The Synthesis and Antilipidperoxidation Activity of 4,4-Diarylbutylamines and 4,4-Diarylbutanamides

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

Faculty of Pharmaceutical Sciences, Fukuoka University,[a] Nanakuma, Jonan-ku, Fukuoka 814-01, Japan and Suntory Institute for Biomedical Research,[b] Wakayamadai, Shimamoto-cho, Mishima-gun, Osaka 618, Japan. *Received October 23, 1989*

A series of 4,4-diarylbutylamine and 4,4-diarylbutanamide derivatives has been synthesized and evaluated for their antilipidperoxidation (ALP) activity and acute toxicity (LD_{50}). Some of them were found to have significant ALP activity.

Keywords 4,4-diarylbutylamine; 4,4-diarylbutanamide; synthesis; antilipidperoxidation; lipid peroxidation; cerebral protective agent

As one of our projects directed toward the development of a new cerebral protective agent which affects cerebral circulation and metabolism in aged brain or in cerebral vascular diseases, we are preparing and evaluating pharmacological profiles of diarylbutylamines and the corresponding acid amides which are rationalized as the general structure (A) (see Fig. 1). Our interest in these compounds lies in the fact that some antipsychotics and antidepressants like pimozide,[1] chlorpromazine[2] and imipramine[3] bear the framework A in common, the latter two being considered as cyclic aza analogues of A.

An assay for antilipidperoxidation (ALP)[4] activity with brain homogenate in rats was designed for use in preliminary screening of the pharmacological activities of synthesized compounds, 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.[5] Acute toxicity (LD_{50}) was also determined.

In this paper, we report the synthesis and the results of screening tests of the target compounds synthesized.

Chemistry The target molecules were synthesized by the routes shown in Chart 1.

Commercially available γ-phenyl-γ-butyrolactone (**1**) is a common starting compound in the preparations. Initial attempts to search for compounds by means of chemical modifications have been focused on dimethylamino and *N*-methylpiperazino groups as the amine moiety to be included in the target molecule A, since the existence of such functionalities is typical in known psychotherapeutic drugs.[6]

The compounds (**3** and **4**)[7] having no substituent on phenyl rings are easily transformed from diphenylbutanoic acid (**2**)[8] obtained from the treatment of the lactone **1** in benzene in the presence of anhydrous aluminum chloride. The phenyl benzoxepin-2-ones (**6**), which are directly obtained from the reaction of lactone **1** and a phenol derivative with polyphosphoric acid (PPA) or by the oxidative ring enlargement (Baeyer–Villiger oxidation with *m*-chloroperbenzoic acid) of the tetralone derivative (**5**)[8] synthesized by the intramolecular ring closure of acid **1**, are useful precursors for the preparation of the compounds (**7**, **8**, **9**, and **10**) having a phenolic hydroxy group in one of the phenyl rings of the designed molecule.

Thus, compound (**6**) was transformed to the amides (**7a—d**) by treatment with appropriate amines, and subsequent reduction of products **7** with lithium aluminum hydride (LAH) afforded the corresponding amines (**8**) in high yield. Methylation of the phenolic hydroxy group in **7d** with diazomethane in the presence of silica-gel[9] gave the compound **9**. The acetate (**10**) was easily obtained by the treatment of **7d** with acetic anhydride in pyridine. The compounds (**11a—k**) listed in Table II were extensively prepared from the compound (**6b**) and appropriate amines by the procedure followed in the synthesis of **7c—d** (see Experimental).

The structures of these compounds were easily determined by spectroscopic data (infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR), and mass (MS) spectra) and elemental analyses. All of these target compounds, except for **4a** and **4b**, showed characteristic absorption bands for C=O and/or OH group (1600—1760 and/or 2900—3200 cm^{-1}, respectively) in IR spectra, and dialkylamino functionalities [−N(R)R′] introduced by the above procedures could be easily confirmed by ^{1}H-NMR (δ: >2.1). The physical data for compounds **3**, **4** and **7—11** are summarized in Tables I and II.

Pharmacological Evaluation The ALP activity and acute toxicity (LD_{50}) of the compounds (**3**, **4**, **7**, **8**, **9**, and **10**) are listed in Table III.

Compounds[7] (**4a** and **4b**) with no substituent on the aromatic ring in the diarylbutylamine had only slight effects on ALP activity (17—37% inhibition at 10^{-4} M) and showed low LD_{50} values.

Introduction of phenolic hydroxy group on a phenyl ring, compounds (**8a** and **8b**), still showed rather weak ALP activity (31—40% inhibition at 10^{-4} M) and rather high acute toxicity (104—205 mg/kg). Compounds (**8c** and **8d**) with an additional methoxy group on the above aromatic ring were found to be of an equivalent grade of acute toxicity (LD_{50} = 147—150 mg/kg), and they both exhibited an

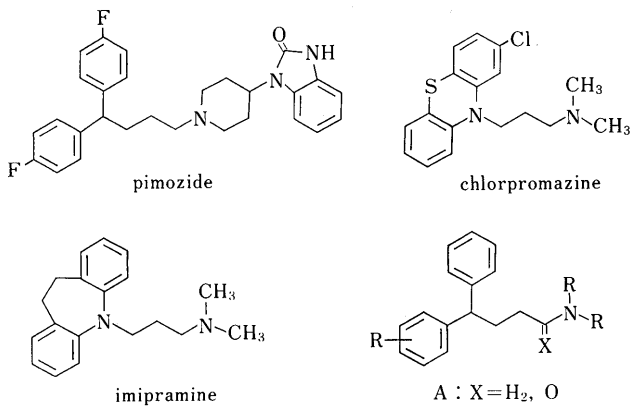
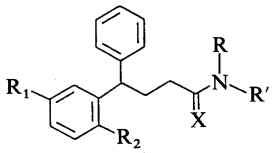
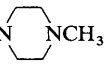
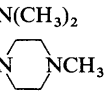
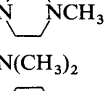
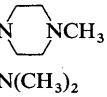
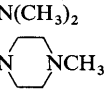
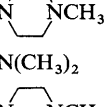
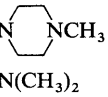
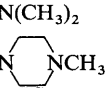


Fig. 1

TABLE I. Physical Properties of 4,4-Diarylbutylamines and 4,4-Diarylbutanamides



Compd.	R_1	R_2	X	–N(R)R′	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
3a	H	H	O	$-N(CH_3)_2$	89—91	73	$C_{18}H_{21}NO$	80.86 (80.88	7.92 7.96	5.24 5.42)
3b	H	H	O		209—212	77	$C_{21}H_{26}N_2O \cdot HCl \cdot 1/10H_2O$	69.93 (69.83	7.60 7.66	7.77 7.75)
4a	H	H	H_2	$-N(CH_3)_2$	149—152[a]	71	$C_{18}H_{23}N \cdot HCl \cdot 1/10H_2O$	74.13 (73.92	8.36 8.20	4.80 5.12)
4b	H	H	H_2		194—199[b]	91	$C_{21}H_{28}N_2 \cdot 2HCl \cdot 1/5H_2O$	65.52 (65.58	7.96 7.93	7.28 7.36)
7a	H	OH	O	$-N(CH_3)_2$	178—180	70	$C_{18}H_{21}NO_2$	76.29 (75.99	7.47 7.49	4.94 4.86)
7b	H	OH	O		99—101	68	$C_{21}H_{27}N_2O_2$[d]	339.2073[g] (339.2150)		
7c	OCH_3	OH	O	$-N(CH_3)_2$	176—178	74	$C_{19}H_{23}NO_3$	72.82 (72.77	7.40 7.45	4.47 4.44)
7d	OCH_3	OH	O		173—174	85	$C_{22}H_{28}N_2O_3$	71.71 (71.55	7.66 7.68	7.60 7.56)
8a	H	OH	H_2	$-N(CH_3)_2$	212—215	65	$C_{18}H_{25}ClNO$[e]	306.1623[g] (306.1609)		
8b	H	OH	H_2		202—204	61	$C_{21}H_{28}N_2O \cdot 2HCl \cdot 1/2H_2O$	62.07 (62.12	7.69 7.68	6.89 7.08)
8c	OCH_3	OH	H_2	$-N(CH_3)_2$	[c]	65	$C_{19}H_{25}NO_2$[f]	299.1884[g] (299.1876)		
8d	OCH_3	OH	H_2		187—190	65	$C_{22}H_{30}N_2O_2 \cdot 2HCl \cdot 1/2H_2O$	60.54 (60.75	7.62 7.38	6.42 6.65)
9	OCH_3	OCH_3	O		189—191.5	49	$C_{23}H_{30}N_2O_3 \cdot HCl$	65.93 (65.73	7.46 7.63	6.69 6.58)
10	OCH_3	$OCOCH_3$	O		105—106	95	$C_{24}H_{30}N_2O_4$	70.22 (70.03	7.37 7.46	6.82 6.81)

a) Lit. mp 153—154 °C.[7b] *b*) See Experimental and lit.[7a] *c*) Not measured because the compound is extremely hygroscopic. *d*) The *m/z* for $(M+H)^+$ of the hydrochloride [FAB-MS]. *e*) The *m/z* for $(M+H+HCl)^+$ of the hydrochloride [FAB-MS]. *f*) The *m/z* for M^+ of the free base. *g*) Determined by high-resolution MS. Upper figure, calcd for the corresponding ion and lower figure, found.

improved ALP activity (100% inhibition at 10^{-4} M), compared with the original compounds (**8a** and **8b**).

Most of the precursor amides, 4,4-diarylbutanamides (**3**, and **7**), on the other hand, showed higher LD_{50} values than those of the amino series (**4** or **8**). The compounds **7c** and **7d** having low toxicity ($LD_{50} > 500$ mg/kg) showed especially high ALP activities. Methylation (**9**) or acetylation (**10**) of the phenolic hydroxy group in compound **7d** led to a reduction of ALP activity accompanied by increased acute toxicity. In a subsequent chemical modification of amide functionality in the molecule **7c** (see compounds **11a—k** in Table II), compound **11f** was found to have remarkable activity and low toxicity (Table III).

Through these screening tests, we revealed that the derivatives of diarylbutylamines and the corresponding acid amides possessed significant ALP activities. With some active compounds (**7d** and **11f**) in the current series, we examined several additional animal models, such as hypobaric hypoxia,[10] global ischemia,[11] normobaric hypoxia,[12] KCN anoxia[13] and hemicholinium-3 anoxia,[14] and scopolamine amnesia.[15] Compounds **7d** and **11f** were also found to show a wide range of activity to such animal models and low toxicity (a wide margin of safety in animal species).

Further experiments of the above candidates are under way and the details will be reported in a separate paper.

Experimental

Melting points were determined on a Yanako melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a JEOL JNM-GX270 spectrometer, using tetramethylsilane as an internal standard, and IR spectra were obtained with either a Hitachi 260-10 or a Nicolet 5DX instrument. Elemental analyses were performed on a Perkin-Elmer 240B elemental analyzer. MS spectra were obtained with a Hitachi M80 instrument with a direct inlet system.

The compounds **11a—k** (Table II) were prepared by a similar procedure for the synthesis of the compound **7c** or **7d**. The compounds (**3, 4, 7a, 7c, 7d, 8b, 8d, 9, 10,** and **11a—k**) were analyzed (C, H, N, and S), and values obtained were within ±0.4% of the theoretical values. Regarding the compounds (**7b, 8a,** and **8c**), those molecular formulas were determined by high resolution MS spectra [electron impact (EI) or fast atom bombardment (FAB) method]. γ-Phenyl-γ-butyrolactone was obtained from Aldrich and used without further purification.

4,4-Diphenylbutyric Acid (2) For preparation of this compound (**2**),[8] the following procedure starting from commercially available γ-phenyl-γ-butyrolactone is conventional and gave a reproducible result. A solution of γ-phenyl-γ-butyrolactone (1.62 g, 10.0 mmol) in dry benzene (50 ml) was added in small portions to anhydrous aluminum chloride (1.46 g, 11.0 mmol). The mixture was stirred at room temperature for 5 h, and then decomposed with 2 N hydrochloric acid. The benzene layer was extracted twice with ether, the combined extracts were washed with water and dried over anhydrous magnesium sulfate. After filtration, evaporation of the

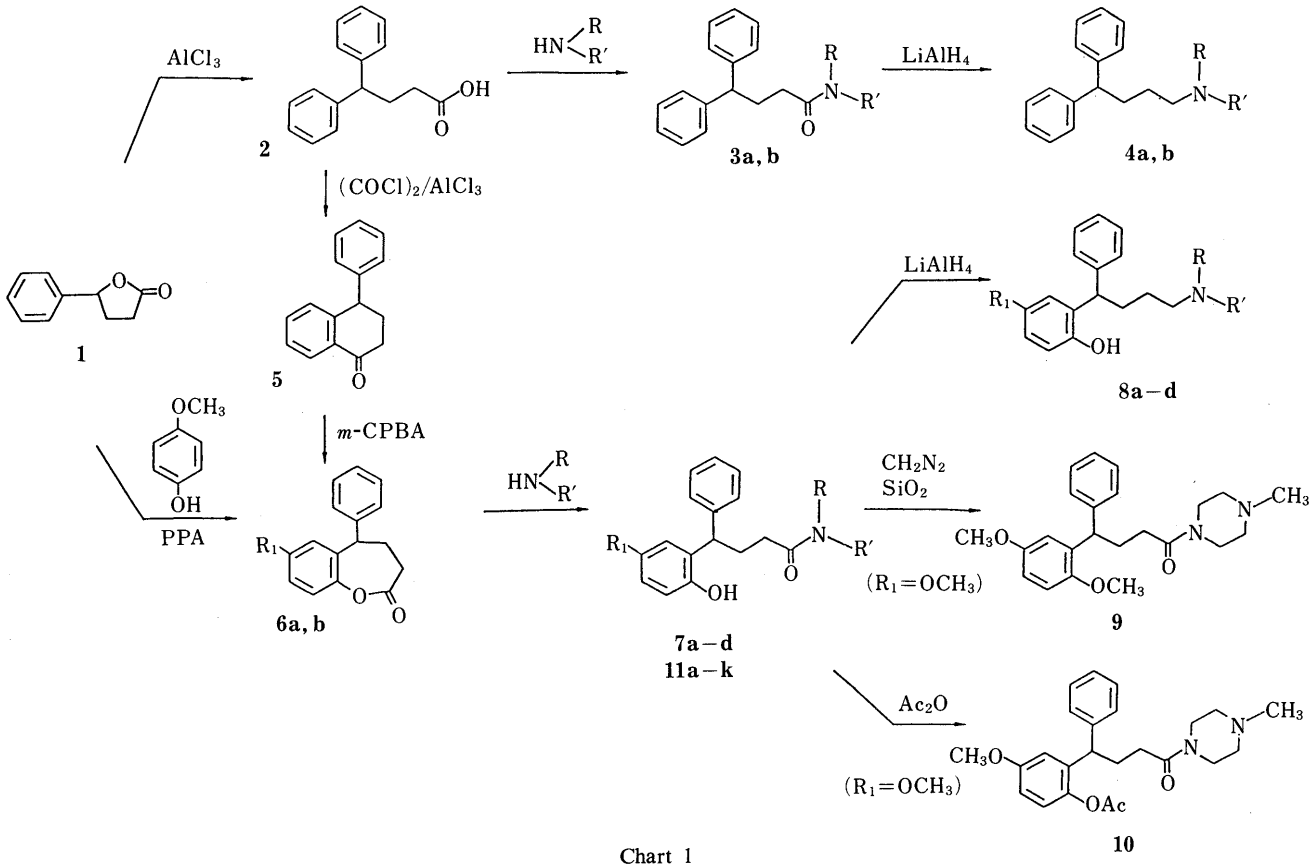
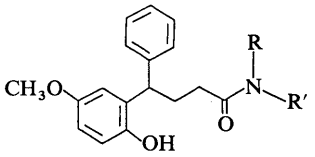


Chart 1

TABLE II. Physical Properties of Amide Derivatives of 4-(2-Hydroxy-5-methoxyphenyl)-4-phenylbutyric Acid



Compd.	–N(R)R′	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found)			
					C	H	N	S
11a	–N(Me)Ph	148—150	70	$C_{24}H_{25}NO_3$	76.77 (76.57	6.71 6.71	3.73 3.70)	
11b	–N(Me)CH$_2$Ph	[a]	94	$C_{25}H_{27}NO_3$	77.09 (76.92	6.99 6.99	3.60 3.65)	
11c	–N⟨⟩	203.5—204	74	$C_{22}H_{27}NO_3$	74.74 (75.05	7.70 7.78	3.96 4.10)	
11d	–N⟨O⟩	172—173.5	90	$C_{21}H_{25}NO_4$	70.96 (70.89	7.09 7.13	3.94 3.89)	
11e	–N⟨S⟩	191—192	97	$C_{21}H_{25}NO_3S$	67.91 (68.04	6.79 6.81	3.77 3.77	8.62 8.57)
11f	–N⟨NCH$_2$CH$_2$OH⟩	90.5—91.5	78	$C_{23}H_{30}N_2O_4$	69.32 (69.69	7.59 7.42	7.03 7.37)	
11g	–N⟨NCH$_2$Ph⟩	171—172	72	$C_{28}H_{32}N_2O_3$	75.65 (75.31	7.26 7.31	6.30 6.25)	
11h	–N⟨N–Ph⟩	148—149	85	$C_{27}H_{30}N_2O_3 \cdot 3/4H_2O$	73.02 (72.84	7.16 7.56	6.30 5.90)	
11i	–N⟨NH⟩	85—87	46	$C_{21}H_{26}N_2O_3$	71.16 (71.16	7.39 7.21	7.90 7.93)	
11j	–N⟨N–Me⟩	179—180[b]	91	$C_{23}H_{30}N_2O_3 \cdot HCl$	65.93 (65.92	7.22 7.50	6.69 6.72)	
11k	–N⟨NH⟩	165—166	35	$C_{22}H_{28}N_2O_3$	71.71 (71.71	7.66 7.52	7.60 7.85)	

a) An oily material. *b*) As monohydrochloride.

TABLE III. Antilipidperoxidation (ALP) Activity and LD_{50} Values of Target Compounds

Compd.	ALP[a]	LD_{50}[b]
3a	10.9	>500
3b	−6.7	143
4a	17.8	120
4b	37.0	140
7a	17.4	>500
7b	30.4	>500
7c	100.0	>500
7d	95.4	>1000
8a	40.0	104
8b	31.1	205
8c	100.0	147
8d	100.0	150
9	35.0	119
10	37.0	337
11f	88.0	>1000

a) Inhibition (%) at 10^{-4} M. *b*) Intraperitoneal (i.p.) administration (mg/kg).

solvent afforded the compound **2** (1.96 g, 82% yield) as colorless crystals: mp 89—91 °C (benzene–petroleum ether) (lit.[8] mp 103—106 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.20—2.50 (4H, m, $-CH_2CH_2-$), 3.97 (1H, t, a benzylic H), 7.00—7.45 (10H, m, ArH). IR (KBr): 1707 (C=O) cm^{-1}. MS *m/z*: 240 (M^+).

4,4-Diphenylbutyric Acid, *N,N*-Dimethyl Amide (3a) To a stirred solution of dimethylamine hydrochloride (1.02 g, 12.5 mmol) and triethylamine (1.26 g, 12.5 mmol) in dry methylene chloride was added the acid **2** (1.50 g, 6.25 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (3.00 g, 15.6 mmol). The mixture was stirred at room temperature for 4 h, and the reaction mixture was then poured into water and extracted with methylene chloride. The combined extracts were dried over anhydrous magnesium sulfate. After filtration and evaporation of methylene chloride, the crude product was purified by flash column chromatography with hexane–ethyl acetate (1 : 1) as solvent. The compound (**3a**) (1.21 g) was obtained as colorless crystals. The physical data are listed in Table I.

4,4-Diphenylbutyric Acid, *N*-Methylpiperazinyl Amide (3b) To a stirred solution of **2** (428 mg, 1.78 mmol) and ethyl chloroformate (232 mg, 2.14 mmol) in dry methylene chloride (20 ml) was added dropwise triethylamine (271 mg) at 0 °C with additional stirring for 1 h. The reaction mixture was filtered and the filtrate was concentrated to leave an oil. The solution was added to *N*-methylpiperazine (190 mg, 1.90 mmol). After refluxing for 1 h, the reaction mixture was concentrated *in vacuo*. The residue was chromatographed by silica-gel column with 3% methanol–methylene chloride as solvent to give **3b** (442 mg), which was converted to the hydrochloride. The physical data are listed in Table I.

4,4-Diphenylbutylamines[7] (4a and 4b) To a stirred suspension of LAH (279 mg, 7.35 mmol) in dry tetrahydrofuran (THF) (25—40 ml) was added a solution of **3** (1.42—1.84 mmol) in THF (10 ml) at 0 °C, and the resulting mixture was stirred at room temperature for 1—6 h. The reaction mixture was quenched by 3 N NaOH with ice-cooling. The THF layer was separated and dried over anhydrous magnesium sulfate. After concentration, the residue was chromatographed by silica-gel column. Elution with (5—7.5%) methanol–methylene chloride gave the compound **4** the structures of which were easily confirmed by spectroscopic methods. The physical data are listed in Table I. The mp (194—199 °C) for the sample **4b** obtained above was much lower than the value (mp 271—272 °C) for the sample with 0.5 mol H_2O reported previously.[7a]

4-Phenyl-1-tetralone (5) For preparation of this compound (**5**),[8] the following procedure is conventional and gave a reproducible result. Thus, the compound (**2**) (1.00 g, 4.17 mmol) was added in small portions to oxalyl chloride (2.64 g) over the course of 30 min and the resulting mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated in vacuo and the resulting acid chloride was dissolved in 1,2-dichloroethane followed by addition of anhydrous aluminum chloride at 0 °C. The mixture was stirred at room temperature for 8 h and was poured into ice-cold 2 N hydrochloric acid. The organic layer was separated and the water layer was extracted with methylene chloride. The combined extracts were washed with 2 N NaOH and brine, and subsequently dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* afforded **5** (655 mg, 71% yield). The structure was confirmed from its spectroscopic data. MS *m/z*: 222 (M^+). IR (KBr): 1683 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.15—2.85 (4H, m, $-CH_2CH_2-$), 4.15—4.40 (1H, m, a benzylic H), 6.98—8.11 (9H, m, ArH).

5-Phenyl-2,3,4,5-tetrahydro-1-benzoxepin-2-one (6a) A mixture of (**5**) (1.86 g, 8.38 mmol) and *m*-chloroperbenzoic acid (5.40 g, 31.3 mmol) in chloroform (100 ml) was stirred at room temperature for 5 d. The reaction mixture was washed with aqueous K_2CO_3 and water. After drying over anhydrous magnesium sulfate, the chloroform layer was concentrated *in vacuo* and the residual oil was purified by flash column chromatography with hexane–ethyl acetate (5 : 1) as solvent to give (**6a**) (1.30 g, 65% yield) as a colorless oil. MS *m/z*: 238 (M^+). IR (KBr): 1754 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.25—2.70 (4H, m, $-CH_2CH_2-$), 4.30—4.55 (1H, m, a benzylic H), 6.72—7.50 (9H, m, ArH).

7-Methoxy-5-phenyl-2,3,4,5-tetrahydro-1-benzoxepin-2-one (6b) A mixture of 4-methoxyphenol (12.4 g, 10 mmol) and γ-phenyl-γ-butyrolactone (16.2 g, 10 mmol) in 75% PPA (350 g) was stirred at room temperature for 5 h. The reaction mixture was poured into ice-cold water and extracted with ether. The combined extracts were washed with 2 N NaOH and water. After drying over anhydrous magnesium sulfate, the ether layer was concentrated *in vacuo* and the residual oil was chromatographed by silica-gel column with hexane–ethyl acetate (5 : 1) as solvent to give (**6b**) (8.03 g, 30% yield) as colorless crystals: mp 65—67 °C. MS *m/z*: 268 (M^+). IR (KBr): 1760 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.33—2.70 (4H, m, $-CH_2CH_2-$), 3.65 (3H, s, CH_3), 4.40 (1H, dd, a benzylic H), 6.28—7.45 (8H, m, ArH).

4-(2-Hydroxyphenyl)-4-phenylbutyric Acid, *N,N*-Dimethyl Amide (7a) A solution of (**6a**) (560 mg, 2.35 mmol) and dimethylamine (50% in water) (20 ml) in dioxane (20 ml) was heated in a sealed tube at 140 °C for 5 h. The reaction mixture was diluted with water and extracted with chloroform. The combined extracts were washed with brine and dried over anhydrous magnesium sulfate. After filtration and concentration of the chloroform layer, the residual oil was purified by flash column chromatography with hexane–ethyl acetate (1 : 1) as solvent to give (**7a**) (468 mg). The physical data are listed in Table I.

4-(2-Hydroxyphenyl)-4-phenylbutyric Acid, *N*-Methylpiperazinyl Amide (7b) A mixture of (**6a**) (622 mg, 2.61 mmol) and *N*-methylpiperazine (784 mg, 7.83 mmol) in toluene was refluxed for 5 h. After concentration of the solvent, the residual oil was chromatographed by silica-gel column with 5% methanol–methylene chloride to give (**7b**) (602 mg) which was converted to hydrochloride. The physical data are listed in Table I.

4-(2-Hydroxy-5-methoxyphenyl)-4-phenylbutyric Acid, *N,N*-Dimethyl Amide (7c) A mixture of dimethylamine hydrochloride (577 mg, 7.1 mmol) and triethylamine (714 mg, 7.1 mmol) in toluene (50 ml) was stirred at room temperature for 30 min. To the above mixture was added (**6b**) (379 mg, 1.41 mmol) and the resulting solution was refluxed for 5 h. The reaction mixture was washed with brine and dried over anhydrous magnesium sulfate. The toluene layer was concentrated and residual oil was purified by flash column chromatography with hexane–ethyl acetate (1 : 1) to afford (**7c**) (327 mg). The physical data are listed in Table I.

4-(2-Hydroxy-5-methoxyphenyl)-4-phenylbutyric Acid, *N*-Methylpiperazinyl Amide (7d) Using a procedure similar to that described above, **7d** (3.13 g, 85%) was obtained from **6b** (2.68 g) and *N*-methylpiperazine (1.20 g). The product was purified by silica gel column with 7% methanol–methylene chloride as solvent. The physical data are listed in Table I.

***N,N*-Dimethyl-4-(2-hydroxyphenyl)-4-phenylbutylamine (8a)** To a stirred suspension of LAH (129 mg) in dry THF (50 ml), the compound (**7a**) (321 mg, 1.13 mmol) was added at 0 °C and the mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with 3 N NaOH with ice-cooling. The THF layer was separated and the residual slurry was washed with THF. The combined THF solutions were concentrated and the residue was dissolved in 1 N hydrochloric acid. The separated aqueous acidic layer was washed with ether and then neutralized with 3 N NaOH, and the product was extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate, and concentrated, and the residual oil was chromatographed by silica-gel column with 5% methanol–methylene chloride as solvent to give (**8a**) (198 mg) which was converted to hydrochloride. The compounds (**8b**, **8c** and **8d**) were also obtained by the procedure described above. The results are summarized in Table I.

4-(2,5-Dimethoxyphenyl)-4-phenylbutyric Acid, *N*-Methylpiperazinyl Amide (9) A solution of (**7d**) (412 mg, 1.12 mmol) in ether (200 ml) was treated with an excess of ethereal diazomethane in the presence of neutral silica-gel at room temperature overnight. After filtration, the ether layer

was concentrated and the residual oil was purified by silica-gel column chromatography with 5% methanol–methylene chloride as solvent to give (**9**) (210 mg) which was converted to hydrochloride. The physical data are listed in Table I.

4-(2-Acetoxy-5-methoxyphenyl)-4-phenylbutyric Acid, *N*-Methylpiperazinyl Amide (10) A mixture of (**7d**) (1.10 g, 2.99 mmol) and acetic anhydride (20 ml) in pyridine (20 ml) was stirred at room temperature for 4 h. The mixture was concentrated and the resulting oil was dissolved in ether. The ether layer was washed with saturated sodium bicarbonate and water. After drying over anhydrous magnesium sulfate, the ether was evaporated and residual oil was purified by silica-gel column chromatography with 5% methanol–methylene chloride as solvent to afford (**10**) (1.16 g) which was converted to hydrochloride. The physical data are listed in Table I.

Pharmacological Evaluations ALP Activity Assay: The supernatant fraction of rat brain homogenates was prepared according to the method reported by Stocks *et al.*[4] The whole brain except the cerebellum of male Wistar rats weighing 200—300 g was obtained after decapitation and homogenated in 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 × *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 addition of 0.2 ml of ice-cold 35% $HClO_4$, the resulting mixture was centrifuged at 1000 × *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. The results are shown in Table III.

Acute Toxicity: Male ddY mice weighing 18—25 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 according to the up-and-down method described by Brownlee *et al.*[16]

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