Nuclear, Dreieich, FRG and Research Biochemicals, Wayland, MA), 5 mg/mL tissue homogenate in 50 mM Tris-HCl buffer containing 4.0 mM $CaCl_2$ and 5.7 mM ascorbic acid, pH 7.5. Binding experiments were started by the addition of tissue homogenate and followed by incubation at 37 °C for 10 min. The incubation mixtures were filtered through Whatman GF/B glass filteres with a Brandel cell harvester (Gaithersburg, MD). The filters were washed twice with 5 mL of ice-cold 50 mM Tris-HCl buffer, pH 7.5, and counted with 5 mL of Ready-solv HP (Beckman) in a Beckman LS 3801 scintillation counter. Nonspecific binding was measured by the addition of 10 μM 5-HT·HCl to the reaction mixture. The binding data were processed by nonlinear least-squares computer analysis.[35] A K_d value of 1.4 nM for the 8-OH-DPAT binding was obtained from the saturated experiments and was used to calculate the K_i values.

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Supplementary Material Available: Lists of intramolecular bond distances and bond angles, involving the non-hydrogen atoms (Tables I and II), hydrogen atomic coordinates with isotropic temperature factors (Table III), and anisotropic thermal parameters of the non-hydrogen atoms (Table IV) for **9**·HCl, and geometries and steric energies of low-energy MMP2 conformations of **3**·HCl (Table V) (6 pages). Ordering information is given on any current masthead page. The list of observed and calculated structure factors is available directly from the authors on request.

Potential Antiatherosclerotic Agents. 6.[1] Hypocholesterolemic Trisubstituted Urea Analogues

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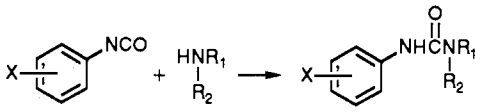
The discovery that a series of *N,N*-dialkyl-*N'*-arylureas were inhibitors of the ACAT enzyme has led to a structure–activity study involving the systematic modification of three sites of the urea backbone. This study culminated in the selection of *N'*-(2,4-dimethylphenyl)-*N*-benzyl-*N*-*n*-butylurea (**115**) for more extensive biological evaluation. ACAT inhibitors are seen as potentially beneficial agents against hypercholesterolemia and atherosclerosis.

The enzyme acyl CoA:cholesterol *O*-acyltransferase (ACAT, EC 2.3.1.26) is responsible for catalyzing the intracellular esterification of cholesterol.[2-4] Studies both in cultured cells[5-9] and in arterial tissue[10-12] have suggested that ACAT activity is increased when cells are exposed to cholesterol-rich lipoproteins. Since the intracellular accumulation of esterified cholesterol is one of the distinctive features of the atherosclerotic plaque, the regulation of ACAT is likely to be of great importance in the progression of atherosclerosis. Furthermore, the ACAT enzyme also plays a crucial role in the intestinal absorption of cholesterol. Despite the fact that free cholesterol is internalized by intestinal mucosal cells,[13] more than 90% of the cholesterol which appears subsequently in the lymph is esterified.[14] Substantial ACAT activity has been observed in intestinal mucosal cells from a variety of animal species[15-18] and man.[19] The site of greatest ACAT activity is the jejunum,[20] which is where the majority of cholesterol absorption occurs. Thus, the inhibition of intestinal ACAT

Scheme I



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would be expected to lead to decreased cholesterol esterification resulting in diminished intestinal absorption. An additional reduction in the intracellular accumulation of cholesteryl esters might also be expected. Therefore, ACAT inhibitors offer potential for exhibiting both hypocholesterolemic and antiatherosclerotic activity.

A number of compounds have previously been reported to inhibit ACAT-catalyzed cholesterol esterification. Bell has reported[21] that the local anesthetics lidocaine, tetracaine, benzocaine, and dibucaine are inhibitors are ACAT activity over the concentration range of 0.25–5 mM. Bell has also reported[22] that chlorpromazine was a somewhat more potent ACAT inhibitor with an IC_{50} of about 0.1 mM in rabbit arterial microsomes. The hypolipidemic agents clofibrate and bezafibrate have also been shown to inhibit cholesterol esterification in cultured smooth-muscle cells,[23] fibroblasts, and macrophages.[24] These hypolipidemics have IC_{50} values in the range of 0.5–2 mM. More potent ACAT inhibitors include progesterone[25] and the experimental drugs 57-118 (the ethyl ester of (*Z*)-*N*-(1-oxo-9-octadecenyl)-D,L-tryptophan)[26] and 58-035 (3-decyldimethylsilyl)-*N*-[2-(4-methylphenyl)-1-phenethyl]propionamide).[27] Among all these compounds, only progesterone, 57-118, and 58-035 are sufficiently potent to offer the potential of affecting ACAT activity at concentrations that conceivably might be achieved in vivo.

In the course of investigating ACAT inhibitors of novel structure, we discovered that *N'*-aryl-*N*,*N*-dialkylureas showed consistent ACAT inhibitory activity as a class. Subsequent synthetic and structure–activity studies resulted in the preparation of *N'*-(2,4-dimethylphenyl)-*N*-benzyl-*N*-*n*-butylurea (**115**), the prototype urea in the series. Extensive biological evaluation and metabolic study of **115** and subsequent analogues will be described in forthcoming publications. The synthesis of a metabolically stable analogue of **115** has been described.[1]

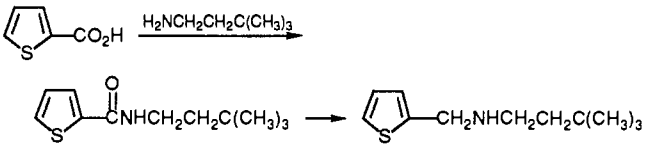
N'-(2,4-dimethylphenyl)-*N*-benzyl-*N*-butylurea (**115**)

The trisubstituted urea analogues described in this paper arose from the systematic variation of the three N-substitution sites on the urea backbone. Compounds were evaluated in vitro as ACAT inhibitors and in vivo as inhibitors of dietary-cholesterol absorption. Structure–activity trends were often well-defined, in particular, with respect to the length of the *N*-*n*-alkyl chain and the nature of the substituent on the aniline ring.

Chemistry

All of the trisubstituted ureas shown in Tables I–IV were prepared as illustrated in Scheme I by reactions of aryl isocyanates with secondary amines (method G).

Scheme II



Many of the secondary amines required for these syntheses were commercially available. Others, for example, were prepared as illustrated in Scheme II. In general, carboxylic acids were converted via activated derivatives to N-substituted carboxamides (Table V) by using methods A–C. These carboxamides were reduced to secondary amines (Table VI) with a variety of reducing agents including diborane (method D), lithium aluminum hydride (method E), and sodium dihydrobis(2-methoxyethoxy)-aluminate (method F).

Biology

The analogues whose syntheses are described in this paper, as well as commercially available analogues relevant to the structure–activity study, were screened for two types of biological activity. First, the compounds were tested in vitro to measure their ability to inhibit ACAT. In the initial test, the percent enzyme inhibition was measured at a compound concentration of 5.2 μg/mL with enzyme derived from rat adrenal glands. Highly active compounds were studied further, and IC_{50} values were obtained with enzyme derived from the same tissue. Selected analogues were then studied with smooth-muscle cells in culture and IC_{50} values for inhibition of ACAT in this system were obtained.

Second, certain analogues were tested in vivo to measure the hypocholesterolemic activity. In these tests, cholesterol-fed rats were dosed with the compounds for 14 days and final values of both serum sterol and liver sterol levels were obtained. In Tables I–IV these values are expressed as a percent of control values.

Table I shows data for a series of *N*,*N*-dialkyl-*N'*-arylureas. An examination of the ACAT inhibition data for compounds in which the substituent X is 2,4-dimethyl and the size of the R substituent is varied reveals that alkyl groups containing from 4 to 10 carbons (**14** and **42–53**) are compatible with activity while smaller (**1–6**) or larger (**54–58**) alkyl groups are incompatible with activity. Data for compounds in which the R groups are *n*-butyl while the substituent X is varied show that a variety of aromatic substituents (**7–41**) are compatible with activity; however, certain polar substituents (**25**, **36**, and **40**) diminish activity. Based on IC_{50} values, compounds **47** and **54** are the most potent ACAT inhibitors shown in the table.

The hypocholesterolemic data of Table I indicates that serum sterol and liver sterol lowering activity cannot generally be predicted on the basis of ACAT inhibitory activity. Some of the more active ACAT inhibitors (e.g. **14** and **18**) exhibit hypocholesterolemic activity while others (e.g. **24** and **31**) fail to show hypocholesterolemic activity. The best combination of ACAT inhibitory and hypocholesterolemic activity was exhibited by compounds in which the R groups contained six to eight carbons (**47**, **48**, and **49**).

Table II shows data for a series of *N*,*N*-dibenzyl-*N'*-arylureas. As with the 1,1-dialkyl congeners of Table I, a wide variety of aryl substituents (X) are compatible with ACAT inhibition activity; however, the presence of a carboxy group (**109**) greatly diminishes activity. The hypocholesterolemic data of Table II shows a somewhat better correlation between ACAT inhibitory activity and serum and liver sterol lowering activity. The analogue with

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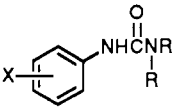
Table I. Physical Data and Biological Activities of *N,N*-Dialkyl-*N'*-arylureas



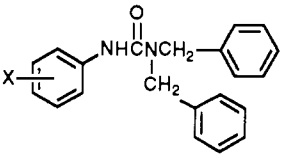
no.	X	R	formula[i,r]	crystn solvent	mp, °C	yld[a]	ACAT inhibn %[b]	ACAT inhibn ADL[c]	ACAT inhibn SMC[d]	sterols LS[e]	sterols SS[f]
1	2,4-dimethyl	methyl					−7				
2	2,4-dimethyl	ethyl	$C_{13}H_{20}N_2O$	EtOAc/pentane	70–80	86	18				
3	2,4-dimethyl	*n*-propyl					8				
4	2,4-dimethyl	isopropyl					−1				
5	2,4-dimethyl	allyl					43				
6	2,4-dimethyl	propargyl	$C_{15}H_{16}N_2O$	hexane	116–118	90	33			93	73
7	hydrogen	*n*-butyl					64			100	121
8	2-methyl	*n*-butyl	$C_{16}H_{26}N_2O$[j]		oil	79	62			111	81
9	3-methyl	*n*-butyl					78	1.25	6.28		
10	4-methyl	*n*-butyl	$C_{16}H_{26}N_2O$	hexane	90–91	94	80				
11	4-isopropyl	*n*-butyl	$C_{18}H_{30}N_2O$	hexane	60–62	87	76				
12	4-butyl	*n*-butyl	$C_{19}H_{32}N_2O$[k]	hexane	44–46	90	94	2.78		100	63
13	2,3-dimethyl	*n*-butyl					88				
14	2,4-dimethyl	*n*-butyl					81	2.72	2.76	78	81
15	2,5-dimethyl	*n*-butyl					96			110	127
16	2,6-dimethyl	*n*-butyl	$C_{17}H_{28}N_2O$[l]	hexane	131–134	67	85				
17	3,4-dimethyl	*n*-butyl	$C_{17}H_{28}N_2O$		74–76	95	49				
18	3,5-dimethyl	*n*-butyl					84	0.98		76	100
19	2,4,6-trimethyl	*n*-butyl	$C_{18}H_{30}N_2O$		119–120	58	74				
20	4-methoxy	*n*-butyl					59			109	127
21	4-ethoxy	*n*-butyl	$C_{17}H_{28}N_2O_2$[m]	hexane	59–60	96	79				
22	3-methylthio	*n*-butyl	$C_{16}H_{26}N_2OS$	hexane	65–66	70	85				
23	4-fluoro	*n*-butyl					56				
24	3-chloro	*n*-butyl					88	2.73	9.08	100	105
25	2-bromo	*n*-butyl					51				
26	3-bromo	*n*-butyl	$C_{15}H_{23}BrN_2O$	hexane	79–80	87	86				
27	4-iodo	*n*-butyl	$C_{15}H_{23}IN_2O$	hexane	113–114	84	83				
28	2,3-dichloro	*n*-butyl					85				
29	3,5-dichloro	*n*-butyl	$C_{15}H_{22}Cl_2N_2O$		80–81	90	79	1.39		93	76
30	3-chloro-2-methyl	*n*-butyl	$C_{16}H_{25}ClN_2O$	hexane	73–75	95	80	1.21		93	87
31	3-chloro-4-methyl	*n*-butyl					91	1.91	3.78	98	110
32	4-chloro-2-methyl	*n*-butyl					88				
33	5-chloro-2-methyl	*n*-butyl	$C_{16}H_{25}ClN_2O$		55–56	89	75				
34	3-chloro-4-fluoro	*n*-butyl	$C_{15}H_{22}ClFN_2O$	hexane	80–81	92	91	343		108	83
35	2,4,5-trichloro	*n*-butyl					62			103	111
36	3-trifluoromethyl	*n*-butyl					75			91	100
37	4-chloro-3-trifluoromethyl	*n*-butyl	$C_{16}H_{22}ClF_3N_2O$	hexane	84–85	78	87	3.69			
38	4-nitro	*n*-butyl					75				
39	3-acetyl	*n*-butyl	$C_{17}H_{26}N_2O_2$	ether	80–81	96	51			100	64
40	4-acetyl	*n*-butyl	$C_{17}H_{26}N_2O_2$	THF	95–96	57	55				
41	4-nitro-2-chloro	*n*-butyl					87				
42	2,4-dimethyl	isobutyl					80				
43	2,4-dimethyl	*sec*-butyl	$C_{17}H_{28}N_2O$	EtOAc/hexane	97–99	37	78				
44	2,4-dimethyl	*n*-pentyl	$C_{19}H_{32}N_2O$		45–46	94	90	0.29		49	82
45	2,4-dimethyl	isopentyl	$C_{19}H_{32}N_2O$		66–68	81	89	1.43		65	66
46	2,4-dimethyl	cyclopentyl	$C_{19}H_{28}N_2O$	hexane	136–138	26	90			113	98
47	2,4-dimethyl	*n*-hexyl	$C_{21}H_{36}N_2O$[n]		oil	85	95	0.11		36	59
48	2,4-dimethyl	*n*-heptyl	$C_{23}H_{40}N_2O$		oil	95	91	0.26		15	65
49	2,4-dimethyl	*n*-octyl	$C_{25}H_{44}N_2O$		oil	91	89	0.55	0.51	22	47
50	2,4-dimethyl	2-ethylhexyl	$C_{25}H_{44}N_2O$	Kugelrohr[g]	36–38	72	86				
51	2,4-dimethyl	*n*-nonyl	$C_{27}H_{48}N_2O$	HPLC[h]	oil	73	90				
52	2,4-dimethyl	3,5,5-trimethylhexyl	$C_{27}H_{48}N_2O$	Kugelrohr[g]	68–70	68	90			70	71
53	2,4-dimethyl	*n*-decyl	$C_{29}H_{52}N_2O$[o]		oil	89	64	0.28		66	71
54	2,4-dimethyl	4-cyclohexylbutyl	$C_{29}H_{48}N_2OP$	petr ether	85–86	55	86	0.19	2.03	106	80
55	2,4-dimethyl	*n*-undecyl	$C_{31}H_{56}N_2O$	HPLC[h]	oil	84	49				
56	2,4-dimethyl	*n*-dodecyl	$C_{33}H_{60}N_2O$[q]	HPLC[h]	oil	86	26			120	86
57	2,4-dimethyl	*n*-tetradecyl	$C_{37}H_{68}N_2O$	HPLC[h]	oil	85	−7			121	107
58	2,4-dimethyl	*n*-octadecyl	$C_{45}H_{84}N_2O$	ether	55–57	48	−6			123	106

[a] Yield (%). [b] Percent inhibition of the rat adrenal ACAT enzyme under the conditions described in the Biological Methods section. [c] IC_{50} (μg/mL) for the rat adrenal enzyme. [d] IC_{50} (μg/mL) for the smooth-muscle enzyme. [e] Liver sterol expressed as a percentage of control values. [f] Serum sterol expressed as a percentage of control values. [g] Purified by bulb to bulb distillation using a Kugelrohr apparatus. [h] Purified by high-pressure liquid chromatography. [i] Satisfactory elemental analyses were obtained for C, H, N (S and halogen where appropriate) unless indicated otherwise. [j] C: calcd, 73.24; found, 73.73. [k] C: calcd, 74.95; found, 75.38. [l] H: calcd, 10.21; found, 9.52. [m] C: calcd, 69.83; found, 70.28. [n] H: calcd, 10.91; found, 10.06. [o] H: calcd, 11.78; found, 12.22. [p] C: calcd, 80.89; found, 79.16; H: calcd 8.89; found, 10.88. [q] H: calcd, 12.07; found, 12.51. [r] When no physical data is given, compounds were commercially available.

the best combination of the two activities (**70**) is comparable to compound **47**.

Shown in Table III are a series of *N*-benzyl-*N*-*n*-butyl-*N'*-arylureas. The most active compounds (**115**, **119**, **120**, and **125**) exhibit a combination of ACAT inhibitory and hypocholesterolemic activity comparable to **47** and **70**.

Table II. Physical Data and Biological Activities of *N,N*-Dibenzyl-*N'*-arylureas



no.	X	formula[g,n]	crystn solvent	mp, °C	yld[a]	ACAT inhibn %[b]	ACAT inhibn ADL[c]	ACAT inhibn SMC[d]	sterols LS[e]	sterols SS[f]
59	hydrogen					90				
60	2-methyl					77				
61	3-methyl	$C_{22}H_{22}N_2O$[h]	hexane	126–128	96	89				
62	4-methyl	$C_{22}H_{22}N_2O$	hexane	170–175	95	87				
63	4-butyl	$C_{25}H_{28}N_2O$	hexane	104–106	92	91			87	62
64	2,3-dimethyl					85			51	65
65	2,4-dimethyl					90	0.59	1.33	31	52
66	2,5-dimethyl					89				
67	2,6-dimethyl					56				
68	3,4-dimethyl					72			60	97
69	2,6-diethyl					72				
70	2,4,5-trimethyl	$C_{24}H_{26}N_2O$	hexane	141–142	89	69	0.16	0.39	20	47
71	2,4,6-trimethyl	$C_{24}H_{26}N_2O$	hexane	163–165	92	37	1.34		28	32
72	2-methyl-6-ethyl					74				
73	2-methoxy					91				
74	3-methoxy					87				
75	4-methoxy					72				
76	2,5-dimethoxy					88				
77	4-ethoxy	$C_{23}H_{24}N_2O_2$	hexane	129–130	95	96	3.47			
78	4-butoxy	$C_{25}H_{28}N_2O_2$	hexane	119–120	87	90				
79	4-phenoxy	$C_{27}H_{24}N_2O_2$[i]	hexane	145–146	86	94	1.32		89	66
80	4-methylthio	$C_{22}H_{22}N_2OS$	hexane	196–198	92	67				
81	2-methoxy-5-methyl					88			44	83
82	2-chloro					88				
83	3-chloro					94	2.72	13.53		
84	4-chloro					78				
85	2-bromo	$C_{21}H_{19}BrN_2O$	hexane	118–119	90	94				
86	3-bromo	$C_{21}H_{19}BrN_2O$	hexane	102–103	94	92	2.28		86	92
87	4-bromo					80				
88	4-iodo	$C_{21}H_{19}IN_2O$[h]	THF	233–235	66	85				
89	2,5-difluoro	$C_{21}H_{18}F_2N_2O$	hexane	67–68	56	72				
90	2,3-dichloro					80				
91	2,4-dichloro					83			72	77
92	2,5-dichloro					82				
93	2,6-dichloro					89				
94	3,4-dichloro					95				
95	3,5-dichloro	$C_{21}H_{18}Cl_2N_2O$	hexane	144–145	94	86	1.53			
96	2-chloro-6-methyl					84				
97	3-chloro-2-methyl	$C_{22}H_{21}ClN_2O$	hexane	138–139	87	84	3.06			
98	3-chloro-4-methyl					94	6.88	1.06	97	84
99	4-chloro-2-methyl					63	1.23		26	53
100	5-chloro-2-methyl					71			66	97
101	2-trifluoromethyl	$C_{22}H_{19}N_2F_3O$	ethanol	114–115	77	68			76	165
102	3-trifluoromethyl					94	1.11	3.65		
103	4-chloro-2-trifluoromethyl	$C_{22}H_{18}ClF_3N_2O$	hexane	82–83	75	82			57	66
104	4-chloro-3-trifluoromethyl	$C_{22}H_{18}ClF_3N_2O$	hexane	146–148	91	92				
105	3-nitro					81				
106	4-nitro					52				
107	3-acetyl	$C_{23}H_{22}N_2O_2$[m]	ether	124–127	85	81				
108	4-carboethoxy	$C_{24}H_{24}N_2O_3$	hexane	91–93	30	93			83	120
109	4-carboxy	$C_{22}H_{20}N_2O_3$	ethanol	210–214		14				
110	hydrogen					82				

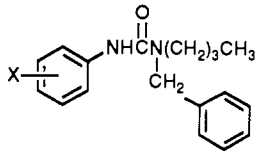
[a] Yield (%). [b] Percent inhibition of the rat adrenal ACAT enzyme under the conditions described in the Biological Methods section. [c] IC_{50} (μg/mL) for the rat adrenal enzyme. [d] IC_{50} (μg/mL) for the smooth-muscle enzyme. [e] Liver sterol expressed as a percentage of control values. [f] Serum sterol expressed as a percentage of control values. [g] Satisfactory elemental analyses were obtained for C, H, N (S and halogen were appropriate) unless indicated otherwise. [h] N: calcd, 8.48; found, 7.89. [i] N: calcd, 6.36; found, 6.84. [j] Footnote deleted in press. [k] C: calcd, 57.03; found, 56.23. [l] Footnote deleted in press. [m] C: calcd, 77.07; found, 77.53. [n] When no physical data is given, compounds were comercially available.

Table IV shows a series of arylureas in which the group R_1 and R_2 are varied independently. It is evident that *N,N*-disubstituted ureas (**135–141**) are generally less active than *N,N,N'*-trisubstituted ureas. It also appears that when R_2 is aryl (**143–145**, **162**, and **163**) ACAT inhibitory activity is diminished. When R_2 is heteroarylmethylene (**156–159**) activity is maintained. In fact, the analogue of Table IV with the best combination of activities (**157**) is a 2-furyl compound.

Of the various types of analogues shown in Tables I–IV, the compounds with the best combination of activities[28]

(28) Biological activity data comparable to that shown in Tables I–IV for the metabolically stable analogue of reference 1 is as follows: ADL, IC_{50} = 0.57 μg/mL; SMC, IC_{50} = 2.02 μg/mL; LS, 24%, and SS, 24%.

Table III. Physical Data and Biological Activities of *N*-Benzyl-*N*-*n*-butyl-*N'*-arylureas



						ACAT inhibn			sterols	
no.	X	formula[i]	crystn solvent	mp, °C	yld[a]	%[b]	ADL[c]	SMC[d]	LS[e]	SS[f]
111	2-methyl	$C_{19}H_{24}N_2O$		48–53	81	79			137	109
112	3-methyl	$C_{19}H_{24}N_2O$	hexane	91–92	87	92				
113	4-methyl	$C_{19}H_{24}N_2O$	hexane	102–103	93	78			107	106
114	2,3-dimethyl	$C_{20}H_{26}N_2O$	hexane	77–78	87	86				
115	2,4-dimethyl	$C_{20}H_{26}N_2O$	pentane	70–71	86	91	1.49	0.57	75	70
116	2,5-dimethyl	$C_{20}H_{26}N_2O$	hexane	87–89	86	93				
117	2,6-dimethyl	$C_{20}H_{26}N_2O$	hexane	125–126	84	83			91	68
118	3,4-dimethyl	$C_{20}H_{26}N_2O$	hexane	94–95	97	87				
119	3,5-dimethyl	$C_{20}H_{26}N_2O$	hexane	108–109	85	94			75	93
120	2,4,6-trimethyl	$C_{21}H_{28}N_2O$	hexane	141–144	85	76			37	63
121	3,4,5-trimethoxy	$C_{21}H_{28}N_2O_4$	hexane	144–145	94	74				
122	3-chloro	$C_{18}H_{21}ClN_2O$	hexane	69–70	89	89				
123	3,4-dichloro	$C_{18}H_{20}Cl_2N_2O$	ethanol	102–105	63	96				
124	3,5-dichloro	$C_{18}H_{20}Cl_2N_2O$	THF/hexane	100–103	88	91			107	120
125	2,4,6-trichloro	$C_{18}H_{19}Cl_3N_2O$	CH_2Cl_2	94–96	75	88		1.37	32	48
126	3-trifluoromethyl	$C_{19}H_{21}F_3N_2O$	hexane	86–87	87	86			104	84
127	2-nitro	$C_{18}H_{21}N_3O_3$	HPLC[g]	oil	79	37				
128	4-chloro-2-methyl	$C_{19}H_{23}ClN_2O$	hexane	83–84	60		2.53		62	72
129	3-chloro-2-methoxy	$C_{19}H_{23}ClN_2O_2$	Kugelrohr[h]	52–54	87	85				
130	5-chloro-2-methoxy	$C_{19}H_{23}ClN_2O_2$	Kugelrohr[h]	61–63	79	81				
131	5-chloro-2-hydroxy	$C_{18}H_{21}ClN_2O_2$	hexane	113–115	90	86				
132	4-amino-3,5-dichloro	$C_{18}H_{21}Cl_2N_3O$	toluene/hexane	121–124	46	61				
133	4-carboxy-2-methyl	$C_{20}H_{24}N_2O_3$	HPLC[g]	156–158	50				88	76
134	4-methyl					14				

[a] Yield (%). [b] Percent inhibition of the rat adrenal ACAT enzyme under the conditions described in the Biological Methods sction. [c] IC_{50} (μg/mL) for the rat adrenal enzyme. [d] IC_{50} (μg/mL) for the smooth-muscle enzyme. [e] Liver sterol expressed as a percentage of control values. [f] Serum sterol expressed as a percentage of control values. [g] Purified by high-pressure liquid chromatography. [h] Purified by bulb to bulb distillation using a Kugelrohr apparatus. [i] Satisfactory elemental analyses were obtained for C, H, N (S and halogen where appropriate) unless indicated otherwise.

are **47**, **70**, **115**, and **157**. On the basis of structural novelty and ease of synthesis as well as its ACAT inhibitory and hypocholesterolemic activity, **115** was the initial choice for further evaluation. In cholesterol-fed rabbits, plasma cholesterol levels were decreased by 44% and 38%, respectively, at doses of 110 and 35 mg/kg of body weight per day after 35 days (Table VII). Despite this modest hypocholesterolemic activity in rabbits, no such effect was noted in cholesterol-fed cynomologous monkeys. At a dose of 85 mg/kg per day, **115** was completely ineffective in lowering serum cholesterol over a 30-week period.

One hypothesis which would account for this lack of activity in the monkey is that **115** undergoes rapid metabolic degradation to an inactive metabolite. On the basis of this hypothesis, a study of the metabolism of **115** was undertaken. The results of this study as well as an investigation of the metabolism of related trisubstituted ureas is the subject of the next paper in this series.

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Ultraviolet spectra were determined in methanol solution with a Hewlett-Packard 8450A spectrophotometer and infrared spectra were determined in potassium bromide disks or as smears between NaCl plates with a Nicolet 7199FT spectrophotometer. Proton magnetic resonance spectra were determined with a Varian 4100 and a Nicolet 300 spectrometer using tetramethylsilane as an internal standard. The high-pressure liquid chromatography purifications were carried out using a Water's Associates Prep 500 HPLC instrument. Analogues in Tables I–IV shown without physical data were purchased from the Alfred Bader Chemical Co.

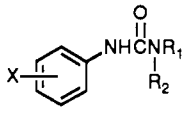
Method A. *N*-(3,3-Dimethylbutyl)-2-thiophenecarboxamide. To a suspension of 3.90 g (30.4 mmol) of 2-thiophenecarboxylic acid in 50 mL of CH_2Cl_2 was added 5.60 mL (9.13 g, 76.7 mmol) of thionyl chloride, and the resulting mixture was stirred at room temperature overnight. The solvent was evaporated to dryness to yield 4.5 g of 2-thiophenecarboxylic acid chloride as a colorless liquid.

To a cold (0 °C) solution of 3.00 g (29.6 mmol) of 3,3-dimethylbutylamine and 8.4 mL (6.10 g, 60.3 mmol) of Et_3N in 40 mL of CH_2Cl_2 was added dropwise a solution of 4.50 g (30.4 mmol) of 2-thiophenecarboxylic acid chloride in 10 mL of CH_2Cl_2. The resulting mixture was stirred at room temperature for 3 h and diluted with water, and the two layers were separated. The organic layer was washed with 5 N HCl and saturated NaCl solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was evaporated to dryness to yield a solid. The solid was triturated with hexane and collected by filtration to yield 5.70 g (91%) of *N*-(3,3-dimethylbutyl)-2-thiophenecarboxamide as a white solid, mp 145–146 °C.

Method B. *N*-Butyl-1,3-benzodioxole-5-carboxamide. A mixture of 16.6 g (0.100 mol) of piperonylic acid, 14.6 g (0.200 mol) of *n*-butylamine, 20.2 g (0.200 mol) of Et_3N, and 24.6 mL (28.4 g, 0.200 mol) of boron trifluoride etherate in 800 mL of toluene was heated under reflux overnight. The mixture was cooled and washed with 10% NaOH, 10% HCl, and water and then dried over anhydrous $MgSO_4$ and filtered. The filtrate was evaporated to yield a brown oil which solidified on standing. The solid was dissolved in CH_2Cl_2, the solution was clarified with Darco, and the filtrate was evaporated to yield an oil which solidified on trituration with hexane. The solid was collected by filtration to yield 10.5 g (47%) of *N*-butyl-1,3-benzodioxole-5-carboxamide as a beige solid, mp 68–70 °C.

Method C. *N*-Heptyl-2-furancarboxamide. A mixture of 4.90 mL (6.50 g, 50.0 mmol) of 2-furoyl chloride, 7.40 mL (5.80 g, 50.0 mmol) of *n*-heptylamine, 7.40 g (70.0 mmol) of anhydrous Na_2CO_3, and 90 mL of 1,2-dimethoxyethane was heated under reflux overnight. The mixture was cooled and filtered and the filtrate was evaporated to dryness to yield 10.4 g of oil. The oil

Table IV. Physical Data and Biological Activities of *N,N*-Disubstituted-*N'*-arylureas



no.	X	R_1	R_2	formula[i,j]	crystn solvent	mp, °C	yld[a]	ACAT inhibn %[b]	ACAT inhibn ADL[c]	ACAT inhibn SMC[d]	sterols LS[e]	sterols SS[f]
135	3-methoxy	H	benzyl					34			94	110
136	2-chloro	H	benzyl					50			96	92
137	2,4-dimethyl	H	benzyl					35				
138	2-methyl-5-chloro	H	benzyl					33				
139	2,4-dimethyl	H	1-methylbenzyl	$C_{17}H_{20}N_2O$	hexane	183–185	94	29				
140	2,4-dimethyl	H	1-methylbenzyl	$C_{17}H_{20}N_2O$[k]	hexane	185–186	97	20				
141	2,4-dimethyl	H	2,4-dimethylphenyl					10			85	100
142	3,4-dichloro	methyl	*n*-butyl					64				
143	2,5-dichloro	methyl	phenyl					48				
144	2-methyl	ethyl	phenyl					9				
145	2,4-dimethyl	*n*-butyl	phenyl					70	6.34	7.95	107	99
146	2,4-dimethyl	*n*-butyl	4-cyclohexylbutyl	$C_{23}H_{38}N_2O$	HPLC[g]	oil	90	40				
147	2,4-dimethyl	*n*-butyl	2-(1-adamantyl)-ethyl	$C_{25}H_{38}N_2O$		134–135	92	56				
148	2,4-dimethyl	*n*-butyl	2,2-diphenylpropyl	$C_{28}H_{34}N_2O$	hexane	159–160	82	97				
149	2,4-dimethyl	*n*-butyl	3,3-diphenylpropyl	$C_{28}H_{34}N_2O$		94–95	89	53				
150	2,4-dimethyl	*n*-butyl	2,2-bis(4-chlorophenyl)ethyl	$C_{27}H_{30}Cl_2N_2O$	hexane	145–146	92	81			84	110
151	2,4-dimethyl	*n*-butyl	2-cyclohexyl-2-phenylethyl	$C_{27}H_{38}N_2O$		112–113	82	74				
152	2,4-dimethyl	*n*-butyl	5-(benzdioxoyl)-methyl	$C_{21}H_{26}N_2O_3$	Kugelrohr[h]	oil	97	88	2.01		46	64
153	2,4-difluoro	2-thienylmethyl	3,3-dimethylbutyl	$C_{18}H_{22}F_2N_2OS$[l]	Kugelrohr[h]	oil	61		2.38	5.97	73	66
154	3-chloro-2-methyl	2-thienylmethyl	3,3-dimethylbutyl	$C_{19}H_{25}ClN_2OS$	Kugelrohr[h]	111–113	64		2.47	2.30	64	62
155	2,4,6-trichloro	2-thienylmethyl	3,3-dimethylbutyl	$C_{18}H_{21}Cl_3N_2OS$	Kugelrohr[h]	118–120	91		0.41	1.07	56	58
156	2,4,5-trimethyl	*n*-heptyl	2-furylmethyl	$C_{22}H_{32}N_2O_2$	hexane	65–67	86	94	0.80	0.05	38	44
157	2,4,6-trichloro	*n*-heptyl	2-furylmethyl	$C_{19}H_{23}Cl_3N_2O_2$	Kugelrohr[h]	oil	87	96	0.17	0.13	34	37
158	2,4,5-trimethyl	*n*-heptyl	2-thienylmethyl	$C_{22}H_{32}N_2OS$	hexane	84–85	94		0.54		25	54
159	2,4,5-trichloro	*n*-heptyl	2-thienylmethyl	$C_{19}H_{23}Cl_3N_2OS$	Kugelrohr[h]	72–73	72		0.21		28	56
160	2,4-dimethyl	oleyl	4-butylbenzyl	$C_{38}H_{60}N_2O$[m]		oil	76	42				
161	2,4-dimethyl	oleyl	4-butylbenzyl	$C_{39}H_{62}N_2O$	HPLC[g]	oil	69	9			87	130
162	4-chloro	benzyl	phenyl					68			102	67
163	2,4-dibromo	benzyl	phenyl	$C_{20}H_{16}Br_2N_2O$	hexane	107–108	85	82				

[a] Yield (%). [b] Percent inhibition of the rat adrenal ACAT enzyme under the conditions described in the Biological Methods section. [c] IC_{50} (μg/mL) for the rat adrenal enzyme. [d] IC_{50} (μg/mL) for the smooth-muscle enzyme. [e] Liver sterol expressed as a percentage of control values. [f] Serum sterol expressed as a percentage of control values. [g] Purified by high-pressure liquid chromatography. [h] Purified by bulb to bulb distillation using a Kugelrohr apparatus. [i] Satisfactory elemental analysis were obtained for C, H, N (S and halogen where appropriate) unless indicated otherwise. [j] When no physical data is given, compounds were comercially available. [k] C: calcd, 76.08; found, 75.59. [l] F: calcd, 10.78; found, 11.26. [m] C: calcd, 81.37; found, 80.96.

Table V. Physical Data for Carboxamide Intermediates

no.	A	B	formula[a]	crystn solvent	mp, °C	method	% yield
164	1-adamantylmethyl	*n*-butyl	$C_{16}H_{27}NO$[b]	Kugelrohr[f]	82–83	B	77
165	1,1-diphenylethyl	*n*-butyl	$C_{19}H_{23}NO$	Kugelrohr[f]	59–60	A	76
166	1,1-bis(4-chlorophenyl)methyl	*n*-butyl	$C_{18}H_{19}Cl_2NO$	Kugelrohr[f]	119–121	B	77
167	1-cyclohexyl-1-phenylmethyl	*n*-butyl	$C_{18}H_{27}NO$[c]	Kugelrohr[f]	79–81	B	64
168	2-thienyl	3,3-dimethylbutyl	$C_{11}H_{17}NOS$	Kugelrohr[f]	145–146	A	91
169	2-furyl	*n*-heptyl	$C_{12}H_{19}NO_2$[d]	Kugelrohr[f]	oil	C	87
170	2-thienyl	*n*-heptyl	$C_{12}H_{19}NOS$	hexane	62–63	A	82
171	4-*n*-butylphenyl	oleyl	$C_{29}H_{49}NO$	HPLC[g]	33–34	A	88
172	5-benzodioxolyl	*n*-butyl	$C_{12}H_{15}NO_3$[e]	Kugelrohr[f]	68–70	B	47
173	2,2-diphenylethyl	*n*-butyl	$C_{19}H_{23}NO$	ether	75–76	B	85

[a] Satisfactory elemental analyses were obtained for C, H, N (S and halogen where appropriate) unless indicated otherwise. [b] C: calcd, 77.06; found 76.46. H: calcd, 10.91; found, 10.43. [c] N: calcd, 5.12; found, 3.64. [d] C: calcd, 68.87; found, 68.17. [e] N: calcd, 6.33; found, 5.91. [f] Purified by bulb to bulb distillation suing a Kugelrohr apparatus. [g] Purified by high-pressure liquid chromatography.

was purified by Kugelrohr distillation to yield 9.00 g (87%) of *N*-heptyl-2-furancarboxamide as a colorless liquid.

Method D. *N*-Heptyl-2-furanmethanamine. A mixture of 9.00 g (43.0 mmol) of *N*-heptyl-2-furancarboxamide, 90.0 mL (90.0 mmol) of borane (1.0 M solution in THF), and 30 mL of anhydrous THF was heated under reflux overnight under argon. A solution of 30.0 mL of 6 N HCl was added dropwise and the resulting mixture was stirred at room temperature overnight. The THF was removed in vacuo, and the residue was diluted with water, rendered alkaline with 10 N NaOH, and extracted with Et_2O. The Et_2O extract was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was evaporated to yield yellow oil. The oil was purified by Kugelrohr distillation to yield 5.60 g (67%) of *N*-heptyl-2-furanmethanamine as a colorless liquid.

Method E. *N*-Heptyl-2-thiophenemethanamine. To a stirred mixture of 30.0 g (79.0 mmol) of lithium aluminum hydride in 100 mL of Et_2O was added dropwise a solution of 8.00 g (35.0 mmol) of *N*-heptyl-2-thiophenecarboxamide in 30 mL of anhydrous THF over a period of 10 min. The resulting mixture was

Table VI. Physical Data for Secondary Amine Intermediates

ACH_2NHB

no.	A	B	formula[a]	crystn solvent[d]	mp, °C	method	% yield
174	1-adamantylmethyl	*n*-butyl	$C_{16}H_{29}N$	Kugelrohr	oil	D	82
175	1,1-diphenylethyl	*n*-butyl	$C_{19}H_{25}N$	Kugelrhor	oil	D	98
176	1,1-di-(4-chlorophenyl)methyl	*n*-butyl	$C_{18}H_{21}Cl_2N$	Kugelrohr	oil	D	72
177	1-cyclohexyl-1-phenylmethyl	*n*-butyl	$C_{18}H_{29}N$	Kugelrohr	oil	D	79
178	2-thienyl	3,3-dimethylbutyl	$C_{11}H_{19}NS$	Kugelrohr	oil	F	85
179	2-furyl	*n*-heptyl	$C_{12}H_{21}NO$[b]	Kugelrohr	oil	D	67
180	2-thienyl	*n*-heptyl	$C_{12}H_{21}NS$	Kugelrohr	oil	E	96
181	4-*n*-butylphenyl	oleyl	$C_{29}H_{51}N$[c]	Kugelrohr	oil	D	40
182	5-benzodioxolyl	*n*-butyl	$C_{12}H_{17}NO_2$	Kugelrohr	oil	D	85
183	2,2-diphenylethyl	*n*-butyl	$C_{19}H_{25}N$	Kugelrohr	oil	D	61

[a] Satisfactory elemental analyses were obtained for C, H, N (S and halogen where appropriate) unless indicated otherwise. [b] C: calcd, 73.79; found, 73.02. [c] C: calcd, 84.19; found 83.24. [d] Purified by bulb to bulb distillation using a Kugelrohr apparatus.

Table VII. Effect of 115 on Rabbit Serum Cholesterol Levels

dose of 115, mg/kg per day	serum cholesterol, mg/dL day 0	day 7	day 21	day 35
110	278 ± 27	230 ± 26	343 ± 65	405 ± 64
35	270 ± 34	255 ± 38	357 ± 58	488 ± 65
11	307 ± 37	340 ± 51	556 ± 89	722 ± 114
control	272 ± 28	412 ± 56	593 ± 82	749 ± 122

heated under reflux overnight under argon. The mixture was cooled to room temperature, treated with sodium sulfate decahydrate in several portions, stirred for 30 min, and filtered. The solid was washed with Et_2O and then evaporated to dryness to yield an oil. The oil was purified by Kugelrohr distillation to yield 7.20 g (96%) of *N*-heptyl-2-thiophenemethanamine as a colorless liquid.

Method F. *N*-(3,3-Dimethylbutyl)-2-thiophenemethanamine. To a solution of 17.0 mL (61.0 mmol) of Vitride (70% solution in toluene) in 50 mL of toluene was added dropwise a solution of 5.00 g (23.7 mmol) of *N*-(3,3-dimethylbutyl)-2-thiophenecarboxamide in 50 mL of anhydrous THF over a period of 15 min under argon. The resulting mixture was heated under reflux for 2 h, cooled, and treated with 30 mL of 2.5 N NaOH solution. This mixture was stirred for 30 min, and the layers were separated. The organic layer was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated to yield 5.00 g of brown liquid. The liquid was purified by Kugelrohr distillation to yield 4.00 g (85%) of *N*-(3,3-dimethylbutyl)-2-thiophenemethanamine as a colorless liquid.

Method G. *N'*-(2,4-Dimethylphenyl)-*N*-benzyl-*N*-butylurea. To a solution of 4.89 g (30.0 mmol) of 2,4-dimethylphenyl isocyanate in 150 mL of hexane was added a solution of 4.41 g (30.0 mmol) of *n*-benzyl-*n*-butylamine in 100 mL of hexane. The resulting solution was stirred at ambient temperature for 2 h. The solvent was evaporated to dryness to yield an oil which was dissolved in pentane and allowed to remain at room temperature overnight. The solid was collected by filtration, washed with pentane, and dried to yield 8.00 g (86%) of *N'*-(2,4-dimethylphenyl)-*N*-benzyl-*N*-butylurea (**115**) as a white solid, mp 70–71 °C.

Biological Methods. Adrenal-Derived ACAT. The compounds were tested for inhibition of fatty acyl CoA:cholesterol *O*-acyltransferase (ACAT)[10] as follows. Rat adrenals were homogenized in 0.2 M monobasic potassium phosphate buffer (pH 7.4) and centrifuged at 1000*g* for 15 min at 5 °C. The supernatant, containing the microsomal fraction, served as the source of the ACAT enzyme. A mixture comprising 50 parts of adrenal supernatant, 10 parts of bovine serum albumin (50 mg/mL), 3 parts of test compound (final concentration 5.2 μg/mL), and 500 parts of buffer was preincubated at 37 °C for 10 min. After treatment with 20 parts of oleoyl-CoA (^{14}C, 0.4 μCi) the mixture was incubated at 37 °C for 30 min. A control mixture, omitting the test compound, was prepared and treated in the same manner. The lipids from the incubation mixture were extracted into an organic solvent and separated by thin-layer chromatography. The cholesteryl ester zone was scraped off the plate and counted in a scintillation counter. The values shown in Tables I–IV are expressed as the mean percent inhibition of the enzyme. Calculations of IC_{50} values were made with data from triplicate assay tubes at each drug concentration. Variation among the individual assay tubes at each concentration was generally less than 10%. IC_{50} values were derived by linear-regression analysis of the means at each drug concentration.

Smooth Muscle Cell Derived ACAT. Smooth-muscle cells (SMC) were cultured from thoracic aorta of African green monkeys as described by Ross.[29] Low-density lipoproteins (LDL) were isolated from the serum of hypercholesterolemic monkeys, by addition of sodium bromide and centrifugation.[30] The 1.017–1.063 density range was isolated as LDL. Cationized LDL (C-LDL) was prepared with 3-(dimethylamino)propylamine (Aldrich) and [1-ethyl-3-(dimethylamino)propyl]carbodiimide hydrochloride (Pierce Chemical Co.) according to the method of Basu et al.[31] Smooth-muscle cells were cultured in 35 cm^2-culture wells (Costar) for 48 h with Dulbecco's modified Eagle medium and 10% fetal-calf serum with LDL plus graded concentrations of the arylurea dissolved in methanol. Albumin-bound [^{14}C]oleate, prepared by the method of St. Clair and Leight[32] from albumin (Pentex) and [^{14}C]oleate (New England Nuclear), was added and the cells were incubated for 2.5 h. Cells were removed from the culture dishes with trypsin–EDTA and the lipids were extracted by using the Folch procedure.[33] [^{14}C]Cholesterol esters were isolated by TLC and counted by liquid scintillation.

Serum and Liver Sterol. The compounds were tested for serum hypolipidemic activity as follows. Male CD-1 Sprague–Dawley (Charles River) rats weighing 140–150 g were fed a 1% cholesterol/0.5% cholic acid diet for 7 days. The drug was mixed in the diet at 0.01%. This results in a daily drug intake of approximately 10 mg/kg of body weight per day. After 7 days on test, the control rat serum cholesterol levels raned from 300–360 mg/dL while liver cholesterol concentrations were 25–30 mg/g. Methods for the determination of liver and serum cholesterol were adapted for use with the Technicon autoanalyzer.[34,35]

Cholesterol-Fed Rabbit. Male New Zealand rabbits weighing 2.5–3.0 kg were placed on a diet consisting of Fisher rabbit pellets supplemented with 0.4% cholesterol (J.T. Baker) and peanut oil. All rabbits received food and water ad libitum during the course of the entire study. After one week, the rabbits were bled and grouped on the basis of plasma sterol. The grouped animals were placed on the following diets: control = cholesterol-containing diet with 6% peanut oil; high dose = control diet with **115** at 0.25% of diet; medium dose = control diet with **115** at 0.075% of diet; low dose = control diet with **115** at 0.025% of diet. The

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resultant doses in the drug-treated rabbits during the subsequent five weeks of the study were 109.6, 34.5, and 11.2 mg/kg per day, respectively. In order to obtain modest hypercholesterolemia in this study, the level of cholesterol in all the diets was varied on the basis of plasma cholesterol levels in the control rabbits on a weekly basis if needed. During the drug administration part of this study, the rabbit received a diet supplemented with 6% peanut oil and 0.35% cholesterol for the first week, 0.30% cholesterol for the second week, 0.35% cholesterol for the third and fourth weeks, and 0.30% cholesterol for the fifth week. As a means to rapidly induce atherosclerotic lesions, the rabbits were subjected to aortic endothelial cell denudation with a 4F pediatric diagnostic balloon catheter seven days after the initiation of drug treatment.[36] Via an incision in the femoral artery, the aortae of all rabbits were deendothelialized with two passes of the balloon catheter inflated to a constant pressure of 500 mmHg.

Registry No. 1, 91430-05-6; 2, 122020-25-1; 3, 122020-26-2; 4, 122020-27-3; 5, 122020-28-4; 6, 122020-29-5; 7, 2589-21-1; 8, 56124-72-2; 9, 86781-16-0; 10, 56124-73-3; 11, 86781-17-1; 12, 86781-18-2; 13, 86781-19-3; 14, 86781-15-9; 15, 86781-20-6; 16, 86781-21-7; 17, 86781-22-8; 18, 86781-23-9; 19, 86781-24-0; 20, 86781-25-1; 21, 86781-26-2; 22, 86781-27-3; 23, 86781-28-4; 24, 15442-04-3; 25, 122020-30-8; 26, 86781-61-5; 27, 86781-29-5; 28, 86781-30-8; 29, 86781-32-0; 30, 86781-36-4; 31, 86781-37-5; 32, 86781-53-5; 33, 86781-58-0; 34, 86781-38-6; 35, 122020-31-9; 36, 86781-62-6; 37, 86781-40-0; 38, 122020-32-0; 39, 86781-34-2; 40, 86781-35-3; 41, 86781-39-7; 42, 122020-33-1; 43, 86781-41-1; 44, 86781-42-2; 45, 86781-43-3; 46, 86781-51-3; 47, 86781-44-4; 48, 86781-45-5; 49, 86781-46-6; 50, 86781-60-4; 51, 86781-50-2; 52, 86781-59-1; 53, 86781-48-8; 54, 86802-60-0; 55, 86781-47-7; 56, 86781-49-9; 57, 122020-34-2; 58, 122020-35-3; 59, 53693-57-5; 60, 86764-28-5; 61, 86764-29-6; 62, 86764-30-9; 63, 86764-31-0; 64, 86764-32-1; 65, 86764-27-4; 66, 86764-33-2; 67, 53099-44-8; 68, 86764-34-3; 69, 86764-72-9; 70, 86764-36-5; 71, 86764-37-6; 72, 86764-71-8; 73, 86764-63-8; 74, 86764-62-7; 75, 86764-38-7; 76, 86764-65-0; 77, 86764-74-1; 78, 86764-39-8; 79, 86764-54-7; 80, 86764-40-1; 81, 86764-69-4; 82, 86764-41-2; 83, 86764-42-3; 84, 86764-43-4; 85, 86764-44-5; 86, 86764-82-1; 87, 86764-45-6; 88, 86764-46-7; 89, 86764-75-2; 90, 86764-47-8; 91, 86764-48-9; 92, 86764-49-0; 93, 86764-66-1; 94, 86764-67-2; 95, 86764-50-3; 96, 86764-70-7; 97, 86764-55-8; 98, 86764-56-9; 99, 86764-68-3; 100, 86764-61-6; 101, 86764-81-0; 102, 86764-51-4; 103, 86764-58-1; 104, 86764-57-0; 105, 86764-64-9; 106, 86764-73-0; 107, 86764-52-5; 108, 86764-53-6; 109, 86764-84-3; 111, 88451-07-4; 112, 88451-08-5; 113, 88451-09-6; 114, 88451-10-9; 115, 88451-06-3; 116, 88451-11-0; 117, 88451-12-1; 118, 88451-13-2; 119, 88451-14-3; 120, 88451-15-4; 121, 88451-16-5; 122, 88452-22-6; 123, 88452-25-9; 124, 88452-26-0; 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ACAT, 9027-63-8; $Ph_2CHCH_2CO_2H$, 606-83-7; $CH_3(CH_2)_4CO_2H$, 142-62-1; *p*-$BuC_6H_4CO_2H$, 20651-71-2; 2,4-$(Me)_2C_6H_3NCO$, 51163-29-2; *o*-MeC_6H_4NCO, 614-68-6; *p*-MeC_6H_4NCO, 622-58-2; *p*-$(Me)_2CHC_6H_4NCO$, 31027-31-3; *p*-BuC_6H_4NCO, 69342-47-8; 2,6-$(Me)_2C_6H_3NCO$, 28556-81-2; 3,4-$(Me)_2C_6H_3NCO$, 51163-27-0; *p*-$EtOC_6H_4NCO$, 32459-62-4; *m*-$MeSC_6H_4NCO$, 28479-19-8; *m*-BrC_6H_4NCO, 23138-55-8; *p*-IC_6H_4NCO, 15845-62-2; 3,5-$(Cl)_2C_6H_3NCO$, 34893-92-0; *m*-AcC_6H_4NCO, 23138-64-9; *p*-AcC_6H_4NCO, 49647-20-3; $(CH_3(CH_2)_3CH(CH_2CH_3)CH_2)_2NH$, 106-20-7; $((CH_3)_3CCH_2CH(CH_3)(CH_2)_2)_2NH$, 926-75-0; $(CH_3(CH_2)_{10})_2NH$, 16165-33-6; $(CH_3(CH_2)_{11})_2NH$, 3007-31-6; $(CH_3(CH_2)_{13})_2NH$, 17361-44-3; $(CH_3(CH_2)_{17})_2NH$, 112-99-2; *m*-MeC_6H_4NCO, 621-29-4; *p*-$BuOC_6H_4NCO$, 28439-86-3; *p*-$PhOC_6H_4NCO$, 59377-19-4; *p*-$MeSC_6H_4NCO$, 1632-84-4; *o*-BrC_6H_4NCO, 1592-00-3; 2,5-$F_2C_6H_3NCO$, 39718-32-6; *o*-$F_3CC_6H_4NCO$, 2285-12-3; *p*-$EtO_2CC_6H_4NCO$, 30806-83-8; *p*-$HO_2CC_6H_4NCO$, 46112-47-4; 2,3-$(Me)_2C_6H_3NCO$, 1591-99-7; 2,5-$(Me)_2C_6H_3NCO$, 40397-98-6; 3,5-$(Me)_2C_6H_3NCO$, 54132-75-1; *m*-ClC_6H_4NCO, 2909-38-8; 3,4-$(Cl)_2C_6H_3NCO$, 102-36-3; *m*-$F_3CC_6H_4NCO$, 329-01-1; *o*-$O_2NC_6H_4NCO$, 3320-86-3; $PhCH(CH_3)NH_2$, 98-84-0; 2,4-$F_2C_6H_3NCO$, 59025-55-7; 2,4-$(Br)_2C_6H_3NCO$, 55076-90-9; 2-thiophenecarboxylic acid, 527-72-0; 2-thiophenecarboxylic acid chloride, 5271-67-0; 3,3-dimethylbutylamine, 15673-00-4; piperonylic acid, 94-53-1; 1-adamantylacetic acid, 4942-47-6; 4-chloro-α-(4-chlorophenyl)benzeneacetic acid, 83-05-6; 1-cyclohexyl-1-phenylacetic acid, 3894-09-5; 2-furoyl chloride, 527-69-5; 2,4,6-trimethylphenyl isocyanate, 2958-62-5; 3-chloro-2-methylphenyl isocyanate, 40397-90-8; 5-chloro-2-methylphenyl isocyanate, 40411-27-6; 3-chloro-4-fluorophenyl isocyanate, 50529-33-4; 4-chloro-3-(trifluoromethyl)phenyl isocyanate, 327-78-6; *N*-(4-cyclohexylbutyl)-(4-cyclohexyl)-1-butanamine, 94874-68-7; 2,4,5-trimethylphenyl isocyanate, 85324-94-3; 4-chloro-2-(trifluoromethyl)phenyl isocyanate, 16588-69-5; 3,4,5-trimethoxyphenyl isocyanate, 1016-19-9; 2,4,6-trichlorophenyl isocyanate, 2505-31-9; 4-chloro-2-methylphenyl isocyanate, 37408-18-7; 3-chloro-2-methoxyphenyl isocyanate, 56309-55-8; 5-chloro-2-methoxyphenyl isocyanate, 55440-54-5; 5-chloro-2-hydroxyphenyl isocyanate, 122020-63-7; 4-amino-3,5-dichlorophenyl isocyanate, 122020-64-8; 4-carboxy-2-methylphenyl isocyanate, 122020-65-9; 4-cyclohexyl-1-butanamine, 4441-59-2; 2,4,5-trichlorophenyl isocyanate, 26328-35-8.

(36) The balloon catheter experiment was conducted to determine whether 115 displayed an antiatherosclerotic effect, independent of the hypocholesterolemic effect of the drug. None was observed.