Inhibitors of Acyl-CoA:Cholesterol Acyltransferase. 1. Synthesis and Hypocholesterolemic Activity of Dibenz[*b,e*]oxepin-11-carboxanilides

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Received August 2, 1993•

A series of *N*-phenyl-6,11-dihydrodibenz[*b,e*]oxepin-11-carboxamides and related derivatives were prepared on the basis of structures of the reported inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). These compounds were tested for their ability to inhibit ACAT (liver microsomes from cholesterol-fed rabbits) in vitro and to decrease serum total cholesterol in cholesterol-fed golden hamsters in vivo. The structure–activity relationships in vitro were as follows. Substitution at positions 2 and 6 in the anilide resulted in potent inhibitory activity, and the potency increased with increasing size of the substituents, with maximum potency being obtained with a 2,6-diisopropyl substitution. The position of the substituent on the dibenz[*b,e*]oxepin ring system influenced the activity, and substitution at position 2 was critical for potent activity. The electronic effect of the substituent at position 2 does not influence activity, but bulkiness seems to be a significant factor. The lipophilicity of the compounds also plays an important role in determining ACAT inhibitory activity. Among the compounds tested, 2-bromo-*N*-(2,6-diisopropylphenyl)-6,11-dihydrodibenz-[*b,e*]oxepin-11-carboxamide (**33**, KF17828) showed significant in vitro activity (rabbit liver microsomes IC_{50} = 23 nM) and the most potent in vivo activity (complete reduction in elevated serum total cholesterol levels at a dose of 10 mg/kg in hamsters).

Hypercholesterolemia is considered to be a major risk factor in the development of atherosclerosis, and recent studies have demonstrated the benefits of lowering plasma cholesterol levels on mortality from myocardial infarction.[1] Acyl-CoA:cholesterol acyltransferase (ACAT, EC 2.3.1.26) is a primary enzyme responsible for the intracellular esterification of cholesterol.[2] This enzyme is thought to play an important role in the absorption of dietary cholesterol from the intestine, the metabolism of cholesterol in the liver, and the accumulation of cholesteryl esters in arterial lesions.[2] It is known that ACAT activity is increased in intestinal mucosal cells when cholesterol is ingested[3] and in arterial cells undergoing atherosclerosis.[4] Inhibition of this enzyme would thus be expected to reduce plasma cholesterol concentration, to reduce the secretion of very low-density lipoproteins (VLDL) into the plasma, and to prevent the formation of foam cells in the arterial walls. In fact, several ACAT inhibitors have been shown to be effective in cholesterol-fed animal models of hypercholesterolemia.[5] Therefore, ACAT inhibitors offer potential as hypocholesterolemic and antiatherosclerotic agents.[6]

At the time we initiated this research, some ACAT inhibitors had been reported, e.g., **1** and **2**,[7,8] which consist of two lipophilic moieties linked with an amide or a urea. Compound **1**, for example, possesses an alkyl-chain moiety and a 1,2-diphenylethyl moiety which are linked with an amide.

During the course of our investigation to find potent ACAT inhibitors of novel structure, we synthesized a new series of *N*-phenyl-6,11-dihydrodibenz[*b,e*]oxepin-11-carboxamide derivatives **3** and their analogs on the basis of the structures of the reported ACAT inhibitors as described above. Compounds prepared were tested for their ability to inhibit ACAT in vitro and to decrease serum total cholesterol in vivo. In the present paper, we have described the synthesis, structure–activity relationships, and biological evaluation of this novel class of ACAT inhibitors.

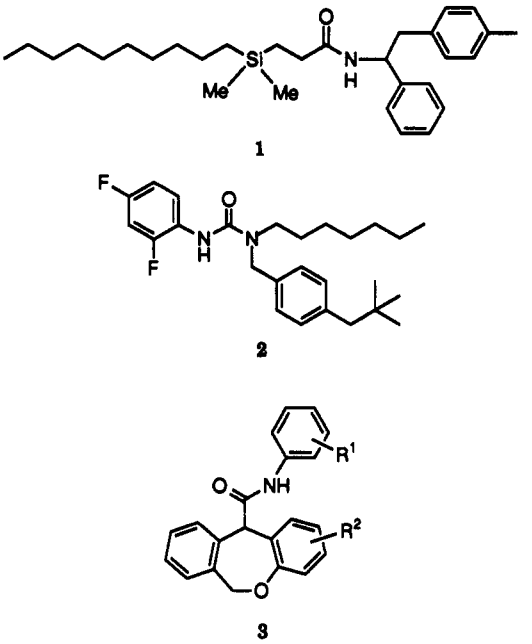

Figure 1.

Chemistry

The general synthetic method of compound **3** and its analogs is shown in Schemes 1 and 2. The key intermediate carboxylic acids **10** were prepared from the ketone **4**[9] using three different methods (Scheme 1). The cyanide **6** obtained by reacting the alcohol **5** with thionyl chloride and then with CuCN was hydrolyzed with HCl–AcOH to afford **10** (method A).[10] The ketone **4** was reacted with

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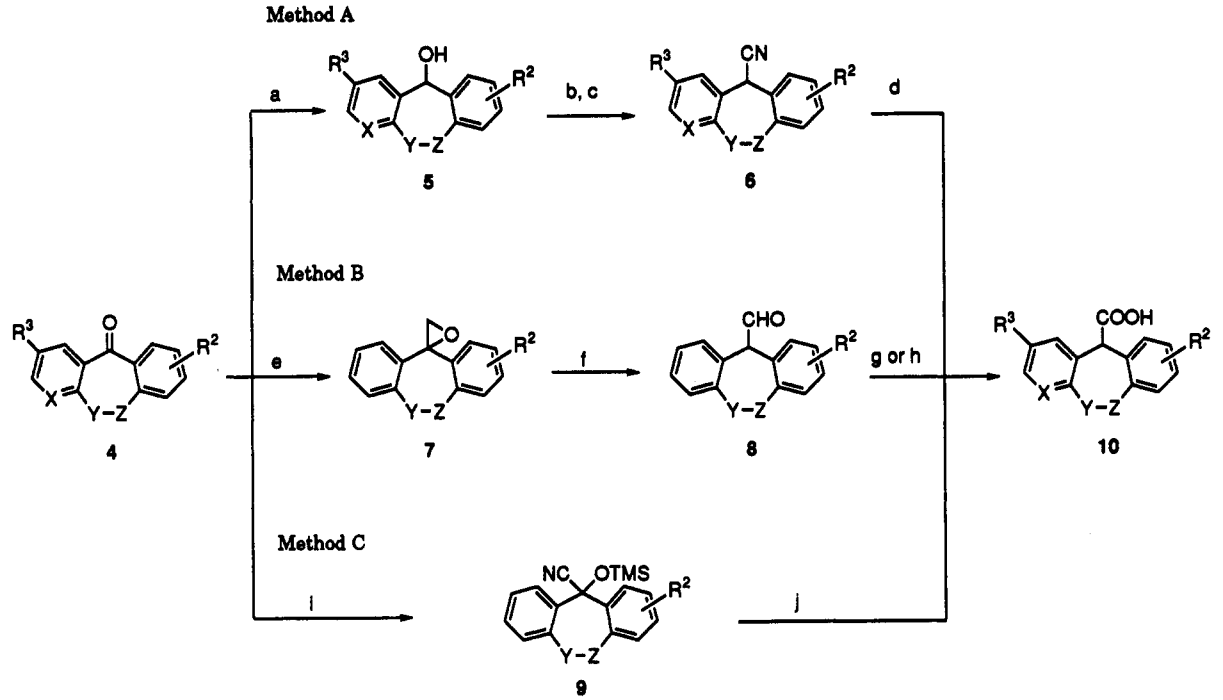
• Abstract published in *Advance ACS Abstracts*, February 15, 1994.

0022-2623/94/1837-0804$04.50/0

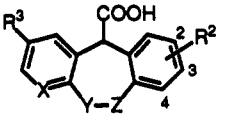
Scheme 1[a]



[a] (a) $NaBH_4$/MeOH; (b) $SOCl_2/CH_2Cl_2$; (c) CuCN/toluene; (d) HCl–AcOH; (e) Me_3SI, NaH/THF–DMSO; (f) $BF_3{\cdot}Et_2O/CH_2Cl_2$; (g) Jones oxidation; (h) $KMnO_4$, *t*-BuOH–acetone, pH 7; (i) Me_3SiCN, ZnI_2/CH_2Cl_2; (j) $SnCl_2$, HCl–AcOH.

the ylid prepared by treating trimethylsulfonium iodide with NaH to afford the epoxide **7**. Conversion of **7** to the corresponding aldehyde **8** was effected by treatment with a catalytic amount of $BF_3{\cdot}Et_2O$.[11] Because oxidation of the aldehyde **8** with Jones' reagent gave the starting ketone **4** as a major product rather than the desired carboxylic acid **10** in some cases, we tried several oxidation methods. After all, we adopted Masamune's method ($KMnO_4$, *t*-BuOH–acetone, pH 7)[12] to obtain the carboxylic acid **10** (method B). Reaction of **4** with TMSCN in the presence

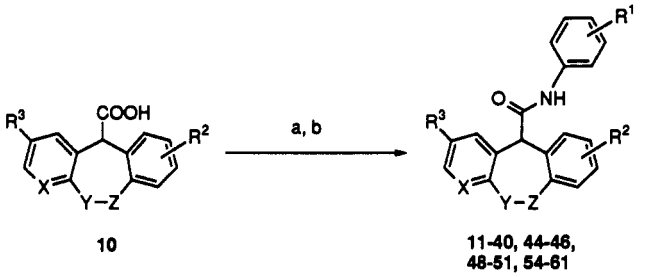
Table 1. Preparation of Carboxylic Acids **10**



no.	R^2	R^3	X	Y-Z	method	formula[a]	mp (°C)
10a	H	H	CH	CH_2O	B	$C_{15}H_{12}O_3$	199.5–201
b	2-Me	H	CH	CH_2O	C	$C_{16}H_{14}O_3$	183–184
c	2-Et	H	CH	CH_2O	B	$C_{17}H_{16}O_3$	154–155
d	2-*i*-Pr	H	CH	CH_2O	B	$C_{18}H_{18}O_3$	161–162
e	2-*t*-Bu	H	CH	CH_2O	B	$C_{19}H_{20}O_3$	197–198
f	2-F	H	CH	CH_2O	B	$C_{15}H_{11}O_3F$	176–177
g	2-Cl	H	CH	CH_2O	B	$C_{15}H_{11}O_3Cl$	182–183
h	2-Br	H	CH	CH_2O	A	$C_{15}H_{11}O_3Br$	174–175.5
i	3-Br	H	CH	CH_2O	B	$C_{15}H_{11}O_3Br$	217–218
j	2-I	H	CH	CH_2O	C	$C_{15}H_{11}O_3I$	191–192
k	2-OMe	H	CH	CH_2O	C	$C_{16}H_{14}O_4$	201–202
l	2-CF_3	H	CH	CH_2O	C	$C_{16}H_{11}O_3F_3$	258–260
m	2-CN	H	CH	CH_2O	B	$C_{16}H_{11}NO_3$	215–217
n	2-NO_2	H	CH	CH_2O	A	$C_{15}H_{11}NO_5$	254–156
o	2-SMe	H	CH	CH_2O	A	$C_{16}H_{14}SO_3$	175–176
p	2,3-$(Me)_2$	H	CH	CH_2O	A	$C_{17}H_{16}O_3$	195.5–196.5
q	2-Me, 4-Br	H	CH	CH_2O	C	$C_{16}H_{13}O_3Br$	196–197
r	2-CO_2Me	H	CH	CH_2O	B	$C_{17}H_{14}O_5$	223–224
s	2-Me, 4-CO_2Me	H	CH	CH_2O	B	$C_{18}H_{16}O_5$	240–242
t	H	Br	CH	CH_2O	A	$C_{15}H_{11}O_3Br$	187–189
u	2-Me	Br	CH	CH_2O	A	$C_{16}H_{13}O_3Br$	168–170
v	2-Br	Br	CH	CH_2O	A	$C_{15}H_{10}O_3Br_2$	179–181.5
w	H	H	N	CH_2O	A	$C_{14}H_{11}NO_3$	139–140
x	2-Br	H	N	CH_2O	A	$C_{14}H_{10}NO_3Br$	126–127
y	2-Br	H	CH	CH_2S	A	$C_{15}H_{11}SO_2Br$	185–186
z	H	H	CH	CH_2CH_2	A	$C_{16}H_{14}O_2$	197–199.5
aa	2-Me	H	CH	CH_2CH_2	C	$C_{17}H_{16}O_2$	185–186
ab	2-Br	H	CH	CH_2CH_2	A	$C_{16}H_{13}O_2Br$	129–131
ac	H	H	CH	CH=CH	A	$C_{16}H_{12}O_2$	244–245
ad	2-Br	H	CH	CON(Me)	B	$C_{16}H_{12}NO_3Br$	240.5

[a] All new compounds had C, H, N microanalyses within 0.4% of theoretical values.

Scheme 2[a]



[a] (a) $SOCl_2/CH_2Cl_2$; (b) R^1-C_6H_5-NH_2, NEt_3/CH_2Cl_2.

of a catalytic amount of ZnI afforded compound **9**, which was refluxed with $SnCl_2$ in HCl–AcOH to give the carboxylic acid **10** (method C).[13]

The anilides **11–40**, **44–46**, **48–51**, and **54–61** were prepared by reacting the appropriate anilines with carboxylic chloride, obtained by the treatment of carboxylic acid with thionyl chloride or oxalyl chloride, in the presence of NEt_3 (Scheme 2; Table 2). The esters **40** and **46** were hydrolyzed to the carboxylic acids **41** and **47**, respectively. The amide **42** was obtained from the corresponding carboxylic acid **41** in the usual manner. Treatment of the carboxylic acid **41** with ethyl chloroformate and NEt_3 followed by reduction with $NaBH_4$ afforded the hydroxymethyl **43**. The thioanilides **52** and **53** were prepared by the reaction of **29** and **33** with Lawesson's reagent, respectively.

Results and Discussion

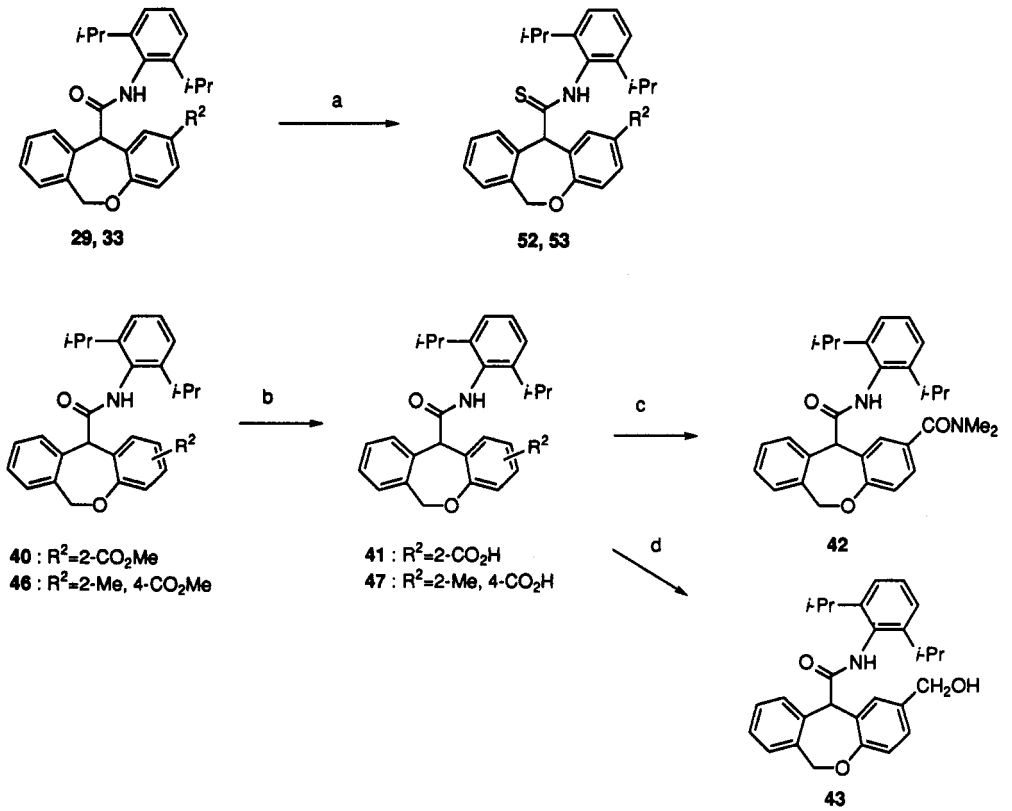
The compounds prepared were evaluated in two primary biological assays. First, the ability to inhibit ACAT in vitro was determined by incubation with [^{14}C]oleoyl-CoA and liver microsomes from cholesterol-fed rabbits.[14] Second, certain compounds were tested in vivo to measure the hypocholesterolemic effect, which was assessed in golden hamsters, fed with a diet containing 2% cholesterol. Each test compound suspended in olive oil was administered orally once a day for 3 days. After 3 days of feeding, serum total cholesterol was measured and the percent change vs the control was determined. The results of ACAT inhibitory activity and hypocholesterolemic activity are shown in Table 2.

The structure–activity relationships in vitro are as follows. It is obvious that 2,6-substitution in the anilide resulted in potent ACAT inhibitory activity and the potency increased with increasing size of the substituents, with maximum potency being obtained with a 2,6-diisopropyl substitution (e.g., **11**, **19**, **23**, and **29**). Although it has been reported that 2,4,6-trimethoxy substitution in a fatty acid anilide provides a good profile of ACAT inhibitory activity,[5] in this study, similar trimethoxy substitution showed weak activity (**18**). Substitution with 2,4-difluorine found to confer optimum potency in aryl ureas also showed low potency (**12**).[15]

The position of the substituent on the dibenz[*b*,*e*]oxepin ring system influenced activity. Compounds substituted with bromine at position 3 were less potent than 2-bromine substitutions (**15** and **34** vs **14** and **33**). Interestingly, 9-bromine derivative **49**, the substituted position of which seemed to be symmetrical to position 2, showed weaker activity than 2-bromine **33**. Although further substitution of compound **49** at position 2 resulted in increased activity, 2,9-dibromine derivative **51** was less potent than **33** (**50** and **51** vs **29** and **33**). These results reveal that substitution at position 9 leads to reduced ACAT activity.

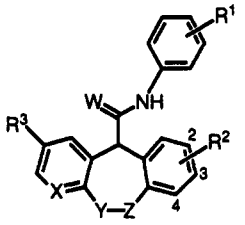
As for the nature of the substituent at position 2, an electronic effect did not influence activity but bulkiness

Scheme 3[a]



[a] (a) Lawesson's reagent; (b) NaOH/EtOH; (c) (i) $SOCl_2/CH_2Cl_2$, (ii) Me_2NH; (d) (i) $ClCO_2Et$, NEt_3/CH_2Cl_2, (ii) $NaBH_4$.

Table 2. *N*-Phenyl-6,11-dihydrodibenz[*b*,*e*]oxepin-11-carboxamides and Related Derivatives



no.	R^1	R^2	R^3	W	X	Y–Z	formula[a]	mp (°C)	ACAT inhibitory activity[b] (IC_{50}, μM)	hypocholesterolemic activity[c] (mg/kg, po) 100	30	10
11	H	2-Me	H	O	CH	CH_2O	$C_{22}H_{19}NO_2$	129–130	(15%)[d]	10		
12	2,4-F_2	2-Br	H	O	CH	CH_2O	$C_{21}H_{14}NO_2F_2Br$	189–191	0.58			
13	2,6-Cl_2	2-Me	H	O	CH	CH_2O	$C_{22}H_{17}NO_2Cl_2$	156–157	0.19	25		
14	2,6-Cl_2	2-Br	H	O	CH	CH_2O	$C_{21}H_{14}NO_2Cl_2Br$	185–187	0.074		0	
15	2,6-Cl_2	3-Br	H	O	CH	CH_2O	$C_{21}H_{14}NO_2Cl_2Br$	169.5–170.5	0.94			
16	2,6-Cl_2	2-*t*-Bu	H	O	CH	CH_2O	$C_{25}H_{23}NO_2Cl_2$	115–117	0.42			
17	2,6-Br_2	2-Me	H	O	CH	CH_2O	$C_{22}H_{17}NO_2Br_2$	183.5–184.5	0.19	6		
18	2,4,6-$(OMe)_3$	2-Me	H	O	CH	CH_2O	$C_{25}H_{25}NO_5$	177–178	0.58			
19	2,6-Me_2	2-Me	H	O	CH	CH_2O	$C_{24}H_{23}NO_2$	162–163	0.35	25		
20	2,6-Me_2	2-*i*-Pr	H	O	CH	CH_2O	$C_{26}H_{27}NO_2$	149.5–150.5	0.36			
21	2,6-Me_2	2-*t*-Bu	H	O	CH	CH_2O	$C_{27}H_{29}NO_2$	116–117	0.5	–42		
22	2,4,6-Me_3	2-Me	H	O	CH	CH_2O	$C_{25}H_{25}NO_2$	148–149	0.11			
23	2,6-Et_2	2-Me	H	O	CH	CH_2O	$C_{26}H_{27}NO_2$	201.5–203	0.27	49		
24	2,6-Et_2	2-*i*-Pr	H	O	CH	CH_2O	$C_{28}H_{31}NO_2$	169.5–170.5	0.5	25		
25	2,6-Et_2	2-Br	H	O	CH	CH_2O	$C_{25}H_{24}NO_2Br$	234.5–235	0.25	64		
26	2-Cl, 6-Me	2-Me	H	O	CH	CH_2O	$C_{23}H_{20}NO_2Cl$	160–161	0.26			
27	2-*i*-Pr	2-Me	H	O	CH	CH_2O	$C_{25}H_{25}NO_2$	180–181	0.73	18		
28	2,6-*i*-Pr_2	H	H	O	CH	CH_2O	$C_{27}H_{29}NO_2$	168–169	0.094	2		
29	2,6-*i*-Pr_2	2-Me	H	O	CH	CH_2O	$C_{28}H_{31}NO_2$	166.5–167	0.05	106	70	
30	2,6-*i*-Pr_2	2-Et	H	O	CH	CH_2O	$C_{29}H_{33}NO_2$	154.5–155.5	0.13	51		
31	2,6-*i*-Pr_2	2-F	H	O	CH	CH_2O	$C_{27}H_{28}NO_2F$	158–159	0.21	53		
32	2,6-*i*-Pr_2	2-Cl	H	O	CH	CH_2O	$C_{27}H_{28}NO_2Cl$	185–186	0.15	97		
33	2,6-*i*-Pr_2	2-Br	H	O	CH	CH_2O	$C_{27}H_{28}NO_2Br$	191.5–193	0.023	143	114	101
34	2,6-*i*-Pr_2	3-Br	H	O	CH	CH_2O	$C_{27}H_{28}NO_2Br$	170.5–171.5	0.18	–2		
35	2,6-*i*-Pr_2	2-I	H	O	CH	CH_2O	$C_{27}H_{28}NO_2I$	201–202	0.035		73	
36	2,6-*i*-Pr_2	2-CF_3	H	O	CH	CH_2O	$C_{28}H_{28}NO_2F_3$	200–201	0.16		63	
37	2,6-*i*-Pr_2	2-OMe	H	O	CH	CH_2O	$C_{28}H_{31}NO_3$	152–153	0.14		22	
38	2,6-*i*-Pr_2	2-SMe	H	O	CH	CH_2O	$C_{28}H_{31}NO_2S$	171.5–172.5	0.007		5	
39	2,6-*i*-Pr_2	2-CN	H	O	CH	CH_2O	$C_{28}H_{28}N_2O_2$	175–176	0.49		–6	
40	2,6-*i*-Pr_2	2-CO_2Me	H	O	CH	CH_2O	$C_{29}H_{31}NO_4$	169.5–170.5	0.18	89		
41	2,6-*i*-Pr_2	2-CO_2H	H	O	CH	CH_2O	$C_{28}H_{29}NO_4$	289–290	(1%)[d]			
42	2,6-*i*-Pr_2	2-$CONMe_2$	H	O	CH	CH_2O	$C_{30}H_{34}N_2O_3$	200–203	0.4			
43	2,6-*i*-Pr_2	2-CH_2OH	H	O	CH	CH_2O	$C_{28}H_{31}NO_3$	157–158	0.58			
44	2,6-*i*-Pr_2	2-NO_2	H	O	CH	CH_2O	$C_{27}H_{28}N_2O_4$	186.5–187.5	0.24			
45	2,6-*i*-Pr_2	2,3-Me_2	H	O	CH	CH_2O	$C_{29}H_{33}NO_2$	164–165	0.064		27	
46	2,6-*i*-Pr_2	2-Me, 4-CO_2Me	H	O	CH	CH_2O	$C_{30}H_{33}NO_4$	135.5–137.5	0.027		84	28
47	2,6-*i*-Pr_2	2-Me, 4-CO_2H	H	O	CH	CH_2O	$C_{29}H_{31}NO_4$	172–172.5	(28%)[d]			
48	2,6-*i*-Pr_2	2-Me, 4-Br	H	O	CH	CH_2O	$C_{28}H_{30}NO_2Br$	172–173	0.1		67	
49	2,6-*i*-Pr_2	H	Br	O	CH	CH_2O	$C_{27}H_{28}NO_2Br$	165–166	0.19		8	
50	2,6-*i*-Pr_2	2-Me	Br	O	CH	CH_2O	$C_{28}H_{30}NO_2Br$	149–151	0.12		17	
51	2,6-*i*-Pr_2	2-Br	Br	O	CH	CH_2O	$C_{27}H_{27}NO_2Br_2$	202–204	0.058		40	
52	2,6-*i*-Pr_2	2-Br	H	S	CH	CH_2O	$C_{27}H_{28}NOSBr$	189.5–191	(33%)[d]			
53	2,6-*i*-Pr_2	2-Me	H	S	CH	CH_2O	$C_{28}H_{31}NOS$	140–141	(15%)[d]			
54	2,6-*i*-Pr_2	2-Br	H	O	CH	CH_2S	$C_{27}H_{28}NOSBr$	189–190	0.15		67	
55	2,6-*i*-Pr_2	H	H	O	N	CH_2O	$C_{26}H_{28}N_2O_2$	154–155	0.64			
56	2,6-*i*-Pr_2	2-Br	H	O	N	CH_2O	$C_{26}H_{27}N_2O_2Br$	151–153	0.078		47	
57	2,6-*i*-Pr_2	H	H	O	CH	CH_2CH_2	$C_{28}H_{31}NO$	140–142 dec	0.04		89	3
58	2,6-*i*-Pr_2	2-Me	H	O	CH	CH_2CH_2	$C_{29}H_{33}NO$	118–120	0.055		93	–1
59	2,6-*i*-Pr_2	2-Br	H	O	CH	CH_2CH_2	$C_{28}H_{30}NOBr$	127–128	0.039			42
60	2,6-*i*-Pr_2	H	H	O	CH	CH=CH	$C_{28}H_{29}NO$	166–166.5	0.025		73	
61	2,6-*i*-Pr_2	2-Br	H	O	CH	CONMe	$C_{28}H_{29}N_2O_2Br$	241–243.5 dec	0.24			
2	(CL277082)								0.32		71	35

[a] All new compounds had C, H, N microanalyses within 0.4% of theoretical values unless otherwise noted. [b] Liver microsomes isolated from cholesterol-fed rabbits. IC_{50} values were determined by a single experiment unless otherwise noted. Each assay was performed in triplicate. [c] Percent reduction in increased serum total cholesterol in golden hamsters fed with a diet containing 2% cholesterol under the condition described in Biological Methods ($n = 5$): % reduction = [(B – A)/(B – C)]100 (A, B, and C represent serum cholesterol levels in the drug-treated, control, and normal groups, respectively). [d] Percent inhibition at 1 μM.

seemed to be a significant factor. Methoxy and nitro derivatives showed almost equipotent moderate activity (**37** and **44**). On the other hand, 2-methyl derivatives were more active than 2-ethyl, 2-isopropyl, or 2-*tert*-butyl derivatives (**13**, **19**, **23**, and **29** vs **16**, **20**, **21**, **24**, and **30**). In the case of a halogen group, a remarkable substituent effect was also observed. Bromine was the most favorable one (F < Cl < I < Br) (**31**–**33** and **35**). Other substituents

Table 3. Effect of 33 on Rat Cholesterol Levels[a]

dose of 33 (mg/kg/day, po)	serum (mg/dL)[b]	liver (mg/g)[b]
normal	61 ± 2	2.5 ± 0.1
control	280 ± 40	24.6 ± 1.0
1	214 ± 15*	19.2 ± 1.5**
3	167 ± 19**	15.0 ± 1.8**
10	114 ± 7**	10.4 ± 1.0**
30	108 ± 4**	6.3 ± 0.4**

[a] Male Sprague–Dawley rats were fed a semisynthetic diet containing 1% cholesterol, 1% cholic acid, 50% sucrose, 12% coconut oil, and 20% casein for 7 days. Compound 33 was orally administered once a day for 7 days. All tabular values are mean ± SEM. All groups contain six animals each. [b] Determined on day 8 of the experiment. * = $P \leq 0.05$. ** = $P \leq 0.01$.

at position 2 bigger than bromine or methyl caused reduced potency. These results indicate a bulk limitation at this position. Methylthio derivative **38** was the only exception, which showed the most potent activity (IC_{50} = 7 nM) in this series of compounds.

Although incorporation of a methoxycarbonyl group at the 4-position of 2-methyl derivative **29** retained activity (IC_{50} = 27 nM), a carboxyl group brought complete loss of activity (28% inhibition at 1 μM) (**46** and **47**). A similar result was shown for 2-methoxycarbonyl, 2-(dimethylamino)carbonyl, and 2-carboxyl ones (**40–42**). This suggests that lipophilicity of the compounds also plays an important role in determining ACAT inhibitory activity. Replacement of an amide bond by a thioamide bond resulted in a complete loss of ACAT activity (**29** and **33** vs **52** and **53**).

In order to determine the potency of the 6,11-dihydrodibenz[*b,e*]oxepin ring system, we prepared and evaluated some other tricyclic systems. 6,11-Dihydrodibenz[*b,e*]thiepin, 5,11-dihydrobenzoxepino[3,4-*b*]pyridine, and 5,11-dihydrodibenz[*b,e*]azepin-6-one derivatives showed reduced activity (**54–56** and **61**). Dibenzosuberane and dibenzosuberenane derivatives showed potent activity independent of the substituents on the tricyclic systems.

The compounds possessing IC_{50} values less than 0.2 μM and some other compounds were further evaluated for in vivo experiment. In general, there was a reasonable correlation between in vitro and in vivo activity except for **14**, **28**, and **38**. The substitution at position 2 was crucial for potent activity in vivo. The unsubstituted derivative **28** that showed moderate activity in vitro (IC_{50} = 94 nM) was inactive in vivo. Compound **38**, which showed the most potent ACAT inhibitory activity in this series of compounds, showed negligible activity in vivo. The reason for this discrepancy is unknown but may be related to poor absorption or metabolism. In vivo activities of dibenzosuberane and dibenzosuberenane derivatives, which showed potent in vitro activity, at a dose of 10 mg/kg were less potent than that of **33** (**57–60**). Thus, a 6,11-dihydrodibenz[*b,e*]oxepin ring system is crucial for potent hypocholesterolemic activity in vivo.

From these compounds, **33**, which showed significant in vitro activity (IC_{50} = 23 nM) and the most potent in vivo activity (complete reduction in elevated serum total cholesterol levels at a dose of 10 mg/kg, po), was selected for further evaluation. In cholesterol-fed rats, both serum and hepatic total cholesterol levels were decreased significantly when **33** was administered orally at doses of more than 1 mg/kg/day for 7 days (Table 3). Compound **33** was reported to inhibit ACAT in a manner noncompetitive with respect to oleoyl-CoA.[16] Furthermore, **33** has also been found to accelerate the regresssion of preestablished hypercholesterolemia in hamsters and to prevent the progression of atherosclerosis in cholesterol-fed rabbits.[16]

In conclusion, we found a novel series of ACAT inhibitors with dibenz[*b,e*]oxepin-11-carboxanilides. The SAR data discussed above can elicit some conclusions about the pharmacophore necessary for potent ACAT activity in this series of compounds. Optimum potency is obtained with 2,6-disubstitution with an isopropyl group in the anilide. Substitution at position 2 on the dibenz[*b,e*]-oxepin ring system with the proper size group is essential for good in vitro activity. This is also critical for potent in vivo activity. With regard to tricyclic systems, 6,11-dihydrodibenz[*b,e*]oxepin is most preferred. Among the compounds tested, **33** (KF17828) showed the most promising activity. A detailed pharmacology of **33** will be reported.

Experimental Section

Melting points were determined with a Büchi-510 melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Jasco IR-810 spectrometer. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Hitachi R-90H (90 MHz) or JEOL JNM GX-270 (270 MHz) spectrometer with Me_4Si as internal standard. Elemental analyses were performed by the analytical department of our laboratories.

Method A. 2-Bromo-6,11-dihydrodibenz[*b,e*]oxepin-11-carboxylic Acid (10h). To a solution of 2-bromo-11-hydroxy-6,11-dihydrodibenz[*b,e*]oxepin (**5h**) (34.5 g, 112 mmol) in 500 mL of CH_2Cl_2 was added dropwise $SOCl_2$ (17.0 mL, 233 mmol) at 0 °C. The resulting solution was stirred at room temperature for 17 h. The solvent was evaporated in vacuo to dryness to yield a solid which was dissolved in 300 mL of toluene. After addition of CuCN (11.6 g, 130 mmol), the mixture was heated under reflux for 2 h, cooled, and filtered through Celite. The filtrate was evaporated in vacuo. The resulting solid was recrystallized from toluene–isopropyl ether to yield 31.3 g of 2-bromo-6,11-dihydrodibenz[*b,e*]oxepin-11-carbonitrile (**6h**): mp 116–116.5 °C; IR (KBr) 3060, 2986, 2902, 2250, 1469, 1377, 1271 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.31 and 5.46 (q, 2H, AB type, J = 14.4 Hz), 5.45 (s, 1H), 6.87 (d, 1H, J = 8.6 Hz), 7.14–7.55 (m, 6H). Anal. ($C_{15}H_{10}NOBr$) C, H, N.

A mixture of **6h** (5.16 g, 17.2 mmol) in 100 mL of HCl–AcOH (1:1) was heated under reflux for 24 h. The mixture was cooled, diluted with water, and extracted with AcOEt. The organic layer was washed with water and extracted with 1 N NaOH three times. The combined aqueous layer was acidified with 4 N HCl to pH 2 and extracted with AcOEt. The organic layer was washed with water and brine, dried, and evaporated in vacuo to yield 4.15 g of **10h** as a white solid. An analytical sample was prepared by recrystallization from toluene–isopropyl ether: mp 174–175.5 °C; IR (KBr) 2992, 2902, 1713, 1691, 1482, 1224 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.62 (s, 1H), 4.86 and 5.56 (q, 2H, AB type, J = 14.2 Hz), 6.84 (d, 1H, J = 8.6 Hz), 7.13–7.35 (m, 6H), 7.94 (br s, 1H). Anal. ($C_{15}H_{11}O_3Br$) C, H.

Method B. 2-(Methoxycarbonyl)-6,11-dihydrodibenz[*b,e*]oxepin-11-carboxylic Acid (10r). To a suspension of NaH (2.11 g of 60% in oil, 88 mmol) in 300 mL of DMSO–THF (1:1) was added portionwise trimethylsulfonium iodide at −5 °C. A solution of 2-(methoxycarbonyl)-6,11-dihydrodibenz[*b,e*]oxepin-11-one (**4r**) (15.7 g, 59 mmol) in 50 mL of DMSO–THF (1:1) was added dropwise and the mixture was stirred at room temperature for 10 h. Ten milliliters of water was added dropwise at 0 °C. The resulting mixture was diluted with 300 mL of water and extracted with ether. The organic layer was washed with brine, dried, and evaporated in vacuo to yield 9.85 g (60%) of 2-(methoxycarbonyl)-6,11-dihydrodibenz[*b,e*]oxepin-11-spiro-2′-oxirane (**7r**) as a white solid: mp 108–109 °C; IR (KBr) 2990, 1712, 1623, 1501, 1440, 1296 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.99 and 3.22 (q, 2H, AB type, J = 6.4 Hz), 3.87 (s, 3H), 5.09 and 5.74 (q, 2H, AB type, J = 12.5 Hz), 6.84 (d, 1H, J = 8.6 Hz), 7.25–7.50 (m, 4H), 7.84 (dd, 1H, J = 8.6 and 2.2 Hz), 8.17 (d, 1H, J = 2.2 Hz). Anal. ($C_{17}H_{14}O_4$) C, H.

This solid was dissolved in 200 mL of CH_2Cl_2. $BF_3{\cdot}Et_2O$ (0.43 mL, 3.5 mmol) was added dropwise at 0 °C, and the mixture was stirred for 5 h. After addition of 10 mL of water, the resulting mixture was diluted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ and brine, dried, and evaporated in vacuo to yield 9.2 g of 2-(methoxycarbonyl)-6,11-dihydrodibenz[*b,e*]-oxepin-11-carboxaldehyde (**8r**) as a white solid: mp 133–134 °C; ^1H NMR ($CDCl_3$) δ 3.86 (s, 3H), 4.62 (s, 1H), 4.82 and 5.25 (q, 2H, AB type, J = 13.8 Hz), 6.95 (d, 1H, J = 8.1 Hz), 7.13–7.92 (m, 6H), 9.84 (s, 1H). Anal. ($C_{17}H_{14}O_4$) C, H.

To a mixture of **8r** (9.1 g, 32 mmol) in 300 mL of acetone–2-methyl-2-propanol (1:1) and 60 mL of phosphate pH standard equimolal solution (pH 6.86) was added dropwise 130 mL of 0.5 M aqueous $KMnO_4$ at 0 °C. The mixture was stirred for 1.5 h, and then saturated aqueous sodium sulfite was added. The resulting mixture was acidified with 4 N HCl to pH 2 and extracted with AcOEt. The organic layer was washed with brine, dried, and evaporated in vacuo to yield 9.42 g of **10r** as a white solid: mp 223–224 °C; IR (KBr) 3148, 2948, 1737, 1726, 1709, 1689, 1667, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H), 4.81 (s, 1H), 4.87 and 5.68 (q, 2H, AB type, J = 13.6 Hz), 6.92 (d, 1H, J = 8.6 Hz), 7.25–7.30 (m, 4H), 7.90 (dd, 1H, J = 8.9 and 5.2 Hz), 7.94 (br s, 1H). Anal. ($C_{17}H_{14}O_5$) C, H.

Method C. 2-Methyl-6,11-dihydrodibenz[*b,e*]oxepin-11-carboxylic Acid (10b). A mixture of 2-methyl-6,11-dihydrodibenz[*b,e*]oxepin-11-one (**4b**) (8.96 g, 40 mmol), trimethylsilyl cyanide (11.9 g, 120 mmol), zinc iodide (1.28 g, 4 mmol), and molecular sieves (4A) (4 g) in 15 mL of CH_2Cl_2 was stirred at room temperature for 72 h. The reaction mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, dried, and evaporated in vacuo to yield 12.1 g of 2-methyl-11-[(trimethylsilyl)oxy]-6,11-dihydrodibenz[*b,e*]oxepin-11-carbonitrile (**9b**) as a colorless oil: IR (liquid film) 2960, 1498, 1256, 893, 847, 759 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.24 (s, 9H), 2.31 (s, 3H), 5.25 and 5.64 (q, 2H, AB type, J = 13.7 Hz), 6.90 (d, 1H, J = 8.3 Hz), 7.08–7.64 (m, 6H).

A mixture of **9b** (11.9 g, 37 mmol) and tin(II) chloride (28.2 g, 120 mmol) in 40 mL of HCl–AcOH (1:1) was heated under reflux for 5 h. The mixture was cooled and extracted with AcOEt. The organic layer was washed with water and brine, dried, and evaporated in vacuo to yield 5.16 g (55%) of **10b** as a white solid: mp 183–184 °C; IR (KBr) 3064, 2894, 1710, 1705, 1689, 1503 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (s, 3H), 4.64 (s, 1H), 4.89 and 5.55 (q, 2H, AB type, J = 14.6 Hz), 6.94–7.23 (m, 7H). Anal. ($C_{16}H_{14}O_3$) C, H.

***N*-(2,6-Diisopropylphenyl)-6,11-dihydrodibenz[*b,e*]oxepin-11-carboxamide (28).** To a solution of 6,11-dihydrodibenz[*b,e*]-oxepin-11-carboxylic acid (**10a**) (1.92 g, 8 mmol) in 30 mL of CH_2Cl_2 was added dropwise oxalyl chloride (7.0 mL, 80 mmol) at 0 °C. After being stirred for 8 h, the reaction mixture was evaporated in vacuo. The residue was dissolved in 10 mL of CH_2Cl_2 and added dropwise to a solution of 2,6-diisopropylaniline (1.65 g, 9.3 mmol), NEt_3 (2.2 mL, 16 mmol), and a catalytic amount of 4-(*N,N*-dimethylamino)pyridine in 30 mL of CH_2Cl_2 at 0 °C. After being stirred at room temperature for 1.5 h, the reaction mixture was diluted with CH_2Cl_2, washed with water, 1 N HCl, and brine, dried, and evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate–hexane (1:5) to afford a colorless solid. Recrystallization from ethyl acetate–hexane yielded 2.08 g (65%) of **28**: mp 168–169 °C; IR (KBr) 3298, 2956, 1658, 1518 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 6H, J = 6.8 Hz), 1.01 (d, 6H, J = 6.8 Hz), 2.63–2.78 (m, 2H), 4.92 (s, 1H), 5.06 and 5.53 (q, 2H, AB type, J = 14.7 Hz), 6.98–7.58 (m, 12H). Anal. ($C_{27}H_{29}NO_2$) C, H, N.

***N*-(2,6-Diisopropylphenyl)-2-methyl-6,11-dihydrodibenz-[*b,e*]oxepin-11-carbothioamide (53).** A mixture of *N*-(2,6-diisopropylphenyl)-2-methyl-6,11-dihydrodibenz[*b,e*]oxepin-11-carboxamide (**29**) (1.09 g, 2.6 mmol) and Lawesson's reagent (1.07 g, 2.6 mmol) in 10 mL of toluene was heated under reflux for 1 h. Upon cooling, the reaction mixture was evaporated in vacuo. The residue was chromatographed on silica gel eluting with ethyl acetate–hexane (1:2) to afford a solid. Recrystallization from ethyl acetate–hexane yielded 1.09 g (96%) of **53**: mp 140–141 °C; IR (KBr) 3248, 2956, 1500, 1442, 1413, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (d, 3H, J = 6.8 Hz), 0.88 (d, 3H, J = 6.8 Hz), 1.0 (d, 3H, J = 6.8 Hz), 1.04 (d, 3H, J = 6.8 Hz), 2.34 (s, 3H), 2.34–2.47 (m, 2H), 5.09 and 5.39 (q, 2H, AB type, J = 15.8 Hz), 5.55 (s, 1H), 7.10–7.77 (m, 10H), 9.87 (br s, 1H). Anal. ($C_{28}H_{31}NOS$) C, H, N.

11-[(2,6-Diisopropylphenyl)carbamoyl]-6,11-dihydrodibenz[*b,e*]oxepin-2-carboxylic Acid (41). A solution of **40** (0.58 g, 1.3 mmol) in 6 mL of 5 N NaOH and 24 mL of MeOH was heated under reflux for 5 min. Upon cooling, the reaction mixture was acidified with 4 N HCl to pH 3 and extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated in vacuo to yield 0.52 g (92%) of **41** as a white solid: mp 289–290 °C; IR (KBr) 3280, 2962, 1690, 1651, 1501, 1259, 1236 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, 12H, J = 6.8 Hz), 2.61–2.93 (m, 2H), 5.18 (s, 3H), 4.84 and 6.26 (q, 2H, AB type, J = 13.0 Hz), 6.89–7.87 (m, 10H), 8.14 (br s, 1H). Anal. ($C_{28}H_{29}NO_4$) C, H, N.

2-(Dimethylcarbamoyl)-*N*-(2,6-diisopropylphenyl)-6,11-dihydrodibenz[*b,e*]oxepin-11-carboxamide (42). To a solution of **41** (0.92 g, 2.1 mmol) and a drop of pyridine in 30 mL of CH_2Cl_2 was added dropwise $SOCl_2$ (0.76 mL, 10.4 mmol) at room temperature. The resulting solution was stirred at room temperature for 24 h and evaporated in vacuo. The residue was dissolved in 15 mL of CH_2Cl_2. A solution of dimethylamine hydrochloride (0.34 g, 4.1 mmol), triethylamine (1.2 mL, 8.3 mmol), and a catalytic amount of 4-(*N,N*-dimethylamino)pyridine in 15 mL of CH_2Cl_2 was added dropwise at 0 °C. The mixtue was stirred at 0 °C for 30 min and then at room temperature for 21 h. The reaction mixture was diluted with CH_2Cl_2, washed with 1 N NaOH, 1 N HCl, and brine, dried, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with ethyl acetate–hexane (1:4) to afford a solid. Recrystallization from toluene yielded 0.7 g (72%) of **42**: mp 200–203 °C; IR (KBr) 3256, 2960, 2928, 1687, 1621, 1489, 1257 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0 (d, 6H, J = 6.8 Hz), 1.04 (d, 6H, J = 6.8 Hz), 2.60–2.90 (m, 2H), 3.05 (s, 6H), 4.93 (s, 1H), 5.01 and 5.64 (q, 2H, AB type, J = 13.6 Hz), 7.0–7.56 (m, 1H). Anal. ($C_{30}H_{34}N_2O_3$) C, H, N.

***N*-(2,6-Diisopropylphenyl)-2-(hydroxymethyl)-6,11-dihydrodibenz[*b,e*]oxepin-11-carboxamide (43).** To a solution of **41** (1.33 g, 3.0 mmol) and triethylamine (1.0 mL, 7.2 mmol) in 10 mL of THF was added ethyl chloroformate (0.39 g, 3.6 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. $NaBH_4$ (0.57 g, 15.0 mmol) was added at 0 °C. The mixture was stirred for 6 h and diluted with ethyl acetate. The resulting solution was washed with water, saturated $NaHCO_3$, and brine, dried, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with ethyl acetate–hexane (1:2) to afford a solid. Recrystallization from ethyl acetate–hexane yielded 1.1 g (84%) of **43**: mp 157–158 °C; IR (KBr) 3318, 3286, 2962, 1659, 1650, 1526, 1502, 1232 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, 6H, J = 6.8 Hz), 1.02 (d, 6H, J = 6.8 Hz), 1.75 (br s, 1H), 2.67–2.82 (m, 2H), 4.62 (s, 2H), 4.89 (s, 1H), 5.03 and 5.54 (q, 2H, AB type, J = 14.8 Hz), 6.99–7.45 (m, 11H). Anal. ($C_{28}H_{31}NO_3$) C, H, N.

Biological Methods. In Vitro ACAT Assay. The compounds were tested for inhibition of ACAT as follows. Male New Zealand rabbits were fed 2% cholesterol chow for 2 months. The liver was homogenized in 0.1 M potassium phosphate buffer (pH 7.4) containing 1 mM EDTA and 2 mM dithiothreitol (DTT). The homogenate was centrifuged at 10000*g* for 15 min. The supernatant was centrifuged at 100000*g* for 60 min. The pellet was resuspended in 0.1 M potassium phosphate buffer and used as the source of ACAT enzyme. Microsomal ACAT activity was measured as the incorporation of [^{14}C]oleoyl-CoA into cholesteryl ester. The reaction mixture included 1.7 mg/mL BSA, 2 mM DTT, and 50 μg of protein of microsome in 180 μL of 0.1 M potassium phosphate buffer (pH 7.4). The test compound was dissolved in 10 μL of methanol and added to the reaction mixture. A control mixture, omitting the test compound, was prepared and treated in the same manner. Cholesterol esterification was started by addition of 45 μM [^{14}C]oleoyl-CoA (10 μL, 44 000 dpm) and run at 37 °C for 40 min. The reaction was stopped by addition of 4 mL of $CHCl_3$:methanol (2:1). Then, lipid was extracted from the reaction mixture and separated by silica gel G thin-layer chromatography. The radioactivity of cholesteryl ester was quantitated with a scintillation counter. The values of percent inhibition were calculated from the mean of triplicate assay tubes.

In Vivo Cholesterol-Fed Hamsters. Male golden hamsters

(Japan SLC Inc., age 6 weeks) were fed a diet supplemented with 2% cholesterol. The drug-treated group of animals was also administered the test compound suspended in olive oil once a day for 3 days. The control group was administered the vehicle. The normal group was fed a basal diet without supplements to determine the basal serum cholesterol concentration. The serum cholesterol levels in the normal group 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 untreated controls enabled the hypolipidemic activity of the compounds to be measured as a reduction percentage that was calculated from the following formula: % reduction = [(B − A)/(B − C)]100 (A, B, and C represent serum choesterol levels in the drug-treated, control, and normal groups, respectively).

Cholesterol-Fed Rats. Male Sprague–Dawley rats (Charles River Japan Inc.) weighing 170–200 g were used. Rats were fed a high-cholesterol diet (1% cholesterol, 1% cholic acid, 20% casein, 50% sucrose, 12% coconut oil, 4% cellulose, 7.5% fishmeal, 4% minerals, and 0.5% vitamins) for 7 days. Throughout the period of experiment, the high-cholesterol diet was available ad libitum. Compound **33** was suspended in 0.3% sodium carboxymethyl cellulose containing 0.2% Tween 80 and orally administered once a day for 7 days. On the eighth day, a blood sample was collected from the descending aorta under anesthesia with sodium pentobarbital, and the cholesterol level in serum was determined by an enzymatic method.

Acknowledgment. We are grateful to Drs. T. Oka and T. Hirata for their continuous support.

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