$CO_2HC_6H_4CH_2CO_2H$, 501-89-3; 5-Cl-2TCH_2CO_2H, 13669-19-7; 5-Me-2TCH_2CO_2H, 70624-30-5; 3TCH_2CO_2H, 6964-21-2; 2PCH_2CO_2H, 13115-43-0; 4PCH_2CO_2H, 28356-58-3; 1-naphthyl CH_2CO_2H, 86-87-3; 2-naphthyl CH_2CO_2H, 581-96-4; 3$TNCH_2CO_2H$, 1131-09-5; 4-$FC_6H_4C(O)CH_3$, 403-42-9; 2TAc, 88-15-3; 2TCHO, 98-03-3; cyclooxygenase, 39391-18-9; 5-lipoxygenase, 80619-02-9; 2,6-dimethylphenol, 576-26-1; 4-acetyl-2,6-dimethylphenol, 5325-04-2.

Synthesis and Ca^{2+} Antagonistic Activity of 2-[2-[(Aminoalkyl)oxy]-5-methoxyphenyl]-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzothiazines

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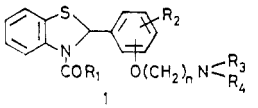
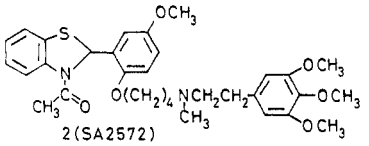
As an extension of the previous investigation (*J. Med. Chem.* **1988**, *31*, 919), we synthesized a series of 2-[2-[(aminoalkyl)oxy]-5-methoxyphenyl]-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzothiazines (**3**) and evaluated their Ca^{2+} antagonistic activities. Ca^{2+} antagonistic activity was measured with isolated depolarized guinea pig taenia cecum. On the basis of their potent Ca^{2+} antagonistic activity, six benzothiazines were selected and further evaluated for their vasocardioselectivity. Among these six compounds, the key compound **15** [3,4-dihydro-2-[5-methoxy-2-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propoxy]phenyl]-4-methyl-3-oxo-2*H*-1,4-benzothiazine hydrogen fumarate] was recognized as having the lowest cardioselectivity. Following optical resolution, the absolute configuration of the compound's optically active enantiomer was determined by means of X-ray crystallography of a synthetic precursor (+)-**4a**. The Ca^{2+} antagonistic activity of **15** was found to reside primarily in (+)-**15** (which was about 7 times more potent than (−)-**15**). The in vitro study showed that (+)-**15** had a low cardioselectivity compared to verapamil and diltiazem. This result suggests that (+)-**15** would exhibit less adverse effects due to cardiac inhibition than diltiazem and verapamil in therapeutic use.

Ca^{2+} antagonists, useful in the treatment of angina pectoris, hypertension, and certain cardiac arrhythmias, are classified structurally into two large groups: the non-dihydropyridines, represented by verapamil and diltiazem, and the dihydropyridines, represented by nifedipine and nicardipine.[1-3] We were interested in both the chemical structures and therapeutic benefit of the former. However, in some patients with impaired ventricular function and/or those undergoing β-adrenergic blocker therapy, non-dihydropyridine type Ca^{2+} antagonists caused several adverse effects (cardiac failure, bradycardia, and/or asystole) due to myocardial suppression and conduction disturbances.[4-7] Accordingly, we anticipate that a novel non-dihydropyridine type Ca^{2+} antagonist having weak cardiac suppression would be safer than conventional ones such as verapamil and diltiazem in clinical use.

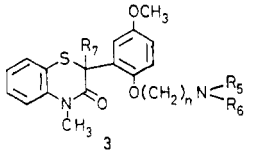
In our previous paper,[8] on our study of the structure–activity relationship of benzothiazoline derivatives **1**, we reported that 3-acetyl-2-[5-methoxy-2-[4-[*N*-methyl-*N*-(3,4,5-trimethoxyphenethyl)amino]butoxy]phenyl]benzothiazoline (**2**: SA2572) was a potent Ca^{2+} antagonist, possessing the same level of activity as diltiazem. Here, we report further developments in our research on new Ca^{2+} antagonists. Anticipating a bioisosteric effect, we changed the benzothiazoline nucleus into benzothiazine's and synthesized 2-[2-[(aminoalkyl)oxy]-5-methoxyphenyl]-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzothiazine (**3**).



1



2 (SA2572)



3

Compound **15**, which was selected from the series of synthesized benzothiazines, was a racemic compound possessing an asymmetric center at the 2-position in the benzothiazine ring. Because differences in the biological activity of enantiomers are often recognized,[9] we resolved **15** by fractional crystallization to produce (+)-**15** and (−)-**15**. A biological evaluation of both enantiomers in vitro suggests that the potent Ca^{2+} antagonistic activity of **15** residues stereoselectively in (+)-**15**.

Chemistry. In the previous publication,[10] we reported the synthetic method for 3,4-dihydro-2-(2-hydroxy-5-methoxyphenyl)-4-methyl-3-oxo-2*H*-1,4-benzothiazines

(1) Fleckenstein, A. *Cir. Res. Suppl. 1* **1983**, *52*, 3.
(2) Singh, B. N.; Baky, S.; Nademanee, K. *Am. J. Cardiol.* **1985**, *55*, 214B.
(3) Millard, R. W.; Lathrop, D. A.; Grupp, G.; Ashraf, M.; Grupp, I. L.; Schwartz, A. *Am. J. Cardiol.* **1982**, *49*, 499.
(4) Singh, B. N.; Ellrodt, G.; Peter, C. T. *Drugs* **1978**, *15*, 169.
(5) Opie, L. H. *Lancet* **1980**, *I*, 806.
(6) Klieman, R. L.; Stephenson, S. H. *Q. Rev. Drug Metab. Drug Interact.* **1985**, *5*, 193.
(7) Gibson, R. S.; Boden, W. E.; Theroux, P.; Strauss, H. D.; Pratt, C. M.; Gheorghiade, M.; Capone, R. J.; Crawford, M. H.; Schlant, R. C.; Kleiger, R. E.; Young, P. M.; Schechtman, K.; Perryman, M. B.; Roberts, R. *N. Engl. J. Med.* **1986**, *315*, 423.
(8) Yamamoto, K.; Fujita, M.; Tabashi, K.; Kawashima, Y.; Kato, E.; Oya, M.; Iso, T.; Iwao, J. *J. Med. Chem.* **1988**, *31*, 919.
(9) Ariens, E. J. *Eur. J. Clin. Pharmacol.* **1984**, *26*, 663.
(10) Fujita, M.; Ota, A.; Ito, S.; Yamamoto, K.; Kawashima, Y. *Synthesis* **1988**, 599.

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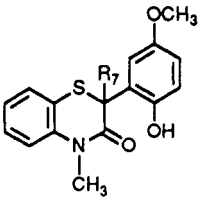
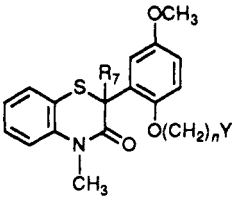
Table I. 3,4-Dihydro-2-(2-hydroxy-5-methoxyphenyl)-4-methyl-3-oxo-2*H*-1,4-benzothiazines (**4**) and 3,4-Dihydro-2-[2-[(haloalkyl)oxy]-5-methoxyphenyl]-4-methyl-3-oxo-2*H*-1,4-benzothiazines (**5**)



4d, e

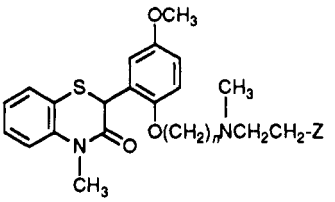


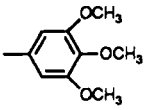
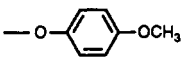
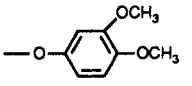
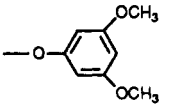
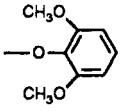
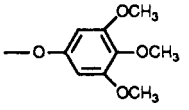
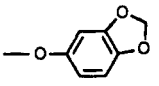
5a–f

compd	R^7	*n*	Y	yield,[a] %	mp, °C	recrystn solvent	formula[b]
4d	OCH_3			85	135–137	MeOH	$C_{17}H_{17}NO_4S$
4e	SCH_3			78	167–168[c]	EtOH	$C_{17}H_{17}NO_3S_2$
5a	H	3	Cl	88	97–99	EtOH	$C_{19}H_{20}ClNO_3S$
5b	H	4	Br	86	103–105	MeOH	$C_{20}H_{22}BrNO_3S$
5c	CH_3	3	Br	40	107–109	MeOH	$C_{20}H_{22}BrNO_3S$
5d	*i*-C_3H_7	3	Br	40	110–111	MeOH	$C_{22}H_{26}BrNO_3S$
5e	OCH_3	3	Cl	85	67–69	MeOH	$C_{20}H_{22}ClNO_4S$
5f	SCH_3	3	Cl	93	135–136	EtOH	$C_{20}H_{22}ClNO_3S_2$

[a] Yield for production of target compound from immediate precursor, **6** or **4a–e**. [b] A satisfactory C, H, and N analysis for all compounds. [c] Decomposition.

Table II. 2-[2-[(Aminoalkyl)oxy]-5-methoxyphenyl]-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzothiazines



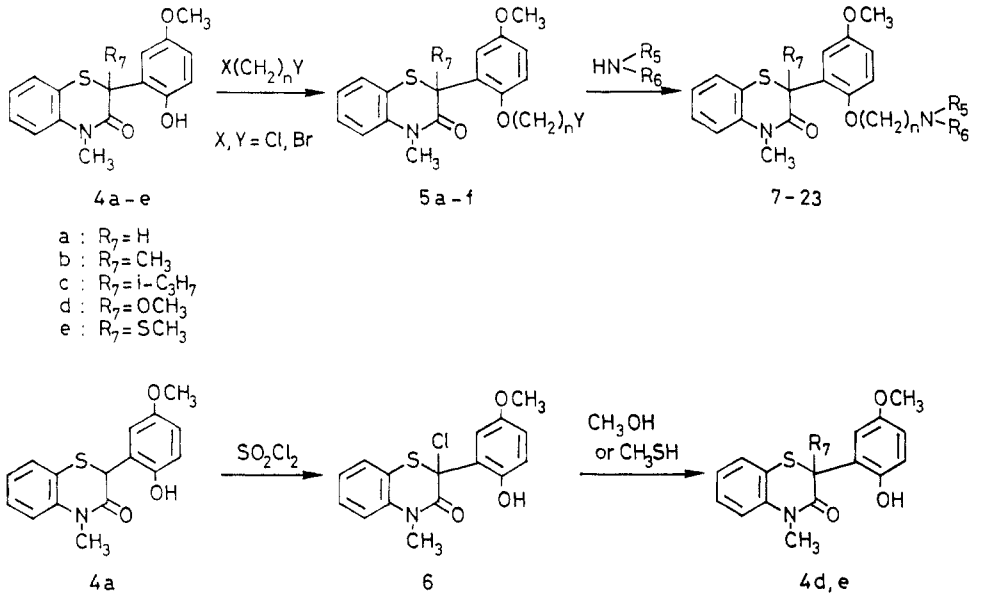
compd	Z	*n*	Ca^{2+}: IC_{50},[a] μM	yield,[b] %	mp, °C	recrystn solvent[c]	formula[d]
7		3	0.27 ± 0.07	60	163–165	Me–Et	$C_{31}H_{38}N_2O_6S{\cdot}C_2H_2O_4$[e]
8		4	0.35 ± 0.06	60	154–156	Et	$C_{32}H_{40}N_2O_6S{\cdot}C_2H_2O_4$[e]
9		4	0.53 ± 0.09	52	149–150	Et–Wt	$C_{30}H_{36}N_2O_5S{\cdot}C_2H_2O_4$[e]
10		4	0.23 ± 0.04	61	167–168	Et–Wt	$C_{31}H_{38}N_2O_6S{\cdot}C_2H_2O_4$[e]
11		3	0.55 ± 0.09	70	144–146	Et	$C_{30}H_{36}N_2O_6S{\cdot}C_4H_4O_4$[f]
12		3	0.51 ± 0.15	62	185–187	Et	$C_{30}H_{36}N_2O_6S{\cdot}HCl$
13		3	0.23 ± 0.04	43	137–139	Et–Ac	$C_{31}H_{38}N_2O_7S{\cdot}C_2H_2O_4$[e]
14		4	0.16 ± 0.03	51	149–151	Et–Wt	$C_{32}H_{40}N_2O_7S{\cdot}C_2H_2O_4$[e]
15		3	0.18 ± 0.01	68	131–133	Et	$C_{29}H_{32}N_2O_6S{\cdot}C_4H_4O_4$[f]
16		4	0.17 ± 0.03	62	149–152	Me	$C_{30}H_{34}N_2O_6S{\cdot}C_4H_4O_4$[f]

[a] Molar concentration required to block Ca^{2+}-induced contraction of K^+-depolarized guinea pig taenia cecum by 50%. Each value indicates the mean ± SEM (n = 4–10). Diltiazem was used as the standard compound; IC_{50} = 0.25 ± 0.08 μM. [b] Yield for production of target compound from immediate precursor, **5a,b**. [c] Et = EtOH; Me = MeOH; Wt = water; Ac = AcOEt. [d] A satisfactory C, H, and N analysis for all compounds. [e] Hydrogen oxalate. [f] Hydrogen fumarate.

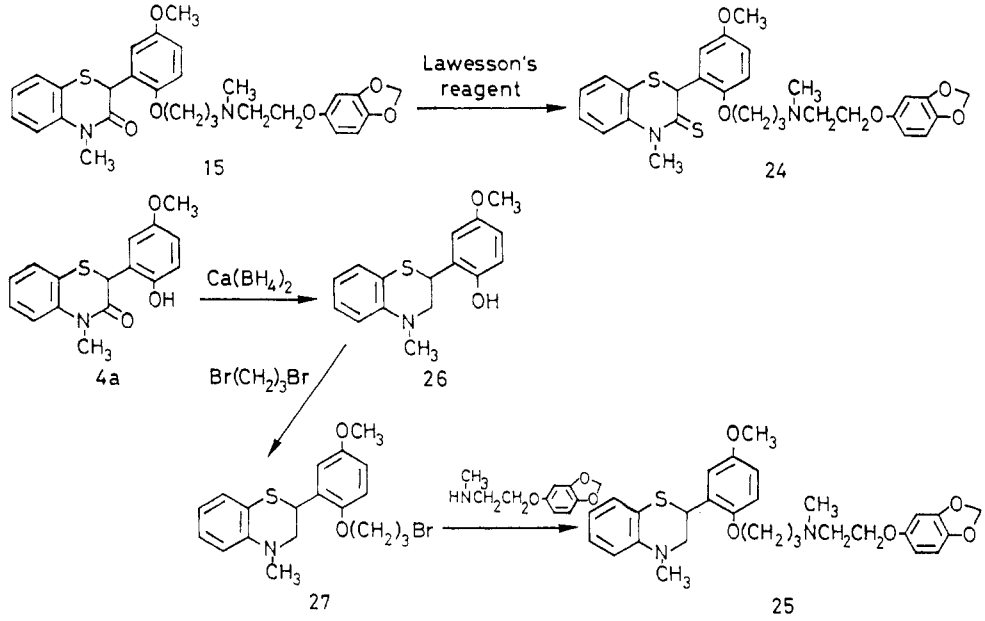
(**4a–c**). Compound **6** was prepared by chlorination of **4a** with sulfuryl chloride. Compounds **4d,e** (Table I) were obtained by the treatment of **6** with methanol or methanethiol. Compounds **7–23** were prepared by substituting halogens of compounds **5a–f** (Table I), which were obtained from **4a–e**, with appropriate amines[11,12] (Scheme I). These compounds (**7–16**) were isolated as hydro-

(11) Kuroda, S.; Koyama, S. *Yakugaku Zasshi* **1943**, *63*, 382.

Scheme I



Scheme II



chlorides, fumarates, or oxalates (Table II). Thiolactam **24** was obtained by treating **15** with Lawesson's reagent[13] and then isolated as a fumarate salt. Deoxo compound **25** was prepared as described in Scheme II; **4a** was treated with calcium borohydride[14] and 1,3-dibromopropane consecutively. The result, **27**, was then treated with *N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amine to yield **25**. Compound **25** was isolated as oxalate salt (Table IV).

Optical Resolution of the Racemate 15. Optical resolution of **15** was performed by way of diastereomeric salt formation with use of optically active mandelic acid, followed by fractional recrystallization. Treatment of the resolved amine–mandelic acid salts with aqueous $NaHCO_3$ produced free bases of (+)-**15** and (−)-**15**, which were isolated in fumarates (method A) (Table V).

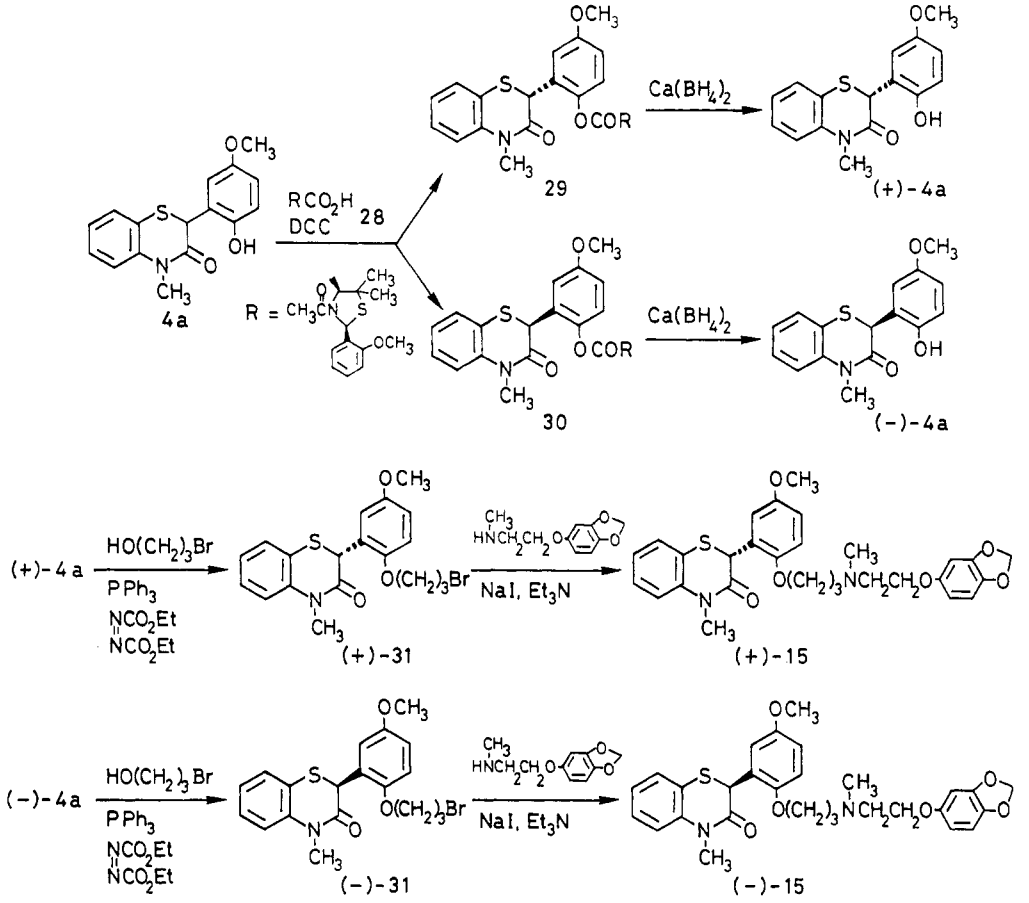
Optical Purity. The enantiomeric purity of (+)-**15** and (−)-**15** was determined by high-performance liquid chromatography with a chiral column[15] composed of cellulose carbamate.

Absolute Configuration. Since the crystals of (+)-**15** were not suitable for X-ray crystallography, we synthesized (+)-**15** via chiral synthetic intermediates (Scheme III), and determined the absolute configuration of (+)-**15** by means of an X-ray crystallographic analysis of a phenol compound (+)-**4a**, the synthetic precursor of (+)-**15**.

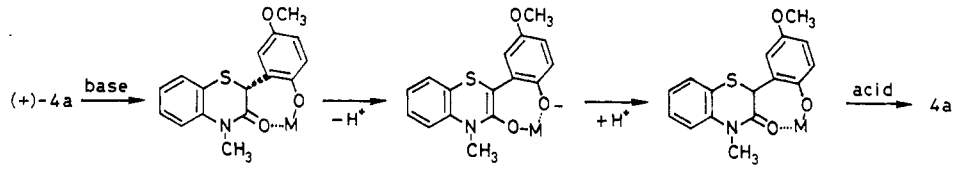
The racemic compound **4a** was separated as follows: 3-acyl-2-aryl-4-thiazolidinecarboxylic acid (**28**),[16] which possessed a rigid five-membered ring having two asymmetric centers, in the 2- and 4-positions, was condensed

(12) Shadbolt, R. S.; Sharpe, C. J.; Brown, G. R.; Ashford, A.; Ross, J. W. *J. Med. Chem.* **1971**, *14*, 836.
(13) Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223.
(14) Harbermehl, G. G.; Ecsy, W. *Heterocycles* **1977**, *7*, 1027.
(15) Okamoto, Y.; Kawashima, M.; Hatada, K. *J. Chromatogr.* **1986**, *363*, 173.
(16) Oya, M.; Kato, E.; Iwao, J.; Yasuoka, N. *Chem. Pharm. Bull.* **1982**, *30*, 484.

Scheme III



Scheme IV



with **4a**, yielding **29** and **30**. This diastereomeric mixture was suitable for separation. The optically pure phenol compound (+)-**4a**, which easily racemized under weak alkaline conditions, was obtained by the reduction of **29** by calcium borohydride[14] (Scheme III). Presumably, the acidity of methine proton at the 2-position was enhanced by a coordination of carbonyl group to counter cation of phenolate anion. The instability of (+)-**4a** was likely due to this rising acidity (Scheme IV).

Compound (+)-**4a** was alkylated via the Mitsunobu reaction[17] to yield the corresponding bromide (+)-**31**. (+)-**31** was then treated with *N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amine to give the (+)-**15** (method B). By the same procedure, (−)-**15** was obtained from **30** (Scheme III). It was convinced that the absolute configuration of the chiral center in (+)-**4a** was maintained through these reactions. The X-ray crystal structure of (+)-**4a**, shown in Figure 1, revealed that the absolute configuration of the 2-position (C1) was *R*, which corresponded to the configuration of the 2-position in (+)-**15**.

Results and Discussion

Ca^{2+} antagonistic activities of benzothiazine derivatives (**7**–**25**) were evaluated through in vitro assay by using isolated depolarized taenia cecum of guinea pigs. *N*-Methyl-*N*-phenethylamino compounds (**7**, **8**), having the same amino group as the benzothiazoline compound (**2**: SA2572),[8] displayed the same or slightly less potent activity than diltiazem (Table II). All the tested *N*-methyl-*N*-(phenoxyethyl)amino compounds (**9**–**16**), with newly designed amino groups, showed potent Ca^{2+} antagonistic

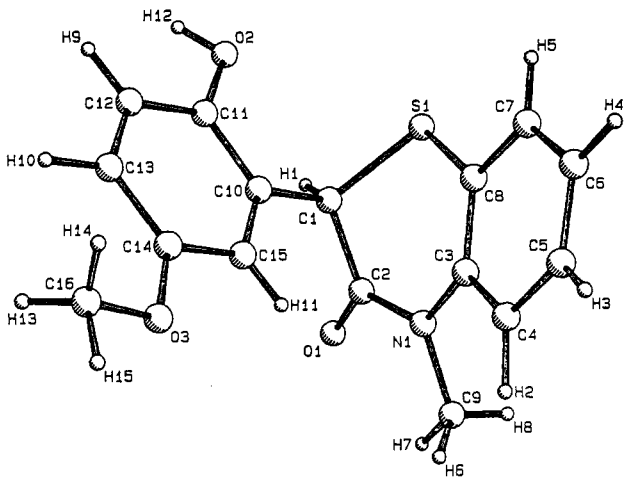


Figure 1. Molecular structure of (+)-**4a** drawn by the PLUTO program.

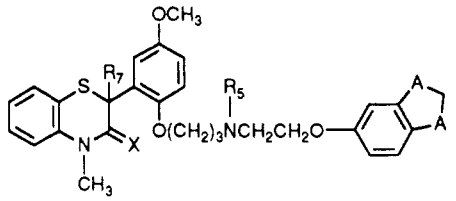
(17) Manhas, M. S.; Hoffman, W. H.; Lal, B.; Bose, A. K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 461.

Table III. Cardiovascular Effects of Compounds **7**, **10**, **13–16**, (+)-**15**, Diltiazem, and Verapamil

compd	guinea pig aorta, Ca^{2+} antagonistic activity: IC_{50},[a] μM	guinea pig right atria: suppressive effect on rate of contraction IC_{50},[b] μM	ratio[c]	guinea pig right atria: suppressive effect on contractile force IC_{50},[d] μM	ratio[e]
7	2.4 (1.3–4.6)	0.40 (0.17–0.94)	6.0	0.52 (0.17–1.6)	4.6
10	2.9 (1.5–5.5)	0.60 (0.21–1.7)	4.8	0.44 (0.19–1.0)	6.6
13	4.1 (1.1–15)	0.50 (0.22–1.1)	8.2	0.37 (0.18–0.77)	11.1
14	1.5 (0.96–2.3)	0.19 (0.09–0.41)	7.9	0.20 (0.096–0.41)	7.5
15	0.66 (0.32–1.4)	0.59 (0.40–0.85)	1.1	0.31 (0.19–0.50)	2.1
16	0.33 (0.19–0.55)	0.19 (0.11–0.32)	1.7	0.094 (0.066–0.13)	3.5
(+)-**15** (sesamodil)	0.23 (0.17–0.31)	0.18 (0.13–0.23)	1.3	0.068 (0.054–0.086)	3.4
diltiazem	4.5 (2.8–7.1)	0.60 (0.46–0.78)	7.5	0.095 (0.063–0.14)	47.4
verapamil	0.62 (0.42–0.91)	0.21 (0.14–0.33)	3.0	0.035 (0.027–0.046)	17.7

[a] Molar concentration required to block Ca^{2+}-induced contraction of K^+-depolarized guinea pig aorta by 50%. Each value indicates the mean and 95% confidence limits (n = 3–6). [b] Molar concentration required to suppress the rate of contraction of guinea pig right atria by 50%. [c] Ratio of (IC_{50} for Ca^{2+} antagonistic activity in aorta)/(IC_{50} for suppressive effect on rate of contraction). [d] Molar concentration required to suppress contractile force of guinea pig right atria by 50%. [e] Ratio of (IC_{50} for Ca^{2+} antagonistic activity in aorta)/(IC_{50} for suppressive effect on contractile force).

Table IV. Related Compounds of Compound **15**



compd	R_5	A	R_7	X	Ca^{2+}: IC_{50},[a] μM	yield,[b] %	mp, °C	recrystn solvent	formula	anal.
17	CH_3	O	CH_3	O	2.1 ± 0.2	88	133–134	AcOEt	$C_{30}H_{34}N_2O_6S \cdot C_4H_4O_4$[c]	C,H,N
18	CH_3	O	i-C_3H_7	O	>10	59	111–112	AcOEt	$C_{32}H_{38}N_2O_6S \cdot C_4H_4O_4$[c]	C,H,N
19	CH_3	O	CH_3O	O	0.25 ± 0.06	62	amorph	–	$C_{30}H_{34}N_2O_7S \cdot C_4H_4O_4$[c]	*e*
20	CH_3	O	CH_3S	O	1.5 ± 0.4	70	amorph	–	$C_{30}H_{34}N_2O_6S_2 \cdot C_4H_4O_4$[c]	*f*
21	H	O	H	O	0.49 ± 0.09	44	176–177	EtOH–AcOEt	$C_{28}H_{30}N_2O_6S \cdot C_2H_2O_4$[d]	C,H,N
22	i-C_3H_7	O	H	O	1.9 ± 0.6	51	amorph	–	$C_{31}H_{36}N_2O_6S \cdot HCl$	*g*
23	CH_3	CH_2	H	O	>10	56	107–109	AcOEt	$C_{31}H_{36}N_2O_4S \cdot C_2H_2O_4$[d]$\cdot 0.5H_2O$	C,H,N
24	CH_3	O	H	S	>10	24	143–145	EtOH–AcOEt	$C_{29}H_{32}N_2O_5S_2 \cdot C_4H_4O_4$[c]	C,H,N
25	CH_3	O	H	H_2	>10	47	101–102[h]	EtOH	$C_{29}H_{34}N_2O_5S \cdot C_2H_2O_4$[d]	C,H,N

[a] See footnote *a* in Table II. [b] Yield for production of target compound from immediate precursor, **5a,c–f**, **15**, or **27**. [c] Hydrogen fumarate. [d] Hydrogen oxalate. [e] m/z (EI, M^+, $C_{30}H_{34}N_2O_7S$) calcd 566.2085, found 566.2083. [f] m/z (EI, M^+, $C_{30}H_{34}N_2O_6S_2$) calcd 582.1856, found 582.1869. [g] m/z (EI, M^+, $C_{31}H_{36}N_2O_6S$) calcd 564.2292, found 564.2306. [h] Decomposition.

Table V. Enantiomer of Compound **15**

compd	Ca^{2+}: IC_{50},[a] μM	configuration of 2-position	$[\alpha]^{25}_D$, deg (c = 1.0, Me_2SO)	mp, °C	recrystn solvent	anal.
(+)-**15** (sesamodil)	0.089 ± 0.018	*R*	+195	134–135	EtOH	C,H,N
(–)-**15**	0.60 ± 0.06	*S*	–195	134–135	EtOH	C,H,N

[a] See footnote a in Table II.

activities. The IC_{50} values of these compounds were in the order of 10^{-7} M, almost the same as diltiazem. Six compounds (**7**, **10**, **13–16**) of this benzothiazine series were further evaluated in vitro for their vasocardioselective activities with use of guinea pig aorta and right atria (Table III). Compounds **15** and **16** showed more potent activity than other benzothiazines in the aorta, but they showed similar activity in the taenia cecum. The methylenedioxy group in the amine moiety probably plays an important role in the potent Ca^{2+} antagonistic activity in the aorta. In terms of cardio-suppressive effects, compounds **14** and **16** displayed the same order of potency. When the vasocardioselectivity was expressed as ratios of IC_{50} values for Ca^{2+} antagonistic activity in aorta to IC_{50} values for the rate of contraction or contractile force in atria, compound **15** showed the smallest value among the benzothiazines, diltiazem, and verapamil. This result indicated that **15** had the highest selectivity for vasodilation among the compounds tested. In light of the adverse effects of the Ca^{2+} antagonists due to cardiosuppression,[4-7] the lesser cardioselectivity is expected to be safer. Accordingly, we selected **15** as the key compound.

To find more potent Ca^{2+} antagonists, compounds related to **15** were examined further. We introduced a methyl, isopropyl, methoxy, or methylthio group into the 2-position of **15**, as in compounds **17–20** and examined the activity of the derivatives. As shown in Table IV, the moieties at the 2-position affected the activity markedly. The potencies were in the following order: H > CH_3O > CH_3S > CH_3 > $CH(CH_3)_2$. When the methyl group in the *N*-methyl-*N*-(phenoxyethyl)amino moiety was replaced with a hydrogen atom, as in **21**, or with an isopropyl group as in **22**, the activity also declined. Replacement of the ring oxygen atoms in the 3,4-(methylenedioxy)phenyl moiety in **15** by methylenes, as in the [(indanyloxy)-ethyl]amino compound **23**, again diminished activity dramatically. Moreover, conversion of the carbonyl group at the 3-position, as in the thiolactam **24** and the deoxo **25** compounds, also resulted in substantially reduced activity. These structural modifications of **15** did not im-

prove its Ca^{2+} antagonistic activity.

In the in vitro study on the enantiomers of **15**, (+)-**15** was about 7 times more potent than (−)-**15** (Table V). It is well known that the pharmacological activities of the Ca^{2+} antagonists, such as verapamil,[18-20] diltiazem,[21] and 1,4-dihydropyridine derivatives,[22-24] are stereoselective. The activities of enantiomers of Ca^{2+} antagonists have been reported to be different, 2–20-fold.[18-23] The difference between the activities of (+)-**15** and (−)-**15** was in the same order as other Ca^{2+} antagonists.

The higher activity of (+)-**15** than (−)-**15** indicated that (+)-**15** was more potent than the racemic compound **15**. This was confirmed with several in vitro assay systems using aorta and atria of guinea pig (Table III).

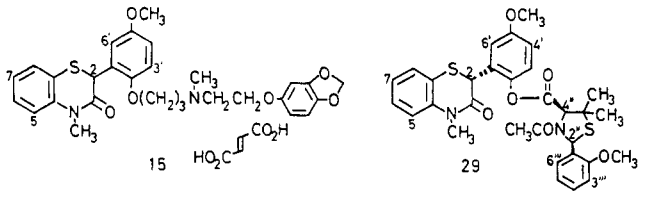
Conclusion

Compound (+)-*R*-**15** was found out from studies on benzothiazine derivative **3** as a novel Ca^{2+} antagonist. In studies with isolated smooth and cardiac muscle, the pharmacological profile of (+)-**15** showed a greater selectivity for vascular smooth muscle than such other well-known non-dihydropyridine type Ca^{2+} antagonists as diltiazem and verapamil. Because the cardio-suppressive effects of the non-dihydropyridines sometimes yield such side effects as bradycardia and atrioventricular block, the pharmacological profile of (+)-**15** is particularly interesting. Research findings suggest that (+)-**15** will yield fewer side effects in therapeutic use.

Compound ((+)-**15**: sesamodil[25]), a novel non-dihydropyridine type Ca^{2+} antagonist, is currently undergoing clinical evaluation.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries with a Yamato MP-21 melting point apparatus and were 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 by using a Hitachi M-80B spectrometer in the EI mode with samples introduced directly into the ion source for spectral determination. NMR spectra were measured by a JEOL PMX-60 spectrometer and a JEOL GSX-400 spectrometer with tetramethylsilane as the internal standard. Compounds **15** and **29** are numerically represented in NMR spectra as follows:



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

2-Chloro-3,4-dihydro-2-(2-hydroxy-5-methoxyphenyl)-4-methyl-3-oxo-2*H*-1,4-benzothiazine (6). To a stirred suspension of 3,4-dihydro-2-(2-hydroxy-5-methoxyphenyl)-4-methyl-3-oxo-2*H*-1,4-benzothiazine (**4a**) (14.0 g, 46.5 mmol) in dry dichloromethane (150 mL) was added dropwise at 0–5 °C sulfuryl chloride (6.59 g, 48.8 mmol). Stirring was continued at room temperature for 1 h. The precipitated crystals were filtered to yield 12.7 g (79%) of **6**. This preparation was used in the next step without further purification because of its instability: mp 121–128 °C dec; IR (KBr) 3248 (OH), 1650 (C=O), 1583 (C=C), 1496 (C=C), 1037 (C—O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.44 (s, 3 H, NCH_3), 3.67 (s, 3 H, OCH_3), 6.4–7.7 (m, 7 H, aromatic), 9.52 (br s, 1 H, OH).

3,4-Dihydro-2-(2-hydroxy-5-methoxyphenyl)-2-methoxy-4-methyl-3-oxo-2*H*-1,4-benzothiazine (4d). Compound **6** (14.0 g, 41.7 mmol) was dissolved in MeOH (200 mL), and the solution was stirred at room temperature for 2 h. The precipitated crystals were filtered, yielding 11.8 g (85%) of **4d**: mp 135–137 °C; IR (KBr) 3436 (OH), 1665 (C=O), 1499 (C=C), 1467 (C=C), 1032 (C—O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.07 (s, 3 H, C-2 OCH_3), 3.31 (s, 3 H, NCH_3), 3.57 (s, 3 H, OCH_3), 6.4–7.4 (m, 7 H, aromatic), 8.90 (s, 1 H, OH).

2-[2-(3-Chloropropoxy)-5-methoxyphenyl]-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzothiazine (5a). A solution of **4a** (30.1 g, 0.10 mol) in dry DMF (60 mL) was added dropwise to a suspension of sodium hydride (60% mineral oil dispersion) (4.80 g, 0.12 mol) in dry DMF (40 mL) at 0 °C. The mixture was stirred at room temperature for 30 min. A solution of 1-bromo-3-chloropropane (18.9 g, 0.12 mol) in dry DMF (30 mL) was added to the mixture with further stirring at room temperature for 2 h. The resulting mixture was poured into H_2O (700 mL) and then extracted with AcOEt. The extract was washed with H_2O and brine, dried ($MgSO_4$), and then concentrated at reduced pressure. The precipitated crystals were washed with MeOH to yield 33.3 g (88%) of **5a**: mp 97–99 °C; IR (KBr) 1653 (C=O), 1582 (C=C), 1497 (C=C), 1238, 1048 (C—O), 1023 (C—O), 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 (dt, 2 H, J = 6.0 Hz, $CH_2CH_2CH_2$), 3.50 (s, 3 H, NCH_3), 3.56 (s, 3 H, OCH_3), 3.69 (t, 2 H, J = 6.0 Hz, CH_2Cl), 4.06 (t, 2 H, J = 6.0 Hz, OCH_2), 4.98 (s, 1 H, C-2 H), 6.4–7.4 (m, 7 H, aromatic).

3,4-Dihydro-2-[5-methoxy-2-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propoxy]phenyl]-4-methyl-3-oxo-2*H*-1,4-benzothiazine Hydrogen Fumarate (15). To a mixture of **5a** (11.3 g, 30.0 mmol) and *N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amine (6.15 g, 31.5 mmol) in dry DMF (60 mL) were added $NaHCO_3$ (7.56 g, 90.0 mmol) and NaI (8.99 g, 60 mmol), and then the mixture was stirred at 70–80 °C for 3 h. After cooling, the mixture was treated with H_2O (200 mL) and extracted with AcOEt. The organic extract was washed with H_2O and brine, dried ($MgSO_4$), and then concentrated in vacuo. The residual oil was chromatographed on silica gel with $CHCl_3$–MeOH (50/1) to yield the free amine of **15** as oil. Its fumarate was prepared by the addition of a solution of a slightly excess amount of fumaric acid in EtOH to a solution of the free amine in AcOEt. The precipitated crystals were filtered and recrystallized from EtOH, yielding 13.3 g (68%) of **15**: IR (KBr) 1654 (C=O), 1498 (C=C), 1474 (C=C), 1239, 1207, 1184, 1033 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.92 (t, 2 H, J = 6.8 Hz, $CH_2CH_2CH_2$), 2.38 (s, 3 H, NCH_3), 2.73 (t, 2 H, J = 6.8 Hz, $CH_2CH_2CH_2N$), 2.86 (t, 2 H, J = 5.4 Hz, NCH_2CH_2O), 3.48 (s, 3 H, N-4 CH_3), 3.53 (s, 3 H, OCH_3), 4.00 (t, 2 H, J = 5.9 Hz, OCH_2), 4.01 (t, 2 H, J = 5.4 Hz, OCH_2), 4.97 (s, 1 H, C-2 H), 5.93 (s, 2 H, OCH_2O), 6.32 (dd, 1 H, J = 2.4, 8.3 Hz, C-6″ H), 6.32 (d, 1 H, J = 2.9 Hz, C-6′ H), 6.59 (d, 1 H, J = 2.4 Hz, C-2″ H), 6.59 (s, 2 H, $CHCO_2 \times 2$), 6.75 (d, 1 H, J = 8.8 Hz, C-5″ H), 6.78 (dd, 1 H, J = 2.9, 8.8 Hz, C-4′ H), 6.92 (d, 1 H, J = 9.3 Hz, C-3′ H), 7.02 (t, 1 H, J = 6.8 Hz, C-7 H), 7.25 (d, 1 H, J = 7.8 Hz, C-5 H), 7.33 (t, 1 H, J = 7.8 Hz, C-6 H), 7.35 (d, 1 H, J = 8.3 Hz, C-8 H), 10.93 (br s, 2 H, $CO_2H \times 2$).

(+)-(*R*)- and (−)-(*S*)-3,4-Dihydro-2-[5-methoxy-2-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propoxy]phenyl]-4-methyl-3-oxo-2*H*-1,4-benzothiazine Hydrogen Fumarate ((+)-15 (Sesamodil Fumarate) and (−)-15) (Method A). To a solution of free amine of **15** (10.73 g, 20.0 mmol) in acetone (15 mL) were added (+)-mandelic acid (1.52 g, 10.0 mmol) and cyclohexane (18 mL). After the mixture was stirred for 1 day at room temperature, the precipitate was formed. This solid was collected and dried, yielding 5.92 g of a white

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(25) This generic name was registered in Japanese Accepted Name (JAN).

powder. This (+)-mandelate salt was recrystallized from acetone, yielding 4.40 g of white crystals: mp 114–115 °C, $[\alpha]^{25}_D$ (c = 1.1, Me_2SO) +206°. The filtrate of the first precipitate was concentrated at reduced pressure. The residual oil was dissolved in CH_2Cl_2 (40 mL), treated with 0.5 N NaOH (20 mL), washed with brine, and dried ($MgSO_4$). After removal of the solvent, the residue was dissolved in acetone (14 mL). (−)-Mandelic acid (1.52 g, 10.0 mmol), and cyclohexane (14 mL) were added to the solution. The mixture was then stirred for 1 h at room temperature and left standing for 2 h in a refrigerator, yielding a precipitate. The solid was collected and dried to give 5.97 g of white powder. This (−)-mandelate salt was recrystallized from acetone, yielding 4.67 g of white crystals: mp 114–115 °C; $[\alpha]^{25}_D$ (c = 1.0, Me_2SO) −214°. A suspension of (+)-mandelate salt (4.40 g, 6.38 mmol) in CH_2Cl_2 (27 mL) was treated with saturated $NaHCO_3$, washed with brine, and dried ($MgSO_4$). After removal of solvent, the residue was dissolved in AcOEt (9 mL). A hot solution of fumaric acid (0.74 g, 6.38 mmol) in EtOH (18 mL) was added to this solution. After the mixture was stirred for 1 h at room temperature and left standing for 10 h in a refrigerator, a precipitate formed. Recrystallization of the precipitate from EtOH (18 mL) gave 3.38 g (26% from **15**) of (+)-**15** (100% ee). Enantiomeric purity was determined by a chiral column (CHIRALCEL OG). HPLC conditions were as follows: mobile phase, EtOH–hexane–Et_2NH (450/50/1); flow rate, 1.5 mL min^{-1}; column temperature, 35 °C; detection wavelength, 300 nm. Retention time of (+)-**15** in the chromatogram was 12.4 min: IR (KBr) 1654 (C=O), 1498 (C=C), 1478, 1239 (C—O), 1184, 1034 (C—O) cm^{-1}. The ^1H NMR spectrum exhibited the same resonances as that of **15**. According to the same procedure, (−)-mandelate salt (4.67 g, 6.78 mmol) was converted to 3.59 g (28% from **15**) of (−)-**15** (100% ee). Retention time of (−)-**15** in the chromatogram was 5.8 min: The IR and the ^1H NMR spectra were identical with those of the enantiomer.

3,4-Dihydro-2-[5-methoxy-2-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propoxy]phenyl]-4-methyl-3-thioxo-2*H*-1,4-benzothiazine Hydrogen Fumarate (24). To a stirred solution of free amine of **15** (1.61 g, 3.00 mmol) in dry toluene (8 mL) was added Lawesson's reagent (0.67 g, 1.65 mmol), and stirring was continued at 80 °C for 4 h. The mixture was poured into H_2O (20 mL) and extracted with AcOEt. The extract was washed with 2 N HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and then concentrated at reduced pressure. The residual oil was chromatographed on silica gel with $CHCl_3$–MeOH (100/1) to yield the free amine of **24** as oil. To a solution of the oil in AcOEt was added a slightly excess amount of fumaric acid in EtOH. Precipitated crystals were filtered to give 0.48 g (24%) of **24**: IR (KBr) 1480 (C=S), 1462 (C=C), 1370, 1238, 1222, 1033 (C—O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.6–2.4 (m, 2 H, $CH_2CH_2CH_2$), 2.42 (s, 3 H, NCH_3), 2.6–3.1 (m, 4 H, CH_2NCH_2), 3.44 (s, 3 H, N-4 CH_3), 3.8–4.3 (4 H, OCH_2 × 2), 4.04 (s, 3 H, OCH_3), 5.58 (s, 1 H, C-2 H), 5.90 (s, 2 H, OCH_2O), 6.0–7.8 (m, 10 H, aromatic), 6.58 (s, 2 H, $CHCO_2$ × 2), 10.5–10.9 (br, 2 H, CO_2H × 2).

3,4-Dihydro-2-(2-hydroxy-5-methoxyphenyl)-4-methyl-2*H*-1,4-benzothiazine (26). $Ca(BH_4)_2$ was prepared in situ by the addition of $NaBH_4$ (13.3 g, 351 mmol) to a stirred suspension of $CaCl_2$ (16.6 g, 150 mmol) in dry THF (600 mL) at 0 °C. Compound **4a** (18.0 g, 60 mmol) was added to the suspension of $Ca(BH_4)_2$ in THF gradually at room temperature, and the mixture was refluxed with stirring for 24 h. After cooling, the reaction mixture was treated with brine (200 mL), and THF was evaporated at reduced pressure. The mixture was extracted with AcOEt. The extract was washed with brine (100 mL), dried ($MgSO_4$), and then concentrated in vacuo. The residue was chromatographed on silica gel with benzene–AcOEt (20/1) to yield 9.33 g (54%) of **26**: mp 111–113 °C; IR (KBr) 3288 (OH), 1586 (C=C), 1495 (C=C), 1033 (C—O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.90 (s, 3 H, NCH_3), 3.23 (dd, 1 H, J = 5.0, 13.0 Hz, C-3 H), 3.51 (dd, 1 H, J = 5.0, 13.0 Hz, C-3 H), 3.67 (s, 3 H, OCH_3), 4.61 (t, 1 H, J = 5.0 Hz, C-2 H), 6.4–7.3 (m, 7 H, aromatic), 7.60 (br s, 1 H, OH). Anal. ($C_{16}H_{17}NO_2S$) C, H, N.

2-[2-(3-Bromopropoxy)-5-methoxyphenyl]-3,4-dihydro-4-methyl-2*H*-1,4-benzothiazine (27). A solution of **26** (4.00 g, 13.9 mmol) in dry DMF (12 mL) was added dropwise to a suspension of sodium hydride (60% mineral oil dispesion) (0.67 g, 16.8 mmol) in dry DMF (8 mL) at 0 °C. The mixture was stirring at room temperature for 30 min. A solution of 1,3-dibromopropane (8.40 g, 41.6 mmol) in dry DMF (5 mL) was then added, and the mixture was stirred at room temperature for 2.5 h. The mixture was treated with 2 N HCl (30 mL) and extracted with AcOEt. The organic layer was washed with 2 N NaOH and brine, dried ($MgSO_4$), and then concentrated at reduced pressure. The residue was chromatographed on silica gel with hexane–AcOEt (3/1) to give 2.73 g (48%) of **27** as oil: IR (film) 1586 (C=C), 1493 (C=C), 1283, 1218, 1042 (C—O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.31 (dt, 2 H, J = 6.0 Hz, $CH_2CH_2CH_2$), 2.94 (s, 3 H, NCH_3), 3.4–3.8 (m, 4 H, CH_2Br and C-3 H_2), 3.67 (s, 3 H, OCH_3), 4.06 (t, 2 H, J = 6.0 Hz, OCH_2), 4.83 (dd, 1 H, J = 5.0, 6.0 Hz, C-2 H), 6.4–7.3 (m, 7 H, aromatic). A portion was converted to the HCl salt and recrystallized from EtOH: mp 172–173 °C dec. Anal. ($C_{19}H_{22}BrNO_2S$·HCl) C, H, N.

3,4-Dihydro-2-[5-methoxy-2-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propoxy]phenyl]-4-methyl-2*H*-1,4-benzothiazine Hydrogen Oxalate (25). To a mixture of **27** (1.53 g, 3.75 mmol) and *N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amine (0.70 g, 3.59 mmol) in dry DMF (6 mL) was added K_2CO_3 (0.78 g, 5.44 mmol). The mixture was then stirred at 60–70 °C for 2 h. After cooling, the mixture was poured into 6 N HCl (20 mL) and washed with AcOEt. The aqueous layer was treated with 6 N NaOH (25 mL) and extracted with AcOEt. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residual oil was chromatographed on silica gel with $CHCl_3$–MeOH (20/1) to yield the free amine of **25** as oil. The oxalate was prepared by the addition of a slightly excess amount of oxalic acid in EtOH to a solution of the free amine in AcOEt. The precipitated crystals were filtered and recrystallized from EtOH to give 1.07 g (47%) of **25**: IR (KBr) 1714 (C=O), 1609 (C=C), 1583 (C=C), 1032 (C—O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.8–2.4 (m, 2 H, $CH_2CH_2CH_2$), 2.70 (s, 3 H, NCH_3), 2.88 (s, 3 H, NCH_3), 2.9–3.7 (m, 6 H, CH_2NCH_2 and C-3 H_2), 3.63 (s, 3 H, OCH_3), 3.8–4.4 (m, 4 H, OCH_2 × 2), 4.74 (dd, 1 H, J = 4.0, 7.0 Hz, C-2 H), 5.87 (s, 2 H, OCH_2O), 6.2–7.2 (m, 10 H, aromatic), 10.32 (br s, 2 H, CO_2H × 2).

(2*S*,4*S*)-3-Acetyl-5,5-dimethyl-2-(2-methoxyphenyl)-4-thiazolidinecarboxylic Acid (28). A solution of 2-methoxybenzaldehyde (40.8 g, 0.30 mol) in EtOH (300 mL) was added to a stirred solution of D-penicillamine (44.8 g, 0.30 mol) in H_2O (500 mL) at room temperature. Stirring was continued at the same temperature for 1 h and then at 0 °C for 3 h. The precipitated crystals were filtered, washed with H_2O–EtOH (8/2) and dried to yield 63.7 g of (4*S*)-5,5-dimethyl-2-(2-methoxyphenyl)-4-thiazolidinecarboxylic acid that was pure enough for the following reaction. To a stirred suspension of this compound (30 g, 0.11 mol) in H_2O (60 mL) was added at 80 °C acetic anhydride (63.6 mL, 0.67 mol) and the mixture was stirred at this temperature for 10 min, then at room temperature for 30 min, and finally at 0 °C for 1 h. The precipitated solid was collected by filtration, washed with H_2O, and dried. Recrystallization from MeOH–H_2O gave 31.1 g (total yield 71% of **28**: mp 215–217 °C dec; $[\alpha]^{25}_D$ (c = 1.0, MeOH) −170°; IR (KBr) 2916, 1740 (C=O), 1585 (C=O), 1490, 1437 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 1.91 (s, 3 H, $COCH_3$), 3.85 (s, 3 H, OCH_3), 4.71 (s, 1 H, 4-H), 6.29 (s, 1 H, 2-H), 6.7–7.4 (m, 3 H, aromatic), 8.11 (dd, 1 H, J = 7.0, 2.0 Hz, 6′-H), 10.68 (s, 1 H, CO_2H). Anal. ($C_{15}H_{19}NO_4S$) C, H, N.

(2*R*)- and (2*S*)-2-[2-[[[(2*S*,4*S*)-3-Acetyl-5,5-dimethyl-2-(2-methoxyphenyl)thiazolidin-4-yl]carbonyl]oxy]-5-methoxyphenyl]-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzothiazine (29, 30). To a stirred solution of **4a** (202.7 g, 673 mmol) and **28** (312.3 g, 1.01 mol) in DMF (850 mL) were added under ice cooling a solution of *N*,*N*′-dicyclohexylcarbodiimide (208.3 g, 1.01 mol) in DMF (500 mL) and 4-(dimethylamino)pyridine (13.3 g, 1.01 mol), and the mixture was stirred at this temperature for 4 h. The mixture was poured into H_2O–AcOEt (6/1, 7 L), and then oxalic acid (30.3 g, 337 mmol) was added while stirring at room temperature for 15 min. Precipitated solid was removed by filtration. The filtrate was separated into two layers, and the aqueous layer was extracted with AcOEt. The pooled organic phases were washed with H_2O and brine, dried ($MgSO_4$), and evaporated, yielding a brown oil. The residue was chromatographed on silica

gel with hexane–benzene–AcOEt (1/5/2), yielding 171.6 g (48%) of **29** and 179.6 g (45%) of **30**. Compound **29**: mp 165–166 °C (AcOEt/hexane); $[\alpha]^{25}_D$ (c = 1.0, $CHCl_3$) −108°; IR (KBr) 1756 (C=O), 1653 (C=O), 1488 (C=C), 1373 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 3 H, C-5″ CH_3), 1.63 (s, 3 H, C-5″ CH_3), 1.72 (s, 3 H, CH_3CO), 3.48 (s, 3 H, N-4 CH_3), 3.67 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.88 (s, 1 H, C-2 H), 5.05 (s, 1 H, C-4″ H), 6.29 (s, 1 H, C-2″ H), 6.7–7.5 (m, 10 H, aromatic), 8.05 (dd, 1 H, J = 7.5, 1.5 Hz, C-6‴ H). Anal. ($C_{13}H_{32}N_2O_6S_2$) C, H, N. Compound **30**: amorphous powder; $[\alpha]^{25}_D$ (c = 1.0, $CHCl_3$) −109°; IR (KBr) 1755 (C=O), 1646 (C=O), 1457 (C=C), 1376 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 3 H, C-5″ CH_3), 1.56 (s, 3 H, C-5″ CH_3), 1.76 (s, 3 H, CH_3CO), 3.42 (s, 3 H, N-4 CH_3), 3.61 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.79 (s, 1 H, C-2 H), 4.91 (s, 1 H, C-4″ H), 6.24 (s, 1 H, C-2″ H), 6.5–7.5 (m, 10 H, aromatic), 8.01 (dd, 1 H, J = 7.5, 1.5 Hz, C-6‴ H); EIMS m/z 592.1694 (calcd 592.1700).

(+)-(*R*)-3,4-Dihydro-2-(2-hydroxy-5-methoxyphenyl)-4-methyl-3-oxo-2*H*-1,4-benzothiazine ((+)-4a). $Ca(BH_4)_2$ was prepared in situ by the addition of $NaBH_4$ (58.6 g, 1.55 mol) to a stirred suspension of $CaCl_2$ (179.8 g, 1.62 mol) in dry THF (460 mL) at 0 °C. A cooled solution of **29** (183.1 g, 309 mmol) in EtOH (1.2 L) and NH_4Cl (165.8 g, 3.10 mol) was added to the suspension of $Ca(BH_4)_2$ in THF at −10 °C, and stirring was continued for 12 h at the same temperature. The mixture was treated with 1 N HCl (2.5 L), concentrated at reduced pressure, and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and then concentrated at reduced pressure. The residue was chromatographed on silica gel with hexane–AcOEt–$CHCl_3$ (1/1/8) and recrystallized from benzene to yield 69.9 g (75%) of (+)-**4a**: mp 161–162 °C; $[\alpha]^{25}_D$ (c = 1.17, $CHCl_3$) +40°; IR (KBr) 3176 (OH), 1621 (C=O), 1500 (C=C), 1424 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.45 (s, 3 H, N-4 CH_3), 3.50 (s, 3 H, OCH_3), 4.94 (s, 1 H, C-2 H), 6.5–7.7 (m, 7 H, aromatic), 7.55 (br s, 1 H, OH). Anal. ($C_{16}H_{15}NO_3S$) C, H, N.

(+)-(*R*)-3,4-Dihydro-2-[2-(3-bromopropoxy)-5-methoxyphenyl]-4-methyl-3-oxo-2*H*-1,4-benzothiazine ((+)-31). A mixture of compound (+)-**4a** (10.0 g, 33.2 mmol) and diethyl azodicarboxylate (17.4 g, 99.6 mmol) in dry dimethoxyethane–THF (10/1, 55 mL) was added dropwise to a stirred mixture of 3-bromo-1-propanol (13.8 g, 99.6 mmol) and triphenylphosphine (26.1 g, 99.6 mmol) in dry DMF (100 mL) in a N_2 atmosphere at 0–5 °C for 25 min. The mixture was treated with 0.5 N HCl (30 mL) and concentrated at reduced pressure. The mixture was then dissolved in Et_2O, washed with brine, dried ($MgSO_4$), and concentrated at reduced pressure. Precipitated crystals were removed and the filtrate was chromatographed on silica gel with hexane–benzene–AcOEt (5/15/1). Recrystallization from *i*-PrOH yielded 2.53 g (18.1%) of (+)-**31**: mp 78–79 °C; $[\alpha]^{25}_D$ (c = 1.0, $CHCl_3$) +198°; IR (KBr) 1647 (C=O), 1584 (C=C), 1492 (C=C), 1465, 1357 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (dt, 2 H, J = 6.0 Hz, $CH_2CH_2CH_2$), 3.53 (s, 3 H, N-4 CH_3), 3.57 (t, 2 H, J = 6.5 Hz, CH_2Br), 3.59 (s, 3 H, OCH_3), 4.07 (t, J = 5.8 Hz, OCH_2), 4.99 (s, 1 H, C-2 H), 6.4–7.4 (m, 7 H, aromatic). Anal. ($C_{19}H_{20}BrNO_3S$) C, H, N.

(+)-15 (Method B). To a stirred solution of (+)-**31** (2.43 g, 5.75 mmol) in acetone (60 mL) was added NaI (8.62 g, 57.5 mmol), and the mixture was refluxed for 20 h. After removal of the solvent, the residue was dissolved in AcOEt, washed with water and brine, and dried ($MgSO_4$). The solvent was evaporated, leaving a residue. To a stirred solution of this residue in dry DMF (25 mL) were added *N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amine (1.46 g, 7.48 mmol) and triethylamine (0.58 g, 5.75 mmol), and the mixture was stirred at 50 °C for 1.5 h. The mixture was poured into water and extracted with AcOEt. The extract was then washed with brine and dried ($MgSO_4$), and the solvent was evaporated off. The residual oil was chromatographed on silica gel with $CHCl_3$–MeOH (50/1) to yield the free amine of (+)-**15** as oil. The fumarate was prepared by adding a slightly excess amount of fumaric acid in EtOH to a solution of the free amine in AcOEt. Precipitated crystals were filtered and recrystallized from EtOH to give 2.11 g (56.2%) of (+)-**15** (9.0% ee).

X-ray Crystallography. X-ray crystallographic data were obtained on the (+)-**4a**, $C_{16}H_{15}NO_3S$, FW = 301.36. Crystals of (+)-**4a** were grown in benzene by allowing the solvent to evaporate slowly at room temperature. A clear, colorless crystal, 0.35 × 0.20 × 0.10 mm, was used for the structural determination. A least-squares refinement, using 25 centered reflections within 40.2 < 2θ < 56.2°, gave the orthorhombic cell a = 11.298 (2) Å, b = 28.100 (2) Å, c = 9.075 (1) Å, V = 2881.4 (7) Å^3, Z = 8 and D_{calcd} = 1.389gm cm^{-3}. A computer-controlled diffractometer (Rigaku AFC5R, with Cu Kα radiation, wavelength = 1.541 78 Å), with an incident beam graphite monochromator, was used for data collection. A total of 5111 reflections were measured in the ω – 2θ mode to $2\theta_{max}$ = 118.1°. Corrections were applied for Lorentz and polarization effects. The structure was solved by direct methods with the aid of the program TEXSTAN,[26] and refined by using the full-matrix least-squares program TEXSTAN.[26] The 500 parameters refined include the coordinates and anisotropic thermal parameters for all nonhydrogen atoms. Hydrogen atoms were refined isotropically. The final R factors for the 2239 reflections ($I > 3\sigma(I)$) observed were R = 0.038 and R_w = 0.052.

Ca^{2+} Antagonistic Activity. Isolated taenia cecum and aorta (about 1.5 cm, from male Hartley guinea pigs weighing 300–450 g) were suspended in a 20-mL organ bath with Krebs–Hensleit solution at 31 ± 1 and 37 ± 1 °C, respectively. The medium was 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 30 min before addition of $CaCl_2$ (2×10^{-3} M). The contraction evoked by $CaCl_2$ was recorded isotonically. The Ca^{2+} antagonistic activity was represented by the concentration of the test compound that elicited 50% inhibition of Ca^+-evoked contraction (IC_{50}).

Effect on Isolated Right Atria of Guinea Pigs. Isolated right atria were suspended in a 20 mL organ bath with Krebs–Henseleit solution at 34 ± 1 °C and bubbled with 5% carbon dioxide in oxygen. The contractile force was measured isometrically with a force–displacement transducer, and the rate of contraction was measured with a heart rate counter (Nihon Kohden, AT-600G). After equilibration, drugs were added cumulatively to the organ baths. The effects on the contractile force and rate of contraction were represented by the concentration required to produce 50% inhibition (IC_{50}).

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Supplementary Material Available: Tables of atomic coordinates, intramolecular distances, and intramolecular bond angles for (+)-**4a** (5 pages). Ordering information is given on any current masthead page.

(26) *TEXSTAN–TEXRAY Structure Analysis Package*, Molecular Structure Corporation, 1985.