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Bioisosterism in Drug Design: Identification of and Structure–Activity Relationships in a Series of Glycine Anilide ACAT Inhibitors†

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Abstract—To examine the effects of bioisosteric replacement on the biological activity of our previously disclosed disubstituted urea inhibitors of the enzyme acyl-CoA:cholesterol acyltransferase (ACAT), we prepared a series of N'-substituted and N',N'-disubstituted glycine anilides. These compounds were tested for the ability to inhibit ACAT *in vitro* and lower plasma total cholesterol in cholesterol-fed rats given a single high-fat, high-cholesterol meal. ACAT inhibitory potency was greatest in compounds containing 2,6-diisopropyl substituents in the anilide portion with the glycine nitrogen substituted by a 1,1-diphenylmethyl moiety. Small improvements in potency *in vitro* were obtained by substitution of electron donating groups in the 2-, 3- or 5-positions of the aryl rings of the 1,1-diphenylmethyl moiety, but not by substitution in the 4-position. *In vitro* potency was maintained, but not improved by acylation of the glycine nitrogen. Through a QSAR analysis of *in vitro* ACAT inhibition for this set of compounds, an equation could be derived which accounted for 85% of the variance in the dataset. An optimal clogp of 6.65 was found, comparable to that found for other series of ACAT inhibitors. In general, compounds from this series displayed inhibitory potency against ACAT *in vitro* and hypocholesterolemic activity in the *in vivo* rat model of hypercholesterolemia comparable to that found with the ureas.

Introduction

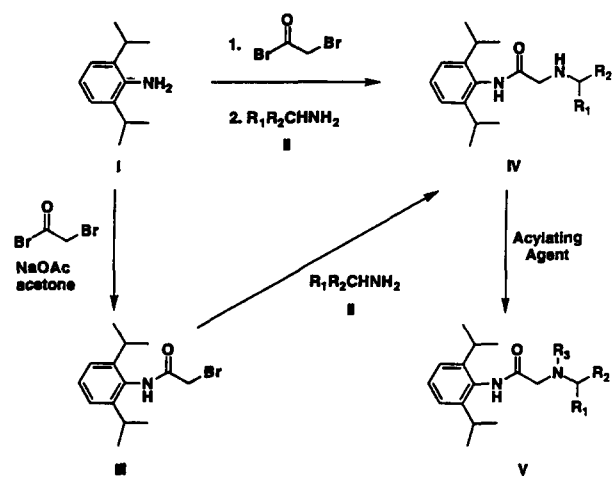
Interest in inhibitors of the enzyme acyl-CoA:cholesterol acyltransferase (ACAT) has increased steadily in recent years owing to the important role of ACAT in the esterification of cholesterol in the key tissues involved in lipoprotein production and clearance.[1,2] Most activity has focused on inhibition of ACAT as a therapeutically valuable means of reducing cholesterol absorption in the intestine,[3,4] VLDL secretion by the liver[5,6] and cholesteryl ester deposition in the artery wall.[7,8] Numerous studies have demonstrated the beneficial effects of ACAT inhibition in a variety of animal models of hypercholesterolemia,[2,6,9–11] including evidence of a direct beneficial effect of ACAT inhibition on arterial lesions.[12–16] Despite the large number of positive studies of ACAT inhibition in animals, in the only study in humans reported to date, no effect was found on cholesterol absorption, sterol excretion rates, plasma lipoprotein levels or distribution in healthy volunteers.[17] Despite the poor efficacy of early inhibitors in man, interest in this therapeutic target has continued and many new compounds possessing a wide range of structures[2,18–20] have emerged.

Because of the profound anti-atherosclerotic activity displayed by our prototype inhibitor, CI-976,[21] in injured, cholesterol-fed rabbits[14] and micropigs,[15] even at doses where levels of plasma total cholesterol were unaffected, we have continued our search for potent, efficacious ACAT inhibitors as safe and effective hypocholesterolemic and anti-atherosclerotic agents. Thus, we reported that bioisosteric modifications of our original series of fatty acid anilides resulted in a potent series of *N*-alkyl-*N*-phenyl ureas[22] and extended the original fatty acid amide series to encompass β-ketoamides.[23] Further studies resulted in the identification of a series of potent ureas that defined a new ACAT inhibitor template[24] distinct from those reported previously.[2,16–23] Extensive structure–activity studies within that series defined the optimal spatial arrangement of the 2,6-diisopropylphenyl and bulky lipophilic moieties for producing potent inhibitors.[24] Subsequent evaluation of these compounds in animal models of hypercholesterolemia suggested that their physical properties were important determinants of their pharmacokinetics and efficacy.[25] To further define the structural features of this template needed for potent ACAT inhibition, we have extended our bioisosteric replacement strategy[22] to these newer ureas, represented by compound **1**,[24] by the transposition of the N'-nitrogen and its α-carbon to produce a series of glycine anilides (Fig. 1). These compounds are potent ACAT inhibitors *in vitro* and effective hypocholesterolemic agents in cholesterol-fed rats *in vivo*.

†Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). Part 9. Presented in part at the 201st ACS National Meeting, Atlanta, GA, 14–19 April, 1991, MEDI 114 and 115.

Chemistry

All compounds were prepared utilizing either the one-pot or two-pot protocols illustrated in Scheme 1. In the two-pot method, the appropriate aniline was acylated with bromoacetyl bromide in the presence of sodium acetate in aqueous acetone at 0 °C. The isolated bromoamide was then reacted with the appropriate amine in the presence of triethylamine in refluxing toluene. Alternatively, the target N-substituted glycine anilides could be synthesized in a one-pot procedure by addition of one equivalent of bromoacetyl bromide to a mixture of one equivalent of aniline and one equivalent of triethylamine in ethyl acetate at room temperature, followed by addition of the requisite amine and a second equivalent of triethylamine and heating the resulting mixture at reflux. Those amines which were not commercially available were prepared by reduction of the oximes, generated from the requisite ketones[26] or by the Leuckart reaction.[27] Ketones which were not commercially available were prepared by addition of the appropriate Grignard reagent to the desired acid chloride.[28] The N',N'-disubstituted glycine anilides were prepared by acylation of the corresponding mono-substituted compounds (IV, Scheme 1).



Scheme 1.

Results

The compounds prepared for this study were evaluated in two primary biological assays. Each compound was evaluated for its ability to inhibit intestinal ACAT *in vitro* by incubation with [1-^{14}C]oleoyl-CoA and microsomes isolated from the intestines of cholesterol-fed rabbits. *In vivo* activity was assessed in rats employing a protocol modified significantly from that reported by us previously.[21] Thus, in previous studies, compounds were admixed in the high fat, high cholesterol diet and administered to rats for one week. In this study, rats (male, Sprague–Dawley strain, 200–225 g) were administered a single oral dose of test compound as a suspension in carboxymethylcellulose (1.5%) and Tween-20 (0.2%) in water.[23,25] The control animals were given vehicle alone. All animals then received *ad libitum*, a chow diet supplemented with peanut oil (5.5%), cholesterol (1.5%) and cholic acid (0.5%). At 8 am the next day, the animals were killed and plasma total cholesterol was measured and the per cent change vs control was determined. Since the animals were 'gang' caged, food intake of individual rats was not determined. However, cages were examined for the presence of food to eliminate false positives.

Owing to the high potency found for *N*-[2,6-bis(1-methylethyl)phenyl]-*N'*-2,2-diphenylethylurea (**1**, IC_{50} = 0.024 μM) in our previous study of disubstituted ureas[24] and the ready commercial availability of relevant starting materials, we selected this compound as the model for our carbon/nitrogen transposition (Fig. 1). This modification, unlike many bioisosteres examined previously,[21,24] resulted in a compound of roughly equivalent ACAT inhibition *in vitro* (**2**, Table 1). Having identified an active bioisostere, a systematic evaluation of each portion of the structure was undertaken.

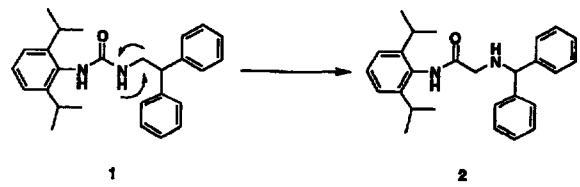
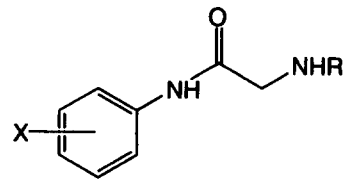


Figure 1.

Examination of the *N*-aryl (Table 1) ring revealed a structure–activity pattern which paralleled that found in the disubstituted ureas. Thus, potency increased with increasing size of the 2 and 6 substituents (compounds **2–4**) while the 2,4-difluoro and 2,4,6-trimethoxy substitution patterns found to be optimal in the trisubstituted ureas[9] and fatty acid anilides,[21] respectively, produced weak ACAT inhibitors *in vitro* in this series (compounds **5** and **6**). It was assumed based on this limited SAR that this portion of the molecule was close to optimal. Thus, no further modifications of the *N*-aryl ring were examined and the 2,6-diisopropylphenyl unit was utilized in the remainder of the study.

When attention was turned to the aralkyl unit, it was found that the 1,1-diphenylmethyl moiety (**2**) was preferred for potent inhibition and that removing one of the phenyls (**7**), inserting a methylene between the diphenylmethyl and amino moieties (**9**) or connecting the two phenyl rings to produce a fluorenyl system (**10**) all resulted in compounds with greatly reduced inhibitory potency. Interestingly, the stereochemistry at the carbon alpha to the glycine nitrogen was found to have a significant effect on potency *in vitro*, with the *R*-isomer consistently four times more potent than the *S*-isomer (**13** and **15** vs **12** and **14**). It should also be noted that compound **15** displays potency equal to the 1,1-diphenylmethyl analog **2**, suggesting the importance of

Table 1

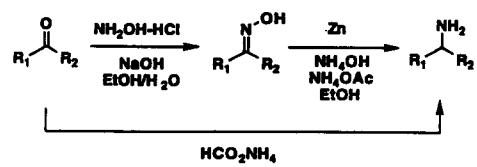


Cpd. No.	X	R	IC_{50} (μM)[a]	%Δ TC APCC[b] (50 mg/kg)	mp (°C)	Formula[c]	clogp[d]
1			0.024	-68**			
2	2,6-iPr_2	-$CH(Ph)_2$	0.055	-40**	182-184	$C_{27}H_{32}N_2O$	5.05
3	2,6-Me_2	-$CH(Ph)_2$	>1.0	-5	143-145	$C_{23}H_{24}N_2O$[f]	
4	2,6-Et_2	-$CH(Ph)_2$	0.10	-16	132-134	$C_{25}H_{30}N_2O$	
5	2,6-F_2	-$CH(Ph)_2$	>5		95-98	$C_{21}H_{18}F_2N_2O$	
6	2,4,6-$(OMe)_3$	-$CH(Ph)_2$	2.3	-9[e]	80-84	$C_{24}H_{27}N_2O_4$	
7	2,6-iPr_2	-CH_2Ph	2.1	NC	117-119	$C_{21}H_{28}N_2O$	3.71
8	2,6-iPr_2	-CH_2CH_2Ph	3.2	NC	94-96	$C_{22}H_{30}N_2O$	3.77
9	2,6-iPr_2	-$CH_2CH(Ph)_2$	2.3	-6[e]	118-120	$C_{28}H_{34}N_2O \cdot 0.25\ H_2O$	5.06
10	2,6-iPr_2	-9-fluorenyl	0.4	-13	194-197	$C_{27}H_{30}N_2O$	5.04
11	2,6-iPr_2	-$C(CH_3)_2CH_2Ph$	2.6	-4[e]	160-161	$C_{24}H_{34}N_2O$[g]	4.48
12	2,6-iPr_2	-(S)-$CH(CH_3)Ph$	1.2	-5	120-121	$C_{22}H_{30}N_2O$[g]	4.01
13	2,6-iPr_2	-(R)-$CH(CH_3)Ph$	0.22	NC	119-120	$C_{22}H_{30}N_2O$[h]	4.01
14	2,6-iPr_2	-(S)-$CH(CH_3)$(1-naphthyl)	0.12	NC	154-155	$C_{26}H_{32}N_2O$[i]	5.19
15	2,6-iPr_2	-(R)-$CH(CH_3)$(1-naphthyl)	0.039	-19*	153-155	$C_{26}H_{32}N_2O$[j]	5.19
16	2,6-iPr_2	-$CH(CH_3)$(2-OMe-Ph)	0.13	-6	68-70	$C_{23}H_{32}N_2O_2$	3.93
17	2,6-iPr_2	-$CH(CH_3)$(2-pyridyl)	4.5	-22	99-101	$C_{21}H_{29}N_3O$	2.54

[a]ACAT inhibition *in vitro*, using intestinal microsomes isolated from cholesterol-fed rabbits. Each determination performed in triplicate. See ref. 22 for experimental details.
[b]Denotes per cent change in plasma total cholesterol in the acute peanut oil (5.5%), cholic acid (0.5%)–cholesterol (1.5%) fed rat (APCC). Compounds dosed as suspensions in carboxymethylcellulose (1.5%) and Tween-20 (0.2%) in water at 50 mg kg^{-1} unless otherwise noted. N = 5/group. See ref. 24 for experimental details. NC = No change.
[c]Analytical results are within 0.4% of theoretical unless otherwise noted.
[d]Calculated using MedChem software, V.3.54.
[e]Dosed at 30 mg kg^{-1}.
[f]C: Calcd, 80.20; found, 79.79.
[g]$[\alpha]_D$ −36° (1.0, $CHCl_3$).
[h]$[\alpha]_D$ +34° (1.1, $CHCl_3$).
[i]$[\alpha]_D^{23}$ −8.6° (1.08, $CHCl_3$).
[j]$[\alpha]_D^{23}$ +8.8° (1.0, $CHCl_3$).
*Significantly different from control, $P < 0.05$. **$P < 0.005$.

overall lipophilicity for high potency (*vide infra*). Unfortunately, none of these modifications led to improved cholesterol lowering *in vivo* over that found with compounds **1** or **2**. We then turned our attention to substituent effects in the phenyls of the 1,1-diphenylmethyl moiety and substitution on the aralkyl nitrogen.

To examine the effects of substitution in the 1,1-diphenylmethyl moiety, a series of substituted analogs was prepared (Table 2). Analogs of **2** further substituted on the glycine nitrogen are listed in Table 3. Since the 1,1-diphenylmethyl amines required for this study were readily available via reductive amination of benzophenone derivatives (Scheme 2), we desired to have an adequate set of substituents for examining the relevance of a standard set of properties. Making use of the cluster schemes reported by Hansch and Leo,[29] we

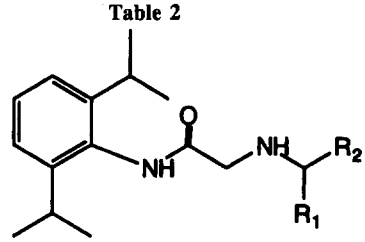


Scheme 2.

selected a group of about 40 analogs from commercially available benzophenones and 1,1-diphenylmethyl amines. Among these were included substituents known to be of interest from earlier ACAT work (e.g. NMe_2).[25] The resulting set also included positional variations and disubstituted analogs. The original design set had a reasonable spread of the major substituent properties pi, sigma and MR. Even though the full design set was not completed, a group sufficiently large to derive significant QSAR correlations from the set of compounds with respect to *in vitro* ACAT inhibition was prepared.

Examination of the SAR indicated that many of the observations made in earlier series could be confirmed here. With respect to ACAT inhibition *in vitro*, acidic substituents were quite detrimental to potency (**23**, **35**). Lipophilicity was related to potency in a non-linear manner and *para* substituents had a slightly negative effect on potency. Consideration of the whole set of 2,6-

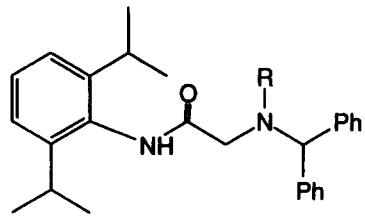
Table 2

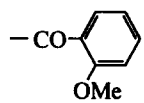
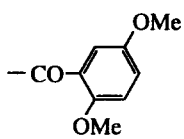
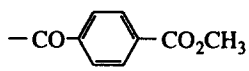
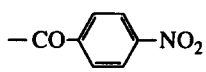
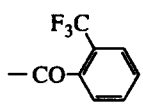
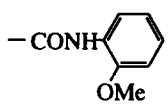
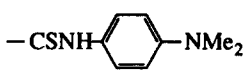
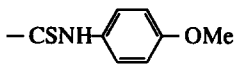


				% Δ TC APCC (mg/kg)[b]				
Cpd No.	R_1	R_2	IC_{50} (μM)[a]	30	50	mp (°C)	Formula[c]	clogp[d]
2	Ph	Ph	0.055	-40***	-40***	182-184	$C_{27}H_{32}N_2O$	5.05
18	2-Cl-Ph	Ph	0.025	-48***		119-121	$C_{27}H_{31}ClN_2O$	5.77
19	2-MeO-Ph	Ph	0.025	-50***	-41**	133-134	$C_{28}H_{34}N_2O_2$	4.97
20	2-Me-Ph	Ph	0.021	-26**		163-164	$C_{28}H_{34}N_2O$	5.55
21	3-Me-Ph	Ph	0.017	-55***	-52***	119-120	$C_{28}H_{34}N_2O$	5.55
22	3-COOMe-Ph	Ph	0.038	-54***		131-132	$C_{29}H_{34}N_2O_3$	5.02
23	3-COOH-Ph	Ph	3.30	-4		190-191	$C_{28}H_{32}N_2O_3$	4.80
24	3-CH_2OH-Ph	Ph	0.058	-7		57-62	$C_{28}H_{34}N_2O_2$	4.02
25	3,5$(OMe)_2$-Ph	Ph	0.017	-56***		111-112	$C_{29}H_{36}N_2O_3$	5.06
26	3,5$(OMe)_2$-Ph	2-Me-Ph	0.020	-62***		138-139	$C_{30}H_{38}N_2O_3$	5.56
27	4-Me-Ph	Ph	0.047	-13	-40**	165-166	$C_{28}H_{34}N_2O$	5.55
28	4-OH-Ph	Ph	0.16	-30***		190-192	$C_{27}H_{32}N_2O_2$	4.39
29	4-OMe-Ph	Ph	0.060	-16	-32*	117-118	$C_{28}H_{34}N_2O_2$	4.97
30	4-Br-Ph	Ph	0.075	-28*	-50***	154-155	$C_{27}H_{31}BrN_2O$	5.92
31	4-F-Ph	Ph	0.083	-30***	-44***	161	$C_{27}H_{31}FN_2O$	5.20
32	4-NO_2-Ph	Ph	0.130	NC		177-179	$C_{27}H_{31}N_3O_3$	4.80
33	4-NMe_2Ph	Ph	0.041	-14		116-117	$C_{29}H_{37}N_3O$	5.25
34	4-COOEt-Ph	Ph	0.11	-24		139-140	$C_{30}H_{36}N_2O_3$	5.55
35	4-COOH-Ph	Ph	25	-7		245-246	$C_{28}H_{32}N_2O_3$	4.80
36	3-CF_3-Ph	3-CF_3-Ph	0.075	-40***		144-145	$C_{29}H_{30}F_6N_2O$	6.82
37	4-F-Ph	4-F-Ph	0.20	-3	-44***	150-151	$C_{27}H_{30}F_2N_2O$	5.34
38	4-Cl-Ph	4-Cl-Ph	0.18	-22	-14	180-181	$C_{27}H_{30}Cl_2N_2$	6.48
39	4-OMe-Ph	4-OMe-Ph	0.12	-34**	-45***	84-85	$C_{29}H_{36}N_2O_3$	4.89
40	2-Naphthyl	Ph	0.054	-35**	-49**	146-148	$C_{31}H_{34}N_2O$	6.23
41	1-Naphthyl	Ph	0.037	43***		149-151	$C_{31}H_{34}N_2O$	6.23
42	2-Thienyl	Ph	0.06	NC	-37**	164-166	$C_{28}H_{30}N_2OS$	4.70
43	2-Pyridyl	Ph	0.14	-19		135-136	$C_{26}H_{31}N_3O$	3.58
44	2-Pyridyl	2-Pyridyl	1.0	-55***	-52***	134-135	$C_{25}H_{30}N_4O$	2.10

[a]ACAT inhibition *in vitro*. See footnote Table 1.
[b]See footnote Table 1. NC = No change.
[c]Analytical results are within 0.4% of theoretical unless otherwise note.
[d]Calculated using MedChem Software, V.3.54.
*P, 0.1. **P, 0.005. ***P, 0.0001.

Table 3



Cpd No.	R	IC_{50}(μM)[a]	% Δ TC APCC (mg/kg)[b] 30	50	mp (°C)	Formula[c]	clogp[d]
2	H	0.055	-40***	-40***	182-184	$C_{27}H_{32}N_2O$	5.05
45	OH	0.905		-12	139-140	$C_{27}H_{32}N_2O_2$	4.73
46	$-COCH_3$	0.069	-21		149-151	$C_{29}H_{34}N_2O_2$[e]	4.93
47	$-CO_2CH_3$	0.029	-41***	-40***	170-171	$C_{29}H_{34}N_2O_3$	5.77
48	$-CONHCH_2CO_2Et$	0.070	-40***		133-136	$C_{32}H_{39}N_3O_4$	5.85
49	-COPh	0.039	-43***	-52***	188-190	$C_{34}H_{36}N_2O_2$	6.22
50		0.057	-19		212-214	$C_{35}H_{38}N_2O_3$	6.16
51		0.092	-23**		148-150	$C_{36}H_{40}N_2O_4$	6.28
52		0.052	NC		210-212	$C_{36}H_{38}N_2O_4$	6.46
53		0.040	-3		205-207	$C_{34}H_{35}N_3O_4$	6.12
54		0.051	-49**		194-197	$C_{35}H_{35}F_3N_2O_2$	7.23
55	$-COC_3F_7$	0 040	-51**		185-187	$C_{31}H_{31}F_7N_2O_2$	7.42
56	-CONHPh	0.039	-8	-32**	231-233	$C_{34}H_{37}N_3O_2$	6.18
57		0.027	NC		238-240	$C_{35}H_{39}N_3O_3$	6.28
58		0.049	-47**	-54**		$C_{36}H_{42}NOS$[f]	6.02
59		0.049	-19		174-177	$C_{35}H_{39}N_3O_2S$	6.79

[a]ACAT inhibition *in vitro*. See footnote Table 1.
[b]See footnote Table 1. NC = No change.
[c]Analytical results are within ±0.4% of theoretical unless otherwise noted.
[d]Calculated using MedChem Sofware, V.3.54.
[e]C: Calcd, 78.70; found, 79.14.
[f]C: Calcd, 74.70; found, 73.62. N: calcd, 9.68; found, 9.06.
*P, 0.005. **P, 0.0005.

diisopropyl anilides (Tables 1–3) indicated that acylation with a variety of groups had very little effect on the potency of **2**. Initial studies indicated that a good correlation could be obtained for the whole set if indicator variables for an acid group (I_acid) and the absence of the proper spacing (I_space = 0 if benzhydryl C two atoms removed from amide CO, 1 if not) were included. A positive effect of increasing size of the 1,1-diphenylmethyl moiety as reflected in MR_bnh was apparent, but seemed not to apply to the *para* substituted analogs. When the Charton steric parameter υ^{31} was included for the *para* substituted analogs, significantly improved correlations resulted. *para* Substituents in the second ring caused an additional loss of activity (I_*para*ring2). Stepwise development of a QSAR equation containing all of these features is shown in Table 4. Compounds **3–6** containing other than 2,6-diisopropyl substitution in the anilide ring were not included. A table of all parameters considered, as well as predicted activities and residuals from equation 7, are included in the Supplementary Material.

All terms were significant at the 99% confidence level or greater. In order to test whether the few compounds taking the indicator variables I_acid, I_space were having undue leverage on the correlation, the analysis was rerun without these five compounds (**8**, **9**, **11**, **22**, **34**) (Table 5). The overall statistics for the resulting equation are somewhat lower, but the same order of entry, significance and coefficients of the parameters in the final equation were observed along with a similar residual standard error, giving confidence in the result obtained for the full set. The correlation matrix for the parameters considered in the stepwise development of the equations is given in Table 6.

Equation 7 accounts for 85% of the variance of this dataset with a reasonable residual standard error. No term for sigma was found to be justified, nor was special consideration of the acyl portion of the molecules needed. This suggests that the 1,1-diphenylmethyl moiety contacts a hydrophobic region of the enzyme, but that the acyl group extends away from the enzyme and does not affect the fit. The optimal clogp was found to be 6.65, in the same range as obtained for other series (e.g. 7.5 for the related urea series[24]). The negative effect of improper spacing in this series was especially large (one order of magnitude; compare the urea series where this factor was about 4–5 fold[24]). The only significant outlier was **45**, the N–OH analog, which was much less active than predicted.

Table 4. Development of QSAR equations (n = 54). Compounds **3–6** not included

Equation			R^2	s	F
1	log (1/IC_{50}) =	4.87 + 0.39 (±0.08) clogp	0.33	0.60	25.7
2	log (1/IC_{50}) =	5.08 + 0.36 (±0.06) clogp - 1.78 (±0.36) I_acid	0.55	0.50	30.9
3	log (1/IC_{50}) =	5.42 + 0.31 (±0.05) clogp - 1.87 (±0.30) I_acid - 1.23 (±0.25) I_space	0.70	0.41	38.0
4	log (1/IC_{50}) =	5.91 + 0.21 (±0.06) clogp - 2.04 (±0.27) I_acid - 1.09 (±0.23) I_space + 0.22 (±0.06) MR_bnh	0.76	0.37	38.3
5	log (1/IC_{50}) =	6.12 + 0.19 (±0.05) clogp - 1.83 (±0.26) I_acid - 1.10 (±0.21) I_space + 0.30 (±0.06) MR_bnh - 0.48 (±0.15) υ_4	0.80	0.34	38.8
6	log (1/IC_{50}) =	4.37 + 0.91 (±0.28) clogp - 0.07 (±0.03) $clogp^2$ - 1.88 (±0.24) I_acid -1.18 (±0.20) I_space + 0.26 (±0.06) MR_bnh - 0.51 (±0.14) υ_4	0.83	0.32	37.6
7	log (1/IC_{50}) =	4.37 + 0.93 (±0.27) clogp - 0.07 (±0.03) $clogp^2$ - 1.94 (±0.23) I_acid -1.20 (±0.19) I_space + 0.27 (±0.06) MR_bnh - 0.47 (±0.13) υ_4 -0.46 (±0.18) I_pararing2 $clogp^0$ = 6.64	0.85	0.30	36.6

Table 5. Development of QSAR equations lacking compounds **3–6**, **8**, **9**, **11**, **23**, **35** (n = 49)

Equation			R^2	s	F
8	log (1/IC_{50}) =	5.40 + 0.32 (±0.05) clogp	0.41	0.41	33.0
9	log (1/IC_{50}) =	5.91 + 0.21 (±0.06) clogp + 0.24 (±0.06) MR_bnh	0.55	0.36	28.7
10	log (1/IC_{50}) =	6.12 + 0.18 (±0.05) clogp + 0.33 (±0.06) MR_bnh - 0.49 (±0.16) υ_4	0.63	0.34	25.4
11	log (1/IC_{50})) =	4.37 + 0.92(±0.28)clogp-0.07 (±0.3)$clogp^2$ + 0.29 (±0.06) MR_bnh - 0.52 (±0.15) υ_4	0.68	0.32	23.5
12	log (1/IC_{50}) =	4.36 + 0.93 (±0.26) clogp - 0.07 (±0.03) $clogp^2$ + 0.30 (±0.06) MR_bnh - 0.47 (±0.15) υ_4 - 0.47 (±0.18) I_pararing2 $clogp^0$ = 6.64	0.73	0.30	22.7

Table 6. Correlation matrix (r) of included and related parameters. Compounds **3–6** not included (n = 54)

	clogp[a]	clogp2	pi_bnh[b]	cmr[a]	MR_bnh[c]	υ_4[d]	σ[e]	I_pararing2[f]	I_space[g]	I_acid[h]
clogp	1									
clogp2	0 99	1								
pi_bnh	0.81	0.75	1							
cmr	0.76	0.77	0.44	1						
MR_bnh	0.50	0.46	0.69	0.49	1					
υ_4	0.04	0.01	0.23	-0.01	0.39	1				
σ	-0.25	-0.20	-0.21	-0.16	-0.01	0.19	1			
I_pararing2	0.07	0.06	0.19	-0.03	0.16	0.16	-0.07	1		
I_space	-0.19	-0.20	-0.15	-0.25	-0.25	-0.11	-0.08	-0.06	1	
I_acid	-0.08	-0.10	-0.03	-0.03	0.11	0.29	0.21	-0.05	-0.05	1
log ($1/IC_{50}$)	0.57	0.55	0.51	0.52	0.48	-0.17	-0.26	-0.04	-0.45	-0.51

[a]Calculated from MedChem Software, V. 3.54.
[b]P_i value for benzhydryl portion of the molecule relative to compound **2**; pi_bnh = clogp – 5.05 for compounds **2–44**, 0 for **45–59**.
[c]MR value for benzhydryl portion of the molecule relative to compound **2**; MR_bnh = cmr – 12.66 for compounds **2–44**, 0 for **45–59**.
[d]Charton steric parameter.[29]
[e]Hammett sigma constant summed for all substituents.[29]
[f]Indicator for presence of non-H substituent at *para* position of bis-substituted analogs.
[g]Indicator for lack of optimal spacing (3 atoms) between amide CO and benzhydryl Ph.
[h]Indicator for the presence of COOH substituent.

This compound differs structurally from all the rest and thus its failure to be properly accommodated in this dataset may not be surprising. In summary, the *in vitro* results are fully consistent with the picture that has emerged from our other series of 2,6-diisopropyl anilide ACAT inhibitors.

With respect to *in vivo* activity, many of the derivatives (**18, 19, 21, 22, 25, 26, 36, 41, 44, 47–49, 54, 55, 58**) displayed hypocholesterolemic activity in the acute rat model of hypercholesterolemia equivalent or superior to that displayed by **2**. In general, there was no clear correlation between *in vitro* and *in vivo* activity and, in fact, **44**, one of the weakest inhibitors *in vitro*, was one of the most effective *in vivo*. Surprisingly, **33**, which contained the 4-Me_2NPh moiety found to impart excellent *in vivo* activity in the chronic rat hypercholesterolemia model in the urea series,[25] displayed weak cholesterol-lowering activity *in vivo* in this series in this acute rat model of hypercholesterolemia. Considerably better activity was found with **58**,which incorporated the 4-Me_2NPh in the *N'*-thiourea moiety. Two compounds (**54** and **55**) proved effective even at the low dose of 3 mg kg^{-1} (51% and 41% lowering, respectively, $P < 0.0005$). From the compounds that displayed efficacy equivalent or superior to **2** in the acute model, a smaller subset (**26, 36, 47, 49, 54, 55**) was selected for testing in the chronic rat model of hypercholesterolemia.[25] Of these, three compounds (**26, 36**, and **55**) were found to produce statistically significant reductions in plasma total cholesterol (35, 22, and 20%, respectively) at the screening dose of 30 mg kg^{-1}, a result comparable to that found in close structural analogs in the urea series.[25]

Discussion

A variety of compounds have been identified as potent inhibitors of ACAT *in vitro*. Many of these compounds closely resemble the fatty acyl-CoA substrate used by ACAT to esterify cholesterol.[6,10,20e, 21–23] In order to better understand the requirements for potent ACAT inhibition for fatty acid based inhibitors, we examined a series of amide bioisosteres and found that only bioisosteres having both hydrogen bond donor and acceptor functionalities yielded compounds which retained ACAT inhibitory potency. Of these, the urea bioisostere provided best inhibitory potency *in vitro* and hypocholesterolemic activity *in vivo*.[22] Recently, we reported a structurally distinct series of disubstituted ureas,[24] represented by compound **1**, which do not possess a fatty acid like moeity, but are potent inhibitors of ACAT *in vitro* and efficacious hypocholesterolemic agents in a cholesterol-fed rat model of hypercholesterolemia. In order to further examine the effects of structural modification in this series on ACAT inhibition *in vitro* and cholesterol lowering *in vivo*, three distinct strategies were developed. Two strategies aimed at changing the pharmacokinetic properties of this series, i.e. introducing ionizable groups on to the aryl ring[25] or into the backbone of the aralkyl moiety,[31] were successful in improving the *in vivo* activity of the original series of highly lipophilic ureas. A study of the effects on biological activity of a bioisosteric replacement, that of transposing the N'-nitrogen of the urea with its α-carbon to create a glycine anilide, is the subject of this report.

Several conclusions can be drawn from the results of this study. First, transposition of the nitrogen and carbon

of the disubstituted ureas does, in fact, result in compounds which are essentially equipotent at inhibiting ACAT *in vitro* (*c.f.* **1** and **2**). This is in contrast to the results found in the fatty acid anilides, where most bioisosteric replacements resulted in significant reductions in potency *in vitro*,[22] but consistent with the results found with other bioisosteres retaining the optimal chain spacing in the urea series represented by **1**.[24] Also, the same overall shape and chain spacing found to be optimal for potent ACAT inhibition in the ureas (i.e. a 1,1-diphenylmethyl moiety separated from a carbonyl by 2 atoms[24]) were found to impart best activity in this series. As found in the ureas, substitution in the aryl rings of the aralkyl substituent was well tolerated with respect to *in vitro* and *in vivo* activity. Additionally, in the glycine anilides, substitution on the aliphatic nitrogen by a variety of carbonyl containing groups is well tolerated, but seems not to be essential for potent inhibition, suggesting that this group may not interact significantly with the enzyme. In general, the requirements for potent ACAT inhibition *in vitro* in this series paralleled the findings in other series, including a high optimal clogp of 6.65. With respect to *in vivo* activity, the presence of the weakly basic nitrogen in this series did not affect *in vivo* activity significantly and these compounds were found to possess hypocholesterolemic activity comparable to that found in the parent ureas. Unlike the disubstituted ureas[25] or the amino and amidoureas[31] developed in the parallel strategies, introduction of a 4-NMe_2 substituent on to one of the aromatic rings in the aralkyl chain in the glycine anilides did not improve *in vivo* activity significantly.

Thus, in the case of the novel template defined by the disubstituted urea ACAT inhibitors reported previously, transposition of the N'-nitrogen and α-carbon yielded a parallel series which demonstrated essentially equivalent ACAT inhibition *in vitro* and hypocholesterolemic activity *in vivo*. Further extension of the bioisosteric strategy reported here to other series of ACAT inhibitors will be the subject of future communications from these laboratories.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Nicolet MX-1 FT-IR spectrophotometer. Nuclear magnetic resonance spectra were determined on either a Varian EM-390, Varian XL-200 or a Bruker 250 MHz 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 were within ±0.4% unless otherwise noted. Yields are unoptimized. Spectral data are consistent with the assigned structures. Statistical analyses were run using the program StatView (v.4.0).

One-pot procedure

N-[2,6-Bis(1-methylethyl)phenyl]-2-[(diphenylmethyl) amino]acetamide (2). A mixture of 2,6-diisopropylaniline (53.1 g, 0.3 mol), Et_3N (45 mL, 0.32 mol), and EtOAc (1000 mL) was cooled to 0 °C and bromoacetyl bromide (26 mL, 0.3 mol) was added dropwise over 30 min. The reaction mixture was stirred at 0 °C for 1 h, then benzhydrylamine (54.9 g, 0.3 mol) and Et_3N(45 mL, 0.32 mol) were added and the mixture was heated on the steambath for 2 h. The reaction mixture was allowed to stand overnight at room temperature and was then heated 1 h on the steambath, filtered, and concentrated to a dark oil which solidified. The solid was slurried in 1:1 (v/v) hexane:EtOAc and collected by filtration, 63.9 g was obtained in 4 crops (53%). An analytical sample was obtained by recrystallization from hexane:EtOAc (1:1). IR (KBr) υ 3238, 3055, 2965, 1656, 1540, 1454, 702 cm^{-1}. ^1H NMR (250 MHz) ($CDCl_3$) δ 1.20 (*d*, 12H, *J* = 6.8 Hz), 3.01 (*m*, 2H), 3.53 (*s*, 2H), 4.99 (*s*, 1H), 7.18–7.43 (*m*, 13H), 8.66 (*br s*, 1H). Anal. ($C_{27}H_{32}N_2O$) C, H, N.

Two-pot procedure

(±)-N-[2,6-Bis(1-methylethyl)phenyl]-2-[[(3,5-dimethoxyphenyl) (2-methylphenyl)methyl] amino]acetamide (26). N-[2,6-Bis(1-methylethyl)phenyl]-2-bromoacetamide (III). To a stirred mixture of 2,6-diisopropylaniline (10.0 g, 56.4 mmol) and sodium acetate trihydrate (15.6 g, 114.8 mmol) in Me_2CO:H_2O (1:1) (50 mL) was added dropwise bromoacetyl bromide (17.0 g, 84.6 mmol) at 0 °C. When addition was completed, the reaction mixture was stirred at room temperature for 1 h, and then diluted with H_2O (100 mL). The product was filtered and washed with cold H_2O, saturated sodium bicarbonate solution, and H_2O. The crude product was dried, and triturated with hexane. The white solid was collected by filtration and dried *in vacuo* to afford 14.5 g (86%) of **III**, mp 170 °C. IR (KBr) υ 1656 cm^{-1}. ^1H NMR (250 MHz) ($CDCl_3$): δ 1.21 (*d*, 12H, *J* = 7 Hz), 3.0 (*septet*, 2H, *J* = 7 Hz), 4.10 (*s*, 2H), 7.00–7.30 (*m*, 3H), 7.70 (*br s*, 1H). Anal. ($C_{14}H_{20}BrNO$) C, H, N, Br.

General procedure for reaction of III with amines

N-[2,6-Bis(1-methylethyl)phenyl]-2-bromoacetamide (**III**, 2.98 g, 1.0 mmol) was added to a solution of Et_3N (1.11 g, 1.1 mmol) and (3,5-dimethoxyphenyl)(2-methylphenyl) methanamine (2.57 g, 1.0 mmol) in toluene (75 mL). The reaction mixture was heated to reflux overnight. After cooling and filtration, the filtrate was concentrated. Flash chromatography on silica gel (1:1 v/v, hexane:EtOAc) provided a white solid, which was recrystallized (hexane:EtOAc) to afford 3.5 g (75%) of **26** as a white solid, mp 138–139 °C. IR (KBr) υ 3446, 3320, 3280, 2932, 2868, 1660, 1596, 1497 cm^{-1}. ^1H NMR (250 MHz) ($CDCl_3$): δ 1.18 (*d*, 6H, *J* = 6.6 Hz), 1.19 (*d*, 6H, *J* = 6.6 Hz), 2.32 (*s*, 3H), 2.95–3.10 (*m*, 2H), 3.58 (*s*, 2H), 3.74 (*s*, 6H), 5.11 (*s*, 1H), 6.35 (*s*, 1H), 6.52 (*s*, 2H), 7.00–7.35 (*m*, 6H), 7.60 (*d*, 1H, *J* = 6.9 Hz), 8.62 (*s*, 1H). Anal. ($C_{30}H_{38}N_2O_3$) C, H, N.

General procedures for preparing the amines (II)

(3,5-Dimethoxyphenyl)(2-methylphenyl)methanamine. To a stirred mixture of 3,5-dimethoxy-2'-methylbenzophenone (10.24 g, 4.0 mmol) and hydroxylamine hydrochloride (4.61 g, 6.64 mmol) in EtOH:H_2O (4:1) (50 mL) was added NaOH (4.0 g). The mixture was heated to reflux until the reaction was completed. After cooling, the mixture was diluted with H_2O (200 mL) and extracted with EtOAc. Drying over $MgSO_4$ and concentration provided the oxime as yellow oil (10.0 g). ^{1}H NMR (90 MHz) ($CDCl_3$): δ 2.25 (*s*, 3H), 3.75 (*s*, 6H), 6.50 (*t*, 1H, *J* = 1 Hz), 6.66 (*d*, 2H, *J* = 1 Hz), 7.1–7.5 (*m*, 3H), 7.75 (*s*, 1H).

Reduction of the oxime (method A)

To a mixture of the crude oxime (9.0 g, 33 mmol), NH_4OAc (3.5 g, 45 mmol), and zinc dust (18.0 g, 275 mmol) in EtOH (65 mL) was added NH_4OH (315 mL) and the mixture was refluxed for 24 h. After cooling, it was extracted with EtOAc, dried and concentrated. Flash chromatography on silica gel (EtOAc) provided 6.2 g (78%) of the amine as an oil.

Reduction of the oxime (method B)

The crude oxime was dissolved in 100 mL of a MeOH solution saturated with NH_3. This solution was treated with Raney nickel (2.0 g, washed with MeOH before use) and hydrogenated in a 500 mL glass reaction bottle on a Parr hydrogenation apparatus at 50.8 psi at room temperature for 22 h. After completion of the reaction, the catalyst was removed by filtration, and the filtrate was concentrated to yield 8.0 g (78%) of an oil. ^{1}H NMR (200 MHz) ($CDCl_3$): δ 1.8 (*s*, 2H), 2.33 (*s*, 3H), 3.73 (*s*, 6H), 5.3 (*s*, 1H), 6.37 (*t*, 1H, *J* = 1 Hz), 6.5 (*d*, 2H, *J* = 1 Hz), 7.1–7.35 (*m*, 3H), 7.5 (*d*, 1H, *J* = 7 Hz).

(4-Methylphenyl)phenylmethaneamine·hydrochloride. A mixture of 4-methylbenzophenone (9.8 g, 50.0 mmol) and ammonium formate (10.5 g, 165 mmol) was heated at 160–165 °C with a distillation apparatus. The temperature of the homogeneous mixture was gradually increased to 180 °C and dry $ZnCl_2$ (100 mg) was added. After heating at 180–185 °C for 3 h, the reaction mixture was cooled and 40 mL of conc HCl was added. The resulting aqueous mixture was refluxed for 1 h. On cooling, a solid salt separated, which was filtered and washed with toluene. Recrystallization from H_2O provided 8.0 gm of a solid, mp 263–264 °C. ^{1}H NMR (200 MHz) (DMSO): δ 2.28 (*s*, 3H), 5.57 (*s*, 1H), 7.10–7.6 (*m*, 9H), 9.2 (*br s*, 2H).

(±)-3-[[[2-[[2,6-Bis(1-methylethyl)phenyl]amino]-2-oxoethyl]amino]phenylmethyl]benzoic acid (23). To a solution of **22** (2.29 g, 5.0 mmol) in MeOH (50 mL) was added NaOH (0.4 g, 10.0 mmol) in H_2O (10 mL). The reaction mixture was stirred at room temperature for 2 days and then refluxed for 6 h. After neutralizing with 10% HCl, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. Recrystallization from EtOAc:hexane provided 1.1 g (50%) of a white solid. Mp 190–191 °C. IR (KBr) υ 3285, 2961, 2931, 1696, 1686, 1669, 1513, 1497 cm^{-1}. ^{1}H NMR (250 MHz) ($CDCl_3$ + DMSO): δ 1.19 (*d*, 12H, *J* = 6.7 Hz), 3.02 (*septet*, 2H, *J* = 6.7 Hz), 3.48 (*s*, 2H), 5.00 (*s*, 1H), 7.10–7.50 (*m*, 10H), 7.62 (*d*, 1H, *J* = 7.7 Hz), 7.95 (*d*, 1H, *J* = 7.7 Hz), 8.14 (*s*, 1H), 8.67 (*s*, 1H). Anal. ($C_{28}H_{32}N_2O_2$) C, H, N.

(±)-N-[2,6-Bis(1-methylethyl)phenyl]-2-[[(3-hydroxymethyl)phenyl]phenylmethyl]amino]acetamide (24). A solution of **22** (11.5 g, 25.0 mmol) in toluene (50 mL) was added dropwise to a suspension of $LiAlH_4$ (1.08 g, 28 mmol) in 100 mL of toluene at room temperature. The reaction mixture was stirred at room temperature for 15 min, quenched with 5.0 mL of water and filtered through Celite. The filtrate was dried and concentrated. Recrystallization from EtOAc:hexane provided 9.0 g (83%) of **24** as a white solid, mp 57–62 °C. IR (KBr) υ 3463, 3455, 3314, 1684, 1670, 1654, 1507, 1497 cm^{-1}. ^{1}H NMR (250 MHz) ($CDCl_3$): δ 1.20 (*d*, 12H, *J* = 7.0 Hz), 3.00 (*septet*, 2H, *J* = 7 Hz), 3.49 (*s*, 2H), 4.67 (*s*, 2H), 4.96 (*s*, 1H), 7.1–7.5 (*m*, 12H), 8.56 (*s*, 1H). Anal. ($C_{28}H_{34}N_2O_2$) C, H, N.

General acylation procedures

N-[2-[[2,6-(1-methylethyl)phenyl]amino]-2-oxoethyl]-N-(diphenylmethyl)acetamide (46). Excess acetic anhydride (40 mL) was added to **2** (0.60 g, 1.5 mmol) and the resulting mixture was concentrated to dryness on the rotary evaporator at 60 °C. A second 40 mL portion of acetic anhydride was added and the mixture was concentrated to a foam. The foam was taken up in hexane:EtOAc (1:1). A white solid precipitated and was collected by filtration, 0.48 g (73%). IR (KBr) υ 2965, 1646, 1634, 1453 cm^{-1}. ^{1}H NMR (250 MHz) ($CDCl_3$): δ 1.09 (*d*, 12H, *J* = 6.8 Hz), 2.33 (*s*, 3H), 2.74 (*m*, 2H), 4.25 (*s*, 2H), 6.35 (*s*, 1H), 7.07–7.39 (*m*, 13H), 7.81 (*br s*, 1H). Anal. ($C_{29}H_{34}N_2O_2$) C, H, N.

Methyl [2-[[2,6-bis(1-methylethyl)phenyl]amino]-2-oxoethyl](diphenylmethyl) carbamate (47). Excess (20 mL) methyl chloroformate was added to **2** (1.80 g, 4.5 mmol) at room temperature. Et_3N was added (1 mL, 7.2 mmol), followed by excess solid $NaHCO_3$ and a large volume of EtOAc. The reaction mixture was allowed to stand 3 days at room temperature, concentrated to dryness, taken up in EtOAc, washed with 1.5 N HCl, saturated aqueous NaCl and dried ($MgSO_4$). The solution was filtered and concentrated to an off-white solid, 0.83 g (40%). IR (KBr) υ 3293, 2962, 1705, 1654, 1497, 1448 cm^{-1}. ^{1}H NMR (250 MHz) ($CDCl_3$): δ 1.06 (*d*, 12H, *J* = 6.8 Hz), 2.57 (*m*, 2H), 3.84 (*s*, 3H), 4.18 (*s*, 2H), 6.80 (*br s*, 1H), 7.07–7.40 (*m*, 13H). Anal. ($C_{29}H_{34}N_2O_3$) C, H, N.

N-[2-[[2,6-Bis(1-methylethyl)phenyl]amino]-2-oxoethyl]-N-(diphenylmethyl) benzamide (49). Benzoyl chloride

(1.5 mL, 13 mmol) was added to a mixture of **2** (1.80 g, 4.5 mmol) and excess Et_3N at room temperature. The reaction mixture was allowed to stand 3 days at room temperature. It was then diluted with EtOAc, washed with 1.5 N HCl, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated. Hexane (50 mL) and EtOAc (1 mL) were added to the residue and the insoluble portion was collected by filtration. The product was obtained as a white solid, 2.05 g (90%). IR (KBr) υ 3290, 2961, 1694, 1622, 1495, 1398, 699 cm^{-1}. ^1H NMR (250 MHz) ($CDCl_3$): δ 1.10 (*d*, 12H, *J* = 6.8 Hz), 2.78 (*m*, 2H), 4.38 (*br s*, 2H), 6.34 (*s*, 1H), 7.08–7.43 (*m*, 18H), 8.03 (*br s*, 1H). Anal. ($C_{34}H_{36}N_2O_2$) C, H, N.

N-[2,6-Bis(1-methylethyl)phenyl]-2-[(diphenylmethyl)[(phenylamino)carbonyl]amino]acetamide (56). Phenyl isocyanate (0.52 mL, 4.8 mmol) was added to **2** (1.80 g, 4.5 mmol) in EtOAc (100 mL) at room temperature. The solution was warmed to 50 °C for 3 min. and was then allowed to stand at room temperature for 2 days. The product precipitated from the reaction mixture as a white solid (2.04 g, 87%) and was collected by filtration. IR (KBr) υ 2964, 1684, 1653, 1522, 1499, 1445 cm^{-1}. ^1H NMR (250 MHz) ($CDCl_3$): δ 1.07 (*d*, 12H, *J* = 6.9 Hz), 2.69 (*m*, 2H), 4.31 (*s*, 2H), 6.86 (*s*, 1H), 6.94–7.39 (*m*, 18H), 7.88 (*s*, 1H), 8.78 (*s*, 1H). Anal. ($C_{34}H_{37}N_3O_2$) C, H, N.

N-[2,6-Bis(1-methylethyl)phenyl]-2-[(diphenylmethyl)-[[(4-methoxyphenyl)amino]thioxomethyl]amino]acetamide (59). A solution of **2** (1.50 g, 3.7 mmol), and 4-methoxyphenyl isothiocyanate (0.62 g, 3.8 mmol) in EtOAc (40 mL) was heated on the steam bath for 2 h and was then allowed to stand at room temperature for 5 days. Hexane was added and the resulting white solid was collected by filtration to afford 1.69 g (80%). An analytical sample was obtained by recrystallization from Et_2O:CH_2Cl_2, mp 174–177 °C. IR (KBr) υ 3296, 2965, 1684, 1663, 1513, 1361, 702 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.11 (*d*, 12H, *J* = 6.86 Hz), 2.78 (*m*, 2H), 3.76 (*s*, 3H), 4.65 (*s*, 2H), 6.78–7.45 (*m*, 18H), 7.66 (*br s*, 1H), 8.60 (*br s*, 1H). Anal. ($C_{35}H_{39}N_3O_2S$) C, H, N.

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