A New Class of Calcium Antagonists. Synthesis and Biological Activity of 11-[(ω-Aminoalkanoyl)amino]-6,6a,7,8,9,10,10a,11-octahydrodibenzo[b,e]thiepin Derivatives

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A series of 11-[(ω-aminoalkanoyl)amino]-6,6a,7,8,9,10,10a,11-octahydrodibenzo[b,e]thiepin derivatives were prepared and found to be a structurally new class of calcium antagonists. The structure–activity relationship studies indicated that the optimum was (6a*R**,10a*R**,11*R**)-11-[[4-[4-(4-fluorophenyl)-1-piperazinyl]butyryl]amino]-6,6a,7,8,9,10,10a,11-octahydrodibenzo[b,e]thiepin (**31**, pA_2 8.16), which was superior to diltiazem (pA_2 7.42) in calcium antagonistic activity. Compound **31** showed antihypertensive activity in anesthetized rats, without a significant effect on the heart rate. It had also antianginal effects in vasopressin-induced ST-depression and methacholine-induced ST-elevation testings in rats. These potencies of **31** were essentially equal to those of diltiazem.

We had previously reported the synthesis of the novel tricyclic compounds, (6a*R**,10a*R**)-6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[b,e]thiepin (**1**) and -oxepin (**2**) (Chart I).[1] As an extension of that work, a propionic acid moiety has been introduced into the phenyl rings of **1** and **2** in order to find novel pharmacologically active compounds; the resulting compounds **3** and **4** were found to show a potent antiinflammatory activity.[2] In continuation of our study on the tricyclic compounds, the 11-amino derivatives **5a–d** and **6**[3], and various 11-(*N*-substituted-amino) derivatives were prepared.[4] Among them, (6a*R**,10a*R**,11*R**)-11-[[3-(4-phenyl-1-piperazinyl)-propionyl]amino]-6,6a,7,8,9,10,10a,11-octahydrodibenzo-[b,e]thiepin (**15**) showed interestingly calcium antagonistic activity against the potassium-depolarized rat aorta.

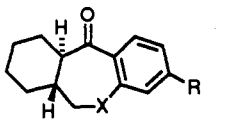
Calcium antagonists such as diltiazem (**7**), nifedipine (**8**), and verapamil (**9**) (Chart II) are drugs newly accepted for the treatment of cardiovascular disorders.[5-7] After introduction of the calcium antagonists to clinical practice, many compounds with the calcium antagonistic activity have been reported,[8,9] most of which were the analogues structurally related to the precedents **7–9**. It seemed therefore to us that compound **15** might be a new prototype for designing a useful calcium antagonists. The present study was undertaken to modify the side chain and the tricyclic system of **15**, in hopes of enhancing its activity; structure–activity relationships (SARs) are the subject for this paper.

Chemistry

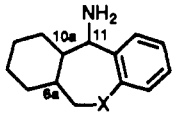
Compounds submitted to the biological evaluation were synthesized from the 11-amino derivatives **5a–d** and **6**[3], or the 2-substituted 11-amino derivatives **12a–d**. The laters were prepared by the Leuckart reaction of the corresponding ketones **10a–d**[10] as shown in Scheme I. The configuration of the resulting amines **12a–d** were determined on the basis of comparison of their proton nuclear magnetic resonance (^{1}H NMR) spectra with those of compounds **5a–d**. Detailed accounts for the configurational assignment will be presented in a separate paper.[3]

A synthetic route to 11-(ω-aminoalkanoyl)octahydrodibenzo[b,e]thiepins (**15**, **18–30**, and **32–43**) was given in Scheme II. Compound **5a** was treated with an appropriate

Chart I

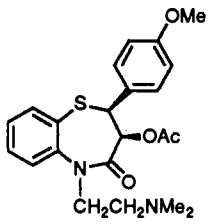


1: X = S; R = H
2: X = O; R = H
3: X = S; R = $CH(CH_3)COOH$
4: X = O; R = $CH(CH_3)COOH$

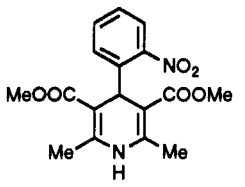


5a (6a*R**, 10a*R**, 11*R**): X = S
5b (6a*R**, 10a*R**, 11*S**): X = S
5c (6a*R**, 10a*S**, 11*R**): X = S
5d (6a*R**, 10a*S**, 11*S**): X = S
6 (6a*R**, 10a*R**, 11*R**): X = O

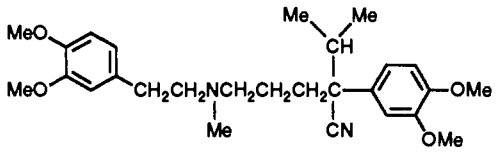
Chart II



7, diltiazem

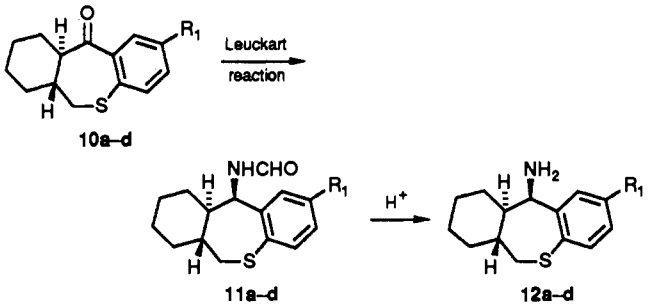


8, nifedipine



9, verapamil

Scheme I



10a–d

11a–d **12a–d**

a, R_1 = Cl; **b**, R_1 = F; **c**, R_1 = Me; **d**, R_1 = OMe

(1) Kurokawa, M.; Yoshida, K.; Uno, H. *Chem. Pharm. Bull.* **1983**, *31*, 4312.
(2) Kurokawa, M.; Uno, H.; Nakamura, H.; Sato, F.; Naruto, S. *J. Med. Chem.* **1990**, *33*, 504.
(3) Kurokawa, M.; Itokawa, A.; Sato, F.; Naruto, S.; Uno, H.; Matsumoto, J., in preparation. This work was presented in part at the 109th Annual Meeting of Pharmaceutical Society of Japan, 1989, Abstract III, p-74.
(4) Kurokawa, M.; Sato, F.; Uno, H. Unpublished results.
(5) Olivari, M. T.; Bartorelli, C.; Polese, A.; Fiorentini, M. P.; Guazzi, M. D. *Circulation* **1979**, *59*, 1056.
(6) Dollery, C. T. *Fed. Pro.* **1983**, *42*, 207.
(7) Resnick, L. M.; Laragh, J. H. *Am. J. Cardiol.* **1985**, *56*, 68H.
(8) Janis, R. A.; Triggle, D. J. *J. Med. Chem.* **1983**, *26*, 775.
(9) Godfraind, T.; Miller, R.; Wibo, M. *Pharmacol. Rev.* **1986**, *38*, 321.
(10) Uno, H.; Nagai, Y.; Kurokawa, M. *Japan Patent Kokai* 55-479, 1983; *Chem. Abstr.* **1989**, *99*, 53624g.

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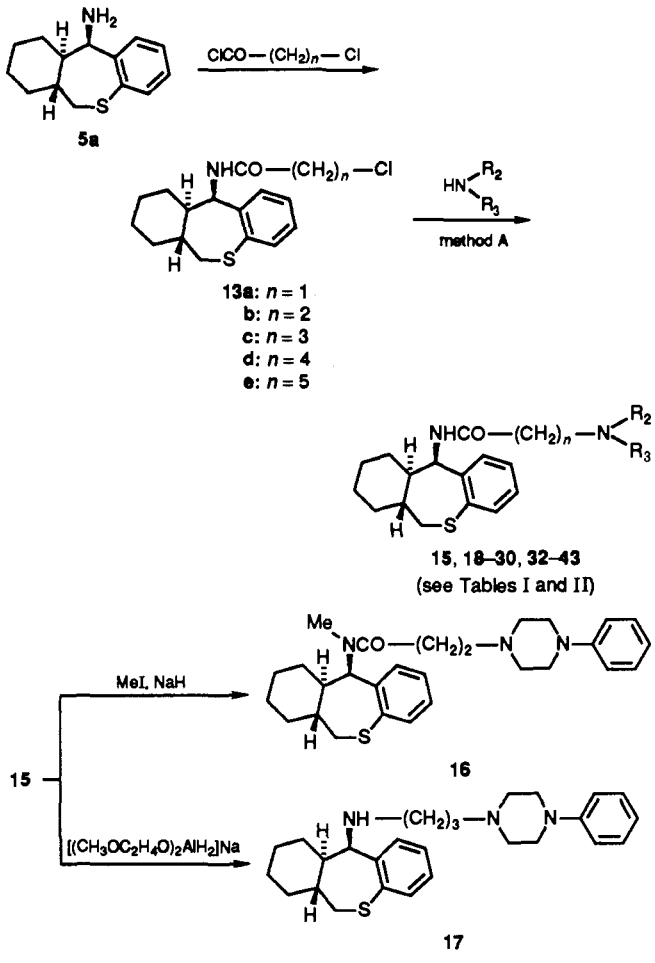
Scheme II



ω-chloroalkanoyl chloride to give 11-[(ω-chloroalkanoyl)-amino]octahydrodibenzo[*b*,*e*]thiepins (**13a–e**), which were then converted into the corresponding derivatives **15**, **18–30**, and **32–43** on replacement on the terminal chlorine atom by an appropriate amine (Tables I and II). Methylation of the amido nitrogen of **15** with methyl iodide in the presence of sodium hydride gave the *N*-methylamido derivatives **16**. Reduction of the amido group of **15** with sodium bis(2-methoxyethoxy)aluminum hydride afforded the secondary derivatives **17**.

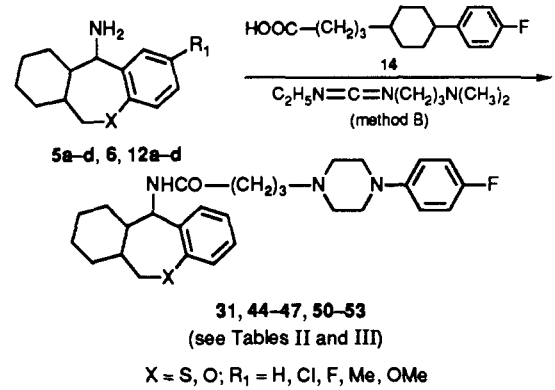
Condensation of **5a–d**, **6**, and **12a–d** with 4-[4-(4-fluorophenyl)-1-piperazinyl]butyric acid (**14**) using a condensing reagent, 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride,[11] gave the 11-[[4-[4-(4-fluorophenyl)-1-piperazinyl]butyryl]amino] derivatives (**31**, **44–47**, and **50–53**) (Scheme III). Oxidation of the sulfur atom of **31** with sodium metaperiodate, followed by chromatography on silica gel, gave two isomeric sulfoxides **48** and **49** in an approximately 2:1 ratio (Scheme IV).

The structures of all compounds thus prepared were confirmed by elemental analysis and infrared and ^{1}H NMR spectra.

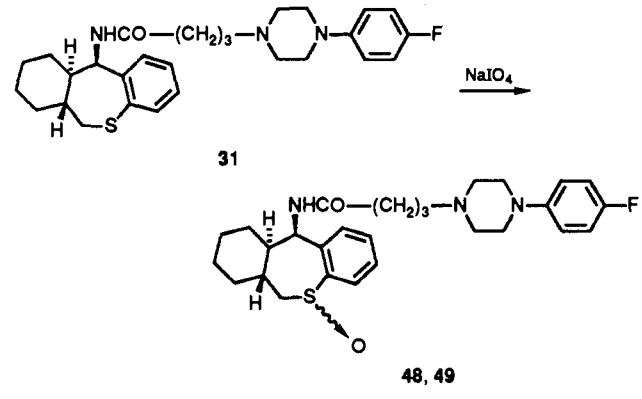
Results and Discussion

In vitro calcium antagonistic activity of compounds prepared in the present study was assessed against calcium-induced constriction of potassium-depolarized rat aorta.[12,13] The results are summarized in Tables I–III and

Scheme III



Scheme IV



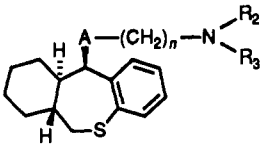
the data for diltiazem was included for comparison of Table I.

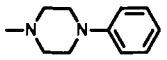
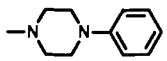
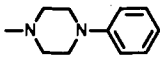
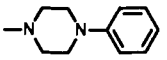
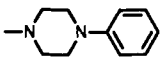
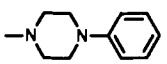
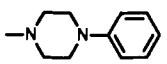
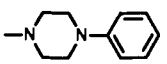
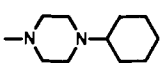
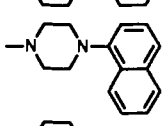
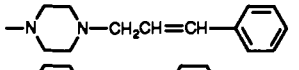
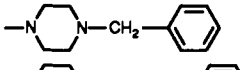
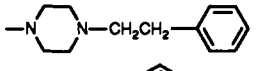
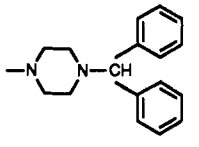
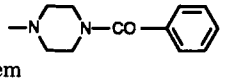
Methylation and reduction of the amido moiety of **15** (yielding **16** and **17**, respectively) caused a decrease in activity (Table I). This finding implies that the receptor might require an acidic hydrogen and a carbonyl group. A decrease in the length of the methylene chain (**15**, n = 2 → **18**, n = 1) resulted in a reduced activity, whereas an increase in the length (**19**, n = 3; **20**, n = 4; **21**, n = 5) led to an increase in activity. Although the differences in the pA_2 value between **19–21** were small, the optimal length of the methylene chain was n = 3. The piperidine derivative **22** was less effective than the piperazine derivative **19**; thus the presence of the piperazinyl nitrogen bound to the phenyl group seemed requisite for biological activity. Saturation of the phenylpiperazine moiety of **19** to a cyclohexylpiperazine group (**23**) significantly reduced activity. Hence, aromaticity of the terminal portion of the side chain might be required. Replacement of the phenyl ring of **19** by a benzyl group, yielding compound **26**, retained the same level of activity. However, an increase in the length of the methylene bridge between the terminal phenyl group and the piperazinyl moiety of **26**, as in the phenethyl group of **27**, resulted in a decrease in activity. When each benzhydryl and benzoyl group was introduced into the piperazinyl nitrogen, the resultant compounds **28** and **29** became less active than the benzyl derivative **26**.

SARs of the substituent (R_4) on the phenyl rings of the phenylpiperazinyl (**30–37**) and benzylpiperazinyl (**38–43**) groups and the substituent (R_1) on the octahydrodibenzo[*b*,*e*]thiepin nucleus (**44–47**) were as follows (Table II). Introduction of the electron-withdrawing group such as chloro (**30**), fluoro (**31** and **32**), and trifluoromethyl (**33**) groups into the phenyl ring of the phenylpiperazinyl group

(11) Sheehan, J.; Cruickshank, P.; Boshart, G. *J. Org. Chem.* **1961**, *26*, 2525.
(12) Godfrand, T.; Kaba, A. *Br. J. Pharmacol.* **1969**, *36*, 549.
(13) Godfrand, T.; Kaba, A. *Arch. Inter. Pharma.* **1972**, *196*, 35.

Table I. Physiochemical and Biological Data for Compounds 15–29



compd[a]	NR_2R_3	n	A	yield,[b] %	mp, °C	recryst solvent	formula[c]	calcium antagonistic activity (n = 4) pA_2[d]
15		2	NHCO	46	233–234	EtOH	$C_{27}H_{35}N_3OS \cdot C_2H_2O_4^e \cdot 0.25H_2O$	7.38 ± 0.06
16		2	N(Me)CO	56	116–119	Et_2O–hexane	$C_{28}H_{37}N_3OS$	6.83 ± 0.05
17		2	$NHCH_2$	33	98–102	AcOEt–hexane	$C_{27}H_{37}N_3S$	6.80 ± 0.07
18		1	NHCO	92	149–151	EtOH	$C_{26}H_{33}N_3OS$	6.98 ± 0.08
19		3	NHCO	47	120–121	EtOH	$C_{28}H_{37}N_3OS \cdot C_2H_2O_4^e \cdot 0.25H_2O$	7.68 ± 0.05
20		4	NHCO	65	104–108	EtOH	$C_{29}H_{39}N_3OS \cdot 0.5H_2O$	7.55 ± 0.07
21		5	NHCO	69	138–141	EtOH	$C_{30}H_{41}N_3OS \cdot C_2H_2O_4^e \cdot 0.2H_2O$	7.52 ± 0.05
22		3	NHCO	44	oil		$C_{28}H_{38}N_{30}S$	7.26 ± 0.16
23		3	NHCO	40	201–202	EtOH–ether	$C_{28}H_{43}N_3OS \cdot 2HCl \cdot 0.75H_2O$	7.34 ± 0.05
24		3	NHCO	24	112–116	EtOH–ether	$C_{32}H_{39}N_3OS \cdot C_2H_2O_4^e \cdot 1.5H_2O$	7.24 ± 0.19
25		3	NHCO	50	205–206	EtOH	$C_{31}H_{41}N_3OS \cdot 2C_2H_2O_4^e \cdot 0.75H_2O$	7.12 ± 0.09
26		3	NHCO	54	192–194	EtOH–ether	$C_{29}H_{39}N_3OS \cdot 2HCl \cdot 0.5H_2O$	7.80 ± 0.08
27		3	NHCO	41	203–204	EtOH–ether	$C_{30}H_{41}N_3OS \cdot 2C_2H_2O_4^e \cdot 1.25H_2O$	7.14 ± 0.01
28		3	NHCO	37	oil		$C_{35}H_{43}N_3OS$	7.39 ± 0.07
29		3	NHCO	45	240–241	EtOH	$C_{29}H_{37}N_3OS \cdot C_2H_2O_4^e \cdot 0.25H_2O$	7.01 ± 0.10
diltiazem								7.42 ± 0.05

[a] All compounds are racemic. [b] Yields were not optimized and refer to the last step in each synthetic sequence. [c] All compounds were analyzed for C, H, N, and, where present, S, Cl, and F; analytical results are within ±0.4% of the theoretical values. [d] Negative logarithm of the molar concentration of the test compounds which causes a shift of factor 2 toward higher concentration in the calcium concentration–response curve. See text and the Experimental Section for details. [e] Oxalate.

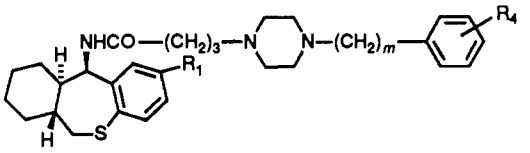
in **19** enhanced activity. It is worth noting that **31** is approximately 5 times more potent than diltiazem. Introduction of the electron-donating group such as methyl (**34**), methoxy (**35** and **36**), and hydroxy (**37**) were, however, less active than the unsubstituted compound **19**. The presence of substituents, as in **38**–**43**, on the phenyl ring of the benzylpiperazine reduced activity. Introduction of the substituent (R_1) on the tricyclic system (**44**–**47**) also caused a considerable decrease in activity compared with **31** (R_1 = H).

Oxidation of the sulfur atom in **31**, providing two isomeric sulfoxides **48** and **49**, considerably decreased activity (Table III). Furthermore, replacement of the sulfur atom by a bioisosteric oxygen atom, giving **50**, resulted in a decrease in activity. Hence, the divalent sulfur atom in the central seven-membered ring of the tricyclic system is prerequisite for calcium antagonistic activity.

The relative configuration of three chiral centers (C6a, C10a, and C11) in the tricyclic system of **31** influenced the activity. Thus compound **53** (6a*R**,10a*S**,11*R**), one of the configurational isomers of **31** (6a*R**,10a*R**,11*R**), was equipotent to **31**, whereas other isomers **51** (6a*R**,10a*R**,11*S**) and **52** (6a*R**,10a*S**,11*S**) were significantly less active than both **31** and **53**. This result indicates that the configuration and hence the spatial structure of the tricyclic system are important to exhibiting the activity.

Among compounds prepared in the present study, **31** was selected for the following pharmacological evaluation. Antihypertensive effect of **31** on anesthetized rats was compared with that of diltiazem as given in Figure 1. Compound **31** decreased the systolic blood pressure (SBP),

Table II. Physiochemical and Biological Data for Compounds 30–47



compd[a]	R_1	R_4	m	yield,[b] %	mp, °C	recryst solvent	formula[c]	calcium antagonistic activity (n = 4) pA_2[d]
30	H	4-Cl	0	27	oil		$C_{28}H_{36}N_3OSCl$	7.82 ± 0.20
31	H	4-F	0	47	95–100	ether	$C_{28}H_{36}N_3OSF \cdot C_4H_6O_6$[e] $\cdot 2H_2O$	8.16 ± 0.13
32	H	3-F	0	44	173–175	EtOH–ether	$C_{28}H_{36}N_3OSF \cdot 1.5C_2H_2O_4$[f] $\cdot H_2O$	7.82 ± 0.12
33	H	4-CF_3	0	51	105–107	EtOH–hexane	$C_{29}H_{36}N_3OSF_3$	8.05 ± 0.05
34	H	4-Me	0	35	123–124	EtOH–ether	$C_{29}H_{39}N_3OS \cdot 2C_2H_2O_4$[f] $\cdot 0.5H_2O$	7.15 ± 0.11
35	H	4-OMe	0	52	122–125	EtOH–ether	$C_{29}H_{39}N_3O_2S \cdot 2C_2H_2O_4$[f] $\cdot 1.5H_2O$	7.60 ± 0.04
36	H	2-OMe	0	46	oil		$C_{29}H_{39}N_3O_2S$	7.33 ± 0.17
37	H	4-OH	0	12	95–101	EtOH–hexane	$C_{28}H_{37}N_3O_2S$	7.16 ± 0.04
38	H	4-Cl	1	46	208–210	EtOH–ether	$C_{29}H_{38}N_3OSCl \cdot HCl \cdot 0.25H_2O$	7.57 ± 0.07
39	H	4-F	1	44	176–180	EtOH	$C_{29}H_{38}N_3OSF \cdot 2HCl \cdot 0.75H_2O$	7.24 ± 0.16
40	H	3-F	1	36	165–167	EtOH	$C_{29}H_{38}N_3OSF \cdot 2HCl \cdot 0.5H_2O$	7.52 ± 0.03
41	H	4-NO_2	1	49	167–170	EtOH–ether	$C_{29}H_{38}N_4O_3S \cdot 2HCl \cdot 0.5H_2O$	7.72 ± 0.13
42	H	4-OMe	1	49	220–221	EtOH–ether	$C_{30}H_{41}N_3O_2S \cdot C_2H_2O_4$[f] $\cdot 0.5H_2O$	7.25 ± 0.08
43	H	4-OH	1	31	oil		$C_{29}H_{39}N_3O_2S$	7.15 ± 0.02
44	Cl	4-F	0	68	208–209	EtOH	$C_{28}H_{36}N_3OSClF \cdot C_2H_2O_4$[f]	7.09 ± 0.13
45	F	4-F	0	71	191–194	EtOH	$C_{28}H_{36}N_3OSF_2 \cdot C_2H_2O_4$[f]	7.11 ± 0.10
46	Me	4-F	0	77	186–189	EtOH	$C_{29}H_{38}N_3OSF \cdot 2C_2H_2O_4$[f]	6.85 ± 0.41
47	OMe	4-F	0	50	110–113	EtOH–ether	$C_{29}H_{38}N_3O_2SF \cdot 2C_2H_2O_4$[f] $\cdot 0.5H_2O$	7.77 ± 0.11

[a–d] See footnotes in Table I. [e] Tartarate. [f] Oxalate.

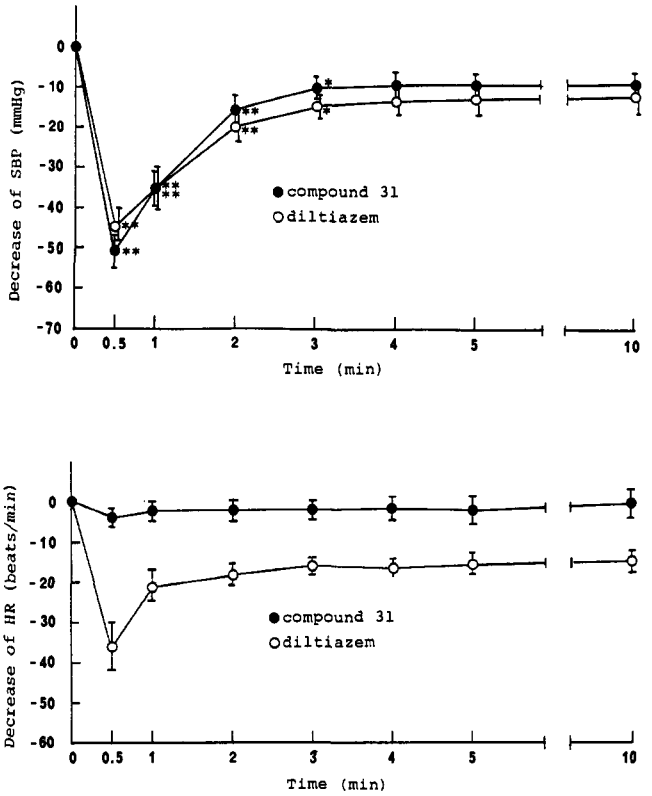


Figure 1. Effects of intravenously administered compound **31** (1.00 mg/kg, n = 6) and diltiazem (1.00 mg/kg, n = 6) on systolic blood pressure (SBP, upper) and heart rate (HR, lower) in anesthetized rats. Each point indicates the mean value and vertical lines represent the standard error of the mean. The asterisks denote that the effect of tested compounds are statistically significant; *, $P < 0.05$; **, $P < 0.01$.

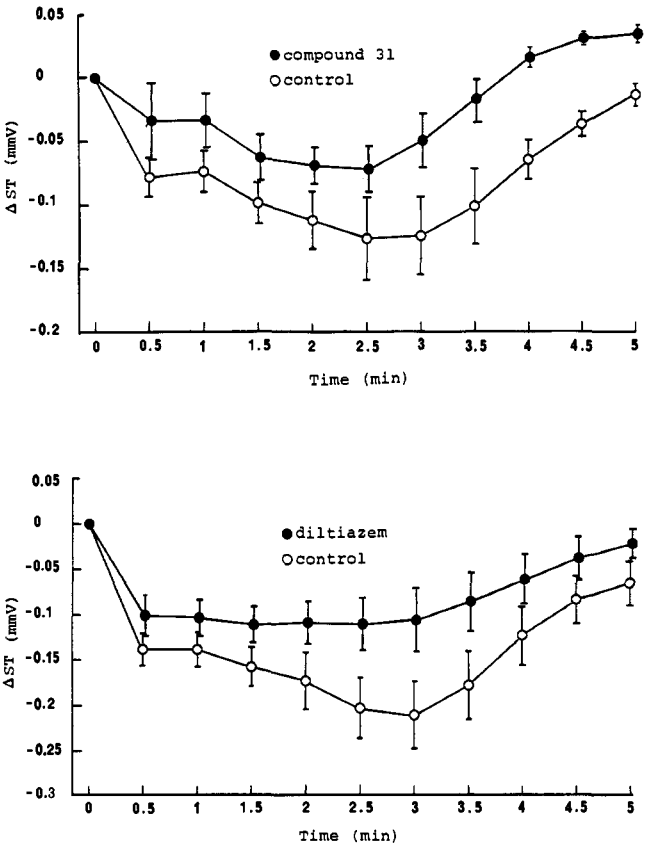


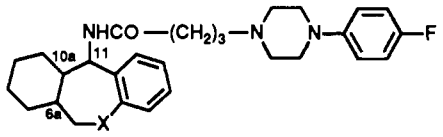
Figure 2. Preventive effects of orally administered compound **31** (upper; 30 mg/kg, n = 5) and diltiazem (lower; 30 mg/kg, n = 5) on vasopressin-induced ST depression in Donryu strain rats. Test compounds were administered 60 min before intravenous administration of vasopressin. Each point indicates the mean value and vertical lines represent the standard error of the mean.

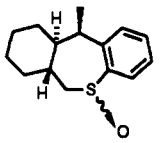
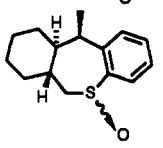
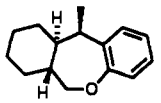
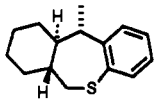
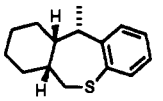
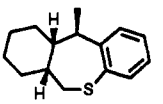
whose potency was essentially the same as that of diltiazem. Interestingly, compound **31** hardly affected the heart rate, unlike diltiazem. Preventive effects on the methacholine-induced ST elevation and the vasopressin-induced ST depression are known to be useful indexes for evaluating an antianginal effect of calcium antagonists.[14–16]

Compound **31** showed the preventive effects on these experimental models (Table IV and Figure 2), and its po-

(14) Hiramatsu, Y.; Izumi, A.; Tezuka, T.; Kurosawa, Y. Japan. *J. Pharmacol.* **1970**, *20*, 313.

Table III. Physiochemical and Biological Data for Compounds 48–53



compd[a]		yield,[b] %	mp, °C	recryst solvent	formula[c]	calcium antagonistic activity (n = 4) pA_2[d]
48[e]		46	oil		$C_{28}H_{36}N_3O_2SF$	6.48 ± 0.06
49[e,f]		22	oil		$C_{28}H_{36}N_3O_2SF$	6.49 ± 0.12
50		77	130–134	ethanol	$C_{28}H_{36}N_3O_2F \cdot C_2H_2O_4$[g]$\cdot 1.5H_2O$	6.86 ± 0.13
51		60	159–161	ethanol	$C_{28}H_{36}N_3OSF \cdot 1.5C_2H_2O_4$[g]$\cdot 0.25H_2O$	7.57 ± 0.08
52		71	199–200	ethanol–hexane	$C_{28}H_{36}N_3OSF \cdot 0.25H_2O$	7.73 ± 0.08
53		65	172–174	ethanol–hexane	$C_{28}H_{36}N_3OSF$	8.15 ± 0.05

[a–d] See footnotes in Table I. [e] Relative stereochemistry of the sulfoxide moiety was not determined. [f] The isomer of 48. [g] Oxalate.

Table IV. Preventive Effects of Compound 31 and Diltiazem on Methacholine-Induced ST Elevation in Anesthetized Rats

compd (1.0 mg/kg, iv)	ST elevation (Δ mV ± SE[a]) control	without test compound	with test compound maximum (0–10 min)
31	−0.140 ± 0.022	+0.212 ± 0.028	+0.069 ± 0.022**[b]
diltiazem	−0.196 ± 0.044	+0.223 ± 0.027	+0.091 ± 0.023**[b]

[a] The results were presented as the mean ± SE from five experiments. [b] ** = significantly different from respective control ($P < 0.01$).

tencies were essentially equal to those of diltiazem.

In conclusion, the series of 11-[(ω-aminoalkanoyl)-amino]-6,6a,7,8,9,10,10a,11-octahydrodibenzo[b,e]thiepin derivatives showed calcium antagonistic activity, despite a remarkable difference in chemical structure from the existing calcium antagonists such as diltiazem (**7**), nifedipine (**8**), and verapamil (**9**). The SAR studies of the side chain of the tricyclic system revealed that the [4-[4-(4-fluorophenyl)-1-piperazinyl]butyryl]amino group was optimal. In the configuration-activity relationships study associated with three chiral centers of the tricyclic system, the spatial structure was found to be crucial to the activity. The most potent was compound **31**, which showed the antihypertensive and antianginal effects with an equipotency to those of diltiazem in the animal models.

(15) Hatano, N.; Nakatsuji, K.; Nose, I.; Shimizu, M. *Pharmacometrics* **1980**, *19*, 311.
(16) Sakai, K.; Akima, M.; Aono, J. *J. Pharmacol. Methods* **1981**, *5*, 325.

Experimental Section

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a Varian XL-300 spectrometer with tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Hitachi 260-10 grating infrared spectrophotometer, and mass (MS) spectra were taken on a JEOL D-300 mass spectrometer. Column chromatography was carried out on Merck Silica gel 60.

The following known compounds were prepared according to the cited literature: (6a*R**,10a*R**,11*R**)-6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[*b*,*e*]thiepin (**1**) and -oxepin (**2**);[1] (6a*R**,10a*R**,11*R**)-, (6a*R**,10a*R**,11*S**)-, (6a*R**,10a*S**,11*R**)-, and (6a*R**,10a*S**,11*S**)-11-amino-6,6a,7,8,9,10,10a,11-octahydrodibenzo[*b*,*e*]thiepins (**5a–d**, respectively);[3] (6a*R**,10a*R**,11*R**)-11-amino-6,6a,7,8,9,10,10a,11-octahydrodibenz[*b*,*e*]oxepin (**6**);[3] (6a*R**,10a*R**,11*R**)-2-chloro-, (6a*R**,10a*R**,11*R**)-2-fluoro-, (6a*R**,10a*R**,11,*R**)-2-methyl-, and (6a*R**,10a*R**,11*R**)-2-methoxy-6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenzo[*b*,*e*]thiepins (**10a–d**, respectively).[10]

(6a*R,10a*R**,11*R**)-2-Chloro-11-(formylamino)-6,6a,7,8,9,10,10a,11-octahydrodibenzo[*b*,*e*]thiepin (11a).** A mixture of **10a** (5.0 g, 19 mmol) and ammonium formate (33 g, 524 mmol) was heated at 220 °C for 5 h and then poured into water. The solution was extracted with ethyl acetate. The extract was successively washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was evaporated to give an oil, which was crystallized from ethyl acetate. Recrystallization of the crude product from ethyl acetate gave **11a** (2.2 g, 40%) as colorless crystals: mp 169–172 °C; IR (KBr) 3300, 1640 (C=O), 1595 cm^{-1}. Anal. ($C_{15}H_{18}NOSCl$) C, H, N, S, Cl.

The following compounds were prepared in a similar manner.

(6a*R,10a*R**,11*R**)-2-Fluoro-11-(formylamino)-6,6a,7,8,9,10,10a,11-octahydrodibenzo[*b*,*e*]thiepin (11b):** 27%

yield; mp 139–142 °C (from ethyl acetate). Anal. ($C_{15}H_{18}NOSF$) C, H, N, S, F.

(6a*R**,10a*R**,11*R**)-11-(**Formylamino**)-**2-methyl**-6,6a,7,8,9,10,10a,11-**octahydrodibenzo[*b*,*e*]thiepin** (**11c**): 34% yield; mp 110–113 °C (from toluene–hexane). Anal. ($C_{16}H_{21}NOS$) C, H, N, S.

(6a*R**,10a*R**,11*R**)-11-(**Formylamino**)-**11-Methoxy**-6,6a,7,8,9,10,10a,11-**octahydrodibenzo[*b*,*e*]thiepin** (**11d**): 40% yield; mp 98–101 °C (from toluene). Anal. ($C_{16}H_{21}NO_2S$) C, H, N, S.

(6a*R**,10a*R**,11*R**)-11-**Amino-2-chloro**-6,6a,7,8,9,10,10a,-11-**octahydrodibenzo[*b*,*e*]thiepin** (**12a**). A solution of **11a** (2.2 g, 7.4 mmol) in ethanol (50 mL) was added to 36% hydrochloric acid (10 mL). The resulting solution was refluxed for 0.5 h, then poured into 5% sodium hydroxide (50 mL), and extracted with toluene. The extract was successively washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was evaporated to give **12a** (1.4 g, 70%) as an oil: ^{1}H NMR (nitrobenzene-d_5, at 130 °C) δ 0.96–1.74 (7 H, m), 1.38 (1 H, dddd, J = 2.8, 2.8, 10.0, and 11.4 Hz), 1.75 (1 H, s), 1.51 (1 H, m), 2.44 (1 H, dd, J = 9.9 and 12.8 Hz), 2.60 (1 H, dd, J = 2.4 and 12.8 Hz), 4.12 (1 H, d, J = 2.8 Hz), 6.97 (1 H, dd, J = 1.7 and 7.5 Hz), 7.25 (1 H, d, J = 1.7), and 7.35 (1 H, d, J = 7.5 Hz). A solution of **12a** in ethanol was treated with ethanolic hydrochloric acid, and the resulting precipitate was filtered off and recrystallized from ethanol to give hydrochloride of **12a** as colorless crystals, mp 225–235 °C. Anal. ($C_{14}H_{18}NSCl$·HCl) C, H, N, S, Cl.

The following compounds were prepared in a similar manner.

(6a*R**,10a*R**,11*R**)-11-**Amino-2-fluoro**-6,6a,7,8,9,10,10a,-11-**octahydrodibenzo[*b*,*e*]thiepin** (**12b**): 18% yield; oil. Hydrochloride of **12b**: mp 250–270 °C (from EtOH). Anal. ($C_{14}H_{18}NSF$·HCl) C, H, N, S, Cl, F.

(6a*R**,10a*R**,11*R**)-11-**Amino-2-methyl**-6,6a,7,8,9,10,10a,-11-**octahydrodibenzo[*b*,*e*]thiepin** (**12c**): 34% yield; oil. Hydrochloride of **12c**: mp 235–240 °C (from EtOH). Anal. ($C_{15}H_{21}NS$·HCl) C, H, N, S, Cl.

(6a*R**,10a*R**,11*R**)-11-**Amino-2-methoxy**-6,6a,7,8,9,10,-10a,11-**octahydrodibenzo[*b*,*e*]thiepin** (**12d**): 27% yield; oil. Hydrochloride of **12d**: mp 260–270 °C (from EtOH–ether). Anal. ($C_{15}H_{21}NOS$·HCl) C, H, N, S, Cl.

(6a*R**,10a*R**,11*R**)-11-[(**Chloroacetyl**)**amino**]-6,6a,7,8,9,10,10a,11-**octahydrodibenzo[*b*,*e*]thiepin** (**13a**). A mixture of **5a** (3.5 g, 15 mmol) and chloroacetyl chloride (1.9 g, 17 mmol) in toluene (100 mL) was refluxed for 6 h, and cooled to room temperature. The mixture was concentrated to dryness under reduced pressure to give an oil, which was chromatographed on silica gel with toluene as an eluent to give **13a** (3.8 g, 81%) as an oil. Anal. ($C_{16}H_{20}NOSCl$) C, H, N, S, Cl.

The following compounds were prepared in a similar manner.

(6a*R**,10a*R**,11*R**)-11-[(**2-Chloropropionyl**)**amino**]-6,6a,7,8,9,10,10a,11-**octahydrodibenzo[*b*,*e*]thiepin** (**13b**): 77% yield; oil. Anal. ($C_{17}H_{22}NOSCl$) C, H, N, S, Cl.

(6a*R**,10a*R**,11*R**)-11-[(**3-Chlorobutyryl**)**amino**]-6,6a,7,8,9,10,10a,11-**octahydrodibenzo[*b*,*e*]thiepin** (**13c**): 79% yield; oil. Anal. ($C_{18}H_{24}NOSCl$) C, H, N, S, Cl.

(6a*R**,10a*R**,11*R**)-11-[(**4-Chloropentenoyl**)**amino**]-6,6a,7,8,9,10,10a,11-**octahydrodibenzo[*b*,*e*]thiepin** (**13d**): 83% yield; oil. Anal. ($C_{19}H_{26}NOSCl$) C, H, N, S, Cl.

(6a*R**,10a*R**,11*R**)-11-[(**5-Chlorohexanoyl**)**amino**]-6,6a,7,8,9,10,10a,11-**octahydrodibenzo[*b*,*e*]thiepin** (**13e**): 80% yield; oil. Anal. ($C_{20}H_{28}NOSCl$) C, H, N, S, Cl.

4-[4-(4-Fluorophenyl)-1-piperazinyl]butyric Acid (**14**). A mixture of ethyl 4-bromobutyrate (50 g, 256 mmol), 1-(4-fluorophenyl)piperazine (46 g, 255 mmol) and sodium carbonate (28 g, 264 mmol) in dimethylformamide (300 mL) was stirred at 80 °C for 10 h. The mixture was cooled to room temperature and filtered to remove the undissolved material. The filtrate was concentrated to dryness. The residue was dissolved in chloroform, and the solution was washed successively with water and brine and dried over anhydrous magnesium sulfate. The solvent was evaporated to give an oily ethyl 4-[4-(4-fluorophenyl)-1-piperazinyl]butyrate (68 g, 91%): MS m/z 294 (M^+); IR (film) 1720 (C=O) cm^{-1}. A mixture of the above oily product (60 g, 204 mmol) and 2 N sodium hydroxide (105 mL, 210 mmol) in ethanol (500 mL) was stirred at room temperature for 1 h. After the solution was concentrated to dryness under reduced pressure, water (300 mL) was added to the residue. The resulting aqueous solution was adjusted to pH 7 with 1 N hydrochloric acid and concentrated to dryness. The residual solid was dissolved in ethyl acetate, and the solution was filtered. The filtrate was concentrated to dryness, and the residual crystals were recrystallized from ethyl acetate to give **14** (46 g, 85%) as colorless crystals, mp 109–110 °C. Anal. ($C_{14}H_{19}N_2O_2F$) C, H, N, F.

11-[(ω-Aminoalkanoyl)amino]-6,6a,7,8,9,10,10a,11-octahydrodibenzo[*b*,*e*]thiepins (**15, 18–47, and 51–53**) **and -oxepin** (**50**). **General Procedures. Method A.** A mixture of **13b** (3.0 g, 9.3 mmol), 1-phenylpiperazine (3.1 g, 19 mmol), and sodium iodide (1.4 g, 9.3 mmol) in dimethylformamide (100 mL) was stirred at 100 °C for 1 h and then diluted with toluene. The resulting solution was successively washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was evaporated to give an oil, which was chromatographed on silica gel with chloroform as an eluent. The resulting oil was dissolved in ether, and the solution was treated with oxalic acid to give **15** (2.3 g, 46%) as colorless crystals: mp 233–234 °C; MS m/z 449 (M^+). Anal. ($C_{27}H_{35}N_3OS$·$C_2H_2O_4$·0.25H_2O) C, H, N, S.

Compound **18–30** and **32–43** were prepared according to method A (Tables I and II).

Method B. A mixture of **5a** (1.9 g, 8.2 mmol), **14** (2.2 g, 8.3 mmol) and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (1.6 g, 8.3 mmol) in dichloromethane (50 mL) was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with chloroform. The extract was successively washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was evaporated to give an oil, which was chromatographed on silica gel with chloroform as an eluent to give a free base of **31**. This was dissolved in ethanol and treated with tartaric acid to give **31** (2.4 g, 47%) as colorless crystals: mp 95–100 °C; MS m/z 481 (M^+). Anal. ($C_{28}H_{36}N_3OSF$·$C_4H_4O_4$·2H_2O) C, H, N, S, Cl, F.

Compounds **44–47** and **50–53** were prepared according to method B (Tables II and III).

(6a*R**,10a*R**,11*R**)-***N***-**Methyl**-11-[[3-(4-**phenyl**-1-**piperazinyl**)**propionyl**]**amino**]-6,6a,7,8,9,10,10a,11-**octahydrodibenzo[*b*,*e*]thiepin** (**16**). Compound **15** (2.6 g, 5.8 mmol) was dissolved in dry dimethylformamide (50 mL) at 40 °C. To the solution was added portionwise sodium hydride (0.14 g, 5.8 mmol). The mixture was stirred at the same temperature for 30 min and then cooled in an ice bath. Methyl iodide (0.9 g, 6.3 mmol) was added dropwise over a period of 5 min. The mixture was then poured into water and extracted with chloroform. The extract was succesively washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was evaporated to give an oil, which was chromatographed on silica gel with 30% toluene in chloroform as an eluent to give solid. Recrystallization of the solid from ether–hexane gave **16** (1.5 g, 56%) as colorless crystals: mp 116–119 °C; MS m/z 463 (M^+). Anal. ($C_{28}H_{37}N_3OS$) C, H, N, S.

(6a*R**,10a*R**,11*R**)-11-[[3-(4-**Phenyl**-1-**piperazinyl**)-**propyl**]**amino**]-6,6a,7,8,9,10,10a,11-**octahydrodibenzo[*b*,*e*]thiepin** (**17**). A solution of **15** (2.5 g, 5.6 mmol) in toluene (50 mL) was treated with sodium bis(2-methoxyethoxy)aluminum hydride (5.0 g, 70% solution in toluene). The mixture was stirred at 80 °C for 2 h and allowed to cool to room temperature. The resulting solution was poured into water and extracted with toluene. The extract was successively washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was evaporated to give an oil, which was chromatographed on silica gel with chloroform as an eluent, giving a pale yellow solid. Recrystallization of the solid from ethyl acetate–hexane gave **17** (0.8 g, 33%) as colorless crystals: mp 98–102 °C; MS m/z 435 (M^+). Anal. ($C_{27}H_{37}N_3S$) C, H, N, S.

(6a*R**,10a*R**,11*R**)-11-[[4-[4-(4-**Fluorophenyl**)-1-**piperazinyl**]**butyryl**]**amino**]-6,6a,7,8,9,10,10a,11-**octahydrodibenzo[*b*,*e*]thiepin 5-Oxides** (**48 and 49**). A solution of **31** (2.1 g, 4.4 mmol) in dioxane (50 mL) and water (20 mL) was treated with sodium metaperiodate (2.8 g, 13 mmol). The mixture was vigorously stirred at room temperature for 1 h and then poured into water. The solution was extracted with chloroform. The extract was successively washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was evaporated to leave an oil. This oil was chromatographed on silica

gel with chloroform as an eluent. The first fraction gave 48 (1.0 g, 46%) as an oil: MS m/z 497 (M^+). Anal. ($C_{28}H_{36}N_3O_2SF$) C, H, N, S, F. The second fraction gave **49** (0.48 g, 22%) as an oil: MS m/z 497 (M^+). Anal. ($C_{28}H_{36}N_3O_2SF$) C, H, N, S, F.

Effect of Calcium-Induced Contraction of Depolarized Arterial Smooth Muscle. Std-Wister rats were killed by a blow on the head. The thoracic aorta was removed and cut into spinal strips 3–4 mm in width and about 30 mm in length. The preparation was mounted under 1.0 g tension in a 10 mL organ containing Krebs–bicarbonate solution aerated with 95% O_2 and 5% CO_2 at 37 °C. Isometric contractions were recorded on a flat recorder with force-displacement transducer. The normal Krebs–bicarbonate solution was composed of the following (mmol): NaCl, 112.0; $CaCl_2 \cdot 2H_2O$, 1.25; KCl, 5.0; $MgSO_4 \cdot 7H_2O$, 1.2; $NaHCO_3$, 25.0; KH_2PO_4, 1.0; glucose 11.5. After the vascular preparations were equilibrated in the normal Krebs–bicarbonate solution, the solution was replaced with the calcium-free, potassium-rich Krebs–bicarbonate solution (excluding $CaCl_2$, and replacing NaCl with an equimolar KCl) to cause a depolarization, and then $CaCl_2$ was cumulatively added to make the Ca^{2+} concentration–response curve. After the test compounds were incubated in the solution for 5 min, the same experiment was carried out. The pA_2 value was calculated according to the method of van Rossum.[17] The pA_2 value is defined as the negative logarithm of the molar concentration of the test compound which will cause a shift of factor 2 toward higher concentration in the Ca^{2+} concentration–response curve.

Effects of Blood Pressure and Heart Rate in Anesthetized Rats. Male rats of Donryu strains, weighting about 200 g, were anesthetized with sodium pentobarbital, 60 mg/kg ip and 30 mg/kg sc. The test compound solution was intravenously administered through a cannula in the right femoral vein. Blood pressure on the right carotid artery was measured by a pressure-displacement transducer (Nihon Koden, MPU-0.5). Heat rate was measured by a pulse-rate tachometer (Nihon Koden, RJG-3004).

Preventive Effect on Vasopressin-Induced ST Depression in Rats. Male rats of Donryu strains, weighting 150–220 g, were anesthetized with sodium pentobarbital, 60 mg/kg ip. The test compound suspended in 0.5% tragacanth solution was administered orally 60 min before intravenous administration of vasopressin. After 60 min, by using the method of Hiramatsu et al.,[14] myocardial hypoxia was produced with vasopressin, which was administered through a cannula in the femoral vein. Electrocardiogram (ECG) was registered in the second lead, and the sensitivity was adjusted to give 20 mm deflection for 1 mV input. As previously described by Hatano et al.,[15] the difference of the amplitudes of ST segment between after vasopressin and just before vasopressin was measured as the depression of ST segment. The amplitude of ST segment was measured at intervals of 30 s for 5 min after administration of vasopressin in each rat.

(17) Van Rossum, J. M. *Arch. Int. Pharmacodyn.* **1963**, *143*, 299.

Preventive Effect on Methacholine-Induced ST Elevation in Rats. Male Sprague–Dawlay rats, weighting about 500 g, were anesthetized with sodium pentobarbital, 60 mg/kg ip. For bolus injection of metacholine at ostia of the left and right coronary arteries, an arterial cannula was introduced through the exposed right carotid artery down closely to the aortic valve. Methacholine solutions (8 μg/kg) administered ia into the aorta by means of microsyringes at before and 0.5 min and every 5 min (until abolish methacholine-induced ST elevation) after test drug administration. Test compound solutions were intravenously administered into the femoral vein. Recording of ECG, sensitivity of ECG, and amplitude of ST segment were achieved by the same method as used with the vasopressin-induced ST-depression assay. Values are represented as mean ± SE. The difference of paired mean values was analyzed by the Student's t test and judged to be significant when p values were less than 0.05.

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Registry No. (±)-**5a**, 130982-55-7; (±)-**5b**, 130982-56-8; (±)-**5c**, 130982-57-9; (±)-**5d**, 130982-58-0; (±)-**6**, 130933-29-8; (±)-*trans*-**10a**, 130933-30-1; (±)-*trans*-**10b**, 130933-31-2; (±)-*trans*-**10c**, 130933-32-3; (±)-*trans*-**10d**, 130933-33-4; (±)-**11a**, 130933-34-5; (±)-**11b**, 130933-35-6; (±)-**11c**, 130933-36-7; (±)-**11d**, 130933-37-8; (±)-**12a**, 130933-38-9; (±)-**12a**·HCl, 130982-59-1; (±)-**12b**, 130933-39-0; (±)-**12b**·HCl, 130982-60-4; (±)-**12c**, 130933-40-3; (±)-**12c**·HCl, 130982-61-5; (±)-**12d**, 130933-41-4; (±)-**12d**·HCl, 130982-62-6; (±)-**13a**, 130933-42-5; (±)-**13b**, 130933-43-6; (±)-**13c**, 130982-63-7; (±)-**13d**, 130933-44-7; (±)-**13e**, 130933-45-8; **14**, 130933-46-9; (±)-**15**·oxalate, 130933-48-1; (±)-**16**, 130933-49-2; (±)-**17**, 130933-50-5; (±)-**18**, 130933-51-6; (±)-**19**·oxalate, 131063-12-2; (±)-**20**, 130933-52-7; (±)-**21**·oxalate, 130933-54-9; (±)-**22**, 130933-55-0; (±)-**23**·2HCl, 130933-56-1; (±)-**24**·oxalate, 130982-65-9; (±)-**25**·2 oxalate, 130982-67-1; (±)-**26**·2 HCl, 130933-57-2; (±)-**27**·2 oxalate, 130933-59-4; (±)-**28**, 130982-68-2; (±)-**29**·oxalate, 131063-14-4; (±)-**30**, 130933-60-7; (±)-**31**·oxalate, 130933-62-9; (±)-**31**·tartrate, 130982-69-3; (±)-**32**·$^3/_2$oxalate, 130933-64-1; (±)-**33**, 130933-65-2; (±)-**34**·2 oxalate, 130933-67-4; (±)-**35**·2 oxalate, 130933-69-6; (±)-**36**, 130933-70-9; (±)-**37**, 130933-71-0; (±)-**38**·HCl, 130933-72-1; (±)-**39**·2 HCl, 130933-73-2; (±)-**40**·2HCl, 130933-74-3; (±)-**41**·2HCl, 130933-75-4; (±)-**42**·oxalate, 130933-77-6; (±)-**43**, 130933-78-7; (±)-**44**·oxalate, 130953-93-4; (±)-**45**·oxalate, 130933-80-1; (±)-**46**·2 oxalate, 130933-82-3; (±)-**47**·2oxalate, 130933-84-5; (±)-**48**, 130933-85-6; (±)-**4**, 130982-70-6; (±)-**50**·oxalate, 130933-87-8; (±)-**51**·$^3/_2$oxalate, 130982-72-8; (±)-**52**, 131063-06-4; (±)-**53**, 130982-73-9; 1-(4-fluorophenyl)piperazine, 2252-63-3; ethyl 4-[4-(4-fluorophenyl)-1-piperazinyl]butyrate, 130933-88-9; ethyl 4-bromobutyrate, 2969-81-5; 1-phenylpiperazine, 92-54-6.