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Synthesis of 2-Phenylthiazolidine Derivatives as Cardiotonic Agents. V.[1] Modification of the Thiazolidine Moiety of 2-(Phenylpiperazinylalkoxyphenyl)thiazolidine-3-thiocarboxamides and the Corresponding Carboxamides

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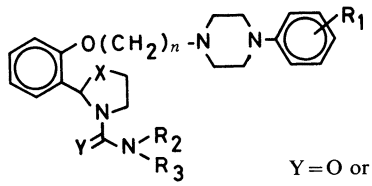
The carba (**2**) and oxa analogues (**3**) of 2-(phenylpiperazinylalkoxyphenyl)thiazolidine-3-carboxamide (**1**, Y=O) and -thiocarboxamide (**1**, Y=S) were synthesized and tested for cardiotonic activity. These analogues (**2** and **3**) were prepared from the aldehydes (**4**) through several intermediates (**7**, **10**, and **13**). In a series of the *N*-methylcarboxamides, positive inotropic activity in anesthetized dogs decreased in the following order: the thiazolidine (**1a**)≫oxazolidine (**3a**)>pyrrolidine (**2a**). In the corresponding thiocarboxamide series, however, the oxazolidine (**3b**) was the most potent, followed by the thiazolidine (**1b**) and the pyrrolidine (**2c**).

Keywords——2-arylthiazolidine-3-thiocarboxamide; 2-arylthiazolidine-3-carboxamide; 2-arylpyrrolidine-3-thiocarboxamide; 2-arylpyrrolidine-3-carboxamide; 2-aryloxazolidine-3-thiocarboxamide; 2-aryloxazolidine-3-carboxamide; cardiotonic agent; positive inotropic activity; structure–activity relationship

Previous papers of this series[1-4] described the synthesis and cardiotonic activity of a series of new 2-phenylthiazolidine-3-carboxamides and thiocarboxamides (**1**). These compounds exhibited marked and sustained positive inotropic activity without producing significant effects on heart rate or blood pressure in anesthetized dogs. Although the effect of various substituents in structure **1** on the activity became apparent through those studies, the effect of modification of the thiazolidine ring remained unclear. Our continued interest in the structure–activity relationships (SAR) of this class of compounds as a new class of cardiotonic agents led us to attempt replacement of the sulfur atom of the thiazolidine ring of **1** with carbon and oxygen. In this report we describe the synthesis and cardiotonic activity of the pyrrolidine (**2**) and oxazolidine (**3**), which are carba and oxa analogues of **1**, respectively.



Y=O or S

1: X=S
2: X=CH_2
3: X=O

Chart 1

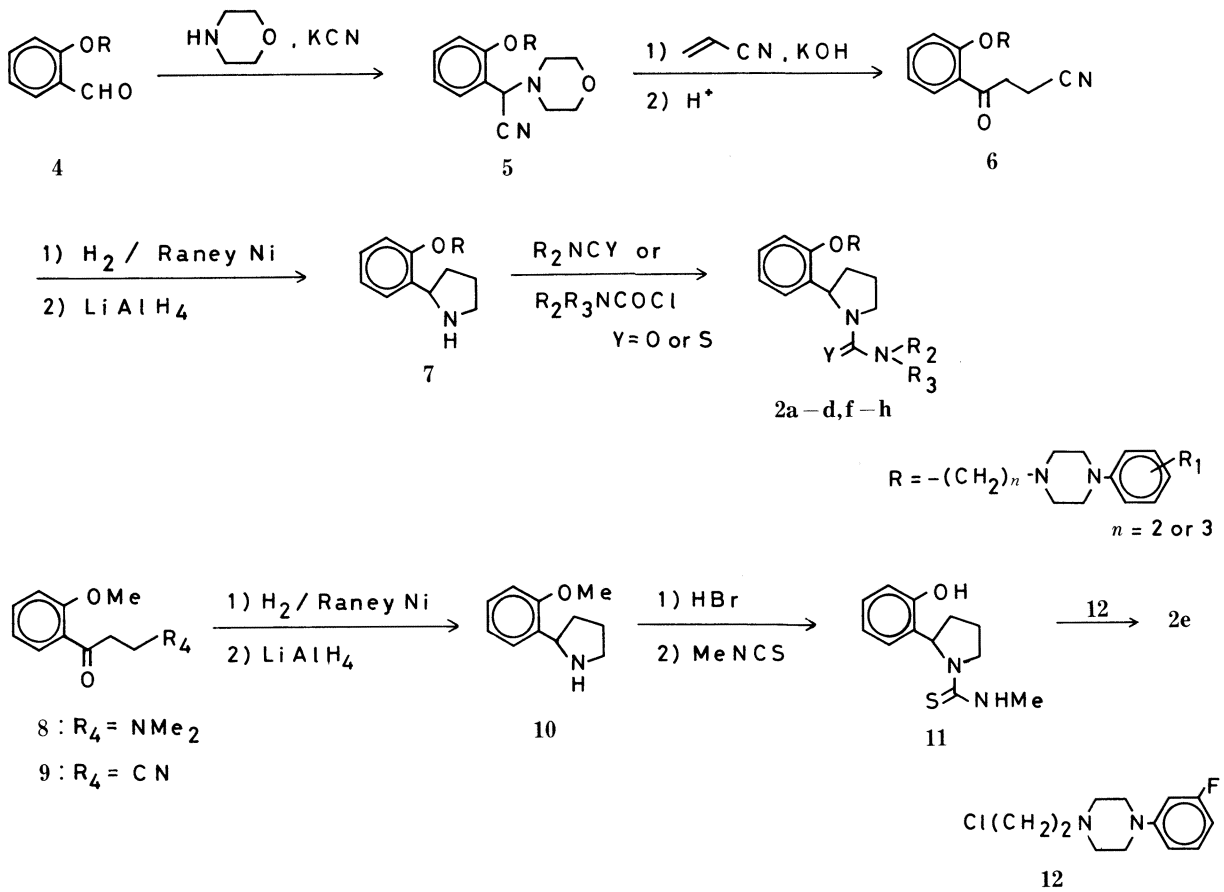
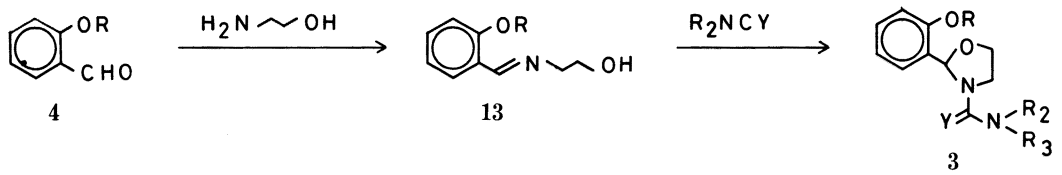

OR
CHO
HN O , KCN
OR
N O
CN
1) CN , KOH
2) H+
OR
CN
O
4
5
6
1) H2 / Raney Ni
2) LiAlH4
OR
N
H
R2NCY or
R2R3NCOCl
Y=O or S
OR
N
Y N R2
R3
7
2a–d,f–h
R = -(CH2)n-N N R1
n = 2 or 3
OMe
R4
O
1) H2 / Raney Ni
2) LiAlH4
OMe
N
H
1) HBr
2) MeNCS
OH
N
S NHMe
12
2e
8 : R4 = NMe2
9 : R4 = CN
10
11
Cl(CH2)2 N N F
12

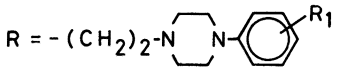
Chart 2

Chemistry

Synthesis of the pyrrolidine analogue (**2**) was carried out through the sequence of reactions outlined in Chart 2. Reaction of the benzaldehyde (**4**)[3] with morpholine and potassium cyanide gave the aminonitrile (**5**). Cyanoethylation of **5** followed by acidic hydrolysis[5] readily gave the ketonitrile (**6**). Catalytic hydrogenation of **6** over Raney Ni and reduction of the resulting pyrroline with lithium aluminum hydride ($LiAlH_4$)[6] gave the pyrrolidine (**7**). Carbamoylation or thiocarbamoylation of **7** by the usual method gave the carboxamide or thiocarboxamide derivatives (**2a**—**d**, **f**—**h**) listed in Table I.

As an alternative route to **2**, introduction of an aminoalkyl side chain into the phenolic thiocarboxamide (**11**) was attempted. The aminoketone (**8**)[7] was converted to the ketonitrile (**9**), which, on hydrogenation over Raney Ni and $LiAlH_4$ reduction, gave the pyrrolidine (**10**). *O*-Demethylation of **10** followed by treatment with methyl isothiocyanate (MeNCS) gave the phenolic thiocarboxamide (**11**). Alkylation of **11** with the aminoethyl chloride (**12**)[3] gave the aminoether (**2e**) (Table I) in only low yield (6.4%), probably due to concomitant *S*-alkylation of the thiocarboxamide group.





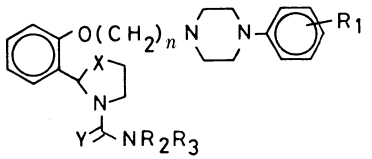
a: Y=O, $R_1=R_3=H$, $R_2=Me$
b: Y=S, $R_1=R_3=H$, $R_2=Me$
c: Y=S, R_1=3-F, $R_2=Me$, $R_3=H$
d: Y=O, $R_1=R_2=R_3=H$
e: Y=O, $R_1=R_3=H$, $R_2=COCH_3$

Chart 3

The oxazolidine analogue (**3**) was also synthesized from the benzaldehyde (**4**) (Chart 3). Condensation of aromatic aldehydes with ethanolamine has been claimed to give oxazolidines directly[8] or Schiff bases[9] without definite structural elucidation. When the aldehyde (**4**) was heated in benzene with continuous removal of water, the Schiff base (**13**) was obtained in quantitative yield. The spectroscopic data of **13** both in solution and in the solid state were in good agreement with the iminocarbinol structure and are given in the experimental section. The structure of **13** ($R_1=H$) was further confirmed by X-ray crystallographic analysis (Fig. 1). On treatment with methyl isocyanate in tetrahydrofuran, the Schiff base (**13**, $R_1=H$) gave the carbamoylated oxazolidine (**3a**) in 82.6% yield. The presence of a singlet at δ 6.36 in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum and absence of an OH absorption in the infrared (IR) spectrum are consistent with the assigned structure. Similar formation of *N*-acyl-2-aryl oxazolidines from benzylideneaminoethanol by treatment with acylating agents has been reported by several workers.[10] Treatment of **13** with MeNCS similarly gave the oxazolidine-3-thiocarboxamide (**3b**, **c**). The unsubstituted 3-carboxamide (**3d**) was obtained from **13** by treatment with trimethylsilyl isocyanate (TMSNCO)[11] followed by hydrolytic work-up.

Acetylation of **3d** with acetyl chloride gave the diacetate of **3d** in 86.8% yield. Hydrolysis of the diacetate with aq. sodium hydroxide solution gave the *N*-acetylurea (**3e**). The physical properties of **3a**—**e** are summarized in Table I. These oxazolidines were quite susceptible to

TABLE I. 2-(2-(Phenylpiperazinoalkoxy)phenyl)pyrrolidines and Oxazolidines (**2** and **3**)



Compd. No.	n	X	Y	R_1	R_2	R_3	Yield (%)	Salt	mp (°C) (Recrystn. solvent)[b]	Analysis (%) Calcd (Found) C H N	Myocardial contractility[g] Anesthetized dog Dose mg/kg i.v.	LVdP/dt_{max} Δ%	Duration (min)
2a	2	CH_2	O	H	CH_3	H	65.4	—	151.5—154 (A)				
								Ox[a]	165—168[c] (B)	$C_{24}H_{32}N_4O_2 \cdot C_2H_2O_4$ 62.64 6.87 11.24 (62.73 6.84 11.20)	0.3	16	17
2b	2	CH_2	O	3-F	CH_3	H	78.8	—	159—163 (A)				
								Ox	180.5—182.5[c] (C)	$C_{24}H_{31}FN_4O_2 \cdot C_2H_2O_4 \cdot H_2O$ 58.42 6.60 10.48 (58.36 6.32 10.26)	0.03	22	20
2c	2	CH_2	S	H	CH_3	H	59.5	—	100—103 (A)				
								Ox	163—168[c] (D)	$C_{24}H_{32}N_4OS \cdot C_2H_2O_4$ 60.68 6.66 10.89 (60.62 6.83 11.08)	0.1	27	25
2d	3	CH_2	O	H	CH_3	H	78.8	—	105—108 (A)				
								Ox	118—123[c] (E)	$C_{25}H_{34}N_4O_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$ 62.17 7.15 10.74 (62.50 7.01 10.56)	0.1	23	15
2e	2	CH_2	S	3-F	CH_3	H	6.4[d]	—	94—99 (A)				
								Ox	149—152[c] (F)	$C_{24}H_{31}FN_4OS \cdot C_2H_2O_4$ 58.63 6.24 10.52 (58.51 6.21 10.34)	0.03	39	40

2f	2	CH_2	O	H	CH_3CO	H	76.0	—	130—131 (A)			0.03	30	27
								Ox	169.5—170[c] (F)	$C_{25}H_{32}N_4O_3 \cdot C_2H_2O_4$	61.59 6.51 10.64 (61.86 6.67 10.69)			
2g	2	CH_2	O	H	H	H	75.3	—	122—124 (A)					
								Ox	136—138[c] (F)	$C_{23}H_{30}N_4O_2 \cdot C_2H_2O_4 \cdot 0.33H_2O$	61.21 6.71 11.42 (61.25 6.96 11.31)	0.03	26	13
2h	2	CH_2	O	H	CH_3	CH_3	85.6	—	Oil —					
								Ox	156—158[c] (F)	$C_{25}H_{34}N_4O_2 \cdot C_2H_2O_4$	63.26 7.08 10.93 (63.02 7.04 10.92)	0.03	27	21
3a	2	O	O	H	CH_3	H	82.6	—	129—132 (A)	$C_{23}H_{30}N_4O_3$	67.29 7.37 13.65 (67.25 7.35 13.71)	0.1	25	21
3b	2	O	S	H	CH_3	H	76.5	—	125—127 (G)	$C_{23}H_{30}N_4O_2S$	67.76 7.09 13.13 (67.89 7.19 13.01)	0.03	20	21
3c	2	O	S	3-F	CH_3	H	57.5	—	83—88 (H)	$C_{23}H_{29}FN_4O_2S$	62.14 6.57 12.60 (62.33 6.62 12.47)	0.01	19	45
3d	2	O	O	H	H	H	30.3	—	165—168 (I)	$C_{22}H_{28}N_4O_3$	66.65 7.12 14.13 (66.35 7.25 14.38)	0.1	32	29
3e	2	O	O	H	CH_3CO	H	55.4[e]	—	123—125 (A)	$C_{24}H_{30}N_4O_4$	65.73 6.90 12.78 (65.99 6.71 12.84)	0.03	27	30
1a[f]	2	S	O	H	CH_3	H						0.003	30	30
1b[f]	2	S	S	H	CH_3	H						0.1	27	20
Amrinone												0.3	25	24

a) Ox represents oxalate. *b*) A = AcOEt–hexane, B = acetone–MeOH–Et_2O, C = acetone–hexane, D = MeOH, E = EtOH–Et_2O, F = acetone, G = AcOEt–Et_2O, H = iso-PrOH–iso-Pr_2O, I = EtOH. *c*) With decomposition. *d*) Yield from **11**. *e*) Yield from **3d**. *f*) See reference 3. *g*) Myocardial contractility was examined with the salts. For methodology, see reference 12.

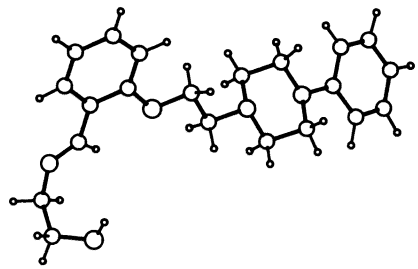


Fig. Perspective Drawing of the Molecule of **13**

acidic hydrolysis and decomposed to the aldehyde (**4**) even during salt formation with oxalic acid. After examination of the stability of various salts of **3**, the D-glucuronate was found to be the most stable salt. The oxazolidines (**3a**—**e**) were, therefore, converted to their D-glucuronates in ether, and the precipitated amorphous powder was used for assessment of cardiotonic activity without purification.

Pharmacology and Structure–Activity Relationships

The positive inotropic activity of the pyrrolidine (**2a**—**h**) and oxazolidine (**3a**—**e**) analogues prepared in the present study was determined by measuring the increase in the maximum derivative of left ventricular pressure ($LVdP/dt_{max}$) after i.v. administration to anesthetized dogs.[12] The results are included in Table I together with comparative data for the corresponding thiazolidine derivatives (**1a**, **b**) and amrinone.

Generally, the pyrrolidine and oxazolidine analogues (**2** and **3**) exhibited stronger positive inotropy than amrinone. The thiocarboxamides (**2c** and **3b**) were more potent than the corresponding carboxamides (**2a** and **3a**) in both the pyrrolidine and oxazolidine series. This constitutes a major deviation from the SAR in the thiazolidine series,[3] where the carboxamide (**1a**) was much more potent than the thiocarboxamide (**1b**). As in the previous case,[3] introduction of a fluoro group onto the benzene ring of the piperazine moiety produced a significant increase in activity (**2a** *vs.* **2b**, **2c** *vs.* **2e**, and **3b** *vs.* **3c**). As for the effect of the substituent on the (thio)carboxamide group, the *N*-acetyl derivatives (**2f** and **3e**) were more active than the corresponding *N*-methyl derivatives (**2a** and **3a**). This tendency was more pronounced in the pyrrolidine series, where the *N*-dimethyl (**2h**) and unsubstituted (**2g**) derivatives also showed potent activity. Finally, the effects of the conversion of the thiazolidine to the oxazolidine and pyrrolidine rings on the activity varied with the nature of the *N*-substituents. Looking at a series of the *N*-methylcarboxamides, one observes that positive inotropic activity decreases in the following order: the thiazolidine (**1a**) $\gg$ oxazolidine (**3a**) > pyrrolidine (**2a**). In the corresponding thiocarboxamide series, however, the oxazolidine (**3b**) was the most potent, followed by the thiazolidine (**1b**) and pyrrolidine (**2c**). This is in sharp contrast with the SAR in a series of simple 2-phenylthiazolidine-3-thiocarboxamides,[4] where the conversion of the thiazolidine ring to the oxazolidine ring caused a marked fall in activity. These results suggest an important role of the phenylpiperazine group in the appearance of positive inotropy in this series of compounds.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Hitachi IR-215 spectrometer. ^{1}H-NMR spectra were taken in $CDCl_3$, unless otherwise noted, 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.

Analytical data are given in Table I, unless otherwise noted.

α-(2-(2-(4-Phenylpiperazinyl)ethoxy)phenyl)-4-morpholineacetonitrile (5, $n=2$, $R_1=H$)——A mixture of mor-

pholine (120 g, 1.38 mol), *p*-toluenesulfonic acid (hydrate, 10.1 g, 0.0531 mol), 2-(2-(4-phenylpiperazinyl)-ethoxy)benzaldehyde[3] (15 g, 0.0484 mol), and tetrahydrofuran (THF) (50 ml) was heated at 80 °C for 1.5 h. Then, a solution of KCN (4.7 g, 0.0722 mol) in H_2O (50 ml) was added to the mixture, and the whole was heated at 100 °C for 1.5 h. After cooling, the reaction mixture was extracted with AcOEt. The AcOEt extracts were washed with water, dried, and evaporated. The residue was digested with a mixture of AcOEt–hexane and filtered to give 18.3 g (93.1%) of **5** ($n=2$, $R_1=H$), mp 108—110 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 1600. MS *m/z*: 406 (M^+), 379, 321, 186. ^{1}H-NMR δ: 2.53—2.94 (10H, m), 3.13—3.29 (4H, m), 3.60—3.75 (4H, m), 4.19 (2H, t, $J=6.2$ Hz), 5.13 (1H, s, >CHCN), 6.82—7.50 (9H, m). *Anal.* Calcd for $C_{24}H_{30}N_4O_2$: C, 70.91; H, 7.44; N, 13.78. Found: C, 71.15; H, 7.49; N, 13.64.

The 3-fluorophenyl analogue (**5**, $n=2$, $R_1=3$-F) was similarly obtained in a quantitative yield as an oil. IR ν_{max}^{liquid} cm^{-1}: 1610, 1580. MS *m/z*: 424 (M^+), 397, 339, 204.

The propyloxy analog (**5**, $n=3$, $R_1=H$) was similarly obtained in 98.6% yield and had mp 109—110 °C (from Et_2O–hexane). *Anal.* Calcd for $C_{25}H_{32}N_4O_2$: C, 71.40; H, 7.67; N, 13.32. Found: C, 71.58; H, 7.60; N, 13.53.

3-(2-(2-(4-Phenylpiperazinyl)ethoxy)benzoyl)propionitrile (6, $n=2$, $R_1=H$)——A methanolic KOH solution (30%, 1 ml) was added to a stirred solution of **5** ($n=2$, $R_1=H$; 35 g, 0.086 mol) in THF (200 ml). A solution of acrylonitrile (6.85 g, 0.129 mol) in THF (50 ml) was then added to the mixture, and the whole was stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* and extracted with AcOEt. The extracts were washed with H_2O, dried, and evaporated. The residue was dissolved in a solution of AcOH (100 ml), H_2O (50 ml), and THF (200 ml) and allowed to stand at room temperature for 20 h. The solution was evaporated, made basic with aq. 10% K_2CO_3, and extracted with AcOEt. The extracts were washed with H_2O, dried, and evaporated. The residue was purified by SiO_2 chromatography (benzene–AcOEt (1 : 1)) and recrystallized from AcOEt–hexane to give 22.6 g (72.2%) of **6** ($n=2$, $R_1=H$), mp 98—100 °C. IR ν_{max}^{Nujol} cm^{-1}: 2240, 1660, 1590. MS *m/z*: 363 (M^+), 189, 175. ^{1}H-NMR δ: 2.58—2.99 (8H, m), 3.08—3.62 (6H, m), 4.24 (2H, t, $J=6.2$ Hz), 6.80—7.95 (9H, m). The oxalate was recrystallized from MeOH and had mp 173.5—174.5 °C (dec.). *Anal.* Calcd for $C_{24}H_{27}N_3O_6$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.50; H, 5.99; N, 9.36.

The 3-fluorophenyl analogue (**6**, $n=2$, $R_1=3$-F) was similarly obtained in 63.7% yield as an oil. IR ν_{max}^{liquid} cm^{-1}: 2220, 1660, 1600, 1580. MS *m/z*: 381 (M^+), 207, 193.

The propyloxy analogue (**6**, $n=3$, $R_1=H$) was similarly obtained in 57.3% yield and had mp 70—72 °C (from AcOEt–hexane). *Anal.* Calcd for $C_{23}H_{27}N_3O_2$: C, 73.18; H, 7.21; N, 11.13. Found: C, 73.31; H, 7.29; N, 11.23.

2-(2-(2-(4-Phenylpiperazinyl)ethoxy)phenyl)pyrrolidine (7, $n=2$, $R_1=H$)——A mixture of **6** ($n=2$, $R_1=H$; 10 g, 0.0275 mol), Raney Ni (40 ml), and EtOH (400 ml) was hydrogenated at room temperature and atmospheric pressure. After 5 h, the catalyst and solvent were removed, and the residue was dissolved in THF (100 ml). The solution was added to a stirred suspension of $LiAlH_4$ (2 g, 0.0527 mol) in THF (20 ml), and the whole was refluxed for 1.5 h. The mixture was decomposed by addition of moist Et_2O, and inorganic materials were filtered off. The filtrate was diluted with AcOEt, washed with H_2O, dried, and evaporated. The residue was purified by chromatography on SiO_2 ($CHCl_3$–MeOH–Et_3N (23 : 1 : 1)) to give 7.93 g (82.1%) of **7** ($n=2$, $R_1=H$) as an oil. IR ν_{max}^{liquid} cm^{-1}: 3300, 1590. MS *m/z*: 351 (M^+), 350, 349, 219, 217. ^{1}H-NMR δ: 1.52—2.24 (4H, m), 2.30—2.96 (8H, m), 3.05—3.49 (5H, m), 4.18 (2H, t, $J=6$ Hz), 3.95—4.55 (1H, m, CH-N), 6.50—7.60 (9H, m).

The 3-fluorophenyl analogue (**7**, $n=2$, $R_1=3$-F) was similarly obtained in 53.8% yield as an oil. IR ν_{max}^{liquid} cm^{-1}: 3300, 1600, 1580. MS *m/z*: 369 (M^+), 259, 245, 233, 219.

The propyloxy analogue (**7**, $n=3$, $R_1=H$) was similarly obtained in 47.3% yield as an oil. IR ν_{max}^{liquid} cm^{-1}: 3300, 1590, 1490, 750. MS *m/z*: 365 (M^+), 364, 233, 231, 173, 162.

***N*-Methyl-2-(2-(2-(4-phenylpiperazinyl)ethoxy)phenyl)pyrrolidine-1-carboxamide (2a)**——According to the method[4] described previously, the title compound (**2a**) was obtained from **7** ($n=2$, $R_1=H$; 1.50 g, 0.00427 mol) and methyl isocyanate (0.29 g, 0.00508 mol) in a yield of 1.14 g (65.4%) as colorless needles. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1630. MS *m/z*: 409, 408 (M^+), 407, 406, 393, 302, 290, 289, 277, 271, 219. ^{1}H-NMR δ: 1.57—2.50 (4H, m), 2.60—3.00 (9H, m), 3.17—3.32 (4H, m), 3.67 (2H, br t, $J=5.2$ Hz), 4.11 (2H, t, $J=8$ Hz), 3.82—4.40 (1H, m), 5.06 (1H, dd, $J=2$, 7 Hz), 6.50—7.50 (9H, m).

Compounds **2b—d**, **f—h** were also prepared from **7** by the reported procedure.[4]

3-(2-Methoxybenzoyl)propionitrile (9)——A mixture of **8**·hydrochloride (28.5 g, 0.117 mol) and potassium cyanide (25 g, 0.384 mol) in H_2O (200 ml) was refluxed for 15 min with stirring. After being cooled, the mixture was made acidic with 10% aq. HCl and extracted with AcOEt. The extract was washed with H_2O, dried, and evaporated. Chromatographic purification of the residue (SiO_2, benzene) gave 7.90 g (35.7%) of **9** as an oil. IR ν_{max}^{liquid} cm^{-1}: 2240, 1665, 1595, 755. MS *m/z*: 189 (M^+), 162, 135. ^{1}H-NMR δ: 2.57—2.80 (2H, m), 3.26—3.50 (2H, m), 3.90 (3H, s), 6.89—7.85 (4H, m).

2-(2-Methoxyphenyl)pyrrolidine (10)——According to the method described for the preparation of **7**, the title compound (**10**) was obtained from **9** (7.90 g, 0.0418 mol) in a yield of 5.96 g (80.6%) as an oil. IR ν_{max}^{liquid} cm^{-1}: 3300 (br), 1590, 750. MS *m/z*: 177 (M^+), 176, 160, 148, 137. ^{1}H-NMR δ: 1.55—2.25 (5H, m), 2.65—3.35 (2H, m), 3.80 (3H, s), 4.23—4.47 (1H, m), 6.74—7.45 (4H, m).

2-(2-Hydroxyphenyl)-*N*-methylpyrrolidine-1-thiocarboxamide (11)——A mixture of **10**·HCl (1.53 g, 0.0072 mol)

and 48% aq. HBr (10 ml) was heated at 120 °C for 4 h and then evaporated. The residue was made basic with aq. $NaHCO_3$ solution and extracted with AcOEt. The extract was dried and evaporated, and the residue was dissolved in EtOH (25 ml). Methyl isothiocyanate (0.7 g, 0.0096 mol) was added to the solution, and the mixture was refluxed for 2 h then evaporated. The residue was purified by SiO_2 chromatography ($CHCl_3$–EtOH (40 : 1)) to give, after recrystallization from MeOH–Et_2O, 0.69 g (40.8%) of **11**, mp 200—202 °C. IR ν_{max}^{Nujol} cm^{-1}: 3320, 3200, 1590, 1530. MS *m/z*: 236 (M^+), 219, 162. ^{1}H-NMR ($CDCl_3$–DMSO-d_6): δ: 1.40—2.30 (4H, m), 3.00 (3H, d, J=5.0 Hz), 3.80—4.15 (2H, m), 5.25—5.40 (1H, m), 5.90 (1H, br), 6.75—7.30 (4H, m), 9.15 (1H, s). *Anal.* Calcd for $C_{12}H_{16}N_2OS$: C, 60.99; H, 6.82; N, 11.85; S, 13.57. Found: C, 61.14; H, 6.78; N, 11.71; S, 13.39.

2-(2-(2-(4-(3-Fluorophenyl)piperazinyl)ethoxy)phenyl)-*N*-methylpyrrolidine-1-thiocarboxamide (2e)——A mixture of **11** (0.64 g, 0.0027 mol), 1-(2-chloroethyl)-4-(3-fluorophenyl)piperazine (**12**) hydrochloride[3] (0.76 g, 0.0027 mol), K_2CO_3 (0.37 g, 0.0027 mol), and NaI (0.405 g, 0.0027 mol) in dimethylformamide (DMF) (10 ml) was heated at 90 °C for 10 h. A further amount of **12**·HCl (0.38 g, 0.0014 mol) was added to the mixture, and the whole was heated at 90 °C for 8 h. The reaction mixture was concentrated, diluted with H_2O, and extracted with AcOEt. The extract was washed with H_2O, dried and evaporated. The residue was purified by chromatography on SiO_2 ($CHCl_3$–Me_2CO (5 : 1)) to give 0.075 g (6.4%) of **2e**, mp 94—99 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3300, 1600, 1550, 1480, 750. MS *m/z*: 442 (M^+), 368, 292, 236, 219, 193, 162, 150.

2-(2-(2-(4-Phenylpiperazinyl)ethoxy)benzylideneamino)ethanol (13)——A solution of **4** (n=2, R_1=H[3]; 10.24 g, 0.033 mol) and ethanolamine (2.12 g, 0.035 mol) in benzene (200 ml) was refluxed for 6 h with continuous removal of H_2O. The solution was washed with sat. NaCl solution, dried, and evaporated. The residue was digested with iso-Pr_2O and filtered to give 11.5 g (98.6%) of **13** (n=2, R_1=H), mp 106—112 °C. The analytical sample was recrystallized from CCl_4 and had mp 115—118 °C. IR ν_{max}^{Nujol} cm^{-1}: 3200 (br), 1630, 1590. MS *m/z*: 353 (M^+), 308, 221, 188, 132, 119. ^{1}H-NMR δ: 2.50—3.26 (11H, m), 3.62—3.77 (4H, m), 4.13 (2H, t, J=6.0 Hz), 6.81—7.49 (8H, m), 7.85—7.99 (1H, m), 8.74 (1H, s). *Anal.* Calcd for $C_{21}H_{27}N_3O_2$: C, 71.36; H, 7.70; N, 11.89. Found: C, 71.52; H, 7.79; N, 11.74.

The 3-fluorophenyl analogue (**13**, n=2, R_1=3-F) was similarly obtained in quantitative yield as an oil. IR ν_{max}^{liquid} cm^{-1}: 3400—3200, 1630, 1610, 1580, 1490, 750. MS *m/z*: 371 (M^+), 326, 221, 206, 204, 193, 191, 150, 137, 122. ^{1}H-NMR δ: 2.45—2.96 (7H, m), 3.13—3.28 (4H, m), 3.56—3.95 (4H, m), 4.18 (2H, t, J=5.8 Hz), 6.41—7.60 (7H, m), 7.89—8.02 (1H, m), 8.77 (1H, s).

***N*-Methyl-2-(2-(2-(4-phenylpiperazinyl)ethoxy)phenyl)oxazolidine-3-carboxamide (3a)**——A mixture of **13** (R_1 = H; 1.98 g, 0.0056 mol), methyl isocyanate (0.48 g, 0.0084 mol), and THF (50 ml) was heated at 50 °C for 3.5 h. Then, a further amount of methyl isocyanate (0.32 g, 0.0056 mol) was added to the mixture, and the whole was heated at 50 °C for 30 min. The reaction mixture was evaporated and the residue was purified by chromatography on SiO_2 to give, after recrystallization from AcOEt–hexane, 1.9 g (82.6%) of **3a**, mp 129—132 °C. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1620. MS *m/z*: 410 (M^+), 395, 353, 278, 221, 132. ^{1}H-NMR δ: 2.66—4.34 (19H, m), 4.59—4.65 (1H, br s), 6.36 (1H, s), 6.80—7.40 (9H, m).

The thiocarboxamides (**3b, c**) were prepared from **13** in the same manner as described above.

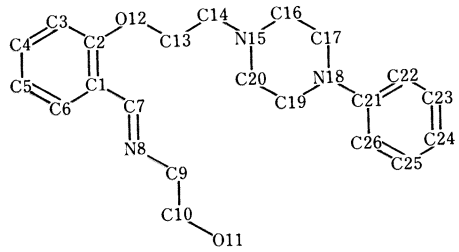
2-(2-(2-(4-Phenylpiperazinyl)ethoxy)phenyl)oxazolidine-3-carboxamide (3d)——A solution of TMSNCO[11] (2.94 g, 0.0255 mol) in CH_2Cl_2 (6 ml) was added to a stirred solution of **13** (R_1 = H; 6 g, 0.017 mol) in CH_2Cl_2 (70 ml) under ice-cooling, and the mixture was stirred at room temperature for 2 d. A further amount (1.96 g, 0.017 mol) of TMSNCO was added to the mixture, and the whole was stirred for 24 h. The reaction mixture was washed with H_2O, dried, and evaporated. The residue was purified by chromatography on SiO_2 ($CHCl_3$–MeOH (30 : 1)) to give 2.04 g (30.3%) of **3d**, mp 165—168 °C (from EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3440, 3420, 3140, 1660. MS *m/z*: 396 (M^+), 381, 353, 221, 188, 175, 132, 119. ^{1}H-NMR δ: 2.64—4.34 (16H, m), 5.02 (2H, br s), 6.44 (1H, s), 6.76—7.50 (9H, m).

***N*-Acetyl-2-(2-(2-(4-phenylpiperazinyl)ethoxy)phenyl)oxazolidine-3-carboxamide (3e)**——Acetyl chloride (0.776 g, 0.0099 mol) was added to a solution of **3d** (0.979 g, 0.0025 mol), Et_3N (1 ml), THF (30 ml), and toluene (20 ml), and the mixture was heated at 80 °C for 45 min. The mixture was evaporated, and the residue was diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried, and evaporated. The residue was purified by chromatography on SiO_2 ($CHCl_3$–MeOH (50 : 1)) to give 1.03 g (86.6%) of the diacetate of **3d** as an amorphous powder. MS *m/z*: 480 (M^+), 465, 352, 189, 175, 132. A solution of NaOH (0.257 g, 0.0064 mol) in H_2O (2.5 ml) was added to a stirred solution of the diacetate (1.03 g, 0.0021 mol) in THF (10 ml) and EtOH (8 ml) under ice-cooling. The mixture was stirred under ice-cooling for 30 min. After addition of sat. NaCl solution (80 ml), the reaction mixture was adjusted to pH 7.0 with 10% aq. HCl solution and extracted with AcOEt. The extract was washed with sat. NaCl solution, dried, and evaporated. The residue was purified by chromatography on SiO_2 ($CHCl_3$–MeOH (50 : 1)) to give, after recrystallization from AcOEt–hexane, 0.6 g, (64%) of **3e**, mp 123—125 °C. IR ν_{max}^{Nujol} cm^{-1}: 3270, 1700, 1680, 1600. MS *m/z*: 438 (M^+), 353, 308, 221, 186, 132. ^{1}H-NMR δ: 2.37 (3H, s), 2.64—4.40 (16H, m), 6.51 (1H, s), 7.22—7.55 (9H, m), 8.02 (1H, m).

Crystal Data for 13——$C_{21}H_{27}N_3O_2$, M_r=353.47, monoclinic, a=21.635 (1), b=8.264 (1), c=11.249 (1) Å, β=104.409 (4)°, V=1948.0 (2) Å^3, D_c=1.205 g/cm^3, space group $P2_1/a$.

X-Ray Analysis——A single crystal of **13** was obtained from CCl_4. The diffraction intensities were measured on a four-circle diffractometer (Rigaku AFC-5) using graphite-monochromated CuK_α radiation. The intensities of 3315 independent reflections were collected and used in the structure determination. The structure was solved by the direct

TABLE II. Fractional Coordinates ($\times 10^4$) and Isotropic Thermal Parameters ($Å^2$) for **13**



Atom	x	y	z	B_{eq}	Atom	x	y	z	B_{eq}
C(1)	4974 (1)	3857 (3)	3215 (2)	4.9 (0.1)	C(14)	4532 (1)	1065 (4)	6495 (3)	5.6 (0.1)
C(2)	4488 (1)	3055 (3)	3596 (2)	4.7 (0.1)	N(15)	4103 (1)	358 (3)	7183 (2)	5.0 (0.1)
C(3)	3873 (1)	2949 (4)	2812 (3)	5.1 (0.1)	C(16)	3723 (2)	1627 (4)	7593 (3)	11.1 (0.2)
C(4)	3759 (2)	3625 (4)	1658 (3)	5.6 (0.1)	C(17)	3286 (2)	907 (5)	8309 (3)	12.4 (0.2)
C(5)	4236 (2)	4414 (4)	1264 (3)	6.7 (0.2)	N(18)	3647 (1)	3 (3)	9364 (2)	7.7 (0.1)
C(6)	4834 (2)	4518 (3)	2041 (3)	6.4 (0.1)	C(19)	4046 (1)	−1224 (3)	8993 (2)	6.4 (0.1)
C(7)	5619 (1)	3942 (3)	4035 (2)	5.0 (0.1)	C(20)	4474 (1)	−467 (4)	8281 (2)	6.2 (0.1)
N(8)	6102 (1)	4288 (3)	3644 (2)	6.1 (0.1)	C(21)	3352 (1)	−354 (3)	10315 (2)	4.9 (0.1)
C(9)	6717 (1)	4289 (4)	4546 (3)	5.0 (0.2)	C(22)	2764 (1)	314 (4)	10360 (3)	5.4 (0.2)
C(10)	7117 (1)	2876 (4)	4307 (3)	5.9 (0.2)	C(23)	2520 (2)	73 (5)	11366 (3)	6.0 (0.2)
O(11)	6873 (1)	1369 (3)	4586 (2)	6.0 (0.1)	C(24)	2836 (2)	−844 (5)	12354 (3)	6.3 (0.2)
O(12)	4662 (1)	2381 (3)	4736 (2)	5.7 (0.1)	C(25)	3406 (2)	−1536 (5)	12307 (3)	8.1 (0.2)
C(13)	4184 (1)	1580 (4)	5214 (3)	5.3 (0.1)	C(26)	3668 (2)	−1322 (4)	11315 (3)	7.7 (0.2)

Isotropic thermal parameters are in the form $B_{eq}=4/3\sum_i\sum_j \beta_{ij}\boldsymbol{a}_i\cdot\boldsymbol{a}_j$.

method using MULTAN and refined by the block-diagonal least-squares method. The final R index was 0.054. Fractional coordinates and thermal parameters are listed in Table II.

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