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Synthesis of 2-Phenylthiazolidine Derivatives as Cardiotonic Agents. I. 2-Phenylthiazolidine-3-thiocarboxamides

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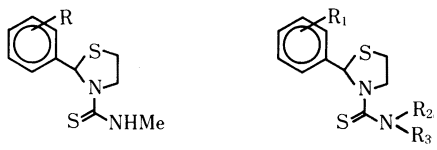
A series of novel 2-phenylthiazolidine-3-thiocarboxamides (II) was synthesized and tested for positive inotropic activity in the isolated guinea pig heart and in anesthetized dogs. Reaction of the benzaldehydes (VI, XI, XIV and XV) with cysteamine followed by treatment with isothiocyanates readily gave II. Structure–activity relationships were investigated by varying the structural parameters. *N*-Methyl-2-phenylthiazolidine-3-thiocarboxamides having an *ortho* substituent such as a Me or OMe group exhibited significant positive inotropic action, which was not blocked by propranolol. Among the various *ortho*-alkoxyphenyl derivatives synthesized, the 2-(2-(3-(4-phenylpiperazino)propoxy)phenyl) derivative (I_{67}) was found to exhibit more potent and longer-lasting activity than amrinone without any significant effect on heart rate or blood pressure.

Keywords——2-phenylthiazolidine-3-thiocarboxamide; positive inotropic activity; structure–activity relationship; cardiotonic agent

Cardiac glycosides and sympathomimetic agents have been used for the treatment of congestive heart failure (CHF) for many years. Although cardiac glycosides such as digitoxin and digoxin have been the principal agents used for CHF, their use is limited by arrhythmogenic liability and very narrow therapeutic index. The use of sympathomimetic agents such as dobutamine and dopamine is also limited because of their chronotropic liability and oral ineffectiveness.[1,2] Thus, the absence of safe, orally effective, positive inotropic agents for the treatment of CHF has stimulated the development of several new nonglycoside, nonsympathomimetic, cardiotonic agents such as amrinone, milrinone, sulmazole, and fenoximone.[3]

In the course of our studies on new antiulcer agents, 2-phenylthiazolidine-3-thiocarboxamides (I), conformationally restricted analogues[4] of metiamide, have been synthesized. Unexpectedly, in the isolated guinea pig heart, these compounds were found to display positive inotropic activity which was not blocked by propranolol. In view of the structural novelty of this class of compounds as cardiotonic agents, we have synthesized a large number of derivatives by varying the structural parameters. In this paper, we report the synthesis and cardiotonic activity of a series of new 2-phenylthiazolidines represented by the general formula II and related compounds.



I II

Chart 1

Chemistry

Our chemical approach was to examine the effects of varying three structural parameters on the activity of I; (1) the position and nature of substituents on the phenyl ring, (2) the effect of substituents on nitrogen, and (3) modification of the thiazolidine ring. These thiazolidine derivatives could be readily obtained from substituted benzaldehydes. The requisite benzaldehydes were synthesized by diverse routes depending on the nature of the substituents (Chart 2) or by known procedures.

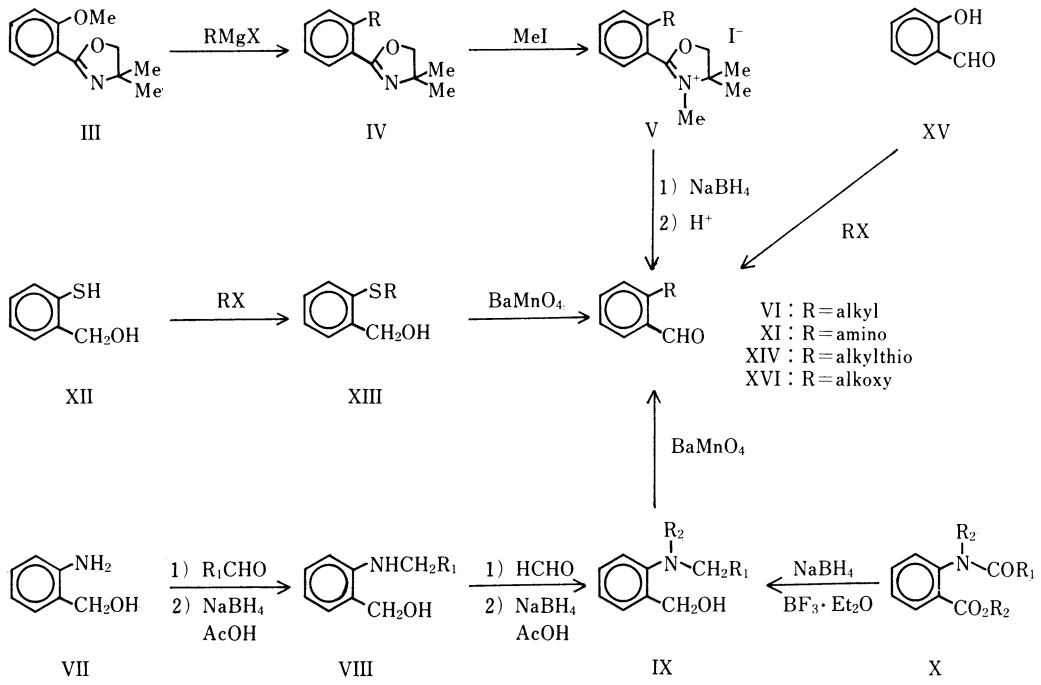


Chart 2

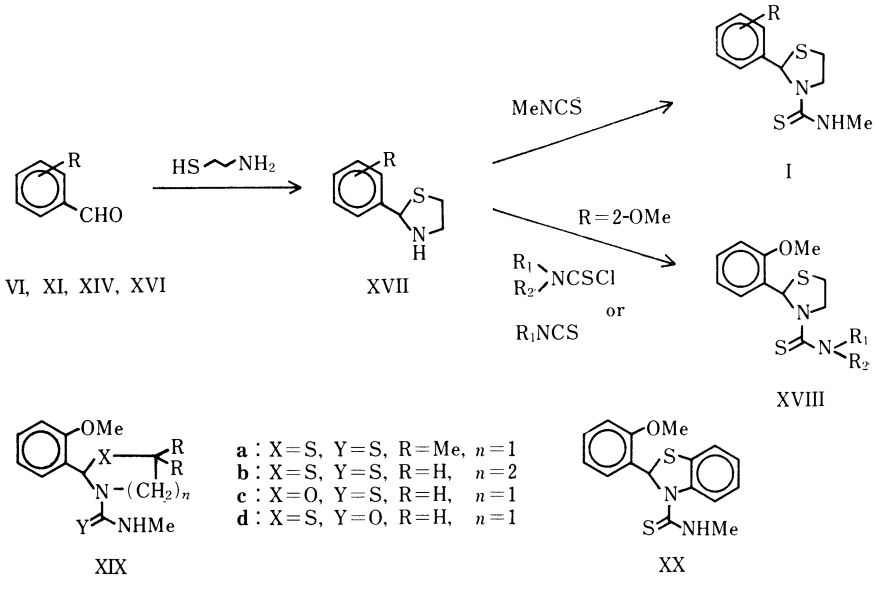
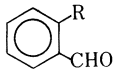


Chart 3

Reaction of the oxazoline (III)[5a] with alkylmagnesium halides according to Meyers and Mihelich[5b] effected the conversion of the methoxy group of III to various alkyl groups, giving the 2-(2-alkylphenyl)oxazolines (IV). Quaternization of IV with methyl iodide followed by reduction with $NaBH_4$[6] gave, after acidic hydrolysis, various 2-alkylbenzaldehydes (VI) listed in Table I.

TABLE I. 2-Substituted Benzaldehydes (VI, XI, XIV, XVI)



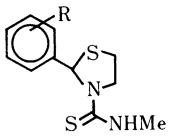
Compd. No.	R	Yield (%)	^{1}H-NMR ($CDCl_3$) δ ppm
VIa	C_2H_5	63[a]	1.25 (3H, t, J=7.5 Hz), 3.06 (2H, q, J=7.5 Hz), 10.27 (1H, s)
VIb	C_3H_7	61[a]	0.98 (3H, t, J=7.0 Hz), 1.51—1.78 (2H, m), 10.28 (1H, s)
VIc	iso-C_3H_7	61[a]	[b]
VId	C_4H_9	57[a]	0.93 (3H, t, J=7.0 Hz), 1.20—1.75 (4H, m), 10.28 (1H, s)
VIe	C_6H_{13}	69[a]	0.88 (3H, t, J=6.0 Hz), 1.10—1.70 (8H, m), 10.29 (1H, s)
VIf[c]	$CH_2N(CH_3)_2$	64	2.24 (6H, s), 3.75 (2H, s), 10.44 (1H, s)
VIg	$(CH_2)_3OCH_3$	28[a]	1.76—2.11 (2H, m), 3.38 (3H, s), 10.25 (1H, s)
XI[d]a	$N(CH_3)(CH_2)_2OCH_3$	55[e]	[b]
XIb	$N(CH_3)(CH_2)_2N(CH_3)_2$	21[e]	2.34 (6H, s), 3.04 (3H, s), 10.39 (1H, s)
XIc	$N(CH_3)(CH_2)_2SCH_3$	57[e]	2.07 (3H, s), 2.91 (3H, s), 10.29 (1H, s)
XId	$N(C_2H_5)_2$	66[f]	1.05 (6H, t, J=7 Hz), 3.18 (4H, q, J=7 Hz), 10.33 (1H, s)
XIe	$N(C_3H_7)_2$	62[f]	0.84 (6H, t, J=7 Hz), 1.20—1.90 (4H, m), 10.37 (1H, s)
XIf	$N(C_4H_9)_2$	55[f]	0.70—1.05 (6H, m), 1.10—1.90 (8H, m), 10.35 (1H, s)
XIV[g]a	$S(CH_2)_2N$ 	79[h]	1.62—2.00 (4H, m), 2.45—3.26 (8H, m), 10.47 (1H, s)
XIVb	$S(CH_2)_2N$ 	34[h]	1.30—1.75 (6H, m), 2.33—3.23 (8H, m), 10.42 (1H, s)
XIVc	$S(CH_2)_2N$ N–CH_3	34[h]	[b]
XIVd	$S(CH_2)_3N$ 	84[h]	1.30—2.08 (8H, m), 2.31—2.98 (8H, m), 10.40 (1H, s)
XVI[i]a	$O(CH_2)_2OCH_3$	82	[b]
XVIb	$O(CH_2)_2SCH_3$	93	2.19 (3H, s), 2.91 (2H, t, J=6.5 Hz), 10.44 (1H, s)
XVIc	$O(CH_2)_2SC_6H_5$	84	3.32 (2H, t, J=6.5 Hz), 4.25 (2H, t, J=6.5 Hz), 10.32 (1H, s)

a) Overall yield from III. *b*) See Experimental. *c*) This compound was prepared by reduction of 2-(dimethylaminocarbonyl)benzoic acid with B_2H_6 and subsequent oxidation with $BaMnO_4$. *d*) 2-Dimethylamino and 2-acetaminobenzaldehyde were prepared by the reported procedures. See reference 9. *e*) Overall yield from VII. *f*) Overall yield from X. *g*) Other known 2-alkylthiobenzaldehydes were prepared by the reported procedures. See reference 10. *h*) Overall yield from XII. *i*) Other known 2-alkoxybenzaldehydes were prepared by the reported procedures. See reference 11.

2-Aminobenzaldehydes (XI) were prepared from 2-aminobenzylalcohol (VII). Two successive reductive alkylations of VII gave IX, which could also be obtained by diborane reduction of the *N*-acyl anthranilates (X). Oxidation of IX with $BaMnO_4$[7] in refluxing $CHCl_3$ readily gave various 2-aminobenzaldehydes (XI) (Table I). 2-Alkylthiobenzaldehydes (XIV, Table I) were prepared by alkylation of 2-mercaptobenzyl alcohol (XII)[8] followed by $BaMnO_4$ oxidation. Alkylation of salicylaldehyde (XV) with alkyl halides gave various 2-alkoxybenzaldehydes (XVI), listed in Table I.

Reaction of substituted benzaldehydes (VI, XI, XIV, and XVI) with cysteamine at room temperature gave the 2-phenylthiazolidines (XVII). Without isolation, the products (XVII) were allowed to react with methyl isothiocyanate (MeNCS) to give the *N*-methylthiocarboxamides (I) (Table II). Since the 2-methoxyphenyl derivative (I_{37}) exhibited sig-

TABLE II. 2-Aryl-*N*-methylthiazolidine-3-thiocarboxamides (I)



Compd. No.	R	Yield (%)	Salt[a]	mp (°C)	Recrystn.[b] solvent	Analysis (%) Calcd (Found)	Myocardial contractility: Anesthetized dog[c] Dose mg/kg i.v.	LVdP/dt_{max} Δ%	Duration min	Isolated guinea pig heart[d] MED[e] μg/heart
						C H N				
						$C_{11}H_{14}N_2S$				
1	H	91	—	168—169	A	55.45 5.92 11.76 (55.52 5.92 11.74)	1	7	<10	3
						$C_{11}H_{13}ClN_2S_2$				
2	2-Cl	90	—	204—205	B	48.43 4.80 10.27 (48.29 4.83 10.29)	1	9.5	<10	10
						$C_{11}H_{13}ClN_2S_2$				
3	3-Cl	57	—	128—130	C	48.43 4.80 10.27 (48.42 4.85 10.15)	1	8.5	3	30
						$C_{11}H_{13}ClN_2S_2$				
4	4-Cl	57	—	141.5—144	C	48.43 4.80 10.27 (48.61 4.91 10.02)	1	12	6	30
						$C_{12}H_{16}N_2S_2$				
5	2-CH_3	58	—	183—184	C	57.10 6.39 11.10 (57.04 6.39 11.12)	1	40	10	3
						$C_{12}H_{16}N_2S_2$				
6	3-CH_3	60	—	131—133	A	57.10 6.39 11.10 (57.21 6.46 11.15)	1	4.5	3	30
						$C_{12}H_{16}N_2S_2$				
7	4-CH_3	52	—	134—135	A	57.10 6.39 11.10 (57.07 6.40 11.11)	1	6.8	3	30
						$C_{13}H_{18}N_2S_2$				
8	2-C_2H_5	68	—	157—159	A	58.61 6.81 10.52 (58.49 6.89 10.56)	1	23	15	10

						$C_{14}H_{20}N_2S_2$				
9	2-C_3H_7	88	—	156—159	A	59.96 7.19 9.99 (60.26 7.29 9.96)	1	20	19	*f*)
						$C_{14}H_{20}N_2S_2$				
10	2-iso-C_3H_7	58	—	184—186	A	59.96 7.19 9.99 (59.69 7.13 9.89)	1	14	11	100
						$C_{15}H_{22}N_2S_2$				
11	2-C_4H_9	81	—	137—139	A	61.18 7.53 9.51 (61.38 7.59 9.50)	1	34	20	10
						$C_{17}H_{26}N_2S_2$				
12	2-C_6H_{13}	73	—	106—108	A	63.33 8.09 8.69 (63.06 8.19 8.87)	1	48	39	100
						$C_{14}H_{21}N_3S_2 \cdot HCl$				
13	2-$CH_2N(CH_3)_2$	88	HCl	193—197 (dec.)	D	50.66 6.68 12.66 (50.48 6.71 12.56)	1	6	1	100
						$C_{15}H_{22}N_2OS_2$				
14	2-$(CH_2)_3OCH_3$	71	—	116—119	A	58.03 7.14 9.02 (58.24 7.20 8.98)	1	33	20	10
						$C_{12}H_{14}N_2O_2S_2$				
15	2-CO_2H	51	—	202—203	E	51.04 5.00 9.92 (50.94 4.98 9.80)	1	0	0	*f*)
						$C_{13}H_{16}N_2O_2S_2$				
16	2-CO_2CH_3	78	—	172—175	C	52.68 5.44 9.45 (52.94 5.58 9.20	1	33	10	3
						$C_{11}H_{15}N_3S_2$				
17	2-NH_2[g]	27	—	159—161	A	52.14 5.97 16.58 (52.15 6.14 16.29)	1	0	0	100
						$C_{13}H_{17}N_3OS_2$				
18	2-$NHCOCH_3$	19	—	191—193	A	52.85 5.80 14.22 (52.89 5.82 14.18)	1	0	0	*f*)
						$C_{13}H_{19}N_3S_2 \cdot H_2SO_4$				
19	2-$N(CH_3)_2$	70	H_2SO_4	141—142.5 (dec.)	F	41.13 5.58 11.07 (41.26 5.70 10.95)	0.3	46	10	3
						$C_{15}H_{23}N_3S_2 \cdot H_2SO_4 \cdot 1/2\,H_2O$				
20	2-$N(C_2H_5)_2$	84	H_2SO_4	114—118 (dec.)	F	43.25 6.29 10.08 (42.96 6.51 9.84)	0.3	20	8.5	10
						$C_{17}H_{27}N_3S_2 \cdot H_2SO_4$				
21	2-$N(C_3H_7)_2$	32	H_2SO_4	143—146 (dec.)	F	46.87 6.71 9.65 (46.98 6.57 9.90)	0.3	16	10	30

TABLE II. (continued)

Compd. No.	R	Yield (%)	Salt[a]	mp (°C)	Recrystn.[b] solvent	Analysis (%) Calcd (Found)			Myocardial contractility			
									Anesthetized dog[c]			Isolated guinea pig heart[d]
						C	H	N	Dose mg/kg i.v.	LV$dP/dt_{max}$ Δ%	Duration min	MED[e] μg/heart
22	2-N(C_4H_9)$_2$	55	H_2SO_4	163—164 (dec.)	F	$C_{19}H_{31}N_3S_2 \cdot H_2SO_4$ 49.22 (49.41)	7.17 (7.29)	9.06 (9.03)	1	60	25	100
23	2-N(CH_2)$_2$N(CH_3)$_2$	43	2HBr	105—110 (dec.)	F	$C_{16}H_{26}N_4S_2 \cdot 2HBr$ 38.41 (38.63)	5.64 (5.72)	11.20 (11.40)	1	2	5	f)
24	2-N(CH_2)$_2$SCH_3	81	HCl	143—145 (dec.)	F	$C_{15}H_{23}N_3S_3 \cdot HCl$ 47.66 (47.47)	6.40 (6.56)	11.12 (10.95)	1	213	22	1
25	2-N(CH_2)$_2$OCH_3	59	HCl	122—128	F	$C_{15}H_{23}N_3S_2 \cdot HCl \cdot H_2O$ 47.41 (47.50)	6.89 (6.82)	11.06 (10.80)	1	43	6	1
26	2-SCH_3	81	—	180—182	C	$C_{12}H_{16}N_2S_3$ 50.69 (50.65)	5.67 (5.70)	9.85 (9.68)	1	30	10	10
27	2-SO_2CH_3	62	—	237—238.5	G	$C_{12}H_{16}N_2O_2S_3$ 45.55 (45.67)	5.10 (5.19)	8.85 (8.84)	1	3	1	f)
28	2-SC_2H_5	76	—	161.5—163.5	A	$C_{13}H_{18}N_2S_3$ 52.31 (52.35)	6.08 (6.11)	9.39 (9.32)	1	16	8.5	100
29	2-SC_3H_7	75	—	143.5—145	A	$C_{14}H_{20}N_2S_3$ 53.81 (54.00)	6.45 (6.55)	8.96 (8.98)	1	26	17.5	100
30	2-SC_4H_9	81	—	162—164	A	$C_{15}H_{22}N_2S_3$ 55.17 (55.06)	6.79 (6.81)	8.58 (8.32)	1	11	11.5	f)
31	2-S(CH_2)$_2$N⟨ ⟩	77	HCl	193—195 (dec.)	D	$C_{17}H_{25}N_3S_2 \cdot HCl$ 50.53 (50.68)	6.49 (6.70)	10.40 (10.19)	1	19	27	30

32	2-S(CH$_2$)$_2$N⟨⟩	30	HCl	186—189 (dec.)	H	$C_{18}H_{27}N_3S_3 \cdot HCl$ 51.71 6.75 10.05 (51.66 6.86 9.84)	1	45	40	100
33	2-S(CH$_2$)$_2$N⟨O⟩	84	HCl	204—206 (dec.)	I	$C_{17}H_{25}N_3OS_3 \cdot HCl$ 48.61 6.24 10.00 (48.70 6.48 9.69)	1	37	10	3
34	2-S(CH$_2$)$_2$N⟨N–CH$_3$⟩	79	2HCl	209—211 (dec.)	F	$C_{18}H_{28}N_4S_3 \cdot 2HCl \cdot 1/2\,H_2O$ 45.18 6.53 11.71 (45.37 6.60 11.44)	1	12	17.5	*f*)
35	2-S(CH$_2$)$_3$N⟨⟩	69	HCl	216—218 (dec.)	F	$C_{19}H_{29}N_3S_3 \cdot HCl$ 52.81 7.00 9.72 (52.67 7.04 9.59)	1	15	37	*h*)
36	2-OH	37	—	177—178	A	$C_{11}H_{14}N_2OS_2$ 51.94 5.55 11.01 (51.87 5.50 11.18)	1	2	1	*f*)
37	2-OCH$_3$	80	—	153—154	A	$C_{12}H_{16}N_2OS_2$ 53.70 6.01 10.44 (53.69 6.03 10.41)	1	30	10	3
38	3-OCH$_3$	86	—	81—82	D	$C_{12}H_{16}N_2OS_2$ 53.70 6.01 10.44 (53.55 5.99 10.28)		NT		*f*)
39	4-OCH$_3$	90	—	104—105	D	$C_{12}H_{16}N_2OS_2$ 53.70 6.01 10.44 (53.75 6.14 10.41)		NT		*f*)
40	2,4-(OCH$_3$)$_2$	54	—	119.5—121	J	$C_{13}H_{18}N_2O_2S_2$ 52.32 6.08 9.39 (52.23 6.13 9.34)	1	4.5	< 10	3
41	2,5-(OCH$_3$)$_2$	84	—	178—180	K	$C_{13}H_{18}N_2O_2S_2$ 52.32 6.08 9.39 (52.21 6.04 9.35)		NT		*f*)
42	2-OC$_2$H$_5$	78	—	169.5—171.5	K	$C_{13}H_{18}N_2OS_2$ 55.29 6.42 9.92 (55.21 6.38 9.76)	1	28	10	10
43	2-OC$_3$H$_7$	89	—	149—152	A	$C_{14}H_{20}N_2OS_2$ 56.72 6.80 9.45 (56.68 6.83 9.39)	1	21	20	30
44	2-OC$_4$H$_9$	60	—	138—140	L	$C_{15}H_{22}N_2OS_2$ 58.03 7.14 9.02 (58.09 7.21 9.01)	1	39	30	30

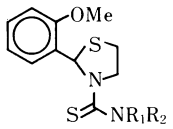
TABLE II. (continued)

Compd. No.	R	Yield (%)	Salt[a]	mp (°C)	Recrystn.[b] solvent	Analysis (%) Calcd (Found)	Myocardial contractility: Anesthetized dog[c] Dose mg/kg i.v.	LV$dP/dt_{max}$ Δ%	Duration min	Myocardial contractility: Isolated guinea pig heart[d] MED[e] μg/heart
						C H N				
45	2-OC_5H_{11}	60	—	117—119	C	$C_{16}H_{24}N_2OS_2$ 59.22 7.45 8.63 (59.32 7.51 8.60)	1	6	8	100
46	2-OC_6H_{13}	62	—	115—118	C	$C_{17}H_{26}N_2OS_2$ 60.30 7.74 8.28 (60.01 7.51 8.20)	1	29	9	*f*)
47	2-$OC_{12}H_{25}$	37	—	109—112	C	$C_{23}H_{38}N_2OS_2$ 67.35 9.06 6.63 (67.08 9.10 6.78)	1	0	0	*f*)
48	2-OC_6H_5	80	—	160—162	C	$C_{17}H_{18}N_2OS_2$ 61.79 5.49 8.48 (61.82 5.47 8.45)	1	32.5	26.5	100
49	2-$OCH_2C_6H_5$	68	—	177.5—181	K	$C_{18}H_{20}N_2OS_2$ 62.76 5.85 8.13 (62.59 5.95 8.10)		NT		30
50	2-$OCH_2CO_2CH_3$	83	—	139.5—140.5	A	$C_{14}H_{18}N_2O_3S_2$ 51.52 5.55 8.58 (51.47 5.62 8.44)	1	8	4	*f*)
51	2-OCH_2CO_2H[i]	61	—	184—185	B	$C_{13}H_{16}N_2O_3S_2$ 49.98 5.16 8.97 (49.96 5.21 8.88)	1	2	2	*f*)
52	2-$O(CH_2)_2OCH_3$	75	—	142—144	A	$C_{14}H_{20}N_2O_2S_2$ 53.80 6.45 9.00 (53.79 6.44 9.02)	1	7	3	100
53	2-$O(CH_2)_2SCH_3$	80	—	153—155	M	$C_{14}H_{20}N_2OS_3$ 51.19 6.14 8.53 (51.40 6.20 8.49)	1	15	12	100
54	2-$O(CH_2)_2SC_6H_5$	86	—	142—145	K	$C_{19}H_{22}N_2OS_3$ 58.43 5.68 7.17 (58.73 5.75 7.15)	1	25	5	*f*)
55	2-$O(CH_2)_2N(CH_3)_2$	52	HCl	209—212 (dec.)	F	$C_{15}H_{23}N_3OS_2 \cdot HCl$ 49.78 6.68 11.61 (49.77 6.68 11.66)	1	−5	—	*f*)

56	2-O$(CH_2)_2N(C_2H_5)_2$	61	HCl	210—211 (dec.)	F	$C_{17}H_{27}N_3OS_2 \cdot HCl$ 52.36 7.24 10.77 (52.12 7.26 10.72)	1	−1	—	*f*)
57	2-O$(CH_2)_2$N⟨ ⟩	81	2HCl	140—145	D	$C_{17}H_{25}N_3OS_2 \cdot 2HCl \cdot 1/2\,H_2O$ 47.10 6.51 9.69 (47.39 6.59 9.51)	1	5	—	*h*)
58	2-O$(CH_2)_2$N⟨ ⟩	41	HCl	209—211 (dec.)	F	$C_{18}H_{27}N_3OS_2 \cdot HCl$ 53.78 7.02 10.45 (53.65 7.02 10.49)	0.3	20	16	*f*)
59	2-O$(CH_2)_2$N⟨ O ⟩	91	HCl	207—208	D	$C_{17}H_{25}N_3O_2S_2 \cdot HCl$ 50.34 6.49 10.40 (50.52 6.48 10.42)	1	6	12.5	100
60	2-O$(CH_2)_3N(CH_3)_2$	73	HCl	213—215 (dec.)	F	$C_{16}H_{25}N_3OS_2 \cdot HCl$ 51.11 6.97 11.18 (50.96 6.96 11.09)	1	−25	5	*f*)
61	2-O$(CH_2)_3N(C_2H_5)_2$	54	HCl	195—196 (dec.)	F	$C_{18}H_{29}N_3OS_2 \cdot HCl$ 53.51 7.48 10.40 (53.57 7.53 10.35)	1	−23	—	*f*)
62	2-O$(CH_2)_3N(C_3H_7)_2$	87	HCl	192—194 (dec.)	F	$C_{20}H_{33}N_3OS_2 \cdot HCl$ 55.60 7.93 9.73 (55.73 7.94 9.76)	1	−12	—	*h*)
63	2-O$(CH_2)_3$N⟨ ⟩	71	2HCl	122—125	D	$C_{18}H_{27}N_3OS_2 \cdot 2HCl \cdot H_2O$ 47.36 6.85 9.21 (47.64 7.04 9.27)	1	2	1	*h*)
64	2-O$(CH_2)_3$N⟨ ⟩	55	2HCl	129—133	D	$C_{19}H_{29}N_3OS_2 \cdot 2HCl \cdot H_2O$ 48.50 7.07 8.93 (48.48 7.37 8.91)	1	−4	—	*h*)
65	2-O$(CH_2)_3$N⟨ O ⟩	72	2HCl	160—165	D	$C_{18}H_{27}N_3O_2S_2 \cdot 2HCl$ 47.57 6.43 9.25 (47.29 6.51 9.08)	1	19	15	*f*)
66	2-O$(CH_2)_3$N⟨ N–CH_3 ⟩	86	2HCl	195—198 (dec.)	D	$C_{19}H_{30}N_4OS_2 \cdot 2HCl \cdot H_2O$ 47.00 7.06 11.54 (47.18 6.95 11.57)	1	2	1	*f*)
67	2-O$(CH_2)_3$N⟨ N–C_6H_5 ⟩	63	Fum	125—128	D	$C_{24}H_{32}N_4OS_2 \cdot C_4H_4O_4$ 58.72 6.34 9.78 (58.28 6.31 9.68)	0.3	68	60	10
	Amrinone						0.3	25	25	10

a) Fum = fumarate. *b*) A = EtOH, B = MeOH–H_2O, C = AcOEt–hexane, D = EtOH–Et_2O, E = MeOH–THF, F = MeOH–Et_2O, G = DMF–iso-Pr_2O, H = iso-PrOH–Et_2O, I = MeOH–iso-Pr_2O, J = EtOH–iso-Pr_2O, K = AcOEt, L = iso-PrOH, M = THF. *c*) For methodology, see reference 14. *d*) For methodology, see reference 2*a*. *e*) Minimum effective dose (minimum dose required to cause an increase in contractile force of more than 0.3 g). *f*) Ineffective at 100 μg/heart. *g*) Prepared from the *N*-acetate (I_{18}) by alkaline hydrolysis. *h*) Caused a decrease in contractile force. *i*) This compound was prepared by alkaline hydrolysis of the ester (I_{50}). NT = not tested.

TABLE III. *N*-Substituted-2-(2-methoxyphenyl)thiazolidine-3-thiocarboxamides (XVIII)



Compd. No.	R_1	R_2	Yield (%)	Salt	mp (°C)	Recrystn.[a] solvent	Analysis (%) Calcd (Found)			Myocardial contractility			
										Anesthetized dog[b]			Isolated guinea pig heart[c] MED[d] μg/heart
							C	H	N	Dose mg/kg i.v.	LV$dP/dt_{max}$ Δ%	Duration min	
							$C_{11}H_{14}N_2OS_2$						
1	H	H	52[e]	—	182.5—184.5	N	51.94 (51.96)	5.55 (5.57)	11.01 (10.96)	1	−3	—	[f]
							$C_{13}H_{18}N_2OS_2$						
2	H	C_2H_5	64	—	131.5—134	D	55.29 (55.49)	6.42 (6.47)	9.92 (9.91)	1	−7	—	[f]
							$C_{15}H_{22}N_2OS_2$						
3	H	iso-C_4H_9	55	—	86—91	H	58.03 (58.14)	7.14 (7.20)	9.02 (9.21)	1	2.3	1	[f]
							$C_{17}H_{18}N_2OS_2$						
4	H	C_6H_5	64	—	142—144	C	61.79 (61.63)	5.49 (5.52)	8.48 (8.46)	1	3.5	1	[f]

5	H	$(CH_2)_2N(CH_3)_2$	82	HCl	182—185 (dec.)	A	$C_{15}H_{23}N_3OS_2 \cdot HCl$ 49.78 6.68 11.61 (49.50 6.83 11.56)	1	−6	—	*f*)
6	H	$CH_2CO_2C_2H_5$	89	—	79—83	J	$C_{15}H_{20}N_2O_3S_2$ 52.92 5.92 8.23 (52.81 5.75 8.11)	1	0	0	*f*)
7	H	CH_2CO_2H	80*g*)	—	145—146 (dec.)	O	$C_{13}H_{16}N_2O_3S_2$ 49.98 5.16 8.97 (50.15 5.18 8.95)	1	0	0	*f*)
8	H	$CO_2C_2H_5$	89	—	139—141.5	N	$C_{14}H_{18}N_2O_3S_2$ 51.51 5.56 8.58 (51.44 5.54 8.58)	1	1.4	1	*f*)
9	H	$COCH_3$	28	—	143—146	K	$C_{13}H_{16}N_2O_2S_2$ 52.68 5.44 9.45 (52.48 5.51 9.32)	1	0	0	*f*)
10	H	COC_6H_5	78	—	142—144.5	C	$C_{18}H_{18}N_2O_2S_2$ 60.31 5.06 7.81 (60.25 4.92 7.74)	1	0	0	*f*)
11	CH_3	CH_3	2	—	170—173	C	$C_{13}H_{18}N_2OS_2$ 55.29 6.42 9.92 (55.49 6.55 9.81)	1	−2	—	*f*)

a) N = MeOH, O = AcOEt–benzene. See also footnote *b* in Table II. *b*—*d*) See footnotes *c*—*e* in Table II, respectively. *e*) Prepared by alkaline hydrolysis of the *N*-acetate ($XVIII_9$). *f*) See footnote *f* in Table II. *g*) Prepared by alkaline hydrolysis of the ester ($XVIII_6$).

nificant cardiotonic activity (see below), the effect of varying the substituents on the thiocarboxamide group was examined with this compound. Reaction of XVII (R=2-OMe) with various isothiocyanates or dimethylthiocarbamoyl chloride gave the *N*-substituted thiocarboxamides (XVIII) listed in Table III.

With regard to modification of the thiazolidine ring, reaction of 2-methoxybenzaldehyde with 2-aminomethyl-2-propanethiol[12] and 3-amino-1-propanethiol followed by treatment with MeNCS gave the *gem*-dimethyl derivative (XIXa) and the 1,3-thiazine derivative (XIXb), respectively (Chart 3). The oxazolidine analogue (XIXc) was prepared by reaction of 2-methoxybenzaldehyde with ethanolamine[13] followed by treatment with MeNCS. The benzothiazoline derivative (XX) was prepared in a similar manner by the use of 2-aminothiophenol. Physical properties of XIX and XX are summarized in Table IV.

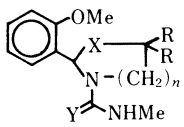
Pharmacology and Structure–Activity Relationships

The positive inotropic activities of the novel 2-phenylthiazolidine derivatives were determined in the isolated guinea pig heart by measuring the increase in cardiac contractile force[2a] and also in anesthetized dogs by measuring percent increase in maximum dP/dt of left ventricular pressure[14] after i.v. administration by the method reported previously. The results are listed in Tables II—IV together with comparative data for amrinone.

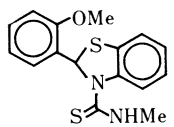
Effects of the substituents on the benzene ring of *N*-methyl-2-phenylthiazolidine-3-thiocarboxamides (I) were examined first (Table II). The presence of substituents such as Me (I_5) and OMe (I_{37}) at the *ortho* position to the thiazolidine group conferred potent positive inotropic activity, which was not blocked by propranolol. Substitution at any other position was ineffective, as exemplified by the corresponding *meta* and *para* isomers ($I_{6,7}$ and $I_{38,39}$). The 2-dimethylamino (I_{19}), 2-methoxycarbonyl (I_{16}), and 2-methylthio (I_{26}) derivatives also exhibited potent activity. On the other hand, introduction of hydrophilic substituents such as OH (I_{36}), NH_2 (I_{17}), NHAc (I_{18}), and CO_2H (I_{15}) at the *ortho* position resulted in disappearance of the activity. In a series of *ortho*-alkoxyphenyl derivatives (I_{37}, I_{42-47}), the duration of action in anesthetized dogs tends to increase with increasing length of the alkylene chain, the butoxy derivative (I_{44}) exhibiting the most prolonged activity. However, lengthening of the alkylene chain in this series caused a major decrease in *in vitro* activity. Similar results were generally observed in the 2-alkyl and 2-alkylthio series. The activity of 2-dialkylaminophenyl derivatives decreased with increasing bulkiness of the *N*-alkyl group. Thus, a change from methyl to butyl (I_{19}—I_{22}) resulted in gradual decrease in both *in vitro* and *in vivo* activities. The positive inotropic activity of these 2-aminophenyl derivatives was invariably accompanied by significant elevation of blood pressure. This was also the case for the 2-((2-methylthio)ethylamino)phenyl derivative (I_{24}), one of the most potent compounds in this series. After examination of a number of *ortho*-alkoxy and -alkylthio derivatives having a hetero atom in the alkylene chain, the phenylpiperazinopropoxy derivative (I_{67}) was found to exhibit more potent and longer-lasting positive inotropic activity than amrinone with only small effects on both heart rate and blood pressure.

The effects of *N*-substituents on the thiocarboxamide group on the activity were examined in a series of 2-methoxyphenyl derivatives (XVIII), listed in Table III. Replacement of the methyl group of I_{37} by hydrogen, a larger alkyl group, or an acyl group all resulted in disappearance of the activity. The *N*-dimethyl derivative ($XVIII_{11}$) was also ineffective. The effect of modifying the thiazolidine moiety was also examined in a series of 2-methoxyphenyl derivatives (Table IV). Introduction of a geminal dimethyl group at C_5 of the thiazolidine ring (XIXa) and conversion of thiazolidine to the 1,3-thiazine (XIXb), oxazolidine (XIXc), or benzothiazoline (XX) all resulted in a marked fall in activity. Finally, conversion of the *N*-methylthiocarboxamide (I_{37}) to the corresponding carboxamide (XIXd) also conferred reduced activity.

TABLE IV. Modified Thiazolizine Analogues (XIX and XX)



XIX



XX

Compd. No.	X	Y	R	*n*	Yield (%)	mp (°C)	Recrystn.[a] solvent	Analysis (%) Calcd (Found) C	H	N	Myocardial contractility: Anesthetized dog[b] Dose mg/kg i.v.	LV$dP/dt_{max}$ Δ%	Duration min	Isolated guinea pig heart[c] MED[d] μg/heart
								$C_{14}H_{20}N_2OS_2$						
XIXa	S	S	CH_3	1	68	139—140	C	56.72 (56.78)	6.80 (6.86)	9.45 (9.39)	1	0	0	100
								$C_{13}H_{18}N_2OS_2$						
XIXb	S	S	H	2	75	141—143	A	55.29 (55.41)	6.42 (6.49)	9.92 (9.95)	1	−6.5		e)
								$C_{12}H_{16}N_2O_2S$						
XIXc	O	S	H	1	63	142—147	A	57.12 (57.10)	6.39 (6.38)	11.10 (11.03)		NT		30
								$C_{12}H_{16}N_2O_2S$						
XIXd	S	O	H	1	75	161—164	D	57.12 (57.39)	6.39 (6.31)	11.10 (11.09)		NT		30
								$C_{16}H_{16}N_2OS_2$						
XX					14	185—186	C	60.73 (66.77)	5.10 (5.04)	8.85 (8.78)	1	0	0	e)

a) See footnote *b* in Table II. *b*—*e*) See footnotes *c*—*f* in Table II, respectively. NT = not tested.

Thus, examination of the positive inotropic activities of a large number of novel 2-phenylthiazolidine-3-thiocarboxamides (II) and related compounds clarified the structure–activity relationship of this series and led to the discovery of the phenylpiperazino derivative (I_{67}) with potent and long-lasting activity. Further modification of this new lead as a cardiotonic agent is in progress and will be the subject of a forthcoming paper.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi IR-215 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60 MHz on a JEOL PMX-60 spectrometer with tetramethylsilane (TMS) as an internal reference. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Mass spectra (MS) were measured with Hitachi RMU-6M instrument.

2-Isopropylbenzaldehyde (VIc)——An ethereal solution of isopropylmagnesium bromide (prepared from isopropyl bromide (9.0 g) and Mg (1.96 g)) was added to a stirred solution of III[5a] (5.0 g, 24.4 mmol) in tetrahydrofuran (THF) (20 ml) at room temperature. The mixture was stirred for 3.5 h, then aq. NH_4Cl solution was added dropwise under ice-cooling, and the aq. layer was extracted with Et_2O. The combined organic layer was washed with water, dried over Na_2SO_4, and evaporated to give IV (R = isopropyl, 5.23 g, 99%) as an oil. IR ν_{max}^{neat} cm^{-1}: 1645 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (6H, d, J=7 Hz, $CH(CH_3)_2$), 1.37 (6H, s, 2×CH_3), 3.69 (1H, m, $CH(CH_3)_2$), 4.05 (2H, s, OCH_2–), 6.99—7.67 (4H, m, Ar-H). MS m/z: 217 (M^+). This oil (1.0 g, 4.6 mmol) was heated with methyl iodide (2.25 ml) in nitromethane (2 ml) at 70 °C overnight. The cooled reaction mixture was diluted with Et_2O. The precipitate was collected, washed with Et_2O, and dried to give V (R = isopropyl, 1.54 g, 96%), mp 153—156 °C. $NaBH_4$ (0.17 g, 4.5 mmol) was added portionwise to a solution of V (R = isopropyl, 1.5 g, 4.3 mmol) in EtOH (10 ml) at room temperature, and the mixture was stirred for 4 h. After removal of the solvent, the residual oil was heated with 5% aq. HCl (10 ml) at 65 °C for 20 min and extracted with Et_2O. The extracts were washed with water, dried, and concentrated. The residue was chromatographed on silica gel with benzene to give VIc (0.41 g, 64%; 61% overall yield from III) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (6H, d, J=7 Hz, $CH(CH_3)_2$), 3.95 (1H, m, $CH(CH_3)_2$), 7.15—7.90 (4H, m, Ar-H), 10.43 (1H, s, CHO). MS m/z: 148 (M^+). Compounds VIa, b, d, e, g were prepared in a similar manner and are listed in Table I.

2-(*N*-(2-Methoxyethyl)-*N*-methylamino)benzyl Alcohol (IX, R_1=CH_2OCH_3, R_2=CH_3)——A mixture of VII (2.0 g, 16.3 mmol) and 2-methoxyacetaldehyde (1.80 g, 24.5 mmol) in MeOH (30 ml) was stirred at room temperature overnight. The MeOH was evaporated off, and the resulting oil was dissolved in THF (10 ml). This solution was added dropwise to a mixture of $NaBH_4$ (1.0 g, 26.4 mmol) in AcOH (8 ml) under ice-cooling, and the mixture was stirred at room temperature for 5 h. The reaction mixture was made alkaline with aq. K_2CO_3 and extracted with AcOEt. The extracts were washed with water, dried, and evaporated. The residue was chromatographed on silica gel with AcOEt–benzene (1 : 4) to give VIII (R_1=CH_2OCH_3, 2.27 g, 77%) as an oil. IR ν_{max}^{neat} cm^{-1}: 3350 (OH), 1600. ^{1}H-NMR ($CDCl_3$) δ: 3.2—4.0 (5H, m, 2×CH_2 and NH), 3.31 (3H, s, OCH_3), 4.54 (2H, s, CH_2O), 4.5—4.8 (1H, br, OH), 6.5—7.4 (4H, m, Ar-H). Treatment of this oil (2.2 g, 12.3 mmol) with 37% HCHO (3 ml) and $NaBH_4$ (1.0 g, 26.4 mmol) in the same manner as described above gave IX (R_1=CH_2OCH_3, R_2=CH_3, 2.0 g, 83.4%; 64.2% overall yield from VII) as an oil. IR ν_{max}^{neat} cm^{-1}: 3400 (OH). ^{1}H-NMR ($CDCl_3$) δ: 2.69 (3H, s, N–CH_3), 3.29 (3H, s, OCH_3), 3.05—3.65 (4H, m, 2×CH_2), 4.66 (2H, s, CH_2O), 5.20 (1H, br s, OH), 7.1—7.4 (4H, m, Ar-H). Compounds IXb, c were prepared in a similar manner.

***N*,*N*-Dibutylaminobenzyl Alcohol (IX: R_1=C_3H_7, R_2=C_4H_9)**——BF_3-etherate (27 g) was added dropwise to a mixture of X (R_1=C_3H_7, R_2=C_4H_9, 12.4 g, 38.9 mmol) and $NaBH_4$ (9.0 g, 238 mmol) in THF (200 ml) with stirring. The mixture was refluxed overnight, then decomposed with water, and extracted with AcOEt. The extracts were washed with water, dried, and evaporated *in vacuo*. The residual oil was chromatographed on silica gel with AcOEt–benzene (1 : 6) to give IX (R_1=C_3H_7, R_2=C_4H_9, 6.29 g, 69%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.65—1.10 (6H, m, 2×CH_2CH_3), 1.10—1.80 (8H, m, 2×CH_2CH_2), 2.80—3.05 (4H, m, 2×CH_2N), 4.80 (2H, s, CH_2O), 6.08 (1H, s, OH), 7.05—7.30 (4H, m, Ar-H).

2-(*N*-(2-Methoxyethyl)-*N*-methylamino)benzaldehyde (XIa)——A mixture of IX (R_1=CH_2OCH_3, R_2=CH_3, 2.00 g, 10.3 mmol) and $BaMnO_4$ (5.23 g) in $CHCl_3$ (40 ml) was refluxed for 6 h with stirring. The inorganic material was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 4) to give XIa (1.7 g, 85.5%; 55% overall yield from VII) as an oil. IR ν_{max}^{neat} cm^{-1}: 1680 (CHO). ^{1}H-NMR ($CDCl_3$) δ: 2.94 (3H, s, NCH_3), 3.31 (3H, s, OCH_3), 3.31—3.80 (4H, m, 2×CH_2), 7.00—7.85 (4H, m, Ar-H), 10.31 (1H, s, CHO). Compounds XIb—f were prepared in a similar manner and are listed in Table I.

2-(2-(4-Methylpiperazino)ethylthio)benzaldehyde (XIVc)——A mixture of 2-mercaptobenzyl alcohol (XII, 3.6 g, 25.7 mmol), 1-chloroethyl-4-methylpiperazine dihydrochloride (6.0 g, 25.7 mmol), and K_2CO_3 (10.5 g, 3×25.7 mmol) in dimethyl formamide (DMF, 25 ml) was stirred overnight under argon, then poured into water. Extraction with AcOEt followed by evaporation of the solvent gave XIII (R = CH_2CH_2N⌒N–CH_3, 4.9 g) as an oil, which was

oxidized with $BaMnO_4$ (15 g) in CH_2Cl_2 (150 ml) under reflux for 4 h. The inorganic material was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (10 : 1) to give XIVc (2.3 g, 34.2% overall yield from XII) as an oil. IR ν_{max}^{neat} cm^{-1}: 1680 (CHO). ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s, NCH_3), 2.47—2.77 (10H, m, $5 \times CH_2$), 2.99—3.24 (2H, m, SCH_2), 7.17—7.92 (4H, m, Ar-H), 10.48 (1H, s, CHO). MS *m/z*: 264 (M^+). Compounds XIVa, b, d were prepared in a similar manner and are listed in Table I.

2-(2-Methoxyethoxy)benzaldehyde (XVIa)——A mixture of XV (2.63 g, 21.6 mmol), 1-bromo-2-methoxyethane (4.00 g, 28.8 mmol), and K_2CO_3 (3.0 g, 21.7 mmol) in DMF (30 ml) was stirred for 16 h at room temperature, then heated at 50 °C for 16 h. The mixture was cooled, diluted with water, and extracted with AcOEt. The extracts were washed with water, dried, and evaporated. The residue was chromatographed on silica gel and eluted with AcOEt–hexane (1 : 9) to give 3.20 g of XVIa as an oil. IR ν_{max}^{neat} cm^{-1}: 1680 (CHO). ^{1}H-NMR ($CDCl_3$) δ: 3.43 (3H, s, OCH_3), 3.70—3.90 (2H, m, CH_2–C), 4.10—4.30 (2H, m, C–CH_2), 6.80—7.90 (4H, m, Ar-H), 10.49 (1H, s, CHO). MS *m/z*: 180 (M^+). Compounds XVIb, c were prepared in a similar manner (Table I).

Preparation of 2-Aryl-*N*-methylthiazolidine-3-thiocarboxamides (I)——The following prodedure is representative. A solution of 2-methoxybenzaldehyde (10.0 g, 73.4 mmol) in EtOH (20 ml) was added to a stirred suspension of cysteamine hydrochloride (8.34 g, 73.4 mmol) and NaOH (3.00 g, 75 mmol) in EtOH (160 ml) under argon. The mixture was refluxed for 1 h, and a solution of methyl isothiocyanate (5.90 g, 80.7 mmol) in EtOH (20 ml) was added, then the whole was refluxed for 3 h. After removal of the solvent, the residue was chromatographed on silica gel with $CHCl_3$–EtOH (30 : 1) to give 14.6 g of 2-(2-methoxyphenyl)-*N*-methylthiazolidine-3-thiocarboxamide (I_{37}), mp 154—155 °C (from EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3365, 3280 (NH). ^{1}H-NMR ($CDCl_3$) δ: 2.99 (3H, d, J=4.5 Hz, $NHCH_3$), 2.90—3.25 (2H, m, SCH_2), 3.93 (3H, s, OCH_3), 4.09—4.80 (2H, m, NCH_2), 5.50 (1H, br, NH), 6.31 (1H, s, S–CH–N), 6.30—7.40 (4H, m, Ar-H). MS *m/z*: 268 (M^+).

2-(2-Aminophenyl)-*N*-methylthiazolidine-3-thiocarboxamide (I_{17})——A mixture of I_{18} (0.95 g, 3.2 mmol) and 20% KOH (5 ml) in MeOH (30 ml) was refluxed for 30 h. The reaction mixture was evaporated *in vacuo* and diluted with water. The precipitate was collected and recrystallized from EtOH to give 0.22 g of I_{17}. mp 159—161 °C. IR ν_{max}^{neat} cm^{-1}: 3445, 3360, 3330 (NH_2). ^{1}H-NMR ($CDCl_3$) δ: 3.00 (3H, d, J=4.5 Hz, $NHCH_3$), 3.00—3.20 (2H, m, SCH_2), 3.8 (2H, br s, NH_2), 4.10—4.70 (2H, m, NCH_2), 5.55 (1H, br s, NH), 6.12 (1H, s, S–CH–N), 6.68—7.27 (4H, m, Ar-H). MS *m/z*: 253 (M^+). Compound $XVIII_1$ was prepared from $XVIII_9$ in a similar manner.

2-(2-Carboxymethoxyphenyl)-*N*-methylthiazolidine-3-thiocarboxamide (I_{51})——A mixture of the ester (I_{50}, 7.00 g, 21.5 mmol) and NaOH (0.945 g, 23.7 mmol) in 50% aq. MeOH (100 ml) was stirred at room temperature overnight. The mixture was acidified with 10% HCl and extracted with AcOEt. The extracts were washed with water, dried over Na_2SO_4, and evaporated. The residue was recrystallized from aq. MeOH to give 4.1 g of I_{51}, mp 184—185 °C. IR ν_{max}^{Nujol} cm^{-1}: 3380 (NH), 1720 (COOH). ^{1}H-NMR (DMSO-d_6) δ: 2.86 (3H, d, J=4 Hz, N–CH_3), 3.00—3.21 (2H, m, –SCH_2), 3.80—4.30 (2H, m, N–CH_2), 4.72 (2H, s, O–CH_2), 6.80—7.30 (5H, m, S–CH–N and Ar-H), 7.50 (1H, br s, NH). MS *m/z*: 312 (M^+). Compound $XVIII_7$ was prepared from $XVIII_6$ in a similar manner.

2-(2-Methoxyphenyl)-*N*,*N*-dimethylthiazolidine-3-thiocarboxamide ($XVIII_{11}$)——A solution of dimethylthiocarbamoyl chloride (2.96 g, 24 mmol) in DMF (10 ml) was added to a solution of 2-(2-methoxyphenyl)thiazolidine (XVII, R=2–OCH_3, 3.90 g, 20 mmol) and 4-dimethylaminopyridine (2.93 g, 24 mmol) in DMF (40 ml) under ice-cooling, and the mixture was stirred at room temprature for 20 h, then poured into water and extracted with AcOEt. The extracts were washed with 5% HCl, sat. $NaHCO_3$, and water, successively and dried over Na_2SO_4. After removal of the solvent, the residual oil was chromatographed on silica gel with benzene–AcOEt (100 : 1) to give 0.10 g of $XVIII_{11}$, mp 170—173 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 1600 (Ar). ^{1}H-NMR ($CDCl_3$) δ: 3.30 (6H, s, $N(CH_3)_2$), 2.93—3.75 (3H, m, S–CH_2, NCH–H), 3.88 (3H, s, OCH_3), 4.50—4.85 (1H, m, NCH–H), 6.59 (1H, s, S–CH–N), 6.76—7.35 (4H, m, Ar-H). MS *m/z*: 282 (M^+).

2-(2-Methoxyphenyl)-*N*-methyloxazolidine-3-thiocarboxamide (XIXc)——A solution of MeNCS (1.40 g, 18.4 mmol) was added to a solution of 2-(2-methoxyphenyl)oxazolidine[13] (3.00 g, 16.7 mmol) in EtOH (30 ml), and the mixture was refluxed for 4 h. The mixture was concentrated *in vacuo*, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried, and evaporated. The crystalline residue was collected by filtration, washed with Et_2O, and recrystallized from EtOH to give 2.66 g of XIXc, mp 142—147 °C. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3250 (NH). ^{1}H-NMR ($CDCl_3$) δ: 3.00 (3H, d, J=4.5 Hz, $NHCH_3$), 3.92 (3H, s, OCH_3), 3.81—4.50 (4H, m, –OCH_2CH_2–N), 5.50 (1H, br, NH), 6.46 (1H, s, O–CH–N), 6.87—7.50 (4H, m, Ar-H). MS *m/z*: 252 (M^+).

2-(2-Methoxyphenyl)-*N*-methylthiazolidine-3-carboxamide (XIXd)——A solution of methyl isocyanate (3.80 g, 66 mmol) in THF (10 ml) was added to a solution of 2-(2-methoxyphenyl)thiazolidine (XVII, R=2–OCH_3, 10.7 g, 55 mmol) in THF. The mixture was refluxed for 4 h and concentrated *in vacuo*, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried, and evaporated. The crystalline residue was collected by filtration, washed with Et_2O, and recrystallized from EtOH–Et_2O to give 10.4 g of XIXd, mp 161—164 °C. IR ν_{max}^{Nujol} cm^{-1}: 3310 (NH), 1635 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.73 (3H, d, J=4.5 Hz, $NHCH_3$), 2.88—3.08 (2H, m, S–CH_2), 3.60—4.50 (3H, m, N–CH_2 and NH), 3.89 (3H, s, OCH_3), 6.16 (1H, s, S–CH–N), 6.78—7.41 (4H, m, Ar-H).

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References and Notes

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