Novel Calcium Antagonists with Both Calcium Overload Inhibition and Antioxidant Activity. 2. Structure−Activity Relationships of Thiazolidinone Derivatives

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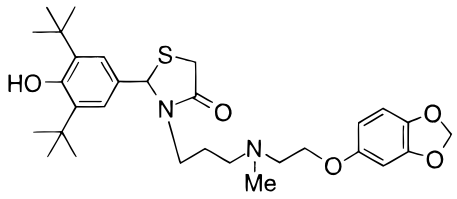
CP-060 (**1**), 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)-phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one, is a novel type of Ca^{2+} antagonist possessing both Ca^{2+} overload inhibition and antioxidant activity. The structure−activity relationships for this series of compounds were studied by synthesizing the analogues and evaluating these three kinds of activity. Ca^{2+} antagonistic activity was largely determined by the lipophilicity of the phenyl group at the 2-position and the length of the alkyl chains. As for the antioxidant activity, it was demonstrated that the phenolic hydroxyl group is an essential structural element. Compounds with potent activity were evaluated for their effect on the coronary blood flow in vivo. Among these compounds, compound **1** was shown to be the most potent. Furthermore, the enantiomers of **1** were resolved by high-performance liquid chromatography with a chiral column. Compound (−)-**1** showed about 10 times higher Ca^{2+} antagonistic activity than (+)-**1**, though both enantiomers had similar potency in Ca^{2+} overload inhibition and antioxidant activity. An X-ray crystal structure determination of (−)-**1** hydrogen fumarate identified (−)-**1** as having *S* configuration at the 2-position.

Introduction

In a previous paper,[1] we reported the design, synthesis, and pharmacological evaluation of a series of 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(aminopropyl)-1,3-thiazolidin-4-ones. These compounds have proved to be a novel class of Ca^{2+} antagonists possessing both Ca^{2+} overload inhibition and antioxidant activity. In particular, 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]-propyl]-1,3-thiazolidin-4-one (**1**) was found to be highly potent and to possess a well-balanced combination of these three actions in vitro. We demonstrated that the Ca^{2+} antagonistic and Ca^{2+} overload inhibitory activities depended on the substituents at the amino group. However, we could not clarify structure−activity relationships (SARs) at other parts of the molecule: substituent type in the phenyl group at the 2-position, R^1−R^4; length of the methylene chain, *m*; substituent type in the amino group, R^5 and R^6; and stereochemistry at the 2-position in the thiazolidinone ring, as shown in the general formula **2**.

In this paper, we describe the synthesis, pharmacological evaluation, and SARs of the 2-aryl-3-(aminoalkyl)-1,3-thiazolidinone derivatives and their optical isomers.



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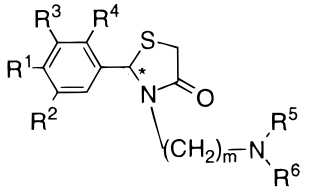

2

Chemistry

The aminoalkylthiazolidinone derivatives **11**−**27** were synthesized by a general method[1] as shown in Scheme 1. Initially, benzaldehydes **3** were condensed with ω-amino alcohols **4** to give imines **5**. A further condensation of the imines **5** with α-mercaptoacetic acid **6** afforded the key intermediates **7a**−**m** (Table 8). Compounds **7a**−**m** were then treated with thionyl chloride or phosphorus tribromide to give the corresponding chlorides **8a**−**m** or bromide **9a** (Table 9). Finally, aminations of **8a**−**m** or **9a** with amines **10** produced the target compounds **11**−**27** (method A or B).

Thiazolidinone derivative **32**, bearing a two-carbon chain ($m = 2$), was prepared as shown in Scheme 2, because the amination was not successful in this case. The possible reason for this is that the chloride **8k** may decompose via intramolecular cyclization. Initially, amination of *N*-(2-bromoethyl)phthalimide (**28**) with amine **10a** gave **29**, and then **29** was transformed into diamine **30** by treatment with methylamine. Subsequently, the diamine **30** was condensed with aldehyde **3a** to give imine **31**, and further condensation of **31** with α-mercaptoacetic acid **6** produced **32**.

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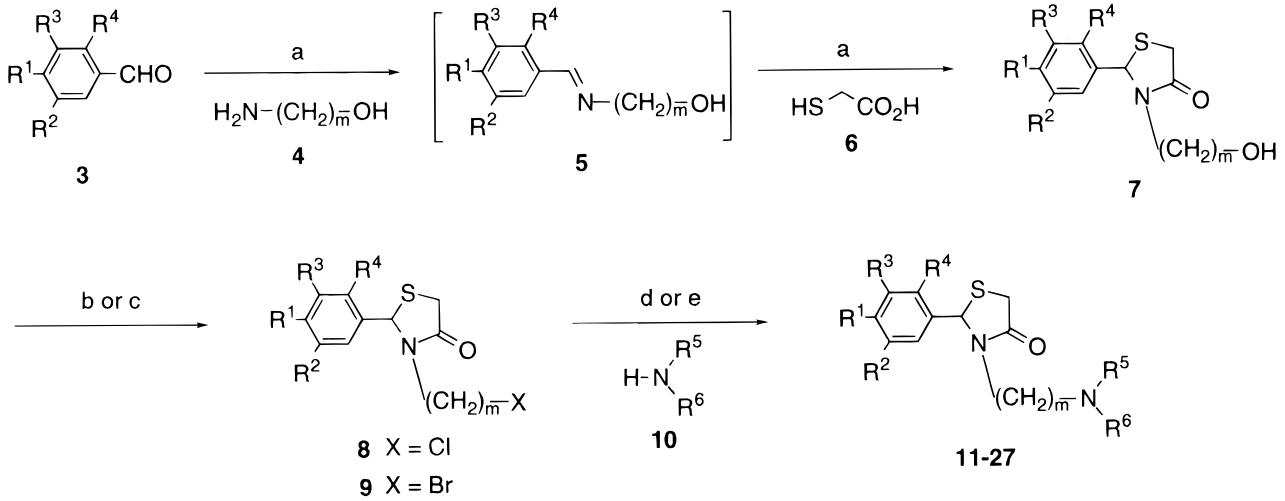
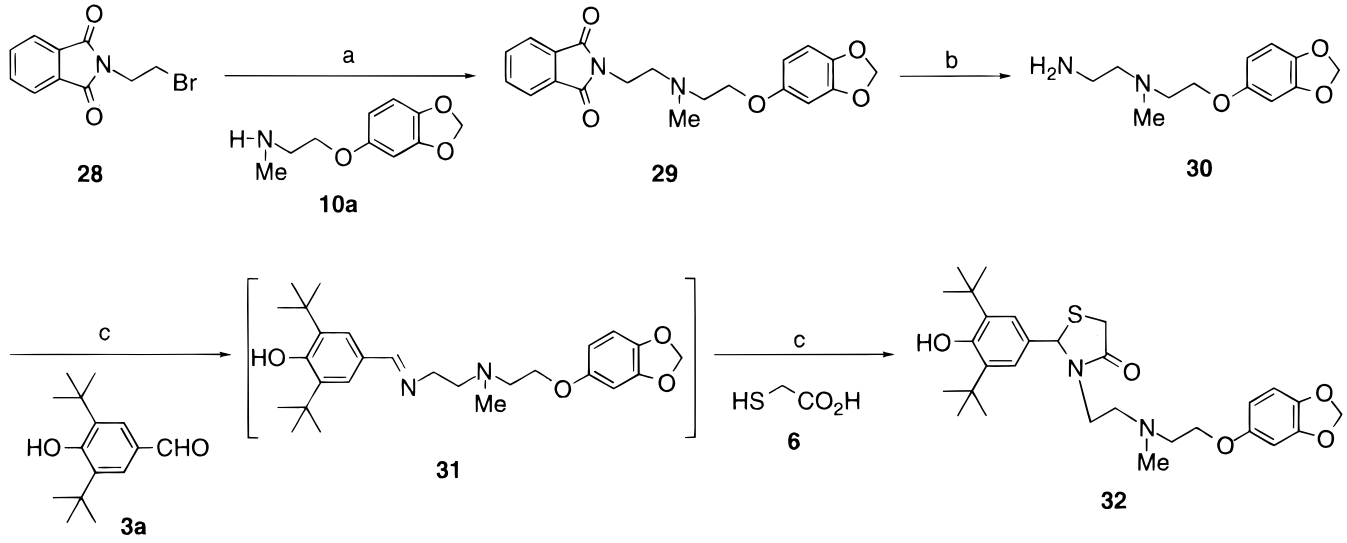
Scheme 1[a]



[a] Reagents and reaction conditions: (a) reflux in benzene with a Dean−Stark trap; (b) for X = Cl, $SOCl_2$, CH_2Cl_2, reflux; (c) for X = Br, PBr_3, Et_2O, rt; (d) for X = Cl, Na_2CO_3, NaI, DMF, 80 °C (method A); (e) for X = Br, K_2CO_3, acetone, reflux (method B).

Scheme 2[a]



[a] Reagents and reaction conditions: (a) K_2CO_3, DMF, 90 °C; (b) $MeNH_2$, MeOH, rt; (c) reflux in benzene with a Dean−Stark trap.

The elimination of a *tert*-butyl group from the phenyl ring of **1** proceeded in HBr/H_2O/AcOH to give **33**. Sulfoxide **34** was prepared by oxidation of **1** with H_2O_2. A thiolactam **35** was obtained by treating **1** with Lawesson's reagent[2] (Scheme 3).

Optical Resolution. The optical resolution of **1** was carried out by using preparative HPLC with a chiral column composed of cellulose 3,5-dimethylphenylcarbamate (Chiralcel OD).[3]

Absolute Configuration. The absolute configuration of (−)-**1** was determined by means of an X-ray crystallographic analysis using its hydrogen fumarate salt. The X-ray crystal structure of (−)-**1** hydrogen fumarate, as shown in Figure 1, revealed that the absolute configuration of the 2-position in the thiazolidinone ring was *S*.

Results and Discussion

The compounds prepared in this study were initially tested for Ca^{2+} antagonistic activity, and some compounds were tested for Ca^{2+} overload inhibitory activity.

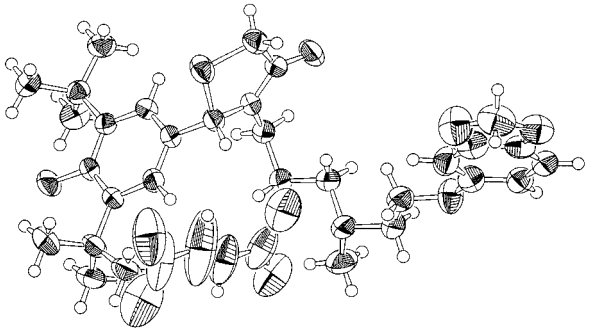
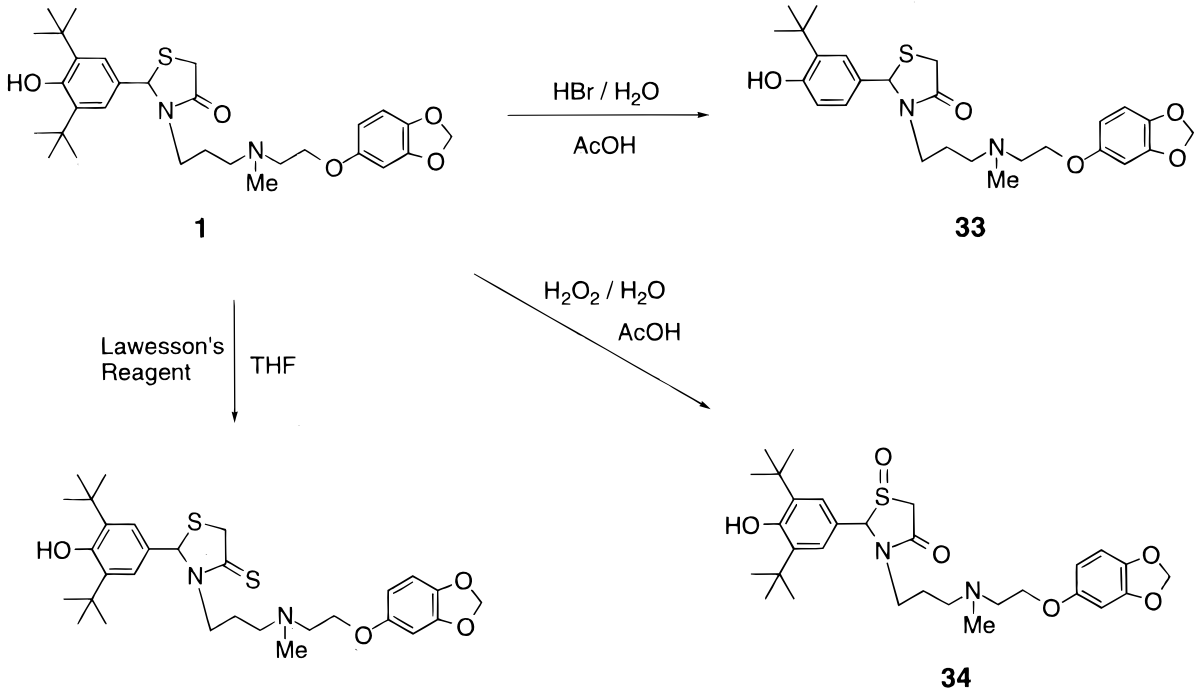


Figure 1. ORTEP drawing of (−)-**1** hydrogen fumarate which establishes its absolute stereochemistry.

The results are summarized in Tables 1−4. The antioxidant activity of representative thiazolidinone derivatives was examined, and the results are summarized in Table 5.

Ca^{2+} Antagonistic Activity. The in vitro Ca^{2+} antagonistic activity of compounds was evaluated by means of a K^+-depolarized isolated rat aorta.[4] As shown in Table 1, substituents in the phenyl group at the

Scheme 3



2-position, R^1−R^4, affected the activity significantly. When R^1 and R^4 were OH and H, respectively, the effects of substituents R^2 and R^3 were shown to be in the following order of potency: ^{t}Bu > ^{i}Pr > Et > Me > H > MeO > Cl. When one *tert*-butyl group of **1** was replaced with a methyl group, as in **17**, or with a hydrogen atom, as in **33**, this activity declined. In contrast, replacement of the phenolic hydroxyl group by a methoxy group, as in **19**, slightly increased the activity. In terms of results, it may be speculated that Ca^{2+} antagonistic activity in this series was enhanced by increased lipophilicity of the phenyl group at the 2-position of the thiazolidinone structure. The carbon chain length (*m*, *n*) was then optimized. The most potent activity was observed with $m = 3$ and $n = 2$−3 as shown in Table 2. The effect of the *N*-methyl substituent in the amine moiety was also examined. As shown in Table 3, the potency order was Me (**1**) = Et (**25**) > H (**24**) > CH_2CH_2OH (**27**) > ^{i}Pr (**26**). Moreover, oxidation of the sulfur atom in the thiazolidinone ring, as in the sulfoxide **34**, and conversion to the thiocarbonyl group at the 4-position, as in the thiolactam **35**, both resulted in a decreased activity.

Ca^{2+} Overload Inhibitory Activity. The Ca^{2+} overload inhibitory activity of compounds was evaluated as the protective effect in a veratridine-induced Ca^{2+} overload model of rat cardiac myocytes.[5] With respect to the substituents of the phenyl group at the 2-position, **11**, having the isopropyl groups in place of the *tert*-butyl groups, exhibited similar potency to that of **1**. Replacement of the phenolic hydroxyl group by a methoxy group, as in **19**, decreased the activity. As for the methylene chain lengths (*m*, *n*), the optimum length of *m* was 3 (**1**); on the other hand, Ca^{2+} overload inhibitory activity was less sensitive to changes in *n* as demonstrated by equipotent compounds **1** ($n = 2$), **22** ($n = 3$), and **23** ($n = 4$), as shown in Table 2. As for the *N*-alkyl substituent in the amine moiety, *N*-ethyl compound **25** had efficacy comparable with that of **1**; however, *N*-isopropyl compound **26** was less potent.

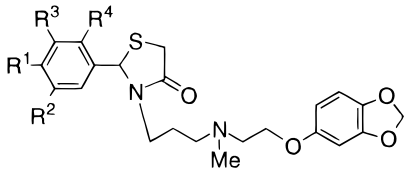
Antioxidant Activity. The antioxidant activity of some compounds was evaluated through the determination of their in vitro inhibitory activity on soybean lipoxygenase-induced lipid peroxidations of rabbit low-density lipoprotein (LDL).[6] All test compounds except for **19** exhibited potency similar to the known antioxidant 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT).[7] In contrast, compound **19**, where the phenolic hydroxyl group was replaced by the methoxy group, showed significantly reduced activity. Therefore, it was suggested that the phenolic hydroxyl group is an essential structure for potent antioxidant activity.

From these results, **1**, **22**, and **25** were regarded as having these three kinds of activity in vitro. We further assessed their effect on coronary blood flows in anesthetized dogs. As shown in Table 6, **1** was found to be the most potent compound for increasing coronary blood flow.

We resolved **1** into its enantiomers. The chiral compound (−)-**1** showed about 10 times more potent Ca^{2+} antagonistic activity than (+)-**1**, though both enantiomers had similar potency in Ca^{2+} overload inhibitory and antioxidant activities. Furthermore, (−)-**1** showed more coronary blood flow-increasing activity than diltiazem.

Compound (−)-**1** was submitted to an extensive pharmacological evaluation as a novel Ca^{2+} antagonist. The binding studies to the L-type Ca^{2+} channel suggested that (−)-**1** interacts with a new binding site distinct from the principal binding sites.[8] On the basis of electrophysiological studies, (−)-**1** inhibited not only a Ca^{2+} current but also a noninactivating Na^+ current without suppressing physiological Na^+ channel activity.[9] This mechanism would be considered to contribute to the cardioprotective effect against ischemic injury caused by Na^+ and Ca^{2+} overload.[10,11] Actually, (−)-**1** inhibited

Table 1. Effect of Substituents R^1, R^2, R^3, and R^4



compd	R^1	R^2	R^3	R^4	Ca^{2+}antagonistic activity; IC_{50},[a] μM (n)	Ca^{2+}overload inhibit.activity; $IC_{>80}$,[b] μM	mp,°C (recryst solv[c])	formula[d]	anal.[e]
1[f]	OH	^{t}Bu	^{t}Bu	H	0.062 ± 0.007 (6)	0.32	70-71 (Ac-iPr)	$C_{30}H_{42}N_2O_5S$	C, H, N
11	OH	^{i}Pr	^{i}Pr	H	0.14 ± 0.03 (2)	0.32	amorph[h]	$C_{28}H_{38}N_2O_5S{\cdot}C_4H_4O_4{\cdot}H_2O$	C, H, N
12	OH	Et	Et	H	0.32 ± 0.16 (2)	N.T.[g]	amorph[h]	$C_{26}H_{34}N_2O_5S{\cdot}C_4H_4O_4{\cdot}1/2H_2O$	C, H, N
13	OH	Me	Me	H	2.3 ± 0.4 (2)	N.T.[g]	amorph[h]	$C_{24}H_{30}N_2O_5S{\cdot}C_4H_4O_4{\cdot}2H_2O$	C, H, N
14	OH	H	H	H	2.6 ± 0.4 (2)	N.T.[g]	amorph[h]	$C_{22}H_{26}N_2O_5S{\cdot}HCl$	[i]
15	OH	OMe	OMe	H	4.1 ± 0.7 (2)	N.T.[g]	amorph[h]	$C_{24}H_{30}N_2O_7S{\cdot}C_4H_4O_4{\cdot}3/2H_2O$	C, H, N
16	OH	Cl	Cl	H	>10 (2)	N.T.[g]	amorph[h]	$C_{22}H_{24}N_2O_5SCl_2{\cdot}HCl{\cdot}3/2H_2O$	C, H, N
17	OH	^{t}Bu	Me	H	0.28 ± 0.13 (2)	N.T.[g]	98-100 (Ac-iPr)	$C_{27}H_{36}N_2O_5S{\cdot}C_4H_4O_4{\cdot}1/2H_2O$	C, H, N
33	OH	^{t}Bu	H	H	0.56 ± 0.27 (2)	N.T.[g]	amorph[h]	$C_{26}H_{34}N_2O_5S{\cdot}HCl$	[j]
18	OH	Me	Me	Me	0.63 ± 0.12 (2)	N.T.[g]	amorph[h]	$C_{25}H_{32}N_2O_5S{\cdot}C_4H_4O_4{\cdot}3/2H_2O$	C, H, N
19	OMe	^{t}Bu	^{t}Bu	H	0.036 ± 0.010 (2)	1.0	102-104 (Ac-iPr)	$C_{31}H_{44}N_2O_5S{\cdot}C_4H_4O_4{\cdot}H_2O$	C, H, N
diltiazem					0.10 ± 0.01 (8)	> 10			
R56865					0.76 ± 0.18 (5)	0.032			

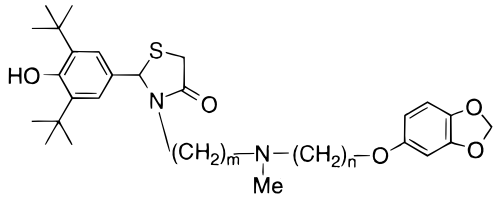
[a] Molar concentration required to inhibit 30 mM K^+ contraction of rat aorta by 50%. Diltiazem was used as a standard compound. Each value indicates a mean ± standard error from 2−8 experiments. The number of experiments performed is shown in parentheses. [b] Molar concentration required to inhibit veratridine-induced rat myocardiac cell death by >80%. The results were determined from 2−8 experiments, and more than 50 rod-shaped myocytes were used in each experiment. [c] Ac, acetone; iPr, diisopropyl ether. [d] $C_4H_4O_4$, fumaric acid. [e] All compounds gave satisfactory elemental analyses (±0.4%) for C, H, and N, unless otherwise noted. [f] See ref 1. [g] N.T., not tested. [h] The parent compound is an oil, and the corresponding salt was prepared as an amorphous solid after trituration with acetone−diisopropyl ether, AcOEt−hexane, or MeOH−water. Compound failed to give crystal. [i] *m/z* (EI, M^+, $C_{22}H_{26}N_2O_5S$) calcd 430.1561, found 430.1562. [j] *m/z* (EI, M^+, $C_{26}H_{34}N_2O_5S$) calcd 486.2225, found 486.2188.

ischemia- and reperfusion-induced arrhythmias in rats and reduced the size of myocardial infarct in dogs.[12,13] These cardioprotective effects seem likely to be explained by synergistically preventing Ca^{2+} overload and/or scavenging oxygen free radicals as well as blocking Ca^{2+} channels.[14] We are convinced that (−)-**1** (CP-060*S*) would be beneficial for patients with ischemic heart diseases.

Experimental Section

General Comments. The melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured with a Hitachi R-24B spectrometer (60 MHz), a JEOL JNM-FX200 spectrometer (200 MHz), or a JEOL JNM-EX270 spectrometer (270 MHz), with tetramethylsilane as the internal standard. Infrared spectra were recorded on a Hitachi Model 270-3 infrared spectrometer. EI mass spectra were determined on a Shimadzu GCMS-QP1000 instrument. HPLC analyses were performed on a Shimadzu SPD-10A (UV detector) with a Shimadzu LC-6AD (pump); a YMC-Pack A-312 S-5 120A ODS column was used; eluent CH_3CN-H_2O−TFA system at a flow rate of 1.0 mL/min. TLC was routinely performed on a Merck Kieselgel 60 F_{254}. Benzene was dried over MS4A before use. Organic extracts were dried over anhydrous sodium sulfate and concentrated by a rotary evaporator.

Table 2. Effect of the Length of the Methylene Chain (*m*, *n*)



compd	m	n	Ca^{2+}antagonistic activity; IC_{50},[a] μM (n)	Ca^{2+}overload inhibit.activity; $IC_{>80}$,[b] μM	mp,°C (recryst solv[c])	formula[d]	anal.[e]
32	2	2	0.36 ± 0.02 (2)	N.T.[g]	102-104 (Ac-iPr)	$C_{29}H_{40}N_2O_5S\cdot C_4H_4O_4\cdot H_2O$	C, H, N
1[f]	3	2	0.062 ± 0.007 (6)	0.32	70-71 (Ac-iPr)	$C_{30}H_{42}N_2O_5S$	C, H, N
20	4	2	0.21 ± 0.12 (2)	1.0	90-93 (Ac-iPr)	$C_{31}H_{44}N_2O_5S\cdot C_4H_4O_4\cdot 1/2H_2O$	C, H, N
21	5	2	0.28 ± 0.11 (2)	N.T.[g]	90-92 (Ac-iPr)	$C_{32}H_{46}N_2O_5S\cdot C_4H_4O_4$	C, H, N
22	3	3	0.078 ± 0.019 (2)	0.32	79-81 (Ac-iPr)	$C_{31}H_{44}N_2O_5S\cdot C_4H_4O_4\cdot 3/2H_2O$	C, H, N
23	3	4	0.20 ± 0.01 (2)	0.32	71-74 (Ac-iPr)	$C_{32}H_{46}N_2O_5S\cdot C_4H_4O_4\cdot 1/2H_2O$	C, H, N

[a−g] See footnotes *a*−*g* for Table 1.

General Procedure for the Preparation of 2-Aryl-3-(ω-hydroxyalkyl)-1,3-thiazolidin-4-one. To a suspension of the appropriate aldehyde **3** (0.10 mol) in dry benzene (150 mL) was added the appropriate ω-amino alcohol **4** (0.10 mol), and the mixture was refluxed for 1.5 h in a flask equipped with a Dean−Stark trap under nitrogen atmosphere. After cooling to room temperature, α-mercaptoacetic acid (**6**) (0.10 mol) was added dropwise to the solution, and the resulting mixture was refluxed for 2 h. It was then cooled and concentrated under reduced pressure. The obtained residue was poured into water and extracted with $CHCl_3$. The extract was dried and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give the corresponding compound.

2-(3,5-Diisopropyl-4-hydroxyphenyl)-3-(3-hydroxypropyl)-1,3-thiazolidin-4-one (7b): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.23 (12H, d, *J* = 6.6 Hz), 1.0−1.8 (2H, m), 2.5−3.8 (7H, m), 3.73 (2H, brs), 5.50 (2H, brs), 6.92 (2H, s); IR (neat) 3400, 2950, 1652 (C=O), 1464, 1200, 760 cm^{-1}; MS *m*/*z* 337 (M^+), 304, 262.

2-(3,5-Diethyl-4-hydroxyphenyl)-3-(3-hydroxypropyl)-1,3-thiazolidin-4-one (7c): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.20 (6H, t, *J* = 7.5 Hz), 1.0−1.7 (2H, m), 2.55 (4H, q, *J* = 7.5 Hz), 2.8−3.6 (5H, m), 3.77 (2H, brs), 5.27 (1H, brs), 5.47 (1H, brs), 6.87 (2H, s); IR (neat) 3400, 2960, 1658 (C=O), 1410, 1200 cm^{-1}; MS *m*/*z* 309 (M^+), 276, 234.

2-(3,5-Dimethyl-4-hydroxyphenyl)-3-(3-hydroxypropyl)-1,3-thiazolidin-4-one (7d): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.4−1.7 (2H, m), 1.68 (1H, brs), 2.26 (6H, s), 2.9−3.1 (1H, m), 3.2−3.3 (1H, m), 3.4−3.8 (2H, m), 3.73 and 3.86 (2H, ABq, *J* = 16 Hz), 5.04 (1H, brs), 5.48 (1H, s), 6.92 (2H, s); IR (KBr) 3300, 2930, 1630 (C=O), 1204, 1150 cm^{-1}; MS *m*/*z* 281 (M^+), 206, 135.

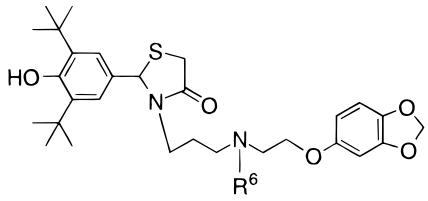
2-(4-Hydroxyphenyl)-3-(3-hydroxypropyl)-1,3-thiazolidin-4-one (7e): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.3−1.7 (2H, m), 2.0 (1H, brs), 2.9−3.2 (1H, m), 3.3−3.8 (3H, m), 3.74 and 3.82 (2H, ABq, *J* = 16 Hz), 5.57 (1H, s), 6.84 (2H, d, *J* = 8.0 Hz), 7.20 (2H, d, *J* = 8.0 Hz), 7.26 (1H, brs); IR (KBr) 3300, 2940, 1640 (C=O), 1450, 1260, 750 cm^{-1}; MS *m*/*z* 253 (M^+), 194, 107.

2-(3,5-Dimethoxy-4-hydroxyphenyl)-3-(3-hydroxypropyl)-1,3-thiazolidin-4-one (7f): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.4−1.7 (2H, m), 2.9−3.2 (1H, m), 3.3−4.1 (4H, m), 3.72 and 3.85 (2H, ABq, *J* = 16 Hz), 3.89 (6H, s), 5.55 (1H, s), 6.07 (1H, brs), 6.56 (2H, s); IR (KBr) 3300, 2950, 1650 (C=O), 1214, 1114 cm^{-1}; MS *m*/*z* 313 (M^+), 238.

2-(3,5-Dichloro-4-hydroxyphenyl)-3-(3-hydroxypropyl)-1,3-thiazolidin-4-one (7g): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.67 (2H, quint, *J* = 6.0 Hz), 2.7−4.0 (7H, m), 5.47 (1H, s), 6.87 (1H, s), 7.17 (2H, s); IR (KBr) 3450, 2950, 1630 (C=O), 1420, 1310, 1234, 1168 cm^{-1}; MS *m*/*z* 321 (M^+), 262, 175.

2-(3-*tert*-Butyl-4-hydroxy-5-methylphenyl)-3-(3-hydroxypropyl)-1,3-thiazolidin-4-one (7h): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.35 (9H, s), 1.0−2.1 (2H, m), 2.22 (3H, s), 2.7−3.8 (5H, m), 3.72 (2H, brs), 5.27 (1H, brs), 5.43 (1H, brs), 6.8−7.2 (2H, m); IR (neat) 3500, 2950, 1658 (C=O), 1434, 1230, 760 cm^{-1}; MS *m*/*z* 323 (M^+), 290, 248.

Table 3. Effect of Substituent R^6 in the Amino Group



compd	R^6	Ca^{2+}antagonistic activity; IC_{50},[a] μM (n)	Ca^{2+}overload inhibit.activity; $IC_{>80}$,[b] μM	mp,°C (recryst solv[c])	formula[d]	anal.[e]
24	H	0.16 ± 0.02 (2)	1.0	111-114 (Ac-iPr)	$C_{29}H_{40}N_2O_5S{\cdot}C_4H_4O_4{\cdot}1/2H_2O$	C, H, N
1[f]	Me	0.062 ± 0.007 (6)	0.32	70-71 (Ac-iPr)	$C_{30}H_{42}N_2O_5S$	C, H, N
25	Et	0.063 ± 0.020 (2)	0.32	amorph[h]	$C_{31}H_{44}N_2O_5S{\cdot}HCl$	[i] [j]
26	^{i}Pr	0.45 ± 0.14 (2)	1.0	amorph[h]	$C_{32}H_{46}N_2O_5S{\cdot}HCl$	
27	CH_2CH_2OH	0.32 ± 0.11 (2)	N.T.[g]	112-115 (Ac-iPr)	$C_{31}H_{44}N_2O_6S{\cdot}C_4H_4O_4{\cdot}1/2H_2O$	C, H, N

[a–h] See footnotes *a–h* for Table 1. [i] *m/z* (EI, M^+, $C_{31}H_{44}N_2O_5S$) calcd 556.2971, found 556.2950. [j] *m/z* (EI, M^+, $C_{32}H_{46}N_2O_5S$) calcd 570.3127, found 570.3136.

2-(2,3,5-Trimethyl-4-hydroxyphenyl)-3-(3-hydroxypropyl)-1,3-thiazolidin-4-one (7i): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.58 (2H, quint, *J* = 6.0 Hz), 2.17 (9H, s), 2.6−3.9 (5H, m), 3.70 (2H, brs), 5.43 (1H, s), 5.83 (1H, brs), 6.72 (1H, s); IR (neat) 3400, 2950, 1660 (C=O), 1218, 760 cm^{-1}; MS *m/z* 295 (M^+), 220, 162.

2-(3,5-Di-*tert*-butyl-4-methoxyphenyl)-3-(3-hydroxypropyl)-1,3-thiazolidin-4-one (7j): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.40 (18H, s), 1.2−1.7 (2H, m), 2.8−3.7 (5H, m), 3.65 (3H, s), 3.72 (2H, brs), 5.50 (1H, brs), 7.13 (2H, s); IR (KBr) 3450, 2950, 1670 (C=O), 1410, 1220 cm^{-1}; MS *m/z* 379 (M^+), 322.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(2-hydroxyethyl)-1,3-thiazolidin-4-one (7k): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.42 (18H, s), 2.6−4.0 (7H, m), 5.37 (1H, s), 5.67 (1H, s), 7.03 (2H, s); IR (KBr) 3450, 2950, 1660 (C=O), 1430, 1232 cm^{-1}; MS *m/z* 351 (M^+), 260.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(4-hydroxybutyl)-1,3-thiazolidin-4-one (7l): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.37 (18H, s), 1.2−1.9 (4H, m), 2.6−3.2 (2H, m), 3.3−3.4 (3H, m), 3.67 (2H, brs), 5.30 (1H, brs), 5.53 (1H, brs), 7.00 (2H, s); IR (KBr) 3350, 2950, 1660 (C=O), 1434, 1070 cm^{-1}; MS *m/z* 379 (M^+), 306, 234.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(5-hydroxypentyl)-1,3-thiazolidin-4-one (7m): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.40 (18H, s), 1.0−1.8 (6H, m), 2.23 (1H, s), 2.4−3.0 (1H, m), 3.2−3.8 (3H, m), 3.68 (2H, brs), 5.33 (1H, s), 5.53 (1H, brs), 7.03 (2H, s); IR (KBr) 3450, 2950, 1658 (C=O), 1430 cm^{-1}; MS *m/z* 393 (M^+), 234.

General Procedure for the Preparation of 2-Aryl-3-(ω-chloroalkyl)-1,3-thiazolidin-4-one. To a solution of the appropriate alcohol **7** (14 mmol) in CH_2Cl_2 (50 mL) was added thionyl chloride (21 mmol) at room temperature under nitrogen atmosphere, and the mixture was refluxed for 1 h. After cooling, the reaction mixture was poured into brine and extracted with $CHCl_3$. The extract was dried and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give the corresponding chloride.

2-(3,5-Diisopropyl-4-hydroxyphenyl)-3-(3-chloropropyl)-1,3-thiazolidin-4-one (8b): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.23 (12H, d, *J* = 6.6 Hz), 1.5−2.1 (2H, m), 2.6−3.8 (6H, m), 3.67 (2H, brs), 5.20 (1H, s), 5.50 (1H, brs), 6.88 (2H, s); IR (KBr) 3400, 2960, 1658 (C=O), 1460, 1202 cm^{-1}; MS *m/z* 355 (M^+), 280.

2-(3,5-Diethyl-4-hydroxyphenyl)-3-(3-chloropropyl)-1,3-thiazolidin-4-one (8c): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.23 (6H, t, *J* = 7.5 Hz), 1.7−2.2 (2H, m), 2.4−3.2 (5H, m), 3.3−3.6 (3H, m), 3.70 (2H, brs), 5.20 (IH, s), 5.50 (1H, brs), 6.87 (2H, s); IR (KBr) 3350, 2960, 1650 (C=O), 1442, 1200 cm^{-1}; MS *m/z* 327 (M^+), 252.

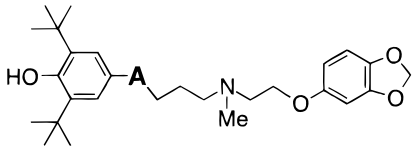
2-(3,5-Dimethyl-4-hydroxyphenyl)-3-(3-chloropropyl)-1,3-thiazolidin-4-one (8d): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.6−2.2 (2H, m), 2.26 (6H, s), 2.8−3.1 (1H, m), 3.47 (2H, t, *J* = 6.5 Hz), 3.5−3.8 (1H, m), 3.67 and 3.82 (2H, ABq, *J* = 16 Hz), 5.23 (1H, brs), 5.53 (1H, s), 6.91 (2H, s); IR (KBr) 3300, 1642 (C=O), 1200, 1142 cm^{-1}; MS *m/z* 299 (M^+), 224.

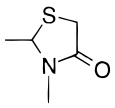
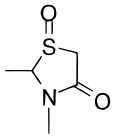
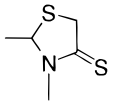
2-(4-Hydroxyphenyl)-3-(3-chloropropyl)-1,3-thiazolidin-4-one (8e): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.7−2.1 (2H, m), 2.8−3.1 (1H, m), 3.48 (2H, t, *J* = 6.6 Hz), 3.5−3.8 (1H, m), 3.69 and 3.83 (2H, ABq, *J* = 16 Hz), 5.59 (2H, brs), 6.86 (2H, d, *J* = 8.0 Hz), 7.22 (2H, d, *J* = 8.0 Hz); IR (KBr) 3100, 1640 (C=O), 1440, 1230 cm^{-1}; MS *m/z* 271 (M^+), 196, 107.

2-(3,5-Dimethoxy-4-hydroxyphenyl)-3-(3-chloropropyl)-1,3-thiazolidin-4-one (8f): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.7−2.1 (2H, m), 2.8−3.1 (1H, m), 3.49 (2H, t, *J* = 6.3 Hz), 3.5−3.7 (1H, m), 3.69 and 3.82 (2H, ABq, *J* = 16 Hz), 3.90 (6H, s), 5.58 (1H, s), 5.82 (1H, brs), 6.56 (2H, s); IR (KBr) 3300, 1658 (C=O), 1104 cm^{-1}; MS *m/z* 331 (M^+), 256.

2-(3,5-Dichloro-4-hydroxyphenyl)-3-(3-chloropropyl)-1,3-thiazolidin-4-one (8g): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.6−2.2 (2H, m), 2.8−3.1 (1H, m), 3.3−3.6 (3H, m), 3.68 and 3.82 (2H, ABq, *J* = 16 Hz), 5.51 (1H, s), 6.37 (1H, s), 7.24 (2H, s); IR (KBr) 3450, 2940, 1656 (C=O), 1280 cm^{-1}; MS *m/z* 341 (M^+ + 2), 339 (M^+), 304, 266.

Table 4. Related Compounds of Compound **1**



compd	A	Ca^{2+}antagonistic activity; IC_{50},[a] μM (n)	Ca^{2+}overload inhibit.activity; $IC_{>80}$,[b] μM	mp,°C (recryst solv[c])	formula[d]	anal.[e]
1[f]		0.062 ± 0.007 (6)	0.32	70-71 (Ac-iPr)	$C_{30}H_{42}N_2O_5S$	C, H, N
34		0.79 ± 0.36 (2)	N.T.[g]	129-130 (Cl-Hex)	$C_{30}H_{42}N_2O_6S$	C, H, N
35		0.16 ± 0.07 (2)	N.T.[g]	100-103 (Ac-iPr)	$C_{30}H_{42}N_2O_4S_2{\cdot}C_4H_4O_4{\cdot}H_2O$	C, H, N

[a,b] See footnotes *a*,*b* for Table 1. [c] Ac, acetone; iPr, diisopropyl ether; Cl, chloroform; Hex, *n*-hexane. [d–g] See footnotes *d*–*g* for Table 1.

Table 5. Antioxidant Activities of Thiazolidinone Derivatives

compd	LDL oxidation (% of control)[a]	
	0.5 μM	5 μM
1	12.9	3.0
21	13.5	5.9
22	16.4	3.9
25	16.8	6.4
35	22.8	11.3
19	91.6	39.7
BHT	19.7	0.9
α-tocopherol	60.2	13.2
diltiazem	109	111

[a] Inhibition of rabbit LDL oxidation induced by soybean lipoxygenase. All results are shown as percent of control.

2-(3-*tert*-Butyl-4-hydroxy-5-methylphenyl)-3-(3-chloropropyl)-1,3-thiazolidin-4-one (8h): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40 (9H, s), 1.7−2.1 (2H, m), 2.26 (3H, s), 2.9−3.1 (1H, m), 3.4−3.5 (2H, m), 3.5−3.7 (1H, m), 3.68 and 3.80 (2H, ABq, *J* = 15 Hz), 5.10 (1H, s), 5.55 (1H, s), 6.97 (1H, s), 7.01 (1H, s); IR (KBr) 3372, 2952, 1670, 1650 (C=O), 1426, 1172 cm^{-1}; MS *m*/*z* 341 (M^+), 304, 266.

2-(2,3,5-Trimethyl-4-hydroxyphenyl)-3-(3-chloropropyl)-1,3-thiazolidin-4-one (8i): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.8−2.2 (2H, m), 2.20 (3H, s), 2.22 (3H, s), 2.23 (3H, s), 2.8−3.0 (1H, m), 3.52 (2H, t, *J* = 6.6 Hz), 3.64 and 3.73 (2H, ABq, *J* = 16 Hz), 3.7−3.9 (1H, m), 4.73 (1H, s), 5.92 (1H, s), 6.74 (1H, s); IR (neat) 3400, 2940, 1656 (C=O), 1408, 1292, 1248, 1090, 752 cm^{-1}; MS *m*/*z* 313 (M^+), 238, 179.

2-(3,5-Di-*tert*-butyl-4-methoxyphenyl)-3-(3-chloropropyl)-1,3-thiazolidin-4-one (8j): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.40 (18H, s), 1.5−2.2 (2H, m), 2.6−3.6 (2H, m), 3.40 (2H, t, *J* = 6.5 Hz), 3.63 (3H, s), 3.68 (2H, brs), 5.52 (1H, brs), 7.13 (2H, s); IR (KBr) 2950, 1690 (C=O), 1404, 1218 cm^{-1}; MS *m*/*z* 397 (M^+), 382, 322.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(2-chloroethyl)-1,3-thiazolidin-4-one (8k): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.43 (18H, s), 3.0−3.2 (1H, m), 3.3−3.5 (1H, m), 3.5−3.7 (1H, m), 3.7−3.9 (1H, m), 3.75 (2H, brs), 5.35 (1H, s), 5.76 (1H, s), 7.11 (2H, s); IR (KBr) 3540, 2956, 1660 (C=O), 1424, 1100 cm^{-1}; MS *m*/*z* 369 (M^+), 354.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(4-chlorobutyl)-1,3-thiazolidin-4-one (8l): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.40

Table 6. Effects on Coronary Blood Flow by Intravenous Administration of Compounds **1**, **22**, **25**, and Diltiazem in Anesthetized Dogs

compd	CBF increasing activity (100 mg/kg, i.v.),[a] %
1	96 ± 16
22	23
25	52
diltiazem	86 ± 5

[a] Each value indicates a mean ± standard error from 5−6 experiments, and the ones without standard errors are the result of a single experiment. Diltiazem was used as a standard compound in all experiments.

Table 7. Enantiomers of Compound **1**

compd	Ca^{2+} antagonist activity; IC_{50},[a] μM (n)	Ca^{2+} overload inhibit.activity; $IC_{>80}$,[b] μM	LDL-ox. (% of control)[c] 0.5 μM	5 μM	CBF[d] %	config. of C(2)[e]	mp,°C (recryst solv[f])	formula[g]	anal.[h]
1	0.062 ± 0.007 (6)	0.32	12.9	3.0	96 ±16		70-71 (Ac-iPr)	$C_{30}H_{42}N_2O_5S$	C, H, N
(+)-**1**	0.34 ± 0.04 (3)	0.32	13.5	5.9	16 ± 3	R	143-145 (Me-Wt)	$C_{30}H_{42}N_2O_5S \cdot C_4H_4O_4$	C, H, N
(-)-**1**	0.033 ± 0.008 (8)	0.32	16.4	3.9	117 ± 2	S	143-144 (Me-Wt)	$C_{30}H_{42}N_2O_5S \cdot C_4H_4O_4$	C, H, N
diltiazem	0.10 ± 0.01 (8)	>10	109	111	86 ± 5				

[a,b] See footnotes *a,b* for Table 1. [c] See footnote *a* for Table 5. [d] See footnote *a* for Table 6. [e] Configuration of the 2-position of the thiazolidinone ring. [f] Ac, acetone; iPr, diisopropyl ether; Me, methanol; Wt, water. [g] $C_4H_4O_4$, fumaric acid. [h] All compounds gave satisfactory elemental analyses (±0.4%) for C, H, and N.

(18H, s), 1.2−2.0 (4H, m), 2.6−3.0 (1H, m), 3.2−3.6 (3H, m), 3.67 (2H, brs), 5.27 (1H, s), 5.50 (1H, brs), 7.02 (2H, s); IR (KBr) 3550, 2960, 1660 (C═O), 1430, 1240, 1110 cm^{-1}; MS *m/z* 397 (M^+), 322.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(5-chloropentyl)-1,3-thiazolidin-4-one (8m): ^1H NMR ($CDCl_3$, 60 MHz) δ 1.40 (18H, s), 1.1−2.0 (6H, m), 2.4−3.0 (1H, m), 3.2−3.8 (3H, m), 3.67 (2H, brs), 5.27 (1H, s), 5.50 (1H, brs), 7.00 (2H, s); IR (KBr) 3570, 2950, 1660 (C═O), 1420, 1230, 1110 cm^{-1}; MS *m/z* 411 (M^+), 336.

General Procedure for the Preparation of 2-Aryl-3-(ω-aminoalkyl)-1,3-thiazolidin-4-one (Method A). To a solution of the appropriate chloride **8** (1.0 mmol) and the appropriate amine (1.0 mmol) in DMF (5 mL), under nitrogen atmosphere, were added Na_2CO_3 (2.0 mmol) and NaI (0.1 mmol), and the mixture was stirred overnight at 80 °C. After cooling, the reaction mixture was poured into water and extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give the free form of the corresponding compound.

General Procedure for the Preparation of 2-Aryl-3-(ω-aminoalkyl)-1,3-thiazolidin-4-one (Method B). To a solution of the appropriate bromide **9** (1.0 mmol) and the appropriate amine (1.2 mmol) in acetone (25 mL), under nitrogen atmosphere, was added K_2CO_3 (1.2 mmol), and the mixture was refluxed for 10 h. After cooling, the reaction mixture was filtered and washed with acetone, and the resulting filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give the free form of the corresponding compound.

A solution of the free form in EtOH was treated with an equimolar amount of fumaric acid and concentrated under reduced pressure. The residue was triturated with $^iPr_2O$, AcOEt−hexane, or MeOH−H_2O, and the precipitated solid was collected by filtration. The obtained solid was dried in vacuo to give the corresponding hydrogen fumarate salt.

2-(3,5-Diisopropyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (11): method A (36%); ^1H NMR ($CDCl_3$, free form, 60 MHz) δ 1.23 (12H, d, *J* = 6.6 Hz), 1.4−1.9 (2H, m), 2.17 (3H, s), 2.3−3.8 (8H, m), 3.67 (2H, brs), 3.87 (2H, t, *J* = 5.7 Hz), 5.00 (1H, brs), 5.57 (1H, s), 5.80 (2H, s), 6.0−6.7 (3H, m), 6.90 (2H, s); IR (KBr) 3450, 2980, 1674 (C═O), 1498, 1198, 1050 cm^{-1}; MS *m/z* 514 (M^+), 363, 320; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 2.9 min (15.3%, fumaric acid) and t_R = 7.4 min (83.7%, free form of **11**), 99.0% pure.

2-(3,5-Diethyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (12): method A (34%); ^1H NMR ($CDCl_3$, free form, 60 MHz) δ 1.18 (6H, t, *J* = 7.2 Hz), 1.4−1.8 (2H, m), 2.17 (3H, s), 2.3−3.1 (9H, m), 3.3−3.8 (1H, m), 3.65 (2H, brs), 3.83 (2H, t, *J* = 5.7 Hz), 5.00 (1H, brs), 5.52 (1H, s), 5.78 (2H, s), 6.0−6.7 (3H, m), 6.80 (2H, s); IR (KBr) 3450, 3000, 1680 (C═O), 1498, 1198, 1050 cm^{-1}; MS *m/z* 486 (M^+), 335, 292; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 2.9 min (14.2%, fumaric acid) and t_R = 5.4 min (84.3%, free form of **12**), 98.5% pure.

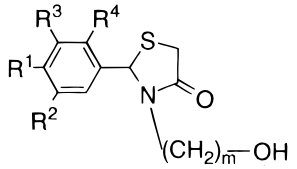
2-(3,5-Dimethyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (13): method A (53%); ^1H NMR ($CDCl_3$, free form, 200 MHz) δ 1.5−1.8 (2H, m), 2.23 (6H, s), 2.26 (3H, s), 2.3−2.5 (2H, m), 2.68 (2H, t, *J* = 5.7 Hz), 2.7−2.9 (1H, m), 3.5−3.7 (1H, m), 3.65 and 3.81 (2H, ABq, *J* = 16 Hz), 3.91 (2H, t, *J* = 5.7 Hz), 4.90 (1H, brs), 5.56 (1H, s), 5.90 (2H, s), 6.2−6.7 (3H, m), 6.88 (2H, s); IR (KBr) 3420, 2940, 1676 (C═O), 1498, 1188, 1040 cm^{-1}; MS *m/z* 458 (M^+), 135; HPLC analysis (CH_3CN-H_2O−TFA (30:70:0.1)) t_R = 3.3 min (9.9%, fumaric acid) and t_R = 7.8 min (89.5%, free form of **13**), 99.4% pure.

2-(4-Hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrochloride (14): method A (35%); ^1H NMR ($CDCl_3$, free form, 200 MHz) δ 1.5−1.8 (2H, m), 2.27 (3H, s), 2.3−2.5 (2H, m), 2.73 (2H, t, *J* = 5.7 Hz), 2.6−3.1 (1H, m), 3.5−3.7 (1H, m), 3.66 and 3.80 (2H, ABq, *J* = 16 Hz), 3.94 (2H, t, *J* = 5.7 Hz), 5.59 (1H, s), 5.88 (2H, s), 6.2−7.2 (8H, m); IR (KBr) 3440, 3240, 2980, 1670 (C═O), 1498, 1198, 1046 cm^{-1}; MS *m/z* 430 (M^+), 279, 236; HPLC analysis (CH_3CN-H_2O−TFA (30:70:0.1)) t_R = 10.2 min (99.4%).

2-(3,5-Dimethoxy-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (15): method A (55%); ^1H NMR ($CDCl_3$, free form, 200 MHz) δ 1.5−1.8 (2H, m), 2.25 (3H, s), 2.3−2.5 (2H, m), 2.70 (2H, t, *J* = 5.7 Hz), 2.7−2.9 (1H, m), 3.6−3.8 (1H, m), 3.67 and 3.79 (2H, ABq, *J* = 16 Hz), 3.85 (6H, s), 3.93 (2H, t, *J* = 5.7 Hz), 5.63 (1H, s), 5.89 (2H, s), 6.2−6.7 (6H, m); IR (KBr) 3440, 2930, 1670 (C═O), 1180, 1108 cm^{-1}; MS *m/z* 490 (M^+), 339, 137; HPLC analysis (CH_3CN-H_2O−TFA (30:70:0.1)) t_R = 3.3 min (9.6%, fumaric acid) and t_R = 10.0 min (90.2%, free form of **15**), 99.8% pure.

2-(3,5-Dichloro-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrochloride (16): method A (36%); ^1H

Table 8. 2-Aryl-3-(ω-hydroxyalkyl)-1,3-thiazolidin-4-ones[a]



compd	R^1	R^2	R^3	R^4	m	yield, %	mp,°C	recryst solv[b]	formula	anal.
7a	OH	^{t}Bu	^{t}Bu	H	3	55	100-101	Cl-Hex	$C_{20}H_{31}NO_3S$	C, H, N
7b	OH	^{i}Pr	^{i}Pr	H	3	24	oil			
7c	OH	Et	Et	H	3	27	oil			
7d	OH	Me	Me	H	3	16	120-123	Cl-Hex	$C_{14}H_{19}NO_3S$	C, H, N
7e	OH	H	H	H	3	14	104-107	Cl-Hex	$C_{12}H_{15}NO_3S$	C, H, N
7f	OH	OMe	OMe	H	3	36	120-123	Cl-Hex	$C_{14}H_{19}NO_5S$	C, H, N
7g	OH	Cl	Cl	H	3	45	129-132	Cl-Hex	$C_{12}H_{13}NO_3SCl_2$	C, H, N
7h	OH	^{t}Bu	Me	H	3	53	oil			
7i	OH	Me	Me	Me	3	16	oil			
7j	OMe	^{t}Bu	^{t}Bu	H	3	88	amorph		$C_{21}H_{33}NO_3S$	C, H, N
7k	OH	^{t}Bu	^{t}Bu	H	2	60	134-136	Cl-Hex	$C_{19}H_{29}NO_3S$	C, H, N
7l	OH	^{t}Bu	^{t}Bu	H	4	60	104-106	Cl-Hex	$C_{21}H_{33}NO_3S$	C, H, N
7m	OH	^{t}Bu	^{t}Bu	H	5	59	128-131	Cl-Hex	$C_{22}H_{35}NO_3S$	C, H, N

[a] Structures of all compounds were confirmed by ^{1}H NMR, IR, and MS spectra. [b] Cl, chloroform; Hex, *n*-hexane.

NMR ($CDCl_3$, free form, 200 MHz) δ 1.5−2.0 (2H, m), 2.37 (3H, s), 2.3−2.9 (3H, m), 2.86 (2H, t, J = 5.7 Hz), 3.5−3.8 (1H, m), 3.64 and 3.79 (2H, ABq, J = 16 Hz), 4.02 (2H, t, J = 5.7 Hz), 5.51 (1H, s), 5.88 (2H, s), 6.1−6.9 (4H, m), 7.14 (2H, s); IR (KBr) 3450, 2940, 1670 (C=O), 1490, 1180, 1040 cm^{-1}; MS *m*/*z* 498 (M^+), 347, 304; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 4.4 min (96.2%).

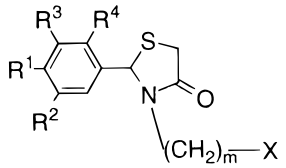
2-(3-*tert*-Butyl-4-hydroxy-5-methylphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (17): method B (58%); ^{1}H NMR ($CDCl_3$, free form, 200 MHz) δ 1.39 (9H, s), 1.2−1.8 (2H, m), 2.21 (3H, s), 2.24 (3H, s), 2.2−2.5 (2H, m), 2.67 (2H, t, J = 5.7 Hz), 2.6−2.9 (1H, m), 3.5−3.8 (1H, m), 3.67 and 3.80 (2H, ABq, J = 16 Hz), 3.91 (2H, t, J = 5.7 Hz), 5.19 (1H, brs), 5.58 (1H, s), 5.88 (2H, s), 6.1−7.1 (5H, m); IR (KBr) 3440, 2980, 1670 (C=O), 1492, 1198, 1046 cm^{-1}; MS *m*/*z* 500 (M^+), 349, 306; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 2.9 min (10.9%, fumaric acid) and t_R = 7.0 min (88.3%, free form of **17**), 99.2% pure.

2-(2,3,5-Trimethyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (18): method A (50%); ^{1}H NMR ($CDCl_3$, free form, 200 MHz) δ 1.5−1.9 (2H, m), 2.17 (3H, s), 2.19 (3H, s), 2.21 (3H, s), 2.29 (3H, s), 2.3−2.5 (2H, m), 2.70 (2H, t, J = 5.7 Hz), 2.6−2.9 (1H, m), 3.4−3.8 (1H, m), 3.61 and 3.76 (2H, ABq, J = 16 Hz), 3.91 (2H, t, J = 5.7 Hz), 5.87 (3H, brs), 5.95 (1H, s), 6.1−6.9 (4H, m); IR (KBr) 3440, 2920, 1674 (C=O), 1486, 1180, 1034 cm^{-1}; MS *m*/*z* 472 (M^+), 321; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 2.9 min (11.9%, fumaric acid) and t_R = 4.4 min (85.7%, free form of **18**), 97.6% pure.

2-(3,5-Di-*tert*-butyl-4-methoxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (19): method A (69%); ^{1}H NMR ($CDCl_3$, free form, 200 MHz) δ 1.41 (18H, s), 1.2−1.8 (2H, m), 2.20 (3H, s), 2.3−2.5 (2H, m), 2.69 (2H, t, J = 5.7 Hz), 2.6−2.9 (1H, m), 3.4−3.7 (1H, m), 3.65 (3H, s), 3.64 and 3.67 (2H, ABq, J = 16 Hz), 3.80 (2H, t, J = 5.7 Hz), 5.57 (1H, s), 5.89 (2H, s), 6.2−6.8 (3H, m), 7.06 (2H, s); IR (KBr) 3470, 2980, 1684 (C=O), 1496, 1198, 1048 cm^{-1}; MS *m*/*z* 556 (M^+), 405, 362; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 2.9 min (14.2%, fumaric acid) and t_R = 31.1 min (84.6%, free form of **19**), 98.8% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[4-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]butyl]-1,3-thiazolidin-4-one hydrogen fumarate (20): method A (48%); ^{1}H NMR ($CDCl_3$, free form, 60 MHz) δ 1.40 (18H, s), 1.1−1.9 (4H, m), 2.22 (3H, s), 2.2−2.8 (3H, m), 2.65 (2H, t, J = 5.7 Hz), 3.2−3.8 (1H, m), 3.65 (2H, brs), 3.88 (2H, t, J = 5.7 Hz), 5.30 (1H, brs), 5.52 (1H, brs), 5.82 (2H, s), 6.1−6.9 (3H, m), 7.00 (2H, s); IR (KBr) 3450, 2970, 1672 (C=O), 1488, 1186, 1040 cm^{-1}; MS *m*/*z* 556 (M^+), 405; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 2.9 min (18.4%, fumaric acid) and t_R = 14.5 min (79.7%, free form of **20**), 98.1% pure.

Table 9. 2-Aryl-3-(ω-haloalkyl)-1,3-thiazolidin-4-ones[a]



compd	R^1	R^2	R^3	R^4	m	X	yield, %	mp,°C	recryst solv[b]	formula	anal.
8a	OH	^{t}Bu	^{t}Bu	H	3	Cl	70	133-134	Cl-Hex	$C_{20}H_{30}NO_2SCl$	C, H, N
9a	OH	^{t}Bu	^{t}Bu	H	3	Br	56	130-131	Cl-Hex	$C_{20}H_{30}NO_2SBr$	C, H, N
8b	OH	^{i}Pr	^{i}Pr	H	3	Cl	60	105-106	Cl-Hex	$C_{18}H_{26}NO_2SCl$	C, H, N
8c	OH	Et	Et	H	3	Cl	95	94-95	Cl-Hex	$C_{16}H_{22}NO_2SCl$	C, H, N
8d	OH	Me	Me	H	3	Cl	70	210-211	Cl-Et	$C_{14}H_{18}NO_2SCl$	C, H, N
8e	OH	H	H	H	3	Cl	67	170-171	Cl-Et	$C_{12}H_{14}NO_2SCl$	C, H, N
8f	OH	OMe	OMe	H	3	Cl	59	95-98	Cl-Hex	$C_{14}H_{18}NO_4SCl$	C, H, N
8g	OH	Cl	Cl	H	3	Cl	61	114-116	Cl-Hex	$C_{12}H_{12}NO_2SCl_3$	C, H, N
8h	OH	^{t}Bu	Me	H	3	Cl	78	152-154	Cl-Hex	$C_{17}H_{24}NO_2SCl$	C, H, N
8i	OH	Me	Me	Me	3	Cl	38	oil			
8j	OMe	^{t}Bu	^{t}Bu	H	3	Cl	88	75-76	Cl-Hex	$C_{21}H_{32}NO_2SCl$	C, H, N
8k	OH	^{t}Bu	^{t}Bu	H	2	Cl	80	152-153	Cl-Hex	$C_{19}H_{28}NO_2SCl$	C, H, N
8l	OH	^{t}Bu	^{t}Bu	H	4	Cl	18	50-53	Cl-Hex	$C_{21}H_{32}NO_2SCl$	C, H, N
8m	OH	^{t}Bu	^{t}Bu	H	5	Cl	60	125-126	Cl-Hex	$C_{22}H_{34}NO_2SCl$	C, H, N

[a] See footnote *a* for Table 8. [b] Cl, chloroform; Hex, *n*-hexane; Et, diethyl ether.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[5-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]pentyl]-1,3-thiazolidin-4-one hydrogen fumarate (21): method A (65%); ^{1}H NMR ($CDCl_3$, free form, 60 MHz) δ 1.40 (18H, s), 1.0−1.8 (6H, m), 2.23 (3H, s), 2.1−3.0 (3H, m), 2.67 (2H, t, *J* = 5.7 Hz), 3.2−3.8 (1H, m), 3.67 (2H, brs), 3.90 (2H, t, *J* = 5.7 Hz), 5.33 (1H, brs), 5.50 (1H, brs), 5.80 (2H, s), 6.1−6.7 (3H, m), 7.02 (2H, s); IR (KBr) 3460, 2970, 1678 (C=O), 1492, 1192, 1042 cm^{-1}; MS *m*/*z* 570 (M^+), 419; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 2.9 min (11.4%, fumaric acid) and t_R = 16.8 min (85.5%, free form of **21**), 96.9% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[3-[3,4-(methylenedioxy)phenoxy]propyl]amino]-propyl]-1,3-thiazolidin-4-one hydrogen fumarate (22): method A (52%); ^{1}H NMR ($CDCl_3$, free form, 200 MHz) δ 1.43 (18H, s), 1.2−2.0 (4H, m), 2.11 (3H, s), 2.2−2.4 (2H, m), 2.40 (2H, t, *J* = 7.1 Hz), 2.7−2.9 (1H, m), 3.4−3.6 (1H, m), 3.66 and 3.80 (2H, ABq, *J* = 16 Hz), 3.87 (2H, t, *J* = 5.7 Hz), 5.31 (1H, s), 5.57 (1H, s), 5.88 (2H, s), 6.2−6.8 (3H, m), 7.07 (2H, s); IR (KBr) 3450, 2950, 1670 (C=O), 1494, 1180, 1034 cm^{-1}; MS *m*/*z* 556 (M^+), 222; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 2.9 min (11.3%, fumaric acid) and t_R = 16.2 min (87.0%, free form of **22**), 98.3% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[4-[3,4-(methylenedioxy)phenoxy]butyl]amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (23): method A (47%); ^{1}H NMR ($CDCl_3$, free form, 200 MHz) δ 1.43 (18H, s), 1.3−1.9 (6H, m), 2.07 (3H, m), 2.1−2.5 (4H, m), 2.6−3.0 (1H, m), 3.4−3.7 (1H, m), 3.67 and 3.80 (2H, ABq, *J* = 16 Hz), 3.86 (2H, t, *J* = 5.7 Hz), 5.30 (1H, s), 5.58 (1H, s), 5.88 (2H, s), 6.1−6.8 (3H, m), 7.07 (2H, s); IR (KBr) 3450, 2960, 1672 (C=O), 1488, 1184, 1038 cm^{-1}; MS *m*/*z* 570 (M^+), 433, 348; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 2.9 min (7.1%, fumaric acid) and t_R = 19.0 min (92.2%, free form of **23**), 99.3% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (24): method A (36%); ^{1}H NMR ($CDCl_3$, free form, 200 MHz) δ 1.42 (18H, s), 1.5−1.7 (3H, m), 2.61 (2H, t, *J* = 6.9 Hz), 2.8−2.9 (1H, m), 2.89 (2H, t, *J* = 5.3 Hz), 3.6−3.7 (1H, m), 3.68 and 3.78 (2H, ABq, *J* = 16 Hz), 3.95 (2H, t, *J* = 5.3 Hz), 5.34 (1H, brs), 5.60 (1H, s), 5.90 (2H, s), 6.2−6.8 (3H, m), 7.08 (2H, s); IR (KBr) 3450, 2970, 1680 (C=O), 1490, 1188, 1040 cm^{-1}; MS *m*/*z* 528 (M^+), 377; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 2.9 min (10.4%, fumaric acid) and t_R = 14.7 min (88.0%, free form of **24**), 98.4% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-ethyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrochloride (25): method A (8%); ^{1}H NMR ($CDCl_3$, free form, 200 MHz) δ 0.97 (3H, t, *J* = 6.8 Hz), 1.43 (18H, s), 1.2−1.8 (2H, m), 2.4−2.6 (4H, m), 2.7−3.0

(1H, m), 2.74 (2H, t, J = 5.7 Hz), 3.4−3.7 (1H, m), 3.66 and 3.79 (2H, ABq, J = 16 Hz), 3.89 (2H, t, J = 5.7 Hz), 5.33 (1H, s), 5.61 (1H, s), 5.89 (2H, s), 6.2−6.8 (3H, m), 7.08 (2H, s); IR (KBr) 3440, 2950, 1668 (C=O), 1482, 1180, 1038 cm^{-1}; MS m/z 556 (M^+), 405, 348; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 17.6 min (97.7%).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-isopropyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrochloride (26): method A (7%); ^1H NMR ($CDCl_3$, free form, 200 MHz) δ 0.93 (6H, d, J = 6.3 Hz), 1.43 (18H, s), 1.2−1.7 (2H, m), 2.41 (2H, t, J = 5.7 Hz), 2.6−3.0 (4H, m), 3.4−3.7 (1H, m), 3.62 and 3.75 (2H, ABq, J = 16 Hz), 3.80 (2H, t, J = 5.7 Hz), 5.33 (1H, s), 5.57 (1H, s), 5.89 (2H, s), 6.2−6.8 (3H, m), 7.06 (2H, s); IR (KBr) 3440, 2960, 1672 (C=O), 1488, 1438, 1184, 1038 cm^{-1}; MS m/z 570 (M^+), 433, 348; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 19.2 min (98.9%).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-(2-hydroxyethyl)-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (27): method B (47%); ^1H NMR ($CDCl_3$, free form, 200 MHz) δ 1.41 (18H, s), 1.4−2.0 (2H, m), 2.4−3.0 (7H, m), 3.4−3.7 (4H, m), 3.64 and 3.77 (2H, ABq, J = 16 Hz), 3.89 (2H, t, J = 5.7 Hz), 5.30 (1H, s), 5.54 (1H, s), 5.89 (2H, s), 6.1−6.8 (3H, m), 7.06 (2H, s); IR (KBr) 3440, 2950, 1664 (C=O), 1488, 1180, 1038 cm^{-1}; MS m/z 572 (M^+), 421, 234; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 2.9 min (11.5%, fumaric acid) and t_R = 12.7 min (87.6%, free form of **27**), 99.1% pure.

***N*-[2-[*N*-Methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]ethyl]phthalimide (29).** A suspension of *N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amine (**10a**) (2.0 g, 10 mmol), *N*-(2-bromoethyl)phthalimide (**28**) (2.7 g, 11 mmol), and K_2CO_3 (1.6 g, 11 mmol) in DMF (20 mL) was stirred overnight at 90 °C under nitrogen atmosphere. After cooling, the reaction mixture was poured into brine and extracted with $CHCl_3$. The extract was dried and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with $CHCl_3$−MeOH (10:1) to give 900 mg (24%) of **29** as a pale-yellow oil: ^1H NMR ($CDCl_3$, 60 MHz) δ 2.85 (3H, s), 3.6−4.4 (8H, m), 5.84 (2H, s), 6.1−6.8 (3H, m), 7.1−8.0 (4H, m).

***N*-(2-Aminoethyl)-*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amine (30).** To a solution of **29** (900 mg, 2.5 mmol) in MeOH (10 mL) was added a solution of 40% $MeNH_2$ in MeOH (10 mL, 116 mmol), and the mixture was stirred for 3 days at room temperature. The reaction mixture was concentrated under reduced pressure. To the residual oil were added $CHCl_3$ and 2 N HCl, and the aqueous layer was separated. The aqueous layer was made basic with 10% Na_2CO_3 solution and extracted with $CHCl_3$. The extract was dried and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with $CHCl_3$−MeOH−NEt_3 (50:50:1) to give 440 mg (75%) of **30** as a pale-orange oil: ^1H NMR ($CDCl_3$, 60 MHz) δ 2.34 (3H, s), 2.0−3.2 (8H, m), 3.90 (2H, t, J = 6 Hz), 5.85 (2H, s), 6.0−6.9 (3H, m).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[2-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]ethyl]-1,3-thiazolidin-4-one Hydrogen Fumarate (32). To a suspension of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**3a**) (410 mg, 1.76 mmol) in dry benzene (30 mL) was added **30** (420 mg, 1.76 mmol), and the mixture was refluxed for 2 h in a flask equipped with a Dean−Stark trap under nitrogen atmosphere. After cooling to room temperature, α-mercaptoacetic acid (**6**) (160 mg, 1.76 mmol) was added dropwise to the solution, and the resulting mixture was refluxed for 2 h. It was then cooled and concentrated under reduced pressure. The obtained residue was poured into water and extracted with $CHCl_3$. The extract was dried and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with $CHCl_3$−MeOH (97:3) to give 200 mg (22%) of the free form of **32** as a pale-brown oil: ^1H NMR ($CDCl_3$, 60 MHz) δ 1.40 (18H, s), 2.20 (3H, s), 2.5−3.0 (5H, m), 3.3−4.1 (3H, m), 3.65 (2H, brs), 5.23 (1H, s), 5.73 (1H, s), 5.82 (2H, s), 6.0−6.8 (3H, m), 7.00 (2H, s).

A solution of the free form of **32** in EtOH was treated with an equimolar amount of fumaric acid and concentrated under reduced pressure. The residue was triturated with AcOEt−hexane, and the precipitated solid was collected by filtration. The obtained solid was dried in vacuo to give **32** as colorless crystals: IR (KBr) 3450, 2950, 1708 (C=O), 1482, 1180, 1034 cm^{-1}; MS m/z 528 (M^+), 208; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 2.9 min (8.1%, fumaric acid) and t_R = 13.7 min (90.6%, free form of **32**), 98.7% pure.

2-(3-*tert*-Butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one Hydrochloride (33). To a solution of **1** (350 mg, 0.65 mmol) in AcOH (5 mL) was added 47% HBr in H_2O (5 mL, 43 mmol), and the mixture was stirred for 7 days at room temperature. The reaction mixture was poured into 5% Na_2CO_3 solution, and extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with $CHCl_3$−MeOH (98:2) to give 50 mg (16%) of the free amine of **33** as a pale-yellow oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.37 (9H, s), 1.2−1.9 (2H, m), 2.26 (3H, s), 2.1−2.5 (2H, m), 2.71 (2H, t, J = 5.7 Hz), 2.6−3.0 (1H, m), 3.4−3.8 (1H, m), 3.67 and 3.80 (2H, ABq, J = 16 Hz), 3.94 (2H, t, J = 5.7 Hz), 5.60 (1H, s), 5.82 (1H, s), 5.88 (2H, s), 6.1−7.0 (5H, m), 7.14 (1H, s).

To a solution of the free amine of **33** in MeOH was added a small excess of 4 N HCl in dioxane, and the mixture was concentrated under the reduced pressure. The residue was triturated with AcOEt−hexane, and the precipitated solid was collected by filtration. The obtained solid was dried in vacuo to give **33** as a colorless amorphous powder: IR (KBr) 3450, 2970, 1672 (C=O), 1492, 1192, 1042 cm^{-1}; MS m/z 486 (M^+), 335, 292; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 6.5 min (97.0%).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one 1-Oxide (34). To a solution of **1** (300 mg, 0.55 mmol) in AcOH (5 mL) was added 35% H_2O_2 in H_2O (200 mg, 3.7 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was poured into *5%* K_2CO_3 solution and extracted with AcOEt. The extract was dried and concentrated under reduced pressure. The residue was purified with chromatography on silica gel with $CHCl_3$−MeOH (98:2) to give 120 mg (39%) of **34** as colorless crystals: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.41 (18H, s), 1.4−2.0 (2H, m), 2.28 (3H, s), 2.3−2.7 (2H, m), 2.72 (2H, t, J = 5.7 Hz), 2.9−3.2 (1H, m), 3.37 and 3.69 (2H, ABq, J = 16 Hz), 3.8−4.2 (3H, m), 5.40 (1H, s), 5.61 (1H, s), 5.87 (2H, s), 6.1−6.8 (3H, m), 6.94 (2H, s); IR (KBr) 3624, 3480, 2950, 1682, 1670 (C=O), 1488, 1184, 1040 cm^{-1}; MS m/z 558 (M^+), 407; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 7.6 min (99.3%).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidine-4-thione Hydrogen Fumarate (35). A suspension of **1** (217 mg, 0.40 mmol) and Lawesson's reagent (194 mg, 0.48 mmol) in THF (5 mL) was stirred for 5 h at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was treated with H_2O and extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with $CHCl_3$−MeOH (99:1) to give 181 mg (81%) of the free amine of **35** as a pale-yellow oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.41 (18H, s), 1.3−1.8 (2H, m), 2.20 (3H, s), 2.3−2.5 (2H, m), 2.70 (2H, t, J = 5.7 Hz), 3.1−3.3 (1H, m), 3.93 (2H, t, J = 5.7 Hz), 3.9−4.1 (1H, m), 4.36 and 4.40 (2H, ABq, J = 16 Hz), 5.34 (1H, s), 6.18 (2H, s), 6.04 (1H, s), 6.2−7.0 (3H, m), 7.07 (2H, s).

A solution of the free form of **35** in EtOH was treated with an equimolar amount of fumaric acid and concentrated under reduced pressure. The residue was recrystallized from $CHCl_3$−hexane to give **35** as colorless crystals: IR (KBr) 3450, 2960, 1688 (C=O), 1482, 1182, 1038 cm^{-1}; MS m/z 558 (M^+), 421, 364; HPLC analysis (CH_3CN-H_2O−TFA (50:50:0.1)) t_R = 2.9

min (7.2%, fumaric acid) and t_R = 25.3 min (88.3%, free form of **35**), 95.5% pure.

Optical Resolution of 1. Compound **1** (400 mg) was dissolved in ^{i}PrOH (8 mL) and injected in 0.1-mL aliquots into a preparative chiral column (Chiralcel OD, i.d. 2 cm × 25 cm). The HPLC condition was as follows: mobile phase, ^{i}PrOH: hexane (20:80); flow rate, 13.2 mL/min; detection wavelength, 280 nm. Two pools of material were isolated with retention times of 11.4 min (180 mg, colorless oil) and 14.1 min (170 mg, colorless oil), respectively. The column isolates were individually treated with an equimolar amount of fumaric acid, and each was then recrystallized from MeOH−H_2O to give the corresponding hydrogen fumarate salts as colorless crystals. Each of them was examined by analytical chiral column (Chiralcel OD, i.d. 0.46 cm × 25 cm) for optical purity. The HPLC condition was as follows: mobile phase, ^{i}PrOH:hexane (20:80); flow rate, 0.7 mL/min; detection wavelength, 280 nm.

(*R*)-(+)-2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]-propyl]-1,3-thiazolidin-4-one hydrogen fumarate ((+)-1): colorless crystals; mp 143−145 °C (MeOH−H_2O); 99.6% ee; $[\alpha]_D$ = +33.3° (*c* = 1.166, EtOH).

(*S*)-(−)-2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]-propyl]-1,3-thiazolidin-4-one hydrogen fumarate ((−)-1): colorless crystals; mp 143−144 °C (MeOH−H_2O); 99.5% ee; $[\alpha]_D$ = −33.5° (*c* = 1.071, EtOH).

Single-Crystal X-ray Analysis of (−)-1. Suitable crystals of (−)-**1**, $C_{30}H_{42}N_2O_5S \cdot C_4H_4O_4$, FW = 658.81, were grown in AcOEt−hexane. A clear, colorless crystal, 0.24 × 0.17 × 0.35 mm, was used for the structural determination. A least-squares refinement, using 25 centered reflections within 59.08° < 2θ < 59.89°, gave the orthorhombic $P2_12_12_1$ cell, a = 11.863-(2) Å, b = 25.798(2) Å, c = 11.348(2) Å, V = 3473.1(7) Å^3, Z = 4, D_{calcd} = 1.260 g cm^{-3}. A Rigaku AFC7R diffractometer with graphite monochromated Cu Kα radiation (λ = 1.54178 Å, T = 296 K) was used for data collection. A total of 6060 reflections were measured in the $\omega - 2\theta$ mode to 2θ_{max} = 120°. Corrections were applied for Lorentz and polarization effects. The structure was solved by direct methods with the aid of the program SHELXS86,[15] and the non-H atoms were refined by using the full-matrix least-squares method. Hydrogen atoms were located on a difference Fourier map and subsequently entered at idealized positions. The final R factors for the 5261 reflections ($I > 3\sigma(I)$) were R = 0.041 and R_w = 0.061.

Calcium Antagonistic Activity. Thoracic aortas were removed from male Sprague−Dawley rats (350−550 g; Charles River Japan Inc.), dissected free from surrounding connective tissue, and cut into ring segments each about 2−3 mm long. Each strip of smooth muscle was mounted for isometric tension recording in an organ bath filled with 10 mL of Krebs-Henseleit (K-H) solution (pH 7.4). This bathing solution was maintained at 37 °C and bubbled with 95% O_2/5% CO_2. The strips were given a stretched tension of 2 g and allowed to equilibrate for more than 30 min. Isometric tension changes were monitored using an isometric transducer (Nihon Kohden Co., Ltd., TB-611T) and recorded on a self-balancing potentiometric recorder (Yokogawa Co., Ltd., 3066). After the equilibration period, a precontraction was produced by changing the solution in the bath to one containing 30 mM K^+. After the contraction was maintained for 20 min, the preparation was washed with K-H solution. Sixty minutes thereafter (the K-H solution was exchanged for a fresh one every 20 min), contraction was again induced in the same manner as described above. After the contraction stabilized, a test compound or diltiazem was added to the system in a cumulative manner in half-log-unit increments to obtain a concentration−response curve. Taking the contraction at 30 mM K^+ as 100%, the concentration of the drug at which the contraction was relaxed to 50% was deemed the IC_{50}. The results obtained are shown in Tables 1−4.

Protective Effects in the Veratridine-Induced Calcium Overload Model. Isolated ventricular myocytes were prepared from the heart of male Sprague−Dawley rats (300-500 g; Charles River Japan Inc.), using an enzyme-perfusion method.[16] The thus obtained rod-shaped normal myocytes were treated with a test compound or diltiazem for 30 min, and 50 μg/mL veratridine was added. Five minutes later, the shape of the cells was observed to obtain a survival rate thereby to evaluate the efficacy of the compound. The results obtained are shown in Tables 1−4.

Inhibitory Action on Lipid Peroxidation. A test compound was added to rabbit LDL prepared according to the method of Havel et al.,[17] and then a soybean lipoxygenase type-IS (SLO) was added to a final concentration of 40 μg/mL. Oxidation of LDL was carried out by incubation at 37 °C in a CO_2 incubator for 24 h. The oxidized LDL solution was analyzed by gel-permeation chromatography, and the fluorescence intensity of the LDL fraction was measured at an excitation wavelength of 360 nm and an emission wavelength of 430 nm. The results of measurements expressed as a percentage of control are shown in Table 5.

Effect on Coronary Blood Flow in Anesthetized Dogs. Male beagle dogs (9−14 kg) were anesthetized with sodium pentobarbital (PB; 35 mg/kg, iv) and maintained by infusion of PB (3-5 mg/kg/h, iv). Polyethylene catheters were inserted into the right cephalic vein for drug administration. After artificial respiration, the thoracotomy was performed through the left fifth intercostal space. The pericardium was opened and reflected to form a cradle for suspending the heart. An electromagnetic flow probe connected to an electromagnetic flow meter (Nihon Kohden Co., Ltd., MFV-2100) was placed around the left circumflex coronary artery to measure coronary blood flow (CBF). After the completion of surgery, the preparation was allowed for stabilization. A test compound was administered intravenously. The CBF-increasing activity was expressed as a maximal percent change from the preadministration value. The results are shown in Table 6.

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Supporting Information Available: Tables of atomic positional parameters, intramolecular bond distances, and intramolecular bond angles for (−)-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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