Preparation and Pharmacological Evaluation of 4-(1,4-Benzoquinon-2-yl)-4-phenylbutanamides as Potential Cerebral Protective Agents[1)]

Toshio TATSUOKA,*[,a] Kenji SUZUKI,[a] Kayoko IMAO,[a] Fumio SATOH,[a] Takafumi ISHIHARA,[a] Ichiro HIROTSU,[a] Tetsuro KIHARA,[a] Mizuho HATTA,[a] Yoshiko HORIKAWA,[a] Kunihiro SUMOTO,[b] and Seiji MIYANO*[,b]

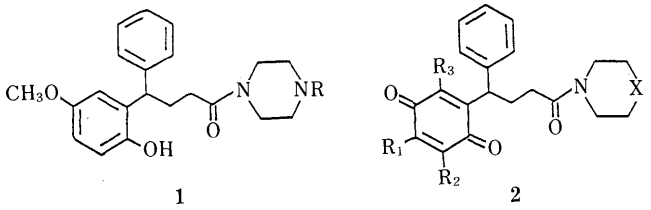
Suntory Institute for Biomedical Research,[a] Wakayamadai, Shimamoto-cho, Mishimagun, Osaka 618, Japan and Faculty of Pharmaceutical Sciences, Fukuoka University,[b] Nanakuma, Jonan-ku, Fukuoka 814-01, Japan. *Received December 16, 1991*

A new series of 4-(1,4-benzoquinon-2-yl)-4-phenylbutanamides (2) were synthesized for evaluation of their pharmacological activities. All these compounds synthesized showed significant antilipidperoxidation (ALP) activities with brain homogenate in rats and some of them possessed a protective effect against hypobaric hypoxia in mice. Especially, a thiomorpholine derivative (2l, SUN-4757) showed a wide efficacy spectrum to a variety of experimental screening assays designed for cerebral protective agents, and it had a high LD_{50} value.

Keywords SUN-4757; 2,3,4,5-tetrahydro-1-benzoxepin-2-one; 4-phenylbutanamide; 1,4-benzoquinone; N-substituted thiomorpholine; antilipidperoxidation; cerebral protective agent

In the course of our studies on cerebral protective agents that affect cerebral blood flow circulation and metabolism in the aged brain or in cerebral vascular disease, we have reported the synthesis and pharmacological evaluation of a novel class of compounds, 4,4-diarylbutanamides and related compounds.[1a)] Many of these compounds showed significant activities in response to the experimental screening assays designed for our project.

Especially, the compounds represented as the structure



1 2

Fig. 1

(**1**) showed a wide spectrum of activity in response to various screening assays such as antilipidperoxidation (ALP), hypobaric hypoxia, global ischemia, and so on. This led us to design new derivatives (**2**) which contain a quinonyl moiety instead of a substituted aryl group in the molecule (**1**) (see Fig. 1).

Our reasoning for this line of investigation hinges on the hypothesis that subtle changes in the lipophilic–hydrophilic nature of such compounds might lead to unique pharmacological properties. Further, we reasoned the compound containing benzoquinone functionality that might be responsible for the biological events such as free radical damage of the brain following ischemia[2)] or redox cycles *in vivo*.[3)]

This paper describes the synthesis and pharmacological evaluation of new 4-(1,4-benzoquinon-2-yl)-4-arylbutanamides (**2**) which demonstrate marked cerebral protective activity.

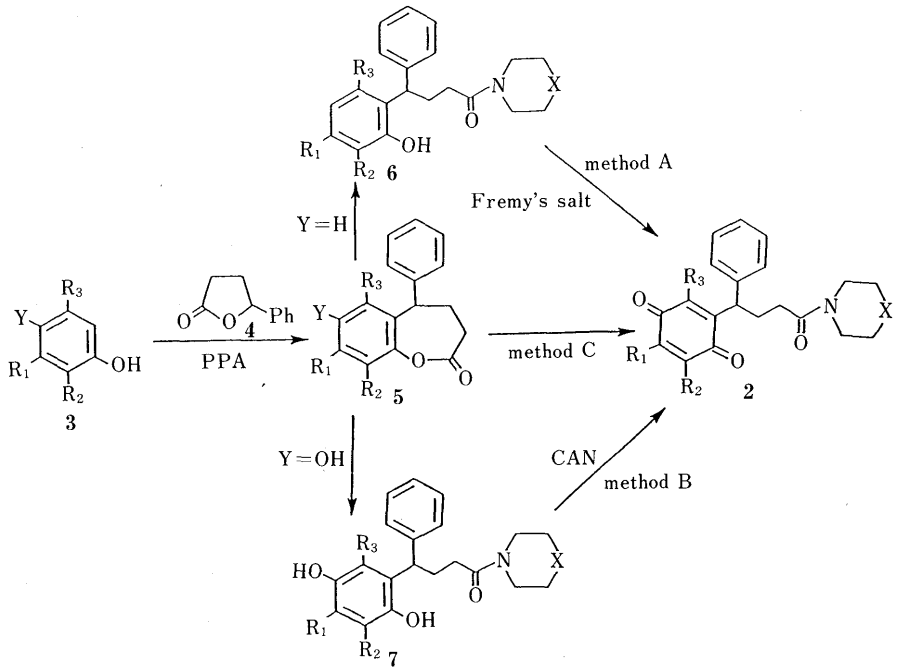


Chart 1

Chemistry

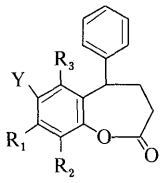
The synthetic procedures for the target compounds are summarized in the Chart 1. The key compounds in the procedure are 5-phenyl-2,3,4,5-tetrahydro-1-benzoxepin-2-ones (**5**) easily obtained from the reaction of hydroquinone or phenol derivatives (**3**) with γ-phenyl-γ-butyrolactone (**4**). Ring opening reaction of (**5**) with various amines, followed by oxidation, gave the title compounds (**2**). In some runs, the intermediate phenol or hydroquinone derivatives (**6**: Y=H or **7**: Y=OH) could be isolated in good yields. The oxidation of hydroquinones (**7**) with cerium ammonium nitrate (CAN) also afforded the title 1,4-benzoquinone derivatives (**2**).

The compounds having no hydroxy group at the *para* position of the starting phenols (**3**: Y=H) afforded ring-opened compounds (**6**), the oxidation of which also can be attained by Fremy's salt to give the target 4-(1,4-benzoquinon-2-yl)-4-phenylbutanamides (**2**).

The sulfoxide **2n** and sulfone **2o** were obtained from oxidation of the sulfide **2l** with *m*-chloroperbenzoic acid (*m*-CPBA) (method D, see Experimental).

The structures of the compounds (**2**) prepared by the above routes were confirmed by spectroscopic infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR), and mass spectrum (MS) and elemental analysis. All compounds showed correct *m/z* for the corresponding molecular ions

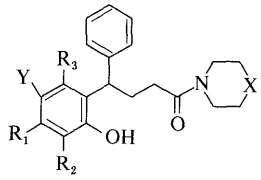
TABLE I. Physical Data for 5-Phenyl-2,3,4,5-tetrahydro-1-benzoxepin-2-ones (**5**)



Compd.	R_1	R_2	R_3	Y	Yield (%)	IR, cm^{-1} (C=O)[a]	^{1}H-NMR (R_1, R_2, R_3)[b]	Formula	Analysis[c] Calcd	Found
5a	H	H	H	OH	27	1760	[b]	$C_{16}H_{14}O_3$	254.0943	254.0929
5b	CH_3	H	H	OH	26	1740	2.20 (3H, s, $-CH_3$)	$C_{17}H_{16}O_3$	268.1100	268.1104
5c	CH_3	CH_3	H	H	24	1742	2.21 (3H, s, $-CH_3$), 2.25 (3H, s, $-CH_3$)	$C_{18}H_{18}O_2$	266.1307	266.1333
5d	H	CH_3	CH_3	H	34	1740	2.20 (3H, s, $-CH_3$), 2.32 (3H, s, $-CH_3$)	$C_{18}H_{18}O_2$	266.1307	266.1353
5e	CH_3	H	CH_3	H	62	1740	2.31 (6H, s, 2×$-CH_3$)	$C_{18}H_{18}O_2$	266.1307	266.1300
5f	CH_3	CH_3	CH_3	OH	46	1734	2.10 (3H, s, $-CH_3$), 2.18 (3H, s, $-CH_3$), 2.20 (3H, s, $-CH_3$)	$C_{19}H_{20}O_3$	296.1412	296.1373
5g	OCH_3	OCH_3	H	OH	21	1752	3.96 (6H, s, 2×$-OCH_3$)	$C_{18}H_{18}O_5$	314.1154	314.1138
5h	OCH_3	OCH_3	CH_3	OH	19	1752	2.21 (3H, s, $-CH_3$), 3.83 (3H, s, $-OCH_3$), 3.99 (3H, s, $-OCH_3$)	$C_{19}H_{20}O_5$	328.1311	328.1266

a) Measured as $CHCl_3$ solution, except for **5a** and **5f** (liq. film). *b*) Measured in $CDCl_3$ using tetramethylsilane as an internal standard. Aromatic protons were observed at δ: 6.12—7.50; other aliphatic protons assignable to the benzoxepin-2-one ring were observed at δ: 2.15—3.95 (4H, m, $-CH_2CH_2-$) and δ: 4.30—4.70 (1H, m, or dd, a benzylic H). Phenolic OH protons disappeared by treatment with D_2O. *c*) Determined by high-resolution mass spectrometry.

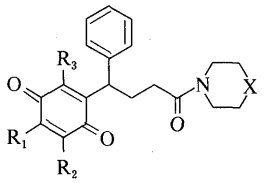
TABLE II. Selected Physical Data for 4,4-Diarylbutanamides (**6** and **7**)



Compd.	R_1	R_2	R_3	X	Y	Yield (%)	IR cm^{-1} (C=O)[a]	^{1}H-NMR (R_1, R_2, R_3)[b]	Formula	Analysis (%) Calcd (Found) C	H	N
6e	CH_3	CH_3	H	S	H	65	1634	2.22 (3H, s, $-CH_3$), 2.24 (3H, s, $-CH_3$)	$C_{22}H_{27}NSO_2$	369.1763[c] (369.1806)		
6f	H	CH_3	CH_3	S	H	60	1624	2.06 (3H, s, $-CH_3$), 2.21 (3H, s, $-CH_3$)	$C_{22}H_{27}NSO_2$	71.51 (71.05	7.36 7.46	3.79 3.59)
6g	CH_3	H	CH_3	S	H	77	1618	2.10 (3H, s, $-CH_3$), 2.22 (3H, s, $-CH_3$)	$C_{22}H_{27}NSO_2$	71.51 (71.45	7.36 7.41	3.79 3.75)
7a	H	H	H	O	OH	92	1611	[b]	$C_{20}H_{23}NO_4$	341.1627[c] (341.1670		
7b	H	H	H	S	OH	62	1630	[b]	$C_{20}H_{23}NSO_3$	357.1399[c] (357.1447)		
7c	H	H	H	NCH_3	OH	72	1610	[b]	$C_{21}H_{26}N_2O_3$	354.1943[c] (354.1931)		

a) Measured as $CHCl_3$ solution (**6e—f**), or KBr tablet (**7a—c**). *b*) Measured in $CDCl_3$ using tetramethylsilane as an internal standard. Aromatic protons were observed at δ: 6.19—7.80; a benzylic proton was observed at δ: 4.10—4.75 (1H, t, or m) and other aliphatic protons were observed at δ: 2.10—4.29. Phenolic OH protons disappeared by treatment with D_2O. The N–CH_3 protons of the compound **7c** was observed at δ: 2.25 as a singlet. *c*) Determined by high-resolution mass spectrometry.

TABLE III. Selected Physical Data for Target Compounds (**2a—o**)



Compd.	R_1	R_2	R_3	X	Method	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
2a	H	H	H	O	B	87	103—105	$C_{20}H_{21}NO_4$	70.78	6.24	4.13	70.30	6.28	4.08
2b	H	H	H	S	B	54	59—61	$C_{20}H_{21}NO_3S$	67.58	6.28	4.08	67.48	6.05	4.86
2c	H	H	H	N-CH_3	B	65	140—142	$C_{21}H_{24}N_2O_3$		352.1787[c]			352.1399	
2d	CH_3	H	H	S	C	69	101—103	$C_{21}H_{23}NO_3S$		369.1399[c]			369.1443	
2e	CH_3	CH_3	H	S	A	83	96—98	$C_{22}H_{25}NO_3S$	68.90	6.57	3.65	68.92	6.53	3.66
2f	H	CH_3	CH_3	S	A	75	109—110	$C_{22}H_{25}NO_3S$	69.90	6.57	3.65	69.76	6.63	3.58
2g	CH_3	H	CH_3	S	A	52	43—45	$C_{22}H_{25}NO_3S$		383.1555[c]			383.1567	
2h	CH_3	CH_3	CH_3	S	C	72	79—80	$C_{23}H_{27}NO_3S$		397.1712[c]			397.1683	
2i	CH_3	CH_3	CH_3	N-CH_3	C	73	203—205[a]	$C_{24}H_{30}N_2O_3$		394.2256[c]			394.2209	
2j	OCH_3	OCH_3	H	S	C	81	[b]	$C_{22}H_{25}NO_5S$		415.1454[c]			415.1503	
2k	OCH_3	OCH_3	CH_3	O	C	68	74—76	$C_{23}H_{27}NO_6$	66.81	6.58	3.39	66.74	6.82	3.34
2l	OCH_3	OCH_3	CH_3	S	C	47	128—129	$C_{23}H_{27}NO_5S$	64.31	6.34	3.26	64.17	6.45	3.21
2m	OCH_3	OCH_3	CH_3	N-CH_3	C	57	97—99[a]	$C_{24}H_{30}N_2O_5$		426.2155[c]			426.2132	
2n	OCH_3	OCH_3	CH_3	SO	D	90	122—124	$C_{23}H_{27}NO_6S$	62.00	6.11	3.14	61.95	6.16	3.10
2o	OCH_3	OCH_3	CH_3	SO_2	D	73	118—121	$C_{23}H_{27}NO_7S$	59.85	5.90	3.04	59.72	5.91	3.02

a) As hydrochloride. *b*) Obtained as an oil. *c*) Determined by high-resolution mass spectrometry.

TABLE IV. Pharmacological Evaluations of Target Compounds (**2a—o**)

Compd.	ALP (%)[a]	ED_{min} (mg/kg)[b]	LD_{50} (mg/kg)[e]
2a	92.3	6.25[c]	100—250
2b	100	6.25[c]	100—250
2c	100	12.5[d]	<100
2d	100	3.13[d]	100—250
2e	98.5	>25	250—500
2f	97.0	25[c]	100—250
2g	98.5	25[d]	100—250
2h	96.2	>25	>500
2i	90.6	>25	>500
2j	100	12.5[d]	250—500
2k	98.5	>25	>500
2l	80.6	6.25[d]	>1000
2m	98.0	25[d]	>500
2n	97.0	>25	>500
2o	95.5	25[d]	>500

a) Antilipidperoxidation activity (% inhibition at 10^{-4} M in rat brain homogenates). *b*) Minimum effective dose against hypobaric hypoxia in mice (i.p.); *c*) and *d*) exhibit significant differences *versus* control (*c*) $p<0.05$; *d*) $p<0.01$). *e*) i.p. administration.

in MS, a characteristic absorption band for an amide group at 1620—1660 cm^{-1} in IR spectra, and all protons could be easily confirmed by ^{1}H-NMR (Tables I—III).

Pharmacological Evaluation

For the purpose of preliminary screening of the pharmacological activities of the compounds synthesized, we set up a simple animal model; *i.e.*, hypobaric hypoxia[4] in mice, together with acute toxicity (LD_{50}). This approach was deemed particularly relevant to our objective since it has been suggested that the cerebral blood flow[5] and oxygen consumption[6] are considered to be closely related to most primary degenerative dementia and multi-infarct dementia (MID).[7] In addition to this screening test, the assay for ALP[8] activity with brain homogenate in rats was also designed, since the generation of free radicals is observed in some cerebral vascular diseases and it is believed that such radical species may damage the cerebral tissues.[9]

All of the target compounds (Table IV) showed significant ALP activity (over 80% inhibition at 10^{-4} M), and some of them showed remarkable activity against hypobaric hypoxia in mice with low toxicity. Among them, the compound **2l** (SUN-4757) showed a wide variety of cerebral protective activity to additional animal models (such as normobaric hypoxia,[10] KCN anoxia,[11] hemicholinium-3 anoxia,[12] global ischemia[13]) designed as extensive screening test, and it had a high LD_{50} value (>1000 mg/kg). Thus a new candidate for our project has been provided.

The selected results for the compound **2l** (SUN-4757) are summarized in Table V.

Further phamacological experiments and preclinical trials are under way and the details will be published in separate papers.

Experimental

Melting points were determined on a Yanako melting point apparatus and are uncorrected. The IR spectra were obtained with either a Hitachi 260-10 or a Nicolet 5DX instrument, and ^{1}H-NMR spectra were recorded on a JEOL JNM-GX270 spectrometer, using tetramethylsilane as an internal standard. Elemental analyses were performed on a Perkin-Elmer 240B elemental analyzer. MS were obtained using a Hitachi M80 instrument with a direct inlet system. The compounds (**2a**, **b**, **e**, **f**, **k**, **l**, **n**, **o**) were analyzed (C, H, and N), and values obtained were within ±0.4% of the theoretical values. Regarding other compounds (**2c**, **d**, **g**, **h**, **i**, **j**, **m**), those molecular formulas were determined by high resolution MS [EI or FAB method]. γ-Phenyl-γ-butyrolactone was obtained from Aldrich and used without purification.

General Procedure for 5-Phenyl-2,3,4,5-tetrahydro-1-benzoxepin-2-ones (5a—h) The mixture of a substituted-phenol or hydroquinone (**3**) (0.1

TABLE V. Pharmacological Evaluation of 4-(3-Methyl-5,6-dimethoxy-1,4-benzoquinon-2-yl)-4-phenylbutylic Acid Thiomorpholine Amide (**2l**: SUN-4757)

ALP[a]	LD_{50}[b]	Hypobaric hypoxia[c,f]	Normobaric hypoxia[c,g]	KCN anoxia[c,h]	Hemicholinium-3 anoxia[c,i]	Global ischemia[c,j]
80.6	>1000	1.31[d] (6.25) 1.75[e] (12.5) 1.42[e] (25.0) 1.60[e] (50.0)	1.39 (12.5) 1.47[d] (25.0)	1.28[d] (6.25) 1.39[e] (12.5) 1.72[e] (25.0)	1.32[d] (6.25) 2.39[e] (12.5) 2.66[e] (25.0)	1.02 (6.25) 1.17[d] (12.5) 1.22[d] (25.0)

a) Inhibition (%) at 10^{-4} M. *b*) Intraperitoneal (i.p.) administration (mg/kg). *c*) Potency ratios (cerebral protective activity) were determined by comparison with that (1.00) obtained in the control group. The values in parentheses are administration dose by i.p. (mg/kg). *d*) and *e*) mean significant differences *versus* control ($p<0.05$ and $p<0.01$, respectively). *f*) Control group, $n=10$; test group, $n=7$. *g*) Control group, $n=10$; test group, $n=7$. *h*) Control group, $n=6$; test groups, $n=11$ (6.25), 6 (12.5), and 6 (25.0). *i*) Control group, $n=10$; test group, $n=10$. *j*) Control group, $n=6$; test group, $n=6$.

mol) and γ-phenyl-γ-butyrolactone (**4**) (0.1 mol) in polyphosphoric acid (PPA) (150 ml) was stirred at room temperature for 5 h. The resulting mixture was poured onto ice-water, and then extracted with ether. The ether layer was washed with water and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the oily residue was submitted to column chromatography on silica gel with an appropriate solvent. Physical data for the compounds obtained with this procedure (**5a**—**h**) are listed in Table I.

Preparation of 4,4-Diarylbutanamide Derivatives (6e—g) from 1-Benzoxepin-2-ones (5c—e) The mixture of 1-benzoxepin-2-one derivative (**5c**) (836 mg) and thiomorpholine (1.62 g) in toluene (80 ml) was refluxed for 5 h. The reaction mixture was concentrated and the residue was chromatographed on silica gel with hexane/ethyl acetate (7 : 2) to give the compound (**6e**) (760 mg) in 65% yield.

Similarly, compounds (**6f** and **6g**) were obtained from the benzoxepinones (**5d** and **5e** in 60 and 77% yield, respectively) and a corresponding amine. The results are summarized in Table II.

Synthesis of Benzoquinone Derivatives (2e—g) by Oxidation of Phenols (6e—g) were Potassium Nitrosodisulfonate (Fremy's Salt) [Method A] To a solution of Compound (**6e**) (857 mg) in acetone (15 ml) were added sodium acetate (294 mg), water (33 ml), and potassium nitrosodisulfonate (3.92 g). The mixture was stirred at room temperature for 2 h. The resulting mixture was poured into water and then extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel with hexane/ethyl acetate (1 : 1) to give the product (**2e**) (743 mg) in 84% yield. Similarly, compounds **2f** and **2g** were obtained from phenol derivatives (**6f** and **6g**) in 75 and 53% yield, respectively. The results are summarized in Table III.

Preparation of 4,4-Diarylbutanamide Derivatives (7a—c) from 1-Benzoxepin-2-one (5a) The mixture of 1-benzoxepin-2-one derivative (**5a**) (2.04 g) and morpholine (1.26 g) in toluene (100 ml) was refluxed for 6 h. After cooling the reaction mixture to room temperature, the precipitated crystalline product (**7a**) (2.53 g) was collected by filtration. The yield was 92%.

Similarly, compounds (**7b** and **7c**) were prepared from compound **5a** and a corresponding amine in 62 and 72% yield, respectively. The data for these products are listed in Table II.

Synthesis of Benzoquinone Derivatives (2a—c) by Oxidation of Hydroquinones (7a—c) with CAN [Method B] The mixture of hydroquinone derivative (**7a**) (815 mg) and CAN (3.28 g) in acetonitrile/water (3 : 1) (55 ml) was stirred at room temperature for 15 min. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel with hexane/ethyl acetate (1 : 1) to give the target 1,4-benzoquinone derivative (**2a**) (723 mg) in 87% yield.

Similarly, compounds (**2b** and **2c**) were obtained from hydroquinones (**7b** and **7c**) in 55 and 65% yield, respectively. The results are summarized in Table III.

Direct Preparation of 4-(Substituted 1,4-benzoquinon-2-yl)-4-phenylbutanamides (2) from 1-Benzoxepin-2-one Derivatives (5) [Method C] The mixture of a benzoxepin-2-one derivative (**5**) (*ca.* 3.5 mol) and an appropriate amine (2—2.5 mol eq) in toluene (*ca.* 60—80 ml) was refluxed for 6 h. After evaporation of the solvent, the residue was dissolved in acetonitrile/water (3 : 1) (*ca.* 40 ml), to which was added CAN (2—2.5 mol eq). The mixture was stirred for 10 min at room temperature, and then the solvent was evaporated to give an oily residue. Purification by column chromatography on silica gel afforded target compounds (**2d** and **2h**—**m**). Physical data of the products are summarized in Table III.

Synthesis of Benzoquinone Derivatives (2n and 2o) by Oxidation of Benzoquinone (2l) with *m*-CPBA [Method D] The mixture of benzoquinone derivative (**2l**) (518 mg) and *m*-CPBA (260 mg) in 1,2-dichloromethane was stirred at room temperature for 5 h. After filtrating the precipitated *m*-CPBA, the filtrate was washed with aqueous sodium sulfinate and then with a saturated sodium bicarbonate solution. The dichloromethane solution was dried over anhydrous magnesium sulfate. Concentration of the solvent gave sulfoxide (**2n**) (483 mg) in 90% yield.

Similarly, the sulfone (**2o**) was obtained from benzoquinone (**2l**) with two equivalents of *m*-CPBA in 73% yield. The data for these products are listed in Table III.

Pharmacological Evaluation ALP Activity Assay: The supernatant fraction of rat brain homogenates was prepared according to the method of Stocks *et al.*[8] The whole brain except the cerebellum of male Wistar rats weighing 200—250 g was obtained after decapitation and was homogenated in an ice-cold phosphate–saline buffer (50 mM, pH 7.4) at a volume of 9 ml per 1 g tissue. The homogenate was centrifuged for 15 min at $1000 \times g$, and the supernatant was stored at −30 °C for later assay. When utilizing the stocked supernatant, the sample was diluted 3-fold with the same phosphate-saline buffer. The diluted sample (1 ml) was incubated at 37 °C for 30 min either with the test compound which was dissolved in 10 μl of dimethyl sulfoxide or with its vehicle. After the addition of 0.2 ml of ice-cold 35% $HClO_4$, the resulting mixture was centrifuged at $1000 \times g$ for 15 min. The lipid peroxide of the supernatant was determined by the thiobarbituric acid (TBA) method and expressed as malondialdehyde (MDA) per mg of protein. All of the compounds showed significant activity (over 80% inhibition at 10^{-4} M).

Acute Toxicity: Male ddY mice weighing 18—25 g were used groups of 5—10 animals for each test compounds. The LD_{50} value was calculated from the lethality within 7 d after an intraperitoneal administration of test compounds according to the up-and-down method.[14]

Other assays for cerebral protective activity are carried out according to the methods described by Nakanishi *et al.*[4] (hypobaric hypoxia), Arnfred *et al.*[10] (normobaric hypoxia), Yasuda *et al.*[11] (KCN anoxia), Domino *et al.*[12] (hemicholinium-3 anoxia), and Holowach-Thurston *et al.*[13] (global ischemia). The ED_{min} was determined as the minimum effective dose at which the drug significantly prolongs the survival time in mice under a hypoxic condition as compared with that of the vehicle-treated group. The initial dose administered was 25 or 50 mg/kg (i.p.) and the subsequent doses were reduced to 1/2 of the initial dose when it was effective.

The statistical evaluation was carried out by means of a variance (*F*-test) followed by the Student's *t*-test. The selected results for **2l** (SUN-4757) are shown in Table V.

Acknowledgment We thank Dr. T. Noguchi (Suntory Institute for Biomedical Research) for his encouragement throughout the investigation.

References and Notes

1) Series on studies of cerebral protective agents. *a*) S. Miyano, T. Tatsuoka, K. Suzuki, K. Imao, F. Satoh, T. Ishihara, I. Hirotsu, T. Kihara, M. Hatta, Y. Horikawa, and K. Sumoto, *Chem. Pharm. Bull.*, **38**, 1570 (1990); *b*) T. Tatsuoka, K. Imao, K. Suzuki, M. Shibata, F. Satoh, S. Miyano, and K. Sumoto, *Heterocycles*, **30**, 749 (1990).
2) K. Kogure, H. Arai, K. Abe, and M. Nakano, "Progress in Brain

Research," Vol. 63, ed. by K. Kogure, K.-H Hossman, B. K. Siesjo, and F. A. Welsh, Elsevier Science Publishers B. V. (Biomedical Division), Amsterdam, 1985, p. 237.
3) *a*) A. R. Boobis, D. J. Fawthrop, and D. S. Davies, *Trends Pharmacol. Science*, **10**, 275 (1989), and related references cited therein; *b*) H. G. Lawford and P. B. Garland, *Biochem. J.*, **130**, 1029 (1972).
4) M. Nakanishi, Y. Yasuda, and T. Tsumagari, *Life Sci.*, **13**, 467 (1973).
5) For example, see *a*) M. E. Raichle, R. L. Grubb, Jr., M. H. Gado, and J. O. Eichling, *Arch. Neurol.*, **33**, 523 (1976); *b*) V. C. Hachinski, L. D. Iliff, E. Zilhka, G. H. Du Bouly, V. L. McAllister, J. Marshall, R. W. R. Russell, and L. Symon, *ibid.*, **32**, 632 (1975).
6) For example, see *a*) N. A. Lassen, O. Munck, and E. R. Tottery, *Arch. Neurol. Psychiat.*, **77**, 126 (1957); *b*) J. L. Patterson, A. Heyman, and F. T. Nichols, *J. Clin. Invest.*, **29**, 1327 (1950).
7) J. S. Mayer, H. Lechner, and M. Reivich, "Cerebral Vascular Diseases," Excerpta Medica, Amsterdam-Oxford, 1977, and related references cited therein.
8) J. Stocks, J. M. C. Gutteridge, R. J. Sharp, and T. L. Dormandy, *Clin. Sci. Mol. Med.*, **47**, 215 (1974).
9) D. Harman, *Aging*, **7**, 111 (1984).
10) I. Arnfred and O. Secher, *Arch. Int. Pharmacodyn.*, **139**, 67 (1962).
11) H. Yasuda, S. Shuto, T. Tsumagari, and A. Nakajima, *Arch. Int. Pharmacodyn. Thr.*, **233**, 136 (1978).
12) E. F. Domino, M. E. Mohrman, A. E. Wilson, and V. B. Harrstad, *Neuropharmacology*, **12**, 549 (1978).
13) J. Holowach-Thurston, R. E. Hauhart, and E. M. Jones, *Pediat. Rev.*, **8**, 238 (1974).