text{-Bu}$, Et_2O , H_2O , 0°C to rt.

Scheme 6.

Reaction conditions: (a) diethyl phosphite, Et₃N, Pd(PPh₃)₄, EtOH, reflux; (b) H₂SO₄, EtOH, reflux; (c) C₈H₁₇SO₂Cl, Et₃N, CH₂Cl₂, 0 °C to rt; (d) TMSBr, CH₂Cl₂, rt.

Scheme 7.

Reaction conditions: (a) RSO₂Cl, pyridine, CH₂Cl₂, 0 °C to rt; (b) K⁺O⁻*t*-Bu, Et₂O, H₂O, 0 °C to rt.

Figure 1.
Comparison of the Proposed GPAT Transition State (**A**) to the Basic Inhibitor Design (**B**)

Table 1*In Vitro* Anti-mtGPAT1 Activity of Sulfonamides **5a-f** and **13a-f**

Compound	X	Y	n	IC ₅₀ (μM) ± SD
5a	<i>p</i> -CO ₂ H	C ₅ H ₁₁	1	252 ± 6.0
5b	<i>p</i> -CO ₂ H	C ₉ H ₁₉	1	129 ± 18.5
5c	<i>m</i> -CO ₂ H	C ₅ H ₁₁	1	310 ± 6.0
5d	<i>m</i> -CO ₂ H	C ₉ H ₁₉	1	83.5 ± 4.7
5e	<i>o</i> -CO ₂ H	C ₅ H ₁₁	1	217 ± 47.3
5f	<i>o</i> -CO ₂ H	C ₉ H ₁₉	1	66.5 ± 3.2
13a	<i>p</i> -CH ₂ PO ₃ H ₂	C ₅ H ₁₁	0	148 ± 29.8
13b	<i>p</i> -CH ₂ PO ₃ H ₂	C ₉ H ₁₉	0	81.3 ± 14.3
13c	<i>m</i> -CH ₂ PO ₃ H ₂	C ₅ H ₁₁	0	141 ± 28.0
13d	<i>m</i> -CH ₂ PO ₃ H ₂	C ₉ H ₁₉	0	62.8 ± 1.9
13e	<i>o</i> -CH ₂ PO ₃ H ₂	C ₅ H ₁₁	0	129 ± 26.2
13f	<i>o</i> -CH ₂ PO ₃ H ₂	C ₉ H ₁₉	0	81.1 ± 16.4

Table 2*In Vitro* Anti-mtGPAT1 Activity of Sulfonamides **15a-i** and **17a-f**

Compound	X	Y	IC ₅₀ (μM) ± SD
15a	<i>p</i> -CO ₂ H	C ₉ H ₁₉	88.9 ± 13.1
15b	<i>p</i> -CO ₂ H	Ph	151 ± 19.1
15c	<i>p</i> -CO ₂ H	4-ClPh	108 ± 4.2
15d	<i>m</i> -CO ₂ H	C ₉ H ₁₉	73.9 ± 8.9
15e	<i>m</i> -CO ₂ H	Ph	138 ± 27.4
15f	<i>m</i> -CO ₂ H	4-ClPh	75.7 ± 3.8
15g	<i>o</i> -CO ₂ H	C ₉ H ₁₉	24.7 ± 2.1
15h	<i>o</i> -CO ₂ H	Ph	146 ± 9.4
15i	<i>o</i> -CO ₂ H	4-ClPh	107 ± 8.0
17a	<i>p</i> -CO ₂ H	CH ₂ Ph	221 ± 39.7
17b	<i>p</i> -CO ₂ H	C ₂ H ₄ Ph	206 ± 42.2
17c	<i>m</i> -CO ₂ H	CH ₂ Ph	178 ± 30.7
17d	<i>m</i> -CO ₂ H	C ₂ H ₄ Ph	164 ± 14.3
17e	<i>o</i> -CO ₂ H	CH ₂ Ph	140 ± 4.1
17f	<i>o</i> -CO ₂ H	C ₂ H ₄ Ph	152 ± 14.7

Table 3*In Vitro* Anti-mtGPAT1 Activity of Sulfonamides **21a-c** and **24a-f**

Compound	X	Y	Z	IC ₅₀ (μM) ± SD
21a	<i>p</i> -PO ₃ H ₂	C ₈ H ₁₇	H	95.3 ± 10.9
21b	<i>m</i> -PO ₃ H ₂	C ₈ H ₁₇	H	72.4 ± 15.5
21c	<i>o</i> -PO ₃ H ₂	C ₈ H ₁₇	H	73.6 ± 7.1
24a	CO ₂ H	CH ₃	H	132 ± 21.2
24b	CO ₂ H	C ₁₄ H ₂₉	H	17.4 ± 1.2
24c	CO ₂ H	C ₁₆ H ₃₃	H	18.3 ± 1.9
24d	CO ₂ H	C ₉ H ₁₉	Cl	31.8 ± 1.9
24e	CO ₂ H	C ₈ H ₁₇	OH	116 ± 12.4
24f	CO ₂ H	C ₈ H ₁₇	F	89.0 ± 7.8