

## Design, Synthesis and Anticonvulsive Activities of Potential Prodrugs Linked by Two-carbon Chain

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For the development of new anticonvulsive agents, GABA mimetics such as nipecotic acid, isonipecotic acid,  $\gamma$ -aminobutyric acid (GABA),  $\gamma$ -vinyl GABA (vigabatrin) and valproic acid were covalently coupled through an ester bond by a two-carbon linker chain as potential prodrugs and evaluated for their anticonvulsive activities.

**Key words:** Anticonvulsants, Prodrugs, Synthesis, Linker chain, Anticonvulsive activities

### INTRODUCTION

Epilepsy is a family of neurological disorders that have in common a transient, recurrent, self-sustained interruption of normal brain functions and a simultaneous, hypersynchronous activation of a large population of neurons in one focal area or generally throughout the brain (Dichter and Ayala, 1987). It has been reported that approximately 1% of the population suffer from some form of epilepsy and 20-40% of epileptic patients have experienced failure to control seizures. Since epilepsy consists of various forms of seizure, combinations of drugs and repeated therapy are required to control such complex convulsions, which result in increased toxicity and adverse side effects of clinically used anticonvulsant drugs.

Many studies have been performed to develop new anticonvulsants such as structurally modified compounds of clinically used drugs (Kwon *et al.*, 1991; Edafiogho *et al.*, 1991), modified amino acids (Kohn *et al.*, 1991; Kohn *et al.*, 1990) and  $\gamma$ -aminobutyric acid (GABA) related compounds (Krogsgaard-Larsen, 1981). However, these compounds cannot provide complete control of complex seizures. Many GABA mimetic substances such as GABA receptor agonists, GABA reuptake inhibitors and GABA metabolism inhibitors have been reported to be potent anticonvulsant agents, and some of these agents have been

clinically used for the treatment of epilepsy (Krogsgaard-Larsen, 1981; Matsuyama *et al.*, 1984). However, these compounds do not readily enter the central nervous system in pharmacologically effective amounts following peripheral administration, since these compounds can not readily pass the blood-brain barrier (BBB), presumably due to their lower lipophilicity (Krogsgaard-Larsen, 1981; Sasaki *et al.*, 1991; Smith and Kwon, 1992). In our previous reports (Jung *et al.*, 1998; Son *et al.*, 1998; Lee *et al.*, 1999; Kim *et al.*, 2000) efforts to overcome such problems were made with particular emphasis on designing new anticonvulsants having a broader spectrum, lower toxicity and increased lipophilicity.

In this report, we described the design, synthesis and biological activity of potentially dual acting prodrugs in which nipecotic acid (**1**), isonipecotic acid (**2**), GABA (**3**), vigabatrin (**4**) and valproic acid (**5**) (Fig. 1) are covalently coupled with an ester bond through a two-carbon linker chain. Nipecotic acid was reported as a GABA reuptake inhibitor, isonipecotic acid as a GABA receptor agonist, vigabatrin as a GABA aminotransferase inhibitor and valproic acid as the most commonly used conventional anticonvulsive agent. It was intended that these prodrugs connected by a two-carbon linker chain could not only readily penetrate to the CNS but also be biotransformed into active components by metabolic hydrolysis. Additionally, the two metabolites are expected to have an increased potency with a synergistic effect and a broader spectrum (Maynert and Kaji, 1962; Frey and Löscher, 1980; Shashoua *et al.*, 1984; Jacob *et al.*, 1985).

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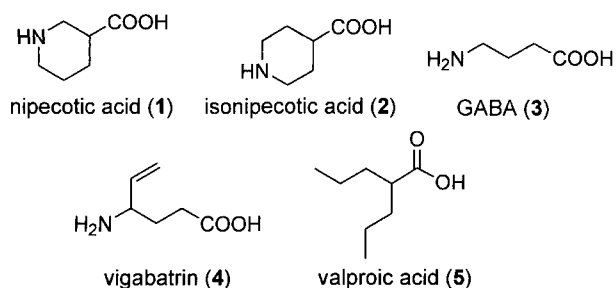


Fig. 1.

## MATERIALS AND METHODS

### Chemistry

Compounds used as starting materials and reagents were obtained from Aldrich Chemical Co, Sigma, Fluka, and Jusei and were used without further purification. Thin-layer chromatography (TLC) and column chromatography were performed with Kieselgel 60 F<sub>254</sub> (Merck) and silica gel Kieselgel 60, (70~230, 230~240 mesh, Merck), respectively. Compounds containing an aromatic ring were visualized on TLC plates with UV light and compounds containing nitrogen were visualized on TLC plates with ninhydrin spray or Cl<sub>2</sub> exposure after spraying with 1% KI starch solution. All prepared compounds were detected on TLC plates with I<sub>2</sub>. <sup>1</sup>H-NMR spectra were taken on a Bruker AMX 250 MHz spectrometer, and tetramethylsilane was used as an internal standard except for the compounds in D<sub>2</sub>O. <sup>13</sup>C-NMR was determined in DMSO-*d*<sub>6</sub> or CDCl<sub>3</sub> solutions with a Bruker AMX 250 spectrometer taken on 62.5 MHz, and peaks positions were given in ppm. Melting points were determined in open capillary tubes on electrothermal 1A 9100 digital melting point apparatus and were uncorrected.

#### Piperidine-1,3-dicarboxylic acid 1-benzyl ester (6)

General procedure: Nipecotic acid (1, 3.0 g, 23.23 mmol) was added to an ice-cold solution of 2 M NaOH (25.55 mL) and dissolved completely. Benzylchloroformate (3.65 mL, 25.25 mmol) was added to the solution dropwise. The temperature was gradually increased to room temperature and the mixture was stirred for 16 h. The mixture was cooled to 0°C and washed with EtOAc (40 mL×3) and the aqueous layer was acidified with aqueous 1 M HCl solution to pH 2. The solution was cooled to 0°C and the aqueous layer was extracted with EtOAc (80 mL×3) and washed with 1 N HCl solution (40 mL×3), water (40 mL×3) and saturated NaCl solution (40 mL×2), and then dried with MgSO<sub>4</sub>. Compound 6 (5.43 g, 20.62 mmol) was obtained as a white crystal at 88.8% yield. mp 94.6~95.8°C; TLC (EtOAc: *n*-hexane: acetic acid = 100:100:1, v:v:v), R<sub>f</sub> = 0.33, TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1, v:v), R<sub>f</sub> = 0.63; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz) 7.38 (s, 5H, CH of phenyl×5), 5.13 (t, J = 17.4

Hz, 2 H, CH<sub>2</sub> of benzyl), 4.19 (dd, J = 14.3, 7.1 Hz, 1 H, -CONCH<sub>2</sub>CH-), 3.98 (br, 1H, -CONCH<sub>2</sub>CH-), 3.11 (d, J = 3.4 Hz, 1H, -CONCH<sub>2</sub>CH<sub>2</sub>-), 2.91 (td, J = 10.8, 2.6 Hz, 1H, -CONCH<sub>2</sub>CH<sub>2</sub>-), 2.49 (m, 2H, -CHCOO), 2.09 (m, 1H, -CH<sub>2</sub>CH<sub>2</sub>CH-), 1.78~1.39 (m, 3H, -CH<sub>2</sub>CH<sub>2</sub>CH-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>).

#### Piperidine-1,4-dicarboxylic acid 1-benzyl ester (7)

Yield: 91.7%, white crystal, mp 66.8~70.7°C; TLC (EtOAc: *n*-hexane: acetic acid = 100:100:1, v:v:v), R<sub>f</sub> = 0.33, TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1, v:v), R<sub>f</sub> = 0.38; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz) δ 7.32 (s, 5H, CH of phenyl×5), 5.13 (t, J = 20.0 Hz, 2H, CH<sub>2</sub> of benzyl), 4.11 (m, 2H, -CONCH<sub>2</sub>CH<sub>2</sub>-), 2.95 (t, J = 11.4 Hz, 1H, -CONCH<sub>2</sub>CH<sub>2</sub>-), 2.49 (tt, J = 10.8, 3.9 Hz, 2H, -CHCOO), 1.95 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH-), 1.60 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>).

#### 4-Benzyloxycarbonylaminobutyric acid (8)

Yield: 92.3%, white crystal, mp 62.8~64.2°C; TLC (EtOAc: *n*-hexane: acetic acid = 100:100:1, v:v:v), R<sub>f</sub> = 0.32, TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1, v:v), R<sub>f</sub> = 0.46; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz) δ 7.29 (s, 5H, CH of phenyl×5), 5.09 (s, 2H, CH<sub>2</sub> of benzyl), 4.97 (br, 1H, HNCO), 3.25 (q, J = 6.5 Hz, 2H, CH<sub>2</sub>NHCO<sub>2</sub>-), 2.38 (t, J = 7.1 Hz, 2H, -CHCOO), 1.83 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>).

#### N-Benzyloxycarbonylpiperidine-3-carboxylic acid 2-(N-Benzyloxycarbonylpiperidine-3-carboxyloxy)-ethyl ester (9)

General procedure: Ethylene glycol (0.11 mL, 1.90 mmol) and 4-dimethylaminopyridine (DMAP, 0.93 g, 7.60 mmol) were added to the solution of compound 6 (2.0g, 7.60 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The solution was cooled to 0°C, and EDC (1.46 g, 7.60 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added dropwise for 5 min. After a further 5 min stirring at 0°C, the mixture was stirred for 3 h at room temperature. The solution was evaporated under reduced pressure and the residue formed was dissolved in EtOAc (100 mL), and the resultant solution was washed with aqueous 5% NaHCO<sub>3</sub> solution (40 mL×3), 5% HCl solution (40 mL×3) and saturated NaCl solution (40 mL×2), and then dried with MgSO<sub>4</sub>. After evaporation under reduced pressure, the residue was purified by silica gel column chromatography in a gradient elution of solvent EtOAc: *n*-hexane = 1:3 to 1:1, v:v. Compound 9 (1.02 g, 1.84 mmol) was obtained as a colorless oil at 97.1% yield. TLC (EtOAc: *n*-hexane = 1:1, v:v), R<sub>f</sub> = 0.44, TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1, v:v), R<sub>f</sub> = 0.81; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz) δ 7.35 (s, 10H, CH of phenyl×10), 5.13 (t, J = 12.6 Hz, 4H, CH<sub>2</sub> of benzyl×2), 4.26 (s, 4H, -COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 3.97 (d, J = 4.3 Hz, 2H, -CH<sub>2</sub>NCO-), 3.07 (br, 2H, -CH<sub>2</sub>NCO-), 2.91 (td, J = 10.9, 2.8 Hz, 2H, -CH<sub>2</sub>NCO-), 2.48 (br, 2H, -CH<sub>2</sub>NCO-), 2.01 (m, 2H, -CHCOO×2), 1.54 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH×2), 1.26 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH×2); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 62.5 MHz) δ 173.72, 171.56 (C=O), 137.14 (tertiary carbon of phenyl), 128.90, 128.42, 128.28 (CH of phenyl), 67.58 (CH<sub>2</sub> of benzyl), 62.69 (-COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 46.04

(-CH<sub>2</sub>NCO-), 44.59 (-CHCOO), 41.59 (-CH<sub>2</sub>NCO-), 27.60, 24.5 $\delta$  (-CH<sub>2</sub>CH<sub>2</sub>CH-). **N-Benzylloxycarbonylpiperidine-4-carboxylic acid 2-(N-Benzylloxycarbonylpiperidine-4-carboxyloxy)-ethyl ester (10)** Yield: 95.0%, colorless oil, TLC (EtOAc: *n*-hexane = 1:1, v:v), R<sub>f</sub> = 0.44, TLC (CH<sub>2</sub>Cl<sub>2</sub>: MeCH = 9:1, v:v), R<sub>f</sub> = 0.81; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  7.35 (s, 10H, CH of phenyl  $\times$ 10), 5.12 (s, 4H, CH<sub>2</sub> of benzyl  $\times$ 2), 4.22 (s, 4H, -COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 4.11 (d, *J* = 13.0 Hz, 4H, -CH<sub>2</sub>NCO- $\times$ 2), 2.88 (t, *J* = 11.2 Hz, 4H, -CH<sub>2</sub>NC=O- $\times$ 2), 2.48 (tt, *J* = 10.9, 4.9 Hz, 2H, -CHCOO $\times$ 2), 1.89 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH- $\times$ 2), 1.57 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH- $\times$ 2); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 62.5 MHz)  $\delta$  174.47, 155.58 (C = O), 37.12 (tertiary carbon of phenyl), 128.92, 128.45, 128.32 (CH of phenyl), 67.58 (CH<sub>2</sub> of benzyl), 62.68 (-COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 43.58 (-CH<sub>2</sub>NCO-), 41.23 (-CHCOO), 28.23 (-CH<sub>2</sub>CH<sub>2</sub>CH-). **N-Benzylloxycarbonyl-4-amino-butyl-oxo)-ethyl ester (11)** Yield: 96.5%, colorless oil, TLC (EtOAc: *n*-hexane = 1:1, v:v), R<sub>f</sub> = 0.23, TLC (CH<sub>2</sub>Cl<sub>2</sub>: MeCH = 9:1, v:v), R<sub>f</sub> = 0.67; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  7.33 (s, 10H, CH of phenyl  $\times$ 10), 5.07 (s, 4H, CH<sub>2</sub> of benzyl  $\times$ 2), 4.26 (s, 4H, -COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 3.22 (q, *J* = 6.5 Hz, 4H, -CH<sub>2</sub>NHCO- $\times$ 2), 2.38 (t, *J* = 7.2 Hz, 4H, -CH<sub>2</sub>COO $\times$ 2), 1.83 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- $\times$ 2); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 62.5 MHz)  $\delta$  173.89, 156.87 (C=O), 136.94 (tertiary carbon of phenyl), 128.93, 128.53 (CH of phenyl), 67.09 (CH<sub>2</sub> of benzyl), 62.62 (-COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 40.68 (-CH<sub>2</sub>NHCO-), 31.65 (-CH<sub>2</sub>COO), 25.43 (-CH<sub>2</sub>CH<sub>2</sub>CH-).

#### Piperidine-3-carboxylic acid 2-(piperidine-3-carboxyloxy)-ethyl ester (12)

General procedure: Compound **9** (1.00 g, 1.81 mmol) was dissolved in absolute MeOH (120 mL), and 10% Pd/C (0.5 g) was added to the solution. The mixture was hydrogenolyzed with H<sub>2</sub> gas for 3 h under 60 *psi*. The mixture was filtered using celite to remove Pd/C and evaporated under reduced pressure. Compound **12** (0.48 g, 1.37 mmol) was obtained as a colorless oil at 92.0% yield. TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 in NH<sub>3</sub> atmosphere, v:v), R<sub>f</sub> = 0.17, TLC (*n*-butanol: acetic acid:EtOAc:H<sub>2</sub>O = 1:1:1:1, v:v:v:v), R<sub>f</sub> = 0.19; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  4.26 (s, 4H, -COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 3.16 (dd, *J* = 12.4, 3.7 Hz, 2H, HNCH<sub>2</sub>CH-), 2.95 (td, *J* = 12.4, 3.7 Hz, 2H, HNCH<sub>2</sub>CH-), 2.82 (dd, *J* = 12.4, 9.2 Hz, 2H, HNCH<sub>2</sub>CH<sub>2</sub>-), 2.65 (td, *J* = 9.2, 3.7 Hz, 2H, HNCH<sub>2</sub>CH<sub>2</sub>-), 2.47 (m, 2H, -CHCOO $\times$ 2), 1.97 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH-), 1.65 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), 1.65 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 62.5 MHz)  $\delta$  174.45 (C=O), 62.40 (-COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 48.85, 46.73 (HNCH<sub>2</sub>CH<sub>2</sub>-), 42.72 (-CHCOO), 27.68, 25.80 (-CH<sub>2</sub>CH<sub>2</sub>CH-). **Piperidine-4-carboxylic acid 2-(piperidine-4-carboxyloxy)-ethyl ester (13)** Yield: 92.0%, colorless oil, TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 in NH<sub>3</sub> atmosphere, v:v), R<sub>f</sub> = 0.16, TLC (*n*-butanol: acetic acid:EtOAc:H<sub>2</sub>O = 1:1:1:1,

v:v:v:v), R<sub>f</sub> = 0.19; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  4.24 (s, 4H, -COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 3.04 (dt, *J* = 12.5, 3.6 Hz, 4H, HNCH<sub>2</sub>CH<sub>2</sub>- $\times$ 2), 2.55 (td, *J* = 12.5, 2.7 Hz, 2H, HNCH<sub>2</sub>CH<sub>2</sub>- $\times$ 2), 2.39 (m, 2H, -CHCOO $\times$ 2), 1.86 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH- $\times$ 2), 1.57 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH- $\times$ 2); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 62.5 MHz)  $\delta$  175.18 (C=O), 62.46 (-COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 46.10 (HNCH<sub>2</sub>CH<sub>2</sub>-), 41.83 (-CHCOO), 29.54 (-CH<sub>2</sub>CH<sub>2</sub>CH-). **4-Aminobutyric acid 2-(4-amino-butyl-oxo)-ethyl ester (14)** Yield: 77.5%, colorless oil, TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 in NH<sub>3</sub> atmosphere, v:v), R<sub>f</sub> = 0.08, TLC (*n*-butanol: acetic acid:EtOAc:H<sub>2</sub>O = 1:1:1:1, v:v:v:v), R<sub>f</sub> = 0.15; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  3.72 (s, 4H, -COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 3.41 (t, *J* = 6.9 Hz, 4H, -CH<sub>2</sub>NH<sub>2</sub>- $\times$ 2), 2.82 (br, 2H, HN), 2.35 (t, *J* = 6.5 Hz, 4H, -CH<sub>2</sub>COO $\times$ 2), 2.16 (q, *J* = 7.3 Hz, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- $\times$ 2); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 62.5 MHz)  $\delta$  179.76 (C=O), 64.11 (-COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 42.69 (-CH<sub>2</sub>NH<sub>2</sub>-), 30.41 (-CH<sub>2</sub>COO), 21.19 (-CH<sub>2</sub>CH<sub>2</sub>CH-).

#### 4-tert-Butoxycarbonylamino-hex-5-enoic acid (15)

To a solution of vigabatrin (**4**, 4.69 g, 36.3 mmol) and triethylamine (TEA, 7.6 mL, 54.4 mmol) in water (35 mL) was added 1,4-dioxane (35 mL) and BOC-ON (9.83 g, 39.9 mmol) at room temperature with continuous stirring. The mixture became homogenous within 15 min and stirring was continued for 3 h at room temperature. After the addition of water (150 mL) and EtOAc (90 mL) to the mixture, the aqueous layer was separated, washed with EtOAc (50 mL $\times$ 2) and then acidified with 5% aqueous citric acid to pH 2-3 and extracted with EtOAc (50 mL $\times$ 2). The extracted organic layer was washed with 5% aqueous citric acid (30 mL $\times$ 2) and saturated NaCl solution (30 mL $\times$ 2), and then dried with MgSO<sub>4</sub> and evaporated under reduced pressure. Compound **15** (7.26 g, 30.0 mmol) was obtained as a colorless crystal at 82.6% yield without further purification. mp 88.7-91.2; TLC (EtOAc: *n*-hexane: acetic acid = 100:100:1, v:v:v), R<sub>f</sub> = 0.33; <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  5.75 (m, 1H, -CHCH<sub>2</sub>), 5.15 (t, *J* = 13.9 Hz, 2H, CH<sub>2</sub>CH-), 4.15 (m, 1H, CH-NHCO), 2.43 (t, *J* = 7.4 Hz, 2H, CH<sub>2</sub>COO), 1.85 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH-), 1.36 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>). **2-vinylpentanedioic acid 5-[2-(4-tert-butoxycarbonyl-1-methylene-hex-5-enoyloxy-ethyl)] ester 1-ethyl ester (16)** This compound was obtained from **15** by the same procedure described for **9**. Yield: 97.1%, colorless oil, TLC (EtOAc: *n*-hexane = 1:1, v:v), R<sub>f</sub> = 0.44, TLC (EtOAc: *n*-hexane = 1:3, v:v), R<sub>f</sub> = 0.21; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  5.75 (m, 2H, -CHCH<sub>2</sub>- $\times$ 2), 5.14 (t, *J* = 9.0 Hz, 4H, CH<sub>2</sub>CH- $\times$ 2), 4.58 (br, 2H, NH $\times$ 2), 4.28 (s, 4H, -COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 4.13 (q, *J* = 7.5 Hz, 2H, CH-NHCO  $\times$ 2), 2.41 (t, *J* = 7.5 Hz, 4H, CH<sub>2</sub>COO $\times$ 2) 1.79 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH-  $\times$ 2) 1.44 (s, 18H, (CH<sub>3</sub>)<sub>3</sub>- $\times$ 2); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 62.5 MHz)  $\delta$  173.42, 155.74 (C=O), 138.56 (-CHCH<sub>2</sub>), 115.55 (CH<sub>2</sub>CH-), 62.63 (-COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 52.70 (CH-NHCO), 31.03 (CH<sub>2</sub>COO), 30.26 (-CH<sub>2</sub>CH<sub>2</sub>CH-), 28.79 ((CH<sub>3</sub>)<sub>3</sub>-).

#### 4-Aminohex-5-enoic acid-2-(4-amino-hex-5-enoyloxy)-ethyl ester (17)

Dimethylsulfide (DMS, 0.50 mL) and trifluoroacetic acid (TFA, 5 mL) were added to a solution of compound **16** (0.80 g, 11.66 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (10 mL) at  $0^\circ\text{C}$ , and the temperature was increased to room temperature. The mixture was stirred for 2 h at room temperature. The organic solvent was evaporated under reduced pressure and the residue formed was treated with 10% diisopropylethylamine (DIEA, 1 mL) in  $\text{CH}_2\text{Cl}_2$  (10 mL). After evaporation under reduced pressure, the residue was purified by silica gel chromatography in a gradient elution of solvent  $\text{CH}_2\text{Cl}_2$ :MeOH = 20:1 to 10:1, v:v. Compound **17** (0.845 g, 1.65 mmol) was obtained as a colorless oil at quantitative yield. TLC ( $\text{CH}_2\text{Cl}_2$ :MeOH = 9:1 in  $\text{NH}_3$  atmosphere, v:v),  $R_f$  = 0.30, TLC (*n*-butanol: acetic acid:EtOAc:H<sub>2</sub>O = 1:1:1:1),  $R_f$  = 0.45;  $^1\text{H-NMR}$  (DMSO-*d*<sub>6</sub>, 250 MHz)  $\delta$  5.78 (m, 2H,  $-\text{CHCH}_2\times 2$ ), 5.45 (t,  $J$  = 8.9 Hz, 4H,  $\text{CH}_2\text{CH}\times 2$ ), 4.33 (s, 4H,  $-\text{COOCH}_2\text{CH}_2\text{OCO}-$ ), 3.82 (m, 2H,  $\text{CHNH}_2\times 2$ ), 2.49 (t,  $J$  = 7.3 Hz, 4H,  $\text{CH}_2\text{COO}\times 2$ ), 2.02 (m, 4H,  $-\text{CH}_2\text{CH}_2\text{CH}\times 2$ );  $^{13}\text{C-NMR}$  (DMSO-*d*<sub>6</sub>, 62.5 MHz)  $\delta$  174.95 (C=O), 132.61 ( $-\text{CHCH}_2$ ), 122.21 ( $\text{CH}_2\text{CH}-$ ), 63.68 ( $-\text{COOCH}_2\text{CH}_2\text{OCO}-$ ), 53.81 ( $\text{CH-NH}_3$ ), 30.03 ( $\text{CH}_2\text{COO}$ ), 27.35 ( $-\text{CH}_2\text{CH}_2\text{CH}-$ ).

#### 2-propylpentanoic acid 2-(2-propyl-pentanoyloxy)-ethyl ester (18)

This compound was obtained from valproic acid (**5**) by the same procedure described for **9**. Yield: 96.5%, colorless oil, TLC (EtOAc: *n*-hexane = 1:2, v:v),  $R_f$  = 0.71, TLC (EtOAc: *n*-hexane = 1:5, v:v),  $R_f$  = 0.46;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  4.36 (s, 4H,  $-\text{COOCH}_2\text{CH}_2\text{OCO}-$ ), 1.61 (m, 2H,  $\text{CH}(\text{CH}_2)_2\times 2$ ), 1.43 (m, 4H,  $\text{CH}_3\text{CH}_2\text{CH}_2\times 2$ ), 1.29 (m, 12H,  $\text{CH}_3\text{CH}_2\text{CH}_2\times 4$ ,  $\text{CH}_3\text{CH}_2\text{CH}_2\times 2$ ), 0.89 (t,  $J$  = 7.2 Hz, 12H,  $\text{CH}_3\text{CH}_2\text{CH}_2\times 2$ );  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 62.5 MHz)  $\delta$  176.67 (C=O), 62.27 ( $-\text{COOCH}_2\text{CH}_2\text{OCO}-$ ), 45.58 ( $\text{OOCCH}(\text{CH}_2)_2$ ), 34.96 ( $\text{CH}_3\text{CH}_2\text{CH}_2$ ), 21.00 ( $\text{CH}_3\text{CH}_2\text{CH}_2$ ), 14.36 ( $\text{CH}_3\text{CH}_2\text{CH}_2$ ).

#### 4-Benzoyloxycarbonylaminobutyric acid 2-hydroxy-ethyl ester (19)

General procedure: Ethylene glycol (2.30 mL, 39.99 mmol) and DMAP (1.62 g, 13.33 mmol) were added to the solution of compound **8** (3.15 g, 7.60 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (50 mL). The solution was cooled to  $0^\circ\text{C}$ , and EDC (3.07 g, 16.00 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (10 mL) was added dropwise for 5 min. After a further 5 min stirring at  $0^\circ\text{C}$ , the solution was stirred for 3 h at room temperature. The solution was evaporated under reduced pressure and the residue formed was dissolved in EtOAc (100 mL) and washed with aqueous 5%  $\text{NaHCO}_3$  solution (40 mL $\times$ 3), aqueous 1 M HCl solution (40 mL $\times$ 3) and saturated NaCl solution (40 mL $\times$ 2), and then dried with  $\text{MgSO}_4$ . After evaporation under reduced pressure, the residue was

purified by silica gel column chromatography in a gradient elution of solvent EtOAc: *n*-hexane = 1:3 to 1:1, v:v. Compound **19** (2.24 g, 7.99 mmol) was obtained as a colorless oil at 95.0% yield. TLC (EtOAc: *n*-hexane = 1:1, v:v),  $R_f$  = 0.19, TLC ( $\text{CH}_2\text{Cl}_2$ :MeOH = 9:1, v:v),  $R_f$  = 0.50;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.34 (s, 5H,  $\text{CH}$  of phenyl $\times$ 5), 5.08 (s, 2H,  $\text{CH}_2$  of benzyl), 4.20 (t,  $J$  = 4.5 Hz, 2H,  $\text{HOCH}_2\text{CH}_2\text{OCO}-$ ), 3.79 (t,  $J$  = 4.5 Hz, 2H,  $\text{HOCH}_2\text{CH}_2\text{OCO}-$ ), 3.24 (q,  $J$  = 6.6 Hz, 2H,  $-\text{CH}_2\text{NHCO}-$ ), 2.40 (t,  $J$  = 6.9 Hz, 2H,  $-\text{CH}_2\text{CH}_2\text{COO}-$ ), 1.80 (m, 2H,  $-\text{CH}_2\text{CH}_2\text{CH}_2-$ ).

#### Piperidine-1,3-dicarboxylic acid 1-benzyl ester 3-[2-(4-benzoyloxycarbonylaminobutyryloxy)-ethyl] ester (20)

General procedure: Compound **19** (1.00 g, 3.57 mmol) and DMAP (0.36 g, 2.97 mmol) were added to the solution of compound **6** (0.78 g, 2.97 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (30 mL). The solution was cooled to  $0^\circ\text{C}$ , and EDC (0.68 g, 3.57 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (10 mL) was added dropwise for 5 min. After a further 5 min stirring at  $0^\circ\text{C}$ , the solution was stirred for 3 h at room temperature. The solution was evaporated under reduced pressure and the residue formed was dissolved in EtOAc (70 mL) and washed with aqueous 5%  $\text{NaHCO}_3$  solution (40 mL $\times$ 3), aqueous 1 M HCl solution (40 mL $\times$ 3) and saturated NaCl solution (40 mL $\times$ 2), and then dried with  $\text{MgSO}_4$ . After evaporation under reduced pressure, the residue was purified by silica gel column chromatography in a gradient elution of solvent EtOAc: *n*-hexane = 1:3 to 1:1, v:v. Compound **20** (1.40 g, 2.67 mmol) was obtained as a colorless oil at 89.7% yield. TLC (EtOAc: *n*-hexane = 1:1, v:v),  $R_f$  = 0.29, TLC ( $\text{CH}_2\text{Cl}_2$ :MeOH = 9:1, v:v),  $R_f$  = 0.68;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.33 (s, 10H,  $\text{CH}$  of phenyl $\times$ 10), 5.08 (d,  $J$  = 9.0 Hz, 4H,  $\text{CH}_2$  of benzyl $\times$ 2), 4.26 (s, 4H,  $-\text{COOCH}_2\text{CH}_2\text{OCO}-$ ), 3.93 (d,  $J$  = 3.3 Hz, 2H,  $-\text{CH}_2\text{NCO}-$ ), 3.23 (d,  $J$  = 5.6 Hz, 2H,  $-\text{CH}_2\text{NCO}-$ ), 2.92 (m, 2H,  $-\text{CH}_2\text{NHCO}-$ ), 2.49 (m, 1H,  $-\text{CHCOO}-$ ), 2.40 (s, 2H,  $-\text{CH}_2\text{COO}$ ), 1.90~1.40 (m, 6H,  $-\text{CH}_2\text{CH}_2\text{CH}\times 2$ ,  $-\text{CH}_2\text{CH}_2\text{CH}-$ );  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 62.5 MHz)  $\delta$  173.39, 173.30, 156.90, 155.59 ( $-\text{C}=\text{O}$ ), 137.08, 137.01 (tertiary carbon of phenyl), 128.90, 128.49, 128.43, 128.29 ( $\text{CH}$  of phenyl), 67.63, 67.01 ( $\text{CH}_2$  of benzyl), 62.63, 62.49 ( $-\text{COOCH}_2\text{CH}_2\text{OCO}-$ ), 46.04, 44.59 ( $-\text{CH}_2\text{NCO}-$ ), 41.55 ( $-\text{CHCOO}$ ), 40.70 ( $-\text{CH}_2\text{NCO}-$ ), 31.63 ( $-\text{CH}_2\text{COO}$ ), 27.45, 25.43, 24.52 ( $-\text{CH}_2\text{CH}_2\text{CH}-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2-$ ). **Piperidine-1,4-dicarboxylic acid 1-benzyl ester 4-[2-(4-benzoyloxycarbonylaminobutyryloxy)-ethyl] ester (21)** Yield: 95.0%, colorless oil, TLC (EtOAc: *n*-hexane = 1:1, v:v),  $R_f$  = 0.31, TLC ( $\text{CH}_2\text{Cl}_2$ :MeOH = 9:1, v:v),  $R_f$  = 0.83;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.35 (s, 10H,  $\text{CH}$  of phenyl $\times$ 10), 5.08 (d,  $J$  = 9.1 Hz, 2H,  $\text{CH}_2$  of benzyl), 5.04 (s, 2H,  $\text{CH}_2$  of benzyl), 4.27 (s, 4H,  $-\text{COOCH}_2\text{CH}_2\text{OCO}-$ ), 4.10 (m, 2H,  $-\text{CH}_2\text{NCO}-$ ), 3.24 (q,  $J$  = 6.5 Hz, 2H,  $-\text{CH}_2\text{NCO}-$ ), 2.92 (t,  $J$  = 11.3 Hz, 2H,  $-\text{CH}_2\text{NHCO}-$ ), 2.50 (tt,  $J$  = 10.9, 3.9 Hz, 1H,  $-\text{CHCOO}-$ ),

2.40 (t,  $J = 7.2$  Hz, 2H,  $-CH_2COO$ ), 1.90~1.50 (m, 6H,  $-CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$ );  $^{13}C$ -NMR ( $CDCl_3$ , 62.5 MHz)  $\delta$  174.58, 173.28, 156.84, 155.59 ( $-C=O$ ), 137.13, 136.92 (tertiary carbon of phenyl), 128.93, 128.91, 128.54, 128.44, 128.30 ( $CH$  of phenyl), 67.56, 67.09 ( $CH_2$  of benzyl), 62.68, 62.60 ( $-COOCH_2CH_2OCO-$ ), 43.48 ( $-CH_2NCO-$ ), 41.18 ( $-CHCOO$ ), 40.68 ( $-CH_2NH-$ ), 31.59 ( $-CH_2COO$ ), 28.22, 25.45 ( $-CH_2CH_2CH-$ ,  $-CH_2CH_2CH_2-$ ). **Piperidine-3-carboxylic acid 2-(4-aminobutyryloxy)-ethyl ester (22)** This compound was obtained from **20** by the same procedure described for **12**. Yield: 82.0%, colorless oil, TLC ( $CH_2Cl_2$ :MeOH = 9:1 in  $NH_3$  atmosphere, v:v),  $R_f = 0.15$ , TLC (*n*-butanol: acetic acid:EtOAc:H<sub>2</sub>O = 1:1:1:1, v:v:v:v),  $R_f = 0.27$ .  $^1H$ -NMR ( $CDCl_3$ , 250 MHz)  $\delta$  4.28 (m, 1H,  $-CH_2CH_2NH-$ ), 4.16 (m, 2H,  $-COOCH_2CH_2OCO-$ ), 3.79 (t,  $J = 4.8$  Hz, 2H,  $-COOCH_2CH_2OCO-$ ), 3.41 (t,  $J = 6.9$  Hz, 2H,  $-CHCH_2NH_2-$ ), 3.12 (dd,  $J = 12.2, 3.7$  Hz, 1H,  $-CHCH_2NH-$ ), 2.91 (m, 2H,  $-CHCH_2NH-$ ), 2.32 (m, 1H,  $-CHCOO-$ ), 2.27 (m, 2H,  $-CH_2COO$ ), 1.90~1.60 (m, 4H,  $-CH_2CH_2CH_2CH_2-$ ), 1.49 (m, 1H,  $-CH_2CH_2CH_2-$ ), 1.27 (t,  $J = 6.5$  Hz, 1H,  $-CH_2CH_2CH_2-$ );  $^{13}C$ -NMR ( $CDCl_3$ , 62.5 MHz)  $\delta$  179.47, 174.91 ( $-C=O$ ), 66.45, 61.08 ( $-COOCH_2CH_2OCO-$ ), 48.88, 43.73 ( $-CH_2NH$ ), 42.58 ( $-CH_2NH_2$ ), 41.87 ( $-CHCOO$ ), 30.32 ( $-CH_2COO$ ), 29.19, 27.44 ( $-CH_2CH_2CH-$ ), 21.23 ( $-CH_2CH_2CH_2-$ ). **Piperidine-4-carboxylic acid 2-(4-aminobutyryloxy)-ethyl ester (23)** Yield: 85.0%, colorless oil, TLC ( $CH_2Cl_2$ :MeOH = 9:1 in  $NH_3$  atmosphere, v:v),  $R_f = 0.19$ , TLC (*n*-butanol: acetic acid: EtOAc:H<sub>2</sub>O = 1:1:1:1, v:v:v:v),  $R_f = 0.38$ ;  $^1H$ -NMR ( $CDCl_3$ , 250 MHz)  $\delta$  4.21 (t,  $J = 4.7$  Hz, 2H,  $-COOCH_2CH_2OCO-$ ), 3.81 (t,  $J = 4.7$  Hz, 2H,  $-COOCH_2CH_2OCO-$ ), 3.41 (t,  $J = 6.9$  Hz, 2H,  $-CHCH_2NH_2-$ ), 3.11 (dt,  $J = 12.6, 3.5$  Hz, 1H,  $-CHCH_2NH-$ ), 2.64 (td,  $J = 12.3, 2.7$  Hz, 2H,  $-CHCH_2NH-$ ), 2.49 (m, 1H,  $-CHCOO-$ ), 2.32 (m, 2H,  $-CH_2COO$ ), 1.90~1.55 (m, 6H,  $-CH_2CH_2CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$ );  $^{13}C$ -NMR ( $CDCl_3$ , 62.5 MHz)  $\delta$  179.47, 175.82 ( $-C=O$ ), 66.44, 61.52 ( $-COOCH_2CH_2OCO-$ ), 46.11 ( $-CH_2NH$ ), 42.53 ( $-CHCOO$ ), 41.91 ( $-CH_2NH$ ), 30.21 ( $-CH_2COO$ ), 29.57 ( $-CH_2CH_2CH-$ ), 21.28 ( $-CH_2CH_2CH_2-$ ). **Piperidine-1,4-dicarboxylic acid 1-benzyl ester-4-(2-hydroxyethyl) ester (24)** This compound was obtained from **7** by the same procedure described for **19**. Yield: 71.3%, colorless oil, TLC (EtOAc: *n*-hexane = 1:1, v:v),  $R_f = 0.13$ , TLC ( $CH_2Cl_2$ : MeOH = 9:1, v:v),  $R_f = 0.46$ ;  $^1H$ -NMR ( $CDCl_3$ , 250 MHz)  $\delta$  7.34 (s, 5H,  $CH$  of phenyl $\times$ 5), 5.12 (s, 2H,  $CH_2$  of benzyl), 4.21 (t,  $J = 4.7$  Hz, 2H,  $HOCH_2CH_2OCO-$ ), 3.80 (t,  $J = 4.7$  Hz, 2H,  $HOCH_2CH_2OCO-$ ), 2.93 (t,  $J = 11.3$  Hz, 2H,  $-CH_2NCO-$ ), 2.51 (tt,  $J = 10.9, 3.9$  Hz, 1H,  $-CHCOO-$ ), 1.90 (m, 2H,  $-CH_2CH_2CH-$ ), 1.68 (m, 2H,  $-CH_2CH_2CH-$ )

**Piperidine-1,3-dicarboxylic acid 1-benzyl ester 3-[2-(4-benzoyloxycarbonylpiperidine-4-carboxyloxy)-ethyl] ester (25)** This compound was obtained from **24** and **6** by

the same procedure described for **20**. Yield: 95.0%, colorless oil, TLC (EtOAc: *n*-hexane = 1:1, v:v),  $R_f = 0.46$ , TLC ( $CH_2Cl_2$ : MeOH = 9:1, v:v),  $R_f = 0.82$ ;  $^1H$ -NMR ( $CDCl_3$ , 250 MHz)  $\delta$  7.35 (s, 10H,  $CH$  of phenyl $\times$ 10), 5.12 (s, 4H,  $CH_2$  of benzyl $\times$ 2), 4.28 (s, 4H,  $-COOCH_2CH_2OCO-$ ), 3.97 (dt,  $J = 13.4, 3.9$  Hz, 2H,  $-CH_2NCO-$ ), 2.87 (td,  $J = 12.1, 2.9$  Hz, 4H,  $-CH_2NCO-$ ), 2.49 (m, 2H,  $-CH_2NCO-$ ), 2.02 (s, 2H,  $-CHCOO-\times$ 2), 1.90~1.30 (m, 8H,  $-CH_2CH_2CH-\times$ 4). **Piperidine-3-carboxylic acid 1-benzyl ester 2-(piperidine-4-carboxyloxy)-ethyl ester (26)** This compound was obtained from **25** by the same procedure described for **22**. Yield: 75.0%, colorless oil, TLC (*i*-propanol: acetic acid:H<sub>2</sub>O:NH<sub>4</sub>OH = 1:0.02:0.5:0.03, v:v:v:v),  $R_f = 0.19$ , TLC (*n*-butanol: acetic acid:EtOAc:H<sub>2</sub>O = 1:1:1:1, v:v:v:v),  $R_f = 0.29$ ;  $^1H$ -NMR ( $CDCl_3$ , 250 MHz)  $\delta$  4.29 (s, 4H,  $-COOCH_2CH_2OCO-$ ), 3.82 (q,  $J = 4.6$  Hz, 2H,  $-CHCH_2NH_2-$ ), 3.71 (d,  $J = 13.4$  Hz, 1H,  $-CHCH_2NH_2-$ ), 3.10 (br, 2H,  $-CHCH_2NH_2-$ ), 2.86 (m, 1H,  $-CHCH_2NH_2-$ ), 2.63 (td,  $J = 12.0, 2.1$  Hz, 2H,  $-CHCH_2NH_2-$ ), 2.45 (m, 2H,  $-CHCOO-\times$ 2), 1.90~1.40 (m, 8H,  $-CH_2CH_2CH-\times$ 2);  $^{13}C$ -NMR ( $CDCl_3$ , 62.5 MHz)  $\delta$  179.47, 174.91 ( $-C=O$ ), 66.41, 62.44 ( $-COOCH_2CH_2OCO-$ ), 48.87, 47.10, 46.20 ( $-CH_2NH$ ), 42.10, 41.87 ( $-CHCOO$ ), 29.64, 29.54, 25.82 ( $-CH_2CH_2CH-$ ). **2-Propylpentanoic acid 2-hydroxyethyl ester (27)** This compound was obtained from valproic acid (**5**) by the same procedure described for **19**. Yield: 83.6%, colorless oil, TLC (EtOAc: *n*-hexane = 1:1, v:v),  $R_f = 0.56$ , TLC (EtOAc: *n*-hexane = 1:3, v:v),  $R_f = 0.23$ ;  $^1H$ -NMR ( $CDCl_3$ , 250 MHz)  $\delta$  4.22 (t,  $J = 4.7$  Hz, 2H,  $-CH_2COO$ ), 3.83 (t,  $J = 4.7$  Hz, 2H,  $CH_2OH$ ), 2.38 (m, 1H,  $CH_2CHCOO-$ ), 1.62 (m, 2H,  $CH_3CH_2CH_2-$ ), 1.45 (m, 2H,  $CH_3CH_2CH_2-$ ), 1.34 (m, 4H,  $CH_3CH_2CH_2-\times$ 2), 0.90 (t,  $J = 7.2$  Hz, 6H,  $CH_3CH_2CH_2-\times$ 2). **Piperidine-1,3-dicarboxylic acid 1-benzyl ester-3-[2-(2-propylpentanoyloxy)-ethyl] ester (28)** This compound was obtained from **27** and **6** by the same procedure described for **20**. Yield: 65.0%, colorless oil, TLC (EtOAc: *n*-hexane = 1:1, v:v),  $R_f = 0.59$ , TLC ( $CH_2Cl_2$ : MeOH = 9:1, v:v),  $R_f = 0.75$ ;  $^1H$ -NMR ( $CDCl_3$ , 250 MHz)  $\delta$  7.35 (s, 5H,  $CH$  of phenyl $\times$ 5), 5.12 (s, 2H,  $CH_2$  of benzyl), 4.31 (s, 4H,  $-COOCH_2CH_2OCO-$ ), 3.98 (d,  $J = 13.3$  Hz, 1H,  $-CH_2NCO-$ ), 3.07 (m, 1H,  $-CH_2NCO-$ ), 2.88 (td,  $J = 10.9, 2.9$  Hz, 1H,  $-CH_2NCO-$ ), 2.47 (br, 1H,  $-CH_2NCO-$ ), 2.40 (m, 1H,  $(CH_2)_2CHCOO-$ ), 2.10 (m, 1H,  $-NCH_2CH_2COO$ ), 1.80~1.35 (m, 6H,  $-CH_2CH_2CH-$ ,  $-CH_3CH_2CH_2-\times$ 2), 1.32 (m, 4H,  $CH_3CH_2CH_2-\times$ 2), 0.88 (t,  $J = 7.2$  Hz, 6H,  $CH_3CH_2CH_2-\times$ 2);  $^{13}C$ -NMR ( $CDCl_3$ , 62.5 MHz)  $\delta$  176.72, 173.35, 155.56 ( $-C=O$ ), 137.10 (tertiary carbon of phenyl), 128.91, 128.44, 128.32 ( $CH$  of phenyl), 67.60 ( $CH_2$  of benzyl), 62.87, 61.98 ( $-COOCH_2CH_2OCO-$ ), 46.01 ( $-CH_2NCO-$ ), 45.56 ( $-NCH_2CHCOO$ ), 44.58 ( $-CH_2NCO-$ ), 41.64 ( $-(CH_2)_2CH_2COO$ ), 35.01 ( $CH_2CHCOO$ ), 27.70 ( $CH_3CH_2CH_2-$ ), 24.60 ( $CH_3CH_2CH_2-$ ), 21.02 ( $CH_3CH_2CH-$ ), 14.47 ( $CH_3CH_2CH_2-$ ). **Piperidine-1,4-dicarboxylic acid 1-benzyl ester-3-[2-(2-**

**propylpentanoyloxy]-ethyl] ester (29)** Yield: 66.1%, colorless oil, TLC (EtOAc: *n*-hexane = 1:1, v:v),  $R_f$  = 0.57, TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1, v:v),  $R_f$  = 0.74; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  7.35 (s, 5H, CH of phenyl $\times$ 5), 5.12 (s, 2H, CH<sub>2</sub> of benzyl), 4.29 (s, 4H, -COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 4.09 (br, 2H, -CH<sub>2</sub>NCO-), 2.77 (t,  $J$  = 11.2 Hz, 2H, -CH<sub>2</sub>NCO-), 2.40 (m, 2H, CHCOO $\times$ 2), 1.91 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH-), 1.67 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH-), 1.58 (m, 2H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), 1.42 (m, 2H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), 1.28 (m, 4H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub> $\times$ 2), 0.91 (t,  $J$  = 7.2 Hz, 6H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub> $\times$ 2); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 62.5 MHz)  $\delta$  176.70, 174.44, 155.57 (-C=O), 137.13 (tertiary carbon of phenyl), 128.90, 128.42, 128.29 (CH of phenyl), 67.55 (CH<sub>2</sub> of benzyl), 62.88, 62.01 (-COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 45.59 (-CHCOO), 45.59 (-CH<sub>2</sub>NCO-), 43.59 (-CH<sub>2</sub>NCO), 41.24 (CHCOO), 35.01 (CH<sub>2</sub>CHCH), 28.21 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), 21.01 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), 14.38 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-). **2-propylpentanoic acid [4-(2-vinylbut-2-enoyloxycarbonylamino)-butyloxy]-ethyl ester (30)** Yield: 83.0%, colorless oil, TLC (EtOAc: *n*-hexane = 1:1, v:v),  $R_f$  = 0.59, TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1, v:v),  $R_f$  = 0.73; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  7.35 (s, 5H, CH of phenyl  $\times$ 5), 5.09 (s, 2H, CH<sub>2</sub> of benzyl), 4.35 (s, 4H, -COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 3.25 (q,  $J$  = 6.5 Hz, 2H, -CH<sub>2</sub>NHCO-), 2.38 (m, 3H, CHCOO-, CH<sub>2</sub>COO-) 1.81 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH-), 1.58 (m, 2H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), 1.42 (m, 2H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), 1.31 (m, 4H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub> $\times$ 2), 0.91 (t,  $J$  = 7.2 Hz, 6H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub> $\times$ 2)

**Piperidine-3-carboxylic acid 2-(2-propylpentanoyloxy)-ethyl ester (31)**

General procedure: 10% Pd/C (0.2 g) and cyclohexene (15 mL) were added to the solution of compound **28** (1.08 g, 2.49 mmol) in absolute MeOH (40 mL). The mixture was refluxed for 15 min and was filtered using celite to remove Pd/C, and the organic solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography in a gradient elution of solvent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 20:1 to 10:1, v:v. Compound **31** (0.65 g, 2.19 mmol) was obtained as a colorless oil at 88.0% yield. TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1, v:v),  $R_f$  = 0.21; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  4.29 (s, 4H, -COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 3.21 (dd,  $J$  = 12.4, 3.4 Hz, 1H, -CH<sub>2</sub>NH-), 2.89 (dt,  $J$  = 12.4, 3.8 Hz, 1H, -CH<sub>2</sub>NH), 2.77 (m, 1H, -CH<sub>2</sub>NH-), 2.50 (m, 1H, -CHCOO-), 2.10 (m, 1H, (CH<sub>2</sub>)<sub>2</sub>CHCOO-), 1.80~1.35 (m, 8H, -CH<sub>2</sub>CH<sub>2</sub>CH $\times$ 2, -CH<sub>3</sub>CH<sub>2</sub>CH $\times$ 2), 1.30 (m, 4H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub> $\times$ 2), 0.91 (t,  $J$  = 7.2 Hz, 6H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub> $\times$ 2); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 62.5 MHz)  $\delta$  176.70, 174.10 (-C=O), 62.72, 62.06 (-COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 48.36, 46.45 (-CH<sub>2</sub>NH), 45.57 (-HNCH<sub>2</sub>COO), 42.23 (-CHCOO), 35.00 (CH<sub>2</sub>CHCOO-), 27.48 (-CH<sub>2</sub>CH<sub>2</sub>CH-), 25.33, 21.01 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), 14.39 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-). **Piperidine-4-carboxylic acid 2-(2-propylpentanoyloxy)-ethyl ester (32)** Yield: 80.9%, colorless oil, TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1, v:v),  $R_f$  = 0.22; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  4.28 (s, 4H,

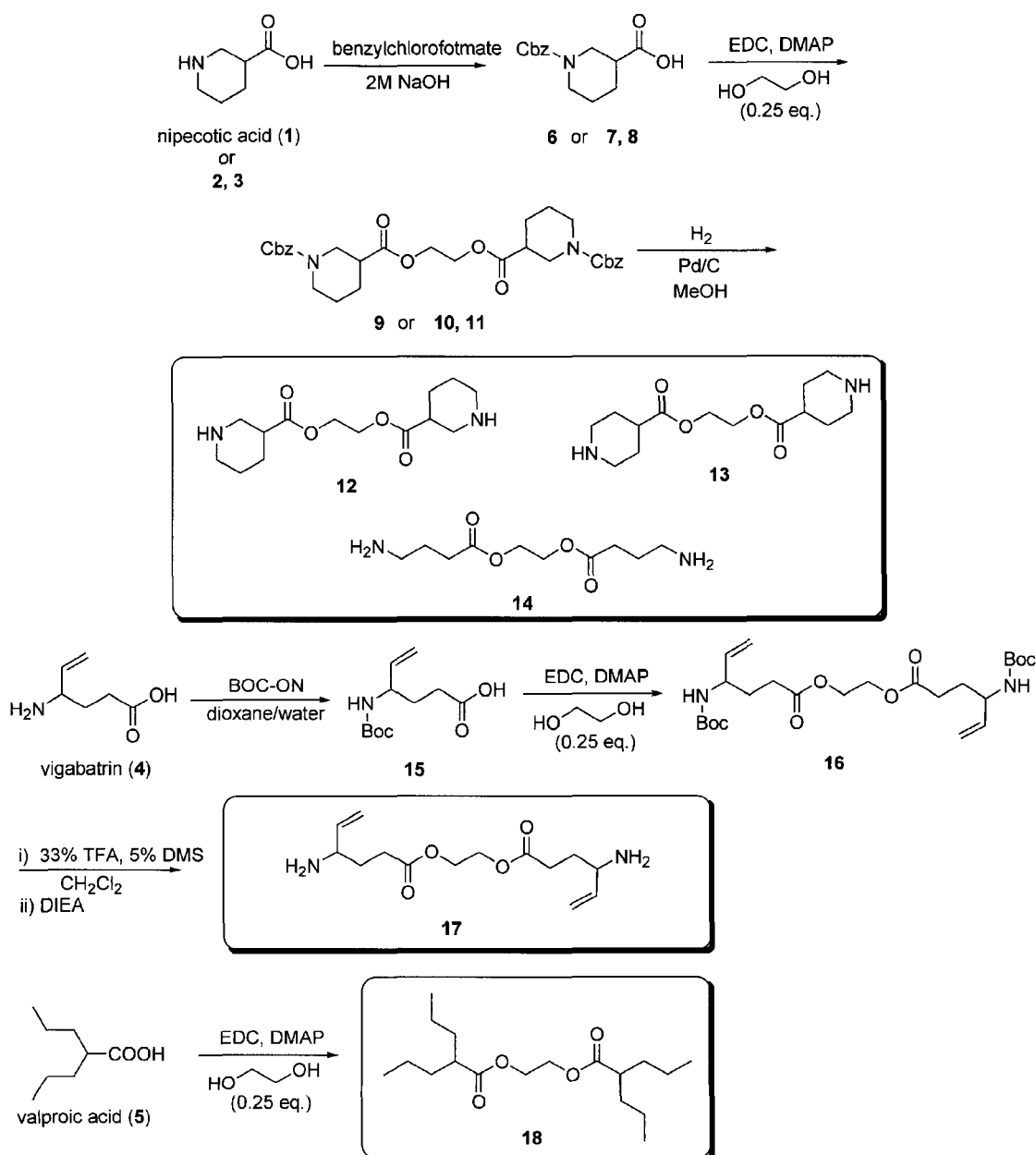
-COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 2.82 (dt,  $J$  = 11.7, 3.5 Hz, 1H, -CH<sub>2</sub>NH), 2.28 (m, 1H, -CH<sub>2</sub>NH-), 2.10 (m, 1H, -CHCOO-), 2.02 (m, 1H, (CH<sub>2</sub>)<sub>2</sub>CHCOO-), 1.90~1.60 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH $\times$ 2), 1.58 (2H, m, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), 1.42 (2H, m, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), 1.29 (m, 4H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub> $\times$ 2), 0.89 (t,  $J$  = 7.2 Hz, 6H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub> $\times$ 2); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 62.5 MHz)  $\delta$  176.71, 175.08 (-C=O), 62.66, 62.08 (-COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 55.26 (-CH<sub>2</sub>NH), 46.70, 45.59 (-CHCOO), 35.01 (-CH<sub>2</sub>CH<sub>2</sub>CH-), 28.47 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), 23.38 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), 14.40 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-). **2-Propylpentanoic acid 2-(4-aminobutyryloxy)-ethyl ester (33)** Yield: 82.0%, colorless oil, TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1, v:v),  $R_f$  = 0.13; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  4.28 (t,  $J$  = 4.7 Hz, 4H, -COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 3.41 (t,  $J$  = 6.9 Hz, 2H, -CHCH<sub>2</sub>NH<sub>2</sub>-), 2.41 (m, 2H, -CH<sub>2</sub>COO-), 2.27 (m, 1H, -CHCOO), 2.14 (q,  $J$  = 7.1 Hz, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH), 1.60 (m, 2H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), 1.43 (m, 2H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), 1.29 (d,  $J$  = 7.8 Hz, 4H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub> $\times$ 2), 0.91 (t,  $J$  = 7.2 Hz, 6H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub> $\times$ 2); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 62.5 MHz)  $\delta$  177.50, 173.40 (-C=O), 66.19, 63.45 (-COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 45.65 (-CH<sub>2</sub>COO-), 45.53 (-CHCH<sub>2</sub>NH<sub>2</sub>-), 35.0 (-CHCOO), 34.97 (-CH<sub>2</sub>CH<sub>2</sub>CH), 29.32 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), 21.05 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-), 11.34 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>-). **4-tert-Butoxycarbonyl aminohex-5-enoic acid 2-(2-propylpentanoyloxy)-ethyl ester (34)** This compound was obtained from **27** and **15** by the same procedure described for **28**. Yield: 74.7%, colorless oil, TLC (EtOAc: *n*-hexane = 1:1, v:v),  $R_f$  = 0.65, TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1, v:v),  $R_f$  = 0.77; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  5.77 (m, 1H, -CH=CH<sub>2</sub>), 5.14 (t,  $J$  = 13.7 Hz, 2H, CH<sub>2</sub>=CH-), 4.56 (br, 1H, NH), 4.28 (s, 4H, -COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 2.45 (m, 3H, -CH<sub>2</sub>COO-, -CHCOO), 1.82 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH-), 1.62~1.35 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> $\times$ 2), 1.44 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>), 1.27 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> $\times$ 2), 0.89 (t,  $J$  = 7.2 Hz, 6H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> $\times$ 2); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 62.5 MHz)  $\delta$  176.73, 173.39 (-C=O), 138.52 (-CH=CH<sub>2</sub>), 115.54 (CH<sub>2</sub>=CH-), 62.75, 62.00 (-COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 45.54 (-CH<sub>2</sub>NHCO-), 35.00 (-CH<sub>2</sub>CH<sub>2</sub>CH-), 31.02 (-CHCOO), 30.24 (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 28.76 ((CH<sub>3</sub>)<sub>3</sub>), 20.97 (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 14.39 (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>). **4-Aminohex-5-enoic acid 2-(2-propylpentanoyloxy)-ethyl ester (35)** This compound was obtained from **34** by the same procedure described for **17**. Yield: quantitative, colorless oil, TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1, v:v),  $R_f$  = 0.27; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$  5.73 (ddd,  $J$  = 17.7, 9.7, 8.1 Hz, 1H, -CH=CH<sub>2</sub>), 5.38 (dd,  $J$  = 15.8, 4.5 Hz, 2H, CH<sub>2</sub>=CH-), 4.27 (m, 4H, -COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 3.49 (d,  $J$  = 2.4 Hz, 1H, -CHNH<sub>2</sub>), 2.49 (m, 3H, -CH<sub>2</sub>COO-, OCCH (CH<sub>2</sub>)<sub>2</sub>), 2.10 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH-), 1.60~1.30 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> $\times$ 2), 1.39 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> $\times$ 2), 0.89 (t,  $J$  = 7.2 Hz, 6H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> $\times$ 2); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 62.5 MHz)  $\delta$  176.99, 174.00 (C=O), 132.79 (-CH=CH<sub>2</sub>), 122.37 (CH<sub>2</sub>=CH-), 63.27, 61.80 (-COOCH<sub>2</sub>CH<sub>2</sub>OCO-), 54.46 (-CH<sub>2</sub>NH<sub>2</sub>-), 45.53 (-CHCOO), 34.93 (-CH<sub>2</sub>COO), 30.24 (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 29.98 (-CH<sub>2</sub>CH<sub>2</sub>CH-), 27.76 (-CH<sub>2</sub>CH<sub>2</sub>CH-),

20.92 (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 14.31 (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>).

### Pharmacology

The pharmacological tests were carried out as follows (Hollanc *et al.*, 1992; Swinyard *et al.*, 1989; Krall *et al.*, 1978). All tested compounds were dissolved in polyethylene glycol 400 and administered intraperitoneally to male ICR mice at doses of 0.25, 0.50, 0.75 and 1.00 mmol/kg. The anticonvulsant tests were performed 30 minutes after the administration in groups of four mice. We had previously determined the lowest dose that could induce seizures in all tested animals during preliminary screening. Seizures

were then artificially induced by either electric shock or chemicals. The MES tests were carried out with a 60-cycle AC current of 50 mA intensity delivered for 0.2 seconds via corneal electrodes with an ECT unit (UGO Basline, Italy). A drop of 0.9% saline was instilled in the eye prior to the application of electrodes. Protection in this test was defined as the abolition of the hind limb tonic extension component of a seizure. The pentylenetetrazole (PTZ), bicuculline (BIC) and picrotoxin (PCR) induced seizure test entailed the administration of 80 mg/kg of PTZ (CD<sub>97</sub>), 3.2 mg/kg of BIC (CD<sub>97</sub>) and 5 mg/kg of PCR (CD<sub>97</sub>) as a 0.5% solution subcutaneously in the posterior midline of



Scheme 1. Synthesis of Compound 13, 14, 17, and 18

the mice, and observation lasted for 30 minutes. Protection was defined as the failure to observe even a threshold seizure, such a seizure being defined as a single episode of chronic spasms that persisted for at least 5 seconds. Quantitative evaluation of the anticonvulsant activity of ED<sub>50</sub> was estimated from dose-response data.

## RESULTS AND DISCUSSION

### Chemistry

Compounds **12**, **13**, **14**, **17** and **18** could be synthesized from protected nipecotic acid (**6**), isonipecotic acid (**7**), GABA (**8**), vigabatrin (**15**) and valproic acid (**5**) with 0.25 equivalence of ethylene glycol in the presence of EDC and DMAP, followed by hydrogenolysis at good yields by known general reactions, as outlined in Scheme 1.

Cbz-protected compounds **6**, **7** and **8** were prepared from corresponding nipecotic acid (**1**), isonipecotic acid (**2**) and GABA (**3**), respectively, by treatment with benzylchloroformate in aqueous 2 N NaOH solution at 88.8~92.3% yields as white crystals. Compounds **9**, **10** and **11** were prepared from ethylene glycol and four equivalences of Cbz-protected compounds **6**, **7** and **8** by treatment with EDC and DMAP, respectively, at 95.0~97.1% yields as colorless oils. Compounds **12**, **13** and **14** were prepared by hydrogenolysis in the presence of 10% Pd/C with H<sub>2</sub> gas at 77.5~92.0% yields as colorless oils.

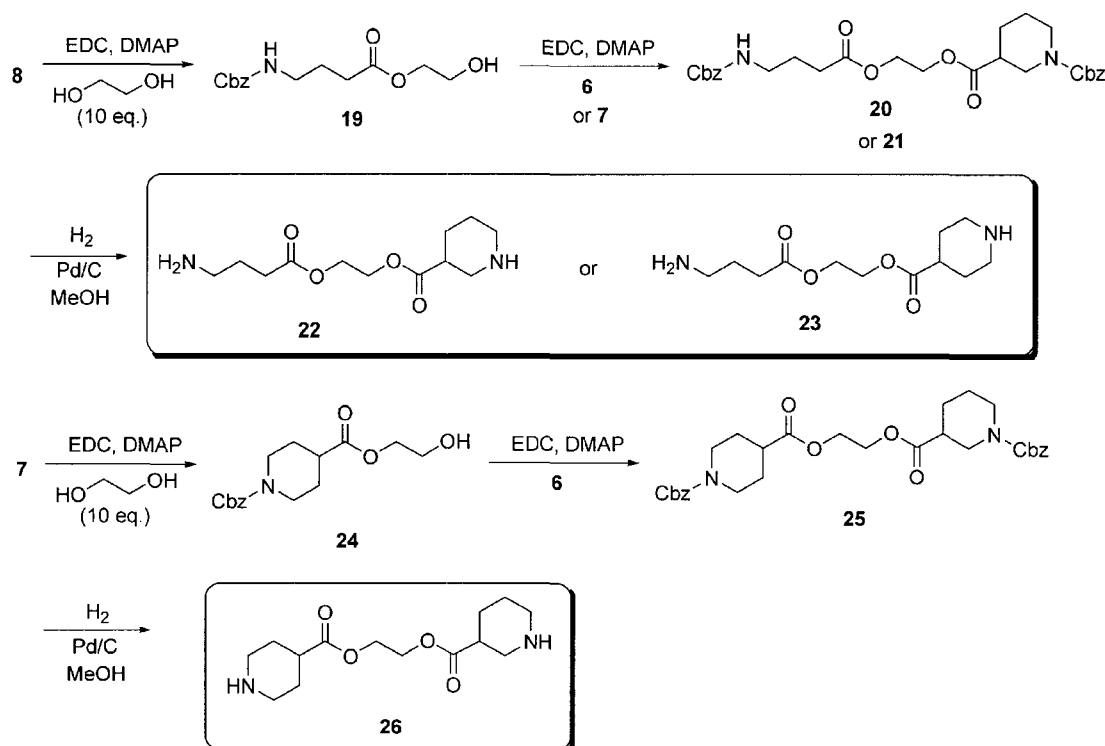
The amino group of vigabatrin (**4**) was protected with

Boc group by treatment with BOC-ON in the presence of TEA in water/dioxane to afford Boc-protected vigabatrin **15** at 82.6% yield as a colorless crystal. Compound **16** was prepared from ethylene glycol and four equivalences of **15** with treatment of EDC and DMAP at 97.1% yield as a colorless oil, followed by the treatment with 33% trifluoroacetic acid (TFA) and 5% dimethylsulfide (DMS) in dichloromethane to afford compound **17** at quantitative yield as a colorless oil.

Compound **18** was prepared from ethylene glycol and four equivalences of valproic acid with treatment of EDC and DMAP at a 97.1% yield as a colorless oil.

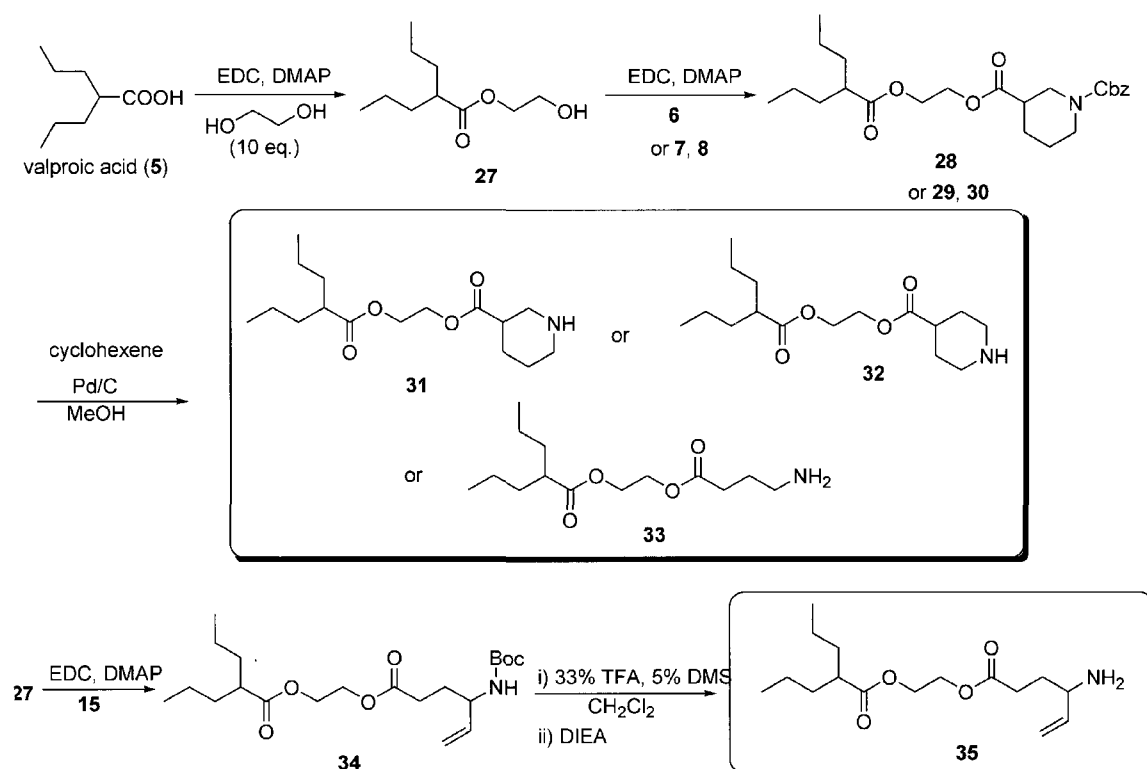
Compounds **22**, **23** and **26** were synthesized, at good yields by known general reactions as outlined in Scheme 2, from protected isonipecotic acid (**7**) and GABA (**8**) with 10 equivalences of ethylene glycol in the presence of EDC and DMAP, followed by treatment with **6** or **7** in the presence of EDC and DMAP to form intermediates **20**, **21** and **25**, and finally by hydrogenolysis.

Cbz-protected GABA **8** and 10 equivalences of ethylene glycol were treated in the presence of EDC and DMAP to form intermediate **19** at 95.0% yield as a colorless oil. Compounds **20** or **21** were prepared from compounds **6** or **7**, and compound **19** with treatment of EDC and DMAP at 89.7 and 95.0% yields as colorless oils, respectively. Compounds **22** and **23** were prepared from compounds **20** and **21** by hydrogenolysis in the presence of 10% Pd/C with H<sub>2</sub> gas at 82.0~85.0% yields as colorless oils,



Scheme 2. Synthesis of **22**, **23**, and **26**





Scheme 3. Synthesis of 31, 32, 33, and 35

respectively.

Compound **26** was prepared with the similar method described above as a colorless oil.

Compounds **31**, **32**, **33** and **35** were synthesized, at good yields by known general reactions as outlined in Scheme 3, from valproic acid (**5**) with 10 equivalents of ethylene glycol in the presence of EDC and DMAP, followed by treatment with **6**, **7**, **8** and **15** in the presence of EDC and DMAP to form intermediates **28**, **29**, **30** and **34**, and finally by hydrogenolysis.

Compound **27** was prepared from 10 equivalents of ethylene glycol and valproic acid (**5**) by treatment of EDC and DMAP at 83.6% yield as a colorless oil. Compound **27** was treated with Cbz-protected compounds **6**, **7** and **8** in the presence of EDC and DMAP to form compounds **28**, **29** and **30**, respectively, at 65.0–83.0% yields as colorless oils, which were deprotected by hydrogenolysis with treatment of cyclohexene and 10% Pd/C to afford compounds **31**, **32** and **33**, respectively, at 88.0–82.0% yields as colorless oils. For the hydrogenolysis, we utilized cyclohexene (Alan and Robert, 1976) instead of H<sub>2</sub> as a hydrogen donor, since the reaction with H<sub>2</sub> did not proceed well.

Compound **34** was prepared from compounds **27** and **15** by treatment of EDC and DMAP at 74.7% yield as a colorless oil, which was deprotected by treatment of 33% TFA and 5% DMS in dichloromethane to afford **35** at

quantitative yield as a colorless oil.

### Anticonvulsive activities

To test the anticonvulsant activity of the prepared compounds in maximal electroshock seizure (MES), pentylenetetrazole (PTZ), bicuculline (BIC) and picrotoxin (PCR) induced seizure tests were carried out according to the protocol of the Antiepileptic Drug Development Program of the National Institute of Neurological Disorders and Stroke (Holland *et al.*, 1992; Swinyard *et al.*, 1989; Krall *et al.*, 1978). It has been reported that the MES test correlates to both generalized tonic-clonic and psychomotor seizures, and that the PTZ test correlates to generalized absence seizure (Swinyard *et al.*, 1989; Krall *et al.*, 1978). BIC and PCR tests have been reported to be selective to a GABA<sub>A</sub> receptor. However, vigabatrin was effective only against BIC and PCR induced seizures (Holland *et al.*, 1992). These seizure tests are meaningful for clinical predictions of anticonvulsive agents and for recognition of a broader clinical spectrum and dual action for prepared compounds. The anticonvulsive activities of compound **18** are shown in Table I, in comparison with the parent compounds.

Most of the prepared compounds did not show significant anticonvulsive activities compared to those of the parent compounds except compound **18**. Compound **18** displayed 3–5 fold stronger anticonvulsive activities, with a broad clinical spectrum against PTZ, BIC and PCR tests,

**Table I.** The Anticonvulsive Activities of **18**

Compound	ED <sub>50</sub> (mmol/kg)			
	MES	PTZ	BIC	PCR
<b>18</b>	n <sup>a</sup>	0.29	0.38	0.43
Vigabatrin	n	n	0.22	0.21
Nipecotric acid	n	n	n	n
Isonipecotric acid	n	n	n	n
Valproic acid(Lin and Sun, 1999)	1.64	0.90	1.78	2.50

<sup>a</sup>n : not effective (>2.0 mmol/kg)

compared to those of the parent compound, valproic acid. This result indicated that the hydrophobicity of **18** was increased by the introduction of the two-carbon linker chain, resulting in easier passage into BBB and ready hydrolysis of the ester linkage bond by metabolizing enzyme. In the case of the other prepared compounds, presumably hydrophobicity was not significantly increased to pass BBB, which resulted in lower anticonvulsive activities.

In conclusion, we have designed and prepared twelve potential anticonvulsive agents as prodrugs linked by a two-carbon chain to increase the potency and to broaden the clinical spectrum. Compound **18** showed the most potent anticonvulsive activity in the PTZ, BIC and PCR tests, thereby indicating a broad clinical spectrum.

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