Heterocyclic Amides: Inhibitors of Acyl-CoA:Cholesterol *O*-Acyl Transferase with Hypocholesterolemic Activity in Several Species and Antiatherosclerotic Activity in the Rabbit

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Received June 6, 1996[⊗]

A series of heterocyclic amides were synthesized and evaluated as inhibitors of acyl-CoA: cholesterol *O*-acyltransferase (ACAT) in vitro and for cholesterol lowering in cholesterol-fed rats. Compounds were evaluated for cell-based macrophage ACAT inhibition, bioactivity, and adrenal toxicity. Candidates were selected for evaluation in cholesterol-fed dogs and, ultimately, the injured cholesterol-fed rabbit model of atherosclerosis. The heterocyclic amides potently inhibited rabbit liver ACAT (IC_{50}'s = 0.014−0.11 μM), and the majority of compounds significantly lowered plasma cholesterol (42−68%) in an acute cholesterol-fed rat model at 3 mg/kg. The most efficacious compounds in the rat were evaluated for bioactivity in vivo and arterial ACAT inhibition in a cell-based macrophage ACAT assay. Two highly bioactive analogs, (±)-2-(3-dodecylisoxazol-5-yl)-2-phenyl-*N*-(2,4,6-trimethoxyphenyl)acetamide (**13a**) and (±)-2-(5-dodecylisoxazol-3-yl)-2-phenyl-*N*-(2,4,6-trimethoxyphenyl)acetamide (**16a**), were selected for further study and were found to be nontoxic in a guinea pig model of adrenal toxicity. Compounds **13a** and **16a** lowered total cholesterol in the cholesterol-fed rat, rabbit, and dog models of pre-established hypercholesterolemia. Compound **13a** in the injured cholesterol-fed rabbit model of atherosclerosis was effective in slowing the development of cholesteryl ester-rich thoracic aortic lesions, reducing lesion coverage by 53% at a dose of 1 mg/kg.

Introduction

Hypercholesterolemia is an independent risk factor definitively linked to coronary heart disease, which is the leading cause of death in nations of the Western hemisphere.[1] Cholesterol in the body is derived from two sources: endogenous biosynthesis and absorption from the diet.[2] Inhibition of either process represents an attractive approach to lowering plasma cholesterol. The HMG-CoA reductase inhibitors, which inhibit the rate-limiting enzyme in cholesterol biosynthesis, have proven clinically effective at lowering total and low-density lipoprotein (LDL) cholesterol. Most recently they have been shown to reduce mortality and morbidity from coronary heart disease (CHD) in both patients with diagnosed CHD[3] and middle-aged men without diagnosed CHD,[4] thus realizing the ultimate goal for a cholesterol-lowering agent.

The enzyme acyl-CoA:cholesterol *O*-acyltransferase (ACAT, EC 2.3.1.26) catalyzes the intracellular formation of cholesteryl esters. Evidence suggests that inhibition of ACAT can prevent absorption of dietary cholesterol and lower plasma total cholesterol (TC) in cholesterol-fed (C-fed) animal models.[5] Additional studies show hepatic cholesteryl ester content is directly proportional to VLDL secretion rate.[6] Recently, ACAT inhibition has been shown to decrease both the secretion rate of cholesteryl esters and apolipoprotein B from perfused monkey livers.[7] Inhibition of ACAT in the arterial wall may reduce the accumulation of cholesteryl esters in monocyte macrophages. These cholesteryl ester-rich cells are the precursors of the foam cells of the early atherosclerotic lesion.[8] The data suggesting a direct role for ACAT in the formation of atherosclerotic lesions has maintained this enzyme as a very attractive target,[2] despite the fact that clinical trials with several ACAT inhibitors have proved disappointing.[9−11]

Previous work in our laboratories[12−17] identified several series of potent ACAT inhibitors which lowered plasma total cholesterol in cholesterol-fed animal models. The early work focused on primarily amide-based inhibitors.[12] This culminated in the discovery of CI-976, which exerted its antiatherosclerotic effects by inhibition of arterial ACAT independent of cholesterol lowering.[2,18] In a related series of tetrazole amides,[19] the compound **2** provided a potent and efficacious lead. Animal studies with enantiomers of **2** suggested that it racemized in vivo.[19] We report here the synthesis and biological evaluation of racemic heterocyclic isosteres of tetrazole **2**. Subsequent to the initiation of our studies, it was determined that **2** was inactive in a rabbit bioassay. We set out to synthesize a variety of heterocyclic isosteres of tetrazole **2**. Our goal was to provide a compound that inhibited both liver and arterial ACAT and was efficacious in cholesterol-lowering animal models, nonadrenotoxic, and bioactive. Such a compound would then be evaluated in an injured cholesterol-fed rabbit model of atherosclerosis.

Chemistry

The compounds examined in this study were prepared by several different methods. The α-unsubstituted 3-alkylisoxazole **10** was synthesized from homologation of the carboxylic acid **4** as shown in Scheme 1. Thus

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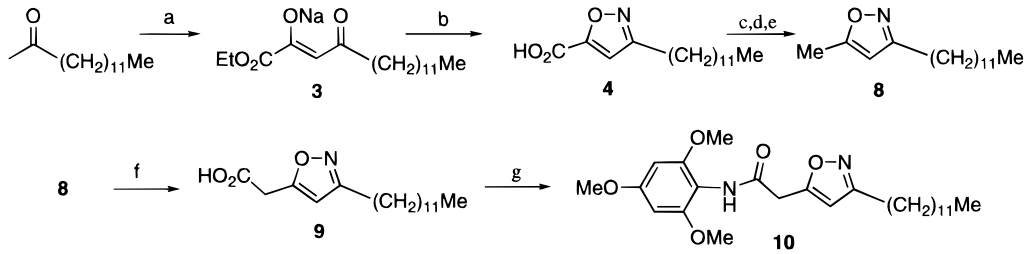
[⊗] Abstract published in *Advance ACS Abstracts,* September 1, 1996.

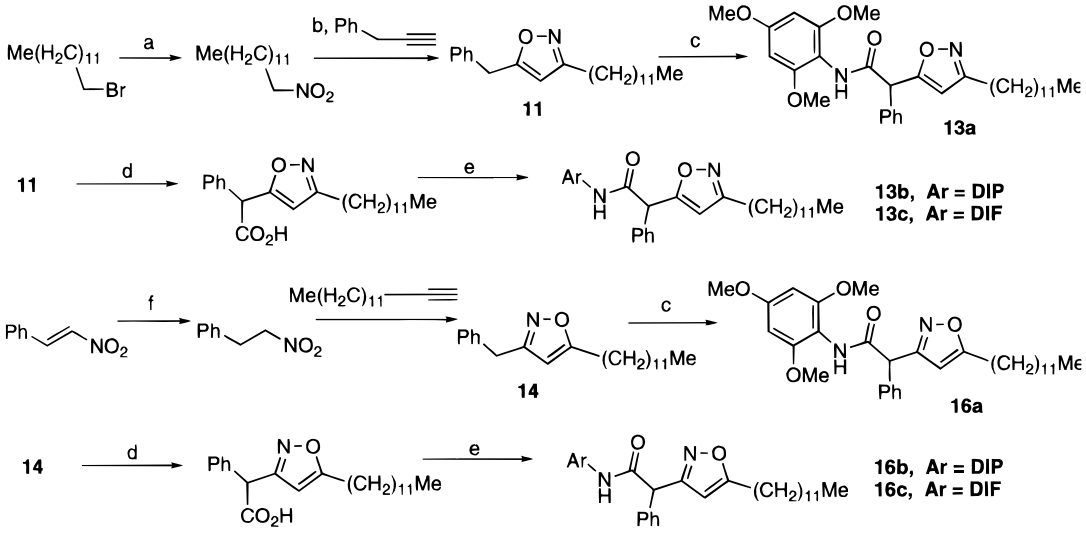
S0022-2623(96)00403-7 CCC: $12.00

Scheme 1[a]

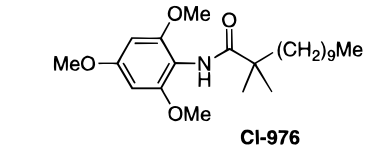


[a] (a) NaOEt, EtOH, $(CO_2Et)_2$; (b) $NH_2OH{\cdot}HCl$, AcOH, H_2O; (c) (i) Et_3N, THF, EtOCOCl; (ii) $NaBH_4$; (d) PBr_3, CH_2Cl_2; (e) $NaBH_4$, DMSO; (f) (i) BuLi, THF; (ii) CO_2; (g) (i) CDI, THF; (ii) $ArNH_2$.

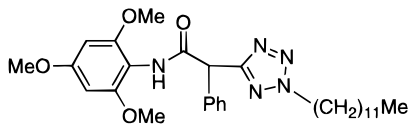
Scheme 2[a]



[a] (a) $NaNO_2$, DMF; (b) Et_3N, 2PhNCO, benzene; (c) (i) *n*-BuLi, THF; (ii) 2,4,6-trimethoxyphenyl isocyanate; (d) (i) *n*-BuLi, THF; (ii) CO_2; (e) (i) CDI, THF; (ii) $ArNH_2$; (f) $ClRh(PPh_3)_3$, H_2, benzene.



CI-976



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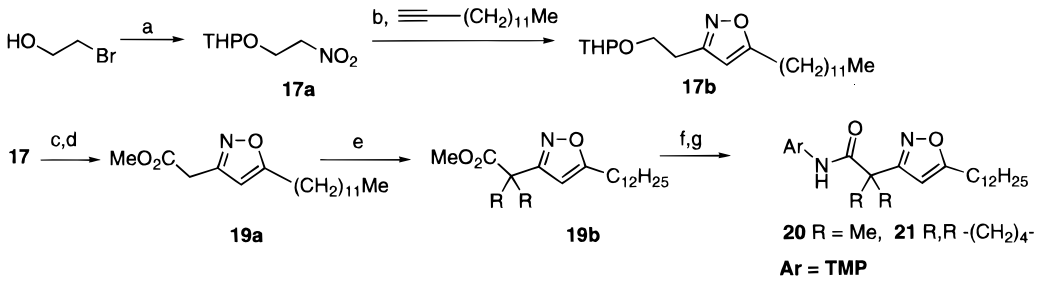
2-tetradecanone was condensed with diethyl oxalate and sodium ethoxide to give the enolate **3**. The isoxazole ring was constructed via cyclization of the sodium enolate **3** and hydroxylamine to give **4** using the method of Seki.[20] The acid **4** was homologated via reduction with sodium borohydride, conversion of the subsequent alcohol to the bromide, and reduction of the methylene bromide to a methyl group using sodium borohydride to give isoxazole **8**. The methylisoxazole **8** was selectively deprotonated at the position α to oxygen[21] and the anion quenched with CO_2 to give the homologated carboxylic acid **9**. The acid **9** was activated with carbonyldiimidazole (CDI), and the imidazolide was coupled with 2,4,6-trimethoxyaniline in situ to yield the α-unsubstituted amide **10**.

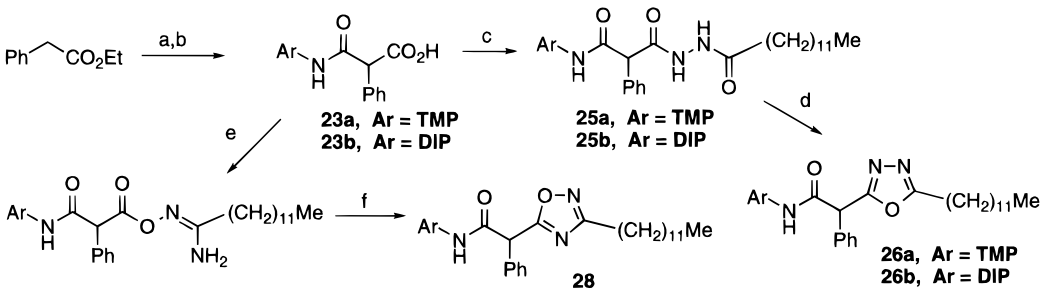
The α-phenyl-substituted 3- and 5-alkylisoxazoles (**13a**−**c**, **16a**−**c**) were synthesized regioselectively as shown in Scheme 2. The [3 + 2] nitrile oxide alkyne cycloaddition has been described[22] for isoxazoles and represents the method of choice for generating the desired regioselectivity. An alkyl halide was converted to a nitroalkane by reaction with sodium nitrite in DMF. The nitroalkane was converted to the nitrile oxide in situ using Mukaiyama conditions[23] (Et_3N/PhNCO) and cyclized with 3-phenyl-1-propyne to afford the 3-alkyl-5-benzylisoxazole **11** regiselectively. Deprotonation of **11** with *n*-BuLi occurred selectively at the benzyl position α to oxygen,[21] and subsequent quenching of the the intermediate in situ with 2,4,6-trimethoxyphenyl isocyanate gave the 3-alkylisoxazole amide **13a**. The reaction when repeated with 2,6-diisopropyl- or 2,4-difluorophenyl isocyanate failed to give the desired amides. Instead, the anion generated from **11** was quenched with CO_2 and the resultant acid was coupled with (2,6-diisopropylphenyl)- or (2,4-difluorophenyl)-aniline using CDI to give the 3-alkylisoxazole amides (**13b**,**c**). The regioisomeric 5-alkylisoxazoles (**16a**−**c**) were prepared in a similar fashion utilizing the appropriate nitroalkane and alkyne in a [3 + 2] cycloaddition. The desired 2-phenylnitroethane was obtained by reduction of 2-phenylnitroethene using $ClRh(PPh)_3$ as described by Birch.[24] The [3 + 2] cycloaddition of the nitrile oxide generated in situ from 2-phenylnitroethane and Et_3N/PhNCO with tetradecyne gave the 5-alkylisoxazole **14**. Deprotonation of **14** with *n*-BuLi occurred selectively at the benzyl position α to nitrogen, and subsequent quenching in situ of the intermediate with 2,4,6-trimethoxyphenyl isocyanate gave the 5-alkylisoxazole amide **16a**. The 3-alkylisoxazole amides **16b** and **16c** were obtained in a manner similar to that for

Scheme 3[a]



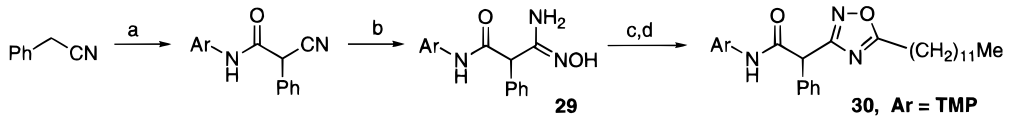
[a] (a) (i) Dihydropyran, heptane, Amberlyst-15; (ii) $NaNO_2$, DMF; (b) Et_3N, 2PhNCO, benzene; (c) TsOH, MeOH; (d) (i) Jones reagent, acetone; (ii) MeOH, HCl(g); (e) NaH, DMF, RX; (f) KOH, MeOH; (g) CDI, THF, ArNCO.

Scheme 4[a]



[a] (a) (i) LDA, THF, −78 °C; (ii) ArNCO; (b) KOH, EtOH; (c) (i) CDI, THF; (ii) $Me(CH_2)_{11}CONHNH_2$; (d) $3P_2O_5$−4EtOH; (e) (i) CDI, THF; (ii) $Me(CH_2)_{11}C(NH_2)NOH$; (f) AcOH.

Scheme 5[a]



[a] (a) (i) NaH, DMF; (ii) ArNCO; (b) $NH_2OH{\cdot}HCl$, Et_3N, EtOH; (c) $Me(CH_2)_{11}COCl$, iPr_2NEt, THF; (d) AcOH.

compounds **13b**,**c.** The anion of **14** was quenched with CO_2, and the resultant acid was coupled with (2,6-diisopropyl-phenyl)- or (2,4-difluorophenyl)aniline using CDI to give the 5-alkylisoxazole amides (**16b**,**c**).

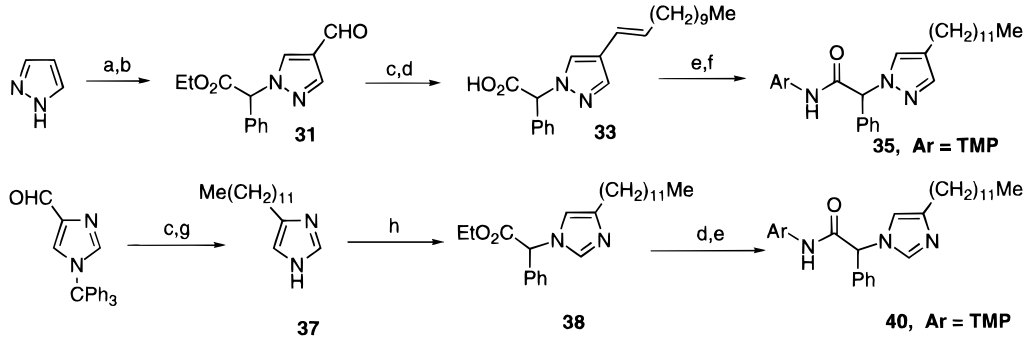
The α,α-dimethyl and spirocyclopentane-substituted isoxazole derivatives (**20**, **21**) were synthesized according to Scheme 3. Thus, 2-bromoethanol was protected as its tetrahydropyranyl ether and the bromide displaced with nitrite to give **17a**. The isoxazole **17b** was constructed via a [3 + 2] cycloaddition with alkyne and the nitrile oxide formed in situ from **17a** and Et_3N/PhNCO. It was necessary to use the alcohol oxidation state since cycloaddition with the appropriate nitrile ester did not proceed. Deprotection of **17b** under acidic conditions gave the alcohol, which was oxidized to the carboxylic acid using Jones reagent. Esterification gave **19a**, which was bis-alkylated α to the ester to give compound **19b**. Saponification and coupling of the resultant acid with (2,4,6-trimethoxyphenyl)aniline using CDI gave the desired isoxazole amides (**20**, **21**).

The 1,3,4-oxadiazole ring system (**26a**,**b**) was synthesized using the known cyclization of a diacyl hydrazide.[25] The 3-alkyl-1,2,4-oxadiazole ring system (**28**) was assembled by cyclization of an *O*-acylamidoxime[26] as depicted in Scheme 4. Ethyl phenylacetate was deprotonated with lithium diisopropylamide (LDA) and then acylated with an isocyanate, and the resultant ester was saponified to afford acid **23**. The acid **23** was coupled with an acylhydrazine to yield the diacyl intermediate, which was cyclodehydrated with a mixture of phosphorus pentoxide and ethanol[27] to afford the 1,3,4-oxadiazole amides (**26a**,**b**). The acid **23** was also utilized to synthesize the 3-alkyl-1,2,4-oxadiazole (**28**) as depicted in Scheme 4. The acid **23** was activated with CDI, and the imidazolide was coupled with a hydroxyamidine, made from a nitrile and hydroxylamine, to give the *O*-acylamidoxime intermediate, which was cyclized with acetic acid to give the 3-alkyl-1,2,4-oxadiazole amide (**28**).

The 5-alkyl-1,2,4-oxadiazole ring system (**30**) was synthesized by cyclization of an *O*-acylamidoxime[26] according to Scheme 5. Benzyl cyanide was deprotonated with LDA and acylated with a 2,4,6-trimethoxyphenyl isocyanate to give a *β*-keto nitrile, which was reacted with hydroxylamine under standard conditions to give the hydroxyamidine **29**. Compound **29** was *O*-acylated with tridecanoyl chloride to give an *O*-acylamidoxime, which was cyclodehydrated with acetic acid to give the 5-alkyl-1,2,4-oxadiazole amide (**30**).

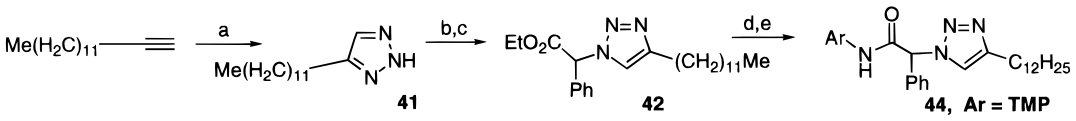
The pyrazole amide **35** was synthesized from a preexisting heterocyclic ring as shown in Scheme 6. Pyrazole was deprotonated with sodium hydride and *N*-alkylated with ethyl α-bromophenylacetate. The *N*-substituted pyrazole was then formylated at the 4-position using standard Vilsmeier−Haack conditions to give the *N*-substituted 4-formylpyrazole **31**. The aldehyde was then elaborated via a Wittig reaction, and the ester functionality was saponified to give the pyrazole acetic acid **33**. The acid **33** was coupled with (2,4,6-trimethoxyphenyl)aniline using dicyclohexylcarbodiimide (DCC) to give an unsaturated pyrazole amide. The alkene at

Scheme 6[a]



[a] (a) NaH, THF, PhCH(Br)CO_2Et; (b) $POCl_3$, DMF; (c) *n*-BuLi, $Ph_3P^+C_{11}H_{23}{\cdot}Br^-$, THF, −78 °C; (d) NaOH, EtOH; (e) DCC, $ArNH_2$; (f) 5% Pd/C, H_2, 50 psi; (g) 20% Pd/C, AcOH, H_2, 50 psi; (h) Et_3N, DMF, PhCH(Br)CO_2Et.

Scheme 7[a]



[a] (a) $TMSN_3$, 150 °C, autoclave; (b) NaH, DMF, PhCH(Br)CO_2Et; (c) chromatography; (d) NaOH, EtOH; (e) $ArNH_2$, DCC, CH_2Cl_2.

the 4-position of the pyrazole was hydrogenated over Pd/carbon to afford the pyrazole amide **35**.

The imidazole amide **40** was synthesized from a preexisting heterocyclic ring as shown in Scheme 6. Thus, 4-(hydroxymethyl)imidazole was oxidized with MnO_2, and the resulting imidazole aldehyde was *N*-protected with a trityl group according to the procedure described by Kelly et al.[28] Wittig reaction of the *N*-protected 4-formyl imidazole with *n*-undecyltriphenylphosphorane, followed by hydrogenation, which removed the trityl group and saturated the side chain, gave **37** (Scheme 6). The alkylimidazole was then deprotonated with sodium hydride and *N*-alkylated with ethyl α-bromophenylacetate to give **38**. The ester **38** was saponified, and the resultant acid was coupled with (2,4,6-trimethoxyphenyl)aniline using DCC to yield the imidazole amide **40**.

The 1,2,3-triazole amide **44** was synthesized as shown in Scheme 7. Cycloaddition of tetradecyne with trimethylsilyl azide according to the general method described by Birkofer[29] yielded the 4-dodecyl-1,2,3-triazole **41**. Deprotonation of **41** with sodium hydride and *N*-alkylation with ethyl α-bromophenylacetate gave a mixture of regioisomers, purified by column chromatography. The major isomer **42** had a proton NMR and MS (loss of N_2 evident) consistent with a 1,4 substitution pattern. The ester **42** was saponified, and the resultant acid was coupled with (2,4,6-trimethoxyphenyl)aniline using DCC to give the triazole amide **44**.

Biological Methods

In Vitro Liver and Macrophage Assays. ACAT inhibition in vitro was determined by incubating the compounds with [1-^{14}C]oleoyl-CoA, and microsomes were isolated from the livers of cholesterol-fed rats.[30] The cell culture assay (MAI) used murine IC-21 macrophages as a model for cells of the arterial wall. The IC-21 mouse macrophages (American Type Culture Collection, Rockville, MD) were preincubated for 16 h in serum-free medium (Dulbecco's modified Eagle medium, DMEM) containing albumin (20 μM) and phosphatidylserine/cholesterol vesicles. The latter were prepared by combining phosphatidylserine (27.4 μmol) and cholesterol (26 μmol) in chloroform and then evaporating in order to disperse the dried lipids into 5 mL of 150 mM NaCl, 5 mM 3-(*N*-morpholino)-propanesulfonic acid (MOPS), 1 mM EDTA (pH 7.4). This suspension was sonicated to form vesicles, which were then sterilized by filtration (0.45 μM filter). Following the preincubation, the media with vesicles was replaced with serum-free DMEM containing the test compound in DMSO and incubated for 1 h, after which ^{14}C-labeled sodium oleate was added for an additional 4 h. The media was removed, and cells were washed and extracted with hexane/2-propanol (3:2 v/v) containing internal standard ([^{14}C]cholesterol). Neutral lipids were separated by TLC followed by isotopic scanning (PhosphorImager, Molecular Dynamics, Sunnyvale, CA). Cell protein concentration was determined by the method of Lowry et al.[31] Data are reported as the concentration (μM) required to inhibit the enzyme activity by 50%.

ACAT Bioassay. 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.[30] Standards were prepared for each drug by adding compound directly to rabbit plasma in DMSO.

In Vivo Rat Assays. In vivo efficacy in rats was examined in an acute assay (APCC) as described by Krause et al.[30] The compounds were administered by gavage in carboxymethylcellulose (1.5%) and Tween-20 (0.2%) in water at either 30 or 3 mg/kg (3−4 pm). The animals were then allowed to consume overnight a diet supplemented with 5.5% peanut oil, 1.5% cholesterol, and 0.5% cholic acid. The data were 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),[30] hypercholesterolemia was first established with a 1 week diet of 5.5% peanut oil/1.5% cholesterol/0.5% cholic acid, followed by administration of the compounds with continued diet for 1 week. In this model changes in TC, HDL cholesterol (HDL-C), and non HDL cholesterol (non HDL-C) were monitored.

In Vivo Dog Assay. In vivo efficacy in cholesterol-fed female Beagle dogs was examined according to the method described by Krause et al.[30] The dogs were dosed with bulk drug in capsules daily before meals for 1 week. Efficacy was expressed as the percent change in plasma TC before and after treatment.

Adrenal Toxicity Assay. Compounds were evaluated for adrenal toxicity in chow-fed guinea pigs. The test compounds were dosed (100 mg/kg) by gavage in an oleic acid vehicle over

2 weeks. Drug-related pathological alterations of the adrenal cortical cells were evaluated as compared with untreated controls.[32]

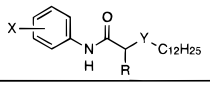
In Vivo Rabbit Assays. Efficacy in cholesterol-fed rabbits was also evaluated in order to attempt to determine a dose which did not lower plasma total cholesterol for the antiatherosclerotic rabbit model. Any subsequent antiatherosclerotic activity at this dose could then be directly attributed to arterial ACAT inhibition and not cholesterol lowering. New Zealand White rabbits were meal-fed a 0.5% cholesterol, 3% peanut oil, 3% coconut oil diet for 1 week prior to administration of the compounds for 2 weeks in the same diet. Blood was obtained from the heart of fasted animals after nitrogen asphyxiation for determining plasma TC concentrations. Antiatherosclerotic activity was evaluated in the injured cholesterol-fed rabbit.[18] Diet-induced (thoracic aorta) and injury-induced (iliac-femoral) atherosclerotic lesions were produced after 9 weeks on a 0.5% cholesterol, 3% peanut oil, 3% coconut oil diet (1 week prior to, and 8 weeks after surgery). The compounds were then dosed for 8 weeks, and lesion area was evaluated.

Results and Discussion

Previous studies from these laboratories demonstrated ACAT inhibition to be optimal in amides with 2,6-diisopropyl-, 2,4,6-trimethoxy-, or 2,4-difluorophenylamide substitution in the aniline ring.[12−14] Thus these were the the substitution patterns employed in this study. The activities in vitro and in vivo of the isoxazole amides, the first analogs prepared, were shown to be optimal in the 2,6-diisopropyl and 2,4,6-trimethoxyphenyl-substituted analogs (**13a**−**b**, **16a**−**b**) depicted in Table 1. However at the 3 mg/kg dose in the APCC rat, the 2,4,6-trimethoxyphenyl **13a** was more effective than 2,6-diisopropylphenyl derivative **13b**. Therefore the 2,4,6-trimethoxyphenyl group was utilized in subsequent analogs. The chain length of the side chain has been previously optimized[33] in related series and was kept constant at 12 carbons. The introduction of α-substitution next to the amide was neccessary because in the related tetrazole amide series, the desphenyl compounds were toxic to the adrenal glands of guinea pigs while the α-phenyl-substituted compounds exemplified by **2** were nontoxic, even when certain analogs in the series were demonstrated to be bioactive.[34] In this series, the one desphenyl analog prepared (**10**) was less potent in vitro and in vivo at 3 mg/kg in the rat than the corresponding α-phenyl-substituted compound (**13a**). However, the bis-alkyl-substituted analogs (**20**, **21**) were significantly less potent in vitro and less efficacious for total cholesterol lowering in the rat than the α-phenyl-substituted compound (**13a**). We set out to examine a variety of heterocyclic replacements for the tetrazole moiety in **2**, keeping the 2,4,6-trimethoxyphenyl, α-phenyl, and C12 substituents constant. We concentrated our efforts on oxygen- and nitrogen-containing heterocycles as these had been shown to be more effective than sulfur-containing heterocycles in a series of related heterocyclic ureas.[35] Both the 3- and 5-dodecylisoxazoles (**13a**, **16a**) were excellent compounds in vitro and vivo in the rat with the 3-dodecylisoxazole **13a** being more efficacious at lowering total cholesterol at 3 mg/kg in the rat (Table 1). When the various oxadiazole isosteres (**26**−**30**) were examined, the 1,3,4-oxadiazole **26a** with a 2,4,6-trimethoxyphenylamide moiety was found to be comparable to the isoxazoles **13a** and **13b**. The 2,6-diisopropyl analog **26b** was comparable in vitro, but in vivo in the rat at 3 mg/kg, efficacy fell off sharply. The 1,2,4-oxadiazole regioisomers (**28**, **30**) were equivalent to each other in vitro and vivo in the acute rat model. When compared with the optimal isoxazoles **13a** and **16a**, the 1,2,4-oxadiazole regioisomers (**28**, **30**) were marginally less potent in vitro, but their efficacy was essentially equivalent at 3 mg/kg in the in vivo APCC rat model. The *N*-alkylated heterocycles (**35**, **40**, and **44**) were chosen as we have previously shown that a free ring NH is detrimental to activity.[35] The 1,2,3-triazole amide derivative **44** was essentially equivalent to the isoxazole **13a** in vitro and in vivo in the rat. The pyrazole amide derivative **35** was less potent in vitro and essentially as efficacious in the rat as the isoxazole **13a**, while the imidazole amide derivative **40** was significantly less potent in vitro and less efficacious in vivo at 3 mg/kg in the rat than the isoxazole **13a**.

Four of the more optimal compounds (**13a**, **16a**, **26a**, **and 44**) were compared in vitro in a cell-based macrophage ACAT assay to assess their ability to penetrate into cells and inhibit ACAT in the target (arterial) tissue. The compounds were also evaluated in a bioassay measuring rat liver microsomal ACAT inhibition in plasma extracts from drug treated rabbits to determine if the compounds were bioactive in plasma. This represents a crude assessment of whether the compound is being absorbed (Table 2). Activity in macrophage ACAT assay and bioassay screens is essential for a compound expected to affect arterial ACAT. All of the compounds (**13a**, **16a**, **26a**, and **44**) inhibited macroph-

Table 1. ACAT Inhibition in Vitro and Hypocholesterolemic Activity in Vivo



Compound	X[a]	R	Y	$IC_{50}(\mu M)$[b]	APCC[c] %ΔTC 30mg/kg	APCC[c] %ΔTC 3mg/kg
10	TMP	H		0.032	-59*	-42*
13a	TMP	Ph		0.015	-68*	-68*
13b	DIP	Ph		0.019	-52*	-10
13c	DIF	Ph		0.051	-50*	ND
16a	TMP	Ph		0.022	-72*	-50*
16b	DIP	Ph		0.024	ND	ND
16c	DIF	Ph		0.10	-29	ND
20	TMP	Me,Me		0.15	-40*	ND
21	TMP	$-(CH_2)_4-$		0.10	-29	ND
26a	TMP	Ph		0.017	-57*	-64*
26b	DIP	Ph		0.014	-64*	-23*
28	TMP	Ph		0.031	-60*	-58*
30	TMP	Ph		0.031	-54*	-56*
35	TMP	Ph		0.046	-72*	-59*
40	TMP	Ph		0.11	-62*	-43*
44	TMP	Ph		0.022	-69*	-66*

[a]TMP = 2,4,6-Trimethoxyphenyl, DIP = 2,6-diisopropylphenyl, DIF = 2,4-difluorophenyl. [b]ACAT inhibition in vitro measured in rat liver microsomes. [c]Denotes percent change in total cholesterol in the acute cholesterol-fed rat model (APCC) of hypercholesterolemia. *Data is statistically significant $p<0.05$. ND = Not determined.

Table 2. ACAT Inhibition in Cell Culture, Bioassay, and Hypocholesterolemic Activity in Vivo

			% ΔTC		
compound	MAI IC_{50} (μM)[a]	ABIO % inhibition[b] at 25 mg/kg	CPCC[c]	CDOG at 10 mg/kg[d]	CFR (mg/kg)[e] % ΔTC
13a	0.17	94	−65*	−44*	−76* (25), −64* (5)
16a	0.31	92	−61*	−44*	−63* (25), −66* (5)
26a	0.048	21	−39	ND	ND
44	0.054	12	ND	ND	ND

[a] MAI is ACAT inhibition in cell culture measured in murine IC-21 macrophages. [b] ABIO denotes the rabbit bioassay. Data represents percent inhibition for rat liver microsomal ACAT inhibition from rabbit plasma. [c] CPCC represents percent change in TC in the chronic rat model. [d] CDOG represents the C-fed female beagle dog model, data is expressed as percent change in TC relative to untreated controls. An asterisk (*) denotes values significantly different from controls, $p < 0.05$.

age ACAT with IC_{50}'s of <1 μM (Table 2). In the bioassay, the isoxazoles (**13a**, **16a**) both gave essentially complete ACAT inhibition when dosed at 25 mg/kg in the rabbit. However, compounds **26a** and **44** were not significantly bioactive, with only 21 and 12% inhibition when dosed at 25 mg/kg. The isoxazoles (**13a, 16a**) were evaluated in several more challenging cholesterol-lowering models. The compounds **13a** and **16a** lowered total cholesterol 65 and 61%, respectively, in the 2 week chronic rat model of pre-established hypercholesterolemia. Compounds **13a** and **16a** could not be distinguished in the cholesterol-fed rabbit model of pre-established hypercholesterolemia, each lowering total cholesterol >60% at a dose of 5 mg/kg. In the cholesterol-fed dog model, which mirrors the clinical situation in that drug is dosed by bulk capsule daily to animals with pre-established hypercholesterolemia, **13a** and **16a** were equivalent, both lowering TC 44%. As a result of the excellent hypocholesterolemic profile, macrophage ACAT inhibition, and bioactivity, **13a** and **16a** were tested in a model to assess adrenal toxicity in guinea pigs in vivo. This toxicity problem has been observed previously with potent lipophilic urea type ACAT inhibitors but was thought not to be related to ACAT inhibition.[32] No adrenal cortical atrophy of the zona fasciculata, necrosis of adrenal cortical cells in the adrenal cortex, or cytoplasmic course vacuolation was observed in the guinea pig with **13a** or **16a** dosed orally at 100 mg/kg for 2 weeks in oleic acid.

The goal of finding potent, bioactive, nontoxic, efficacious cholesterol-lowering ACAT inhibitors having been achieved, the two isoxazoles were evaluated in a long-term rabbit model of atherosclerosis. The compounds (**13a**, **16a**) were compared against CI-976, our prototypical ACAT inhibitor which is antiatherosclerotic at 5 mg/kg, a dose at which there is generally no effect on plasma cholesterol in this rabbit model of atherosclerosis.[18] The 3-alkylisoxazole (**13a**) was effective in slowing the development of cholesteryl ester-rich thoracic aortic lesions, showing a significant effect at all doses (Table 3). The 5-alkylisoxazole **16a** only produced a statistical effect on lesion area at the high dose of 25 mg/kg. Interestingly, the 3-alkylisoxazole **13a** blocks lesion progression at a dose (1 mg/kg) at which it is inactive in the bioassay, suggesting that total cholesterol lowering of 26% may be responsible for the lesion effects. The isoxazole **13a** was equivalent to CI-976, our prototypical ACAT inhibitor in this model.[18] Unfortunately, however, significant hypertriglyceridemia was observed

Table 3. Effect of ACAT Inhibitors in a Rabbit Model of Atherosclerosis

compound	dose (mg/kg)	bioassay % inhibition[a]	thoeracic aortic lesion coverage (%)[b]	% ΔTC[c]	plasma TG[d] % Δ
CI-976	25	46	−41*	−24*	−7
13a	1	0	−53*	−26*	+1
13a	5	46	−46*	−32*	+111*
13a	25	94	−32*	−26*	+168*
16a	1	0	−20	−17*	+24
16a	5	68	−29	−27*	+66*
16a	25	92	−36*	−27*	+157*

[a] Bioassay in chow fed rabbits, data represents percent inhibition of rat liver microsomal ACAT in the plasma drawn from rabbits. [b] Data expressed as percent change in lesion coverage relative to control in the thoracic aorta. [c] Denotes percent change in plasma total cholesterol. [d] Denotes percent change in plasma triglyceride levels. An asterisk (*) denotes value significantly different from control, $p < 0.05$ using a Student's *t*-test.

at 5 and 25 mg/kg, which complicates the intepretation of the data at these doses. The hypertriglyceridemia may be a consequence of potent liver ACAT inhibition by **13a**, as with no cholesteryl ester, the liver has only triglyceride to package into lipoproteins. Presumably, at the 1 mg/kg dose, where no hypertriglyceridemia is observed, **13a** and **16a** are not bioactive and not inhibiting liver ACAT. Neither compound affected the more complex cholesteryl ester (CE)-poor injury-induced iliac femoral lesions. This observation is not suprising given the nature of the iliac femoral lesion, which consists primarily of smooth muscle cells and matrix with a low CE-rich macrophage content.

Conclusion

The majority of heterocyclic amides synthesized here inhibited liver ACAT in vitro (IC_{50}'s = 0.014−0.11 μM), suggesting that ACAT is insensitive to changes in this part of the molecule which do not introduce a free heterocyclic ring NH.[35] The heterocyclic amides were all efficacious in lowering plasma cholesterol (40−68%) in an acute cholesterol-fed rat model at 30 mg/kg. Several compounds were efficacious at 3 mg/kg in this model. Two optimal isoxazoles (**13a**, **16a**) inhibited macrophage ACAT in a cell-based assay, were bioactive in a rabbit bioassay and were nontoxic to the adrenal glands of guinea pigs in vivo. Both compounds significantly lowered cholesterol in models with pre-established hypercholesterolemia in cholesterol-fed rats, cholesterol-fed rabbits, and cholesterol-fed dogs. These two compounds were selected for evaluation in a long-term model of atherosclerosis. Compound **13a** was effective in the injured cholesterol-fed rabbit model of atherosclerosis in slowing the development of cholesteryl ester (CE)-rich thoracic aortic lesions, reducing lesion coverage 53% at 1 mg/kg and was equivalent to CI-976, our prototypical ACAT inhibitor, in this model.[18] The hypertriglyceridemia observed at 5 and 25 mg/kg in this model may be a consequence of potent liver ACAT inhibition, thus with no CE the liver has only TG to package into lipoproteins. The significance of hypertriglyceridemia in the rabbit model of atherosclerosis is unknown. Further studies of **13a** and related compounds in models of atherosclerosis designed to avoid the hypertriglyceridemia observed in this study will be the subject of future communications from these laboratories.

Experimental Section

Unless otherwise noted, all reagents were obtained from commercial suppliers and were 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. Chemical shifts (δ) are expressed in ppm, relative to internal tetramethylsilane. Mass spectra were obtained on a VG Masslab Trio-2A, 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%.

2,4-Dioxohexadecanoic Acid, Ethyl Ester, Monosodium Salt (3). To a stirred volume of absolute ethanol (260 mL) at 5 °C under nitrogen was added portionwise sodium metal (4.3 g, 0.19 mol) over 45 min, and the mixture was allowed to warm to room temperature. To the resulting solution was added a suspension of 2-tetradecanone (39.1 g, 0.184 mol) in diethyloxalate (25 mL, 0.184 mol). The mixture was heated at 60 °C for 5 h and allowed to cool. The resulting suspension was chilled (3 °C), filtered off, and washed with ethanol. The solids were recrystallized from ethanol to give **3** (25.9 g, 39%) as a pale yellow solid: 200 MHz ^{1}H NMR (DMSO-d_6) δ 5.4 (br s, 1H), 4.0 (q, 2H), 2.2 (m, 2H), 1.4 (m, 2H), 1.2 (m, 21H), 0.85 (t, 3H) ppm; EIMS m/z 313 (M − 23 + 2$^+$). Anal. ($C_{18}H_{31}NaO_4$) C, H.

3-Dodecylisoxazole-5-carboxylic Acid (4). To a stirred solution of **3** (15.5 g, 0.046 mol) in glacial acetic acid (125 mL) at 55 °C was added dropwise a solution of hydroxylamine hydrochloride (6.45 g, 0.093 mol) in water (32 mL) over 10 min, and the mixture was stirred at 60 °C for 25 h. The mixture was allowed to cool and partitioned between water (250 mL) and chloroform (400 mL). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in toluene and concentrated in vacuo and the residue recrystallized from chloroform and then toluene to give **4** (5.62 g, 43%) as a white solid: mp 119−122 °C; 200 MHz ^{1}H NMR (DMSO-d_6) δ 14.2 (br s, 1H), 7.1 (s, 1H), 2.66 (t, 2H), 1.64 (m, 2H), 1.3 (m, 18H), 0.84 (t, 3H) ppm; EIMS m/z 282 (MH$^+$). Anal. ($C_{16}H_{27}NO_3$) C, H, N.

3-Dodecyl-5-(hydroxymethyl)isoxazole (6). To a stirred solution of **4** (24.3 g, 0.0863 mol) and triethylamine (12.0 mL, 0.0861 mol) in THF (600 mL) at 3 °C under nitrogen was added in one portion a chilled (3 °C) solution of ethyl chloroformate (8.25 mL, 0.0863 mol) in THF (30 mL). A white precipitate formed immediately. The suspension was stirred for 1.25 h before sodium borohydride (6.54 g, 0.173 mol) was added in portions over 10 min. The mixture was stirred for 1.5 h while warming to room temperature. The mixture was chilled and carefully quenched with water (350 mL). The organic layer was diluted with dichloromethane. The aqueous layer was extracted with THF−dichloromethane and then dichloromethane. The organic solutions were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with 10% acetone in petroleum ether. Fractions containing product were concentrated, and the residue was dissolved in dichloromethane, concentrated and dried in vacuo to give **6** (11.1 g, 48%) as a white solid: mp 57−59 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 6.10 (s, 1H), 4.73 (d, 2H), 2.64 (t, 2H), 2.48 (t, 1H), 1.64 (m, 2H), 1.25 (m, 18H), 0.88 (t, 3H) ppm. EIMS m/z 268 (MH$^+$). Anal. ($C_{16}H_{29}NO_2$) C, H, N.

5-(Bromomethyl)-3-dodecylisoxazole (7). To a stirred solution of **6** (1.0 g, 0.0037 mol) in dichloromethane (20 mL) at 3 °C was added in one portion phosphorus tribromide (0.13 mL, 0.0014 mol), and the solution was stirred for 1.5 h and then at room temperature for 3 days. The mixture was washed carefully with saturated sodium bisulfite, saturated sodium bicarbonate, and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to a yellow oil. The oil was purified by column chromatography on silica gel, eluting with 3% acetone in hexanes to give **7** (0.47 g, 39%) as an off-white solid: mp 35.5−37.5 °C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.16 (s, 1H), 4.43 (s, 2H), 2.64 (t, 2H), 1.65 (m, 2H), 1.26 (m, 18H), 0.88 (t, 3H) ppm; EIMS m/z 330 (M$^+$). Anal. ($C_{16}H_{28}BrNO$) C, H, N.

3-Dodecyl-5-methylisoxazole (8). A suspension of **7** (9.99 g, 0.030 mol) in DMSO (100 mL) was warmed to give a cloudy solution and allowed to cool to room temperature. Sodium borohydride (1.2 g, 0.032 mol) was added in one portion, and the mixture was stirred for 3 days under nitrogen. The mixture was poured into 0.1 M HCl (900 mL) and extracted with ethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with 3% acetone in petroleum ether. The product was concentrated and dried in vacuo to give **8** (3.96 g, 52%) as a white solid: mp 35−38 °C; 200 MHz ^{1}H NMR ($CDCl_3$) δ 5.80 (s, 1H), 2.60 (t, 2H), 2.37 (s, 3H), 1.63 (m, 2H), 1.25 (m, 18H), 0.87 (t, 3H) ppm; EIMS m/z 252 (MH$^+$). Anal. ($C_{16}H_{29}NO$) C, H, N.

2-(3-Dodecylisoxazol-5-yl)acetic Acid (9). To a stirred suspension of **8** (3.40 g, 0.0135 mol) in dry THF (900 mL) at −78 °C was added in one portion a 1.6 M solution of *n*-butyllithium in hexanes (8.5 mL, 0.014 mol), and the mixture was stirred for 1.5 h. The mixture was poured onto freshly crushed dry ice and allowed to warm overnight. The mixture was concentrated, and the residue was partitioned between petroleum ether and 0.5 M NaOH. The aqueous layer was washed with petroleum ether, acidified with concentrated HCl to pH ∼1−2, and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concentrated to give a waxy solid which was recrystallized from toluene to give **9** (0.65 g, 16%) as a white solid: mp 79−80 °C; 200 MHz ^{1}H NMR (DMSO-d_6) δ 12.8 (br s, 1H), 6.29 (s, 1H), 3.85 (s, 2H), 2.58 (t, 2H),1.59 (m, 2H), 1.25 (m, 18H), 0.87 (t, 3H) ppm; EIMS m/z 296 (MH$^+$). Anal. ($C_{17}H_{29}NO_3$) C, H, N.

2-(3-Dodecylisoxazol-5-yl)-*N*-(2,4,6-trimethoxyphenyl)acetamide (10). To a stirred solution of **9** (0.64 g, 0.0022 mol) in dry THF (20 mL) at room temperature under nitrogen was added in one portion 1,1′-carbonyldiimidazole (CDI) (0.38 g, 0.0024 mol), and the mixture was stirred for 2 h. To this solution were added 2,4,6-trimethoxyaniline hydrochloride (0.48 g, 0.0022 mol) and triethylamine (0.33 mL, 0.0024 mol) in THF (30 mL). The mixture was stirred for 2 days. The solution was concentrated, and the residue was dissolved in dichloromethane. The solid was filtered through silica gel, eluting with 25% acetone in petroleum ether. The filtrate was concentrated in vacuo to give an oil which crystallized on standing to give **10** (0.96 g, 96%) as a pale yellow solid: mp 107−109 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 6.71 (br s, 0.67 H), 6.42 (br s, 0.33H), 6.22 (0.67 H), 6.14 (s, 2.33H), 3.79−3.87 (m, 11H), 2.65 (m, 2H), 1.67 (m, 2H), 1.25 (m, 18H), 0.88 (t, 3H) ppm; EIMS m/z 460 (M$^+$). Anal. ($C_{26}H_{40}N_2O_5$) C, H, N.

3-Dodecyl-5-(phenylmethyl)isoxazole (11). To a stirred suspension of sodium nitrite (227 g, 3.29 mol) in DMF (3.8 L) was added 1-bromotridecane (514.5 g, 1.95 mol), and the mixture was stirred for 6 h at room temperature. The mixture was poured into cold water (8 L) and extracted with petroleum ether (2 × 2 L). The organic layer was washed with water (2 L) and brine, dried ($MgSO_4$), and concentrated. The residue was distilled in vacuo (bp 101−120 °C, 0.2 mmHg) to give 171.9 g of an oil which was purified by column chromatography on silica gel, eluting with 1% ethyl acetate in petroleum ether to give 1-nitrotridecane (109.8 g, 24.5%) as a clear colorless oil which was not further purified. To a stirred solution of 3-phenyl-l-propyne (54.9 g, 0.472 mol) and phenyl isocyanate (104 mL, 0.957 mol) in benzene (800 mL) at room temperature under nitrogen was added dropwise over 30 min a solution of the l-nitrotridecane (109.1 g, 0.476 mol) and triethylamine (6.7 mL, 0.048 mol) in benzene (400 mL). The mixture was stirred for 1 h, refluxed for 6 h, allowed to cool, and chilled. The solid that precipitated was filtered, and the filtrate was concentrated to an oil which was purified by column chromatography on silica gel, eluting with 4% ether in petroleum ether to give **11** (57.8 g, 37%) as an off-white solid: mp 45−47 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 5H), 5.74 (s, 1H), 4.04 (s, 2H), 2.59 (t, 2H), 1.58 (m, 2H), 1.25 (m, 18H), 0.88 (t, 3H) ppm; EIMS m/z 328 (MH$^+$). Anal. ($C_{22}H_{33}NO$) C, H, N.

(±)-2-(3-Dodecylisoxazol-5-yl)-2-phenyl-*N*-(2,4,6-trimethoxyphenyl)acetamide (13a). A stirred solution of **11** (38.3 g, 0.117 mol) in THF (600 mL) was cooled to −78 °C under nitrogen. To the resulting suspension was added dropwise a 2.01 M solution of *n*-butyllithium in hexanes (58 mL, 0.12 mol) over 10 min. The mixture was stirred for 1.25 h before a solution of 2,4,6-trimethoxyphenyl isocyanate[13] (24.4 g, 0.117 mol) in THF (350 mL) was added dropwise over 30 min. The mixture was stirred for 45 min and then quenched with the dropwise addition of 1 M HCl (235 mL, 0.235 mol) followed by ethyl ether (500 mL). The mixture was allowed to warm to room temperature. The organic layer was washed with 0.2 M HCl, water, saturated aqueous sodium bicarbonate, and brine, dried ($MgSO_4$), and concentrated to a solid which was recrystallized from diisopropyl ether and chromatographed on silica gel eluting with 30% ethyl acetate in petroleum ether to give **13a** (40.7 g, 65%) as a white solid: mp 106−107 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.1−7.5 (m, 5H), 6.68 (s, 1H), 6.27 (s, 1H), 6.11 (s, 2H), 5.19 (s, 1H), 3.6−3.8 (m, 9H), 2.63 (t, 2H), 1.64 (m, 2H), 1.25 (m, 18H), 0.88 (t, 3H) ppm; EIMS *m*/*z* 536 (M^+). Anal. ($C_{32}H_{44}N_2O_5$) C, H, N.

(±)-2-(3-Dodecylisoxazol-5-yl)-2-phenylacetic Acid (12). A stirred solution of **11** (6.03 g, 0.0184 mol) in THF (120 mL) was cooled to −78 °C under nitrogen, and to the resulting suspension was added dropwise a 2.1 M solution of *n*-butyllithium in hexanes (8.8 mL, 0.018 mol) over 5 min. The mixture was stirred for 1 h, then transferred via canula onto freshly crushed dry ice, and allowed to warm overnight. The mixture was partitioned between 0.2 M HCl and ethyl ether. The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated to give a solid which was crystallized from hexanes−ethyl ether to give **12** (5.16 g, 76%) as a white solid: mp 110−111.5 °C; 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.37 (m, 5H), 6.11 (s, 1H), 5.10 (s, 1H), 2.62 (dd, 2H), 1.62 (m, 2H), 1.21−1.34 (m, 18H), 0.88 (t, 3H) ppm; CIMS *m*/*z* 372 (MH^+). Anal. ($C_{23}H_{33}NO_3$) C, H, N.

(±)-*N*-(2,6-Diisopropylphenyl)-2-(3-dodecylisoxazol-5-yl)-2-phenylacetamide (13b). To a stirred solution of **12** (0.30 g, 0.000 81 mol) in THF (15 mL) at room temperature under nitrogen was added CDI (0.14 g, 0.000 85 mol), and the mixture was stirred for 2 h. To the solution was added 2,6-diisopropylaniline (0.18 mL, 0.000 96 mol), and the mixture was stirred at room temperature for 1 day and at reflux for 6 days. The reaction mixture was partitioned between ethyl ether and 1 M HCl. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel, eluting with 6% acetone in petroleum ether. The product was dissolved in CH_2Cl_2, concentrated, and dried in vacuo to give **13b** (0.245 g, 57%) as a white solid: mp 115−117 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.46 (m, 5H), 7.26 (d, 1H), 7.13 (d, 2H), 6.91 (br s, 1H), 6.23 (s, 1H), 5.24 (s, 1H), 2.85 (m, 2H), 2.66 (t, 2H), 1.66 (m, 2H), 1.25 (m, 18H), 1.09 (m, 12H), 0.88 (t, 3H) ppm; EIMS *m*/*z* 531 (MH^+). Anal. ($C_{35}H_{50}N_2O_2 \cdot 0.25H_2O$) C, H, N.

(±)-*N*-(2,4-Difluorophenyl)-2-(3-dodecylisoxazol-5-yl)-2-phenylacetamide (13c). According to the procedure described for **13b**, compound **13c** (91%) was synthesized as a yellow solid: mp 68−70 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 8.20 (m, 1H), 7.55 (br s, 1H), 7.41 (m, 5H), 6.83 (m, 2H), 6.15 (s, 1H), 5.16 (s, 1H), 2.64 (t, 2H), 1.64 (m, 2H), 1.25 (m, 18H), 0.85 (t, 3H) ppm; EIMS *m*/*z* 483 (MH^+). Anal. ($C_{29}H_{36}F_2N_2O_2$) C, H, N.

5-Dodecyl-3-(phenylmethyl)isoxazole (14). To a stirred solution of l-tetradecyne (29.9 g, 0.154 mol) and phenyl isocyanate (33.4 mL, 0.307 mol) in benzene (450 mL) at room temperature was added dropwise a solution of 2-phenylnitroethane[24] (35.2 g,0.154 mol) and triethylamine (2.15 mL, 0.0154 mol) in benzene (150 mL) over 10 min under nitrogen. The mixture was stirred for 1 h, then refluxed for 10 h, cooled, and filtered. The filtrate was concentrated, and the residue was chromatographed on silica gel, eluting with 2% ethyl acetate in petroleum ether to give **14** (20.6 g, 41%) as a yellow crystalline solid: mp 41−45 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5H), 5.72 (s, 1H), 3.97 (s, 2H), 2.66 (t, 2H), 1.64 (m, 2H), 1.25 (m, 18H), 0.88 (t, 3H) ppm; EIMS *m*/*z* 327 (M^+). Anal. ($C_{22}H_{33}NO$) C, H, N.

(±)-2-(5-Dodecylisoxazol-3-yl)-2-phenyl-*N*-(2,4,6-trimethoxyphenyl)acetamide (16a). According to the procedure described for **13a**, compound **16a** (59%) was synthesized as a white solid: mp 90−91.5 °C; 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 2H), 7.36 (m, 2H), 7.29 (m, 1H), 7.02 (br s, 1H), 6.17 (s, 1H), 6.11 (s, 2H), 5.17 (s, 1H), 3.78 (s, 3H), 3.74 (s, 6H), 2.69 (t, 2H), 1.66 (m, 2H), 1.25 (m, 18H), 0.88 (t, 3H) ppm; EIMS *m*/*z* 536 (M^+). Anal. ($C_{32}H_{44}N_2O_5$) C, H, N.

(±)-2-(5-Dodecylisoxazol-3-yl)-2-phenylacetic Acid (15). According to the procedure described for compound **12**, compound **15** (86%) was synthesized as a white solid: mp 84−85 °C; 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.37 (m, 5H), 6.05 (s, 1H), 5.16 (s, 1H), 2.69 (t, 2H), 1.66 (m, 2H), 1.25 (m, 18H), 0.88 (t, 3H) ppm; CIMS *m*/*z* 372 (MH^+). Anal. ($C_{23}H_{33}NO_3$) C, H, N.

(±)-*N*-(2,6-Diisopropylphenyl)-2-(5-dodecylisoxazol-3-yl)-2-phenylacetamide (16b). According to the procedure described for **13b**, compound **16b** (56%) was synthesized as a white solid: mp 107−108 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.72 (br s, 1H), 7.53 (d, 2H), 7.38 (m, 3H), 7.24 (d, 1H), 7.12 (d, 2H), 6.07 (s, 1H), 5.18 (s, 1H), 2.85 (m, 2H), 2.74 (t, 2H), 1.67 (m, 2H), 1.25 (m, 18H), 1.06 (m, 12H), 0.88 (t, 3H) ppm; EIMS *m*/*z* 531 (MH^+). Anal. ($C_{35}H_{50}N_2O_2$) C, H, N.

(±)-*N*-(2,4-Difluorophenyl)-2-(5-dodecylisoxazol-3-yl)-2-phenylacetamide (16c). According to the procedure described for **13b**, compound **16c** (81%) was synthesized as a yellow solid: mp 54−57 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 8.47 (br s, 1H), 8.21 (m 1H), 7.41 (m, 5H), 6.84 (t, 2H), 6.01 (s, 1H), 5.11 (s, 1H), 2.72 (t, 2H), 1.67 (m 2H), 1.25 (m, 18H), 0.87 (t, 3H) ppm; EIMS *m*/*z* 483 (MH^+). Anal. ($C_{29}H_{36}F_2N_2O_2$) C, H, N.

5-Dodecyl-3-[2-(tetrahydropyran-2-yloxy)ethyl]isoxazole (17b). Dihydropyran (78.5 mL, 0.86 mol) was added dropwise to a mechanically stirred, ice-cooled mixture of 3-bromopropanol (100 g, 0.72 mol), Amberlyst-15 (5 g) and heptane (1 L). The mixture was stirred for 18 h at room temperature, filtered, and concentrated to afford a crude oil which was diluted with DMF (500 mL), stirred for 18 h with sodium nitrite (84.5 g, 1.22 mol), poured into water, and extracted with ethyl acetate (2 × 500 mL). The combined organic extracts were washed with water, dried over Na_2SO_4, and chromatographed on silica gel, eluting with 20% ethyl acetate in hexanes to afford an oil **17a** (36.7 g) which was not further purified but diluted with benzene (400 mL), tetradecyne (53.5 g, 0.28 mol), and phenyl isocyanate (65.7 g, 0.55 mol). Triethylamine (3.9 mL, 0.028 mol) was added to the mixture, which was refluxed for 3 h and stirred at room temperature for a further 12 h. The mixture was filtered and washed with benzene (100 mL) and the filtrate chromatographed on silica gel, eluting with 15% ethyl acetate in hexane to give the title compound as an oil (35.7 g, 13%): 400 MHz ^{1}H NMR ($CDCl_3$) δ 5.91 (s, 1H), 4.63 (m, 1H), 4.01 (m, 1H), 3.81 (m, 1H), 3.68 (m, 1H), 3.52−3.47 (m, 1H), 2.94 (t, J = 6.8 Hz, 2H), 2.70 (t, J = 7.8 Hz, 2H), 1.85−1.48 (m, 6H), 1.26 (s, 20H), 0.88 (t, J = 6.8 Hz, 3H) ppm; CIMS *m*/*z* 366 (MH^+). Anal. ($C_{22}H_{39}NO_3 \cdot 0.08H_2O$) C, H, N.

2-(5-Dodecylisoxazol-3-yl)ethanol (18). Compound **17b** (20.2 g, 0.055 mol) was diluted with methanol (300 mL) and *p*-toluenesulfonic acid (0.2 g) added. The mixture was stirred for 18 h at room temperature, concentrated in vacuo, and partitioned between ethyl acetate and dilute aqueous $NaHCO_3$, and the organic layer was washed with brine and chromatographed on silica gel, eluting with 10% ethyl acetate in hexane, to give the title compound as a white solid (15.4 g, 99%): 400 MHz ^{1}H NMR ($CDCl_3$) δ 5.88 (s, 1H), 3.95 (m, 2H), 2.89 (t, J = 5.8 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.20 (t, J = 5.8 Hz, 1H), 1.68 (m, 2H), 1.26 (s, 18H), 0.88 (t, J = 6.8 Hz, 3H) ppm; EIMS *m*/*z* 282 (MH^+). Anal. ($C_{17}H_{31}NO_2$) C, H, N.

2-(5-Dodecylisoxazol-3-yl)-2-methylpropionic Acid Methyl Ester (19b). A solution of Jones reagent (112 mL, 1.25 M) was added dropwise over 1 h to **18** (15.1 g, 0.054 mol) in acetone at 0 °C. The mixture was stirred for a further 4 h and allowed to warm to room temperature, and the reaction was quenched with 2-propanol (10 mL). The mixture was poured into water (500 mL), concentrated in vacuo to remove acetone and extracted with ethyl acetate (2 × 600 mL). The organics were washed with brine, dried over $MgSO_4$, and

concentrated to afford a white solid (14.8 g) which was dissolved in methanol (600 mL). Gaseous HCl was bubbled into the solution for 30 s, and the solution was stirred for 12 h, concentrated in vacuo, and partitioned between ethyl acetate and water. The organic layer was washed with brine and chromatographed on silica gel, eluting with 10, 20, and 30% ethyl acetate in hexane to afford **19a**, 10.8 g as an oil, 2.8 g of which was diluted with DMF and methyl iodide (5.7 g, 0.0405 moL) under N_2. NaH (0.97 g, 60% dispersion in mineral oil) was added to the ice-cooled solution and the mixture stirred for 12 h at room temperature. The mixture was poured into ethyl acetate/brine and the organic layer dried over $MgSO_4$ and chromatographed on silica gel, eluting with 5% ethyl acetate in hexane to afford the title compound as an oil (2.5 g, 64%): 400 MHz ^{1}H NMR ($CDCl_3$) δ 5.92 (s, 1H), 3.70 (s, 3H), 2.70 (t, J = 7.6 Hz, 2H), 1.66 (m, 2H), 1.60 (s, 6H), 1.26 (s, 18H), 0.88 (t, J = 6.8 Hz, 3H) ppm; EIMS m/z 388 (MH^+). Anal. ($C_{20}H_{35}NO_3$) C, H, N.

2-(5-Dodecylisoxazol-3-yl)-*N*-(2,4,6-trimethoxyphenyl)-isobutyramide (20). Compound **19** (1.36 g, 0.0039 mol) was refluxed with KOH (0.34 g, 0.006 mol) in methanol (100 mL) for 24 h, acidified with 1 M HCl, and extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and concentrated to afford a white solid (2.27 g), which was dissolved in a solution of THF (200 mL) and CDI (1.30 g, 0.008 mol). The mixture was refluxed under N_2 for 2 h to give the imidazolide in situ. Trimethoxyaniline hydrochloride (1.77 g, 0.008 mol) and Et_3N (1.12 mL, 0.008 mol) were stirred in THF (50 mL) for 30 min, and the slurry was added to the imidazolide. The mixture was refluxed for 2 weeks, quenched with water, concentrated to remove THF, extracted with $CHCl_3$ (200 mL), dried over $MgSO_4$, and chromatographed on silica gel, eluting with 30% ethyl acetate in hexane to afford the title compound as a white solid (2.42 g, 68%): mp 58−60 °C; 400 MHz ^{1}H NMR ($CDCl_3$) δ 6.84 (s br, 2H), 6.11 (s, 2H), 6.05 (s, 1H), 3.78 (s, 3H), 3.74 (s, 6H), 2.74 (t, J = 7.6 Hz, 2H), 1.76−1.70 (m, 2H), 1.68 (s, 6H), 1.39−1.28 (m, 2H), 1.25 (s, 16H), 0.88 (t, J = 7.0 Hz, 3H) ppm; CIMS m/z 489 (MH^+). Anal. ($C_{28}H_{44}N_2O_5$) C, H, N.

1-(5-Dodecylisoxazol-3-yl)cyclopentanecarboxylic Acid (2,4,6-Trimethoxyphenyl)amide (21). The title compound was prepared by a method analogous to the method for **20**, replacing methyl iodide with 1,4-dibromobutane to give the title compound: 400 MHz ^{1}H NMR ($CDCl_3$) δ 6.74 (s br, 1H), 6.10 (s, 2H), 6.01 (s, 1H), 3.78 (s, 3H), 3.73 (s, 6H), 2.73 (t, J = 7.8 Hz, 2H), 2.52−2.47 (m, 2H), 2.28−2.24 (m, 2H), 1.86−1.67 (m, 6H), 1.39−1.28 (m, 2H), 1.25 (s, 16H), 0.88 (t, J = 6.8 Hz, 3H); CIMS m/z 515 (MH^+). Anal. ($C_{30}H_{46}N_2O_5$) C, H, N.

(±)-2-Phenyl-*N*-(2,4,6-trimethoxyphenyl)malonamic Acid Ethyl Ester (22). To a stirred solution of diisopropylamine (43.4 mL, 0.310 mol) in dry THF (1.2 L) at room temperature was added a 2.5 M solution of *n*-butyllithium in hexanes (124 mL, 0.31 mol) in one portion, and the mixture was cooled to −78 °C. To the solution was added a solution of phenylacetic acid ethyl ester (50.8 g, 0.309 mol) in THF (500 mL) over 15 min under N_2, and the mixture was stirred for 2 min. A solution of 2,4,6-trimethoxyphenyl isocyanate[13] (64.9 g, 0.310 mol) in THF (500 mL) was added over 10 min. After 1.5 h, the reaction was quenched with 1 M HCl (310 mL, 0.310 mol), and the mixture was allowed to warm to room temperature.The mixture was concentrated to remove THF and partitioned between water and $CHCl_3$. The organic layer was washed with 1 M HCl and brine, dried (Na_2SO_4), and chromatographed on silica gel, eluting with 50% ethyl acetate in petroleum ether, and the product was crystallized from ethanol−ethyl ether to give **22** (46.9 g, 41%) as a white solid: mp 109−111 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.94 (br s, 1H), 7.58 (d, 2H), 7.36 (m, 3H), 6.12 (s, 2H), 4.68 (s, 1H), 4.24 (m, 2H), 3.79 (s, 3H), 3.75 (s, 6H), 1.28 (t, 3H) ppm; EIMS m/z 373 (M^+). Anal. ($C_{20}H_{23}NO_6$) C, H, N.

(±)-2-Phenyl-*N*-(2,4,6-trimethoxyphenyl)malonamic Acid (23a). To a stirred solution of KOH (10.70 g, 0.191 mol) in absolute ethanol (1.1 L) was added **22** (55.3 g, 0.148 mol), and the mixture was stirred for 2 days. The resulting suspension was diluted with water (900 mL) and concentrated to remove ethanol. The solution was washed with ethyl acetate and acidified with the dropwise addition of 1 M HCl (265 mL). The resulting precipitate was filtered, washed with water, and dried in vacuo to give **23a** (48.4 g, 100%) as an off-white solid: mp 111−113 °C (gas evolution); 250 MHz ^{1}H NMR (DMSO-d_6) δ 12.6 (br s, 1H), 8.99 (s, 1H), 7.20−7.66 (m, 5H), 6.22 (s, 2H), 4.77 (s, 1H), 3.76 (s, 3H), 3.65 (s, 6H) ppm; CIMS m/z 346 (MH^+). Anal. ($C_{18}H_{19}NO_6 \cdot 0.2H_2O$) C, H, N.

Tridecanoic Acid Hydrazide (24). A solution of tridecanoic acid methyl ester (24.6 g, 0.108 mol) and anhydrous hydrazine (3.40 mL, 0.108 mol) in absolute ethanol (150 mL) was stirred at room temperature for 24 h and then refluxed for 2 days. The solution was allowed to cool, and the solid that crystallized was filtered, washed, and dried in vacuo to give **24** (18.6 g, 75%) as a white solid: mp 101−104 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 8.90 (br s, 1H), 4.14 (s, 2H), 1.98 (t, 2H), 1.47 (m, 2H), 1.23 (m, 18H), 0.85 (t, 3H) ppm; EIMS m/z 229 (MH^+). Anal. ($C_{13}H_{28}N_2O$) C, H, N.

(±)-2-Phenyl-*N*-(tridecanoylamino)-*N*′-(2,4,6-trimethoxyphenyl)malonamide (25a). A solution of **23a** (46.7 g, 0.135 mol) and CDI (24.7 g, 0.152 mol) in anhydrous THF (1.0 L) was stirred at room temperature under nitrogen for 2 h. To the resulting suspension was added **24** (30.9 g, 0.135 mol), and the mixture was stirred at room temperature for 17 h and then at 40 °C for 21 h. The mixture was chilled to 5 °C and filtered, and the residue was washed with THF, ethyl ether, and then water and air-dried to give **25a** (54.4 g, 72%) as a white solid: mp 175−180 °C; 250 MHz ^{1}H NMR (DMSO) δ 10.2 (m, 2H), 9.1 (s, 1H), 7.55 (d, 2H), 7.37 (m, 3H), 6.26 (s, 2H), 4.64 (s, 1H), 3.79 (s, 3H), 3.72 (s, 6H), 2.13 (t, 2H), 1.51 (m, 2H), 1.25 (m, 18H), 0.87 (t, 3H) ppm; CIMS m/z 556 (MH^+). Anal. ($C_{31}H_{45}N_3O_6$) C, H, N.

(±)-2-(5-Dodecyl[1,3,4]oxadiazol-2-yl)-2-phenyl-*N*-(2,4,6-trimethoxyphenyl)acetamide (26a). To a flask charged with granular phosphorus pentoxide (470 g, 3.31 mol) was added dropwise over 30 min absolute ethanol (260 mL, 4.43 mol) under nitrogen. The mixture was heated on a steam bath with periodic stirring for 3 h and allowed to cool. To the mixture were added **25a** (53.6 g, 0.0964 mol) and DMF (700 mL), and the mixture was stirred at 95 °C for 12 h. The resulting solution was allowed to cool, poured into water (5 L), and extracted twice with CH_2Cl_2. The organics were washed with water and brine, dried ($MgSO_4$), and chromatographed on silica gel, eluting with 20% acetone in petroleum ether. The product was concentrated and crystallized from ethanol−water to give **26a** (7.37 g, 14%) as a white solid: mp 120−121 °C; 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.85 (br s, 1H), 7.58 (d, 2H), 7.38 (m, 3H), 6.11 (s, 2H), 5.31 (s, 1H), 3.79 (s, 3H), 3.74 (s, 6H), 2.82 (t, 2H), 1.76 (m, 2H), 1.25 (m, 18H), 0.88 (t, 3H) ppm; EIMS m/z 538 (MH^+). Anal. ($C_{31}H_{43}N_3O_5$) C, H, N.

(±)-*N*-(2,6-Diisopropylphenyl)-2-phenylmalonamic Acid (23b). According to the procedures described for **22** and **23a**, compound **23b** was synthesized as a white solid: mp 198−199 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 12.8 (br s, 1H), 9.56 (s, 1H), 7.47 (d, 2H), 7.34 (m, 3H), 7.23 (m, 1H), 7.12 (m, 2H), 4.87 (s, 1H), 3.23 (br s, 1H), 2.60 (br s, 1H), 0.80−1.2 (m, 12H) ppm; CIMS m/z 340 (MH^+). Anal. ($C_{21}H_{25}NO_3 \cdot 0.33H_2O$) C, H, N.

(±)-*N*-(2,6-Diisopropylphenyl)-2-phenyl-*N*′-(tridecanoylamino)malonamide (25b). According to the procedure described for **25a**, compound **25b** (84%) was synthesized as a white solid: mp 182−184 °C; 250 MHz ^{1}H NMR (DMSO-d_6) δ 10.2 (br s, 1H), 10.0 (br s, 1H), 9.42 (s, 1H), 7.50 (d, 2H), 7.36 (m, 3H), 7.22 (m, 1H), 7.11 (d, 2H), 4.76 (s, 1H), 2.93 (br s, 2H), 2.13 (t, 2H), 1.50 (m, 2H), 1.23 (m, 18H), 1.02 (d, 12H), 0.85 (t, 3H) ppm; CIMS m/z 550 (MH^+). Anal. ($C_{34}H_{51}N_3O_3$) C, H, N.

(±)-*N*-(2,6-Diisopropylphenyl)-2-(5-dodecyl[1,3,4]-oxadiazol-2-yl)-2-phenylacetamide (26b). According to the procedure described for **26a**, the title compound was synthesized as an oil after concentration from $CHCl_3$. The oil was dried in vacuo and crystallized on standing to give **26b** (30%) as a yellow solid: mp 82−84 °C; 200 MHz ^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1H), 7.10−7.51 (m, 8H), 5.29 (s, 1H), 2.86 (m, 4H), 1.79 (m, 2H), 1.25 (m, 18H), 1.06 (m, 12H), 0.87 (m, 3H) ppm; EIMS m/z 532 (MH^+). Anal. ($C_{34}H_{49}N_3O_2 \cdot 0.03CHCl_3$) C, H, N.

2-(3-Dodecyl[1,2,4]oxadiazol-5-yl)-2-phenyl-*N*-(2,4,6-trimethoxyphenyl)acetamide (28). Hydroxylamine hydrochloride (0.90 g, 0.013 mol) was added to a mixture of Et_3N (1.79 mL, 0.013 mol) and 50% aqueous EtOH (4 mL). The mixture was stirred for 2 min, then tridecanenitrile (2.02 g, 0.0104 mol) dissolved in EtOH (10 mL) was added, and the mixture was refluxed for 2 h and then poured into water (100 mL). The precipitate was filtered and washed with hexanes (2 × 10 mL) to afford *N*-hydroxytridecanimidamide (0.63 g) (**27**) as a white solid which was not further purified.

CDI (0.28 g, 0.0017 mol) was added to a solution of **23a** (0.56 g, 0.0016 mol) in THF (20 mL) and the mixture stirred at room temperature for 1 h. Compound **27** (0.37 g, 1.63 mmol) was added to the heterogeneous mixture, which was stirred a further 1.5 h. The pale green solution was concentrated in vacuo, redissolved in AcOH (20 mL), and refluxed for 1.5 h. The mixture was concentrated in vacuo, diluted with toluene (20 mL), concentrated, and partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic layer was washed with water and brine, dried over $MgSO_4$, concentrated, and recrystallized from EtOH/water to give the title compound **28** (0.14 g, 16%) as a white solid: mp 117−119 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 8.06 (s, 1H), 7.61−7.58 (m, 2H), 7.39−7.37 (m, 3H), 6.12 (s, 2H), 5.35 (s, 1H), 3.79 (s, 3H), 3.75 (s, 6H), 2.75 (t, J = 7.5 Hz, 2H), 1.82−1.73 (m, 2H), 1.24 (s, 18H), 0.88 (t, J = 6.5 Hz, 3H) ppm; EIMS m/z 538 (MH^+). Anal. ($C_{31}H_{43}N_3O_5$) C, H, N.

α-[(Hydroxyamino)iminomethyl]-*N*-(2,4,6-trimethoxyphenyl)benzeneacetamide (29). Benzyl nitrile (20.3 mL, 0.18 mol) was added dropwise to an ice-cooled solution of NaH (7.04 g, 60% in mineral oil, 0.18 mol) in dry DMF (200 mL) and the mixture stirred for 15 min. 2,4,6-Trimethoxyphenyl isocyanate (36.8 g, 0.18 mol) was added portionwise over 2 min, and the mixture was stirred for 0.5 h while being warmed to room temperature, poured into water (500 mL), and filtered. The residue was dried in vacuo then stirred with hexanes (200 mL), filtered, and air-dried to afford a pale purple solid of 2-cyano-2-phenyl-*N*-(2,4,6-trimethoxyphenyl)acetamide (46.7 g) which was not further purified.

Hydroxylamine hydrochloride (11.9 g, 0.17 mol) was added to a solution of Et_3N (23.9 mL, 0.17 mol) in 50% aqueous EtOH (40 mL) and stirred for 0.5 h. 2-Cyano-2-phenyl-*N*-(2,4,6-trimethoxyphenyl)acetamide (44.9 g, 0.14 mol) in EtOH (300 mL) was added, and the mixture was refluxed for 8 h, allowed to cool, and poured into water (1 L). The aqueous solution was decanted, concentrated to half volume, and allowed to crystallize to afford the title compound as a white solid (33.7 g, 52%): 250 MHz ^{1}H NMR (DMSO) δ 9.34 (s br, 1H), 9.21 (s, 1H), 7.49−7.23 (m, 5H), 6.25 (s, 2H), 5.47 (s br, 2H), 4.49 (s, 1H), 3.78 (s, 3H), 3.71 (s, 6H) ppm; EIMS m/z 360 (MH^+). Anal. ($C_{18}H_{21}N_3O_5$) C, H, N.

2-(5-Dodecyl[1,2,4]oxadiazol-3-yl)-2-phenyl-*N*-(2,4,6-trimethoxyphenyl)acetamide (30). Tridecanoyl chloride (15.1 g, 0.061 mol) was added to a solution of **29** (19.8 g, 0.055 mol) and diisopropylethylamine (10.6 mL, 0.061 mol) in THF (200 mL). The mixture was stirred for 2 h, concentrated in vacuo, redissolved in glacial AcOH (100 mL), and refluxed for 2 h. The mixture was concentrated in vacuo, azeotroped with toluene (2 × 250 mL), chromatographed on silica gel, eluting with 35% ethyl acetate in hexane, and recrystallized from EtOH/water to afford the title compound (13.8 g, 47%) as a white solid: mp 98−99 °C; 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.76 (s br, 1H), 7.61 (m, 2H), 7.37−7.30 (m, 3H), 6.12 (s, 2H), 5.27 (s br, 1H), 3.79 (s, 3H), 3.75 (s, 6H), 2.88 (t, J = 7.6 Hz, 2H), 1.80 (m, 2H), 1.24 (s, 18H), 0.88 (t, J = 6.5 Hz, 3H) ppm; EIMS m/z 537 (M^+). Anal. ($C_{31}H_{43}N_3O_5$) C, H, N.

(±)-Ethyl 4-Formyl-α-phenyl-1*H*-pyrazole-1-acetate (31). A solution of pyrazole (2.80 g, 0.041 mol) in 75 mL of THF was added dropwise to a suspension of NaH (1.65 g, 0.041 mol) in 100 mL of THF at −15 °C under an atmosphere of N_2. The cloudy solution was warmed to room temperature for 15 min, resulting in a clear solution. The mixture was cooled to −15 °C and added to a solution of ethyl α-bromophenylacetate (7.2 mL, 0.041 mol) in 50 mL of THF. The resulting yellow suspension was warmed to room temperature for 16 h and then concentrated in vacuo. The residue was partitioned between water and dichloromethane. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a light green oil which was chromatographed on silica gel, eluting with 10% ethyl acetate in hexanes to give 5.54 g (58%) of (±)-α-phenyl-1*H*-pyrazole-1-acetate as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.58 (s, 1H), 7.41 (s, 6H), 6.27 (s, 1H), 6.23 (s, 1H), 4.31−4.24 (m, 2H), 1.30−1.24 (t, 3H); CIMS m/z 231 (MH^+).

Phosphorus oxychloride (7.0 mL, 0.075 mol) was added dropwise to 14 mL DMF at 0 °C under an atmosphere of N_2. The resulting solution was stirred for 30 min, and then a solution of ethyl (±)-α-phenyl-1*H*-pyrazole-1-acetate (5.76 g, 0.025 mol) in 5 mL of DMF was added dropwise. The resulting orange solution was warmed to 70 °C for 16 h. The reaction mixture was cooled to 0 °C, carefully quenched with saturated aqueous Na_2CO_3, and partitioned between water and diethyl ether. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give an orange oil which was chromatographed on silica gel, eluting with 15% ethyl acetate in hexanes to give 5.73 g (89%) of the title compound as a yellow/green oil which solidified upon standing: mp 68−70 °C; ^{1}H NMR ($CDCl_3$) δ 9.82 (s, 1H), 8.03 (s, 1H), 7.91 (s, 1H), 7.49−7.42 (m, 5H), 6.22 (s, 1H), 4.36−4.27 (m, 2H), 1.30−1.24 (t, 3H) ppm; CIMS m/z 259 (MH^+). Anal. ($C_{14}H_{14}N_2O_3 \cdot 0.2H_2O$) C, H, N.

(±)-Ethyl 4-(1-Dodecenyl)-α-phenyl-1*H*-pyrazole-1-acetate (32). A solution of *n*-BuLi (127 mL, 0.254 mol, 2.0 M in hexanes) was added dropwise to a suspension of *n*-undecyltriphenylphosphonium bromide (121.6 g, 0.244 mol, obtained from triphenylphosphine and undecyl bromide) in 500 mL of THF at −78 °C under an atmosphere of N_2. The resulting orange solution was stirred for 1 h before a solution of (±)-ethyl 4-formyl-α-phenyl-1*H*-pyrazole-1-acetate in 250 mL of THF was added dropwise. The mixture was warmed to room temperature and stirred for 16 h, quenched with water (150 mL), and concentrated in vacuo. The residue was partitioned between water and dichloromethane, and the organic layer was dried over $MgSO_4$, filtered, and concentrated to give an oily tan solid which was triturated with boiling hexanes and filtered to remove triphenylphosphine oxide. The filtrate was concentrated and chromatographed on silica gel, eluting with 10% ethyl acetate in hexanes to give the title compound as a yellow oil (1:2 *E*/*Z* mixture, 44.4 g, 50%): ^{1}H NMR ($CDCl_3$) δ 7.59 (s, 1H), 7.40−7.26 (m, 6H), 6.17 (s, 1H), 6.16−6.10 (m, 1H), 5.96−5.84 (dt, 0.33H), 5.53−5.43 (dt, 0.66H), 4.34−4.22 (m, 2H), 2.26−2.04 (m, 2H), 1.42−1.26 (m, 19H), 0.90−0.85 (t, 3H) ppm; CIMS m/z 397 (MH^+). Anal. ($C_{25}H_{36}N_2O_2$) C, H, N.

(±)-4-(1-Dodecenyl)-α-phenyl-*N*-(2,4,6-trimethoxyphenyl)-1*H*-pyrazoleacetamide (34). Solid NaOH (6.72 g, 0.168 mol) was added to a solution of (±)-ethyl 4-(1-dodecenyl)-α-phenyl-1*H*-pyrazole-1-acetate (44.4 g, 0.112 mol) in 500 mL of 95% ethanol. The resulting yellow solution was stirred for 1 h and then concentrated in vacuo. The residue was partitioned between water and ether, and the aqueous layer was acidified with concentrated HCl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give (±)-4-(1-dodecenyl)-α-phenyl-1*H*-pyrazole-1-acetic acid (**33**) as a yellow oil (43.4 g) which was used without further purification.

Triethylamine (18 mL, 0.13 mol) was added to a suspension of 2,4,6-trimethoxyaniline hydrochloride (28.48 g, 0.13 mol) in 500 mL of THF and stirred for 1 h before filtering to remove triethylamine hydrochloride. The filtrate was concentrated and redissolved in 500 mL of dichloromethane with **33** (43.43 g, 0.118 mol) at −15 °C. Dicyclohexylcarbodiimide (25.53 g, 0.124 mol) was added in one portion, and the resulting suspension was warmed to room temperature and stirred for 16 h. The mixture was filtered to remove a white solid and the filtrate partitioned between dichloromethane and 1 M HCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give an oily tan solid which was recrystallized from hexanes to give the title compound as a tan solid (45.43 g, 72%): mp 82−85 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1H), 7.65−7.26 (m, 7H), 6.19−6.13 (m, 4H), 5.58−5.48 (m, 1H), 3.79 (s, 3H), 3.76 (s, 6H), 2.28−2.08 (m, 2H), 1.45−1.26 (m, 16H), 0.90−0.85 (t, 3H) ppm; CIMS m/z 534 (MH^+). Anal. ($C_{32}H_{43}N_3O_4 \cdot 0.2H_2O$) C, H, N.

(±)-4-Dodecyl-α-phenyl-*N*-(2,4,6-trimethoxyphenyl)-1*H*-pyrazole-1-acetamide (35). Compound **34** (0.46 g, 0.9 mmol) was dissolved in 75 mL of THF, and 5% Pd/C (0.1 g) was added. Hydrogen gas (50 psi) was added, and the reaction mixture was stirred at room temperature for 2 h. The mixture was filtered to remove the catalyst and the filtrate concentrated to give an oil which was triturated with hexanes to give the title compound as a cream-colored solid (0.45 g, 97%): mp 77−79 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.54−7.26 (m, 7H), 6.19−6.13 (s, 3H), 3.79 (s, 3H), 3.76 (s, 6H), 2.44 (t, 2H), 1.57−1.51 (m, 2H), 1.25 (s, 18H), 0.90−0.85 (t, 3H) ppm; CIMS *m*/*z* 536 (MH^+). Anal. ($C_{32}H_{45}N_3O_4$) C, H, N.

4-(1-Dodecenyl)-1-(triphenylmethyl)imidazole (36). A solution of *n*-BuLi (4.1 mL, 0.0065 mol, 1.6 M in hexanes) was added dropwise to a suspension of *n*-undecyltriphenylphosphonium bromide (3.09 g, 0.0062 mol, obtained from triphenylphosphine and undecyl bromide) in 100 mL of THF at −78 °C under an atmosphere of N_2. The resulting orange solution was stirred for 45 min before a solution of 1-(triphenylmethyl)-4-imidazolecarboxaldehyde[28] (2.0 g, 0.0059 mol, in 75 mL of THF was added dropwise. The mixture was warmed to room temperature and stirred for 16 h, quenched with saturated aqueous NH_4Cl (50 mL), and concentrated. The residue was partitioned between water and dichloromethane, and the organic layer was dried over $MgSO_4$, filtered, and concentrated to give a yellow oil which was chromatographed on silica gel, eluting with 10% ethyl acetate in hexanes to give the title compound (1.8 g, 64%) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.46 (s, 1H), 7.35−7.12 (m, 15H), 6.75 (s, 1H), 6.29−6.25 (d, 1H), 5.62−5.52 (dt, 1H), 2.33−2.24 (m, 2H), 1.38−1.23 (m, 16H), and 0.90−0.85 (t, 3H) ppm; CIMS *m*/*z* 477 (MH^+). Anal. ($C_{34}H_{40}N_2 \cdot 0.26H_2O$) C, H, N.

4-Dodecylimidazole (37). 20% Pd/C (1 g) was added to a solution of 4-(1-dodecenyl)-1-(triphenylmethyl) imidazole (2.39 g, 0.005 mol) in glacial acetic acid (100 mL) and 50 psi of hydrogen gas. The mixture was stirred for 16 h and concentrated in vacuo and the residue made basic with saturated aqueous Na_2CO_3 and neutralized with 1 M HCl. The reaction was extracted with diethyl ether, dried over $MgSO_4$, filtered, and concentrated to give an oily white solid which was recrystallized from hexanes to give the title compound as a white solid (1.06 g, 90%): mp 69−71 °C; ^{1}H NMR ($CDCl_3$) δ 9.02 (s, 1H), 7.57 (s, 1H), 6.78 (s, 1H), 2.64−2.58 (t, 2H), 1.66−1.58 (m, 2H), 1.30−1.25 (s, 18H), 0.90−0.85 (t, 3H) ppm; CIMS *m*/*z* 237 (MH^+). Anal. ($C_{15}H_{28}N_2 \cdot 0.4H_2O$) C, H, N.

(±)-Ethyl 4-Dodecyl-α-phenyl-1*H*-imidazole-1-acetate (38). A solution of ethyl α-bromophenylacetate (5.14 g, 0.021 mol) in DMF (50 mL) was added dropwise to a suspension of 4-dodecylimidazole (5.0 g, 0.021 mol) and triethylamine (3.0 mL, 0.021 mol) in DMF (100 mL). The mixture was stirred for 16 h at room temperature and concentrated in vacuo. The residue was partitioned between ethyl acetate and water, and the organic layer was dried over $MgSO_4$, filtered, and concentrated to give an orange oil which was chromatographed on silica gel, eluting with 10% ethyl acetate in hexanes to give 4.57 g (54%) of the title compound as an orange oil: ^{1}H NMR ($CDCl_3$) δ 7.52 (s, 1H), 7.41−7.25 (m, 5H), 6.73 (s, 1H), 5.83 (s, 1H), 4.32−4.24 (q, 2H), 2.57−2.50 (t, 2H), 1.64−1.56 (m, 2H), 1.31−1.25 (m, 21H), and 0.90−0.85 (t, 3H) ppm; CIMS *m*/*z* 399 (MH^+). Anal. ($C_{25}H_{38}N_2O_2 \cdot 0.57H_2O$) C, H, N.

(±)-4-Dodecyl-α-phenyl-1H-imidazole-1-acetic acid (39). Solid NaOH (0.9 g, 0.0226 mol) was added to a solution of ethyl (±)-4-dodecyl-α-phenyl-1*H*-imidazole-1-acetate (4.5 g, 0.0113 mol) in 95% ethanol (150 mL). The resulting solution was stirred for 2 h and then concentrated in vacuo. The residue was partitioned between water and ether, and the aqueous layer was acidified with concentrated HCl and extracted with dichloromethane. The dichloromethane solution was dried over $MgSO_4$, filtered, and concentrated to give a white solid (2.53 g, 55%): mp 110−118 °C; ^{1}H NMR (DMSO-d_6) δ 14.00 (bs, 1H), 9.18 (s, 1H), 7.56−7.49 (m, 6H), 6.63 (s, 1H), 2.64−2.59 (t, 2H), 1.58 (m, 2H), 1.24 (m, 18H), 0.89−0.84 (t, 3H) ppm; CIMS *m*/*z* 371 (MH^+). Anal. ($C_{23}H_{34}N_2O_2 \cdot HCl$) C, H, N.

(±)-4-Dodecyl-α-phenyl-*N*-(2,4,6-trimethoxyphenyl)-1*H*-imidazole-1-acetamide (40). Excess triethylamine (2 mL) was added to a suspension of 2,4,6-trimethoxyaniline hydrochloride (1.6 g, 0.0073 mol) in THF (500 mL) and stirred for 1 h before being filtered to remove triethylamine hydrochloride. The filtrate was concentrated and redissolved in dichloromethane (500 mL) with (±)-4-dodecyl-α -phenyl-1*H*-imidazole-1-acetic acid (2.45 g, 0.0066 mol) at 0 °C. Dicyclohexylcarbodiimide (1.43 g, 0.0069 mol) was added in one portion, and the resulting suspension was warmed to room temperature and stirred for 16 h. The mixture was filtered and the filtrate partitioned between dichloromethane and 1 M HCl. The organic layer was washed with 1 M NaOH, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was chromatographed on silica gel, eluting with 20% ethyl acetate in hexanes to give the title compound as a white solid (1.25 g, 35%): mp 95−102 °C; ^{1}H NMR ($CDCl_3$) δ 7.53−7.29 (m, 6H), 6.75 (s, 2H), 6.12 (s, 2H), 5.96 (s, 1H), 3.79 (s, 9H), 2.57−2.52 (t, 2H), 1.64−1.57 (m, 2H), 1.29−1.24 (m, 18H), 0.89−0.85 (t, 3H); CIMS *m*/*z* 536 (MH^+). Anal. ($C_{32}H_{45}N_3O_4 \cdot 0.45H_2O$) C, H, N.

4-Dodecyl-1,2,3-triazole (41). A mixture of 1-tetradecyne (6.6 g, 0.034 mol) and trimethylsilyl azide (4.1 g, 0.035 mol) was autoclaved at 135 °C for 14 h and then at 150 °C for 14 h. The resulting mixture was rinsed with ether, and the ether solution was washed with water, dried over $MgSO_4$, filtered, and concentrated to give a brown oil which was triturated with cold hexanes to give the title compound as a tan solid (4.02 g, 50%): mp 64−67 °C; ^{1}H NMR ($CDCl_3$) δ 8.45 (bs, 1H), 7.53 (s, 1H), 2.78−2.72 (t, 2H), 1.71−1.66 (m, 2H), 1.31−1.25 (s, 18H), 0.90−0.85 (t, 3H) ppm; CIMS *m*/*z* 238 (MH^+). Anal. ($C_{14}H_{27}N_3$) C, H, N.

(±)-Ethyl 4-Dodecyl-α-phenyl-1*H*-1,2,3-triazole-1-acetate (42). A solution of 4-dodecyl-1,2,3-triazole (0.99 g, 0.0042 mol) in THF (50 mL) was added dropwise to a suspension of sodium hydride (0.18 g, 0.0046 mol, 60% dispersion in mineral oil) in THF (50 mL) at 0 °C. The resulting suspension was warmed to room temperature, stirred for 1 h, and then cooled to 0 °C. A solution of ethyl α-bromophenylacetate (1.01 g, 0.0042 mol) in THF (50 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 16 h, concentrated in vacuo, and partitioned between water and ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a clear oil which was chromatographed on silica gel, eluting with 10% ethyl acetate in hexanes to give the title compound as a white solid (0.61 g, 36%): mp 68−70 °C; ^{1}H NMR ($CDCl_3$) δ 7.44−7.40 (m, 6H), 6.54 (s, 1H), 4.37−4.23 (q, 2H), 2.71−2.65 (t, 2H), 1.66−1.61 (m, 2H), 1.32−1.24 (m, 21H), 0.90−0.85 (t, 3H) ppm; CIMS *m*/*z* 400 (MH^+). Anal. ($C_{24}H_{37}N_3O_2$) C, H, N.

(±)-4-Dodecyl-α-phenyl-1*H*-1,2,3-triazole-1-acetic Acid (43). Solid NaOH (0.44 g, 0.011 mol) was added to a solution of ethyl (±)-4-dodecyl-α-phenyl-1*H*-1,2,3-triazole-1-acetate (2.92 g, 7.3 mmol) in 95% ethanol (100 mL). The resulting yellow solution was stirred for 1 h and then concentrated in vacuo. The residue was partitioned between water and ether. The aqueous layer was acidified with concentrated HCl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give an off-white solid (2.74 g, 99%): mp 94−98 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1H), 7.46−7.37 (m, 5H), 6.59 (s, 1H), 2.68−2.62 (t, 2H), 1.60−1.54 (m, 2H), 1.24 (s, 18H), 0.90−0.85 (t, 3H) ppm; CIMS *m*/*z* 372 (MH^+). Anal. ($C_{22}H_{33}N_3O_2$) C, H, N.

(±)-4-Dodecyl-α-phenyl-*N*-(2,4,6-trimethoxyphenyl)-1*H*-1,2,3-triazole-1-acetamide (44). Triethylamine (1.2 mL, 0.0084 mol) was added to a suspension of 2,4,6-trimethoxyaniline hydrochloride (1.68 g, 0.0077 mol) in THF (100 mL), and the mixture was stirred for 1 h before filtering to remove triethylamine hydrochloride. The filtrate was concentrated and redissolved in dichloromethane (100 mL) with (±)-4-dodecyl-α-phenyl-1*H*-1,2,3-triazole-1-acetic acid (2.59 g, 0.007 mmol) at 0 °C. Dicyclohexylcarbodiimide (1.51 g, 0.0073 mol) was added in one portion, and the resulting suspension was warmed to room temperature and stirred for 16 h. The mixture was filtered and the filtrate partitioned between chloroform and 1 M HCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a pale lavender solid which was recrystallized from ethyl acetate−hexanes (4:1) to

give the title compound as a white solid (2.8 g, 75%): mp 123−125 °C; ^{1}H NMR ($CDCl_3$) δ 7.70−7.19 (m, 7H), 6.70 (s, 1H), 6.10 (s, 2H), 3.78 (s, 3H), 3.73 (s, 6H), 2.67−2.61 (t, 2H), 1.61−1.55 (m, 2H), 1.24 (s, 18H), 0.90−0.85 (t, 3H) ppm; CIMS *m/z* 537 (MH^+). Anal. ($C_{31}H_{44}N_4O_4 \cdot 0.27H_2O$) C, H, N.

Acknowledgment. We thank Dr. G. A. McClusky and staff for spectral and analytical determinations.

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JM9604033