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Synthesis of Novel 2-Chloro-1,4-dihydropyridines by Chlorination of 2-Hydroxy-1,4-dihydropyridines with Phosphorus Oxychloride

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Novel 2-chloro-1,4-dihydropyridine derivatives were synthesized by chlorination of 2-hydroxy-1,4-dihydropyridines with $POCl_3$. The dihydropyridines chlorinated at position 2 exhibited more potent vasodilative and hypotensive activities than the dihydropyridines (nicardipine and nitrendipine) with a methyl group at position 2.

Keywords 1,4-dihydropyridine; phosphorus oxychloride; chlorination; calcium antagonist; 2-chloro-1,4-dihydropyridine; 2-hydroxy-1,4-dihydropyridine; antihypertension

Generally, chlorinations of dihydroheterocycles with phosphorus oxychloride ($POCl_3$) give oxidized chloroheterocycles but not chloro-dihydroheterocycles. For instance, $POCl_3$ chlorination of dihydropyrazinones A or a dihydropyridazinone B afforded chloropyrazines C or a chloropyridazine D, respectively.[1] Folkers and Johnson[2] reported that chlorination of dihydropyrimidines E with $POCl_3$ did not yield the desired dihydropyrimidine derivatives F (Chart 1).

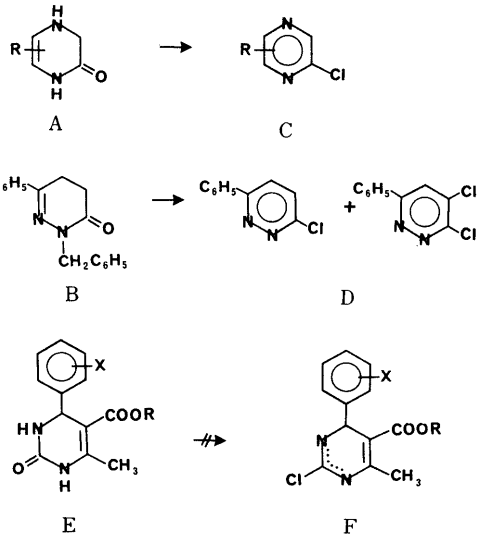


Chart 1

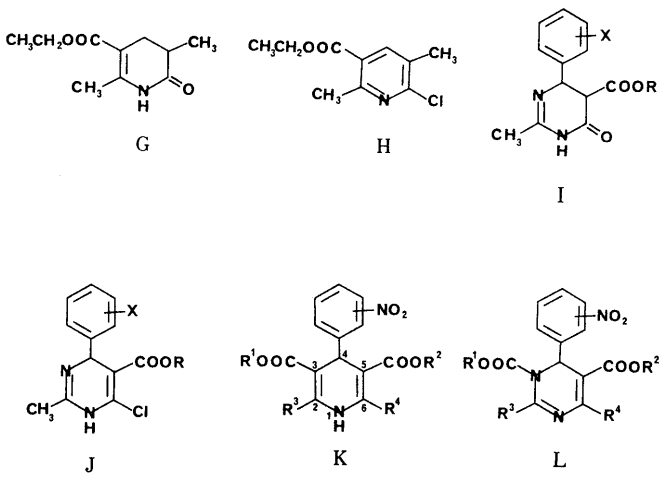


Chart 2

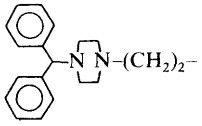
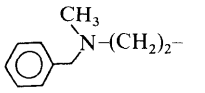
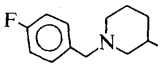
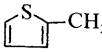
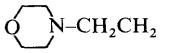
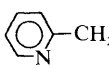
Recently, Doehner[3] reported that the chlorination of the dihydropyridine G with $POCl_3$ afforded the chloropyridine derivative H due to spontaneous air oxidation or the successive reactions of chlorination and dehydrochlorination. However, we[4] reported the first successful chlorination of dihydropyrimidinones I with $POCl_3$ to yield chloro-dihydropyrimidines J. Therefore, we investigated the applicability of the method to dihydropyridine synthesis, despite the unsuccessful results with the dihydropyridine G described above, which may have been due to the substituents on the dihydropyridone ring. Namely, when an electron withdrawing group is situated at the β carbon of the enamine moiety of the chlorinated product, the molecule should be stable, but in the case of an electron donating group (methyl group in compound G) the dihydro form should be unstable, so that air oxidation should easily occur (Chart 2).

Since 1967, much attention has been paid to the synthesis of the 1,4-dihydropyridine derivatives K which are calcium antagonists in the cardiovascular system.[5] A calcium antagonist selectively blocks the calcium channel in the smooth muscle and the cardiac muscle. Therefore, it is effective against hypertension and angina pectoris.[6] A number of pharmaceutical companies synthesized a variety of derivatives K in search of compounds with more potent activity and longer duration of action. The most common substituents on the dihydropyridine skeleton are 2,6-dimethyl, 4-substituted phenyl, and 3,5-diester groups. In other cases, R^3 can be amino, substituted amino, cyano, higher alkyl, alkoxymethyl, or hydroxymethyl group, while R^4 is a lower alkyl group (usually a methyl group).

In the present paper, we wish to report the facile synthesis of new 2-chloro-1,4-dihydropyridine derivatives **3**, which exhibit more potent calcium antagonistic activity and longer duration of action than nifedipine[7] (o-NO_2, $R^1=R^2=R^3=R^4=Me$), nicardipine[8] (m-NO_2, $R^1=CH_2CH_2N(CH_3)CH_2C_6H_5$, $R^2=R^3=R^4=Me$), nitrendipine[9] (m-NO_2, $R^1=Et$, $R^2=R^3=R^4=Me$) and so on.

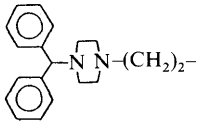
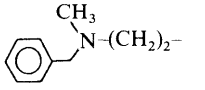
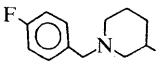
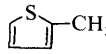
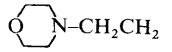
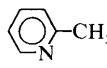
The reason why we chose a chlorine arom instead of a methyl group at position 2 was as follows. Firstly, the methyl group and the chlorine atom seem to have approximately the same size. Secondly, chlorine atom cannot be metabolized, whereas the methyl group can be oxidized to a hydroxymethyl group, whose γ-lactonization with the ester group results in loss of activity. Thirdly, the electron density of the enamino double bond should be changed by replacement of the methyl group with a chlorine atom.

TABLE I. Hydroxy 1,4-Dihydropyridines **1**

Compd.	X	R^1	R^2	Yield (%)	Method
a	*m*-NO_2	Me	Me	95	A-a, b
b	*o*-NO_2	Me	Me	24	B-a
c	*m*-NO_2		Me	94	A-a
d	*m*-NO_2		Me	62	A-a
e	*m*-NO_2		Me	75	A-a
f	*m*-NO_2	*n*-C_7H_{15}	Me	62	A-a
g	*m*-NO_2	iso-Pr	Me	88	A-a
h	*m*-NO_2		Me	50	A-a
i	*m*-NO_2	$MeOCH_2CH_2$	Me	98	A-a
j	*m*-NO_2		Me	26	B-b
k	*o*-NO_2		Et	51	A-b
l	*m*-NO_2		Me	85	A-a
m	*m*-NO_2	Me	Et	80	A-a

Methods: A-a, 1) EtOH or MeOH reflux, 2) Et_3N–EtOH or MeOH reflux; A-b, 1) EtOH or MeOH reflux, 2) K_2CO_3–DMF, 80 °C; B-a, iso-PrOH reflux; B-b, Et_3N–iso-PrOH reflux.

TABLE II. Chloro 1,4-Dihydropyridines **3**

Compd.	X	R^1	R^2	Yield (%)
a	*m*-NO_2	Me	Me	44
b	*o*-NO_2	Me	Me	6
c	*m*-NO_2		Me	52
d	*m*-NO_2		Me	14
e	*m*-NO_2		Me	51
f	*m*-NO_2	*n*-C_7H_{15}	Me	30
g	*m*-NO_2	iso-Pr	Me	11
h	*m*-NO_2		Me	5
i	*m*-NO_2	$MeOCH_2CH_2$	Me	2
j	*m*-NO_2		Me	9
k	*o*-NO_2		Et	16
l	*m*-NO_2		Me	0

Therefore, it was expected that the compound might exhibit different pharmacological activity and longer duration of action.

Hence, we carried out cyclization reactions of dialkyl benzylidenemalonates **5** with 3-aminocrotonates **6**, followed by chlorination reactions of the resulting 2-hydroxy-1,4-dihydropyridines **1**.

Thus, a solution of dimethyl 3-nitrobenzylidenemalonate **5** and methyl 3-aminocrotonate **6** in anhydrous MeOH was heated under reflux for 5 h to afford **2a**. This was dissolved in MeOH–Et_3N and refluxed for 16 h to give hydroxy 1,4-dihydropyridine **1a**. In most cases, compound **1** could be prepared more conveniently without isolation of **2**. However, in this case [Method A-a] triethylamine must be added after Michael addition is completed, otherwise the reaction proceeds to give the desired compound **1** contaminated with undefined by-products. Alternatively [Method A-b], ring formation of **2** could also be achieved in K_2CO_3–dimethylformamide (DMF) at 80 °C for several hours. However, in the case of starting materials bearing an *o*-nitrophenyl group, steric hindrance prevented Michael addition. Without any base, direct ring formation could not be completely achieved in MeOH or EtOH, yielding intermediate **2** with a trace of compound **1**. However, the use of 2-propanol afforded compound **1b** in low yield after 5 d

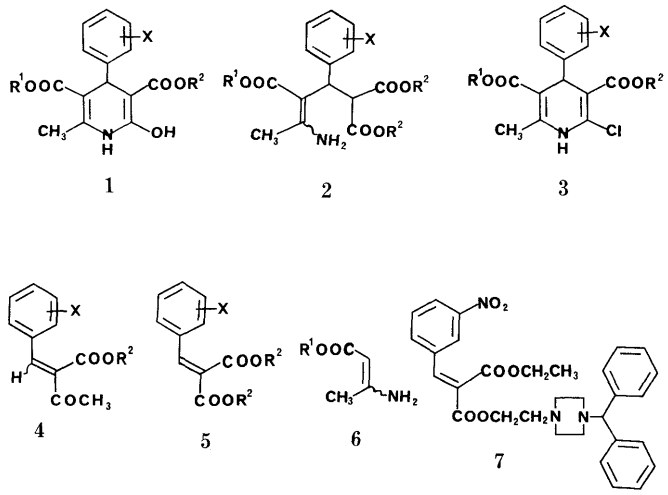


Chart 3

[Method B-a]. When triethylamine was added to the reaction mixture after Michael addition was completed, the direct ring formation in 2-propanol proceeded overnight to yield **1j** [Method B-b]. Thus, a series of 2-hydroxy 1,4-dihydropyridines **1** were obtained as shown in Table I. Their chemical structures were supported by the proton

TABLE III. Vasodilative Effects of Dihydropyridines on Vertebral Vascular Bed in Anesthetized Dogs

	3a	3b	3c	3d	3e	3f	3g	3h	Nifedipine	Nicardipine	Nitrendipine
ED_{30}	1.2	0.59	3.3	3.3	2.8	2.2	0.28	0.2	0.5	3.0	1.2
$T_{1/2}$	3.1	1.4	30	17	32	21	10.6	7.2	2.5	5.6	7.4

ED_{30} = Dose that lowered vascular resistance to 30% of the control value (μg/kg; administered intravenously). $T_{1/2}$ = Time to 50% recovery (min).

nuclear magnetic resonance (^{1}H-NMR) spectra; the methine proton at position 4 was observed as a broad singlet between δ 4.66 and 4.93 (*m*-NO_2) or in lower field at δ *ca.* 5.18 (*o*-NO_2).

Since most of compounds **1** obtained by this procedure have a larger ester moiety ($COOR^1$) on the side opposite to the hydroxy group, we next tried to obtain a different type of dihydropyridines which have the larger ester group ($COOR^2$) on the same side as the hydroxy group. For this purpose, the reaction of 2-[4-(benzhydryl)piperazin-1-yl]ethyl ethyl 3-nitrobenzylidenemalonate **7** and methyl 3-aminocrotonate **6** in 2-propanol was undertaken. However, the amino group of the Michael donor did not attack the ethyl ester carbonyl carbon but the larger alkyl ester carbonyl carbon to give the undesired dihydropyridine **1m** and 2-[4-(benzhydryl)piperazin-1-yl]ethanol. The desired type of dihydropyridine derivatives has not been obtained to data (Tables I and II).

Next, $POCl_3$ chlorination of hydroxy dihydropyridines **1** was investigated. A solution of **1** in $POCl_3$ was refluxed for 3 h to provide 2-chloro-1,4-dihydropyridines **3**, whose chemical structures were clearly demonstrated by the fact that the ^{1}H-NMR signal of the methine proton at position 4 appeared as a broad singlet between δ 5.15 and 5.32 (*m*-NO_2) or in lower field (δ 5.87—5.95) (*o*-NO_2) (see Table II). Although no pyridine derivative was observed in this case, the yields of compound **3h-1** were poor, because R^2 of the ester group was sensitive to acidic phosphorus oxychloride. Most of compounds **3** prepared above were fairly stable to light and oxygen in the solid state, but in K_2CO_3 aqueous solution hydrolysis of **3** occurred to give **1**. As had been expected, the chlorinated dihydropyridines **3** showed more potent calcium antagonistic activity and a longer duration of action than nifedipine, nicardipine and nitrendipine (see Table III and the experimental section on the pharmacological procedure).

Namely, **3b**, **3g** and **3h** exhibited very potent vasodilative activity on the vertebral artery of anesthetized dogs. In addition, the actions of compounds chlorinated at position 2 (**3c**, **3d**, **3e**, **3f** and **3g**) were long-lasting. In particular, the durations of action of **3d** and **3g** were much longer than those of dihydropyridines without a chlorine atom at position 2 such as nicardipine and nitrendipine.

Therefore, these chlorinated dihydropyridines were subjected to pharmacological testing for hypotensive effect in conscious spontaneously hypertensive rats (SHR). As shown in Fig. 1, oral administrations of **3g** and nitrendipine (10 mg/kg) caused a decrease in mean blood pressure and an increase in heart rate. When the peak responses were compared, the activity of **3g** was almost the same as that of nitrendipine. The hypotensive action of nitrendipine reached the maximum immediately after administration, while that of **3g** reached the maximum 2 h after administration. In other words, the onset of hypotensive action in the case of the chloro dihydropyridine was slower than that in the case of the 2,6-dimethyl dihydropyridine.

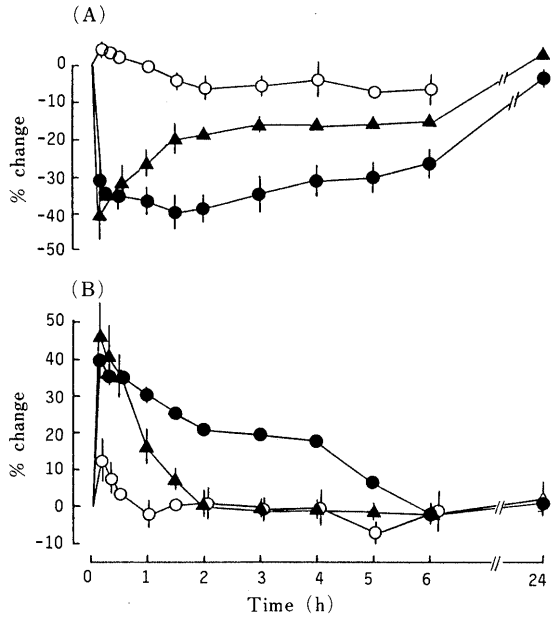


Fig. 1. Effects of 3 g and Nitrendipine on Mean Blood Pressure (A) and Heart Rate (B) in Conscious Spontaneously Hypertensive Rats

—○—, control (10% EtOH), $n=5$; —●—, comp. **3g**, 10 mg/kg, *p.o.*, $n=4$; —▲—, nitrendipine, 10 mg/kg, *p.o.*, $n=5$.

These results strongly suggest that the vasodilative and hypotensive actions of dihydropyridines chlorinated at position 2 could be more potent and longer-lasting than those of usual dihydropyridines with a methyl group at position 2.

Experimental

General Methods Melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded with a JEOL GX-270 (270 MHz) spectrometer in $CDCl_3$ solution with tetramethylsilane (Me_4Si) as an internal standard. IR spectra were recorded on a Hitachi 260-10 infrared spectrometer in $CHCl_3$ and high-resolution mass spectra (HRMS) were obtained with a JEOL JMS-01SG-2 spectrometer with an ionizing voltage of 70 eV. Column chromatography was performed on Merck silica gel (70—230 mesh). Typical procedures for the preparation of the dihydropyridines **1** and **3** are given below.

2-Hydroxy-3,5-bis(methoxycarbonyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine (1a) Method A: An aqueous solution of 28% ammonium hydroxide (5 ml) was added to a stirred solution of 5.0 g of methyl acetoacetate in 20 ml of MeOH, and the mixture was refluxed for 16 h. The reaction mixture was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated to leave 4.75 g (96%) of colorless needles. A solution of 151 mg of the crystals and 318 mg of dimethyl 3-nitrobenzylidenemalonate in 13 ml of anhydrous MeOH was refluxed for 4.5 h. After cooling of the reaction mixture, 285 mg of crystalline **2a** was obtained.

Method A-a: Triethylamine (1.5 ml) was added to a stirred solution of 175 mg of **2a** in 6 ml of anhydrous MeOH, and the solution was refluxed for 16 h. After evaporation of the solvents, the residue was chromatographed on SiO_2 (2% MeOH in $CHCl_3$) to afford crude crystals, which were recrystallized from $CHCl_3$–Et_2O to yield 152 mg (95%) of compound

1a.

Method A-b: Anhydrous K_2CO_3 powder (2.42 g) was added to a stirred solution of 1.33 g of **2a** in 20 ml of anhydrous DMF. The mixture was vigorously stirred at 80 °C for 2.5 h, then poured into ice-water and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to leave 1.1 g (91%) of **1a**.

2-Hydroxy-3,5-bis(methoxycarbonyl)-6-methyl-4-(2-nitrophenyl)-1,4-dihydropyridine (1b) Method B-a: A solution of 0.78 g of methyl 3-amino-2-butenoate and 1.79 g of dimethyl 2-nitrobenzylidenemalonate in 30 ml of anhydrous 2-propanol was refluxed for 5 d. After evaporation of the solvent, the residue was purified by SiO_2 column chromatography (5% MeOH in $CHCl_3$) to give 0.56 g (24%) of **1b**.

2-Hydroxy-3-methoxycarbonyl-6-methyl-4-(3-nitrophenyl)-5-[2-(2-thienyl)ethoxycarbonyl]-1,4-dihydropyridine (1j) Method B-b: Triethylamine (27 ml) was added to a stirred solution of 1.8 g of 2-(2-thienyl)-ethyl 3-amino-2-butenoate and 2.25 g of dimethyl 3-nitrobezylidenemalonate in 80 ml of 2-propanol. The solution was refluxed for 21 h, and after cooling, the solvent was evaporated off to leave the residue, which was chromatographed on SiO_2 (5% MeOH in $CHCl_3$) to give 1.0 g (26%) of compound **1j**.

1a: Pale yellow crystals, mp 150—152 °C ($CHCl_3$–Et_2O). IR cm^{-1}: 3390, 1740, 1705. ^{1}H-NMR δ: 2.47 (3H, s), 3.59 (1H, s), 3.66 (3H, s), 3.81 (3H, s), 4.79 (1H, s), 7.47—8.13 (4H, m). HRMS Calcd for $C_{16}H_{16}N_2O_7$ *m/z*: 348.3140. Found: 348.3138.

1b: Pale yellow crystals, mp 180—184 °C ($CHCl_3$–*n*-hexane). IR cm^{-1}: 3400, 1740, 1710.^{1}H-NMR δ: 2.48 (3H, s), 3.56 (3H, s), 3.82 (3H, s), 3.85 (1H, s), 5.18 (1H, s), 7.21—7.92 (4H, m). HRMS Calcd for $C_{16}H_{16}N_2O_7$ *m/z*: 348.3140. Found: 348.3142.

1c: A colorless powder. IR cm^{-1}: 3390, 1740, 1710. ^{1}H-NMR δ: 2.20—2.60 (8H, m), 2.46 (3H, s), 2.52 (2H, t, J=6 Hz), 3.56 (1H, s), 3.77 (3H, s), 4.14 (1H, s), 4.20—4.30 (2H, m), 4.76 (1H, s), 7.1—8.1 (14H, m). HRMS Calcd for $C_{34}H_{36}N_4O_7$ *m/z*: 612.6861. Found: 612.6866.

1d: A pale yellow oil. IR cm^{-1}: 3395, 1740, 1710. ^{1}H-NMR δ: 2.12 (3H, s), 2.44 (3H, s), 2.58 (2H, t, J=6 Hz), 3.42 (2H, s), 3.60 (1H, s), 3.79 (3H, s), 4.20 (2H, t, J=6 Hz), 4.80 (1H, s), 7.2—8.1 (9H, m), 8.72 (1H, s). HRMS Calcd for $C_{25}H_{27}N_3O_7$ *m/z*: 481.5080. Found: 481.5081.

1e: A pale yellow oil. As a 1 : 1 isomeric mixture; IR cm^{-1}: 3395, 1745, 1710. ^{1}H-NMR δ: 1.1—2.7 (8H, m), 2.45 and 2.46 (total 6H, each s), 3.30—3.55 (2H, m), 3.59 and 3.60 (total 2H, each s), 4.82 (1H, s), 4.80—4.95 (1H, m), 6.9—8.2 (8H, m). HRMS Calcd for $C_{27}H_{28}FN_3O_7$ *m/z*: 525.5366. Found: 525.5371.

1f: A pale yellow oil. IR cm^{-1}: 3400, 1720, 1705. ^{1}H-NMR δ: 0.85 (3H, t, J=7 Hz), 1.10—1.80 (10H, m), 2.47 (3H, s), 3.81 (3H, s), 4.05 (2H, t, J=7 Hz), 4.78 (1H, s), 7.42—8.30 (4H, m). HRMS Calcd for $C_{22}H_{28}N_2O_7$ *m/z*: 432.4757. Found: 432.4759.

1g: Pale yellow crystals, mp 152—154 °C ($CHCl_3$–*n*-hexane). IR cm^{-1}: 3390, 1740, 1700. ^{1}H-NMR δ: 1.05 (3H, s), 1.23 (3H, s), 2.45 (3H, s), 3.60 (1H, s), 3.81 (3H, s), 4.77 (1H, s), 4.8—5.1 (1H, m), 7.4—8.3 (4H, m). HRMS Calcd for $C_{18}H_{20}N_2O_7$ *m/z*: 376.3679. Found: 376.3683.

1h: A pale yellow oil. IR cm^{-1}: 3400, 1720, 1710. ^{1}H-NMR δ: 0.10—0.25 (2H, m), 0.40—0.60 (2H, m), 0.95—1.10 (1H, m), 2.48 (3H, s), 3.82 (3H, s), 3.90 (2H, d, J=7 Hz), 4.81 (1H, br s), 7.45—8.20 (4H, m). HRMS Calcd for $C_{19}H_{20}N_2O_7$ *m/z*: 388.3791. Found: 388.3789.

1i: Colorless crystals, mp 135—136 °C ($CHCl_3$–*n*-hexane). IR cm^{-1}: 3390, 1740, 1700. ^{1}H-NMR δ: 2.45 (3H, s), 3.26 (3H, s), 3.4—3.6 (2H, m), 3.60 (1H, s), 3.81 (3H, s), 4.1—4.3 (2H, m), 4.79 (1H, s), 7.4—8.2 (4H, m), 8.70 (1H, s). HRMS Calcd for $C_{18}H_{20}N_2O_8$ *m/z*: 392.3673. Found: 392.3669.

1j: A pale yellow oil. IR cm^{-1}: 3400, 1720, 1710.^{1}H-NMR δ: 2.44 (3H, s), 3.07 (2H, t, J=6 Hz), 3.80 (3H, s), 4.20—4.40 (2H, m), 4.77 (1H, s), 6.68—8.20 (7H, m). HRMS Calcd for $C_{21}H_{20}N_2O_7S$ *m/z*: 444.4654. Found: 444.4656.

1k: A pale yellow oil. IR cm^{-1}: 3400, 1720, 1705. ^{1}H-NMR δ: 1.31 (3H, t, J=7 Hz), 2.20—2.55 (6H, m), 2.49 (3H, s), 3.55 (4H, t, J=5 Hz), 4.00—4.35 (4H, m), 5.17 (1H, s), 7.22—8.00 (4H, m). HRMS Calcd for $C_{22}H_{27}N_3O_8$ *m/z*: 461.4739. Found: 461.4741.

1l: A colorless oil. IR cm^{-1}: 3410, 1750, 1720. ^{1}H-NMR δ: 2.36 (3H, s), 3.02 (2H, t, J=6 Hz), 3.52 (1H, s), 3.78 (3H, s), 4.49 (2H, t, J=6 Hz), 4.66 (1H, s), 6.9—8.5 (8H, m), 8.72 (1H, brs). HRMS Calcd for $C_{22}H_{21}N_3O_7$ *m/z*: 439.4271. Found: 439.4273.

5-[2-(4-Benzhydrylpiperazin-1-yl)ethoxycarbonyl]-2-chloro-3-methoxycarbonyl-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine (3c) A solution of 390 mg of **1c** in 5 ml of $POCl_3$ was refluxed for 3 h. Excess $POCl_3$ was removed thoroughly under reduced pressure to leave the residue, which was diluted with saturated aqueous K_2CO_3 solution and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to leave the residue, which was chromatographed on SiO_2 (1% MeOH in $CHCl_3$) to give the crude crystals. Recrystallization from *n*-hexane–$CHCl_3$–iso-Pr_2O afforded 210 mg (57%) of **3c**.

3a: Pale yellow crystals, mp 225—228 °C ($CHCl_3$–*n*-hexane). IR cm^{-1}: 3420, 1700. ^{1}H-NMR δ: 2.40 (3H, s), 3.66 (3H, s), 3.70 (3H, s), 5.25 (1H, s), 6.08 (1H, s), 7.39-8.12 (4H, m). HRMS Calcd for $C_{27}H_{27}ClFN_3O_6$ *m/z*: 574.0566. Found: 574.0561.

3b: Pale yellow crystals, mp 162—164 °C ($CHCl_3$–*n*-hexane). IR cm^{-1}: 3425, 1700. ^{1}H-NMR δ: 2.36 (3H, s), 3.60 (3H, s), 3.65 (3H, s), 5.87 (1H, s), 5.95 (1H, s), 7.28—7.73 (4H, m). HRMS Calcd for $C_{16}H_{15}ClN_2O_6$ *m/z*: 574.0566. Found: 574.0570.

3c: Pale yellow crystals, mp 131—134 °C ($CHCl_3$–*n*-hexane– iso-Pr_2O). IR cm^{-1}: 3425, 1700. ^{1}H-NMR δ: 2.3—2.6 (8H, m), 2.38 (3H, s), 2.5—2.7 (2H, m), 3.67 (3H, s), 4.1—4.2 (2H, m), 4.19 (1H, s), 5.23 (1H, s), 6.07 (1H, s), 7.1—8.1 (14H, m). HRMS Calcd for $C_{34}H_{35}ClN_4O_6$ *m/z*: 631.1318. Found: 631.1324.

3d: A pale yellow oil. IR cm^{-1}: 3425, 1700. ^{1}H-NMR δ: 2.20 (3H, s), 2.37 (3H, s), 2.5—2.7 (2H, m), 3.50 (1H, s), 3.69 (3H, s), 4.18 (2H, t, J=6 Hz), 5.27 (1H, s), 6.27 (1H, s), 7.2—8.2 (9H, m). HRMS Calcd for $C_{25}H_{26}ClN_3O_6$ *m/z*: 499.9537. Found: 499.9532.

3e: A colorless oil. As a 1 : 1 isomeric mixture. IR cm^{-1}: 3450, 1700. ^{1}H-NMR δ: 1.2—2.8 (8H, m), 2.36 (3H, s), 3.30—3.65 (2H, m), 3.71 and 3.72 (total 6H, each s), 4.70—4.90 (1H, m), 5.23 (1H, s), 6.37 (1H, s), 6.90—8.20 (8H, m). HRMS Calcd for $C_{27}H_{27}ClFN_{36}$ *m/z*: 543.9823. Found: 543.9819.

3f: A pale yellow powder. IR cm^{-1}: 3400, 1700, 1695. ^{1}H-NMR δ: 0.87 (3H, t, J=7 Hz), 1.15—1.75 (10H, m), 2.40 (3H, s), 3.71 (3H, s), 3.98—4.24 (2H, m), 5.25 (1H, s), 7.42 (1H, t, J=8 Hz), 7.65 (1H, d, J=8 Hz), 8.14 (1H, d, J=8 Hz), 8.14 (1H, s). HRMS Calcd for $C_{22}H_{27}ClN_2O_6$ *m/z*: 450.9214. Found: 450.9220.

3g: A pale yellow oil. IR cm^{-1}: 3430, 1700. ^{1}H-NMR δ: 1.10 (3H, d, J=6.5 Hz), 1.26 (3H, d, J=6.5 Hz), 2.38 (3H, s), 3.70 (3H, s), 4.97 (1H, quintet, J=6 Hz), 5.22 (1H, s), 6.30 (1H, s), 7.4—8.1 (4H, m). HRMS Calcd for $C_{18}H_{19}ClN_2O_6$ *m/z*: 394.8136. Found: 394.8142.

3h: A pale yellow oil. IR cm^{-1}: 3440, 1715, 1705. ^{1}H-NMR δ: 0.10—0.30 (2H, m), 0.50—0.60 (2H, m), 1.00—1.18 (1H, m), 2.40 (3H, s), 3.70 (3H, s), 5.27 (1H, s), 7.38—8.25 (4H, m). HRMS Calcd for $C_{19}H_{19}ClN_2O_6$ *m/z*: 654.1867. Found: 654.1866.

3i: A pale yellow oil. IR cm^{-1}: 3440, 1710. ^{1}H-NMR δ: 2.39 (3H, s), 3.34 (3H, s), 3.5—3.6 (2H, m), 3.69 (3H, s), 4.1—4.3 (2H, m), 5.26 (1H, s), 6.31 (1H, s), 7.3—8.2 (4H, m). HRMS Calcd for $C_{18}H_{19}ClN_2O_7$ *m/z*: 410.8130. Found: 410.8135.

3j: A pale yellow oil. IR cm^{-1}: 3430, 1710, 1700. ^{1}H-NMR δ: 2.36 (3H, s), 3.12 (2H, t, J=6 Hz), 3.71 (3H, s), 4.31 (2H, t, J=6 Hz), 5.24 (1H, s), 6.76—8.20 (7H, m). HRMS Calcd for $C_{21}H_{19}ClN_2O_6S$ *m/z*: 462.9111. Found: 462.9108.

3k: A pale yellow oil. IR cm^{-1}: 3430, 1705, 1700. ^{1}H-NMR δ: 1.19 (3H, t, J=7 Hz), 2.35 (3H, s), 2.20—2.60 (6H, m), 3.61 (4H, t, J=5 Hz), 4.00—4.30 (4H, m), 5.95 (1H, s), 7.25—7.80 (4H, m). HRMS Calcd for $C_{22}H_{26}ClN_3O_7$ *m/z*: 479.9196. Found: 479.9201.

Vasodilative Effect on Vertebral Artery Blood Flow in Anesthetized Dogs Mongrel dogs weighing 7—15 kg of either sex were anesthetized with an intravenous (i.v.) or intraperitoneal injection (i.p.) of 30 mg/kg of sodium thiopental followed by a combination of urethane 400 mg/kg (i.v.) and α-chloralose 60 mg/kg (i.v.). The anesthetized animal was artificially ventilated with a positive pressure respirator after tracheal intubation. After left thoracotomy, the vertebral artery was exposed and blood flow was measured with an implantable flow probe connected to an electromagnetic flow meter. Mean arterial blood pressure was measured from the right femoral artery. Vascular resistance of the vertebral artery was computed from the mean arterial blood pressure and mean vertebral blood flow, and was recorded continuously on a polygraph. The test compounds were dissolved in ethanol and the solution was administered intravenously into the cannulated femoral vein in a volume of 0.05 ml/kg. The dose required to decrease vertebral vascular resistance by 30% (ED_{30}) and the half recovery time ($T_{1/2}$) of the vascular resistance decrease at ED_{30} were determined.

Hypotensive Effect in Conscious Spontaneously Hypertensive Rats Male spontaneously hypertensive rats, more than 15 weeks of age, were used. More than one day before the experiment, an indwelling catheter was inserted into the distal aorta *via* the left femoral artery for blood pressure measurement under light ether anesthesia. The catheter was filled with heparin sodium solution (300 U/ml) to prevent blood coagulation. About 1 h before the experiment, each animal was transferred into

an individual translucent cylindrical box. Systemic blood pressure was measured from the previously implanted catheter with the aid of a pressure transducer, and heart rate, with a cardiotachometer, triggered by the blood pressure pulse under conscious and unrestrained conditions. The test compounds were dissolved in 10% ethanol and the solution was administered orally.

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