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

Seiji Miyano,*,a Toshio Tatsukau,b Kenji Suzuki,b Kayoko Imao,a Fumio Satoh,b Takaumi Ishihara,a Ichiro Hirotsu,b Tetsuro Kihara,b Mizuho Hatba,b Yoshiko Horikawab,a and Kunihiro Sumota,a

Faculty of Pharmaceutical Sciences, Fukuoka University,* Nanakuma, Jonan-ku, Fukuoka 814-01, Japan and Santory Institute for Biomedical Research,† 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 (LD₅₀). 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 chlorpromazine⁰ and imipramine³⁰ bear the framework A in common, the latter two being considered as cyclic aza analogues of A.

An assay for antilipidperoxidation (ALP)²⁶ 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.⁴ Acute toxicity (LD₅₀) 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-butyro lactone (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-methylpipеразин групс as the amine moiety to be included in the target molecule A, since the existence of such functionalities is typical in known psychotherapeutic drugs.⁵

The compounds (3 and 4)⁷ having no substituent on phenyl rings are easily transformed from diphenylbutanionic 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 aluminium 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-gel⁹ 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 (¹H-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 dikalaymino functionalities [−N(R)R'] introduced by the above procedures could be easily confirmed by ¹H-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 (LD₅₀) of the compounds (3, 4, 7, 8, 9, and 10) are listed in Table III.

Compounds (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 LD₅₀ 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 (LD₅₀ = 147–150 mg/kg), and they both exhibited an
TABLE I. Physical Properties of 4,4-Diarylbutaamines and 4,4-Diarylbutanamides

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R₁</th>
<th>R₂</th>
<th>X</th>
<th>-N(R)R’</th>
<th>mp (°C)</th>
<th>Yield (%)</th>
<th>Formula</th>
<th>Analysis (%)</th>
<th>Calcd (Found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>-N(CH₃)₂</td>
<td>89–91</td>
<td>73</td>
<td>C₁₈H₂₁NO</td>
<td>80.86</td>
<td>7.92</td>
</tr>
<tr>
<td>3b</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>-N(CH₃)₂</td>
<td>209–212</td>
<td>77</td>
<td>C₁₂H₁₆N₂O·HCl·1·1OH₂O</td>
<td>69.93</td>
<td>7.60</td>
</tr>
<tr>
<td>4a</td>
<td>H</td>
<td>H</td>
<td>H₃</td>
<td>-N(CH₃)₂</td>
<td>149–152a</td>
<td>71</td>
<td>C₁₈H₂₃N·HCl·1·1OH₂O</td>
<td>74.13</td>
<td>8.36</td>
</tr>
<tr>
<td>4b</td>
<td>H</td>
<td>H</td>
<td>H₃</td>
<td>-N(CH₃)₂</td>
<td>194–199b</td>
<td>91</td>
<td>C₁₂H₁₈N₂·2HCl·1·1H₂O</td>
<td>65.52</td>
<td>7.96</td>
</tr>
<tr>
<td>7a</td>
<td>H</td>
<td>OH</td>
<td>O</td>
<td>-N(CH₃)₂</td>
<td>178–180</td>
<td>70</td>
<td>C₁₈H₂₁NO₂</td>
<td>76.29</td>
<td>7.47</td>
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<tr>
<td>7b</td>
<td>H</td>
<td>OH</td>
<td>O</td>
<td>-N(CH₃)₂</td>
<td>99–101</td>
<td>68</td>
<td>C₁₂H₁₇N₂O₂</td>
<td>75.99</td>
<td>7.49</td>
</tr>
<tr>
<td>7c</td>
<td>OCH₃</td>
<td>OH</td>
<td>O</td>
<td>-N(CH₃)₂</td>
<td>176–178</td>
<td>74</td>
<td>C₁₂H₁₃NO₃</td>
<td>72.82</td>
<td>7.40</td>
</tr>
<tr>
<td>7d</td>
<td>OCH₃</td>
<td>OH</td>
<td>O</td>
<td>-N(CH₃)₂</td>
<td>173–174</td>
<td>85</td>
<td>C₁₂H₁₃N₂O₃</td>
<td>71.71</td>
<td>7.66</td>
</tr>
<tr>
<td>8a</td>
<td>H</td>
<td>OH</td>
<td>H₃</td>
<td>-N(CH₃)₂</td>
<td>212–215</td>
<td>65</td>
<td>C₁₂H₁₃ClNO</td>
<td>71.59</td>
<td>7.68</td>
</tr>
<tr>
<td>8b</td>
<td>H</td>
<td>OH</td>
<td>H₃</td>
<td>-N(CH₃)₂</td>
<td>202–204</td>
<td>61</td>
<td>C₁₂H₁₃N₂O₂·2HCl·1·1H₂O</td>
<td>62.07</td>
<td>7.69</td>
</tr>
<tr>
<td>8c</td>
<td>OCH₃</td>
<td>OH</td>
<td>H₃</td>
<td>-N(CH₃)₂</td>
<td>212–215</td>
<td>65</td>
<td>C₁₂H₁₃N₂O₂</td>
<td>62.12</td>
<td>7.68</td>
</tr>
<tr>
<td>8d</td>
<td>OCH₃</td>
<td>OH</td>
<td>H₃</td>
<td>-N(CH₃)₂</td>
<td>187–190</td>
<td>65</td>
<td>C₁₂H₁₃N₂O₂·2HCl·1·1H₂O</td>
<td>60.54</td>
<td>7.62</td>
</tr>
<tr>
<td>9</td>
<td>OCH₃</td>
<td>OCH₃</td>
<td>O</td>
<td>-N(CH₃)₂</td>
<td>189–191.5</td>
<td>49</td>
<td>C₁₂H₁₃N₂O₃·HCl</td>
<td>65.93</td>
<td>7.46</td>
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<tr>
<td>10</td>
<td>OCH₃</td>
<td>OCH₃</td>
<td>O</td>
<td>-N(CH₃)₂</td>
<td>105–106</td>
<td>95</td>
<td>C₁₂H₁₃N₂O₄</td>
<td>70.22</td>
<td>7.37</td>
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</table>

a) Lit. mp 153–154°C. b) See Experimental and lit. 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 LD₅₀ values than those of the amino series (4 or 8). The compounds 7c and 7d having low toxicity (LD₅₀ > 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 diarylbutaamines 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, global ischemia, normobaric hypoxia, KCN anoxia, and hemicholinium-3 anoxia, and scopolamine amnesia. 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 1H-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 7e 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), 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
TABLE II. Physical Properties of Amide Derivatives of 4-(2-Hydroxy-5-methoxyphenyl)-4-phenylbutyric Acid

<table>
<thead>
<tr>
<th>Compd.</th>
<th>-N(R)R'</th>
<th>mp (°C)</th>
<th>Yield (%)</th>
<th>Formula</th>
<th>Analysis (% Calcd/Found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11a</td>
<td>-NMe</td>
<td>148-150</td>
<td>70</td>
<td>C_{22}H_{22}NO_3</td>
<td>76.77/6.71/3.73 (76.57/6.71/3.70)</td>
</tr>
<tr>
<td></td>
<td>-NPh</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11b</td>
<td>-NMe</td>
<td></td>
<td>94</td>
<td>C_{22}H_{22}NO_3</td>
<td>77.09/6.99/3.60 (76.92/6.99/3.65)</td>
</tr>
<tr>
<td></td>
<td>-CH_2Ph</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11c</td>
<td>-NN</td>
<td>203.5-204</td>
<td>74</td>
<td>C_{22}H_{22}NO_3</td>
<td>74.74/7.70/3.96 (75.05/7.78/4.10)</td>
</tr>
<tr>
<td>11d</td>
<td>-NO</td>
<td>172-173.5</td>
<td>90</td>
<td>C_{22}H_{22}NO_4</td>
<td>70.96/7.09/3.94 (70.89/7.13/3.89)</td>
</tr>
<tr>
<td>11e</td>
<td>-NS</td>
<td>191-192</td>
<td>97</td>
<td>C_{22}H_{22}NO_2S</td>
<td>67.91/6.79/3.77 (68.04/6.81/3.77)</td>
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<tr>
<td>11f</td>
<td>-NCH_2CH_2OH</td>
<td>90.5-91.5</td>
<td>78</td>
<td>C_{22}H_{22}NO_4</td>
<td>69.32/7.59/3.90 (69.69/7.42/3.77)</td>
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<tr>
<td>11g</td>
<td>-NCH_2Ph</td>
<td>171-172</td>
<td>72</td>
<td>C_{22}H_{22}NO_3</td>
<td>75.65/7.26/6.30 (75.31/7.31/6.25)</td>
</tr>
<tr>
<td>11h</td>
<td>-NPh</td>
<td>148-149</td>
<td>85</td>
<td>C_{22}H_{22}NO_3·3H_2O</td>
<td>73.02/7.16/6.30 (72.84/7.56/5.90)</td>
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<tr>
<td>11i</td>
<td>-NH</td>
<td>85-87</td>
<td>46</td>
<td>C_{22}H_{22}NO_3</td>
<td>71.16/7.39/7.90 (71.16/7.21/7.93)</td>
</tr>
<tr>
<td>11j</td>
<td>-NMe</td>
<td>179-180°b</td>
<td>91</td>
<td>C_{22}H_{22}NO_3·HCl</td>
<td>65.93/7.22/6.69 (65.92/7.50/6.72)</td>
</tr>
<tr>
<td>11k</td>
<td>-NH</td>
<td>165-166</td>
<td>35</td>
<td>C_{22}H_{22}NO_3</td>
<td>71.71/7.66/7.60 (71.71/7.52/7.85)</td>
</tr>
</tbody>
</table>

a) An oily material.  b) As monohydrochloride.
TABLE III. Antilipid Peroxidation (ALP) Activity and LD₅₀ Values of Target Compounds

<table>
<thead>
<tr>
<th>Compd.</th>
<th>ALPᵃ</th>
<th>LD₅₀ᵇ</th>
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<tr>
<td>3a</td>
<td>10.9</td>
<td>&gt;500</td>
</tr>
<tr>
<td>3b</td>
<td>6.7</td>
<td>143</td>
</tr>
<tr>
<td>4a</td>
<td>17.8</td>
<td>120</td>
</tr>
<tr>
<td>4b</td>
<td>37.0</td>
<td>&gt;500</td>
</tr>
<tr>
<td>7a</td>
<td>17.4</td>
<td>&gt;500</td>
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<tr>
<td>7b</td>
<td>30.4</td>
<td>&gt;500</td>
</tr>
<tr>
<td>7c</td>
<td>100.0</td>
<td>&gt;500</td>
</tr>
<tr>
<td>7d</td>
<td>95.4</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>8a</td>
<td>40.0</td>
<td>104</td>
</tr>
<tr>
<td>8c</td>
<td>31.1</td>
<td>205</td>
</tr>
<tr>
<td>8e</td>
<td>100.0</td>
<td>147</td>
</tr>
<tr>
<td>9</td>
<td>35.0</td>
<td>119</td>
</tr>
<tr>
<td>10</td>
<td>37.0</td>
<td>337</td>
</tr>
<tr>
<td>11f</td>
<td>88.0</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

ᵃ Inhibition (%) at 10⁻⁴ M. ᵇ Intraperitoneal (i.p.) administration (mg/kg).

(655 mg, 71% yield). The structure was confirmed from its spectroscopic data. MS m/z: 222 (M⁺). IR (KBr): 1683 (C=O) cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.15–2.85 (4H, m, –CH₂–CH₂–), 4.15–4.40 (1H, m, a benzyllic H), 6.98–8.11 (3H, m, ArH).

5-Phenyl-2,3,4,5-tetrahydro-1-benzoxin-2-one (6a) A mixture of (5) (1.86 g, 8.38 mmol) and m-chloroperozoic acid (5.40 g, 31.3 mmol) in chloroform (100 ml) was stirred at room temperature for 5d. The reaction mixture was washed with aqueous K₂CO₃ 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. ¹H-NMR (CDCl₃) δ: 2.25–2.70 (4H, m, –CH₂–CH₂–), 4.30–4.55 (1H, m, a benzyllic H), 6.72–7.50 (3H, m, ArH).

7-Methoxy-5-phenyl-2,3,4,5-tetrahydro-1-benzoxin-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 5h. 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. ¹H-NMR (CDCl₃) δ: 2.33–2.70 (4H, m, –CH₂–CH₂–), 3.65 (3H, s, CH₃), 4.40 (1H, dd, a benzyllic H), 6.28–7.45 (3H, 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 5h. 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) (261 mg, 1.91 mmol) and N-methylpiperazine (784 mg, 7.83 mmol) in toluene was refluxed for 5h. 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 (6a) (261 mg, 1.91 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 5h. 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-1-(2-hydroxyphenyl)-4-phenylbutyramide (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 resulting solution was stirred at room temperature for 2h. The reaction mixture was quenched with 3N 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 1N hydrochloric acid. The separated aqueous layer was washed with ether and then neutralized with 3N NaOH, and the product was extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate, the residue was 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

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*Note: The text contains a table and a list of chemical compounds with their ALP activity and LD₅₀ values. The compounds are listed with their corresponding ALP and LD₅₀ values, followed by a description of the chemical reactions and the isolation of the compounds. The table includes compounds 3a, 3b, 3a, 7b, 7c, 7d, 8a, 8c, 8d, 9, 10, and 11f, along with their associated ALP and LD₅₀ values.*
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-Acetoxyl-5-methoxyphenyl)-4-phenylbutyric Acid, N-Methylpipera
tzyl 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.44 The whole brain except the cerebellum of male
Wistar rats weighing 200—300 g was obtained after decapitation and
homogenized in ice-cold phosphate-saline buffer (50 mm, pH 7.4) at a
volume of 9 ml per 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% HClO4, 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 LD₅₀ 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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