*Arch. Pharm. Res.* **13**(3), 240-245

# Synthesis of 1,4-Dihydropyridine Derivatives with Vasodilating Activities (I)

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*(Received April 18, 1990)*

**Abstract**□Asymmetric 2,6-dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylate with [N-(3,4-methylenedioxybenzyl)-N-methyl] aminoethyl group as the ester moiety and related 1,4-dihydropyridine derivatives were prepared and tested for the effects on vascular smooth muscles. 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[N-(3', 4'-methylenedioxybenzyl)-N-methyl] aminoethyl ester 5-methyl ester (**11**) and 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[N-2',3'-methylenedioxybenzyl)-N-methyl] aminoethyl ester 5-ethyl ester (**15**) showed potent vasodilating activities. $IC_{50}$ ($10^{-8}$ M) was 2.6 and 2.7 for **11** and **15**, compared with 3.5 for nicardipine.

**Keywords**□1,4-Dihydropyridines, vasodilating activities, nicardipine.

Since nifedipine (**1**) was introduced for the treatment of angina pectoris and hypertension[1,2], a number of symmetrically and asymmetrically substituted ester derivatives of 1,4-dihydropyridine have been synthesized and developed[3,4]. In a recent study the pharmacological activities of the asymmetrically substituted 3-nitrophenyl derivatives were shown to be superior to those of the corresponding symmetrically substituted derivatives in many cases[5,6]. At present, nicardipine (**2**), methyl 2-(N-benzyl-N-methyl amino) ethyl-2,6-dimethyl-1,4-dihydropyridine-4-(3'-nitrophenyl)-3,5-dicarboxylate, is widely used for the treatment of celebral ischemia and hypertension[7]. Thus, as a part of our continuing effort to develop novel 1,4-dihydropyridine compounds, we tried to modify the structure of nicardipine.

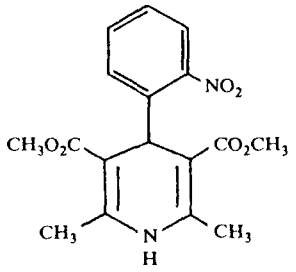
In this paper we report the modification of (N-benzyl-N-methylamino ethanol and the synthesis of new 1,4-dihydropyridines.

One of the modified alcohols, 2-[N-methyl-N-(3,4-methylenedioxybenzyl) amino] ethanol (**6a**), was prepared as follows. Piperonal (**3a**) was reacted with methylamine to give Schiff base **4a**. **4a** was hydrogenated with Pd on C to afford N-(3,4-methylenedioxybenzyl)-N-methylamine (**5a**). **5a** was reacted with ethylene bromohydrin to give **6a** in 54% yield (Scheme 1).

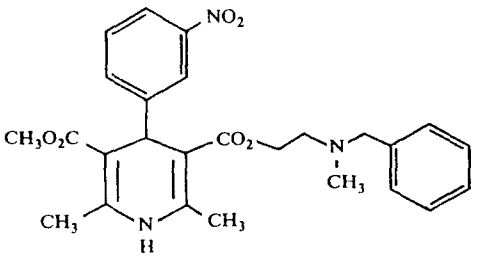
Using the same procedure, the alcohol **6b**,**6c**,**6d**,**6e** and **6f** were obtained in moderate to good yield as shown in Fig. 2.

2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[N-(3',4'-methylenedioxybenzyl)-N-methyl] amino ethyl ester 5-methyl ester (**11**) was prepared in 63.2% yield from 3-(2-hydroxyethyl) 5-methyl 1,4-dihydropyridine-2,6-dimethyl-4-(3'-nitrophenyl)-3,5-dicarboxylate (**7**) and **5a** through mesylate **8**.

As the same procedure, **12** was obtained in 18%

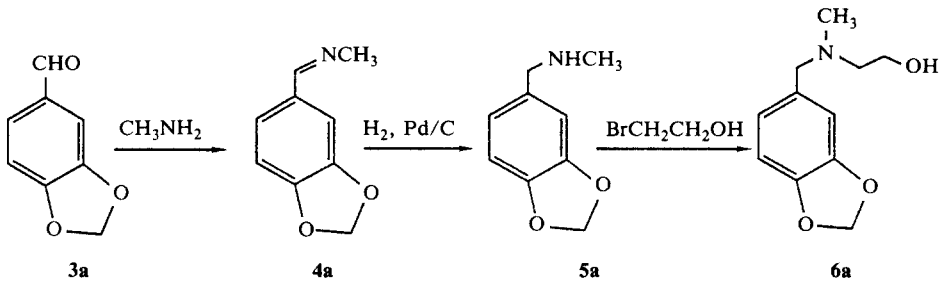



**1**



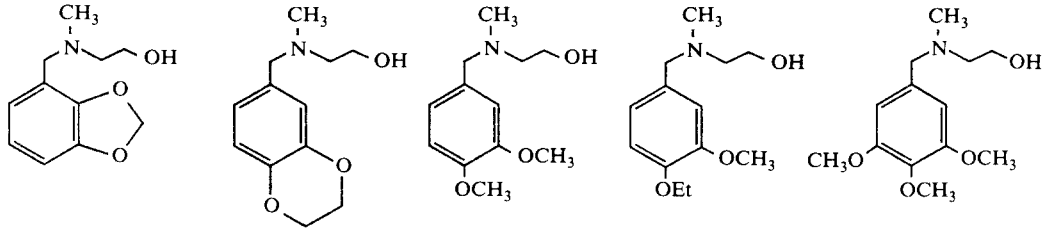

**2**

**Fig. 1.**




**3a** **4a** **5a** **6a**

**Scheme 1**




**6b** **6c** **6d** **6e** **6f**

**Fig. 2.**

yield.

On the other hand, 2,6-dimethyl-4-(2',3'-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[N-(3',4'-methylenedioxybenzyl)-N-methyl] amino ethyl ester 5-methyl ester (**13**) was prepared in 26.3% from 2,6-dimethyl-4-(2',3'-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 5-methyl ester (**9**) and **6a** via acid chloride **10**.

The same synthetic application gave **14,15,16,17,18** and **19** in moderate to good yield as indicated in Scheme 2.

In this studies, we examined the effects of compound **11-19** on the vascular smooth muscles in *in-vitro* preparations of experimental animals. Two compound **11** and **15** showed potent vasodilating activities. $IC_{50}$ ($10^{-8}$ M) was 2.6 and 2.7 for **11** and **15**, compared with 3.5 for nicardipine (Table I).

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Capillary melting point apparatus and are uncorrected. The pmr spectra were recorded on a Hitachi R-600 (60 MHz). Chemical shifts are reported in ppm from TMS as an internal standard. The IR spectra were recorded with a Shimazu IR 435 spectrometer.

### *N-(3,4-methylenedioxybenzyl)-N-methylamine (5a)*

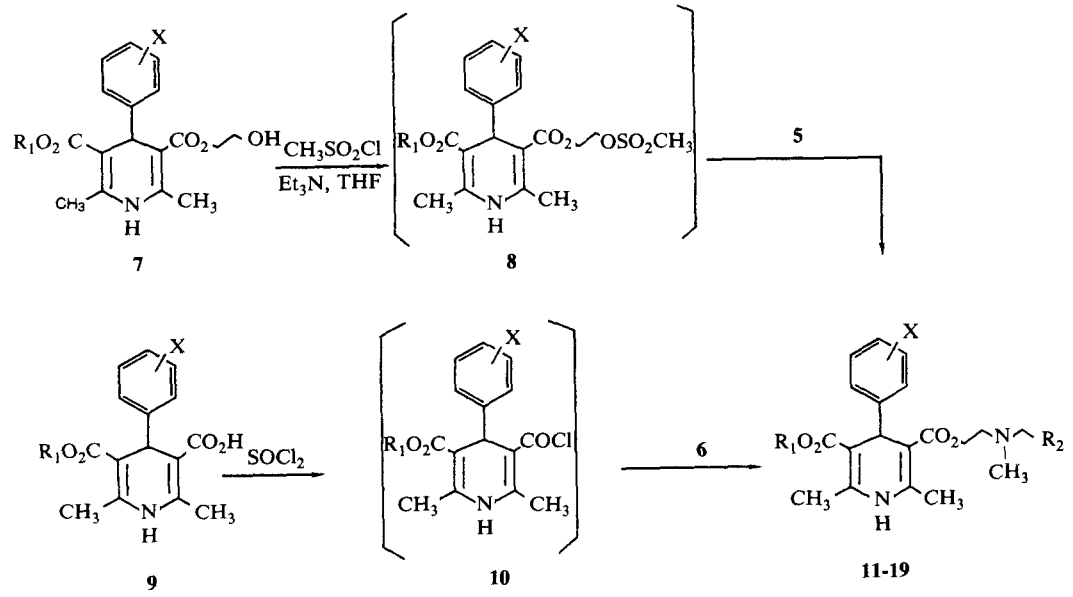
To a solution of piperonal (**3**, 22.5g) in EtOH (30 m*l*) was added 40% aqueous $CH_3NH_2$ (30 m*l*). The reaction mixture was heated at 70°C for 1 hr and stirred overnight at room temperature. The solvent was evaporated in vacuo and the residue was extracted with $Et_2O$. The organic layer was dried over anhydrous $MgSO_4$ and filterd. After the solvent was evaporated, the residue was hydrogenated with Pd on C. The crude product was distilled in vacuo to give **5a** (16.2g, 65.5%) as an oil.

NMR ($CDCl_3$): $\delta$ 1.25 (s, 1H, NH), 2.42 (s, 3H, N-$CH_3$), 3.65 (s, 2H, $ArCH_2N$), 5.91 (s, 2H, $OCH_2O$), 6.7-7.9 (m, 3H, Ar)

### *2-[N-methyl-N-(3,4-methylenedioxybenzyl) amino] ethanol (6a)*

To a solution of N-(3,4-methylenedioxybenzyl)-N-methylamine (5a, 7g) in toluene (50 m*l*) was added $K_2CO_3$ (6g), KI (7g) and ethylene bromohydrine (3.5 m*l*) at room temperature. The reaction mixture was heated to reflux for 16 hrs, and cooled.

The mixture was washed with water and extracted with EtOAc. The solvent was evaporated in vacuo to afford oily residue (5.2g), which was purified on silica gel column (EtOAc/n-Hexane = 1:1, thereafter EtO-



Scheme 2

Ac/$CH_3OH$ = 4:1) to give **6a** (5.3g, 54%) as an oily product.

NMR ($CDCl_3$): 2.23 (s, 3H, N-$CH_3$), 2.48 (t, 2H, $NCH_2$), 3.51 (t, 2H, $CH_2OH$), 3.58 (s, 2H, $ArCH_2N$), 5.94 (s, 2H, $OCH_2O$), 6.82 (m, 3H, Ar)

***2-[N-methyl-N-(2,3-methylenedioxybenzyl) amino] ethanol (6b)***

Yield: 34% (liq.)

NMR ($CDCl_3$): $\delta$ 2.26 (s, 3H, $NCH_3$), 2.4-3.0 (m, 4H, $NCH_2CH_2OH$), 3.56 (s, 2H, $ArCH_2N$), 5.92 (s, 2H, $OCH_2O$), 6.76 (s, 3H, Ar)

***2-[N-methyl-N-(3,4-ethylenedioxybenzyl) amino] ethanol (6c)***

Yield: 78% (liq.)

NMR ($CDCl_3$): $\delta$ 2.21 (s, 3H, $NCH_3$), 2.50 (t, 2H, $NCH_2$), 3.50 (m, 4H, $ArCH_2N$, $CH_2OH$), 4.20 (s, 4H, $OCH_2CH_2O$), 6.70 (s, 3H, Ar)

***2-[N-methyl-N-(3,4-dimethoxybenzyl) amino] ethanol (6d)***

Yield: 55.6% (liq.)

NMR ($CDCl_3$): $\delta$ 2.21 (s, 3H, $NCH_3$), 2.58 (t, 2H, $NCH_2$), 3.49 (s, 2H, $ArCH_2N$), 3.62 (t, 2H, $CH_2OH$), 3.90 (s, 6H, 2x$OCH_3$), 6.80 (m, 3H, Ar)

***2-[N-methyl-N-(3-methoxy-4-ethoxybenzyl) amino] ethanol (6e)***

Yield: 61% (liq.)

NMR ($CDCl_3$): $\delta$ 1.5 (t, 3H, $OCH_2CH_3$), 2.2 (s, 3H, $NCH_3$), 2.6 (t, 2H, $NCH_2$), 3.5 (t, 2H, $CH_2OH$), 3.8 (s, 2H, $ArCH_2N$), 4.2 (q, 5H, $OCH_3$, $OCH_2CH_3$), 6.8 (s, 3H, Ar)

***2-[N-methyl-N-(3,4,5-trimethoxybenzyl) amino] ethanol (6f)***

Yield: 61% (liq.)

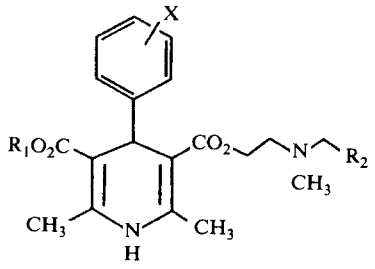
NMR ($CDCl_3$): $\delta$ 2.3 (s, 3H, $NCH_3$), 2.7 (t, 2H, $NCH_2$), 3.6 (m, 4H, $ArCH_2N$, $CH_2OH$) 3.9 (s, 9H, 3x$OCH_3$), 6.6 (s, 2H, Ar)

***2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[N-(3',4'-methylenedioxybenzyl)-N-methyl]aminoethyl ester 5-methyl ester · HCl (11)[8]***

To a solution of 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarhoxylic acid 3-(2-hydroxyethyl) ester 5-methyl ester (**7**, 5g) and TEA (5 m*l*) in THF (50 m*l*) was dropwise added methanesulfonyl chloride (3g) on an ice bath. The reaction mixture was stirred for 30 min. and then poured into cold d-HCl. The mixture was extracted with $CH_2Cl_2$. The $CH_2Cl_2$ layer was washed with water, dried over $MgSO_4$, and evaporated in vacuo to give 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2-methanesulfonyl oxyethyl) ester 5-methyl ester (**8**, 6g) as pale yellow oil.

A mixture of **8** (6g), **5a** (6 m*l*) and toluene (50 m*l*) was heated to reflux for 3 hrs. The excess **5a** and to-

**Table I. Vasodilating activities of 1,4-dihydrogpyridines**



| Compound | X | $R_1$ | $R_2$ | $IC_{50}$ ($10^{-8}$ M) |
|---|---|---|---|---|
| Nicardipine | 3-$NO_2$ | Me |  | 3.5 |
| 11 | 3-$NO_2$ | Me |  | 2.6 |
| 12 | 3-$NO_2$ | Et |  | 9.2 |
| 13 | 2,3-Cl | Me |  | 16 |
| 14 | 3-$NO_2$ | Me |  | 6.7 |
| 15 | 3-$NO_2$ | Et |  | 2.7 |
| 16 | 3-$NO_2$ | Me |  | 10.1 |
| 17 | 3-$NO_2$ | Et |  | 10.6 |
| 18 | 3-$NO_2$ | Me |  | 5.9 |
| 19 | 3-$NO_2$ | Me |  | 10 |

luene were evaporated *in vacuo*. The residue was dissolved in $CH_2Cl_2$ and the solution was washed with water. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was separated on silica gel column (EtOAc/n-Hexane). The separated pale yellow oil was dissolved in IPA and the solution was treated with 3.6 N HCl/IPA solution. The mixture was evaporated in vacuo and the residual oil was triturated with $Et_2O$ and the precipitate was separated and recrystallized from acetone/$CH_3OH$.

Yield: 4.7g (63.2%), mp: 139-142°C

IR (KBr) $cm^{-1}$: 1701 (C=O), 1690 (C=O), 1526 ($NO_2$)

NMR (DMSO-$d_6$): $\delta$ 2.1 (s, 3H, $NCH_3$), 2.3 (d, 6H, 2x$CH_3$), 3.3 (s, 3H, $CH_3O$), 3.52 (s, 2H, Ar $CH_2N$), 4.0-4.5 (m, 4H, $OCH_2CH_2N$), 5.0 (s, 1H, $C_4$-H), 6.05 (s, 2H, $OCH_2O$), 6.95-7.92 (m, 7H, Ar), 9.36 (s, 1H, NH)

***2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[N-(3',4'-methylenedioxybenzyl)-N-methyl]aminoethyl ester 5-ethyl ester·HCl (12)***

Yield: 18%, mp: 217-218°C

IR (KBr) $cm^{-1}$: 1695 (C=O), 1527 ($NO_2$)

NMR (DMSO-$d_6$): $\delta$ 1.2(t, 3H, $CH_3CH_2O$), 2.36 (d, 6H, 2x$CH_3$), 2.62 (s, 3H, $NCH_3$) 3.0-3.7 (t, 2H, $OCH_2CH_2N$), 3.7-4.7 (m, 6H, $CH_2OCO$, $OCH_2CH_2$-N, $ArCH_2N$), 5.0 (s, 1H, $C_4$-H), 6.1 (s, 2H, $OCH_2$-O), 6.95-8.0 (m, 7H, Ar), 9.25 (s, 1H, NH)

***2,6-Dimethyl-4-(2',3'-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[N-(3',4'-methylenedioxybenzyl)-N-methyl] amino ethyl ester 5-methyl ester·HCl (13)***[9-11].

To a suspension of 2,6-dimethyl-4-(2',3'-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 5-methyl ester (**9**, 2.15g) in mixed solvent ($CH_2Cl_2$/DMF = 4:1, 14 m*l*) was added thionyl chloride (0.5 m*l*) under ice cooling.

After being stirred for 1 hr. **6a** was added and the reaction mixture was stirred for 2.5 hrs.

The reaction mixture was washed with water and brine. The organic layer was dried over anhydrous $Na_2SO_4$. The solvent was evaporated and the residual oil was separated on silica gel column (EtOAc/n-Hexane). The eluent was evaporated in vacuo and the residue was treated with 3 N-HCl ethanolic solution. The solvent was removed in vacuo. The residue was dissolved in acetone and stirred overnight under cooling. The ppt was filtered and recrystallized from acetone.

Yield: 0.92g (26.3%), mp: 196-199°C

IR (KBr) $cm^{-1}$: 1689 (C=O)

NMR (DMSO-$d_6$): $\delta$ 2.3 (d, 6H, 2x$CH_3$), 2.6 (S, 3H, $NCH_3$), 3.38 (s, 3H, $CH_3O$), 3.5 (s, 2H, Ar-$CH_2N$), 4.0-4.6 (m, 4H, $OCH_2CH_2N$), 5.3 (s, 1H, $C_4$-H), 6.1 (s, 2H, $OCH_2O$), 6.8-7.6 (m, 6H, Ar), 9.25 (s, 1H, NH)

***2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[N-(2',3'-methylenedioxybenzyl)-N-methyl] aminoethyl ester 5-methyl ester·HCl (14)***

Yield: 78%, mp. 108-113°C

IR (KBr) $cm^{-1}$: 3409 (NH), 1690 (C=O)

NMR ($CDCl_3$ + DMSO-$d_6$): $\delta$ 2.4 (d, 6H, 2x$CH_3$), 2.66 (s, 3H, $NCH_3$), 3.04-3.42 (m, 2H, $CH_2CH_2N$),

3.64 (s, 3H, $CH_3O$) 4.10 (b·s, 2H, $OCH_2CH_2N$), 4.60 (b.s, 2H, $ArCH_2N$), 5.04 (s, 1H, $C_4$ – H), 6.0 (s, 2H, $OCH_2O$), 6.60-8.20 (m, 7H, Ar), 8.80 (s, 1H, NH)

***2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[N-(2',3'-methylenedioxybenzyl)-N-methyl] aminoethyl ester 5-ethyl ester·HCl (15)***

Yield: 45%, mp: 101-110°C

IR (KBr) $cm^{-1}$: 3415 (NH), 1689 (C=O)

NMR ($CDCl_3$ + DMSO-$d_6$): $\delta$ 1.2 (t, 3H, $CH_3$-$CH_2O$), 2.40 (d, 6H, 2x$CH_3$), 2.70 (s, 3H, $NCH_3$), 3.10-3.60 (m, 2H, $OCH_2CH_2N$), 3.80-4.40 (m, 4H, $CH_3CH_2O$, $OCH_2CH_2N$), 4.40-4.80 (b·s, 2H, Ar-$CH_2N$), 5.0 (s, 1H, $C_4$-H), 6.0 (s, 2H, $OCH_2O$), 6.70-8.10 (m, 7H, Ar), 9.0 (s, 1H, NH)

***2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[N-(1',4'-benzodioxan-2-yl) methyl-N-methyl] aminoethyl ester 5-methyl ester·HCl (16)***

Yield: 20.6%, mp: 123-125°C

IR (KBr) $cm^{-1}$: 3430 (NH), 1706 (C=O)

NMR ($CDCl_3$ + DMSO-$d_6$): $\delta$ 2.10 (s, 3H, $NCH_3$), 2.40 (s, 6H, 2x$CH_3$), 2.60 (b·s, 2H, $OCH_2CH_2N$), 3.40 (b·s, 2H, $OCH_2CH_2N$), 3.60 (s, 3H, $CH_3O$), 4.0-4.60 (m, 6H, $ArCH_2N$, $OCH_2CH_2O$), 5.0 (s, 1H, $C_4$-H), 6.60-8.0 (m, 7H, Ar), 9.20 (b·s, 1H, NH)

***2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[N-(3',4'-dimethoxybenzyl)-N-methyl] aminoethyl ester 5-ethyl ester (17)***

Yield: 50%, mp. 125-126°C

IR (KBr) $cm^{-1}$: 3425 (NH), 1693 (C=O)

NMR ($CDCl_3$): $\delta$ 1.21 (t, 3H, $CH_2CH_3$), 2.10 (s, 3H, $NCH_3$), 2.34 (s, 6H, 2x$CH_3$), 2.62 (t, 2H, $NCH_2$-$CH_2$), 3.44 (s, 2H, $ArCH_2N$), 3.87 (s, 6H, 2x$OCH_3$), 4.11 (q, 2H, $OCH_2CH_3$), 4.19 (t, 2H, $OCH_2CH_2O$), 5.13 (s, 1H, $C_4$-H), 5.83 (s, 1H, NH) 6.81-8.14 (m, 7H, Ar)

***2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[N-(3'-methoxy-4'-ethoxybenzyl)-N-methyl] aminoethyl ester 5-methyl ester·HCl (18)***

Yield: 57%, mp: 131-133°C

IR (KBr) $cm^{-1}$: 3411 (NH), 1693 (C=O)

NMR ($CDCl_3$): $\delta$ 1.45 (t, 3H, $OCH_2CH_3$), 2.38 (s, 6H, 2x$CH_3$), 2.66 (s, 3H, $NCH_3$), 3.40 (b.d, 2H, $OCH_2CH_2N$), 3.64 (s, 3H, $COOCH_3$) 3.91-4.19 (t, 7H, $OCH_3$, $ArCH_2N$, $OCH_2CH_2CH_3$, 4.58 (b.d, 2H, $OCH_2CH_2N$), 5.09 (s, 1H, $C_4$-H), 6.85-8.10 (m, 8H, Ar, NH)

***2,6-Dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[N-(3',4',5'-trimethoxybenzyl)-N-methyl] aminoethyl ester 5-methyl ester·HCl (19)***

Yield: 54%, mp: 144-149°C

IR (KBr) $cm^{-1}$: 3437 (NH), 1691 (C=O)

NMR ($CDCl_3$): $\delta$ 2.42 (s, 6H, 2x$CH_3$), 2.66 (s, 3H, $NCH_3$), 3.32 (b.d, 2H, $OCH_2CH_2N$), 3.68 (s, 3H, $COOCH_3$), 3.91 (d, 11H, 3x$OCH_3$, $ArCH_2$), 4.65 (b.d, 2H, $OCH_2CH_2N$), 5.09 (s, 1H, $C_4$-H), 6.95-8.14 (m, 7H, Ar, NH)

***Effect on vascular smooth muscle[12]***

New Zealand white rabbits of either sex weighing 2.5-3.0 kg were killed by a sharp blow to the base of the skull. The descending thoracic aorta was excised immediately, cleared of connective tissue, and cut into rings 2-3 mm wide. These rings were suspended by means of stainless steel hooks in 20 m*l* organ baths containing a Krebs-Henseleit (KH) solution of following composition (in mM): NaCl, 118; KCl, 4.7; $MgSO_4 \cdot 7H_2O$, 1.2; $CaCl_2 \cdot 2H_2O$, 2.5; $NaHCO_3$, 25; $KH_2PO_4$, 1.2; glucose, 10.1. The tension of the rings was recorded isometrically with electromechanical transducers (Narco Bio-Systems, myograph F-60) on a pen recorder (Narco Bio Systems, Narcotrace 80). At the beginning of the experiments, the rings were stretched to an initial tension of 2g and allowed to relax for 90 min. until a stable baseline tension was reached. The bathing medium was changed every 15 min. to prevent accumulation of metabolites. After submaximal contractions were induced by KCl, cumulative concentration-response curves for the contractile effects of KCl were determined by a stepwise increase in the concentration of stimulant as soon as a steady response to the preceeding concentration had been obtained. Test compound was introduced to the bath 10 min. prior to another cumulative concentration-response curves and the vascular relaxing effects were expressed as percentages of control response.

## ACKNOWLEDGEMENT

This research was partly supported by the special research project, Ministry of Science and Technology, Korea.

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