Analogues of Platelet Activating Factor. 7. Bis-Aryl Amide and Bis-Aryl Urea Receptor Antagonists of PAF

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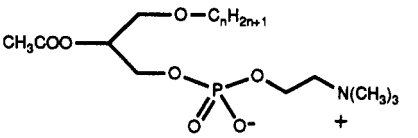
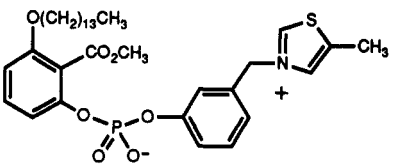
A series of bis-aryl amide (13–57 and 66–81) and bis-aryl urea (58 and 85) antagonists of platelet-activating factor (PAF) was prepared that contain, separating the two aromatic rings, linear amide linkages of the form $-(CH_2)_nCONH-$ (n = 0–2), $-OCH_2CONH-$, and $-(CH_2)_nNHCO-$ (n = 0–1), branched amide linkages of the form $-(CH_2)_nN(COR)-$ (n = 1–3, R = CH_3 or n-C_3H_7), and $-N(COCH_3)CH_2-$, and urea linkages of the form $-NHCONH-$ and $-CH_2N(CONHCH_3)-$. These compounds were examined for their ability to inhibit PAF-induced platelet aggregation of rabbit platelets. These in vitro data were compared to similar data obtained for a number of known PAF antagonists. The compounds were evaluated in vivo, in the mouse, for their ability to prevent death induced by a lethal challenge of PAF. The relationships between the biological activity and the nature, lipophilicity, and position of substituents of the aromatic rings were studied. Best activity was observed for compounds having linkages of the type $-CH_2CONH-$, $-CH_2N(COR)-$, and $-CH_2NHCO-$. Many of these compounds inhibit PAF-induced platelet aggregation with IC_{50}'s under 1 μM.

Platelet-activating factor (PAF, 1) is a naturally occurring alkyl ether phospholipid that was first described by Benveniste in 1972.[1] The structure determination of this substance followed seven years later.[2] Over the succeeding years, a vast amount of information has become available concerning the role of PAF in a number of pathological conditions. Evidence has accumulated that implicates PAF as a mediator in asthma, septic (endotoxic) shock, ischemia, and gastric ulceration.[3] It is possible that an antagonist to this substance may prove useful in the treatment of these and other inflammatory diseases. For this reason, a number of groups have been engaged in the design and preparation of PAF receptor antagonists with the result that a variety of antagonists having different structural features have been described.[4]



1 (PAF) n = 16, 18



2 (CL 184005)

In an earlier communication,[5] we reported on a series of bis-aryl phosphate receptor antagonists of PAF. One member of this series, 2 (CL 184005), is presently undergoing clinical trials as a potential therapeutic agent for the treatment of septic shock in man. In this communication, we will describe a further extension of this series of compounds by addressing the question concerning what functionality other than a phosphate group can be used to separate the two aromatic rings in compounds such as 2. Initially, we have elected to look at various types of amide and urea linkages connecting the two aromatic rings. We will describe the use of linear amide linkages of the form $-(CH_2)_nCONH-$ (n = 0–2), $-OCH_2CONH-$, and $-(CH_2)_nNHCO-$ (n = 0, 1) as well as some branched amide linkages of the type $-(CH_2)_nN(COR)-$ (n = 1–3) and $-N(COCH_3)CH_2-$. The urea linkages that we will describe include those exhibiting a linear connectivity between the aromatic rings (–NHCONH–) as well as those that are

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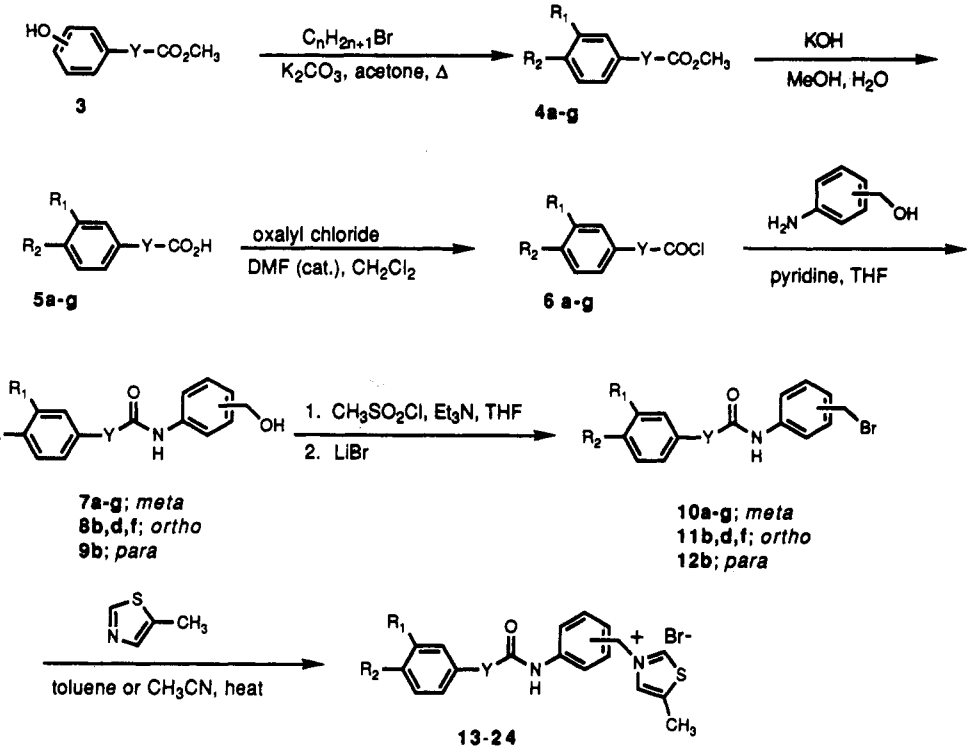
Scheme I [a]



	R_1	R_2	Y
a.	H	$OC_{16}H_{33}$	CH_2
b.	H	$OC_{14}H_{29}$	CH_2
c.	H	$OC_{12}H_{25}$	CH_2
d.	$OC_{14}H_{29}$	H	CH_2
e.	H	$OC_{14}H_{29}$	CH_2CH_2
f.	H	$OC_{16}H_{33}$	OCH_2
g.	H	$OC_{14}H_{29}$	–

[a] The substitution patterns for compounds 13–24 are given in Table II.

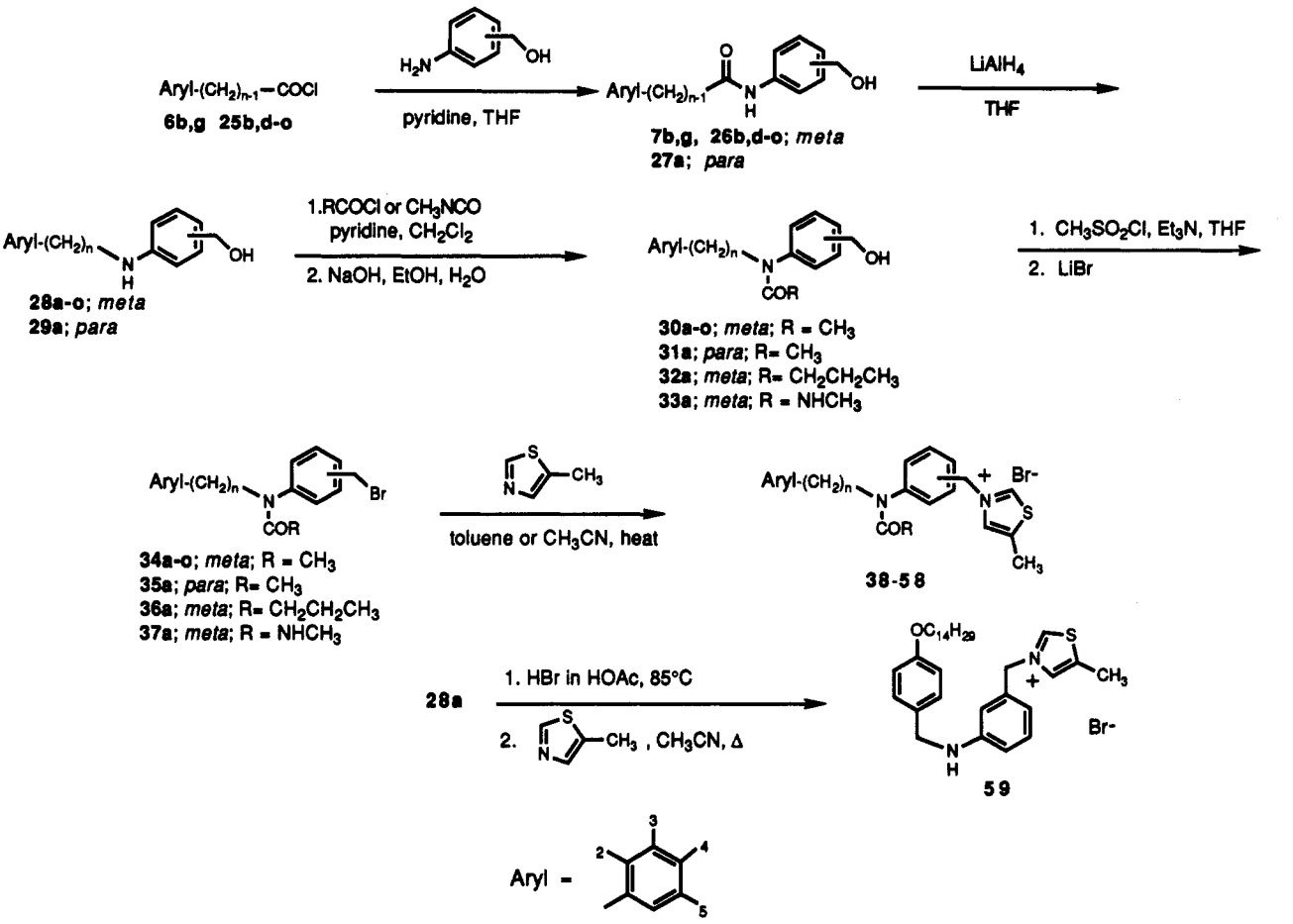
branched ($-CH_2N(CONHCH_3)-$). The relationships between structure and PAF antagonist activity that have been uncovered for this group of bis-aryl amide and urea PAF antagonists will be described.

Chemistry

The synthesis of antagonists that contain a $-(CH_2)_n$-CONH– or $-OCH_2CONH-$ amide linkage separating the two aromatic rings is outlined in Scheme I. Alkylation of the phenolic esters **3** with an alkyl bromide and potassium carbonate in refluxing acetone gave the substituted aromatic esters **4a–g**. Basic hydrolysis followed by acid chloride formation using oxalyl chloride and a catalytic amount of DMF in methylene chloride furnished **6a–g**. Selective reaction of these acid chlorides with either *o*-, *m*-, or *p*-aminobenzyl alcohol at the amino position was accomplished by slow addition of a THF solution of the acid chloride to an ice-cold stirring solution of the amino alcohol and pyridine and then warming to room temperature. Workup resulted in the compounds **7a–g** of the meta series, **8b,d,f** of the ortho series, and **9b** of the para series. If the order of addition is reversed or the reactants are added too rapidly, product mixtures resulting from both reaction at the amine and at the alcohol groups are observed. The benzylic alcohols were efficiently converted to the benzylic bromides **10a–g**, **11b,d,f**, and **12b** by the two-step process involving formation of the mesylate using mesyl chloride and triethylamine in THF followed by the addition of an excess of anhydrous lithium bromide. In the final step of the sequence, the benzylic bromides were heated in toluene or acetonitrile with an excess of 5-methylthiazole to furnish the antagonists **13–15**, **18**, **20**, and **22–24** with meta substitution, **16**, **19**, and **21** with ortho substitution, and **17** with para substitution in the right-hand aromatic ring. The choice of a 5-methylthiazolium group as the positively charged moiety to terminate the antagonists described herein is based on structure–activity relationships uncovered in our earlier study of the bis-aryl phosphate series.[5]

The antagonists that contain a branched amide linkage of the type $-(CH_2)_nN(COR)-$ and the branched urea linkage of the type $-CH_2N(CONHCH_3)-$ are prepared as shown in Scheme II. The aryl carboxylic acid chlorides **6b,g** and **25b,d–o** were reacted with either *m*- or *p*-aminobenzyl alcohol in the presence of pyridine to give the intermediates in the meta series **7b,g** and **26b,d–o**, and the intermediate **27a** in the para series. Reduction with lithium aluminum hydride in THF then gave the amines **28a–o** and **29a**, respectively. The reaction of these amines with an excess of acetyl chloride, butanoyl chloride, or methyl isocyanate followed by basic hydrolysis of the ester or carbamate groups furnished the amides **30a–o** and **32a** with meta substitution, the amide **31a** with para substitution, and the branched urea **33a** with meta substitution,

Scheme II [a]



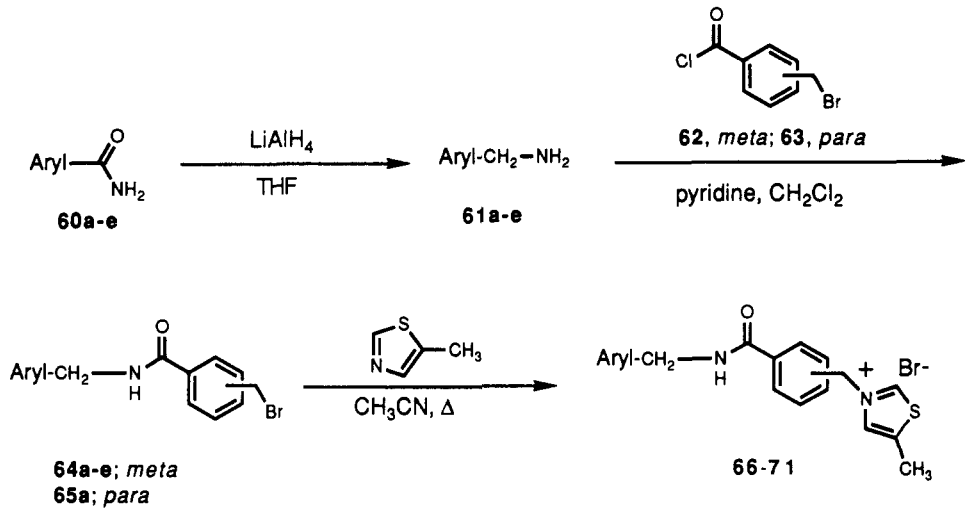
	2	3	4	5	n
a.	H	H	$OC_{14}H_{29}$	H	1
b.	H	H	$OC_{14}H_{29}$	H	3
c.	H	H	$OC_{14}H_{29}$	H	2
d.	H	$OC_{14}H_{29}$	H	H	1
e.	H	Cl	$OC_{14}H_{29}$	H	1
f.	H	$C(CH_3)_3$	$OC_{14}H_{29}$	H	1
g.	H	$OC_{14}H_{29}$	OCH_3	H	1
h.	H	$OC_{14}H_{29}$	H	OCH_3	1
i.	$OC_{14}H_{29}$	H	H	OCH_3	1
j.	$OC_{14}H_{29}$	H	OCH_3	H	1
k.	H	OCH_3	$OC_{14}H_{29}$	OCH_3	1
l.	H	OCH_3	OC_5H_{11}	OCH_3	1
m.	$OC_{14}H_{29}$	CH_3	H	H	1
n.	$OC_{14}H_{29}$	H	H	CH_3	1
o.	H	CH_3	$OC_{14}H_{29}$	CH_3	1

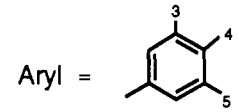
[a] The substitution patterns for compounds **38–58** are given in Table II.

respectively. As described above, these benzylic alcohols were converted to the bromides using mesyl chloride and triethylamine in THF followed by lithium bromide. In the last step of the sequence, the benzylic bromides were refluxed in acetonitrile containing an excess of 5-methylthiazole to furnish the branched amide antagonists **38–57** and the branched urea antagonist **58**. Also shown in Scheme II is the preparation of compound **59**, a potential antagonist that contains an unacylated amino group; this compound was prepared by heating **28a** in 40% hydrogen bromide in acetic acid. Removal of the excess reagents gave the benzylic bromide as the hydrogen bromide salt. Without purification, this was refluxed in acetonitrile containing an excess of 5-methylthiazole to furnish **59**.

Reversal of the linear amide linkage previously described results in antagonists that have a linkage of the form $-CH_2-NHCO-$; the synthesis of such compounds is illustrated in Scheme III. Reduction of the primary aryl amides **60a–e** with lithium aluminum hydride in THF gave the benzylic amines **61a–e**. The reaction of these amines with either acid chloride **62** or **63** using pyridine in methylene chloride resulted in the intermediates **64a–e** with meta substitution and intermediate **65a** with para substitution, respectively.

Scheme III [a]





	3	4	5
a.	H	$OC_{14}H_{29}$	H
b.	OCH_3	$OC_{14}H_{29}$	H
c.	$C(CH_3)_3$	$OC_{14}H_{29}$	H
d.	$OC_{14}H_{29}$	H	OCH_3
e.	CH_3	$OC_{14}H_{29}$	CH_3

[a] The substitution patterns for compounds 66–71 are given in Table II.

As before, heating with an excess of the thiazole reagent gave the desired antagonists **66–71**.

An antagonist that has a shorter amide linkage of the form –NHCO– was prepared as shown in Scheme IV. Alkylation of *p*-nitrophenol with tetradecyl bromide using phase-transfer conditions resulted in **73** which on catalytic reduction gave the aniline **74**. The reaction of **74** with acid chloride **62** resulted in the formation of intermediate **75**. As described above, heating with 5-methylthiazole furnished the antagonist **76**.

Also shown in Scheme IV is the preparation of an antagonist with a branched amide linkage of the type $-N(COCH_3)CH_2-$. Refluxing a DMF solution of the benzylic bromide **75** with an excess of sodium formate led to substitution of the bromine atom with a formyl group. Reduction of **77** with lithium aluminum hydride then gave the amino alcohol **78**. Bis-acetylation followed by ester hydrolysis furnished the branched amide **79**. As before, this was converted to the benzylic bromide **80** using the mesyl chloride–lithium bromide method. Refluxing **80** in acetonitrile containing an excess of 5-methylthiazole then gave the desired antagonist **81**.

The preparation of an antagonist that contains a linear urea linkage of the form –NHCONH– separating the two aromatic rings is illustrated in Scheme V. The aniline **74** was converted to the isocyanate **82** using triphosgene and base. The reaction of **82** with 3-aminobenzyl alcohol and pyridine in THF gave the urea **83**. The synthesis was then completed as described above to furnish the urea-containing antagonist **85**.

Biology

The test compounds were evaluated for their PAF antagonist properties both in vitro and in vivo. In our primary assay, we examined their ability to inhibit PAF-induced platelet aggregation in rabbit platelet rich plasma (PRP). The data are expressed as a micromolar IC_{50}, the concentration of antagonist needed to inhibit platelet aggregation induced by a standard challenge concentration (usually 5.0×10^{-8} M) of PAF by 50%. Multiple determinations of the IC_{50} values were averaged to give the values shown in Tables I and II.

In order to facilitate the comparison of the new compounds presented herein with other antagonists in

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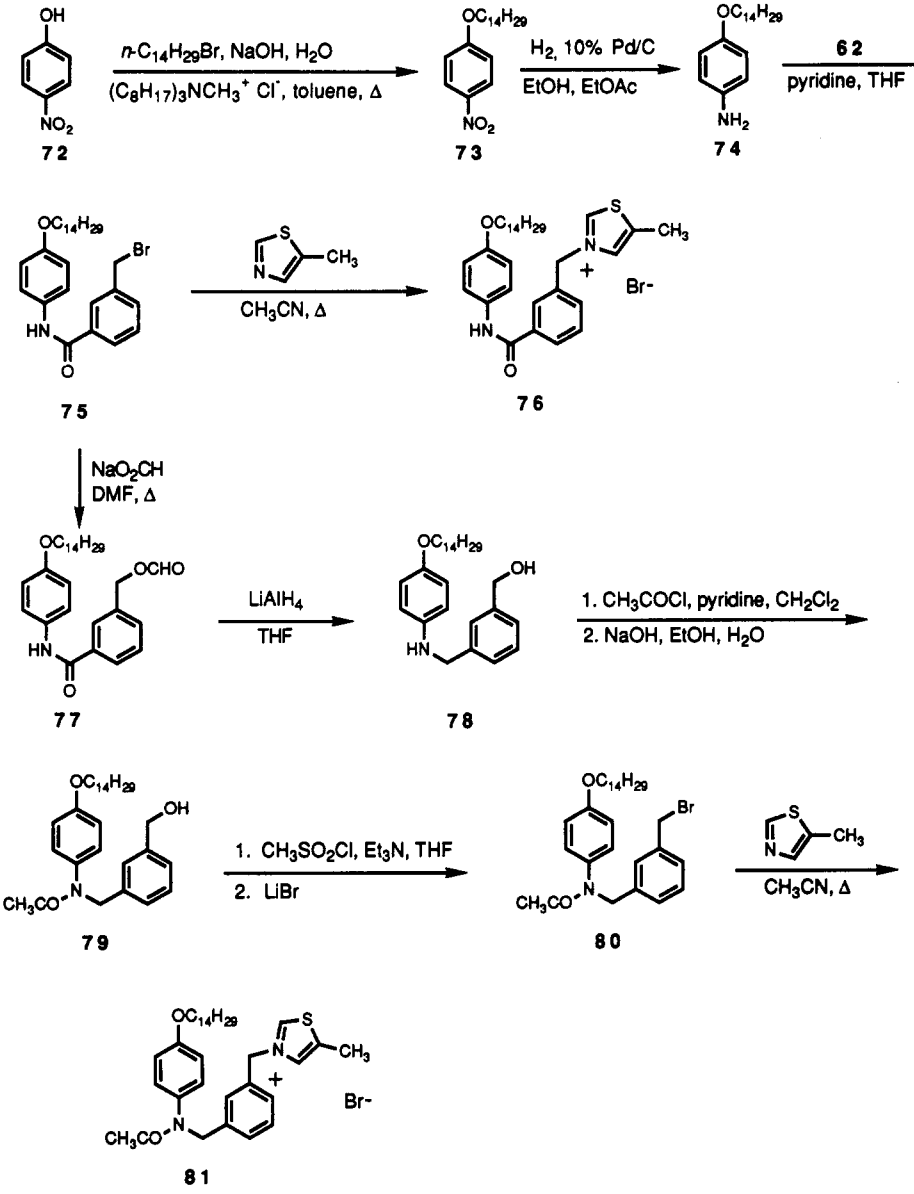
Scheme IV



the literature, we have included similar data generated in our laboratory for a number of these antagonists (see Table I). For comparisons of our IC_{50} values with those in the literature to be meaningful, it is important to note the PAF challenge concentrations used and whether washed platelets or, as is the case in this study, PRP was used. We generally find that the IC_{50} values are about 10-fold lower when washed platelets are used.

For selected compounds, we also evaluated their potential for PAF antagonism in vivo by evaluating their ability to prevent death resulting from a lethal challenge of PAF in the mouse. These results are presented in Table III.

Results and Discussion

Since an important objective of the present study was to determine which amide or urea linkages could be used to replace the phosphate group in our earlier series of bisaryl phosphate antagonists,[5] one of the initial questions that we wanted to address concerned the best choice for the chain length of the lipophilic group that is on the left-hand aromatic ring. We wanted to decide on a specific chain length early on and then keep it constant for the remaining analogues. In order to accomplish this, the homologous series of linear amides **13–15** were prepared. It is readily apparent that within this series, the best activity is observed with the C_{14} homologue. One can also see the effect of varying the chain length of the alkoxy chain in the branched amide antagonists when comparing compounds **51** and **52**; for these two compounds decreasing the chain length from C_{14} to C_5 leads to a 4-fold decline

(10) Shen, T. Y.; Hwang, S-B.; Chang, M. N.; Doebber, T. W.; Lam, M-H. T.; Wu, M. S.; Wang, X.; Han, G.; Li, R. Characterization of a Platelet-activating Factor Receptor Antagonist Isolated from Haifenteng (Piper futokadsura): Specific Inhibition of *In vitro* and *In vivo* Platelet-activating Factor-induced Effects. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 672–676.

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Scheme V

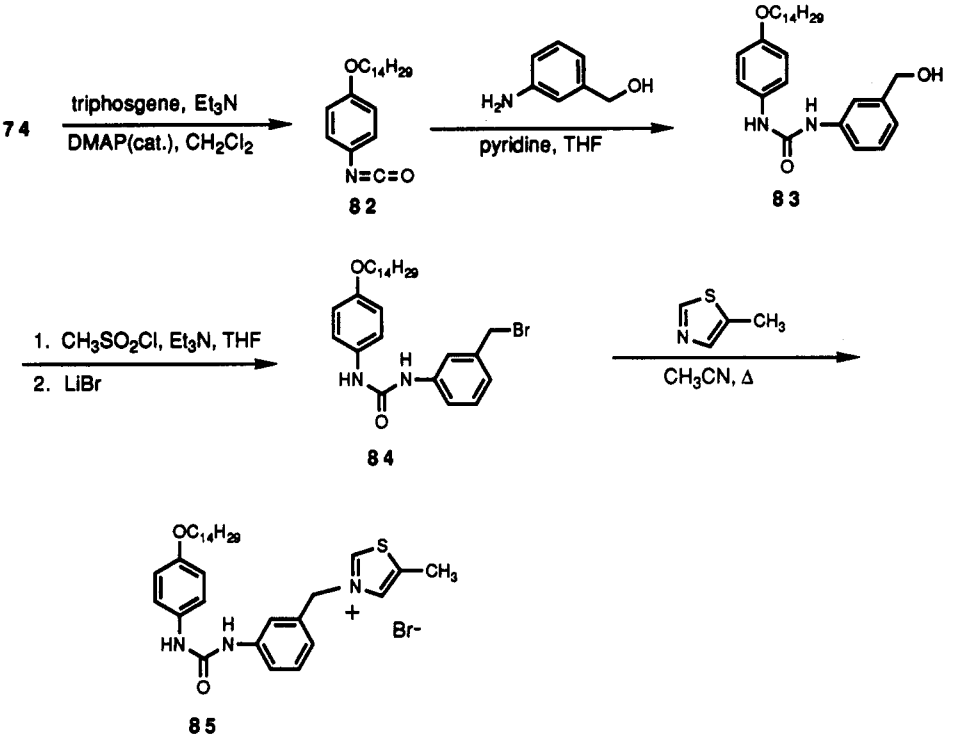


Table I. Inhibition of PAF-Induced Platelet Aggregation: Literature Standards

compound	inhibition of platelet agg, IC_{50} (μM)[a]	ref
CV 3988	25.9 (n = 4)	6
CV 6209	0.02 (n = 3)	7
Triazolam	11.1 (n = 3)	8
Alprazolam	41.2 (n = 2)	8
WEB 2086	0.34 (n = 6)	9
Kadsurenone	3.3 (n = 2)	10
L 652731	1.6 (n = 3)	11
SRI 63072	16.7 (n = 1)	12
SRI 63441	2.1 (n = 1)	13
CL 184005	0.54 (n = 12)	5

[a] Concentration needed to inhibit PAF-induced platelet aggregation in rabbit PRP by 50%; the PAF challenge concentration was 5×10^{-8} M; the n value in parentheses is the number of separate determinations of the IC_{50} from the concentration-response curves.

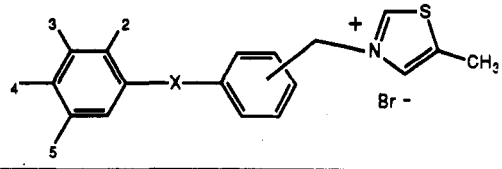
in activity. It is possible that this observation is the result of either a change in the lipophilicity or steric bulk of the alkoxy chain. Because of the above results, most of the remaining compounds were prepared with a C_{14}-alkoxy chain.

For the series of linear amides of the form $-(CH_2)_n$-CONH- (**13–20**, **23**, and **24**), we examined compounds where n was varied from 0 to 2. The best activity is obtained for compound **14** (n = 1); removing the methylene group results in compound **23** (n = 0) that is 19 times less potent than **14**. Adding an additional methylene group results in compound **20** (n = 2) that is also significantly (about 24-fold) less active than **14**. In contrast, **22**, a compound that has the $-OCH_2CONH-$ linkage separating the aromatic rings, shows comparable activity to **13** which lacks the additional oxygen atom.

For the series of antagonists having a linear amide group of the type $-(CH_2)_nCONH-$ (n = 0, 1), we examined the effect on activity of varying the position of substitution on each of the aromatic rings. With respect to the position of the lipophilic chain on the left-hand ring, we find that compounds that have the lipophilic chain at the meta or para positions show comparable activity (compare **14** with **18**, and **23** with **24**). With respect to the right-hand aromatic ring, there appears to be a significant effect on the activity when the position of substitution is changed. Consider the isomeric series of meta, ortho, and para derivatives **14**, **16**, and **17**, respectively; we find that while the meta and para compounds **14** and **17** show similar activity (about a 2-fold difference), the ortho-substituted isomer **16** shows far less, if any, activity. Similarly, in comparing the isomers **18** and **19** we find that the meta isomer **18** is much more active than the ortho isomer **19**. This particular outcome of altering the position of aromatic substitution in the right-hand ring is in contrast to what we observed in our earlier bis-aryl phosphate series[5] where we found that the difference in activity between the meta and ortho isomers was usually small. Conceivably, the greater sensitivity of the amide series of antagonists to changes in the substitution pattern in the right-hand ring may be the result of the greater conformational rigidity of the typically planar amide linkage compared to a phosphate linkage. It may simply be too costly in energy for the amide compounds having an ortho substitution pattern in the right-hand ring to accommodate a conformation consistent with efficient binding to the PAF receptor.

For the series of antagonists having a branched amide group of the type $-(CH_2)_nN(COR)-$ (n = 1–3), we also studied the effects on activity of alteration of the number of methylene groups. Compared to **40** (n = 1), increasing the number of methylene groups by one or two, resulting in compounds **39** and **38**, respectively, leads to a 12–16-fold decrease in activity. With respect to the position of the lipophilic chain on the left-hand ring, we find that compounds with this chain at the meta or para positions show similar activity (compare **40** with **41**; about a 2-fold difference). Compounds with the lipophilic chain in the ortho position of the left-hand ring, **48–50**, **53**, and **54**,

Table II. Inhibition of PAF-Induced Platelet Aggregation



compd	aromatic substituents 2	3	4	5	X	substn[a]	inhibn of platelet agg, IC_{50} (μM)[b]	formula[c]	anal.[d]
13	H	H	$OC_{16}H_{33}$	H	CH_2CONH	meta	5.3 (n = 3)	$C_{35}H_{51}N_2BrO_2S(1.5H_2O)$	C,H,N,Br,S
14	H	H	$OC_{14}H_{29}$	H	CH_2CONH	meta	0.31 (n = 3)	$C_{33}H_{47}N_2BrO_2S$	H,N,Br,S;C[h]
15	H	H	$OC_{12}H_{25}$	H	CH_2CONH	meta	2.9 (n = 2)	$C_{31}H_{43}N_2BrO_2S(1.0H_2O)$	C,H,N,Br,S
16	H	H	$OC_{14}H_{29}$	H	CH_2CONH	ortho	f (n = 2)	$C_{33}H_{47}N_2BrO_2S$	H,N,Br,S;C[i]
17	H	H	$OC_{14}H_{29}$	H	CH_2CONH	para	0.60 (n = 3)	$C_{33}H_{47}N_2BrO_2S$	H,N,Br,S;C[q]
18	H	$OC_{14}H_{29}$	H	H	CH_2CONH	meta	0.55 (n = 2)	$C_{33}H_{47}N_2BrO_2S$	C,H,N,Br,S
19	H	$OC_{14}H_{29}$	H	H	CH_2CONH	ortho	g (n =1)	$C_{33}H_{47}N_2BrO_2S$	C,H,N,Br,S
20	H	H	$OC_{14}H_{29}$	H	$(CH_2)_2CONH$	meta	7.3 (n = 1)	$C_{34}H_{48}N_2BrO_2S$	C,H,N,Br,S
21	H	H	$OC_{16}H_{33}$	H	OCH_2CONH	ortho	11.2 (n = 1)	$C_{35}H_{51}N_2BrO_3S$	C,H,N,Br,S
22	H	H	$OC_{16}H_{33}$	H	OCH_2CONH	meta	5.0 (n = 1)	$C_{35}H_{51}N_2BrO_3S$	C,H,N,Br,S
23	H	H	$OC_{14}H_{29}$	H	CONH	meta	5.9 (n = 1)	$C_{32}H_{45}N_2BrO_2S$	C,H,N,Br,S
24	H	$OC_{14}H_{29}$	H	H	CONH	meta	4.2 (n = 1)	$C_{32}H_{45}N_2BrO_2S(0.5H_2O)$	C,H,N,Br,S
38	H	H	$OC_{14}H_{29}$	H	$(CH_2)_3N(COCH_3)$	meta	3.1 (n = 1)	$C_{36}H_{52}N_2BrO_2S$	C,H,N,Br,S
39	H	H	$OC_{14}H_{29}$	H	$(CH_2)_2N(COCH_3)$	meta	4.3[h] (n = 1)	$C_{35}H_{51}N_2BrO_2S(0.3H_2)$	C,H,N,Br,S
40	H	H	$OC_{14}H_{29}$	H	$CH_2N(COCH_3)$	meta	0.26 (n = 3)	$C_{34}H_{49}N_2BrO_2S$	C,H,N,Br,S
41	H	$OC_{14}H_{29}$	H	H	$CH_2N(COCH_3)$	meta	0.74 (n = 1)	$C_{34}H_{49}N_2BrO_2S(0.5H_2O)$	C,H,N,Br,S
42	H	H	$OC_{14}H_{29}$	H	$CH_2N(COCH_3)$	para	2.1 (n = 1)	$C_{34}H_{49}N_2BrO_2S$	C,H,N,Br,S
43	H	Cl	$OC_{14}H_{29}$	H	$CH_2N(COCH_3)$	meta	0.13 (n = 1)	$C_{34}H_{48}N_2BrClO_2S(0.4H_2O)$	C,H,N,Br,Cl,S
44	H	$C(CH_3)_3$	$OC_{14}H_{29}$	H	$CH_2N(COCH_3)$	meta	0.35[e] (n = 1)	$C_{38}H_{57}N_2BrO_2S$	C,H,N,Br,S
45	H	OCH_3	$OC_{14}H_{29}$	H	$CH_2N(COCH_3)$	meta	0.32 (n = 2)	$C_{35}H_{51}N_2BrO_3S$	C,H,N,Br,S
46	H	$OC_{14}H_{29}$	OCH_3	H	$CH_2N(COCH_3)$	meta	0.37 (n = 1)	$C_{35}H_{51}N_2BrO_3S(0.7H_2O)$	C,H,N,Br,S
47	H	$OC_{14}H_{29}$	H	OCH_3	$CH_2N(COCH_3)$	meta	0.96 (n = 1)	$C_{35}H_{51}N_2BrO_3S$	C,H,N,Br,S
48	$OC_{14}H_{29}$	H	H	OCH_3	$CH_2N(COCH_3)$	meta	0.32 (n = 1)	$C_{35}H_{51}N_2BrO_3S$	C,H,N,Br,S
49	$OC_{14}H_{29}$	H	OCH_3	H	$CH_2N(COCH_3)$	meta	1.4 (n = 2)	$C_{35}H_{51}N_2BrO_3S$	C,H,N,Br,S
50	$OC_{14}H_{29}$	OCH_3	H	H	$CH_2N(COCH_3)$	meta	2.5 (n = 1)	$C_{35}H_{51}N_2BrO_3S$	C,H,N,Br,S
51	H	OCH_3	$OC_{14}H_{29}$	OCH_3	$CH_2N(COCH_3)$	meta	0.57 (n = 1)	$C_{36}H_{53}N_2BrO_4S(0.8H_2O)$	C,H,N,Br,S
52	H	OCH_3	OC_5H_{11}	OCH_3	$CH_2N(COCH_3)$	meta	2.3 (n = 1)	$C_{27}H_{35}N_2BrO_4S$	C,H,N,Br,S
53	$OC_{14}H_{29}$	CH_3	H	H	$CH_2N(COCH_3)$	meta	3.2 (n = 1)	$C_{35}H_{51}N_2BrO_2S$	C,H,N,Br,S
54	$OC_{14}H_{29}$	H	H	CH_3	$CH_2N(COCH_3)$	meta	1.5 (n = 2)	$C_{35}H_{51}N_2BrO_2S$	C,H,N,Br,S
55	H	$OC_{14}H_{29}$	CH_3	H	$CH_2N(COCH_3)$	meta	6.7 (n = 1)	$C_{35}H_{51}N_2BrO_2S(0.5H_2O)$	C,H,N,Br,S
56	H	CH_3	$OC_{14}H_{29}$	CH_3	$CH_2N(COCH_3)$	meta	0.71 (n = 1)	$C_{36}H_{53}N_2BrO_2S$	C,H,N,Br,S
57	H	H	$OC_{14}H_{29}$	H	$CH_2N(CO\text{-}n\text{-}C_3H_7)$	meta	0.26 (n = 3)	$C_{34}H_{49}N_2BrO_2S$	C,H,N,Br,S
58	H	H	$OC_{14}H_{29}$	H	$CH_2N(CONHCH_3)$	meta	0.53 (n = 2)	$C_{34}H_{50}N_3BrO_2S$	C,H,N,Br,S
59	H	H	$OC_{14}H_{29}$	H	CH_2NH	meta	7.1 (n = 1)	$C_{32}H_{47}N_2BrOS$	H,N,S;C[n],Br[o]
66	H	H	$OC_{14}H_{29}$	H	CH_2NHCO	meta	0.40 (n = 2)	$C_{33}H_{47}N_2BrO_2S$	C,H,N,Br,S
67	H	H	$OC_{14}H_{29}$	H	CH_2NHCO	para	2.9 (n = 1)	$C_{33}H_{47}N_2BrO_2S(0.5H_2O)$	C,H,N,S;Br[p]
68	H	OCH_3	$OC_{14}H_{29}$	H	CH_2NHCO	meta	0.96 (n = 1)	$C_{34}H_{49}N_2BrO_3S(1.2H_2O)$	C,H,N,Br,S
69	H	$C(CH_3)_3$	$OC_{14}H_{29}$	H	CH_2NHCO	meta	3.5 (n = 1)	$C_{37}H_{55}N_2BrO_2S$	C,H,N,Br,S
70	H	$OC_{14}H_{29}$	H	OCH_3	CH_2NHCO	meta	j (n = 1)	$C_{34}H_{49}N_2BrO_3S$	H,N,S;C[q],Br[r]
71	H	CH_3	$OC_{14}H_{29}$	CH_3	CH_2NHCO	meta	3.1 (n = 1)	$C_{35}H_{51}N_2BrO_2S$	C,H,N,Br,S
76	H	H	$OC_{14}H_{29}$	H	NHCO	meta	2.7 (n = 1)	$C_{32}H_{45}N_2BrO_2S$	C,H,N,Br,S
81	H	H	$OC_{14}H_{29}$	H	$N(COCH_3)CH_2$	meta	1.0 (n = 1)	$C_{34}H_{49}N_2BrO_2S$	H,N,Br,S;C[s]
85	H	H	$OC_{14}H_{29}$	H	NHCONH	meta	1.5 (n = 1)	$C_{32}H_{46}N_3BrO_2S$	C,H,N,S;Br[t]

[a] Refers to the position of substitution in the right-hand aromatic ring. [b] Concentration needed to inhibit PAF-induced platelet aggregation in rabbit PRP by 50%; unless indicated, the PAF challenge concentration was 5×10^{-8} M; the n value in parentheses is the number of determinations. [c] Empirical formula. The amount of water of hydration is given in parentheses. All compounds showed the expected M^+–Br ion in the FAB mass spectrum. [d] Analytical results for the indicated elements are within ±0.4% of the calculated values, unless indicated otherwise. [e] PAF challenge concentration was 1×10^{-7} M. [f] No inhibition observed at a compound concentration up to 10 μM. [g] 23% inhibition at a dose of 10 μM. [h] PAF challenge concentration was 5×10^{-7} M. [i] PAF challenge concentration was 1×10^{-8} M. [j] 43% inhibition at a dose of 10 μM. [k] C: calcd, 64.37; found, 65.40. [l] C: calcd, 64.37; found, 65.82. [m] C: calcd, 64.37; found, 67.09. [n] C: calcd, 65.40; found, 65.95. [o] Br: calcd, 13.60; found, 12.00. [p] Br: calcd, 12.79; found, 13.50. [q] C: calcd, 63.24; found, 61.24. [r] Br: calcd, 12.37; found, 14.44. [s] C: calcd, 64.85; found, 65.66. [t] Br: calcd, 12.96; found, 13.61.

show moderate to good antagonist activity. In contrast to the linear amides discussed above, there appears to be a larger decrease (about 8-fold) in activity when the position of substitution in the right-hand aromatic ring is changed from meta to para (compare **40** with **42**). In this branched amide series (n = 1), we also prepared a number of antagonists containing other substituents, in addition to the lipophilic chain, on the left-hand ring; these substituents do not appear to have a significant effect on the measured potency (compare **43–45** with **40**, and **46** and **47** with **41**). Further, we also looked at the effect of altering the acyl substituent within the branched amide series. As is apparent, changing the acyl moiety from acetyl to butanoyl had no effect on the activity (compare **40** with **57**). Removal of the acyl substituent as in **59**, however, leads to a significant loss of activity (about 27-fold) compared to the acetylated counterpart **40**.

Inverting the orientation of the branched amide linkage of the form $-CH_2N(COCH_3)-$ gives a linkage of the type $-N(COCH_3)CH_2-$ where the nitrogen atom is now associated with the left-hand ring; this leads to almost a 4-fold decrease in activity (compare **40** with **81**).

We also prepared antagonists that encompass a linear amide linkage between the two aromatic rings of the form

Table III. Protection of PAF-Induced Lethality in the Mouse[a]

compd	% lethality	dead/total
control	90	2345/2599
14	50	6/12
15	55	6/11
17	80	8/10
18	100	12/12
20	50	5/10
38	58	14/24
40	38	9/24
43	59	10/17
46	27	4/15
48	59	16/27
49	73	11/15
50	85	11/13
53	20	2/10
54	39	9/23
55	86	12/14
57	79	11/14
58	62	8/13
59	42	5/12
67	31	12/39
CL 184005	15	48/312
CV 6209	10	1/10

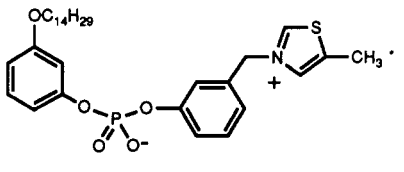
[a] Compound was given ip at a dose of 1.0 mg/Kg in saline 0.5 h before the lethal iv PAF challenge (75–150 μg/Kg). Survival was assessed 90 min after challenge and did not change thereafter. The control is an accumulated group of saline treated mice that showed 90% lethality from PAF.

$-(CH_2)_nNHCO-$ ($n = 0, 1$) where the amide group now has a reversed orientation compared to the linear amides described above ($-(CH_2)_nCONH-$). We see that for n = 1, both types of linkage have nearly identical activity (compare **14** with **66**) and for $n = 0$ there is only a 2-fold difference in potency (compare **23** and **76**).

With respect to the position of substitution on the left-hand ring for antagonists having a $-CH_2NHCO-$ group, we observe about a 7-fold decrease in activity in going from the meta isomer **66** to the para isomer **67**. We have also made compounds in this series that possess, in addition to the lipophilic alkoxy chain, other substituents on the left-hand aromatic ring; it appears that these substituted derivatives differ in potency but none of them are more potent than the unsubstituted compound **66** (compare with **68–71**).

Compounds that contain both a linear urea (**85**, $-NHCONH-$) as well as a branched urea (**58**, $-CH_2N(CONHCH_3)-$) were prepared. Comparing **85** to its amide counterpart **14**, we find about a 5-fold decrease in activity; comparing **58** with its amide counterpart **40**, we find only a 2-fold decrease.

Finally, it is of interest to compare the amide compounds of the present study directly with **86**, a close analogue from our earlier bis-aryl phosphate series that has an IC_{50} of 9.9 μM. As is apparent from the data in Table II, both the linear amide **18** and the branched amide **41** show considerably greater potency than **86**.



86, IC_{50} = 9.9μM

We assessed selected antagonists for their ability to prevent death resulting from a lethal intravenous challenge of PAF in the mouse. These results are presented in Table III. In vivo, PAF has a multitude of biological effects including platelet aggregation, activation of other inflammatory cells and release of mediators, alteration of vascular permeability, hypotension, and death. Insofar as PAF-induced death is the result of various receptor-mediated processes, one would expect that an antagonist of PAF would show some efficacy in forestalling death. All the compounds tested in the in vivo assay were also active, to varying degrees, in the in vitro platelet assay. As can be seen (Table III), many of the compounds at a dose of 1.0 mg/kg showed significant protection against a lethal challenge of PAF.

The lack of good in vivo activity for some of the compounds that have been found to be excellent antagonists in our in vitro platelet assay (for example, **18** and **57**) is likely due to factors (such as bioavailability and metabolism) that are unrelated to the ability of these compounds to bind to the PAF receptors.

In conclusion, a number of bis-aryl amide and bis-aryl urea antagonists of PAF have been prepared. We have found that replacement of the phosphate group, as found in our earlier bis-aryl phosphate series,[5] with various amide and urea linkages results in retention of the antagonist activity in both in vitro and in vivo assays. The best replacements were found to be linkages of the form $-CH_2CONH-$, $-CH_2N(COR)-$ (R = CH_3 or n-C_3H_7), and $-CH_2NHCO-$. Many of these compounds inhibit PAF induced platelet aggregation with IC_{50}'s under 1 μM and therefore show excellent in vitro activity compared to other antagonists described in the literature (see Table I). In addition to the PAF antagonist data that has been presented herein, we have evaluated many of the active antagonists in models of septic (endotoxic) shock; these data will be reported at a future date.

Experimental Section

Inhibition of PAF-Induced Platelet Aggregation. About 60–100 mL of blood was collected by cardiac puncture or ear bleeding from unanesthetized male New Zealand rabbits with the use of sodium citrate anticoagulant (1 part of 3.2% citrate for 10 parts of blood). All syringes and pipets were plastic. Platelet-rich plasma (PRP) was recovered from 20 mL of blood centrifuged at 800 rpm × 15 min at room temperature. Dilutions (1:3000) of PRP in Isoton diluent were made and the platelet count was determined on a Coulter Thrombocounter. Platelet counts ranged from 350 000–550 000 per μL.

The L isomer of C16-PAF (**1**) was obtained from Boehringer-Mannheim and diluted in CH_3OH to give a 10 mg/mL solution. Aliquots were used to make working serial dilutions in saline. The test compounds were diluted in CH_3OH to give 1 mg/mL stock solutions, and then serially diluted in saline. All working solutions were made fresh in plastic tubes and kept on ice.

Incubation mixtures consisted of 400 μL of PRP, 50 μL of saline or test compound, and 50 μL of L-PAF agonist. Breifly, 400 μL of PRP was stabilized in a cuvette for 1–2 min at 37 °C in a Chronolog aggregometer to achieve a stable baseline. Test compound (final concentration ranging from 10^{-8} to 10^{-5} M) or 50 μL of saline was added and incubated for 5 min. Controls and test samples were run in parallel. At 5 min, the challenge concentration of PAF was added (5×10^{-8} M or 1×10^{-7} M) as determined from a PAF dose response. The dose response for each test compound was determined and the IC_{50} value (the dose required for 50% inhibition of the magnitude of aggregation) was determined. The aggregation response was recorded and analyzed as previously described.[14]

(14) Wissner, A.; Sum, P-E.; Schaub, R. E.; Kohler, C. A.; Goldstein, B. M. Analogs of Platelet Activating Factor (PAF). 1. Some Modifications of the Alkoxy Chain. *J. Med. Chem.* **1984**, *27*, 1174–1184.

Prevention of PAF-Induced Lethality in Mice. A stock solution containing 7.5–15 μg/mL of racemic C16-PAF in saline was prepared. Female Swiss-Webster mice weighing 20–25 g (Charles River Labs Inc.) were dosed ip with test compound in saline at 10 mL/Kg. Control animals were dosed only with saline. Thirty minutes later the mice were injected with PAF stock solution as an intravenous bolus in a tail vein at 10 mL/Kg (resulting in a dose of 75–150 μg/Kg of PAF). Survival was monitored at 1.5 h and did not change thereafter. There was a day to day variability in the sensitivity of mice to the PAF challenge; several small test groups were done to select the appropriate dose for the experiment. The racemic PAF was indistinguishable from the stereochemically pure compound when the overall concentration was adjusted for the inactive isomer.

Chemistry. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Fast-atom-bombardment (FAB) mass spectra were determined on a VG-ZAB SE mass spectrometer. Electron-impact (EI) and chemical-ionization (CI) mass spectra were determined on a Finnigan MAT-90 mass spectrometer. IR spectra were recorded on a Nicolet 20SXB FT-IR spectrophotometer. ^{1}H NMR spectra were determined at 300 MHz using a Nicolet QE-300 WB spectrometer; chemical shifts (δ) given are in parts per million relative to tetramethylsilane. NMR spectra of all thiazolium salts were determined in DMSO-d_6; it was usually found that adding several drops of CF_3CO_2D to the sample improved the resolution of the spectrum. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical value.

Unless otherwise noted all reagents and solvents obtained from commercial suppliers were used without further purification.

4-(Tetradecyloxy)benzeneacetic Acid Methyl Ester (4b). A solution of 102 g (613.8 mmol) of *p*-hydroxyphenyl acetic acid methyl ester and 170.2 g (613.8 mmol) of 1-tetradecyl bromide in 1 L of acetone containing 93.3 g of powdered K_2CO_3 was refluxed for 24 h. Two more 33.9 g (245.5 mmol) amounts of K_2CO_3 were added at 24-h intervals resulting in a total reflux time of 72 h. The mixture was filtered, and the solvent was evaporated in vacuo. The residue was dissolved in ether. The ether solution was washed with dilute NaOH and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was recrystallized from hexanes giving 170 g (76%) of **4b** as a white solid: mp 36–38 °C; ^{1}H NMR ($CDCl_3$) δ 7.05 (AA'BB', 4 H, aromatic), 3.93 (t, 2 H, CH_2O), 3.68 (s, 3 H, CH_3), 3.56 (s, 2 H, CH_2CO), 1.75 (m, 2 H, CH_2CH_2O), 1.26 (m, 22 H, $(CH_2)_{11}$), 0.88 (t, 3 H, terminal CH_3); mass spectrum (EI) *m/e* 362 (M^+). Anal. ($C_{23}H_{38}O_3$) C, H.

4-(Tetradecyloxy)benzeneacetic Acid (5b). A mixture of 30 g (82.7 mmol) of **4b** and 13.9 g (248.2 mmol) of KOH in 300 mL of ethanol and 15 mL of H_2O was refluxed for 18 h. The solvent was evaporated in vacuo. The residue was acidified with dilute HCl and extracted with ether. The ether solution was dried ($MgSO_4$). The solvent was removed, and the residue was recrystallized from hexanes–CCl_4, giving 23.7 g (82%) of **5b** as a white solid: mp 84–86 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (s, 1 H, CO_2H), 7.03 (AA'BB', 4 H, aromatic), 3.93 (t, 2 H, CH_2O), 3.58 (s, 2 H, CH_2CO), 1.74 (m, 2 H, CH_2CH_2O), 1.26 (m, 22 H, $(CH_2)_{11}$), 0.88 (t, 3 H, terminal CH_3); mass spectrum (EI) *m/e* 348 (M^+). Anal. ($C_{22}H_{36}O_3$) C, H.

4-(Tetradecyloxy)benzeneacetyl Chloride (6b). A solution of 21.7 g (62.2 mmol) of **5b** and several drops of DMF in 250 mL of CH_2Cl_2 was stirred as 11.9 g (93.3 mmol) of oxalyl chloride was added dropwise. The mixture was stirred for 18 h, and the solvent was evaporated in vacuo. The residue was redissolved in ether and filtered. The solvent was removed, and the residue was maintained under reduced pressure giving 22.5 g (99%) of **6b** as a white solid. This material was used without additional purification.

***N*-[3-(Hydroxymethyl)phenyl]-4-(tetradecyloxy)benzeneacetamide (7b).** To a stirring solution of 15.5 g (125.9 mmol) of 3-aminobenzyl alcohol and 36.2 g (457.8 mmol, 37 mL) of pyridine in 250 mL of THF was added at 0 °C a solution of **6b** in 250 mL of THF over a 40-min period. The mixture was then stirred a room temperature overnight. The THF was evaporated in vacuo, and the residue was mixed with $CHCl_3$ and H_2O. The mixture was heated to dissolve solids. The hot organic layer was washed with warm H_2O and dilute HCl. While still warm, the solution was dried ($MgSO_4$). The solvent was evaporated in vacuo, and the residue was recrystallized from CCl_4, giving 40 g (77%) of a white solid: mp 120–125 °C; ^{1}H NMR ($CDCl_3$) δ 7.40–6.80 (ms, 9 H, aromatic, NH), 4.64 (s, 2 H, CH_2OH), 3.97 (t, 2 H, CH_2O), 3.67 (s, 2 H, CH_2CO), 1.74 (m, 2 H, CH_2CH_2O), 1.26 (m, 22 H, $(CH_2)_{11}$), 0.88 (t, 3 H, terminal CH_3); mass spectrum (EI) *m/e* 453 (M^+). Anal. ($C_{29}H_{43}NO_3$) C, H, N.

***N*-[3-(Bromomethyl)phenyl]-4-(tetradecyloxy)benzeneacetamide (10b).** To a stirred solution of 4.0 g (8.8 mmol) of **7b** in 100 mL of THF was added 1.34 g (11.7 mmol, 0.91 mL) of methanesulfonyl chloride followed by 1.19 g (11.7 mmol, 1.6 mL) of triethylamine. The mixture was stirred for 1.5 h and 7.7 g (88.2 mmol) of anhydrous LiBr was added. The mixture was stirred overnight. The solvent was evaporated in vacuo, and the residue was mixed with H_2O and $CHCl_3$. The organic layer was washed with saturated $NaHCO_3$ and then dried ($MgSO_4$). The solution was passed through a short plug of silica gel. The solvent was evaporated in vacuo, and the residue was recrystallized from hexanes–CCl_4 giving 4.1 g (90%) of **10b** as a white powder: mp 116–118 °C; ^{1}H NMR ($CDCl_3$) δ 7.50–6.90 (ms, 9 H, aromatic, NH), 4.43 (s, 2 H, CH_2N), 3.95 (t, 2 H, CH_2O), 3.67 (s, 2 H, CH_2Br), 1.80 (m, 2 H, CH_2CH_2O), 1.26 (m, 22 H, $(CH_2)_{11}$), 0.88 (t, 3 H, terminal CH_3); mass spectrum (EI) *m/e* 517 (M^+). Anal. ($C_{29}H_{42}NBrO_2$) C, H, N, Br.

5-Methyl-3-[[3-[[[4-(tetradecyloxy)phenyl]acetyl]amino]phenyl]methyl]thiazolium Bromide (14). A solution of 3.6 g (7 mmol) of **10b** and 3.5 g (34.9 mmol) of 5-methylthiazole in 25 mL of toluene was refluxed with stirring under argon for 2 h. The solution was cooled and poured into 200 mL of ether. The solid was collected by filtration and washed several times with ether giving 3.8 g (89%) of **14** as an off-white powder: mp 173–175 °C; ^{1}H NMR (DMSO-d_6) δ 10.29 (s, 1 H, thiazole), 8.32 (s, 1 H, thiazole), 7.87–6.80 (ms, 9 H, aromatic, NH), 5.76 (s, 2 H, CH_2N^+), 3.93 (t, 2 H, CH_2O), 3.61 (s, 2 H, CH_2CO), 2.56 (s, 3 H, CH_3), 1.72 (m, 2 H, CH_2CH_2O), 1.26 (m, 22 H, $(CH_2)_{11}$), 0.87 (t, 3 H, terminal CH_3); mass spectrum (FAB) *m/e* 535 (M – Br). Anal. ($C_{33}H_{47}N_2BrO_2S$) H, N, Br, S; C: calcd, 64.37; found, 65.40.

3-[[[4-(Tetradecyloxy)phenyl]methyl]amino]benzenemethanol (28a). To a stirring solution of 8 g (18.2 mmol) of **7b** in 80 mL of THF at 0 °C under argon was added 36.4 mL of a 1 M solution of $LiAlH_4$ in THF. The mixture was stirred 1 h at room temperature and then refluxed for 7 h. The solution was cooled and the excess $LiAlH_4$ was destroyed by slowly adding ethyl acetate. A concentrated solution of NaOH was slowly added until solids formed. The mixture was diluted with ether and filtered. The solvent was evaporated in vacuo from the filtrate, and the residue was recrystallized from hexanes giving 6.7 g (86%) of **28a** as a white solid: mp 72–75 °C; ^{1}H NMR ($CDCl_3$) δ 7.40–6.50 (ms, 8 H, aromatic), 4.60 (s, 2 H, CH_2OH), 4.25 (s, 2 H, CH_2N), 3.94 (t, 2 H, CH_2O), 1.75 (m, 2 H, CH_2CH_2O), 1.26 (m, 22 H, $(CH_2)_{11}$), 0.88 (t, 3 H, terminal CH_3); mass spectrum (EI) *m/e* 425 (M^+). Anal. ($C_{28}H_{43}NO_2$) C, H, N.

***N*-[3-(Hydroxymethyl)phenyl]-*N*-[[4-(tetradecyloxy)phenyl]methyl]acetamide (30a).** To a stirred solution of 6.4 g (15 mmol) of **28a** and 4.8 g (60 mmol, 4.9 mL) of pyridine in 60 mL CH_2Cl_2 at 0 °C was added dropwise 4.1 g (52.6 mmol, 3.7 mL) of acetyl chloride in 10 mL CH_2Cl_2. The mixture was stirred at room temperature for 1.5 h. The mixture was diluted with $CHCl_3$ and washed with dilute HCl and saturated $NaHCO_3$. The solvent was evaporated in vacuo, and the residue was stirred in 60 mL of ethanol containing 1 mL of H_2O and 0.84 g (21 mmol) of NaOH for 35 min. The mixture was poured into H_2O and extracted with ether. The solution was dried ($MgSO_4$), the solvent was evaporated in vacuo, and the residue was recrystallized from hexanes giving 6.7 g (95%) of **30a** as a white solid: mp 65–67 °C; ^{1}H NMR ($CDCl_3$) δ 7.40–6.60 (ms, 9 H, aromatic, OH), 4.81 (s, 2 H, CH_2N), 4.66 (d, 2 H, CH_2OH), 3.90 (t, 2 H, CH_2O), 1.86 (s, 3 H, $COCH_3$), 1.75 (m, 2 H, CH_2CH_2O), 1.26 (m, 22 H, $(CH_2)_{11}$), 0.88 (t, 3 H, terminal CH_3); mass spectrum (EI) *m/e* 467 (M^+). Anal. ($C_{30}H_{45}NO_3$) C, H, N.

***N*-[3-(Hydroxymethyl)phenyl]-*N'*-methyl-*N*-[[4-(tetradecyloxy)phenyl]methyl]urea (33a).** A solution of 8 g (18.8 mmol) of **28a** and 3.2 g (56.4 mmol, 3.3 mL) of methyl isocyanate in 10 mL of pyridine and 20 mL of ether was stirred overnight. The mixture was poured into H_2O and extracted with ether containing a small amount of THF. The organic extract was

washed with dilute HCl and brine. The solution was dried ($MgSO_4$), and the solvent was evaporated in vacuo giving 8.7 g of a white solid: mp 107–109 °C; mass spectrum (EI) *m/e* 539 (M^+). This product is the result of methyl isocyanate reaction at both the amino and alcohol sites.

A 7.8-g (14.5 mmol) portion of this material was stirred at reflux 6 h in 100 mL of ethanol containing 10 mL of H_2O and 0.77 g (19.2 mmol) of NaOH. The mixture was poured into H_2O and extracted with ether–THF. The extract was washed with brine. The solution was dried ($MgSO_4$), the solvent was evaporated in vacuo, and the residue was recrystallized from CCl_4–hexanes, giving 6.9 g of **33a** as a white solid: ^1H NMR (DMSO-d_6) δ 7.35–6.70 (ms, 8 H, aromatic), 5.62 (m, 1 H, NH), 5.15 (t, 1 H, OH), 4.72 (s, 2 H, CH_2N), 4.45 (d, 2 H, CH_2OH), 3.88 (t, 2 H, CH_2O), 2.55 (d, 3 H, CH_3), 1.67 (m, 2 H, CH_2CH_2O), 1.24 (m, 22 H, $(CH_2)_{11}$), 0.85 (t, 3 H, terminal CH_3); IR (KBr) 1629, 1605, 1587 cm^{-1}; mass spectrum (EI) *m/e* 482 (M^+). Anal. ($C_{30}H_{46}N_2O_3$) C, H, N.

***N*-[3-(Bromomethyl)phenyl]-*N*-[[4-(tetradecyloxy)phenyl]methyl]acetamide (34a).** To a stirred solution of 6 g (12.8 mmol) of **30a** in 100 mL of THF was added 1.76 g (15.4 mmol, 1.19 mL) of methanesulfonyl chloride followed by 1.56 g (15.4 mmol, 2.15 mL) of triethylamine. The mixture was stirred for 1.5 h, and 11.1 g (128.3 mmol) of anhydrous LiBr was added. The mixture was stirred 1 h, poured into H_2O, and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ and brine and then dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was recrystallized from petroleum ether, giving 6.6 g (97%) of **34a** as a white powder: mp 56–58 °C; ^1H NMR ($CDCl_3$) δ 7.40–6.70 (ms, 8 H, aromatic), 4.80 (s, 2 H, CH_2N), 4.41 (s, 2 H, CH_2Br), 3.91 (t, 2 H, CH_2O), 1.75 (m, 2 H, CH_2CH_2O), 1.26 (m, 22 H, $(CH_2)_{11}$), 0.88 (t, 3 H, terminal CH_3); IR (KBr) 1648 cm^{-1}; mass spectrum (EI) *m/e* 531 (M^+). Anal. ($C_{30}H_{44}NBrO_2$) H, N, Br; C: calcd, 67.91; found, 68.66.

3-[[3-[Acetyl[[4-(tetradecyloxy)phenyl]methyl]amino]phenyl]methyl]-5-methylthiazolium Bromide (40). A solution of 3 g (5.65 mmol) of **34a** and 2.2 g (22.6 mmol) of 5-methylthiazole in 40 mL of toluene was refluxed with stirring under argon for 4 h. The solution was cooled and poured into 60 mL of ether. The mixture was allowed to stand overnight. The solid was collected by filtration and washed three times with ether, giving 3.1 g (87%) of **40** as a white powder: mp 130–134 °C; ^1H NMR (DMSO-d_6) δ 10.20 (s, 1 H, thiazole), 8.23 (s, 1 H, thiazole), 7.45–6.70 (ms, 8 H, aromatic), 5.71 (s, 2 H, CH_2N^+), 4.80 (s, 2 H, CH_2NCO), 3.91 (t, 2 H, CH_2O), 2.55 (s, 3 H, CH_3), 1.83 (s, 3 H, $COCH_3$), 1.70 (m, 2 H, CH_2CH_2O), 1.25 (m, 22 H, $(CH_2)_{11}$), 0.86 (t, 3 H, terminal CH_3); IR (KBr) 1657, 1609 cm^{-1}; mass spectrum (FAB) *m/e* 549 (M – Br). Anal. ($C_{34}H_{49}N_2BrO_2S$) C, H, N, Br, S.

5-Methyl-3-[[3-[[[4-(tetradecyloxy)phenyl]methyl]amino]phenyl]methyl]thiazolium Bromide (59). A solution of 4.4 g (10.3 mmol) of **28a** in 50 mL of 40% HBr in acetic acid was stirred at 85 °C for 5 h. The solvent was evaporated in vacuo at reduced pressure. The residue was suspended in 40 mL of CH_3CN containing 4.6 g (46.5 mmol) of 5-methylthiazole. The mixture was refluxed for 5 h, and the solvent was evaporated in vacuo. The residue was dissolved in CH_3OH, and the solution was passed through a column of Amberlyst A-21 resin (weakly basic) and the CH_3OH was removed. The residue was chromatographed on silica gel eluting with $CHCl_3$–CH_3OH 20:1 to give 0.44 g (7%) of **59** as an oil: ^1H NMR (DMSO-d_6) δ 10.14 (s, 1 H, thiazole), 8.23 (s, 1 H, thiazole), 7.40–6.50 (ms, 8 H, aromatic), 5.60 (s, 2 H, CH_2N^+), 4.23 (s, 2 H, CH_2NH), 3.92 (t, 2 H, CH_2O), 2.51 (s, 3 H, CH_3), 1.68 (m, 2 H, CH_2CH_2O), 1.24 (m, 22 H, $(CH_2)_{11}$), 0.89 (t, 3 H, terminal CH_3); mass spectrum (FAB) *m/e* 507 (M – Br). Anal. ($C_{32}H_{47}N_2BrOS$) C, H, N, S; Br: calcd, 13.60; found, 12.00.

4-(Tetradecyloxy)benzenemethanamine (61a). To a stirring suspension of 38 g (113.9 mmol) of **60a** in 300 mL of THF at 0 °C under argon was added 171 mL of a 1 M solution of $LiAlH_4$ in THF over 40 min. The mixture was stirred at reflux for 11 h. The solution was cooled and the excess $LiAlH_4$ was destroyed by slowly adding ethyl acetate. A solution of NaOH (6 g in 50 mL) was slowly added until solids formed. The mixture was diluted with ether and filtered. The solvent was evaporated in vacuo from the filtrate, and the residue was chromatographed on silica gel eluting first with ethyl acetate to remove less polar impurities and then with ethyl acetate–CH_3OH 4:1, giving 18.4 g (51%) of **61a** as a white solid: mp 62–64 °C; ^1H NMR ($CDCl_3$) δ 7.05 (AA′BB′, 4 H, aromatic), 3.94 (t, 2 H, CH_2O), 3.79 (s, 2 H, CH_2N), 1.77 (m, 2 H, CH_2CH_2O), 1.26 (m, 22 H, $(CH_2)_{11}$), 0.88 (t, 3 H, terminal CH_3); mass spectrum (EI) *m/e* 319 (M^+). Anal. ($C_{21}H_{37}NO$) C, H, N.

3-(Bromomethyl)-*N*-[[4-(tetradecyloxy)phenyl]methyl]benzamide (64a). To a stirring solution of 12 g (37.6 mmol) of **61a** and 2.97 g (37.6 mmol, 3.04 mL) of pyridine in 70 mL of CH_2Cl_2 was added at 0 °C a solution of **62** in 70 mL of CH_2Cl_2. The mixture was then stirred a room temperature for 2.5 h, poured into H_2O, and extracted with ethyl acetate. The organic solution was washed with dilute HCl and saturated $NaHCO_3$ and then dried ($MgSO_4$). The filtrate was passed through a short column of silica gel. The solvent was evaporated in vacuo and the residue was recrystallized from CCl_4–hexanes, giving 7.6 g (39%) of **64a** as a tan solid: mp 97–100 °C; ^1H NMR ($CDCl_3$) δ 7.80–6.90 (ms, 8 H, aromatic) 6.40 (m, 1 H, NH), 4.60 (m, 2 H, CH_2N), 4.49 (s, 2 H, CH_2Br), 3.94 (t, 2 H, CH_2O), 1.79 (m, 2 H, CH_2CH_2O), 1.26 (m, 22 H, $(CH_2)_{11}$), 0.88 (t, 3 H, terminal CH_3); IR (KBr) 1641, 1613, 1584 cm^{-1}; mass spectrum (EI) *m/e* 517 (M^+). Anal. ($C_{29}H_{42}NBrO_2$) H, N; C: calcd, 67.43; found, 70.02; Br: calcd, 15.47; found, 14.92.

5-Methyl-3-[[3-[[[[4-(tetradecyloxy)phenyl]methyl]amino]carbonyl]phenyl]methyl]thiazolium Bromide (66). A solution of 2.5 g (4.8 mmol) of **64a** and 1.4 g (14.2 mmol) of 5-methylthiazole in 20 mL of CH_3CN was refluxed with stirring under argon for 6 h. The solution was cooled and allowed to stand for 17 h. The solid was collected by filtration and washed several times with ether. The solid was redissolved in hot CH_3CN, treated with Norite, and filtered. The solution was diluted with an equal volume of ether and the mixture was cooled in the freezer. Solid was collected by filtration, giving 2.8 g (89%) of **66** as a white powder: mp 168–170 °C; ^1H NMR (DMSO-d_6) δ 10.30 (s, 1 H, thiazole), 8.39 (s, 1 H, thiazole), 8.40–6.80 (ms, 9 H, aromatic, NH), 5.82 (s, 2 H, CH_2N^+), 4.44 (s, 2 H, CH_2NHCO), 3.93 (t, 2 H, CH_2O), 2.55 (s, 3 H, CH_3), 1.70 (m, 2 H, CH_2CH_2O), 1.25 (m, 22 H, $(CH_2)_{11}$), 0.88 (t, 3 H, terminal CH_3); IR (KBr) 1640, 1611, 1587 cm^{-1}; mass spectrum (FAB) *m/e* 535 (M – Br). Anal. ($C_{33}H_{47}N_2BrO_2S$) C, H, N, Br, S.

4-(Tetradecyloxy)benzenamine (74). A mixture of 75 g (539 mmol) of 4-nitrophenol, 149.5 g (539 mmol) of tetradecyl bromide, 26.96 g (674 mmol) of NaOH, and 2.2 g (5.4 mmol) of the phase-transfer catalyst $(C_8H_{17})_3NCH_3^+Cl^-$ was refluxed in a mixture of 400 mL of toluene and 400 mL of H_2O for 65 h. The organic layer was separated and washed with 1 N NaOH and dilute HCl. The solution was dried ($MgSO_4$), the solvent was evaporated in vacuo, and the residue was recrystallized from hexanes giving 30 g of **73** as a white solid: mp 57–60 °C; ^1H NMR ($CDCl_3$) δ 7.57 (AA′BB′, 4 H, aromatic), 4.04 (t, 2 H, CH_2O), 1.82 (m, 2 H, CH_2CH_2O), 1.26 (m, 22 H, $(CH_2)_{11}$), 0.88 (t, 3 H, terminal CH_3); mass spectrum (EI) *m/e* 335 (M^+).

A mixture of 30 g (89.4 mmol) of **73** and 2 g of 10% Pd/C in 150 mL of ethanol and 20 mL of ethyl acetate was shaken in a Parr apparatus under 40 psi of hydrogen overnight. The mixture was filtered, and the solvent was evaporated in vacuo. The residue was recrystallized from hexanes, giving 25.7 g of **74** as a white solid: mp 65–68 °C; ^1H NMR ($CDCl_3$) δ 7.28 (s, 2 H, NH_2), 6.60 (AA′BB′, 4 H, aromatic), 3.89 (t, 2 H, CH_2O), 1.73 (m, 2 H, CH_2CH_2O), 1.26 (m, 22 H, $(CH_2)_{11}$), 0.88 (t, 3 H, terminal CH_3); mass spectrum (EI) *m/e* 305 (M^+). Anal. ($C_{20}H_{35}NO$) H, N; C: calcd, 78.63; found, 77.76.

3-[(Formyloxy)methyl]-*N*-[4-(tetradecyloxy)phenyl]benzamide (77). A mixture of 10 g (19.9 mmol) of **75** and 9.61 g (139.3 mmol) of sodium formate was refluxed in 150 mL of DMF for 2 h. The mixture was poured into H_2O. The solid was collected by filtration and recrystallized from acetone, giving 8.5 g (91%) of **77** as a white solid: mp 105–106 °C; ^1H NMR ($CDCl_3$) δ 8.16 (s, 1 H, CHO), 7.90–6.90 (ms, 9 H, aromatic, NH), 5.27 (s, 2 H, CH_2OCHO), 3.95 (t, 2 H, CH_2O), 1.76 (m, 2 H, CH_2CH_2O), 1.26 (m, 22 H, $(CH_2)_{11}$), 0.88 (t, 3 H, terminal CH_3); mass spectrum (EI) *m/e* 467 (M^+). Anal. ($C_{29}H_{41}NO_4$) C, H, N.

3-[[[4-(Tetradecyloxy)phenyl]amino]methyl]benzenemethanol (78). To a stirring solution of 8 g (17.1 mmol) of **77** in 100 mL of THF at 0 °C under argon was added 34.2 mL of a 1 M solution of $LiAlH_4$ in THF over 10 min. The mixture was

stirred at reflux for 6 h. The solution was cooled, and the excess $LiAlH_4$ was destroyed by slowly adding ethyl acetate. A solution of Na_2SO_4 was slowly added until solids formed. The mixture was diluted with ether and filtered through a pad of silica gel. The solvent was evaporated in vacuo, and the residue was recrystallized from hexanes giving 5.6 g (77%) of **78** as a white solid: mp 88–90 °C; ^1H NMR ($CDCl_3$) δ 7.41–6.23 (ms, 3 H, aromatic), 6.68 (AA'BB', 4 H, aromatic), 4.69 (s, 2 H, CH_2OH), 4.28 (s, 2 H, NCH_2), 3.67 (t, 2 H, CH_2OH), 1.75 (m, 2 H, CH_2CH_2O), 1.26 (m, 22 H, $(CH_2)_{11}$), 0.88 (t, 3 H, terminal CH_3); mass spectrum (EI) *m/e* 425 (M^+). Anal. ($C_{29}H_{41}NO_4$) C, H, N.

***N*-[3-(Hydroxymethyl)phenyl]-*N'*-[4-(tetradecyloxy)-phenyl]urea (83).** To a stirring solution of 8.74 g (29.5 mmol) of triphosgene [bis(trichloromethyl)carbonate] in 125 mL of CH_2Cl_2 at 0 °C under argon was added dropwise a solution of 12 g (39.3 mmol) of **74**, 7.95 g (78.56 mmol) of triethylamine, and 0.24 g (2 mmol) of DMAP in 125 mL of CH_2Cl_2 over a 35-min period. The mixture was stirred for 4 h at room temperature. The solvent was evaporated in vacuo. The residue was mixed with ether, and the resulting mixture was filtered. The solvent was removed from the filtrate, giving the isocyanate **82** which was used without additional purification.

To a solution of **82** in a mixture of 30 mL of pyridine and 70 mL of THF was added at 0 °C a solution of 7.24 g (58.8 mmol) of 3-aminobenzyl alcohol in 70 mL of THF. The mixture was stirred 1 h at room temperature and then heated until all solids dissolved. The mixture was then stirred at room temperature overnight. To the stirring mixture was added H_2O. The suspended solid was collected by filtration and washed with dilute HCl and H_2O. The product was recrystallized from ethanol, giving 13.1 g (74%) of **83** as a light pink solid: mp 156–158 °C; ^1H NMR (DMSO-d_6) δ 8.55 (s, 1 H, NH), 8.41, (s, 1 H, NH), 7.50–6.30 (ms, 8 H, aromatic), 5.16 (t, 1 H, OH), 4.45 (d, 2 H, CH_2OH), 3.90 (t, 2 H, CH_2O), 1.75 (m, 2 H, CH_2CH_2O), 1.24 (m, 22 H, $(CH_2)_{11}$), 0.85 (t, 3 H, terminal CH_3); IR (KBr) 1635, 1602, 1591 cm^{-1}; mass spectrum (EI) *m/e* 454 (M^+). Anal. ($C_{28}H_{42}N_2O_3$) C, H, N.

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