by vortexing the block for 10 s. After a 10-min preincubation at 37 °C in a water bath, 25 μL of the solutions of the radioactively labeled amines was added to the two rows with a Titrertec Multichannel pipette, type 12-channel (Flow Laboratories). The reaction was immediately started by vortexing the block for 10 s on a Super-Mixer, and the incubation was continued for 2 min at 37 °C. The uptake reaction was stopped by filtration and washing for 15 s with ice-cold 0.15 M NaCl through a Whatman GF/B glass filter paper in a 24-channel cell harvester (Brandel) with use of the standard harvesting probe. The filters were left to dry at room temperature for about 1 h. The punched filters were transformed to counting vials, 10 mL of the scintillation liquid (Aquasol, NEN) was added, and vials were shaken and allowed to stand for 1 h before counting. The radioactivity was measured in a Packard TriCarb liquid scintillation photometer. The active uptake of the amines was defined as the difference between the accumulation of the radioactivity in the absence (triplicates) and the presence (triplicates) of selective uptake inhibitors, determined at each incubation. These inhibitors were citalopram (0.3 μM) for the serotonin uptake and maprotiline (1 μM) for the norepinephrine uptake. The inhibition was calculated in percent of the active uptake. The IC_{50} values were obtained from log concentration–response curves. The SEM of the control values (n = 24) was for the NE uptake ±0.9% of the mean and for the 5-HT uptake ±3%. The difference between the duplicates expressed in percent of the mean was determined for the nine concentrations in each experiment. The mean (±SEM) of this difference was for the NE uptake 6.4 ± 1.6% or less and for the 5-HT uptake 7.2 ± 2.0% or less.

Acknowledgment. We thank Dr. Lucy Rényi and Ingrid Fagervall for performing uptake experiments. Research support was provided by the National Institutes of Health (Grant GM22988), the University of Kansas General Research Fund, and by a grant from the State of Kansas Advanced Technology Commission (with matching funds provided by Astra Alab). J.D.B. was the recipient of a predoctoral traineeship (NIH Grant GM 07775). A gift of the SYBYL software to the University of Kansas from Tripos Associates, St. Louis, MO, is gratefully acknowledged.

Registry No. (*Z*)-**1**, 56775-88-3; (*E*)-**1**, 56775-89-4; (*Z*)-**3**, 112969-63-8; (*Z*)-**3**·oxalate, 112969-66-1; (*E*)-**3**, 112969-64-9; (*E*)-**3**·oxalate, 112969-65-0; (*Z*)-**4**, 112969-67-2; (*Z*)-**4**·oxalate, 112969-68-3; (*E*)-**4**, 112969-69-4; (*E*)-**4**·oxalate, 112969-70-7; **7**, 14548-45-9; **8**, 112969-71-8; (*Z*)-**9**, 112969-72-9; (*E*)-**9**, 112969-73-0; **10**, 112969-74-1; (*E*)-**11**, 112969-75-2; (*Z*)-**11**, 112969-76-3; **12**, 112969-77-4; NE, 51-41-2; 5-HT, 50-67-9; PCl_5, 10026-13-8; PCl_3, 7719-12-2; $SOCl_2$, 7719-09-7; HCl, 7647-01-0; $ZnCl_2$, 7646-85-7; PBr_5, 7789-69-7; PBr_3, 7789-60-8; HBr, 10035-10-6; HOAc, 64-19-7; cyclopropyl bromide, 4333-56-6.

Novel Calcium Antagonists. Synthesis and Structure–Activity Relationship Studies of Benzothiazoline Derivatives

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A series of novel compounds having a benzothiazoline skeleton was studied for their structure–activity relationship (SAR) with respect to Ca^{2+} antagonistic activity. As test compounds, analogues of 3-acyl-2-arylbenzothiazolines (**3**) were synthesized. Benzothiazoline derivatives (**3**) exerted higher Ca^{2+} antagonistic activity than the corresponding thiazolidine derivatives (**2**). Effects of substituents R_1–R_4, the substitution position of the aminoalkoxy group and R_2, and the length of the methylene chain on biological activities were examined. Compound **4** [3-acetyl-2-[5-methoxy-2-[4-[*N*-methyl-*N*-(3,4,5-trimethoxyphenethyl)amino]butoxy]phenyl]benzothiazoline hydrochloride] showed a potent Ca^{2+} antagonistic activity in vitro and dual inhibition on the fast Na^+ inward channel and the slow Ca^{2+} inward channel in Langendorff perfused rabbit hearts. Compound **4** also showed a long-acting hypotensive effect in spontaneously hypertensive rats and prevented acute pulmonary thrombotic death in mice.

Ca^{2+} antagonists are highly valued as therapeutic agents for essential hypertension and angina pectoris because of their excellent profiles.[1-10] There are only a few Ca^{2+} antagonists on the market (**5–8**), but their structures are fundamentally different from each other.[11] The structure–activity relationships (SAR) of 1,4-dihydropyridine derivatives[2,12-14] and verapamil derivatives[15-17] have been

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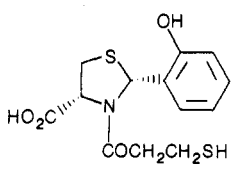
described. We report our studies on the SAR in a series of newly synthesized benzothiazolines from which a potent Ca^{2+} antagonist, **4**, was found.



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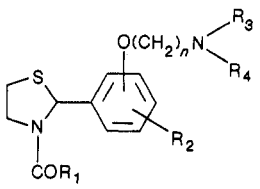

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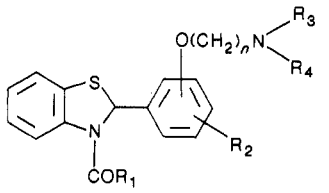

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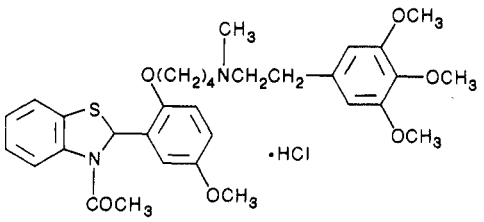

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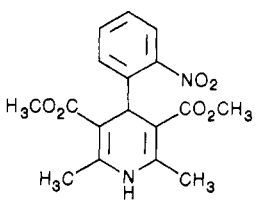

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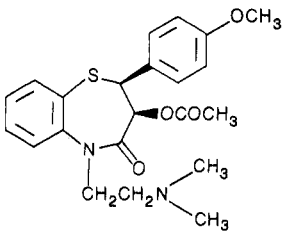

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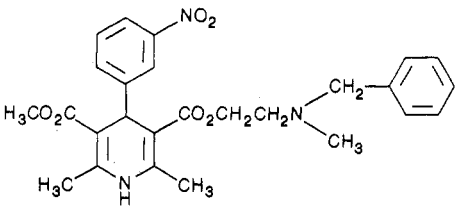
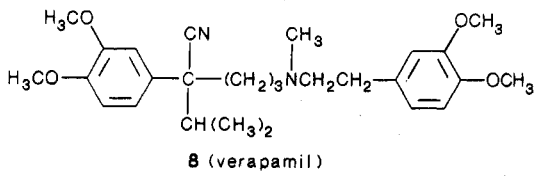


7 (nicardipine)

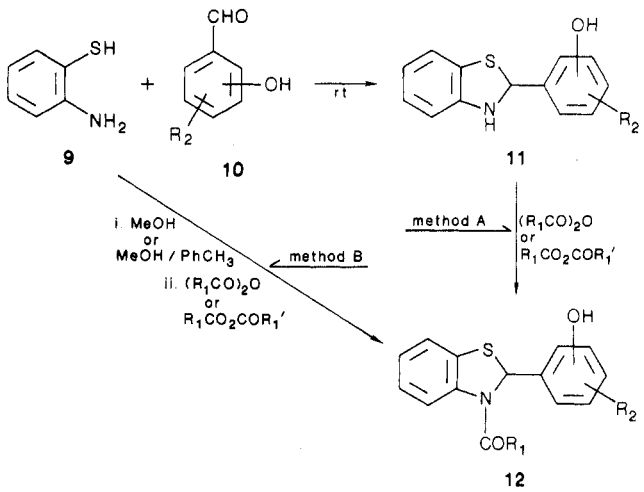


8 (verapamil)

Our earlier work led to the development of a new angiotensin I converting enzyme inhibitor **1** with a thiazolidine skeleton.[18] In successive studies on thiazolidine derivatives, we synthesized 3-aralkyl-2-arylthiazolidine derivatives having platelet aggregation inhibitory (PAI) activity.[19]

We further developed the derivatives to dually active 3-acyl-2-arylthiazolidine derivatives (**2**), which have Ca^{2+} antagonistic activity in addition to PAI activity.[20] Aiming at improving their stability under acidic conditions and

Scheme I



increasing crystallinity, we examined a series of benzo homologues of the thiazolidine ring. Consequently, benzothiazoline derivatives (**3**) thus obtained did show better stability and high crystallizing ability; furthermore, they were more potent than those of the corresponding thiazolidine derivatives (**2**).

Among the benzothiazoline derivatives (**3**) examined, 3-acetyl-2-[5-methoxy-2-[4-[*N*-methyl-*N*-(3,4,5-trimethoxyphenethyl)amino]butoxy]phenyl]benzothiazoline hydrochloride (**4**) was found to have a potent (IC_{50} = 1.3 × 10^{-7} M) Ca^{2+} antagonistic activity. An electrophysiological study revealed that compound **4** has dual inhibitory effects on the fast and slow channels. In the in vivo biological study, compound **4** showed a long-acting hypotensive effect on the spontaneously hypertensive rat (SHR) (po) and a preventive effect on pulmonary thrombotic death induced by collagen in mice.

Chemistry. Many studies on benzothiazoline have been made because of their structural interest. Namely, they contain two different heteroatoms linked by one carbon. There is considerable literature on their synthesis and chemistry. Concerning the 3-position of 2-arylbenzothiazolines, unsubstituted[21-26] and 3-alkyl[24,25,27-33] derivatives have been described previously. 3-Acyl derivatives were disclosed by Breuer,[34] Chioccara,[35,36] and Horr[37-40] et

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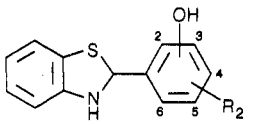
Table I. 2-Arylbenzothiazolines

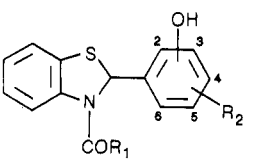


11

compd	position of OH	R_2	yield, %	mp, °C	recrystn solvent[a]	formula[b]
11-1	2	H	91	141–144[c]	Ac–Hx	$C_{13}H_{11}NOS$
11-2	3	H	58	122–125	Me	$C_{13}H_{11}NOS$
11-3	4	H	96	amorph	Me	$C_{13}H_{11}NOS$
11-4	2	3-OCH_3	62	109–112	Me	$C_{14}H_{13}NO_2S$
11-5	2	5-Cl	73	142–144 dec[d]	Me	$C_{13}H_{10}ClNOS$
11-6	2	5-OCH_3	79	125–127	Cl	$C_{14}H_{13}NO_2S$

[a] Ac = AcOEt; Cl = $CHCl_3$; Hx = *n*-hexane; Me = MeOH. [b] Satisfactory analysis were not obtained (all compounds could not be purified by recrystallization because of their instability, but their spectral data (NMR and IR) supported their structure). [c] Literature[23] mp 140–141 °C. [d] Literature[24] mp 155–156 °C.

Table II. 3-Acyl-2-arylbenzothiazolines



12

compd	position of OH	R_1	R_2	yield, % method A	yield, % method B	mp, °C	recrystn solvent[a]	formula[b]
12-1	2	H	H	87[c] (79)[d]		172.5–174	Me–Ac–Hx	$C_{14}H_{11}NO_2S$
12-2	2	CH_3	H	99[c] (90)[d]		218–219 dec	Me–Ac–Hx	$C_{15}H_{13}NO_2S$
12-3	3	CH_3	H	95[c] (55)[d]	56[d]	185–186	Me–Ac–Hx	$C_{15}H_{13}NO_2S$
12-4	2	H	5-OCH_3	81[c] (64)[d]		189.5–191	Me–Ac–Hx	$C_{15}H_{13}NO_3S$
12-5	2	CH_3	5-OCH_3	96[c] (76)[d]	79[d]	205.5–206.5	Me–Ac–Hx	$C_{16}H_{15}NO_3S$
12-6	2	C_2H_5	5-OCH_3		37[d]	155.5–157	Ac–Hx	$C_{17}H_{17}NO_3S$
12-7	2	CH_3	5-Cl	45[c] (33)[d]		215–220 dec	Wt–Me–At	$C_{15}H_{12}ClNO_2S$
12-8	2	CH_3	5-NO_2		47[d]	214–215 dec	Me–Dm	$C_{15}H_{12}N_2O_4S$
12-9	4	CH_3	3,5-OCH_3		52[d]	175–177	Me–Ac–Eo	$C_{17}H_{17}NO_4S$

[a] Ac = AcOEt; At = acetone; Dm = DMF; Eo = Et_2O; Hx = *n*-hexane; Me = MeOH; Wt = H_2O. [b] A satisfactory C, H, and N analysis for all compounds. [c] Yield of acylation from **11** to **12**. [d] Total yield from **10** to **12**.

al. However, in these examples substituents at the 2-position were limited to simple ones, for example, lower alkyl and halophenyl groups. Those compounds were reported to have antiinflammatory[29,32,34] or antibacterial[25] activity. 3-Acyl-2-[[(substitutedamino)alkoxy]phenyl]-benzothiazoline derivatives (**3**) have not been disclosed, and our description of this series of derivatives is the first one.

The benzothiazoline ring was formed by condensation of 2-aminobenzenethiol (**9**) with a substituted benzaldehyde (**10**) as shown in Scheme I. By mixing equimolar amounts of **9** and **10** in a polar solvent or without a solvent, an exothermic reaction occurs and crystals of the corresponding benzothiazoline derivative (**11**) are obtained[23-26] (Table I). Acylation of the 3-amino group was achieved by using acid anhydrides[34,39] (method A). This condition prevented the ring opening in an acidic medium in the same manner as acylation of the phenolic hydroxyl group. 3-Unsubstituted benzothiazoline derivatives (**11**) are generally unstable, particularly in solution, and are easily air oxidized to the corresponding benzothiazole derivatives.[22,25,26] When the yield was low due to the poor stability of **11** after acylation, the two steps (ring closure → acylation) were performed in one pot (method B). The results are shown in Table II.

The substituted aminoalkyl group was introduced on the phenolic hydroxyl group by one of the following three methods. method C, direct alkylation; method D, introduction of an alkyl group containing an acetal function, followed by hydrolysis to an aldehyde and reductive amination; method E, introduction of a haloalkyl group followed by amination.

Though methods D and E require one step more than method C, they have an advantage that various amino groups can be introduced via the same intermediate. In method D, when the acetal was a propanal derivative, attempts to prepare the aldehyde with use of mineral acid or organic acid under homogeneous conditions led to β-elimination as the preferred reaction. In such cases the target aldehyde was obtained by using a strong acidic resin (Amberlite CG-120). Since this aldehyde was very unstable, it was passed to the next step without further purification.

In method E, chloro derivatives obtained by the use of α-bromo-ω-chloroalkane or α-chloro-ω-[(methylsulfonyl)-oxy]alkane (to minimize the formation of bissubstituted derivatives in the first step) were less reactive in the next amination step. Therefore, to synthesize highly reactive derivatives, we used excess α,ω-dibromoalkane and obtained the bromoalkoxy derivatives in good yields (bissubstituted products were negligible) (Scheme II, Table III).

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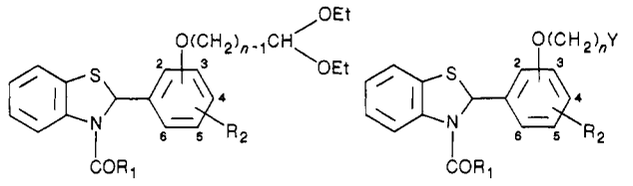
Table III. Acetal and (Haloalkoxy)benzothiazolines

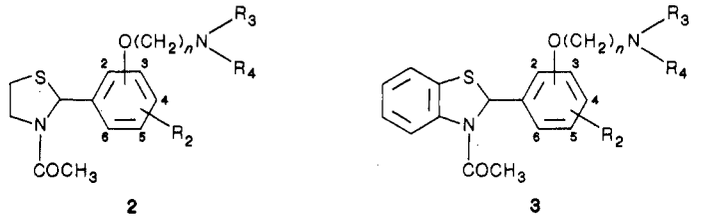


13-1 13-2–13-14

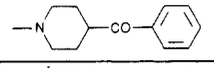
compd	position[a]	R_1	R_2	n	Y	method	yield, %	mp, °C	recrystn solvent[b]	formula	anal.
13-1	2	CH_3	H	3		D	76	oil		$C_{22}H_{27}NO_4S$	
13-2	2	CH_3	H	2	Cl	E	59	121–122	Me	$C_{17}H_{16}ClNO_2S$	C, H, N
13-3	3	CH_3	H	3	Cl	E	76	oil		$C_{18}H_{18}ClNO_2S$	
13-4	4	CH_3	3,5-OCH_3	3	Cl	E	48	oil		$C_{20}H_{22}ClNO_4S$	
13-5	2	CH_3	H	4	Cl	E	58	121–122	Ac	$C_{19}H_{20}ClNO_2S$	C, H, N
13-6	2	H	5-OCH_3	5	Br	E	80	82.5–84.5	Et	$C_{20}H_{22}BrNO_3S$	C, H, N
13-7	2	CH_3	5-OCH_3	3	Cl	E	88	92–94	Me	$C_{19}H_{20}ClNO_3S$	C, H, N
13-8	2	CH_3	5-OCH_3	4	Cl	E	62	113–114	Et	$C_{20}H_{22}ClNO_3S$	C, H, N
13-9	2	CH_3	5-OCH_3	4	Br	E	80	114.5–116	Me	$C_{20}H_{22}BrNO_3S$	C, H, N
13-10	2	CH_3	5-OCH_3	5	Br	E	63	81.5–83	Me	$C_{21}H_{24}BrNO_3S$	C, H, N
13-11	2	C_2H_5	5-OCH_3	4	Br	E	65	105.5–106.5	Et	$C_{21}H_{24}BrNO_3S$	C, H, N
13-12	2	CH_3	5-Cl	4	Cl	E	47	128–129.5	Me-Cl	$C_{19}H_{19}Cl_2NO_2S$	C, H, N
13-13	2	CH_3	5-NO_2	4	Cl	E	76	135–138	Me-Cl	$C_{19}H_{19}ClN_2O_4S$[c]	C, H, N
13-14	2	CH_3	5-NO_2	6	Cl	E	78	139–140.5	Me-Cl	$C_{21}H_{23}ClN_2O_4S$	C, H, N

[a] Substitution position of alkyl ether. [b] Ac = AcOEt; Cl = $CHCl_3$; Et = EtOH; Me = MeOH. [c] Analytical data were calculated as $C_{19}H_{19}ClN_2O_4S \cdot 0.2H_2O$.

Table IV. Thiazolidines and Benzothiazolines



2 3

compd	type[a]	position of alkyl ether	R_2	$-N(R_3)(R_4)$	n	Ca^{2+} IC_{50}[b]	mp, °C	recrystn solvent[c]	formula	anal.
2-1	T	2	H	$-N(CH_3)_2$	2	$>10^{-4}$	174–177	Et-Ac	$C_{15}H_{22}N_2O_2S \cdot HCl \cdot 0.2H_2O$	C, H, N
3-1	B					1.7×10^{-5}	209–210	Me-Ac	$C_{19}H_{22}N_2O_2S \cdot HCl \cdot 0.3H_2O$	C, H, N
2-2	T	4	H	$-N(CH_3)_2$	2	$>10^{-4}$	amorph		$C_{15}H_{22}N_2O_2S \cdot HCl$	*d*
3-2	B					3.6×10^{-5}	amorph		$C_{19}H_{22}N_2O_2S \cdot HCl$	*e*
2-3	T	2	5-NO_2	$-N(CH_3)_2$	3	4.1×10^{-4}	128.5–130.5	Ac	$C_{16}H_{23}N_3O_4S$	C, H, N
3-3	B					6.2×10^{-6}	159–160 dec	Me-An	$C_{20}H_{23}N_3O_4S \cdot 1.5C_4H_4O_4$[f]	C, H, N
2-4	T	2	5-OCH_3		4	4.1×10^{-6}	127–129	Et	$C_{28}H_{36}N_2O_4S \cdot C_4H_4O_4$[g]	C, H, N
3-4	B					1.4×10^{-6}	182–184	Me-An	$C_{32}H_{36}N_2O_4S \cdot C_2H_2O_4$[h]	C, H, N

[a] T = thiazolidine; B = benzothiazoline. [b] Molar concentration required to block Ca^{2+}-induced contraction of K^+-depolarized taenia cecum by 50%. Diltiazem was used as the standard compound; $IC_{50} = 1.7 \times 10^{-7}$ M, standard deviation ±0.5. [c] Ac = AcOEt; An = MeCN; Et = EtOH; Me = MeOH. [d] *m/z* (CI, MH^+; $C_{15}H_{23}N_2O_2S$) calcd 295.1479, found 295.1446. [e] *m/z* (CI, MH^+; $C_{19}H_{23}N_2O_2S$) calcd 343.1479, found 343.1472. [f] Hydrogen fumarate. [g] Hydrogen maleate. [h] Hydrogen oxalate.

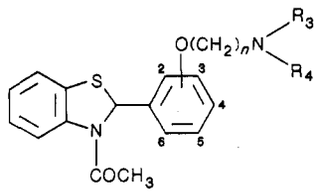
More complicated treatment was involved in the synthesis of amino derivatives (**3**) from acetal derivative **13-1** than from the corresponding halo derivatives **13-2–13-14**. Furthermore, by method E, compounds with the objective length of the methylene chain were easily obtained because of the availability of various kinds of haloalkanes. Therefore, we synthesized most of the amino derivatives (**3**) by method E. Final amino compounds (**3**) were isolated mainly as hydrochlorides or organic acid salts (maleate, fumarate, oxalate).

Structure–Activity Relationships. A series of benzothiazoline derivatives (**3**) was examined for their Ca^{2+} antagonistic activity. Ca^{2+} antagonistic activity in vitro was measured by using an isolated depolarized taenia cecum of guinea pigs as reported in the Experimental Section. Structure–activity relationships were studied in terms of the following: (1) benzothiazolines and thiazolidines; (2) substitution position of aminoalkoxy group; (3) type and substitution position of the substituent on the benzene ring, R_2; (4) type of 3-acyl group, COR_1; (5) length of the methylene chain, n; (6) type of substituents on the amino group, R_3, R_4.

(1) Benzothiazoline derivatives (**3**) and the corresponding thiazolidine derivatives (**2**) were compared with respect to activity. As the results in the Table IV show, the activity of the **3** series is greater than that of the corresponding **2** as Ca^{2+} antagonists, suggesting that fusion of a benzene ring with the thiazolidine ring is responsible for the increased activity.

(2) With the acyl group COR_1 fixed as acetyl and R_2 as

Table V. Substitution Position of Aminoalkoxy Group

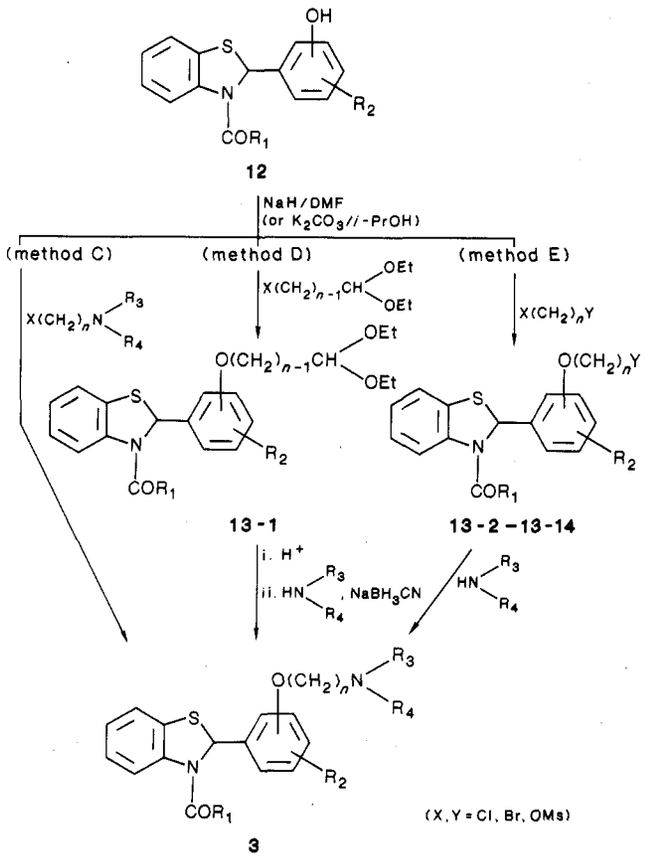


3

compd	$-N(CH_3)_2$	substit position	n	Ca^{2+} IC_{50}[a]	mp, °C	recrystn solvent[b]	formula	anal.
3-1		2	2	*c*	*c*	*c*	*c*	*c*
3-2		4	2	*c*	*c*	*c*	*c*	*c*
3-5		2	3	1.0×10^{-5}	177.5–178.5	Me–Ac	$C_{20}H_{24}N_2O_2S$·HCl	C, H, N
3-6		3	3	1.1×10^{-5}	162–164	Me	$C_{20}H_{24}N_2O_2S$·$C_4H_4O_4$[d]	C, H, N
3-7		4	3	5.5×10^{-6}	amorph		$C_{20}H_{24}N_2O_2S$·HCl	*e*
3-8		2	3	1.7×10^{-6}	130–142	Me–Ac	$C_{25}H_{32}N_2O_2S$·HCl·MeOH	C, H, N
3-9		4	3	4.4×10^{-6}	amorph		$C_{25}H_{32}N_2O_2S$·HCl	*f*

[a] See footnote *b* in Table IV. [b] Ac = AcOEt; Me = MeOH. [c] Data are given in Table IV. [d] Hydrogen fumarate. [e] *m/z* (CI, MH^+; $C_{20}H_{25}N_2O_2S$) calcd 357.1635, found 357.1596. [f] *m/z* (CI, MH^+; $C_{25}H_{33}N_2O_2S$) calcd 425.2261, found 425.2224.

Scheme II



H, the effect of the substitution position of the aminoalkoxy chain on the activity was examined. As shown in Table V, ortho (2)-substituted derivatives showed more potent activity than meta- or para-substituted derivatives.

(3) With the acyl group COR_1 fixed as acetyl and the substitution position of the aminoalkoxy group in the ortho position, the effect of the type and substitution position of R_2 on the activity was examined. As shown in Table VI, the activity was greatest when R_2 was 5-OCH_3.

(4) From the results of the above studies, the substitution position of the aminoalkoxy group and the type of substituent R_2 were fixed as the ortho position and 5-OCH_3, respectively, and the effect of the acyl group COR_1 on the activity was examined. As shown in Table VII and Figure 1, acetyl compounds showed a higher activity than formyl or propionyl compounds.

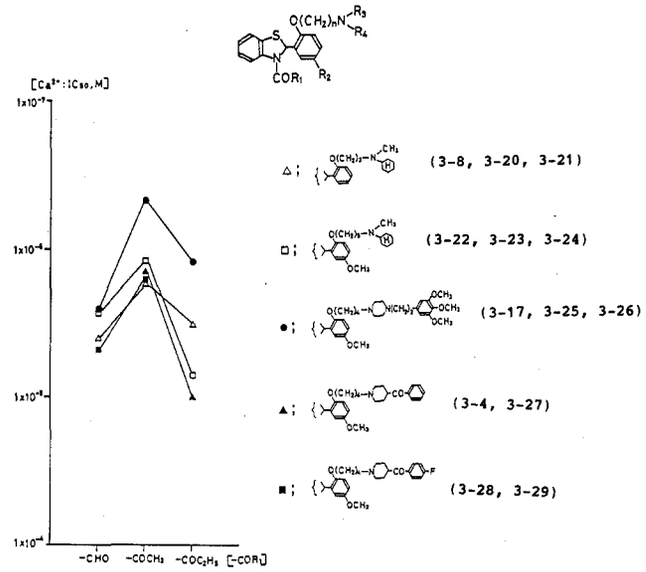


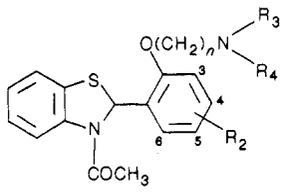
Figure 1. Effect of acyl group COR_1 on Ca^{2+} antagonistic activity visualized by using the data of Table VII. Ca^{2+} antagonistic activity was shown as the logarithm.

(5) The type of acyl group COR_1, substituent R_2, and substitution position of aminoalkoxy group were fixed to acetyl, 5-OCH_3, and the ortho position, respectively. The length of the methylene chain (n) was altered, while the same amino group was kept, and their biological activities were examined. In all cases, with the exception of cyclohexylmethylamines, the most potent activity was obtained when n equaled 4 (Table VIII and Figure 2).

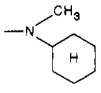
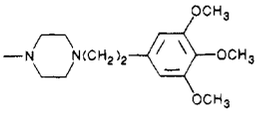
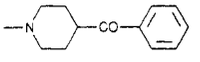
(6) From the results of studies 1–5, the type of acyl group COR_1, substituent R_2, number of methylene groups (n), and substitution position of aminoalkoxy group were fixed as acetyl, 5-OCH_3, 4, and ortho position, respectively, and the effects of various substituents (R_3 and R_4) on the activity were examined (Table IX).

In this examination, *N*-methyl-*N*-phenethylamine derivatives (**4**, **3-39**, **3-42**) were found to have a potent Ca^{2+} antagonistic activity. In particular, compound **4** showed an activity equivalent to those of diltiazem (**6**) and vera-

Table VI. Effect of Substituent R_2

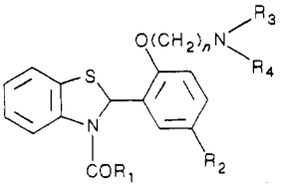


3

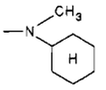
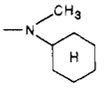
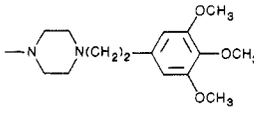
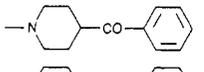
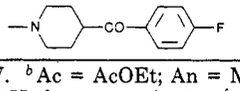
compd	$-N(R_3)R_4$	n	R_2	Ca^{2+} IC_{50}[a]	mp, °C	recrystn solvent[b]	formula	anal.
3-5		3	H	1.0×10^{-5}	*c*	*c*	*c*	*c*
3-10		3	3-OCH_3	1.3×10^{-5}	221–222	Me	$C_{21}H_{26}N_2O_3S$·HCl	C, H, N
3-11		3	5-Cl	3.8×10^{-6}	193–195.5	Pr–Eo	$C_{20}H_{23}ClN_2O_2S$·HCl·0.2H_2O	C, H, N
3-3		3	5-NO_2	6.2×10^{-6}	*d*	*d*	*d*	*d*
3-12		3	5-OCH_3	1.6×10^{-6}	165.5–166	Me	$C_{21}H_{26}N_2O_3S$·$C_4H_4O_4$[e]	C, H, N
3-13		4	3-OCH_3	8.8×10^{-6}	197–198	Me–Ac	$C_{27}H_{36}N_2O_3S$·HCl·0.3H_2O	C, H, N
3-14		4	5-NO_2	5.4×10^{-6}	176.5–178 dec	Me–An	$C_{26}H_{33}N_3O_4S$·$C_4H_4O_4$[f]	C, H, N
3-15		4	5-OCH_3	4.0×10^{-6}	147–148 dec	An	$C_{27}H_{36}N_2O_3S$·$C_2H_2O_4$[g]	C, H, N
3-16		4	5-Cl	2.3×10^{-6}	193.5–195	Me–An	$C_{34}H_{42}ClN_3O_5S$·2$C_4H_4O_4$[e]	C, H, N
3-17		4	5-OCH_3	4.7×10^{-7}	239–240 dec	Wt–Et	$C_{35}H_{45}N_3O_6S$·2HCl·H_2O	C, H, N
3-18		4	5-Cl	1.3×10^{-5}	108–109	Ac–Eo	$C_{31}H_{33}ClN_2O_3S$	C, H, N
3-19		4	5-NO_2	4.8×10^{-6}	165–168	An–Et	$C_{31}H_{33}N_3O_5S$·$C_4H_4O_4$[e]	C, H, N
3-4		4	5-OCH_3	1.4×10^{-6}	*d*	*d*	*d*	*d*

[a] See footnote *b* in Table IV. [b] Ac = AcOEt; An = MeCN; Eo = Et_2O; Et = EtOH; Me = MeOH; Pr = *i*-PrOH; Wt = H_2O. [c] Data are given in Table V. [d] Data are given in Table IV. [e] Hydrogen maleate. [f] Hydrogen fumarate. [g] Hydrogen oxalate.

Table VII. Effect of Acyl Group COR_1



3

compd	R_1	R_2	n	$-N(R_3)R_4$	Ca^{2+} IC_{50}[a]	mp, °C	recrystn solvent[b]	formula	anal.
3-20	H	H	3		4.0×10^{-6}	153.5–155	Me–An	$C_{24}H_{30}N_2O_2S$·$C_4H_4O_4$[c]	C, H, N
3-8	CH_3	H	3		1.7×10^{-6}	*d*	*d*	*d*	*d*
3-21	C_2H_5	H	3		3.2×10^{-6}	150–152	Pr	$C_{26}H_{34}N_2O_2S$·HCl·1.5H_2O	C, H, N
3-22	H	OCH_3	5		2.7×10^{-6}	amorph		$C_{27}H_{36}N_2O_3S$·$C_4H_6O_4$[e]	*f*
3-23	CH_3	OCH_3	5		1.2×10^{-6}	155.5–157.5	Me–Eo	$C_{28}H_{38}N_2O_3S$·$C_4H_4O_4$[c]	C, H, N
3-24	C_2H_5	OCH_3	5		7.0×10^{-6}	160–162	Et	$C_{29}H_{40}N_2O_3S$·$C_4H_4O_4$[c]	C, H, N
3-25	H	OCH_3	4		2.6×10^{-6}	162–164 dec	Me	$C_{34}H_{43}N_3O_6S$·2$C_4H_4O_4$[g]	C, H, N
3-17	CH_3	OCH_3	4		4.7×10^{-7}	*h*	*h*	*h*	*h*
3-26	C_2H_5	OCH_3	4		1.2×10^{-6}	190–192.5 dec	Me–An	$C_{36}H_{47}N_3O_6S$·2$C_4H_4O_4$[g]	C, H, N
3-4	CH_3	OCH_3	4		1.4×10^{-6}	*i*	*i*	*i*	*i*
3-27	C_2H_5	OCH_3	4		1.0×10^{-5}	197–198.5 dec	Me–An	$C_{33}H_{38}N_2O_4S$·$C_4H_4O_4$[g]	C, H, N
3-28	H	OCH_3	4		4.8×10^{-6}	160–161 dec	Me–An	$C_{31}H_{33}FN_2O_4S$·$C_4H_4O_4$[c]	C, H, N
3-29	CH_3	OCH_3	4		1.6×10^{-6}	146–149	Et–Ac	$C_{32}H_{35}FN_2O_4S$·$C_4H_4O_4$[g]	C, H, N

[a] See footnote *b* in Table IV. [b] Ac = AcOEt; An = MeCN; Eo = Et_2O; Et = EtOH; Me = MeOH; Pr = *i*-PrOH. [c] Hydrogen fumarate. [d] Data are given in Table V. [e] Hydrogen succinate. [f] *m/z* (CI, MH^+; $C_{27}H_{37}N_2O_3S$) calcd 469.2523, found 469.2526. [g] Hydrogen maleate. [h] Data are given in Table VI. [i] Data are given in Table IV.

pamil (**8**). Therefore, further examinations were focused on these types of compounds.

At first, effects of the number and substitution position of methoxy groups on the phenethyl part were examined. Calcium antagonism activity was in the order 3,4,5-trimethoxy (**4**) > 2,3,4-trimethoxy (**3-42**) > 3,4-dimethoxy (**3-39**). Bulky methylene chains (**3-53**) and branched methylene chains (**3-54**) on the phenethyl residue reduced the activity.

Primary (**3-46**) and secondary amino derivatives (**3-47**, **3-49**) were synthesized, and the effects of degree of substitution on the amino group on the activity were examined. The activity was in the order of tertiary > secondary ≫ primary.

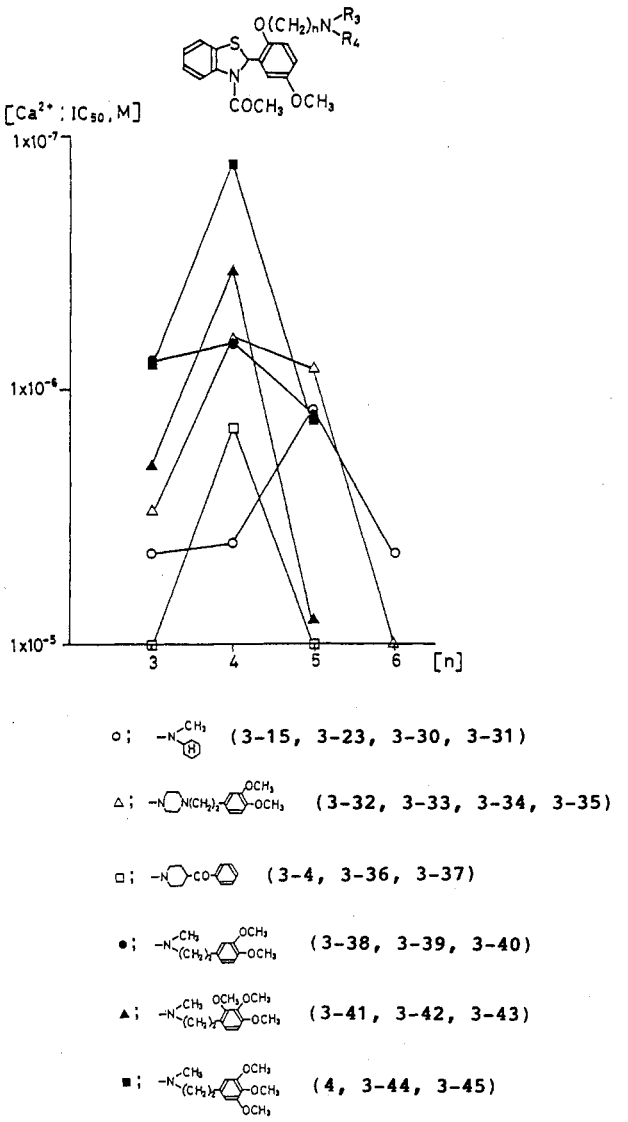


Figure 2. Effect of number of methylene (n) on Ca^{2+} antagonistic activity visualized by using the data of Table VIII. Ca^{2+} antagonistic activity was shown as the logarithm.

Lastly, the N-methyl substituent was changed to an N-ethyl (**3-50**), N-isopropyl (**3-51**), or N-cyclopropyl (**3-52**) group. All of these modifications resulted in a decrease in potency.

As the result of these examinations, compound **4** was selected as the most suitable compound.

Electrophysiological Study (Langendorff Perfused Rabbit Hearts). In Langendorff perfused rabbit hearts electrically driven at 2 Hz, compound **4** (5×10^{-8}–10^{-6} M) prolonged an atrio–His bundle conduction time (A–H interval; mediated mainly by the slow inward current) and a His bundle ventricular conduction time (H–V interval; mediated mainly by the fast inward current). On the other hand, other Ca^{2+} antagonists (**5–8**) also prolonged the A–H interval but did not produce significant effects on the H–V interval even at the concentrations that blocked the A–H interval (Table X). Therefore, compound **4**, unlike other Ca^{2+} antagonists (**5–8**), has dual inhibitory effects on the fast channel and slow channel.

In Vivo Biological Activities. To evaluate in vivo biological activities of compound **4**, hypotensive activity in SHR and the preventive effect on acute thrombotic death induced by collagen (mice) were examined.

Hypotensive Effect. The hypotensive effect of compound **4** in conscious SHR was evaluated in comparison with diltiazem (**6**) and verapamil (**8**). Compound **4** and other Ca^{2+} antagonists (**6**, **8**) lowered the systolic blood pressure (SBP) in SHR (Table XI). The maximum decrease of SBP by compound **4** (100 mg/kg, po) appeared later than that by diltiazem (**6**) (100 mg/kg, po) and verapamil (**8**) (30 mg/kg, po), and the hypotensive effect of compound **4** persisted until 24 h after administration (Figure 3). Neither compound showed any effect on heart rate in these examinations (Figure 3).

PAI Activity. The preventive effect on acute thrombotic death (mice) is one of the indexes for the PAI activity in vivo. Compound **4** was examined by using the method as described in the Experimental Section. As shown in Table XII, compound **4** showed a more potent preventive effect than other Ca^{2+} antagonists (**5–8**).

Conclusion

Structure–activity relationships of novel Ca^{2+} antagonist benzothiazoline derivatives (**3**) were studied. Various parts of the structure were modified, and the Ca^{2+} antagonistic activity was examined.

Compound **4** had the most potent Ca^{2+} antagonistic activity in vitro and showed a long-acting hypotensive effect in conscious SHR (po). It also showed a superior preventive effect on acute thrombotic death in mice to that of other Ca^{2+} antagonists (**5–8**).

Unlike other Ca^{2+} antagonists, however, compound **4** was found to block both the fast sodium channel as well as the slow calcium channel at equivalent doses. This dual inhibitory activity could limit its utility as an antihypertensive agent, but might enhance its potential as an an-

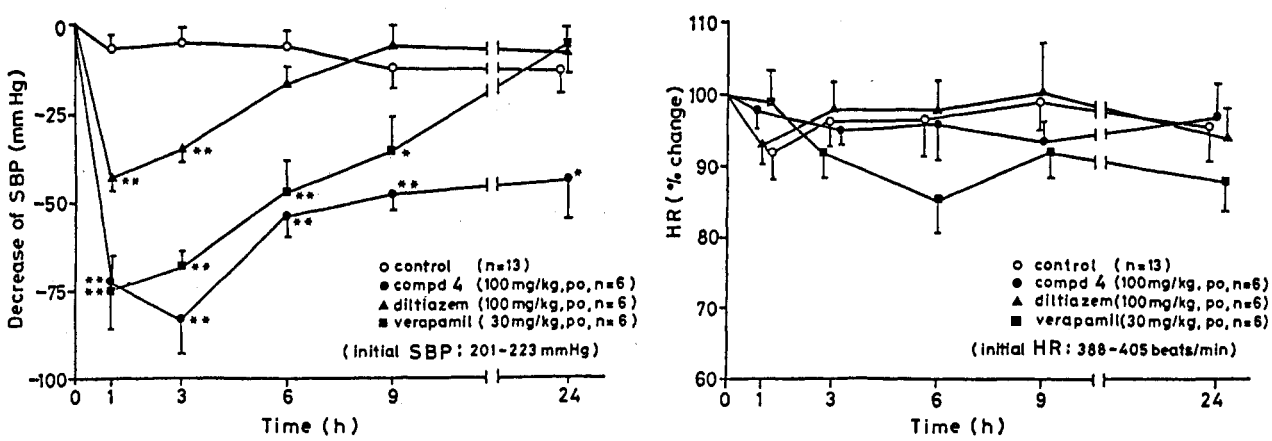
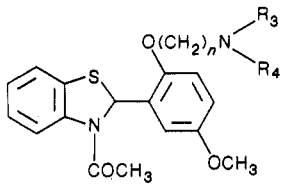


Figure 3. Effects of orally administered compound **4**, diltiazem, verapamil, and methylcellulose (control) on systolic blood pressure (SBP) and heart rate (HR) in conscious SHR. Data indicate the mean ± SEM of 6–13 animals. Test groups were compared statistically to control group values by Dunnett's multiple comparison test: *, $0.01 < p \leq 0.05$; **, $p \leq 0.01$.

Table VIII. Effect of the Length of Methylene (*n*)



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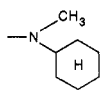
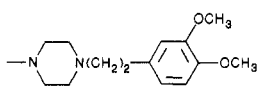
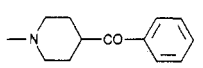
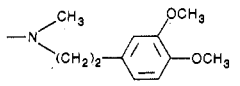
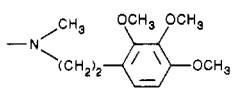
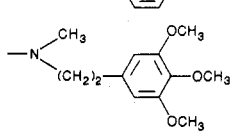
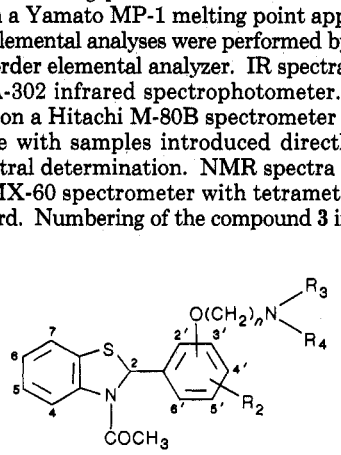
compd	$-N(R_3)R_4$	*n*	Ca^{2+} IC_{50}[a]	mp, °C	recrystn solvent[b]	formula	anal.
3-30		3	4.2×10^{-6}	191.5–192 dec	Me–An	$C_{26}H_{34}N_2O_3S \cdot C_2H_2O_4$[c]	C, H, N
3-15		4	4.0×10^{-6}	*d*	*d*	*d*	*d*
3-23		5	1.2×10^{-6}	*e*	*e*	*e*	*e*
3-31		6	4.2×10^{-6}	145.5–146.5	Et	$C_{29}H_{40}N_2O_3S \cdot C_2H_2O_4 \cdot 0.5H_2O$	C, H, N
3-32		3	3.0×10^{-6}	181–182 dec	Me–An	$C_{33}H_{41}N_3O_5S \cdot 2C_4H_4O_4$[f]	C, H, N
3-33		4	6.4×10^{-7}	197.5–198.5 dec	Me–An	$C_{34}H_{43}N_3O_5S \cdot 2C_4H_4O_4$[g]	C, H, N
3-34		5	8.2×10^{-7}	195.5–197.5	An–Cl	$C_{35}H_{45}N_3O_5S \cdot 2C_4H_4O_4$[f]	C, H, N
3-35		6	1.1×10^{-5}	188–189	Me–An	$C_{36}H_{47}N_3O_5S \cdot 2C_4H_4O_4$[f]	C, H, N
3-36		3	1.1×10^{-5}	180–182.5	Me–An	$C_{31}H_{34}N_2O_4S \cdot C_2H_2O_4$[c]	C, H, N
3-4		4	1.4×10^{-6}	182–184	Me–An	$C_{32}H_{36}N_2O_4S \cdot C_2H_2O_4$[c]	C, H, N
3-37		5	1.7×10^{-5}	173–175	Wt–Et	$C_{33}H_{38}N_2O_4S \cdot C_4H_4O_4 \cdot H_2O$	C, H, N
3-38		3	7.8×10^{-7}	164.5–166.5	Et	$C_{30}H_{36}N_2O_5S \cdot HCl$	C, H, N
3-39		4	6.6×10^{-7}	155–157	Ac	$C_{31}H_{38}N_2O_5S \cdot HCl$	C, H, N
3-40		5	1.3×10^{-6}	amorph		$C_{32}H_{40}N_2O_5S \cdot HCl$	*h*
3-41		3	2.0×10^{-6}	159–161	Pr	$C_{31}H_{38}N_2O_6S \cdot HCl$	C, H, N
3-42		4	3.4×10^{-7}	168.5–171.5	Pr	$C_{32}H_{40}N_2O_6S \cdot HCl \cdot 0.5H_2O$	C, H, N
3-43		5	8.0×10^{-6}	amorph		$C_{33}H_{42}N_2O_6S \cdot HCl$	*i*
3-44		3	7.8×10^{-7}	amorph		$C_{31}H_{38}N_2O_6S \cdot HCl$	*j*
4		4	1.3×10^{-7}	190–190.5	Et	$C_{32}H_{40}N_2O_6S \cdot HCl$	C, H, N
3-45		5	1.3×10^{-6}	amorph		$C_{33}H_{42}N_2O_6S \cdot HCl$	*k*

[a] See footnote *b* in Table IV. [b] Ac = AcOEt; An = MeCN; Cl = $CHCl_3$; Et = EtOH; Me = MeOH; Pr = *i*-PrOH; Wt = H_2O. [c] Hydrogen oxalate. [d] Data are given in Table VI. [e] Data are given in Table VII. [f] Hydrogen maleate. [g] Hydrogen fumarate. [h] *m/z* (EI, M^+; $C_{32}H_{40}N_2O_5S$) calcd 564.2656, found 564.2647. [i] *m/z* (EI, M^+; $C_{33}H_{42}N_2O_6S$) calcd 594.2761, found 594.2810. [j] *m/z* (EI, M^+; $C_{31}H_{38}N_2O_6S$) calcd 566.2448, found 566.2456. [k] *m/z* (EI, M^+; $C_{33}H_{42}N_2O_6S$) calcd 594.2761, found 594.2728.

tiarrythmic agent. This latter possibility is under investigation.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries with a Yamato MP-1 melting point apparatus and are uncorrected. Elemental analyses were performed by a Yanagimoto MT-3 CHN Corder elemental analyzer. IR spectra were recorded on a JASCO A-302 infrared spectrophotometer. Mass spectra were obtained on a Hitachi M-80B spectrometer in the EI or CI (i-C_4H_{10}) mode with samples introduced directly into the ion source for spectral determination. NMR spectra were measured by a JEOL PMX-60 spectrometer with tetramethylsilane as an internal standard. Numbering of the compound **3** in NMR spectra is as follows:



Merck silica gel 60 (70–230 mesh) was used for column chromatography.

2-(2-Hydroxy-5-methoxyphenyl)benzothiazoline (11-6). To a stirred solution of 2-aminobenzenethiol (**9**) (16.2 g, 0.129 mol) in MeOH (40 mL) was added a solution of 2-hydroxy-5-methoxybenzaldehyde (19.7 g, 0.129 mol) in MeOH (40 mL). The mixture was stirred at room temperature for 1 h and allowed to stand at 0 °C for 1 h. The precipitate was filtered to give 26.4 g (79%) of **11-6**: mp 125–127 °C; IR (KBr) 3240 (OH, NH), 1500 (C=C), 1460, 1225 (C—O), 1034 (C—O), 750 cm^{-1}; ^1H NMR ($CDCl_3$–Me_2SO-d_6) δ 3.65 (s, 3 H, OCH_3), 5.38 (br s, 1 H, NH), 6.27–7.17 (m, 8 H, aromatic and C-2H), 8.76 (s, 1 H, OH).

3-Acetyl-2-(2-hydroxy-5-methoxyphenyl)benzothiazoline (12-5). Method A. A suspension of 2-(2-hydroxy-5-methoxyphenyl)benzothiazoline (**11-6**) (20 g, 0.077 mol) in acetic anhydride (36 mL, 0.38 mol) was stirred at room temperature for 4 h. Ether (100 mL) was added to the reaction mixture, and the precipitated crystals were filtered to give 22.2 g (96%) of **12-5** (though these crystals were pure enough for further reaction, they were recrystallized from MeOH–AcOEt–*n*-hexane): mp 205.5–206.5 °C; IR (KBr) 3212 (OH), 1621 (C=O), 1377, 1201 (C—O), 1038 (C—O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.17 (s, 3 H, $COCH_3$), 3.50 (s, 3 H, OCH_3), 6.38–7.40 (m, 7 H, aromatic and C-2 H), 7.67–8.17 (br s, 1 H, C-4 H), 9.58 (s, 1 H, OH). Anal. ($C_{16}H_{15}NO_3S$) C, H, N.

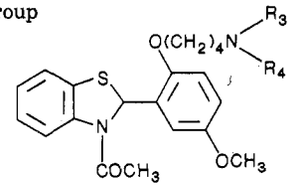
Method B. To a stirred solution of 2-aminobenzenethiol (**9**) (16.3 g, 0.13 mol) in toluene–MeOH (9/1, 20 mL) was added a solution of 2-hydroxy-5-methoxybenzaldehyde (19.8 g, 0.13 mol) in the same solvent (20 mL), and the mixture was stirred at room temperature for 1 h. Acetic anhydride (53.0 g, 0.52 mol) was added to the reaction mixture and the resultant mixture was stirred at room temperature for 1.5 h. The precipitated crystals were filtered after being cooled at 0 °C for 30 min, and 31.0 g (79%) of **12-5** was obtained.

3-Formyl or 3-propionyl derivatives were synthesized by using acetic–formic anhydride[41] or propionic anhydride instead of acetic anhydride.

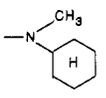
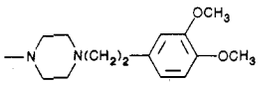
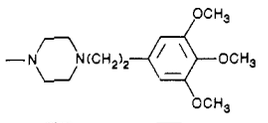
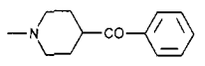
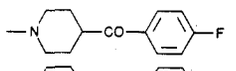
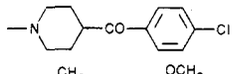
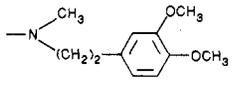
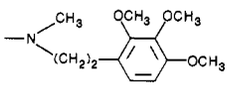
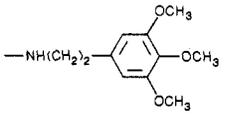
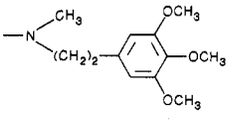
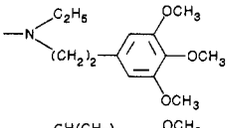
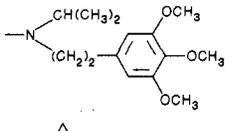
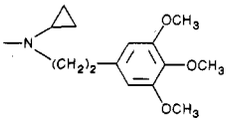
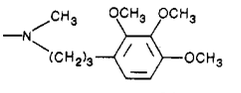
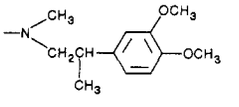
3-Acetyl-2-[2-(3,3-diethoxypropoxy)phenyl]benzothiazoline (13-1). Method D. To a stirred suspension of NaH (50% oil dispersion; 6.6 g, 0.138 mol) in dry DMF (100 mL) was added dropwise a solution of 3-acetyl-2-(2-hydroxyphenyl)-

(41) Krimen, L. I.; Sacage, J.; Yates, P. In *Organic Syntheses*; Wiley: New York, 1970; Vol. 50, p 1.

Table IX. Type of Substituents R_3, R_4 on Amino Group



3

compd	$-NR_3R_4$	yield,[a] %	Ca^{2+} IC_{50}[b]	mp, °C	recrystn solvent[c]	formula	anal.
3-46	$-NH_2$	34	$>10^{-5}$	148.5–151	Pr	$C_{20}H_{24}N_2O_3S\cdot C_4H_4O_4$[d]	C, H, N
3-47	$-NHCH_3$	18	2.0×10^{-6}	133–134	Pr	$C_{21}H_{26}N_2O_3S\cdot C_4H_4O_4$[d]	C, H, N
3-15		56	4.0×10^{-6}	*e*	*e*	*e*	*e*
3-33		51	6.4×10^{-7}	*f*	*f*	*f*	*f*
3-17		51	4.7×10^{-7}	*e*	*e*	*e*	*e*
3-4		62	1.4×10^{-6}	*g*	*g*	*g*	*g*
3-29		26	1.6×10^{-6}	*h*	*h*	*h*	*h*
3-48		86	8.7×10^{-6}	180–181	Me–An	$C_{32}H_{35}ClN_2O_4S\cdot C_4H_4O_4$[d]	C, H, N
3-39		70	6.6×10^{-7}	*f*	*f*	*f*	*f*
3-42		60	3.4×10^{-7}	*f*	*f*	*f*	*f*
3-49		45	6.5×10^{-6}	179–181 dec	Pr	$C_{31}H_{38}N_2O_6S\cdot C_2H_2O_4$[i]	C, H, N
4 (SA2572)		80	1.3×10^{-7}	*f*	*f*	*f*	*f*
3-50		53	1.0×10^{-6}	amorph		$C_{33}H_{42}N_2O_6S\cdot HCl$	*j*
3-51		17	1.3×10^{-6}	amorph		$C_{34}H_{44}N_2O_6S\cdot HCl$	*k*
3-52		51	1.2×10^{-6}	amorph		$C_{34}H_{42}N_2O_6S\cdot HCl$	*l*
3-53		48	1.2×10^{-6}	168–169	Et–Ac	$C_{33}H_{42}N_2O_6S\cdot HCl$	C, H, N
3-54		17	1.6×10^{-6}	amorph		$C_{32}H_{40}N_2O_5S\cdot HCl$	*m*
diltiazem (**6**)			1.7×10^{-7}				
verapamil (**8**)			1.0×10^{-7}				

[a] Calculated from the corresponding haloalkyl derivatives (**13**) by using method E. [b] See footnote *b* in Table IV. [c] Ac = AcOEt; An = MeCN; Et = EtOH; Me = MeOH; Pr = *i*-PrOH. [d] Hydrogen maleate. [e] Data are given in Table VI. [f] Data are given in Table VIII. [g] Data are given in Table IV. [h] Data are given in Table VII. [i] Hydrogen oxalate. [j] *m/z* (EI, M^+; $C_{33}H_{42}N_2O_6S$) calcd 594.2761, found 594.2749. [k] *m/z* (EI, M^+; $C_{34}H_{44}N_2O_6S$) calcd 608.2918, found 608.2938. [l] *m/z* (EI, M^+; $C_{34}H_{42}N_2O_6S$) calcd 606.2761, found 606.2792. [m] *m/z* (EI, M^+; $C_{32}H_{40}N_2O_5S$) calcd 564.2656, found 564.2611.

Table X. Electrophysiological Effects of Compound 4 and Other Ca^{2+} Antagonists in Isolated Rabbit Hearts

compd	A–H interval: EC_{30}[a]	H–V interval: EC_{10}[b]	H–V(EC_{10})/ A–H(EC_{30})
4	$(3.0 \pm 0.7) \times 10^{-7}$	$(2.0 \pm 0.2) \times 10^{-7}$	1.0 ± 0.3
diltiazem	$(4.4 \pm 0.6) \times 10^{-7}$	$(2.6 \pm 0.7) \times 10^{-6}$	6.5 ± 2.1
verapamil	$(8.7 \pm 1.2) \times 10^{-8}$	c	
nifedipine	$(2.2 \pm 0.7) \times 10^{-8}$	c	
nicardipine	$(5.2 \pm 1.0) \times 10^{-8}$	c	

[a] Molar concentration that prolongs the atrio–His bundle (A–H) conduction time by 30%. Data represent mean ± SE of three to five experiments. [b] Molar concentration that prolongs the His bundle ventricular (H–V) conduction time by 10%. Data represent the mean ± SEM of three to five experiments. [c] These drugs did not produce significant effects on H–V conduction time even on concentrations at which A–H blocks were observed.

Table XI. Hypotensive Effect of Compound 4 and Other Ca^{2+} Antagonists in SHR

compd	decrease of SBP,[a] mmHg		
	10 mg/kg, po	30 mg/kg, po	100 mg/kg, po
4	ND[b]	48.3 ± 5.3	87.5 ± 9.0
diltiazem	ND[b]	22.5 ± 7.7	44.2 ± 3.3
verapamil	24.2 ± 5.2	83.3 ± 4.0	ND[b]

[a] Each value indicates the mean ± SEM of maximum decrease of systolic blood pressure (SBP) after oral administration in six animals. [b] Not determined.

Table XII. Effect of Compound 4 on Acute Thrombotic Death Induced by Collagen in Mice

compd	ID_{50},[a] mg/kg, po	compd	ID_{50},[a] mg/kg, po
4 (SA2572)	12	nifedipine	>30
diltiazem	>30	nicardipine	>30
verapamil	>30	ticlopidine[d]	260

[a] ID_{50} was calculated by using the following formula: % inhibition = $(S_t^b - S_c^c)/(100 - S_c^c)$. [b] Survival ratio (%) of treated group ($n = 8$). [c] Survival ratio (%) of control group ($n = 12$). [d] Platelet aggregation inhibitor.

benzothiazoline (**12-2**) (33.9 g, 0.125 mol) in dry DMF (150 mL) under ice cooling and then stirred at room temperature for 20 min. 3-Chloropropionaldehyde diethyl acetal (25.0 g, 0.15 mol) was added to the mixture, and this mixture was heated at 60 °C for 2 h. The reaction mixture was poured onto ice–water and extracted with AcOEt. The organic extract was washed with 1 N NaOH, H_2O, and brine, dried ($MgSO_4$), and concentrated at a reduced pressure. The residual oil (56 g) was chromatographed on silica gel with benzene–AcOEt (10/1) to give 38 g (76%) of **13-1** as oil: IR (film) 1680 (C=O), 1468, 1380, 1124 (C—O), 1102 (C—O), 1060 (C—O), 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, 6 H, J = 7.0 Hz, 2 CH_2CH_3), 1.9–2.3 (m, 2 H, OCH_2CH_2), 2.20 (s, 3 H, $COCH_3$), 3.3–3.9 (m, 4 H, 2 CH_2CH_3), 4.17 (t, 2 H, J = 6.0 Hz, OCH_2), 4.83 (t, 1 H, J = 6.0 Hz, OCHO), 6.7–7.4 (m, 8 H, aromatic and C-2 H), 7.8–8.4 (br, 1 H, C-4 H).

3-Acetyl-2-[2-(4-bromobutoxy)-5-methoxyphenyl]benzothiazoline (13-9). Method E. To a stirred solution of 3-acetyl-2-(2-hydroxy-5-methoxyphenyl)benzothiazoline (**12-5**) (26.8 g, 0.089 mol) and K_2CO_3 (24.6 g, 0.178 mol) in i-PrOH (180 mL) was added 1,4-dibromobutane (192.2 g, 0.89 mol), and the mixture was refluxed for 2 h. The cooled reaction mixture was poured onto water (600 mL) and then extracted with AcOEt. The organic extract was washed with brine and dried ($MgSO_4$), and the solvent was evaporated. Excess 1,4-dibromobutane was recovered by distillation [50–51 °C/(4 mmHg)] to give 148.5 g (86% recovery). The residue of the distillation was chromatographed on silica gel with CH_2Cl_2 and recrystallized from MeOH to give 27.0 g (70%) of **13-9**: mp 114.5–116 °C; IR (KBr) 1655 (C=O), 1467, 1368, 1279 (C—O), 1205 (C—O), 1046 (C—O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7–2.3 (m, 4 H, $OCH_2CH_2CH_2$), 2.20 (s, 3 H, $COCH_3$), 3.49 (t, 2 H, J = 6.0 Hz, CH_2Br), 3.59 (s, 3 H, OCH_3), 4.01 (t, 2 H, J = 5.0 Hz, OCH_2), 6.50, (d, 1 H, J = 2.2 Hz, C-6′ H), 6.6–7.2 (m, 6 H, aromatic and C-2 H), 7.6-8.3 (br, 1 H, C-4 H). Anal. ($C_{20}H_{22}BrNO_3S$), C, H, N.

Chloroalkoxy derivatives were synthesized by using α-bromo-ω-chloroalkane or α-chloro-ω-[(methylsulfonyl)oxy]alkane (1.1 molar equiv of **12**) instead of α,ω-dibromoalkane.

3-Acetyl-2-[5-chloro-2-[3-(dimethylamino)propoxy]phenyl]benzothiazoline Hydrochloride (3-11). Method C. To a stirred suspension of NaH (50% oil dispersion; 0.53 g, 0.011 mol) in dry DMF (10 mL) was added dropwise a solution of 3-acetyl-2-(5-chloro-2-hydroxyphenyl)benzothiazoline (**12-7**) (3.06 g, 0.010 mol) in dry DMF (10 mL), and the mixture was stirred at room temperature for 20 min. To the mixture was added a solution of 3-(dimethylamino)propyl chloride (1.46 g, 0.012 mol) in dry DMF (15 mL) and stirred at about 60 °C for 2 h. The reaction mixture was poured onto ice-cooled 2 N HCl and washed with AcOEt. The aqueous solution was alkalized (pH >10) and extracted with AcOEt. The organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in MeOH, and HCl (gas)–AcOEt was added to acidify (pH <2). The solvent was evaporated, and the residual solid was recrystallized from i-PrOH–Et_2O to give 2.85 g (67%) of **3-11**: mp 193–195.5 °C; IR (KBr) 3420, 1678 (C=O), 1466, 1376 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.1–2.4 (m, 2 H, OCH_2CH_2), 2.28 (s, 3 H, $COCH_3$), 2.76 (s, 3 H, NCH_3), 2.83 (s, 3 H, NCH_3), 3.1–3.5 (m, 2 H, CH_2N), 4.21 (t, 2 H, J = 5.5 Hz, OCH_2), 6.8–7.4 (m, 7 H, aromatic and C-2 H), 7.7–8.1 (br, 1 H, C-4 H), 11.0–11.9 (br, 1 H, HCl). Anal. ($C_{20}H_{23}ClN_2O_2S \cdot HCl \cdot 0.2H_2O$) C, H, N.

3-Acetyl-2-[2-[3-(methylamino)propoxy]phenyl]benzothiazoline Hydrogen Fumarate.[42] Method D. To a stirred solution of 3-acetyl-2-[2-(3,3-diethoxypropoxy)phenyl]benzothiazoline (**13-1**) (5.0 g, 0.0125 mol) in acetone–H_2O (5/1, 30 mL) was added Amberlite CG-120 (type 1, 10.0 g), and the mixture was stirred at 50 °C for 2 h. After filtration of the resin, the filtrate was diluted with AcOEt. The solution was washed with H_2O and brine, dried ($MgSO_4$), and evaporated in vacuo to give 3.9 g of 3-acetyl-2-[2-(3-oxopropoxy)phenyl]benzothiazoline as oil. The purity of this aldehyde compound was about 70% from its ^1H NMR spectrum: ^1H NMR ($CDCl_3$) δ 2.23 (s, 3 H, $COCH_3$), 2.93 (dt, 2 H, J = 6.0 and 1.0 Hz, CH_2CHO), 4.37 (t, 2 H, J = 6.0 Hz, OCH_2), 6.7–7.4 (m, 8 H, aromatic and C-2 H), 7.7–8.4 (br, 1 H, C-4 H), 9.83 (t, 1 H, J = 1.0 Hz, CHO). (This aldehyde, very unstable, was used directly without further purification.)

To the solution of this aldehyde (2.5 g, about 0.0061 mol) were added methylamine hydrochloride (2.47 g, 0.0366 mol), pulverized 3A molecular sieves (3 g) and sodium cyanoborohydride (0.383 g, 0.0061 mol), and the solution was stirred for 1 h at room temperature. The aqueous solution was washed with AcOEt, alkalized with 5 N NaOH (pH >11), and extracted with AcOEt. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated at a reduced pressure to give an oily residue (1.0 g). It was chromatographed on silica gel with AcOEt–MeOH (20/1) to give 440 mg of pure product as an oil. To a solution of this oil (440 mg, 0.0013 mol) in AcOEt (5 mL) was added solution of fumaric acid (150 mg, 0.0013 mol) in MeOH (5 mL), and the mixture was concentrated in vacuo to give 307 mg (11%) of the desired compound: mp 111–113 °C; IR (KBr) 3420, 1674 (C=O), 1458, 1370 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.9–2.5 (m, 2 H, OCH_2CH_2), 2.20 (s, 3 H, $COCH_3$), 2.58 (s, 3 H, NCH_3), 2.9–3.4 (m, 2 H, CH_2N), 4.18 (t, 2 H, J = 6.0 Hz, OCH_2), 6.48 (s, 2 H, fumaric acid HC=CH), 6.5–7.5 (m, 8 H, aromatic and C-2 H), 7.8–8.2 (br, 1 H, C-4 H), 9.13 (br s, 3 H, NH and 2 CO_2H).

3-Acetyl-2-[5-methoxy-2-[4-[*N*-methyl-*N*-(3,4,5-trimethoxyphenethyl)amino]butoxy]phenyl]benzothiazoline Hydrochloride (4, SA2572). Method E. To a solution of 3-acetyl-2-[2-(4-bromobutoxy)-5-methoxyphenyl]benzothiazoline (**13-9**) (10.5 g, 0.024 mol) and *N*-methyl-3,4,5-trimethoxyphenethylamine (5.9 g, 0.026 mol) in dry DMF (36 mL) was added K_2CO_3 (6.6 g, 0.048 mol), and the mixture was stirred at 60 °C for 2 h. The reaction mixture was poured onto H_2O and extracted with AcOEt. The organic extract was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The residual oil was chromatographed on silica gel with $CHCl_3$–MeOH (50/1) to give

(42) Ca^{2+} antagonistic activity (IC_{50}, M) of this compound was 1.9×10^{-5}.

the free amine of **4** as oil (11.7 g, 84%). The oil was dissolved in $CHCl_3$ and washed with 1 N HCl and H_2O and dried over $MgSO_4$. The solvent was removed, and the residue was recrystallized from EtOH to give 11.9 g (80.0%) of **4**: mp 190–190.5 °C; IR (KBr) 2436 (ammonium salt), 1669 (C=O), 1590, 1494, 1458, 1418, 1380, 1235 (C—O), 1213 (C—O), 1121 (C—O), 1038 (C—O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60–2.53 (m, 4 H, $OCH_2CH_2CH_2$), 2.22 (s, 3 H, $COCH_3$), 2.70–3.00 (m, 3 H, NCH_3), 3.00–3.56 (m, 6 H, $CH_2NCH_2CH_2Ar$), 3.59 (s, 3 H, 5'-OCH_3), 3.75 (s, 9 H, phenethyl part 3 OCH_3), 4.03 (br t, 2 H, J = 5.0 Hz, OCH_2), 6.42 (s, 2 H, aromatic of phenethyl part), 6.40–7.20 (m, 7 H, aromatic and C-2 H), 7.50–8.12 (m, 1 H, C-4 H), 12.00–12.67 (br, 1 H, HCl). Anal. ($C_{32}H_{40}N_2O_6S$·HCl) C, H, N.

Biological Activities in Vitro. Ca^{2+} Antagonistic Activity. Isolated taenia cecum (about 1.5 cm; from male Hartley guinea pig weighing 300–450 g) was suspended in a 20-mL organ bath with Krebs–Hensleit solution at 31 ± 1 °C and bubbled with 5% carbon dioxide in oxygen. After equilibration, the muscle was washed with Ca^{2+}-free high-K^+ Krebs solution. The muscle was exposed to test compounds for 5 min before addition of $CaCl_2$, and the contraction evoked by $CaCl_2$ (3×10^{-4} M) was recorded isotonically. The Ca^{2+} antagonistic activity was represented by the concentration of the test compound that elicited 50% inhibition of Ca^{2+}-evoked contraction (IC_{50}).

Electrophysiological Study (Langendorff Perfused Rabbit Hearts). The hearts were rapidly removed, and cannula were inserted into the aorta for Langendorff perfusion. The preparations were perfused at a constant flow rate (20 mL/min) with Krebs bicarbonate solution equilibrated with 5% carbon dioxide in oxygen. The solution had the following composition in mM: NaCl, 120.3; KCl, 5.0; $CaCl_2$, 1.2; $MgSO_4$, 7, H_2O, 1.3; NaH_2PO_4, 1.2; $NaHCO_3$, 24.2; and glucose, 5.5 (pH 7.4). The temperature of the perfusate entering the heart was maintained at 33 ± 0.5 °C. Bipolar silver wire electrodes (200 μm in diameter) with an interpolar distance of 1.0 mm were inserted through a small incision made in the atria so as to record His-bundle electrograms (HBE). The signal was amplified at a frequency response from 100 to 500 Hz with a time constant of 0.003 s and displayed on the oscilloscope (Tektronix 5113A). The same electrodes as for HBE recording were placed on the atrium close to the coronary sinus region. The hearts were electrically driven at a constant rate of 2.0 Hz through the stimulating electrodes on the right atrium. The pulses for stimulation were 5 ms in duration and twice the diastolic threshold in intensity. The atrio–His bundle conduction time (A–H interval) was defined as the period from the onset of the first rapid atrial deflection (A) to the first rapid His bundle deflection (H) on HBE, and the His bundle–ventricular conduction time (H–V interval) from H to the beginning of the ventricular activity (V). The preparations were allowed to equilibrate for at least 40 min. The actions of the drugs were evaluated after 30 min of exposure to the preparations at each concentration.

Biological Activities in Vivo. Hypotensive Effect in Conscious SHR. The experiments were performed in 6–13 male SHR weighing 300–400 g. (SHR had been given by the courtesy of Professor K. Okamoto, Department of Pathology, Kinki University School of Medicine. They were inbred thereafter in our laboratory.) Systolic blood pressure (SBP) was measured in a conscious state by a tail cuff plethysmographic method with an electrosphygmomanometer (Narco, PE-300) at 0, 1, 3, 6, 9, and 24 h after administration. Heart rate was calculated from the pulse for 4 s. Test compounds were orally administered as a 0.5% methylcellulose suspension.

Statistical analysis of the data was performed by using the Dunnett's multiple comparison test with significance achieved at the indicated level (Figure 3).

Acute Thrombotic Death in Mice. Animals used were male ddY mice weighing 20–30 g. Collagen solution (3 mg/mL) was prepared as follows. The solution of collagen (Sigma Chemical Co., type III; 30 mg) in 0.5 M acetic acid (2.5 mL) was diluted with Tris buffer (pH 7.4, 7.5 mL). Acute pulmonary thrombosis was induced in mice by a rapid intravenous injection (tail vain) of collagen solution in 2 s according to the reports by Nordöy[43] and Nishizawa.[44] The dose of collagen was determined to about 30 mg/kg so that 10–20% of the control mice died within 3 min after the injection. Test compounds were orally administered as a 0.5% tragacanth suspension at 3 h before the injection of collagen.

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Registry No. **2-1**·HCl, 87181-95-1; **2-2**·HCl, 87181-97-3; **2-3**, 87182-06-7; **2-4**·$C_4H_4O_4$, 112968-92-0; **3-1**, 112947-04-3; **3-1**·HCl, 86135-07-1; **3-2**, 112947-05-4; **3-2**·HCl, 86135-57-1; **3-3**, 86135-36-6; **3-3**·$^3/_2C_4H_4O_4$, 112946-45-9; **3-4**, 86136-36-9; **3-4**·$C_2H_2O_4$, 86136-37-0; **3-5**, 86135-08-2; **3-5**·HCl, 112946-46-0; **3-6**, 86135-49-1; **3-6**·$C_4H_4O_4$, 86135-50-4; **3-7**, 112947-06-5; **3-7**·HCl, 86135-58-2; **3-8**, 86136-58-5; **3-8**·HCl, 86135-09-3; **3-9**, 112947-07-6; **3-9**·HCl, 86135-60-6; **3-10**, 112947-08-7; **3-10**·HCl, 86135-16-2; **3-11**, 112947-09-8; **3-11**·HCl, 86135-34-4; **3-12**, 86135-21-9; **3-12**·$C_4H_4O_4$, 86135-22-0; **3-13**, 112947-10-1; **3-13**·HCl, 86135-20-8; **3-14**, 86135-40-2; **3-14**·$C_4H_4O_4$, 86135-41-3; **3-15**, 86135-25-3; **3-15**·$C_2H_2O_4$, 86135-26-4; **3-16**, 112946-47-1; **3-16**·$2C_4H_4O_4$, 112946-48-2; **3-17**, 86136-61-0; **3-17**·2HCl, 86135-92-4; **3-18**, 112946-49-3; **3-19**, 112946-50-6; **3-19**·$C_4H_4O_4$, 112946-51-7; **3-20**, 112946-52-8; **3-20**·$C_4H_4O_4$, 112946-53-9; **3-21**, 112947-11-2; **3-21**·HCl, 112946-54-0; **3-22**, 112946-55-1; **3-22**·$C_4H_6O_4$, 112946-56-2; **3-23**, 86135-27-5; **3-23**·$C_4H_4O_4$, 86135-28-6; **3-24**, 112946-57-3; **3-24**·$C_4H_4O_4$, 112946-58-4; **3-25**, 112946-59-5; **3-25**·$2C_4H_4O_4$, 112946-60-8; **3-26**, 112946-61-9; **3-26**·$2C_4H_4O_4$, 112946-62-0; **3-27**, 112946-63-1; **3-27**·$C_4H_4O_4$, 112946-64-2; **3-28**, 99320-45-3; **3-28**·$C_4H_4O_4$, 112946-65-3; **3-29**, 99320-53-3; **3-29**·$C_4H_4O_4$, 112946-66-4; **3-30**, 86135-23-1; **3-30**·$C_2H_2O_4$, 86135-24-2; **3-31**, 86135-29-7; **3-31**·$C_2H_2O_4$, 86135-30-0; **3-32**, 86135-82-2; **3-32**·$2C_4H_4O_4$, 86135-83-3; **3-33**, 86135-84-4; **3-33**·$2C_4H_4O_4$, 86135-85-5; **3-34**, 86135-86-6; **3-34**·$2C_4H_4O_4$, 86135-87-7; **3-35**, 86135-88-8; **3-35**·$2C_4H_4O_4$, 86135-89-9; **3-36**, 112946-67-5; **3-36**·$C_2H_2O_4$, 112946-68-6; **3-37**, 112946-69-7; **3-37**·$C_4H_4O_4$, 112946-70-0; **3-38**, 112947-12-3; **3-38**·HCl, 112946-71-1; **3-39**, 86136-62-1; **3-39**·HCl, 86135-31-1; **3-40**, 112947-13-4; **3-40**·HCl, 112946-72-2; **3-41**, 112947-14-5; **3-41**·HCl, 112946-73-3; **3-42**, 112947-15-6; **3-42**·HCl, 112946-74-4; **3-43**, 112947-16-7; **3-43**·HCl, 112946-75-5; **3-44**, 112947-17-8; **3-44**·HCl, 112946-76-6; **3-45**, 112947-18-9; **3-45**·HCl, 112946-77-7; **3-46**, 112946-78-8; **3-46**·$C_4H_4O_4$, 112946-79-9; **3-17**, 112946-80-2; **3-47**·$C_4H_4O_4$, 112946-81-3; **3-48**, 99320-49-7; **3-48**·$C_4H_4O_4$, 112946-82-4; **3-49**, 112946-83-5; **3-49**·$C_2H_2O_4$, 112946-84-6; **3-50**, 112947-19-0; **3-50**·HCl, 112946-85-7; **3-51**, 112947-20-3; **3-51**·HCl, 112946-86-8; **3-52**, 112947-21-4; **3-52**·HCl, 112946-87-9; **3-53**, 112947-22-5; **3-53**·HCl, 112946-88-0; **3-54**, 112947-23-6; **3-54**·HCl, 112946-89-1; **4**, 105148-98-9; **4**·HCl, 112946-90-4; **9**, 137-07-5; **10**(2-OH, R_2 = H), 90-02-8; **10**(3-OH, R_2 = H), 100-83-4; **10**(4-OH, R_2 = H), 123-08-0; **10**(2-OH, R_2 = 3-OCH_3), 148-53-8; **10**(2-OH, R_2 = 5-Cl), 635-93-8; **10**(2-OH, R_2 = 5-OCH_3), 672-13-9; **10**(2-OH, R_2 = 5-NO_2), 97-51-8; **10**(4-OH, R_2 = 3,5-OCH_3), 134-96-3; **11-1**, 7361-94-6; **11-2**, 56248-80-7; **11-3**, 112946-91-5; **11-4**, 41570-03-0; **11-5**, 6266-11-1; **11-6**, 41570-02-9; **12-1**, 112946-92-6; **12-2**, 86136-50-7; **12-3**, 112946-93-7; **12-4**, 112946-94-8; **12-5**, 105129-60-0; **12-6**, 112946-95-9; **12-7**, 112946-96-0; **12-8**, 112946-97-1; **12-9**, 112946-98-2; **13-1**, 112946-99-3; **13-2**, 86136-55-2; **13-3**, 93264-89-2; **13-4**, 112947-00-9; **13-5**, 93264-99-4; **13-6**, 112947-01-0; **13-7**, 93264-85-8; **13-8**, 93265-04-4; **13-9**, 99320-58-8; **13-10**, 86136-53-0; **13-11**, 112947-02-1; **13-12**, 112947-03-2; **13-13**, 93265-06-6; **13-14**, 93264-92-7; $Cl(CH_2)_2Br$, 107-04-0; $Cl(CH_2)_3Br$, 109-70-6; $Cl(CH_2)_4Br$, 6940-78-9; $Br(CH_2)_2Br$, 111-24-0; $Br(CH_2)_4Br$, 110-52-1; $Cl(CH_2)_6Br$, 6294-17-3; H_3CNH_2·HCl, 593-51-1; H_3CNHCH_3, 124-40-3; $H_3CNHC_6H_{11}$, 100-60-7; $Cl(CH_2)_2CH(OEt)_2$, 35573-93-4; $(H_3C)_2N(CH_2)_3Cl$, 109-54-6; 3-acetyl-2-[2-[3-(methylamino)propoxy]phenyl]benzothiazoline, 86135-02-6; 3-acetyl-2-[2-[3-(methylamino)propoxy]phenyl]benzothiazoline hydrogen fumarate, 86135-03-7; 3-acetyl-2-[2-(3-oxopropoxy)phenyl]benzothiazoline, 86136-52-9; *N*-(2-(3,4,5-trimethoxyphenethyl))piperazine, 93847-87-1; 4-

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(phenylcarbonyl)piperidine, 37586-22-4; 4-((4-fluorophenyl)-carbonyl)piperidine, 56346-57-7; *N*-(2-(3,4-dimethoxyphenyl))-piperazine, 86136-56-3; *N*-methyl-3,4-dimethoxyphenethylamine, 3490-06-0; *N*-methyl-2,3,4-trimethoxyphenethylamine, 32042-11-8; *N*-methyl-3,4,5-trimethoxyphenethylamine, 4838-96-4; methylamine, 74-89-5; 4-((4-chlorophenyl)carbonyl)piperidine, 53220-41-0; 2-(3,4,5-trimethoxyphenyl)ethylamine, 54-04-6; *N*-ethyl-3,4,5-trimethoxyphenylethylamine, 112947-24-7; *N*-(methylethyl)-3,4,5-trimethoxyphenylethylamine, 58418-70-5; *N*-cyclopropyl-3,4,5-trimethoxyphenylethylamine, 112947-25-8; *N*-methyl-2,3,4-trimethoxyphenylpropylamine, 112947-26-9; *N*-methyl-2-(3,4-dimethoxyphenyl)propylamine, 112947-27-0.

Synthesis and Pharmacological Evaluation of 5,6-*exo*-Epoxy-7-oxabicyclo[2.2.1]heptane Derivatives[1]

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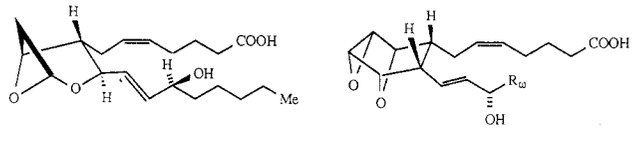
[1α,2β(5*Z*),3β(1*E*,3*S*),4α,5α,6α]-7-[5,6-Epoxy-3-(3-cyclohexyl-3-hydroxy-3-methyl-1-propenyl)-7-oxabicyclo[2.2.1]-hept-2-yl]-5-heptenoic acid (**31**) and [1α,2β(5*Z*),3β(1*E*,3*S*),4α,5α,6α]-7-[5,6-epoxy-3-[3-hydroxy-5-(*p*-hydroxyphenyl)-1-pentenyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid (**37**) were found to be selective TxA_2 antagonists at the platelet and pulmonary thromboxane receptors. An efficient stereospecific synthesis of these compounds and a series of structural analogues is described. Compounds **31** and **37** both inhibited the bronchoconstriction induced by arachidonic acid in the anesthetized guinea pig.

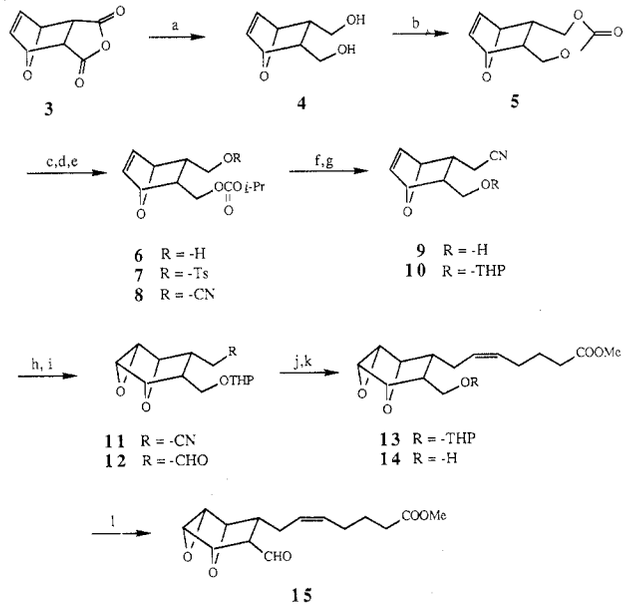
Arachidonic acid (AA) is metabolized by platelets into thromboxane A_2 (TxA_2),[2] which is a powerful inducer of platelet aggregation[3] and of vascular[4] and pulmonary[5] smooth muscle contraction. Overproduction of TxA_2 has been implicated in several pathophysiological conditions including thrombosis, asthma, ischemia, and myocardial infarction.[6] In recent years considerable efforts have been directed toward identification of agents that would either inhibit TxA_2 biosynthesis[7] or block its action at the thromboxane receptor.[8] Over the past few years several 7-oxabicyclo[2.2.1]heptane derivatives have been reported to be potent TxA_2 antagonists.[9-15] Inspection of Dreiding models indicated a striking resemblance between the proposed structure of TxA_2 and that of the 7-oxabicyclo-

Chart I



1 2

Scheme I[a]



3 4 5

6 R = -H
7 R = -Ts
8 R = -CN

9 R = -H
10 R = -THP

11 R = -CN
12 R = -CHO

13 R = -THP
14 R = -H

15

[a] (a) LAH/THF; (b) $COCl_2$ (1 equiv)/THF, 0 °C; Py/CH_2Cl_2, −50 °C; (c) *i*-PrOH/TsOH (cat.), Δ; (d) Py/TsCl, room temperature; (e) NaCN (2 equiv)/DMSO, 90–95 °C; (f) 1% K_2CO_3/MeOH–H_2O, room temperature; (g) CH_2Cl_2/DHP/TsOH (cat.); (h) MCPBA/CH_2Cl_2, room temperature; (i) DIBAH/toluene, −78 °C; (j) K-*tert*-amylate/Ph_3P·Br$(CH_2)_4$COOH/THF–toluene, −20 °C; CH_2N_2/ether; (k) MeOH/amberlyst, room temperature; (l) PCC/CH_2Cl_2, room temperature.

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