Novel 1,4-Dihydropyridine Calcium Antagonists. II. Synthesis and Antihypertensive Activity of 3-[4-(Substituted Amino)phenylalkyl]ester Derivatives

Atsuyuki Ashimori, Taizo Ono, Yoshihisa Inoue, Satoshi Morimoto, Masahiro Eda, Takeshi Uchida, Yutaka Ohtaki, Yoshiyuki Fujino, Hideaki Kido, Yasushi Ogura, Chikara Fukaya, Masahiro Watanabe, and Kazumasa Yokoyama

Research Division, The Green Cross Corporation, 1180-1, Shodaigai 2-chome, Hirakata-shi, Osaka 573, Japan. Received June 11, 1990

Novel 1,4-dihydropyridine derivatives bearing 3-[4-(substituted amino)phenylalkyl]ester side chains were prepared and tested for their antihypertensive activity in spontaneously hypertensive rats. Most compounds showed a more potent antihypertensive effect and a longer duration of action than nicardipine. The derivatives with a benzhydrylpiperazinyl and a benzhydrylpiperidinyl group were distinctive. 2-[4-(4-Benzhydryl-1-piperazinyl)phenyl]ethanol methyl 1,4-dihydridro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (4e), its 4-(4-cyano-2-pyridyl) analogue (4f), its 3-[4-(4-benzhydryl-1-piperazinyl)phenyl]propyl ester analogue (4h), its 2-[44-(4-benzhydryl-1-piperidinyl)phenyl]ethyl ester analogue (4j), and its 2-[4-(1-benzhydryl-4-piperidinyl)phenyl]ethyl ester analogue (4k) were selected as candidates for further pharmacological investigations.

Keywords 1,4-dihydropyridine-3-[4-(substituted amino)phenylalkyl]ester; calcium antagonist; antihypertensive effect; benzhydrylpiperazinyl group; benzhydrylpiperidinyl group; spontaneously hypertensive rat

Introduction
In a previous paper,1) we reported the syntheses and hypotensive effects of 4-(substituted pyridyl)-1,4-dihydropyridine derivatives, and three compounds (1, 2, and 3) were selected as candidates for further elaboration of their structures (Fig. 1).

We prepared 1,4-dihydropyridine calcium antagonists which have a novel ester side chain containing one or more amine functions and a benzene ring placed between the amine and the alkylene groups, expecting that the metabolism could be delayed to some extent by introducing such functions. We are interested in how the lipophilic benzene ring interacts with a receptor and influence its pharmacological properties. Although there are a few reports2) on such derivatives bearing alkyl-, alkoxy-, or halo-substituted phenylalkyl ester side chains, their pharmacological profiles have never been reported in detail. Alkylamino and aralkylamino, in particular, either piperidinyl or piperazinyl with a benzhydryl group were selected as functional groups for the substituent on the benzene ring, because this type of moiety has been employed in some vasodilating drugs (e.g., cinnarizine3) and flunarizine3) and a dihydropyridine calcium antagonist CY-4093 (manidipine).4)

Thus, we synthesized the series of compounds shown in Fig. 2 and some related compounds and tested for their antihypertensive effects in spontaneously hypertensive rats (SHR); the results are described in this paper.

Chemistry Methods for the Construction of 1,4-Dihydropyridine Skeleton Prepared compounds (4a–m) were listed in Table I. For the substituent at the 4-position of the 1,4-dihydropyridine ring, we employed 4-cyano-2-pyridyl and 2-trifluoromethyl-3-pyridyl groups, which were originally developed in our laboratory,5) in addition to the most popular 3-nitrophenyl group. They were synthesized either via the Hantzsch reaction (method A),5) its modified reaction (method B), or through the esterification reaction of 1,4-dihydropyridine monocarboxylic acid (9) with alcohols (10) (method C)6) (Chart 1).

Method for the Synthesis of Side Chains Alcohols employed in the preparation of the ester side chains of each derivative were synthesized as shown in Charts 2, 3 and 4.

Preparation of Side Chains of 4c–g, 4i, 4j and 4l (Charts 2 and 3) Compound 10b, the side chain of 4e and 4d, were obtained by direct dibenzylzation of p-aminophenethyl alcohol (12). Compounds 10c and 10d, the side chains of 4e–g and 4i, were easily derived from 12 by treatment with bis(2-chloroethyl)amine hydrochloride in refluxing BuOH,7) and the following benzhydrylation with benzhydryl bromide and 4,4'-difluorobenzhydryl bromide, respectively. Compound 10e, the side chain of 4j, was also synthesized from 12 via 15. The reductive amination of 14 with 12 using NaBH₄ and NH₃ as a reducing agent gave 15 in moderate yield.8) Compound 15 was then methylated by reductive alkylation

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with HCHO. Aldehyde 14 was derived from aminoalcohol 16 by N-benzhydrylation, followed by oxidation of the obtained intermediate 17. The method for the synthesis of 10, the side chain of 4i, was as follows: Compound 18 derived from 12 by known methods was reduced with NaBH₄ to give the corresponding alcohol 19, which was treated with p-toluenesulfonyl chloride in pyridine. The toslyoxy leaving group of 20 was replaced by a cyano group by the method of Henbest and Jackson, namely, 20 was treated with NaCN in N-methyl-2-pyrrolidone and tert-BuOH at 80—90 °C to give 21 in moderate yield. After the protecting group of the primary alcohol of 21 was changed into a tetrahydropyranyl (THP) group, 22 was treated with phenylmagnesium bromide twice to afford 24 in good yield. Dehydration and a concomitant exchange of THP for acetyl (Ac) was performed by treatment of 24 with H₂SO₄—AcOH.
Chart 3

A) NaBH₄/MeOH, r.t. (96%)  B) TsCl/pyridine, r.t. (81%)  C) NaCN/N-methyl-2-pyrrolidone and tert-ButOH, 80-90°C (45%)  D) i) K₂CO₃/MeOH, r.t.; ii) DHP, TsOH/CH₂Cl₂, r.t. (80%)  E) i) PhMgBr/Et₂O, r.t.; ii) 12N H₂SO₄, ice-water cooling (66%)  F) i) PhMgBr/Et₂O-THF, r.t.; ii) 25% NH₄Cl (96%)  G) H₂SO₄-AcOH (2:8), r.t. (66%)  H) H₂, 10% Pd on charcoal/AcOH/HClO₄, 65-70°C (79%)  I) K₂CO₃/MeOH, r.t. (91%)

Chart 4

A) i) H₂, 5% Pd on charcoal/MEOH, r.t.; ii) HCl/MeOH, refl.; iii) LiAlH₄/THF, 22-23°C (91%)  B) (CICH₂CH₂)₂NH·HCl/MeOH, refl. (62%)  C) (Ph₂)CHBr, K₂CO₃/DMF, r.t. (60%)  D) i) BuLi/THF, < -60°C; ii) 1-benzyl-4-piperidone (31), -60-40°C; iii) 10% HCl/MeOH, r.t. (76%)  E) H₂SO₄-AcOH (2:8), r.t. (51%)  F) H₂, 10% Pd on charcoal/AcOH-HClO₄, 65-70°C (96%)  G) (Ph₂)CHBr, K₂CO₃/DMF, r.t. (73%)  H) K₂CO₃/MeOH, r.t. (89%)  I) i) MsCl, NEt₃/THF-CH₂Cl₂, r.t.; ii) 1-benzhydrylpiperazine, K₂CO₃/DMF, r.t. (30%)
TABLE I. Physical and Biological Data of 1,4-Dihydropyridines (4)

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Ar</th>
<th>Method</th>
<th>R</th>
<th>n</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Recryst. solvent</th>
<th>HR-SIMS&lt;sup&gt;3&lt;/sup&gt; Found (Calcd)</th>
<th>Max. reduction of SBP (%)</th>
<th>Duration (h)</th>
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<tbody>
<tr>
<td>4a</td>
<td>4-CN-2-Py</td>
<td>A</td>
<td>NMe₂</td>
<td>2</td>
<td>45</td>
<td>184—186</td>
<td>M</td>
<td>461.2255 (461.2187)</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>4b</td>
<td>2-CF₃-3-Py</td>
<td>A</td>
<td>NMe₂</td>
<td>2</td>
<td>43</td>
<td>199—204</td>
<td>M</td>
<td>504.2131 (504.2109)</td>
<td>19</td>
<td>5</td>
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<tr>
<td>4c</td>
<td>4-CN-2-Py</td>
<td>A</td>
<td>NBn₃</td>
<td>2</td>
<td>40</td>
<td>194.5—197</td>
<td>M-C</td>
<td>613.2842 (613.2813)</td>
<td>20</td>
<td>11</td>
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<tr>
<td>4d</td>
<td>2-CF₃-3-Py</td>
<td>A</td>
<td>NBn₃</td>
<td>2</td>
<td>37</td>
<td>141—142</td>
<td>IPE-M-C</td>
<td>656.2703 (656.2733)</td>
<td>13</td>
<td>—</td>
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<tr>
<td>4e</td>
<td>3-NO₂-Ph</td>
<td>A, B, C</td>
<td>NCH(Ph)₃</td>
<td>2</td>
<td>92&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Amorph.</td>
<td>—</td>
<td>668.3234 (668.3234)</td>
<td>35</td>
<td>13</td>
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<tr>
<td>4f</td>
<td>4-CN-2-Py</td>
<td>A, B</td>
<td>NCH(Ph)₂</td>
<td>2</td>
<td>48&lt;sup&gt;a&lt;/sup&gt;</td>
<td>218—220</td>
<td>IPE-C</td>
<td>668.3234 (668.3234)</td>
<td>29</td>
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<td>A</td>
<td>NCH(Ph)₂</td>
<td>2</td>
<td>13</td>
<td>Amorph.</td>
<td>—</td>
<td>711.3196 (711.3156)</td>
<td>29</td>
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<tr>
<td>4h</td>
<td>3-NO₂-PH</td>
<td>C</td>
<td>NCH(Ph)₂</td>
<td>3</td>
<td>73</td>
<td>Amorph.</td>
<td>—</td>
<td>637.2994 (637.3023)</td>
<td>46</td>
<td>22</td>
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<tr>
<td>4i</td>
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<td>C</td>
<td>NCH(p-F-Ph)₂</td>
<td>2</td>
<td>94</td>
<td>Amorph.</td>
<td>—</td>
<td>701.3385 (701.3337)</td>
<td>34</td>
<td>16</td>
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<tr>
<td>4j</td>
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<td>C</td>
<td>CH₂CH₂NCH(Ph)₂</td>
<td>2</td>
<td>75</td>
<td>Amorph.</td>
<td>—</td>
<td>723.3027 (723.2992)</td>
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<td>20</td>
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<tr>
<td>4k</td>
<td>3-NO₂-PH</td>
<td>C</td>
<td>N(Ph)₃</td>
<td>2</td>
<td>48</td>
<td>Amorph.</td>
<td>—</td>
<td>686.3263 (686.3228)</td>
<td>42</td>
<td>&gt;24</td>
</tr>
<tr>
<td>4l</td>
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<td>C</td>
<td>NMeCH₂CH₂NMeCH(Ph)₂</td>
<td>2</td>
<td>53</td>
<td>Amorph.</td>
<td>—</td>
<td>686.3204 (686.3228)</td>
<td>38</td>
<td>4</td>
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<tr>
<td>4n</td>
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<td>A</td>
<td>CH₂CH₂NCH(Ph)₂</td>
<td>2</td>
<td>27</td>
<td>Amorph.</td>
<td>—</td>
<td>689.3358 (689.3337)</td>
<td>12</td>
<td>—</td>
</tr>
</tbody>
</table>

Nicardipine·HCl
Manidipine·2HCl

<sup>a</sup> 4-CN-2-Py, 4-cyano-2-pyridyl; 2-CF₃-3-Py, 2-trifluoromethyl-3-pyridyl; 3-NO₂-Ph, 3-nitrophenyl.  b) C, CHCl₃; IPE, isopropyl ether; M, MeOH.  c) Compounds were converted to corresponding hydrochlorides and then analyzed. The method of conversion was described in Experimental section.  d) The yield by method C.  e) The yield by method B.  f) Whole ester group.  g) Compound 4e was converted to dihydrochloride and used for elemental analysis. The data are shown in Experimental section. Amorph. = amorphous.

(2:8, v/v) to afford 25, which was hydrogenated in AcOH using 10% Pd on charcoal in the presence of HClO₄ to yield 26. Compound 26 was hydrolyzed in a methanolic base to afford 10f in high yield.

**Preparation of Side Chain of 4h, 4k and 4m (Chart 4)**
Successive treatment of 27 with H₂ over 5% Pd on charcoal in MeOH, dry HCl in MeOH, and LiAlH₄ in tetrahydrofuran (THF) gave 28 in high yield. Compound 10g, the side chain of 4h, was derived from 28 as in the case of 12. Compound 10h, the side chain of 4k, was obtained in the following manner. Lithiated 30<sup>11</sup> was treated with N-benzyl-4-piperidone (31), and the following deprotection of the primary alcohol gave 32, which was dehydrated and acetylated at the same time by treatment with H₂SO₄—AcOH (2:8, v/v) to give 33. Treatment of 33 with H₂ over 10% of Pd on charcoal in AcOH—HClO₄ was followed by benzoylation of the secondary amine to give 35. Compound 10h was obtained by hydrolysis of 35 with K₂CO₃ in MeOH. Compound 10i, the side chain of 4m, was obtained by one pot reaction of (E)-2-butene-1,4-diol (36) with methanesulfonyl chloride in THF followed by an amination with 1-benzylpiperazine. 2-(4-Dimethylaminophenyl)ethyl alcohol (10a) is commercially available.

In cases where 1,4-dihydropyridine derivatives were
prepared by method A or B, the corresponding alcohols obtained above were converted to acetoacetic acid esters by treatment with diketene in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) in THF or Et₂O as shown in Chart 5.  

**Results and Discussion**

Antihypertensive activity and duration of action of the 1,4-dihydropyridine derivatives (4a–m) are shown in Table I. Most of the compounds synthesized except 4a have more potent antihypertensive activity than nicardipine which was used as a control compound.

Concerning the substituent at the 4-position of the 1,4-dihydropyridine ring, the derivatives with 2-trifluoromethyl-3-pyridyl group showed longer duration than those with a 4-cyano-2-pyridyl or a 3-nitrophenyl group (e.g., 4a < 4b, 4e < 4d, and 4c, 4f < 4g) like the previous examples (e.g., 1 < 3). However, there seems to be no distinct relationship between the potency of antihypertensive effect and the substituents used at 4-position.

The derivatives which have a piperazine moiety with a benzhydryl group (4e–g) showed more potent and longer lasting antihypertensive activity than the compounds without such a group (4a–d), and when the alkylene was lengthened from ethylene to trimethylene (n = 2 → n = 3, i.e., 4e → 4h) the antihypertensive effect and duration were increased. However, the introduction of a fluorine atom into the 4-position on each benzene ring of the benzhydryl moiety had little influence on the antihypertensive action (4e vs. 4i).

Interestingly, replacement of either nitrogen atom of the piperazine ring in 4e by a carbon atom gave rise to increased antihypertensive effect and, in particular, prolongation of the duration of action (4j and 4k). From these results, neither nitrogen atom of the piperazine ring is necessarily required for the antihypertensive activity. In addition, the fact that the straight chain analogue 4l preserves activity suggests the structural flexibility of this portion of the molecule to show the antihypertensive activity.

Although manidipine (Fig. 3), which will soon come onto the market, showed a potent antihypertensive activity, the duration of action was not as long (ca. 6 h; see Table I). It is remarkable to note that compound 4e, in which a benzene ring is introduced between the alkylene and the piperazine ring of manidipine, has somewhat less antihypertensive activity and yet the duration of action is more than twice as long as manidipine. This would be due, at least in part, to a tardiness of the metabolism or an increase of the affinity to a drug receptor caused by the introduced benzene ring.

Among the compounds described above, 4e (AE0047), 4f, 4h, 4i, and 4k were selected as candidates for further pharmacological investigations. One of the investigations indicated that AE0047 had a potent and selective vasodilating action to canine vertebral artery, and this property is thought to be an additional benefit to an antihypertensive drug.

**Experimental**

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-420 spectrometer. 1H-Nuclear magnetic resonance (1H-NMR) spectra were determined on a Hitachi R-24 (60 Mc) or a BRUKER AC-200 spectometer with tetramethylsilane (TMS) as an internal standard. Secondary ion mass spectra (SIMS) were measured on a Hitachi M-2000 instrument, and precise mass analysis were performed by high resolution SIMS (HR-SIMS). Extraction solvents were dried over anhydrous MgSO₄. Silica gel 60, 230—400 mesh (Nacalai Tesque) was used for flash column chromatography, and Kieselgel 60, F₂₅₄ (Merek) plates were used for thin layer chromatography (TLC).

2-(4-Dibenzylnaminoethyl) Alcohol (10b) To a solution of 12 (10.15 g, 74 mmol) in N,N-dimethylformamide (DMF) (9 ml), K₂CO₃ (4.20 g, 30 mmol) and benzyl bromide (2.99 g, 18 mmol) were added successively at room temperature, and the mixture was stirred at the same temperature for 2.5 h. After addition of H₂O, the resulting solution was extracted with Et₂O. The extract was washed with brine, dried, and the solvent was removed. The residue was chromatographed on silica gel with CHCl₃–MeOH (98:2, v/v) to give the product (10b) as a pale yellow oil (2.28 g, 94%). IR (film): 3350, 3205, 1620, 1520, 1495 cm⁻¹. 1H-NMR (CDCl₃): δ: 1.48 (1H, t, J = 6 Hz), 2.69 (2H, t, J = 6 Hz), 3.72 (2H, t, J = 6 Hz), 4.56 (4H), 6.62, 6.92 (4H, Ar—CH₃, J = 8.5 Hz), 7.18 (10H, s).

2-[4-(1-Piperaziny1)phenyl]ethyl Alcohol (13) A mixture of 12 (10.15 g, 74 mmol), bis(2-chloroethyl)amine hydrochloride (6.61 g, 37 mmol) and BuOH (66 ml) was refluxed for 23.5 h. After cooling to room temperature, the resulting solution was poured into H₂O, which was made alkaline with 3.5% NaOH to pH 10–11 with ice-water cooling. The resulting mixture was extracted with CHCl₃, the extract was washed with brine, dried, and the solvent was removed. The residue was chromatographed on silica gel with CHCl₃–MeOH (1:1, v/v) to yield the product (13) as a pale yellow solid (6.09 g, 79%). IR (KBr): 3300, (1615, 1515, 1450 cm⁻¹. 1H-NMR (CDCl₃): δ: 2.10 (2H, s), 2.75 (2H, t, J = 6 Hz), 2.8–3.2 (8H, m), 3.77 (2H, t, J = 6 Hz), 6.7–6.95 (2H, m), 6.95–7.15 (2H, m).

2-[4-(4-Benzylhydr zi-1-piperaziny1)phenyl]ethyl Alcohol (10c) To a solution of 13 (6.09 g, 29 mmol) in DMF (33 ml) were added successively, K₂CO₃ (8.03 g, 58 mmol) and benzyl bromide (7.54 g, 31 mmol) at room temperature, and the mixture was stirred at the same temperature for 2 h. The resulting mixture was poured into H₂O, and then extracted with CHCl₃. The extract was washed with brine, dried, and the solvent was removed. The product (10c) was isolated by chromatography on silica gel with AcOEt–hexane (1:1, v/v) to give a colorless oil (6.19 g, 57%). IR (CHCl₃): 3600, 2950, 1615, 1490, 1430 cm⁻¹. 1H-NMR (CDCl₃): δ: 1.71 (1H, s), 2.35–2.65 (4H, m), 2.71 (2H, t, J = 6 Hz), 2.95–3.3 (4H, m), 3.72 (2H, t, J = 6 Hz), 4.23 (1H, s), 6.65–6.92 (2H, m), 6.9–7.55 (12H, m).

2-[4-(4,4-Difluorobenzylid 1-piperaziny1)phenyl]ethyl alcohol (10d) was obtained by similar treatment of 13 with 4,4'-difluorobenzyl bromide as a colorless solid (yield 50%). IR (KBr): 3300, 2850, 1605, 1505, 1455 cm⁻¹. 1H-NMR (CDCl₃): δ: 1.50 (1H, brs), 2.72 (2H, t, J = 6 Hz), 2.4–2.6 (4H, m), 3.0–3.2 (2H, m), 3.75 (2H, t, J = 6 Hz), 4.20 (1H, s), 6.7–7.5 (12H, m).

2-(4-Benzylhydr zi-1-N-methylamin oethyl) alcohol (17) was obtained by similar treatment of N-methylthanolaminol (16) with benzyl bromide as a colorless oil (yield 95%). IR (film): 3300, 2950, 2750, 1590, 1490, 1450 cm⁻¹. 1H-NMR (CDCl₃): δ: 2.18 (3H, s), 2.70 (2H, t, J = 7 Hz), 3.48 (2H, t, J = 7 Hz), 4.37 (3H, s), 7.0–7.5 (10H, brs).

2-(4-N-Benzylhydr zi-1-N-methylamin oethyl)phenyl]ethyl Alcohol (15) To a solution of 17 (5.00 g, 21 mmol) and N,N-dicyclohexylcarbodiimide (16.50 g, 80 mmol) in dimethyl sulfoxide (DMSO) (100 ml) was added, 1.0 M H₂PO₄ in DMSO (10 ml) at room temperature, and the mixture was stirred at the same temperature for 2.5 h. After removing the precipitated dicyclohexylurea by filtration, 1.0 M K₂CO₃ was added to the filtrate, and the resulting mixture was extracted with CH₂Cl₂. The extract was washed with brine, dried, and the solvent was removed. The obtained residue was chromatographed on silica gel with AcOEt–hexane (1:5, v/v).
to give aldehyde 14 (1.54 g, 30%), which was used immediately in the next reaction. To a solution of aldehyde 14 (780 mg, 3.3 mmol) and 12 (1.34 g, 9.8 mmol) in MeOH (50 mL), NaBH₄CN (163 mg, 2.6 mmol) was added at room temperature, and the mixture was stirred at the same temperature for 2.5 h. After the solvent was removed, the residue was purified by chromatography on silica gel with AcOEt-hexane (1:1, v/v). The product was obtained as a pale yellow oil (606 mg, 51%). IR (film): 3300, 2875, 1610, 1495, 1450 cm⁻¹. H-NMR (CDCl₃): δ 1.21 (6H, s), 2.36 (2H, J = 6 Hz), 2.74 (2H, J = 6 Hz), 3.17 (2H, J = 6 Hz), 3.77 (2H, J = 7 Hz), 4.44 (4H, J = 6.6), 6.53 (4H, J = 4.6, H₂A₈B₂Q₂, J = 8.5 Hz), 7.16–7.20 (10H, m).

2-[2-(2-N-Benzhydryl-N-methylamino)ethyl]-N-methylamino)phenyl]ethyl Alcohol (10e) To a solution of 15 (44 mg, 0.12 mmol) in CH₂Cl₂ (10 mL) were added successively, 37% aqueous HCHO (10 mg, 0.1 mmol) and NaBH₄CN (8 mg, 0.10 mmol) at room temperature. After the resulting mixture was stirred at the same temperature for 2 h, the solvent was removed. H₂O was added to the mixture, and then the mixture was extracted with Et₂O. The extract was washed with brine and dried. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt-hexane (1:1, v/v) to give the product (16a) as a pale yellow oil (30 mg, 66%). IR (film): 3300, 2850, 1610, 1500, 1450 cm⁻¹. H-NMR (CDCl₃): δ 2.35 (2H, J = 6 Hz), 2.77 (2H, J = 6 Hz), 3.17 (2H, J = 6 Hz), 3.77 (2H, J = 7 Hz), 7.20 (2H, J = 7 Hz), 7.27–7.40 (10H, m).

2-[4-(Hydroxy-1-piperidinyl)phenyl]ethyl Acetate (19) To a solution of 18 (2.27 g, 8.9 mmol) in MeOH (22 mL), NaBH₄CN (168 mg, 4.25 mmol) was added, and the mixture was stirred at the same temperature for 30 min, the resulting solution was poured into H₂O, and extracted with CH₂Cl₂. The extract was washed with brine and dried, and then the solvent was removed. Purification by chromatography on silica gel with AcOEt-hexane (1:1, v/v) gave the product (19) as a pale yellow oil (2.10 g, 96%). IR (film): 3400, 2975, 1740, 1620, 1520, 1470, 1245 cm⁻¹. H-NMR (CDCl₃): δ 1.68 (2H, J = 6 Hz), 1.78–1.87 (4H, m), 2.67 (2H, J = 6 Hz), 2.78 (3H, J = 6 Hz), 2.84 (3H, J = 6 Hz), 3.14 (2H, J = 7 Hz), 3.50 (2H, J = 6 Hz), 4.09 (4H, J = 6.9 Hz), 5.96 (1H, J = 7 Hz), 5.87–6.12 (10H, m).

2-[4-[p-Toluenesulfonyloxy]-1-piperidinyl]phenyl]ethyl Acetate (20) A solution of 19 (100 mg, 0.38 mmol) in pyridine (1 mL), p-toluenesulfonyl chloride (109 mg, 0.57 mmol) was added with ice-water cooling. The reaction mixture was stirred at room temperature for 17 h under N₂ atmosphere. After evaporation of H₂O to the mixture and purification with 5% NaHCO₃ to ca. pH 4, the resulting mixture was extracted with Et₂O. The extract was washed with brine, and then the solvent was removed. Purification by chromatography on silica gel with AcOEt-hexane (2:1, v/v) gave the product (20) as a pale yellow oil (115 mg, 81%). IR (film): 2950, 1735, 1615, 1515, 1360, 1240, 1180 cm⁻¹ H-NMR (CDCl₃): δ 2.68–2.84 (4H, m), 3.57–3.71 (2H, m), 3.86 (2H, J = 7 Hz), 5.94 (1H, J = 7 Hz), 5.68–5.85 (9H, m), 7.10–7.22 (10H, m).

2-[2-(Cyano-1-[4-[2-(tetrfluoropyran-2-yloxy)ethyl]phenyl]peripederine] (21) To a solution of 20 (2.47 g, 5.9 mmol) in N-methyl-2-pyrrolidone (161 mL) and tert-ButOH (8.5 mL), NaN₃ (3.48 g, 71 mmol) was added at room temperature and stirred at 80–90°C for 15 h under N₂ atmosphere. The resulting solution was poured into crushed ice and the mixture was extracted with Et₂O. The extract was washed with brine, and then the solvent was removed. The product was isolated by chromatography on silica gel with AcOEt-hexane (1:2, v/v) to afford 21 as a pale yellow oil (731 mg, 45%). IR (film): 2975, 2250, 1740, 1615, 1500, 1425, 1240 cm⁻¹. H-NMR (CDCl₃): δ 1.95–2.14 (4H, m), 2.03 (3H, J = 27–285 (1H, m), 2.86 (2H, J = 7 Hz), 3.03–3.15 (2H, m), 3.35–3.45 (2H, m), 4.23 (2H, J = 7 Hz), 6.85–6.95 (9H, m), 7.10–7.22 (10H, m).

4-Cyaeno-1-[4-[2-(tetrfluoropyran-2-yloxy)ethyl]phenyl]peripederine (22) To a solution of 21 (719 mg, 2.6 mmol) in MeOH (10 mL), a catalytic amount of K₂CO₃ (ca. 3 mol%) was added at room temperature, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was poured into 10% K₂CO₃, and then was extracted with CH₂Cl₂. The extract was washed with brine, and then the mixture was removed. After the obtained residue (600 mg) was dissolved in CH₂Cl₂ (10 mL), 3,4-dihydro-2H-pyran (DHP) (328 mg, 4.6 mmol), p-toluenesulfonyl acid (644 mg, 3.4 mmol), and pulverized molecular sieves 3A (350 mg) were added successively to the solution, and then the mixture was stirred at room temperature for 1 h. After the reaction mixture was filtered, and the filtrate was poured into 10% K₂CO₃, and then was extracted with CH₂Cl₂. The mixture was washed with brine, and then the solvent was removed. Purification of the residue by chromatography on silica gel with AcOEt-hexane (2:5, v/v) gave the product (22) as a colorless solid (387 mg, 91%). IR (KBr): 3235, 2900, 1610, 1515, 1490, 1450 cm⁻¹. H-NMR (CDCl₃): δ 1.25–1.45 (3H, m), 1.62 (2H, m), 2.25 (2H, J = 7 Hz, 7.5 Hz), 2.77 (2H, J = 6.5 Hz, 6.5 Hz, d, J = 11 Hz), 3.55–3.65 (2H, m), 3.80 (2H, brs), 6.8–6.9 (2H, m), 7.05–7.15 (2H, m), 7.15–7.45 (10H, m).
Table II. Yields and Spectral Data of Acetoacetic Acid Esters (6)

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>Yield (%)</th>
<th>IR (cm⁻¹)</th>
<th>δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>NMe₂</td>
<td>76</td>
<td>2.20 (3H, s), 2.84 (2H, t, J = 7 Hz), 2.89 (6H, s), 3.38 (2H, s), 4.27 (2H, t, J = 7 Hz), 4.63, 7.03 (2H, ABq, J = 9 Hz)</td>
<td>-</td>
</tr>
<tr>
<td>6b</td>
<td>NBn₂</td>
<td>82</td>
<td>2.15 (3H, s), 2.81 (2H, t, J = 6 Hz), 3.36 (2H, s), 4.25 (2H, t, J = 6 Hz), 4.57 (4H, s), 6.5-6.75 (2H, m), 6.8-7.1 (2H, m), 7.19 (10H, s)</td>
<td>-</td>
</tr>
<tr>
<td>6c</td>
<td>CH₂CH₂CH=CH₂N(CH₂)₂</td>
<td>100</td>
<td>2.18 (3H, s), 2.4-2.7 (4H, m), 2.85-2.9 (2H, t, J = 6 Hz), 3.0-3.35 (4H, m), 3.39 (2H, s), 4.24 (1H, s), 4.29 (2H, t, J = 6 Hz), 6.65-6.85 (2H, m), 6.9-7.2 (2H, m)</td>
<td>-</td>
</tr>
<tr>
<td>6d</td>
<td>CH₂CH₂CH=CH₂N(CH₂)₂</td>
<td>75</td>
<td>2.20 (3H, s), 2.44 (8H, brs), 5.64 (2H, d, J = 5.5 Hz), 3.41 (2H, s), 4.22 (1H, s), 4.59 (2H, d, J = 5.5 Hz), 5.69 (1H, ddd, J = 15.5, 6, 5.5 Hz), 5.83 (1H, ddd, J = 15.5, 6, 5.5 Hz), 7.1-7.4 (10H, m)</td>
<td>-</td>
</tr>
</tbody>
</table>

a) Whole ester group.

General Method for the Synthesis of Acatocyctic Acid Esters (6) To a THF or Et₂O solution of 10, diketene (1.2 equiv of 10) and a catalytic amount of DMAP were added with ice-salt cooling. After the addition of the reagents, the reaction mixture was stirred at the same temperature for 30 min and at room temperature for 3-16 h. To the mixture, 0.1% NaOH was added.

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was added and then the resulting mixture was extracted with 

\[ \text{CH}_2\text{Cl}_2 \]. The extract was washed with 0.1% NaOH (twice) and brine, dried, and the solvent was evaporated to dryness. The residue was chromatographed on silica gel. Yields and spectral data are shown in Table II.

**Typical Procedure for Method A** 2-(4-Dimethylaminophenyl)ethyl Methyl 4-(4-Cyano-2-pyridyl)-1,1-dihydro-2,6-dimethyl-3,5-pyridinedicarbonylate (4a). A solution of 4-cyano-2-pyridinecarboxaldehyde (1.01 g, 7.6 mmol) and 2-(4-dimethylaminophenyl)ethyl acetate (6a, 1.90 g, 7.6 mmol), and methyl 3-aminoacetanilide (7, 903 mg, 7.6 mmol) in 2-pro

\[ \text{panol} (10 \text{mL}) \] was stirred at 45–45°C for 26 h. The solvent was remov

ed and the residue was chromatographed on silica gel with AcOEt-hexane (9:1, v/v). The product (4a) was recrystallized from MeOH to obtain colorless needles (1.5 g, 45%).

**The other compounds were similarly prepared, except for 4e for which refluxing temperature was necessary.**

**Typical Procedure for Method B** 2-[4-(Benzhydryl-1-piperazinyl)phenyl]ethyl Methyl 4-(4-Cyano-2-pyridyl)-1,1-dihydro-2,6-dimethyl-3,5-pyridinedicarbonylate (4f). A solution of 4-cyano-2-pyridinecarboxaldehyde (828 mg, 6.3 mmol) and 2-[4-(benza

hydryl-1-piperazinyl)phenyl]ethyl acetate (6c, 2.86 g, 6.3 mmol) in benzene (14 mL) containing piperidine (107 mg, 1.3 mmol) and AcOEt (376 mg, 3.6 mmol) was refluxed for 1 h with azeotropic removal of H₂O using a Dean Stark trap. After cooling to room temperature, the mixture was washed with H₂O, aqueous saturated NaHCO₃, and brine. After drying, the solvent was evaporated to dryness, and the residue was chromatographed on silica gel with AcOEt-hexane (2:3, v/v) to give 2-[4-(benza

hydryl-1-piperazinyl)phenyl]ethyl 2-(4-cyano-2-pyridymethylidene)acetamide (2.36 g) as an amorphous solid. A solution of the amorphous solid and methyl 3-aminoacetanilide (7, 447 mg, 3.9 mmol) in 2-propano

l (18 mL) was stirred for 4 h. The solvent was distilled off and the residue was chromatographed on silica gel with AcOEt-hexane (3:1, v/v). The product (4f) was recrystallized from isopropyl ether-CHCl₃ to give a slightly yellow powder (2.55 g, 59%).

**Compound 4e was prepared similarly by method B.**

**Typical Procedure for Method C** 2-[4-(Benzhydryl-1-piperazinyl)phenyl]ethyl Methyl 1,1-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarbonylate (4g): To a suspension of carboxylic acid (9, 3.00 g, 9.0 mmol) in CHCl₃ (24 mL) and DMF (6 mL) was added SOCl₂ (1.18 g, 9.9 mmol) at 4–5°C with ice-water cooling and this was then stirred for 2 h at the same temperature. The solution of 10c (3.36 g, 9.0 mmol) in CHCl₃ (6 mL) was added to the reaction mixture at 5–7°C and stirred for 1 h at 4–5°C. The reaction mixture was diluted with CHCl₃ (30 mL), washed with 1 N NaOH and brine, dried, and the solvent was removed. The residue was purified by chromatography on silica gel with AcOEt-hexane (2:3, v/v) to give the product (4g) as a yellow amorphous powder (5.70 g, 92%). Anal. Calcd for C₃₅H₃₅N₂O₂: 2HCl: C, 62.77; H, 6.10; N, 5.14; Cl 9.04. Found: C, 63.01; H, 6.08; N, 7.05; Cl 8.76.

The other compounds were prepared similarly by method C. Spectral data of 4 are shown in Table III.

**Method for the Preparation of Hydrochlorides of 4** To a solution of 4 (2.30 mmol) in CHCl₃ (30 mL), a solution of HCl in dioxane (the same equivalent of HCl with 18 mL) was added at room temperature. After the solution was stirred at the same temperature for 2.5 h, the solvent was removed. The residue was dissolved in EtOH (25 mL) and then the solvent

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>1R (KBr) νmax (cm⁻¹)</th>
<th>¹H-NMR (CDCl₃) δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>3200, 3100, 2950, 2225, 1705, 1665, 1620, 1600, 1520, 1500, 1440</td>
<td>2.25 (6H, s), 2.80 (2H, t, J = 6 Hz), 2.91 (6H, s), 3.63 (3H, s), 4.24 (2H, t, J = 6 Hz), 5.14 (1H, s), 6.62, 7.00 (4H, Ar-H), 7.85 (1H, s), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz), 7.15–7.4 (2H, m), 8.52 (1H, d, J = 5 Hz)</td>
</tr>
</tbody>
</table>
was evaporated to dryness to give the hydrochloride of 4. All hydrochlorides of 4 were obtained as amorphous solids and subjected to pharmacological testing.

Biological Test\textsuperscript{13} The experiments were performed in groups of 3—6 male SHR (10 to 11 weeks old). Systolic blood pressure (SBP) was measured in a conscious state by a tail cuff plethysmographic method with an electrophysiomonometer (PE-300, Narco Bio-System) at 0, 1, 2, 4, 7 and 24 h after administration. The test compounds were converted to hydrochlorides and were prepared as a solution or a suspension in aqueous 0.3% Tween 80 solution and orally administered at a dose of 5 mg/kg (10 ml/kg). Antihypertensive effects are shown as maximum reductions in SBP (%) from 0 h values. Duration of antihypertensive effects, carefully estimated by time course curves of SBP, is shown in hours by which SBP recovered to half maximum reductions.

References and Notes
8) C. F. Lane, Synthesis, 1975, 135 and references cited therein.
13) Dihydrochloride of 4e was prepared in the following manner. 4e (7.0 mmol) was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (20 ml) and HCl gas was bubbled into the solution at its reflux temperature for 30 min and then with ice-salt cooling for 20 min to give a precipitated solid. The mixture was allowed to warm to room temperature and then the precipitate was collected by filtration to afford 4e·2HCl (4.5 g) as a pale yellow powder. Dihydrochloride of 4e was elementarily analyzed. Calculated values were made assuming 3.19% water content determined by Karl Fisher method.
14) Concentration of HCl was determined by titration with 1 N NaOH using phenolphthalein as an indicator.