# Acyl-CoA:Cholesterol *O*-Acyltransferase (ACAT) Inhibitors. 2. 2-(1,3-Dioxan-2-yl)-4,5-diphenyl-1*H*-imidazoles as Potent Inhibitors of ACAT

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The second in this series of papers concerns our further investigations into the search for a potent bioavailable acyl-CoA:cholesterol *O*-acyltransferase (ACAT) inhibitor suitable for the treatment of atherosclerosis. The design, synthesis, and structure−activity relationship for a series of ACAT inhibitors based on the 2-(1,3-dioxan-2-yl)-4,5-diphenyl-1*H*-imidazole pharmacophore are described. Compounds such as **13a** bearing simple alkyl or hydroxymethyl substituents at the 5-position of the 1,3-dioxane ring are potent bioavailable inhibitors of the rat hepatic microsomal enzyme *in vitro* ($IC_{50}$ < 100 nM) but are only weak inhibitors of the human hepatic enzyme. We have found however that 1,3-dioxanes substituted at the 5-*cis* position with pyrazolylalkyl or aminoalkyl groups are potent inhibitors *in vitro* of human macrophage ACAT, the potency depending on the nature of the terminal heterocycle and the length of the alkyl chain. An *ex vivo* bioassay described herein demonstrates that potent inhibitors such as **13t** ($IC_{50}$ = 10 nM) which contain lipophilic terminal heterocycles do not appear to be systemically available. Less potent but more water soluble compounds such as **13h** ($IC_{50}$ = 60 nM) and **13n** ($IC_{50}$ = 70 nM) are absorbed following oral dosing and achieve plasma levels significantly in excess of their $IC_{50}$ for ACAT inhibition. These compounds are therefore possible candidates for further investigation as oral antiatherosclerotic agents.

## Introduction

Part 1 in this series identified the 4,5-diphenyl-1*H*-imidazole moiety as a potent pharmacophore for *in vitro* inhibition of the rat liver acyl-CoA:cholesterol *O*-acyltransferase (ACAT, EC 2.3.1.26) and described moderately lipophilic 2-(alkylthio)-4,5-diphenyl-1*H*-imidazoles which were good inhibitors of ACAT *in vitro* and reduced plasma cholesterol levels in the cholesterol-fed rat.[1] ACAT is responsible for catalyzing the intracellular esterification of cholesterol by acyl-CoA's derived from long chain fatty acids, principally oleic acid, and as such plays a key role in the absorption and metabolism of cholesterol.[2] It has been postulated that the inhibition of ACAT is a rational and efficient approach to the design of novel hypocholesterolemic agents interfering with the intestinal absorption of cholesterol.[3] In addition, the consequences of ACAT inhibition in the artery by a systemically available agent might lead to direct antiatherosclerotic effects. Arterial macrophages possess a scavenger receptor for oxidatively modified low-density lipoprotein (LDL) particles.[4] The ingested lipid particles are metabolized via the cholesteryl ester (CE) cycle to release their burden of cholesterol.[5] After digestion of the LDL particle, lysosomal hydrolysis by acidic cholesterol ester hydrolase produces free cholesterol (FC) which is immediately re-esterified by ACAT. The scavenger receptor is unregulated, and since cells do not generally excrete CE,[4,5] arterial macrophages can accumulate considerable quantities of lipid. The resulting CE-laden foam cells comprise a major component of the atherosclerotic plaque,[6] so the prevention, or reduction, of the accumulation of CE in macrophages by the inhibition of ACAT might be beneficial in the treatment of atherosclerosis. Recent reports have also implicated ACAT in the release of VLDL particles from the liver, and inhibition of this hepatic activity might also be expected to bring about a beneficial hypocholesterolemic response.[7]

A number of structurally diverse compounds showing potent *in vitro* and *in vivo* inhibition of ACAT have been described.[8] Many reported inhibitors are lipophilic, water-insoluble, and unlikely to exhibit significant bioavailability following oral dosing. These include, for example: the amide RP 64477 (**1**),[9] the urea CL 227,082 (**2**),[10] and the diphenylimidazole DuP 128 (**3**)[11] which has been examined in the clinic.[12] These compounds were designed to limit cholesterol absorption by inhibiting ACAT in the intestinal mucosa without being systemically available. More recently, ACAT inhibitors such as CI-976 (**4**),[13] CP-105191 (**5**),[14] and PD-132301 (**6a**)[15] possessing moderate systemic bioavailability have been reported, and a water-soluble ACAT inhibitor has been synthesized at Parke-Davis.[16] Studies carried out in the DuPont laboratories to obtain a systemically available ACAT inhibitor based on **3** have also been described in a recent series of papers.[17] In addition to a hypocholesterolemic benefit, these systemic inhibitors have the potential to exert a direct antiatherosclerotic effect on the artery wall. In confirmation of this hypothesis, it has been reported that **4** inhibits the progression of atherosclerotic lesions independently of its effect on plasma cholesterol concentration.[18] The search for bioavailable ACAT inhibitors has recently been reviewed by Sliscovic.[19]

Our objective was to develop a novel, potent, systemically available ACAT inhibitor that might produce a direct disease-modifying effect by inhibition of the action of the arterial enzyme in addition to any beneficial hypocholesterolemic response occasioned by the inhibition of the intestinal and/or hepatic enzymes. Research in our laboratories identified the 2-(alkylthio)-substituted 4,5-diphenyl-1*H*-imidazole RP 70676 (**7**) as a bioavailable ACAT inhibitor which exhibited a hypocholesterolemic effect in the cholesterol-fed rabbit and reduced

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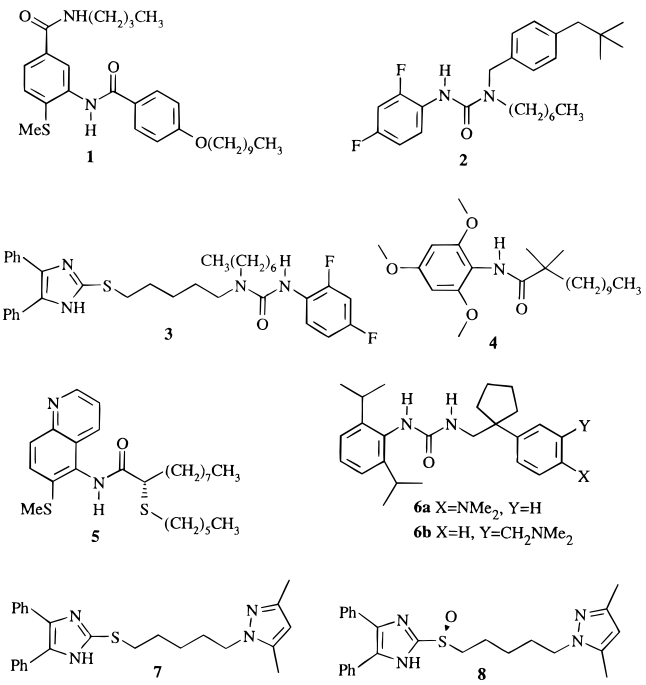
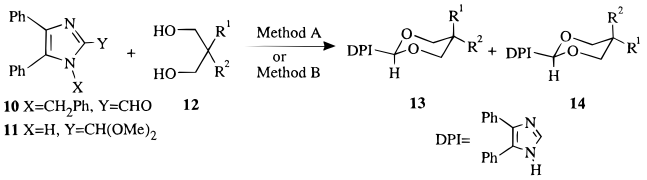
**Chart 1**



the accumulation of cholesterol and cholesterol ester in rabbit aorta and thoracic artery.[20] This compound was found to be a potent *in vitro* inhibitor of ACAT derived from a number of species and tissues including the human hepatic enzyme ($IC_{50}$ = 40 nM). It was observed however that **7** is rapidly metabolized in mammals to the corresponding enantiomeric sulfoxides. Synthesis and testing of each enantiomer showed that only the (*S*)-(−)-isomer RP 73163 (**8**) was responsible for ACAT inhibition. When **8** was tested *in vitro* against the human THP-1 macrophage enzyme[21] however, the level of inhibition was only moderate ($IC_{50}$ = 160−300 nM). This was disappointing since the human arterial macrophage enzyme was considered the ultimate target for an oral antiatherosclerotic ACAT inhibitor. The chemistry and hypolipidemic properties of this compound have recently been reported by these laboratories.[22,23]

This paper outlines some of our investigations in the search for a novel series of systemic ACAT inhibitors to act as a backup to RP 73163 (**8**). The aim was to obtain a compound which would possess a 5−10-fold increase in potency over **8** against the human macrophage enzyme *in vitro* while maintaining a comparable or improved systemic bioavailability in a suitable animal model. Our strategy for modifying the structure of **8** was as follows: (1) The 4,5-diphenyl-1*H*-imidazole pharmacophore was considered essential for ACAT inhibition[1] and would remain unchanged; (2) the effect of varying the terminal dimethylpyrazole ring to other polar/basic heterocycles would be examined; and (3) the sulfoxide linkage would be replaced with a conformationally less flexible group, ideally heterocyclic, that might restrain the side chain in its enzyme-bound conformation and increase inhibitory activity. This replacement would also remove a potential site of metabolic deactivation (oxidation to the sulfone level), previous studies having shown that conversion of the thioether to a sulfone significantly reduced *in vitro* activity.[1]

**Scheme 1.** General Synthesis of 1,3-Dioxanes **13a−d,f,h,i,k−y** and **14d,f**[a]



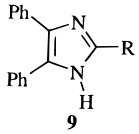
[a] Method A: (i) **10**, **12**, PPTS, toluene, reflux; (ii) Na, $NH_3$, THF. Method B: **11**, **12**, PTSA, toluene, 100−110 °C.

**Identification of the 1,3-Dioxane Pharmacophore.** To determine the functionality that could be tolerated at the 2-position, a number of simple 2-substituted 4,5-diphenyl-1*H*-imidazoles **9** were tested for their ability to inhibit the catalytic activity of rat liver microsomal ACAT (Table 1). It was noted that the carbocyclic compounds **9a**,**b**[24] possessed a good level of inhibitory activity; however, these groups were deemed to be too lipophilic in nature to facilitate oral absorption. To improve water solubility, some cyclic ethers of varying ring size (**9c**−**g**[25−27]) were prepared. The optimum substituents were found to be the six-ring tetrahydropyran-2-yl and 1,3-dioxan-2-yl groups (compounds **9c**,**d**, respectively, $IC_{50}$ ∼ 100 nM). It was decided to initiate a program of work based around the 2-(1,3-dioxan-2-yl)-4,5-diphenyl-1*H*-imidazole pharmacophore[26] due to its potency, its synthetic accessibility, and its symmetrical, hydrophilic properties.

## Chemistry

The general synthesis of the 1,3-dioxanes described in this paper is illustrated in Scheme 1 and their characterization summarized in Table 2. The key step in the synthetic route was the formation of the dioxane ring from the benzyl-protected imidazole-2-carboxaldehyde **10**[26] and a suitably substituted diol, **12** (method

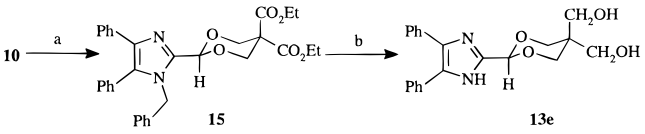
**Table 1.** Preparation and *in Vitro* ACAT Inhibition of 2-Substituted 4,5-Diphenyl-1*H*-imidazoles **9**



| no. | R | prep | formula[a] | mp (°C) | rat liver ACAT $IC_{50}$ (nM)[b] |
|---|---|---|---|---|---|
| **9a** | phenyl | *c* | $C_{21}H_{16}N_2$ | 272−5 | 260 |
| **9b** | cyclohexyl | *d* | $C_{21}H_{22}{}^{e}N_2$ | 227−9 | 910 |
| **9c** | tetrahydropyran-2-yl | *f* | $C_{20}H_{20}N_2O$ | 295−7 | 110 |
| **9d** | 1,3-dioxan-2-yl | *g* | $C_{19}H_{18}N_2O_2$ | 193−4 | 100 |
| **9e** | 1,3-dioxolan-2-yl | *h* | $C_{18}H_{16}N_2O_2$ | 248−50 | 4800 |
| **9f** | tetrahydro-1,3-dioxepin-2-yl | *h* | $C_{20}H_{20}N_2O_2$ | 203−5 | 180 |
| **9g** | furan-2-yl | *i* | $C_{19}H_{14}N_2O$ | 233−4 | 290 |

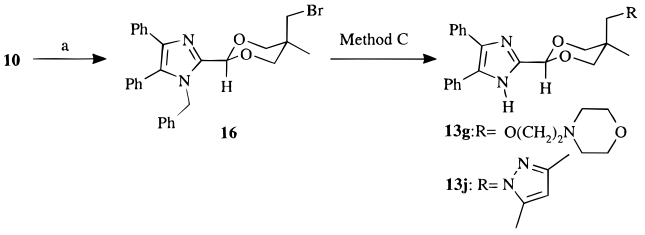
[a] Satisfactory microanalyses were obtained (±0.4%) for C, H, N. [b] ACAT inhibition *in vitro*. [c] Commercially available. [d] See ref 24. [e] Calcd, 7.33; found, 6.60. [f] See ref 25. [g] See ref 26. [h] See the Experimental Section. [i] See ref 27.

**Scheme 2.** Synthesis of Dioxane **13e**[a]



[a] (a) $(HOCH_2)_2C(CO_2Et)_2$, PTSA, toluene, reflux; (b) (i) $LiAlH_4$, THF, (ii) Na, $NH_3$, THF.

**Scheme 3.** Synthesis of Dioxanes **13g**,**i**[a]



[a] (a) $BrCH_2C(CH_3)(CH_2OH)_2$, PPTS, toluene, reflux. Method C: (i) RH, NaH, DMF, reflux; (ii) Na, $NH_3$, THF.

A). Acetal formation was achieved by reaction with an acid catalyst (pyridinium *p*-toluenesulfonate or *p*-toluenesulfonic acid) in an inert solvent (usually toluene) with azeotropic removal of water. Cleavage of the 1-benzyl group to give the required 1*H*-imidazole was carried out with sodium in liquid ammonia.[28] Transacetalization of the unprotected dimethylacetal **11**[26] with diol **12** (method B) was generally used to prepare compounds in which substituents on the 5-position of the dioxane ring were considered to be incompatible with the reductive deprotection step. The 1,3-dioxanes **13e**,**g**,**j** were prepared by an extension of the above general methods (Schemes 2 and 3).

In the majority of the cases, the substituents on the diol **12** were not identical ($R^1 \neq R^2$ and $R^1$ larger than $R^2$), leading to the formation of a mixture of *cis* and *trans* isomers (**13** and **14**, respectively). In general, the *cis* isomer predominated over the *trans* with ratios varying from 2:1 to 10:1. The *cis* and *trans* isomers could routinely be separated by flash chromatography, the *cis* isomer invariably being the more mobile component of the mixture. In a few cases it proved possible to separate the isomers by fractional crystallization. Isomerically pure compounds could be re-equilibrated to *cis*/*trans* mixtures under acid catalysis, but this required an inert solvent at elevated temperatures (usually refluxing toluene). The chemical stability of the 1,3-dioxane ring with respect to acid-mediated isomerization and hydrolysis was crucial if oral administration was to be achieved. We believed that rapid protonation of the imidazole ring in acidic media precluded further protonation of the dioxane ring oxygen atoms. Since this is the first step in the mechanism of acetal hydrolysis,[29] the dioxane is rendered resistant to ring opening.

The assignment of stereochemistry of the dioxane ring was based on the relative chemical shifts in the $^1$H-NMR spectra of the groups at the 5-position. The stereochemistry of **13d** and **14d**, for example, was assigned using this argument (see Figure 1) and confirmed when the X-ray structure of **13d** was acquired. It was assumed that the ring adopts a chair conformation with the bulky imidazole group equatorial. An axial group at the 5-position should resonate downfield relative to an equatorial group on account of the 1,3-diaxial interactions it experiences with the lone pairs on the oxygen atoms. As a result of this deshielding effect by the

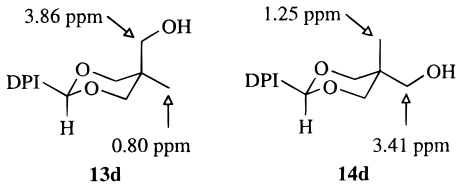
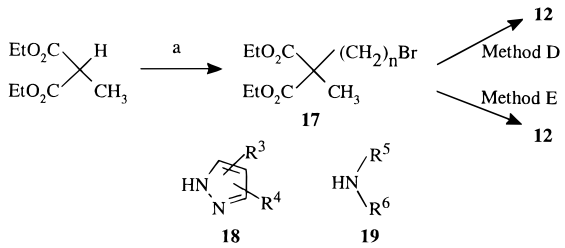


**Figure 1.** Stereochemical assignment of *cis* and *trans* dioxanes by $^1$H NMR.

**Scheme 4.** Synthesis of 1,3-Diols **12f**,**h**,**i**,**k**−**y** ($R^2$ = $CH_3$)[a]



[a] (a) NaH, THF, $Br(CH_2)_nBr$ ($n$ = 3−5), reflux. Method D: (i) NaH, THF, **18** or $HOCH_2Ph$, reflux; (ii) $LiAlH_4$, THF, room temperature. Method E: (i) **19**, THF, reflux; (ii) $LiAlH_4$, THF, reflux.

oxygen lone pairs, the hydroxymethylene protons resonate at 3.86 ppm in the axial position of isomer **13d** and at 3.41 ppm when equatorial as in **14d**. Similarly, the axial methyl protons in **14d** resonate 0.45 ppm further downfield than the equatorial methyl group in **13d** (Figure 1).

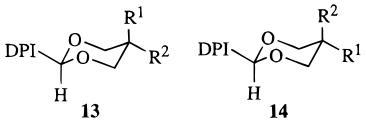
The diol starting materials **12a**,**b**,**d** were commercially available, and **12c** was prepared by a literature method.[30] Scheme 4 outlines the synthesis of the diols **12f**,**h**,**i**,**k**−**y** for which $R^2$ = $CH_3$. Diethyl methyl malonate was alkylated with the appropriate dibromoalkane to give a bromoalkyl diester intermediate (**17**).[31] This was then reacted with either (a) an anion derived from a suitably substituted pyrazole (**18**) or alcohol (method D) or (b) a secondary amine (**19**) in an inert refluxing solvent (method E). The resultant diesters were reduced with lithium aluminum hydride to the required propane-1,3-diol derivatives **12**.

## Biological Results and Discussion

Compounds **13a**−**f** were tested initially for *in vitro* activity against rat liver microsomal ACAT using a standard radioassay.[32] This assay system has been adopted by many research groups as a primary screen for the optimization of ACAT inhibition. The inherent problems associated with handling human tissue dissuaded us from using a human enzyme as a routine screen. The systemic availability of potent inhibitors was then determined in the rabbit following an oral dose of 10 mg/kg, since this was the animal model to be used for *in vivo* evaluation of promising compounds. The results are displayed in Table 3 along with data for RP 70676 (**7**) and RP 73163 (**8**) for the purposes of comparison.

We began by adding simple substituents to the "lead" compound **9d**, the 5-position of the 1,3-dioxane ring being the obvious starting point since the complication of optical isomers would not arise. Substitution by small alkyl groups significantly improved *in vitro* activity against the rat liver enzyme, the 5,5-diethyl analogue **13b** being 8 times and the spirane **13c** 13 times more active than the parent **9d**. These substitutions however were accompanied by a concomitant decrease in peak

**Table 2.** Preparation of 1,3-Dioxanes **13** and **14**



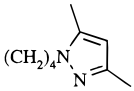
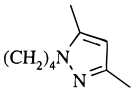
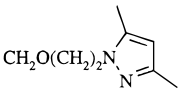
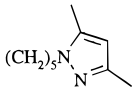
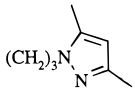
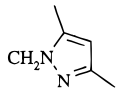
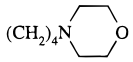
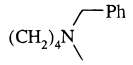
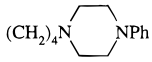
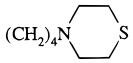
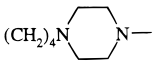
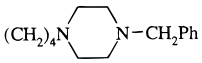
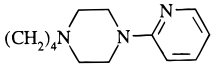
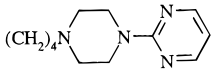
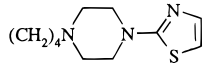
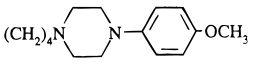
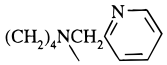
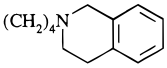
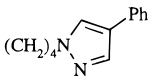
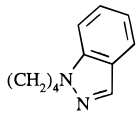
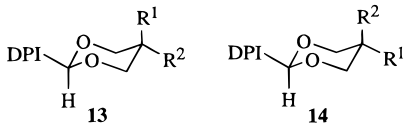

| no. | $R^1$ | $R^2$ | method | formula[a] | mp/°C (solvent)[b] |
|---|---|---|---|---|---|
| **13a** | $CH_3$ | $CH_3$ | A | $C_{21}$[c]$H_{22}N_2O_2$ | 166-7 (T/P) |
| **13b** | $CH_2CH_3$ | $CH_2CH_3$ | A | $C_{23}H_{26}N_2O_2$ | 210-2 (C) |
| **13c** | $-CH_2CH_2CH_2CH_2CH_2-$ | | A | $C_{24}H_{25}N_2O_2$ HCl $0.5H_2O$[d] | 245-7 |
| **13d** | $CH_2OH$ | $CH_3$ | A | $C_{21}$[e]$H_{22}N_2O_3$ | 205-7 (C) |
| **14d** | $CH_2OH$ | $CH_3$ | A | $C_{21}H_{22}N_2O_3$ | 208-10 (C) |
| **13e** | $CH_2OH$ | $CH_2OH$ | *f* | $C_{21}H_{22}N_2O_4$ | 228-30 (C) |
| **13f** |  | $CH_3$ | A | $C_{29}H_{34}N_4O_2$ $0.5C_6H_{12}$ | dec. >180 (C) |
| **14f** |  | $CH_3$ | A | $C_{29}H_{34}N_4O_2$ | 155-6 |
| **13g** |  | $CH_3$ | C | $C_{28}H_{32}N_4O_3$ | 152-4 (C) |
| **13h** |  | $CH_3$ | A | $C_{30}H_{36}N_4O_2$ $0.1C_6H_{12}$ $0.3H_2O$ | 98-100 (C) |
| **13i** |  | $CH_3$ | A | $C_{28}H_{32}N_4O_2$ | 186-9 (EA/C) |
| **13j** |  | $CH_3$ | C | $C_{26}H_{28}N_4O_2$ | 173-4 (T/C) |
| **13k** |  | $CH_3$ | A | $C_{28}H_{35}N_3O_3$ $0.2C_6H_{12}$ | 93-6 (EA/C) |
| **13l** |  | $CH_3$ | A | $C_{32}H_{37}N_3O_2$ | 111-2 (P) |
| **13m** |  | $CH_3$ | A | $C_{34}H_{40}N_4O_2$ | 156-7 (EA/C) |
| **13n** |  | $CH_3$ | B | $C_{28}H_{35}N_3O_2S$[g] | 144-6 (H) |
| **13o** |  | $CH_3$ | A | $C_{29}H_{38}N_4O_2$ | 168-70 (EA) |
| **13p** |  | $CH_3$ | B | $C_{35}H_{42}N_4O_2$ $3C_4H_4O_4$[h] $H_2O$ | 174-6 ($H_2O$) |
| **13q** |  | $CH_3$ | B | $C_{33}H_{39}N_5O_2$ | 120-8 (EA/H) |
| **13r** |  | $CH_3$ | B | $C_{22}H_{38}N_6O_2$ | 155-7 (H) |
| **13s** |  | $CH_3$ | B | $C_{31}H_{33}N_5O_2S$[g] | 152-4 (EA) |
| **13t** |  | $CH_3$ | B | $C_{35}H_{42}N_4O_3$ | 186-9 (EA/C) |
| **13u** |  | $CH_3$ | B | $C_{31}H_{36}N_4O_2$ | 178-82 |
| **13v** |  | $CH_3$ | B | $C_{33}$[i]$H_{37}N_3O_2$ | 138-9 (C) |
| **13w** |  | $CH_3$ | B | $C_{33}H_{34}N_4O_2$ | 158-9 (EA/C) |

**Table 2.** (Continued)

| no. | $R^1$ | $R^2$ | method | formula[a] | mp/°C (solvent)[b] |
|---|---|---|---|---|---|
| **13x** |  | $CH_3$ | B | $C_{31}H_{32}N_4O_2$ | 117-9 (EA/C) |
| **13y** | $(CH_2)_4OCH_2Ph$ | $CH_3$ | B | $C_{31}H_{34}N_2O_3$ | 129-30 (C) |

[a] Satisfactory microanalyses (±0.4%) were obtained for C, H, N unless otherwise indicated. [b] Recrystallization solvent: P = pentane, C = cyclohexane, EA = ethyl acetate, H = heptane. [c] Calcd, 75.42; found, 75.90. [d] Hydrochloride salt (C, H, N, Cl). [e] Calcd, 71.98; found, 71.5. [f] See the Experimental Section. [g] C, H, N, S. [h] Trimaleate salt. [i] Calcd, 78.1; found, 77.5.

**Table 3.** *In Vitro* ACAT Inhibition and Systemic Availability of Compounds **13a**−**f** and **14f**

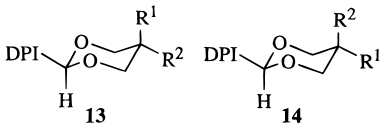


**13** **14**

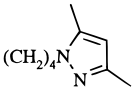
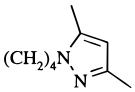
| no. | $R^1$ | $R^2$ | rat liver ACAT $IC_{50}$ (nM)[a] | plasma level[b] $C_{max}$ (nM)[c] |
|---|---|---|---|---|
| **7** | RP 70676 | | 25 | |
| **8** | RP 73163 | | 85 | 2100 |
| **9d** | H | H | 100 | 500 |
| **13a** | $CH_3$ | $CH_3$ | 75 | 300 |
| **13b** | $CH_2CH_3$ | $CH_2CH_3$ | 15 | 150 |
| **13c** | $-CH_2CH_2CH_2CH_2CH_2-$ | | 4 | 40 |
| **13d** | $CH_2OH$ | $CH_3$ | 90 | 8700 |
| **14d** | $CH_2OH$ | $CH_3$ | 110 | 8700 |
| **13e** | $CH_2OH$ | $CH_2OH$ | 275 | 5460 |

[a] ACAT inhibition *in vitro*. [b] In the rabbit following 10 mg/kg dose po. [c] Maximum concentration of compound in the plasma.

**Table 4.** Activity against ACAT from Various Species/Tissues for Compounds **13a,b,f** and **14f**



**13** **14**

| | | | ACAT $IC_{50}$ (nM)[a] | | |
|---|---|---|---|---|---|
| no. | $R^1$ | $R^2$ | rat liver | rabbit liver/artery | human |
| **7** | RP 70676 | | 25 | 40/40 | 40[b] |
| **8** | RP 73163 | | 85 | 75/150 | 240[b]/300[c] |
| **13a** | $CH_3$ | $CH_3$ | 75 | 3500/3700 | 430[b] |
| **13b** | $CH_2CH_3$ | $CH_2CH_3$ | 15 | 20%[d]/− | 1300[b] |
| **13d** | $CH_2OH$ | $CH_3$ | 90 | 4300/4450 | |
| **14d** | $CH_2OH$ | $CH_3$ | 110 | >8500/>8500 | |
| **13f** |  | $CH_3$ | 55 | 20/25 | 75[c] |
| **14f** |  | $CH_3$ | 250 | 20%[d]/20%[d] | >500[c] |

[a] ACAT inhibition *in vitro*. [b] Hepatic microsomal enzyme. [c] THP-1 macrophage enzyme. [d] Inhibition at 0.1 μg/mL.

plasma level in the rabbit, presumably due to the increased lipophilicity. In an effort to improve water solubility, the more hydrophilic hydroxymethyl group was introduced. The two diastereomeric *cis* and *trans* alcohols **13d** and **14d** were both equiactive with **9d** but more importantly showed peak levels of parent compound of 8700 nM in rabbit plasma. This was in excess of the value achieved by RP 73163 (**8**). Reducing lipophilicity further (compound **13e**) led to a marginal decrease in potency but without the expected increase in bioavailability. It was encouraging to observe that the 1,3-dioxane ring was sufficiently chemically and metabolically stable to survive passage through the gut and the liver to allow oral administration.

Despite their moderate *in vitro* potency, the high plasma levels achieved by these simple dioxanes made them interesting compounds for evaluation in a cholesterol-fed rabbit model of atherosclerosis. Prior to *in vivo* testing however, compounds **13a**,**b** and the isomers **13d**/**14d** were screened *in vitro* against rabbit liver and arterial microsomal ACAT.[22] The results are presented in Table 4 along with values for **7** and **8** for the purposes of comparison. A significant species selectivity was observed for the dioxanes with those compounds examined being at least 50 times less active against the rabbit enzymes than the rat liver enzyme under comparable assay conditions. To answer the question as to which, if either, species enzyme was representative of human ACAT, the dioxanes **13a**,**b** were screened *in vitro* against the human liver microsomal enzyme[22] (Table 4). This highlighted a further species difference with both of these compounds being sufficiently weaker inhibitors of the human liver than the rat liver enzyme. These dioxanes should be contrasted to RP 70676 (**7**) which inhibits the rat, rabbit, and human liver enzymes at a similar level with an $IC_{50}$ of 20−40 nM. We hypothesized therefore that the rat liver enzyme was particularly sensitive to inhibition by the dioxanyldiphenylimidazole moiety but that the pyrazolylalkyl group present in **7** was required for good *in vitro* inhibition of the rabbit and human liver enzymes. This prompted the synthesis of the isomeric compounds **13f** and **14f** which contained a (3,5-dimethylpyrazol-1-yl)-butyl substituent on the 5-*cis* and 5-*trans* positions of the 1,3-dioxane ring. The *cis* dioxane **13f** was found to be a potent inhibitor of the rat liver, rabbit liver, and rabbit arterial enzymes (20−55 nM); the *trans* isomer **14f** however was only moderately active against rat liver ACAT and virtually inactive against the rabbit enzymes (Table 4).

In the light of the unexpected species selectivity exhibited by the dioxanyl compounds, the human THP-1 macrophage enzyme[21] was adopted as the tool for primary *in vitro* screening of synthetic molecules since this enzyme was the desired target of an oral antiatherosclerotic ACAT inhibitor. A cellular and a microsomal preparation of the THP-1 enzyme was examined with similar levels of ACAT inhibition being found for standard compounds in both assay systems. It could be argued that a cellular *in vitro* assay would be desirable since it takes into account the ability of a compound to enter the macrophage as well as its inhibitory properties. In general it has been our experience with the diphenylimidazole series of inhibitors that cellular and microsomal activity correlates well with few

exceptions. In this instance, a cellular ACAT assay was found to be most appropriate for routine screening. The *cis* dioxane **13f** inhibited the THP-1 macrophage enzyme with an $IC_{50}$ of 75 nM, whereas the *trans* isomer **14f** was at least 10-fold less potent (Table 4). Since RP 73163 (**8**) was only moderately active against this enzyme with an $IC_{50}$ of 160−300, it was felt that **13f** was a good starting point for further optimization.

The pyrazolylbutyl group appeared to be crucial for activity against human enzymes, and so the nature of this heteroarylalkyl group on the 5-*cis* position of **13f** was explored by varying the terminal heterocycle and the connecting chain. An *ex vivo* bioassay using rat plasma samples taken 90 min after dosing with test compound at 10 mg/kg po (see Biological Methods) was developed to allow routine estimation of systemic bioavailability. This method would allow us to compare the systemic bioavailability of test compounds with RP73163 (**8**) and obtain a rank order. A very high plasma level of 7570 nM (25 times the $IC_{50}$ for THP-1 enzyme inhibition) was measured for **8** in this assay. Results from *in vitro* screening and the *ex vivo* bioassay are displayed in Table 5. The *trans* dioxane isomers, when they could be obtained, were always found to be 10−20 times less potent than the corresponding *cis* compounds (data not shown).

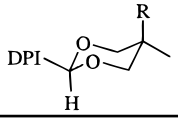
Dioxanes **13g**−**j** were synthesized to vary the connecting butyl group. A four- or five-carbon atom chain appeared to be the optimum for linking the terminal pyrazole to the dioxane ring, **13f**,**h** being equipotent. The plasma levels of both of these compounds in the *ex vivo* bioassay were estimated to be 20−25 times their $IC_{50}$ for enzyme inhibition. Attempts to introduce polar groups into the chain to improve water solubility as in the ether **13g** were deleterious to potency.

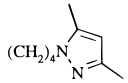
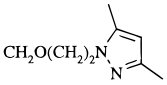
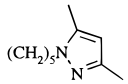
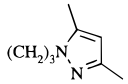
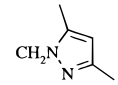
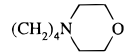
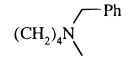
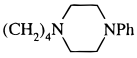
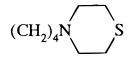
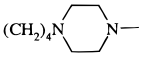
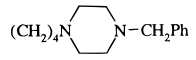
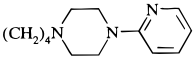
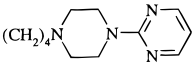
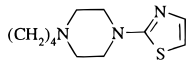
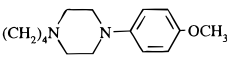
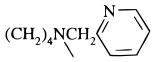
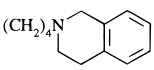
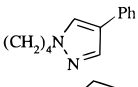
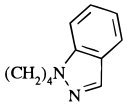
The terminal heterocycle could be replaced by a variety of basic groups, the most active being the morpholine **13k**, the benzylamine **13l**, and the arylpiperazine **13m**. We decided to focus on this terminal position as the most likely area for optimization of *in vitro* potency and/or bioavailability maintaining the connecting group as butyl to minimize lipophilicity.

The morpholine **13k** was found to achieve a high plasma level of 1450 nM in the bioassay but was only moderately active against human macrophage ACAT. The morpholine ring was therefore systematically varied to other cyclic amines. The thiomorpholine **13n** proved to be an excellent replacement in terms of potency ($IC_{50}$ = 70 nM) and systemic availability showing a plasma level of 2280 nM. Oxidation of this compound to the more polar sulfoxide and sulfone levels abolished activity (data not shown). The *N*-methylpiperazine **13o** was poorly active, although reintroduction of an aromatic ring as in **13p** restored inhibitory potency but not systemic availability. The lipophilic *N*-arylpiperazine **13m** was similarly very poorly bioavailable although moderately potent *in vitro*. Introduction of heteroatoms into the aryl ring (compounds **13q**−**s**) had little effect on *in vitro* activity but unfortunately did not lead to an improvement in systemic availability despite the decrease in lipophilicity.

The effect of substituents in the phenyl ring of **13m** was examined, and it was found that H-bond acceptor groups (F, $NO_2$, OMe) at the *para* position generally improved activity. The methoxy derivative **13t** was the most potent dioxane ACAT inhibitor obtained against the human macrophage enzyme *in vitro*. The plasma level achieved by this compound was low (~400 nM) when compared to that of **8**, but this was still 40 times the $IC_{50}$ for inhibition of the THP-1 enzyme.

**Table 5.** *In Vitro* ACAT Inhibition and Systemic Availability of Compounds **13f**−**y**




| no. | R | human macrophage ACAT[a] $IC_{50}$[b] (nM) | plasma concentration[c] (nM) |
|---|---|---|---|
| **8** | RP 73163 | 300 | 7570 |
| **13f** |  | 75 | 1820 |
| **13g** |  | 30%[d] | ND[e] |
| **13h** |  | 60 | 1325 |
| **13i** |  | 30%[d] | ND |
| **13j** |  | 10%[d] | ND |
| **13k** |  | 300 | 1450 |
| **13l** |  | 220 | 445 |
| **13m** |  | 70 | 820 |
| **13n** |  | 70 | 2280 |
| **13o** |  | 20%[d] | ND |
| **13p** |  | 90 | 730 |
| **13q** |  | 105 | 220 |
| **13r** |  | 75 | 615 |
| **13s** |  | 50 | 185 |
| **13t** |  | 10 | 400 |
| **13u** |  | 50 | 0 |
| **13v** |  | 60 | 225 |
| **13w** |  | 110 | 570 |
| **13x** |  | 130 | 495 |
| **13y** | $(CH_2)_4OCH_2Ph$ | 300 | ND |

[a] THP-1 macrophage enzyme. [b] ACAT inhibition *in vitro*. [c] In the rat 90 min following 10 mg/kg dose po. [d] Inhibition at 300 nM. [e] Not determined.

The pyridyl derivative **13u** was 4 times more potent than the parent benzylamine **13l**, but compound was not detectable in rat plasma following oral dosing. It was thought that *in vivo* N-demethylation of these amines might be occurring, but the potentially metabolically more stable tetrahydroisoquinoline **13v** was still poorly bioavailable in the rat.

Phenyl substitution at the terminal position appeared to be beneficial to *in vitro* potency; however, introduction of aromatic groups into the pyrazole ring (compounds **13w**,**x**) did not produce any significant improvement in activity in this series and led to poor oral absorption, as shown in the bioassay. It was thought unusual that the terminal heterocyclic pharmacophore could encompass a neutral pyrazole molecule and a series of basic amine derivatives. It was postulated therefore that the amines were binding to ACAT in their un-ionized forms. This hypothesis was partially confirmed by the observation that the benzyloxy derivative **13y** and the benzylamine **13l** were equipotent against human macrophage ACAT.

## Conclusion

In our search for therapeutically useful bioavailable ACAT inhibitors for the treatment of atherosclerosis, we have discovered the 2-(1,3-dioxan-2-yl)-4,5-diphenyl-1*H*-imidazole system to be a potent pharmacophore for enzyme inhibition. A series of these dioxanes (**13** and **14**) were prepared (Table 2) and their biological activity and oral bioavailability assayed (Tables 3 and 5). Our goal was to obtain a compound which was 5−10 times more potent than the sulfoxide RP 73163 (**8**) against the human macrophage enzyme with comparable or improved systemic availability. Compound **13** substituted at the 5-position of the dioxane ring with simple alkyl groups were potent inhibitors *in vitro* ($IC_{50}$ < 100 nM) of the rat liver microsomal enzyme and possessed good oral bioavailability in the rabbit but were significantly less active *in vitro* against the human enzyme. For potent inhibition of the human macrophage enzyme, a more complex pyrazolylalkyl or aminobutyl substituent was required at the 5-*cis* position. The corresponding *trans* isomers **14** were generally much less active *in vitro*. Human ACAT has only recently been purified to homogeneity, cloned, and expressed and a sequence obtained.[33] Until this analysis is extended to the rat and rabbit enzymes, the structural origin of this species selectivity will remain unknown. By varying the nature of the terminal heterocyclic group, we were able to obtain extremely potent *in vitro* inhibitors of human macrophage ACAT, such as the (4-methoxyphenyl)-piperazine **13t** ($IC_{50}$ = 10 nM). *In vitro* potency however could only be increased at the expense of oral bioavailability; we were not able to obtain plasma levels in the rat for the dioxane series following oral dosing comparable to those obtained for RP 73163 (**8**). For a number of moderately potent compounds (the pyrazoles **13f**,**h** and the thiomorpholine **13n**) however, we were able to demonstrate plasma levels of biologically active compound after oral dosing in the rat significantly in excess of their $IC_{50}$ for enzyme inhibition. We hope to use this series of compounds to further test the hypothesis that an orally bioavailable ACAT inhibitor will have a direct disease-modifying effect at the artery wall on the formation and progression of atherosclerosis.

During the course of this research, the development of the sulfoxide RP 73163 (**8**) as an antiatherosclerotic and hypocholesterolemic agent was halted due to its adrenal toxicity in the dog.[22] This adverse side effect was also observed by scientists at Parke-Davis for PD-132301 (**6a**). The toxicity of **6a** was reported to be related to inhibition of mitochondrial respiration in adrenal cells[19] and may have been overcome through the synthesis of the methyleneamino analogue **6b** which is devoid of adrenal toxicity.[15,19] The higher basicity and lower lipophilicity of **6b** are the only obvious differences to **6a** since they are equipotent *in vitro* against the rabbit intestinal enzyme. Whether the adrenal toxicity of RP 73163 (**8**) is mechanism or compound related is unclear at present. We hopt to address this problem using the 1,3-dioxane series of ACAT inhibitors **13** detailed above since the structural and overall physicochemical differences to **8** may lead to different side effect profiles. The results of *in vivo* and toxicological studies on these dioxane compounds will be the subject of furture communications from these laboratories.

## Experimental Section

**Biological Methods. ACAT Assays: (1) Microsomal Assay.** ACAT activity was determined using procedures previously described in the literature.[22,32] Inhibitors were added as solutions in DMSO (final solvent concentration = 0.5%, v/v). For calculation of $IC_{50}$ values (the concentration required to inhibit ACAT activity by 50%), each compound was examined in triplicate at five concentrations.

**(2) Cellular Assay.** Human THP-1 cells (purchased from the ECACC at Porton Down) were routinely cultured in RPMI-1640 medium supplemented with 50 $\mu$M mercaptoethanol and 10% (v/v) fetal calf serum. THP-1 cells ($1.5 \times 10^6$ cells) were differentiated by incubation for 72 h in 2 mL of medium (as above) containing 80 nM phorbol 12-myristate 13-acetate (PMA). The cells were loaded with cholesterol by incubation for a further 24 h in 1 mL of fresh medium containing 80 nM PMA and 100 ng/mL acetylated human LDL. ACAT activity was determined over the final 5 h of the incubation period following addition of [$^{14}$C]oleate/albumin complex to give a final concentration of 200 $\mu$M oleate (with a specific activity of 5 $\mu$Ci/$\mu$mol) and 100 $\mu$M albumin. Test compounds or vehicle control (0.2%, v/v, dimethyl sulfoxide, ethanol, or distilled water) were added for the final 6 h of the 24 h incubation period. ACAT activity was measured as the incorporation of [$^{14}$C]oleate into [$^{14}$C]cholesteryl oleate per microgram of cell protein during the 5 h incubation period. Cellular lipids (including [$^3$H]cholesterol oleate added as an internal standard) were extracted using the Folch procedure;[34] labeled cholesteryl oleate was separated by high-performance thin layer chromatography and quantitated by dual label liquid scintillation counting. ACAT activity was calculated as nanomoles of [$^{14}$C]oleate incorporated into [$^{14}$C]cholesteryl oleate per microgram of cell protein. Results were calculated as the mean ± SEM of four experiments. $IC_{50}$ values, the concentration of compound required to inhibit ACAT activity by 50%, were calculated from their inhibition curves.

**Oral Bioavailability: (1) Rabbit.** Three male NZW rabbits were dosed with the test compound at 10 mg/kg po. Blood samples were obtained predose and at intervals up to 24 h. The corresponding plasma samples were assayed following solvent extraction by reverse phase HPLC with UV detection.

**(2) Rat.** The microsomal assay was also used to determine systemic bioavailability by measuring ACAT inhibitory activity in plasma obtained from treated rats.[22] Compounds were suspended in 1% sodium carboxymethyl cellulose and 0.2% Tween and administered orally (2 mL/kg) to male Sprague−Dawley rats at a dose of 10 mg/kg. Animals were sacrificed after 90 min and blood samples obtained. Aliquots of plasma (5−20 $\mu$L) were preincubated with rat hepatic microsomes in phosphate buffer (pH 7.4) for 20 min prior to the addition to radiolabeled oleolyl CoA. The ACAT activity of the plasma samples was determined as above. Concentration−response curves were obtained by incubating microsomes with various

concentrations of test compound (dissolved in DMSO) in the presence of the appropriate volume of plasma from vehicle-treated rats using the above conditions. These standard curves were used to estimate the concentration of compound in the plasma sample.

**Chemical Methods.** Reagents, starting materials, and solvents were purchased from common commercial suppliers and used as received or distilled from the appropriate drying agent. All organic solutions were dried over magnesium sulfate and concentrated at reduced pressure under aspirator vacuum using a Buchi rotary evaporator. Reaction products were purified, when necessary, by flash chromatography on silica gel (40−63 $\mu$m) with the solvent system indicated. Yields are not optimized. Melting points were determined on a Gallenkamp 595 apparatus and are uncorrected. $^1$H-NMR spectra were acquired on Varian VXR-400 and XL-200 spectrometers; peak positions are reported in parts per million relative to internal tetramethylsilane on the $\delta$ scale. Elemental analyses were performed by the Analytical Department at Rhone-Poulenc Rorer. The structure and purity of all compounds were confirmed by microanalytical and/or spectroscopic methods. Satisfactory microanalyses (±0.4%) were obtained for C, H, N unless otherwise stated.

**2-(1,3-Dioxolan-2-yl)-4,5-diphenyl-1*H*-imidazole (9e).** A mixture of **11** (1.24 g, 5 mmol), ethylene glycol (5 mL), *p*-toluenesulfonic acid monohydrate (0.12 g, 0.6 mmol), and toluene (120 mL) was heated at reflux for 18 h with azeotropic removal of water. The solid which separated on cooling was collected and purified by flash chromatography (dichloromethane−methanol, 98:2) on silica gel to give **9e** as a white solid (0.4 g, 27%) after recrystallization from acetonitrile: mp 248−50 °C; $^1$H NMR (200 MHz) ($CDCl_3$) 4.06 (m, 2H), 4.24 (m, 2H), 5.98 (s, 1H), 7.28−7.50 (m, 10H). Anal. ($C_{18}H_{16}N_2O_2$) C, H, N.

**2-(4,5,6,7-Tetrahydro-1,3-dioxepin-2-yl)-4,5-diphenyl-1*H*-imidazole (9f).** A mixture of **10** (10 g, 29.5 mmol), 2-butene-1,4-diol (17 g), pyridinium *p*-toluenesulfonate (0.5 g), and toluene (250 mL) was heated at reflux for 18 h with azeotropic removal of water. The reaction mixture was cooled and washed with water (3 × 100 mL) and the organic layer dried and concentrated. The residue was recrystallized from ethyl acetate to give 1-benzyl-2-(4,7-dihydro-1,3-dioxepin-2-yl)-4,5-diphenylimidazole as a white solid (10 g, 83%): mp 168−70 °C.

A portion (5.0 g, 12 mmol) of this material was stirred at room temperature in ethyl acetate (300 mL) with 5% palladium on carbon (0.8 g) under an atmosphere of hydrogen. After 30 min, the reaction mixture was filtered through a pad of diatomaceous earth and concentrated. The residue was recrystallized from ethyl acetate to give 1-benzyl-2-(4,5,6,7-tetrahydro-1,3-dioxepin-2-yl)-4,5-diphenylimidazole as a white solid (2.5 g, 50%): mp 149−51 °C. Anal. ($C_{27}H_{26}N_2O_2$) C, H, N.

This material was dissolved in dry tetrahydrofuran (200 mL), and approximately 400 mL of liquid ammonia was condensed into the flask. Sodium metal (0.63 g, 27 mmol) was added portionwise over 15 min to the stirred, refluxing reaction mixture. The reaction mixture was quenched with solid ammonium chloride (6.0 g) and the ammonia allowed to evaporate. The residue was partitioned between saturated aqueous ammonium chloride (200 mL) and ethyl acetate (200 mL) and the aqueous layer extracted with a further 3 × 200 mL of ethyl acetate. The combined organics were washed with water (4 × 200 mL), dried, and concentrated. The residue was recrystallized from toluene to give **9f** (1.6 g, 94%) as a colorless solid: mp 203−5 °C; $^1$H NMR (200 MHz) ($CDCl_3$) 1.84 (m, 4H), 3.96 (m, 4H), 5.84 (s, (1H), 7.26−7.50 (m, 10H). Anal. ($C_{20}H_{20}N_2O_2$) C, H, N.

**(*r*)-2-(4,5-Diphenyl-1*H*-imidazol-2-yl)-5-*cis*-(hydroxymethyl)-5-methyl-1,3-dioxane (13d) and (*r*)-2-(4,5-Diphenyl-1*H*-imidazol-2-yl)-5-*trans*-(hydroxymethyl)-5-methyl-1,3-dioxane (14d). Method A.** A mixture of **10** (67.7 g, 174 mmol), 1,1,1-tris(hydroxymethyl)ethane (120 g), pyridinium *p*-toluenesulfonate (2.0 g), and toluene (500 mL) was heated at reflux for 18 h with azeotropic removal of water. The reaction mixture was cooled and washed with water (4 × 100 mL) and brine (3 × 50 mL) and the organic layer dried and concentrated. The residue was subjected to flash chromatography (ethyl acetate−cyclohexane, 1:1) to give 1-benzyl-(*r*)-2-(4,5-diphenylimidazol-2-yl)-5-*cis*-(hydroxymethyl)-5-methyl-1,3-dioxane as a white solid (15 g, 20%) after recrystallization from cyclohexane: mp 224−6 °C.

There was then eluted 1-benzyl-(*r*)-2-(4,5-diphenylimidazol-2-yl)-5-*trans*-(hydroxymethyl)-5-methyl-1,3-dioxane which was obtained as a fluffy white solid (1 g) after recrystallization from cyclohexane: mp 198−200 °C.

The *cis* isomer (3.0 g, 6.8 mmol) was dissolved in dry tetrahydrofuran (50 mL), and approximately 200 mL of liquid ammonia was condensed into the flask. Sodium metal (0.62 g, 27 mmol) was added portionwise to the stirred, refluxing reaction mixture over 40 min. The reaction was quenched with 8.0 g of solid ammonium chloride and the ammonia allowed to evaporate. The residue was partitioned between dichloromethane (250 mL) and brine (100 mL) and the organic layer washed with brine (100 mL) and water (100 mL). The organic layer was dried and concentrated to leave a residue which was recrystallized from cyclohexane to give **13d** (1.8 g, 76%) as a white solid: mp 205−7 °C; $^1$H NMR (200 MHz) ($CDCl_3$) 0.8 (s, 3H), 3.62 (d, $J$ = 12 Hz, 2H), 3.86 (s, 2H), 4.07 (d, $J$ = 12 Hz, 2H), 5.66 (s, 1H), 7.28−7.56 (m, 10H). Anal. ($C_{21}H_{22}N_2O_3$) C, H, N.

The *trans* isomer was debenzylated in a similar manner to give **14** as a white solid after recrystallization from cyclohexane: mp 208−10 °C; $^1$H NMR (200 MHz) ($CDCl_3$) 1.25 (s, 3H), 3.41 (s, 2H), 3.90 (m, 4H), 5.65 (s, 1H), 7.26−7.50 (m, 10H). Anal. ($C_{21}H_{22}N_2O_3$) C, H. N.

**1-Benzyl-2-[5,5-bis(ethoxycarbonyl)-1,3-dioxan-2-yl]-4,5-diphenylimidazole (15).** A mixture of **10** (16.8 g, 50 mmol), diethyl bis(hydroxymethyl)malonate (11.0 g, 50 mmol), and pyridinium *p*-toluenesulfonate (0.5 g) was heated at reflux for 18 h with azeotropic removal of water. A further equivalent of diethyl bis(hydroxymethyl)malonate was added and reflux continued for 18 h. The reaction mixture was cooled and washed with water (3 × 100 mL) and brine before being dried and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane−ethyl acetate, 2:1) to give **15** as a colorless solid (12 g, 46%) after recrystallization from cyclohexane: mp 129−31 °C; $^1$H NMR (400 MHz) ($CDCl_3$) 1.01 (t, $J$ = 8 Hz, 3H), 1.25 (t, $J$ = 8 Hz, 3H), 3.64 (d, $J$ = 12 Hz, 2H), 3.93 (q, $J$ = 8 Hz, 2H), 4.13 (d, $J$ = 12 Hz, 2H), 4.18 (q, $J$ = 8 Hz, 2H), 5.21 (s, 2H), 5.60 (s, 1H), 6.82−7.43 (m, 15H). Anal. ($C_{32}H_{32}N_2O_6$) C, H. N.

**2-[5,5-Bis(hydroxymethyl)-1,3-dioxan-2-yl]-4,5-diphenyl-1*H*-imidazole (13e).** To a stirred solution of **15** (6.0 g, 10.3 mmol) in dry tetrahydrofuran (200 mL) under an atmosphere of nitrogen was added a 1.0 M solution of lithium aluminum hydride in tetrahydrofuran (16 mL, 16 mmol) dropwise over 20 min. The reaction mixture was stirred at ambient temperature for 2 h and the reaction quenched by the dropwise addition of 3% aqueous sodium hydroxide (8 mL). The resultant precipitate was removed by filtration through diatomaceous earth. The filtrate was concentrated and the resultant residue recrystallized from ethyl acetate to give 1-benzyl-2-[5,5-bis(hydroxymethyl)-1,3-dioxan-2-yl]-4,5-diphenylimidazole (3.45 g, 73%) as a colorless solid: mp 186−8 °C. Anal. ($C_{28}H_{28}N_2O_4$) C, H, N.

This material (2.9 g, 6.4 mmol) was dissolved in dry tetrahydrofuran (20 mL), and approximately 300 mL of liquid ammonia was condensed into the flask. Sodium metal (0.68 g, 30 mmol) was added portionwise to the stirred, refluxing reaction mixture over 50 min. The reaction was quenched with 6.0 g of solid ammonium chloride and the ammonia allowed to evaporate. Saturated aqueous ammonium chloride solution (20 mL) was added and the mixture extracted with dichloromethane (4 × 100 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL) before drying and concentration. The residue was recrystallized from cyclohexane to give **13e** (1.5 g, 65%) as a colorless solid: mp 228−30 °C; $^1$H NMR (200 MHz) (DMSO) 3.32 (s, 2H), 3.41 (s, 2H), 3.90 (m, 4H), 5.65 (s, 1H), 7.26−7.50 (m, 10H). Anal. ($C_{21}H_{22}N_2O_4$) C, H, N.

**(*r*)-2-(4,5-Diphenyl-1*H*-imidazol-2-yl)-5-methyl-5-*cis*-[4-(thiomorpholin-1-yl)but-1-yl]-1,3-dioxane (13n). Method B.** A mixture of **11** (2.94 g, 10 mmol), **12n** (2.97 g, 12 mmol),

and *p*-toluenesulfonic acid (2.28 g, 12 mmol) in toluene (150 mL) was heated at 110 °C for 30 min. The reaction mixture cooled, diluted with ethyl acetate (100 mL), and treated with 200 mL of 10% aqueous potassium carbonate before stirring a further 20 min at ambient temperature. The organic layer was separated, washed with water (250 mL), dried, and concentrated. The residue was purified by flash chromatography on silica gel (dichloromethane−methanol, 19:1) to give the *cis* isomer **13n** as a white solid (1.5 g, 31%) after recrystallization from heptane: mp 144−6 °C; $^1$H NMR (400 MHz) ($CDCl_3$) 0.73 (s, 3H), 1.30 (m, 2H), 1.55 (m, 2H), 1.72 (m, 2H), 2.44 (br t, $J$ = 6 Hz, 2H), 2.72 (br m, 8H), 3.63, (d, $J$ = 12 Hz, 2H), 5.66 (s, 1H), 7.25−7.65 (br m, 10H). Anal. ($C_{28}H_{35}N_2O_2S$) C, H, N, S.

**1-Benzyl-(*r*)-2-(4,5-diphenylimidazol-2-yl)-5-*cis*-(bromomethyl)-5-methyl-1,3-dioxane (16).** A mixture of **10** (33.8 g, 100 mmol), 2-(bromomethyl)-2-methylpropane-1,3-diol[35] (27.5 g, 150 mmol), pyridinium *p*-toluenesulfonate (2.0 g), and toluene (500 mL) was heated at reflux overnight. The reaction mixture was cooled, washed with water (3 × 250 mL), dried, and concentrated. The residue was recrystallized from 2-propanol to give **16** as a white solid (33.3 g, 66%): mp 141 °C; $^1$H NMR (400 MHz) ($CDCl_3$) 0.82 (s, 3H), 3.57 (s, 2H), 3.70 (d, $J$ = 12 Hz, 2H), 4.09 (d, $J$ = 12 Hz, 2H), 5.28 (s, 2H), 5.78 (s, 1H), 6.90−7.47 (m, 15H). Anal. ($C_{28}H_{27}BrN_2O_2$) C, H, N.

**(*r*)-2-(4,5-Diphenyl-1*H*-imidazol-2-yl)-5-*cis*-[(3,5-dimethylpyrazol-1-yl)methyl]-5-methyl-1,3-dioxane (13j). Method C.** To a stirred suspension of sodium hydride (1.76 g of a 60% dispersion, w/w, in mineral oil, 44 mmol) in dry dimethylformamide (250 mL) was added 3,5-dimethylpyrazole (4.23 g, 44 mmol) in small portions. After stirring at ambient temperature for 30 min, **16** (20.1 g, 40 mmol) was added in one portion and the reaction mixture stirred at reflux for 45 min. After cooling, the mixture was concentrated and water (500 mL) added. The resultant solid was collected and recrystallized from ethanol to give 1-benzyl-(*r*)-2-(4,5-diphenylimidazol-2-yl)-5-*cis*-[(3,5-dimethylpyrazol-1-yl)methyl]-5-methyl-1,3-dioxane as white solid (13.0 g, 63%): mp 214−6 °C. Anal. ($C_{33}H_{34}N_4O_2$) C, H, N.

This material (10 g, 19.3 mmol) was dissolved in tetrahydrofuran (50 mL) and approximately 250 mL of liquid ammonia condensed into the flask. Sodium metal was added to the stirring, refluxing reaction mixture until TLC showed that no starting material was present. Solid ammonium chloride (5 g) was added and the ammonia allowed to evaporate. The residue was partitioned between dichloromethane (100 mL) and water (100 mL) and the organic layer dried and concentrated. The residue was recrystallized from toluene/cyclohexane to give **13j** as a white powder (2.88 g, 35%: mp 173−4 °C; $^1$H NMR (400 MHz) ($CDCl_3$) 0.8 (s, 3H), 2.22 (s, 3H), 2.27 (s, 3H), 3.68 (d, $J$ = 12 Hz, 2H), 4.05 (d, $J$ = 12 Hz, 2H), 4.30 (s, 2H), 5.72 (s, 1H), 5.80 (s, 1H), 7.18−7.60 (m, 10H). Anal. ($C_{26}H_{28}N_4O_2$) C, H, N.

**Diethyl (4-Bromobutyl)methylmalonate (17, *n* = 4).** A solution of diethyl methylmalonate (87 g, 500 mmol) in dry tetrahydrofuran (700 mL) was treated portionwise with sodium hydride (19.2 g of a 60% dispersion, w/w, in mineral oil, 500 mmol) with cooling. The reaction mixture was stirred for 30 min at ambient temperature and treated with 1,4-dibromobutane (162 g, 750 mmol). The mixture was heated to reflux for 3 h and cooled before being concentrated to dryness. The residue was partitioned between diethyl ether (500 mL) and water (500 mL) and the organic layer dried and concentrated. The residue was purified by fractional distillation to give **17** ($n$ = 4) as a colorless oil (98 g, 63%): bp 104−16 °C/0.2 mbar; $^1$H NMR (400 MHz) ($CDCl_3$) 1.23 (m, 2H), 1.25 (t, $J$ = 8 Hz, 6H), 1.43 (s, 3H), 1.88 (m, 4H), 3.41 (t, $J$ = 6 Hz, 2H), 4.18 (q, $J$ = 8 Hz, 4H).

The bromo malonates **17** ($n$ = 3 and 5) were prepared in a similar manner from the appropriate dibromoalkane.

**2-[4-(3,5-Dimethylpyrazol-1-yl)but-1-yl]-2-methylpropane-1,3-diol (12f). Method D.** To a stirred suspension of sodium hydride (6 g of a 60% dispersion, w/w, in mineral oil, 150 mmol) in dry tetrahydrofuran (250 mL) was added 3,5-dimethylpyrazole (14.4 g, 150 mmol) in small portions. After stirring at ambient temperature for 15 min, **17** ($n$ = 4) (50.7 g, 170 mmol) was added in one portion and the reaction mixture stirred at reflux for 8 h. The reaction mixture was concentrated and partitioned between diethyl ether (300 mL) and water (150 mL). The organic layer was washed with water (2 × 100 mL), dried, and concentrated. The residue was purified by flash chromatography (diethyl ether−pentane, 1:1) to give diethyl [4-(3,5-dimethylpyrazol-1-yl)but-1-yl]methylmalonate as a colorless oil (28.8 g, 52%). Anal. ($C_{17}H_{24}N_2O_4$) C, H, N.

This material (28.8 g, 90 mmol) was dissolved in dry tetrahydrofuran (50 mL) and added dropwise to a stirred 1.0 M solution of lithium aluminum hydride (110 mL, 110 mmol). The reaction mixture was stirred at ambient temperature for 18 h and then cooled to 0 °C. A 3% aqueous sodium hydroxide solution (22 mL) was added dropwise and the mixture stirred for 15 min before being filtered through a pad of diatomaceous earth. The filtrate was dried and concentrated to leave **12f** as an oil (21.2 g, 98%): $^1$H NMR (400 MHz) ($CDCl_3$) 0.72 (s, 3H), 1.29 (m, 2H), 1.62 (m, 2H), 1.78 (m, 2H), 2.22 (s, 3H), 2.28 (s, 3H), 3.56 (m, 4H), 4.12 (t, $J$ = 6 Hz, 2H), 5.83 (s, 1H).

**2-[4-(Thiomorpholin-1-yl)but-1-yl]-2-methylpropane-1,3-diol (12n). Method E.** A mixture of thiomorpholine (21 g, 200 mmol), **17** ($n$ = 4) (32.7 g, 100 mmol), and tetrahydrofuran (200 mL) was heated at reflux for 18 h before being cooled and concentrated. The residue was partitioned between ethyl acetate (250 mL) and 5% aqueous potassium carbonate (250 mL) and the organic layer dried and concentrated. The residue was purified by fractional distillation to give diethyl [4-(thiomorpholin-1-yl)but-1-yl]methylmalonate (24.2 g, 72%) as a yellow oil: bp 150−2 °C/0.2 Torr.

This material (24.2 g, 73 mmol) was dissolved in dry tetrahydrofuran (20 mL) and added dropwise to a solution of lithium aluminum hydride (3.88 g, 102 mmol) in tetrahydrofuran (350 mL). The reaction mixture was heated to reflux for 4 h and cooled to 0 °C and the reaction quenched dropwise with 3% aqueous sodium hydroxide (14 mL). Stirring was continued for 1 h at ambient temperature and the reaction mixture filtered through a pad of diatomaceous earth. The filtrate was dried and concentrated to leave **12n** as a white solid (15.5 g, 86%): mp 54−6 °C; $^1$H NMR (400 MHz) ($CDCl_3$) 0.78 (s, 3H), 1.60 (br m, 4H), 1.51 (m, 2H), 2.40 (t, $J$ = 6 Hz, 2H), 2.70 (br s, 8H), 3.51 (s, 4H), 3.65, (br m, 2H).

**1-(Thiazol-2-yl)piperazine (19r).** A mixture of 2-bromothiazole (19.9 g, 121 mmol), piperazine (20.9 g, 243 mmol), and *n*-butanol (400 mL) was heated at reflux for 18 h. The reaction mixture was cooled, concentrated, and treated with 150 mL of 10% aqueous potassium carbonate. The mixture was extracted with ethyl acetate (4 × 250 mL), and the combined extracts were dried and concentrated to leave **19** as a brown oil (17.9 g, 88%) which was used without further purification: $^1$H NMR (400 MHz) ($CDCl_3$) 2.99 (m, 4H), 3.47 (m, 4H), 6.58 (d, $J$ = 3 Hz, 1H), 7.19 (d, $J$ = 3 Hz, 1H).

All other heterocycles **18** and **19** were obtained from commercial sources.

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## References

(1) Harris, N. V.; Smith, C.; Ashton, M. J.; Bridge, A. W.; Bush, R. C.; Coffee, E. C. J.; Dron, D. I.; Harper, M. F.; Lythgoe, D. J.; Newton, C. G.; Riddell, D. Acyl-CoA:cholesterol *O*-Acyl Transferase (ACAT) Inhibitors. 1. 2-(Alkylthio)-4,5-diphenyl-1*H*-imidazoles as Potent inhibitors of ACAT. *J. Med. Chem.* **1992**, *35*, 4384−4392.

(2) Billheimer, J. T.; Gillies, P. J. Intracellular Cholesterol Esterification. In *Advances in Cholesterol Research*; Esfahani, M., Swaney, J. B., Eds.; Telford Press: Caldwell, NJ, 1990; pp 7−45.

(3) Sliskovic, D. R.; White, A. D. Therapeutic Potential of ACAT Inhibitors as Lipid Lowering and Anti-Atherosclerotic Agents. *Trends Pharmacol. Sci.* **1991**, *12*, 194−199. O'Brien, P. M.; Sliskovic, D. R. ACAT Inhibitors: A Potential New Approach to the Treatment of Hypercholesterolaemia and Atherosclerosis. *Curr. Opin. Ther. Patents* **1992**, *2*, 507−526.

(4) Brown, M. S.; Goldstein, J. L. Lipoprotein Metabolism in the Macrophage. *Annu. Rev. Biochem.* **1983**, *52*, 223−261.

(5) Glick, J. M. Intracellular Cholesteryl Ester Hydrolysis and Clearance in Cholesterol Research. In *Advances in Cholesterol Research*; Esfahani, M., Swaney, J. B., Eds.; Telford Press: Caldwell, NJ, 1990; pp 171−200.
(6) Gillies, P. J.; Robinson, C. S.; Rathgeb, K. A. Regulation of ACAT Activity by a Cholesterol Substrate Pool During the Progression and Regression of Atherosclerosis: Implications for Drug Discovery. *Atherosclerosis* **1990**, *83*, 177−185.
(7) Krause, B. R.; Anderson, M.; Bisgaier, C. L.; Bocan, T.; Bousley, R.; DeHart, P.; Essenburg, A.; Hamelehle, K.; Homan, R.; Kieft, K.; McNally, W.; Stanfield, R.; Newton, R. S. In vivo Evidence that the Lipid-Regulating Activity of the ACAT inhibitor CI-976 in Rats is Due to Inhibition of Both Intestinal and Liver ACAT. *J. Lipid Res.* **1993**, *34*, 279−294.
(8) Roark, W. H.; Roth, B. D. ACAT Inhibitors: Preclinical Profiles of Clinical Candidates. *Exp. Opin. Invest. Drugs* **1994**, *3*, 1143−1152.
(9) Parrott, D. P.; Bright, C. P.; Burton, B.; Riddell, D.; Sims, A. F. G. RP 64477: a Potent Inhibitor of ACAT in Human Cells. Abstracts of the 11th International Symposium on Drugs Affecting Lipid Metabolism, Florence, Italy, 1992; p 89. Ashton, M. J.; Bridge, A. W.; Bush, R. C.; Dron, D. I.; Joannou, P. P.; Riddell, D.; Roberts, S.; Stevenson, G. V. W.; Warne, P. J. RP 64477: a Potent Inhibitor of Acyl-CoA:cholesterol *O*-Acyl Transferase (ACAT). Abstracts of the 9th International Symposium on Atherosclerosis, Chicago, IL, 1991; p 183.
(10) Largis, E. E.; Wang, C. H.; DeVries, V. G.; Schaffer, S. A. CL 277,082: A Novel Inhibitor of ACAT-Catalysed Cholesterol Esterification and Cholesterol Absorption. *J. Lipid. Res.* **1989**, *30*, 681−690.
(11) Higley, C. A.; Wilde, R. G.; Maduskuie, T. P.; Johnson, A. L.; Pennev, P.; Billheimer, J. T.; Robinson, C. S.; Gillies, P. J.; Wexler, R. R. Acyl CoA:Cholesterol Acyltransferase Inhibitors: Synthesis and Structure-Activity Relationship Studies of a New Series of Trisubstituted Imidazoles. *J. Med. Chem.* **1994**, *37*, 3511−3522.
(12) Hainer, J. W.; Terry, J. G.; Connell, J. M.; Zyruk, H.; Jenkins, R. M.; Shand, D. L.; Gillies, P. J.; Livak, K. J.; Hunt, T. L.; Crouse, J. R. Effect of the Acyl-CoA:Cholesterol Acyltransferase Inhibitor DuP 128 on Cholesterol Absorption and Cholesterol in Humans. *Clin. Pharmacol. Ther.* **1994**, *52*, 65−74.
(13) Roth, B. D.; Blankley, C. J.; Hoefle, M. L.; Holmes, A.; Roark, W. H.; Trivedi, B. K.; Essenburg, A. D.; Kieft, K. A.; Krause, B. R.; Stanfield, R. L. Inhibitors of Acyl-CoA:Cholesterol Acyltransferase. 1. Identification of a Structure Activity Relationships of a Novel Series of Fatty Acid Anilide Hypocholesterolaemic Agents. *J. Med. Chem.* **1992**, *35*, 1609−1617. For the description of more recent compounds related to CI-976, see: O'Brien, P. M.; Sliskovic, D. R.; Anderson, M. K.; Bousley, R. F.; Krause, B. R.; Stanfield, R. L. Inhibitors of Acyl CoA:Cholesterol Acyltransferase (ACAT) as Hypocholesterolemic Agents 12. Syntheses and Biological Activity of Structurally Novel Tetrazole Amides. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 289−294 and subsequent papers in that issue.
(14) McCarthy, P. A.; Hamanaka, M. S.; Marzetta, C. A.; Bamberger, M. J.; Gaynor, B. J.; Chang, G.; Kelly, S. E.; Inskeep, P. B.; Mayne, J. T.; Beyer, T. A.; Walker, F. J.; Goldberg, D. I.; Savoy, Y. E.; Davis, K. M.; Diaz, C. L.; Freeman, A. M.; Johnson, D. A.; LaCour, T. G.; Long, C. A.; Maloney, M. E.; Martingano, R. J.; Pettini, J. L.; Sand, T. M.; Wint, L. T. Potent, Selective, and Systemically-Available Inhibitors of Acyl-Coenzyme A:Cholesterol Acyl Transferase (ACAT). *J. Med. Chem.* **1994**, *37*, 1252−1255.
(15) Trivedi, B. K.; Purchase, T. S.; Holmes, A.; Augelli-Szafran, C. E.; Essenburg, A. D.; Hamelehle, Stanfield, R. L.; Bousley, R. F.; Krause, B. R. Inhibitors of Acyl-CoA:Cholesterol Acyltransferase (ACAT). 7. Development of a Series of Substituted *N*-Phenyl-*N*′-[(1-phenylcyclopentyl)methyl]ureas with Enhanced Hypocholesterolemic Activity. *J. Med. Chem.* **1994**, *37*, 1652−1659.
(16) Sliskovic, D. R.; Krause, B. R.; Picard, J. A.; Anderson, M.; Bousley, R. F.; Hamelehle, K. L.; Homan, R.; Julian, T. N.; Rashidbaigi, Z. A.; Stanfield, R. L. Inhibitors of Acyl-CoA: Cholesterol *O*-Acyl Transferase (ACAT) as Hypocholesterolemic Agents. 6. The First Water-Soluble ACAT Inhibitor with Lipid Regulating Activity. *J. Med Chem.* **1994**, *37*, 560−562.
(17) Wilde, R. G.; Billheimer, J. T.; Germain, S. J.; Gillies, P. J.; Higley, C. A.; Kezar, H. S.; Maduskuie, T. P.; Shimshick, E. S.; Wexler, R. R. Acyl-CoA:Cholesterol Acyltransferase (ACAT) Inhibitors: Ureas Bearing Heterocyclic Groups Bioisosteric for an Imidazole. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 167−172. Wilde, R. G.; Billheimer, J. T. Acyl-CoA:Cholesterol Acyltransferase (ACAT) Inhibitors: Ureas Bearing Two Heterocyclic Head Groups. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 173−176. Wilde, R. G.; Klaczkiewicz, J. D.; Billheimer, J. T.; Wexler, R. R.; Gillies, P. J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 177−180.
(18) Brown, T. M. A.; Mueller, S. B.; Uhlendorf, P. D.; Newton, R. S.; Krause, B. Comparison of CI-976, an ACAT Inhibitor, and Selected Lipid Lowering Agents for Antiatherosclerotic Activity in Iliac-Femoral and Thoracic Lesions. *Arteriosclerosis Thrombosis* **1991**, *11*, 1830−1843.
(19) Sliskovic, D. R.; Trivedi, B. T. ACAT Inhibitors: Potential Antiatherosclerotic Agents. *Curr. Med. Chem.* **1994**, *1*, 204−225.
(20) Ashton, M. J.; Bridge, A. W.; Bush, R. C.; Dron, D. I.; Harris, N. V.; Jones, G. D.; Lythgoe, D. J.; Riddell, D.; Smith, C. RP 70676: A Potent Systemically Available Inhibitor of Acyl-CoA: Cholesterol *O*-Acyl Transferase (ACAT). *Bioorg. Med. Chem. Lett.* **1992**, *2*, 375−380.
(21) THP-1 cells are a human monocyte leukemia cell line that can be stimulated to differentiate in culture in the presence of phorbol ester. Differentiated THP-1 cells have macrophage-like characteristic including scavenger receptor activity. Via, D. P.; Pons, L.; Dennison, D. K.; Fanslow, A. E.; Bernini, F. Induction of Acetyl-LDL-Receptor Activity by Phorbol Ester in Human Monocyte Cell Line THP-1. *J. Lipid Res.* **1989**, *30*, 1515−1524.
(22) Smith, C.; Ashton, M. J.; Bush, R. C.; Facchini, V.; Harris, N. V.; Hart, T.; Jordan, R.; MacKenzie, R.; Riddell, D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 47−50. Riddell, D.; Bright C.; Burton, B. J.; Bush, R. C.; Harris, N. V.; Hele, D.; Moore, U. M.; Naik, K.; Parrott, D. P.; Smith, C.; Williams, R. J. Hypolipidaemic Properties of RP 73163, a Potent and Systemically Bioavailable Inhibitor of ACAT, in Animals Fed Diets Low in Cholesterol. *Biochem. Pharmacol.* **1996**, in press.
(23) Pitchen, P. The Asymmetric Synthesis of a Biologically Active Sulphoxide. *Chem. Ind. (London)* **1994**, 636−639.
(24) Stoeck, V.; Schunack, W. Synthesis of Imidazoles With Liquid Ammonia. 4. N-Substituted Imidazoles From Aldehydes, 1,2-Diketones, Primary Amines, and Liquid Ammonia. *Arch. Pharm.* **1974**, *307*, 922−925.
(25) Bridge, A. W.; Harris, N. V.; Lythgoe, D. J.; Smith, C. Imidazole Derivatives. WO 9205148-A, 1991.
(26) Harris, N. V.; Smith, C. Preparation of 2-(4,5-Diphenyl-2-imidazolyl)-1,3-Dioxanes as Antiatherosclerotics. EP 424195-A, 1991. Ashton, M. J.; Dron, D. I.; Harris, N. V.; Hart, T. W.; Riddell, D.; Smith, C.; Walsh, R. J. A. Inhibition of ACAT by 4,5-Diphenylimidazoles Substituted at the 2-Position by an Acetal Function. Abstracts of the 7th RSC-SCI Medicinal Chemistry Symposium, Cambridge, U.K., 1993; P46.
(27) Yartseva, S. V.; Tanaseichuk, B. S. Nitrogen Containing Heterocyclic Free Radicals. XII. 2-(α-Furyl)-4(5)-(5)-Phenyl-5(4)-p-X-Phenylimidazoles. *J. Org. Chem. USSR (Engl. Transl.)* **1971**, *7*, 1558−1561.
(28) Jones, R. G. Studies on Imidazole Compounds. 1. A Synthesis of Imidazoles with Functional Groups in the 2-Position. *J. Am. Chem. Soc.* **1949**, *71*, 383−386.
(29) Kreevoy, M. M.; Taft, R. W. Acid-Catalysed Hydrolysis of Acetal and Chloroacetal. *J. Am. Chem. Soc.* **1955**, *77*, 3146−3148.
(30) Searles, S.; Nickerson, R. G.; Witsiepe, W. K. Oxetanes. IX. Structural and Solvent Effects in the Reaction of χ-Bromoalcohols With Base. *J. Org. Chem.* **1959**, *24*, 1839−1844.
(31) Crowley, J. I.; Rapoport, H. Unidirectional Dieckmann Cyclizations on a Solid Phase and in Solution. *J. Org. Chem.* **1980**, *45*, 3215−3227.
(32) Lichtenstein, A. H.; Brecher, P. Properties of Acyl-CoA:Cholesterol Acyltransferase in Rat Liver Microsomes. *J. Biol. Chem.* **1980**, *255*, 9098−9104.
(33) Becker, A.; Bottcher, A.; Lackner, K. J.; Fehringer, P.; Notka, F.; Aslanidis, C.; Schmitz, G. Purification, Cloning and Expression of a Human Enzyme with Acyl Coenzyme A:Cholesterol Acyltransferase Activity, Which is Identical to Liver Carboxylesterase. *Arteriosclerosis Thrombosis* **1994**, *14*, 1346−1355. Chang, T. Y.; Chang, C. C. Y.; Cadigan, K. M. The Structure of Acyl Coenzyme A-Cholesterol Acyltransferase and its Potential Relevance to Atherosclerosis. *Trends Cardiovasc. Med.* **1994**, *4*, 223−230.
(34) Folch, J.; Less, M.; Stanley, G. H. S. A Simple Method for the Isolation and Purification of Total Lipid from Animal Tissues. *J. Biol. Chem.* **1957**, *226*, 497−509.
(35) Reiff, H.; Dieterich, D.; Braden, R.; Ziemen, H. New 1,3-Propanediols by Nucleophilic Cleavage of 3-Alkyl-3-Hydroxymethyl Oxetanes. *Justus Liebig Ann. Chem.* **1973**, 43, 365−374.

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