# Synthesis and Pharmacological Effects of Optically Active 2-[4-(4-Benzhydryl-1-piperazinyl)phenyl]-ethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate Hydrochloride

Atsuyuki ASHIMORI, Takeshi UCHIDA, Yutaka OHTAKI, Mikio TANAKA, Kazuhito OHE, Chikara FUKAYA,* Masahiro WATANABE, Masao KAGITANI, and Kazumasa YOKOYAMA

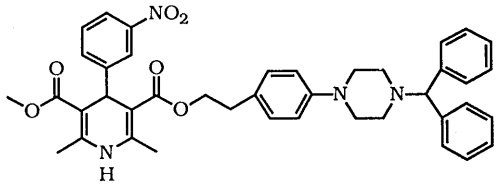
*Research Division, The Green Cross Corporation, 1180–1, Shodaiotani 2-chome, Hirakata-shi, Osaka 573, Japan.* *Received June 21, 1990*

**Optically active 2-[4-(4-benzhydryl-1-piperazinyl)phenyl]ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate [(*S*)-(+)-1 and (*R*)-(−)-1] hydrochlorides were synthesized with high optical purities from (*R*)-(−)- and (*S*)-(+)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylic acids [(*R*)-(−)-6 and (*S*)-(+)-6], which are available from (±)-6 by optical resolution using quinidine and cinchonidine, respectively. From pharmacological investigations of (*S*)-(+)-1 and (*R*)-(−)-1 such as the antihypertensive effect on spontaneously hypertensive rats and inhibition of [$^3$H]nimodipine binding to rat cardiac membrane homogenate, the active form of 1 was defined to be the (4*S*)-(+)-enantiomer of 1.**

**Keywords** 1,4-dihydropyridine; calcium antagonist; antihypertensive effect; receptor binding assay; optically active compound; AE0047

## Introduction

In a previous paper,[1] we reported the synthesis and antihypertensive activity of 1,4-dihydropyridine derivatives with 3-[4-(substituted amino)phenylalkyl] ester, and that among them, 2-[4-(4-benzhydryl-1-piperazinyl)phenyl]ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate dihydrochloride (**1**·2HCl, AE0047) had long lasting antihypertensive activity and selective vasodilating activity on canine vertebral artery. AE0047 has been selected as a promising candidate from other pharmacological investigations also. Since **1** has an asymmetric center at C-4 of the dihydropyridine ring, it is a racemic mixture (Fig. 1). We have been interested in biological activities of each enantiomer of **1** because a number of reports described that one optical isomer of 1,4-dihydropyridine derivatives showed much more potent biological activities than the other.[2–8] Therefore, we synthesized each enantiomer of **1**, and investigated the difference of *in vivo* and *in vitro* biological activities, namely antihypertensive activity on spontaneously hypertensive rats (SHR) and the effect on the binding of [$^3$H]nimodipine to rat cardiac membranes.



1

Fig. 1

In this paper, we report the synthesis of each enantiomer of **1** and their biological activities.

**Synthesis** Method for synthesis of each enantiomer of **1** is shown in Charts 1 and 2.

Optically active nicardipine[3] and other such 1,4-dihydropyridine derivatives[6–8] were synthesized from (+)- and (−)-**6** which were obtained by an optical resolution of 1-ethoxymethylated (±)-**6** and subsequent removal of the ethoxymethyl group. Tamazawa *et al.*[6] and Kajino *et al.*[8] independently determined the absolute configuration of **6** by X-ray crystallographic analysis of its derivatives to assign unambiguously that (+)-**6** and (−)-**6** have *S* and *R* configurations at C-4, respectively.

We tried to ascertain the utility of the direct optical resolution of (±)-**6** reported by Genain.[9] Several hundreds of grams of (±)-**6** was easily prepared from ethylene

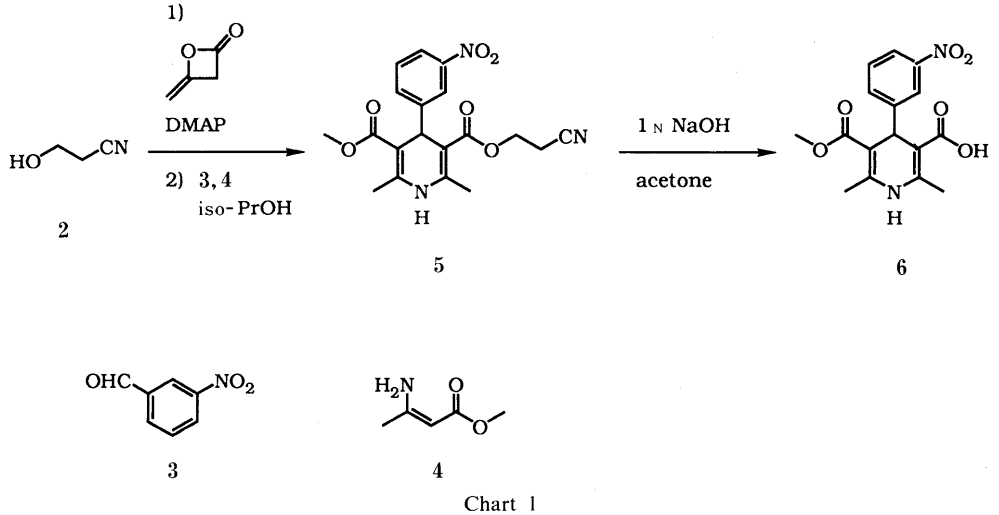


Chart 1

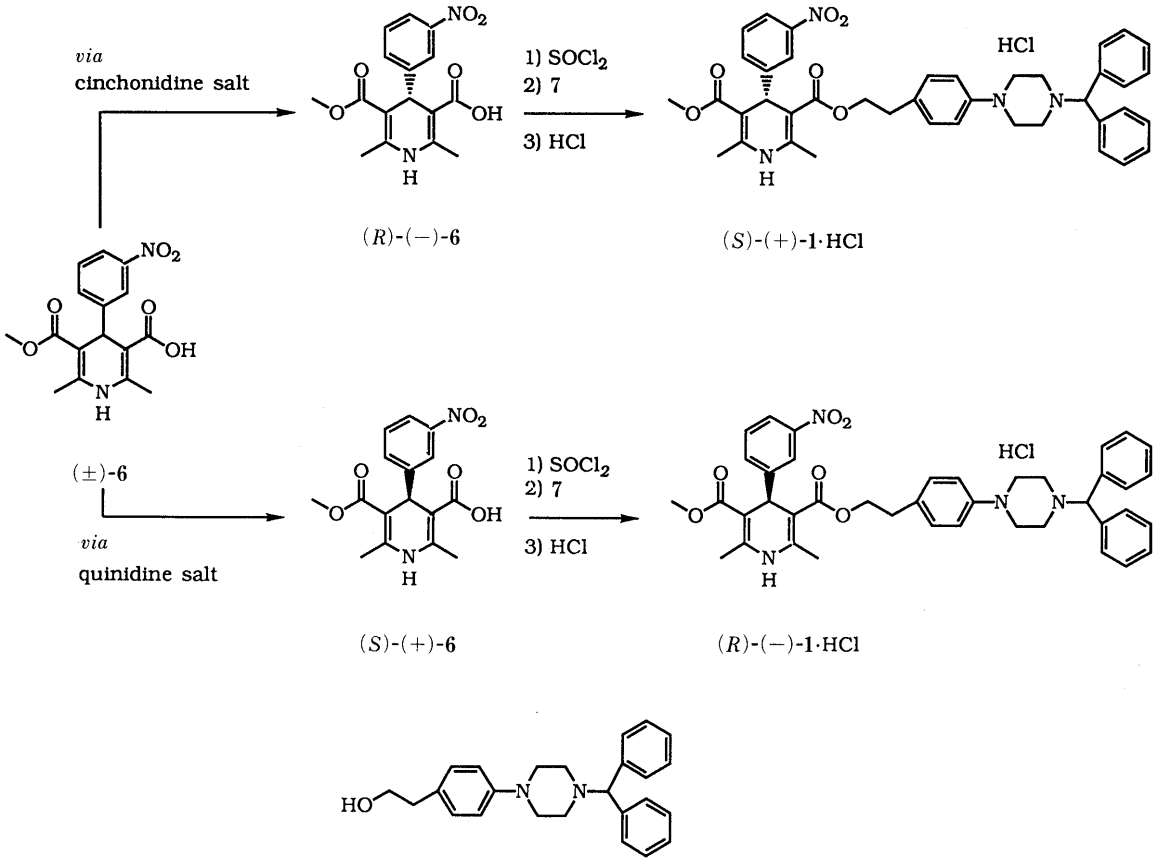



Chart 2

cyanohydrin (**2**) *via* 1,4-dihydropyridine **5** in a *ca.* 60% overall yield without chromatographical purification (Chart 1).[10] The compound (*S*)-(+)-**6** was obtained in a 46% yield from a quinidine salt of **6** in pure form by recrystallizing it to a constant optical rotation. On the other hand, **6** recovered from the mother liquor gave (*R*)-(−)-**6** by recrystallizing it as cinchonidine salt (yield 48%). Treatment of (*R*)-(−)-**6** and (*S*)-(+)-**6** with $SOCl_2$, and a subsequent reaction with **7** gave (*S*)-(+)-**1** and (*R*)-(−)-**1**, respectively. They were treated with a solution of hydrogen chloride in 1,2-dimethoxyethane (DME) in $Et_2O$–$CH_2Cl_2$ (90 : 10, v/v) to afford monohydrochlorides, (*S*)-(+)-**1**·HCl, 62%, mp 143.5—147 °C, $[\alpha]_D^{20}$ +31.0° (*c* = 0.50, acetone) and (*R*)-(−)-**1**·HCl, 59%, mp 145—149 °C, $[\alpha]_D^{20}$ −31.4° (*c* = 0.50, acetone) (Chart 2).

**Determination of Optical Purities of (*S*)-(+)-1 and (*R*)-(−)-1** The optical purities of (*S*)-(+)-**1**·HCl and (*R*)-(−)-**1**·HCl were determined by high performance liquid chromatography (HPLC) analyses using chiral stationary phase columns, Chiralcel OF® (4.6 mm i.d. × 250 mm) [column temperature, 50 °C; mobile phase, hexane–2-propanol–trifluoroacetic acid (50 : 50 : 0.05, v/v); flow rate, 1.0 ml/min; detection, ultraviolet (UV) at 254 nm] and Chiralpak AD® (4.6 mm i.d. × 250 mm) [column temperature, 40 °C; mobile phase, hexane–ethanol (9 : 1, v/v); flow rate, 1.0 ml/min; detection, UV at 254 nm] purchased from Daicel Chemical Industries, Tokyo, Japan. Retention times of the compounds are as follows: in Chiralcel OF®, (*S*)-(+)-**1**, 22.5 min; (*R*)-(−)-**1**, 50.3 min; in Chiralpak AD®, (*S*)-(+)-**1**, 23.1 min; (*R*)-(−)-**1**, 27.0 min. Since in both cases the peaks of antipodal compounds were not detected at all, the optical purities of each compound were concluded to be almost 100% ee.

TABLE I. Effects of (±)-**1**, (*S*)-(+)-**1**, and (*R*)-(−)-**1** on SBP in SHR (*p.o.* Administration)

| Drug and dose (mg/kg) | *n* | Reduction of SBP (%) (mean ± S.E.) | | | | |
|---|---|---|---|---|---|---|
| | | Before | 1 h[b] | 2 h[b] | 4 h[b] | 7 h[b] |
| Vehicle[a] | 6 | 0 | 0±2 | 1±2 | 0±1 | 3±2 |
| (±)-**1** | | | | | | |
| 1 | 6 | 0 | 10±3 | 14±2 | 16±2 | 12±2 |
| 3 | 6 | 0 | 31±1 | 36±3 | 35±1 | 26±1 |
| 10 | 6 | 0 | 41±2 | 43±2 | 41±2 | 38±1 |
| (*S*)-(+)-**1** | | | | | | |
| 0.3 | 6 | 0 | 1±3 | 11±2 | 5±3 | 8±3 |
| 1 | 6 | 0 | 19±3 | 21±2 | 17±2 | 15±2 |
| 3 | 3 | 0 | 43±4 | 51±2 | 41±1 | 33±4 |
| (*R*)-(−)-**1** | | | | | | |
| 30 | 6 | 0 | 4±2 | 11±2 | 11±3 | 11±3 |

*a*) 0.3% Tween 80 solution. *b*) Time after administration.

**Pharmacological Results and Discussion** The antihypertensive effects of (±)-AE0047 and each enantiomer of AE0047 on SHR are shown in Table I. The compound (*S*)-(+)-**1** showed a dose dependent potent antihypertensive effect, particularly at doses of 1 and 3 mg/kg, and the duration was estimated to be over 7 h, whereas at a dose of 30 mg/kg the antihypertensive effect of (*R*)-(−)-**1** was barely comparable to the effect of (*S*)-(+)-**1** at a dose of 0.3 mg/kg. Although the antihypertensive effect of (±)-**1**

Table II. Inhibition of [$^3$H]Nimodipine Binding to Rat Cardiac Membrane Homogenate

| Drug | Concentrations required for 50% inhibition (nM) |
|---|---|
| (±)-**1** | 0.26 |
| (*S*)-(+)-**1** | 0.13 |
| (*R*)-(−)-**1** | 18.2 |
| (±)-Nicardipine | 0.48 |

was less than (*S*)-(+)-**1**, it had enough potency at doses 3 and 10 mg/kg. The doses necessary for a 30% reduction of systolic blood pressure (SBP) ($ED_{30}$) obtained from the dose–response curves were 1.1 mg/kg in (*S*)-(+)-**1** and 2.6 mg/kg in (±)-**1**, respectively. These results indicate that the antihypertensive effect of (±)-**1** depends mostly on (*S*)-(+)-**1**, which is supported by the fact that the $ED_{30}$ value of (*S*)-(+)-**1** is about a half of the value of (±)-**1**.

We performed a receptor binding assay to evaluate phamacological profiles of these compounds *in vitro*. Drug concentrations required for 50% inhibition of [$^3$H]nimodipine binding to rat cardiac membrane homogenate ($IC_{50}$) of these compounds and (±)-nicardipine are shown in Table II. The compound (*S*)-(+)-**1** shows the highest affinity to the receptor, and the affinity was decreased in the following order; (±)-**1** (0.26 nM) > (±)-nicardipine (0.48 nM) > (*R*)-(−)-**1** (18.2 nM). The affinity of (*S*)-(+)-**1** was found to be 140-fold higher than (*R*)-(−)-**1** and to be 2-fold higher than (±)-**1**. This result is consistent with the potency of the antihypertensive effects obtained in the *in vivo* study.

## Conclusion

We synthesized the compounds (*S*)-(+)-**1** and (*R*)-(−)-**1** with high optical purities from (*R*)-(−)-**6** and (*S*)-(+)-**6**, respectively, which were obtained by the direct optical resolution of (±)-**6** through its quinidine and cinchonidine salts. From pharmacological investigations *in vivo* and *in vitro*, the active form of **1** was defined to be the (4*S*)-(+)-enantiomer of **1**. The 4*S* configuration of **1** was found to be important for interaction with the 1,4-dihydropyridine receptor, as is found in other 1,4-dihydropyridine enantiomers.

### Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-420 spectrophotometer. $^1$H-Nuclear magnetic resonance ($^1$H-NMR) spectra were determined on a BRUKER AC-200 spectrometer with tetramethylsilane (TMS) as an internal standard. Optical rotations were measured on a JASCO DIP-181 digital polarimeter. Extraction solvents were dried over anhydrous $MgSO_4$. Silica gel 60, 230—400 mesh (Nacalai Tesque) was used for flash column chromatography, and Kieselgel 60, $F_{254}$ (Merck) plates were used for thin layer chromatography (TLC).

**(±)-1,4-Dihydro-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylic Acid [(±)-6]** Diketene (106 ml, 1.36 mol) was added dropwise to ethylene cyanohydrin (**2**, 96.5 g, 1.36 mmol) preheated at about 80 °C at temperatures between 75 and 100 °C over 1.5 h. After the addition was completed, the mixture was stirred at 70—80 °C for 2.5 h. After dissolving the resulting mixture in 2-propanol (450 ml), *m*-nitrobenzaldehyde (**3**, 205.2 g, 1.36 mmol), methyl 3-aminocrotonate (**4**, 156.3 g, 1.36 mmol) and 2-propanol (510 ml) were added to the solution, and then refluxed for 7 h, stirred at room temperature for 11 h, and with ice-water cooling for 3 h. A precipitated solid was collected by filtration, and rinsed with 2-propanol. After drying *in vacuo* at 50 °C overnight, the compound **5** was obtained as a yellow powder (332.4 g). To a solution of **5** obtained above in acetone (1300 ml) was added 1 N NaOH (2600 ml at a time) with water cooling. After the mixture was stirred at 28 °C for 1 h, the resulting solution was diluted with water (2600 ml) and then washed with $CH_2Cl_2$ (three times). With ice-water cooling, the aqueous layer was acidified with 35% HCl to pH 1—2, and stirred for 3 h to afford a precipitated solid. The solid collected by filtration was rinsed with water and then dried *in vacuo* at 50 °C for 4 d to give the product [(±)-**6**] as a slightly yellow powder (268.9 g, 60%), mp 199—200 °C. IR (KBr): 3325, 2925, 2700, 2600, 1670, 1655, 1605, 1525, 1480, 1435, 1350 cm$^{-1}$. $^1$H-NMR [DMSO-$d_6$+$CDCl_3$ (10:1, v/v)] $\delta$: 2.29, 2.30 (each 3H, s), 3.56 (3H, s), 5.00 (1H, s), 7.45—7.65 (2H, m), 7.9—8.05 (2H, m), 8.94 (1H, s), 11.82 (1H, br s). *Anal.* Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.74; H, 4.67; N, 8.33.

**Optical Resolution of (±)-1,4-Dihydro-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylic Acid [(±)-6]** Quinidine (293.66 g, 0.91 mol) was added portionwise to a suspension of (±)-**6** (300.81 g, 0.91 mol) in *N*,*N*-dimethylformamide (DMF) (500 ml) with warming. After the addition was completed, further DMF (370 ml) was added to the mixture, and the remaining solid was completely dissolved at about 85 °C. Hot water (*ca.* 60—70 °C, 580 ml) was added portionwise to the solution, and then kept at room temperature for 53 h. The crystals formed were collected by filtration and recrystallized from DMF–water (3:2, v/v) to give the (*R*)-(−)-**6**-quinidine salt (151.4 g) as yellow needles, mp 199—200 °C, $[\alpha]_D^{20}$ +96.4° (*c*=0.50, acetone). IR (KBr): 3350, 3225, 2950, 1645, 1620, 1590, 1570, 1530, 1510, 1485, 1440, 1330 cm$^{-1}$. *Anal.* Calcd for $C_{36}H_{40}N_4O_8$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.85; H, 6.17; N, 8.46. The obtained (*R*)-(−)-**6**-quinidine salt was suspended in 0.47 N NaOH (507 ml, containing 1.03 eq of NaOH), and then washed with $CH_2Cl_2$ (three times). With ice-water cooling, the aqueous layer was acidified with 35% HCl to pH 1—2, and then stirred for 1.5 h. A precipitated solid was collected by filtration, and dried *in vacuo* at about 60 °C to afford (*R*)-(−)-**6** (72.11 g, 48%) as a slightly yellow powder, mp 169—170 °C, $[\alpha]_D^{20}$ −24.6° (*c*=0.50, acetone) [lit.[3] $[\alpha]_D^{20}$ −19.6° (*c*=0.542, acetone)]. *Anal.* Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.98; H, 4.79; N, 8.34. The mother liquor obtained after the first recrystallization was concentrated and the residue was worked up in the same way used in the case of (*R*)-(−)-**6**-quinidine salt. The obtained (*S*)-(+)-**6** (141.3 g, 0.43 mol) was treated with cinchonidine (125.2 g, 0.43 mol) in a similar manner used for the preparation of (±)-**6**-quinidine salt to give (*S*)-(+)-**6**-cinchonidine salt (144.2 g) as pale yellow fine needles, mp 188—189 °C, $[\alpha]_D^{20}$ −45.0° (*c*=0.50, MeOH). IR (KBr): 3350, 3075, 2950, 1670, 1640, 1610, 1590, 1525, 1490, 1440, 1345 cm$^{-1}$. *Anal.* Calcd for $C_{35}H_{38}N_4O_7$: C, 67.08; H, 6.11; N, 8.94. Found: C, 67.23; H, 6.21; N, 8.72. By the same work up described above, (*S*)-(+)-**6** was obtained as a slightly yellow powder (69.46 g, 46%), mp 168.5—170 °C, $[\alpha]_D^{20}$ +24.4° (*c*=0.50, acetone) [lit.[3] $[\alpha]_D^{20}$ +19.1° (*c*=0.556, acetone)]. *Anal.* Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 58.04; H, 4.85; N, 8.25.

**(4*S*)-(+)-2-[4-(4-Benzhydryl-1-piperazinyl)phenyl]ethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate [(*S*)-(+)-1] Hydrochloride** To a suspension of (*R*)-(−)-**6** (62.32 g, 0.188 mol) in $CH_2Cl_2$ (400 ml) and DMF (100 ml) was added $SOCl_2$ (22.31 g, 0.188 mol) at 5—9 °C with ice-water cooling under $N_2$ atmosphere, and then stirred for 2.5 h at the same temperature. The solution of **7** (67.76 g, 0.182 mol) in $CH_2Cl_2$ (120 ml) was added to the reaction mixture and stirred for 16 h at about 5 °C. The resulting mixture was diluted with $CH_2Cl_2$ (500 ml) and then washed with water and brine, dried, and removed. After the addition of AcOEt to the residue, the mixture was washed with 5% $K_2CO_3$ and brine, and then dried. Concentration of the solvent following chromatography on silica gel with $C_6H_6$–AcOEt (4:1, v/v) afforded (*S*)-(+)-**1** as a yellow powder (107.45 g, 83%). IR (KBr). 3325, 3025, 2950, 2800, 1680, 1645, 1610, 1520, 1485, 1450, 1430, 1345 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.30, 2.35 (each 3H, s), 2.55 (4H, br t, *J*=5 Hz), 2.82 (2H, t, *J*=7 Hz), 3.15 (4H, br t, *J*=5 Hz), 3.64 (3H, s), 4.23 (2H, t, *J*=7 Hz), 4.26 (1H, s), 5.07 (1H, s), 5.80 (1H, s), 6.80, 7.04 (4H, $A_2B_2$q, *J*=8.5 Hz), 7.1—7.6 (12H, m), 7.97 (1H, ddd, *J*=8, 2.5, 1 Hz), 8.06 (1H, t, *J*=2.5 Hz). To a solution of (*S*)-(+)-**1** (105.45 g) obtained above in $Et_2O$–$CH_2Cl_2$ (9:1, v/v) (2000 ml) was added dropwise a solution of hydrogen chloride in DME (2.45 N, 69 ml) at room temperature. After the addition was completed, the mixture was stirred at room temperature for 40 min. A precipitated solid was collected by filtration, which was

rinsed with $Et_2O$, and then dried *in vacuo* to give (*S*)-(+)-**1**·HCl (83.69 g, 75%) as a yellow powder, mp 143.5—147 °C, $[\alpha]_D^{20}$ +31.0° (*c*=0.50, acetone). IR (KBr): 3375, 3050, 2925, 2550, 1690, 1610, 1520, 1485, 1455, 1435, 1350 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.25, 2.36 (each 3H, s), 2.82 (2H, t, *J*=6.5 Hz), 3.0—3.2 (2H, br), 3.35—3.6 (4H, br), 3.64 (3H, s), 3.75—4.05 (2H, br), 4.24 (2H, t, *J*=6.5 Hz), 4.88 (1H, br d, *J*=7 Hz), 5.06 (1H, s), 6.42 (1H, s), 6.76, 7.00 (4H, $A_2B_2q$, *J*=8 Hz), 7.2—7.65 (8H, m), 7.8—8.1 (6H, m), 13.10 (1H, br s). *Anal.* Calcd for $C_{41}H_{42}N_4O_6$·HCl: C, 68.09; H, 5.99; N, 7.75. Found: C, 68.43; H, 5.83; N, 7.65.

**(4*R*)-(−)-2-[4-(4-Benzhydryl-1-piperazinyl)phenyl]ethyl Methyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate [(*R*)-(−)-1] Hydrochloride** The compound (*R*)-(−)-**1**·HCl was prepared from (*S*)-(+)-**6** by the same method employed for the synthesis of (*S*)-(+)-**1**·HCl; yield 59%, mp 145—149 °C, $[\alpha]_D^{20}$ −31.4° (*c*=0.50, acetone). *Anal.* Calcd for $C_{41}H_{42}N_4O_6$·HCl: C, 68.09; H, 5.99; N, 7.75. Found: C, 68.07; H, 5.85; N, 7.74.

**Biological Tests** Antihypertensive Activity[11]: The experiments were performed in groups of 3—6 male SHR. SBP was measured in a conscious state by a tail cuff plethysmographic method with an electrosphygmomanometer (PS-200A, Riken-Kaihatsu) at 0, 1, 2, 4 and 7 h after oral administration. The test compounds were prepared as follows: A compound was dissolved in EtOH (0.3 ml) and Tween 80 (0.1 ml) and then diluted with distilled water for the volume of administration to be 10 ml/kg. Antihypertensive effects are shown as reductions in SBP (%) from 0 h values.

**Receptor Binding Assay** Rat cardiac membrane for the assay was prepared by the same method reported by Ishii *et al.*[12]

To a solution of a test compound in 0.5 ml of 50 mM Tris buffer (pH 7.4) containing 0.1% albumin was added 0.05 ml of [$^3$H]nimodipine (4.729 TBq/mmol) in 10% EtOH (160000 dpm) and 0.5 ml of cardiac membrane homogenate. After incubation at 25 °C for 3 h in the dark, the incubation mixture was filtered under vacuum through a glass fiber filter (Whatman GF/F), and washed twice with 1 ml of 50 mM Tris buffer (pH 7.4) which was used for washing the test tube, and three times with another 5 ml of Tris buffer (pH 7.4). After the addition of 2 ml of Soluene-350 (Packard) to the cardiac membrane homogenate, and standing overnight, 13 ml of Hionic-Fluor was added to the mixture, and kept in a cool and dark place for 24 h. Subsequently, the radio activity was measured by liquid scintillation counter (Tri-carb Model 4640CD, Packard). Non-specific binding was determined by the result of measurement in the presence of 100 ng/ml of (±)-**1**.

**References and Notes**


1) A. Ashimori, T. Ono, Y. Inoue, S. Morimoto, M. Eda, T. Uchida, Y. Ohtaki, Y. Fujino, H. Kido, Y. Ogura, C. Fukaya, M. Watanabe, and K. Yokoyama, *Chem. Pharm. Bull.*, **39**, 91 (1991).
2) R. Towart, E. Wehinger, and H. Meyer, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **317**, 183 (1981).
3) T. Shibanuma, M. Iwanami, K. Okuda, T. Takenaka, and M. Murakami, *Chem. Pharm. Bull.*, **28**, 2809 (1980).
4) T. Takenaka, I. Miyazaki, M. Asano, S. Higuchi, and H. Maeno, *Jpn. J. Pharmacol.*, **32**, 665 (1982).
5) R. Towart, E. Wehinger, H. Meyer, and S. Kazda, *Arzneim.-Forsch.*, **32**, 338 (1982).
6) T. Tamazawa, H. Arima, T. Kojima, Y. Isomura, M. Okada, S. Fujita, T. Furuya, T. Takenaka, O. Inagaki, and M. Terai, *J. Med. Chem.*, **29**, 2504 (1986).
7) K. Muto, T. Kuroda, H. Kawato, A. Karasawa, K. Kubo, and N. Nakamizo, *Arzneim.-Forsch.*, **38**, 1662 (1988).
8) M. Kajino, T. Wada, Y. Nagai, A. Nagaoka, and K. Meguro, *Chem. Pharm. Bull.*, **37**, 2225 (1989).
9) G. Genain, Eur. Patent 273349 (1988) [*Chem. Abstr.*, **109**, 190260*z* (1988)].
10) E. Wehinger and F. Bossert, Ger. Patent 2847237 (1980) [*Chem. Abstr.*, **93**, 150124*c* (1980)].
11) D. Pruneau and F. Roy, *Arzneim.-Forsch.*, **37**, 416 (1987).
12) A. Ishii, K. Nishida, T. Oka, and N. Nakamizo, *Arzneim.-Forsch.*, **38**, 1733 (1988).