Structure–Activity Relationship of a Series of Phenylureas Linked to 4-Phenylimidazole. Novel Potent Inhibitors of Acyl-CoA:Cholesterol *O*-Acyltransferase with Antiatherosclerotic Activity. 2

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In our continuing search to find systemically bioavailable ACAT (acyl-CoA:cholesterol *O*-acyltransferase) inhibitors with more potent antiatherosclerotic effect than *N*-[2-(dimethylamino)-6-[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]phenyl]-*N'*-pentylurea (**3**), a series of phenylureas linked to 4-phenylimidazole were synthesized and evaluated for in vitro inhibitory activity toward both aortic and intestinal ACATs, and for in vivo hypocholesterolemic activity. The structure–activity relationships (SARs) were studied by strategic modification of five regions in the molecule of **3**, i.e., by introducing functional groups or exchanging carbon atoms for heteroatoms. The SAR studies allowed us to select optimum substituents in the five regions, as follows. (1) Dimethylamino was convertible into nitro, methyl, ethyl, propyl, isopropyl, and chloro. On the basis of preliminary pharmacokinetic studies, the methyl group in the ortho-position of the phenylurea was selected. (2) Butyl, pentyl, isopentyl, and neopentyl were better substituents in the urea moiety. (3) Propoxy was the optimal moiety in the bridging portion. (4) Proton, methyl, ethyl, isopropyl, hydroxymethyl, and chloro were better substituents at the 5-position of the imidazole moiety. (5) An unsubstituted phenyl ring was selected as the phenyl group of phenylimidazole. The subsequent comparison studies of compounds containing various combinations of the optimum substituents in each region resulted in the selection of two compounds (**67**, **68**) for further pharmacological and toxicological testing. These compounds were orally bioavailable, and possessed potent in vitro aortic ACAT inhibitory activity (IC_{50} = 0.16 and 0.012 μM, respectively) and in vivo cholesterol lowering effect (46% and 52% at 1 mg/kg po, respectively). In particular, **68** was 10-fold more potent in the in vitro aortic ACAT assay and 5-fold more potent with respect to hypocholesterolemic activity in vivo than **3**.

In recent studies on atherosclerosis, it has been found that the enzyme ACAT (acyl-CoA:cholesterol *O*-acyltransferase) present in the arterial wall plays as an important role in the formation of macrophage-enriched fatty streaks.[1,2] That is, the formation of cholesteryl esters on the arterial wall appears to be catalyzed by ACAT, whose activation is implicated in the excess accumulation of cholesterol esters.[3] ACAT is also known to participate in the intestinal absorption of cholesterol, since its activity is greatest in the jejunum, where the majority of cholesterol absorption occurs,[1,4] and in vitro and ex vivo inhibition of ACAT activity is correlated with the inhibition of cholesterol absorption, at least in rats[5] and rabbits.[6] A nonabsorbable ACAT inhibitor (one that is not detected in plasma after oral administration) may retard the progression of atherosclerosis only by reducing serum cholesterol levels, whereas a systemically bioavailable ACAT inhibitor may delay or impede the progression of atherosclerosis by both reducing serum cholesterol levels and directly preventing the accumulation of esterified cholesterol in arterial tissue.[7-11]

As described in our previous paper,[12] *N*-[2-(dimethylamino)-6-[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]-phenyl]-*N'*-pentylurea (**3**) is a novel, potent, and systemically bioavailable ACAT inhibitor with an antiatherosclerotic effect. Although it is not clear whether or not the antiatherosclerotic effect is at least partly due to a direct effect on the arterial wall, we hoped that a systemically bioavailable ACAT inhibitor with more potent aortic ACAT inhibitory activity and hypocholesterolemic effect than **3** might have a more potent antiatherosclerotic effect. In order to find such a compound, we divided molecule **3** into five regions and strategically modified each of them by introducing functional groups and converting carbon atoms in the molecule into heteroatoms on the basis of the structural requirements established in our previous investigation (Chart I).[12] Since the aim of the present study was to discover more effective antiatherosclerotic agents, compounds containing various combinations of the selected substituents in each region were subjected to comparative study in order to identify compounds showing a desirable balance of in vitro aortic ACAT inhibitory activity, in vivo hypocholesterolemic effect, and oral bioavailability.

In this paper, we report the structure–activity relationships at the five regions, and we present the results of the comparative studies, leading to the selection of two compounds for further testing.

Chemistry

Scheme I shows the preparation of the final compounds by route I. The 2-nitroanisole derivatives **1a–l** were prepared by the standard methods. The imidazole derivatives **3a–s** required for these syntheses were prepared by various reported methods.[12-15] The preparation of 2-(*N'*-pentylureido)phenol derivatives **2a–l** from 2-nitroanisoles **1a–l** by method A and subsequent preparation of the final compounds by method B have been reported in our previous paper.[12] Compound **5** was prepared from *N*-[2-(*N*-benzyl-*N*-methylamino)-6-[3-(5-methyl-4-phen-

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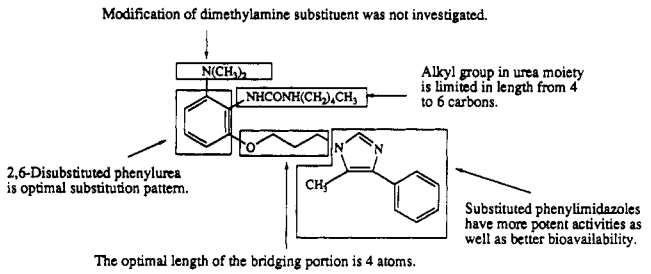
Chart I. Summary of Structure–Activity Relationships of the Lead Compound 3 Found Previously[12]



yl-1*H*-imidazol-1-yl)propoxy]phenyl]-*N'*-pentylurea (**4**) by catalytic hydrogenolysis. The sulfonamide analogues **43**, **46**, and **48** were prepared from the nitro derivatives **42**, **45**, and **47** by catalytic hydrogenation followed by treatment with methanesulfonic anhydride (method C). Preparation of the 5-[(dimethylamino)methyl] (**57**) and 5-[(methylthio)methyl] (**59**) derivatives was accomplished by chlorination of the hydroxymethyl analogue **56** with thionyl chloride and subsequent treatment with either dimethylamine or sodium thiomethoxide (method D). The (methylsulfonyl)methyl analogue **60** was obtained by oxidation of **59** with *m*-chloroperoxybenzoic acid (mcpba) (method I). The carboxylic acid (**62**) and amide (**63**) derivatives were prepared from the ester analogue **61** by the standard methods.

Scheme II shows the preparation of **6**, **7**, **8**, and **10** by route II. Reaction of 2-amino-3-nitrophenol with 1-(3-chloropropyl)-5-methyl-4-phenylimidazole (**3a**) in the presence of sodium iodide and potassium carbonate afforded 2-[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]-6-nitroaniline (**79**). Reaction of **79** with phenyl chloroformate in pyridine followed by treatment with pentylamine in toluene gave the nitro analogue **10**. Catalytic hydrogenation of **10** gave the aniline analogue **6**. Sulfonamide analogues **7** and **8** were obtained by treatment of **6** with either methanesulfonic anhydride or trifluoromethanesulfonic anhydride.

Scheme III shows the preparation of compounds **11–14** and **24–30** by route III. Alkylation of commercially available nitrophenols with **3a** followed by catalytic hydrogenation gave the aniline derivatives **80a–d** (method E). Treatment of **80a–d** with either alkyl isocyanates (method F) or phenyl chloroformate followed by reaction with the corresponding amine (method G) afforded the final compounds.

In order to examine the effect of the bridging portion in the key compound **12**, the compounds listed in Table III were prepared as illustrated in Schemes IV–VII. Scheme IV shows the preparation of the sulfur derivatives **31–33** by route IV. The sulfide analogue **31** was prepared from 3-chloro-2-nitrotoluene by a similar procedure to that reported in our previous paper.[12] The sulfoxide analogue **32** was obtained by oxidation of **31** with 1 equiv of mcpba in CH_2Cl_2 (method H), while the sulfone analogue **33** was afforded by oxidation with 2 equiv of mcpba (method I).

Scheme V shows the preparation of benzyl type compounds **34–37** by route V. Reaction of 3-methyl-2-nitrobenzyl bromide with 1-(2-heteroethyl)-5-methyl-4-phenylimidazoles (**3u,v**), which were prepared by reported methods,[12] in the presence of NaH gave the benzyl ether (**82**) and benzyl thioether (**83**) derivatives (method J). Reduction of **82** or **83** with zinc in acetic acid followed by treatment with pentyl isocyanate gave the benzyl analogues **34** and **35** (method K). Oxidation of the sulfur derivative **35** by method H or I afforded sulfoxide (**36**) and sulfone (**37**) analogues.

Scheme VI shows the preparation of the amide derivative **38** by route VI. Reaction of 3-methyl-2-nitrobenzoyl chloride with 1-(2-aminoethyl)-5-methyl-4-phenylimidazole (**3w**), prepared as reported,[12] in the presence of Et_3N afforded the amide compound **84**. Catalytic hydrogenation of **84** and subsequent reaction with pentyl isocyanate gave the amide analogue **38**.

Compound **39**, which is a hydroxy group analogue of **12**, was prepared by the procedure illustrated in Scheme VII (route VII). Alkylation of 3-methyl-2-nitrophenol with epibromohydrin followed by treatment with the sodium salt of 5-methyl-4-phenylimidazole gave **85**. The final compound **39** was obtained from **85** by catalytic hydrogenation and subsequent reaction with pentyl isocyanate.

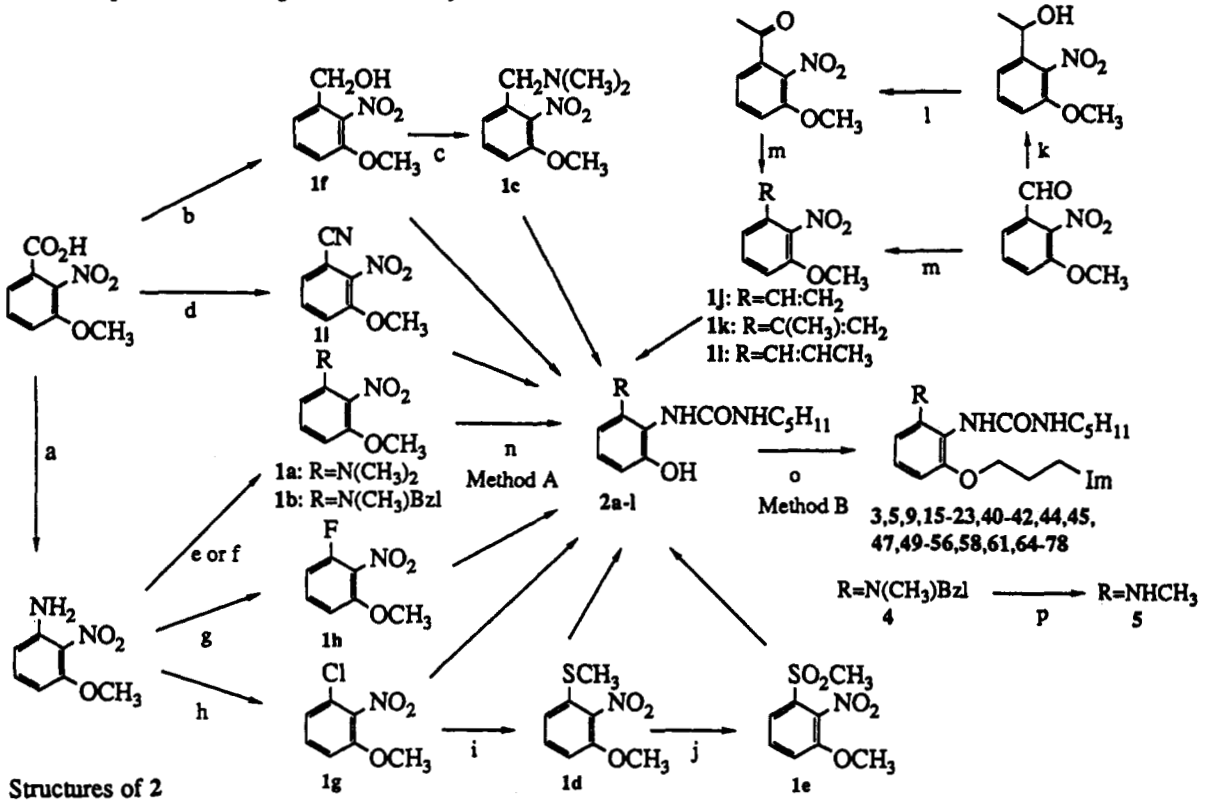
The regioisomers of the imidazole moiety were previously identified by analysis of the ^{1}H-NMR spectral data.[12] Structural confirmation of the analogues of the present investigation was obtained by alternative synthesis as shown in Scheme VIII (route VIII). Alkylation of 3-methyl-2-nitrophenol with 1-bromo-3-chloropropane in the presence of potassium carbonate in DMF gave **86**. Reaction of **86** with sodium diformylamide followed by treatment with a catalytic amount of KOH in EtOH afforded the formamide compound **87**.[16] Alkylation of **87** with 2-bromoalkyl phenyl ketones in the presence of NaH in DMF and subsequent cyclization to the imidazole ring in formic acid, formamide, and ammonium formate[17] gave **88a–c**. The final compounds **12**, **67**, and **68** were prepared from **88a–c** by catalytic hydrogenation and subsequent reaction with alkyl isocyanate. The physical data of the final compounds **12**, **67**, and **68** prepared by this method (route VIII) coincided with those of the compounds prepared by route I.

Biological Results and Structure–Activity Relationship

Our aim is to find a compound able to act on both intestinal and aortic ACATs to prevent absorption of cholesterol in the intestine and the accumulation of cholesteryl esters in the arterial wall. Since Lange et al.[18] had suggested the possibility of the existence of isozymes of ACAT, the synthesized compounds were evaluated for in vitro ACAT inhibitory activity according to the method of Heider et al.[6] using two enzyme sources, rabbit aorta homogenate and rabbit small intestinal microsomes. The potency of activity was expressed as the micromolar concentration of a compound required to inhibit the enzyme activity by 50% (IC_{50}). IC_{50} values were calculated from concentration-inhibition curves derived from assay of triplicate tubes at each drug concentration.

The analogues with potent in vitro intestinal inhibitory activity were then tested for in vivo hypocholesterolemic activity. In vivo serum cholesterol lowering activity was assessed in male Sprague–Dawley rats (5-weeks-old) fed a hypercholesterolemic diet along with a test compound, administered orally, once a day for 2 days. Cholesterol-lowering activity was expressed as a percentage of the control value. We added compound **3** as an active control in all experiments. Test compounds were compared by the mean values. For the compounds listed in Table VII, ED_{30} values, the mg/kg dose of a compound required to decrease the serum cholesterol level to 30% of the control

Scheme I. Preparation of Target Molecules by Route I[a]

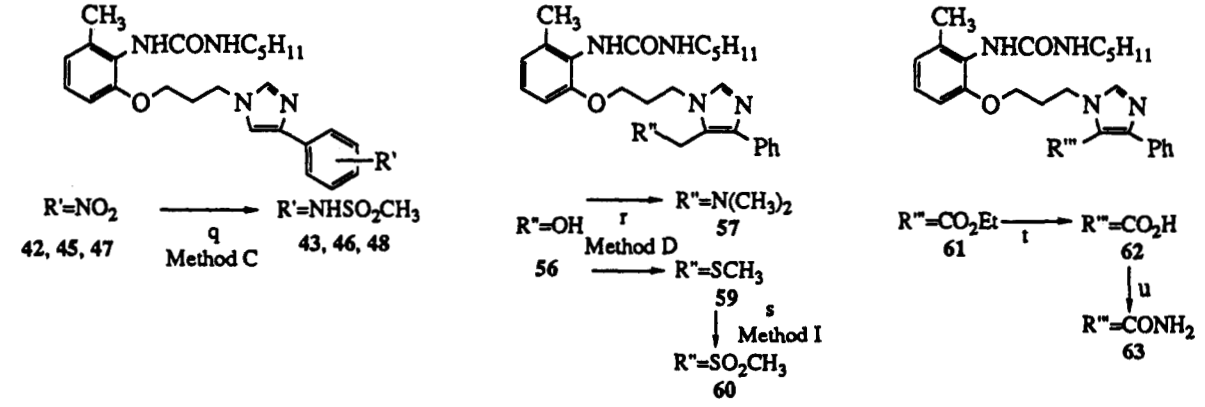


Structures of 2

no.	R
a	$N(CH_3)_2$
b	$N(CH_3)Bzl$
c	$CH_2N(CH_3)_2$
d	SCH_3
e	SO_2CH_3
f	CH_2OH
g	Cl
h	F
i	CN
j	C_2H_5
k	$CH(CH_3)_2$
l	C_3H_7

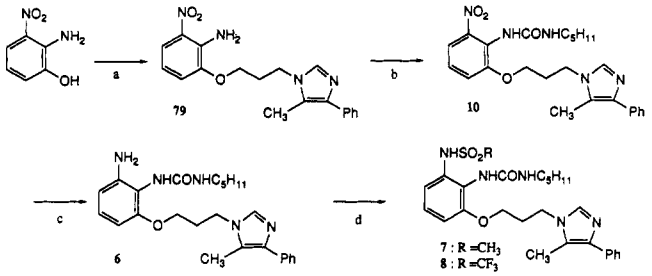
Structures of 3

no	Im.	no	Im
3a	5-methyl-4-phenylimidazole	3k	4-(3,4,5-trimethoxyphenyl)imidazole
3b	4-phenylimidazole	3l	5-ethyl-4-phenylimidazole
3c	4-(2-methyphenyl)imidazole	3m	5-propyl-4-phenylimidazole
3d	4-(2-nitrophenyl)imidazole	3n	5-isopropyl-4-phenylimidazole
3e	4-(2-sulfonylmethylphenyl)imidazole	3o	5-hydroxymethyl-4-phenylimidazole
3f	4-(3-nitrophenyl)imidazole	3p	5-methoxymethyl-4-phenylimidazole
3g	4-(4-nitrophenyl)imidazole	3q	5-ethoxycarbonyl-4-phenylimidazole
3h	4-(4-chlorophenyl)imidazole	3r	5-chloro-4-phenylimidazole
3i	4-(2,4-difluorophenyl)imidazole	3s	(1H, 8H, 9H)-naphtho[2,1-d]imidazole
3j	4-(2,4,6-trimethoxyphenyl)imidazole		



[a] Reagents: (a) (1) $SOCl_2$, (2) NaN_3/acetone–H_2O, (3) Δ/benzene, (4) NaOH, (5) HCl; (b) B_2H_6/THF; (c) (1) $PBr_3/CHCl_3$, (2) $HN(CH_3)_2$/DMF; (d) (1) $SOCl_2$, (2) NH_4OH/CH_2Cl_2, (3) $SOCl_2$; (e) MeI, K_2CO_3/DMF; (f) (1) HCO_2H, (2) BzlBr, NaH/DMF, (3) HCl/1,4-dioxane, (4) MeI, NaH/DMF; (g) (1) $NaNO_2$/HCl, (2) $NaSbF_6$, (3) Δ/SiO_2; (h) (1) $NaNO_2$/HCl, (2) $CuCl_2$; (i) $NaSCH_3$/DMF; (j) mcpba/CH_2Cl_2; (k) MeLi/THF; (l) (1) oxalyl chloride, DMSO/CH_2Cl_2, (2) NEt_3; (m) Ph_3P^+alkylI^-, nBuLi/THF; (n) (1) H_2, Pd–C/EtOAc, (2) pentyl isocyanate/$CHCl_3$, (3) BBr_3/CH_2Cl_2 or (1) H_2, Pd-C/EtOAc, (2) $ClCO_2Ph$/pyridine, (3) pentylamine/toluene, (4) BBr_3/CH_2Cl_2; (o) **3a–s**, K_2CO_3, NaI/DMF; (p) H_2, Pd–C/EtOH; (q) (1) H_2, Pd–C/EtOH, (2) $(CH_3SO_2)_2O$, Et_3N/CH_2Cl_2; (r) (1) $SOCl_2$, $Et_3N/CHCl_3$, (2) $HN(CH_3)_2$ or $NaSCH_3$/DMF; (s) mcpba/CH_2Cl_2; (t) 10 N NaOH/MeOH; (u) (1) $SOCl_2/CH_2Cl_2$, (2) $NH_4OH/CHCl_3$.

Scheme II. Preparation of Target Molecules by Route II[a]



[a] Reagents: (a) **3a**, K_2CO_3, NaI/DMF; (b) (1) $ClCO_2Ph$/pyridine, (2) pentylamine/toluene; (c) H_2, Pd–C/AcOH; (d) $(RSO_2)_2O$, Et_3N/CH_2Cl_2.

value, were obtained. ED_{30} values were calculated from dose–response curves derived from experiments performed with more than three dosages (n = 4 or 5).

In our previous paper,[12] we described the allowable limitations in modifying five regions of the lead compound **3**, and the SARs of **3** are summarized in Chart I. (1) Modification of the dimethylamine substituent was not investigated. (2) In the urea moiety, the L lengths of STERIMOL parameters in the alkyl group were limited to the range from 6.17 Å (butyl) to 8.22 Å (hexyl) based on in vitro ACAT inhibitory activity, in vivo hypocholesterolemic activity, and pharmacokinetic data. (3) In the bridging portion, the length of four atoms was optimal. (4) Although various heterocycles were tolerated in the arylated heterocycle moiety, only the phenylimidazole moiety provided potent activity as well as high bioavailability. (5) In the phenylurea nucleus, 2,6-disubstituted phenylurea was the optimal substitution pattern.

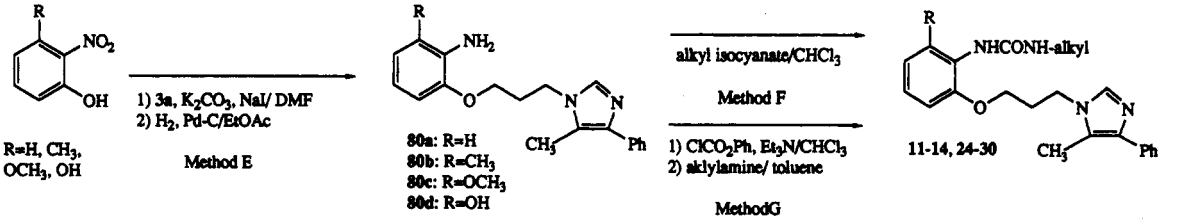
To study further the structure–activity relationships, we modified the parent compound **3** on the basis of the above findings. The synthesized compounds were compared for in vitro ACAT inhibitory activity and in vivo hypocholesterolemic effect. The results are shown in Tables I–V. First, the importance of ortho substituents of phenylureas was examined (Table I). Removing the dimethylamino group (**11**) reduced in vitro and in vivo activity. This indicates that introduction of a substituent at the ortho-position of phenylurea may increase the activity. Next, we varied the substituents at the ortho-position of phenylurea to examine lipophilic–hydrophilic, electronic, and steric factors. Conversion of the dimethylamino group (**3**) to methylamino (**5**), amino (**6**), (methylsulfonyl)amino (**7** and **8**), (dimethylamino)methyl (**9**), hydroxy (**14**), and hydroxymethyl (**17**) (hydrophilic group) reduced the potency. When electron-donating and electron-withdrawing substituents were compared, the in vitro aortic activity decreased in the order thiomethyl (**15**) > sulfonylmethyl (**16**) > nitro (**10**) > fluoro (**19**) > chloro (**18**) ≥ dimethylamino (**3**) > methoxy (**13**), in vitro intestinal activity decreased in the order dimethylamino (**3**) ≥ nitro (**10**) > fluoro (**19**) > chloro (**18**) > methoxy (**13**) > sulfonylmethyl (**16**) > thiomethyl (**15**), and in vivo hypocholesterolemic activity decreased in the order nitro (**10**) ≥ chloro (**18**) ≥ dimethylamino (**3**) ≥ methoxy (**13**) ≥ sulfonylmethyl (**16**) ≥ fluoro (**19**). Since the thiomethyl substituent (**15**) was the most potent substituent for in vitro aortic activity but was much less potent for in vitro intestinal activity, we did not examine in vivo hypocholesterolemic effect. The cyano substituent (**20**) almost abolished the activities both in vitro and in vivo.

These results suggest that the inhibitor-binding site of ACAT repels hydrophilic substituents, and electronic factors did not correlate with activities in vitro and in vivo. We therefore speculated that the potent activity of the nitro substituent (**10**) might not depend on the electron-withdrawing property, but rather might depend on the steric factor. In order to examine steric and lipophilic factors, **12** and **21–23** were compared. The order of in vitro aortic and in vivo hypocholesterolemic activity was methyl (**12**) < ethyl (**21**) ≥ isopropyl (**22**) > propyl (**23**). The order of in vitro intestinal activity was methyl (**12**) > isopropyl (**22**) ≥ ethyl (**21**) > propyl (**23**). These results suggest the existence of an optimal size of the substituent in this region. We investigated the relationships between the activities and some physiological parameters (CLOGP,[19] STERIMOL parameters,[20] Es values, van der Waals radius, and Hammett substituent constant values[21]); however, no correlation was found. We found that the dimethylamino substituent was convertible into nitro, methyl, ethyl, isopropyl, propyl, and chloro substituents in this region. Of these substituents, the methyl group was selected as the most favorable on the basis of a preliminary pharmacokinetic study.[22] Further comparisons of the activity of various analogues were made within the methyl-substituted series.

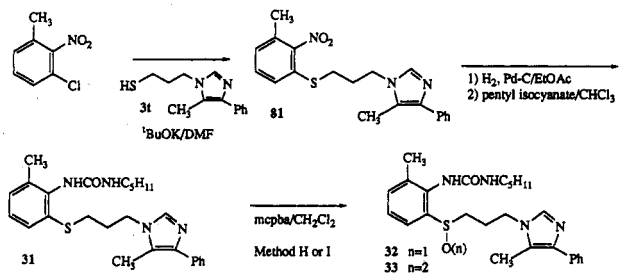
In our previous study,[12] we found that in vivo hypocholesterolemic effect correlated with the L length of STERIMOL parameters of alkyl groups, and lengthening the alkyl chain resulted in a reduction of the plasma concentration of the compound after oral administration. The limitation of carbon length was confirmed in the methyl-substituted series (Table II). The conversion from butyl to hexyl (**24**, **12**, and **25**) caused almost no change in in vitro intestinal activity and in vivo hypocholesterolemic activity, while in vitro aortic activity increased in the order butyl (**24**) < pentyl (**12**) < hexyl (**25**). Since the plasma level of compounds after oral administration was found to decrease in the order butyl (**24**) > pentyl (**12**) ≫ hexyl (**25**) in a preliminary experiment,[22] we discontinued studies on compounds with substituents longer than hexyl (**25**) in the methyl series as well as in the dimethylamino series. Although replacement of the linear alkyl group with a cycloalkyl group (**26**) or branched alkyl groups (**27** and **28**) slightly reduced in vitro activity, in vivo hypocholesterolemic activity increased. When a carbon in the alkyl chain was replaced with oxygen (**29** and **30**), the activity was nearly abolished. In the urea moiety, butyl, pentyl, isopentyl, and neopentyl were chosen as candidates for further comparison studies.

In order to examine hydrophilic and conformational tolerance in the bridging portion, the phenyl ether moiety was varied (Table III). When oxygen was replaced with sulfide, sulfoxide, and sulfone, the in vitro aortic activity decreased in the order S (**31**) > O (**12**) ≫ SO_2 (**33**) > SO (**32**), and in vitro intestinal activity decreased in the order O (**12**) > S (**31**) ≫ SO_2 (**33**) > SO (**32**). The sulfide analogue **31** possessed much lower in vivo hypocholesterolemic activity as compared with in vitro intestinal activity. Although the reason for this was not examined, it may be due to the metabolic instability of compound **31**, since the sulfur compound was expected to be metabolized to the much less active SO and SO_2 derivatives. When phenyl ether (**12** and **31**) was replaced with benzyl ether (**34–37**), compounds **34**, **35**, and **37** retained the in vitro aortic activity, while in vitro intestinal and in vivo hypocholesterolemic activity decreased. The amide type compound

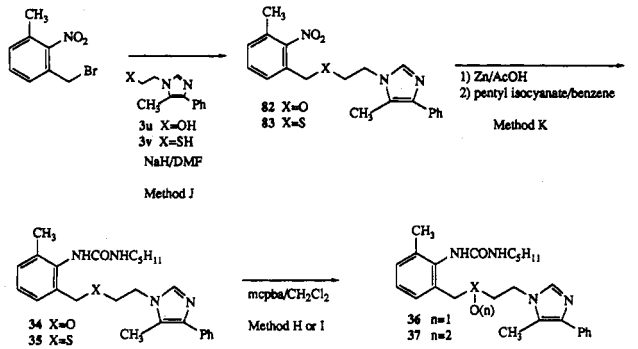
Scheme III. Preparation of Target Molecules by Route III



Scheme IV. Preparation of Target Molecules by Route IV



Scheme V. Preparation of Target Molecules by Route V



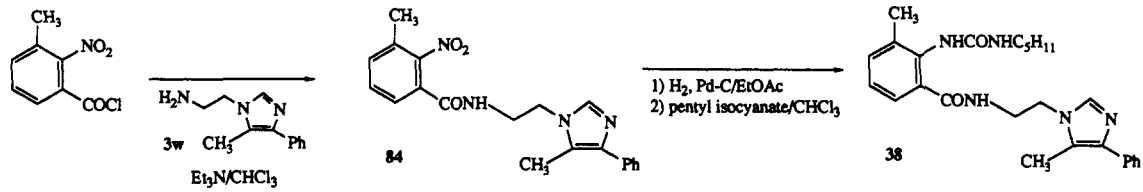
38 was half as potent as 12. Introduction of a hydroxy group (39) into the propoxy moiety did not increase the activity. Therefore, the propoxy group was selected for further comparison studies.

Our previous paper[12] reported that phenylimidazole analogues had potent in vitro and in vivo activity, and introduction of substituents into the phenylimidazole moiety increased the in vivo potency. To examine in more detail the substituent effects, various substituents were introduced into the phenyl ring and imidazole ring in the phenylimidazole moiety. The substituent effects in the phenyl ring are shown in Table IV. The ortho-substituted methyl analogue 41 showed about a 3-fold increase in in vitro aortic activity compared with the unsubstituted analogue 40, while this compound did not have improved in vitro intestinal activity or in vivo activity. To investigate electronic and hydrophilic factors, nitro, methylsulfonyl, (methylsulfonyl)amino, methoxy, and halogen substituents were introduced. Introduction of a nitro group (42) at the ortho-position increased the in vivo activity, and introduction at the meta- (45) or para-position (47) increased the in vitro intestinal activity. The introduction of a sulfonylamino (43) did not increase the activity, and in particular, introduction at the meta- (46) or para-position (48) nearly abolished the activity. Introduction of a methylsulfonyl group (44) reduced the in vitro aortic and in vivo hypocholesterolemic activity. Introduction of halogen atoms (49 and 50) resulted in almost no change in the vitro activity, while introduction of a methoxy group (51 and 52) reduced the activity. The chloro analogue 49 had increased in vivo activity. Since the introduction of substituents did not greatly increase the activity, unsubstituted phenyl was selected as the preferred phenyl ring moiety.

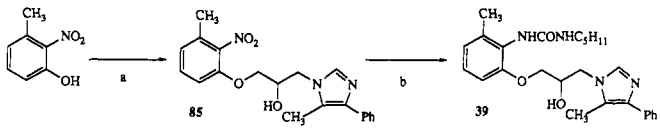
The effects of the substituents in the imidazole ring of the phenylimidazole moiety are shown in Table V. To investigate the optimum length of the 5-substituted alkyl group, compounds 12, 40, and 53–55 were compared. The isopropyl substituent (55) gave the most potent in vitro aortic activity. The methyl substituent (12) gave the most potent in vitro intestinal activity. The propyl substituent (54) gave the most potent in vivo hypocholesterolemic activity. However, 54 was not detected in plasma after oral administration in the preliminary experiment.[22] Polar substituents (56–63) were also assessed. The hydroxymethyl substituent (56) had similar in vitro and in vivo potencies to those of 40. Although (dimethylamino)methyl (57), methoxymethyl (58) and (methylthio)methyl (59) derivatives retained the in vitro aortic activity, in vitro intestinal activity and in vivo hypocholesterolemic activity were reduced. The methylsulfonyl analogue 60 lacked in vitro aortic activity. The ester analogue 61 had more potent in vitro activity than 40. However, the ester analogue 61 was not examined in vivo, because it was expected that the ester would be rapidly hydrolyzed to carboxylic acid (62) by esterase after administration, leading to loss of activity. The amide analogue 63 lacked in vitro aortic activity. The chloro analogue 64 showed increased in vitro and in vivo activity. To investigate the influence of the torsional angle between the imidazole and phenyl rings, compound 53, in which the phenyl and imidazole rings were nearly perpendicular, was compared with 65, in which these rings were nearly planar. Although the two compounds were not dramatically different in activity, 53 was obviously superior to 65 in oral bioavailability.[22] These results indicate that the basicity of imidazole and the torsional angle between imidazole and phenyl did not contribute greatly to the activity, whereas hydrophilicity did contribute to the activity. Hydrophilic tolerance was limited near the phenylimidazole moiety, and increasing the lipophilicity increased the potency. Proton, methyl, ethyl, isopropyl, and chloro substituents were selected for further comparison studies.

The optimum substituents are illustrated in Chart II. Our next objective was to find compounds giving a well-balanced combination of high in vitro aortic ACAT inhibitory activity, potent in vivo hypocholesterolemic effect, and good bioavailability. Since we found that activity was inversely correlated with bioavailability (for example, in vitro aortic activity 24 < 25 < 26 vs plasma level of the compound after oral administration 24 > 25 > 26), comparison studies were performed to identify the desired compounds. In the urea moiety, butyl, pentyl, isopentyl, and neopentyl groups were examined. In the 5-position of the imidazole moiety, proton, methyl, ethyl, isopropyl, chloro, and hydroxymethyl substituents were

Scheme VI. Preparation of Target Molecules by Route VI

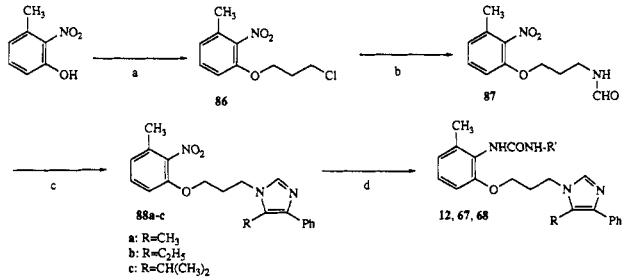


Scheme VII. Preparation of Target Molecules by Route VII[a]



[a] Reagents: (a) (1) epibromohydrin, K_2CO_3, NaI/DMF; (2) 5-methyl-4-phenylimidazole, NaH/DMF; (b) (1) H_2, Pd–C/EtOAc, (2) pentyl isocyanate/$CHCl_3$.

Scheme VIII. Preparation of Target Molecules by Route VIII[a]



[a] Reagents: (a) 1-bromo-3-chloropropane, K_2CO_3/DMF; (b) (1) $NaN(CHO)_2$/DMF, (2) 0.01 eq KOH/EtOH; (c) (1) NaH/DMF, (2) 2-bromoalkylphenylketone, (3) HCO_2NH_4, HCO_2NH_2, HCO_2H; (d) (1) H_2, Pd-C/EtOAc, (2) alkyl isocyanate/$CHCl_3$.

tried. The results are shown in Table VI. We first sorted these compounds according to in vivo hypocholesterolemic activity. Compounds **64, 67, 68, 70**, a series of isopentyl analogues (**27** and **71–75**), and a series of neopentyl analogues (**28** and **76–78**) were selected as potent hypocholesterolemic compounds. Compounds **70, 71**, and **74**, with less potent in vitro aortic ACAT inhibitory activity, were dropped. Next, the selected compounds (**27, 28, 64, 67, 68, 72, 73, 75–78**) were assessed in preliminary pharmacokinetic studies. Since compounds **67** and **68** gave higher plasma concentration after oral administration than the other compounds,[22] they were selected for study of antiatherosclerotic effect as ACAT inhibitors with the best balance of the required properties in this series. The in vitro ACAT inhibitory activity and in vivo hypocholesterolemic activity of these compounds (**67** and **68**) are summarized in Table VII. Compounds **67** and **68** were found to prevent the accumulation of cholesterol in the arterial wall and to reduce aortic ACAT activity at the dosage of 0.02% in diet (approximately 7 mg/kg, one-fifth of the necessary dosage of **3**[12]). The effectiveness of these compounds may have been partly due to a direct antiatherosclerotic effect.[23] At present, we are continuing further investigation in order to clarify the direct effect on the arterial wall.

In summary, in order to find more effective antiatherosclerotic agents than **3**, **3** was strategically modified and the resulting compounds were evaluated as ACAT inhibitors. Structure–activity relationship studies revealed optimum groups in each of five regions of the molecule, and comparison studies were performed to identify the compounds giving the desired combination of potent activities and high bioavailability. Compounds **67** and **68** were selected for further pharmacological and toxicological studies.

Experimental Section

The purity of each product was checked by thin-layer chromatography (TLC) on silica gel plates (Kieselgel 60 F_{254}, thickness 0.25 mm). Column chromatography was performed on silica gel (Merck; particle size 0.063–0.200 mm for normal chromatography and 15 μm for flash chromatography). All melting points (mp) were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured on JEOL JNM-FX90Q (90 MHz) and Varian UNITY 400 (400 MHz) instruments. Chemical shifts are reported in δ units from tetramethylsilane as an internal standard; coupling constants are reported in hertz. Mass spectra were obtained on a JEOL HX100 mass spectrometer and data are tabulated as *m/e*. Elemental analyses were performed at the Analytical Chemistry Section of Eisai Tsukuba Research Laboratories.

Route I. 3-Chloro-2-nitroanisole (1g). To a solution of 3-methoxy-2-nitroaniline (10.0 g, 59.5 mmol) in 98% sulfuric acid (50 mL) and acetic acid (120 mL) was added a suspension of sodium nitrate (4.50 g) in acetic acid (10 mL) at below 10 °C, and the mixture was stirred at this temperature. After 1 h, a solution of cuprous chloride (13.0 g) in 36% HCl (120 mL) was added to the mixture below 10 °C. The mixture was stirred at room temperature for 1 h and poured into water (500 mL). The resulting precipitate was collected and washed with water to give 8.75 g (78%) of **1g**: ^{1}H NMR ($CDCl_3$) δ 3.90 (3H, s), 6.94 (1H, d, *J* = 8.0), 7.04 (1H, d, *J* = 8.0), 7.37 (1H, t, *J* = 8.0).

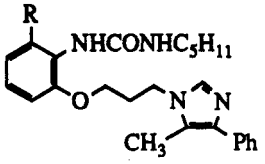
2-Nitro-3-(methylthio)anisole (1d). To a solution of **1g** (1.00 g, 5.33 mmol) in DMF was added a solution of sodium methanethiol (15% water solution, 10 mL), and the mixture was stirred at 100 °C for 2 h. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (hexane–EtOAc 2:1) to give 370 mg (35%) of **1d**: ^{1}H NMR ($CDCl_3$) δ 2.46 (3H, s), 3.88 (3H, s), 6.83 (1H, d, *J* = 8.0), 6.97 (1H, d, *J* = 8.0), 7.38 (1H, t, *J* = 8.0).

2-Nitro-3-(methylsulfonyl)anisole (1e). To a solution of **1d** (2.36 g, 11.9 mmol) in CH_2Cl_2 was added mcpba (85% purity, 5.11 g) at room temperature, and the mixture was stirred overnight. The mixture was poured into water, neutralized with 1 N NaOH, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (hexane–EtOAc 1:1) to give 1.69 g (61%) of **1e**: ^{1}H NMR ($CDCl_3$) δ 3.22 (3H, s), 3.98 (3H, s), 7.38 (1H, dd, *J* = 7.2, 6.5), 7.64 (1H, d, *J* = 6.5), 7.65 (1H, d, *J* = 7.2).

Method A. 2-(*N'*-Pentylureido)-3-(methylsulfonyl)phenol (2e). A solution of **1e** (1.69 g, 7.32 mmol) in EtOAc was hydrogenated over 10% palladium on carbon (100 mg) at 1 atm for 1 h. The catalyst was filtered off and the filtrate was evaporated in vacuo to give 1.50 g (99%) of 2-methoxy-6-(methylsulfonyl)aniline.

A solution of the aniline (1.50 g, 7.46 mmol) and phenyl chloroformate (1.4 mL) in pyridine (30 mL) was heated at 60 °C for 2 h and the solvent was removed in vacuo. The residue was dissolved in toluene (20 mL) and pentylamine (720 mg). The solution was heated under reflux for 1 h and cooled to room temperature. The resulting precipitate was collected and washed with benzene to give 740 mg (32%) of *N*-[2-methoxy-6-(methylsulfonyl)phenyl]-*N'*-pentylurea.

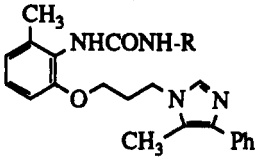
Table I. Physical Data and Biological Activites of *N*-[2-[3-(5-Methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]-6-substitutedphenyl]-*N'*-pentylureas



no.	R	yield[a] (route)	mp (°C)	formula[b]	ACAT inhibn aorta[c]	ACAT inhibn intestine[d]	cholesterol lowering (%)[e]
3	$N(CH_3)_2$	69 (I)	128–130	$C_{27}H_{37}N_5O_2$	0.11	0.043	−42
5	$NHCH_3$	86 (I)	93–94	$C_{26}H_{35}N_5O_2$	0.60	0.15	−35
6	NH_2	83 (II)	86–87	$C_{25}H_{33}N_5O_2$	0.59	0.10	−21
7	$NHSO_2CH_3$	59 (II)	123–124	$C_{26}H_{35}N_5O_4S$	0.48	0.14	+3.6
8	$NHSO_2CF_3$	46 (II)	111–113	$C_{26}H_{32}N_5O_4SF_3$	>10[f]	>1[f]	NT[g]
9	$CH_2N(CH_3)_2$	22 (I)	103–105	$C_{28}H_{39}N_5O_2$	2.6	1.3	NT[g]
10	NO_2	53 (II)	135–136	$C_{25}H_{31}N_5O_4$	0.060	0.044	−52
11	H	87 (III)	115–116	$C_{25}H_{32}N_4O_2$	0.39	0.23	+3.9
12	CH_3	47 (III)	130–134	$C_{26}H_{34}N_4O_2$	0.12	0.050	−51 (−38)
13	OCH_3	34 (III)	125–127	$C_{26}H_{34}N_4O_3$	0.22	0.090	−34
14	OH	44 (III)	120–121	$C_{25}H_{32}N_4O_3$	0.96	0.46	NT[g]
15	SCH_3	5 (I)	111–112	$C_{26}H_{34}N_4O_2S$	0.019	0.23	NT[g]
16	SO_2CH_3	40 (I)	175–176	$C_{26}H_{34}N_4O_4S$	0.050	0.14	−33
17	CH_2OH	13 (I)	*h*	$C_{26}H_{34}N_4O_3$[i]	3.3	>1[f]	NT[g]
18	Cl	56 (I)	92–93	$C_{25}H_{31}N_4O_2Cl$	0.10	0.073	−49
19	F	46 (I)	128–129	$C_{25}H_{31}N_4O_2F$	0.071	0.069	−30
20	CN	16 (I)	45–50	$C_{26}H_{31}N_5O_2$	1.9	>1[f]	NT[g]
21	CH_2CH_3	19 (I)	122–124	$C_{27}H_{36}N_4O_2$	0.044	0.080	−60 (−51)
22	$CH(CH_3)_2$	24 (I)	153–154	$C_{28}H_{38}N_4O_2$	0.045	0.071	−59 (−40)
23	$CH_2CH_2CH_3$	36 (I)	116–121	$C_{28}H_{38}N_4O_2$	0.098	0.17	−50 (−34)

[a] Yield (%) of final step. [b] Satisfactory elemental analyses were obtained for C, H, N unless otherwise indicated. [c] IC_{50} (μM) for the enzyme derived from rabbit aorta homogenate. [d] IC_{50} (μM) for the enzyme derived from rabbit intestine microsomes. [e] Compounds were administered to rats at 4 mg/kg once a day for 2 days. Cholesterol-lowering activity was expressed as a percentage of the control value (n ≥ 4). Values in parentheses are cholesterol-lowering activity observed when compounds were administered to rats at 1 mg/kg once a day for 2 days. [f] A greater-than sign (>) denotes no effect at the concentration indicated. [g] Not tested. [h] Compound obtained as an oil. [i] Elemental analysis was not obtained. Spectral data were consistent with the indicated structure. See Experimental Section.

Table II. Physical Data and Biological Activities of *N*-Alkyl-*N'*-[2-methyl-6-[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]phenyl]ureas



no.	R	yield[a] (route)	mp (°C)	formula[b]	ACAT inhibn aorta[c]	ACAT inhibn intestine[d]	cholesterol lowering (%)[e]
24	C_4H_9	99 (III)	139–140	$C_{25}H_{32}N_4O_2$	0.48	0.073	−45 (−34)
12	C_5H_{11}	47 (III)	130–134	$C_{26}H_{34}N_4O_2$	0.12	0.050	−51 (−38)
25	C_6H_{13}	40 (III)	139–140	$C_{27}H_{36}N_4O_2$	0.068	0.084	−46 (−43)
26	c-C_6H_{11}	57 (III)	166–167	$C_{27}H_{34}N_4O_2$	0.18	0.10	−53 (−42)
27	$CH_2CH_2CH(CH_3)_2$	54 (III)	127–128	$C_{26}H_{34}N_4O_2$	0.10	0.14	−63 (−59)
28	$CH_2CH(CH_3)_3$	39 (III)	150–151	$C_{26}H_{34}N_4O_2$	0.14	0.21	(−64)
29	$CH_2(CH_2)_2OCH_3$	49 (III)	123–124	$C_{25}H_{32}N_4O_3$	>1[f]	0.30	NT[g]
30	$CH_2CH_2OC_2H_5$	44 (III)	121–122	$C_{25}H_{32}N_4O_3$	>1[f]	0.34	NT[g]

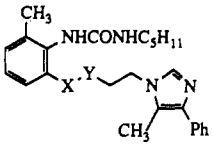
[a–g] See corresponding footnotes of Table I.

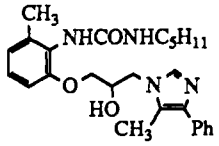
To a solution of the urea (740 mg, 2.36 mmol) in CH_2Cl_2 was added a solution of BBr_3 (2 M CH_2Cl_2 solution, 2.5 mL) at 0 °C. The mixture was heated under reflux for 2 h. The mixture was neutralized with aqueous sodium hydrogen carbonate and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give 730 mg (99%) of **2e**. ^1H NMR ($CDCl_3$) δ 0.87 (3H, t, *J* = 6.8), 1.23–1.58 (6H, m), 3.11 (3H, s), 3.21 (2H, q, *J* = 6.8), 3.85 (3H, s), 4.98 (1H, brt), 6.81 (1H, brs), 7.19 (1H, d, *J* = 7.8), 7.35 (1H, t, *J* = 7.8), 7.75 (1H, d, *J* = 7.8).

Method B. *N*-[2-[3-(5-Methyl-4-phenyl-1*H*-imidazol-1-yl)-propoxy]-6-(methylsulfonyl)phenyl]-*N'*-pentylurea (16). A solution of 1-(3-chloropropyl)-5-methyl-4-phenylimidazole (**3a**, 571 mg) in DMF was added dropwise to a suspension of **2e** (730 mg, 2.43 mmol), sodium iodide (70 mg), and potassium carbonate (670 mg) in DMF at 60 °C over 1 h. The mixture was stirred at the same temperature for 2 h. Then the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography (benzene–acetone 2:1), and recrystallized from EtOAc–hexane to give 480 mg (40%) of **16**: mp 175–176 °C; MS *m/e* (FAB) 499 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, *J* = 6.8), 1.23–1.52 (6H, m), 2.19 (2H, quintet, *J* = 5.6), 2.38 (3H, s), 3.11 (3H, s), 3.21 (2H, q, *J* = 6.8), 3.99 (2H, t, *J* = 5.6), 4.14 (2H, t, *J* = 5.6), 5.46 (1H, brt), 7.10 (1H, brs), 7.10–7.64 (9H, m). Anal. ($C_{26}H_{34}N_4O_4S$) C, H, N.

***N*-[2-(Methylamino)-6-[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]phenyl]-*N'*-pentylurea (5).** A solution of *N*-[2-(*N*-benzyl-*N*-methylamino)-6-[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]phenyl]-*N'*-pentylurea (**4**, 1.00 g, 1.86 mmol) in EtOH was hydrogenated over 10% palladium on carbon for 5 h. The catalyst was filtered off and the filtrate was evaporated in vacuo. The crude product was recrystallized from EtOAc to give 710 mg (86%) of **5**: mp 93–94 °C; MS *m/e* (FAB) 450 $(M + H)^+$;

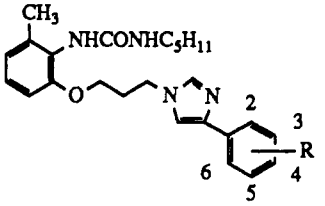
Table III. Physical Data and Biological Activities of *N*-[2-Methyl-6-[(5-methyl-4-phenyl-1H-imidazol-1-yl)heteroalkyl]phenyl]-*N'*-pentylureas



no.	X	Y	yield[a] (route)	mp (°C)	formula[b]	ACAT inhibn: aorta[c]	ACAT inhibn: intestine[d]	cholesterol lowering (%)[e]
12	O	CH_2	47 (III)	130–134	$C_{26}H_{34}N_4O_2$	0.12	0.050	−51
31	S	CH_2	51 (IV)	111–113	$C_{26}H_{34}N_4OS$	0.086	0.077	−7
32	SO	CH_2	97 (IV)	*h*	$C_{26}H_{34}N_4O_2S$[i]	>1[f]	>1[f]	NT[g]
33	SO_2	CH_2	74 (IV)	45–47	$C_{26}H_{34}N_4O_3S$	0.73	0.60	NT[g]
34	CH_2	O	60 (V)	72–73	$C_{26}H_{34}N_4O_2$	0.10	0.88	+2.0
35	CH_2	S	64 (V)	130–131	$C_{26}H_{34}N_4OS$	0.070	0.57	−11
36	CH_2	SO	73 (V)	116–118	$C_{26}H_{34}N_4OS$	0.44	>1[f]	NT[g]
37	CH_2	SO_2	85 (V)	168–170	$C_{26}H_{34}N_4O_3S$	0.090	>1[f]	NT[g]
38	CO	NH	45 (VI)	179–180	$C_{26}H_{33}N_5O_2$	0.28	0.097	−25
39			32 (VII)	182–184	$C_{26}H_{34}N_4O_3$	0.17	0.16	−43

[a–i] See corresponding footnotes of Table I.

Table IV. Physical Data and Biological Activities of *N*-[2-[3-(4-Aryl-1*H*-imidazol-1-yl)propoxy]-6-methylphenyl]-*N'*-pentylureas



no.	R	yield[a] (route)	mp (°C)	formula[b]	ACAT inhibn: aorta[c]	ACAT inhibn: intestine[d]	cholesterol lowering (%)[e]
40	H	28 (I)	121–122	$C_{25}H_{32}N_4O_2$	0.31	0.25	−52 (−28)
41	2-CH_3	45 (I)	90–91	$C_{26}H_{34}N_4O_2$	0.10	0.26	−48 (−25)
42	2-NO_2	28 (I)	96–97	$C_{25}H_{31}N_5O_4$	0.17	0.21	−66 (−46)
43	2-$NHSO_2CH_3$	39 (I)	65–70	$C_{26}H_{35}N_5O_4S$	0.24	0.45	−39
44	2-SO_2CH_3	14 (I)	100–101	$C_{26}H_{34}N_4O_4S$	0.41	0.16	−19
45	3-NO_2	41 (I)	181–182	$C_{25}H_{31}N_5O_4$	0.29	0.13	(−15)
46	3-$NHSO_2CH_3$	40 (I)	165–167	$C_{26}H_{35}N_5O_4S$	>1[f]	>1[f]	NT[g]
47	4-NO_2	37 (I)	174–175	$C_{25}H_{31}N_5O_4$	0.56	0.070	−33 (−31)
48	4-$NHSO_2CH_3$	13 (I)	86–88	$C_{26}H_{35}N_5O_4S$	>1[f]	>1[f]	NT[g]
49	4-Cl	35 (I)	141–144	$C_{25}H_{31}N_4O_2Cl$	0.26	0.12	−59 (−43)
50	2,4-F_2	10 (I)	147–148	$C_{25}H_{30}N_4O_2F_2$	0.12	0.29	−48 (−23)
51	2,4,6-$(OCH_3)_3$	24 (I)	*h*	$C_{28}H_{38}N_4O_5$[i]	>1[f]	>1[f]	NT[g]
52	3,4,5-$(OCH_3)_3$	25 (I)	*h*	$C_{28}H_{38}N_4O_5$[i]	0.90	0.51	NT[g]

[a–i] See corresponding footnotes of Table I.

^{1}H NMR ($CDCl_3$) δ 0.85 (3H, t, *J* = 7.2), 1.21–1.45 (6H, m), 2.21 (2H, quintet, *J* = 5.6), 2.38 (3H, s), 2.84 (3H, s), 3.16 (2H, q, *J* = 7.2), 3.94 (2H, t, *J* = 5.6), 4.13 (2H, t, *J* = 5.6), 4.85 (1H, brt), 5.40 (1H, brs), 6.21–7.64 (10H, m). Anal. ($C_{26}H_{35}N_5O_2$) C, H, N.

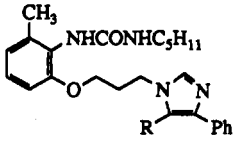
Method C. *N*-[2-Methyl-6-[3-[4-[2-[(methylsulfonyl)amino]phenyl]-1*H*-imidazol-1-yl]propoxy]phenyl]-*N'*-pentylurea (43). A solution of **42** (1.18 g, 2.53 mmol) in EtOH was hydrogenated over 10% palladium on carbon for 2 h. The catalyst was filtered off and the filtrate was evaporated in vacuo to give crude *N*-[2-[3-[4-(2-aminophenyl)-1*H*-imidazol-1-yl]propoxy]-6-methylphenyl]-*N'*-pentylurea.

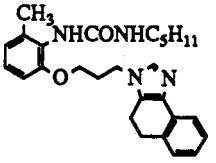
To a solution of the above compound and NEt_3 (0.53 mL) in CH_2Cl_2 was added a solution of methanesulfonic anhydride (660 mg) in CH_2Cl_2 at 0 °C. The mixture was stirred at room temperature for 1 h and poured into water. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to remove solvent. The residue was purified by column chromatography (benzene–acetone 1:2), and the resulting solid was recrystallized from EtOAc to give 370 mg (39%) of **43**: mp 65–70 °C; MS *m/e* (FAB) 514 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, t, *J* = 7.2), 1.18–1.50 (6H, m), 2.27 (2H, quintet, *J* = 5.6), 2.32 (3H, s), 2.90 (3H, s), 3.20 (2H, q, *J* = 7.2), 3.93 (2H, t, *J* = 5.6), 4.24 (2H, t, *J* = 5.6), 4.45 (1H, brt), 5.73 (1H, brs), 6.67–7.68 (10H, m). Anal. ($C_{26}H_{35}N_5O_4S$) C, H, N.

Method D. *N*-[2-[3-[5-[(Dimethylamino)methyl]-4-phenyl-1*H*-imidazol-1-yl]propoxy]-6-methylphenyl]-*N'*-pentylurea (57). To a solution of **56** (800 mg, 1.77 mmol) and Et_3N (0.38 mL) in $CHCl_3$ was added thionyl chloride (0.2 mL), and the mixture was heated under reflux for 1 h. The excess reagent was removed in vacuo to give crude *N*-[2-[3-[5-(chloromethyl)-4-phenyl-1*H*-imidazol-1-yl]propoxy]-6-methylphenyl]-*N'*-pentylurea.

A solution of the crude compound and the dimethylamine (50% water solution, 8.0 mL) in DMF was stirred at room temperature for 2 h. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated to remove the solvent. The residue was dissolved in toluene (20 mL) and pentylamine (500 mg). The mixture was refluxed for 1 h and concentrated under reduced pressure. The

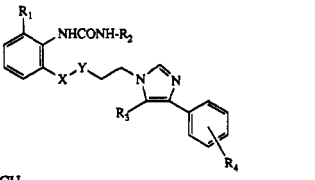
Table V. Physical Data and Biological Activities of *N*-[2-Methyl-6-[3-(4-phenyl-5-substituted-1*H*-imidazol-1-yl)propoxy]phenyl]-*N'*-pentylureas



no.	R	yield[a] (route)	mp (°C)	formula[b]	ACAT inhibn: aorta[c]	ACAT inhibn: intestine[d]	cholesterol lowering (%)[e]
40	H	28 (I)	121–122	$C_{25}H_{32}N_4O_2$	0.31	0.25	−52 (−28)
12	CH_3	47 (III)	130–134	$C_{26}H_{34}N_4O_2$	0.12	0.050	−51 (−38)
53	C_2H_5	47 (I)	108–109	$C_{27}H_{36}N_4O_2$	0.079	0.17	−49 (−28)
54	C_3H_7	19 (I)	107–108	$C_{28}H_{38}N_4O_2$	0.063	0.16	−56 (−49)
55	$CH(CH_3)_2$	29 (I)	132–134	$C_{28}H_{38}N_4O_2$	0.031	0.18	−49 (−30)
56	CH_2OH	58 (I)	114–116	$C_{26}H_{34}N_4O_3$	0.20	0.21	−55 (−29)
57	$CH_2N(CH_3)_2$	54 (I)	*h*	$C_{28}H_{39}N_5O_2$[i]	0.31	0.67	−10
58	CH_2OCH_3	14 (I)	116–117	$C_{27}H_{36}N_4O_3$	0.29	0.48	−47 (+18)
59	CH_2SCH_3	51 (I)	128–130	$C_{27}H_{36}N_4O_2S$	0.12	0.54	−33 (−20)
60	$CH_2SO_2CH_3$	51 (I)	108–110	$C_{27}H_{36}N_4O_4S$	>1[f]	0.41	NT[g]
61	$CO_2C_2H_5$	40 (I)	111–112	$C_{28}H_{36}N_4O_4$	0.055	0.15	NT[g]
62	CO_2H	98 (I)	131–132	$C_{26}H_{32}N_4O_4$	>1[f]	>1[f]	NT[g]
63	$CONH_2$	93 (I)	176–177	$C_{26}H_{33}N_5O_3$	>1[f]	0.18	(−20)
64	Cl	38 (I)	133–134	$C_{25}H_{31}N_4O_2Cl$	0.084	0.049	(−41)
65		35 (I)	146–147	$C_{27}H_{34}N_4O_2$	0.22	0.22	−56 (−30)

[a–i] See corresponding footnotes of Table I.

Chart II. Optimum Substituents in Each of Five Regions (see Chart I)



R_1: CH_3
R_2: C_4H_9, C_5H_{11}, $CH_2CH_2CH(CH_3)_2$, $CH_2C(CH_3)_3$
R_3: H, CH_3, C_2H_5, CH_2OH, Cl, $CH(CH_3)_2$
R_4: H
X: O
Y: CH_2

residue was purified by column chromatography (benzene–acetone 1:1) to give 460 mg (54%) of **57** as an oil: MS *m/e* (FAB) 478 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, *J* = 6.8), 1.19–1.51 (6H, m), 2.14 (6H, s), 2.28 (3H, s), 2.31 (2H, quintet, *J* = 6.0), 3.18 (2H, q, *J* = 6.8), 3.54 (2H, s), 4.00 (2H, t, *J* = 6.0), 4.32 (2H, t, *J* = 6.0), 4.82 (1H, brt), 5.63 (1H, brs), 6.67–7.63 (9H, m).

***N*-[2-[3-(5-Carboxy-4-phenyl-1*H*-imidazol-1-yl)propoxy]-6-methylphenyl]-*N'*-pentylurea (62).**

A solution of **61** (5.52 g, 11.2 mmol) and 10 N NaOH (11.2 mL) in MeOH (10 mL) was stirred at room temperature for 5 h. The mixture was neutralized with 36% HCl and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated to remove solvent. The resulting crystal was washed with Et_2O to give 5.07 g (98%) of **62**: mp 131–132 °C; MS *m/e* (FAB) 465 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.82 (3H, t, *J* = 7.6), 1.18–1.48 (6H, m), 2.21 (2H, quintet, *J* = 5.6), 2.30 (3H, s), 3.16 (2H, t, *J* = 7.6), 3.90 (2H, t, *J* = 5.6), 4.00 (1H, brs), 4.51 (2H, t, *J* = 5.6), 6.67–7.75 (11H, m). Anal. ($C_{26}H_{32}N_4O_4$) C, H, N.

***N*-[2-[3-(5-Carbamoyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]-6-methylphenyl]-*N'*-pentylurea (63).** To a solution of **62** (300 mg, 0.65 mmol) in CH_2Cl_2 was added thionyl chloride (0.071 mL) at 0 °C. The mixture was heated under reflux for 1 h. Then the excess reagent and solvent were removed in vacuo to give crude acid chloride.

To a solution of the above acid chloride in $CHCl_3$ was added NH_4OH (1.0 mL) at 0 °C. The reaction mixture was stirred vigorously for 30 min and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated to remove the solvent. The product was recrystallized from EtOAc to give 280 mg (93%) of **63**: mp 176–177 °C; MS *m/e* (FAB) 464 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.84 (3H, t, *J* = 7.2), 1.18–1.50 (6H, m), 2.27 (2H, quintet, *J* = 6.0), 2.30 (3H, s), 3.17 (2H, t, *J* = 7.2), 3.97 (2H, t, *J* = 6.0), 4.56 (2H, t, *J* = 6.0), 4.80 (1H, brt), 5.97 (1H, brs), 6.02 (1H, brs), 6.45 (1H, brs), 6.69–7.64 (9H, m). Anal. ($C_{26}H_{33}N_5O_3$) C, H, N.

***N*-[2-(Hydroxymethyl)-6-[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]phenyl]-*N'*-pentylurea (17):** MS *m/e* (FAB) 433 $(M - OH)^+$; ^1H NMR ($CDCl_3$) δ 0.87 (3H, t, *J* = 6.8), 1.21–1.36 (4H, m), 1.50–1.60 (2H, m), 2.18–2.25 (2H, m), 2.39 (3H, s), 3.28–3.36 (2H, m), 4.03 (2H, t, *J* = 5.6), 4.23 (2H, t, *J* = 5.6), 5.08 (2H, s), 6.59–7.65 (12H, m).

***N*-[2-Methyl-6-[3-[4-(2,4,6-trimethoxyphenyl)-1*H*-imidazol-1-yl]propoxy]phenyl]-*N'*-pentylurea (51).** MS *m/e* (FAB) 511 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.85 (3H, t, *J* = 7.2), 1.23–1.45 (6H, m), 2.28 (2H, m), 2.27 (3H, s), 3.16 (2H, q, *J* = 7.2), 3.70 (6H, s), 3.83 (3H, s), 3.99 (2H, t, *J* = 5.2), 4.20 (2H, t, *J* = 5.2), 5.25 (1H, brt), 5.75 (1H, brs), 6.17 (2H, s), 6.65–7.69 (5H, m).

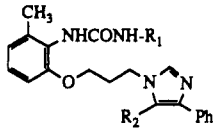
***N*-[2-Methyl-6-[3-[4-(3,4,5-trimethoxyphenyl)-1*H*-imidazol-1-yl]propoxy]phenyl]-*N'*-pentylurea (52):** MS *m/e* (FAB) 511 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.84 (3H, t, *J* = 6.8), 1.17–1.42 (6H, m), 2.18 (2H, quintet, *J* = 7.2), 2.27 (3H, s), 3.16 (2H, q, *J* = 6.8), 3.83–3.90 (2H, m), 3.85 (3H, s), 3.88 (6H, s), 4.14 (2H, t, *J* = 7.2), 4.89 (1H, brt), 6.17 (1H, brs), 6.66 (1H, dd, *J* = 8.0, 1.5), 6.84 (1H, dd, *J* = 8.0, 1.5), 6.98 (2H, s), 7.08 (1H, t, *J* = 8.0), 7.18 (1H, s), 7.49 (1H, s).

***N*-(2,2-Dimethylpropyl)-*N'*-[2-[3-(5-ethyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]-6-methylphenyl]urea (77):** MS *m/e* (FAB) 449 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.83 (9H, s), 1.88 (3H, t, *J* = 7.4), 2.11–2.20 (2H, m), 2.25 (3H, s), 2.74 (2H, q, *J* = 7.4), 2.98 (2H, d, *J* = 6.0), 3.91 (2H, t, *J* = 5.4), 4.06 (2H, t, *J* = 5.4), 5.31 (1H, brt), 6.28 (1H, brs), 6.61–7.63 (9H, m).

Route II. *N*-[2-[3-(5-Methyl-4-phenyl-1*H*-imidazol-1-yl)-propoxy]-6-nitrophenyl]-*N'*-pentylurea (10). A mixture of 2-amino-3-nitrophenol (25.0 g, 0.162 mol), **3a** (38.0 g), sodium iodide (100 mg), and potassium carbonate (24.6 g) in DMF was stirred at 60 °C for 2 h. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (benzene–acetone 2:1) to give 34.6 g (61%) of 2-[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)-propoxy]-6-nitroaniline (**79**).

To a solutioin of **79** (21.0 g, 59.5 mmol) in pyridine was added

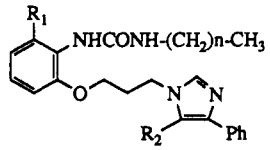
Table VI. Comparison Studies of Optimum Substituents



no.	R_2	yield[a] (route)	mp (°C)	formula[b]	ACAT inhibn: aorta[c]	ACAT inhibn: intestine[d]	cholesterol lowering[g] (%)
	$R_1 = C_5H_{11}$						
40	H	28 (I)	121–122	$C_{25}H_{32}N_4O_2$	0.31	0.25	−28
12	CH_3	47 (III)	130–134	$C_{26}H_{34}N_4O_2$	0.12	0.050	−38
53	C_2H_5	47 (I)	108–109	$C_{27}H_{36}N_4O_2$	0.079	0.17	−28
55	$CH(CH_3)_2$	29 (I)	132–134	$C_{28}H_{38}N_4O_2$	0.031	0.18	−30
56	CH_2OH	58 (I)	114–116	$C_{26}H_{34}N_4O_3$	0.20	0.21	−29
64	Cl	38 (I)	133–134	$C_{25}H_{31}N_4O_2Cl$	0.084	0.049	−41
	$R_1 = C_4H_9$						
66	H	84 (I)	102–110	$C_{24}H_{30}N_4O_2$	0.31	0.048	−7
24	CH_3	99 (III)	139–140	$C_{25}H_{32}N_4O_2$	0.48	0.073	−34
67	C_2H_5	55 (I)	114–115	$C_{26}H_{34}N_4O_2$	0.16	0.088	−46
68	$CH(CH_3)_2$	38 (I)	122–123	$C_{27}H_{36}N_4O_2$	0.012	0.13	−52
69	CH_2OH	40 (I)	128–130	$C_{25}H_{32}N_4O_3$	0.59	0.19	−21
70	Cl	54 (I)	151–155	$C_{24}H_{29}N_4O_2Cl$	0.21	0.055	−40
	$R_1 = CH_2CH_2CH(CH_3)_2$						
71	H	58 (I)	55–57	$C_{25}H_{32}N_4O_2$	0.37	0.23	−41
27	CH_3	54 (III)	127–128	$C_{26}H_{34}N_4O_2$	0.10	0.14	−59
72	C_2H_5	54 (I)	110–111	$C_{27}H_{36}N_4O_2$	0.072	0.22	−46
73	$CH(CH_3)_2$	42 (I)	136–137	$C_{28}H_{38}N_4O_2$	0.019	0.28	−40
74	CH_2OH	47 (I)	154–155	$C_{26}H_{34}N_4O_3$	0.19	0.23	−52
75	Cl	38 (I)	136–137	$C_{25}H_{31}N_4O_2Cl$	0.088	0.14	−59
	$R_1 = CH_2C(CH_3)_3$						
76	H	48 (I)	159–161	$C_{25}H_{32}N_4O_2$	0.073	0.32	−46
28	CH_3	39 (III)	150–151	$C_{26}H_{34}N_4O_2$	0.14	0.21	−64
77	C_2H_5	47 (I)	*e*	$C_{27}H_{36}N_4O_2$[f]	0.068	0.46	−55
78	Cl	51 (I)	171–172	$C_{25}H_{31}N_4O_2Cl$	0.048	0.20	−43

[a–d] See footnotes of Table I. [e] See footnote *h* of Table I. [f] See footnote *i* of Table I. [g] Compounds were administered to rats at 1 mg/kg once a day for 2 days. Cholesterol-lowering activity was expressed as a percentage of the control value ($n \geq 4$).

Table VII. Biological Activities of Selected Compounds



no.	R_1	R_2	*n*	ACAT inhibn: aorta[a]	ACAT inhibn: intestine[b]	hypocholesterolemic activity (ED_{30}, mg/kg)[c]
3	$N(CH_3)_2$	CH_3	4	0.11	0.043	1.9
67	CH_3	C_2H_5	3	0.16	0.088	0.5
68	CH_3	$CH(CH_3)_2$	3	0.012	0.13	0.4
89	CL-277082			0.90	0.18	1.5

[a] See footnote *c* of Table I. [b] See footnote *d* of Table I. [c] The values are effective dose required to decrease serum total cholesterol to 30% of the control value, calculated from dose–response curves derived from experiments with more than three doses ($n = 4$ or 5). Each compound was administered orally as a suspension in methylcellulose solution for 2 days.

phenyl chloroformate (9.32 g). The mixture was stirred at 100 °C for 3 h. The solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography (benzene–acetone 2:1) to give 19.7 g (70%) of phenyl *N*-[2-[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]-6-nitrophenyl]carbamate.

A solution of the above carbamate derivative (19.7 g, 41.7 mmol) and pentylamine (4.00 g) in toluene was heated under reflux for 1 h. The mixture was poured into 1 N NaOH solution and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The resulting solid was recrystallized from EtOAc to give 8.56 g (44%) of **10**: mp 135–136 °C; MS *m/e* (FAB) 466 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.87 (3H, t, $J = 7.2$), 1.18–1.41 (6H, m), 2.27 (2H, quintet, $J = 5.2$), 2.38 (3H, s), 3.04 (2H, q, $J = 7.2$), 4.09 (2H, t, $J = 5.2$), 4.15 (2H, t, $J = 5.2$), 6.03 (1H, brt), 6.90 (1H, brs), 6.92–7.64 (9H, m). Anal. ($C_{25}H_{31}N_5O_4$) C, H, N.

***N*-[2-Amino-6-[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]phenyl]-*N'*-pentylurea (6).** A solution of **10** (5.00 g, 10.8 mmol) in AcOH was hydrogenated over palladium on carbon at 5 kg/cm^2. The catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was neutralized with aqueous sodium hydrogen carbonate and extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The resulting solid was recrystallized from EtOAc to give 3.86 g (83%) of **6**: mp 86–87 °C; MS *m/e* (FAB) 436 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, $J = 7.2$), 1.22–1.46 (6H, m), 2.23 (2H, quintet, $J = 6.0$), 2.39 (3H, s), 3.15 (2H, q, $J = 7.2$), 3.96 (2H, t, $J = 6.0$), 4.13 (2H, t, $J = 6.0$), 5.15 (1H, brt), 5.56 (1H, brs), 6.23–7.64 (11H, m). Anal. ($C_{25}H_{33}N_5O_2$) C, H, N.

***N*-[2-[3-(5-Methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]-6-[(methylsulfonyl)amino]phenyl]-*N'*-pentylurea (7).** To a solution of **6** (500 mg, 1.15 mmol) and NEt_3 (0.32 mL) in CH_2Cl_2 was added methanesulfonic anhydride (500 mg) at −78 °C. The mixture was stirred at 0 °C for 1 h and then quenched with aqueous sodium hydrogen carbonate. The mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography (benzene–acetone 2:1) and the product was recrystallized from EtOAc–hexane to give 350 mg (59%) of **7**: mp 123–124 °C; MS *m/e* (FAB) 514 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.92 (3H, t, $J = 7.2$), 1.24–1.57 (6H, m), 2.36 (2H, quintet, $J = 4.8$), 2.38 (3H, s), 2.49 (3H, s), 3.15 (2H, q, $J = 7.2$), 4.12 (2H, t, $J = 4.8$), 4.20 (2H, t, $J = 4.8$), 5.77 (1H, brs), 6.60–7.75 (10H, m), 8.82 (1H, brs). Anal. ($C_{26}H_{35}N_5O_4S$) C, H, N.

Route III. Method E. 2-Methyl-6-[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]aniline (80b). A mixture of 3-methyl-2-nitrophenol (45.0 g, 0.29 mol), **3a** (69.0 g), potassium carbonate (81.0 g), and sodium iodide (1.00 g) in DMF was stirred at 60 °C for 2 h. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified

by silica gel column chromatography (hexane–EtOAc 1:3 and 1:5) to give 86.3 g (84%) of 3-[3-(5-methyl-4-phenyl-1H-imidazol-1-yl)propoxy]-2-nitrotoluene.

To a solution of the above compound (86.3 g, 0.25 mol) in AcOH was added zinc powder (150 g) at below 50 °C. After complete addition of the zinc powder, the mixture was stirred for 1 h. The excess reagent was filtered off and the filtrate was concentrated under reduced pressure. The residue was neutralized with 1 N NaOH and extracted with EtOAc. The separated organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (EtOAc only) to give 39.7 g (50%) of **80b**: ^{1}H-NMR ($CDCl_3$) δ 2.20 (3H, s), 2.28 (2H, q, J = 5.6), 2.39 (3H, s), 3.73 (2H, brs), 4.03 (2H, t, J = 5.6), 4.18 (2H, t, J = 5.6), 6.62–7.63 (9H, m).

Method F. *N*-[2-Methyl-6-[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]phenyl]-*N'*-pentylurea (12). A solution of **80b** (39.7 g, 0.12 mol) and pentyl isocyanate (15.4 g) in $CHCl_3$ was heated under reflux for 12 h. The solvent and excess reagent were removed in vacuo. The resulting crude solid was recrystallized from EtOAc to give 33.0 g (61%) of **12**: mp 130–134 °C; MS m/e (FAB) 435 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, t, J = 7.0), 1.19–1.46 (6H, m), 2.20 (2H, quintet, J = 5.6), 2.28 (3H, s), 2.37 (3H, s), 3.15 (2H, q, J = 7.0), 3.94 (2H, t, J = 5.6), 4.12 (2H, t, J = 5.6), 4.77 (1H, brt), 5.80 (1H, brs), 6.60–7.64 (9H, m). Anal. ($C_{26}H_{34}N_4O_2$) C, H, N.

Method G. *N*-Hexyl-*N'*-[2-methyl-6-[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]phenyl]urea (25). A solution of **80b** (2.07 g, 6.45 mmol), phenyl chloroformate (1.21 g), and Et_3N (780 mg) in chloroform was stirred at room temperature for 3 h. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with 1 N NaOH and brine, dried over $MgSO_4$, and evaporated. The residue was dissolved with toluene (10 mL) and hexylamine (720 mg), and the mixture was heated under reflux for 1 h. The mixture was poured into 1 N NaOH (20 mL) and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography (benzene–acetone 2:1) and the product was recrystallized from EtOAc to give 1.16 g (40%) of **25**: mp 139–140 °C; MS m/e (FAB) 449 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, t, J = 6.0), 1.17–1.48 (8H, m), 2.23 (2H, quintet, J = 5.6), 2.30 (3H, s), 2.39 (3H, s), 3.15 (2H, q, J = 6.0), 3.96 (2H, t, J = 5.6), 4.14 (2H, t, J = 5.6), 4.65 (1H, brt), 5.62 (1H, brs), 6.67–7.65 (9H, m). Anal. ($C_{27}H_{36}N_4O_2$) C, H, N.

Route IV. *N*-[2-Methyl-6-[[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propyl]thio]phenyl]-*N'*-pentylurea (31). A mixture of 3-chloro-2-nitrotoluene (2.45 g, 14.3 mmol), 5-methyl-4-phenyl-1-(3-propylthio)imidazole (**3t**, 3.12 g) and potassium *tert*-butoxide (1.77 g) was stirred at 50 °C for 1 h. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to remove solvent. The residue was purified by column chromatography (benzene–acetone 2:1) to give 1.64 g (31%) of 3-[[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propyl]thio]-2-nitrotoluene (**81**).

A solution of **81** (1.64 g, 4.47 mmol) in EtOAc was hydrogenated over 10% palladium on carbon (100 mg) at 1 atm for 5 h. The catalyst was filtered off and the filtrate was evaporated in vacuo to give 1.47 g (98%) of 2-methyl-6-[[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propyl]thio]aniline.

A solution of the aniline (1.45 g, 4.36 mmol) and pentyl isocyanate (740 mg) in $CHCl_3$ was heated under reflux for 10 h. The mixture was evaporated under reducing conditions to remove the excess reagent and solvent. The residue was purified by column chromatography (benzene–acetone 1:1), and the product was recrystallized from EtOAc–hexane to give 1.00 g (51%) of **31**: mp 111–113 °C; MS m/e (FAB) 451 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, J = 7.2), 1.18–1.50 (6H, m), 2.09 (2H, m), 2.30 (3H, s), 2.36 (3H, s), 2.84 (2H, t, J = 7.2), 3.18 (2H, q, J = 7.2), 4.07 (2H, t, J = 6.8), 4.46 (1H, brt), 5.90 (1H, brs), 7.08–7.77 (9H, m). Anal. ($C_{26}H_{34}N_4OS$) C, H, N.

Method H. *N*-[2-Methyl-6-[[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propyl]sulfinyl]phenyl]-*N'*-pentylurea (32). To a solution of **31** (24 mg, 0.053 mmol) in CH_2Cl_2 was added a solution of mcpba (80% purity, 12 mg) in CH_2Cl_2 at −78 °C. The mixture was stirred for 2.5 h at room temperature. The mixture was diluted with Et_2O, and 1 M sodium sulfate (5 mL) was added. The organic layer was separated and the water layer was extracted with ether. The combined organic layer was washed with sodium hydrogen carbonate and brine, dried over $MgSO_4$, and evaporated to remove solvent. The residue was purified by chromatography (CH_2Cl_2–MeOH 20:1) to give 24 mg (97%) of **32** as an oil: MS m/e (FAB) 467 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, J = 6.8), 1.20–1.50 (6H, m), 2.01 (2H, m), 2.18 (3H, s), 2.37 (3H, s), 2.83 (1H, dt, J = 13.2, 7.2), 3.02 (1H, dt, J = 13.2, 7.2), 3.15 (2H, m), 4.01 (2H, t, J = 7.2), 4.48 (1H, brt), 5.58 (1H, brs), 7.20–7.60 (9H, m).

Method I. *N*-[2-Methyl-6-[3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propyl]sulfonyl]phenyl]-*N'*-pentylurea (33). To a solution of **31** (700 mg, 1.55 mmol) in CH_2Cl_2 was added a solution of mcpba (80% purity, 540 mg) in CH_2Cl_2 at 0 °C. The mixture was stirred for 1 h at room temperature. To the mixture was added 1 M sodium sulfate (10 mL), and the organic layer was separated. The water layer was extracted with CH_2Cl_2. The combined organic layer was washed with sodium hydrogen carbonate and brine, dried over $MgSO_4$, and evaporated to remove solvent. The residue was purified by column chromatography (CH_2Cl_2–MeOH 20:1), and the product was recrystallized from EtOAc–hexane to give 560 mg (74%) of **33**: mp 45–47 °C; MS m/e (FAB) 483 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, J = 6.8), 1.18–1.52 (6H, m), 2.15 (2H, quintet, J = 7.2), 2.32 (3H, s), 2.34 (3H, s), 3.14 (2H, t, J = 7.2), 3.17 (2H, q, J = 6.8), 4.01 (2H, t, J = 7.2), 5.10 (1H, brt), 7.21–7.83 (10H, m). Anal. ($C_{26}H_{34}N_4O_3S$) C, H, N.

Route V. Method J. 3-[[2-(5-Methyl-4-phenyl-1*H*-imidazol-1-yl)ethoxy]methyl]-2-nitrotoluene (82). To a solution of 3-methyl-2-nitrobenzyl bromide (1.70 g, 7.39 mmol) and 1-(2-hydroxyethyl)-5-methyl-4-phenylimidazole (**3u**, 1.50 g) in DMF was added NaH (55% oil suspension, 390 mg) at 0 °C. The mixture was stirred at room tempertaure for 10 min, poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to remove solvent. The residue was purified by column chromatography (benzene–acetone 7:3) to give 1.40 g (54%) of **82**: ^{1}H NMR ($CDCl_3$) δ 2.17 (3H, s), 2.40 (3H, s), 3.68 (2H, t, J = 5.2), 4.09 (2H, t, J = 5.2), 4.34 (2H, s), 7.05–7.95 (9H, m).

Method K. *N*-[2-Methyl-6-[[2-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)ethoxy]methyl]phenyl]-*N'*-pentylurea (34). To a solution of **82** (1.40 g, 3.99 mmol) in AcOH was added zinc powder (5.10 g) at below 10 °C. The mixture was stirred for 30 min at room temperature. The excess reagent was filtered off and the filtrate was neutralized with saturated sodium hydrogen carbonate. The mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated to remove solvent. The residue was purified by column chromatography (benzene–acetone 7:3) to give 580 mg (45%) of 2-methyl-6-[[2-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)ethoxy]methyl]aniline.

A solution of the aniline derivative (580 mg, 1.81 mmol) and pentyl isocyanate (5.0 mL) in benzene was heated under reflux for 1.5 h. The mixture was concentrated in vacuo. The residue was purified by chromatography (acetone only), and the product was recrystallized from EtOAc–hexane to give 474 mg (60%) of **34**: mp 72–73 °C; MS m/e (FAB) 435 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, t, J = 7.6), 1.19–2.04 (6H, m), 2.16 (3H, s), 2.32 (3H, s), 3.00 (2H, q, J = 7.6), 3.68 (2H, t, J = 5.2), 4.09 (2H, t, J = 5.2), 4.34 (2H, s), 4.80 (1H, brs), 5.89 (1H, brt), 7.07–7.65 (9H, m). Anal. ($C_{26}H_{34}N_4O_2$) C, H, N.

Route VI. 3-Methyl-2-(*N'*-pentylureido)-*N*-[2-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)ethyl]benzamide (38). A solution of 3-methyl-2-nitrobenzoyl chloride (1.03 g) in $CHCl_3$ was added dropwise to a solution of 1-(2-aminoethyl)-5-methyl-4-phenylimidazole (**3w**, 1.03 g, 5.12 mmol) and NEt_3 (620 mg) in $CHCl_3$ at 0 °C. The mixture was stirred at room temperature for 1 h and poured into water. The mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography (benzene–acetone 1:2) to give 1.31 g (70%) of 3-methyl-2-nitro-*N*-[2-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)ethyl]benzamide (**84**).

A solution of **84** (1.31 g, 3.60 mmol) in THF–EtOH was hydrogenated over 10% palladium on carbon at 5 kg/cm^2 for 3 h. The catalyst was filtered off and the filtrate was evaporated

in vacuo to give 1.25 g (100%) of 2-amino-3-methyl-*N*-[2-(5-methyl-4-phenyl-1*H*-imidazol-1-yl]benzamide.

A mixture of the benzamide derivative (1.25 g, 3.74 mmol) and pentyl isocyanate (630 mg) in $CHCl_3$ was refluxed for 5 h. The excess pentyl isocyanate and solvent were removed under reduced pressure. The residue was purified by column chromatography (benzene–acetone 1:1), and the product was recrystallized from EtOAc–hexane to give 750 mg (45%) of **38**: mp 179–180 °C; MS *m/e* (FAB) 448 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, J = 6.8), 1.16–1.41 (6H, m), 2.17 (3H, s), 2.34 (3H, s), 3.06 (2H, q, J = 6.8), 3.51 (2H, q, J = 6.0), 4.03 (2H, t, J = 6.0), 5.27 (1H, brt), 7.09–7.58 (9H, m), 7.72 (1H, brs), 7.79 (1H, brt). Anal. ($C_{26}H_{33}N_5O_2$) C, H, N.

Route VII. *N*-[2-[2-Hydroxy-3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]-6-methylphenyl]-*N'*-pentylurea (39). A suspension of 3-methyl-2-nitrophenol (20.0 g, 131 mmol), epibromohydrin (20.0 g), and potassium carbonate (20.0 g) in THF–DMF was stirred at room temperature for 2 h. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to remove the solvent. The crude oil was used without further purification.

A solution of 5-methyl-4-phenylimidazole (7.60 g, 47.8 mmol) in DMF was added dropwise to a suspension of NaH (55% oil suspension, 2.1 g) in DMF at 0 °C. The mixture was stirred at 60 °C for 1 h. The above crude oil (10.0 g, 47.8 mmol) was added to it at room temperature. The mixture was stirred at 60 °C for 2 h and poured into water. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to remove solvent. The residue was purified by column chromatography (EtOAc only) to give 3.29 g (19%) of 3-[2-hydroxy-3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]-2-nitrotoluene (**85**).

A solution of **85** (3.20 g, 8.72 mmol) in EtOAc was hydrogenated over 10% palladium on carbon. The catalyst was filtered off and the filtrate was evaporated to give crude 2-[2-hydroxy-3-(5-methyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]-6-methylaniline.

A solution of the aniline derivative (2.10 g, 6.23 mmol) and pentyl isocyanate (1.06 g) in MeOH–$CHCl_3$ was heated under reflux for 3 h. The excess reagent and solvent were removed. The resulting solid was recrystallized from EtOAc to give 2.41 g (86%) of **39**: mp 182–184 °C; MS *m/e* (FAB) 451 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, J = 6.8), 1.20–1.50 (6H, m), 2.30 (3H, s), 2.39 (3H, s), 3.18 (2H, m), 3.86 (1H, m), 4.10 (4H, m), 6.70–7.60 (12H, m). Anal. ($C_{26}H_{34}N_4O_3$) C, H, N.

Route VIII. *N*-Butyl-*N'*-[2-[3-(5-ethyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]-6-methylphenyl]urea (67). A mixture of 3-methyl-2-nitrophenol (50.0 g, 0.327 mol), 1-bromo-3-chloropropane (51.5 g), and potassium carbonate (90.3 g) in DMF was stirred at 60 °C for 2 h to conduct a reaction. After the completion of the reaction, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give 73.8 g (98%) of 3-(3-chloropropoxy)-2-nitrotoluene (**86**).

A mixture of **86** (63.8 g, 0.278 mol), sodium diformylamide (31.7 g), and sodium iodide (4.17 g) in DMF was stirred at 100 °C for 1 h. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to remove the solvent. The resulting solid was recrystallized from EtOH to give 66.8 g (90%) of 3-[3-(diformylamino)propoxy]-2-nitrotoluene.

The product was dissolved in EtOH followed by the addition of potassium hydroxide (300 mg). The mixture was stirred at room temperature for 10 minutes. The reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to remove the solvent. The obtained product was washed with ether and hexane to give 51.2 g (86%) of 3-(3-formamidopropoxy)-2-nitrotoluene (**87**).

A solution of **87** (20.0 g, 84.0 mmol) in DMF was added to a suspension of NaH (55% oil suspension, 3.67 g) in DMF, and the mixture was stirred under heating at 60 °C for 1 h. The mixture was dripped into a solution of 2-bromobutyrophenone (19.1 g, 84.0 mmol) in DMF over a period of 1 h. After the completion of the dropping, the mixture was stirred for 1 h and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give a crude oil. The obtained oil was added dropwise to a mixture of ammonium formate (6.65 g), formic acid (1.60 g), and formamide (2.1 g) at 120 °C. The mixture was stirred at 120 °C for 2 h. Then the mixture was cooled to room temperature, and ether and water were added to it. The obtained mixture was vigorously stirred for 15 min and allowed to stand at 0 °C for 1 h. The resulting precipitate was collected and washed with water and ether to give 8.20 g (27%) of 3-[3-(5-ethyl-4-phenyl-1*H*-imidazol-1-yl)-propoxy]-2-nitrotoluene (**88b**).

A solution of **88b** (8.20 g, 22.4 mmol) in EtOAc and EtOH was hydrogenated over 10% palladium on carbon for 3 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give 6.36 g (85%) of 2-[3-(5-ethyl-4-phenyl-1*H*-imidazol-1-yl)propoxy]-6-methylaniline.

A solution of the aniline derivative (6.36 g, 17.4 mmol) and butyl isocyanate (1.90 g) in $CHCl_3$ was heated under reflux for 12 h. The excess reagent and solvent were removed in vacuo. The resulting solid was recrystallized from EtOAc–hexane to give 8.20 g (99%) of **67**: mp 114–115 °C; MS *m/e* (FAB) 435 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.84 (3H, t, J = 7.2), 1.17–1.29 (2H, m), 1.19 (3H, t, J = 7.4), 1.34–1.41 (2H, m), 2.09–2.16 (2H, m), 2.22 (3H, s), 2.74 (2H, q, J = 7.6), 3.10–3.16 (2H, m), 3.88 (2H, t, J = 5.4), 4.04 (2H, t, J = 6.6), 5.31 (1H, brt), 6.42 (1H, brs), 6.62 (1H, d, J = 7.6), 6.79 (1H, d, J = 7.6), 7.02 (1H, t, J = 7.6), 7.20–7.62 (6H, m). Anal. ($C_{26}H_{34}N_4O_2$) C, H, N.

Assay of ACAT Activity. The intestinal microsomes were prepared according to the method of Field et al.[24] Briefly, the intestinal mucosa of an NZW rabbit was homogenized in a buffered sucrose solution (0.1 N sucrose, 0.05 M KCl, 0.04 M KH_2PO_4, 0.03 M ETDA, pH 7.4) in a glass Dounce homogenizer. The whole homogenate was spun at 10000*g* for 20 min at 4 °C. The resulting supernatant was centrifuged at 105000*g* for 1 h at 4 °C. The microsomal pellet thus obtained was rehomogenized in cold buffered sucrose solution and used as intestinal ACAT.

Arterial ACAT was prepared as follows. The aortae of cholesterol-fed NZW rabbits were homogenized in 154 mM potassium phosphate buffer (pH 7.4) containing 2.4 mg/mL BSA. The whole homogenate was spun at 300*g* for 5 min to remove cellular debris. The resulting supernatant was used as arterial ACAT.

ACAT activity was determined essentially by the method described by Heider et al.[6] Endogenous cholesterol (of microsomal fraction or homogenate) and exogenous [1-^{14}C]oleoyl-CoA were used as the substrates. The reaction mixture for intestinal ACAT consisted of 250 μL of K_2HPO_4 buffer (pH 7.4) containing 2.4 mg/mL BSA and 40 μM [1-^{14}C]oleoyl-CoA, and the reaction mixture for arterial ACAT consisted of 250 μL of the same buffer containing 2.4 mg/mL BSA and 5 μM [1-^{14}C]oleoyl-CoA. Then, 30 μL of test compound solution was added, and the mixture was preincubated at 37 °C for 3 min before the addition of 20 μL of the enzyme (8 mg of protein/mL). The reaction mixture was incubated for a certain time (5 min for aorta and 2 min for intestine), and then the reaction was terminated by the addition of 3 mL of chloroform–methanol (2:1; v/v) and 500 μL of 0.04 N HCl. After shaking, the chloroform phase was taken to dryness and the residue was separated by thin-layer chromatography on plastic sheets (TLC plastic sheets, silica gel 60, Merck Co.) using heptane–diethyl ether–acetic acid (90:30:1; v/v/v). Cholesteryl oleate was visualized with iodine vapor, and the cholesterol ester zone was cut out and placed directly in a scintillation vial for counting. The values are expressed as IC_{50} values. Calculation of IC_{50} values was performed with data from triplicate assay tubes at each drug concentration.

Serum Cholesterol Level. Male Sprague–Dawley rats (5-weeks-old) were fed a standard rat chow, MF (oriental Yeast Co., Ltd., Tokyo, Japan), containing 1% cholesterol and 0.5% cholic acid. At the same time, the drug suspended in methylcellulose was administered orally once a day. Rats were starved for 5 h after the last administration and bled via the abdominal aorta while under ether anesthesia. Serum concentration of total cholesterol was determined enzymatically using the Iatrolipo TC kit (Iatron Lab, Tokyo, Japan). After the last day of the test, the control rat serum cholesterol levels were in the range of 180–230 mg/dL, while the normal rat serum cholesterol levels were in the range of 50–60 mg/dL. The values shown in Tables I–VI are expressed as percentage of control value, while the values

shown in Table VII are ED_{30} (mg/kg). The values of ED_{30} were calculated from the dose–response curve derived from experiments with at least three doses (n = 4 or 5).

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References

(1) Suckling, K. E.; Stange, E. F. Role of Acyl-CoA:Cholesterol Acyltransferase in Cellular Cholesterol Metabolism. *J. Lipid Res.* **1985**, *26*, 647–671.
(2) Brown, M. S.; Goldstein, J. L. Lipoprotein Metabolism in the Macrophage: Implications for Cholesterol Deposition in Atherosclerosis. *Annu. Rev. Biochem.* **1983**, *52*, 223–261.
(3) Bell, F. P.; Schaub, R. G. Chlorpromazine Inhibits Arterial ACAT and Reduces Arterial Cholesterol and Cholesteryl Ester Accumulation in Cholesterol-Fed Rabbits. *Arteriosclerosis* **1986**, *6*, 42–49.
(4) Helgerud, P.; Saarem, K.; Norum, K. R. Acyl-CoA:Cholesterol Acyltransferase in Human Small Intestine: Its Activity and Some Properties of the Enzyme Reaction. *J. Lipid Res.* **1981**, *22*, 271–277.
(5) 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.
(6) Heider, J. G.; Pickens, C. E.; Kelly, L. A. Role of Acyl CoA: Cholesterol Acyltransferase in Cholesterol Absorption and Its Inhibition by 57-118 in the Rabbit. *J. Lipid Res.* **1983**, *24*, 1127–1134.
(7) Gammill, R. B.; Bell, F. P.; Bell, L. T.; Bisaha, S. N.; Wilson, G. J. Antiatherosclerotic Agents. A Structurally Novel Bivalent Inhibitor of AcylCoA:Cholesterol O-Acyltransferase with Systemic Activity. *J. Med. Chem.* **1990**, *33*, 2685–2687.
(8) Rucker, W.; Prop, G.; Huther, A. M. Antiatherosclerotic and Antihyperlipidemic Effects of Octimibate Sodium in Rabbits. *Atherosclerosis* **1988**, *69*, 155–162.
(9) DeVries, V. G.; Schaffer, S. A.; Largis, E. E.; Dutia, M. D.; Wang, C.; Bloom, J. D.; Katocs, A. S. Potential Antiatherosclerotic Agents. 5. An Acyl-CoA:Cholesterol O-Actyltransferase Inhibitor with Hypocholesterolemic Activity. *J. Med. Chem.* **1986**, *29*, 1131–1133.
(10) Sliskovic, D. R.; White, A. D. Therapeutic Potential of ACAT Inhibitors as Lipid Lowering and Anti-atherosclerotic Agents. *Trends Pharmacol. Sci.* **1991**, *12*, 194–199.
(11) Bocan, T. M. A.; Mueller, S. B.; Uhlendorf, P. D.; Newton, R. S.; Krause, B. R. Comparison of CI-976, an ACAT Inhibitor, and Selected Lipid-Lowering Agents for Antiatherosclerotic Activity in Iliac-Femoral and Thoracic Aortic Lesions. *Arterioscler. Thromb.* **1991**, *11*, 1830–1843.
(12) Kimura, T.; Takase, Y.; Hayashi, K.; Tanaka, H.; Ohtsuka, I.; Kogushi, M.; Fujimori, T.; Saitou, I.; Akasaka, K. *J. Med. Chem.*, preceding paper in this issue.
(13) Bredereck, H.; Theilig, G. *Ber. Dtsch. Chem. Ges.* **1953**, *86*, 88–96.
(14) Gante, J.; Kurmeier, H. A. Pharmacologically Active Basically Substituted Phenyl Ether(s). DE-2842759, 1980.
(15) Furukawa, Y.; Kishimoto, S.; Nishikawa, K. 1,2-Disubstituted-4-halo-5-carboxymethyl-imidazole Derivatives. JP-56071074, 1981.
(16) Yinglin, H.; Hongwen, H. A Convenient Synthesis of Primary Amines Using Sodium Diformylamide as a Modified Gabriel Reagent. *Synthesis* **1990**, 122–124.
(17) Kim, C. S.; Lee, K. J.; Kim, H. S.; Chae, Y. B. Synthesis of 4(5)-Hydroxymethylimidazoles by Hydroxymethylation and Decarboxylation of Imidazole-4(5)-carboxylic acids. *Heterocycl. Chem.* **1983**, *20*, 1417–1418.
(18) Kinnunen, P. M.; DeMichele, A.; Lange, L. G. Chemical Modification of Acyl-CoA:Cholesterol O-Acyltransferase. 1. Identification of Acyl-CoA:Cholesterol O-Acyltransferase Subtypes by Differential Diethyl Pyrocarbonate Sensitivity. *Biochemistry* **1988**, *27*, 7344–7350.
(19) Leo, A. The Octanol-Water Partition Coefficient of Aromatic Solutes: the Effect of Electronic Interactions, Alkyl Chains, Hydrogen Bonds, and *ortho*-Substitution. *J. Chem. Soc. Perkin Trans. 2* **1983**, 825–838.
(20) Verloop, A.; Hoogenstraaten, M.; Tipker, J. *Drug Design*; Ariens, E. J., Ed.; Academic Press: New York, 1976; Vol. VII, pp 180–185.
(21) Exner, O. *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978; Chapter 10.
(22) Nose, K.; et al. After oral administration of test compounds (30 mg/kg) to male Sprague–Dawley rats (n = 2), C_{max} (ng/mL) values were measured and expressed as the mean value from two experiments. The C_{max} values of compounds **10**, **12**, **21**, **22**, **23**, **24**, **25**, **54**, **65**, **67**, and **68** were 385, 521, <30, <30, <30, 690, <30, <30, <30, 1657, and 1834 ng/mL, respectively (unpublished results).
(23) Tanaka, H.; Ohtsuka, I.; Kogushi, M.; Kimura, T.; Hayashi, K.; Saeki, T.; Saitou, I.; Yamatsu, I. Effect of A Novel ACAT Inhibitor (E5324) on Experimental Atherosclerosis in Rabbits. *Abstracts of the XI International Symposium on Drugs Affecting Lipid Metabolism.* Florence, Italy, May 13–16, 1992.
(24) Field, F. J.; Mathur, S. N. β-Sitosterol: Esterification by Intestinal Acylcoenzyme A:Cholesterol Acyltransferase (ACAT) and Its Effect on Cholesterol Esterification. *J. Lipid Res.* **1983**, *24*, 409–417.