Heterocyclic Ureas: Inhibitors of Acyl-CoA:Cholesterol *O*-Acyltransferase as Hypocholesterolemic Agents[1]

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A series of diaryl-substituted heterocyclic ureas was prepared, and their ability to inhibit acyl-CoA:cholesterol *O*-acyltransferase (ACAT) in vitro and to lower plasma total cholesterol in cholesterol-fed animal models in vivo was examined. *N*-(2,6-Diisopropylphenyl)-*N*′-tetrazole- or isoxazole-substituted heterocyclic ureas proved optimal. A carbon chain of 11−14 carbons substituted 1,3 with respect to the amine provided the optimal side chain. Substitution of the alkyl chain generally lowered activity. Tetrazole urea **2i** dosed at 3 mg/kg lowered plasma total cholesterol (TC) 67% in an acute, cholesterol-fed (C-fed) rat model of hypercholesterolemia and 47% in C-fed dogs. Tetrazole **2i**, dosed at 10 mg/kg, also lowered TC 52% and raised HDL cholesterol 113% in rats with pre-established hypercholesterolemia.

Introduction

Coronary heart disease is the leading cause of death among nations of the Western hemisphere. Elevated levels of plasma low-density lipoprotein cholesterol represent an independent risk factor definitively linked to coronary heart disease (CHD).[2] The body obtains cholesterol from only two sources: one-third via absorption from the diet and the balance from endogenous biosynthesis.[3] Inhibition of either process represents an approach to lowering plasma cholesterol. Notably HMG-CoA reductase inhibitors, which inhibit the rate-limiting enzyme in cholesterol biosynthesis, have proven clinically effective at lowering total cholesterol and, most recently, have been shown to reduce CHD and total mortality in men with[4] or without[5] previously diagnosed CHD.

Evidence suggests that inhibition of the enzyme acyl-CoA:cholesterol *O*-acyltransferase (ACAT, EC 2.3.1.26), which catalyzes the intracellular formation of cholesteryl esters, may have beneficial effects on plasma total cholesterol by preventing the absorption of dietary cholesterol.[6] Additional studies show hepatic cholesteryl ester content is directly proportional to very-low-density lipoprotein (VLDL) secretion rate.[7] Recently ACAT inhibition has been shown to decrease both the secretion rate of cholesteryl esters and apolipoprotein B from perfused monkey livers.[8] Inhibition of ACAT in the arterial wall may reduce accumulation of cholesteryl ester (CE) in monocyte macrophages. These CE rich cells are the precursors of the foam cells of the early atherosclerotic lesion.[9] The additional data suggesting a role for ACAT in the liver and at the artery wall have maintained this enzyme as a very attractive target for pharmacological intervention even though ACAT inhibition has yet to be proven clinically relevant for the treatment of hypercholesterolemia.[10]

Previous work in our laboratories[11−16] identified several series of potent ACAT inhibitors which lowered plasma total cholesterol in cholesterol-fed animal models. The early work focused on primarily amide inhibitors.[11] This culminated in the discovery of CI-976, which exerted its antiatherosclerotic effects by inhibition of arterial ACAT independent of cholesterol lowering.[3,17] The urea moiety was later found to be an excellent isosteric replacement for amide.[12] Among these ureas, the secondary urea moiety containing a sterically hindered *N*-2,6-disubstituted aryl moiety provided optimal activity.[13] A surprising variety of substitutions is then tolerated on the other nitrogen.[3] Initially we chose the tetrazole moiety to furnish a more polar linker as compared with our previous compounds.[12,18] We reasoned this would yield a compound with improved pharmacokinetic properties that would inhibit arterial ACAT. We discovered a series of potent compounds upon alkylation of the tetrazole ring and sought to optimize the tetrazole ring substitution with respect to biological activity. In an effort to investigate the importance of the tetrazole moiety as a linker, we synthesized a series of heterocyclic replacements for tetrazole. A comparison of the tetrazoles and 2- and 3-heteroatom-containing heterocyclic replacements is presented here together with synthetic and biological data.

Chemistry

The heterocyclic ureas were generally synthesized via coupling of an isocyanate with an amino heterocycle. The substitution on the amino heterocyclic ring could be put in place before or after reaction with isocyanate, depending on the heterocycle. Tetrazole ureas were synthesized by the routes illustrated in Schemes 1 and 2. Reaction of 5-aminotetrazole with an aryl isocyanate in the presence of base gave a good yield of tetrazole urea **1**. Alkylation of the tetrazole urea with an alkyl halide and triethylamine gave the 2-substituted tetrazole urea **2** as the major product (Scheme 1). A small amount of 1-alkyltetrazole urea **3** was sometimes ob-

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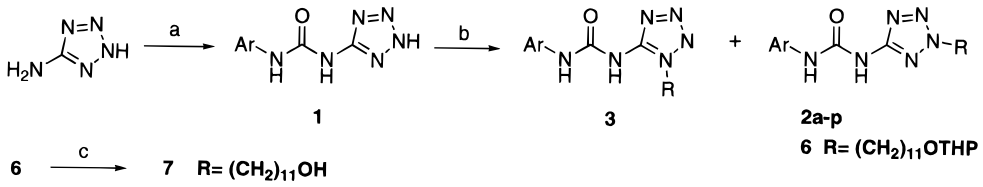
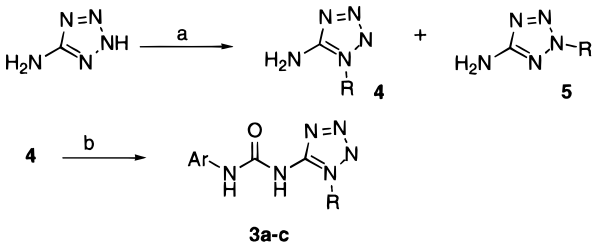
Scheme 1[a]



[a] (a) ArNCO, Et_3N, MeCN; (b) RBr, Et_3N, MeCN; (c) *p*-TSA, MeOH.

Scheme 2[a]



[a] (a) RBr, NaOH, EtOH/H_2O; (b) ArNCO, Et_3N, MeCN.

served. The 1-substituted tetrazole was obtained in a synthetically useful quantity via alkylation of 5-aminotetrazole with an alkyl halide in basic aqueous ethanol to give a mixture of the 1- and 2-alkylated aminotetrazoles **4** and **5**, respectively. The ratio of isomers varied. For R = $C_{12}H_{25}$, a 2:1 ratio was observed favoring the 2-isomer. For R = benzyl, only the 1-isomer was observed under the reaction conditions. The isomers were easily separable by crystallization or column chromatography.

The 1-alkyl-5-aminotetrazole was coupled with an aryl isocyanate in the presence of triethylamine to give the 1-substituted urea **3** (Scheme 2). The 2-substituted isomers could also be synthesized by this route. The regioisomers were assigned based on their NMR chemical shifts. The 2-isomer *N*-methylene protons are always downfield (~0.3 ppm) from the 1-isomer. The terminally substituted 2-alkyl tetrazoles **2m** and **6** were synthesized via alkylation of the intermediate **1** with an appropriately substituted bromo alcohol. Deprotection of **6** gave the terminal alcohol **7** (Scheme 1).

The methylene-spaced tetrazole ureas **10** and **11** were synthesized from tetrazoleacetic acid ethyl ester (**7a**),[19] via alkylation and chromatography to separate the 1- (**8b**) and 2- (**8a**) isomers. Saponification of **8a** afforded the acid **9**, which was subjected to a Curtius rearrangement with diphenyl phosphorazidate. Trapping the isocyanate with the requisite aniline yielded the ureas **10** and **11** (Scheme 3).

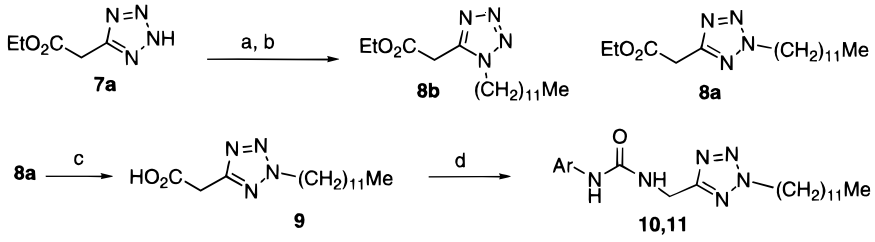
The 1,3,4-thiadiazole ureas **14a**−**c** were obtained from an alkyl carboxylic acid, which was converted to the acyl thiosemicarbazide **12** and then cyclized under acidic conditions[20] to give the alkyl amino 1,3,4-thiadiazole **13** which was coupled with an isocyanate to give the ureas (Scheme 4).

The 1,3,4-oxadiazole urea **16** was assembled via conversion of a carboxylic acid to an acyl hydrazide via reaction of the methyl ester with hydrazine. Subsequent base-induced cyclization of the acyl hydrazide with cyanogen bromide[21] yielded the 5-alkyl-2-amino-1,3,4 oxadiazole **15** which was coupled with an isocyanate by the same method used for the tetrazole ureas to give urea **16** (Scheme 5).

The *C*-alkylated triazole derivative **19** was obtained via cyclization of aminoguanidine and tridecanoic acid to afford the triazole **17**. Reaction with an aryl isocyanate afforded the undesired ring-acylated product **17a**. Prior ring acylation with acetyl chloride to give **18** and subsequent reaction with isocyanate followed by deprotection was necessary to obtain the urea **19** in good overall yield (Scheme 6).

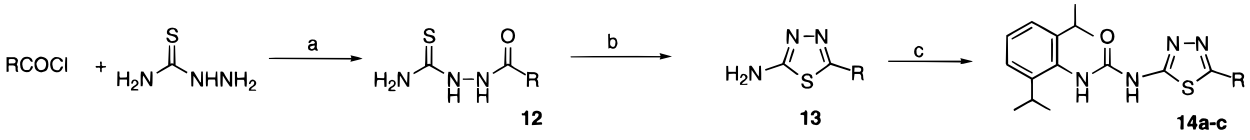
The *N*-alkylated 1,2,4-triazole derivatives **21a**−**c** were obtained via functionalization of a preformed triazole ring. The *N*-alkyl derivatives were obtained via alkylation of 3-amino-1,2,4-triazole with an alkyl bromide to give a mixture of the three ring-alkylated regioisomers **20a**−**c**). After separation by column chromatography, the assignment of regiochemistry was based on analogy with the known methyl-substituted regioiso-

Scheme 3[a]



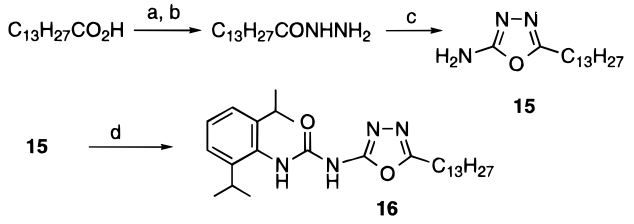
[a] (a) $Me(CH_2)_{11}Br$, Et_3N, MeCN; (b) chromatography; (c) KOH, EtOH; (d) diphenyl phosphorazidate, $ArNH_2$.

Scheme 4[a]



[a] (a) THF, 18 h; (b) $MeSO_3H$, toluene; (c) 2,6-(*i*-Pr)$_2$PhNCO, MeCN.

Scheme 5[a]



[a] (a) MeOH, HCl; (b) NH_2NH_2, MeOH; (c) BrCN, $KHCO_3$, dioxane; (d) 2,6-(*i*-Pr)$_2$PhNCO, MeCN.

mers (Scheme 7).[22] The aminotriazoles **20a**−**c** were coupled in good yield with 2,6-diisopropylphenyl isocyanate to afford the ureas **21a**−**c**.

The thioalkyl derivatives **24**−**27** were synthesized via alkylation of 3-amino-5-mercapto-1,2,4-triazole, which occurred selectively on sulfur. Subsequent reaction with an aryl isocyanate yielded only acylation on the triazole ring. This was overcome by prior ring *N*-acylation with acetyl chloride to give **23** and reaction of the exocyclic nitrogen with an aryl isocyanate to yield **24** and subsequent deprotection to give **25**. Oxidation of **25** with 1 or 2 equiv of *m*-CPBA afforded the sulfoxide (**26**) and sulfone (**27**) derivatives, respectively, in good yield (Scheme 8).

The 3,5-disubstituted isoxazole ureas **30a**−**d** and **32** were synthesized from the appropriate isoxazole amines and 2,6-diisopropylphenyl isocyanate. The isoxazole amines were assembled from an alkylacetylene via conversion to a cyanoacetylene (**28**) with phenyl cyanate.[23] Cyclization of the cyanoacetylene **28** with hydroxylamine[24] gave the 3-alkyl-5-aminoisoxazole **29**; conversely, the 5-alkyl-3-amino regioisomer **31** was obtained via cyclization with hydroxylamine and base. The regiospecific cyclizations occur because, in the absence of base, hydroxylamine adds to the acetylene; however, with base present addition to nitrile occurs faster to afford cyclization via the amidoxime (Scheme 9).

The oxazole urea **35** was sythesized from an appropriately substituted methyl ketone. Conversion to the silyl enol ether under standard conditions and oxidation with acidic workup yielded an α-hydroxy ketone (**33**). Base-induced cyclization of **33** with cyanamide[25] gave the oxazole amine **34** which was converted to the urea **35** in the manner previously described (Scheme 10).

The imidazole urea **37** was synthesized from 4-nitroimidazole. Alkylation under basic conditions of the tetrabutylammonium salt of 4-nitroimidazole[26] followed by reduction of the nitro group yielded the 1-alkyl-4-aminoimidazole. Coupling with an aryl isocyanate under normal conditions yielded the urea **37**, which was isolated as the HCl salt (Scheme 11).

The thiazole ureas **39a,b** were prepared by heating thiourea with an iodo ketone, which was generated in situ from the appropriately substituted methyl ketone and iodine.[27] The regioisomeric mixture of thiazole amines **38a,b** obtained was separable by column chromatography. Coupling with an aryl isocyanate gave the desired ureas **39a,b** (Scheme 12).

Biological Methods

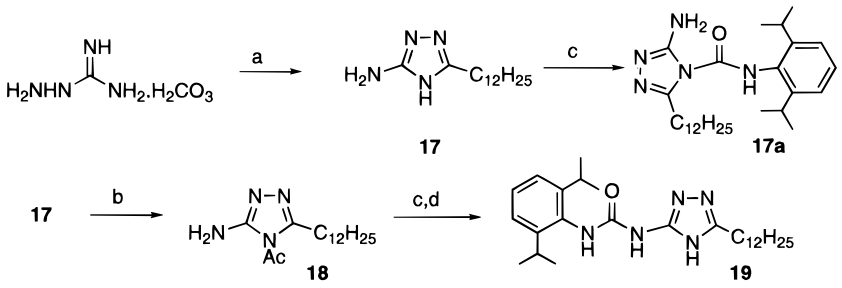
ACAT inhibition in vitro (designated as IAI) was determined via incubation of ^{14}C-labeled oleoyl-CoA with intestinal microsomes from cholesterol-fed rabbits.[11] The degree of activity was expressed as the micromolar concentration required to inhibit enzyme activity 50% (IC_{50}).

In vivo efficacy was examined in an acute assay (APCC).[14] The compounds were administered in carboxymethylcellulose (1.5%) and Tween-20 (0.2%) in water at either 3 or 30 mg/kg. The animals were then allowed to consume a diet supplemented with cholesterol. The data are expressed as percent decrease of total cholesterol (TC) relative to controls. This model measures the ability of the compound to prevent the overnight rise in plasma TC induced by a high-fat high-cholesterol meal. In a 2 week chronic model (CPCC),[28] hypercholesterolemia was first established with 1 week on a high-fat high-cholesterol diet followed by administration of the compounds for 1 week. In this model changes in TC, HDL cholesterol (HDL-C), and non-HDL cholesterol (non-HDL-C) were monitored.

Bioactivity was assessed in male New Zealand white rabbits. The animals were conditioned to meal feeding for 1 week and then given a meal containing the drug at 25 mg/kg in an oil vehicle (3% peanut oil/3% coconut oil). Blood samples were obtained at time zero (before drug) and 1, 2, and 4 h postdrug meal. The plasma samples (0.2 mL) were extracted into hexane, dried, dissolved in chloroform/methanol (2:1, v/v), and assayed for microsomal liver ACAT inhibition.[28] Standards were prepared for each drug by adding compound directly to rabbit plasma in DMSO.

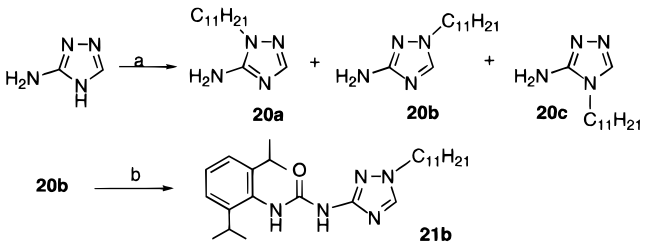
In vivo efficacy in cholesterol-fed female Beagle dogs was examined according to the method described by Krause et al.[28] The dogs were dosed as bulk drug in capsules daily before meals for 1 week. Efficacy is expressed as the percent change in plasma TC before and after treatment. Plasma blood drug levels were determined in the dog with an HPLC assay. Animals were dosed orally once daily for 1 week. Single blood samples were taken 6 h post dose on the last day. The

Scheme 6[a]



[a] (a) $C_{12}H_{25}CO_2H$, $PhNMe_2$, toluene; (b) AcCl, THF, Et_3N; (c) 2,6-(*i*-Pr)$_2$PhNCO, MeCN; (d) MeOH.

Scheme 7[a]



[a] (a) (i) $C_{11}H_{21}Br$, NaOMe, MeOH, (ii) chromatography; (b) 2,6-(*i*-Pr)$_2$PhNCO, MeCN.

HPLC method comprised a Grom Spherisorb C8 column with acetonitrile/water (4:1 v/v) as eluent and detection at 190 nm. Retention times were 6.3 min for **2h** and 7.6 min for **2i**. Both compounds served as internal standards alternately. The minimum quantitation limit was 40 ng/mL.

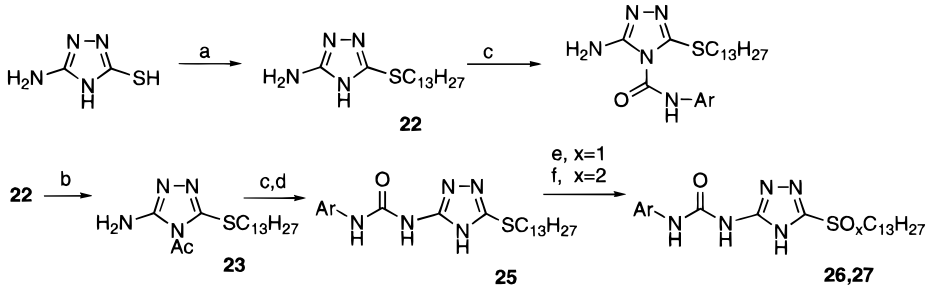
Results and Discussion

On the basis of the inactivity of compound **1** (Table 1), alkylation of the tetrazole NH is essential for activity. However alkylation with the benzyl group produced a compound (**2a**) of modest potency (IAI $IC_{50} = 0.37\ \mu M$). A 3-fold increase in potency in vitro was obtained with the 2-butyl group (**2b**) (IAI $IC_{50} = 0.092\ \mu M$). This compound however possessed little in vivo activity. We had observed in other series[14,16] a threshold lipophilicity (CLOGP = calculated lipophilicity)[29] of greater than 6 was required for good in vivo efficacy. Further extension of the alkyl side chain increased the lipophilicity and revealed a series of extremely potent compounds in vitro and in vivo (**2f**−**k**). The in vivo activity of compounds **2c**−**k** at a dose of 30 mg/kg was essentially equivalent. At a dose of 3 mg/kg in the APCC rat model, the undecyl to tetradecyl side chains (**2g**−**j**) were still effective in lowering total cholesterol. Activity was maximal with the C13 side chain analog **2i** and declined with a further increase in chain length. This probably resulted from the compounds being extremely lipophilic and consequently not being absorbed. The in vitro activity of the 2-decyl to the 2-tetradecyl compounds **2f**−**j** was $IC_{50} \leq 0.014\ \mu M$. The effect of substitution on the alkyl chain was examined. Terminal tetrahydropyranyl ether (**6**) and hydroxyl (**7**) substituents resulted in compounds less active in vivo though still retaining good potency in vitro. The 2-geranyl derivative **2n** was equipotent in vitro with the unsubstituted analog of similar length (**2b**). However efficacy fell off in vivo with the more substituted geranyl side chain. A terminal ester functionality (**2m**) imparted a significant loss of in vitro and in vivo activity. However, possible hydrolysis under the assay conditions would yield a carboxylic acid function, which has been shown in other series to have a detrimental effect on activity both in vitro and in vivo.[16]

To examine which regioisomeric substitution on the tetrazole was optimal, we compared the 1-substituted isomers **3b,c** with the corresponding 2-substituted isomers **2h,p** and discovered the 2-substituted isomers were optimal. Although in one case the 2,4,6-trimethoxyphenyl analog (**2p** vs **2h**) was more efficacious in vivo than the 2,6-diisopropyl, we decided to expand the tetrazole series using 2-substitution on the tetrazole ring of the parent *N*-(2,6-diisopropylphenyl)-*N*′-tetrazoyl urea moiety (**1**).

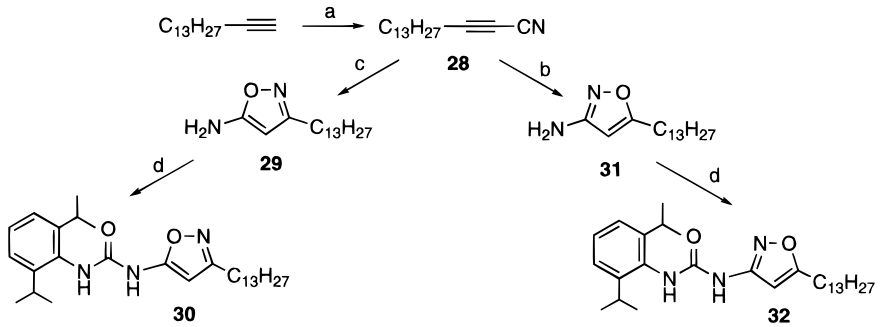
In order to determine which aryl moiety was optimal in the heterocyclic ureas, we compared several 2,4,6-trimethoxyphenyl (**2p, 3c**) and 2,6-diisopropylphenyl (**2h, 3b**) analogs in the aminotetrazole series (Table 1) and tetrazole methyleneamino series (**10, 11**) (Table 2) and compared their abilities to inhibit ACAT in vitro

Scheme 8[a]



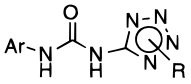
[a] (a) $C_{13}H_{27}Br$, Et_3N, MeCN; (b) AcCl, Et_3N, THF; (c) ArNCO, MeCN; (d) MeOH; (e) *m*CPBA (1 equiv), CH_2Cl_2; (f) *m*-CPBA (2 equiv), CH_2Cl_2.

Scheme 9[a]



[a] (a) *n*-BuLi, Et_2O, −78 °C, PhOCN; (b) $NH_2OH{\cdot}HCl$, NaOH (2 equiv), EtOH; (c) $NH_2OH{\cdot}HCl$, NaOH (1 equiv), EtOH; (d) 2,6-(*i*-Pr)$_2$PhNCO, MeCN.

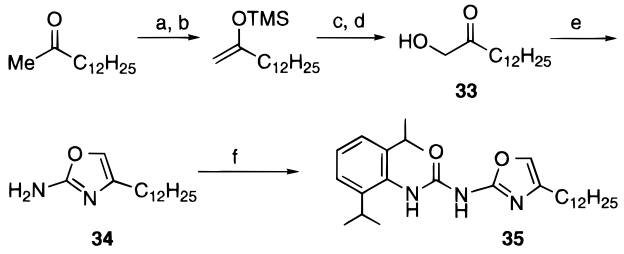
Table 1. Tetrazole Ureas: ACAT Inhibition in Vitro and Hypocholesterolemic Activity in Vivo



compd	Ar[a]	R	IAI[b] IC_{50} (μM)	APCC[c] % ΔTC 30 mg/kg	APCC[c] % ΔTC 3 mg/kg	CLOGP[d]
1	DIP	H	>10	−19	ND	2.02
2a	DIP	2- CH_2Ph	0.37	−27*	ND	3.63
2b	DIP	2-$(CH_2)_3Me$	0.092	−26	ND	3.65
2c	DIP	2-$(CH_2)_5Me$	0.073	−59*	−21	4.71
2d	DIP	2-$(CH_2)_7Me$	0.059	−67*	−24	5.77
2e	DIP	2-$(CH_2)_8Me$	0.031	−65*	+1	6.30
2f	DIP	2-$(CH_2)_9Me$	0.014	−62*	−35*	6.83
2g	DIP	2-$(CH_2)_{10}Me$	0.009	−70*	−63*	7.36
2h	DIP	2-$(CH_2)_{11}Me$	0.014	−67*	−61*	7.88
2i	DIP	2-$(CH_2)_{12}Me$	0.009	−67*	−67*	8.41
2j	DIP	2-$(CH_2)_{13}Me$	0.012	−65*	−56*	8.94
2k	DIP	2-$(CH_2)_{15}Me$	0.057	−67*	−43*	10.00
2m	DIP	2-$(CH_2)_{10}CO_2Me$	4.7	−23	ND	5.79
2n	DIP	2-geranyl	0.063	−27	ND	5.60
2p	TMP	2-$(CH_2)_{11}Me$	0.066	−75*	−69*	6.23
3a	DIP	1-$(CH_2)_9Me$	0.18	−65*	−22	7.17
3b	DIP	1-$(CH_2)_{11}Me$	0.21	−57*	−45*	8.23
3c	TMP	1-$(CH_2)_{11}Me$	28% @ 1 μM	ND	ND	6.40
6	DIP	2-$(CH_2)_{11}OTHP$	0.037	−53*	−28*	6.67
7	DIP	2-$(CH_2)_{11}OH$	0.032	−28*	ND	5.37

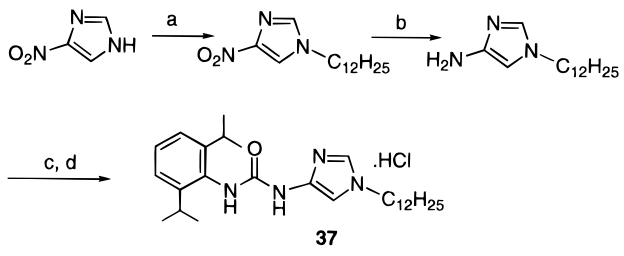
[a] DIP = 2,6-diisopropylphenyl, TMP = 2,4,6-trimethoxyphenyl. [b] ACAT inhibition in vitro measured in rabbit intestinal microsomes. [c] Denotes percent change in plasma TC in an acute C-fed rat model of hypercholesterolemia, with $p < 0.05$* and ND = not determined. [d] Reference 29, CLOGP refers to calculated lipophilicity.

Scheme 10[a]



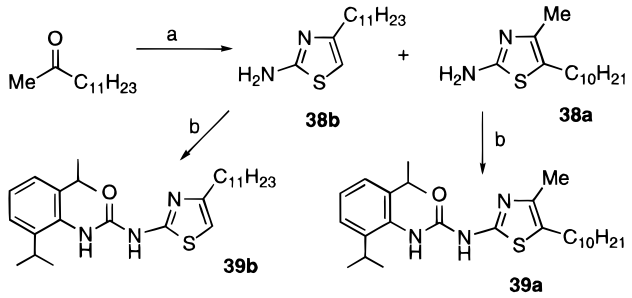
[a] (a) LDA, THF; (b) TMSCl; (c) *m*-CPBA; (d) HCl, Et_2O; (e) H_2NCN, THF/H_2O, NaOH, Bu_4NOH; (f) 2,6-(*i*-Pr)$_2$PhNCO, MeCN, Et_3N.

Scheme 11[a]



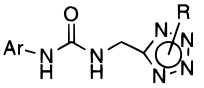
[a] (a) $C_{12}H_{25}Br$, NaOH, MeOH; (b) 5% Pd/C, H_2, MeOH; (c) 2,6-(*i*-Pr)$_2$PhNCO, EtOAc; (d) HCl, Et_2O.

Scheme 12[a]



[a] (a) Thiourea, I_2, 100 °C; (b) 2,6-(*i*-Pr)$_2$PhNCO, Et_3N, MeCN.

Table 2. Tetrazole Ureas: ACAT Inhibition in Vitro and Hypocholesterolemic Activity in Vivo



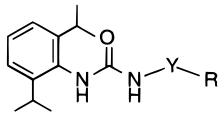
compd	Ar[a]	R	IAI[b] IC_{50} (μM)	APCC[c] % ΔTC 30 mg/kg	APCC[c] % ΔTC 3 mg/kg	CLOGP[d]
10	DIP	2-$(CH_2)_{11}Me$	0.012	−58*	−31*	7.86
11	TMP	2-$(CH_2)_{11}Me$	0.15	−40*	ND	6.21

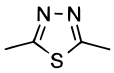
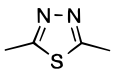
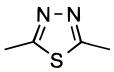
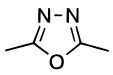
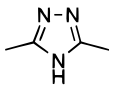
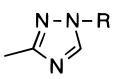
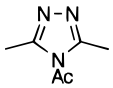
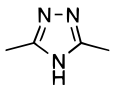
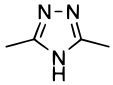
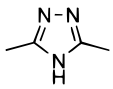
[a–d] See corresponding footnotes in Table 1.

and lower plasma TC in the acute C-fed rat assay. The 2,4,6-trimethoxyphenyl analogs **2p, 3c,** and **11** were all less potent in vitro than the corresponding 2,6-diisopropylphenyl analogs **2h, 3b,** and **10**. The 2,6-diisopropylphenyl analog **2h** and the corresponding 2,4,6-trimethoxyphenyl **2p** were equivalent in vivo. However the 2,4,6-trimethoxyphenyl analog **11** was less efficacious than 2,6-diisopropyl analog **10**. There was a general trend toward better overall activity with the 2,6-diisopropyl substitution; thus, this was chosen.

The potency of the tetrazole ureas necessitated an examination of the role of the heterocyclic linker. The tetrazole ring was replaced by various other heterocycles bearing 2- and 3-heteroatom replacements. From the tetrazole urea studies, the 2,6-diisopropylphenyl and the C11−14 alkyl chain were the substituents of choice when assessing the viability of the heterocyclic replacements for tetrazole. The 3-heteroatom replacements were examined, and the results are depicted in Table 3. The 1,3,4-thiadiazole **14a** was 3-fold less active in vitro and also less active in vivo than the corresponding tetrazole **2i**. The 1,3,4-oxadiazole **16** proved an excellent bioisosteric replacement for tetrazole in vitro and in the APCC rat at a dose of 30 mg/kg. However lower

Table 3. 3-Heteroatom Heterocyclic Ureas: ACAT Inhibition in Vitro and Hypocholesterolemic Activity in Vivo



Compound	Y	R	IAI[b] $IC_{50}(\mu M)$	%Δ APCC[c] 30mg/kg	%Δ APCC[c] 3mg/kg	CLOGP[d]
14a		$(CH_2)_{12}Me$	0.036	-46*	ND	10.03
14b		$(CH_2)_{10}Me$	0.039	-61*	ND	8.97
14c		$(CH_2)_8Me$	0.15	-39*	ND	7.91
16		$(CH_2)_{12}Me$	0.018	-62*	-34*	9.20
19		$(CH_2)_{11}Me$	4.2	+12	ND	9.01
21a		$(CH_2)_{11}Me$	0.25	-36*	ND	8.74
21b		$(CH_2)_{11}Me$	0.12	-30*	ND	8.74
21c		$(CH_2)_{11}Me$	1.5	-28*	ND	8.37
24		$S(CH_2)_{12}Me$	0.68	-21	ND	10.05
25		$S(CH_2)_{12}Me$	0.39	+12	ND	10.37
26		$SO(CH_2)_{12}Me$	1.7	-6	ND	8.40
27		$SO_2(CH_2)_{12}Me$	4.7	-11	ND	8.43

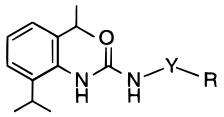
[a–d] See corresponding footnotes in Table 1.

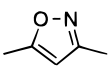
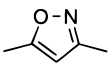
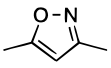
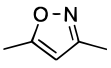
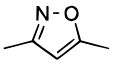
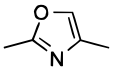
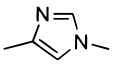
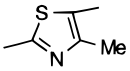
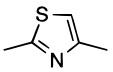
efficacy was observed at 3 mg/kg in vivo. The triazole ureas **19**−**27** were considerably less active in vitro than the tetrazoles. A comparison of the long chain regioisomers showed N-alkylation (**21a**−**c**) to be superior to *C*-alkylation (**19**). *C*-Alkylation presents a free NH, the presence of which may lower activities in vitro and in vivo.[16] The *N*-alkylated 1,3-substituted regioisomer **21b** imparted more activity than 1,2-substitution (**21c**) in vitro, in agreement with the structure-activity relationship (SAR) observed with 1- and 2-alkylated tetrazoles, with relative 1,3-substitution being optimal. However, in contrast **21b** was essentially equipotent with the other 1,2-regioisomer **21a**.

Insertion of a sulfur in the alkyl chain on the triazoles (**25**) improved the in vitro activity over the *C*-alkylated series (**19**). Further oxidation of sulfur decreased in vitro activity (**26**, **27**). The presence of the free ring NH in these derivatives is also detrimental to in vivo activity. Only when the ring nitrogen was acylated (**24**) was some in vivo activity observed, although this was not statistically significant.

When the 2-heteroatom replacements for tetrazole were examined (Table 4), the isoxazole (**30a**−**d, 32**) moiety proved optimal in vitro and in vivo. The 3-alkyl (**30b**) regioisomer when compared with the 5-alkyl (**32**) showed no difference between the two regioisomers. The

Table 4. 2-Heteroatom Heterocyclic Ureas: ACAT Inhibition in Vitro and Hypocholesterolemic Activity in Vivo



Compound	Y	R	IAI[b] $IC_{50}(\mu M)$	%Δ APCC[c] 30mg/kg	%Δ APCC[c] 3mg/kg	CLOGP[d]
30a		$(CH_2)_{13}Me$	0.028	-64*	-44*	10.67
30b		$(CH_2)_{12}Me$	0.013	-62*	-51*	10.14
30c		$(CH_2)_{11}Me$	0.019	-61*	-58*	9.61
30d		$(CH_2)_9Me$	0.029	-69*	-61*	8.55
32		$(CH_2)_{12}Me$	0.014	-62*	-59*	10.14
35		$(CH_2)_{11}Me$	0.063	-55*	ND	8.83
37		$(CH_2)_{11}Me$	0.035	ND	ND	9.11
39a		$(CH_2)_9Me$	0.12	-33*	ND	9.25
39b		$(CH_2)_{10}Me$	0.15	-29*	ND	9.56

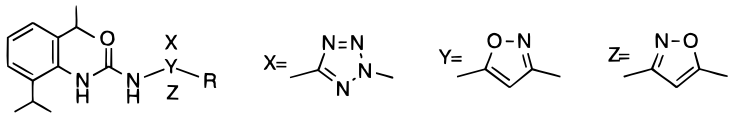
[a–d] See corresponding footnotes in Table 1.

optimal isoxazoles **30c,d** and **32** were essentially equipotent and efficacious with the optimal tetrazoles **2g–j** in vitro and in the APCC rat model when dosed at 3 mg/kg. The imidazole replacement **37** ($IC_{50} = 0.035\ \mu M$) displayed good in vitro activity but was not as potent as the tetrazole **2h** in vivo in the APCC rat model dosed at 30 mg/kg. The oxazole ring replacement **35** ($IC_{50} = 0.063\ \mu M$) was weaker in vitro and in the APCC rat model when dosed at 30 mg/kg than both tetrazole **2i** ($IC_{50} = 0.009\ \mu M$)] and the closely related isoxazole **30c** ($IC_{50} = 0.020\ \mu M$). The latter observation is suprising, as lipophilicity is similar and the three compounds all present 1,3-substitution on the heterocycle. The thiazole ring (**39a,b**) was the least active of the 2-heteroatom replacements, significantly less active both in vitro and in vivo in the APCC rat dosed at 30 mg/kg. This correlates with the 3-heteroatom replacement SAR, at least in vivo, where lower activity was observed with the sulfur-containing 1,3,4-thiadiazoles **14a–c** in the APCC rat model dosed at 30 mg/kg.

Efficacy in the Chronic Rat Model of Preestablished Hypercholesterolemia. The acute APCC rat model was not sufficient to distinguish between the more potent tetrazole ureas **2h–j** and isoxazole ureas **30a–d** and **32**. The compounds were evaluated in the chronic rat model. The tetrazole ureas **2h–j** were all efficacious and essentially equivalent at lowering both TC and non-HDL-C at all doses tested as shown in Table 5. A dose dependent rise in HDL-C was also observed, being significant at the 10 and 30 mg/kg doses. The oxadiazole ureas were all evaluated at a single dose of 30 mg/kg. The isoxazole ureas **30b,c** were essentially equivalent to the tetrazoles. However, for the C10 and C14 analogs **30d**,**a**, efficacy fell off sharply. The 3-amino-5-alkyl regioisomer **30b** was superior to the 5-alkyl-3-aminooxadiazole **32**, especially for HDL-C elevation.

Efficacy in Cholesterol-Fed Dogs and Adrenal Toxicity. The compounds **2h–j** were evaluated in cholesterol-fed dogs at a dose of 3 mg/kg po (Table 6). All compounds lowered plasma TC in a statistically significant manner. Compound **2i** containing the C13 side chain was the most effective at lowering TC. Plasma drug blood levels were determined by HPLC in the dog for **2i**,**h** (Table 6); both compounds are present in plasma although there is significant variability consistent with the compounds being very lipophilic. The assay could not determine levels below 40 ng/mL, and the results (Table 6) represent a mean of 6 animals. As a result of the excellent in vivo activity displayed by these compounds, several were tested in a model to assess adrenal toxicity in guinea pigs in vivo.[30] This problem has been observed previously with potent lipophilic urea ACAT inhibitors but was thought to be unrelated to ACAT inhibition.[30] Unfortunately, **2i,h**

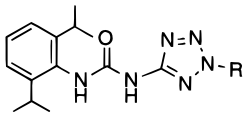
Table 5. Efficacy in the Rat Model of Pre-established Hypercholesterolemia



				CPCC		
compd	heterocycle	R	dose[a] (mg/kg)	% ΔTC[b]	% ΔHDL-C[c]	% Δnon-HDL-C[d]
2h	X	$(CH_2)_{11}Me$	30	−69*	+93*	−78*
2h	X	$(CH_2)_{11}Me$	10	−64*	+87*	−72*
2h	X	$(CH_2)_{11}Me$	3	−43*	+20	−47*
2i	X	$(CH_2)_{12}Me$	30	−66*	+113*	−76*
2i	X	$(CH_2)_{12}Me$	10	−64*	+113*	−73*
2i	X	$(CH_2)_{12}Me$	3	−52*	+21*	−47*
2j	X	$(CH_2)_{13}Me$	30	−61*	+93*	−68*
2j	X	$(CH_2)_{13}Me$	10	−53*	+87*	−61*
2j	X	$(CH_2)_{13}Me$	3	−43*	+47	−48*
30a	Y	$(CH_2)_{13}Me$	30	−16	+16	−18
30b	Y	$(CH_2)_{12}Me$	30	−53	+111*	−65*
30c	Y	$(CH_2)_{11}Me$	30	−56*	+100*	−68*
30d	Y	$(CH_2)_9Me$	30	−13	−6	−14
32	Z	$(CH_2)_{12}Me$	30	−40	+33	−45

[a] Dose of compound administered daily for 1 week, after 1 week on high-C diet. [b] Denotes percent change in plasma TC in the chronic C-fed rat model of pre-established hypercholesterolemia. [c] Denotes percent change in HDL-C. [d] Denotes percent change in non-HDL-C. The percent change in TC, HDL-C, and non-HDL-C was statistically significant from control with $p < 0.05$*.

Table 6. Tetrazole Ureas: Efficacy in Cholesterol-Fed Dogs at 3 mg/kg



compd	R	%Δ plasma cholesterol[a]	plasma levels[b] (ng/mL)
2h	$(CH_2)_{11}Me$	−39*	29.3 ± 45.8
2i	$(CH_2)_{12}Me$	−47*	76.7 ± 65.6
2j	$(CH_2)_{13}Me$	−22	ND

[a] Represents mean percent change in plasma TC relative to controls dosed at 3 mg/kg, statistically significant, $p < 0.05$* using paired, two-tailed *t*-test ($n = 6$). [b] Mean blood drug concentration in the dog, compound dosed at 3 mg/kg. ND = not determined.

caused adrenal cortical atrophy of the zona fasciculata and necrosis of adrenal cortical cells in the adrenal cortex. The isoxazole urea **30c** was also examined and found not to be overtly toxic. However it did increase cytoplasmic coarse vacuolation in the zona fasciculata. The significance of this finding has yet to be established.

Conclusion

This study has identified a series of ACAT inhibitors which are extremely potent in vitro and effective at lowering plasma cholesterol in cholesterol-fed rats and dogs. The activity is optimized by having the substituent on the heterocycle 1,3-oriented. In vivo, certain examples from the isoxazoles were shown to be equivalent to the tetrazole at 30 mg/kg in cholesterol-fed rats. The triazoles and thiazoles were significantly less active. A heterocycle containing nitrogen and/or oxygen seems to be desirable as a linker, except when this heterocycle is triazole or even less optimal when it furnishes a free ring NH. A sulfur atom in the heterocycle leads to compounds of lower activity.

In general the tetrazole-substituted ureas were the most potent in vitro and the most effective at lowering plasma TC in vivo. The optimal tetrazole urea **2i** when dosed at 3 mg/kg lowered total cholesterol 49% in an acute cholesterol-fed rat model and 47% in cholesterol-fed dogs. Tetrazole **2i** also lowered TC 52% and raised HDL-C 113% in rats with pre-established hypercholesterolemia dosed at 10 mg/kg, but was adrenotoxic in guinea pigs. The isoxazole urea **30c** was not overtly toxic. Our efforts to exploit the inherent activity of the heterocycle and overcome the toxicities observed with this series will be the subject of future publications.

Experimental Section

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Column chromatography was performed on Merck silica gel 60 (230−400 mesh). Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were determined on a Brucker 250 MHz, VarianXL 300 MHz, or Varian Unity 400 MHz instrument. Chemical shifts (δ) are expressed in ppm, relative to internal tetramethylsilane. Mass spectra were obtained on a VG Masslab Trio-2A, or VG Analytical 7070E/HF, or Finnigan 4500 mass spectrometer. Elemental analyses were determined on a Perkin-Elmer 240C elemental analyzer and were within ±0.4%.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(1*H*-tetrazol-5-yl)-urea (1).** 5-Aminotetrazole hydrate (45 g, 0.44 mol) was refluxed in toluene (300 mL) in the presence of a Dean−Stark trap. After removal of the theoretical amount of water (7.9 mL), the mixture was allowed to cool and concentrated in vacuo and the resulting solid stirred with acetonitrile (500 mL). Triethylamine (61 mL, 0.44 mol) and 2,6-diisopropylphenyl isocyanate (89.3 mL, 0.44 mol) were added sequentially, and the mixture was refluxed for 4 h. The mixture was then allowed to cool and concentrated in vacuo to about 200 mL, and acidified with l M citric acid. The solid was filtered, washed with water (l L) and ethyl acetate (1 L), and pumped in vacuo for 12 h to give the title compound, 87.6 g (69% yield): mp >240 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 1.14 (d, $J = 7.5$ Hz, 12H), 3.11 (m, 2H), 7.18 (d, $J = 7$ Hz, 2H), 7.27−7.32 (m, 1H), 8.12 (s, 1H), 10.63 (s, 1H), 15.45 (s br, 1H); EIMS *m*/*z* 288 (M^+). Anal. ($C_{14}H_{20}N_6O$) C, H, N.

***N*-[2,6-bis(1-methylethyl)phenyl]-*N′*-(2-tetradecyl-2*H*-tetrazol-5-yl)urea (2j).** 1-Bromotetradecane (26.1 g, 0.094 mol) was added to a refluxing solution of **1** (24.8 g, 0.086 mol), triethylamine (9.51 g, 0.094 mol), and acetonitrile (300 mL). The mixture was allowed to reflux for 18 h, cooled, and filtered, and the solid obtained recrystallized from hot acetonitrile to give a white solid (25.0 g, 60%): mp 112−114 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 7$ Hz, 3H), 1.20 (s, 22H), 2.00 (m, 2H),

3.17 (heptet, $J = 7$ Hz 2H), 4.54 (t, $J = 7$ Hz, 2H), 7.19−7.35 (m, 3H), 8.70 (s, 1H), 9.03 (s, 1H); EIMS m/z 485 (MH^+). Anal. ($C_{28}H_{48}N_6O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(2-nonyl-2*H*-tetrazol-5-yl)urea (2e).** The compound was prepared as in the above procedure for **2j** using l-bromononane (17% yield): mp 128−130 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 0.84 (t, $J = 7$ Hz, 3H), 1.14 (d, $J = 7.5$ Hz, 12H), 1.22 (s, 12H), 1.89 (m, 2H), 3.13 (m, 2H), 4.58 (t, $J = 7$ Hz, 2H), 7.16−7.31 (m, 3H), 8.44 (s, 1H), 10.18 (s, 1H); CIMS m/z 414 (MH^+). Anal. ($C_{23}H_{38}N_6O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(2-dodecyl-2*H*-tetrazol-5-yl)urea (2h).** The compound was prepared as in the above procedure for **2j** using l-bromododecane (30% yield): mp 117−119 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 7$ Hz, 3H), 1.25 (s sh, 30H), 2.00 (m, 2H), 3.19 (m, 2H), 4.54 (t, $J = 7$ Hz, 2H), 7.19−7.35 (m, 3H), 8.43 (s, 1H), 9.01 (s, 1H); CIMS m/z 457 (MH^+). Anal. ($C_{26}H_{44}N_6O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(2-hexadecyl-2*H*-tetrazol-5-yl)urea (2k).** The compound was prepared as in the above procedure for **2j** using l-bromohexadecane (43% yield): mp 108−111 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 0.85 (t, $J = 7$ Hz, 3H), 1.14 (d, $J = 7.5$ Hz, 12H), 1.23 (s, 26H), 1.89 (m, 2H), 3.12 (m, 2H), 4.57 (t, $J = 7$ Hz, 2H), 7.16−7.31 (m, 3H), 8.43 (s, 1H), 10.15 (s, 1H); EIMS m/z 513 (MH^+). Anal. ($C_{30}H_{52}N_6O$) C, H, N.

***N*-(2,4,6-Trimethoxyphenyl)-*N′*-(2-dodecyl-2*H*-tetrazol-5-yl)urea (2p).** The compound was prepared as in the above procedure for **2j** and **1** using *N*-(2,4,6-trimethoxyphenyl)-isocyanate.[12] The crude reaction mixture was allowed to cool; the precipitate obtained was filtered and chromatographed on silica gel eluting with 50% ethyl acetate in hexanes to give an off-white solid as the title compound (25% yield): mp 161−166 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 0.85 (t, $J = 7$ Hz, 3H), 1.23 (s, 18H), 1.87 (m, 2H), 3.74 (s, 6H), 3.79 (s, 3H), 4.56 (t, $J = 7$ Hz, 2H), 6.27 (s, 2H), 7.79 (s, 1H), 9.88 (s, 1H); EIMS m/z 462 (M^+). Anal. ($C_{23}H_{38}N_6O_4$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(2-tridecyl-2*H*-tetrazol-5-yl)urea (2i).** 1-Bromotridecane (5.48 g, 0.022 mol) was added to a refluxing solution of **1** (6.0 g, 0.021 mol), triethylamine (2.1 g, 0.021 mol), and acetonitrile (175 mL). The solution was refluxed for 6 days, cooled, concentrated, and partitioned between l M citric acid and ethyl acetate. The organics were washed with water, dried over Na_2SO_4, concentrated in vacuo, and chromatographed on silica gel eluting with 15% ethyl acetate in hexane to give a white solid (1.2 g, 12%): mp 110−114 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 0.85 (t, $J = 7$ Hz, 3H), 1.14 (d, $J = 7.5$ Hz, 12H), 1.23 (s, 20H), 1.89 (m, 2H), 3.13 (m, 2H), 4.58 (t, $J = 7$ Hz, 2H), 7.16−7.31 (m, 3H), 8.43 (s, 1H), 10.18 (s, 1H); CIMS m/z 471 (MH^+). Anal. ($C_{27}H_{46}N_6O_4$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-[2-(phenylmethyl)-2*H*-tetrazol-5-yl]urea (2a).** The compound was prepared as in the above procedure for **2i** using benzyl bromide. The crude reaction mixture was cooled, concentrated in vacuo, and partitioned between ethyl acetate/1 M HCl. The organics were dried over $MgSO_4$ and concentrated and the solid obtained recrystallized from hot acetonitrile (29% yield): mp 180−181 °C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.19 (s br, 12H), 3.15 (m, 2H), 5.70 (s, 2H), 7.16−7.43 (m, 8H), 7.94 (s, 1H), 8.92 (s, 1H); CIMS m/z 379 (MH^+). Anal. ($C_{21}H_{26}N_6O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(2-butyl-2*H*-tetrazol-5-yl)urea (2b).** The compound was prepared as in the above procedure for **2i** using 1-bromobutane and chromatographed on silica gel eluting with 50% ethyl acetate in hexane (23% yield): mp 174−179 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 0.90 (t, $J = 7$ Hz, 3H), 1.14 (d, $J = 7.5$ Hz, 12H), 1.29 (m, 2H), 1.88 (m, 2H), 3.11 (m, 2H), 4.59 (t, $J = 7$ Hz, 2H), 7.16−7.31 (m, 3H), 8.41 (s, 1H), 10.12 (s, 1H); EIMS m/z 345 (MH^+). Anal. ($C_{18}H_{28}N_6O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(2-hexyl-2*H*-tetrazol-5-yl)urea(2c).** The compound was prepared as in the above procedure for **2i** using 1-bromohexane, refluxed for 3 days, allowed to cool, and concentrated in vacuo. The mixture was partitioned between ethyl acetate and 1 M HCl and the organic layer dried over $MgSO_4$, concentrated, and recrystallized from acetonitrile (48% yield): mp 154−156 °C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.90 (t, $J = 7$ Hz, 3H), 1.24 (s br, 14H), 1.35 (s, 4H), 2.02 (m, 2H), 3.19 (m, 2H), 4.55 (t, $J = 7$ Hz, 2H), 7.21−7.33 (m, 3H), 7.53 (s, 1H), 8.99 (s, 1H); EIMS 372 (M^+). Anal. ($C_{20}H_{32}N_6O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(2-undecyl-2H-tetrazol-5-yl)urea (2g).** The compound was prepared as in the above procedure for **2i** using 1-bromoundecane and chromatographed on silica gel eluting with 15% ethyl acetate in hexane (25% yield): mp 119−121 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 0.85 (t, $J = 7$ Hz, 3H), 1.14 (d, $J = 7.5$ Hz, 12H), 1.22 (s, 16H), 1.89 (m, 2H), 3.09 (m, 2H), 4.58 (t, $J = 7$ Hz, 2H), 7.16−7.31 (m, 3H), 8.42 (s, 1H), 10.12 (s, 1H). EIMS m/z 443 (MH^+). Anal. ($C_{25}H_{42}N_6O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-[2-[10-(methoxycarbonyl)decyl]-2*H*-tetrazol-5-yl]urea (2m).** The compound was prepared as in the above procedure for **2i** using 11-bromoundecanoic acid methyl ester and chromatographed on silica gel eluting with 20% ethyl acetate in hexane (19% yield): mp 80−85 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 1.25 (m, 24H), 1.61 (m, 2H), 1.99 (m, 2H), 2.30 (t, $J = 8$ Hz, 2H), 3.19 (m, 2H), 3.66 (s, 3H), 4.54 (t, $J = 7$ Hz, 2H), 7.19−7.34 (m, 3H), 8.58 (s, 1H), 9.02 (s, 1H); CIMS m/z 487 (MH^+). Anal. ($C_{26}H_{42}N_6O_3$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-[2-(3,7-dimethyl-2,6-octadienyl)-2*H*-tetrazol-5-yl]urea (2n).** The compound was prepared as in the above procedure for **2i** using geranyl bromide and chromatographed on silica gel eluting with 20% ethyl acetate in hexane (33% yield): mp 98−107 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 1.21 (m, 15H), 1.58 (s, 3H), 1.66 (s, 3H), 1.81 (s, 2H), 1.97 (m, 1H), 2.08 (s, 3H), 3.19 (m, 2H), 4.70 (m, 1H), 5.05 (m, 1H), 5.14 (d, $J = 7$ Hz, 2H), 5.49 (t, $J = 7$ Hz, 1H), 7.21−7.34 (m, 3H), 8.84 (s, 1H), 9.07 (s, 1H); EIMS m/z 424 (M^+). Anal. ($C_{24}H_{36}N_6O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(2-octyl-2*H*-tetrazol-5-yl)urea (2d).** A mixture of **1** (2.0 g, 6.94 mmol), l-bromooctane (1.8 mL, 10.4 mmol), and triethylamine (1.0 mL, 7 mmol) in a 1:1 mixture of dimethylformamide/toluene (100 mL) was heated to reflux for 18 h and then cooled and partitioned between l N HCl and ethyl acetate. The organic layer was washed three times with water, dried over $MgSO_4$, and filtered and the filtrate evaporated to dryness. The remaining solid was chromatographed on silica gel in ethyl acetate/hexane to give the title compound (0.94 g, 34%): mp 139−140 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 7$ Hz, 3H), 1.24 (m, 22H), 2.00 (m, 2H), 3.19 (m, 2H), 4.54 (t, $J = 7$ Hz, 2H), 7.19−7.35 (m, 3H), 8.44 (s, 1H), 9.02 (s, 1H); EIMS m/z 401 (MH^+). Anal. ($C_{22}H_{36}N_6O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(2-decyl-2*H*-tetrazol-5-yl)urea (2f).** Solid $NaHCO_3$ (2 g, 0.02 mol) and 1-bromodecane (2 mL, 0.01 mol) were added to a solution of **1** in DMF (30 mL). The mixture was stirred at 80 °C for 6 h, allowed to cool, diluted with DMF (100 mL), and extracted with Et_2O. The organic layer was washed three times with water, dried with $MgSO_4$, concentrated, and chromatographed on silica gel in ethyl acetate/hexane to yield a greasy solid which was recrystallized from Et_2O/hexane to give the title compound (0.76 g, 34%): mp 123−124 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 7$ Hz, 3H), 1.26 (m, 26H), 2.00 (m, 2H), 3.18 (m, 2H), 4.54 (t, $J = 7$ Hz, 2H), 7.18−7.32 (m, 3H), 7.96 (s, 1H), 9.00 (s, 1H); EIMS m/z 429 (MH^+). Anal. ($C_{24}H_{40}N_6O$) C, H, N.

5-Amino-1-dodecyltetrazole (4) and 5-Amino-2-dodecyltetrazole (5). 1-Bromododecane (46.8 g, 0.188 mol) was added in one portion to a refluxing solution of hydrated 5-aminotetrazole (20.0 g, 0.19 mol) and sodium hydroxide (8 g, 0.2 mol) in 550 mL of ethanol/water (4:1.5, v/v). The resulting mixture was refluxed for 18 h, allowed to cool, filtered, and washed with ethanol (2 × 50 mL), and the resulting solid was dried in vacuo to give 17.85 g of a mixture of isomers. The mixture was recrystallized from acetonitrile (250 mL) to give 6.85 g (14%) of 5-amino-1-dodecyltetrazole: mp 159−160 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 0.86 (t, $J = 7$ Hz, 3H), 1.24 (s, 18H), 1.69 (m, 2H), 4.06 (t, $J = 7$ Hz, 2H), 6.66 (s, 2H); EIMS m/z 254 (MH^+). Anal. ($C_{13}H_{27}N_5$) C, H, N.

The crude reaction filtrate from above was concentrated to two-thirds volume in vacuo and allowed to crystallize. The mixture was filtered to yield a solid, which was dried in vacuo to give 9.95 g (21%) of 5-amino-2-dodecyltetrazole: mp 62.5−63.5 °C; 400 MHz ^{1}H NMR (DMSO-d_6) δ 0.85 (t, J = 6.8 Hz, 3H), 1.23 (s, 18H), 1.80 (m, 2H), 4.35 (t, J = 6.8 Hz, 2H), 5.98 (s, 2H); CIMS m/z 254 (MH^+). Anal. ($C_{13}H_{27}N_5$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(1-dodecyl-1H-tetrazol-5-yl)urea (3b).** Triethylamine (2.50 mL, 18.0 mmol) was added to a slurry of **4** (4.56 g, 18.0 mmol) in acetonitrile (150 mL). The mixture was heated to reflux, and upon dissolution of the solid 2,6-diisopropylphenyl isocyanate (3.90 mL, 18.1 mmol) was added in one portion. The solution was refluxed for 18 h and allowed to cool. The resultant precipitate was filtered and the filtrate concentrated in vacuo and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated in vacuo, and chromatographed on silica gel, eluting with 10% and then 15% ethyl acetate in hexanes to give an oil which solidified on standing to give the title compound as a white solid (1.95 g, 24%): mp 80−88 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 0.5 (t, J = 6 Hz, 3H), 1.15 (d, J = 7.5 Hz, 12H), 1.24 (s, 18H), 1.80 (m, 2H), 3.13 (m, 2H), 4.30 (t, J = 7 Hz, 2H), 7.17−7.32 (m, 3H), 8.93 (s, 1H), 10.24 (s, 1H); EIMS m/z 457 (MH^+). Anal. ($C_{26}H_{44}N_6O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(1-decyl-1*H*-tetrazol-5-yl)urea (3a).** 5-Amino-1-decyltetrazole (3.5 g, 0.0155 mol), made in a manner similar to **4**, and 2,6-diisopropylphenyl isocyanate (3.65 mL, 0.017 mol) were dissolved in 1,2-dichloroethane (100 mL) to which triethylamine (2.4 mL) was added. The reaction mixture was heated to reflux for 8 h, stirred overnight, and then partitioned between saturated aqueous ammonium chloride and methylene chloride. The organic layer was washed twice with water and then dried over $MgSO_4$, filtered, and evaporated to give a solid which was chromatographed on silica gel in ethyl acetate/hexane to give a white solid which was recrystallized from hexane at −78 °C to give the title compound (35% yield): mp 135−136 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7 Hz, 3H), 1.21 (m, 28H), 3.16 (m, 2H), 4.08 (t, J = 7 Hz, 2H), 7.13−7.35 (m, 3H), 9.96 (s, 1H), 11.22 (s, 1H); EIMS m/z 429 (MH^+). Anal. ($C_{24}H_{40}N_6O$) C, H, N.

***N*-(2,4,6-Trimethoxyphenyl)-*N′*-(2-dodecyl-1*H*-tetrazol-5-yl)urea (3c).** Triethylamine (0.85 mL, 6.1 mmol) and 2,4,6-trimethoxyphenyl isocyanate[12] (1.44 g, 6.1 mmol) were added to a solution of **4** (1.55 g, 6.1 mmol) in acetonitrile (50 mL). The mixture was refluxed for 18 h and allowed to cool; the resulting precipitate was recrystallized from CH_3CN to give the title compound as needles (0.46 g, 17%): mp 139−140 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 0.88 (t, J = 7 Hz, 3H), 1.06−1.25 (m, 18H), 1.68 (m, 2H), 3.79 (s, 6H), 3.83 (s, 3H), 4.24 (t, J = 7 Hz, 2H), 6.15 (s, 2H), 9.39 (s br, 1H), 11.15 (s br, 1H); FABMS m/z 463 (MH^+). Anal. ($C_{23}H_{38}N_6O_4$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-[2-[[(tetrahydro-2*H*-pyran-2-yl)oxy]undecyl]-2*H*-tetrazol-5-yl]urea (6).** 11-Bromoundecan-1-ol (11.2 g, 44.7 mmol) was added to a vigorously stirred solution of dihydropyran (4.9 mL, 53.7 mmol) and Amberlyst H15 (0.5 g; Aldrich D10, 620-8) in hexane (100 mL). After 3 h dihydropyran (4.9 mL) was added and the solution stirred for a further 15 h. The mixture was then filtered, and the filtrate was concentrated in vacuo and chromatographed on silica gel, eluting with 2% ethyl acetate in hexane to give 16.6 g of 2-[(11-bromoundecyl)oxy]tetrahydropyran as an oil, which was added to a refluxing mixture of **1** (11.6 g, 40.2 mmol), triethylamine (6.2 mL, 44.2 mmol), and acetonitrile (250 mL). The mixture was allowed to reflux for 18 h, allowed to cool, and concentrated to one-third volume. The slurry obtained was filtered and the filtrate concentrated in vacuo and recrystallized from acetonitrile to give the title compound as a white solid (4.72 g, 19%): mp 105−111 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 1.27 (m, 26H), 1.54 (m, 6H), 1.82−1.71 (m, 2H), 2.00 (m, 2H), 3.18 (m, 2H), 3.39 (m, 1H), 3.52 (m, 1H), 3.73 (m, 1H), 3.87 (m, 1H), 4.54 (m, 3H), 7.35−7.19 (m, 3H), 8.19 (s, 1H), 9.00 (s, 1H); FABMS m/z 543 (MH^+). Anal. ($C_{30}H_{50}N_6O_3$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-N′-[2-(11-hydroxyundecyl)-2*H*-tetrazol-5-yl]urea (7).** Compound **6** (24.6 g, 0.045 mol) was stirred at room temperature with *p*-toluenesulfonic acid (0.5 g) in methanol (200 mL) for 1.5 h. The solution was then concentrated in vacuo and redissolved in ethyl acetate (20 mL). Hexane (200 mL) was added and the resultant precipitate filtered. The residue was chromatographed on silica gel, eluting with 35% ethyl acetate in hexanes to give the title compound as a white solid (6.73 g, 33%): mp 84−87 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 1.15 (d, J = 7 Hz, 12H), 1.24 (m, 14H), 1.40 (m, 2H), 1.90 (m, 2H), 3.13 (heptet, J = 7 Hz, 2H), 3.37 (m, 2H), 4.32 (br t, 1H), 4.58 (t, J = 7 Hz, 2H), 7.31−7.7.17 (m, 3H), 8.43 (s, 1H), 10.35 (s, 1H); EIMS m/z 459 (MH^+). Anal. ($C_{25}H_{42}N_6O_2$) C, H, N.

2-Dodecyltetrazoleacetic Acid Ethyl Ester (8a) and 1-Dodecyltetrazoleacetic Acid Ethyl Ester (8b). 1-Bromododecane (8.78 g, 0.035 mol) was added to a refluxing solution of the tetrazoleacetic acid ethyl ester (5 g, 0.032 mol)[19] and triethylamine (3.56 g, 0.035 mol) in acetonitrile (150 mL). The mixture was refluxed for 18 h, allowed to cool, and filtered. The filtrate was concentrated in vacuo and partitioned between ethyl acetate (150 mL) and water (150 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$, and then filtered, concentrated, and chromatographed on silica gel, eluting with 10% and then 20% ethyl acetate in hexanes to give **8a** as an oil (5.40 g, 52%): R_f 0.66, 50% ethyl acetate/hexane; 250 MHz ^{1}H NMR (DMSO-d_6) δ 4.65(t, J = 6.9 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 4.04 (s, 2H), 1.90 (m, 2H), 1.23 (s, H), 0.85 (t, J = 7.1 Hz, 3H); EIMS m/z 325 (MH^+). Anal. ($C_{17}H_{32}N_4O_2$) C, H, N. **8b** was obtained as a solid (3.39 g, 33%): mp 59−62 °C; R_f 0.50, 50% ethyl acetate/hexane; 250 MHz ^{1}H NMR (DMSO-d_6) δ 4.34 (t, J = 7.3 Hz, 2H), 4.27 (s, 2H), 4.14 (q, J = 7.0 Hz, 2H), 1.81 (m, 2H), 1.24 (s, H), 0.86 (t, J = 7.0 Hz, 3H); EIMS m/z 325 (MH^+). Anal. ($C_{17}H_{32}N_4O_2$) C, H, N.

2-Dodecyltetrazoleacetic Acid (9). A solution of KOH (4.21 g, 0.075 mol) in water (10 mL) was added to a solution of **8a** (23.2 g, 0.0715 mol) in ethanol (250 mL). The mixture was stirred at room temperature for 3 h, concentrated in vacuo to 50 mL, diluted with water (200 mL), and washed with ethyl acetate (100 mL). The aqueous layer was acidified with 1 M HCl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a white solid (18.0 g, 85%): mp 70−71.5 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 4.60 (t, J = 7.2 Hz, 2H), 4.04 (s, 2H), 2.01 (m, 2H), 1.32 (m, 2H), 1.25 (s, 16H), 0.88 (t, J = 6.8 Hz, 3H); CIMS m/z 297 (MH^+). Anal. ($C_{15}H_{28}N_4O_2$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-[(2-dodecyl-2*H*-tetrazol-5-yl)methyl]urea (10).** Triethylamine (0.84 mL, 6.1 mmol) was added to a mixture of **9** (1.5 g, 5.0 mmol) and diphenyl phosphorazidate (1.64 mL, 7.6 mmol) in dioxane (50 mL). The mixture was stirred for 15 min at room temperature and then heated to reflux for 20 min and cooled, and 2,6-diisopropylphenylamine (1.2 mL, 6.1 mmol) was added. The mixture was stirred for 15 min at room temperature and then heated to reflux for 30 min, allowed to cool, and poured into ethyl acetate/water. The organic layer was washed with 1 M HCl, water, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and chromatographed on silica gel eluting with 40% ethyl acetate in hexanes to give the title compound (0.76 g, 31%): mp 87−90 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.14−1.28 (m, 30H), 1.94 (m, 3H), 3.28 (m, 2H), 4.51 (t, J = 7 Hz, 2H), 4.68 (s, 2H), 6.13 (s br, 1H), 7.13−7.37 (m, 3H); EIMS m/z 471 (MH^+). Anal. ($C_{27}H_{46}N_6O$) C, H, N.

***N*-(2,4,6-Trimethoxyphenyl)-*N′*-[(2-dodecyl-2*H*-tetrazol-5-yl)methyl]urea (11).** The compound was prepared as in the above procedure for compound **10** using 2,4,6-trimethoxyphenylaniline[12] and chromatographed on silica gel eluting with 60% ethyl acetate in hexanes to give the title compound (46%): mp 139−143.5 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 0.85 (t, J = 7 Hz, 3H), 1.23 (s, 18H), 1.88 (m, 2H), 3.70 (s, 6H), 3.76 (s, 3H), 4.47 (d, J = 6 Hz, 2H), 4.62 (t, J = 7 Hz, 2H), 6.22 (s, 2H), 6.49 (t, J = 6 Hz, 1H), 6.96 (s, 1H); CIMS m/z 477 (MH^+). Anal. ($C_{24}H_{40}N_6O_4$) C, H, N.

Dodecanoic Acid 2-(Aminothioxomethyl)hydrazide (12). Lauroyl chloride (12.9 g, 0.06 mol) in THF (70 mL) was

added dropwise to a vigorously stirred suspension of thiosemicarbazide (10.9 g, 0.12 mol) in THF (300 mL) at 0 °C. After the addition was complete, the mixture was allowed to warm to room temperature and stirred for 24 h. The mixture was concentrated in vacuo to one-fourth of the original volume and filtered through silica gel, eluting with ethyl acetate (500 mL). The filtrate was concentrated to 250 mL and filtered, and the residue was washed with ethyl acetate and dried in vacuo to give a white solid (12.0 g, 73%): 250 MHz ^{1}H NMR (DMSO-d_6) δ 9.63 (s, 1H), 9.15 (s, 1H), 7.83 (s, 1H), 7.37 (s, 1H), 2.09 (t, J = 7.3 Hz, 2H), 1.48 (br m, 2H), 1.24 (s, 16H), 0.86 (t, J = 6.5 Hz, 3H); EIMS m/z 273 (M^+). Anal. ($C_{13}H_{25}N_3O$) C, H, N.

5-Undecyl-1,3,4-thiadiazol-2-amine (13). Methanesulfonic acid (6.26 g, 0.065 mol) was added in one portion to a slurry of **12** (11.9 g, 0.044 mol) in toluene (300 mL) at 0 °C. After 5 min, the mixture was heated to reflux for 18 h, allowed to cool to 0 °C, and filtered, and the residue was washed with cold toluene (50 mL at 5 °C). The solid was dried in vacuo, suspended in water (200 mL), and made basic with 0.1 M ammonium hydroxide while stirring vigorously. The resulting solid was filtered, washed with water, and dried in vacuo to give the title compound as a white solid (4.5 g, 41%): mp 176−177.5 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 7.02 (br s, 2H), 2.77 (t, J = 7.4 Hz, 2H), 1.59 (m, 2H), 1.24 (s, 16H), 0.85 (t, J = 6.8 Hz, 3H); EIMS m/z 256 (MH^+). Anal. ($C_{13}H_{25}N_3O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(5-undecyl-1,3,4-thiadiazol-2-yl)urea (14b).** 2,6-Diisopropylphenyl isocyanate (3.85 g, 0.019 mol) was added to a solution of **13** (4.4 g, 0.017 mol) in acetonitrile (150 mL). The mixture was refluxed for 1 h and then allowed to stand at room temperature overnight, concentrated to three-fourths volume, and filtered. The residue obtained was washed with acetonitrile (50 mL) and hexanes (200 mL) to give 5.9 g of the title compound as a white solid (75% yield): mp 111−113 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 11.93 (br s, 1H), 8.17 (s, 1H), 7.32−7.16 (m, 3H), 3.09 (m, 2H), 2.90 (t, J = 7.4 Hz, 2H), 1.66 (m, 2H), 1.23 (s, 16H), 1.15 (s, 6H), 1.13 (s, 6H), 0.85 (t, J = 6.9 Hz, 3H); EIMS m/z 459 (MH^+). Anal. ($C_{26}H_{42}N_4OS\cdot0.1H_2O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(5-tridecyl-1,3,4-thiadiazol-2-yl)urea (14a).** The compound (63% yield) was prepared as in the above procedure for **14b**: mp 85−91 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 10.90 (br s, 1H), 8.08 (br s, 1H), 7.29−7.16 (m, 3H), 3.07 (m, 2H), 2.89 (t, J = 7.3 Hz, 2H), 1.65 (m, 2H), 1.23 (s, 20H), 1.13 (d, J = 7.5 Hz, 12H), 0.85 (t, J = 6.8 Hz, 3H); EIMS m/z 487 (MH^+). Anal. ($C_{28}H_{46}N_4OS$) C, H, N, S.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(5-nonyl-1,3,4-thiadiazol-2-yl)urea (14c).** The compound (6.6 g, 76%) was prepared as in the above procedure for **14b**: mp 94−98 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 10.91 (br s, 1H), 8.07 (br s, 1H), 7.32−7.16 (m, 3H), 3.07 (m, 2H), 2.89 (t, J = 7.4 Hz, 2H), 1.66 (m, 2H), 1.23 (s, 12H), 1.13 (d, J = 7.5 Hz, 12H), 0.85 (t, J = 6.8 Hz, 3H); EIMS m/z 431 (MH^+). Anal. ($C_{24}H_{38}N_4OS$) C, H, N, S.

2-Amino-5-tridecyl-1,3,4-oxadiazole (15). Hydrazine (1.9 mL, 0.058 mol) was added to a solution of methyl tetradecanoate (13.96 g, 0.058 mol) in methanol (300 mL) and the solution refluxed for 3 days. The mixture was allowed to cool and filtered to yield hydrazide (6.17 g, 44%), mp 107−111 °C. Cyanogen bromide (2.9 g, 0.027 mol) was added to a mixture of hydrazide (6.1 g, 0.025 mmol) and $KHCO_3$ (2.8 g, 0.028 mol) in dioxane/water (1:1, 50 mL) at room temperature. The mixture was refluxed for 1 h, allowed to cool, filtered, washed with dioxane/water (1:1, 20 mL) and then water (50 mL), and dried in vacuo. The solid was recrystallized from chloroform to yield the title compound (4.16 g, 27% yield) as a white solid: mp 147−150 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 6.82 (br s, 2H), 2.60 (t, J = 6.9 Hz, 2H), 1.59 (m, 2H), 1.24 (s, 20H), 0.86 (t, J = 6.8 Hz, 3H); EIMS m/z 268 (MH^+). Anal. ($C_{15}H_{29}N_3O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(5-tridecyl-1,3,4-oxadiazol-2-yl)urea (16).** Triethylamine (1.67 g, 0.017 mol) was added to a solution of **15** (4.0 g, 0.015 mol) in acetonitrile (200 mL) and the mixture refluxed until the solution became homogeneous. 2,6-Diisopropylphenyl isocyanate (3.71 g, 0.018 mol) was then added, the mixture was refluxed for 18 h, allowed to cool, concentrated, diluted with water (20 mL), and filtered, and the solid was chromatographed on silica gel, eluting with 20% ethyl acetate in hexanes to give the title compound (0.54 g, 8% yield) as a white solid: mp 114−116.5 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 11.02 (br s, 1H), 8.99 (br s, 1H), 7.33−7.17 (m, 3H), 3.09 (m, 2H), 2.76 (t, J = 7.3 Hz, 2H), 1.67 (m, 2H), 1.24 (s, 20H), 1.15 (s, 6H), 1.13 (s, 6H), 0.85 (t, J = 6.7 Hz, 3H); EIMS m/z 471 (MH^+). Anal. ($C_{28}H_{46}N_4O_2$) C, H, N.

3-Amino-5-dodecyl-1*H*-1,2,4-triazole (17). A slurry of aminoguanidine bicarbonate (15.24 g, 112 mmol), tridecanoic acid (12.0 g, 56.0 mmol), and *N*,*N*-dimethylaniline (0.1 mL, 0.8 mmol) in toluene (100 mL) was heated under reflux with the azeotropic removal of water (72 h). The resulting slurry was cooled (25 °C) and concentrated in vacuo. The residue was partitioned between ethyl acetate (300 mL) and saturated sodium bicarbonate (300 mL). The aqueous layer was back-extracted with ethyl acetate. After filtration, the combined organic extracts were washed with brine (1 × 250 mL) and then dried ($MgSO_4$) and concentrated in vacuo. The resulting solid was dissolved in hot chloroform and chromatographed on silica eluting with ethyl acetate and then 90:10 chloroform/methanol to give an off-white powder (4.4 g, 31% yield): mp 118−127 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 2.38 (br t, J = 7.2 Hz, 2H), 1.55 (m, 2H), 1.24 (br s, 18H), 0.85 (t, J = 6.4 Hz, 3H); EIMS m/z 253 (MH^+). Anal. ($C_{14}H_{28}N_4$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(2-acetyl-5-dodecyl-2*H*-1,2,4-triazol-3-yl) urea (18).** Acetyl chloride (1.18 mL, 16.6 mmol) was added in one portion to a slurry of **17** (4.0 g, 15.8 mmol) in THF (100 mL). The resulting slurry was stirred (1 h, 25 °C) and then concentrated in vacuo. The residue was suspended in ethyl acetate (350 mL), washed with ice cold water (2 × 100 mL) and ice cold brine (1 × 100 mL), and then dried ($MgSO_4$) and concentrated to yield a waxy solid, 2-acetyl-3-amino-5-dodecyl-2*H*-1,2,4-triazole (4.2 g, 90% yield): 250 MHz ^{1}H NMR (DMSO-d_6) δ 7.40 (s, 2H), 2.48 (s, 3H), 2.40 (t, J = 7.5 Hz, 2H), 1.59 (m, 2H), 1.24 (br s, 20H), 0.85 (t, J = 6.4 Hz, 3H). Without further purification a slurry of 2-acetyl-3-amino-5-dodecyl-2*H*-1,2,4-triazole (4.1 g, 13.9 mmol) in acetonitrile (300 mL) was warmed until homogeneous. 2,6-Diisopropylphenyl isocyanate (3.0 mL, 13.9 mmol) was added, and the solution was heated under reflux for 15 h. The resulting solution was cooled (25 °C) and concentrated in vacuo. The residue was chromatographed on silica gel eluting with hexane and then 85:15 hexane/ethyl acetate to yield a clear oil (4.2 g, 61% yield): 250 MHz ^{1}H NMR (DMSO-d_6) δ 10.05 (s, 1H), 9.42 (s, 1H), 7.35−7.10 (m, 3H), 3.16 (heptet, J = 6.9 Hz, 2H), 2.67 (s, 3H), 2.60 (t, J = 7.6 Hz, 2H), 1.69 (m, 2H), 1.24 (br s, 30H), 0.88 (t, J = 6.6 Hz, 3H); EIMS m/z 498 (MH^+). Anal. ($C_{29}H_{47}N_5O_2$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(5-dodecyl-1*H*-1,2,4-triazol-3-yl)urea (19).** A solution of **18** (4.1 g, 8.2 mmol) in methanol (100 mL) was stirred for 16 h at 25 °C. The slurry was cooled (−20 °C); then the resulting precipitate was collected by filtration, washed with cold methanol, and dried in vacuo (16 h, 40 °C) to yield the title compound as a white powder (3.35 g, 89% yield): mp 154−164 °C; 400 MHz ^{1}H NMR (DMSO-d_6) δ 7.20 (t, J = 7.7 Hz, 1H), 7.10 (d, J = 7.7 Hz, 2H), 3.04 (heptet, J = 6.8 Hz, 2H), 2.55 (br s, 2H), 1.57 (m, 2H), 1.14 (m, 30H), 0.79 (t, J = 6.8 Hz, 3H); EIMS m/z 455(M^+). Anal. ($C_{27}H_{45}N_5O$) C, H, N.

3-Amino-2-dodecyl-1,2,4-triazole (20a), 3-Amino-1-dodecyl-1,2,4-triazole (20b), and 3-Amino-4-dodecyl-1,2,4-triazole (20c). A methanol solution of sodium methoxide was generated by dissolving sodium (2.73 g, 0.119 mol) in methanol (400 mL). 3-Amino-1,2,4-triazole (10.0 g, 0.119 mol) was added and the resulting solution was stirred (10 min, 25 °C). Dodecyl bromide (28.6 mL, 0.119 mol) was then added, and the resulting solution was heated under reflux for 24 h. The solution was cooled (25 °C) and concentrated in vacuo. The residue was taken up in ethyl acetate (450 mL), washed with brine (2 × 150 mL), and then dried ($MgSO_4$) and concentrated in vacuo. The resulting solid was dissolved in a minimal amount of chloroform and chromatographed on silica gel eluting with 2% chloroform in methanol to yield **20a** (4.5 g,

15% yield): mp 75−80 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 7.29 (s, 1H), 6.12 (s, 2H), 3.81 (t, J = 7.0 Hz, 2H), 1.63 (m, 2H), 1.24 (br s, 18H), 0.86 (t, J = 6.4 Hz, 3H); EIMS m/z 252 (M^+). Anal. ($C_{14}H_{28}N_4$) C, H, N; **20b** (4.0 g, 13% yield): mp 101−107 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 7.64 (s, 1H), 4.17 (br s, 2H), 3.93 (t, J = 7.1 Hz, 2H), 1.81 (m, 2H), 1.25 (br s, 18H), 0.88 (t, J = 6.4 Hz, 3H); EIMS m/z 252 (M^+). Anal. ($C_{14}H_{28}N_4$) C, H, N. **20c** (2.0 g, 7% yield): 250 MHz ^{1}H NMR (DMSO-d_6) δ 7.89 (s, 1H), 5.75 (s, 2H), 3.71 (t, J = 7.2 Hz, 2H), 1.60 (m, 2H), 1.24 (br s, 18H), 0.86 (t, J = 6.2 Hz, 3H). **20c** was used without further purification in the synthesis of **21c**.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(2-dodecyl-1*H*-1,2,4-triazol-3-yl) urea (21a).** A solution of **20a** (4.43 g, 0.176 mol) and 2,6-diisopropylphenyl isocyanate (3.75 mL, 0.176 mol) in acetonitrile (100 mL) was heated under reflux (8 h). The resulting solution was cooled (25 °C) and concentrated in vacuo. The oil was chromatographed on silica gel eluting with 1% methanol in chloroform to give an oil, which was triturated with acetonitrile to give a solid, which was dried in vacuo to yield the title compound as a white solid (4.0 g, 50% yield): mp 128−140 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 10.74 (s, 1H), 10.44 (s, 1H), 7.57 (s, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 7.6 Hz, 2H), 3.90 (t, J = 7.4 Hz, 2H), 3.19 (heptet, J = 6.9 Hz, 2H), 1.49 (m, 2H), 1.21 (m, 30H), 0.89 (t, J = 6.6 Hz, 3H); EIMS m/z 456 (MH^+). Anal. ($C_{27}H_{45}N_5O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(1-dodecyl-1*H*-1,2,4-triazol-3-yl)urea (21b).** The compound was prepared as in the above procedure for **21a** using **20b** (5.30g, 74% yield): mp 191−207 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 9.38 (s, 1H), 8.80 (s, 1H), 7.87 (s, 1H), 7.25 (m, 3H), 4.10 (t, J = 7.0 Hz, 2H), 3.23 (heptet, J = 6.9 Hz, 2H), 1.85 (m, 2H), 1.25 (br s, 30H), 0.88 (t, J = 6.6 Hz, 3H); EIMS m/z 456 (MH^+). Anal. ($C_{27}H_{45}N_5O$) C, H, N.

***N*-[2,6-bis(1-methylethyl)phenyl]-*N′*-(4-dodecyl-4H-1,2,4-triazol-3-yl)urea (21c).** The compound was prepared as in the above procedure for **21a** using **20c** (1.3 g, 38% yield): 250 MHz ^{1}H NMR ($CDCl_3$) δ 10.74 (br s, 1H), 10.42 (br s, 1H), 7.81 (s, 1H), 7.23 (m, 3H), 3.77 (t, J = 7.2 Hz, 2H), 3.21 (heptet, J = 6.8 Hz, 2H), 1.43 (m, 2H), 1.23 (m, 30H), 0.90 (t, J = 6.6 Hz, 3H); EIMS m/z 456 (MH^+). Anal. ($C_{27}H_{45}N_5O$) C, H, N.

2-(Tridecylthio)-5-amino-1,2,4-triazole (22). 1-Bromotridecane (45.2 mL, 0.18 mol) was added to a slurry of 3-amino-5-mercapto-1,2,4-triazole (18.66 g, 0.16 mol) and triethylamine (24.6 mL, 0.18 mol) in acetonitrile (250 mL). The mixture was allowed to reflux for 2 h and cooled, and the precipitate was filtered and recrystallized from acetonitrile to give the title compound as a tan solid (47.7g, 95%): mp 101−103 °C; 300 MHz ^{1}H NMR (DMSO-d_6) δ 11.85 (br s, 1H), 6.00 (br s, 2H), 2.90 (t, J = 7.2 Hz, 2H), 1.57 (m, 2H), 1.21 (s, 20H), 0.83 (t, J = 6.9 Hz, 3H); CIMS m/z 299 (MH^+) Anal. ($C_{15}H_{30}N_4S$) C, H, N.

1-Acetyl-2-(tridecylthio)-5-aminotriazole (23). Acetyl chloride (13.8 mL, 0.19 mol) was added to a cooled (0 °C) solution of **22** (46.7 g, 0.185 mol) and triethylamine (27 mL, 0.185 mol) in THF (600 mL). The mixture was stirred for 1 h at 0 °C, poured into ethyl acetate, and filtered, and the residue was washed with water and dried in vacuo to give the title compound as a white solid (14.9 g, 23%): mp 99−102 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 6.60 (br s, 2H), 3.06 (t, J = 7.3 Hz, 2H), 2.58 (s, 3H), 1.73 (m, 2H), 1.42 (m, 2H), 1.26 (s, 18H), 0.8 (t, J = 6.9 Hz, 3H); EIMS m/z 340 (M^+). Anal. ($C_{17}H_{32}N_4OS$) C, H, N.

***N*-[4-Acetyl-5-(tridecylthio)-4z-1,2,4-triazol-3-yl]-*N′*-[2,6-bis(1-methylethyl)phenyl]urea (24).** 2,6-Diisopropylphenyl isocyanate (8.35 mL, 0.039 mol) was added to a solution of **23** (9.27 g, 0.030 mol) in THF (250 mL), the mixture was refluxed for 24 h, concentrated in vacuo to 50 mL, and filtered, and the filtrate was concentrated in vacuo and chromatographed on silica gel, eluting with 5−10 ethyl acetate in hexanes to give the title compound as an oil (4.83 g, 30%): 250 MHz ^{1}H NMR (DMSO-d_6) δ 10.20 (s, 1H), 8.93 (s, 1H), 7.36−7.14 (m, 3H), 3.15 (m, 2H), 2.54 (m, 3H), 1.69 (m, 2H), 1.24 (s, 18H), 1.16 (s, 6H), 1.13 (s, 6H), 0.86 (t, J = 6.1 Hz, 3H); EIMS m/z 544 (MH^+). Anal. ($C_{30}H_{49}N_5O_2S$) C, H, N, S.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-[5-(tridecylthio)-1*H*-1,2,4-triazol-3-yl]urea (25).** The urea **24** (4.4 g, 0.0081 mol) was stirred in methanol (100 mL) at room temperature for 2 h; the solution was then allowed to stand overnight. The solid obtained was filtered and dried in vacuo to give a white solid (2.57 g, 63%): mp 131−135 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 7.27−7.15 (m, 3H), 3.13−2.95 (m, 4H), 1.63 (m, 2H), 1.23 (s, 18H), 1.14 (d, J = 7.5 Hz, 12H), 0.85 (t, J = 7 Hz, 3H); EIMS m/z 502 (MH^+). Anal. ($C_{28}H_{47}N_5OS$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-[5-(tridecylsulfinyl)-1*H*-1,2,4-triazol-3-yl]urea (26).** *m*-Chloroperbenzoic acid (0.26 g, 1.49 mmol) was added to a cooled (0 °C) solution of the compound **25** (0.5 g, 1.0 mmol) in dichloromethane (25 mL). The solution was allowed to warm to room temperature and stirred for 4 h. The mixture was diluted with dichloromethane (100 mL), washed with aqueous $NaHSO_3$, water, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, concentrated, triturated with hexane, filtered, and dried in vacuo to give a white solid as the title compound (0.42 g, 81%): mp 178−181 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 13.67 (br s, 1H), 10.45 (br s, 1H), 8.16 (br s, 1H), 7.32−7.17 (m, 3H), 3.19−3.05 (m, 4H), 1.56 (m, 2H), 1.35 (m, 2H), 1.24 (s, 18H), 1.16 (s, 6H), 1.14 (s, 6H), 0.85 (t, J = 8 Hz, 3H); CIMS m/z 518 (MH^+). Anal. ($C_{28}H_{47}N_5O_2S\cdot0.5H_2O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(5-tridecylsulfonyl)-1*H*-1,2,4-triazol-3-yl]urea (27).** *m*-Chloroperbenzoic acid (0.52 g, 3.0 mmol) was added to a cooled (0 °C) suspension of **25** (0.5 g, 1 mmol) in dichloromethane (25 mL), and the procedure for **26** was followed to give the title compound as a white solid (0.36 g, 68%): mp 136−138 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 13.93 (br s, 1H), 10.56 (br s, 1H), 8.15 (br s, 1H), 7.29−7.16 (m, 3H), 3.35 (t, 2H), 3.11 (m, 2H), 1.63 (m, 2H), 1.23 (s, 20H), 1.14 (d, J = 7.5 Hz, 12H), 0.85 (t, J = 6.8 Hz, 3H); FABMS m/z 534 (MH^+). Anal. ($C_{28}H_{47}N_5O_3S$) C, H, N.

2-Pentadecynenitrile (28). *n*-Butyllithium (2.2 M, 24.3 mL, 0.054 mol) was added dropwise to a cooled (−78 °C) slurry of tetradecyne (10.3 g, 0.053 mol) in anhydrous ether (60 mL) at such a rate that the temperature did not rise above −40 °C. The resulting slurry was stirred (5 min, −70 °C); then phenyl cyanate[23] (6.9 g, 0.058 mol) was added dropwise at such a rate that the temperature did not rise above −60 °C. The slurry was stirred (45 min, −78 °C) and then warmed to room temperature, diluted with ether (140 mL), washed with 1.5 M NaOH (2 × 100 mL) and brine, (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The oil was chromatographed on silica gel eluting with 5% ether in pentane to give a pale yellow liquid (9.0 g, 78%): ^{1}H NMR ($CDCl_3$) δ 2.35 (t, J = 7.0 Hz, 2H), 1.60 (m, 2H), 1.38 (m, 2H), 1.27 (br s, 16H), 0.88 (t, J = 6.5 Hz, 3H); EIMS m/z 220 (MH^+). Anal. ($C_{15}H_{25}N$) C, H, N.

5-Amino-3-dodecylisoxazole (29). A solution of **28** (10.0 g, 0.046 mol) in ethanol (50 mL) was added to a stirred solution of hydroxylamine hydrochloride (3.8 g, 0.055 mmol) in 2.5 M NaOH (20.0 mL, 0.05 mol). The mixture was diluted with ethanol (100 mL), stirred for 22 h at room temperature, concentrated, and then partitioned between ethyl acetate (300 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo, and chromatographed on silica gel eluting with 5−30% ethyl acetate in hexane to yield the title compound as a waxy solid (8.2 g, 71%): mp 48.5−49.5 °C; ^{1}H NMR ($CDCl_3$) δ 4.98 (s, 1H), 4.41 (br s, 2H), 2.50 (t, J = 7.6 Hz, 2H), 1.60 (m, 2H), 1.25 (br s, 18H), 0.88 (t, J = 6.6 Hz, 3H); EIMS m/z 253 (MH^+). Anal. ($C_{15}H_{28}N_2O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(3-dodecyl-5-isoxazolyl)urea (30c).** A slurry of **29** (1.44 g, 5.71 mmol) in acetonitrile (50 mL) was warmed until homogeneous. 2,6-Diisopropylphenyl isocyanate (1.22 mL, 5.71 mmol) was then added in one portion, the resulting solution was heated under reflux for 24 h and cooled to −20 °C, and the precipitate was collected by filtration and chromatographed on silica gel eluting with 30% ethyl acetate in hexane to give a solid which was recrystallized from acetonitrile to yield the title compound as white needles (0.53 g, 20%): mp 112.5−114 °C; ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 3H), 6.91 (br s, 1H), 6.85 (br s, 1H), 6.06 (br s, 1H), 3.24 (m, 2H), 2.54 (t, J = 7.7 Hz, 2H), 1.61 (m, 2H), 1.25 (m, 30H), 0.88 (t, J = 6.5 Hz, 3H); EIMS m/z 456 (MH^+). Anal. ($C_{28}H_{45}N_3O_2$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(3-tetradecyl-5-isoxazolyl)urea (30a).** The compound was prepared as in the above procedure for **30c** (1.1 g, 19% yield): mp 104−106 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 3H), 7.06 (br s, 1H), 6.85 (br s, 1H), 6.06 (br s, 1H), 3.24 (m, 2H), 2.53 (t, J = 7.6 Hz, 2H), 1.61 (m, 2H), 1.25 (br s, 34H), 0.88 (t, J = 6.5 Hz, 3H); EIMS m/z 484 (MH^+). Anal. ($C_{30}H_{49}N_3O_2$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(3-tridecyl-5-isoxazolyl)urea (30b).** The compound was prepared as in the above procedure for **30c** (1.55 g, 18% yield): mp 101−104 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 3H), 6.84 (br s, 1H), 6.56 (br s, 1H), 6.08 (br s, 1H), 3.23 (m, 2H), 2.55 (t, J = 7.6 Hz, 2H), 1.64 (m, 2H), 1.19 (m, 32H), 0.88 (t, J = 6.5 Hz, 3H); EIMS m/z 469 (MH^+). Anal. ($C_{29}H_{47}N_3O_2$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(3-decyl-5-isoxazolyl)urea (30d).** The compound was prepared as in the above procedure for **30c** (5.9 g, 32% yield): mp 112−114 °C; ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 3H), 7.06 (br s, 1H), 6.86 (br s, 1H), 6.05 (br s, 1H), 3.24 (m, 2H), 2.53 (t, J = 7.6 Hz, 2H), 1.60 (m, 2H), 1.21 (m, 26H), 0.88 (t, J = 6.5 Hz, 3H); EIMS m/z 427 (MH^+). Anal. ($C_{26}H_{41}N_3O_2$) C, H, N.

3-Amino-5-tridecylisoxazole (31). A solution of 2-hexadecynenitrile (7.35 g, 0.032 mmol), synthesized in a manner similar to **28**, in ethanol (115 mL) was added to a stirred solution of hydroxylamine hydrochloride (2.26 g, 0.038 mol) in 2.5 M NaOH (27.7 mL, 0.069 mol). The slurry was stirred for 16 h at room temperature and filtered, and the crystals were washed with cold water and dried in vacuo at 40 °C (24 h) to yield the title compound as a white solid (5.6 g, 67%): mp 83−84.5 °C; ^{1}H NMR ($CDCl_3$) δ 5.53 (s, 1H), 3.95 (br s, 2H), 2.60 (t, J = 7.6 Hz, 2H), 1.64 (m, 2H), 1.26 (br s, 20H), 0.88 (t, J = 6.5 Hz, 3H); EIMS m/z 267 (MH^+). Anal. ($C_{16}H_{30}N_2O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(5-tridecyl-3-isoxazolyl)urea (32).** The compound was prepared as in the above procedure for **30c** using **31** (4.4 g, 47% yield): mp 85−100 °C; ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 3H), 5.75 (br s, 1H), 3.21 (m, 2H), 2.65 (t, J = 7.4 Hz, 2H), 1.67 (m, 2H), 1.27 (m, 32H), 0.89 (t, J = 6.5 Hz, 3H); EIMS m/z 469 (M^+). Anal. ($C_{29}H_{47}N_3O_2$) C, H, N.

1-Hydroxy-2-tridecanone (33). A solution of *n*-butyllithium (12.6 mL, 0.028 mol, 2.2 M in hexane) was added dropwise via syringe to a cooled (−78 °C) solution of diisopropylamine (4.1 mL, 0.029 mol) in dry THF (200 mL). The solution was stirred (15 min −78 °C); then a solution of 2-tridecanone (5.0 g, 0.025 mol) in dry THF (50 mL) was added dropwise via a dropping funnel. The mixture was stirred (30 min, −78 °C); then a solution of chlorotrimethylsilane (3.5 mL, 0.028 mol) in dry THF (40 mL) was added in one portion. The mixture was allowed to warm to 10 °C; then the reaction was quenched with saturated $NaHCO_3$ (100 mL). Dichloromethane (400 mL) and water (80 mL) were added, and the organic layer was washed with brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo to yield 2-[(trimethylsilyl)oxy]-1-tridecene (6.7 g, 98%) which was used without further purification. *m*-Chloroperoxybenzoic acid (8.5 g, 0.025 mol) was added in one portion to a cooled (0 °C) solution of 2-[(trimethylsilyl)oxy]-1-tridecene in hexane (200 mL). The ice bath was removed, and the slurry was stirred for 4 h at room temperature. Ether (200 mL) and 1.5 M HCl (130 mL) were added, and the resulting two-phase mixture was stirred vigorously for 4.5 h. The organic layer was washed with saturated $NaHCO_3$ (2 × 130 mL) and brine (130 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel eluting with 10% ethyl acetate in hexane and concentrated in vacuo. The solid was washed with cold hexane and collected by filtration to yield the title compound as a white solid (1.5 g, 29%): mp 52−54 °C; ^{1}H NMR ($CDCl_3$) δ 4.24 (s, 2H), 3.15 (br s, 1H), 2.41 (t, J = 7.5 Hz, 2H), 1.63 (m, 2H), 1.26 (br s, 16H), 0.88 (t, J = 6.5 Hz, 3H); EIMS m/z 215 (MH^+). Anal. ($C_{13}H_{26}O_2$) C, H.

2-Amino-4-undecyloxazole (34). To a solution of **33** (1.0 g, 4.7 mmol) and cyanamide (0.2 g, 4.7 mmol) in THF (3.0 mL) were added aqueous sodium acetate (2.0 mL, 1.0 M), tetra-*n*-butylammonium hydroxide (0.6 mL, 0.4 M, 0.2 mmol), and 1 M sodium hydroxide (0.2 mL, 0.2 mmol) sequentially. The resulting two-phase mixture was stirred for 48 h at room temperature and then redissolved in ethyl acetate (200 mL), washed with brine (2 × 65 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel eluting with chloroform and then 5% methanol in chloroform to give the title compound as an off-white powder (0.70 g, 63%): mp 55−58 °C; ^{1}H NMR (DMSO-d_6) δ 7.01 (s, 1H), 6.40 (s, 2H), 2.22 (t, J = 7.4 Hz, 2H), 1.48 (m, 2H), 1.24 (br s, 16H), 0.86 (t, J = 6.3 Hz, 3H); EIMS m/z 239 (MH^+). Anal. ($C_{14}H_{26}N_2O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(4-undecyl-2-oxazolyl)urea (35).** 2,6-Diisopropylphenyl isocyanate (0.57 g, 0.0028 mol) was added to a refluxing mixture of **34** (0.56 g, 0.0024 mol), triethylamine (0.26 g, 0.0026 mol), and acetonitrile (50 mL). The mixture was refluxed for 2.5 h under nitrogen, allowed to cool, and concentrated in vacuo. The residue was partitioned between ethyl acetate (100 mL) and water (75 mL). The organic layer was washed with brine, dried with Na_2SO_4, filtered, concentrated, and triturated with acetonitrile to give a yellow solid which was dried in vacuo to give the title compound (0.73 g, 70%): mp 104−108 °C; ^{1}H NMR (DMSO-d_6) δ 10.82 (s, 1H), 9.85 (s, 1H), 7.27−7.16 (m, 3H), 3.06 (heptet, J = 6.8 Hz, 2H), 2.37 (t, J = 7.2 Hz, 2H), 1.52 (m, 2H), 1.18−1.12 (m, 28H), 0.83 (t, J = 6.8 Hz, 3H); EIMS m/z 442 (MH^+). Anal. ($C_{27}H_{43}N_3O_2$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N′*-(dodecyl-1*H*-imidazol-4-yl)urea Monohydrochloride (37).** To a solution of 4-nitro(tetrabutylammoniumyl)imidazole[26] (**36**) (0.5 g, 1.4 mmol) in DMF (10 mL) was added the dodecyl bromide (0.35 g, 1.4 mmol). The mixture was stirred at room temperature for 18 h, concentrated in vacuo, diluted with water (50 mL), and extracted with 1:1 ethyl acetate/hexane (2 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to yield 1-dodecyl-4-nitroimidazole which was used without further purification. The 1-dodecyl-4-nitroimidazole (1.5 g, 5.3 mmol) was treated with 5% Pd/C in methanol at 50 psi of hydrogen for 6 h at 22−28 °C in a Parr apparatus. The crude reaction mixture containing 1-dodecyl-4-aminoimidazole was concentrated and used without further purification. To a solution of 1-dodecyl-4-aminoimidazole in ethyl acetate (5 mL) was added the 2,6-diispropylphenyl isocyanate (0.64 g, 3.2 mmol). The resulting mixture was stirred for 3 h at room temperature, diluted with water (10 mL), and stirred for 30 min. The organic layer was separated, washed with saturated $NaHCO_3$ and brine, and dried ($MgSO_4$). The mixture was filtered, concentrated, and column chromatographed on silica gel eluting with 10%, 20%, 30%, 40%, and 60% ethyl acetate in hexane. The brown oil obtained was treated with saturated ethereal HCl, concentrated, and dissolved in methanol, and water was added. The mixture was concentrated in vacuo and then lyophilized overnight to yield the title compound (0.25 g, 16%): foam; 250 MHz ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 5.88 Hz, 3H), 1.12−1.34 (m, 30H), 1.73 (br t, 2H), 3.15 (hept, 2H), 4.04 (br t, 2H), 7.03−7.51 (m, 4H), 8.47 (br s, 1H), 9.79 (br s, 1H); EIMS m/z 454 (M^+). Anal. ($C_{28}H_{46}N_4O\cdot HCl$) C, H, N.

2-Amino-4-methyl-5-decylthiazole (38a) and 2-Amino-4-undecylthiazole (38b). 2-Tridecanone (19.3 g, 0.1 mol) and thiourea (15.24 g, 0.2 mol) were stirred at 40 °C until a slurry was obtained. Iodine (25.4 g, 0.1 mol) was added in one portion, and the mixture was heated at 100 °C for 18 h, allowed to cool, and diluted with water (50 mL). The aqueous solution was made basic with saturated aqueous NH_4OH solution, precipitating a white gum which was partitioned into ethyl acetate (200 mL). The organic layer was washed with saturated $NaHSO_3$, dried with Na_2SO_4, and concentrated in vacuo to give an oil which was chromatographed on silica gel, eluting with 20%, 25%, and 50% ethyl acetate in hexanes to yield 2-amino-4-methyl-5-decylthiazole (**38a**) (4.95 g, 19%): mp 39−40 °C; 400 MHz ^{1}H NMR (DMSO-d_6) δ 6.52 (s, 2H), 2.47 (t, J = 7.4 Hz, 2H), 1.95 (s, 3H), 1.42 (m, 2H), 1.24 (s, 14H), 0.85 (t, J = 6.8 Hz, 3H); CIMS m/z 255 (MH^+). Anal. ($C_{14}H_{26}N_2S$) C, H, N. Also eluted was 2-amino-4-undecylthiazole (**38b**) (13.5 g, 53%): mp 60−61.5 °C; 400 MHz ^{1}H NMR (DMSO-d_6) δ 6.77 (s, 2H), 6.07 (s, H), 2.36 (t, J = 7.0 Hz, 2H), 1.53 (m,

2H), 1.24 (s, 16H), 0.85 (t, J = 6.8 Hz, 3H); CIMS m/z 255 (MH^+). Anal. ($C_{14}H_{26}N_2S$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-(5-decyl-4-methyl-2-thiazolyl)urea (39a).** 2,6-Diisopropylphenyl isocyanate (11.2 g, 0.055 mol) was added to a solution of **38a** (13.4 g, 0.053 mol) in ethyl acetate (200 mL). The mixture was stirred for 2 h at room temperature; then acetonitrile (50 mL) was added, the mixture was refluxed for a further 2 h and concentrated, and the resulting oil was crystallized from acetonitrile (10 mL), filtered, and washed with hexane (200 mL) to give the title compound as a white solid (8.38 g, 35%): mp 101−108 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.22 (m, 26H), 1.57 (m, 2H), 2.12 (s, 3H), 2.60 (t, J = 7 Hz, 2H), 3.20 (m, 2H), 7.10−7.43 (m, 3H); EIMS m/z 458 (MH^+). Anal. ($C_{27}H_{43}N_3OS$) C, H, N, S.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-(4-undecyl-2-thiazolyl)urea (39b).** 2,6-Diisopropylphenyl isocyanate (4.0 g, 0.02 mol) was added to a solution of **38b** (4.78 g, 0.019 mol) in ethyl acetate (150 mL) and the mixture refluxed for 18 h. The precipitate obtained was filtered and the filtrate concentrated and chromatographed on silica gel, eluting with 5−10% ethyl acetate in hexanes to give the title compound as an oil (4.57 g): 300 MHz ^{1}H NMR (DMSO-d_6) δ 0.83 (t, J = 6.2 Hz, 3H), 1.11 (d, J = 7.5 Hz, 12H), 1.21 (s, 16H), 1.57 (br m, 2H), 2.51 (t, 2H), 3.07 (m, 2H), 6.57 (s, 1H), 7.15 (m, 2H), 7.26 (m, 1H), 8.15 (br s, 1H), 10.54 (br s, 1H); EIMS m/z 458 (MH^+). Anal. ($C_{27}H_{43}N_3O$) C, H, N.

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