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

Michael P. Trova,* Allan Wissner, Marion L. Carroll, Suresh S. Kerwar, Walter C. Pickett, Robert E. Schaub, Lawrence W. Torley, and Constance A. Kohler

Oncology and Immunology Section, Medical Research Division, American Cyanamid Company, Lederle Laboratories, Pearl River, New York 10965

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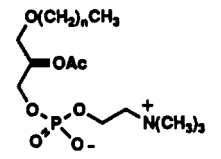
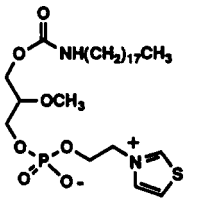
A series of platelet activating factor (PAF) antagonists containing a quaternary pyridinium ring connected through an amide, imide, or carbamate linkage to a substituted aromatic ring was prepared. Of these compounds, those containing a branched imide linkage of the form (CON(COCH$_3$)CH$_2$, **37–51**, 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 (IC$_{50}$ <0.1 μM) provide excellent protection against an LD$_{97}$ 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]

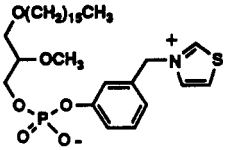
Terashita et al.[6] reported the first PAF antagonist CV-3988 (**2**) in 1983. In our earlier antagonist work, we combined some structural features present in CV-3988 with other features that we uncovered in our earlier SAR studies on PAF analogues.[7] This resulted in the synthesis of compounds such 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)



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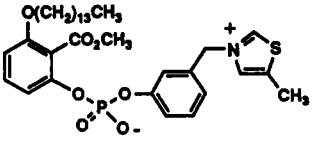

CL 184,005 (4)

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 **7**[10] and Nakamura on antagonists **8** and **9**,[11] describe antagonists that all contain the group OCON(COCH$_3$)CH$_2$(2-pyridinium). Apparently, this particular structural feature is consistent with potent PAF antagonism; CV-6209 is among the most potent antagonists

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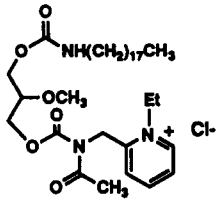
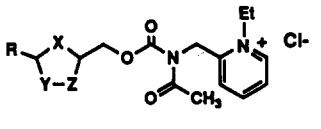
known. Additionally, Terashita et al. has disclosed TCV-309 (10),[12] wherein a 3-pyridinium group is connected through the carbonyl carbon atom of an amide to the rest of the molecule. These literature observations prompted our own investigation into antagonists having these important structural components, 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.

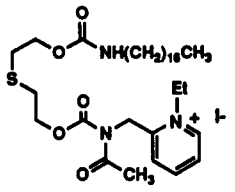


CV-6209 (5)



6

X, Y, Z = O, CH_2
R = Alkyl, O-Alkyl, etc.



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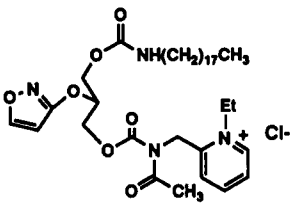
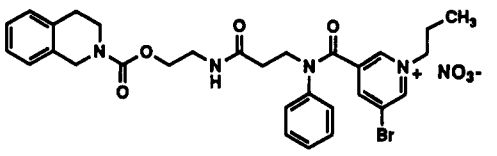


R-75319 (R) (8)
R-75828 (S) (9)



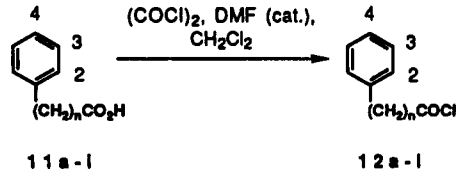
TCV-309 (10)

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 known[9] esters **15a** or **15b** or the known[9] 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.

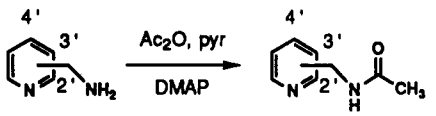
Amide compounds **20–23** were prepared as described in Scheme II. Acid chlorides **12a** and **12i** were allowed to react with 2-(aminoalkyl)pyridines **13a** or **18** in the presence of pyridine in methylene chloride solution to provide amides **19a–d**. The quaternary salts of amides **19a–d** were 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

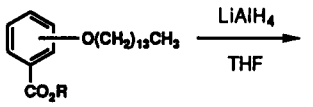


11a-l **12a-l**

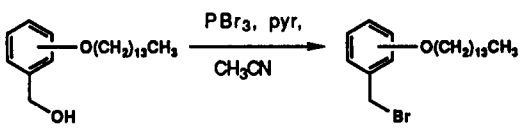
Entry	2	3	4	n
a	H	H	$O(CH_2)_{13}CH_3$	0
b	H	OCH_3	$O(CH_2)_{13}CH_3$	0
c	H	$O(CH_2)_{13}CH_3$	$O(CH_2)_{13}CH_3$	0
d	H	$C(CH_3)_3$	$O(CH_2)_{13}CH_3$	0
e	H	$C(CH_3)_3$	$O(CH_2)_9CH_3$	0
f	H	$O(CH_2)_{13}CH_3$	OCH_3	0
g	H	$O(CH_2)_{13}CH_3$	H	0
h	H	$O(CH_2)_6CH_3$	$O(CH_2)_6CH_3$	0
i	H	H	$O(CH_2)_{13}CH_3$	1



13a 2' **13b** 3' **13c** 4' **14a** 2' **14b** 3' **14c** 4'



15a *ortho*; R = CH_3
15b *para*; R = CH_3
11g *meta*; R = H

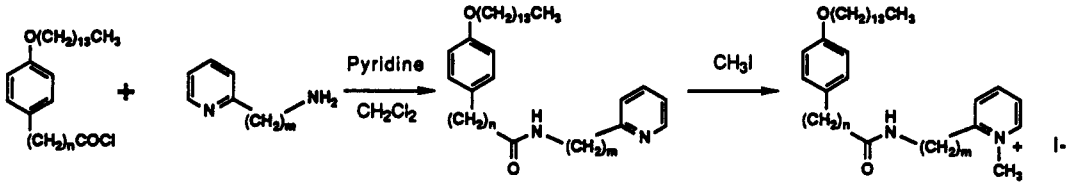


16a *ortho* **17a** *ortho*
16b *para* **17b** *para*
16c *meta* **17c** *meta*

The synthesis of compounds in which the linkage is reversed with respect to amide compounds **20–23** is described in Scheme III. Benzylamine **24**[9] 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.

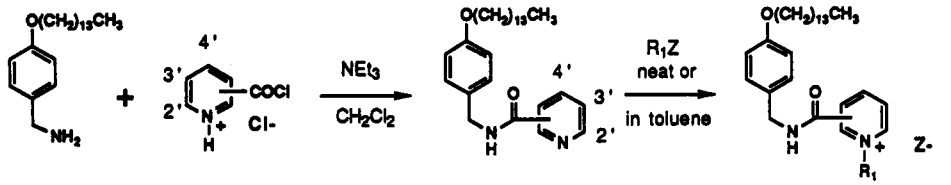
A series of amide containing antagonists was prepared

Scheme II



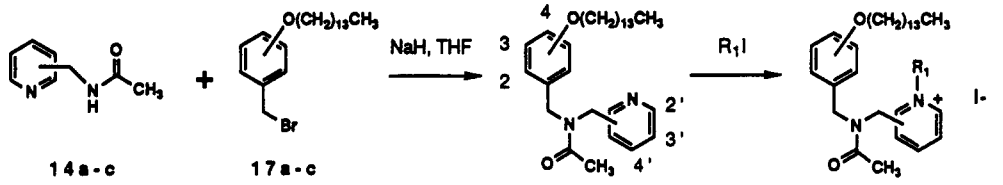
12a,l 13a 18 m = 2 19a n = 0; m = 1 19b n = 0; m = 2 19c n = 1; m = 1 19d n = 1; m = 2 20-23

Scheme III



24 25a 2' 25b 3' 25c 4' 26a 2' 26b 3' 26c 4' 27-29

Scheme IV



14a-c 17a-c

30a 4-O(CH2)13CH3; 2'-pyridyl
30b 4-O(CH2)13CH3; 3'-pyridyl
30c 4-O(CH2)13CH3; 4'-pyridyl
30d 3-O(CH2)13CH3; 2'-pyridyl
30e 2-O(CH2)13CH3; 2'-pyridyl

31-35

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 ^{13}C 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 disilyl **54** with oxalyl chloride[13] 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.

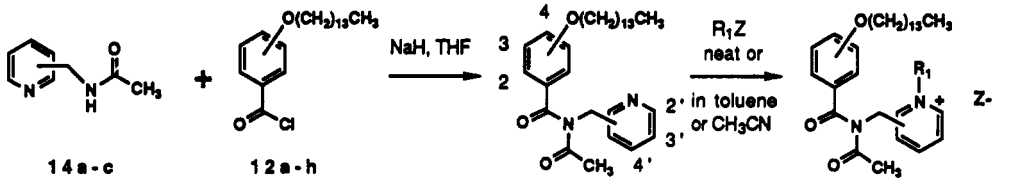
The synthesis of compounds **62** and **63**, in which an unbranched imide linkage connects the two aromatic rings, is described in Scheme VII. Commercially available isonicotinamide (**60a**) or nicotinamide (**60b**) were allowed to react with sodium hydride in THF/hexamethylphosphoramide (HMPA) solution 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

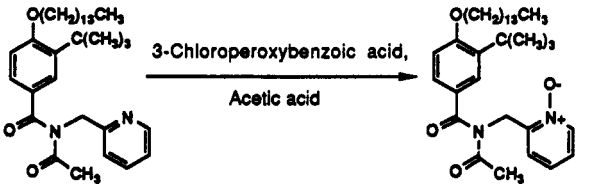
The compounds were evaluated for their PAF antagonist properties both in vitro and in vivo. In one assay, we examined their ability to inhibit PAF-induced platelet aggregation in rabbit platelet rich plasma (PRP). The data are expressed as a molar IC_{50}, the concentration of antagonist needed to inhibit 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. 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



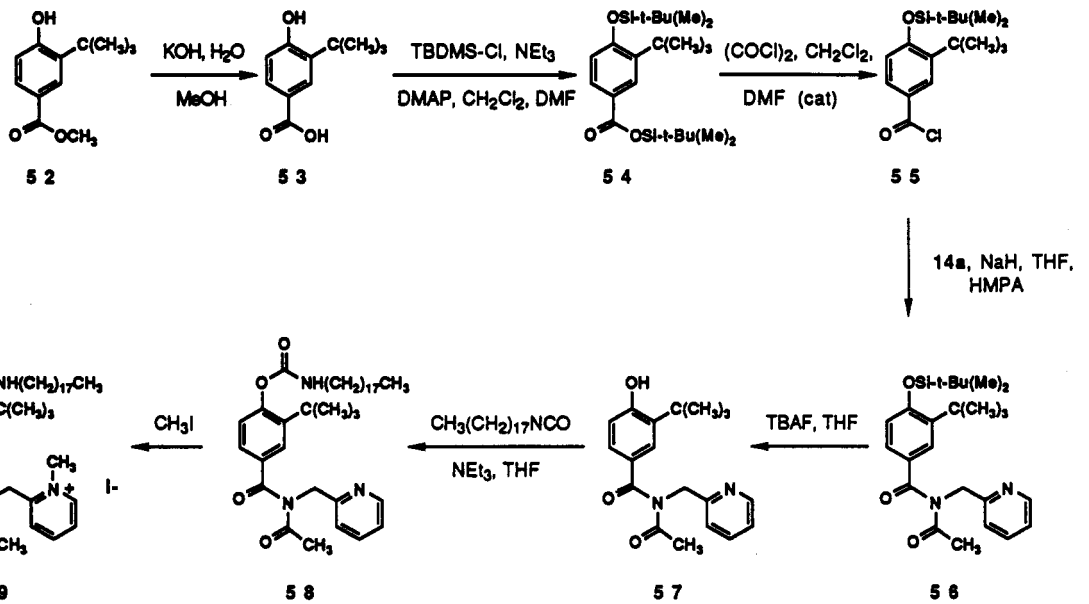
14a-c 12a-h 36a-k 37-50

Entry	Aromatic Substitution 3	4	Pyridyl Position
36a	H	$O(CH_2)_{13}CH_3$	2'
36b	$O(CH_2)_{13}CH_3$	H	2'
36c	H	$O(CH_2)_{13}CH_3$	3'
36d	$C(CH_3)_3$	$O(CH_2)_{13}CH_3$	2'
36e	$C(CH_3)_3$	$O(CH_2)_9CH_3$	2'
36f	$C(CH_3)_3$	$O(CH_2)_{13}CH_3$	3'
36g	$C(CH_3)_3$	$O(CH_2)_{13}CH_3$	4'
36h	OCH_3	$O(CH_2)_{13}CH_3$	2'
36i	$O(CH_2)_{13}CH_3$	OCH_3	2'
36j	$O(CH_2)_{13}CH_3$	$O(CH_2)_{13}CH_3$	2'
36k	$O(CH_2)_6CH_3$	$O(CH_2)_6CH_3$	2'



36d 51

Scheme VI[a]



52 53 54 55 56 57 58 59

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

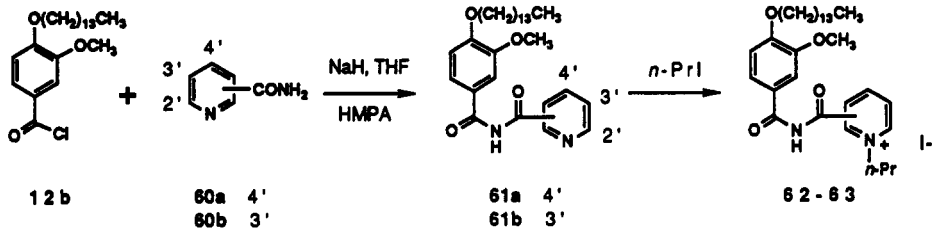
For comparative purposes, we have included data generated in our laboratory for a number of antagonists reported in the literature (see Table I). For comparisons of our IC_{50} values with those in the literature to be meaningful, it is important to note the PAF challenge concentrations used, the species of platelets, and whether washed platelets or, as is the case in this study, PRP was used. We have generally found that the IC_{50} 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

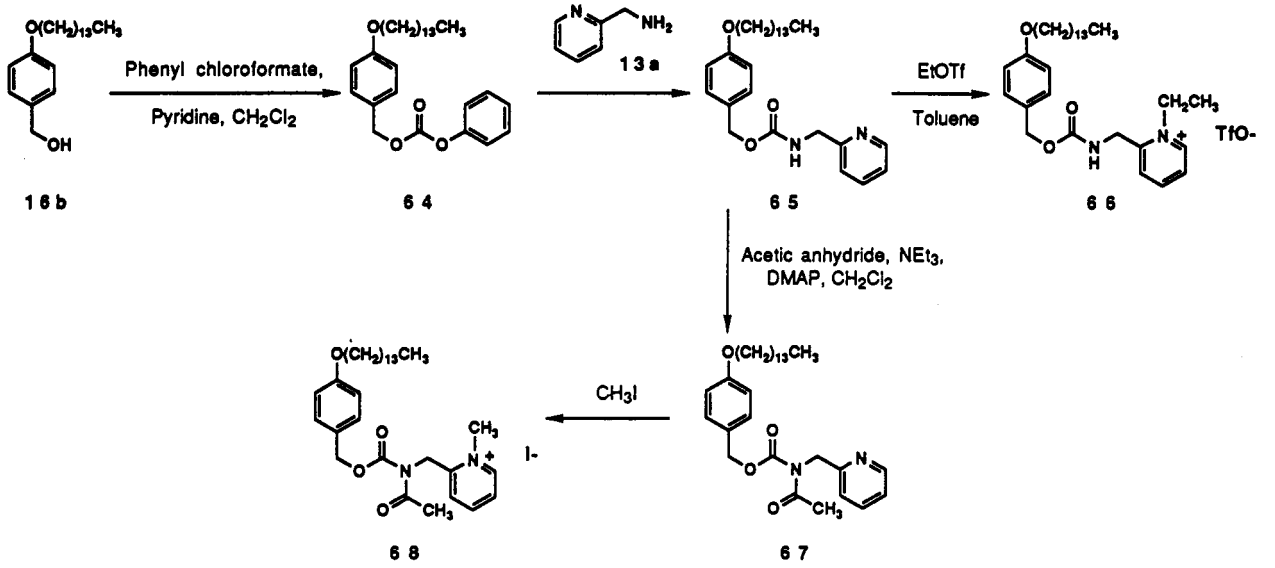
As evident from the in vitro PAF antagonist data presented in Table II, a number of trends in the activity of our compounds are apparent. Because of results gleaned in our earlier PAF antagonist studies,[7,9] we spent little time examining the SAR of the lipophilic side chain. For most of the antagonists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

Scheme VII



12b 60a 4' 60b 3' 61a 4' 61b 3' 62-63

Scheme VIII



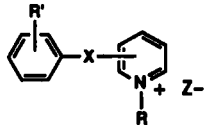
16b 64 65 66 67 68

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^{-8} M; the value in parentheses is the number of determinations. For $n = 2$, the range of IC_{50} 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

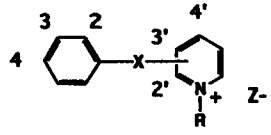
Of major significance to activity is variation of the X group. We found that a simple unbranched amide linkage between the two aromatic rings was not consistent with good PAF antagonism. For example, compounds **20–23** and **27–29** are essentially devoid of activity, independent of the orientation of the amide group ($CONHCH_2$ vs CH_2NHCO) 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 ($CH_2N(COCH_3)CH_2$) 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 $4\text{-}O(CH_2)_{13}CH_3$ 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 ($CON(COCH_3)CH_2$) 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 2	3	4	X	pyridine subst	R	Z	inhibition of platelet agg, IC_{50} (μM)[a]	n[a]	formula[b]	anal.[c]
20	H	H	$O(CH_2)_{13}CH_3$	$CONH(CH_2)$	2′	methyl	I	>10	2	$C_{28}H_{43}N_2O_2I$	C,H,N,I
21	H	H	$O(CH_2)_{13}CH_3$	$CONH(CH_2)_2$	2′	methyl	I	>10	1	$C_{29}H_{45}N_2O_2I$	C,H,N,I
22	H	H	$O(CH_2)_{13}CH_3$	$(CH_2)CONH(CH_2)$	2′	methyl	I	>10	1	$C_{29}H_{45}N_2O_2I$	C,H,N,I
23	H	H	$O(CH_2)_{13}CH_3$	$(CH_2)CONH(CH_2)_2$	2′	methyl	I	15	1	$C_{30}H_{47}N_2O_2I$ (0.25H_2O)	C,H,N,I
27	H	H	$O(CH_2)_{13}CH_3$	$(CH_2)NHCO$	2′	ethyl	OTf	>10	1	$C_{30}H_{45}N_2O_5SF_3$[d]	C,H,N,F,S
28	H	H	$O(CH_2)_{13}CH_3$	$(CH_2)NHCO$	3′	methyl	I	120	1	$C_{28}H_{43}N_2O_2I$	H,N; C[e], I[f]
29	H	H	$O(CH_2)_{13}CH_3$	$(CH_2)NHCO$	4′	methyl	I	60	1	$C_{28}H_{43}N_2O_2I$	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	$C_{31}H_{49}N_2O_2I$	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	$C_{30}H_{47}N_2O_2I$ (0.75H_2O)	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	$C_{30}H_{47}N_2O_2I$ (0.50H_2O)	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	$C_{30}H_{47}N_2O_2I$ (0.25H_2O)	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	$C_{30}H_{47}N_2O_2I$	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]	$C_{30}H_{45}N_2O_3I$	C,H,I; N[i]
38	H	$O(CH_2)_{13}CH_3$	H	$CON(COCH_3)CH_2$	2′	methyl	I	>10	2	$C_{30}H_{45}N_2O_3I$	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	$C_{30}H_{45}N_2O_3I$	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	$C_{34}H_{53}N_2O_3I$ (0.20H_2O)	C,H,N,I
41	H	$C(CH_3)_3$	$O(CH_2)_9CH_3$	$CON(COCH_3)CH_2$	2′	methyl	I	>10	1	$C_{30}H_{45}N_2O_3I$ (0.25H_2O)	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	$C_{34}H_{53}N_2O_3I$	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	$C_{34}H_{53}N_2O_3I$ (0.25H_2O)	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	$C_{31}H_{47}N_2O_4I$	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	$C_{32}H_{49}N_2O_4I$ (0.50H_2O)	C,H,N; I[m]
46	H	OCH_3	$O(CH_2)_{13}CH_3$	$CON(COCH_3)CH_2$	2′	*n*-propyl	OTf	0.10	1	$C_{34}H_{51}N_2O_7SF_3$	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	$C_{31}H_{47}N_2O_4I$	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	$C_{44}H_{73}N_2O_4I$ (0.50H_2O)	C,H,N,I
49	H	$O(CH_2)_6CH_3$	$O(CH_2)_6CH_3$	$CON(COCH_3)CH_2$	2′	methyl	I	3.7	1	$C_{30}H_{45}N_2O_4I$	C,H,N; I[n]
50	H	H	$O(CH_2)_{13}CH_3$	$CON(COCH_3)CH_2$	2′	benzyl	Br	330	1	$C_{36}H_{49}N_2O_3Br$	C,H,N,Br
51	H	$C(CH_3)_3$	$O(CH_2)_{13}CH_3$	$CON(COCH_3)CH_2$	2′	oxygen		>10	1	$C_{33}H_{50}N_2O_4$ (1.0H_2O)	C,H; N[o]
59	H	$C(CH_3)_3$	$OCONHC_{18}H_{37}$	$CON(COCH_3)CH_2$	2′	methyl	I	>10	2	$C_{39}H_{62}N_3O_4I$	C,H,N,I
62	H	OCH_3	$O(CH_2)_{13}CH_3$	CONHCO	4′	*n*-propyl	I	>10	1	$C_{31}H_{47}N_2O_4I$	C,H,N; I[p]
63	H	OCH_3	$O(CH_2)_{13}CH_3$	CONHCO	3′	*n*-propyl	I	>10	1	$C_{31}H_{47}N_2O_4I$	H,N; C[q], I[r]
66	H	H	$O(CH_2)_{13}CH_3$	$CH_2OCONH(CH_2)$	2′	ethyl	OTf	>10	1	$C_{31}H_{47}N_2O_6SF_3$	C,H,N,F,S
68	H	H	$O(CH_2)_{13}CH_3$	$CH_2OCON(COCH_3)CH_2$	2′	methyl	I	>10	2	$C_{31}H_{47}N_2O_4I$	C,H; N[s], I[t]

[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 IC_{50} 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 IC_{50} 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] $IC_{50} = 0.025 \pm 0.011$ μM when PAF challenge was 1×10^{-7} M ($n = 2$). [l] $IC_{50} = 2.4 \pm 2.0$ 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^{-8} M. [b] Compound was given ip at a dose of 1 mg/kg in saline 0.5 h prior to an LD_{90} 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 antagonists[9] 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. OCH_3, $C(CH_3)_3$) 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 $O(CH_2)_{13}CH_3$ into the 3-position, as in 48, led to a significant loss in activity. Additionally, compound 49, bearing 3,4-$[O(CH_2)_6CH_3]_2$ disubstitution, was somewhat less active than 37, which has only a single 4-$O(CH_2)_{13}CH_3$ 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-$O(CH_2)_{13}CH_3$; 4-OCH_3) led to an activity decrease of 2500-fold. Lastly, replacement of the 4-$O(CH_2)_{13}CH_3$ of 40 by an $OC(O)NH(CH_2)_{17}CH_3$ 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 $IC_{50} > 10$ 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 LD_{90} 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 ^{13}C 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 CF_3CO_2D 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 ±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. ($C_8H_{10}N_2O$) 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 **11g**[9] (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. ($C_{21}H_{36}O_2$) 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. ($C_{21}H_{35}BrO$) 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 **12a**[9] (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. ($C_{27}H_{40}N_2O_2$) 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 microneedles, 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 ($M^+ - I$). Anal. ($C_{28}H_{43}N_2O_2I$) 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 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. ($C_{27}H_{40}N_2O_2$) 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 (2 s, 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 ($M^+ - C_6H_6N$). Anal. ($C_{29}H_{44}N_2O_2$) 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 iodoethane.

Compound **31** was isolated as cream-colored crystal (98%): mp 108–110 °C; IR (KBr) 2920, 2851, 1643, 1628 cm^{-1}; ^1H NMR (d_6-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, CH_2-NCH_2, NCH_2CH_3), 3.96 (t, 2 H, J = 7 Hz, OCH_2), 2.27, 2.09 (2 s, 3 H, $COCH_3$), 1.79–1.69 (m, 2 H, OCH_2CH_2), 1.50 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.49–1.26 (m, 22 H), 0.87 (t, 3 H, J = 6 Hz, CH_3); mass spectrum (FAB) m/e 481 (M^+ – I). Anal. ($C_{31}H_{49}N_2O_2I$) 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 ($CDCl_3$) 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, NCH_2), 3.99 (t, 2 H, J = 7 Hz, OCH_2), 2.21 (s, 3 H, $COCH_3$), 1.79 (quintet, 2 H, J = 8 Hz, OCH_2CH_2), 1.50–1.26 (m, 22 H), 0.88 (t, 3 H, J = 6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$) 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. ($C_{29}H_{42}N_2O_3$) 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 ($CDCl_3$) 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, NCH_2), 4.78 (s, 3 H, NCH_3), 4.04 (t, 2 H, J = 7 Hz, OCH_2), 2.12 (s, 3 H, $COCH_3$), 1.81 (quintet, 2 H, J = 7 Hz, OCH_2CH_2), 1.48–1.26 (m, 22 H), 0.88 (t, 3 H, J = 7 Hz, CH_3); ^{13}C NMR ($CDCl_3$) 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. ($C_{30}H_{45}N_2O_3I$) 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 ($CDCl_3$) 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, NCH_2), 4.05 (t, 2 H, J = 7 Hz, OCH_2), 2.29 (s, 3 H, $COCH_3$), 1.86 (quintet, 2 H, J = 7 Hz, OCH_2CH_2), 1.37 (s, 9 H, $C(CH_3)_3$), 1.53–1.26 (m, 22 H), 0.88 (t, 3 H, J = 7 Hz, CH_3); mass spectrum (FAB) m/e 539 (M^+ + H). Anal. ($C_{33}H_{50}N_2O_4 \cdot 1.0H_2O$) C, H; N: calcd, 5.03; found, 4.52.

3-(1,1-Dimethylethyl)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]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 ($CDCl_3$) 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, $CC(CH_3)_3$), 1.04 (s, 9 H, $SiC(CH_3)_3$), 1.02 (s, 9 H, $SiC(CH_3)_3$), 0.356 (s, 6 H, $Si(CH_3)_2$), 0.355 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$) 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. ($C_{23}H_{42}O_3Si_2$) C, H.

3-(1,1-Dimethylethyl)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]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 ($CDCl_3$) 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, $CC(CH_3)_3$), 1.05 (s, 9 H, $SiC(CH_3)_3$), 0.38 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$) 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. ($C_{17}H_{27}O_2SiCl$) 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)-dimethylsilyl]oxy]-*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 ($CDCl_3$) 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, NCH_2), 2.24 (s, 3 H, $COCH_3$), 1.32 (s, 9 H, $CC(CH_3)_3$), 1.03 (s, 9 H, $SiC(CH_3)_3$), 0.35 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$) 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. ($C_{25}H_{36}N_2O_3Si$) 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 ($CDCl_3$) 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, NCH_2), 2.31 (s, 3 H, $COCH_3$), 1.32 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) 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. ($C_{19}H_{22}N_2O_3$) 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 ($CDCl_3$) 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, $C(CH_3)_3$), 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 ($M^+ - C_{19}H_{37}NO$). Anal. ($C_{38}H_{59}N_3O_4$) C, H, N.

2-[[Acetyl[3-(1,1-dimethylethyl)-4-[[(octadecylamino)carbonyl]oxy]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, $C(CH_3)_3$), 1.37–1.24 (m, 30 H), 0.85 (t, 3 H, J = 6.7 Hz, CH_3); mass spectrum (FAB) m/e 636 (M^+ - I). Anal. ($C_{39}H_{62}N_3O_4I$) 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 × 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. ($C_{28}H_{40}N_2O_4$) 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 (hextet, 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, $NCH_2CH_2CH_3$), 0.87 (t, 3 H, J = 6.7 Hz, CH_2CH_3); mass spectrum (FAB) m/e 511 (M^+ - I). Anal. ($C_{31}H_{47}N_2O_4I$) 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 × 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. ($C_{28}H_{40}O_4$) 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. ($C_{28}H_{42}N_2O_3$) 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 (M^+ - OTf). Anal. ($C_{31}H_{47}N_2O_6SF_3$) 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, NCH_2 + 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 ($M^+ - C_9H_8N_2O_2$). Anal. ($C_{30}H_{44}N_2O_4$) C, H, N.

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