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Trisubstituted Benzene Leukotriene B_4 Receptor Antagonists: Synthesis and Structure–Activity Relationships

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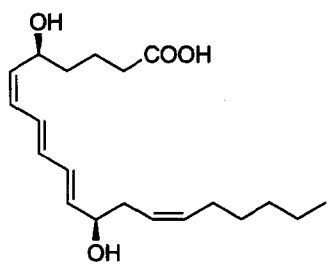
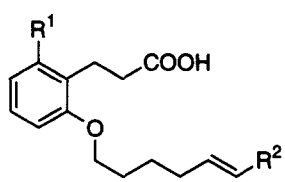
Abstract—A series of trisubstituted benzenes which demonstrate leukotriene B_4 (LTB_4, **1**) receptor affinity was prepared. Previous trisubstituted benzenes from our laboratory showed high affinity to the LTB_4 receptor but demonstrated agonist activity in functional assays. Compound **3a**, the initial lead compound of this new series, showed only modest affinity (IC_{50} = 0.20 μM). However, **3a** was a receptor antagonist with no demonstrable agonist activity up to 30 μM. Further modification of the lipid tail and aryl head groups region led to the discovery of **3b** (ONO-4057). This compound, free of agonist activity, possesses high affinity to the LTB_4 receptor (K_i = 3.7±0.9 nM). © 1997 Elsevier Science Ltd.

Introduction

We have designed and synthesized compounds that demonstrate high affinity to LTB_4 receptors on the basis of the specific conformation of LTB_4 (**1**, Chart 1).[1] These compounds exhibited LTB_4 receptor agonist activity in the functional assay. One of the analogues in this study, disubstituted benzene **3a** (Chart 1), was identified as an antagonist. In this report, we describe the structure–activity relationship (SAR) for a large group of trisubstituted benzene analogues that have potent LTB_4 receptor affinity. These compounds may be useful for treating inflammatory diseases in which LTB_4 is thought to be a major chemical mediator.



LTB_4 (1)



2 R^1 = H, R^2 = $CH(OH)^nC_8H_{17}$
3a R^1 = H, R^2 = (4-MeO)C_6H_4
3b R^1 = $O(CH_2)_4COOH$, R^2 = (4-MeO)C_6H_4
(ONO-4057)

Chart 1. LTB_4 (**1**) and di- and trisubstituted benzenes.

Chemistry

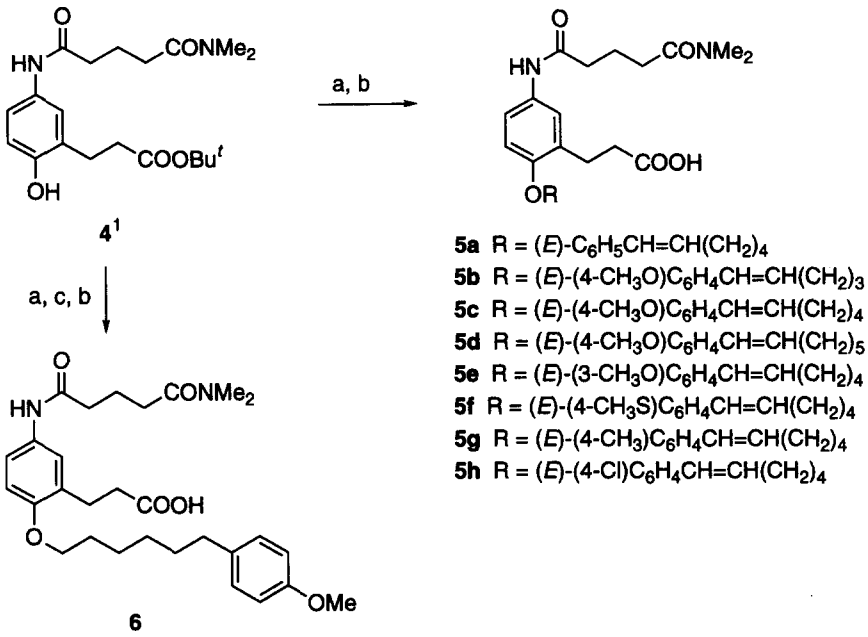
The trisubstituted benzene analogues of this study were prepared as outlined in Schemes 1–17. Schemes 1–6, 8, 9, 11, 14, and 15 illustrate the modifications of the lipid chain of 1,2,5-trisubstituted benzene analogues.

The *O*-alkylation of **4**[1] in the presence of sodium hydride followed by the deprotection of *t*-butyl ester provided **5a–h**. The catalytic hydrogenation of the *O*-alkylated product of **4** followed by deprotection afforded **6** (Scheme 1).

Scheme 2 illustrates the modification of the acid chain of 1,2,5-trisubstituted benzene analogues. The *N*-acylation of **7** with the acid chloride followed by acid treatment afforded **8a**. The Wittig reaction of **8a** with the ylides **61** and **62** afforded **8b** and **8c**, respectively. The sodium borohydride reduction of **8c** gave **8d**. The *O*-alkylation of **8b**, **8d**, and **8e**[1] with **60b** in the presence of sodium hydride provided **9a**, **9b**, and **9c**, respectively. Compounds **10a–c** were prepared by the alkaline hydrolysis of **9a–c**, respectively.

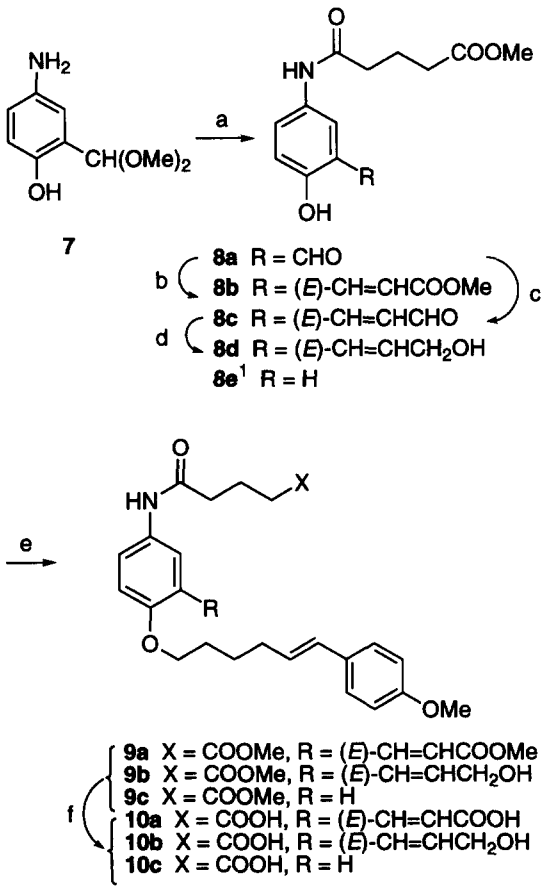
Scheme 3 illustrates the modification of the amide chain of 1,2,5-trisubstituted benzene analogues. The *O*-alkylation of **11a–d**,[2] prepared from ethyl-2′-hydroxy-5′-nitrocinnamate by the conventional method, with **60b** gave **12a–d**, respectively. The *O*-alkylation of **11e**[1] with **60i** gave **12e**. Compounds **13a–e** were prepared by the alkaline hydrolysis of **12a–e**, respectively.

Scheme 4 illustrates another modification of the amide chain and acid chain of 1,2,5-trisubstituted benzene



[a] Reagent: (a) **60a-h**, NaH; (b) HCOOH; (c) H_2, Pd-C

Scheme 1. Synthesis of compounds **5a–b** and **6**.[a]



[a] Reagent: (a) $ClCO(CH_2)_3COOMe$ then H^+;
(b) Ph_3P=CHCOOMe (**61**); (c) Ph_3P=CHCHO (**62**);
(d) $NaBH_4$; (e) **60b**, NaH; (f) aq. NaOH

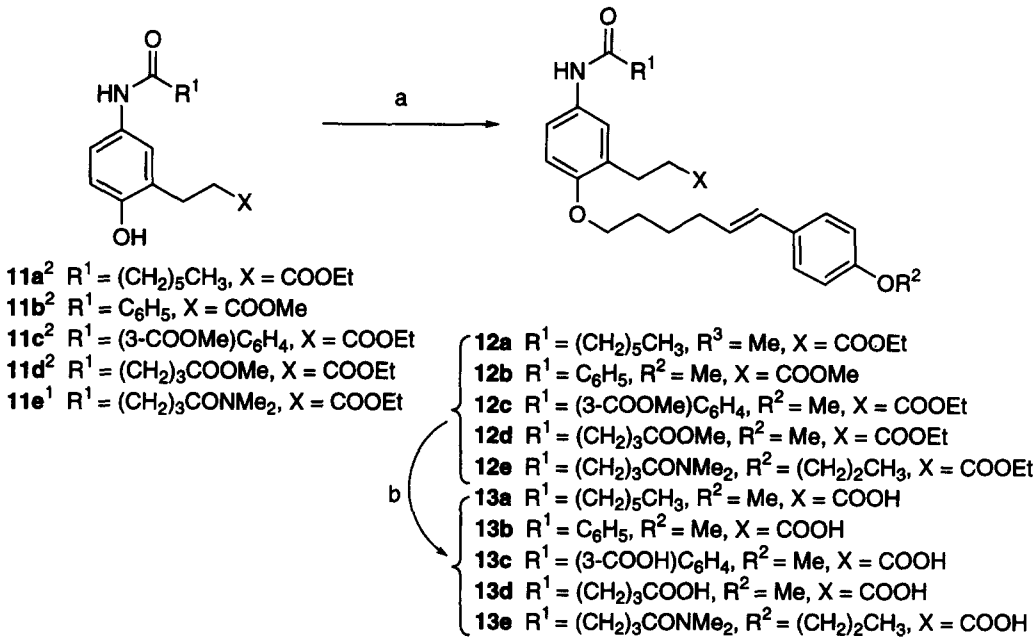
Scheme 2. Synthesis of compounds **10a–c**.[a]

analogues. Compound **15a** was prepared from **14a**[3] by the sequential reactions: *O*-alkylation with **60b** in the presence of sodium hydride; alkaline hydrolysis; amide formation with dimethylamine; deprotection with formic acid. Compounds **15b** and **15c** were also prepared from **14a** and **14b**,[3] respectively, by the sequential reactions: *O*-alkylation; alkaline hydrolysis of methyl ester; reduction of the formed carboxylic acid function; deprotection of the *t*-butyl ester; alkaline hydrolysis of the formed formate. Compound **17** was prepared from **15d**, which was prepared by the *O*-alkylation of **14b** followed by the acidic deprotection of *t*-butyl ester, by amide formation with dimethylamine followed by alkaline hydrolysis.

Compounds **20a–b** were prepared from **19a**, which was prepared from **18**[4] by the conventional method, as outlined in Scheme 5. Compound **19a** was acetylated to **19b** or phthaloyled to **19c**. The deprotection of **19b** and **19c** provided **20a** and **20b**, respectively. As shown in Scheme 6, sulfonamide analogues **22a–c** were prepared by the sulfonylation of **19a** followed by deprotection.

The synthesis of 1,2,6-trisubstituted benzene analogue **26**[5] is illustrated in Scheme 7. The catalytic hydrogenation of **23**,[5] which was prepared from 6-nitrosalicylaldehyde by the conventional method, afforded **24a**. The acylation of **24a** with glutaric anhydride followed by amide formation with dimethylamine gave **24c**. The *O*-alkylation of **24c** followed by alkaline hydrolysis provided **26**.

Compounds **30a–b** and **32a–b** were synthesized as outlined in Scheme 8. Compound **27**, which was prepared by the Friedel-Crafts acylation of methyl-3-(2-methoxyphenyl)propionate followed by demethyl-



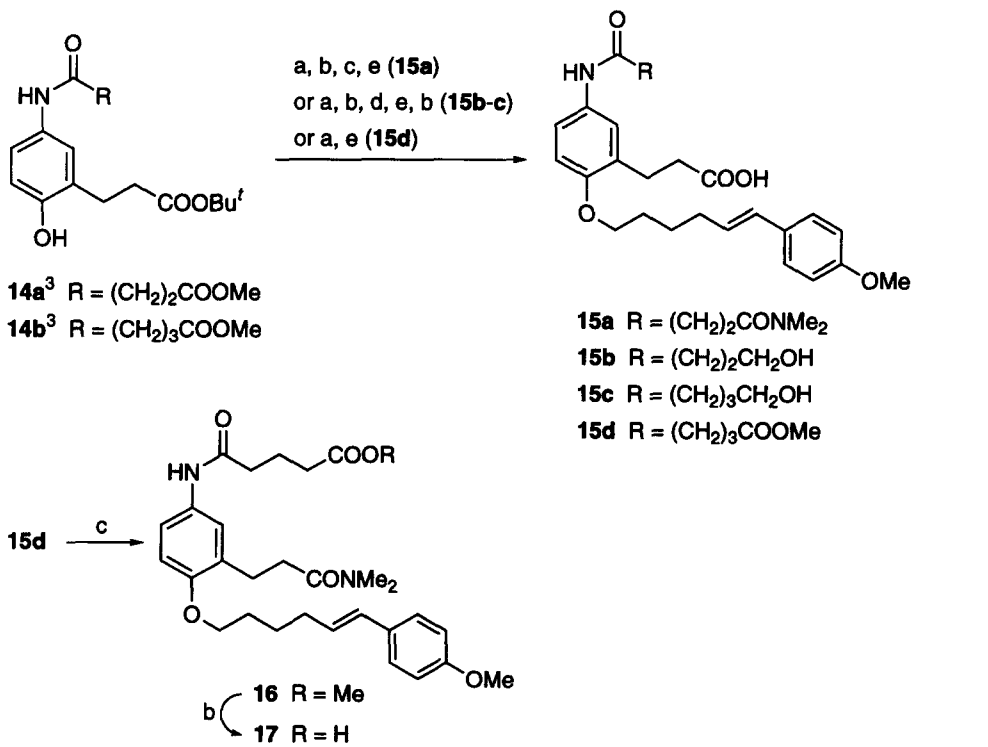
[a] Reagent: (a) **60b** or **60l**, NaH; (b) aq. NaOH

Scheme 3. Synthesis of compounds **13a–e**.[a]

ation,[6] was either esterified to **28a** or converted to **28b** by the sequential reactions: lactonization; ethanolysis; amide formation. Compounds **28a** and **28b** were converted to **30a** and **30b**, respectively, under standard conditions. The sodium borohydride reduction of **29a** and **29b** followed by alkaline hydrolysis gave **32a** and **32b**, respectively. Compound **32a** was isolated as a disodium salt to avoid intramolecular lactonization.

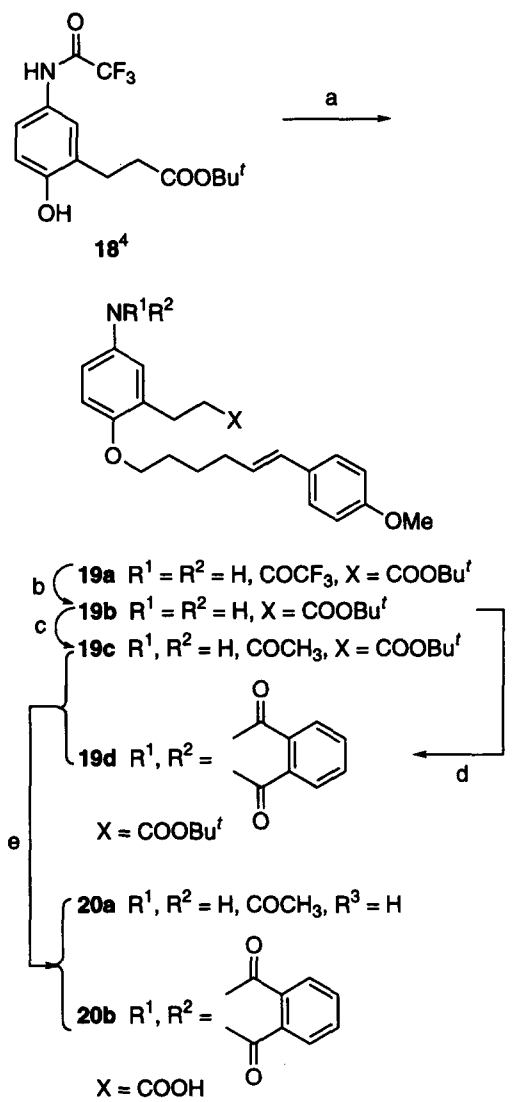
Compounds **35a–b** were synthesized as outlined in Scheme 9. Compounds **33a–b**[1] were alkylated with the desired lipid chain **60b**, and the compounds formed, **34a–b**, were hydrolyzed under alkaline conditions, giving **35a** and **35b**, respectively.

Schemes 10, 12, and 13 illustrate the other modifications of 1,2,6-trisubstituted benzene analogues. The



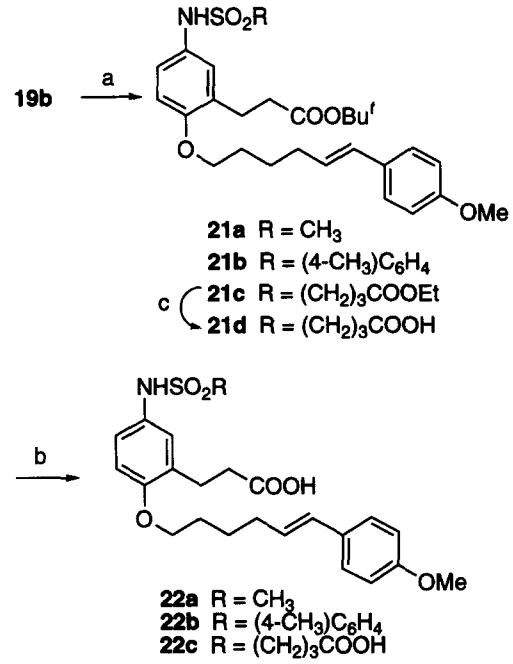
[a] Reagent: (a) **60b**, NaH; (b) aq. NaOH; (c) ClCOOEt, $HNMe_2$; (d) ClCOOEt, $NaBH_4$; (e) HCOOH

Scheme 4. Synthesis of compounds **15a–c** and **17**.[a]



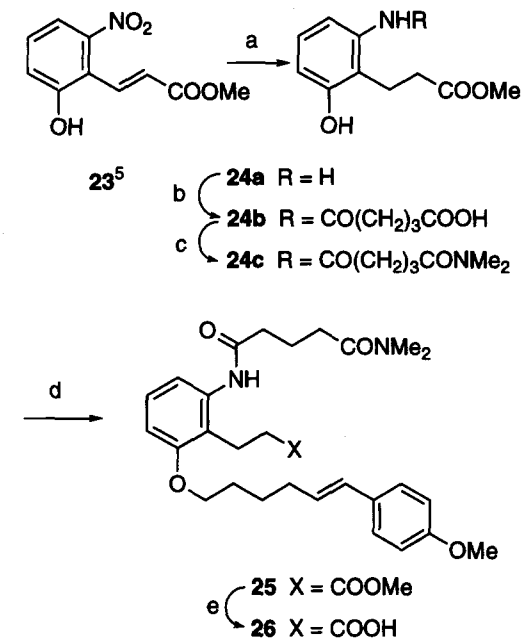
[a] Reagent: (a) **60b**, NaH; (b) K_2CO_3, aq. MeOH; (c) CH_3COCl; (d) phthalic anhydride; (e) HCOOH

Scheme 5. Synthesis of compounds **20a–b**.



[a] Reagent: (a) RSO_2Cl; (b) HCOOH; (c) aq. NaOH

Scheme 6. Synthesis of compounds **22a–c**.[a]



[a] Reagent: (a) H_2, Pd-C; (b) glutaric anhydride; (c) ClCOOEt, $HNMe_2$; (d) **60b**, NaH; (e) aq. NaOH

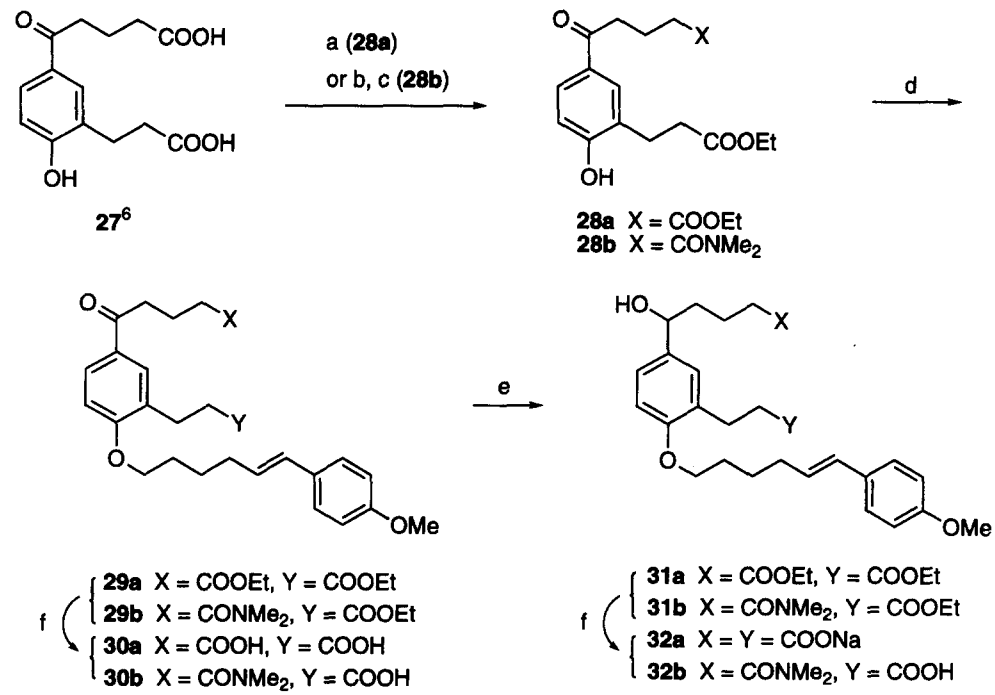
Scheme 7. Synthesis of compound **26**.[a]

selective reduction of **36** with sodium borohydride followed by the Wittig reaction, esterification with diazomethane, and then catalytic hydrogenation afforded **37a**. Compound **37a** was converted to **38** by the sequential reactions: oxidation of the hydroxyl group with pyridinium dichromate; Horner–Emmons reaction; catalytic hydrogenation; demethylation with pyridinium hydrochloride. Compound **38** was converted to **40a** by esterification under acidic conditions. Dimethylamide analogue **40b** was prepared from **38** by the sequential reactions: lactonization; amide formation with dimethylamine; ethanolysis of the lactone. Compounds **40a** and **40b** were converted to **42a** and **42b**, respectively, by the same method as that outlined above.

As shown in Scheme 11, compound **43**[1] was converted to **45** by the conventional method.

The synthetic routes used in the preparation of **47**, **49a–b**, **3b**, and **52** are outlined in Schemes 12 and 13.

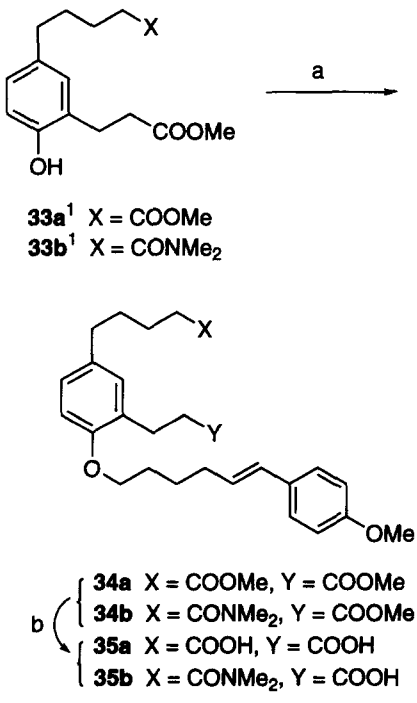
The alkaline hydrolysis of **46**, prepared by the alkylation of 5-hydroxy-3,4-dihydrocoumarin,[7] gave **47**. The preparation of **49a–b** and **3b** was achieved under standard conditions. As shown in Scheme 13, the ring opening of **50**[8] with ethoxide followed by *O*-alkylation with **60b** gave **51**, which was converted to **52** under standard conditions.



[a] Reagent: (a) EtOH, HCl; (b) Resin (H^+ form) then EtOH; (c) ClCOOEt, $HNMe_2$; (d) **60b**, NaH; (e) $NaBH_4$; (f) aq. NaOH

Scheme 8. Synthesis of compounds **31a–b** and **32a–b**.[a]

Schemes 14 and 15 illustrate the synthetic routes used in the preparation of another type of 1,2,5-trisubstituted benzene analogue, **54b**, and the 1,2,4-trisubstituted benzene analogue **57c**. Alkylation of the phenolic hydroxyl group of **53**, prepared from 6-hydroxy-3,4-dihydrocoumarin by the conventional method,[9] was achieved under standard conditions, giving **54a**. The hydrolysis of **54a** provided **54b**. The alcoholysis of **55**, prepared by the *O*-alkylation of 7-hydroxycoumarin,[10] gave **56**, which was converted to **57c** under standard conditions.



[a] Reagent: (a) **60b**, NaH; (b) aq. NaOH

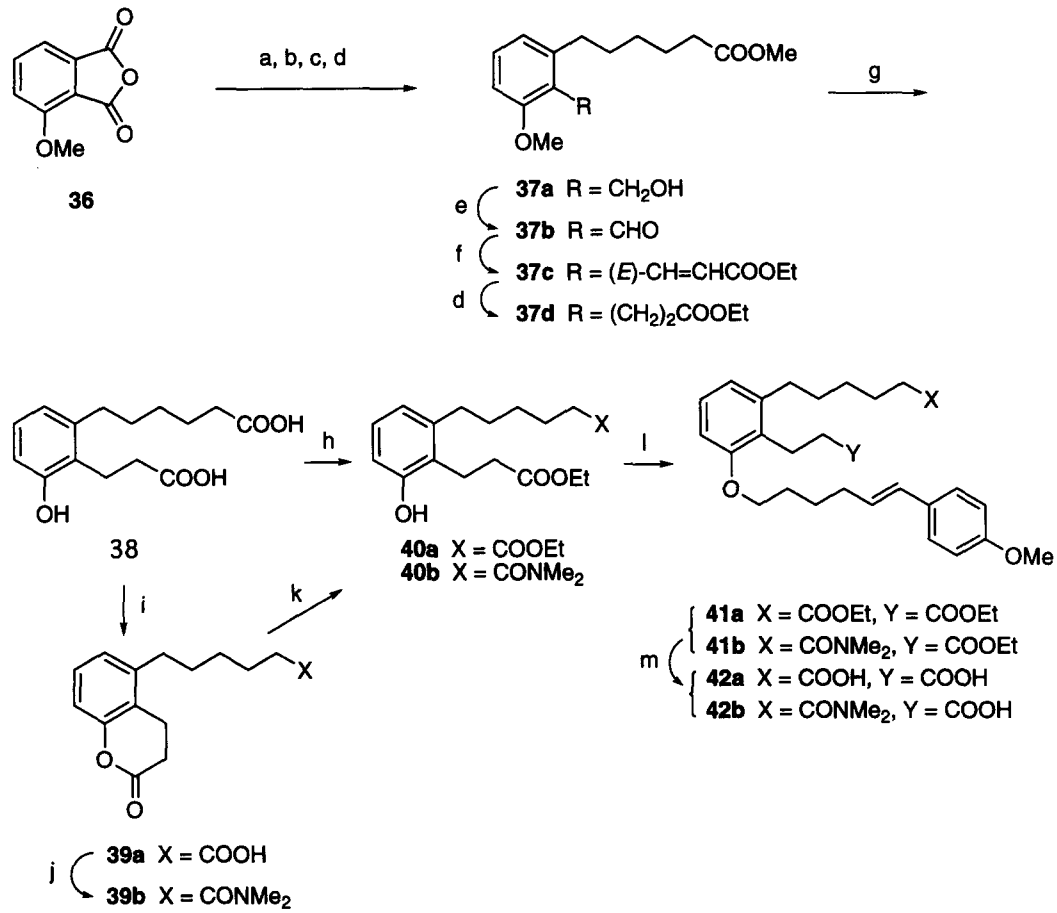
Scheme 9. Synthesis of compounds **35a–b**.[a]

The synthesis of the lipid chains used in *O*-alkylation is illustrated in Scheme 16. The introduction of *trans*-double bond was achieved by the Wittig reaction of the desired benzaldehydes, giving **58a–i**. The reduction of the ester group followed by methanesulfonylation provided **60a–i**.

An alternative synthetic method of **59b** is described in Scheme 17. The Friedel–Crafts acylation with 6-acetoxyhexanoyl chloride, which was prepared by the ring opening of ε-caprolactone with acetyl chloride, gave **63**. The alkaline hydrolysis of **63** followed by sodium borohydride reduction provided **64**, which was dehydrated by heating to give **59b**.

Results and Discussion

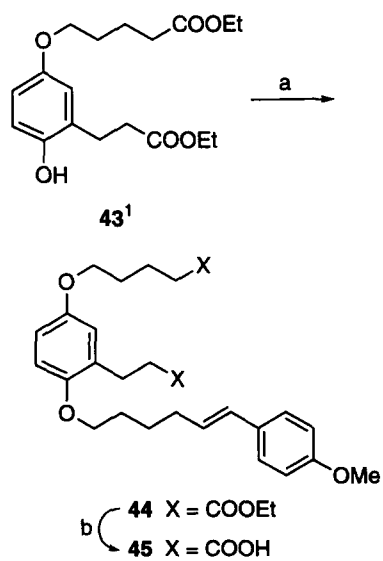
The LTB_4 receptor affinities of the test compounds were determined by evaluating the ability of the compounds to compete with the binding of [^{3}H] LTB_4 to receptors on intact human neutrophils.[11] For the present study, the human neutrophil binding assay served as our primary test system to determine structure–activity relationships. For antagonist activity, the ability of the selected compounds to inhibit the LTB_4-induced aggregation of human neutrophils was used (Table 6).[11] All compounds in this series were free of LTB_4 receptor agonist activity at concentrations up to 30 μM.



[a] Reagent: (a) $NaBH_4$; (b) DIBAH; (c) $Ph_3P^+(CH_2)_4COOH\ Br^-$, *t*-BuOK then CH_2N_2; (d) H_2, Pd-C; (e) PCC; (f) $(EtO)_2P(O)CH_2COOEt$, NaH; (g) pyridine hydrochloride; (h) EtOH, HCl; (i) Resin (H^+ form); (j) ClCOOEt, $HNMe_2$; (k) EtOH, K_2CO_3; (l) **60b**, NaH; (m) aq. NaOH

Scheme 10. Synthesis of compounds **42a–b**.[a]

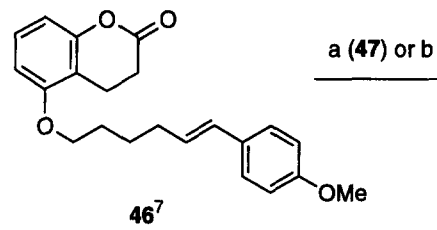
Our initial drug design utilized a structural template based on the presumed conformation of LTB_4 (**1**, Chart 1). This approach led to the discovery of compounds possessing high affinity for the LTB_4 receptor.[1] However, these compounds demonstrated agonist activity at the LTB_4 receptor. Our previous work led us to believe that the agonist activity may be triggered by a combination of the C-12 allylic alcohol (LTB_4 numbering) and the lipophilic tail. In addition, the optimization of the three-dimensional distance between the C-1 carboxylic acid (LTB_4 numbering) and C-12 allylic alcohol was discovered to be important for potent binding affinity. As we have reported, the removal of the C-5 hydroxyl group had no effect on the binding affinity of the compounds.

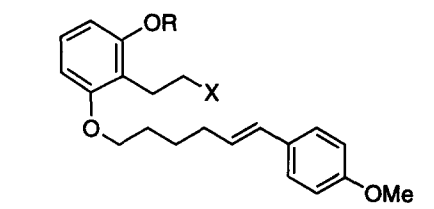


[a] Reagent: (a) **60b**, NaH; (b) aq. NaOH

Scheme 11. Synthesis of compound **45**.[a]

The examination of compounds **2** and **3a**, prepared in our earlier study, revealed that the lipophilic binding pocket may be able to accept changes in the lipid chain. Compound **3a**, the first compound in this series which was found to be an LTB_4 receptor antagonist, was strongly suggested to be a lead compound for the development of a unique antagonist. As such, modifications of the lipophilic part of the compounds possessing general formula I were undertaken (Table 1). The alkyl chain length was chosen to maintain an overall length roughly consistent with that of LTB_4. In addition, the corresponding C-12 allylic alcohol (LTB_4 numbering) moiety was replaced by various kinds of lipophilic



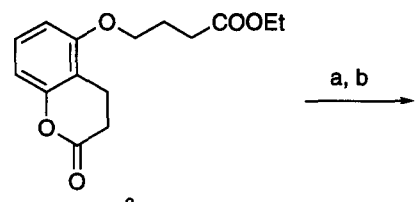


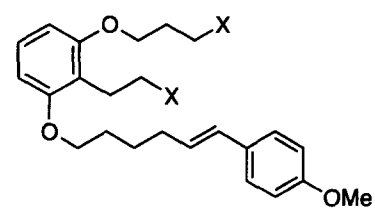
47 R = H, X = COONa
48a R = H, X = COOEt
48b R = CH_2COOEt, X = COOEt
48c R = $(CH_2)_4COOEt$, X = COOEt
48d R = $(CH_2)_5COOEt$, X = COOEt
49a R = CH_2COOH, X = COOH
3b R = $(CH_2)_4COOH$, X = COOH
49b R = $(CH_2)_4COOH$, X = COOH

[a] Reagent: (a) aq. NaOH; (b) EtOH, K_2CO_3; (c) $Br(CH_2)_nCOOEt$ (n = 1, 4 and 5), NaH

Scheme 12. Synthesis of compounds **47**, **49a–b**, and **3b**.[a]

moieties. The resulting compounds described in Table 1 were our first synthetic targets in this new series of compounds. Compounds **5b–d** showed moderate to potent LTB_4 receptor affinity (Table 1). Among them, **5c** was the most optimized in its length of lipid chain. The saturation of the double bond of **5c** provided **6** with reduced receptor affinity. The removal of the *p*-methoxy group of **5c** gave **5a**, with a marked decrease in the receptor affinity. The tri-dimensional length of the lipid chain between the ether oxygen and terminal phenyl

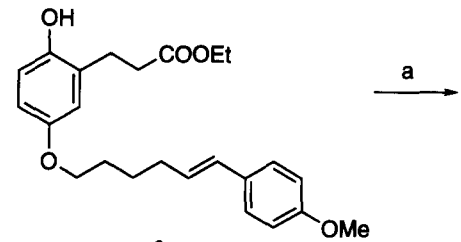


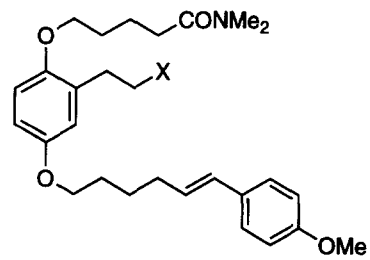


c → **51** X = COOEt
c → **52** X = COOH

[a] Reagent: (a) EtOH, K_2CO_3; (b) **60b**, NaH; (c) aq. NaOH

Scheme 13. Synthesis of compound **52**.[a]



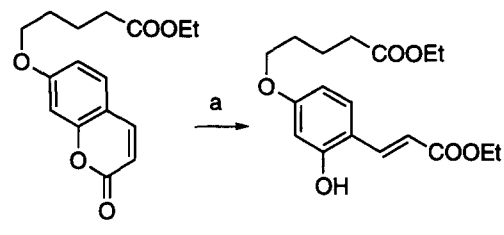


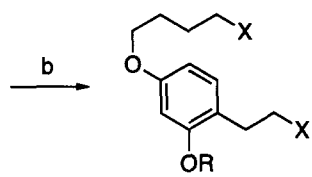
b → **54a** X = COOEt
b → **54b** X = COOH

[a] Reagent: (a) $Br(CH_2)_4CONMe_2$, NaH; (b) aq. NaOH

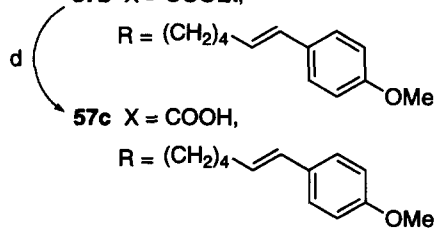
Scheme 14. Synthesis of compound **54b**.[a]

moiety was also found to be strictly limited. Replacing the *p*-methoxy group with *p*-methylthio, *p*-propyloxy, *p*-methyl, and *p*-chloro residues provided compounds **5f**, **13e**, **5g**, and **5h**, respectively. Our evaluation of these



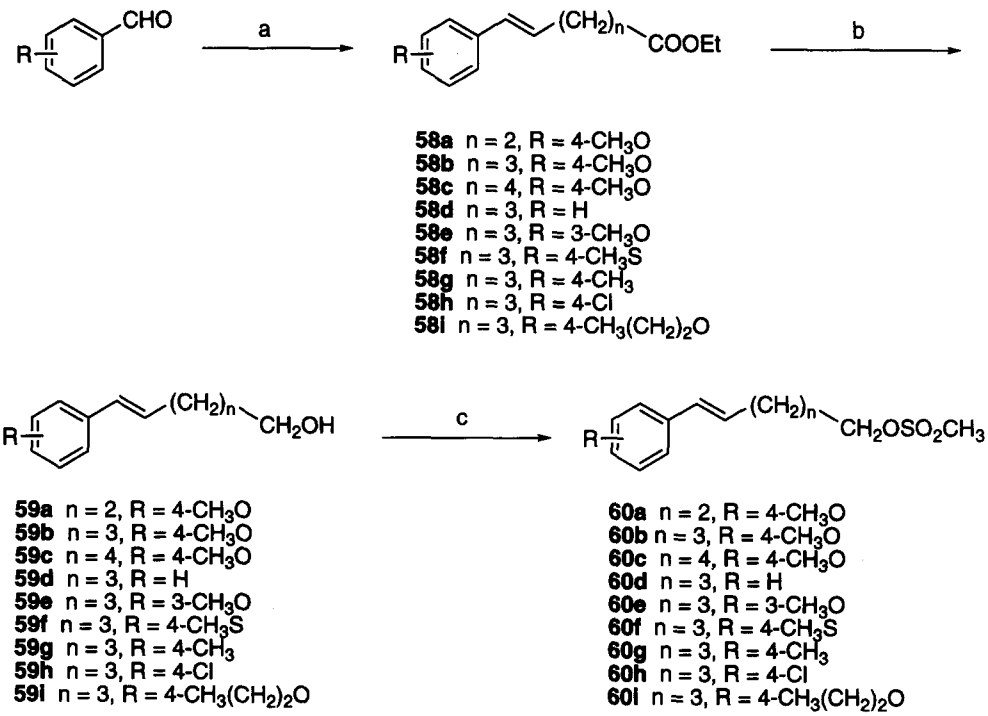


c → **57a** X = COOEt, R = H
c → **57b** X = COOEt, R = $(CH_2)_4$
d → **57c** X = COOH, R = $(CH_2)_4$



[a] Reagent: (a) EtONa; (b) H_2, Pd-C; (c) **60b**, NaH; (d) aq. NaOH

Scheme 15. Synthesis of compounds **57c**.[a]

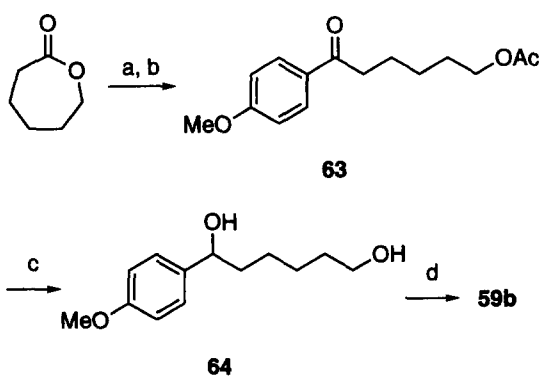


[a] Reagent: (a) $Ph_3P^+(CH_2)_nCOOH\ Br^-$ (n = 3-5), *t*-BuOK then EtOH, HCl; (b) $LiAlH_4$; (c) CH_3SO_2Cl

Scheme 16. Synthesis of compounds **60a–i**.[a]

compounds revealed that the *p*-methoxy group of the lipid tail could be replaced with a *p*-methylthio or *p*-lower alkoxy group without loss of the potent receptor affinity, although the *p*-methyl and *p*-chloro groups had a slightly negative effect on the receptor binding. The replacement of the *p*-methoxyphenyl moiety of **5c** with the *m*-methoxyphenyl moiety provided **5e** with a 10-times less potent affinity to the LTB_4 receptor. As such, the substituents and their arrangement on the terminal benzene nucleus of the lipid chain afforded a substantial effect on the receptor affinity.

Remaining within the 1,2,5-trisubstituted series and utilizing the (5*E*)-(*p*-methoxyphenyl)hexenyl lipid chain, the compounds in Table 2 were prepared.

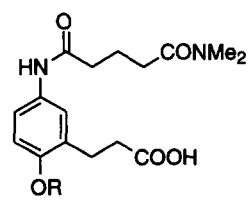


[a] Reagent: (a) anisole, CH_3COCl, H_2SO_4; (b) $AlCl_3$; (c) aq. NaOH then $NaBH_4$; (d) heat

Scheme 17. Alternative synthesis of compound **59b**.[a]

Compound **13d**, the corresponding carboxylic acid analogue of **5c**, maintained potent receptor affinity. The transformation of the carboxylic acid function of **13d** to alcohol provided **15c** with quite potent receptor affinity. The shortening of the amide chain of **5c** and **15c** gave **15a** and **15b**, respectively, with potent receptor affinity. Benzoylamide derivative **13b** showed 5-times less affinity compared to **13d**; however, the conversion to the *m*-carboxybenzoylamide derivative **13c** restored

Table 1. Inhibition of $[^3H]LTB_4$ binding to human neutrophils

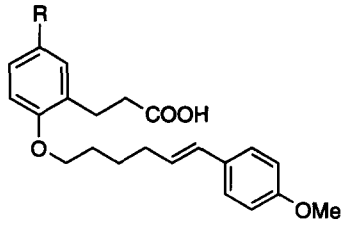


I

Compd	R	IC_{50}, μM[a]
5b	(*E*)-(4-CH_3O)C_6H_4CH=$CH(CH_2)_3$	4.0
5c	(*E*)-(4-CH_3O)C_6H_4CH=$CH(CH_2)_4$	0.045
5d	(*E*)-(4-CH_3O)C_6H_4CH=$CH(CH_2)_5$	0.20
6	(4-CH_3O)$C_6H_4(CH_2)_6$	0.20
5a	(*E*)-C_6H_4CH=$CH(CH_2)_4$	>3.0
5f	(*E*)-(4-CH_3S)C_6H_4CH=$CH(CH_2)_4$	0.050
13e	(*E*)-[4-$CH_3(CH_2)_2O$)C_6H_4CH=$CH(CH_2)_4$	0.080
5e	(*E*)-(3-CH_3O)C_6H_4CH=$CH(CH_2)_4$	0.50
5g	(*E*)-(4-CH_3)C_6H_4CH=$CH(CH_2)_4$	0.17
5h	(*E*)-(4-Cl)C_6H_4CH=$CH(CH_2)_4$	0.22

[a] IC_{50} values were obtained from four concentration–response curves.

Table 2. Inhibition of [^{3}H]LTB_4 binding to human neutrophils



II

Compd	R	IC_{50}, μM[a]
13d	$NHCO(CH_2)_3COOH$	0.040
15c	$NHCO(CH_2)_4OH$	0.090
15a	$NHCO(CH_2)_2CONMe_2$	0.12
15b	$NHCO(CH_2)_3OH$	0.15
13c	$NHCO(3\text{-}COOH)C_6H_4$	0.020
20a	$NHCOCH_3$	0.050
13a	$NHCO(CH_2)_5CH_3$	0.17
13b	$NHCOC_6H_5$	0.20
20b	$N(CO)_2C_6H_4$ (phthalimine)	0.045
22c	$NHSO_2(CH_2)_3COOH$	0.030
22a	$NHSO_2CH_3$	0.030
22b	$NHSO_2(4\text{-}CH_3)C_6H_4$	0.10
30a	$CO(CH_2)_3COOH$	0.034
30b	$CO(CH_2)_3CONMe_2$	0.030
32a	$CH(OH)(CH_2)_3COONa$	0.060
32b	$CH(OH)(CH_2)_3CONMe_2$	0.0036
35a	$(CH_2)_4COOH$	0.036
35b	$(CH_2)_4CONMe_2$	0.025
45	$O(CH_2)_4COOH$	0.070

[a]IC_{50} values were obtained from four concentration–response curves.

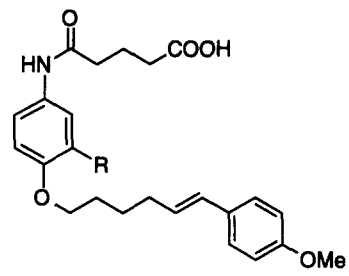
an affinity level comparable to that of **13d**. *N*-Acetyl derivative **20a** and *N*-phthaloyl derivative **20b** showed receptor affinities comparable to that of **13d**, while the more lipophilic *N*-heptanoyl derivative **13a** showed a decrease in receptor affinity. This kind of change did not result in compounds with substantially improved receptor affinities.

The other non-anilide analogues had relatively higher receptor affinities than the compounds described in Table 1. The sulfonanilide analogues **22a** and **22c** showed binding affinities comparable to those of **20a** and **13d**, respectively. Compound **22b** showed nearly the same potency as that of **13b**.

The replacement of the amide chain of **13d** with an acyl chain provided **30a**, with the maintenance of receptor affinity. Compound **30a** and its dimethylamide analogue **30b** demonstrated little difference in their receptor binding. The sodium borohydride reduction of the carbonyl group of **30a** provided **32a**, with slightly less receptor affinity. Interestingly, its dimethylamide equivalent, **32b**, had nearly 20-times higher receptor affinity than that of **32a**.

The replacement of the amide moiety with the methylene moiety provided **35a**, with a receptor affinity comparable to that of **13d**. The *N,N*-dimethylamide analogue **35b** showed the same potency as that of **30b**.

Table 3. Inhibition of [^{3}H]LTB_4 binding to human neutrophils



III

Compd	R	IC_{50}, μM[a]
10c	H	>3.0
10a	(*E*)-CH=CHCOOH	0.20
10b	(*E*)-CH=$CHCH_2OH$	0.60
17	$CH_2CH_2CONMe_2$	2.0

[a]IC_{50} values were obtained from four concentration–response curves.

The ether analogue **45** also exhibited a binding affinity comparable to that of **13d**.

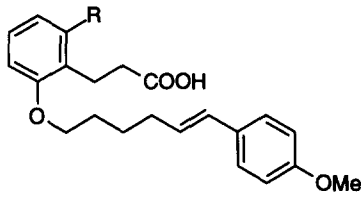
To examine the effect of the acid chain *R* in general formula III (Table 3) on receptor affinity, chemical modifications of *R* were made. Compound **10c** without the acid chain showed no binding affinity at 3 μM. Since all of the modifications of the acid chain afforded greatly reduced receptor affinity, as revealed by compounds **10a–b** and **17**, the propanoic acid moiety was indicated to be indispensable for potent receptor binding.

Maintaining the benzene nucleus, the amide chain of **5c** was moved to the 3-position of the benzene ring, providing **26**, with the maintenance of the binding affinity. The analogous structural changes in **35a** and **35b** afforded **42a** and **42b**, respectively, also with the maintenance of the binding affinity. The ether analogues **49a**, **52**, **3b**, and **49b** demonstrated potent receptor affinity. Maximum potency was obtained in **3b** and **49b**. Based on the moderate receptor affinity of **47** with no chain, the *R* group in the general formula IV was found not to be indispensable for receptor affinity. Due to the similarity in the binding affinities of the compounds described in Tables 2 and 4, it is apparent that the *R* groups in the general formulas II and IV play a minor role in the in vitro receptor binding of the series.

The transformation from 1,2,5- and 1,2,6-trisubstituted to another type of 1,2,5- and 1,2,4-trisubstituted benzene analogues (Table 5) provided compounds **54b** and **57c** with LTB_4 receptor affinity, albeit with greatly reduced receptor affinity.

The inhibitory effects of the selected 1,2,5- and 1,2,6-trisubstituted benzene analogues on LTB_4-induced human neutrophil aggregation are described in Table 6. The potency of the receptor binding affinity does not always reflect that of antagonist activity. Interestingly,

Table 4. Inhibition of [^{3}H]LTB$_4$ binding to human neutrophils



IV

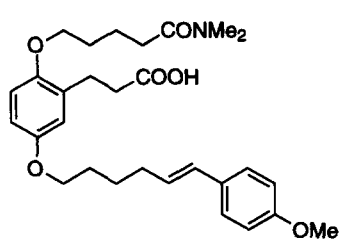
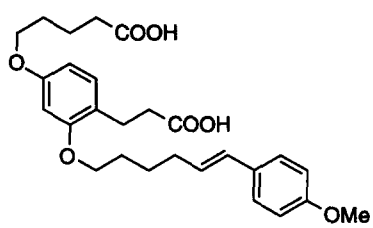
Compd	R	IC$_{50}$, μM[a]
26	NHCO(CH$_2$)$_3$CONMe$_2$	0.050
42a	(CH$_2$)$_5$COOH	0.015
42b	(CH$_2$)$_5$CONMe$_2$	0.020
47	OH (sodium salt)	0.48
49a	OCH$_2$COOH	0.085
52	O(CH$_2$)$_3$COOH	0.040
3b	O(CH$_2$)$_4$COOH	0.014
49b	O(CH$_2$)$_5$COOH	0.012

[a]IC$_{50}$ values were obtained from four concentration–response curves.

compounds **13d** and **35b** did not show antagonist activity up to 10 μM. Compound **32b**, which possesses the most potent binding affinity, demonstrated nearly the same potency as that of the other compounds. Among the compounds **32b**, **42b**, and **3b**, which showed relatively higher antagonist activity compared to the other candidates, compound **3b** was selected for further evaluation because of its greater metabolic stability and longer duration of action in the in vivo model than those of **32b** or **42b**.

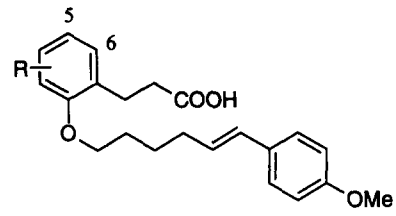
In summary, all of the compounds selected for the evaluation of antagonist activity (Table 6) demonstrated competitive LTB$_4$ receptor antagonist activity in binding to human neutrophils with no detectable agonist activity in the neutrophils. This work led to the discovery of novel, high-affinity LTB$_4$ receptor antagonists such as **3b** (ONO-4057).[11] This compound is now under further evaluation using in vivo models of inflammation and allergy, among other conditions. The results of these studies will be reported in due course. These studies will help disclose the therapeutic potential of LTB$_4$ receptor antagonists.

Table 5. Inhibition of [^{3}H]LTB$_4$ binding to human neutrophils

Compd	R	IC$_{50}$, μM[a]
54b		1.5
57c		1.0

[a]IC$_{50}$ values were obtained from four concentration–response curves.

Table 6. Inhibitory activities of trisubstituted benzene analogues on LTB$_4$-induced human neutrophil aggregation



V

Compd	R	IC$_{50}$, μM[a]
5c	5-NHCO(CH$_2$)$_3$CONMe$_2$	3.6
13d	5-NHCO(CH$_2$)$_3$COOH	>10
13c	5-NHCO(3-COOH)C$_6$H$_4$	3.0
32b	5-CH(OH)(CH$_2$)$_3$CONMe$_2$	1.7
35b	5-(CH$_2$)$_4$CONMe$_2$	>10
26	6-NHCO(CH$_2$)$_3$CONMe$_2$	5.4
42b	6-(CH$_2$)$_5$CONMe$_2$	0.81
52	6-O(CH$_2$)$_3$COOH	6.0
3b	6-O(CH$_2$)$_4$COOH	3.0
49b	6-O(CH$_2$)$_5$COOH	5.3

[a]IC$_{50}$ values were obtained from four concentration–response curves.

Experimental

Chemistry: general directions

Melting points (mp) were taken on a Yanaco micro melting-point apparatus and are uncorrected. All proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained with a JEOL FX-90-Q or a Varian VXR-200 spectrometer. Infrared spectra (IR) were recorded on a Perkin–Elmer 1760X FT-IR spectrometer with neat or KBr disks. Mass spectral data (MS) were determined with a JEOL JMS-DX303HF mass spectrometer. High-resolution mass spectra were within +3 μMu of the theoretical values. All solvents were freshly distilled prior to use.

General procedure A

Preparation of methyl 4-[3-(2-methoxycarbonyl-(*E*)-ethenyl)-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl-aminocarbonyl]butanoate (9a). A solution of **8b** (157 mg, 0.49 mmol) in DMF (2.0 mL) was slowly added to a stirred suspension of sodium hydride (0.49 mmol) in DMF (1.0 mL) at 0 °C under an argon atmosphere. After the addition was completed, the mixture was allowed to warm to 25 °C and was then stirred for 30 min. A solution of **60b** (140 mg, 0.49 mmol) in DMF (1.0 mL) was then added to the above mixture with stirring. After stirring at 60 °C for 2 h, the mixture was

poured into a mixture of crushed ice (10 g) and 1N HCl (10 mL), and extracted with 50% Et_2O in AcOEt (50 mL × 2). The combined extract was washed with satd aq $NaHCO_3$ and then brine, dried over $MgSO_4$, and evaporated in vacuo. Chromatography of the residual oil on a silica gel column (AcOEt:hexane, 2:1) afforded 117 mg (47%) of **9a** as a pale yellow oil. R_f 0.30 (AcOEt:hexane, 2:1). ^1H NMR ($CDCl_3$) δ 1.60 (m, 2H), 1.80 (m, 2H), 2.05 (m, 2H), 2.25 (m, 2H), 2.40 (m, 4H), 3.70 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 4.03 (t, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.55 (d, J = 16 Hz, 1H), 6.85 (m, 3H), 7.28 (d, J = 8 Hz, 2H), 7.50 (dd, J = 8 Hz and 2 Hz, 1H), 7.60 (d, J = 2 Hz, 1H), 7.75 (d, J = 16 Hz, 1H).

The following compounds were prepared from the indicated starting materials and the methanesulfonates or bromides by using the procedure described above.

Methyl-4-[3-(3-hydroxy-(1*E*)-pentenyl)-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenylaminocarbonyl]butanoate (9b). The title compound was prepared from **8d** and **60b**: 39% yield; yellow oil; R_f 0.70 (AcOEt:hexane, 5:1). ^1H NMR ($CDCl_3$) δ 1.60 (m, 2H), 1.82 (m, 2H), 2.05 (m, 2H), 2.25 (m, 2H), 2.40 (m, 4H), 3.70 (s, 3H), 3.82 (s, 3H), 4.00 (t, J = 7 Hz, 2H), 4.30 (s, 2H), 6.05 (dt, J = 16 Hz and 7 Hz, 1H), 6.25–6.52 (m, 2H), 6.70–7.00 (m, 4H), 7.15–7.60 (m, 5H); MS (EI) m/z 481 (M^+).

Methyl-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxyphenylaminocarbonyl]butanoate (9c). The title compound was prepared from **8e**[1] and **60b**: 49% yield; white solid; R_f 0.30 (AcOEt:hexane, 1:1). ^1H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.80 (m, 2H), 2.05 (m, 2H), 2.25 (m, 2H), 2.45 (m, 4H), 3.70 (s, 3H), 3.80 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.85 (m, 4H), 7.30 (d, J = 8 Hz, 2H), 7.40 (d, J = 8 Hz, 2H); MS (EI) m/z 425 (M^+).

Ethyl-3-[2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]-5-*n*-heptanoylaminophenyl]propanoate (12a). The title compound was prepared from **11a**[3] and **60b**: 60% yield; white solid; R_f 0.50 (hexane:AcOEt, 2:1). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.20 (t, J = 7 Hz, 3H), 1.30 (m, 6H), 1.70 (m, 4H), 1.82 (m, 2H), 2.28 (m, 4H), 2.40 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 4.10 (q, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 6.97 (s, 1H), 7.20 (d, J = 2 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 7.40 (dd, J = 8 Hz, and 2 Hz, 1H); MS (EI) m/z 509 (M^+).

Methyl-3-[2-[6-(4-Methoxyphenyl)-(5*E*)-hexenyloxy]-5-benzoylaminophenyl]propanoate (12b). The title compound was prepared from **11b**[3] and **60b**: 59% yield; white needles; R_f 0.40 (AcOEt:hexane, 1:1). ^1H NMR ($CDCl_3$) δ 1.67 (m, 2H), 1.85 (m, 2H), 2.28 (m, 2H), 2.65 (t, J = 7 Hz, 2H), 2.95 (t, J = 7 Hz, 2H), 3.65 (s, 3H), 3.80 (s, 3H), 4.00 (t, J = 7 Hz, 2H), 6.07 (dt, J = 16 Hz and 7 Hz, 1H), 6.38 (d, J = 16 Hz, 1H), 6.83 (m, 3H), 7.22–7.38 (m, 3H), 7.40–7.60 (m, 4H), 7.70 (s, 1H), 7.85 (dd, J = 8 Hz and 2 Hz, 2H); MS (EI) m/z 487 (M^+).

Methyl-3-[5-[3-(methoxycarbonyl)benzoylamino]-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoate (12c). The title compound was prepared from **11c**[3] and **60b**: 41% yield; pale yellow oil; R_f 0.25 (hexane:AcOEt, 2:1). ^1H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.85 (m, 2H), 2.28 (m, 2H), 2.65 (t, J = 7 Hz, 2H), 2.95 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.97 (s, 3H), 4.13 (q, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.38 (d, J = 16 Hz, 1H), 6.85 (m, 3H), 7.27 (d, J = 8 Hz, 2H), 7.37 (d, J = 2 Hz, 1H), 7.55 (dd, J = 8 Hz and 2 Hz, 1H), 7.57 (t, J = 8 Hz, 1H), 7.85 (s, 1H), 8.13 (d, J = 8 Hz, 1H), 8.20 (d, J = 8 Hz, 1H), 8.47 (s, 1H); MS (EI) m/z 559 (M^+).

Methyl-4-[3-(2-ethoxycarbonylethyl)-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenylaminocarbonyl]butanoate (12d). The title compound was prepared from **11d**[3] and **60b**: 17% yield; colorless oil; R_f 0.50 (AcOEt:hexane, 2:1). ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.65 (m, 2H), 1.82 (m, 2H), 2.05 (m, 2H), 2.25 (m, 2H), 2.42 (m, 4H), 2.60 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.70 (s, 3H), 3.80 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 4.10 (q, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.78 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.10 (d, J = 2 Hz, 1H), 7.27 (d, J = 8 Hz, 2H), 7.40 (dd, J = 8 Hz and 2 Hz, 1H); MS (EI) m/z 525 (M^+).

Ethyl-3-[2-[6-(4-*n*-propyloxyphenyl)-(5*E*)-hexenyloxy]-5-[4-(dimethylaminocarbonyl)butanoylamino]phenyl]-propanoate (12e). The title compound was prepared from **11e**[1] and **60i**: 80% yield; pale yellow oil; R_f 0.20 (AcOEt:MeOH, 19:1). ^1H NMR ($CDCl_3$) δ 1.02 (t, J = 7 Hz, 3H), 1.22 (t, J = 7 Hz, 3H), 1.65 (m, 2H), 1.80 (m, 4H), 2.05 (m, 2H), 2.25 (m, 2H), 2.45 (m, 4H), 2.60 (t, J = 7 Hz, 2H), 2.92 (t, J = 7 Hz, 2H), 2.98 (s, 3H), 3.02 (s, 3H), 3.95 (m, 4H), 4.12 (q, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.25 (m, 3H), 7.40 (dd, J = 8 Hz and 2 Hz, 1H), 8.00 (s, 1H); MS (EI) m/z 566 (M^+).

***tert*-Butyl-3-[2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]-5-(trifluoroacetylamino)phenyl]propanoate (19a)**. The title compound was prepared from **18**[5] and **60b**: 68% yield; white solid. ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.68 (m, 2H), 1.85 (m, 2H), 2.28 (m, 2H), 2.52 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 4.00 (t, J = 7 Hz, 2H), 6.07 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.85–6.90 (m, 3H), 7.20–7.32 (m, 3H), 7.43 (dd, J = 8 Hz and 2 Hz, 1H), 7.80 (s, 1H); MS (EI) m/z 521 (M^+).

Methyl-3-[2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]-6-[4-(dimethylaminocarbonyl)butanoylamino]phenyl]-propanoate (25). The title compound was prepared from **24c** and **60b**: 36% yield; pale yellow oil; R_f 0.35 (AcOEt:MeOH, 9:1). ^1H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.85 (m, 2H), 2.10 (m, 2H), 2.25 (m, 2H), 2.53 (m, 4H), 2.75 (m, 2H), 2.85 (m, 2H), 2.95 (s, 3H), 3.02 (s, 3H),

3.63 (s, 3H), 3.80 (s, 3H), 3.98 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.65 (d, J = 8 Hz, 1H), 6.85 (d, J = 8 Hz, 2H), 7.18 (t, J = 8 Hz, 1H), 7.28 (d, J = 8 Hz, 2H), 7.40 (d, J = 8 Hz, 1H), 9.20 (s, 1H); MS (EI) m/z 524 (M^+).

Ethyl-4-[3-[2-(ethoxycarbonyl)ethyl]-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenylcarbonyl]butanoate (29a). The title compound was prepared from **28a** and **60b**: quantitative yield; colorless oil; R_f 0.40 (hexane:AcOEt, 2:1); MS (EI) m/z 524 (M^+).

Ethyl-3-[2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]-5-[4-(dimethylaminocarbonyl)butanoyl]phenyl]propanoate (29b). The title compound was prepared from **28b** and **60b**: 95% yield; colorless oil; R_f 0.50 (AcOEt). ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.65 (m, 2H), 1.90 (m, 2H), 2.05 (m, 2H), 2.30 (m, 2H), 2.42 (t, J = 7 Hz, 2H), 2.60 (t, J = 7 Hz, 2H), 2.95 (s, 3H), 2.98 (m, 4H), 3.02 (s, 3H), 3.80 (s, 3H), 4.05 (t, J = 7 Hz, 2H), 4.10 (q, J = 7 Hz, 2H), 6.07 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.83 (m, 3H), 7.25 (t, J = 8 Hz, 2H), 7.82 (d, J = 2 Hz, 1H), 7.87 (dd, J = 8 Hz and 2 Hz, 1H); IR (neat) 2937, 1732, 1674, 1646, 1601, 1511, 1252 cm^{-1}; MS (EI) m/z 523 (M^+). EI HRMS m/z 523.2928 ($C_{31}H_{41}NO_6$ 523.2934).

Methyl-5-[3-[2-(methoxycarbonyl)ethyl]-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]pentanoate (34a). The title compound was prepared from **33a** and **60b**: 42% yield; yellow oil; R_f 0.65 (hexane:AcOEt, 2:1). ^{1}H NMR ($CDCl_3$) δ 1.50–1.75 (m, 6H), 1.75–1.92 (m, 2H), 2.20–2.40 (m, 4H), 2.45–2.70 (m, 4H), 2.92 (m, 2H), 3.65 (s, 3H), 3.67 (s, 3H), 3.80 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 6.85 (d, J = 8 Hz, 2H), 6.90-7.00 (m, 2H), 7.27 (d, J = 8 Hz, 2H); MS (EI) m/z 482 (M^+).

Methyl-3-[5-[4-(dimethylaminocarbonyl)butyl]-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoate (34b). The title compound was prepared from **33b** and **60b**: 48% yield; pale yellow oil; R_f 0.60 (AcOEt). ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 6H), 1.80 (m, 2H), 2.30 (m, 4H), 2.60 (m, 4H), 2.93 (m, 2H), 2.95 (s, 3H), 3.00 (s, 3H), 3.65 (s, 3H), 3.80 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.72 (d, J = 8 Hz, 1H), 6.83 (d, J = 8 Hz, 2H), 6.97 (m, 2H), 7.27 (d, J = 8 Hz, 2H); MS (EI) m/z 495 (M^+).

Ethyl-6-[2-[2-(ethoxycarbonyl)ethyl]-3-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]hexanoate (41a). From **40a** and **60b** the title compound was obtained as: 83% yield; pale yellow oil; R_f 0.25 (hexane:AcOEt, 5:1). ^{1}H NMR ($CDCl_3$) δ 1.22 (m, 6H), 1.40 (m, 2H), 1.65 (m, 6H), 1.83 (m, 2H), 2.30 (m, 4H), 2.50 (m, 2H), 2.62 (t, J = 7 Hz, 2H), 2.98 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.97 (t, J = 7 Hz, 2H), 4.12 (m, 4H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.70 (d, J = 8 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 6.83 (d, J = 8 Hz, 2H), 7.08 (t, J = 8 Hz, 1H), 7.25 (d, J = 8 Hz, 2H); MS (EI) m/z 524 (M^+).

Ethyl-3-[6-[5-(dimethylaminocarbonyl)pentyl]-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoate (41b). The title compound was prepared from **40b** and **60b**: 84% yield; pale yellow oil; R_f 0.50 (AcOEt). ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.40 (m, 2H), 1.65 (m, 6H), 1.82 (m, 2H), 2.30 (m, 4H), 2.50 (t, J = 7 Hz, 2H), 2.62 (t, J = 7 Hz, 2H), 2.95 (m, 2H), 2.97 (s, 3H), 3.00 (s, 3H), 3.80 (s, 3H), 3.97 (t, J = 7 Hz, 2H), 4.12 (q, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.08 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 2H); MS (EI) m/z 523 (M^+).

Ethyl-5-[3-[2-(ethoxycarbonyl)ethyl]-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyloxy]pentanoate (44). The title compound was prepared from **43**[1] and **60b**: 65% yield; pale yellow oil; R_f 0.25 (hexane:AcOEt, 4:1). ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3H), 1.25 (t, J = 7 Hz, 3H), 1.65 (m, 2H), 1.80 (m, 6H), 2.27 (m, 2H), 2.38 (m, 2H), 2.60 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.90 (m, 4H), 4.10 (m, 4H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.70 (m, 3H), 6.82 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H); IR (neat) 2937, 1734, 1511, 1247, 1221, 1176, 1037 cm^{-1}; MS (EI) m/z 526 (M^+); EI HRMS m/z 526.2919 ($C_{31}H_{42}O_7$ 526.2931).

Ethyl-3-[2-(ethoxycarbonylmethoxy)-6-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoate (48b). The title compound was prepared from **48a** and ethyl bromoacetate: quantitative yield; colorless oil; R_f 0.20 (benzene:AcOEt, 19:1). ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.28 (t, J = 7 Hz, 3H), 1.65 (m, 2H), 1.85 (m, 2H), 2.25 (m, 2H), 2.55 (t, J = 7 Hz, 2H), 3.07 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.97 (t, J = 7 Hz, 2H), 4.12 (q, J = 7 Hz, 2H), 4.23 (q, J = 7 Hz, 2H), 4.62 (s, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.34 (d, J = 8 Hz, 1H), 6.36 (d, J = 16 Hz, 1H), 6.55 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.07 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 2H); MS (EI) m/z 484 (M^+).

Ethyl-5-[2-[2-(ethoxycarbonyl)ethyl]-3-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenoxy]pentanoate (48c). The title compound was prepared from **48a** and ethyl 5-bromopentanoate: 84% yield; white crystals (from hexane:AcOEt, 9:1); mp 52.5–54.0 °C; R_f 0.60 (hexane:AcOEt, 2:1). ^{1}H NMR ($CDCl_3$) δ 1.23 (m, 6H), 1.58–1.95 (m, 8H), 2.25 (m, 2H), 2.40 (m, 2H), 2.45 (m, 2H), 3.00 (m, 2H), 3.80 (s, 3H), 3.95 (m, 4H), 4.10 (m, 4H), 6.07 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.48 (m, 2H), 6.82 (d, J = 8 Hz, 2H), 7.08 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 2H); IR (KBr) 1738, 1594, 1515, 1466, 1250, 1181, 1106 cm^{-1}; MS (EI) m/z 526 (M^+). Anal. calcd for $C_{31}H_{42}O_7$: C, 70.70; H, 8.04%. Found: C, 70.67; H, 7.87%.

Ethyl-6-[2-[2-(ethoxycarbonyl)ethyl]-3-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenoxy]hexanoate (48d). The title compound was prepared from **48a** and ethyl 6-bromohexanoate: 92% yield; colorless oil; R_f 0.50 (hexane:AcOEt, 2:1). ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J =

7 Hz, 3H), 1.24 (t, J = 7 Hz, 3H), 1.55 (m, 2H), 1.65 (m, 4H), 1.80 (m, 4H), 2.25 (m, 2H), 2.32 (t, J = 7 Hz, 2H), 2.45 (t, J = 7 Hz, 2H), 3.00 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.95 (m, 4H), 4.10 (m, 4H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.48 (m, 2H), 6.82 (d, J = 8 Hz, 2H), 7.08 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 2H); MS (EI) m/z 540 (M^+).

Ethyl-3-[2-[4-(dimethylaminocarbonyl)butoxy]-5-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoate (54a). The title compound was prepared from **53**[10] and *N,N*-dimethyl-5-bromopentanoamide: 59% yield; pale yellow oil; R_f 0.40 (AcOEt). ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3H), 1.50–1.95 (m, 8H), 2.25 (m, 2H), 2.40 (m, 2H), 2.58 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 2.96 (s, 3H), 3.01 (s, 3H), 3.80 (s, 3H), 3.90 (m, 4H), 4.10 (q, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.70 (m, 3H), 6.82 (d, J = 8 Hz, 2H), 7.26 (d, J = 8 Hz, 2H); MS (EI) m/z 525 (M^+).

Ethyl-5-[4-[2-(ethoxycarbonyl)ethyl]-3-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenoxy]pentanoate (57b). The title compound was prepared from **57a** and **60b**: 77% yield; pale yellow oil; R_f 0.50 (hexane:AcOEt, 2:1). ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3H), 1.25 (t, J = 7 Hz, 3H), 1.65 (m, 2H), 1.80 (m, 6H), 2.27 (m, 2H), 2.38 (m, 2H), 2.55 (t, J = 7 Hz, 2H), 2.87 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.95 (m, 4H), 4.12 (m, 4H), 6.07 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (m, 3H), 6.83 (d, J = 8 Hz, 2H), 7.02 (d, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 2H); MS (EI) m/z 526 (M^+).

General procedure B

Preparation of 5-[2-(2-carboxyethyl)-3-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenoxy]pentanoic acid (3b). A solution of NaOH (40 g, 1.0 mol) in water (100 mL) was added in one portion to a stirred solution of **48c** (195 g, 0.37 mol) in EtOH (300 mL) at 60 °C. The mixture was refluxed for 1 h, concentrated in vacuo, and then diluted with water (500 mL). The resulting mixture was extracted with Et_2O (500 mL × 2). The aqueous layer was acidified with concentrated (concd) HCl, and extracted with AcOEt (1 L × 2). The combined AcOEt layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give a white solid. Recrystallization of the solid from AcOE:hexane (1:1) afforded 166 g (95 %) of **3b** as white platelets. Mp 112–113 °C; R_f 0.50 (AcOEt:MeOH, 9:1). ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.84 (m, 2H), 1.86 (m, 2H), 1.90 (m, 2H), 2.25 (m, 2H), 2.47 (t, J = 7 Hz, 2H), 2.55 (t, J = 7 Hz, 2H), 3.05 (t, J = 7 Hz, 2H), 3.78 (s, 3H), 3.98 (m, 4H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.49 (d, J = 8 Hz, 1H), 6.51 (d, J = 8 Hz, 1H), 6.83 (d, J = 8 Hz, 2H), 7.10 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 18.6, 22.0, 26.0, 28.8, 28.9, 32.6, 33.6, 34.0, 55.3, 67.6, 68.0, 104.1, 104.4, 113.9, 117.0, 127.0, 127.2, 128.3, 129.5, 130.6, 157.5, 157.6, 158.6, 180.2, 180.5. IR (KBr) 1702, 1596, 1511, 1466, 1260, 1107 cm^{-1}; MS (EI) m/z 470 (M^+). Anal. calcd for $C_{27}H_{34}O_7$: C, 68.92; H, 7.28%. Found: C, 69.02; H, 7.03%.

The following compounds were prepared from the indicated starting materials by using the procedure described above.

4-[3-(2-Carboxy-(*E*)-ethenyl)-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenylaminocarbonyl]butanoic acid (10a). From **9a** the title compound was obtained as: 78% yield; pale yellow powder (from AcOEt); R_f 0.40 ($CHCl_3$:MeOH:AcOH, 100:10:1). ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 1.70 (m, 2H), 1.90 (m, 2H), 2.02 (m, 2H), 2.28 (m, 2H), 2.40 (m, 4H), 3.80 (s, 3H), 4.10 (t, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.52 (d, J = 16 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 6.95 (d, J = 8 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 7.52 (dd, J = 8 Hz and 2 Hz, 1H), 7.73 (d, J = 2 Hz, 1H), 7.98 (d, J = 16 Hz, 1H); IR (KBr) 3249, 1699, 1665, 1513, 1247 cm^{-1}; MS (EI) m/z 463 (M^+-H_2O).

4-[3-(3-Hydroxy-(1*E*)-pentenyl)-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenylaminocarbonyl]butanoic acid (10b). From **9b** the title compound was obtained as: 73% yield; white powder (from AcOEt); R_f 0.30 (AcOEt:MeOH, 6:1). ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 1.60–2.50 (m, 12H), 3.80 (s, 3H), 4.02 (t, J = 7 Hz, 2H), 4.25 (dd, J = 7 Hz and 2 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (m, 2H), 6.80–6.95 (m, 4H), 7.28 (d, J = 8 Hz, 2H), 7.57 (dd, J = 8 Hz and 2 Hz, 1H), 7.62 (d, J = 2 Hz, 1H); IR (KBr) 3313, 1706, 1658, 1511, 1247 cm^{-1}; MS (EI) m/z 467 (M^+).

4-[4-[6-(4-Methoxyphenyl)-(5*E*)-hexenyloxy]phenylaminocarbonyl]butanoic acid (10c). The title compound was prepared from **9c**: 98% yield; white powder (from AcOEt); mp 150–151 °C; R_f 0.15 (AcOEt:MeOH, 9:1). ^{1}H NMR (DMSO-d_6) δ 1.60 (m, 2H), 1.80 (m, 4H), 2.25 (m, 6H), 3.77 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.12 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.85 (m, 4H), 7.32 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 2H), 9.70 (s, 1H). IR (KBr) 3289, 1693, 1659, 1512, 1245 cm^{-1}; MS (EI) m/z 411 (M^+). Anal. calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40%. Found: C, 70.28; H, 6.89; N, 3.57%.

3-[5-(*n*-Heptanoylamino)-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (13a). From **12a** the title compound was obtained as: 75% yield; white solid (from hexane:AcOEt, 4:1); mp 110–111 °C; R_f 0.40 (AcOEt). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.30 (m, 6H), 1.70 (m, 4H), 1.82 (m, 2H), 2.30 (m, 4H), 2.65 (t, J = 7 Hz, 2H), 2.95 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.98 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.78 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.15 (s, 1H), 7.20 (d, J = 2 Hz, 1H), 7.27 (d, J = 8 Hz, 2H), 7.40 (dd, J = 8 Hz and 2 Hz, 1H). IR (KBr) 3269, 1732, 1607, 1512, 1252 cm^{-1}; MS (EI) m/z 481 (M^+). Anal. calcd for $C_{29}H_{39}NO_5$: C, 72.32; H, 8.16; N, 2.91%. Found: C, 72.20; H, 7.87; N, 2.80%.

3-[5-(Benzoylamino)-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (13b). From **12b** the title compound was obtained as: 75% yield; white needles (from AcOEt:hexane, 1:1); mp 142.5–143 °C; R_f 0.60 (AcOEt). ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 2H), 1.82 (m, 2H), 2.25 (m, 2H), 2.65 (t, J = 7 Hz, 2H), 2.92 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 4.00 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.30 (m, 3H), 7.50 (m, 4H), 7.82 (m, 3H); IR (KBr) 3277, 1698, 1643, 1510, 1248 cm^{-1}; MS (EI) m/z 473 (M^+); Anal. calcd for $C_{29}H_{31}NO_5$: C, 73.55; H, 6.60; N, 2.96%. Found: C, 73.66; H, 6.40; N, 2.92%.

3-[5-(3-Carboxybenzoylamino)-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (13c). The title compound was prepared from **12c**: 72% yield; white powder (from AcOEt:hexane:MeOH, 9:9:1); R_f 0.70 ($CHCl_3$:MeOH:AcOH, 85:10:5). ^{1}H NMR (DMSO-d_6) δ 1.62 (m, 2H), 1.70 (s, 1H), 1.80 (m, 2H), 2.25 (m, 2H), 2.50 (t, J = 7 Hz, 2H), 2.80 (t, J = 7 Hz, 2H), 3.77 (s, 3H), 4.00 (t, J = 7 Hz, 2H), 6.15 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.87 (d, J = 8 Hz, 2H), 6.95 (d, J = 8 Hz, 1H), 7.30 (d, J = 8 Hz, 2H), 7.55 (d, J = 2 Hz, 1H), 7.60 (dd, J = 8 Hz and 2 Hz, 1H), 7.63 (t, J = 8 Hz, 1H), 8.12 (d, J = 8 Hz, 1H), 8.17 (dd, J = 8 Hz and 2 Hz 1H), 8.52 (s, 1H), 10.25 (s, 1H); IR (KBr) 3281, 1702, 1643, 1510, 1247 cm^{-1}; MS (EI) m/z 517 (M^+).

4-[3-(2-Carboxyethyl)-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenylaminocarbonyl]butanoic acid (13d). The title compound was prepared from **12d**: 65% yield; white powder (from AcOEt:hexane, 2:1); mp 156–159 °C; R_f 0.70 ($CHCl_3$:MeOH:AcOH, 85:10:5). ^{1}H NMR (DMSO-d_6) δ 1.60 (m, 2H), 1.77 (m, 4H), 2.22 (m, 2H), 2.25 (t, J = 7 Hz, 2H), 2.30 (t, J = 7 Hz, 2H), 2.45 (t, J = 7 Hz, 2H), 2.75 (t, J = 7 Hz, 2H), 3.75 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.15 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.85 (m, 3H), 7.30 (m, 3H), 7.40 (dd, J = 8 Hz and 2 Hz, 1H), 9.68 (s, 1H). IR (KBr) 3276, 1702, 1650, 1609, 1541, 1512, 1245, 1223 cm^{-1}; MS (FAB) m/z 484 (MH^+). Anal. calcd for $C_{27}H_{33}NO_7$: C, 67.06; H, 6.88; N, 2.90%. Found: C, 67.00; H, 6.66; N, 2.81%.

3-[5-[4-(Dimethylaminocarbonyl)butanoylamino]-2-[6-(4-*n*-propyloxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (13e). From **12e**, the title compound was obtained as: 69% yield; white powder (from AcOEt:hexane, 4:1); mp 99.5–100.5 °C; R_f 0.30 ($CHCl_3$:MeOH, 9:1). ^{1}H NMR ($CDCl_3$) δ 1.03 (t, J = 7 Hz, 3H), 1.65 (m, 2H), 1.82 (m, 4H), 2.05 (m, 2H), 2.25 (m, 2H), 2.45 (m, 4H), 2.70 (t, J = 7 Hz, 2H), 2.95 (m, 5H), 3.00 (s, 3H), 3.95 (m, 4H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz 1H), 6.80 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.20 (d, J = 2 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 7.70 (dd, J = 8 Hz and 2 Hz, 1H), 8.42 (s, 1H); IR (KBr) 3285, 1712, 1645, 1600, 1510, 1249 cm^{-1}; MS (EI) m/z 538 (M^+). Anal. calcd for $C_{31}H_{42}N_2O_6$: C, 69.12; H, 7.86; N, 5.20%. Found: C, 69.22; H, 7.71; N, 5.11%.

4-[3-[2-(Dimethylaminocarbonyl)ethyl]-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenylaminocarbonyl]butanoic acid (17). The title compound was prepared from **16**: 96% yield; pale yellow solid (from AcOEt:hexane, 2:1); mp 123.5–124.5 °C; R_f 0.35 (AcOEt:MeOH, 6:1). ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 2H), 1.80 (m, 2H), 2.03 (m, 2H), 2.25 (m, 2H), 2.43 (m, 4H), 2.60 (t, J = 7 Hz, 2H), 2.93 (s, 3H), 2.95 (s, 3H), 2.97 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.97 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 6.80 (d, J = 8 Hz, 2H), 7.18 (d, J = 2 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 7.58 (dd, J = 8 Hz and 2 Hz, 1H), 8.22 (s, 1H); IR (KBr) 3345, 1706, 1682, 1598, 1511, 1182 cm^{-1}; MS (EI) m/z 510 (M^+). Anal. calcd for $C_{29}H_{38}N_2O_6$: C, 68.21; H, 7.50; N, 5.49%. Found: C, 68.10; H, 7.23; N, 5.60%.

3-[6-[4-(Dimethylaminocarbonyl)butanoylamino]-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (26). Using **25** as the starting material, the title compound was obtained as: 95% yield; colorless oil; R_f 0.50 (CH_2Cl_2:MeOH, 4:1); ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 2H), 1.82 (m, 2H), 2.05 (m, 2H), 2.27 (m, 2H), 2.47 (m, 4H), 2.70 (m, 2H), 2.95 (m, 5H), 3.02 (s, 3H), 3.80 (s, 3H), 3.98 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.60 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.12 (t, J = 8 Hz, 1H), 7.28 (d, J = 8 Hz, 2H), 7.50 (d, J = 8 Hz, 1H), 9.43 (s, 1H); IR (neat) 1608, 1511, 1248 cm^{-1}; MS (EI) m/z 510 (M^+); FAB HRMS m/z 511.2778 (MH^+, $C_{29}H_{39}N_2O_6$ 511.2808).

4-[3-[2-(Carbohydroxy)ethyl]-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenylcarbonyl]butanoic acid (30a). From **29a** the title compound was obtained as: 75% yield; white solid (hexane:AcOEt, 2:1); mp 118.5–119.5 °C; R_f 0.20 (AcOEt:MeOH, 9:1). ^{1}H NMR (CD_3OD) δ 1.70 (m, 2H), 1.90 (m, 4H), 2.28 (m, 2H), 2.40 (t, J = 7 Hz, 2H), 2.60 (t, J = 7 Hz, 2H), 3.00 (m, 4H), 3.77 (s, 3H), 4.10 (t, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.80 (d, J = 8 Hz, 2H), 6.98 (d, J = 8 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 7.85 (m, 2H); IR (KBr) 1697, 1682, 1603, 1510, 1258, 1242, 1117 cm^{-1}; MS (EI) m/z 468 (M^+). Anal. calcd for $C_{27}H_{32}O_7$: C, 69.21; H, 6.88%. Found: C, 69.40; H, 6.85%.

3-[5-[4-(Dimethylaminocarbonyl)butanoyl]-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (30b). From **29b**, the title compound was obtained as: 84% yield; white solid (from hexane:AcOEt, 3:2); mp 84.5–85 °C; R_f 0.20 (AcOEt). ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.88 (m, 2H), 2.05 (m, 2H), 2.27 (m, 2H), 2.43 (t, J = 7 Hz, 2H), 2.65 (t, J = 7 Hz, 2H), 2.95 (s, 3H), 2.98 (t, J = 7 Hz, 2H), 3.00 (s, 3H), 3.80 (s, 3H), 4.05 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.83 (d, J = 8 Hz, 2H), 6.85 (d, J = 8 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 7.85 (m, 3H); IR (KBr) 1713, 1674, 1602, 1511, 1255 cm^{-1}; MS (EI) m/z 495 (M^+). Anal. calcd for $C_{29}H_{37}NO_6$: C, 70.28; H, 7.52; N, 2.83%. Found: C, 70.21; H, 7.32; N, 2.93%.

3-[5-[4-(Dimethylaminocarbonyl)-1-hydroxybutyl]-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (32b). The title compound was obtained from **31b**: 59% yield; pale yellow oil; R_f 0.50 (AcOEt:MeOH, 9:1). ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 2H), 1.65 (m, 4H), 1.85 (m, 2H), 2.30 (m, 4H), 2.60 (t, J = 7 Hz, 2H), 2.93 (s, 3H), 3.00 (m, 2H), 3.00 (s, 3H), 3.80 (s, 3H), 4.00 (t, J = 7 Hz, 2H), 4.65 (m, 1H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 6.83 (d, J = 8 Hz, 2H), 7.15 (m, 2H), 7.27 (d, J = 8 Hz, 2H); IR (neat) 1723, 1609, 1511, 1249 cm^{-1}; MS (FAB) *m/z* 498 (MH^+); FAB HRMS *m/z* 480.2732 (MH^+-H_2O, $C_{29}H_{38}NO_5$ 480.2750).

5-[3-(2-Carboxyethyl)-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]pentanoic acid (35a). From **34a** the title compund was obtained as: 21% yield; white needles (from hexane:AcOEt, 4:1); mp 89–90 °C; R_f 0.70 (AcOEt:MeOH, 6:1). ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 6H), 1.82 (m, 2H), 2.27 (m, 2H), 2.35 (m, 2H), 2.55 (m, 2H), 2.65 (t, J = 7 Hz, 2H), 2.92 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 6.95 (m, 2H), 7.28 (d, J = 8 Hz, 2H); IR (KBr) 1702, 1514, 1503, 1250 cm^{-1}; MS (EI) *m/z* 454 (M^+). Anal. calcd for $C_{27}H_{34}O_6$: C, 71.34; H, 7.54%. Found: C, 71.06; H, 7.28%.

3-[5-[4-(Dimethylaminocarbonyl)butyl]-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (35b). The title compund was obtained from **34b**: 74% yield; colorless oil; R_f 0.50 (AcOEt). ^{1}H NMR ($CDCl_3$) δ 1.40–1.55 (m, 8H), 1.82 (m, 2H), 7.27 (d, J = 8 Hz, 2H), 2.28 (m, 4H), 2.60 (m, 4H), 2.95 (s, 3H), 2.98 (t, J = 7 Hz, 2H), 3.00 (s, 3H), 3.80 (s, 3H), 3.97 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 6.95 (dd, J = 8 Hz and 2 Hz, 1H), 7.00 (d, J = 2 Hz, 1H). IR (neat) 1729, 1609, 1510, 1249 cm^{-1}; MS (EI) *m/z* 481 (M^+); FAB HRMS *m/z* 482.2946 (MH^+, $C_{29}H_{30}NO_5$ 482.2907).

6-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]hexanoic acid (42a). From **41a** the title compund was obtained as: 92% yield; white solid; R_f 0.30 ($CHCl_3$:MeOH, 9:1). ^{1}H NMR ($CDCl_3$) δ 1.40–1.80 (m, 8H), 1.85 (m, 2H), 2.25 (m, 2H), 2.38 (t, J = 7 Hz, 2H), 2.60 (m, 4H), 3.00 (m, 2H), 3.80 (s, 3H), 3.98 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 6.80 (d, J = 8 Hz, 2H), 7.10 (t, J = 8 Hz, 1H), 7.28 (d, J = 8 Hz, 2H). IR (neat) 1707, 1511, 1458, 1248 cm^{-1}; MS (EI) *m/z* 468 (M^+); FAB HRMS *m/z* 469.2586 (MH^+, $C_{28}H_{37}O_6$ 469.2590).

3-[6-[5-(Dimethylaminocarbonyl)pentyl]-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (42b). The title compund was obtained from **41b**: 84% yield; colorless oil; R_f 0.50 ($CHCl_3$:MeOH, 9:1). ^{1}H NMR ($CDCl_3$) δ 1.23 (m, 2H), 1.65 (m, 6H), 1.83 (m, 2H), 2.27 (m, 2H), 2.35 (t, J = 7 Hz, 2H), 2.60 (m, 4H), 2.95 (s, 3H), 3.00 (s, 3H), 3.05 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.98 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.70 (d, J = 8 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.10 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 2H). IR (neat) 1724, 1609, 1510, 1458, 1249 cm^{-1}; MS (EI) *m/z* 495 (M^+); FAB HRMS *m/z* 496.3048 (MH^+, $C_{30}H_{42}NO_5$ 496.3063).

5-[3-(2-Carboxyethyl)-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyloxy]pentanoic acid (45). The title compound was obtained from **44**: 93% yield; white powder (from hexane:AcOEt, 2:1); mp 112.5–113 °C; R_f 0.35 ($CHCl_3$:MeOH, 9:1). ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 2H), 1.80 (m, 6H), 2.25 (m, 2H), 2.42 (t, J = 7 Hz, 2H), 2.65 (t, J = 7 Hz, 2H), 2.92 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.93 (m, 4H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.75 (m, 3H), 6.82 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H). IR (KBr) 1695, 1510, 1227 cm^{-1}; MS (EI) *m/z* 470 (M^+). Anal. calcd for $C_{27}H_{34}O_7$: C, 68.92; H, 7.28%. Found: C, 69.02; H, 7.12%.

3-[2-(Carboxymethoxy)-6-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (49a). The title compound was obtained from **48b**: 61% yield; white solid (from hexane:AcOEt, 3:2); mp 111–112 °C; R_f 0.30 ($CHCl_3$:MeOH:AcOH, 85:10:5). ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.85 (m, 2H), 2.25 (m, 2H), 2.60 (t, J = 7 Hz, 2H), 3.10 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 4.00 (t, J = 7 Hz, 2H), 4.60 (s, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.38 (d, J = 8 Hz, 1H), 6.55 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.12 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 2H). IR (KBr) 1716, 1596, 1511, 1467, 1244, 1126 cm^{-1}; MS (EI) *m/z* 428 (M^+). Anal. calcd for $C_{24}H_{28}O_7$: C, 67.28; H, 6.59%. Found: C, 67.31; H, 6.30%.

6-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenoxy]hexanoic acid (49b). The title compound was obtained from **48d**: 70% yield; white powder (from hexane:AcOEt, 2:1); mp 76.5–77 °C; R_f 0.60 (AcOEt:MeOH, 9:1). ^{1}H NMR ($CDCl_3$) δ 1.50–1.90 (m, 10H), 2.25 (m, 2H), 2.40 (t, J = 7 Hz, 2H), 2.52 (t, J = 7 Hz, 2H), 3.03 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.97 (m, 4H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.50 (m, 2H), 6.82 (d, J = 8 Hz, 2H), 7.10 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 2H). IR (KBr) 1703, 1462, 1251, 1108 cm^{-1}; MS (EI) *m/z* 484 (M^+). Anal. calcd for $C_{28}H_{36}O_7$: C, 69.40; H, 7.49%. Found: C, 69.27; H, 7.24%.

4-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenoxy]butanoic acid (52). The title compound was obtained from **51**: 90% yield; white crystals (from AcOEt:hexane, 1:1); mp 70–73 °C; R_f 0.35 ($CHCl_3$:MeOH, 9:1). ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 2H), 1.82 (m, 2H), 2.15 (m, 2H), 2.25 (m, 2H), 2.58 (m, 4H), 3.00 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 4.00 (m, 4H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.47 (d, J = 8 Hz, 1H), 6.50 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.10 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 2H). IR (KBr) 2931, 1703, 1596, 1511, 1461, 1251, 1108 cm^{-1}; MS (EI) *m/z* 456 (M^+). Anal. calcd for

$C_{26}H_{32}O_7$: C, 68.40; H, 7.06%. Found: C, 68.14; H, 7.11%.

3-[2-[4-(Dimethylaminocarbonyl)butoxy]-5-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (54b). The title compound was obtained from **54a**: 53% yield; white solid (from hexane:AcOEt, 5:1); mp 105–106.5 °C; R_f 0.20 (AcOEt:MeOH, 9:1). ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 2H), 1.80 (m, 6H), 2.25 (m, 2H), 2.40 (m, 2H), 2.63 (t, J = 7 Hz, 2H), 2.95 (m, 5H), 3.02 (s, 3H), 3.80 (s, 3H), 3.92 (m, 4H), 6.07 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.65–6.80 (m, 3H), 6.82 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H). IR (KBr) 1726, 1636, 1608, 1511, 1250, 1226 cm^{-1}; MS (EI) m/z 497 (M^+). Anal. calcd for $C_{29}H_{39}NO_6$: C, 70.00; H, 7.90; N, 2.81%. Found: C, 69.74; H, 7.75; N, 3.01%.

5-[4-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenoxy]pentanoic acid (57c). The title compound was obtained from **57b**: 84% yield; white powder (from hexane:AcOEt, 2:1); mp 107.5–108 °C; R_f 0.35 ($CHCl_3$:MeOH, 9:1). ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.80 (m, 6H), 2.25 (m, 2H), 2.42 (m, 2H), 2.62 (t, J = 7 Hz, 2H), 2.87 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.95 (m, 4H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (m, 3H), 7.02 (d, J = 8 Hz, 1H), 7.25 (d, J = 8 Hz, 2H). IR (KBr) 1707, 1610, 1510, 1254 cm^{-1}; MS (EI) m/z 470 (M^+). Anal. calcd for $C_{27}H_{34}O_7$: C, 68.92; H, 7.28%. Found: C, 68.70; H, 7.10%.

Preparation of sodium 3-[2-hydroxy-6-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoate (47). A 0.40 mmol quantity of 0.1 N sodium hydroxide was added to a stirred solution of **46**[8] (140 mg, 0.40 mmol) in MeOH (10 mL). After refluxing for 1 h, the mixture was evaporated in vacuo to give white precipitates. The precipitates were collected by filtration, washed with distilled water, and dried in a desiccator (P_2O_5) under reduced pressure, giving 105 mg (67%) of **47** as a white powder. R_f 0.50 (AcOEt); ^{1}H NMR (CD_3OD) δ 1.68 (m, 2H), 1.83 (m, 2H), 2.27 (m, 2H), 2.48 (t, J = 7 Hz, 2H), 2.85 (t, J = 7 Hz, 2H), 3.75 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.40 (m, 2H), 6.82 (d, J = 8 Hz, 2H), 6.93 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 2H). IR (KBr) 3462, 1606, 1558, 1510, 1250 cm^{-1}; MS (FAB) m/z 393 (MH^+); FAB HRMS m/z 415.1501 (MNa^+, $C_{22}H_{25}O_5Na_2$ 415.1498).

Sodium 5-hydroxy-5-[4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]-3-[2-(sodiumcarboxy)ethyl]phenyl]pentanoate (32a). The title compound was prepared from **31a** with 2.0 equiv of NaOH by using the same procedure as described above: 89% yield; white powder; R_f 0.20 (AcOEt:MeOH, 9:1). ^{1}H NMR (CD_3OD) δ 1.60–2.00 (m, 8H), 2.20 (m, 2H), 2.30 (t, J = 7 Hz, 2H), 2.43 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.78 (s, 3H), 4.00 (t, J = 7 Hz, 2H), 4.50 (m, 1H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.82 (m, 3H), 7.10 (m, 2H), 7.28 (d, J = 8 Hz, 2H); IR (KBr) 3401, 1558, 1409, 1249 cm^{-1}; MS (FAB) m/z 515 (MH^+); FAB HRMS m/z 537.1860 (MNa^+, $C_{27}H_{32}O_7Na_3$ 537.1842).

General procedure C

Preparation of 3-[5-(acetylamino)-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (20a). A solution of **19c** (160 mg, 0.34 mmol) in formic acid (10 mL) was stirred at 25 °C for 30 min, and the mixture was then evaporated in vacuo. Chromatography of the residue on a silica gel column (AcOEt) afforded a white solid, which was recrystallized from AcOEt:hexane (4:1) to give 95 mg (67%) of **20a** as a white fluffy solid. Mp 138–139 °C; R_f 0.40 (AcOEt:MeOH, 9:1); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 1.63 (m, 2H), 1.82 (m, 2H), 2.15 (s, 3H), 2.25 (m, 2H), 2.60 (t, J = 7 Hz, 2H), 2.93 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.97 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.78 (d, J = 8 Hz, 1H), 6.83 (d, J = 8 Hz, 2H), 7.18 (d, J = 2 Hz, 1H), 7.30 (d, J = 8 Hz, 2H), 7.45 (dd, J = 8 Hz and 2 Hz, 1H), 7.87 (s, 1H); IR (KBr) 3326, 1709, 1636, 1510, 1248 cm^{-1}; MS (EI) m/z 411 (M^+). Anal. calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40%. Found: C, 70.09; H, 6.86; N, 3.50%.

The following compounds were prepared from the indicated starting materials by using the procedure described above.

3-[2-[6-(4-Methoxyphenyl)-(5*E*)-hexenyloxy]-5-(phthalimino)phenyl]propanoic acid (20b). The title compound was obtained from **19d**: 52% yield; pale yellow powder (from AcOEt); mp 180–182 °C; R_f 0.50 (AcOEt). ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.87 (m, 2H), 2.30 (m, 2H), 2.70 (t, J = 7 Hz, 2H), 3.00 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 4.03 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 6.92 (d, J = 8 Hz, 1H), 7.23 (m, 2H), 7.50 (d, J = 8 Hz, 2H), 7.78 (m, 2H), 7.95 (m, 2H). IR (KBr) 3215, 1756, 1702, 1511, 1256 cm^{-1}; MS (EI) m/z 499 (M^+). Anal. calcd for $C_{30}H_{29}NO_6$: C, 72.13; H, 5.85; N, 2.80%. Found: C, 71.88; H, 5.57; N, 2.54%.

3-[5-(Methanesulfonylamino)-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (22a). From **21a** the title compound was obtained as: 70% yield; white solid (from hexane:AcOEt, 2:1); mp 113.5–114 °C; R_f 0.30 (AcOEt). ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.85 (m, 2H), 2.27 (m, 2H), 2.68 (t, J = 7 Hz, 2H), 2.90 (s, 3H), 2.93 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.98 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 6.85 (s, 1H), 7.07 (d, J = 2 Hz, 1H), 7.13 (dd, J = 8 Hz and 2 Hz, 1H), 7.27 (d, J = 8 Hz, 2H); IR (KBr) 3259, 1697, 1511, 1249, 1152 cm^{-1}; MS (EI) m/z 447 (M^+). Anal. calcd for $C_{23}H_{29}NSO_6$: C, 61.73; H, 6.53; N, 31.30; S, 7.16%. Found: C, 61.95; H, 6.81; N, 3.34; S, 7.30%.

3-[2-[6-(4-Methoxyphenyl)-(5*E*)-hexenyloxy]-5-[(4-methylphenyl)sulfonylamino]phenyl]propanoic acid (22b). The title compound was prepared from **21b**: 59% yield; white solid (from hexane:AcOEt, 2:1); mp 107–109 °C; R_f 0.30 (AcOEt:hexane, 2:1). ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 2H), 1.82 (m, 2H), 2.25 (m, 2H), 2.40 (s, 3H), 2.58

(t, J = 7 Hz, 2H), 2.85 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.93 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.67 (d, J = 8 Hz, 1H), 6.80 (s, 1H), 6.82 (d, J = 8 Hz, 2H), 6.95 (dd, J = 8 Hz and 2 Hz, 1H), 6.98 (d, J = 2 Hz, 1H), 7.20 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 2H); IR (KBr) 3264, 1708, 1511, 1248, 1160 cm^{-1}; MS (EI) m/z 523 (M^+). Anal. calcd for $C_{29}H_{33}NSO_6$: C, 66.52; H, 6.35; N, 2.67; S, 6.12%. Found: C, 66.38; H, 6.28; N, 2.59; S, 6.15%.

3-[5-[4-(Dimethylaminocarbonyl)butanoylamino]-2-(6-phenyl-5*E*-hexenyloxy)phenyl]propanoic acid (5a). The title compound was prepared from **4**[1] according to general procedure A followed by general procedure C: 17% yield; white powder (from AcOEt); R_f 0.50 (AcOEt:MeOH, 6:1). ^1H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.82 (m, 2H), 2.05 (m, 2H), 2.27 (m, 2H), 2.45 (m, 4H), 2.65 (t, J = 7 Hz, 2H), 2.97 (m, 5H), 3.00 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.22 (dt, J = 16 Hz and 7 Hz, 1H), 6.40 (d, J = 16 Hz, 1H), 6.78 (d, J = 8 Hz, 1H), 7.10–7.40 (m, 6H), 7.70 (dd, J = 8 Hz and 2 Hz, 1H), 8.52 (1H, s); IR (KBr) 3282, 1711, 1646, 1600, 1502, 1230 cm^{-1}; MS (EI) m/z 480 (M^+); FAB HRMS m/z 481.2719 (MH^+, $C_{28}H_{37}N_2O_5$ 481.2702).

3-[5-[4-(Dimethylaminocarbonyl)butanoylamino]-2-[5-(4-methoxyphenyl)-(4*E*)-pentenyloxy]phenyl]propanoic acid (5b). The title compound was prepared from **4**[1] according to general procedure A followed by general procedure C: 30% yield; white solid; R_f 0.20 (AcOEt: MeOH, 6:1). ^1H NMR ($CDCl_3$) δ 2.00 (m, 4H), 2.45 (m, 6H), 2.70 (t, J = 7 Hz, 2H), 2.97 (m, 5H), 3.02 (s, 3H), 3.80 (s, 3H), 4.00 (t, J = 7 Hz, 2H), 6.08 (dd, J = 16 Hz and 7 Hz, 1H), 6.38 (d, J = 16 Hz, 1H), 6.78 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.20 (d, J = 2 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 7.68 (dd, J = 8 Hz and 2 Hz, 1H), 8.45 (1H, s). IR (KBr) 3289, 1730, 1658, 1633, 1609, 1511, 1501, 1240 cm^{-1}; MS (EI) m/z 496 (M^+); FAB HRMS m/z 497.2651 (MH^+, $C_{28}H_{37}N_2O_6$ 497.2652).

3-[5-[4-(Dimethylaminocarbonyl)butanoylamino]-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (5c). The title compound was prepared from **4**[1] according to general procedure A followed by general procedure C: 23% yield; white platelets (from AcOEt); mp 123–123.5 °C; R_f 0.30 (AcOEt:MeOH, 6:1). ^1H NMR ($CDCl_3$) δ 1.62 (m, 2H), 1.82 (m, 2H), 2.05 (m, 2H), 2.25 (m, 2H), 2.45 (m, 4H), 2.65 (t, J = 7 Hz, 2H), 2.95 (m, 5H), 3.00 (s, 3H), 3.80 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.78 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.20 (d, J = 2 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 7.65 (dd, J = 8 Hz and 2 Hz, 1H), 8.52 (s, 1H). IR (KBr) 3357, 1714, 1683, 1601, 1508, 1245 cm^{-1}; MS (EI) m/z 510 (M^+). Anal. calcd for $C_{29}H_{38}N_2O_6$: C, 68.21; H, 7.50; N, 5.49%. Found: C, 68.04; H, 7.25; N, 5.37%.

3-[5-[4-(Dimethylaminocarbonyl)butanoylamino]-2-[7-(4-methoxyphenyl)-(6*E*)-heptenyloxy]phenyl]propanoic acid (5d). The title compound was prepared from **4**[1] according to general procedure A followed by general procedure C: 17% yield; white solid (from AcOEt:hexane, 2:1); mp 120–123 °C; R_f 0.30 (AcOEt:MeOH, 6:1). ^1H NMR ($CDCl_3$) δ 1.50 (m, 4H), 1.80 (m, 2H), 2.05 (m, 2H), 2.23 (m, 2H), 2.45 (m, 4H), 2.65 (t, J = 7 Hz, 2H), 2.97 (m, 5H), 3.02 (s, 3H), 3.80 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.07 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.78 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.20 (d, J = 2 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 7.70 (dd, J = 8 Hz and 2 Hz, 1H), 8.50 (1H, s). IR (KBr) 3273, 1711, 1650, 1601, 1511, 1248, 1229 cm^{-1}; MS (EI) m/z 524 (M^+). Anal. calcd for $C_{30}H_{40}N_2O_6$: C, 68.68; H, 7.68; N, 5.34%. Found: C, 68.62; H, 7.62; N, 5.14%.

3-[5-[4-(Dimethylaminocarbonyl)butanoylamino]-2-[6-(3-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (5e). The title compound was prepared from **4**[1] according to general procedure A followed by general procedure C: 57% yield; yellow oil; R_f 0.40 (AcOEt: MeOH, 6:1). ^1H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.82 (m, 2H), 2.05 (m, 2H), 2.28 (m, 2H), 2.45 (m, 4H), 2.65 (t, J = 7 Hz, 2H), 2.97 (m, 5H), 3.02 (s, 3H), 3.80 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.22 (dt, J = 16 Hz and 7 Hz, 1H), 6.40 (d, J = 16 Hz, 1H), 6.75 (m, 2H), 6.90 (m, 2H), 7.20 (m, 2H), 7.68 (dd, J = 8 Hz and 2 Hz, 1H), 8.52 (s, 1H); IR (neat) 3301, 1723, 1607, 1503, 1236 cm^{-1}; MS (EI) m/z 510 (M^+).

3-[5-[4-(Dimethylaminocarbonyl)butanoylamino]-2-[6-(4-methylthiophenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (5f). The title compound was prepared from **4**[1] according to general procedure A followed by general procedure C: 37% yield; white powder; R_f 0.30 (AcOEt:MeOH, 6:1). ^1H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.83 (m, 2H), 2.05 (m, 2H), 2.27 (m, 2H), 2.47 (t, J = 7 Hz, 2H), 2.50 (s, 3H), 2.65 (t, J = 7 Hz, 2H), 2.95 (m, 5H), 3.02 (s, 3H), 3.97 (t, J = 7 Hz, 2H), 6.20 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 7.20 (m, 3H), 7.25 (d, J = 8 Hz, 2H), 7.68 (dd, J = 8 Hz and 2 Hz, 1H), 8.50 (s, 1H). IR (KBr) 3279, 3120, 1733, 1650, 1624, 1500, 1243, 1176 cm^{-1}; MS (EI) m/z 526 (M^+); FAB HRMS m/z 549.2424 (MNa^+, $C_{29}H_{38}N_2O_5SNa$ 549.2399).

3-[5-[4-(Dimethylaminocarbonyl)butanoylamino]-2-[6-(4-methylphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (5g). The title compound was prepared from **4**[1] according to general procedure A followed by general procedure C: 35% yield; colorless oil; R_f 0.35 (AcOEt: MeOH, 6:1). ^1H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.83 (m, 2H), 2.05 (m, 2H), 2.30 (m, 2H), 2.32 (s, 3H), 2.45 (m, 4H), 2.65 (m, 2H), 2.95 (m, 5H), 3.02 (s, 3H), 3.97 (t, J = 7 Hz, 2H), 6.15 (dt, J = 16 Hz and 7 Hz, 1H), 6.38 (d, J = 16 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 7.10 (d, J = 8 Hz, 2H), 7.13 (d, J = 2 Hz, 1H), 7.22 (d, J = 8 Hz, 2H), 7.65 (dd, J = 8 Hz and 2 Hz, 1H), 8.48 (1H, s); IR (neat) 3301, 1723, 1616, 1504, 1235 cm^{-1}; MS (EI) m/z 494 (M^+); EI HRMS m/z 494.2788 ($C_{29}H_{38}N_2O_5$ 494.2781).

3-[2-[6-(4-Chlorophenyl)-(5*E*)-hexenyloxy]-5-[4-(dimethylaminocarbonyl)butanoylamino]phenyl]propanoic acid (5h). The title compound was prepared from **4**[1] according to general procedure A followed by general procedure C: 37% yield; colorless oil; R_f 0.40 (AcOEt:MeOH, 6:1). ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.82 (m, 2H), 2.05 (m, 2H), 2.27 (m, 2H), 2.45 (m, 4H), 2.65 (t, J = 7 Hz, 2H), 2.95 (m, 5H), 3.02 (s, 3H), 3.97 (t, J = 7 Hz, 2H), 6.20 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 7.15-7.30 (m, 5H), 7.67 (dd, J = 8 Hz and 2 Hz, 1H), 8.50 (s, 1H). IR (neat) 3300, 1714, 1615, 1503, 1234 cm^{-1}; MS (EI) *m/z* 514 (M^+); EI HRMS *m/z* 514.2261 ($C_{28}H_{35}N_2O_5Cl$ 514.2235).

3-[5-[4-(Methoxycarbonyl)butanoylamino]-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (15d). The title compound was prepared from **14b**[4] according to general procedure A followed by general procedure C: quantitative yield; pale yellow oil; R_f 0.15 (AcOEt:hexane, 1:1). ^{1}H NMR ($CDCl_3$) δ 1.60–2.50 (m, 12H), 2.65 (t, J = 7 Hz, 2H), 2.93 (t, J = 7 Hz, 2H), 3.68 (s, 3H), 3.80 (s, 3H), 3.97 (t, J = 7 Hz, 2H), 6.07 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.55–7.40 (m, 8H); MS (EI) *m/z* 497 (M^+).

Preparation of 4-[3-(2-carboxyethyl)-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenylaminosulfonyl]butanoic acid (22c). Compound **22c** was prepared from **21c** via 4-[3-[2-(*tert*-butoxycarbonyl)ethyl]-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenylaminosulfonyl]butanoic acid **21d**, according to general procedure B followed by general procedure C: 72% yield; pale yellow oil; R_f 0.10 (AcOEt:MeOH, 9:1). ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 2H), 1.82 (m, 2H), 2.10 (m, 2H), 2.25 (m, 2H), 2.50 (t, J = 7 Hz, 2H), 2.65 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.10 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.97 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.00 (d, J = 2 Hz, 1H), 7.18 (dd, J = 8 Hz and 2 Hz, 1H), 7.27 (2H, d, J = 8 Hz, 2H). IR (neat) 3270, 1713, 1608, 1504, 1299, 1153 cm^{-1}; MS (EI) *m/z* 519 (M^+).

Preparation of methyl-4-(3-formyl-4-hydroxyphenylaminocarbonyl)butanoate (8a). Methyl 4-chloroformylbutanoate (0.53 mL, 3.84 mmol) was added dropwise to a stirred solution of **7** (690 mg, 3.76 mmol) and pyridine (3.0 mL, 37 mmol) in CH_2Cl_2 (20 mL) at 25 °C. After being stirred for 15 min, the mixture was poured into 1 N HCl (40 mL). The resulting mixture was extracted with AcOEt (100 mL). The extract was washed with satd aq $NaHCO_3$ and then brine, dried over $MgSO_4$, and evaporated in vacuo. Chromatography of the residue on a silica gel column (AcOEt:hexane, 2:1) afforded 660 mg (66%) of **8a** as a pale yellow oil; R_f 0.45 (AcOEt:hexane, 3:2). ^{1}H NMR ($CDCl_3$) δ 2.07 (m, 2H), 2.45 (m, 4H), 3.72 (s, 3H), 6.95 (d, J = 8 Hz, 1H), 7.40 (dd, J = 8 Hz and 2 Hz, 1H), 7.45 (s, 1H), 8.05 (d, J = 2 Hz, 1H), 9.88 (s, 1H), 10.87 (s, 1H); MS *m/z* 265 (M^+).

Preparation of methyl-4-[4-hydroxy-3-(2-methoxycarbonyl-(*E*)-ethenyl)phenylaminocarbonyl]butanoate (8b). A phosphorane, **61** (180 mg, 5.4 mmol) was added to a stirred solution of **8a** (130 mg, 0.49 mmol) in CH_2Cl_2 (10 mL). After being stirred at 25 °C for 2 h, the mixture was concentrated in vacuo. Chromatography of the residue on a silica gel column (AcOEt:hexane, 3:1) afforded 157 mg (quantitative yield) of **8b** as a pale yellow oil. R_f 0.50 (AcOEt:hexane, 4:1); ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 2.03 (m, 2H), 2.42 (m, 4H), 3.40 (s, 3H), 3.80 (s, 3H), 6.57 (d, J = 16 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 7.45 (dd, J = 8 Hz and 2 Hz, 1H), 7.52 (d, J = 2 Hz, 1H), 7.95 (d, J = 16 Hz, 1H).

Methyl-4-[3-(2-formyl-(*E*)-ethenyl)-4-hydroxyphenylaminocarbonyl]butanoate (8c). Compound **8c** was prepared from **8a** and the phosphorane **62** by using the procedure described above. Quantitative yield; pale yellow oil; R_f 0.30 (AcOEt:hexane, 4:1). ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 2.05 (m, 2H), 2.45 (m, 4H), 3.70 (s, 3H), 6.70–6.85 (m, 2H), 7.25–7.35 (m, 2H), 7.80 (d, J = 16 Hz, 1H), 9.62 (d, J = 8 Hz, 1H); MS (EI) *m/z* 291 (M^+).

General procedure D

Preparation of methyl-4-[4-hydroxy-3-(3-hydroxy-(1*E*)-propenyl)phenylaminocarbonyl]butanoate (8d). Sodium borohydride (80 mg, 2.1 mmol) was added to a stirred solution of **8c** (170 mg, 0.58 mmol) in THF (2.0 mL) and MeOH (0.5 mL) at 0 °C. After stirring at 0 °C for 20 min, the mixture was poured into cold water (10 mL) and extracted with AcOEt (50 mL). The extract was washed with satd aq $NaHCO_3$ and then brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt:hexane, 5:1), providing 120 mg (71%) of **8d** as a colorless oil. R_f 0.15 (AcOEt:hexane, 5:1); ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 2.02 (m, 2H), 2.42 (m, 4H), 3.68 (s, 3H), 4.25 (d, J = 7 Hz, 2H), 6.32 (dt, J = 16 Hz and 7 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 7.27 (dd, J = 8 Hz and 2 Hz, 1H), 7.45–7.68 (m, 2H).

The following compounds were prepared from the indicated starting materials by using the procedure described above.

Ethyl-5-[3-[2-(ethoxycarbonyl)ethyl]-5-hydroxy-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]pentanoate (31a). From **29a** the title compound was obtained as: 84% yield; colorless oil; R_f 0.40 (AcOEt:hexane, 1:1). ^{1}H NMR ($CDCl_3$) δ 1.25 (m, 6H), 1.50–1.95 (m, 6H), 2.20–2.38 (m, 4H), 2.60 (t, J = 7 Hz, 2H), 2.95 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.98 (t, J = 7 Hz, 2H), 4.10 (m, 4H), 4.58 (m, 1H), 6.07 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 6.83 (d, J = 8 Hz, 2H), 7.15 (m, 2H), 7.27 (d, J = 8 Hz, 2H); MS (EI) *m/z* 526 (M^+).

Ethyl-3-[5-[4-(dimethylaminocarbonyl)-1-hydroxybutyl]-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoate (31b). The title compound was obtained from **29b**: 98% yield; colorless oil; R_f 0.20 (AcOEt). ^{1}H NMR

($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.55–1.95 (m, 8H), 2.22–2.40 (m, 4H), 2.60 (t, J = 7 Hz, 2H), 2.95 (t, J = 7 Hz, 2H), 2.95 (s, 3H), 3.00 (s, 3H), 3.80 (s, 3H), 3.97 (t, J = 7 Hz, 2H), 4.10 (q, J = 7 Hz, 2H), 4.60 (m, 1H), 6.07 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 6.83 (d, J = 8 Hz, 2H), 7.15 (m, 2H), 7.25 (d, J = 8 Hz, 2H); MS (EI) m/z 525 (M^+).

Preparation of *tert*-butyl 3-[5-amino-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoate (19b). Potassium carbonate (2.80 g, 20.0 mmol) was added to a stirred solution of **19a** (5.30 g, 10.0 mmol) in MeOH (30 mL) and water (5.0 mL). After being stirred at 25 °C for 16 h, the mixture was diluted with water (100 mL). The resulting mixture was extracted with AcOEt (100 mL × 2). The combined extract was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel (hexane:AcOEt, 3:2) to give 3.50 g (78%) of **19b** as a pale yellow oil. R_f 0.20 (hexane:AcOEt, 2:1). ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.65 (m, 2H), 1.80 (m, 2H), 2.25 (m, 2H), 2.50 (t, J = 7 Hz, 2H), 2.80 (t, J = 7 Hz, 2H), 3.40 (s, 2H), 3.80 (s, 3H), 3.90 (t, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.50 (dd, J = 8 Hz and 2 Hz, 1H), 6.55 (d, J = 2 Hz, 1H), 6.65 (d, J = 8 Hz, 1H), 6.85 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H). IR (neat) 3367, 2934, 1726, 1510, 1247, 1149 cm^{-1}; MS (EI) m/z 425 (M^+); EI HRMS m/z 425.2564 ($C_{26}H_{35}NO_4$ requires 425.2566).

Preparation of *tert*-butyl-3-[5-acetylamino-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoate (19c). Acetyl chloride (0.031 mL, 0.43 mmol) was added dropwise to a stirred solution of **19b** (153 mg, 0.36 mmol) and triethylamine (0.075 mL, 0.54 mmol) in CH_2Cl_2 (4.0 ml) at 0 °C under an argon atmosphere. After being stirred at 0 °C for 30 min, the mixture was poured into ice-cooled 1 N HCl (10 mL). The resulting mixture was extracted with AcOEt (50 mL). The extract was washed with satd aq $NaHCO_3$ and then brine, dried over $MgSO_4$, and evaporated in vacuo. Purification of the residue by column chromatography on silica gel (AcOEt:hexane, 3:2) afforded 160 mg (95%) of **19c** as a white solid; R_f 0.15 (AcOEt:hexane, 1:1). ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.65 (m, 2H), 1.85 (m, 2H), 2.15 (s, 3H), 2.25 (m, 2H), 2.50 (t, J = 7 Hz, 2H), 2.88 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.97 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 6.83 (d, J = 8 Hz, 2H), 7.00 (s, 1H), 7.18 (d, J = 2 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 7.37 (dd, J = 8 Hz and 2 Hz, 1H); MS (EI) m/z 467 (M^+).

Preparation of *tert*-butyl-3-[2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]-5-phthaliminophenyl]propanoate (19d). Phthalic anhydride (120 mg, 0.83 mmol) was added to a stirred solution of **19b** (176 mg, 0.41 mmol) in $CHCl_3$ (5 mL). After being refluxed for 24 h, the mixture was evaporated in vacuo. Purification of the residue by column chromatography on silica gel (CH_2Cl_2:AcOEt, 9:1) gave 130 mg (58%) of **19d** as a pale yellow oil. R_f 0.20 (hexane:AcOEt, 4:1); ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.70 (m, 2H), 1.90 (m, 2H), 2.30 (m, 2H), 2.55 (t, J = 7 Hz, 2H), 2.95 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 4.05 (t, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.85 (d, J = 8 Hz, 2H), 6.95 (d, J = 8 Hz, 1H), 7.20 (m, 2H), 7.30 (d, J = 8 Hz, 2H), 7.80 (m, 2H), 7.95 (m, 2H); MS (EI) m/z 555 (M^+).

General procedure E

Preparation of *tert*-butyl 3-[5-(methanesulfonylamino)-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoate (21a). Methanesulfonyl chloride (0.030 mL, 0.38 mmol) was added dropwise to a stirred solution of **19b** (150 mg, 0.35 mmol) and triethylamine (0.072 mL, 0.52 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C. After stirring at 0 °C for 30 min, the mixture was poured into ice-cooled 1 N HCl (5 mL). The resulting mixture was extracted with AcOEt (50 mL). The extract was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. Purification of the residue was carried out by column chromatography on silica gel (hexane:AcOEt, 2:1), yielding 160 mg (91%) of **21a** as a colorless oil. R_f 0.50 (AcOEt:hexane, 1:1); ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.65 (m, 2H), 1.85 (m, 2H), 2.25 (m, 2H), 2.50 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 2.95 (s, 3H), 3.80 (s, 3H), 4.00 (q, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.20 (s, 1H), 6.35 (d, J = 16 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 6.85 (d, J = 8 Hz, 2H), 7.05 (d, J = 2 Hz, 1H), 7.10 (dd, J = 8 Hz and 2 Hz, 1H), 7.25 (d, J = 8 Hz, 2H); MS (EI) m/z 503 (M^+).

The following compounds were prepared from the indicated starting materials and the sulfonyl chlorides by the procedure described above.

***tert*-Butyl-3-[2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]-5-(4-methylphenyl)sulfonylaminophenyl]propanoate (21b).** The title compound was obtained from **19b**: 90% yield; colorless oil; R_f 0.30 (hexane:AcOEt, 2:1). ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.60 (m, 2H), 1.80 (m, 2H), 2.25 (m, 2H), 2.40 (s, 3H), 2.40 (t, J = 7 Hz, 2H), 2.80 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.15 (s, 1H), 6.35 (d, J = 16 Hz, 1H), 6.65 (d, J = 8 Hz, 1H), 6.75 (d, J = 2 Hz, 1H), 6.80 (d, J = 8 Hz, 2H), 6.85 (dd, J = 8 Hz and 2 Hz, 1H), 7.20 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 2H); MS (EI) m/z 579 (M^+).

Ethyl-4-[3-[2-(*tert*-butoxycarbonyl)ethyl]-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenylaminosulfonyl]butanoate (21c). From **19b** the title compound was obtained as: 78% yield; pale yellow oil; R_f 0.25 (hexane:AcOEt, 2:1). ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3H), 1.40 (s, 9H), 1.65 (m, 2H), 1.85 (m, 2H), 2.15 (m, 2H), 2.25 (m, 2H), 2.50 (m, 4H), 2.90 (t, J = 7 Hz, 2H), 3.10 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 4.00 (t, J = 7 Hz, 2H), 4.15 (q, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.30 (s, 1H), 6.35 (d, J = 16 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 6.85 (d, J = 8 Hz, 2H), 7.10 (m, 2H), 7.25 (d, J = 8 Hz, 2H); MS (EI) m/z 603 (M^+).

General procedure F

Preparation of methyl 4-[3-[2-(dimethylaminocarbonyl)-ethyl]-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl-aminocarbonyl]butanoate (16). Ethyl chloroformate (0.017 mL, 0.18 mmol) was added dropwise to a stirred solution of **15d** (61 mg, 0.12 mmol) and triethylamine (0.033 mL, 0.24 mmol) in THF (1.0 mL) at −10 °C under an argon atmosphere. The mixture was stirred at −10 °C for 5 min, and then dimethylamine (0.5 mL of 40% aqueous solution) was added to the above mixture. After being stirred at 25 °C for 5 min, the mixture was poured into ice-cooled 2 N HCl (10 mL). The resulting mixture was extracted with AcOEt (50 mL). The organic layer was washed with satd aq $NaHCO_3$ and then brine, dried over $MgSO_4$, and evaporated in vacuo. Chromatography of the residue on a silica gel column ($CHCl_3$:MeOH, 19:1) afforded 52 mg (81%) of **16** as a colorless oil. R_f 0.50 (AcOEt:MeOH, 6:1); ^{1}H NMR ($CDCl_3$) δ 1.63 (m, 2H), 1.82 (m, 2H), 2.05 (m, 2H), 2.25 (m, 2H), 2.43 (m, 4H), 2.60 (t, J = 7 Hz, 2H), 2.93 (m, 8H), 3.70 (s, 3H), 3.80 (s, 3H), 3.98 (t, J = 7 Hz, 2H), 6.07 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 6.83 (d, J = 8 Hz, 2H), 7.15 (d, J = 2 Hz, 1H), 7.27 (d, J = 8 Hz, 2H), 7.42 (s, 1H), 7.50 (dd, J = 8 Hz and 2 Hz, 1H); MS (EI) m/z 524 (M^+).

The following compounds were prepared from the indicated starting materials by the procedure described above.

Methyl-3-[6-[4-(dimethylaminocarbonyl)butanoylamino]-2-hydroxyphenyl]propanoate (24c). From **24b**, the title compound was obtained as: 43% yield; R_f 0.30 (AcOEt:MeOH, 19:1). ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 2.03 (m, 2H), 2.42–2.75 (m, 6H), 2.88 (m, 2H), 2.97 (s, 3H), 3.10 (s, 3H), 3.67 (s, 3H), 6.65 (d, J = 8 Hz, 1H), 6.93 (d, J = 8 Hz, 1H), 7.02 (t, J = 8 Hz, 1H); MS (EI) m/z 336 (M^+).

5-(5-Dimethylaminocarbonyl)hexyl-3,4-dihydrocoumarin (39b). The title compound was obtained from **39a**: 91% yield; pale yellow oil; R_f 0.40 (AcOEt). ^{1}H NMR ($CDCl_3$) δ 1.40 (m, 2H), 1.50–1.80 (m, 4H), 2.30 (t, J = 7 Hz, 2H), 2.62 (t, J = 7 Hz, 2H), 2.78 (m, 2H), 2.95 (m, 2H), 2.97 (s, 3H), 3.00 (s, 3H), 6.93 (d, J = 8 Hz, 1H), 6.97 (d, J = 8 Hz, 1H), 7.18 (t, J = 8 Hz, 1H); MS (EI) m/z 289 (M^+).

Preparation of 3-[5-[3-(dimethylaminocarbonyl)propanoylamino]-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]-phenyl]propanoic acid (15a). Compound **15a** was prepared from **14a**[4] according to general procedures A, B, F, and C described above: 12% yield; white powder (from AcOEt:hexane, 2:1); mp 134–136 °C; R_f 0.55 (AcOEt:MeOH, 6:1). ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 2H), 1.82 (m, 2H), 2.25 (m, 2H), 2.70 (m, 6H), 2.95 (m, 5H), 3.02 (s, 3H), 3.80 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.17 (d, J = 2 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 7.55 (dd, J = 8 Hz and 2 Hz, 1H), 8.65 (s, 1H); IR (KBr) 1695, 1676, 1609, 1511, 1245 cm^{-1}; MS (EI) m/z 496 (M^+). Anal. calcd for $C_{28}H_{36}N_2O_6$: C, 67.72; H, 7.31; N, 5.64%. Found: C, 67.59; H, 7.25; N, 5.79%.

General procedure G

Preparation of ethyl-4-[3-[2-(ethoxycarbonyl)ethyl]-4-hydroxyphenylcarbonyl]butanoate (28a). Concd sulfuric acid (2 drops) was added to a stirred solution of **27**[7] (2.17 g, 7.05 mmol) in EtOH (50 mL). After being refluxed for 16 h, the reaction mixture was evaporated in vacuo. The residue was diluted with water (50 mL), and the resulting mixture was extracted with AcOEt (200 mL). The organic layer was washed with satd aq $NaHCO_3$ and then brine, dried over $MgSO_4$, and concentrated. Chromatography of the residue on a silica gel column afforded 2.13 g (90%) of **28a** as a colorless oil. R_f 0.40 (AcOEt:hexane, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.25 (M, 6H), 2.05 (m, 2H), 2.45 (t, J = 7 Hz, 2H), 2.75 (m, 2H), 3.00 (m, 4H), 4.15 (m, 4H), 6.90 (d, J = 8 Hz, 1H), 7.75 (dd, J = 8 Hz and 2 Hz, 1H), 7.80 (d, J = 2 Hz, 1H), 8.20 (s, 1H); IR (KBr) 3359, 1737, 1721, 1662, 1583, 1282, 1185, 1156, 1121 cm^{-1}; MS (EI) m/z 336 (M^+); EI HRMS m/z 336.1573 ($C_{18}H_{24}O_6$ 336.1573).

Preparation of methyl-6-[2-[2-(ethoxycarbonyl)-(*E*)-ethenyl]-3-methoxyphenyl]hexanoate (37c). Pyridinium chlorochromate (460 mg, 2.20 mmol) was added to a mixture of **37a** (290 mg, 1.10 mmol) and silica gel (460 mg) in CH_2Cl_2 (10 mL). The mixture was stirred at 25 °C for 40 min. The precipitates were filtered off and washed with 50 mL of AcOEt:hexane (1:1). The combined filtrate was evaporated in vacuo to give 290 mg (quantitative yield) of **37b** as a pale yellow oil; R_f 0.75 (AcOEt:hexane, 1:1). The material prepared in this manner was used for further transformations without purification.

A solution of triethyl phosphonoacetate (470 mg, 1.78 mmol) in THF (5.0 mL) was added dropwise to a stirred suspension of sodium hydride (1.65 mmol) in THF (1.0 mL) at 0 °C under an argon atmosphere, and stirred at 25 °C for 30 min. A solution of **37b** (290 mg, 1.10 mmol) in THF (5.0 mL) was then added in one portion to the above mixture at 0 °C. After being stirred at 25 °C for 30 min, the reaction mixture was acidified with glacial acetic acid. The precipitates were removed by filtration through a silica gel mat and washed with AcOEt (50 mL). The combined filtrate was evaporated in vacuo. The residue was purified by chromatography on a silica gel column (hexane:AcOEt, 4:1) to yield 310 mg (84%) of **37c** as a pale yellow oil. R_f 0.50 (hexane:AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3H), 1.40 (m, 2H), 1.65 (m, 4H), 2.30 (t, J = 7 Hz, 2H), 2.73 (t, J = 7 Hz, 2H), 3.65 (s, 3H), 3.87 (s, 3H), 4.25 (q, J = 7 Hz, 2H), 6.68 (d, J = 16 Hz, 1H), 6.80 (m, 2H), 7.20 (t, J = 8 Hz, 1H), 7.85 (d, J = 16 Hz, 1H); MS (EI) m/z 334 (M^+).

General procedure H

Preparation of methyl-6-[2-[2-(ethoxycarbonyl)ethyl]-3-methoxyphenyl]hexanoate (37d). A solution of **37d** (440 mg, 1.32 mmol) in EtOH (10 mL) was hydrogenated over 5% Pd charcoal (130 mg) at 25 °C for 1 h

under atmospheric pressure. The catalyst was then removed by filtration. Evaporation of the filtrate in vacuo gave 425 mg (97%) of **37d** as a colorless oil, which was used for further transformation without purification. R_f 0.60 (hexane:AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3H), 1.40 (m, 2H), 1.65 (m, 4H), 2.30 (t, J = 7 Hz, 2H), 2.50 (t, J = 7 Hz, 2H), 2.62 (t, J = 7 Hz, 2H), 2.95 (t, J = 7 Hz, 2H), 3.65 (s, 3H), 3.80 (s, 3H), 4.15 (q, J = 7 Hz, 2H), 6.70 (d, J = 8 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 7.12 (t, J = 8 Hz, 1H); MS (EI) m/z 336 (M^+).

Ethyl-5-[4-[2-(ethoxycarbonyl)ethyl]-3-hydroxyphenoxy]-pentanoate (57a). The title compound was prepared from **56** by the procedure described above: 95% yield; R_f 0.40 (hexane:AcOEt, 2:1). ^{1}H NMR ($CDCl_3$) δ 1.15–1.30 (m, 6H), 1.80 (m, 4H), 2.38 (m, 2H), 2.67 (m, 2H), 2.80 (m, 2H), 3.90 (m, 2H), 4.05–4.22 (m, 4H), 6.38–6.47 (m, 2H), 6.93 (d, J = 8 Hz, 1H), 7.45 (s, 1H); MS (EI) m/z 338 (M^+).

Preparation of 3-[5-[4-(dimethylaminocarbonyl)butanoylamino]-2-[6-(4-methoxyphenyl)hexyloxy]phenyl]-propanoic acid (6). Compound **6** was prepared from **4** according to general procedures A, H, and C, described above: 10% yield; pale yellow solid; R_f 0.50 (AcOEt:-MeOH, 6:1). ^{1}H NMR ($CDCl_3$) δ 1.40 (m, 4H), 1.60 (m, 2H), 1.78 (m, 2H), 2.05 (m, 2H), 2.45 (m, 4H), 2.55 (t, J = 7 Hz, 2H), 2.68 (t, J = 7 Hz, 2H), 2.97 (m, 5H), 3.02 (s, 3H), 3.80 (s, 3H), 3.92 (t, J = 7 Hz, 2H), 6.78 (d, J = 8 Hz, 1H), 6.80 (d, J = 8 Hz, 2H), 7.08 (d, J = 8 Hz, 2H), 7.20 (d, J = 2 Hz, 1H), 7.70 (dd, J = 8 Hz and 2 Hz, 1H), 8.52 (s, 1H). IR (neat) 3304, 1727, 1613, 1512, 1504, 1245 cm^{-1}; MS (EI) m/z 512 (M^+); EI HRMS m/z 512.2888 ($C_{29}H_{40}N_2O_6$ 512.2887).

General procedure I

Preparation of ethyl-3-[6-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]-2-hydroxyphenyl]propanoate (48a). Anhydrous potassium carbonate (6.8 g, 49.2 mmol) was added to a solution of **46**[8] (172 g, 489 mmol) in a 1:1 mixture of EtOH and THF (1.0 L), and stirred at 50 °C for 2 h. The potassium carbonate was removed by filtration and washed with AcOEt (1.0 L). The combined filtrate was evaporated in vacuo. The residue was taken up in AcOEt (5 L). The resulting mixture was washed successively with diluted HCl (1 L), satd aq $NaHCO_3$ (1 L) and brine (1 L). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give a white solid, which was recrystallized from hexane:AcOEt (5:1) to give 184 g (95%) of **48a** as a white solid. Mp 61.5–62.0 °C; R_f 0.40 (hexane:AcOEt, 2:1). ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3H), 1.65 (m, 2H), 1.85 (m, 2H), 2.27 (m, 2H), 2.70 (m, 2H), 2.90 (m, 2H), 3.80 (s, 3H), 3.95 (t, J = 7 Hz, 2H), 4.12 (q, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.42 (d, J = 8 Hz, 1H), 6.58 (d, J = 8 Hz, 1H), 6.85 (d, J = 8 Hz, 2H), 7.05 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 2H), 7.87 (s, 1H). IR (KBr) 3458, 1718, 1604, 1509, 1463, 1251, 1191, 1078 cm^{-1}; MS (EI) m/z 398 (M^+). Anal. calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59%. Found: C, 72.22; H, 7.38%.

Ethyl-3-[6-[5-(dimethylaminocarbonyl)pentyl]phenyl]-2-hydroxypropanoate (40b). The title compound was prepared from **39b** by the procedure described above: 89% yield; R_f 0.70 (AcOEt). ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3H), 1.40 (m, 2H), 1.65 (m, 4H), 2.33 (t, J = 7 Hz, 2H), 2.60 (t, J = 7 Hz, 2H), 2.65 (t, J = 7 Hz, 2H), 2.97 (t, J = 7 Hz, 2H), 2.97 (s, 3H), 3.00 (s, 3H), 4.13 (q, J = 7 Hz, 2H), 6.75 (m, 2H), 7.05 (t, J = 8 Hz, 1H), 7.30 (s, 1H); MS (EI) m/z 335 (M^+).

Preparation of ethyl-4-[2-[2-(ethoxycarbonyl)ethyl]-3-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenoxy]butanoate (51). Compound **51** was prepared from **50**[9] according to general procedure I followed by general procedure A, described above: 75% yield; R_f 0.30 (hexane:AcOEt, 5:1). ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.25 (t, J = 7 Hz, 3H), 1.65 (m, 2H), 1.83 (m, 2H), 2.15 (m, 2H), 2.25 (m, 2H), 2.50 (m, 4H), 3.00 (t, J = 7 Hz, 2H), 3.80 (s 3H), 4.00 (m, 4H), 4.12 (m, 4H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.50 (m, 2H), 6.82 (d, J = 8 Hz, 2H), 7.08 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 2H); MS (EI) m/z 512 (M^+).

Preparation of 3-[5-(4-hydroxybutanoylamino)-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (15b). Compound **14a**[4] was converted to 3-[3-[2-(*tert*-butoxycarbonyl)ethyl]-4-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenylaminocarbonyl]propanoic acid in 55% yield according to general procedures A and B. Ethyl chloroformate (0.018 mL, 0.19 mmol) was added dropwise to a stirred solution of carboxylic acid (90 mg, 0.17 mmol) and triethylamine (0.028 mL, 0.20 mmol) in THF (1.0 mL) at −10 °C under an argon atmosphere, and stirred at −10 °C for 10 min. Sodium borohydride (25 mg, 0.67 mmol) and MeOH (0.30 mL) were added to the mixture. After being stirred at 25 °C for 15 min, the mixture was poured into ice-cooled 1 N HCl (10 mL), and extracted with AcOEt (50 mL). The extract was washed with satd aq $NaHCO_3$ and then brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt:hexane, 3:1) to give 51 mg (60%) of *tert*-butyl-3-[5-(4-hydroxybutanoylamino)-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoate, which was converted to 3-[5-[4-(formyloxy)butanoylamino]-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid with HCOOH in quantitative yield according to general procedure C. A 1.0 mmol quantity of 1 N sodium hydroxide was added to a stirred solution of the formate (0.10 mmol) in MeOH (5 mL). After being stirred at 25 °C for 1 h, the mixture was acidified with 1 N HCl. The resulting mixture was extracted with AcOEt (50 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. Chromatography of the residue on a silica gel column ($CHCl_3$:MeOH, 19:1) afforded 10 mg (22%) of **15b** as a pale yellow powder; R_f 0.65 (AcOEt:MeOH, 6:1). ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 1.70 (m, 2H), 1.90 (m, 4H), 2.28 (m, 2H), 2.45 (t, J = 7 Hz, 2H), 2.60 (t, J = 7 Hz, 2H), 2.92 (t, J =

7 Hz, 2H), 3.63 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 4.00 (t, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.82 (m, 3H), 7.27 (m, 3H), 7.37 (dd, J = 8 Hz and 2 Hz, 1H). IR (KBr) 3288, 1698, 1663, 1555, 1509, 1248, 1235 cm^{-1}; MS (FAB) m/z 456 (MH^+).

3-[5-(5-Hydroxypentanoylamino)-2-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoic acid (15c). The title compound was prepared from **14b**[4] by the procedure described above: 12% yield; white powder; R_f 0.50 (AcOEt:MeOH, 7:1). ^1H NMR ($CDCl_3$ + CD_3OD) δ 1.65 (m, 4H), 1.80 (m, 4H), 2.30 (m, 4H), 2.60 (t, J = 7 Hz, 2H), 2.92 (t, J = 7 Hz, 2H), 3.65 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.97 (t, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.78 (d, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 2H), 7.20 (d, J = 2 Hz, 1H), 7.23 (d, J = 8 Hz, 2H), 7.38 (dd, J = 8 Hz and 2 Hz, 1H). IR (KBr) 3361, 1733, 1655, 1508, 1245 cm^{-1}; MS (EI) m/z 469 (M^+).

Preparation of 4-[3-hydroxy-2-[2-(methoxycarbonyl)-ethyl]phenylaminocarbonyl]butanoic acid (24b). Compound **23**[6] was hydrogenated in MeOH (10 mL) over 10% Pd charcoal (30 mg) at 25 °C for 3 h, giving **24a**. Glutaric anhydride (102 mg, 0.90 mmol) was then added to the solution, and the reaction mixture was stirred at 25 °C for 30 min. The catalyst was removed by filtration, and the filtrate was evaporated in vacuo. The residue was subjected to silica gel chromatography (CH_2Cl_2:MeOH, 9:1), giving 175 mg (63%) of **24b** as a colorless oil. R_f 0.45 (CH_2Cl_2:MeOH, 4:1); ^1H NMR (CD_3OD) δ 2.00 (m, 2H), 2.45 (m, 4H), 2.63 (m, 2H), 2.85 (m, 2H), 3.65 (s, 3H), 6.67 (d, J = 8 Hz, 1H), 6.85 (d, J = 8 Hz, 1H), 7.02 (t, J = 8 Hz, 1H); MS (EI) m/z 309 (M^+).

Preparation of ethyl-3-[5-[4-(dimethylaminocarbonyl)-butanoyl]-2-hydroxyphenyl]propanoate (28b). Dowex 50W × 8 (H^+ form, 20 mL) and benzene (100 mL) were added to a solution of **27**[7] (1.14 g, 4.07 mmol) in 1,4-dioxane (10 mL). The mixture was refluxed for 2.5 h under a Dean–Stark apparatus. The resin was removed by filtration, and the filtrate was evaporated in vacuo. The residue was diluted with EtOH (20 mL), and the mixture was concentrated to give 843 mg (67%) of 4-[3-[2-(ethoxycarbonyl)ethyl-4-hydroxyphenyl]carbonyl]-butanoic acid, which was converted to **28b** by general procedure F in 98% yield. White solid (from AcOEt:hexane, 1:1); mp 123–123.5 °C; R_f 0.40 (AcOEt). ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 2.10 (m, 2H), 2.45 (t, J = 7 Hz, 2H), 2.68 (t, J = 7 Hz, 2H), 2.97 (s, 3H), 3.00 (m, 4H), 3.02 (s, 3H), 4.10 (q, J = 7 Hz, 2H), 6.80 (d, J = 8 Hz, 1H), 7.60 (dd, J = 8 Hz and 2 Hz, 1H), 7.70 (d, J = 2 Hz, 1H), 8.75 (s, 1H). IR (KBr) 1713, 1669, 1589, 1510, 1401, 1266, 1119, 1034, 820 cm^{-1}; MS (EI) m/z 335 (M^+). Anal. calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18%. Found: C, 64.17; H, 7.36; N, 4.43%.

Preparation of methyl-6-[2-(hydroxymethyl)-3-methoxyphenyl]hexanoate (37a). Sodium borohydride (640 mg, 3.60 mmol) was added to a stirred solution of 3-methoxyphthalic anhydride (640 mg, 3.60 mmol), prepared from 3-hydroxyphthalic anhydride with diazomethane, in acetic acid (0.43 mL, 7.20 mmol) and THF (20 mL) at 25 °C. The mixture was stirred at 50 °C for 2 h. A 7.0 mL quantity of 1 N HCl was then added to the cooled reaction mixture, and the resulting mixture was stirred at 25 °C for 15 min. The mixture was evaporated in vacuo. Purification of the residue by chromatography on a silica gel column (AcOEt:hexane, 1:1) afforded 216 mg (37%) of 4-methoxyphthalide as a pale yellow oil (R_f 0.25, AcOEt:hexane, 1:1). 7-Methoxyphthalide was also isolated (314 mg, 53%, R_f 0.60, AcOEt:hexane, 1:1).

Diisobutylaluminum hydride (0.58 mL of 1.76 M solution in toluene, 1.02 mmol) was added dropwise to a stirred solution of 4-methoxyphthalide (140 mg, 0.85 mmol) in toluene (15 mL) at −70 °C under an argon atmosphere. The mixture was stirred for 30 min, quenched with satd aq Na_2SO_4 (0.25 mL) and warmed to 25 °C with stirring. The resulting precipitates were removed by filtration and washed with AcOEt (100 mL). The combined filtrate was evaporated in vacuo to give 140 mg (quantitative yield) of the lactol, which was used for further transformation without purification. R_f 0.40 (AcOEt:hexane, 1:1).

A mixture of (4-carboxy-*n*-butyl)triphenylphosphonium bromide (1.33 g, 3.0 mmol) and potassium *tert*-butoxide (670 mg, 6.0 mmol) was stirred at 80 °C for 1.5 h under an argon atmosphere. A solution of the lactol prepared above (140 mg, 0.85 mmol) in toluene (5.0 mL) was added in one portion at 25 °C. After stirring for 1.5 h, the mixture was poured into ice-cooled 1 N HCl (20 mL), and extracted with AcOEt (100 mL). The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. Diazomethane was added to a solution of the residue in AcOEt (10 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min, and then evaporated in vacuo. Chromatography of the residue on a silica gel column (AcOEt:hexane, 1:1) afforded 99 mg (44%) of methyl 6-[2-(hydroxymethyl)-3-methoxyphenyl]-(5*E*)-hexanoate, which was converted to **37a** by general procedure H in 99% yield. Pale yellow oil; R_f 0.40 (AcOEt:hexane, 1:1); ^1H NMR ($CDCl_3$) δ 1.40 (m, 2H), 1.80 (m, 4H), 2.32 (t, J = 7 Hz, 2H), 2.65 (t, J = 7 Hz, 2H), 3.65 (s, 3H), 3.82 (s, 3H), 4.50 (d, J = 7 Hz, 2H), 6.75 (d, J = 8 Hz, 1H), 6.80 (d, J = 8 Hz, 1H), 7.20 (t, J = 8 Hz, 1H); MS (EI) m/z 266 (M^+).

Preparation of 6-(3,4-dihydrocoumarin-5-yl)hexanoic acid (39a). A mixture of **37d** (325 mg, 0.97 mmol) and pyridine hydrochloride (4.0 g) was heated at 190 °C for 2.5 h. The mixture was then cooled to 25 °C, and then 1 N HCl (20 mL) was added. The resulting mixture was extracted with AcOEt (50 mL × 3). The combined extract was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give 272 mg (quantitative yield) of **38** as a pale yellow oil. R_f 0.10 ($CHCl_3$:MeOH, 9:1).

Resin (100 mg of Dowex 50W × 8; H^+ form) was added to a mixture of **38** (272 mg) and benzene (30 mL). The mixture was refluxed under a Dean–Stark apparatus for 2 h. The resin was then removed by filtration and washed with benzene (20 mL). Evaporation of the combined filtrate afforded 247 mg (97%) of **39a** as a pale yellow oil. R_f 0.10 (AcOEt); ^1H NMR ($CDCl_3$) δ 1.20–1.90 (m, 6H), 2.37 (t, J = 7 Hz, 2H), 2.42 (t, J = 7 Hz, 2H), 2.77 (m, 2H), 2.97 (m, 2H), 6.93 (d, J = 8 Hz, 1H), 6.95 (d, J = 8 Hz, 1H), 7.15 (t, J = 8 Hz, 1H); MS (EI) m/z 262 (M^+).

Preparation of ethyl-6-[2-[2-(ethoxycarbonyl)ethyl]-3-hydroxyphenyl]hexanoate (40a). Compound **37d** (100 mg, 0.30 mmol) was converted to **38** by the procedure described for the preparation of **39a**. Compound **38** (85 mg, 0.30 mmol) was dissolved in 2 N HCl of EtOH solution (5.0 mL). After being stirred at 25 °C for 30 min, the mixture was concentrated in vacuo. Chromatography of the residue on a silica gel column (hexane:AcOEt, 2:1) afforded 87 mg (86%) of **40a** as a colorless oil. R_f 0.50 (hexane:AcOEt, 2:1); ^1H NMR ($CDCl_3$) δ 1.22 (m, 6H), 1.40 (m, 2H), 1.65 (m, 4H), 2.30 (t, J = 7 Hz, 2H), 2.57 (t, J = 7 Hz, 2H), 2.65 (t, J = 7 Hz, 2H), 2.95 (t, J = 7 Hz, 2H), 4.12 (m, 4H), 6.75 (m, 2H), 7.03 (t, J = 8 Hz, 1H), 7.20 (s, 1H); MS (EI) m/z 336 (M^+).

Preparation of ethyl-5-[4-[2-(ethoxycarbonyl)-(*E*)-ethenyl]-3-hydroxyphenoxy]pentanoate (56). EtOH (10 mL) was added dropwise to a stirred suspension of sodium hydride (4.5 mmol) at 0 °C, and the mixture was stirred at 25 °C for 30 min under an argon atmosphere. A solution of **55**[11] (650 mg, 2.20 mmol) in EtOH (10 mL) was added to the mixture at 25 °C. The mixture was refluxed for 4 h and acidified with glacial acetic acid (6.0 mmol). The resulting mixture was evaporated in vacuo. The residue was diluted with water (20 mL), and the resulting mixture was extracted with Et_2O (100 mL). The organic layer was washed with water (20 mL × 3) and then brine, dried over $MgSO_4$, and evaporated in vacuo. Chromatography of the residual oil on a silica gel column (hexane:AcOEt, 4:1) afforded 220 mg (30%) of **56** as a white solid. R_f 0.35 (hexane:AcOEt, 2:1); ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3H), 1.33 (t, J = 7 Hz, 3H), 1.82 (m, 4H), 2.40 (m, 2H), 3.98 (m, 2H), 4.15 (q, J = 7 Hz, 2H), 4.25 (q, J = 7 Hz, 2H), 6.28 (d, J = 2 Hz, 1H), 6.42 (dd, J = 8 Hz and 2 Hz, 1H), 6.45 (d, J = 16 Hz, 1H), 6.48 (s, 1H), 7.38 (d, J = 8 Hz, 1H), 7.92 (d, J = 16 Hz, 1H); MS (EI) m/z 336 (M^+).

Preparation of methanesulfonate of 6-(4-methoxyphenyl)-(5*E*)-hexenol (60b). A mixture of potassium *tert*-butoxide (55 g, 0.49 mol) and (4-carboxy-*n*-butyl)-triphenylphosphonium bromide (109 g, 0.245 mol) in toluene (650 mL) was refluxed for 30 min under an argon atmosphere. A solution of 4-methoxybenzaldehyde (30 mL, 0.245 mol) in toluene (100 mL) was added to the orange–red solution in one portion. After stirring at 100 °C for 10 min, the mixture was poured into water (1 L) and extracted with Et_2O (1 L). The aqueous layer was acidified by the addition of 2 N HCl. The resulting mixture was extracted with AcOEt (2 L). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. Concd sulfonic acid (5.0 mL) was added to a solution of the residue in MeOH (150 mL). The mixture was stirred at 80 °C for 1 h and then evaporated in vacuo. The residue was taken up in AcOEt (1 L), and the solution was washed with satd aq $NaHCO_3$ and then brine, dried over $MgSO_4$ and evaporated to give a yellow oil, which was distilled under reduced pressure, affording 44.3 g (77%) of ethyl 6-(4-methoxyphenyl)-(5*E*)-hexanoate **58b** as a colorless oil (bp 151–153 °C at 1.0 mmHg).

A solution of **58b** (11.8 g, 50.6 mmol) in THF (100 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (4.0 g, 105 mmol) in THF (400 mL) at 0 °C under an argon atmosphere, and the mixture was stirred for 30 min at 25 °C. Satd aq Na_2SO_4 (100 mL) was added dropwise at 25 °C, and the resulting mixture was stirred for 2 h. The resulting white precipitates were removed by filtration and washed with AcOEt (1 L). Evaporation of the filtrate gave a white solid, which was recrystallized from AcOEt:hexane (1:1) to afford 71 g (68%) of **59b** as a white solid. R_f 0.50 (AcOEt:hexane, 1:1); ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 1H), 1.40–1.70 (m, 4H), 2.20 (q, J = 7 Hz, 2H), 3.65 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.85 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H); MS (EI) m/z 206 (M^+).

Methanesulfonyl chloride (0.67 mL, 8.7 mmol) was added dropwise to a stirred solution of **59b** (900 mg, 4.35 mol) and triethylamine (1.8 mL, 13 mmol) in CH_2Cl_2 (10 mL) at 10 °C under an argon atmosphere. After being stirred for 1 h, the mixture was poured into a mixture of crushed ice (5.0 g) and 1 N HCl (5.0 mL) and extracted with AcOEt (100 mL). The organic layer was washed with satd aq $NaHCO_3$ and then brine, dried over $MgSO_4$, and evaporated in vacuo. Chromatography of the residue on a silica gel column (hexane:AcOEt, 3:2) afforded 1.14 g (92%) of **60b** as a pale yellow solid. R_f 0.50 (hexane:AcOEt, 1:1); ^1H NMR ($CDCl_3$) δ 1.60 (m, 2H), 1.80 (m, 2H), 2.25 (q, J = 7 Hz, 2H), 3.00 (s, 3H), 3.80 (s, 3H), 4.25 (t, J = 7 Hz, 2H), 6.05 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.85 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H); MS (EI) m/z 284 (M^+).

The following compounds were prepared from the indicated benzaldehydes and the phosphonium salts by the procedure described above.

Methanesulfonate of 5-(4-methoxyphenyl)-(4*E*)-pentenol (60a). The title compound was obtained from 4-methoxybenzaldehyde and (3-carboxy-*n*-propyl)triphenylphosphonium bromide; 73% yield; colorless oil; R_f 0.35 (hexane:AcOEt, 3:2). ^1H NMR ($CDCl_3$) δ 2.00 (m, 2H), 2.45 (m, 2H), 3.00 (s, 3H), 3.80 (s, 3H), 4.25 (t, J = 7 Hz, 2H), 6.05 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.85 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H); MS (EI) m/z 270 (M^+).

Methanesulfonate of 7-(4-methoxyphenyl)-(6*E*)-heptenol (60c). From 4-methoxybenzaldehyde and (5-carboxy-*n*-pentyl)triphenylphosphonium bromide, the title compound was obtained as: 94% yield; colorless oil; R_f 0.35 (hexane:AcOEt, 3:2). ^{1}H NMR ($CDCl_3$) δ 1.50 (m, 4H), 1.80 (m, 2H), 2.25 (m, 2H), 3.00 (s, 3H), 3.80 (s, 3H), 4.25 (t, J = 7 Hz, 2H), 6.05 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.85 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H); MS (EI) *m/z* 298 (M^+).

Methanesulfonate of 6-phenyl-(5*E*)-hexenol (60d). The title compound was obtained from benzaldehyde and (4-carboxy-*n*-butyl)triphenylphosphonium bromide: 51% yield; colorless oil; R_f 0.35 (hexane:AcOEt, 3:2). ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 2H), 1.80 (m, 2H), 2.25 (q, J = 7 Hz, 2H), 3.00 (s, 3H), 3.80 (s, 3H), 4.25 (t, J = 7 Hz, 2H), 6.20 (dt, J = 16 Hz and 7 Hz, 1H), 6.40 (d, J = 16 Hz, 1H), 7.10–7.40 (m, 5H); MS (EI) *m/z* 254 (M^+).

Methanesulfonate of 6-(3-methoxyphenyl)-(5*E*)-hexenol (60e). The title compound was obtained from 3-methoxybenzaldehyde and (4-carboxy-*n*-butyl)triphenylphosphonium bromide: 66% yield; colorless oil; R_f 0.35 (hexane:AcOEt, 3:2). ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 2H), 1.80 (m, 2H), 2.25 (q, J = 7 Hz, 2H), 3.00 (s, 3H), 3.80 (s, 3H), 4.25 (t, J = 7 Hz, 2H), 6.20 (dt, J = 16 Hz and 7 Hz, 1H), 6.40 (d, J = 16 Hz, 1H), 6.80–7.20 (m, 4H); MS (EI) *m/z* 284 (M^+).

Methanesulfonate of 6-(4-methylthiophenyl)-(5*E*)-hexenol (60f). The title compound was obtained from 4-methylthiobenzaldehyde and (4-carboxy-*n*-butyl)triphenylphosphonium bromide: 75% yield; pale yellow oil; R_f 0.35 (hexane:AcOEt, 2:1). ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 2H), 1.80 (m, 2H), 2.25 (m, 2H), 2.50 (s, 3H), 3.00 (s, 3H), 4.25 (t, J = 7 Hz, 2H), 6.15 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 7.22 (m, 4H); MS (EI) *m/z* 300 (M^+).

Methanesulfonate of 6-(4-methylphenyl)-(5*E*)-hexenol (60g). From *p*-tolaldehyde and (4-carboxy-*n*-butyl)triphenylphosphonium bromide, the title compound was obtained as: quantitative yield; pale yellow oil; R_f 0.35 (hexane:AcOEt, 2:1). ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 2H), 1.80 (m, 2H), 2.28 (m, 2H), 2.32 (s, 3H), 3.00 (s, 3H), 4.25 (t, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.38 (d, J = 16 Hz, 1H), 7.10 (d, J = 8 Hz, 2H), 7.22 (d, J = 8 Hz, 2H); MS (EI) *m/z* 268 (M^+).

Methanesulfonate of 6-(4-chlorophenyl)-(5*E*)-hexenol (60h). The title compound was obtained from 4-chlorobenzaldehyde and (4-carboxy-*n*-butyl)triphenylphosphonium bromide; quantitative yield; pale yellow oil; R_f 0.35 (hexane:AcOEt, 2:1). ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 2H), 1.80 (m, 2H), 2.27 (m, 2H), 3.00 (s, 3H), 4.25 (t, J = 7 Hz, 2H), 6.10 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 7.25 (m, 4H); MS (EI) *m/z* 288 (M^+).

Methanesulfonate of 6-(4-*n*-Propoxyphenyl)-(5*E*)-hexenol (60i). The title compound was obtained from 4-*n*-propoxybenzaldehyde and (4-carboxy-*n*-butyl)triphenylphosphonium bromide as a pale yellow oil; R_f 0.35 (hexane:AcOEt, 2:1). ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J = 7 Hz, 3H), 1.60 (m, 2H), 1.80 (m, 4H), 2.25 (m, 2H), 3.00 (s, 3H), 3.65 (s, 3H), 3.90 (t, J = 7 Hz, 2H), 4.25 (t, J = 7 Hz, 2H), 6.05 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.80 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H).

Alternative preparation of 6-(4-methoxyphenyl)-(5*E*)-hexenol (59b). Concd sulfuric acid (1.3 mL) was added dropwise to a stirred mixture of ε-caprolactone (22.8 g, 0.20 mol) and acetyl chloride (28.4 mL, 0.40 mol) at 25 °C. The temperature was allowed to rise to 35 °C. The mixture was then refluxed for 1 h. Excess acetyl chloride was removed in vacuo to give 6-acetoxyhexanoyl chloride. A solution of anisole (26 g, 0.36 mol) in $ClCH_2CH_2Cl$ (20 mL) was added dropwise to a stirred suspension of anhydrous aluminum chloride (48 g, 0.36 mol) in $ClCH_2CH_2Cl$ (240 mL) at 15 °C, and the mixture was stirred at 15 °C for 1 h. The solution of 6-acetoxyhexanoyl chloride prepared above in $ClCH_2CH_2Cl$ (30 mL) was added dropwise to the reaction mixture at 12 °C. After being stirred at 15 °C for 1.5 h, the mixture was poured into cold water (320 mL) and stirred at 25 °C for 0.5 h. *iso*-Propylalcohol (130 mL) was added to the mixture, and the resulting mixture was separated. The aqueous layer was extracted with $ClCH_2CH_2Cl$ (100 mL). The combined $ClCH_2CH_2Cl$ layer was concentrated under reduced pressure to give 44.7 g (85%) of 4-[6-acetoxyhexanoyl]-1-methoxybenzene **63** as a pale yellow oil, which was used for further modification without purification. R_f 0.60 (AcOEt:hexane, 2:1); ^{1}H NMR ($CDCl_3$) δ 1.40–1.90 (m, 6H), (m, 16H), 2.05 (s, 3H), 2.90 (t, J = 7 Hz, 2H), 3.85 (s, 3H), 4.10 (t, J = 7 Hz, 2H), 6.90 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H); MS (EI) *m/z* 264 (M^+).

A 0.33 mol quantity of 5 N sodium hydroxide was added to a stirred solution of **63** (44 g, 0.17 mol) in MeOH (185 mL) at 25–35 °C and stirred at 25 °C for 1 h. A solution of sodium borohydride (7.9 g, 0.21 mol) in water (41 mL) was added dropwise to the stirred mixture at 25 °C and stirred at 25 °C for 30 min, and then at 65 °C for an additional 30 min. After the addition of acetone (73 mL) at 15 °C, the mixture was stirred at 15 °C for 1 h and then concentrated in vacuo, and the residue was diluted with water (110 mL). The resulting mixture was extracted with AcOEt (200 mL × 3). The combined extract was washed with brine, dried over $MgSO_4$, and evaporated to give 28.6 g (77%) of 6-(4-methoxyphenyl)-1,6-hexadiol **64** as a yellow oil, which was used for further modification without purification. R_f 0.20 (AcOEt:hexane, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.20–1.90 (m, 8H), (m, 16H), 2.50 (s, 2H), 3.60 (t, J = 7 Hz, 2H), 3.85 (s, 3H), 4.55 (t, J = 7 Hz, 1H), 6.90 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H); MS (EI) *m/z* 224 (M^+).

A mixture of **64** (125 g, 0.56 mol), KCl (21 g, 0.28 mol), and DMSO (600 mL) was heated at 170 °C for 4 h. After cooling to 25 °C, the reaction mixture was poured into water (1.5 L) to give a white solid. The solid was collected by filtration, washed with water, dried in a vacuum desiccator, and recrystallized from hexane: AcOEt (4:1) to yield 84 g (73%) of **59b** as a white solid.

Biological methods

Materials. Tritiated LTB_4 preparations with a specific activity of 32 Ci/mmol and a radiochemical purity of >95% were purchased from New England Nuclear Corp. (Boston, MA, USA). Nonradioactive LTB_4 was prepared according to E. J. Corey et al.'s method.[12] Ficoll-paque was purchased from Pharmacia LKB (Uppsala, Sweden). All other chemicals were commercial reagent-grade materials.

Neutrophil preparation. Human neutrophils were isolated from the citrated peripheral blood of normal volunteers by dextran sedimentation, followed by Ficoll-paque gradient centrifugation and hypotonic lysis of erythrocytes.

Binding assay studies. The effectiveness of compounds in the inhibition of the binding of [^{3}H]LTB_4 to neutrophils was measured by using an adaptation of a radioligand-binding assay reported by R. R. Gorman and A. H. Lin.[13] The following were added to polypropylene tubes in a final volume of 1.0 mL: 10 μL DMSO containing different amounts of tested compounds, 100 μL of 10 nM [^{3}H] LTB_4 (final concentration of 1.0 nM), and 0.5 mL of neutrophils enriched to 95% purity suspended at a concentration of 2×10^7 cells/mL in ice-cold Hank's balanced salt solution (HBSS) pH 7.4 and 0.39 mL of HBSS. The tubes were then incubated at 0 °C for 20 min. The reaction was terminated by the addition of ice-cold HBSS (2.5 mL) followed by vacuum filtration through Whatman CF/C glass-fiber filters. The radioactivity retained in the filters was measured by liquid scintillation spectrometry. Nonspecific binding was defined as [^{3}H]LTB_4 bound in the presence of 3.0-μM unlabeled LTB_4. The specific binding was determined by subtracting the nonspecific binding from the total binding. The concentration of the compounds which inhibited 50% of the specific [^{3}H]LTB_4 binding was identified as the IC_{50} value. The inhibitory constant (K_i value) for the competition studies was calculated from the equation $K_i = IC_{50}/[1 + (C)/K_d]$, where K_d is the dissociation constant of [^{3}H]LTB_4 binding obtained from the scatter plot, and C is the added radioligand.

Aggregation assay studies. Human neutrophils (10^7 cells/mL) in HBSS containing 0.5% bovine serum albumin (pH 7.4) were preincubated in the presence or absence of 10 μL of DMSO containing different amounts of tested compounds at 37 °C for 1 min prior to the addition of 10-nM LTB_4. Aggregation was monitored as the change in light transmission using a multichannel aggregometer (HEMA TRACER 1, Nikou Bio Science, Tokyo, Japan). The concentration of the compounds which inhibited 50% of the aggregation by 10-nM LTB_4 was identified as the IC_{50} value.

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2. Physical and spectroscopic data of ethyl 3-(5-heptanoylamino-2-hydroxyphenyl)propanoate **11a**: white solid; R_f 0.40 (AcOEt:hexane, 1:1). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 3H), 1.25 (t, J = 7 Hz, 2H), 1.30 (m, 6H), 1.70 (m, 2H), 2.35 (t, J = 7 Hz, 2H), 2.70 (t, J = 7 Hz, 2H), 2.85 (t, J = 7 Hz, 2H), 4.15 (q, J = 7 Hz, 2H), 6.80 (d, J = 8 Hz, 1H), 7.05 (s, 1H), 7.10 (dd, J = 8 Hz and 2 Hz, 1H), 7.35 (s, 1H), 7.40 (d, J = 2 Hz, 1H); MS (EI) m/z 321 (M^+). Physical and spectroscopic data of methyl 3-(5-benzoylamino-2-hydroxyphenyl)propanoate **11b**: colorless oil; R_f 0.25 (AcOEt:hexane, 1:1). ^{1}H NMR ($CDCl_3$) δ 2.75 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.70 (s, 3H), 6.85 (d, J = 8 Hz, 1H), 7.25 (dd, J = 8 Hz and 2 Hz, 1H), 7.75 (s, 1H), 7.85 (m, 2H). Physical and spectroscopic data of ethyl-3-[2-hydroxy-5-[3-(methoxycarbonyl)benzoylamino]-phenyl]propanoate **11c**: white solid; R_f 0.20 (AcOEt:hexane, 1:1). ^{1}H NMR (CD_3OD) δ 1.25 (t, J = 7 Hz, 3H), 2.65 (t, J = 7 Hz, 2H), 2.90 (t, J = 7 Hz, 2H), 3.95 (s, 3H), 4.10 (q, J = 7 Hz, 2H), 6.75 (d, J = 8 Hz, 1H), 7.35 (m, 2H), 7.60 (t, J = 8 Hz, 1H), 8.15 (m, 2H), 8.55 (s, 1H); MS (EI) m/z 371 (M^+). Physical and spectroscopic data of methyl-4-[3-[2-(ethoxycarbonyl)ethyl]-2-hydroxyphenylaminocarbonyl]butanoate **11d**: pale yellow oil; R_f 0.25 (AcOEt:hexane, 2:1). ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3H), 2.10 (m, 2H), 2.20–3.00 (m, 8H), 3.70 (s, 3H), 4.10 (q, J = 7 Hz, 2H), 6.80 (d, J = 8 Hz, 1H), 7.10 (dd, J = 8 Hz and 2 Hz, 1H), 7.30 (m, 2H); MS (EI) m/z 337 (M^+).

3. Physical and spectroscopic data of methyl-3-[3-[2-(*tert*-butoxycarbonyl)ethyl]-4-hydroxyphenylaminocarbonyl]-propanoate **14a**: pale brown solid; mp 125–130 °C; R_f 0.50 (AcOEt:hexane, 2:1). ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 2.60–2.82 (m, 8H), 3.72 (s, 3H), 6.83 (d, J = 8 Hz, 1H), 7.07 (dd, J = 8 Hz and 2 Hz, 1H), 7.38 (m, 2H), 7.68 (s, 1H); IR (KBr) 3328, 1723, 1698, 1673, 1561, 1511, 1367, 1237, 1171, 1150 cm^{-1}; MS (EI) m/z 351 (M^+). Physical and spectroscopic data of methyl-4-[3-[2-(*tert*-butoxycarbonyl)ethyl]-4-hydroxyphenyl-aminocarbonyl]butanoate **14b**: pale brown oil; R_f 0.50 (AcOEt:hexane, 2:1). ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 2.05 (m, 2H), 2.42 (m, 4H), 2.62 (m, 2H), 2.80 (m, 2H), 3.70 (s, 3H), 6.82 (d, J = 8 Hz, 1H), 7.05 (dd, J = 8 Hz and 2 Hz, 1H), 7.37 (d, J = 2 Hz, 1H), 7.70 (s, 1H). IR (neat) 3305, 2978, 1716, 1652, 1616, 1557, 1505, 1435, 1369, 1151, 1108 cm^{-1}; MS (EI) m/z 365 (M^+); EI HRMS m/z 365.1854 ($C_{19}H_{27}NO_6$ 365.1839).

4. Physical and spectroscopic data of *tert*-butyl 3-[2-hydroxy-5-(trifluoroacetylamino)phenyl]propanoate **18**: R_f 0.30 (hexane: AcOEt, 2:1); white needles (from hexane:AcOEt, 9:1); mp 122–123.5 °C. ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 2.65 (m, 2H), 2.80 (m, 2H), 6.90 d, J = 8 Hz, 1H), 7.20 (dd, J = 8 Hz and 2 Hz, 1H), 7.40 (d, J = 2 Hz, 1H), 7.80 (s, 1H), 7.90 (s, 1H); IR (KBr) 3282, 1706, 1560, 1370, 1252, 1166 cm^{-1}; MS m/z 333 (M^+); EI HRMS m/z 333.1189 ($C_{15}H_{18}F_3NO_4$ 333.1188). Anal. calcd for $C_{15}H_{18}F_3NO_4$: C, 54.05; H, 5.44; N, 4.20; F, 17.10%. Found: C, 54.37; H, 5.39; N, 4.11; F, 17.36%.

5. Physical and spectroscopic data of methyl-3-(2-hydroxy-6-nitrophenyl)-(*E*)-propanoate **23**: yellow platelets (from AcOEt); mp 229.5–230 °C; R_f 0.40 (AcOEt:hexane, 2:1). ^{1}H

NMR ($CDCl_3$ + CD_3OD) δ 3.80 (s, 3H), 6.83 (d, J = 16 Hz, 1H), 7.15 (m, 1H), 7.30 (m, 2H), 7.70 (d, J = 16 Hz, 1H); IR (KBr) 3323, 1693, 1632, 1524 cm^{-1}; EI HRMS m/z 223.0478 ($C_{10}H_9NO_5$ 223.0481). Anal. calcd for $C_{10}H_9NO_5$5: C, 53.82; H, 3.91; N, 6.03%. Found: C, 53.67; H, 3.98; N, 6.23%.

6. Physical and spectroscopic data of 4-[3-(2-carboxyethyl)-4-hydroxyphenylcarbonyl]butanoic acid **27**: pale gray powder (from AcOEt); mp 167–168 °C; R_f 0.45 ($CHCl_3$:MeOH, 5:1). ^1H NMR (CD_3OD) δ 1.95 (m, 2H), 2.20–2.70 (m, 4H), 2.92 (t, J = 7 Hz, 2H), 3.00 (t, J = 7 Hz, 2H), 6.80 (d, J = 8 Hz, 1H), 7.63–7.82 (m, 2H); IR (KBr) 3377, 2951, 1703, 1663, 1593, 1510, 1289, 1253, 1157, 1122 cm^{-1}; MS (EI) m/z 280 (M^+).

7. Physical and spectroscopic data of 5-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]-3,4-dihydrocoumarin **46**: white needles (from hexane:AcOEt, 3:1); mp 64.5–65.0 °C; R_f 0.50 (hexane:AcOEt, 2:1). ^1H NMR ($CDCl_3$) δ 1.70 (m, 2H), 1.90 (m, 2H), 2.27 (m, 2H), 2.73 (t, J = 7 Hz, 2H), 2.98 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 4.00 (t, J = 7 Hz, 2H), 6.07 (dt, J = 16 Hz and 7 Hz, 1H), 6.37 (d, J = 16 Hz, 1H), 6.65 (d, J = 8 Hz, 1H), 6.70 (d, J = 8 Hz, 1H), 6.83 (d, J = 8 Hz, 2H), 7.17 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 2H). IR (KBr) 1753, 1612, 1595, 1511, 1461, 1257, 1161, 1077 cm^{-1}; MS (EI) m/z 352 (M^+). Anal. calcd for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86%. Found: C, 74.92; H, 6.71%.

8. Physical and spectroscopic data of ethyl-4-(3,4-dihydrocoumarin-5-yl)oxybutanoate **50**: pale yellow oil; R_f 0.55 (hexane:AcOEt, 2:1). ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3H), 2.15 (m, 2H), 2.52 (t, J = 7 Hz, 2H), 2.75 (t, J = 7 Hz, 2H), 2.98 (t, J = 7 Hz, 2H), 4.05 (t, J = 7 Hz, 2H), 4.15 (q, J = 7 Hz, 2H), 6.65 (d, J = 8 Hz, 1H), 6.70 (d, J = 8 Hz, 1H), 7.18 (t, J = 8 Hz, 1H).

9. Physical and spectroscopic data of ethyl 3-[2-hydroxy-5-[6-(4-methoxyphenyl)-(5*E*)-hexenyloxy]phenyl]propanoate **53**: pale yellow oil; R_f 0.30 (hexane:AcOEt, 2:1). ^1H NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3H), 1.65 (m, 2H), 1.80 (m, 2H), 2.25 (m, 2H), 2.68 (t, J = 7 Hz, 2H), 2.85 (t, J = 7 Hz, 2H), 3.80 (s, 3H), 3.90 (t, J = 7 Hz, 2H), 4.12 (q, J = 7 Hz, 2H), 6.08 (dt, J = 16 Hz and 7 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 6.65 (m, 2H), 6.80 (m, 3H), 7.25 (d, J = 8 Hz, 2H); MS (EI) m/z 398 (M^+).

10. Physical and spectroscopic data of ethyl-5-(coumarin-7-yl)-oxypentanoate **55**: pale yellow oil; R_f 0.40 (hexane:AcOEt, 2:1). ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7 Hz, 3H), 1.85 (m, 4H), 2.40 (t, J = 7 Hz, 2H), 4.03 (m, 2H), 4.13 (q, J = 7 Hz, 2H), 6.25 (d, J = 10 Hz, 1H), 6.77–6.87 (m, 2H), 7.35 (d, J = 8 Hz, 1H), 7.62 (d, J = 10 Hz, 1H); MS (EI) m/z 290 (M^+).

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