Communications to the Editor

Potent, Selective, and Systemically-Available Inhibitors of Acyl-Coenzyme A:Cholesterol Acyl Transferase (ACAT)[1]

Peter A. McCarthy,* Ernest S. Hamanaka, Carol A. Marzetta, Mark J. Bamberger, B. J. Gaynor, George Chang, Sarah E. Kelly, Philip B. Inskeep, James T. Mayne, Thomas A. Beyer, Frederick J. Walker, Dennis I. Goldberg, Yvette E. Savoy, Kim M. Davis, Christina L. Diaz, Ann M. Freeman, David A. Johnson, Thomas G. LaCour, Catherine A. Long, Mary E. Maloney, Robert J. Martingano, Judy L. Pettini, Thomas M. Sand, and Lewin T. Wint

Central Research, Pfizer Inc., Groton, Connecticut 06340

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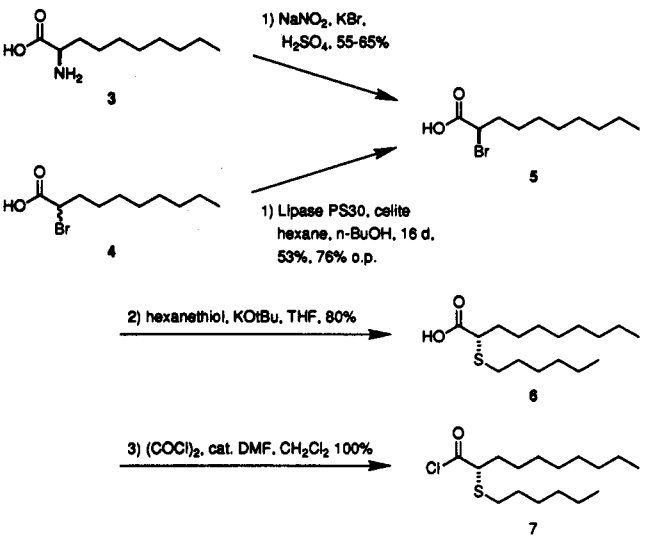
Acyl-coenzyme A:cholesterol acyl transferase (ACAT, EC 2.3.1.26)[2] is the enzyme responsible for intracellular esterification of cholesterol.[3] ACAT-mediated cholesterol esterification is believed to play a key role in intestinal absorption of cholesterol, hepatic production of lipoproteins, and the deposition of cholesteryl esters in atherosclerotic lesions.[4] As such, ACAT inhibitors are hypothesized to generate enhanced effects on atherosclerosis compared to those achievable with agents that only lower plasma cholesterol concentrations. For this reason, inhibition of ACAT is an attractive target for new treatments of hypercholesterolemia and atherosclerosis.[5] Our interest in this area has led to the discovery of a new series of potent, selective, and systemically-available ACAT inhibitors. This communication presents the key chemical, pharmacologic, and pharmacokinetic characteristics of the two most interesting compounds, (S)-*N*-(2,4-bis(methylthio)-6-methylpyridin-3-yl)-2-(hexylthio)-decanoic acid amide (**1**, CP-113,818) and (S)-*N*-(6-(methylthio)quinolin-5-yl)-2-(hexylthio)decanoic amide (**2**, CP-105,191).[6]

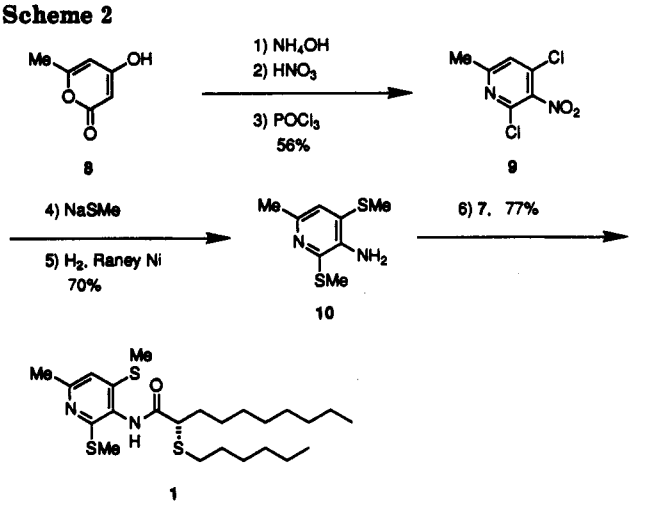
The synthesis of the acyl side chain contained in both **1** and **2** is shown in Scheme 1.[7] Commercially available (*R*)-2-aminodecanoic acid (**3**)[8] was diazotized and displaced with potassium bromide to give (*R*)-2-bromodecanoic acid (**5**). Alternatively, racemic 2-bromodecanoic acid could be resolved by enantioselective enzymatic esterification of the (*S*)-enantiomer to give **5**. Interestingly, this process provides the opposite enantioselectivity from that predicted by the literature.[9] A careful survey of displacement conditions identified potassium *tert*-butoxide in tetrahydrofuran as optimum for yield and enantiomeric purity in converting **5** into the sulfide acid **6**. The enantiomeric purity of this intermediate was judged by conversion to an amide of (*R*)-naphthylethylamine and separation by HPLC. The chemical and enantiomeric purity of **6** could be improved by recrystallization of the dicyclohexylamine salt. Conversion of **6** to the corresponding acid chloride **7** prepared it for coupling with the heterocyclic amines.

To synthesize 3-amino-2,4-bis(methylthio)-6-methylpyridine (**10**, Scheme 2), 4-hydroxy-6-methyl-α-pyrone (**8**) was converted to the corresponding pyridone, selectively

Scheme 1



Scheme 2



nitrated and chlorinated to give nitropyridine **9**. Displacement of both chlorines with methanethiolate, followed by reduction of the nitro group, provided **10**. Coupling of **10** with **7** provided **1**. To synthesize 5-amino-6-(methylthio)quinoline (**13**, Scheme 3), 4-chloroaniline (**11**) was subjected to Skraup cyclization conditions followed by nitration to give nitroquinoline **12**. Chloride displacement with methanethiol followed by nitro group reduction gave **13**. Coupling of **13** with **7** provided **2**. Both **1** and **2** could be enantio-enriched through recrystallization.[10]

1 and **2** were examined for *in vitro* potency and specificity. *In vitro* potency measurements were determined using ACAT in liver microsomes isolated from chow-fed Sprague–Dawley rats according to Billheimer.[11] Under these conditions, **1** and **2** demonstrated IC_{50}'s of 22 ± 2 and 135 ± 33 nM, respectively. The enantiomers of **1** and **2** demonstrated IC_{50}'s of 160 and 750 nM, respectively. For comparison, 2,2-dimethyl-*N*-(2,4,6-trimethoxyphenyl)dodecanoic acid amide (**14**, CI-976)[12] demonstrated an IC_{50} of 900 nM in this same assay system. **1** and **2** have demonstrated similar inhibitory potency against ACAT

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Scheme 3

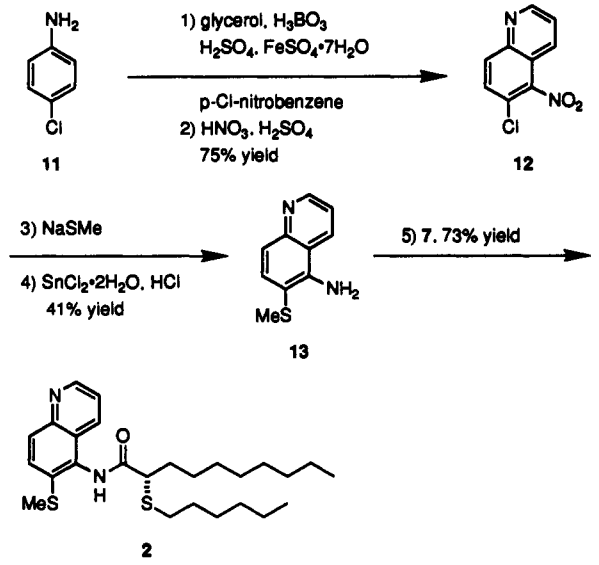

Table 1. *In Vitro* Effects of 1 and 2

	inhibition (concn, μM)	
enzyme	1	2
ACAT	50% (0.022)	50% (0.135)
LCAT[a]	no effect (300)	no effect (30)[b]
PCE[d]	no effect (300)	–[c]
PL[e]	50% (300)	50% (100)
HCR[f]	–[c]	no effect (100)[b]

[a] Lecithin:cholesterol acyl transferase. [b] Data on racemate. [c] Not determined. [d] Pancreatic cholesterol esterase. [e] Pancreatic lipase. [f] 3-Hydroxy-3-methylglutaryl coenzyme A reductase.

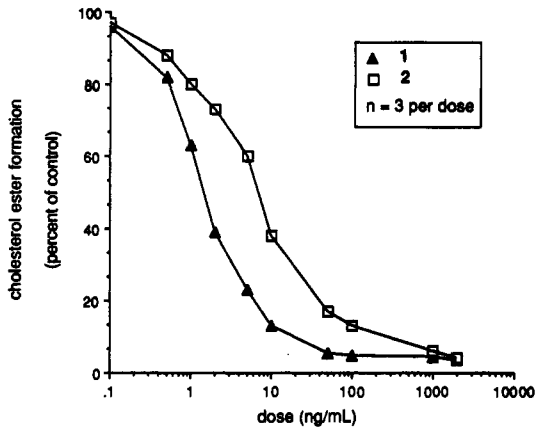

Figure 1. Effects on cholesterol ester formation in Caco-2 cells.

isolated from other tissues and species. For instance, 1 demonstrated an IC_{50} of 30 nM against human intestinal ACAT in a single determination. *In vitro* specificity measurements have been made relative to other enzymes involved in lipid metabolism (Table 1). Of these, significant effects were noted only against pancreatic lipase at concentrations 700–13 000-fold higher than those necessary to inhibit ACAT.

1 and 2 have been evaluated for their ability to inhibit cholesterol esterification in Caco-2 cells, a human intestinal cell line. As shown in Figure 1, 1 and 2 effectively blocked the incorporation of tritiated oleate into cholesteryl oleate. This incorporation fell below 50% of control at 2 and 10 ng/mL, respectively. These inhibitors were also studied for specificity of effect in Caco-2 cells. At 2 μg/mL, 1 and 2 maximally inhibited cholesterol ester formation. At this

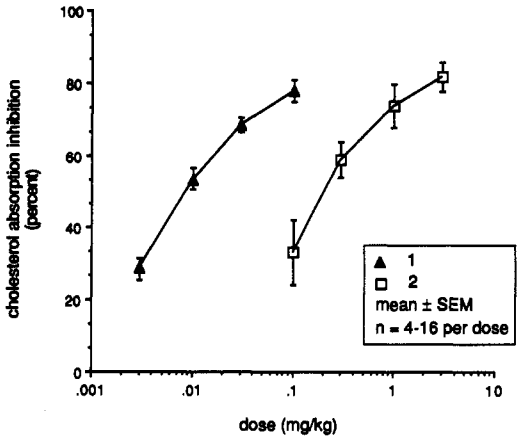

Figure 2. Effects on cholesterol absorption in hamsters.

Table 2. Plasma Cholesterol Lowering in Rabbits

compd	plasma cholesterol level (mg/dL)[a]
control	418 ± 220
1 (5 mg/kg)	98 ± 48[b]
2 (5 mg/kg)	123 ± 19[b]

[a] Mean ± standard deviation, $n = 5$ per group. [b] $p < 0.02$ vs controls.

same dose, no significant effect was observed on oleate incorporation into cellular or secreted phospholipids or triglycerides. No effect on either apo A1 or apo B production was detected in these cells at the same concentrations.[13] Results similar to those describe for Caco-2 cells were also found using the human hepatoma cell line, Hep-G2.

In order to assess the ability of these compounds to inhibit cholesterol absorption *in vivo*, we have examined inhibition of radiolabeled cholesterol absorption in cholesterol-fed hamsters.[14] Radiolabeled cholesterol is administered in a liquid diet with drug to cholesterol-fed hamsters. Twenty-four hours later, the animals are sacrificed and cholesterol absorption inhibition is estimated by comparing plasma and liver counts with those of untreated controls. In dose–response studies (Figure 2), 2 demonstrated an ED_{50} of 0.24 mg/kg, while 1 demonstrated an ED_{50} of 0.009 mg/kg. For comparison, 14 demonstrated an ED_{50} of 9.2 mg/kg in this same assay system. 1 and 2 are also efficacious in chow-fed animals, but at a somewhat higher doses (ED_{50}'s of 0.025 and 0.90 mg/kg, respectively).

1 and 2 were also evaluated for their effects on total plasma cholesterol concentrations in cholesterol-fed rabbits. New Zealand White rabbits were fed a diet containing 0.4% cholesterol and 5% peanut oil for 4 weeks and drug was administered for the final 3 weeks. Shown in Table 2 are single-dose data for 1 and 2 compared with untreated controls. Relative to these controls, the total plasma cholesterol concentrations were lowered more than 70% in animals dosed with either inhibitor at 5 mg/kg.

The pharmacokinetics of 1 and 2 have been studied in the dog. The bioavailability of both compounds were found to increase in the fed state as compared with the fasted state. Figure 3 shows a time course for plasma drug levels in fed dogs administered 50 mg of each inhibitor. It should be noted that the peak plasma drug concentrations exceed the *in vitro* rat liver IC_{50} concentrations by a factor of 3 with 2 and a factor of 150 with 1. Even at the 24-h time point, the plasma concentrations of 1 exceed its *in vitro* rat liver IC_{50} concentration.

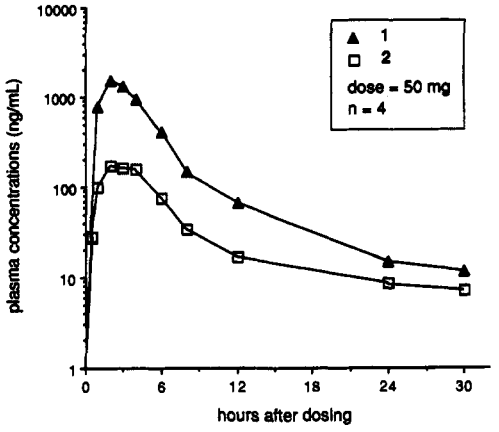

Figure 3. Mean plasma concentrations in fed dog.

The data shown demonstrate that 1 and 2 are potent and selective inhibitors of ACAT *in vitro* and of cholesterol esterification in Caco-2 cells. These inhibitors demonstrate cholesterol absorption inhibition in hamsters and plasma cholesterol lowering in cholesterol-fed rabbits, two *in vivo* endpoints consistent with inhibition of intestinal ACAT. Additional hypocholesterolemic and antiatherosclerotic benefits are postulated from inhibition of hepatic and aortic ACAT. The pharmacokinetic data demonstrate the potential for such effects, especially with 1.

In recent years, several laboratories have discovered ACAT inhibitors, many of which appear to be comparable to 14.[15] The data shown above clearly indicate the superior *in vitro* and *in vivo* potency of 1 and 2. Of those inhibitors that are also superior to 14, none have been reported to demonstrate pharmacokinetics comparable to 1. Thus, 1 appears to represent a breakthrough in terms of systemically-available ACAT inhibitors.

With the advent of new cholesterol-lowering therapies, especially HMG-CoA reductase inhibitors, new research has focused on modalities for producing a more rapid and pronounced effect on atherosclerosis and, ultimately, coronary heart disease. Because of its hypothesized potential for both hypocholesterolemic and direct antiatherosclerotic effects, systemic ACAT inhibition could be a superior treatment modality. The data in this communication demonstrate that 1 has the pharmacologic and pharmacokinetic credentials to test the ACAT inhibition hypothesis *in vivo*. Further details on this new series will be reported in due course.

Supplementary Material Available: Experimental procedures and physical data for the compounds in Schemes 1-3 and data for Figures 1-3 (14 pages). Ordering information is given on any current masthead page.

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