# Studies on Cerebral Protective Agents. IV.[1a] Synthesis of Novel 4-Arylpyridine and 4-Arylpyridazine Derivatives with Anti-anoxic Activity

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**In a search for new cerebral protective agents, a series of 4-(3- or 4-nitrophenyl)-6-phenylpyridines (or pyridazines) and 2-(3-nitrophenyl)-6-phenylpyridines, possessing an amino moiety at the C-3 position of the pyridine (or pyridazine) ring, were synthesized through the corresponding novel 1,4-dihydro derivatives and tested for anti-anoxic (AA) activity in mice. Four compounds (2c, 2f, 3a, 4a) possessed significant AA activity at a dose of 32 mg/kg, i.p. These results suggest that four-atom linkages between the C-3 position of the pyridine (or pyridazine) ring and the nitrogeneous basic moiety also seems to be a prerequisite for the expression of AA activity.**

**Keywords** cerebral protective agent; 4-arylpyridine; 4-arylpyridazine; 1,4-dihydro-3-pyridinecarboxylate; 1,4-dihydro-3-pyridazinecarboxylate; 2-arylpyridine

## Introduction

In the previous paper[1b] we reported that the 4-aryl-5-pyrimidinecarboxamide derivatives (**1**) had potent cerebral protective activities in animal models (*i.e.* anti-anoxic (AA) activity, anti-lipid peroxidation (ALP) activity and a protective effect on arachidonate-induced cerebral edema in rats). The 4-(3- or 4-nitrophenyl)-2-phenylpyrimidine system (part A) and a nitrogeneous basic amide group at the C-5 position of the pyrimidine ring (part B) appeared to be a prerequisite for the expression of ALP and AA activity, respectively (Fig. 1).[1b,c] Among these compounds, **1a**, FK 360 was the most effective example on the above mentioned three assays and had low acute toxicity in mice ($LD_{50} > 560$ mg/kg, i.p.). In order to investigate more fully the structure–activity relationships on AA activity and look for back-up compounds of FK 360, we decided to synthesize related six-membered ring systems (*e.g.* **2**—**4** types) (Fig. 2).

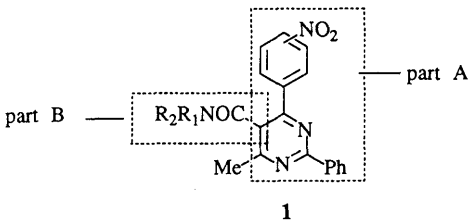
For the synthesis of these target compounds (**2**—**4**), alkyl 1,4-dihydro-3-pyridine(or pyridazine)carboxylate derivatives (**5**—**7**) were considered to be the key intermediate compounds, respectively. Despite many reports on the synthesis of 4-aryl-1,4-dihydro-3,5-pyridine(or pyridazine)dicarboxylates, we could not find any report on the synthesis of 4-aryl-1,4-dihydro-3-pyridine(or pyridazine)carboxylates.

In this paper we described the preparation of the key intermediates (**5**—**7**) and the evaluation of **2**—**4** and their analogues in regard to AA activity.

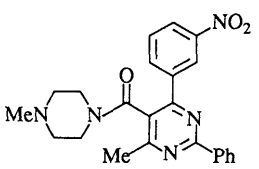
## Chemistry

The synthesis of the target compounds (**2a**—**e**) and their analogues (**2f**, **12**) was accomplished through the novel 1,4-dihydropyridine derivatives (**5a**, **b**) by the routes shown in Chart 1.

The reaction of 3-(3- or 4-nitrophenyl)-1-phenyl-2-propen-1-one (**8**)[2] with ethyl 3-aminocrotonate in refluxing 1-butanol (*n*-BuOH) provided **5**. Although the existence of a variety of isomers in dihydroazines (*i.e.* dihydropyridines, dihydropyridazines, dihydropyrimidines *etc.*)[3] is known, on the basis of 200 MHz $^1$H-NMR measurements in DMSO-$d_6$, dihydropyridine **5a** was found

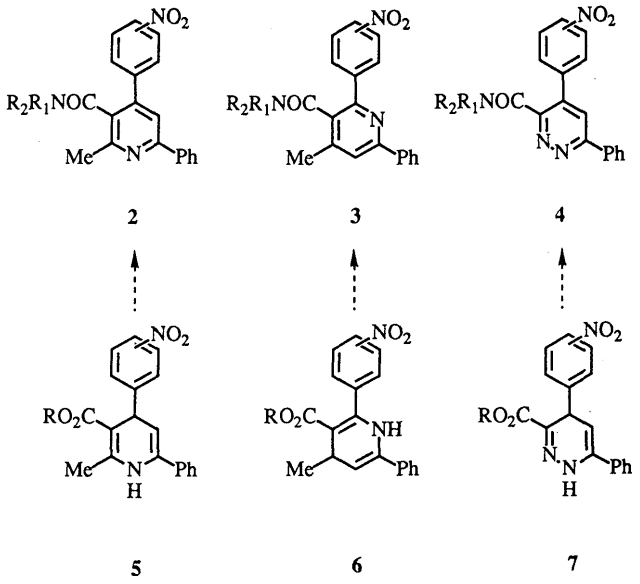



**1**




**1a**: FK 360

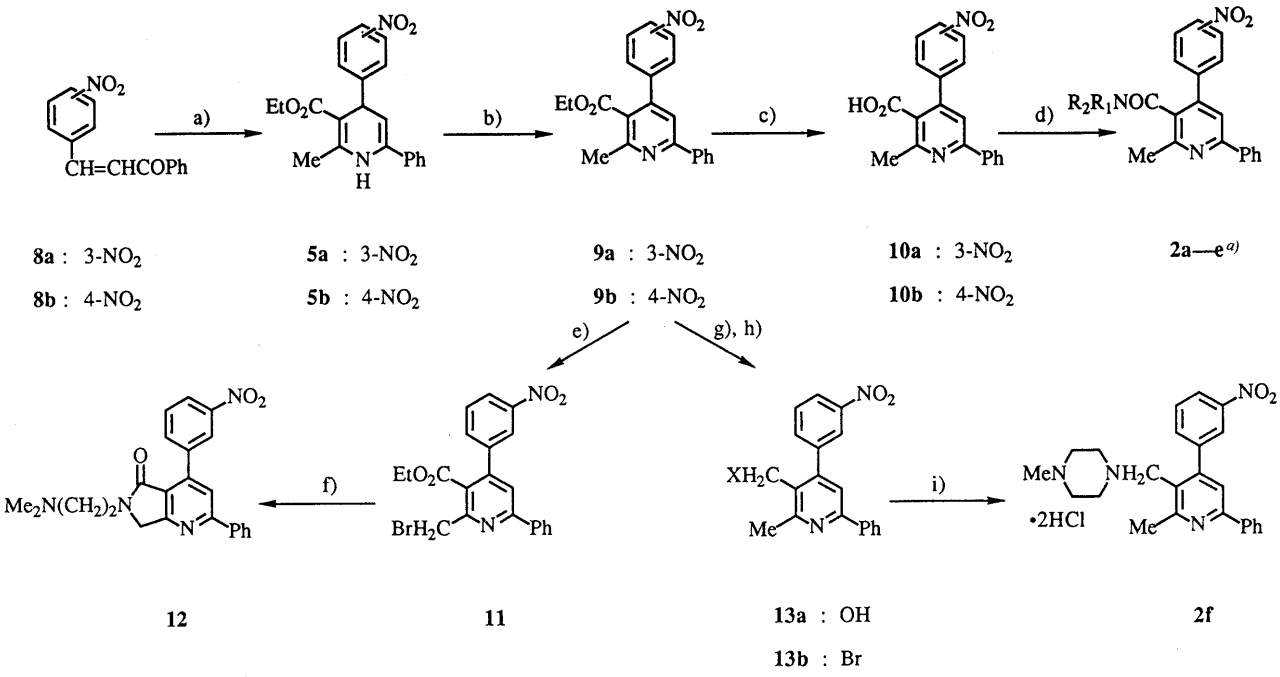
Fig. 1




**5**,**7** : R = Et

**6** : R = Me

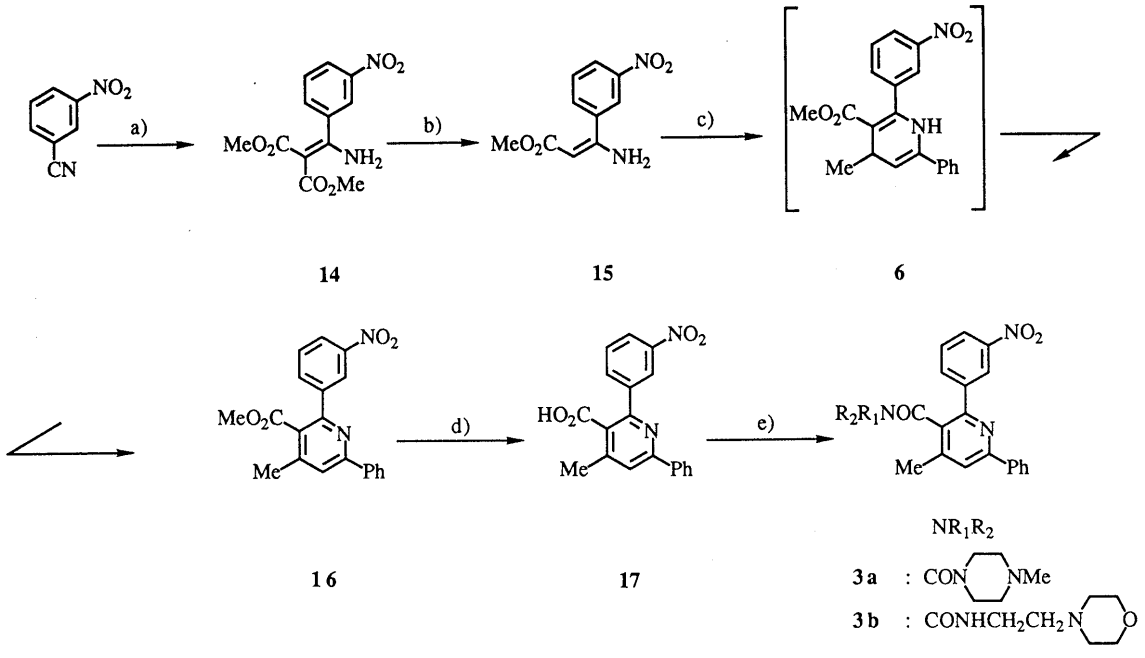
Fig. 2




a) ethyl 3-aminocrotonate / *n*-BuOH; b) $MnO_2$ / $CHCl_3$; c) KOHaq. / EtOH; d) $SOCl_2$ / DMF—$CH_2Cl_2$, amines; e) *N*-bromosuccinimide, benzoylperoxide / $CCl_4$; f) 2-dimethylaminoethylamine / iso-PrOH; g) $LiAlH_4$ / $Et_2O$—THF; h) $PBr_3$ / THF; i) 1-methylpiperazine / iso-PrOH

*a*) The position of $NO_2$, $NR_1R_2$ are as listed in Table I.

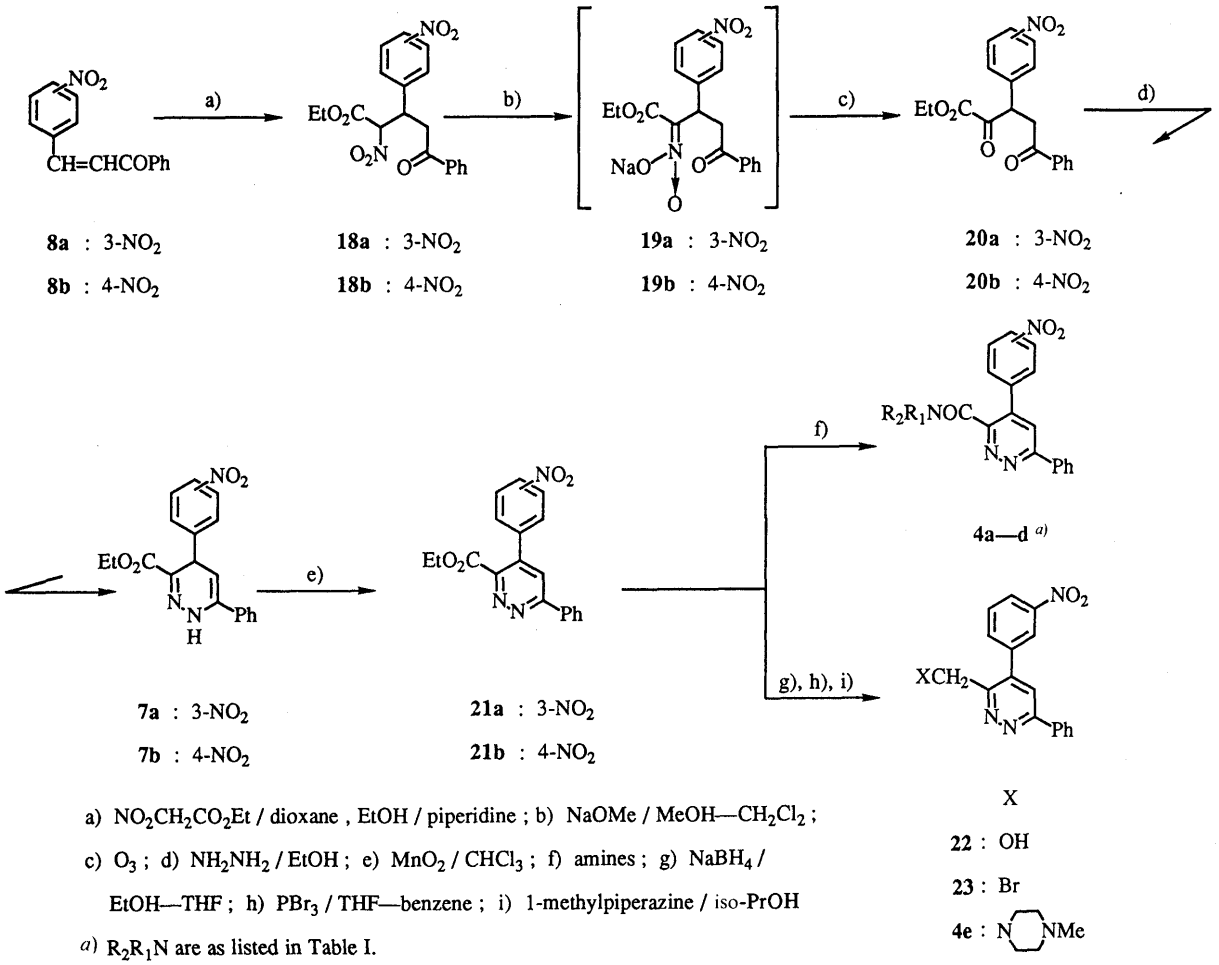
Chart 1




a) dimethyl malonate, $SnCl_4$ / 1,2-dichloroethane; b) KOH / $H_2O$—MeOH; c) 1-phenyl-2-buten-1-one / *n*-BuOH; d) NaOH aq. / dioxane-MeOH; e) $SOCl_2$ / DMF—$CH_2Cl_2$, amines

Chart 2

solely in the 1,4-dihydro form under these conditions. Thus, the proton signal of $C_4$-H ($\delta$ 4.77) of **5a** was coupled with the proton $C_5$-H ($\delta$ 5.21) at the value of 5.7 Hz. Further, the signal of $C_5$-H was also long-range coupled with the proton of $N_1$-H ($\delta$ 8.53) at 1.7 Hz, which disappeared on the addition of $D_2O$. Oxidation of **5** with activated manganese (IV) oxide ($MnO_2$) afforded **9**, which followed by hydrolysis with ethanolic KOH aq. gave **10**. The amide derivatives (**2a—e**) were synthesized according to the same procedures which we have reported




a) $NO_2CH_2CO_2Et$ / dioxane , EtOH / piperidine ; b) NaOMe / MeOH—$CH_2Cl_2$ ;
c) $O_3$ ; d) $NH_2NH_2$ / EtOH ; e) $MnO_2$ / $CHCl_3$ ; f) amines ; g) $NaBH_4$ /
EtOH—THF ; h) $PBr_3$ / THF—benzene ; i) 1-methylpiperazine / iso-PrOH

a) $R_2R_1N$ are as listed in Table I.

Chart 3

previously.[1b] Thus, **10** was reacted with $SOCl_2$ in a mixture of *N*,*N*-dimethylformamide (DMF) and $CH_2Cl_2$ under ice cooling, and the resultant acid chloride intermediate was allowed to react with excess amine to afford **2a**—**e**.

Reaction of bromide (**11**), prepared from **9a** by treatment with *N*-bromosuccinimide in the presence of benzoylperoxide, with 2-dimethylaminoethylamine afforded the lactam derivative (**12**).

The alcohol (**13a**), obtained by $LiAlH_4$ reduction of **9a**, reacted with phosphorus tribromide ($PBr_3$) to give bromide (**13b**), which was converted to **2f** by reaction with 1-methylpiperazine.

Next target compounds (**3a, b**) were obtained by the routes shown in Chart 2.

Propanedioate derivative (**14**) was prepared according to the same procedures reported by Helquist *et al.*[4] Thus, reaction of equimolar amounts of dimethyl malonate and 3-nitrobenzonitrile in the presence of tin(IV) chloride ($SnCl_4$) gave a white tin complex, which was hydrolyzed with NaOH aq. to afford **14**. The 2-propenoate derivative (**15**), obtained by alkaline hydrolysis of **14**, reacted with 1-phenyl-2-buten-1-one[5] in refluxing *n*-BuOH to afford (**16**) directly in low yield. We could not isolate the 1,4-dihydropyridine derivative (**6**). The acid (**17**), obtained by hydrolysis of **16**, was converted to the amides (**3a, b**) by the same procedures as in the preparation of **2a**—**e**.

The synthesis of the pyridazine derivatives (**4a**—**e**) was accomplished by the routes shown in Chart 3.

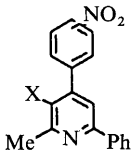
A Michael addition of ethyl nitroacetate to **8** in the presence of piperidine provided the adduct (**18**). The diketoester (**20**) was obtained by means of modified Nef reaction.[6] Thus, compound **18** was converted to the nitronate (**19**) by treatment with NaOMe, followed by ozonolysis of **19** at −60 °C to afford **20**. Condensation of **20** with hydrazine hydrate afforded the key intermediate (**7**). On the basis of 200 MHz $^1$H-NMR measurements in DMSO-$d_6$, dihydropyridazine (**7a** and **7b**) were found soley in the 1,4-dihydro form under these conditions. Thus for example, the proton signal of $C_4$-H ($\delta$ 4.94) of **7a** was coupled with the proton $C_5$-H ($\delta$ 5.37) at a value of 5.7 Hz. Further, the signal of $C_5$-H was also long-range coupled with the proton of $N_1$-H (10.85) at 2.4 Hz, which disappeared on the addition of $D_2O$. Oxidation of **7** with activated $MnO_2$ gave **21**.

The pyridazine amides (**4a**—**d**) were obtained by heating **21** with appropriate amines at 90 °C. The alcohol (**22**), obtained by $NaBH_4$ reduction of **21a**, was allowed to react with $PBr_3$ to afford bromide (**23**), which was converted to **4e** by reaction with 1-methylpiperazine.

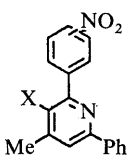
## Pharmacological Results and Discussion

The compounds listed in Table I were tested for AA activity in mice as described previously.[1c] Since we pointed out in the previous pyrimidinecarboxamide series that four-atom linkages between the pyrimidine C-5 position

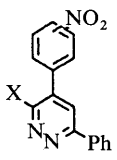
TABLE I. Physical Properties and AA Activity of Pyridine Derivatives (**2a—f**, **3a**, **3b**, **12**) and Pyridazine Derivatives (**4a—e**)



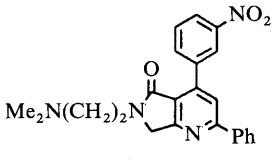
**2x**



**3x**



**4x**



**12**

| Compound No. | Position of $-NO_2$ | X | Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10 | 32 | mp (°C) (Recryst. solv.) | Yield | Formula | Analysis (%) Calcd (Found) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| **2a** | 3 | CON◯NMe | | 108 | 169—172 ($Et_2O$) | 25.6 | $C_{24}H_{24}N_4O_3$ | 69.21 (69.08) | 5.81 5.83 | 13.45 13.23) |
| **2b** | 3 | $CONH(CH_2)_2N$◯O | | 101 | 137—139 (EtOH–$Et_2O$) | 52.4 | $C_{25}H_{26}N_4O_4$ | 67.25 (66.98) | 5.87 6.09 | 12.55 12.67) |
| **2c** | 3 | $CONH(CH_2)_2NMe_2$ | 109 | 116[b] | 143—145 ($Et_2O$) | 36.8 | $C_{23}H_{24}N_4O_3$ | 68.30 (68.26) | 5.98 5.86 | 13.85 14.10) |
| **2d** | 3 | $CONH(CH_2)_2N$◯S ·fumarate | | 110 | 182—184 (dec.) (EtOH) | 32.3 | $C_{25}H_{26}N_4O_3S$ $\cdot C_4H_4O_4\cdot 0.2H_2O$ | 59.82 (59.60) | 5.26 5.21 | 9.62 9.45) |
| **2e** | 4 | $CONH(CH_2)_2NMe_2$ ·fumarate | | 93 | 185—187 (EtOH) | 12.4 | $C_{23}H_{24}N_4O_3$ $\cdot C_4H_4O_4\cdot H_2O$ | 60.21 (60.14) | 5.61 5.40 | 10.40 10.30) |
| **2f** | 3 | $CH_2N$◯NMe·2HCl | 102 | 135[b] | 250 (dec.) (EtOH) | 98.2 | $C_{24}H_{26}N_4O_2$ $\cdot 2HCl\cdot 1.5H_2O$ | 57.37 (57.20) | 6.22 6.20 | 11.15 11.05) |
| **12** | 3 | | | 116 | 179—181 (EtOH) | 35.8 | $C_{23}H_{22}N_4O_3$ $\cdot 0.25H_2O$ | 67.88 (67.82) | 5.57 5.41 | 13.77 13.77) |
| **3a** | 3 | CON◯NMe | 108 | 143[b] | 127—129 (EtOH–$Et_2O$) | 55.6 | $C_{24}H_{24}N_4O_3$ | 69.21 (69.42) | 5.81 5.38 | 13.45 13.41) |
| **3b** | 3 | $CONH(CH_2)_2N$◯O | | 113 | 147—148 (EtOH–$Et_2O$) | 66.1 | $C_{25}H_{26}N_4O_4$ | 67.25 (67.23) | 5.87 5.82 | 12.55 12.52) |
| **4a** | 3 | CON◯NMe | 115[c] | 142[b] | 180—181 (EtOH) | 11.6 | $C_{22}H_{21}N_5O_3$ | 65.50 (65.76) | 5.25 5.15 | 17.36 17.06) |
| **4b** | 3 | $CONH(CH_2)_2N$◯O | | 102 | 134—135 (EtOH) | 88.7 | $C_{23}H_{23}N_5O_4$ | 63.73 (63.54) | 5.35 5.21 | 16.16 16.08) |
| **4c** | 3 | $CONH(CH_2)_2NMe_2$ | | 98 | 157—158 ($Et_2O$) | 92.9 | $C_{21}H_{21}N_5O_3$ $\cdot 0.2H_2O$ | 63.85 (63.56 | 5.46 5.66 | 17.72 17.72) |
| **4d** | 4 | CON◯NMe | | 92 | 101—103 (EtOH) | 25.1 | $C_{22}H_{21}N_5O_3$ $\cdot 0.5EtOH$ | 64.78 (65.02 | 5.67 5.53 | 16.42 16.58) |
| **4e** | 3 | $CH_2N$◯NMe | | 114 | 157—159 (EtOH) | 50.7 | $C_{22}H_{23}N_5O_2$ | 67.85 (67.98 | 5.95 5.67 | 17.98 17.92) |

*a*) Each value represents the mean of 5 to 10 animals compared with the control group. *b*) $p<0.01$. *c*) $p<0.05$.

and the nitrogenous basic moiety ($-CONRCH_2CH_2NR'R''$) seemed to be a prerequisite for the expression of AA activity, in the synthesis of the pyridine carboxamides we selected the following five representatives (**2a—e**) from the point of view that the substituents (*i.e.* X of **2a—e** in Table I) were the most effective ones in the pyrimidine derivatives (**1**).[1b] However, the pyridine derivatives (**2a—e**) diminished or abolished AA activity compared to that of the pyrimidine ones.

One plausible approach was to prepare the 5-(4-methylpiperazin-1-ylmethyl) derivative (**2f**), due to the fact that the compound which has this substituent at the C-5 position of the pyrimidine ring was shown to increase AA activity compared to the 4-methylpiperazin-1-ylcarbonyl derivative,[1a] also proved to be effective for the expression of significant AA activity. Compound **12**, which is considered to be a semirigid analogue of **2c** was also effective by this type modification in the pyrimidine series,[1a] however, the activity of **12** was not significant at the dose tested. Compound **3a**, which is transposed the pyridine nitrogen of **2a** from the 1- to the 5-position, possessed significant activity.

In the pyridazine series, only **4a** had significant AA activity. In this pyridine and pyridazine series, modifications of the substituents seemed generally not to be well tolerated compared to that of the pyrimidine series. Therefore, we curtailed any additional synthesis regarding variation in the substituents. Incongruous failures for the expression of AA activity in these series occurred in several of the pyrimidine series and may reflect either negative pharmacokinetic issues resulting from metabolic degradation or low penetration into the brain.

Three compounds **2f**, **3a** and **4a** were further evaluated for acute toxicity in mice and/or AA activity in the oral-administration test in mice. Compounds **2f** and **3a** were more toxic (all mice were dead at 560 mg/kg, i.p.) than FK 360 ($LD_{50}>560$ mg/kg, i.p.). Compound **4a** was less toxic ($LD_{50}>1000$ mg/kg, i.p.), however, it proved not to be superior to FK 360 in the oral-administration test on AA assay (details not presented here).

In summary and conclusion, novel 1,4-dihydro-3-pyridine(or pyridazine)carboxylates were synthesized and converted to the target compounds through a few steps. Some of these target compounds were effective on AA

assay. These results suggest that four-atom linkages between the C-3 position of the pyridine (or pyridazine) ring and nitrogeneous basic moiety seems to be a prerequisite for the expression of AA activity as well as pyrimidine derivatives. These data may be useful for the future design and synthesis of new AA agents.

## Experimental

Melting points were determined using a Thomas–Hoover capillary melting point apparatus and are uncorrected. $^1$H-NMR spectra were obtained on a Varian EM-390 NMR (90 MHz) or a Hitachi R90-H NMR (90 MHz) or a Bruker AC-200P (200 MHz) using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Hitachi 260-10 or Shimadzu IR-420 spectrophotometer. Mass spectral measurements (MS) were made on a Hitachi M-80 or a JEOL-D300 mass spectrometer.

**Ethyl 1,4-Dihydro-2-methyl-4-(3-nitrophenyl)-6-phenyl-3-pyridinecarboxylate (5a)** A mixture of **8a** (2.0 g), ethyl 3-aminocrotonate (1.2 g) and *n*-BuOH (20 ml) was refluxed for 6 h. After allowing to cool to room temperature, the reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel ($SiO_2$) (75 g) with benzene–AcOEt (30 : 1) as eluent. The fractions containing **5a** were evaporated *in vacuo* and the residual crystalline material was recrystallized from EtOH to afford **5a** (0.6 g, 20.8%), mp 141—142 °C. IR (Nujol): 3375, 1675, 1638 cm$^{-1}$. MS *m/z*: 364 ($M^+$). $^1$H-NMR (200 MHz, DMSO-$d_6$) $\delta$: 1.06 (3H, t, $J$=7.1 Hz), 2.38 (3H, s), 3.93 (2H, q, $J$=7.1 Hz), 4.77 (1H, d, $J$=5.7 Hz), 5.21 (1H, dd, $J$=5.7, 1.7 Hz), 7.35—7.80 (7H, m), 8.00—8.10 (2H, m), 8.53 (1H, s). *Anal.* Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.29. Found: C, 69.19; H, 5.44; N, 7.59. Compound **5b** was synthesized by the same procedures employed in the preparation of **5a**.

Ethyl 1,4-Dihydro-2-methyl-4-(4-nitrophenyl)-6-phenyl-3-pyridinecarboxylate (**5b**): Yield 48.6%, mp 109—110 °C. IR (Nujol): 3330, 1640, 1608, 1515, 1350 cm$^{-1}$. MS *m/z* 364 ($M^+$). $^1$H-NMR (90 MHz, $CDCl_3$) $\delta$: 1.13 (3H, t, $J$=7 Hz), 2.41 (3H, s), 4.00 (2H, q, $J$=7 Hz), 4.78 (1H, d, $J$=6 Hz), 5.07 (1H, dd, $J$=6, 2 Hz), 5.80 (1H, s), 7.33 (5H, s), 7.42 (2H, d, $J$=9 Hz), 8.10 (2H, d, $J$=9 Hz). *Anal.* Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.29. Found: C, 69.21; H, 5.33; N, 7.56.

**Ethyl 2-Methyl-4-(3-nitrophenyl)-6-phenyl-3-pyridinecarboxylate (9a)** To a solution of **5a** (0.5 g) in $CHCl_3$ (5 ml) was added activated $MnO_2$ (2 g) and the mixture was refluxed for 1 h with vigorous stirring. After being cooled to room temperature, the $MnO_2$ was filtered off and the filtrate was evaporated *in vacuo*. The residual precipitates were recrystallized from EtOH to afford **9a** (0.25 g, 50.3%), mp 110—112 °C. IR (Nujol): 1720, 1595, 1360 cm$^{-1}$. MS *m/z*: 362 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.10 (3H, t, $J$=7 Hz), 2.73 (3H, s), 4.17 (2H, q, $J$=7 Hz), 7.20—8.30 (10H, m). *Anal.* Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.00, N, 7.73. Found: C, 69.90; H, 4.97; N. 7.48. Compound **9b** was synthesized by the same procedures employed in the preparation of **9a**.

Ethyl 2-Methyl-4-(4-nitrophenyl)-6-phenyl-3-pyridinecarboxylate (**9b**): Yield 15.5%, mp 132—133 °C. IR (Nujol): 1722, 1583, 1550, 1522, 1350 cm$^{-1}$. MS *m/z*: 362 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.06 (3H, t, $J$=7 Hz), 2.73 (3H, s), 4.15 (2H, q, $J$=7 Hz), 7.35—7.73 (6H, m), 7.95—8.40 (4H, m). *Anal.* Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.00; N, 7.73. Found: C, 69.75; H, 4.62; N, 7.79.

**2-Methyl-4-(3-nitrophenyl)-6-phenyl-3-pyridinecarboxylic Acid (10a)** A mixture of **9a** (4.6 g), KOH aq. (1.07 g KOH in 200 ml $H_2O$) and EtOH (92 ml) was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was washed with AcOEt (150 ml × 2). The aqueous layer was adjusted to pH 3.0 with 10% HCl aq. To this mixture was added AcOH (40 ml) and the whole was stirred for 30 min under ice cooling. The resulting precipitates were collected by filtration, washed with $H_2O$ and dried *in vacuo* to afford **10a** (1.98 g, 46.6%), mp 274—276 °C. IR (Nujol): 1710, 1600 cm$^{-1}$. MS *m/z*: 334 ($M^+$). $^1$H-NMR ($CF_3COOD$) $\delta$: 3.20 (3H, s), 7.50—8.10 (8H, m), 8.23 (1H, s), 8.30—8.60 (1H, m). *Anal.* Calcd for $C_{19}H_{14}N_2O_4 \cdot 1/4H_2O$: C, 67.35; H, 4.31; N, 8.27. Found: C, 67.59; H, 4.20; N, 8.13. Compound **10b** was synthesized by the same procedures employed in the preparation of **10a**.

2-Methyl-4-(4-nitrophenyl)-6-phenyl-3-pyridinecarboxylic Acid (**10b**): Yield 86.7%, mp 260—263 °C. IR (Nujol): 1710, 1595, 1545, 1345 cm$^{-1}$. MS *m/z*: 334 ($M^+$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.65 (3H, s), 7.30—7.90 (6H, m), 8.05—8.50 (4H, m). *Anal.* Calcd for $C_{19}H_{14}N_2O_4 \cdot 1/4H_2O$: C, 67.35; H, 4.31; N, 8.27. Found: C, 67.48; H, 4.25; N, 8.18.

**Typical Example for the Preparation of Amide Derivatives (2a—e)** *N*-(2-Dimethylaminoethyl)-2-methyl-4-(3-nitrophenyl)-6-phenyl-3-pyridinecarboxamide (**2c**): To a mixture of **10a** (1.98 g), $CH_2Cl_2$ (20 ml) and DMF (4 ml) was added a solution of $SOCl_2$ (0.47 ml) in $CH_2Cl_2$ (2 ml) at 7 °C under ice cooling. After being stirred for 2.5 h at the same conditions, a solution of 2-dimethylaminoethylamine (1.3 g) in $CH_2Cl_2$ (20 ml) was added thereto and stirred for 2 h at the same temperature. After the addition of $H_2O$ (150 ml) and $CH_2Cl_2$ (150 ml), the mixture was adjusted to pH 9.0 with 10% NaOH aq. The organic layer was separated, successively washed with $H_2O$ and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on alumina ($Al_2O_3$) (70 g) with $CHCl_3$ as eluent. The fractions containing **2c** were evaporated *in vacuo*. The residue was recrystallized from $Et_2O$ to afford **2c** (0.88 g, 36.8%), mp 143—145 °C. IR (Nujol): 3275, 1640 cm$^{-1}$. MS *m/z*: 404 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 2.01 (6H, s), 2.17 (2H, t, $J$=6 Hz), 2.73 (3H, s), 3.27 (2H, td, $J$=6, 6 Hz), 6.27 (1H, br), 7.30—8.40 (10H, m). Compounds **2a** and **2b** were prepared by the same procedures employed in the preparation of **2c**.

2-Methyl-3-(4-methylpiperazin-1-ylcarbonyl)-4-(3-nitrophenyl)-6-phenylpyridine (**2a**): Yield 25.6%, mp 169—172 °C. IR (Nujol): 1628, 1535, 1350 cm$^{-1}$. MS *m/z*: 416 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.60—2.40 (4H, m), 2.17 (3H, s), 2.67 (3H, s), 2.80—3.20 (2H, m), 3.40—3.80 (2H, m), 7.20—8.50 (10H, m).

*N*-(2-Morpholinoethyl)-2-methyl-4-(3-nitrophenyl)-6-phenyl-3-pyridinecarboxamide (**2b**): Yield 52.4%, mp 137—139 °C. IR (Nujol): 3180, 1620, 1560, 1520, 1355 cm$^{-1}$. MS *m/z*: 446 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 2.15—2.40 (6H, m), 2.74 (3H, s), 3.20—3.70 (6H, m), 6.16 (1H, br), 7.40—7.75 (5H, m), 7.80—8.10 (3H, m), 8.15—8.43 (2H, m). According to a manner similar to that of **2c**, 2-methyl-4-(3-nitrophenyl)-6-phenyl-*N*-(2-thiomorpholinoethyl)-3-pyridinecarboxamide was obtained and was treated with slight excess fumaric acid to give precipitates of fumarate (**2d**) thereof as crystal. Yield 32.3%, mp 182—184 °C (dec.). IR (Nujol): 3300, 1665, 1590 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.19 (2H, t, $J$=6 Hz), 2.50 (8H, s), 2.56 (3H, s), 3.15 (2H, td, $J$=6, 6 Hz), 6.57 (2H, s), 7.00—8.50 (11H, m). According to a similar manner to that of **2d**, *N*-(2-dimethylaminoethyl)-2-methyl-4-(4-nitrophenyl)-6-phenyl-3-pyridinecarboxamide fumarate (**2e**) was obtained. Yield 12.4%, mp 185—187 °C. IR (Nujol): 3450, 1710, 1660, 1350 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.23 (6H, s), 2.30—2.50 (2H, m), 2.61 (3H, s), 3.25 (2H, td, $J$=6, 6 Hz), 6.56 (2H, s), 7.30—7.90 (4H, m), 7.79 (2H, d, $J$=8 Hz), 8.32 (2H, d, $J$=8 Hz), 8.00—8.20 (2H, m), 8.51 (1H, br). Elemental analysis data of these compounds are listed in Table I.

**Ethyl 2-Bromomethyl-4-(3-nitrophenyl)-6-phenyl-3-pyridinecarboxylate (11)** A mixture of **9a** (5.0 g), *N*-bromosuccinimide (5.9 g) and benzoyl peroxide (0.1 g) in $CCl_4$ (200 ml) was refluxed for 5 h. The reaction mixture was poured into ice water (100 ml). The organic layer was successively washed with $NaHCO_3$ aq. and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on $SiO_2$ (150 g) with *n*-hexane–$CHCl_3$ (1 : 2) as eluent. The fractions containing **11** were combined and evaporated *in vacuo* to afford **11** (2.0 g, 32.8%), mp 125—128 °C. IR (Nujol): 1710, 1590, 1570, 1520, 1350 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.00 (3H, t, $J$=7 Hz), 4.16 (2H, q, $J$=7 Hz), 4.88 (2H, s), 7.40—8.60 (10H, m). This compound was further purified or analyzed before use in the next step.

**6-(2-Dimethylaminoethyl)-4-(3-nitrophenyl)-2-phenyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-5-one (12)** A mixture of **11** (1.5 g) and 2-dimethylaminoethylamine (0.6 g) in iso-PrOH (15 ml) was refluxed for 1 h. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in a mixture of $H_2O$ (20 ml) and $CHCl_3$ (40 ml). The organic layer was washed with $H_2O$ and dried over $MgSO_4$. After evaporating the solvent, the residue was purified by column chromatography on $SiO_2$ (50 g) with $CHCl_3$–MeOH (50 : 1) as eluent. The fractions containing **12** were combined and evaporated *in vacuo*. The crystalline residue was recrystallized from EtOH to afford **12** (0.49 g, 35.8%), mp 179—181 °C. IR (Nujol): 1675, 1585, 1565, 1525, 1345 cm$^{-1}$. MS *m/z*: 402 ($M^+$). $^1$H-NMR ($CDCl_3$ + DMSO-$d_6$) $\delta$: 2.29 (6H, s), 2.60 (2H, t, $J$=6 Hz), 3.73 (2H, t, $J$=6 Hz), 4.64 (2H, s), 7.30—7.78 (5H, m), 7.90—8.35 (4H, m), 8.40—8.58 (1H, m). Elemental analysis data are listed in Table I.

**3-Hydroxymethyl-2-methyl-4-(3-nitrophenyl)-6-phenylpyridine (13a)** To a suspension of $LiAlH_4$ (0.32 g) in a mixture of dry tetrahydrofuran (THF) (4 ml) and $Et_2O$ (8 ml) was dropwise added a solution of **9a** (1.0 g) in dry THF (4 ml) at −20 to −10 °C. The excess $LiAlH_4$ was decomposed by a careful addition to ice water. Then AcOEt (25 ml) was added and the organic layer was successively washed with 10% $H_2SO_4$ aq. (15 ml), saturated $NaHCO_3$ aq., brine, dried over $MgSO_4$ and

evaporated *in vacuo*. The residue was purified by column chromatography on $SiO_2$ (50 g) with $CHCl_3$ as eluent. The fractions containing **13a** were combined and evaporated *in vacuo*. The residue was crystallized from $Et_2O$ to afford **13a** (0.27 g, 30.7%), mp 212—214 °C. IR (Nujol): 3200, 1720, 1590, 1520, 1350 $cm^{-1}$. $^1$H-NMR ($CDCl_3$ + DMSO-$d_6$) $\delta$: 2.81 (3H, s), 4.45 (2H, d, $J$=5 Hz), 4.84 (1H, t, $J$=5 Hz), 7.20—8.50 (10H, m). This compound was not further purified or analyzed before use in the next step.

**3-Bromomethyl-2-methyl-4-(3-nitrophenyl)-6-phenylpyridine (13b)** To a solution of $PBr_3$ (0.93 g) in THF (10 ml) was dropwise added a suspension of **13a** (1.65 g) in THF (10 ml) at 5—10 °C. After being stirred for 1.5 h at the same temperature, the reaction mixture was poured into ice water (20 ml), adjusted to pH 9.5 with saturated $K_2CO_3$ aq. and extracted with AcOEt (40 ml). The organic layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on $SiO_2$ (80 g) with $CHCl_3$ as eluent. The fractions containing **13b** were combined and evaporated *in vacuo* to afford **13b** (0.49 g, 24.9%), mp 155—157 °C. IR (Nujol): 1580, 1570, 1520, 1345 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.82 (3H, s), 4.38 (2H, s), 7.20—8.50 (10H, m). This compound was not further purifiied or analyzed before use in the next step.

**2-Methyl-3-(4-methylpiperazin-1-ylmethyl)-4-(3-nitrophenyl)-6-phenylpyridine Dihydrochloride (2f)** A mixture of **13b** (0.45 g), 1-methylpiperazine (0.26 g) in iso-PrOH (4.5 ml) was refluxed for 1 h. The reaction mixture was poured into ice water (50 ml) and extracted with $CHCl_3$ (60 ml). The organic layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue and conc. HCl aq. (0.3 ml) were dissolved in EtOH (3 ml). The resulting crystals were collected by filtration and dried *in vacuo* to afford **2f** (0.55 g, 98.2%), mp 250 °C (dec.). IR (Nujol): 1580, 1520, 1350 $cm^{-1}$. $^1$H-NMR ($D_2O$) $\delta$: 2.1—3.65 (8H, m), 2.84 (3H, s), 2.99 (3H, s), 3.77 (2H, s), 7.50—8.00 (8H, m), 8.30—8.53 (2H, m). Elemental analysis data are listed in Table I.

**Dimethyl [Amino(3-nitrophenyl)methylene]propanedioate (14)** To a mixture of dimethyl malonate (100 g) and 3-nitrobenzonitrile (112 g) in 1,2-dichloroethane (500 ml) was added $SnCl_4$ (177 g) at once with a syringe and it was refluxed for 1 h with stirring. The white precipitates were collected by filtration, dissolved in a mixture of acetone (2 l) and $H_2O$ (2 l) and adjusted to pH 9.0 with 20% NaOH aq. The resulting white solid was filtered off, and the filtrate was extracted with $CH_2Cl_2$ (2 l). The extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The resulting precipitates were recrystallized from $Et_2O$–$CH_2Cl_2$ to afford **14** (139.5 g, 67.8%), mp 113—115 °C. IR (Nujol): 3350, 3175, 1670 $cm^{-1}$. MS *m/z*: 280 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 3.38 (3H, s), 3.78 (3H, s), 7.60—7.80 (2H, m), 8.20—8.40 (2H, m). *Anal.* Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.32; N, 9.99. Found: C, 51.52; H, 3.95; N, 9.97.

**Methyl 3-Amino-3-(3-nitrophenyl)-2-propenoate (15)** A mixture of **14** (120 g) and KOH (56.5 g) in a mixture of MeOH (1.2 l) and $H_2O$ (120 ml) was refluxed for 8 h. The reaction mixture was concentrated under reduced pressure to a volume of 200 ml. The resulting crystals were collected by filtration and recrystallized from MeOH to afford **15** (50.2 g, 52.8%), mp 97—99 °C. IR (Nujol): 3500, 3325, 1680, 1660, 1615 $cm^{-1}$. MS *m/z*: 222 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 3.74 (3H, s), 5.02 (1H, s), 6.10—6.90 (2H, br), 7.50—8.50 (4H, m). *Anal.* Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.16; H, 4.27; N, 12.61.

**Methyl 4-Methyl-2-(3-nitrophenyl)-6-phenyl-3-pyridinecarboxylate (16)** A mixture of **15** (45 g) and 1-phenyl-2-buten-1-one (44 g) in *n*-BuOH (450 ml) was refluxed for 4 h. After being cooled to room temperature, the reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography on $SiO_2$ (500 g) with benzene as eluent. The fractions containing **16** were evaporated *in vacuo*. The residual crystalline was recrystallized from MeOH to afford **16** (4.10 g, 5.9%), mp 105—106 °C. IR (Nujol): 1685 $cm^{-1}$. MS *m/z*: 348 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 2.52 (3H, s), 3.76 (3H, s), 7.40—7.75 (4H, m), 7.66 (1H, s), 7.90—8.40 (4H, m), 8.55—8.65 (1H, m). *Anal.* Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 69.15; H, 4.42; N, 8.01.

**4-Methyl-2-(3-nitrophenyl)-6-phenyl-3-pyridinecarboxylic Acid (17)** A mixture of **16** (4.08 g), NaOH aq. (0.94 g NaOH in 10 ml $H_2O$), dioxane (20 ml) and MeOH (80 ml) was refluxed for 14 h. After being cooled to room temperature, the reaction mixture was poured into a mixture of $H_2O$ (150 ml) and $CHCl_3$ (100 ml). The aqueous layer was adjusted to pH 2.9 with 10% HCl aq. To this mixture was added AcOH (15 ml) and the whole was stirred for 30 min under ice cooling. The resulting precipitates were collected by filtration, washed with $H_2O$ and dried *in vacuo* to afford **17** (2.80 g, 71.6%), mp 191—192 °C. IR (Nujol): 1690, 1530 $cm^{-1}$. MS *m/z*: 334 ($M^+$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.50 (3H, s), 7.40—7.60 (3H, m), 7.70—8.60 (7H, m). *Anal.* Calcd for $C_{19}H_{14}N_2O_4$: C, 68.25; H, 4.22; N, 8.38. Found: C, 67.92; H, 3.97; N, 8.24.

**4-Methyl-3-(4-methylpiperazin-1-ylcarbonyl)-2-(3-nitrophenyl)-6-phenylpyridine (3a)** To a mixture of **17** (1.4 g), $CH_2Cl_2$ (14 ml) and DMF (2.8 ml) was added a solution of $SOCl_2$ (0.33 ml) in $CH_2Cl_2$ (3 ml) at 7 °C under ice cooling. After being stirred for 2 h at the same conditions, a solution of 1-methylpiperazine (1.05 g) in $CH_2Cl_2$ (7 ml) was added and the mixture was stirred for 2 h at the same temperature. After adding water (100 ml) and $CH_2Cl_2$ (50 ml), the mixture was adjusted to pH 8.5 with 10% NaOH aq. The organic layer was separated, successively washed with $H_2O$ and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from a mixture of EtOH and $Et_2O$ to afford **3a** (0.97 g, 55.6%), mp 127—129 °C. IR (Nujol): 1625, 1520 $cm^{-1}$. MS *m/z*: 416 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.50—3.80 (8H, m), 2.15 (3H, s), 2.45 (3H, s), 7.35—7.70 (4H, m), 7.67 (1H, s), 7.90—8.35 (4H, m), 8.65—8.80 (1H, m). Compound **3b** was prepared by the same procedures employed in the preparation of **3a**.

4-Methyl-*N*-(2-morpholinoethyl)-2-(3-nitrophenyl)-6-phenyl-3-pyridinecarboxamide (**3b**): Yield 66.1%, mp 147—148 °C. IR (Nujol): 3280, 1625, 1525 $cm^{-1}$. MS *m/z* 446 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 2.10—2.40 (6H, m), 2.51 (3H, s), 3.20—3.70 (6H, m), 6.20 (1H, br), 7.35—7.70 (5H, m), 7.90—8.35 (4H, m), 8.65—8.80 (1H, m). Elemental analysis data of these compounds are listed in Table I.

**Ethyl 2-Nitro-3-(3-nitrophenyl)-5-oxo-5-phenylpentanoate (18a)** A mixture of **8a** (0.5 g), ethyl nitroacetate (0.29 g) and piperidine (3 drops) in a mixture of dioxane (5 ml) and EtOH (5 ml) was refluxed for 2 h. After being cooled to room temperature, the reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography on $SiO_2$ (50 g) with benzene as eluent. The fractions containing **18a** were evaporated *in vacuo*, and the residual crystalline material was recrystallized from EtOH to afford **18a** (0.15 g, 19.7%), mp 102—104 °C. IR (Nujol): 1750, 1685, 1565, 1538 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.12, 1.26 (total 3H, each t, $J$=7 Hz), 3.50—4.80 (2H, m), 4.12, 4.27 (total 2H, each q, $J$=7 Hz), 4.40—4.80 (1H, m), 5.57, 5.66 (total 1H, each d, $J$=6 Hz), 7.25—8.30 (9H, m). *Anal.* Calcd for $C_{19}H_{18}N_2O_7$: C, 59.06; H, 4.70; N, 7.25. Found: C, 59.47; H, 4.65; N, 7.25. Compound **18b** was synthesized by the same procedures employed in the preparation of **18a**.

Ethyl 2-Nitro-3-(4-nitrophenyl)-5-oxo-5-phenylpentanoate (**18b**): Yield 83.1%, mp 118—121 °C. IR (Nujol): 1730, 1680, 1550 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.23 (3H, t, $J$=7 Hz), 3.50—3.80 (2H, m), 4.30 (2H, q, $J$=7 Hz), 4.40—4.90 (1H, m), 5.50—5.80 (1H, m), 7.40—8.33 (9H, m). *Anal.* Calcd for $C_{19}H_{18}N_2O_7$: C, 59.06; H, 4.70; N, 7.25. Found: C, 59.26; H, 4.86; N, 7.20.

**Ethyl 2,5-Dioxo-3-(3-nitrophenyl)-5-phenylpentanoate (20a)** To a solution of **18a** (2.0 g) in a mixture of MeOH (30 ml) and $CH_2Cl_2$ (30 ml) was added NaOMe (0.28 g) and stirred for 10 min at 20 °C. The reaction mixture was then cooled to −60 °C, and a stream of ozone-oxygen was passed through until the reaction mixture was light blue. After 30 min, the reaction mixture was purged with nitrogen stream to remove excess ozone, and then treated with dimethyl sulfide (1 ml) at −60 °C and slowly allowed to come to room temperature. Then the reaction mixture was poured into a mixture of $CH_2Cl_2$ (50 ml) and $H_2O$ (50 ml). The organic layer was separated, washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from EtOH to afford **20a** (1.57 g, 85.3%), mp 70—71 °C. IR (Nujol): 1733, 1685, 1535 $cm^{-1}$. MS *m/z*: 356 ($M^+$ + 1). $^1$H-NMR ($CDCl_3$) $\delta$: 1.37 (3H, t, $J$=7 Hz), 3.20—4.10 (2H, m), 4.30 (2H, q, $J$=7 Hz), 5.10—5.40 (1H, m), 7.30—8.30 (9H, m). *Anal.* Calcd for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 64.60; H, 4.61; N, 3.94. Compound **20b** was synthesized by the same procedures employed in the preparation of **20a**.

Ethyl 2,5-Dioxo-3-(4-nitrophenyl)-5-phenylpentanoate (**20b**): Yield 73.6%, mp 77—80 °C. IR (Nujol): 1745, 1715, 1505, 1345 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.33 (3H, t, $J$=7 Hz), 3.50 (1H, dd, $J$=18, 4.5 Hz), 4.05 (1H, dd, $J$=18, 10 Hz), 4.30 (2H, q, $J$=7 Hz), 5.25 (1H, dd, $J$=10, 4.5 Hz), 7.30—7.75 (5H, m), 7.80—8.30 (4H, m). *Anal.* Calcd for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 64.59; H, 4.89; N, 3.86.

**Ethyl 1,4-Dihydro-4-(3-nitrophenyl)-6-phenyl-3-pyridazinecarboxylate (7a)** A mixture of **20a** (1.5 g) and hydrazine monohydrate (0.24 g) in EtOH (30 ml) was refluxed for 5.5 h. After evaporating the solvent *in vacuo*, the residue was purified by column chromatography on $SiO_2$ (50 g) with benzene–AcOEt (50 : 1) as eluent. The fractions containing **7a** were evaporated *in vacuo* and the residual crystalline material was

recrystallized from EtOH to afford **7a** (0.52 g, 34.6%), mp 133—134 °C. IR (Nujol): 3300, 1710, 1535 $cm^{-1}$. $^1$H-NMR (200 MHz, DMSO-$d_6$) $\delta$: 1.21 (3H, t, $J$=7.1 Hz), 4.13, 4.15 (total 2H, each q, $J$=7.1 Hz), 4.94 (1H, d, $J$=5.7 Hz), 5.37 (1H, dd, $J$=5.7, 2.4 Hz), 7.40—7.71 (7H, m), 8.00—8.15 (2H, m), 10.84 (1H, d, $J$=2.4 Hz). *Anal.* Calcd for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 65.17; H, 5.02; N, 12.02. Compound **7b** was synthesized by the same procedures employed in the preparation of **7a**.

Ethyl 1,4-Dihydro-4-(4-nitrophenyl)-6-phenyl-3-pyridazinecarboxylate (**7b**): Yield 97.9%, mp 139—142 °C. IR (Nujol): 1695, 1585 $cm^{-1}$. $^1$H-NMR (200 MHz, DMSO-$d_6$) $\delta$: 1.21 (3H, t, $J$=7.1 Hz), 4.13, 4.15 (total 2H, each q, $J$=7.1 Hz), 4.90 (1H, d, $J$=5.7 Hz), 5.33 (1H, dd, $J$=5.7, 2.3 Hz), 7.35—7.60 (7H, m), 8.21 (2H, d, $J$=8.8 Hz), 10.83 (1H, d, $J$=2.3 Hz). *Anal.* Calcd for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 65.14; H, 5.09; N, 12.10.

**Ethyl 4-(3-Nitrophenyl)-6-phenyl-3-pyridazinecarboxylate (21a)** To a solution of **7a** (0.4 g) in $CHCl_3$ (6 ml) was added activated $MnO_2$ (2 g) and the mixture was refluxed for 30 min with vigorous stirring. After being cooled to room temperature, the $MnO_2$ was filtered off. The filtrate was evaporated *in vacuo*, and the residual precipitate was recrystallized from EtOH to afford **21a** (0.2 g, 50.3%), mp 121—122 °C. IR (Nujol): 1738, 1530 $cm^{-1}$. MS *m/z*: 349 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.30 (3H, t, $J$=7 Hz), 4.38 (2H, q, $J$=7 Hz), 7.40—7.80 (5H, m), 7.88 (1H, s), 8.00—8.40 (4H, m). *Anal.* Calcd for $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.33; N, 12.03. Found: C, 65.66; H, 4.32; N, 12.11. Compound **21b** was synthesized by the same procedures employed in the preparation of **21a**.

Ethyl 4-(4-Nitrophenyl)-6-phenyl-3-pyridazinecarboxylate (**21b**): Yield 75.4%, mp 162—164 °C. IR (Nujol): 1715, 1505, 1350 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.28 (3H, t, $J$=7 Hz), 4.34 (2H, q, $J$=7 Hz), 7.40—7.60 (3H, m), 7.57 (2H, d, $J$=9 Hz), 7.80 (1H, s), 8.00—8.20 (2H, m), 8.28 (2H, d, $J$=9 Hz). *Anal.* Calcd for $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.33; N, 12.03. Found: C, 65.51; H, 4.35; N, 12.14.

**Typical Example for the Preparation of Amide Derivatives (4a—d)** *N*-(2-Dimethylaminoethyl)-4-(3-nitrophenyl)-6-phenyl-3-pyridazinecarboxamide (**4c**): A mixture of **21a** (1.0 g) and 2-dimethylaminoethylamine (0.75 g) was heated at 90 °C for 30 min. After being cooled to room temperature the resulting crystalline material was recrystallized from $Et_2O$ to afford **4c** (1.04 g, 92.9%), mp 157—158 °C. IR (Nujol): 1658, 1590, 1535 $cm^{-1}$. MS *m/z*: 391 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 2.28 (6H, s), 2.53 (2H, t, $J$=6 Hz), 3.50 (2H, td, $J$=6, 6 Hz), 7.35—7.75 (5H, m), 7.81 (1H, s), 7.95—8.40 (4H, m), 8.45 (1H, t, $J$=6 Hz). The following compounds were synthesized by the same procedures employed in the preparation of **4c**.

3-(4-Methylpiperazin-1-ylcarbonyl)-4-(3-nitrophenyl)-6-phenylpyridazine (**4a**): Yield 11.6%, mp 180—181 °C. IR (Nujol): 1635, 1545, 1353 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.33 (3H, s), 2.40 (2H, t, $J$=5.5 Hz), 2.46 (2H, t, $J$=5.5 Hz), 3.50 (2H, t, $J$=5.5 Hz), 3.80 (2H, t, $J$=5.5 Hz), 7.40—7.65 (3H, m), 7.76 (1H, dd, $J$=9, 9 Hz), 7.87 (1H, ddd, $J$=9, 2, 2 Hz), 7.91 (1H, s), 8.00—8.20 (2H, m), 8.31 (1H, ddd, $J$=9, 2, 2 Hz), 8.35 (1H, dd, $J$=2, 2 Hz). MS *m/z*: 403 ($M^+$).

*N*-(2-Morpholinoethyl)-4-(3-nitrophenyl)-6-phenylpyridazinecarboxamide (**4b**): Yield 88.7%, mp 134—135 °C. IR (Nujol): 3280, 1640, 1535 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.35—2.65 (4H, m), 2.60 (2H, t, $J$=6 Hz), 3.53 (2H, td, $J$=6, 6 Hz), 3.60—3.85 (4H, m), 7.40—7.75 (5H, m), 7.81 (1H, s), 8.00—8.40 (4H, m), 8.43 (1H, t, $J$=6 Hz). MS *m/z*: 433 ($M^+$).

3-(4-Methylpiperazin-1-ylcarbonyl)-4-(4-nitrophenyl)-6-phenylpyridazine (**4d**): Yield 25.1%, mp 101—103 °C. IR (Nujol): 1628, 1525 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.25 (3H, s), 2.15—2.50 (4H, m), 3.25—3.45 (2H, m), 3.55—3.85 (2H, m), 7.40—7.60 (3H, m), 7.68 (2H, d, $J$=9 Hz), 7.85 (1H, s), 7.95—8.20 (2H, m), 8.26 (2H, d, $J$=9 Hz). MS *m/z*: 403 ($M^+$). Elemental analysis data of **4a—e** are listed in Table I.

**3-Hydroxymethyl-4-(3-nitrophenyl)-6-phenylpyridazine (22)** To a solution of **21a** (1.0 g) in a mixture of EtOH (10 ml) and THF (10 ml) was added $NaBH_4$ (0.22 g) and the mixture was stirred for 3 h at room temperature. Then the reaction mixture was poured into a mixture of AcOEt (100 ml) and $H_2O$ (50 ml). The organic layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on $SiO_2$ (50 g) with benzene–AcOEt (5 : 1) as eluent. The fractions containing **22** were evaporated *in vacuo*. The residue was recrystallized from EtOH–$CHCl_3$ to afford **22** (0.19 g, 21.6%), mp 162—164 °C. IR (Nujol): 3300, 1525, 1360 $cm^{-1}$. MS *m/z*: 307 ($M^+$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 4.75 (2H, d, $J$=6 Hz), 5.60 (1H, t, $J$=6 Hz), 7.35—7.60 (3H, m), 7.76 (1H, dd, $J$=8, 8 Hz), 8.00—8.40 (4H, m), 8.18 (1H, s), 8.58 (1H, dd, $J$=2, 2 Hz). *Anal.* Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.68. Found: C, 66.46; H, 4.11; N, 13.80.

**3-Bromomethyl-4-(3-nitrophenyl)-6-phenylpyridazine (23)** A solution of **22** (0.86 g) in THF (5 ml) was dropwise added to a solution of $PBr_3$ (0.18 ml) in a mixture of THF (10 ml) and benzene (5 ml) under ice cooling. After stirring for 4 h at the same temperature, the reaction mixture was poured into ice-water (50 ml), adjusted to pH 9.0 with saturated $K_2CO_3$ aq. and extracted with AcOEt (50 ml). The organic layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on $SiO_2$ (50 g) with $CHCl_3$–acetone (5 : 1) as eluent. The fractions containing **23** were evaporated *in vacuo*. The residue was recrystallized from $Et_2O$ to afford **23** (0.73 g, 70.4%), mp 139—140 °C (dec.). IR (Nujol): 1520, 1355 $cm^{-1}$. MS *m/z*: 368 ($M^+ - 1$). $^1$H-NMR ($CDCl_3$) $\delta$: 4.77 (2H, s), 7.77 (1H, s), 7.40—8.60 (9H, m). *Anal.* Calcd for $C_{17}H_{12}BrN_3O_2$: C, 55.16; H, 3.27; N, 11.35. Found: C, 54.87; H, 2.90; N, 11.17.

**3-(4-Methylpiperazin-1-ylmethyl)-4-(3-nitrophenyl)-6-phenylpyridazine (4e)** A mixture of **23** (0.6 g), 1-methylpiperazine (0.36 g) in iso-PrOH (6 ml) was refluxed for 30 min. After evaporating the solvent, the residue was dissolved in $CH_2Cl_2$ (50 ml), washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and the residue was purified by column chromatography on $SiO_2$ (50 g) with $CHCl_3$–MeOH (20 : 1) as eluent. The fractions containing **4e** were combined and evaporated *in vacuo*. The residue was recrystallized from EtOH to afford **4e** (0.32 g, 50.7%), mp 157—159 °C. IR (Nujol): 1520, 1355 $cm^{-1}$. MS *m/z*: 389 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 2.27 (3H, s), 2.20—2.80 (8H, m), 3.76 (2H, s), 7.40—8.50 (8H, m), 7.80 (1H, s), 8.80—9.00 (1H, m). Elemental analysis data are listed in Table I.

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**References and Notes**

1) *a*) Part III: A. Kuno, K. Katsuta, H. Sakai, M. Ohkubo, Y. Sugiyama, and H. Takasugi, *Chem. Pharm. Bull.*, **41**, 139 (1993); *b*) Part II: A. Kuno, Y. Sugiyama, K. Katsuta, H. Sakai, and H. Takasugi, *ibid.*, **40**, 2423 (1992); *c*) Part I: A. Kuno, Y. Sugiyama, K. Katsuta, T. Kamitani, and H. Takasugi, *ibid.*, **40**, 1452 (1992).
2) B. R. Baker, B-H. Ho, and G. J. Lourens, *J. Pharm. Sci.*, **56**, 737 (1967).
3) A. L. Weis, "Advances in Heterocyclic Chemistry," Vol. 38, ed. by A. R. Katritzky FRS, Academic Press, Inc., Florida, 1985, pp. 1—101.
4) F. Scavo and P. Helquist, *Tetrahedron Lett.*, **26**, 2603 (1985).
5) S. Wattanaisin and W. S. Murphy, *Synthesis*, **8**, 647 (1980).
6) J. E. McMurry, J. Melton, and H. Padgett, *J. Org. Chem.*, **39**, 259 (1974).