

Analogues of Platelet Activating Factor. 8. Antagonists of PAF Containing an Aromatic Ring Linked to a Pyridinium Ring

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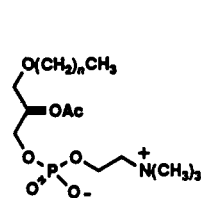
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A series of platelet activating factor (PAF) antagonists containing a quaternary pyridinium ring connected through an amide, imide, or carbamate linkage to a substituted aromatic ring was prepared. Of these compounds, those containing a branched imide linkage of the form (CON-(COCH₃)CH₂, 37-51, and 59) generally showed excellent PAF antagonist properties *in vitro*. Structure-activity relationships within this series of compounds were studied extensively with respect to substituents and the position of substitution in both the aromatic and pyridinium rings. Several of these compounds (40 and 44) showed *in vitro* PAF antagonism at less than 0.1 μM and are as potent as CV-6209, the most potent PAF antagonist reported in the literature. Less active PAF antagonists were those bearing simple amide linkages (20-23, 27-29, and 31-35), linear imide linkages (62-63), or carbamate linkages (66 and 68), between the two aromatic rings. A number of our PAF antagonists were tested *in vivo* in mice and rabbits for their ability to protect these animals against a lethal injection of PAF. Those antagonists that are particularly potent (IC₅₀ < 0.1 μM) provide excellent protection against an LD₉₇ dose of PAF in rabbits. The relationships between structure and activity *in vitro* and *in vivo* are presented and compared to literature standards.

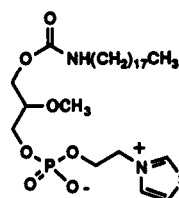
Platelet activating factor (PAF, 1), first described biologically in 1972,¹ was structurally defined in 1979 independently by Benveniste et al.² and by Hanahan et al.³ Interestingly, PAF, while having a potent ability to aggregate platelets, also has many other significant inflammatory effects.⁴ Because PAF has been invoked as a possible mediator in a number of human diseases by binding to a specific receptor,⁴ the idea that a receptor antagonist to PAF may block its effects has been proposed. Consequently, a vast number of structurally diverse PAF antagonists have been prepared or isolated from natural sources, and many of these antagonists are being evaluated for the treatment of asthma, graft rejection, stroke, inflammatory diseases, and septic shock.⁵

Terashita et al.⁶ reported the first PAF antagonist CV-3988 (2) in 1983. In our earlier antagonist work, we combined some structural features present in CV-3988 with other features that we uncovered in our earlier SAR studies on PAF analogues.⁷ This resulted in the synthesis of compounds such as 3 which bear an aromatic ring separating the charged heterocycle from the lipophilic portion of the molecule. Additionally, it is reported in several studies that the configuration of the C-2 carbon atom (of glycerol based and other types) of PAF antagonists has little influence on their antagonist properties.⁸ These literature observations suggested to us that since an asymmetric center with a defined configuration is not a requirement for antagonist activity, perhaps we could dispense with the glycerol backbone all together. We, therefore, decided to replace the glycerol backbone of our aryl phosphoglyceride antagonists such as 3 with a simple aromatic backbone to give, for example, CL 184,005 (4), and the results of this study have been published.⁷ This highly potent series of antagonists provided a number of compounds that have proven efficacious in our animal models of endotoxic shock; CL 184,005 (4) is presently undergoing clinical trials for the treatment of septic shock

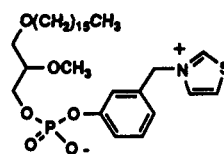
in humans. More recently, we have reported on a new series of aromatic PAF antagonists that contain an amide linkage (instead of the phosphate linkage) separating the two aromatic rings.⁹



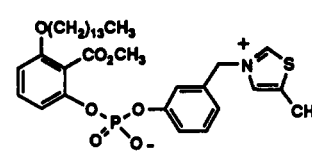
PAF (1, n = 15,17)



CV-3988 (2)



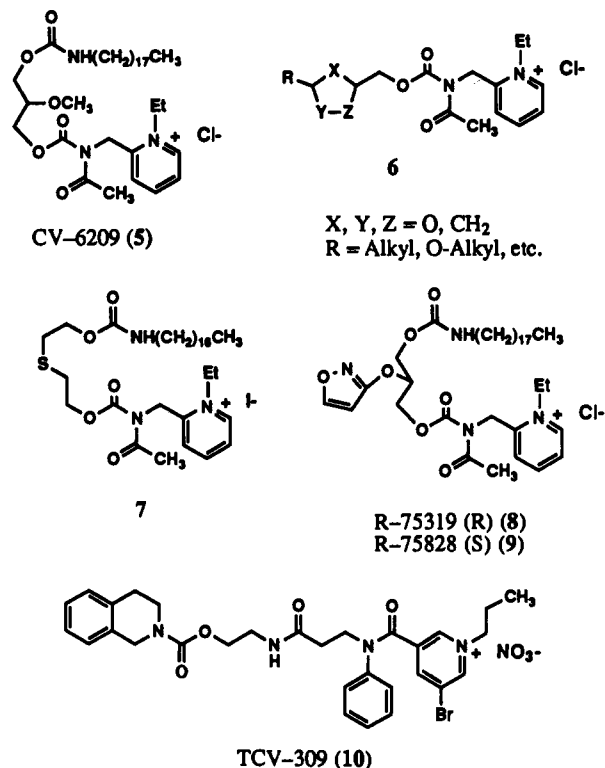
3



CL 184,005 (4)

In our continuing studies to discover novel PAF antagonists, we attempted to improve on the activities of compounds bearing the amide linkage between the aromatic ring and the polar end. A number of PAF antagonists have been disclosed that contain a charged pyridine ring as a key structural unit, linked via an amide or a carbamate moiety to a lipophilic side chain. Reports by Takatani et al. on the PAF antagonist properties of CV-6209 (5),^{8d} and subsequent reports by Forn et al. on antagonists such as 6 and 7¹⁰ and Nakamura on antagonists 8 and 9,¹¹ describe antagonists that all contain the group OCON(COCH₃)CH₂(2-pyridinium). Apparently, this particular structural feature is consistent with potent PAF antagonism; CV-6209 is among the most potent antagonists

known. Additionally, Terashita et al. has disclosed TCV-309 (10),¹² wherein a 3-pyridinium group is connected through the carbonyl carbon atom of an amide to the rest of the molecule. These literature observations prompted our own investigation into antagonists having these important structural components, and in this report we wish to disclose another series of aryl-containing PAF antagonists that contain a pyridinium ring as a key structural unit.

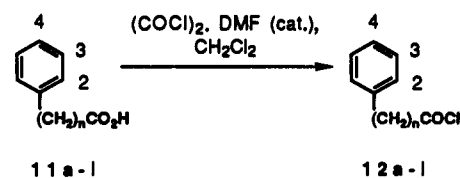


Chemistry

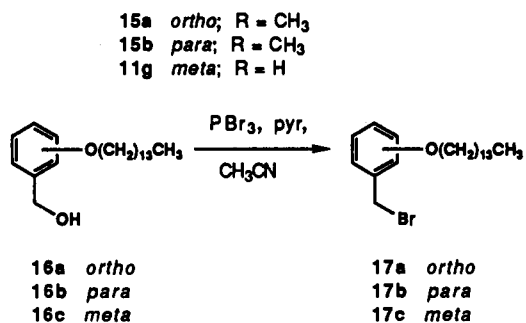
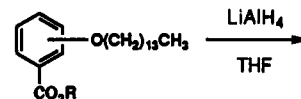
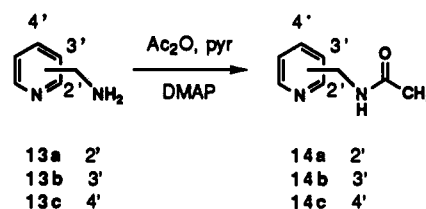
A number of important intermediates were prepared and repeatedly used in the synthesis of a variety of the compounds described in this communication. Aromatic acid chlorides 12a-i (Scheme I) were prepared from the corresponding carboxylic acids, by a procedure described earlier,⁹ by reaction with oxalyl chloride in methylene chloride solution in the presence of a catalytic amount of dimethylformamide (DMF).¹³ Amides 14a-c were prepared from commercially available (aminomethyl)pyridines 13a-c by reacting these with acetic anhydride in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP). Benzyl bromides 17a-c were prepared by first reduction of the known⁹ esters 15a or 15b or the known⁹ acid 11g with lithium aluminum hydride (LAH) to give benzyl alcohols 16a-c. Alcohols 16a-c were then transformed into bromides 17a-c by reaction with phosphorus tribromide in acetonitrile. The moderately labile benzyl bromides were usually prepared immediately prior to use to avoid decomposition.

Amide compounds 20-23 were prepared as described in Scheme II. Acid chlorides 12a and 12i were allowed to react with 2-(aminoalkyl)pyridines 13a or 18 in the presence of pyridine in methylene chloride solution to provide amides 19a-d. The quaternary salts of amides 19a-d were isolated after reaction with iodomethane at 90-110 °C in the absence of solvent. Recrystallization from methanol provided pure pyridinium-containing compounds 20-23.

Scheme I



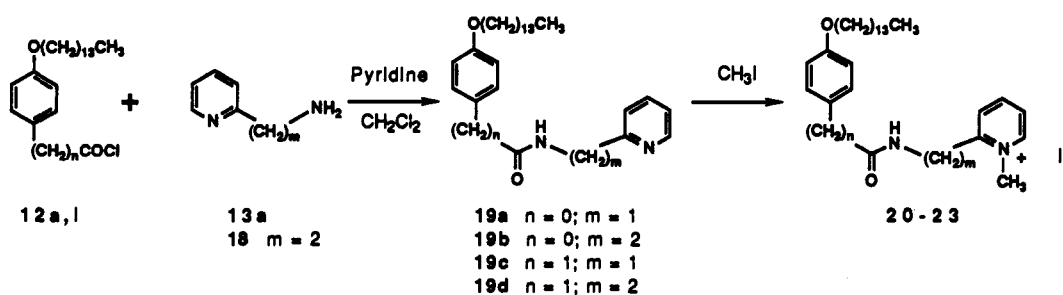
Entry	2	3	4	n
a	H	H	O(CH ₂) ₁₃ CH ₃	0
b	H	OCH ₃	O(CH ₂) ₁₃ CH ₃	0
c	H	O(CH ₂) ₁₃ CH ₃	O(CH ₂) ₁₃ CH ₃	0
d	H	C(CH ₃) ₃	O(CH ₂) ₁₃ CH ₃	0
e	H	C(CH ₃) ₃	O(CH ₂) ₉ CH ₃	0
f	H	O(CH ₂) ₁₃ CH ₃	OCH ₃	0
g	H	O(CH ₂) ₁₃ CH ₃	H	0
h	H	O(CH ₂) ₆ CH ₃	O(CH ₂) ₆ CH ₃	0
i	H	H	O(CH ₂) ₁₃ CH ₃	1



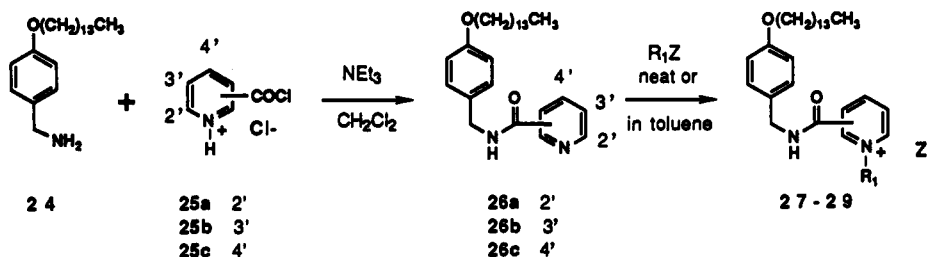
The synthesis of compounds in which the linkage is reversed with respect to amide compounds 20-23 is described in Scheme III. Benzylamine 24⁹ was allowed to react with commercially available acid chlorides 25a-c in methylene chloride solution in the presence of triethylamine. Amides 26a-c, isolated after column chromatography, were then allowed to react with various electrophiles at 65-100 °C to provide compounds 27-29. Interestingly, while the 4'-isomer 26c and the 3'-isomer 26b reacted readily with iodomethane at 100 °C, the 2'-isomer 26a showed considerable resistance to alkylation with iodomethane even under forcing conditions. Quaternization was realized when 26a was allowed to react with the more potent alkylating agent ethyl trifluoromethanesulfonate (EtOTf) in toluene at 65-70 °C, although the product invariably contained some unreacted starting material.

A series of amide containing antagonists was prepared

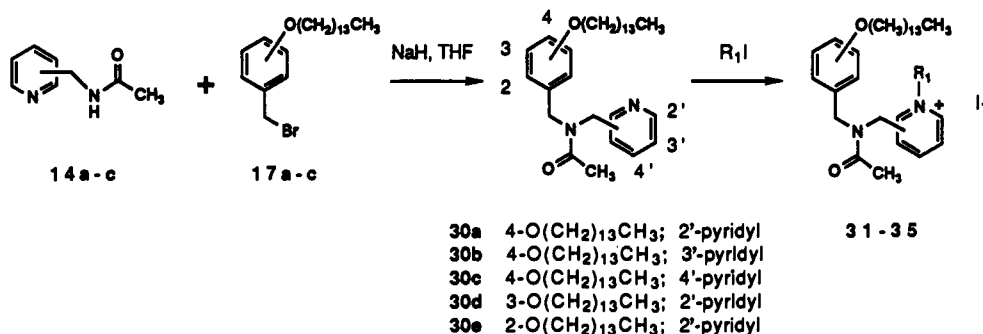
Scheme II



Scheme III



Scheme IV



in which the amide linkage was external to the backbone of the molecule. The synthesis of these compounds is outlined in Scheme IV. The anions of amides 14a-c, prepared by reaction with sodium hydride in tetrahydrofuran (THF), were allowed to react with benzyl bromides 17a-c at ambient temperature or above, providing amides 30a-e. The amides were then heated at 100–115 °C in the presence of an alkyl iodide to provide pyridinium salts 31–35. Interestingly, these compounds exhibit slow amide rotation in solution as evidenced by their ¹H and ¹³C NMR spectra when recorded in *d*₆-DMSO/trifluoroacetic acid.

Those compounds bearing branched imide linkages between the aromatic rings were synthesized as described in Schemes V and VI. Imides 36a-k were isolated after reaction of the anions of amides 14a-c (prepared as described above) with acid chlorides 12a-h. Attempts to prepare the same imides by reaction of amides 19a-d and others not shown with various acylating agents were unsuccessful. Lastly, pyridinium salts 37–50 were obtained by heating the imides with an alkyl iodide or triflate in toluene or acetonitrile. Pyridine *N*-oxide 51 was prepared from 36d by oxidation with 3-chloroperbenzoic acid in acetic acid.

Compound 59 was prepared from commercially available phenol 52 as shown in Scheme VI. Of note, we prepared acid chloride 55 by reaction of diacyl 54 with oxalyl chloride¹³ and then treated 55 with the anion derived from amide 14a in THF solution. Compound 59 was obtained from 56 in a three-step procedure.

The synthesis of compounds 62 and 63, in which an

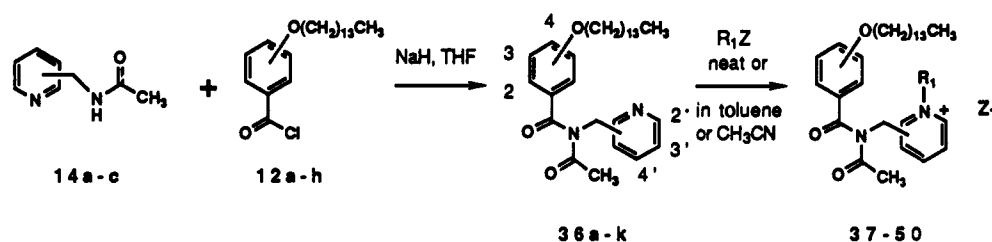
unbranched imide linkage connects the two aromatic rings, is described in Scheme VII. Commercially available isonicotinamide (60a) or nicotinamide (60b) were allowed to react with sodium hydride in THF/hexamethylphosphoramide (HMPA) solution followed by treatment with acid chloride 12b giving imides 61a,b. Alkylation with 1-iodopropane at 90–95 °C produced 62 and 63.

Carbamate 66 and acyl carbamate 68 were synthesized from benzyl alcohol 16b as shown in Scheme VIII. Displacement of phenol from 64 by amine 13a was accomplished in the absence of solvent at 105 °C, providing carbamate 65 in 96% yield. After acylation of 65 with acetic anhydride, triethylamine, and DMAP, in methylene chloride, the desired products 66 and 68 were synthesized as described before.

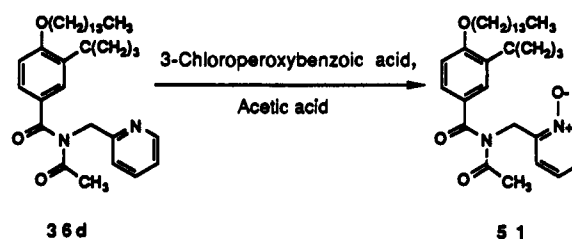
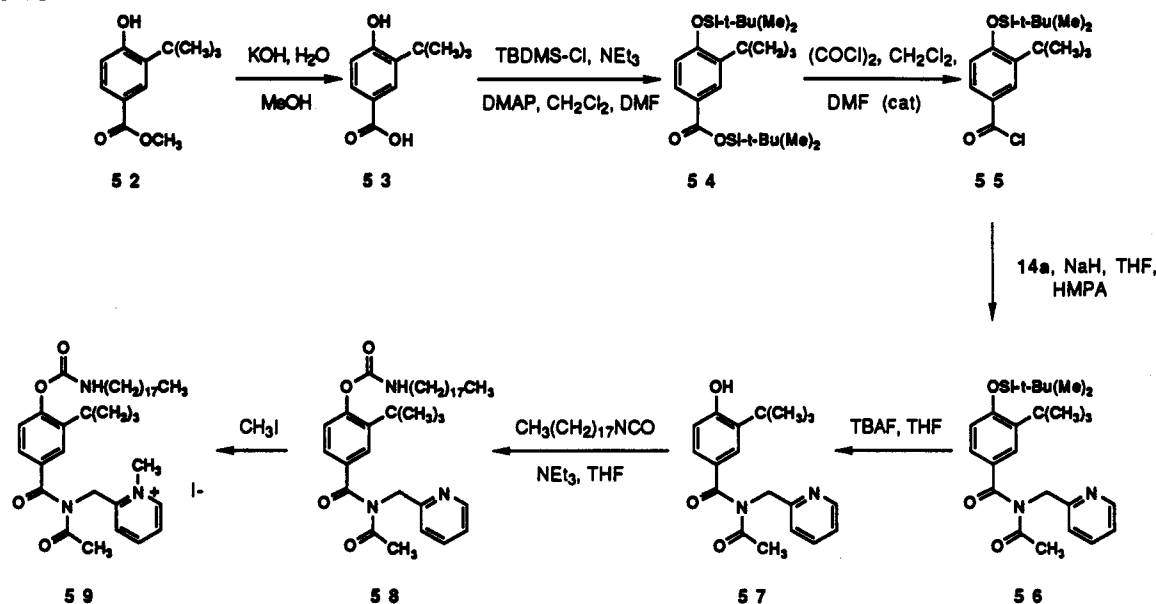
Biology

The compounds were evaluated for their PAF antagonist properties both *in vitro* and *in vivo*. In one assay, we examined their ability to inhibit PAF-induced platelet aggregation in rabbit platelet rich plasma (PRP). The data are expressed as a molar IC₅₀, 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 IC₅₀ values were averaged to give the values shown in Tables I and II. Each compound was evaluated for agonist activity; none of the compounds in Table I or II showed agonist activity at the indicated doses.

Scheme V



Entry	Aromatic Substitution		Pyridyl Position
	3	4	
36 a	H	O(CH ₂) ₁₃ CH ₃	2'
36 b	O(CH ₂) ₁₃ CH ₃	H	2'
36 c	H	O(CH ₂) ₁₃ CH ₃	3'
36 d	C(CH ₃) ₃	O(CH ₂) ₁₃ CH ₃	2'
36 e	C(CH ₃) ₃	O(CH ₂) ₆ CH ₃	2'
36 f	C(CH ₃) ₃	O(CH ₂) ₁₃ CH ₃	3'
36 g	C(CH ₃) ₃	O(CH ₂) ₁₃ CH ₃	4'
36 h	OCH ₃	O(CH ₂) ₁₃ CH ₃	2'
36 i	O(CH ₂) ₁₃ CH ₃	OCH ₃	2'
36 j	O(CH ₂) ₁₃ CH ₃	O(CH ₂) ₁₃ CH ₃	2'
36 k	O(CH ₂) ₆ CH ₃	O(CH ₂) ₆ CH ₃	2'


 Scheme VI^a


^a TBDMS-Cl is *tert*-butyldimethylsilyl chloride; DMAP is 4-(dimethylamino)pyridine; TBAF is tetrabutylammonium fluoride.

For comparative purposes, we have included data generated in our laboratory for a number of antagonists reported in the literature (see Table I). For comparisons of our IC₅₀ values with those in the literature to be meaningful, it is important to note the PAF challenge concentrations used, the species of platelets, and whether washed platelets or, as is the case in this study, PRP was used. We have generally found that the IC₅₀ values are about 10-fold lower when washed rabbit platelets are used.

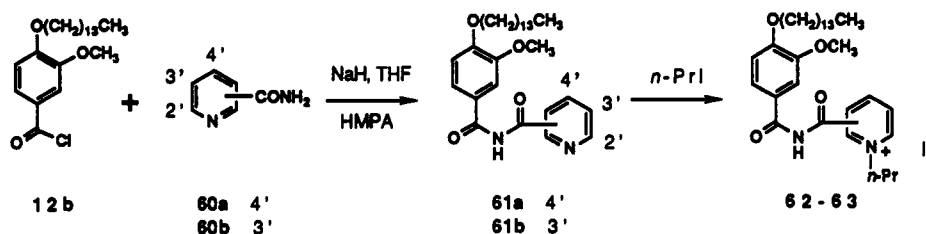
For selected compounds, we also evaluated their ability *in vivo* to prevent death resulting from a lethal challenge

of intravenous PAF in both mice and rabbits. These results are presented in Table III.

Results and Discussion

As evident from the *in vitro* PAF antagonist data presented in Table II, a number of trends in the activity of our compounds are apparent. Because of results gleaned in our earlier PAF antagonist studies,^{7,9} we spent little time examining the SAR of the lipophilic side chain. For most of the antagonists prepared, a chain length of 14 carbon atoms was used. We did, however, vary this

Scheme VII



Scheme VIII

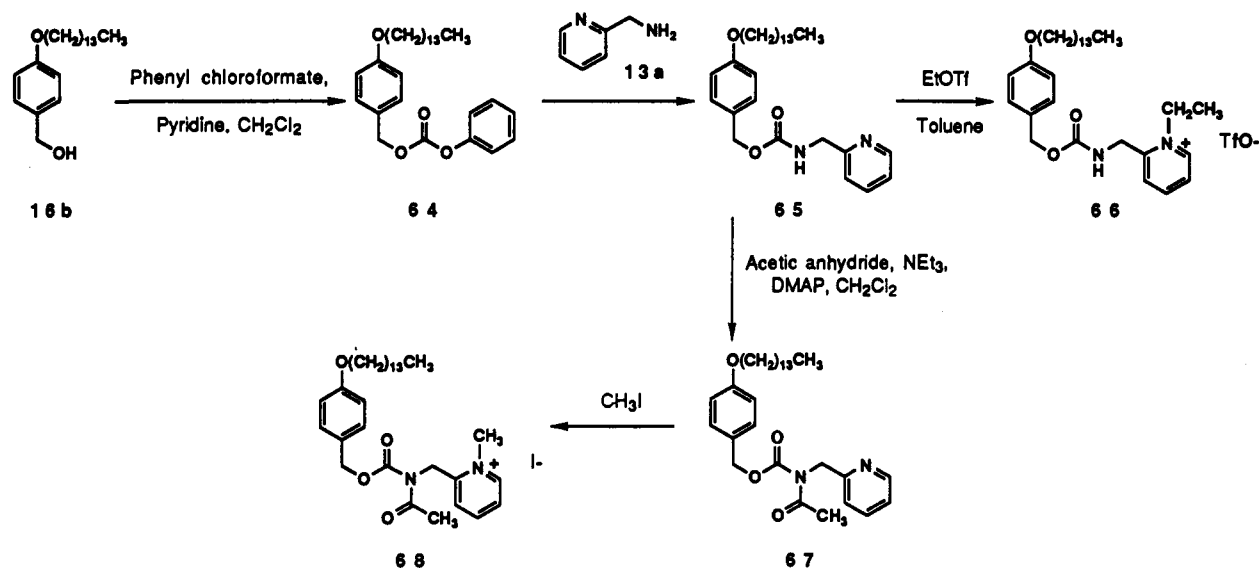
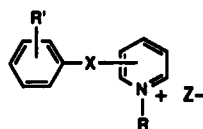


Table I. Inhibition of PAF-Induced Platelet Aggregation: Literature Standards

compd	inhibition of platelet agg IC ₅₀ (μM) ^a	ref
CV-3988	25.9 ± 39.6 (4)	6
CV-6209	0.02 ± 0.01 (3)	8b
Triazolam	11.1 ± 3.7 (3)	15
Alprazolam	22.0 ± 19.2 (2)	15
WEB-2086	0.34 ± 0.27 (6)	16
Kadsurenone	3.3 ± 0.7 (2)	17
L-652731	1.6 ± 0.68 (3)	18
SRI-63072	16.7 (1)	19
SRI-63441	2.1 (1)	20
CL 184,005	0.54 ± 0.3 (12)	7

^a Concentration needed to inhibit PAF-induced platelet aggregation in rabbit PRP by 50%; the PAF challenge concentration was 5.0×10^{-6} M; the value in parentheses is the number of determinations. For $n = 2$, the range of IC₅₀ is given; for $n > 2$, the standard deviation is given.

parameter in conjunction with multiple aromatic ring substitutions. We concentrated on examining structure-activity relationships predominantly on modifications of four structural parameters (refer to 69): substitution of the aromatic ring (R' groups), variation of the X group between the two aromatic rings, substitution pattern of the pyridinium ring, and variation of the R group attached to the nitrogen of the pyridinium ring.



69

Of major significance to activity is variation of the X group. We found that a simple unbranched amide linkage

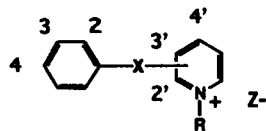
between the two aromatic rings was not consistent with good PAF antagonism. For example, compounds 20–23 and 27–29 are essentially devoid of activity, independent of the orientation of the amide group (CONHCH₂ vs CH₂NHCO) or the length of the chain between the rings.

Moderate PAF antagonist activity was observed for the series of compounds 31–35 which contain a branched amide linkage (CH₂N(COCH₃)CH₂) between the aromatic rings. Compounds within this series containing a pyridinium ring substituted in the 2'- or 4'-position exhibited activity, while compounds with 3'-substitution were totally devoid of activity. Within the 2'-substituted series (i.e., 31, 34, and 35), the antagonist bearing the 4-O(CH₂)₁₃CH₃ substituent in the aromatic ring was the most active, a trend observed in several other series discussed below.

The most active series described in this report were those bearing a branched imide linkage (CON(COCH₃)-CH₂) between the two aromatic rings. This particular functional group is closely related to those found in the most active PAF antagonists described in the literature;^{8d,10,11} the only difference is that our antagonists are imides while the literature antagonists are *N*-acetyl carbamates. If one compares the PAF antagonist activities of the series of compounds 20–23, 27, 31, 37, 66, and 68, which differ predominantly in the X group, one can see that 37 is the most active. A related observation was made by Takatani et al.^{8d} wherein a carbamate antagonist exhibited moderate activity while the analogous *N*-acetyl carbamate showed superior activity. Interestingly, compound 68, which contains the same *N*-acetyl carbamate linkage, is devoid of activity.

Compounds bearing a linear imide X group (CONHCO), compounds 62 and 63, were also inactive. Particularly disappointing in this regard was 3'-substituted derivative

Table II. Inhibition of PAF-Induced Platelet Aggregation



compd no.	aromatic substituents			pyridine subst	R	Z	inhibition of platelet agg, IC ₅₀ (μM) ^a	n ^a	formula ^b	anal. ^c	
	2	3	4 X								
20	H	H	O(CH ₂) ₁₃ CH ₃	CONH(CH ₂)	2'	methyl	I	>10	2	C ₂₈ H ₄₃ N ₂ O ₂ I	C,H,N,I
21	H	H	O(CH ₂) ₁₃ CH ₃	CONH(CH ₂) ₂	2'	methyl	I	>10	1	C ₂₉ H ₄₆ N ₂ O ₂ I	C,H,N,I
22	H	H	O(CH ₂) ₁₃ CH ₃	(CH ₂)CONH(CH ₂)	2'	methyl	I	>10	1	C ₂₉ H ₄₆ N ₂ O ₂ I	C,H,N,I
23	H	H	O(CH ₂) ₁₃ CH ₃	(CH ₂)CONH(CH ₂) ₂	2'	methyl	I	15	1	C ₃₀ H ₄₇ N ₂ O ₂ I (0.25H ₂ O)	C,H,N,I
27	H	H	O(CH ₂) ₁₃ CH ₃	(CH ₂)NHCO	2'	ethyl	OTf	>10	1	C ₃₀ H ₄₆ N ₂ O ₆ SF ₃ ^d	C,H,N,F,S
28	H	H	O(CH ₂) ₁₃ CH ₃	(CH ₂)NHCO	3'	methyl	I	120	1	C ₂₈ H ₄₃ N ₂ O ₂ I	H,N; C ^e , I ^f
29	H	H	O(CH ₂) ₁₃ CH ₃	(CH ₂)NHCO	4'	methyl	I	60	1	C ₂₈ H ₄₃ N ₂ O ₂ I	H,N,I; C ^g
31	H	H	O(CH ₂) ₁₃ CH ₃	(CH ₂)N(COCH ₃)CH ₂	2'	ethyl	I	8.3 ± 8	2	C ₃₁ H ₄₉ N ₂ O ₂ I	C,H,N,I
32	H	H	O(CH ₂) ₁₃ CH ₃	(CH ₂)N(COCH ₃)CH ₂	3'	methyl	I	>10	1	C ₃₀ H ₄₇ N ₂ O ₂ I (0.75H ₂ O)	C,H,N,I
33	H	H	O(CH ₂) ₁₃ CH ₃	(CH ₂)N(COCH ₃)CH ₂	4'	methyl	I	1.0	1	C ₃₀ H ₄₇ N ₂ O ₂ I (0.50H ₂ O)	C,H,N,I
34	H	O(CH ₂) ₁₃ CH ₃	H	(CH ₂)N(COCH ₃)CH ₂	2'	methyl	I	17	1	C ₃₀ H ₄₇ N ₂ O ₂ I (0.25H ₂ O)	C,H,N,I
35	O(CH ₂) ₁₃ CH ₃	H	H	(CH ₂)N(COCH ₃)CH ₂	2'	methyl	I	43	1	C ₃₀ H ₄₇ N ₂ O ₂ I	C,H,N,I
37	H	H	O(CH ₂) ₁₃ CH ₃	CON(COCH ₃)CH ₂	2'	methyl	I	0.95 ± 0.25	6 ^h	C ₃₀ H ₄₆ N ₂ O ₂ I	C,H,I; N ⁱ
38	H	O(CH ₂) ₁₃ CH ₃	H	CON(COCH ₃)CH ₂	2'	methyl	I	>10	2	C ₃₀ H ₄₆ N ₂ O ₂ I	C,H,N; I ^j
39	H	H	O(CH ₂) ₁₃ CH ₃	CON(COCH ₃)CH ₂	3'	methyl	I	6.8	1	C ₃₀ H ₄₆ N ₂ O ₂ I	C,H,N,I
40	H	C(CH ₃) ₃	O(CH ₂) ₁₃ CH ₃	CON(COCH ₃)CH ₂	2'	methyl	I	0.022 ^k	1	C ₃₄ H ₅₃ N ₂ O ₃ I (0.20H ₂ O)	C,H,N,I
41	H	C(CH ₃) ₃	O(CH ₂) ₉ CH ₃	CON(COCH ₃)CH ₂	2'	methyl	I	>10	1	C ₃₀ H ₄₆ N ₂ O ₃ I (0.25H ₂ O)	C,H,N,I
42	H	C(CH ₃) ₃	O(CH ₂) ₁₃ CH ₃	CON(COCH ₃)CH ₂	3'	methyl	I	20	1	C ₃₄ H ₅₃ N ₂ O ₃ I	C,H,N,I
43	H	C(CH ₃) ₃	O(CH ₂) ₁₃ CH ₃	CON(COCH ₃)CH ₂	4'	methyl	I	1.1	1	C ₃₄ H ₅₃ N ₂ O ₃ I (0.25H ₂ O)	C,H,N,I
44	H	OCH ₃	O(CH ₂) ₁₃ CH ₃	CON(COCH ₃)CH ₂	2'	methyl	I	0.064 ^l	1	C ₃₁ H ₄₇ N ₂ O ₄ I	C,H,N,I
45	H	OCH ₃	O(CH ₂) ₁₃ CH ₃	CON(COCH ₃)CH ₂	2'	ethyl	I	0.16 ± 0.08	2	C ₃₂ H ₄₆ N ₂ O ₄ I (0.50H ₂ O)	C,H,N; I ^m
46	H	OCH ₃	O(CH ₂) ₁₃ CH ₃	CON(COCH ₃)CH ₂	2'	<i>n</i> -propyl	OTf	0.10	1	C ₃₄ H ₅₁ N ₂ O ₇ SF ₃	C,H,N,F,S
47	H	O(CH ₂) ₁₃ CH ₃	OCH ₃	CON(COCH ₃)CH ₂	2'	methyl	I	160	1	C ₃₁ H ₄₇ N ₂ O ₄ I	C,H,N,I
48	H	O(CH ₂) ₁₃ CH ₃	O(CH ₂) ₁₃ CH ₃	CON(COCH ₃)CH ₂	2'	methyl	I	>10	1	C ₄₄ H ₇₃ N ₂ O ₄ I (0.50H ₂ O)	C,H,N,I
49	H	O(CH ₂) ₆ CH ₃	O(CH ₂) ₆ CH ₃	CON(COCH ₃)CH ₂	2'	methyl	I	3.7	1	C ₃₀ H ₄₆ N ₂ O ₄ I	C,H,N; I ⁿ
50	H	H	O(CH ₂) ₁₃ CH ₃	CON(COCH ₃)CH ₂	2'	benzyl	Br	330	1	C ₃₆ H ₄₉ N ₂ O ₃ Br	C,H,N,Br
51	H	C(CH ₃) ₃	O(CH ₂) ₁₃ CH ₃	CON(COCH ₃)CH ₂	2'	oxygen	I	>10	1	C ₃₃ H ₅₀ N ₂ O ₄ (1.0H ₂ O)	C,H; N ^o
59	H	C(CH ₃) ₃	OCONHC ₁₈ H ₃₇	CON(COCH ₃)CH ₂	2'	methyl	I	>10	2	C ₃₉ H ₆₂ N ₃ O ₄ I	C,H,N,I
62	H	OCH ₃	O(CH ₂) ₁₃ CH ₃	CONHCO	4'	<i>n</i> -propyl	I	>10	1	C ₃₁ H ₄₇ N ₂ O ₄ I	C,H,N; I ^p
63	H	OCH ₃	O(CH ₂) ₁₃ CH ₃	CONHCO	3'	<i>n</i> -propyl	I	>10	1	C ₃₁ H ₄₇ N ₂ O ₄ I	H,N; C ^q , I ^r
66	H	H	O(CH ₂) ₁₃ CH ₃	CH ₂ CONH(CH ₂)	2'	ethyl	OTf	>10	1	C ₃₁ H ₄₇ N ₂ O ₆ SF ₃	C,H,N,F,S
68	H	H	O(CH ₂) ₁₃ CH ₃	CH ₂ CON(COCH ₃)CH ₂	2'	methyl	I	>10	2	C ₃₁ H ₄₇ N ₂ O ₄ I	C,H; N ^r , I ^s

^a Concentration needed to inhibit PAF induced platelet aggregation in rabbit PRP by 50%; the PAF challenge was 5 × 10⁻⁸ M; *n* is the number of determinations. For *n* = 2, the range of IC₅₀ is given; for *n* > 2, the standard deviation is given. ^b Empirical formula with amount of water of hydration. All compounds showed the expected M + H-X⁺ ion in the FAB mass spectrum. ^c Analytical results for the indicated elements are within ±0.4% of the calculated values, unless indicated otherwise. ^d Isolated and analyzed as a 1:1 mixture of 26a/27. ^e C: calcd, 59.36; found, 58.24. ^f I: calcd, 22.40; found, 23.49. ^g C: calcd, 59.36; found, 58.70. ^h Average IC₅₀ determined on four trials, the remaining two determinations showed no inhibition of platelet aggregation. ⁱ N: calcd, 4.60; found, 4.11. ^j I: calcd, 20.85; found, 20.34. ^k IC₅₀ = 0.025 ± 0.011 μM when PAF challenge was 1 × 10⁻⁷ M (*n* = 2). ^l IC₅₀ = 2.4 ± 2.0 μM when PAF challenge was 1 × 10⁻⁷ M (*n* = 3). ^m I: calcd, 19.18; found, 20.45. ⁿ I: calcd, 20.32; found, 19.42. ^o N: calcd, 5.03; found, 4.52. ^p I: calcd, 19.87; found, 18.81. ^q C: calcd, 58.30; found, 58.80. ^r I: calcd, 19.87; found, 18.32. ^s N: calcd, 4.39; found, 3.63. ^t I: calcd, 19.87; found, 22.15.

Table III. Protection of PAF-Induced Lethality in the Mouse and Rabbit

compd	in vitro IC ₅₀ (μM) ^a	% survival in mouse ^b	% survival in rabbit ^b
control		10 (2599)	3 (33)
27	>10	36 (11)	ND ^c
31	8.3	40 (10)	ND
32	>10	38 (13)	ND
33	1.0	ND	0 (2)
35	43	23 (13)	ND
37	0.95	27 (11)	ND
40	0.022	64 (11)	100 (4)
41	>10	50 (12)	ND
42	20	17 (12)	ND
43	1.1	27 (11)	ND
44	0.064	58 (24)	75 (4)
45	0.16	58 (24)	33 (3)
46	0.10	47 (30)	ND
47	160	21 (14)	ND
48	>10	36 (14)	ND
49	3.7	45 (11)	0 (3)
50	330	0 (15)	ND
59	>10	29 (14)	ND
62	>10	33 (12)	ND
63	>10	42 (12)	ND
66	>10	36 (11)	ND
68	>10	40 (15)	ND
CL 184005	0.54	85 (312)	53 (17)

^a Concentration needed to inhibit PAF induced platelet aggregation in rabbit PRP by 50%; the PAF challenge was 5×10^{-6} M. ^b Compound was given ip at a dose of 1 mg/kg in saline 0.5 h prior to an LD₅₀ of PAF. Number in parentheses is number of animals treated. ^c ND = not determined.

63, which in spite of its having some structurally similar components to the literature antagonist TCV-309 (10)¹² was inactive. These results are somewhat contrary to our earlier diaryl amide antagonists⁹ where considerable structural variability was consistent with activity.

Within the series of antagonists bearing a branched imide linker between the two aromatic rings, i.e. 37–51 and 59, several interesting structure–activity relationships are evident. We found maximal activity when the 14-carbon chain was para to the X group (37 vs 38). Introduction of a relatively small group (e.g. OCH₃, C(CH₃)₃) into the 3-position of the carbocyclic ring led to a 15–40-fold increase in activity (compare 37, 40, and 44). However, introducing a large group such as O(CH₂)₁₃CH₃ into the 3-position, as in 48, led to a significant loss in activity. Additionally, compound 49, bearing 3,4-[O(CH₂)₆CH₃]₂ disubstitution, was somewhat less active than 37, which has only a single 4-O(CH₂)₁₃CH₃ substituent. Decreasing the chain length of the lipophilic group led to a decrease in activity of >450-fold (40 vs 41). Reversing the aromatic substitution pattern of 44 to give 47 (3-O(CH₂)₁₃CH₃; 4-OCH₃) led to an activity decrease of 2500-fold. Lastly, replacement of the 4-O(CH₂)₁₃CH₃ of 40 by an OC(O)NH(CH₂)₁₇CH₃ group, present in a number of literature antagonists,^{6,8d,10,11} provided compound 59 and a concomitant decrease in activity by >450-fold. It should be noted at this point that compounds 40 and 44 are as potent as the most active PAF antagonist reported in the literature, CV-6209.

Variation on the substitution of the pyridine ring paralleled the results described above. Among the series 40, 42, and 43, which differ by the position of pyridine substitution, we found highest activity for the 2'- and 4'-substituted compounds, with the former being clearly superior. Compound 42 with 3'-substitution was 20 times less active than 43 (4'-substitution) and 1000 times less active than 40 (2'-substitution).

Variation of the R group on the positively charged pyridinium ring (44–46) was examined with respect to methyl, ethyl, and propyl. While 44 containing a methyl substituent was the most active, ethyl- and propyl-substituted antagonists 45 and 46, respectively, still maintained significant activity. Apparently, some variability of the R group is permitted without significant erosion of PAF antagonism.

A large number of these PAF antagonists (even those with an IC₅₀ > 10 μM in vitro) were tested in vivo for their ability to protect mice and rabbits against a lethal injection of PAF. These results are presented in Table III. In mice, there appears to be no correlation between in vitro PAF antagonism and in vivo protection against an LD₅₀ challenge of PAF. Even the best PAF antagonists, 40 and 44, were only marginally more protective than some other compounds that are weak PAF antagonists, such as 41, 49, and 63. Interestingly, compound 50 actually seems to amplify the deleterious effects of PAF, resulting in death of all mice.

We observed a better correlation between in vitro PAF antagonism and in vivo protection in rabbits; those antagonists that are particularly potent in vitro provide excellent protection. These findings could be related to the fact that rabbit platelets bear high-affinity receptors for PAF and are particularly sensitive to the effects of PAF, while mice are less sensitive to PAF because their platelets do not have the same numbers of PAF receptors or have lower affinity to PAF.^{4d,14} PAF administration elicits a number of biological responses and different species may respond to each of these responses differently.^{4,5} Following a lethal injection of PAF in the rabbit, platelets aggregate in the lungs and contribute to death by asphyxia. In mice lethal effects of PAF are more related to vascular permeability, leakage, and hypotension. Therefore, the species variation we observed with respect to a lethal challenge of PAF may be due to species variation of the receptor, bioavailability, metabolism, or mode of death.

In conclusion, we have prepared and evaluated a new series of PAF antagonists that contain a substituted aromatic ring connected via an amide linkage to a charged pyridine ring. A number of these antagonists are particularly effective in preventing PAF-induced platelet aggregation in vitro. Some of these compounds are as good as the most potent antagonists reported in the literature. Additionally, several of these antagonists have been tested in our animal models for reduction of PAF induced lethality; in general, those antagonists that are particularly potent provide excellent protection in rabbits. Testing of some of these compounds in models of septic shock will be reported elsewhere.

Experimental Section

Biology. Our methodology for assessing inhibition of PAF-induced platelet aggregation, prevention of PAF-induced lethality in mice, and prevention of PAF-induced lethality in rabbits has been described previously.⁷

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 spectrometer. ¹H NMR spectra were determined at 300 MHz, and ¹³C NMR spectra were determined at 75 MHz, using a Nicolet QE-300 WB spectrometer; chemical shifts (δ) are

recorded in parts per million relative to tetramethylsilane. Apparent couplings are given in hertz. NMR spectra of some of the hygroscopic quaternary salts were determined in d_6 -DMSO; it was usually found that adding several drops of $\text{CF}_3\text{CO}_2\text{D}$ to the sample improved the resolution of the resulting spectrum. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within $\pm 0.4\%$ of the theoretical value. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ.

Unless otherwise noted all reagents and solvents obtained from commercial suppliers were used without further purification. All nonaqueous reactions were performed in dry glassware under an inert atmosphere of dry argon or nitrogen.

N-(3-Pyridinylmethyl)acetamide (14b). To a stirred solution of 13b (50.0 g, 462 mmol) and 4-(dimethylamino)pyridine (DMAP, 2.26 g, 18 mmol) in 150 mL of dry pyridine was added acetic anhydride (50 mL, 532 mmol) dropwise during 15 min. After being stirred at room temperature for 92 h, the mixture was carefully poured into a saturated aqueous solution of sodium bicarbonate and extracted with chloroform (5×250 mL). The combined organic phases were washed with brine (300 mL), dried over anhydrous sodium sulfate, and filtered, and the solvent was evaporated in vacuo. The residue was purified on silica gel (800 g, elution with 20% MeOH/ CHCl_3) to give 14b as a pale yellow oil, 31.8 g (46%): IR (neat) 3290, 1659, 1550 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.51 (d, 2 H, $J = 2.7$ Hz, aromatic), 7.64 (dt, 1 H, $J = 8, 2$ Hz, aromatic), 7.26–7.24 (m, 1 H, aromatic), 6.18 (br s, 1 H, CONH), 4.44 (d, 2 H, $J = 5.9$ Hz, CH_2), 2.04 (s, 3 H, CH_3); ^{13}C NMR (CDCl_3) δ 170.44, 148.65, 148.23, 135.66, 134.23, 123.49, 40.79, and 22.82 ppm; mass spectrum (EI) m/e 150 (M^+). Anal. ($\text{C}_9\text{H}_{10}\text{N}_2\text{O}$) C, H, N.

3-(Tetradecyloxy)benzenemethanol (16c). To a room temperature solution of lithium aluminum hydride (LAH, 7.94 g, 209 mmol) in 100 mL of dry tetrahydrofuran (THF) was added 11g⁹ (20.0 g, 59.8 mmol) dissolved in dry THF (100 mL) during 30 min. The reaction mixture was stirred at room temperature for 60 h and quenched by the careful addition of a saturated aqueous solution of sodium sulfate. The white solids that precipitated were separated by filtration. The filtrate was concentrated in vacuo, giving 16c as a colorless solid, 18.8 g (98%): mp 49–50 °C; IR (KBr) 2921, 2849 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.26 (t, 1 H, $J = 8$ Hz, aromatic), 6.93–6.91 (m, 2 H, aromatic), 6.84–6.81 (m, 1 H, aromatic), 4.67 (d, 2 H, $J = 5.6$ Hz, CH_2OH), 3.96 (t, 2 H, $J = 6.6$ Hz, OCH_2), 1.82–1.74 (m, 2 H, OCH_2CH_2), 1.69–1.63 (m, 1 H, OH), 1.49–1.26 (m, 22 H), 0.88 (t, 3 H, $J = 6.7$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 159.38, 142.42, 129.51, 118.86, 113.78, 112.84, 67.94, 65.26, 31.90, 29.66, 29.59, 29.38, 29.36, 29.26, 26.03, 22.68, and 14.11 ppm; mass spectrum (EI) m/e 320 (M^+). Anal. ($\text{C}_{21}\text{H}_{36}\text{O}_2$) C, H.

1-(Bromomethyl)-3-(tetradecyloxy)benzene (17c). To a 0 °C solution of 16c (1.0 g, 3.1 mmol) dissolved in dry acetonitrile (5 mL) and dry pyridine (136 mg, 1.72 mmol) was added phosphorus tribromide (845 mg, 3.1 mmol) during 3 min. The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 30 min. The reaction mixture was concentrated in vacuo, and the residue was purified on silica gel (20 g, elution with hexane) providing 17c as colorless needles, 1.00 g (83%): mp 34–35 °C; IR (KBr) 2850, 2915, 2950 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.24–7.21 (m, 1 H, aromatic), 6.97–6.92 (m, 2 H, aromatic), 6.85–6.81 (m, 1 H, aromatic), 4.46 (s, 2 H, CH_2Br), 3.95 (t, 2 H, $J = 6.5$ Hz, OCH_2), 1.84–1.72 (m, 2 H, OCH_2CH_2), 1.49–1.26 (m, 22 H), 0.88 (t, 3 H, $J = 6.5$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 159.31, 139.03, 129.71, 121.02, 115.01, 114.64, 67.99, 33.55, 31.91, 29.68, 29.66, 29.59, 29.38, 29.35, 29.23, 26.03, 22.70, and 14.12 ppm; mass spectrum (EI) m/e 382/384 (M^+). Anal. ($\text{C}_{21}\text{H}_{35}\text{BrO}$) C, H, Br.

N-(2-Pyridinylmethyl)-4-(tetradecyloxy)benzamide (19a). To a 0 °C solution of 2-(aminomethyl)pyridine (674 mg, 6.23 mmol) and pyridine (1.83 mL, 22.7 mmol) in 20 mL of dry methylene chloride was added 12a⁹ (2.0 g, 5.67 mmol) dissolved in dry methylene chloride (25 mL) during 20 min. The reaction mixture was stirred at 0 °C for 2 h and at room temperature for 17 h. The reaction mixture was diluted with chloroform (150 mL) and washed successively with saturated aqueous sodium bicarbonate (150 mL), water (150 mL), and brine (150 mL) prior to drying over anhydrous magnesium sulfate and filtration. The filtrate was concentrated in vacuo and the residue purified on

silica gel (125 g, elution with 75% EtOAc/hexane), providing 19a as a colorless solid, 1.51 g (63%): mp 91–93 °C; IR (KBr) 2851, 1637, 1606 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.59 (d, 1 H, $J = 5$ Hz, aromatic), 7.84–7.82 (m, 2 H, aromatic), 7.72–7.66 (m, 1 H, aromatic), 7.48–7.41 (br s, 1 H, CONH), 7.33 (d, 1 H, $J = 7.7$ Hz, aromatic), 7.25–7.20 (m, 1 H, aromatic), 6.94–6.92 (m, 2H, aromatic), 4.75 (d, 2 H, $J = 4.8$ Hz, CH_2NH), 4.00 (t, 2 H, $J = 6.6$ Hz, OCH_2), 1.80 (quintet, 2 H, $J = 8$ Hz, OCH_2CH_2), 1.50–1.26 (m, 22 H), 0.88 (t, 3 H, $J = 6.7$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 166.91, 161.78, 156.51, 148.96, 136.73, 128.81, 126.41, 122.31, 122.16, 114.19, 68.16, 44.73, 31.89, 29.63, 29.56, 29.54, 29.41, 29.35, 29.33, 29.13, 25.97, 22.66, and 14.08 ppm; mass spectrum (EI) m/e 424 (M^+). Anal. ($\text{C}_{27}\text{H}_{40}\text{N}_2\text{O}_2$) C, H, N.

1-Methyl-2-[[[4-(tetradecyloxy)benzoyl]amino]methyl]pyridinium Iodide (20). A solution of 19a (1.0 g, 2.4 mmol) and iodomethane (7.3 mL, 118 mmol) was heated at 100–120 °C in a sealed glass vessel for 22 h. Unreacted iodomethane was removed in vacuo, and the residue was crystallized from methanol to give 20 as pale yellow microcrystals, 1.15 g (86%): mp 108–110 °C; IR (KBr) 3266, 2921, 2849, 1630, 1605 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.87–8.83 (m, 1 H, aromatic), 8.75–8.73 (m, 1 H, aromatic), 8.35–8.30 (m, 2 H, aromatic), 8.08–8.05 (m, 2 H, aromatic), 7.75–7.69 (m, 1 H, aromatic), 6.94–6.91 (m, 2 H, aromatic), 5.09 (d, 2 H, $J = 6$ Hz, CH_2NH), 4.66 (s, 3 H, NCH_3), 3.98 (t, 2 H, $J = 7$ Hz, OCH_2), 1.84–1.74 (m, 2 H, OCH_2CH_2), 1.49–1.26 (m, 22 H), 0.88 (t, 3 H, $J = 7$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 167.67, 162.50, 156.68, 145.72, 144.92, 129.82, 129.35, 126.16, 123.97, 114.30, 68.24, 47.60, 40.99, 31.86, 29.62, 29.53, 29.36, 29.30, 29.08, 25.95, 22.63, and 14.06 ppm; mass spectrum (FAB) m/e 439 ($\text{M}^+ - \text{I}$). Anal. ($\text{C}_{28}\text{H}_{43}\text{N}_2\text{O}_2\text{I}$) C, H, N, I.

N-[[4-(Tetradecyloxy)phenyl]methyl]-2-pyridinecarboxamide (26a). 26a was prepared by the procedure described for 19a (except for the replacement of pyridine by triethylamine) by reaction of 25a and amine 24.⁹ Compound 26a was isolated as a pale yellow solid (80%): mp 51–52 °C; IR (KBr) 3387, 2290, 2850, 1666, 1514 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.52 (ddd, 1 H, $J = 5, 1.7, 1.7$ Hz, aromatic), 8.29 (br s, 1 H, NH), 8.23 (dt, 1 H, $J = 7.8, 1$ Hz, aromatic), 7.85 (td, 1 H, $J = 7.8, 1.7$ Hz, aromatic), 7.44–7.39 (m, 1 H, aromatic), 7.31–7.26 (m, 2 H, aromatic), 6.89–6.84 (m, 2 H, aromatic), 4.59 (d, 2 H, $J = 6$ Hz, CH_2NH), 3.94 (t, 2 H, $J = 6.5$ Hz, OCH_2), 1.82–1.72 (m, 2 H, OCH_2CH_2), 1.50–1.26 (m, 22 H), 0.88 (t, 3 H, $J = 6.8$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 164.05, 158.55, 149.70, 148.01, 137.29, 130.01, 129.17, 126.10, 122.27, 114.62, 68.02, 42.98, 31.90, 29.67, 29.64, 29.58, 29.55, 29.37, 29.34, 29.22, 26.02, 22.68, 22.66, and 14.11 ppm; mass spectrum (EI) m/e 424 (M^+). Anal. ($\text{C}_{27}\text{H}_{40}\text{N}_2\text{O}_2$) C, H, N.

N-(2-Pyridinylmethyl)-N-[[4-(tetradecyloxy)phenyl]methyl]acetamide (30a). To a 0 °C slurry of sodium hydride (NaH, 88.1 mg of a 50% oil dispersion, 1.84 mmol) and dry THF (2 mL) was added amide 14a (704 mg, 1.84 mmol) dissolved in dry THF (6 mL) during 5 min. After a 15-min stirring period at 0 °C, the reaction mixture was warmed to room temperature. Bromide 17a (262 mg, 1.74 mmol) dissolved in THF (4 mL) was added by syringe, and the reaction mixture was stirred at room temperature for 3.5 h. The reaction mixture was diluted with water (50 mL) and then extracted with methylene chloride (3×70 mL). The combined organic fractions were washed with brine (50 mL), dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated in vacuo and the residue purified on silica gel (50 g, elution with 5% MeOH/EtOAc), providing 30a as a pale yellow solid as a mixture of two amide rotamers in a 1:1 ratio, 0.70 g (84%): mp 66–67 °C; IR (KBr) 2290, 2850, 1641 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.60–8.51 (m, 1 H, aromatic), 7.70–7.61 (m, 1 H, aromatic), 7.31–7.07 (m, 4 H, aromatic), 6.89–6.81 (m, 2 H, aromatic), 4.68–4.52 (m, 4 H, CH_2NCH_2), 3.96–3.90 (m, 2 H, OCH_2), 2.23, 2.18 (2s, 3 H, COCH_3), 1.82–1.72 (m, 2 H, OCH_2CH_2), 1.50–1.26 (m, 22 H), 0.88 (t, 3 H, $J = 6.9$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 171.03, 170.79, 158.44, 158.38, 157.35, 156.66, 149.68, 148.96, 136.64, 136.39, 129.59, 128.89, 127.86, 127.56, 122.54, 122.24, 122.22, 121.96, 120.36, 114.61, 114.30, 67.81, 67.75, 52.41, 51.32, 50.10, 47.94, 31.71, 29.46, 29.40, 29.19, 29.06, 25.84, 22.48, 21.63, 21.45, and 13.93 ppm; mass spectrum (EI) m/e 452 (M^+), 360 ($\text{M}^+ - \text{C}_2\text{H}_5\text{N}$). Anal. ($\text{C}_{28}\text{H}_{44}\text{N}_2\text{O}_2$) C, H, N.

2-[[Acetyl[[4-(tetradecyloxy)phenyl]methyl]amino]methyl]-1-ethylpyridinium Iodide (31). 31 was prepared by the procedure described for 20 by reaction of 30a and iodomethane.

Compound 31 was isolated as cream-colored crystal (98%): mp 108–110 °C; IR (KBr) 2920, 2851, 1643, 1628 cm⁻¹; ¹H NMR (d₆-DMSO/TFA) δ 9.15–9.06 (m, 1 H, aromatic), 8.58–8.45 (m, 1 H, aromatic), 8.10–7.83 (m, 2 H, aromatic), 7.28–7.22 (m, 2 H, aromatic), 6.95–6.86 (m, 2 H, aromatic), 5.08–4.58 (m, 6 H, CH₂-NCH₂, NCH₂CH₃), 3.96 (t, 2 H, J = 7 Hz, OCH₂), 2.27, 2.09 (2 s, 3 H, COCH₃), 1.79–1.69 (m, 2 H, OCH₂CH₂), 1.50 (t, 3 H, J = 7 Hz, CH₂CH₃), 1.49–1.26 (m, 22 H), 0.87 (t, 3 H, J = 6 Hz, CH₃); mass spectrum (FAB) *m/e* 481 (M⁺ - I). Anal. (C₃₁H₄₉N₂O₂) C, H, N, I.

N-Acetyl-*N*-(2-pyridinylmethyl)-4-(tetradecyloxy)benzamide (36a). 36a was prepared by the procedure described for 30a by the reaction of 14a, sodium hydride, and 12a. Compound 36a was isolated as a pale yellow solid (51%): mp 68–70 °C; IR (KBr) 2922, 2849, 1706, 1660 cm⁻¹; ¹H NMR (CDCl₃) δ 8.51–8.50 (m, 1 H, aromatic), 7.73–7.71 (m, 2 H, aromatic), 7.62 (td, 1 H, J = 7, 1.8 Hz, aromatic), 7.26–7.23 (m, 1 H, aromatic), 7.16–7.12 (m, 1 H, aromatic), 6.93–6.89 (m, 2 H, aromatic), 5.11 (s, 2 H, NCH₂), 3.99 (t, 2 H, J = 7 Hz, OCH₂), 2.21 (s, 3 H, COCH₃), 1.79 (quintet, 2 H, J = 8 Hz, OCH₂CH₂), 1.50–1.26 (m, 22 H), 0.88 (t, 3 H, J = 6.4 Hz, CH₃); ¹³C NMR (CDCl₃) δ 173.84, 173.32, 162.82, 156.80, 149.24, 136.47, 131.23, 127.27, 122.02, 121.41, 114.42, 68.30, 51.08, 31.88, 29.61, 29.54, 29.51, 29.30, 29.03, 25.93, 22.64, and 14.07 ppm; mass spectrum (EI) *m/e* 466 (M⁺). Anal. (C₂₆H₄₂N₂O₃) C, H, N.

2-[[Acetyl[4-(tetradecyloxy)benzoyl]amino]methyl]-1-methylpyridinium iodide (37). 37 was prepared by the procedure described for 20 by the reaction of 36a and iodoethane. Compound 37 was isolated as pale yellow crystals (100%): mp 84–88 °C; IR (KBr) 2920, 2851, 1711, 1692, 1630, 1603 cm⁻¹; ¹H NMR (CDCl₃) δ 9.41 (d, 1 H, J = 6 Hz, aromatic), 8.50–8.44 (m, 1 H, aromatic), 8.02–7.96 (m, 2 H, aromatic), 7.79–7.74 (m, 2 H, aromatic), 7.03–6.98 (m, 2 H, aromatic), 5.42 (s, 2 H, NCH₂), 4.78 (s, 3 H, NCH₃), 4.04 (t, 2 H, J = 7 Hz, OCH₂), 2.12 (s, 3 H, COCH₃), 1.81 (quintet, 2 H, J = 7 Hz, OCH₂CH₂), 1.48–1.26 (m, 22 H), 0.88 (t, 3 H, J = 7 Hz, CH₃); ¹³C NMR (CDCl₃) δ 172.74, 172.58, 164.01, 154.51, 147.14, 145.80, 131.98, 127.14, 126.76, 125.11, 115.17, 68.59, 47.71, 46.98, 31.82, 29.57, 29.50, 29.46, 29.26, 28.95, 26.09, 25.87, 22.56, and 14.01 ppm; mass spectrum (FAB) *m/e* 481 (M⁺ - I). Anal. (C₃₀H₄₅N₂O₃I) C, H, I, N: calcd, 4.60; found, 4.11.

N-Acetyl-3-(1,1-dimethylethyl)-*N*-(2-pyridinylmethyl)-4-(tetradecyloxy)benzamide *N*-Oxide (51). A solution of 36d (0.25 g, 0.48 mmol), 3-chloroperbenzoic acid (165 mg of a 50% by weight solid, 0.48 mmol), and glacial acetic acid (2 mL) was heated at 50 °C for 18 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (100 mL) and extracted with chloroform (4 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified on silica gel (50 g, elution with 90% EtOAc/hexane) to give 51 as a pale yellow oil, 0.102 g (39%): IR (neat) 2924, 2854, 1696, 1599 cm⁻¹; ¹H NMR (CDCl₃) δ 8.30–8.28 (m, 1 H, aromatic), 7.67–7.54 (m, 2 H, aromatic), 7.45–7.40 (m, 1 H, aromatic), 7.30–7.20 (m, 2 H, aromatic), 6.90–6.86 (m, 1 H, aromatic), 5.11 (s, 2 H, NCH₂), 4.05 (t, 2 H, J = 7 Hz, OCH₂), 2.29 (s, 3 H, COCH₃), 1.86 (quintet, 2 H, J = 7 Hz, OCH₂CH₂), 1.37 (s, 9 H, C(CH₃)₃), 1.53–1.26 (m, 22 H), 0.88 (t, 3 H, J = 7 Hz, CH₃); mass spectrum (FAB) *m/e* 539 (M⁺ + H). Anal. (C₃₃H₅₀N₂O₄·1.0H₂O) C, H, N: calcd, 5.03; found, 4.52.

3-(1,1-Dimethylethyl)-4-[[[(1,1-dimethylethyl)dimethylsilyloxy]benzoic Acid (1,1-Dimethylethyl)dimethylsilyl Ester (54). To a 0 °C solution of 53 (8.0 g, 41.2 mmol), commercially available or prepared by hydrolysis of 52 according to the procedure described earlier,⁹ dry methylene chloride (50 mL), dry DMF (3 mL), DMAP (252 mg, 2.1 mmol), and triethylamine (28.7 mL, 206 mmol) was added a solution of *tert*-butyldimethylsilyl chloride (TBDMS-Cl, 13.04 g, 86.5 mmol) dissolved in dry methylene chloride (50 mL). The cooling bath was removed, and the reaction mixture was stirred at room temperature for 18 h and then at reflux temperature for 18 h. The cooled reaction mixture was diluted with half-saturated aqueous sodium bicarbonate (200 mL) and extracted with methylene chloride (3 × 50 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified on silica gel (250 g, elution

with 5% EtOAc/hexane) to give 54 as colorless crystals, 10.0 g (57%): mp 74–75 °C; IR (KBr) 1694, 1601 cm⁻¹; ¹H NMR (CDCl₃) δ 8.04 (d, 1 H, J = 2.2 Hz, aromatic), 7.78 (dd, 1 H, J = 8, 2.2 Hz, aromatic), 6.83 (d, 1 H, J = 8 Hz, aromatic), 1.39 (s, 9 H, C(CH₃)₃), 1.04 (s, 9 H, SiC(CH₃)₃), 1.02 (s, 9 H, SiC(CH₃)₃), 0.356 (s, 6 H, Si(CH₃)₂), 0.355 (s, 6 H, Si(CH₃)₂); ¹³C NMR (CDCl₃) δ 166.74, 158.89, 139.35, 129.79, 129.34, 123.36, 118.41, 34.78, 29.57, 26.25, 25.67, 18.78, 17.77, -3.52, and -4.75 ppm; mass spectrum (EI) *m/e* 365 (M⁺ - *t*-Bu). Anal. (C₂₃H₄₂O₃Si₂) C, H.

3-(1,1-Dimethylethyl)-4-[[[(1,1-dimethylethyl)dimethylsilyloxy]benzoyl Chloride (55). To a 0 °C solution of 54 (9.1 g, 21.5 mmol) and dry DMF (10 drops) in dry methylene chloride (75 mL) was added oxalyl chloride (2.44 mL, 28 mmol) dropwise. The reaction mixture was warmed to room temperature and maintained there for 18 h. Following concentration of the volatiles in vacuo, the residue was dissolved in dry ether (200 mL) and filtered through a pad of Celite, and the filtrate was concentrated, providing 55 as pale cream-colored crystals, 7.0 g (100%): mp 43–44 °C; IR (KBr) 2930, 1753, 1682, 1598 cm⁻¹; ¹H NMR (CDCl₃) δ 8.05 (d, 1 H, J = 2.3 Hz, aromatic), 7.91 (dd, 1 H, J = 8.6, 2.3 Hz, aromatic), 6.87 (d, 1 H, J = 8.6 Hz, aromatic), 1.40 (s, 9 H, C(CH₃)₃), 1.05 (s, 9 H, SiC(CH₃)₃), 0.38 (s, 6 H, Si(CH₃)₂); ¹³C NMR (CDCl₃) δ 167.51, 161.28, 140.33, 131.76, 131.18, 124.91, 118.92, 34.92, 29.43, 26.18, 18.80, and -3.53 ppm; mass spectrum (EI) *m/e* 326 (M⁺), 269 (M⁺ - *t*-Bu). Anal. (C₁₇H₂₇O₂SiCl) H, Si, C: calcd, 62.45; found, 63.22; Cl: calcd, 10.84; found, 9.60.

N-Acetyl-3-(1,1-dimethylethyl)-4-[[[(1,1-dimethylethyl)dimethylsilyloxy]-*N*-(2-pyridinylmethyl)benzamide (56). 56 was prepared by the procedure described for 30a by the reaction of 14a, sodium hydride, 55, and the addition of 0.2 equiv of HMPA. Compound 56 was isolated as a yellow oil (46%): IR (neat) 2957, 1701, 1663, 1597 cm⁻¹; ¹H NMR (CDCl₃) δ 8.52–8.50 (m, 1 H, aromatic), 7.70 (d, 1 H, J = 2.4 Hz, aromatic), 7.63 (td, 1 H, J = 7.7, 1.8 Hz, aromatic), 7.51 (dd, 1 H, J = 8.5, 2.4 Hz, aromatic), 7.24 (d, 1 H, J = 7.7 Hz, aromatic), 7.16–7.12 (m, 1 H, aromatic), 6.82 (d, 1 H, J = 8.5 Hz, aromatic), 5.10 (s, 2 H, NCH₂), 2.24 (s, 3 H, COCH₃), 1.32 (s, 9 H, C(CH₃)₃), 1.03 (s, 9 H, SiC(CH₃)₃), 0.35 (s, 6 H, Si(CH₃)₂); ¹³C NMR (CDCl₃) δ 174.35, 173.48, 158.83, 156.91, 149.30, 140.01, 136.49, 128.82, 128.56, 126.88, 121.99, 121.30, 118.72, 51.23, 34.84, 29.49, 26.20, 25.95, 18.76, and -3.53 ppm; mass spectrum (EI) *m/e* 440 (M⁺). Anal. (C₂₅H₃₆N₂O₃Si) C, H, N, Si.

N-Acetyl-3-(1,1-dimethylethyl)-4-hydroxy-*N*-(2-pyridinylmethyl)benzamide (57). To a 0 °C solution of 56 (13.52 g, 30.7 mmol) dissolved in dry THF (50 mL) was added tetrabutylammonium fluoride (TBAF, 46 mL of a 1 M THF solution, 46 mmol). The reaction mixture was stirred at 0 °C for 15 min and at room temperature for 3 h, diluted with water (500 mL), and extracted with methylene chloride (4 × 500 mL). The combined organic phases were washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo, and purified on silica gel (600 g, gradient elution with 40–60% EtOAc/hexane), to provide 57 as colorless crystals, 8.10 g (81%): mp 150–151 °C; IR (neat) 1693, 1598 cm⁻¹; ¹H NMR (CDCl₃) δ 9.05 (br, 1 H, OH), 8.51–8.49 (m, 1 H, aromatic), 7.73 (td, 1 H, J = 7.7, 1.5 Hz, aromatic), 7.56 (d, 1 H, J = 2.1 Hz, aromatic), 7.35–7.21 (m, 3 H, aromatic), 6.44 (d, 1 H, J = 8.3 Hz, aromatic), 5.13 (s, 2 H, NCH₂), 2.31 (s, 3 H, COCH₃), 1.32 (s, 9 H, C(CH₃)₃); ¹³C NMR (CDCl₃) δ 174.45, 173.74, 160.75, 156.72, 148.41, 137.57, 137.01, 128.89, 128.86, 124.55, 122.55, 121.88, 116.15, 51.03, 34.70, 29.13, and 25.50 ppm; mass spectrum (EI) *m/e* 326 (M⁺). Anal. (C₁₉H₂₂N₂O₃) C, H, N.

4-[[Acetyl(2-pyridinylmethyl)amino]carbonyl]-2-(1,1-dimethylethyl)phenyl Octadecylcarbamate (58). To a solution of phenol 57 (2.0 g, 6.13 mmol), freshly distilled octadecyl isocyanate (2.14 mL, 6.13 mmol), and dry THF (30 mL) was added triethylamine (0.85 mL, 6.13 mmol). The reaction mixture was stirred at room temperature for 22 h, diluted with saturated aqueous sodium bicarbonate (100 mL), and extracted with methylene chloride (3 × 50 mL). The combined methylene chloride layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated in vacuo. The residue was purified on silica gel (250 g, elution with 50% EtOAc/hexane) to provide 58 as a colorless oil, 3.36 g (88%): IR (neat) 2923, 2853, 1748, 1704, 1665, 1593 cm⁻¹; ¹H NMR (CDCl₃) δ 8.52–8.50 (m, 1 H, aromatic), 7.75

(d, 1 H, $J = 2$ Hz, aromatic), 7.65–7.58 (m, 2 H, aromatic), 7.21–7.11 (m, 3 H, aromatic), 5.08 (s, 2 H, NCH_2), 3.32–3.26 (m, 2 H, NHCH_2), 2.30 (s, 3 H, COCH_3), 1.60–1.50 (m, 2 H, NCH_2CH_2), 1.30 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 1.35–1.26 (m, 30 H), 0.88 (t, 3 H, $J = 7$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 174.00, 173.57, 156.48, 153.72, 152.82, 149.31, 141.96, 136.47, 131.98, 128.05, 127.43, 124.44, 122.06, 121.40, 50.96, 41.39, 34.74, 31.91, 29.98, 29.86, 29.68, 29.55, 29.34, 29.22, 26.68, 26.25, 22.67, and 14.11 ppm; mass spectrum (EI) m/e 326 ($\text{M}^+ - \text{C}_{18}\text{H}_{37}\text{NO}$). Anal. ($\text{C}_{38}\text{H}_{59}\text{N}_3\text{O}_4$) C, H, N.

2-[[Acetyl[3-(1,1-dimethylethyl)-4-[[octadecylamino]carbonyloxy]benzoyl]amino]methyl]-1-methylpyridinium Iodide (59). 59 was prepared by the procedure described for 20 by the reaction of 58 and iodoethane. Compound 59 was isolated as pale yellow crystals (100%): mp (softens/dec) 110–130 °C; IR (KBr) 2922, 2851, 1723, 1667, 1631 cm^{-1} ; ^1H NMR (d_6 -DMSO/TFA) δ 9.02 (d, 1 H, $J = 5.6$ Hz, aromatic), 8.55 (td, 1 H, $J = 8, 1.2$ Hz, aromatic), 8.05–7.94 (m, 2 H, aromatic), 7.70–7.65 (m, 1 H, aromatic), 7.12–7.16 (m, 2 H, aromatic), 5.34 (s, 2 H, NCH_2), 4.34 (s, 3 H, NCH_3), 3.40–3.06 (m, 2 H, NCH_2), 2.17 (s, 3 H, COCH_3), 1.53–1.44 (m, 2 H, NCH_2CH_2), 1.33 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 1.37–1.24 (m, 30 H), 0.85 (t, 3 H, $J = 6.7$ Hz, CH_3); mass spectrum (FAB) m/e 636 ($\text{M}^+ - \text{I}$). Anal. ($\text{C}_{39}\text{H}_{62}\text{N}_3\text{O}_4\text{I}$) C, H, N, I.

N-[3-Methoxy-4-(tetradecyloxy)benzoyl]-4-pyridinecarboxamide (61a). To a room temperature slurry of NaH (0.864 g of a 50% oil dispersion, 18 mmol) in dry THF (10 mL) was added 60a (1.0 g, 8.2 mmol) in one portion. HMPA (1.4 mL, 8.2 mmol) was added to the reaction mixture after a 30-min period. After an additional stirring period of 30 min, acid chloride 12b (3.14 g, 8.2 mmol) dissolved in dry THF (10 mL) was added. The reaction mixture was stirred at room temperature for 1.5 h, poured into saturated aqueous ammonium chloride (200 mL), and extracted with methylene chloride (3 \times 100 mL). The combined organic phases were washed with brine (75 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo, and purified on silica gel (250 g, elution with 90% EtOAc/hexane) to provide 61a as a colorless solid, 2.73 g (71%): mp 116–117 °C; IR (KBr) 2922, 2853, 1727, 1681, 1599 cm^{-1} ; ^1H NMR (CDCl_3) δ 9.11 (s, 1 H, NH), 8.80 (d, 2 H, $J = 5.5$ Hz, aromatic), 7.62–7.60 (m, 2 H, aromatic), 7.46–7.43 (m, 2 H, aromatic), 6.91 (d, 1 H, $J = 8.6$ Hz, aromatic), 4.08 (t, 2 H, $J = 7$ Hz, OCH_2), 3.91 (s, 3 H, OCH_3), 1.88 (quintet, 2 H, $J = 7$ Hz, OCH_2CH_2), 1.49–1.26 (m, 22 H), 0.88 (t, 3 H, $J = 6.5$ Hz, CH_2CH_3); ^{13}C NMR (CDCl_3) δ 167.39, 165.44, 153.37, 150.36, 149.49, 141.33, 124.21, 121.60, 121.38, 111.56, 111.29, 69.16, 56.10, 31.86, 29.60, 29.54, 29.49, 29.30, 28.88, 25.85, 22.63, and 14.07 ppm; mass spectrum (EI) m/e 468 (M^+). Anal. ($\text{C}_{28}\text{H}_{40}\text{N}_2\text{O}_4$) C, H, N.

4-[[[3-Methoxy-4-(tetradecyloxy)benzoyl]amino]carbonyl]-1-propylpyridinium Iodide (62). A solution of 61a (0.75 g, 1.6 mmol) and 1-iodopropane (5.5 mL, 56 mmol) was heated at 90–95 °C for 4.5 h and then maintained at room temperature for 18 h. The unreacted 1-iodopropane was removed in vacuo, and the residue was recrystallized from methanol to give 62 as orange-colored crystals, 1.02 g (100%): mp (softens/dec) 68–88 °C; IR (KBr) 2921, 2851, 1735, 1678, 1599 cm^{-1} ; ^1H NMR (d_6 -DMSO/TFA) δ 9.27 (d, 2 H, $J = 6.7$ Hz, aromatic), 8.41 (d, 2 H, $J = 6.7$ Hz, aromatic), 7.69 (dd, 1 H, $J = 8.5, 2.1$ Hz, aromatic), 7.60 (d, 2 H, $J = 2.1$ Hz, aromatic), 7.10 (d, 1 H, $J = 8.6$ Hz, aromatic), 4.67 (t, 2 H, $J = 7$ Hz, NCH_2), 4.08 (t, 2 H, $J = 7$ Hz, OCH_2), 3.86 (s, 3 H, OCH_3), 2.02 (hexet, 2 H, $J = 7$ Hz, NCH_2CH_2), 1.77 (quintet, 2 H, $J = 7$ Hz, OCH_2CH_2), 1.46–1.26 (m, 22 H), 0.95 (t, 3 H, $J = 7.3$ Hz, $\text{NCH}_2\text{CH}_2\text{CH}_3$), 0.87 (t, 3 H, $J = 6.7$ Hz, CH_2CH_3); mass spectrum (FAB) m/e 511 ($\text{M}^+ - \text{I}$). Anal. ($\text{C}_{31}\text{H}_{47}\text{N}_2\text{O}_4\text{I}$) C, H, N; I: calcd, 19.87; found, 18.81.

Phenyl [4-(Tetradecyloxy)phenyl]methyl Carbonate (64). To a 0 °C slurry of benzyl alcohol 16b (9.0 g, 28 mmol), pyridine (4.5 mL, 56 mmol), and dry methylene chloride (70 mL) was added phenyl chloroformate (4.2 mL, 33.7 mmol) by syringe. The reaction mixture was stirred at 0 °C for 15 min and room temperature for 30 min, prior to dilution with saturated aqueous sodium bicarbonate (200 mL). The aqueous phase was extracted with methylene chloride (4 \times 100 mL); the combined organic phases were washed with brine (200 mL), dried over anhydrous magnesium sulfate, filtered, concentrated in vacuo, and purified on silica gel (250 g, gradient elution with 0–5% EtOAc/hexane) to give 64 as colorless prisms, 12.4 g (100%): mp 34–35 °C; IR

(KBr) 2917, 2849, 1758 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.40–7.35 (m, 4 H, aromatic), 7.26–7.15 (m, 3 H, aromatic), 6.92–6.89 (m, 2 H, aromatic), 5.20 (s, 2 H, CO_2CH_2), 3.96 (t, 2 H, $J = 6.5$ Hz, OCH_2), 1.79 (quintet, 2 H, $J = 7$ Hz, OCH_2CH_2), 1.46–1.26 (m, 22 H), 0.88 (t, 3 H, $J = 6.6$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 159.61, 153.66, 151.11, 130.50, 129.39, 126.60, 125.93, 121.01, 114.54, 70.27, 68.02, 31.90, 29.64, 29.58, 29.37, 29.35, 29.20, 26.01, 22.68, and 14.11 ppm; mass spectrum (EI) m/e 440 (M^+). Anal. ($\text{C}_{28}\text{H}_{40}\text{O}_4$) C, H.

[4-(Tetradecyloxy)phenyl]methyl (2-Pyridinylmethyl)-carbamate (65). A mixture of carbonate 64 (3.0 g, 6.8 mmol) and 13a (1.1 g, 10.2 mmol) was heated at 100 °C for 80 min. The crude reaction mixture was purified on silica gel (250 g, elution with 50% EtOAc/hexane) to give 65 as colorless crystals, 2.99 g (96%): mp 67–68 °C; IR (KBr) 3336, 2917, 2850, 1690 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.53 (d, 1 H, $J = 4$ Hz, aromatic), 7.68–7.63 (m, 1 H, aromatic), 7.31–7.16 (m, 4 H, aromatic), 6.87 (d, 2 H, $J = 8.5$ Hz, aromatic), 5.79 (br s, 1 H, NH), 5.07 (s, 2 H, CO_2CH_2), 4.51 (d, 2 H, $J = 5$ Hz, NCH_2), 3.94 (t, 2 H, $J = 6.5$ Hz, OCH_2), 1.82–1.72 (m, 2 H, OCH_2CH_2), 1.46–1.26 (m, 22 H), 0.88 (t, 3 H, $J = 6.5$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 159.08, 156.88, 156.70, 149.05, 136.69, 129.93, 128.31, 122.27, 121.67, 114.40, 67.98, 66.69, 45.99, 31.89, 29.64, 29.57, 29.36, 29.33, 29.20, 25.99, 22.67, and 14.10 ppm; mass spectrum (EI) m/e 454 (M^+). Anal. ($\text{C}_{29}\text{H}_{42}\text{N}_2\text{O}_3$) C, H, N.

1-Ethyl-2-[[[[4-(tetradecyloxy)phenyl]methoxy]carbonyl]amino]methyl]pyridinium Salt with Trifluoromethanesulfonic Acid (1:1) (66). A solution of carbamate 65 (1.0 g, 2.2 mmol), ethyl trifluoromethanesulfonate (EtOTf, 0.31 mL, 2.4 mmol), and dry toluene (3 mL) was heated at 65–70 °C for 12 h. The cooled reaction mixture was concentrated in vacuo and purified on silica gel (70 g, elution with 50% EtOAc/hexane) followed by MeOH) to give 66 as a gummy solid, 0.255 g (18%): IR (neat) 2918, 2850, 1711, 1674, 1631, 1615, 1584 cm^{-1} ; ^1H NMR (d_6 -DMSO/TFA) δ 9.07 (d, 1 H, $J = 5.6$ Hz, aromatic), 8.73–8.55 (m, 1 H, aromatic), 8.09–8.00 (m, 2 H, aromatic), 7.32–7.29 (m, 2 H, aromatic), 6.94–6.91 (m, 2 H, aromatic), 5.02 (s, 2 H, CO_2CH_2), 4.71–4.61 (m, 4 H, NCH_2 , NHCH_2), 3.95 (t, 2 H, $J = 6.4$ Hz, OCH_2), 1.71 (quintet, 2 H, $J = 7$ Hz, OCH_2CH_2), 1.52 (t, 3 H, $J = 7$ Hz, NCH_2CH_3), 1.46–1.26 (m, 22 H), 0.86 (t, 3 H, $J = 6.6$ Hz, CH_3); mass spectrum (FAB) m/e 483 ($\text{M}^+ - \text{OTf}$). Anal. ($\text{C}_{31}\text{H}_{47}\text{N}_2\text{O}_6\text{SF}_3$) C, H, N, S, F.

[4-(Tetradecyloxy)phenyl]methyl Acetyl(2-pyridinylmethyl)carbamate (67). A mixture of carbamate 65 (3.0 g, 6.6 mmol), acetic anhydride (12.5 mL, 132 mmol), DMAP (80 mg, 0.66 mmol), triethylamine (4.6 mL, 33 mmol), and dry methylene chloride (25 mL) was heated at 100 °C for 54 h in a sealed glass vessel. The crude reaction mixture was shaken with saturated aqueous sodium bicarbonate (100 mL); the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified on silica gel (150 g, elution with 20% EtOAc/hexane) to give 67 as colorless crystals, 1.42 g (43%): mp 52–53 °C; IR (KBr) 2919, 2850, 1738, 1698, 1614 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.50–8.49 (m, 1 H, aromatic), 7.56 (td, 1 H, $J = 7.7, 1.8$ Hz, aromatic), 7.15–7.02 (m, 4 H, aromatic), 6.81–6.77 (m, 2 H, aromatic), 5.09, 5.08 (2 s, 4 H, $\text{NCH}_2 + \text{OCH}_2$), 3.92 (t, 2 H, $J = 6.6$ Hz, OCH_2), 2.61 (s, 3 H, COCH_3), 1.77 (quintet, 2 H, $J = 7$ Hz, OCH_2CH_2), 1.46–1.26 (m, 22 H), 0.88 (t, 3 H, $J = 6.7$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 172.97, 159.29, 156.94, 154.47, 149.21, 136.34, 129.93, 126.75, 121.83, 120.41, 114.35, 68.43, 67.98, 48.48, 31.88, 29.63, 29.57, 29.35, 29.18, 26.57, 25.99, 22.66, and 14.09 ppm; mass spectrum (EI) m/e 320 ($\text{M}^+ - \text{C}_9\text{H}_9\text{N}_2\text{O}_2$). Anal. ($\text{C}_{30}\text{H}_{44}\text{N}_2\text{O}_4$) C, H, N.

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