Articles

Design, Synthesis, and Structure–Activity Relationship Studies for a New Imidazole Series of J774 Macrophage Specific Acyl-CoA:Cholesterol Acyltransferase (ACAT) Inhibitors

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Acyl-CoA:cholesterol acyltransferase (ACAT) is the primary enzyme involved in intracellular cholesterol esterification. Arterial wall infiltration by macrophages and subsequent uncontrolled esterification of cholesterol leading to foam cell formation is believed to be an important process which leads to the development of fatty streaks. Inhibitors of the ACAT enzyme may retard this atherogenic process. We have recently discovered a series of imidazoles which are potent *in vitro* ACAT inhibitors in the J774 macrophage cell culture assay. This paper will describe the design, synthesis, and structure–activity relationship for this very potent series of compounds.

Introduction

Hypercholesterolemia is an established risk factor in the development of atherosclerosis.[1] Dietary cholesterol can increase the level of serum cholesterol to levels which place an individual at increased risk for the development or exacerbation of atherosclerosis. Therapeutic agents which control the level of serum cholesterol have proven to be an effective treatment for coronary artery disease.[2] Since much of the cholesterol absorbed by intestinal mucosal cells is esterified by acyl-CoA:cholesterol acyltransferase (ACAT) prior to its incorporation and secretion into the bloodstream, inhibitors of ACAT can limit the absorption of dietary cholesterol.[3] In addition to the role of cholesterol ester in cholesterol absorption, the deposition of cholesterol ester in the arterial wall is believed to be an important process in the development of atherosclerosis. Much of the accumulation is in lipid rich macrophages (foam cells) formed through increased ACAT esterification in infiltrating macrophages.[4] Inhibition of the ACAT enzyme at the intestinal wall and/or the arterial wall may retard this atherogenic process or even reverse existing atherosclerosis.

A series of diarylimidazoles that inhibit ACAT was discovered in these labs.[5] The lead compound, DuP 128 (**1**), has been shown to be a potent *in vitro* inhibitor of hepatic ACAT and an effective agent in lowering serum cholesterol levels in several cholesterol-fed animal models but had limited efficacy in initial human studies.[6] Although **1** is an intestinally active ACAT inhibitor, limited bioavailability and decreased potency against macrophage ACAT suggest it would not be an effective systemic therapeutic agent. Therefore the goal of this program was to further elaborate the core structure of **1**, to develop a bioavailable, arterial active ACAT inhibitor. Prior investigations suggest that liver/intestinal ACAT may not be identical with arterial ACAT, and two putative ACAT proteins dissimilar in amino acid composition have recently been isolated.[6c-e] Because of this, ACAT inhibition was tested both in a hepatic microsomal assay and in a J774 macrophage cell culture assay.

This paper will detail the preparation of a series of substituted diarylimidazole compounds which have been found to be specific, very potent *in vitro* ACAT J774 macrophage cell inhibitors. The initial design concept of this series was to explore the substitution effect on the imidazole, particularly to optimize the aromatic substituent. It was believed that these groups would have a large effect on parameters such as basicity of the imidazole group, spatial conformation of the aromatic rings, and site specific interactions with the binding pocket. Any of these might prove important for macrophage cell ACAT inhibition.

A second design approach was to vary the structural elements within the alkyl chains of compound **1**. Earlier work[5] established the optimal tether lengths for the internal methylene chain connecting the sulfide and the urea to be five carbons and for the outer alkyl chain on the urea nitrogen atom to be seven carbons. Substitution on the carbon chains was considered, but early compounds with this feature were not particularly potent. Instead, carbon atoms in these chains were replaced with oxygen and nitrogen atoms. It was reasoned that this would not greatly affect the length or conformation of the chains but might change the physical properties of the molecule such as lipophilicity and pK_a, which in turn may alter the macrophage ACAT inhibitory potency.

Chemistry

Many of the compounds in this work were prepared (Scheme 1) by reaction of heptylamine with γ-valerolactone in refluxing toluene to give 5-hydroxypentanamide **2** as crystalline white plates. The 5-hydroxypentanamide **2** was reduced with lithium aluminum hydride

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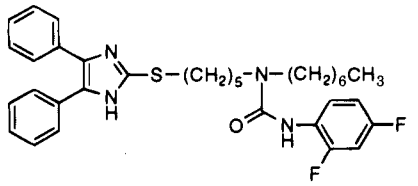
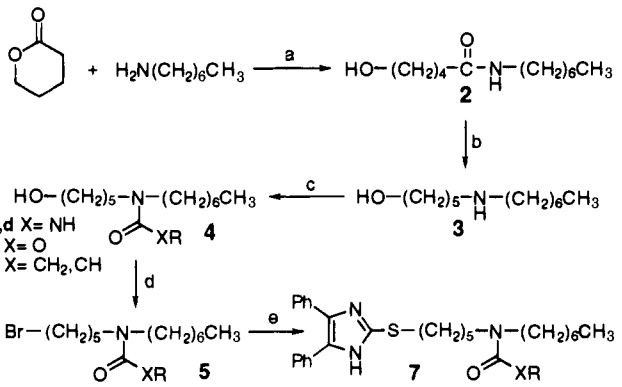


Figure 1. DuP 128 (1).

Scheme 1[a]



[a] Reagents: (a) toluene, reflux (99%); (b) $LiAlH_4$, THF (90%); (c) isocyanate, acid chloride or chloroformate, CH_2Cl_2; (d) $(C_6H_5)_3P$, CBr_4, CH_2Cl_2; (e) **6**, NaH, DMF (75%).

in refluxing tetrahydrofuran to give the 5-hydroxypentylamine **3** as a white crystalline powder. This 5-hydroxypentylamine **3** was reacted with an appropriately substituted isocyanate, chloroformate, or acid chloride in methylene chloride to give the 5-hydroxypentylureas **4a,d**, where X is NH, 5-hydroxypentyl carbamate **4b**, where X is O, and 5-hydroxypentylamide **4c**, where X is CH_2 or CH, respectively.

The hydroxy compound **4** was converted to the bromide by treatment with carbon tetrabromide and triphenylphosphine in methylene chloride to give the key intermediate **5**. The final product **7** was produced by the reaction of the sodium salt of the 4,5-disubstituted-2-mercaptoimidazole **6**, generated with sodium hydride in *N,N*-dimethylformamide, with the bromo intermediate **5**.

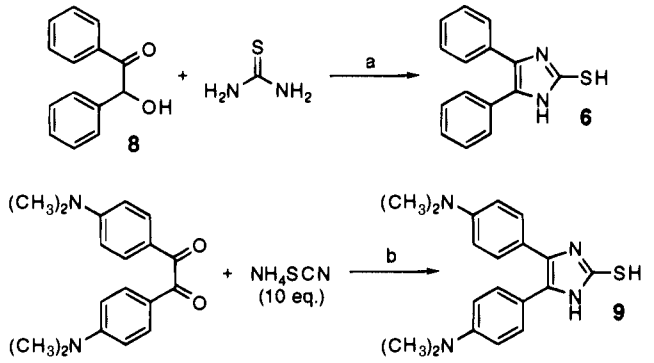
The 4,5-disubstituted-2-mercaptoimidazoles were prepared by classical chemistry,[7] condensing the α-hydroxy ketone[8] **8** with thiourea or ammonium thiocyanate in *N,N*-dimethylformamide or hexanol. An improved procedure for the synthesis of 4,5-bis[4-(*N,N*-dimethylamino)phenyl]-2-mercaptoimidazole (**9**) used 4,4′-bis(dimethylamino)benzil (Kodak) with 10 equiv of ammonium thiocyanate in hexanol at 160 °C to give imidazole **9**. The 4,5-disubstituted-imidazole compounds **10**–**33** shown in Tables 1–6 were synthesized *via* a synthetic sequence analogous to that shown in Schemes 1 and 2.

Preparation of compounds with an ether linkage in the "inner" chain (connecting the imidazole sulfide and the urea groups) began with the acylation of a commercially available hydroxyalkoxyamine to give amide **34** (Scheme 3). Reduction to amine **35**, functionalization to **36**, conversion to bromide **37**, and imidazolethiol *S*-alkylation proceeded analogously to the previous series.

Compounds with an ether linkage in the "outer" chain off of the urea (*e.g.*, the heptyl group in **1**) were prepared in the manner outlined in Scheme 4. Various functionalized alcohols **42** were converted first to bromides **43** using PBr_3 and then to azides **44** by the action of NaN_3 in DMF. The azides were then reduced by the Staudinger method,[9] involving treatment with triphenylphosphine and hydrolysis of the phosphine imine intermediate. The resulting amines **45** were acylated with 5-bromovaleryl chloride to give bromo amides **46**. The imidazole groups were introduced by *S*-alkylation of the imidazolethiols in the usual manner to give amides **47**. Reduction to the amines **48** was best accomplished by the use of sodium bis(methoxyethoxy)aluminum hydride (Red-Al), which facilitated removal of aluminum salts from the product. In this case, amine functionalization to compounds **49**–**60** was performed as the final step.

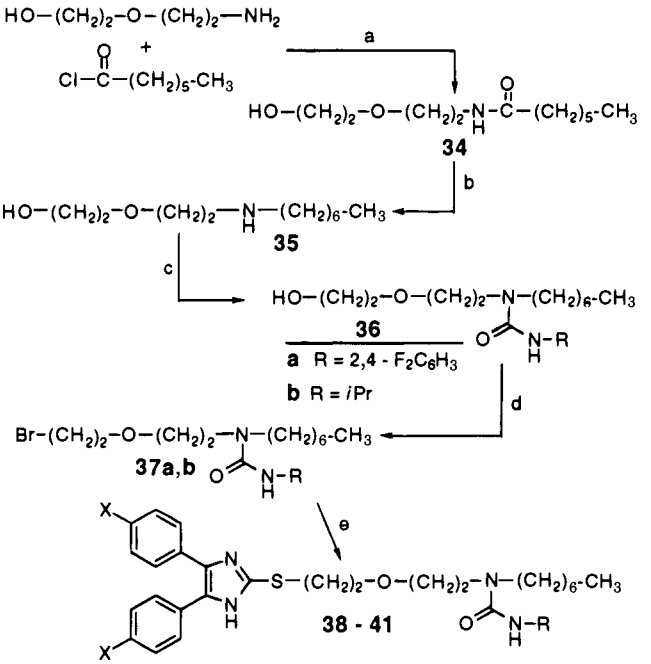
Amine groups in the outer chain could be introduced by the procedure shown in Scheme 5. Carboxylic acids of structure **63** were prepared in the manner of Higley *et al.*[5] They could be coupled to various diamines using dicyclohexylcarbodiimide (DCC) with 1-hydroxybenzotriazole hydrate (HOBT) as a catalyst according to the method of Windridge and Jorgensen.[10] Reduction of the amides **64** to the amines **65**, followed by conversion to the final products **66**–**69**, proceeded as described earlier.

Scheme 2[a]



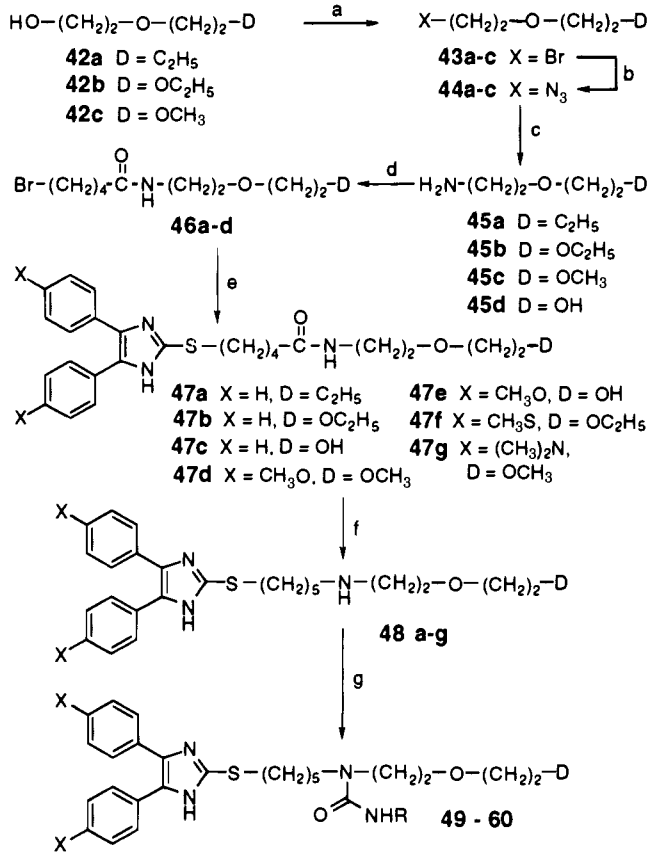
[a] Reagents: (a) *n*-hexanol, DMF, 160 °C; (b) *n*-hexanol, 160 °C.

Scheme 3[a]



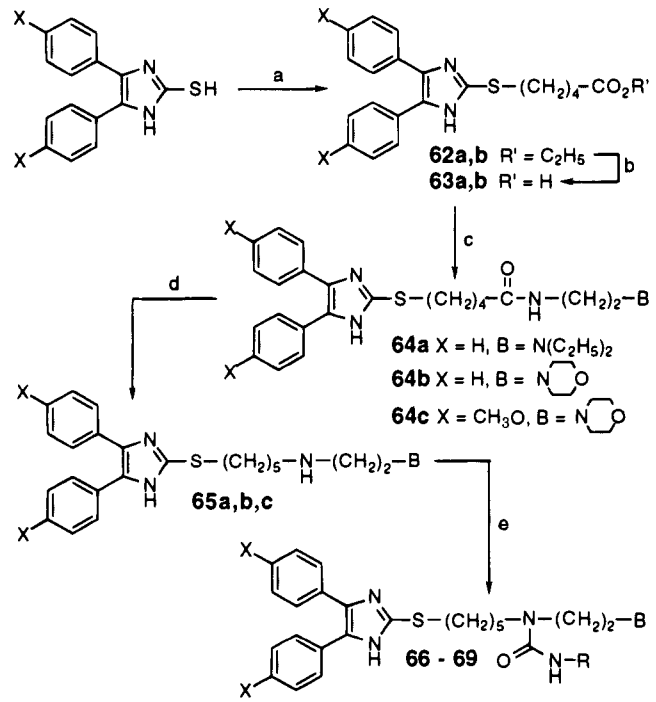
[a] Reagents: (a) Et_3N; (b) $LiAlH_4$; (c) R–N=C=O; (d) CBr_4, Ph_3P; (e) 4,5-diaryl-1*H*-imidazole-2-thiol, K_2CO_3, cat. Bu_4NI.

Scheme 4[a]



[a] Reagents: (a) PBr_3, cat. pyridine; (b) NaN_3; (c) Ph_3P, H_2O; (d) 5-bromovaleryl chloride, Et_3N; (e) 4,5-diaryl-1*H*-imidazole-2-thiol, K_2CO_3, cat. Bu_4NI; (f) Red-Al; (g) R–N=C=O.

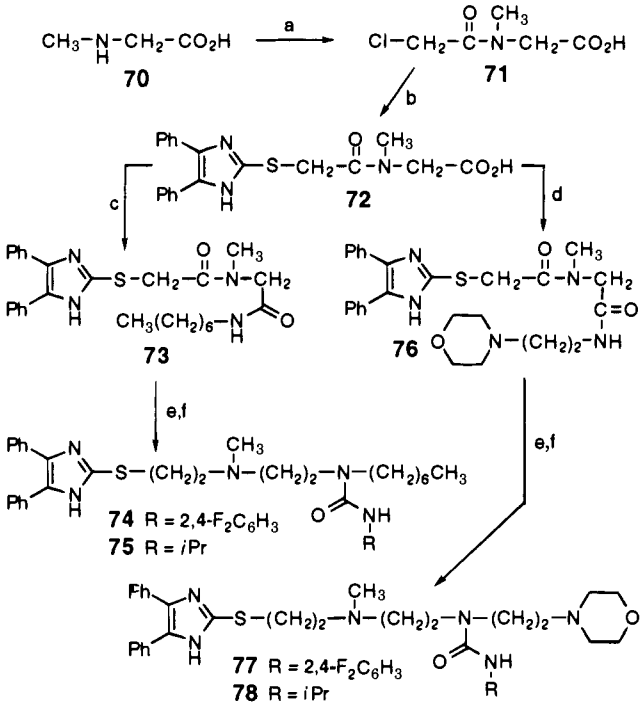
Scheme 5[a]



[a] Reagents: (a) ethyl bromovalerate, K_2CO_3, cat. Bu_4NI; (b) NaOH; (c) B-$(CH_2)_2NH_2$, DCC, HOBT; (d) Red-Al; (e) R–N=C=O.

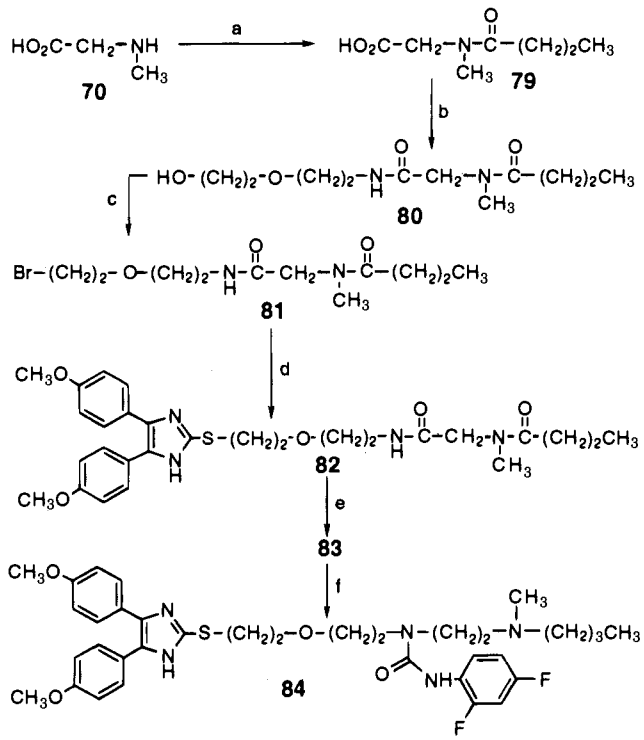
The synthesis of compounds with a nitrogen atom in the inner chain (Scheme 6) began with the acylation of sarcosine (**70**), and thiol alkylation of the resulting chloride **71** gave acid **72**. This could be coupled (DCC/HOBT) to various amines to give dipeptides **73** and **76**. Reduction/functionalization gave the final products **74**, **75**, **77**, and **78**. Sarcosine was also used as the starting material for compound **84** (Scheme 7), which contains both an ether and an amine linkage.

Scheme 6[a]



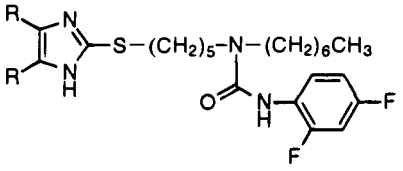
[a] Reagents: (a) chloroacetyl chloride, NaOH; (b) **6**, K_2CO_3; (c) heptylamine, DCC, HOBT; (d) 4-(2-aminoethyl)morpholine, DCC, HOBT; (e) Red-Al; (f) R–N=C=O.

Scheme 7[a]



[a] Reagents: (a) butyryl chloride, Et_3N; (b) 2-(2-aminoethoxy)-ethanol, DCC, HOBT; (c) Ph_3P, CBr_4; (d) 4,5-bis(4-methoxyphenyl)-1*H*-imidazole-2-thiol, K_2CO_3, cat. Bu_4NI; (e) Red-Al; (f) 2,4-difluorophenyl isocyanate.

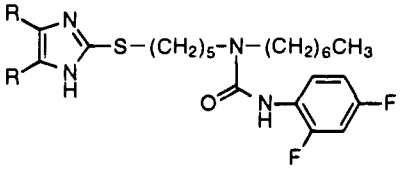
Table 1. Effect on *in Vitro* ACAT and J774 Inhibition by Dialkylimidazole



no.	R	IC_{50}, μM ACAT[a]	IC_{50}, μM J774[b]
1	C_6H_5	0.010	1.0
10	$CH_3(CH_2)_2$	0.06	2.70
11	$(CH_3)_2CH$	0.02	0.64
12	c-C_6H_{11}	0.02	0.64

[a] *In vitro* rat liver microsomal ACAT inhibition IC_{50}, μM. [b] *In vitro* J774 macrophage cell culture ACAT inhibition IC_{50}, μM.

Table 2. Effect on *in Vitro* ACAT and J774 Inhibition by Diheterocycleimidazole



no.	R	IC_{50}, μM ACAT	IC_{50}, μM J774
13	2-thienyl	0.06	0.94
14	2-furanyl	0.20	0.45
15	2-pyridyl	1.0	2.25

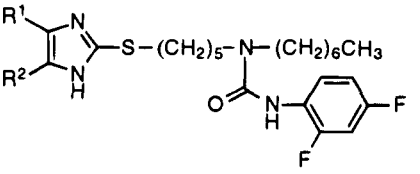
Pharmacological Results and Discussion

The substituted imidazoles were evaluated in an ACAT rat liver microsome radioassay[11] and a J774 macrophage cell culture assay[12] previously described.[5] The *in vitro* ACAT assay assesses the intrinsic inhibitory potency against the hepatic enzyme. The J774 macrophage assay assesses inhibition against the target cells of systemic antiatherosclerotic agents. A whole cell assay aids in identifying compounds with enhanced cellular uptake or which are more active against macrophage ACAT if isozymes or different ancillary proteins exist. Therefore, results from the *in vitro* macrophage assay were used to direct compound design.

The *in vitro* results have shown that the 4,5-diphenyl groups on the imidazole can be replaced (Table 1) with simpler alkyl groups, such as *n*-propyl for compound **10**, isopropyl for **11**, or cyclohexyl for **12**, with only a modest 2–6-fold loss of *in vitro* ACAT activity and a slight improvement in the *in vitro* J774 macrophage IC_{50} in the case of the branched alkyl groups (*i.e.*, isopropyl and cyclohexyl). The 4,5-diphenyl groups on the imidazole can be replaced with heterocycles (Table 2) such as the 2-thienyl compound **13** or 2-furanyl **14** with only a modest loss in the *in vitro* ACAT activity and a slight improvement in the *in vitro* J774 macrophage assay. The 2-pyridyl compound **15** was found to be significantly less active than the lead compound **1** in both the *in vitro* ACAT and J774 macrophage assays.

In an attempt to explore the orientation of the phenyl rings relative to the plane of the imidazole ring, several compounds in which the phenyl rings are linked together (Table 3) were synthesized. These analogues were designed to restrict the rotation of the phenyl groups by varying the connecting chain length and thus

Table 3. *In Vitro* ACAT and J774 Inhibition by Conformationally Restricted Diphenylimidazoles



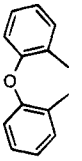
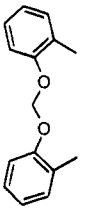
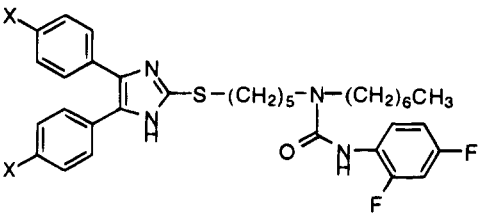
no.	R^1, R^2	IC_{50}, μM ACAT	IC_{50}, μM J774
16		0.06	1.72
17		0.03	0.84

Table 4. Effect on *in Vitro* ACAT and J774 Inhibition by Substitution on the Diphenylimidazole

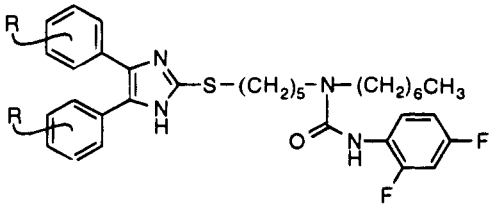


no.	X	IC_{50}, μM ACAT	IC_{50}, μM J774
18	CF_3	39.9	25.0
19	CH_3	0.08	0.29
20	F	0.04	3.50
21	OCH_3	0.14	0.08
22	OH	2.4	4.75
23	$N(CH_3)_2$	0.05	0.08
24	SCH_3	0.07	0.05
25	SO_2CH_3	>50	2.02

the out-of-plane dihedral angle. The ether-bridged compound **16**, which holds the rings to a nearly coplanar configuration, had reduced activity in both the *in vitro* ACAT and J774 macrophage assays. To our surprise, X-ray analysis of the longer methylenedioxy-bridged system **17** revealed that the phenyl rings adopt a parallel propeller orientation with the bridging methylene lying in the plane of the imidazole. The phenyl ring to imidazole ring dihedral angles are 24.4° and 24.5°, very similar to the orientation found for the phenyl rings in compound **1**.

Substitution on the phenyl rings with a variety of electron-withdrawing and -donating groups gave us a series of compounds with dramatic differences in biological activity (Table 4). It was found that strong electron-withdrawing groups, as in 4,5-bis[4-(trifluoromethyl)phenyl]imidazole **18**, are not tolerated, with a 500-fold loss in the *in vitro* ACAT activity and a 86-fold loss in the *in vitro* J774 macrophage activity, compared to the 4,5-bis(4-methylphenyl)imidazole analogue **19**. The 4,5-bis(4-fluorophenyl)imidazole **20** is

Table 5. *In Vitro* ACAT and J774 Inhibition by Regioisomers of 4,5-Bis(Methoxyphenyl)imidazole



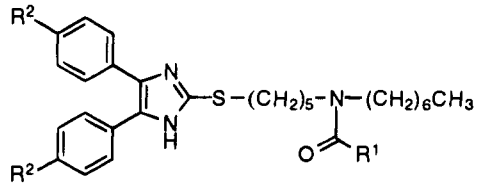
no.	R	IC_{50}, μM ACAT	J774
21	4-OCH_3	0.14	0.08
26	3-OCH_3	0.04	0.36
27	2-OCH_3	0.35	2.07

about 4-fold less active in both the *in vitro* ACAT and *in vitro* J774 macrophage assays compared to **1**. Electron-donating groups, such as methoxy in the 4,5-bis-(4-methoxyphenyl)imidazole **21**, gave a 14-fold loss in the *in vitro* ACAT assay but a 12-fold improvement in the *in vitro* J774 macrophage assay as compared to **1**. The 4,5-bis(4-methoxyphenyl)imidazole **21** is preferred over the 4,5-bis(4-hydroxyphenyl)imidazole **22** which is significantly less potent. The preferred substitution was found to be the electron-donating groups of 4,5-bis[4-(*N*,*N*-dimethylamino)phenyl]imidazole **23**, for which was seen a 4-fold loss in the *in vitro* ACAT activity as compared to **1** but again an improved *in vitro* J774 macrophage activity equivalent to the 4,5-bis(4-methoxyphenyl)imidazole compound **21**. The methylthio groups of compound **24** have an effect similar to the other analogues bearing electron-donating substituents (*i.e.*, **21** and **23**). Oxidation of the sulfide groups to sulfones (as in **25**) eliminates *in vitro* ACAT activity and significantly reduces the *in vitro* J774 activity. It appears that any substitution on the phenyl ring decreases the intrinsic enzyme inhibition potency. Strong electron-withdrawing groups as in **18** dramatically decrease potency in both assays, but electron-donating groups only marginally decrease intrinsic enzyme potency while having a significant effect on inhibition of whole cell intracellular ACAT. It appears that aprotic electron-donating groups provide the best balance of intrinsic hepatic potency and whole cell macrophage activity.

The positional preference for substitution on the phenyl groups was investigated using the *o*-, *m*-, and *p*-methoxyphenyl analogues (Table 5). The 4,5-bis(3-methoxyphenyl)imidazole analogue **26** was slightly better in the *in vitro* ACAT but 5-fold less active in the J774 macrophage assay compared to the *para* isomer **21**. The 4,5-bis(2-methoxyphenyl)imidazole analogue **27** was less active in both the *in vitro* ACAT and J774 macrophage assays.

To further improve the *in vitro* macrophage activity, a series of compounds with modification in the side chain, incorporating the 4,5-bis(4-methoxyphenyl)imidazole and 4,5-bis[4-(*N*,*N*-dimethylamino)phenyl]imidazole groups, were synthesized (Table 6). Replacing the (2,4-difluorophenyl)urea with a phenyl carbamate as in compounds **28** and **29** resulted in less activity in the *in vitro* ACAT assay and a small improvement in potency in the *in vitro* J774 macrophage assay. Replacing the urea with an acetamido group, as in compounds **30** and **31**, gave a 10-fold improvement in the *in vitro*

Table 6. Effect on *in Vitro* ACAT and J774 Inhibition by Modifying the Urea Tail

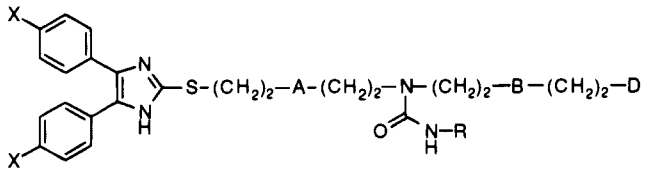


no.	R^1	R^2	IC_{50}, μM ACAT	J774
21	NH-C_6H_3-2,4-F_2	OCH_3	0.14	0.08
23	NH-C_6H_3-2,4-F_2	$N(CH_3)_2$	0.05	0.08
28	O-C_6H_5	OCH_3	0.64	0.032
29	O-C_6H_5	$N(CH_3)_2$	0.12	0.06
30	CH_2-c-C_6H_{11}	OCH_3	0.011	0.029
31	CH_2-c-C_6H_{11}	$N(CH_3)_2$	0.05	0.016
32	$NHCH(CH_3)_2$	OCH_3	0.16	0.004
33	$NHCH(CH_3)_2$	$N(CH_3)_2$	0.08	0.003

ACAT activity for **30** but no change in potency for **31**. However, the *in vitro* J774 macrophage activity did improve 2–5-fold, as compared to the 2,4-difluorophenyl analogues **21** and **23**. Finally, replacing the (2,4-difluorophenyl)urea with an isopropyl urea as in **32** and **33** produced a substantial improvement in the *in vitro* J774 macrophage assay activity; for the 4,5-bis(4-methoxyphenyl)imidazole **32**, IC_{50} = 0.004 μM, and for 4,5-bis[4-(*N*,*N*-dimethylamino)phenyl]imidazole **33**, IC_{50} = 0.003 μM. Compound **32** has about the same potency in the *in vitro* microsomal ACAT assay as compound **21**, and compound **33** is less than 2-fold less active than compound **23**. But compounds **32** and **33** are about 20-fold more active in the *in vitro* J774 macrophage assay than the respective analogue **21** or **23**. These compounds are 40- and 25-fold more potent in J774 macrophage cell culture assay than in the microsomal ACAT activity and 250- and 300-fold more active than **1** in the *in vitro* J774 macrophage assay, respectively.

The compounds with ether and amine replacements within the alkyl chains, Tables 7 and 8, also show a similar imidazole structure–activity relationship (SAR). Substitution of the imidazole phenyl groups with methoxy or dimethylamino always lowered *in vitro* ACAT activity but almost always increased *in vitro* J774 activity (the exception being compound **60**). The effect of changing the urea group from 2,4-difluorophenyl to isopropyl was not consistent in these series with respect to either *in vitro* ACAT or J774 assay, and any improvements in *in vitro* J774 activity were not nearly as dramatic as that seen in the all-carbon series (above). Replacement of methylene groups with oxygen atoms in the inner chain always resulted in significant loss of potency in both the *in vitro* ACAT and J774 assays. Similar replacement in the outer chain resulted in loss of activity in both assays, but the degree of loss was generally smaller. In fact, improvements in *in vitro* ACAT activity were seen in a few examples (*e.g.*, **49** to **50** and **52** to **53**). Why the introduction of ether groups generally had reduced potency in the *in vitro* J774 macrophage ACAT assay relative to the microsomal ACAT is unclear at this point. The best ether-containing compound was **59**, which bears *p*-methylthio substitution on the phenyl groups. None of the amine-bearing compounds **66–84** was more potent *in vitro* inhibitors of macrophage ACAT than either **32** or **33**, which seemed to indicate that amine groups were not

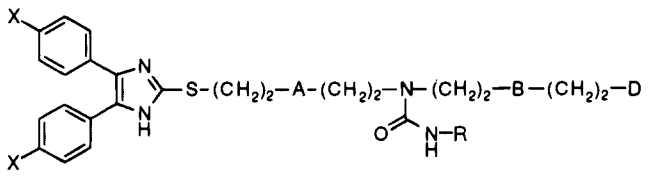
Table 7. *In Vitro* ACAT and J774 Inhibition by Ether and Alcohol Compounds



						IC$_{50}$, μM	
no.	X	A	B	D	R	ACAT	J774
38	H	O	CH_2	C_2H_5	2,4-$F_2C_6H_3$	0.08	3.98
39	H	O	CH_2	C_2H_5	*i*-Pr	0.19	0.99
40	CH_3O	O	CH_2	C_2H_5	2,4-$F_2C_6H_3$	2.30	0.50
41	CH_3O	O	CH_2	C_2H_5	*i*-Pr	0.85	0.34
49	H	CH_2	O	C_2H_5	2,4-$F_2C_6H_3$	0.07	1.75
50	H	CH_2	O	OC_2H_5	2,4-$F_2C_6H_3$	0.05	4.01
51	H	CH_2	O	OH	2,4-$F_2C_6H_3$	0.04	6.74
52	H	CH_2	O	C_2H_5	*i*-Pr	0.19	0.84
53	H	CH_2	O	OC_2H_5	*i*-Pr	0.03	3.02
54	H	CH_2	O	OH	*i*-Pr	0.09	6.84
55	CH_3O	CH_2	O	OCH_3	2,4-$F_2C_6H_3$	0.34	0.25
56	CH_3O	CH_2	O	OH	2,4-$F_2C_6H_3$	0.23	0.84
57	CH_3O	CH_2	O	OCH_3	*i*-Pr	0.50	0.36
58	CH_3O	CH_2O	O	OH	*i*-Pr	0.48	2.42
59	CH_3S	CH_2	O	OC_2H_5	*i*-Pr	0.28	0.04
60	$(CH_3)_2N$	CH_2	O	OCH_3	*i*-Pr	inactive	7.51
61	CH_3O	CH_2	CH_2	OH	*i*-Pr	*a*	1.00

[a] Assay not performed.

Table 8. *In Vitro* ACAT and J774 Inhibition by Amine Compounds



						IC$_{50}$, μM	
no.	X	A	B	D	R	ACAT	J774
66	H	CH_2	NC_2H_5	H	2,4-$F_2C_6H_3$	0.08	2.18
67	H	CH_2			2,4-$F_2C_6H_3$	0.07	0.88
68	H	CH_2	NC_2H_5	H	*i*-Pr	0.66	0.58
69	CH_3O	CH_2			2,4-$F_2C_6H_3$	0.27	1.34
74	H	NCH_3	CH_2	C_2H_{5c}	2,4-$F_2C_6H_3$	0.17	1.47
75	H	NCH_3	CH_2	C_2H_5	*i*-Pr	0.26	2.40
77	H	NCH_3			2,4-$F_2C_6H_5$	0.24	2.74
78	H	NCH_3			*i*-Pr	0.35	6.28
84	CH_3O	O	NCH_3	C_2H_5	2,4-$F_2C_6H_3$	1.50	0.63

well-tolerated in any location except as phenyl substitution. However, *in vitro* microsomal ACAT inhibition was largely retained. Interestingly, substitution of the phenyl rings with methoxy in this series did not improve *in vitro* J774 macrophage potency (see entries for **67** and **69**).

Several of the compounds demonstrated greater inhibition in the *in vitro* J774 assay than the *in vitro* hepatic microsomal assay (Tables 1–8) with specific compounds **32** and **33** showing 30–40-fold greater potency. This is unusual since in general potency is often decreased when going from a broken cell to an intact cell assay: the plasma membrane may act as a barrier to uptake of the compound or the compound may

Table 9. Inhibition of Hepatic and Macrophage ACAT by Compounds **1** and **33**

	IC$_{50}$, nM	
	33	1
hepatic ACAT[a]	80	10
macrophage CE[b]	4	1000
macrophage ACAT[a]	0.6	25

[a] *In vitro* mirosomal ACAT assay. [b] Intact cell cholesterol esterification assay.

be metabolized within the cell. There are several possibilities for the increased potency in the macrophage assay: (a) differential solubility of compound in the two assay media, (b) preferential concentration of some compounds in the endoplasmic reticulum, (c) cellular metabolism to a more potent compound, (d) presence of different ACAT isozymes in the liver and macrophage, or (e) different microenvironments which affect activity, or combinations of the above. In both assays the inhibitor is dissolved in DMSO and added to an aqueous environment so it is not thought that differential solubility (a) plays a role. To assess the other possibilities, the potencies of compounds **1** and **33** were tested in an *in vitro* microsomal assay where J774 macrophage microsomes were substituted for liver microsomes (Table 9). Compound **33** had a slightly lower IC$_{50}$ in the macrophage microsomal assay (0.6 nM) than was observed in the intact macrophage assay (4 nM) and was 150 times lower than obtained in the hepatic microsomal assay (80 nM). In contrast, compound **1** showed a similar IC$_{50}$ in both microsomal assays (10 and 25 nM). These data suggest that the increased potency for compound **33** is unlikely due to preferential concentration in the endoplasmic reticulum or cellular metabolism to a more potent inhibitor (b and c above) and suggest that there may be ACAT isozymes or ancillary factors affecting inhibitor activity. Definitive studies into the possibility of isozymes must await the purification of ACAT.

Conclusions

We have been able to significantly improve the *in vitro* J774 macrophage ACAT potency relative to the *in vitro* hepatic ACAT activity by substituting aprotic electron-donating groups on the phenyl rings of the imidazole, *i.e.*, $-OCH_3$, $-N(CH_3)_2$, and $-SCH_3$. Substitution on the phenyl rings in the *para* position balanced the preference for an electron-donating group and flexibility for the phenyl rings to assume the preferred conformation relative to the imidazole ring. In conjunction with modification on the diarylimidazole, *in vitro* macrophage ACAT inhibition can be further enhanced by incorporating an isopropylurea group in place of the difluorophenylurea. The later series of compounds in this paper, bearing the optimal imidazole and urea groups and oxygen or nitrogen atom replacements within the alkyl chains, unfortunately lost much of the potency for both intrinsic ACAT inhibition and inhibition in the cell culture. Any potential gains in absorption (and bioavailability) anticipated for the ether and amine compounds would be canceled by this potency loss.

Compounds **32** and **33** are the most active analogues reported in terms of the *in vitro* J774 macrophage cell culture assay. The large difference in activity for compound **33** against macrophage ACAT relative to liver ACAT suggests the enzyme from the two tissues may

not be identical, although proof must await purification of ACAT. Unfortunately, the preliminary pharmacokinetics data do not show improved bioavailability, relative to compound **1**. Further reports will detail ongoing efforts and investigations to identify a bioavailable ACAT inhibitor.

Experimental Section

All reactions detailed below were performed using reagent-grade materials and solvents under a dry nitrogen atmosphere. All solvents were distilled prior to use or stored over 4 Å molecular sieves. The phrase "flash chromatography" and related phrases refer to the separation methods reported by Still *et al.*[13] Melting points were determined in a open capillary on a Thomas Scientific melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Varian VXR-300A spectrometer, and chemical shifts are reported in ppm (δ) using tetramethylsilane as reference. IR spectra were obtained on a Perkin Elmer 1600 FTIR spectrometer. Mass spectra were obtained on a Hewlett-Packard 5988A MS spectrometer. Microanalysis were determined by Quantitative Technologies, Inc., Bound Brook, NJ.

Preparation of *N*-Heptyl-5-Hydroxypentanamide (2). A solution of γ-valerolactone (25.0 g, 0.249 mol) in toluene (50 mL) and *n*-heptylamine (35.96 g, 0.312 mol) was heated to reflux for 18 h under a nitrogen atmosphere. The reaction mixture was allowed to cool to ambient temperature, diluted with ethyl acetate (300 mL), washed with 1 N aqueous HCl (50 mL), water, and brine, dried over magnesium sulfate, and concentrated to give a white solid. The product was crystallized from ethyl ether:hexane to give *N*-heptyl-5-hydroxypentanamide (41.8 g, 0.194 mol, 78%) as white plates, mp 55–56 °C. ^{1}H NMR ($CDCl_3$): δ 6.06 (br s, 1H), 3.61 (t, 2H), 3.24 (q, 2H), 3.19 (br s, 1H), 2,19 (t, 2H), 1.80–1.23 (m, 14H), 0.87 (t, 3H). MS (CI–CH_4): *m/e* 216 (M + H). IR (KBr): 3446, 3322, 3002, 2931, 2858, 1630, 1522, 1459 cm^{-1}.

Preparation of *N*-(5-Hydroxypentyl)-*N*-heptylamine (3). To a solution of lithium aluminum hydride (6.7 g, 0.176 mol) in dry tetrahydrofuran (300 mL) was added dropwise a solution of *N*-heptyl-5-hydroxypentanamide (**2**) (19.0 g, 0.088 mol) in dry tetrahydrofuran (100 mL) under a nitrogen atmosphere. The reaction mixture was heated to reflux for 18 h, allowed to cool to room temperature, and poured slowly into a stirred mixture of 10% aqueous sodium sulfate (400 mL) and ice (200 mL). The resulting slurry was filtered through a bed of Celite, and the filtrate was extracted with ethyl acetate (2 × 500 mL). The combined organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated to give a viscous yellow oil. The product was crystallized from hexane to give *N*-(5-hydroxypentyl)-*N*-heptylamine (**3**) (15.2 g, 0.075 mol, 85%) as a white powder, mp 47–48 °C. ^{1}H NMR ($CDCl_3$): δ 3.63 (t, 2H), 2.63 (q, 4H), 2.39 (br s, 2H), 1.66–1.24 (m, 16H), 0.91 (t, 3H). MS (CI–CH_4): *m/e* 202 (M + H). IR (KBr): 2916, 2858, 1458, 1210 cm^{-1}.

Preparation of *N'*-(2,4-Difluorophenyl)-*N*-heptyl-*N*-(5-hydroxypentyl)urea (4a). To a solution of *N*-(5-hydroxypentyl)-*N*-heptylamine (**3**) (11.65 g, 0.0578 mol) in methylene chloride (75 mL) under a nitrogen atmosphere cooled to 0 °C was added slowly 2,4-difluorophenyl isocyanate (8.97 g, 0.0578 mol). The reaction mixture was stirred for 1 h, poured into 1 N aqueous HCl (200 mL), and extracted with ethyl acetate (300 mL). The combined organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated to give *N'*-(2,4-difluorophenyl)-*N*-heptyl-*N*-(5-hydroxypentyl)urea (**4a**) as a pale yellow oil (20.0 g, 0.056 mol, 97%). ^{1}H NMR ($CDCl_3$): δ 8.03 (m, 1H), 6.88–6.59 (m, 2H), 6.45 (br s, 1H), 3.68 (t, 2H), 3.33 (m, 4H), 1.81–1.22 (m, 16H), 0.91 (t, 3H). MS (CI–CH_4): *m/e* 357 (M + H).

Preparation of *N*-(5-Bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (5a). To a solution of *N'*-(2,4-difluorophenyl)-*N*-heptyl-*N*-(5-hydroxypentyl)urea (**4a**) (15.0 g, 0.042 mol) and carbon tetrabromide (16.75 g, 0.051 mol) in methylene chloride (350 mL) under a nitrogen atmosphere at ambient temperature was added slowly a solution of triphenylphosphine (13.24 g, 0.051 mol) in methylene chloride (100 mL). The reaction mixture was stirred for 3 h and concentrated *in vacuo* to give a crude viscous oil. The product was purified by flash chromatography on silica gel (400 mL) eluting with hexane: ethyl acetate (v:v, 90:10) to give *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**) as a viscous colorless oil (17.5 g, 0.042 mol, 100%). ^{1}H NMR ($CDCl_3$): δ 8.14–8.00 (m, 1H), 6.92–6.79 (m, 2H), 6.35 (br s, 1H), 3.49–3.25 (m, 6H), 1.99–1.26 (m, 16H), 0.92 (t, 3H). MS (CI–CH_4): *m/e* 419, 421 (M + H), 339, 156.

Preparation of *N*-[5-[[4,5-Bis(4-methoxyphenyl)-1*H*-imidazol-2yl]thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (21). To a suspension of sodium hydride (0.88 g, 60% mineral oil dispersion, 2.2 mmol) (washed free of mineral oil with hexane) in *N,N*-dimethylformamide (15 mL) under a nitrogen atmosphere, cooled to 0 °C, was added slowly a solution of 4,5-bis(4-methoxyphenyl)-1*H*-imidazole-2-thiol (**6**) (0.63 g, 2.0 mmol) in *N,N*-dimethylformamide (5 mL). The reaction mixture was stirred for 2 h, and then a solution of *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (0.845 g, 2.0 mmol) in *N,N*-dimethylformamide (3 mL) was added. The reaction mixture was allowed to warm to ambient temperature, stirred for an additional 2 h, poured into water (50 mL), and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with water and brine, dried over magnesium sulfate, and concentrated to give a viscous oil. The product was purified by flash chromatography on silica gel (100 mL) eluting with hexane:ethyl acetate (v:v, 70:30) to give compound **21** as a pure yellow foam (0.98 g, 1.50 mmol, 75%), mp 54–58 °C. ^{1}H NMR ($CDCl_3$): δ 10.15 (br s, 1H), 7.87–7.76 (m, 1H), 7.51 (d, 2H), 7.30 (d, 2H), 6.86–6.60 (m, 6H), 6.42 (d, 1H), 3.80 (s, 6H), 3.40 (t, 2H), 3.26 (t, 2H), 2.99 (t, 2H), 1.84–1.25 (m, 16H), 0.89 (t, 3H). MS (DCI–*i*-C_4H_{10}): *m/e* 651 (M + H), 496. IR (KBr): 2928, 2855, 1612, 1521, 1502, 1246 cm^{-1}.

Preparation of 4,5-Bis[4-(*N,N*-dimethylamino)phenyl]-1*H*-imidazole-2-thione (9). A suspension of 4,4′-bis(dimethylamino)benzil (57.2 g, 192.0 mmol) and ammonium thiocyanate (145.9 g, 1.92 mol) in hexanol (600 mL) under a nitrogen atmosphere was heated to 155 °C in a preheated oil bath for 35 min. The reaction mixture was allowed to cool to room temperature and diluted with diethyl ether (1200 mL) to give a precipitate. The solids were collected and washed with diethyl ether, and then methylene chloride until the washings were colorless. The solids were suspended in methylene chloride, heated to reflux, and filtered hot. The filtrate was then suspended in 1,4-dioxane (300 mL), heated to 85 °C, and decanted. The dioxane step was repeated until all of the product was leached from the solid residue. The dioxane layers were concentrated to give 4,5-bis[4-(*N,N*-dimethylamino)phenyl]-1*H*-imidazole-2-thiol (**9**) as a pale green yellow solid (24.2 g, 72.0 mmol, 37%), mp >265 °C. ^{1}H NMR (DMSO-d_6): δ 12.10 (s, 2H), 7.16 (d, 4H), 6.64 (d, 4H), 2.90 (s, 12H). MS (CI–CH_4): *m/e* 339 (M + H), 307. IR (KBr): 3010, 2901, 1613, 1521, 1484, 1362 cm^{-1}.

Preparation of *N*-[5-[[4,5-Di(1-propyl)-1*H*-imidazol-2-yl]thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (10). This product was prepared using similar methods described for the preparation of **21** but using 4,5-di(1-propyl)-1*H*-imidazole-2-thiol (0.275 g, 1.49 mmol) and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**) (0.625 g, 1.49 mmol) to give **10** as white needles crystallized from petroleum ether (0.435 g, 0.83 mmol, 56%), mp 78–80 °C. ^{1}H NMR ($CDCl_3$): δ 8.00–7.88 (m, 1H), 6.88–6.76 (m, 2H), 6.44 (d, 1H), 3.37–3.22 (m, 4H), 2.87 (t, 2H), 2.44 (t, 4H), 1.71–1.23 (m, 21H), 0.89 (t, 9H). IR (KBr): 2959, 2931, 1661, 1528 cm^{-1}.

Preparation of *N*-[5-[[4,5-Di(2-propyl)-1*H*-imidazol-2-yl]thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (11). This product was prepared using similar methods described for the preparation of **21** but using 4,5-di(2-propyl)-1*H*-imidazole-2-thiol (0.20 g, 1.09 mmol) and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**) (0.455 g, 1.09 mmol). Compound 11 was prepared as a crystalline white powder (0.385 g, 0.736 mmol, 67%), mp 91–93 °C. ^{1}H NMR ($CDCl_3$): δ 9.91–9.05 (br, 1H), 8.04–7.85 (m, 1H), 6.90–6.71 (m, 2H), 6.41 (br s, 1H), 3.41–3.19 (m, 4H), 3.02–2.78 (m, 4H), 2.23–

1.83 (br, 1H), 1.75–1.09 (m, 27H), 0.92 (t, 3H). MS (CI–CH_4): *m/e* 523 (M + H), 368, 156. IR (KBr): 2930, 1662, 1528 cm^{-1}.

Preparation of *N*-[5-[(4,5-Dicyclohexyl-1*H*-imidazol-2-yl)thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (12). This product was prepared using similar methods described for the preparation of **21** but using 4,5-dicyclohexyl-1*H*-imidazole-2-thiol (0.40 g, 1.51 mmol) and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**) (0.54 g, 1.51 mmol). Compound **12** was purified by flash chromatography on silica gel eluting with hexane:ethyl acetate (v:v, 7:3) to give a viscous colorless oil (0.64 g, 1.06 mmol, 70%). ^1H NMR ($CDCl_3$): δ 9.50–9.18 (br s, 1H), 7.97 (m, 1H), 6.80 (m, 2H), 6.41 (br s, 1H), 3.31 (m, 4H), 2.86 (t, 2H), 2.68–2.37 (m, 2H), 1.91–1.13 (m, 36H), 0.89 (t, 3H). MS (DCI–NH_3): *m/e* 603 (M + H), 448. IR (KBr): 2926, 2852, 1515 cm^{-1}.

Preparation of *N*-[5-[[4,5-Di(2-thienyl)-1*H*-imidazol-2-yl]thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (13). This product was prepared using similar methods described for the preparation of **21** but using 4,5-di(2-thienyl)-1*H*-imidazole-2-thiol (0.275 g, 1.04 mmol) and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**) (0.436 g, 1.04 mmol). Compound **13** was precipitated as the hydrochloride salt from ethyl ether to give a white powder (0.358 g, 0.559 mmol, 54%), mp 75–80 °C. ^1H NMR ($CDCl_3$): δ 9.76–8.89 (v vr, 1H), 7.75–7.60 (m, 1H), 7.47 (d, 2H), 7.28 (d, 2H), 7.01–6.97 (m, 2H), 6.76–6.66 (m, 3H), 3.35–3.21 (m, 6H), 1.60–1.30 (m, 16H), 0.85 (t, 3H). MS (EI): *m/e* 447, 264, 205, 155. IR (KBr): 2930, 1659, 1528 cm^{-1}.

Preparation of *N*-[5-[[4,5-Di(2-furanyl)-1*H*-imidazol-2-yl]thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (14). This product was prepared using similar methods described for the preparation of **21** but using 4,5-di(2-furanyl)-1*H*-imidazole-2-thiol (0.69 g, 3.0 mmol) and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**) (1.26 g, 3.0 mmol). Compound **14** was purified by flash chromatography on silica gel eluting with hexane:ethyl acetate (v:v, 70:30) to give **14** as an oil (0.30 g, 0.526 mmol, 17%). ^1H NMR ($CDCl_3$): δ 10.35–10.15 (br s, 1H), 7.95 (m, 1H), 7.50–7.36 (m, 2H), 6.98–6.69 (m, 4H), 6.49–6.38 (m, 3H), 3.35 (t, 2H), 3.25 (t, 2H), 3.05 (t, 2H), 1.79–1.27 (m, 16H), 0.90 (t, 3H). MS (DCI–CH_4): *m/e* 571 (M + H), 416, 156. IR (KBr): 3120, 2928, 1649, 1529, 1430, 1403 cm^{-1}.

Preparation of *N*-[5-[[4,5-Di(2-pyridinyl)-1*H*-imidazol-2-yl]thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (15). This product was prepared using similar methods described for the preparation of **21** but using 4,5-di(2-pyridinyl)-1*H*-imidazole-2-thiol (0.30 g, 1.18 mmol) and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**) (0.495 g, 1.18 mmol). Compound **15** was purified by flash chromatography eluting with methylene chloride:methanol (v:v, 95:5) to give **15** as an amber oil (0.35 g, 0.59 mmol, 50%). ^1H NMR ($CDCl_3$): δ 8.79–7.63 (m, 7H), 7.29–7.12 (m, 2H), 6.86–6.73 (m, 2H), 6.44 (br s, 1H), 3.34–3.08 (m, 6H), 1.83–1.18 (m, 16H), 0.86 (t, 3H). MS (DCI–NH_3): *m/e* 593 (M + H), 438, 156. IR (KBr): 2930, 1663, 1591, 1528 cm^{-1}.

Preparation of *N'*-[5-[(1*H*-Dibenz[2,3:6,7]oxepino[4,5-*d*]imidazol-2-yl)thio]pentyl]-*N*-(2,4-difluorophenyl)-*N*-heptylurea (16). This product was prepared using similar methods described for the preparation of **21** but using 1*H*-dibenz[2,3:6,7]oxepino[4,5-*d*]imidazole-2-thiol and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**). Compound **16** was isolated as a white powder (0.36 g, 0.59 mmol, 63%), mp 82–87 °C. ^1H NMR ($CDCl_3$): δ 9.75–8.50 (br s, 2H), 7.84–7.59 (m, 3H), 7.43–7.05 (m, 6H), 5.13–6.53 (m, 3H), 3.43–3.13 (m, 6H), 1.75–1.20 (m, 16H), 0.88 (t, 3H). MS (EI): *m/e* 604, 449, 266. IR (KBr): 2858, 1657, 1635, 1611, 1517, 1462, 1431 cm^{-1}.

Preparation of *N*-[5-[(1*H*,9*H*-Dibenzo[4,5:8,9][1,3]dioxonino[6,7-*d*]imidazol-2-yl)thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (17). Part A. To a suspension of sodium hydride (washed free of mineral oil with hexane) (2.45 g, 80% oil dispersion, 0.081 mol) in dry *N,N*-dimethylformamide (50 mL) under a nitrogen atmosphere, cooled to 0 °C, was added slowly a solution of salicylaldehyde (10.0 g, 81.9 mmol) in dry *N,N*-dimethylformamide (10 mL). The reaction mixture was stirred at 0 °C for 2 h, and diiodomethane (11.3 g, 0.041 mol) was added. The reaction mixture was allowed to warm to ambient temperature for 18 h and then warmed to 60 °C for 20 h. The reaction mixture was allowed to cool to ambient temperature, poured into 1 N aqueous HCl (100 mL), and extracted with ethyl acetate (2 × 100 mL). The combined organic extract was washed with water and brine, dried over magnesium sulfate, and concentrated to give a solid. The product was purified by flash chromatography on silica gel (300 mL) eluting with methylene chloride (100%) to give 2,2'-(methylenedioxy)bis(2-benzaldehyde) as a white crystalline solid (5.1 g, 0.0199 mol, 48%), mp 131–133 °C. ^1H NMR ($CDCl_3$): δ 10.47 (s, 2H), 7.87 (d, 2H), 7.68–7.54 (m, 2H), 7.21 (d, 2H), 7.15 (t, 2H), 6.02 (s, 2H). MS (DCI–NH_3): *m/e* 274 (M + NH_4).

Part B. A mixture of 2,2'-(methylenedioxy)bis(2-benzaldehyde) (5.0 g, 0.0195 mol) and potassium cyanide (0.63 g, 0.0975 mol) in ethanol (75 mL) and water (50 mL) was heated to reflux for 6 h. The reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo*, and the resultant aqueous residue was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated to give a viscous oil. The product was purified by flash chromatography on silica gel (250 mL) eluting with hexane:ethyl acetate (80:20, v:v) to give 13-hydroxydibenzo[*d,h*][1,3]dioxonin-12(13*H*)-one as a crystalline solid (2.5 g, 0.00975 mol, 50%), mp 129–130 °C. ^1H NMR (DMSO-d_6): δ 7.49 (t, 2H), 7.29–7.08 (m, 6H), 6.40 (d, 1H), 5.97 (d, 1H), 5.92 (d, 1H), 5.24 (d, 1H). MS (DCI–NH_4): *m/e* 257 (M + H), 239, 227, 211. IR (KBr): 3474, 1669, 1598, 1487, 1448 cm^{-1}.

Part C. A solution of 13-hydroxydibenzo[*d,h*][1,3]dioxonin-12(13*H*)-one (2.0 g, 0.0078 mol), thiourea (0.82 g, 0.0108 mol), and hexanol (25 mL), equipped with a column of 4 Å sieves and a condenser, was heated to 160 °C for 20 h under a nitrogen atmosphere. The reaction mixture was allowed to cool to ambient temperature and diluted with ethyl ether (100 mL) to give a solid. The solid was washed with ethyl ether and dried to give 1*H*,9*H*-dibenzo[4,5:8,9][1,3]dioxonino[6,7-*d*]-imidazole-2-thione as a white crystalline powder (1.6 g, 0.00539 mol, 69%), mp >250 °C. ^1H NMR (DMSO-d_6): δ 12.50 (s, 2H), 7.43–7.08 (m, 8H), 6.20–5.00 (br d, 2H). MS (DCI–CH_4): *m/e* 297 (M + H). IR (KBr): 3044, 2976, 2901, 2815, 1652, 1505, 1484 cm^{-1}.

Part D. This product **17** was prepared using similar methods described for the preparation of **21** but using 1*H*,9*H*-dibenzo[4,5:8,9][1,3]dioxonino[6,7-*d*]imidazole-2-thione and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**). The title compound **17** was isolated as a white foam (0.85 g, 0.00134 mol), mp 65–70 °C. ^1H NMR ($CDCl_3$): δ 10.35–10.10 (br s, 1H), 7.56 (m, 1H), 7.30–6.95 (m, 10H), 6.40 (d, 1H), 5.70–5.20 (br s, 2H), 3.40–3.19 (m, 4H), 3.08 (t, 2H), 1.85–1.23 (m, 16H), 0.88 (t, 3H). MS (DCI–NH_4): *m/e* 635 (M + H), 480.

Preparation of *N*-[5-[[4,5-Bis[4-(trifluoromethyl)phenyl]-1*H*-imidazol-2-yl]thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (18). This product was prepared using similar methods described for the preparation of **21** but using 4,5-bis-[4-(trifluoromethyl)phenyl]-1*H*-imidazole-2-thiol (0.30 g, 0.77 mmol) and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**) (0.32 g, 0.77 mmol). Compound **18** was purified by flash chromatography eluting with hexane:ethyl acetate (v:v, 70:30) to give a viscous colorless oil (0.31 g, 0.43 mmol, 55%). ^1H NMR ($CDCl_3$): δ 11.68 (br s, 1H), 7.67–7.20 (m, 9H), 6.68 (m, 1H), 6.48 (m, 1H), 6.33 (m, 1H), 3.46 (t, 2H), 3.27 (t, 2H), 2.99 (t, 2H), 1.83–1.20 (m, 16H), 0.90 (t, 3H). MS (DCI–NH_3): *m/e* 727 (M + H), 572. IR (KBr): 2931, 1616, 1517, 1325 cm^{-1}.

Preparation of *N*-[5-[[4,5-Bis(4-methylphenyl)-1*H*-imidazol-2-yl]thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (19). This product was prepared using similar methods described for the preparation of **21** but using 4,5-bis-(4-methylphenyl)-1*H*-imidazole-2-thiol (0.84 g, 3.0 mmol) and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**) (1.25 g, 0.3 mmol). Compound **19** was purified by flash chromatography eluting with toluene:tetrahydrofuran (v:v, 90:10) to give an off-white solid (0.10 g, 0.16 mmol, 5%), mp 63–

65 °C. ^{1}H NMR ($CDCl_3$): δ 10.25 (br s, 1H), 7.80–7.73 (m, 1H), 7.50 (d, 2H), 7.26 (m, 2H), 7.10 (br s, 4H), 6.83–6.56 (m, 2H), 6.40 (d, 1H), 3.40 (t, 2H), 3.25 (t, 2H), 3.00 (t, 2H), 2.33 (br s, 6H), 1.83–1.20 (m, 19H), 0.93 (t, 3H). MS (CDI–CH_4): *m/e* 619 (M + H).

Preparation of *N*-[5-[[4,5-Bis(4-fluorophenyl)-1*H*-imidazol-2-yl]thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (20). This product was prepared using similar methods described for the preparation of **21** but using 4,5-bis-(4-fluorophenyl)-1*H*-imidazole-2-thiol (0.30 g, 1.04 mmol) and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**) (0.436 g, 1.04 mmol). Compound **20** was purified by flash chromatography eluting with hexane:ethyl acetate (v:v, 70:30) to give a viscous colorless oil which was then recrystallized from petroleum ether to give a white powder (0.43 g, 0.686 mmol, 66%), mp 82–84 °C. ^{1}H NMR ($CDCl_3$): δ 11.03 (br s, 1H), 7.74–7.60 (m, 1H), 7.53–7.40 (m, 2H), 7.26 (m, 2H), 7.03–6.80 (m, 4H), 6.67 (m, 1H), 6.62–6.40 (m, 1H), 6.39 (d, 1H), 3.40 (t, 2H), 3.25 (t, 2H), 2.95 (t, 2H), 1.77–1.31 (m, 16H), 0.88 (t, 3H). IR (KBr): 2931, 2860, 1657, 1522 cm^{-1}.

Preparation of *N*-[5-[[4,5-Bis(4-hydroxyphenyl)-1*H*-imidazol-2-yl]thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (22). To a stirred solution of *N*-[5-[[4,5-bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**21**) (0.78 g, 0.0012 mol) in methylene chloride (30 mL) cooled to −78 °C under a nitrogen atmosphere was added 1 M boron tribromide in methylene chloride (3.6 mL). The reaction mixture was stirred for 1 h at 0 °C, poured over ice (100 mL), and extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with 10% aqueous $NaHCO_3$ (50 mL), water, and brine, dried over magnesium sulfate, and concentrated *in vacuo* to give the crude oil. The product was purified by flash chromatography on silica gel (100 mL) eluting with hexane:ethyl acetate (40:60, v:v) to give a white foam (0.5 g, 0.80 mmol, 67%), mp 110–112 °C. ^{1}H NMR (DMSO-d_6): δ 12.22 (br s, 1H), 9.55 (br s, 1H), 9.32 (br s, 1H), 7.92 (s, 1H), 7.45–6.60 (m, 11H), 3.24 (m, 4H), 3.06 (t, 2H), 1.77–1.17 (m, 16H), 0.88 (t, 3H). MS (DCI–NH_3): *m/e* (M + H), 468. IR (KBr): 3253, 2928, 2856, 1649, 1613, 1524, 1503, 1258 cm^{-1}.

Preparation of *N*-[5-[[4,5-Bis[4-(*N*,*N*-dimethylamino)-phenyl]-1*H*-imidazol-2-yl]thiol]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (23). This product was prepared using similar methods described for the preparation of **21** but using 4,5-bis[4-(*N*,*N*-dimethylamino)phenyl]-1*H*-imidazole-2-thiol (**9**) (0.60 g, 1.77 mmol) and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**) (0.74 g, 1.77 mmol). Compound **23** was purified by flash chromatography eluting with hexane:ethyl acetate (v:v, 60:40) to give a pale amber foam (0.42 g, 0.62 mmol, 35%), mp 68–70 °C. ^{1}H NMR ($CDCl_3$): δ 10.03–9.55 (br s, 1H), 7.86 (m, 1H), 7.58–7.20 (br m, 4H), 6.82–6.61 (m, 6H), 6.42 (br s, 1H), 3.30–3.21 (m, 2H), 2.94 (br s, 14H), 1.78–1.26 (m, 16H), 0.88 (t, 3H). MS (CDI–NH_3): *m/e* 677 (M + H), 5.22. IR (KBr): 2927, 1615, 1529, 1512, 1352 cm^{-1}.

Preparation of *N*-[5-[[4,5-Bis[4-(methylthio)phenyl]-1*H*-imidazol-2-yl]thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (24). This product was prepared using similar methods described for the preparation of **21** but using 4,5-bis-[4-(methylthio)phenyl]-1*H*-imidazole-2-thiol (2.06 g, 5.99 mmol) and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**) (2.51 g, 5.99 mmol). Compound **24** was purified by flash chromatography eluting with chloroform:ethyl acetate (v:v, 90:10) to give an amorphous solid (1.89 g, 2.77 mmol, 47%), mp 48–52 °C. ^{1}H NMR ($CDCl_3$): δ 7.7–7.6 (m, 1H), 7.4–7.0 (m, 9H), 6.7–6.6 (m, 1H), 6.55–6.5 (m, 1H), 6.3 (s, 1H), 3.35 (t, 2H, *J* = 6.8 Hz), 3.2 (t, 2H, *J* = 7.7 Hz), 2.9 (t, 2H, *J* = 6.4 Hz), 2.4 (s, 6H, 1.8–1.1 (m, 16H), 0.8 (t, 3H, *J* = 6.6 Hz). MS (DCI–NH_3): *m/e* 683 (M + H). IR (KBr): 3463, 3080, 2926, 2856, 1712, 1650, 1516, 1430 cm^{-1}.

Preparation of *N*-[5-[[4,5-Bis[4-(methylsulfonyl)phenyl]-1*H*-imidazol-2-yl]thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (25). This product was prepared using similar methods described for the preparation of **21** but using 4,5-bis-[4-(methylsulfonyl)phenyl]-1*H*-imidazole-2-thiol (0.45 g, 1.1 mmol) and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**) (0.46 g, 1.1 mmol). Compound **24** was purified by flash chromatography eluting with pentane:ethyl acetate (v:v, 25:75) to give an amorphous solid (725 mg, 971 μmol, 91%). ^{1}H NMR ($CDCl_3$): δ 7.9–7.75 (m, 6H), 7.55–7.45 (m, 2H), 6.75–6.65 (m, 1H), 6.55–6.45 (m, 1H), 3.5 (t, 2H, *J* = 6.2 Hz), 3.3 (t, 2H, *J* = 7.9 Hz), 3.15 (s, 3H), 3.05 (s, 3H), 2.95 (t, 2H, *J* = 6.2 Hz), 1.9–1.5 (m, 10H), 1.4–1.2 (m, 8H), 0.95–0.85 (m, 3H). MS (DCI–NH_3): *m/e* 747 (M + H). IR (KBr): 3267, 3079, 2930, 2858, 1634, 1598, 1516, 1313 cm^{-1}.

Preparation of *N*-[5-[[4,5-Bis(3-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (26). This product was prepared using similar methods described for the preparation of **21** but using 4,5-bis-(3-methoxyphenyl)-1*H*-imidazole-2-thiol (0.39 g, 1.25 mmol) and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**) (0.52 g, 1.25 mmol). Compound **26** was crystallized from hexane:ethyl ether to give an off-white crystalline powder (0.35 g, 0.54 mmol, 43%), mp 100–102 °C. ^{1}H NMR ($CDCl_3$): δ 10.45 (br s, 1H), 7.76 (m, 1H), 7.28–6.54 (m, 10H), 6.37 (d, 1H), 3.69 (br s, 6H), 3.42 (t, 2H), 3.26 (t, 2H), 3.00 (t, 2H), 1.86–1.23 (m, 16H), 0.88 (t, 3H). MS (DCI–NH_3): *m/e* 651 (M + H), 496.

Preparation of *N*-[5-[[4,5-Bis(2-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentyl]-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (27). This product was prepared using similar methods described for the preparation of **21** but using 4,5-bis-(2-methoxyphenyl)-1*H*-imidazole-2-thiol (0.37 g, 1.20 mmol) and *N*-(5-bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (**5a**) (0.50 g, 1.21 mmol). Compound **27** was purified by flash chromatography eluting with acetonitrile:chloroform (v:v, 20:80) to give a colorless oil (0.6 g, 0.92 mmol, 76%). ^{1}H NMR ($CDCl_3$): δ 12.17 (br s, 1H), 7.94 (br s, 1H), 7.43–6.77 (m, 11H), 3.57 (s, 3H), 3.24 (m, 4H), 3.19 (s, 3H), 3.07 (t, 2H), 1.76–1.18 (m, 16H), 0.85 (t, 3H). MS (CDI–NH_3): *m/e* 651 (M + H), 496.

Preparation of Phenyl *N*-(5-Hydroxypentyl)-*N*-heptylcarbamate (4b). This product was prepared using similar methods described for the preparation of **4a** but using phenyl chloroformate (1.56 g, 10.0 mmol) and *N*-(5-hydroxypentyl)-*N*-heptylamine (**3**) (2.01 g, 10.0 mmol). Compound **4b** was purified by flash chromatography eluting with hexane:ethyl acetate (v:v, 30:70) to give a colorless oil (3.1 g, 9.36 mmol, 94%). ^{1}H NMR ($CDCl_3$): δ 7.4–7.06 (m, 5H), 3.68–3.63 (m, 2H), 3.42–3.27 (m, 4H), 2.08–1.95 (m, 1H), 1.75–1.26 (m, 16H), 0.90 (t, 3H). MS (DCI–NH_3): *m/e* 322 (M + H).

Preparation of Phenyl *N*-(5-Bromopentyl)-*N*-heptylcarbamate (5b). This product was prepared using similar methods described for the preparation of **5a** but using phenyl *N*-(5-hydroxypentyl)-*N*-heptylcarbamate (**4b**) (3.2 g, 10.0 mmol). Compound **5b** was purified by flash chromatography eluting with hexane:ethyl acetate (v:v, 70:30) to give the title compound **5b** as a pale yellow oil (3.5 g, 8.7 mmol, 87%). ^{1}H NMR ($CDCl_3$): δ 7.39 (m, 5H), 3.47–3.28 (m, 6H), 1.97–1.89 (m, 2H), 1.75–1.26 (m, 16H), 0.88 (t, 3H). MS (DCI–CH_4): *m/e* 384, 386 (M + H), 304. IR (KBr): 2929, 2857, 1721, 1467, 1417 cm^{-1}.

Preparation of Phenyl *N*-[5-[[4,5-Bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentyl]-*N*-heptylcarbamate (28). This product was prepared using similar methods described for the preparation of **21** but using 4,5-bis(4-methoxyphenyl)-1*H*-imidazole-2-thiol (0.50 g, 1.60 mmol) and phenyl *N*-(5-bromopentyl)-*N*-heptylcarbamate (**5b**) (0.61 g, 1.60 mmol). Compound **28** was purified by flash chromatography eluting with hexane:ethyl acetate (v:v, 70:30) to give a colorless oil (0.25 g, 0.41 mmol, 25%). ^{1}H NMR (DMSO-d_6): δ 12.34 (s, 1H), 7.39–7.22 (m, 6H), 7.19 (t, 1H), 7.06 (d, 2H), 6.84 (d, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 3.40–3.20 (m, 4H), 3.09 (m, 2H), 1.75–1.17 (m, 16H), 0.84 (m, 3H). MS (DCI–CH_4): *m/e* 616 (M + H). IR (KBr): 2930, 2856, 1719, 1694, 1521, 1502, 1466, 1247 cm^{-1}.

Preparation of Phenyl *N*-[5-[[4,5-Bis[4-(*N*,*N*-dimethylamino)phenyl]-1*H*-imidazol-2-yl]thio]pentyl]-*N*-heptylcarbamate (29). This product was prepared using similar methods described for the preparation of **21** but using 4,5-bis-[4-(*N*,*N*-dimethylamino)phenyl]-1*H*-imidazole-2-thio (**9**) (0.142 g, 0.42 mmol) and phenyl *N*-(5-bromopentyl)-*N*-heptylcarbamate (**5b**) (0.16 g, 0.42 mmol). Compound **29** was purified by

flash chromatography eluting with hexane:ethyl acetate (v:v, 60:40) to give an amber oil (0.2 g, 0.31 mmol, 74%). ^{1}H NMR ($CDCl_3$): δ 10.00–9.90 (br s, 1H), 7.57–7.03 (m, 9H), 6.63 (m, 4H), 3.43–3.26 (m, 4H), 3.09–2.86 (br s, 14H), 1.81–1.25 (m, 16H), 0.89 (t, 3H). MS (DCI–NH_3): *m/e* 642 (M + H). IR (KBr): 3467, 2927, 2855, 1719, 1615, 1530, 1510, 1352, 1205, 1164 cm^{-1}.

Preparation of *N*-Heptyl-*N*-(5-hydroxypentyl)cyclohexaneacetamide (4c). This product was prepared using similar methods described for the preparation of **4a** but using 2-cyclohexylacetyl chloride (0.85 g, 10.0 mmol) and *N*-(5-hydroxypentyl)-*N*-heptylamine (**3**) (2.01 g, 10.0 mmol). Compound **4c** was purified by flash chromatography eluting with hexane:ethyl acetate (v:v, 30:70) to give an oil (1.5 g, 0.0046 mol, 97%). ^{1}H NMR ($CDCl_3$): δ 3.70–3.61 (m, 2H), 3.37–3.18 (m, 4H), 2.03 (d, 2H), 1.97–1.08 (m, 26H), 1.02–0.86 (m, 4H). MS (DCI–CH_4): *m/e* 326 (M + H). IR (KBr): 2924, 2854, 1624, 1449, 1424 cm^{-1}.

Preparation of *N*-(5-Bromopentyl)-*N*-heptylcyclohexaneacetamide (5c). This product was prepared using similar methods described for the preparation of **5a** but using *N*-heptyl-*N*-(5-hydroxypentyl)cyclohexaneacetamide (**4c**) (1.5 g, 4.6 mmol). Compound **5c** was purified by flash chromatography eluting with hexane:ethyl acetate (v:v, 70:30) to give an oil (1.3 g, 3.3 mmol, 73%). ^{1}H NMR ($CDCl_3$): δ 3.47–3.39 (m, 2H), 3.36–3.18 (m, 4H), 2.17 (d, 2H), 1.96–0.86 (m, 30H). MS (DCI–NH_3): *m/e* 383, 390 (M + H). IR (KBr): 2929, 2857, 1721, 1467, 1417, 1206 cm^{-1}.

Preparation of *N*-[5-[[4,5-Bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentyl]-*N*-heptylcyclohexaneacetamide (30). This product was prepared using similar methods described for the preparation of **21** but using 4,5-bis(4-methoxyphenyl)-1*H*-imidazole-2-thiol (0.40 g, 1.3 mmol) and *N*-(5-bromopentyl)-*N*-heptylcyclohexaneacetamide (**5c**) (0.44 g, 1.3 mmol). Compound **30** was purified by flash chromatography eluting with hexane:ethyl acetate (v:v, 60:40) to give an oil (0.46 g, 0.74 mmol, 57%). ^{1}H NMR (DMSO-d_6): δ 12.34 (s, 1H), 7.36 (d, 2H), 7.29 (d, 2H), 6.95 (d, 2H), 6.84 (d, 2H), 3.77 (s, 3H), 3.73 (s, 3H), 3.18 (m, 4H), 3.07 (m, 2H), 2.09 (d, 2H), 1.73–0.81 (m, 30H). MS (DCI–NH_3): *m/e* 620 (M + H). IR (KBr): 2926, 2853, 1613, 1521, 1502, 1463, 1246 cm^{-1}.

Preparation of *N*-[5-[[4,5-Bis[4-(*N*,*N*-dimethylamino)-phenyl]-1*H*-imidazol-2-yl]thio]pentyl]-*N*-heptylcyclohexaneacetamide (31). This product was prepared using similar methods described for the preparation of **21** but using 4,5-bis-[4-(*N*,*N*-dimethylamino)phenyl]-1*H*-imidazole-2-thiol (**9**) (0.338 g, 1.0 mmol) and *N*-(5-bromopentyl)-*N*-heptylcyclohexaneacetamide (**5c**) (0.388 g, 1.0 mmol). Compound **31** was purified by flash chromatography eluting with hexane:ethyl acetate (v:v, 50:50) to give an amber oil (0.4 g, 0.62 mmol, 62%). ^{1}H NMR (DMSO-d_6): δ 12.12 (s, 1H), 7.31 (d, 2H), 7.20 (d, 2H), 6.70 (d, 2H), 6.63 (d, 2H), 3.18 (m, 4H), 3.03 (m, 2H), 2.91 (s, 6H), 2.86 (s, 6H), 2.08 (d, 2H), 1.64–0.82 (m, 30H). MS (DCI–NH_3): *m/e* 646 (M + H). IR (KBr): 2920, 2852, 2801, 1614, 1529, 1509, 1445, 1351 cm^{-1}.

Preparation of *N*-Heptyl-*N*-(5-hydroxypentyl)-*N'*-(1-methylethyl)urea (4d). This product was prepared using similar methods described for the preparation of **4a** but using isopropyl isocyanate (0.85 g, 10.0 mmol) and *N*-(5-hydroxypentyl)-*N*-heptylamine (**3**) (2.01 g, 10.0 mmol). Compound **4d** was purified by flash chromatography eluting with hexane:etyl acetate (v:v, 30:70) to give an oil (2.79 g, 9.7 mmol, 97%). ^{1}H NMR ($CDCl_3$): δ 4.15–4.07 (m, 1H), 4.01–3.90 (m, 1H), 3.65 (t, 2H), 3.19 (t, 2H), 3.12 (t, 2H), 2.54–2.28 (v br, 1H), 1.66–1.24 (m, 16H), 1.15 (s, 6H), 0.90 (t, 3H). MS (DCI–CH_4): *m/e* 287 (M + H).

Preparation of *N*-(5-Bromopentyl)-*N*-heptyl-*N'*-(1-methylethyl)urea (5d). This product was prepared using similar methods described for the preparation of **4a** but using *N*-heptyl-*N*-(5-hydroxypentyl)-*N'*-(1-methylethyl)urea (**4d**) (2.8 g, 10.0 mmol). Compound **5d** was purified by flash chromatography eluting with hexane:ethyl acetate (v:v, 65:35) to give a pale yellow oil (2.7 g, 7.7 mmol, 77%). ^{1}H NMR ($CDCl_3$): δ 4.05–3.90 (m, 2H), 3.42 (t, 2H), 3.20 (t, 2H), 3.12 (t, 2H), 1.97–1.86 (m, 2H), 1.60–1.26 (m, 14H), 1.14 (s, 6H), 0.88 (t, 3H). MS (DCI–CH_4): *m/e* 349, 351 (M + H). IR (KBr): 3347, 2958, 2928, 1620, 1530, 1490, 1459 cm^{-1}.

Preparation of *N*-[5-[[4,5-Bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentyl]-*N*-heptyl-*N'*-(1-methylethyl)-urea (32). This product was prepared using similar methods described for the preparation of **21** but using 4,5-bis(4-methoxyphenyl)-1*H*-imidazole-2-thiol (16.1 g, 51.5 mmol) and *N*-(5-bromopentyl)-*N*-heptyl-*N'*-(1-methylethyl)urea (**5d**) (18.0 g, 51.5 mmol). Compound **32** was purified by flash chromatography eluting with hexane:ethyl acetate (v:v, 50:50) to give a pale yellow foam (19.5 g, 33.6 mmol, 65%), mp 50–55 °C. ^{1}H NMR ($CDCl_3$): δ 7.47 (d, 4H), 6.84 (d, 4H), 4.12 (d, 1H), 3.84 (m, 1H), 3.80 (s, 6H), 3.33 (t, 2H), 3.07 (t, 2H), 2.96 (t, 2H), 1.80–1.24 (m, 16H), 1.08 (d, 6H), 0.90 (t, 3H). MS (DCI–NH_3): *m/e* 581 (M + H), 496. IR (KBr): 2929, 2856, 1615, 1521, 1502, 1246 cm^{-1}.

Preparation of *N*-[5-[[4,5-Bis[4-(*N*,*N*-dimethylamino)-phenyl]-1*H*-imidazol-2-yl]thio]pentyl]-*N*-heptyl-*N'*-(1-methylethyl)urea (33). This product was prepared using similar methods described for the preparation of **21** but using 4,5-bis[4-(*N*,*N*-dimethylamino)phenyl]-1*H*-imidazole-2-thiol (0.42 g, 1.23 mmol) and *N*-(5-bromopentyl)-*N*-heptyl-*N'*-(1-methylethyl)urea (**5d**) (0.43 g, 1.23 mmol). Compound **33** was purified by flash chromatography eluting with methylene chloride:ethyl acetate (v:v, 60:40) to give a foam which was crystallized from ether/hexane to give white needles (0.54 g, 0.89 mmol, 72%), mp 70–72 °C. ^{1}H NMR ($CDCl_3$): δ 7.56–7.33 (br s, 4H), 6.67 (d, 4H), 4.11 (d, 1H), 3.89 (m, 1H0, 3.30 (t, 2H), 3.08 (t, 2H), 2.95 (br s, 14H), 1.84–1.25 (m, 16H), 1.10 (d, 6H), 0.90 (t, 3H). MS (DCI–NH_3): *m/e* 607 (M + H). IR (KBr): 2927, 2855, 1616, 1529, 1510, 1352 cm^{-1}.

Preparation of 2-[2-(*N*-Heptylamino)ethoxy]ethanol (35). A solution of heptanoyl chloride (20.0 mL, 129 mmol) in THF (80 mL) was cooled to 0 °C, and a solution of 2-(2-aminoethoxy)ethanol (Aldrich; 10.0 mL, 139 mmol) and triethylamine (20.0 mL, 143 mmol) in THF (200 mL) was added dropwise. After stirring overnight, the solution was poured into water (400 mL), and this mixture was extracted with ether (400 mL) and then with CH_2Cl_2 (400 mL). The extracts were washed with brine, combined, dried over $MgSO_4$, and evaporated to afford sufficiently pure product (**34**) as an oil (25.8 g, 119 mmol, 92%). A slurry of $LiAlH_4$ (9.21 g, 243 mmol) in THF (100 mL) was cooled to 0 °C, and a solution of compound **34** (16.1 g, 74.1 mmol) in THF (100 mL) was added dropwise over 30 min. The ice bath was removed and the mixtured heated to reflux for 18 h. The solution was recooled to 0 °C and the reaction quenched by sequential addition of water (10 mL), aqueous NaOH (30 mL, 15%), and water (30 mL). The resulting mixture was filtered through a pad of Celite, which was in turn washed with additional THF. The solution was dried over K_2CO_3, filtered, and evaporated to give the product as a clear, colorless oil (13.3 g, 65.2 mmol, 88%). ^{1}H NMR ($CDCl_3$): δ 3.7 (2H, m), 3.6 (4H, m), 2.8 (2H, t), 2.6 (2H, t), 2.5 (2H, br s), 1.5 (2H, m), 1.3 (8H, m), 0.9 (3H, t).

Preparation of 3-(2,4-Difluorophenyl)-1-heptyl-1-[2-(2-hydroxyethoxy)ethyl]urea (36a). The amine compound **35** (6.63 g, 32.6 mmol) was converted to the title product as a clear, colorless oil (8.07 g, 22.5 mmol, 69%), using the same procedure used for the conversion of **3** to **4a**. ^{1}H NMR ($CDCl_3$): δ 7.99–7.90 (2H, m), 6.84–6.77 (2H, m), 3.80–3.62 (6H, m), 3.58–3.50 (2H, m), 3.32 (2H, dd, J = 7.8, 7.6 Hz), 2.27 1H, dd, J = 5.9, 2.6 Hz), 1.66–1.53 (2H, m), 1.33–1.23 (8H, m), 0.88 (3H, t, J = 6.9 Hz). MS (DCI–NH_3): *m/e* 359 (100), 341 (4), 286 (16), 227 (2), 184 (3), 142 (4).

Preparation of 1-Heptyl-1-[2-(2-hydroxyethoxy)ethyl]-3-(1-methylethyl)urea (36b). The same procedure used to prepare compound **4a** was employed here. Thus, compound **35** (6.63 g, 32.6 mmol) and isopropyl isocyanate (3.20 mL, 32.6 mmol) gave, after chromatography (1:1 ethyl acetate–hexane), the product as an oil (4.71 g, 16.3 mmol, 50%). ^{1}H NMR ($CDCl_3$): δ 5.01 (1H, br s), 3.94–3.88 (1H, m), 3.75 (2H, t, J = 4.6 Hz), 3.62–3.60 (4H, m), 3.39 (2H, t, J = 5.0 Hz), 3.20 (2H, t, J = 7.7 Hz), 2.43 (1H, br s), 1.57–1.50 (2H, m), 1.35–1.26 (8H, m), 1.13 (6H, d, J = 6.6 Hz), 0.88 (3H, t, J = 5.6 Hz). MS (DCI–NH_3): *m/e* 289 (100), 227 (3), 204 (8), 186 (1).

Preparation of 1-[2-(2-Bromoethoxy)ethyl]-3-(2,4-di-

fluorophenyl)-1-heptylurea (37a). The same procedure used to convert **4a** to **5a** was employed here. Thus, compound **36a** (6.98 g, 19.5 mmol) gave, after workup and chromatography, the title product as a clear, colorless oil (7.17 g, 17.0 mmol, 87%). ^{1}H NMR ($CDCl_3$): δ 8.00–7.94 (1H, m), 7.84 (1H, br s), 6.85–6.77 (2H, m), 3.87 (2H, t, J = 6.2 Hz), 3.73 (2H, t, J = 4.6 Hz), 3.55–3.47 (4H, m), 3.34 (2H, dd, J = 8.0, 7.4 Hz), 1.66–1.56 (2H, m), 1.35–1.21 (8H, m), 0.88 (3H, t, J = 7.0 Hz). MS (DCI–NH_3): *m/e* 423 (98), 421 (100), 403 (4), 341 (16), 297 (5), 266 (4), 186 (28).

Preparation of 1-[2-(2-Bromoethoxy)ethyl]-1-heptyl-3-(1-methylethyl)urea (37b). The same general procedure used for compound **5a** was employed here. Thus, compound **36b** (3.81 g, 13.2 mmol) afforded the title compound as a clear, colorless oil (4.20 g, 11.9 mmol, 90%). ^{1}H NMR ($CDCl_3$): δ 5.03 (1H, br s), 3.91 (1H, heptet, J = 6.5 Hz), 3.79 (2H, t, J = 6.0 Hz), 3.62 (2H, t, J = 5.0 Hz), 3.46 (2H, t, J = 5.9 Hz), 3.39 (2H, t, J = 5.0 Hz), 3.22 (2H, dd, J = 8.1, 7.3 Hz), 1.58–1.51 (2H, m), 1.39–1.30 (8H, m), 1.15 (6H, d, J = 6.5 Hz), 0.88 (3H, t, J = 6.6 Hz). MS (DCI–NH_3): *m/e* 353 (94), 351 (100), 271 (18), 186 (17).

Preparation of 3-(2,4-Difluorophenyl)-1-[2-[2-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]ethoxy]ethyl]-1-heptylurea (38). A modification of the following procedure may be used for alkylation of many 2-mercaptoimidazoles with bromide-bearing compounds. A mixture of 4,5-diphenyl-2-mercapto-1*H*-imidazole (931 mg, 3.69 mmol), compound **37a** (1.93 g, 4.76 mmol), K_2CO_3 (674 mg, 4.88 mmol), and tetra-*n*-butylammonium iodide (360 mg, 0.97 mmol) in anhydrous THF (50 mL) was heated to gentle reflux for 2 h and then cooled and poured into water (200 mL). This mixture was extracted with ethyl acetate (2 × 200 mL), and the extracts were washed with brine (200 mL), combined, dried over $MgSO_4$, filtered, and evaporated. The residue was separated by flash chromatography (3:7 ethyl acetate–hexane) to afford the product as a solid, which was recrystallized from ether–hexane to give the pure title product, mp 106–108 °C (1.53 g, 2.58 mmol, 70%). ^{1}H NMR ($CDCl_3$): δ 7.84–7.76 (2H, m), 7.46–7.40 (4H, m), 7.32–7.19 (7H, m), 6.75–6.64 (2H, m), 3.82 (2H, t, J = 6.0 Hz), 3.68 (2H, t, J = 4.5 Hz), 3.48 (2H, t, J = 4.5, Hz), 3.28–3.23 (4H, m), 1.61–1.54 (2H, m), 1.27–1.18 (8H, m), 0.87 (3H, t, J = 6.1 Hz). ^{13}C NMR ($CDCl_3$): δ 157.1, 156.5, 152.3, 139.2, 128.4, 127.8, 127.5, 127.3, 124.1, 122.3, 110.5, 103.3, 70.4, 70.3, 47.9, 47.8, 33.7, 31.7, 29.0, 28.1, 26.8, 22.5, 14.0. MS (DCI–NH_3): *m/e* 593 (100), 503 (4), 438 (46), 343 (5), 253 (20). IR (KBr): 3323, 2928, 1655, 1612, 1512, 1490, 1466, 1448, 1430, 1406, 1258, 1201, 1140, 1101, 962, 765 cm^{-1}.

Preparation of 1-[2-[2-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]ethoxy]ethyl]-1-heptyl-3-(1-methylethyl)urea (39). The same general procedure used for compound **38** was employed here. Thus, 4,5-diphenyl-2-mercapto-1*H*-imidazole (718 mg, 2.84 mmol) and compound **37b** (1.06 g, 3.02 mmol) gave, after workup, chromatography, and recrystallization from ether–hexane, the title compound, mp 92–93 °C (1.48 g, 2.83 mmol, 99%). ^{1}H NMR ($CDCl_3$): δ 7.55–7.51 (4H, m), 7.46–7.20 (6H, m), 4.75 (1H, br d, J = 6.9 Hz), 3.91–3.79 (1H, m), 3.75 (2H, t, J = 5.7 Hz), 3.62 (2H, t, J = 5.1 Hz), 3.42 (2H, t, J = 7.7 Hz), 3.20 (2H, t, J = 5.7 Hz), 3.12 (2H, t, J = 7.7 Hz), 1.55–1.43 (2H, m), 1.33–1.14 (8H, m), 1.09 (6H, d, J = 6.2 Hz), 0.87 (3H, t, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 158.2, 139.5, 128–126, 70.1, 70.0, 47.5, 46.8, 42.4, 34.5, 31.7, 29.0, 28.2, 26.8, 23.4, 22.5, 14.0. MS (DCI–NH_3): *m/e* 524 (38), 523 (100), 438 (4), 253 (14). IR (KBr): 3366, 2928, 1623, 1535, 1510, 1490, 1466, 1449, 1366, 1114, 765, 697 cm^{-1}.

Preparation of 1-[2-[2-[4,5-Bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]ethoxy]ethyl]-3-(2,4-difluorophenyl)-1-heptylurea (40). The same general procedure used for compound **38** was employed here. Thus, 4,5-bis(4-methoxyphenyl)-2-mercapto-1*H*-imidazole (1.22 g, 3.91 mmol) and compound **37a** (2.25 g, 5.55 mmol) gave, after workup, chromatography, and recrystallization from ether–hexane, the title product, mp 100–102 °C (1.59 g, 2.44 mmol, 62%). ^{1}H NMR ($CDCl_3$): δ 7.84–7.73 (2H, m), 7.38 (4H, d, J = 8.8 Hz), 6.83 (4H, d, J = 8.8 Hz), 6.79–6.66 (2H, m), 3.98–3.76 (4H, m), 3.81 (6H, s), 3.50 (2H, t, J = 4.2 Hz), 3.32–3.24 (4H, m), 1.63–1.53 (2H, m), 1.30–1.20 (8H, m), 0.87 (3H, t, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 157.0, 156.5, 150.5, 138.2, 128.7, 124.2, 122.2, 113.8, 110.9. 103.3, 70.4, 70.3, 55.1, 47.9, 47.8, 33.9, 31.7, 29.0, 28.1, 26.8, 22.5, 14.0. MS (DCI–NH_3): *m/e* 653 (52), 498 (100), 343 (7), 313 (8). IR (KBr): 3323, 2930, 1656, 1613, 1522, 1503, 1465, 1431, 1294, 1247, 1201, 1175, 1100, 834 cm^{-1}.

Preparation of 1-[2-[2-[[4,5-Bis(4-methoxyphenyl)-1-*H*-imidazol-2-yl]thio]ethoxy]ethyl]-1-heptyl-3-(1-methylethyl)urea (41). The same general procedure used for compound **38** was employed here. Thus, 4,5-bis(4-methoxyphenyl)-2-mercapto-1*H*-imidazole (624 mg, 2.00 mmol) and compound 37b (1.00 g, 2.85 mmol) gave, after workup, chromatography, and recrystallization from ether–hexane, the title compound, mp 85–87 °C (1.11 g, 1.90 mmol, 95%). ^{1}H NMR ($CDCl_3$): δ 7.44 (4H, d, J = 8.6 Hz), 6.84 (4H, d, J = 8.6 Hz), 4.77 (1H, d, J = 6.6 Hz), 3.83 (1H, heptet, J = 6.6 Hz), 3.80 (6H, s), 3.73 (2H, t, J = 5.8 Hz), 3.61 (2H, t, J = 5.1 Hz), 3.41 (2H, t, J = 5.1 Hz), 3.18 (2H, t, J = 5.8 Hz), 3.12 (2H, t, J = 7.6 Hz), 1.55–1.43 (2H, m), 1.30–1.18 (8H, m), 1.10 (6H, d, J = 6.6 Hz), 0.87 (3H, t, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 158.3, 138.6, 128.8, 113.7, 70.3, 55.0, 47.6, 47.1, 42.3, 34.1, 31.7, 30.8, 29.0, 28.2, 26.8, 23.4, 22.4, 13.9. MS (DCI–NH_3): *m/e* 584 (40), 583 (100), 498 (31), 313 (30), IR (KBr): 3365, 2929, 1616, 1522, 1503, 1465, 1294, 1247, 1175, 834 cm^{-1}.

Preparation of 2-Bromoethyl Butyl Ether (43a). A solution of PBr_3 (5.20 mL, 54.8 mmol) in benzene (10 mL) was cooled to 0 °C and treated with pyridine (2.3 mL). After 5 min, a solution of 2-hydroxyethyl butyl ether ("butyl cellosolve"; 20.0 mL, 153 mmol) and pyridine (0.8 mL) in benzene (10 mL) was added dropwise over 1 h. After stirring for an additional 56 h, the mixture was carefully poured into ice water. The mixture was allowed to melt and then extracted with ethyl acetate (2 × 200 mL). The extracts were dried over saturated brine, combined, dried over K_2CO_3, filtered, and evaporated to yield sufficiently pure title product as a liquid (11.0 g, 61.1 mmol, 40%). ^{1}H NMR ($CDCl_3$): δ 3.67 (2H, t, J = 6.4 Hz), 3.45–3.37 (4H, m), 1.56–1.45 (2H, m), 1.38–1.26 (2H, m), 0.86 (3H, t, J = 7.3 Hz).

Preparation of 2-(2-Bromoethoxy)ethyl Ethyl Ether (43b). The same procedure used for compound **43a** was employed here. Thus, 2-(2-ethoxyethoxy)ethanol (20.0 mL, 149 mmol), PBr_3 (5.10 mL, 53.7 mmol), and pyridine (3.10 mL, 38.3 mmol) gave, after workup, the title product as a liquid (18.9 g, 96.4 mmol, 65%). ^{1}H NMR ($CDCl_3$): δ 3.82 (2H, t, J = 6.4 Hz), 3.69–3.66 (2H, m), 3.62–3.46 (6H, m), 1.22 (3H, t, J = 7.0 Hz).

Preparation of *N*-(2-Butoxyethyl)-5-bromopentanamide (46a). A solution of compound **43a** (11.0 g, 61.1 mmol), sodium azide (5.27 g, 81.1 mmol), and sodium iodide (2.26 g, 15.1 mmol) in DMF (70 mL) was heated to 60 °C for 18 h and then cooled and poured into ethyl acetate (300 mL). This mixture was washed with water (3 × 300 mL), dried over $MgSO_4$, filtered, and evaporated to afford the crude intermediate azide (**44a**) as an oil (8.73 g, 61 mmol, 100%). Compound **44a** (8.73 g, 61 mmol) was dissolved in THF (60 mL) and cooled to 0 °C. Solid triphenylphosphine (17.6 g, 67.2 mmol) was added in small portions over 5 min, and the mixture was allowed to warm to ambient temperature and stirred for 10 h. Water (2.0 mL, 110 mmol) was added, and the mixture was allowed to stir for an additional 24 h. At this point, the intermediate amine compound **45a** was not isolated but the remaining reaction performed directly in the same reaction vessel. Solid K_2CO_3 (14.3 mmol, 103 mmol) was first added, and the solution was stirred for 2 h. Then, a solution of 5-bromovaleryl chloride (10.0 mL, 75.2 mmol) in THF (10 mL) was added dropwise over 30 min. After stirring for an additional 4 h, the mixture was poured into water (400 mL) and extracted with ethyl acetate (2 × 400 mL). The extracts were combined, dried over $MgSO_4$, filtered, and evaporated. Chromatography (3:7 ethyl acetate–hexane) then afforded the title product as an oil (10.6 g, 37.9 mmol, 62%). ^{1}H NMR ($CDCl_3$): δ 5.93 (1H, br s), 3.58–3.42 (8H, m), 2.23 (2H, t, J = 7.1 Hz), 1.96–1.88 (2H, m), 1.88–1.77 (2H, m), 1.61–1.51 (2H, m), 1.43–1.26 (2H, m), 0.93 (3H, t, J = 7.3 Hz). MS (DCI–NH_3): *m/e* 282 (97), 280 (100), 238 (16), 236 (47), 200 (64).

Preparation of *N*-[2-(2-Ethoxyethoxy)ethyl]-5-bromopentanamide (46b). The same procedure used for com-

pound **46a** was employed here. Thus, compound **43b** (18.9 g, 96.4 mmol) was used to prepare the title compound as an oil (16.7 g, 56.5 mmol, 59%). ^{1}H NMR ($CDCl_3$): δ 6.12 (1H, br s), 3.69–3.39 (12H, m), 2.22 (2H, t, J = 7.0 Hz), 1.93–1.75 (4H, m), 1.23 (3H, t, J = 7.0 Hz). MS (DCI–NH_3): *m/e* 298 (46), 296 (48), 254 (33), 252 (100), 216 (54), 162 (20), 101 (80).

Preparation of *N*-[2-(2-Methoxyethoxy)ethyl]-5-bromopentanamide (46c). The same set of procedures used in the preparation of compound **46a** were employed here. Thus, bromide compound **43c** (10.0 mL, 73.6 mmol) was used to prepare the title product as a colorless oil (9.34 g, 33.1 mmol, 53%). ^{1}H NMR ($CDCl_3$): δ 6.12 (1H, br s), 3.63 (2H, td, J = 3.8, 1.5 Hz), 3.60–3.54 (4H, m), 3.52–3.38 (4H, m), 3.40 (3H, s), 2.22 (2H, t, J = 7.1 Hz), 1.94–1.78 (4H, m). MS (DCI–NH_3): *m/e* 284 (7), 282 (7), 280 (20), 279 (100).

Preparation of *N*-[2-(2-Hydroxyethoxy)ethyl]-5-bromopentanamide (46d). A solution of 2-(2-aminoethoxy)-ethanol (10.0 mL, 139 mmol) and triethylamine (20.0 mL, 143 mmol) in THF (100 mL) was cooled to 0 °C and treated with a solution of 5-bromovaleryl chloride (10.0 mL, 75.2 mmol) in THF (30 mL) dropwise over 20 min. The mixture was allowed to stir for 48 h and then poured into water (400 mL). This mixture was extracted with CH_2Cl_2 (2 × 400 mL), and the extracts were combined, dried over $MgSO_4$, filtered, and evaporated. The residual oil was separated by flash chromatography (3:7 acetone–hexane) to afford the product as an oil (6.43 g, 24.0 mmol, 32%). IR (KBr): 3500, 3298, 1649 cm^{-1}.

Preparation of *N*-(2-Butoxyethyl)-5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentanamide (47a). The same procedure used for compound **38** was employed here. Thus, compound **46a** (3.89 g, 13.9 mmol) was used to produce the title product (8.69 g) as an oil.

Preparation of *N*-[2-(2-Ethoxyethoxy)ethyl]-5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentanamide (47b). The same procedure used for compound **38** was employed here. Thus, compound **46b** (4.89 g, 16.5 mmol) was used to prepare the title product (11.4 g) as an oil.

Preparation of *N*-[2-(2-Hydroxyethoxy)ethyl]-5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentanamide (47c). The general procedure detailed for the preparation of compound **38** was used here. Thus, compound **46d** (6.43 g, 24.0 mmol) was used to prepare, after workup and chromatography (1:1 acetone–hexane), the product as a solid, mp 176–178 °C (10.1 g, 23.0 mmol, 96%). ^{1}H NMR ($CDCl_3$): δ 7.58–7.50 (4H, m), 7.35–7.25 (6H, m), 6.32 (1H, br s), 3.69 (2H, t, J = 4.4 Hz), 3.50 (2H, t, J = 4.4 Hz), 3.39 (2H, t, J = 5.0 Hz), 3.24 (2H, q, J = 5.1 Hz), 3.01 (2H, t, J = 6.5 hz), 2.29 (2H, t, J = 6.6 Hz), 1.98–1.88 (2H, m), 1.75–1.63 (4H, m).

Preparation of *N*-[2-(2-Methoxyethoxy)ethyl]-5-[4,5-bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentanamide (47d). The standard alkylation procedure used above for compound **38** was employed here. Thus, compound **46c** (9.20 g, 32.6 mmol) was used in the preparation of the title compound, which was obtained after workup and chromatography (1:1 acetone–hexane) as an oil (15.7 g, 30.5 mmol, 94%). ^{1}H NMR ($CDCl_3$): δ 7.43 (4H, d, J = 8.8 Hz), 6.81 (4H, d, J = 8.8 Hz), 6.42 (1H, br t, J = 4 Hz), 3.79 (6H, s), 3.56–3.49 (4H, m), 3.38 (2H, t, J = 5.1 Hz), 3.34 (3H, s), 3.28–3.21 (2H, m), 2.95 (2H, t, J = 6.5 Hz), 2.23 (2H, t, J = 6.8 Hz), 1.90–1.81 (2H, m), 1.69–1.59 (2H, m). MS (DCI–NH_3): *m/e* 515 (37), 514 (100), 281 (12), 242 (11).

Preparation of *N*-[2-(2-Hydroxyethoxy)ethyl]-5-[[4,5-bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentanamide (47e). The same general procedure used to prepare compound **38** was employed here. Thus, compound **46d** (3.46 g, 12.9 mmol) was used to make, after workup and chromatography, the title compound as an amorphous solid (6.31 g, 12.6 mmol, 98%). ^{1}H NMR ($CDCl_3$): δ 7.40 (4H, d, J = 8.8 Hz), 6.82 (4H, d, J = 8.8 Hz), 6.63 (1H, t, J = 5.3 Hz), 3.79 (6H, s), 3.67 (2H, dd, J = 5.9, 4.0 Hz), 3.49–3.46 (2H, m), 3.40 (2H, t, J = 5.0 Hz), 3.26 (2H, q, J = 5.1 Hz), 2.94 (2H, t, J = 6.6 Hz), 2.22 (2H, t, J = 6.6 Hz), 1.90–1.79 (2H, m), 1.66–1.57 (2H, m). MS (DCI–NH_3): *m/e* 501 (34), 500 (100).

Preparation of *N*-[2-(2-Ethoxyethoxy)ethyl]-5-[[4,5-bis-[4-(methylthio)phenyl]-1*H*-imidazol-2-yl]thio]pentanamide (47f). A solution of compound **46b** (1.36 g, 4.61 mmol), 4,5-bis[4-(methylthio)phenyl]-2-mercapto-1*H*-imidazole (1.20 g, 3.49 mmol), K_2CO_3 (0.63 g, 4.56 mmol), and sodium iodide (40 mg) in THF (25 mL) was heated to reflux for 16 h. The mixture was cooled and poured into water (120 mL). This mixture was extracted with ethyl acetate (2 × 120 mL), and the extracts were combined, dried over MgSO4, filtered, and evaporated. The oily residue was separated by flash chromatography (1:3 pentane–ethyl acetate) to afford the title product (1.28 g, 2.29 mmol, 66%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.5 (4H, d, J = 8.0 Hz), 7.15 (4H, d, J = 8.4 Hz), 6.3–6.2 (1H, m), 3.6 (6H, s), 3.35 (2H, t, J = 5.0 Hz), 3.2 (2H, t, J = 5.1 Hz), 2.95 (2H, t, J = 6.2 Hz), 2.3 (2H, t, J = 6.2 Hz), 1.95 (2H, pentet, J = 7.1 Hz), 1.6 (2H, pentet, J = 7.0 Hz), 1.25–1.15 (4H, m). MS (DCI–NH_3): *m/e* 560 (100). IR (KBr): 3166, 3076, 2973, 2921, 1645, 1504, 1488, 1104 cm^{-1}.

Preparation of *N*-[2-(2-Methoxymethoxy)ethyl]-5-[[4,5-bis(4-dimethylamino)-1*H*-imidazol-2-yl]thio]pentanamide (47g). The standard alkylation procedure used for compound **38** was employed here. Thus, compound **46c** (2.12 g, 7.51 mmol) was used in the preparation of the title compound, which was obtained after workup and chromatography (1:4 2-propanol–ethyl acetate) as a gum (2.92 g, 5.41 mmol, 79%). ^{1}H NMR ($CDCl_3$): δ 7.44 (4H, d, J = 8.8 Hz), 6.67 (4H, d, J = 8.8 Hz), 6.16 (1H, br t, J = 5 Hz), 3.58–3.47 (4H, m), 3.37 (3H, s), 3.36–3.27 (2H, m), 3.26–3.18 (2H, m), 3.00–2.90 (2H, m), 2.95 (12H, s), 2.24 (2H, t, J = 6.6 hz), 1.99–1.88 (2H, m), 1.74–1.62 (2H, m). MS (DCI–NH_3): *m/e* 541 (34), 540 (100), 307 (7), 236 (17).

Preparation of 2-[[5-[(2-Butoxyethyl)amino]pentyl]-thio]-4,5-diphenyl-1*H*-imidazole (48a). Amide compound **47a** (8.69 g) was dissolved in toluene (50 mL) and cooled to 0 °C. A solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in toluene (15.0 mL, 3.40 M, 51.0 mmol) was added dropwise by syringe, and the reaction mixture was taken out of the ice bath and warmed to reflux for 4 h. It was cooled again to 0 °C and the reaction quenched by the dropwise addition of aqueous NaOH (15 mL, 2 N). The mixture was washed with brine, dried over K_2CO_3, filtered, and evaporated to afford the title product as an oil (4.98 g).

Preparation of 2-[[5-[[2-(2-Ethoxyethoxy)ethyl]amino]-pentyl]thio]-4,5-diphenyl-1*H*-imidazole (48b). Amide compound **47b** (11.4 g) was treated in a manner similar to that to make **48a** to afford the title product as an oil (5.91 g).

Preparation of 4,5-Diphenyl-2-[[5-[[2-(2-hydroxyethoxy)ethyl]amino]pentyl]thio]-1*H*-imidazole (48c). The same general procedure used for compound **48a** was employed here. Thus, compound **47c** (6.59 g, 15.0 mmol) was used to prepare the title compound as a crude oil, which was used directly in the next step (6.27 g, 14.7 mmol, 98%).

Preparation of 4,5-Bis(4-methoxyphenyl)-2-[[5-[*N*-[2-(2-hydroxyethoxy)ethyl]amino]pentyl]thio]-1*H*-imidazole (48e). The same reduction procedure used for compound **48a** was employed here. Thus, compound **47e** (3.90 g, 7.81 mmol) was used to prepare the title compound as a semisolid (3.79 g, 7.81 mmol, 100%). ^{1}H NMR ($CDCl_3$): δ 7.33 (2H, br s), 7.17 (2H, d, J = 7.7 Hz), 7.10 (2H, d, J = 7.3 Hz), 6.76 (4H, br d, J = 8 Hz), 3.73 (6H, s), 3.60–3.40 (10H, m), 2.95 (2H, t, J = 6.5 Hz), 1.63–1.44 (6H, m). MS (DCI–NH_3): *m/e* 487 (32), 486 (100), 399 (12), 313 (5).

Preparation of 4,5-Bis[4-(methylthio)phenyl]-2-[[5-[[2-(2-ethoxyethoxy)ethyl]amino]pentyl]thio]-1*H*-imidazole (48f). The reduction procedure used for compound **3** was employed here. Thus, compound **47f** (1.12 g, 2.00 mmol) was used in the preparation of the title compound, which was obtained after workup and chromatography (1:3 methanol–ethyl acetate) as an oil (1.15 g, 2.00 mmol, 100%). ^{1}H NMR ($CDCl_3$): δ 7.5–7.3 (4H, m), 7.2–7.1 (4H, m), 3.6 (4H, s), 3.55–3.45 (4H, m), 3.1 (2H, t, J = 6.6 Hz), 2.70 (2H, t, J = 4.9 Hz), 2.65–2.55 (2H, m), 2.5 (6H, s), 1.8–1.5 (6H, m), 1.15 (3H, t, J = 7.0 Hz). MS (DCI–NH_3): *m/e* 546 (100). Ir (KBr): 3637, 3075, 2923, 2864, 1604, 1507, 1490, 1437, 1371 cm^{-1}.

Preparation of 4,5-Bis[4-(dimethylamino)phenyl]-2-[[5-[[2-(2-methoxyethoxy)ethyl]amino]pentyl]thio]-1*H*-imidazole (48g). The reduction procedure used for compound **3** was employed here. Thus, compound **47g** (2.92 g, 5.41 mmol) was used in the preparation of the title compound, which was

obtained after workup as an oil (2.81 g, 5.35 mmol, 99%). ^{1}H NMR ($CDCl_3$): δ 7.39 (4H, br s), 6.68 (4H, d, J = 8.8 Hz), 3.60–3.50 (6H, m), 3.38 (3H, s), 3.03 (2H, t, J = 7 Hz), 2.95 (12H, s), 2.74 (2H, t, J = 6 Hz), 2.60 (2H, t, J = 6 Hz), 1.78–1.62 (2H, m), 1.52–1.41 (4H, m). MS (DCI–NH_3): *m/e* 527 (34), 526 (100), 307 (19), 188 (91).

Preparation of 1-(2-Butoxyethyl)-3-(2,4-difluorophenyl)-1-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]urea (49). The same procedure used for compound **4a** was employed here. Thus, compound **48a** (2.49 g, 5.69 mmol) and 2,4-difluorophenyl isocyanate (0.70 mL, 5.91 mmol) gave, after evaporation of the reaction mixture and chromatography (1:3 ethyl acetate–hexane), the title product as a crystalline solid, mp 69–71 °C (2.01 g, 3.39 mmol, 60%). ^{1}H NMR ($CDCl_3$): δ 11.18 (1H, br s), 8.33 (1H, s), 7.62–7.50 (4H, m), 7.35 (1H, br s), 7.31–7.24 (6H, m), 6.72–6.64 (1H, m), 6.54–6.47 (1H, m), 3.63–3.44 (8H, m), 2.97 (2H, t, J = 6.6 Hz), 1.81–1.72 (2H, m), 1.71–1.49 (6H, m), 1.42–1.28 (2H, m), 0.91 (3H, t, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 157.4, 157.2, 153.0, 140.0, 128.2, 127.7, 126.9, 124.2, 122.9, 110.5, 103.1, 71.8, 70.5, 48.6, 46.8, 35.5, 31.1, 29.0, 27.2, 24.6, 19.1, 13.7. MS (DCI–NH_3): *m/e* 594 (45), 593 (100), 438 (12). IR (KBr): 3316, 2934, 1656, 1612, 1538, 1508, 1490, 1465, 1430, 1405, 1364, 1256, 1229, 1202, 1140, 1095, 962, 765, 697 cm^{-1}.

Preparation of 3-(2,4-Difluorophenyl)-1-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-1-[2-(2-ethoxyethoxy)ethyl]urea (50). The same procedure used for compound **4a** was employed here. Thus, compound **48b** (2.95 g, 6.50 mmol) and 2,4-difluorophenyl isocyanate (0.80 mL, 6.75 mmol) gave, after evaporation of the reaction mixture and chromatography (3:7 ethyl acetate–hexane), the title product as a semisolid (3.81 g, 6.26 mmol, 96%). ^{1}H NMR ($CDCl_3$): δ 11.28 (1H, br s), 8.25 (1H, s), 7.64–7.52 (3H, m), 7.39–7.30 (2H, m), 7.27–7.17 (6H, m), 6.71–6.63 (1H, m), 6.55–6.49 (1H, m), 3.73–3.69 (4H, m), 3.67–3.59 (2H, m), 3.56–3.43 (6H, m), 2.97 (2H, t, J = 6.6 Hz), 1.80–1.71 (2H, m), 1.70–1.60 (2H, m), 1.59–1.47 (2H, m), 1.13 (3H, t, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 157.5, 157.2, 153.1, 140.0, 128.2, 127.7, 126.9, 124.1, 123.2, 110.5, 103.1, 71.4, 71.0, 69.5, 66.5, 48.4, 46.8, 35.5, 29.0, 27.2, 24.6, 14.9. IR (KBr): 3307, 2931, 1656, 1612, 1540, 1509, 1490, 1463, 1448, 1431, 1406, 1374, 1257, 1232, 1202, 1140, 1096, 1072, 962, 846, 764, 697 cm^{-1}. MS (DCI–NH_3): *m/e* 610 (39), 609 (100), 454 (22).

Preparation of 3-(2,4-Difluorophenyl)-1-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-1-[2-(2-hydroxyethoxy)ethyl]urea (51). The same procedure used for compound **4a** was employed here. Thus, compound **48c** (2.92 g, 6.86 mmol) and 2,4-difluorophenyl isocyanate (0.90 mL, 7.60 mmol) were used to prepare the title compound as an amorphous solid, mp <100 °C (3.14 g, 5.41 mmol, 79%). ^{1}H NMR ($CDCl_3$): δ 8.09 (1H, br s), 7.64 (1H, td, J = 9.2, 5.8 Hz), 7.50–7.40 (4H, m), 7.29–7.20 (6H, m), 6.75–6.67 (1H, m), 6.56 (1H, br t, J = 7.8 Hz), 3.80 (2H, t, J = 4.6 Hz), 3.72 (2H, t, J = 4.4 Hz), 3.68 (2H, t, J = 5.1 Hz), .53 (2H, t, J = 4.4 Hz), 3.46 (2H, t, J = 7.0 Hz), 3.01 (2H, t, J = 6.4 Hz), 1.80–1.49 (6H, m). ^{13}C NMR ($CDCl_3$): δ 157.3, 157.0, 152.9, 139.9, 128.2, 127.7, 127.0, 124.1, 123.1, 110.7, 103.2, 73.1, 71.3, 61.3, 48.6, 47.1, 35.4, 28.9, 27.3, 24.6. MS (DCI–NH_3): *m/e* 582 (15), 581 (32), 426 (100), 253 (4). IR (KBr): 3287, 3150, 2933, 1656, 1612, 1513, 1490, 1463, 1448, 1431, 1406–1000 (13 peaks), 962, 766, 697 cm^{-1}.

Preparation of 1-(2-Butoxyethyl)-1-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-3-(1-methylethyl)urea (52). The same procedure used for compound **4a** was employed here. Thus, compound **48a** (2.49 g, 5.69 mmol) and isopropyl isocyanate (0.60 mL, 6.11 mmol) gave, after evaporation of the reaction mixture and chromatography (3:7 ethyl acetate–hexane), the title product as a semisolid (2.75 g, 5.26 mmol, 92%). ^{1}H NMR ($CDCl_3$): δ 12.12 (1H, br s), 7.62 (2H, d, J = 8.1 Hz), 7.52 (2H, d, J = 8.1 Hz), 7.33–7.17 (6H, m), 5.84 (1H, d, J = 7.4 Hz), 3.70 (1H, heptet, J = 6.6 Hz), 3.52 (2H, t, J = 4.2 Hz), 3.45 (2H, t, J = 6.6 Hz), 3.39 (2H, t, J = 6.6 Hz), 3.33 (2H, t, J = 4.4 Hz), 2.96 (2H, t, J = 6.4 Hz), 1.78–1.68 (2H, m), 1.61–1.37 (8H, m), 1.01 (6H, d, J = 6.6 hz), 0.92 (3H, t, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 159.2, 140.2, 138.4, 134.9, 131.0, 129.2, 128.3, 128.0, 127.9, 127.8, 127.1, 126.5, 71.4, 71.1, 60.2, 48.1, 46.5, 42.2, 35.4, 31.6, 29.0, 27.4, 24.5, 23.2, 19.2, 13.7. IR (KBr): 3351, 2961, 2932, 1624, 1539, 1510, 1490, 1466, 1448, 1404, 1366, 1318, 1276, 1241, 1190, 1109, 1072, 764, 696 cm^{-1}. MS (DCI–NH_3): *m/e* 524 (37), 523 (100), 438 (2).

Preparation of 1-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-1-[2-(2-ethoxyethoxy)ethyl]-3-(1-methylethyl)urea (53). The same procedure used for compound **4a** was employed here. Thus, compound **48b** (2.95 g, 6.50 mmol) and isopropyl isocyanate (0.70 mL, 7.12 mmol) gave, after evaporation of the reaction mixture and chromatography (3:7 ethyl acetate–hexane), the title product as a semisolid (3.24 g, 6.02 mmol, 93%). ^{1}H NMR ($CDCl_3$): δ 7.52–7.42 (4H, m), 7.27–7.16 (7H, m), 5.62 (1H, d, J = 6.9 Hz), 3.73 (1H, heptet, J = 6.6 Hz), 3.60–3.52 (6H, m), 3.49 (2H, q, J = 7.0 Hz), 3.32–3.26 (4H, m), 2.95 (2H, t, J = 6.9 Hz), 1.71–1.63 (2H, m), 1.55–1.46 (2H, m), 1.43–1.36 (2H, m), 1.20 (3H, t, J = 7.0 Hz), 1.03 (6H, d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 159.0, 140.2, 128.1, 127.8, 126.8, 71.5, 70.8, 69.6, 60.3, 47.8, 46.5, 42.2, 35.3, 29.0, 27.3, 24.6, 23.2, 15.0. MS (DCI–NH_3): *m/e* 540 (34), 539 (100), 454 (3), 253 (2). IR (KBr): 3349, 2971, 1620, 1536, 1490, 1465, 1448, 1404, 1366, 1318, 1272, 1241, 1107, 1070, 765, 697 cm^{-1}.

Preparation of 1-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-1-[2-(2-hydroxyethoxy)ethyl]-3-(1-methylethyl)urea (54). The same procedure used for compound **4a** was employed here. Thus, compound **48c** (3.35 g, 7.87 mmol) and isopropyl isocyanate (0.90 mL, 9.16 mmol) were used to prepare the title compound, after chromatography (1:1 acetone–hexane), as an amorphous solid (4.02 g, 7.87 mmol, 100%). ^{1}H NMR ($CDCl_3$): δ 11.73 (1H, br s), 7.55 (4H, br s), 7.31–7.21 (6H, m), 5.47 (1H, d, J = 6 Hz), 3.79–3.70 (3H, m), 3.64–3.58 (4H, m), 3.40–3.33 (4H, m), 2.98 (2H, t, J = 7 Hz), 2.44 (1H, br s), 1.80–1.69 (2H, m), 1.61–1.46 (4H, m), 1.06 (6H, d, J = 7 Hz). ^{13}C NMR ($CDCl_3$): δ 158.8, 140.1, 128.2, 127.8, 126.9, 72.7, 71.2, 61.7, 47.9, 46.8, 42.3, 35.3, 28.9, 27.4, 24.6, 23.2. MS (DCI–NH_3): *m/e* 512 (34), 511 (100), 426 (20). IR (KBr): 3348, 2931, 1625, 1538, 1510, 1490, 1465, 1448, 1403–1027 (9 peaks), 765, 697 cm^{-1}.

Preparation of 1-[5-[[4,5-Bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentyl]-3-(2,4-difluorophenyl)-1-[2-(2-methoxyethoxy)ethyl]urea (55). The reduction reaction used in the synthesis of amine compound **48a** was employed in the generation of intermediate compound **48d**. Thus, amide compound **47d** (15.4 g, 30.0 mmol) and Red-Al (20.0 mL of a 3.4 M solution in toluene, 68.0 mmol) were used to make amine **48d** (13.9 g, 27.9 mmol, 93%), which was taken on directly in the next step. The procedure used was that employed for compound **4a**, so that compound **48d** (6.97 g, 13.9 mmol) and 2,4-difluorophenyl isocyanate (2.00 mL, 16.9 mmol) gave, after chromatography (1:3 acetone–hexane), the title product as a semisolid (7.48 g, 11.4 mmol, 82%). ^{1}H NMR ($CDCl_3$): δ 8.21 (1H, br s), 7.60 (1H, td, J = 9.2, 5.9 Hz), 7.54 (2H, br s), 7.27 (2H, br s), 6.80 (4H, d, J = 8.8 Hz), 6.69 (1H, td, J = 8.4, 2.5 Hz), 6.60–6.51 (1H, m), 3.80 (6H, s), 3.76–3.69 (4H, m), 3.59–3.51 (4H, m), 3.45 (2H, t, J = 6.6 Hz), 3.32 (3H, s), 2.97 (2H, t, J = 6.4 hz), 1.80–1.51 (6H, m). ^{13}C NMR ($CDCl_3$): δ 158.5, 157.4, 153.0, 138.9, 128.9, 124.1, 123.3, 113.6, 111.6, 103.1, 71.5, 71.4, 70.9, 58.7, 55.1, 48.3, 46.8, 35.7, 29.0, 27.1, 24.5. MS (DCI–NH_3): *m/e* 656 (4), 655 (10), 500 (71), 156 (100). IR (KBr): 3154, 2933, 1657, 1613, 1521, 1503, 1464, 1431, 1404, 1293, 1247, 1202, 1175, 1140, 1096, 1032, 835 cm^{-1}.

Preparation of 1-[5-[[4,5-Bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentyl]-3-(2,4-difluorophenyl)-1-[2-(2-hydroxyethoxy)ethyl]urea (56). The same procedure used for the synthesis of compound **4a** was employed here. Thus, compound **48e** (1.90 g, 3.91 mmol) and 2,4-difluorophenyl isocyanate (0.50 mL, 4.22 mmol) were used to prepare the title compound as a gum (1.41 g, 2.20 mmol, 56%). ^{1}H NMR ($CDCl_3$): δ 8.09 (1H, br s), 7.67 (1H, dt, J = 9.2, 3.3 Hz), 7.37 (4H, br s), 6.80 (4H, d, J = 9.8 Hz), 6.79–6.55 (3H, m), 3.79 (6H, s), 3.75–3.65 (6H, m), 3.54 (2H, t, J = 4.4 Hz), 3.44 (2H, t, J = 6.6 Hz), 2.98 (2H, t, J = 6.5 Hz), 2.50 (1H, br s), 1.80–1.49 (6H, m). ^{13}C NMR ($CDCl_3$): δ 158.5, 157.2, 157.0, 153.0, 139.0, 128.9, 124.1, 123.0, 113.6, 111.0, 103.3, 73.1, 71.2, 61.1, 55.0, 48.5, 47.2, 35.3, 29.0, 27.3, 24.8. IR (KBr): 3294, 2935, 1656, 1613, 1522, 1504, 1464, 1431, 1293, 1248, 12020–963

(7 peaks), 835 cm^{-1}. MS (DCI–NH_3): *m/e* 642 (6), 641 (19), 486 (100), 313 (4).

Preparation of 1-[5-[[4,5-Bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentyl]-1-[2-(2-methoxyethoxy)ethyl]-3-(1-methylethyl)urea (57). The same procedure used to make compound **4a** was employed here. Thus, compound **48d** (3.98 g, 7.97 mmol) and isopropyl isocyanate (2.00 mL, 20.4 mmol) were used to prepare, after workup and chromatography (1:3 acetone–hexane), the title product as a solid, mp <50 °C (3.81 g, 6.52 mmol, 82%). ^1H NMR ($CDCl_3$): δ 11.81 (1H, br s), 7.44 (4H, br s), 6.82 (4H, d, J = 8.4 Hz), 5.65 (1H, d, J = 7.4 Hz), 3.80 (6H, s), 3.75 (1H, m, J = 6.2 Hz), 3.65–3.51 (6H, m), 3.36 (3H, s), 3.36–3.30 (4H, m), 2.94 (2H, t, J = 7.2 Hz), 1.78–1.68 (2H, m), 1.59–1.43 (4H, m), 1.04 (6H, d, J = 6.2 Hz). ^{13}C NMR ($CDCl_3$): δ 159.1, 139.0, 129.0, 113.6, 71.6, 70.6, 58.8, 55.1, 47.7, 45.9, 42.3, 36.2, 28.7, 27.1, 23.9, 23.2. MS (DCI–NH_3): *m/e* 586 (35), 585 (100), 500 (12), 279 (4). IR (KBr): 3352, 2932, 1615, 1574, 1522, 1503, 1464, 1442, 1404, 1366, 1294, 1246, 1175, 1106, 1033, 834, 754 cm^{-1}.

Preparation of 1-[5-[[4,5-Bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentyl]-1-[2-(2-hydroxyethoxy)ethyl]-3-(1-methylethyl)urea (58). The same procedure used for the synthesis of compound **4a** was employed here. Thus, compound **48e** (1.90 g, 3.91 mmol) and isopropyl isocyanate (0.50 mL, 5.09 mmol) were used to prepare the title compound as a gum (1.73 g, 3.03 mmol, 78%). ^1H NMR ($CDCl_3$): δ 7.45 (4H, br d, J = 8.5 Hz), 6.83 (4H, d, J = 8.5 Hz), 5.46 (1H, br d, J = 7.3 Hz), 3.80 (6H, s), 3.80–3.72 (3H, m), 3.63–3.58 (4H, m), 3.41–3.34 (4H, m), 2.96 (2H, t, J = 6.4 Hz), 1.79–1.69 (2H, m), 1.63–1.46 (4H, m), 1.05 (6H, d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 158.8, 139.2, 129.0, 113.6, 72.7, 71.1, 61.0, 55.0, 47.8, 46.9, 42.3, 35.2, 29.0, 27.5, 24.8, 23.2. MS (DCI–NH_3): *m/e* 572 (27), 571 (7), 486 (100), 313 (23). IR (KBr): 3348, 2932, 1616, 1522, 1503, 1464, 1442–1294 (4 peaks), 1247, 1176, 1123–967 (4 peaks), 834 cm^{-1}.

Preparation of 1-[5-[[4,5-Bis[4-(methylthio)phenyl]-1*H*-imidazol-2-yl]thio]pentyl]-1-[2-(2-ethoxyethoxy)ethyl]-3-(1-methylethyl)urea (59). The same procedure used for the synthesis of compound **4a** was employed here. Thus, compound **48f** (0.65 g, 1.19 mmol) and isopropyl isocyanate (0.16 mL, 1.65 mmol) were used in the preparation of the title compound, which was obtained after workup and chromatography (1:3 pentane–ethyl acetate) as an amorphous solid (0.64 g, 1.01 mmol, 85%). ^1H NMR ($CDCl_3$): δ 7.5 (4H, d, J = 8.5 Hz), 7.15 (4H, d, J = 8.5 Hz), 5.9–5.8 (1H, m), 3.7–3.3 (13H, m), 3.05–2.95 (2H, m), 2.5 (6H, s), 1.8–1.7 (2H, m), 1.65–1.25 (4H, m), 1.2 (3H, t, J = 7.0 Hz), 1.05 (6H, d, J = 6.6 Hz). MS (DCI–NH_3): *m/e* 631 (100). IR (KBr): 3348, 3126, 2923, 2868, 1621, 1540, 1506, 1489, 1367 cm^{-1}.

Preparation of 1-[5-[[4,5-Bis[4-(dimethylamino)phenyl]-1*H*-imidazol-2-yl]thio]pentyl]-1-[2-(2-methoxyethoxy)ethyl]-3-(1-methylethyl)urea (60). The same procedure used for the synthesis of compound **4a** was employed here. Thus, compound **48g** (2.81 g, 5.35 mmol) and isopropyl isocyanate (0.70 mL, 7.13 mmol) were used in the preparation of the title compound, which was obtained as a solid foam (mp 63–65 °C) after workup, chromatography (ethyl acetate), and evaporation from ether solution (1.13 g, 1.85 mmol, 35%). ^1H NMR ($CDCl_3$): δ 10.89 (1H, br s), 7.60–7.30 (4H, br), 6.68 (4H, d, J = 8.4 Hz), 5.61 (1H, br d, J = 4.0 Hz), 3.81 (1H, m, J = 6.6 Hz), 3.67–3.52 (6H, m), 3.41–3.31 (2H, m), 3.37 (3H, s), 3.02–2.92 (18H, m), 1.80–1.40 (6H, m), 1.07 (6H, d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 159.0, 149.2, 138.0, 128.5, 112.2, 71.6, 71.5, 70.6, 58.8, 47.8, 46.4, 42.2, 40.4, 36.1, 29.0, 27.4, 24.4, 23.2. MS (DCI–NH_3): *m/e* 612 (8), 611 (20), 526 (15), 307 (100). IR (KBr): 3352, 2928, 1616, 1530, 1510, 1466, 1444, 1352, 1272, 1238, 1194, 1166, 1130, 1062, 946, 820 cm^{-1}.

Preparation of Ethyl 5-[[4,5-Bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentanoate (62b). The same general alkylation procedure used for compound **38** was employed here. Thus, 4,5-bis(4-methoxyphenyl)-2-mercapto-1*H*-imidazole (10.0 g, 32.0 mmol), ethyl 5-bromovalerate (5.10 mL, 32.0 mmol), K_2CO_3 (5.75 g, 41.6 mmol), and tetra-*n*-butylammonium iodide (2.36 g, 6.40 mmol) were used to prepare, after workup and chromatography (1:2 ethyl acetate–hexane), the title product as a solid, mp 102–104 °C (10.3 g, 23.5 mmol, 73%). ^1H NMR ($CDCl_3$): δ 9.76 (1H, br s), 7.52 (2H, d, J = 8.1 Hz), 7.35 (2H, d, J = 8.1 hz), 6.87 (2H, d, J = 8.1 Hz), 6.82 (2H, d, J = 8.1 Hz), 4.05 (2H, q, J = 7.3 Hz), 3.82 (3H, s), 3.80 (3H, s), 3.01 (2H, t, J = 6.6 Hz), 2.37 (2H, t, J = 6.2 Hz), 1.92–1.80 (2H, m), 1.78–1.63 (2H, m), 1.20 (3H, t, J = 7.3 Hz). MS (DCI–NH_3): *m/e* 442 (28), 441 (100), 313 (1), 281 (1).

Preparation of 5-[[4,5-Bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentanoic Acid (63b). The method of Higley *et al.*[5] was employed here. Thus, compound **62b** (10.1 g, 23.0 mmol) was used to prepare the title compound as a semisolid (9.40 g, 99%). ^1H NMR ($CDCl_3$): δ 8.61 (1H, br s), 7.30 (4H, d, J = 8.8 Hz), 6.74 (4H, d, J = 8.8 Hz), 3.73 (6H, s), 2.95 (2H, t, J = 5.6 Hz), 2.26 (2H, br t, J = 5.9 Hz), 1.78–1.60 (4H, m). MS (DCI–NH_3): *m/e* 414 (27), 413 (100).

Preparation of *N*-[2-(*N*′,*N*′-Diethylamino)ethyl]-5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentanamide (64a). A solution of acid **63a** (3.73 g, 10.6 mmol) in DMF (40 mL) was treated with 1-hydroxybenzotriazole hydrate (HOBT) (1.77 g, 13.1 mmol). Then, a solution of *N*,*N*-diethylethylenediamine (2.00 mL, 14.2 mmol) in DMF (20 mL) was added dropwise. This solution was stirred at ambient temperature for 20 min, cooled to 0 °C, and treated with dicyclohexylcarbodiimide (DCC) (2.81 g, 13.6 mmol) portionwise over 10 min. The mixture was allowed to warm to ambient temperature and stirred for 48 h and then poured into ethyl acetate (150 mL) and washed with water (3 × 150 mL). The water phases were back-extracted in sequence with ethyl acetate (150 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and evaporated. The oily residue was separated by flash chromatography (1:9 methanol–CH_2Cl_2) to afford the product as an amorphous solid (3.77 g, 8.37 mmol, 79%). ^1H NMR ($CDCl_3$): δ 7.56–7.49 (4H, m), 7.33–7.17 (6H, m), 6.91 (1H, br s), 3.16 (2H, br d, J = 6 Hz), 2.97 (2H, t, J = 7 Hz), 2.68–2.49 (6H, m), 2.29 (2H, t, J = 6 Hz), 2.00–1.57 (4H, m), 1.02 (6H, t, J = 7 Hz). IR (KBr): 3323, 2931, 1642, 1604, 1560, 1510, 1490, 1448, 1372, 1243, 1183, 787 cm^{-1}.

Preparation of *N*-[2-(Morpholin-4-yl)ethyl]-5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentanamide (64b). The same general procedure used for compound **64a** was employed here. Thus, compound **63a** (1.73 g, 4.91 mmol), 4-(2-aminoethyl)morpholine (1.00 mL, 7.62 mmol), HOBT hydrate (867 mg, 6.42 mmol), and DCC (1.37 g, 6.64 mmol) were used to prepare the title product as an amorphous solid (2.26 g, 4.86 mmol, 99%).

Preparation of *N*-[2-(Morpholin-4-yl)ethyl]-5-[[4,5-(bis-(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentanamide (64c). The coupling procedure used for compound **64a** was employed here. Thus, compound **63b** (1.91 g, 4.63 mmol), HOBT hydrate (890 mg, 6.59 mmol), 4-(2-aminoethyl)morpholine (1.00 mL, 7.62 mmol), and DCC (1.42 g, 6.88 mmol) were used to prepare the title compound as a semisolid (1.77 g, 3.37 mmol, 73%). ^1H NMR ($CDCl_3$): δ 7.42 (4H, d, J = 9 Hz), 6.82 (4H, d, J = 9 Hz), 6.22 (1H, br t, J = 4 Hz), 3.80 (6H, s), 3.65–3.60 (4H, m), 3.15 (2H, q, J = 6 Hz), 2.98 (2H, t, J = 7 Hz), 2.38–2.24 (8H, m), 1.96–1.85 (2H, m), 1.70–1.60 (2H, m). MS (DCI–NH_3): *m/e* (526 (34), 525 (100), 500 (3), 313 (3).

Preparation of 2-[[5-[[2-(*N*,*N*-Diethylamino)ethyl]amino]pentyl]thio]-4,5-diphenyl-1*H*-imidazole (65a). The same general procedure to prepare compound **48a** was employed here. Thus, compound **64a** (2.19 g, 4.66 mmol) and Red-Al (3.00 mL of a 3.7 M solution in toluene, 11.1 mmol) afforded the title compound as an oil (2.01 g, 4.60 mmol, 99%). ^1H NMR ($CDCl_3$): δ 7.50–7.07 (10H, m), 3.00 (2H, t, J = 7.0 Hz), 2.58–2.37 (10H, m), 1.65–1.18 (6H, m), 0.89 (6H, t, J = 7.0 Hz).

Preparation of 1-[2-(Diethylamino)ethyl]-3-(2,4-difluorophenyl)-1-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]urea (66). The same procedure used for compound **4a** was employed here. Thus, compound **65a** (1.01 g, 2.30 mmol) and 2,4-difluorophenyl isocyanate (0.28 mL, 2.36 mmol) gave the product as a solid, recrystallized from hexane–ethyl acetate, mp 65–66 °C (1.20 g, 2.03 mmol, 88%). ^1H NMR ($CDCl_3$): δ 11.03 (1H, br s), 7.57–7.20 (13H, m), 3.49–3.41 (4H, m), 3.00–2.94 (2H, m), 2.70–2.60 (6H, m), 1.81–1.71 (2H, m), 1.69–1.54 (4H, m), 1.28–1.23 (6H, m). ^{13}C NMR ($CDCl_3$): δ 158.4, 157.2, 153.4, 139.7, 138.5, 134.8, 130.8, 129.1, 128.3, 128.0, 127.8, 127.2, 126.6, 124.6, 110.6, 103.3, 54.1, 48.3, 46.7, 36.3,

28.8, 27.2, 24.2, 11.1. MS (DCI−NH_3): *m/e* 592 (82), 437 (100). IR (KBr): 2971, 2934, 1656, 1613, 1555, 1510, 1490, 1466, 1448, 1430, 1408, 1242, 1206, 1140, 963, 765, 697 cm^{-1}.

Preparation of 3-(2,4-Difluorophenyl)-1-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-1-[2-(morpholin-4-yl)ethyl]urea (67). The general reduction procedure used for compound **48a** was used to prepare intermediate amine compound **65b**. Thus, compound **64b** (2.26 g, 4.86 mmol) and Red-Al (5.00 mL of a 3.40 M toluene solution, 17.0 mmol) were used to make compound **65b** as an amorphous solid. This material was then subjected directly to the same procedure as used for compound **4a**, using 2,4-difluorophenyl isocyanate (1.00 mL, 8.44 mmol). Workup and chromatography afforded the title product as a solid, mp 70−72 °C (1.76 g, 2.91 mmol, 60%). ^1H NMR ($CDCl_3$): δ 11.18 (1H, br s), 9.78 (1H, br s), 7.58 (2H, d, J = 8.1 Hz), 7.40 (1H, dt, J = 9.2, 6.0 Hz), 7.35−7.23 (8H, m), 6.64 (1H, br t, J = 10.9 Hz), 6.52 (1H, br t, J = 7.7 Hz), 3.68 (4H, t, J = 4.6 Hz), 3.53−3.42 (4H, m), 2.97 (2H, t, J = 6.1 Hz), 2.70−2.59 (4H, m), 1.86−1.55 (6H, m). ^{13}C NMR ($CDCl_3$): δ 158.2, 157.8, 154.1, 139.8, 128.3, 128.0, 127.9, 127.2, 125.7, 123.6, 110.7, 103.5, 77.3, 66.3, 59.9, 54.3, 47.1, 46.0, 35.7, 29.0, 27.2, 24.5. MS (DCI−NH_3): *m/e* 607 (10), 606 (27), 451 (100), 253 (3). IR (KBr): 3136, 2934, 1654, 1604, 1511, 1490, 1467, 1448, 1430, 1409−1011 (12 peaks), 964, 697 cm^{-1}.

Preparation of 1-[2-(Diethylamino)ethyl]-1-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-3-(methylethyl)urea (68). The same general procedure used for compound **4a** was employed here. Thus, compound **65a** (1.01 g, 2.30 mmol) and isopropyl isocyanate (0.23 mL, 2.34 mmol) gave the product as a solid, which was recrystallized from hexane−ethyl acetate, mp 58−59 °C (1.13 g, 2.17 mmol, 94%). ^1H NMR ($CDCl_3$): δ 7.57−7.53 (4H, m), 7.33−7.18 (6H, m), 3.81−3.70 (1H, m), 3.38−3.24 (4H, m), 2.98 (2H, t, J = 6.4 Hz), 2.65−2.62 (6H, m), 1.85−1.68 (2H, m), 1.59−1.46 (4H, m), 1.10 (6H, t, J = 6.9 Hz), 1.06 (6H, d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 159.5, 140.0, 128.2, 127.8, 126.8, 126.7, 126.6, 54.3, 47.6, 47.4, 46.5, 42.1, 36.0, 28.7, 27.4, 24.2, 23.4, 11.0. MS (DCI−NH_3): *m/e* 594 (14), 593 (37), 592 (83), 437 (100). IR (KBr): 2969, 2933, 1623, 1560, 1509, 1490, 1466, 1448, 1384, 1364, 1258, 1220, 765, 697 cm^{-1}.

Preparation of 1-[5-[[4,5-Bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]pentyl]-3-(2,4-difluorophenyl)-1-[2-(morpholin-4-yl)ethyl]urea (69). The procedure previously used for the preparation of compound **48a** was first used to make amine intermediate **65c**. Thus, amide compound **64c** (1.77 g, 3.37 mmol) and Red-Al (2.20 mL of a 3.4 M toluene solution, 7.48 mmol) gave **65c** after workup as a gummy semisolid. This material was sufficiently pure for the next step, which used the procedure previously employed for compound **4a**. Thus, the amine and 2,4-difluorophenyl isocyanate (0.50 mL, 4.22 mmol) were used to prepare the title compound, after workup and chromatography, as a solid, mp <50 °C (1.89 g, 2.84 mmol, 84%). ^1H NMR ($CDCl_3$): δ 9.68 (1H, s), 7.52−7.26 (5H, m), 6.79 (4H, d, J = 8.8 Hz), 6.73−6.55 (2H, m), 3.79 (6H, s), 3.75−3.67 (4H, m), 3.42 (4H, br s), 2.93 (2H, t, J = 6.4 Hz), 2.64−2.58 (6H, m), 1.80−1.44 (6H, m). ^{13}C NMR ($CDCl_3$): δ 158.4, 158.0, 157.6, 154.0, 138.9, 128.9, 125.5, 123.5, 113.6, 111.6, 103.3, 66.2, 59.8, 55.0, 54.2, 47.2, 46.0, 35.5, 29.0, 27.2, 24.7. MS (DCI−NH_3): *m/e* 667 (5), 666 (14), 511 (100), 313 (84). IR (KBr): 3182, 2934, 1656, 1613, 1521, 1503, 1465, 1430, 1295, 1247, 1175, 1140, 1118, 1033, 835 cm^{-1}.

Preparation of *N*-(Chloroacetyl)sarcosine (71). A solution of sarcosine (32.4 g, 363 mmol) in aqueous NaOH (4 N, 90 mL) was cooled to −5 °C and treated dropwise simultaneously with chloroacetyl chloride (32.0 mL, 402 mmol) and aqueous NaOH (4 N, 110 mL) with vigorous stirring over 30 min. After warming to ambient temperature and stirring for 34 h, the solution was acidified to pH 2 with concentrated aqueous HCl, saturated with NaCl, and extracted with ethyl acetate (2 × 400 mL). The extracts were combined, dried over $MgSO_4$, filtered, and evaporated to afford the product as a pale yellow oil (39.3 g, 238 mmol, 65%). ^1H NMR ($CDCl_3$): δ 10.83 (1H, br s), 4.19 (2H, s), 4.14 (2H, s), 3.20 (3H, s).

Preparation of 4,5-Diphenyl-2-[[2-[*N*-methyl-*N*-[2-(*N*-heptylamino)ethyl]amino]ethyl]thio]-1*H*-imidazole (73). A mixture of compound **71** (6.45 g, 39.0 mmol), 4,5-diphenyl-1*H*-imidazole-2-thiol (9.83 g, 39.0 mmol), and K_2CO_3 (11.8g, 85.7 mmol) in 100 mL of dry THF was heated to reflux for 14 h. The mixture was cooled, poured into water (200 mL), washed with ether (150 mL), acidified to pH 5 with concentrated aqueous HCl, saturated with NaCl, and extracted with ethyl acetate (3 × 200 mL). The extracts were combined, dried over $MgSO_4$, filtered, and evaporated to afford compound **72** as an off-white solid (13.0 g, 34.1 mmol, 87%). A solution of compound **72** (6.83 g, 17.9 mmol) was coupled to heptylamine (4.00 mL, 27.0 mmol) using DCC (5.05 g, 24.5 mmol) and HOBT (3.14 g, 23.2 mmol) using the same procedure as employed for compound **64a**. The resulting diamide compound (6.56 g, 13.7 mmol) was sufficiently pure after flash chromatography (2:98 methanol:CH_2Cl_2) for use in the next step. This compound was dissolved in toluene (100 mL) and added dropwise to a solution of Red-Al in toluene (29.0 mL, 3.70 M, 107 mmol) at 0 °C. The ice bath was removed, and the solution was heated to gentle reflux for 15 h. The solution was then cooled to 0 °C and the reaction quenched by the dropwise addition of aqueous NaOH (60 mL, 1 N). The phases were separated, and the aqueous phase was saturated with NaCl and extracted with CH_2Cl_2 (3 × 50 mL). The organic phases were combined, dried over K_2CO_3, filtered, and evaporated. The oily residue was separated by flash chromatography (1:4 methanol−CH_2Cl_2) to afford the product as an oil (2.05 g, 4.55 mmol, 33%). ^1H NMR ($CDCl_3$): δ 7.51 (4H, d, J = 7.4 Hz), 7.32−7.21 (7H, m), 3.07−3.04 (2H, m), 2.80−2.66 (6H, m), 2.58 (2H, t, J = 7.3 Hz), 2.28 (3H, s), 1.43−1.35 (2H, m), 1.33−1.11 (8H, m), 0.83 (3H, t, J = 7.0 Hz). IR (KBr): 3260, 2924, 2852, 1603, 1510, 1492, 1449, 1121, 1071, 966, 764, 696 cm^{-1}.

Preparation of 3-(2,4-Difluorophenyl)-1-heptyl-1-[2-[*N*-methyl-*N*-[2-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]ethyl]amino]ethyl]urea (74). The same method used for compound **4a** was employed here. Thus, compound **73** (1.02 g, 2.27 mmol) and 2,4-difluorophenyl isocyanate (0.30 mL, 2.53 mmol) gave, after flash chromatography (1:19 methanol−CH_2Cl_2), the product as a solid (1.27 g, 2.10 mmol, 92%), which was recrystallized to purity with toluene, mp 151−152 °C. ^1H NMR ($CDCl_3$): δ 7.85−7.77 (1H, m), 7.57−7.46 (4H, m), 7.32−7.18 (7H, m), 6.80−6.72 (2H, m), 3.54−3.49 (2H, m), 3.30−3.22 (4H, m), 3.07−2.99 (2H, m), 2.95−2.88 (2H, m), 2.58 (3H, s), 1.58−1.54 (2H, m), 1.30−1.17 (8H, m), 0.87 (3H, t, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 157.2, 157.0, 152.2, 139.5, 128.4, 127.5, 126.5, 124.9, 122.6, 110.7, 103.3, 57.9, 57.3, 48.1, 46.9, 43.1, 31.8, 31.7, 29.0, 28.1, 26.8, 22.5, 14.0. MS (DCI−NH_3): *m/e* 606 (16), 452 (20), 451 (64), 155 (100). IR (KBr): 3416, 3180, 2929, 1658, 1619, 1601, 1563, 1508, 1489, 1472, 1448, 1430, 1411, 1314, 1257, 1208, 1138, 1100, 959, 841, 768, 698 cm^{-1}.

Preparation of 1-[2-[*N*-[2-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]ethyl]-*N*-methylamino]ethyl]-1-heptyl-3-(1-methylethyl)urea (75). The same method used for compound **4a** was employed here. Thus, compound **73** (1.03 g, 2.27 mmol) and isopropyl isocyanate (0.22 mL, 2.24 mmol) afforded, after chromatography (1:19 methanol−CH_2Cl_2), the product as a solid, which was recrystallized from ether−hexane, mp 122−124 °C (1.10 g, 2.05 mmol, 92%). ^1H NMR ($CDCl_3$): δ 7.52 (4H, d, J = 6.9 Hz), 7.33−7.21 (7H, m), 4.95 (1H, br s), 3.85 (1H, heptet, J = 6.6 Hz), 3.36 (2H, t, J = 6.5 Hz), 3.17 (2H, t, J = 5.8 Hz), 3.03 (2H, t, J = 7.7 Hz), 2.92 (2H, t, J = 6.0 Hz), 2.70 (2H, t, J = 6.3 Hz), 2.43 (3H, s), 1.48−1.40 (2H, m), 1.38−1.20 (8H, m), 1.09 (6H, d, J = 6.6 Hz), 0.87 (3H, t, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 158.2, 140.4, 128.3, 127.5, 127.0, 58.3, 56.5, 47.7, 45.4, 42.8, 42.3, 31.8, 31.7, 29.0, 28.3, 26.8, 23.4, 22.5, 14.0. MS (DCI−NH_3): *m/e* 536 (100), 439 (12), 253 (8), 145 (4). IR (KBr): 3061, 2931, 1616, 1600, 1491, 1448, 1029, 768 cm^{-1}.

Preparation of *N'*-[2-(Morpholin-4-yl)ethyl]-*N*-[[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]acetyl]sarcosinamide (76). The same general procedure used for compound **64a** was employed here. Thus, compound **72** (4.08 g, 10.7 mmol), 4-(2-aminoethyl)morpholine (2.00 mL, 15.2 mmol), HOBT hydrate (1.78 g, 13.2 mmol), and DCC (3.02 g, 14.7 mmol) were used to prepare the title compound as a semisolid after workup and chromatography (2.69 g, 5.45 mmol, 51%). MS (DCI−NH_3): *m/e* 495 (30), 494 (100).

Preparation of 3-(2,4-Difluorophenyl)-1-[2-[*N*-[2-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]ethyl]-*N*-methylamino]-ethyl]-1-[2-(morpholin-4-yl)ethyl]urea (77). The dipeptide reduction procedure that was used to prepare compound **74** was employed here. Thus, compound **76** (1.35 g, 2.72 mmol) and Red-Al (4.00 mL of a 3.4 M solution in toluene, 13.6 mmol) generated the diamine intermediate upon workup. This compound was used directly without further purification along with 2,4-difluorophenyl isocyanate (0.35 mL, 2.95 mmol) to make, after workup and chromatography, the title compound as a semisolid (910 mg, 1.47 mmol, 54%). ^{1}H NMR ($CDCl_3$): δ 9.95 (1H, br s), 7.60–7.20 (11H, m), 6.76–6.62 (3H, m), 3.64 (4H, t, J = 4.6 Hz), 3.47 (2H, t, J = 5.9 Hz), 3.39 (2H, t, J = 5.4 Hz), 3.14 (2H, t, J = 5.7 Hz), 2.85 (2H, t, J = 5.9 Hz), 2.71 (2H, t, J = 5.7 Hz), 2.56 (2H, t, J = 5.4 Hz), 2.55–2.45 (4H, m), 2.39 (2H, s). ^{13}C NMR ($CDCl_3$): δ 158.2, 157.9, 153.0, 140.0, 128.3, 127.5, 124.1, 110.7, 103.3, 66.5, 57.8, 54.0, 46.9, 46.2, 46.0, 43.0, 32.6, 32.3. MS (DCI–NH_3): *m/e* 622 (10), 621 (27), 466 (100), 253 (5). IR (KBr): 3176, 2948, 2852, 1657, 1612, 1551, 1509, 1467, 1448, 1430, 1406, 1365, 1304, 1256, 1206, 1140, 1118, 964, 848, 766 cm^{-1}.

Preparation of 1-[2-[*N*-[2-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]ethyl]-*N*-methylamino]ethyl]-3-(1-methylethyl)-1-[2-(morpholin-4-yl)ethyl]urea (78). The dipeptide reduction procedure that was used to prepare compound **74** was employed here. Thus, compound **76** (1.35 g, 2.72 mmol) and Red-Al (4.00 mL of a 3.4 M solution in toluene, 13.6 mmol) generated the diamine intermediate upon workup. This compound was used directly without further purification along with isopropyl isocyanate (0.30 mL, 3.05 mmol) to make, after workup and chromatography, the title compound as a semisolid (982 mg, 1.78 mmol, 65%). ^{1}H NMR ($CDCl_3$): δ 7.53 (4H, d, J = 7.0 Hz), 7.35–7.25 (6H, m), 6.86 (1H, br d, J = 7.0 Hz), 3.82 (1H, m, J = 6.6 Hz), 3.68 (4H, t, J = 4.6 Hz), 3.35 (2H, t, J = 6.6 Hz), 3.19 (2H, t, J = 5.1 Hz), 3.11 (2H, t, J = 5.7 Hz), 2.84 (2H, t, J = 5.7 Hz), 2.63 (2H, t, J = 6.6 Hz), 2.49–2.41 (6H, m), 2.36 (3H, s), 1.11 (6H, d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 159.1, 140.4, 128.2, 127.6, 126.9, 66.6, 58.3, 57.9, 56.4, 53.9, 46.4, 45.9, 42.6, 42.5, 42.1, 31.6, 23.6. MS (DCI–NH_3): *m/e* 552 (36), 551 (100), 466 (10), 253 (4). IR (KBr): 2965, 1625, 1557, 1509, 1490, 1466, 1406, 1383, 1364, 1301, 1270, 1118, 766, 697 cm^{-1}.

Preparation of *N*-Butyrylsarcosine (79). The Schotten–Baumann procedure used in the preparation of compound **71** was employed here. Thus, sarcosine (14.9 g, 168 mmol), butyryl chloride (20.0 mL, 193 mmol), and NaOH (84.0 mL, 4 N aqueous solution, 336 mmol) were used to make the title product as an oil (19.7 g, 123 mmol, 74%). ^{1}H NMR ($CDCl_3$): δ 11.10 (1H, br s), 4.17 (2H, s), 3.10 (3H, s), 2.33 (2H, t, J = 7.3 Hz), 1.75–1.61 (2H, m), 0.97 (3H, t, J = 7.3 Hz). MS (DCI–NH_3): *m/e* 161 (9), 160 (100), 142 (5), 90 (41).

Preparation of *N*-Butyryl-*N'*-[2-(2-hydroxyethoxy)ethyl]sarcosinamide (80). The DCC coupling procedure used for **64a** was also used here. Thus, compound **79** (10.9 g, 68.6 mmol), HOBT hydrate (10.5 g, 77.7 mmol), 2-(2-aminoethoxy)-ethanol (6.00 mL, 83.3 mmol), and DCC (20.3 g, 98.4 mmol) were used to prepare the title compound, after chromatography (1:19 methanol–CH_2Cl_2), as a gum (3.98 g, 16.2 mmol, 24%). ^{1}H NMR ($CDCl_3$): δ 6.55 (1H, br s), 5.92 (1H, br s), 3.99 (2H, s), 3.78–3.71 (2H, m), 3.60–3.52 (4H, m), 3.50–3.40 (2H, s), 3.12 (3H, s), 2.35 (2H, t, J = 7.5 Hz), 1.71–1.57 (2H, m), 0.95 (3H, t, J = 7.3 Hz). MS (DCI–NH_3): *m/e* 248 (5), 247 (34), 176 (41), 142 (100).

Preparation of *N*-Butyryl-*N'*-[2-[2-[[4,5-bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]ethoxy]ethyl]sarcosinamide (82). The intermediate bromide-bearing compound **81** was prepared using the same procedure employed for the synthesis of bromide **5a**. Thus, compound **80** (3.04 g, 12.3 mmol), carbon tetrabromide (4.95 g, 14.9 mmol), and triphenylphosphine (3.92 g, 14.9 mmol) were used in the preparation of compound **81**, obtained after chromatography (1:1 acetone–hexane) as an oil (2.05 g, 6.67 mmol, 54%). The procedure used previously to prepare compound **38** was then employed. Thus, compound **81** (2.05 g, 6.67 mmol), 4,5-bis(4-methoxyphenyl)-2-mercapto-1*H*-imidazole (2.08 g, 6.66 mmol), K_2CO_3 (1.20 g, 8.68 mmol), and tetra-*n*-butylammonium iodide (0.49 g, 1.33 mmol) were used to prepare the title compound, which was isolated after workup and chromatography (1:4 2-propanol–ethyl acetate) as a gum (2.68 g, 4.96 mmol, 74%). NMR spectroscopy showed the presence of two amide rotomers. ^{1}H NMR ($CDCl_3$): δ 7.50–7.40 (4H, m), 6.91–6.80 (4H, m), 4.02 (1.53H, s), 4.01 (0.47H, s), 3.81 (6H, s), 3.80–3.25 (8H, m), 3.10 (2.30H, s), 3.06 (0.70H, s), 2.32 (1.53H, t, J = 7.3 Hz), 2.30 (0.47H, t, J = 6.9 Hz), 1.75–1.60 (2H, m), 1.02 (0.70H, t, J = 7.3 Hz), 0.88 (2.30H, t, J = 7.3 Hz). MS (DCI–NH_3): *m/e* 542 (33), 541 (100), 364 (16), 142 (22).

Preparation of 4,5-Bis(4-methoxyphenyl)-2-[[2-[2-[*N*-[2-(*N*-butyl-*N*-methylamino)ethyl]amino]ethoxy]ethyl]-thio]-1*H*-imidazole (83). The reduction procedure used for compound **48a** was employed here. Thus, compound **82** (2.68 g, 4.96 mmol) and Red-Al (9.00 mL of a 3.4 M toluene solution, 30.6 mmol) were used in the preparation of the title compound, which was obtained after workup and chromatography (1:9 methanol–CH_2Cl_2) as a semisolid (870 mg, 1.70 mmol, 34%). ^{1}H NMR ($CDCl_3$): δ 7.43 (4H, d, J = 8.8 Hz), 6.84 (4H, d, J = 8.8 Hz), 3.80 (6H, s), 3.77–3.67 (4H, m), 3.12 (2H, t, J = 5.3 Hz), 2.88 (2H, t, J = 5.0 Hz), 2.66 (2H, t, J = 6.9 Hz), 2.53–2.43 (2H, m), 2.37 (2H, t, J = 5.9 Hz), 2.10 (3H, s), 1.55–1.41 (1H, m), 1.38–1.18 (4H, m), 0.85 (3H, t, J = 7.4 Hz). MS (DCI–NH_3): *m/e* 514 (32), 513 (100), 412 (25), 356 (6).

Preparation of 1-[2-[2-[[4,5-Bis(4-methoxyphenyl)-1*H*-imidazol-2-yl]thio]ethoxy]ethyl]-1-[2-(*N*-butyl-*N*-methylamino)ethyl]-3-(2,4-difluorophenyl)urea (84). The same procedure used for compound **4a** was employed here. Thus, compound **83** (811 mg, 1.58 mmol) and 2,4-difluorophenyl isocyanate (0.20 mL, 1.69 mmol) were used in the preparation of the title compound, which was obtained as a gum (606 mg, 0.91 mmol, 57%) after workup and chromatography (1:19 methanol–CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 7.64–7.55 (1H, m), 7.54–7.23 (4H, br s), 6.82 (4H, d, J = 8.4 Hz), 6.72–6.63 (1H, m), 6.62–6.55 (1H, m), 3.80 (6H, s), 3.79–3.70 (4H, m), 3.60 (2H, br t, J = 4.8 Hz), 3.49–3.40 (2H, m), 3.12 (2H, t, J = 5.3 Hz), 2.64 (2H, br s), 2.45 (2H, br t, J = 7.7 Hz), 2.33 (3H, s), 1.52–1.40 (2H, m), 1.33–1.21 (2H, m), 0.86 (3H, t, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$): δ 158.2, 157.3, 153.2, 138.5, 128.8, 124.3, 123.7, 113.7, 110.7, 103.3, 69.7, 69.0, 58.2, 58.0, 55.1, 48.2, 47.7, 42.7, 35.5, 28.5, 20.4, 13.8. MS (DCI–NH_3): *m/e* 669 (4), 668 (10), 513 (100). HRMS *m/e* 512 (M + H). IR (KBr): 3784, 2957, 1658, 1614, 1551, 1521, 1503, 1466, 1430, 1293, 1247, 1207, 1174, 1097, 963, 834, 728 cm^{-1}.

***In Vitro* ACAT Assay (IC_{50}).** ACAT activity was determined in rat hepatic microsomes by measuring the formation of labeled cholesteryl oleate (pmol/min/mg) from [^{14}C]oleoyl-CoA as described previously. Inhibitors were added in 5 μL of DMSO. The data are expressed as the concentration at which ACAT activity is inhibited by 50% (IC_{50}). IC_{50}'s were obtained from assays performed in duplicate containing a minimum of four inhibitor concentrations which bracket the IC_{50}. The average range of replicates was ±17%. To determine macrophage ACAT activity, J774 cells were grown as described below and harvested and microsomes prepared. ACAT activity was determined as described previously,[11c] and IC_{50}'s were determined.

Materials. All cell culture reagents including media, supplements, and salt solutions were purchased from Gibco Laboratories. Tissue culture ware was obtained from Falcon. Radioisotopes were obtained from New England Nuclear. Human acetylated human low-density lipoprotein (ac-LDL) was purchased from Biotechnology Research Institute (Rockville, MD). Silica gel-impregnated glass fiber chromatography plates (ITLC) were obtained from Gelman Sciences Inc. J774A.1 cells were obtained from the American Type Culture Collection. Cells were tested routinely and found to be free of mycoplasma contamination.

J774A.1 Cell Culture Studies. J774A.1 cells were grown in high-glucose Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) in a humidity-controlled incubator maintained at 37 °C and 6% CO_2. Cells were subcultured at confluence by scraping. Cells were seeded at 3 × 10^4 cells/cm^2 and grown for 36 h prior to being loaded with 50 mg/mL ac-LDL in 10% FBS-DMEM for 17 h. After

loading, cholesterol esterification was determined in the presence or absence of inhibitors.

Drugs of interest were dissolved in DMSO and incubated with the cells for 4 h. The concentration of DMSO was maintained at 1.0%. J774 cells were incubated with 100 mM [^{14}C]oleate (10 000 dpm/nmol), complexed with an equimolar amount of BSA, for the last 2 h of the drug incubation. At the end of the labeling period, all cells were washed three times with PBS at 4 °C. Quantitation of cholesteryl ester formation (nmol/h/mg) was performed as described.[12] Cells were extracted with hexane:2-propanol (3:2) for 30 min in the presence of [^{3}H]cholesteryl oleate as the internal standard. Extracts were collected and dried under nitrogen. Lipids were separated by thin layer chromatography using silica gel plates and a mobile phase of hexane:diethyl ether:acetic acid (85:15:1) and quantified by liquid scintillation counting. Protein was solubilized with 0.2 N sodium hydroxide for 60 min. Protein was determined by the Lowry protein assay[12] using BSA as a standard. The data are expressed as the concentration at which cholesterol esterification is inhibited by 50% (IC_{50}). The average range of replicate assays was 23%.

References

(1) Meittinen, T. A.; Kesaniem, Y. A. Cholesterol Absorption: Regulation of Cholesterol Synthesis and Elimination Within Population Variations of Serum Cholesterol Levels. *Am. J. Clin. Nutr.* **1989**, *49*, 629–635.

(2) (a) Heider, J. G. Agents Which Inhibit Cholesterol Esterification in the Intestine and Their Potential Value in the Treatment of Hypercholesterolaemia. In *Pharmacological Control of Hyperlipidaemia*; Fears, R., Ed.; J. R. Prous Science Publishers: Barcelona, Spain, 1986; pp 423–438. (b) Largis, E. E.; Wang, C. H.; DeVries, V. G.; Schaffer, S. A. CL277,082: A Novel Inhibitor of ACAT-Catalyzed Cholesterol Esterification and Cholesterol Absorption. *J. Lipid Res.* **1989**, *30*, 681–690. (c) Sliskovic, D. R.; White, A. D. Therapeutic Potential of ACAT Inhibitors as Lipid Lowering and Antiatherosclerotic Agents. *Trends Pharmacol. Sci.* **1991**, *12*, 194–199.

(3) (a) Billheimer, J. T.; Gillies, P. J. Intracellular Cholesterol Esterification. In *Advances in Cholesterol Research*; Esfaham, M., Swaney, J. B., Eds.; Telford Press: London, 1990; pp 1–45. (b) Chang, T. Y.; Doolittle, G. M. Acyl Coenzyme A:Cholesterol O-Acyltransferase. In *The Enzymes*, 3rd ed.; Boyer, P. D., Ed.; Academic Press: New York, 1985; Vol. XVI, pp 523–539. (c) Billheimer, J. T.; Wilde, R. G. ACAT Inhibitors: Potential Antihypercholesterolemic Agents. *Current Drugs* **1991**, B5–B19.

(4) (a) Kelley, J. L.; Svenram, C. A.; Schaffer, J. A.; Schwartz, C. J. Influence of the Acyl-CoA:Cholesterol O-Acyltransferase Inhibitor, CL277082, on Cholesteryl Ester Accumulation in Rabbit Macrophage-Rich Granulomas and Heptic Tissue. *Biochem. Biophys. Acta* **1988**, *960*, 83–90. (b) Rucker, W.; Prop, G.; Hather, A. M. Antiatherosclerotic and Antihyperlipidemic Effects of Octimibate Sodium in Rabbits. Atherosclerosis **1988**, *69*, 155–160.

(5) (a) Billheimer, J. T.; Gillies, P. J.; Higley, C. A.; Maduskuie, T. P.; Wexler, R. R. U.S. Patent No. 5,166,214, 1992. (b) Wexler, R. R.; Higley, C. A.; Maduskuie, T. P.; Pennev, P.; Billheimer, J. T.; Gillies, P. J. Acyl CoA:Cholesterol Acyltransferase (ACAT) Inhibitors: Synthesis and SAR Studies of a New Series of Trisubstituted Imidazoles. 201st Am. Chem. Soc. Meeting, Atlanta, 1991; Abstract MEDI 87. (c) Higley, C. A.; Maduskuie, T. P.; Pennev, P.; Billheimer, J. T.; Gillies, P. J. Acyl CoA: Cholesterol Acyltransferase (ACAT) Inhibitors: Synthesis and SAR Studies of a New Series of Trisubstituted Imidazoles. *J. Med. Chem.* **1994**, *37*, 3511–3522.

(6) (a) Gillies, P. J.; Robinson, C. A.; Wexler, R. R.; Billheimer, J. T. Inhibition of Intestinal Acyl CoA:Cholesterol Acyltransferase by DuP 128 in a Cholesterol-fed Hamster model of Hypercholesterolemia. 9th Int. Symp. on Atherosclerosis, Chicago, IL, 1991; Abstract 93. (b) Hainer, J. W.; Tery, J. G.; Connell, J. M.; Zyruk, H.; Jenkins, R. M.; Shand, D. L.; Gillies, P. J.; Livak, K. J.; Hunt, T. L.; Crouse, J. R. Effect of acyl:CoA cholesterol acyltransferase inhibitor DuP 128 on cholesterol absorption and serum cholesterol in humans. *Clin. Pharmacol. Ther.* **1994**, *56*, 65–74. (c) Becker, A.; Bottcher, A.; Lackner, K.; Fehringer, P.; Notka, F.; Aslanidis, C.; Schmitz, G. Purification, Cloning, and Expression of a Human Enzyme with Acyl coenzyme A: Cholesterol Acyltransferase Activity, which is Identical to Liver Carboxlesterase. *Arterioscler. Thromb.* **1994**, *14*, 1346–1355. (d) Chang, C.; Huh, H.; Cadigan, K.; Chang, T. Y. Molecular Cloning and Functional Expression of Human Acyl-Coenzyme A: Cholesterol Acyltransferase cDNA in Mutant Chinese Hamster Ovary Cells. *J. Biol. Chem.* **1993**, *268*, 20747–20755. (e) Kinnunen, P.; DeMichele, A.; Lange, L. Chemical modification of Acyl-CoA: Cholesterol Acyltransferase. 1. Identification of Acyl-CoA: Cholesterol Acyltransferase Subtypes by Differential Diethyl Pyrocarbonate Sensitivity, *Biochemistry* **1988**, *27*, 7344–7350.

(7) (a) Hoffman, K. *Chem. Heterocycl. Compds. Imidazoles, Part 1* **1953**, *6*, 79–80. (b) Sharpe, T. R.; Cherkovsky, S. C.; Hewes, W. E.; Smith, D. H.; Gregory, W. A.; Haber, S. B.; Leadbetter, M. R.; Whitney, J. G. Preparation and Antiarthritic and Analgesic Activity of 4,5-Diaryl-2-(substitutedthio)-1*H*-imidazoles and Their Sulfoxides and Sulfones. *J. Med. Chem.* **1985**, *28*, 1188–1194.

(8) (a) Ide, W. S.; Buck, J. S. *Org. React.* **1948**, *4*, 269–304. (b) Irvine, J. C. Preparation of *o*-Dimethoxybenzoin and a New Method of Preparing Salicylaldehyde Methyl Ether. *J. Chem. Soc.* **1901**, *79*, 668–672. (c) Hodgson, H. H.; Rosenberg, W. The Influence of Substituents on the Benzoin Condensation. *J. Chem. Soc.* **1930**, 14–18.

(9) Review: Barluenga, J.; Palacios, F. Synthesis and Reactivity of λ^5-Phosphazenes. Use as Synthetic Intermediates. *Org. Prep. Proc. Int.* **1991**, *23*, 1–65.

(10) Windridge, G. C.; Jorgensen, E. C. 1-Hydroxybenzotriazole as a Racemization-Suppressing Reagent for the Incorporation of *im*-Benzyl-L-histidine into Peptides. *J. Am. Chem. Soc.* **1971**, *93*, 6318.

(11) (a) Billheimer, J. T.; Gillies, P. J.; Higley, C. A.; Maduskuie, T. P.; Wexler, R. R. U.S. Patent No. 5,166,214, 1992. (b) Billheimer, J. T.; Tavani, D.; Nes, W. R. Effect of a Dispersion of Cholesterol in Triton WR-1339 on Acyl CoA:Cholesterol Acyltransferase in Rat Liver Microsomes. *Anal. Biochem.* **1981**, *111*, 331–335. (c) Gillies, P. J.; Rathgeb, K.; Perri, M.; Robinson, C. Regulation of Acyl-CoA: Cholesterol Acyltransferase Activity in Normal and Atherosclerotic Rabbit Aortas: Role of a Substrate Pool. *Exp. Mol. Pathol.* **1986**, *44*, 329–339.

(12) (a) Schmitz, G.; Neimann, R.; Brennhauser, B.; Krause, R.; Assman, G. Regulation of High Density Lipoprotein Receptors in Cultured Macrophages: Role of Acyl CoA:Cholesterol Acyltransferase. *EMBO J.* **1985**, *4*, 2773–2779. (b) Mazzone, T.; Gump, H.; Diller, P.; Getz, J. Macrophage Free Cholesterol Content Regulates Apolipoprotein E Synthesis. *J. Biol. Chem.* **1987**, *262*, 11657–11662.

(13) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separation with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923.

(14) Lowry, O. H.; Randall, R. J.; Rosebrough, N. J.; Farr, A. L. Protein Measurement with the Folin Phenol Method. *J. Biol. Chem.* **1951**, *193*, 265–275.

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