Novel Calcium Antagonists with Both Calcium Overload Inhibition and Antioxidant Activity. 1. 2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(aminopropyl)thiazolidinones

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A series of 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(aminopropyl)thiazolidinones was synthesized in order to explore novel calcium antagonists with potent antiischemic activity. These compounds were designed to have, in addition to Ca^{2+} antagonistic activity, both Ca^{2+} overload prevention and antioxidant activity in one molecule. These three kinds of activity were evaluated by using a K^+-depolarized rat aorta, a veratridine-induced Ca^{2+} overload model of rat cardiomyocytes, and a soybean lipoxygenase-induced lipid peroxidation model of rabbit low-density lipoprotein, respectively. 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 (**7o**) was found to be highly potent and possessed a well-balanced combination of these actions in vitro.

Introduction

A profound imbalance between supply and demand for oxygen in the myocardium plays a critical role in ischemic heart diseases (IHD) such as angina pectoris and myocardial infarction.[1] Ca^{2+} antagonists, which increase oxygen supply and decrease oxygen consumption in myocardium, have been widely used in the treatment of IHD.[2] They have been advocated as cardioprotective agents against ischemia on the basis of animal experiments.[3] However, it has not yet been demonstrated that Ca^{2+} antagonists significantly impact mortality in long-term clinical studies after infarction.[4]

On reperfusion of the ischemic heart tissue, a marked increase in the generation of oxygen free radicals (oxidative stress) and an extraordinary accumulation of intracellular calcium ions (Ca^{2+} overload) have been observed.[5] Recent studies suggest that both the oxidative stress and the Ca^{2+} overload are causally related to the resultant structural damage of cardiomyocytes and functional failure of the heart that occur under such pathological conditions.[6] Existing Ca^{2+} antagonists, however, have little or no inhibitory effect against Ca^{2+} overload or oxidative stress.[7]

These considerations have led us to design and synthesize novel Ca^{2+} antagonists with both Ca^{2+} overload inhibition and antioxidant activity, in order to discover a more effective drug than existing Ca^{2+} antagonists in the treatment of IHD.

A Ca^{2+} overload inhibitor, R56865 (**1**), reportedly has not only a potent veratridine-induced Ca^{2+} overload inhibitory activity in vitro but also myocardial protective activity in various experimental models.[8] From a structural consideration of **1**, its Ca^{2+} overload inhibitory effect was thought to be in correlation with the distance between the benzothiazolylaminopiperidine moiety and the phenyl group. As for the antioxidant activity, a 3,5-di-*tert*-butyl-4-hydroxyphenyl group is known to be an important moiety of the antioxidant 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) (**2**).[9] At present there is a substantial number of Ca^{2+} antagonists in use in the clinic;[10] in particular, diltiazem (**3**) is widely used for the treatment of IHD.[11] From a study of the structural features of diltiazem (**3**) and related compounds (e.g., SA2572 (**4**) and semotiadil (**5**)),[12] a sulfur- and nitrogen-containing heterocycle linked to a phenyl ring and an amine group were identified as probable important elements for the activity of Ca^{2+} antagonism.

Therefore, we formed the hypothesis that if in **1** we carried out a replacement of the phenyl group with the 3,5-di-*tert*-butyl-4-hydroxyphenyl group and an incorporation of the heterocyclic structure into the methylene spacer, this might lead to compounds that would exhibit all of the three desired pharmacological effects, as mentioned above (Chart 1).

On the basis of this hypothesis, we designed and synthesized derivatives of **1**, bearing various kinds of heterocycles. At the beginning of this study, it was found that a thiazolidinone derivative (**6**) had the three desired activities. We paid particular attention to the thiazolidinone structure and extensively synthesized the 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(aminopropyl)-1,3-thiazolidin-4-one derivatives shown in the general formula **7**. In this paper, we describe the synthesis and pharmacological evaluation of the thiazolidinone derivatives **6** and **7**.

HO S N O N N S N Me

6

HO S N O N R1 R2

7

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Chart 1. Drug Design

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).

Chemistry

The syntheses of the aminopropylthiazolidinone derivatives **6** and **7b–q** are presented in Scheme 1. Initially, the aldehyde **8** was condensed with 3-aminopropanol **(9)** to give imine **10**. A further condensation of imine **10** with α-mercaptoacetic acid **11** afforded the key intermediate **12**.[13] Compound **12** was then treated with thionyl chloride or phosphorus tribromide to give the corresponding chloride **13a** or bromide **13b**. Finally, aminations of **13a** or **13b** with amines **14** produced **6** or **7b–q**, respectively (method A or B).

Exceptionally, the primary amine **7a** was indirectly prepared from **12** by the Mitsunobu reaction as shown in Scheme 2.[14] As shown in Scheme 3, reactions of **7b** with epoxides produced **7r**,**s**, bearing the 3-phenoxy-2-hydroxypropylamine structure (method C).

Results and Discussion

The compounds prepared in this study were tested for Ca^{2+} antagonistic activity by means of a K^+-depolarized isolated rat aorta.[15] For Ca^{2+} overload inhibitory activity, we tested the protective effect in a veratridine-induced Ca^{2+} overload model of rat cardiac myocytes.[7b,16] The antioxidant activity of representative thiazolidinone derivatives was evaluated through a determination of their in vitro inhibitory activity on soybean lipoxyge-

Scheme 2

Scheme 3

nase-induced lipid peroxidations of rabbit low-density lipoprotein (LDL).[17]

At the beginning of this study; we found that the 4-(*N*-methyl-*N*-benzothiazolylamino)piperidinyl compound **6**, having the same amino group as R56865 (**1**), exhibited a protective effect against Ca^{2+} overload with an $IC_{>80}$ of 1 μM, a slightly less potent Ca^{2+} antagonistic activity than diltiazem (Table 1), and an inhibition of lipid peroxidation similar to that of BHT (Table 2). These data encouraged us to perform derivatizations of **6,** aimed at a potentiation of each of its pharmacological effects.

In our extensive program to develop novel cardioprotective drugs, we have focused on the 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(aminopropyl)thiazolidinone structure, considering it to be essential, and hence synthesized several amino-substituted derivatives (**7a**−**s**). In terms of results, all compounds exhibited Ca^{2+} antagonistic activity to various extents, as shown in Table 1. Of particular note was the finding that **7k**,**o** were more potent than diltiazem and 8 and 12 times more potent than the parent R56865, respectively. Interestingly, the terminal amino moieties of **7k**,**o** were the same as those of the existing Ca^{2+} antagonists, verapamil and semotiadil. A comparison of the terminal amine moieties ($-NR^1R^2$) showed the potency order to be **7c** (tertiary amine) > **7b** (secondary amine) > **7a** (primary amine). In addition, the Ca^{2+} antagonistic activity of the phenylalkylamine derivatives (**7h**−**k**) was higher than that of the alkylamine derivatives (**7c**−**g**). These results suggest that the terminal substituent at the amine may either hydrophobically or aromatically interact with a target receptor.

Certain of these compounds were evaluated as Ca^{2+} overload inhibitors. Importantly, the most effective Ca^{2+} antagonist, **7o**, also exhibited the most effective Ca^{2+} overload inhibition as well.

Antioxidative assay of **6** and **7k**,**o** was performed, and their activities were evidently suggested to be comparable to that of BHT, most likely because the common structural component, the 3,5-di-*tert*-butyl-4-hydroxyphenyl group, possesses essential antioxidant activity.

It is important to note that the novel cardioprotective compound **7o** (CP-060) has three types of action, and these are well-balanced. We believe that a novel drug with such a profile could turn out to be of great benefit for patients with IHD.[18] Further studies shall be needed to determine whether this hypothesis shall be borne out in the clinic.

Experimental Section

General. 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 recorded 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 and was eluted with CH_3CN-H_2O-TFA (50:50:0.1) at a flow rate of 1.0 mL/min. TLC was routinely performed on Merck Kieselgel 60 F_{254}. Organic extracts were dried over anhydrous sodium sulfate and concentrated by a rotary evaporator.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(3-hydroxypropyl)-1,3-thiazolidin-4-one (12). To a suspension of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde **(8)** (23.4 g, 0.10 mol) in dry benzene (150 mL) was added 3-aminopropanol **(9)** (7.51 g, 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 (**11**) (9.21 g, 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 H_2O (100 mL) and extracted with $CHCl_3$. The extract was dried and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with $CHCl_3-MeOH$ (99:1) and recrystallized from $CHCl_3$−hexane to give 20.2 g (55%) of **12** as colorless crystals: mp 100−101 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42 (18H, s), 1.2−1.6 (2H, m), 3.0−3.2 (1H, m), 3.3−3.6 (4H, m), 3.70 and 3.83 (2H, ABq, J = 16 Hz), 5.39 (lH, s), 5.54 (1H, s), 7.11 (2H, s); IR (KBr) 3750, 2950, 1660 (C=O), 1424, 1120 cm^{-1}; MS m/z 365 (M^+), 332, 290. Anal. ($C_{20}H_{31}NO_3S$) C, H, N.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(3-chloropropyl)-1,3-thiazolidin-4-one (13a). To a solution of **12** (5.09 g, 13.9 mmol) in CH_2Cl_2 (50 mL) was added thionyl chloride

Table 1. Ca^{2+} Antagonistic and Ca^{2+} Overload Inhibitory Activities of Novel Thiazolidinone Derivatives

HO, S, N, O, N, R^1, R^2

compd	$-N(R^1)R^2$	Ca^{2+} antagonistic activity; IC_{50},[a] µM	Ca^{2+} overload inhibit. activity; $IC_{>80}$,[b] µM	mp, °C (recryst solv[c])	formula[d]	anal.[e]
6	—N, N, Me, N, S	0.23 ± 0.09	1.0	amorph[f]	$C_{33}H_{46}N_4O_2S_2 \cdot 2HCl$	C, H, N
7a	—NH2	4.4 ± 1.4	N.T.	amorph[f]	$C_{20}H_{32}N_2O_2S \cdot C_4H_4O_4 \cdot 3/2H_2O$	C, H, N
7b	—NHMe	2.4 ± 0.4	N.T.	195-196 (Cl-Hex)	$C_{21}H_{34}N_2O_2S \cdot HBr$	C, H, N
7c	—N(Me)2	1.5 ± 0.4	N.T.	97-98 (Cl-Hex)	$C_{22}H_{36}N_2O_2S \cdot 3/2H_2O$	C, H, N[g]
7d	—N(Me), OH	3.3 ± 1.2	N.T.	amorph[f]	$C_{23}H_{38}N_2O_3S \cdot C_4H_4O_4 \cdot H_2O$	C, H, N
7e	—N(Me), OEt	0.84 ± 0.51	N.T.	amorph[f]	$C_{25}H_{42}N_2O_3S \cdot C_4H_4O_4 \cdot H_2O$	C, H, N
7f	—N(Me)	1.2 ± 0.7	N.T.	amorph[f]	$C_{25}H_{40}N_2O_2S \cdot C_4H_4O_4 \cdot H_2O$	C, H, N
7g	—N(Me), NMe2	1.7 ± 0.5	N.T.	amorph[f]	$C_{25}H_{43}N_3O_2S \cdot 2HCl \cdot 2H_2O$	C, H, N
7h	—N(Me)	0.60 ± 0.38	N.T.	amorph[f]	$C_{28}H_{40}N_2O_2S \cdot C_4H_4O_4 \cdot H_2O$	C, H, N
7i	—N(Me), O, O	0.25 ± 0.07	N.T.	amorph[f]	$C_{29}H_{40}N_2O_4S \cdot C_4H_4O_4 \cdot 6/5H_2O$	C, H, N
7j	—N(Me), OMe, OMe	0.12 ± 0.01	1.0	amorph[f]	$C_{30}H_{44}N_2O_4S \cdot C_4H_4O_4 \cdot H_2O$	C, H, N
7k	—N(Me), OMe, OMe	0.093 ± 0.029	1.0	amorph[f]	$C_{31}H_{46}N_2O_4S \cdot C_4H_4O_4 \cdot 1/2H_2O$	C, H, N
7l	—N(Me), O, OMe	0.23 ± 0.09	N.T.	amorph[f]	$C_{30}H_{44}N_2O_4S \cdot C_4H_4O_4$	C, H, N
7m	—N(Me), O, OMe, OMe	0.18 ± 0.07	1.0	amorph[f]	$C_{31}H_{46}N_2O_5S \cdot C_4H_4O_4 \cdot 1/2H_2O$	C, H, N
7n	—N(Me), O, OMe, OMe, OMe	0.30 ± 0.03	N.T.	135-136 (Ac-iPr)	$C_{32}H_{48}N_2O_6S \cdot C_4H_4O_4$	C, H, N
7o	—N(Me), O, O, O	0.062 ± 0.007	0.32	70-71 (Ac-iPr)	$C_{30}H_{42}N_2O_5S$	C, H, N

Table 1 (Continued)

compd	$-N(R^1)(R^2)$	Ca^{2+} antagonistic activity; IC_{50},[a] μM	Ca^{2+} overload inhibit. activity; $IC_{>80}$,[b] μM	mp, °C (recryst solv[c])	formula[d]	anal.[e]
7p		0.20 ± 0.03	1.0	amorph[f]	$C_{31}H_{44}N_2O_4S \cdot C_4H_4O_4 \cdot H_2O$	C, H, N
7q		0.21 ± 0.12	0.32	amorph[f]	$C_{32}H_{46}N_2O_2S \cdot C_4H_4O_4 \cdot 1/2H_2O$	C, H, N
7r		0.42 ± 0.12	N.T.	amorph[f]	$C_{30}H_{44}N_2O_4S \cdot C_4H_4O_4 \cdot H_2O$	C, H, N
7s		0.43 ± 0.14	N.T.	amorph[f]	$C_{31}H_{44}N_2O_6S \cdot C_4H_4O_4 \cdot H_2O$	C, H, N
diltiazem		0.10 ± 0.01	> 10			
R56865		0.76 ± 0.18	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 2–6 experiments. [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] Cl, chloroform; Hex, *n*-hexane; 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] The parent compound is an oil, and the corresponding salt was prepared as an amorphous solid after trituration with diethyl ether, diisopropyl ether, or *n*-hexane. Compound failed to give crystal. [g] Anal. C, N; H: calcd, 9.37; found, 8.77.

Table 2. Antioxidant Activities of Thiazolidinone Derivatives

compd	LDL oxidation (% of control)[a] 0.5 μM	5 μM
6	25.8	4.9
7k	8.7	0.6
7o	12.9	3.0
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.

(2.5 g, 21.0 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 with CH_2Cl_2 and recrystallized from $CHCl_3$–hexane to give 3.75 g (70%) of **13a** as pale-yellow crystals: mp 133–134 °C; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.40 (18H, s), 1.5–2.0 (2H, m), 2.6–3.6 (2H, m), 3.40 (2H, t, J = 6.5 Hz), 3.68 (2H, brs), 5.27 (1H, s), 5.50 (1H, s), 7.02 (2H, s); IR (KBr) 3560, 2980, 1664 (C=O), 1410, 1298, 1110 cm^{-1}; MS m/z 383 (M^+), 368, 308. Anal. ($C_{20}H_{30}NO_2SCl$) C,H, N.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(3-bromopropyl)-1,3-thiazolidin-4-one (13b). To a solution of **12** (2.0 g, 5.47 mmol) in Et_2O (20 mL) was added phosphorus tribromide (0.74 g, 2.73 mmol) at room temperature under nitrogen atmosphere, and the mixture was stirred for 6 h. The reaction mixture was poured into ice–water (10 mL) and extracted with Et_2O. The extract was washed with brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with $CHCl_3$ and recrystallized from $CHCl_3$–hexane to give 1.31 g (56%) of **13b** as pale-yellow crystals: mp 130–131 °C; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.43 (18H, s), 1.6–2.2 (2H, m), 2.6–3.6 (2H, m), 3.28 (2H, t, J = 6.5 Hz), 3.70 (2H, brs), 5.28 (1H, s), 5.53 (1H, s), 7.05 (2H, s); IR (KBr) 3540, 2950, 1652 (C=O), 1408, 1100 cm^{-1}; MS m/z 429 (M^+ + 2), 427 (M^+), 354, 352. Anal. ($C_{20}H_{30}NO_2SBr$) C, H, N.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-1,3-thiazolidin-4-one Hydrogen Fumarate (7k) (Method A). To a solution of **13a** (384 mg, 1.00 mmol) and 2-(3,4-dimethoxyphenyl)-*N*-methylethylamine (196 mg, 1.00 mmol) in DMF (5 mL) were added Na_2CO_3 (211 mg, 2.00 mmol) and NaI (15 mg, 0.10 mmol) under nitrogen atmosphere, and the mixture was stirred overnight at 80 °C. After cooling, the reaction mixture was poured into water (50 mL) 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 355 mg (65%) of the free form of **7k** as a colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.41 (18H, s), 1.3–1.8 (2H, m), 2.53 (3H, s), 2.2–2.9 (7H, m), 3.4–3.7 (1H, m), 3.66 and 3.81 (2H, ABq, J = 16 Hz), 3.83 (3H, s), 3.84 (3H, s), 5.31 (1H, s), 5.60 (1H, s), 6.6–6.9 (3H, m), 7.10 (2H, s).

A solution of the free form of **7k** 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 **7k** as a colorless powder: IR (KBr) 3500, 2980, 1684 (C=O), 1530, 1276, 1250, 1040 cm^{-1}; MS m/z 543 (M^+ + 1), 542 (M^+), 391; HPLC analysis (CH_3CN–H_2O–TFA (50:50:0.1)) t_R = 2.9 min (11.1%, fumaric acid) and t_R = 11.8 min (86.6%, free form of **7k**), 97.7% pure.

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 (7o) (Method B). To a solution of **13b** (89.3 mg, 0.21 mmol) and *N*-methyl-*N*-[2-[3,4-(methylenedi-

oxy)phenoxy]ethyl]amine (48.8 mg, 0.25 mmol) in acetone (5 mL) was added K_2CO_3 (34.6 mg, 0.25 mmol) under nitrogen atmosphere, 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 with $CHCl_3$−MeOH (97:3) and recrystallized from AcOEt−hexane to give 67.4 mg (60%) of **7o** as colorless crystals: mp 70−71 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42 (18H, s), 1.4−1.7 (2H, m), 2.20 (3H, s), 2.3−2.5 (2H, m), 2.68 (2H, t, J = 5.9 Hz), 2.7−2.9 (1H, m), 3.5−3.6 (1H, m), 3.66 and 3.80 (2H, ABq, J= 16 Hz), 3.92 (2H, t, J = 5.9 Hz), 5.32 (1H, s), 5.66 (1H, s), 5.90 (2H, s), 6.2−7.1 (5H, m); IR (KBr) 3570, 2920, 1660 (C=O), 1490, 1240, 1190, 1102, 1042 cm^{-1}; MS m/z 542 (M$^+$), 391, 348; HPLC analysis (CH_3CN−H_2O−TFA (50:50:0.1)) t_R = 13.6 min (99.3%). The following compounds were prepared from **13a** (method A) or **13b** (method B) via an amination reaction with the corresponding amine.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[4-(*N*-methyl-*N*-benzothiazol-2-ylamino)piperidino]propyl]-1,3-thiazolidin-4-one hydrochloride (6): method A (50%); ^{1}H NMR ($CDCl_3$, free form, 60 MHz) δ 1.43 (18H, s), 1.0−3.2 (15H, m), 3.00 (3H, s), 3.67 (2H, brs), 5.27 (1H, s), 5.56 (1H, s), 6.7−8.0 (6H, m); IR (KBr) 3450, 2950, 1664 (C=O), 1614, 1432, 762 cm^{-1}; MS m/z 594 (M$^+$), 446, 429; HPLC analysis (CH_3CN−H_2O−TFA (50:50:0.1)) t_R = 8.0 min (99.0%).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-(*N,N*-dimethylamino)propyl]-1,3-thiazolidin-4-one (7c): method B (66%); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.43 (18H, s), 1.7−1.9 (2H, m), 2.40 (6H, s), 2.3−2.7 (2H, m), 2.8−3.0 (1H, m), 3.5−3.7 (1H, m), 3.68 and 3.79 (2H, ABq, J = 15.8 Hz), 5.34 (1H, s), 5.65 (1H, s), 7.12 (2H, s); IR (KBr) 3420, 2950, 1684 (C=O), 1430, 1410, 1232, 1218 cm^{-1}; MS m/z 392 (M$^+$), 306; HPLC analysis (CH_3CN−H_2O−TFA (50:50:0.1)) t_R = 6.4 min (99.7%).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-(2-hydroxyethyl)amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (7d): method B (49%); ^{1}H NMR ($CDCl_3$, free form, 270 MHz) δ 1.43 (18H, s), 1.4−1.8 (2H, m), 1.6−2.2 (1H, m), 2.12 (3H, s), 2.32 (2H, t, J = 6.9 Hz), 2.43 (2H, t, J = 5.3 Hz), 2.7−3.0 (1H, m), 3.53 (2H, t, J = 5.3 Hz), 3.5−3.7 (1H, m), 3.68 and 3.79 (2H, ABq, J= 15.5 Hz), 5.33 (1H, s), 5.57 (1H, s), 7.09 (2H, s); IR (KBr) 3420, 2960, 1664 (C=O), 1434, 982, 648 cm^{-1}; MS m/z 422 (M$^+$), 391; HPLC analysis (CH_3CN−H_2O−TFA (50:50:0.1)) t_R = 2.9 min (14.1%, fumaric acid) and t_R = 5.6 min (82.6%, free form of **7d**), 96.7% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-(2-ethoxyethyl)amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (7e): method B (57%); ^{1}H NMR ($CDCl_3$, free form, 270 MHz) δ 1.17 (3H, t, J = 6.9 Hz), 1.43 (18H, s), 1.4−1.8 (2H, m), 2.16 (3H, s), 2.2−2.4 (2H, m), 2.49 (2H, t, J = 5.9 Hz), 2.7−2.9 (IH, m), 3.4−3.5 (2H, m), 3.5−3.7 (1H, m), 3.67 and 3.79 (2H, ABq, J = 15.5 Hz), 5.31 (1H, s), 5.61 (1H, s), 7.09 (2H, s); IR (KBr) 3480, 2980, 1688 (C=O), 1450, 1138, 1000, 662 cm^{-1}; MS m/z 450 (M$^+$), 391; HPLC analysis (CH_3CN−H_2O−TFA (50:50:0.1)) t_R = 2.9 min (13.6%, fumaric acid) and t_R = 9.5 min (84.1%, free form of **7e**), 97.7% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-(cyclopropylmethyl)amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (7f): method B (51%); ^{1}H NMR ($CDCl_3$, free form, 270 MHz) δ 0.0−0.1 (2H, m), 0.4−0.6 (2H, m), 0.7−0.9 (IH, m), 1.43 (18H, s), 1.4−1.8 (2H, m), 2.14 (2H, d, J = 6.6 Hz), 2.18 (3H, s), 2.2−2.4 (2H, m), 2.7−2.9 (1H, m), 3.5−3.7 (1H, m), 3.67 and 3.79 (2H, ABq, J = 15.5 Hz), 5.31 (1H, s), 5.62 (1H, s), 7.09 (2H, s); IR (KBr) 3590, 2950, 1658 (C=O), 1432, 1240, 980 cm^{-1}; MS m/z 432 (M$^+$); HPLC analysis (CH_3CN−H_2O−TFA (50:50:0.1)) t_R = 2.9 min (14.2%, fumaric acid) and t_R = 9.0 min (84.5%, free form of **7f**), 98.7% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-(*N,N*-dimethylaminoethyl)amino]propyl]-1,3-thiazolidin-4-one hydrochloride (7g): method B (66%); ^{1}H NMR ($CDCl_3$, free form, 200 MHz) δ 1.42 (18H, s), 1.4−1.8 (2H, m), 2.11 (3H, s), 2.20 (6H, s), 2.2−2.5 (6H, m), 2.7−2.9 (1H, m), 3.4−3.7 (1H, m), 3.65 and 3.78 (2H, ABq, J = 16 Hz), 5.31 (1H, s), 5.58 (1H, s), 7.06 (2H, s); IR (KBr) 3450, 2970, 2660, 1674 (C=O), 1442 cm^{-1}; MS m/z 449 (M$^+$), 391; HPLC analysis (CH_3CN−H_2O−TFA (50:50:0.1)) t_R = 3.6 min (97.7%).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-(*N*-methyl-*N*-benzylamino)propyl]-1,3-thiazolidin-4-one hydrogen fumarate (7h): method B (50%); ^{1}H NMR ($CDCl_3$, free form, 60 MHz) δ 1.43 (18H, s), 1.2−2.0 (2H, m), 2.05 (3H, s), 2.0−3.3 (4H, m), 3.40 (2H, s), 3.70 (2H, brs), 5.30 (1H, s), 5.57 (1H, s), 7.07 (2H, s), 7.20 (5H, s); IR (KBr) 3470, 2980, 1680 (C=O), 1444, 1252, 1000 cm^{-1}; MS m/z 468 (M$^+$), 377; HPLC analysis (CH_3CN−H_2O−TFA (50:50:0.1)) t_R = 2.9 min (14.0%, fumaric acid) and t_R = 13.0 min (84.5%, free form of **7h**), 98.5% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[3,4-(methylenedioxy)phenyl]methylamino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (7i): method B (75%); ^{1}H NMR ($CDCl_3$, free form, 200 MHz) δ 1.41 (18H, s), 1.5−1.8 (2H, m), 2.00 (3H, s), 2.1−2.4 (2H, m), 2.6−3.0 (1H, m), 3.27 (2H, s), 3.4−3.7 (1H, m), 3.63 and 3.77 (2H, ABq, J= 16.0 Hz), 5.31 (1H, s), 5.56 (1H, s), 5.90 (2H, s), 6.5−6.8 (3H, m), 7.09 (2H, s); IR (KBr) 3470, 2980, 1680 (C=O), 1460, 1264, 1050, 662 cm^{-1}; MS m/z 512 (M$^+$), 164; HPLC analysis (CH_3CN−H_2O−TFA (50:50:0.1)) t_R = 2.9 min (9.0%, fumaric acid) and t_R = 12.8 min (90.0%, free form of **7i**), 99.0% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-(3,4-dimethoxyphenyl)methylamino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (7j): method A (90%); ^{1}H NMR ($CDCl_3$, free form, 200 MHz) δ 1.43 (18H, s), 1.2−1.9 (2H, m), 2.06 (3H, s), 2.1−2.4 (2H, m), 2.6−3.0 (1H, m), 3.34 (2H, s), 3.4−3.7 (1H, m), 3.64 and 3.78 (2H, ABq, J = 16.0 Hz), 3.84 (3H, s), 3.86 (3H, s), 5.31 (1H, s), 5.56 (1H, s), 6.6−6.9 (3H, m), 7.06 (2H, s); IR (KBr) 3450, 2950, 1670 (C=O), 1518, 1432, 1260, 1022 cm^{-1}; MS m/z 528 (M$^+$), 180, 151; HPLC analysis (CH_3CN−H_2O−TFA (50:50:0.1)) t_R = 2.9 min (9.0%, fumaric acid) and t_R = 11.1 min (88.2%, free form of **7j**), 97.2% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-(4-methoxyphenoxy)ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (7l): method A (25%); ^{1}H NMR ($CDCl_3$, free form, 200 MHz) δ 1.43 (18H, s), 1.1−1.8 (2H, m), 2.21 (3H, s), 2.3−2.5 (2H, m), 2.70 (2H, t, J = 5.7 Hz), 2.6−3.0 (1H, m), 3.4−3.9 (3H, m), 3.76 (3H, s), 3.96 (2H, t, J = 5.7 Hz), 5.30 (1H, s), 5.64 (1H, s), 6.79 (4H, s), 7.09 (2H, s); IR (KBr) 3450, 2960, 1674 (C=O), 1504, 1234 cm^{-1}; MS m/z 528 (M$^+$), 391; HPLC analysis (CH_3CN−H_2O−TFA (50:50:0.1)) t_R = 2.9 min (12.1%, fumaric acid) and t_R = 15.9 min (85.8%, free form of **7l**), 97.9% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-(3,4-dimethoxyphenoxy)ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (7m): method A (28%); ^{1}H NMR ($CDCl_3$, free form, 60 MHz) δ 1.38 (18H, s), 1.2−1.9 (2H, m), 2.18 (3H, s), 2.3−2.5 (2H, m), 2.6−3.2 (3H, m), 3.2−4.2 (3H, m), 3.67 (2H, brs), 3.76 (6H, s), 5.22 (1H, s), 5.57 (1H, s), 6.2−6.9 (3H, m), 7.00 (2H, s); IR (KBr) 3460, 2970, 1678 (C=O), 1520, 1234, 1202 cm^{-1}; MS m/z 558 (M$^+$), 391; HPLC analysis (CH_3CN−H_2O−TFA (50:50:0.1)) t_R = 2.9 min (12.0%, fumaric acid) and t_R = 11.9 min (85.9%, free form of **7m**), 97.9% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-(3,4,5-trimethoxyphenoxy)ethyl]amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (7n): method A (45%); ^{1}H NMR ($CDCl_3$, free form, 200 MHz) δ 1.43 (18H, s), 1.3−1.9 (2H, m), 2.23 (3H, s), 2.3−2.5 (2H, m), 2.71 (2H, t, J = 5.7 Hz), 2.6−3.0 (1H, m), 3.4−3.9 (3H, m), 3.77 (3H, s), 3.83 (6H, s), 3.97 (2H, t, J= 5.7 Hz), 5.30 (1H, s), 5.63 (1H, s), 6.12 (2H, s), 7.08 (2H, s); IR (KBr) 3480, 2980, 1682 (C=O), 1610, 1250, 1142 cm^{-1}; MS m/z 588 (M$^+$), 391, 348; HPLC analysis (CH_3CN−H_2O−TFA (50:50:0.1)) t_R = 2.9 min (10.5%, fumaric acid) and t_R = 12.5 min (89.0%, free form of **7n**), 99.5% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)propyl]-1,3-thiazolidin-4-one hydrogen fumarate (7p): method A (69%); ^{1}H NMR ($CDCl_3$, free form, 60 MHz) δ 1.37 (18H, s), 1.5−2.0 (2H, m), 2.1−3.1 (8H, m), 3.42 (2H, s), 3.65 (2H, brs),

3.75 (6H, s), 5.39 (1H, s), 5.57 (1H, s), 6.42 (1H, s), 6.50 (1H, s), 7.02 (2H, s); IR (KBr) 3460, 2980, 1680 (C=O), 1526, 1272, 1132 cm^{-1}; MS *m/z* 540 (M$^+$), 192; HPLC analysis (CH_3CN–H_2O–TFA (50:50:0.1)) t_R = 2.9 min (10.6%, fumaric acid) and t_R = 10.5 min (86.9%, free form of **7p**), 97.5% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-(4-benzylpiperidino)propyl]-1,3-thiazolidin-4-one hydrogen fumarate (7q): method A (60%); ^{1}H NMR ($CDCl_3$, free form, 200 MHz) δ 1.36 (18H, s), 1.1–1.9 (9H, m), 2.1–2.3 (2H, m), 2.50 (2H, d, J = 6.6 Hz), 2.7–2.9 (3H, m), 3.4–3.6 (1H, m), 3.66 and 3.79 (2H, ABq, J = 16 Hz), 5.32 (1H, s), 5.62 (1H, s), 7.0–7.3 (7H, m); IR (KBr) 3470, 2980, 1678 (C=O), 1442, 1248 cm^{-1}; MS *m/z* 522 (M$^+$), 188; HPLC analysis (CH_3CN–H_2O–TFA (50:50:0.1)) t_R = 2.9 min (12.2%, fumaric acid) and t_R = 23.9 min (87.3%, free form of **7q**), 99.5% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-(1,3-dioxoisoindolin-2-yl)propyl]-1,3-thiazolidin-4-one (15). To a solution of **12** (3.00 g, 8.20 mmol), phthalimide (1.81 g, 12.3 mmol), and triphenylphosphine (3.23 g, 12.3 mmol) in dry THF (100 mL) was added diethyl azodicarboxylate (2.14 g, 12.3 mmol) at 0 °C under nitrogen atmosphere. The mixture was stirred for 3 h at room temperature, and the reaction mixture was concentrated under reduced pressure. The obtained residue was poured into water and extracted with AcOEt. The extract was washed with brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with AcOEt–hexane (3:7) and recrystallized from $CHCl_3$–hexane to give 3.04 g (75%) of **15** as pale-purple crystals: mp 146–147 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.40 (18H, s), 1.6–2.0 (2H, m), 2.7–2.9 (1H, m), 3.5–3.8 (3H, m), 3.68 and 3.76 (2H, ABq, J = 15.2 Hz), 5.29 (1H, s), 5.65 (1H, s), 7.08 (2H, s), 7.6–7.9 (4H, m); IR (KBr) 3570, 2950, 1712 (C=O), 1664 (C=O), 1400, 1116, 720 cm^{-1}; MS *m/z* 494 (M$^+$), 306.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(3-aminopropyl)-1,3-thiazolidin-4-one Hydrogen Fumarate (7a). To a suspension of **15** (1.00 g, 2.02 mmol) in MeOH (5 mL) was added 40% $MeNH_2$ in MeOH (4 mL, 41 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel with $CHCl_3$–MeOH (80:20) to give 0.67 g (91%) of the free form of **7a** as a colorless oil: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.43 (18H, s), 1.48 (2H, brs), 1.2–1.8 (2H, m), 2.5–2.7 (2H, m), 2.7–3.0 (1H, m), 3.6–3.8 (1H, m), 3.69 and 3.80 (2H, ABq, J = 15.2 Hz), 5.33 (1H, s), 5.57 (1H, s), 7.09 (2H, s).

A solution of the free form of **7a** 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 **7a** as a colorless powder: IR (KBr) 3480, 2980, 1670 (C=O), 1444 cm^{-1}; MS *m/z* 364 (M$^+$), 306; HPLC analysis (CH_3CN–H_2O–TFA (50:50:0.1)) t_R = 2.9 min (14.7%, fumaric acid) and t_R = 5.6 min (84.4%, free form of **7a**), 99.1% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-(*N*-methylamino)propyl]-1,3-thiazolidin-4-one Hydrobromide (7b). A mixture of **13b** (1.10 g, 2.57 mmol) and 40% $MeNH_2$ in MeOH (20 mL, 232 mmol) in CH_3CN (15 mL) was stirred for 15 h at room temperature under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel with $CHCl_3$–MeOH (95:5) to give 0.90 g (76%) of **7b** as pale-orange crystals which were characterized as hydrobromide: mp 195–196 °C ($CHCl_3$–hexane); ^{1}H NMR ($CDCl_3$, free form, 60 MHz) δ 1.37 (1H, s), 1.42 (18H, s), 1.6–2.2 (2H, m), 2.67 (3H, s), 2.6–3.6 (4H, m), 3.77 (2H, brs), 5.33 (1H, s), 5.63 (1H, s), 7.08 (2H, s); IR (KBr) 3450, 2950, 2720, 1660 (C=O), 1436 cm^{-1}; MS *m/z* 378 (M$^+$), 306; HPLC analysis (CH_3CN–H_2O–TFA (50:50:0.1)) t_R = 6.0 min (98.6%).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-hydroxy-3-[3,4-(methylenedioxy)phenoxy]propyl]amino]propyl]-1,3-thiazolidin-4-one Hydrogen Fumarate (7s) (Method C). To a solution of **7b** (500 mg, 1.32 mmol) in CH_3CN (10 mL) was added 2,3-(epoxypropyl)-3,4-(methylenedioxy)phenyl ether (260 mg, 1.32 mmol), and the mixture was refluxed for 8 h. After cooling, the reaction mixture was poured into ice–water and extracted with AcOEt. 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 0.72 g (95%) of the free form of **7s** as a colorless oil: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.43 (18H, s), 1.4–1.8 (2H, m), 2.17 (3H, s), 2.2–2.6 (4H, m), 2.7–3.0 (1H, m), 3.4–3.7 (1H, m), 3.67 and 3.80 (2H, ABq, J = 16 Hz), 3.8–4.1 (4H, m), 5.33 (1H, s), 5.57 (1H, s), 5.91 (2H, s), 6.2–6.8 (3H, m), 7.09 (2H, s).

A solution of the free form of **7s** 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 **7s** as a colorless powder: IR (KBr) 3440, 2960, 1674 (C=O), 1488, 1188, 1040 cm^{-1}; MS *m/z* 572 (M$^+$), 391; HPLC analysis (CH_3CN–H_2O–TFA (50:50:0.1)) t_R = 2.9 min (12.1%, fumaric acid) and t_R = 12.9 min (86.7%, free form of **7s**), 98.8% pure.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (7r): method C (57%); ^{1}H NMR ($CDCl_3$, free form, 200 MHz) δ 1.43 (18H, s), 1.4–1.8 (2H, m), 2.19 (3H, s), 2.2–3.0 (6H, m), 3.3–3.7 (1H, m), 3.66 and 3.79 (2H, ABq, J = 16 Hz), 3.8–4.2 (3H, m), 5.31 (1H, s), 5.54 (1H, s), 6.7–7.0 (3H, m), 7.06 (2H, m), 7.1–7.5 (2H, m); IR (KBr) 3450, 2980, 1678 (C=O), 1252, 766 cm^{-1}; MS *m/z* 528 (M$^+$), 391; HPLC analysis (CH_3CN–H_2O–TFA (50:50:0.1)) t_R = 2.9 min (11.5%, fumaric acid) and t_R = 14.0 min (87.3%, free form of **7r**), 98.8% pure.

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 Table 1.

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 Table 1.

Inhibitory Action on Lipid Peroxidation. A test compound was added to rabbit LDL prepared according to the method of Havel et al.,[17a] 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 2.

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