Articles

Substituted (1,2-Diarylethyl)amide Acyl-CoA:Cholesterol Acyltransferase Inhibitors: Effect of Polar Groups on *in Vitro* and *in Vivo* Activity

John W. Clader,* Joel G. Berger, Robert E. Burrier, Harry R. Davis, Martin Domalski, Sundeep Dugar, Timothy P. Kogan,† Brian Salisbury, and Wayne Vaccaro

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033-0539

Received August 26, 1994®

Substituted (1,2-diarylethyl)amides have been prepared and evaluated for their ability to inhibit microsomal acyl-CoA:cholesterol acyltransferase activity *in vitro* and to lower hepatic cholesteryl ester content *in vivo* in a cholesterol-fed hamster. Simple unsubstituted (diarylethyl)amides were potent inhibitors *in vitro* but showed poor activity *in vivo*. Introduction of polar groups at specific locations on the diarylethylamine moiety decreased *in vitro* activity but increased *in vivo* activity. Both effects were highly structure dependent, suggesting specific interactions which were mediating activity in each model. Optimization of these opposing effects led to compounds which were potent in both models.

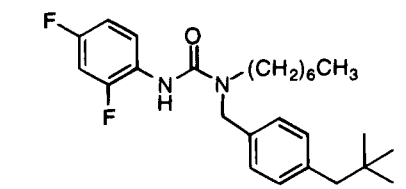
Introduction

Atherosclerotic coronary artery disease (CAD) remains a major cause of death and morbidity in the western world. Among the many risk factors for CAD which have been identified, high serum cholesterol levels have received considerable public attention. A high level of dietary saturated fat and cholesterol has been singled out both as a major determinant of risk and as an important first-line intervention for hyperlipidemia.[1] Despite compelling evidence that reduced levels of dietary fat and cholesterol can significantly lower serum lipid levels, successful dietary therapy is achieved only in a minority of patients due in part to the inability of many patients to remain on a strict dietary regimen. Although drug therapy, particularly the use of bile acid sequestrants, is known to inhibit intestinal cholesterol absorption, the spectrum of unpleasant side effects associated with these drugs has led to poor patient compliance.[2] Thus, there is an ongoing need for safe and effective inhibitors of cholesterol absorption for control of serum lipids.

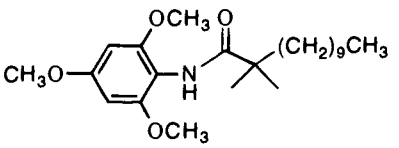
Acyl-CoA:cholesterol acyltransferase (ACAT; EC 2.3.1.26) is a microsomal enzyme responsible for conversion of free cholesterol into fatty acid cholesteryl esters.[3] In enterocytes, intestinally derived free cholesterol is esterified *via* ACAT prior to packaging into chylomicrons and secretion into the lymph. Inhibition of intestinal ACAT activity has been shown to significantly inhibit intestinal cholesterol absorption and reduce serum lipid levels in animal models of hypercholesterolemia. Furthermore, since ACAT-derived cholesterol esters have been implicated in the formation of atherosclerotic plaques, ACAT inhibition may inhibit progression and promote regression of plaques.

Many classes of compounds have been shown to inhibit ACAT activity *in vitro* (Chart 1).[4] These include various anilide and urea derivatives such as CI-976[4c] and Cl 227,082[4d] as well as amides of diphenylethylamine such as compounds 1 (Sa-58,035)[4e] and **2**.[4f] As part of a broad chemical effort directed at understanding factors affecting both *in vitro* and *in vivo* activity, we have investigated structure–activity relationships of

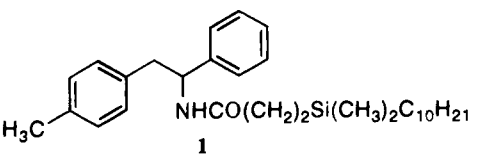
Chart 1. Prototypical ACAT Inhibitors



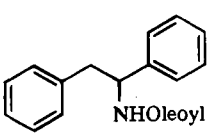
CL 277,082



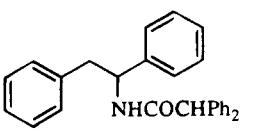
CI-976



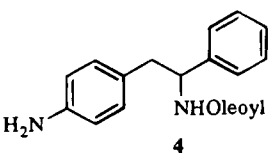
1
(SA-58,035)



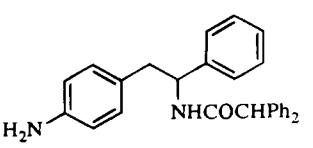
2



3



4



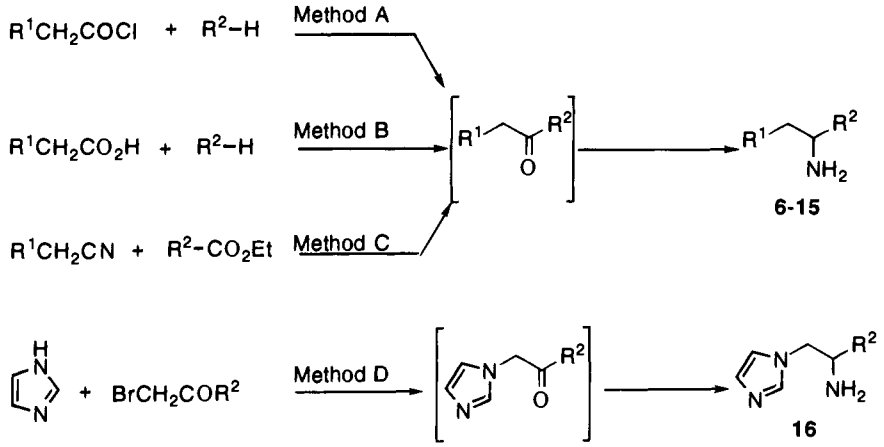
5

† Present address: Texas Biotechnology, 7000 Fannin, Suite 720, Houston, TX.

® Abstract published in *Advance ACS Abstracts*, April 15, 1995.

0022-2623/95/1838-1600$09.00/0

Scheme 1. Preparation of Amines **6**–**16**[a]



[a] (A) i. $AlCl_3$, benzene, 0 °C, overnight; ii. hydroxylamine hydrochloride, pyridine, 3.5 h, 0–23 °C; iii. 50 psi H_2, 10% Pd/C, ethanol. (B) P_2O_5/CH_3SO_3H (10/1, w/w), 50–60 °C, 90 min, and then method A, steps ii and iii. (C) Sodium ethoxide/ethanol, reflux, 2.5 h, and then method A, steps ii and iii. (D) THF, room temperature, 1.5 h, and then method A, steps ii and iii.

Table 1. Biological Activity of Prototypical Compounds

compound	*in vitro* ACAT assay IC_{50} (μM)	cholesterol-fed hamster assay: % change serum cholesterol	% change cholesteryl esters	dose (mpk)
1	0.30	−5	0	100
2	0.15	−4	−23	100
3	0.46	0	−15	50
4	0.36	−24	−54	100
5	1.8	−13	−60[a]	50
CI-976	6.0	−10	−67[b]	50
CL 277,082	3.2	−29	−85[c]	50

[a] ED_{50} = 21 mg/kg. [b] ED_{50} = 20 mg/kg. [c] ED_{50} = 15 mg/kg.

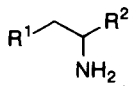
derivatives of **2** and a related series of diphenylacetamides, **3**, using both an *in vitro* microsomal ACAT assay and a cholesterol-fed hamster model. Biological data for some prototypical compounds are shown in Table 1. In general, simple amides of 1,2-diphenylethylamine show potent ACAT inhibitory activity in the microsomal ACAT assay, but unlike CI-976 and Cl 277,082, they show poor activity in the cholesterol-fed hamster model of hyperlipidemia (cf. compounds 1–**3**). We were therefore pleasantly surprised to find that the introduction of a single amino group on the diphenylethylamine moiety significantly improved the *in vivo* profile of these compounds (cf. compounds **4** and **5**). This effect was particularly profound for diphenylacetamides (**3** vs **5**). In light of this finding, we undertook a systematic exploration of the effect of polar groups on *in vitro* and *in vivo* activity for a series of compounds related to **3**. Our results point to two distinct and opposing structure–activity relationships governing *in vitro* and *in vivo* activity which, when optimized, yield compounds which are potent inhibitors in both models.

Chemistry

Substituted (1,2-diarylethyl)amide derivatives were prepared from the amines listed in Table 2. Amines **6**–**16** were prepared by reduction of the corresponding ketoxime as shown in Scheme 1. In the cases where R^1 or R^2 contains a nitro group, concurrent reduction of this group to the amine occurred. The ketone precursors of these oximes were prepared *via* a variety of methods as described in Scheme 1. Most ketones were prepared by method A or B: Friedel–Crafts reaction between a substituted arylacetic acid or acid chloride and a substituted benzene. Alternatively, ketones could be made by method C: Claisen condensation between an arylacetonitrile and an aryl ester followed by decarboxylation.[5] Imidazole derivative **16** was prepared by reaction of imidazole with bromoacetophenone followed by oxime formation and reduction (method D).

Amines **17**–**24** were prepared by method E, F, or G as described in Scheme 2. In method E, Horner–Emmons condensation of a carbamoylphosphonate with an aromatic aldehyde produced the enamide shown which was reduced under catalytic conditions to give the desired amine.[6] In method F, an organolithium or Grignard reagent was added to a (trimethylsilyl)imine to give the desired amine after hydrolytic workup.[7] Alternatively (method G), the organolithium or Grignard reagent could be added to a nitrile followed by sodium borohydride reduction to give the desired amine.

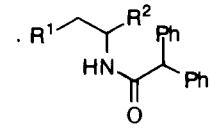
Table 2. Substituted Ethylamines



no.	R^1	R^2	preparation method
(±)-**6**	4-NH_2-C_6H_4	C_6H_5	A
(−)-**6**	4-NH_2-C_6H_4	C_6H_5	*a*
(+)-**6**	4-NH_2-C_6H_4	C_6H_5	*a*
7	3-NH_2-C_6H_4	C_6H_5	A
8	4-CH_3O-C_6H_4	C_6H_5	*b*
9	3,4-$(CH_3O)_2$-C_6H_3	C_6H_5	A
10	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4	A
11	C_6H_5	4-CH_3O-C_6H_4	B
12	4-pyridinyl	C_6H_5	B
13	C_6H_5	4-pyridinyl	C
14	C_6H_5	4-CO_2H-C_6H_4	C
15	C_6H_5	3-pyridinyl	C
16	1-imidazolyl	C_6H_5	D
17	C_6H_5	4-NH_2-C_6H_4	E
18	4-CH_3CO_2-C_6H_4	C_6H_5	E
19	1-SEM-2-imidazolyl	C_6H_5	F
20	1-*n*-heptyl-2-imidazolyl	C_6H_5	F
21	C_6H_5	1-SEM-2-imidazolyl	F
22	C_6H_5	3-CH_3O-C_6H_4	G
23	C_6H_5	2-CH_3O-C_6H_4	G
24	4-CH_3O-C_6H_4	3-CH_3O-C_6H_4	G

[a] Prepared *via* crystallization of the di-*p*-toluoyltartaric acid salt of (±)-**6**. See the Experimental Section for details. [b] Commercially available.

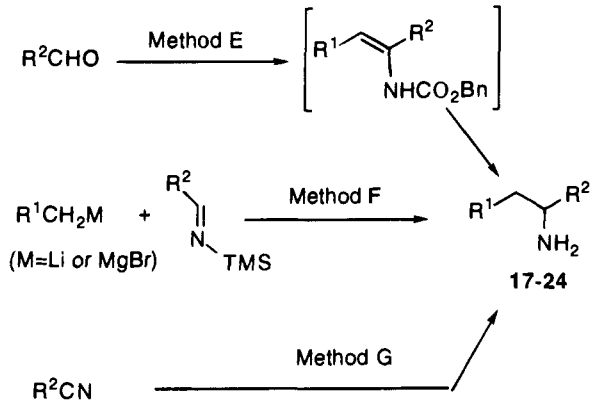
Table 3. *In Vitro* and *in Vivo* Data



no.	R^1	R^2	microsomal ACAT IC_{50} (μM)	cholesterol-fed hamster[a], % change: serum cholesterol	cholesterol-fed hamster[a], % change: cholesteryl esters
(±)-**5**	4-NH_2-C_6H_4	C_6H_5	1.8	−13	−60
(−)-**5**	4-NH_2-C_6H_4	C_6H_5	0.9	0	−81
(+)-**5**	4-NH_2-C_6H_4	C_6H_5	1.4	0	0
25	3-NH_2-C_6H_4	C_6H_5	5	−15	−31
26	C_6H_5	4-NH_2-C_6H_4	2.8	0	−24
27	4-CH_3SO_2NH-C_6H_4	C_6H_5	0.36	−17	−32
28	4-CH_3CONH-C_6H_4	C_6H_5	0.35	−12	0
29	4-CH_3O-C_6H_4	C_6H_5	1.6	−14	−65
30	3,4-$(CH_3O)_2$-C_6H_3	C_6H_5	0.5	−21	−26
31	C_6H_5	4-CH_3O-C_6H_4	1.5	−14	−69
32	C_6H_5	3-CH_3O-C_6H_4	1.5	0	0
33	C_6H_5	2-CH_3O-C_6H_4	1.8	0	−51
34	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4	>10	0	−32
35	4-CH_3O-C_6H_4	3-CH_3O-C_6H_4	2.4	−20	0
36	4-HO-C_6H_4	C_6H_5	0.8	0	0
37	C_6H_5	4-HO-C_6H_4	1	−14	−69
38	C_6H_5	3-HO-C_6H_4	88% at 10 μM	−17	−19
39	4-HO-C_6H_4	4-HO-C_6H_4	97% at 10 μM	−20	−40
40	4-CO_2H-C_6H_4	C_6H_5	>10	ND	ND
41	C_6H_5	4-CO_2H-C_6H_4	10	0	0
42	4-CH_3CO_2-C_6H_4	C_6H_5	>10	ND	ND
43	4-pyridinyl	C_6H_5	1.8	−10	−52
44	C_6H_5	4-pyridinyl	2.3	−13	−29
45	C_6H_5	3-pyridinyl	4	−9	0
46	C_6H_5	4-pyridinyl *N*-oxide	>10	0	−28
47	1-SEM-2-imidazolyl	C_6H_5	5	0	−24
48	2-imidazolyl	C_6H_5	>10	ND	ND
49	1-*n*-heptyl-2-imidazolyl	C_6H_5	5	0	0
50	1-imidazolyl	C_6H_5	3.5	0	0
51	C_6H_5	1-SEM-2-imidazolyl	>10	ND	ND
52	C_6H_5	2-imidazolyl	>10	ND	ND

[a] All compounds were tested at 50 mg/kg po. ND = not determined.

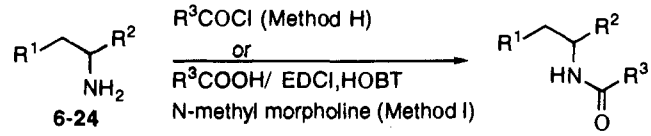
Scheme 2. Preparation of Amines **17**−**24**[a]



[a] (E) i. $(PhO)_3P$, $PhCH_2O(CO)NH_2$, acetic acid, 75−80 °C, 2 h; ii. 10% KOH, methanol−THF, −40 °C, 90 min, and then R^1CHO, −40 °C, 20 min; iii. 50 psi H_2, 10% Pd/C, methanol. (F) THF−ether, −78 °C to rt overnight. (G) R^1CH_2MgCl, THF, 0−23 °C, 18 h, and then $NaBH_4$/methanol, 0 °C.

Amides were prepared from the amines listed in Table 2 by standard procedures as described in Scheme 3. In cases where the groups R^1 or R^2 contain an aromatic amine, minor amounts of the bis-amide product were removed chromatographically. In some cases, additional functional group manipulations such as removal of protecting groups were accomplished under standard conditions as described in the Experimental Section. Physical data for all new amides are listed in Table 4.

Scheme 3. Preparation of Amides

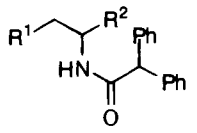


Discussion of Results

Compounds were evaluated for *in vitro* ACAT inhibitory activity using a rat liver microsomal ACAT assay and for *in vivo* activity using a 7-day cholesterol-fed hamster. Details of both models are given in the Experimental Section. Results from this study are reported in Table 3. As reported previously,[13] the change in hepatic cholesteryl ester content proved to be the most sensitive and reproducible measure of *in vivo* efficacy. This end point has also been shown to correlate well with the degree of inhibition of cholesterol absorption in this model.

In general, introduction of a polar group attenuates the *in vitro* ACAT activity, with the extent of this attenuation roughly following the polarity of the group. Thus, introduction of an amino group into **3** to give **5** decreases the *in vitro* activity, but conversion of the amine to an amide or sulfonamide as in **27** or **28** restores the *in vitro* potency. Imidazole derivatives **48** and **52** are probably too polar to effectively bind to the enzyme and are inactive. The extent of attenuation by polar groups is only slightly affected by the location of the

Table 4. Preparation and Analytical Data for Diphenylacetamides of Substituted Ethylamines



no.	R^1	R^2	mp (°C)	formula[a]	amide preparation method
(±)-**5**	4-NH_2-C_6H_4	C_6H_5	161–163	$C_{28}H_{26}N_2O$	I
(−)-**5**	4-NH_2-C_6H_4	C_6H_5	oil	$C_{28}H_{26}N_2O$	I
(±)-**5**	4-NH_2-C_6H_4	C_6H_5	oil	$C_{28}H_{26}N_2O$	I
25	3-NH_2-C_6H_4	C_6H_5	140–144	$C_{28}H_{26}N_2O$	I
26	C_6H_5	4-NH_2-C_6H_4	oil	$C_{28}H_{26}N_2O$	I
27	4-CH_3SO_2NH-C_6H_4	C_6H_5	200–202	$C_{29}H_{28}N_2O_3S$	*b*
28	4-CH_3CONH-C_6H_4	C_6H_5	247–249	$C_{30}H_{28}N_2O_2$	*b*
29	4-CH_3O-C_6H_4	C_6H_5	169–171	$C_{29}H_{27}NO_2$	I
30	3,4-$(CH_3O)_2$-C_6H_3	C_6H_5	166–169	$C_{30}H_{29}NO_3$	I
31	C_6H_5	4-CH_3O-C_6H_4	oil	$C_{29}H_{27}NO_2 \cdot 5H_2O$	I
32	C_6H_5	3-CH_3O-C_6H_4	185–186	$C_{29}H_{27}NO_2$	H
33	C_6H_5	2-CH_3O-C_6H_4	179–180	$C_{29}H_{27}NO_2$	H
34	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4	197–197.5	$C_{30}H_{29}NO_3$	I
35	4-CH_3O-C_6H_4	3-CH_3O-C_6H_4	167–168	$C_{30}H_{29}NO_3$	H
36	4-HO-C_6H_4	C_6H_5	oil	$C_{28}H_{25}NO_2 \cdot {}^1/_3H_2O$	*b*
37	C_6H_5	4-HO-C_6H_4	67–69	$C_{28}H_{25}NO_2$	*b*
38	C_6H_5	3-HO-C_6H_4	140–141	$C_{28}H_{25}NO_2$	*b*
39	4-HO-C_6H_4	4-HO-C_6H_4	199–200	$C_{28}H_{25}NO_3$	*b*
40	4-CO_2H-C_6H_4	C_6H_5	245–248	$C_{29}H_{25}NO_3$	*b*
41	C_6H_5	4-CO_2H-C_6H_4	226–228	$C_{29}H_{25}NO_3$	H
42	4-CO_2CH_3-C_6H_4	C_6H_5	181–183	$C_{30}H_{27}NO_3$	I
43	4-pyridinyl	C_6H_5	164–165	$C_{27}H_{24}N_2O$	I
44	C_6H_5	4-pyridinyl	145–148	$C_{27}H_{24}N_2O$	I
45	C_6H_5	3-pyridinyl	152–153	$C_{27}H_{24}N_2O$	I
46	C_6H_5	4-pyridinyl *N*-oxide	83–85	$C_{27}H_{24}N_2O_2$	*b*
47	1-SEM-2-imidazolyl	C_6H_5	123.123.5	$C_{31}H_{37}N_3O_2Si$	I
48	2-imidazolyl	C_6H_5	246.5–247	$C_{25}H_{23}N_3O$[c]	*b*
49	1-*n*-heptyl-2-imidazolyl	C_6H_5	116–117	$C_{32}H_{37}N_3O$	I
50	1-iomidazolyl	C_6H_5	156–158	$C_{25}H_{23}N_3O$[d]	I
51	C_6H_5	1-SEM-2-imidazolyl	147–147.5	$C_{31}H_{37}N_3O_2Si$	H
52	C_6H_5	2-imidazolyl	oil	$C_{25}H_{23}N_3O$	*b*

[a] Analyses for C, H, and N are within ±0.4% of theoretical values. [b] Made by functional group transformations on other compounds. See the Experimental Section for details. [c] N: calcd, 11.01; found, 10.36. HRMS: calcd, 382.1919; found, 382.1910. [d] C: calcd, 78.71; found, 79.43. HRMS: calcd, 382.1919; found, 382.1906.

group (cf. compounds **29**, **31**–**33**), suggesting that this is probably due to an overall decrease in the lipophilicity of the compound rather than specific unfavorable interactions in the enzyme active site.

Unlike *in vitro* activity, the *in vivo* activity is extremely sensitive to the position of polar substitution. This effect is shown most dramatically in the series of 4-, 3-, and 2-methoxyphenyl derivatives **31**–**33**. While all three compounds are roughly equipotent *in vitro*, only the 2- and 4-methoxy compounds are active *in vivo*. Polar moieties at the 3-position of R^2 appear to be incompatible with *in vivo* activity (cf. **35** and **45**). The optimal position for a polar group is dependent upon the choice of substituent. Thus, while R^1-substituted 4-amino- (**5**), 4-methoxy- (**29**), and 4-hydroxyphenyl (**36**) derivatives are roughly equipotent *in vitro*, only **5** and **29** show significant *in vivo* activity. By contrast, the R^2-substituted 4-amino (**26**), 4-methoxy (**31**), and 4-hydroxyphenyl (**37**) derivatives have comparable *in vitro* activity, but **31** and **37** are considerably more potent *in vivo* than **26**. Another example of the divergence of *in vitro* and *in vivo* activity comes from an examination of enantiomeric compounds, (+)- and (−)-**5**. While both compounds are potent ACAT inhibitors *in vitro*, only (−)-**5** displays significant activity *in vivo*.

While it is impossible at this time to say exactly what factors are influencing the *in vivo* activity of these compounds, clearly the polarity of substituent groups is influencing *in vitro* and *in vivo* activity in opposing ways which need to be balanced for optimal activity. The fact that in *vivo* activity is so highly dependent upon the site of substitution makes it unlikely that the effect of polar groups on *in vivo* activity is due entirely to physicochemical effects such as solubility or lipophilicity, and no correlation with any physicochemical parameter such as log *P* could be demonstrated. While differences in metabolism cannot be ruled out, differences in drug delivery are likely to be an important factor. Both cholesterol and, presumably, inhibitors must be effectively delivered to the site of ACAT activity on the endoplasmic reticulum of cells. The mechanisms by which cholesterol is delivered to this site are poorly understood at this time.[8] Differences in the ability of various inhibitors to be delivered *via* these or alternate mechanisms may be an important determinant of *in vivo* activity. Whatever the cause, the structure-sensitive nature of both *in vitro* and *in vivo* activity produces two distinct structure–activity relationships which must be optimized. Further insight into the nature of these relationships and definition of both the *in vitro* and *in vivo* pharmacophores will be the subject of future reports.

Experimental Section

All melting points were taken on a Thomas-Hoover melting point apparatus and are reported uncorrected. Chromatography was performed over Universal Scientific or Selecto Scientific flash silica gel, 32–63 mesh. ^{1}H NMR spectra were determined with a Varian VXR 200 MHz or Gemini 300 MHz instrument using tetramethylsilane as an internal standard. High-resolution mass spectra were determined on a JEOL HX110A mass spectrometer in fast atom bombardment mode. Elemental analyses are within 0.4% of the theoretical values unless noted.

2-(4-Aminophenyl)-1-phenylethylamine (6). General Method A. To a solution of 4-nitrophenylacetic acid (200 g, 1.1 mol) in benzene (1.5 L) was added oxalyl chloride (200 mL, 2.2 mol). The mixture was warmed to 50–60 °C for 2 h after which time benzene and excess oxalyl chloride were distilled off under vacuum at 50 °C until a final volume of 500 mL was achieved. The residue was diluted with benzene (1 L) and cooled to 0 °C. To this was added anhydrous aluminum chloride (160 g) portionwise over 15 min. Thereafter, the mixture was stirred overnight at room temperature. The reaction mixture was poured over a mixture of ice (3 L) and concentrated HCl (1 L). The resulting slurry was filtered through Celite and the precipitate washed with ethyl acetate. The combined filtrates were washed with water, saturated sodium bicarbonate, and brine, dried over sodium sulfate, and evaporated to give 2-(4-nitrophenyl)-1-phenylethanone (227 g).

To a solution of 220 g of the above product in pyridine (2.5 L) at 0 °C was added hydroxylamine hydrochloride (70 g, 1 mol). The reaction mixture was stirred for 3.5 h while coming slowly to room temperature. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with water, dried over sodium sulfate, and evaporated. The crude product was filtered through a bed of silica gel eluting with dichloromethane:hexane (2:1). The solvent was evaporated, and the residue was crystallized from ether/hexane to give the oxime (160 g). This was hydrogenated over 10% Pd/C at 50 psi in ethanol to give, after filtration and evaporation, 128 g of **6** (60%): ^{1}H NMR ($CDCl_3$) δ 1.59 (bs, 2H), 2.7 (dd, 1H), 2.9 (dd, 1H), 3.5 (s, 2H), 4.11 (dd, 1H), 6.62 (d, 2H), 6.95 (d, 2H), 7.18–7.4 (m, 5H). Compounds **7**, **9**, and **10** were prepared by an analogous procedure.

2-(3-Aminophenyl)-1-phenylethylamine (7): ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 2H), 2.7 (dd, 1H), 2.95 (dd, 1H), 3.5 (s, 2H), 4.19 (dd, 1H), 6.5–6.68 (m, 3H), 7.04–7.46 (m, 6H).

2-(3,4-Dimethoxyphenyl)-1-phenylethylamine (9): ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 2H), 2.78 (dd, 1H), 2.98 (dd, 1H), 3.79 (s, 3H), 3.87 (s, 3H), 4.18 (dd, 1H), 6.55–6.61 (m, 1H), 6.69–6.84 (m, 2H), 7.72–7.42 (m, 5H).

2-(4-Methoxyphenyl)-1-(4-methoxyphenyl)ethylamine (10): ^{1}H NMR ($CDCl_3$) δ 3.03 (m, 1H), 3.28 (dd, 1H), 4.38 (s, 1H), 3.68 (s, 3H), 3.68 (s, 3H), 3.73 (s, 3H), 4.38 (s, 1H), 6.90 (m, 6H), 7.34 (d, 2H), 8.55 (s, 2H).

(+)- and (−)-2-(4-Aminophenyl)-1-phenylethylamine [(+)-6 and (−)-6]. A solution of 10 g (21.1 mmol) of racemic **6** in 300 mL of hot ethanol was treated with a solution of 18.2 g (47.1 mmol) of di-*p*-toluoyl-L-tartaric acid in ethanol. The resulting suspension was heated to reflux and an additional 1000 mL of ethanol added until the suspension dissolved. The solution was allowed to cool slowly to ambient temperature and then was refrigerated for 2 days. The resulting crystals of tartrate salt were filtered, washed with cold ethanol followed by ethyl acetate, and dried. The salt was recrystallized once from 725 mL of hot ethanol and then treated with 1 N aqueous NaOH. The oily suspension was extracted with ethyl acetate, washed with water and brine, dried over magnesium sulfate, and evaporated to give (−)-2-(4-aminophenyl)-1-phenylethylamine, $[\alpha]^{26}_D = -56.01°$ (c = 1, methanol). The (+)-isomer, $[\alpha]^{26}_D = +55.80°$ (c = 1, methanol), was similarly prepared from di-*p*-toluoyl-D-tartaric acid. Enantiomeric excess of each amine was determined to be greater than 95% based on the NMR of the corresponding (*R*)-α-methoxyphenylacetamide.

1-(4-Methoxyphenyl)-2-phenylethylamine (11). General Method B. A mixture of methanesulfonic acid (100 g) and P_2O_5 (10 g) was stirred at 50–60 °C until solution was complete and then cooled to room temperature. To this were added phenylacetic acid (2.0 g, 14.7 mmol) and anisole (4.00 g, 37.0 mmol). The mixture was stirred at 50–60 °C for 90 min, cooled to room temperature, and poured into ice water (1.2 L). The solution was made basic by gradual addition of solid sodium bicarbonate and then extracted into ethyl acetate (800 mL). The ethyl acetate was dried over magnesium sulfate and concentrated, and the crude product was chromatographed on silica gel eluting with 2% ethyl acetate in hexane to give 1-(4-methoxyphenyl)-2-phenylethanone (2.92 g, 76%). This was converted to the oxime and reduced as described in method A to give 2.46 g (84%) of 11: ^{1}H NMR ($CDCl_3$) δ 3.09 (m, 1H), 3.38 (m, 1H), 3.72 (s, 3H), 4.44 (s, 1H), 7.13 (m, 9H), 8.62 (s, 2H). Compound **12** was prepared by an analogous procedure.

2-(4-Pyridinyl)-1-phenylethylamine (12): ^{1}H NMR ($CDCl_3$) δ 3.18 (s, 1H), 3.45 (q, 1H), 3.72 (q, 1H), 7.34 (d, 3H), 7.57 (d, 2H), 7.93 (d, 2H), 8.82 (d, 2H), 9.02 (s, 2H).

1-(4-Pyridinyl)-2-phenylethylamine (13). General Method C. To a solution of 0.11 mol of sodium ethoxide (prepared from 2.56 g of sodium metal) in ethanol (50 mL) were added ethyl isonicotinate (10.0 g, 0.066 mol) and phenylacetonitrile (8.54 g, 0.073 mol), and the mixture was heated at reflux for 2.5 h. After cooling to room temperature, the mixture was poured into ice water and brough to pH 3 by addition of concentrated HCl. The resulting precipitate was collected, washed with water, and dried under vacuum to give the crude cyano ketone (13.6 g, 92%).

A solution of 5.0 g of the above product was suspended in 48% HBr (30 mL) and the mixture heated at reflux for 5 h. After cooling in an ice bath, the mixture was made basic by addition of concentrated ammonia and the mixture was extracted with ethyl acetate (200 mL). The combined organic layers were washed with water and brine, dried over magnesium sulfate, and evaporated to give 1-(4-pyridinyl)-2-phenylethanone (2.71 g, 61%). This was converted to its oxime and reduced as described in method A to give **13** (2.01 g, 74%): ^{1}H NMR ($CDCl_3$) δ 2.82 (m, 2H), 3.33 (s, 2H), 4.03 (t, 1H), 7.20 (m, 7H), 8.43 (d, 2H). Compounds 14 and **15** were prepared by an analogous procedure.

1-(4-Carboxyphenyl)-2-phenylethylamine (14): ^{1}H NMR ($CDCl_3$) δ 3.12 (m, 1H), 3.42 (dd, 2H), 7.13 (m, 5H), 7.55 (m, 2H), 7.88 (m, 2H), 8.89 (s, 2H).

1-(3-Pyridinyl)-2-phenylethylamine (15): ^{1}H NMR ($CDCl_3$) δ 2.87 (d, 2H), 4.10 (t, 1H), 7.20 (m, 6H), 7.72 (d, 1H), 8.39 (m, 2H).

Synthesis of 2-(1*H*-Imidazol-1-yl)-1-phenylethylamine (16). General Method D. To a solution of imidazole (5.88 g, 0.086 mol) in THF (100 mL) was added 2-bromoacetophenone (6.84 g, 0.034 mol). After 1.5 h the mixture was transferred to a separatory funnel, washed with saturated sodium bicarbonate, water, and brine, dried over sodium sulfate, and evaporated. The residue was passed through a short silica gel column, eluting with 10% methanol in dichloromethane to give a yellow solid (4.51 g). This was converted to the oxime and reduced as described in Method A to give **16** (2.1 g, 33%). This amine was converted to amide **50** without purification according to procedure I.

1-(4-Aminophenyl)-2-phenylethylamine (17). General Method E. A mixture of 4-nitrobenzaldehyde (5.0 g, 0.033 mol), triphenyl phosphite (8.53 g, 0.027 mol), and benzylcarbamate (4.16 g, 0.027 mol) in glacial acetic acid (5 mL) was stirred at 75–80 °C for 2 h. The resulting thick solid was dissolved in chloroform (80 mL), and methanol (320 mL) was added. The resulting cloudy solution was refrigerated overnight. The precipitate was collected, washed with cold methanol, and vacuum-dried to give the crude product (9.45 g). This was crystallized from methanol:chloroform (4:1) to give diphenyl [[[[(4-nitrophenyl)-2-benzyl]oxy]carbonyl]amino]methylphosphonate (8.28 g, 56%).

A solution of the above phosphonate (4.0 g) in THF (50 mL) was cooled to −40 °C, and 4.3 g of 10% KOH in methanol was added dropwise over 0.5 h. The deep-purple solution was stirred for 1.5 h, after which a solution of benzaldehyde (10.89 g, 0.103 mol) in THF (10 mL) was added in portions while maintaining the reaction temperature at −30 to −40 °C. After

the addition was complete, the mixture was maintained at −40 °C for 20 min and then allowed to warm to ambient temperature. The solvent was removed under vacuum, and the residue was extracted into ethyl acetate. The ethyl acetate was washed with water, aqueous sodium bicarbonate, and brine, dried over magnesium sulfate, and concentrated. The residue was chromatographed over silica gel eluting with ethyl acetate:hexane (2:8) to give 1-(4-nitrophenyl)-1-[[(benzyloxy)carbonyl]amino]-2-phenylethylene (1.8 g, 64%).

A solution of the above product (0.50 g) in ethanol (70 mL) and methanol (40 mL) was hydrogenated at 50 psi over 10% palladium on carbon (0.1 g) for 2 h at room temperature. After filtering through Celite, the solvent was removed to give **17** (0.28 g, 98%): ^{1}H NMR (DMSO-d_6) δ 2.88 (m, 2H), 3.62 (s, 2H), 4.10 (q, 1H), 6.66 (d, 2H), 7.21 (m, 7H). Compound **18** was prepared by an analogous procedure.

2-(4-Carbomethoxyphenyl)-1-phenylethylamine (18): ^{1}H NMR ($CDCl_3$) δ 2.98 (m, 2H), 3.89 (s, 3H), 4.22 (t, 1H), 7.26 (m, 7H), 7.90 (m, 2H).

1-Phenyl-2-[1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-imidazol-2-yl]ethylamine (19). General Method F. 2-Methylimidazole (5.02 g, 0.06 mol) in THF (100 mL) was added to a 0 °C suspension of sodium hydride (1.88 g, 0.078 mol) in THF (100 mL). After gas evolution ceased, the mixture was warmed to room temperature for 1 h and then recooled to 0 °C. [2-(Trimethylsilyl)ethoxy]methyl chloride (11.0 mL, 0.062 mol) was added, and the mixture was allowed to warm to room temperature overnight. The reaction was quenched with saturated sodium bicarbonate and the mixture extracted with ethyl acetate. The extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was chromatographed on silica gel (5% MeOH/CH_2Cl_2) to provide 2-methyl-1-[[(trimethylsilyl)ethoxy]methyl]-imidazole (10.9 g, 84%) as a clear slighty yellow liquid: ^{1}H NMR ($CDCl_3$) δ 6.90 (1H, s), 5.19 (s, 2H), 3.48 (2H, t), 2.43 (s, 3H), 0.89 (2H, t), 0.02 (s, 9H).

A solution of 2-methyl-1-[[(trimethylsilyl)ethoxy]methyl]-imidazole (2.04 g) in dry THF (25 mL) was cooled to −78 °C and treated with *t*-BuLi (5.14 mL, 1.7 M in pentane). The cooling bath was removed for 10 min; the mixture was recooled to −78 °C and transferred *via* cannula to a −78 °C solution of *N*-(trimethylsilyl)benzaldimine[7b] (1.31 mL) in THF (25 mL). The reaction mixture was allowed to warm slowly to ambient temperature overnight (~18 h). The reaction was quenched with saturated ammonium chloride solution and the mixture extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was chromatographed on silica gel, eluting with MeOH/CH_2Cl_2 (5/95) followed by concentrated NH_4OH/MeOH/CH_2Cl_2 (5/5/90) to provide **19** (1.02 g, 33%) as a deep-red oil: ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 1H), 7.02 (s, 1H), 6.92 (s, 1H), 5.02 (q, 2H), 4.62 (t, 1H), 3.45 (t, 2H), 2.64 (bs, 2H), 0.89 (t, 2H), 0.02 (s, 9H).

1-Phenyl-2-(1-heptyl-1*H*-imidazol-2-yl)ethylamine (20). To a solution of 2-methylimidazole (4.52 g, 0.055 mol) and heptyl bromide (8.65 mL, 0.055 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added 1.52 g (0.063 mmol) of sodium hydride, and the mixture was allowed to warm to room temperature overnight. The reaction was quenched with saturated sodium bicarbonate and the mixture transferred to a separatory funnel, diluted with methylene chloride, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was chromatographed on silica gel (5% MeOH/CH_2Cl_2) to provide 1-heptyl-2-methylimidazole (3.34 g, 34%) as clear golden liquid: ^{1}H NMR ($CDCl_3$) δ 6.89 (1H, s), 6.80 (s, 1H), 3.80 (2H, t), 2.36 (s, 3H), 1.71 (2H, m), 1.29 (8H, m), 0.88 (3H, m).

Benzoyl chloride (0.67 mL) was dropwise added to a 0 °C solution of 1-heptyl-2-methylimidazole (0.47 g, 2.6 mmol) and triethylamine (1.1 mL) in acetonitrile (5 mL).[9] The cooling bath was removed, and the mixture was stirred overnight. The solvent was removed in vacuo; the residue was taken up in methylene chloride, transferred to a separatory funnel, washed with water, dried over anhydrous sodium sulfate, and concentrated to give 1.1 g of an amber oil. Chromatography on silica gel (50% EtOAc/hexane) provided 2-(1-heptylimidazol-2-yl)-acetophenone (0.72 g, 96%) as an amber oil: ^{1}H NMR ($CDCl_3$) δ 9.94 (~1H, bs, enol form), 8.08 (2H, d), 7.45 (3H, m), 7.08 (1H, bs), 6.84 (1h, bs), 4.67 (~1.5H, bs, keto form), 3.85 (2H, t), 1.72 (2H, m), 1.23 (8H, m), 0.88 (3H, m).

Conversion to the corresponding oxime [^{1}H NMR ($CDCl_3$) δ 8.45 (1H, bs), 8.25 (1H, d), 7.70 (1H, m), 7.50 (1H, m), 7.28 (2H, m), 6.98 (1H, s), 6.75 (1H, s), 4.48 (2H, s), 3.84 (2H, t), 1.63 (2H, m), 1.24 (8H, m), 0.86 (3H, m)] and reduction as described in method A gave **20**: ^{1}H NMR ($CDCl_3$) δ 8.06 (1H, d), 7.50 (1H, m), 7.40 (1H, m), 7.28 (2H), 7.01 (1H, s), 6.79 (1H, s), 5.65 (2H, bs), 4.69 (1H, dd), 3.61 (2H, dt), 3.23 (1H, dd), 3.06 (1H, dd), 1.54 (2H, m), 1.22 (8H, m), 0.86 (3H, t).

2-Phenyl-1-[1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-imidazol-2-yl]ethylamine (21). *n*-BuLi (1.66 mL, 1.6 M in hexanes) was dropwise added to a −78 °C solution of hexamethyldisilazine (0.59 mL, 2.8 mmol) in THF (5 mL). The cooling bath was removed, and the mixture was warmed to room temperature for 10 min. The clear solution was recooled to −78 °C and transferred *via* cannula to a −78 °C solution of 1-[[2-(trimethylsilyl)ethoxy]methyl]-2-formyl-1*H*-imidazole[10] (0.54 g, 2.7 mmol) in THF (5 mL). The light pink solution was warmed to −20 °C for 1 h; the resulting yelow solution was recooled to −78 °C. Benzylmagnesium chloride (3.61 mL, 1 M in diethyl ether) was dropwise added. The reaction mixture was allowed to warm to room temperature overnight. Quenching with 1 N NaOH, transferring to a separatory funnel, extracting with ether, washing with brine, drying over anhydrous sodium sulfate, and concentrating gave 1.14 g of a clear orange liquid. Chromatography on silica gel, eluting with 5% MeOH/CH_2Cl_2 followed by 1% NH_4OH/5% MeOH/CH_2Cl_2, gave **21** (0.46 g, 54%) as an orange oil: ^{1}H NMR ($CDCl_3$) δ 7.23 (5H, m), 7.04 (1H, s), 6.90 (1H, s), 5.14 (1H, d), 4.99 (1H, d), 4.31 (1H, t), 3.42 (2H, t), 3.28 (1H, dd), 3.13 (1H, dd), 2.62 (2H, bs), 0.87 (2H, dd), 0.01 (9H, s).

Synthesis of 1-(3-Methoxyphenyl)-2-phenylethylamine (22). General Method G. To a solution of 3-methoxybenzonitrile (5.01 g, 0.038 mol) in dry THF (150 mL) at 0 °C was added benzylmagnesium chloride (47 mL of a 2 M solution in THF). The mixture was stirred overnight while coming to room temperature. The resulting mixture was again cooled to 0 °C and treated with methanol (100 mL) followed by sodium borohydride (3.56 g) added slowly in portions. After stirring for another 1 h, the mixture was diluted with water and exhaustively extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over sodium sulfate, and concentrated. The crude was dissolved in ether and extracted with 3 N HCl. The acidic extracts were washed with ether, made basic with NaOH, and exhaustively extracted with ether. The combined ether layers were washed with water, dried over sodium sulfate, and evaporated to give **22** (5.95 g, 69%): ^{1}H NMR ($CDCl_3$) δ 7.28 (6H, m), 6.96 (2H, m), 6.82 (1H, m), 4.20 (1H, dd), 3.82 (3H, s), 3.04 (1H, dd), 2.86 (1H, dd), 1.93 (2H, s). Compounds **23** and **24** were prepared by an analogous procedure.

1-(2-Methoxyphenyl)-2-phenylethylamine (23): ^{1}H NMR ($CDCl_3$) δ 7.27 (6H, m), 6.92 (3H, m), 4.52 (1H, dd), 3.86 (3H, s), 3.17 (1H, dd), 2.89 (1H, dd), 2.71 (2H, bs).

1-(3-Methoxyphenyl)-2-(4-methoxyphenyl)ethylamine (24): ^{1}H NMR ($CDCl_3$) δ 7.25 (1H, m), 7.09 (2H, d), 6.93 (2H, m), 6.82 (3H, m), 4.13 (1H, dd), 3.81 (3H, s), 3.79 (3H, s), 2.96 (1H), 2.76 (1H, dd), 1.74 (2H, bs).

Synthesis of *N*-[2-(4-Aminophenyl)-1-phenylethyl]-2,2-dimethyl-9-(*Z*)-octadecenamide (4). General Method H. To a solution of 2-(4-aminophenyl)-1-phenylethylamine (0.155 g) in THF at 0 °C was added 2,2-dimethyl-9-(*Z*)-octadecanoyl chloride (0.2 g), and the reaction mixture was stirred overnight while warming to ambient temperature. The reaction was quenched by pouring the mixture into water:saturated aqueous sodium bicarbonate (1:1). The resultant solution was extracted into ethyl acetate; the organic layer was dried over magnesium sulfate and concentrated. The residue was purified by chromatography on silica gel, eluting with hexane:ethyl acetate (1:1) to obtain 4 (0.24 g, 65%).

***N*-[1-Phenyl-2-(4-aminophenyl)ethyl]-α-phenylbenzeneacetamide (5). General Method I.** 2-(4-Aminophenyl)-1-phenylethylamine (**6**) (0.40 g, 1.88 mmol) and diphenylacetic

acid (0.40 g, 1.88 mmol) were dissolved in DMF (4 mL) at room temperature. To this were added HOBT (0.26 g, 1.92 mmol), NMM (0.19 g, 1.88 mmol), and EDCI (0.36 g, 2.28 mmol), and the mixture was stirred at room temperature for 18 h. DMF was removed under vacuum, and the oily residue was taken up in ethyl acetate (100 mL). The ethyl acetate was washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated. The crude product was purified on a silica gel column eluting with dichloromethane to give **5** (0.512 g, 67%): mp = 161–163 °C; ^{1}H NMR ($CDCl_3$) δ 2.72 (dd, 1H, J = 7, 13 Hz), 2.98 (dd, 1H, J = **4**, 13 Hz), 3.60 (bs, 2H), 4.89 (s, 1H), 5.20–5.35 (m, 1H), 5.85 (bd, 1H), 6.55 (m, 2H), 6.68 (m, 2H), 7.0–7.15 (m, 6H), 7.20–7.40 (m, 9H).

Starting with (−)-**6** yields (−)-**5**, $[\alpha]^{26}_D$ = −1.9° (c = 1, methanol), while (+)-**6** yields (+)-**5**, $[\alpha]^{26}_D$ = +2.1° (c = 1, methanol). The oily pure enantiomers were otherwise spectroscopically identical to the racemate.

***N*-[1-Phenyl-2-[4-[(methylsulfonyl)amino]phenyl]ethyl]-α-phenylbenzeneacetamide (27).** Compound **5** (0.5 g, 1.23 mmol) was treated with methanesulfonyl chloride (0.11 mL, 0.16 g, 1.39 mmol) in dichloromethane (3 mL) containing triethylamine (0.14 g, 1.38 mmol) to obtain **27** (0.43 g, 72%).

***N*-[1-Phenyl-2-(4-acetamidophenyl)ethyl]-α-phenylbenzeneacetamide (28).** Compound **5** (0.2 g, 0.49 mmol) was acylated with acetyl chloride (0.04 mL, 0.56 mmol) in pyridine (4 mL) to obtain **28** (0.22 g, 100%).

α-Phenyl-*N*-[1-phenyl-2-(4-hydroxyphenyl)ethyl]benzeneacetamide (36). Compound **29** (66.1 mg, 0.157 mmol) was treated with boron tribromide (0.32 mL of a 1 M solution) in dichloromethane (1 mL) at 0 °C for 1.5 h. The reaction was quenched with saturated sodium bicarbonate and the reaction mixture extracted with dichloromethane. The dichloromethane was washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was purified by silica gel chromatography, eluting with hexane:ethyl acetate (1:1) to give **36** (53 mg, 83%). Compounds **37–39** were prepared by an analogous procedure from compounds **31**, **32**, and **34**, respectively.

***N*-[1-Phenyl-2-(4-carboxyphenyl)ethyl]-α-phenylbenzeneacetamide (40).** Compound **42** (0.3 g, 0.67 mmol) was dissolved in ethanol (15 mL), treated with 1 N sodium hydroxide solution (1.35 mL), and heated at reflux to give **40** (0.27 g, 93%).

***N*-[1-(4-Pyridyl 1-oxide)-2-phenylethyl]-α-phenylbenzeneacetamide (46).** A solution of **44** (0.53 g, 1.35 mmol) in dichloromethane (10 mL) was treated with 0.46 g of 50–60% 3-chloroperbenzoic acid in 4.5 mL of dichloromethane. After 3.5 h the reaction mixture was washed with 10% sodium sulfite solution and dried over magnesium sulfate. The solvent was removed, and the crude was purified on a silica gel column eluting first with ethyl acetate/dichloromethane (1/1–4/1) followed by dichloromethane/methanol (98/2–96/4) to give **46** (0.38 g, 69%).

***N*-[1-Phenyl-2-(1*H*-imidazol-2-yl)ethyl]-α-phenylbenzeneacetamide (48).** A solution of tetrabutylammonium fluoride (5 mL, 1 M in THF) was added to compound **47** (0.31 g, 0.61 mmol) and the reaction mixture heated at reflux overnight.[10] At the end of this time the reaction mixture was cooled to ambient temperature and concentrated and the residue chromatographed on a silica gel column eluting with methanol/dichloromethane (5/95) to give **48** (0.24 g, 96%). Compound **52** was prepared in a analogous procedure from compound **51**.

Microsomal ACAT Assay. Assays for acyl CoA:cholesterol acyltransferase (ACAT; EC 2.3.1.26) activity were performed by measuring the formation of cholesteryl [^{3}H]oleate from cholesterol and [^{3}H]oleoyl CoA in rat liver microsomes using the incubation conditions described previously.[11] The incubation mixtures contained 90 μM bovine serum albumin (essentially fatty acid free) and 12.5 μg of rat hepatic microsomal protein in a buffer containing 0.1 M potassium phosphate and 2 mM dithiothreitol (pH 7.4) in a total volume of 50 μL. Exogenous compound was introduced into the incubations using small volumes (1 μL) of concentrated stock solutions in dimethyl sulfoxide (DMSO). After a preincubation at 37 °C for 15 min, [^{3}H]oleoyl-CoA (10 μM final concentration, 1 μCi/ incubation mixture) was added, and incubations were continued at 37 °C for 15 min. Assays were terminated by the addition of a 15 μL aliquot of each incubation to a silica gel G thin layer chromatographic (TLC) plate. The plates were allowed to dry for several minutes and then developed using a solvent containing petroleum ether:diethyl ether:acetic acid (90:10:1, v/v/v). Regions corresponding to the migration position of authentic cholesteryl oleate were scraped, and the radioactivity was quantified by liquid scintillation spectrometry. Data are reported either as the micromolar concentration required to produce 50% inhibition (IC_{50}) or alternatively as the percent inhibition at 10 μM. Percent inhibitions are the average of three determinations.

Cholesterol-Fed Hamsters. Unless indicated, all animals used in these studies were allowed access to food (chow pellets) and water *ad libitum*. All animals were housed, treated, and cared for according to NIH guidelines for humane treatment of laboratory animals and the Animal Welfare Act in a program accredited by the American Association for Accreditation of Laboratory Animal Care. Male golden Syrian hamsters (Charles Riber Labs, Wilmington, MA), weighing between 100 and 125 g, were fed rodent chow and provided water *ad libitum*. Treatment protocols consisted of feeding chow which had been supplemented with 0.5% cholesterol for 7 days. During this period the animals were gavaged once daily with test compounds (at 50 mpk) dissolved in 0.2 mL of corn oil. On the last day the animals were sacrificed and liver samples taken for lipid analyses. Samples of liver were extracted for neutral lipid analysis by the method of Folch *et al.*[12] Hepatic neutral lipid composition was determined subsequently using a HPLC method which has been described previously.[13] Data are reported as percent change in hepatic cholesterol ester content versus control animals receiving the high-cholesterol diet (oral gavaged in 0.2 mL of corn oil/day) without drug.

Acknowledgment. We would like to thank Drs. D. Burnett, T. Fevig, and B. Tait for their helpful discussions and assistance during this study. We also thank Dr. P. Das for the high-resolution mass spectral data.

References

(1) (a) The Nutrition Committee of the American Heart Association. Dietary guidelines for healthy American adults: a statement for physicians and health professionals. *Circulation* **1988**, *77*, 721A–724A. (b) Denke, M. A.; Grundy, S. M. Individual Responses to a Cholesterol-Lowering Diet in 50 Men with Moderate Hypercholesterolemia. *Arch. Intern. Med.* **1994**, *154*, 317–325. (c) The Expert Panel. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* **1993**, *269*, 3015–3023.

(2) Grundy, S. M. Bile Acid Sequestrants: Do they have a future? In *Drugs Affecting Lipid Metabolism*; Paoletti, R., Kritchevsky, D., Holmes, M. L., Eds.; Springer-Verlag: Berlin, 1987; pp 34–41.

(3) Suckling, K. E.; Strange, E. F. Role of Acyl-CoA Cholesterol Acyltransferase in Cellular Cholesterol Metabolism. *J. Lipid Res.* **1985**, *26*, 647–671.

(4) (a) Sliskovic, D. R.; White, A. D. Therapeutic Potential of ACAT Inhibitors as Lipid Lowering and Antiatherosclerotic Agents. *Trends Pharmacol. Sci.* **1991**, 194–199. (b) Larsen, S. D.; Spilman, C. H. New Potential Theraples for Treatment of Atherosclerosis. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1993; Vol. 28, pp 217–226. (c) Roth, B. D.; Blankley, C. J.; Hoefle, M. L.; Holmes, A.; Roark, W. H.; Trivedi, B. K.; Essenburg, A. D.; Kieft, K. A.; Krause, B. R.; Stanfield, R. L. Inhibitors of Acyl-CoA: Cholesterol Acyltransferase. 1. Identification and Structure-Activity Relationships of a Novel Series of Fatty Acid Anilide Hypocholesterolemic Agents. *J. Med. Chem.* **1992**, *35*, 1609–1617. (d) Largis, E. E.; Wang, C. H.; DeVries, V. G.; Schaffer, S. A. CL 277,082: A novel inhibitor of ACAT-catalyzed cholesterol esterification and cholesterol absorption. *J. Lipid Res.* **1989**, *30*, 681–690. (e) Ross, A. C.; Go, K. J.; Helder, J. G.; Rothblatt, G. H. Selective Inhibition of Acyl Coenzyme A:Cholesterol Acyltransferase by Compounds 58-035. *J. Biol. Chem.* **1984**, *259*, 815–819. (f) Fukumaru, T.; Hamma, N.; Nakatani, H.; Fukushima, H.; Toki, K. Fatty acid amide derivatives. U.S. Patent 3784577, 1974. (g) Tawada, H.; Harcourt, M.; Kawamura, N.; Kajino, M.; Ishikawa, E.; Sugiyama, Y.; Ikeda, H.;

Meguro, K. Novel Acyl-CoA:Cholesterol Acyltransferase Inhibitors. Synthesis and Biological Activity of 3-Quinolylurea Derivatives. *J. Med. Chem.* **1994**, *37*, 2079–2084. (h) Kumzawa, T.; Yanase, M.; Harakawa, H.; Obase, H.; Shirakura, S.; Ohishi, E.; Oda, S.; Kubo, K.; Yamda, K. Inhibitors of Acyl-CoA: Cholesterol Acyltransferase. 1. Synthesis and Hypocholesterolemic Activity of Dibenz[*b*,*e*]oxepin-11-carboxanilides. *J. Med. Chem.* **1994**, *37*, 804–810.

(5) Lantos, I.; Gombatz, K.; McGuire, M.; Pridgen, L.; Remich, J.; Shilcrat, S. Synthetic and Mechanistic Studies on the Preparation of Pyridyl-substituted Imidazolthiazoles. *J. Org. Chem.* **1988**, *53*, 4223–4227.

(6) (a) Redmore, D. Chemistry of Phosphorus Acid: New Routes to Phosphonic Acids and Phosphate Esters. *J. Org. Chem.* **1978**, *43*, 992–996. (b) Zimmer, H.; Bercz, J. P. Synthesis with α-Aminoalkylphophonic Esters. *Liebigs Ann. Chem.* **1965**, *686*, 107–114.

(7) (a) Hirao, A.; Hattori, I.; Yamaguchi, K.; Nakahama, S. Synthesis of Secondary and Tertiary Carbinamines from N-(Trimethylsilyl)-imines and Organolithium Reagents. *Synthesis* **1982**, 461. (b) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. Preparation of Primary Amines and 2-Azetidinones *via* N-Trimethylsilyl Imines. *J. Org. Chem.* **1983**, *48*, 289.

(8) Lange, Y.; Strebel, F.; Steck, T. L. Role of the Plasma Membrane in Cholesterol Esterification in Rat Hepatoma Cells. *J. Biol. Chem.* **1993**, *268*, 13838–13843 and references contained therein.

(9) Knoler, H.-J.; Boese, R.; Hitzemann, R. Imidazole Derivatives. Part II. *Heterocycles* **1989**, *29* (8), 1551–1558.

(10) Vaccaro, W. Heterocycles in Synthesis. Part I: α,α-Dialkylated Amino Acid Derivitives via Imidazoles. Part II: Approaches to the Cyclopeptide Alkaloids. Ph.D. Dissertation, University of California, Santa Barbara, 1987.

(11) Burrier, R. E.; Deren, S.; McGregor, D. G.; Hoos, L. M.; Smith, A. A.; Davis, H. R., Jr. Demonstration of a Direct Effect on Hepatic Acyl CoA:Cholesterol Acyl Transferase (ACAT) Activity by an Orally Administered Enzyme Inhibitor in the Hamster. *Biochem. Pharmacol.* **1994**, *47*, 1545–1551.

(12) Folch, J.; Lees, M.; Sloan-Stanley, G. H. A Simple Method for Isolation and Purification of Total Lipids from Animal Tissue. *J. Biol. Chem.* **1956**, *266*, 497–509.

(13) Schnitzer-Polokoff, R.; Compton, D.; Boykow, G.; Davis, H.; Burrier, R. Effects of Acyl-CoA: cholesterol O-Acyltransferase Inhibition on Cholesterol Absorption and Plasma Lipoprotein Composition in Hamsters. *Comp. Biochem. Physiol.* **1991**, *99A*, 665–670.

JM940564B