Acyl-CoA:cholesterol O-Acyl Transferase (ACAT) Inhibitors. 1. 2-(Alkylthio)-4,5-diphenyl-1H-imidazoles as Potent Inhibitors of ACAT

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A potent, bioavailable ACAT inhibitor may have beneficial effects in the treatment of atherosclerosis by (i) reducing the absorption of dietary cholesterol, (ii) reducing the secretion of very low density lipoproteins into plasma from the liver, and (iii) preventing the transformation of arterial macrophages into foam cells. We have found that a mevalonate derivative **2**, which contains a 4,5-diphenyl-1*H*-imidazol-2-yl moiety, inhibits rat hepatic microsomal ACAT in vitro and produces a significant hypocholesterolemic effect in the cholesterol-fed rat. Structure–activity relationships for analogues of **2** demonstrate that the 4,5-diphenyl-1*H*-imidazole moiety is a pharmacophore for inhibition of rat microsomal ACAT.

Introduction

Atherosclerosis is a progressive disease of medium and large arteries which is characterized by a progressive thickening of the arterial intima. The occlusion of these vessels may lead ultimately to myocardial infarction. Hypercholesterolemia has been identified as an independent risk factor for coronary heart disease, and recent studies have demonstrated the benefits of lowering plasma cholesterol levels on morbidity and mortality from myocardial infarction.[1] Cholesterol in humans is derived from two sources: by absorption from the diet and by endogenous synthesis, principally in the liver and intestine.[2] Acyl-CoA:cholesterol *O*-acyl transferase (EC 2.3.1.26, ACAT), the enzyme principally responsible for the intracellular esterification of cholesterol,[3] plays a key role in the absorption and metabolism of cholesterol. The esterification within the enterocyte of dietary cholesterol appears to play a pivotal role in chylomicron assembly and subsequent secretion into the lymphatic system.[3] In the liver, ACAT has been implicated in the secretion of very low density lipoproteins (VLDL) into plasma. Studies carried out in vitro have shown that the concentration of cholesterol esters in VLDL is directly correlated with ACAT activity[4] and that the enzyme is necessary for the secretion of apo-B containing lipoproteins by cultured hepatocytes.[5,6] In addition, in the aortic intima ACAT is involved in the formation of monocyte-macrophage foam cells which are an integral component of the atherosclerotic lesion.[7]

A potent bioavailable ACAT inhibitor might have beneficial therapeutic effects in atherosclerosis by acting at three different sites: (i) in the gut, by reducing cholesterol absorption, (ii) in the liver, by reducing the secretion of VLDL particles, and (iii) in the artery, by reducing cholesterol ester deposition and thereby directly arresting the progression of atheromatous plaques. A number of potent intestinal ACAT inhibitors, of widely diverse structures, are known which are extremely effective in preventing the absorption of cholesterol in cholesterol-fed animals.[8] Some of these compounds are currently undergoing development as hypolipidemic agents.[9] More recently, a systemically available ACAT inhibitor has been claimed to reduce atherosclerotic lesion progression and enhance regression in hypercholesterolemic rabbits by a direct mechanism which is independent of effects on serum cholesterol levels.[10] In this series of papers we describe our progress toward the discovery of therapeutically useful bioavailable ACAT inhibitors for the treatment of atherosclerosis. (A preliminary account of some of this work has been published previously[11].)

Specific properties that might be considered desirable for such an agent include (i) potent inhibition of microsomal ACAT in vitro ($IC_{50} \leq 100$ nM) and a hypocholesterolemic response in an appropriate animal model, (ii) sufficient chemical and metabolic stability for the compound to survive passage through the gut, thus allowing oral administration, (iii) moderate lipophilicity (preferably $\log P \leq 4$) and adequate water solubility in order to achieve

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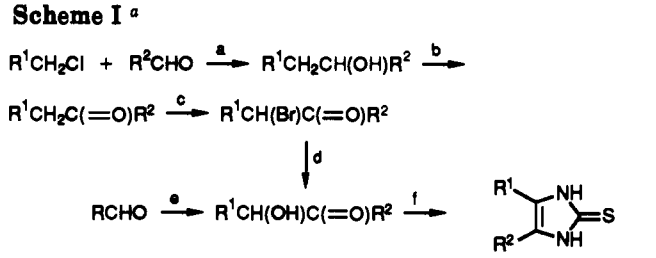
Scheme I [a]



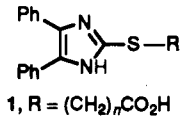
6, $R^1 = R^2$ = 4-MeOPh
7, $R^1 = R^2$ = 2-ClPh
8, $R^1 = R^2$ = 2-MeOPh

[a] (a) Mg/Et_2O; (b) MnO_2/Et_2O; (c) Br_2/CCl_4; (d) NaOEt/EtOH; (e) cat./Et_3N/EtOH (f) $H_2NC(=S)NH_2$/DMF.

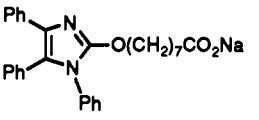
good systemic availability,[12] and finally (iv) it should be possible to demonstrate a therapeutic concentration of the compound in the plasma for an extended period of time after oral dosing.

A series of 4,5-diphenylimidazoles substituted at the 2-position by (carboxyalkyl)thio groups **1**, structurally related to octimibate **3**,[13] were screened for inhibition of the enzyme hydroxymethylglutaryl-CoA reductase. Some of these compounds showed weak activity, and following work described by Ferres et al.[14] the acid group in **1** was replaced with a mevalonate moiety in an attempt to improve activity against HMG-CoA reductase. These lactones were inactive as HMG-CoA reductase inhibitors, but one analogue (**2**) was active in our ACAT screen (IC_{50} = 170 nM) and showed an effective hypocholesterolemic response in the cholesterol-fed rat (see below for details). (Note that in our hands octimibate is a very poor ACAT inhibitor: $IC_{50} > 50$ μM against the rat liver enzyme.) In this paper the work directed toward the elucidation of a pharmacophore for ACAT inhibition embedded in the structure of **2** is described; subsequent papers will report the elaboration of that pharmacophore into compounds that are potent ACAT inhibitors with significant systemic availability.

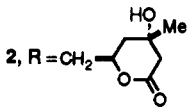
Subsequent to the work described in this and following papers, a group from DuPont Merck reported the synthesis of a series of 2-(alkylthio)-4,5-diphenyl-1*H*-imidazoles.[15] These compounds, structurally related to known ACAT inhibitors such as octimibate (**3**) and CL 277082 (**4**),[8] are very potent inhibitors of ACAT from rat liver microsomes (IC_{50}s ≤ 10 nM[16]); one analogue (DuP 128, **5**) is currently in development as an hypocholesterolemic agent.[16]

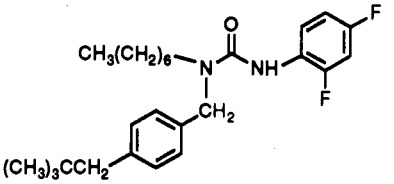


1, R = $(CH_2)_nCO_2H$

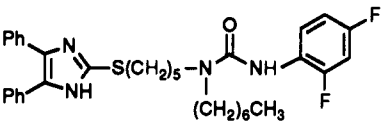


3 (octimibate)





4 (CL 277082)



5 (DuP 128)

Chemistry

4,5-Bis(aryl)-2,3-dihydro-1*H*-imidazole-2-thiones were prepared by the cyclization of the appropriately substituted benzoin with thiourea in DMF. Symmetrically substituted benzoins were prepared from the benzaldehyde by a benzoin condensation catalyzed by 3,4-dimethyl-5-(hydroxyethyl)thiazolium iodide.[17] Unsymmetrical analogues were obtained in five steps from the appropriately substituted benzyl chloride and benzaldehyde[18] (Scheme I).

Diastereoisomeric mevalonate analogues **10** and **11** were prepared by the alkylation of the potassium salt of heterocyclic thiols with epoxy ester **9**;[14] acidic workup gave the lactones as mixtures of diastereoisomers, the trans isomers predominating (Scheme II). Purification by fractional crystallization or flash chromatography allowed the isolation of seven trans (**2**, **13**, **16**, **21**, **22**, **25**, and **28**) and three cis (**12**, **14**, and **29**) diastereoisomers; other compounds were obtained as mixtures of isomers (Table I). Intermediate *tert*-butyl esters **32** and **33** were isolated in two instances; treatment of **32** with trifluoroacetic acid gave the trans lactone **15** (Scheme II).

Reaction of the lactone **2** with sodium methoxide gave the dehydration product **35** in low yield, rather than the expected ring-opened hydroxy ester. Formation of other dihydropyranones **36**–**40** (Table II) was more readily achieved by acylation of the hydroxy lactone followed by treatment with DBU. The hydroxy ester **34** was obtained by alkylation of sodium salt **41** (Scheme III).

Oxidation of **2** with 2 equiv of 3-chloroperoxybenzoic acid gave the sulfone **42** (Scheme IV). Reduction of **2** with DIBAL in THF gave the lactol **43** as a mixture of two diastereoisomers. Subsequent conversion of **43** to the methyl glycosides **44** and **45** allowed the separation of the two isomers (Scheme IV); the stereochemistry at the anomeric center was tentatively assigned from the ^1H NMR spectra of the two isomers. The preparation of the analogous desmethyl compounds **46** and **47** by the alkylation of the thione with an iodomethyl-substituted glycoside has been described previously.[19]

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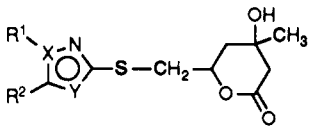
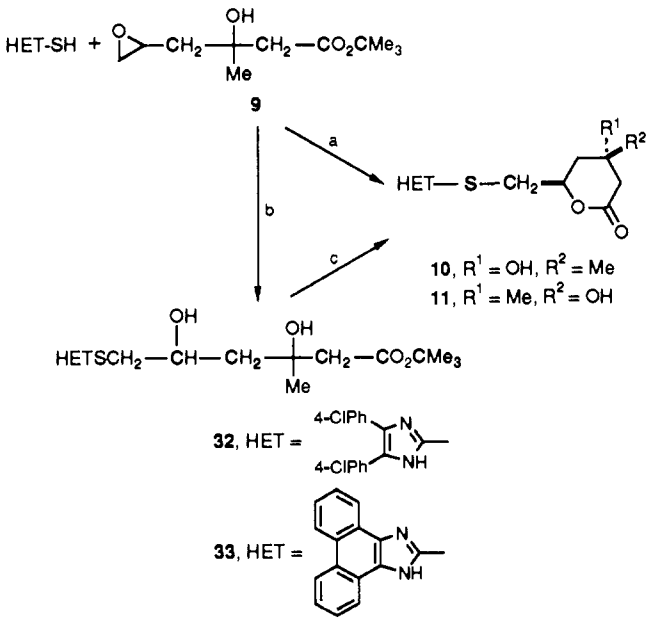
Table I. Preparation of



no.	R^1	R^2	X	Y	isomer	method	mp (°C)	anal.
2	Ph	Ph	C	NH	trans	A	201–2	C,H,N,S
12	Ph	Ph	C	NH	cis	A	203–5	C,H,N,S
13	4-$MeOC_6H_4$	4-$MeOC_6H_4$	C	NH	trans	A	214–5	C,H,N,S
14	4-$MeOC_6H_4$	4-$MeOC_6H_4$	C	NH	cis	A	*a*	C,H,N,S
15	4-ClC_6H_4	4-ClC_6H_4	C	NH	trans	*b*	190–1	C,H,N,Cl
16	4-FC_6H_4	4-FC_6H_4	C	NH	trans	A	174–8	C,H,F,N
17	4-$CF_3C_6H_4$	4-$CF_3C_6H_4$	C	NH	t:c = 5:2	A	205	C,H,N
18	4-*i*-PrC_6H4	4-*i*-PrC_6H_4	C	NH	t:c = 1:1	A	89–91	H,N,S;C[c]
19	4-*t*-BuC_6H_4	4-*t*-BuC_6H_4	C	NH	t:c = 2:1	A	134–151	C,H,N,S
20	4-MeC_6H_4	4-MeC_6H_4	C	NH	t:c = 3:2	A	205–7	C,H,N
21	3-ClC_6H_4	3-ClC_6H_4	C	NH	trans	A	178	C,H,N,S
22	3-$MeOC_6H_4$	3-$MeOC_6H_4$	C	NH	trans	A	148	H,N;C[d]
23	3-MeC_6H_4	3-MeC_6H_4	C	NH	t:c = 3:7	A	86–8	C,H,N
24	2-$MeOC_6H_4$	2-$MeOC_6H_4$	C	NH	t:c = 2:1	A	108–10	C,H,N;S[e]
25	2-ClC_6H_4	2-ClC_6H_4	C	NH	trans	A	100	C,H,Cl,N
26	Ph	Ph	C	NMe	t:c = 3:2	A	91–4	C,H,N
27	Ph	Ph	C	NPh	t:c = 2:1	A	165–7	C,H,N,S
28	Ph	H	C	NH	trans	A	184–5	H,N;C[f]
29	Ph	Ph	N	N	cis	A	92–4	C,H,N,S
30	Ph	Ph	C	S	t:c = 3:2	A	123–4	C,H,N
31	Ph	Ph	C	O	t:c = 4:3	A	108–10	C,H,N,S

[a] Noncrystalline solid, no sharp melting point. [b] See Experimental Section for details. [c] Calcd: 70.26. Found: 69.8. [d] Calcd: 62.7. Found: 62.2. [e] Calcd: 5.90. Found: 6.37. [f] Calcd: 60.35. Found: 59.9.

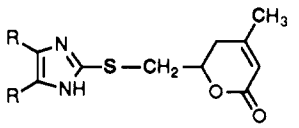
Scheme II [a]



[a] (a) KOH/EtOH; (b) NaOMe/MeOH; (c) CF_3CO_2H.

The preparation of lactones and lactams **48–53** was achieved by iodo cyclization[20] of ω-carboxy- or ω-carboxamidoalkenes followed by reaction of the intermediate 6-(iodomethyl) lactones or lactams with 2,3-dihydro-4,5-diphenyl-1*H*-imidazole-2-thione (Table III). Pyrans, acetals, and thioethers were also prepared by the alkylation of thiones with commercially available alkyl halides (Table III). Dioxane **58**, for which the appropriate alkyl halide was not readily available, was obtained by the transacetalization of **63** with 1,3-propanediol; also obtained as a byproduct in this reaction was the fused bicycle **72** (Scheme V). Alkylation with epoxy ester **73**[21] gave the hydroxy acid **74** rather than the expected lactone (Scheme V).

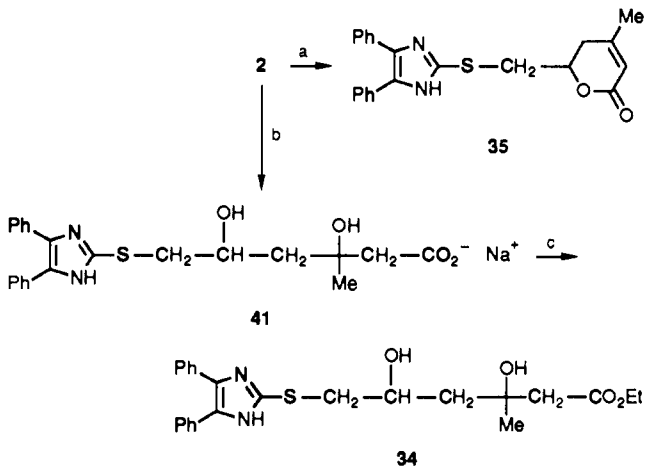
Table II. Preparation of



no.	R	method	mp (°C)	anal.
35	Ph	*a*	70–1	H,N,S;C[b]
36	4-FC_6H_4	B	123–6	C,H,F,N
37	4-ClC_6H_4	B	175–6	C,H,Cl,N
38	4-MeC_6H_4	B	191	C,H,N,S
39	3-ClC_6H_4	B	132–5	C,H,Cl,N
40	2-ClC_6H_4	B	126–7	C,H,N,Cl

[a] See Experimental Section for details. [b] Calcd: 70.19. Found: 69.7.

Scheme III [a]

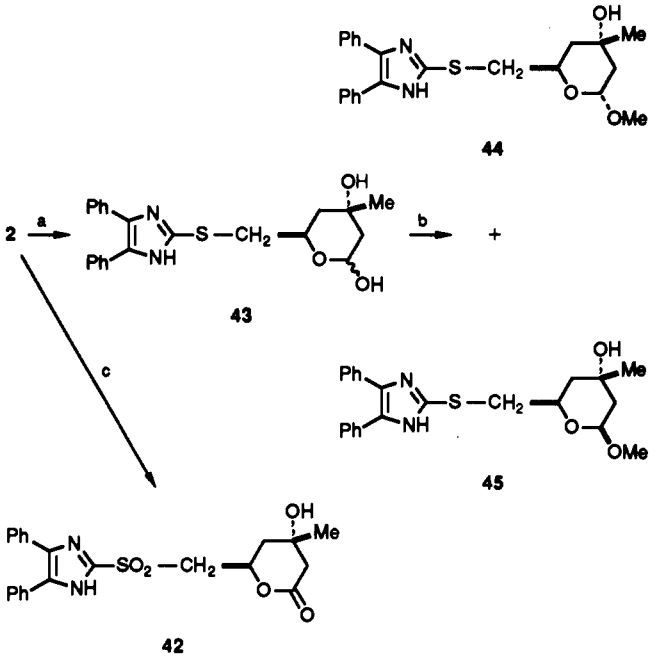


[a] (a) NaOMe/MeOH; (b) $NaOH/H_2O$; (c) EtI/DMF.

Biology and Results

The ability of compounds to inhibit ACAT was determined using hepatic microsomes from cholesterol-fed rats as the enzyme source. All compounds were originally tested at a single fixed concentration (either 1 or 10 μg/

Scheme IV [a]



[a] (a) DIBAL/THF; (b) BF_3·Et_2O/MeOH; (c) *m*-CPBA/CH_2Cl_2.

mL) and the results expressed in the form of percent inhibition of enzyme activity (Table IV). For 43 of the analogues the IC_{50}, which is the concentration that inhibited 50% of the enzyme activity, was also determined (Table IV). In comparison to the lead compound **2**, 12 analogues were more active, the most potent being **46**, 6 times more active than **2**. A detailed consideration of the structure–activity relationships allowed identification of the pharmacophore for ACAT inhibition for this series of compounds.

A number of the more potent compounds were also tested in an in vivo model. In this test rats received a diet supplemented with cholesterol and cholic acid in order to elevate their plasma cholesterol levels. Test compounds were coadministered as an additional supplement of 0.03% w/w (approximately equivalent to 30 mg/kg per day) and the effect on plasma cholesterol concentration determined. In cholesterol-fed animal models such as this any effect produced on plasma cholesterol concentration by a systemically acting ACAT inhibitor cannot be separated from the hypolipidemic response associated with the inhibition of ACAT in the gut. Of the 17 analogues subjected to this test, 9 showed a statistically significant hypocholesterolemic effect (Table IV).

Structure–Activity Relationships

The compounds prepared can be described by the general structural formula give in Figure 1. Considering each part of the formula in turn, the following structure–activity relationships for in vitro inhibition of rat liver microsomal ACAT are apparent.

(i) Modification of R^1/R^2: in the lead compound **2**, $R^1 = R^2$ = Ph. The presence of both phenyl rings was essential; compare **28** with **2**.

Symmetrical substitution by chloro or methyl at either the 2-, 3-, or 4-position of both phenyl rings gave compounds (**15**, **20**, **21**, and **25**) of comparable activity to **2**, and in one case (**23**) a 3-fold improvement in activity was observed. In comparison, substitution by methoxy (**13**, **14**, **22**, and **24**) reduced activity. Reductions in activity were also observed for the fluoro (**16**), trifluoromethyl (**17**), and *tert*-butyl (**19**) derivatives. Substitution in only one of the phenyl rings in pyran **54** offered no advantage; compare **54** with **55**, **56**, and **57**.

Replacement of both phenyl rings in the acetal **63** by heterocycles significantly reduced activity; compare **63** with **65** and **66**. In one example, ester **33**, where the two phenyl rings were joined together at the 2-position to give a planar quadricyclic system, activity compared to the corresponding bis(4-chlorophenyl) ester **32** was reduced.

(ii) Modification of X/Y: **2** is a 1*H*-imidazole (X = C, Y = NH); when the 1-position was substituted with a methyl group (Y = NMe, **26**), activity was reduced 15-fold relative to **2**. A much greater reduction in activity was observed when this position was substituted with a phenyl group (compound **27**). Compounds in which the imidazole ring was replaced by other azoles (**29**, **30**, and **31**) had very weak inhibitory activities.

(iii) Variation in *m*: oxidation of **2** to the sulfone **42** reduced activity significantly.

(iv) Variation in *n*: in most of the compounds described here, *n* = 1. There was some evidence that activity could be improved by increasing the chain length. For example, when Z = 1,3-dioxan-2-yl, **60** (*n* = 3) was more active than **58** (*n* = 1) and **59** (*n* = 2), and when Z = diethoxymethyl, **64** (*n* = 2) was more active than **63** (*n* = 1). Imidazole-2-thiols **6**, **7**, **8** (*n* = 0, Z = H) had little inhibitory activity.

(v) Modification of Z: for the mevalonate analogues where both diastereoisomers **10** and **11** were isolated, little difference in activity between the isomers was observed (compare **2** with **12**, and **13** with **14**). Removing either the methyl group or both the methyl and hydroxy groups together from the 3-position of the lactone ring reduced activity 4–5-fold (compare **48** and **50** with **2**), whereas replacing the 3-hydroxy group with another methyl group to give the dimethyl analogue **51** resulted in a small improvement in activity. In the dihydropyranone series the effects on activity of substitution in the phenyl rings were variable: the chloro analogues (**37**, **39**, and **40**) were less active than the corresponding mevalonate derivatives (**15**, **21**, and **25**). When the rings were unsubstituted or were substituted at their 4-positions by a fluoro or methyl group (**35**, **36**, and **38**), this modification had little effect on activity relative to the corresponding compound in the mevalonate series.

Reduction of the lactone ring of **2** to the corresponding lactols **43** had little effect on activity. In the two sets of anomeric methyl glycosides (compounds **44** and **45**, and **46** and **47**) the α-anomer was 3 times more active than its corresponding β-isomer. The most potent of these four glycosides **46** was 5–6 times more active than **2**. It is interesting to note that the more hydrophilic mannopyranoside derivative **70** was less active.

In comparison to the metabolically labile δ-lactone **48**, activity was retained with the more stable δ-lactam **49**. Analogues in which Z comprised other stable six-membered rings (e.g. pyran **54**, cyclohexyl **67**, and phenyl **68**) showed good activity. The relatively hydrophilic 1,3-dioxane **58** also retained this level of activity.

Effective ACAT inhibition is not restricted to com-

(19) Coffee, E. C. J. Preparation of (2S,4R,6S)- and (2R,4R,6S)-6-[(4,5-Diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2*H*-pyran as Antiatherosclerotic Agents. EP 391796 (*Chem. Abstr.* **1990**, *114*, 101991).

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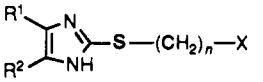
Table III. Preparation of



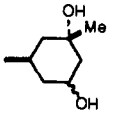
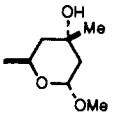
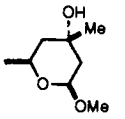
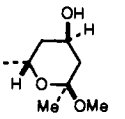
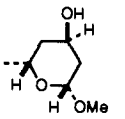
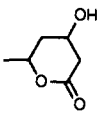
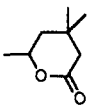
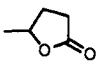
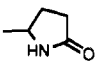
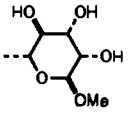
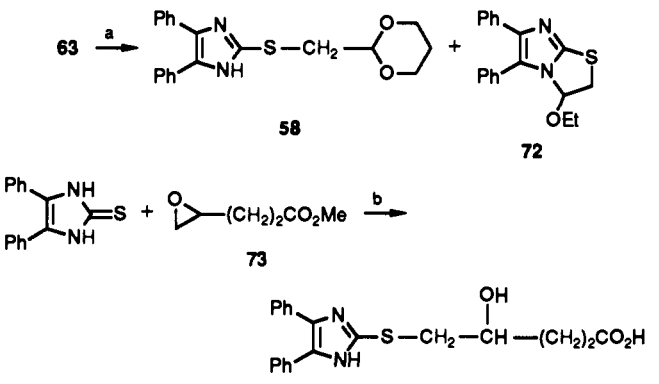
no.	R^1	R^2	n	X	method	mp (°C)	anal.
43	Ph	Ph	1		a	134–151	C,H,N,S
44	Ph	Ph	1		a	46	C,H,N,S
45	Ph	Ph	1		a	163–6	C,H,N,S
46	Ph	Ph	1		b	80–108	C,H,N,S
47	Ph	Ph	1		b	202–3	C,H,N,S
48	Ph	Ph	1		C	*c*	C,H,N,S
49	Ph	Ph	1		C	209–10	C,H,N,S
50	Ph	Ph	1		C	191–2	C,H,N,S
51	Ph	Ph	1		C	130–1	C,H,S;N[d]
52	Ph	Ph	1		C	118–20	C,H,N,S
53	Ph	Ph	1		C	218	C,H,N,S
54	Ph	Ph	1		D	143–5	C,H,N,S
55	4-ClC_6H_4	Ph	1		D	127–9	C,H,N
56	3-ClC_6H_4	Ph	1		D	113–5	C,H,N,S
57	2-ClC_6H_4	Ph	1		D	58–60	C,H,Cl,N
58	Ph	Ph	1		*a*	153–5	C,H,N,S
59	Ph	Ph	2		D	153–5	C,H,N
60	Ph	Ph	3		D	151	N,H,S;C[e]
61	Ph	Ph	1		D	139–40	C,H,N,S
62	Ph	Ph	1	$CH(OMe)_2$	D	162–3	C,H,N,S
63	Ph	Ph	1	$CH(OEt)_2$	D	90–4	C,H,N,S
64	Ph	Ph	2	$CH(OEt)_2$	D	100–2	C,H,N,S
65	2-pyridyl	2-pyridyl	1	$CH(OEt)_2$	D	*f*	C,H,N,S

Table III (Continued)

no.	R^1	R^2	n	X	method	mp (°C)	anal.
66	2-furanyl	2-furanyl	1	$CH(OEt)_2$	D	*f*	C,H,N,S
67	Ph	Ph	1	cyclohexyl	D	169–71	C,H,N,S
68	Ph	Ph	1	Ph	D	181–9	C,H,N,S
69	Ph	Ph	1	Me	D	190[g]	C,H,N,S
70	Ph	Ph	1		D	120–2	H,N;C[h]
71	2-ClC_6H_4	2-ClC_6H_4	0	$(CH_2)_5CO_2H$	*a*	78–80	C,H,N,S

[a] See Experimental Section for details. [b] See ref 19. [c] Noncrystalline solid, no sharp melting point. [d] Calcd: 7.14. Found: 6.6 [e] Calcd: 69.44. Found: 69.9. [f] Oil. [g] Lit:[28] mp 189–190.5 °C. [h] Calcd: 61.7. Found: 61.2.

Scheme V [a]



[a] (a) $HO(CH_2)_3OH$/PPTS (cat.)/toluene; (b) KOH/EtOH.

pounds in which Z is a cyclic group—the diethyl acetal **63** was approximately equipotent with the cyclic acetal **58**,

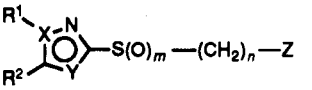


Figure 1. General formula for discussion of structure–activity relationships.

although the dimethyl acetal **62** was less active. Similarly, the esters **32** and **34** were only slightly less active than the corresponding lactones (compounds **15** and **2**, respectively). However, acid groups were not tolerated: the sodium salt **41** of **2** and long chain acids **71** and **74** were only weakly active.

Conclusions

From these SAR data it is possible to draw some conclusions about the pharmacophore necessary for potent in vitro ACAT activity in this series of compounds. It would appear that two phenyl rings ($R^1 = R^2 = Ph$) are essential for activity. These rings may be substituted by

Table IV. Biological Activities

	ACAT activity in vitro			effect on plasma cholesterol in vivo, % change[a]		ACAT activity in vitro			effect on plasma cholesterol in vivo, % change[a]
no.	concn (μg/mL)	% inhibn	IC_{50}(nM)		no.	concn. (μg/mL)	% inhibn	IC_{50}(nM)	
2	10	98	170	−105[b]	**41**	10	66		−33[c]
6	10	42			**42**	10	23		
7	10	27			**43**	1	94	160	
8	1	0			**44**	1	89	280	
12	10	98	140	−35	**45**	1	93	82	
13	10	87	420		**46**	0.1	85	30	−40[b]
14	10	96	340		**47**	1	92	90	
15	10	98	180	−11	**48**	10	95	740	+16
16	10	97	790		**49**	1	86	610	
17	10	95	1000		**50**	1	89	910	
18	1	90	230		**51**	1	94	100	−17
19	1	32			**52**	10	78		
20	10	99	170		**53**	1	87	360	
21	1	93	110		**54**	1	92	210	−38[c]
22	10	97	570		**55**	1	87		
23	1	94	64	−64[b]	**56**	1	90	560	
24	1	29			**57**	1	76		
25	10	99	140		**58**	10	97	180	−10
26	10	90	2600		**59**	1	80	730	
27	10	32			**60**	1	96	47	−57[b]
28	10	0			**61**	10	98	530	−29
29	1	12			**62**	10	99	580	
30	10	4			**63**	10	99	250	−37[c]
31	10	13			**64**	1	95	69	+4
32	10	97	250	−53[c]	**65**	10	15		
33	1	41			**66**	1	34		
34	1	91	280		**67**	1	95	100	−92[b]
35	10	98	200	+27	**68**	1	90	290	
36	10	96	610		**69**	10	99	770	
37	1	77			**70**	1	52		
38	10	97	280		**71**	10	20		
39	10	98	440		**74**	10	76		
40	10	95	1700						

[a] 0.03% in the diet. [b] Significantly different from untreated controls ($p < 0.01$, Student's *t*-test). [c] Significantly different from untreated controls ($p < 0.05$, Student's *t*-test).

small groups without any significant effect on potency. A 1*H*-imidazole ring (X = C, Y = NH) is also essential for good activity. It is difficult to speculate on the apparent requirement for a free NH group (Y = NH): the lack of activity of the oxazole, thiazole, and triazole analogues may suggest that this group is functioning as a hydrogen-bond donor. In the *N*-methyl analogue **26**, however, where hydrogen bonding is no longer possible, some activity is retained. (Attempts to prepare a diphenylpyrrole analogue, in order probe the importance of the NH moiety, were unsuccessful.) If this methyl group is replaced by a phenyl group (compound **27**), activity is very significantly reduced (compare the inhibition at 10 μg/mL of **26** and **27**); this may be a steric effect. The lack of activity exhibited by 1*H*-imidazole-2-thiols ($n = 0$) may be because these compounds actually exist as 2,3-dihydro-1*H*-imidazole-2-thiones.[22] Replacement of the sulfur atom at position 2 by other atoms such as carbon and nitrogen will be described in a subsequent paper. (The DuPont Merck group have published preliminary results on the replacement of sulfur in their series[23].)

The SARs for the other part of the molecule are less clear. Effective ACAT inhibition is achieved in compounds in which Z is both cyclic and acyclic, chiral and nonchiral, both aromatic and alicyclic, and in compounds in which the calculated lipophilicity[24] of Z differs by a factor of more than 25 000. In the majority of the compounds reported Z is a six-membered ring, but even when the 2-position of the imidazole ring is substituted by a simple ethylthio group (compound **69**), useful activity is achieved. It is difficult to identify precise structure–activity relationships for the Z group, partly because profound changes in the structure of Z have rather small effects on activity (compare, for example, analogues in which Z is a simple methyl group (compound **69**) and a six-membered ring with three chiral centers (compound **45**); these analogues differ in activity by a factor of less than 10). There is some evidence that the shape of Z may be important, because compounds with similar skeletons have similar activities (e.g. **2** and **51**, **48** and **49**, and **54**, **58**, **67**). Particularly important, in view of our interest in developing bioavailable inhibitors, is the fact that the lipophilicity of Z does not correlate with activity: the 1,3-dioxane **58** and the cyclohexyl analogue **67**, which have similar activities and must have very similar shapes, differ in calculated log *P*[24] by more than 3 log units.

Relatively hydrophilic analogues such as **45** and **46** are inhibitors of rat liver microsomal ACAT in vitro, although not as potent as the (very lipophilic) amides and ureas described by DuPont Merck.[15] Other analogues (e.g. **2**, **23**, and **67**) show an effective hypocholesterolemic response in the cholesterol-fed rat. The combination of these properties in compound **60** encourages us to believe that a potent, bioavailable ACAT inhibitor can be discovered on the basis of the 4,5-diphenyl-1*H*-imidazole pharmacophore.

Experimental Section

Biological Methods. The rat liver microsomal enzyme screen was based on a method described in the literature[25] with some modifications: assays were performed using 60 μg of microsomal protein in a reaction volume of 200 μL with a concentration of 90 μM of oleoyl-CoA. Conversion of radiolabeled oleoyl-CoA to cholesterol ester was determined by scintillation counting after separation of the reaction products by TLC.

For the in vivo screen, male Sprague-Dawley rats (200 g body weight, $n = 8$ per group) obtained from Charles River UK Ltd. were fed a diet supplemented with 0.5% w/w cholesterol and 0.25% w/w cholic acid for 3 days. One group of animals also received the test compound at a concentration of 0.03% w/w in the diet (approximately equivalent to 30 mg/kg per day). Food intake and body weight gains were routinely monitored to ensure that animals received the stated dose. Another group ($n = 4$) was fed basal diet without supplements to determine the basal plasma cholesterol concentration. The plasma cholesterol levels of undosed control animals receiving cholesterol and cholic acid rose from 2 mM to about 5 mM. The plasma cholesterol levels in basal fed rats were very reproducible, and so for screening purposes this level was subtracted from that in cholesterol-fed animals to define the hyperlipidemic response to cholesterol feeding. Comparison of the response in drug treated animals with that in undosed controls enabled the hypolipidemic activity of the compounds to be measured as a percentage change. Plasma cholesterol concentrations were determined by a standard enzymatic method (Cholesterol-C system, Product no. 237574, Boehringer Mannheim GmbH) using a COBAS Bio centrifugal analyzer.

Chemical Methods. All organic solutions were dried over $MgSO_4$. The structures and purities of all compounds described were confirmed by microanalytical and spectroscopic analysis. Melting points were obtained on an Electrothermal apparatus and are uncorrected. ^1H NMR spectra were acquired on Varian XL-200 or XL-400 machines at 200 or 400 MHz, respectively; peak positions are reported in parts per million relative to internal tetramethylsilane on the delta (δ) scale.

4,5-Bis(2-chlorophenyl)-2,3-dihydro-1*H*-imidazole-2-thione (7). A mixture of 2-chlorobenzaldehyde (28.1 g, 0.20 mol), Et_3N (3.6 mL), and 3,4-dimethyl-5-(2-hydroxyethyl)-thiazolium iodide (2.75 g, 20 mmol) in EtOH (150 mL) was stirred at reflux under N_2 in the absence of light for 24 h. The mixture was evaporated to dryness and the residue taken up into CH_2Cl_2 (75 mL). This solution was washed with H_2O (50 mL), dried, and evaporated. Purification by flash chromatography (CH_2Cl_2) gave 2,2′-dichlorobenzoin as a pale yellow oil: 11.3 g (40%). A solution of 2,2′-dichlorobenzoin (11.3 g, 40 mmol) in DMF (30 mL) was treated with thiourea (4.56 g, 60 mmol) and the mixture stirred at reflux for 6 h. The mixture was allowed to stand at room temperature overnight and then the crystalline precipitate was collected by filtration and washed with EtOH to give **7** as a white powder: 8.6 g (69%); mp 285–286 °C. Anal. ($C_{15}H_{10}Cl_2N_2S$) H, N; C: calcd, 56.1; found, 56.6.

4(5)-(4-Chlorophenyl)-2,3-dihydro-5(4)-phenyl-1*H*-imidazole-2-thione. A mixture of 1-(4-chlorophenyl)-1-hydroxy-2-oxo-2-phenylethane[18] (8.9 g, 36 mmol) and thiourea (3.0 g, 40 mmol) in DMF (100 mL) was stirred at reflux for 7 h. After cooling to room temperature, the mixture was poured into H_2O (1 L) and the yellow precipitate collected by filtration and washed thoroughly with H_2O to give 4(5)-(4-chlorophenyl)-2,3-dihydro-5(4)-phenyl-1*H*-imidazole-2-thione as a white powder: 2.4 g (23%), mp 287–290 °C. Anal. ($C_{15}H_{11}ClN_2S$) C, H, Cl, N.

4,5-Diphenylthiazole-2-thiol. Desyl chloride (23.1 g, 0.10 mol) was added portionwise over 15 min to a stirred suspension of ammonium dithiocarbamate (16.5 g, 0.15 mol) in absolute EtOH (100 mL); there was a mild exotherm, the internal temperature reaching ~40 °C. The mixture was stirred at room temperature for 30 min and then at 60–65 °C for 2 h. After cooling to room temperature, the mixture was poured with stirring onto ice (200 g) and H_2O (1000 mL). After stirring for 1 h, the mixture was filtered and the residue washed with H_2O (200 mL) and crystallized from EtOH to give 4,5-diphenylthiazole-2-thiol as a white powder: 12.1 g (45%); mp 223–225 °C.

(22) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. The Tautomerism of Heterocycles. *Adv. Heterocycl. Chem.* Suppl. 1, 1976, 400–401.

(23) 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. Poster presented at the 9th International Symposium on Atherosclerosis; Chicago, 6–11 October 1991.

(24) Pomona College Medicinal Chemistry Project, MedChem Software, Release 3.63.

(25) Lichtenstein, A. H.; Brecher, P. Properties of Acyl-CoA:Cholesterol Acyltransferase in Rat Liver Microsomes. *J. Biol. Chem.* 1980, *255*, 9098–9104.

4,5-Diphenyloxazole-2-thiol[26] and 1,5-diphenyl-1,2,4-triazole-3-thiol[27] were prepared following the published procedures.

6-[[(4,5-Diphenyloxazol-2-yl)thio]methyl]-4-hydroxy-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (31). Method A. 4,5-Diphenyloxazole-2-thiol (20.0 g, 80 mmol) was added to a stirred solution of KOH pellets (85%, 5.8 g, 88 mmol) in EtOH (300 mL) at room temperature. After 20 min 1,1-dimethylethyl 5,6-epoxy-3-hydroxy-3-methylhexanoate (25.9 g, 0.12 mol) was added and the mixture stirred at room temperature overnight. The solvent was evaporated off and the oily residue dissolved in H_2O (500 mL). Acidification with HCl to pH 1 precipitated a gum, which was taken up into CH_2Cl_2 (500 mL). This solution was washed with H_2O (250 mL), dried, and evaporated. Purification of the residue by flash chromatography (CH_2Cl_2/MeOH mixture, 40:1 by volume) followed by crystallization from EtOAc/hexane gave white microcrystals of compound **31** as a 4:3 mixture of trans and cis isomers: 12.9 g (41%); mp 108–110 °C. Anal. ($C_{22}H_{21}NO_4S$) C, H, N, S. ^1H NMR ($CDCl_3$) 1.28 and 1.36 (3 H, 2 s, CH_3), 1.92 (2 H, m, $CHCH_2C(OH)(CH_3)$), 2.60 (2 H, m, $C(=O)CH_2C(OH)(CH_3)$), 3.68 (2 H, m, SCH_2), 4.62 (0.43 H, m, SCH_2CH, cis isomer), 5.08 (0.57 H, m, SCH_2CH, trans isomer), 7.15–7.75 (10 H, m, $(C_6H_5)_2$).

1,1-Dimethylethyl 6-[[4,5-Bis(4-chlorophenyl)-1*H*-imidazol-2-yl]thio]-3,5-dihydroxy-3-methylhexanoate (32). Sodium methoxide (1.04 g, 19 mmol) was added to a stirred suspension of 4,5-bis(4-chlorophenyl)-2,3-dihydro-1*H*-imidazole-2-thione (6.1 g, 19 mmol) in MeOH (150 mL). After 45 min 1,1-dimethylethyl 5,6-epoxy-3-hydroxy-3-methylhexanoate (6.04 g, 28 mmol) was added and the mixture stirred at room temperature overnight. Evaporation of the mixture gave a yellow semisolid, which was partitioned between EtOAc (100 mL) and H_2O (50 mL). The layers were separated, and the organic layer was dried and evaporated. TLC analysis (EtOAc/CH_2Cl_2 mixture, 1:1 by volume) showed a complex mixture containing at least three major spots. The product was combined with the product from a previous reaction on a 6.2-mmol scale and the mixture was purified by flash chromatography (EtOAc/CH_2Cl_2 mixture, 3:7 to 2:3 by volume). Fractions containing pure top spot were combined and crystallized from cyclohexane to give compound **32** as a white crystalline solid: 2.6 g (19%); mp 152–153 °C. Anal. ($C_{26}H_{30}Cl_2N_2O_4S$) C, H, N. ^1H NMR ($CDCl_3$) 1.31 (3 H, s, $C(OH)(CH_3)$), 1.48 (9 H, s, $C(CH_3)_3$), 1.64 and 2.01 (2 H, 2 dd, $CH(OH)CH_2C(\ )(CH_3)$, J = 10 Hz, 2 Hz), 2.43 and 2.69 (2 H, 2 d, $C(OH)(CH_3)CH_2CO_2C(CH_3)_3$, J = 14 Hz), 3.10 (2 H, m, SCH_2), 4.40 (1 H, m, $CH(OH)$), 7.2–7.4 (8 H, m, $(C_6H_4Cl)_2$).

***r*-6-[[[4,5-Bis(4-chlorophenyl)-1*H*-imidazol-2-yl]thio]methyl]-*t*-4-hydroxy-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (15).** Trifluoroacetic acid (20 mL) was cooled in an ice bath and compound **32** (4.0 g, 7.4 mmol) was added. The cooling bath was removed and the clear solution allowed to stand at room temperature for 1 h. The solution was carefully poured into 5% $NaHCO_3$ solution (250 mL) and the product then extracted into EtOAc (200 mL). This solution was washed with H_2O (100 mL), dried, and evaporated. The resulting amorphous foam was dissolved in CH_2Cl_2 (50 mL) and the solution kept at 0 °C overnight. The mixture was filtered and the residue was washed with a little fresh ice-cold CH_2Cl_2 to give compound **15** as a white crystalline solid: 2.3 g (67%); mp 190–191 °C. Anal. ($C_{22}H_{20}Cl_2N_2O_3S$) C, H, Cl, N. ^1H NMR ($CDCl_3$–DMSO-d_6) 1.28 (3 H, s, $C(OH)(CH_3)$), 2.06 and 2.14 (2 H, 2 dd, $CHCH_2C(\ )(CH_3)$, J = 12 Hz, 6 Hz), 2.48 and 2.56 (2 H, 2 d, $C(=O)CH_2C(OH)(CH_3)$, J = 16 Hz), 3.37 and 3.89 (2 H, 2 dd, SCH_2, J = 12 Hz, 6 Hz), 4.78 (1 H, m, SCH_2CH, J = 6 Hz), 7.3–7.5 (8 H, m, $(C_6H_4Cl)_2$).

Sodium 3,5-Dihydroxy-6-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]-3-methylhexanoate 1.5-Hydrate (41). A mixture of **2** (2.6 g, 6.7 mmol) and 1.0 M NaOH (6.7 mL, 6.7 mmol) in H_2O (50 mL) was warmed at 60 °C for 10 min. The almost clear solution was filtered and the filtrate evaporated to dryness. The residue was warmed at 60–70 °C under high vacuum to remove last traces of moisture to give **41** as a pale yellow powder: 1.8 g (58%); mp 172–174 °C. Anal. ($C_{22}H_{23}N_2NaO_4S\cdot1.5H_2O$) C, H, N, S. ^1H NMR (d_6-DMSO) 1.12 (3 H, s, CH_3), 1.63 (2 H, m, $CH(OH)CH_2C(\ )CH_3$), 2.11 (2 H, m, $C(OH)C(CH_3)CH_2CO_2C_2H_5$), 3.10 (2 H, m, SCH_2), 4.04 (1 H, m, $CH(OH)$), 7.2–7.5 (10 H, m, $(C_6H_5)_2$).

Ethyl 3,5-Dihydroxy-6-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]-3-methylhexanoate (34). A mixture of **2** (4.2 g, 10.7 mmol) and 1.0 M NaOH (10.6 mL, 10.6 mmol) in H_2O (70 mL) was warmed at 60 °C for 10 min. The almost clear solution was filtered and the filtrate evaporated to dryness. The residue was warmed at 60–70 °C under high vacuum to remove last traces of moisture. The glassy product was suspended in DMF (40 mL) and the mixture treated with ethyl iodide (2.1 g, 14 mmol). After stirring at room temperature for 2 h, the mixture was partitioned between EtOAc (200 mL) and H_2O (100 mL). The layers were separated, and the organic layer was washed with H_2O (100 mL), dried, and evaporated to dryness. Purification of the residue by flash chromatography (EtOAc/CH_2Cl_2 mixture, 1:1 by volume) gave **34** as a light yellow foam: 2.5 g (53%); no sharp melting point. Anal. ($C_{24}H_{28}N_2O_4S$) H, N, S; C: calcd, 65.4; found, 64.9. ^1H NMR ($CDCl_3$) 1.26 (3 H, t, CH_2CH_3, J = 8 Hz), 1.38 (3 H, s, $C(OH)C(CH_3)$), 1.59 and 2.00 (2 H, 2 m, $CH(OH)CH_2C(OH)CH_3$)), 2.58 (2 H, m, $C(OH)C(CH_3)CH_2CO_2C_2H_5$), 3.06 (2 H, m, SCH_2), 4.17 (2 H, q, CH_2CH_3, J = 8 Hz), 4.45 (1 H, m, $CH(OH)$), 7.2–7.5 (10 H, m, $(C_6H_5)_2$).

5,6-Dihydro-6-[[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]methyl]-4-methyl-2*H*-pyran-2-one (35). NaOMe (34 mg, 0.63 mmol) was added to a solution of compound **2** (250 mg, 0.63 mmol) in anhydrous MeOH (20 mL) and the mixture stirred at reflux. After 4.5 h further NaOMe (34 mg) was added and refluxing continued for another 2 h. The mixture was evaporated to dryness and the residue dissolved in H_2O (25 mL). Acidification with AcOH gave a colorless gum, which was extracted with CH_2Cl_2 (4 × 20 mL). The combined extracts were dried and evaporated, and the residue was purified by flash chromatography (EtOAc/hexane mixture, 1:1 by volume) to give **35** as a white amorphous powder: 15 mg (6%); mp 70–71 °C. Anal. ($C_{22}H_{20}N_2O_2S$) H, N, S; C: calcd, 70.2; found, 69.7. ^1H NMR ($CDCl_3$) 1.99 (3 H, s, CH_3), 2.36 and 2.52 (2 H, 2 dd, $C(=O)CH=C(CH_3)CH_2$, J = 16 Hz, 4 Hz), 3.37 (2 H, m, SCH_2), 4.74 (1 H, m, SCH_2CH), 5.82 (1 H, s, $C(=O)CH=C$), 7.2–7.5 (10 H, m $(C_6H_5)_2$).

6-[[4,5-Bis(4-methylphenyl)-1*H*-imidazol-2-yl]thio]methyl]-5,6-dihydro-4-methyl-2*H*-pyran-2-one (38). Method B. NaOMe (3.3 g, 60 mmol) was added to a stirred suspension of 2,3-dihydro-4,5-bis(4-methylphenyl)-1*H*-imidazole-2-thione (17.0 g, 60 mmol) in MeOH (600 mL). After 15 min 1,1-dimethylethyl 5,6-epoxy-3-hydroxy-3-methylhexanoate (19.7 g, 90 mmol) was added and the mixture stirred at room temperature overnight. The mixture was filtered through Filter-aid and the residue evaporated to dryness and partitioned between EtOAc (400 mL) and 2 M aqueous AcOH (400 mL). The layers were separated, and the organic layer was dried and evaporated. The resulting brown gum was triturated with Et_2O (500 mL) until crystallization was complete. Filtration gave 4.7 g of a white powder, pure by TLC (EtOAc/CH_2Cl_2, 1:1 by volume). A suspension of this hydroxy lactone in anhydrous CH_2Cl_2 (250 mL) was cooled in an ice bath and treated slowly with trifluoroacetic anhydride (6.3 g); complete solution occurred. After standing at room temperature for 2 h, the light yellow solution was washed with 5% $NaHCO_3$ solution (2 × 150 mL), dried, and evaporated. The resulting brown gum was dissolved in toluene (200 mL) and treated with DBU (4.5 g). After standing at room temperature for 2 h, the clear solution was washed with H_2O (3 × 100 mL), dried, and evaporated. Crystallization of the resulting white foam from EtOAc containing a little MeOH gave compound **38** as white crystals: 2.1 g (9%); mp 191 °C. Anal. ($C_{24}H_{24}N_2O_2S$) C, H, N, S. ^1H NMR ($CDCl_3$) 1.92 (3 H, s, $CCH_3=CH$), 2.30 (6 H, s, $(C_6H_4(CH_3))_2$), 2.54 (2 H, 2 dd, $CHCH_2C(CH_3)=CH$, J = 7 Hz,

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2 Hz), 3.47 (2 H, d, SCH_2, J = 6 Hz), 4.70 (1 H, m, SCH_2CH), 5.78 (1 H, d, $C(=O)CH=C$, J = 2 Hz), 7.1–7.4 (8 H, m, $(C_6H_4(CH_3))_2$).

r-6-[[(4,5-Diphenyl-1*H*-imidazol-2-yl)sulfonyl]methyl]-*t*-4-hydroxy-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (42). 3-Chloroperoxybenzoic acid (80%, 273 mg, 1.3 mmol) was added to a stirred suspension of **2** (250 mg, 0.63 mmol) in CH_2Cl_2 (25 mL) at room temperature; complete solution occurred almost immediately. After 3 h the solution was washed successively with 5% Na_2SO_3 solution (25 mL) and 5% $NaHCO_3$ solution (25 mL), dried, and evaporated. Trituration of the residue with Et_2O gave **42** as a white powder: 230 mg (85%); mp 216–217 °C. Anal. ($C_{22}H_{22}N_2O_5S$) C, H, N, S. ^1H NMR (DMSO-d_6) 1.20 (3 H, s, CH_3), 1.85 (2 H, m, $C(=O)CH_2C(OH)(CH_3)CH_2$), 2.42 (2 H, m, $OC(=O)CH_2$), 3.95 (2 H, m, SO_2CH_2), 4.12 (1 H, m SO_2CH_2CH), 7.3–7.5 (10 H, m, $(C_6H_5)_2$).

r-6-[[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]methyl]-2-hydroxy-*t*-4-hydroxy-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran (43). A solution of **2** (3.9 g, 10 mmol) in anhydrous THF (80 mL) was flushed with argon and cooled in a cardice–acetone bath (internal temperature < −70 °C). A solution of DIBAL in THF (1.0 M, 50 mL, 50 mmol) was added dropwise at such a rate as to keep the internal temperature below −60 °C. After 3 h at −70 °C the mixture was poured onto ice (50 g), H_2O (200 mL), and AcOH (25 mL). The mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the combined extracts were washed with 5% $NaHCO_3$ solution (100 mL), dried, and evaporated to give **43** as a white powder: 2.8 g (71%); mp 134–151 °C. Anal. ($C_{22}H_{24}N_2O_3S$) C, H, N, S. ^1H NMR (DMSO-d_6) 1.16 (3 H, s, CH_3), 1.21 (2 H, m, $OCH(OH)CH_2$), 1.63 (2 H, m, $OCH_2C(CH_3)$), 3.25 (2 H, m, SCH_2), 3.95 (1 H, m, SCH_2CH), 4.85 (1 H, d, $OCH(OH)$, J = 6 Hz), 7.2–7.4 (10 H, m, $(C_6H_5)_2$).

r-6-[[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]methyl]-*t*-4-hydroxy-2-methoxy-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran (44 and 45). A mixture of **43** (1.9 g, 4.8 mmol) and $BF_3{\cdot}Et_2O$ (3.0 mL) in MeOH (150 mL) was allowed to stand at room temperature for 24 h. The solution was poured onto 5% $NaHCO_3$ solution (100 mL) and extracted with EtOAc (200 mL). The layers were separated, and the organic layer was washed with water (2 × 100 mL), dried, and evaporated. TLC analysis (EtOAc/cyclohexane mixture, 3:1 by volume) showed two new components, no starting material. Purification by flash chromatography (EtOAc/cyclohexane, 2:1 by volume) gave **44** and **45**. (1) Compound **44**: the higher running component, tentatively identified from the ^1H NMR spectrum as the β-anomer, as a white foam; 0.51 g (26%); mp 46 °C. Anal. ($C_{23}H_{26}N_2O_3S$) C, H, N, S. ^1H NMR ($CDCl_3$) 1.23 (3 H, s, $C(OH)(CH_3)$), 1.6–1.95 (4 H, m, $OCH(OCH_3)CH_2C(OH)(CH_3)CH_2$), 3.16 (1 H, dd, SCH_2, J = 16 Hz, 8 Hz), 3.27 (1 H, dd, SCH_2, J = 12 Hz, 2 Hz), 3.47 (3 H, s, OCH_3), 4.35 (1 H, m, SCH_2CH), 5.02 (1 H, d, $OCH(OCH_3)$, J = 4 Hz), 7.2–7.6 (10 H, m, $(C_6H_5)_2$). (2) Compound **45**: the lower running component, tentatively identified as the α-anomer, as a white powder; 0.83 g (42%); mp 163–166 °C. Anal. ($C_{23}H_{26}N_2O_3S$) C, H, N, S. ^1H NMR ($CDCl_3$) 1.34 (3 H, s, $C(OH)CH_3$)), 1.5–1.9 (4 H, m, $OCH(OCH_3)CH_2C(OH)(CH_3)CH_2$), 3.04 (1 H, dd, SCH_2, J = 16 Hz, 6 Hz), 3.26 (1 H, dd, SCH_2, J = 16 Hz, 2 Hz), 3.32 (3 H, s, OCH_3), 4.22 (1 H, m, SCH_2CH), 4.79 (1 H, dd, $OCH(OCH_3)$, J = 10 Hz, 2 Hz), 7.2–7.6 (10 H, m, $(C_6H_5)_2$).

6-[[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]methyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (48). Method C. Iodine (82.3 g, 0.33 mol) was added to a stirred solution of hex-5-enoic acid (9.3 g, 81 mmol) in MeCN (200 mL) at 0 °C. After stirring at 0 °C for 3 h, solid $NaHCO_3$ (5 g) was added, followed by Et_2O (150 mL). The mixture was carefully washed with 10% Na_2SO_3 solution (3 × 100 mL), 5% $NaHCO_3$ solution (2 × 50 mL), and H_2O (100 mL), dried, and evaporated to give 6-(iodomethyl)-3,4,5,6-tetrahydro-2*H*-pyran-2-one as a yellow oil, 5.5 g (28%). A mixture of 2,3-dihydro-4,5-diphenyl-1*H*-imidazole-2-thione (4.5 g, 18 mmol) and K_2CO_3 (1.5 g, 11 mmol) in DMF (50 mL) was stirred at room temperature for 30 min. The iodo lactone (5.5 g, 23 mmol) was added and the mixture stirred at room temperature overnight. After concentrating to dryness, the residue was partitioned between H_2O (100 mL) and CH_2Cl_2 (100 mL). The layers were separated, and the organic layer was dried and evaporated. Purification of the residue by flash chromatography (EtOAc/CH_2Cl_2 mixture, 3:7 by volume) gave **48** as a white amorphous solid: 2.7 g (42%); no sharp melting point. Anal. ($C_{21}H_{20}N_2O_2S$) C, H, N, S. ^1H NMR ($CDCl_3$) 1.8–2.0 (4 H, m, $OC(=O)CH_2CH_2CH_2$), 2.50 (2 H, m, $OC(=O)CH_2$), 3.36 (2 H, m, SCH_2), 4.63 (1 H, , SCH_3), 7.2–7.5 (10 H, $(C_6H_5)_2$).

2-[(2,2-Diethoxy-1-ethyl)thio]-4,5-diphenyl-1*H*-imidazole (63). Method D. A mixture of 2,3-dihydro-4,5-diphenyl-1*H*-imidazole-2-thione (41.1 g, 0.16 mol) and anhydrous K_2CO_3 (44.2 g, 0.32 mol) in anhydrous DMF (250 mL) was stirred at room temperature for 30 min. Bromoacetaldehyde diethyl acetal (64.3 g, 0.32 mol) was added and the mixture stirred at room temperature overnight. The reaction mixture was poured into H_2O (1500 mL) and extracted with EtOAc (500 mL). The layers were separated, and the organic layer was washed with H_2O (250 mL), dried, and evaporated. Crystallization of the residue from aqueous EtOH gave **63** as a fine white powder: 42.4 g (70%); mp 90–94 °C. Anal. ($C_{21}H_{24}N_2O_2S$) C, H, N, S. ^1H NMR ($CDCl_3$) 1.22 (6 H, t, CH_2CH_3, J = 7 Hz), 3.21 (2 H, d, SCH_2, J = 6 Hz), 3.64 and 3.79 (4 H, 2 m, CH_2CH_3), 4.78 (1 H, t, SCH_2CH, J = 6 Hz), 7.2–7.5 (10 H, $(C_6H_5)_2$).

6-[[4,5-Bis(2-chlorophenyl)-1*H*-imidazol-2-yl]thio]hexanoic Acid (71). 4,5-Bis(2-chlorophenyl)-2,3-dihydro-1*H*-imidazole-2-thione (10.0 g, 31 mmol) was added to a solution of Na (700 mg, 31 mmol) in anhydrous MeOH (400 mL). After the mixture was stirred at room temperature for 2 h, methyl 6-bromohexanoate (6.5 g, 31 mmol) was added and the resulting mixture stirred at room temperature overnight. The mixture was concentrated to dryness and the residue diluted with Et_2O (800 mL). This solution was washed with H_2O (4 × 60 mL), dried, and evaporated to give 13.4 g of an oil. A portion of this product (11 g) was dissolved in MeOH (150 mL) and treated with 1.0 M NaOH (80 mL). After stirring at room temperature overnight, the mixture was concentrated to dryness and the residue acidified with 2.0 M AcOH (100 mL). The product was extracted into CH_2Cl_2 (4 × 50 mL), and the combined extracts were washed with H_2O (2 × 50 mL), dried, and evaporated to give **71** as a white powder: 6.5 g (50%); mp 78–80 °C. Anal. ($C_{21}H_{20}Cl_2N_2O_2S$) C, H, N, S; Cl: calcd, 16.3; found, 15.7. ^1H NMR ($CDCl_3$) 1.5–1.8 (6 H, m, $SCH_2(CH_2)_3CH_2$), 2.29 (2 H, t, $SCH_2(CH_2)_3CH_2$, J = 6 Hz), 3.14 (2 H, t, $SCH_2(CH_2)_3CH_2$, J = 6 Hz), 7.2–7.4 (8 H, m, $(C_6H_4Cl)_2$).

2-[[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]methyl]-1,3-dioxane (58). A mixture of **63** (10.0 g, 27 mmol), 1,3-propanediol (2.1 g, 27 mmol), and pyridinium 4-toluenesulfonate (1.5 g, 6 mmol) in toluene (500 mL) was stirred at reflux under a Dean and Stark water separator. Approximately every hour the solvent in the trap was run off and an equal volume of fresh toluene added to the reaction flask. After 24 h the solution was washed with H_2O (250 mL), dried, and evaporated. TLC analysis (EtOAc/CH_2Cl_2 mixture, 1:3 by volume) of the residue showed two major components. Purification by flash chromatography (EtOAc/CH_2Cl_2 mixtures, 1:9 to 2:3 by volume) allowed the separation of two products, **72** and **58**. (1) The higher running fraction was identified as 2,3-dihydro-5,6-diphenyl-3-ethoxyimidazo[2,1-*b*]-thiazole (**72**): 0.82 g (9%); mp 132 °C. Anal. ($C_{19}H_{18}N_2OS$) C, H, N, S. ^1H NMR ($CDCl_3$) 1.03 (3 H, t, CH_2CH_3, J = 7 Hz), 3.26 (2 H, m, CH_2CH_3), 3.64 (1 H, d, SCH_2, J = 12 Hz), 4.07 (1 H, dd, SCH_2, J = 12 Hz, 6 Hz), 5.61 (1 H, d, $CH(OC_2H_5)$, J = 6 Hz), 7.2–7.5 (10 H, m, $(C_6H_5)_2$). (2) The lower running fraction was crystallized from EtOAc and identified as compound **58**: 2.3 g (24%); mp 153–155 °C. Anal. ($C_{20}H_{20}N_2O_2S$) C, H, N, S. ^1H NMR ($CDCl_3$) 1.38 and 2.12 (2 H, 2 m, $OCH_2CH_2CH_2O$), 3.19 (2 H, d, SCH_2, J = 6 Hz), 3.87 and 4.16 (4 H, 2 m, $OCH_2CH_2CH_2O$), 4.89 (1 H, t, SCH_2CH, J = 6 Hz), 7.2–7.5 (10 H, m, $(C_6H_5)_2$).

5-[(4,5-Diphenyl-1*H*-imidazol-2-yl)thio]-4-hydroxypentanoic Acid (74). 2,3-Dihydro-4,5-diphenyl-1*H*-imidazole-2-thione (3.2 g, 13 mmol) was added to a stirred solution of KOH (85%, 1.3 g, 20 mmol) in EtOH (100 mL). After 10 min methyl 4,5-epoxypentanoate[20] (2.5 g, 19 mmol) was added and the mixture stirred at room temperature overnight. The mixture was concentrated to dryness and the residue stirred with 2.0 M AcOH (100 mL). The product was extracted into CH_2Cl_2 (3 × 100 mL); considerable quantities of solid remained in the aqueous layer. This solid was collected by filtration and crystallized from acetone to give **74** as cream crystals: 0.77 g (11%); mp 160–161 °C. Anal. ($C_{20}H_{20}N_2O_3S$) C, H, N. ^1H NMR (DMSO-d_6) 1.93 (2 H, m, $SCH_2CH(OH)CH_2CH_2$), 2.52 (2 H, m, $SCH_2CH(OH)CH_2CH_2$), 3.20 (2 H, m, SCH_2), 4.05 (1 H, $SCH_2CH(OH)$), 7.2–7.5 (10 H, m, $(C_6H_5)_2$).