Studies on Cerebral Protective Agents. VII.[1a] Synthesis of Novel 4-Arylazole Derivatives with Anti-anoxic Activity

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Novel 4-arylazole (*i.e.* thiazole, oxazole, and imidazole) derivatives, possessing an amino moiety at the C-5 position of the azole ring, were prepared and tested for anti-anoxic (AA) activity in mice. Among them, 5-(4-methylpiperazin-1-yl)methyl-4-(3-nitrophenyl)-2-phenylthiazole (3b, FR75094) possessed significant AA activity (10 mg/kg, i.p. and 100 mg/kg, *p.o.*, respectively), and was also effective on anti-lipid peroxidation (ALP) assay and inhibited arachidonate-induced cerebral edema in rats. Structure–activity relationships in regard to AA activity of this series of compounds are discussed.

Key words cerebral protective agent; anti-anoxia; structure–activity relationship; 4-(3-nitrophenyl)thiazole; FK360

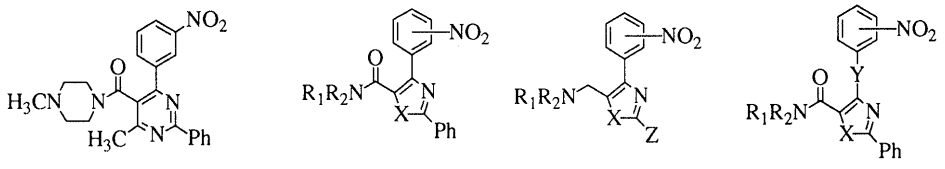
In the course of searching for new cerebral protective agents, we found that a 4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxamide derivative (**1**, FK360) (Fig. 1) exhibited potent anti-anoxic (AA) and anti-lipid peroxidation (ALP) activities with low acute toxicity in mice.[1b] We have also reported that some six-membered ring (*i.e.* pyridine and pyridazine) analogues of FK360 exhibited significant AA activity.[1c] In order to investigate the effects of replacing the pyrimidine ring of FK360 with a five-membered ring (*i.e.* thiazole, oxazole or imidazole) on the AA activity, three types of novel 4-arylazole derivatives (**2**—**4**) (Fig. 1) were prepared and evaluated for AA activity. We describe here the preparation of these 4-arylazole derivatives and their structure–activity relationships (SARs) in regard to AA activity.

Chemistry

The 4-aryl-5-azolecarboxamide derivatives (**2a**—**j**) were prepared *via* the routes shown in Chart 1.

Bromination of ethyl 4-(3- or 4-nitrobenzoyl)acetate (**5a, b**) with pyridinium bromide perbromide followed by cyclization with thiobenzamide or benzamide afforded ethyl 4-(3- or 4-nitrophenyl)-5-azolecarboxylates (**6a, b** and **7a, b**), which were hydrolyzed with aqueous NaOH to afford the corresponding acids (**8a, b** and **9a, b**). The acids were converted into the corresponding acid chlorides according to the method described in the previous reports,[1a,2] and these were condensed with appropriate amines to afford the corresponding amide derivatives (**2a**—**j**).

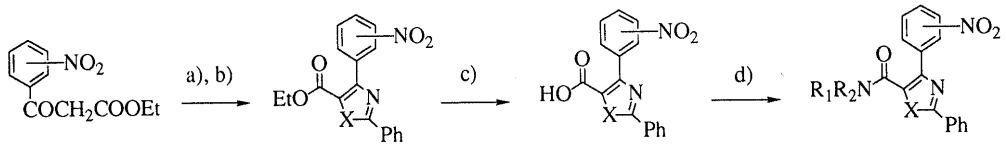
The 4-aryl-5-(4-methylpiperazin-1-yl)methylazole derivatives (**3a**—**k**) were alternatively prepared *via* the routes



1 : FK360 **2** **3** **4**

(X = S, O, NH; Y = CH_2, CO; Z = Ph, NH_2)

Fig. 1



5a : 3-NO_2 **6a, b** : X = S **8a, b** : X = S **2a—j**

5b : 4-NO_2 **7a, b** : X = O **9a, b** : X = O

a) pyridinium bromide perbromide, HBr-AcOH / CH_2Cl_2; b) thiobenzamide or benzamide / EtOH; c) NaOH / H_2O-MeOH-THF; d) $SOCl_2$-DMF / CH_2Cl_2, then amines

Chart 1

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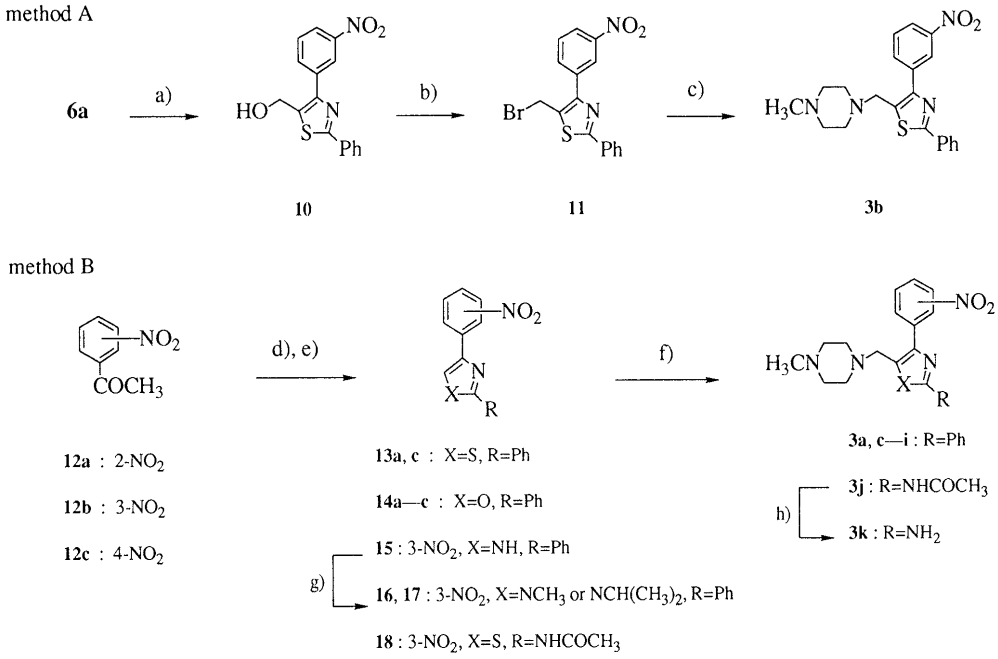
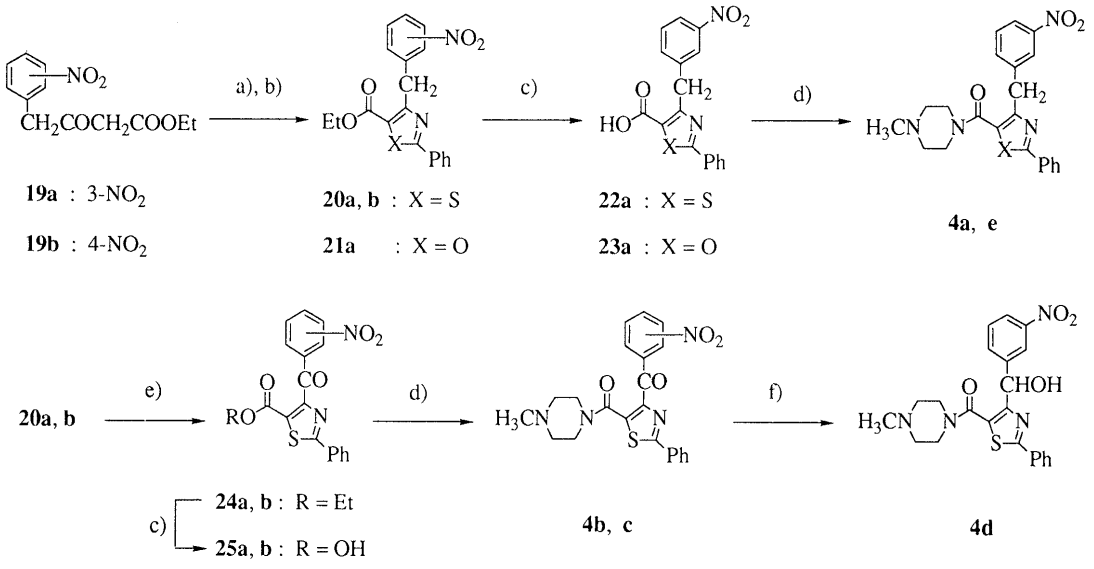


a) $LiAlH_4$ / THF-ether; b) PBr_3 / THF; c) *N*-methylpiperazine / IPA; d) pyridinium bromide perbromide, HBr-AcOH / CH_2Cl_2; e) thiobenzamide, benzamide or benzamidine / EtOH; f) paraformaldehyde, *N*-methylpiperazine / AcOH; g) NaH, alkyl halide / DMF; h) conc. HCl / EtOH

Chart 2



a) pyridinium bromide perbromide, HBr-AcOH / CH_2Cl_2; b) thiobenzamide / EtOH or benzamide; c) NaOH / H_2O-MeOH-THF; d) $SOCl_2$-DMF / CH_2Cl_2, then *N*-methylpiperazine; e) SeO_2 / dioxane; f) $NaBH_4$ / MeOH-THF

Chart 3

shown in Chart 2 (methods A and B).

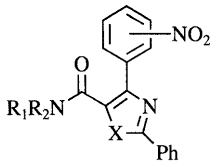
Method A: Reduction of the ester (**6a**) with lithium aluminum hydride ($LiAlH_4$) afforded the desired alcohol (**10**). This was brominated with phosphorus tribromide (PBr_3) to afford **11**, which was condensed with *N*-methylpiperazine to afford **3b**.

Method B: Bromination of acetophenones (**12a—c**) with pyridinium bromide perbromide followed by cyclization with thiobenzamide, benzamide, benzamidine or *N*-acetylthiourea afforded the 4-arylazoles (**13—15** and **18**, respectively). The 1-alkylimidazoles (**16** and **17**) were obtained by alkylation of **15** with appropriate alkyl halides and sodium hydride (NaH). The Mannich reaction[3] at the C-5 position of the azole rings of **13—18** with *N*-methylpiperazine afforded **3a** and **3c—j**. Compound **3j** was hydrolyzed with concentrated HCl to afford the 2-aminothiazole (**3k**).

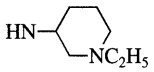
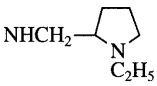
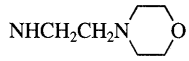
Compounds **4a—d** were prepared *via* the routes shown in Chart 3.

The esters (**20a, b** and **21a**) were prepared from ethyl 4-(3- or 4-nitrophenyl)-3-oxobutanoate (**19a, b**)[1a] according to the routes described in the preparation of **6** and **7**.

Table 1. Physical Properties and AA Activity of 5-Azolecarboxamide Derivatives (**2a—j**)



2a—j

Compd. No.	X	Position of $-NO_2$	NR_1R_2	Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10	32	Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N
2a	S	3		98	120[b]	64.3	136—138 (Ether)	$C_{21}H_{20}N_4O_3S \cdot 0.3H_2O$	60.94 (60.94)	5.02 4.94	13.54 13.51)
2b	S	3	$NHCH_2CH_2N(CH_3)_2$		106	63.1	113—116 (Ether)	$C_{20}H_{20}N_4O_3S \cdot 0.1H_2O$	60.32 (60.18)	5.11 5.12	14.07 14.06)
2c	S	3	$N(CH_3)CH_2CH_2N(CH_3)_2$		121[c]	44.5	215—216 (Ether–EtOH)	$C_{21}H_{22}N_4O_3S \cdot HCl$	56.43 (56.50)	5.19 5.21	12.54 12.73)
2d	S	3			124[c]	35.3	151—152 (Ether)	$C_{22}H_{22}N_4O_4S$	60.26 (60.54)	5.06 5.02	12.78 12.52)
2e	S	3			110	39.2	154—156 (Ether)	$C_{23}H_{24}N_4O_3S$	63.28 (63.01)	5.54 5.56	12.83 12.70)
2f	S	3			104	42.9	130—131 (Ether)	$C_{23}H_{24}N_4O_3S$	63.28 (63.60)	5.54 5.52	12.83 12.65)
2g	S	4			112[c]	71.1	166—267 (Ether)	$C_{21}H_{20}N_4O_3S \cdot 0.1H_2O$	61.48 (61.28)	4.96 4.92	13.66 13.61)
2h	S	4			107	67.9	170—172 (Ether)	$C_{22}H_{22}N_4O_4S$	60.26 (60.10)	5.06 5.15	12.78 12.70)
2i	O	3			114	37.5	180—181 (Ether)	$C_{21}H_{20}N_4O_4$	64.27 (64.40)	5.14 5.22	14.28 14.37)
2j	O	4			111[c]	65.2	186—187 (Ether)	$C_{21}H_{20}N_4O_4$	64.27 (64.35)	5.14 5.08	14.28 14.32)

a) Each value represents the mean of 5 to 10 animals compared with the control group. *b*) $p<0.01$. *c*) $p<0.05$. Values without superscripts are not statistically significant.

The 4-benzoylthiazoles (**24a, b**) were obtained by oxidation of **20a, b** with selenium oxide (SeO_2). The 5-azolecarboxamides (**4a—c**) were obtained by condensation of the acids (**22a** and **25a, b**) with *N*-methylpiperazine according to the routes described in the preparation of **2a—j**. Reduction of **4b** with sodium borohydride ($NaBH_4$) afforded **4d**.

Pharmacological Results and Discussion

The compounds listed in Tables 1—3 were tested for AA activity in mice according to the method described previously.[1d] The results for the 5-azolecarboxamide derivatives (**2a—j**) are shown in Table 1.

4-(3-Nitrophenyl)-5-(4-methylpiperazin-1-yl)carbonyl-2-phenylthiazole (**2a**), which is the thiazole analogue of FK360 (**1**), exhibited significant AA activity, comparable to that of FK360 at an i.p. dose of 32 mg/kg. The result suggests that the pyrimidine ring is exchangeable with the thiazole ring without adversely affecting AA activity. Other thiazole derivatives (**2c, d**) also exhibited AA activity comparable to that of **2a**. But the oxazole analogue (**2i**) showed diminished AA activity.

In order to investigate the effects of an aminomethyl group at the C-5 position of the azole ring on AA activity, the 5-(4-methylpiperazin-1-yl)methylazole derivatives (**3a—k**) were prepared and tested for AA activity, and the results are shown in Table 2.

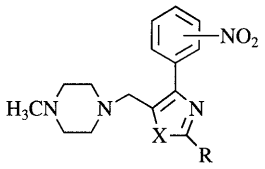
Among them, the thiazole derivatives (**3a, b**) and the oxazole derivative (**3d**) exhibited more potent AA activity than that of the 5-thiazolecarboxamide (**2a**). But in the case of imidazole derivatives (**3g—i**), only **3i** exhibited AA activity comparable to that of the 5-thiazolecarboxamide (**2a**). The 2-aminothiazole derivative (**3k**), in which the phenyl group at the C-2 position of the thiazole ring was replaced with an amino group, also exhibited significant AA activity. The result suggests that the phenyl group is not essential for the expression of AA activity.

We have reported that the 4-(4-nitrobenzoyl)pyrimidine derivatives exhibited AA activity more potent than that of FK360.[1a] We further synthesized the 4-arylcarbonyl-5-azolecarboxamide derivatives and related compounds (**4a—e**), which were tested for AA activity (Table 3).

Only the 4-(3-nitrobenzoyl)-5-thiazolecarboxamide (**4b**) exhibited AA activity as potent as that of the 5-thiazolecarboxamide (**2a**), but less potent than that of the 4-(3-nitrophenyl)-5-aminomethylthiazole (**3b**). Other derivatives (**4a** and **4c—e**) showed diminished AA activity.

Compound **3b** (FR75094) was further evaluated for AA activity by oral administration, ALP assay,[1d] and

Table 2. Physical Properties and AA Activity of 5-(4-Methylpiperazin-1-yl)methylazole Derivatives (**3a**—**k**)

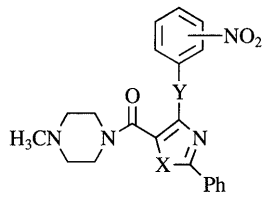


3a—**k**

Compd. No.	X	Position of $-NO_2$	R	Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10	32	Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N
3a	S	2	Ph	106	152[b]	6.4	141—143 (Ether)	$C_{21}H_{22}N_4O_2S \cdot 2HCl \cdot 1.0H_2O$	51.96 (51.71)	5.40 5.36	11.54 11.39)
3b	S	3	Ph	116[c]	143[b]	46.2	116—118 (Ether)	$C_{21}H_{22}N_4O_2S$	63.94 (64.21)	5.62 5.79	14.20 14.19)
3c	S	4	Ph		102	11.1	138—140 (Ether)	$C_{21}H_{22}N_4O_2S \cdot 0.1H_2O$	63.65 (63.50)	5.65 5.61	14.14 14.08)
3d	O	2	Ph	117[c]	160[d]	70.2	250 (dec.) (Ether–EtOH)	$C_{21}H_{22}N_4O_3 \cdot 2HCl$	53.74 (54.13)	5.58 5.63	11.93 12.04)
3e	O	3	Ph		119	67.9	138—139 (Ether)	$C_{21}H_{22}N_4O_3$	66.65 (66.46)	5.86 5.48	14.81 14.77)
3f	O	4	Ph		105	60.0	185—186 (Ether)	$C_{21}H_{22}N_4O_3$	66.65 (66.46)	5.86 5.64	14.81 14.78)
3g	NH	3	Ph		99	40.6	144—147 (Ether)	$C_{21}H_{23}N_5O_2 \cdot 0.3H_2O$	65.88 (65.93)	6.21 6.49	18.29 18.19)
3h	NCH_3	3	Ph		118	64.3	121—122 (Ether)	$C_{22}H_{25}N_5O_2 \cdot 0.4H_2O$	66.28 (66.22)	6.52 6.63	17.57 17.40)
3i	$NCH(CH_3)_2$	3	Ph	110[c]	119[d]	24.0	168 (dec.) (Ether–EtOH)	$C_{24}H_{29}N_5O_2 \cdot 3HCl \cdot 5.5H_2O$	45.91 (45.96)	6.90 6.88	11.15 11.07)
3j	S	3	$NHCOCH_3$		107	43.5	249—251 (Ether)	$C_{17}H_{21}N_5O_3S$	54.39 (54.29)	5.64 5.66	18.65 18.57)
3k	S	3	NH_2		115[c]	18.8	146—148 (Ether)	$C_{15}H_{19}N_5O_2S$	54.04 (53.95)	5.74 5.55	21.01 20.62)

a) Each value represents the mean of 5 to 10 animals compared with the control group. *b*) $p<0.01$. *c*) $p<0.05$. *d*) $p<0.001$. Values without superscripts are not statistically significant.

Table 3. Physical Properties and AA Activity of 4-Benzoyl-5-azolecarboxamide Derivatives and Related Compounds (**4a**—**e**)



4a—**e**

Compd. No.	X	Y	Position of $-NO_2$	Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10	32	Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N
4a	S	CH_2	3		112	30.6	168—170 (Ether)	$C_{22}H_{22}N_4O_3S$	62.54 (62.83)	5.25 5.41	13.26 13.31)
4b	S	CO	3	101	120[b]	63.6	179—181 (Ether)	$C_{22}H_{20}N_4O_4S \cdot 0.2H_2O$	60.04 (60.05)	4.67 4.44	12.73 12.60)
4c	S	CO	4		109	74.7	197—199 (Ether)	$C_{22}H_{20}N_4O_4S$	60.54 (60.74)	4.62 4.78	12.84 12.39)
4d	S	CHOH	3		108	57.3	193—194 (Ether)	$C_{22}H_{22}N_4O_4S \cdot 0.1H_2O$	60.01 (59.95	5.08 5.08	12.72 12.71)
4e	O	CH_2	3		116	43.1	161—162 (Ether)	$C_{22}H_{22}N_4O_4S \cdot 0.25H_2O$	64.30 (64.50	5.52 5.36	13.62 13.57)

a) Each value represents the mean of 5 to 10 animals compared with the control group. *b*) $p<0.001$. Values without superscripts are not statistically significant.

Table 4. Pharmacological Data of 5-(4-Methylpiperazin-1-yl)methyl-4-(3-nitrophenyl)-2-phenylthiazole (**3b**) and FK360 (**1**)

Compound No.	Anti-anoxia (% of control) (mg/kg) 10	32	Upper; i.p. Lower; *p.o.* 100	Lipid peroxidation (% of control) (g/ml) 10^{-5}	Inhibition of arachidonate-induced cerebral edema[a] (% of control) 32 mg/kg, i.p.	Acute toxicity[b] LD_{50} (mg/kg, i.p.)
3b	116[c]	143[c]		96.0[d]	48[c]	440
	100	110	144[e]			
FK360 (**1**)	104	126[d]	168[d]	80.0[d]	63[d]	>560
		114	125[d]			

a) Each value represents the mean of 5 rats. *b*) Male ICR mice weighing 25—30 g were used in groups of 5—10 animals for each test drug. The LD_{50} value was calculated from the lethality within 7 d after an intraperitoneal administration of a test compound. *c*) $p<0.05$. *d*) $p<0.01$. *e*) $p<0.001$. Values without superscripts are not statistically significant.

arachidonate-induced cerebral edema in rats,[1d] and for acute toxicity in mice (Table 4).

Compound **3b** exhibited more potent AA activity than that of FK360 on intraperitoneal administration at a low dose (10 mg/kg) and also exhibited significant AA activity on oral administration (100 mg/kg). It was also effective in ALP assay (96% inhibition at 10^{-5} g/ml) and inhibited arachidonate-induced cerebral edema (48% inhibition at 32 mg/kg i.p.), which were comparable to the effects of FK360.

In conclusion, by replacing the pyrimidine ring of FK360 (**1**) with five-membered rings (*i.e.* thiazole, oxazole and imidazole), we found that the 4-arylthiazole derivative (**3b**, FR75094) exhibited more potent AA activity than that of FK360. The result suggests that the thiazole ring is superior to the pyrimidine ring for the expression of AA activity. The data may be useful for design of new AA agents.

Experimental

Melting points were determined using a Thomas–Hoover capillary melting point apparatus and are uncorrected. ^{1}H-Nuclear magnetic resonance (^{1}H-NMR) spectra were recorded at 90 MHz on a Varian EM-390 NMR spectrometer or a Hitachi R90-H NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrophotometer. Mass spectral (MS) measurements were made on a Hitachi M-80 or a JEOL-D300 mass spectrometer.

Ethyl 4-(3-Nitrophenyl)-2-phenyl-5-thiazolecarboxylate (6a) A mixture of ethyl (3-nitrobenzoyl)acetate (**5a**) (9.5 g, 40.0 mmol), pyridinium bromide perbromide (15.6 g, 48.8 mmol) and 25% hydrobromide–acetic acid solution (10 ml) in acetic acid (100 ml) was stirred for 4 h at room temperature, then poured into water (100 ml) and extracted with ethyl acetate (300 ml). The extract was washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue and thiobenzamide (8.2 g, 59.7 mmol) were dissolved in EtOH (100 ml). The solution was refluxed for 4 h, and allowed to cool to room temperature. The resulting precipitates were collected by filtration and recrystallized from EtOH to afford **6a** (5.8 g, 40.9%) as a pale yellow solid, mp 152—155 °C. IR (Nujol): 1710, 1510 cm^{-1}. ^{1}H-NMR ($CD_3OD+CDCl_3$) δ: 1.33 (3H, t, J=7 Hz), 4.33 (2H, q, J=7 Hz), 7.30—7.66 (3H, m), 7.65 (1H, d, J=9 Hz), 7.90—8.36 (4H, m), 8.74 (1H, t, J=2 Hz). MS *m/z*: 354 (M^+). The following compound was prepared from ethyl (4-nitrobenzoyl)acetate (**5b**) and thiobenzamide by the same procedures as employed for the preparation of **6a**. Compounds **6a, b** were not further purified or analyzed before use in the next steps.

Ethyl 4-(4-Nitrophenyl)-2-phenyl-5-thiazolecarboxylate (**6b**): Yield 42.3% as a pale yellow solid, mp 152—153 °C (EtOH). IR (Nujol): 1715, 1603 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7 Hz), 3.97 (2H, q, J=7 Hz), 7.29—7.79 (3H, m), 7.83—8.17 (2H, m), 7.93 (2H, d, J=9 Hz), 8.40 (2H, d, J=9 Hz). MS *m/z*: 354 (M^+). The following compounds were prepared from 2- or 4-nitroacetophenone (**12a, b**) and thiobenzamide by the same procedures as employed for the preparation of **6a** and were not further purified or analyzed before use in the next steps.

4-(2-Nitrophenyl)-2-phenylthiazole (**13a**): Yield 64.5% as a yellow solid, mp 225—227 °C (EtOH–ether). IR (Nujol): 1570 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.46 (1H, s), 7.48—7.57 (3H, m), 7.62—7.69 (2H, m), 7.75—7.85 (2H, m), 7.89—7.98 (2H, m). MS *m/z*: 252 (M^+).

4-(4-Nitrophenyl)-2-phenylthiazole (**13c**): Yield 72.8% as a yellow solid, mp 126—127 °C (EtOH). IR (Nujol): 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.45—7.52 (3H, m), 7.69 (1H, s), 8.02—8.07 (2H, m), 8.18 (2H, d, J=9 Hz), 8.30 (2H, d, J=9 Hz). MS *m/z*: 252 (M^+).

The following compounds were prepared from ethyl 4-(3- or 4-nitrophenyl)-3-oxobutanoate (**19a, b**)[1a] and thiobenzamide by the same procedures as employed for the preparation of **6a** and were not further purified or analyzed before use in the next steps.

Ethyl 4-[(3-Nitrophenyl)methyl]-2-phenyl-5-thiazolecarboxylate (**20a**): Yield 28.0% as a pale yellow solid, mp 83—84 °C (ether). IR (Nujol): 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7 Hz), 3.83 (2H, s), 4.20 (2H, q, J=7 Hz), 7.30—7.45 (3H, m), 7.55 (1H, dd, J=7, 7 Hz), 7.73—7.93 (3H, m), 8.10—8.38 (2H, m). MS *m/z*: 368 (M^+).

Ethyl 4-[(4-Nitrophenyl)methyl]-2-phenyl-5-thiazolecarboxylate (**20b**): Yield 18.0% as a yellow solid, mp 119—120 °C (EtOH–ether). IR (Nujol): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 3.85 (2H, s), 4.25 (2H, q, J=7 Hz), 7.35—7.55 (3H, m), 7.75 (2H, d, J=8 Hz), 7.85—8.05 (2H, m), 8.30 (2H, d, J=8 Hz). MS *m/z*: 368 (M^+).

2-Acetylamino-4-(3-nitrophenyl)thiazole (**18**)[4] was prepared in 81.0% yield from 3-nitroacetophenone and *N*-acetylthiourea by the same procedures as employed for the preparation of **6a**.

Ethyl 4-(3-Nitrophenyl)-2-phenyl-5-oxazolecarboxylate (7a) A mixture of ethyl (3-nitrobenzoyl)acetate (**5a**) (3.0 g, 12.6 mmol), pyridinium bromide perbromide (4.9 g, 15.3 mmol) and 25% hydrobromide–acetic acid solution (2 ml) in acetic acid (30 ml) was stirred at room temperature for 1 h, then poured into water and extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was heated with benzamide (2.0 g, 16.5 mmol) at 150 °C for 2 h, then cooled to room temperature. The whole was dissolved in $CHCl_3$, washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from ethyl ether to afford **7a** (0.9 g, 20.6%) as a pale yellow solid, mp 114—115 °C. IR (Nujol): 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7 Hz), 4.45 (2H, q, J=7 Hz), 7.35—7.70 (4H, m), 8.05—8.60 (4H, m), 8.95—9.15 (1H, m). MS *m/z*: 338 (M^+). The following compound was prepared from ethyl (4-nitrobenzoyl)acetate (**5b**) and benzamide by the same procedures as employed for the preparation of **7a**. Compound **7a** was not further purified or analyzed before use in the next steps.

Ethyl 4-(4-Nitrophenyl)-2-phenyl-5-oxazolecarboxylate (**7b**): Yield 20.3% as a pale yellow solid, mp 128—130 °C (ether). IR (Nujol): 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7 Hz), 4.42 (2H, q, J=7 Hz), 7.35—7.68 (3H, m), 7.93—8.42 (6H, m). MS *m/z*: 338 (M^+). *Anal.* Calcd for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 64.16; H, 3.87; N, 8.30.

The following compounds were prepared from 2- or 3- or 4-nitroacetophenone (**12a—c**) and benzamide by the same procedures

as employed for the preparation of **7a**. Compound **14a** was not further purified or analyzed before use in the next steps.

4-(2-Nitrophenyl)-2-phenyloxazole (**14a**): Yield 17.0% as a yellow solid, mp 108—109 °C (ether). IR (Nujol): 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.30—8.25 (10H, m). MS *m/z*: 266 (M^+).

4-(3-Nitrophenyl)-2-phenyloxazole (**14b**): Yield 46.7% as a yellow solid, mp 160—161 °C (EtOH–ether). IR (Nujol): 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.30—7.85 (4H, m), 7.90—8.35 (5H, m), 8.65—8.80 (1H, m). MS *m/z*: 266 (M^+). *Anal.* Calcd for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.79; N, 10.52. Found: C, 67.94; H, 3.52; N, 10.47.

4-(4-Nitrophenyl)-2-phenyloxazole (**14c**): Yield 42.1% as a pale yellow solid, mp 173—174 °C (EtOH–ether). IR (Nujol): 1600, 1515 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.30—7.70 (3H, m), 8.09 (1H, s), 7.75—8.50 (6H, m). MS *m/z*: 266 (M^+). *Anal.* Calcd for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.79; N, 10.52. Found: C, 67.68; H, 3.60; N, 10.54.

The following compound was prepared from ethyl 4-(3-nitrophenyl)-3-oxobutanoate (**19a**) and benzamide by the same procedures as employed for the preparation of **7a** and was not further purified or analyzed before use in the next steps.

Ethyl 4-[(3-Nitrophenyl)methyl]-2-phenyl-5-oxazolecarboxylate (**21a**): Yield 7.5% as a pale yellow solid, mp 133—135 °C (EtOH–ether). IR (Nujol): 1720, 1520 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7 Hz), 3.85 (2H, s), 4.22 (2H, q, J=7 Hz), 7.40—7.70 (4H, m), 7.90—8.23 (4H, m), 8.48—8.53 (1H, m). MS *m/z*: 352 (M^+).

4-(3-Nitrophenyl)-2-phenylimidazole (15) A suspension of benzamidine hydrochloride (4.7 g, 30.0 mmol) in H_2O (5 ml)–$CHCl_3$ (10 ml) was adjusted to pH 13 with 4 N aqueous NaOH, then the organic layer was separated and dried over $MgSO_4$. Insoluble materials were removed by filtration, then 2-bromo-1-(3-nitrophenyl)ethanone (2.44 g, 10.0 mmol) was added to the filtrate. The mixture was stirred for 2 h at room temperature, poured into water (100 ml), then extracted with $CHCl_3$ (50 ml). The organic solution was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$ and the fractions containing **15** were combined and evaporated *in vacuo*. The crystalline residue was recrystallized from isopropyl ether to afford **15** (0.94 g, 35.5%) as a pale yellow solid, mp 153—164 °C. IR (Nujol): 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.33—7.70 (4H, m), 7.92—8.15 (4H, m), 8.30—8.50 (2H, m), 8.70 (1H, s). MS *m/z*: 265 (M^+). Compound **15** was not further purified or analyzed before use in the next steps.

4-(3-Nitrophenyl)-2-phenyl-5-thiazolecarboxylic Acid (8a) A mixture of **6a** (5.7 g, 16.1 mmol) and 1 N aqueous NaOH (32.5 ml) in MeOH (40 ml)–THF (20 ml) was refluxed for 1 h, then the mixture was evaporated *in vacuo*. The residue was dissolved in water (20 ml) and the solution was acidified to pH 2 with 10% aqueous HCl, then extracted with ethyl acetate (100 ml). The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was triturated with ethyl ether to afford **8a** (4.45 g, 84.7%) as a white powder, mp 228 °C (dec.). IR (Nujol): 1665, 1515 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.36—7.70 (3H, m), 7.78 (1H, d, J=8 Hz), 7.90—8.20 (2H, m), 8.30 (1H, dd, J=2, 8 Hz), 8.67 (1H, t, J=2 Hz). MS *m/z*: 326 (M^+). The following compounds were prepared by the same procedures as employed for the preparation of **8a**. Compounds **8a**, **8b**, **22a**, **23a**, **25a** and **25b** were not further purified or analyzed before use in the next steps.

4-(4-Nitrophenyl)-2-phenyl-5-thiazolecarboxylic Acid (**8b**): Yield 49.2% as a white powder, mp 232—233 °C (ether). IR (Nujol): 1680, 1655, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.33—7.83 (3H, m), 7.83—8.33 (2H, m), 8.03 (2H, d, J=9 Hz), 8.30 (2H, d, J=9 Hz). MS *m/z*: 326 (M^+).

4-(3-Nitrophenyl)-2-phenyl-5-oxazolecarboxylic Acid (**9a**): Yield 81.9% as a pale yellow powder, mp 247—249 °C (ether). IR (Nujol): 1680, 1540 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.50—8.75 (8H, m), 9.02—9.25 (1H, m). MS *m/z*: 310 (M^+). *Anal.* Calcd for $C_{16}H_{10}N_2O_5$: C, 61.94; H, 3.25; N, 9.03. Found: C, 61.93; H, 3.33; N, 9.08.

4-(4-Nitrophenyl)-2-phenyl-5-oxazolecarboxylic Acid (**9b**): Yield 46.7% as a white powder, mp 254—257 °C (ether). IR (Nujol): 1690, 1660 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.40—7.75 (3H, m), 7.85—8.15 (2H, m), 8.15—8.45 (4H, m). MS *m/z*: 310 (M^+). *Anal.* Calcd for $C_{16}H_{10}N_2O_5$: C, 61.94; H, 3.25; N, 9.03. Found: C, 62.02; H, 3.66; N, 9.09.

4-[(3-Nitrophenyl)methyl]-2-phenyl-5-thiazolecarboxylic Acid (**22a**): Yield 77.2% as a white powder, mp 160—162 °C (ether). IR (Nujol): 1682 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.90 (2H, s), 7.30—7.75 (3H, m), 7.85—8.20 (4H, m), 8.25—8.50 (2H, m). MS *m/z*: 340 (M^+).

4-[(3-Nitrophenyl)methyl]-2-phenyl-5-oxazolecarboxylic Acid (**23a**): Yield 88.3% as a white powder, mp 238—240 °C (ether). IR (Nujol): 1720 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.90 (2H, s), 7.50—7.90 (4H, m), 8.00—8.35 (4H, m), 8.45—8.52 (1H, m). MS *m/z*: 324 (M^+).

4-(3-Nitrobenzoyl)-2-phenyl-5-thiazolecarboxylic Acid (**25a**): Yield 86.2% as a pale yellow powder, mp 217—220 °C (ether). IR (Nujol): 1740, 1675 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.55—7.70 (3H, m), 7.82—8.20 (4H, m), 8.30—8.60 (2H, m). MS *m/z*: 354 (M^+).

4-(4-Nitrobenzoyl)-2-phenyl-5-thiazolecarboxylic Acid (**25b**): Yield 86.2% as a pale yellow powder, mp 115—118 °C (ether). IR (Nujol): 1730, 1690 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.55—7.70 (3H, m), 7.86—8.10 (4H, m), 8.38 (2H, d, J=9 Hz). MS *m/z*: 354 (M^+).

5-(4-Methylpiperazin-1-yl)carbonyl-4-(3-nitrophenyl)-2-phenylthiazole (2a) $SOCl_2$ (0.92 g, 7.7 mmol) was added dropwise to a mixture of **8a** (2.3 g, 7.1 mmol) and *N*,*N*-dimethylformamide (DMF) (4.6 ml) in CH_2Cl_2 (23 ml) at 0 °C, and the whole was stirred for an additional 1 h, then added to a solution of *N*-methylpiperazine (1.75 g, 17.4 mmol) in CH_2Cl_2 (30 ml) at 0 °C, and stirred for 2 h at the same temperature. The mixture was poured into water (50 ml), adjusted to pH 8.0 with 20% aqueous K_2CO_3, and extracted with CH_2Cl_2 (100 ml). The extract was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from ethyl ether to afford **2a** (1.85 g, 64.3%) as a pale yellow solid. Compounds **2b**—**j** and **4a**—**e** were prepared by the same procedures as employed for the preparation of **2a**. Physical properties and spectral data of these compounds are listed in Tables 1, 3 and 5.

5-Hydroxymethyl-4-(3-nitrophenyl)-2-phenylthiazole (10a) A solution of **6a** (3.54 g, 10.0 mmol) in tetrahydrofuran (THF) (50 ml) was added dropwise to a suspension of $LiAlH_4$ (0.76 g, 20.0 mmol) in THF (50 ml)–ethyl ether (50 ml) at −40 °C. The reaction mixture was stirred at −40 °C for an additional 30 min, then a solution of THF (30 ml) and water (30 ml) was added dropwise, and the whole was acidified with 4 N aqueous HCl, and extracted with ethyl acetate. The extract was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from ethyl ether to afford **10a** (1.55 g, 49.6%) as a white solid, mp 144—145 °C. IR (Nujol): 1520 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.87 (2H, d, J=6 Hz), 6.06 (1H, t, J=6 Hz), 7.40—7.65 (3H, m), 7.74—8.13 (3H, m), 8.13—8.43 (2H, m), 8.63 (1H, t, J=2 Hz). MS *m/z*: 312 (M^+). Compound **10a** was not further purified or analyzed before use in the next steps.

5-Bromomethyl-4-(3-nitrophenyl)-2-phenylthiazole (11) A solution of **10a** (4.5 g, 14.4 mmol) in THF (50 ml) was added dropwise to a solution of PBr_3 (3.9 g, 14.4 mmol) in THF (30 ml) at 0 °C. The reaction mixture was stirred for an additional 1 h at the same temperature, then poured into isopropyl ether (100 ml) and washed with water. The organic layer was separated and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$ to afford **11** (1.57 g, 29.1%) as a yellow solid, mp 142—144 °C. IR (Nujol): 1530 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.43 (2H, s), 7.33—7.73 (3H, m), 7.74—8.10 (3H, m), 8.10—8.43 (2H, m), 8.60 (1H, m). MS *m/z*: 374, 376 (M^+). Compound **11** was not further purified or analyzed before use in the next steps.

5-(4-Methylpiperazin-1-yl)methyl-4-(3-nitrophenyl)-2-phenylthiazole (3b) A mixture of **11** (1.3 g, 3.46 mmol) and *N*-methylpiperazine (1.0 g, 10.2 mmol) in isopropanol (15 ml) was stirred at 80 °C for 2 h. The reaction mixture was allowed to cool to room temperature, then poured into a mixture of $CHCl_3$ (50 ml) and water (30 ml). The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from a mixture of isopropyl ether and ethyl acetate to afford **3b** (0.63 g, 46.2%) as a pale yellow solid. Physical properties and spectral data of this compound are listed in Tables 2 and 5.

5-(4-Methylpiperazin-1-yl)methyl-4-(4-nitrophenyl)-2-phenylthiazole (3c) A mixture of **13c** (0.53 g, 2.1 mmol), paraformaldehyde (0.53 g, 17.7 mmol) and *N*-methylpiperazine hydrochloride (2.1 g, 15.4 mmol) in acetic acid (20 ml) was refluxed for 6 h. The reaction mixture was allowed to cool to room temperature and evaporated *in vacuo*. The residue was dissolved in water (20 ml), then adjusted to pH 9.0 with 20% aqueous K_2CO_3 and extracted with $CHCl_3$. The extract was washed with water, and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$–MeOH (97 : 3) to afford **3c** (0.44 g, 11.1%) as a pale yellow solid. Compounds **3a**, **d**—**j** were prepared by the same procedures as employed for the preparation of **3c**. Physical properties and spectral data of these

compounds are listed in Tables 2 and 5.

2-Amino-5-(4-methylpiperazin-1-yl)methyl-4-(3-nitrophenyl)thiazole (3k) A mixture of **3j** (3.0 g, 8.0 mmol) and concentrated HCl (15 ml) in EtOH (15 ml) was refluxed for 1 h. The reaction mixture was allowed to cool to room temperature, then neutralized with saturated aqueous K_2CO_3 and extracted with ethyl acetate. The extract was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$–MeOH (95 : 5) to afford **3k** (0.5 g, 18.8%) as a yellow solid. Physical properties and spectral data of this compound are listed in Tables 2 and 5.

1-Methyl-4-(3-nitrophenyl)-2-phenylimidazole (16) NaH (60% in oil suspension) (0.14 g, 3.5 mmol) was added to a solution of **15** (1.0 g, 3.7 mmol) in DMF (10 ml), and the mixture was stirred for 1 h at room temperature, then methyl iodide (0.36 ml, 5.8 mmol) was added. The whole was stirred for 3 h, then poured into water and extracted with ethyl acetate. The extract was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from ethyl ether to afford **16** (0.7 g, 66.7%) as a yellow solid, mp 99—105 °C. IR (Nujol): 1515 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.77 (3H, s), 7.25—7.75 (7H, m), 7.87—8.23 (2H, m), 8.45—8.60 (1H, m). MS *m/z*: 279 (M^+). Compound **17** was prepared by the same procedures as employed for the preparation of **16**. Compounds **16** and **17** were not further purified or analyzed before use in the next steps.

1-Isopropyl-4-(-3-nitrophenyl)-2-phenylimidazole (**17**): Yield 25.3% as a pale yellow solid, mp 111—114 °C (ether). IR (Nujol): 1515 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (6H, d, J=7 Hz), 4.35—4.85 (1H, m) 7.35—7.80 (7H, m), 7.85—8.35 (2H, m), 8.53—8.35 (1H, m). MS *m/z*: 307 (M^+).

Ethyl 4-(3-Nitrobenzoyl)-2-phenyl-5-thiazolecarboxylate (24a) A mixture of **20a** (0.3 g, 0.8 mmol), SeO_2 (0.14 g, 1.3 mmol) and H_2O (0.1 ml) in dioxane (5 ml) was refluxed for 6 h. The insoluble materials were removed by filtration, then the filtrate was evaporated *in vacuo*. The

Table 5. Spectral Data for the Azole Derivatives (**2—4**)

Compd. No.	MS *m/z*, M^+	IR (Nujol) cm^{-1}	Solvent[a]	^{1}H-NMR (ppm)[b]
2a	408	1620, 1532	A	2.36 (3H, s), 2.02—2.60 (4H, m), 3.16—3.93 (4H, m), 7.22—7.58 (4H, m), 7.86—8.38 (4H, m), 8.72 (1H, t, J=2 Hz)
2b	396	3250, 1636, 1525	A	2.04 (6H, s), 2.17—2.45 (2H, m), 3.23—3.52 (2H, m), 6.53 (1H, m), 7.36—7.60 (3H, m), 7.70 (1H, d, J=8 Hz), 7.85—8.53 (4H, m), 8.68 (1H, d, J=8 Hz)
2c	410	1630, 1530	A	2.90 (3H, s), 2.95 (3H, s), 2.97 (3H, s), 3.10—3.55 (2H, m), 3.86—4.20 (2H, m), 7.33—7.77 (4H, m), 7.80—8.50 (5H, m)
2d	438	3250, 1630, 1520	A	2.15—2.57 (6H, m), 3.25—3.63 (6H, m), 6.45—6.55 (1H, m), 7.38 —7.76 (4H, m), 7.82—8.35 (4H, m), 8.54—8.76 (1H, m)
2e	435	3250, 1620, 1520	A	0.84 (3H, t, J=7 Hz), 1.22—2.75 (9H, m), 2.25 (2H, q, J=7 Hz), 4.05—4.33 (1H, m), 6.42—6.65 (1H, m), 7.36—7.75 (4H, m), 7.88—8.40 (4H, m), 8.53—8.72 (1H, m)
2f	435	3280, 1635, 1525	A	0.87 (3H, t, J=7 Hz), 1.0—3.9 (11H, m), 6.15—6.65 (1H, m), 7.1—8.5 (8H, m), 8.5—8.8 (1H, m)
2g	408	1630, 1520	A	2.00—2.43 (4H, m), 2.23 (3H, s), 3.05—3.95 (4H, m), 7.40—7.62 (3H, m), 8.06 (2H, dd, J=2, 8 Hz), 7.90—8.15 (2H, m), 8.33 (2H, dd, J=2, 8 Hz)
2h	438	3275, 1635, 1600, 1540	A	2.15—2.58 (6H, m), 3.2—3.6 (6H, m), 6.1—6.5 (1H, m), 7.28—7.57 (3H, m), 7.8—8.4 (6H, m)
2i	392	1620, 1510	A	2.33 (3H, s), 2.2—2.7 (4H, m), 3.3—4.1 (4H, m), 7.4—7.8 (4H, m), 8.0—8.5 (4H, m), 8.8—9.0 (1H, m)
2j	392	1620, 1560	A	2.33 (3H, s), 2.2—2.7 (4H, m), 3.3—4.1 (4H, m), 7.4—7.7 (3H, m), 8.0—8.4 (2H, m), 8.22—8.33 (4H, m)
3a	394	1575	C	3.21 (3H, s), 3.20—4.00 (8H, m), 4.63 (2H, s), 7.46—7.86 (4H, m), 7.86—8.23 (4H, m), 8.45 (1H, dd, J=2, 8 Hz)
3b	394	1537	A	2.32 (3H, s), 2.36—2.93 (8H, m), 3.75 (2H, s), 7.30—7.55 (3H, m), 7.65 (1H, d, J=8 Hz), 7.80—8.09 (2H, m), 8.10—8.33 (2H, m), 8.93 (1H, m)
3c	394	1600	A	2.31 (3H, s), 2.16—2.93 (8H, m), 3.80 (2H, s), 4.38 (2H, s), 7.33—7.60 (3H, m), 7.85—8.13 (2H, m), 8.00 (2H, d, J=8 Hz), 8.33 (2H, d, J=8 Hz)
3d	378	1520	B	2.60 (3H, s), 3.1—3.7 (8H, m), 4.42 (2H, s), 7.5—8.3 (9H, m)
3e	378	1520	A	2.28 (3H, s), 2.3—2.8 (8H, m), 3.75 (2H, s), 7.3—7.6 (4H, m), 7.95—8.35 (4H, m), 8.85—9.02 (1H, m)
3f	378	1600	A	2.28 (3H, s), 2.3—2.8 (8H, m), 3.78 (2H, s), 7.35—7.55 (3H, m), 7.95—8.35 (6H, m)
3g	377	1620, 1570, 1540	D	2.32 (3H, s), 2.55 (8H, s), 3.67 (2H, s), 7.22—7.58 (4H, m), 7.7—8.2 (4H, m), 8.65—8.77 (1H, m)
3h	391	1520	A	2.27 (3H, s), 2.3—2.7 (8H, m), 3.66 (2H, s), 7.25—7.75 (6H, m), 7.95—8.27 (2H, m), 8.75—8.86 (1H, m)
3i	419	1530	B	1.42 (6H, d, J=7 Hz), 2.4—3.7 (8H, m), 2.67 (3H, s), 3.95 (2H, s), 4.65—5.10 (1H, m), 7.5—8.7 (9H, m)
3j	375	1680, 1575	B	2.38 (3H, s), 2.40—2.65 (8H, m), 3.30 (3H, s), 3.72 (2H, s), 7.60—8.30 (3H, m), 8.73—8.82 (1H, m)
3k	333	1630, 1520	A	2.28 (3H, s), 2.48—2.60 (8H, m), 3.55 (2H, s), 5.25 (2H, br), 7.25—7.70 (1H, m), 7.98—8.24 (2H, m), 8.70—8.78 (1H, m)
4a	422	1620	A	2.38 (3H, s), 2.40—2.65 (4H, m), 3.65—3.90 (4H, m), 3.92 (2H, s), 7.40—8.40 (8H, m), 8.50—8.60 (1H, m)
4b	436	1680, 1640	A	2.30 (3H, s), 2.35—2.60 (4H, m), 3.38—3.83 (4H, m), 7.45—8.13 (7H, m), 8.28—8.60 (2H, m)
4c	436	1680, 1635	A	2.30 (3H, s), 2.50—2.70 (4H, m), 3.50—3.95 (4H, m), 7.48—7.65 (3H, m), 7.86 (2H, d, J=8 Hz), 7.90—8.05 (4H, m)
4d	438	1650	A	2.25 (3H, s), 2.20—2.50 (4H, m), 2.80—3.20 (2H, m), 3.50—3.80 (2H, m), 5.28 (1H, s), 7.40—7.56 (3H, m), 7.68—8.40 (5H, m), 8.45—8.55 (1H, m)
4e	406	1625, 1520	A	2.32 (3H, s), 2.35—2.65 (4H, m), 352—3.90 (4H, m), 3.92 (2H, s), 7.45—7.82 (4H, m), 8.05—8.50 (4H, m), 8.72 (1H, m)

a) A, $CDCl_3$; B, DMSO-d_6; C, D_2O; D, $CDCl_3$+CD_3OD. *b*) Listed as chemical shifts (number of protons, multiplicity, constant).

residue was dissolved in $CHCl_3$, and the solution was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from ethyl ether to afford **24a** (0.1 g, 32.7%) as a pale yellow solid, mp 139—140 °C. IR (Nujol): 1730, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7 Hz), 4.45 (2H, q, J=7 Hz), 7.36—8.00 (7H, m), 8.18—8.48 (2H, m). MS m/z: 382 (M^+). The following compound was prepared by the same procedures as employed for the preparation of **24a**. Compounds **24a**, **b** were not further purified or analyzed before use in the next steps.

Ethyl 4-(4-Nitrobenzoyl)-2-phenyl-5-thiazolecarboxylate (**24b**): Yield 59.8% as a pale yellow solid, mp 126—128 °C (ether). IR (Nujol): 1730, 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7 Hz), 4.50 (2H, q, J=7 Hz), 7.45—7.63 (3H, m), 7.85 (2H, d, J=9 Hz), 7.88—8.05 (2H, m), 8.30 (2H, d, J=9 Hz). MS m/z: 382 (M^+).

5-(4-Methylpiperazin-1-yl)carbonyl-4-[hydroxy(3-nitrophenyl)methyl]-2-phenylthiazole (4d) $NaBH_4$ (0.07 g, 1.8 mmol) was added to a mixture of **4b** (0.8 g, 1.8 mmol) in MeOH (5 ml)–THF (10 ml) at 0 °C. The reaction mixture was stirred for 30 min, then poured into water and the whole was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$–MeOH (50 : 1) to afford **4d** (0.59 g, 74.7%) as a white solid. Physical properties and spectral data of this compound are listed in Tables 2 and 5.

Anti-anoxic (100% N_2) Activity in Mice[1d] Two male ICR mice of the same age were maintained in a closed glass chamber in which a current of nitrogen gas was circulated, and their survival time was measured. One mouse was pretreated with the test compound, and the other with the vehicle 30 min before the experiment.

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References and Notes

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