Acyl CoA:Cholesterol Acyltransferase (ACAT) Inhibitors: Synthesis and Structure–Activity Relationship Studies of a New Series of Trisubstituted Imidazoles

C. Anne Higley,* Richard G. Wilde, Thomas P. Maduskuie, Alexander L. Johnson, Pennio Pennev, Jeffrey T. Billheimer, Candy S. Robinson, Peter J. Gillies, and Ruth R. Wexler

The DuPont Merck Research Laboratories, P.O. Box 80402, Wilmington, Delaware 19880-0402

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A series of 4,5-diaryl-2-(substituted thio)-1*H*-imidazoles has been synthesized and demonstrated to be potent inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). The design, synthesis, and structure–activity relationships for this series are reported herein. One of the compounds from this series, *N'*-(2,4-difluorophenyl)-*N*-[5-[(4,5-diaryl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptylurea (DuP 128), was selected for development as an intestinally active ACAT inhibitor. DuP 128 is a potent ACAT inhibitor *in vitro* and *in vivo*, inhibiting ACAT in rat hepatic microsomes with an IC_{50} = 10 nM and possessing potent antihypercholesterolemic activity *in vivo*.

Introduction

Animal studies and recent clinical studies have led to the recognition that hypercholesterolemia is a major risk factor for atherosclerosis and coronary heart disease (CHD) and that therapeutic lowering of serum cholesterol will decrease this risk. Since dietary cholesterol contributes to the degree of hypercholesterolemia and risk of coronary artery disease,[1] agents have therefore been sought which would inhibit the absorption of cholesterol. An approach that has received intensive research attention in recent years focuses on interference with the incorporation of cholesterol into chylomicrons which are required for transport of cholesterol from the intestine into the circulation. One mechanism for doing such is by inhibiting acyl-CoA:cholesterol acyltransferase (ACAT), which catalyzes the intracellular esterification of cholesterol to cholesteryl ester (CE).[2-5] It has been demonstrated that potent inhibitors of intestinal ACAT both decrease the absorption of dietary cholesterol and reduce plasma total cholesterol (TC) concentrations in cholesterol-fed animal models of hypercholesterolemia and therefore have potential to be benefical in the treatment of hypercholesterolemia in humans.[6-8]

Recently, the implications for inhibiting ACAT in other tissues (*e.g.*, liver, artery wall) for the treatment of hypercholesterolemia and atherosclerosis are also becoming more clear. In addition to affecting serum cholesterol levels by inhibiting cholesterol absorption, ACAT inhibitiors targeted at the liver may also affect cholesterol levels by inhibiting the synthesis and/or secretion of apo-B. This is supported by recent preliminary studies in hepatocytes and isolated perfused liver.[9,10] This would result in fewer apo-B-containing lipoprotein particles and a decrease in serum cholesterol. Another recent prospect is the possibility that bioavailable ACAT inhibitors may exert an antiatherosclerotic effect by inhibiting foam cell formation in the arterial wall.[11,12] Macrophage-derived foam cells play a major role in lesion progression. Systemic inhibitors should prevent CE deposition in the macrophage and promote cholesterol efflux, thereby preventing the progression of atherosclerosis.[13]

It is the central involvement of ACAT in cholesterol homeostatic mechanisms in a variety of tissues and cells which has prompted a large number of pharmaceutical companies to pursue ACAT inhibitors as a potential therapeutic target for the treatment of both hypercholesterolemia and atherosclerosis. Earlier, we reported on a series of ω-[(4,5-diarylimidazol-2-yl)thio]alkanoic acids and esters.[14] Herein, we report on the synthesis and biological activity of a series of 4,5-diaryl-2-(substituted thio)-1*H*-imidazoles which were designed to be intestinally active ACAT inhibitors.[15]

Our clinical candidate, DuP 128, **1**, is a potent ACAT inhibitor that inhibits ACAT in rat hepatic microsomes with an IC_{50} of 10 nM. The compound is also a potent antihypercholesterolemic agent as evidenced by serum cholesterol lowering in cholesterol-fed hamsters when dosed orally (ED_{50} = 3 mg/kg).[16,17]

Chemistry

The synthesis of **1** is illustrated in Scheme 1. Alkylation of 4,5-diphenyl-2-imidazolethiol (**2**) with bromide **3** in the presence of potassium carbonate and catalytic sodium iodide in tetrahydrofuran resulted in the amide **4**. Reduction of the amide **4** to the amine **5** was accomplished with Red-Al (Aldrich) in toluene at reflux, which in turn was condensed with 2,4-difluorophenyl isocyanate in hexane to afford **1**. *N*-Methylation of **1** with iodomethane using sodium hydride in *N,N*-dimethylformamide provided **6**. Compounds **12–13**, **24–25**, **29–33**, **35–59**, and **61–71** were prepared in analogous fashion. In cases wherein the requisite mercaptoimidazole was not commercially available, the starting material was prepared via condensation of the appropriately substituted benzoin or α-hydroxy ketone or α-amino ketone compound with the appropriately substituted thiourea in *N,N*-dimethylformamide or with ammonium thiocyanate in 1-propanol.[18,19]

An alternative synthesis of **1** and related compounds is depicted in Scheme 2. The hydroxy amide **7** was prepared from γ-valerolactone and *n*-heptylamine in toluene at reflux. Reduction of the amide **7** with lithium aluminum hydride followed by condensation with 2,4-

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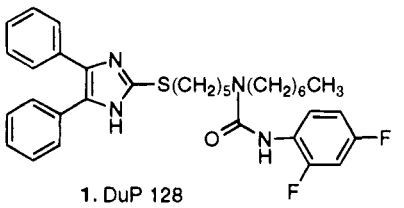


1. DuP 128

Figure 1.

difluorophenyl isocyanate afforded the urea **9**. The hydroxy group was converted to the bromide **10** using carbon tetrabromide and triphenylphosphine in dichloromethane and was followed by alkylation of the diarylimidazolethione (**2**) which proceeded smoothly to afford **1**. Compounds **26**–**28**, **34**, and **60** were prepared analogously.

As shown in Scheme 3, the amine **5** was reacted with the requisite isothiocyanate, acid chloride, or chloroformate to afford thioureas (**11a**), amides (**11b**), or carbamates (**11c**), respectively.

The sulfoxide **12** was readily prepared from 1 by oxidation with *m*-chloroperbenzoic acid (1 equiv) in dichloromethane at −78 °C. The corresponding sulfone (**13**) was prepared via oxidation of **1** with Oxone (2 equiv) in methanol (Scheme 4).

Compound **19**, wherein the 2-thio group of 1 has been replaced by a methylene group, was prepared as illustrated in Scheme 5. Protection of the imidazole nitrogen atom in **14** followed by lithiation with *n*-butyllithium and subsequent alkylation with 1,6-dibromohexane afforded bromide **16**. Treatment of **16** with heptylamine followed by condensation with 2,4-difluorophenyl isocyanate and subsequent deprotection gave the methylene analog **19**.

The corresponding 2-aminoimidazole **23**, was prepared as shown in Scheme 6. Amine **21** was obtained via bromination of 4,5-diphenylimidazole at the imidazole 2-position followed by displacement of the bromide with 1,5-diaminopentane. Alkylation with heptanoyl chloride followed by reduction with lithium aluminum hydride and condensation with 2,4-difluorophenyl isocyanate gave **23**.

Pharmacological Results and Discussion

1 and compounds **6**, **12**–**13**, and **24**–**71** were tested for ACAT inhibitory activity *in vitro* in a rat liver microsome radioassay.[15,20] The data obtained from these assays are displayed in Tables 1–6. Examination of the data yields several conclusions regarding the SAR of this series. In probing the effect of imidazole ring substitution on ACAT inhibition (Table 1), **1**, the diarylimidazole, was found to be 50 times more potent in the *in vitro* assay than the monoarylimidazole **24** and was in turn approximately 300 times more active than the corresponding 4,5-unsubstituted imidazole **25**. *N*-Methylation on the imidazole nitrogen of **1** (**6**) resulted in a 350-fold decrease in potency. An even greater decrease in potency was observed with the diaryl-substituted imidazole when the ring nitrogen was substituted with phenyl (**26**). The requirement of the imidazole NH for good potency was further borne out by a decrease in activity of the 1,4-diphenylimidazole **27**, which was a much poorer ACAT inhibitor than its counterpart possessing the free NH. Additionally, as one might anticipate, the 1,4,5-triphenyl analog **28** is a poor inhibitor of ACAT.

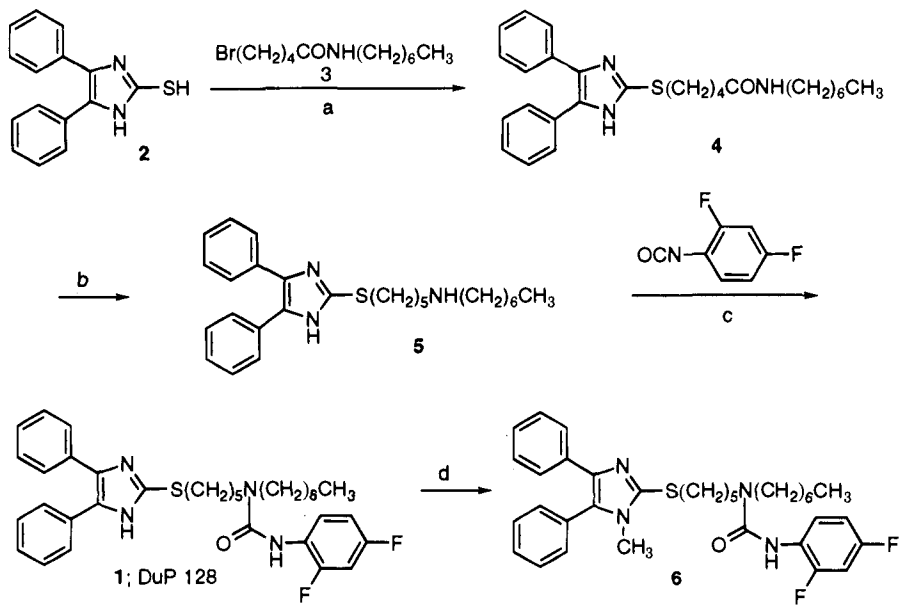
Having identified the 4,5-diarylimidazole as optimal, we focused our attention on the X-linker at the 2-position of the imidazole. As illustrated in Table 2, the sulfide (**1**), sulfoxide (**12**), and sulfone (**13**) maintain essentially equipotent inhibitory activity. Compounds **12** and **13** were originally prepared as potential metabolites of **1** and indeed were found to be metabolites of **1** from intravenous studies in rats.[21] When sulfur was replaced by carbon (**19**) and nitrogen (**23**), hepatic ACAT activity decreased in the order of sulfur (SO ≥ S > SO_2) > carbon > nitrogen; hence, theoretically, the sulfur is presumed to be involved in electronically modifying the pK_a of the imidazole.

In order to determine the optimal bridging distance between the sulfur and the tertiary nitrogen, compounds having two, five, and eight methylene groups were synthesized and evaluated (Table 3). The results of this investigation demonstrate that ACAT inhibitory activity was improved significantly for a length of five or more carbon atoms, suggesting a preference for flexibility in the chain between the sulfur atom and the urea group. The addition of rigidifying elements into the sulfur-to-nitrogen chain was also investigated. For example, the introduction of the positional isomers of phenylene gave compounds **31**–**33** which ranked in increasing potency in the order *ortho* < *para* < *meta*. The *meta* isomer would most likely mimic the extended pentamethylene chain of compounds like **1**, but it is not known if this represents the optimal ground-state conformation for inhibitors of this class. The *gem*-dimethyl group was introduced into compound **34**, with some resulting loss of *in vitro* potency. Geminal dialkyl groups are thought to cause preference for "folded" conformations, due to the Thorpe–Ingold effect,[22] but if the ground state conformation of **34** is folded, then this conformation clearly does not result in a more potent inhibitor.

As shown in Table 4, replacement of the urea group of **1** and **35** with a thiourea group (**36** and **37**) resulted in a 2–4-fold decrease in activity. Replacement of the urea of **38** with the more basic guanidine functionality (**39**) resulted in a greater than 100-fold decrease in potency.

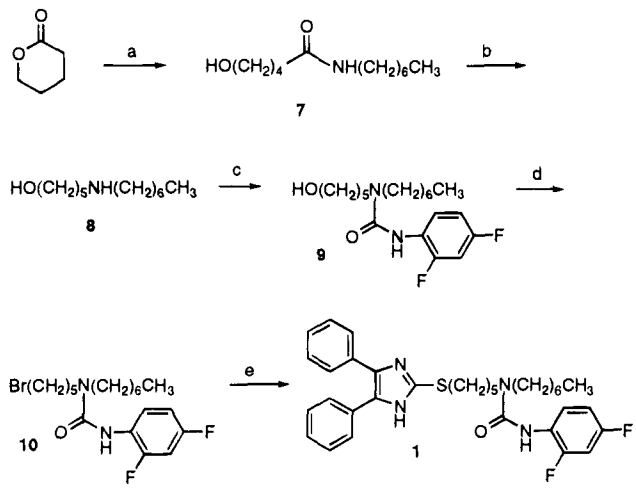
The substituents on the urea R position of the representative compounds shown in Table 5 were chosen to examine lipophilic–hydrophlic, electronic, and steric factors. The effect of the majority of substituted phenyl analogs as well as *n*-alkyl, branched alkyl, and cycloalkyl analogs resulted in an array of *in vitro* potent analogs. Preferred substitutents on the urea were phenyl, polyfluorophenyl, or branched alkyl groups, although almost any substituent tried was well-tolerated. Apparently, electron-withdrawing groups, such as fluorinated or nitrated phenyl groups (**1**, **40**), give potency to the resulting ureas. However, bulky groups, such as branched alkyls, were also successful substituents. This suggests that more than one mode of the inhibitor interacting with the enzyme may be occurring. Other bulky groups such as biphenyl, **41** and **42**, and diisopropylphenyl, **43**, may have provided steric hinderance to the molecules. Only **44** , the unsubstituted urea, was substantially less active than the other analogs prepared. Additionally, replacement of the urea group, **1** and **45**–**47**, with an amide group, **49**–**54**, or carbamate group, **55**–**57**, resulted in almost unchanged *in vitro* hepatic ACAT activity.

Scheme 1. Preparation of DuP 128[a]



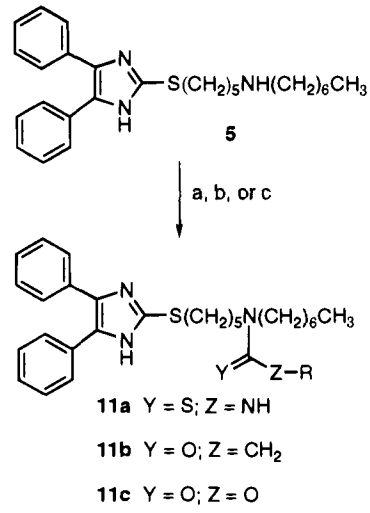
[a] Reagents: (a) K_2CO_3, NaI, THF; (b) Red-Al, THF, reflux; (c) hexane; (d) CH_3I, K_2CO_3, THF.

Scheme 2. Alternative Method for Preparation of DuP 128[a]



[a] Reagents: (a) *n*-heptylamine, toluene, reflux; (b) $LiAlH_4$, THF, reflux; (c) 2,4-$F_2C_6H_4N$=C=O, CH_2Cl_2; (d) Ph_3P, CBr_4, CCl_4; (e) 4,5-diaryl-1*H*-imidazole-2-thiol, NaH, DMF.

Scheme 3. Preparation of Thioureas, Amides, and Carbamates[a]



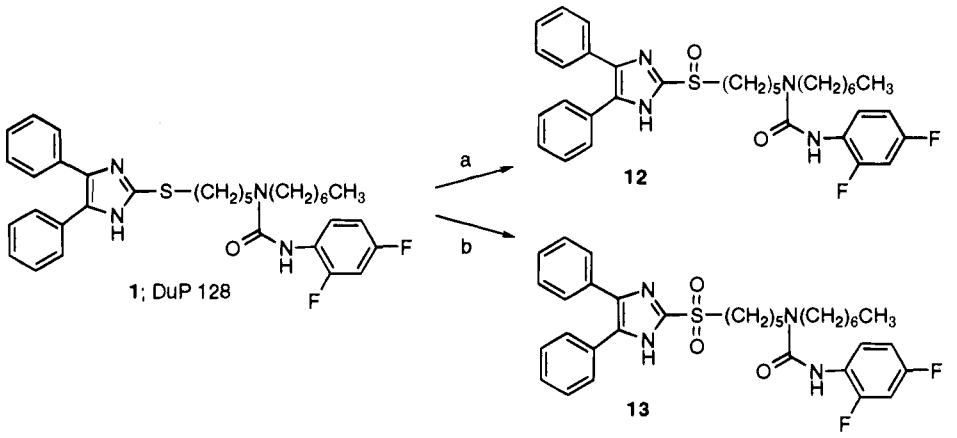
[a] Reagents: (a) SCN-R; (b) HOC(O)R or ClC(O)R; (c) ClC(O)OR.

The effect of shortening the heptyl group in the disubstituted nitrogen atom of **1** is shown in Table 6. A variety of groups were acceptable substitutes for the heptyl group, but the longer chain alkyl group proved superior. Elimination of this group, resulting in the disubstituted urea **59**, resulted in a 400-fold decrease in *in vitro* potency. The consistent loss of *in vitro* potency observed in going from heptyl (**1**) to propyl (**58**) to hydrogen (**59**) was seen for other structural types as well. For example, when the urea aromatic group was changed to 2,6-diisopropylphenyl, elimination of the heptyl chain (going from compound **43** to **60**) lowered *in vitro* potency 2-fold. The compound corresponding to heptyl group removal in the *m*-phenylene rigidified compound **31** was also prepared (**61**, Figure 2). A sizeable drop in potency was recorded (IC_{50} – 2.80 μM). Although this position in this chemical series can tolerate a variety of groups, apparently short alkyl chains (or just a hydrogen atom) are not acceptable.

A series of compounds was prepared which contain an arylalkyl group at the R^1 position (**62**–**66**). Once again, more potent compounds are observed when the overall length of the R^1 group reaches about six carbon–carbon bonds (*e.g.*, **64**). This is consistent with the all-alkyl examples discussed above; perhaps the spacial parameters of the inhibitor–receptor interaction require a group of that minimal length in that position. The potency of a compound bearing a shorter arylalkyl group (*e.g.*, **66**) can be increased, however, if the R^2 group is made to be a longer chain alkyl, which apparently also satisfies the "six-bond length" requirement.

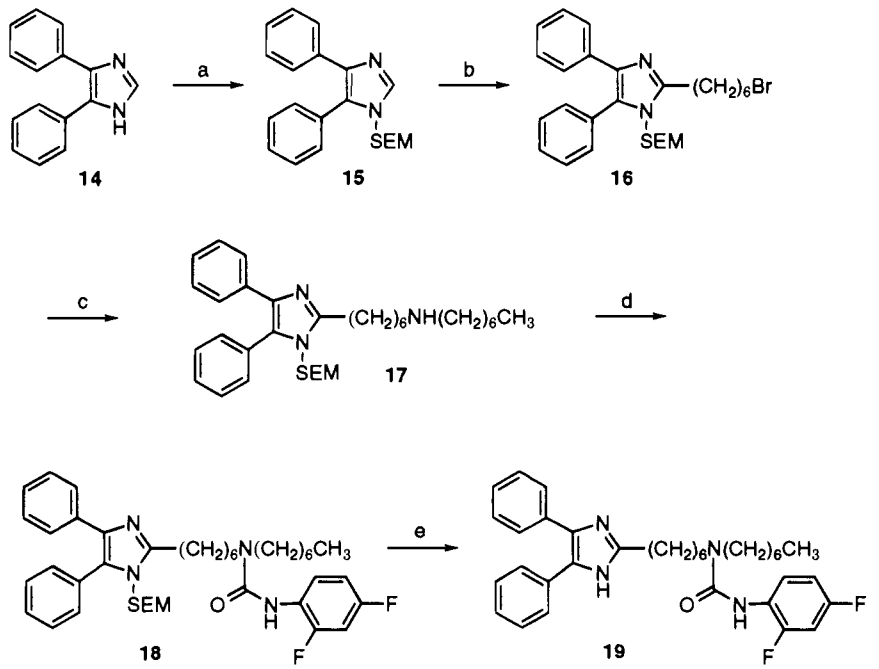
To evaluate potential influences of rotational or conformational changes at the disubstituted nitrogen, the position of both lipophilic branches with respect to each other was examined. The observation that the IC_{50} remains intact well within 1 order of magnitude between compounds containing the reversed substitution to each other (**67** and **1**, **68** and **38**, **69** and **35**) implies a certain amount of flexibility in the interaction between inhibitor molecule and its binding pocket. Once again,

Scheme 4. Preparation of Sulfide and Sulfone Analogs[a]



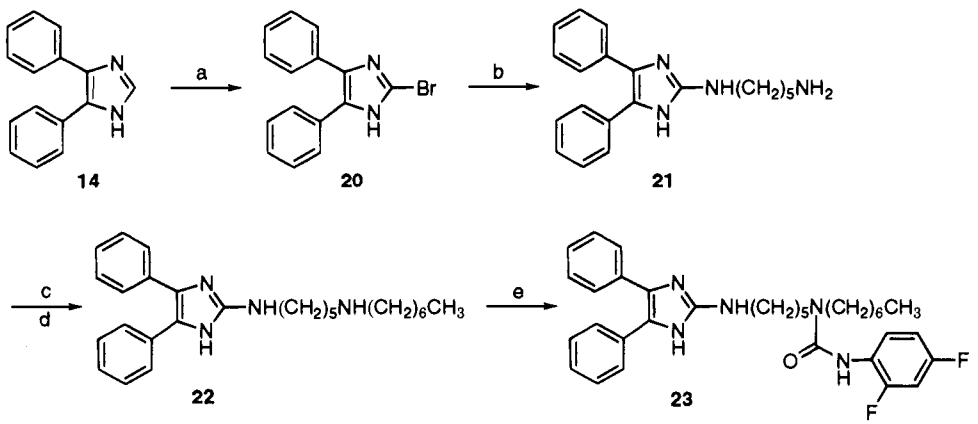
[a] Reagents: (a) *m*-CPBA, CH_2Cl_2, −78 °C; (b) Oxone, CH_3OH.

Scheme 5. Preparation of Carbon-Linker Analogs[a]



[a] Reagents: (a) $ClCH_2O(CH_2)_2(CH_3)_3$, NaH, DMF; (b) $Br(CH_2)_6Br$, *n*-BuLi, THF, −78 °C; (c) $H_2N(CH_2)_6CH_3$, CH_3CN, 60 °C; (d) 2,4-difluorophenyl isocyanate, CH_2Cl_2; (e) $(Bu)_4NF$, THF.

Scheme 6. Preparation of Nitrogen-Linker Analogs[a]

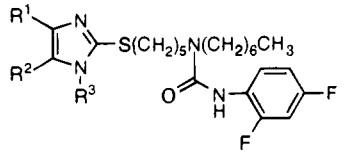


[a] Reagents: (a) Br_2, $CHCl_3$; (b) 1,5-diaminopentane, reflux; (c) $ClC(O)(CH_2)_5CH_3$, Et_3N, CH_2Cl_2; (d) $LiAlH_4$, THF; (e) 2,4-difluorophenyl isocyanate, CH_2Cl_2.

the compounds in this series bearing short alkyl chains (**70**–**71**) are less potent than their homologous counterparts (**1**, **38**).

The analogues with potent *in vitro* ACAT inhibitory activity (IC_{50} < 50 nM) were then evaluated in the cholesterol-fed hamster model for *in vivo* hypocholes-

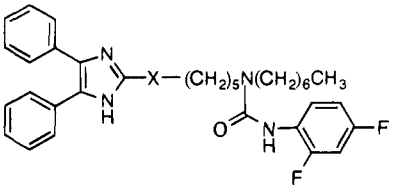
Table 1. Effect of Varying Imidazole Substituents on *in Vitro* ACAT Inhibition



no.	R^1	R^2	R^3	yield[a]	formula[b]	mp (°C)	ACAT[c]
1	Ph	Ph	H	63	$C_{34}H_{40}F_2N_4OS$	96–98	0.010
6	Ph	Ph	CH_3	52	$C_{35}H_{42}F_2N_4OS$	*d*	3.6
24	Ph	H	H	89	$C_{28}H_{36}F_2N_4OS$	*d*	0.49
25	H	H	H	41	$C_{22}H_{32}F_2N_4OS$	*d*	2.9
26	H	Ph	Ph	85	$C_{34}H_{40}F_2N_4OS$	*d*	7.2
27	Ph	H	Ph	73	$C_{34}H_{40}F_2N_4OS$	*d*	42
28	Ph	Ph	Ph	73	$C_{40}H_{44}F_2N_4OS$	99–101	>50

[a] Yield (%) of final step. [b] Satisfactory elemental analyses were obtained for C, H, N unless otherwise indicated. [c] IC_{50} (μM) for the enzyme obtained from rat hepatic microsomes. [d] Compound obtained as an oil.

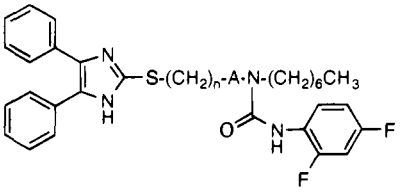
Table 2. Effect of Varying X-Linker on *in Vitro* ACAT Inhibition



no.	X	yield[a]	formula[b]	mp (°C)	ACAT[c]
1	S	63	$C_{34}H_{40}F_2N_4OS$	96–98	0.010
12	SO	71	$C_{34}H_{40}F_2N_4O_2S$	77–79	0.008
13	SO_2	51	$C_{34}H_{40}F_2N_4O_3S$	66–68	0.016
19	CH_2	53	$C_{35}H_{42}F_2N_4O$	*d*	0.280
23	NH	29	$C_{34}H_{41}F_2N_5O$	*d*	3.50

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

Table 3. Effect of Varying Internal Chain Length on *in Vitro* ACAT Inhibition



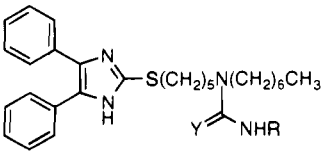
no.	n	A	yield[a]	formula[b]	mp (°C)	ACAT[c]
1	5		63	$C_{34}H_{40}F_2N_4OS$	96–98	0.010
29	8		44	$C_{37}H_{46}F_2N_4OS$	89–91	0.008
30	2		51	$C_{31}H_{34}F_2N_4OS$	144–146	0.070
31	1	*m*-$C_6H_4CH_2$	31	$C_{36}H_{36}F_2N_4OS$	148–149	0.030
32	1	*p*-$C_6H_4CH_2$	31	$C_{36}H_{46}F_2N_4OS$	149–150	0.20
33	1	*o*-$C_6H_4CH_2$	42	$C_{36}H_{36}F_2N_4OS$	87–89	3.6
34	2	$C(CH_3)_2CH_2$	82	$C_{36}H_{44}F_2N_4OS$	138–139	0.070

[a–c] See corresponding footnotes of Table 1.

terolemic activity. The antihypercholesterolemic activity of **1** and several of its analogs is shown in Table 7. Compounds **1**, **35**, and **47** are potent antihypercholesterolemic compounds having a greater than 50% antihypercholesterolemic value (AHV) at 10 mg/kg. However, not all compounds, such as **29** and **68**, which have equivalent *in vitro* activity to **1**, show *in vivo* antihypercholesterolemic activity. Additional structural requirements for potent *in vivo* activity are currently being pursued.

Direct comparisons among various ACAT inhibitors

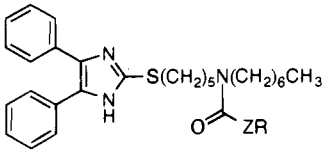
Table 4. Physical Properties and *in Vitro* ACAT Inhibition Potencies of Ureas vs Thioureas and Guanidines



no.	Y	R	yield[a]	formula[b]	mp (°C)	ACAT[c]
1	O	2,4-$F_2C_6H_3$	63	$C_{34}H_{40}F_2N_4OS$	96–98	0.010
35	O	2,4,6-$F_3C_6H_2$	34	$C_{34}H_{39}F_3N_4OS$	78–80	0.016
36	S	2,4-$F_2C_6H_3$	76	$C_{34}H_{40}F_2N_4S_2$	116–118	0.058
37	S	2,4,6-$F_3C_6H_2$	67	$C_{34}H_{39}F_3N_4S_2$	124–126	0.030
38	O	C_6H_5	71	$C_{34}H_{42}N_4OS$	58–62	0.023
39	NH	C_6H_5	63	$C_{34}H_{43}N_5S$	135–136	3.16

[a–c] See corresponding footnotes of Table 1.

Table 5. Effect of Ureas, Amides, Carbamates on *in Vitro* ACAT Inhibition



no.	Z	R	yield[a]	formula[b]	mp (°C)	ACAT[c]
1	NH	2,4-$F_2C_6H_3$	63	$C_{34}H_{40}F_2N_4OS$	96–98	0.010
40	NH	4-$NO_2C_6H_4$	85	$C_{34}H_{41}N_5O_3S$	65–67	0.080
41	NH	$C_6H_4C_6H_5$	65	$C_{40}H_{46}N_4OS$	119–121	0.070
42	CH_2	$C_6H_4C_6H_5$	44	$C_{41}H_{47}N_3OS$	*d*	0.160
43	NH	2,6-*i*$Pr_2C_6H_3$	94	$C_{40}H_{54}N_4OS$	185–187	0.230
44	NH	H	76	$C_{28}H_{38}N_4OS$	133–135	0.910
45	NH	C_6H_{11}	88	$C_{34}H_{48}N_4OS$	95–97	0.010
46	NH	$CH(CH_3)_2$	86	$C_{31}H_{44}N_4OS$	84–86	0.020
47	NH	$CH_2CH_2CH_3$	19	$C_{31}H_{44}N_4OS$	77–80	0.010
48	NH	CH_3	67	$C_{29}H_{40}N_4OS$	93–96	0.040
49	CH_2	2,4-$F_2C_6H_3$	88	$C_{35}H_{41}F_2N_3OS$	*d*	0.025
50	CH_2	C_6H_{11}	84	$C_{35}H_{49}N_3OS$	*d*	0.030
51	CH_2	$(CH_3)_2$	72	$C_{31}H_{43}N_3OS$	*d*	0.10
52	CH_2	CH_2CH_3	92	$C_{31}H_{43}N_3OS$	*d*	0.030
53		2,4-$F_2C_6H_3$	88	$C_{34}H_{39}F_2N_3OS$	*d*	0.060
54		C_6H_5	92	$C_{34}H_{41}N_3OS$	*d*	0.050
55	O	$CH_2CH_2CH_3$	35	$C_{31}H_{43}N_3O_2S$	*d*	0.034
56	O	C_6H_{11}	55	$C_{34}H_{47}N_3O_2S$	*d*	0.050
57	O	C_6H_5	21	$C_{34}H_{41}N_3O_2S$	*d*	0.020

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

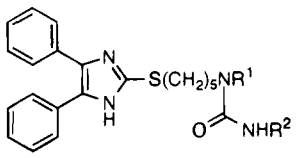
are difficult. The percent lowering of serum cholesterol is affected by animal species, the level of hypercholesterolemia achieved in control animals, and the length of the study. Bearing this in mind, the above compounds compare very favorably with other ACAT inhibitors that have been looked at in the cholesterol-fed hamster. Octimibate, S58–035, and CL277,082 show less than 20% lowering of plasma cholesterol at doses of 50–100 mg/kg.[23,24] CI-976 lowers serum cholesterol 38% at 20 mg/kg, and YM17E has an ED_{50} of 19 mg/kg.[25,26]

Substituents on the aromatic rings of the diarylimidazole were explored extensively, and a variety of modifications were made to 1 that improve bioavailability properties of the molecule. These topics will be discussed in subsequent papers.

Conclusion

In conclusion, in an attempt to develop a novel, potent ACAT inhibitor with minimal systemic bioavailability, a large series of trisubstituted imidazoles was prepared. The results of the SAR study in this series of compounds

Table 6. Effect of Replacing Terminal Heptyl Group on *in Vitro* ACAT Inhibition



no.	R^1	R^2	yield[a]	formula[b]	mp (°C)	ACAT[c]
1	$(CH_2)_6CH_3$	2,4-$F_2C_6H_3$	63	$C_{34}H_{40}F_2N_4OS$	96–98	0.01
58	$(CH_2)_2CH_3$	2,4-$F_2C_6H_3$	75	$C_{30}H_{32}F_2N_4OS$	68–70	0.03
59	H	2,4-$F_2C_6H_3$	26	$C_{27}H_{26}F_2N_4OS$	187–189	0.40
60	H	2,6-*i*$Pr_2C_6H_3$	92	$C_{33}H_{40}N_4OS$	199–201	0.51
62	$CH_2C_6H_5$	2,4-$F_2C_6H_3$	64	$C_{34}H_{32}F_2N_4OS$	86–88	0.20
63	$(CH_2)_2C_6H_5$	2,4-$F_2C_6H_3$	57	$C_{35}H_{34}F_2N_4OS$	78–80	0.17
64	$(CH_2)_3C_6H_5$	2,4-$F_2C_6H_3$	54	$C_{36}H_{36}F_2N_4OS$	76–78	0.03
65	$(CH_2)_4C_6H_5$	2,4-$F_2C_6H_3$	25	$C_{37}H_{38}F_2N_4OS$	69–71	0.05
66	$CH_2C_6H_5$	$(CH_2)_7CH_3$	84	$C_{36}H_{46}N_4OS$	*d*	0.15
67	2,4-$F_2C_6H_3$	$(CH_2)_7CH_3$	28	$C_{35}H_{42}F_2N_4OS$	*d*	0.04
68	C_6H_5	$(CH_2)_7CH_3$	56	$C_{35}H_{44}N_4OS$	74–76	0.01
69	2,4,6-$F_3C_6H_3$	$(CH_2)_7CH_3$	80	$C_{35}H_{41}F_3N_4OS$	95–97	0.02
70	2,4-$F_2C_6H_3$	$CH(CH_3)_2$	86	$C_{30}H_{32}F_2N_4OS$	46–50	0.04
71	C_6H_5	$CH(CH_3)_2$	73	$C_{30}H_{34}N_4OS$	55–59	0.08

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

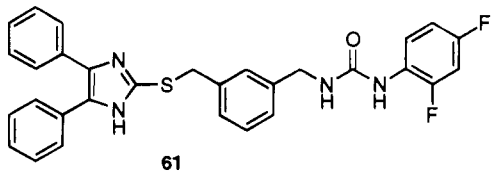


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Figure 2.

Table 7. Antihypercholesterolemic Activity of ACAT Inhibitors in the Cholesterol-Fed Hamster

no.	dose[a] (mg/kg/day)	serum cholesterol (mg%)[b] treated	serum cholesterol (mg%)[b] control	AHV[c] (%)
1	10[d]	253 ± 16	383 ± 23	59
1	10[e]	205 ± 8	275 ± 8	61
12	10[d]	278 ± 12	383 ± 23	49
13	10[d]	318 ± 22	383 ± 23	30
29	10[e]	271 ± 13	253 ± 4	NS
35	10[e]	218 ± 22	279 ± 29	51
40	25[d]	277 ± 13	350 ± 13	38
47	10[d]	199 ± 8	308 ± 10	74
52	10[d]	245 ± 5	308 ± 10	43
68	10[e]	268 ± 5	275 ± 10	NS

[a] Animals were orally gavaged with drug suspended in a methylcellulose vehicle. Control animals received vehicle only. [b] Blood was obtained from the orbital sinus of each animal and serum was analyzed for total serum cholesterol on a DuPont aca Clinical Analyzer. Values are the mean ± SEM. [c] Antihypercholesterolemic value (AHV) is the ratio of the observed reduction in serum cholesterol to the difference between the control and baseline levels × 100. An AHV of 0 indicates the drug had no effect; an AHV of 100 indicates it was completely effective. NS = not statistically significant at $p = 0.05$. [d] Male Golden Syrian hamsters ($n = 10$) were fed a 0.8% cholesterol-supplemented chow diet for 7 days. [e] Male Golden Syrian hamsters ($n = 10$) were fed a 2.5% cholesterol-supplemented diet for 3 days.

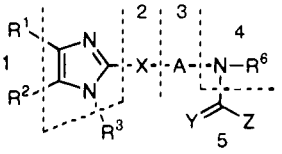

Figure 3. SAR summary of the DuP 128 series.

may be summarized in the diagram presented in Figure 3. Region 1: optimized R^1 and R^2 groups were found to be phenyl rings, wherein optimally, R^3, is a hydrogen atom. Region 2: the preferred X group is sulfur (of any oxidation state) over carbon or nitrogen. Region 3: the A group has a required minimum length of three atoms, but potency improves significantly with a length of five or more atoms, and rigidifying groups are not generally well tolerated. Region 4: alkyl, aryl and arylalkyl groups are acceptable, but long alkyl chains are preferred. Region 5: ureas are favored over amides, thioureas, guanidines, or tertiary amines, and the preferred substituents on the urea are difluorophenyl, trifluorophenyl, and branched alkyl groups (although a number of types of groups were acceptable). The most potent compound, *N'*-(2,4-difluorophenyl)-*N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptylurea (**1**) was chosen to undergo clinical investigation.

Future reports from this group will disclose our efforts to improve oral bioavailability with the goal of identifying a systemic bioavailable ACAT inhibitor from this series.

Experimental Section

Physical Methods. Melting points were determined in an open capillary on a Thomas Scientific melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrophotometer. ^1H NMR spectra were obtained using a Varian VXR-300a using tetramethylsilane (TMS) as an internal standard. Microanalyses were performed by Quantitative Technologies, Inc., Bound Brook, NJ, and were within ±0.4% of the calculated values. Mass spectra were obtained on a HP 5988A MS/HP Particle Beam Interface. Analytical thin-layer chromatography (TLC) was carried out on Merck precoated silica gel 60 F-354 plates. Flash column chromatography was preformed using silica gel 60 (230–400 mesh; EM Reagents).

***In Vitro* ACAT Assay (IC_{50}).** Inhibition of ACAT-catalyzed cholesterol esterification was determined in rat hepatic microsomes by measuring the formation of labelled cholesterol oleate (pmol/min/mg) from oleoyl-CoA as described previously.[15,20] 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%.

Antihypercholesterolemic Activity in Cholesterol-Fed Hamster Model. Male Golden Syrian hamsters ($n = 10$) weighing approximately 100 g were maintained on a diet supplemented with either 0.8% cholesterol for 7 days or 2.5% cholesterol for 3 days. The treatment group received 10 mg/kg po of the test compound suspended in methylcellulose vehicle. The control group was pair-fed to the treatment group and dosed with the vehicle only. Blood was obtained from the orbital sinus of each animal, and total serum cholesterol was determined on a DuPont aca IV Clinical Analyzer. The data were expressed in terms of mg of cholesterol/100 mL of serum (mg%). The antihypercholesterolemic value (AHV), which is the ratio of the observed reduction in serum cholesterol to the difference between the control and baseline levels × 100, was also determined. An AHV of 0% indicates the drug had no effect; an AHV of 100% indicates it was completely effective. The average baseline serum cholesterol (non-cholesterol diet) was 160 ± 1.4 mg%.

5-Bromo-*N*-heptylpentanamide (3). To a solution of bromovaleryl chloride (6.98 g, 0.035 mol) in dichloromethane (50 mL) at 0 °C was added, dropwise, a solution of heptylamine (5.04 mL, 3.92 g, 0.034 mol) in dichloromethane (10 mL), and the reaction mixture was stirred at 0 °C for 30 min and then stirred at ambient temperature for 1 h. The reaction mixture was poured into water and then extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum. The residue was distilled to give **3** (5.00 g, 0.018 mol, 53%) as a clear liquid, bp 138–142 °C. ^1H NMR ($CDCl_3$): δ 7.1 (s, 1H), 3.9 (d, 2H, J = 6 Hz), 3.3 (m, 2H), 1.6 (m, 2H), 0.9 (t, 3H, J = 7 Hz). MS: 279 (M + H).

5-[(4,5-Diphenyl-*1H*-imidazol-2-yl)thio]-*N*-heptylpentanamide (4). A portion of sodium hydride, 60% in mineral oil (0.4 g, 0.01 mol), was washed twice with hexane (10 mL), and the hexane was replaced with DMF (50 mL). To this solution was added, portionwise as a solid, sodium iodide (0.04 g, 0.0003 mol) and then, dropwise, a solution of **2** (2.52 g, 0.01 mol) in DMF (10 mL) followed by the dropwise addition of a solution of **3** (2.78 g, 0.01 mol) in DMF (10 mL). The reaction mixture was stirred at reflux for 18 h, cooled, poured, carefully, into ice water, and then extracted with ethyl acetate. The combined organic extracts were backwashed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography (hexane–ethyl acetate, 1:1) and the resulting solid was recrystallized from acetonitrile to give **4** (2.82 g, 0.0063 mol, 63%) as a white solid, mp 104–106 °C. ^1H NMR ($CDCl_3$): δ 12.6 (s, 1H), 8.3 (s, 1H), 7.5–7.1 (m, 10H), 3.8 (s, 2H), 3.0 (q, 2H, J = 7.5 Hz), 1.4 (sextet, 2H, J = 9 Hz), 0.8 (t, 3H, J = 6 Hz). MS: 450 (M + H).

***N*-[5-[(4,5-Diphenyl-*1H*-imidazol-2-yl)thio]pentyl]-1-heptanamine (5).** A solution of **4** (9.80 g, 0.022 mol) in toluene (50 mL) was added, dropwise, to a solution of Red-Al (3.4 M in toluene, 13.88 mL, 9.58 g, 0.047 mol) in toluene (100 mL), and the reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was cooled to 0 °C and quenched by the slow and careful addition of a 5% solution of NaOH (8.5 mL). The layers were separated, and the aqueous layer was extracted with toluene. The combined organic layers were backwashed with water and brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography (ethyl acetate–methanol, 1:0 and 3:1 and 1:1). The resulting yellow oil was triturated with cold hexane to give **5** (7.22 g , 0.017 mol, 77%) as a white solid, mp 80–83 °C. ^1H NMR ($CDCl_3$): δ 9.3 (s, 2H), 7.7–7.3 (m, 10H), 3.7–3.5 (m, 2H), 3.0–2.7 (m, 4H), 2.0–1.2 (m, 16H), 0.9 (t, 3H, J = 8 Hz). MS: 436 (M + H).

Method A. *N'*-(2,4-Difluorophenyl)-*N*-[5-[(4,5-diphenyl-*1H*-imidazol-2-yl)thio]pentyl]-*N*-heptylurea (1). A solution of 2,4-difluorophenyl isocyanate (0.296 mL, 0.39 g, 0.0025 mol) in hexane (25 mL) was added, dropwise, to a solution of **5** (1.0 g, 0.0024 mol) in hexane (50 mL), and the reaction mixture was stirred at ambient temperature for 3 h. The reaction mixture was concentrated under vacuum, and the residue was purified by flash chromatography (hexane–ethyl acetate, 7:3) to give 1 (0.86 g, 0.0015 mol, 60%) as a white solid, mp 96–98 °C. ^1H NMR ($CDCl_3$): δ 10.8 (s, 1H), 7.7–7.1 (m, 14H), 3.4 (t, 2H, J = 7 Hz), 3.2 (t, 2H, J = 7 Hz), 3.0 (t, 2H, J = 7 Hz), 1.9–1.4 (m, 16H), 0.9 (t, 3H, J = 8 Hz). MS: 591 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-heptyl-*N*-[5-[(1-methyl-4,5-diphenyl-*1H*-imidazol-2-yl)thio]pentyl]urea (6).** A solution of **5** (0.25 g, 0.00042 mol) and potassium carbonate (0.056 g, 0.00042 mol) in dry tetrahydrofuran (10 mL) was stirred at ambient temperature for 10 min. To this reaction mixture was added, dropwise, methyl iodide (0.039 mL, 0.09 g, 0.00063 mol), and the reaction mixture was stirred for 18 h at ambient temperature. The reaction mixture was then treated with DMF (1.0 mL) and methyl iodide (0.1 mL), and the reaction mixture was stirred at reflux for an additional 24 h. The reaction mixture was cooled, poured into water, and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography (hexane–ethyl acetate, 3:7) to give **6** (0.13 g, 0.000 22 mol, 52%) as a yellow oil. ^1H NMR ($CDCl_3$): δ 8.1–8.0 (m, 1H), 7.5–7.1 (m, 10H), 6.9–6.7 (m, 2H), 6.4 (s, 1H), 3.5 (s, 3H), 3.4–3.2 (m, 5H), 1.9–1.2 (m, 17H), 0.9 (t, 3H, J = 8 Hz). MS: 605 (M + H).

***N*-Heptyl-5-hydroxypentanamide (7).** A solution of γ-valerolactone (25.0 g, 0.25 mol) in toluene (50 mL) and *n*-heptylamine (35.96 g, 0.31 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, washed with 1 N HCl, water, and brine, dried over $MgSO_4$, and concentrated under vacuum. The product was crystallized from ethyl ether and hexane to give **7** (41.8 g, 0.19 mol, 78%) as a white solid, mp 55–56 °C. ^1H 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), 0.866 (t, 3H). MS: 216 (M + H).

***N*-(5-Hydroxypentyl)-*N*-heptylamine (8).** To a solution of lithium aluminum hydride (6.7 g, 0.18 mol) in dry THF (300 mL) was added, dropwise, a solution of **7** (19.0 g, 0.088 mol) in dry THF (100 mL) under a nitrogen atmosphere. The reaction mixture was heated to reflux for 18 h, allowed to cool to ambient temperature, and poured slowly into a stirred mixture of Na_2SO_4 (10%, 400 mL) and ice (200 mL). The resulting slurry was filtered through a bed of Celite, and the filtrate was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under vacuum to give a viscous yellow oil. The product was crystallized from hexane to give **8** (15.2 g, 0.075 mol, 85%) as a white powder, mp 47–48 °C. ^1H NMR ($CDCl_3$): δ 3.63 (t, 2H), 2.63 (q, 4H), 2.39 (br s, 2H), 1.66–1.24 (m, 16H), 0.905 (t, 3H). MS: 202 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-heptyl-*N*-(5-hydroxypentyl)urea (9).** To a solution of **8** (11.65 g, 0.058 mol) in dichloromethane (75 mL) under a nitrogen atmosphere cooled to 0 °C was added, dropwise, 2,4-difluorophenyl isocyanate (8.97 g, 0.058 mol). The reaction mixture was stirred for 1 h, poured into 1 N HCl, and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under vacuum to give **9** as a pale yellow oil (20.0 g, 0.056 mol, 97%). ^1H 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), 0.907 (t, 3H). MS: 357 (M + H).

***N*-(5-Bromopentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (10).** To a solution of **9** (15.0 g, 0.042 mol) and carbon tetrabromide (16.75 g, 0.051 mol) in dichloromethane (350 mL) under a nitrogen atmosphere at ambient temperature, was added, dropwise, a solution of triphenylphosphine (13.24 g, 0.051 mol) in dichloromethane (100 mL). The reaction mixture was stirred for 3 h and was concentrated under vacuum to give a crude viscous oil. The product was purified by flash chromatography (hexane–ethyl acetate, 9:1) to give **10** as a viscous, colorless oil (17.5 g, 0.042 mol, 99%). ^1H 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: 420 (M + H).

Method B. *N'*-(2,4-Difluorophenyl)-*N*-[5-[(4,5-diphenyl-*1H*-imidazol-2-yl)thio]pentyl]-*N*-heptylurea (1). To a suspension of sodium hydride (0.88 g, 60% mineral oil dispersion, 0.0022 mol) (washed free of mineral oil with hexane) in DMF (15 mL) under a nitrogen atmosphere, cooled to 0 °C, was added, dropwise, a solution of 4,5-diphenyl-*1H*-imidazole-2-thione (**2**, 0.63 g, 0.002 mol) in DMF (5 mL). The reaction mixture was stirred for 2 h, and then a solution of **10** (0.845 g, 0.002 mol) in DMF (3 mL) was added. The reaction mixture was allowed to warm to ambient temperature, stirred for 2 h, poured into water, and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated under vacuum to give a viscous oil. The product was purified by flash chromatography (hexane–ethyl acetate, 7:3) to give 1 as a pure yellow foam (0.98 g, 0.0015 mol, 75%). ^1H NMR ($CDCl_3$): δ 10.15 (br s, 1H), 7.87–7.76 (m, 1H), 7.51 (d, 2H), 7.3 (d, 2H), 6.86–6.6 (m, 6H), 6.42 (d, 1H), 3.8 (s, 6H), 3.4 (t, 2H), 3.26 (t, 2H), 2.99 (t, 2H), 1.84–1.25 (m, 16H), 0.89 (t, 3H). MS: 591 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[5-[(4,5-diphenyl-*1H*-imidazol-2-yl)sulfinyl]pentyl]-*N*-heptylurea (12).** To a solution of 1 (0.59 g, 0.001 mol) in dichloromethane (50 mL) cooled to −78 °C was added, dropwise, a solution of *m*-chloroperbenzoic acid (0.286 g, 0.0017 mol) in dichloromethane (10 mL). The reaction mixture was stirred at −78 °C for 1 h and then allowed to warm to ambient temperature. The reaction mixture was then cooled to 0 °C, and a solution of saturated sodium bisulfite was added, dropwise. The layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography (hexane–ethyl acetate, 1:1) to give **12** (0.43 g, 0.00071 mol, 71%) as a yellow solid, mp 77–79 °C. ^1H NMR ($CDCl_3$): δ 8.1–7.9 (m, 1H), 7.6–7.2

(m, 1H), 6.9–6.7 (m, 2H), 6.4 (d, 1H, J = 3.3 Hz), 3.4–3.1 (m, 6H), 2.0–1.1 (m, 18H), 0.9 (t, 3H, J = 6.4 Hz). MS: 607 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[5-[(4,5-diphenyl-*1H*-imidazol-2-yl)sulfonyl]pentyl]-*N*-heptylurea (13).** To a solution of 1 (0.11 g, 0.000 19 mol) in methanol (5 mL) was added, portionwise as a solid, Oxone (0.234 g, 0.000 38 mol), and the reaction mixture was stirred at ambient temperature for 7 h. The solids were filtered and washed with methanol. The filtrate was concentrated under vacuum, and the residue was purified by flash chromatography (hexane–ethyl acetate, 6:4) to give **13** (0.06 g, 0.0000 96 mol, 51%) as a glassy, colorless solid, mp 66–68 °C. ^{1}H NMR ($CDCl_3$): δ 7.85–7.75 (m, 1H), 7.6–7.1 (m, 11H), 6.8–6.6 (m, 2H), 6.4 (s, 1H), 3.4 (t, 4H, J = 10 Hz), 3.25 (t, 2H, J = 7 Hz), 1.9–1.75 (m, 2H), 1.75–1.4 (m, 6H), 1.4–1.1 (m, 8H), 0.9 (t, 3H, J = 8 Hz). MS: 623 (M + H).

4,5-Diphenyl-1-[[2-(trimethylsilyl)ethoxy]methyl]-*1H*-imidazole (15). A portion of sodium hydride, 60% in mineral oil (0.55 g, 0.014 mol), was washed twice with hexane (10 mL), the hexane was replaced with DMF (15 mL), and the solution was cooled to 0 °C. To this solution was added, dropwise, a solution of **14** (3.0 g, 0.014 mol) in DMF (10 mL), and the reaction mixture was stirred for 45 min. Then [2-(trimethylsilyl)ethoxy]methyl chloride (2.27 g, 0.014 mol) was added, dropwise. The reaction mixture was stirred for 1 h, poured, carefully, into ice water, and extracted with ethyl acetate. The combined organic extracts were backwashed with H_2O and brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography (hexane–ethyl acetate, 7:3). The residue was triturated with hexane to give **15** (3.77 g, 0.011 mol, 79%) as a white solid, mp 73-75 °C. ^{1}H NMR ($CDCl_3$): δ 7.76 (s, 1H), 7.5–7.4 (m, 7H), 7.3–7.16 (m, 3H), 5.2 (s, 2H), 3.5 (t, 2H), 0.9 (t, 2H). MS: 351 (M + H).

6-Bromo-1-[4,5-diphenyl-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazol-2-yl]hexane (16). To a solution of **15** (2.5 g, 0.0073 mol) in dry THF (50 mL) cooled to −78 °C under a nitrogen atmosphere was added slowly n-butyllithium in hexane (2.5 M, 0.0073 mol). The reaction mixture was stirred for 1 h, and 1,6-dibromohexane (2.68 g, 0.0011 mol) was added rapidly, the mixture was then stirred for 30 min, allowed to warm to ambient temperature, and stirred for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under vacuum to give a viscous oil. The product was purified by flash chromatography (hexane–ethyl acetate, 7:3) to give **16** as an oil (2.18 g, 0.0042 mol, 58%). ^{1}H NMR ($CDCl_3$): δ 7.53–7.16 (m, 10H), 5.1 (s, 2H), 3.48 (t, 2H), 3.34 (t, 2H), 2.9 (t, 2H), 1.99–1.5 (m, 8H), 0.88 (t, 2H), 0.08 (s, 9H). MS: 514 (M + H).

***N*-[6-[4,5-Diphenyl-1-[[2-(trimethylsilyl)ethoxy]methyl]-*1H*-imidazol-2-yl]hexyl]-*N*-heptylamine (17).** A solution of **16** (1.0 g, 0.002 mol) and n-heptylamine (0.45 g, 0.0039 mol) in acetonitrile (25 mL) was heated to 60 °C for 8 h. The reaction mixture was poured into 10% aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated under vacuum to give **17** as a colorless viscous oil (1.04 g, 0.0019 mol). ^{1}H NMR ($CDCl_3$): δ 7.52–7.2 (m, 10H), 5.11 (s, 2H), 4.7–4.2 (br s, 1H), 3.3 (t, 2H), 2.93–2.70 (m, 6H), 1.95–1.34 (m, 18H), 0.93 (t, 3H), 0.86 (t, 2H), 0.01 (s, 9H). MS: 548 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[6-[4,5-diphenyl-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazole-2-yl]hexyl]-*N*-heptylurea (18).** This product was prepared from **17** in a similar manner to that described in method A and was isolated as a viscous oil (1.40 g, 0.0012 mol). ^{1}H NMR ($CDCl_3$): δ 8.12 (m, 1H), 7.53–7.16 (m, 10H), 6.88 (m, 2H), 6.48 (d, 1H), 5.1 (s, 2H), 3.33 (m, 6H), 2.90 (t, 2H), 2.0–1.34 (m, 18H), 0.88 (t, 3H), 0.79 (t, 2H), 0.06 (s, 9H). MS: 704 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[6-(4,5-diphenyl-*1H*-imidazol-2-yl)hexyl]-*N*-heptylurea (19).** To a solution of **18** (0.60 g, 0.000 85 mol) in dry tetrahydrofuran (10 mL) under a nitrogen atmosphere was added tetrabutylammonium fluoride (1 M in tetrahydrofuran, 3.41 mL), and the reaction mixture was heated to reflux for 7 h. The reaction mixture was cooled, poured into water (50 mL), and extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography (hexane–ethyl acetate, 6:4) to give **19** as a viscous oil (0.26 g, 0.000 45 mol, 53%). ^{1}H NMR ($CDCl_3$): δ 9.5–9.0 (br s, 1H), 7.87 (m, 1H), 7.5–7.2 (m, 10H), 6.83–6.7 (m, 2H), 6.4 (d, 1H), 3.28 (m, 4H), 2.67 (t, 2H), 1.75–1.26 (m, 18H), 0.88 (t, 3H). MS: 573 (M + H).

2-Bromo-4,5-diphenyl-*1H*-imidazole (20). Bromine was added, dropwise, to a solution of **14** (5.0 g, 0.023 mol) in CH_2Cl_2 (30 mL) that was cooled to 0 °C. The reaction mixture was stirred for 1 h, allowed to warm to ambient temperature, and stirred for 16 h. The reaction mixture was diluted with ether (100 mL), and a precipitate formed. The solid was collected and triturated with CH_2Cl_2. This solid was recrystallized from CH_3CN to give **20** (6.02 g, 0.02 mol, 87%) as a white solid, mp 153–155 °C. ^{1}H NMR ($CDCl_3$): δ 8.0–7.6 (m, 3H), 7.5–7.33 (m, 7H). MS: 300 (M + H).

5-[(4,5-Diphenyl-*1H*-imidazol-2-yl)amino]-1-aminopentane (21). A solution of **20** (3.5 g, 0.012 mol) in 1,5-diaminopentane (20 mL) was heated to reflux for 48 h. The reaction mixture was concentrated under vacuum to give a viscous oil which was taken up in dichloromethane (60 mL), washed with 10% aqueous $NaHCO_3$, water (2 × 50 mL), and brine, dried over $MgSO_4$, and concentrated under vacuum to give **21** as a viscous oil (3.5 g, 0.011 mol, 93%). ^{1}H NMR ($CDCl_3$): δ 7.55–7.09 (m, 10H), 4.79–3.79 (br s, 3H), 3.14 (t, 2H), 2.59 (t, 2H), 1.79–1.22 (m, 6H). MS: 321 (M + H).

***N*-[5-[(4,5-Diphenyl-*1H*-imidazol-2-yl)amino]pentyl]-*N*-heptylamine (22).** To a solution of **21** (1.7 g, 0.0053 mol) and triethylamine (0.58 g, 0.0058 mol) in dichloromethane cooled to 0 °C under a nitrogen atmosphere was added, dropwise, heptanoyl chloride (0.79 g, 0.0053 mol). The reaction mixture was stirred for 1 h at 0 °C, poured into water, and extracted with dichloromethane (2 × 50 mL). The combined organic extract was washed with water and brine, dried over $MgSO_4$, and concentrated under vacuum to give *N*-[5-[(4,5-diphenyl-*1H*-imidazol-2-yl)amino]pentyl]heptanamide as a viscous oil. This intermediate was purified by flash chromatography (dichloromethane–methanol, 95:5) to give an amber foam (1.3 g, 0.003 mol, 56%). ^{1}H NMR ($CDCl_3$): δ 7.43–7.15 (m, 10H), 6.3 (m, 1H), 3.24–3.1 (m, 4H), 2.09 (t, 2H), 1.6–1.16 (m, 14H), 0.84 (t, 3H). The product (**22**) was prepared from *N*-[5-[(4,5-diphenyl-*1H*-imidazol-2-yl)amino]pentyl]heptanamide in a similar manner to that described in method A and was obtained as an amber oil (1.00 g, 0.002 38 mol, 45%). ^{1}H NMR ($CDCl_3$): δ 7.56–6.85 (m, 10H), 3.23 (m, 2H), 2.49 (m, 4H), 1.68–0.90 (m, 16H), 0.88 (t, 3H). MS: 419 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[5-[(4,5-diphenyl-*1H*-imidazol-2-yl)amino]pentyl]-*N*-heptylurea (23).** This product was prepared from **22** in a similar manner to that described in method A and was obtained as a viscous oil (0.395 g, 0.000 69 mol, 29%). ^{1}H NMR ($CDCl_3$): δ 8.37–7.1 (m, 11H), 6.9–6.67 (m, 2H), 6.44 (d, 1H), 4.53 (br s, 1H), 3.27 (m, 6H), 1.74–1.23 (m, 16H), 0.89 (t, 3H). MS: 574 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-heptyl-*N*-[5-[(4-phenyl-*1H*-imidazol-2-yl)thio]pentyl]urea (24).** This product was prepared from *N*-[5-[(4-phenyl-*1H*-imidazol-2-yl)thio]pentyl]-1-heptanamine in a similar manner to that described in method A and was obtained as an oil (0.13 g, 0.000 25 mol, 89%). ^{1}H NMR ($CDCl_3$): δ 10.8–10.7 (m, 1H), 8.0–7.2 (m, 7H), 6.9–6.6 (m, 2H), 6.0–5.9 (m, 1H), 3.4 (t, 2H, J = 6.6 Hz), 3.3 (t, 2H, J = 7.6 Hz), 3.0 (t, 2H, J = 6.5 Hz), 1.9–1.2 (m, 18H), 0.9 (t, 3H, J = 7.2 Hz). MS: 574 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-heptyl-*N*-[5-(1*H*-imidazol-2-ylthio)pentyl]-*N*-heptylurea (25).** This product was prepared from *N*-[5-(1*H*-imidazol-2-ylthio)pentyl]-1-heptanamine (0.25 g, 0.000 88 mol) in a similar manner to that described in method A and was obtained as an oil (0.16 g, 0.000 46 mol, 41%). ^{1}H NMR ($CDCl_3$): δ 10.4–10.1 (m, 1H), 8.0–7.8 (m, 1H), 7.2–6.9 (m, 2H), 6.9–6.75 (m, 2H), 6.5–6.4 (m, 1H), 3.4–3.2 (m, 4H), 3.0 (t, 2H, J = 7.0 Hz), 1.9–1.1 (m, 19H), 0.9 (t, 3H, J = 8.0 Hz). MS: 439 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[5-[(1,5-diphenyl-*1H*-imidazol-2-yl)thio]pentyl]-*N*-heptylurea (26).** This product was

prepared from 1,5-phenyl-1*H*-imidazole-2-thione (0.25 g, 0.001 mol) in a similar manner to that described in method B and was obtained as an oil (0.50 g, 0.000 85 mol, 85%). ^{1}H NMR ($CDCl_3$): δ 8.1–8.0 (m, 1H), 7.5–7.3 (m, 3H), 7.3–7.1 (m, 4H), 7.1–7.0 (m, 1H), 6.9–6.8 (m, 1H), 6.5 (d, 1H, J = 3.3 Hz), 3.3 (q, 4H, J = 7.4 Hz), 3.1 (t, 2H, J = 7.2 Hz), 1.8–1.2 (m, 18H), 0.9–0.8 (m, 3H). MS: 591 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[5-[(1,4-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptylurea (27).** This product was prepared from 1,4-phenyl-1*H*-imidazole-2-thione (0.25 g, 0.001 mol) in a similar manner to that described in method B and was obtained as an oil (0.43 g, 0.000 73 mol, 73%). ^{1}H NMR ($CDCl_3$): δ 8.0–7.9 (m, 1H), 7.85–7.80 (m, 2H), 7.55–7.40 (m, 7H), 7.3–7.2 (m, 2H), 6.9–6.8 (m, 2H), 6.4 (d, 1H, J = 3.3 Hz), 3.25 (sextet, 4H, J = 5.1 Hz), 3.15 (t, 2H, J = 7.2 Hz), 1.8–1.2 (m, 16H), 0.9–0.8 (m, 3H). MS: 591 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[5-[(1,4,5-triphenylimidazol-2-yl)thio]pentyl]-*N*-heptylurea (28).** This product was prepared from 1,4,5-triphenylimidazole-2-thione (0.30 g, 0.0009 mol) in a similar manner to that described in method B and was triturated with petroleum ether to give **28** (0.44 g, 0.000 66 mol, 73%) as a white solid, mp 99–101 °C. ^{1}H NMR ($CDCl_3$): δ 8.1–7.9 (m, 1H), 7.55–7.0 (m, 15H), 6.8–6.75 (m, 2H), 6.4 (d, 1H), 3.3–3.1 (m, 6H), 1.7–1.2 (m, 17H), 0.9 (t, 3H). MS: 667 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[8-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]octyl]-*N*-heptylurea (29).** This product was prepared in a similar manner to that described in method A using 8-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]-*N*-heptyl-1-octanamine (0.5 g, 0.001 mol) to give a solid which was triturated with cold ethyl acetate and then hexane to give **29** (0.18 g, 0.000 28 mol, 20%) as a white solid, mp 89–91 °C. ^{1}H NMR (DMSO-d_6): δ 12.5 (s, 1H), 7.9 (s, 1H), 7.5–7.1 (m, 10H), 3.3–3.1 (m, 5H), 1.8–1.2 (m, 17H), 0.9 (t, 3H, J = 8.0 Hz). MS: 633 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[2-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]ethyl]-*N*-heptylurea (30).** This product was prepared in a similar manner to that described in method A using 2-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]-*N*-heptyl-1-ethylamine (0.35 g, 0.0009 mol) to give a solid which was triturated with cold chlorobutane to give **30** (0.25 g, 0.000 46 mol, 51%) as a white solid, mp 144–146 °C. ^{1}H NMR ($CDCl_3$): δ 11.6–11.2 (br s, 1H), 7.9–7.7 (br s, 1H), 7.6–7.0 (m, 11H), 6.8–6.6 (m, 2H), 3.7 (t, 2H, J = 6.3 Hz), 3.3 (t, 2H, J = 7.6 Hz), 3.2 (t, 2H, J = 7.3 Hz), 1.75–1.2 (m, 10H), 0.8 (t, 3H, J = 6.3 Hz). MS: 549 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[3-[[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]methyl]benzyl]-*N*-heptylurea (31).** This product was prepared in a similar manner to that described in method A using 4,5-diphenyl-2-[[3-[(heptylamino)methyl]benzyl]thio]-1*H*-imidazole (2.0 g, 0.0044 mol) to give a solid which was recrystallized from ether–hexane to give **31** (0.85 g, 0.001 36 mol, 31%) as a white solid, mp 148–149 °C. ^{1}H NMR ($CDCl_3$): δ 10.55 (br s, 1H), 7.93–7.84 (m, 1H), 7.59–7.44 (br s, 2H), 7.25–7.08 (m, 12H), 6.79–6.66 (m, 2H), 6.41 (br d, 1H, J = 3.3 Hz), 4.45 (s, 2H), 4.15 (s, 2H), 3.26 (t, 2H, J = 7.1 Hz), 1.62–1.52 (m, 2H), 1.35–1.22 (m, 8H), 0.87 (t, 3H, J = 6.9 Hz). MS: 625 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[4-[[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]methyl]benzyl]-*N*-heptylurea (32).** This product was prepared in a similar manner to that described in method A using 4,5-diphenyl-2-[[4-[(heptylamino)methyl]benzyl]thio]-1*H*-imidazole (5.07 g, 0.011 mol) to give a solid which was recrystallized from ether–hexane to give **32** (2.11 g, 0.0034 mol, 31%) as a white solid, mp 149–150 °C. ^{1}H NMR ($CDCl_3$): δ 9.76 (br s, 1H), 7.96 (td, 1H, J = 9.0, 6.2 Hz), 7.34–7.12 (m, 10H), 6.80–6.67 (m, 2H), 6.40 (d, 1H, J = 3.3 Hz), 4.51 (s, 2H), 4.21 (s, 2H), 3.29 (t, 2H, J = 7.7 Hz), 1.65–1.55 (m, 2H), 1.35–1.20 (m, 8H), 0.87 (t, 3H, J = 6.8 Hz). MS: 625 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[2-[[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]methyl]benzyl]-*N*-heptylurea (33).** This product was prepared in a similar manner to that described in method A using 4,5-diphenyl-2-[[2-[(heptylamino)methyl]benzyl]thio]-1*H*-imidazole (6.70 g, 0.014 mol) to give a solid which was recrystallized from acetonitrile to give **33** (3.72 g, 0.006 mol, 42%) as a white solid, mp 87–89 °C. ^{1}H NMR ($CDCl_3$): δ 7.51–7.38 (m, 2H), 7.36–7.30 (m, 3H), 7.28–7.20 (m, 8H), 7.18–7.15 (m, 2H), 6.76 (br s, 1H), 6.71–6.62 (m, 1H), 6.35–6.31 (m, 1H), 4.96 (s, 2H), 4.34 (s, 2H), 3.37 (t, 2H, J = 7.7 Hz), 1.69–1.59 (m, 2H), 1.38–1.26 (m, 8H), 0.88 (t, 3H, J = 6.9 Hz). MS: 625 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[3,3-dimethyl-5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptylurea (34).** This product was prepared in a similar manner to that described in method B using *N*-(5-bromo-3,3-dimethylpentyl)-*N'*-(2,4-difluorophenyl)-*N*-heptylurea (1.60 g, 0.003 58 mol) and 4,5-diphenyl-1*H*-imidazolethiol (0.82 g, 0.003 25 mol) to give a solid which was recrystallized from ether–hexane to give **34** (1.64 g, 0.002 65 mol, 82%) as a white solid, mp 138–139 °C. ^{1}H NMR ($CDCl_3$): δ 10.98 (br s, 1H), 7.74–7.66 (m, 1H), 7.60–7.51 (br s, 2H), 7.34–7.26 (m, 2), 7.24–7.14 (m, 6H), 6.86–6.78 (m, 1H), 6.75–6.69 (m, 1H), 6.44 (br s, 1H), 3.23–3.14 (m, 6H), 1.80–1.66 (m, 2H), 1.62–1.54 (m, 4H), 1.39–1.27 (m, 8H), 0.94 (s, 6H), 0.90 (t, 3H, J = 6.6 Hz). MS: 619 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptyl-*N'*-(2,4,6-trifluorophenyl)urea (35).** This product was prepared in a similar manner to that described in method A using 2,4,6-trifluorophenyl isocyanate (0.25 g, 0.0014 mol) to give **35** (0.27 g, 0.000 44 mol, 34%) as a white solid, mp 78–80 °C. ^{1}H NMR ($CDCl_3$): δ 10.8 (s, 1H), 7.7–7.4 (m, 2H), 7.4–7.2 (m, 8H), 6.8–6.7 (m, 1H), 6.5–6.3 (t, 2H, J = 8.0 Hz), 5.8 (s, 1H), 3.5 (t, 2H, J = 6.2 Hz), 3.3 (t, 2H, J = 7.7 Hz), 2.9 (t, 2H, J = 6.0 Hz), 1.9–1.0 (m, 16H), 1.0–0.8 (m, 3H). MS: 609 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptylthiourea (36).** This product was prepared in a similar manner to that described in method A using 2,4-difluorophenyl isothiocyanate (0.71 g, 0.0041 mol) to give **36** (1.57 g, 0.0026 mol, 76%) as a white solid, mp 115–117 °C. ^{1}H NMR ($CDCl_3$): δ 9.7 (s, 1H), 7.7–7.2 (m, 10H), 7.1–6.8 (m, 3H), 3.9–3.6 (m, 4H), 3.6 (t, 2H, J = 7.8 Hz), 3.2 (m, 2H), 2.0–1.2 (m, 17H), 1.0–0.8 (m, 3H). MS: 607 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptyl-*N'*-(2,4,6-trifluorophenyl)thiourea (37).** This product was prepared in a similar manner to that described in method A using 2,4,6-trifluorophenyl isothiocyanate (0.25 g, 0.000 57 mol) to give **37** (0.24 g, 0.000 38 mol, 67%) as a white solid, mp 124–126 °C. ^{1}H NMR ($CDCl_3$): δ 9.7–9.2 (br s, 1H), 7.6–7.2 (m, 10H), 6.8–6.6 (m, 2H), 6.5 (s, 1H), 3.8–3.7 (m, 4H), 3.1 (t, 2H, J = 7.0 Hz), 1.9–1.2 (m, 18H), 0.9 (t, 3H, J = 6.4 Hz). MS: 625 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptyl-*N'*-(2,4,6-trifluorophenyl)thiourea (38).** This product was prepared in a similar manner to that described in method A using phenyl isocyanate (0.27 mL, 0.25 g, 0.0025 mol) to give **38** (0.5 g, 0.0009 mol, 38%) as a white solid, mp 58–62 °C. ^{1}H NMR ($CDCl_3$): δ 11.0 (br s, 1H), 7.7–6.9 (m, 14H), 6.4 (s, 1H), 3.4 (t, 2H, J = 7.0 Hz), 3.2 (t, 2H, J = 7.0 Hz), 3.0 (t, 2H, J = 7.0 Hz), 1.9–1.1 (m, 16H), 0.9 (t, 3H, J = 8.0 Hz). MS: 555 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]-pentyl]-*N*-heptyl-*N'*-phenylguanidine (39).** A solution of **5** (0.50 g, 0.0012 mol) and *S*-methyl *N*-phenylcarbamimidothioate hydrochloride (0.34 g, 0.0012 mol) in acetonitrile (10 mL) and triethylamine (0.5 mL) was heated to reflux under a nitrogen atmosphere for 4 h. The reaction was allowed to cool to ambient temperature, diluted with ethyl acetate, washed with 10% aqueous $NaHCO_3$, water, and brine, dried over $MgSO_4$, and concentrated under vacuum to give a crude oil. The product was crystallized from acetonitrile to give **39** (0.4 g, 0.000 72 mol, 63%) as a white powder, mp 135–136 °C. ^{1}H NMR ($CDCl_3$): δ 7.45 (m, 4H), 7.23 (m, 8H), 6.94 (t, 1H), 6.82 (d, 2H), 3.3 (t, 2H), 3.16 (t, 2H), 3.03 (t, 2H), 1.7–1.16 (m, 16H), 0.87 (t, 3H). MS: 554 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptyl-*N'*-(4-nitrophenyl)urea (40).** This product was prepared in a similar manner to that described in method A using 4,5-diphenyl-2-[[5-(heptylamino)pentyl]thio]-1*H*-imidazole (3.00 g, 0.0069 mol) to give a solid which was recrystallized from ether to give **40** (3.50 g, 0.0058 mol, 85%) as a white solid, mp

65–67 °C. ^{1}H NMR ($CDCl_3$): δ 9.91 (br s, 1H), 8.02 (d, 2H, J = 8.9 Hz), 7.60–7.50 (m, 2H), 7.44 (d, 2H, J = 8.9 Hz), 7.42–7.24 (m, 8H), 7.04 (br s, 1H), 3.43 (t, 2H, J = 7.1 Hz), 3.27 (t, 2H, J = 7.5 Hz), 3.05 (t, 2H, J = 7.0 Hz), 1.87–1.72 (m, 2H), 1.70–1.60 (m, 2H), 1.57–1.49 (m, 2H), 1.39–1.21 (m, 10H), 0.89 (t, 3H, J = 6.6 Hz). MS: 600 (M + H).

***N'*-([1,1'-Biphenyl]-4-yl)-*N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptylurea (41).** To a solution of **5** (0.44 g, 0.001 mol) in hexane (25 mL) was added 4-phenylphenyl isocyanate (0.29 g, 0.0015 mol), and the reaction mixture was stirred at ambient temperature for 18 h. The reaction mixture was concentrated under vacuum, and the residue was purified by flash chromatography (hexane–ethyl acetate, 7:3). The resulting solid was triturated with hexane to give **41** (0.41 g, 0.000 65 mol, 65%) as a white solid, mp 119–121 °C. ^{1}H NMR ($CDCl_3$): δ 10.8 (s, 1H), 7.7–7.1 (m, 19H), 6.4 (s, 1H), 3.45 (t, 2H, J = 6.5 Hz), 3.25 (t, 2H, J = 7.6 Hz), 3.0 (t, 2H, J = 6.4 Hz), 1.9–1.2 (m, 16H), 0.9 (t, 3H, J = 6.8 Hz). MS: 631 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptyl-[1,1'-biphenyl]-4-acetamide (42).** To a solution of **5** (2.2 g, 0.005 mol), hydroxybenzotriazole hydrate (0.81 g, 0.006 mol), and 4-biphenylacetic acid (1.38 g, 0.0065) in DMF (50 mL), cooled to 0 °C, was added dicyclohexylcabodiimide (1.24 g, 0.006 mol) and the reaction mixture was stirred 0 °C for 2.5 h and then at ambient temperature for 18 h. The reaction mixture was filtered, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography (hexane–ethyl acetate, 7:3) to give **42** (1.38 g, 0.0022 mol, 44%) as a clear oil. ^{1}H NMR ($CDCl_3$): δ 11.4–11.3 (br s, 1H), 7.7–7.1 (m, 19H), 3.7 (s, 2H), 3.5 (t, 2H, J = 6.3 Hz), 3.3 (t, 2H, J = 7.8 Hz), 2.9 (t, 2H, J = 6.1 Hz), 1.9–1.1 (m, 18H), 0.85 (t, 3H, J = 6.5 Hz). MS: 630 (M + H).

***N'*-[2,6-Bis(1-methylethyl)phenyl]-*N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptylurea (43).** This product was prepared in a similar manner to that described in method A using 4,5-diphenyl-2-[[5-(heptylamino)pentyl]-thio]-1*H*-imidazole (3.05 g, 0.007 mol) to give a solid which was recrystallized from hexane to give **43** (4.22 g, 0.0066 mol, 94%) as a white solid, mp 185–187 °C. ^{1}H NMR ($CDCl_3$): δ 11.54 (br s, 1H), 7.52 (d, 2H, J = 7.0 Hz), 7.24–7.00 (m, 11H), 5.70 (br s, 1H), 3.41 (t, 2H, J = 6.4 Hz), 3.29 (br t, 2H, J = 7.5 Hz), 3.16 (t, 2H, J = 7.0 Hz), 2.91 (t, 2H, J = 6.3 Hz), 1.75–1.58 (m, 6H), 1.54–1.44 (m, 2H), 1.40–1.26 (m, 8H), 1.15 (d, 12H, J = 7.0 Hz), 0.89 (t, 3H, J = 6.6 Hz). MS: 639 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptylurea (44).** This product was prepared in a similar manner to that described in method A using 4,5-diphenyl-2-[[5-(heptylamino)pentyl]thio]-1*H*-imidazole (0.77 g, 0.0018 mol) and trimethylsilyl isocyanate to give, upon aqueous workup and chromatography, a solid which was recrystallized from ether to give **44** (0.64 g, 0.0013 mol, 76%) as a white solid, mp 133–135 °C. ^{1}H NMR ($CDCl_3$): δ 7.60 (d, 2H, J = 7.0 Hz), 7.48 (d, 2H, J = 7.0 Hz), 7.37–7.18 (m, 6H), 4.30 (br s, 2H), 3.31 (t, 2H, J = 6.6 Hz), 3.10 (t, 2H, J = 7.7 Hz), 3.03 (t, 2H, J = 6.6 Hz), 1.81–1.71 (m, 2H), 1.69–1.43 (m, 8H), 1.35–1.22 (m, 8H), 0.88 (t, 3H, J = 6.9 Hz). MS: 479 (M + H).

***N'*-Cyclohexyl-*N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)-thio]pentyl]-*N*-heptylurea (45).** This product was prepared in a similar manner to that described in method A using cyclohexyl isocyanate (0.18 g, 0.0015 mol) to give **45** (0.49 g, 0.000 88 mol, 88%) as a white solid, mp 95–97 °C. ^{1}H NMR ($CDCl_3$): δ 7.7–7.1 (m, 11H), 4.2 (d, 1H, J = 7.7 Hz), 3.3 (t, 2H, J = 3.3 Hz), 3.1–2.9 (m, 4H), 1.8–1.0 (m, 27H), 0.9 (t, 3H, J = 5.4 Hz). MS: 561 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptyl-*N'*-(1-methylethyl)urea (46).** This product was prepared in a similar manner to that described in method A using isopropyl isocyanate (0.13 g, 0.0015 mol) to give **46** (0.45 g, 0.000 86 mol, 86%) as a white solid, mp 84–86 °C. ^{1}H NMR ($CDCl_3$): δ 11.7–11.5 (br s, 1H), 7.7–7.1 (m, 10H), 4.2–4.1 (m, 1H), 3.9–3.7 (m, 1H), 3.4 (t, 2H, J = 6.3 Hz), 3.2–2.9 (m, 4H), 2.0–1.0 (m, 23H), 0.9 (t, 3H, J = 3.1 Hz). MS: 521 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptyl-*N'*-propylurea (47).** To a solution of **5** (0.36 g, 0.0008 mol) in hexane (15 mL) was added propyl isocyanate (0.094 mL, 0.085 g, 0.001 mol), and the reaction mixture was stirred at ambient temperature for 4 h. The reaction mixture was then treated with additional propyl isocyanate (0.094 mL, 0.085 g, 0.001 mol) and stirred at ambient temperature for 16 h and then at reflux for 72 h. The reaction mixture was concentrated under vacuum, and the residue was purified by flash chromatography (hexane–ethyl acetate, 2:8). The resulting oil was triturated with hexane to give **46** (0.8 g, 0.000 15 mol, 19%) as a white solid, mp 78–80 °C. ^{1}H NMR ($CDCl_3$): δ 7.6–7.2 (m, 10H), 4.4 (t, 1H, J = 7.0 Hz), 3.4–2.9 (m, 8H), 1.9–1.1 (m, 19H), 1.0–0.75 (m, 6H). MS: 521 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptyl-*N'*-methylurea (48).** To a solution of **5** (0.30 g, 0.0007 mol) in hexane (15 mL) was added methyl isocyanate (0.06 mL, 0.057 g, 0.001 mol), and the reaction mixture was stirred at ambient temperature for 18 h. The reaction mixture was concentrated under vacuum, and the residue was purified by flash chromatography (hexane–ethyl acetate, 1:1). The resulting oil was triturated with hexane to give **48** (0.23 g, 0.000 47 mol, 67%) as a white solid, mp 93–96 °C. ^{1}H NMR ($CDCl_3$): δ 7.6–7.2 (m, 11H), 3.45–2.7 (m, 9H), 1.9–1.2 (m, 16H), 0.9 (t, 3H, J = 8.0 Hz). MS: 493 (M + H).

2,4-Difluoro-*N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]-pentyl]-*N*-heptylbenzeneacetamide (49). To a solution of **5** (2.2 g, 0.005 mol), 1-hydroxybenzotriazole hydrate (0.81 g, 0.006 mol), and 2,4-difluorophenylacetic acid (1.12 g, 0.0065 mol) in DMF (50 mL) at 0 °C was added, portionwise as a solid, dicyclohexylcarbodiimide (1.24 g, 0.006 mol). The reaction mixture was stirred at 0 °C for 2.5 h and then at ambient temperature for 72 h. The solids were filtered and washed with chloroform. The filtrate was concentrated under vacuum, and the residue was purified by flash chromatography (hexane–ethyl acetate, 7:3) to give **49** (2.59 g, 0.0044 mol, 88%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.6–7.0 (m, 11H), 6.8–6.5 (m, 2H), 3.7 (d, 2H, J = 13.7 Hz), 3.5 (t, 2H, J = 6.4 Hz), 3.4–3.0 (m, 3H), 2.9 (t, 2H, J = 6.1 Hz), 1.8–1.1 (m, 17H), 0.9 (t, 3H, J = 6.6 Hz). MS: 590 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptylcyclohexaneacetamide (50).** To a solution of **5** (2.2 g, 0.005 mol), 1-hydroxybenzotriazole hydrate (0.81 g, 0.006 mol), and cyclohexylacetic acid (1.07 g, 0.0075 mol) in DMF (50 mL) at 0 °C was added, portionwise as a solid, dicyclohexylcarbodiimide (1.24 g, 0.006 mol). The reaction mixture was stirred at 0 °C for 2.5 h and then at ambient temperature for 72 h. The solids were filtered and washed with chloroform. The filtrate was concentrated under vacuum and the residue was purified by flash chromatography (hexane–ethyl acetate, 75:25) to give **50** (2.36 g, 0.0042 mol, 84%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.6–7.1 (m, 11H), 3.4-2.9 (m, 6H), 2.2–2.1 (m, 2H), 1.8–1.0 (m, 27H), 0.9–0.8 (m, 3H). MS: 560 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptyl-2-methylpropanamide (51).** To a solution of **5** (1.1 g, 0.0025 mol) in CH_2Cl_2 (10 mL) at −15 °C was added, dropwise, a solution of isobutyryl chloride (0.26 mL, 0.27 g, 0.0025 mol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at 0 °C for 0.5 h and then at ambient temperature for 96 h. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2. The organic layer was backwashed with H_2O and brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography (hexane–ethyl acetate, 1:1) to give **51** (0.89 g, 0.0018 mol, 72%) as an oil. ^{1}H NMR ($CDCl_3$): δ 11.8 (s, 1H), 7.7–7.2 (m, 11H), 3.5 (t, 2H, J = 6.4 Hz), 3.3–3.1 (m, 3H), 2.95 (t, 2H, J = 6.1 Hz), 2.85–2.7 (m, 1H), 1.9–1.2 (m, 14H), 1.1–1.0 (m, 6H), 0.9–0.8 (m, 3H). MS: 506 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptylbutanamide (52).** To a solution of **5** (2.2 g, 0.005 mol), 1-hydroxybenzotriazole hydrate (0.81 g, 0.006 mol), and butyric acid (0.67 mL, 0.64 g, 0.0073 mol) in DMF (50 mL) at 0 °C was added, portionwise as a solid, dicyclohexylcarbodiimide (1.24 g, 0.006 mol). The reaction mixture was stirred at 0 °C for 2.5 h and then at ambient temperature for 72 h. The solids were filtered and washed with chloroform. The filtrate was concentrated under vacuum, and the residue was purified by flash chromatography (hexane–ethyl acetate, 7:3) to give **52**

(2.60 g, 0.005 mol, 92%) as an oil. ^{1}H NMR ($CDCl_3$): δ 11.7–11.6 (br s, 1H), 7.7–7.1 (m, 10H), 3.4 (t, 2H, J = 7.0 Hz), 3.3–3.2 (m, 2H), 2.9 (t, 2H, J = 7.0 Hz), 2.35–2.25 (m, 2H), 1.8–1.1 (m, 18H), 1.0–0.8 (m, 6H). MS: 506 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-2,4-difluoro-*N*-heptylbenzamide (53).** To a solution of **5** (2.2 g, 0.005 mol) in CH_2Cl_2 (20 mL) at −15 °C was added, dropwise, a solution of 2,4-difluorobenzoyl chloride (0.68 mL, 0.97 g, 0.0055 mol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred over 30 min, allowed to warm to ambient temperature, and stirred over 4 h. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2. The organic layer was backwashed with H_2O and brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography (hexane–ethyl acetate, 9:1) to give **53** (2.51 g, 0.0044 mol, 88%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.6–7.2 (m, 11 H), 6.9–6.8 (m, 2H), 3.7–3.4 (m, 2H), 3.2–3.0 (m, 4H), 1.9–1.0 (m, 17H), 0.9–0.8 (m, 3H). MS: 576 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-heptylbenzamide (54).** To a solution of **5** (2.2 g, 0.005 mol) in CH_2Cl_2 (20 mL) at −15 °C was added, dropwise, a solution of benzoyl chloride (0.64 mL, 0.77 g, 0.0055 mol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred over 30 min, allowed to warm to ambient temperature, and stirred over 4 h. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2. The organic layer was backwashed with H_2O and brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography (hexane–ethyl acetate, 7:3) to give **54** (2.50 g, 0.0046 mol, 92%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.6–7.1 (m, 16 H), 3.6–3.4 (m, 2H), 3.3–2.9 (m, 4H), 1.9–1.0 (m, 16H), 0.9–0.8 (m, 3H). MS: 540 (M + H).

Propyl [5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-heptylcarbamate (55). To a solution of **5** (0.87 g, 0.002 mol) in toluene (10 mL) at 0 °C was added, dropwise, a solution of propyl chloroformate (0.23 mL, 0.25 g, 0.002 mol) in toluene (5 mL). The reaction mixture was allowed to warm to ambient temperature, stirred over 16 h, and then poured into H_2O. The organic layer was separated, backwashed with brine, dried over $MgSO_4$, and concentrated under vacuum to give **55** (0.37 g, 0.0007 mol, 35%) as a clear oil. ^{1}H NMR ($CDCl_3$): δ 10.9 (s, 1H), 7.75–7.1 (m, 10H), 4.0 (q, 2H, J = 6.9 Hz), 3.3 (t, 2H, J = 9.6 Hz), 3.2 (t, 2H, J = 7.5 Hz), 3.0 (t, 2H, J = 7.8 Hz), 1.8–1.1 (m, 18H), 0.9 (t, 3H, J = 7.2 Hz). MS: 522 (M + H).

Cyclohexyl [5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]-pentyl]heptylcarbamate (56). To a solution of **5** (0.87 g, 0.002 mol) and sodium bicarbonate (5%, 1 mL) in toluene (10 mL) at 0 °C was added, dropwise, a solution of cyclohexyl chloroformate (0.32 g, 0.002 mol) in toluene (5 mL). The reaction mixture was allowed to warm to ambient temperature and stirred over 16 h. The solvent was removed under vacuum. The residue was purified by flash chromatography (hexane–ethyl acetate, 7:3) to give **56** (0.61 g, 0.0011 mol, 55%) as an oil. ^{1}H NMR ($CDCl_3$): δ 11.1 (br s, 1H), 7.7–7.2 (m, 10H), 4.6 (br s, 1H), 3.3 (t, 2H, J = 5.1 Hz), 3.2 (t, 2H, J = 7.5 Hz), 3.0 (t, 2H, J = 5.2 Hz), 1.9–1.2 (m, 26H), 0.9–0.8 (m, 3H). MS: 562 (M + H).

Phenyl[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-heptylcarbamate (57). To a solution of **5** (0.87 g, 0.002 mol) in toluene (10 mL) at 0 °C was added, dropwise, a solution of phenyl chloroformate (0.25 mL, 0.31 g, 0.002 mol) in toluene (5 mL). The reaction mixture was allowed to warm to ambient temperature and stirred over 2 h. The reaction mixture was filtered, and the filtrate was backwashed with H_2O, 1 N HCl, and brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography (hexane–ethyl acetate, 7:3) to give **57** (0.23 g, 0.000 41 mol, 21%) as an oil. ^{1}H NMR ($CDCl_3$): δ 10.6 (s, 1H), 7.7–7.0 (m, 15 H), 3.4 (q, 4H, J = 4.7 Hz), 2.9 (t, 2H, J = 5.8 Hz), 1.8-1.2 (m, 16H), 0.95–0.75 (m, 3H). MS: 556 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-propylurea (58).** This product was prepared from 5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]-*N*-propyl-1-pentanamine in a similar manner to that described in method A to give **58** (0.25 g, 0.000 47 mol, 75%) as an off-white solid, mp 68–70 °C. ^{1}H NMR ($CDCl_3$): δ 10.4 (s, 1H), 7.8–7.1 (m, 12H), 6.8–6.2 (m, 3H), 3.4 (t, 2H, J = 6.7 Hz), 3.25 (t, 2H, J = 7.8 Hz), 3.0 (t, 2H, J = 6.3 Hz), 1.8–1.4 (m, 10H), 0.95 (t, 3H, J = 7.4 Hz). MS: 535 (M + H).

***N*-(2,4-Difluorophenyl)-*N'*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]urea (59).** This product was prepared from 5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]-1-pentanamine in a similar manner to that described in method A to give **59** (0.13 g, 0.000 26 mol, 26%) as an off-white solid, mp 187–189 °C. ^{1}H NMR (DMSO-d_6): δ 12.5 (s, 1H), 8.2–8.0 (m, 2H), 7.5–7.1 (m, 11H), 7.0–6.9 (m, 1H), 6.6–6.5 (m, 1H), 3.2–3.0 (m, 4H), 1.8–1.3 (m, 6H). MS: 493 (M + H).

***N'*-[2,6-Bis(1-methylethyl)phenyl]-*N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]urea (60).** This product was prepared in a similar manner to that described in method B using 4,5-diphenyl-2-mercapto-1*H*-imidazole (2.73 g, 0.011 mol) and *N*-[2,6-bis(1-methylethyl)phenyl]-*N'*-(5-bromopentyl)-urea to give, upon aqueous workup and chromatography, a solid which was recrystallized from ether to give **60** (0.58 g, 0.0011 mol, 10%) as a white solid, mp 199–201 °C. ^{1}H NMR ($CDCl_3$): δ 11.73 (br s, 1H), 11.59 (br s, 1H), 7.60–7.17 (m, 13H), 6.19 (br s, 1H), 3.26 (heptet, 2H, J = 6.6 Hz), 3.20 (br s, 2H), 3.01 (t, 2H, J = 6.6 Hz), 1.75–1.61 (m, 2H), 1.55–1.40 (m, 4H), 1.16 (br s, 12H). MS: 541 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[3-[[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]methyl]benzyl]-*N*-heptylurea (61).** This product was prepared in a similar manner to that described in method A using 4,5-diphenyl-2-[[3-(aminomethyl)benzyl]thio]-1*H*-imidazole (3.50 g, 0.009 42 mol) to give a solid which was recrystallized from acetonitrile to give **61** (4.15 g, 0.007 88 mol, 84%) as a white solid, mp 214–215 °C. ^{1}H NMR ($CDCl_3$): δ 11.80 (br s, 1H), 8.01–7.92 (m, 1H), 7.85 (s, 1H), 7.38 (d, 2H, J = 7.3 Hz), 7.20–6.97 (m, 13H), 6.65–6.55 (m, 2H), 4.18 (d, 2H, J = 5.8 Hz), 4.14 (s, 2H). MS: 527 (M + H).

***N*-Benzyl-*N'*-(2,4-Difluorophenyl)-*N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]urea (62).** This product was prepared in a similar manner to that described in method A using 4,5-diphenyl-2-[[5-(benzylamino)pentyl]thio]-1*H*-imidazole (3.04 g, 0.0071 mol) to afford, after workup and chromatography, **62** (2.64 g, 0.0045 mol, 64%) as a solid, mp 86–88 °C. ^{1}H NMR ($CDCl_3$): δ 11.51 (br s, 1H), 7.78–7.69 (m, 1H), 7.56 (br s, 2H), 7.40–7.18 (m, 13H), 6.69–6.59 (m, 2H), 6.51 (br d, 1H, J = 3 Hz), 4.49 (s, 2H), 3.39 (t, 2H, J = 5 Hz), 2.95 (t, 2H, J = 6 Hz), 1.71–1.56 (m, 4H), 1.47–1.33 (m, 2H). MS: 583 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-(2-phenylethyl)urea (63).** This product was prepared in a similar manner to that described in method A using 4,5-diphenyl-2-[[5-[(2-phenylethyl)amino]pentyl]thio]-1*H*-imidazole (2.67 g, 0.0061 mol) to afford, after workup and chromatography, **63** (2.07 g, 0.0035 mol, 57%) as a solid, mp 78–80 °C. ^{1}H NMR ($CDCl_3$): δ 7.73–7.63 (m, 1H), 7.51–7.39 (m, 4H), 7.32–7.15 (m, 11H), 6.77–6.59 (m, 2H), 6.32 (br s, 1H), 3.48 (t, 2H, J = 7 Hz), 3.25 (t, 2H, J = 6 Hz), 2.97–2.84 (m, 4H), 1.71–1.36 (m, 6H). MS: 597 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-(3-phenylpropyl)urea (64).** This product was prepared in a similar manner to that described in method A using 4,5-diphenyl-2-[[5-[(3-phenylpropyl)amino]-pentyl]thio]-1*H*-imidazole (3.88 g, 0.008 56 mol) to afford, after workup and chromatography, **64** (2.84 g, 0.004 65 mol, 54%) as a solid, mp 76–78 °C. ^{1}H NMR ($CDCl_3$): δ 10.28 (br s, 1H), 7.79–7.55 (m, 3H), 7.41–7.17 (m, 13H), 6.73 (br t, 1H, J = 8 Hz), 6.60 (br t, 1H, J = 8 Hz), 6.23 (br s, 1H), 3.40 (t, 2H, J = 5.5 Hz), 3.28 (t, 2H, J = 7.7 Hz), 3.02 (t, 2H, J = 6.2 Hz), 2.68 (t, 2H, J = 7.4 Hz), 2.08–1.98 (m, 2H), 1.82–1.47 (m, 6H). MS: 611 (M + H).

***N'*-(2,4-Difluorophenyl)-*N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N*-(4-phenylbutyl)urea (65).** This product was prepared in a similar manner to that described in method A using 4,5-diphenyl-2-[[5-[(4-phenylbutyl)amino]-pentyl]thio]-1*H*-imidazole (5.02 g, 0.011 mol) to afford, after workup and chromatography, **65** (1.67 g, 0.0027 mol, 25%) as a solid, mp 69–71 °C. ^{1}H NMR ($CDCl_3$): δ 10.50 (br s, 1H), 7.79–7.69 (m, 1H), 7.60–7.14 (m, 15H), 6.79–6.70 (m, 1H) 6.68–6.59 (m, 1H), 6.34 (br s, 1H), 3.36 (t, 2H, J = 7.0 Hz),

3.26 (br s, 2H), 3.01 (t, 2H, J = 6.6 Hz), 2.66 (br s, 2H), 1.81–1.45 (m, 10H). MS: 625 (M + H).

***N*-Benzyl-*N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N'*-octylurea (66).** This product was prepared in a similar manner to that described in method A using 4,5-diphenyl-2-[[5-(benzylamino)pentyl]thio]-1*H*-imidazole (3.04 g, 0.0071 mol) to afford, after workup and chromatography, **66** (3.50 g, 0.006 mol, 84%) as an amorphous solid. ^{1}H NMR ($CDCl_3$): δ 11.33 (br s, 1H), 7.60 (d, 2H, J = 6.6 Hz), 7.50–7.17 (m, 13H), 4.40 (s, 2H), 4.33 (t, 2H, J = 6.6 Hz), 3.46 (t, 2H, J = 6.6 Hz), 3.32–3.10 (m, 4H), 3.01 (t, 2H, J = 6.6 Hz), 1.87–0.99 (m, 18H), 0.86 (t, 3H, J = 7.3 Hz). MS: 583 (M + H).

***N*-(2,4-Difluorophenyl)-*N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N'*-octylurea (67).** This product was prepared in a similar manner to that described in method A using *N*-[5-[(4,5-diphenyl-1*H*-imidazole-2-yl)thio]pentyl]-2,4-difluorophenylamine (0.45 g, 0.001 mol) to afford, after workup and chromatography (hexane–ethyl acetate, 7:3), **67** (0.17 g, 0.000 28 mol, 28%) as an amorphous solid. ^{1}H NMR ($CDCl_3$): δ 7.7–6.9 (m, 14H), 4.41 (t, 1H, J = 5.4 Hz), 3.8–3.65 (m, 2H), 3.1–2.9 (m, 4H), 1.9–1.0 (m, 18H), 0.85 (t, 3H, J = 6.7 Hz). MS: 605 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N'*-octyl-*N*-phenylurea (68).** This product was prepared in a similar manner to that described in method A using *N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]phenylamine (0.41 g, 0.001 mol) to afford, after workup and chromatography (hexane–ethyl acetate, 7:3), **68** (0.32 g, 0.000 56 mol, 56%) as a white solid, mp 74–76 °C. ^{1}H NMR ($CDCl_3$): δ 11.8 (s, 1H), 7.75–7.1 (m, 15H), 4.3 (t, 1H, J = 6.0 Hz), 3.8 (t, 2H, J = 7.0 Hz), 3.0 (quintet, 4H, J = 6.0 Hz), 1.9–0.9 (m, 18H), 0.8 (t, 3H, J = 7.0 Hz). MS: 569 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N'*-octyl-*N*-(2,4,6-trifluorophenyl)urea (69).** This product was prepared in a similar manner to that described in method A using *N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-2,4,6-trifluorophenylamine (0.48 g, 0.001 mol) to afford, after workup and chromatography (hexane–ethyl acetate, 75:25), **69** (0.50 g, 0.0008 mol, 80%) as a white solid, mp 95–97 °C. ^{1}H NMR ($CDCl_3$): δ 11.1 (s, 1H), 7.7–7.2 (m, 10H), 6.9–6.75 (m, 2H), 4.4–4.1 (m, 1H), 3.7 (t, 2H, J = 7.0 Hz), 3.2–2.95 (m, 4H), 1.9–1.0 (m, 18H), 0.9–0.8 (m, 3H). MS: 623 (M + H).

***N*-(2,4-Difluorophenyl)-*N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N'*-(1'-methylethyl)urea (70).** This product was prepared in a similar manner to that described in method A using *N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]-pentyl]-2,4-difluorophenylamine (0.63 g, 0.0014 mol) to afford, after workup and chromatography (hexane–ethyl acetate, 6:4), **70** (0.625 g, 0.0012 mol, 86%) as an amorphous solid, mp 46–50 °C. ^{1}H NMR ($CDCl_3$): δ 7.7–7.2 (m, 11H), 7.0–6.9 (m, 2H), 3.9–3.6 (m, 3H), 3.1–2.9 (m, 2H), 1.9–1.4 (m, 8H), 1.0–0.8 (m, 6H). MS: 535 (M + H).

***N*-[5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]pentyl]-*N'*-(1'-methylethyl)-*N*-phenylurea (71).** This product was prepared in a similar manner to that described in method A using *N*-[5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]pentyl]phenylamine (0.30 g, 0.000 73 mol) to afford, after workup and chromatography (hexane–ethyl acetate, 1:1), **71** (0.45 g, 0.0009 mol, 73%) as an amorphous solid, mp 55–59 °C. ^{1}H NMR ($CDCl_3$): δ 7.7–7.2 (m, 15H), 4.1–4.0 (m, 1H), 3.9–3.7 (m, 3H), 3.0 (t, 2H, J = 6.1 Hz), 1.9–1.4 (m, 7H), 0.9 (d, 6H, J = 6.6 Hz). MS: 499 (M + H).

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