Pergamon

Bioorganic & Medicinal Chemistry 9 (2001) 1479–1491

BIOORGANIC & MEDICINAL CHEMISTRY

Studies on Selectin Blocker. 9. SARs of Non-Sugar Selectin Blocker against E-, P-, L-Selectin Bindings

Hideki Moriyama, Yasuyuki Hiramatsu, Takao Kiyoi, Toshio Achiha, Yoshimasa Inoue and Hirosato Kondo*

Department of Chemistry, Nippon Organon K.K., R&D Laboratories, 1-5-90 Tomobuchi-Cho, Miyakojima-Ku, Osaka 534-0016, Japan

Received 18 August 2000; accepted 20 January 2001

Abstract—As a part of study of selectin blockers, we have already reported that a non-sugar selectin antagonist (**3**) was successfully discovered using a computational screening (Hiramatsu, Y.; Tsukida, T.; Nakai, Y.; Inoue, Y.; Kondo, H. *J. Med. Chem.* **2000**, *43*, 1476). To investigate the SARs of compound **3** against E-, P-, and L-selectins, we synthesized the derivatives of compound **3** and evaluated their inhibitory activities toward selectin bindings. The structural diversity of compound **3** contained the following: (1) a modification of the spacer unit (**4**–**7**), (2) a modification of the tail unit (**8**–**11**), (3) a modification of the head unit (**12**–**18**). As a result, it was found that a non-sugar based selectin blocker (**3**) could be a potential lead compound for E-, P-, and L-selectin blockers and some of the derivatives showed broad and/or selective inhibitory activities toward the E-, P-, and L-selectins. In addition, it was found that the experimental evidence well supported that the computational screening using 3D-pharmacophore model could be useful methodology to find out a new lead for the several type of selectin blockers, which included a broad and/or a selective inhibitor. © 2001 Published by Elsevier Science Ltd.

Introduction

Recently, it has been clarified that oligosaccharides play an important role in significant vital functions, such as cancer metastasis and leukocytes invasion,[1–9] and oligosaccharides have been one of the best targets for new drug discovery. In addition, synthetic[10–17] and biological[18–22] studies of oligosaccharide have made remarkable progress, however, there are still some problems for application of oligosaccharide as a drug, because of difficulty of a large scale synthesis, absorption by oral administration and/or rapid metabolism in the body. Thus, current studies of oligosaccharides with potentially biological activities focus on their mimic to overcome the problems as described above. In the series of our studies on selectin blocker,[23–29] we have designed and synthesized some sugar mimetics in order to find an applicable methodology for the conversion of the sugar moiety into a simple molecular structure. From them, it has already been found that the lactose unit of 3′-sulfated Le^x derivative (**1**) (Chart 1) could be replaced with a simple dipeptide, D-Ser-L-Glu (**2a**) or L-Ser-D-Glu (**2b**), characterized by a type II and/or type II′ β-turn formation (Fig. 1).[27] This finding indicated that β-turn dipeptide would be an active scaffold to conserve three groups (fucose, branched alkyl chain, carboxylic acid), necessary for E-selectin binding. From the SAR study and the docking study toward E-selectin of compounds **1** and **2**, the function of these three groups, namely (1) coordination to calcium on E-selectin, (2) hydrophobic interaction with the hydrophobic region on E-selectin, and (3) interaction with basic residue on E-selectin, would be crucial for E-selectin binding.[24,25,27–30] This knowledge hinted at the possibility of new lead generation. Actually, we have focused on the discovery of non-sugar lead compounds based on an E-selectin complex model using the computational screening and have successfully found a new lead of selectin blocker (**3**, Chart 1) that had a good inhibitory activity against E-selectin binding.[31]

Incidentally, although a selectin blocker based on an E-selectin complex model could be a good inhibitor against P- and L-selectin bindings, there are still few

*Corresponding author. Tel.: +81-6-6921-8920; fax: +81-6-6921-9078; e-mail: kondo.hirosato@organon.co.jp

0968-0896/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0968-0896(01)00023-2

reports concerning their systematic SAR studies. For example, it has been reported that sugar-based selectin blockers such as sLe^X did not always show the same SAR against E-, P-, and L-selectin bindings. However, concerning non-sugar based selectin blockers, there are very few SAR studies against E-, P-, and L-selectins. In addition, the SAR studies of a non-sugar lead compound against E-, P-, and, L-selectins would be useful for discovery of potential selectin blockers, for example a selectin blocker with broad or a selective spectrum against E-, P-, and/or L-selectins. Therefore, we focused on the non-sugar lead compound **3** using the computational screening that we have originally constructed and investigated the biological profiles of analogues of compound **3** against E-, P-, and L-selectins.

In this paper, we describe the syntheses of compound **3** and its related derivatives, and their SAR studies.

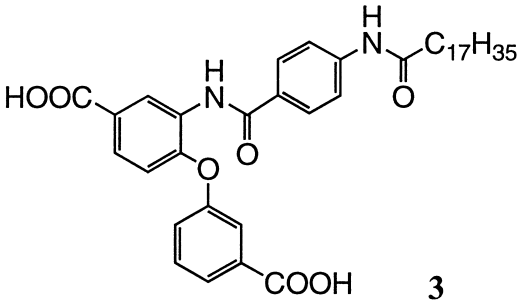


Chart 1.

Results and Discussion

Chemistry

Our interest was to investigate the SAR of compound **3**, and to verify the result of computer simulation. The SAR map of compound **3** is illustrated in Figure 2.

The preparation of diphenylether moiety was carried out according to a literature,[32] namely, methyl 4-fluoro-3-nitrobenzoate (**19**) was treated with methyl 3-hydroxybenzoate (**20**) in the presence of potassium carbonate to afford diphenylether derivative **21** in 92% yield. Next, compound **21** was subjected to catalystic reduction in the presence of a catalyst, 10% palladium-carbon, under hydrogen atmosphere to give compound **22**. The condensation of **22** with various acyl chloride **23a–e** afforded compounds **24a–e** in 19–100% yields. The hydrogenation of nitro group of compounds **24a,b,d,e** or the removal of Z group of **24c** using a catalyst, 10%

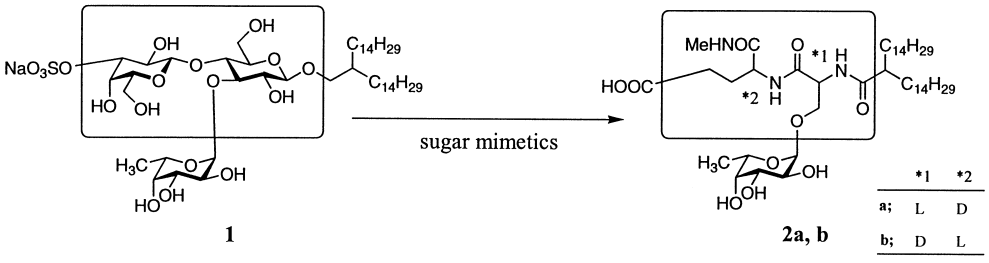


Figure 1. Successful sLe^x mimetics **1** and **2a,b**.

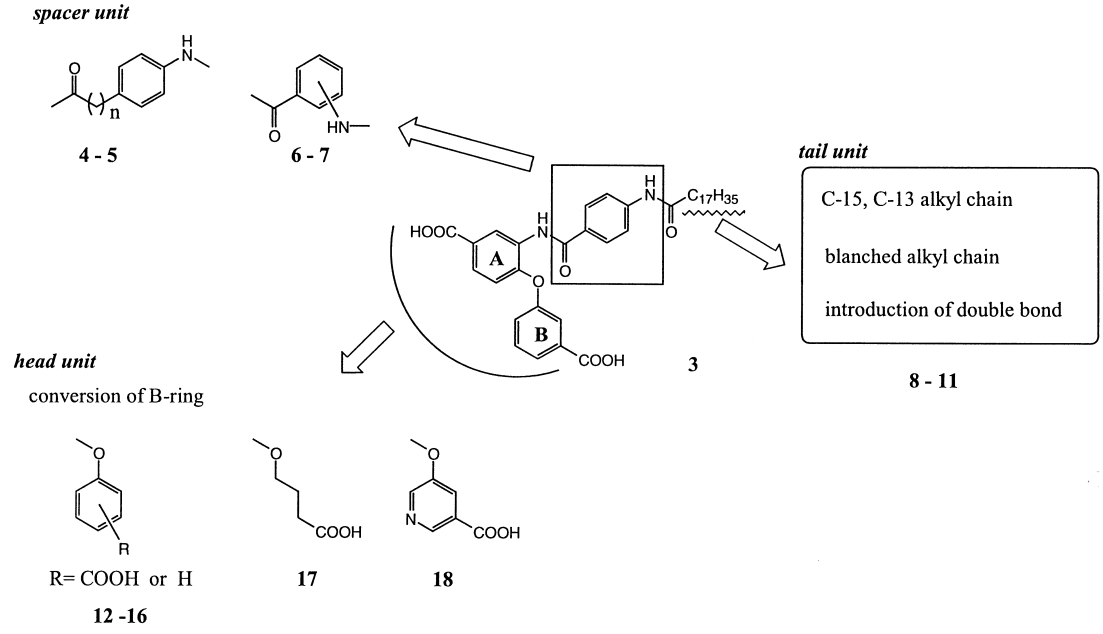


Figure 2. SAR map of non-sugar blocker (**3**).

palladium-carbon followed by the coupling with various acyl chloride in the presence of triethylamine afforded compounds **25a–e** and **26–29** in moderate yields. Finally, compounds **25a–e** and **26–29** were treated with 1N sodium hydroxide aqueous solution (1 N-NaOH aq) to provide the desired compounds **3–11**, as shown in Scheme 1.

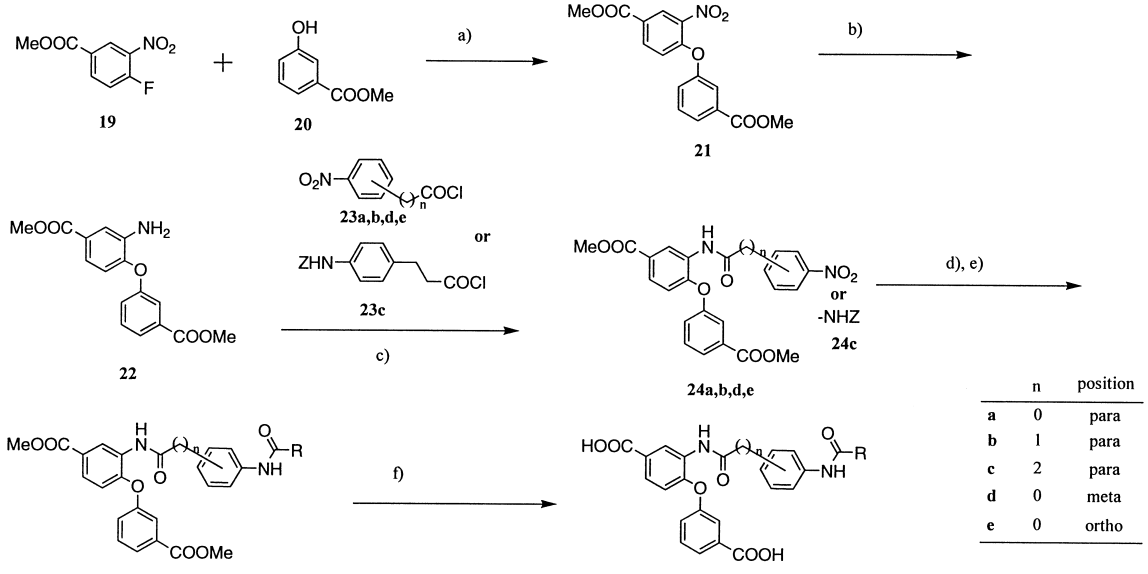
According to the same manner in Scheme 1, methyl 4-fluoro-3-nitrobenzoate (**19**) was treated with phenol derivatives **30a–c,e** in the presence of potassium carbonate to afford diphenylether derivatives **31a–c,e** in 68–97% yields. Next, compounds **31a–c,e** were subjected to catalystic reduction under hydrogen atmosphere to give aniline derivatives **32a–c,e**. The condensation of **32a–e** with 4-nitrobenzoyl chloride afforded compounds **33a–f** in moderate yields. The reduction of nitro group of compounds **33a–f** using 10% palladium-carbon for **33a–d,f** or 2M stannyl chloride in N,N-dimethylformamide for **33e** followed by the coupling with stearoyl chloride in the presence of triethylamine afforded compounds **34a–f** in 12–100% yields. Finally, compounds **34a–f** were treated with 1 N NaOH aq to provide the desired compounds **12–16** and **18** (Scheme 2).

For the synthesis of compound **17**, intermediate **37** was prepared according to Scheme 3, namely, methyl 4-hydroxy-3-nitrobenzoate **35** was substituted with ethyl 4-bromobutanoate **36** in the presence of potassium carbonate to provide compound **37** in 98% yield. Compound **37** was transformed into the target compound **17**, according to the same manner in Scheme 1.

Biological activities

The method using selectin-IgG chimeras reported by Foxall et al. was followed.[33] To explore the SAR of compound **3** and the related compounds, we have synthesized the several derivatives as illustrated in Figure 2 and have investigated their inhibitory activities against E-, P-, L-selectins (Tables 1–3): (1) a modification of the spacer unit (**3–7**), (2) a modification of the tail unit (**3**, **8–11**), (3) a modification of the head unit (**3**, **12–18**).

First, we focused on the modification of the spacer unit of compound **3**. As shown in Table 1, *meta*- and *ortho*-substituted derivatives (**6**, **7**) showed very weak activities compared to *para*-substituted compound **3** against E-, P-, and L-selectins, IC_{50} values of **3**, **6** and **7** were 86, >500, $>500\,\mu M$ against E-selectin, 6.1, >500, $>500\,\mu M$ against P-selectin, and 30, >500, $>500\,\mu M$ against L-selectin, respectively. Next, we investigated the relationships between the methylene length in the spacer unit and the inhibitory activity against E-, P-, L-selectins, compounds **3–5** corresponded to $n=0$, 1, and 2, respectively (Table 1). Against E-selectin, the in vitro activities of compounds **4** and **5** were decreased compared to that of compound **3**, however, against P- and L-selectins, all compounds **3–5** showed the potent inhibitory activities, interestingly, $n=1$ was the most optimized length for the inhibition against P- and L-selectins as shown in Table 1. These findings indicated that the spacer unit played an important role in keeping the desirable orientation and distance of three crucial



25a-e (R = $-C_{17}H_{35}$)
26 (n = 0, para ,R = $-C_{15}H_{31}$)
27 (n = 0, para, R = $-C_{13}H_{27}$)
28 (n = 0, para, R = $-CH(C_7H_{15})_2$)
29 (n = 0, para, R = $-(CH_2)_7CH{=}CHCH_2CH{=}CHC_5H_{11}$, Z,Z isomer)

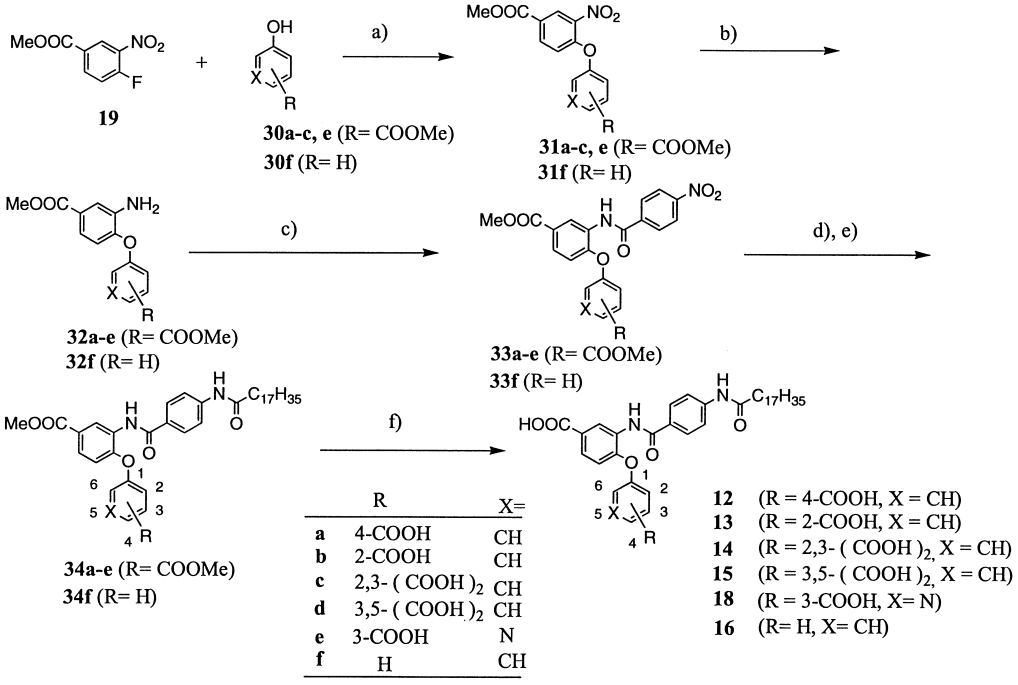
3 (n = 0, para, R = $-C_{17}H_{35}$)
4 (n = 1, para, R = $-C_{17}H_{35}$)
5 (n = 2, para, R = $-C_{17}H_{35}$)
6 (n = 0, meta, R = $-C_{17}H_{35}$)
7 (n = 0, ortho, R = $-C_{17}H_{35}$)

8 (n = 0, para ,R = $-C_{15}H_{31}$)
9 (n = 0, para, R = $-C_{13}H_{27}$)
10 (n = 0, para, R = $-CH(C_7H_{15})_2$)
11 (n = 0, para, R = $-(CH_2)_7CH{=}CHCH_2CH{=}CHC_5H_{11}$, Z,Z isomer)

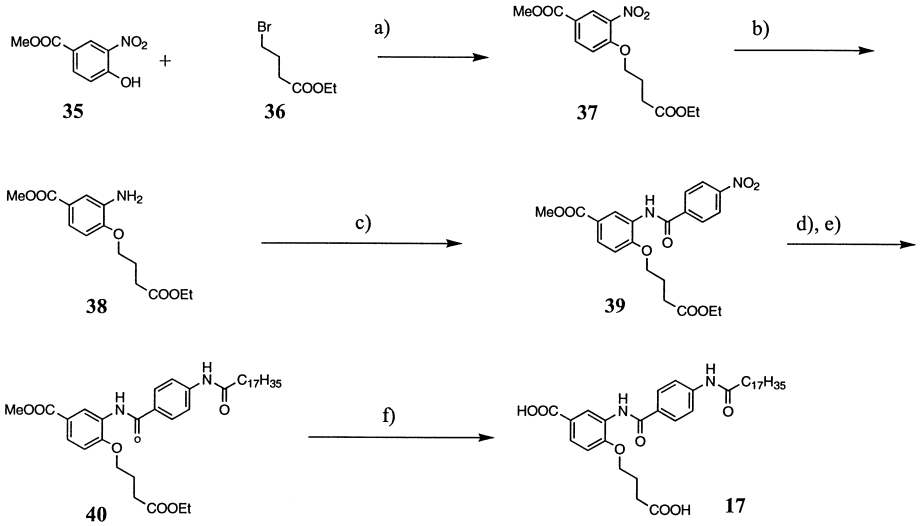
Scheme 1. Condition: (a) K_2CO_3/DMF, 92%; (b) H_2/Pd-C; (c) **23a–e**, Et_3N, 19–100% from **21**; (d) H_2/Pd-C; (e) RCOCl, Et_3N, 8–79% from **24a–e**; (f) 1 N NaOH, 9–99%.

functions, namely, two carboxylic acids and hydrophobic part necessary for binding to E-, P-, and L-selectins.

Next, we investigated modifications of hydrophobic parts (the tail unit) such as compounds **3** and **8**–**11**. Compounds **8** and **9** including a shorter single alkyl chain, 15- and 13-carbon lengths, respectively, were not active toward all selectin bindings. In addition to them, compound **10** having a branched alkyl chain, 2-heptylnonanoyl group also showed very weak activity, IC_{50} $>500\,\mu M$. Interestingly, though compound **11** had a similar carbon length to compound **3**, it did not exhibit potent inhibitory activity. Actually, a direction and/or a stable conformation of C-17 alkyl chain containing the unsaturated carbon atoms might be much different from that of a saturated C-17 alkyl chain, because the C-17 chain of compound **11** was incorporated with two double bonds, characterized by Z-isomer.[34] Namely, this finding also indicated that keeping the desirable orientation of alkyl chains as well as the carbon length of hydrophobic part was essential for the binding into E-, P-, and L-selectins (Table 2). According to the complex model of compound **11** with E-selectin, it was suggested that the edge of the long alkyl chain of compound **11** could not direct in the same position as that of compound **3** (Figs 3 and 4). Therefore, compound **11** wouldn't bind to E-selectin, because the long alkyl chain moiety of compound **11** could not interact with the

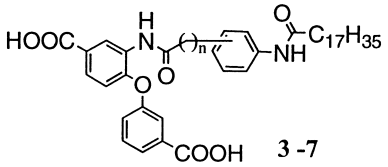


Scheme 2. Condition: (a) K_2CO_3/DMF, 68–97%; (b) H_2/Pd-C, 94% from **31f**; (c) 4-nitrobenzoyl chloride, Et_3N, 42–83% from **31a–c,e**, 73–93% from **32d,f**; (d) H_2/Pd-C, or 2 M $SnCl_2$/DMF; (e) stearoyl chloride, Et_3N, 12–100% from **32a**–**e**; (f) 1 N NaOH, 23–99%.



Scheme 3. Condition: (a) K_2CO_3/DMF, 98%; (b) H_2/Pd-C; (c) 4-nitrobenzoyl chloride, Et_3N, 91% from **37**; (d) H_2/Pd-C; (e) stearyl chloride, Et_3N, 87% from **39**; (f) 1 N NaOH, 73%.

Table 1. Blocking activity of compounds **3**–**7**



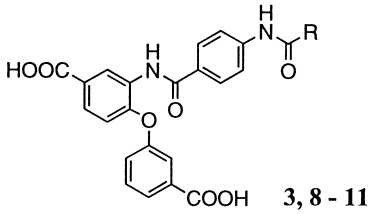
3 -7

compound	IC_{50} (μM)		
	E-selectin	P-selectin	L-selectin
3 ($n=0$, *para*)	86	6.1	30
4 ($n=1$, *para*)	320	3.7	5.3
5 ($n=2$, *para*)	270	38	91
6 ($n=0$, *meta*)	> 500	> 500	> 500
7 ($n=0$, *ortho*)	> 500	> 500	> 500

shallow hydrophobic region on E-selectin. This finding would suggest the weak in vitro activity of compound **11** toward E-selectin.

Finally, we studied on the modification of head unit of compound **3**. To know the relationships between the position of the carboxylic acid on head unit and their inhibitory activities against selectins, we synthesized compounds **12** and **13** with 2-carboxylic acid and 4-carboxylic acid, respectively. As shown in Table 3, both IC_{50} values (> 500 μM) of **12** and **13** toward the E-selectin were decreased compared to **3** (86 μM). In the previous study, we reported that the position of carboxylic acid, coordinated to the calcium is crucial for the inhibitory activity against E-selectin. According to the complex model between E-selectin and compound **3**,

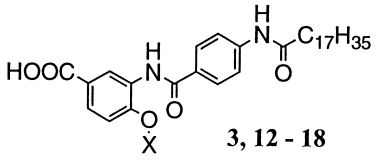
Table 2. Blocking activities of compounds **3** and **8**–**11**



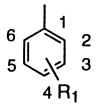
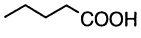
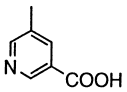
3, 8 - 11

Compound	IC_{50} (μM)		
	E-selectin	P-selectin	L-selectin
3 R = -$C_{17}H_{35}$	86	6.1	30
8 R = -$C_{15}H_{31}$	> 500	280	260
9 R = -$C_{13}H_{27}$	> 500	400	> 500
10 R = -$CH(C_7H_{15})_2$	> 500	400	> 500
11 R = -$(CH_2)_7CH{=}CHCH_2CH{=}CHC_5H_{11}$	> 500	> 500	> 500

Table 3. Blocking activities of compounds **3** and **12**–**18**



3, 12 - 18

Compound	X=		IC_{50} (μM)		
			E-selectin	P-selectin	L-selectin
3		R_1 = 3-COOH	86	6.1	30
12		R_1 = 4-COOH	> 500	14	47
13		R_1 = 2-COOH	> 500	> 500	> 500
14		R_1 = 2,3-$(COOH)_2$	> 500	> 500	> 500
15		R_1 = 3,5-$(COOH)_2$	> 500	> 500	> 500
16		R_1 = H	> 150[a]	2.7	2.0
17			> 500	21	37
18			19	11	4.2
1			280	30	100

[a]Due to the low solubility

the position of 2- or 4-carboxylic acid were not oriented to the same position of the 3-carboxylic acid. Therefore, compound **12** and **13** would not be able to coordinate to the calcium. This finding can explain the weak in vitro activity of compounds **12** and **13**. On the other hand, toward the P- and L-selectins, these compounds exhibited a little bit different profile, namely, the inhibitory activity was decreased in order of *meta*-, *para*-, *ortho*-substituted derivatives, IC_{50} values were 6.1 μM (P), 30 μM (L) for **3**, 14 μM (P), 47 μM (L) for **12**, and >500 μM (P, L) for **13**, respectively. This finding indicated that the position of the negatively charged group on the head unit of compound **3** might play an important role in recognition of E-, P-, and L-selectins, which could be useful information for the design of a broad and/or a selective selectin antagonist. Next, compounds **14** and **15** substituted with 2,3- and 3,5-dicarboxylic acids showed very weak activities toward all selectins. Although compounds **14** and **15** have the carboxylic acid in the desirable 3-position, these compounds show weak activity against E-selectin. In the previous paper, we described that compound **15** exhibited weak in vitro activity because the binding conformation of **15** would not be stable compared to lead compound **3**. Compound **14** might also show weak activity because of the same reason of **15**. In addition, in order to clarify the biological importance of carboxylic acid on the head unit of compound **3**, we synthesized compound **16**, eliminated the carboxylic acid group and evaluated the in vitro activity toward the E-, P-, and L-selectins. It was of interest to note that the inhibitory activities of **16** toward the P- and L-selectins were more potent than

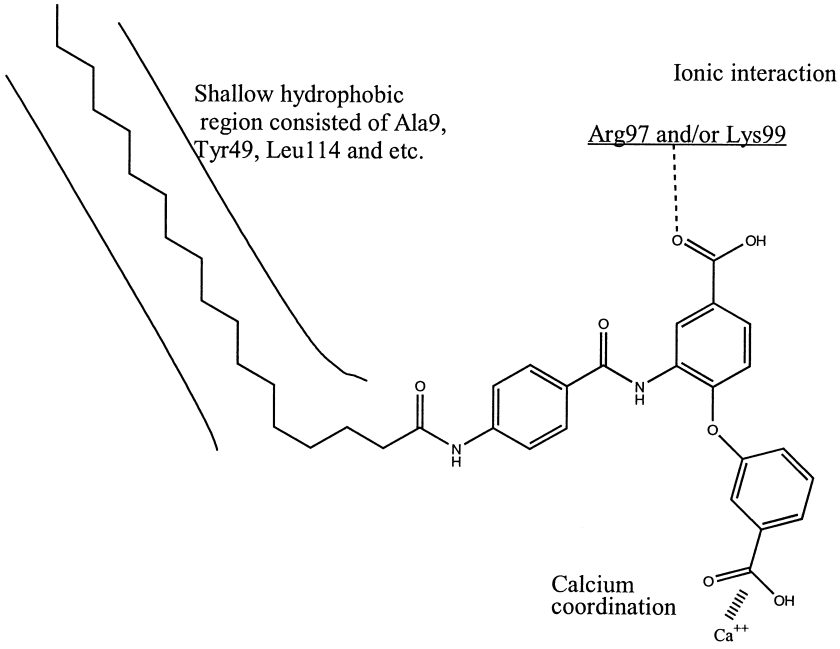


Figure 3. The scheme of the complex model of compound **3** and E-selectin based on the three points of interaction: (1) one of the carboxylic acids of isophthalic acid coordinates to calcium; (2) the carboxylic acid in the benzoic moiety forms the electric interaction with Arg97 and/or Lys99; (3) a C17 long alkyl chain interacts with the shallow hydrophobic region consisted of Leu114, Ala9, Tyr49, and so on on E-selectin.

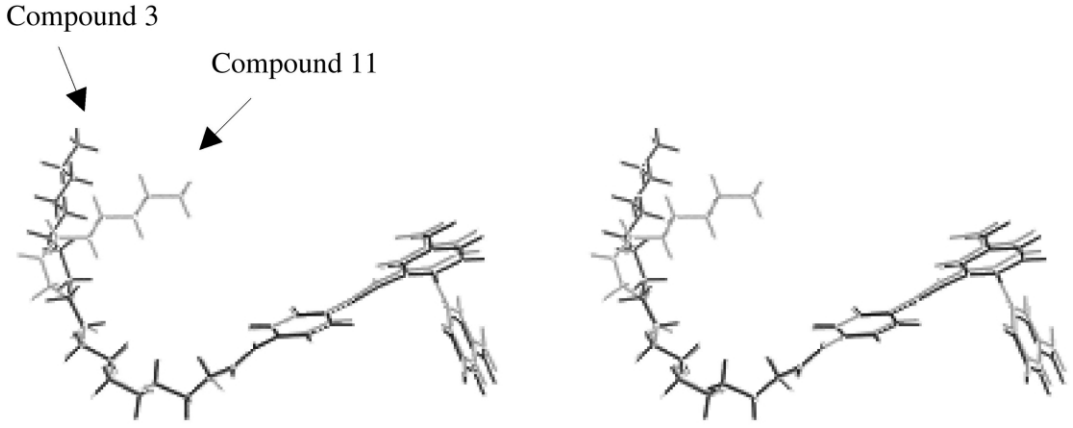


Figure 4. The stereoview of the superimpose between compounds **3** and **11** of the bindingconformation toward E-selectin. The conformation of compound **3** was retrieved from the complex model with E-selectin. The conformation of compound **11** was constructed by means of changing the rotatable bonds to fit the binding conformation of compound **3**. However, the edge of the long alkyl chain of the compound **11** does not fit to that of compound **3**, because two Z-double bonds restricted the conformation. As the interaction point on E-selectin of the long alkyl chain is shallow, compound **11** cannot bind to E-selectin tightly.

that of compound **3**, the IC_{50} values of **16** were 2 times more potent and 15 times more potent than that of compound **3**, against P- and L-selectin, respectively. This SAR information would be helpful to make sure the possible recognition sites of this series of compounds.

Next, to investigate the biological importance of the head aromatic ring of compound **3**, compounds **17** and **18** were synthesized. The IC_{50} value for butanoic acid derivative **17** was $>500\,\mu M$ toward E-selectin, but toward P- and L-selectins it showed favorably potent activities; the IC_{50} were 21 μM (P) and 37 μM (L). Presumably, the flexibility of butanoic acid moiety in the head unit would be disadvantage for E-selectin binding. On the other hand, compound **18** exhibited the potent inhibitory activity as well as compound **3**. This finding suggested that the negatively charged group attached at the 3-position on the rigid aromatic ring such as the phenyl or pyridyl ring would be necessary for binding to selectins, especially E-selectin.

Conclusion

For the preliminarly structural optimization of compound **3**, we have synthesized and evaluated the inhibitory activities of compound **3** analogues toward the E-, P-, and L-selectins. In the spacer unit, the difference in methylene length reflects on the selectivity of P- and L-selectins against E-selectin. In the tail unit, the length and the orientation of the long alkyl chain are very important for the activity against all selectins. In the head unit, the position of the carboxylic acid is very important for the activity toward E-selectin, but this is not necessary for the activity toward P- and L-selectins. From these results, we clarified that the preliminary SAR of the non-sugar-based compounds and the difference of the activity toward each selectin. In addition, we found that a non-sugar based selectin blocker (**3**) discovered using the computational screening could be a potential lead compound for E-, P-, and L-selectin blockers.

Experimental

Inhibition assay of selectin-sLe^x bindings

The construction of the selectin–immunoglobulin was carried out according to a previous paper.[23]

A solutoin of sLe^x pentasaccharide ceramide analogue in a 1:1 mixture of methanol and distilled water was pipetted into microtiter plate wells (96 wells; Falcon Pro-Bind) at 100 pmol/50 μL/well and was adsorbed by evaporating the solvent. The wells were washed twice with distilled water, blocked with 5% BSA (bovine serum albumin)–1 mM $CaCl_2$/50 mM imidazole buffer (pH 7.2) for 1 h at rt, and washed three times with 50 mM imidazole buffer (pH 7.2).

Separately, a 1:1 volumetric mixture of 1:500 dilution in 1% BSA–1 mM $CaCl_2$/50 mM imidazole buffer (pH 7.2) of biotinylated goat F(ab)2 anti-human IgG(g)/streptavidin-alkaline phosphatase (Zymed Lab Inc.) and a selectin–immunoglobuline fusion protein (selectin–Ig) was incubated at rt for 30 min to form a complex. The test compounds were dissolved in DMSO at 10 mM and finally diluted by 1 mM $CaCl_2$/50 mM imidazole buffer (pH 7.2) to final concentrations at 1000, 500, 250, 125, 62.5, 31.3, 15.6, 7.8 μM, respectively. Reactant solutions were prepared by incubating 30 μL of this solution at each concentration with 30 μL of the above complex solution for 30 min at rt. This reactant solution was then added to the above microtiter wells at 50 μL/well and incubeted at 37 °C for 45 min. The wells were washed three times with 50 mM imidazole buffer (pH 7.2) and diluted water, respectively, followed by addition of *p*-nitrophenyl phosphate (1 mg/mL) and 0.01% $MgCl_2$ in 1M diethanolamine (pH 9.8) at 50 μL/well. The reactant mixture was developed for 120 min at rt, and absorbance at 405 nm was measured. Percent binding was calculated by the following equation:

$$\%\ \text{binding} = (X - C/A - C) \times 100$$

wherein X is the absorbance of wells containing the test compounds at each concentration, C is the absorbance of wells not containing the selectin–Ig and test compounds, and A is the absorbance of control wells not containing the test compounds. The results of inhibitory activities are presented in Tables 1–3 as IC_{50} values. The number of replicates is 2.

General procedure for the preparation of 21, 31a–c, 31e and 37: dimethyl 3-nitro-3′,4-oxydibenzoate (21).[32] To a solution of methyl 4-fluoro-3-nitrobenzoate (**19**) (1.99 g, 10 mM) and methyl 3-hydroxybenzoate (**20**) (1.52 g, 10 mM) in DMF (20 mL) was added K_2CO_3 (1.38 g, 10 mM), and the mixture was stirred for 6 h at rt. AcOEt was added to the solution, and the mixture was washed with water and brine successively, dried over Na_2SO_4, and concentrated. To the resulting residue *n*-hexane and Et_2O was added, and the precipitate was filtered to afford the title compound **21** (3.04 g, 91.8%) as a colorless solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.96 (s, 3H), 6.99 (d, 1H, $J=8.7$ Hz), 7.31 (dd, 1H, $J=8.1$, 2.5 Hz), 7.51 (t, 1H, $J=7.9$ Hz), 7.74 (s, 1H), 7.93 (d, 1H, $J=8.2$ Hz), 8.14 (ddd, 1H, $J=8.8$, 2.2, 0.5 Hz), 8.62 (d, 1H, $J=2.2$ Hz); TOF-MS 354 ($M^+ + Na$), 380 ($M^+ + K$).

Dimethyl 3-nitro-4,4′-oxydibenzoate (31a). Yield 97.2% as a colorless solid ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.93 (s, 3H), 3.96 (s, 3H), 7.09 (d, 1H, $J=8.7$ Hz), 7.11 (d, 2H, $J=6.8$ Hz), 8.10 (d, 2H, $J=6.8$ Hz), 8.19 (dd, 1H, $J=8.7$, 2.1 Hz), 8.63 (d, 1H, $J=2.1$ Hz); TOF–MS 354 ($M^+ + Na$), 380 ($M^+ + K$).

Dimethyl 3-nitro-2′,4-oxydibenzoate (31b). Yield 70.0% as a pale yellow solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.94 (s, 3H), 6.75 (d, 1H, $J=9.0$ Hz), 7.22 (dd, 1H, $J=8.0$, 1.0 Hz), 7.40 (td, 1H, $J=6.0$, 1.0 Hz), 7.64 (td, 1H, $J=6.0$, 2.0 Hz), 8.00–8.15 (m, 2H), 8.63 (d, 1H, $J=2.0$ Hz); TOF–MS 354 ($M^+ + Na$), 380 ($M^+ + K$).

Dimethyl 3-(4-methoxycarbonyl-2-nitrophenoxy)phthalate (31c). Yield 86.0% as a pale yellow solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.86 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 6.96 (d, 1H, J = 9.0 Hz), 7.27 (dd, 1H, J = 8.0, 1.0 Hz), 7.53 (t, 1H, J = 8.0 Hz), 7.92 (dd, 1H, J = 8.0, 1.0 Hz), 8.12 (dd, 1H, J = 9.0, 2.0 Hz), 8.57 (d, 1H, J = 2.0 Hz); TOF-MS 412 (M^+ + Na), 428 (M^+ + K).

Methyl 5-(4-methoxycarbonyl-2-nitrophenoxy)nicotinate (31e). yield 68.1% as a colorless solid; mp 90–91 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.96 (s, 3H), 3.98(s, 3H), 7.07 (d, 1H, J = 8.6 Hz), 7.93 (dd, 1H, J = 2.8, 1.7 Hz), 8.22 (dd, 1H, J = 8.6, 2.1 Hz), 8.64 (d, 1H, J = 2.8 Hz), 8.66 (d, 1H, J = 2.1 Hz), 9.09 (d, 1H, J = 1.7 Hz); TOF–MS 355 (M^+ + Na), 381 (M^+ + K).

Ethyl 4-(4-methoxycarbonyl-2-nitrophenoxy)butanoate (37). yield 98.0% as a syrup; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.2 Hz), 2.13–2.23 (m, 2H), 2.55–2.61 (m, 2H), 3.93 (s, 3H), 4.15 (q, 2H, J = 7.1 Hz), 4.23–4.28 (m, 2H), 7.13 (d, 1H, J = 8.8 Hz), 8.20 (dd, 1H, J = 8.8, 2.2 Hz), 8.51 (d, 1H., J = 2.2 Hz); TOF–MS 334 (M^+ + Na), 350 (M^+ + K).

Methyl 3-amino-4-phenoxybenzoate (32f). To a solution of methyl 4-fluoro-3-nitrobenzoate (**19**) (2.12 g, 10.6 mM) and phenol (**30f**) (1.00 g, 10.6 mM) in DMF (20 mL) was added K_2CO_3 (1.47 g, 10.6 mM), and the mixture was stirred for 1 h at rt. AcOEt was added to the solution, and the mixture was washed with water and brine successively, dried over Na_2SO_4, and concentrated. To the resulting residue was added *n*-hexane and Et_2O, and the precipitate was filtered to afford the title compound **31f** (2.57 g, 88.3%) as a colorless solid. To a solution of methyl 3-nitro-4-phenoxybenzoate (**31f**) (2.57 g, 9.4 mM) in MeOH (100 mL) and 1,4-Dioxane (10 mL) was added 10% Pd-C (250 mg), and the mixture was stirred for 2 h under 3 atmospheric pressure of hydrogen at room temperature. The precipitate was filtered off, and the filtrate was concentrated in vacuo to afford title compound **32f** (2.17 g, 94.4%) as a syrup: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.88 (s, 3H), 3.95(bs, 2H), 6.78 (d, 1H, J = 8.4 Hz), 7.02 (d, 2H, J = 7.3 Hz), 7.13 (t, 1H, J = 7.4 Hz), 7.30–7.40 (m, 3H), 7.50 (d, 1H, J = 2.0 Hz).

General procedure for the preparation of 24a–e, 33a–f and 39: dimethyl 3-(4-nitrobenzoylamino)-3′,4-oxydibenzoate (24a). To a solution of dimethyl 3-nitro-3′,4-oxydibenzoate (**21**) (4.37 g, 13.19 mM) in MeOH (100 mL) and 1,4-Dioxane (50 mL) was added 10% Pd-C (100 mg), and the mixture was stirred for 1 h under 3 atmospheric pressure of hydrogen at rt. The precipitate was filtered off, and the filtrate was concentrated *in* vacuo to afford dimethyl 3-amino-3′,4-oxydibenzoate (**22**) as a syrup.

In contrast, 4-nitrobenzoic acid (0.90 g, 5.39 mM) was added thionyl chloride (20 g), and the mixture was stirred for 2 h at 50 °C and then for 1 h at 75 °C. The mixture was co-evaporated with toluene to give 4-nitrobenzoyl chloride (**23a**) as a syrup. The resulting residue (**23a**) and **22** (864 mg, 2.87 mM) were dissolved in $CHCl_3$ (20 mL), and triethylamine (653 mg, 6.45 mM) was added to the solution, and the mixture was stirred for 20 h at rt. $CHCl_3$ (50 mL) was added to the solution, and the mixture was washed with 1 N HCl, saturated sodium carbonate and brine successively, dried over $MgSO_4$, and concentrated. The resulting precipitate was filtered to afford **24a** (700 mg, 54.3%) as a colorless crystal: mp 185–187 °C (*n*-hexane); ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.83 (s, 3H), 3.87 (s, 3H), 7.07 (d, 1H, J = 8.6 Hz), 7.35–7.45 (m, 1H), 7.50–7.60 (m, 2H), 7.77 (d, 1H, J = 7.6 Hz), 7.85 (dd, J = 2.2, 8.7 Hz), 8.07 (d, 2H, J = 8.6 Hz), 8.32 (d, 2H, J = 8.6 Hz), 8.35–8.43 (m, 1H), 10.37 (s, 1H); TOF-MS 473 (M^+ + Na), 489 (M^+ + K). Anal. ($C_{23}H_{18}N_2O_8$) Calcd. for C, 61.33; H, 4.03; N, 6.22, Found C, 61.13; H, 3.92; N, 6.35.

Dimethyl 3-[(4-nitrophenyl)acetylamino]-3′,4-oxydibenzoate (24b). Compound **24b** was prepared from dimethyl 3-amino-3′,4-oxydibenzoate (**22**) and 4-nitrophenyl acetic acid as described above: yield 19.4% as a solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.86 (s, 2H), 3.90 (s, 3H), 3.93 (s, 3H), 6.82 (d, 1H, J = 8.6 Hz), 7.05–7.20 (m, 1H), 7.35–7.55 (m, 3H), 7.55–7.65 (m, 1H), 7.65–7.85 (m, 2H), 7.88 (d, 1H, J = 7.7 Hz), 8.10–8.20 (m, 2H), 9.04 (d, 1H, J = 1.6 Hz); TOF–MS 487 (M^+ + Na), 503 (M^+ + K).

Dimethyl 3-[3-(4-benzyloxycarbonylaminophenyl)propionylamino]-3′,4-oxy-dibenzoate (24c). Compound **24c** was prepared from dimethyl 3-amino-3′,4-oxydibenzoate (**22**) and 3-(4-benzyloxycarbonylaminophenyl)propionic acid as described above: yield 72.4% as a colorless solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.70 (t, 2H, J = 7.4 Hz), 3.01 (t, 2H, J = 7.3 Hz), 3.89 (s, 6H), 5.17 (s, 2H), 6.66 (bs, 1H), 6.71 (d, 1H, J = 8.6 Hz), 7.10–7.50 (m, 11H), 7.60 (bs, 1H), 7.60–7.65 (m, 1H), 7.65–7.75 (m, 1H), 7.86 (d, 1H, J = 7.8 Hz), 9.06 (s, 1H); TOF–MS 605 (M^+ + Na), 621 (M^+ + K).

Dimethyl 3-(3-nitrobenzoylamino)-3′,4-oxydibenzoate (24d). Compound **24d** was prepared from dimethyl 3-amino-3′,4-oxydibenzoate (**22**) and 3-nitrobenzoic acid as described above: yield 73.6% as a pale brown amorphous; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.92 (s, 3H), 3.94 (s, 3H), 6.86 (d, 1H, J = 9.0 Hz), 7.33 (ddd, 1H, J = 8.0, 3.0, 1.0 Hz), 7.52 (t, 1H, J = 8.0 Hz), 7.70 (t, 1H, J = 8.0 Hz), 7.78 (dd, 1H, J = 3.0, 2.0 Hz), 7.82 (dd, 1H, J = 9.0, 2.0 Hz), 7.93 (dt, 1H, J = 1.0, 8.0 Hz), 8.21 (dt, 1H, J = 1.0, 8.0 Hz), 8.35–8.45 (m, 1H), 8.48 (bs, 1H), 8.69 (t, 1H, J = 2.0 Hz), 9.20 (d, 1H, J = 2.0 Hz); TOF-MS 473 (M^+ + Na), 489 (M^+ + K).

Dimethyl 3-(2-nitrobenzoylamino)-3′,4-oxydibenzoate (24e). Compound **24e** was prepared from dimethyl 3-amino-3′,4-oxydibenzoate (**22**) and 2-nitrobenzoyl chloride (**23e**) as described above: yield 100% as a syrup; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.94 (s, 3H), 3.97 (s, 3H), 6.81 (d, 1H, J = 8.6 Hz), 7.24–7.33 (m, 1H), 7.49 (t, 1H, J = 7.9 Hz), 7.58–7.84 (m, 5H), 7.92 (dt, 1H, J = 7.9, 1.4 Hz), 8.08 (bs, 1H), 8.14 (dd, 1H, J = 8.3, 1.3 Hz), 9.19 (bs, 1H); TOF–MS 473 (M^+ + Na), 489 (M^+ + K).

Dimethyl 3-(4-nitrobenzoylamino)-4,4′-oxydibenzoate (33a). Compound **33a** was prepared from dimethyl 3-nitro-4,4′-oxydibenzoate (**31a**) and 4-nitrobenzoyl chloride (**23a**) as described above: yield 73.5% as a solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.94 (s, 3H), 3.95 (s, 3H), 6.95 (d, 1H, J = 8.6 Hz), 7.15 (d, 1H, J = 8.8 Hz), 7.85 (dd, 1H, J = 8.6, 2.1 Hz), 8.01 (d, 2H, J = 8.8 Hz), 8.12 (d, 2H, J = 8.8 Hz), 8.35 (d, 2H, J = 8.8 Hz), 9.22 (d, 1H, J = 2.1 Hz); TOF-MS 473 (M^+ + Na), 489 (M^+ + K).

Dimethyl 3-(4-nitrobenzoylamino)-2′,4-oxydibenzoate (33b). Compound **33b** was prepared from dimethyl 3-nitro-2′,4-oxydibenzoate (**31b**) and 4-nitro-benzoyl chloride (**23a**) as described above: yield 53.8% as a pale yellow solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.93 (s, 3H), 6.88 (d, 1H, J = 9.0 Hz), 7.15–7.35 (m, 2H), 7.50–7.70(m, 1H), 7.80 (dd, 1H, J = 9.0, 2.0 Hz), 7.98 (dd, 1H, J = 8.0, 2.0 Hz), 8.16 (d, 2H, J = 9.0 Hz), 8.33 (d, 2H, J = 9.0 Hz), 9.17 (d, 1H, J = 2.0 Hz), 9.31 (s, 1H); TOF–MS 473 (M^+ + Na), 489 (M^+ + K).

Dimethyl 3-(4-methoxycarbonyl-2-nitrophenoxy)phthalate (33c). Compound **33c** was prepared from dimethyl 3-(4-methoxycarbonyl-2-nitrophenoxy)phthalate (**31c**) and 4-nitrobenzoyl chloride (**23a**) as described above: yield 83.0% as a syrup; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 7.05–7.20 (m, 2H), 7.45 (t, 1H, J = 8.0 Hz), 7.76 (d, 1H, J = 7.0 Hz), 7.89 (dd, 1H, J = 8.0, 2.0 Hz), 8.05 (d, 2H, J = 7.0 Hz), 8.30 (d, 2H, J = 9.0 Hz), 8.86 (bs, 1H), 9.13 (d, 1H, J = 2.0 Hz); TOF–MS 531 (M^+ + Na), 547 (M^+ + K).

Dimethyl 5-[4-Methoxycarbonyl-2-(4-nitrobenzoylamino)-phenoxy]isophthalate (33d). Compound **33d** was prepared from dimethyl 5-[3-amino-4-methoxy-carbonylphenoxy]-isophthalate (**32d**) and 4-nitrobenzoyl chloride (**23a**) as described above: yield 72.9% from **32d** as a solid; mp 226–229 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.87 (s, 6H), 3.88 (s, 3H), 7.18 (d, 1H, J = 8.6 Hz), 7.82 (d, 2H, J = 1.5 Hz), 7.87 (dd, 1H, J = 8.6, 2.2 Hz), 8.06 (d, 2H, J = 8.9 Hz), 8.25 (t, 1H, J = 1.5 Hz), 8.31 (d, 2H, J = 8.8 Hz), 8.39 (d, 1H, J = 2.1 Hz), 10.4 (s, 1H). Anal. ($C_{25}H_{20}N_2O_{10}$) Calcd. for C, 59.06; H, 3.96; N, 5.51; found C, 58.86; H, 3.88; N, 5.53.

Methyl 5-[4-methoxycarbonyl-2-(4-nitrobenzoylamino)-phenoxy]nicotinate (33e). Compound **33e** was prepared from methyl 5-(4-methoxycarbonyl-2-nitrophenoxy)-nicotinate (**31e**) and 4-nitrobenzoyl chloride (**23a**) as described above: yield 42.2% as a solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.95 (s, 3H), 3.97 (s, 3H), 6.85 (d, 1H, J = 8.6 Hz), 7.85 (dd, 1H, J = 8.6, 2.1 Hz), 8.00–8.20 (m, 3H), 8.36 (d, 2H, J = 8.8 Hz), 8.46 (bs, 1H), 8.70 (d, 1H, J = 2.8 Hz), 9.12 (d, 1H, J = 1.6 Hz), 9.22 (d, 1H, J = 2.0 Hz); TOF-MS 474 (M^+ + Na), 490 (M^+ + K).

Methyl 3-(4-nitrobenzoylamino)-4-phenoxybenzoate (33f). Compound **33f** was prepared from methyl 3-amino-4-phenoxybenzoate (**32f**) and 4-nitrobenzoyl chloride (**23a**) as described above: yield 92.7% as a colorless solid; mp 156–157 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.93 (s, 3H), 6.85 (d, 1H, J = 8.6 Hz), 7.12 (d, 2H, J = 7.4 Hz), 7.20–7.35 (m, 1H), 7.40–7.50 (m, 2H), 7.79 (dd, 1H, J = 8.7, 2.1 Hz), 8.04 (d, 1H, J = 8.9 Hz), 8.34 (d, 1H, J = 8.9 Hz), 8.60 (bs, 1H), 9.21 (d, 1H, J = 2.1 Hz); TOF–MS 415 (M^+ + Na), 431 (M^+ + K).

Ethyl 4-[4-Methoxycarbonyl-2-(4-nitrobenzoylamino)-phenoxy]butanoate (39). Compound **39** was prepared from ethyl 4-(4-methoxycarbonyl-2-nitrophenoxy)-butanoate (**37**) and 4-nitrobenzoyl chloride (**23a**) as described above: yield 91.0% as a colorless solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15 (t, 3H, J = 7.1 Hz), 2.20–2.30 (m, 2H), 2.53 (t, 2H, J = 6.3 Hz), 3.92 (s, 3H), 3.92–4.02 (m, 2H), 4.22 (t, 2H, J = 6.0 Hz), 6.97 (d, 1H, J = 8.6 Hz), 7.87 (dd, 1H, J = 8.6, 2.0 Hz), 8.16 (d, 2H, J = 8.8 Hz), 8.38 (d, 2H, J = 8.8 Hz), 8.68 (s, 1H), 9.15 (d, 1H, J = 2.0 Hz); TOF–MS 453 (M^+ + Na), 469 (M^+ + K).

General procedure for the preparation of 25a–e, 26–29, 34a–f and 40: dimethyl 3-(4-Octadecanoylamino-benzoylamino)-3′,4-oxydibenzoate (25a). To a solution of **24a** (650 mg, 1.44 mM) in MeOH-1,4-dioxane (10–10 mL) was added 10% Pd-C (200 mg), and the mixture was stirred for 2 h under hydrogen atmosphere at rt. The precipitate was filtered off, and the filtrate was concentrated in vacuo to afford dimethyl 3-aminobenzoylamino-3′,4-oxydibenzoate as a syrup. On the other hand, to stearic acid sodium salt (607 mg, 1.98 mM) was added thionyl chloride (20 mL), and the mixture was stirred for 2 h at rt. The mixture was co-evaporated with toluene to give stearoyl chloride as a syrup. To a solution of stearoyl chloride in $CHCl_3$ (10 mL) was added a solution of dimethyl 3-aminobenzoylamino-3′,4-oxydibenzoate in $CHCl_3$ (10 mL) and triethylamine (240 mg, 2.37 mM), and then the mixture was stirred for 21 h at rt. $CHCl_3$ (50 mL) was added to the solution, and the mixture was washed with 1 N HCl, saturated sodium carbonate and brine successively, dried over $MgSO_4$, and concentrated. The residue was purified by thin-layer chromatography developing with 1:1 AcOEt/*n*-hexane to afford **25a** (310 mg, 31.3%) as a colorless solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.70–0.90 (m, 3H), 1.25 (s, 28H), 1.40–1.80 (m, 2H), 2.20–2.40 (m, 2H), 3.80–3.95 (m, 6H), 6.70–6.90 (m, 1H), 7.15–7.30 (m, 3H), 7.30–7.95 (m, 7H), 8.44 (bs, 1H), 9.24 (bs, 1H); TOF–MS 709 (M^+ + Na), 725 (M^+ + K).

Dimethyl 3-[(4-octadecanoylaminophenyl)acetylamino]-3′,4-oxydibenzoate (25b). Yield 7.9% as a solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz), 1.10–1.45 (m, 28H), 1.65–1.85 (m, 2H), 2.37 (t, 2H, J = 7.1 Hz), 3.70 (s, 2H), 3.91 (s, 3H), 3.94 (s, 3H), 6.87 (d, 1H, J = 8.5 Hz), 7.02 (ddd, 1H, J = 8.2, 2.6, 1.0 Hz), 7.16 (d, 2H, J = 8.5 Hz), 7.30–7.50 (m, 5H), 7.66 (bs, 1H), 7.74 (dd, 1H, J = 8.5, 2.1 Hz), 7.75–7.85 (m, 1H), 9.06 (d, 1H, J = 1.9 Hz); TOF–MS 723 (M^+ + Na), 739 (M^+ + K).

Dimethyl 3-[3-(4-octadecanoylaminophenyl)propionylamino]-3′,4-oxy-dibenzoate (25c). To a solution of **24c** (500 mg, 0.858 mM) in MeOH-1,4-dioxane (6–9 mL) was added 10% Pd-C (150 mg) and the mixture was stirred for 2 h under hydrogen atmosphere at rt. The

precipitate was filtered off, and the filtrate was concentrated in vacuo to afford dimethyl 3-[3-(4-aminophenyl)propionylamino]-3′,4-oxydibenzoate as a syrup.

As described above, the obtained syrup was subjected to the acyl condensation with stearoyl chloride in the presence of triethylamine to afford **25c** (420 mg, 68.4%) as a colorless solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz), 1.20–1.40 (m, 28H), 1.60–1.80 (m, 2H), 2.29–2.35 (m, 2H), 2.69–2.75 (m, 2H), 3.00–3.06 (m, 2H), 3.91 (s, 3H), 3.93 (s, 3H), 6.73 (d, 1H, J = 8.6 Hz), 7.10–7.30 (m, 4H), 7.40 (d, 2H, J = 8.3 Hz), 7.48 (t, 1H, J = 8.0 Hz), 7.60–7.70 (m, 2H), 7.70 (dd, 1H, J = 8.6, 2.1 Hz), 7.88–7.92 (m, 1H), 9.05–9.10 (m, 1H); TOF-MS 737 (M^+ + Na), 753 (M^+ + K).

Dimethyl 3-(3-octadecanoylaminobenzoylamino)-3′,4-oxydibenzoate (25d). Yield 61.0% as a colorless amorphous; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 8.0 Hz), 1.20–1.80 (m, 30H), 2.37 (t, 2H, J = 8.0 Hz), 3.92 (s, 3H), 3.93 (s, 3H), 6.85 (d, 1H, J = 9.0 Hz), 7.31 (ddd, 1H, J = 8.0, 3.0, 1.0 Hz), 7.35–7.55 (m, 3H), 7.70–7.85 (m, 2H), 7.85–7.95 (m, 3H), 8.45 (bs, 1H), 9.21 (d, 1H, J = 2.0 Hz); TOF-MS 709 (M^+ + Na), 725 (M^+ + K).

Dimethyl 3-(2-octadecanoylaminobenzoylamino)-3′,4-oxydibenzoate (25e). Yield 78.9% as a solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.75–0.95 (m, 3H), 1.13–1.47 (m, 28H), 1.65–1.88 (m, 2H), 2.45 (t, 2H, J = 7.3 Hz), 3.92 (s, 3H), 3.96 (s, 3H), 6.83 (d, 1H, J = 8.6 Hz), 7.11 (td, 1H, J = 7.7, 1.2 Hz), 7.29–7.38 (m, 1H), 7.44–7.64 (m, 3H), 7.73–7.83 (m, 2H), 7.87–8.00 (m, 1H), 8.50 (bs, 1H), 8.68(dd, 1H, J = 8.6, 1.0 Hz), 9.13(d, 1H, J = 2.1 Hz), 10.82 (bs, 1H); TOF–MS 709 (M^+ + Na), 725 (M^+ + K).

Dimethyl 3-(4-hexadecanoylaminobenzoylamino)-3′,4-oxydibenzoate (26). Yield 31.3% as a solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.70–0.90 (m, 3H), 1.25 (s, 24H), 1.40–1.80 (m, 2H), 2.20–2.40 (m, 2H), 3.80–3.95 (m, 6H), 6.70–6.90 (m, 1H), 7.15–7.30 (m, 3H), 7.30–7.95 (m, 7H), 8.44 (bs, 1H), 9.24 (bs, 1H).

Dimethyl 3-(4-tetradecanoylaminobenzoylamino)-3′,4-oxydibenzoate (27). Yield 30.7% as a solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.75–1.00 (m, 6H), 1.00–1.45 (m, 20H), 1.45–1.85 (m, 2H), 2.34 (t, 2H, J = 7.6 Hz), 3.80–4.00 (m, 6H), 6.83 (d, 1H, J = 8.6 Hz), 7.05 (d, 1H, J = 8.7 Hz), 7.20–7.60 (m, 2H), 7.60–8.10 (m, 6H), 8.44 (d, 1H, J = 7.1 Hz), 8.90 (s, 1H), 9.15–9.30 (m, 1H).

Dimethyl 3-[4-(2-heptylnonanoyl)aminobenzoylamino]-3′,4-oxydibenzoate (28). Yield 35.0% as a syrup; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.75–0.95 (m, 6H), 1.10–1.40 (m, 22H), 1.60–1.85 (m, 2H), 2.10–2.25 (m, 1H), 3.92 (s, 3H), 3.93 (s, 3H), 6.86 (d, 1H, J = 8.6 Hz), 7.10–7.40 (m, 2H), 7.50 (t, 1H, J = 8.1 Hz), 7.67 (d, 2H, J = 8.6 Hz), 7.75–8.00 (m, 5H), 8.45 (s, 1H), 9.26 (s, 1H).

Dimethyl 3-[4-[(9Z,12Z)-9,12-octadecadienoylamino]benzoylamino]-3′,4-oxydibenzoate (29). Yield 74.0% as a colorless amorphous; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz), 1.20–1.50 (m, 14H), 1.60–1.80 (m, 2H), 2.00–2.10 (m, 4H), 2.37 (t, 2H, J = 7.0 Hz), 2.76 (t, 2H, J = 6.0 Hz), 3.91 (s, 3H), 3.92 (s, 3H), 5.20–5.50 (m, 4H), 6.84 (d, 1H, J = 9.0 Hz), 7.15–7.35 (m, 2H), 7.49 (t, 1H, J = 8.0 Hz), 7.62 (d, 2H, J = 9.0 Hz), 7.70–8.00 (m, 5H), 8.41 (s, 1H), 9.24 (d, 1H, J = 1.0 Hz); TOF–MS 705 (M^+ + Na), 721 (M^+ + K).

Dimethyl 3-(4-octadecanoylaminobenzoylamino)-4,4′-oxydibenzoate (34a). Yield 91.9% as a solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz), 1.20–1.75 (m, 30H), 2.37 (t, 2H, J = 7.0 Hz), 3.92 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 6.95 (d, 1H, J = 8.6 Hz), 7.12 (d, 2H, J = 8.9 Hz), 7.21 (bs, 1H), 7.62 (d, 2H, J = 8.7 Hz), 7.78 (d, 2H, J = 8.7 Hz), 7.79 (dd, 1H, J = 8.6, 2.1 Hz), 8.09 (d, 2H, J = 8.9 Hz), 8.32 (bs, 1H), 9.24 (d, 1H, J = 2.1 Hz); TOF–MS 709 (M^+ + Na), 725 (M^+ + K).

Dimethyl 3-(4-octadecanoylaminobenzoylamino)-2′,4-oxydibenzoate (34b). Yield 42.0% as a colorless solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz), 1.10–1.40 (m, 28H), 1.70 (q, 2H, J = 7.0 Hz), 2.37 (t, 2H, J = 8.0 Hz), 3.77 (s, 3H), 3.91 (s, 3H), 6.80 (d, 1H, J = 9.0 Hz), 7.10–7.35 (m, 3H), 7.50–7.70 (m, 3H), 7.73 (dd, 1H, J = 9.0, 1.0 Hz), 7.90–8.00 (m, 3H), 8.97 (s, 1H), 9.21 (s, 1H); TOF–MS 709 (M^+ + Na), 725 (M^+ + K).

Dimethyl 3-[4-methoxycarbonyl-2-(4-octadecanoylaminobenzoylamino)-phenoxy]phthalate (34c). Yield 100% as a colorless solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz), 1.20–1.40 (m, 28H), 1.73 (quint, 2H, J = 7.0 Hz), 2.37 (t, 2H, J = 8.0 Hz), 3.84 (s, 3H), 3.92 (s, 3H), 7.02 (d, 1H, J = 9.0 Hz), 7.10–7.30 (m, 2H), 7.44 (d, 1H, J = 9.0 Hz), 7.62 (d, 2H, J = 9.0 Hz), 7.75–7.85 (m, 2H), 7.87 (d, 2H, J = 9.0 Hz), 8.57 (s, 1H), 9.20 (d, 1H, J = 2.0 Hz).

Dimethyl 5-[4-methoxycarbonyl-2-(4-octadecanoylaminobenzoylamino)-phenoxy]isophthalate (34d). yield 58.2% as a solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.80–0.95 (m, 3H), 1.1–1.8 (m, 30H), 2.3–2.4 (m, 2H), 3.92 (s, 3H), 3.94 (s, 6H), 6.84 (d, 1H, J = 8.6 Hz), 7.37 (bs, 1H), 7.64 (d, 2H, J = 8.7 Hz), 7.77 (dd, 1H, J = 8.7, 2.1 Hz), 7.83 (d, 1H, J = 8.7 Hz), 7.94 (d, 2H, J = 1.4 Hz), 8.41 (bs 1H), 8.54 (t, 1H, J = 1.4 Hz), 9.24 (d, 1H, J = 2.0 Hz); TOF-MS 767 (M^+ + Na), 783 (M^+ + K).

Methyl 5-[4-methoxycarbonyl-2-(4-octadecanoylaminobenzoylamino)phenoxy]-nicotinate (34e). 33e (390 mg, 0.864 mM) was dissolved in 2 M $SnCl_2$ DMF solution (10 mL), and then the solution was stirred for 3 h at rt. To the reaction mixture was added saturate sodium carbonate, and it was extracted with EtOAc. The organic layer was washed with saturated sodium carbonate, dried over $MgSO_4$ and concentrated. The residue was purified by thin-layer chromatography developing with 10:1 $CHCl_3$/MeOH to afford methyl 5-[4-methoxycarbonyl-2-(4-aminobenzoylamino)phenoxy]-nicotinate.

As described above, the obtained aniline derivative was subjected to the acyl condensation with stearoyl

chloride in the presence of triethylamine to afford **34e** (70 mg, 11.8%) as a colorless solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.80–0.95 (m, 3H), 1.15–1.45 (m, 28H), 1.65–1.80 (m, 2H), 2.37 (t, 2H, J = 7.0 Hz), 3.93 (s, 3H), 3.95 (s, 3H), 6.85 (d, 1H, J = 8.5 Hz), 7.20 (s, 2H), 7.63 (d, 2H, J = 8.7 Hz), 7.75–7.85 (m, 3H), 7.97 (dd, 1H, J = 2.6, 1.7 Hz), 8.33 (s, 1H), 8.67 (d, 1H, J = 2.0 Hz), 9.08 (s, 1H), 9.23 (d, 1H, J = 2.1 Hz); TOF–MS 710 (M^+ + Na), 726 (M^+ + K).

Methyl 3-(4-octadecanoylaminobenzoylamino)-4-phenoxybenzoate (34f). yield 80.7% as a solid; mp 103–107 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.1 Hz), 1.10–1.45 (m, 28H), 1.60–1.85 (m, 2H), 2.39 (t, 2H, J = 7.1 Hz), 3.92 (s, 3H), 6.84 (d, 1H, J = 8.6 Hz), 7.11 (d, 2H, J = 7.5 Hz), 7.20–7.50 (m, 4H), 7.65 (d, 2H, J = 8.5 Hz), 7.75 (dd, 1H, J = 8.5, 2.0 Hz), 7.84 (d, 2H, J = 8.7 Hz), 8.53 (bs, 1H), 9.25 (d, 1H, J = 2.0 Hz). Anal. ($C_{39}H_{52}N_2O_5$) calcd for C, 74.49; H, 8.33; N, 4.45; found C, 74.39; H, 8.22; N, 4.55.

Ethyl 4-[4-methoxycarbonyl-2-(4-octadecanoylaminobenzoylamino)-phenoxy]butanoate (40). Yield 87.1% as a solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.1 Hz), 1.20 (t, 3H, J = 7.1 Hz), 1.20–1.80 (m, 30H), 2.15–2.30 (m, 2H), 2.38 (t, 2H, J = 7.6 Hz), 2.52 (t, 2H, J = 6.8 Hz), 3.90 (s, 3H), 4.09 (q, 2H, J = 7.1 Hz), 4.20 (t, 2H, J = 6.2 Hz), 6.93 (d, 1H, J = 8.6 Hz), 7.21 (s, 1H), 7.67 (d, 2H, J = 8.7 Hz), 7.81 (dd, 1H, J = 8.6, 2.1 Hz), 7.91 (d, 2H, J = 8.7 Hz), 8.48 (s, 1H), 9.15 (d, 1H, J = 2.1 Hz); TOF–MS 689 (M^+ + Na), 705 (M^+ + K).

General procedure for the preparation of 3–18: 3-(4-Octadecanoylamino-benzoylamino)-3′,4-oxydibenzoic acid (3). 25a (300 mg, 0.44 mM) was dissolved in 1,4-dioxane–MeOH (9–3 mL), and 1 N NaOH (4.1 mL) was added to the solution, and then the mixture was stirred for 5.5 h at rt. Cold water (30 mL) was added to the mixture, the resulting mixtute was adjusted to pH 1 using c HCl, and then extracted with AcOEt. The organic layer was washed with water and brine successively, dried over $MgSO_4$, and concentrated. The resulting precipitate was washed with *n*-hexane (30 mL), and then purified by HPLC eluting with 9:1 CH_3CN/0.1% TFA aq to afford **3** (63 mg, 21.9%) as a colorless powder: mp 240 °C (dec.); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.80–0.85 (m, 3H), 1.10–1.34 (m, 28H), 1.46–1.65 (m, 2H), 2.30 (t, 2H, J = 7.4 Hz), 7.00 (d, 1H, J = 8.6 Hz), 7.30–7.40 (m, 1H), 7.45–7.60 (m, 2H), 7.60–7.85 (m, 6H), 8.37 (d, 1H, J = 2.2 Hz), 9.79 (s, 1H), 10.07 (s, 1H); TOF–MS 681(M^+ + Na). Anal. ($C_{39}H_{50}N_2O_7$*H_2O) calcd for C, 69.21; H, 7.74 ; N, 3.95; found C, 68.95; H, 7.57; N, 4.23.

3-[(4-Octadecanoylaminophenyl)acetylamino]-3′,4-oxydibenzoic acid (4). Yield 29.7% as a colorless solid; mp 225–231 °C (dec.); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.84 (t, 3H, J = 7.3 Hz), 1.00–1.50 (m, 28H), 1.40–1.70 (m, 2H), 2.27 (t, 2H, J = 7.4 Hz), 3.65 (s, 2H), 6.97 (d, 1H, J = 8.5 Hz), 7.16 (d, 2H, J = 8.5 Hz), 7.20–7.40 (m, 1H), 7.40–7.60 (m, 4H), 7.67 (dd, 1H, J = 8.6, 2.1 Hz), 7.77 (d, 1H, J = 7.7 Hz), 8.50–8.70 (m, 1H), 9.79 (s, 1H), 9.81 (s, 1H); TOF–MS 695 (M^+ + Na).

3-[3-(4-Octadecanoylaminophenyl)propionylamino]-3′,4-oxydibenzoic acid (5). Yield 99.1% as a colorless solid; mp 209–213 °C (dec.); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.75–0.90 (m, 3H), 1.10–1.70 (m, 30H), 2.25 (t, 2H, J = 7.4 Hz), 2.60–2.70 (m, 2H), 2.70–2.80 (m, 2H), 6.95 (d, 1H, J = 8.6 Hz), 7.11 (d, 2H, J = 8.3 Hz), 7.25–7.35 (m, 1H), 7.46 (d, 1H, J = 8.3 Hz), 7.50–7.60 (m, 1H), 7.60–7.70 (m, 1H), 7.70–7.80 (m, 1H), 8.61 (bs, 1H), 9.60 (s, 1H), 9.73 (s, 1H); TOF–MS 709 (M^+ + Na).

3-(3-Octadecanoylaminobenzoylamino)-3′,4-oxydibenzoic acid (6). Yield 42.0% as a colorless solid; mp 168–169 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.83 (t, 3H, J = 7.0 Hz), 1.10–1.70 (m, 30H), 2.28 (t, 2H, J = 7.0 Hz), 6.98 (d, 1H, J = 9.0 Hz), 7.30–7.40 (m, 2H), 7.45–7.60 (m, 3H), 7.70–7.90 (m, 3H), 8.00–8.05 (m, 1H), 8.32 (d, 1H, J = 2.0 Hz), 9.98 (bs, 1H), 10.03 (bs, 1H); TOF–MS 681(M^+ + Na).

3-(2-Octadecanoylaminobenzoylamino)-3′,4-oxydibenzoate (7). Yield 23.0% as a colorless powder; mp 180–183 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.70–0.95 (m, 3H), 1.00–1.38 (m, 28H), 1.40–1.63 (m, 2H), 2.21 (t, 2H, J = 7.4 Hz), 7.01 (d, 1H, J = 8.5 Hz), 7.15 (t, 1H, J = 7.6 Hz), 7.35 (dd, 1H, J = 8.1, 2.2 Hz), 7.40–7.59 (m, 3H), 7.64 (d, 1H, J = 7.8 Hz), 7.75 (d, 1H, J = 7.6 Hz), 7.80 (dd, 1H, J = 8.5, 2.1 Hz), 8.10 (d, 1H, J = 8.3 Hz), 8.38 (d, 1H, J = 2.0 Hz), 10.14 (s, 1H), 10.53 (s, 1H); TOF–MS 681(M^+ + Na).

3-(4-Hexadecanoylaminobenzoylamino)-3′,4-oxydibenzoic acid (8). Yield 8.7% as a colorless powder; mp 239–240 °C (dec.); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.75–0.95 (m, 3H), 1.10–1.45 (m, 24H), 1.50–1.70 (m, 2H), 2.32 (t, 2H, J = 6.8 Hz), 7.02 (d, 1H, J = 8.5 Hz), 7.35 (dd, 1H, J = 8.1, 2.6 Hz), 7.45–7.60 (m, 2H), 7.60–7.90 (m, 6H), 8.38 (d, 1H, J = 2.6 Hz), 9.78 (s, 1H), 10.06 (s, 1H); TOF–MS 653 (M^+ + Na).

3-(4-Tetradecanoylaminobenzoylamino)-3′,4-oxydibenzoic acid (9). Yield 22.8% as a pale red solid; mp > 216 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.80–0.95 (m, 3H), 1.15–1.40 (m, 22H), 2.25–2.40 (m,2H), 7.01 (d, 1H, J = 8.5 Hz), 7.30–7.40 (m, 1H), 7.45–7.60 (m, 2H), 7.60–7.85 (m, 5H), 8.37 (d, 1H, J = 2.3 Hz), 9.77 (s, 1H), 10.05 (s, 1H); TOF–MS 625 (M^+ + Na).

3-[4-(2-Heptylnonanoylamino)benzoylamino]-3′,4-oxydibenzoic acid (10). Yield 70.6% as a colorless solid; mp 235–237 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.70–0.95 (m, 6H), 1.00–1.45 (m, 22H), 1.45–1.70 (m, 2H), 2.25–2.45 (m, 1H), 7.02 (d, 1H, J = 8.6 Hz), 7.25–7.40 (m, 1H), 7.40–7.60 (m, 2H), 7.60–7.90 (m, 6H), 8.37 (d, 1H, J = 1.6 Hz), 9.79 (bs, 1H), 10.04 (bs, 1H); TOF–MS 653 (M^+ + Na).

3-[4-[(9Z,12Z)-9,12-Octadecadienoylamino]benzoylamino]-3′,4-oxydibenzoic acid (11). yield 32.2% as a colorless solid; mp 224–226 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.83 (t, 3H, J = 7.0 Hz), 1.20–1.40 (m, 14H), 1.55–1.65 (m, 2H), 1.95–2.05 (m, 4H), 2.31 (t, 2H, J = 7.0 Hz), 2.72 (t, 2H, J = 5.0 Hz), 5.20–5.40 (m, 4H), 7.01 (d, 1H, J = 9.0 Hz), 7.30–7.40 (m, 1H), 7.52 (d, 1H, J = 8.0 Hz),

7.55–7.60 (m, 1H), 7.65 (d, 1H, $J=9.0$ Hz), 7.70–7.85 (m, 4H), 8.37 (d, 1H, $J=2.0$ Hz), 9.74 (s, 1H), 10.02 (s, 1H), 12.90 (s, 2H); TOF–MS 677 ($M^+ + Na$).

3-(4-Octadecanoylaminobenzoylamino)-4,4′-oxydibenzoic acid (12). Yield 66.8% as a colorless solid; mp >250 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.85 (t, 3H, $J=7.4$ Hz), 1.18–1.70 (m, 30H), 2.32 (m, 2H), 7.11 (d, 2H, $J=8.7$ Hz), 7.13 (d, 1H, $J=8.5$ Hz), 7.65 (d, 2H, $J=8.7$ Hz), 7.76 (d, 2H, $J=8.7$ Hz), 7.81 (dd, 1H, $J=8.5$, 2.0 Hz), 7.95 (d, 2H, $J=8.7$ Hz), 8.38 (d, 1H, $J=2.0$ Hz), 9.76 (s, 1H), 10.03 (s, 1H); TOF–MS 681 ($M^+ + Na$).

3-(4-Octadecanoylaminobenzoylamino)-2′,4-oxydibenzoic acid (13). Yield 56.0% as a colorless powder; mp 199–202 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.84 (t, 3H, $J=7.0$ Hz), 1.10–1.40 (m, 28H), 1.50–1.65 (m, 2H), 2.32 (t, 2H, $J=7.0$ Hz), 6.83 (d, 1H, $J=9.0$ Hz), 7.24 (d, 1H, $J=8.0$ Hz), 7.34 (t, 1H, $J=8.0$ Hz), 7.55–7.75 (m, 4H), 7.80–7.95 (m, 3H), 8.68 (d, 1H, $J=2.0$ Hz), 9.51 (s, 1H), 10.03 (s, 1H), 12.78 (bs, 1H); TOF–MS 681($M^+ + Na$).

3-[4-Carboxy-2-(4-octadecanoylaminobenzoylamino)phenoxy]phthalic acid (14). Yield 49.1% as a colorless solid; mp 205–207 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.83 (t, 3H, $J=7.0$ Hz), 1.20–1.40 (m, 28H), 1.50–1.65 (m, 2H), 2.31 (t, 2H, $J=7.0$ Hz), 6.95 (d, 1H, $J=9.0$ Hz), 7.32 (d, 1H, $J=8.0$ Hz), 7.53 (t, 1H, $J=8.0$ Hz), 7.65–7.80 (m, 4H), 7.84 (d, 2H, $J=9.0$ Hz), 8.50–8.55 (m, 1H), 9.58 (bs, 1H), 10.05 (bs, 1H), 13.10 (bs, 1H); TOF–MS 725 ($M^+ + Na$).

5-[4-Carboxy-2-(4-octadecanoylaminobenzoylamino)phenoxy]isophthalic acid (15). Yield 97.0% as a pale yellow solid; mp >250 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.75–0.95 (m, 3H), 1.23 (s, 28H), 1.40–1.70 (m, 2H), 2.25-2.4 (m, 2H), 7.12 (d, 1H, $J=8.6$ Hz), 7.66 (d, 1H, $J=8.8$ Hz), 7.7-7.85 (m, 5H), 8.20–8.30 (m, 1H), 8.35-8.4 (m,1H), 9.84 (s, 1H), 10.07 (s, 1H) TOF-MS 725 ($M^+ + Na$).

3-(4-Octadecanoylaminobenzoylamino)-4-phenoxybenzoic acid (16). yield 99.3% as a colorless solid; mp 202–204 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.85 (t, 3H, $J=7.4$ Hz), 1.05–1.40 (m, 28H), 1.45–1.70 (m, 2H), 2.32 (t, 2H, $J=7.3$ Hz), 6.94 (d, 1H, $J=8.5$ Hz), 7.00–7.25 (m, 3H), 7.35–7.50 (m, 2H), 7.68 (d, 2H, $J=8.7$ Hz), 7.75 (dd, 1H, $J=8.6$, 2.1 Hz), 7.82 (d, 2H, $J=8.8$ Hz), 8.40 (bs, 1H), 9.68 (s, 1H), 10.05 (s, 1H); TOF–MS 637 ($M^+ + Na$).

5-[4-Carboxy-2-(4-octadecanoylaminobenzoylamino)phenoxy]nicotinic acid (18). yield 22.6% as a colorless solid; mp >221 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.75–0.90 (m, 3H), 1.15–1.40 (m, 28H), 1.50–1.65 (m, 2H), 2.31 (t, 2H, $J=7.3$ Hz), 7.15 (d, 1H, $J=8.7$ Hz), 7.66 (d, 2H, $J=8.9$ Hz), 7.70–7.85 (m, 4H), 8.34 (s, 1H), 8.62 (d, 1H, $J=2.9$ Hz), 8.83 (d, 1H, $J=1.5$ Hz), 9.80–9.90 (m, 1H), 10.00–10.10 (m, 1H); TOF–MS 682 ($M^+ + Na$), 698 ($M^+ + K$).

4-[4-Carboxy-2-(4-octadecanoylaminobenzoylamino)phenoxy]butanoic acid (17). Yield 72.5% as a colorless solid; mp 215–218 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.85 (t, 3H, $J=6.9$ Hz), 1.18–1.70 (m, 30H), 1.90–2.05 (m, 2H), 2.34 (t, 2H, $J=7.4$ Hz), 2.44 (t, 2H, $J=7.2$ Hz), 4.16 (t, 2H, $J=6.2$ Hz), 7.17 (d, 1H, $J=8.4$ Hz), 7.74 (d, 2H, $J=8.7$ Hz), 7.76 (dd, 1H, $J=8.4$, 2.2 Hz), 7.91 (d, 2H, $J=8.7$ Hz), 8.48 (d, 1H, $J=2.2$ Hz), 9.27 (bs, 1H), 10.12 (bs, 1H); TOF–MS 647 ($M^+ + Na$), 663 ($M^+ + K$).

References and Notes

1. Berg, E. L.; Yoshino, T.; Rott, L. S.; Robinson, M. K.; Warnock, R. A.; Kishimoto, T. K.; Picker, L. J.; Butcher, E. C. *J. Exp. Med.* **1999**, *174*, 1461.
2. Picker, L. J.; Kishimoto, T. K.; Smith, C. W.; Warnock, R. A.; Butcher, E. C. *Nature* **1991**, *349*, 796.
3. Lorant, D. E.; Topham, M. K.; Whatley, R. E.; McEver, R. P.; Mclntyre, T. M.; Prescott, S. M.; Zimmerman, G. A. *J. Clin. Invest*. **1993**, *92*, 559.
4. Symon, F. A.; Walsh, G. M.; Watson, S. R.; Wardlaw, A. J. *J. Exp. Med.* **1994**, *80*, 371.
5. Akbar, A. N.; Salmon, M.; Janossy, G. *Immunol. Today* **1991**, *12*, 184.
6. Duijvestijn, A. M.; Horst, E.; Pals, S. T.; Rouse, B. N.; Steere, A. C.; Picker, L. J.; Meijer, C. J. L. M.; Butcher, E. C. *Am. J. Pathol.* **1988**, *130*, 147.
7. Nguyen, M.; Eilber, F. R.; DeFrees, S. *Biophys. Res. Commun.* **1996**, *228*, 716. Kannagi, R. *Glycoconjugate J.* **1997**, *14*, 577.
8. McEver, R. P. *Glycoconjugate J.* **1997**, *14*, 585.
9. Austrup, F.; Vestweber, D.; Borges, E.; Löhning, M.; Bräuer, R.; Herz, U.; Renz, H.; Hollmann, R.; Scheffold, A.; Radbruch, A.; Hamann, A. *Nature* **1997**, *385*, 81.
10. Kondo, H.; Ichikawa, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **1992**, *114*, 8748.
11. Halcomb, R. L.; Huang, H.; Wong, C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 11315.
12. Mehta, S.; Pinto, B. M. *J. Org. Chem.* **1993**, *58*, 3269.
13. Raghavan, S.; Kahne, D. A. *J. Am. Chem. Soc.* **1993**, *115*, 1580.
14. Yamada, H.; Harada, T.; Takahashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 7919.
15. Kanie, O.; Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 12073.
16. Madsen, R.; Udodong, U.; Roberts, C.; Mootoo, D.; Mootoo, U. D. R.; Konradsson, P.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 1554.
17. Tsukida, T.; Yoshida, M.; Kurokawa, K.; Nakai, Y.; Achiha, T.; Kiyoi, T.; Kondo, H. *J. Org. Chem.* **1997**, *62*, 6876.
18. Mulligan, M. S.; Lowe, J. B.; Larsen, R. D.; Paulson, J.; Zheng, Z.; DeFrees, S.; Maemura, K.; Fukuda, M.; Ward, P. *J. Exp. Med.* **1993**, *178*, 623.
19. Springer, T. A.; Lasky, L. A. *Nature* **1991**, *349*, 196.
20. Fukushima, K.; Ohkura, T.; Kanai, M.; Kuroki, M.; Matsuoka, Y.; Kobata, A.; Yamashita, K. *Glycobiology* **1995**, *5*, 105.
21. Feizi, T.; Larkin, M. *Glycobiology* **1990**, *1*, 17.
22. Nguyen, M.; Eilber, F. R.; DeFrees, S. *Biochem. Biophys. Res. Commun.* **1996**, *228*, 716.
23. Ohmoto, H.; Nakamura, K.; Inoue, T.; Kondo, N.; Inoue, Y.; Yoshino, K.; Kondo, H.; Ishida, H.; Kiso, M.; Hasegawa *J. Med. Chem.* **1996**, *39*, 1339.
24. Wada, Y.; Saito, T.; Matsuda, N.; Ohmoto, H.; Yoshino, K.; Ohashi, M.; Kondo, H.; Ishida, H.; Kiso, M.; Hasegawa, A. *J. Med. Chem.* **1996**, *39*, 2055.
25. Hiramatsu, Y.; Tsujishita, H.; Kondo, H. *J. Med. Chem.* **1996**, *39*, 4547.

26. Yoshino, K.; Ohmoto, H.; Kondo, N.; Tsujishita, H.; Hiramatsu, Y.; Inoue, Y.; Kondo, H.; Ishida, H.; Kiso, M.; Hasegawa, A. *J. Med. Chem.* **1997**, *40*, 455.
27. Tsukida, T.; Hiramatsu, Y.; Tsujishita, H.; Kiyoi, T.; Yoshida, M.; Kurokawa, K.; Moriyama, H.; Ohmoto, H.; Wada, Y.; Saito, T.; Kondo, H. *J. Med. Chem.* **1997**, *40*, 3534.
28. Hiramatsu, Y.; Moriyama, H.; Kiyoi, T.; Tsukida, T.; Inoue, Y.; Kondo, H. *J. Med. Chem.* **1998**, *41*, 2302.
29. Tsukida, T.; Moriyama, H.; Kurokawa, K.; Achiha, T.; Inoue, Y.; Kondo, H. *J. Med. Chem.* **1998**, *41*, 4279.
30. Tsujishita, H.; Hiramatsu, Y.; Kondo, N.; Ohmoto, H.; Kondo, H.; Kiso, M.; Hasegawa, A. *J. Med. Chem.* **1997**, *40*, 362.
31. Hiramatsu, Y.; Tsukida, T.; Nakai, Y.; Inoue, Y.; Kondo, H. *J. Med. Chem.* **2000**, *43*, 1476.
32. Beugelmans, R.; Singh, G. P.; Zhu, J. *Tetrahedron Lett.* **1993**, *34*, 7741.
33. Erbe, D.; Watson, S. R.; Presta, L. G.; Wolitzky, B. A.; Foxall, C.; Brandley, B. K.; Lasky, L. A. *J. Cell. Biol.* **1995**, *120*, 1227.
34. Compound **11** was derived from linoleic acid, which was characterized by Z-isomer.