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Synthesis of 2-Phenylthiazolidine Derivatives as Cardiotonic Agents. II.[1] 2-(Phenylpiperazinoalkoxyphenyl)thiazolidine-3-thiocarboxamides and the Corresponding Carboxamides

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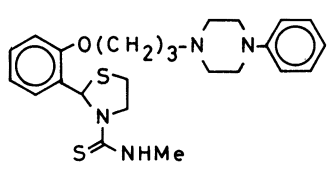
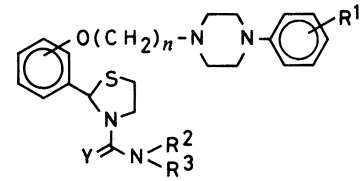
A large number of 2-(phenylpiperazinoalkoxyphenyl)thiazolidine-3-thiocarboxamides and the corresponding carboxamides (II) were synthesized and tested for inotropic activity in anesthetized dogs. Compounds II were prepared from a hydroxybenzaldehyde (III) through the intermediates (IV, V, and X). Structure–activity relationships (SAR) were investigated by varying the structural parameters. Transposition of the piperazinoalkoxyl group to the *meta* or *para* position from the *ortho* position caused a marked fall in activity. Conversion of the thiocarboxamido to a carboxamido group caused a marked increase in activity. This tendency was generally observed in this series of compounds and constitutes a major deviation from the SAR in the simple 2-phenylthiazolidine series. With regard to effects of the length of the aminoalkoxy chain, the ethoxy derivatives were generally more potent than higher analogues. Lengthening of the *N*-alkyl group in the (thio)carboxamido group generally caused a decrease in activity. Among the various derivatives synthesized, II_{15} was found to be approximately one hundred times more potent than amrinone with a long duration of action.

Keywords——2-phenylthiazolidine-3-carboxamide; 2-(phenylpiperazinoalkoxyphenyl)thiazolidine-3-thiocarboxamide; 2-(phenylpiperazinoalkoxyphenyl)thiazolidine-3-carboxamide; positive inotropic activity; structure–activity relationship; cardiotonic agent

The preceding paper[1] of this series described the synthesis and cardiotonic activity of a series of new 2-phenylthiazolidine-3-thiocarboxamides. After examination of the structure–activity relationships (SAR) of numerous derivatives, *N*-methyl-2-(2-(3-(4-phenylpiperazino)-propoxy)phenyl)thiazolidine-3-thiocarboxamide (I) was found to exhibit potent and long-lasting positive inotropic activity in anesthetized dogs. Further exploration of this new lead compound (I) as a cardiotonic agent led to the synthesis of a large number of derivatives represented by general formula (II). This paper describes the synthesis and positive inotropic



I



II

Chart 1

activity of II, and the SAR are discussed in terms of the effect of varying the substituents (R^1, R^2, R^3, and Y), the position of the aminoalkoxyl group, and the length of the alkylene chain (*n*).

Chemistry

The thiazolidine-3-(thio)carboxamides (II) were synthesized through the sequence of reactions shown in Chart 2. Reaction of hydroxybenzaldehydes (III) with cysteamine followed by treatment with methyl isocyanate (MeNCO) or methyl isothiocyanate (MeNCS) readily gave the phenolic *N*-methylthiazolidine-3-carboxamides or thiocarboxamides (IV). Alkylation of IV with alkylene dihalides or tosyloxyalkyl halides in the presence of potassium carbonate (K_2CO_3) in dimethylformamide (DMF) gave the haloalkoxy derivatives (V) (method A). The reverse procedure (alkylation first followed by thiazolidine formation) also effected the conversion of III to V *via* the aldehydes (VI) (method B). The physical properties of V are summarized in Table I. Treatment of the aldehydes (VI) with ethylene glycol gave the acetals (VII), which in turn were heated with substituted phenylpiperazines[2] and K_2CO_3 in DMF to give, after acidic hydrolysis, the piperazinoalkoxybenzaldehydes (IX) (method C). Alternatively, IX could also be obtained by the condensation of a hydroxybenzaldehyde (III) with the haloalkylpiperazines (VIII) (method D). The physical properties of IX are listed in Table II. Condensation of the halides (V) with various phenylpiperazines (method F) or the reaction of the aldehydes (IX) with cysteamine followed by treatment with MeNCO or MeNCS (method G) gave II (Y=O, S, R^2=H, R^3=Me). Condensation of the phenols (IV, Y=S) with the haloalkylpiperazines (VIII) also gave II (Y=S, R^2=H, R^3=Me) (method E). The physical properties of the *N*-methylthiazolidine-3-carboxamides or thiocarboxamides (II, Y=O, S, R^2=H, R^3=Me) thus obtained are summarized in Table III.

The *N*-alkyl, *N*-phenyl, or *N*-acetylthiazolidine-3-carboxamides or thiocarboxamides (II, Y=O, S, R^2=H, R^3=alkyl, phenyl, or acetyl) were similarly prepared (method G) by the

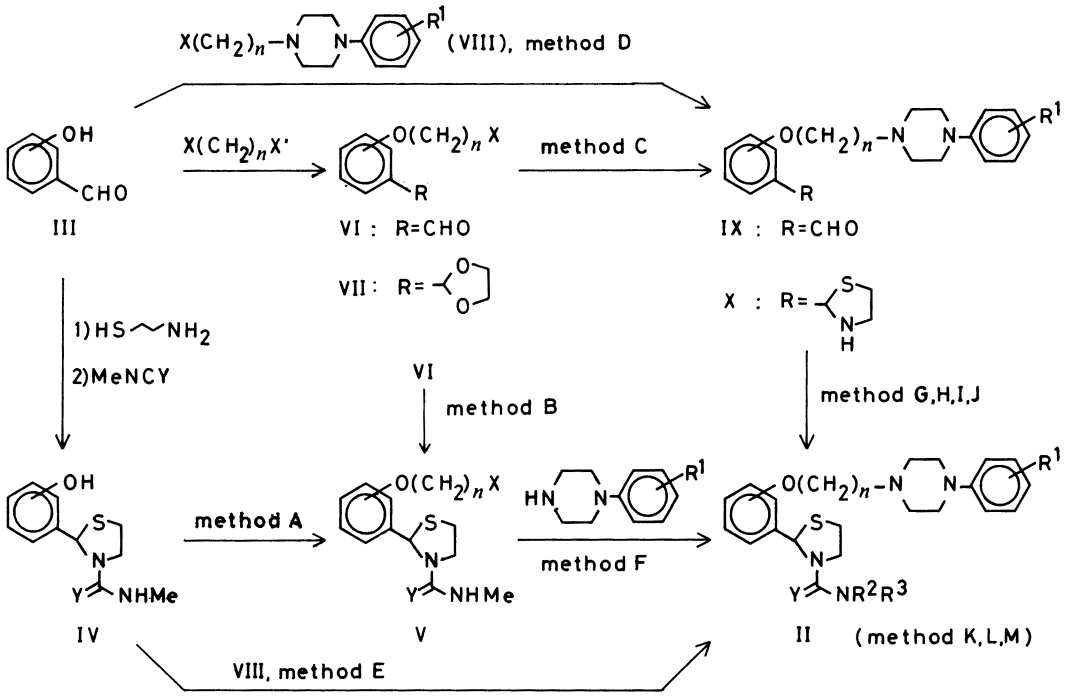


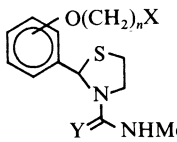
Chart 2

reaction of the intermediate thiazolidines (X) with appropriate isocyanates or isothiocyanates. Alkaline hydrolysis of the *N*-acetylthiocarboxamides (II, Y=S, R^2=H, R^3=Ac) gave the unsubstituted thiocarboxamides (II, Y=S, R^2=R^3=H) (method L). The corresponding carboxamides (II, Y=O, R^2=R^3=H) were obtained by the reaction of X with sodium cyanate (NaOCN) and acetic acid in ethanol (method H). Carbamoylation of X with dimethylcarbamoyl chloride in the presence of K_2CO_3 in DMF gave the *N*,*N*-dimethylcarboxamides (II, Y=O, R^2=R^3=Me) (method I). The reaction of X with thiophosgene followed by treatment with dimethylamine gave the *N*,*N*-dimethylthiocarboxamides (II, Y=S, R^2=R^3=Me) (method J). Acetylation of the *N*-methylthiocarboxamides (II, Y=S, R^2=H, R^3=Me) with acetyl chloride in the presence of sodium hydride in DMF gave the *N*-acetyl[3] derivatives (II, Y=S, R^2=Ac, R^3=Me) (method K). The *N*-acetyl-*N*-methylcarboxamides (II, Y=O, R^2=Ac, R^3=Me) were prepared similarly. Acetylation of the carboxamides (II, Y=O, R^2=R^3=H) with acetyl chloride and triethylamine gave diacetyl compounds,[4] which were hydrolyzed with aqueous sodium hydroxide to give the *N*-acetyl derivatives (II, Y=O, R^2=H, R^3=Ac) (method M). The physical properties of these *N*-substituted thiazolidine-3-carboxamides or thiocarboxamides are listed in Table IV.

Pharmacology and Structure–Activity Relationships

The positive inotropic activity of a series of 2-(phenylpiperazinoalkoxyphenyl)-thiazolidine-3-(thio)carboxamides (II) was determined by measuring the increase in the maximum derivative of left ventricular pressure ($LVdP/dt_{max}$) after i.v. administration to anesthetized dogs by the method reported previously.[5] The results are included in Tables III

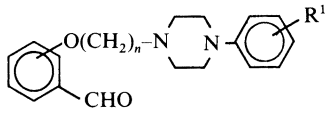
TABLE I. 2-(Haloalkoxyphenyl)-*N*-methylthiazolidine-3-(thio)carboxamides (V)



Compd. No.	Position[a]	*n*	X	Y	Method	Yield (%)	mp (°C) Recrystn. solvent[b]	Formula	Analysis (%) Calcd (Found)		
									C	H	N
a	2	2	Cl	S	B	71	153—154.5 (A)	$C_{13}H_{17}ClN_2OS_2$	49.28 (49.37	5.41 5.36	8.84 8.77)
b	2	2	Cl	O	B	70	166—167 (A)	$C_{13}H_{17}ClN_2O_2S$	51.91 (52.12	5.70 5.65	9.31 9.27)
c	2	3	Cl	S	B	53	118—120 (B–C)	$C_{14}H_{19}ClN_2OS_2$	50.82 (50.92	5.79 5.71	8.47 8.55)
d	2	3	Cl	O	B	63	128—130 (D–E)	$C_{14}H_{19}ClN_2O_2S$	53.41 (53.58	6.08 6.05	8.90 8.93)
e	2	4	Cl	S	B	47	137—143 (A)	$C_{15}H_{21}ClN_2OS_2$	52.23 (52.32	6.14 6.12	8.12 8.14)
f	4	2	Cl	S	A	67	114—116 (A)	$C_{13}H_{17}ClN_2OS_2$	49.28 (49.33	5.41 5.36	8.84 8.87)
g	4	2	Br	O	B	72	96—98.5 (B–C)	$C_{13}H_{17}BrN_2O_2S$	45.23 (45.49	4.96 4.93	8.11 8.20)
h	4	3	Cl	O	B	87	75—78 (B–C)	$C_{14}H_{19}ClN_2O_2S$	53.41 (53.63	6.08 6.12	8.90 9.05)

a) The position of the haloalkoxy group. *b*) A=EtOH, B=AcOEt, C=hexane, D=MeOH, E=Et_2O.

TABLE II. 2-(4-Phenylpiperazinoalkoxy)benzaldehydes (IX)



Compd. No.	Position[a]	n	R^1	Method	Yield (%)	mp (°C) (Recrystn. solvent[b])	^{1}H-NMR δ ($CDCl_3$, J=Hz)
1	2	2	H	C	63	79—82 (F)	2.96—2.84 (6H, m), 3.16—3.30 (4H, m), 4.24 (2H, t, J=5.5), 6.84—7.93 (9H, m), 10.52 (1H, s)
2	2	2	2-Cl	C	35	Oil	2.5—3.4 (10H, m), 4.27 (2H, t, J=6), 6.7—8.1 (8H, m), 10.53 (1H, s)
3	2	2	3-Cl	C	44	Oil	2.6—3.4 (10H, m), 4.25 (2H, t, J=6), 6.60—7.95 (8H, m), 10.49 (1H, s)
4	2	2	4-Cl	C	65	95—105 (E)	2.65—3.26 (10H, m), 4.25 (2H, t, J=6), 6.73—7.92 (8H, m), 10.48 (1H, s)
5	2	2	2-F	C	62	Oil	2.6—3.2 (10H, m), 4.27 (2H, t, J=6), 6.8—7.9 (8H, m), 10.58 (1H, s)
6	2	2	3-F	D	57	76—78 (E–C)	2.6—3.5 (10H, m), 4.30 (2H, t, J=6), 6.35—8.00 (8H, m), 10.52 (1H, s)
7	2	2	4-F	C	67	68—74 (E–C)	2.65—3.30 (10H, m), 4.25 (2H, t, J=6), 6.80—7.95 (8H, m), 10.47 (1H, s)
8	2	2	3-Me	C	38	Oil	2.32 (3H, s), 2.71—3.26 (10H, m), 4.26 (2H, t, J=5.5), 6.66—7.90 (8H, m), 10.52 (1H, s)
9	2	2	4-Me	C	44	Oil	2.26 (3H, s), 2.71—3.21 (10H, m), 4.27 (2H, t, J=5.5), 6.79—7.89 (8H, m), 10.52 (1H, s)
10	2	2	2-OMe	C	57	78—80 (E–C)	2.7—3.2 (10H, m), 3.80 (3H, s), 4.22 (2H, t, J=6), 6.85—7.95 (8H, m), 10.46 (1H, s)
11	2	2	3-OMe	C	51	Oil	2.68—3.26 (10H, m), 3.77 (3H, s), 4.25 (2H, t, J=5.5), 6.34—7.89 (8H, m), 10.51 (1H, s)
12	2	2	4-OMe	C	34	Oil	2.85—3.35 (10H, m), 3.75 (3H, s), 4.39 (2H, t, J=5), 6.88—7.92 (8H, m), 10.46 (1H, s)
13	2	2	4-NO_2	C	45	139—142 (B–C)	2.67—3.03 (6H, m), 3.36—3.52 (4H, m), 4.27 (2H, t, J=5.5), 6.71—8.19 (8H, m), 10.49 (1H, s)
14	2	3	2-Cl	C	54	Oil	1.8—2.4 (2H, m), 2.5—2.9 (6H, m), 3.0—3.3 (4H, m), 4.19 (2H, t, J=6), 6.8—8.0 (8H, m), 10.52 (1H, s)
15	2	3	3-Cl	D	61	86—90 (E–C)	1.85—2.40 (2H, m), 2.5—2.9 (6H, m), 3.1—3.4 (4H, m), 4.15 (2H, t, J=6), 6.65—8.00 (8H, m), 10.46 (1H, s)
16	2	3	4-Cl	C	25	Oil	2.01—2.26 (2H, m), 2.50—2.67 (6H, m), 2.97—3.22 (4H, m), 4.15 (2H, t, J=6), 6.78, 7.13 (2H, each, ABq, J=9), 6.8—7.9 (4H, m), 10.44 (1H, s)
17	2	3	2-F	C	68	81—84 (F)	1.95—2.40 (2H, m), 2.55—2.90 (6H, m), 3.05—3.35 (4H, m), 4.18 (2H, t, J=6), 6.90—8.00 (8H, m), 10.50 (1H, s)
18	2	3	3-F	D	63	65—79 (E–C)	1.8—2.4 (2H, m), 2.5—2.8 (6H, m), 3.1—3.35 (4H, m), 4.17 (2H, t, J=6), 6.8—7.95 (8H, m), 10.52 (1H, s)
19	2	3	4-F	C	80	54—57 (E–C)	1.9—2.3 (2H, m), 2.52—2.79 (6H, m), 3.00—3.24 (4H, m), 4.16 (2H, t, J=6), 6.84—7.93 (8H, m), 10.49 (1H, s)
20	2	3	3-Me	D	59	53—54 (E–C)	1.8—2.3 (2H, m), 2.31 (3H, s), 2.45—2.90 (6H, m), 3.15—3.40 (4H, m), 4.16 (2H, t, J=6), 6.55—7.95 (8H, m), 10.47 (1H, s)

TABLE II. (continued)

Compd. No.	Position[a]	n	R^1	Method	Yield (%)	mp (°C) (Recrystn. solvent[b])	^{1}H-NMR δ ($CDCl_3$, J=Hz)
21	2	3	4-Me	C	89	46—51 (E–C)	2.00—2.25 (2H, m), 2.25 (3H, s), 2.52—2.68 (6H, m), 3.06—3.22 (4H, m), 4.15 (2H, t, J=6), 6.70—7.90 (8H, m), 10.45 (1H, s)
22	2	3	2-OMe	C	67	104—108 (B–C)	1.9—2.3 (2H, m), 2.45—2.90 (6H, m), 2.95—3.30 (4H, m), 3.85 (3H, s), 4.18 (2H, t, J=6), 6.80—7.95 (8H, m), 10.49 (1H, s)
23	2	3	3-OMe	C	46	Oil	1.90—2.20 (2H, m), 2.52—3.26 (10H, m), 3.78 (3H, s), 4.16 (2H, t, J=6), 6.34—7.88 (8H, m), 10.51 (1H, s)
24	2	3	4-OMe	C	52	58—62 (E–C)	1.97—2.28 (2H, m), 2.55—2.71 (6H, m), 2.99—3.19 (4H, m), 3.76 (3H, s), 4.18 (2H, t, J=6), 6.87—7.95 (8H, m), 10.53 (1H, s)
25	2	3	4-NO_2	C	62	121—123.5 (B–C)	1.85—2.35 (2H, m), 2.52—2.75 (6H, m), 3.34—3.51 (4H, m), 4.18 (2H, t, J=6), 6.70—8.16 (8H, m), 10.49 (1H, s)
26	3	3	H	D	30	Oil	1.94—2.25 (2H, m), 2.63—2.85 (6H, m), 3.27—3.43 (4H, m), 4.24 (2H, t, J=6), 6.85—7.50 (9H, m), 10.10 (1H, s)
27	4	3	H	D	30	Oil	1.90—2.27 (2H, m), 2.50—2.94 (6H, m), 3.14—3.30 (4H, m), 4.14 (2H, t, J=6), 6.85—7.92 (9H, m), 9.87 (1H, s)
28	2	5	H	C	61	Oil	1.48—1.97 (6H, m), 2.37—2.67 (6H, m), 3.17—3.27 (4H, m), 4.10 (2H, t, J=6), 6.84—7.88 (9H, m), 10.52 (1H, s)

a) The position of the phenylpiperazinoalkoxy group. *b*) F=isopropyl ether and see also footnote *b*) in Table I.

and IV together with comparative data for amrinone.

The effects of varying the position of the piperazinoalkoxyl group in the benzene ring of I were examined first. Transposition of this group to the *meta* position (II_{41}) from the *ortho* position (I) caused a marked fall in activity. On the other hand, the *para* thiocarboxamides ($II_{42,44}$) retained a considerable degree of activity. In the carboxamide series, the *ortho* isomers ($II_{15,36}$) exhibited highly potent activity, whereas the corresponding *para* isomers ($II_{43,45}$) rather decreased the contractile force. The favorable effect of the *ortho* substitution is consistent with our earlier finding in the simple 2-phenyl derivatives.[1)]

Conversion of the thiocarboxamido group of I to a carboxamide group caused a marked increase in activity. The carboxamide (II_{36}) was approximately ten times as potent as I. An about thirtyfold increase in activity was also occasioned by the conversion of the thiocarboxamide (II_1) to the corresponding carboxamide (II_{15}). This tendency was generally observed in this series of compounds and constitutes a major deviation from the SAR in the 2-methoxyphenyl series, where the conversion of the thiocarboxamido group to the carboxamido group caused a marked decrease in activity.[1)]

With regard to the effect of the length of the aminoalkoxy chain on activity, the ethoxy derivatives were generally more potent than the propoxy analogues. This tendency was more pronounced in the carboxamide series (*e.g.* II_{15} *vs.* II_{36} and II_{17} *vs.* II_{37}) than in the thiocarboxamide series (*e.g.* II_1 *vs.* I and II_5 *vs.* II_{26}). Further lengthening of the alkylene chain caused a decrease in activity as shown by the pentyloxythiocarboxamide (II_{40}).

The effects of substitution on the benzene ring of the piperazine moiety were extensively examined in the thiocarboxamide series (II_{1-14} and II_{23-35}). Although no clear SAR can be

deduced, introduction of a fluoro group (II_{5-7} and II_{26-28}) tends to have a favorable effect. In the carboxamide series, the unsubstituted phenyl (II_{15}) and 2-fluorophenyl (II_{17}) derivatives exhibited the most potent activity. This was followed by the 3-fluoro (II_{18}), 4-fluoro (II_{19}), and 2-methyl (II_{20}) derivatives.

The effect of modifying the *N*-substituent in the (thio)carboxamido group was examined in a series of the *ortho* piperazinoethoxy derivatives listed in Table IV. The unsubstituted ($II_{46,49,57}$) and *N*-acetyl ($II_{47,52,55,61}$) derivatives exhibited potent activity, comparable to the corresponding *N*-methyl derivatives. This also constitutes a deviation from the SAR in the 2-methoxyphenyl series.[1] The extraordinarily long-lasting positive inotropic action with a slow onset induced by the *N*-acetate (II_{61}) may arise, at least in part, from its metabolic transformation. Lengthening of the *N*-alkyl group generally caused a decrease in activity ($II_{50-51,58,59}$). *N*-Dimethyl substitution in the carboxamido group caused a decrease in activity ($II_{48,54}$), while the corresponding thiocarboxamides ($II_{56,63}$) exhibited activity comparable to the corresponding monomethyl derivatives. Thus, there are some discrepancies in the SAR between the carboxamide and thiocarboxamide series and also between the 2-methoxyphenyl[1] and the piperazinoalkoxyphenyl series.

As a consequence of the above SAR, *N*-methyl-2-(2-(2-(4-phenylpiperazino)-ethoxy)phenyl)thiazolidine-3-carboxamide (II_{15}), which was approximately one hundred times more potent than amrinone, was selected for further study. In the isolated guinea pig heart, its minimum effective dose (MED) to cause an increase in contractile force[6] was 3 μg/heart (MED for amrinone = 10 μg/heart). After intraduodenal administration of 0.1 mg/kg to anesthetized dogs, II_{15} produced a 45% increase in LV$dP/dt_{max}$ with a 20% increase in heart rate; the positive inotropic action persisted for more than 2 h without affecting mean blood pressure. Oral administration of 0.3 mg/kg of II_{15}[7] to conscious instrumented dogs also produced potent positive inotropic action (a 26% increase in LV$dP/dt_{max}$) lasting for 5 h. Compound (II_{15}) had low toxicity in mice ($LD_{50} > 1000$ mg/kg *p.o.*).

Further studies on the synthesis and SAR of 2-phenylthiazolidine-3-(thio)carboxamides as new cardiotonic agents are in progress.

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 a Hitachi RMU-6M instrument.

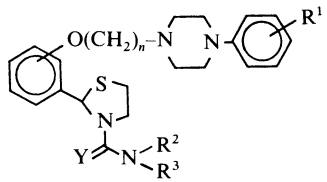
2-(2-Hydroxyphenyl)-*N*-methylthiazolidine-3-carboxamide (IVa, *o*-Isomer, Y = O)——This compound was prepared according to the reported procedure[1] from salicylaldehyde, cysteamine, and methyl isocyanate in 75% yield. mp 186—188 °C (dec.) (EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3430, 3350, 3280, 1620. ^{1}H-NMR ($CDCl_3$) δ: 2.70 (3H, d, J = 4.5 Hz), 2.90—3.25 (2H, m), 3.45—4.40 (2H, m), 5.60 (1H, br), 6.32 (1H, s), 6.62—7.35 (4H, m), 9.59 (1H, s). MS *m/z*: 238 (M^+). *Anal.* Calcd for $C_{11}H_{14}N_2O_2S$: C, 55.44; H, 5.92; N, 11.76; S, 13.45. Found: C, 55.43; H, 5.90; N, 11.80; S, 13.32. The following compounds were prepared in a similar manner.

2-(4-Hydroxyphenyl)-*N*-methylthiazolidine-3-carboxamide (IVb, *p*-Isomer, Y = O)——68% yeild. mp 218—220 °C (EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3410, 3310, 1620. ^{1}H-NMR ($CDCl_3$) δ: 2.68 (3H, d, J = 4.5 Hz), 2.90—3.13 (2H, m), 3.55—4.35 (2H, m), 5.30 (1H, br), 6.08 (1H, s), 6.76, 7.11 (2H each, ABq, J = 9 Hz), 8.94 (1H, s). MS *m/z*: 238 (M^+). *Anal.* Calcd for $C_{11}H_{14}N_2O_2S$: C, 55.44; H, 5.92; N, 11.76; S, 13.45. Found: C, 55.28; H, 5.84; N, 11.69; S, 13.41.

2-(4-Hydroxyphenyl)-*N*-methylthiazolidine-3-thiocarboxamide (IVc, *p*-Isomer, Y = S)——58% yield. mp 152—153 °C (EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3280, 1610. MS *m/z*: 254 (M^+). *Anal.* Calcd for $C_{11}H_{14}N_2OS_2$: C, 51.94; H, 5.55; N, 11.01. Found: C, 52.09; H, 5.52; N, 11.19.

2-(4-(2-Chloroethoxy)phenyl)-*N*-methylthiazolidine-3-thiocarboxamide (Vf, *p*-Isomer, *n* = 2, X = Cl, Y = S)——Method A: A mixture of IVc (*p*-isomer, Y = S, 5.0 g, 19.6 mmol), 1-chloro-2-tosyloxyethane (4.6 g, 19.6 mmol), and K_2CO_3 (4.0 g, 29.0 mmol) in DMF (20 ml) was stirred at 50 °C overnight. The mixture was diluted with water and

TABLE III. 2-(4-Phenylpiperazinoalkoxyphenyl)thiazolidine-3-(thio)carboxamides (II, $R^2 = H$, $R^3 = CH_3$)



Compd. No.	Position[a]	n	Y	R^1	Method	Yield (%)	Salt[b]	mp (°C) (Recrystn. solvent[c])	Analysis (%)[e] Calcd (Found)			Myocardial contractility Anesthetized dog[f]		
									C	H	N	Dose (mg/kg) i.v.	LVdP/dt_{max} (Δ%)	Duration (min)
1	2	2	S	H	G	72	—	124—126 (B–C)	$C_{27}H_{34}N_4OS_2$			0.1	27	20
							fum	166—168[d] (A–G)	58.04 (58.02	6.03 6.03	9.92 9.92)			
2	2	2	S	2-Cl	G	79	—	145—151 (E–C)	$C_{27}H_{33}ClN_4O_5S_2$			0.3	22	14
							fum	180—181[d] (D–G–C)	54.67 (54.76	5.61 5.66	9.45 9.49)			
3	2	2	S	3-Cl	G	58	—	147—148 (D–E)	$C_{27}H_{33}ClN_4O_5S_2$			0.1	17	> 30
							fum	151—153[d] (D–E)	54.67 (54.47	5.61 5.67	9.45 9.50)			
4	2	2	S	4-Cl	G	52	—	130—133 (E)	$C_{27}H_{33}ClN_4O_5S_2$			0.3	21	30
							fum	155—160[d] (G–E)	54.67 (54.40	5.61 5.61	9.45 9.55)			
5	2	2	S	2-F	G	70	—	143—145 (B–C)	$C_{27}H_{33}FN_4O_5S_2$			0.1	37	> 30
							fum	178—179[d] (D–E)	56.23 (56.06	5.77 5.72	9.72 9.72)			

6	2	2	S	3-F	G	92	—	132—134 (B–C)	$C_{27}H_{33}FN_4O_5S_2$			0.1	38	> 30
							fum	164[d] (D–G)	56.23 (55.98	5.77 5.75	9.72 9.63)			
7	2	2	S	4-F	G	65	—	132—133 (B–C)	$C_{27}H_{33}FN_4O_5S_2$			0.1	20	22
							fum	163—164[d] (D–G–C)	56.23 (56.11	5.77 5.72	9.72 9.68)			
8	2	2	S	2-CH_3	G	68	—	171—174 (B–A)	$C_{28}H_{36}N_4O_5S_2$			0.1	41	60
							fum	186—188[d] (G)	58.72 (58.58	6.34 6.28	9.78 9.81)			
9	2	2	S	3-CH_3	G	41	—	132—136 (A)	$C_{28}H_{36}N_4O_5S_2 \cdot 1/2\,H_2O$			0.1	23	27
							fum	157—160[d] (G)	57.81 (57.64	6.41 6.20	9.63 9.63)			
10	2	2	S	4-CH_3	G	71	—	157—160 (A)	$C_{26}H_{34}N_4O_5S_2 \cdot 1/2\,H_2O$			0.3	27	42
							1/2 fum	170—171.5[d] (A)	59.63 (60.01	6.74 6.71	10.70 10.55)			
11	2	2	S	2-OCH_3	G	86	—	161—162.5 (E)	$C_{28}O_{36}N_4O_6S_2 \cdot H_2O$			0.3	20	8.5
							fum	181—183[d] (D–G–C)	55.43 (55.38	6.31 6.13	9.23 9.27)			
12	2	2	S	3-OCH_3	G	50	—	135—138 (A–F)	$C_{28}H_{36}N_4O_6S_2$			0.1	27	40
							fum	155—159[d] (A–F)	57.12 (57.24	6.16 6.24	9.52 9.61)			
13	2	2	S	4-OCH_3	G	55	—	135—137 (B–C)	$C_{28}H_{36}N_4O_6S_2$			0.3	30	65
							fum	155—160[d] (A)	57.12 (57.37	6.16 6.36	9.52 9.80)			
14	2	2	S	4-NO_2	G	80	—	116—119 (H–B–C)	$C_{23}H_{30}ClN_5O_3S_2$			1	14	13
							HCl	218—220[d] (I–B)	52.71 (52.54	5.77 5.91	13.36 13.55)			

TABLE III. (continued)

Compd. No.	Position[a]	n	Y	R^1	Method	Yield (%)	Salt[b]	mp (°C) (Recrystn. solvent[c])	Analysis (%)[e] Calcd (Found)			Myocardial contractility Anesthetized dog[f]		
									C	H	N	Dose (mg/kg) i.v.	LV$dP/dt_{max}$ (Δ%)	Duration (min)
15	2	2	O	H	F	58	—	127—129 (B–C)	$C_{25}H_{32}N_4O_6S \cdot 1/2\,H_2O$			0.003	30	30
							ox	152—153.5[d] (G)	57.13 (57.08	6.33 6.12	10.66 10.76)			
16	2	2	O	3-Cl	F	66	—	119—121 (B–E)	$C_{25}H_{31}ClN_4O_6S$			0.03	20	10
							ox	138—139[d] (A–E)	54.49 (54.46	5.67 5.67	10.17 10.20)			
17	2	2	O	2-F	F	90	—	Oil	$C_{25}H_{31}FN_4O_6S$			0.003	20	30
							ox	175—176[d] (G)	56.17 (55.95	5.84 5.80	10.48 10.60)			
18	2	2	O	3-F	G	90	—	156—157 (G–C)	$C_{25}H_{31}FN_4O_6S$			0.01	40	35
							ox	173—175[d] (G)	56.17 (56.11	5.84 5.81	10.48 10.40)			
19	2	2	O	4-F	F	77	—	134—136 (B–C)	$C_{25}H_{31}FN_4O_6S$			0.01	25	20
							ox	120—123[d] (G)	56.17 (56.04	5.81 5.78	10.48 10.52)			
20	2	2	O	2-CH_3	F	73	—	162—163 (H–E)	$C_{26}H_{34}N_4O_6S$			0.01	30	>30
							ox	183—184[d] (A)	58.85 (59.09	6.46 6.47	10.56 10.68)			
21	2	2	O	3-CH_3	F	71	—	112—114 (B–E)	$C_{26}H_{34}N_4O_6S$			0.1	30	10
							ox	153—154[d] (A–E)	58.85 (58.98	6.46 6.56	10.56 10.73)			

22	2	2	O	3-OCH_3	F	78	—	123—124 (H–E)	$C_{26}H_{34}N_4O_7S$			0.1	45	> 30
							ox	151—152[d] (A–E)	57.13 (57.32	6.27 6.30	10.25 10.33)			
23	2	3	S	2-Cl	G	86	—	111—116 (E–C)	$C_{28}H_{35}ClN_4O_5S_2$			0.3	35	50
							fum	149—151.5[d] (G–C)	55.39 (55.34	5.81 5.87	9.23 9.08)			
24	2	3	S	3-Cl	E	52	—	151—153.5 (B–C)	$C_{28}H_{35}ClN_4O_5S_2$			0.3	22	21
							fum	143.5—145[d] (G–C)	55.39 (55.05	5.81 5.82	9.23 9.15)			
25	2	3	S	4-Cl	G	65	—	126—130 (B–C)	$C_{28}H_{35}ClN_4O_5S_2$			0.3	29	25
							fum	133—138 (A–E)	55.39 (55.29	5.81 5.77	9.23 9.17)			
26	2	3	S	2-F	G	71	—	116—118 (B–C–E)	$C_{28}H_{35}FN_4O_5S_2$			0.1	20	34
							fum	138—140[d] (G–C)	56.93 (56.74	5.97 5.94	9.48 9.56)			
27	2	3	S	3-F	G	85	—	133—134 (A–J)	$C_{28}H_{35}FN_4O_5S_2$			0.1	30	> 50
							fum	147—148[d] (G–C)	56.93 (56.83	5.97 6.02	9.48 9.37)			
28	2	3	S	4-F	G	78	—	113—116 (B–C)	$C_{28}H_{35}FN_4O_5S_2$			0.3	20	17
							fum	115—118[d] (A–E–G)	56.93 (56.78	5.97 5.93	9.48 9.24)			
29	2	3	S	2-CH_3	F	91	—	110—112 (E–C)	$C_{29}H_{38}N_4O_5S_2$			0.3	33	> 40
							fum	162—164[d] (G–C)	59.36 (59.36	6.53 6.50	9.55 9.54)			
30	2	3	S	3-CH_3	G	91	—	140—141.5 (A–J)	$C_{29}H_{38}N_4O_5S_2$			0.3	24	35
							fum	140—142 (G–C)	59.36 (59.19	6.53 6.58	9.55 9.37)			

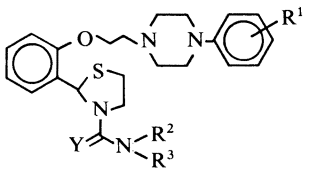
TABLE III. (continued)

Compd. No.	Position[a]	n	Y	R^1	Method	Yield (%)	Salt[b]	mp (°C) (Recrystn. solvent[c])	Analysis (%)[e] Calcd (Found)			Myocardial contractility Anesthetized dog[f]		
									C	H	N	Dose (mg/kg) i.v.	LV$dP/dt_{max}$ (Δ%)	Duration (min)
31	2	3	S	4-CH_3	G	84	—	163—165 (B–C)	$C_{29}H_{38}N_4O_5S_2$			0.3	26	34
							fum	135—138[d] (A–E–G)	59.36 (59.28	6.53 6.59	9.55 9.30)			
32	2	3	S	2-OCH_3	G	69	—	110—115 (E–C)	$C_{29}H_{38}N_4O_6S_2$			0.3	34	25
							fum	159—161 (G–C)	57.78 (57.67	6.35 6.44	9.30 9.07)			
33	2	3	S	3-OCH_3	G	63	—	149—154 (B–C)	$C_{27}H_{36}N_4O_6S_2$			0.3	30	24
							ox	154—157[d] (D–E)	56.23 (56.26	6.29 6.30	9.72 9.63)			
34	2	3	S	4-OCH_3	G	83	—	158—161 (B–C)	$C_{29}H_{38}N_4O_6S_2$			0.3	28	20
							fum	129—132 (A–G)	57.78 (57.53	6.35 6.44	9.30 8.99)			
35	2	3	S	4-NO_2	G	77	—	191—193 (H–B–C)	$C_{26}H_{33}N_5O_7S_2$			0.3	25	42
							ox	197—199[d] (D–E)	52.78 (52.48	5.62 5.56	11.84 12.01)			
36	2	3	O	H	F	66	—	85.5—90 (B–C–E)	$C_{26}H_{34}N_4O_6S$			0.03	26	21
							ox	118—130[d] (A–E)	58.85 (58.75	6.46 6.51	10.56 10.54)			
37	2	3	O	2-F	F	58	—	121—129 (K–B–C)	$C_{26}H_{33}FN_4O_6S$			0.3	20	30
							ox	126—134[d] (A–E)	56.92 (56.87	6.06 6.09	10.21 10.27)			

38	2	3	O	3-F	F	68	—	103—105 (B–C)	$C_{26}H_{33}FN_4O_6S$			0.1	25	30
							ox	150—151.5[d] (A–E–G)	56.92 (56.85	6.06 6.10	10.21 10.21)			
39	2	4	S	H	F	40	—	105—110 (K)	$C_{29}H_{38}N_4O_5S_2$			0.3	34	40
							fum	145—147 (G–C)	59.36 (59.56	6.53 6.49	9.55 9.44)			
40	2	5	S	H	G	34	—	121.5—123.5 (K–F)	$C_{28}H_{38}N_4O_5S_2$			1	−8	
							ox	173—175[d] (A–D–E)	58.51 (58.31	6.66 6.59	9.75 9.73)			
41	3	3	S	H	G	72	—	Oil	$C_{28}H_{36}N_4O_5S_2$			1	5	8
							fum	144—148[d] (A–E–G)	58.72 (58.81	6.34 6.60	9.78 9.64)			
42	4	2	S	H	F	66	—	Oil	$C_{23}H_{33}Cl_3N_4OS_2$			0.3	24	20
							3HCl	164—167[d] (A–E–G)	50.04 (50.15	6.06 6.13	10.15 10.17)			
43	4	2	O	H	F	79	—	85—91 (B–C)	$C_{25}H_{32}N_4O_6S$			1	−8	
							ox	125—130[d] (G)	58.12 (57.98	6.24 6.20	10.85 10.63)			
44	4	3	S	H	G	69	—	146—149 (K)	$C_{26}H_{34}N_4O_5S_2$			0.3	27	65
							ox	115—120 (D–E)	57.12 (56.90	6.27 6.22	10.25 9.99)			
45	4	3	O	H	F	70	—	129—130 (B–C)	$C_{26}H_{34}N_4O_6S$			0.03	−15	
							ox	122—127[d] (G)	58.85 (58.65	6.46 6.41	10.56 10.44)			
I[g]	2	3	S	H								0.3	68	60
Amrinone												0.3	25	25

a) The position of the phenylpiperazinoalkoxy group. *b*) fum = fumarate, ox = oxalate. *c*) G = acetone, H = chloroform, I = dimethylformamide, J = H_2O, K = isopropanol. See also footnote *b* in Tables I and II. *d*) With decomposition. *e*) Elemental analysis for the salt. *f*) Myocardial contractility was examined with the salts. For methodology, see reference 5. *g*) See reference 1.

TABLE IV. 2-(2-(2-(4-Phenylpiperazino)ethoxy)phenyl)thiazolidine-3-(thio)carboxamides (II, *o*-Isomer, $n=2$)



Compd. No.	Y	R^1	R^2	R^3	Method	Yield (%)	Salt[a]	mp (°C) (Recrystn. solvent[b])	Analysis (%)[d] Calcd (Found)			Myocardial contractility Anesthetized dog[e]		
									C	H	N	Dose (mg/kg) i.v.	LV$dP/dt_{max}$ (Δ%)	Duration (min)
46	O	H	H	H	H	82	—	137—139 (B)	$C_{24}H_{30}N_4O_6S$			0.003	34	45
							ox	146—150.5[c] (D–G)	57.35 (57.64	6.06 6.37	11.15 10.95)			
47	O	H	H	$COCH_3$	M	46	—	137—139 (B–C)	$C_{25}H_{31}N_4O_4S \cdot 1/2\,H_2O$			0.003	28	20
							1/2 ox	164—168[c] (G)	59.03 (58.75	6.34 6.02	11.02 10.72)			
48	O	H	CH_3	CH_3	I	58	—	100—102 (F)	$C_{26}H_{34}N_4O_6S$			0.1	21	25
							ox	167—168.5[c] (G)	58.85 (58.83	6.46 6.45	10.56 10.43)			
49	O	3-F	H	H	H	88	—	142—143 (B–E)	$C_{24}H_{29}FN_4O_6S$			0.01	38	20
							ox	104—105[c] (D–E)	55.37 (55.40	5.62 5.60	10.76 10.64)			
50	O	3-F	H	C_2H_5	G	89	—	116—118 (B–C)	$C_{26}H_{33}FN_4O_6S$			0.03	22	23
							ox	197—198[c] (J–G–E)	56.92 (57.08	6.06 6.06	10.21 10.28)			

51	O	3-F	H	C_4H_9	G	71	—	93—95.5 (E–F–C)	$C_{30}H_{39}FN_4O_6S$			0.1	28	3
							fum	165—167[c] (A–F)	59.78 (59.64	6.52 6.52	9.30 9.33)			
52	O	3-F	H	$COCH_3$	M	50	—	142—143 (B–E)	$C_{26}H_{31}FN_4O_7S$			0.01	26	40
							ox	165—166[c] (A)	55.50 (55.60	5.55 5.63	9.96 10.01)			
53	O	3-F	$COCH_3$	CH_3	K	29	—	Oil	$C_{27}H_{33}FN_4O_7S$			0.03	39	35
							ox	110—117[c] (D–G–C)	56.24 (56.45	5.77 5.79	9.72 9.58)			
54	O	3-F	CH_3	CH_3	I	50	—	90.5—93 (F)	$C_{26}H_{33}FN_4O_6S$			0.03	74	33
							ox	171—172.5[c] (A–G–E)	56.92 (56.96	6.06 6.09	10.21 10.19)			
55	S	H	H	$COCH_3$	G	56	—	139—140.5 (B–C)	$C_{26}H_{32}N_4O_6S_2$			0.1	22	25
							ox	156—157[c] (G)	55.69 (55.72	5.75 5.83	9.99 9.77)			
56	S	H	CH_3	CH_3	J	46	—	Oil	$C_{26}H_{34}N_4O_5S_2$			0.1	32	30
							ox	90—100 (G)	57.12 (57.14	6.27 6.30	10.25 10.13)			
57	S	3-F	H	H	L	90	—	136—137 (E)	$C_{24}H_{29}FN_4O_3S$			0.03	44	23
							1/2 fum	164—165[c] (A–E)	57.12 (57.24	5.79 5.84	11.10 11.06)			
58	S	3-F	H	C_2H_5	G	99	—	Oil	$C_{26}H_{33}FN_4O_5S_2$			0.3	30	25
							ox	148—151[c] (G)	55.30 (55.01	5.89 6.08	9.92 9.65)			
59	S	3-F	H	C_4H_9	G	94	—	Oil	$C_{30}H_{39}FN_4O_5S_2 \cdot 1/2\,H_2O$			0.3	27	32
							fum	168—170.5[c] (G–C)	57.40 (57.65	6.42 6.25	8.92 8.79)			

TABLE IV. (continued)

Compd. No.	Y	R^1	R^2	R^3	Method	Yield (%)	Salt[a]	mp (°C) (Recrystn. solvent[b])	Analysis (%)[d] Calcd (Found)			Myocardial contractility Anesthetized dog[e]		
									C	H	N	Dose (mg/kg) i.v.	LVdP/dt_{max} (Δ%)	Duration (min)
60	S	3-F	H	C_6H_5	G	62	—	124—126 (B–C)	$C_{32}H_{35}FN_4O_5S_2$			0.3	29	7
							fum	161.5—164[c] (A–D)	60.17 (59.94	5.52 5.42	8.77 8.70)			
61	S	3-F	H	$COCH_3$	G	49	—	151—152 (A–E)	$C_{26}H_{31}FN_4O_6S_2$			0.1	50	190
							ox	121—122[c] (A–E)	53.96 (53.71	5.40 5.47	9.68 9.66)			
62	S	3-F	$COCH_3$	CH_3	K	77	—	Oil	$C_{27}H_{33}FN_4O_6S_2$			0.1	30	20
							ox	106—109[c] (G–E)	54.71 (54.61	5.61 5.63	9.45 9.47)			
63	S	3-F	CH_3	CH_3	J	60	—	Oil	$C_{26}H_{33}FN_4O_5S_2$			0.1	36	20
							ox	79—84 (G)	55.30 (55.59	5.89 5.82	9.92 10.00)			

a—*e*) See footnote *b*—*f*, respectively, in Table III.

extracted with AcOEt. The extracts were washed successively with 10% aq. NaOH and water, and evaporated. The residue was purified by silica gel chromatography with AcOEt–$CHCl_3$ (1 : 4) and recrystallized from EtOH to give 3.95 g of Vf as colorless prisms. IR ν_{max}^{Nujol} cm^{-1}: 3325. ^{1}H-NMR ($CDCl_3$) δ: 3.02 (3H, d, J = 4 Hz), 2.98—3.20 (2H, m), 3.79 (2H, t, J = 5 Hz), 4.22 (2H, t, J = 5 Hz), 4.13—4.74 (2H, m), 5.44 (1H, br), 6.21 (1H, s), 6.88, 7.22 (2H each, ABq, J = 9 Hz), MS m/z: 318, 316 (M^+).

2-(2-Chloroethoxy)benzaldehyde (VIa, *o*-Isomer, *n* = 2, X = Cl)——A mixture of salicylaldehyde (40 g, 0.328 mol), 1-chloro-2-tosyloxyethane (84 g, 0.358 mol), and K_2CO_3 (50 g, 0.362 mol) in DMF (270 ml) was stirred at room temperature for 68 h. The mixture was poured into water and the liberated oil was extracted with Et_2O. The extracts were washed with 10% aq. NaOH, H_2O, dried, and evaporated. The residue was distilled under reduced pressure to give 51.8 g (86%) of VIa[8] as an oil. bp 116—118 °C (0.2 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 3.84 (2H, t, J = 5.5 Hz), 4.33 (2H, t, J = 5.5 Hz), 6.86—7.87 (4H, m), 10.47 (1H, s). The following compounds were prepared in a similar manner.

2-(3-Chloropropoxy)benzaldehyde (VIb, *o*-Isomer, *n* = 3, X = Cl)——85% yield. bp 125—129 °C (0.3 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 2.30 (2H, m), 3.76 (2H, t, J = 6 Hz), 4.24 (2H, t, J = 6 Hz), 6.80—7.89 (4H, m), 10.44 (1H, s).

2-(4-Chlorobutoxy)benzaldehyde (VIc, *o*-Isomer, *n* = 4, X = Cl)——95% yield. bp 142—144 °C (0.35 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.93—2.11 (4H, m), 3.63 (2H, distorted t, J = 6 Hz), 4.12 (2H, distorted t, J = 6 Hz), 6.88—7.89 (4H, m), 10.47 (1H, s).

2-(5-Bromopentyloxy)benzaldehyde (VId, *o*-Isomer, *n* = 5, X = Br)——72% yield. bp 148—157 °C (0.35 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.45—2.10 (6H, m), 3.44 (2H, t, J = 6.5 Hz), 4.10 (2H, t, J = 5.8 Hz), 6.91—7.88 (4H, m), 10.51 (1H, s).

4-(2-Bromoethoxy)benzaldehyde (VIe, *p*-Isomer, *n* = 2, X = Br)——21% yield. bp 119—132 °C (0.4 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 3.63 (2H, t, J = 6 Hz), 4.35 (2H, t, J = 6 Hz), 6.95, 7.77 (2H each, ABq, J = 9 Hz), 9.81 (1H, s).

4-(3-Chloropropoxy)benzaldehyde (VIf, *p*-Isomer, *n* = 3, X = Cl)——77% yield. bp 130—140 °C (0.35 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 2.26 (2H, m), 3.75 (2H, t, J = 6 Hz), 4.20 (2H, t, J = 6 Hz), 7.00, 7.82 (2H, each ABq, J = 9 Hz), 9.86 (1H, s).

2-(2-(2-Chloroethoxy)phenyl)-*N*-methylthiazolidine-3-thiocarboxamide (Va, *o*-Isomer, *n* = 2, X = Cl, Y = S)——Method B: This compound was prepared from VIa, cysteamine, and methyl isothiocyanate by the method of the preceding paper.[1] IR ν_{max}^{Nujol} cm^{-1}: 3325. ^{1}H-NMR ($CDCl_3$) δ: 3.02 (3H, d, J = 4.5 Hz), 3.10 (2H, t, J = 5 Hz), 3.80—4.01 (2H, m), 4.12—4.85 (4H, m), 5.50 (1H, br), 6.41 (1H, s), 6.85—7.47 (4H, m). Compounds Vb—e, g, h were prepared in a similar manner and their physical properties are summarized in Table I.

2-(2-Chloroethoxy)benzaldehyde Ethylene Acetal (VIIa, *o*-Isomer, *n* = 2, X = Cl)——A solution of VIa (46.5 g, 0.25 mol), ethylene glycol (33.2 g, 0.53 mol), and 85% phosphoric acid (0.5 ml) in benzene (500 ml) was refluxed for 18 h with a Dean-Stark water separator. The reaction mixture was cooled to room temperature and washed with aq. $NaHCO_3$. The organic layer was washed with water, dried, and evaporated. The residue was distilled under reduced pressure to afford 56 g (97%) of VIIa as an oil. bp 130—135 °C (0.3 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 3.71—4.37 (8H, m), 6.18 (1H, s), 6.80—7.60 (4H, m). The following compounds were prepared in a similar manner.

2-(3-Chloropropoxy)benzaldehyde Ethylene Acetal (VIIb, *o*-Isomer, *n* = 3, X = Cl)——94% yield. bp 136—137 °C (0.2 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 2.32 (2H, m), 3.81 (2H, t, J = 6 Hz), 4.13 (4H, m), 4.22 (2H, t, J = 6 Hz), 6.20 (1H, s), 6.79—7.63 (4H, m).

2-(4-Chlorobutoxy)benzaldehyde Ethylene Acetal (VIIc, *o*-Isomer, *n* = 4, X = Cl)——90% yield. bp 165—167 °C (0.4 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.65—2.25 (4H, m), 3.48—3.80 (2H, m), 3.90—4.20 (6H, m), 6.15 (1H, s), 6.80—7.59 (4H, m).

2-(5-Bromopentyloxy)benzaldehyde Ethylene Acetal (VIId, *o*-Isomer, *n* = 5, X = Br)——88% yield. bp 160—165 °C (0.35 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.72—2.12 (6H, m), 3.34 (2H, t, J = 6 Hz), 3.84—4.17 (6H, m), 6.04 (1H, s), 6.71—7.49 (4H, m).

4-(2-Bromoethoxy)benzaldehyde Ethylene Acetal (VIIe, *p*-Isomer, *n* = 2, X = Br)——90% yield. bp 144—155 °C (0.4 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 3.10 (2H, t, J = 6 Hz), 3.90—4.40 (6H, m), 5.72 (1H, s), 6.85, 7.39 (2H each, ABq, J = 9 Hz).

4-(3-Chloropropoxy)benzaldehyde Ethylene Acetal (VIIf, *p*-Isomer, *n* = 3, X = Cl)——85% yield. bp 151—156 °C (0.3 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 2.19 (2H, m), 3.69 (2H, t, J = 6 Hz), 3.90—4.30 (7H, m), 5.72 (1H, s), 6.87, 7.38 (2H each, ABq, J = 9 Hz).

2-(2-(4-Phenylpiperazino)ethoxy)benzaldehyde (IX_1)——Method C: A mixture of VIIa (18.3 g, 80 mmol), *N*-phenylpiperazine (13.6 g, 84 mmol), NaI (12.0 g, 80 mmol), and K_2CO_3 (12.2 g, 88 mmol) in DMF (200 ml) was stirred at 100 °C for 5 h under an argon atmosphere. The mixture was concentrated to one-third of the initial volume and poured into water. The liberated oil was extracted with AcOEt. The extracts were washed with water, dried, and evaporated *in vacuo*. The residue was dissolved in a mixture of tetrahydrofuran (THF) (50 ml) and 10% aq. HCl (30 ml). After being stirred for 1 h at room temperature, the mixture was made alkaline with 10% aq. NaOH, diluted with water, and extracted with AcOEt. The extracts were washed with water, dried, and evaporated. The residue was purified by silica gel chromatography with AcOEt–benzene (1 : 1) and recrystallized from isopropyl ether to give 15.5 g of IX_1. IR ν_{max}^{Nujol} cm^{-1}: 1680. MS m/z: 310 (M^+). Compounds $IX_{2-5,7-14,16,17,19,21-25,28}$ were prepared in a similar manner and their physical properties are listed in Table II.

1-(2-Chloroethyl)-4-(3-fluorophenyl)piperazine (VIIIa, $n=2$, $R^1=$3-F, X=Cl)——Thionyl chloride (12 g) was added dropwise to a stirred solution of 4-(3-fluorophenyl)-1-piperazinoethanol[9] (5.90 g, 26.3 mmol) in $CHCl_3$ (120 ml). The mixture was refluxed for 1 h and evaporated to dryness. The residue was recrystallized from EtOH–Et_2O to give 6.70 g (91.2%) of the dihydrochloride of VIIIa as needles, mp 215—217 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 2000—2550, 1610, 1510. MS *m/z*: 242 (M^+), 206, 150. ^{1}H-NMR (D_2O) δ: 3.40—4.15 (12H, m), 6.75—7.55 (4H, m).

1-(3-Chlorophenyl)-4-(3-chloropropyl)piperazine (VIIIb, $n=3$, $R^1=$3-Cl, X=Cl)——A mixture of 4-(3-chlorophenyl)-1-piperazinopropanol[9] (2.0 g, 7.86 mmol) and triphenylphosphine (2.06 g, 7.86 mmol) in CCl_4 (20 ml) was refluxed overnight. After cooling, the precipitate was filtered off, and the filtrate was concentrated. The residue was chromatographed on silica and eluted with AcOEt–benzene (1 : 4) to give 1.50 g (70%) of VIIIb as an oil. MS *m/z*: 274, 272 (M^+), 211, 209. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.2 (2H, m), 2.4—2.9 (6H, m), 3.1—3.4 (4H, m), 3.60 (2H, t, $J=6$ Hz), 6.65—7.50 (4H, m). The following compounds were prepared in a similar manner.

1-(3-Chloropropyl)-4-(3-fluorophenyl)piperazine (VIIIc, $n=3$, $R^1=$3-F, X=Cl)——72% yield. Oil. ^{1}H-NMR ($CDCl_3$) δ: 1.84—2.15 (2H, m), 2.25—2.75 (6H, m), 3.04—3.45 (4H, m), 3.58 (2H, t, $J=6$ Hz), 6.30—7.45 (4H, m).

1-(3-Chloropropyl)-4-(3-methylphenyl)piperazine (VIIId, $n=3$, $R^1=$3-CH_3, X=Cl)——79% yield. Oil. ^{1}H-NMR ($CDCl_3$) δ: 1.90—2.29 (2H, m), 2.30 (3H, s), 2.35—2.80 (6H, m), 3.10—3.40 (4H, m), 3.61 (2H, t, $J=6$ Hz), 6.60—7.60 (4H, m).

1-(3-Chloropropyl)-4-phenylpiperazine (VIIIe, $n=3$, $R^1=$H, X=Cl)——74% yield. Oil. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.2 (2H, m), 2.3—2.8 (6H, m), 3.1—3.4 (4H, m), 3.61 (2H, t, $J=6$ Hz), 6.5—7.5 (5H, m).

2-(3-(4-(3-Chlorophenyl)piperazino)propoxy)benzaldehyde (IX_{15})——Method D: A mixture of salicylaldehyde (0.67 g, 5.5 mmol), VIIIb (1.50 g, 5.5 mmol), and K_2CO_3 (0.76 g) in DMF (10 ml) was stirred at 60 °C overnight. The mixture was diluted with water and extracted with AcOEt. The extracts were washed with water, dried, and evaporated. The residue was purified by silica gel chromatography with AcOEt–benzene (1 : 4) and recrystallized from Et_2O–hexane to give 1.20 g of IX_{15}. IR ν_{max}^{Nujol} cm^{-1}: 1680. Compounds $IX_{6,18,20,26,27}$ were prepared in a similar manner and their physical properties are listed in Table II.

2-(2-(3-(4-(3-Chlorophenyl)piperazino)propoxy)phenyl)-*N*-methylthiazolidine-3-thiocarboxamide (II_{24})——Method E: A mixture of IV[1] (*o*-isomer, Y=S, 0.51 g, 2.2 mmol), VIIIb (0.60 g, 2.2 mmol), K_2CO_3 (0.28 g, 2 mmol), and NaI (0.29 g, 2 mmol) in DMF (10 ml) was stirred at 80 °C overnight. The mixture was concentrated, diluted with water, and extracted with AcOEt. The extracts were washed successively with 10% aq. NaOH and water, and evaporated. The residue was purified by silica gel chromatography with AcOEt–benzene (2 : 3) and recrystallized from AcOEt–hexane to give 0.51 g of II_{24} as needles. IR ν_{max}^{Nujol} cm^{-1}: 3400. MS *m/z*: 490 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.75—2.4 (2H, m), 2.5—2.81 (6H, m), 2.9—3.4 (9H, m), 4.0—4.7 (4H, m), 5.4 (1H, br), 6.31 (1H, s), 6.6—7.5 (8H, m).

***N*-Methyl-2-(2-(2-(4-(2-methylphenyl)piperazino)ethoxy)phenyl)thiazolidine-3-carboxamide (II_{20})**——Method F: A mixture of Vb (2.10 g, 7 mmol), 1-(2-methylphenyl)piperazine (1.23 g, 7 mmol), K_2CO_3 (0.97 g, 7 mmol), and NaI (1.05 g, 7 mmol) in DMF (20 ml) was heated at 80 °C for 20 h. After removal of the solvent, the residue was diluted with water and extracted with AcOEt. The extracts were washed with water, dried, and evaporated. The residue was purified by silica gel chromatography with AcOEt–MeOH (40 : 1) and recrystallized from $CHCl_3$–Et_2O to give 2.26 g of II_{20}. IR ν_{max}^{Nujol} cm^{-1}: 3280, 1630. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s), 2.50—3.30 (15H, m), 3.50—4.80 (5H, m), 6.22 (1H, s), 6.80—7.50 (8H, m). MS *m/z*: 440 (M^+). Compounds $II_{15-17,19,21,22,29,36-39,42,43,45}$ were prepared in a similar manner and their properties are listed in Table III.

***N*-Methyl-2-(2-(2-(4-phenylpiperazino)ethoxy)phenyl)thiazolidine-3-thiocarboxamide (II_1)**——Method G: This compound was prepared according to the reported procedure[1] from IX_1, cysteamine, and methyl isothiocyanate. IR ν_{max}^{Nujol} cm^{-1}: 3375. MS *m/z*: 442 (M^+), 369. ^{1}H-NMR ($CDCl_3$) δ: 2.69—3.33 (12H, m), 3.01 (3H, d, $J=4.5$ Hz), 4.24 (2H, t, $J=5$ Hz), 4.24—4.83 (2H, m), 5.56 (1H, br), 6.37 (1H, s), 6.70—7.42 (9H, m). Compounds $II_{2-14,18,23,25-28,30-35,40,41,44,50,51,55,58-61}$ were prepared in a similar manner and their properties are listed in Tables III and IV.

2-(2-(2-(4-Phenylpiperazino)ethoxy)phenyl)thiazolidine-3-carboxamide (II_{46})——Method H: A solution of acetic acid (2.46 g, 41 mmol) in EtOH (5 ml) was added dropwise to a suspension of X (*o*-isomer, $n=2$, $R^1=$H; 3.03 g, 8.2 mmol, prepared from the corresponding benzaldehyde and cysteamine) and sodium cyanate (1.07 g, 16.4 mmol) in EtOH (40 ml). After being stirred for 2 h at room temperature, the mixture was made alkaline with 10% aq. K_2CO_3, concentrated, and extracted with AcOEt. The extracts were washed with water, dried over Na_2SO_4, and evaporated. The residue was recrystallized from AcOEt to give 2.22 g of II_{46}. IR ν_{max}^{Nujol} cm^{-1}: 1640. ^{1}H-NMR ($CDCl_3$) δ: 2.66—3.30 (12H, m), 3.57—4.43 (4H, m), 4.81 (2H, br s), 6.25 (1H, s), 6.83—7.38 (9H, m). MS *m/z*: 412 (M^+). Compound II_{49} was prepared in a similar manner and its properties are listed in Table IV.

***N,N*-Dimethyl-2-(2-(2-(4-phenylpiperazino)ethoxy)phenyl)thiazolidine-3-carboxamide (II_{48})**——Method I: A mixture of X (*o*-isomer, $n=2$, $R^1=$H; 2.00 g, 5.4 mmol), dimethylcarbamoyl chloride (0.87 g, 8.1 mmol), and K_2CO_3 (1.19 g, 8.6 mmol) in DMF (20 ml) was heated at 50 °C for 5 h. The mixture was poured into water and extracted with AcOEt. The extracts were washed with water, dried, and evaporated. The residue was purified by silica gel chromatography with AcOEt–benzene (5 : 1) and recrystallized from isopropyl ether to give 1.39 g of II_{48}. IR ν_{max}^{Nujol} cm^{-1}: 1620. ^{1}H-NMR ($CDCl_3$) δ: 2.68—3.74 (12H, m), 2.81 (6H, s), 3.94—4.58 (4H, m), 6.24 (1H, s), 6.69—7.32 (9H, m). Compound II_{54} was prepared in a similar manner and its properties are listed in Table IV.

***N*,*N*-Dimethyl-2-(2-(2-(4-phenylpiperazino)ethoxy)phenyl)thiazolidine-3-thiocarboxamide (II_{56})**——Method J: A solution of X (*o*-isomer, $n=2$, $R^1=H$; 1.60 g, 4.3 mmol) in THF (30 ml) was added to a stirred solution of thiophosgene (1.00 g, 8.6 mmol) in THF (20 ml) under ice-cooling over a period of 3 h, and then dimethylamine (1.56 g, 34.6 mmol) in toluene (15 ml) was added to the mixture. After being stirred for 30 min at room temperature, the mixture was poured into 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–benzene (1 : 1) to give 0.90 g of II_{56} as an oil. IR ν_{max}^{film} cm^{-1}: 1600, 1500. ^{1}H-NMR ($CDCl_3$) δ: 2.70—3.65 (12H, m), 3.13 (6H, s), 3.75—3.89 (1H, m), 4.21 (2H, t, $J=6$ Hz), 4.45—4.90 (1H, m), 6.66—7.34 (10H, m). MS *m/z*: 456 (M^+). Compound II_{63} was prepared in a similar manner and its properties are listed in Table IV.

***N*-Acetyl-2-(2-(2-(4-(3-fluorophenyl)piperazino)ethoxy)phenyl)-*N*-methylthiazolidine-3-thiocarboxamide (II_{62})**——Method K: A solution of II_6 (1.90 g, 4.1 mmol) in DMF (10 ml) was added to a suspension of NaH (60% oil dispersion, 0.18 g, 4.5 mmol) in DMF (5 ml) under ice-cooling, and the mixture was stirred for 20 min under an argon atmosphere. A solution of acetyl chloride (0.36 g, 4.5 mmol) in Et_2O (10 ml) was added to the mixture, and the whole was stirred at room temperature overnight. After dilution with water, the mixture was 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 : 1) to afford 1.60 g of II_{62} as an oil. IR ν_{max}^{film} cm^{-1}: 1670. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s), 2.30—3.50 (15H, m), 4.00—4.80 (4H, m), 6.10—7.50 (9H, m). MS *m/z*: 502 (M^+). Compound II_{53} was prepared in a similar manner and its properties are listed in Table IV.

2-(2-(2-(4-(3-Fluorophenyl)piperazino)ethoxy)thiazolizine-3-thiocarboxamide (II_{57})——Method L: This compound was prepared according to the reported procedure[1] from II_{61} and 10% aq. NaOH. IR ν_{max}^{Nujol} cm^{-1}: 3430, 3310, 3180. ^{1}H-NMR ($CDCl_3$) δ: 2.60—3.40 (12H, m), 4.10—4.80 (4H, m), 5.76 (2H, br s), 6.35 (1H, s), 6.30—7.50 (8H, m).

***N*-Acetyl-2-(2-(2-(4-phenylpiperazino)ethoxy)phenyl)thiazolidine-3-carboxamide (II_{47})**——Method M: A mixture of II_{46} (1.49 g, 3.5 mmol), triethylamine (0.55 g, 5.4 mmol), and acetyl chloride (0.42 g, 5.4 mmol) in benzene (60 ml) was heated at 80 °C for 1.5 h. An additional amount of triethylamine (0.55 g, 5.4 mmol) and acetyl chloride (0.42 g, 5.4 mmol) was added to the mixture, and the whole was heated at 80 °C for 1 h. The mixture was concentrated, diluted with water, and extracted with AcOEt. The extracts were washed with water, dried, and evaporated. The residue was purified by silica gel chromatography with AcOEt–benzene (1 : 1) and recrystallized from $CHCl_3$–Et_2O to give 1.25 g (70%) of the diacetate of II_{46}[4] as crystals, mp 120—123.5 °C. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1700, 1680. MS *m/z*: 496 (M^+), 368, 189, 175, 132. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (6H, m), 2.67—2.32 (12H, m), 3.98—4.31 (4H, m), 6.85—7.47 (10H, m). The diacetate (1.19 g, 2.4 mmol) was hydrolyzed by treatment with a mixture of NaOH (0.29 g, 7.2 mmol), H_2O (2.7 ml), EtOH (20 ml), and THF (20 ml) under ice-cooling for 1.5 h. The mixture was concentrated, diluted with water, and extracted with AcOEt. The extracts were washed with water, dried, and evaporated. The residue was purified by silica gel chromatography with AcOEt–$CHCl_3$ (5 : 1) and recrystallized from AcOEt–hexane to give 0.72 g (67%) of II_{47} as colorless prisms. IR ν_{max}^{Nujol} cm^{-1}: 3260, 1690, 1680, 1660, 1600. MS *m/z*: (M^+ was not observed) 369, 309, 237, 186, 175, 132. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 2.67—3.38 (12H, m), 3.72—4.49 (4H, m), 6.44 (1H, s), 6.88—7.44 (9H, m), 7.94 (1H, s). Compounds II_{52} was prepared in a similar manner from II_{49} and its properties are listed in Table IV.

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