# Studies on Cerebral Protective Agents. VI.[1a] Synthesis of Novel 4-(4-Nitrobenzoyl)pyrimidine and Related Compounds with Anti-anoxic Activity

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**Novel pyrimidine derivatives, possessing linkages between the aryl group and the pyrimidine nucleus at the C-4 position, were prepared and tested for anti-anoxic (AA) activity in mice. Among them, 5-(4-methylpiperazin-1-ylcarbonyl)-4-(4-nitrobenzoyl)-2-phenylpyrimidine (2f, FR76659) possessed significant AA activity (10—100 mg/kg, i.p.) with low acute toxicity ($LD_{50}$ >1000 mg/kg, i.p.). Structure–activity relationships in regard to AA activity of this series of compounds were examined.**

**Keywords** cerebral protective agent; anti-anoxia; anti-lipid peroxidation; structure–activity relationship; 4-(4-nitrobenzoyl)pyrimidine; FK360

We have reported that 6-methyl-5-(4-methylpiperazin-1-ylcarbonyl)-4-(3-nitrophenyl)-2-phenylpyrimidine (**1**: FK360) (Fig. 1) exhibited cerebral protective activities in animal models [*i.e.* anti-anoxic (AA) activity and anti-lipid peroxidation (ALP) activity].[1b] The effects of synthetic modification at the C-2, C-5 and C-6 positions of the pyrimidine nucleus of **1** on AA activity have been studied.[1a,c]

In order to investigate more fully the structure–activity relationships (SARs) for AA activity and to find back-up compounds of FK360 (**1**), we have prepared new series of pyrimidine derivatives (**2** and **3**) substituted with a 3- or 4-nitrobenzoyl or a related group at the C-4 position of the pyrimidine nucleus, as shown in Fig. 1. In this paper we describe the preparation of these 4-(4-nitrobenzoyl)-pyrimidine and related compounds and the SARs in regard to AA activity of these pyrimidine derivatives.

## Chemistry

Compounds **2a**—**g** were synthesized *via* the routes shown in Charts 1 and 2.

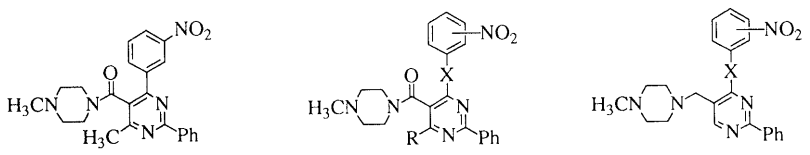
Acylation of Meldrum's acid with 3- or 4-nitrophenylacetyl chloride followed by ethanolysis afforded β-keto esters (**4a, b**).[2] The Wittig reaction of 3- or 4-nitrobenzaldehyde with (2-ethoxy-3-ethoxycarbonyl-2-(*E*)-propenyl)triphenylphosphonium iodide[3] followed by hydrolysis afforded (*E*)-γ,δ-unsaturated β-keto esters (**4c, d**). These β-keto esters (**4a**—**d**) were treated with *N*,*N*-dimethylformamide dimethylacetal and then condensed with benzamidine to afford ethyl 4-(3- or 4-nitrophenyl)-methyl-5-pyrimidinecarboxylates (**5a**—**d**), which were oxidized with selenium oxide ($SeO_2$) to afford the 4-benzoylpyridmidines (**7a, b**). The esters (**5a**—**d**, and **7a, b**) were hydrolyzed with aqueous NaOH to afford the 5-pyrimidinecarboxylic acids (**6a**—**d** and **8a, b**), which were converted into the corresponding acid chlorides according to Zollinger's method.[4] Condensation of the acid chlorides with *N*-methylpiperazine afforded the corresponding amide derivatives (**2a**—**f**). Reduction of **2e** and **2f** with sodium borohydride ($NaBH_4$) afforded the 4-arylhydroxymethylpyrimidines (**2g, h**).

The 5-aminomethylpyrimidines (**3a**—**e**) were synthesized *via* the routes shown in Chart 3.

Reduction of the esters (**5a, b**) with lithium borohydride ($LiBH_4$) afforded the 5-hydroxymethylpyrimidines (**9a, b**). These were treated with phosphorus tribromide ($PBr_3$) to afford the 5-bromomethylpyrimidines (**10a, b**), which were then condensed with *N*-methylpiperazine to afford the 5-aminomethylpyrimidines (**3a, b**). The 4-benzoylpyrimidine derivatives (**3c, d**) and the 4-arylhydroxymethylpyrimidine derivative (**3e**) were obtained according to the route described for the preparation of **2e**—**h**.

The 4-arylthiopyrimidines (**2i, j**) were synthesized *via* the routes shown in Chart 4.

Condensation of ethyl 4-mercapto-6-methyl-2-phenyl-5-pyrimidinecarboxylate (**11**), which was synthesized

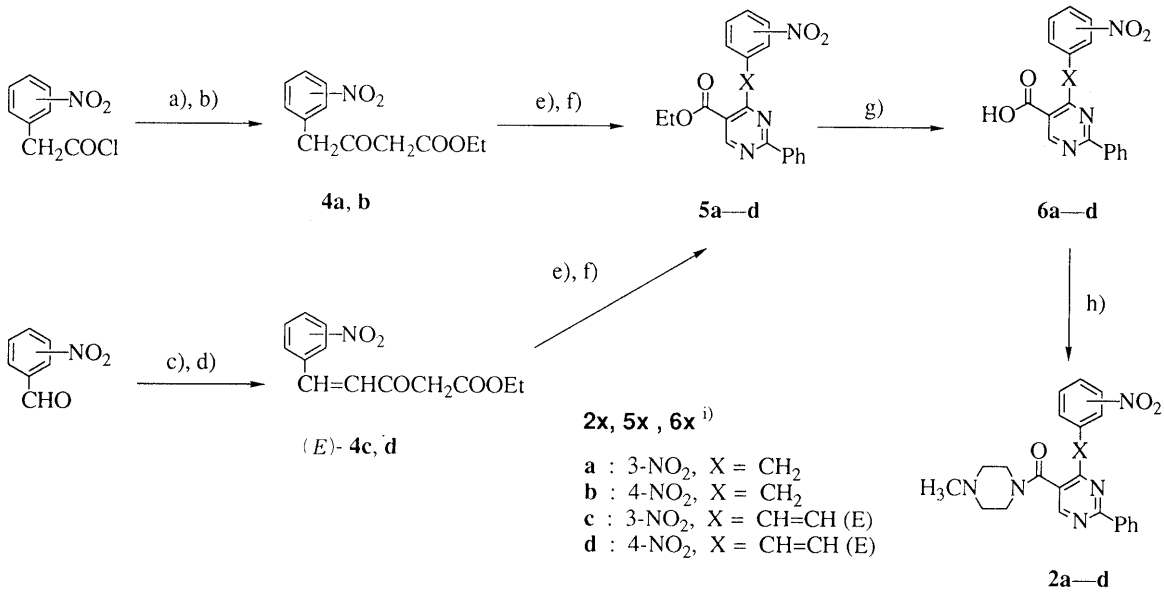


**1** (FK360) **2** **3**

X = $CH_2$, CH=CH (E), CO, CHOH, S, NH

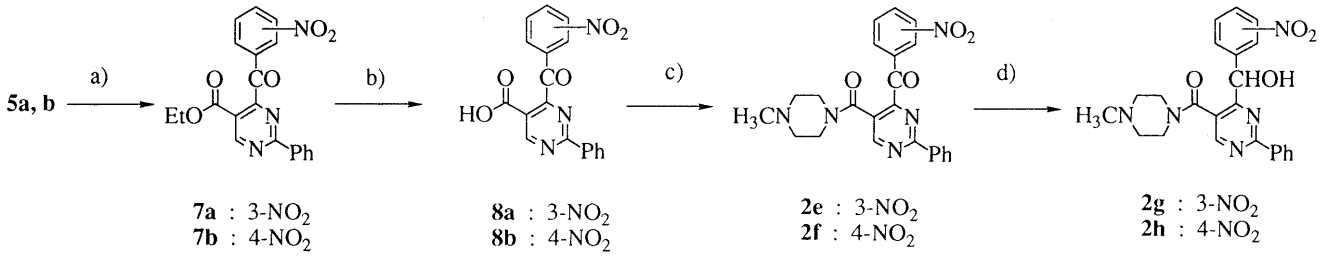
R = H or $CH_3$

Fig. 1



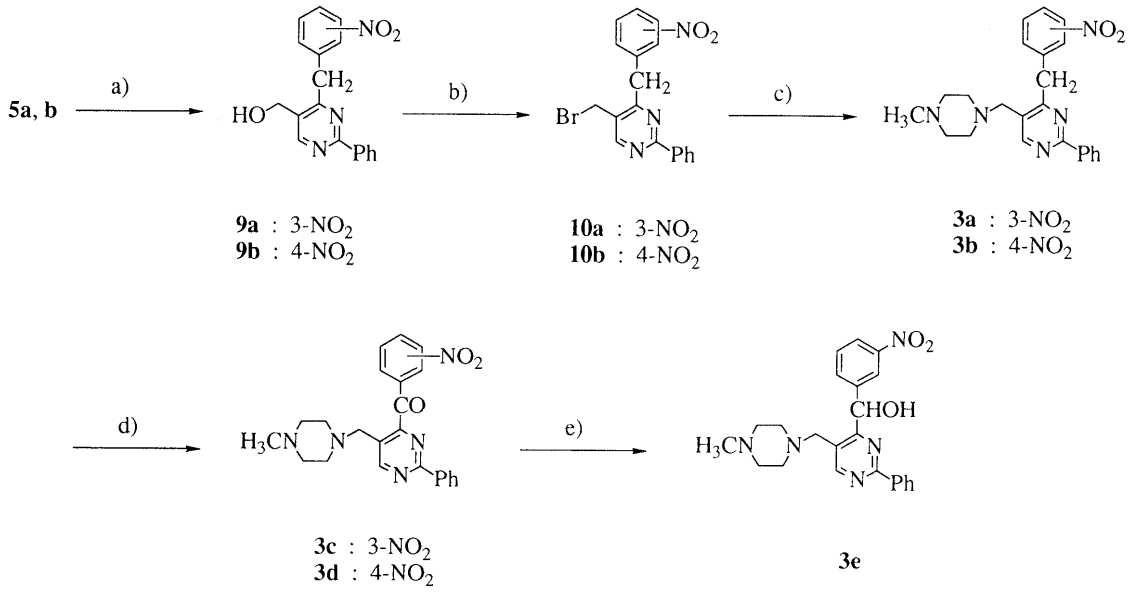

a) Meldrum's acid / pyridine, $CH_2Cl_2$ ; b) EtOH; c) (*E*)-$Ph_3P^+CH_2C(OEt)$=CHCOOEt $I^-$ / THF, NaOH aq.; d) 0.1 N $H_2SO_4$ aq. / dioxane; e) *N*,*N*-dimethylformamide dimethylacetal / benzene; f) benzamidine hydrochloride, $Et_3N$ / *n*-BuOH; g) NaOH aq. / EtOH; h) $SOCl_2$—DMF / $CH_2Cl_2$ then *N*-methylpiperazine; i) The letters assigned to compounds **2**, **5** and **6** correspond to each other.

Chart 1



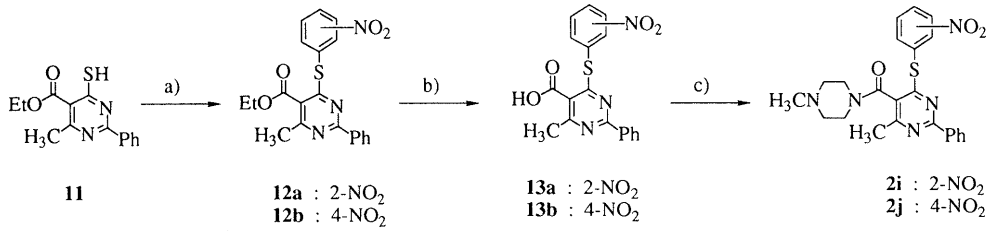

a) $SeO_2$ / dioxane; b) NaOH aq. / EtOH; c) $SOCl_2$—DMF / $CH_2Cl_2$, then *N*-methylpiperazine; d) $NaBH_4$ / MeOH

Chart 2



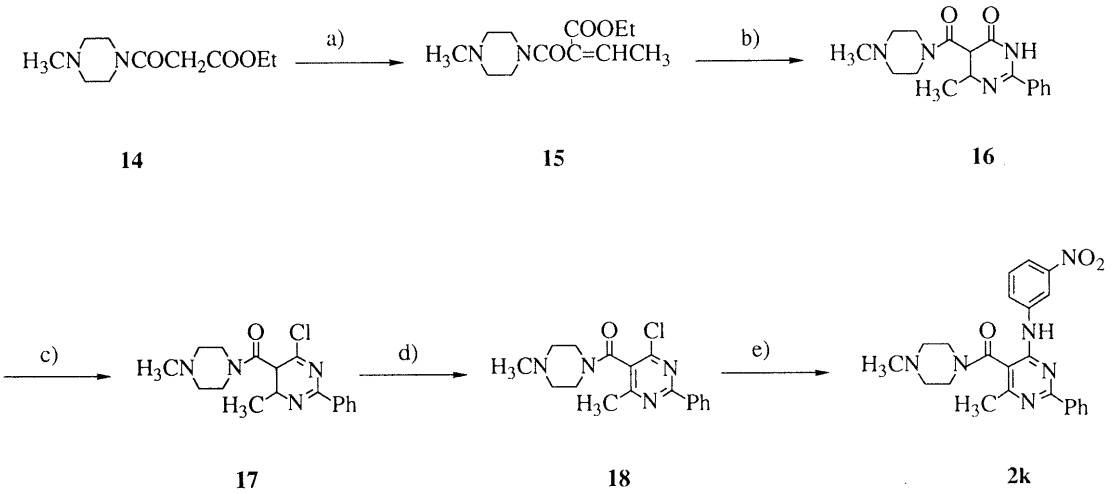

a) $LiBH_4$ / THF—IPE; b) $PBr_3$ / THF; c) *N*-methylpiperazine / IPA; d) $SeO_2$ / dioxane; e) $NaBH_4$ / MeOH

Chart 3



a) 2- or 4-chloronitrobenzene, NaH / DMF; b) NaOH aq. / MeOH; c) $SOCl_2$—DMF / $CH_2Cl_2$, then *N*-methylpiperazine

Chart 4



a) $CH_3CHO$, $TiCl_4$, pyridine / dioxane; b) benzamidine hydrochloride, EtONa / EtOH; c) $POCl_3$ / 1,2-dichloroethane; d) $MnO_2$ / $CHCl_3$; e) 3-nitroaniline, $K_2CO_3$, CuO

Chart 5

according to the literature,[5] with 2- or 4-nitrochlorobenzene afforded 4-arylthio-5-pyrimidinecarboxylates (**12a, b**). Compounds **2i** and **2j** were obtained from the esters (**12a, b**) according to the routes described for the preparation of **2a**—**f**.

The 4-arylaminopyrimidine (**2k**) was synthesized *via* the routes shown in Chart 5.

The Knoevenagel condensation[6] of **14** with acetaldehyde afforded the ethylidene (**15**), which was then converted into the 5,6-dihydropyrimidin-4(3*H*)-one (**16**) by condensation with benzamidine. Chlorination of **16** with phosphorus oxychloride ($POCl_3$) afforded the 4-chloro-5,6-dihydropyrimidine (**17**). This was oxidized with activated manganese (IV) oxide ($MnO_2$) to afford the 4-chloropyrimidine (**18**), which was then condensed with 3-nitroaniline to afford **2k**.

## Pharmacological Results and Discussion

The compounds (**2a**—**k** and **3a**—**e**) listed in Table I were tested for AA activity in mice according to the method described previously.[1d]

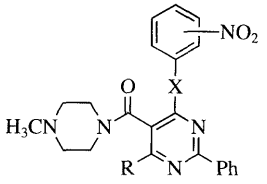
In 5-pyrimidinecarboxamide derivatives (**2a**—**k**), 4-[(4-nitrophenyl)ethenyl]pyrimidine (**2d**), 4-(4-nitrobenzoyl)-pyrimidine (**2f**), 4-[(3- or 4-nitrophenyl)hydroxymethyl]-pyrimidines (**2g, h**) and 4-[(3-nitrophenyl)amino]pyrimidine (**2k**) exhibited significant activity on AA assay by intraperitoneal administration at the dose of 32 mg/kg. Among them, compound **2f** exhibited the most potent activity, being the only compound to show significant activity at the dose of 10 mg/kg. A comparison of the results in the Table I suggests that the 4-nitrobenzoyl group at the C-4 position of the pyrimidine nucleus is the optimal substituent for the expression of AA activity in this series.

Among the 5-aminomethylpyrimidine derivatives (**3a**—**e**), only 4-(4-nitrobenzoyl)pyrimidine derivative (**3d**) exhibited significant AA activity, but the activity was decreased as compared to that of the 4-(4-nitrobenzoyl)-5-pyrimidinecarboxamide derivative (**2f**).

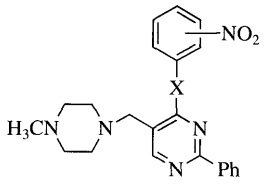
Compound **2f** (FR76659) was further evaluated for AA activity by oral administration, acute toxicity in mice and ALP activity (Table II). Compound **2f** exhibited AA activity by intraperitoneal administration at a lower dose (10 mg/kg) than that of FK360 (**1**), and also showed significant AA activity by oral administration (100 mg/kg) with lower acute toxicity ($LD_{50} > 1000$ mg/kg, i.p.) than that of FK360 ($LD_{50} > 560$ mg/kg, i.p.). This compound also exhibited ALP activity ($IC_{50} = 1.0 \times 10^{-6}$ M) more potent than that of FK360 ($IC_{50} = 6.7 \times 10^{-6}$ M).

In conclusion, 4-(4-nitrobenzoyl)pyrimidine (**2f**) exhibited significant cerebral protective activities with low

TABLE I. Physical Properties and AA Activity for 5-Pyrimidinecarboxamide Derivatives (**2a—k**) and 5-Aminomethylpyrimidine Derivatives (**3a—e**)



**2a—k**



**3a—e**

| Compound No. | X | Position of $-NO_2$ | R | Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10 | 32 | Yield (%) | mp (°C) (Recryst. solv.) | Formula | Analysis (%) Calcd (Found) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **2a** | $CH_2$ | 3 | H | | 106 | 40.1 | 133—135 (MeOH) | $C_{23}H_{23}N_5O_3 \cdot HCl \cdot H_2O$ | 58.53 (58.16 | 5.55 5.74 | 14.84 14.75) |
| **2b** | $CH_2$ | 4 | H | | 112 | 33.4 | 141—142 (Ether) | $C_{23}H_{23}N_5O_3$ | 66.17 (65.85 | 5.55 5.58 | 16.78 16.62) |
| **2c** | CH=CH(E) | 3 | H | | 111 | 86.3 | 194—195 (Ether) | $C_{24}H_{23}N_5O_3 \cdot 0.5H_2O$ | 65.81 (66.14 | 5.52 5.63 | 15.99 16.20) |
| **2d** | CH=CH(E) | 4 | H | 107 | 123[d] | 66.5 | 173—174 (Ether) | $C_{24}H_{23}N_5O_3$ | 67.12 (67.38 | 5.40 5.61 | 16.31 16.25) |
| **2e** | CO | 3 | H | | 108 | 64.3 | 187—188 (Ether) | $C_{23}H_{21}N_5O_4$ | 64.03 (63.91 | 4.91 5.15 | 16.23 15.79) |
| **2f** | CO | 4 | H | 119[b] | 127[b] | 46.8 | 169—170 (Ether) | $C_{23}H_{21}N_5O_4$ | 64.03 (64.12 | 4.91 4.90 | 16.23 16.03) |
| **2g** | CHOH | 3 | H | | 118[b] | 25.9 | 146—147 (Ether) | $C_{23}H_{23}N_5O_4$ | 63.73 (64.02 | 5.35 5.51 | 16.16 16.19) |
| **2h** | CHOH | 4 | H | 108 | 120[c] | 8.8 | 163—165 (Ether) | $C_{23}H_{23}N_5O_4$ | 63.73 (63.27 | 5.35 5.57 | 16.16 15.80) |
| **2i** | S | 2 | $CH_3$ | 103 | 106 | 56.1 | 122—123 (Ether) | $C_{23}H_{23}N_5O_3S$ | 61.45 (61.47 | 5.16 5.27 | 15.58 15.77) |
| **2j** | S | 4 | $CH_3$ | | 95 | 81.8 | 202—203 (EtOH) | $C_{23}H_{23}N_5O_3S$ | 61.45 (60.84 | 5.16 5.24 | 15.58 15.45) |
| **2k** | NH | 3 | $CH_3$ | 101 | 119[b] | 18.4 | 176—177 (EtOH) | $C_{23}H_{24}N_6O_3$ | 63.87 (64.23 | 5.59 5.72 | 19.43 19.46) |
| **3a** | $CH_2$ | 3 | — | | 101 | 59.6 | 85—87 (Ether) | $C_{23}H_{25}N_5O_2 \cdot 0.2H_2O$ | 67.86 (67.74 | 6.29 6.49 | 17.20 17.02) |
| **3b** | $CH_2$ | 4 | — | | 115 | 82.6 | 103—104 (Ether) | $C_{23}H_{25}N_5O_2$ | 68.46 (68.06 | 6.25 6.00 | 17.36 17.50) |
| **3c** | CO | 3 | — | | 109 | 24.6 | 143—144 (Ether) | $C_{23}H_{23}N_5O_3$ | 66.17 (65.77 | 5.55 5.28 | 16.78 16.47) |
| **3d** | CO | 4 | — | | 116[d] | 28.7 | 126—127 (Ether) | $C_{23}H_{23}N_5O_3$ | 66.17 (66.03 | 5.55 5.30 | 16.78 16.52) |
| **3e** | CHOH | 3 | — | | 114 | 62.0 | 138—139 (Ether) | $C_{23}H_{25}N_5O_3$ | 65.85 (65.69 | 6.01 5.82 | 16.70 16.63) |

*a*) Each value represents the mean of 5 to 10 animals compared with the control group. *b*) $p<0.05$. *c*) $p<0.01$. *d*) $p<0.001$. Values without superscripts are not statistically significantly different from the control.

TABLE II. Pharmacological data for 4-(4-Nitrobenzoyl)-2-phenylpyrimidine (**2f**) and FK360 (**1**)

| Compd. No. | Anti-anoxia (% of control) (mg/kg) 10 | 32 | Upper; i.p. Lower; *p.o.* 100 | Lipid peroxidation $IC_{50}$ (M) | Acute toxicity[a] $LD_{50}$ (mg/kg, i.p.) |
|---|---|---|---|---|---|
| **2f** | 119[b] | 127[b] | 122[c] | $1.0 \times 10^{-6}$ | >1000 |
| FK360 (**1**) | 105 | 100 | 115[d] | $6.7 \times 10^{-6}$ | >560 |
| | 104 | 125[c] | 168[c] | | |
| | | 114 | 125[c] | | |

*a*) Male ICR mice weighing 25—30 g were used in groups of 5—10 animals for each test drug. The $LD_{50}$ value was calculated from the lethality within 7 d after intraperitoneal administration of a test compound. *b*) $p<0.05$. *c*) $p<0.01$. *d*) $p<0.001$. Values without superscripts are not statistically significantly different from the control.

acute toxicity. These results showed that replacement of the 3-nitrophenyl group at the C-4 position of the pyrimidine nucleus of FK360 (**1**) with a 4-nitrobenzoyl group is beneficial for the expression of AA and ALP activities. The SAR information obtained may be useful for the design and synthesis of new cerebral protective agents.

## Experimental

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

**Ethyl 3-Oxo-4-(4-nitrophenyl)butanoate (4b)** A solution of 4-

nitrophenylacetyl chloride (82.2 g, 412 mmol) in $CH_2Cl_2$ (500 ml) was added dropwise to a mixture of Meldrum's acid (49.6 g, 343 mmol) and pyridine (55.5 ml) in $CH_2Cl_2$ (200 ml) at 0 °C over 1 h. The mixture was stirred at room temperature for 1 h, then poured into water (500 ml) and acidified to pH 2.0 with 10% aqueous HCl. The organic layer was washed with brine (100 ml), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was dissolved in EtOH (500 ml) and refluxed for 1 h. The solution was evaporated *in vacuo* to give a residue, which was recrystallized from EtOH to afford **4b** (27.8 g, 26.9%) as a pale yellow solid, mp 79—81 °C. IR (Nujol): 1730, 1710 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.28 (3H, q, $J$=7 Hz), 3.52 (2H, s), 4.00 (2H, s), 4.25 (2H, t, $J$=7 Hz), 7.42 (2H, d, $J$=9 Hz), 8.23 (2H, d, $J$=9 Hz). MS $m/z$: 251 ($M^+$). Compound **4a** was prepared by the same procedures as employed for the preparation of **4b**. Compounds **4a** and **4b** were not further purified or analyzed before use in the next step.

Ethyl 3-Oxo-4-(3-nitrophenyl)butanoate (**4a**): Yield 28.9% as white needles, mp 56—57 °C (EtOH). IR (Nujol): 1745, 1710 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.30 (3H, q, $J$=7 Hz), 3.58 (2H, s), 4.04 (2H, s), 4.26 (2H, t, $J$=7 Hz), 7.50—7.65 (2H, m), 8.10—8.22 (2H, m). MS $m/z$: 251 ($M^+$).

**Ethyl 3-Oxo-5-(3-nitrophenyl)-4-(*E*)-pentenoate (4c)** A mixture of 3-nitrobenzaldehyde (7.6 g, 50.0 mmol) and (3-ethoxycarbonyl-2-ethoxy-2-(*E*)-propenyl)triphenylphosphonium iodide (28.5 g, 52.5 mmol) in tetrahydrofuran (THF) (76 ml) and water (38 ml) was adjusted to pH 11.0 with aqueous 4 N NaOH, stirred at room temperature for 1 h, and extracted with ethyl acetate (200 ml). The extract was washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was dissolved in ethyl acetate (20 ml) and the insolubles were filtered off. The filtrate was evaporated *in vacuo* and the residue was dissolved in a mixture of dioxane (100 ml) and aqueous 0.1 N $H_2SO_4$ (100 ml), and refluxed for 4 h. The reaction mixture was extracted with ethyl acetate (200 ml). The extract was washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from *n*-hexane to afford **4c** (5.3 g, 40.3%) as a yellow solid, mp 99—101 °C. IR (Nujol): 1650, 1620 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.35 (3H, q, $J$=7 Hz), 4.26 (2H, t, $J$=7 Hz), 5.25 (2H, s), 7.50—7.72 (5H, m), 8.10 (1H, d, $J$=15 Hz), 8.20 (1H, d, $J$=15 Hz), 8.40—8.68 (4H, m), 9.34 (1H, s). MS $m/z$: 263 ($M^+$). Compound **4d** was prepared by the same procedures as employed for the preparation of **4c**. Compounds **4d** and **4c** were not further purified or analyzed before use in the next step.

Ethyl 3-Oxo-4-(4-nitrophenyl)-4-(*E*)-pentenoate (**4d**): Yield 30.5% as a yellow solid, mp 112—114 °C (*n*-hexane). IR (Nujol): 1640, 1605 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.30 (3H, q, $J$=7 Hz), 4.23 (2H, t, $J$=7 Hz), 5.20 (2H, s), 6.56 (1H, d, $J$=14 Hz), 7.48 (1H, d, $J$=14 Hz), 7.66 (2H, d, $J$=9 Hz), 8.24 (2H, d, $J$=9 Hz). MS $m/z$: 263 ($M^+$).

**Ethyl 4-[(4-Nitrophenyl)methyl]-2-phenyl-5-pyrimidinecarboxylate (5b)** A mixture of **4b** (9.8 g, 39 mmol) and *N*,*N*-dimethylformamide dimethylacetal (6.22 ml, 47 mmol) in benzene (138 ml) was stirred at room temperature for 3 h. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in a mixture of $CHCl_3$ (200 ml) and $H_2O$ (100 ml). The organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent by evaporation, the residue was dissolved in *n*-BuOH (100 ml). Benzamidine hydrochloride (6.1 g, 39 mmol) and triethylamine (6.5 ml) were added, and the mixture was refluxed for 40 min. It was evaporated *in vacuo* to afford a residue, which was dissolved in a mixture of ethyl acetate (200 ml) and $H_2O$ (100 ml). The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was recrystallized from diisopropyl ether to afford **5b** (3.2 g, 22.6%) as a white solid, mp 122—123 °C. IR (Nujol): 1705 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.42 (3H, q, $J$=7 Hz), 4.40 (2H, t, $J$=7 Hz), 4.69 (2H, s), 7.55—7.66 (5H, m), 8.10—8.70 (4H, m), 9.24 (1H, s). MS $m/z$: 363 ($M^+$). *Anal.* Calcd for $C_{20}H_{17}N_3O_4 \cdot 0.3H_2O$: C, 65.14; H, 4.73; N, 11.39. Found: C, 65.06; H, 4.84; N, 11.13. The following compounds were prepared by the same procedures as employed for the preparation of **5b**. Compound **5c** was not further purified or analyzed before use in the next step.

Ethyl 4-[(3-Nitrophenyl)methyl]-2-phenyl-5-pyrimidinecarboxylate (**5a**): Yield 61.5% as a white solid, mp 114—115 °C (ether). IR (Nujol): 1725 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.43 (3H, t, $J$=7 Hz), 4.46 (2H, q, $J$=7 Hz), 4.74 (2H, s), 7.3—7.6 (4H, m), 7.7—7.9 (1H, m), 8.0—8.2 (1H, m), 8.3—8.6 (3H, m), 9.31 (1H, s). MS $m/z$: 363 ($M^+$). *Anal.* Calcd for $C_{20}H_{17}N_3O_4$: C, 66.11; H, 4.72; N, 11.57. Found: C, 66.30; H, 4.66; N, 11.80.

Ethyl 4-[(*E*)-2-(3-Nitrophenyl)ethenyl]-2-phenyl-5-pyrimidinecarboxylate (**5c**): Yield 56.5% as a pale yellow solid, mp 138—140 °C (ether–EtOH). IR (Nujol): 1715, 1630 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.49 (3H, t, $J$=7 Hz), 4.51 (2H, q, $J$=7 Hz), 7.4—7.7 (4H, m), 7.9—8.3 (2H, m), 8.40 (2H, m), 8.45—8.72 (3H, m), 9.34 (1H, s). MS $m/z$: 375 ($M^+$).

Ethyl 4-[(*E*)-2-(4-Nitrophenyl)ethenyl]-2-phenyl-5-pyrimidinecarboxylate (**5d**): Yield 38.9% as a yellow solid, mp 150—151 °C (EtOH). IR (Nujol): 1705 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.43 (3H, t, $J$=7 Hz), 4.47 (2H, q, $J$=7 Hz), 7.47—8.63 (11H, m), 9.27 (1H, s). MS $m/z$: 375 ($M^+$). *Anal.* Calcd for $C_{21}H_{17}N_3O_4$: C, 67.19; H, 4.56; N, 11.19. Found: C, 67.03; H, 4.36; N, 11.16.

**Ethyl 4-(4-Nitrobenzoyl)-2-phenyl-5-pyrimidinecarboxylate (7b)** A mixture of **5b** (5.9 g, 16 mmol) and $SeO_2$ (2.88 g, 26 mmol) in dioxane (60 ml) and $H_2O$ (0.2 ml) was refluxed for 4 h. After filtration to remove insoluble material, the filtrate was evaporated *in vacuo*. The residue was dissolved in $CHCl_3$ and this solution was washed with $H_2O$, brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was recrystallized from diethyl ether to afford **7b** (4.55 g, 74.4%) as a pale yellow solid, mp 125—126 °C. IR (Nujol): 1705, 1695 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.23 (3H, t, $J$=7 Hz), 4.31 (2H, q, $J$=7 Hz), 7.40—7.70 (3H, m), 8.06 (2H, d, $J$=8 Hz), 8.34 (2H, d, $J$=8 Hz), 8.45—8.65 (2H, m), 9.47 (1H, s). MS $m/z$: 377 ($M^+$). *Anal.* Calcd for $C_{20}H_{15}N_3O_4$: C, 63.66; H, 4.01; N, 11.14. Found: C, 63.40; H, 3.84; N, 11.06. Compounds **3c**, **3d** and **7a** were prepared by the same procedures as employed for the preparation of **7b**. Physical properties and spectral data of **3c** and **3d** are listed in Tables I and III. Compound **7a** was not further purified or analyzed before use in the next step.

Ethyl 4-(3-Nitrobenzoyl)-2-phenyl-5-pyrimidinecarboxylate (**7a**): Yield 38.5% as a white solid, mp 135—137 °C (ether). IR (Nujol): 1716, 1695 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.23 (3H, t, $J$=7 Hz), 4.36 (2H, q, $J$=7 Hz), 7.4—7.6 (3H, m), 7.71 (1H, dd, $J$=8, 8 Hz), 8.23 (1H, ddd, $J$=2, 2, 8 Hz), 8.3—8.6 (3H, m), 8.71 (1H, dd, $J$=2, 2 Hz), 9.47 (1H, s). MS $m/z$: 377 ($M^+$).

**4-[(4-Nitrophenyl)methyl]-2-phenyl-5-pyrimidinecarboxylic Acid (6b)** A mixture of **5b** (0.3 g, 6.4 mmol) and aqueous NaOH (0.04 g in 3 ml $H_2O$) in EtOH (10 ml) was stirred at 40 °C for 10 min. After removal of the solvent by evaporation, the residue was dissolved in $H_2O$ (50 ml) and the solution was adjusted to pH 2.5 with 10% aqueous HCl. The resulting precipitate was collected by filtration, washed with $H_2O$ and dried to afford **6b** (0.2 g, 72.2%) as a white powder, mp 275—277 °C. IR (Nujol): 1685, 1600 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 4.75 (2H, s), 7.4—7.7 (5H, m), 8.0—8.6 (4H, m), 9.21 (1H, s). MS $m/z$: 335 ($M^+$). *Anal.* Calcd for $C_{18}H_{13}N_3O_4$: C, 64.48; H, 3.91; N, 12.51. Found: C, 64.39; H, 3.96; N, 12.38. The following compounds were prepared by the same procedures as employed for the preparation of **6b**. Compounds **6a**, **6c**, **8a**, **8b** and **13a** were not further purified or analyzed before use in the next step.

4-[(3-Nitrophenyl)methyl]-2-phenyl-5-pyrimidinecarboxylic Acid (**6a**): Yield 97.6% as a white powder, mp 263 °C (dec.) (ether). IR (Nujol): 1680 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 4.70 (2H, s), 7.46—7.92 (5H, m), 8.00—8.43 (4H, m), 9.20 (1H, s). MS $m/z$: 335 ($M^+$).

4-[2-(*E*)-(3-Nitrophenyl)ethenyl]-2-phenyl-5-pyrimidinecarboxylic Acid (**6c**): Yield 86.5% as a pale yellow powder, mp 243—245 °C (ether). IR (Nujol): 1680, 1620 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 7.3—8.8 (11H, m), 9.28 (1H, s). MS $m/z$: 347 ($M^+$).

4-[2-(*E*)-3-Nitrophenyl)ethenyl]-2-phenyl-5-pyrimidinecarboxylic Acid (**6d**): Yield 83.2% as a white powder, mp 281—283 °C (dec.) (ether). IR (Nujol): 1690 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 7.50—7.77 (3H, m), 7.86—8.70 (8H, m), 9.23 (1H, s). MS $m/z$: 347 ($M^+$). *Anal.* Calcd for $C_{19}H_{13}N_3O_4$: C, 65.70; H, 3.77; N, 12.00. Found: C, 65.55; H, 3.64; N, 12.09.

4-(3-Nitrobenzoyl)-2-phenyl-5-pyrimidinecarboxylic Acid (**8a**): Yield 88.0% as a yellow powder, mp 215 °C (dec.) (ether). IR (Nujol): 1675 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 7.25—7.98 (5H, m), 8.15—8.60 (4H, m), 9.42 (1H, s). MS $m/z$: 349 ($M^+$).

4-(4-Nitrobenzoyl)-2-phenyl-5-pyrimidinecarboxylic Acid (**8b**): Yield 92.2% as a pale yellow powder, mp 249—250 °C (ether). IR (Nujol): 1680 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 7.50—7.70 (3H, m), 8.14 (2H, $J$=9 Hz), 8.25—8.55 (4H, m), 9.50 (1H, s). MS $m/z$: 349 ($M^+$).

6-Methyl-4-[(2-nitrophenyl)thio]-2-phenyl-5-pyrimidinecarboxylic Acid (**13a**): Yield 67.8% as a white powder, mp 235—237 °C (ether). IR (Nujol): 1660 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.71 (3H, s), 7.31—7.50 (3H, m), 7.76—7.90 (5H, m), 8.10—8.20 (1H, m). MS $m/z$: 367 ($M^+$).

6-Methyl-4-[(4-nitrophenyl)thio]-2-phenyl-5-pyrimidinecarboxylic Acid (**13**): Yield 59.9% as a white powder, mp 220—224 °C (ether). IR

(Nujol): 1675 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.70 (3H, s), 7.33—7.46 (3H, m), 7.88 (2H, d, $J$=9 Hz), 7.83—7.88 (2H, m), 8.31 (2H, d, $J$=9 Hz). MS $m/z$: 367 ($M^+$). *Anal.* Calcd for $C_{18}H_{13}N_3O_4S$: C, 58.85; H, 3.57; N, 11.44. Found: C, 59.19; H, 3.60; N, 11.38.

**5-(4-Methylpiperazin-1-ylcarbonyl)-4-(4-nitrobenzoyl)-2-phenylpyrimidine (2f)** Thionyl chloride (0.25 ml, 3.4 mmol) was added dropwise to a mixture of **8b** (0.9 g, 2.6 mmol) and *N*,*N*-dimethylformamide (DMF) (2 ml) in $CH_2Cl_2$ (10 ml) under ice cooling. The mixture was stirred for 2 h under the same conditions, then a solution of *N*-methylpiperazine (0.65 g, 6.5 mmol) in $CH_2Cl_2$ (10 ml) was added dropwise and the whole was stirred for 30 min. The reaction mixture was then poured into water and adjusted to pH 8.5 with saturated aqueous $K_2CO_3$. The organic layer was successively washed with $H_2O$ and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$–MeOH (50 : 1) and the fractions containing **2f** were combined and evaporated *in vacuo*. The crystalline residue was recrystallized from diethyl ether to afford **2f** (0.5 g, 76.8%) as a pale yellow solid. Compounds **2a—e** and **2i—j** were prepared by the same procedures as employed for the preparation of **2f**. Physical properties and spectral data of these compounds are listed in Tables I and III.

**5-(4-Methylpiperazin-1-ylcarbonyl)-4-[hydroxy(4-nitrophenyl)methyl]-2-phenylpyrimidine (2h)** $NaBH_4$ (0.31 g, 8 mmol) was added to a solution of **2f** (4.45 g, 10 mmol) in MeOH (15 ml) and THF (50 ml) under ice cooling. The reaction mixture was stirred for 30 min under the same conditions, then poured into $H_2O$ (100 ml) and ethyl acetate (100 ml). The organic layer was successively washed with $H_2O$ and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (100 g) with $CHCl_3$–MeOH (50 : 1) and the fractions containing **2h** were combined and evaporated *in vacuo*. The crystalline residue was recrystallized from diethyl ether to afford **2h** (0.4 g, 8.8%) as a white solid. Compounds **2g** and **3e** were prepared by the same procedures as employed for the preparation of **2h**. Physical properties and spectral data of these compounds are listed in Tables I and III.

**5-Hydroxymethyl-4-[(4-nitrophenyl)methyl]-2-phenylpyrimidine (9b)** $LiBH_4$ (0.02 g, 0.8 mmol) was added to a solution of **5b** (0.15 g, 0.4 mmol) in isopropyl ether (IPE) (3 ml) and THF (3 ml) at room temperature. The reaction mixture was stirred for 1.5 h under the same conditions, then poured into $H_2O$ (30 ml) and ethyl acetate (30 ml) and adjusted to pH 2.0 with 10% aqueous HCl. The organic layer was successively washed with $H_2O$ and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The crystalline residue was recrystallized from diethyl ether to afford **9b** (0.03 g, 23.3%) as a pale yellow solid, mp 118—119 °C. IR (Nujol): 1350 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 4.56 (2H, s), 4.80 (2H, s), 7.48—7.68 (5H, m), 8.12—8.56 (4H, m), 8.75 (1H, s). MS $m/z$: 321 ($M^+$).

Compound **9a** was prepared by the same procedures as employed for the preparation of **9b**. Compounds **9a** and **9b** were not further purified or analyzed before use in the next step.

5-Hydroxymethyl-4-[(3-nitrophenyl)methyl]-2-phenylpyrimidine (**9a**): Yield 45.5% as a white solid, mp 110—111 °C (ether). IR (Nujol): 1355 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 4.30 (2H, s), 4.75 (2H, s), 7.28—7.80 (5H, m), 7.98—8.45 (4H, m), 8.63 (1H, s). MS $m/z$: 321 ($M^+$).

**5-Bromomethyl-4-[(4-nitrophenyl)methyl]-2-phenylpyrimidine (10b)** A solution of $PBr_3$ (0.6 ml, 6.2 mmol) in THF (20 ml) was added to a solution of **9b** (2.0 g, 6.2 mmol) in THF (20 ml) at 5 °C. The reaction mixture was stirred for 30 min under the same conditions, then poured into $H_2O$ (50 ml) and ethyl acetate (50 ml) and adjusted to pH 8.0 with saturated aqueous $K_2CO_3$. The organic layer was successively washed with $H_2O$ and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The crystalline residue was recrystallized from diethyl ether to afford **10b** (0.9 g, 37.8%) as a white solid, mp 162—163 °C. IR (Nujol): 1350 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 4.42 (2H, s), 4.47 (2H, s), 7.26—7.57 (5H, m), 8.20 (2H, d, $J$=9 Hz), 8.37—8.44 (2H, m), 8.70 (1H, s). MS $m/z$: 384 ($M^+$). Compound **10a** was isolated by the same procedures as employed for the preparation of **10b**. Compounds **10a** and **10b** were not further purified or analyzed before use in the next step.

5-Bromomethyl-4-[(3-nitrophenyl)methyl]-2-phenylpyrimidine (**10a**): Yield 41.9% as a white solid, mp 97—98 °C (ether). IR (Nujol): 1355 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 4.41 (2H, s), 4.50 (2H, s), 7.44—7.51 (4H, m), 7.73 (1H, d, $J$=8 Hz), 8.14 (1H, d, $J$=8 Hz), 8.30—8.70 (3H, m), 9.27 (1H, s). MS $m/z$: 384 ($M^+$).

**5-[(4-Methylpiperazin-1-yl)methyl]-4-[(4-nitrophenyl)methyl]-2-phenylpyrimidine (3b)** A mixture of **10b** (0.8 g, 2.1 mmol) and *N*-methylpiperazine (0.5 ml, 4.6 mmol) in IPA (10 ml) was refluxed for 30 min, then poured into a mixture of $H_2O$ (20 ml) and $CHCl_3$ (50 ml). The organic layer was successively washed with $H_2O$ and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The crystalline residue was recrystallized from diethyl ether to afford **3b** (0.7 g, 82.6%) as a pale yellow solid. Compound **3a** was prepared by the same procedures as employed for the preparation of **3b**. Physical properties and spectral data of these compounds are listed in Tables I and III.

**Ethyl 4-[(4-Nitrophenyl)thio]-6-methyl-2-phenyl-5-pyrimidinecarboxylate (12b)** NaH (0.15 g, 3.7 mmol; 60% in mineral oil) was added to a solution of **11** (1.0 g, 3.7 mmol) in DMF (10 ml) at room temperature. The reaction mixture was stirred for 30 min, then 4-chloro-1-nitrobenzene (0.58 g, 3.7 mmol) was added and the whole was heated at 100 °C for 3 h. The reaction mixture was poured into a mixture of $CHCl_3$ (50 ml) and $H_2O$ (20 ml). The organic layer was successively washed with $H_2O$ and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The crystalline residue was recrystallized from ethanol to afford **12b** (0.5 g, 34.6%) as a pale yellow solid, mp 170—171 °C. IR (Nujol): 1680 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.49 (3H, t, $J$=7 Hz), 2.73 (3H, s), 4.50 (2H, q, $J$=7 Hz), 7.26—7.35 (3H, m), 7.84 (2H, d, $J$=9 Hz), 7.93—8.03 (2H, m), 8.25 (2H, d, $J$=9 Hz). MS $m/z$: 395 ($M^+$).

Compound **12a** was isolated by the same procedures as employed for the preparation of **12b**. Compounds **12a** and **12b** were not further purified or analyzed before use in the next step.

Ethyl 4-[(2-Nitrophenyl)thio]-6-methyl-2-phenyl-5-pyrimidinecarboxylate (**12a**): Yield 15.3% as a yellow solid, mp 97—99 °C (EtOH). IR (Nujol): 1695 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.46 (3H, t, $J$=7 Hz), 2.71 (3H, s), 4.46 (2H, q, $J$=7 Hz), 7.16—7.25 (3H, m), 7.51—7.76 (3H, m), 7.86—8.06 (3H, m). MS $m/z$: 395 ($M^+$).

**Ethyl 2-[(4-Methylpiperazin-1-yl)carbonyl]-2-butenoate (15)** A solution of $TiCl_4$ (3.07 ml, 28.8 mmol) in $CCl_4$ (7 ml) was added dropwise to dioxane (56 ml) at 0 °C. Then a mixture of ethyl 3-oxo-3-(4-methylpiperazin-1-yl)propanoate (**14**) (3.0 g, 14.0 mmol) and acetaldehyde (0.94 ml, 16.8 mmol) in dioxane (7 ml) was added to the above solution at 0 °C. The whole was stirring for 1 h, pyridine (4.52 ml, 56.0 mmol) was added, and the reaction mixture was again stirred at 0 °C for 12 h. It was poured into water (50 ml) and $CHCl_3$ (50 ml) and adjusted to pH 8.0 with aqueous 4 N NaOH. The organic layer was separated, washed with $H_2O$ and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$–MeOH (50 : 1) and the fractions containing **15** were combined and evaporated *in vacuo* to afford **15** (1.9 g, 56.5%) as a colorless oil. IR (film): 3450, 1710, 1620 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.26 (3H, t, $J$=7 Hz), 1.84 (3H, d, $J$=7 Hz), 4.30 (3H, s), 2.32—2.46 (4H, m), 3.28—3.40 (2H, m), 3.65—3.76 (2H, m), 4.16 (2H, q, $J$=7 Hz). MS $m/z$: 240 ($M^+$).

**5,6-Dihydro-5-(4-methylpiperazin-1-ylcarbonyl)-6-methyl-2-phenylpyrimidin-4(3*H*)-one (16)** Benzamidine hydrochloride (1.24 g, 7.9 mmol) was added to a solution of Na (0.18 g, 7.9 mmol) in EtOH (20 ml) at room temperature. The mixture was stirred for 10 min, then a solution of **15** (1.9 g, 7.9 mmol) in EtOH (2 ml) was added and stirring was continued for 1 h. The resultant mixture was poured into $CHCl_3$ (100 ml) and water (50 ml). The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from EtOH–ether to afford **16** (1.26 g, 50.7%) as a white solid, mp 157—160 °C. IR (Nujol): 1720, 1655, 1645 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.43 (3H, d, $J$=7 Hz), 2.29 (3H, s), 2.40—2.50 (4H, m), 3.48 (1H, d, $J$=11 Hz), 3.51—3.83 (4H, m), 4.23—4.39 (1H, m), 7.38—7.53 (3H, m), 7.76—7.79 (2H, m), 9.02 (1H, br). MS $m/z$: 314 ($M^+$). *Anal.* Calcd for $C_{17}H_{22}N_4O_2$: C, 64.95; H, 7.05; N, 17.82. Found: C, 64.69; H, 7.23; N, 17.83.

**4-Chloro-5,6-dihydro-5-(4-methylpiperazin-1-ylcarbonyl)-6-methyl-2-phenylpyrimidine (17)** Phosphorus oxychloride (0.44 ml, 4.77 mmol) was added to a solution of **16** (1.0 g, 3.18 mmol) in 1,2-dichloroethane (10 ml) at room temperature. The resultant mixture was stirred overnight, then evaporated *in vacuo*. The residue was dissolved in ethyl acetate (20 ml) and the solution was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$–MeOH (50 : 1) and the fractions containing **17** were combined and evaporated *in vacuo* to afford **17** (0.75 g, 70.9%) as a yellow oil. IR ($CHCl_3$): 1620, 1600 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.31 (3H, d, $J$=6 Hz), 2.33 (3H, s), 2.40—2.65 (4H, m), 3.52—3.83 (4H, m), 4.80—4.85 (1H, m), 6.24—6.30 (1H, m), 7.37—7.54 (3H, m), 7.74—7.79 (2H, m). MS $m/z$: 333 ($M^+$).

TABLE III. Spectral Data for Pyrimidine Derivatives (**2**, **3**)

| Compd. No. | MS *m/z*, $M^+$ | IR (Nujol) $cm^{-1}$ | Solvent[a] | $^1$H-NMR (ppm)[b] |
|---|---|---|---|---|
| **2a** | 417 | 1630, 1350 | B | 2.72 (3H, s), 2.98—3.68 (8H, m), 4.32 (2H, s), 7.43—7.85 (5H, m), 8.00—8.36 (4H, m), 8.83 (1H, s) |
| **2b** | 417 | 1620, 1345 | A | 2.04—2.56 (7H, m), 3.00—3.32 (2H, m), 3.65—3.92 (2H, m), 4.38 (2H, s), 7.45—7.70 (5H, m), 8.13—8.60 (5H, m) |
| **2c** | 429 | 1620, 1355 | A | 2.00—2.30 (2H, m), 2.32 (3H, s), 2.45—2.70 (2H, m), 3.25—3.55 (2H, m), 3.80—4.05 (2H, m), 7.27 (1H, d, $J$=15 Hz), 7.45—7.71 (4H, m), 8.35 (1H, d, $J$=15 Hz), 7.86—8.63 (5H, m), 8.77 (1H, s) |
| **2d** | 429 | 1620, 1340 | A | 2.40 (3H, s), 2.45—2.78 (4H, m), 3.35—3.60 (2H, m), 3.85—4.10 (2H, m), 7.48—7.90 (6H, m), 8.22—8.76 (6H, m) |
| **2e** | 431 | 1660, 1615 | A | 2.35 (3H, s), 2.42—2.54 (4H, m), 3.35—3.85 (4H, m), 7.36—7.72 (4H, m), 8.25—8.48 (4H, m), 8.83 (1H, s), 8.96—9.03 (1H, m) |
| **2f** | 431 | 1670, 1630, 1600 | A | 2.41 (3H, s), 2.4—2.7 (4H, m), 3.4—3.9 (4H, m), 7.4—7.6 (3H, m), 8.2—8.6 (6H, m), 8.94 (1H, s) |
| **2g** | 433 | 1625 | A | 1.90—2.15 (2H, m), 2.26 (3H, s), 2.30—2.45 (2H, m), (2H, m), 2.60—3.30 (2H, m), 3.40—3.90 (2H, m), 5.65 (1H, br), 6.20 (1H, s), 7.42—7.82 (5H, m), 8.06—8.30 (2H, m), 8.43—8.60 (3H, m) |
| **2h** | 433 | 1645 | A | 1.82—2.08 (2H, m), 2.18 (3H, s), 2.23—2.43 (2H, m), 2.80—3.25 (2H, m), 3.50—3.80 (2H, m), 5.60 (1H, br), 6.20 (1H, s), 7.52—7.66 (5H, m), 8.16—8.63 (5H, m) |
| **2i** | 449 | 1630, 1350 | A | 2.35 (3H, s), 2.50 (3H, s), 2.43—2.60 (4H, m), 3.33—3.50 (2H, m), 3.72—4.13 (2H, m), 7.26—7.36 (3H, m), 7.55—7.77 (3H, m), 7.93—8.13 (3H, m) |
| **2j** | 449 | 1610, 1355 | A | 2.35 (3H, s), 2.52 (3H, s), 2.40—2.60 (4H, m), 3.32—3.45 (2H, m), 3.83—3.95 (2H, m), 7.30—7.40 (3H, m), 7.76 (2H, d, $J$=9 Hz), 8.05—8.15 (2H, m), 8.23 (2H, d, $J$=9 Hz) |
| **2k** | 432 | 1605, 1355 | A | 2.33 (3H, s), 2.47 (3H, s), 2.45—2.70 (4H, m), 3.40—4.25 (4H, m), 7.40—7.53 (4H, m), 7.83—7.96 (3H, m), 8.36—8.46 (2H, m), 9.01—9.05 (1H, m) |
| **3a** | 403 | 1350 | A | 2.34 (3H, s), 2.52—2.56 (8H, m), 3.58 (2H, s), 4.45 (2H, s), 7.45—7.62 (4H, m), 7.73—8.26 (2H, m), 8.40—8.55 (3H, m), 8.60 (1H, s) |
| **3b** | 403 | 1350 | A | 2.25 (3H, s), 2.38—2.42 (8H, m), 3.45 (2H, s), 4.38 (2H, s), 7.36—7.55 (5H, m), 8.06—8.42 (4H, m), 8.52 (1H, s) |
| **3c** | 417 | 1675, 1350 | A | 1.65—1.95 (4H, m), 1.98 (3H, s), 2.20—2.50 (4H, m), 3.56 (2H, s), 7.40—7.80 (4H, m), 8.15—8.55 (4H, m), 8.70—8.80 (2H, m) |
| **3d** | 417 | 1690, 1350 | A | 1.76—2.05 (7H, m), 2.20—2.45 (4H, m), 3.55 (2H, s), 7.30—7.54 (4H, m), 7.94—8.48 (5H, m), 8.75 (1H, s) |
| **3e** | 419 | 1350 | A | 2.32 (3H, s), 2.50—2.54 (8H, m), 3.28 (2H, s), 6.12 (1H, s), 7.45—7.85 (5H, m), 8.05—8.55 (5H, m) |

a) $CDCl_3$; B, DMSO-$d_6$. b) Listed as chemical shifts (number of protons, multiplicity, constant).

**4-Chloro-5-(4-methylpiperazin-1-ylcarbonyl)-6-methyl-2-phenylpyrimidine (18)** A mixture of **17** (9.4 g, 28.2 mmol) and activated $MnO_2$ (60 g) in $CHCl_3$ was refluxed for 30 min, then cooled to room temperature. Insoluble precipitates were filtered off. The filtrate was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$–MeOH (50 : 1) and the fractions containing **18** were combined and evaporated *in vacuo* to afford **18** (2.8 g, 30.0%) as a pale yellow solid, mp 117—118 °C. IR (Nujol): 1630, 1550 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.33 (3H, s), 2.45—2.54 (4H, m), 2.57 (3H, s), 3.23—3.36 (4H, m), 3.85—3.89 (4H, m), 7.43—7.53 (3H, m), 8.42—8.45 (2H, m). MS *m/z*: 330 ($M^+$). *Anal.* Cacld for $C_{17}H_{22}N_4O_2$: C, 61.72; H, 5.79; N, 16.94. Found: C, 62.16; H, 5.93; N, 17.01.

**5-(4-Methylpiperazin-1-ylcarbonyl)-6-methyl-4-[(3-nitrophenyl)-amino]-2-phenylpyrimidine (2k)** A mixture of **18** (1.0 g, 3.02 mmol), 3-nitroaniline (2.5 g, 18.1 mmol), $K_2CO_3$ (0.46 g, 3.32 mmol) and a catalytic amount of CuO (12 mg) was heated at 150 °C for 2 h under stirring. The resultant mixture was dissolved in $CHCl_3$ (100 ml) and the solution was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$–MeOH (50 : 1) and the fractions containing **2k** were combined and evaporated *in vacuo* to afford **2k** (0.50 g, 38.3%) as a pale yellow solid. Physical properties and spectral data of this compound are listed in Tables I and III.

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**References and Notes**

1) *a*) Part V: A Kuno, H. Sakai, M. Ohkubo, H. Takasugi, *Chem. Pharm. Bull.*, **41**, 163 (1993); *b*) Part II: A. Kuno, Y. Sugiyama, K. Katsuta, H. Sakai, H. Takasugi, *ibid.*, **40**, 2423 (1992); *c*) Part III: A. Kuno, K. Katsuta, H. Sakai, M. Ohkubo, Y. Sugiyama, H. Takasugi, *ibid.*, **41**, 139 (1993); *d*) Part I: A. Kuno, Y. Sugiyama, K. Katsuta, T. Kamitani, H. Takasugi, *ibid.*, **40**, 1452 (1992).
2) Y. Okikawa, K. Sugano, O. Yonemitsu, *J. Org. Chem.*, **43**, 2087 (1978).
3) D. Zhao, G. Li, *Zhejiang Yike Daxue Xuebao*, **19**, 211 (1990) [*Chem. Abstr.*, **115**, 29065*d* (1990)].
4) H. H. Bosshard, R. Mory, M. Schmid, H. Zollinger, *Helv. Chim. Acta.*, **42**, 1653 (1959).
5) J. Goerdeler, J. Pohland, *Chem. Ber.*, **96**, 526 (1963).
6) W. Lehnert, *Tetrahedron Lett.*, **1970**, 4723.