Inhibitors of Acyl-CoA:Cholesterol *O*-Acyltransferase. 17. Structure−Activity Relationships of Several Series of Compounds Derived from *N*-Chlorosulfonyl Isocyanate[1]

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Received December 27, 1995[⊗]

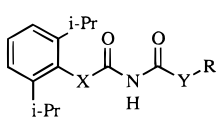
Several series of acyl-CoA:cholesterol *O*-acyltransferase inhibitors were prepared by the stepwise addition of nitrogen, oxygen, and sulfur nucleophiles to *N*-chlorosulfonyl isocyanate. The (aminosulfonyl)ureas **3**−**44** were the most potent inhibitors in vitro, with several compounds having IC_{50} values < 1 μM. Although the other series of compounds were not as potent in vitro, many compounds did display good in vivo activity in cholesterol-fed rats. Several of the oxysulfonyl carbamates (including CI-999, **115**) showed excellent lipid-lowering activity in the chronic in vivo screen, demonstrating significant cholesterol lowering in a pre-established hypercholesterolemic state.

Introduction

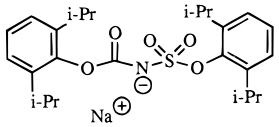
The possibility that an acyl-CoA:cholesterol *O*-acyltransferase (ACAT) inhibitor may significantly regulate lipid levels in hypercholesterolemic animals has resulted in extensive drug discovery efforts to identify a clinically effective ACAT inhibitor.[2] Early work in this area concentrated on identifying inhibitors of the intestinal enzyme. Such inhibitors were designed to mimic fatty acyl-CoA, the natural substrate of ACAT, and prevent the absorption of dietary cholesterol.

However, with the recent failure of a number of lipophilic inhibitors in the clinic[3] (designed to inhibit cholesterol absorption), the focus has switched from inhibition of intestinal ACAT to inhibition of ACAT in the liver and at the arterial wall. It has been proposed that inhibition of ACAT in the liver would decrease apoB secretion from the liver and also decrease the cholesteryl ester content (and therefore the atherogenicity) of plasma low-density lipoproteins (LDL).[4] Additionally, ACAT inhibition in the macrophages of the artery wall is predicted to be beneficial by preventing foam cell and fatty streak formation in the developing atheroma.[4a] Inhibition at these peripheral sites requires compounds that are well absorbed, as opposed to the intestinal ACAT inhibitors which in general were lipophilic and poorly absorbed. Lipophilicity and ionization potential are two important factors that contribute to the disposition of a drug after oral dosing.[5] Our most recent approach has been to functionalize some of our lipophilic inhibitors to alter these physical properties, thereby altering their ability to reach the peripheral sites of interest.

In a recent report on a series of *N*-carbonyl-functionalized ureas, carbamates, and thiocarbamates (**1**), we indicated the possibility that the acidic proton on the central nitrogen atom is important for in vivo activity.[6] We have also recently reported a communication describing the design and synthesis of the first water soluble ACAT inhibitor, CI-999, in which a base addition salt is formed at a central acidic site.[7]



1 X,Y = O, NH, S



CI-999

In this paper we present the full structure−activity relationship (SAR) leading up to the identification of the novel lipid regulator CI-999 (**115**) and several related series in which we continue to elaborate the structural motif (nitrogen substituted with carbonyl and sulfonyl) previously identified.[7,8]

Chemistry

N-Chlorosulfonyl isocyanate (**2**, CSI) is a very reactive and versatile reagent whose applications have been extensively reviewed.[9] For our purposes, it provided a convenient route to a variety of (oxy- or aminosulfonyl)-ureas and -carbamates (Scheme 1). Reaction of an oxygen or nitrogen nucleophile (**I**) at the isocyanate moiety of CSI in an inert solvent (e.g., diethyl ether) at 0 °C gave a stable (chlorosulfonyl)carbamate or -urea intermediate (**II**) in >90% yields. Reaction of **II** with a second oxygen or nitrogen nucleophile in the presence of an acid-scavenging base (e.g., triethylamine) afforded four distinct series of compounds: (aminosulfonyl)ureas (Table 1), (oxysulfonyl)ureas (Table 2), (aminosulfonyl)-carbamates (Table 3), and (oxysulfonyl)carbamates (Tables 4 and 5).

Some of the compounds in the oxysulfonyl series (Tables 2, 4, and 5) could be synthesized by an alternate route (Scheme 2) via an oxysulfonyl isocyanate. It has been reported that the intermediate (chlorosulfonyl)-carbamate **IIb**, formed when some phenols react with CSI at room temperature, will rearrange at elevated temperatures (>100 °C) to give an oxysulfonyl isocyanate (**III**).[10] This highly reactive intermediate may then be combined with nitrogen nucleophiles to give the (oxysulfonyl)ureas, oxygen nucleophiles to give the (oxysulfonyl)carbamates, or sulfur nucleophiles to give the (oxysulfonyl)carbamothioates. Additionally, compounds in which the same nucleophile is added to both sides of CSI can easily be synthesized in one step, using 2 equiv of the requisite nucleophile.

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⊗ Abstract published in *Advance ACS Abstracts,* March 1, 1996.

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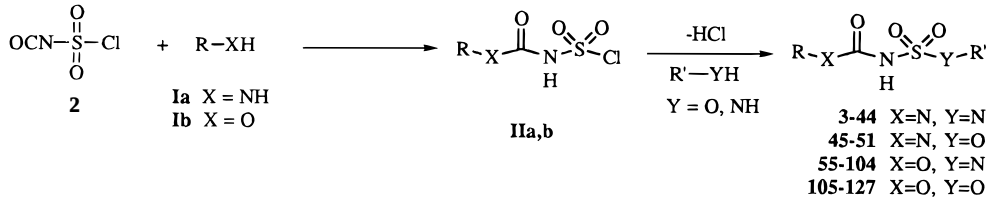
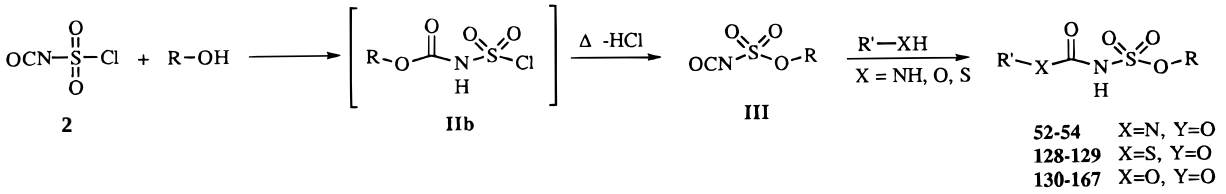
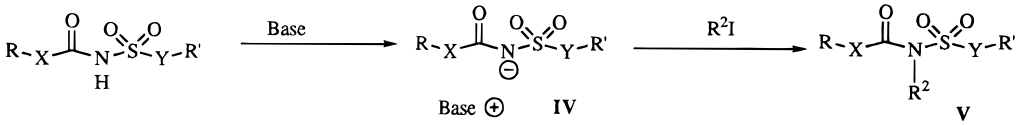
Scheme 1. Stepwise Addition of Nucleophiles to CSI



Scheme 2. Alternate Route to Oxysulfonyl Compounds



Scheme 3. Functionalization of the Central Nitrogen Atom



Members of these series possess an acidic proton on the nitrogen atom situated between the carbonyl and sulfonyl groups. The acidic nature of this proton allows the formation of base addition salts (**IV**) or treatment of the anion with alkylating agents to give N-alkylated products (**V**; Scheme 3).

Biology

The in vitro ACAT inhibitory activity was determined by measuring the incorporation of [1-^{14}C]oleoyl-CoA into cholesterol esters in microsomes isolated from rat liver. Results are reported as the micromolar concentration of drug required to inhibit the enzymatic activity by 50% (IC_{50}).[11] The in vivo hypocholesterolemic activity was measured in an acute, cholesterol-fed rat model. This acute screen measures the ability of a single dose of drug to prevent the rise in plasma cholesterol induced by a single cholesterol-rich meal (5.5% peanut oil, 1.5% cholesterol, and 0.5% cholic acid). The drugs were administered by gavage at a dose of 30 or 3 mg/kg, and the animals (n = 5/group/cage) were then fed the test diet overnight. Plasma cholesterol levels were measured by standard enzymatic methods, and the results are expressed as the percent change from the levels observed in control animals given vehicle (CMC/Tween in water) and diet only.[11]

Compounds which showed good potency in the acute in vivo screen were tested in a chronic screen which measured the drugs ability to affect a pre-established hypercholesterolemic state (Table 6). In the chronic screen, rats were fed the cholesterol-rich diet, described above, for 1 week to elevate plasma cholesterol levels. The 30 mg/kg dose of drug was then given daily by gavage for a second week while continuing the cholesterol-rich diet. Total plasma cholesterol (TC) levels were measured, and the concentration of plasma high-density lipoproteins (HDL) was calculated. The results were compared to control animals given only vehicle and the cholesterol-rich diet for 2 weeks.[11]

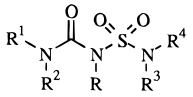
Results and Discussion

In several previous series of ACAT inhibitors developed in our laboratories, we demonstrated that the 2,6-diisopropylphenyl group imparts good ACAT inhibitory activity to a variety of amides, ureas, and carbamates.[2b] In order to identify potent ACAT inhibitors in the compounds of the present work, we incorporated the 2,6-diisopropylphenyl group into each of the series of compounds examined.

Table 1 shows a series of (aminosulfonyl)ureas (X = N, Y = N) with in vitro potencies between 0.1 and 69 μM. The most potent compounds (IC_{50} < 1.0 μM) were those which contained the (2,6-diisopropylphenyl)urea in combination with an (*N*,*N*-dialkylamino)sulfonyl group (e.g., **14**−**16**, **18**−**20**, and **22**−**26**). Compounds in which the *N*,*N*-dialkylamino group contains six carbon atoms or less (**3**−**13**) are less potent than the longer chain analogues. In addition, in vitro potency decreased when the number of carbons in the *N*,*N*-dialkylamino group exceeded 15 (**30**−**33**). The exceptions to these trends are compound **21** (with an *N*-methyl, *N*-octyl substitution pattern), which falls within the optimal rnage of carbon atoms but is about 10-fold less potent than other compounds within the range, and compound **32** (with a *N*,*N*-didecylamino group), which displayed an unexpected potency of 0.72 μM despite having a total of 20 carbon atoms in its *N*,*N*-dialkylamino group. Branching of the alkyl groups (especially α to the nitrogen atom) resulted in increased in vitro potency, as seen by comparing **14** and **20** to their *n*-alkyl isomers **10** and **16**.

Aminosulfonyl compounds with aryl or aryl-substituted alkyl substituents (**34**−**42**) were not very potent in vitro. Compound **41** however, which possessed a benzyl moiety as one of the groups on the aminosulfonyl and an isopropyl as the other group, did display good potency in vitro (0.40 μM), presumably due to the branched alkyl group. Compounds **43** and **44** (where the 2,6-diisopropylphenyl group is incorporated into the aminosulfonyl side of the molecule) are 7-fold less potent in vitro, compared to the corresponding (2,6-diisopropylphenyl)urea isomers **39** and **35**. The importance of the ionizable proton on the central nitrogen of these molecules is indicated by compounds **17** and **18**. The central nitrogen of compound **16** was methylated to give compound **17**, which abolished the in vitro and in vivo

Table 1. (Aminosulfonyl)ureas



compd	R	R^1	R^2	R^3	R^4	in vitro IC_{50} (μM)[b]	acute in vivo (% ΔTC) 30 mg/kg	acute in vivo (% ΔTC) 3 mg/kg	formula[d]	mp (°C)
3	H	2,6-(*i*-Pr)$_2$Rh	H	Me	Me	3.9	NT	NT	$C_{15}H_{25}N_3O_3S$	144−147
4	H	2,6-(*i*-Pr)$_2$Ph	H	H	*i*-Pr	18	−17	NT	$C_{16}H_{27}N_3O_3S$	177−179
5	H	2,6-(*i*-Pr)$_2$Ph	H	Et	Et	2.5	−19*	NT	$C_{17}H_{29}N_3O_3S$	139−142
6	H	2,6-(*i*-Pr)$_2$Ph	H	−(CH$_2$)$_4$−		15	−49***	NT	$C_{17}H_{27}N_3O_3S$	153−155
7	H	2,6-(*i*-Pr)$_2$Ph	H	Me	*n*-Bu	2.3	−56****	−37**	$C_{18}H_{31}N_3O_3S$	109−110
8	H	2,6-(*i*-Pr)$_2$Ph	H	Et	allyl	2.1	−48***	NT	$C_{18}H_{29}N_3O_3S$[e]	124−128
9	H	2,6-(*i*-Pr)$_2$Ph	H	allyl	allyl	2.7	−67****	2	$C_{19}H_{29}N_3O_3S$	142−145
10	H	2,6-(*i*-Pr)$_2$Ph	H	*n*-Pr	*n*-Pr	1.1	−60****	−51***	$C_{19}H_{33}N_3O_3S$	119−121
11	H	2,6-(*i*-Pr)$_2$Ph	H	Et	*n*-Bu	1.2	−70****	−29*	$C_{19}H_{33}N_3O_3S$[f]	101−104
12	H	2,6-(*i*-Pr)$_2$Ph	H	H	*n*-hexyl	8.1	−19*	NT	$C_{19}H_{33}N_3O_3S$	161−162.5
13	H	2,6-(*i*-Pr)$_2$Ph	H	−(CH$_2$)$_5$−		17	−13	NT	$C_{18}H_{29}N_3O_3S$	159−161
14	H	2,6-(*i*-Pr)$_2$Ph	H	*i*-Pr	*i*-Pr	0.24	−59[c] ****	NT	$C_{19}H_{33}N_3O_3S$	151−153
15	H	2,6-(*i*-Pr)$_2$Ph	H	*i*-Pr	*t*-Bu	0.14	−17****	−55****	$C_{20}H_{35}N_3O_3S$	146−147
16	H	2,6-(*i*-Pr)$_2$Ph	H	*n*-Bu	*n*-Bu	0.36	−66[c] ****	−52***	$C_{21}H_{37}N_3O_3S$	98−101
17	Me	2,6-(*i*-Pr)$_2$Ph	H	*n*-Bu	*n*-Bu	>5.0	−8	NT	$C_{22}H_{39}N_3O_3S$[g]	oil
18	Na^+	2,6-(*i*-Pr)$_2$Ph	H	*n*-Bu	*n*-Bu	0.53	−68****	−64****	$C_{21}H_{36}NaN_3O_3S$[h]	217−219
19	H	2,6-(*i*-Pr)$_2$Ph	H	*i*-Bu	*i*-Bu	0.42	−75****	−61****	$C_{21}H_{37}N_3O_3S$	122−125
20	H	2,6-(*i*-Pr)$_2$Ph	H	*s*-Bu	*s*-Bu	0.10	−71****	−65****	$C_{21}H_{37}N_3O_3S$	144−146
21	H	2,6-(*i*-Pr)$_2$Ph	H	Me	*n*-octyl	3.8	−59***	−57****	$C_{22}H_{39}N_3O_3S$	oil
22	H	2,6-(*i*-Pr)$_2$Ph	H	*i*-Pr	cyclohexyl	0.36	−68****	−60****	$C_{22}H_{37}N_3O_3S$	162−164
23	H	2,6-(*i*-Pr)$_2$Ph	H	*n*-pentyl	*n*-pentyl	0.42	−76****	−68****	$C_{23}H_{41}N_3O_3S$	93−95
24	H	2,6-(*i*-Pr)$_2$Ph	H	*i*-pentyl	*i*-pentyl	0.42	−60****	−66****	$C_{23}H_{41}N_3O_3S$	106−110
25	H	2,6-(*i*-Pr)$_2$Ph	H	*n*-hexyl	*n*-hexyl	0.51	−77****	−63****	$C_{25}H_{45}N_3O_3S$	70−73
26	H	2,6-(*i*-Pr)$_2$Ph	H	cyclohexyl	cyclohexyl	0.23	−64****	−60****	$C_{25}H_{41}N_3O_3S$	163−165
27	H	2,6-(*i*-Pr)$_2$Ph	H	CH$_2$-2-THF[a]	CH$_2$-2-THF[a]	1.7	−53***	−45***	$C_{23}H_{37}N_3O_3S$	oil
28	H	2,6-(*i*-Pr)$_2$Ph	H	(CH$_2$)$_3$N(Me)$_2$	(CH$_2$)$_3$N(Me)$_2$	55	−30**	NT	$C_{23}H_{43}N_5O_3S$	oil
29	H	2,6-(*i*-Pr)$_2$Ph	H	Me	*n*-tetradecyl	0.33	−65****	−65****	$C_{28}H_{51}N_3O_3S$	49−52
30	H	2,6-(*i*-Pr)$_2$Ph	H	*n*-octyl	*n*-octyl	1.9	−53****	−38**	$C_{29}H_{53}N_3O_3S$	70−72
31	H	2,6-(*i*-Pr)$_2$Ph	H	Me	*n*-octadecyl	1.9	−60***	−18	$C_{32}H_{59}N_3O_3S$	59−59
32	H	2,6-(*i*-Pr)$_2$Ph	H	*n*-decyl	*n*-decyl	0.72	−57****	−17	$C_{33}H_{61}Ni_3O_3Si$[i]	35−37
33	H	2,6-(*i*-Pr)$_2$Ph	H	*n*-dodecyl	*n*-dodecyl	69	5	NT	$C_{37}H_{69}N_3O_3S$	oil
34	H	2,6-(*i*-Pr)$_2$Ph	H	H	2,6-(*i*-Pr)$_2$Ph	11	−54[c] ****	NT	$C_{25}H_{37}N_3O_3S$	169−172
35	H	2,6-(*i*-Pr)$_2$Ph	H	H	benzhydryl	4.1	−14[c]	NT	$C_{26}H_{30}N_3O_3S$	182−185
36	H	2,6-(*i*-Pr)$_2$Ph	H	H	9-fluorene	25	−4[c]	NT	$C_{26}H_{28}N_3O_3S$	224−227
37	H	2,6-(*i*-Pr)$_2$Ph	H	H	CH$_2$CH(Ph)$_2$	5.9	−20[c] *	NT	$C_{27}H_{32}N_3O_3S$	190−191
38	H	2,6-(*i*-Pr)$_2$Ph	H	Ph	Ph	16	−37**	−27***	$C_{25}H_{29}N_3O_3S$	169−170
39	H	2,6-(*i*-Pr)$_2$Ph	H	CH$_2$Ph	CH$_2$Ph	2.2	−36**	−18*	$C_{27}H_{33}N_3O_3S$	123−126
40	H	2,6-(*i*-Pr)$_2$Ph	H	Me	(CH$_2$)$_2$Ph	1.7	−71****	−38*	$C_{22}H_{31}N_3O_3S$	128−133
41	H	2,6-(*i*-Pr)$_2$Ph	H	*i*-Pr	CH$_2$Ph	0.40	−60[c] ****	NT	$C_{23}H_{33}N_3O_3S$	142−144
42	H	2,6-(*i*-Pr)$_2$Ph	H	4-Ph-piperidine		10.4	−67****	−17	$C_{24}H_{34}N_3O_3S$	154−159
43	H	CH$_2$Ph	CH$_2$Ph	H	2,6-(*i*-Pr)$_2$Ph	16	−44**	NT	$C_{27}H_{33}N_3O_3S$	140−142
44	H	H	benzhydryl	H	2,6-(*i*-Pr)$_2$Ph	30	NT	−5	$C_{26}H_{30}N_3O_3S$	92−95

[a] THF = tetrahydrofuryl. [b] In vitro ACAT Inhibition determined in rat liver microsomes. [c] Dosed at 50 mg/kg. [d] C,H,N analysis within 0.4% unless otherwise noted. [e] C: calcd, 58.83; found, 59.50. [f] C: calcd, 62.08; found, 62.75. [g] C: calcd, 59.50; found, 59.95. [h] N: calcd, 9.69; found, 8.74. [i] C: calcd, 59.50; found, 59.95. *Significantly different from control using the unpaired, two-tailed *t*-test: $p < 0.1$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$. NT = not tested.

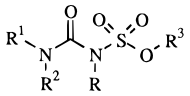
activity. Conversely, ionization of the proton of this central nitrogen, as in the sodium salt **18**, retained in vitro potency and in vivo efficacy.

Several compounds in this series were very efficacious in the acute in vivo screen, with changes in total plasma cholesterol up to −77% when dosed at 30 mg/kg. An examination of these compounds at lower doses established the superiority of several examples. The (*N*,*N*-dialkylamino)sulfonyl compounds (i.e., **15** and **18**−**26**), which were the most potent compounds in vitro, also demonstrated the best potency in vivo, with changes in total cholesterol ranging from −55% to −68% when dosed at 3 mg/kg in the acute screen. Several of these potent (*N*,*N*-dialkylamino)sulfonyl compounds (**19**, **20**, and **22**−**25**) were also effective in the chronic in vivo screen, with 62−69% decreases in total cholesterol, coupled with 86−207% increases in HDL cholesterol (Table 6).

Replacing the aminosulfonyl group with an oxysulfonyl gave the series of (oxysulfonyl)ureas **45**−**54** shown in Table 2. Although the (2,6-diisopropylphenyl)urea functionality was maintained, the most potent compounds in this series were 1 order of magnitude less potent in vitro than the (aminosulfonyl)ureas discussed above. Surprisingly, some of the compounds in this series possessed good in vivo efficacy despite having IC_{50} values in the micromolar range. The (2,6-diisopropylphenyl)urea, in combination with a long chain alkoxysulfonyl group, gave maximum in vitro and in vivo potency with a chain length of 12 carbon atoms (**49**). Compound **50** demonstrated that the generation of the base addition salt at the acidic central nitrogen had no adverse effect on the biological profile in this series. Incorporating an (aryloxy)sulfonyl group with the (2,6-diisopropylphenyl)urea moiety also gave efficacious compounds (**52** and **53**). Incorporation of the 2,6-diisopropylphenyl group into the oxysulfonyl portion of the molecule and the alkyl group into the urea half (**54**) resulted in a much less efficacious compound in vivo.

Like the (aminosulfonyl)urea compounds (Table 1), the (*N*,*N*-dialkylamino)sulfonyl substitution pattern also gave the most potent compounds in the (aminosulfonyl)-carbamate series (Table 3). However, the (aminosulfonyl)carbamates were typically 1 order of magnitude less potent than the corresponding urea compounds. The in vitro potency of the (*N*,*N*-dialkylamino)sulfonyl com-

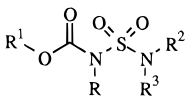
Table 2. (Oxysulfonyl)ureas



compd	R	R^1	R^2	R^3	in vitro IC_{50} (μM)[a]	acute in vivo (% Δ TC) 30 mg/kg	acute in vivo (% Δ TC) 3 mg/kg	formula[b]	mp (°C)
45	H	2,6-(*i*-Pr)$_2$Ph	H	*n*-hexyl	27	−56***	−8	$C_{19}H_{32}N_2O_4S$	148−151
46	H	2,6-(*i*-Pr)$_2$Ph	H	2-octyl	35	−51**	+10	$C_{21}H_{36}N_2O_4S$	109−113
47	H	2,6-(*i*-Pr)$_2$Ph	H	*n*-decyl	>10	−31*	NT	$C_{23}H_{40}N_2O_4S$	133−135
48	H	2,6-(*i*-Pr)$_2$Ph	H	2-dodecyl	16	−68***	−48***	$C_{25}H_{44}N_2O_4S$	110−112
49	H	2,6-(*i*-Pr)$_2$Ph	H	*n*-dodecyl	6.8	−75****	−53****	$C_{25}H_{44}N_2O_4S$	112−115
50	Na^+	2,6-(*i*-Pr)$_2$Ph	H	*n*-dodecyl	5	−60****	−34****	$C_{25}H_{43}N_2O_4SNa$	foam
51	H	2,6-(*i*-Pr)$_2$Ph	H	*n*-octadecyl	14	−42**	−5	$C_{31}H_{56}N_2O_4S$	95−98
52	H	2,5-(*i*-Pr)$_2$Ph	H	2,6-(*i*-Pr)$_2$Ph	8.7	−43*	−1	$C_{25}H_{36}N_2O_4S$	186−189
53	H	2,4,6-(*i*-Pr)$_3$Ph	H	2,6-(*i*-Pr)$_2$Ph	23	−68****	−51***	$C_{28}H_{42}N_2O_4S$	202−203
54	H	*s*-Bu	*s*-Bu	2,6-(*i*-Pr)$_2$Ph	12	−20	NT	$C_{21}H_{36}N_2O_4S$[c]	oil

[a] In vitro ACAT inhibition determined in rat liver microsomes. [b] C, H, N analysis within 0.4% unless otherwise noted. [c] C: calcd, 61.13; found, 60.57. *Significantly different from control using the unpaired, two-tailed, *t*-test: $p < 0.1$, **$p < 0.01$, *** $p < 0.001$, and ****$p < 0.001$. NT = not tested.

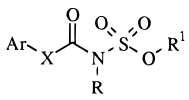
Table 3. (Aminosulfonyl)carbamates



compd	R	R^1	R^2	R^3	in vitro IC_{50} (μM)[b]	acute in vivo (% Δ TC) 30 mg/kg	acute in vivo (% Δ TC) 3 mg/kg	formula[d]	mp (°C)
55	H	2,6-(*i*-Pr)$_2$Ph	−(CH$_2$)$_4$−		53	−53***	−4	$C_{17}H_{26}N_2O_4S$	89−91
56	H	2,6-(*i*-Pr)$_2$Ph	−(CH$_2$)$_5$−		>100	−11	NT	$C_{18}H_{28}N_2O_4S\cdot 0.5H_2O$[e]	86−88
57	H	2,6-(*i*-Pr)$_2$Ph	−(CH$_2$)$_2$O(CH$_2$)$_2$−		>100	−14	NT	$C_{17}H_{26}N_2O_5S$	185−187
58	H	2,6-(*i*-Pr0$_2$Ph	N-Me-piperazine·HCl		>100	−21*	NT	$C_{18}H_{29}N_3O_4S\cdot HCl$[f]	179 dec
59	H	2,6-(*i*-Pr)$_2$Ph	indoline		43	−77****	−31**	$C_{21}H_{26}N_2O_4S$	127−128
60	H	2,6-(*i*-Pr)$_2$Ph	*i*-Pr	*i*-Pr	15	−76****	−65****	$C_{19}H_{32}N_2O_4S$	126−131
61	H	2,6-(*i*-Pr)$_2$Ph	H	*n*-hexyl	21	−58****	−12	$C_{19}H_{32}N_2O_4S$	105−106.5
62	H	2,6-(*i*-Pr)$_2$Ph	*n*-Bu	*n*-Bu	1.9	−57****	−47****	$C_{21}H_{36}N_2O_4S$	94−97
63	Na^+	2,6-(*i*-Pr)$_2$Ph	*n*-Bu	*n*-Bu	1.9	−66****	−64****	$C_{21}H_{35}N_2O_4SNa$	162−166
64	H	2,6-(*i*-Pr)$_2$Ph	*i*-Pr	cyclohexyl	5.1	−60****	−49****	$C_{22}H_{36}N_2O_4S$[g]	133−135
65	H	2,6-(*i*-Pr)$_2$Ph	Me	*n*-octyl	22	−60****	−57****	$C_{22}H_{38}N_2O_4S$	32−35
66	H	2,6-(*i*-Pr)$_2$Ph	*n*-pentyl	*n*-pentyl	1.3	−74****	−66****	$C_{23}H_{40}N_2O_4S$	69−70
67	H	2,6-(*i*-Pr)$_2$Ph	*n*-hexyl	*n*-hexyl	4.2	−62****	−74****	$C_{25}H_{44}N_2O_4S$	57−61
68	H	2,6-(*i*-Pr)$_2$Ph	*n*-octyl	*n*-octyl	58	−70****	−67****	$C_{29}H_{52}N_2O_4S$	64−67
69	H	2,6-(*i*-Pr)$_2$Ph	*i*-Pr	CH$_2$Ph	12	−70****	−59****	$C_{23}H_{32}N_2O_4S$	156−159
70	H	2,6-(*i*-Pr)$_2$Ph	Ph	Ph	58	−67****	−46****	$C_{25}H_{28}N_2O_4S$	149−151
71	H	2,6-(*i*-Pr)$_2$Ph	CH$_2$Ph	CH$_2$Ph	20	−43****	−17**	$C_{27}H_{32}N_2O_4S$	143−146
72	H	2,6-(*i*-Pr)$_2$Ph	H	Ph	38.1	−55[c] ****	NT	$C_{19}H_{24}N_2O_4S$	165−168
73	H	2,6-(*i*-Pr)$_2$Ph	H	2,6-(*i*-Pr)$_2$Ph	25.8	−65[c] ****	NT	$C_{25}H_{36}N_2O_4S$	154−159
74	H	2,6-(*i*-Pr)$_2$Ph	H	2-benzimidazole	52	8[c]	NT	$C_{20}H_{24}N_4O_4S$	159−162
75	H	2,6-(*i*-Pr)$_2$Ph	H	benzhydryl	10.6	46[c] ***	NT	$C_{26}H_{30}N_2O_4S$	185−187
76	H	2,6-(*i*-Pr)$_2$Ph	H	CH$_2$CH(Ph)$_2$	49	−29[c] **	NT	$C_{27}H_{32}N_2O_4S$	103−105
77	H	2,6-(*t*-Bu)$_2$Ph	CH$_2$Ph	CH$_2$Ph	11	−3[c]	NT	$C_{29}H_{36}N_2O_4S$[h]	182−183
78	H	2,6-(*t*-Bu)$_2$Ph	H	Ph	19	−26[c] ***	NT	$C_{21}H_{28}N_2O_4S$	169−172
79	H	2,6-(*t*-Bu)$_2$Ph	H	2,6-(*i*-Pr)$_2$Ph	16.8	−57[c] ****	NT	$C_{27}H_{40}N_2O_4S$[i]	180−181
80	H	2,6-(*t*-Bu)$_2$Ph	H	benzhydryl	11.4	−35[c] **	NT	$C_{28}H_{34}N_2O_4S$	162−166
81	Me	2,6-(*t*-Bu)$_2$Ph	H	banzhydryl	4.6	4	NT	$C_{29}H_{36}N_2O_4S$	175−178
82	H	2,6-(*t*-Bu)$_2$Ph	H	CH$_2$CH(Ph)$_2$	21.8	−32[c] *	NT	$C_{29}H_{36}N_2O_4S$[j]	147−150
83	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	*i*-Pr	*i*-Pr	3.2	−19*	NT	$C_{22}H_{38}N_2O_4S$	198−199
84	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	H	*n*-hexyl	19.4	−52***	−10	$C_{22}H_{38}N_2O_4S$	123−128
85	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	*n*-Bu	*n*-Bu	3.2	−4	NT	$C_{24}N_{42}N_2O_4S$	134−135
86	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	Me	*n*-octyl	18	−55**	1	$C_{25}H_{44}N_2O_4S$	65−68
87	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	*n*-pentyl	*n*-pentyl	2.2	−42**	NT	$C_{26}H_{46}N_2O_4S$	107−108
88	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	*n*-hexyl	*n*-hexyl	4.3	−40**	NT	$C_{28}H_{50}N_2O_4S$	66−68
89	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	*n*-octyl	*n*-octyl	2.7	0	NT	$C_{32}H_{58}N_2O_4S$	53−55
90	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	*n*-decyl	*n*-decyl	89	−4	NT	$C_{36}H_{66}N_2O_4S$	63−65
91	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	(CH$_2$)$_3$N(Me)$_2$	(CH$_2$)$_3$N(Me)$_2$	164	−13	NT	$C_{26}H_{48}N_4O_4S$	oil
92	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	CH$_2$-2-THF[a]	CH$_2$-2-THF[a]	21	2	NT	$C_{26}H_{42}N_2O_6S$	108−111
93	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	Me	(CH$_2$)$_2$-2-pyridyl·HCl	31	−10	NT	$C_{24}H_{36}N_3ClO_4S$[k]	178−181
94	Na^+	2,6-(*t*-Bu)$_2$-4-Me-Ph	Me	(CH$_2$)$_2$-2-pyridyl	31	−22*	NT	$C_{24}H_{34}N_3O_4SNa$	133−136
95	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	H	Ph	23.4	−33[c] ****	NT	$C_{22}H_{30}N_2O_4S$	186−188
96	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	H	2,6-(*i*-Pr)$_2$Ph	13.5	−56[c] ****	NT	$C_{28}H_{42}N_2O_4S$	176−178
97	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	H	benzhydryl	11.5	−42[c] ****	NT	$C_{29}H_{36}N_2O_4S$	150−152
98	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	H	CH$_2$CH(Ph)$_2$	24.4	−54[c] ****	NT	$C_{30}H_{38}N_2O_4S$	142−144
99	H	2,6-(*t*-Bu)$_2$-4-MeO-Ph	H	2,6-(*i*-Pr)$_2$Ph	15	−77****	−29*	$C_{28}H_{42}N_2O_5S$	155−158
100	H	2,6-(*t*-Bu)$_2$-4-MeO-Ph	H	CH$_2$CH(Ph)$_2$	82	−55****	−15	$C_{30}H_{38}N_2O_5S$	132−138
101	H	2,6-(Ph)$_2$Ph	H	2,6-(*i*-Pr)$_2$Ph	>25	−39**	NT	$C_{31}H_{32}N_2O_4S$	166−168
102	H	Me	H	2,6-(*i*-Pr)$_2$Ph	>100	NT	NT	$C_{14}H_{22}N_2O_4S$	152−155
103	H	*n*-dodecyl	H	2,6-(*i*-Pr)$_2$Ph	33	0	NT	$C_{25}H_{44}N_2O_4S$	82−84
104	H	*n*-dodecyl	H	2,4,6-(MeO)$_3$Ph	30	−8	NT	$C_{22}H_{38}N_2O_7S$	133−136

[a] THF = tetrahydrofuran. [b] In vitro ACAT inhibition determined in rat liver microsomes. [c] Dosed at 50 mg/kg. [d] C,H,N analysis within 0.4% unless otherwise noted. [e] N: calcd, 10.00; found 8.68. [f] N: calcd, 7.42; found 6.98. [g] C: calcd, 62.23; found, 62.65. [h] C: calcd, 68.47; found, 68.05. [i] C: calcd, 66.36; found, 65.75. [j] C: calcd, 68.47; found, 67.98. [k] C: calcd, 57.87; found, 57.32. *Significantly different from control using the unpaired, two-tailed, *t*-test: $p < 0.1$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$. NT = not tested.

Table 4. Oxysulfonyl *O*-Aryl Carbamates and *S*-Aryl Thiocarbamates



						acute in vivo (% Δ TC)			
compd	X	R	Ar	R^1	in vitro IC_{50} (μM)[a]	30 mg/kg	3 mg/kg	formula[b]	mp (°C)
105	O	H	2,6-(*i*-Pr)$_2$Ph	*n*-hexyl	40	−52**	−18*	$C_{19}H_{31}NO_5S$	110−111
106	O	H	2,6-(*i*-Pr)$_2$Ph	*n*-dodecyl	13	−68****	−63****	$C_{25}H_{43}NO_5S$[c]	69−72
107	O	H	2,6-(*i*-Pr)$_2$Ph	*n*-hexadecyl	10.3	−60****	−42****	$C_{29}H_{51}NO_5S$	69−72
108	O	H	2,6-(*i*-Pr)$_2$Ph	Ph	>50	−26**	NT	$C_{19}H_{23}NO_5S$[d]	100−104
109	O	H	2,6-(*i*-Pr)$_2$Ph	2,4-F$_2$Ph	>50	−11	NT	$C_{19}H_{21}F_2NO_5S$	78−81
110	O	H	2,6-(*i*-Pr)$_2$Ph	2,6-F$_2$Ph	38	9	NT	$C_{19}H_{21}F_2NO_5S$[e]	137−142
111	O	H	2,6-(*i*-Pr)$_2$Ph	2,6-(Me)$_2$Ph	>50	−58**	−37**	$C_{21}H_{27}NO_5S$	134−137
112	O	H	2,6-(*i*-Pr)$_2$Ph	2,6-(MeO)$_2$Ph	>50	−70****	−63****	$C_{21}H_{27}NO_7S$	132−133
113	O	H	2,6-(*i*-Pr)$_2$Ph	2,4,6-(MeO)$_3$Ph	>50	−61***	−37**	$C_{22}H_{29}NO_8S$	130−132
114	O	H	2,6-(*i*-Pr)$_2$Ph	2,6-(*i*-Pr)$_2$Ph	9.4	−70****	−54****	$C_{25}H_{35}NO_5S$	132−133.5
115	O	Na^+	2,6-(*i*-Pr)$_2$Ph	2,6-(*i*-Pr)$_2$Ph	5.3	−74****	−59****	$C_{25}H_{34}NO_5SNa$	252−255
116	O	Me	2,6-(*i*-Pr)$_2$Ph	2,6-(*i*-Pr)$_2$Ph	50	−64****	−18	$C_{26}H_{37}NO_5S$	95−101
117	O	H	2,6-(*i*-Pr)$_2$Ph	2,6-(*t*-Bu)$_2$Ph	50	−55****	−46***	$C_{27}H_{39}NO_5S$	173−176
118	O	H	2,6-(*i*-Pr)$_2$Ph	2,4,6-(*i*-Pr)$_3$Ph	29	−67****	−63****	$C_{28}H_{41}NO_5S$	126−128
119	O	H	2,6-(*i*-Pr)$_2$Ph	2,6-(*i*-Pr)$_2$-4-OH-Ph	>50	−15*	NT	$C_{25}H_{35}NO_6S$[f]	oil
120	O	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	*n*-hexyl	95	−56****	−14	$C_{22}H_{37}NO_5S$	118−121
121	O	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	*n*-dodecyl	52	−65****	−41***	$C_{28}H_{49}NO_5S$	85−87
122	O	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	Ph	90	−65****	−15	$C_{22}H_{29}NO_5S$	122−125
123	O	H	2,6-(*t*-Bu)$_2$-4-Me-Ph	2,6-(*i*-Pr)$_2$Ph	7.7	−72****	−52****	$C_{28}H_{41}NO_5S$	140−142
124	O	H	2,4,6-(*i*-Pr)$_3$Ph	2,6-(*i*-Pr)$_2$Ph	14	−79****	−57****	$C_{28}H_{41}NO_5S$	122−123
125	O	H	2,4,6-(*i*-Pr)$_3$Ph	2,4,6-(*i*-Pr)$_3$Ph	22	−65****	−32****	$C_{31}H_{47}NO_5S$	144−146
126	O	H	2,6-(*t*-Bu)$_2$Ph	2,6-(*i*-Pr)$_2$Ph	12	−70****	−50***	$C_{27}H_{39}NO_5S$[g]	109−114
127	O	H	2,6-(*t*-Bu)$_2$Ph	2,6-(*t*-Bu)$_2$Ph	30	−18*	NT	$C_{29}H_{43}NO_5S$	195−197
128	S	H	2,6-(*i*-Pr)$_2$Ph	*n*-dodecyl	48	−9	NT	$C_{25}H_{43}NO_4S_2$	83−84
129	S	H	2,6-(*i*-Pr)$_2$Ph	2,6-(*i*-Pr)$_2$Ph	8.7	−17*	NT	$C_{25}H_{35}NO_4S_2$[h]	92−94

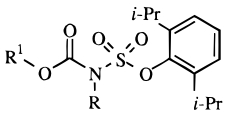
[a] In vitro ACAT inhibition determined in rat liver microsomes. [b] C,H,N analysis within 0.4% unless otherwise noted. [c] C: calcd, 63.93; found, 62.61. [d] C: calcd, 60.46; found, 59.78. [e] C: calcd, 55.20; found, 54.77. [f] C: calcd, 62.87; found, 62.26. [g] N: calcd, 2.86; found, 2.38. [h] N: calcd, 2.93; found, 2.42. *Significantly different from control using the unpaired, two-tailed, *t*-test: $p < 0.1$, $**p < 0.01$, $***p < 0.001$, and $****p < 0.0001$. NT = not tested.

pounds was examined in the 2,6-diisopropylphenyl carbamates **55**−**76** as well as for a series of 2,6-di-*tert*-butyl-4-methylphenyl carbamates (**83**−**98**). As in the (aminosulfonyl)ureas, the most potent compounds were those in which the number of carbons in the alkyl chains of the (*N*,*N*-dialkylamino)sulfonyl group totaled more than six but less than 16 (**62**−**68** and **85**−**88**). The in vitro activities of the 2,6-di-*tert*-butyl-4-methylphenyl carbamates **83**−**98** parallelled the activity observed with the 2,6-diisopropylphenyl carbamates except that the (*N*,*N*-diisopropylamino)sulfonyl group gave in vitro potency when coupled with a 2,6-di-*tert*-butyl-4-methylphenyl carbamate (**83**) but not when coupled with a 2,6-diisopropylphenyl carbamate (**60**). Interestingly, the (*N*-methyl-*N*-octylamino)sulfonyl group, which was unexpectedly inactive in the (aminosulfonyl)urea series, was also inactive in this series (**65** and **86**). As in the (aminosulfonyl)ureas, incorporation of an aryl or aryl-substituted alkyl substituent into the aminosulfonyl group (**69**−**82** and **92**−**101**) resulted in a decrease in the in vitro activity. Replacement of the aryl carbamate with an alkyl carbamate (**102**−**104**) also resulted in no significant in vitro or in vivo activity.

The in vivo activity of this series reveals some interesting results. Despite being roughly 1 order of magnitude less potent in vitro, the 2,6-diisopropylphenyl carbamates **55**−**76** show a similar in vivo activity profile as observed in the corresponding (2,6-diisopropylphenyl)ureas (Table 1). Indeed, several of the 2,6-diisopropylphenyl carbamates possessing the (*N*,*N*-dialkylamino)sulfonyl group (**60** and **62**−**68**) were very potent in the acute in vivo screen and also demonstrated excellent efficacy in the chronic in vivo screen. Inexplicably, within this series, the corresponding 2,6-di-*tert*-butyl-4-methylphenyl carbamates **83**−**98** possessed no in vivo potency, although they were just as potent in vitro as the corresponding 2,6-diisopropylphenyl carbamates **55**−**76**.

The 2,6-diisopropylphenyl carbamate group that gave excellent in vivo activity in the (aminosulfonyl)carbamates (Table 3) was included in several examples of (oxysulfonyl)carbamates (**105**−**119**; Table 4). Several compounds in this series possessed in vitro IC_{50} values in the micromolar range yet possessed excellent efficacy in the acute and chronic in vivo screens (e.g., **106**, **112**, **114**, **118**, **121**, **123**, **124**, and **126**). For the alkoxysulfonyl examples **105**−**107**, the long chain (i.e., dodecyl and hexadecyl) compounds were two of the more potent examples in vitro, in this series. In addition, they possessed good efficacy in vivo. Compounds in which the oxysulfonyl group was an unsubstituted phenyl (**108**) or a phenyl substituted with fluorine atoms (**109** and **110**) possessed no significant activity in vitro or in vivo. As larger substituents were incorporated onto the phenoxysulfonyl group (i.e., CH_3, CH_3O, *i*-Pr, and *t*-Bu), modest in vitro potency was observed in combination with good in vivo efficacy. The (2,6-diisopropylphenoxy)-sulfonyl compound **114** gave exceptional in vivo potency. In this series, as in those previously discussed, methylation of the nitrogen atom in the center of the molecule (**116**) had a detrimental effect on the activity profile, while formation of the base addition salt at the nitrogen atom (**115**) had little effect on the activity profile. Four 2,6-di-*tert*-butyl-4-methylphenyl carbamate examples (**120**−**123**) were examined and displayed similar activity patterns to the corresponding 2,6-diisopropylphenyl carbamates **105**, **106**, **108**, and **114**. The (2,6-diisopropylphenoxy)sulfonyl compound **123** displayed good in

Table 5. [(2,6-Diisopropylphenoxy)sulfonyl]carbamates



				acute in vivo (% Δ TC)			
compd	R	R^1	in vitro IC_{50} (μM)[a]	30 mg/kg	3 mg/kg	formula[b]	mp (°C)
130	H	Me	>100	NT	NT	$C_{14}H_{21}NO_5S$[c]	92−95
131	H	Et	>50	−14*	NT	$C_{15}H_{23}NO_5S$	72−74
132	Na^+	Et	>50	17	NT	$C_{15}N_{22}NO_5SNa\cdot0.5H_2O$	230−239
133	H	2-octyl	26	−32*	NT	$C_{21}H_{35}NO_5S$	74−76
134	H	*n*-dodecyl	13	−62****	1	$C_{25}H_{43}NO_5S$[d]	32−35
135	H	cyclohexyl	38	−38***	NT	$C_{19}H_{29}NO_5S$	119−121
136	H	1-adamantyl	13	−10	NT	$C_{23}H_{33}NO_5S$	foam
137	H	2-adamantyl	23	−36*	NT	$C_{23}H_{33}NO_5S$	185−187
138	H	(±)-menthyl	21	−40**	NT	$C_{23}H_{37}NO_5S$	115−117
139	H	*trans*-2,6-(*i*-Pr)$_2$-cyclohexyl	5.7	−35**	NT	$C_{25}H_{41}NO_5S$	115−118
140	H	*cis*-2,6-(*i*-Pr)$_2$-cyclohexyl	3.6	−70****	−29**	$C_{25}H_{41}NO_5S$	122−126
141	H	3-pyridyl	>50	−2	NT	$C_{18}H_{22}N_2O_5S$	150−155
142	H	4-FPh	>50	−21**	NT	$C_{19}H_{22}FNO_5S$	137−139
143	H	4-ClPh	97	−8	NT	$C_{19}H_{22}ClNO_5S$	121−125
144	H	2,4-F_2Ph	>50	−5	NT	$C_{19}H_{21}F_2NO_5S$	143−146
145	H	2,6-F_2Ph	65	−27	NT	$C_{19}H_{21}F_2NO_5S$	113−115
146	H	F_5Ph	66	−5	NT	$C_{19}H_{18}F_5NO_5S$	93−97
147	H	2,6-Me_2Ph	>50	−37**	NT	$C_{21}H_{27}NO_5S$	97−100
148	H	2,6-Et_2PhCH$_2$	20	−2	NT	$C_{24}H_{33}NO_5S$	57−61
149	H	2,3,5,6-Me_4Ph	>50	−17*	NT	$C_{23}H_{31}NO_5S$	120−128
150	H	2-(*i*-Pr)Ph	>50	−37*	NT	$C_{23}H_{29}NO_5S$	143−145
151	H	2-(*t*-Bu)-6-Me-Ph	49	−15	NT	$C_{24}H_{33}NO_5S$	114−116
152	H	2,6-(MeO)$_2$Ph	>50	−61***	−4	$C_{21}H_{27}NO_7S$	151−153
153	Na^+	2,6-(MeO)$_2$Ph	48	−49***	−12	$C_{21}H_{26}NO_7SNa$	200−204
154	H	2,4,6-(MeO)$_3$Ph	>25	−5	NT	$C_{22}H_{29}NO_8S$	87−92
155	H	2,4-(*i*-Pr)$_2$Ph	>50	6	NT	$C_{25}H_{35}NO_5S$	95−98
156	H	2,6-(*i*-Pr)$_2$-4-(*t*-Bu)Ph	8.8	−58***	−55***	$C_{29}H_{43}NO_5S$[e]	146−148
157	H	2,6-(*i*-Pr)$_2$-4-(MeO)Ph	>25	−56****	1	$C_{26}H_{37}NO_6S$[f]	81−83
158	H	2,6-(*i*-Pr)$_2$-4-(NO_2)Ph	>50	18	NT	$C_{25}H_{34}N_2O_7S$	124−127
159	H	2,6-(*i*-Pr)$_2$-4-Br-Ph	31	−29*	NT	$C_{25}H_{34}BrNO_5S$	117−120
160	H	2,6-(*i*-Pr)$_2$-4-Cl-Ph	42	2	NT	$C_{25}H_{34}ClNO_5S$	108−111
161	H	2,6-(*i*-Pr)$_2$-4-F-Ph	>50	−72****	NT	$C_{25}H_{34}FNO_5S$	161−163
162	H	2,6-(*i*-Pr)$_2$-4-(OH)Ph	>50	−55****	−5	$C_{25}H_{35}NO_6S$	oil
163	H	2,6-(*i*-Pr)$_2$-4-(MeCO)Ph	41.8	−16	NT	$C_{27}H_{37}NO_6S$	164−167
164	H	2,3,5,6-(*i*-Pr)$_4$-4-F-Ph	13	−71****	−47****	$C_{31}H_{46}FNO_5S$	155−158
165	H	2,6-(*t*-Bu)$_2$-4-(MeO)Ph	4.8	−72****	−58****	$C_{28}H_{41}NO_6S$	137−139
166	Na^+	2,6-(*t*-Bu)$_2$-4-(MeO)Ph	10	−60****	−42***	$C_{28}H_{40}NO_6SNa$	276−279
167	H	2,4,6-(*t*-Bu)$_3$Ph	26	−76****	−69****	$C_{31}H_{47}NO_5S$	149−150
168	H	2,6-(*t*-Bu)$_2$-4-($CH_2N(Me)_2$)Ph	22	2	NT	$C_{30}H_{46}N_2O_5S$	125−130
169	H	2,6-(Ph)$_2$Ph	12	−46***	NT	$C_{31}H_{31}NO_5S\cdot C_4H_{10}O$	140−142

[a] In vitro ACAT inhibition determined in rat liver microscomes. [b] C,H,N analysis within 0.4% unless otherwise noted. [c] N: calcd, 4.44; found, 3.80. [d] N: calcd, 2.98; found, 2.45. [e] N: calcd, 2.71; found, 2.29. [f] C: calcd, 63.52; found, 64.06. *Significantly different from control using the unpaired, two-tailed *t*-test: $p < 0.1$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$. NT = not tested.

vitro activity coupled with exceptional in vivo efficacy. The (2,6-diisopropylphenoxy)sulfonyl group gave similar results when coupled to two other aryl carbamates (**124** and **126**). With these aryl carbamates, deviating from the (2,6-diisopropylphenoxy)sulfonyl group (**125** and **127**) resulted in a decrease in in vivo potency.

A comparison of the *S*-aryl thiocarbamates **128** and **129** with the corresponding *O*-aryl carbamates **106** and **114** demonstrated that the replacement of an oxygen atom by a sulfur atom led to a significant loss of in vivo activity.

The excellent efficacy observed with the (2,6-diisopropylphenoxy)sulfonyl carbamates **114**−**116**, **123**, **124**, and **126** prompted us to examine a variety of carbamate groups while keeping the (2,6-diisopropylphenoxy)-sulfonyl group constant (Table 5). Several alkyl and cycloalkyl carbamates (**130**−**140**) were synthesized. The *n*-dodecyl carbamate **134** and some of the cycloalkyl carbamates (**136**, **139**, and **140**) possessed modest in vitro potency, but none of these compounds displayed the excellent in vivo efficacy shown above in the aryl carbamates (Table 4). The 3-pyridyl carbamate **141** and several halogenated phenyl carbamates (**142**−**146**) were completely inactive both in vitro and in vivo. Surprisingly, several alkyl- and alkoxyphenyl carbamates (**147**−**155**) were also inactive in vitro and in vivo. The striking difference between these phenyl carbamates and the extremely efficacious examples (**114**, **123**, **124**, and **126**; Table 4) is the absence of large (isopropyl or *tert*-butyl) substituents in the 2- and 6-positions. It is interesting to note that the 2,6-diethyl compound **148** and the large 2,6-diphenyl compound **169** gave some activity in vitro but not in vivo, indicating a lower and upper limit to the size of the 2,6-disubstituents. It was also shown that neither the 2-isopropyl (**150**) or the 2-*tert*-butyl, 6-methyl (**151**) substitution patterns gave good activity. A pair of 'flanking' isopropyl or *tert*-butyl groups apparently are required for good efficacy and potency. The 2,6-diisopropyl substitution pattern in combination with an electron-withdrawing group in the 4-position (**158**−**161**) produced inactive compounds, with the exception of the 4-fluoro compound **161** which was very efficacious in vivo. Interestingly, the addition of two more isopropyl groups to the 3- and 5-positions

with an electron-withdrawing fluorine atom in the 4-position (**164**) retained the in vivo efficacy while also improving the in vitro potency. Alkyl groups are tolerated in the 4-position (**156** and **167**), while polar groups such as hydroxy (**162**) or (dimethylamino)-methylene (**168**) are not. Inexplicably, a 4-methoxy substituent completely abolished the in vitro and in vivo activity of the 2,6-diisopropylphenyl series (**157**) but gives a very potent and efficacious compound in the 2,6-di-*tert*-butylphenyl series (**165**).

Conclusion

Some general trends are observed in the five series of compounds presented here. In the two series of aminosulfonyl compounds (Tables 1 and 3), the (*N*,*N*-dialkylamino)sulfonyl group gave the most potent and efficacious compounds in vitro and in vivo. Optimal potency was observed when the total number of carbon atoms in the (*N*,*N*-dialkylamino)sulfonyl group was between 6 and 16 and especially if the alkyl chains were branched. A comparison of the (2,6-diisopropylphenyl)-urea compounds in Table 1 to the corresponding 2,6-diisopropylphenyl carbamate analogues in Table 3 reveals a distinct difference in in vitro activity. Each (aminosulfonyl)carbamate was roughly 1 order of magnitude less potent in vitro than the corresponding (aminosulfonyl)urea, although the in vivo efficacy of the compounds in the two series was similar (cf. **14** and **60**, **16** and **63**, **25** and **67**, etc.). Inexplicably, the *N*-methyloctylamine group had a significantly negative effect on the in vitro activity in both the ureas (**21**) and carbamates (**65** and **86**).

Unlike the aminosulfonyl compounds, in the two series of oxysulfonyl compounds, the activity of the ureas (Table 2) was very similar to the activities observed in the carbamates (Table 4). Compounds containing the (*n*-dodecyloxy)sulfonyl (i.e., **49**, **106**, and **121**) or the (2,6-diisopropylphenoxy)sulfonyl (i.e., **52**, **53**, **114**, **123**, **124**, and **126**) groups gave the best potency in vitro and in vivo. Replacement of an oxygen in the (oxysulfonyl)carbamate series by a sulfur atom was not tolerated (cf. **128** and **106**, **129** and **114**).

Overall, alkylation of the central nitrogen atom resulted in a significant loss of activity. This same result has also been observed in a structurally similar series of acylurea and -carbamate[6] and sulfonylurea[8] ACAT inhibitors. Conversely, generation of the sodium salt had very little effect on the biological activity, while it did increase the aqueous solubility of the compounds.

The (aminosulfonyl)ureas (Table 1) are the only series of compounds presented here which possessed significant in vitro potency, coupled with good in vivo efficacy in cholesterol-fed rats. Three other series of compounds (Tables 2−5) only gave modest potency in vitro (>1.0 μM), although excellent in vivo effects were obtainable in each of the series. One possible explanation for the lack of correlation between ACAT inhibition in vitro and hypocholesterolemic activity in vivo is that ACAT inhibition may not be the primary mechanism by which these drugs are acting. To search for other possible mechanisms of action, compound **115** was tested and found to be inactive against several acyltransferases and other enzymes involved in lipid metabolism (i.e., acyl-CoA:monoglyceride acyltransferase, lecithin:cholesterol acyltransferase, acyl-CoA:retinol acyltransferase, carnitine acyltransferase, pancreatic cholesterolester hydrolase, hepatic lipase, and HMG-CoA reductase).[12] However, the involvement of ACAT inhibition is further supported by the fact that **115** inhibits cholesterol absorption in a rat lymph-fistula model.[4c] In this model, the lymphatic transport of ACAT-derived cholesterol esters was inhibited 50−60% after a single 10 mg/kg dose of **115**.

To date, ACAT inhibition remains our best explanation for the dramatic in vivo lipid-regulating effects

Table 6. Chronic Hypocholesterolemic Effect of Selected Compounds in Cholesterol-Fed Rats

compd	% Δ TC	% Δ HDL
10	−53***	78
14	−38***	83
15	−48*	43
16	−40****	167
18	−52***	82
19	−62***	122
20	−62**	86
21	−64***	123
22	−63**	94
23	−67****	193
24	−68****	133
25	−69****	207
26	−35**	92
27	−56**	123
29	−51*	19
30	−56****	150
34	−37***	80
38	−36*	170
39	−28**	183
40	−45***	43
41	−41****	150
49	−52**	67
50	−55***	11
51	−38*	−30
52	−43**	5
53	−59****	18
60	−59**	82
62	−72****	113
63	−69****	109
64	−71**	188
65	−64**	88
66	−73****	166
67	−75**	144
68	−80**	156
69	−69****	114
70	−37*	320
72	−33	240
73	−9	388
79	−28*	200
80	−46*	50
96	−38***	156
97	−25*	100
98	−51**	144
99	−47***	86
106	−56*	31
112	−62**	208
113	−37*	62
114	−68***	345
115	−64*	233
118	−61****	295
121	−33*	23
123	−66**	205
124	−74****	153
125	−62****	129
126	−64**	25
156	−72**	177
157	−12	−8
161	−52**	143
162	−25	95
164	−74**	208
165	−76***	380
166	−62***	108
167	−78****	108
169	−38*	21

[a] Significantly different from control using the unpaired, two-tailed *t*-test: $p < 0.1$, $^{**}p < 0.01$, $^{***}p < 0.001$, and $^{****}p < 0.0001$.

observed with these drugs. Since the structural design of these compounds was based on a series of sulfonylurea hypoglycemics, it is possible that these compounds possess similar physical characteristics (i.e., protein binding, log *P*, pK_a, etc.). It is conceivable that enhanced absorption of these compounds (the structurally related hypoglycemics are typically >90% bioavailable after oral dosing[13]) could explain the excellent in vivo lipid-lowering effects observed despite the modest in vitro activity. Several mechanistic studies are ongoing in a variety of animal models to further elucidate a possible alternate mechanism and elaborate upon the enhanced in vivo effect observed with these compounds. Results of these studies will be reported in due course.

Experimental Section

Unless otherwise noted, reagents and solvents obtained from commercial sources were used without further purification. All amines and alcohols were commercially available except the following, which could be readily synthesized according to literature methods: 2,4,6-triisopropylaniline, 2,6-diisopropylhydroquinone, 2,6-diisopropyl-4-methoxyphenol, 4-chloro-2,6-diisopropylphenol, 4-bromo-2,6-diisopropylphenol, 2,6-diisopropyl-4-nitrophenyl, 3′,5′-diisopropyl-4′-hydroxyacetophenone, and 2,6-diisopropylcyclohexanol. Additionally, 4-fluoro-2,3,5,6-tetraisopropylphenol and 2,6-diisopropyl-4-fluorophenol were previously unknown in the literature, and their syntheses are provided below.

Column chromatography was performed on Merck silica gel 60 (230−400 mesh). Proton NMR spectra were recorded with a Gemini 300 spectrometer, and chemical shifts are expressed in parts per million (ppm) relative to internal tetramethylsilane. Melting points were measured with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer model 240C elemental analyzer and are ±0.4% of the theoretical values unless otherwise noted.

Representative experimental procedures are given below for each of the four series of compounds described in this paper. Analytical data and melting points for all of the final compounds are given in Tables 1−5.

4-Fluoro-2,3,5,6-tetraisopropylphenol. 4-Fluorophenol (27.35 g, 0.244 mol) was dissolved in 55 mL of concentrated sulfuric acid at 65 °C. 2-Propanol (112 mL, 1.46 mol) was added dropwise, and the resulting mixture was heated at 70 °C for 1 h. An additional 30 mL of sulfuric acid was added, and heating was continued for an additional 5 h. The reaction mixture was cooled to room temperature and stirred for 3 days. The reaction mixture was extracted with diethyl ether, and the ether extracts were then washed with saturated sodium bicarbonate solution followed by brine. The ether layer was dried over $MgSO_4$, filtered, and concentrated to give a black oily solid. Silica gel chromatography (10% ethyl acetate/hexanes) gave 4.53 g (7%) of the title compound as a yellow solid: mp 180−182 °C; ^{1}H-NMR (DMSO-d_6) δ 3.56 (hept, 2H), 3.33 (hept, 2H), 1.27 (dd, 24H). Anal. ($C_{18}H_{29}FO$) C,H,N.

2,6-Diisopropyl-4-fluorophenol. 4-Fluorophenol (10.9 g, 0.097 mol) and aluminum turnings (81 mg, 0.003 mol) were combined in a sealed vessel and heated to 165 °C for 30 min. This was then cooled to room temperature, and propylene (19.0 g, 0.451 mol) was added. The vessel was resealed, heated to 240 °C for 2 h, and then cooled to room temperature. The vessel was washed with hexanes and the mixture concentrated to give a black oil. The residue was chromatographed on silica gel (1% ethyl acetate in hexanes) to give 6.92 g (36%) of 2,6-diisopropyl-4-fluorophenol as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ 6.74 (d, 2H), 4.54 (s, 1H), 3.14 (hept, 2H), 1.24 (d, 6H). Anal. ($C_{12}H_{17}FO$) C,H,N.

General Method for the Synthesis of the (Chlorosulfonyl)urea Intermediates IIa: Preparation of [[[2,6-Bis(1-methylethyl)phenyl]amino]carbonyl]sulfamoyl Chloride. A solution of 2,6-diisopropylaniline (30.0 g, 0.169 mol) in 150 mL of diethyl ether was added dropwise to a solution of *N*-chlorosulfonyl isocyanate (14.73 mL, 0.169 mol) in 100 mL of diethyl ether at −15 °C under an atmosphere of nitrogen. The resulting off-white suspension was stirred at −15 °C for 1 h. The solid was collected by vacuum filtration, washed with hexanes, and air-dried to give 53.79 g (99%) of the title compound as a white solid: mp 130−134 °C; ^{1}H-NMR ($CDCl_3$) δ 7.23 (m, 3H), 3.01 (hept, 2H), 1.19 (d, 12H). Anal. ($C_{13}H_{19}ClN_2O_3S$) C,H,N.

General Method for the Synthesis of the (Chlorosulfonyl)carbamate Intermediates IIb: Preparation of 2,6-Bis(1-methylethyl)phenyl (Chlorosulfonyl)carbamate. A solution of 2,6-diisopropylphenol (37.1 mL, 0.2 mol) in 200 mL of diethyl ether was added dropwise to a solution of *N*-chlorosulfonyl isocyanate (17.4 mL, 0.2 mol) in 200 mL of diethyl ether at −15 °C under an atmosphere of nitrogen. The reaction mixture was maintained at −15 °C for 16 h and then concentrated in vacuo to give an orange oil. This was triturated with hexanes, and the solid was collected by vacuum filtration to give 55.64 g (87%) of the title compound as a white solid: mp 78−81 °C; ^{1}H-NMR ($CDCl_3$) δ 7.21 (m, 3H), 2.99 (hept, 2H), 1.23 (d, 12H). Anal. ($C_{13}H_{18}ClNO_4S$) N; C: calcd, 48.82; found, 49.59. H: calcd, 5.67; found, 6.08.

In a similar manner, the following (chlorosulfonyl)carbamates were also obtained.

2,6-Bis(1,1-dimethylethyl)phenyl (chlorosulfonyl)carbamate: mp 135−137 °C; ^{1}H-NMR ($CDCl_3$) δ 7.26 (m, 3H), 1.36 (s, 18H). Anal. ($C_{15}H_{22}ClNO_4S$) C,H,N.

2,6-Bis(1,1-dimethylethyl)-4-methylphenyl (chlorosulfonyl)carbamate: mp 138−140 °C; ^{1}H-NMR ($CDCl_3$) δ 7.13 (s, 2H), 2.33 (s, 3H), 1.35 (s, 18H). Anal. ($C_{16}H_{24}ClNO_4S$) C,H,N.

1,1′:3,1″-Terphenyl-2′-yl (chlorosulfonyl)carbamate: mp 159−162 °C; ^{1}H-NMR (DMSO-d_6) δ 7.43 (m, 13H), 6.90 (bs, 1H). Anal. ($C_{19}H_{14}ClNO_4S$) H,N; C: calcd, 58.84; found, 57.27.

2,6-Bis(1,1-dimethylethyl)-4-methoxyphenyl (chlorosulfonyl)carbamate: oil; ^{1}H-NMR ($CDCl_3$) δ 6.86 (s, 2H), 3.81 (s, 3H), 1.35 (s, 18H). Anal. ($C_{16}H_{24}ClNO_5S$).

General Method for the Reaction of an Amine with (Chlorosulfonyl)urea Intermediate IIa To Give an (Aminosulfonyl)urea (Table 1): Preparation of *N*-[2,6-Bis(1-methylethyl)phenyl]-*N*′-[(dibutylamino)sulfonyl]urea (16). A solution of [[[2,6-bis(1-methylethyl)phenyl]amino]carbonyl]-sulfamoyl chloride (25.0 g, 0.078 mol) in 250 mL of tetrahydrofuran was added dropwise to a solution of di-*n*-butylamine (10.13 g, 0.078 mol) and excess triethylamine (∼12 mL) in 250 mL of tetrahydrofuran at 25 °C under an atmosphere of nitrogen. This was stirred at 25 °C for 16 h and then concentrated in vacuo to give an oily residue which was partitioned between 1 M HCl and ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a brown oil. Silica gel chromatography (10% ethyl acetate/hexanes) gave a tan oil which was triturated with hexanes to give 12.21 g (38%) of the title compound as a white solid: mp 98−101 °C; ^{1}H-NMR ($CDCl_3$) δ 8.68 (s, 1H), 7.74 (s, 1H), 7.26 (m, 3H), 3.26 (q, 4H), 3.10 (hept, 2H), 1.61 (m, 4H), 1.19 (m, 16H), 0.93 (t, 6H). Anal. ($C_{21}H_{37}N_3O_3S$) C,H,N.

General Method for the Alkylation of the Central Nitrogen Atom: Preparation of *N*′-[2,6-Bis(1-methylethyl)phenyl]-*N*-methyl[(dibutylamino)sulfonyl]urea (17). 1,8-Diazabicyclo[5.4.0]undec-7-ene (1.6 mL, 0.010 mol) was added dropwise to a solution of *N*-[2,6-bis(1-methylethyl)-phenyl]-*N*′-[(dibutylamino)sulfonyl]urea (**16**; 4.0 g, 0.0097 mol) and methyl iodide (1.52 g, 0.010 mol) in 100 mL of acetonitrile at −15 °C. The resulting mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was concentrated in vacuo and partitioned between 1 M HCl and ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give an orange oil. Silica gel chromatography (10% ethyl acetate/hexanes) gave 3.34 g (81%) of the title compound **17** as a clear oil: ^{1}H-NMR (DMSO-d_6) δ 8.57 (s, 1H), 7.18 (m, 3H), 3.21 (m, 7H), 3.05 (hept, 2H), 1.52 (m, 4H), 1.27 (m, 4H), 1.13 (d, 12H), 0.99 (t, 6H). Anal. ($C_{22}H_{39}N_3O_3S$) H,N; C: calcd, 62.08; found, 62.75.

General Method for the Formation of the Sodium Salt: Preparation of *N*-[2,6-Bis(1-methylethyl)phenyl]-*N*′-[(dibutylamino)sulfonyl]urea, Monosodium Salt (18). A solution of *N*-[2,6-bis(1-methylethyl)phenyl]-*N*′-[(dibutylamino)-sulfonyl]urea (**16**; 15.0 g, 0.036 mol) in 150 mL of tetra-

hydrofuran was added dropwise to a suspension of hexane-washed sodium hydride (1.53 g, 60% dispersion in mineral oil, 0.038 mol) in 50 mL of tetrahydrofuran at 0 °C under an atmosphere of nitrogen. The resulting solution was warmed to room temperature and stirred for 16 h. The reaction mixture was concentrated in vacuo, and the residue was triturated with diethyl ether and filtered to remove inorganic impurities. The filtrate was concentrated, and the resulting solid was slurried in hexanes and filtered to give 9.16 g (58%) of **18** as a white solid: mp 217−219 °C; ^{1}H-NMR (DMSO-d_6) δ 7.37 (bs, 1H), 7.04 (m, 3H), 3.34 (hept, 2H), 2.97 (m, 4H), 1.47 (m, 4H), 1.24 (m, 4H), 1.10 (d, 12H), 0.88 (t, 6H). Anal. ($C_{21}H_{36}N_3O_3SNa$) C,H; N: calcd, 9.69; found, 8.74.

General Method for the Reaction of an Alcohol with (Chlorosulfonyl)urea Intermediate IIa To Give an (Oxysulfonyl)urea (Table 2): Preparation of Dodecyl [[[2,6-Bis(1-methylethyl)phenyl]amino]carbonyl]sulfamate (49). A solution of [[[2,6-bis(1-methylethyl)phenyl]amino]carbonyl]-sulfamoyl chloride (5.0 g, 0.016 mol) in 75 mL of tetrahydrofuran was added dropwise to a solution of *n*-dodecanol (2.92 g, 0.016 mol) and excess triethylamine (∼3 mL) in 75 mL of tetrahydrofuran at ambient temperature, under an atmosphere of nitrogen. The resulting suspension was stirred for 16 h and concentrated in vacuo, and the residue was partitioned between 1 M HCl and ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a yellow/green oil. Trituration with cold hexanes gave 2.35 g (32%) of **49** as a white solid: mp 112−115 °C; ^{1}H-NMR (DMSO-d_6) δ 8.01 (s, 1H), 7.18 (m, 3H), 4.24 (q, 2H), 3.06 (hept, 2H), 1.66 (m, 2H), 1.24 (m, 18H), 1.13 (d, 12H), 0.86 (t, 3H). Anal. ($C_{25}H_{44}N_2O_4S_1$) C,H,N.

General Method for the Reaction of an Amine with (Chlorosulfonyl)carbamate Intermediate IIb To Give an (Aminosulfonyl)carbamate (Table 3): Preparation of 2,6-Bis(1-methylethyl)phenyl [(Dipentylamino)sulfonyl]carbamate (66). A solution of 2,6-bis(1-methylethyl)phenyl (chlorosulfonyl)carbamate (5.0 g, 0.016 mol) in 50 mL of tetrahydrofuran was added dropwise to a solution of di-*n*-pentylamine (2.46 g, 0.016 mol) and triethylamine (1.74 g, 0.017 mol) in 100 mL of tetrahydrofuran at −15 °C under an atmosphere of nitrogen. This was then warmed to ambient temperature and stirred for 16 h. The reaction mixture was concentrated in vacuo, and the residue was partitioned between 1 M HCl and ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. Silica gel chromatography (10% ethyl acetate/hexanes) gave 1.22 g (18%) of **66** as a white solid: mp 69−70 °C; ^{1}H-NMR (DMSO-d_6) δ 11.98 (s, 1H), 7.22 (m, 3H), 3.24 (q, 4H), 2.93 (hept, 2H), 1.56 (m, 4H), 1.27 (m, 8H), 1.15 (d, 12H), 0.88 (t, 6H). Anal. ($C_{23}H_{40}N_2O_4S_1$) C,H,N.

General Method for the Reaction of an Alcohol with (Chlorosulfonyl)carbamate Intermediate IIb To Give an (Oxysulfonyl)carbamate (Tables 4 and 5): Preparation of 2,6-Bis(1-methylethyl)phenyl [(Dodecyloxy)sulfonyl]-carbamate (106). A solution of 2,6-bis(1-methylethyl)phenyl (chlorosulfonyl)carbamate (5.0 g, 0.016 mol) in 75 mL of tetrahydrofuran was added dropwise to a solution of *n*-dodecyl alcohol (2.91 g, 0.016 mol) and triethylamine (1.74 g, 0.017 mol) in 100 mL of tetrahydrofuran at −15 °C under an atmosphere of nitrogen and then warmed to ambient temperature and stirred for 16 h. The reaction mixture was concentrated in vacuo, and the residue was partitioned between 1 M HCl and ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a colorless oil. Trituration with hexanes gave 5.02 g (69%) of **106** as a white solid: mp 69−72 °C; ^{1}H-NMR ($CDCl_3$) δ 7.99 (s, 1H), 7.18 (m, 3H), 4.54 (q, 2H), 2.98 (hept, 2H), 1.78 (m, 2H), 1.23 (m, 30H), 0.88 (t, 3H). Anal. ($C_{25}H_{43}N_1O_5S_1$) H,N; C: calcd, 63.93; found, 62.61.

General Method for the Synthesis of the Oxysulfonyl Isocyanate Intermediates III: Preparation of [2,6-Bis(1-methylethyl)phenoxy]sulfonyl Isocyanate. A solution of *N*-chlorosulfonyl isocyanate (15.4 mL, 0.177 mol) in 75 mL of toluene was added dropwise to a solution of 2,6-diisopropylphenol (30.0 g, 0.168 mol) in 75 mL of toluene at 45 °C. After complete addition, the reaction mixture was heated to reflux for 16 h and concentrated in vacuo to remove the toluene. The residue was distilled (109−114 °C at 0.9 mmHg) to give 42.62 g (89%) of the title compound as a clear, pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ 7.30 (m, 3H), 3.39 (hept, 2H), 1.78 (m, 2H), 1.26 (d, 12H). This compound is extremely moisture sensitive and was stored under nitrogen to limit rapid decomposition.

Alternative Synthesis of the (Oxysulfonyl)ureas (Table 2). Reaction of an Amine with Oxysulfonyl Isocyanate Intermediate III: Preparation of 2,6-Bis(1-methylethyl)-phenyl [[Bis(1-methylpropyl)amino]carbonyl]sulfamate (54). *N*,*N*-Di-*sec*-butylamine (1.81 mL, 0.011 mol) was added dropwise to a solution of [2,6-bis(1-methylethyl)phenoxy]-sulfonyl isocyanate (3.0 g, 0.011 mol) in 100 mL of diethyl ether at ambient temperature under an atmosphere of nitrogen. The reaction mixture was stirred for 16 h and then concentrated in vacuo. Silica gel chromatography (20% ethyl acetate/hexanes) gave 3.40 g (78%) of **54** as a white foam: ^{1}H-NMR (DMSO-d_6) δ 7.15 (m, 3H), 3.72 (m, 2H), 3.12 (m, 2H), 1.71 (m, 2H), 1.44 (m, 2H), 1.12 (m, 18H), 0.88 (t, 3H), 0.82 (t, 3H). Anal. ($C_{21}H_{36}N_2O_4S_1$) H,N; C: calcd, 61.13; found, 60.57.

Alternative Synthesis of the (Oxysulfonyl)carbamates (Tables 4 and 5). Reaction of an Alcohol with Oxysulfonyl Isocyanate Intermediate III: Preparation of 2,4,6-Trimethoxyphenyl [[2,6-Bis(1-methylethyl)phenoxy]sulfonyl]carbamate (154). 2,4,6-Trimethoxyphenol (1.30 g, 0.007 mol) was added dropwise to a solution of [2,6-bis(1-methylethyl)phenoxy]sulfonyl isocyanate (2.0 g, 0.007 mol) in 50 mL of diethyl ether at ambient temperature under an atmosphere of nitrogen. The reaction mixture was stirred for 16 h and then concentrated in vacuo. Silica gel chromatography (20% ethyl acetate/hexanes) gave 2.30 g (70%) of **154** as a white powder: mp 87−92 °C; ^{1}H-NMR ($CDCl_3$) δ 8.37 (bs, 1H), 7.20 (m, 3H), 6.17 (s, 2H), 3.80 (s, 9H), 3.51 (hept, 2H), 1.23 (d, 12H). Anal. ($C_{22}H_{29}N_1O_8S_1$) C,H,N.

Synthesis of the (Oxysulfonyl)carbamothioates (Table 4). Reaction of a Thiol with Oxysulfonyl Isocyanate Intermediate III: Preparation of *S*-2,6-Bis(1-methylethyl)phenyl [[2,6-Bis(1-methylethyl)phenoxy]sulfonyl]carbamothioate (129). A solution of 2,6-diisopropylthiophenol (2.26 g, 0.012 mol) in 50 mL of diethyl ether was added dropwise to a solution of [2,6-bis(1-methylethyl)phenoxy]-sulfonyl isocyanate (3.0 g, 0.011 mol) in 100 mL of diethyl ether at room temperature under a nitrogen atmosphere. The mixture was allowed to stir for 16 h and then concentrated in vacuo. The residue was triturated with hexanes, and the solid was collect to give 2.52 g (50%) of **129** as a white solid: mp 92−94 °C; ^{1}H-NMR ($CDCl_3$) δ 8.76 (bs, 1H), 7.48 (t, 1H), 7.26 (m, 4H), 7.17 (d, 1H), 3.59 (hept, 2H), 3.44 (hept, 2H), 1.23 (d, 24H). Anal. ($C_{25}H_{35}N_1O_4S_2$) C,H; N: calcd, 2.93; found, 2.42.

General Method for the One-Pot Synthesis of Compounds Possessing the Same Nucleophile on Both Sides of the Molecule: Preparation of 2,6-Bis(1-methylethyl)-phenyl [[2,6-Bis(1-methylethyl)phenoxy]sulfonyl]carbamate (114). A solution of 2,6-diisopropylphenol (150.0 g, 0.841 mol) and triethylamine (64.5 mL, 0.463 mol) in 600 mL of tetrahydrofuran was added dropwise to a solution of *N*-chlorosulfonyl isocyanate (38.5 mL, 0.442 mol) in 500 mL of tetrahydrofuran at −15 °C under an atmosphere of nitrogen. The reaction mixture was warmed to ambient temperature, stirred for 72 h, and then concentrated in vacuo. The residue was partitioned between 1 M HCl and ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give an oily solid. Silica gel chromatography (10% ethyl acetate/hexanes) gave 139.9 g (72%) of **114** as a white solid: mp 132−133.5 °C; ^{1}H-NMR ($CDCl_3$) δ 7.20 (m, 6H), 3.53 (hept, 2H), 3.06 (hept, 2H), 1.25 (d, 12H), 1.22 (d, 12H). Anal. ($C_{25}H_{35}N_1O_5S_1$) C,H,N.

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JM9509455