A New Class of Antituberculosis Agents

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Long-chain lipid envelopes are characteristic of mycobacteria such as those that cause tuberculosis and leprosy. Inhibition of fatty acid synthesis or elongation is a strategy demonstrated to be clinically effective against *M. tuberculosis*. A new class of compounds designed to inhibit the β-ketoacyl synthase reaction of fatty acid synthesis has been developed. Of >30 compounds described, the most active were acetamides containing alkylsulfonyl substituents. Inhibitory activities were acutely sensitive to net charge, chain length, and degree of unsaturation. The most active compound **5** (alkyl = C_{10}) contained a single methylene spacer between the sulfone and carboxamide and exhibited an MIC of 0.75−1.5 μg/mL, comparable to first-line antituberculosis drugs. These compounds are species-specific, exhibiting no significant activity against bacterial species other than *M. tuberculosis* and closely related strains. The synthesis, biological activity, and specificity of these compounds are described.

Introduction

Tuberculosis (TB) is the leading cause of death from a single infectious agent in the world. Approximately one-third of the world's population harbors latent TB,[1] and 3 million will die from its effects this year. Despite the fact that it is treatable and preventable, the disease has been spreading at a steady rate over the past decade.[2] Two developments make the resurgence in TB especially alarming. The first is pathogenic synergy with HIV. The overall incidence of TB in HIV-positive patients is 50 times that of the rate for HIV-negative individuals.[3] The second is the emergence of drug-resistant and multi-drug-resistant TB (MDRTB). The term MDRTB is used to describe strains that are resistant to two or more of the five first-line anti-TB drugs (isoniazid, rifampin, pyrizinamide, ethambutol, and streptomycin).[4−6] Little has changed in our arsenal for TB treatment in more than 30 years when the last anti-TB drug (rifampin) was introduced. There is a pressing need for new chemotherapeutic agents to combat the emergence of resistance and, ideally, shorten the duration of therapy (currently ≥6 months).

Mycobacteria produce a wide array of complex fatty acids, such as mycocerosic acid and mycolic acids, not found in mammalian cells.[7−9] These long-chain acids form a thick hydrophobic outer barrier and constitute 30% dry weight of the cell.[10] Significantly, mycolic acid biosynthesis is essential for mycobacterial survival as evidenced by the bactericidal properties of drugs that inhibit mycolic acid synthesis such as isoniazid and ethionamide.[11−13] Thus, while the synthesis of fatty acids occurs in all living organisms, mycobacteria possess accessory fatty acid synthase (FAS) enzymes with specialized substrate and product specificities that are attractive targets for drug development.

Although the mechanism of fatty acid biosynthesis is essentially the same in all organisms, FASs are organized into two types.[3,14] In type I FAS the catalytic sites are assembled into complexes of multidomain enzymes. These large, polyfunctional type I synthases are most commonly found in eukaryotes. In contrast, type II FASs are comprised of smaller, monofunctional proteins that carry out fatty acid synthesis in transient acyl carrier protein (ACP)-dependent complexes. Type II systems are found primarily in bacteria and plants. Mycobacteria possess both type I and type II FASs, as well as mycocerosic acid synthase, which synthesizes long-chain, multi-methyl-branched fatty acids. These fatty acids make up components of waxes and some acylated trehaloses found in the outer cell wall of some slow-growing mycobacteria.[7,9]

It has been shown in *Mycobacterium smegmatis* that the type I FAS is located in the cytosolic protein fraction and synthesizes C_{16}−C_{18} and C_{24}−C_{26} fatty acyl-CoA chains in a bimodal distribution. The ACP-dependent type II synthase functions primarily as an elongation system, utilizing C_{16} fatty acid primers to produce C_{24}−C_{30} fatty acyl-ACPs. Although capable of producing fatty acids with chain lengths of C_{30}, neither of these cytosolic systems is capable of producing fatty acids of sufficient length required for mycolic acids. This observation suggests the presence of additional FASs.[15,16] While no other FAS enzymes have been definitively identified, several studies support their existence.[17−19] Furthermore, examination of the *Mycobacterium tuberculosis* genome reveals that there are approximately 5 times as many FAS-related enzymes as in *E. coli*.[19]

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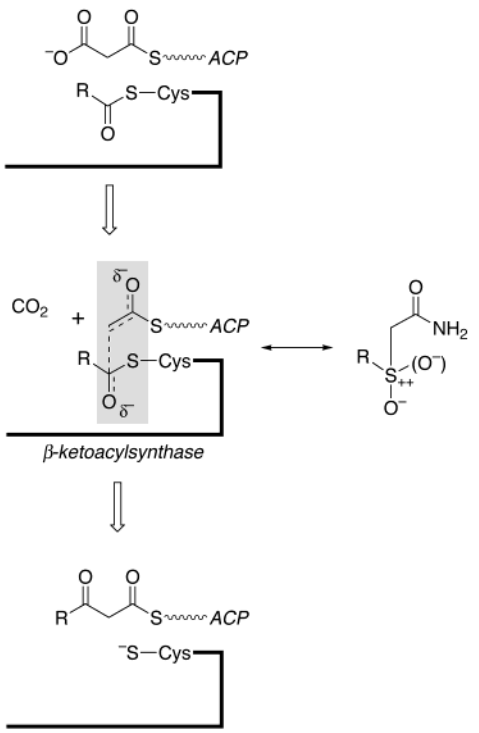
Scheme 1



Chemistry

We chose to target β-ketoacyl synthase (KAS) for inhibitor design. This domain catalyzes the most mechanistically complex of the sequence of FAS reactions yet is definable with respect to geometry and charge. In addition, this reaction, unlike the others involved in fatty acid synthesis, is found only in FAS and polyketide synthase (PKS)-type enzymes. Cerulenin and thiolactomycin, two naturally occurring inhibitors of this chain extension reaction, are known.[20−25] Cerulenin irreversibly inactivates both type I and type II FASs by alkylating the strictly conserved active site cysteine thiol of KAS. Thiolactomycin, on the other hand, while also acting against KAS, reversibly inhibits only type II FAS. Both thiolactomycin[18] and cerulenin[26] are active in vitro against *M. tuberculosis*.

In the KAS-mediated step, malonyl-ACP homologates an existing fatty acid by two carbons. Scheme 1 shows how this is accomplished. Decarboxylation of malonyl-ACP provides the enolate of acetyl-ACP, which is positioned to undergo a Claisen reaction with the cysteine-bound thioester of the growing fatty acyl chain. This addition generates the classical tetrahedral intermediate. The latter, in turn, collapses to give an extended β-keto thioester and the resting state of KAS. While loss of carbon dioxide drives this reaction thermodynamically, it is likely that the enzyme has evolved an architecture that stabilizes formation of the tetrahedral intermediate. Our initial attempts to design an inhibitor of mycobacterial growth were directed to molecules that geometrically and electronically mimic the presumed transition state of this reaction.

Central to realization of this goal are the five boxed atoms in the structures depicted in Scheme 1. A generalized inhibitor structure is shown beside the putative transition state of the thio Claisen reaction. A carboxylic acid, ester, amide, sulfone, or sulfonamide was planned to mimic the acetyl enolate formed after decarboxylation of malonyl-ACP. This component of the reaction must, at some point, add to the thioester of the extending fatty acyl chain to form a tetrahedral intermediate via a one-atom spacer. Structural mimics of this key reactive intermediate could be visualized in a phosphinate, sulfone, or sulfoxide, among others. Bearing in mind, however, that charged, small molecules are generally excluded by the highly lipophilic mycobacterial cell wall,[8] neutral, albeit polar, analogues of the tetrahedral and acetyl centers were sought in the design of potential inhibitors. Using this structural model as a guide, the family of compounds shown in Table 1 was synthesized.

Synthesis. Most of the compounds shown in Table 1 were prepared in a straightforward manner (Scheme 2). Alkylation of the appropriate thiol **32** was carried out with 2-bromoacetate derivatives **33**, followed by oxidation of the resulting thioether **34** and conversion to the desired acyl derivative. If necessary, the thiol could be prepared by Mitsunobu reaction of the corresponding alcohol **35** with thiolacetic acid to give the thioacetate **36**, which was readily hydrolyzed. Alternatively, alkyl bromides **37** could be reacted using methyl thioglycolate (**38**) to thioether **39**, which could be oxidized to the sulfone **40** and substituted at the acyl center as necessary.

Synthesis of the α,β-unsaturated sulfones **10** and **11** was accomplished as shown in Scheme 3. Formation of a thioacetal **42** from methyl thioglycolate **38** and nonyl aldehyde **41** proceeded smoothly using boron trifluoride as a catalyst. Oxidation of **42** to obtain the monosulfoxide **43**, as a mixture of diastereomers, was carried out using *m*-CPBA in 61% yield. This sulfoxide could be converted to the vinyl sulfide **44** in refluxing toluene in the presence of sodium bicarbonate. The vinyl sulfide **44** was obtained as an inseparable mixture of *E*- and *Z*-isomers in 75% yield. Ammonolysis of this ester provided the primary amides **45*E*/*Z***, which could be separated by preparative TLC. Oxidation to the sulfones using *m*-CPBA was carried out in 87% and 91% yield for the *E*- and *Z*-isomers **10** and **11**, respectively.

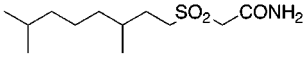
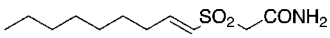
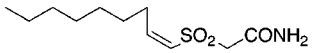
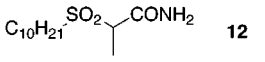
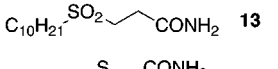
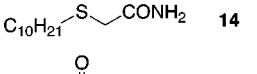
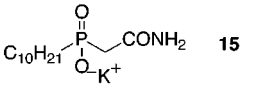
The phosphinate **15** was prepared by the method of Regan.[27−29] Ammonium hypophosphonate was heated under an inert atmosphere with a slight excess of hexamethyldisilazane (HMDS) to give bis(trimethylsilyl)phosphonite (**46**). Alkylation with 1-iododecane followed by resilylation with HMDS and a second alkylation with methyl bromoacetate afforded ester **47** as the ammonium salt in 30% overall yield. Ammonolysis of the ester was readily achieved followed by conversion to the potassium salt **15**.

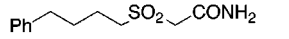
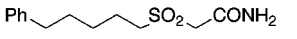
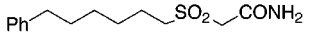
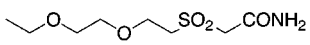
Synthesis of the sulfonamides **28**−**30** was carried out in one step from commercially available octanesulfonyl chloride and either urea, methanesulfonamide, or sulfamide.[30] The anion was formed using sodium hydride in DMF. These compounds were obtained in 70%, 82%, and 69% yields, respectively.

Biological Results and Discussion

The compounds shown in Table 1 were tested for activity against *M. tuberculosis* (H37Rv) using the standard BACTEC radiometric growth assay.[31] All but a few of these compounds (**1**, **7**, **15**, and **27**−**31**)

Table 1. Anti-TB (H37Rv) Activity

		MIC μg/ml
isoniazid		0.1-0.4
ethambutol		2
rifampin		2
pyrizinamide		100
streptomycin		2
thiolactomycin		25
cerulenin		0.5-1.5
$C_6H_{13}SO_2CONH_2$	**1**	> 50
$C_7H_{15}SO_2CONH_2$	**2**	>25
$C_8H_{17}SO_2CONH_2$	**3***	6.25
$C_9H_{19}SO_2CONH_2$	**4***	3.0
$C_{10}H_{21}SO_2CONH_2$	**5***	0.75 - 1.5
$C_{12}H_{25}SO_2CONH_2$	**6**	12.5
$C_{18}H_{37}SO_2CONH_2$	**7**	> 50
$(CH_3)_2CH(CH_2)_7SO_2CONH_2$	**8***	1.5
	**9***	6.25
	**10***	12.5
	**11***	12.5
	**12**	> 25
	**13**	> 25
	**14**	25
	**15**	> 50

		MIC μg/ml
$C_{10}H_{21}SOCONH_2$	**16***	6.25
$C_9H_{19}SOCONH_2$ *rac*	**17***	25
$C_9H_{19}SOCONH_2$ *R*		25
$C_9H_{19}SOCONH_2$ *S*		25
$C_9H_{19}SOCO_2Me$ *rac*	**18***	> 25
$C_9H_{19}SOCO_2Me$ *R*		> 25
$C_9H_{19}SOCO_2Me$ *S*		> 25
$C_8H_{17}SOCO_2Me$	**19***	12.5
$C_8H_{17}SO_2CO_2Me$	**20***	> 25
$C_8H_{17}SOCO_2Bn$	**21***	6.25
$C_8H_{17}SO_2CO_2Bn$	**22***	12.5
$C_8H_{17}SO_2CO_2H$	**23**	> 25
	**24**	> 25
	**25**	12.5 - 25
	**26**	12.5
	**27**	> 25
$C_8H_{17}SO_2NHCONH_2$	**28**	> 25
$C_8H_{17}SO_2NHSO_2CH_3$	**29**	> 25
$C_8H_{17}SO_2NHSO_2NH_2$	**30**	> 25
$C_{10}H_{21}OCONH_2$	**31**	> 25

displayed activity against *M. tuberculosis*. Minimum inhibitory concentrations (MIC) ranged from less than 1 to 25 μg/mL for the active compounds. Compounds in this family consist of four structural elements. These are an acyl derivative, spacer, tetrahedral mimic, and hydrophobic tail. The effects of each element on antimycobacterial activity are discussed below.

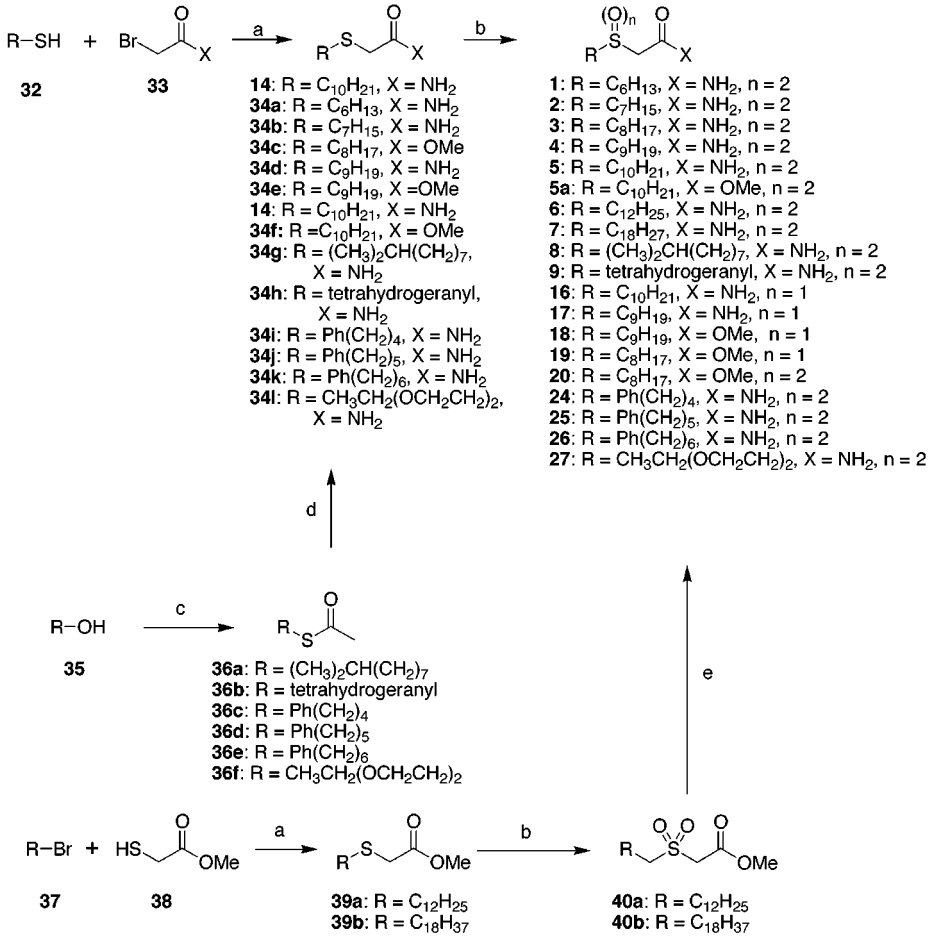
Most of the compounds in Table 1 have a primary amide as the acyl derivative. The exceptions are a methyl ester (**19**, **20**), benzyl ester (**21**, **22**), carboxylic acid (**23**), sulfone (**29**), or sulfamide (**30**). Both methyl and benzyl esters were active against *M. tuberculosis* but had decreased activity relative to the corresponding amides. As the benzyl esters were slightly more active than the corresponding methyl esters, it seems reasonable to suggest that this segment of the molecule occupies a large, flexible binding site or is protruding into solution. The carboxylic acid **23**, phosphinate **15**, and sulfonimide derivatives **28**−**30** are likely to be ionized in the assay buffer (pH 7.2). As noted earlier, it is likely these molecules are not able to enter the mycobacterial cell.[8]

Most of the compounds shown in Table 1, and all active compounds, have a single methylene spacer between the tetrahedral mimic and acyl center. The exceptions, **12**, **13,** and **28**−**30**, are inactive against H37Rv. Thus, a methyl branch at this site, extension to two methylenes, or replacement by a readily ionized N-H is strongly unfavorable. This finding is consistent with the original design as any spacing greater than one atom would alter both the geometrical and electronic similarity between a potential inhibitor and the putative KAS transition state depicted in Scheme 1.

With two exceptions the tetrahedral mimic employed by compounds in Table 1 is a sulfone or a sulfoxide. In general, a sulfone appears to give superior activity relative to the corresponding sulfoxide. For example, the MICs for **5** (sulfone) and **16** (sulfoxide) are 0.75 and 6.25 μg/mL, respectively. However, in the case of compounds having an ester as the acyl derivative, a sulfoxide is slightly more active than the corresponding sulfone. Comparison of **21** and **22**, with MICs of 6.25 and 12.5 μg/mL, respectively, demonstrates this behavior. There is no explanation apparent for this difference between the amide and ester. In the case of the sulfoxides, activity was unaffected by the stereochemistry of the sulfur. Both the *R*- and *S*-enantiomers of **17** and **18** were prepared using the method of Naso.[32] Each enantiomer showed the same level of activity against H37Rv as the racemate.

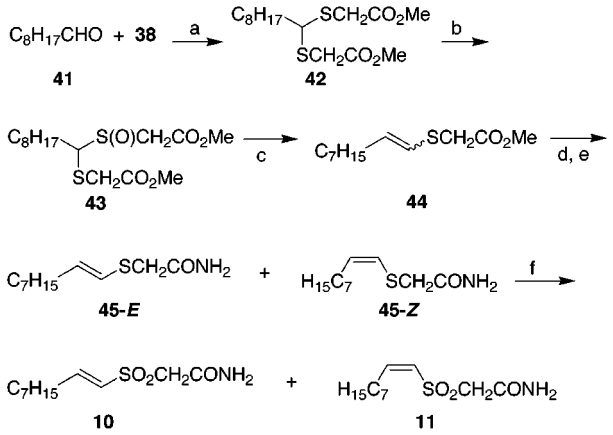
It is not known whether these compounds undergo oxidation to the sulfone under the conditions of the

Scheme 2[a]



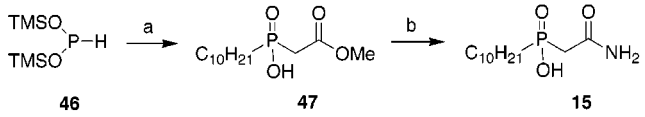
[a] (a) K_2CO_3, DMSO/acetone; (b) *m*-CPBA, CH_2Cl_2; (c) PPh_3, DIAD, CH_3COSH, THF; (d) K_2CO_3, MeOH, $BrCH_2CONH_2$; (e) aq NH_3, MeOH.

Scheme 3[a]



[a] (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2 0 °C; (b) 0.9 equiv *m*-CPBA, CH_2Cl_2; (c) toluene, $NaHCO_3$, 110 °C; (d) aq NH_3, MeOH; (e) PTLC; (f) *m*-CPBA, CH_2Cl_2.

Scheme 4[a]



[a] (a) 1. HMDS, $C_{10}H_{21}I$, THF, 2. HMDS, $BrCH_2CO_2Me$; (b) aq NH_3, *i*-PrOH.

assay. Possibly in keeping with this suggestion, the simple thioether **14** displays low, but measurable, activity against *M. tuberculosis* and may itself be oxidized under the prolonged period of the assay. This proposed background oxidation is supported by the negative control that ether **31** displays extremely low activity. The sharp decrease in activity for both **14** and **31**, and for shorter- and longer-chain sulfones, argues against inhibition of β-oxidation as one possible mechanism of action of the compounds described in this paper. That β-oxidation inhibition is not occurring was also borne out in BACTEC assays of *M. smegmatis*, which were still able to oxidize palmitate to carbon dioxide (data not shown).

The most varied element in the set of compounds studied was side chain length. The vast majority of the compounds have a hydrocarbon tail, although one, **27**, has a glycol tail. This comparatively hydrophilic compound, freely soluble in water, was completely inactive against H37Rv. The most striking structural requirement for these compounds was the length of the side chain. Compounds in Table 1 with a chain length between 8 and 10 carbons were the most active. The difference between a 7-carbon tail (**2**, MIC > 25 μg/mL) and an 8-carbon tail (**3**, MIC = 6.25 μg/mL) was dramatic. A less abrupt loss of activity was observed in the transition from a 10-carbon tail (**5**, MIC = 0.75 μg/mL) to a 12-carbon tail (**6**, MIC = 12.5 μg/mL). However, **7** with a longer, 18-carbon tail was completely inactive against H37Rv.

Regardless of additional substitution, the requirement for an 8−10-carbon side chain appears to hold. Two compounds having alkyl branches (**8**, MIC = 1.5 μg/mL; and **9**, MIC = 6.25 μg/mL) inhibited H37Rv growth. Three compounds have a ω-phenyl substituent (**24**−**26**). While none of these compounds was highly active relative to the compounds lacking a phenyl group, the most active of the three was **26**, having a 10-carbon tail (counting along the phenyl ring).

Two compounds were prepared that have an α,β-unsaturated sulfone, **10** and **11**. Surprisingly, these two isomers (*E* and *Z*, respectively) were approximately equal in their activity against H37Rv. Although an NMR sample of **11** in 1:1 DMSO-d_6:50 mM K_2HPO_4 (pH 8.0) did not show any isomerization in 5 days, the addition of an equivalent of a thiol (**38**) led to loss of the vinyl proton signals from the ^{1}H NMR spectrum within 30 min. This behavior suggests that, in vivo, an addition−elimination reaction by nucleophiles in the cell (such as glutathione, cysteine, etc.) could serve to convert both **10** and **11** to the same equilibrium mixture, which would then display similar MIC values. However, these minimal experiments do not rule out the possibility that both **10** and **11** act as electrophiles and interfere with some vital cell function with equivalent effectiveness.

As the criteria for calculating MIC data using the BACTEC assay system are rigid, compounds with equal MICs may have different activity depending on the conditions of the assay. For this reason, 14 compounds (marked by asterisks, Table 1) were selected and assayed against aliquots of a standard culture of H37Rv at a concentration of 6.25 μg/mL. The results of these assays are shown in Figure 1. With the exception of **20** and **22**, all of these compounds effectively inhibited mycobacterial growth for 10 days. However, for the most active compounds even this assay did not adequately distinguish which was the most active.

To make this distinction, four of the most active compounds were tested against aliquots of a standard H37Rv culture at a concentration of 3.0 μg/mL. The growth curves generated in this assay are shown in Figure 2. Compound **3**, having an 8-carbon tail, was clearly the least active of this group. The activity of **4** fell between **3** and the other two compounds. The two remaining compounds, **5** and **8**, were both highly active against H37Rv, completely inhibiting mycobacterial growth over 5 days.

The compounds marked with an asterisk in Table 1 were also tested against other bacterial strains including *Staphylococcus aureus* (ATCC 29213), *Enterococcus faecalis* (ATCC 29212), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853). None exhibited any activity against these bacteria at concentrations up to 50 μg/mL. In addition, **3** did not show activity against *M. smegmatis* at concentrations as high as 200 μg/mL.

Preliminary studies indicate that **3**, but not cerulenin, is active in the presence of serum.[33] These studies also demonstrated that **21** is a moderate inhibitor of mycobacterial type I FAS and that **3** inhibits the synthesis of mycolic acids. The results of mechanistic and biochemical experiments conducted using the compounds described in this paper will soon be reported elsewhere.[34]

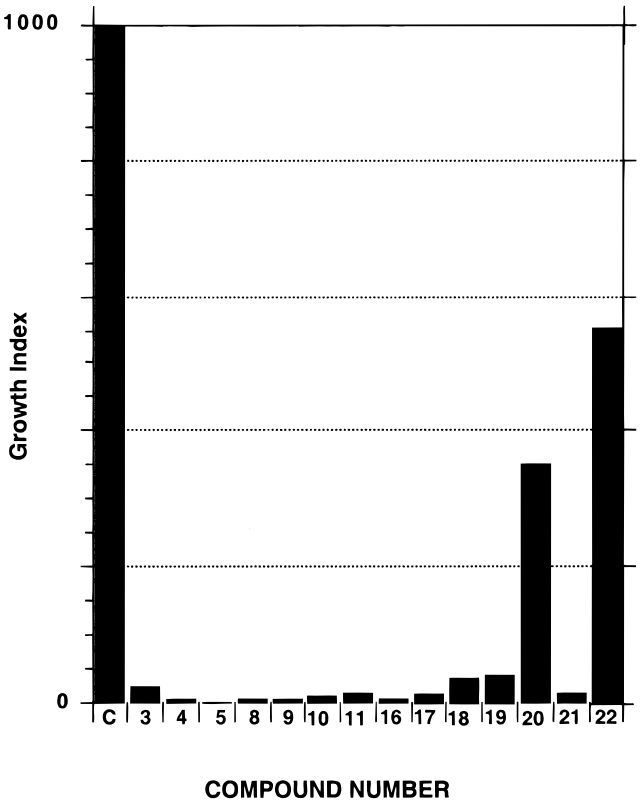


Figure 1. Activity of compounds as numbered in Table 1 at 6.25 μg/mL against *M. tuberculosis* strain H37Rv on day 10 posttreatment. Growth index in BACTEC units. Abbreviation: C, untreated control.

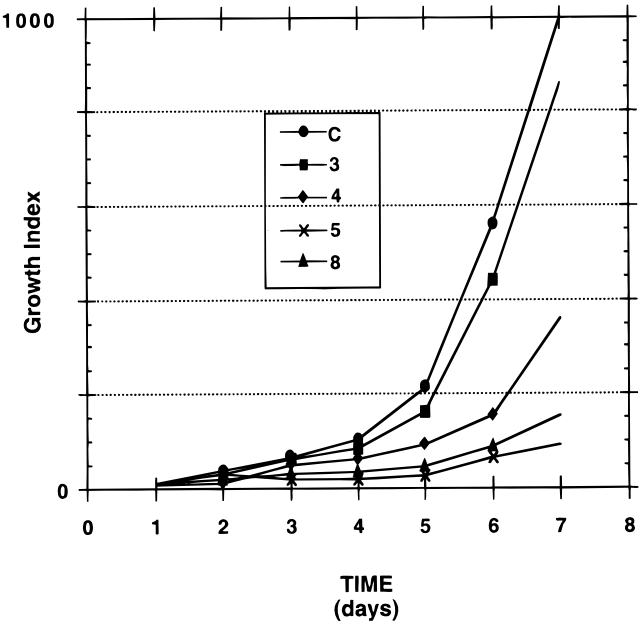


Figure 2. Seven-day BACTEC growth curves of *M. tuberculosis* strain H37Rv in the presence of 3.0 mg/mL of the four most potent compounds listed in Table 1. Abbreviation: C, untreated control.

Conclusion

A new class of readily synthesized compounds with anti-TB activity has been prepared. The most active

members of this group are amide derivatives of 3-sulfonyl fatty acids with an alkyl tail of between 8 and 10 carbons in length. The MICs for these compounds are comparable to those of the first-line anti-TB drugs. The efficacy of these compounds is very sensitive to variations in alkyl tail length, charge and relative position of the sulfone to the amide. Designed to be transition-state mimics of the KAS step of fatty acid biosynthesis, these compounds are highly species-specific, showing no activity against other bacteria including strains of nonpathogenic mycobacteria, such as *M. smegmatis*.

Experimental Section

Melting points are uncorrected. Chemicals for which a synthesis is not reported were purchased commercially. All ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded using a Varian Unity-400 spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C, unless otherwise noted. Infrared spectra were recorded using a Perkin-Elmer 1600 series FTIR and a 0.1 mM NaCl solution cell or KBr disk. Elemental analyses were performed by Atlantic Microlabs (Atlanta, GA).

Representative Alkylation Procedure: 3-Thiononanamide (34a). To a suspension of potassium carbonate (4.00 g, 30 mmol) in acetone/DMSO (30 mL/10 mL) was added bromoacetamide (1.38 g, 10 mmol) followed by hexanethiol (1.4 mL, 1.18 g, 10 mmol). The resulting mixture stirred at ambient temperature for 24 h. The contents were then partitioned between EtOAc (100 mL) and 1 N HCl (200 mL). The aqueous layer was extracted twice more with EtOAc (30 mL each) and the combined organic layers were washed with 1 N HCl (5 × 50 mL), water (2 × 50 mL), brine (1 × 50 mL), and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo to give a white powder that was used without purification: ^{1}H NMR ($CDCl_3$, ppm) 6.77 (bs, 1H), 6.46 (bs, 1H), 3.16 (s, 2H), 2.52 (t, J = 7.2 Hz, 2H), 1.57 (m, 2H), 1.25 (m, 6H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 172.31, 35.76, 33.00, 31.23, 28.97, 28.33, 22.41, 13.91.

3-Thiodecanamide (34b). Bromoacetamide (1.38 g, 10 mmol); heptanethiol (1.53 mL, 1.32 g, 10 mmol): 1.85 g, 9.8 mmol, 98%; mp 73−74 °C; ^{1}H NMR ($CDCl_3$, ppm) 6.79 (bs, 1H), 5.80 (bs, 1H), 3.20 (s, 2H), 2.56 (t, J = 7.2 Hz, 2H), 1.58 (m, 2H), 1.15 (m, 8H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 172.32, 35.76, 33.00, 31.59, 29.02, 28.73, 28.63, 22.49, 13.98. Anal. ($C_9H_{19}NOS$) C, H, N, S.

Methyl 3-Thioundecanoate (34c). Octanethiol (2.50 mL, 14.4 mmol); methyl bromoacetate (1.36 mL, 14.4 mmol): 2.91 g, 13.3 mmol, 93%; ^{1}H NMR ($CDCl_3$, ppm) 3.69 (s, 3H), 3.18 (s, 2H), 2.58 (t, J = 7.4 Hz, 2H), 1.56 (m, 2H), 1.33 (m, 2H), 1.25 (m, 8H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 170.98, 52.24, 38.39, 32.66, 31.71, 29.08, 29.06, 28.90, 28.67, 22.56, 14.00.

3-Thiododecanamide (34d). Bromoacetamide (860 mg, 6.23 mmol); nonanethiol (1.2 mL, 1 g, 6.23 mmol); used without purification: ^{1}H NMR ($CDCl_3$, ppm) 6.78 (bs, 1H), 5.87 (bs, 1H), 3.20 (s, 2H), 2.56 (t, J = 7.2 Hz, 2H), 1.59 (m, 2H), 1.27 (m, 12H), 0.87 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 173.03, 36.91, 34.20, 32.92, 30.53, 30.31, 30.24, 30.20, 29.85, 23.74, 15.19.

Methyl 3-Thiododecanoate (34e). Nonanethiol (15 g, 93.6 mmol); methyl bromoacetate (14.3 g, 93.6 mmol): 20.2 g, 89.4 mmol, 96%; ^{1}H NMR ($CDCl_3$, ppm) 3.72 (s, 3H), 3.21 (s, 2H), 2.61 (t, J = 7.2 Hz, 2H), 1.57 (m, 2H), 1.38 (m, 2H), 1.24 (m, 10H), 0.86 (t, J = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 171.06, 52.33, 33.46, 32.72, 31.84, 29.43, 29.23, 29.16, 28.95, 28.72, 22.64, 14.09.

3-Thiotridecanamide (14). Bromoacetamide (1.66 g, 12 mmol); *n*-decanethiol (1.74 g, 10 mmol); the product was purified by recrystallization from hot hexane/EtOAc: 1.98 g, 9.12 mmol, 91%; mp 80−81 °C; ^{1}H NMR ($CDCl_3$, ppm) 6.76 (bs, 1H), 5.92 (bs, 1H), 3.19 (s, 2H), 2.54 (t, J = 7.5 Hz, 2H), 1.57 (m, 2H), 1.1−1.3 (m, 14H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 171.97, 35.80, 33.10, 31.85, 29.50, 29.46, 29.26, 29.13, 29.08, 28.74, 22.65, 14.09. Anal. ($C_{12}H_{25}NOS$) C, H, N, S.

Methyl 3-Thiotridecanoate (34f). Methyl thioglycolate (2.43 mL, 27.1 mmol); 1-bromodecane (5.0 g, 22.6 mmol); the residue was chromatographed over silica gel (10% EtOAc in hexane) to give a white solid: 5.4 g, 22.1 mmol, 99%; ^{1}H NMR ($CDCl_3$, ppm) 3.71 (s, 3H), 3.20 (s, 2H), 2.60 (t, J = 7.4 Hz, 2H), 1.57 (m, 2H), 1.36 (m, 2H), 1.25 (m, 12H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 171.03, 33.45, 32.72, 31.85, 29.51 (2 signals), 29.46, 29.27, 29.15, 28.94 (2 signals), 22.64, 14.07.

Methyl 3-Thiopentadecanoate (39a). Methyl thioglycolate (1.79 mL, 20.1 mmol); 1-bromododecane (5.0 g, 20.1 mmol); the residue was chromatographed over silica gel (9% EtOAc/hexane) to give a white solid that was used without further purification: 5.0 g, 18.3 mmol, 91%; ^{1}H NMR ($CDCl_3$, ppm) 3.68 (s, 3H), 3.16 (s, 2H), 2.57 (t, J = 7.4 Hz, 2H), 1.53 (m, 2H), 1.22 (m, 18H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 170.88, 52.14, 33.31, 32.60, 31.80, 29.53, 29.51, 29.47, 29.39, 29.23, 29.07, 28.86, 28.63, 22.57, 13.98.

Methyl 3-Thioheneicosanoate (39b). Methyl thioglycolate (1.59 g, 15.0 mmol); 1-bromooctadecane (5.0 g, 15.0 mmol); the residue was chromatographed over silica gel (7.5% EtOAc/hexane) to give a white, waxy solid: 4.85 g, 13.5 mmol, 90%; mp 33−35 °C; ^{1}H NMR ($CDCl_3$, ppm) 3.70 (s, 3H), 3.19 (s, 2H), 2.59 (t, J = 7.4 Hz, 2H), 1.56 (m, 2H), 1.34 (m, 2H), 1.22 (m, 28H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 170.99, 52.25, 33.41, 32.69, 31.88, 29.66 (multiple signals), 29.55, 29.46, 29.32, 29.14, 28.93, 28.70, 22.65, 14.06.

Ethyl 4-Thiotetradecanoate (48). *n*-Decanethiol (2.1 mL, 1.74 g, 10.0 mmol); ethyl 3-bromopropionate (1.3 mL, 1.81 g, 10.0 mmol): 2.56 g (oil), 9.3 mmol, 93%; ^{1}H NMR ($CDCl_3$, ppm) 4.12 (q, J = 7.2 Hz, 2H), 2.73 (t, J = 7.2 Hz, 2H), 2.54 (t, J = 7.4 Hz, 2H), 2.48 (t, J = 7.4 Hz, 2H), 1.52 (m, 2H), 1.28 (m, 17H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 171.91, 60.50, 34.89, 32.08, 31.80, 29.49, 29.47, 29.44, 29.22, 29.14, 28.79, 26.90, 22.59, 14.12, 14.02.

General Thioacetylation Procedure: *S*-Acetyl 5-Phenylpentanethiol (36d). To a solution of triphenylphosphine (5.25 g, 20 mmol) in THF (50 mL) cooled to 0 °C was added a solution of diisopropyl azodicarboxylate (4.17 g, 20 mmol) in THF (15 mL) dropwise. The resulting solution stirred for 30 min during which time a yellow precipitate formed. Thiolacetic acid (1.5 g, 20 mmol), 5-phenylpentanol (1.64 g, 10 mmol) in THF (25 mL) were then added dropwise. The solution became green. After stirring for 30 min at 0 °C, the solution was allowed to warm to ambient temperature over the course of 1 h. The solution was transferred to a separatory funnel and washed with 0.5 M NaOH (2 × 100 mL), water (1 × 100 mL), brine (1 × 100 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was chromatographed over silica (7.5% EtOAc in hexane) to give a yellow oil: 1.84 g, 8.3 mmol, 83%; ^{1}H NMR ($CDCl_3$, ppm) 7.28 (m, 2H), 7.18 (m, 3H), 2.87 (t, J = 7.3 Hz, 2H), 2.61 (t, J = 7.3 Hz, 2H), 2.32 (s, 3H), 1.63 (m, 4H). 1.42 (m, 2H); ^{13}C NMR ($CDCl_3$, ppm) 195.84, 142.34, 128.30, 128.19, 125.60, 35.67, 30.86, 30.55, 29.33, 29.95, 28.34.

***S*-Acetyl 8-Methylnonanethiol (36a).** 8-Methylnonanol[35] (1.24 g, 7.85 mmol); silica chromatography (0−5% EtOAc in hexane) gave the product as a colorless oil: 1.50 g, 6.94 mmol, 88%; ^{1}H NMR ($CDCl_3$, ppm) 2.83 (t, J = 7.5 Hz, 2H), 2.29 (s, 3H), 1.52 (m, 3H), 1.08−1.40 (bm, 10H), 0.83 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, ppm) 195.98, 38.93, 30.58, 29.68, 29.46, 29.11 (2 signals), 28.78, 27.90, 27.26, 22.60.

***S*-Acetyl 3,7-Dimethyloctanethiol (36b).** 3,7-Dimethyloctanol (1.58 g, 10 mmol); the product was isolated by repetitive crystallization of the contaminant triphenylphosphine oxide; a yellow oil was obtained: 875 mg, 4.05 mmol, 41%; ^{1}H NMR ($CDCl_3$, ppm) 2.82 (complex multiplet, 2H), 2.29 (s, 3H), 1.51 (m, 3H), 1.38 (m, 1H), 1.23 (m, 4H), 1.09 (m, 4H), 0.87 (d, J = 6.4 Hz, 3H), 0.84 (m, 6H); ^{13}C NMR ($CDCl_3$, ppm) 195.97, 39.17, 36.78, 36.51, 32.29, 30.58, 27.90, 27.06, 24.56, 22.65, 22.56, 19.21.

***S*-Acetyl 4-Phenylbutanethiol (36c).** 4-Phenylbutanol (1.50 g, 10 mmol); silica chromatography (5−10% EtOAc in hexane) gave the product as a yellow oil: 2.05 g, 9.86 mmol, 99%; ^{1}H NMR ($CDCl_3$, ppm) 7.27 (m, 2H), 7.18 (m, 3H), 2.90 (t, J = 7.4 Hz, 2H), 2.63 (t, J = 7.4 Hz, 2H), 2.32 (s, 3H), 1.65 (m, 4H); ^{13}C NMR ($CDCl_3$, ppm) 195.77, 141.93, 128.28, 128.22, 125.69, 35.27, 30.52, 30.40, 29.02, 28.81.

***S*-Acetyl 6-Phenylhexanethiol (36e).** 6-Phenylhexanol (1.00 g, 5.62 mmol); silica chromatography (2% EtOAc in hexane) gave the product as a yellow oil: 1.02 g, 4.31 mmol, 77%; ^{1}H NMR ($CDCl_3$, ppm) 7.27 (m, 2H), 7.18 (m, 3H), 2.85 (t, J = 7.4 Hz, 2H), 2.60 (t, J = 7.4 Hz, 2H), 2.31 (s, 3H), 1.60 (m, 4H). 1.36 (m, 4H); ^{13}C NMR ($CDCl_3$, ppm) 196.01, 142.60, 128.32, 128.19, 125.56, 35.80, 31.24, 30.59, 29.38, 29.06, 28.70, 28.60.

***S*-Acetyl 3,6-Dioxooctanethiol (36f).** Ethylene glycol ethyl ether (3.35 g, 25 mmol); silica chromatography (30% EtOAc in hexane) gave the product as a yellow oil: 3.52 g, 18.3 mmol, 91%; ^{1}H NMR ($CDCl_3$, ppm) 3.52 (m, 8H), 3.04 (t, J = 6.4 Hz, 2H), 2.29 (s, 3H), 1.16 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 195.45, 72.21, 70.27, 69.67, 66.58, 30.47, 28.70, 15.06.

General in Situ Alkylation Procedure: 8-Methyl-3-thiododecanamide (34g). *S*-Acetyl-8-methylnonanethiol (**36a**) (910 mg, 4.2 mmol) was dissolved in methanol (20 mL) and the solution degassed by bubbling argon for 1 h. Potassium carbonate (2.17 g, 16 mmol) was added in one portion. The suspension stirred for 6 h at ambient temperature. Bromoacetamide (830 mg, 6 mmol) was added in one portion and the resulting mixture stirred for 18 h. The pinkish mixture was partitioned between ethyl acetate and water. The organic layer was washed with 4 × 125 mL water, 1 × 125 mL aqueous NH_4Cl, 1 × 125 mL water, 1 × 125 mL brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a white solid that was used without further purification: ^{1}H NMR (ppm, $CDCl_3$) 6.80 (bs, 1H), 5.53 (bs, 1H), 3.28 (s, 2H), 2.46 (t, J = 7.2 Hz, 2H), 1.2−1.6 (m, 13H), 0.92 (d, J = 7.8 Hz, 6H); ^{13}C NMR (ppm, $CDCl_3$) 171.89, 38.95, 35.79, 33.10, 29.71, 29.16, 29.09, 28.75, 27.93, 27.28, 22.62.

6,10-Dimethyl-3-thioundecanamide (34h). *S*-Acetyl 3,7-dimethyloctanethiol (**36b**) (875 mg, 4.05 mmol); silica chromatography (0−20% EtOH in CH_2Cl_2) afforded a viscous oil: 430 mg, 1.86 mmol, 46%; ^{1}H NMR (ppm, $CDCl_3$) 6.78 (bs, 1H), 6.10 (bs, 1H), 3.19 (s, 2H), 2.55 (m, 2H), 1.0−1.6 (m, 10H), 0.84 (m, 9H); ^{13}C NMR (ppm, $CDCl_3$) 172.09, 39.14, 36.83, 36.22, 35.83, 32.14, 30.95, 27.88, 24.58, 22.65, 22.55, 19.22.

7-Phenyl-3-thioheptamide (34i). *S*-Acetyl 4-phenylbutanethiol (**36c**) (1.08 g, 5.19 mmol); the product was isolated crude and used without further purification: 747 mg, 3.35 mmol, 65%; ^{1}H NMR (ppm, $CDCl_3$) 7.29 (m, 2H), 7.16 (m, 3H), 6.70 (bs, 1H), 6.06 (bs, 1H), 3.17 (s, 2H), 2.59 (m, 4H), 1.67 (m, 4H); ^{13}C NMR (ppm, $CDCl_3$) 171.96, 141.87, 128.32, 128.30, 125.80, 38.91, 35.33, 32.87, 30.37, 28.53.

8-Phenyl-3-thiooctanamide (34j). *S*-Acetyl 5-phenylpentanethiol (**36d**) (588 mg, 2.61 mmol); the product was isolated crude and used without further purification: 427 mg, 1.80 mmol, 69%; ^{1}H NMR (ppm, $CDCl_3$) 7.28 (m, 2H), 7.16 (m, 3H), 6.72 (bs, 1H), 6.30 (bs, 1H), 3.17 (s, 2H), 2.60 (t, J = 7.6 Hz, 2H), 2.54 (t, J = 7.6 Hz, 2H), 1.62 (m, 4H), 1.42 (m, 2H); ^{13}C NMR (ppm, $CDCl_3$) 172.17, 142.25, 128.29, 128.20, 125.63, 38.87, 35.65, 32.87, 30.86, 28.87, 28.24.

9-Phenyl-3-thiononamide (34k). *S*-Acetyl 6-phenylpentanethiol (**36e**) (464 mg, 1.85 mmol); the product was isolated crude and used without further purification: 466 mg, 1.65 mmol, 89%; ^{1}H NMR (ppm, $CDCl_3$) 7.26 (m, 2H), 7.16 (m, 3H), 6.75 (bs, 1H), 6.40 (bs, 1H), 3.18 (s, 2H), 2.59 (t, J = 7.7 Hz, 2H), 2.54 (t, J = 7.3 Hz, 2H), 1.61 (m, 4H), 1.38 (m, 4H); ^{13}C NMR (ppm, $CDCl_3$) 172.24, 142.47, 128.29, 128.16, 125.55, 35.72, 32.91, 29.00, 28.88, 28.64, 28.49, 28.24.

6,9-Oxo-3-thioundecanamide (34l). *S*-Acetyl-3,6-dioxooctanethiol (**36f**) (2.23 g, 11.6 mmol); a clear oil was obtained, which was a hydrate of the desired compound and used without further purification: ^{1}H NMR (ppm, $CDCl_3$) 7.05 (bs, 1H), 5.77 (bs, 1H), 3.72 (t, 2H, J = 7.2 Hz), 3.59 (m, 4H), 3.52 (q, J = 7.4 Hz, 2H), 3.22 (s, 2H), 2.75 (t, J = 7.2 Hz, 2H), 1.17 (t, J = 7.4 Hz, 3H); ^{13}C NMR (ppm, $CDCl_3$) 175.50, 72.02, 71.25, 70.84, 67.58, 36.20, 32.91, 15.42.

Representative Oxidation (Sulfone) Procedure: 3-Sulfonylnonanamide (1). To a solution of 3-thiononamide (**34a**) (1.69 g, 9.6 mmol) in 200 mL dichloromethane was added *m*-CPBA (6.8 g, 40 mmol) slowly at ambient temperature. After stirring for 12 h, the reaction mixture was concentrated in vacuo. The white powdery residue was redissolved in EtOAc (300 mL) and this solution washed with saturated potassium carbonate (5 × 200 mL), water (1 × 100 mL), and brine (1 × 100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give the sulfone as a white solid which was recrystallized from hot hexane to give white flakes: 964 mg, 4.7 mmol, 49%; mp 133−134 °C; ^{1}H NMR (CD_3OD, ppm) 3.96 (s, 2H), 3.28 (t, J = 8.0 Hz, 2H), 1.80 (m, 2H), 1.48 (m, 2H), 1.33 (m, 4H), 0.90 (t, J = 8.2 Hz, 3H); ^{13}C NMR (CD_3OD, ppm) 166.80, 54.42, 49.80, 32.52, 29.26, 23.56, 22.88, 14.45. Anal. ($C_8H_{17}NO_3S$) C, H, N, S.

3-Sulfonyldecanamide (2). 3-Thiodecanamide (**34b**) (500 mg, 2.64 mmol); a white solid was obtained which was recrystallized from 100 mL boiling 3:1 EtOAc:hexane; white needles were obtained: 490 mg, 2.21 mmol, 84%; mp 140−140.5 °C; ^{1}H NMR ($CDCl_3$, ppm) 6.51 (bs, 1H), 5.60 (bs, 1H), 3.86 (s, 2H), 3.14 (t, J = 7.5 Hz, 2H), 1.88 (m, 2H), 1.35 (m, 8H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 162.99, 58.50, 53.38, 31.38, 28.63, 28.25, 22.48, 21.88, 14.00. Anal. ($C_9H_{19}NO_3S$) C, H, N, S.

Methyl 3-Sulfonylundecanoate (20). Methyl 3-thioundecanoate (**34c**) (560 mg, 2.56 mmol): 626 mg (oil), 2.51 mmol, 98%; ^{1}H NMR ($CDCl_3$, ppm) 3.93 (s, 2H), 3.76 (s, 3H), 3.19 (t, J = 8.0 Hz, 2H), 1.80 (m, 2H), 1.41 (m, 2H), 1.25 (m, 8H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 163.46, 56.98, 53.37, 53.18, 31.51, 28.80, 28.73, 28.15, 22.41, 21.65, 13.89. Anal. ($C_{11}H_{22}O_4S$) C, H, S.

3-Sulfonyldodecanamide (4). 3-Thiododecanamide (**34d**) (1.34 g, 6.18 mmol); a fluffy white solid was obtained after recrystallization from hot hexane:EtOAc (150 mL, 2:1): 1.10 g, 4.64 mmol, 75%; mp 145−146 °C; ^{1}H NMR ($CDCl_3$, ppm) 6.50 (bs, 1H), 5.58 (bs, 1H), 3.84 (s, 2H), 3.12 (t, J = 8.0 Hz, 2H), 1.85 (m, 2H), 1.42 (m, 2H), 1.25 (m, 10H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 162.94, 58.49, 53.40, 31.76, 29.17, 29.12, 28.97, 28.30, 22.62, 21.89, 14.08. Anal. ($C_{11}H_{23}NO_3S$) C, H, N, S.

3-Sulfonyltridecanamide (5). 3-Thiotridecanamide **(14)** (6.31 g, 27.3 mmol); a white solid was obtained which was recrystallized from hot EtOAc to give shiny, white crystals: 4.37 g, 16.6 mmol, 61%; mp 141−142 °C; ^{1}H NMR (DMSO-d_6, ppm) 7.70 (bs, 1H), 7.40 (bs, 1H), 3.95 (s, 2H), 3.19 (t, J = 8.0 Hz, 2H), 1.64 (m, 2H), 1.33 (m, 2H), 1.22 (m, 12H), 0.83 (t, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, ppm) 163.84, 57.79, 52.54, 31.33, 28.96, 28.78, 28.72, 28.54, 27.73, 22.13, 21.08, 13.95. Anal. ($C_{12}H_{25}NO_3S$) C, H, N, S.

Methyl 3-Sulfonyltridecanoate (5a). Methyl 3-thiotridecanoate (**34f**) (3.0 g, 12.2 mmol); a brown solid was obtained that was recrystallized from hot hexane/EtOAc to give white, shiny crystals: 2.66 g, 9.54 mmol, 78%; mp 45−47 °C; ^{1}H NMR ($CDCl_3$, ppm) 3.94 (s, 2H), 3.80 (s, 3H), 3.22 (t, J = 8.0 Hz, 2H), 1.82 (m, 2H), 1.42 (m, 2H), 1.25 (m, 12H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 163.55, 57.09, 53.48, 53.27, 31.78, 29.37, 29.17, 28.94 (2 signals), 28.26, 22.59, 21.80, 14.03.

Methyl 3-Sulfonylpentadecanoate (40a). Methyl 3-thiopentadecanoate (**39a**) (4.82 g, 17.6 mmol); a brown solid was obtained and recrystallized from hot hexane to give white, shiny crystals: 3.99 g, 13.1 mmol, 74%; mp 58−60 °C; ^{1}H NMR ($CDCl_3$, ppm) 3.94 (s, 2H), 3.81 (s, 3H), 3.23 (t, J = 8.0 Hz, 2H), 1.84 (m, 2H), 1.44 (m, 2H), 1.23 (m, 16H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 163.58, 57.12, 53.52, 53.32, 31.87, 29.55 (2 signals), 29.45, 29.29, 29.20, 28.98, 28.30, 22.65, 21.85, 14.09.

Methyl 3-Sulfonylheneicosanoate (40b). Methyl 3-thioheneicosanoate (**39b**) (3.0 g, 8.4 mmol); a white solid was obtained: 2.5 g, 6.4 mmol, 76%; mp 71−73 °C; ^{1}H NMR ($CDCl_3$, ppm) 3.94 (s, 2H), 3.81 (s, 3H), 3.23 (t, J = 8.0 Hz, 2H), 1.85

(m, 2H), 1.44 (m, 2H), 1.26 (m, 28H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 163.58, 57.14, 53.53, 31.91, 29.68 (multiple signals), 29.57, 29.47, 29.35, 29.22, 29.00, 28.32, 22.68, 21.87, 14.11.

8-Methyl-3-sulfonyldodecanamide (8). 8-Methyl-3-thiododecanamide (**34g)** (0.960 g, 4.2 mmol); a white solid was obtained which was recrystallized from hot EtOAc:hexane (1:3) to give white crystals: 573 mg, 2.18 mmol, 52%; mp 136−137 °C; ^{1}H NMR (ppm, $CDCl_3$) 6.56 (bs, 1H), 5.68 (bs, 1H), 3.85 (s, 2H), 3.13 (t, J = 8.1 Hz, 2H), 1.84 (m, 2H), 1.2−1.6 (m, 9H), 0.83 (d, J = 6.8 Hz, 6H); ^{13}C NMR (ppm, $CDCl_3$) 163.02, 58.49, 53.38, 38.88, 30.93, 29.46, 29.00, 28.30, 27.91, 27.20, 22.61. Anal. ($C_{12}H_{25}NO_3S$) C, H, N, S.

Ethyl 4-Sulfonyltetradecanoate (51). Ethyl 4-thiotetradecanoate (**48)** (2.56 g, 9.3 mmol); a white solid was obtained and used without further purification: 2.48 g, 8.10 mmol, 87%; ^{1}H NMR ($CDCl_3$, ppm) 4.15 (q, J = 7.2 Hz, 2H), 3.26 (t, J = 7.4 Hz, 2H), 2.95 (t, J = 7.8 Hz, 2H), 2.83 (t, J = 7.4 Hz, 2H), 1.82 (m, 2H), 1.40 (m, 2H), 1.23 (m, 15H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 170.40, 61.39, 53.39, 47.82, 31.75, 29.36, 29.15 (2 signals), 28.94, 28.36, 26.80, 22.56, 21.86, 14.04, 14.01.

6,10-Dimethyl-3-sulfonylundecanamide (9). 6,10-Dimethyl-3-thioundecanamide (**34h)** (430 mg, 1.86 mmol); the product was purified by recrystallization from hot hexane followed by recrystallization from water/MeOH (3:1): 341 mg, 1.3 mmol, 70%; mp 99.5−100 °C; ^{1}H NMR (DMSO-d_6, ppm) 7.73 (bs, 1H), 7.43 (bs, 1H), 3.99 (s, 2H), 3.25 (m, 2H), 1.70 (m, 2H), 1.51 (m, 2H), 1.22 (m, 3H), 1.18 (m, 3H), 0.85 (m, 9H); ^{13}C NMR (DMSO-d_6, ppm) 163.83, 57.71, 50.63, 38.64, 36.07, 31.28, 27.57, 27.37, 23.97, 22.56, 22.48, 19.08. Anal. ($C_{12}H_{25}NO_3S$) C, H, N, S.

7-Phenyl-3-sulfonylheptamide (24). 7-Phenyl-3-thioheptamide (**34i)** (747 mg, 3.35 mmol); the product was purified by recrystallization from hot hexane: 399 mg, 1.56 mmol, 47%; mp 112−113 °C; ^{1}H NMR (ppm, $CDCl_3$) 7.29 (m, 2H), 7.16 (m, 3H), 6.51 (bs, 1H), 5.70 (bs, 1H), 3.85 (s, 2H), 3.17 (t, J = 8.2 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 1.91 (m, 2H), 1.69 (m, 2H); ^{13}C NMR (ppm, $CDCl_3$) 163.05, 141.04, 128.49, 128.34, 126.12, 58.54, 53.18, 35.23, 29.98, 21.49. Anal. ($C_{12}H_{17}NO_3S$) C, H, N, S.

8-Phenyl-3-sulfonyloctanamide (25). 8-Phenyl-3-thiooctamide (**34j)** (160 mg, 0.68 mmol); the product was purified by recrystallization from hot hexane: 92 mg, 0.34 mmol, 50%; mp 134−135 °C; ^{1}H NMR (ppm, $CDCl_3$) 7.28 (m, 2H), 7.18 (m, 3H), 6.52 (bs, 1H), 5.78 (bs, 1H), 3.88 (s, 2H), 3.14 (t, J = 8.2 Hz, 2H), 2.63 (t, J = 7.5 Hz, 2H), 1.90 (m, 2H), 1.67 (m, 2H), 1.49 (m, 2H); ^{13}C NMR (ppm, $CDCl_3$) 163.00, 141.83, 128.36 (2 signals), 125.87, 58.52, 53.23, 35.43, 30.73, 27.82, 21.76. Anal. ($C_{13}H_{19}NO_3S$), C, H, N, S.

9-Phenyl-3-sulfonylnonamide (26). 9-Phenyl-3-thiononamide (**34k)** (170 mg, 0.67 mmol); the product was purified by recrystallization from hot hexane: 116 mg, 0.41 mmol, 61%; mp 116−117 °C; ^{1}H NMR (ppm, $CDCl_3$) 7.26 (m, 2H), 7.14 (m, 3H), 6.52 (bs, 1H), 5.71 (bs, 1H), 3.86 (s, 2H), 3.12 (t, J = 8.1 Hz, 2H), 2.60 (t, J = 7.5 Hz, 2H), 1.87 (m, 2H), 1.62 (m, 2H), 1.49 (m, 2H), 1.44 (m, 2H); ^{13}C NMR (ppm, $CDCl_3$) 166.79, 143.92, 129.56, 129.43, 126.83, 54.38, 49.50, 36.88, 32.53, 29.84, 29.39, 22.90. Anal. ($C_{14}H_{21}NO_3S$), C, H, N, S.

6,9-Oxo-3-sulfonylundecanamide (27). 6,9-Dioxo-3-thioundecanamide (**34l)** (143 mg, 0.69 mmol); the product was purified by flash chromatography (silica gel, 5% MeOH in EtOAc) to give a clear oil: 61 mg, 0.26 mmol, 38%; ^{1}H NMR (ppm, CD_3OD) 4.13 (s, 2H), 3.93 (t, J = 5.0 Hz, 2H), 3.5−3.7 (m, 8H), 1.17 (t, J = 7.0 Hz, 3H); ^{13}C NMR (ppm, CD_3OD) 166.73, 71.48, 70.71, 67.63, 65.91, 61.05, 54.67, 15.61. Anal. ($C_8H_{17}NO_5S$) H, N, S; calcd C, 40.16; found C, 39.38.

Methyl 2-Methyl-3-sulfonyltridecanoate (49). Methyl 3-sulfonyltridecanoate (**5a)** (278 mg, 1.0 mmol) was dissolved in dry methanol (12 mL) and sodium (23 mg, 1 mmol) was added. The solution stirred until homogeneous (approximately one h) and the solution was yellow. Methyl iodide (142 mg, 62 μL, 1 mmol) was added via syringe. After 1 h a precipitate had formed and the color had dissipated. The reaction was allowed to stir at ambient temperature for a further 12 h. The mixture was partitioned between EtOAc (50 mL) and water (50 mL). The aqueous layer was extracted with additional EtOAc (3 × 50 mL). The combined organic layers were washed with water (3 × 50 mL), brine (100 mL), dried over sodium sulfate, and concentrated in vacuo to give a white solid: 231 mg, 0.79 mmol, 79%; ^{1}H NMR ($CDCl_3$, ppm) 3.91 (q, J = 7.0 Hz, 1H), 3.81 (s, 3H), 3.15 (m, 2H), 1.82 (m, 2H), 1.62 (d, J = 7.0 Hz, 3H), 1.41 (m, 2H), 1.21 (m, 12H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 167.23, 62.62, 53.28, 51.08, 31.81, 29.41, 29.20 (2 signals), 29.02, 28.47, 22.62, 21.18, 14.06, 10.57.

General Ammonolysis Procedure: 3-Sulfonylundecanamide (3). Methyl 3-sulfonylundecanoate (**20)** (40 mg, 0.16 mmol) was dissolved in methanol (1 mL) and concentrated aqueous ammonia (0.3 mL) was added causing the reaction to turn yellow. The reaction was stirred at ambient temperature for 18 h during which time an off-white precipitate formed. The mixture was diluted with EtOAc (15 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with additional EtOAc (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to an off-white solid: 22 mg, 0.94 mmol, 59%; mp 140−142 °C; ^{1}H NMR ($CDCl_3$, ppm) 6.56 (bs, 1H), 5.69 (bs, 1H), 3.87 (s, 2H), 3.15 (t, J = 8.0 Hz, 2H), 1.87 (m, 2H), 1.46 (m, 2H), 1.35 (m, 8H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (CD_3-OD, ppm) 166.78, 54.40, 49.60, 33.05, 30.27, 30.10, 29.57, 23.82, 22.90, 14.55. Anal. ($C_{10}H_{21}NO_3S$) C, H, N, S.

3-Sulfonylpentadecanamide (6). Methyl 3-sulfonylpentadecanoate (**40a)** (2.95 g, 9.67 mmol); a white solid was obtained which was recrystallized from hot EtOAc (100 mL) to give shiny, white crystals: 1.74 g, 6.0 mmol, 62%; mp 144−145 °C; ^{1}H NMR (DMSO-d_6, ppm) 7.70 (bs, 1H), 7.40 (bs, 1H), 3.95 (s, 2H), 3.21 (t, J = 8.0 Hz, 2H), 1.66 (m, 2H), 1.32 (m, 2H), 1.21 (m, 16H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, ppm) 163.80, 57.75, 52.47, 31.30, 29.01 (2 signals), 28.96, 28.72 (2 signals), 28.50, 27.69, 22.10, 21.06, 13.96. Anal. ($C_{14}H_{29}NO_3S$) C, H, N, S.

3-Sulfonylheneicosanamide (7). Methyl 3-sulfonylheneicosanoate **(40b)** (350 mg, 0.9 mmol); a white solid was obtained which was recrystallized from hot EtOAc to give shiny, white crystals: 236 mg, 0.63 mmol, 70%; mp 139−140 °C; ^{1}H NMR (DMSO-d_6, ppm) 7.73 (bs, 1H), 7.44 (bs, 1H), 3.98 (s, 2H), 3.26 (t, J = 8.0 Hz, 2H), 1.68 (m, 2H), 1.38 (m, 2H), 1.24 (m, 28H), 0.85 (t, J = 7.2 Hz, 3H). Anal. ($C_{20}H_{41}NO_3S$) C, H, N, S.

3-Sulfenyldodecanamide (17). Methyl 3-sulfenyldodecanoate (**18**) (0.79 g, 2.86 mmol); a white solid was obtained which was recrystallized from a hot hexane/EtOAc mixture: 336 mg, 1.44 mmol, 50%; mp 127−128 °C; ^{1}H NMR ($CDCl_3$, ppm) 6.98 (bs, 1H), 5.72 (bs, 1H), 3.66 (d, J = 14.4 Hz, 1H), 3.25 (d, J = 14.4 Hz, 1H), 2.91 (m, 1H), 2.76 (m, 1H), 1.80 (m, 2H), 1.44 (m, 2H), 1.23 (m, 10H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 166.08, 53.06, 51.49, 31.76, 29.23, 29.13, 29.10, 28.67, 22.87, 22.60, 14.06. Anal. ($C_{11}H_{23}NO_3S$) C, H, N, S.

4-Sulfonyltetradecanamide (13). Ethyl 4-sulfonyltetradecanoate (**51)** (2.4 g, 7.84 mmol); the product was purified by recrystallization from water/MeOH to give a white powder: 1.16 g, 4.23 mmol, 54%; mp 138−139 °C; ^{1}H NMR (DMSO-d_6, ppm) 7.46 (bs, 1H), 6.98 (bs, 1H), 3.22 (t, J = 8.0 Hz, 2H), 3.06 (t, J = 8.0 Hz, 2H), 2.48 (t, J = 8.0 Hz, 2H), 1.62 (m, 2H), 1.80 (m, 2H), 1.33 (m, 2H), 1.22 (m, 10H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 170.89, 51.73, 47.79, 31.29, 28.91, 28.77, 28.67, 28.49, 27.73, 27.17, 22.10, 21.28, 13.96. Anal. ($C_{13}H_{27}NO_3S$) C, H, N, S.

2-Methyl-3-sulfonyltridecanamide (12). Methyl 2-methyl-3-sulfonyltridecanoate (**49)** (225 mg, 0.75 mmol); the product was purified by recrystallization from hot hexane: 161 mg, 0.58 mmol, 77%; mp 115−116 °C; ^{1}H NMR (DMSO-d_6, ppm) 7.71 (bs, 1H), 7.42 (bs, 1H), 3.88 (q, J = 7.0 Hz, 1H), 3.05 (m, 2H), 2.48 (t, J = 8.0 Hz, 2H), 1.62 (m, 2H), 1.38 (d, J = 7.0 Hz, 3H), 1.36 (m, 2H), 1.21 (m, 10H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, ppm) 167.26, 62.72, 48.96, 31.28, 28.90,

28.75, 28.67, 28.53, 27.80, 22.09, 20.33, 13.96, 11.64. Anal. ($C_{13}H_{27}NO_3S$) C, H, N, S.

Representative Oxidation (Sulfoxide) Procedure: Methyl 3-Sulfenylundecanaoate (19). Methyl 3-thioundecanoate (**34c)** (5.37 g, 24.8 mmol) was dissolved in CH_2Cl_2 (150 mL) and cooled to 0 °C in an ice−water bath. *m*-CPBA (3.85 g, 0.9 equiv) was added slowly in several portions. The solution stirred for 45 min and then the reaction was quenched by addition of 0.5 N NaOH (200 mL). The layers were separated and the organic layer was washed once more with 0.5 N NaOH, once with brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The white residue was recrystallized from boiling hexane to give white crystals: 2.76 g, 13.1 mmol, 53%; mp 43−44 °C; ^{1}H NMR (ppm, $CDCl_3$) 3.79 (s, 3H), 3.68 (s, 2H), 3.25 (AB_q, J_{AB} = 15.4 Hz, 2H), 1.79 (m, 2H), 1.46 (m, 2H), 1.2−1.35 (m, 8H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (ppm, $CDCl_3$) 165.54, 55.64, 52.96, 52.85, 31.68, 29.10, 28.96, 28.69, 22.57, 22.36, 14.04. Anal. ($C_{11}H_{22}O_3S$) C, H, S.

Methyl 3-Sulfenyldodecanoate (18). Methyl 3-thiododecanaoate (**34e)** (20.0 g, 88.5 mmol): 11.3 g, 46.7 mmol, 56%; mp 124−125 °C; ^{1}H NMR (ppm, $CDCl_3$) 3.79 (s, 3H), 3.67 (AB_q, J_{AB} = 14.2 Hz, 2H), 2.74 (dt, J = 14.3, 2.8 Hz, 2H), 1.78 (m, 2H), 1.45 (m, 2H), 1.2−1.35 (m, 10H), 0.86 (t, J = 6.7 Hz, 3H); ^{13}C NMR (ppm, $CDCl_3$) 165.57, 55.63, 52.94, 52.81, 31.73, 29.21, 29.10 (2 signals), 28.65, 22.57, 22.32, 14.03. Anal. ($C_{12}H_{24}O_3S$) C, H, S.

3-Sulfenyltridecanamide (16). 3-thiotridecanamide (**14)** (250 mg, 1.1 mmol); the sulfoxide was recrystallized from hot hexane/EtOAc: 197 mg, 0.8 mmol, 80%; mp 127−128 °C; ^{1}H NMR ($CDCl_3$, ppm) 7.60 (bs, 1H), 7.26 (bs, 1H), 3.52 (AB_q, J_{AB} = 13.3 Hz, 2H), 2.76 (m, 2H), 1.61 (m, 2H), 1.38 (m, 2H), 1.24 (m, 12H), 0.83 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 166.33, 57.08, 51.16, 31.30, 28.94, 28.83, 28.70, 28.70, 28.10, 22.11, 21.85, 13.97. Anal. ($C_{12}H_{25}NO_2S$) C, H, N, S.

General Hydrolysis Procedure: 3-Sulfenylundecanoic Acid (50). Methyl 3-sulfenylundecanoate (**19)** (2.02 g, 8.70 mmol) was dissolved in 70 mL MeOH and 0.5 N NaOH(aq) (100 mL) was added. The mixture was stirred at ambient temperature for 2 h, extracted with ether (100 mL), acidified (concentrated aqueous HCl), and extracted with EtOAc (3 × 100 mL). The combined EtOAC extracts were washed with water (5 × 100 mL), brine (1 × 100 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to give the acid as a white solid which was used without further purification: 1.74 g, 7.90 mmol, 91%; ^{1}H NMR ($CDCl_3$, ppm) 9.55 (bs, 1H), 3.62 (ABq, J_{AB} = 14.6 Hz, 2H), 3.05 (m, 1H), 2.85 (m, 1H), 1.78 (m, 2H), 1.46 (m, 2H), 1.2−1.4 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 166.83, 54.40, 51.65, 31.59, 28.98, 28.87, 28.48, 22.47, 22.36, 13.95.

3-Sulfonylundecanoic Acid (23). Methyl 3-sulfonylundecanoate **(20)** (3.75 g, 15 mmol); the acid was recrystallized from hot hexane: 1.78 g, 7.6 mmol, 51%; mp 92−94 °C; ^{1}H NMR ($CDCl_3$, ppm) 9.87 (bs, 1H), 4.01 (s, 2H), 3.27 (t, J = 8.1 Hz, 2H), 1.87 (m, 2H), 1.46 (m, 2H), 1.2−1.4 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 166.93, 56.99, 53.79, 31.64, 28.94, 28.86, 28.27, 22.56, 21.83, 14.04. Anal. ($C_{10}H_{20}SO_4$) C,H,S.

General EDC Coupling Procedure: Benzyl 3-Sulfenylundecaoate (21). To a stirring solution of 3-sulfenylundecanoic acid (**50)** (600 mg, 2.72 mmol) in chloroform (50 mL) were added DMAP (33 mg, 0.27 mmol 10 mol %) and benzyl alcohol (324 mg, 3 mmol). To this solution was added, in several portions, EDC (574 mg, 3 mmol). The solution stirred at ambient temperature for 18 h and then was diluted with EtOAc (250 mL). The mixture was washed 3 × 100 mL saturated aqueous sodium bicarbonate, 3 × 0.5 N aqueous HCl, 2 × 100 mL water, and 1 × 100 mL brine. The organic layer was dried over anhydrous $MgSO_4$ and was concentrated in vacuo. The residue was chromatographed over silica gel (30−100% EtOAc in hexane) to give a white powder that was recrystallized from boiling hexane: 428 mg, 1.38 mmol, 51%; mp 44−45 °C; ^{1}H NMR ($CDCl_3$, ppm) 7.34 (m, 5H), 5.18 (s, 2H), 3.68 (s, 2H), 2.75 (m, 2H), 1.73 (m, 2H), 1.39 (m, 2H), 1.26 (m, 8H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 164.85, 134.71, 128.56, 128.55, 128.41, 67.59, 55.74, 52.78, 31.58, 28.97, 28.86, 28.55, 22.48, 22.19, 13.96. Anal. ($C_{17}H_{26}O_3S$) C, H, S.

Benzyl 3-Sulfonylundecanoate (22). 3-Sulfonylundecanoic acid **(23)** (236 mg, 1.0 mmol): 310 mg, 0.92 mmol, 92%; mp 39−40 °C; ^{1}H NMR ($CDCl_3$, ppm) 7.36 (m, 5H), 5.21 (s, 2H), 3.96 (s, 2H), 3.17 (t, J = 8.1 Hz, 2H), 1.79 (m, 2H), 1.2−1.4 (m, 10H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 162.88, 134.37, 128.77, 128.68, 128.51, 68.23, 57.28, 53.54, 31.61, 28.87, 28.83, 28.23, 22.53, 21.79, 14.01. Anal. ($C_{17}H_{26}O_4S$) C, H, S.

***n*-Decyl Acetoxymethylphosphinic Acid (47).** Dry ammonium phosphinate (ammonium hypophosphonate; 1.64 g, 19.8 mmol) was heated to 100 °C for 20 h under argon with hexamethyldisilazane (4.4 mL, 21 mmol). After cooling in an ice−water bath, dichloromethane (20 mL) was added and the reaction mixture was stirred for 10 min, at which time *n*-decyl iodide (4.2 mL, 19.8 mmol) was added over 10 min and stirring was continued for 2 days at ambient temperature. The reaction was then cooled to 0 °C and additional hexamethyldisilazane (4.4 mL, 19.8 mmol) was added. After 2 h at 0 °C, methyl bromoacetate (1.87 mL, 19.8 mmol) was added slowly over 10 min. The reaction mixture was stirred for 2 h at 0 °C, brought to room temperature and stirred for 2 days. The reaction was quenched by the addition of methanol (2 mL), filtered through Celite and concentrated in vacuo. The residue was purified by silica gel chromatography (2:5:93 formic acid:methanol:acetonitrile) to give a viscous white oil: 1.57 g 5.64 mmol, 29%; ^{1}H NMR ($CDCl_3$, ppm) 10.00 (bs, 1H), 3.74 (s, 3H), 2.96 (d, J = 16.8 Hz, 2H), 1.77 (m, 2H), 1.62 (m, 2H), 1.26 (m, 14H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 167.84, 52.14, 37.13 (d, J = 78.6 Hz), 31.87, 30.82 (d, J = 16.8 Hz), 29.57, 29.46, 29.31, 29.28 (d, J = 98.4 Hz), 29.17, 22.65, 21.68 (d, J = 3.1 Hz), 14.08.

***n*-Decyl Acetoamidophosphonic Acid (15).** Methyl ester **47** (150 mg, 0.54 mmol) was dissolved in a 1:1 solution of 2-propanol and aqueous ammonia (3 mL) and sealed in a pressure tube. After heating overnight at 75 °C, the solution was transferred to a round-bottomed flask and cooled in an ice−water bath. To this solution was added 0.5 N KOH (1.5 mL) and stirred for 2 h. After acidification to pH = 1 with 0.5 N HCl and cooling for 4 h at 4 °C, the precipitated product was collected by vacuum filtration as white crystals: 116 mg, 0.44 mmol, 82%; mp 150−153 °C; ^{1}H NMR (D_2O, ppm) 2.63 (d, J = 16.3 Hz, 2H), 1.55 (m, 4H), 1.26 (m, 14H), 0.81 (t, J = 6.3 Hz, 3H); ^{13}C NMR (D_2O, ppm) 174.56, 40.44 (d, J = 73.2 Hz), 31.33, 30.44 (d, J = 16.0 Hz), 30.10 (d, J = 96.1 Hz), 28.87, 28.75, 28.62, 28.41, 22.19, 21.94 (d, J = 3.8 Hz), 13.56; exact mass m/z 281.2001, $C_{12}H_{26}O_3NP$ requires 281.1994.

Potassium *n*-Decyl Acetoamidophosphonate (15). The amide above was dissolved in 1 mL deionized water and potassium hydroxide (1.0 equiv) was added. After stirring for 30 min, lyophilization yielded the potassium salt in quantitative yield.

3-Oxotridecanamide (31). Sodium hydride (60% in mineral oil, 480 mg, 20 mmol) was suspended in dry DMF (15 mL). Decyl alcohol (5 mL, 26.2 mmol) was added and the mixture stirred at ambient temperature for 30 min as gas evolved. After gas evolution ceased, chloroacetamide (2 g, 21.5 mmol) was added in one portion. The reaction stirred at ambient temperature for 12 h. The reaction mixture was then partitioned between 0.1 N HCl (300 mL) and chloroform (100 mL). The aqueous layer was extracted twice more with chloroform (100 mL each) and the combined organic layers were washed with brine (150 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was dissolved in ether (20 mL) and toluene (20 mL) and cooled to −15 °C. White crystals formed and were collected and dried in vacuo to give the product: 3.96 g, 18.4 mmol, 92%; mp 83−84 °C; ^{1}H NMR ($CDCl_3$, ppm) 6.52 (bs, 1H), 6.04 (bs, 1H), 3.90 (s, 2H), 3.48 (t, J = 7.2 Hz, 2H), 1.56 (m, 2H), 1.22 (m, 14H), 0.83 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 173.03, 71.85, 69.97, 31.84, 29.52, 29.48, 29.36, 29.27, 26.00, 26.64, 22.64, 14.07. Anal. ($C_{12}H_{25}NO_3$) C, H, N.

Nonyl Aldehyde Dimethylacetylthioacetal (42). Nonyl aldehyde (**41**) (0.85 mL, 5 mmol) was dissolved in chloroform (10 mL) and cooled to 0 °C. Boron trifluoride etherate (5.5 mmol) was added and the mixture stirred for 5 min. Methyl thioglycolate (0.9 mL, 10 mmol) was added neat to the yellow solution. The solution stirred for 1 h at 0 °C. The reaction was quenched by addition of ice and partitioned between water and chloroform. The organic layer was washed with 2 × 50 mL aqueous sodium bicarbonate, 2 × 50 mL aqueous ammonium chloride, 2 × 50 mL water, 1 × 50 mL brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give pure thioacetal: 1.48 g, 4.75 mmol, 95%; ^{1}H NMR (ppm, $CDCl_3$) 4.06 (t, J = 6.0 Hz, 1H), 3.68 (s, 6H), 3.35 (AB_q, J_{AB} = 14.6 Hz, 4H), 1.75 (m, 2H), 1.47 (m, 2H), 1.23 (m, 10H), 0.84 (t, 3H, J = 6.6 Hz); ^{13}C NMR (ppm, $CDCl_3$) 170.87, 53.05, 52.46, 35.24, 31.85, 31.82, 29.36, 29.20, 29.00, 27.32, 22.64, 14.09.

Methyl 3-Sulfenyl-3-(carbomethoxythiomethyl)dodecanoate (43). Thioacetal **42** (320 mg, 1.03 mmol) was dissolved in methylene chloride (8 mL) and treated with *m*-CPBA (172 mg, 1 mmol) at ambient temperature. The resulting solution stirred for 18 h. It was then partitioned between aqueous sodium bicarbonate and chloroform. The organic layer was washed 4 × 50 mL aqueous sodium bicarbonate, 1 × 50 mL water, 1 × 50 mL brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed over silica (10−25% MeCN−chloroform) to give the desired product (a mixture of diastereomers) as a colorless oil: 199 mg, 0.62 mmol, 61%; ^{1}H NMR (ppm, $CDCl_3$, mixture of diastereomers with the following signals) 4.14 (dd, J = 3.6, 14.0 Hz, 0.5H), 4.01 (d, J = 14.0 Hz, 0.5H), 3.94 (dd, J = 7.2, 26.0 Hz, 0.5H), 3.85 (bs, 1.5H), 3.78 (s, 2H), 3.77 (s, 1H), 3.72 (s, 1H), 3.71 (s, 2H), 3.55−3.65 (m, 1H), 3.33 (dd, J = 15.6, 18.0 Hz, 1H), 2.20 (m, 0.4H), 1.98 (m, 0.6H), 1.2−1.8 (bm, 13H), 0.82 (t, J = 7.2 Hz, 3H).

(*E,Z*)-Methyl 3-Thiadodec-4-enoate (44). Monosulfoxide **43** (1.15 g, 3.5 mmol) was dissolved in toluene (120 mL) and heated to reflux in the presence of sodium bicarbonate (1.4 g). After 3.5 h, TLC indicated there was no starting material remaining. The solution was washed 3 × 50 mL water, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give an oil. The oil was chromatographed over silica (4% ethyl acetate/hexane) to give the desired olefin (1:1 mixture of geometric isomers) as a clear, colorless oil: 600 mg, 2.61 mmol, 75%; ^{1}H NMR (ppm, $CDCl_3$) 5.94 (m, 1H), 5.58−5.75 (m, 1H), 3.71 (2 singlets, 3H), 3.30 (s, 2H), 2.05 (m, 2H), 1.2−1.5 (m, 10H), 0.84 (t, J = 7.2 Hz, 3H).

(*E,Z*)-3-Thiadodec-4-enamide (45). Methyl ester **44** (600 mg, 3.5 mmol) was dissolved in methanol (12 mL) and ammonium hydroxide (5 mL) was added. The cloudy mixture stirred at ambient temperature for 36 h. The mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted 2 × 40 mL ethyl acetate and the combined organic layers were washed 2 × aqueous sodium bicarbonate, 1 × 50 mL water, 1 × 50 mL brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a yellow-white solid, which was the desired amide (487.4 mg, 2.27 mmol, 65%). The geometric isomers were separated by preparative TLC (4 plates of 200 μm thickness). The plates were eluted in the following manner: 1 × 60% hexane/ether, 2 × 50% hexane/ether, 1 × 40% hexane/ether, 1 × 30% hexane/ether, 2 × 25% hexane/ether. The compound was visualized with UV and the two bands were cleanly separated. The lead band had an R_f under the above eluting conditions of 0.6 while the trailing band had an R_f of 0.45.

(*E*)-3-Thiododec-4-enamide (45*E*). Leading band: ^{1}H NMR (ppm, $CDCl_3$) 6.60 (bs, 1H), 5.96 (bs, 1H), 5.83 (d, J = 15.0 Hz, 1H), 5.71 (dt, J = 6.9, 15.0 Hz, 1H), 3.30 (s, 2H), 2.02 (m, 2H), 1.2−1.4 (m, 10H), 0.83 (t, J = 6.8 Hz, 3H).

(*Z*)-3-Thiododec-4-enamide (45*Z*). Trailing band: ^{1}H NMR (ppm, $CDCl_3$) 6.52 (bs, 1H), 6.04 (bs, 1H), 5.80 (dt, J = 1.2, 9.3 Hz, 1H), 5.71 (dt, J = 7.1, 9.3 Hz, 1H), 3.33 (s, 2H), 2.10 (m, 2H), 1.2−1.4 (m, 10H), 0.83 (t, J = 6.8 Hz, 3H).

(*E*)-3-Sulfonyldodec-4-enamide (10). Amide **45*E*** (154 mg, 0.62 mmol) was dissolved in CH_2Cl_2 (10 mL) and treated with *m*-CPBA (1.8 mmol, 310 mg). The mixture stirred at ambient temperature for 24 h. The solution was diluted with chloroform and washed 3 × 150 mL aqueous sodium bicarbonate, 1 × 50 mL water, 1 × 50 mL brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give the desired sulfone as a white solid: 134 mg, 0.54 mmol, 87%; mp 106−108 °C; ^{1}H NMR (ppm, $CDCl_3$) 6.97 (dt, J = 6.9, 15.1 Hz, 1H), 6.68 (bs, 1H), 6.37 (dt, J = 1.4, 15.1 Hz, 1H), 5.96 (bs, 1H), 3.87 (s, 2H), 2.28 (m, 2H), 1.47 (m, 2H), 1.2−1.4 (m, 8H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (ppm, $CDCl_3$) 162.90, 151.89, 126.76, 60.46, 31.71, 31.61, 28.96, 28.91, 27.44, 22.57, 14.04. Anal. ($C_{11}H_{21}NO_3S$) C, H, N, S.

(*Z*)-3-Sulfonyldodec-4-enamide (11). Amide **45*Z*** (134 mg, 0.54 mmol) was dissolved in CH_2Cl_2 (10 mL) and treated with *m*-CPBA (1.8 mmol, 310 mg). The mixture stirred at ambient temperature for 24 h. The solution was diluted with chloroform and washed 3 × 150 mL aqueous sodium bicarbonate, 1 × 50 mL water, 1 × 50 mL brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give the desired sulfone as a white solid: 121 mg, 0.49 mmol, 91%; mp 99−100 °C; ^{1}H NMR (ppm, $CDCl_3$) 6.58 (bs, 1H), 6.47 (dt, J = 7.1, 10.9 Hz, 1H), 6.26 (dt, J = 1.6, 10.9 Hz, 1H), 5.60 (bs, 1H), 3.88 (s, 2H), 2.63 (qd, J = 1.6, 7.6 Hz, 2H), 1.47 (m, 2H), 1.2−1.4 (m, 8H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR (ppm, $CDCl_3$) 162.85, 151.35, 126.51, 61.25, 31.65, 29.11, 28.94, 28.69, 28.12, 22.57, 14.08. Anal. ($C_{11}H_{21}NO_3S$) C, H, N, S.

***N*-Octanesulfonyl Methanesulfonamide (29).** Sodium hydride (280 mg, 11.7 mmol) was suspended in dry DMF (10 mL). Methanesulfonamide (969 mg, 10.2 mmol, 4 equiv) was added in one portion. Gas evolved and the gray solution turned slightly yellow. After 90 min octanesulfonyl chloride was added via syringe. Heat and gas were again generated. The reaction stirred at ambient temperature for 20 h. The mixture was diluted with water (10 mL) and concentrated HCl (10 drops) was added. The mixture was poured into 1 N HCl and extracted 3 × 50 mL EtOAc. The combined organic layers were washed with 1 N HCl (3 × 50 mL), water (2 × 50 mL), brine (1 × 50 mL), and dried over sodium sulfate. Solvent was removed in vacuo to give a white solid which was recrystallized from 50 mL boiling hexane: yield 570 mg, 2.10 mmol, 82%; mp 80−81 °C; ^{1}H NMR ($CDCl_3$, ppm) 3.42 (t, J = 8.0 Hz, 2H), 3.33 (s, 3H), 1.87 (m, 2H), 1.44 (m, 2H), 1.28 (m, 8H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 55.50, 43.53, 31.65, 28.89 (2 signals), 27.94, 23.15, 22.56, 14.04. Anal. ($C_9H_{21}NO_4S_2$) C, H, N, S.

***N*-Octanesulfonylsulfamide (30).** Sodium hydride (306 mg, 12.8 mmol) was suspended in dry DMF (10 mL). Sulfamide (1.0 g, 10.4 mmol) was added in one portion. Gas evolved as the reaction stirred at ambient temperature under an argon atmosphere. After 45 min gas evolution had ceased and octanesulfonyl chloride (0.5 mL, 2.55 mmol) was added via syringe. Heat and gas were again evolved. After 2.5 h the mixture was diluted with water (15 mL) and then 1 N HCl (20 mL). The mixture was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with 1 N HCl (6 × 50 mL), water (2 × 40 mL), brine (3 × 50 mL), and dried over sodium sulfate. Solvent was removed in vacuo to give a white solid. This solid was recrystallized from 50 mL boiling hexane: EtOAc (25:1) to give white flakes: 480 mg, 1.76 mmol, 69%; mp 121−122 °C; ^{1}H NMR ($CDCl_3$, ppm) 5.40 (bs, 2H), 3.41 (t, J = 8.0 Hz, 2H), 1.86 (m, 2H), 1.45 (m, 2H), 1.28 (m, 8H), 0.88 (t, J = 8.0 Hz, 3H); ^{13}C NMR (CD_3OD, ppm) 54.45, 32.84, 30.06, 30.03, 29.04, 24.32, 23.62, 14.39. Anal. ($C_8H_{20}N_2O_4S_2$) C, H, N, S.

Susceptibility Testing. Susceptibility testing and MIC determination for *M. tuberculosis* (H37Rv) were carried out at least in duplicate using the standard BACTEC radiometric growth system (Becton Dickinson, Sparks, MD). Initial stock solutions (1 mg/mL) and subsequent dilutions of test compounds were prepared in DMSO (Sigma). Stock concentrations (0.1 mL) were then added to individual 4.0-mL BACTEC bottles resulting in the following final concentrations (μg/mL): 50, 25, 12.5, 6.25, 3.0, 1.5. A 1.0 McFarland suspension of *M. tuberculosis* (H37Rv) was prepared and 0.1 mL was

added to each of the following bottles: a direct control (bottle containing diluent, DMSO, but no test compound), a control containing a 1:100 organism dilution (also without test compound), and each concentration with the test compound. All bottles were incubated at 37 °C, and the growth index (GI) of each bottle was recorded daily until the GI of the 1:100 control reached 30. The MIC of each isolate was determined using the following criterion: once the GI of the 1:100 control bottle had reached 30, the GI change (Δ) was calculated for a 1-day period at each concentration tested. The MIC was defined as the lowest inhibitor concentration that yielded a growth index change less than that of the 1:100 control bottle.

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Supporting Information Available: Elemental analyses for compounds **1**−**31** and **34b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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