Inhibitors of Acyl-CoA:Cholesterol Acyltransferase. 4. A Novel Series of Urea ACAT Inhibitors as Potential Hypocholesterolemic Agents[1]

Bharat K. Trivedi,* Ann Holmes, Terri L. Stoeber, C. John Blankley, W. Howard Roark, Joseph A. Picard, Mary K. Shaw,† Arnold D. Essenburg,† Richard L. Stanfield,† and Brian R. Krause†

Departments of Medicinal Chemistry and Pharmacology, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan 48105

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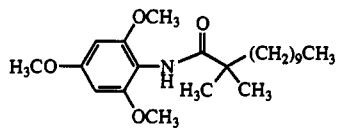
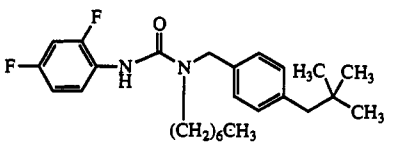
We have synthesized a series of *N*-phenyl-*N'*-aralkyl and *N*-phenyl-*N'*- (1-phenylcycloalkyl)ureas as inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). This intracellular enzyme is thought to be responsible for the esterification of dietary cholesterol; hence inhibition of this enzyme could reduce diet-induced hypercholesterolemia. For this series of compounds, the *in vitro* ACAT inhibitory activity was improved by increasing the bulk of the 2,6-substituents on the phenyl ring. Additionally, we found that spacing of the aromatic rings was critical for ACAT inhibitory activity. A phenyl ring five atoms away from the requisite 2,6-diisopropylphenyl moiety was optimal for *in vitro* activity. Substitution α to the *N'*-phenyl moiety enhanced *in vitro* potency. In the case of phenylcycloalkyl ureas, ACAT inhibitory activity was independent of the size of the cycloalkyl ring. From this series of analogs, compound **25**, which had excellent *in vitro* potency for inhibiting ACAT, was found to lower plasma cholesterol by 73% *in vivo* when administered in the diet at 50 mg/kg in an animal model of hypercholesterolemia. In this model, compound **25** lowered plasma cholesterol dose dependently and was as efficacious as the Lederle ACAT inhibitor CL 277082.

The enzyme acyl-CoA:cholesterol acyltransferase (ACAT, EC 2.3.1.26) is responsible for catalyzing the intracellular esterification of cholesterol in all mammalian cells.[2] Several lines of evidence suggest that ACAT in the intestine is involved in the absorption of dietary cholesterol.[3] The most convincing evidence is the observation that specific inhibitors of the enzyme inhibit cholesterol absorption and reduce plasma total cholesterol in several animal models of hypercholesterolemia.[4] These observations have given a tremendous impetus to the development of ACAT inhibitors as novel lipid-regulating drug candidates.[5] We have recently disclosed a fatty acid anilide (CI-976)[6] (Figure 1), which inhibits not only intestinal ACAT, but also liver ACAT.[7] In addition, since CI-976 both slows the progression and enhances the regression of atherosclerotic lesions in the absence of plasma cholesterol reduction, it can be considered as having direct antiatherosclerotic activity.[8] Due to this interesting biological activity, we have continued our efforts, identifying a novel series of 2,6-alkylanilides[6] and phenylureas[9] of fatty acids as potent ACAT inhibitors. A simple series of *N,N'*-diphenylureas have also been shown to be potent ACAT inhibitors.[10] In this paper, we disclose a novel series of urea derivatives which are potent inhibitors of the enzyme *in vitro* and also possess excellent hypocholesterolemic activity *in vivo*.



CI-976



CL-277082

Figure 1.

Chemistry

Most of the compounds were synthesized by reacting commercially available isocyanates and amines in ethyl acetate at room temperature. The β,β-disubstituted amines were synthesized by first alkylating the benzyl cyanide, and then reducing the nitrile catalytically. Reaction of these amines with appropriate phenylisocyanates yielded the desired urea derivatives (Scheme I). For certain spirocyclic analogs, commercially available nitriles were catalytically reduced to the corresponding amines and then reacted with the appropriate isocyanates to yield the required ureas. Compound **52** was synthesized as follows (Scheme II): 1,3-dichloro-2-nitrobenzene[11] (**77**) was reacted with dimethylamine in toluene in an autoclave at 160 °C for 24 h to afford *N,N,N',N'*-tetramethyl-2-nitro-1,3-benzenediamine (**78**). Compound **78** was catalytically reduced over Ra-Ni in methanolic ammonia to afford the corresponding aniline derivative (**79**), which in turn, was reacted with the appropriate isocyanate to yield compound **52**.

Compound **70** was synthesized as shown in Scheme III. The potassium sulfamate derivative (**81**), obtained from the corresponding catechol derivative **80**,[12] was converted to the sulfamoyl chloride **82** by reacting with PCl_5. Reaction of **82** with 2,6-diisopropylaniline afforded **70**. The guanidine analog **73** (Scheme IV) was synthesized from the corresponding thiourea analog (**72**) by first reacting with dicyclohexyl carbodiimide (DCC) followed by the addition of ammonia to the carbodiimide (**83**) according to the literature procedure.[13] Reaction of the intermediate carbodiimide with cyanamide afforded **74**.

† Department of Pharmacology.
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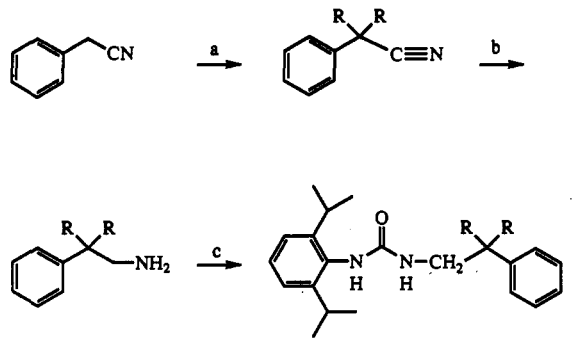
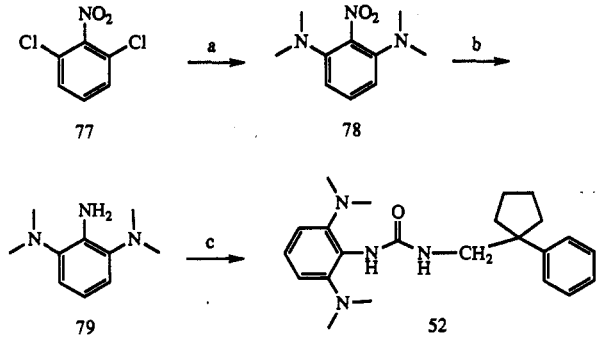
Scheme I[a]



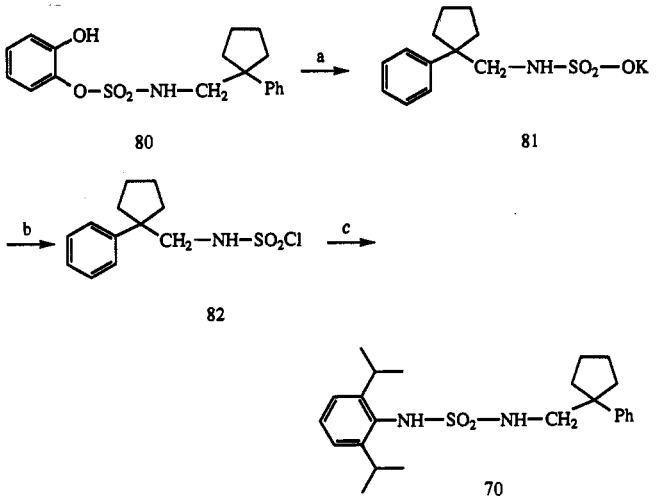
[a] (a) NaH/DMSO, RX; (b) H_2, Ra-Ni; (c) 2,6-diisopropylphenyl isocyanate, ethyl acetate, room temperature.

Scheme II[a]



[a] $HNMe_2$, toluene, 160 °C; (b) Ra-Ni/H_2/MeOH; (c) $CH_2CH_2CH_2CH_2C(Ph)CH_2N{=}C{=}O$, EtOAc.

Scheme III[a]

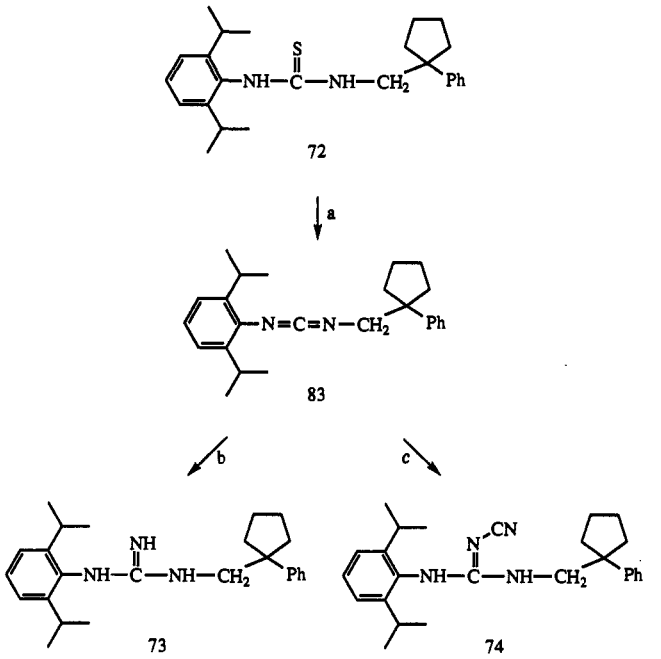


[a] (a) KOH; (b) PCl_5, benzene, reflux; (c) 2,6-diisopropylaniline, Et_3N, THF.

Results and Discussion

Structure–activity relationship studies on related series of compounds[9,10] demonstrated the need for bulky 2,6-dialkyl substituents, such as a 2,6-diisopropyl moiety, on the phenyl ring for high potency *in vitro*. Thus, we prepared and evaluated a series of aralkyl analogs having the 2,6-diisopropylphenyl moiety (Table I). Initial SAR indicated that for optimal ACAT inhibitory activity *in vitro*, phenyl ring spacing was crucial. Thus, compounds in which the phenyl ring was five atoms away from the required 2,6-diisopropylphenyl moiety were more potent than the corresponding lower or higher homologs (**3** vs **2**, **4** or **8** vs **7**, **9**). This was further substantiated by the observation that the 2-tetralin analog (**12**) was significantly more potent than the corresponding 1-tetralin analog (**13**). Conformational aspects of this favorable spacing were explored by embedding the phenyl ring in a variety of conformationally constrained environments (**5**, **6**, **11**, **12**, **14**). Most of these analogs maintained good activity with the notable exception of **14**. This analog is constrained to adopt an extended conformation. Since the other analogs can access various bent conformers, it seems that the latter may be favored for this series.

Scheme IV[a]

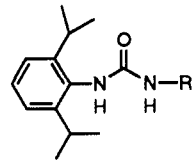


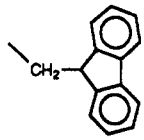
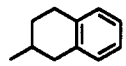
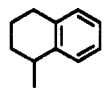
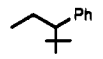
[a] (a) DCC, $(i\text{-Pr})_2NEt$, CH_3CN; (b) NH_3–ether, room temp; (c) H_2NCN, $(i\text{-Pr})_2NEt$, CH_3CN.

The *in vitro* activity was improved 4-fold by incorporation of a substituent such as a phenyl ring in the α- (**10**) or the β-position (**8**). However, dialkyl substitution in the β-position (**17**) improved the ACAT inhibitory activity significantly compared to the corresponding α,α-disubstituted analog **16**, suggesting that steric crowding near the urea moiety was disfavored for optimal interaction at the enzyme site. On the basis of these observations, we synthesized a series of β,β-dialkyl substituted analogs. The *in vitro* ACAT inhibitory activity was excellent for this series of compounds (**17**–**21**). However, there is a limit to the increase in size or lipophilicity in this part of the molecule, as exemplified by compound **22**. Encouraged by this data, we synthesized and evaluated a series of spirocyclic analogs (Table II) (**23**–**31**). These analogs maintained the *in vitro* potency of the corresponding acyclic analogs. Additionally, ACAT inhibitory activity was independent of the size of the spirocycle (**23**–**26**). The pyridyl analog **27**, having a basic nitrogen, was more than 5-fold less active than the corresponding phenyl analog (**23**), whereas the thienyl analogs (**28**,**29**) were equipotent. Once again it is important to note that the "extended" 2-naphthyl analog **30** was significantly less active than the corresponding 1-naphthyl derivative **31**.

To confirm whether a 2,6-diisopropyl substituent was also optimal for this series of ACAT inhibitors, we systematically evaluated the effect of mono-, di-, and trisubstitution on the *N*-phenyl ring. In the series of spirocyclohexyl analogs, substituents such as methoxy (**33**), methyl (**34**), isopropyl (**35**), and trifluoromethyl (**36**) in the ortho position improved the ACAT inhibitory activity

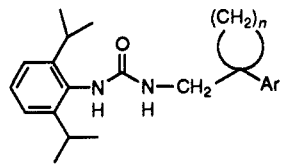
Table I. *N*-Phenyl-*N'*-aralkylureas

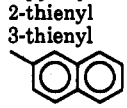
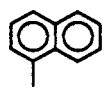


example	R	formula	mp (°C)	IC_{50} (μM)[a]
1	Ph	$C_{19}H_{24}N_2O$	236–237	0.91
2	CH_2Ph	$C_{20}H_{26}N_2O$	186–188	0.36
3	$(CH_2)_2Ph$	$C_{21}H_{28}N_2O$	231–233	0.088
4	$(CH_2)_3Ph$	$C_{22}H_{30}N_2O$	205–207	0.191
5	1-naphthylethyl	$C_{25}H_{30}N_2O$	174–176	0.041
6	2-naphthylethyl	$C_{25}H_{30}N_2O$	207–209	0.039
7	$CH(Ph)_2$	$C_{26}H_{30}N_2O$	245–246	0.045
8	$CH_2CH(Ph)_2$	$C_{27}H_{32}N_2O$	175–176	0.024
9	$(CH_2)_2CH(Ph)_2$	$C_{28}H_{34}N_2O$	212–214	0.14
10	$CH(Ph)CH_2Ph$	$C_{27}H_{32}N_2O$	219–221	0.031
11		$C_{27}H_{30}N_2O$	217–219	0.027
12		$C_{23}H_{30}N_2O$	214–215	0.041
13		$C_{23}H_{30}N_2O$	230–231	0.85
14		$C_{22}H_{28}N_2O$	193–194	2.0
15		$C_{25}H_{36}N_2O$	176–178	0.16
16	$C(Me)_2CH_2Ph$	$C_{23}H_{32}N_2O$	137–138	0.077
17	$CH_2C(Me)_2Ph$	$C_{23}H_{32}N_2O$	153–158	0.026
18	$CH_2C(Et)_2Ph$	$C_{25}H_{36}N_2O$	170–173	0.017
19	$CH_2C(n\text{-}Pr)_2Ph$	$C_{27}H_{40}N_2O$	149–151	0.030
20	$CH_2C(n\text{-}Bu)_2Ph$	$C_{29}H_{44}N_2O$	76–81	0.030
21	$CH_2C(n\text{-pentyl})_2Ph$	$C_{31}H_{48}N_2O$	viscous oil	0.026
22	$CH_2C(n\text{-hexyl})_2Ph$	$C_{33}H_{52}N_2O$	viscous oil	0.12

[a] In vitro ACAT inhibition was measured using intestinal microsomes isolated from cholesterol-fed rabbits. Each determination was performed in triplicate. See ref 6 for the complete protocol.

Table II. *N*-Phenyl-*N'*-(cycloalkyl)phenylurea

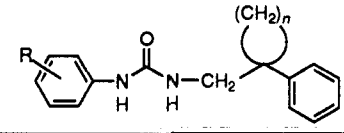


example	*n*	Ar	formula	mp (°C)	IC_{50} (μM)[a]
23	2	Ph	$C_{23}H_{30}N_2O$	138–142	0.018
24	3	Ph	$C_{24}H_{32}N_2O$	170–173	0.028
25	4	Ph	$C_{25}H_{34}N_2O$	181–183	0.017
26	5	Ph	$C_{26}H_{36}N_2O$	168–170	0.021
27	4	3-pyridyl	$C_{24}H_{33}N_3O$	186–187	0.097
28	4	2-thienyl	$C_{23}H_{32}N_2OS$	173–174	0.012
29	4	3-thienyl	$C_{23}H_{32}N_2OS$	184–186	0.018
30	4		$C_{29}H_{36}N_2O$	152–154	0.260
31	4		$C_{26}H_{36}N_2O$	171–173	0.034

[a] ACAT inhibition in vitro. See footnote *a* of Table I.

compared to the unsubstituted analog **32**. However, the polar carboethoxy substituent in the ortho position (**37**) was deleterious toward activity. It is the only group capable of forming an internal hydrogen bond with the urea function. This leads to a planar orientation of the urea group with respect to the phenyl ring rendering the compound less active. Substitution in the meta or para position (**38–45**) did not improve the activity of the parent compound **32**. A series of disubstituted analogs (**46–53**) confirmed the preference for 2,6-substitution (**51,52**) for enhanced potency. The 2,6-bis(dimethylamino) analog (**52**) was evaluated as a surrogate of 2,6-diisopropyl functionality. Although compound **52** demonstrated good *in vitro* activity, it was less active than the corresponding 2,6-diisopropyl analog **25**.

Table III. Phenyl Substitution SAR



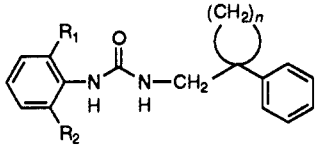
example	R	*n*	formula	mp (°C)	IC_{50} (μM)[a]
32	H	5	$C_{20}H_{24}N_2O$	162–164	2.3
33	2-OMe	5	$C_{21}H_{26}N_2O_2$	155–157	0.27
34	2-Me	5	$C_{22}H_{26}N_2O_2$	164–165	0.64
35	2-iPr	5	$C_{22}H_{28}N_2O$	154–155	0.39
36	2-CF_3	5	$C_{21}H_{23}F_3N_2O$	142–144	0.2
37	2-CO_2Et	5	$C_{23}H_{28}N_2O_3$	99–101	4.2
38	3-OMe	5	$C_{21}H_{26}N_2O_2$	120–122	2.5
39	3-Me	5	$C_{21}H_{26}N_2O$	145–147	2.8
40	4-OMe	5	$C_{21}H_{26}N_2O_2$	155–157	4.9
41	4-Me	5	$C_{21}H_{26}N_2O$	135–137	4.5
42	4-iPr	5	$C_{23}H_{30}N_2O$	151–153	1.5
43	4-Cl	5	$C_{20}H_{23}ClN_2O$	164–166	2.2
44	4-I	5	$C_{20}H_{23}IN_2O$	184–190	2.3
45	4-CO_2Et	5	$C_{23}H_{28}N_2O_3$	163–164	6.1
46	2,4-Me_2	5	$C_{22}H_{28}N_2O$	140–142	5.5
47	2,5-Me_2	5	$C_{22}H_{28}N_2O$	202–203	0.47
48	2,3-Cl_2	5	$C_{20}H_{22}Cl_2N_2O$	214–215	1.3
49	3,4-Cl_2	5	$C_{20}H_{22}Cl_2N_2O$	180–181	3.8
50	2,5-Cl_2	5	$C_{20}H_{22}Cl_2N_2O$	208–210	2.7
51	2,6-Cl_2	4	$C_{19}H_{20}Cl_2N_2O$	193–194	0.24
52	2,6-$(NMe_2)_2$	4	$C_{23}H_{32}N_4O$	85–87	0.11
53	2,4-F_2	4	$C_{19}H_{20}F_2N_2O$	160–161	1.3
54	2,4,6-F_3	4	$C_{19}H_{19}F_3N_2O$	194–195	0.87
55	2,4,6-Cl_3	4	$C_{19}H_{19}Cl_3N_2O$	177–179	0.96
56	2,4,6-Me_3	4	$C_{22}H_{28}N_2O$	151–154	3.3
57	2,4,6-$(OMe)_3$	4	$C_{22}H_{28}N_2O_4$	143–145	1.4

[a] ACAT inhibition in vitro. See footnote *a* of Table I.

Scientists from Lederle have reported extensive work on another series of urea ACAT inhibitors.[4b-e] These differ from the current series in being trisubstituted ureas, but otherwise appear to contain many similar features, such as a side chain aralkyl functionality and high hydrophobicity. In order to test whether this series might share some of the aryl SAR with their series, we prepared analogs **53–56**, which contain several of their preferred substitution patterns. All of these were at least 2 orders of magnitude less active *in vitro* than the best members of this series, or, for that matter, than their best compounds. This strongly suggests that the Lederle series must bind to ACAT in a different manner or at a different site than this series of ureas. It may also be noted that the SAR for the aryl portion of these ureas resembles that of the straight chain amide series we reported earlier,[6] but not that of the α-substituted subseries related to CI-976, where 2,4,6-trimethoxyphenyl was found to be optimum. In this case, the corresponding analog **57** had quite weak activity.

In order to further establish the steric effects of the 2,6-substituents, we prepared the analogs shown in Table IV. Increasing the size of the alkyl substituents not only improved the ACAT inhibitory activity *in vitro* but also tended to improve cholesterol lowering activity *in vivo*.

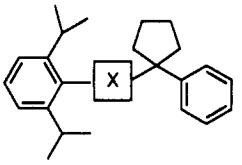
Table IV. 2,6-Dialkylphenyl Substitution SAR



example	R_1	R_2	n	formula	mp (°C)	IC_{50} (μM)[a]	% ΔTC[b]
58	Me	Me	4	$C_{21}H_{26}N_2O$	201–202	0.19	
59	Et	Et	4	$C_{23}H_{30}N_2O$	165–167	0.056	-63**
25	iPr	iPr	4	$C_{25}H_{34}N_2O$	181–183	0.017	-73***
60	Me	Me	5	$C_{22}H_{28}N_2O$	207–208	0.12	-44*
61	Et	Et	5	$C_{24}H_{32}N_2O$	185–186	0.051	-60***
26	iPr	iPr	5	$C_{26}H_{36}N_2O$	168–170	0.021	-73***
62	Me	iPr	4	$C_{23}H_{30}N_2O$	157–159	0.016	-65***
63	Me	tBu	4	$C_{24}H_{32}N_2O$	196–197	0.018	-61***
64	Et	iPr	4	$C_{24}H_{32}N_2O$	152–154	0.025	-59***
65	Me	iPr	5	$C_{24}H_{32}N_2O$	158–160	0.058	-56***
66	Me	tBu	5	$C_{25}H_{34}N_2O$	196–197	0.054	-51***
67	Et	iPr	5	$C_{25}H_{34}N_2O$	178–180	0.020	-70***

[a] ACAT inhibition *in vitro*. See footnote *a* of Table I. [b] Denotes percent change in total cholesterol in cholic acid (0.3%), cholesterol (1.5%), and peanut oil (5.5%) fed rats. All compounds were dosed at 0.05% of the diet for one week. For details see ref 6. * Significantly different from control, $P < 0.005$. ** Significantly different from control, $P < 0.0005$. *** Significantly different from control, $P < 0.0001$.

Table V. Urea SAR



example	X	formula	mp (°C)	IC_{50} (μM)[a]
25	$-NHCONHCH_2-$	$C_{25}H_{34}N_2O$	181–183	0.017
68	-NHCONH-	$C_{24}H_{32}N_2O$	199–200	0.065
69	-NHCONHCO-	$C_{25}H_{32}N_2O_2$	203–204	0.16
70	$-NHSO_2NHCH_2$	$C_{24}H_{34}N_2O_2S\cdot 16H_2O$	91–92	0.18
71	$-OCONHCH_2$	$C_{25}H_{33}NO_2$	62–65	0.049
72	$-NHCSNHCH_2-$	$C_{25}H_{34}N_2S$	143–145	2.33
73	-NHC(=NH)-NHCH$_2$-	$C_{25}H_{25}N_3\cdot 0.5H_2O$	159–161	12.0
74	-NHC(=NCN)-NHCH$_2$-	$C_{26}H_{34}N_4$	202–204	10.0

[a] ACAT inhibition in vitro. See footnote *a* of Table I.

The enhancement of both *in vitro* and *in vivo* activity was similar for the spirocyclopentyl and spirocyclohexyl analogs. Unsymmetrical substitution (**62–67**) also rendered the compounds highly potent both *in vitro* and *in vivo*. Thus, this data suggests that for optimal interactions at the active site of the enzyme, a certain spatial arrangement of the requisite carbonyl moiety is necessary, which is achieved by having a bulky 2,6-disubstituent on the phenyl ring.

We then looked briefly at a series of urea bioisosteres based on **25** (Table V). The lower homolog (**68**) and the acyl urea derivative (**69**) were 4- and 10-fold less active, respectively, than **25**. The sulfamide analog **70**, having the bulkier SO_2 functionality, also showed a 10-fold loss in activity *in vitro*. The carbamate analog (**71**) maintained excellent ACAT inhibitory activity, suggesting that, for activity, only one NH of the urea moiety is required. Conversion of the urea to thiourea, however, produced a significantly less active inhibitor (**72**). Similarly, the guanidine (**73**) and cyanoguanidine (**74**) analogs were essentially inactive.

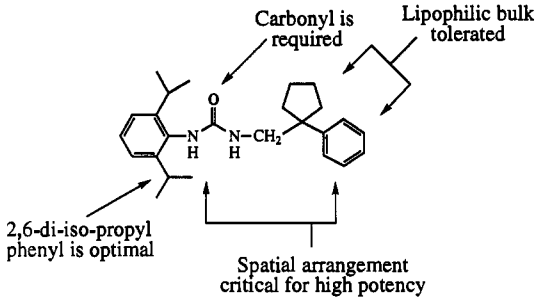


Figure 2. Summary of SAR.

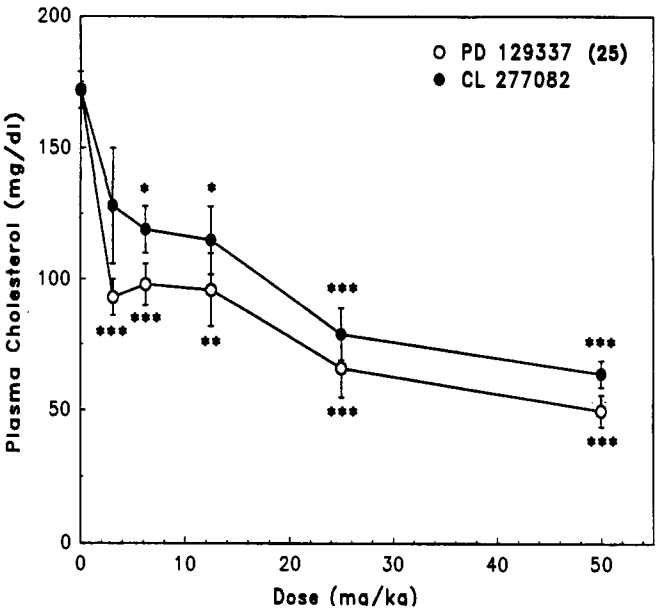


Figure 3. Dose–responses for PD 129337 and CL 277082 in cholesterol-fed rats. Values are the mean ± SEM for six animals/group. The degree of significance from control was determined using unpaired, two-tailed *t*-tests. *$P < 0.01$. **$P < 0.001$. ***$P < 0.0001$.

It is interesting to compare the effect of these urea mimetics with the results obtained in the classical work on H_2 antagonists.[14] In the latter work, the SAR in a similar series of analogs was just the opposite from what we found in the ACAT series; i.e., thiourea and cyanoguanidine were much preferred over urea. In the H_2 work, these preferences have been proposed to be related to conformational and dipole properties,[14,15] which are thought to optimize a critical H-bonding role of this group at the receptor. In our ACAT series as well, an H-bonding function appears critical for inhibitor binding, but this is optimized by urea and amide functions[6,9] and is disfavored by thiourea and guanidine groups. The preferences found here largely parallel those reported by us for a related series of straight chain ACAT inhibitors.[9] We will report separately a more detailed study of these and related ACAT isosteres.

Most of the compounds in Table IV produced good reductions in plasma total cholesterol when administered in the diet in the cholesterol-fed rat assay as described previously.[6] Compound **25** (PD 129337), one of the most potent analogs, was chosen for more extensive evaluation. When PD 129337 was compared with the Lederle inhibitor CL 277082, both compounds were found to reduce plasma cholesterol in a dose-dependent manner when administered in the diet (Figure 3).

Table VI. Development of QSAR Equations (n = 67)

eq		R^2	s	F
1	$\log(1/IC_{50}) = 5.83 + 1.93(\pm0.21)\upsilon\_6$	0.56	0.57	84.0
2	$\log(1/IC_{50}) = 6.14 + 1.53(\pm0.21)\upsilon_6 - 0.79(\pm0.19)$I_4	0.66	0.51	61.8
3	$\log(1/IC_{50}) = 5.26 + 1.74(\pm0.19)\upsilon_6 - 0.80(\pm0.17)$I_4 + 0.87(±0.20)I_βPh	0.74	0.45	58.7
4	$\log(1/IC_{50}) = 3.26 + 2.02(\pm0.19)\upsilon_6 - 0.82(\pm0.15)$I_4 + 0.67(±0.20)I_βPh + 0.89(±0.24)(pi_sc) - 0.09(±0.02)(pi_sc)^2	0.78	0.42	44.1

Table VII. Correlation Matrix of Variables (n = 67)

	CLOGP	pi_sc	pi_ar	I_βPh	I_4	F_26	υ_26	υ_2	υ_6
CLOGP	1								
pi_sc	0.83	1							
pi_ar	0.45	−0.13	1						
I_βPh	0.15	0.33	−0.26	1					
I_4	0.03	0.10	−0.20	0.14	1				
F_26	−0.16	0.03	−0.34	0.16	0.20	1			
υ_26	0.19	−0.19	0.64	−0.25	−0.58	−0.37	1		
υ_2	0.14	−0.15	0.49	−0.17	−0.62	−0.17	0.9	1	
υ_6	0.19	−0.20	0.66	−0.28	−0.45	−0.49	0.92	0.65	1
$\log(1/IC_{50})$	0.24	−0.02	0.46	0.05	−0.61	−0.41	0.80	0.71	0.75

QSAR

The above generalizations on in vitro potency could be supported by a quantitative (QSAR) analysis. Parameters to characterize the various features of both the aryl ring and the aralkyl side chain were examined. For the aryl ring, steric parameters for the ortho substituents, electronic parameters for both ortho substituents and the whole aryl ring, and a steric or an indicator variable for para substitution were chosen. These included MR[16] and Charton ν,[17] as possible steric parameters, and Hammett σ or modified Swain–Lupton F and R[18] for electronic effects. For side-chain characterization, relative lipophilicity as determined from CLOGP[16] was chosen. The apparent special benefit of a properly spaced phenyl group was included as an indicator variable. The data and parameters used are listed in the supplementary material of this paper.

As expected, equations accounting for a high percentage of the variance in the *in vitro* biological data could be obtained. Table VI shows the development of one of the best relations obtained. This incorporates all of the features observed as statistically significant contributors. All the ureas from Tables I–IV are included.

In these equations, log ($1/IC_{50}$) is the log of the molar IC_{50}, pi_sc is the relative lipophilicity of the aralkyl portion of the urea, I_βPh is an indicator for the presence of the five-atom aryl spacing, υ_6 is the Charton steric parameter for the smaller ortho substituent, and I_4 is an indicator for the presence of a non-hydrogen substituent in the para position of the urea aryl ring. The coefficients are shown with their standard errors. Equation 4 confirms the large steric contribution of ortho substituents, indicating in addition that this is not simply additive, but that the addition of a second non-hydrogen ortho group, as implied by a nonzero υ_6, has a very much greater positive effect on activity than the first, even if this latter is fairly large (e.g., *tert*-butyl as in **63** and **66**). The parameter for υ_2, the larger of the two ortho groups, enters the equation as a nonsignificant contributor (<95% confidence level, not shown). This is most consistent with the interpretation that these groups serve to ensure an orthogonal disposition of the urea function relative to the aryl ring for best activity. A significant negative effect of para substituents is shown by the indicator for substitution in this position, I_4. Other steric parameters were examined (MR_4, υ_4), but the simple indicator gave the best result. This may indicate that this apparent "para effect" is not simply steric in origin. An electronic effect on activity for substituents in this ring could not be justified statistically. The approach to characterizing ortho effects proposed by Fujita and Nishioka[19] wherein a steric parameter was combined with an electronic parameter for this purpose was also tried, but gave an inferior result to that reported above. Table VII shows the correlation matrix for key variables considered.

For the aralkyl portion, the aryl spacing effect as parameterized by the indicator, I_βPh, was highly significant. In addition, however, a second-order dependence on the relative side chain lipophilicity as calculated by the CLOGP algorithm[16] was also observed. A similar relation was obtained whether side chain π (pi_sc) or whole molecule CLOGP was used. Since separate examination of aryl ring lipophilicity, pi_ar (not shown), showed no significant contribution from this variable, pi_sc was chosen to represent this effect. In either case, the side chain lipophilicity accounts for only a small portion of the variance in this dataset. The calculated optimum for this effect is located at a fairly high level (pi_sc^0 = 4.9) and may very well signal a nonspecific interaction with hydrophobic regions of the enzyme or the membrane in which it is located. This optimum corresponds to a straight alkyl chain of 9–10 carbon atoms, shorter than was found to be optimal in linear amide and urea ACAT series.[6,9] This dataset does not allow a distinction to be made between size (as represented by MR) and lipophilicity (as represented by CLOGP) since the two measures are highly correlated (R^2 = 0.83). Of interest, however, is the fact that **14** and **30** are the worst outliers in this analysis, each being less active than predicted by greater than 2.5 standard deviations. This supports the idea that special geometric requirements probably exist for proper interaction with the enzyme, most likely with respect to the placement of the side chain aryl group, and that these latter compounds are either unable to access the favorable regions (**14**) or project volume into forbidden space (**30**). We have carried out a more detailed molecular modeling examination of the whole question of optimal aryl placement in the side chain which supports this contention and which will be reported separately.[20]

In comparing the results reported here with those of the

amide series of ACAT inhibitors reported by us previously,[6] it is interesting to note that eq 1, at least as it relates to the aryl portion, bears some similarity to the equation for the straight chain amide series, which also showed a strong preference for bulky ortho substitution, but not to the α-substituted subset for which 2,4,6-trimethoxy substitution was optimal. Given the different collection of substituents actually used in the two series, it is not certain whether the somewhat different parameters included in eq 4 and those reported for the straight chain amide series truly point to a different binding mode for these two series. Separate QSAR analyses of these and other structurally related series of ACAT inhibitors suggest that there may in fact be smaller, but significant, differences in the aryl SAR for the straight chain amide and aralkyl urea series.[20] As has already been noted, the aryl SAR of this series bears no resemblance to that reported for the more structurally divergent, trisubstituted urea ACAT inhibitors reported by the Lederle group.[4i] In the latter series, aryl substitutions with small, electron withdrawing groups such as F or Cl seem optimum, there is no requirement for bulky ortho substitution to obtain high potency and efficacy, and there is frequently a beneficial effect on potency with small para substituents, all in marked contrast to the series reported here. Indeed, the compounds which contain some of the best aryl substitutions reported for the trisubstituted ureas, e.g., **46**, **53**, and **56**, are among the weakest compounds here. For this reason, it seems reasonable to presume that compounds in the two series interact in a different manner or at a different site on the enzyme but can produce similar in vivo efficacy.

Conclusion

In conclusion, we have identified a simple, novel series of urea derivatives as potent ACAT inhibitors *in vitro* and hypocholesterolemic agents *in vivo*. For this series of compounds, a certain spatial arrangement of the functional groups is necessary for optimal enzyme inhibitory activity (Figure 2). Thus, a five atom spacer between the two phenyl rings is required for high potency *in vitro*. Additionally, bulky substituents in the 2,6-positions are essential for orienting the requisite carbonyl moiety out of plane of the phenyl ring for optimal interactions with the enzyme, thus confirming our previous results.[9] Isosteric replacement of the urea moiety renders significantly less active compounds (10–1000-fold). However, the carbamate analog maintains activity. The SAR study in the *N*-phenyl ring showed marked divergence from that of a series of trisubstituted urea ACAT inhibitors developed by Lederle. A systematic comparison of these two distinct series of urea ACAT inhibitors, as well as studies detailing efforts to improve the absorption of these compounds, will be the subjects of future papers from these laboratories.

Experimental Section

Materials used were obtained from commercial suppliers and were used without purification, unless otherwise noted. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined on a Varian XL-200 spectrometer. Chemical shifts are expressed as parts per million downfield from internal tetramethylsilane. Elemental analyses were determined on a Perkin-Elmer Model 240C elemental analyzer and are within 0.4% of theory unless otherwise noted.

The following synthesis of **19** represents a general scheme for the synthesis of related analogs.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-(2-phenyl-2-propylpentyl)urea (19). a. α,α-Dipropylbenzeneacetonitrile (75).** Sodium hydride (50% dispersion on mineral oil, 8.5 g, 0.177 mol) was washed with hexane. The hexane was decanted off. The hydride was then suspended in 200 mL of anhydrous DMF under a nitrogen atmosphere. Benzeneacetonitrile (10.0 g, 0.085 mol) and 1-iodopropane (18.3 mL, 0.188 mol) were dissolved together in 100 mL of ether and added dropwise to the stirring suspension and the temperature was kept between 25 and 35 °C. After the addition was complete, the reaction mixture was stirred at room temperature under nitrogen for 20 h. Excess sodium hydride was quenched by careful dropwise addition of 20 mL of methanol. The reaction mixture was filtered and the filter cake was washed well with ether. The filtrates were then concentrated *in vacuo*. The residue was taken up in ether and washed with water followed by dilute sodium bisulfite, then saturated sodium carbonate. The organic extracts were dried over magnesium sulfate, filtered, and concentrated. Distillation under high vacuum (boiling point 85–89 °C/0.1 mmHg) afforded 12.69 g (74%) of **75**: ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 6H, J = 7.2 Hz), 1.13 (m, 2H); 1.48 (m, 2H); 1.90 (m, 4H); 7.36 (m, 5H, phenyl). Anal. ($C_{14}H_{19}N$) C, H, N.

b. β,β-Dipropylbenzeneethanamine Monohydrochloride (76). Compound **75** (11.86 g, 0.059 mol) was dissolved in 100 mL of a methanol solution saturated with ammonia. This solution was treated with Raney nickel (6 g, washed with methanol before use) and hydrogenated in a 500-mL glass reaction bottle on a Parr hydrogenation apparatus at 50 psi and room temperature for 16 h. An additional portion of Raney nickel (6 g) was added and hydrogenation was continued with heating to 40 °C for an additional 24 h. An aliquot was removed and analyzed by thin layer chromatography, which showed the reaction to be complete. The catalyst was removed by filtration, and the filtrates were concentrated under vacuum. This afforded 11.9 g (98%) of the free amine as a pale green oil. The crude amine was immediately converted to the hydrochloride salt by treating with ethereal HCl. The resulting precipitate was collected and oven-dried, affording 6.71 g (47%) of **76**: mp 200–203 °C; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 6H, J = 6.7 Hz), 1.08 (m, 4H); 1.76 (t, 4H, J = 8.1 Hz), 3.21 (bs, 2H); 7.3 (m, 5H, phenyl); 8.17 (bs, 3H, NH_3^+). Anal. ($C_{14}H_{23}N$·HCl) C, H, N.

c. *N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-(2-phenyl-2-propylpentyl)urea (19). Compound **76** (1.41 g, 0.0058 mol) was suspended in 100 mL of ether, and 100 mL of 2 N NaOH was added. The mixture was stirred for 10 min; the layers were separated. The aqueous layer was extracted with 3 × 100 mL ether. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give 1.10 g (0.0054 mol) of the free amine as a clear, colorless oil. The amine was immediately dissolved in 50 mL of ethyl acetate and 2,6-diisopropylphenyl isocyanate (990 mg, 0.0049 mol) was added. The reaction was stirred at room temperature for 20 h and then concentrated under vacuum. The residue was suspended in hexane and collected. Drying under vacuum afforded 1.53 g (70%) of **19**: mp 149–151 °C, ^{1}H NMR ($CDCl_3$) δ 0.80 (t, 6H, J = 7.1 Hz), 1.07 (m, 16H); 1.47 (m, 4H); 3.13 (septet, 2H, J = 6.8 Hz), 3.39 (d, 2H, J = 5.4 Hz), 3.75 (bs, 1H); 5.73 (s, 1H); 7.17 (m, 8H, phenyl). Anal. ($C_{27}H_{40}N_2O$) C, H, N.

***N*-[2,6-Bis(dimethylamino)phenyl]-*N'*-[(1-phenylcyclopentyl)methyl]urea (52). a. *N,N,N',N'*-Tetramethyl-2-nitro-1,3-benzenediamine (78).** 2,6-Dichloronitrobenzene[11] (20.95 g, 0.11 mol) (**77**) and dimethylamine (50 g) were dissolved in 50 mL of toluene. A trace of copper was added and the mixture was autoclaved for 24 h at 160 °C. The resulting brown solution was cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between chloroform and 5% K_2CO_3 solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in 10% ethyl acetate–hexane and filtered through a pad of silica gel to yield 14.1 g (62%) of **78** as an oil.

b. N^1,N^1,N^3,N^3-Tetramethyl-1,2,3-benzenetriamine (79). Raney nickel (2.0 g) was added to a solution of 2,6-bis(dimethylamino)nitrobenzene (12.23 g, 0.059 mol) (**78**) in 400 mL of methanol and the reaction was shaken for 21 h at room temperature at 50 psi. The methanol solution was filtered, concentrated, and the residue was dissolved in 10% ethyl acetate–

hexane and filtered through a pad of silica gel. Removal of solvent from the filtrate gave 7.2 g (69%) of **79**.

c. *N*-[2,6-Bis(dimethylamino)phenyl]-*N'*-[(1-phenylcyclopentyl)methyl]urea (52). A solution of **79** (1.75 g, 0.0098 mol) in 50 mL of ethyl acetate was added dropwise to a solution of (1-phenylcyclopentyl)methyl isocyanate (1.96 g, 0.0098 mol) in 75 mL of ethyl acetate. An additional 1.5 g of the isocyanate was added after 2 h at 85 °C, and the reaction was heated for an additional 2 h. It was cooled to room temperature and filtered, and solvent was evaporated from the filtrate. Crude material thus obtained was purified by flash column chromatography using 20% ethyl acetate–hexane, yielding 2.02 g (54%) of **52**: mp 85–87 °C; ^{1}H NMR ($CDCl_3$) δ 1.68–1.89 (m, 8H), 2.46 (s, 12H), 3.46–3.48 (d, 2H); 6.72–6.75 (m, 3H); 7.07–7.17 (m, 6H); 7.66 (t, 1H). Anal. ($C_{23}H_{32}N_4O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-[(1-phenylcyclopentyl)methyl]sulfamide (70). a. (1-Phenylcyclopentyl)methanesulfamoyl Chloride (82).** The sulfamate ester **80**, (3.47 g, 0.01 mol), prepared according to DuBois et al.,[12a] was taken up in 40 mL of water and heated at reflux for 0.75 h with 10 mL of 1 M KOH solution. It was cooled to room temperature. The clear aqueous solution was concentrated in vacuo. The residue was triturated with boiling ether. The solid obtained was filtered and dried (2.5 g, 89%). This salt was suspended in benzene (25 mL), and PCl_5 (1.78 g, 0.0086 mol) was added. Reaction was refluxed for 2 h, cooled, and filtered. Evaporation of volatiles from the filtrate followed by trituration with ether gave 2.1 g of **82**, mp 90–91 °C.

b. *N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-[(1-phenylcyclopentyl)methyl]sulfamide (70). To a solution of 2,6-diisopropylaniline (1.4 g, 0.008 mol) and triethylamine (0.8 g, 0.008 mol) in 25 mL of THF was added a solution of **82** (2.1 g, 0.0076 mol) in 25 mL THF. The reaction was refluxed for 0.5 h and then stirred at room temperature overnight. The reaction mixture was filtered and solvent was removed from the filtrate. The residue was dissolved in ethyl acetate (200 mL) and washed with 5 N HCl and saturated $NaHCO_3$, followed by water. It was dried over $MgSO_4$, filtered, and evaporated to dryness. Treatment with hexane yielded **70**: mp 91–92 °C; ^{1}H NMR ($CDCl_3$) δ 1.11 (d, 12H, J = 6.8 Hz), δ 1.78–2.08 (m, 8H); 3.25–3.35 (m, 4H); δ 3.89 (bt, 1H); 5.49 (S, 1H); 7.09–7.37 (m, 8H). Anal. ($C_{24}H_{34}N_2O_2S \cdot 0.16H_2O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-[(1-phenylcyclopentyl)methyl]guanidine (73). a. *N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-[(1-phenylcyclopentyl)methyl] methanediimine (83).** To a solution of the thiourea **72** (5.0 g, 0.0126 mol) in 50 mL of acetonitrile were added dicyclohexyl methanediimine (3.9 g, 0.019 mol) and 0.5 mL of N-ethyldiisopropylamine. The reaction mixture was stirred at room temperature for 24 h. The precipitated dicyclohexyl urea was then filtered. The filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel using 5% ethyl acetate–hexane as eluant to yield 3.9 g (86%) of **83**, which was used immediately in the next reaction.

b. *N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-[(1-phenylcyclopentyl) methyl]guanidine (73). Into a solution of **83** (0.5 g, 0.0014 mol) in 10 mL of ether was bubbled ammonia for 1 min and the reaction was stirred at room temperature for 30 h. Volatiles were removed and the residue was treated with ethyl acetate–hexane (1:2, 15 mL) to give 0.28 g (53%) of **73**: mp 159–160 °C; ^{1}H NMR ($CDCl_3$) δ 1.11–1.16 (bd, 12H); 1.6–2.2 (m, 8H); 3.0 (m, 2H); 3.5 (s, 1H); 7.0–7.4 (m, 8H). Anal. ($C_{25}H_{25}N_3 \cdot 0.5H_2O$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N''*-cyano-*N'*-[(1-phenylcyclopentyl) methyl]guanidine (74).** To a solution of **83** (0.5 g, 0.0014 mol) in 5 mL of acetonitrile were added cyanamide (0.09 g, 0.0021 mol) and 0.4 mL of *N*-ethyldiisopropylamine, and the reaction was heated at 60 °C for 6 h. Volatiles were removed, and the residue, when treated with ethyl acetate, gave solid material. It was filtered and dried to yield 0.41 g (73%) of **74**: mp 202–204; ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 6H; J = 6.9 Hz), 1.10 (d, 6H; J = 7.2 Hz), 1.6–1.8 (m; 8H); 2.91 (s; 2H; J = 6.9 Hz), 3.24 (d; 2H; J = 5.0 Hz), 3.9 (bt, 1H); 6.65 (s, 1H); 6.8–7.4 (m, 8H). Anal. ($C_{26}H_{34}N_4$) C, H, N.

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Supplementary Material Available: Table of parameters employed in QSAR study (3 pages). Ordering information is given on any current masthead page.

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