Structure−Activity Relationships of (*E*)-3-(1,4-Benzoquinonyl)-2-[(3-pyridyl)-alkyl]-2-propenoic Acid Derivatives That Inhibit Both 5-Lipoxygenase and Thromboxane A_2 Synthetase

Shigeki Hibi, Yasushi Okamoto,* Katsuya Tagami, Hirotoshi Numata, Naoki Kobayashi, Masanobu Shinoda, Tetsuya Kawahara, Koukichi Harada, Kaname Miyamoto, and Isao Yamatsu

Tsukuba Research Laboratories, Eisai Company, Ltd., 1-3, Tokodai 5-chome, Tsukuba-shi, Ibaraki 300-26, Japan

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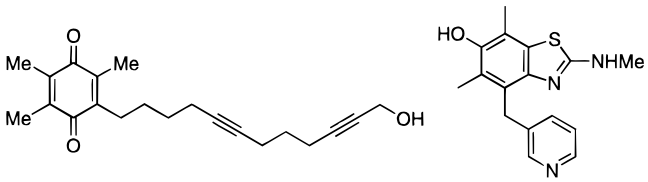
As part of our research for the development of novel antiinflammatory drug candidates, we have designed and synthesized a series of (*E*)-3-(1,4-benzoquinonyl)-2-[(3-pyridyl)alkyl]-2-propenoic acid derivatives as dual inhibitors of 5-lipoxygenase (5-LO) and thromboxane (TX) A_2 synthetase. In order to increase the absorption after oral administration, we introduced a carboxylic acid moiety into the 1,4-benzoquinone skeleton, which has 5-LO-inhibitory character. Introduction of a 3-pyridylalkyl group at the double bond of the 1,4-benzoquinonyl propenoic acid moiety afforded good to moderate inhibitory activities against the production of leukotriene (LT) B_4 and TXA_2 while not significantly inhibiting that of prostaglandin E_2 by glycogen-induced peritoneal cells of rat (*in vitro*). The length of the methylene chain of the 3-pyridylalkyl group influenced the inhibition of LTB_4 and TXB_2 production. An increase of lipophilicity by introducing a more lipophilic alkoxy group did not markedly increase the inhibitory activity on LTB_4 production. The position of an alkoxy group on the 1,4-benzoquinone skeleton played an important role in TXA_2 synthetase inhibition. Compounds such as **20c** (E6700) with an appropriate alkoxy group and proper length of methylene side chain, together with a polar substituent (carboxylic acid), showed good inhibition of both 5-LO and TXA_2 synthetase and possess a variety of pharmacologically beneficial effects.

Introduction

Since the roles of arachidonic acid metabolites, such as leukotrienes (LTs), prostaglandins (PGs), and thromboxanes (TXs), as mediators of the inflammatory reaction were clarified, much effort has been made to develop inhibitors of the production of these chemical mediators as antiinflammatory agents.[1−4] These mediators also play important roles in some inflammatory or allergic diseases, acting either alone or in combination,[4,5] and inhibitors of 5-lipoxygenase (5-LO) and/or cyclooxygenase (CO) may be useful for the treatment of asthma, psoriasis, and rheumatoid arthritis, for example.[6−9] Dual inhibitors of CO and 5-LO have been under development,[6−9] but none has entered clinical use yet, and only nonsteroidal antiinflammatory drugs (NSAIDs) are used clinically. It should be noted that NSAIDs are not effective in some inflammatory diseases such as asthma and hepatitis, suggesting that inflammatory mediators other than PGs may play important roles in the pathology of these diseases.

Recently we have reported that 3-pyridylmethyl-substituted 2-amino-6-hydroxybenzothiazole derivatives showed dual 5-LO and thromboxane A_2 (TXA_2) synthetase inhibitory activity and were effective for the treatment of an inflammatory bowel disease model due to their characteristic distribution.[10] However, compounds with better absorption are required to treat a wide variety of inflammatory diseases. Triple-functional compounds which specifically inhibit both 5-LO and TXA_2 synthetase as well as scavenging active oxygen species were reported by Terao et al. as candidates for the treatment of inflammatory diseases such as nephrosis.[11−14]

Chart 1



AA-861 **E3040**

In this paper, we describe the design, synthesis, and pharmacological properties of a novel series of (*E*)-3-(1,4-benzoquinonyl)-2-[(3-pyridyl)alkyl]-2-propenoic acid derivatives. These compounds have potent inhibitory activities toward both 5-LO and TXA_2 synthetase, and they showed good absorption into the circulation after po administration in preclinical and clinical studies.

Design

For the past several years, we have been searching for superior 5-LO inhibitors among compounds with redox character, since the enzyme reaction involves oxidation as well as reduction steps of the iron atom. AA-861, which has a 1,4-benzoquinone skeleton, is a typical redox-type inhibitor[14] (Chart 1). Electronic equivalents of 1,4-benzoquinone such as 2-amino-6-hydroxybenzothiazoles (e.g., E3040) also inhibit 5-LO.[10] (Chart 1).

In designing a novel dual inhibitor of 5-LO and TXA_2 synthetase, we planned to introduce a 3-pyridyl residue, which is known to selectively inhibit TXA_2 synthetase,[15,16] into the 1,4-benzoquinone skeleton, which suppresses 5-LO activity[14] (Chart 2). As lipophilicity is important for 5-LO inhibition, the effects on the 5-LO activity of various combinations of three substituents attached to the 1,4-benzoquinone skeleton were examined. In order to increase the absorption from digestive organs, a

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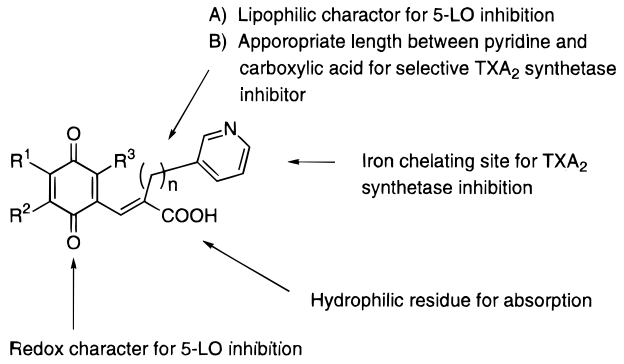
Chart 2



carboxylic acid moiety was also introduced into the structure. To synthesize the designed compounds, we planned to utilize the Wittig−Horner reaction between 1,4-benzoquinone precursors and 3-pyridylalkyl-bearing phosphonoacetates. The length of the methylene chain in Wittig−Horner reagents was varied from three to six to investigate the selectivity in TXA_2 synthetase inhibition and the role of lipophilicity in 5-LO inhibition.

Chemistry

The general synthetic pathways for preparation of the compounds listed in Table 1 are shown in Schemes 1−3. The starting materials, Wittig−Horner reagents **6a**−**d**, and 1,4-dimethoxybenzaldehydes **10**, **14**, and **17** were synthesized by known or general procedures outlined in Schemes 1 and 2, respectively.

The Wittig−Horner reagents **6a**−**d** were prepared from the corresponding chloride or mesylate of the alcohol **5**[17] derived from **4** and triethyl phosphonoacetate in the presence of base (Scheme 1). The alcohol **5** was obtained by the coupling of 3-bromopyridine (**1**) and the lactone **2** in the presence of *n*-butyllithium or magnesium to give keto alcohol **4**.[18] In an alternative route, the keto alcohol **4** was also prepared via Claisen condensation and decarboxylation of methyl nicotinate (**3**) and the lactone **2** in good yield.[19,20]

The trialkoxy-substituted aldehydes **10**,[21] **14**,[21] and **17** were generally synthesized from the corresponding 1,4-hydroquinone dimethyl ethers **7** and **11** or phenol **15**,[22] respectively. The 1,4-hydroquinone dimethyl ethers **7** and **11** were subjected to formylation, Bayer−Villiger rearrangement, and hydrolysis to afford the phenol derivatives **8** and **12**. Phenol derivatives **8**, **12**, and **15** were alkylated by alkyl halides with base, and the resulting ethers **9**, **13**, and **16** were formylated to afford the aldehydes **10**, **14**, and **17** (Scheme 2).

The coupling of the aldehydes **10**, **14**, and **17** and the Wittig−Horner reagents **6a**−**d** was performed in the presence of an appropriate base such as NaH or *t*-BuOK, affording **18** in fairly good yield. After hydrolysis of **18**, the resultant carboxylic acids **19** were oxidized by using cerium(IV) ammonium nitrate (CAN)[23] to afford the 1,4-benzoquinone derivatives **20**. The yields in the oxidation by CAN were somewhat low because the extraction of the product from the reaction mixture was difficult (Scheme 3). The reduction of the benzoquinones to corresponding hydroquinones **21** was easily achieved by using sodium hydrosulfite (Scheme 3).

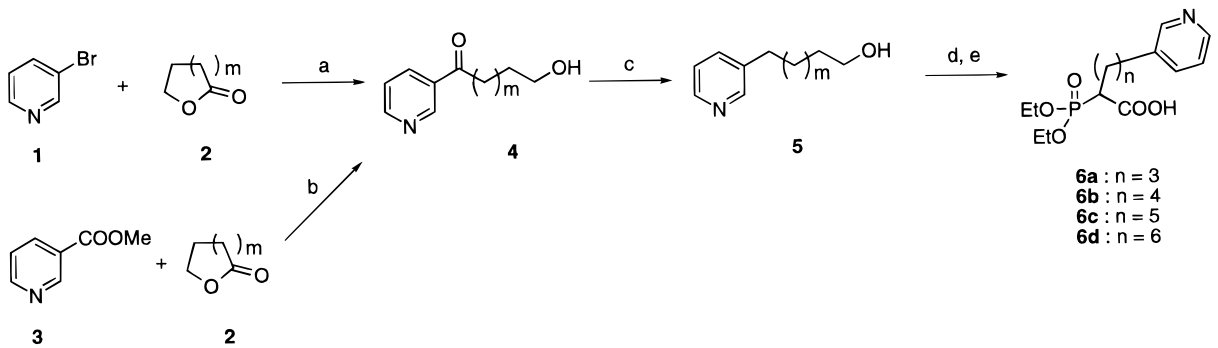
Pharmacological Results and Discussion

(1) *In Vitro* Studies (GPEC). We initially evaluated the inhibitory activities of the obtained (*E*)-3-(1,4-benzoquinonyl)-2-[(3-pyridyl)alkyl]-2-propenoic acid derivatives **20** and **21** by monitoring the inhibition of both LTB_4 and TXB_2 production from glycogen-induced peritoneal cells of rats (GPEC) as we have previously reported[10] (*in vitro*). The results are summarized in Table 1.

As shown in Table 1, the IC_{50} values for the inhibition of LTB_4 production by (*E*)-3-(1,4-benzoquinonyl)-2-[(3-pyridyl)alkyl]-2-propenoic acid derivatives **20a**−**q** varied from 0.17 (**20n**) to 11.7 (**20q**) μM, while those for inhibition of TXB_2 production were under 1.0 μM for all compounds examined, suggesting that the structural changes greatly affect the inhibition of LTB_4 production. In general, introduction of a polar substituent such as carboxylic acid is known to reduce inhibitory activity against LTB_4 production,[24] but these (*E*)-3-(1,4-benzoquinonyl)-2-[(3-pyridyl)alkyl]-2-propenoic acid derivatives exhibit potent inhibition of LTB_4 production by GPEC. The inhibitory activity of LTB_4 production generally increased with increasing length of the alkyl chain, indicating that the lipophilicity of the compound is also an important factor for the inhibition of LTB_4 production by propenoic acid derivatives **20** (Figure 1).

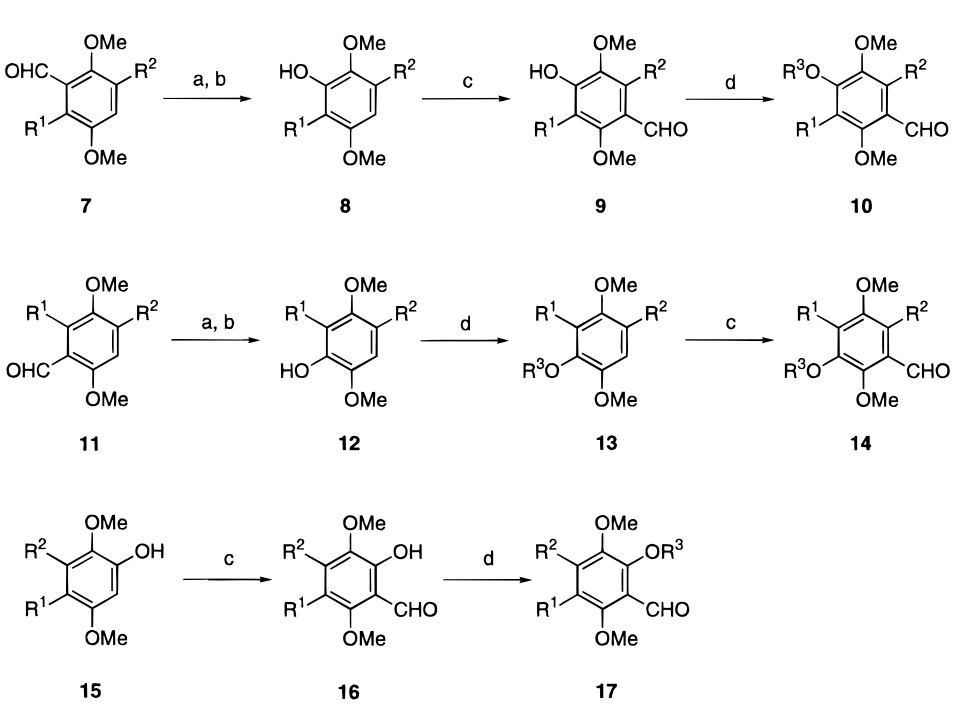
As shown in Figure 1 and Table 1, the compounds with a shorter methylene side chain (e.g., **20a**,**i**) showed weaker inhibitory activities on LTB_4 production, suggesting that the lipophilicity of the alkyl side chain is important. In contrast, an increase of lipophilicity by introduction of a longer alkoxy chain residue at R^1 (**20e**,**f**) reduced the inhibitory activity on LTB_4 production compared with the corresponding methoxy-substituted derivative **20c**. However, similar lipophilic alkoxy group substitution on R^2 (**20j**−**m**) did not markedly

Scheme 1. Synthesis of the Wittig−Horner Reagents **6a**−**d**[a]



[a] Reagents: (a) *n*-BuLi or Mg; (b) *t*-BuOK, *t*-BuOH, then heat; (c) NH_2NH_2, NaOH; (d) $SOCl_2$ or MsCl; (e) $(EtO)_2P(O)CH_2COOEt$, NaI, NaH.

Scheme 2. Synthesis of the Aldehydes **10**, **14**, and **17**[a]



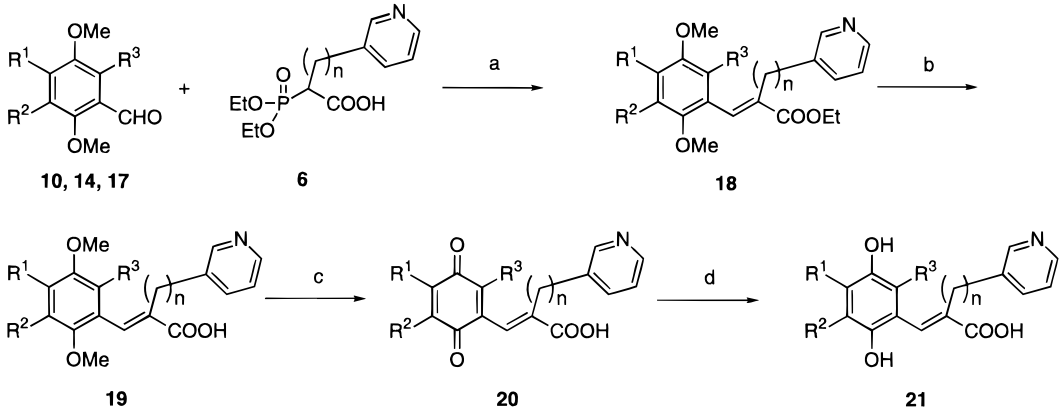
	R^1	R^2	R^3
10a	Me	Me	Me
10b	Me	Me	Et
10c	Me	Me	*n*-Heptyl

	R^1	R^2	R^3
14a	Me	Me	Me
14b	Me	Me	*n*-Butyl
14c	Me	Me	Et
14d	Me	Me	*n*-Heptyl
14e	Me	Me	Cyclohexyl

	R^1	R^2	R^3
17a	Me	Me	Me
17b	Me	H	Me

[a] Reagents: (a) *m*-CPBA; (b) NaOH, H_2O; (c) Cl_2CHOCH_3, $TiCl_4$; (d) R^3X, base.

Scheme 3. Synthesis of 1,4-Benzoquinone Derivatives **20** and Hydroquinone Derivatives **21**[a]



[a] Reagents: (a) NaH, DMF or *t*-BuOK, *t*-BuOH; (b) NaOH, H_2O; (c) $(NH_4)_2Ce(NO_3)_6$; (d) $Na_2S_2O_4$.

reduce the inhibition compared with the corresponding methoxy-substituted derivative **20g**. Among the three monomethoxy compounds with $n = 5$ (**20c**,**g**,**n**), **20n** showed somewhat stronger inhibition of LTB_4 production than **20c**,**g**.

Introduction of an extra methoxy group into the benzoquinone skeleton (**20q**) resulted in decreased inhibition of LTB_4 production compared with the corresponding monomethoxy compounds **20c**,**g**,**n**. These results could also be attributable to the decrease in the lipophilicity of the molecules. Thus, we conclude that the positions of alkoxy substituents on the 1,4-benzoquinone skeleton markedly affected the inhibitory activity on LTB_4 production, probably due to steric and electronic interactions, while lipophilic character around the propenoic acid residue generally increased the inhibitory activity.

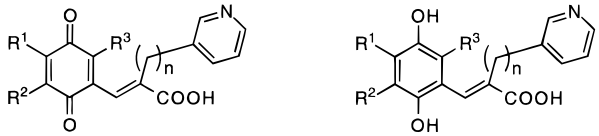
As shown in Table 1 and Figure 1, the inhibition of TXB_2 production decreased only when the length of the methylene side chain was short ($n = 3$) in this series. The structure−activity relationship of TXA_2 synthetase inhibitors has already been well established, and the distance between the carboxylic acid and the nitrogen atom of pyridine or imidazole is critical.[15,16] In the cases of **20a**,**i**, this distance may be too short to allow efficient binding to the enzyme.

It should be noted that none of the compounds examined inhibited the production of PGE_2 at the dose at which the production of TXB_2 is almost completely suppressed. This can be attributed to the inhibition of TXA_2 synthetase without affecting CO.

Hydroquinones **21c**,**g**,**n** showed decreased inhibitory activities on both LTB_4 and TXB_2 production compared with the corresponding 1,4-benzoquinones **20c**,**g**,**n**. Considering that **21c** showed almost the same activities as **20c** in cell-free *in vitro* experiments (see below), the observed differences in the activities could be attributed to differences of transmembrane permeation ability.

(2) *In Vitro* Studies (Human cells).[10] We next conducted *in vitro* assays using human whole blood, human neutrophils, and human platelets for **20c** and **21c**. In these experiments the representative 5-LO and

Table 1. Inhibitory Activity against Eicosanoid Production by Glycogen-Induced Peritoneal Cells of Rat (GPEC)[a]



20 **21**

					IC_{50} (mM)[b]				
compd	R^1	R^2	R^3	*n*	LTB_4	TXB_2	PGE_2	mp (°C)[c]	formula[d]
20a	MeO	Me	Me	3	3.2	0.48	100 (75%)[e]	140−142	$C_{20}H_{21}NO_5 \cdot 0.5H_2O$
20b	MeO	Me	Me	4	1.4	0.09	>100[f]	124−125	$C_{21}H_{23}NO_5 \cdot 0.4H_2O$
20c	MeO	Me	Me	5	0.82	0.07	19[g]	134−135	$C_{22}H_{25}NO_5 \cdot 0.3H_2O$
20d	MeO	Me	Me	6	0.59	0.12	100 (100%)[e]	119−121	$C_{23}H_{27}NO_5 \cdot 0.5H_2O$
20e	EtO	Me	Me	5	4.4	0.32	100 (76%)[e]	116−118	$C_{23}H_{27}NO_5 \cdot 0.3H_2O$
20f	n-$C_7H_{15}O$	Me	Me	5	3.2	0.16	>100[e]	oil	$C_{28}H_{37}NO_5$[h]
20g	Me	MeO	Me	5	0.54	0.18	>100[g]	128−130	$C_{22}H_{25}NO_5 \cdot 0.3H_2O$
20h	Me	MeO	Me	6	0.18	<0.1 (55%)	100 (100%)[e]	108−110	$C_{23}H_{27}NO_5 \cdot 0.1H_2O$
20i	Me	n-C_4H_9O	Me	3	1.8	0.89	NT	92−95	$C_{23}H_{27}NO_5$[h,i]
20j	Me	n-C_4H_9O	Me	5	1.0	<0.1 (61%)	100 (100%)[e]	97−100	$C_{25}H_{31}NO_5 \cdot 0.5H_2O$
20k	Me	EtO	Me	5	0.84	0.12	100 (93%)[g]	105−108	$C_{23}H_{27}NO_5$,[h,j]
20l	Me	n-$C_7H_{15}O$	Me	5	0.27	<0.1 (77%)	NT	oil	$C_{28}H_{37}NO_5$[h]
20m	Me	(cyclohexylmethyl)oxy	Me	5	0.27	<0.1	>100[f]	oil	$C_{28}H_{35}NO_5$[h]
20n	Me	Me	MeO	5	0.17	0.11	NT	148−149	$C_{22}H_{25}NO_5 \cdot 0.5AcOEt$[h,k]
20o	Me	Me	MeO	6	0.22	0.42	NT	64−66	$C_{23}H_{27}NO_5 \cdot 0.7H_2O$[h,l]
20p	H	Me	MeO	5	0.75	0.50	NT	110−112	$C_{21}H_{23}NO_5$[h]
20q	MeO	MeO	Me	5	11.7	0.41	>100[f]	oil	$C_{22}H_{25}NO_6$[h]
21c	MeO	Me	Me	5	4.9	0.40	>100[f]	amorphous	$C_{22}H_{27}NO_5 \cdot HCl$[m]
21g	Me	MeO	Me	5	>3.0	1.5	>100[f]	amorphous	$C_{22}H_{27}NO_5$[h]
21n	Me	Me	MeO	5	2.1	0.14	>100[f]	amorphous	$C_{22}H_{27}NO_5$[h]

[a] Aliquots (5×10^5 cells) of rat peritoneal leukocytes were incubated (5 min, 37 °C) with test compounds prior to addition of A23187 (4 μM, 10 min, 37 °C). Aliquots of the supernatant were analyzed for LTB_4, TXB_2, and PGE_2. See the Experimental Section for details. [b] IC_{50} values were derived from inhibition experiments in which data points were measured in duplicate, and concentration−effect curves were calculated by the probit method. Values in parentheses indicate the inhibition (%) at the dose. [c] The solid was recrystallized from n-hexane−AcOEt. [d] Elemental analyses for C, H, and N are within ±0.4% of the theoretical values. [e] The production of PGE_2 was potentiated at 0.1−1 μM. [f] The production of PGE_2 was potentiated at 0.1−10 μM. [g] The production of PGE_2 was potentiated at 0.1−100 μM. [h] Formula was obtained by high-resolution mass spectroscopy. [i] C: calcd, 69.50; found, 65.83. [j] C: calcd, 69.50; found, 67.57. [k] H: calcd, 6.84; found, 6.33. [l] H: calcd, 6.98; found, 6.44. [m] Elemental analysis by using HCl salt. NT: not tested.

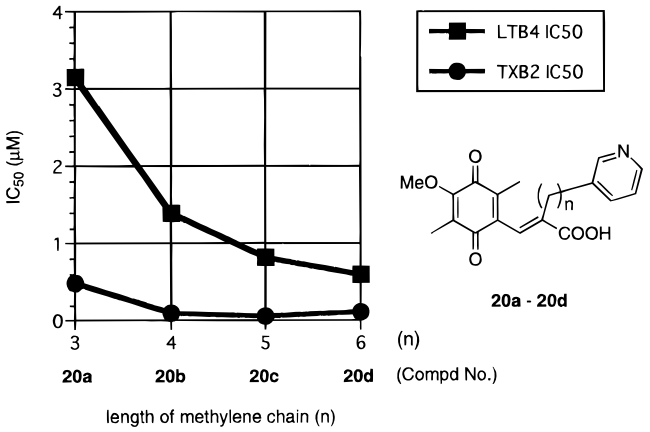


Figure 1. Relationship between the length of the methylene chain and IC_{50}.

TXA_2 synthetase inhibitors Zileuton[25] and Ozagrel,[26] respectively, were also evaluated (Table 2).

As shown in Table 2, both **20c** and the corresponding hydroquinone **21c** inhibited LTB_4 and TXB_2 production, except for LTB_4 production in human whole blood in the case of **21c**. The selective 5-LO inhibitor Zileuton exhibited 2−4 times higher activity than **20c** in the inhibition of LTB_4 production. Ozagrel selectively inhibited TXA_2 production in human whole blood as compared with **20c** and **21c**. However, the inhibition of TXB_2 production by both **20c** and **21c** in human plateletes was almost as potent as that of the selective TXA_2 inhibitor Ozagrel.

Table 2. *In Vitro* Activities in Human Cells (IC_{50}, μM)[a]

	human whole blood[b]		human neutrophils,[c]	human platelets,[d]
compd	LTB_4	TXB_2	LTB_4	TXB_2
20c	5.8	3.2	0.90	0.39
21c	>100	3.0	1.9	1.9
Zileuton	1.3	>100	0.42	NT
Ozagrel	>100	<0.1	>100	1.9

[a] IC_{50} values were derived from inhibition experiments in which data points were measured in duplicate, and concentration−effect curves were calculated by the probit method. [b] Human whole blood (0.4 mL) was incubated (5 min, 37 °C) with test compounds prior to addition of A23187 (40 μM, 20 min, 37 °C). Aliquots of plasma were analyzed for LTB_4, TXB_2, and PGE_2. [c] Human PMNs ($1 \times$ 105 cells) were incubated (5 min, 37 °C) with test compounds prior to addition of A23187 (4 mM, 10 min, 37 °C). Aliquots of the supernatant were analyzed for LTB_4. [d] Human platelets (6×107 cells) were incubated (5 min, 25 °C) with test compounds prior to addition of PGH_2 (1 μg/mL, 3 min, 25 °C). Aliquots of the supernatant were analyzed for TXB_2. NT: not tested.

(3) *In Vitro* Studies (Cell-free enzyme assay).[10] The cell-free *in vitro* assay of 5-LO from RBL-1 and TXA_2 synthetase from microsome human platelets was performed to confirm that the biological activities were due to direct enzyme inhibition (Table 3).

As shown in Table 3, **20c** and **21c** exhibited both 5-LO and TXA_2 synthetase inhibitory activities. In contrast to the *in vitro* cell studies (Tables 1 and 2), **21c** exhibited more potent inhibition than **20c** against 5-LO in microsomes of RBL-1 cells. Thus, the observed difference of *in vitro* activity might be attributed to a difference of transmembrane permeation ability but not to a differ-

Table 3. *In Vitro* Cell-Free Enzyme Assay (IC_{50}, μM)[a]

	enzyme source	
compd	microsome of RBL-1 cells,[b] 5-LO	microsome of human platelets,[c] TXA_2 synthetase
20c	16.3	0.026
21c	4.8	0.033
Zileuton	0.41	NT
Ozagrel	NT	0.006

[a] IC_{50} values were derived from inhibition experiments in which data points were measured in duplicate, and concentration−effect curves were calculated by the probit method. [b] Homogenates of RBL-1 cells were incubated (5 min, 37 °C) with test compounds prior to addition of arachidonic acid (0.2 mM, 10 min, 37 °C). Aliquots of the reaction mixtures were analyzed for 5-HETE. [c] Microsomes fraction (20 μg of protein) from human platelets was incubated (5 min, 25 °C) with test compounds prior to addition of PGH_2 (1 μg/mL, 1 min, 25 °C). Aliquots of the reaction mixtures were analyzed for TXB_2. NT: not tested.

ence of intrinsic inhibitory potency toward 5-LO. These two compounds (**20c** and **21c**) did not show any significant difference in inhibitory activity against cell-free *in vitro* TXA_2 synthetase in microsomes of human platelets.

In conclusion, in spite of the introduction of a polar carboxylic acid moiety into the 1,4-benzoquinone skeleton, compounds **20c**,**g**,**n** exhibited well-balanced inhibition of the production of both LTB_4 and TXB_2 but did not inhibit production of PGE_2 in *in vitro* screening. The compounds showed good absorption into the systemic circulation after po administration in preclinical studies (data not shown). Dual-function compounds such as **20c** (E6700) that specifically inhibit both 5-LO and TXA_2 synthetase could possess a variety of pharmacologically beneficial effects, and clinical studies are in progress.

Experimental Section

Chemistry. Reagents and solvents were purchased from the usual commercial sources. Silica gel (Kieselgel 60, Merck) was used for column chromatography and silica gel (Kieselgel 60 F_{254}, Merck) for analytical thin layer chromatography (TLC). Compounds were detected on TLC plates by exposure to UV light (254 nm). Melting points were measured on a Yanagimoto micromelting point apparatus without correction. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 400 spectrometer, and chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) as an internal reference. Infrared spectra were recorded on a Jasco FT/IR-330E spectrometer. Mass spectra (MS) were obtained on a JEOL JMS-HX100 mass spectrometer. All organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed with a rotary evaporator under reduced pressure.

Ethyl 2-(Diethylphosphono)-7-(3-pyridyl)heptanoate (6c). Mesyl chloride (161 g, 1.41 mol) was added dropwise to a mixture of 5-(3-pyridyl)pentanol (**5c**) (221 g, 1.34 mol) and triethylamine (142 g, 1.40 mol) in dichloromethane (2 L) under cooling with ice. The mixture was stirred for 1 h at the same temperature; then the organic layer was separated, washed with brine twice, dried, and evaporated to give the chloride as a pale red oil. Triethyl phosphonoacetate (300 g, 1.34 mol) was added dropwise to a suspension of sodium hydride (55% oil suspension, 59 g, 1.35 mol) in *N*,*N*-dimethylformamide (500 mL) under 60 °C, and the mixture was stirred at room temperature for 1 h. To this mixture was added dropwise a solution of the above chloride in *N*,*N*-dimethylformamide (500 mL) at 60 °C. The reaction mixture was stirred for 12 h at 60 °C, and then ethyl acetate (3 L) was added. The organic layer was washed with brine, dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: ethyl acetate−*n*-hexane = 1:2−1:1, ethyl acetate−methanol (5%)) to afford **6c** (226 g, 0.61 mol, 45%) as a pale red oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.50 (m, 11H), 1.55−2.04 (m, 4H), 2.05−2.30 (m, 2H), 2.57 (t, J = 7.6 Hz, 2H), 2.89 (ddd, J = 22.4, 10.8, 4.0 Hz, 1H), 4.07−4.24 (m, 6H), 7.19 (dd, J = 8.0, 4.8 Hz, 1H), 7.44−7.48 (m, 1H), 8.38−8.43 (m, 2H).

Ethyl 2-(Diethylphosphono)-5-(3-pyridyl)pentanoate (6a). 5-(3-Pyridyl)propanol (**5a**) (6.9 g, 50.3 mmol) was treated according to the same procedure described for the preparation of **6c** to afford **6a** (7.0 g, 20.4 mmol, 41%) as a dark brown oil: ^{1}H NMR ($CDCl_3$) δ 1.22−1.40 (m, 11H), 1.60−2.10 (m, 4H), 2.65 (t, J = 7.6 Hz, 2H), 2.89−3.02 (m, 1H), 4.07−4.30 (m, 6H), 7.20 (dd, J = 8.0, 4.8 Hz, 1H), 7.42−7.50 (m, 1H), 8.40−8.46 (m, 2H).

Ethyl 2-(Diethylphosphono)-6-(3-pyridyl)hexanoate (6b). 5-(3-Pyridyl)butanol (**5b**) (15.0 g, 99.1 mmol) was treated according to the same procedure described for the preparation of **6c** to afford **6b** (7.9 g, 22.4 mmol, 23%) as a dark brown oil.

Ethyl 2-(Diethylphosphono)-8-(3-pyridyl)octanoate (6d). 5-(3-Pyridyl)heptanol (**5d**) (25.5 g, 0.142 mol) was treated according to the same procedure described for the preparation of **6c** to afford **6d** (25.0 g, 0.066 mol, 46%) as a dark brown oil.

General Procedure for the Synthesis of the Aldehydes 10, 14, and 17: Representative Route to the Aldehyde 10a. 2,5-Dimethoxy-3,6-dimethylphenol (8a). *m*-Chloroperbenzoic acid (70%, 130 g, 0.53 mol) was added portionwise to a solution of 2,5-dimethoxy-3,6-dimethylbenzaldehyde (**7a**) (94 g, 0.48 mol) in dichloromethane (660 mL) with stirring at room temperature. The mixture was heated to reflux for 30 min, then ice (200 g) and a saturated solution of sodium thiosulfate (200 mL) were added. The resulting solid were filtered off and washed with a small amount of dichloromethane. The combined organic layer was washed successively with 1 N sodium hydroxide and brine, dried, and evaporated. The residue was dissolved in methanol (250 mL). To the solution was added 28% sodium methoxide in methanol (120 mL, 0.59 mol), and the mixture was stirred at room temperature for 30 min. Ice-water (300 mL) was added to the reaction mixture, and then the mixture was neutralized with 2 N hydrochloric acid affording white precipitates. The solid was collected by filtration, washed with water, and dried to afford crude **8a** (75 g, 0.41 mol, 81%) as a white solid, which was used for the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.27 (s, 3H), 3.75 (s, 3H), 3.77 (s, 3H), 5.73 (br s, 1H), 6.29 (s, 1H).

4-Hydroxy-2,5-dimethoxy-3,6-dimethylbenzaldehyde (9a). To the solution of 2,5-dimethoxy-3,6-dimethylphenol (**8a**) (31 g, 0.28 mol) in dichloromethane (330 mL) was added titanium(IV) chloride (40 mL, 0.36 mol) under 10 °C, and the resulting deep purple solution was stirred for an additional 15 min at 0 °C. α,α-Dichloromethyl methyl ether (39 mL, 0.43 mol) was added to the solution under 15 °C, and the mixture was stirred at room temperature for 2.5 h. The reaction was quenched carefully with 300 mL of ice−water and the mixture extracted with ethyl acetate twice. The organic layer was washed successively with saturated sodium hydrogen carbonate and brine, dried, and evaporated. The residue was treated with ether, and the resulting solid was collected by filtration and washed with a small amount of ethanol and *n*-hexane (1:1) to afford **9a** (38 g, 0.18 mol, 65%) as a white solid, which was used for the next step without further purification: mp 168−169 °C (EtOH−*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.52 (s, 3H), 3.75 (s, 3H), 3.81 (s, 3H), 6.40 (s, 1H), 10.39 (s, 1H).

2,4,5-Trimethoxy-3,6-dimethylbenzaldehyde (10a). To the solution of 4-hydroxy-2,5-dimethoxy-3,6-dimethylbenzaldehyde (**9a**) (38 g, 0.18 mol) in *N*,*N*-dimethylformamide (300 mL) was added sodium hydride (60% oil suspension, 8.0 g, 0.20 mol) with stirring in an ice bath. After 15 min, iodomethane (12.5 mL, 0.20 mol) was added dropwise to the reaction mixture at room temperature. The mixture was stirred for an additional 3 h, the reaction was quenched with water, and the mixture was extracted with ethyl acetate twice. The organic layer was washed with brine, dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: ethyl acetate−*n*-hexane = 1:9) to afford **10a** (41 g, 0.18 mol, >99%) as a yellow solid: mp 29−30 °C (ethyl acetate−*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ

2.20 (s, 3H), 2.48 (s, 3H), 3.75 (s, 3H), 3.79 (s, 3H), 3.92 (s, 3H), 10.43 (s, 1H).

Ethyl (*E*)-3-(2,4,5-Trimethoxy-3,6-dimethylphenyl)-2-[5-(3-pyridyl)pentyl]-2-propenoate (18c). A solution of ethyl 2-(diethylphosphono)-7-(3-pyridyl)heptanoate (**6c**) (222 g, 0.60 mol) in *N*,*N*-dimethylformamide (300 mL) was added dropwise to a suspension of sodium hydride (60% oil suspension, 24 g, 0.6 mol) in *N*,*N*-dimethylformamide (200 mL) at 0 °C. After completion of the dropping, the mixture was stirred at room temperature for 1 h; then a solution of 2,4,5-trimethoxy-3,6-dimethylbenzaldehyde (**10a**) (122 g, 0.54 mol) in *N*,*N*-dimethylformamide (200 mL) was added dropwise. The reaction mixture was stirred overnight under heating at 50 °C and then poured onto 1 L of ice−water. The whole mixture was extracted with 1 L of ethyl acetate twice. The organic layer was separated, dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: *n*-hexane−ethyl acetate = 1:9−3:7) to afford **18c** (177 g, 0.40 mol, 74%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (tt, J = 7.5, 7.5 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H), 1.38 (tt, J = 7.5, 7.5 Hz, 2H), 1.46 (tt, J = 7.5, 7.5 Hz, 2H), 2.07 (s, 3H), 2.16 (t, J = 7.5 Hz, 2H), 2.16 (s, 3H), 2.48 (t, J = 7.5 Hz, 2H), 3.54 (s, 3H), 3.76 (s, 3H), 3,82 (s, 3H), 4.12 (q, J = 7.1 Hz, 2H), 7.16 (dd, J = 5.5, 7.8 Hz, 1H), 7.39 (dt, J = 1.5, 7.8 Hz, 1H), 7.45 (s, 1H), 8.36 (d, J = 1.5 Hz, 1H), 8.39 (dd, J = 1.5, 5.5 Hz, 1H).

(*E*)-3-(2,4,5-Trimethoxy-3,6-dimethylphenyl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (19c). A solution of ethyl (*E*)-3-(2,4,5-trimethoxy-3,6-dimethylphenyl)-2-[5-(3-pyridyl)-pentyl]-2-propenoate (**18c**) (177 g, 0.39 mol) in ethanol (500 mL) was treated with 5 N sodium hydroxide solution (100 mL). The mixture was heated under reflux for 1 h followed by the addition of 1 L of ice. The whole was neutralized with 6 N hydrochloric acid and extracted with 1 L of ethyl acetate twice. The organic layer was washed with brine, dried, and evaporated to afford **19c** (159 g, 0.39 mol, >99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (tt, J = 7.6, 7.6 Hz, 2H), 1.47 (tt, J = 7.6, 7.6 Hz, 2H), 1.52 (tt, J = 7.6, 7.6 Hz, 2H), 2.09 (s, 3H), 2.17 (s, 3H), 2.20 (t, J = 7.6 Hz, 2H), 2.54 (t, J = 7.6 Hz, 2H), 3.57 (s, 3H), 3.78 (s, 3H), 3,83 (s, 3H), 7.23 (dd, J = 5.0, 7.6 Hz, 1H), 7.48 (br d, J = 7.6 Hz, 1H), 7.59 (s, 1H), 8.46 (br s, 2H).

(*E*)-3-(2,4,5-Trimethoxy-3,6-dimethylphenyl)-2-[3-(3-pyridyl)propyl]-2-propenoic Acid (19a). 2,4,5-Trimethoxy-3,6-dimethylbenzaldehyde (**10a**) (2.2 g, 10.0 mmol) and Wittig−Horner reagent **6a** (3.4 g, 10.0 mmol) were treated according to the same procedure described for the preparation of **19c** to afford **19a** (800 mg, 2.2 mmol, 22%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (tt, J = 7.6, 7.6 Hz, 2H), 2.10 (s, 3H), 2.23 (s, 3H), 2.25 (t, J = 7.6 Hz, 2H), 2.57 (t, J = 7.6 Hz, 2H), 3.56 (s, 3H), 3.80 (s, 3H), 3.87 (s, 3H), 7.21 (t, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.60 (s, 1H), 8.46 (br s, 1H), 8.58 (br s, 1H).

(*E*)-3-(2,4,5-Trimethoxy-3,6-dimethylphenyl)-2-[4-(3-pyridyl)butyl]-2-propenoic Acid (19b). 2,4,5-Trimethoxy-3,6-dimethylbenzaldehyde (**10a**) (1.6 g, 7.1 mmol) and Wittig−Horner reagent **6b** (2.5 g, 7.1 mmol) were treated according to the procedure described for the preparation of **19c** to afford **19b** (1.0 g, 2.5 mmol, 35%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41−1.58 (m, 4H), 2.08 (s, 3H), 2.18 (s, 3H), 2.25 (t, J = 7.2 Hz, 2H), 2.53 (t, J = 7.2 Hz, 2H), 3.55 (s, 3H), 3.78 (s, 3H), 3.85 (s, 3H), 7.21 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.59 (s, 1H), 8.44 (br s, 2H).

(*E*)-3-(2,4,5-Trimethoxy-3,6-dimethylphenyl)-2-[6-(3-pyridyl)hexyl]-2-propenoic Acid (19d). 2,4,5-Trimethoxy-3,6-dimethylbenzaldehyde (**10a**) (1.4 g, 6.3 mmol) and Wittig−Horner reagent **6d** (2.4 g, 6.3 mmol) were treated according to the same procedure described for the preparation of **19c** to afford **19d** (1.4 g, 3.3 mmol, 52%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, J = 3.5 Hz, 4H), 1.41 (t, J = 7.6 Hz, 2H), 1.53 (t, J = 7.6 Hz, 2H), 2.10 (s, 3H), 2.18 (s, 3H), 2.19 (t, J = 7.6 Hz, 2H), 2.55 (t, J = 7.6 Hz, 2H), 3.57 (s, 3H), 3.79 (s, 3H), 3.85 (s, 3H), 7.23 (t, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.58 (s, 1H), 8.47 (br s, 2H).

(*E*)-3-(4-Ethoxy-2,5-dimethoxy-3,6-dimethylphenyl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (19e). 4-Ethoxy-2,5-dimethoxy-3,6-dimethylbenzaldehyde (**10b**) (1.34 g, 5.6 mmol) and Wittig−Horner reagent **6c** (2.1 g, 5.6 mmol) were treated according to the procedure described for the preparation of **19c** to afford **19e** (400 mg, 0.94 mmol, 17%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (m, 2H), 1.39 (t, J = 7.0 Hz, 3H), 1.46 (m, 2H), 1.52 (m, 2H), 2.08 (s, 3H), 2.17 (s, 3H), 2.20 (t, J = 8.0 Hz, 2H), 2.53 (t, J = 8.0 Hz, 2H), 3.56 (s, 3H), 3.78 (s, 3H), 4.03 (t, J = 7.0 Hz, 2H), 7.21 (br s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.58 (s, 1H), 8.43 (br s, 2H).

(E)-3-[4-(*n*-Heptyloxy)-2,5-dimethoxy-3,6-dimethylphenyl]-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (19f). 4-(*n*-Heptyloxy)-2,5-dimethoxy-3,6-dimethylbenzaldehyde (**10c**) (1.0 g, 3.2 mmol) and Wittig−Horner reagent **6c** (1.2 g, 3.2 mmol) were treated according to the procedure described for the preparation of **19c** to afford **19f** (350 mg, 0.7 mmol, 22%) as a colorless oil.

(*E*)-3-(2,3,5-Trimethoxy-4,6-dimethylphenyl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (19g). 2,3,5-Trimethoxy-4,6-dimethylbenzaldehyde (**14a**) (1.4 g, 6.2 mmol) and Wittig−Horner reagent **6c** (2.3 g, 6.2 mmol) were treated according to the procedure described for the preparation of **19c** to afford **19g** (390 mg, 2.2 mmol, 34%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (tt, J = 8.0, 8.0 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H), 1.40 (t, J = 8.0 Hz, 2H), 1.48 (tt, J = 8.0, 8.0 Hz, 2H), 2.07 (s, 3H), 2.15 (t, J = 8.0 Hz, 2H), 2.21 (s, 3H), 2.49 (t, J = 8.0 Hz, 2H), 3.65 (s, 3H), 3.70 (s, 3H), 3.77 (s, 3H), 4.28 (q, J = 7.2 Hz, 2H), 7.16 (dd, J = 4.8, 7.6 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H), 8.36 (d, J = 1.6 Hz, 1H), 8.40 (dd, J = 1.6, 4.8 Hz, 1H).

(*E*)-3-(2,3,5-Trimethoxy-4,6-dimethylphenyl)-2-[6-(3-pyridyl)hexyl]-2-propenoic Acid (19h). 2,3,5-Trimethoxy-4,6-dimethylbenzaldehyde (**14a**) (1.4 g, 5.1 mmol) and Wittig−Horner reagent **6d** (2.0 g, 5.3 mmol) were treated according to the procedure described for the preparation of **19c** to afford **19h** (220 mg, 0.52 mmol, 10%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.27 (m, 4H), 1.42 (tt, J = 8.0, 8.0 Hz, 2H), 1.55 (tt, J = 8.0, 8.0 Hz, 2H), 2.11 (s, 3H), 2.19 (t, J = 8.0 Hz, 2H), 2.23 (s, 3H), 2.58 (t, J = 8.0 Hz, 3H), 3.69 (s, 3H), 3.71 (s, 3H), 3.82 (s, 3H), 7.26 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.58 (s, 1H), 8.50 (br s, 2H).

(*E*)-3-[3-(*n*-Butyloxy)-2,5-dimethoxy-4,6-dimethylphenyl]-2-[3-(3-pyridyl)propyl]-2-propenoic Acid (19i). 3-(*n*-Butyloxy)-2,5-dimethoxy-4,6-dimethylbenzaldehyde (**14b**) (2.8 g, 11.2 mmol) and Wittig−Horner reagent **6a** (3.8 g, 11.2 mmol) were treated according to the procedure described for the preparation of **19c** to afford **19i** (1.3 g, 3.0 mmol, 27%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 8.0 Hz, 3H), 1.51 (q, J = 7.6 Hz, 2H), 1.71−1.85 (m, 4H), 2.04 (s, 3H), 2.22 (br s, 5H), 2.52 (t, J = 7.6 Hz, 2H), 3.66 (s, 6H), 3.90 (t, J = 8.0 Hz, 2H), 7.16 (br s, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.56 (s, 1H), 8.42 (br s, 1H), 8.51 (br s, 1H).

(*E*)-3-[3-(*n*-Butyloxy)-2,5-dimethoxy-4,6-dimethylphenyl]-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (19j). 3-(Butyloxy)-2,5-dimethoxy-4,6-dimethylbenzaldehyde (**14b**) (3.0 g, 12.0 mmol) and Wittig−Horner reagent **6c** (4.4 g, 12.0 mmol) were treated according to the procedure described for the preparation of **19c** to afford **19j** (1.1 g, 2.4 mmol, 20%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 8.0 Hz, 3H), 1.13 (br s, 2H), 1.40−1.55 (m, 4H), 1.71 (tt, J = 7.6, 7.6 Hz, 2H), 2.05 (s, 3H), 2.13 (t, J = 7.6 Hz, 2H), 2.19 (s, 3H), 2.48 (t, J = 7.6 Hz, 2H), 3.62 (br s, 6H), 3.86 (t, J = 8.0 Hz, 2H), 7.17 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.51 (s, 1H), 8.44 (s, 2H).

(*E*)-3-(3-Ethoxy-2,5-dimethoxy-4,6-dimethylphenyl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (19k). 3-Ethoxy-2,5-dimethoxy-4,6-dimethylbenzaldehyde (**14c**) (5.5 g, 23.1 mmol) and Wittig−Horner reagent **6c** (9.3 g, 25.4 mmol) were treated according to the procedure described for the preparation of **19c** to afford **19k** (5.0 g, 11.7 mmol, 51%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (tt, J = 8.0, 8.0 Hz, 2H), 1.35 (t, J = 8.0 Hz, 3H), 1.40−1.52 (m, 4H), 2.08 (s, 3H), 2.18 (t, J = 8.0 Hz, 2H), 2.21 (s, 3H), 2.53 (t, J = 8.0 Hz, 2H), 3.66 (s, 3H), 3.69 (s, 3H) 3.99 (q, J = 8.0 Hz, 2H), 7.24 (dd, J = 4.8, 7.6 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.58 (s, 1H), 8.43 (s, 1H), 8.46 (s, 1H).

(*E*)-3-[3-(*n*-Heptyloxy)-2,5-dimethoxy-4,6-dimethylphenyl]-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (19l). 3-(*n*-Heptyloxy)-2,5-dimethoxy-4,6-dimethylbenzaldehyde (**14d**) (2.4 g, 7.8 mmol) and Wittig−Horner reagent **6c** (2.9 g, 7.8 mmol) were treated according to the procedure described for the preparation of **19c** to afford **19l** (560 mg, 1.1 mmol, 14%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 8.0 Hz, 3H), 1.20−1.38 (m, 10H), 1.41−1.54 (m, 4H), 1.76 (tt, J = 7.6, 7.6 Hz, 2H), 2.08 (s, 3H), 2.18 (t, J = 7.6 Hz, 2H), 2.21 (s, 3H), 2.53 (t, J = 7.6 Hz, 2H), 3.67 (s, 3H), 3.69 (s, 3H), 3.90 (t, J = 8.0 Hz, 3H), 7.23 (t, J = 7.6 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.58 (s, 1H), 8.46 (br s, 2H).

(*E*)-3-[3-(Cyclohexyloxy)-2,5-dimethoxy-4,6-dimethylphenyl]-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (19m). 3-(Cyclohexyloxy)-2,5-dimethoxy-4,6-dimethylbenzaldehyde (**14e**) (1.0 g, 3.3 mmol) and Wittig−Horner reagent **6c** (1.8 g, 4.9 mmol) were treated according to the procedure described for the preparation of **19c** to afford **19m** (380 mg, 0.8 mmol, 24%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (dq, J = 4.0, 12.0 Hz, 2H), 1.17−1.34 (m, 4H), 1.42−1.55 (m, 4H), 1.67−1.82 (m, 5H), 1.90 (br d, J = 12.0 Hz, 2H), 2.10 (s, 3H), 2.18 (t, J = 8.0 Hz, 2H), 2.20 (s, 3H), 2.54 (t, J = 8.0 Hz, 2H), 3.67 (s, 3H), 3.68 (s, 3H), 3.70 (d, J = 4.0 Hz, 2H), 7.22 (t, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.58 (s, 1H), 8.43 (br s, 2H).

(*E*)-3-(2,5,6-Trimethoxy-3,4-dimethylphenyl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (19n). 2,5,6-Trimethoxy-3,4-dimethylbenzaldehyde (**17a**) (2.0 g, 9.0 mmol) and Wittig−Horner reagent **6c** (3.7 g, 10.0 mmol) were treated according to the procedure described for the preparation of **19c** to afford **19n** (1.9 g, 4.6 mmol, 51%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (tt, J = 7.6, 7.6 Hz, 2H), 1.42−1.52 (m, 4H), 2.15 (s, 3H), 2.19 (s, 3H), 2.28 (t, J = 7.6 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H), 3.56 (s, 3H), 3.72 (s, 3H), 3.76 (s, 3H), 7.24 (m, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.64 (s, 1H), 8.43 (br s, 2H).

(*E*)-3-(2,5,6-Trimethoxy-3,4-dimethylphenyl)-2-[6-(3-pyridyl)hexyl]-2-propenoic Acid (19o). 2,5,6-Trimethoxy-3,4-dimethylbenzaldehyde (**17a**) (1.3 g, 5.9 mmol) and Wittig−Horner reagent **6d** (2.5 g, 6.5 mmol) were treated according to the procedure described for the preparation of **19c** to afford **19o** (1.3 g, 3.0 mmol, 51%) as a colorless oil.

(*E*)-3-(2,5,6-Trimethoxy-3-methylphenyl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (19p). 2,5,6-Trimethoxy-3-methylbenzaldehyde (**17b**) (2.1 g, 9.8 mmol) and Wittig−Horner reagent **6c** (4.0 g, 10.7 mmol) were treated according to the procedure described for the preparation of **19c** to afford **19p** (2.5 g, 6.3 mmol, 64%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 8.0 Hz, 2H), 1.30−1.55 (m, 4H), 2.25 (s, 3H), 2.30 (t, J = 8.0 Hz, 2H), 2.53 (t, J = 8.0 Hz, 2H), 3.58 (s, 3H), 3.68 (s, 3H), 3.83 (s, 3H), 6.60 (s, 1H), 7.21 (dd, J = 5.0, 7.0 Hz, 1H), 7.47 (dd, J = 1.0, 9.0 Hz, 1H), 7.64 (s, 1H), 8.43 (br s, 2H).

(*E*)-3-[2,3,4-Trimethoxy-5-(methoxymethoxy)-6-methylphenyl]-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (19q). 2,3,4-Trimethoxy-5-(methoxymethoxy)-6-methylbenzaldehyde (1.0 g, 3.7 mmol) and Wittig−Horner reagent **6c** (1.4 g, 3.7 mmol) were treated according to the procedure described for the preparation of **19c** to afford **19q** (760 mg, 1.6 mmol, 43%) as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.09−1.86 (m, 6H), 2.00−2.34 (m, 2H), 2.09 (s, 3H), 2.37−2.71 (m, 2H), 3.56 (s, 3H), 3.69 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 5.03 (s, 2H), 5.57−6.31 (m, 2H), 7.03−7.57 (m, 3H), 8.29−8.51 (m, 2H).

(*E*)-3-(2-Methoxy-3,6-dimethyl-1,4-benzoquinon-5-yl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (20c). An aqueous solution (700 mL) of cerium(IV) ammonium nitrate (527 g, 0.96 mol) was added to a solution of (*E*)-3-(2,4,5-trimethoxy-3,6-dimethylphenyl)-2-[5-(3-pyridyl)pentyl]-2-propenoic acid (**19c**) (159 g, 0.39 mol) in an acetonitrile (800 mL)/water (400 mL) mixture with cooling in an ice bath. The mixture was stirred for 30 min, and the pH thereof was adjusted to 5 with a saturated solution of sodium hydrogen carbonate followed by the addition of 3 L of water. The whole was extracted with 6 L of ethyl acetate twice. The organic layer was washed with brine, dried, and evaporated. The obtained oil was crystallized from a small amount of ethyl acetate to give crude **20c** (114 g, 0.29 mol, 74%) as yellow crystals. This product was recrystallized from an ethanol−water mixture to afford **20c** (90 g, 0.24 mol, 62%) as a yellow solid: mp 122−128 °C (EtOH−H_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (tt, J = 7.0, 7.0 Hz, 2H), 1.50 (tt, J = 7.0, 7.0 Hz, 2H), 1.61 (tt, J = 7.0, 7.0 Hz, 2H), 1.95 (s, 3H), 1.96 (s, 3H), 2.12 (t, J = 7.0 Hz, 2H), 2.60 (t, J = 7.0 Hz, 2H), 4.01 (s, 3H), 7.26 (s, 1H), 7.27 (dd, J = 5.0, 8.5 Hz, 1H), 7.55 (br d, J = 8.5 Hz, 1H), 8.44 (br d, J = 5.0 Hz, 1H), 8.50 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.9, 13.4, 27.9, 28.8, 29.1, 30.7, 32.7, 60.9, 123.8, 128.9, 131.1, 137.3, 138.6, 139.0, 139.7, 139.8, 145.5, 148.3, 155.6, 169.8, 183.3, 186.7; IR (KBr) 1700, 1650, 1635, 1600 cm^{-1}. Anal. ($C_{22}H_{25}NO_5 \cdot 0.3H_2O$) C, H, N.

(*E*)-3-(2-Methoxy-3,6-dimethyl-1,4-benzoquinon-5-yl)-2-[3-(3-pyridyl)propyl]-2-propenoic Acid (20a). Compound **19a** (800 mg, 2.2 mmol) was treated according to the procedure described for the preparation of **20c** to afford **20a** (300 mg, 0.8 mmol, 38%) as a yellow solid: mp 105−108 °C (*n*-hexane−AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (tt, J = 8.0, 8.0 Hz, 2H), 1.95 (s, 3H), 1.97 (s, 3H), 2.17 (t, J = 8.0 Hz, 2H), 2.63 (t, J = 8.0 Hz, 2H), 4.04 (s, 3H), 7.26 (s, 1H), 7.28 (dd, J = 4.5, 7.5 Hz, 1H), 7.56 (br d, J = 7.5 Hz, 1H), 8.47 (br d, J = 4.5 Hz, 1H), 8.64 (br s, 1H). Anal. ($C_{20}H_{21}NO_5 \cdot 0.5H_2O$) C, H, N.

(*E*)-3-(2-Methoxy-3,6-dimethyl-1,4-benzoquinon-5-yl)-2-[4-(3-pyridyl)butyl]-2-propenoic Acid (20b). Compound **19b** (1.0 g, 2.5 mmol) was treated according to the procedure described for the preparation of **20c** to afford **20b** (390 mg, 1.1 mmol, 44%) as a yellow solid: mp 124−125 °C (*n*-hexane−AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42−1.63 (m, 4H), 1.95 (s, 6H), 2.17 (t, J = 7.0 Hz, 2H), 2.62 (t, J = 7.0 Hz, 2H), 4.03 (s, 3H), 7.25 (s, 1H), 7.31 (dd, J = 5.0, 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 8.46 (br d, J = 5.0 Hz, 1H), 8.48 (br s, 1H). Anal. ($C_{21}H_{23}NO_5 \cdot 0.4H_2O$) C, H, N.

(*E*)-3-(2-Methoxy-3,6-dimethyl-1,4-benzoquinon-5-yl)-2-[6-(3-pyridyl)hexyl]-2-propenoic Acid (20d). Compound **19d** (1.4 g, 3.3 mmol) was treated according to the procedure described for the preparation of **20c** to afford **20d** (480 mg, 1.2 mmol, 36%) as a yellow solid: mp 119−121 °C (*n*-hexane−AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15−1.34 (m, 4H), 1.44 (tt, J = 7.5, 7.5 Hz, 2H), 1.58 (tt, J = 7.5, 7.5 Hz, 2H), 1.95 (s, 6H), 2.12 (t, J = 7.5 Hz, 2H), 2.60 (t, J = 7.5 Hz, 2H), 4.03 (s, 3H), 7.25 (s, 1H), 7.32 (dd, J = 5.5, 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 8.47 (dd, J = 1.0, 5.5 Hz, 1H), 8.50 (d, J = 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.9, 13.5, 28.0, 28.7, 29.2, 30.8, 33.0, 60.9, 123.9, 128.9, 131.1, 137.5, 138.8, 139.1, 139.71, 139.74, 145.3, 148.0, 155.6, 169.9, 183.4, 186.8. Anal. ($C_{23}H_{27}NO_5 \cdot 0.5H_2O$) C, H, N.

(*E*)-3-(2-Ethoxy-3,6-dimethyl-1,4-benzoquinon-5-yl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (20e). Compound **19e** (400 mg, 0.94 mmol) was treated according to the procedure described for the preparation of **20c** to afford **20e** (125 mg, 0.31 mmol, 34%) as a yellow solid: mp 116−118 °C (*n*-hexane−AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23−1.29 (m, 2H), 1.38 (t, J = 7.0 Hz, 3H), 1.46−1.55 (m, 2H), 1.56−1.64 (m, 2H), 1.95 (s, 3H), 1.96 (s, 3H), 2.12 (t, J = 8.0 Hz, 2H), 2.60 (t, J = 8.0 Hz, 2H), 4.28 (q, J = 7.0 Hz, 2H), 7.25−7.29 (m, 2H), 7.55 (dt, J = 1.0, 8.0 Hz, 1H), 8.45 (dd, J = 1.0, 5.0 Hz, 1H), 8.50 (d, J = 1.0 Hz, 1H). Anal. ($C_{23}H_{27}NO_5 \cdot 0.3H_2O$) C, H, N.

(*E*)-3-[2-(*n*-Heptyloxy)-3,6-dimethyl-1,4-benzoquinon-5-yl]-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (20f). Compound **19f** (350 mg, 0.7 mmol) was treated according to the procedure described for the preparation of **20c** to afford **20f** (100 mg, 0.21 mmol, 31%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (t, J = 7.0 Hz, 3H), 1.20−1.40 (m, 8H), 1.40−1.55 (m, 4H), 1.60 (tt, J = 7.0, 7.0 Hz, 2H), 1.74 (tt, J = 7.0, 7.0 Hz, 2H), 1.95 (s, 3H), 1.99 (s, 3H), 2.13 (t, J = 7.0 Hz, 2H), 2.60 (t, J = 7.0 Hz, 2H), 4.20 (t, J = 7.0 Hz, 2H), 7.23 (s, 1H), 7.25 (dd, J = 5.0, 8.0 Hz, 1H), 7.53 (br d, J = 8.0 Hz, 1H), 8.43 (d, J = 5.0 Hz, 1H), 8.49 (br s, 1H); HRMS ($C_{28}H_{37}NO_5$) calcd 468.2750 (MH^+), found, 468.2740.

(*E*)-3-(3-Methoxy-2,6-dimethyl-1,4-benzoquinon-5-yl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (20g). Compound **19g** (390 mg, 2.2 mmol) was treated according to the procedure described for the preparation of **20c** to afford **20g** (280 mg, 0.73 mmol, 33%) as a yellow solid: mp 128−130 °C

(*n*-hexane−AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (tt, J = 7.6, 7.6 Hz, 2H), 1.51 (tt, J = 7.6, 7.6 Hz, 2H), 1.61 (tt, J = 7.6, 7.6 Hz, 2H), 1.97 (s, 3H), 1.98 (s, 3H), 2.13 (t, J = 7.2 Hz, 2H), 2.61 (t, J = 8.0 Hz, 2H), 3.98 (s, 3H), 7.23 (s, 1H), 7.28 (dd, J = 2.4, 7.2 Hz, 1H), 8.45 (d, J = 4.8 Hz, 1H), 8.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0, 14.0, 27.9, 28.9, 29.2, 30.7, 32.7, 61.0, 123.8, 128.6, 130.4, 137.4, 138.8, 139.2, 141.8, 145.3, 148.1, 155.5, 169.6, 182.0, 188.0. Anal. ($C_{22}H_{25}NO_5 \cdot 0.3H_2O$) C, H, N.

(*E*)-3-(3-Methoxy-2,6-dimethyl-1,4-benzoquinon-5-yl)-2-[6-(3-pyridyl)hexyl]-2-propenoic Acid (20h). Compound **19h** (220 mg, 0.52 mmol) was treated according to the procedure described for the preparation of **20c** to afford **20h** (31 mg, 0.08 mmol, 15%) as a yellow solid: mp 108−110 °C (*n*-hexane−AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19−1.33 (m, 4H), 1.45 (tt, J = 7.2, 7.2 Hz, 2H), 1.58 (tt, J = 6.8, 6.8 Hz, 2H), 1.97 (s, 3H), 1.98 (s, 3H), 2.13 (t, J = 7.6 Hz, 2H), 2.60 (t, J = 8.0 Hz, 2H), 4.99 (s, 3H), 7.24 (d, J = 1.2 Hz, 1H), 7.29 (dd, J = 2.4, 7.2 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 8.46 (d, J = 4.8 Hz, 1H), 8.49 (s, 1H). Anal. ($C_{23}H_{27}NO_5 \cdot 0.1H_2O$) C, H, N.

(*E*)-3-[3-(*n*-Butyloxy)-2,6-dimethyl-1,4-benzoquinon-5-yl]-2-[3-(3-pyridyl)propyl]-2-propenoic Acid (20i). Compound **19i** (1.3 g, 3.0 mmol) was treated according to the procedure described for the preparation of **20c** to afford **20i** (460 mg, 1.2 mmol, 39%) as a yellow solid: mp 92−95 °C (*n*-hexane−AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 6.8 Hz, 3H), 1.45 (q, J = 7.2 Hz, 2H), 1.70 (tt, J = 4.8, 4.8 Hz, 2H), 1.90 (br s, 2H), 1.95 (s, 3H), 1.99 (s, 3H), 2.13−2.27 (m, 2H), 2.53−2.66 (m, 2H), 4.12 (t, J = 7.6 Hz, 2H), 7.25 (br s, 2H), 7.53 (d, J = 6.0 Hz, 1H), 8.43 (br s, 1H), 8.61 (br s, 1H); HRMS ($C_{23}H_{27}NO_5$) calcd 397.1889 (M^+), found 397.1904. Anal. ($C_{23}H_{27}NO_5$) H, N; C: calcd, 69.50; found, 65.83.

(*E*)-3-[3-(*n*-Butyloxy)-2,6-dimethyl-1,4-benzoquinon-5-yl]-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (20j). Compound **19j** (1.1 g, 2.4 mmol) was treated according to the procedure described for the preparation of **20c** to afford **20j** (410 mg, 0.96 mmol, 40%) as a yellow solid: mp 97−100 °C (*n*-hexane−AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.4 Hz, 3H), 1.26 (tt, J = 7.6, 7.6 Hz, 2H), 1.40−1.52 (m, 4H), 1.60 (tt, J = 7.6, 7.6 Hz, 2H), 1.70 (tt, J =7.6, 7.6 Hz, 2H), 1.99 (s, 3H), 2.00 (s, 3H), 2.13 (t, J = 8.0 Hz, 2H), 2.60 (t, J = 8.0 Hz, 2H), 4.20 (t, J = 8.0 Hz, 2H), 7.24 (s, 1H), 7.28 (dd, J = 2.4, 7.6 Hz, 1H), 7.55 (d, J = 6.4 Hz, 1H), 8.45 (d, J = 4.0 Hz, 1H), 8.49 (s, 1H). Anal. ($C_{25}H_{31}NO_5 \cdot 0.5H_2O$) C, H, N.

(*E*)-3-(3-Ethoxy-2,6-dimethyl-1,4-benzoquinon-5-yl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (20k). Compound **19k** (5.0 g, 11.7 mmol) was treated according to the procedure described for the preparation of **20c** to afford **20k** (2.0 g, 5.0 mmol, 43%) as a yellow solid: mp 105−108 °C (*n*-hexane−AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (tt, J = 7.6, 7.6 Hz, 2H), 1.34 (t, J = 6.8 Hz, 3H), 1.50 (tt, J = 7.6, 7.6 Hz, 2H), 1.59 (tt, J = 7.6, 7.6 Hz, 2H), 1.97 (s, 3H), 1.98 (s, 3H), 2.13 (t, J = 7.2 Hz, 2H), 2.59 (t, J = 8.0 Hz, 2H), 4.26 (q, J = 7.2 Hz, 2H), 7.24 (s, 1H), 7.29 (dd, J = 2.8, 7.6 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 8.46 (d, J = 4.8 Hz, 1H), 8.48 (s, 1H); HRMS ($C_{23}H_{27}NO_5$) calcd 397.1889 (M^+), found 397.1886. Anal. ($C_{23}H_{27}NO_5$) H, N; C: calcd, 69.50; found, 67.57.

(*E*)-3-[3-(Heptyloxy)-2,6-dimethyl-1,4-benzoquinon-5-yl]-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (20l). Compound **19l** (560 mg, 1.1 mmol) was treated according to the procedure described for the preparation of **20c** to afford **20l** (100 mg, 0.21 mmol, 19%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 8.0 Hz, 3H), 1.22−1.36 (m, 8H), 1.39 (tt, J = 7.6, 7.6 Hz, 2H), 1.49 (tt, J = 7.6, 7.6 Hz, 2H), 1.60 (tt, J = 7.6, 7.6 Hz, 2H), 1.70 (q, J = 8.0 Hz, 2H), 1.97 (s, 3H), 1.99 (s, 3H), 2.14 (t, J = 7.6 Hz, 2H), 2.60 (t, J = 7.6 Hz, 2H), 4.08 (t, J = 8.0 Hz, 2H), 7.24 (t, J = 4.8 Hz, 1H), 7.28 (s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 8.44 (d, J = 4.8 Hz, 1H), 8.48 (s, 1H); HRMS ($C_{28}H_{37}NO_5$) calcd 468.2750 (MH^+), found 468.2746.

(*E*)-3-[3-(Cyclohexyloxy)-2,6-dimethyl-1,4-benzoquinon-5-yl]-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (20m). Compound **19m** (380 mg, 0.8 mmol) was treated according to the procedure described for the preparation of **20c** to afford **20m** (100 mg, 0.22 mmol, 27%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (dq, J = 4.0, 12.0 Hz, 2H), 1.20−1.30 (m, 4H), 1.49 (tt, J = 8.0, 8.0 Hz, 2H), 1.59 (tt, J = 8.0, 8.0 Hz, 2H), 1.65−1.85 (m, 7H), 1.95 (s, 3H), 1.98 (s, 3H), 2.12 (t, J = 8.0 Hz, 2H), 2.59 (t, J = 8.0 Hz, 2H), 3.99 (d, J = 8.0 Hz, 2H), 7.23 (s, 1H), 7.27 (d, J = 7.2 Hz, 1H), 7.53 (d, J = 7.2 Hz, 1H), 8.45 (br s, 1H), 8.49 (br s, 1H); HRMS ($C_{28}H_{35}NO_5$) calcd 466.2593 (MH^+), found 466.2572.

(*E*)-3-(6-Methoxy-2,3-dimethyl-1,4-benzoquinon-5-yl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (20n). Compound **19n** (1.9 g, 4.6 mmol) was treated according to the procedure described for the preparation of **20c** to afford **20n** (150 mg, 0.36 mmol, 8%) as a yellow solid: mp 148−149 °C (*n*-hexane−AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (tt, J = 7.5, 7.5 Hz, 2H), 1.51 (tt, J = 7.5, 7.5 Hz, 2H), 1.60 (tt, J = 7.5, 7.5 Hz, 2H), 2.03 (s, 3H), 2.04 (s, 3H), 2.18 (t, J = 7.5 Hz, 2H), 2.59 (t, J = 7.5 Hz, 2H), 3.96 (s, 3H), 7.27 (dd, J = 5.0, 8.0 Hz, 1H), 7.30 (s, 1H), 7.55 (br d, J = 8.0 Hz, 1H), 8.45 (dd, J = 1.5, 5.0 Hz, 1H), 8.48 (d, J = 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 12.7, 27.7, 28.8, 29.4, 30.6, 32.7, 61.1, 120.3, 123.8, 129.3, 137.5, 138.8, 139.1, 139.3, 141.2, 145.3, 148.1, 154.6, 170.0, 183.3, 186.5; HRMS ($C_{22}H_{25}NO_5$) calcd 383.1733 (M^+), found 383.1748. Anal. ($C_{22}H_{25}NO_5 \cdot 0.5$AcOEt) C, N; H: calcd, 6.84; found, 6.33.

(*E*)-3-(6-Methoxy-2,3-dimethyl-1,4-benzoquinon-5-yl)-2-[6-(3-pyridyl)hexyl]-2-propenoic Acid (20o). Compound **19o** (1.3 g, 3.0 mmol) was treated according to the procedure described for the preparation of **20c** to afford **20o** (175 mg, 0.44 mmol, 15%) as a yellow solid: mp 64−66 °C (*n*-hexane−AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.31 (m, 4H), 1.43 (tt, J = 7.5, 7.5 Hz, 2H), 1.56 (tt, J = 7.5, 7.5 Hz, 2H), 2.01 (s, 3H), 2.03 (s, 3H), 2.15 (t, J = 7.5 Hz, 2H), 2.55 (t, J = 7.5 Hz, 2H), 3.94 (s, 3H), 7.25 (t, J = 8.0 Hz, 1H), 7.27 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 8.46 (br s, 2H); HRMS ($C_{23}H_{27}NO_5$) calcd 397.1889 (M^+), found 397.1904. Anal. ($C_{23}H_{27}NO_5 \cdot 0.7H_2O$) C, N; H: calcd, 6.98; found, 6.44.

(*E*)-3-(6-Methoxy-3-methyl-1,4-benzoquinon-5-yl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (20p). Compound **19p** (2.5 g, 6.3 mmol) was treated according to the procedure described for the preparation of **20c** to afford **20p** (100 mg, 0.27 mmol, 4%) as a yellow solid: mp 110−112 °C (*n*-hexane−AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (tt, J = 8.0, 8.0 Hz, 2H), 1.34 (tt, J = 8.0, 8.0 Hz, 2H), 1.45 (tt, J = 8.0, 8.0 Hz, 2H), 1.93 (s, 3H), 2.03 (t, J = 8.0 Hz, 2H), 2.48 (t, J = 8.0 Hz, 2H), 3.91 (s, 3H), 6.67 (s, 1H), 6.99 (s, 1H), 7.24 (dd, J = 4.0, 7.0 Hz, 1H), 7.53 (dt, J = 1.0, 4.0 Hz, 1H), 8.34 (br s, 2H); HRMS ($C_{21}H_{23}NO_5$) calcd 370.1654 (MH^+), found 370.1650.

(*E*)-3-(2,3-Dimethoxy-6-methyl-1,4-benzoquinon-5-yl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (20q). A solution of (*E*)-3-[2,3,4-trimethoxy-5-(methoxymethoxy)-6-methylphenyl]-2-[5-(3-pyridyl)pentyl]-2-propenoic acid (**19q**) (760 mg, 1.6 mmol) in acetone (20 mL) was treated with concentrated HCl (5 mL) with cooling in an ice bath. The mixture was stirred for 1 h, and the pH thereof was adjust to 5 with a saturated solution of sodium hydrogen carbonate. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried, and evaporated to afford (*E*)-3-(2,3,4-trimethoxy-5-hydroxy-6-methylphenyl)-2-[5-(3-pyridyl)pentyl]-2-propenoic acid (760 mg, 1.6 mmol, >99%) as a colorless oil. To a solution of this product in ethyl acetate (30 mL) was added iron(III) chloride hexahydrate (3 g) at room temperature. The mixture was stirred for 1 h followed by the addition of water, and the whole was extracted with ethyl acetate twice. The organic layer was washed with brine, dried, and evaporated. The crude residue was purified by flash column chromatography on silica gel (solvent: ethyl acetate−*n*-hexane = 1:2−1:1) to afford **20q** (200 mg, 0.5 mmol, 31%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07−1.86 (m, 6H), 1.94 (s, 3H), 1.95−2.77 (m, 4H), 3.97 (s, 3H), 4.00 (s, 3H), 6.77−7.60 (m, 3H), 8.29−8.57 (m, 2H); HRMS ($C_{22}H_{25}NO_6$) calcd 400.1760 (MH^+), found 400.1747.

(*E*)-3-(2,5-Dihydroxy-4-methoxy-3,6-dimethylphenyl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (21c). (*E*)-3-(2-Methoxy-3,6-dimethyl-1,4-benzoquinon-5-yl)-2-[5-(3-pyridyl)-pentyl]-2-propenoic acid (**20c**) (1.0 g, 2.6 mmol) was suspended in ethyl acetate (150 mL), and the suspension was well mixed with a solution of sodium hydrosulfite (2 g) in water (50 mL). The organic layer was separated, dried, and evaporated to give

the hydroquinone **21c** (660 mg, 1.7 mmol, 66%) as a white amorphous substance: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (tt, J = 7.0, 7.0 Hz, 2H), 1.44 (tt, J = 7.0, 7.0 Hz, 2H), 1.51 (tt, J = 7.0, 7.0 Hz, 2H), 2.06 (s, 3H), 2.17 (s, 3H), 2.23 (t, J = 7.0 Hz, 2H), 2.54 (t, J = 7.0 Hz, 2H), 3.76 (s, 3H), 5.22 (br s, 2H), 7.26 (dd, J = 5.5, 7.0 Hz, 1H), 7.43 (s, 1H), 7.51 (dd, J = 1.5, 7.0 Hz, 1H), 8.40−8.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.5, 12.9, 27.7, 27.8, 28.3, 30.3, 32.6, 60.8, 114.9, 118.4, 119.6, 123.9, 134.0, 137.8, 139.0, 139.4, 140.7, 143.6, 144.9, 145.5, 147.6, 171.1. IR (KBr) 3340, 1690, 1635 cm^{-1}. Anal. ($C_{22}H_{27}NO_5$·HCl) C, H, N (elemental analysis by using HCl salt).

***(E)*-3-(2,5-Dihydroxy-3-methoxy-4,6-dimethylphenyl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (21g).** Compound **20g** (220 mg, 0.57 mmol) was treated according to the procedure described for the preparation of **21c** to afford **21g** (180 mg, 0.45 mmol, 79%) as a white amorphous substance: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (tt, J = 7.0, 7.0 Hz, 2H), 1.38−1.52 (m, 4H), 2.03 (s, 3H), 2.22 (t, J = 7.0 Hz, 2H), 2.23 (s, 3H), 2.49 (t, J = 7.0 Hz, 2H), 3.73 (s, 3H), 7.21 (dd, J = 5.2, 8.0 Hz, 1H), 7.45 (br d, J = 8.0 Hz, 1H), 7.56 (br s, 2H), 8.24 (d, J = 2.0 Hz, 1H), 8.40 (dd, J = 1.6, 4.8 Hz, 1H); HRMS ($C_{22}H_{27}NO_5$) calcd 385.1889 (M^+), found 385.1928.

***(E)*-3-(2,5-Dihydroxy-6-methoxy-3,6-dimethylphenyl)-2-[5-(3-pyridyl)pentyl]-2-propenoic Acid (21n).** Compound **20n** (100 mg, 0.26 mmol) was treated according to the procedure described for the preparation of **21c** to afford **21n** (80 mg, 0.21 mmol, 80%) as a white amorphous substance: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (tt, J = 7.0, 7.0 Hz, 2H), 1.30−1.40 (m, 4H), 2.00 (s, 3H), 2.02 (s, 3H), 2.13 (t, J = 7.0 Hz, 2H), 2.41 (t, J = 7.0 Hz, 2H), 3.46 (s, 3H), 7.26 (dd, J = 5.5, 7.0 Hz, 1H), 7.34 (s, 1H), 7.50 (dd, J = 1.5, 7.0 Hz, 1H), 7.64 (s, 1H), 8.03 (s, 1H), 8.31−8.36 (m, 2H); HRMS ($C_{22}H_{27}NO_5$) calcd 385.1889 (M^+), found 385.1916.

Inhibition of Eicosanoid Production (*in Vitro*). Glycogen-Induced Peritoneal Cells of Rats. Mixed peritoneal leukocytes, including polymorphonuclear leukocytes (PMNs) and mononuclear leukocytes, were elicited from male F344 rats (Charles River) by an ip injection of 10 mL of 6% glycogen solution (type II; Sigma), according to Moroney et al.[27] The cells were suspended in Hanks balanced salt solution (HBSS) free of Ca^{2+} and Mg^{2+} at a concentration of 5×10^6 cells/mL. Aliquots (0.1 mL) of the cell suspensions were preincubated for 5 min at 37 °C with test compound or vehicle (0.1% DMSO/0.1% BSA) in 96-well plates (Costar). The reaction was initiated by adding A23187 (4 μM). At the end of incubation (10 min at 37 °C), the reaction was terminated by adding BW755C (100 μM). The incubation mixtures were centrifuged (110*g*, 5 min), and aliquots of the supernatants were analyzed for LTB_4, TXB_2, and PGE_2 by radioimmunoassay (Amersham, NEM).

Human Whole Blood. Fresh blood was obtained from healthy volunteers and anticoagulated with heparin (10 U/mL). Aliquots (0.4 mL) were preincubated with test compound or vehicle (0.1% DMSO/0.1% BSA) for 5 min at 37 °C. A23187 (40 μM; Calbiochem, CA) was added, and the blood samples were incubated for an additional 20 min. Plasma was separated by centrifugation and analyzed for LTB_4, TXB_2, and PGE_2 by radioimmunoassay.

Human Peripheral Blood Neutrophils. Human blood was anticoagulated with heparin (10 U/mL). Red cells were first removed by dextran sedimentation (6% dextran, 37 °C, 60 min). Neutrophils were sedimented by Percoll (Sigma) density gradient centrifugation and resuspended in Hanks balanced salt solution (HBSS) free of Ca^{2+} and Mg^{2+} at a concentration of 1×10^6 cells/mL. Aliquots (0.1 mL) were preincubated with test compound or vehicle (0.1% DMSO/0.1% BSA) for 5 min at 37 °C. Eicosanoid synthesis was induced by adding A23187 (4 μM). After 10 min, the cells were pelleted by centrifugation (110*g*, 10 min). Cell-free supernatants were assayed for LTB_4 by radioimmunoassay.

RBL-1 Cell 5-Lipoxygenase. RBL-1 cells (2×10^6 cells/mL), suspended in 50 mM phosphate buffer, pH 7.4, containing 0.25 M sucrose and 1 mM EDTA, were homogenized by sonication (Branson Sonifier 185, 5 microtip setting) at 0 °C. Aliquots (0.5 mL) of the homogenates were preincubated for 5 min at 37 °C with test compound or vehicle (0.1% DMSO/0.1% BSA) in the presence of 2 mM glutathione. The reaction was initiated by addition of arachidonic acid (0.2 mM). After incubation for 10 min at 37 °C, the reaction was stopped by adding 0.05 μL of 2 N formic acid. Then, 0.2 mL of $CHCl_3$/MeOH (4:1) and 0.2 mL of saturated NaCl solution were added. The samples were centrifuged for 5 min at 110*g*, and the organic phases were analyzed for 5-HETE by HPLC (C18ODS, Nucleosil, MeOH:H_2O:AcOH (75:25:0.01), 1.5 mL/min).

Human Platelets. Platelet-rich plasma was obtained from citrated whole blood by centrifugation (110*g*, 10 min) and mixed with anticoagulant solution (ACD-A solution, Terumo Co., Ltd., Japan). The platelet suspension was centrifuged (1000*g*, 10 min) and resuspended in Tris-HCl−saline, pH 7.4, containing 10 μM indomethacin at a concentration of 3×10^8 cells/mL. Aliquots (0.2 mL) of the platelet suspension were preincubated with test compound or vehicle alone (0.1% DMSO/0.1% BSA) for 5 min at 25 °C before addition of PGH_2 (1 μg/mL). After 3 min at 25 °C, the reaction was terminated by adding 0.8 mL of 55 mM citrate/100% ethanol solution. The cell suspensions were centrifuged (110*g*, 10 min), and the supernatants were assayed for TXB_2 by radioimmunoassay.

Human Platelet Thromboxane Synthetase. Platelets were separated from platelet-rich plasma by centrifugation (1000*g*, 10 min, 4 °C), as described above, and resuspended in phosphate-buffered saline (Dulbecco's PBS), pH 7.4. Platelets were homogenized by sonication (Branson Sonifier 185, 5 microtip setting) at 0 °C. The microsome fraction was separated by centrifugation (105000*g*, 60 min) and resuspended in 50 mM Tris-HCl−saline, pH 7.4, containing 10 μM indomethacin. Aliquots (20 μg of protein) of the enzyme preparation were preincubated for 5 min at 25 °C with test compound or vehicle (0.1% DMSO/0.1% BSA). The reaction was initiated by adding PGH_2 (1 μg/mL). After incubation for 1 min at 25 °C, the reaction was terminated by adding 0.8 mL of 55 mM citric acid/100% ethanol solution. The incubation mixture was assayed for TXB_2 by radioimmunoassay.

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