Studies on Cerebral Protective Agents. VIII.[1a] Synthesis of 2-Aminothiazoles and 2-Thiazolecarboxamides with Anti-anoxic Activity

Mitsuru OHKUBO,*,[a] Atsushi KUNO,[a] Isao NAKANISHI,[b] and Hisashi TAKASUGI[a]

New Drug Research Laboratories[a] and R&D Information,[b] Fujisawa Pharmaceutical Co., Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532, Japan. Received February 15, 1995; accepted April 25, 1995

Various 2-aminothiazoles (2a—s and 3a—g) and 2-thiazolecarboxamides (4a—h), possessing a nitrogenous basic moiety at the C-2 position of the thiazole ring, were prepared and tested for anti-anoxic (AA) activity in mice. Among them, *N*-[2-(4-morpholinyl)ethyl]-4-(3-trifluoromethylphenyl)-2-thiazolecarboxamide hydrochloride (4e, FR108143) (minimum effective doses of 3.2 mg/kg i.p. and 10 mg/kg *p.o.*, respectively) exhibited more potent AA activity than either FK360 or compound 1, each of which has a nitrogenous basic moiety at the C-5 position. The structure–activity relationships with regard to AA activity of this series of compounds are discussed, and the three-dimensional electrostatic potentials (3D-MEP) around the basic nitrogen atom of FK360 and the thiazole derivative (4e) are compared.

Key words cerebral protective agent; anti-anoxia; 2-aminothiazole; 2-thiazolecarboxamide; structure–activity relationship; FK360

In the previous paper,[1a] we reported that the 4-(3-nitrophenyl)-2-phenylthiazole derivative (**1**, FR75039) (Fig. 1) exhibited more potent anti-anoxic (AA) activity than that of FK360 (Fig. 1). Our study has been focused on exploring this thiazole prototype (**1**) in order to increase AA activity further. In this paper, the influence of positional change of a nitrogenous basic moiety in the thiazole ring on AA activity was investigated by preparing the thiazole derivatives (**2**—**4**) (Fig. 2), possessing the nitrogenous basic moiety at the C-2 position instead of the C-5 position. We describe the structure–activity relationships (SARs) with regard to AA activity of these thiazole derivatives. The three-dimensional molecular electrostatic potentials (3D-MEP) around the basic nitrogen atoms of FK360 and the thiazole derivative (**4e**), the most effective example in this series, are also compared.

Chemistry

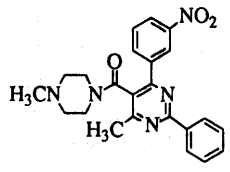
The 2-aminothiazole derivatives (**2a—s**, **3a—g**) were synthesized *via* the routes shown in Chart 1.

The 2-aminothiazoles (**5a—t**) were prepared by using the Hantzsch method.[2] Bromination of appropriate ketones with pyridinium bromide perbromide followed by cyclization with thioamide, *N*-methylthioamide, and *N*-acetylthioamide afforded the 2-aminothiazoles (**5a—m**), the 2-methylaminothiazole (**5n**), and the 2-acetylaminothiazoles (**5o—t**), respectively. Acylation of the 2-aminothiazoles (**5a—n**) with bromoacetyl bromide gave the 2-(bromoacetyl)aminothiazoles (**6a—n**), which were condensed with appropriate amines to afford **2a—e, h—s**. Catalytic hydrogenation of **2c** afforded **2f**, which was treated with methanesulfonyl chloride to afford **2g**. Alkylation of the 2-acetylaminothiazoles (**5o—t**) with 2-morpholinoethyl chloride and sodium hydride (NaH) afforded **3b—g**. Hydrolysis of **3b** with concentrated HCl afforded **3a**.

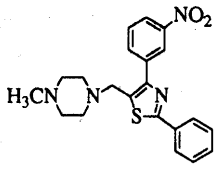
The 2-thiazolecarboxylic acid ethyl esters (**7a—h**) were prepared by cyclization of appropriate acetophenones with ethyl thioxamate[3] according to the routes described for the preparation of the 2-aminothiazoles. The esters were then condensed with morpholinoethylamine to afford the 2-thiazolecarboxamide derivatives (**4a—h**), as shown in Chart 2.

Pharmacological Results and Discussion

The compounds listed in Tables 1—4 were tested for AA activity in mice according to the method described previously.[1b] The results for the 2-aminothiazole derivatives (**2a—s**, **3a—g**), each possessing the nitrogenous basic moiety at the C-2 position of the thiazole ring, are shown

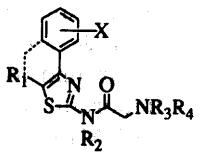


FK360



1 (FR75039)

Fig. 1



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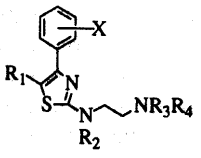

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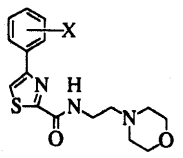

4

(4e : X = 3-CF_3)

Fig. 2

* To whom correspondence should be addressed.

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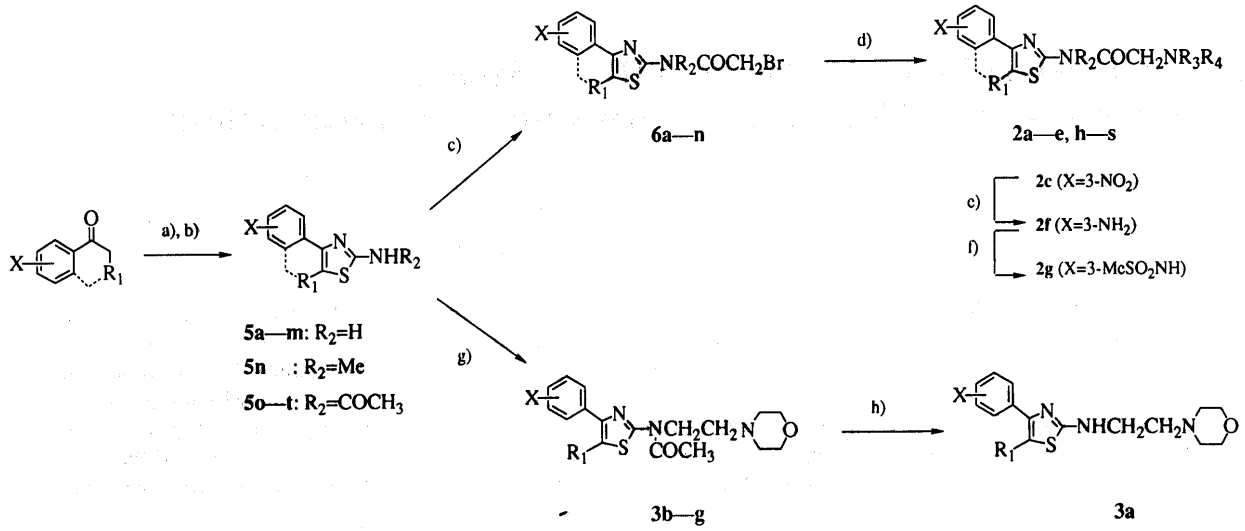
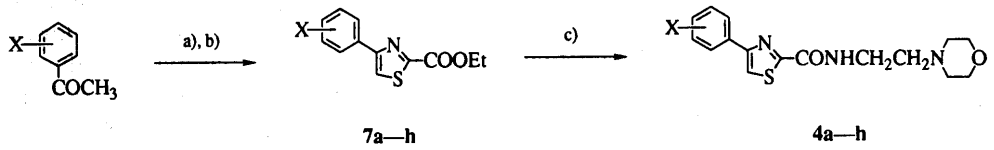


a) pyridinium bromide perbromide, HBr-AcOH/AcOH; b) thiourea or *N*-methylthiourea or *N*-acetylthiourea/DMF; c) bromoacetyl bromide, Et_3N/CH_2Cl_2; d) amine/CH_2Cl_2; e) H_2/10%Pd-C in EtOH; f) $MeSO_2Cl$, Et_3N/CH_2Cl_2; g) morpholinoethyl chloride, NaH/DMF; h) conc. HCl/EtOH

Chart 1



a) pyridinium bromide perbromide, HBr-AcOH/CH_2Cl_2; b) ethyl thioxamate/EtOH; c) morpholinoethylamine

Chart 2

in Tables 1—3.

The results show that the nitrogenous basic moiety at the C-2 position instead of the C-5 position was tolerated for AA activity. Compound **2c**[4] (Table 1) exhibited significant AA activity, comparable to that of the parent compound **1**, at the dose of 32 mg/kg i.p. The analogues **2h—k** (Table 1) bearing the substituents at the C-5 position showed decreased AA activity, while the conformationally rigid analogue **2p** (Table 2) of **2c** maintained AA activity. In the cases of **2h—k**, energy calculation showed that a coplanar conformation of the thiazole ring and the aryl group at the C-4 position was unfavorable because of the steric hindrance between the aryl group and the substituents at the C-5 position.[5] These results suggest that the aryl group at the C-4 position and the thiazole ring may be nearly coplanar in the active conformation for the expression of AA activity. The closely related compound **3a** (Table 3), which was constructed by converting the amide linkage at the C-2 position to an alkylamino linkage, also exhibited significant AA activity, comparable to that of **2c**.

In order to obtain information about the influence of the distance between the basic nitrogen atom and the thiazole ring on AA activity, the *N*-[2-(4-morpholinyl)-ethyl]-2-thiazolecarboxamide derivatives (**4a—h**), possessing four-atom linkages between the basic nitrogen atom and the thiazole ring, were tested for AA activity, and the results are shown in Table 4.

Compound **4e** exhibited more potent AA activity than that of the 2-aminothiazole (**2c**) with the three-atom linkage; **4e** prolonged survival time on AA assay to twice that of the control group at the dose of 32 mg/kg i.p. This result suggests that the four-atom linkage between the basic nitrogen atom and the thiazole ring is more beneficial for AA activity than the three-atom linkage in the case of this series of thiazole derivatives.[1c]

Compounds **2c** and **4e** were further evaluated for AA activity in mice by intraperitoneal administration at a lower dose and oral administration, as well as for anti-lipid peroxidation (ALP) activity in rat brain mitochondria,[1b] and acute toxicity in mice. The results for these compounds, together with those for FK360 and compound **1** as reference compounds, are shown in Table 5.

Compound **4e** (FR108143) exhibited more potent AA activity than either FK360 or **1** at lower doses i.p. and *p.o.*; its minimum effective doses were 3.2 mg/kg i.p. and 10 mg/kg *p.o.* The results show that the nitrogenous basic moiety at the C-2 position of the thiazole ring is beneficial for AA activity. While the parent compound 1 exhibited significant ALP activity, the result of diminished ALP activity for **2c** and **4e** suggested that the 2-phenylthiazole moiety would be necessary for ALP activity.[1b]

Although the structure of **4e** was considerably different from that of FK360, **4e** also exhibited potent AA activity. In order to explain this result, the 3D-MEP around the basic nitrogen atom of **4e** was compared with that of FK360. The 3D-MEP around the basic nitrogen atom is known to be very important at the recognition site for AA activity.[1c,d] The 3D-MEP was calculated by using the electrostatic potential calculation routine of the program MOPAC 7.[6,7] The isopotential surfaces of -5 kcal/mol for the 3D-MEPs of **4e** and FK360, and the superimposition of them are represented in Fig. 3a—c, respectively.

The negative isopotential surfaces of the 3D-MEPs

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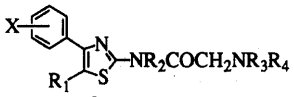
Table 1. Physical Properties and AA Activity of 2-Aminothiazole Derivatives (**2a—o**)

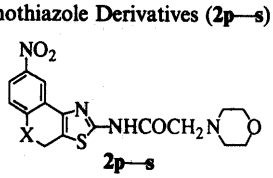


2a—o

Compd. No.	X	R_1	R_2	NR_3R_4	Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10	32	Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N
2a	H	H	H	N⬡O	109[b]	121[b]	59.5	254 (dec.)[c] (EtOH–H_2O)	$C_{15}H_{17}N_3O_2S\cdot HCl$	53.01 (53.18)	5.34 5.31	12.36 12.42)
2b	2-NO_2	H	H	N⬡O	112	123[b]	78.8	230—232 (EtOH)	$C_{15}H_{16}N_4O_4S\cdot HCl\cdot C_2H_5OH$	47.39 (47.29)	5.38 5.14	13.00 13.13)
2c	3-NO_2	H	H	N⬡O	131[d]	143[d]	51.6	268—270[e] (EtOH–H_2O)	$C_{15}H_{16}N_4O_4S\cdot HCl$	46.82 (46.78)	4.45 4.34	14.56 14.54)
2d	4-NO_2	H	H	N⬡O	128[f]	131[f]	61.6	>300 (EtOH–H_2O)	$C_{15}H_{16}N_4O_4S\cdot HCl$	46.82 (46.81)	4.45 4.32	14.56 14.67)
2e	3-CF_3	H	H	N⬡O	107[b]	129[f]	53.0	259—262 (EtOH–H_2O)	$C_{16}H_{16}F_3N_3O_2S\cdot HCl$	47.12 (46.88)	4.20 4.23	10.30 10.29)
2f	3-NH_2	H	H	N⬡O	108[b]	123[d]	82.7	130 (dec.) (EtOH–H_2O)	$C_{15}H_{18}N_4O_2S\cdot 2HCl\cdot 3H_2O$	40.45 (40.31)	5.88 5.48	12.58 12.71)
2g	3-CH_3SO_2NH	H	H	N⬡O		117	72.8	258 (dec.) (EtOH–H_2O)	$C_{16}H_{20}N_4O_4S_2\cdot HCl$	44.39 (44.26)	4.89 5.01	12.94 12.92)
2h	3-NO_2	CH_3	H	N⬡O		109	78.8	177—178 (Et_2O)	$C_{16}H_{18}N_4O_4S$	53.03 (53.31)	5.01 4.93	15.46 15.43)
2i	3-NO_2	$COOC_2H_5$	H	N⬡O		115	47.3	164—165 (Et_2O)	$C_{18}H_{20}N_4O_6S$	51.42 (51.65)	4.79 4.63	13.33 13.33)
2j	4-NO_2	CH_3	H	N⬡O		117[b]	64.2	234 (dec.) (EtOH–H_2O)	$C_{16}H_{18}N_4O_4S\cdot HCl\cdot 0.25H_2O$	47.64 (47.63)	4.87 4.88	13.89 13.66)
2k	4-NO_2	$COOC_2H_5$	H	N⬡O		108[f]	47.3	238 (dec.) (EtOH–H_2O)	$C_{18}H_{20}N_4O_6S\cdot HCl$	47.32 (47.54)	4.63 4.78	12.26 12.32)
2l	3-NO_2	H	CH_3	N⬡O		108	66.9	151—152 (EtOH)	$C_{16}H_{18}N_4O_4S$	53.03 (53.06)	5.01 4.82	15.46 15.34)
2m	3-NO_2	H	H	N⬡S		114[b]	70.4	185—188 (Et_2O)	$C_{15}H_{16}N_4O_3S_2$	49.44 (49.17)	4.43 4.28	15.37 15.18)
2n	3-NO_2	H	H	N⬡	110[b]	141[f]	37.6	175—177 (Et_2O)	$C_{16}H_{18}N_4O_3S$	55.48 (55.55)	5.24 5.13	16.17 15.99)
2o	3-NO_2	H	H	N⬡	114[d]	141[f]	51.5	144—145 (Et_2O)	$C_{15}H_{16}N_4O_3S\cdot 0.1H_2O$	53.91 (53.56)	4.89 4.50	16.77 16.80)

a) Each value represents the mean of 5 to 10 animals compared with the control group. *b*) $p<0.05$. *c*) Lit.[4] mp 180 °C. *d*) $p<0.001$. Values without superscripts are not statistically significantly different from the control. *e*) Lit.[4] mp 124 °C. *f*) $p<0.01$.

Table 2. Physical Properties and AA Activity of 2-Aminothiazole Derivatives (**2p—s**)



2p—s

Compound No.	X	Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10	32	Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N
2p	CH_2	114[b]	131[c]	72.6	258 (dec.) (EtOH–H_2O)	$C_{17}H_{18}N_4O_4S\cdot HCl\cdot 0.8H_2O$	48.01 (48.38)	4.88 4.96	13.17 12.84)
2q	CH_2CH_2	109	116[b]	84.9	225 (dec.) (EtOH–H_2O)	$C_{18}H_{20}N_4O_4S\cdot HCl\cdot H_2O$	48.81 (48.57)	5.23 5.33	12.65 12.42)
2r	S	119[c]	118[b]	91.1	>300 (EtOH–H_2O)	$C_{16}H_{16}N_4O_4S_2\cdot HCl\cdot 2.0H_2O$	41.34 (41.49)	4.55 4.42	12.05 12.14)
2s	O		109	65.9	278 (dec.) (EtOH–H_2O)	$C_{16}H_{16}N_4O_5S\cdot HCl\cdot H_2O$	44.60 (44.28)	4.44 4.75	13.00 12.88)

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

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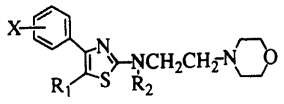
Table 3. Physical Properties and AA Activity of 2-Aminothiazole Derivatives (**3a—g**)

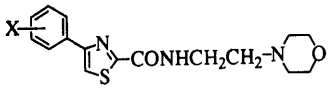


3a—g

Compound No.	X	R_1	R_2	Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10	32	Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N
3a	3-NO_2	H	H	128[b]	147[c]	78.3	222—224 (EtOH–H_2O)	$C_{15}H_{18}N_4O_3S\cdot HCl$	48.58 (48.63)	5.16 5.15	15.10 15.03)
3b	3-NO_2	H	$COCH_3$	121[b]	143[b]	64.6	265—268 (EtOH–H_2O)	$C_{17}H_{20}N_4O_4S\cdot HCl$	49.15 (49.53)	5.13 5.07	13.57 13.63)
3c	3-CF_3	H	$COCH_3$	106	124[b]	50.3	242 (dec.) (EtOH–H_2O)	$C_{18}H_{20}F_3N_3O_2S\cdot HCl\cdot H_2O$	47.63 (47.63)	5.11 4.86	9.26 9.29)
3d	3-NO_2	CH_3	$COCH_3$		113[d]	36.3	232—235 (EtOH–H_2O)	$C_{18}H_{22}N_4O_4S\cdot HCl\cdot 0.5H_2O$	49.60 (49.48)	5.55 5.56	12.85 12.89)
3e	3-NO_2	$COOC_2H_5$	$COCH_3$		108	59.6	229—230 (EtOH–H_2O)	$C_{20}H_{24}N_4O_6S\cdot HCl\cdot H_2O$	47.76 (47.96)	5.41 5.12	11.14 11.32)
3f	4-NO_2	CH_3	$COCH_3$	107[d]	112[d]	27.3	265 (dec.) (EtOH–H_2O)	$C_{18}H_{22}N_4O_4S\cdot HCl$	50.64 (50.72)	5.43 5.28	13.12 13.37)
3g	4-NO_2	$COOC_2H_5$	$COCH_3$		105	59.5	256 (dec.) (EtOH–H_2O)	$C_{20}H_{24}N_4O_6S\cdot HCl$	49.54 (49.60)	5.20 4.97	11.55 11.52)

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

Table 4. Physical Properties and AA Activity of 2-Thiazolecarboxamide Derivatives (**4a—h**)



4a—h

Compound No.	X	Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10	32	Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N
4a	H		104	31.8	221—223 (EtOH)	$C_{16}H_{19}N_3O_2S\cdot HCl\cdot 0.3H_2O$	53.49 (53.44	5.78 5.77	11.70 11.63)
4b	2-NO_2		107	35.2	254—246 (EtOH–H_2O)	$C_{16}H_{18}N_4O_4S\cdot HCl$	48.18 (48.02	4.80 4.84	14.05 14.20)
4c	3-NO_2	108[b]	126[c]	94.2	250—252 (EtOH–H_2O)	$C_{16}H_{18}N_4O_4S\cdot HCl\cdot H_2O$	46.10 (46.30	5.08 5.01	13.44 13.46)
4d	4-NO_2	131[c]	157[c]	83.3	258—260 (EtOH–H_2O)	$C_{16}H_{18}N_4O_4S\cdot HCl\cdot 1.5H_2O$	45.12 (45.01	5.21 5.10	13.16 13.24)
4e	3-CF_3	132[d]	212[c]	49.3	219—220 (EtOH)	$C_{17}H_{18}F_3N_3O_2S\cdot HCl$	48.40 (48.04	4.54 4.50	9.96 9.95)
4f	3-Cl	115[c]	139[c]	43.3	215—216 (EtOH)	$C_{16}H_{18}ClN_3O_2S\cdot HCl$	49.49 (49.56	4.93 4.98	10.82 10.77)
4g	3-CH_3		114	23.9	219—220 (EtOH)	$C_{17}H_{21}N_3O_2S\cdot HCl\cdot 0.5H_2O$	54.18 (54.00	6.15 6.12	11.15 11.10)
4h	3-NO_2, 6-MeO	114[d]	110[d]	82.5	246—247 (EtOH–H_2O)	$C_{17}H_{20}N_4O_5S\cdot HCl$	47.61 (47.41	4.94 4.85	13.06 13.13)

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

around the basic nitrogen atoms of **4e** and FK360 overlapped in part as shown in Fig. 3. The result suggests that the negative MEPs of the basic nitrogen atoms of **4e** and FK360 can act on the same recognition site for AA activity.

In conclusion, i) the nitrogenous basic moiety at the C-2 position of thiazole ring is beneficial for the expression of AA activity, and ii) the 3D-MEP study suggests that **4e** and FK360 can act on the same recognition site for AA activity. These results will be useful for the 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 on a Varian EM-390 NMR (90 MHz), a Hitachi R90-H NMR (90 MHz) or a Bruker AC-200P (200 MHz) instrument using tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrophoto-

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Table 5. Pharmacological Data for **2c**, **4e**, **1** and FK360

Compound No.	Anti-anoxia (% of control) (mg/kg) 3.2	10	Upper; i.p. Lower; *p.o.* 32	100	Lipid peroxidation (% of control) (g/ml) 10^{-5}	Acute toxicity[a] LD_{50} (mg/kg, i.p.)
2c	108 110	131[b] 113[b]	143[b] 128[c]	175[b]	36.0	>560
4e	115[c] 105	132[c] 111[c]	212[b] 122[b]		9.0	>100<320
1		116[d] 100	143[c] 110	144[b]	96.0[c]	440
FK360		104	126[c] 114	168[c] 125[c]	80.0[c]	>560

a) 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. *b*) $p<0.001$. *c*) $p<0.01$. *d*) $p<0.05$. Values without superscripts are not statistically significantly different from the control.

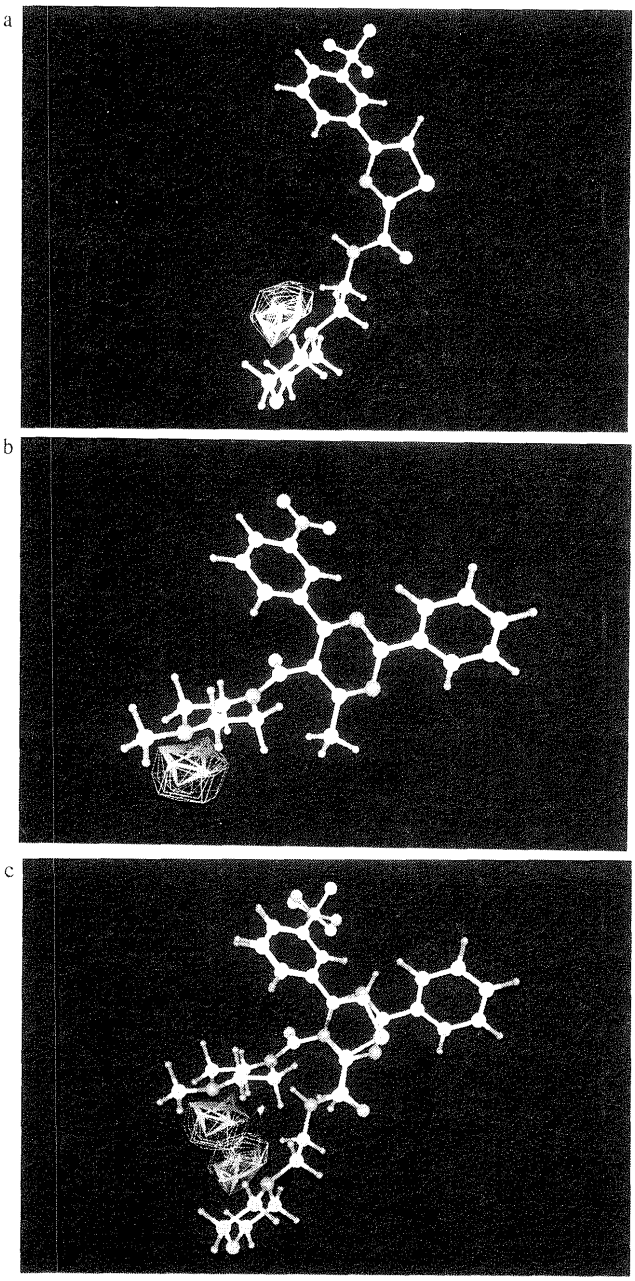

Fig. 3. (a) The 3D-MEP around the Basic Nitrogen Atom of **4e**, (b) 3D-MEP around the Basic Nitrogen Atom of FK360, (c) Superimposition of (a) and (b)

The contours each denote the isopotential surface of −5 kcal/mol.

meter. Mass spectral (MS) measurements were made on a Hitachi M-80 or a JEOL-D300 mass spectrometer.

2-Amino-4-(3-trifluoromethylphenyl)thiazole (5e) A mixture of 3-trifluoromethylacetophenone (5.0 g, 26.6 mmol), pyridinium bromide perbromide (10.0 g, 26.6 mmol) and 25% hydrobromide–acetic acid solution (5 ml) in acetic acid (50 ml) was stirred at room temperature for 30 min, then poured into water (50 ml) and extracted with ethyl acetate (100 ml). The extract was washed with saturated aqueous $NaHCO_3$, H_2O and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was dissolved in EtOH (5 ml), then thioamide (3.0 g, 39.9 mmol) was added. The whole was refluxed for 30 min, then poured into H_2O (50 ml) and extracted with ethyl acetate (100 ml). The extract was washed with H_2O and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The resulting solid was recrystallized from EtOH to afford **5e** (3.65 g, 56.2%) as a pale yellow solid, mp 84—85 °C. IR (Nujol) 3450, 3280, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.40 (2H, br), 6.79 (1H, s), 7.43—7.59 (2H, m), 7.83—8.13 (2H, m). MS *m/z*: 244 (M^+). The following compounds (**5a—d, f—t**) were prepared from appropriate ketones and thioamides by the same procedures as those noted for the preparation of **5e**, and these compounds were not further purified or analyzed before use in the next step.

2-Amino-4-phenylthiazole (**5a**)[8]: 85.1% yield.

2-Amino-4-(2-nitrophenyl)thiazole (**5b**)[9]: 59.4% yield.

2-Amino-4-(3-nitrophenyl)thiazole (**5c**)[10]: 85.6% yield.

2-Amino-4-(4-nitrophenyl)thiazole (**5d**)[10]: 77.2% yield.

2-Amino-5-methyl-4-(3-nitrophenyl)thiazole (**5f**)[11]: 88.1% yield.

2-Amino-5-ethoxycarbonyl-4-(3-nitrophenyl)thiazole (**5g**): 76.6% yield as a pale yellow solid, mp 228—230 °C (EtOH). IR (Nujol) 3400, 3300, 1690, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7 Hz), 4.15 (2H, q, J=7 Hz), 7.70 (1H, t, J=7 Hz), 8.00 (2H, br), 8.10—8.37 (2H, m), 8.53 (1H, d, J=2 Hz). MS *m/z*: 293 (M^+).

2-Amino-5-methyl-4-(4-nitrophenyl)thiazole (**5h**)[11]: 88.4% yield.

2-Amino-5-ethoxycarbonyl-4-(4-nitrophenyl)thiazole (**5i**)[12]: 60.9% yield.

2-Amino-4,5-dihydro-8-nitronaphtho[1,2-*d*]thiazole (**5j**): **5j** was prepared from 3,4-dihydro-7-nitro-1(2*H*)-naphtalenone[13] in 80.9% yield as an orange solid, mp 230—231 °C (EtOH). IR (Nujol): 3440, 3370, 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.86 (2H, t, J=7.0 Hz), 3.10 (2H, t, J=7.0 Hz), 7.15 (2H, br), 7.50 (1H, d, J=7.6 Hz), 7.98 (1H, dd, J=2.4, 7.6 Hz), 8.25 (1H, d, J=2.4 Hz).

2-Amino-5,6-dihydro-9-nitro-4*H*-benzo[6,7]cyclohepta[1,2-*d*]thiazole (**5k**): **5k** was prepared from 6,7,8,9-tetrahydro-3-nitro-5*H*-benzocyclohepten-5-one[14] in 79.6% yield as a yellow solid, mp 222—224 °C (EtOH). IR (Nujol): 3440, 3380, 1635 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.91—2.03 (2H, m), 2.80—3.07 (4H, m), 7.04 (2H, br), 7.43 (1H, d, J=8.0 Hz), 7.97 (1H, dd, J=2.6, 8.0 Hz), 8.82 (1H, d, J=2.6 Hz).

2-Amino-8-nitro-4*H*-[1]benzothiopyrano[4,3-*d*]thiazole (**5l**): **5l** was prepared from 2,3-dihydro-6-nitro-4*H*-1-benzothiopyran-4-one[15] in 78.5% yield as a red solid, mp >270 °C (EtOH). IR (Nujol): 3440, 3370, 1635 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.30 (2H, s), 7.29 (2H, br), 7.50 (1H, d, J=8.6 Hz), 7.94 (1H, dd, J=2.6, 8.6 Hz), 8.40 (1H, d, J=2.6 Hz).

2-Amino-8-nitro-4*H*-[1]benzopyrano[4,3-*d*]thiazole (**5m**): **5m** was prepared from 2,3-dihydro-6-nitro-4*H*-1-benzopyran-4-one[16] in 38.9% yield as a yellow solid, mp 215—217 °C (EtOH). IR (Nujol): 3450, 3350,

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1680, 1600 cm^{-1}.

2-Methylamino-4-(3-nitrophenyl)thiazole (**5n**): 79.5% yield as a pale yellow solid, mp 155—158 °C (EtOH). IR (Nujol): 3300, 1600, 1560 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.09 (1H, d, J=4 Hz), 5.73 (1H, br), 6.92 (1H, s), 7.60 (1H, dd, J=8, 8 Hz), 8.09—8.29 (2H, m), 8.73 (1H, d, J=2 Hz). MS m/z: 235 (M^+).

2-Acetylamino-4-(3-nitrophenyl)thiazole (**5o**)[10]: 77.6% yield.

2-Acetylamino-4-(3-trifluoromethylphenyl)thiazole (**5p**): 73.2% yield as a pale yellow solid, mp 230—231 °C (EtOH). IR (Nujol): 3170, 3060, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 7.67—7.70 (2H, m), 7.86 (1H, s), 8.19—8.24 (2H, m), 12.33 (1H, s).

2-Acetylamino-5-methyl-4-(3-nitrophenyl)thiazole (**5q**): 43.6% yield as a yellow solid, mp 245—246 °C (EtOH). IR (Nujol): 3170, 3060, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.15 (3H, s), 2.54 (3H, s), 7.75 (1H, dd, J=8.0, 8.0 Hz), 8.11 (1H, d, J=8.0 Hz), 8.19 (1H, dd, J=1.8, 8.0 Hz), 8.50 (1H, d, J=1.8Hz), 12.20 (1H, s).

2-Acetylamino-5-ethoxycarbonyl-4-(4-nitrophenyl)thiazole (**5r**): 84.2% yield as a white solid, mp 224—225 °C (EtOH). IR (Nujol): 3240, 3190, 17010, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (3H, t, J=7.2 Hz), 2.21 (3H, s), 4.21 (3H, q, J=7.2 Hz), 7.97 (2H, d, J=8.8 Hz), 8.29 (1H, d, J=8.8 Hz), 12.76 (1H, br).

2-Acetylamino-5-ethoxycarbonyl-4-(3-nitrophenyl)thiazole (**5s**) and 2-acetylamino-5-methyl-4-(4-nitrophenyl)thiazole (**5t**) were not isolated before use in the next step.

2-Bromoacetylamino-4-(3-trifluoromethylphenyl)thiazole (6e) Bromoacetyl bromide (0.64 ml, 7.37 mmol) was added to a mixture of **5e** (1.5 g, 6.14 mmol) and pyridine (0.69 ml, 7.37 mmol) in toluene (20 ml) at 10 °C. The whole was stirred at room temperature for 1 h, then poured into H_2O (20 ml) and extracted with ethyl acetate (50 ml). The extract was washed with H_2O and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The resulting solid was recrystallized from ether to afford **6e** (1.62 g, 72.3%) as a yellow solid, mp 177—178 °C. IR (Nujol): 3180, 1650, 1550 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.06 (2H, s), 7.26 (1H, s), 7.46—7.63 (2H, m), 7.89—8.11 (2H, s), 9.92 (1H, br). MS m/z: 364, 366 (M^+). The following compounds (**6a—d, f—n**) were prepared by the same procedures as those noted for the preparation of **6e**, and these compounds were not further purified or analyzed before use in the next step.

2-Bromoacetylamino-4-phenylthiazole (**6a**): 78.6% yield as a white solid, 181—182 °C (Et_2O). IR (Nujol): 3160, 1645, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.97 (2H, s), 7.29—7.49 (3H,m), 7.60 (1H, s), 7.89—7.93 (2H, m), 12.71 (1H, br).

2-Bromoacetylamino-4-(2-nitrophenyl)thiazole (**6b**): 80.2% yield as a pale yellow solid, 148—150 °C (Et_2O). IR (Nujol): 3150, 1645, 1600, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.18 (2H, s), 7.52—7.65 (1H, m), 7.64 (1H, s), 7.70—7.92 (2H, m), 12.63 (1H, br).

2-Bromoacetylamino-4-(3-nitrophenyl)thiazole (**6c**): 80.5% yield as a yellow solid, 223—224 °C (Et_2O). IR (Nujol): 3150, 1640, 1605, 1555 cm^{-1}. ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 4.06 (2H, s), 7.48 (1H, s), 7.57—7.70 (1H, m), 8.05—8.30 (2H, m), 8.72—8.80 (1H, m). MS m/z: 341, 343 (M^+).

2-Bromoacetylamino-4-(4-nitrophenyl)thiazole (**6d**): 87.7% yield as a yellow solid, 204—205 °C (Et_2O). IR (Nujol): 3340, 1690, 1645, 1595 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.21 (2H, s), 7.98 (1H, s), 8.16 (2H, d, J=8.8 Hz), 8.31 (2H, d, J=8.8 Hz), 12.82 (1H, br).

2-Bromoacetylamino-5-methyl-4-(3-nitrophenyl)thiazole (**6f**): 89.8% yield as a pale yellow solid, 172—171 °C (Et_2O). IR (Nujol): 3240, 1660, 1540 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.56 (3H, s), 4.02 (2H, s), 7.61 (1H, dd, J=8, 8 Hz), 8.02 (1H, d, J=8 Hz), 8.23 (1H, d, J=8 Hz), 8.53 (1H, m). MS m/z: 355, 357 (M^+).

2-Bromoacetylamino-5-ethoxycarbonyl-4-(3-nitrophenyl)thiazole (**6g**): 33.4% yield as a pale yellow solid, 155—157 °C (Et_2O). IR (Nujol): 3200, 1705, 1660, 1520 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7 Hz), 4.12 (2H, s), 4.35 (2H, q, J=7 Hz), 7.63 (1H, dd, J=8, 8 Hz), 8.13—8.40 (2H, m), 8.66 (1H, m). MS m/z: 413, 415 (M^+).

2-Bromoacetylamino-5-methyl-4-(4-nitrophenyl)thiazole (**6h**): 91.5% yield as a pale yellow solid, 226—227 °C (Et_2O). IR (Nujol): 3160, 1640, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.57 (3H, s), 4.17 (2H, s), 7.95 (2H, d, J=8.8 Hz), 8.32 (1H, d, J=8.8 Hz).

2-Bromoacetylamino-5-ethoxycarbonyl-4-(4-nitrophenyl)thiazole (**6i**) was not isolated before use in the next step.

2-Bromoacetylamino-*N*-methyl-4-(4-nitrophenyl)thiazole (**6j**): 88.1% yield as a pale yellow solid, mp 119—121 °C (Et_2O). IR (Nujol): 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.92 (3H, s), 4.23 (2H, s), 7.40 (1H, s), 7.57 (1H, dd, J=8, 8 Hz), 8.06—8.33 (2H, m), 8.73 (1H, d, J=2 Hz). MS m/z: 357, 415 (M^+).

2-Bromoacetylamino-4,5-dihydro-8-nitronaphtho[1,2-*d*]thiazole (**6k**): 82.1% yield as a yellow solid, mp 227—229 °C (Et_2O). IR (Nujol): 3150, 3050, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.01—3.07 (2H, m), 3.12—3.16 (2H, m), 4.19 (2H, s), 7.56 (2H, d, J=8.4 Hz), 8.06 (1H, dd, J=2.6, 8.4 Hz), 8.37 (1H, d, J=2.6 Hz).

2-Bromoacetylamino-5,6-dihydro-9-nitro-4*H*-benzo[6,7]cyclohepta-[1,2-*d*]thiazole (**6l**): 93.0% yield as a pale yellow solid, mp 219—220 °C (Et_2O). IR (Nujol): 3180, 3080, 1660 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.99—2.08 (2H, m), 2.96—3.11 (4H, m), 4.18 (2H, s), 7.52 (1H, d, J=8.4 Hz), 8.05 (1H, dd, J=2.4, 8.4 Hz), 8.85 (1H, d, J=2.4 Hz).

2-Bromoacetylamino-8-nitro-4*H*-[1]benzothiopyrano[4,3-*d*]thiazole (**6m**): 80.7% yield as a yellow solid, mp 270—272 °C (Et_2O). IR (Nujol): 3230, 1665 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.43 (2H, s), 4.48 (2H, s), 7.61 (1H, d, J=8.8 Hz), 8.02 (1H, dd, J=2.4, 8.6 Hz), 8.52 (1H, d, J=2.4 Hz).

2-Bromoacetylamino-8-nitro-4*H*-[1]benzopyrano[4,3-*d*]thiazole (**6n**): 81.0% yield as a yellow solid, mp 244—245 °C (EtOH). IR (Nujol): 1635 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.20 (2H, s), 5.71 (2H, s), 7.13 (1H, d, J=8.6 Hz), 8.10 (1H, dd, J=2.4, 8.6 Hz), 8.31 (1H, d, J=2.4 Hz).

2-(4-Morpholinyl)acetylamino-4-(3-trifluoromethylphenyl)thiazole Hydrochloride (2e) Morpholine (5.97 ml, 68.0 mmol) was added to a solution of **6e** (10.0 g, 27.0 mmol) in CH_2Cl_2 (100 ml) at 5 °C. The reaction mixture was stirred at room temperature for 2 h, then poured into water (50 ml) and extracted with CH_2Cl_2 (100 ml). The extract was washed with H_2O and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was dissolved in EtOH (80 ml) and a solution of 4 mM HCl in EtOH (7.86 ml) was added at 5 °C. The whole was stirred at room temperature for 1 h, and then evaporated *in vacuo*. The resulting solid was recrystallized from a mixture of EtOH (40 ml) and H_2O (7 ml) to afford **2e** (5.48 g, 53.0%) as a yellow solid. The compounds (**2a—d, h—s**) were prepared by the same procedures as those noted for the preparation of **2e**. Physical properties and spectral data of these compounds are listed in Tables 1, 2 and 6.

2-(4-Morpholinyl)acetylamino-4-(3-aminophenyl)thiazole Dihydrochloride (2f) HCl (1.6 mmol) in EtOH (0.4 ml) was added to a mixture of **2c** (0.5 g, 1.3 mmol) and 10% Pd–C (0.15 g) in EtOH (30 ml)–H_2O (10 ml), and hydrogenation was conducted at atmospheric pressure of hydrogen for 1 h. The insoluble materials were removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from EtOH–H_2O to afford **2f** (0.3 g, 72.3%) as a pale yellow solid. Physical properties and spectral data of this compound are listed in Tables 1 and 6.

2-(4-Morpholinyl)acetylamino-4-(3-methanesulfonylaminophenyl)thiazole Hydrochloride (2g) Methanesulfonyl chloride (0.27 ml, 3.45 mmol) was added to a mixture of **2f** (1.0 g, 3.14 mmol) and pyridine (0.56 ml, 6.98 mmol) in CH_2Cl_2 at room temperature. The whole was stirred for 1 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 dissolved in a solution of HCl (4.5 mmol) in EtOH (10 ml), and then evaporated *in vacuo*. The resulting solid was collected by filtration and recrystallized from EtOH–H_2O to afford **2g** (1.99 g, 72.8%) as a pale yellow solid. Physical properties and spectral data of these compounds are listed in Tables 1 and 6.

***N*-Acetyl-2-[2-(4-morpholinyl)ethyl]amino-4-(3-nitrophenyl)thiazole Hydrochloride (3b)** NaH (60% suspension in oil) (1.1 g, 27.4 mmol) was added to a solution of **5o** (3.0 g, 11.4 mmol) in *N*,*N*-dimethylformamide (DMF) (30 ml) at 5 °C. The reaction mixture was stirred at room temperature for 30 min, and then morpholinoethyl chloride (2.54 g, 13.7 mmol) was added. The whole was heated at 60 °C for 2 h, then poured into water (50 ml) and extracted with ethyl acetate (100 ml). The extract was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was dissolved in a solution of HCl in EtOH, and then evaporated *in vacuo*. The resulting solid was recrystallized from EtOH–H_2O to afford **3b** (0.47 g, 74.0%) as a pale yellow solid. The compounds (**3c—g**) were prepared by the same procedures as those noted for the preparation of **3b**. Physical properties and spectral data of these compounds are listed in Tables 3 and 6.

2-[2-(4-Morpholinyl)ethyl]amino-4-(3-nitrophenyl)thiazole Hydrochloride (3a) A solution of **3b** (0.2 g) in a mixture of concentrated HCl (1 ml) and EtOH (2 ml) was refluxed for 3 h. The whole was allowed to cool to room temperature, then evaporated *in vacuo*. The resulting precipitates were collected by filtration and recrystallized from EtOH–H_2O to afford **3a** (0.47 g, 74.0%) as a pale yellow solid. Physical

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Table 6. Spectral Data for Thiazoles (2, 3 and 4)

Compd. No.	MS, m/z, M^+	IR (Nujol) cm^{-1}	Solvent[a]	^{1}H-NMR (ppm)[b]
2a	303	3120, 1695	A	3.46—3.64 (4H, m), 3.95—4.15 (4H, m), 4.48 (2H, s), 7.40—7.58 (3H, m), 7.70 (1H, s), 7.88—8.05 (2H, m)
2b	348	3260, 1685, 1560	A	3.22—3.50 (4H, m), 3.75—3.95 (4H, m), 4.29 (2H, s), 7.53—7.92 (4H, m), 7.65 (1H, s), 12.82 (1H, br)
2c	348	3250, 1685	A	3.45—2.62 (4H, m), 4.25—4.80 (4H, m), 4.40 (2H, s), 3.10—3.55 (2H, m), 7.66—8.83 (5H,m)
2d	348	1680, 1585	A	3.25—3.45 (4H, m), 3.75—3.95 (4H, m), 4.30 (2H, s), 8.25 (1H, s), 8.18 (2H, d, J=8 Hz), 8.35 (2H, d, J=8 Hz)
2e	371	1690	A	3.35—3.50 (4H, m), 3.85—4.00 (4H, m), 4.35 (2H, s), 7.64—7.74 (2H, m), 8.00 (1H, s), 8.15—8.25 (2H, m), 13.05 (1H, br)
2f	318	3320, 1695, 1550	A	3.35—3.60 (4H, m), 3.95—4.15 (4H, m), 4.46 (2H, s), 7.49—7.73 (2H, m), 7.86 (1H, s), 7.90—8.04 (2H, m), 13.05 (1H, br)
2g	396	1685, 1600	A	3.03 (3H, s), 3.40—3.55 (4H, m), 3.85—4.10 (4H, m), 4.41 (2H, s), 7.28—7.48 (2H, m), 7.53—7.68 (1H, m), 7.60 (1H, s), 7.84—7.86 (1H, m), 9.98 (1H, s)
2h	362	1680	B	2.63 (3H, s), 2.64—2.80 (4H, m), 3.30 (2H, s), 3.73—3.96 (4H, m), 7.50—8.60 (4H, m), 10.40 (1H, s)
2i	420	1705, 1690	B	1.30 (3H, t, J=7 Hz), 2.55—2.75 (4H, m), 3.22 (2H, s), 3.72—3.92 (4H, m), 7.30 (2H, q, J=7 Hz), 7.83—8.73 (4H, m)
2j	362	3580, 3420, 1695, 1590	A	2.68 (3H, s), 3.40—3.53 (4H, m), 3.82—4.05 (4H, m), 4.39 (2H, s), 7.92 (2H, d, J=8 Hz), 8.28 (2H, d, J=8 Hz)
2k	420	1705, 1685	A	1.57 (3H, t, J=7 Hz), 3.33—3.52 (4H, m), 3.85—4.10 (4H, m), 4.32 (2H, q, J=7 Hz), 4.41 (2H, s), 8.02 (2h, d, J=8 Hz), 8.38 (2H, d, J=8 Hz)
2l	362	1650	B	2.50—2.66 (4H, m), 3.43 (2H, s), 3.63—3.79 (4H, m), 3.86 (3H, s), 7.33 (1H, s), 7.53 (1H, dd, J=8 Hz), 8.00—8.26 (2H, m), 8.67—8.69 (1H, m)
2m	364	1635	A	2.50—2.86 (8H, m), 3.39 (2H, s), 7.63—8.83 (5H, m)
2n	346	1680	A	1.40—1.58 (6H, m), 2.52—2.60 (4H, m), 3.32 (2H, s), 7.60—8.75 (5H, m)
2o	332	1695	A	1.65—1.80 (4H, m), 2.50—2.70 (4H, m), 3.44 (2H, s), 7.70—8.72 (5H, m)
2p	374	1685	A	3.05—3.15 (4H, m), 3.30—3.60 (4H, m), 3.82—3.94 (4H, m), 4.29 (2H, s), 7.53 (1H, d, J=8 Hz), 8.04 (1H, dd, J=8 Hz), 8.34 (1H, d, J=2 Hz)
2q	388	1690, 1560	A	1.96—2.16 (2H, m), 2.81—3.04 (4H, m), 3.52—3.60 (4H, m), 4.00—4.12 (4H, m), 4.35 (2H, s), 7.46 (1H, d, J=8 Hz), 7.95 (1H, dd, J=2, 8 Hz), 8.52 (1H, d, J=2 Hz)
2r	392	3360, 1680	A	3.15—3.35 (4H, m), 3.77—3.90 (4H, m), 4.18 (2H, s), 4.45 (2H, s), 7.54 (1H, d, J=8 Hz), 7.97 (1H, dd, J=2, 8 Hz), 8.48 (1H, d, J=2 Hz)
2s	376	3400, 1680, 1560	A	3.30—3.45 (4H, m), 3.82—3.96 (4H, m), 4.32 (2H, s), 5.70 (2H, s), 7.08 (1H, d, J=8 Hz), 8.05 (1H, dd, J=2, 8 Hz), 8.26 (1H, d, J=2 Hz)
3a	334	3160, 1620, 1600	A	3.30—3.55 (6H, m), 3.75—4.05 (6H, m), 7.48 (1H, s), 7.70 (1H, dd, J=8, 8 Hz), 8.06—8.38 (2H, m), 8.60—8.63 (1H, m)
3b	376	3360, 1660	A	2.53 (3H, s), 3.40—3.70 (6H, m), 3.90—4.10 (4H, m), 4.56—4.94 (2H, m), 7.74 (1H, dd, J=8, 8 Hz), 8.03 (1H, s), 8.14—8.38 (1H, m), 8.44—8.66 (1H, m), 8.72—8.76 (1H, m)
3c	399	3440, 1660	A	2.52 (3H, s), 3.40—3.70 (6H, m), 3.90—4.10 (4H, m), 4.64—4.88 (2H, m), 7.66—7.77 (2H, m), 7.97 (1H, s), 8.30—8.38 (2H, m)
3d	390	3450, 3380, 1655	A	2.53 (3H, s), 2.57 (3H, s), 3.35—3.70 (6H, m), 3.90—4.10 (4H, m), 4.60—4.85 (2H, m), 7.76 (1H, dd, J=8, 8 Hz), 8.16—8.38 (2H, m), 8.56—8.60 (1H, m)
3e	448	3400, 1690, 1650	A	1.24 (3H, t, J=7 Hz), 2.58 (3H, s), 3.35—3.70 (6H, m), 3.85—3.98 (4H, m), 4.26 (2H, q, J=7 Hz), 4.60—4.76 (2H, m), 7.78 (1H, dd, J=8, 8 Hz), 8.28—8.43 (2H, m), 8.72—8.75 (1H, m)
3f	390	1660, 1595	A	2.52 (3H, s), 2.56 (3H, s), 3.35—3.70 (6H, m), 3.90—4.10 (4H, m), 4.56—4.82 (2H, m), 8.10 (2H, d, J=8 Hz), 8.56 (2H, d, J=8 Hz)
3g	448	1720, 1675, 1600	A	1.26 (3H, t, J=7 Hz), 2.56 (3H, s), 3.23—3.65 (6H, m), 3.76—3.94 (4H, m), 4.24 (2H, q, J=7 Hz), 4.60—4.76 (2H, m), 8.18 (2H, d, J=8 Hz), 8.38 (2H, d, J=8 Hz)
4a	316	3250, 1665	A	3.20—3.54 (6H, m), 3.72—4.02 (6H, m), 7.38—7.58 (3H, m), 8.17—8.22 (2H, m), 8.46 (1H, s), 9.23—9.36 (1H, m)
4b	362	3200, 1660	A	3.34—3.50 (8H, m), 3.72—4.08 (4H, m), 7.83—8.08 (4H, m), 8.30 (1H, s), 9.00—9.08 (1H, m)
4c	362	3300,1650	A	3.35—3.65 (6H, m), 3.95—4.15 (6H, m), 7.84 (1H, dd, J=8, 8 Hz), 8.22—8.93 (3H, m), 8.85 (1H, s), 9.35—9.50 (1H, m)
4d	362	3380, 1665, 1600	A	3.25—3.40 (8H, m), 3.67—3.96 (4H, m), 8.22—8.43 (4H, m), 8.72 (1H, s), 9.28—9.40 (1H, m)
4e	385	3220, 1660	A	3.32—3.56 (6H, m), 3.70—4.08 (6H, m), 7.72—7.80 (2H, m), 8.43—8.54 (2H, m), 8.74 (1H, s), 9.31—9.50 (1H, m)
4f	349	3300, 1665	A	3.20—3.56 (8H, m), 3.68—4.00 (4H, m), 7.45—7.54 (2H, m), 8.05—8.15 (1H, m), 8.24—8.26 (1H, m), 8.60 (1H, s), 9.26—9.38 (1H, m)
4g	331	3450, 3340, 3240, 1640	A	2.38 (3H, s), 3.15—3.60 (8H, m), 3.68—4.00 (4H, m), 7.14—7.42 (2H, m), 7.83—7.94 (2H, m), 8.39 (1H, s), 9.18—9.32 (1H, m)
4h	392	3380, 1655, 1580	A	3.26—3.53 (6H, m), 3.60—3.96 (6H, m), 4.10 (3H, s), 7.38 (1H, d, J=8 Hz), 8.26 (1H, dd, J=2, 8 Hz), 8.53 (1H, s), 9.12 (1H, d, J=2 Hz), 9.20—9.34 (1H, m)

a) A, DMSO-d_6; B, $CDCl_3$. b) Listed as chemical shifts (number of protons, multiplicity, constant).

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properties and spectral data of these compounds are listed in Tables 3 and 6.

Ethyl 4-(3-Trifluoromethylphenyl)-2-thiazolecarboxylate (7e) A mixture of 3-trifluoromethylacetophenone (2.0 g, 10.6 mmol), pyridinium bromide perbromide (3.78 g, 10.6 mmol) and 25% hydrobromide–acetic acid solution (2 ml) in acetic acid (20 ml) was stirred at room temperature for 30 min, then poured into H_2O (30 ml) and extracted with ethyl acetate (60 ml). The extract was washed with saturated aqueous $NaHCO_3$, H_2O and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was dissolved in EtOH (20 ml), and then ethyl thioxamate[3] (1.55 g, 11.7 mmol) was added. The whole was refluxed for 30 min, then poured into H_2O (30 ml) and extracted with ethyl acetate (60 ml). The extract was washed with H_2O and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The resulting solid was recrystallized from Et_2O to afford **7e** (1.80 g, 56.6%) as a white solid, mp 108—109 °C. IR (Nujol): 1720 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.48 (3H, t, J=7.0 Hz), 4.52 (2H, q, J=7.0 Hz), 7.53—7.66 (2H, m), 7.84 (1H, s), 8.15 (1H, d, J=7.2 Hz), 8.21 (1H, s). The following compounds (**7a—c, d—h**) were prepared by the same procedures as those noted for the preparation of **7e**, and these compounds were not further purified or analyzed before use in the next step.

Ethyl 4-Phenyl-2-thiazolecarboxylate (**7a**)[17]: 73.5% yield.

Ethyl 4-(2-Nitrophenyl)-2-thiazolecarboxylate (**7b**): 33.8% yield as a white solid, mp 86—88 °C (Et_2O). IR (Nujol): 1720 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7.0 Hz), 4.49 (2H, q, J=7.0 Hz), 7.51—7.62 (2H, m), 7.65 (1H, s), 7.69—7.74 (1H, m), 7.90 (1H, dd, J=1.2, 8.0 Hz).

Ethyl 4-(3-Nitrophenyl)-2-thiazolecarboxylate (**7c**): 83.3% yield as a pale yellow solid, mp 143—144 °C (Et_2O). IR (Nujol): 1720 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.46 (3H, t, J=7.0 Hz), 4.48 (2H, q, J=7.0 Hz), 7.60 (1H, dd, J=8.0, 8.0 Hz), 7.90 (1H, s), 8.18—8.40 (2H, m), 8.75 (1H, d, J=2.0 Hz).

Ethyl 4-(4-Nitrophenyl)-2-thiazolecarboxylate (**7d**): 76.3% yield as a pale yellow solid, mp 182—183 °C (Et_2O). IR (Nujol): 1720 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.46 (3H, t, J=7.0 Hz), 4.57 (2H, q, J=7.0 Hz), 8.00 (1H, s), 8.17 (2H, d, J=8.0 Hz), 8.40 (2H, d, J=8.0 Hz).

Ethyl 4-(3-Chlorophenyl)-2-thiazolecarboxylate (**7f**): 70.2% yield as a white solid, mp 84—85 °C (Et_2O). IR (Nujol): 1720 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.47 (3H, t, J=7.0 Hz), 4.52 (2H, q, J=7.0 Hz), 7.31—7.38 (2H, m), 7.77 (1H, s), 7.80—7.97 (1H, m), 8.24 (1H, s).

Ethyl 4-(3-Methylphenyl)-2-thiazolecarboxylate (**7g**) was not isolated before use in the next step.

Ethyl 4-(6-Methoxy-3-nitrophenyl)-2-thiazolecarboxylate (**7h**): 79.6% yield as a white solid. IR (Nujol): 1720 cm^{-1}.

***N*-[2-(4-Morpholinyl)ethyl]-4-(3-trifluoromethylphenyl)-2-thiazolecarboxamide Hydrochloride (4e)** A mixture of **7e** (1.0 g, 3.32 mmol) and morpholine (1.3 ml) was heated at 100 °C for 30 min, and then poured into H_2O (20 ml) and extracted with ethyl acetate (50 ml). The extract was washed with H_2O and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was dissolved in a solution of HCl (4.0 mmol) in EtOH (10 ml), then the whole was evaporated *in vacuo*. The resulting precipitates were collected by filtration and recrystallized from EtOH to afford **4e** (0.69 g, 49.3%) as a pale yellow solid. The other compounds (**4a—d, f—h**) were prepared by the same procedures as those noted for the preparation of **4e**. Physical properties and spectral data of these compounds are listed in Tables 4 and 6.

AA (100% N_2) Activity in Mice[1b] 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.

ALP Activity in Rat Brain Mitochondria[1b] Brain mitochondria obtained from a male Wistar rat were incubated with 100 μM ascorbic acid, 20 μM $FeSO_4$ and the test compound for 1 h at 37 °C. Malondialdehyde formed in the incubation mixture was measured by the thiobarbituric acid method according to Shimada and Yasuda.[18] Test compounds were dissolved in EtOH.

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References and Notes

1) *a*) Part VII: Ohkubo M., Kuno A., Sakai H., Sugiyama Y., Takasugi H., *Chem. Pharm. Bull.*, **43**, 947 (1995); *b*) Part I: Kuno A., Sugiyama Y., Katsuta K., Kamitani T., Takasugi H., *ibid.*, **40**, 1452 (1992); *c*) Part V: Kuno A., Sakai H., Ohkubo M., Takasugi H., *ibid.*, **41**, 163 (1993); *d*) Part III: Kuno A., Katsuta K., Sakai H., Ohkubo M., Sugiyama Y., Takasugi H., *ibid.*, **41**, 139 (1993).
2) Metzger J. V., Vincent E. J., Chouteau J., Mille G., *Chem. Heterocycl. Comp.*, **34**, 23 (1979).
3) Boon W. R., *J. Chem. Soc.*, **1945**, 601.
4) Bhargava P. N., Ram P., Singh K. I., *J. Indian Chem. Soc.*, **39**, 396 (1962).
5) The energy maps of **2c** and **2h** on bond rotation between the phenyl at the C-4 position and the thiazole ring each gave two energy minima. The perpendicular conformation of **2h** was observed almost at the energy minima. The energy of the coplanar conformation was about 3.5 kcal/mol higher than that of the perpendicular conformation. On the other hand, the coplanar conformation of **2c** was observed nearly at the energy minima. These calculations were carried out by using the program AM1(MOPAC 7).[6]
6) Stewart J. J. P., *QCPE Bull.*, **13**, 42 (1993).
7) The calculations were made on the free base, although the nitrogen atom could be protonated at the recognition site.
8) Bhargava P. N., Ram P., Singh K. I., *J. Indian Chem. Soc.*, **37**, 241 (1960).
9) Okamiya J., *Nippon Kagaku Zasshi*, **82**, 87 (1961) [*Chem. Abstr.*, **56**, 10122 (1962)].
10) King L. C., Hlavacek R. J., *J. Am. Chem. Soc.*, **72**, 3722 (1950).
11) Silberg A. E., Frenkel Z., Szotyori L., Axente V., *Farm. Bucharest*, **22**, 305 (1974).
12) Balog A., Benko A., *Studia Univ. Babes Bolyai*, **1**, 155 (1960); [*Chem. Abstr.*, **58**, 4534 (1963)].
13) Nichols D. E., Cassady J. M., Persons P. E., Yeung M. C., Clemens J. A., Smalstig E. B., *J. Med. Chem.*, **32**, 2128 (1989).
14) Smith P. A. S., Berry W. L., *J. Org. Chem.*, **26**, 27 (1961).
15) Young T. E., Scott P. H., *J. Org. Chem.*, **30**, 3613 (1965).
16) Patton J. R., Gurusamy N., Eur. Patent Appl., EP228172 [*Chem. Abstr.*, **108**, 112230 (1988)].
17) Kempter G., Schaefer H., Sarodnick G., *Z. Chem.*, **10**, 460 (1970).
18) Shimada O., Yasuda H., *Biochim. Biophys. Acta*, **489**, 163 (1977).

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