Studies on Cognitive Enhancing Agents. III.[1a,b] Antiamnestic and Antihypoxic Activities of a Series of 1-Bicycloaryl-2-(ω-aminoalkoxy)ethanols

Satoshi ONO,* Tetsuo YAMAFUJI, Hisaaki CHAKI, Hajime MORITA, Yozo TODO, Naomi OKADA, Mutsuko MAEKAWA, Kazunori KITAMURA, Masaru TAI, and Hirokazu NARITA

Research Laboratories, Toyama Chemical Co., Ltd., 2-4-1 Shimookui, Toyama 930, Japan.
Received January 5, 1995; accepted May 17, 1995

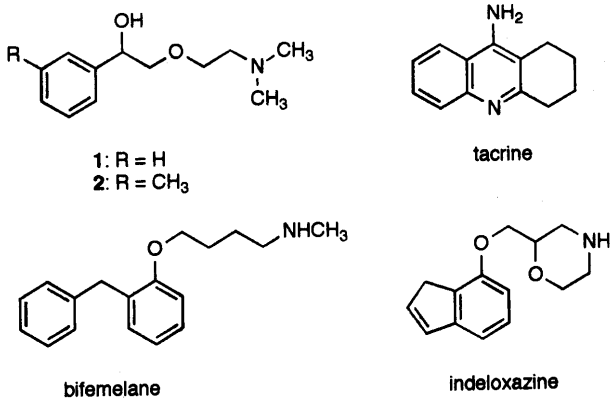
2-(2-Aminoethoxy)-1-hydroxyethyl derivatives of bicyclic arenes (naphthalene, thianaphthene, benzofuran, and indole) were prepared and screened for antiamnestic (AA) and antihypoxic (AH) activities which were evaluated by measuring the reversing potency in electroconvulsion-induced amnesia and the protective effect against hypoxia, respectively, in mice. Compound 3o, 1-(benzo[*b*]thiophen-5-yl)-2-(2-diethylaminoethoxy)ethanol, showed the best AA and AH activity profile, being superior to our prototype compound, 2-(2-dimethylaminoethoxy)-1-phenylethanol (1). Elongation of the ethylene linkage in the side chain of 3o to 3- and 4-carbon moieties brought about a significant decrease in AH activity. Compound 3o was further investigated for its protective effect against CO_2-induced memory impairment and for acute toxicity in mice. It is ten-fold more potent than tacrine in the amnesia-reversal assay and is considerably less toxic than tacrine.

Key words antiamnestic activity; antihypoxic activity; acute toxicity; 1-bicycloaryl-2-(aminoethoxy)ethanol; 1-(benzo[*b*]thiophen-5-yl)-2-(2-diethylaminoethoxy)ethanol

Our continuing efforts directed toward developing a new cognition-enhancing agent, which would be more effective than currently available drugs (tacrine,[2] bifemelane,[3] and indeloxazine,[4] have resulted in the discovery of a lead compound **1**.[1a] The structure of **1** is characterized by the presence of a 2-phenyl-2-hydroxyethyl ether group, quite different from bifemelane and indeloxazine, which are aryl ethers and do not have a hydroxy function. We also reported that, in the assay of antihypoxic (AH) and antiamnestic (AA) activities, the 3-methyl derivative of **1** (**2**) was found to be most active among a variety of benzene ring-substituted compounds, but compound **2** proved much less active than tacrine in its reversing effect on CO_2-induced learning impairment in mice.[1b] Thus, in order to find more active compounds by further structural modifications of **1**, we focused our attention on a series of bicyclic aryl analogues **3** (Chart 1). This paper reports the discovery of the thianaphthenyl compound **3o**, which is much more effective than the three reference drugs (Chart 1) in reversing the memory impairment generated by CO_2 anoxia in mice.

Chemistry

All compounds except the indole derivative **3k** were prepared from arylcarboxaldehyde (**4**) by means of the two-step reaction shown in Chart 2, *i.e.*, the same method as described for the preparation of **1**.[1a] To obtain **3k**, an indirect route was devised, since the aldehyde **7** derived from the *N*-protected dihydroindole (**6**) in two steps failed to produce an oxirane intermediate (**5**) on reaction with dimethylsulfonium methylid. Thus, the aldehyde **7** was allowed to react with (2-chloroethoxy)magnesium



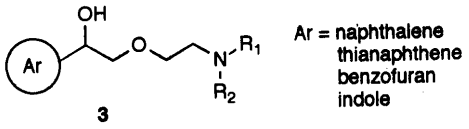


Chart 1

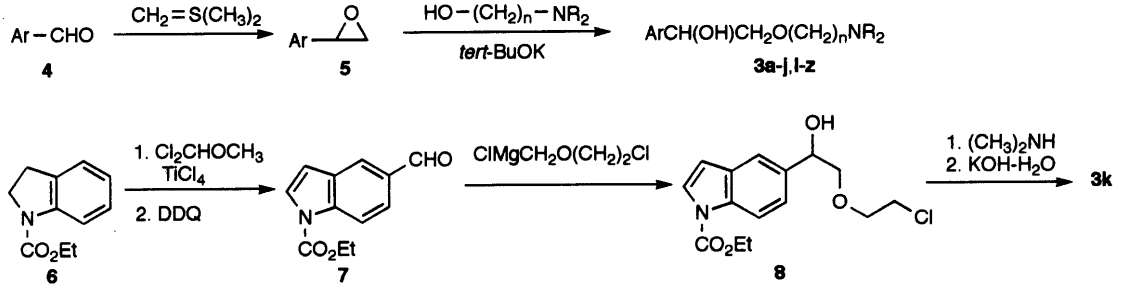


Chart 2

* To whom correspondence should be addressed.

Table 1. Characterization Data for **3a—z**

Compd.	Yield[a] (%)	Formula	mp (°C) (Solvent for crystallization)[b]	Combustion analysis Calcd (Found) (%) C	H	N	^{1}H-NMR spectral data δ in D_2O solvent, J in Hz
3a	17	$C_{16}H_{21}NO_2 \cdot HCl$	196—197 (EtOH)	64.96 (64.90	7.50 7.43	4.75 4.74)	2.85 (6H, s), 3.2—3.5 (2H, m), 3.7—4.0 (4H, m), 5.79 (1H, t, J=5.5), 7.5—7.8 (4H, m), 7.9—8.3 (3H, m)
3b	23	$C_{18}H_{25}NO_2 \cdot HCl \cdot 0.25H_2O$	155.5—157 (IPA)	65.84 (65.81	8.13 8.20	4.27 4.31)	1.24 (6H, t, J=7), 3.15 (4H, q, J=7), 3.2—3.4 (2H, m), 3.7—4.0 (4H, m), 5.80 (1H, t, J=5.5)
3c	23	$C_{19}H_{25}NO_2 \cdot HCl$	174—174.5 (EtOH–Et_2O)	67.94 (67.86	7.80 7.96	4.17 4.18)	1.2—2.0 (6H, m), 2.5—3.6 (6H, m), 3.6—4.41 (4H, m), 5.79 (1H, t, J=5.5), 7.5—7.8 (4H, m), 7.9—8.4 (3H, m)
3d	16	$C_{16}H_{21}NO_2 \cdot HCl$	116.5—118 (Me_2CO)	64.97 (64.95	7.50 7.73	4.74 4.72)	3.08 (6H, s), 3.4—3.7 (2H, m), 3.8—4.1 (4H, m), 5.28 (1H, t, J=5.5), 7.5—7.9 (3H, m), 7.9—8.3 (4H, m)
3e	5	$C_{18}H_{25}NO_2 \cdot HCl$	100.5—101.5 (IPA–Et_2O)	66.75 (66.45	8.09 8.39	4.33 4.29)	1.15 (6H, t, J=7), 2.8—3.4 (6H, m), 3.7—3.9 (4H, m), 5.13 (1H, t, J=5.5), 7.4—7.7 (3H, m)
3f	14	$C_{19}H_{25}NO_2 \cdot HCl \cdot 0.25H_2O$	156.5—158 (EtOH–Et_2O)	67.06 (67.35	7.50 7.79	4.12 4.24)	1.3—1.8 (6H, m), 2.8—3.3 (6H, m), 3.7—4.0 (4H, m), 5.13 (1H, t, J=5.5), 7.4—7.8 (3H, m), 7.8—8.1 (4H, m)
3g	24	$C_{15}H_{23}NO_2 \cdot HCl$	198—199.5 (IPA)	63.04 (62.97	8.46 8.62	4.90 4.85)	1.8—2.3 (2H, m), 2.7—3.1 (10H, m), 3.2—3.5 (2H, m), 3.6—4.0 (4H, m), 4.92 (1H, t, J=6), 7.0—7.4 (3H, m)
3h	7	$C_{14}H_{21}NO_3 \cdot HCl \cdot 0.2H_2O$	168.5—169.5 (IPA)	57.70 (57.99	7.75 7.80	4.81 4.66)	2.92 (6H, s), 3.0—3.5 (4H, m), 3.6—4.0 (4H, m), 4.4—4.8 (2H, m), 4.90 (1H, t, J=6), 6.80 (1H, d, J=8), 7.0—7.4 (2H, m)
3i	11	$C_{14}H_{21}NO_2S \cdot HCl$	207.5—210 (EtOH)	55.34 (55.01	7.30 7.28	4.61 4.44)	2.63 (6H, s), 2.9—3.9 (10H, m), 4.0—5.2 (3H, m), 6.9—7.3 (3H, m)
3j	16	$C_{14}H_{19}NO_3 \cdot HCl$	168—169.5 (IPA–AcOEt)	58.84 (58.56	7.05 7.15	4.90 4.69)	2.87 (6H, s), 3.2—3.5 (2H, m), 3.7—4.0 (4H, m), 5.07 (1H, t, J=6), 6.94 (1H, d, J=1.5), 7.2—7.6 (2H, m), 7.6—7.8 (2H, m)
3k	73	$C_{14}H_{20}N_2O_2 \cdot$ (0.5fumaric acid)	197—200 (dec.) (MeOH)	62.70 (62.59	7.23 7.44	9.18 9.02)	2.81 (6H, s), 3.1—3.4 (2H, m), 3.6—4.0 (4H, m), 5.01 (1H, t, J=6), 6.56 (1H, s), 6.60 (1H, d, J=2), 7.22 (1H, dd, J=9, 2), 7.4—7.5 (2H, m), 7.6—7.7 (1H, m)
3l	18	$C_{12}H_{15}NO_2S \cdot$ (0.5fumaric acid)	204.5—205.5 (MeOH–EtOH)	56.93 (56.64	5.80 5.64	4.74 4.87)	3.1—3.4 (2H, m), 3.6—3.9 (4H, m), 5.09 (1H, t, J=6), 6.54 (1H, s), 7.2—7.5 (2H, m), 7.63 (1H, d, J=5.5), 7.8—8.1 (2H, m)
3m	43	$C_{14}H_{19}NO_2S \cdot HCl$	194—195 (MeOH)	55.71 (55.58	6.68 6.80	4.64 4.47)	1.31 (3H, t, J=7.5), 2.9—3.4 (4H, m), 3.7—4.0 (4H, m), 5.12 (1H, t, J=5.5), 7.3—7.5 (2H, m), 7.68 (1H, d, J=5.5), 7.8—8.1 (2H, m)
3n	6	$C_{14}H_{19}NO_2S \cdot HCl$	191.5—192.5 (EtOH–Me_2CO)	55.71 (55.81	6.68 6.73	4.64 4.06)	2.85 (6H, s), 3.2—3.4 (2H, m), 3.6—3.9 (4H, m), 5.09 (1H, t, J=6), 7.3—7.5 (2H, m), 7.63 (1H, d, J=6), 7.8—8.1 (2H, m)
3o	52	$C_{16}H_{23}NO_2S \cdot HCl$	138.5—139 (IPA)	58.25 (58.10	7.33 7.47	4.25 3.98)	1.18 (6H, t, J=7.5), 2.9—3.4 (6H, m), 3.6—3.9 (4H, m), 5.08 (1H, t, J=5.5), 7.3—7.5 (2H, m), 7.63 (1H, d, J=5.5), 7.8—8.1 (2H, m)
3p	6	$C_{18}H_{27}NO_2S \cdot HCl$	167—168 (IPA)	60.40 (60.26	7.89 8.06	3.91 3.63)	1.24 (12H, d, J=6.5), 3.1—3.4 (2H, m), 3.4—3.9 (6H, m), 5.07 (1H, t, J=5.5), 7.2—7.5 (2H, m), 7.67 (1H, d, J=5.5), 7.8—8.1 (2H, m)
3q	8	$C_{17}H_{23}NO_2S \cdot HCl$	168.5–170 (EtOH–AcOEt)	59.72 (59.80	7.08 7.08	4.10 4.08)	1.2—1.9 (6H, m), 2.7—3.4 (6H, m), 3.6—4.0 (4H, m), 5.10 (1H, t, J=6), 7.3—7.5 (2H, m), 7.63 (1H, d, J=6), 7.8—8.1 (2H, m)
3r	11	$C_{16}H_{21}NO_3S \cdot HCl$	166.5—167.5 (EtOH–Me_2CO)	54.46 (54.29	6.57 6.54	3.97 4.08)	3.0—3.4 (6H, m), 3.5—4.0 (8H, m), 5.09 (1H, t, J=5.5), 7.3—7.5 (2H, m), 7.63 (1H, d, J=5), 7.8—8.1 (2H, m)
3s	7	$C_{17}H_{24}N_2O_2S \cdot 2HCl$	232—234 (EtOH–Me_2CO)	51.91 (52.14	6.66 6.26	7.12 7.02)	2.94 (3H, s), 3.2—3.6 (10H, m), 3.7—4.0 (4H, m), 5.12 (1H, t, J=5.5), 7.3—7.5 (2H, m), 7.65 (1H, d, J=5.5), 7.8—8.1 (2H, m)
3t	2	$C_{14}H_{19}NO_2S \cdot HCl$	188.5—189 (EtOH–AcOEt)	55.71 (55.59	6.68 6.78	4.64 4.39)	2.86 (6H, s), 3.2—3.5 (2H, m), 3.7—4.0 (4H, m), 5.30 (1H, t, J=6), 7.3—7.6 (3H, m), 7.7—8.1 (2H, m)
3u	29	$C_{14}H_{19}NO_2S \cdot HCl$	210—211 (EtOH)	55.71 (55.83	6.68 6.97	4.64 4.82)	2.86 (6H, s), 3.1—3.5 (2H, m), 3.7—4.0 (4H, m), 5.39 (1H, t, J=5.5), 7.3—7.6 (3H, m), 7.8—8.1 (2H, m)
3v	23	$C_{14}H_{19}NO_2S \cdot HCl$	190.5—192 (EtOH–IPA)	55.71 (55.44	6.68 6.95	4.64 4.63)	2.87 (6H, s), 3.2—3.5 (2H, m), 3.6—4.0 (4H, m), 5.50 (1H, t, J=6), 7.2—8.1 (5H, m)
3w	18	$C_{14}H_{19}NO_2S \cdot HCl$	171—172 (IPA–AcOEt)	55.71 (55.45	6.68 6.92	4.64 4.43)	2.87 (6H, s), 3.2—3.5 (2H, m), 3.6—4.0 (4H, m), 5.09 (1H, t, J=5.5), 7.2—7.5 (2H, m), 7.63 (1H, d, J=6), 7.8—8.1 (2H, m)
3x	19	$C_{14}H_{19}NO_2S \cdot HCl \cdot 0.25H_2O$	168.5—169.5 (IPA–AcOEt)	54.90 (54.75	6.70 6.69	4.58 4.65)	2.93 (6H, s), 3.2—3.5 (2H, m), 3.8—4.0 (4H, m), 5.30 (1H, t, J=6), 7.3—8.0 (5H, m)
3y	30	$C_{17}H_{25}NO_2S$	59.5—60.5 (IPA)	66.41 (66.07	8.20 8.34	4.56 4.64)	1.04 (6H, t, J=7), 1.5—2.0 (2H, m), 2.3—2.8 (6H, m), 3.2—3.8 (4H, m), 4.02 (1H, br s), 4.99 (1H, dd, J=8.5, 3.5), 7.2—7.5 (3H, m), 7.7—7.9 (2H, m)[c]
3z	9	$C_{18}H_{27}NO_2S \cdot HCl$	86—88 (Me_2CO–AcOEt)	60.40 (60.25	7.89 7.80	3.91 4.02)	1.14 (6H, t, J=7.5), 1.3—1.7 (4H, m), 2.7—3.2 (6H, m), 3.4—3.8 (4H, m), 5.02 (1H, t, J=6), 7.3—7.7 (3H, m), 7.8—8.1 (2H, m)

a) Overall yield from the arylaldehyde **4**, except for **3k** (% from yield from **8**). *b*) IPA: iso-PrOH. *c*) DMSO-d_6.

chloride to give the indolyl carbinol **8**, which was then converted to **3k** by aminolysis with dimethylamine followed by *N*-deprotection (72% overall yield). Characterization data for all new compounds are given in Table 1.

Pharmacological Results and Discussion

All of the new compounds prepared in this study were screened for AA and AH activities in mice according to the procedures described in a previous paper,[1a] *i.e.*, assay for reversing effect on electroconvulsive shock-induced learning impairment[5] and measurement of the survival time under hypoxia, respectively. As shown in Table 2, all the compounds (**3a—z**) except **3h** and **3m** showed AH activity at oral dose of 100 mg/kg, being mostly superior or comparable to **1** and indeloxazine. At 30 mg/kg, however, only three compounds (**3n, o, w**), which are thianaphthenyl analogues of **1**, were more potent than **1** and reference drugs, and the AH activity of compound **3o** is much greater than that of **3n** or **3w**.

On the other hand, AA activity proved quite sensitive to the structure of the aryl group as well as the *N*-alkyl group, as can be seen in the data for 1- and 2-naphthyl compounds (**3a—f**) and for indan and its heterocyclic analogues (**3g—k**). Furthermore, none of **3a—k** showed AH activity at 30 mg/kg. Compounds **3y** and **3z**, which are methylene homologs of **3o**, exhibited good AA activities at 3 mg/kg as well as 0.3 mg/kg, but they again failed to show acceptable AH activity. Among thianaphthen-5-yl compounds (**3l—s**), only **3n** (*N,N*-dimethyl) and **3o** (*N,N*-diethyl) showed both AA and AH activities superior to indeloxazine and bifemelane. Lastly, compound **3w**, a side chain-positional isomer of **3n**, showed well-balanced AA and AH activities comparable to those of **3n**.

Based on the results in the preliminary bioassay described above, three 1-thianaphthenyl-2-(2-aminoethoxy)-ethanols (**3n, o, w**) were evaluated for their reversing activity in CO_2-induced memory impairment by a passive avoidance technique, and for acute toxicity in mice. As shown in Table 3, the best efficacy was obtained with **3o**. Its minimum effective dose (MED) (0.1 mg/kg) was found to be some 300-fold smaller than that of the prototype compound **1** (30 mg/kg) or indeloxazine (>30 mg/kg), a cerebral metabolism enhancer. Moreover, **3o** proved to be 10-fold more potent than tacrine (a cholinesterase inhibitor). Other notable features of **3o** in comparison with tacrine are its low toxicity (LD_{50}: 300 mg/kg *vs.* 68 mg/kg) and better brain-to-serum ratio.

In conclusion, the present study on structural modifications of our prototype compound **1** in its benzene ring has been rewarded by the discovery of the thianaphthen-5-yl compound **3o** that displays excellent AA and AH activities in mice and yet has remarkably low acute toxicity. Optical resolution of the racemate and the pharmacological properties of the enantiomers will be reported in due course.

Table 2. Antiamnestic and Antihypoxic Activities of 1-Bicycloaryl-2-(ω-aminoalkoxy)ethanols in Mice

Compound	Antiamnestic activity[a] (mg/kg, i.p. dosing)		Antihypoxic activity[b] (mg/kg, *p.o.* dosing)	
	0.3	3	30	100
1	+	++	+	++
2	−	+++	+	+++
3a	−	−	−	++
3b	−	+	−	++++
3c	−	++	−	++
3d	−	+	−	++
3e	+	+	−	+++
3f	−	−	−	+
3g	−	++	−	+++
3h	−	+	−	−
3i	−	−	−	++++
3j	−	−	−	++++
3k	−	−	−	++
3l	+	+	−	+
3m	++	−	−	−
3n	+	−	++	++++
3o	+	−	++++	++++
3p	−	+	−	++
3q	−	−	+	++++
3r	−	−	+	++
3s	+	−	+	++++
3t	+	+	−	++
3u	−	−	−	+++
3v	−	+	+	++
3w	−	++	++	++++
3x	+	++	−	++++
3y	+	+	−	++
3z	++	++	−	+
Tacrine	++	−	+	ND[c]
Indeloxazine	−	−	+	++
Bifemelane	−	−	−	+

a) Determined by testing reversal of electroconvulsive shock-induced amnesia. Symbols represent mean latency: −, <60 s; +, 60—100 s; ++, 101—150 s; +++, 151—300 s. *b*) Determined with hypoxia models. Symbols represent % increase in survival time against control: −, <25%; +, 25—50%; ++, 51—75%; +++, 76—100%; ++++, >100%. *c*) Not determined.

Experimental[6]

1-(Benzo[*b*]thiophen-5-yl)-2-[2-(*N,N*-diethylamino)ethoxy]ethanol Hydrochloride (3o) (General Procedure) A mixture of dimethyl sulfate (34 g, 0.27 mol) and dimethyl sulfide (18.5 g, 0.30 mol) in CH_3CN (90 ml) was stirred at 0—5 °C for 2 h, then at room temperature for 10 h before addition of sodium methoxide (16 g, 0.30 mol). The reaction mixture was stirred at 10—15 °C for 1 h, and a solution of benzo[*b*]thiophene-5-carboxaldehyde (30 g, 185 mmol) in CH_3CN (60 ml) was added at 5—10 °C over a period of 30 min. The reaction mixture was stirred at 10—15 °C for 1 h, then poured into ice-water (250 ml) and extracted with Et_2O (200 m × 2). The ether extract was washed with brine, dried, and concentrated to give 5-(1,2-epoxyethyl)benzo[*b*]thiophene (32.6 g, 99%). A small amount of this material was purified by distillation under reduced pressure to give a colorless oil, bp 115—120 °C/0.7 Torr, which solidified on standing at room temperature, mp 48—51 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.80 (1H, dd, J=5.5, 2.5 Hz), 3.14 (1H, dd, J=5.5, 4 Hz), 3.94 (1H, dd, J=4, 2.5 Hz), 7.0—7.5 (3H, m), 7.6—7.9 (2H, m). *Anal.* Calcd for $C_{10}H_8OS$: C, 68.15; H, 4.58. Found: C, 68.14; H, 4.50.

A solution of the oxirane (5.4 g, 31 mmol) obtained above in dimethyl sulfoxide (DMSO) (5 ml) was added to a mixture of potassium *tert*-butoxide (10.4 g, 93 mmol) and *N,N*-diethylethanolamine (22 g, 188 mmol) in DMSO (15 ml) at 60—65 °C. The mixture was stirred at the same temperature for 1 h, then poured into a stirred mixture of ice-water (100 ml) and toluene (100 ml). The whole was acidified to pH 2 with 6 N HCl, and the layers were separated. The aqueous layer was brought to pH 10 by addition of K_2CO_3 and extracted with AcOEt (100 ml × 2). The combined extracts were washed with water (50 ml × 5) and then brine, dried, and concentrated. A solution of the residual oil in acetone (20 ml) was treated with ethanolic HCl (6 M, 3.5 ml, 21 mmol) at 10—20 °C before dilution with AcOEt (25 ml). Precipitated crystals were collected by filtration and recrystallized from iso-PrOH to give **3o**

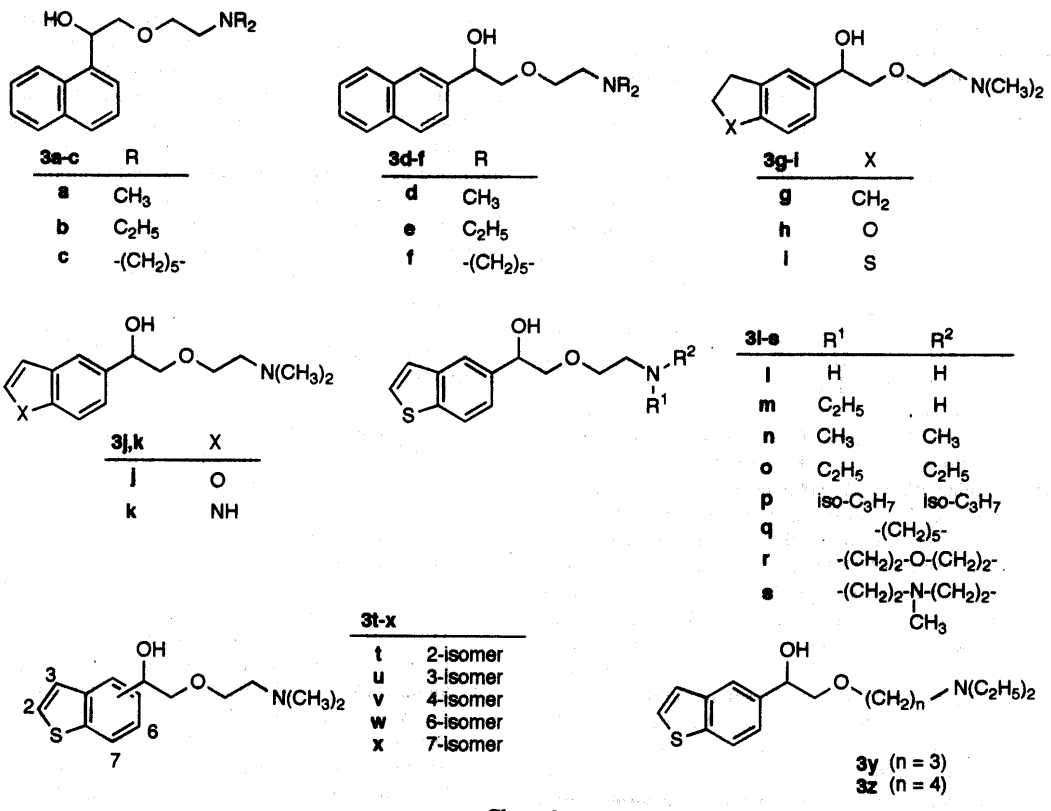
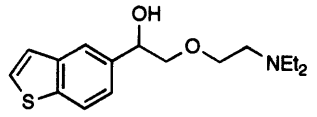


Chart 3

Table 3. Learning Impairment-Ameliorating Activity, Acute Toxicity, and Brain-to-Serum Ratio of 1-Thianaphthenyl-2-(2-aminoethoxy)ethanols (3n, o, w) in Oral Administration

Compound	Reversal of learning impairment in mice[a] MED[b] (mg/kg)	Acute toxicity in mice[c] LD_{50} (mg/kg)	Brain/serum ratio in rats[d]
1	30	>500	4.96
3n	30	>500	13.5
3o	0.1	300	11.5
3w	>30	>500	ND[g]
Tacrine	1	68	8.47
Indeloxazine	>30	444[e]	18.5
Bifemelane	>100	1034[f]	ND[g]

a) Amnesia was induced by exposure to CO_2 immediately after the acquisition trial. *b*) Minimum effective dose. *c*) LD_{50} were calculated from lethality during 7 d after dosing. *d*) Rats were killed 30 min after administration of samples (30 mg/kg). *e*) Ref. 9. *f*) Ref. 10. *g*) Not determined.



3o

Chart 4

(5.1 g, 52%) as colorless prisms, mp 138.5—139 °C.

Characterization data of new aryloxirane intermediates used for the preparation of 3h, i, and 3v—x are given below.

5-(1,2-Epoxyethyl)-2,3-dihydrobenzofuran: 100% yield, bp 95—99 °C/0.45 Torr. ^{1}H-NMR ($CDCl_3$) δ: 2.76 (1H, dd, J=5.5, 2.5 Hz), 2.9—3.3 (3H, m), 3.77 (1H, dd, J=4, 2.5 Hz), 4.53 (2H, t, J=8.5 Hz), 6.5—6.8 (1H, m), 6.9—7.2 (2H, m). *Anal.* Calcd for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22. Found: C, 73.71; H, 6.17.

5-(1,2-Epoxyethyl)-2,3-dihydrobenzo[*b*]thiophene: 92% yield, bp 125—135 °C/3 Torr. ^{1}H-NMR ($CDCl_3$) δ: 2.78 (1H, dd, J=5.5, 2.5 Hz), 3.0—3.5 (5H, m), 3.83 (1H, dd, J=4, 2.5 Hz), 6.8—7.2 (3H, m). *Anal.* Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65. Found: C, 67.18; H, 5.63.

4-(1,2-Epoxyethyl)benzo[*b*]thiophene: 94% yield, bp 102—106 °C/0.18 Torr. ^{1}H-NMR ($CDCl_3$) δ: 2.83 (1H, dd, J=5.5, 2.5 Hz), 3.16 (1H, dd, J=5.5, 4 Hz), 4.24 (1H, dd, J=4, 2.5 Hz), 7.0—8.0 (5H, m). *Anal.* Calcd for $C_{10}H_8OS$: C, 68.15; H, 4.58. Found: C, 68.22; H, 4.61.

6-(1,2-Epoxyethyl)benzo[*b*]thiophene: 95% yield, bp 120—125 °C/0.9 Torr (mp 36—40 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.78 (1H, dd, J=5.5, 2.5 Hz), 3.11 (1H, dd, J=5.5, 4 Hz), 3.90 (1H, dd, J=4, 2.5 Hz), 7.1—7.5 (3H, m), 7.6—7.9 (2H, m). *Anal.* Calcd for $C_{10}H_8OS$: C, 68.15; H, 4.58. Found: C, 67.96; H, 4.63.

7-(1,2-Epoxyethyl)benzo[*b*]thiophene: 95% yield, bp 95—98 °C/0.18 Torr. ^{1}H-NMR ($CDCl_3$) δ: 2.95 (1H, dd, J=5.5, 2.5 Hz), 3.15 (1H, dd, J=5.5, 4 Hz), 4.12 (1H, dd, J=4, 2.5 Hz), 7.1—7.5 (4H, m), 7.5—7.8 (1H, m). *Anal.* Calcd for $C_{10}H_8OS$: C, 68.15; H, 4.58. Found: C, 67.88; H, 4.56.

1-(Ethoxycarbonyl)-1*H*-indole-5-carboxaldehyde (7) Titanium(IV) chloride (11.7 g, 62 mmol) was added to a stirred and cooled (ice-water) solution of 6 (4.0 g, 21 mmol) in dry CH_2Cl_2 (40 ml) at 0—5 °C over a period of 5 min before addition of dichloromethyl methyl ether (2.9 g, 25 mmol). The reaction mixture was stirred at the same temperature for 1 h, then poured into a stirred mixture of ice-water (60 ml) and 6 N HCl (4 ml). The layers were separated, and the organic layer was washed with brine, dried, and concentrated. The residue was subjected to silica gel chromatography (elution with hexane : AcOEt = 10 : 1) to give 1-ethoxycarbonyl-5-formyl-2,3-dihydro-1*H*-indole (2.4 g, 52%) as a white solid. An analytical sample was obtained by recrystallization from iso-PrOH as colorless needles, mp 94—95 °C. IR (KBr): 1704, 1682 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7 Hz), 2.9—3.3 (2H, m), 3.8—4.5 (4H, m), 7.5—7.9 (3H, m), 9.85 (1H, s). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.63; H, 5.98; N, 6.37.

A mixture of the dihydroindole obtained above (6.5 g, 30 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.0 g, 45 mmol) in benzene (65 ml) was refluxed for 4 h. After having been cooled to room temperature, the mixture was filtered and the remaining solid was washed with benzene. The combined filtrates were washed successively with aqueous 10% K_2CO_3 and brine, dried, and concentrated. The residue was purified by silica gel chromatography (elution with hexane : AcOEt = 5 : 1) to give 7 (4.2 g, 65%) as a white solid. A small amount of this solid was recrystallized from iso-PrOH to give colorless needles, mp 70—71 °C. IR (KBr): 1736, 1681 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, t, J=7 Hz), 4.54 (2H, q, J=7 Hz), 6.71 (1H, d, J=3.5 Hz), 7.6—8.5 (4H, m), 10.10 (1H, s). *Anal.* Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10;

N, 6.45. Found: C, 66.43; H, 5.12; N, 6.38.

2-(2-Chloroethoxy)-1-[1-(ethoxycarbonyl)-1*H*-indol-5-yl]ethanol (8) 1-Chloromethoxy-2-chloroethane (4.5 g, 35 mmol) was added dropwise to a stirred suspension of Mg turnings (0.85g, 35 mmol) and $HgCl_2$ (0.10 g, 0.4 mmol) in tetrahydrofuran (THF) (10 ml) at 0—5 °C. After 30 min, the resulting Grignard reagent was added to a solution of **7** (3.0 g, 14 mmol) in THF (30 ml) at −50——40 °C over a period of 5 min. After 15 min, the reaction mixture was poured into a mixture of NH_4Cl (3.1 g, 58 mmol), ice-water (100 ml), and AcOEt (100 ml), then the whole was acidified to pH 2 with 6 N HCl. The layers were separated, and the organic layer was washed with brine, dried, and concentrated. The residue was subjected to silica gel chromatography (elution with hexane : AcOEt = 10 : 1) to give **8** (4.3 g, 99%) as a white solid, mp 40.5—42 °C. IR (KBr): 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, t, J = 7 Hz), 2.92 (1H, br s), 3.3—3.9 (6H, m), 4.46 (2H, q, J = 7 Hz), 4.95 (1H, dd, J = 7.5, 4.5 Hz), 6.54 (1H, d, J = 4 Hz), 7.1—7.4 (1H, m), 7.4—7.6 (2H, m), 8.07 (1H, d, J = 8.5 Hz). *Anal.* Calcd for $C_{15}H_{18}ClNO_4$: C, 57.78; H, 5.82; N, 4.51. Found: C, 57.64; H, 5.80; N, 4.55.

2-[2-(*N*,*N*-Dimethylamino)ethoxy]-1-(1*H*-indol-5-yl)ethanol Fumarate (3k) A mixture of **8** (1.5 g, 4.8 mmol), aqueous Me_2NH (50%, 5 ml, 95 mmol), and KI (0.8 g, 4.8 mmol) in EtOH (4.5 ml) was refluxed for 3 h before addition of a solution of KOH (0.6 g, 11 mmol) in water (2 ml). After 15 min the reaction mixture was cooled to room temperature, poured into ice-water (20 ml), and extracted with $CHCl_3$ (30 ml × 2). The combined extracts were washed with brine, dried, and concentrated. The residue was subjected to silica gel chromatography (elution with $CHCl_3$: MeOH = 1 : 1) to give a colorless oil. This material was dissolved in MeOH (20 ml) and the solution was treated with fumaric acid (0.3 g, 2.6 mmol). The resulting crystals were collected by filtration and recrystallized from MeOH to give **3k** (1.2 g, 73%), mp 197—200 °C (dec.).

Reversal of Electroconvulsive Shock (ECS)-Induced Impairment of a Passive Avoidance Response Groups of 10 male ddY mice, 6—7 weeks old and weighing 26—37 g, were used. Assay was carried out according to a reported procedure[7] by using a two-compartment step-through passive avoidance apparatus consisting of an illuminated compartment (10 × 13 × 15 cm) and a darkened grid-floor-equipped compartment (25 × 13 × 23 cm) with an opening (3 × 4 cm) between them. The passive avoidance training was given by application of 1.5 mA current for 3 s to the grid. Each test compound dissolved in physiological saline was dosed intraperitoneally 1 h before the training. Immediately after the training, a 20 mA current was administered to the eyes for 0.5 s, then after 24 h, retention of the inhibitory avoidance response was measured over a period of 300 s.

Antihypoxic Activity Groups of 10 female ddY mice (6 weeks old) were used. Two mice were placed in a 300 ml glass container into which a 4 : 96 (v/v) mixed gas of O_2 and N_2 was passed continuously at a flow rate of 5 l/min. A test compound was orally administered 30 min before this treatment. Time in seconds to respiratory interception was recorded as the survival time.

Reversal of CO_2-Induced Impairment of a Passive Avoidance Response Groups of 10 male ddY mice (6—7 weeks old) were used. This assay was performed according to a published procedure.[8] Immediately after being given the passive avoidance training described in the foregoing section, each mouse was brought to suspended animation by placing it in a 300 ml glass container into which CO_2 gas was passed continuously at a flow rate of 5 l/min for 30 s. The mouse was then animated by artificial respiration, and test compound was administered orally prior to evaluation for retention of the passive avoidance response. Dosages for MED determination were: **1** = 1.0, 3.0, 10 and 30 mg/kg; **3n** = 3.0, 10 and 30 mg/kg; **3o** = 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg; **3w** = 1.0, 3.0, 10 and 30 mg/kg; tacrine = 0.1, 0.3, 1.0, 3.0, and 10 mg/kg; indeloxazine = 1.0, 3.0, 10, and 30 mg/kg; bifemelane = 10, 30, and 100 mg/kg. Values of MED as determined by the Kruskal–Wallis test followed by the Mann–Whitney U-test were statistically significant ($p < 0.05$).

Acknowledgment The authors are grateful to Professor E. Yoshii, Toyama Medical and Pharmaceutical University, for his help and useful suggestions during the preparation of the manuscript.

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