A Novel Class of Platelet Activating Factor (PAF) Antagonists. I. Synthesis and Structure–Activity Studies on PAF-Sulfonamide Isosteres

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New platelet activating factor (PAF) antagonists, 3 were synthesized by replacing the charged phosphate and trimethylammonium moieties with sulfonamide and heterocyclic quarternary ammonium functionalities, respectively (PAF-sulfonamide isosteres). Darmstoff phosphatidic acid analogues of this class (Darmstoff-sulfonamide isosteres), 6 were also synthesized.

The activity of these compounds as PAF antagonists was evaluated from their *in vitro* inhibitory effect on PAF-induced platelet aggregation in rabbit platelet-rich plasma. Among the compounds tested, some of the 2-methoxypropane derivatives with an octadecylcarbamoyloxy or octadecylcarbamoylthio side chain at the 1-position and a propylsulfonamide function bearing a terminal polar substituent such as a quarternary quinolinium or substituted quinolinium group at the 3-position were found to be the most potent (IC_{50} = 0.3—0.6 μM).

Keywords platelet activating factor; receptor antagonist; platelet activating factor-sulfonamide isostere; Darmstoff phosphatidic acid; Darmstoff-sulfonamide isostere; platelet aggregation

Platelet activating factor (PAF) is a potent phospholipid mediator released from rabbit basophile through an immunoglobulin E (IgE)-dependent mechanism.[1] It has the structure of 1-*O*-alkyl-2-*O*-acetyl-*sn*-glycero-3-phosphocholine (**1**) (Fig. 1).[2]

It is also released from a number of stimulated cells, including platelets, macrophages, basophiles, neutrophiles and endothelium cells.[3]

After the characterization of natural PAF, extensive studies have been conducted on its pathophysiological roles, revealing its diverse biological actions in platelet aggregation, hypotension, bronchoconstriction, induction of chemotaxis and increase of vascular permeability.[4] Thus, although its precise mechanism of action remains to be clarified, PAF is believed to play important roles in various diseases, such as acute allergy, asthma, inflammation, disseminated intravascular coagulation,[4] and even cancer.[5]

The development of a PAF-specific antagonist might yield not only an effective tool for pathophysiological studies, but also promising therapeutic agents for various diseases caused by PAF. Much effort has been devoted toward obtaining synthetic PAF analogues which can act as specific antagonists, and CV-3988 (**2**)[6] was first described as a compound of this category. A number of attempts have also been made to synthesize new antagonists with better potency and bioavailability and with less agonist property and toxicity. These efforts have led to the classification of three types of PAF antagonists[7]: (1) PAF analogues,[8-12] (2) natural plants products,[13a,b] and (3) synthetic compounds not structurally related to the PAF framework.[14] During the course of our research on PAF analogues, several compounds of type (3) have been reported, and it was shown that they were generally superior to PAF analogues with respect to their oral absorption, duration of plasma level, and so on. On the other hand, increasing interest has been focused on PAF-related alkyl lysophospholipids (APL) regarding their antineoplastic properties. Although the mechanism of action has not yet been clarified, there are several reports[5] which discussed the relationship between PAF related activity and antitumor activity. Therefore, we thought that it would still be interesting to study the biological properties of PAF related analogues.

In trying to modify the structure of the natural PAF molecule, work has been focused on the modification of the phosphocholine moiety at the 3-position of the glycerol backbone of PAF, and some analogues have been prepared

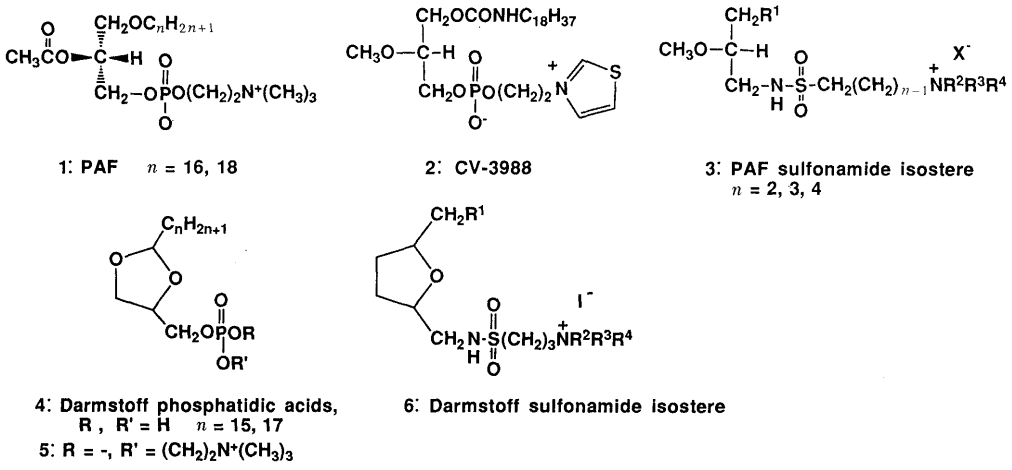


Fig. 1

in which the charged phosphate moiety had been replaced by other functional groups, such as ester,[9] ether,[10] carbamoyl[11] and sulfonyl[12] groups. In the present paper, we report on the syntheses and biological activities of new PAF analogues represented by general formula **3**, in which the phosphocholine moiety of PAF is replaced by as yet unreported alkylsulfonamide groups bearing several aliphatic, alicyclic and aromatic quarternary ammonium groups at the terminal position.

In recent years, Darmstoff phosphatidic acids (**4**), the acetal phosphatidic acid derivatives, have been isolated[15] and shown to contract certain visceral smooth muscles, including taenia coli strips, and to cause platelet aggregation. Their choline ester **5** was synthesized by Marx *et al.*[16] and shown to cause dose-dependent relaxation of taenia coli strips and contraction of the whole trachea, similarly to PAF. Therefore, we also tried to synthesize corresponding sulfonamide analogues in which the 1,3-dioxolane ring is replaced by the tetrahydrofuran backbone represented by general formula **6**.

Chemistry For the substituent at the 1-position of the glycerol backbone of PAF analogues, we selected mainly alkyl ether or alkylcarbamate functional groups, both of which have been introduced at this position as a typical side chain of PAF antagonists. We also introduced alkylthio ether and alkyl carbamoylthio functions at this position for some limited derivatives. For the substituent at the 2-position, we selected the methoxy group as a stable acetoxy equivalent. To investigate the effect of the polar head group at the 3-position, several quarternary ammonium functions of both aliphatic, alicyclic and aromatic amines were introduced. The chain length between the sulfonamide group and polar head moiety was also modified to examine the effect of the distance between these functions on PAF antagonist activity.

Using these design strategies, the PAF sulfonamide isosteres were synthesized as outlined in Chart 1.

2-Methoxy-3-propanol derivatives bearing appropriate substituents such as octadecylcarbamoyloxy-(**7a**),[6] octadecylcarbamoylthio-(**7b**),[8a] hexadecyloxy-(**7c**)[17a] and hexadecylthio-(**7d**)[17b] at the 1-position were converted into primary amines **9a—d** by conventional transformation *via* the reaction of hydrazine with phthalimide intermediates **8a—d**[18] which were obtained by the Mitsunobu reaction[19] of **7a—d** with phthalimide, diethyl azodicarboxylate (DEAD) and triphenylphosphine (PPh_3) in tetrahydrofuran (THF). Coupling of the primary amines **9a—d** with 3-chloropropanesulfonyl chloride or 4-chlorobutanesulfonyl chloride[20] in the presence of triethylamine (Et_3N) in dichloromethane (CH_2Cl_2), followed by iodination of the resulting products **10a—d** and **11a** with sodium iodide (NaI) in methyl ethyl ketone (MEK), led to the corresponding iodoalkylsulfonamide derivatives **12a—d** and **13a**, respectively.

For the preparation of 2-iodoethanesulfonamide derivative **14a**, coupling of **9a** with 2-chloroethanesulfonyl chloride reagent could not be done because the reagent was labile under the coupling condition. Therefore, **14a** was alternatively prepared from **10a** by subtracting one carbon unit *via* the sequential transformations described in Chart 2.

Reaction of **10a** with sodium phenylselenide, freshly prepared from diphenyldiselenide and sodium borohydride ($NaBH_4$) in EtOH, gave phenylselenyl derivative **15a**. This was converted to the olefin **16a** by reaction with hydrogen peroxide, followed by thermolysis of the resulting phenylselenoxide derivative. Ozonolysis of **16a**, followed by

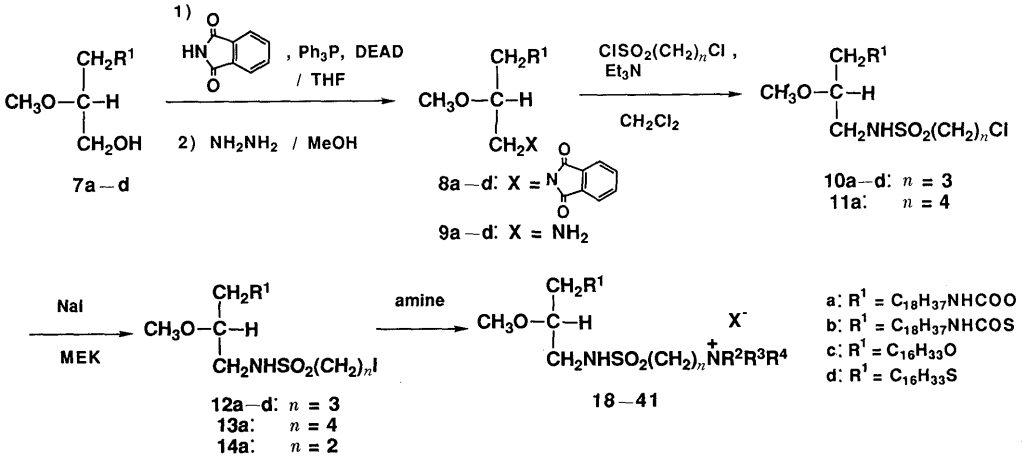


Chart 1

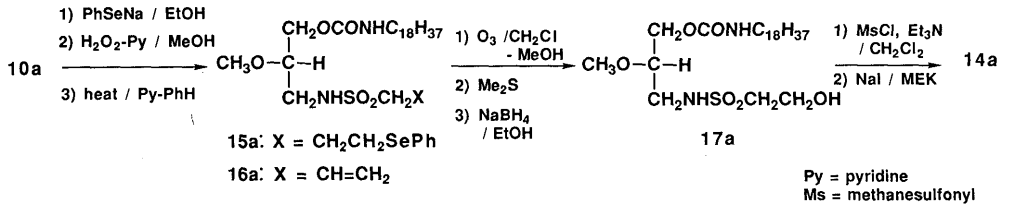


Chart 2

treatment of the ozonide with dimethyl sulfide and subsequent reduction of the resulting aldehyde with $NaBH_4$, gave alcohol **17a**. Conversion of **17a** to iodoalkylsulfonamide derivative **14a** was carried out *via* the reaction of its mesylate intermediate with NaI in MEK. Compounds **12a—d**, **13a** and **14a**, thus prepared, were finally allowed to react with appropriate amines to give quarternary ammonium iodide derivatives **19—33** and **36—41** as a series of PAF sulfonamide isosteres. For some limited derivatives, the corresponding quarternary ammonium chloride derivatives **18**, **34** and **35** were prepared by treating quarternary ammonium iodide derivatives with aq. HCl in $CHCl_3$. These PAF-sulfonamide isosteres are listed in Table I.

Since these procedures for the preparation of PAF sulfonamide isosteres are by no means satisfactory from the standpoint of efficacy and practicability, being especially unsuitable for large-scale preparation, we also investigated the method for direct conversion of the primary alcohol **7a—d** using the Mitsunobu reaction with appropriate sulfonamide reagents to chloroalkylsulfonamide or iodoalkylsulfonamide derivatives (Chart 3).

The Mitsunobu reaction of **7a** with 3-chloropropanesulfonamide (**43**), which was prepared by treating 3-chloropropanesulfonyl chloride (**42**) with ammonia, was found to be unsuccessful, probably due to the lack of sufficient acidity of the amide proton. We therefore tried to use the *N*-substituted sulfonamide reagents **44—46** which have increased acidity of the amide proton. *N*-Acetylchloropropanesulfonamide (**44**) was prepared by acetylation of **43** with acetic anhydride (Ac_2O) in lutidine. *N*-Benzyloxycarbonylchloropropanesulfonamide (**45**) and *N-tert*-butoxycarbonylchloropropanesulfonamide (**46**) were prepared directly from **42** by treatment with 2 equimolar amounts of lithium benzylcarbamate or lithium *tert*-butylcarbamate, respectively. In the reaction of **7a** with *N*-acetylsulfonamide (**44**), PPh_3 and DEAD in THF, a considerable amount (28%) of isomeric imino-ether **50a** was formed, together with the desired compound **47a** (65%). However, the Mitsunobu reaction of **7a** with *N*-benzyloxycarbonylsulfonamide (**45**) or *N-tert*-butyloxycarbonylsulfonamide (**46**) proceeded smoothly and yielded only the desired coupling products **48a** and **49a** in 89 and 90% yields, respectively.

Compounds **48a** or **49a** were converted to **12a** by successive treatment with hydrazine (or trifluoroacetic acid) and NaI. More conveniently, treatment of **48a** with a large excess of

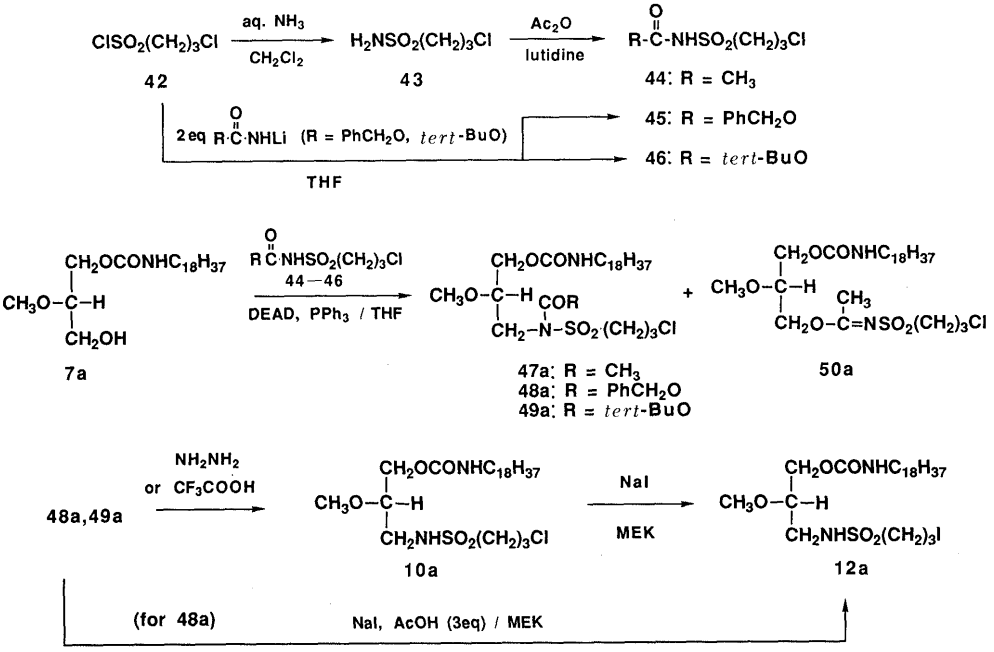


Chart 3

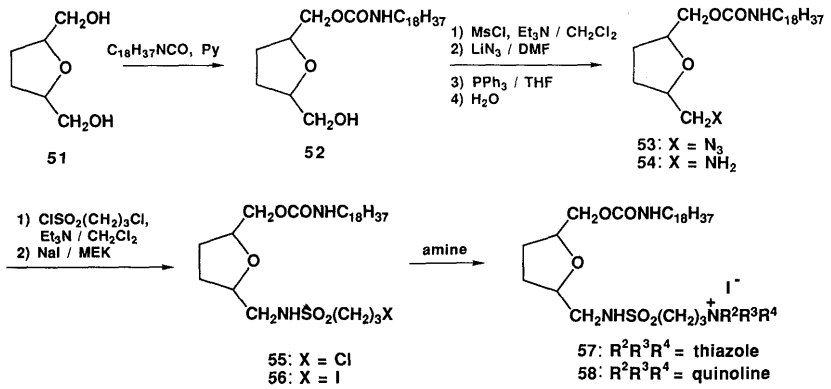


Chart 4

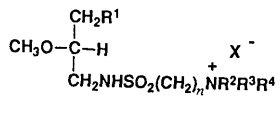
NaI in the presence of 3 molar eq of acetic acid (AcOH) resulted in conversion to the iodide **12a** with simultaneous deprotection of the *N*-benzyloxycarbonyl function and conversion of the chloride to the iodide (Chart 3). This two-step conversion of **7a** gave **12a** in about 80% yield.

In order to obtain new PAF antagonists with greater potencies, we tried preparing the Darmstoff sulfonamide analogues **57** and **58** by modification of the glycerol backbone of the PAF sulfonamide isosteres as summarized in Chart 4. *cis*-2,5-Bis(hydroxymethyl)tetrahydrofuran (**51**)[20] was converted to the octadecylcarbamoyloxy derivative **52** by reaction with octadecyl isocyanate in pyridine. Alcohol **52** was converted to the corresponding mesylate intermediate, which was allowed to react with lithium azide (LiN_3) in dimethylformamide (DMF) to give azido derivative **53**. This derivative **53** was converted to the amine derivative **54** by reaction with PPh_3 in THF, followed by reaction with H_2O. Finally, compounds **57** and **58** (Table I) were obtained from **54** according to the procedures used for the conversion of **9a** to **18**—**41**.

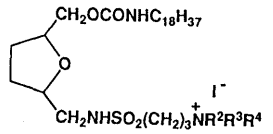
Results and Discussion

The *in vitro* PAF-antagonist activity of the PAF- and Darmstoff-sulfonamide isosteres, **18**—**41**, **57** and **58** was evaluated by their inhibitory effect on PAF-induced platelet aggregation of rabbit platelet-rich plasma which was examined using the method of Born.[22] These results are summarized in Table I.

TABLE I. Inhibitory Activity on PAF-Induced Rabbit Platelet Aggregation by PAF- and Darmstoff-Sulfonamide Isosteres



18—**41**



57, **58**

Compound	R^1	$NR^2R^3R^4$	X^-	n	IC_{50}, μM[a]
2 (CV-3988)					18.5
18	$OCONHC_{18}H_{37}$	Trimethylamine	Cl	3	48.1
19	$OC_{16}H_{33}$	Trimethylamine	I	3	79.9
20	$SC_{16}H_{33}$	Trimethylamine	I	3	82.1
21	$OCONHC_{18}H_{37}$	*N*-Methylmorpholine	I	3	64.2
22	$OCONHC_{18}H_{37}$	Morpholine	None	3	Negative
23	$OCONHC_{18}H_{37}$	*N*-Methylimidazole	I	3	5.88
24	$OCONHC_{18}H_{37}$	Thiazole	I	2	5.95
25	$OCONHC_{18}H_{37}$	Thiazole	I	3	1.89
26	$OCONHC_{18}H_{37}$	Thiazole	I	4	1.77
27	$OC_{16}H_{33}$	Thiazole	I	3	2.97
28	$SC_{16}H_{33}$	Thiazole	I	3	3.64
29	$SCONHC_{18}H_{37}$	Thiazole	I	3	1.93
30	$OCONHC_{18}H_{37}$	Pyridine	I	3	5.20
31	$OCONHC_{18}H_{37}$	Pyrazine	I	3	45.4
32	$OCONHC_{18}H_{37}$	Quinoline	I	3	0.65
33	$OCONHC_{18}H_{37}$	Quinoline	I	4	1.29
34	$OCONHC_{18}H_{37}$	Quinoline	Cl	3	0.74
35	$OCONHC_{18}H_{37}$	Quinoline	Cl	4	7.36
36	$SCONHC_{18}H_{37}$	Quinoline	I	3	0.36
37	$OCONHC_{18}H_{37}$	Isoquinoline	I	4	13.5
38	$OCONHC_{18}H_{37}$	5,6,7,8-Tetrahydroquinoline	I	3	0.84
39	$OCONHC_{18}H_{37}$	*N*-Methyl-1,2,3,4-tetrahydroquinoline	I	3	1.54
40	$OCONHC_{18}H_{37}$	6-Methoxyquinoline	I	3	0.36
41	$OCONHC_{18}H_{37}$	Benzothiazole	I	4	Negative
57	$OCONHC_{18}H_{37}$	Thiazole	I	3	6.35
58	$OCONHC_{18}H_{37}$	Quinoline	I	3	2.21

a) Micromolar concentration of a test compound for 50% inhibition of rabbit platelet aggregation induced by C_{16}-PAF (20 nM).

Comparison with CV-3988 showed most of the sulfonamide derivatives to be more potent, clearly demonstrating that the isostere of the charged phosphate function of PAF is responsible for the antagonist activity.

For the polar head group, aromatic quarternary ammonium functions were evidently superior to the aliphatic and alicyclic ammonium group, among them the quinolinium or the substituted quinolinium group being the most effective. The *in vitro* PAF antagonist activity seems to also be dependent on the chain length between the sulfonamide function and the quarternary ammonium group. In the case of compounds with the thiazolium polar head group, the propylene and butylene groups were superior to the ethylene group (comparison of **24**, **25** and **26**), and in the case of compounds with the quinolinium polar head group, the propylene group was found to be more effective than the butylene group (comparison of **32** *vs.* **33** and **34** *vs.* **35**). As for the quarternary ammonium counter anion, there was no difference in the biological activity between iodide and chloride (comparison of **32** *vs.* **34** and **33** *vs.* **35**). For the substituent at the 1-position, there was no significant difference between the alkylcarbamoyloxy and the alkylthiocarbamate functions. The alkylcarbamoyloxy function seems to be only slightly more effective than that of alkylether (comparison of **25** *vs.* **27**). This is also applicable for the corresponding thio analogues, and the compound with alkylcarbamoylthio function **29** is more potent than that with alkylthioether function **28**. There was no improvement in biological activity following modification of the glycerol backbone to the *cis*-2,5-bis(methyl)-tetrahydrofuranyl ring (comparison of **32** *vs.* **58**). The specificity of the PAF-antagonist action was confirmed for the two representative derivatives **25** and **32** by displacement experiments using ^{3}H-PAF, showing IC_{50} values of 0.15 and 0.066 μM, respectively.[24] Furthermore, these compounds were found to show no significant inhibitory activity at concentrations up to 100 μM in platelet aggregations caused by several stimuli such as adenosine diphosphate (ADP) (10 μM), collagen (10 μM), arachidonic acid (200 μM) and calcium ionophore A 23187 (4 μM) (data not shown). These results clearly show that the PAF sulfonamide analogues act in a PAF-specific manner.

Conclusions

Novel PAF and Darmstoff analogues bearing sulfonamide functionality at the 3-position of the glycerol backbone were synthesized and found to be potentially active as specific PAF-antagonists.

Among the PAF-sulfonamide analogues described in this paper, compounds which have an octadecylcarbamoyloxy or octadecylcarbamoylthio side chain at the 1-position and also a propylene sulfonamide function bearing a terminal polar substituent such as quinolinium or a substituted quinolinium group at the 3-position were found to be more potent (IC_{50} = 0.3—0.6 μM) than CV-3988 (IC_{50} = 18.5 μM), and their *in vitro* activity proved to be PAF-specific.

Experimental

Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere with dry solvents being used under anhydrous conditions and with anhydrous $MgSO_4$ being used as a drying agent for extracts. The organic solvents were removed by evaporation under reduced pressure with a rotary evaporator. Medium-pressure column chromatographies on

Merck "Lobar" prepacked columns packed with LiChroprep Si 60 [size A (240-10 mm, 40—63 μm), size B (310—25 mm, 40—63 μm), and size C (440—37 mm, 40—63 μm)] were carried out for separation and purification of the products. Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were determined with a Hitachi Model 260—10 spectrophotometer, and nuclear magnetic resonance (NMR) spectra were determined on a Varian VXR-200 spectrometer.

3-Amino-2-methoxy-1-octadecylcarbamoyloxypropane (9a)[6b] According to the literature,[6b] compound **9a** was prepared from **7a** *via* the phthalimide **8a**. To an ice-cooled and stirred solution of **7a** (4.0 g, 10 mmol), phthalimide (2.21 g, 15 mmol) and PPh_3 (3.93 g, 15 mmol) in THF (200 ml), was added DEAD (2.36 ml, 15 mmol), and the mixture was stirred at room temperature overnight. After removal of the solvent, the residue was purified by silica gel column chromatography using an AcOEt–hexane (1 : 2) mixture as an eluent. **8a** (5.07 g, 96%) was obtained on recrystallization from isopropyl ether (iso-Pr_2O) as colorless needles, mp 79—80 °C. *Anal.* Calcd for $C_{31}H_{50}N_2O_5$: C, 70.15; H, 9.50; N, 5.28. Found: C, 69.94; H, 9.53; N, 5.66.

To the solution of the above compound (5.07 g, 9.6 mmol) in MeOH (100 ml) was added $NH_2NH_2 \cdot H_2O$ (0.5 ml), and the mixture was refluxed for 3 h. After removal of the insoluble material by passage through a pad of Celite, the filtrate was concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography using a CH_2Cl_2–MeOH (9 : 1) mixture as an eluent, and **9a** (2.7 g, 70%) was obtained as a pale yellow powder. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (30H, s), 1.40—1.70 (4H, br), 2.70—2.92 (2H, m), 3.05—3.25 (2H, m), 3.25—3.45 (1H, m), 3.46 (3H, s), 4.10—4.25 (2H, m), 4.70—4.90 (1H, br). IR ($CHCl_3$): 3450, 2915, 2845, 1715, 1515, 1230, 1095 cm^{-1}. MS m/z: 402 (MH^+).

Compounds **9b—d** were also prepared similarly.

2-Methoxy-1-octadecylcarbamoylthio-3-*N*-phthaloylpropylamine (8b) Yield 73%. Colorless powder. mp 109—110 °C. *Anal.* Calcd for $C_{31}H_{50}N_2O_4S$: C, 68.09; H, 9.22; N, 5.12; S, 5.86. Found: C, 68.05; H, 9.15; N, 5.11; S, 5.85.

3-Amino-2-methoxy-1-octadecylcarbamoylthiopropane (9b) Yield 54%. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (30H, s), 1.40—1.62 (2H, m), 2.65—2.94 (2H, m), 2.95—3.17 (1H, m), 3.17—3.30 (1H, m), 3.30—3.42 (1H, m), 3.45 (3H, s). IR ($CHCl_3$): 3425, 2930, 2850, 1665, 1500, 1190, 1100 cm^{-1}. MS m/z: 417 (MH^+).

1-Hexadecyloxy-2-methoxy-3-*N*-phthaloylpropylamine (8c) Yield 88%. Colorless powder. mp 57.0—57.5 °C. *Anal.* Calcd for $C_{28}H_{45}NO_4$: C, 73.16; H, 9.87; N, 3.05. Found: C, 73.27; H, 9.83; N, 3.20.

3-Amino-1-hexadecyloxy-2-methoxypropane (9c) Yield 76%. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (26H, s), 1.48—1.68 (2H, m), 2.70—2.96 (6H, m), 3.28—3.37 (1H, m), 3.45 (3H, s), 3.40—3.60 (6H, m). IR ($CHCl_3$): 3380, 2920, 2845, 1580, 1465, 1360, 1240, 1115, 860 cm^{-1}. MS m/z: 330 (MH^+).

1-Hexadecylthio-2-methoxy-3-*N*-phthaloylpropylamine (8d) Yield 82%. Colorless powder. mp 58—59 °C. *Anal.* Calcd for $C_{28}H_{45}NO_3S$: C, 70.69; H, 9.53; N, 2.94; S, 6.74. Found: C, 69.94; H, 9.49; N, 2.96; S, 6.71.

3-Amino-1-hexadecylthio-2-methoxypropane (9d) Yield 88%. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (26H, s), 1.48—1.68 (2H, m), 2.50—3.00 (6H, m), 3.25—3.38 (1H, m), 3.43 (3H, s). IR ($CHCl_3$): 3380, 2930, 2850, 1465, 1380, 1230, 1110 cm^{-1}. MS m/z: 346 (MH^+).

3-(3-Chloropropylsulfonylamino)-2-methoxy-1-octadecylcarbamoyloxypropane (10a) To an ice-cooled and stirred solution of **9a** (1.2 g, 3.0 mmol) and Et_3N (0.54 ml, 3.9 mmol) in CH_2Cl_2 (25 ml) was added 3-chloropropanesulfonyl chloride (0.4 ml, 3.3 mmol), and the mixture was stirred at room temperature overnight. The product was isolated by CH_2Cl_2 extraction. The CH_2Cl_2 layer was washed with saturated aqueous $NaHCO_3$ and saturated NaCl and then dried and evaporated. The product was purified by silica gel column chromatography using an AcOEt–hexane (2 : 3) mixture as an eluent, and **10a** (1.39 g, 85%) was obtained on reprecipitation from $CHCl_3$–hexane as a colorless powder, mp 64.5—66.0 °C. NMR ($CDCl_3$) δ: 0.86 (3H, t, J=6.5 Hz), 1.24 (30H, s), 1.40—1.60 (2H, m), 2.10—2.50 (2H, m), 2.90—3.60 (7H, m), 3.44 (3H, s), 3.67 (2H, t, J=6.0 Hz), 4.10—4.25 (2H, m), 4.80—4.95 (1H, m), 5.02—5.18 (1H, m). IR ($CHCl_3$): 3445, 2920, 2850, 1715, 1510, 1460, 1330, 1220, 1145 cm^{-1}. *Anal.* Calcd for $C_{26}H_{53}ClN_2O_5S$: C, 57.70; H, 9.87; Cl, 6.55; N, 5.18; S, 5.92. Found: C, 57.51; H, 9.84; Cl, 6.82; N, 5.34; S, 5.95. MS m/z: 540 (M^+, Cl^{35}).

3-(3-Iodopropylsulfonylamino)-2-methoxy-1-octadecylcarbamoyloxypropane (12a) To a solution of **10a** (972 mg, 1.8 mmol) in MEK (10 ml) was added NaI (500 mg, 3.38 mmol), and the mixture was refluxed for 3 h, then cooled to room temperature and poured into 0.5 N $Na_2S_2O_3$. The product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated NaCl, then dried and evaporated. The product was purified by silica gel column chromatography using an AcOEt–hexane (1 : 1) mixture as an eluent, and **12a** (972 mg, 86%) was obtained on reprecipitation from $CHCl_3$–hexane as a colorless powder, mp 61.5—62.5 °C. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (30H, s), 1.40—1.60 (2H, m), 2.25—2.40 (2H, m), 3.10—3.30 (4H, m), 3.31 (2H, t, J=6.6 Hz), 3.46 (3H, s), 3.45—3.60 (1H, m), 4.05—4.30 (2H, m), 4.75—4.90 (1H, m), 5.00 (1H, t, J=6.0 Hz). IR ($CHCl_3$): 3450, 2940, 2855, 1725, 1510, 1470, 1335, 1230, 1145 cm^{-1}. *Anal.* Calcd for $C_{26}H_{53}IN_2O_5S$: C, 49.12; H, 8.44; I, 20.08; N, 4.56; S, 5.34. Found: C, 49.36; H, 8.44; I, 20.10; N, 4.43; S, 5.07. MS m/z: 505 ($M^+ - I$).

3-(4-Chlorobutylsulfonylamino)-2-methoxy-1-octadecylcarbamoyloxypropane (11a) To an ice-cooled and stirred solution of **9a** (1.2 g, 3.0 mmol) and Et_3N (500 μl, 3.6 mmol) in CH_2Cl_2 (25 ml) was added 4-chlorobutanesulfonyl chloride (0.75 g, 3.93 mmol), and the mixture was stirred at room temperature overnight. The product was isolated by CH_2Cl_2 extraction. The CH_2Cl_2 layer was washed with saturated aqueous $NaHCO_3$ and saturated NaCl, then dried and evaporated. The product was purified by silica gel column chromatography using an AcOEt–hexane (2 : 3) mixture as an eluent, and **11a** (1.28 g, 77%) was obtained on reprecipitation from CH_2Cl_2–hexane as a colorless powder, mp 57.5—58.5 °C. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.25 (30H, s), 1.40—1.60 (2H, m), 1.80—2.10 (4H, m), 3.00—3.40 (6H, m), 3.45 (3H, s), 3.40—3.55 (1H, m), 3.58 (2H, t, J=6.0 Hz), 4.05—4.30 (2H, m), 4.75—4.85 (1H, br), 4.94 (1H, t, J=6.0 Hz). IR ($CHCl_3$): 3450, 2930, 2850, 1720, 1510, 1330, 1225, 1140, 1040 cm^{-1}. *Anal.* Calcd for $C_{27}H_{55}ClN_2O_5S$: C, 58.41; H, 9.98; Cl, 6.38; N, 5.05; S, 5.77. Found: C, 58.15; H, 9.98; Cl, 6.71; N, 5.16; S, 5.89. MS m/z: 554 (M^+, Cl^{35}).

Almost the same procedures as described above were used for the conversion of **9b—d** to **10b—d**, **10b—d** to **12b—d** and **11a** to **13a**, respectively.

3-(3-Chloropropylsulfonylamino)-2-methoxy-1-octadecylcarbamoylthiopropane (10b) Yield 67%. Colorless powder. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (30H, s), 1.40—1.60 (2H, m), 2.20—2.37 (2H, m), 2.93—3.40 (8H, m), 3.44 (3H, s), 3.40—3.55 (1H, m), 3.69 (2H, t, J=5.3 Hz), 5.17—5.35 (1H, m), 5.37—5.54 (1H, br). IR ($CHCl_3$): 3420, 2930, 2850, 1670, 1495, 1460, 1335, 1185, 1150, 1090 cm^{-1}.

3-(3-Iodopropylsulfonylamino)-2-methoxy-1-octadecylcarbamoylthiopropane (12b) Yield 86%. Colorless powder. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (30H, s), 1.42—1.62 (2H, m), 2.25—2.42 (2H, m), 2.95—3.50 (8H, m), 3.44 (3H, s), 3.50—3.58 (1H, m), 5.18—5.34 (1H, br), 5.38—5.57 (1H, br). IR ($CHCl_3$): 3425, 2925, 2850, 1670, 1500, 1460, 1325, 1185, 1140, 1100 cm^{-1}.

3-(3-Chloropropylsulfonylamino)-1-hexadecyloxy-2-methoxypropane (10c) Yield 86%. Colorless powder. mp 49—50 °C (MeOH). NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (26H, s), 1.45—1.65 (2H, m), 2.20—2.38 (2H, m), 3.15—3.60 (9H, m), 3.44 (3H, s), 3.68 (2H, t, J=6.2 Hz), 4.79 (1H, t, J=6.0 Hz). IR ($CHCl_3$): 3375, 2920, 2845, 1465, 1410, 1335, 1265, 1145 cm^{-1}. *Anal.* Calcd for $C_{23}H_{48}ClNO_4S$: C, 58,76; H, 10.29; Cl, 7.54; N, 2.98; S, 6.82. Found: C, 58.63; H, 10.20; Cl, 7.47; N, 3.00; S, 6.72. MS m/z: 469 (M^+, Cl^{35}).

1-Hexadecyloxy-3-(3-iodopropylsulfonylamino)-2-methoxypropane (12c) Yield 77%. Colorless powder. mp 46—47 °C (MeOH). NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (26H, s), 1.45—1.65 (2H, m), 2.25—2.40 (2H, m), 3.10—3.60 (9H, m), 3.30 (2H, t, J=6.6 Hz), 3.44 (3H, s), 4.81 (1H, t, J=6.0 Hz). IR ($CHCl_3$): 3380, 2930, 2855, 1470, 1410, 1335, 1270, 1150 cm^{-1}. *Anal.* Calcd for $C_{23}H_{48}INO_4S$: C, 49.19; H, 8.61; I, 22.60; N, 2.49; S, 5.71. Found: C, 49.11; H, 8.54; I, 22.48; N, 2.53; S, 6.00. MS m/z: 562 (M^+).

3-(3-Chloropropylsulfonylamino)-1-hexadecylthio-2-methoxypropane (10d) Yield 89%. Colorless powder. mp 49—50 °C ($CHCl_3$–hexane). NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (26H, s), 1.48—1.68 (2H, m), 2.20—2.40 (2H, m), 2.55 (2H, t, J=7.4 Hz), 2.53—2.80 (2H, m), 3.10—3.30 (3H, m), 3.42 (3H, s), 3.40—3.60 (2H, m), 3.69 (3H, t, J=6.2 Hz), 4.60—4.80 (1H, br). IR ($CHCl_3$): 3380, 2930, 2850, 1470, 1410, 1330, 1150, 1095 cm^{-1}. *Anal.* Calcd for $C_{23}H_{48}ClNO_3S_2$: C, 56.82; H, 9.95; Cl, 7.29; N, 2.88; S, 13.19. Found: C, 56.76; H, 9.89; Cl, 7.18; N, 3.18; S, 12.94. MS m/z: 485 (M^+, Cl^{35}).

1-Hexadecylthio-3-(3-iodopropylsulfonylamino)-2-methoxypropane (12d) Yield 87%. Oil. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (26H, s), 1.45—1.70 (2H, m), 2.22—2.40 (2H, m), 2.55 (2H, t, J=7.4 Hz), 2.53—2.81 (2H, m), 3.11—3.26 (3H, m), 3.31 (2H, t, J=6.6 Hz), 3.43 (3H, s), 3.41—3.56 (1H, m), 4.65 (1H, t, J=6.0 Hz). IR ($CHCl_3$): 3370, 2920, 2850, 1460, 1405, 1325, 1145, 1090 cm^{-1}. *Anal.* Calcd for $C_{23}H_{48}INO_3S_2$: C,

47.82; H, 8.38; I, 21.97; N, 2.42; S, 11.10. Found: C, 47.62; H, 8.28; I, 22.18; N, 2.50; S, 11.09. MS *m/z*: 577 (M^+).

3-(4-Iodobutylsulfonylamino)-2-methoxy-1-octadecylcarbamoyloxypropane (13a) Yield 81%. Colorless powder. mp 71.0—72.0 °C (CH_2Cl_2–hexane). NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (30H, s), 1.40—1.60 (2H, m), 1.90—2.00 (4H, m), 3.00—3.40 (10H, m), 3.46 (3H, s), 3.45—3.60 (1H, m), 4.10—4.30 (2H, m), 4.70—4.85 (1H, br), 4.87 (1H, t, J=6.6 Hz). IR ($CHCl_3$): 3450, 2925, 2850, 1720, 1510, 1330, 1230, 1140 cm^{-1}. *Anal.* Calcd for $C_{27}H_{55}IN_2O_5S$: C, 50.15; H, 8.57; I, 19.62; N, 4.33; S, 4.96. Found: C, 50.09; H, 8.45; I, 19.33; N, 4.41; S, 5.26. MS *m/z*: 647 (M^+).

2-Methoxy-1-octadecylcarbamoyloxy-3-(2-propenesulfonylamino)propane (16a) To an ice-cooled and stirred solution of diphenyl diselenide (1.52 g, 4.9 mmol) in EtOH (25 ml) was added $NaBH_4$ (0.37 g, 9.78 mmol), and the mixture was stirred until the solution became clear. AcOH (0.56 ml, 9.78 mmol) and **10a** (0.88 g, 1.63 mmol) in THF (20 ml) were added to the mixture, which was stirred for 1.5 h at room temperature. The product was isolated by AcOEt extraction. The AcOEt layer was washed with 1 N HCl, saturated aqueous $NaHCO_3$ and saturated NaCl, then dried and evaporated. The product was purified by silica gel column chromatography using an AcOEt–hexane (1 : 2) mixture as an eluent, and phenylselenyl derivative **15a** (1.06 g, 98%) was obtained as an oil. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (30H, s), 1.40—1.60 (2H, m), 2.10—2.24 (2H, m), 3.01 (2H, t, J=7 Hz), 3.08—3.32 (6H, m), 3.42 (3H, s), 3.40—3.52 (1H, m), 4.00—4.28 (2H, m), 4.73—4.90 (2H, m), 7.24—7.34 (3H, m), 7.45—7.57 (2H, m). IR ($CHCl_3$): 3450, 2930, 2850, 1720, 1515, 1460, 1330, 1220, 1145 cm^{-1}. MS *m/z*: 662 (M^+, Se^{80}). To a solution of **15a** (1.03 g, 1.55 mmol) in a CH_2Cl_2–MeOH (5 : 1) mixture (30 ml) were added pyridine (0.25 ml, 3.16 mmol) and H_2O_2 (2 ml), and the mixture was stirred at room temperature for 5 h. The mixture was isolated by AcOEt extraction and the organic layer was washed with 1 N HCl, saturated aqueous $NaHCO_3$ and saturated NaCl, then dried and evaporated. Benzene (30 ml) and pyridine (0.25 ml, 3.16 mmol) were added to the residue and the mixture was heated at 50 °C for 1 h. After removal of the solvent, the product was purified by silica gel column chromatography using an AcOEt–hexane (1 : 2) mixture as an eluent, and **16a** (624 mg, 80%) was obtained on reprecipitation from CH_2Cl_2–hexane as a colorless powder, mp 74.0—75.5 °C. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (30H, s), 1.40—1.60 (2H, m), 3.10—3.40 (4H, m), 3.74—3.82 (2H, m), 3.45 (3H, s), 3.45—3.55 (1H, m), 4.05—4.30 (2H, m), 4.70—4.90 (1H, m), 4.93 (1H, t, J=6.0 Hz), 5.35—5.50 (2H, m), 5.82—6.04 (1H, m). IR ($CHCl_3$): 3460, 2930, 2850, 1725, 1520, 1475, 1340, 1240, 1150 cm^{-1}. *Anal.* Calcd for $C_{26}H_{52}N_2O_5S$: C, 61.87; H, 10.38; N, 5.55; S, 6.35. Found: C, 61.68; H, 10.34; N, 5.73; S, 6.20.

3-(2-Hydroxyethylsulfonylamino)-2-methoxy-1-octadecylcarbamoyloxypropane (17a) A cooled and stirred solution of **16a** (600 mg, 1.19 mmol) in a CH_2Cl_2–MeOH (5 : 1) mixture (22 ml) at −78 °C was bubbled with ozone gas until the color of the solution became blue. After removal of the ozone by bubbling N_2 gas through the mixture, the ozonide was decomposed by dimethyl sulfide (0.5 ml). After removal of the solvent, the crude residue was dissolved in EtOH (20 ml), then $NaBH_4$ (300 mg, 7.93 mmol) was added to the mixture. The mixture was stirred for 2 h at room temperature, and the product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated NaCl and then dried and evaporated. The product was purified by silica gel column chromatography using an AcOEt–hexane (1 : 3) mixture as an eluent, and **17a** (300 mg, 50%) was obtained as an oil. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (30H, s), 1.40—1.60 (2H, m), 1.70—2.50 (1H, br), 3.05—3.35 (6H, m), 3.45 (3H, s), 3.45—3.60 (1H, m), 4.02—4.12 (2H, m), 4.12—4.27 (2H, m), 4.80—5.00 (1H, m), 5.12—5.27 (1H, m). IR ($CHCl_3$): 3450, 2920, 2850, 1710, 1510, 1465, 1330, 1220, 1135 cm^{-1}. MS *m/z*: 509 (MH^+).

3-(3-Iodoethylsulfonylamino)-2-methoxy-1-octadecylcarbamoyloxypropane (14a) To an ice-cooled and stirred solution of **17a** (298 mg, 0.586 mmol) and Et_3N (106 μl, 0.761 mmol) in CH_2Cl_2 (6 ml) was added methanesulfonyl chloride (50 μl, 0.654 mmol), and the mixture was stirred at room temperature for 2 h. The product was isolated by CH_2Cl_2 extraction. The CH_2Cl_2 layer was washed with saturated aqueous $NaHCO_3$ and saturated NaCl, then dried and evaporated. The product was purified by silica gel column chromatography using an AcOEt–hexane (1 : 1) mixture as an eluent, and crude mesylate (287 mg, 83%) was obtained as an oil. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (30H, s), 1.40—1.60 (2H, m), 3.11 (3H, s), 3.10—3.50 (4H, m), 3.45 (3H, s), 3.50 (2H, t, J=6.0 Hz), 4.15—4.28 (2H, m), 4.61 (2H, t, J=6.0 Hz), 4.85—4.95 (1H, m), 5.19 (1H, t, J=6.2 Hz). IR ($CHCl_3$): 3460, 2930, 2850, 1725, 1520, 1470, 1345, 1235, 1180, 1155, 1000, 970 cm^{-1}. To a solution of the above compound (200 mg, 0.34 mmol) in MEK (5 ml) was added NaI (200 mg, 1.33 mmol), and the mixture was refluxed for 5 h, then cooled to room temperature. After removal of the solvent, the product was purified by silica gel column chromatography using an AcOEt–hexane (1 : 2) mixture as an eluent, and **14a** (188 mg, 87%) was obtained as a pale yellow powder. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (30H, s), 1.40—1.60 (2H, m), 3.10—3.30 (4H, m), 3.46 (3H, s), 3.30—3.60 (5H, m), 4.10—4.30 (2H, m), 4.76—4.85 (1H, m), 5.10 (1H, t, J=6.3 Hz). IR ($CHCl_3$): 3450, 2935, 2855, 1720, 1515, 1460, 1410, 1335, 1220, 1145, 1090, 1050 cm^{-1}.

3-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]propyltrimethylammonium Chloride (18) To a solution of **12a** (633 mg, 1.0 mmol) in toluene (5 ml) was added a toluene solution of trimethylamine (Me_3N) (10 ml/15 ml), and the mixture was allowed to react at room temperature overnight. After removal of the solvent and Me_3N, the crude residue was washed with Et_2O to obtain an iodo derivative (550 mg, 80%). The iodo derivative was dissolved in $CHCl_3$–MeOH mixture and 1 N HCl was added to the solution, which was then vigorously shaken in a separatory funnel. The organic layer was washed with H_2O and saturated NaCl, dried and evaporated. **18** (300 mg, 50%) was obtained on reprecipitation from Et_2O as a colorless powder, mp 60—62 °C. NMR ($CDCl_3$) δ: 0.86 (3H, t, J=6.5 Hz), 1.25 (30H, s), 1.40—1.60 (2H, m), 2.00—2.50 (2H, m), 3.20 (9H, s), 3.00—3.40 (6H, m), 3.46 (3H, s), 3.40—3.80 (3H, m), 4.10—4.20 (2H, m). IR ($CHCl_3$): 3450, 2925, 2850, 1710, 1460, 1320, 1220, 1140 cm^{-1}. *Anal.* Calcd for $C_{29}H_{62}N_3ClO_5S \cdot 1.5H_2O$: C, 55.52; H, 10.44; Cl, 5.65; N, 6.70; S, 5.11. Found: C, 55.49; H, 10.42; Cl, 5.78; N, 6.78; S, 4.85.

3-[3-Hexadecyloxy-2-(methoxy)propylaminosulfonyl]propyltrimethylammonium Iodide (19) To a solution of **12c** (600 mg, 1.07 mmol) in toluene (5 ml) was added a toluene solution of Me_3N (10 ml/25 ml), and the mixture was left standing in a sealed tube at room temperature overnight. After removal of the solvent, **19** (577 mg, 87%) was obtained on reprecipitation from Et_2O as a colorless powder, mp 80.5—82.5 °C. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (26H, s), 1.45—1.65 (2H, m), 2.30—2.50 (2H, m), 3.15—3.65 (9H, m), 3.42 (9H, s), 3.47 (3H, s), 3.80—3.95 (2H, m), 6.30 (1H, t, J=6.0 Hz). IR ($CHCl_3$): 3380, 2925, 2850, 1470, 1325, 1230, 1145 cm^{-1}. *Anal.* Calcd for $C_{26}H_{57}IN_2O_3S$: C, 50.31; H, 9.26; I, 20.44; N, 4.51; S, 5.17. Found: C, 50.20; H, 9.25; I. 20.48; N, 4.63; S, 5.29.

By almost the same procedure, using an appropriate amine with or without a solvent, **20**—**41** were prepared.

3-[3-Hexadecylthio-2-(methoxy)propylaminosulfonyl]propyltrimethylammonium Iodide (20) Yield 60%. Colorless powder. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (26H, s), 1.48—1.68 (2H, m), 2.30—2.50 (2H, m), 2.56 (2H, t, J=7.2 Hz), 3.20—3.65 (5H, m), 3.43 (9H, s), 3.45 (3H, s), 3.85—3.93 (2H, m), 6.20 (1H, t, J=6.0 Hz). IR ($CHCl_3$): 3375, 2925, 2850, 1470, 1330, 1230, 1150, 1090, 1055, 1030 cm^{-1}. *Anal.* Calcd for $C_{26}H_{57}O_3S_2 \cdot 0.4H_2O$: C, 48.49; H, 9.05; I. 19.71; N, 4.35; S, 9.96. Found: C, 48.66; H, 8.85; I, 19.47; N, 4.47; S, 10.19.

3-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]propyl-*N*-methylmorphorinium Iodide (21) Yield 56%. Colorless powder. mp 61—62 °C (acetone–hexane). NMR ($CDCl_3+CD_3OD$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (30H, s), 1.40—1.60 (2H, m), 2.25—2.45 (2H, m), 3.12 (1H, t, J=7.0 Hz), 3.20—3.40 (6H, m), 3.47 (3H, s), 3.50—3.70 (5H, m), 3.73 (3H, s), 3.80—4.00 (2H, m), 4.00—4.10 (2H, m), 4.10—4.20 (2H, m). IR ($CHCl_3$): 3450, 2930, 2850, 1715, 1510, 1330, 1220, 1150 cm^{-1}. *Anal.* Calcd for $C_{31}H_{64}IN_3O_6S \cdot 1.0H_2O$: C, 49.52; H, 8.85; I, 16.88; N, 5.59; S, 4.26. Found: C, 49.44; H, 8.79; I, 16.90; N, 5.71; S, 4.47.

2-Methoxy-3-(3-morphorinopropylsulfonylamino)-1-octadecylcarbamoyloxypropane (22) Yield 87%. Colorless wax. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (30H, s), 1.40—1.60 (2H, m), 1.90—2.10 (2H, m), 2.40—2.50 (6H, m), 3.05—3.30 (6H, m), 3.45 (3H, s), 3.48—3.60 (1H, m), 3.65—3.75 (4H, m), 4.05—4.30 (2H, m), 4.75—4.90 (1H, br), 5.42 (1H, t, J=6.4 Hz). IR ($CHCl_3$): 3450, 2920, 2850, 1715, 1510, 1450, 1325, 1220, 1145, 1120 cm^{-1}. MS *m/z*: 591 (M^+).

4-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]butyl-*N*-methylimidazolium Iodide (23) Yield 69%. Colorless powder. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.25 (30H, s), 1.40—1.60 (2H, m), 1.75—2.00 (2H, m), 2.00—2.20 (2H, m), 3.00—3.50 (6H, m), 3.44 (3H, s), 3.50—3.65 (1H, m), 4.06 (3H, s), 4.00—4.30 (2H, m), 4.47 (2H, t, J=6.7 Hz), 5.21 (1H, t, J=6 Hz), 5.93 (1H, t, J=6 Hz), 7.38 (1H, s), 7.62 (1H, s), 9.71 (1H, s). IR ($CHCl_3$): 3450, 2920, 2850, 1715, 1460, 1325, 1220, 1140 cm^{-1}. *Anal.* Calcd for $C_{31}H_{62}IN_4O_5S$: C, 51.09; H, 8.44; I, 17.41; N, 7.69; S, 4.40. Found: C, 50.79; H, 8.36; I, 17.41; N, 7.67; S, 4.71.

2-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]ethylthiazolium Iodide (24) Yield 14%. Amorphous powder. NMR ($CDCl_3+CD_3OD$) δ: 0.88 (3H, t, J=6.5 Hz), 1.25 (30H, s), 1.40—1.60 (2H, m), 3.05—3.20 (2H, m), 3.20—3.40 (2H, m), 3.46 (3H, s), 3.50—3.70 (1H, m),

3.90—4.00 (2H, m), 4.00—4.30 (2H, m), 5.20—5.35 (2H, m), 5.50—5.60 (1H, m), 6.75—6.90 (1H, m), 8.17 (1H, d, J=3.8 Hz), 8.70 (1H, d, J=3.8 Hz), 10.60—10.70 (1H, m). IR ($CHCl_3$): 3360, 2920, 2850, 1700, 1535, 1460, 1335, 1255, 1150 cm^{-1}. MS m/z: 576 (M^+-I).

3-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]propylthiazolium Iodide (25) Yield 55%. Colorless powder. mp 116—118 °C (CH_2Cl_2–acetone). NMR ($CDCl_3$) δ: 0.86 (3H, t, J=6.5 Hz), 1.24 (30H, s), 1.30—1.50 (2H, m), 2.20—2.40 (2H, m), 2.90—3.20 (6H, m), 3.32 (3H, s), 3.30—3.45 (1H, m), 3.80—4.15 (2H, m), 4.67 (2H, t, J=7.2 Hz), 7.15 (1H, t, J=5.6 Hz), 7.33 (1H, t, J=5.8 Hz), 8.35—8.42 (1H, m), 8.60 (1H, d, J=3.8 Hz), 10.20 (1H, s). IR ($CHCl_3$): 3360, 2855, 1685, 1565, 1470, 1310, 1280, 1145, 1130 cm^{-1}. *Anal.* Calcd for $C_{29}H_{56}IN_3O_5S_2\cdot 0.2H_2O$: 48.28; H, 7.88; I, 17.59; N, 5.82; S, 8.89. Found: C, 48.37; H, 7.88; I, 17.38; N, 6.00; S, 9.22.

4-[2-Methoxy-1-(octadecylcarbamoyloxy)propylaminosulfonyl]butylthiazolium Iodide (26) Yield 41%. Pale yellow powder. mp 59.5—61.5 °C (CH_2Cl_2–Et_2O). NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.25 (30H, s), 1.40—1.65 (2H, m), 1.80—2.05 (2H, m), 2.05—2.40 (2H, m), 3.00—3.40 (6H, m), 3.44 (3H, s), 3.50—3.65 (1H, m), 4.00—4.30 (2H, m), 4.80—4.95 (2H, m), 5.35—5.50 (1H, br), 6.10—6.25 (1H, br), 8.30—8.40 (1H, m), 8.60—8.70 (1H, m), 10.55 (1H, s). IR ($CHCl_3$): 3400, 2930, 2850, 1715, 1465, 1430, 1320, 1235, 1140 cm^{-1}. *Anal.* Calcd for $C_{30}H_{58}IN_3O_5S_2\cdot 0.5H_2O$: C, 48.64; H, 8.03; N, 5.67; S, 8.66. Found: C, 48.46; H, 7.99; I, 17.02; N, 5.77; S, 8.87.

3-[3-Hexadecyloxy-2-(methoxy)propylaminosulfonyl]propylthiazolium Iodide (27) Yield 66%. Colorless powder. mp 52—53 °C (CH_2Cl_2–Et_2O). NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.25 (26H, s), 1.45—1.65 (2H, m), 2.50—2.70 (2H, m), 3.10—3.60 (9H, m), 3.45 (3H, s), 5.06 (2H, t, J=6.8 Hz), 6.18 (1H, t, J=5.7 Hz), 8.27 (1H, t, J=3.0 Hz), 8.76 (1H, d, J=1.7 Hz), 10.69 (1H, s). IR ($CHCl_3$): 3400, 2930, 2850, 1460, 1320, 1220, 1140 cm^{-1}. *Anal.* Calcd for $C_{26}H_{51}IN_2O_4S_2\cdot 0.5H_2O$: C, 47.62; H, 7.99; I, 19.35; N, 4.27; S, 9.78. Found: C, 47.73; H, 7.84; I, 19.15; N, 4.46; S. 9.94.

3-[3-Hexadecylthio-2-(methoxy)propylaminosulfonyl]propylthiazolium Iodide (28) Yield 56%. Colorless powder. mp 70—73 °C (acetone). NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (26H, s), 1.48—1.68 (2H, m), 2.55 (2H, t, J=7.3 Hz), 2.70 (2H, d, J=5.6 Hz), 2.50—2.70 (2H, m), 3.10—3.50 (4H, m), 3.43 (3H, s), 3.48—3.62 (1H, m), 5.04 (2H, t, J=7.4 Hz), 6.26 (1H, t, J=6.0 Hz), 8.29—8.32 (1H, m), 8.72—8.75 (1H, m), 10.59—10.60 (1H, m). IR ($CHCl_3$): 3375, 2930, 2850, 1460, 1325, 1220, 1140, 1090 cm^{-1}. *Anal.* Calcd for $C_{26}H_{51}IN_2O_3S_3\cdot H_2O$: C, 46.99; H, 7.76; I, 19.10; N, 4.21; S, 14.47. Found: C, 46.79; H, 7.71; I, 19.01; N, 4.25; S, 14.42.

3-[2-Methoxy-3-(octadecylcarbamoylthio)propylaminosulfonyl]propylthiazolium Iodide (29) Yield 37%. Amorphous powder. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.25 (30H, s), 1.40—1.62 (2H, m), 2.50—2.75 (2H, m), 2.95—3.60 (9H, m), 3.42 (3H, s), 4.95—5.20 (2H, m), 6.07—6.29 (2H, m), 8.20—8.30 (2H, m), 9.70—9.80 (1H, m), 10.20—10.32 (1H, m). IR ($CHCl_3$): 3420, 2925, 2850, 1670, 1465, 1330, 1150 cm^{-1}. MS m/z: 606 (M^+-I).

3-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]propylpyridinium Iodide (30) Yield 41%. Colorless needles. mp 80—81 °C (AcOEt : AcOH : H_2O = 4 : 1 : 1). NMR (DMSO-d_6) δ: 0.85 (3H, t, J=6.5 Hz), 1.23 (30H, s), 1.30—1.45 (2H, m), 2.20—2.40 (2H, m), 2.85—3.20 (6H, m), 3.32 (3H, s), 3.30—3.45 (1H, m), 3.80—4.15 (2H, m), 4.71 (2H, t, J=7.3 Hz), 7.18 (1H, t, J=6.0 Hz), 7.25—7.40 (1H, m), 8.19 (2H, d, J=6.8 Hz), 8.63 (1H, d, J=7.6 Hz), 9.08 (1H, d, J=5.4 Hz). IR ($CHCl_3$): 3360, 2855, 1685, 1565, 1470, 1310, 1280, 1145, 1130 cm^{-1}. *Anal.* Calcd for $C_{29}H_{56}IN_3O_5S_2\cdot 0.2H_2O$: C, 48.28; H, 7.88; I, 17.59; N, 5.82; S, 8.89. Found: 48.37; H, 7.88; I, 17.38; N, 6.00; S. 9.22.

3-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]propylpyradinium Iodide (31) Yield 56%. Yellow powder. mp 113.5—115 °C (CH_2Cl_2–acetone). NMR (DMSO-d_6) δ: 0.86 (3H, t, J=6.5 Hz), 1.24 (30H, s), 1.30—1.50 (2H, m), 2.30—2.50 (2H, m), 2.85—3.05 (2H, m), 3.05—3.15 (2H, m), 3.15—3.30 (2H, m), 3.30—3.50 (2H, m), 3.80—4.20 (2H, m), 4.02 (3H, s), 4.78 (2H, t, J=7.2 Hz), 7.13 (1H, t, J=5.0 Hz), 7.35 (1H, t, J=6.0 Hz), 9.20—9.30 (2H, m), 9.50—9.60 (2H, m). IR ($CHCl_3$): 3450, 2930, 2850, 1710, 1520, 1445, 1320, 1220, 1145 cm^{-1}. *Anal.* Calcd for $C_{30}H_{57}IN_4O_5S\cdot H_2O$: C, 50.43; H, 8.07; I, 17.76, N, 7.84; S, 4.49. Found: C, 50.27; H, 7.98; I, 17.75; N, 7.83; S, 4.79.

3-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]propylquinolinium Iodide (32) A solution of **12a** (200 mg, 0.32 mmol) in quinoline (300 mg, 2.3 mmol) was allowed to react at 50 °C overnight. Et_2O was added to the mixture and the precipitate was isolated by filtration. **32** (125 mg, 51%) was obtained on reprecipitation from CH_2Cl_2–Et_2O as a yellow powder, mp 56.5—58.0 °C. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5) 1.25 (30H, s), 1.40—1.60 (2H, m), 2.60—2.85 (2H, m), 3.00—3.20 (2H, m), 3.20—3.40 (2H, m), 3.50—3.70 (3H, m), 3.41 (3H, s), 4.00—4.20 (2H, m), 5.32 (1H, t, J=6 Hz), 5.60 (2H, t, J=8.1 Hz) 6.06 (1H, t, J=6 Hz), 7.97 (1H, t, J=8 Hz), 8.10—8.40 (3H, m), 8.71 (1H, d, J=9.2 Hz), 9.03 (1H, d, J=8.2 Hz), 10.27 (1H, d, J=5.4 Hz). IR ($CHCl_3$): 3445, 2920, 2850, 1710, 1520, 1460, 1320, 1230, 1140 cm^{-1}. *Anal.* Calcd for $C_{35}H_{60}IN_3O_5S\cdot 0.75H_2O$: C, 54.22; H, 7.99; I, 16.37; N, 5.42; S, 4.16. Found: C, 54.18; H, 7.92; I, 16.65; N, 5.50; S, 4.26.

4-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]butylquinolinium Iodide (33) Yield 63%. Yellow powder. mp 56.0—59.0 °C (acetone). NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.25 (30H, s), 1.40—1.60 (2H, m), 2.00—2.30 (2H, m), 2.30—2.50 (2H, m), 3.00—3.20 (2H, m), 3.20—3.40 (4H, m), 3.42 (3H, s), 3.48—3.60 (1H, m), 4.00—4.30 (2H, m), 5.28 (1H, t, J=5.5 Hz), 5.46 (2H, t, J=7.6 Hz), 5.85 (1H, t, J=6.0 Hz), 7.97 (1H, t, J=8.0 Hz), 8.05—8.40 (3H, m), 8.68 (1H, d, J=9.6 Hz), 9.01 (1H, d, J=8.2 Hz), 10.25 (1H, d, J=5.4 Hz). IR ($CHCl_3$): 3450, 2925, 2850, 1715, 1520, 1460, 1325, 1220, 1140 cm^{-1}. *Anal.* Calcd for $C_{36}H_{62}IN_3O_5S$: C, 55.09; H, 8.09; I, 16.17; N, 5.35; S, 4.08. Found: C, 54.88; H, 7.95; I, 16.25; N, 5.41; S, 4.33.

3-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]propylquinolinium Chloride (34) Yield 60%. Pale yellow powder. mp 57—59 °C (CH_2Cl_2–Et_2O). NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.25 (30H, s), 1.40—1.60 (2H, m), 2.15—2.35 (2H, m), 3.00—3.20 (2H, m), 3.2—3.35 (2H, m), 3.35—3.50 (1H, m), 3.37 (3H, s), 3.50—3.70 (2H, m), 4.00—4.30 (2H, m), 5.55—5.80 (3H, m), 7.75 (1H, t, J=6.0 Hz), 7.94 (1H, t, J=7.6 Hz), 8.15—8.40 (3H, m), 8.74 (1H, d, J=9.0 Hz), 8.97 (1H, d, J=8.2 Hz), 10.48 (1H, d, J=5.6 Hz). IR ($CHCl_3$): 3455, 2930, 2855, 1715, 1530, 1470, 1325, 1220, 1140 cm^{-1}. *Anal.* Calcd for $C_{35}H_{60}ClN_3O_5S\cdot 1.2H_2O$: C, 60.75; H, 9.09; Cl, 5.12; N, 6.07; S, 4.63. Found: C, 60.66; H, 9.09; Cl, 4.89; N, 6.23; S, 4.51.

4-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]butylquinolinium Chloride (35) Yield 64%. Pale yellow powder. mp 57.0—59.0 °C (acetone). NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.25 (30H, s), 1.40—1.60 (2H, m), 2.00—2.30 (2H, m), 2.30—2.50 (2H, m), 3.00—3.20 (2H, m), 3.20—3.40 (4H, m), 3.39 (3H, s), 3.53—3.63 (1H, m), 4.00—4.30 (2H, m), 5.40—5.65 (3H, m), 6.85 (1H, t, J=7.0 Hz), 7.93 (1H, t, J=7.2 Hz), 8.00—8.40 (3H, m), 8.65 (1H, t, J=9.0 Hz), 9.01 (1H, d, J=8.2 Hz), 10.35 (1H, d, J=5.2 Hz). IR ($CHCl_3$): 3450, 2925, 2850, 1715, 1520, 1465, 1320, 1220, 1140 cm^{-1}. *Anal.* Calcd for $C_{36}H_{62}ClN_3O_5S\cdot 1.5H_2O$: C, 60.78; H, 9.21; Cl, 4.98; N, 5.91; S, 4.51. Found: C, 60.94; H, 9.02; Cl, 4.58; N, 5.91; S, 4.78.

3-[2-Methoxy-3-(octadecylcarbamoylthio)propylaminosulfonyl]propylquinolinium Iodide (36) Yield 56%. Yellow amorphous powder. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.25 (30H, s), 1.40—1.62 (2H, m), 2.62—2.85 (2H, m), 2.90—3.65 (9H, m), 3.39 (3H, s), 5.56 (2H, t, J=8.1 Hz), 5.80—6.25 (2H, br), 7.99 (1H, t, J=7.4 Hz), 8.13—8.37 (3H, m), 8.67 (1H, d, J=8.8 Hz), 9.07 (1H, d, J=8.2 Hz), 10.14 (1H, d, J=5.2 Hz). IR ($CHCl_3$): 3430, 3150, 2930, 2855, 1670, 1500, 1465, 1330, 1150 cm^{-1}. MS m/z: 650 (M^+-I).

4-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]butylisoquinolinium Iodide (37) Yield 75%. Pale yellow powder. mp 59.0—60.0 °C (Et_2O–acetone). NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.25 (30H, s), 1.40—1.60 (2H, m), 1.95—2.15 (2H, m), 2.30—2.50 (2H, m), 3.00—3.20 (2H, m), 3.20—3.40 (4H, m), 3.41 (3H, s), 3.50—3.65 (1H, m), 4.00—4.30 (2H, m), 5.13 (2H, t, J=7.6 Hz), 5.32 (1H, t, J=6 Hz), 5.90 (1H, t, J=6.0 Hz), 7.90—8.10 (1H, m), 8.10—8.20 (2H, m), 8.37 (1H, d, J=6.8 Hz), 8.65 (1H, d, J=8.4 Hz), 8.86—8.98 (1H, m), 10.69 (1H, s). IR ($CHCl_3$): 3450, 2930, 2850, 1715, 1460, 1320, 1220, 1140 cm^{-1}. *Anal.* Calcd for $C_{36}H_{62}IN_3O_5S\cdot 0.1H_2O$: C, 55.60; H, 8.06; I, 16.32; N, 5.40; S, 4.12. Found: C, 55.35; H, 8.04; I, 16.16; N, 5.58; S, 4.47.

3-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]propyl-5,6,7,8-tetrahydroquinolinium Iodide (38) Yield 69%. Yellow amorphous powder. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.25 (30H, s), 1.40—1.65 (2H, m), 1.80—2.00 (2H, m), 2.00—2.20 (2H, m), 2.40—2.70 (2H, m), 2.90—3.05 (2H, m), 3.12 (2H, q, J=6.8 Hz), 3.20—3.40 (2H, m), 3.44 (1H, s), 3.40—3.70 (3H, m), 4.00—4.30 (2H, m), 4.90—5.10 (2H, m), 5.25—5.40 (1H, br), 5.90—6.05 (1H, br), 7.80—8.00 (1H, m), 8.10 (1H, d, J=7.6 Hz), 9.35—9.50 (1H, m). IR ($CHCl_3$): 3450, 3350, 2920, 2845, 1710, 1510, 1460, 1320, 1210, 1135, 1090 cm^{-1}. MS m/z: 638 (M^+-I).

3-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]propyl-*N*-methyl-1,2,3,4-tetrahydroquinolinium Iodide (39) Yield 70%. Yellow powder. mp 55—57 °C (CH_2Cl_2–Et_2O). NMR ($CDCl_3$) δ: 0.86 (3H, t, J=6.5 Hz), 1.25 (30H, s), 1.40—1.55 (2H, m), 1.90—2.60 (4H, m), 2.90—3.70 (9H, m), 3.41 (3H, s), 3.81 (3H, s), 4.00—4.40 (4H, m), 4.40—4.60 (2H, m), 5.25—5.40 (1H, m), 6.05—6.25 (1H, m), 7.27—7.55 (3H, m), 8.05 (1H, d, J=8.2 Hz). IR ($CHCl_3$): 3450, 2940, 2860, 1715,

1520, 1470, 1330, 1230, 1150 cm^{-1}. *Anal.* Calcd for $C_{36}H_{66}IN_3O_5S \cdot 0.75H_2O$: C, 54.50; H, 8.57; I, 15.99; N, 5.30; S, 4.04. Found: C, 54.31; H, 8.45; I, 15.70; N, 5.62; S, 4.25.

3-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]propyl-6-methoxyquinolinium Iodide (40) Yield 55%. Yellow powder. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.25 (30H, s), 1.40—1.60 (2H, m), 2.58—2.78 (2H, m), 3.11 (2H, q, J=6.4 Hz), 3.20—3.40 (2H, m), 3.40 (3H, s), 3.50—3.70 (4H, m), 4.03 (3H, s), 4.05—4.25 (2H, m), 5.34 (1H, t, J=5.5 Hz), 5.40—5.60 (2H, m), 6.02 (1H, t, J=6.0 Hz), 7.58 (1H, d, J=2.8 Hz), 7.84 (1H, dd, J=2.8, 9.8 Hz), 8.08 (1H, dd, J=5.8, 8.6 Hz), 8.61 (1H, d, J=9.8 Hz), 8.96 (1H, d, J=8.6 Hz), 9.93 (1H, d, J=5.8 Hz). IR ($CHCl_3$): 3380, 2925, 2850, 1710, 1630, 1530, 1460, 1430, 1400, 1330, 1270, 1220, 1140 cm^{-1}. *Anal.* Calcd for $C_{36}H_{62}IN_3O_6S \cdot 0.5H_2O$: C, 53.99; H, 7.93; I, 15.85; N, 5.25; S, 4.00. Found: C, 53.75; H, 7.87; I, 16.07; N, 5.26; S, 4.14.

4-[2-Methoxy-3-(octadecylcarbamoyloxy)propylaminosulfonyl]butylbenzothiazolium Iodide (41) Yield 67%. Pale yellow powder. mp 59.0—61.0 °C (Et_2O). NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.25 (30H, s), 1.40—1.60 (2H, m), 2.00—2.25 (2H, m), 2.25—2.50 (2H, m), 3.00—3.20 (2H, m), 3.20—3.40 (4H, m), 3.40 (3H, s), 3.50—3.65 (1H, m), 4.00—4.30 (2H, m), 5.10—5.35 (3H, m), 5.98 (1H, t, J=6.0 Hz), 7.80—8.00 (2H, m), 8.30—8.45 (2H, m), 11.35 (1H, s). IR ($CHCl_3$): 3450, 2930, 2850, 1715, 1510, 1460, 1430, 1330, 1220, 1140 cm^{-1}. *Anal.* Calcd for $C_{34}H_{60}IN_3O_5S_2 \cdot 0.5H_2O$: C, 51.63; H, 7.77; I, 16.05; N, 5.31; S, 8.10. Found: C, 51.43; H, 7.83; I, 16.02; N, 5.38; S, 8.39.

3-Chloropropanesulfonamide (43) To an ice-cooled and stirred solution of 3-chloropropanesulfonyl chloride (**42**) (12.2 ml, 0.1 mol) in CH_2Cl_2 (100 ml) was added 28% aqueous NH_3 (50 ml), and the mixture was allowed to stand at room temperature for 1 h. After removal of the solvent, the residue was dissolved in CH_2Cl_2, and the insoluble material was filtered off by passage through a pad of Celite. The filtrate was concentrated, and **43** (15.5 g, 100%) was obtained as a colorless powder. NMR ($CDCl_3$) δ: 2.27—2.45 (2H, m), 3.28—3.38 (2H, m), 3.71 (2H, t, J=6.2 Hz), 4.70—4.95 (2H, br).

***N*-Acetyl-3-chloropropanesulfonamide (44)** To a solution of **43** (1.53 g, 9.71 mmol) in lutidine (5 ml) was added acetic anhydride (3 ml), and the mixture was stirred at 40 °C aor 8 h. After removal of the reagents, **44** (1.33 g, 68%) was obtained on reprecipitation from CH_2Cl_2–hexane as a colorless powder, mp 68—69 °C. NMR ($CDCl_3$ + CD_3OD) δ: 2.17 (3H, s), 2.20—2.40 (2H, m), 3.10—3.80 (4H, m). IR ($CHCl_3$): 3250, 3020, 1720, 1440, 1405, 1340, 1205, 1150 cm^{-1}. *Anal.* Calcd for $C_5H_{10}ClNO_3S$: C, 30.08; H, 5.05; Cl, 17.76; N, 7.02; S, 16.06. Found: C, 29.85; H, 5.00; Cl, 17.66; N, 7.13; S, 15.97.

***N*-Benzyloxycarbonyl-3-chloropropanesulfonamide (45)** To an ice-cooled and stirred solution of benzylcarbamate (60.5 g, 0.4 mol) in THF (400 ml) with a dry ice-acetone bath at −70 °C was added 1 mol/l of lithium hexamethyldisilazide in THF (400 ml), and the mixture was stirred for 1 h. **42** (24.3 ml, 0.2 mol) was added to the mixture at −70 °C, then the mixture was allowed to warm to room temperature. After concentration of the solution to half its original volume, iso-Pr_2O (500 ml) was added to the mixture. The organic layer was washed with H_2O. The aqueous layer was acidified with 1 N HCl and the product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated NaCl and then dried and evaporated, and **45** (54.1 g, 93%) was obtained on reprecipitation from hexane as a colorless powder, mp 77—78 °C. NMR ($CDCl_3$) δ: 2.22—2.40 (2H, m), 3.55—3.70 (4H, m), 5.22 (2H, s), 7.30—7.40 (5H, m), 7.40—7.45 (1H, br). IR ($CHCl_3$): 3380, 3120, 1745, 1420, 1450, 1220, 1145 cm^{-1}. *Anal.* Calcd for $C_{11}H_{14}ClNO_4S$: C, 45.29; H, 4.84; Cl, 12.15; N, 4.80; S, 10.99. Found: C, 45.06; H, 4.83; Cl, 12.06; N, 5.09; S, 10.71.

***N*-*tert*-Butoxycarbonyl-3-chloropropanesulfonamide (46)** Yield 65%. Colorless powder. NMR ($CDCl_3$) δ: 1.52 (9H, s), 2.25—2.40 (2H, m), 3.55—3.65 (2H, m), 3.70 (2H, t, J=6.2 Hz).

3-(3-Chloropropylbenzyloxycarbonylsulfonimide)-2-methoxy-1-octadecylcarbamoyloxypropane (48a) To an ice-cooled and stirred solution of **7a** (200 mg, 0.5 mmol), **45** (175 mg, 0.6 mmol) and PPh_3 (157 mg, 0.6 mmol) in THF (5 ml) was added DEAD (95 μl, 0.6 mmol), and the mixture was stirred at room temperature overnight. After removal of the solvent, the residue was purified by silica gel column chromatography using an AcOEt–hexane (1 : 3) mixture as an eluent, and **48a** (300 mg, 89%) was obtained as a white wax. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz), 1.26 (30H, s), 1.40—1.55 (2H, m), 2.25—2.40 (2H, m), 3.05—3.20 (2H, m), 3.37 (3H, s), 3.50—3.74 (5H, m), 3.74—4.28 (4H, m), 4.60—4.80 (1H, br), 5.28 (2H, s), 7.32—7.45 (5H, m). IR ($CHCl_3$): 3450, 2930, 2850, 1725, 1510, 1455, 1360, 1230, 1140 cm^{-1}. MS *m/z*: 674 (M^+).

Almost the same procedure was used for the conversion of **7a** to **47a** and **49a**.

To a solution of **48a** (11.5 g, 16.7 mmol) in MEK (10 ml) were added NaI (25 g, 167 mmol) and AcOH (2.87 ml, 50.1 mmol), and the mixture was refluxed for 3 h, then cooled to room temperature and poured into 0.5 N $Na_2S_2O_3$. The product was isolated by AcOEt extraction. The AcOEt layer was washed with saturated NaCl, then dried and evaporated. The product was purified by silica gel column chromatography using an AcOEt–hexane (1 : 1) mixture as an eluent, and **12a** (9.28 g, 86%) was obtained on reprecipitation from iso-Pr_2O as a colorless powder.

***cis*-5-Hydroxymethyl-2-octadecylcarbamoyloxymethyltetrahydrofuran (52)** To a stirred solution of *cis*-2,5-bishydroxymethyltetrahydrofuran (**51**) (6.61 g, 50 mmol) in pyridine (150 ml), octadecyl isocyanate (14.8 g, 50 mmol) was added, and the mixture was stirred at 60 °C for 15 h. The mixture was poured into 2 N HCl and the product was isolated by AcOEt extraction. The AcOEt layer was washed with H_2O, saturated aqueous $NaHCO_3$ and saturated NaCl, then dried and evaporated. The product was purified by silica gel column chromatography using an AcOEt–hexane (2 : 1) mixture as an eluent, and **52** (4.85 g, 23%) was obtained as a colorless powder. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.8 Hz), 1.26 (30H, s), 1.40—1.58 (2H, m), 1.62—2.10 (4H, m), 2.50—2.75 (1H, br), 3.17 (2H, q, J=6.4 Hz), 3.68—3.86 (1H, m), 3.96—4.28 (4H, m), 4.76 (1H, br). IR ($CHCl_3$): 1710 cm^{-1}.

***cis*-5-Azidomethyl-2-octadecylcarbamoyloxymethyltetrahydrofuran (53)** To an ice-cooled and stirred solution of **52** (641 mg, 1.50 mmol) and Et_3N (273 μl, 1.95 mmol) in CH_2Cl_2 (20 ml) was added methanesulfonyl chloride (128 μl, 1.65 mmol), and the mixture was stirred at room temperature for 30 min. The product was isolated by CH_2Cl_2 extraction. The CH_2Cl_2 layer was washed with 2 N HCl, saturated aqueous $NaHCO_3$ and saturated NaCl and then dried and evaporated to obtain crude mesylate (762 mg). NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.8 Hz), 1.26 (30H, s), 1.43—1.54 (2H, m), 1.67—1.91 (2H, m), 1.92—2.15 (2H, m), 3.07 (3H, s), 3.17 (2H, q, J=6.4 Hz), 3.99—4.34 (6H, m), 4.87—5.04 (1H, br). IR ($CHCl_3$): 1720 cm^{-1}. To a solution of the crude mesylate (762 mg) in DMF (30 ml) was added LiN_3 (1.5 g, 31 mmol), and the mixture was stirred at 70 °C for 15 h. The product was isolated by AcOEt extraction. The AcOEt layer was washed with water (×4) and then dried and evaporated. The product was purified by silica gel column chromatography using an AcOEt–hexane (1 : 2) mixture as an eluent, and the azide derivative **53** (614 mg, 90% from **52**) was obtained as an oil. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.8 Hz), 1.26 (30H, s), 1.40—1.57 (2H, m), 1.65—1.88 (2H, m), 1.88—2.13 (2H, m), 3.06—3.57 (4H, m), 3.91—4.33 (4H, m), 4.61—4.87 (1H, br). IR ($CHCl_3$): 2100, 1720 cm^{-1}.

***cis*-5-Aminomethyl-2-octadecylcarbamoyloxymethyltetrahydrofuran (54)** To a solution of **53** in THF (10 ml) was added PPh_3 (409 mg, 1.56 mmol) and the mixture was stirred at room temperature for 63 h. H_2O (0.2 ml) was added and the mixture was refluxed for 1 h. After removal of the solvent, the residue was purified by silica gel column chromatography using a $CHCl_3$–MeOH (9 : 1) mixture as an eluent, and **54** (475 mg, 93%) was obtained as an oil. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.8 Hz), 1.26 (30H, s), 1.40—1.58 (2H, m), 1.58—1.77 (4H, m), 1.84—2.08 (2H, m), 2.62—2.96 (2H, m), 3.17 (2H, q, J=6.4 Hz), 3.86—4.06 (2H, m), 4.06—4.27 (2H, m), 4.72—4.97 (1H, br).

***cis*-5-(3-Chloropropylsulfonylamino)methyl-2-octadecylcarbamoyloxymethyltetrahydrofuran (55)** Yield 69%. Colorless powder. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.8 Hz), 1.26 (30H, s), 1.40—1.58 (2H, m), 1.40—1.58 (2H, m), 1.80—2.12 (4H, m), 2.21—2.40 (2H, m), 3.08—3.46 (6H, m), 3.70 (2H, t, J=6.2 Hz), 3.97—4.40 (4H, m), 5.33—5.59 (2H, m). IR ($CHCl_3$): 1720, 1325, 1150 cm^{-1}.

***cis*-5-(3-Iodopropylsulfonylamino)methyl-2-octadecylcarbamoyloxymethyltetrahydrofuran (56)** Yield 94%. Colorless powder. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.8 Hz), 1.26 (30H, s), 1.42—1.59 (2H, m), 1.80—2.13 (4H, m), 2.24—2.43 (2H, m), 3.07—3.45 (8H, m), 3.97—4.40 (4H, m), 5.31—5.58 (2H, m). IR ($CHCl_3$): 1720, 1325, 1150 cm^{-1}.

***cis*-3-[Tetrahydro-5-(octadecylcarbamoyloxymethyl)furan-2-yl]methylaminosulfonyl]propylthiazolinium Iodide (57)** Yield 90%. Amorphous powder. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.8 Hz), 1.26 (30H, s), 1.40—1.60 (2H, m), 1.63—1.85 (2H, m), 1.85—2.12 (2H, m), 2.50—2.78 (2H, m), 3.00—3.52 (6H, m), 3.90—4.30 (4H, m), 4.96—5.23 (2H, m), 5.30—5.46 (1H, br), 6.24—6.40 (1H, br), 8.16—8.23 (1H, m), 8.77 (1H, d, J=4.2 Hz), 10.84 (1H, s). IR ($CHCl_3$): 3440, 2920, 2850, 1705, 1520, 1460, 1320, 1230, 1140, 1085 cm^{-1}. MS *m/z*: 616 ($M^+ - I$).

***cis*-3-[Tetrahydro-5-(octadecylcarbamoyloxymethyl)furan-2-yl]methylaminosulfonyl)]propylquinolinium Iodide (58)** Yield 85%. Yellow amorphous powder. NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.8 Hz), 1.26 (30H, s), 1.38—1.67 (2H, m), 1.63—2.10 (4H, m), 2.63—2.89 (2H, m), 3.00—3.70

(6H, m), 3.98—4.30 (4H, m), 5.23—5.43 (1H, br), 5.57—5.76 (2H, m), 5.91—6.06 (1H, m), 8.00 (1H, t, $J=8.4$ Hz), 8.09—8.21 (1H, m), 8.22—8.37 (2H, m), 8.67 (1H, d, $J=9.6$ Hz), 8.98 (1H, d, $J=8.4$ Hz), 10.55 (1H, d, $J=6.0$ Hz). IR ($CHCl_3$): 3440, 2920, 2850, 1710, 1525, 1460, 1375, 1320, 1230, 1145, 1090 cm^{-1}. MS *m/z*: 660 (M^+-I).

Biological Methods Materials: C_{16}-PAF and CV-3988 were synthesized at Shionogi Research Laboratories, Osaka, Japan. Bovine serum albumin (BSA) was purchased from Sigma, St. Louis.

Inhibitory Effect on Rabbit Platelet-Rich Plasma (PRP) Aggregation: Preparation of Rabbit PRP Mature male rabbits (NIBS-JW) weighting 2.2—2.6 kg were used. With the animal under sodium pentobarbital anesthesia (Somnopentyl, Pitman Moore, *ca.* 20 mg/kg, i.v.), blood was withdrawn from the carotid artery through a cannulation tube using a syringe containing sodium citrate (3.8%, 1/10 volume). The blood was centrifuged at 200 *g* for 10 min at 22 °C to obtain PRP. The remaining blood was centrifuged at 3000 rpm for 10 min to obtain platelet-poor plasma (PPP).

Measurement of Inhibition of Platelet Aggregation Platelet aggregation was examined by the method of Born,[21] using an aggregometer (NKK Hema tracer 1, model; PAT-6A, Niko Bioscience Co., Ltd., Tokyo) as reported by Uchida *et al.*[22] A pair of samples of PRP (230 μl) placed in a cuvette were warmed at 37 °C for 1 min with stirring (1100 rpm), and then a dimethyl sulfoxide (DMSO) solution of the test compound (1 μl) with saline (9 μl) was added. Exactly 2 min later, 10 μl of C_{16}-PAF (500 nM), which was dissolved in a saline solution containing 0.25% BSA, was added to each of the samples, and the changes in light transmission were recorded. The light transmission for PRP and PPP were taken as 0% and 100%, respectively, with the maximum light transmission after the addition of C_{16}-PAF as the maximum aggregation. The percent inhibition α was expressed as the difference between 1 and the ratio of the maximum aggregation with the test compound to that with the saline-DMSO.

The IC_{50} value for each compound was obtained by regression analysis of the concentration-inhibition relationship among 9—12 points of α covering 3—4 concentrations and ranging from 10% to 100%, obtained by three experiments.

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24) [^{3}H]-PAF Binding Assays in Rabbit Platelets: Rabbit washed

platelets were prepared by the gel filtration method as described by Hanasaki *et al.*,[25] and suspended in a buffer (137 mM NaCl, 2.7 mM KCl, 1.0 mM $MgCl_2$, 3.8 mM NaH_2PO_4, 3.8 mM Hepes, 5.6 mM glucose, 0.035% BSA and 1 μM prostaglandin E_1, pH 7.35). The assay for [^{3}H]-PAF binding to the platelets was performed according to the method of Iñarrea *et al.*[26] with slight modification. Briefly, washed rabbit platelets (5×10^7 cells) were incubated with 0.6 nM [^{3}H]-PAF in the presence of various concentrations of compounds for 30 min at 24 °C, then bound radioligand was separated from the free ligands by the rapid filtration method as described in the literature.[25] Specific binding is defined as the difference between binding in the presence and absence of 10 μM CV-3988. The percent inhibition of PAF-receptor specific binding in the presence of a known amount of the compound was expressed as a percentage inhibition of the specific binding in the absence of these compounds. The IC_{50} value was defined as the inhibitor concentration required to block 50% of the specific [^{3}H]-PAF binding to rabbit platelet membranes.

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