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Article

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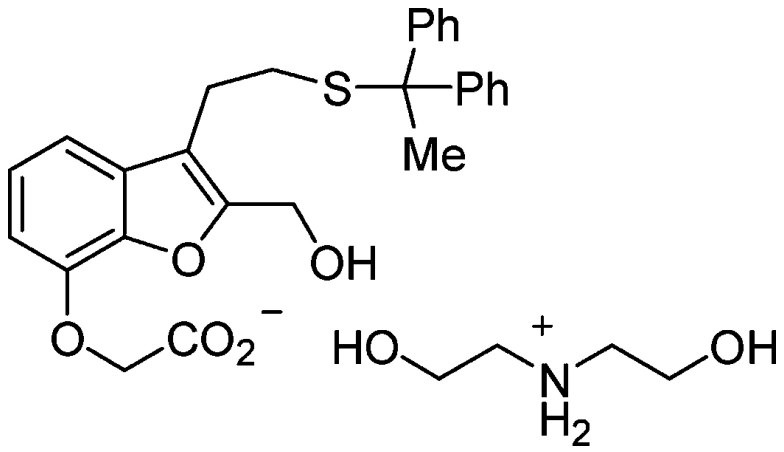

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Development of Dual-Acting Benzofurans for Thromboxane A_2 Receptor Antagonist and Prostacyclin Receptor Agonist: Synthesis, Structure−Activity Relationship, and Evaluation of Benzofuran Derivatives

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Prostacyclin (PGI_2) is an unstable, powerful endogenous inhibitor of platelet aggregation, and thromboxane A_2 (TXA_2) is an unstable endogenous arachidonic acid metabolite that plays a pivotal role in platelet aggregation and vasoconstriction. The balance between TXA_2 and PGI_2 greatly affects maintenance of the homeostasis of the circulatory system. A novel series of benzofuran-7-yloxyacetic acid derivatives was discovered as potent dual-acting agents to block the thromboxane A_2 receptor and to activate the prostacyclin receptor. Synthesis, structure−activity relationship, and in vitro and ex vivo pharmacology of this series of compounds are described. The most potent in the series was {3-[2-(1,1-diphenylethylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy}acetic acid diethanolamine salt (**7**) with K_i of 4.5 nM for thromboxane receptor antagonism and K_i of 530 nM for prostacyclin receptor agonism. Remarkably, compound **7** is a promising candidate for novel treatment as an antithrombotic agent with other cardiovascular actions to avoid hypotensive side effects.

Introduction

Thromboxane A_2 (TXA_2) (**1**), discovered by Samuelsson, is an unstable endogenous arachidonic acid metabolite that plays a pivotal role in platelet aggregation and vasoconstriction[1] and has been implicated as a contributor to cardiovascular, renal, and pulmonary diseases.[2,3] Because of the lack of clinical efficacy with these agents,[4] a combined therapy using thromboxane receptor antagonists (TRAs) and thromboxane synthase inhibitors (TSIs) has been developed. This therapy has the advantage that its TSI activity would prevent the biosynthesis of TXA_2 while the accumulated PGH_2 would be redirected to produce beneficial prostaglandin metabolites such as prostacyclin (PGI_2), PGD_2, and PGE_2. However, this conventional TRA/TSI therapy exhibits unsatisfactory clinical effects.[5]

Prostacyclin (**2**), discovered by Vane, is a powerful endogenous inhibitor of platelet aggregation and also plays an important role in biological homeostasis as an endogenous autacoid distributed widely in various tissues.[6] Although these actions attract notice in the cardiovascular field, the therapeutic application of PGI_2 itself is limited by both chemical and metabolic instability because of its labile enol−ether moiety. Thus, the extensive efforts that have been focused on the synthesis of PGI_2 mimics were directed toward the stabilization of the enol−ether moiety (i.e., **3**).[7,8] Recently, nonprostanoids PGI_2 mimetics with chemical and metabolic instability have been reported (i.e., **4**)[9−14] (Chart 1).

TXA_2 and PGI_2, both of which are synthesized from arachidonic acid, have opposite effects on platelet aggregation. Also, the balance between TXA_2 and PGI_2 greatly affects maintenance of the homeostasis of the circulatory system. In the case of ischemic disorders, the TXA_2/PGI_2 balance is shifted to the TXA_2 side, and phenomena such as platelet activation, subsequent thrombogenesis, and vascular contraction appear. Thus, it is clinically important to achieve the proper TXA_2/PGI_2 balance. A combination of an agent for inhibiting TXA_2 activity and an agent acting as a PGI_2 receptor agonist is thought to be effective. Moreover, researchers at Schering AG reported that the PGI_2 mimetic **5** (iloprost) showed strong antithrombotic action when it was combined with the TXA_2/PGH_2 receptor antagonist **6** (sulotroban).[15,16] Therefore, we are interested in developing agents that combine the TXA_2 receptor (TP) antagonist activity with prostacyclin receptor (IP) agonist activity within a single molecule. Such agents would not only maximize the beneficial effects of each agent but also address the potential clinical problem of using two drugs with different pharmacokinetics. Moreover, one could expect a synergistic effect from combining two therapeutic actions in a single chemical entity to avoid the hypotensive effect of PGI_2.

Chart 1. Chemical Structures of Thromboxane A_2, Prostacyclin, Prostacyclin Mimetics, and Thromboxane A_2 Antagonists

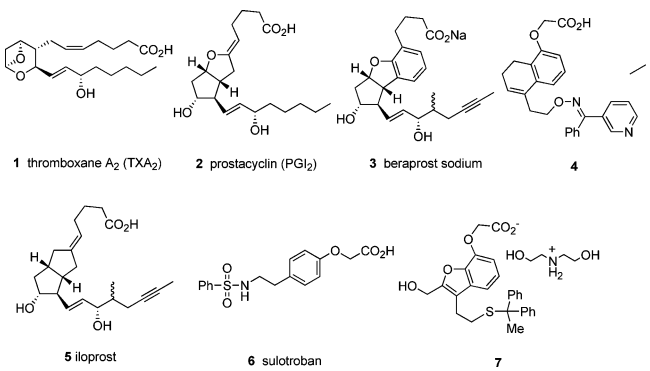

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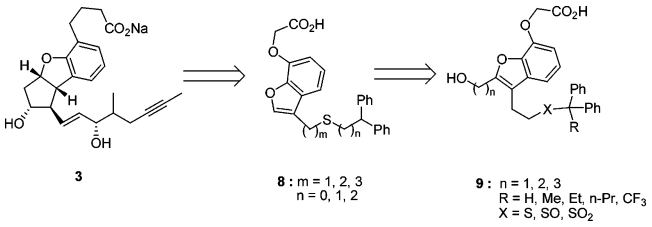
Chart 2. Molecular Design of Benzofuran Derivatives from **3**



In this paper, we report the first dual-acting benzofuran **7** that possesses TXA_2 antagonism and PGI_2 agonism within a single molecule. We describe the design, synthesis, and the biological evaluation of benzofuran derivatives.

Chemistry

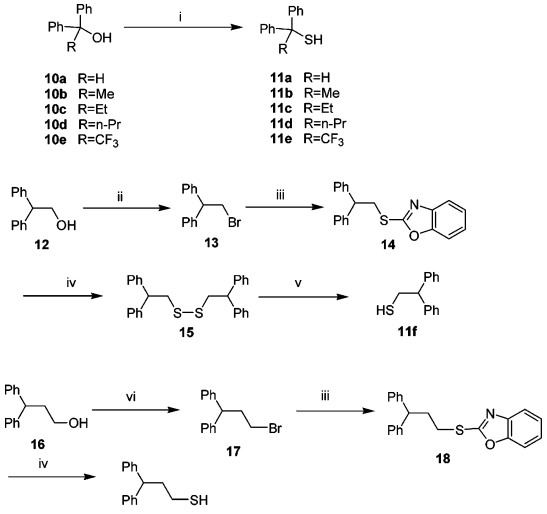
We started to design our new compounds from **3**. To avoid enantiomeric problems, we chose benzofuran, which is regarded as a characteristic structure of **3**, for our scaffold. We chose an oxyacetic acid group for the α-chain and attached it at the 7-position of benzofuran for the following reasons: (1) This derivatization at the 7-position is known to maintain the PGI_2 agonistic properties. (2) This derivatization can avoid ω-oxidation as a route of metabolic degradation of the α-chain. (3) It enables us to shorten synthetic steps. For comparison, we also attached the ω-side chain at the 3-position of benzofuran. A wide range of ω-side chains was screened from a series of functional groups, which we examined in the course of research on **3**. We began with the synthesis and evaluation of compound **8**, which have a sulfide ω-side chain, because some thromboxane antagonists have sulfide groups or sulfonamide groups (i.e., **6**) in their ω-chains.

In the following optimization, we introduced a hydroxyl group at the 2-position of compound **8** through the carbon chain and designed compound **9** to enhance the TXA_2 antagonism and/or the PGI_2 agonism. The hydroxyl group at the 2-position of benzofuran corresponds to that of the 11-position of PGI_2. The product in which the sulfide in compound **9** was oxidized was also screened in the optimization (Chart 2).

Compounds in Tables 1 and 2 were prepared as described in Schemes 1−8. The exploration of conventional methods for thiol synthesis was the first key objective of this project. First, we tried to synthesize thiols **11a**−**e** by alkali hydrolysis of the 2-alkylated isothioureas but only succeeded in the case of **11a**. Isothioureas for **11b**−**e** have undergone elimination reactions to produce styrenes under hydrolytic conditions. Primary thiols (**11f** and **11g**) were synthesized by hydrolysis of 2-mercaptobenzoxazole derivatives. Compounds **11b**−**d** were also obtained in poor yield by this method.

Nishio reported the single-step conversion from secondary and tertiary alcohols to the corresponding thiols by treatment with Lawesson's reagent.[17,18] The original procedure, reported by Nishio, worked well for **11a** but gave low yields for **11b**−**d**. We isolated styrene-type byproducts in the reaction mixtures of **11b**−**d**, which suggests that the thiols produced had undergone elimination reactions to produce styrenes. Moreover, the reaction rate under the original conditions (using DME)

Scheme 1[a]



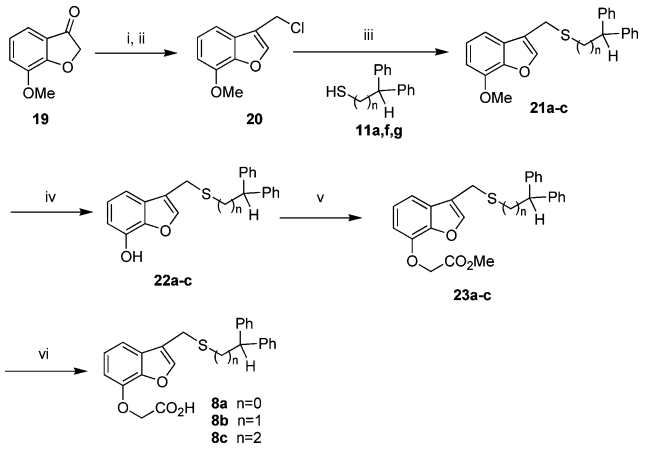
[a] Reagents: (i) Lawesson's reagent, toluene−H_2O; (ii) Ph_3P, CBr_4; (iii) 2-mercaptobenzoxazole, K_2CO_3; (iv) NaOH; (v) Zn, AcOH; (vi) Ph_3P, NBS.

was fast, and the thiol conversion reaction at room temperature was complete within 15 min, which made the control of the reaction difficult. We later found that the addition of a small amount of the water would slow both the thiol conversion and the elimination reactions. By heating the corresponding alcohols with Lawesson's reagent in toluene with water (1 equiv for Lawesson's reagent), we succeeded in obtaining **11b**−**e** in good yield, and our condition also enabled the large-scale preparation of **11b**.

The second key objective of this project was the synthesis of 3-substituted 7-oxybenzofurans. The preparation of compounds **8a**−**c** is described in Scheme 2. We began the synthesis from 7-methoxy-2*H*-benzofuran-3-one (**19**), which was easily prepared by the procedure of Bryant.[19] Thus, compound **19** was treated with lithium chloromethylene to obtain compound **20** in 10% yield. The low yield occurred because the carbonyl group of **19** was easily enolized upon treatment with base, and compound **19** was subject to intermolecular aldol condensation. Compound **20** was coupled with thiols, and the methyl protection of the phenol group at the 7-position of **21a**−**c** was removed using *n*-PrSK. Compounds **22a**−**c** were treated with methyl bromoacetate to introduce the oxyacetic α-chain moiety. Methyl esters of **23a**−**c** were hydrolyzed to give **8a**−**c**.

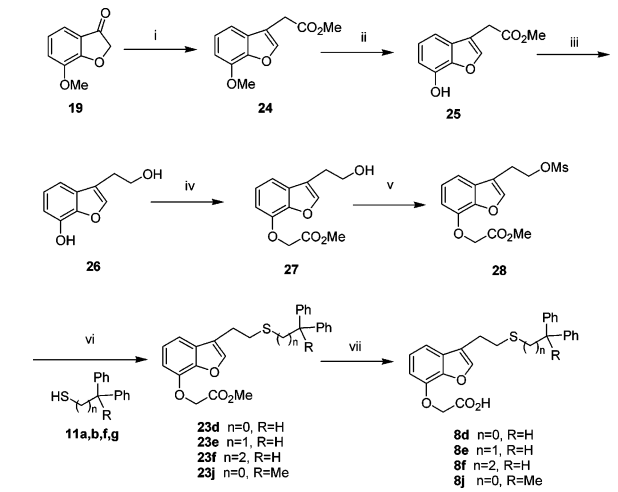
The preparation of compounds **8d**−**f** and **8j** is described in Scheme 3. To avoid the aldol side reaction described in the synthesis of **8a**−**c**, we used the stable Wittig ylide for the preparation of compound **24**. Since this reagent was isolated as a neutral salt-free form, the reaction did not require any base, resulting in the isolation of compound **24** in 46% yield. By use of BBr_3, the methyl protection of phenol group at the 7-position of **24** was selectively removed. The methyl ester of **25** was reduced to the alcohol using $LiAlH_4$, and the resulting compound **26** was treated with methyl bromoacetate to selectively introduce the oxyacetic α-chain moiety at the 7-position of **26**. The alcohol **27** was treated with mesyl chloride, and the resulting mesylate **28** was coupled with thiols. Compounds **8d**−**f** and **8j**

Scheme 2[a]



[a] Reagents: (i) *n*-BuLi, CH_2BrCl; (ii) *p*-toluenesulfonic acid, toluene; (iii) *t*-BuOK, thiols, DMF; (iv) *t*-BuOK, *n*-PrSH, DMF; (v) $BrCH_2CO_2Me$, K_2CO_3, DMF; (vi) NaOH.

Scheme 3[a]



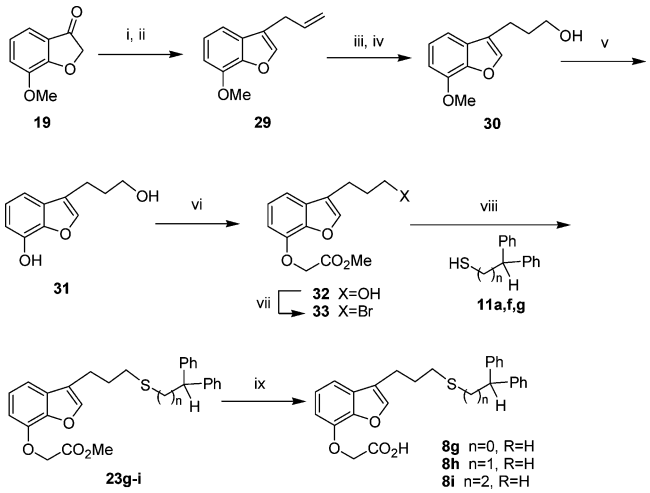
[a] Reagents: (i) Ph_3PCHCO_2Me, xylene; (ii) BBr_3, CH_2Cl_2; (iii) $LiAlH_4$, THF; (iv) $BrCH_2CO_2Me$, K_2CO_3, DMF; (v) methanesulfonyl chloride, Et_3N; (vi) *t*-BuOK, thiols, DMF; (vii) NaOH.

were obtained upon hydrolysis of the methyl ester groups of **23d**−**f** and **23j**.

The preparation of compounds **8g**−**i** is described in Scheme 4. To avoid aldol side reactions described in the synthesis of **8a**−**c**, we used an organocerium reagent, which was prepared in situ from $CeCl_3$ and allylmagnesium bromide.[20,21] Since the basicity of the allylcerium reagent was lower than that in Grignard reagent, compound **29** was obtained in 72% yield, including the dehydration step. The alcohol group was introduced using a hydroboration procedure on **29**. After cleaving the methyl protection of the phenol group at the 7-position of **30** using BBr_3, the oxyacetic α-chain moiety was introduced selectively at the 7-position of **31** by treating with methyl bromoacetate. The alcohol group of **32** was converted to bromine using *N*-bromosuccinimde-Ph_3P, and the resulting compound **33** was coupled with thiols. Compounds **8g**−**i** were obtained by hydrolysis of the methyl ester groups of **23g**−**i**.

The preparation of compounds **9a**−**e** is described in Scheme 5. The 2-substituted benzofuran scaffold was synthesized from **34** using a Dieckmann condensation. The methyl ester of **35** was selectively reduced to the

Scheme 4[a]



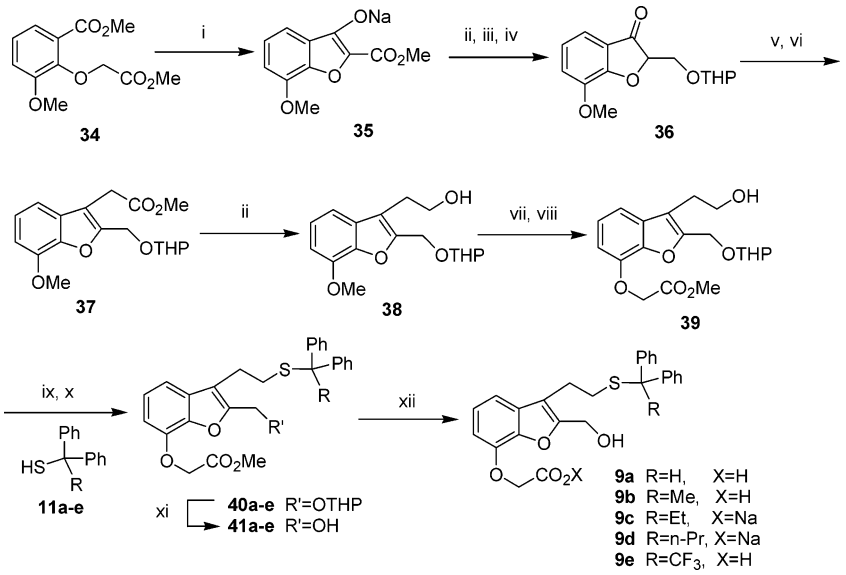
[a] Reagents: (i) allylmagnesium bromide, $CeCl_3$, THF; (ii) *p*-toluenesulfonic acid, benzene; (iii) BH_3-Me_2S, THF; (iv) H_2O_2, NaOH; (v) BBr_3, CH_2Cl_2; (vi) $BrCH_2CO_2Me$, K_2CO_3, DMF; (vii) Ph_3P, *N*-bromosuccinimde; (viii) *t*-BuOK, thiols, DMF; (ix) NaOH.

alcohol using $LiAlH_4$ because the carbonyl group of the 3-position was protected as sodium enolate. During the acidic workup, the carbonyl group of the 3-position was restored. After the protection of the primary alcohol at the 2-position of benzofuran by THP, compound **36** was obtained in 75% yield as a 1:1 mixture of diastereomers. In the synthesis of this series, we also tried a Wittig reaction using the stable ylides to avoid the aldol side reaction as described in the synthesis of **8d**, but the stable Wittig ylide did not react with **36** because of the steric interference by 2-position substitution. Then we performed Reformatski reaction. The reactivity of the Reformatski reagent with each diastereomer was similar, so we used the 1:1 diastereomers mixture of **36** for the scale-up synthesis. The dehydration of the Reformatski product was achieved by using Tf_2O−pyridine in toluene, and compound **37** was obtained in 78% yield in two steps. The methyl ester of compound **37** was reduced to the alcohol using $LiAlH_4$. After cleaving the methyl protection of the phenol group at the 7-position of **38** was cleaved using *n*-PrSK, the oxyacetic α-chain moiety was introduced selectively at this position by treating with methyl bromoacetate. The alcohol **39** was coupled with thiols **11a**−**e** via the mesylate. The THP group of **40a**−**e** was removed under mild acidic conditions, and compounds **9a**−**e** were obtained by hydrolysis of methyl ester groups of **41a**−**e**.

The preparation of compounds **7** and **9h**−**i** is described in Scheme 6. Compound **7** was obtained in 71% yield by treating **9b** with diethanolamine and crystallizing from ethanol. The sulfoxide analogue **9h** was synthesized by direct oxidation of **9b** with H_2O_2. The sulfone analogue **9i** was synthesized by oxidation of **41b** with *m*-CPBA followed by hydrolysis of the methyl ester.

The preparation of **9f** is described in Scheme 7. The 2-hydroxyethylbenzofuran scaffold was also synthesized from **35**, and the side chain at the 2-position of benzofuran was introduced using a Claisen rearrangement. First, the hydroxyl group of enolate **35** was allylated by treating with allyl bromide, and the allylic group then migrated to the 2-position upon heating to give **43**. The ester group of compound **43** underwent hydrolysis

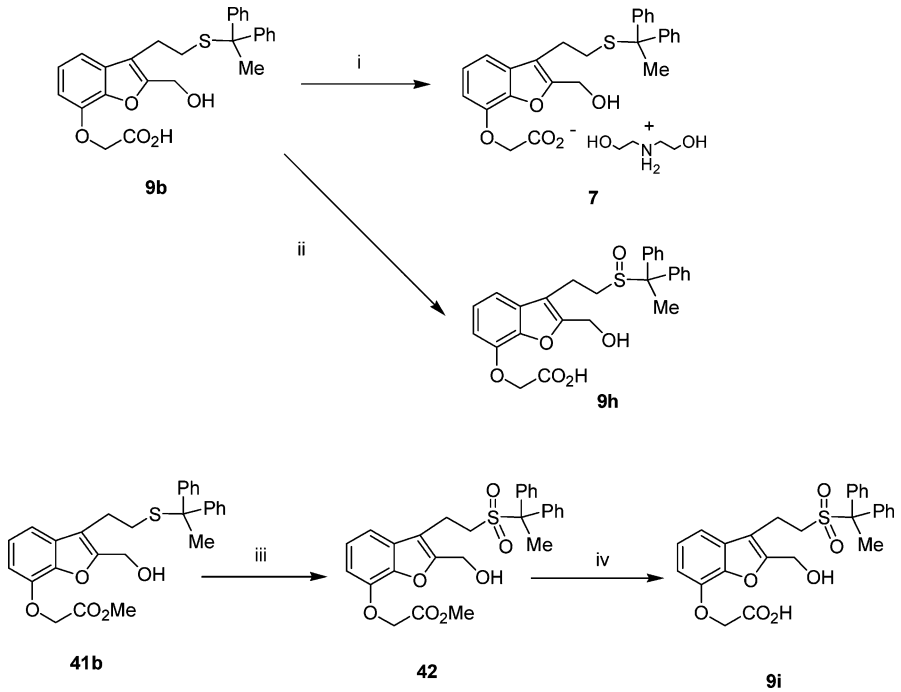
Scheme 5[a]



34 35 36 37 38 39 11a-e

[a] Reagents: (i) NaH, toluene; (ii) $LiAlH_4$, THF; (iii) HCl (aq); (iv) 3,4-dihydro-2*H*-pyran, pyridinium *p*-toluenesulfonate; (v) Zn, $BrCH_2CO_2Me$; (vi) Tf_2O, pyridine; (vii) *t*-BuOK, *n*-PrSH, DMF; (viii) $BrCH_2CO_2Me$, K_2CO_3, DMF; (ix) methanesulfonyl chloride, Et_3N; (x) *t*-BuOK, thiols, DMF; (xi) pyridinium *p*-toluenesulfonate, MeOH; (xii) NaOH.

Scheme 6[a]



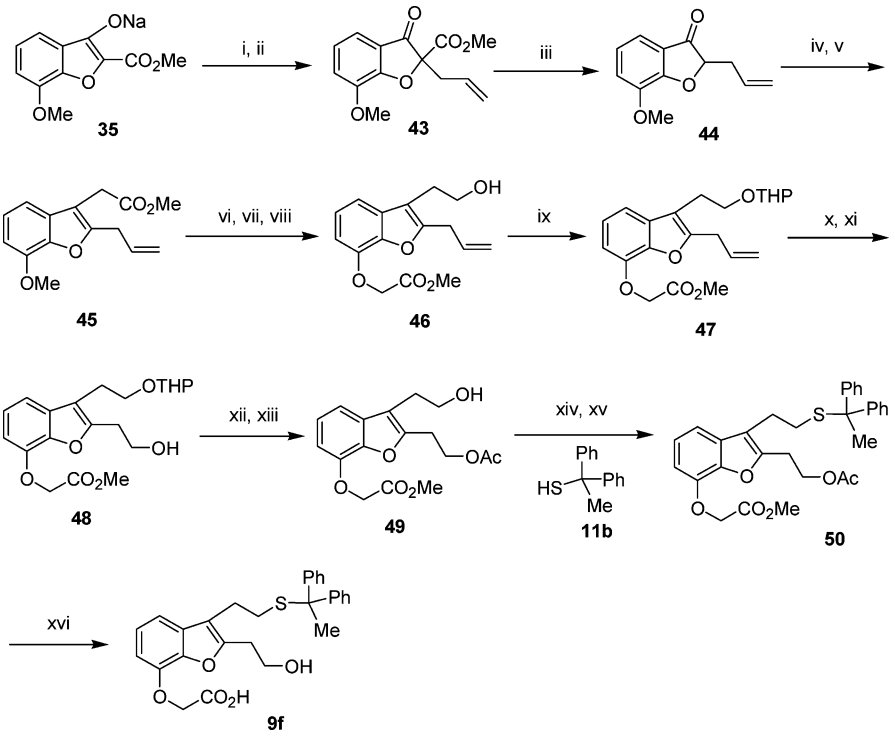
9b 7 9h 41b 42 9i

[a] Reagents: (i) diethanol amine, EtOH; (ii) H_2O_2, MeOH; (iii) *m*-CPBA; (iv) NaOH.

and decarboxylation under acidic condition. The side chain at the 3-position of benzofuran was introduced using Reformatski reaction, and the dehydration of the Reformatski product was performed using *p*-toluenesulfonic acid. After cleaving the methyl protection of the phenol group at the 7-position of **45** using BBr_3, the methyl ester was reduced to the alcohol by $LiAlH_4$. Then, the oxyacetic α-chain moiety was introduced selectively at the 7-position by treating with methyl bromoacetate. The primary alcohol of **46** was protected with THP, followed by cleavage of the olefin at the 2-position of **47** using OsO_4−$NaIO_4$. The alcohol of the 2-position side chain of compound **48** was protected with acetyl group, and the THP group was removed. After the coupling with thiol **11b** via the mesylate of **49**, compound **9f** was obtained by hydrolysis of the methyl ester and the acetyl group.

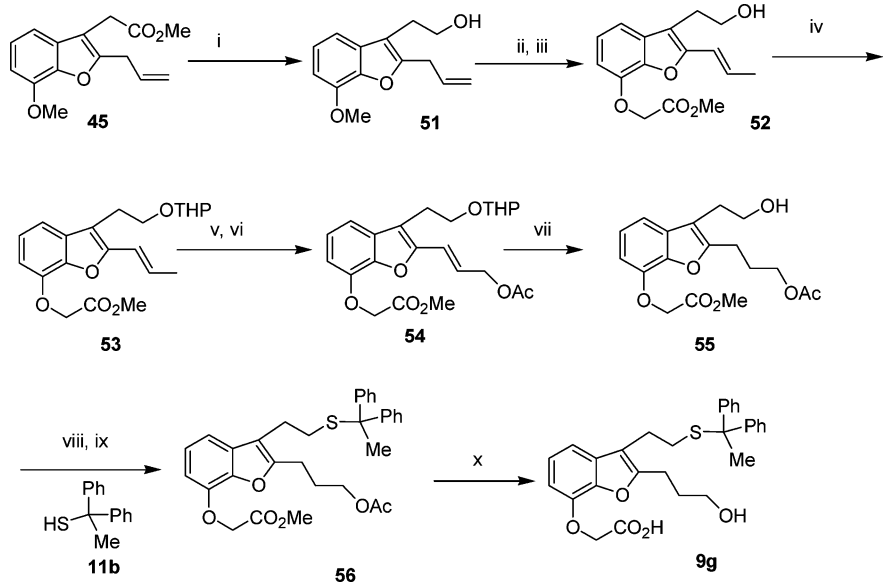
The preparation of **9g** is described in Scheme 8. We planned to introduce a hydroxyl group by using hydroboration of the olefin. After the reduction of the methyl ester on the side chain of compound **45** to alcohol **51** by $LiAlH_4$, the methyl protection of the phenol group at 7-position was removed using *n*-PrSK instead of BBr_3, which was accompanied by double bond isomerization of the olefin at the 2-position. Then, we changed the original plan by introducing the hydroxyl group via bromination at the allylic position. We isolated **52** after the introduction of the oxyacetic α-chain moiety at the

Scheme 7[a]



[a] Reagents: (i) allyl bromide; (ii) toluene, reflux; (iii) H_2SO_4, *t*-BuOH; (iv) Zn, $BrCH_2CO_2Me$; (v) *p*-toluenesulfonic acid; (vi) BBr_3, CH_2Cl_2; (vii) $LiAlH_4$, THF; (viii) $BrCH_2CO_2Me$, K_2CO_3, DMF; (ix) 3,4-dihydro-2*H*-pyran, *p*-toluenesulfonic acid; (x) OsO_4, $NaIO_4$; (xi) $NaBH_4$, THF; (xii) Ac_2O, pyridine; (xiii) HCl, MeOH; (xiv) methanesulfonyl chloride, Et_3N; (xv) *t*-BuOK, **11b**, DMF; (xvi) NaOH.

Scheme 8[a]



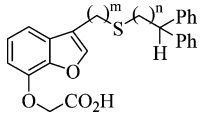
[a] Reagents: (i) $LiAlH_4$, THF; (ii) *t*-BuOK, *n*-PrSH, DMF; (iii) $BrCH_2CO_2Me$, K_2CO_3, DMF; (iv) 3,4-dihydro-2*H*-pyran, pyridinium *p*-toluenesulfonate; (v) *N*-bromosuccinimide, AIBN; (vi) AcOK, DMF; (vii) H_2, 10% Pd/C, MeOH; (viii) methanesulfonyl chloride, Et_3N; (ix) NaH, **11b**, DMF; (x) NaOH.

7-position by treating with methyl bromoacetate. After THP protection of the primary alcohol on the side chain, the allylic position on the side chain of **53** was brominated by *N*-bromosuccinimide and compound **54** was obtained by treatment with potassium acetate. The double bond on the side chain was reduced by catalytic hydrogenation, which was accompanied by removal of the THP group. After coupling with thiol **11b** via mesylate of **55**, compound **9g** was obtained by hydrolysis of the methyl ester and the acetyl group.

Pharmacology

All compounds synthesized were evaluated as the sodium salt, diethanolamine salt, or free acid. Compounds synthesized were evaluated in terms of inhibition of aggregation in human platelet rich plasma (PRP) induced by the P2Y receptor agonist adenosine diphosphate (ADP) or by a stable TXA_2 agonist (U46619). To confirm the mechanistic profile of these compounds, we also performed receptor binding assays in the

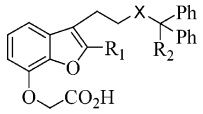
Table 1. In Vitro Activities of Benzofuran Sulfides



compd	*m*	*n*	antiaggregatory activity IC_{50} (μM)[a] ADP[b]	antiaggregatory activity IC_{50} (μM)[a] U46619[c]	receptor affinty K_i (μM) IP	receptor affinty K_i (μM) TP
8a	1	0	>100	>100	4.7 ± 1.4	5.1 ± 0.4
8b	1	1	19.9 ± 6.4	17.3 ± 0.6	0.68 ± 0.07	2.5 ± 0.1
8c	1	2	12.8 ± 3.2	10.0 ± 3.6	0.58 ± 0.02	3.1 ± 0.2
8d	2	0	5.9 ± 1.8	0.56 ± 0.02	0.41 ± 0.05	0.31 ± 0.02
8e	2	1	0.73 ± 0.24	0.51 ± 0.01	0.08 ± 0.02	3.1 ± 0.2
8f	2	2	5.2 ± 1.4	5.4 ± 0.14	0.56 ± 0.09	>10
8g	3	0	1.9 ± 0.2	1.6 ± 0.1	0.27 ± 0.03	3.1 ± 0.3
8h	3	1	1.7 ± 0.3	1.4 ± 0.2	0.40 ± 0.07	>15
8i	3	2	>100	>100	2.9 ± 0.5	>15

[a] IC_{50} represents the concentration that inhibits induced aggregation by 50%. [b] Inhibition of platelet aggregation induced by ADP (5 μM) in human platelet rich plasma. [c] Inhibition of platelet aggregation induced by U46619 (2μM) in human platelet rich plasma.

Table 2. In Vitro Activities of 2-Substituted Benzofuran Sulfides



compd	R_1	R_2	X	antiaggregatory activity IC_{50} (μM)[a] ADP[b]	antiaggregatory activity IC_{50} (μM)[a] U46619[c]	receptor affinty K_i (μM) IP	receptor affinty K_i (μM) TP
8d	H	H	S	5.9 ± 1.8	0.56 ± 0.02	0.41 ± 0.05	0.31 ± 0.02
8j	H	Me	S	8.1 ± 1.1	0.58 ± 0.03	0.57 ± 0.07	0.026 ± 0.001
9a	CH_2OH	H	S	3.3 ± 0.6	0.46 ± 0.08	0.75 ± 0.07	0.088 ± 0.012
9b	CH_2OH	Me	S	2.2 ± 0.4	0.17 ± 0.01	0.53 ± 0.07	0.0045 ± 0.0002
9c[d]	CH_2OH	Et	S	56 ± 8	3.8 ± 0.8	3.40 ± 0.15	0.180 ± 0.01
9d[d]	CH_2OH	*n*-Pr	S	>100	56 ± 2	>2.3	>5.9
9e	CH_2OH	CF_3	S	1.5 ± 0.2	0.52 ± 0.01	0.76 ± 0.19	0.150 ± 0.04
9f	$(CH_2)_2OH$	Me	S	0.71 ± 0.07	0.54 ± 0.01	0.21 ± 0.01	0.078 ± 0.008
9g	$(CH_2)_3OH$	Me	S	9.0 ± 0.7	2.9 ± 0.2	5.80 ± 0.09	0.072 ± 0.003
9h	CH_2OH	Me	SO	7.9 ± 1.7	1.7 ± 0.1	>10	0.051 ± 0.012
9i	CH_2OH	Me	SO_2	3.0 ± 0.8	0.31 ± 0.09	1.90 ± 0.22	0.0043 ± 0.0004

[a] IC_{50} represents the concentration that inhibits induced aggregation by 50%. [b] Inhibition of platelet aggregation induced by ADP (5 μM) in human platelet rich plasma. [c] Inhibition of platelet aggregation induced by U46619 (2 μM) in human platelet rich plasma. [d] This compound was provided as sodium salt.

human platelet membrane fraction. These receptor binding assays were carried out by using [^{3}H]-SQ-29548 (a selective TXA_2 receptor (TP) antagonist) and [^{3}H]-APS314d sodium salt (a selective PGI_2 receptor (IP) agonist), which is one of the component of **3**. Scatchard analysis of binding of [^{3}H]-SQ-29548 revealed a single binding site (K_d = 10.2 ± 0.51 nM, B_{max} = 5.89 ± 0.62 nM/mg protein). [^{3}H]-APS314d sodium salt also had one binding site (K_d = 14.3 ± 0.51 nM, B_{max} = 6.08 ± 0.60 nM/mg protein).

Results and Discussion

We screened a wide range of ω-side chain functionality based on our work with **3**. We identified lead compound **8e**, which contains sulfide in its ω-side chain. The sulfide side chain in conjunction with the benzofuran scaffold results in a PGI_2 receptor agonist. To probe the width and depth of the ω-side chain binding pocket, various lengths of carbon chains were tested (Table 1).

In this series, compound **8e** possesses the lowest inhibitory potency of ADP-induced platelet aggregation, which was derived from its agonism at the PGI_2 receptor. Compound **8d** possesses the second lowest inhibitory potency of U46619-induced platelet aggregation, which was derived from its antagonism at the TXA_2 receptor and its agonism at the PGI_2 receptor. Agonism at PGI_2 receptor proved to be tolerated on the length of the side chain, and compounds **8b**−**h** showed inhibitory potency (induced by ADP). On the other hand, TXA_2 receptor antagonism is very sensitive to the length of the side chain. Only compound **8d** shows significant TXA_2 antagonistic property (K_i = 0.31 μM) (Table 1).

Compound **8j**, which has a diphenylethyl sulfide group at the end of its side chain, and compound **9a**, which has a hydroxymethyl group at the 2-position of benzofuran, also display TXA_2 receptor antagonistic and PGI_2 receptor agonistic properties (Table 2). This is evidence of the utility of terminal sulfide group on the ω-side chain in the search for dual prostanoids.

We investigated the influence of alkyl substitution groups at the end of the side chain on compound **9a**. The methyl analogue **9b**, ethyl analogue **9c**, *n*-propyl analogue **9d**, and trifluoromethyl analogue **9e** were synthesized. Compound **9b** shows excellent potency as both a PGI_2 receptor agonist and a TXA_2 receptor

Table 3. Solubility of Compound **9b** with Diethanolamine Salt and Sodium Salt

salt form of **9b**	solubility (mg/mL) in distilled H_2O	saline	5% xylitol
diethanolamine salt (**7**)	>30	<0.5[a]	10
sodium salt	10	<0.5	1

[a] The compound was precipitated as a sodium salt.

antagonist. Other compounds were not as potent as **9b** at these receptors. Compound **9b** is the best dual prostanoid in this series.

Next we checked the influence of carbon chain length of the hydroxymethyl group attached to the 2-position on the benzofuran ring, which was designed to correspond to the 11-position hydroxyl group of PGI_2. Compound **8j**, which lacks the hydroxymethyl group, has almost the same agonist potency as compound **9b** at the PGI_2 receptor, but it is less potent as a TXA_2 receptor antagonist. In contrast, compound **9f**, which bears a hydroxyethyl group instead of hydroxymethyl, is more potent than compound **9b** as a PGI_2 receptor agonist but is also less potent as a TXA_2 receptor antagonist. The hydroxypropyl-bearing compound **9g** is less potent in both properties.

We also tested oxidized forms of the sulfide in compound **9b**. The sulfoxide analogue **9h** and the sulfone analogue **9i** were synthesized. Compound **9h** completely loses efficacy at the PGI_2 receptor and is a pure TXA_2 receptor antagonist. Compound **9i** has almost the same potency as compound **9b** as a TXA_2 receptor antagonist, but its potency as a PGI_2 receptor agonist is less than that of compound **9b**.

In the next study, we examined the pharmacological profile of compound **9b** in terms of its antiplatelet effects. Compound **9b** is a novel compound having potent TXA_2 receptor antagonistic activity together with a moderate PGI_2 receptor agonist activity. In fact, compound **9b** shows 117-fold higher affinity compared to TP receptor than to IP receptor, as evidenced by the K_d values determined in binding assays using human platelet membrane.

To eliminate the effect of DMSO in pharmacological experiments, we made the sodium salt and the diethanolamine salt and compared the solubility of these salts. (Table 3). Both salts dissolve well in distilled water. Compound **9b** having two aromatic rings at the end of the side chain, however, is highly lipophilic, so sodium salt does not dissolve well in saline and 5% xylitol. Otherwise, the diethanolamine salt of compound **9b** (**7**), which could be easily crystallized from ethanol, showed excellent solubility in the 5% xylitol. In saline, neither salt dissolved more than 0.5 mg/mL, since the diethanolamine salt turned into the sodium salt. From these results, we found out that compound **7** with 5% xylitol is the practical formula for pharmacological experiments.

The TXA_2 receptor antagonistic and PGI_2 receptor agonistic activities of compound **7** were examined in in vitro platelet aggregation (Table 4). Compound **7** exhibited inhibitory effects on the ADP and U46619-induced aggregation. The IC_{50} value of inhibitory effects on the ADP-induced aggregation was about 18-fold less potent than that on the U46619-induced aggregation. A similar tendency was observed with the TXA_2 receptor antagonist SQ-29548. On the other hand, the IC_{50} value of inhibitory effects by the selective PGI_2 receptor agonists **3** and compound **4** were almost the same on both ADP and U46619 induced platelet aggregation. These results are consistent with the fact that compound **7** has PGI_2 receptor agonistic activity in addition to the TXA_2 receptor antagonistic activity. This is also supported by the evidence that these results, together with the results of binding assay, indicate that the PGI_2 receptor agonistic activity of compound **7** is relatively weaker than its TXA_2 receptor antagonistic activity.

Table 4. Effects of Compounds **7**, **3**, **4**, and SQ-29548 on in Vitro Platelet Aggregation in Human PRP[a]

aggregating agent	IC_{50} (nM) **7**	**3**	**4**	SQ-29548
U46619	120 ± 30	7.6 ± 0.7	170 ± 11	21 ± 3
ADP	2200 ± 320	5.7 ± 1.0	170 ± 3	>10000

[a] The platelet aggregation was induced by U46619 (4 μM) or by ADP (5 μM). Values are the mean ± SE of three to four determinations.

To confirm the antithrombotic character of compound **7**, we tried ex vivo platelet aggregation experiment by monitoring blood pressure and heart rate. The inhibitory effects observed with cynomolgus monkey PRP were $IC_{50} = 3.7 \pm 1.5$ μM (induced by 5 μM of ADP) and $IC_{50} = 0.14 \pm 0.20$ μM (induced by 600 μM of arachidonic acid). Since these data were quite similar to those observed with human PRP, the ex vivo experiment was carried out in monkeys (Figure 1). In the ex vivo experiment, the arachidonic acid induced aggregation was completely inhibited by the infusion of compound **7** even at the lowest dose examined (3 μg kg^{-1} min^{-1}). Infusion of **7** also caused dose-dependent inhibitions of the ADP-induced platelet aggregation, which was completely inhibited at the highest dose examined (30 μg kg^{-1} min^{-1}). In the similar manner, the IP receptor agonist **4** showed dose-dependent inhibition of ADP-induced platelet aggregation but did not show clear inhibition of arachidonic acid induced aggregation. Furthermore, compound **4** showed a dose-dependent decrease in blood pressure in the examined dose range, and the decrease was accompanied by an increase in heart rate. The antiplatelet activity of compound **4** is linked to its potent vasodilation. On the other hand, compound **7** does not show any significant change in blood pressure and heart rate even at the highest dose examined (30 μg kg^{-1} min^{-1}). These results suggest that the antiplatelet activity of compound **7** is not related to vasodilation.

In conclusion, a variety of benzofuran-7-oxyacetic acid analogues with many kinds of 2- and 3-position side chains were prepared by versatile synthetic routes, which allow large-scale preparation. Among the benzofuran analogues synthesized, we found the first dual-acting benzofuran **7** possessing a potent TXA_2 antagonism and a moderate PGI_2 agonism. The TP receptor antagonistic and IP receptor agonistic activities of compound **7** are also demonstrated in in vitro platelet aggregation induced by various platelet stimulating agents. The ex vivo experiment of compound **7** illustrated the beneficial properties of PGI_2 stable mimetics in terms of avoiding hypotensive side effects. Remarkably, compound **7** was found to be a promising

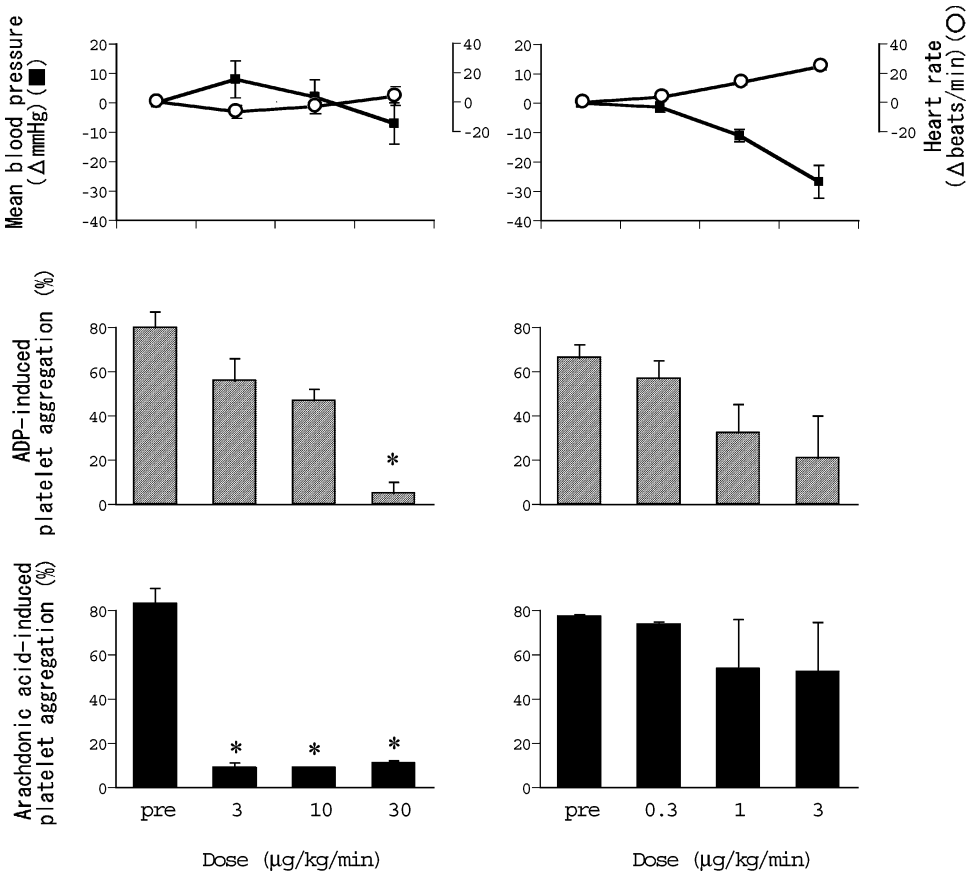


Figure 1. Effects of compound **7** (left) and compound **4** (right) on blood pressure, heart rate, and ex vivo platelet aggregation in monkey. Drugs were infused for 30 min at each of the doses in a dose-escalation manner. Platelet aggregation was induced by ADP (10 μM) or by arachidonic acid (600 μM). Data are expressed as the mean ± SE of three to four determinations: (*) significantly different from the vehicle group ($p < 0.01$).

candidate as novel medicine in antithrombotic and cardiovascular fields. Further experimental evaluations are now in progress on pharmacological properties.

Experimental Section

All of the reagents and solvents used were reagent grade or were purified by standard methods before use. All melting points were obtained with Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were measured on a JASCO FT/IR-410 infrared spectrophotometer. ^{1}H NMR spectra were recorded with Varian Gemini-2000 spectrometer (300 MHz) with tetramethylsilane as an internal standard. Low mass spectra (MS) or high-resolution mass spectra (HR-MS) were obtained with a JEOL JMS-DX303 mass spectrometer. The fast atom bombardment mass spectra (FAB-MS) were obtained by using glycerol as the matrix. Optical rotations were determined at the sodium D line using a HORIBA high-sensitivity polarimeter. Elemental analysis was performed by Toray Research Center. Thin-layer chromatography was performed on precoated TLC plates (silica gel 60 F-254, layer thickness of 0.25 mm, or DIOL F-254s) manufactured by E. Merck. Silica gel column chromatography was performed on silica gel 60 (0.063−0.200 mm) manufactured by E. Merck. Synthetic reagents were purchased from Aldrich (Milwaukee, WI), Kanto Kagaku Co. (Tokyo, Japan), TCI (Tokyo, Japan), and Sigma Chemical Co. (St. Louis, MO). Anhydrous tetrahydrofuran, methanol, dichloromethane, dimethylformamide, and pyridine were purchased from Kanto Kagaku Co. (Tokyo, Japan). The active isomer of beraprost, [^{3}H]APS-314d sodium, and [^{3}H]SQ-29548 were synthesized at Daiichi Pure Chemicals (Tokyo, Japan). SQ-29548 and U46619 were purchased from Cayman Chemical (MI), ADP from Sigma (MO), 3.8% sodium citrate was purchased from Yamanouchi Pharmaceutical (Tokyo, Japan), and a low molecular weight heparin sodium dalteparin was purchased from Kissei Pharmaceutical (Nagano, Japan).

In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise mentioned. All reactions that required anhydrous conditions were performed under argon or nitrogen, and all glassware was either oven-dried or flame-dried before use.

[3-[2-(1,1-Diphenylethylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid Diethanolamine Salt (7). To a stirred solution of **9b** (886 mg, 1.92 mmol) in EtOH (10 mL) was added diethanolamine (230 mg, 2.19 mmol) in EtOH (3 mL), which was stood at room temperature. The resulting crystals were collected and were washed with small amount of cold EtOH to afford **7** (776 mg, 71%). Colorless plates, mp 181.5 °C; ^{1}H NMR (D_2O) δ 1.95 (3H, s), 2.61 (4H, m), 3.36 (4H, bs), 4.01 (4H, bs), 4.61 (2H, s), 4.71 (2H, s), 6.79 (2H, m), 7.04 (1H, m), 7.18 (6H, bs), 7.36 (4H, bs). Anal. ($C_{31}H_{37}NO_7S$) C, H, N, S.

General Procedure for Hydrolysis of Methyl Ester. [3-Benzhydrylsulfanylmethylbenzofuran-7-yloxy]acetic Acid (8a). To a stirred solution of **23a** (73 mg, 0.17 mmol) in MeOH (3.0 mL) was added 1.0 N NaOH (aq) (0.010 mL, 0.49 mmol) and stirred at room temperature for 1 h. The reaction mixture was poured into 1 N HCl (aq) and was extracted with AcOEt. The organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was recrystallized from AcOEt/*n*-hexane to afford **8a** (70 mg, 99%). White powder, mp 135.5−137 °C; ^{1}H NMR ($CDCl_3$) δ 3.64 (2H, d, $J = 1.0$ Hz), 4.92 (2H, s), 5.00 (1H, s), 6.83 (1H, d, $J = 6.0$ Hz), 7.14−7.39 (13H, m); IR (KBr) 1742 cm^{-1} (COOH); LR-MS (EI) 404 (M^+). Anal. ($C_{24}H_{20}O_4S$) C, H, N, S.

[3-(2,2-Diphenylethylsulfanylmethyl)benzofuran-7-yloxy]acetic Acid (8b). Compound **8b** (70%) was prepared from **23b**. White powder, mp 91.0−93.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.13 (2H, d, J = 8.0 Hz), 3.65 (2H, s), 4.11 (1H, t, J = 8.0 Hz), 4.92 (2H, s), 6.83 (1H, d, J = 8.0 Hz), 7.13−7.31 (13H, m); IR (KBr) 1738 cm^{-1} (COOH); LR-MS (EI) 418 (M^+). Anal. ($C_{25}H_{22}O_4S$) C, H, N, S.

[3-(3,3-Diphenylpropylsulfanylmethyl)benzofuran-7-yloxy]acetic Acid (8c). Compound **8c** (96%) was prepared from **23c**. White powder, mp 154.5−155.5 °C; ^{1}H NMR (DMSO-d_6) δ 2.15−2.35 (4H, m), 3.82 (2H, s), 4.02 (1H, t, J = 6.0 Hz), 4.85 (2H, s), 6.84 (1H, d, J = 8.0 Hz), 7.10−7.30 (13H, m), 7.70 (1H, s); IR (KBr) 1748 cm^{-1} (COOH); LR-MS (EI) 432 (M^+). Anal. ($C_{26}H_{24}O_4S$) C, H, N, S.

[3-(2-Benzhydrylsulfanylethyl)benzofuran-7-yloxy]acetic Acid (8d). Compound **8d** (97%) was prepared from **23d**. Colorless prisms, mp 139−141 °C; ^{1}H NMR ($CDCl_3$) δ 2.57 (2H, t, J = 8.0 Hz), 2.88 (2H, t, J = 8.0 Hz), 4.90 (2H, s), 5.17 (1H, s), 6.78 (1H, dd, J = 1.0, 8.0 Hz), 6.97 (1H, dd, J = 1.0, 8.0 Hz), 7.09 (1H, t, J = 8.0 Hz), 7.21−7.41 (11H, m); IR (KBr) 1738 cm^{-1} (COOH); LR-MS (EI) 418 (M^+). Anal. ($C_{25}H_{22}O_4S$) C, H, N, S.

{3-[2-(2,2-Diphenylethylsulfanyl)ethyl]benzofuran-7-yloxy}acetic Acid (8e). Compound **8e** (78%) was prepared from **23e**. Colorless prisms, mp 116−118 °C; ^{1}H NMR ($CDCl_3$) δ 2.74−2.79 (2H, m), 2.87−2.91 (2H, m), 3.24 (2H, d, J = 8.0 Hz), 4.16 (1H, t, J = 8.0 Hz), 4.91 (2H, s), 6.82 (1H, dd, J = 2.0, 7.0 Hz), 7.12−7.32 (12H, m), 7.40 (1H, m); IR (KBr) 1744 cm^{-1} (COOH); LR-MS (EI) 432 (M^+). Anal. ($C_{26}H_{24}O_4S$) C, H, N, S.

{3-[2-(3,3-Diphenylpropylsulfanylmethyl)ethyl]-benzofuran-7-yloxy}acetic Acid (8f). Compound **8f** (97%) was prepared from **23f**. White powder, mp 61−62 °C; ^{1}H NMR ($CDCl_3$) δ 2.29−2.36 (2H, m), 2.49 (2H, dd, J = 7.0, 9.0 Hz), 2.78−2.89 (4H, m), 4.07 (1H, t, J = 8.0 Hz), 4.91 (2H, s), 6.82 (1H, dd, J = 2.0, 7.0 Hz), 7.11−7.30 (12H, m), 7.44 (1H, m); IR (KBr) 1734 cm^{-1} (COOH); LR-MS (EI) 446 (M^+). Anal. ($C_{27}H_{26}O_4S$) C, H, N, S.

[3-(3-Benzhydrylsulfanylpropyl)benzofuran-7-yloxy]-acetic Acid (8g). Compound **8g** (85%) was prepared from **23g**. Colorless needles, mp 116−118 °C; ^{1}H NMR ($CDCl_3$) δ 1.93 (2H, sept, J = 7.0 Hz), 2.46 (2H, t, J = 7.0 Hz), 2.72 (2H, t, J = 7.0 Hz), 4.91 (2H, s), 5.14 (1H, s), 6.81 (1H, d, J = 7.0 Hz), 7.10−7.42 (13H, m); IR (KBr) 1738 cm^{-1} (COOH); LR-MS (EI) 432 (M^+). Anal. ($C_{26}H_{24}O_4S$) C, H, N, S.

{3-[3-(2,2-Diphenylethylsulfanyl)propyl]benzofuran-7-yloxy}acetic Acid (8h). Compound **8h** (84%) was prepared from **23h**. Colorless needles, mp 94 °C; ^{1}H NMR ($CDCl_3$) δ 1.94 (2H, quint, J = 7.0 Hz), 2.51 (2H, t, J = 7.0 Hz), 2.72 (2H, t, J = 7.0 Hz), 3.21 (2H, d, J = 8.0 Hz), 4.17 (1H, t, J = 8.0 Hz), 4.92 (2H, s), 6.81 (1H, d, J = 7.0 Hz), 7.10−7.40 (13H, m); IR (KBr) 1740 cm^{-1} (COOH); LR-MS (EI) 446 (M^+). Anal. ($C_{27}H_{26}O_4S$) C, H, N, S.

{3-[3-(3,3-Diphenylpropylsulfanyl)propyl]benzofuran-7-yloxy}acetic Acid (8i). Compound **8i** (85%) was prepared from **23i**. Colorless prisms, mp 94 °C; ^{1}H NMR ($CDC1_3$) δ 1.92 (2H, quint, J = 7.0 Hz), 2.32 (2H, q, J = 7.0 Hz), 2.45 (2H, t, J = 7.0 Hz), 2.54 (2H, t, J = 7.0 Hz), 2.74 (2H, t, J = 7.0 Hz), 4.08 (1H, t, J = 8.0 Hz), 4.91 (2H, s), 6.81 (1H, d, J = 7.0 Hz), 7.10−7.40 (13H, m); IR (KBr) 1738 cm^{-1} (COOH); LR-MS (EI) 460 (M^+). Anal. ($C_{28}H_{28}O_4S$) C, H, N, S.

{3-[2-(1,1-Diphenylethylsulfanyl)ethyl]benzofuran-7-yloxy}acetic Acid (8j). Compound **8j** (70%) was prepared from **23j**. Colorless prisms, mp 117 °C; ^{1}H NMR ($CDC1_3$) δ 2.11 (3H, s), 2.60 (2H, m), 2.70 (2H, m), 4.89 (2H, s), 6.79 (1H, dd, J = 1.0, 7.5 Hz), 6.99 (1H, dd, J = 1.0, 7.5 Hz), 7.10 (1H, t, J = 7.5 Hz), 7.18−7.33 (6H, m), 7.38−7.43 (5H, m); IR (KBr) 1740 cm^{-1} (COOH); LR-MS (EI) 432 (M^+). Anal. ($C_{26}H_{24}O_4S$) C, H, N, S.

[3-(2-Benzhydrylsulfanylethyl)-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid (9a). Compound **9a** (80%) was prepared from **41a**. Colorless plates, mp 144 °C; ^{1}H NMR ($CDC1_3$) δ 2.66 (2H, t, J = 7.0 Hz), 2.88 (2H, t, J = 7.0 Hz), 4.65 (2H, s), 4.85 (2H, s), 5.04 (1H, s), 6.77 (1H, d, J = 8.0 Hz), 6.92 (1H, d, J = 8.0 Hz), 7.07 (1H, t, J = 8.0 Hz), 7.19−7.36 (10H, m); IR (KBr) 1736 cm^{-1} (COOH); LR-MS (EI) 448 (M^+). Anal. ($C_{26}H_{24}O_5S$) C, H, N, S.

[3-[2-(1,1-Diphenylethylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid (9b). Compound **9b** (89%) was prepared from **41b**. Colorless plates, mp 140.5 °C; ^{1}H NMR ($CDC1_3$) δ 2.00 (3H, s), 2.59 (2H, m), 2.67 (2H, m), 4.62 (2H, s), 4.85 (2H, s), 6.76 (1H, d, J = 7.0 Hz), 6.92 (1H, d, J = 7.0 Hz), 7.06 (1H, t, J = 7.0 Hz), 7.16−7.28 (6H, m), 7.33 (4H, m); IR (KBr) 1742 cm^{-1} (COOH); LR-MS (FAB, negative) 461 (M^+ − H). Anal. ($C_{27}H_{26}O_5S$) C, H, N, S.

[3-[2-(1,1-Diphenylpropylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid Sodium Salt (9c). Compound **9c** (83%) was prepared from **41c**. White powder, mp 193 °C; ^{1}H NMR (D_2O) δ 0.52 (3H, bs), 2.07 (2H, bs), 2.20 (2H, m), 2.35 (2H, m), 4.34 (2H, s), 4.46 (2H, s), 6.50 (1H, m), 6.58 (1H, m), 6.80 (1H, m), 6.97 (6H, bs), 7.10 (4H, bs); LR-MS (FAB, negative) 475 (M^+ − Na). Anal. ($C_{28}H_{27}O_5SNa$) C, H, N, S.

[3-[2-(1,1-Diphenylbutylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid Sodium Salt (9d). Compound **9d** (76%) was prepared from **41d**. Colorless needles, mp 178 °C; ^{1}H NMR (D_2O) δ 0.48 (3H, m), 0.93 (2H, m), 2.02 (2H, m), 2.22 (4H, m), 4.21 (2H, bs), 4.36 (2H, s), 6.35 (1H, s), 6.48 (1H, m), 6.67 (1H, m), 6.90 (6H, m), 7.09 (4H, m); LR-MS (FAB, positive) 513 (M^+ + H). Anal. ($C_{29}H_{29}O_5SNa$) C, H, N, S.

{2-Hydroxymethyl-3-[2-(2,2,2-trifluoro-1,1-diphenylethylsulfanyl)ethyl]benzofuran-7-yloxy}acetic Acid (9e). Compound **9e** (93%) was prepared from **41e**. Colorless prisms, mp 129−131 °C; ^{1}H NMR ($CDCl_3$) δ 2.61 (2H, m), 2.74 (2H, m), 4.64 (2H, s), 4.89 (2H, s), 6.77 (1H, dd, J = 0.8, 8.0 Hz), 6.83 (1H, dd, J = 0.8, 8.0 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.24−7.29 (6H, m), 7.32−7.39 (4H, m); IR (KBr) 1738 cm^{-1} (COOH); LR-MS (EI) 516 (M^+). Anal. ($C_{27}H_{23}F_3O_5S$) C, H, N, S.

[3-[2-(1,1-Diphenylethylsulfanyl)-ethyl]-2-(2-hydroxyethyl)benzofuran-7-yloxy]acetic Acid (9f). Compound **9f** was prepared from **50** (87%). Colorless prisms, mp 129−131 ° C; ^{1}H NMR (CD_3OD) δ 2.01 (3H, s), 2.56 (2H, m), 2.69 (2H, m), 2.89 (2H, t, J = 6.9 Hz), 3.83 (2H, t, J = 6.9 Hz), 4.83 (2H, s), 6.74 (1H, dd, J = 7.8, 1.0 Hz), 6.81 (1H, dd, J = 7.8, 1.0 Hz), 7.01 (1H, t, J = 7.8 Hz), 7.15−7.40 (10H, m); IR (KBr) 1742 cm^{-1} (COOH); LR-MS (EI) 476 (M^+). Anal. ($C_{28}H_{28}O_5S$) C, H, N, S.

[3-[2-(1,1-Diphenylethylsulfanyl)ethyl]-2-(3-hydroxypropyl)benzofuran-7-yloxy]acetic Acid (9g). Compound **9g** was prepared from **55** (84%). Colorless prisms, mp 152−153 ° C; ^{1}H NMR (CD_3OD) δ 1.90 (2H, m), 2.00 (3H, s), 2.54 (2H, m), 2.66 (2H, m), 2.74 (2H, t, J = 7.5 Hz), 3.57 (2H, t, J = 6.4 Hz), 4.84 (2H, s), 6.73 (1H, dd, J = 7.8, 1.0 Hz), 6.81 (1H, dd, J = 7.8, 1.0 Hz), 7.01 (1H, t, J = 7.8 Hz), 7.15−7.39 (10H, m); IR (KBr) 1748 cm^{-1} (COOH); LR-MS (EI) 490 (M^+). Anal. ($C_{29}H_{30}O_5S$) C, H, N, S.

{3-[2-(Diphenylethanesulfonyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy}acetic Acid (9i). Compound **9i** (84%) was prepared from **42**. Colorless prisms, mp 156−158 °C; ^{1}H NMR (CD_3OD) δ 2.20 (3H, s), 2.96−3.10 (4H, m), 4.60 (2H, s), 4.83 (2H, s), 6.80 (1H, dd, J = 0.8, 8.0 Hz), 6.86 (1H, dd, J = 0.8, 8.0 Hz), 7.07 (1H, t, J = 8.0 Hz), 7.33−7.42 (6H, m), 7.55−7.64 (4H, m); IR (KBr) 1740 cm^{-1} (COOH); LR-MS (EI) 494 (M^+). Anal. ($C_{27}H_{26}O_7S$) C, H, N, S.

{3-[2-(Diphenylethanesulfinyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy}acetic Acid (9h). To a stirred solution of **9b** (197 mg, 0.43 mmol) in MeOH (3 mL) was added 30% H_2O_2 (0.5 mL), and the reaction mixture was stirred at room temperature for 4.5 h. The reaction mixture was poured into 1 N HCl (aq) and was extracted with AcOEt. The organic layer was sequentially washed with water and brine and dried over $MgSO_4$. Removal of the solvent gave an oily residue, which was recrystallized from AcOEt/*n*-hexane to afford **9h** (164 mg, 81%). Colorless prisms, mp 131−132 °C; ^{1}H NMR (CD_3OD) δ 1.94 (3H, s), 2.51 (2H, t, J = 7.4 Hz), 3.00−3.10 (2H, m), 4.62 (2H, s), 4.86 (2H, s), 6.82 (1H, dd, J = 0.8, 7.9 Hz), 6.83 (1H, dd, J = 0.8, 7.9 Hz), 7.04 (1H, t, J = 7.9 Hz), 7.20−7.42

(10H, m); IR (KBr) 1745 cm^{-1} (COOH); LR-MS (EI) 478 (M^+). Anal. ($C_{27}H_{26}O_6S$) C, H, N, S.

1,1-Diphenylpropane-1-ol (10c). To a stirred solution of benzophenone (3.50 g, 19.2 mmol) in THF (30 mL) was added 1.0 M EtMgBr in THF (24.5 mL, 24.5 mmol), and the mixture was stirred at 0 °C for 5.0 h. The reaction mixture was poured into 5% citric acid (aq) and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and was dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/4) to afford **10c** (635 mg, 16%). Colorless oil; ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, J = 7.5 Hz), 2.08 (1H, s), 2.32 (2H, q, J = 7.5 Hz), 7.19−7.34 (6H, m), 7.39−7.44 (4H, m); LR-MS (EI) 212 (M^+).

1,1-Diphenylbutane-1-ol (10d). By the procedure used in **10c**, compound **10d** (80%) was prepared from benzophenone and *n*-PrMgBr. Colorless oil; ^1H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.0 Hz), 1.30 (2H, m), 2.09 (1H, s), 2.26 (2H, m), 7.19−7.33 (6H, m), 7.39−7.43 (4H, m); LR-MS (EI) 226 (M^+).

2,2,2-Trifluoro-1,1-diphenylethanol (10e). By the procedure used in **10c**, compound **10e** (96%) was prepared from trifluoroacetophenone and PhMgBr. Colorless oil; ^1H NMR ($CDCl_3$) δ 2.87 (1H, s), 7.33−7.39 (6H, m), 7.46−7.53 (4H, m); LR-MS (EI) 252 (M^+).

General Procedure for Preparation of Thiols. 1,1-Diphenylethanthiol (11b). To solution of 1,1-diphenylethane-1-ol (50 g) and Lawesson's reagent (50 g) in toluene (1300 mL) was added water (6.5 mL), and the reaction mixture was stirred at 50 °C. Water (200 mL) was added, and the resulting mixture was cooled to room temperature. The organic layer was separated and sequentially washed with saturated $NaHCO_3$ (200 mL) and brine (200 mL). The organic layer was dried over Na_2SO_4 and evaporated. The resulting oil was purified by silica gel chromatography (eluent: *n*-hexane), which afforded **11b** (25.0 g, 46%). Colorless solid; ^1H NMR ($CDCl_3$) δ 2.16 (3H, s), 2.49 (1H, s), 7.20−7.34 (6H, m), 7.41−7.45 (4H, m); LR-MS (CI) 213 ($M^+ - H$).

Diphenylmethanethiol (11a). Compound **11a** (94%) was prepared from diphenylmethanol. Colorless oil; ^1H NMR ($CDCl_3$) δ 2.27 (1H, d, J = 5.0 Hz), 5.44 (1H, d, J = 5.0 Hz), 7.20−7.45 (10H, m); LR-MS (FAB) 200 (M^+), 199 ($M^+ - H$).

1,1-Diphenylpropane-1-thiol (11c). Compound **11c** (49%) was prepared from **10c**. Colorless oil; ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, J = 7.0 Hz), 2.25 (1H, s), 2.51 (2H, q, J = 7.0 Hz), 7.19−7.40 (10H, m); LR-MS (EI) 228 (M^+).

1,1-Diphenylbutane-1-thiol (11d). Compound **11d** (44%) was prepared from **10d**. Colorless oil; ^1H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 7.0 Hz), 1.24 (2H, m), 1.55 (1H, s), 2.42 (2H, m), 7.16−7.40 (10H, m); LR-MS (EI) 242 (M^+).

2,2,2-Trifluoro-1,1-diphenylethanol (11e). Compound **11e** (20%) was prepared from **10e**. Colorless oil; ^1H NMR ($CDCl_3$) δ 2.86 (1H, s), 7.30−7.39 (6H, m), 7.40−7.49 (4H, m); LR-MS (EI) 268 (M^+).

2,2-Diphenylethanethiol (11f). To a stirred solution of **15** (30 mg, 0.07 mmol) in AcOH (5 mL) was added zinc powder (5 mg, 0.08 mmol), and the reaction mixture was stirred at 90 °C for 1 h. The reaction mixture was filtered, and the solvent was removed under reduced pressure. The resulting oily residue was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/5) to afford **11f** (27 mg, 90%). Colorless oil; ^1H NMR ($CDCl_3$) δ 1.35 (1H, t, J = 8.0 Hz), 3.18 (2H, q, J = 8.0 Hz), 4.13 (1H, t, J = 8.0 Hz), 7.10−7.42 (10H, m); LR-MS (EI) 214 (M^+).

3,3-Diphenylpropane-1-thiol (11g). To a stirred solution of **18** (5.16 g, 15 mmol) in EtOH (50 mL) and H_2O (20 mL) was added NaOH (950 mg, 24 mmol), and the reaction mixture was refluxed for 5.5 h. The solvent was removed, and the residue was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/12) to afford **11g** (2.94 g, 86%). Colorless oil; ^1H NMR ($CDCl_3$) δ 2.28−2.51 (5H, m), 4.09 (1H, t, J = 8.0 Hz), 7.15−7.32 (10H, m); LR-MS (EI) 228 (M^+).

1-Bromo-2,2-diphenylethane (13). To a stirred solution of 2,2-diphenylethanol (**12**) (10.0 g, 50 mmol) in dichloromethane (200 mL) was added Ph_3P (16.0 g, 61 mmol) and CBr_4 (25 g, 75.6 mmol). After being stirred at room temperature for 4 h, the reaction mixture was sequentially washed with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and evaporated. The resulting oil was distilled under reduced pressure to afford **13** (10.9 g, 83%). Colorless oil, bp 170−171 °C at 0.40 mmHg; ^1H NMR ($CDCl_3$) δ 3.87−4.00 (2H, m), 4.29−4.40 (1H, m), 7.00−7.50 (10H, m); LR-MS (EI) 260, 262 (M^+) (relative peak height ratio is 1:1).

2-(2,2-Diphenylethylsulfanyl)benzoxazole (14). To a stirred solution of **13** (2.03 g, 7.77 mmol) in DMF (15 mL) was added 2-mercaptobenzoxazole (1.31 g, 8.66 mmol) and K_2CO_3 (1.47 g, 10.6 mmol), and the reaction mixture was stirred at room temperature for 4 h. Saturated aqueous NH_4Cl (5 mL) was added to the reaction mixture and was extracted with AcOEt. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue that was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/50 to 1/20) to afford **14** (694 mg, 27%). Colorless prisms, mp 89.0−90.5 °C; ^1H NMR ($CDCl_3$) δ 3.95−4.05 (2H, m), 4.42−4.52 (1H, m), 7.00−7.70 (14H, m); LR-MS (EI) 331(M^+).

Di-(2,2-diphenylethyl) Disulfide (15). To a stirred solution of **14** (110 mg, 0.33 mmol) in EtOH (5 mL) and THF (1 mL) was added 1 N NaOH (1.0 mL), and the reaction mixture was stirred at 40 °C for 4 h. Saturated aqueous NH_4Cl (5 mL) was added to the reaction mixture and was extracted with AcOEt. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue that was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/25) to afford **15** (60 mg, 85%). Colorless oil; ^1H NMR ($CDCl_3$) δ 3.31 (4H, d, J = 8.0 Hz), 4.28 (2H, t, J = 8.0 Hz), 7.16−7.30 (20H, m); LR-MS (EI) 426 (M^+).

1-Bromo-3,3-diphenylpropane (17). To a stirred solution of 3,3-diphenylpropan-1-ol (**16**) (10.8 g, 48 mmol) and Ph_3P (15.2 g, 58 mmol) in THF (120 mL) was added *N*-bromosuccinimide (10.1 g, 57 mmol). After being stirred at 0 °C for 2 h, the reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (dichloromethane) to afford **17** (13.4 g, 96%). Colorless plates, mp 35−37 °C; ^1H NMR ($CDCl_3$) δ 2.58 (2H, q, J = 7.0 Hz), 3.32 (2H, t, J = 7.0 Hz), 4.20 (1H, t, J = 7.0 Hz), 7.15−7.34 (10H, m); LR-MS (EI) 274, 276 (M^+) (relative peak height ratio is 1:1).

2-(3,3-Diphenylpropylsulfanyl)benzoxazole (18). By the procedure used in **14**, compound **18** (90%) was prepared from **17**. Colorless plates, mp 91 °C; ^1H NMR ($CDCl_3$) δ 2.61 (2H, q, J = 7.0 Hz), 3.23 (2H, t, J = 7.0 Hz), 4.20 (1H, t, J = 7.0 Hz), 7.15−7.60 (14H, m); LR-MS (EI) 345 (M^+).

3-Chloromethyl-7-methoxybenzofuran (20). To a solution of 7-methoxy-2*H*-benzofuran-3-one (**19**) (7.13 g, 43.4 mmol) and bromochloromethane (11.3 mL) in THF (200 mL) was added *n*-BuLi (1.6 M in *n*-hexane) (80 mL, 128 mmol) at −78 °C, and the reaction mixture was stirred at −78 °C for 2 h. AcOH (7.3 mL) was added to the reaction mixture, and the solvent was removed. To the resulting oil was added toluene (100 mL) and *p*-toluenesulfonic acid monohydrate (20 mg), and the mixture was stirred at 50 °C for 2 h. The reaction mixture was sequentially washed with saturated $NaHCO_3$ and brine and was dried over Na_2SO_4 and evaporated. The resulting oil was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/8 then 1/4) to afford **20** (0.88 g, 10%). Colorless prisms, mp 43−44 °C; ^1H NMR ($CDCl_3$) δ 4.00 (3H, s), 4.72 (2H, d, J = 3.0 Hz), 6.80 (1H, d, J = 3.0 Hz), 6.87 (1H, d, J = 3.0 Hz), 7.11−7.27 (1H, m), 7.65 (1H, s); LR-MS (EI) 196 (M^+).

General Procedure for Coupling with Thiols. 3-Benzhydrylsulfanylmethyl-7-methoxybenzofuran (21a). To a solution of diphenylmethanethiol (**11a**) (121 mg, 0.604 mmol) in DMF (2.0 mL) was added *t*-BuOK (81 mg, 0.722 mmol) and **20** (118 mg, 0.600 mmol), and the reaction mixture was stirred at room temperature for 1 h. Saturated aqueous NH_4Cl was added to the reaction mixture and was extracted with AcOEt. The combined organic layer was sequentially washed with

water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue that was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/20) to afford **21a** (183 mg, 85%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.63 (2H, s), 4.02 (3H, s), 5.00 (1H, s), 6.83 (1H, dd, J = 1.0, 8.0 Hz), 7.15−7.39 (13H, m); LR-MS (EI) 360 (M^+).

3-(2,2-Diphenylethylsulfanylmethyl)-7-methoxybenzofuran (21b). Compound **21b** (99%) was prepared from **20**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.12 (2H, d, J = 8.0 Hz), 3.65 (2H, s), 4.00 (3H, s), 4.11 (1H, t, J = 8.0 Hz), 6.82 (1H, d, J = 8.0 Hz), 7.13−7.29 (12H, m), 7.46 (1H, s); LR-MS (EI) 374 (M^+).

3-(3,3-Diphenylpropylsulfanylmethyl)-7-methoxybenzofuran (21c). Compound **21c** (62%) was prepared from **20**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.20−2.60 (4H, m), 3.74 (2H, s), 4.00 (3H, s), 3.90−4.20 (1H, m), 6.81 (1H, dd, J = 2.0, 8.0 Hz), 7.10−7.50 (12H, m), 7.47 (1H, s); LR-MS (EI) 388 (M^+).

General Procedure for Deprotection of Methyl on Phenolic Hydroxyl Group Using *n*-PrSH. 3-Benzhydrylsulfanylmethylbenzofuran-7-ol (22a). To a solution of **21a** (45 mg, 0.125 mmol) in DMF (3.0 mL) was added *t*-BuOK (47 mg, 0.42 mmol) and *n*-PrSH (0.20 mL), and the reaction mixture was stirred at 100 °C for 4 h. Saturated aqueous NH_4Cl was added to the reaction mixture and was extracted with AcOEt. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue that was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/5) to afford **22a** (26 mg, 60%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.63 (2H, s), 5.02 (1H, s), 5.47 (1H, s), 6.85 (1H, dd, J = 1.0, 8.0 Hz), 7.15−7.39 (13H, m); LR-MS (EI) 346 (M^+).

3-(2,2-Diphenylethylsulfanylmethyl)benzofuran-7-ol (22b). Compound **22b** (98%) was prepared from **21b**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.13 (2H, d, J = 7.5 Hz), 3.65 (2H, d, J = 1.0 Hz), 4.12 (1H, t, J = 7.5 Hz), 5.26 (1H, s), 6.83−6.86 (1H, m), 7.11−7.30 (12H, m), 7.45 (1H, s); LR-MS (EI) 360 (M^+).

3-(3,3-Diphenylpropylsulfanylmethyl)benzofuran-7-ol (22c). Compound **22c** (89%) was prepared from **21c**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.10−2.60 (4H, m), 3.74 (2H, d, J = 1.0 Hz), 3.90−4.20 (1H, m), 5.60−6.20 (1H, s), 6.70−6.90 (1H, m), 6.90−7.40 (13H, m); LR-MS (EI) 374 (M^+).

General Procedure for Reaction with Methyl Bromoacetate. [3-Benzhydrylsulfanylmethylbenzofuran-7-yloxy]acetic Acid Methyl Ester (23a). To a solution of **22a** (67 mg, 0.19 mmol) in DMF (2.0 mL) was added methyl bromoacetate (0.18 mL) and K_2CO_3 (145 mg, 1.05 mmol), and the reaction mixture was stirred at room temperature for 1.5 h. Saturated aqueous NH_4Cl was added to the reaction mixture and was extracted with AcOEt. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue that was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/5) to afford **23a** (73 mg, 90%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.63 (2H, d, J = 0.5 Hz), 3.82 (3H, s), 4.88 (2H, s), 5.00 (1H, s), 7.12−7.40 (14H, m); IR (neat) 1748 cm^{-1} (COOMe); LR-MS (EI) 418 (M^+).

[3-(2,2-Diphenylethylsulfanylmethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (23b). Compound **23b** (93%) was prepared from **22b**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.12 (2H, d, J = 7.5 Hz), 3.64 (2H, d, J = 1.0 Hz), 3.81 (3H, s), 4.11 (1H, t, J = 7.5 Hz), 4.88 (2H, s), 6.78 (1H, d, J = 7.0 Hz), 7.11−7.30 (12H, m), 7.47 (1H, s); IR (neat) 1760 cm^{-1} (COOMe); LR-MS (EI) 432 (M^+).

[3-(3,3-Diphenylpropylsulfanylmethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (23c). Compound **23c** (70%) was prepared from **22c**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.20−2.60 (4H, m), 3.78 (2H, d, J = 2.0 Hz), 3.80 (3H, s), 3.90−4.20 (1H, m), 4.86 (2H, s), 6.77 (1H, dd, J = 1.0, 7.5 Hz), 7.00−7.50 (13H, m); IR (neat) 1763 cm^{-1} (COOMe); LR-MS (EI) 446 (M^+).

[3-(2-Benzhydrylsulfanylethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (23d). By the procedure used in **21a**, compound **23d** (80%) was prepared from **28**. Colorless prisms, mp 94−95 °C; ^{1}H NMR ($CDCl_3$) δ 2.59−3.02 (4H, m), 3.79 (3H, s), 4.87 (2H, s), 5.17 (1H, s), 6.69−7.45 (14H, m); IR (KBr) 1763 cm^{-1} (COOMe); LR-MS (EI) 432 (M^+).

{3-[2-(2,2-Diphenylethylsulfanyl)ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (23e). By the procedure used in **21a**, compound **23e** (80%) was prepared from **28**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.73−2.80 (2H, m), 2.85−2.92 (2H, m), 3.24 (2H, d, J = 8.0 Hz), 3.80 (3H, s), 4.17 (1H, t, J = 8.0 Hz), 4.88 (2H, s), 6.76−6.79 (1H, m), 7.12−7.33 (12H, m), 7.40 (1H, m); IR (neat) 1736 cm^{-1} (COOMe); LR-MS (EI) 446 (M^+).

{3-[2-(3,3-Diphenylpropylsulfanylmethyl)ethyl]-benzofuran-7-yloxy}acetic Acid Methyl Ester (23f). By the procedure used in **21a**, compound **23f** (29%) was prepared from **28**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.30−2.36 (2H, m), 2.46−2.52 (2H, m), 2.76−2.89 (4H, m), 3.80 (3H, s), 4.08 (1H, t, J = 8.0 Hz), 4.87 (2H, s), 6.77 (1H, dd, J = 2.0, 7.0 Hz), 7.11−7.31 (12H, m), 7.44 (1H, m); IR (neat) 1742 cm^{-1} (COOMe); LR-MS (EI) 460 (M^+).

[3-(3-Benzhydrylsulfanylpropyl)benzofuran-7-yloxy]-acetic Acid Methyl Ester (23g). By the procedure used in **21a**, compound **23g** (89%) was prepared from **33**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.93 (2H, sept, J = 7.0 Hz), 2.46 (2H, t, J = 7.0 Hz), 2.72 (2H, t, J = 7.0 Hz), 3.82 (3H, s), 4.88 (2H, s), 5.13 (1H, s), 6.77 (1H, dd, J = 2.0, 6.0 Hz), 7.00−7.50 (13H, m); IR (neat) 1763 cm^{-1} (COOMe); LR-MS (EI) 446 (M^+).

{3-[3-(2,2-Diphenylethylsulfanyl)propyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (23h). By the procedure used in **21a**, compound **23h** (67%) was prepared from **33**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.94 (2H, quint, J = 7.0 Hz), 2.50 (2H, t, J = 7.0 Hz), 2.71 (2H, t, J = 7.0 Hz), 3.20 (2H, d, J = 8.0 Hz), 3.81 (3H, s), 4.15 (1H, t, J = 8.0 Hz), 4.89 (2H, s), 6.77 (1H, dd, J = 1.0, 7.0 Hz), 7.09−7.34 (13H, m); IR (neat) 1765 cm^{-1} (COOMe); LR-MS (EI) 460 (M^+).

{3-[3-(3,3-Diphenylpropylsulfanyl)propyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (23i). By the procedure used in **21a**, compound **23i** (53%) was prepared from **33**. Colorless oil; ^{1}H NMR ($CDC1_3$) δ 1.92 (2H, quint, J = 7.0 Hz), 2.31 (2H, q, J = 7.0 Hz), 2.45 (2H, t, J = 7.0 Hz), 2.54 (2H, t, J = 7.0 Hz), 2.74 (2H, t, J = 7.0 Hz), 3.81 (3H, s), 4.08 (1H, t, J = 8.0 Hz), 4.88 (2H, s), 6.77 (1H, d, J = 7.0 Hz), 7.05−7.35 (12H, m), 7.39 (1H, s); IR (neat) 174 cm^{-1} (COOMe); LR-MS (EI) 474 (M^+)

{3-[2-(1,1-Diphenylethylsulfanyl)ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (23j). By the procedure used in **21a**, compound **23j** (74%) was prepared from **28**. Colorless oil; ^{1}H NMR ($CDC1_3$) δ 2.07 (3H, s), 2.61 (2H, m), 2.70 (2H, m), 3.80 (3H, s), 4.87 (2H, s), 6.75 (1H, dd, J = 1.0, 8.0 Hz), 6.97 (1H, dd, J = 1.0, 8.0 Hz), 7.08 (1H, t, J = 8.0 Hz), 7.19−7.34 (6H, m), 7.38−7.43 (5H, m); IR (neat) 1765 cm^{-1} (COOMe); LR-MS (EI) 446 (M^+).

(7-Methoxybenzofuran-3-yl)acetic Acid Methyl Ester (24). To a solution of 7-mehtoxy-3(2*H*)-benzofuranone (**19**) (1.80 g, 11.0 mmol) in xylene (40 mL) was added $Ph_3PCHCOOMe$ (4.10 g, 12.3 mmol), and the mixture was stirred at 140 °C for 18 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/3) to afford **24** (1.11 g, 46%). Pale-yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.70 (2H, d, J = 1.0 Hz), 3.73 (3H, s), 4.01 (3H, s), 6.82 (1H, dd, J = 2.0, 7.0 Hz), 7.15 (1H, dd, J = 2.0, 7.0 Hz), 7.19 (1H, t, J = 7.0 Hz), 7.64 (1H, s); IR (KBr) 1742 cm^{-1} (COOMe); LR-MS (EI) 220 (M^+).

(7-Hydroxybenzofuran-3-yl)acetic Acid Methyl Ester (25). To a solution of **24** (5.35 g, 24.3 mmol) in dichloromethane (100 mL) was added 1.0 M BBr_3 in dichloromethane (55 mL, 55 mmol) at −78 °C, and the mixture was stirred at 0 °C for 90 min. The reaction mixture was poured into water and was extracted with dichloromethane. The combined organic layer was sequentially washed with water and brine and dried over $MgSO_4$. Removal of the solvent afforded **25** (5.00 g, 99%). Pale-brown prisms, mp 48−50 °C; ^{1}H NMR ($CDCl_3$) δ 3.71 (2H, d, J = 1.0 Hz), 3.74 (3H, s), 5.30 (1H, bs), 6.82−6.88 (1H, m), 7.10−7.17 (2H, m), 7.64 (1H, t, J = 1.0 Hz); IR (KBr) 1696 cm^{-1} (COOMe); LR-MS (EI) 206 (M^+).

3-(2-Hydroxyethyl)benzofuran-7-ol (26). To a solution of **25** (8.11 g, 39 mmol) in THF (600 mL) was added $LiAlH_4$ (1.53 g, 40 mmol) at 0 °C and was stirred at 0 °C for 6 h. The reaction mixture was poured into 1.0 N HCl and was extracted with AcOEt. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. The solvent was removed, and the residue was recrystallized from AcOEt to afford **26** (5.37 g, 77%). Colorless prisms, mp 113.0 °C; ^{1}H NMR ($CDCl_3$) δ 2.94 (2H, dt, J = 1.0, 6.0 Hz), 3.94 (2H, t, J = 6.0 Hz), 5.26 (1H, bs), 6.85 (1H, m), 7.12−7.14 (2H, m), 7.52 (1H, d, J = 1.0 Hz); LR-MS (EI) 178 (M^+).

[3-(2-Hydroxyethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (27). By the procedure used in **23a**, compound **27** (80%) was prepared from **26**. Pale-yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.94 (2H, dt, J = 1.0, 6.0 Hz), 3.81 (3H, s), 3.93 (2H, t, J = 6.0 Hz), 4.89 (2H, s), 6.79 (1H, dd, J = 1.0, 8.0 Hz), 7.15 (1H, t, J = 8.0 Hz), 7.22 (1H, dd, J = 1.0, 8.0 Hz), 7.54 (1H, d, J = 1.0 Hz); IR (KBr) 1746 (COOMe); LR-MS (EI) 250 (M^+).

[3-(2-Methanesulfonyloxyethyl)benzofuran-7-yloxy]-acetic Acid Methyl Ester (28). To a stirred solution of **27** (4.12 g, 16.5 mmol) in CH_2C1_2 (120 mL) was added Et_3N (3.0 mL, 21.6 mmol) and methanesulfonyl chloride (1.35 mL, 17.4 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 3.5 h. The solvent was removed under reduced pressure, and the residue was poured into 1 N HCl and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water, saturated $NaHCO_3$, water, and brine and dried over Na_2SO_4. The solvent was removed, and the residue was recrystallized from AcOEt/*n*-hexane to afford **28** (5.25 g, 97%). Colorless prisms, mp 102.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.15 (2H, dt, J = 1.0, 7.0 Hz), 3.81 (3H, s), 3.92 (3H, s), 4.48 (2H, t, J = 7.0 Hz), 4.89 (2H, s), 6.79 (1H, dd, J = 1.5, 7.5 Hz), 7.17 (1H, t, J = 7.5 Hz), 7.21 (1H, dd, J = 1.5, 7.5 Hz), 7.56 (1H, s); IR (KBr) 1763 (COOMe); LR-MS (EI) 328 (M^+).

3-Allyl-7-methoxybenzofuran (29). $CeCl_3$ (5.63 g, 22.8 mmol) was dried with stirring at 150 °C for 4 h under reduced pressure. Anhydrous THF (30 mL) was added to this flask and was stirred at room temperature overnight. Allylmagnesium bromide (0.79 M in diethyl ether) (28.9 mL, 22.8 mmol) was added to this suspension at 0 °C dropwise, which afforded an orange suspension. To this suspension was added **19** (2.5 g, 22.8 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 1.5 h. The reaction mixture was poured into water (200 mL) and AcOH (3.0 mL) and was extracted with ethyl acetate. The combined organic layer was sequentially washed with saturated $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was removed, and to the residue was added benzene (20 mL) and *p*-TsOH (50 mg). The mixture was stirred at 60 °C for 0.5 h. The reaction mixture was sequentially washed with saturated $NaHCO_3$ and brine and was dried over Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/20) to afford **29** (2.05 g, 72%). Pale-yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.40−3.44 (2H, m), 4.10 (3H, s), 5.09−5.23 (2H, m), 5.95−6.10 (1H, m), 6.80 (1H, dd, J = 3.0, 6.0 Hz), 7.13−7.16 (2H, m), 7.42 (1H, s); LR-MS (EI) 188 (M^+).

3-(7-Methoxybenzofuran-3-yl)propan-1-ol (30). To a stirred solution of **29** (2.19 g, 11.65 mmol) in THF (25 mL) was added BH_3-Me_2S (2.0 M in THF) (6.1 mL, 12.2 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. To the reaction mixture was added EtOH (20 mL), 3 N NaOH (5 mL), and 30% H_2O_2 (1.5 mL), and the resulting solution was stirred at room temperature for 30 min. The reaction mixture was poured into saturated NH_4Cl and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water, saturated $NaHCO_3$, water, and brine and dried over Na_2SO_4. The solvent was removed and the residue was purified by silica gel chromatography (AcOEt/cyclohexane = 1/3) to afford **30** (1.42 g, 59%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.49 (1H, bs), 1.98 (2H, m), 2.77 (2H, dt, J = 1.0, 8.0 Hz), 3.74 (2H, t, J = 6.0 Hz), 4.01 (3H, s), 6.81 (1H, m), 7.16 (2H, m), 7.44 (1H, s); LR-MS (EI) 206 (M^+).

3-(3-Hydroxypropyl)benzofuran-7-ol (31). By the procedure used in **25**, compound **31** (90%) was prepared from **30**. Colorless prisms, mp 101.0−101.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.90 (2H, quint, J = 7.0 Hz), 2.72 (2H, t, J = 7.0 Hz), 3.62 (2H, t, J = 7.0 Hz), 6.70 (1H, dd, J = 2.0, 7.0 Hz), 7.03 (2H, m), 7.49 (1H, s); LR-MS (EI) 192 (M^+).

[3-(3-Hydroxypropyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (32). By the procedure used in **23a**, compound **32** (83%) was prepared from **31**. Colorless powder, mp 72−73 °C; ^{1}H NMR ($CDCl_3$) δ 1.98 (2H, quint, J = 6.0 Hz), 2.78 (2H, t, J = 6.0 Hz), 3.74 (2H, t, J = 6.0 Hz), 3.82 (3H, s), 4.89 (2H, s), 6.78 (1H, d, J = 7.0 Hz), 7.14 (1H, m), 7.22 (1H, m), 7.45 (1H, s); IR (KBr) 1715 cm^{-1} (COOMe); LR-MS (EI) 264 (M^+).

[3-(3-Bromopropyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (33). By the procedure used in **17**, compound **33** (95%) was prepared from **32**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.24 (2H, quint, J = 6.0 Hz), 2.86 (2H, t, J = 6.0 Hz), 3.45 (2H, t, J = 6.0 Hz), 3.82 (3H, s), 4.89 (2H, s), 6.78 (1H, dd, J = 1.0, 8.0 Hz), 7.15 (1H, t, J = 8.0 Hz), 7.21 (1H, dd, J = 1.0, 8.0 Hz), 7.48 (1H, s); IR (neat) 1769 cm^{-1} (COOMe); LR-MS (EI) 326, 328 (M^+) (relative peak hight ratio is 1:1).

7-Methoxy-2-(tetrahydropyran-2-yloxymethyl)benzofuran-3-one (36). Sodium hydride (60% in mineral oil, 5.60 g, 0.140 mmol), which was washed with *n*-hexane before use, was suspended in toluene (100 mL). To this suspension was added a solution of 3-methoxy-2-methoxycarbonylmethoxybenzoic acid methyl ester (**34**) (35.6 g, 0.140 mol) in toluene (400 mL), and the reaction mixture was refluxed for 22 h. After the mixture was cooled to room temperature, the precipitate was collected and washed with a small amount of toluene to give **35** (34.18 g, 100%) as pale-red powder.

To a stirred solution of **35** (11.3 g, 46.4 mmol) in THF (1100 mL) was added $LiAlH_4$ (1.83 g, 49 mmol) in four portions at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and 1 N HCl (200 mL) and brine (200 mL) were added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was dissolved in CH_2Cl_2 (180 mL). To this solution was added 3,4-dihydro-2*H*-pyran (7.26 g, 86 mmol) and pyridinium *p*-toluenesulfonate (2.50 g, 110 mmol), and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with CH_2Cl_2 (180 mL) and was sequentially washed with water and brine and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/3) to afford **36** (9.71 g, 75%) as a 1:1 mixture of two diastereomers.

Polar Isomer of 36. Pale-yellow solid; ^{1}H NMR ($CDCl_3$) δ 1.35−1.65 (6H, m), 3.50 (1H, m), 3.78 (1H, m), 3.97 (3H, s), 3.99 (1H, dd, J = 2.7, 11.5 Hz), 4.21 (1H, dd, J = 4.1, 11.5 Hz), 4.67 (1H, m), 4.76 (1H, dd, J = 2.7, 4.1 Hz), 7.03 (1H, t, J = 7.8 Hz), 7.13 (1H, dd, J = 1.2, 7.8 Hz), 7.27 (1H, dd, J = 1.2, 7.8 Hz); LR-MS (EI) 278 (M^+).

Less Polar Isomer of 36. Pale-yellow liquid; ^{1}H NMR ($CDCl_3$) δ 1.42−1.65 (6H, m), 3.52 (1H, m), 3.84 (1H, dd, J = 5.8, 11.5 Hz), 3.85 (1H, m), 3.97 (3H, s), 4.29 (1H, dd, J = 2.5, 11.5 Hz), 4.69 (1H, m), 4.82 (1H, dd, J = 2.5, 5.8 Hz), 7.02 (1H, t, J = 7.7 Hz), 7.12 (1H, dd, J = 1.4, 7.7 Hz), 7.25 (1H, dd, J = 1.4, 7.7 Hz); LR-MS (EI) 278 (M^+).

[7-Methoxy-2-(tetrahydropyran-2-yloxymethyl)benzofuran-3-yl]acetic Acid Methyl Ester (37). To a stirred suspension of zinc powder (7.81 g, 120 mmol) and catalytic amount of iodine in THF (10 mL) was added a solution of **36** (16.1 g, 58 mmol) and methyl bromoacetate (11.0 mL, 116 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 60 min and at 50 °C for 30 min. The reaction was quenched by addition of acetic acid (5.5 mL), and the mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was dissolved in toluene (140 mL) and pyridine (140 mL). The solution was cooled to 0 °C, and Tf_2O (14.5 mL, 88 mmol) was added. The reaction mixture was stirred at 0 °C for 90 min. The reaction was

quenched by addition of brine (400 mL), and the mixture was extracted with ethyl acetate. The combined organic layer was sequentially washed with water, 5% citric acid, water, and brine and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/2) to afford **37** (15.0 g, 78%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.45−1.90 (6H, m), 3.56 (1H, m), 3.69 (3H, s), 3.76 (2H, s), 3.90 (1H, m), 4.01 (3H, s), 4.70 (1H, d, J = 13.0 Hz), 4.72 (1H, t, J = 3.0 Hz), 4.85 (1H, d, J = 13.0 Hz), 6.81 (1H, dd, J = 1.0, 8.0 Hz), 7.11−7.20 (2H, m); IR (neat) 1742 cm^{-1} (COOMe); LR-MS (EI) 334 (M^+).

2-[7-Methoxy-2-(tetrahydropyran-2-yloxymethyl)benzofuran-3-yl]ethanol (38). By the procedure used in **26**, compound **38** (51%) was prepared from **37**. Pale-yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.49−1.87 (6H, m), 2.98 (2H, t, J = 6.0 Hz), 3.57 (1H, m), 3.87 (2H, t, J = 6.0 Hz), 3.92 (1H, m), 4.01 (3H, s), 4.64 (1H, d, J = 13.0 Hz), 4 81 (1H, t, J = 3.0 Hz), 4.86 (1H, d, J = 13.0 Hz), 6.83 (1H, dd, J = 1.0, 8.0 Hz), 7.12 (1H, dd, J = 1.0, 8.0 Hz), 7.17 (1H, t, J = 8.0 Hz); IR (neat) 1734 cm^{-1} (COOMe); LR-MS (EI) 306 (M^+).

[3-(2-Hydroxyethyl)-2-(tetrahydropyran-2-yloxymethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (39). To a stirred mixture of *t*-BuOK (9.71 g, 87 mmol) and **38** (7.67 g, 25 mmol) in DMF (150 mL) was added *n*-PrSH (8.50 mL, 94 mmol), and the reaction mixture was stirred at 140 °C for 1 h. The solvent was removed under reduced pressure, and the residue was poured into 5% citric acid and extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was dissolved in DMF (100 mL). To this solution was added K_2CO_3 (10.23 g, 74 mmol) and methyl bromoacetate (5.0 mL, 54 mmol), and the reaction mixture was stirred at room temperature for 15 h. The solvent was removed under reduced pressure, and the residue was poured into 5% citric acid and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/1, then 2/1) to afford **39** (7.54 g, 84%). Pale-yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.47−1.88 (6H, m), 2.31 (1H, t, J = 3.0 Hz), 2.98 (2H, t, J = 6.0 Hz), 3.81 (3H, s), 3.83−3.96 (3H, m), 4.65 (1H, d, J = 13.0 Hz), 4.81 (1H, t, J = 3.0 Hz), 4.85 (1H, d, J = 13.0 Hz), 4.90 (2H, s), 6.78 (1H, dd, J = 1.5, 7.5 Hz), 7.14 (1H, t, J = 7.5 Hz), 7.18 (1H, dd, J = 1.5, 7.5 Hz); IR (neat) 1763 cm^{-1} (COOMe); LR-MS (EI) 364 (M^+).

[3-[2-(1,1-Diphenylethylsulfanyl)ethyl]-2-(tetrahydropyran-2-yloxymethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (40b). Compound **39** was mesylated by the procedure used in **28**. And by the procedure used in **23d**, compound **40b** (80% in two steps) was synthesized from **39**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.47−1.82 (6H, m), 2.04 (3H, s), 2.57 (2H, t, J = 7.0 Hz), 2.77 (2H, t. J = 7.0 Hz), 3.54 (1H, m), 3.80 (3H, s), 3.89 (1H, m), 4.55 (1H, d, J = 13.0 Hz), 4.68 (1H, t, J = 3.0 Hz), 4.73 (1H, d, J = 13.0 Hz), 4.87 (2H, s), 6.74 (1H, dd, J = 1.0, 8.0 Hz), 6.89 (1H, dd, J = 1.0, 8.0 Hz), 7.06 (1H, t. J = 8.0 Hz), 7.18−7.30 (6H, m), 7.39 (4H, m); LR-MS (FAB, positive) 583 (M^+ + Na).

[3-(2-Benzhydrylsulfanylethyl)-2-(tetrahydropyran-2-yloxymethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (40a). By the procedure used in **40b**, compound **40a** (73%) was synthesized from **39**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.47−1.82 (6H, m), 2.66 (2H, t, J = 7.0 Hz), 2.95 (2H, t, J = 7.0 Hz), 3.54 (1H, m), 3.80 (3H, s), 3.89 (1H, m), 4.54 (1H, d, J = 13.0 Hz), 4.68 (1H, t, J = 3.0 Hz), 4.72 (1H, d, J = 13.0 Hz), 4.88 (2H, s), 5.15 (1H, s), 6.78 (1H, dd, J = 1.0, 8.0 Hz), 6.83 (1H, dd, J = 1.0, 8.0 Hz), 7.08 (1H, t, J = 8.0 Hz), 7.19−7.33 (6H, m), 7.37−7.41 (4H, m); LR-MS (FAB, positive) 569 (M^+ + Na).

[3-[2-(1,1-Diphenylpropylsulfanyl)ethyl]-2-(tetrahydropyran-2-yloxymethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (40c). By the procedure used in **40b**, compound **40c** (40%) was synthesized from **39**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.77 (3H, t, J = 7.0 Hz), 1.45−1.82 (6H, m), 2.33 (2H, q, J = 7.0 Hz), 2.40 (2H, t, J = 7.0 Hz), 2.69 (2H, t, J = 7.0 Hz), 3.54 (1H, m), 3.80 (3H, s), 3.88 (1H, m), 4.52 (1H, d, J = 13.0 Hz), 4.68 (1H, t, J = 3.0 Hz), 4.71 (1H, d, J = 13.0 Hz), 4.87 (2H, s), 6.73 (1H, dd, J = 1.0, 8.0 Hz), 6.84 (1H, dd, J = 1.0, 8.0 Hz), 7.05 (1H, t, J = 8.0 Hz), 7.16−7.29 (m, 6H), 7.33 (m, 4H); LR-MS (FAB, positive) 597 (M^+ + Na).

[3-[2-(1,1-Diphenylbutylsulfanyl)ethyl]-2-(tetrahydropyran-2-yloxymethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (40d). By the procedure used in **40b**, compound **40d** (86%) was synthesized from **39**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.82 (3H, t, J = 7.0 Hz), 1.14 (2H, m), 1.45−1.88 (6H, m), 2.25 (2H, m), 2.41 (2H, t, J = 7.0 Hz), 2.68 (2H, t, J = 7.0 Hz), 3.53 (1H, m), 3.80 (3H, s), 3.88 (1H, m), 4.52 (1H, d, J = 13.0 Hz), 4.68 (1H, t, J = 3.0 Hz), 4.70 (1H, d, J = 13.0 Hz), 4.87 (2H, s), 6.73 (1H, dd, J = 1.0, 8.0 Hz), 6.84 (1H, dd, J = 1.0, 8.0 Hz), 7.45 (1H, t, J = 8.0 Hz), 7.16−7.28 (6H, m), 7.34 (4H, m); LR-MS (FAB, positive) 611 (M^+ + Na).

{2-(Tetrahydropyran-2-yloxymethyl)-3-[2-(2,2,2-trifluoro-1,1-diphenylethylsulfanyl)ethyl]benzofuran-7-yloxy}-acetic Acid Methyl Ester (40e). By the procedure used in **40b**, compound **40e** (56%) was synthesized from **39**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.42−1.95 (6H, m), 2.59 (2H, m), 2.78 (2H, m), 3.56 (1H, m), 3.80 (3H, s), 3.89 (1H, m), 4.53 (1H, d, J = 13.0 Hz), 4.68 (1H, t, J = 3.3 Hz), 4.72 (1H, d, J = 13.0 Hz), 4.87 (2H, s), 6.73 (1H, dd, J = 0.8, 7.9 Hz), 6.78 (1H, dd, J = 0.8, 7.9 Hz), 7.03 (1H, t, J = 8.0 Hz), 7.25−7.30 (6H, m), 7.36−7.42 (4H, m); LR-MS (EI) 614 (M^+).

General Procedure for Deprotection of the THP Group. [3-[2-(1,1-Diphenylethylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid Methyl Ester (41b). To a stirred solutoin of **40b** (550 mg, 0.98 mmol) in THF (10 mL) and MeOH (10 mL) was added pyridinium *p*-toluenesulfonate (103 mg, 0.41 mmol), and the reaction mixture was stirred at 80 °C for 6.5 h. The solvent was removed under reduced pressure, and the residue was poured into 5% citric acid and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and was dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/1) to afford **41b** (387 mg, 83%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.00 (3H, s), 2.26 (1H, t, J = 6.5 Hz), 2.60 (2H, m), 2.69 (2H, m), 3.81 (3H, s), 4.63 (2H, d, J = 6.5 Hz), 4.88 (2H, s), 6.74 (1H, dd, J = 1.0, 7.0 Hz), 6.92 (1H, dd, J = 1.0, 7.0 Hz), 7.07 (1H, t, J = 7.0 Hz), 7.16−7.29 (6H, m), 7.34 (m, 4H); LR-MS (FAB, positive) 477 (M^+ + H).

[3-(2-Benzhydrylsulfanylethyl)-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid Methyl Ester (41a). Compound **41a** (73%) was prepared from **40a**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.15 (1H, t, J = 7.0 Hz), 2.67 (2H, t, J = 7.0 Hz), 2.92 (2H, t, J = 7.0 Hz), 3.80 (3H, s), 4.68 (2H, d, J = 7.0 Hz), 4.88 (2H, s), 5.04 (1H, s), 6.81 (1H, dd, J = 1.0, 8.0 Hz), 6.89 (1H, dd, J = 1.0, 8.0 Hz), 7.11 (1H, t, J = 8.0 Hz), 7.18−7.36 (10H, m); LR-MS (FAB, positive) 463 (M^+ + H).

[3-[2-(1,1-Diphenylpropylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid Methyl Ester (41c). Compound **41c** (78%) was prepared from **40c**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.73 (3H, t, J = 7.0 Hz), 2.27 (1H, t, J = 6.0 Hz), 2.31 (2H, q, J = 7.0 Hz), 2.47 (2H, m), 2.55 (2H, m), 3.81 (3H, s), 4.59 (2H, d, J = 6.0 Hz), 4.88 (2H, s), 6.74 (1H, dd, J = 1.0, 8.0 Hz), 6.88 (1H, dd, J = 1.0, 8.0 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.14−7.32 (10H, m); LR-MS (FAB, positive) 491 (M^+ + H).

[3-[2-(1,1-Diphenylbutylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid Methyl Ester (41d). Compound **41d** (91%) was prepared from **40d**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.80 (3H, t, J = 7.0 Hz), 1.11 (2H, m), 2.23 (2H, m), 2.26 (1H, t, J = 6.5 Hz), 2.48 (2H, m), 2.55 (2H, m), 3.81 (3H,s), 4.59 (2H, d, J = 6.5 Hz), 4.88 (2H, s), 6.74 (1H, dd, J = 1.0, 8.0 Hz), 6.88 (1H, dd, J = 1.0, 8.0 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.15−7.32 (10H, m); LR-MS (FAB, positive) 505 (M^+ + H).

{**2-Hydroxymethyl-3-[2-(2,2,2-trifluoro-1,1-diphenylethylsulfanyl)ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (41e).** Compound **41e** (84%) was prepared from **40e**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.98 (1H, t, J = 6.3 Hz), 2.57−2.65 (2H, m), 2.70−2.78 (2H, m), 3.81 (3H, s), 4.64 (2H, d, J = 6.3 Hz), 4.87 (2H, s), 6.73 (1H, dd, J = 0.8, 8.0 Hz), 6.81 (1H, dd, J = 0.8, 8.0 Hz), 7.05 (1H, t, J = 8.0 Hz), 7.24−7.29 (6H, m), 7.35−7.40 (4H, m); LR-MS (EI) 530 (M^+).

2-(3-(2-(1,1-Diphenylethylsulfonyl)ethyl)-2-(hydroxymethyl)benzofuran-7-yloxy)acetic Acid Methyl Ester (42). To a stirred solution of **41b** (216 mg, 0.45 mmol) in dichloromethane (3 mL) was added *m*-CPBA (196 mg) at 0 °C. The reaction mixture was stirred at this temperature for 3.5 h and was poured into water. The organic layer was separated, and the water layer was extracted twice with dichloromethane. The combined organic layer was sequentially washed with water and brine and dried over $MgSO_4$. Removal of the solvent gave an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 2/3) to afford **42** (183 mg, 79%). Colorless prisms, mp 53−54 °C; ^{1}H NMR ($CDCl_3$) δ 2.17 (3H, s), 2.49 (1H, t, J = 6.3 Hz), 2.97−3.12 (4H, m), 3.80 (3H, s), 4.69 (2H, d, J = 6.3 Hz), 4.87 (2H, s), 6.78 (1H, dd, J = 0.8, 8.0 Hz), 6.88 (1H, dd, J = 0.8, 8.0 Hz), 7.08 (1H, t, J = 8.0 Hz), 7.32−7.40 (6H, m), 7.52−7.60 (4H, m); LR-MS (EI) 508 (M^+).

2-Allyl-7-methoxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylic Acid Methyl Ester (43). Compound **35** (18.6 g, 76.4 mmol) was dissolved in DMF (150 mL). To this solution was added allyl bromide (8.6 mL, 99 mmol), and the reaction mixture was stirred at room temperature for 15.5 h. Acetic acid (2.0 mL) was added to the reaction mixture, and the solvent was removed under reduced pressure. The residue was dissolved in toluene (200 mL) and was refluxed for 1 h. The reaction mixture was cooled to room temperature and poured into water (200 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was sequentially washed with saturated $NaHCO_3$, water, and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/3) to afford **43** (18.4 g, 92%). Colorless oil; ^{1}H NMR ($CDC1_3$) δ 2.91 (1H, ddt, J = 14.5, 7.0, 1.0 Hz), 3.08 (1H, ddt, J = 14.5, 7.0, 1.0 Hz), 3.75 (3H, s), 3.99 (3H, s), 5.11−5.07 (1H, m), 5.27−5.20 (1H, m), 5.67 (1H, ddt, J = 17.0, 10.0, 7.0 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.15 (1H, dd, J = 8.0, 1.5 Hz), 7.24 (1H, dd, J = 8.0, 1.5 Hz); LR-MS (EI) 262 (M^+).

2-Allyl-7-methoxybenzofuran-3-one (44). To a solution of **43** (18.42 g, 70 mmol) in *t*-BuOH (150 mL) was added concentrated H_2SO_4 (2 mL), and the mixture was refluxed for 22.5 h. The reaction mixture was cooled to room temperature and was poured into saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was sequentially washed with saturated aqueous $NaHCO_3$, water, and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/4) to afford **44** (11.39 g, 80%). Colorless oil; ^{1}H NMR ($CDC1_3$) δ 2.55−2.66 (1H, m), 2.78−2.89 (1H, m), 3.96 (3H, s), 4.68 (1H, dd, J = 7.0, 5.0 Hz), 5.09−5.14 (1H, m), 5.24 (1H, ddd, J = 7.0, 2.0, 1.5 Hz), 5.82 (1H, ddt, J = 17.0, 10.0, 7.0 Hz), 7.02 (1H, t, J = 8.0 Hz), 7.15 (1H, dd, J = 8.0, 1.0 Hz), 7.24 (1H, dd, J = 8.0, 1.0 Hz); LR-MS (EI) 204 (M^+).

(2-Allyl-7-methoxybenzofuran-3-yl)acetic Acid Methyl Ester (45). By the procedure used in **37**, the Reformatski reaction of compound **44** was performed. The intermediate was dissolved in toluene (100 mL), and *p*-toluenesulfonic acid monohydrate (536 mg, 2.8 mmol) was added. The reaction mixture was stirred at room temperature for 2 h and was poured into water and extracted with ethyl acetate. The combined organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/3) and was recrystallized from AcOEt/*n*-hexane to afford **45** (5.23 g, 67%). Colorless prisms, mp 65−66 °C; ^{1}H NMR ($CDC1_3$) δ 3.57 (2H, dt, J = 6.0, 1.5 Hz), 3.63 (2H, s), 3.68 (3H, s), 3.99 (3H, s), 5.15 (1H, dq, J = 25.0, 1.5 Hz), 5.24 (1H, m), 5.82 (1H, ddt, J = 17.0, 10.0, 6.0 Hz), 6.77 (1H, dd, J = 7.7, 1.4 Hz), 7.09 (1H, dd, J = 7.7, 1.4 Hz), 7.15 (1H, t, J = 7.7 Hz); LR-MS (EI) 260 (M^+).

[2-Allyl-3-(2-hydroxyethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (46). To a solution of **45** (464 mg, 1.78 mmol) in dichloromethane (4 mL) was added 1.0 M BBr_3 dichloromethane solution (3.9 mL, 3.9 mmol) at −78 °C, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was poured into saturated $NaHCO_3$ and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was dissolved in THF (15 mL). To this solution was added $LiAlH_4$ (91 mg, 2.40 mmol), and the mixture was stirred at 0 °C for 30 min and at room temperature for 1.5 h. The reaction mixture was poured into saturated $NaHCO_3$ and extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was dissolved in DMF (5 mL). To this solution was added methyl bromoacetate (0.5 mL, 5.28 mmol) and K_2CO_3 (606 mg, 4.38 mmol), and the mixture was stirred at room temperature for 17 h. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/1) to afford **46** (450 mg, 87%). Colorless oil; ^{1}H NMR ($CDC1_3$) δ 2.89 (2H, t, J = 6.3 Hz), 3.56 (2H, dt, J = 6.0, 1.5 Hz), 3.81 (3H, s), 3.85 (2H, t, J = 6.3 Hz), 4.89 (2H, s), 5.10−5.19 (2H, m), 5.99 (1H, ddt, J = 17.0, 10.0, 6.0 Hz), 6.73 (1H, dd, J = 7.0, 1.5 Hz), 7.08−7.16 (2H, m); LR-MS (EI) 290 (M^+).

{**2-Allyl-3-[2-(tetrahydropyran-2-yloxy)ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (47).** To a solution of **46** (450 mg, 1.55 mmol) in THF (2 mL) were added 3,4-dihydro-2*H*-pyran (0.21 mL, 2.30 mmol) and *p*-toluenesulfonic acid monohydrate (15 mg, 0.08 mmol), and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was poured into water and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/3) to afford **47** (544 mg, 94%). Colorless oil; ^{1}H NMR ($CDC1_3$) δ 1.45−1.84 (6H, m), 2.92 (2H, t, J = 7.0 Hz,), 3.41−3.49 (1H, m), 3.53−3.61 (3H, m), 3.72−3.80 (1H, m), 3.81 (3H, s), 3.94 (1H, dt, J = 9.5, 7.0 Hz), 4.57−4.59 (1H, m), 4.88 (2H, s), 5.09−5.20 (2H, m), 5.98 (1H, ddt, J = 17.0, 10.2, 6.3 Hz), 6.70 (1H, dd, J = 8.0, 1.0 Hz), 7.09 (1H, t, J = 8.0 Hz), 7.16 (1H, dd, J = 8.0, 1.0 Hz); LR-MS (EI) 374 (M^+).

{**2-(2-Hydroxyethyl)-3-[2-(tetrahydropyran-2-yloxy)-ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (48).** To a solution of **47** (0.97 g, 2.59 mmol) in dioxane (15 mL) and water (5 mL) was added 0.07 M OsO_4 in *t*-BuOH (0.37 mL, 26 umol) at 0 °C. $NaIO_4$ (1 38 g 6 45 mmol) was added to this solution in several portions, and the mixture was stirred at 0 °C for 30 min and at room temperature for 30 min. The reaction mixture was filtered, and the filtrate was diluted with THF (12 mL). To this solution was added $NaBH_4$ (98 mg, 2.59 mmol), and the mixture was stirred at room temperature for 40 min. The reaction mixture was poured into water and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/1) to afford **48** (412 mg, 42%). Colorless oil; ^{1}H NMR ($CDC1_3$) δ 1.42−1.76 (6H, m), 2.96 (2H, t, J = 6.0 Hz), 3.05 (2H, t, J = 5.8 Hz), 3.35−3.43 (1H, m), 3.58−3.71 (2H, m), 3.81 (3H, s), 3.93 (2H, t, J = 5.8 Hz), 4.04−4.11 (1H, m), 4.52−4.54 (1H, m), 4.87 (2H, s), 6.70 (1H, dd, J =

8.0, 1.5 Hz), 7.09 (1H, t, J = 8.0 Hz), 7.14 (1H, dd, J = 8.0, 1.5 Hz); LR-MS (EI) 378 (M^+).

[2-(2-Acetoxyethyl)-3-(2-hydroxyethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (49). To a solution of **48** (403 mg, 1.06 mmol) in THF (5 mL) were added pyridine (0.13 mL, 1.61 mmol) and acetic anhydride (0.3 mL, 3.18 mmol). The reaction mixture was stirred at room temperature for 16 h and was poured into water and extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was dissolved in MeOH (4 mL). To this solution was added 1 N HCl (1 mL), and the reaction mixture was stirred at room temperature for 2 h and was poured into water and extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 2/1) and recrystallized from AcOEt/*n*-hexane to afford **49** (283 mg, 79%). Colorless prisms, mp 80−81 °C; ^{1}H NMR ($CDC1_3$) δ 2.03 (3H, s), 2.90 (2H, t, J = 6.3 Hz), 3.13 (2H, t, J = 6.6 Hz), 3.81 (3H, s), 3.87 (2H, t, J = 6.3 Hz), 4.43 (2H, t, J = 6.6 Hz), 4.88 (2H, s), 6.74 (1H, dd, J = 7.5, 2.5 Hz), 7.09−7.14 (2H, m); LR-MS (EI) 336 (M^+).

{2-(2-Acetoxyethyl)-3-[2-(1,1-diphenylethylsulfanyl)-ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (50). By the procedure used in the preparation of **40b**, compound **50** (87%) was prepared from **49** and **11b**. Colorless oil; ^{1}H NMR ($CDC1_3$) δ 1.99 (3H, s), 2.04 (3H, s), 2.50−2.59 (2H, m), 2.62−2.70 (2H, m), 2.98 (2H, t, J = 6.6 Hz), 3.81 (3H, s), 4.32 (2H, t, J = 6.6 Hz), 4.87 (2H, s), 6.69 (1H, dd, J = 8.0, 1.0 Hz), 6.85 (1H, dd, J = 8.0, 1.0 Hz), 7.04 (1H, t, J = 8.0 Hz), 7.18−7.32 (6H, m), 7.36−7.42 (4H, m); LR-MS (EI) 532 (M^+).

2-(2-Allyl-7-methoxybenzofuran-3-yl)ethanol (51). By the procedure used in **26**, compound **51** (86%) was prepared from **45**. Colorless oil; ^{1}H NMR ($CDC1_3$) δ 2.90 (2H, t, J = 6.4 Hz), 3.56 (2H, dt, J = 4.6, 1.6 Hz), 3 86 (2H, t, J = 6.4 Hz), 4.00 (3H, s), 5.09−5.15 (1H, m), 5.18 (1H, q, J = 1.6 Hz), 5.99 (1H, ddt, J = 17.0, 9.9, 6.3 Hz), 6.77 (1H, dd, J = 7.4, 1.4 Hz), 7.08−7.17 (2H, m); LR-MS (EI) 232 (M^+).

[3-(2-Hydroxyethyl)-2-propenylbenzofuran-7-yloxy]-acetic Acid Methyl Ester (52). By the procedure used in **39**, compound **52** (35%) was prepared from **51**. Colorless oil; ^{1}H NMR ($CDC1_3$) δ 1.94 (3H, dd, J = 6.6, 1.4 Hz), 2.93 (2H, t, J = 6.5 Hz), 3.82 (3H, s), 3.85 (2H, t, J = 6.5 Hz), 4.92 (2H, s), 6.38−6.61 (2H, m), 6.76 (1H, dd, J = 7.0, 1.5 Hz), 7.08−7.14 (2H, m); LR-MS (EI) 290 (M^+).

{2-Propenyl-3-[2-(tetrahydropyran-2-yloxy)ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (53). By the procedure used in **47**, compound **53** (92%) was prepared from **52**. Colorless oil; ^{1}H NMR ($CDC1_3$) δ 1.44−1.86 (6H, m), 1.93 (3H, d, J = 5.2 Hz), 2.95 (2H, t, J = 7.0 Hz), 3.40−3.48 (1H, m), 3.58 (1H, dt, J = 9.5, 7.0 Hz), 3.72−3.82 (1H, m), 3.81 (3H, s), 3.93 (1H, dt, J = 9.5, 7.0 Hz), 4.56−4.59 (1H, m), 4.91 (2H, s), 6.35−6.56 (2H, m), 6.73 (1H, dd, J = 8.0, 1.0 Hz), 7.07 (1H, t, J = 8.0 Hz), 7.15 (1H, dd, J = 8.0, 1.0 Hz); LR-MS (EI) 374 (M^+).

{2-(3-Acetoxypropenyl)-3-[2-(tetrahydropyran-2-yloxy)ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (54). To a solution of **53** (523 mg, 1.40 mmol) in benzene (5 mL) were added *N*-bromosuccimide (299 mg, 1.68 mmol) and AIBN (23 mg. 0.14 mmol). The reaction mixture was stirred at room temperature for 4 h and was poured into water and extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was dissolved in DMF (4 mL). To this solution was added KOAc (205 mg, 2.09 mmol), and the mixture was stirred at room temperature for 50 min. The reaction mixture was poured into water and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/2) to afford **54** (217 mg, 36%). Colorless oil; ^{1}H NMR ($CDC1_3$) δ 1.44−1.84 (6H, m), 2.12 (3H, s), 2.98 (2H, t, J = 7.0 Hz), 3.39−3.47 (1H, m), 3.59 (1H, dt, J = 9.5, 7.0 Hz), 3.69−3.77 (1H, m), 3.82 (3H, s), 3.95 (1H, dt, J = 9.5, 7.0 Hz), 4.57 (1H, m), 4.77 (2H, dd, J = 6.0, 1.5 Hz), 4.90 (2H, s), 6.52 (1H, dt, J = 16.0, 6.0 Hz), 6.69 (1H, dt, J = 16.0, 1.5 Hz), 6.77 (1H, dd, J = 8.0, 1.0 Hz), 7.10 (1H, t, J = 8.0 Hz), 7.18 (1H, dd, J = 8.0, 1.0 Hz); LR-MS (EI) 432 (M^+).

[2-(3-Acetoxypropyl)-3-(2-hydroxyethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (55). To a solution of **54** (199 mg, 0.460 mmol) in MeOH (4 mL) was added 5% Pd/C (28 mg), and the reaction mixture was stirred at room temperature for 50 min under hydrogen atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/1) to afford **55** (80 mg, 50%). Colorless oil; ^{1}H NMR ($CDC1_3$) δ 2.03 (3H, s), 2.09 (2H, quint, J = 7.0 Hz), 2.87 (4H, m), 3.81 (3H, s), 3.86 (2H, t, J = 7.0 Hz), 4.12 (2H, t, J = 7.0 Hz), 4.88 (2H, s), 6.71 (1H, dd, J = 7.0, 2.0 Hz), 7.07−7.14 (2H, m); LR-MS (EI) 350 (M^+).

{2-(3-Acetoxypropyl)-3-[2-(1,1-diphenylethylsulfanyl)-ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (56). By the procedure used in the preparation of **40b**, compound **56** (78%) was prepared from **55**. Colorless oil; ^{1}H NMR ($CDC1_3$) δ 1.92 (2H, m), 2.01 (3H, s), 2.05 (3H, s), 2.50−2.57 (2H, m), 2.65−2.70 (2H, m), 2.76 (2H, t, J = 7.3 Hz), 3.80 (s, 3H), 4.05 (2H, t, J = 6.0 Hz), 4.86 (2H, s), 6.68 (1H, dd, J = 8.0, 1.0 Hz), 6.86 (1H, dd, J = 8.0, 1.0 Hz), 7.04 (1H, t, J = 8.0 Hz), 7.18−7.31 (6H, m), 7.36−7.41 (4H, m); LR-MS (EI) 546 (M^+).

Blood Samples. Blood samples were collected from healthy male human volunteers under the approval by the Institutional Ethics Committee of the Pharmaceutical Research Laboratories, Toray Industries, Inc. Written informed consent was obtained from each of the volunteers. The volunteers did not take any drugs at least within 2 weeks before their participation in this study. Blood samples were also collected from male cynomolgus monkeys (Japan SLC, Shizuoka, Japan) in accordance with the guidelines for the animal care and use established at the Pharmaceutical Research Laboratories, Toray Industries, Inc.

Binding Assay for TP and IP Receptors in Human Platelet Membrane. Blood was collected from human volunteers by venous puncture. An amount of nine volumes of the collected blood was mixed with one volume of a solution containing 85 mM sodium citrate, 65 mM citric acid, 2% glucose, and 0.1 mM indomethacin. Platelet-rich plasma (PRP) was prepared by centrifugation at 120*g* for 10 min at 4 °C. The platelets were washed twice in washing buffer, pH 6.5, containing 115 mM NaCl, 4.3 mM K_2HPO_4, 24.4 mM Na_2HPO_4, 5 mM glucose, 1 mM EDTA-2Na, and 0.01 mM indomethacin, and resuspended in 10 mM Tris buffer, pH 7.4, containing 5 mM $MgCl_2$, and 2 mM EDTA-2Na. The platelets were alternately frozen and thawed three times and then centrifuged at 40000*g* for 20 min at 4 °C. The membrane preparation was resuspended at 4 °C in assay buffer, pH 7.4, containing 50 mM Tris and 5 mM $MgCl_2$, and stored at −80 °C until use. For TP receptor binding assay, human platelet membrane (10 μg of protein) was incubated in assay buffer in the presence of the selective TP receptor antagonist, [^{3}H]SQ-29548, and **7** for 30 min at 25 °C. For IP receptor binding assay, human platelet membrane (10 μg of protein) was incubated in assay buffer in the presence of the selective IP receptor agonist, [^{3}H]APS-314d sodium, and **7** for 60 min at 4 °C. The reaction mixture was separated into bound and free radiolabeled ligand by rapid filtration through GF/C filters presoaked in 10 mM Tris-HCl buffer. Filters were washed, and the residual [^{3}H]SQ-29548 or [^{3}H]APS-314d sodium bound to the filter was determined by liquid scintillation counting. Specific binding was defined as the difference between total binding and nonspecific binding, which was determined in the presence of 10 μM SQ-29548 or 10 μM APS-314d sodium. K_i was calculated using the equation $K_i = IC_{50}/(1 + L/K_d)$, where L is the concentration of ligand.

Platelet Aggregation in PRP. Nine volumes of blood collected from human volunteers were mixed with one volume of 3.8% sodium citrate in a tube. The citrated blood samples were immediately centrifuged at 90−140*g* for 10 min at room temperature. The resulting supernatant was used as the PRP fraction. The remaining blood was further centrifuged at 1400*g* for 10 min. The resulting supernatant was used as the platelet-poor plasma fraction. Human PRP were pretreated with compound at various concentrations for 1 min before the addition of U46619 (2 μM), arachidonic acid (600 μM), collagen (1 μg/mL), or ADP (5 μM). The platelet stimulation with ADP was carried out in the presence or absence of SQ-29548 (10 μM).

Platelet aggregation was monitored by recording transmittance on a four-channel light transmission aggregometer (NBS Hematracer 601, MC Medical, Japan) for 5 min after the addition of a platelet-stimulating agent. For evaluating the effect of the test drugs, the percent inhibition values of platelet aggregation were calculated from the increases in transmittance observed with the test drugs ($N = 3$), on the assumption that no inhibition was observed in the control incubation of PRP with vehicle alone. And the optical density of platelet-poor plasma was taken to represent 100% aggregation.

Blood Pressure, Heart Rate, and ex Vivo Platelet Aggregation in Monkeys. Cynomolgus monkeys were anesthetized with sodium pentobarbital (35 mg/kg iv) and given compound **7** at doses of 3, 10, and 30 $\mu g\ kg^{-1}\ min^{-1}$ or compound **4** at doses of 0.3, 1, and 3 $\mu g\ kg^{-1}\ min^{-1}$ both in a manner of dose escalation by infusion for 30 min for each dose via the catheter inserted into the forearm or saphenous vein. Arterial blood pressure and heart rate were monitored with a polygraph system through a femoral catheter and during the infusion period, and the blood pressure and heart rate were recorded at baseline and at the end of the infusion at each dose. Arterial blood was drawn to examine ex vivo platelet aggregation at baseline and at the end of the infusion at each dose. The collected blood samples were processed to prepare PRP for determining by the light transmission method, as described above.

Statistics. The data are shown as the mean ± standard error. Statistical comparisons between mean values were performed by one-way ANOVA and Dunnett's test at a significance level of $p < 0.05$.

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Supporting Information Available: Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Hamberg, M.; Svensson, J.; Samuelsson, B. Thromboxanes: A new group of biologically active compounds derived from prostaglandin endoperoxides. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2994−2998.

(2) Hall, S. E. Thromboxane A_2 receptor antagonists. *Med. Res. Rev.* **1991**, *11* (5), 503−579.

(3) Rote, W. E.; Mu, D. X.; Lucchesi, B. R. Thromboxane antagonism in experimental canine carotid artery thrombosis. *Stroke* **1993**, *24*, 820−828.

(4) Serruys, P. W.; Rutsch, W.; Heyndrickx, G. R.; Danchin, N.; Mast, E. G.; Wijns, W.; Rensing, B. J.; Vos, J.; Stibbe, J. (CARPORT Study Group). Prevention of restenosis after percutaneous transluminal coronary angioplasty with thromboxane A_2 receptor blockade. *Circulation* **1991**, *84*, 1568−1580.

(5) The RAPT Investigators (Van de Werf, F.). Randomized trial of ridogrel, a combined thromboxane A_2 synthase inhibitor and thromboxane A_2/prostaglandin endoperoxide receptor antagonist, versus aspirin as adjunct to thrombolysis in patient with acute myocardial infarction. *Circulation* **1994**, *89*, 588−595.

(6) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature* **1976**, *263*, 663−665.

(7) Collins, P. W.; Djuric, S. W. Synthesis of therapeutic useful prostaglandin and prostacyclin analogs. *Chem. Rev*. **1993**, *93*, 1533−1564.

(8) Narita, S.; Takahashi, A.; Aoki, T.; Sato, H.; Satoh, S.; Yamada, S.; Kudo, M.; Yamaguchi, T.; Kogi, K.; Shibasaki, M. Syntehsis and biological activities of chemically stable prostacyclin mimics with *cis*-bicyclo[4.3.0]nonene ring system: the novel homoisocarbacyclin analogues. *Bioorg. Med. Chem.* **1993**, *1* (2), 77−118.

(9) Meanwell, N. A.; Romine, J. L.; Seiler, S. M. Non-prostanoid prostacyclin mimetics. *Drugs Future* **1994**, *19* (4), 361−385.

(10) Wise, H.; Jones, R. L. Focus on prostacyclin and its novel mimetics. *Trends. Pharmacol. Sci.* **1996**, *17*, 17−21.

(11) Hayashi, K.; Nagamatsu, T.; Oka, T.; Suzuki, Y. Modulation of anti-glomerular basement membrane nephritis in rats by ONO-1301, a non-prostanoid prostaglandin I_2 mimetic compound with inhibitory activity against thromboxane A_2 synthase. *Jpn. J. Pharmacol*. **1997**, *73* (1), 73−82.

(12) Minamoto, K. Beneficial effect of a stable PGI_2 analogue (ONO-1301) on prostanoid release after reperfusion in canine left single lung allotransplantation model. *Nippon Kyobu Geka Gakkai Zasshi*. **1997**, *45* (12), 1931−1942.

(13) Kondo, K.; Hamanaka, N. Prostacyclin mimetics with non-prostanoid structure. *Folia Pharmacol. Jpn*. **1995**, *106*, 181−191.

(14) Tsubaki, K.; Taniguchi, K.; Tabuchi, S.; Okitsu, O.; Hattori, K.; Seki, J.; Sakane, K.; Tanaka, H. A novel pyridazinone derivative as a nonprostanoid PGI_2 agonist. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2787−2790.

(15) Sturzebecher, S.; Witt, W. The PGI_2-analogue iloprost and the TXA_2-receptor antagonist sulotroban synergistically inhibit TXA_2-dependent platelet activation. *Prostaglandins* **1988**, *36*, 751−760.

(16) Klar, U.; Pletsch, A.; Rehwinkel, H.; Schreyer, R. An attempt to synthesize prostanoid thromboxane A_2 antagonists with an additional prostacyclin like quality. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1215−1218.

(17) Nishio, T. A novel transformation of alcohols to thiol. *J. Chem. Soc., Chem. Commum*. **1989**, 205−206.

(18) Nishio, T. Direct conversion of alcohol into thiols. *J. Chem. Soc., Perkin. Trans. 1* **1993**, 1113−1117.

(19) Bryant, W. M., III; Huhn, G. F. A practical preparation of 7-methoxy-3(2*H*)-benzofuranone. *Synth. Commun.* **1995**, *25* (6), 915−920.

(20) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, K.; Kamiya, Y. Reactions of carbonyl compounds with Grignard reagents in the presence of cerium chloride. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398.

(21) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. Carbon−carbon bond-forming reactions using cerium metal or organocerium(III) reagents. *J. Org. Chem*. **1984**, *49*, 3904−3912.

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