Inhibitors of Acyl-CoA:Cholesterol Acyltransferase (ACAT). 7. Development of a Series of Substituted *N*-Phenyl-*N'*-[(1-phenylcyclopentyl)methyl]ureas with Enhanced Hypocholesterolemic Activity‡

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We recently described our initial structure–activity relationship (SAR) studies on a series of *N*-phenyl-*N'*-aralkyl- and *N*-phenyl-*N'*-(1-phenylcycloalkyl)ureas as inhibitors of acyl-CoA: cholesterol acyltransferase (ACAT). From this series of analogs, compound 1 (PD 129337) was identified as a potent inhibitor of ACAT with an IC_{50} value of 17 nM. It was also shown to dose-dependently lower plasma cholesterol in cholesterol-fed rats. However, further investigation led to the suggestion that this compound was poorly absorbed, due to a lack of efficacy when administered by gavage in an aqueous vehicle. To overcome this deficiency, we continued our SAR study on this novel series of ACAT inhibitors using an acute in vivo screen in which the compounds are administered to rats in an aqueous, CMC/Tween suspension vehicle. Modification of the *N'*-phenyl moiety by incorporating functional groups which were amenable to forming salts and/or polar groups to reduce lipophilicity led to the identification of several inhibitors which displayed excellent efficacy employing this protocol. Overall, substitution on the phenyl ring in the ortho, meta, or para positions led to inhibitors with only a slight decrease in potency in vitro compared to the parent unsubstituted compound. Bulkier groups in the para position tended to lower the ACAT inhibitory activity in vitro. Polar groups, such as carboxyl (**33**, **34**), lowered in vitro activity significantly, suggesting that polar–ionic interactions are disfavored for the enzyme activity. From this series, compound **28** was evaluated further in secondary in vivo screens. In a chronic cholesterol-fed rat model of hypercholesterolemia, compound **28** dose-dependently reduced nonHDL cholesterol and significantly elevated HDL cholesterol. It showed significantly greater aqueous solubility than the parent compound 1. However, it was shown to cause adrenal toxicity in guinea pigs. This led us to design a series of homologs (**44–51**) with increased basicity and lower lipophilicity. Some of these compounds were more potent ACAT inhibitors in vitro and demonstrated excellent hypocholesterolemic activity in vivo. Interestingly, compound **45**, unlike **28**, did not produce adrenal toxicity in guinea pigs and demonstrated excellent lipid-modulating activity in the chronic model of preestablished dyslipidemia in rats.

Introduction

Considerable recent evidence suggests that acyl-CoA: cholesterol acyltransferase (ACAT) plays an important role in the regulation of lipoprotein secretion by the liver[1-4] and that inhibition of arterial macrophage ACAT can directly inhibit lesion progression.[5,6] Therefore, we and others have been actively involved in the design and development of potent ACAT inhibitors.[7-9] Recently, we described several series of potent ACAT inhibitors[10-13] including *N*-phenyl-*N'*-(1-phenylcycloalkyl)ureas.[14] From this series, compound 1 (PD 129337) was identified as a potent inhibitor of rabbit intestinal ACAT with an IC_{50} value of 17 nM. Furthermore, 1 was also found to effectively lower plasma total cholesterol when tested in a dose–response fashion in a chronic model of hypercholesterolemia in rats as a diet admixture.[14] In this paper, we disclose further structure–activity relationship (SAR) studies that led to the discovery of potent, orally efficacious ACAT inhibitors, including PD 132301-2 (**28**), the activity of which correlates with plasma drug concentrations in both rat and canine models of hypercholesterolemia.[15]

Chemistry

Most of the compounds prepared for this study were synthesized as previously described.[14] Substituted benzeneacetonitriles were first spiroalkylated and then catalytically reduced to the corresponding amines which in turn were reacted with appropriate isocyanates to yield the requisite urea derivatives. Compounds **23–25** were synthesized from the corresponding nitro analogs (**20–22**) by Raney Ni reduction. Reaction of **25** with ethylene oxide in methanol gave a mixture of **29** and **30** which were separated by flash chromatography. Compound **28** was synthesized as shown in Scheme 1. Commercially available *p*-nitrophenylacetonitrile was spiroalkylated using 1,4-dibromobutane and NaH in DMSO at room temperature.[14] The nitro group was reductively alkylated to afford **53**. The cyano functionality was then catalytically reduced using Raney Ni in methanol–ammonia to yield **54**. Reaction of **54** with 2,6-diisopropylphenyl isocyanate gave **27** which was converted to the hydrochloride salt **28** by treatment with HCl.

The synthesis of compound **51** (Scheme 2) represents the general synthetic scheme for the compounds listed in Table 3. Bromination of benzyl cyanide **55** with NBS in

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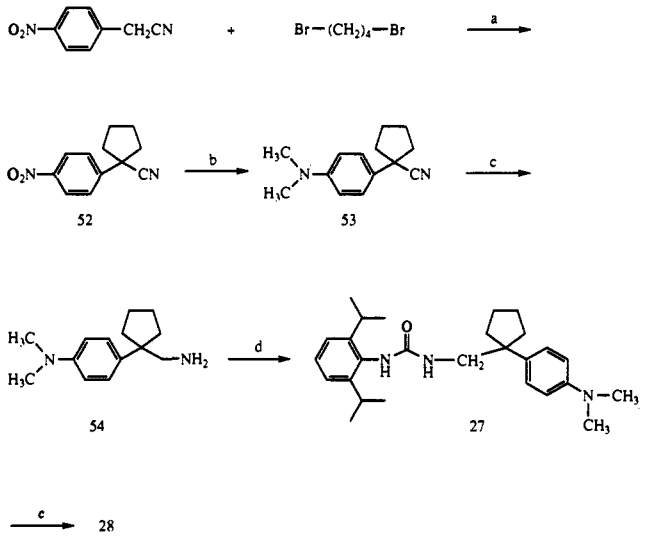
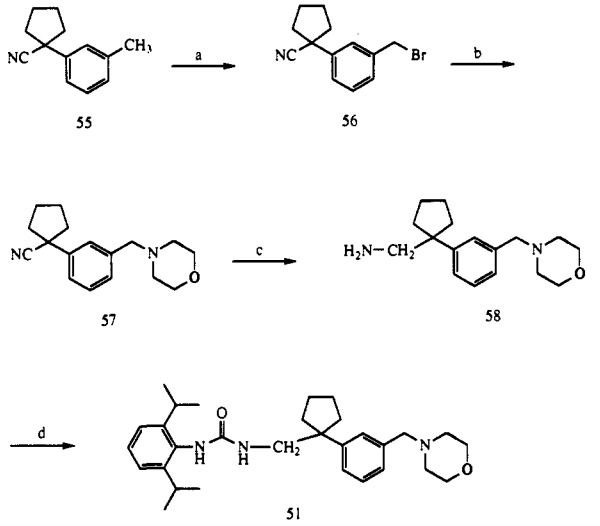
Scheme 1[a]



[a] (a) NaH/DMSO; (b) HCHO, Pd/C; (c) Raney Ni, MeOH–NH_3; (d) 2,6-diisopropylphenyl isocyanate, ethyl acetate; (e) HCl.

Scheme 2[a]



[a] (a) NBS/CCl_4; (b) morpholine, CH_2Cl_2; (c) Raney Ni, H_2; (d) 2,6-diisopropylphenyl isocyanate, ethyl acetate.

refluxing carbon tetrachloride afforded compound **56**. Bromide **56** was then reacted with morpholine in dichloromethane to yield the morpholino derivative **57**. Catalytic reduction using Raney Ni in methanolic ammonia followed by reaction with 2,6-diisopropylphenyl isocyanate yielded the desired urea **51** in 47% overall yield.

Results and Discussion

Efficacy studies with compound 1 suggested that it did not lower plasma total cholesterol when dosed as an aqueous suspension by gavage. Thus, compound 1 was effective only when administered in a lipid-rich diet or with an oil vehicle but not with an aqueous vehicle (Table 1). Specifically, at the lowest dose tested (25 mg/kg) compound 1 was inactive when administered by gavage in an aqueous vehicle; however, at the same dose, it lowered plasma cholesterol by 49% using the oil vehicle or 59% when administered in the diet. Marked differences in efficacy were also observed at higher doses using these different models of drug dosing. Since it is widely recognized that the absorption of poorly absorbed drugs can be enhanced by the use of lipid adjuvants or vehicles[16]

Table 1. Efficacy of Compound 1 (PD 129337) in Cholesterol-Fed Rats (PCC): Effect of Mode of Administration and Vehicle

dose (mg/kg)	mode	vehicle[a]	% reduction in plasma cholesterol[b]
25	gavage	CMC/T	−5*
25	gavage	OA	−49
25	diet		−59
50	gavage	CMC/T	−13*
50	gavage	OA	−46
50	diet		−76
100	gavage	CMC/T	−29
100	gavage	OA	−55
100	diet		−71

[a] CMC/T = 1.5% carboxymethylcellulose (Sigma C-8758)/0.2% Tween-20 (Aldrich 27,434-8) in water. OA = oleic acid (Mallinckrodt 2744). [b] All reductions in plasma cholesterol are significantly different ($p < 0.05$) from those of untreated control animals using the same mode/vehicle except those indicated by *.

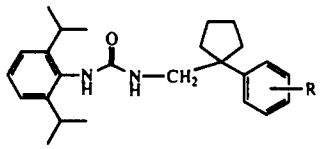
and that lipophilic compounds with poor water solubility generally have low systemic bioavailability,[17] these data suggested that compound 1 might be poorly absorbed. This conclusion was subsequently strengthened by a study in dogs in which blood–drug concentrations of 1 were higher when dosed in oleic acid compared to bulk drug. Thus, these data prompted us to continue our structure–activity relationship studies on this series of compounds using an aqueous, CMC/Tween suspension vehicle in an acute cholesterol-fed animal model.

For the in vitro ACAT inhibitory activity, we had optimized the structure of our inhibitor having a 2,6-diisopropylphenyl functionality and a 1-phenylspirocyclopentyl moiety. Further functionalization in the 4-position of the *N'*-phenyl moiety with a large number of functional groups (**4–11, 14, 16, 19, 22, 25, 27, 32, 34**) afforded ACAT inhibitors with a wide range of electronic and steric effects (Table 2). Compounds with a significantly high steric bulk (**7**) and ionic carboxyl functionality (**33–34**) lost ACAT inhibitory activity 10–100 fold, while the other analogs maintained the in vitro ACAT inhibitory activity. On the basis of the initial in vivo activity of some of these compounds, a few disubstituted analogs (**37–41**) were also synthesized. These compounds were also potent ACAT inhibitors in vitro. For certain functional groups, such as Me, OMe, CF_3, NO_2, NH_2, and NMe_2, the corresponding regioisomeric analogs were also equally effective in inhibiting ACAT in vitro. Incorporation of polar, flexible functional groups afforded analogs **29** and **30** with excellent ACAT inhibitory activity.

All of these ACAT inhibitors were evaluated for their ability to lower plasma cholesterol in the acute cholesterol-fed rat model using an aqueous vehicle.[13,15] When dosed at 50 mg/kg in this acute screen, compound 1 lowered plasma cholesterol by 38% (Table 2). This activity is greater than that seen in the chronic screen using the aqueous, CMC/Tween suspension vehicle (−13%, Table 1). Most of these compounds lowered plasma cholesterol as effectively or better than the parent compound PD 129337 (1). In this screen, most weak ACAT inhibitors (>100 nM) (**32, 34**) were inactive with the exceptions of **7** and **33** which showed good in vivo activity. Compounds having an amino or alkylamino substituent (**23–28**) showed greater cholesterol-lowering activity than the parent unsubstituted compound (1).

We then prepared the hydrochloride salt of **27** (**28**, PD 132301-2) and compared it with the parent unsubstituted compound PD 129337. The physicochemical properties

Table 2. *N'*-Phenyl Substitution



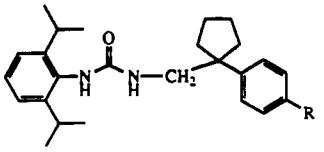
example	R	formula[a]	mp (°C)	IC_{50} [μM][b]	% ΔTC[c]
1	H	$C_{25}H_{34}N_2O$	181–183	0.017	−38**
2	2-Me	$C_{26}H_{36}N_2O$	147–150	0.017	−73***
3	3-Me	$C_{26}H_{36}N_2O$	138–140	0.015	−52***
4	4-Me	$C_{26}H_{36}N_2O$	159–161	0.025	−70***
5	4-*i*-Pr	$C_{28}H_{40}N_2O$	133–141	0.048	−63***
6	4-*t*-Bu	$C_{29}H_{42}N_2O$	160–162	0.063	−48**
7	4-$CH_2C(Me)_3$	$C_{30}H_{44}N_2O$	145–148	0.159	−53***
8	4-F	$C_{25}H_{33}FN_2O$	188–191	0.023	−57***
9	4-Cl	$C_{28}H_{33}ClN_2O$	189–192	0.032	−64***
10	4-Br	$C_{25}H_{33}BrN_2O$	191–193	0.029	−59***
11	4-OH	$C_{25}H_{34}N_2O_2$	109–112	0.042	−31**
12	2-OMe	$C_{26}H_{36}N_2O_2$	132–135	0.023	−53***
13	3-OMe	$C_{28}H_{36}N_2O_2$	128–129	0.013	−42**
14	4-OMe	$C_{26}H_{36}N_2O_2$	144–147	0.031	−41**
15	3-OBn	$C_{32}H_{40}N_2O_2$	179–182	0.030	−73***
16	4-OBn	$C_{32}H_{40}N_2O_2$	122–124	0.034	−33**
17	2-CF_3	$C_{26}H_{33}F_3N_2O$	156–159	0.018	−50***
18	3-CF_3	$C_{26}H_{33}F_3N_2O$	166–169	0.027	−45***
19	4-CF_3	$C_{26}H_{33}F_3N_2O$	196–197	0.066	−39**
20	2-NO_2	$C_{25}H_{33}N_3O_3$	158–160	0.027	−45***
21	3-NO_2	$C_{25}H_{33}N_3O_3$	174–175	0.051	−51***
22	4-NO_2	$C_{25}H_{33}N_3O_3$	205–206	0.131	
23	2-NH_2	$C_{25}H_{35}N_3O{\cdot}0.33H_2O$	87–89	0.14	−58***
24	3-NH_2	$C_{28}H_{35}N_3O$	149–150	0.021	−75***
25	4-NH_2	$C_{25}H_{35}N_3O$	178–179	0.029	−76***
26	3-NMe_2	$C_{27}H_{39}N_3O$	124–126	0.033	−63***
27	4-NMe_2	$C_{27}H_{39}N_3O$	128–130	0.037	−65***
28	4-NMe_2·HCl	$C_{27}H_{39}N_3O{\cdot}HCl$	228–229	0.052	−77***
29	4-$NH(CH_2)_2OH$	$C_{27}H_{39}N_3O_2{\cdot}0.5H_2O$	159–161	0.025	−63***
30	4-$N(CH_2CH_2OH)_2$	$C_{29}H_{43}N_3O_3$	139–141	0.021	−50***
31	3-CO_2Me	$C_{27}H_{36}N_2O_3$	144–147	0.034	−51***
32	4-CO_2Me	$C_{27}H_{36}N_2O_3$	130–135	0.36	−3
33	3-CO_2H	$C_{26}H_{34}N_2O_3$	225–228	0.62	−40**
34	4-CO_2H	$C_{26}H_{34}N_2O_3$	213–214	3.1	−8
35	3-CH_2OH	$C_{26}H_{36}N_2O_2$	75–80	0.015	−40**
36	4-CH_2OH	$C_{26}H_{36}N_2O_2{\cdot}0.25H_2O$	168–170	0.026	19
37	2,4-di-Me	$C_{27}H_{36}N_2O$	152–154	0.050	−50***
38	2,5-di-Me	$C_{27}H_{38}N_2O$	70–74	0.039	−48***
39	2,4,6-tri-Me	$C_{28}H_{40}N_2O$	173–176	0.056	−24**
40	3,5-di-CF_3	$C_{27}H_{32}F_6N_2O$	159–162	0.057	−32**
41	2-CF_3, 4-NMe_2	$C_{28}H_{33}F_3N_3O$	74–78	0.050	

[a] Analytical results are within ±0.4% of the theoretical values, unless otherwise noted. [b] ACAT inhibition in vitro, intestinal microsomes isolated from cholesterol-fed rabbits. Each determination performed in triplicate. See ref 10 for complete protocol. [c] Denotes percent change in total cholesterol in peanut oil (5.5%)–cholic acid (0.3%)–cholesterol (1.5%)-fed rats after a single dose (acute screen). See ref 13 for complete protocol. Compounds dosed as suspension in CMC (1.5%) and Tween-20 (0.2%) in water at 50 mg/kg dose: (*) $p < 0.05$, (**) $p < 0.01$, and (***) $p < 0.001$ (Student's *t*-test).

of these analogs are given in Table 3. It is interesting to note that the lipophilicity of both compounds is quite high, as indicated by the log *P* values. However, the hydrochloride salt (**28**) has greater aqueous solubility than the parent compound, which is completely insoluble in water. In addition, at lower pH, the log *P* values for **27** are significantly lower than those at pH 7.4; thus, in an acidic environment, it will exist in a salt form with lower lipophilicity and increased aqueous solubility. This may be one of the reasons that we do not see significant differences in in vivo activity between **27** and **28**. Compounds **1** and **28** were then evaluated in a chronic, cholesterol-fed rat model (Figure 1). For comparison, the Lederle ACAT inhibitor CL277082 was also tested. The compounds were administered by gavage using aqueous CMC/Tween suspension at 3, 10, and 30 mg/kg doses. PD 129337 reduced nonHDL cholesterol (nonHDL-C) only at the highest dose. The Lederle ACAT inhibitor CL 277082 was effective in lowering nonHDL-C at all doses but failed to elevate HDL cholesterol (HDL-C). Compound **28** lowered nonHDL-C in a dose-dependent manner, resulting in values of nonHDL-C that were lower than those for CL 277082 at both 10 and 30 mg/kg. At the 10 mg/kg dose, the differences reached statistical significance. The most interesting aspect of the PD 132301-2 profile was its HDL-C elevation. It elevated HDL-C significantly at both the 10 and 30 mg/kg doses and elevated HDL-C at the high dose to a level approaching that found in rats switched to a chow diet during the second week (CF → chow).

PD 132301-2 was then extensively evaluated in other animal models of dyslipidemia and exhibited excellent lipid-regulating activity.[15] Moreover, in a canine model, efficacy was correlated with blood–drug concentrations.[15] However, further in vivo evaluation in toxicological studies revealed that PD 132301-2 was an inhibitor of mitochondrial respiration in adrenal cells and caused atrophy of the zona fasciculata.[18,19] Furthermore, the narrow margin between toxic and efficacious doses in the dog precluded

Table 3. Physicochemical Data for PD 129337 (1), PD 132301 (27), and Its Hydrochloride Salt (28)



1 R = H
27 R = $N(Me)_2$
28 R = $N(Me)_2 \cdot HCl$

		example		
		1 (PD 129337)	27 (PD 132301)	28 (PD 132301-2)
solubility (mg/mL):	water		<0.01	0.7
	pH 7.4	<0.001	<0.01	<0.05
	pH 4.0	<0.001	<0.01	1.33
	0.1 N HCl	<0.001	<0.01	6.4
log *P*:[a]	pH 7.4	5.16	5.59	NT
	pH 4.0	NT	2.89	NT
	pH 1.0	NT	2.18	NT

[a] log *P* values were determined at pH 7.4 by HPLC correlation method.[20]

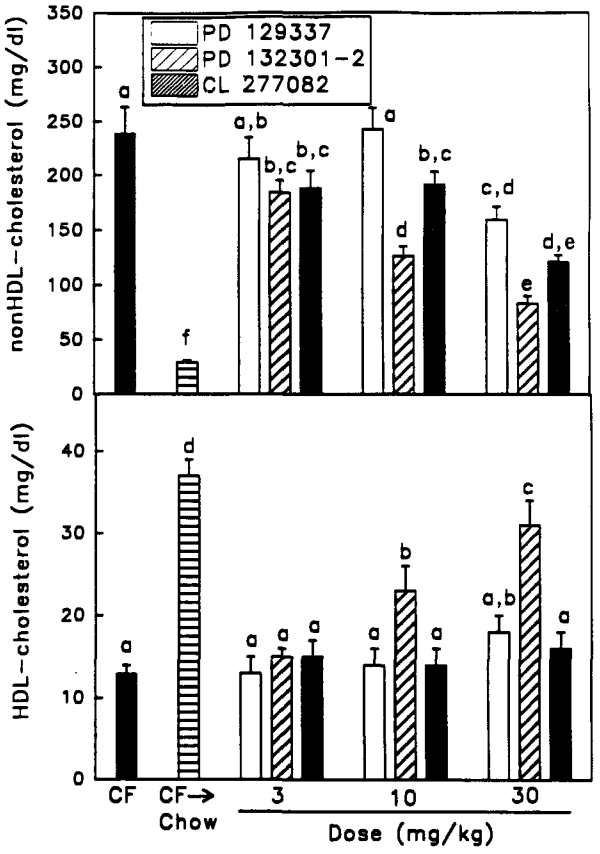
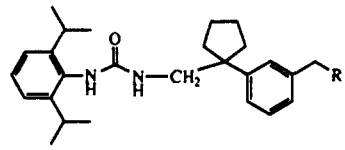


Figure 1. Effect of PD 129337 (1), PD 132301-2 (28), and CL 277082 in the chronic cholesterol-fed rat model. Values sharing a common superscript are not significantly different ($p > 0.05$) using ANOVA followed by a protected least-significant difference test ($n = 12$/group). CF = cholesterol-fed controls (2 weeks); CF → chow = rats switched to normal chow for the second week.

further development of this compound. Thus, we continued our search for other ACAT inhibitors which would have the lipid-regulating activity of PD 132301-2 but not the adrenal toxicity. Since this series of ACAT inhibitors exhibited an excellent overall profile, we chose to further manipulate the parent molecule by incorporating an alkylamino function onto the *N'*-phenyl moiety to make these molecules more polar and basic in nature. Additionally, our SAR in this series of analogs (Table 1) suggested that there was essentially no difference in in vitro and in vivo activity for the regioisomeric meta- and para-substituted analogs. Thus, a series of meta-substituted analogs were synthesized in which we introduced a polar alkylamino function onto the *N'*-phenyl moiety (Table 4). Evaluation of the intermediate bromide (**42**) and nitrile (**43**) showed that both were relatively potent ACAT inhibitors with IC_{50} values of 44 and 24 nM, respectively. However, in the acute overnight model of hypercholesterolemia,[13] both of the compounds were less efficacious. Interestingly, the homolog of **27** (**45**) and its hydrochloride salt (**46**) both maintained in vitro potency for inhibition of ACAT. Incorporation of a bis-hydroxyethyl function (**47**) to introduce polarity gave us a compound with the lowest log *P* value, 3.55, for this series of compounds, and it was very effective in lowering total cholesterol at both 3 and 30 mg/kg. The *N,N*-dibutyl analog (**49**) was one of the most potent analogs in vitro as well as in vivo. Finally, we prepared the *N*-methylpiperazino (**50**) and morpholino (**51**) analogs. Both of these compounds demonstrated excellent in vitro ACAT inhibitory activity and cholesterol-lowering activity in vivo. Compound **51** was slightly more potent at both doses tested. It should be noted that this compound has a log *P* value of 4.37 which is comparable to that for **45** (log *P* = 4.8) and considerably lower than that for **27** (log *P* = 5.59).

On the basis of the excellent in vitro potency and hypocholesterolemic activity in the acute screen, a few of these analogs were then compared with PD 132301-2 in the chronic cholesterol-fed rat model in a dose-response fashion (Table 5). Compound **50**, although effective in lowering total cholesterol, was ineffective in elevating HDL-C except at the highest dose. Compound **49** significantly reduced nonHDL-C and elevated HDL-C at 3 mg/kg but failed to show enhanced activity at the highest dose. Interestingly, the morpholino analog (**51**) was as efficacious as PD 132301-2 not only at lowering total cholesterol but also at elevating HDL-C. Thus, at the highest dose of 10 mg/kg tested, compound **51** had a lipid modulating profile very similar to PD 132301-2 (**28**). Compound **45**, the homolog of PD 132301, showed excellent cholesterol-lowering activity, and at the 30 mg/kg dose level, it had comparable activity to PD132301-2 (**28**). Compound **45** lowered nonHDL-C by 76% and elevated HDL-C by 154%. It is important to note that the HDL-C

Table 4. N'-Alkylamino Analogs



example	R	formula[a]	mp (°C)	IC_{50} [μM][b]	% Δ TC[c] 3 mg/kg	% Δ TC[c] 30 mg/kg	log P[d]
42	Br	$C_{26}H_{35}BrN_2O$	178–181	0.044		−26*	5.23
43	CN	$C_{27}H_{35}N_3O$	150–155	0.024		−31**	3.61
44	NH_2	$C_{26}H_{37}N_3O$	176–180	0.44		−49***	3.64
45	NMe_2	$C_{28}H_{41}N_3O$	109–115	0.063	−22	−55***	4.80
46	NMe_2·HCl	$C_{28}H_{41}N_3O$·HCl	182–186	0.067	−44**	−46**	4.87
47	$N(CH_2CH_2OH)_2$	$C_{30}H_{45}N_3O_3$·0.7$CHCl_3$[e]	amorphous solid	0.047	−33*	−63***	3.55
48	$N(CH_2CH_2OAc)_2$	$C_{34}H_{49}N_3O_5$·0.3$CHCl_3$[f]	amorphous solid	0.033	−35**	−71***	4.55
49	$N(CH_2CH_2CH_2CH_3)_2$	$C_{34}H_{53}N_3O$	oil	0.016	−25	−63***	6.05
50		$C_{31}H_{46}N_4O$	158–161	0.016	−21	−66***	5.28
51		$C_{30}H_{43}N_3O_2$	136–137	0.011	−47**	−70***	4.37

[a–c] Refer to footnotes in Table 2. [d] log P values were determined at pH 7.4 by HPLC correlation method.[20] [e] High-resolution MS calcd, 496.3539; found, 496.3538. [f] High-resolution MS calcd, 579.3672; found, 579.3676.

Table 5. Comparison of PD 132301-2 (28) and Related Analogs in Rats with Preestablished Dyslipidemia

treatment group	dose (mg/kg)	TC	% Δ[a]	HDL-C	% Δ	nonHDL-C	% Δ
		Experiment 1					
controls (c-fed)		314 ± 49		12 ± 1		303 ± 50	
controls (CF→chow)		65 ± 2*	−79	38 ± 1*	230	27 ± 2*	−91
28 (PD 132301-2)	0.3	252 ± 22	−20	17 ± 2	44	235 ± 22	−22
	1.0	222 ± 30	−29	15 ± 2	32	206 ± 31*	−32
	3.0	251 ± 40	−20	16 ± 2*	38	235 ± 42	−23
	10.0	115 ± 5*	−64	31 ± 1*	167	84 ± 6*	−72
49	0.3	271 ± 36	−14	12 ± 1	16	258 ± 37	−15
	1.0	276 ± 31	−12	10 ± 2	−16	266 ± 32	−12
	3.0	206 ± 13*	−34	12 ± 1	8	194 ± 13*	−36
	10.0	302 ± 18	−4	9 ± 1	−21	293 ± 18	−3
50	0.3	325 ± 28	3	12 ± 1	2	313 ± 28	3
	1.0	209 ± 22*	−33	15 ± 1	27	195 ± 22*	−36
	3.0	239 ± 31	−34	12 ± 1	8	227 ± 32	−25
	10.0	154 ± 13*	−51	19 ± 1*	60	135 ± 14*	−55
51	0.3	237 ± 31	−24	14 ± 2	16	224 ± 33	−26
	1.0	273 ± 37	−13	13 ± 1	10	260 ± 38	−14
	3.0	218 ± 25*	−31	16 ± 1*	40	202 ± 26*	−33
	10.0	118 ± 9*	−63	30 ± 4*	162	84 ± 7*	−71
		Experiment 2					
controls (c-fed)		297 ± 39		13 ± 1		284 ± 40	
controls (CF→chow)		57 ± 11*	−81	43 ± 2*	231	23 ± 1*	−92
28 (PD 132301-2)	30	91 ± 6*	−69	36 ± 1*	177	56 ± 7*	−80
45	1	292 ± 30	N/C	14 ± 2	8	278 ± 31	N/C
	3	229 ± 20*	−23	17 ± 2	31	212 ± 22*	−25
	10	200 ± 27*	−33	23 ± 2*	77	177 ± 29*	−38
	30	101 ± 9*	−66	33 ± 2*	154	68 ± 8*	−76

[a] Denotes percent change in total cholesterol in cholic acid (0.3%)–cholesterol (1.5%)–peanut oil (5.5%)-fed rats. * = significantly different from c-fed controls, $p < 0.05$.

elevating activity was independent of the ACAT-inhibitory activity and it was generally associated with compounds having electron-donating functionalities on the N'-phenyl ring. A few of these analogs were evaluated in the guinea pig to assess adrenal toxicity. After two weeks of oral dosing of compound 28 (100 mg/kg) using an oleic acid vehicle, marked cytotoxic atrophy, increased coarse vacuolation, and single-cell necrosis were observed in all animals ($n = 6$), as previously described,[18,19] and compound 51 produced increased coarse vacuolation (6/6 animals). However, under identical conditions, adrenal lesions were not seen with compound 45.

Conclusion

In summary, we have synthesized a series of analogs of PD 129337 (1) in an attempt to improve the pharmacological and physicochemical profile. Synthesis of a series of N'-phenyl-substituted analogs revealed that incorporation of a dimethylamino function onto the N'-phenyl moiety was beneficial in improving the in vivo profile. This strategy led to the identification of 27. The hydrochloride salt (28, PD 132301-2) showed an increase in water solubility which may contribute towards its overall improved profile compared to the parent unsubstituted compound 1. Compound 28 potently lowers plasma total cholesterol in various animal models of hypercholesterolemia[17] but is an adrenal toxicant.[18,19] Continued SAR studies revealed a series of homologated analogs, such as 51, having an excellent biological profile in vitro as well as in vivo. These analogs have slightly lower log P's and enhanced basicity compared to PD 132301 (27). Indeed, compound 45 possessed an excellent overall profile. It is

important to note, however, that seemingly minor changes in the molecule have affected certain key parameters, such as lipophilicity and basicity, and this may play a significant role in modulating compound absorption, transport, and/or distribution. However, it is difficult to explain why **51** displayed toxicity similar to that of **28** (PD 132301-2), whereas **45** was nontoxic. Details of further SAR study, in this regard, will be the subject of future communications from this laboratory.

Experimental Section

Materials used were obtained from commercial suppliers and 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.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-[[1-[4-(dimethylamino)phenyl] cyclopentyl]methyl]urea Hydrochloride (28).** **a. 1-(4-Nitrophenyl)cyclopentanecarbonitrile (52).** To 79.2 g (1.65 mol) of 50% sodium hydride, suspended in 750 mL of DMSO, was added dropwise a mixture of 121.6 g (0.75 mol) of *p*-nitrophenylacetonitrile and 161.7 mL (0.75 mol) of 1,4-dibromobutane in 750 mL of a 50:50 mixture of DMSO and diethyl ether. The temperature was held between 25 and 30 °C. The reaction mixture was stirred at room temperature overnight and then cooled to 10 °C. Thirty-eight milliliters of isopropyl alcohol was added followed by the cautious addition of 2.8 L of water. Air was bubbled through the black reaction mixture to remove most of the ether. The black solid was filtered and taken up in diethyl ether. The ether solution was washed two times with 2 N HCl and two times with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting dark solid was extracted six times with boiling hexane. The hexane solution was concentrated to a small volume to yield 127.5 g of **52**, mp 76-77 °C.

b. 1-[4-(Dimethylamino)phenyl]cyclopentanecarbonitrile (53). In a pressure reactor was placed 127.5 g (0.59 mol) of 1-(4-nitrophenyl)cyclopentanecarbonitrile (**52**) and 1600 mL of methanol. One gram of 10% Pd/C was added to the reactor which was then charged with hydrogen. The reaction mixture was shaken at room temperature until the theoretical amount of hydrogen had been taken up. The reactor was vented, and 100.5 g of 37% formaldehyde and 5 g of 10% Pd/C was added and the mixture shaken at room temperature for 16 h. The reaction mixture was filtered and the filtrate concentrated in vacuo to give a sticky solid. The solid was taken up in ether and washed two times with a sodium bisulfite solution and two times with brine, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by chromatography, using a hexane-ethyl acetate gradient to yield 94 g (73%) of 1-cyano-1-[4-(dimethylamino)-phenyl]cyclopentane(**53**), mp 73-74 °C.

c. 4-[1-(Aminomethyl)cyclopentyl]-*N*,*N*-dimethylbenzenamine (54). In a pressure reactor were placed 281.2 g (1.3 mol) of 1-[4-(dimethylamino)phenyl]cyclopentanecarbonitrile (**53**), 3500 mL of methanol, 600 g of anhydrous ammonia, and 200 g of Raney nickel. Hydrogen was charged into the stirred reaction vessel. The reaction mixture was stirred at room temperature until the theoretical amount of hydrogen had been taken up. The reaction mixture was filtered and the filtrate concentrated in vacuo to yield 284.4 g (99%) of **54**, mp 87-89 °C.

d. *N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-[[1-[4-(dimethylamino)phenyl]cyclopentyl]methyl]urea (27). To 137.2 g (0.63 mol) of **54** in ethyl acetate (2800 mL) was added 2,6-diisopropylphenyl isocyanate (127.75 g, 0.63 mol), and the reaction mixture was stirred at room temperature for 20 h. Volatiles were removed to yield 258.2 g (97%) of **27**, mp 132-133 °C. ^{1}H NMR ($CDCl_3$): δ 1.05 (bs, 12H), 1.8 (m, 8H), 2.95 (s, 6H), 3.2 (m, 4H), 3.95 (bt, 1H), 5.9 (s, 1H), 6.41 (d, 2H, J = 8.5 Hz), 6.76 (d, 2H, J = 8.5 Hz), 7.1 (d, 2H, J = 8.2 Hz); 7.24 (m, 1H). Anal. ($C_{27}H_{39}N_3O$) C, H, N.

e. *N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-[[1-[4-(dimethylamino)phenyl]cyclopentyl]methyl]urea Hydrochloride (28). To 40 g (0.045 mol) of **27** in toluene (350 mL) was added, with stirring, 8.13 mL (0.095 mol) of concentrated HCl. A gummy solid separated. The reaction mixture was heated to boiling to azeotrope off water. It was cooled to room temperature. The solid obtained was filtered, washed with acetone and ether, and dried in vacuo at 60 °C to yield 42.4 g (97%) of **28**, mp 230-231 °C. ^{1}H NMR ($CDCl_3$): δ 1.09 (b s, 12H), 1.8 (m, 8H), 3.08 (b s, 8H), 3.39 (b s, 2H), 5.98 (b s, 1H), 7.1 (m, 3H), 7.6 (b m, 4H). Anal. ($C_{27}H_{39}N_3O$·HCl) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-[[1-[4-[(2-hydroxyethyl)amino]phenyl]cyclopentyl]methyl]urea (29) and *N*-[[1-[4-[Bis(2-hydroxyethyl)amino]phenyl]cyclopentyl]methyl]-*N'*-[2,6-bis(1-methylethyl)phenyl]urea (30).** Compound **25** (2.93 g, 0.01 mol) was dissolved in 10 mL of methanol. Ethylene oxide was bubbled into the reaction for 15 min. The reaction mixture was then refluxed for 3 h. Ethylene oxide was bubbled again, and the reaction mixture was refluxed for 2 h. It was allowed to stir at room temperature overnight. Volatiles were removed under reduced pressure, and the residue was purified by flash chromatography on silica gel using 90% ethyl acetate-hexane to yield 900 mg (20%) of **29**, mp 159-161 °C. ^{1}H NMR ($CDCl_3$) δ 1.05 (b s, 12H), 1.8 (m, 8H), 3.17 (m, 4H), 3.23 (t, 2H, J = 5.2 Hz), 3.81 (t, 2H, J = 5.2 Hz), 3.89 (b s, 1H), 5.82 (s, 1H), 6.33 (d, 2H, J = 8.4 Hz), 6.69 (d, 2H, J = 8.4 Hz), 7.1 (d, 2H, J = 7.6 Hz), 7.27 (d, 1H, J = 6.5Hz). Anal. ($C_{27}H_{39}N_3O_2$·0.5H_2O) C, H, N.

Also obtained was 1.6 g (33%) of **30**, mp 139-141 °C. ^{1}H NMR ($CDCl_3$) δ 1.05 (b s, 12H), 1.8 (m, 8H), 3.14 (m, 5H), 3.51 (t, 4H, J = 4.7 Hz), 3.83 (t, 4H, J = 4.7 Hz), 5.61 (s, 1H), 6.38 (d, 2H, J = 8.5 Hz), 6.75 (d, 2H, J = 8.5 Hz), 7.1 (d, 2H, J = 7.6 Hz), 7.27 (d, 1H, J = 7.5 Hz). Anal. ($C_{29}H_{43}N_3O_3$) C, H, N.

***N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-[[1-[3-(4-morpholinylmethyl)phenyl]cyclopentyl]methyl]urea (51).** **a. 1-(3-Methylphenyl)cyclopentanecarbonitrile (55).** A 50% dispersion of sodium hydride on mineral oil (45.7 g, 0.952 mol) was suspended in 750 mL of anhydrous dimethyl sulfoxide under nitrogen. A solution of 1,4-dibromobutane (98.8 g, 0.457 mol) and 3-methylphenylacetonitrile (50 g, 0.381 mol) dissolved in 250 mL of anhydrous diethyl ether was added slowly to the stirring suspension, cooling as necessary to keep the temperature between 25 and 35 °C. After addition was complete, the reaction mixture was stirred for 20 h at room temperature. The reaction mixture was cooled to 15 °C, and 200 mL of water was added cautiously. To this mixture was added 500 mL of ether, and the layers were separated. The aqueous layer was extracted with 2 × 500 mL of ether. The combined organic extracts were washed with 500 mL of brine, dried over magnesium sulfate, and concentrated. The crude product was purified by flash column chromatography in ethyl acetate-hexane to give 63.2 g (90%) of **55** as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.03 (m, 6H), 2.37 (s, 3H), 2.45 (m, 2H), 7.20 (m, 4H).

b. 1-[3-(Bromomethyl)phenyl]cyclopentanecarbonitrile (56). Nitrile **55** (31.0 g, 0.167 mol) was dissolved in 400 mL of carbon tetrachloride. *N*-Bromosuccinimide (32.8 g, 0.184 mol) was added followed by benzoyl peroxide (0.892 g, 3.7mmol) dissolved in 100 mL of carbon tetrachloride. The stirring mixture was heated to reflux under nitrogen for 4.5 h and then stirred at room temperature for 20 h. The reaction was filtered and washed with additional carbon tetrachloride (<100 mL). The filtrates were concentrated under vacuum, and the resulting crude product was purified by flash column chromatography using ethyl acetate-hexane. This afforded 38.2 g (86%) of the desired bromide **56** as a brown oil. ^{1}H NMR ($CDCl_3$): δ 2.02 (m, 6H), 2.50 (m, 2H), 4.50 (s, 2H), 7.48 (m, 4H).

c. 1-[3-(4-Morpholinylmethyl)phenyl]cyclopentanecarbonitrile (57). Bromide **56** (35.0 g, 0.132 mol) was dissolved in 1000 mL of dichloromethane. To this mixture was added, in one portion, 50 mL (0.574 mol) of morpholine; the reaction became slightly exothermic, and a precipitate formed almost immediately. This reaction mixture was stirred under a nitrogen atmosphere for 20 h. The reaction mixture was treated with 500 mL of 1 N NaOH and stirred vigorously for 10 min. The layers were separated, and the aqueous layer was extracted with 500 mL of dichloromethane. The combined organic extracts were dried over

Na_2SO_4, filtered, and concentrated in vacuo. This crude material was purified by flash column chromatography, eluting gradiently with ethyl acetate–hexane. This afforded 25.1 g (70%) of **57**. ^1H NMR (DMSO-d_6): δ 2.03 (m, 6H), 2.44 (m, 6H), 3.51 (s, 2H), 3.72 (t, 4H, J = 4.6 Hz), 7.34 (m, 4H).

d. 1-[3-(4-Morpholinylmethyl)phenyl]cyclopentanemethanamine (58). Nitrile **57** (1.97 g, 0.0073 mol) was dissolved in 75 mL of a methanol solution saturated with ammonia. This solution was treated with Raney nickel (2 g, washed with methanol before use) and hydrogenated in a 500-mL glass reaction bottle on a Parr hydrogenation apparatus at 50 psig and room temperature for 18 h. The catalyst was removed by filtration, and the filtrates were concentrated under vacuum to yield 1.92 g (96%) of **58** as a clear oil. ^1H NMR ($CDCl_3$): δ 1.96 (m, 8H), 2.44 (t, 4H, J = 4.3 Hz), 3.51 (s, 2H), 3.70 (t, 4H, J = 4.3 Hz), 7.22 (m, 4H).

e. *N*-[2,6-Bis(1-methylethyl)phenyl]-*N'*-[[1-[3-(4-morpholinylmethyl)phenyl]cyclopentyl]methyl]urea (51). To amine **58** (1.75 g, 0.0064 mol) dissolved in 50 mL of ethyl acetate was added 1.38 mL (6.4 mmol) of 2,6-diisopropylphenyl isocyanate. The reaction mixture was stirred at room temperature for 20 h, and then concentrated in vacuo to afford crude product as a yellow gel. The material was purified by flash column chromatography, eluting gradiently in ethyl acetate–hexane. The resulting pale yellow gel was then crystallized from hexane to give 2.31 g (75%) of **51**, mp 135–137 °C. ^1H NMR ($CDCl_3$): δ 1.07 (m, 12H), 1.74 (m, 8H), 2.36 (t, 4H, J = 4.5 Hz), 3.14 (septet, 2H, J = 6.8 Hz), 3.24 (d, 2H, J = 5.4 Hz), 3.30 (s, 2H), 3.68 (t, 4H, J = 4.6 Hz), 3.82 (b s, 1H), 5.91 (s, 1H), 7.02 (m, 7H). Anal. ($C_{30}H_{43}N_3O_2$) C, H, N.

Biological Methods. In Vitro ACAT Assay. Inhibition of ACAT activity in vitro was performed exactly as described previously using intestinal microsomes from cholesterol-fed rabbits and [1-^{14}C]oleoyl-CoA.[10,15]

Acute Cholesterol-Fed Rat Model. As a rapid, acute test of in vivo activity, rats (male Sprague–Dawley, 200–225 g) were dosed po at 4 p.m. with test compound suspended in carboxymethylcellulose (CMC, 1.5%) and Tween-20 (0.2%) in water. The control group received vehicle alone (n = 5–7 rats/group). Immediately after dosing, all animals received ad libitum a chow diet supplemented with peanut oil (5.5%), cholesterol (1.5%), and cholic acid (0.5%). At 8 a.m. the following day, the rats were anaesthetized with ether and exsanguinated via cardiac puncture. Total serum cholesterol concentration was determined using an Abbott VP analyzer with Abbott reagents. The data were expressed as percent decrease relative to controls. Statistically significant changes from vehicle controls were determined using unpaired, two-tailed t-tests.

Chronic Cholesterol-Fed Rat Model. Male Sprague–Dawley rats (200–225 g) were fed ad libitum the diet described above for 2 weeks dosed daily (a.m.) with compounds by gavage during the second week using an aqueous CMC/Tween suspension vehicle. Two control groups were included; one group of rats was fed the cholesterol diet for 2 weeks (cholesterol-fed rats) and one group was fed the cholesterol diet the first week and normal chow during the second week. Animals were then anaesthetized with ether and exsanguinated via cardiac puncture at 8 a.m., 24 h after the last dose. Plasma total HDL cholesterol and nonHDL cholesterol were determined using an Abbott VP analyzer with Abbott reagents (cholesterol reagent and dextran sulfate precipitating reagent). Data are expressed as both absolute mg/dL values and percent change from control. Multiple comparisons (Figure 1) were performed using analysis of variance followed by a protected least significant difference test. Values (bars) sharing a common superscript or letter are not significant, $p > 0.05$.

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