

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 (LD₅₀ > 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 iodide³⁾ followed by hydrolysis afforded (*E*)- γ,δ -unsaturated β -keto esters (**4c, d**). These β -keto esters (**4a–d**) were treated with *N,N*-di-

methylformamide dimethylacetal and then condensed with benzamide to afford ethyl 4-(3- or 4-nitrophenyl)-methyl-5-pyrimidinecarboxylates (**5a–d**), which were oxidized with selenium oxide (SeO₂) to afford the 4-benzoylpyrimidines (**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 (NaBH₄) 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 (LiBH₄) afforded the 5-hydroxymethylpyrimidines (**9a, b**). These were treated with phosphorus tribromide (PBr₃) 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

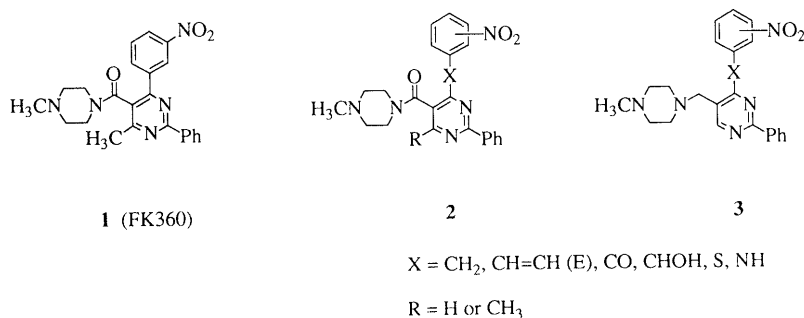
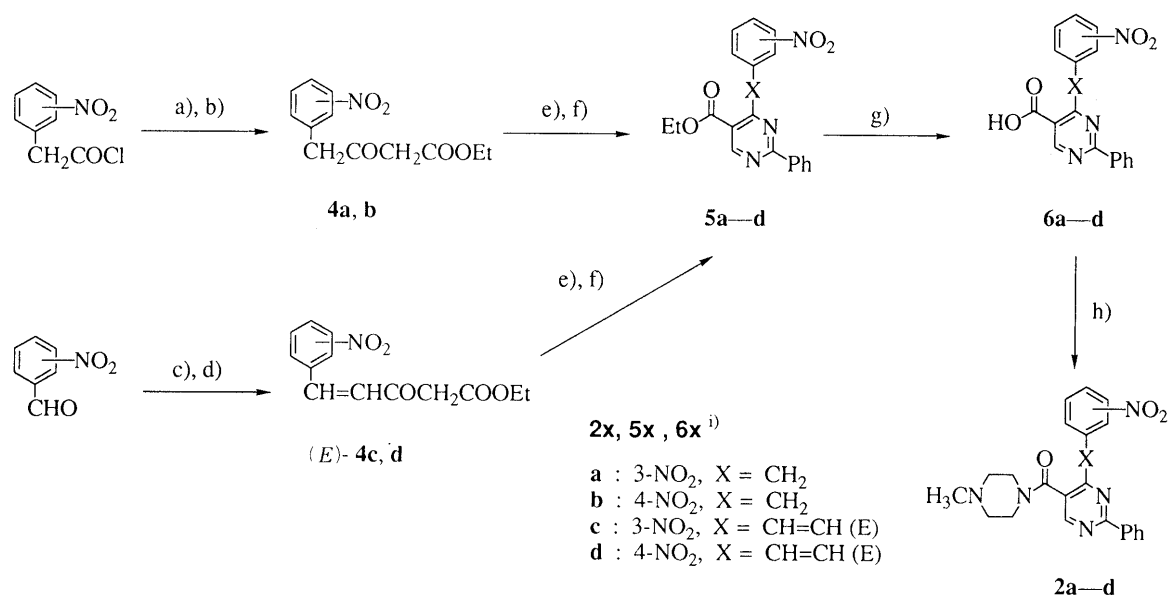
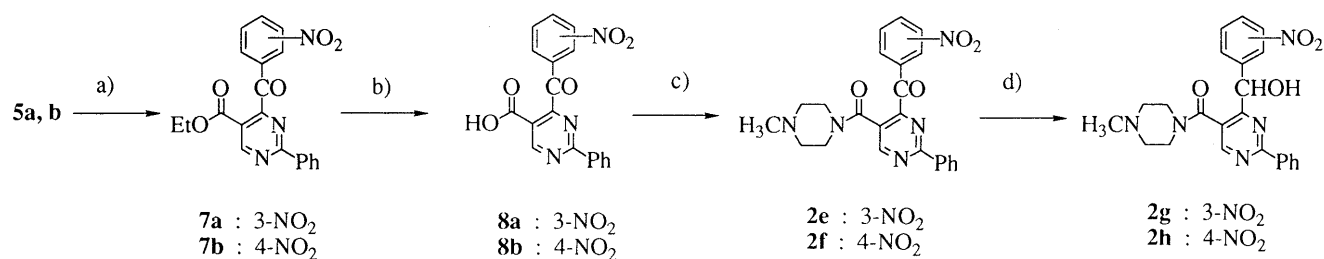


Fig. 1



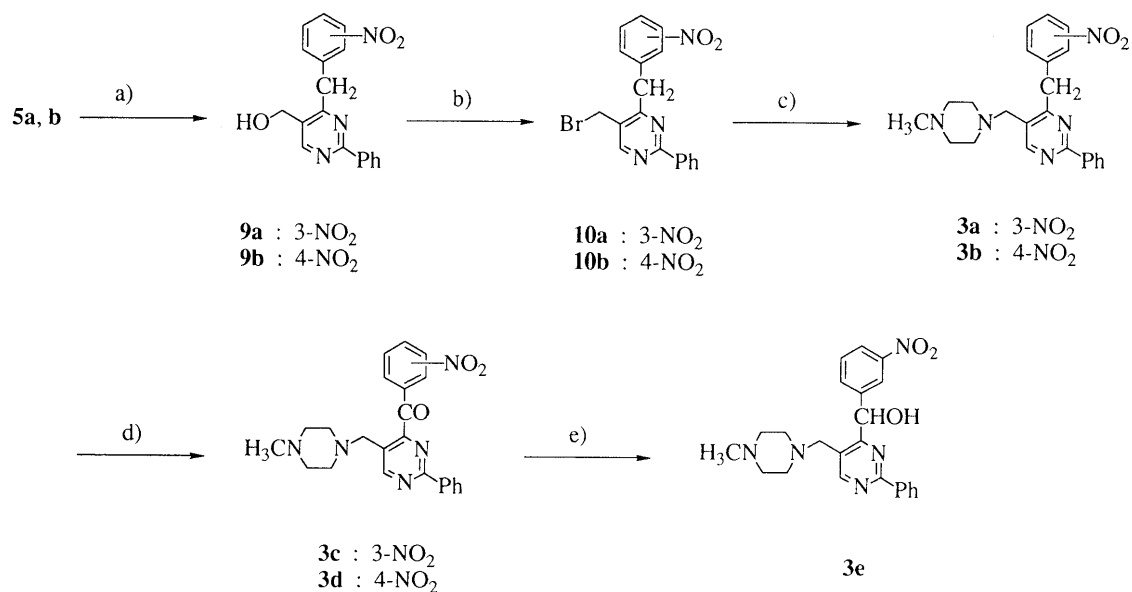
a) Meldrum's acid / pyridine, CH₂Cl₂; b) EtOH; c) (*E*)-Ph₃P⁺CH₂C(OEt)=CHCOOEt⁻ / THF, NaOH aq.; d) 0.1 N H₂SO₄ aq. / dioxane;
 e) *N,N*-dimethylformamide dimethylacetal / benzene; f) benzamidine hydrochloride, Et₃N / *n*-BuOH; g) NaOH aq. / EtOH;
 h) SOCl₂—DMF / CH₂Cl₂ then *N*-methylpiperazine; i) The letters assigned to compounds 2, 5 and 6 correspond to each other.

Chart 1



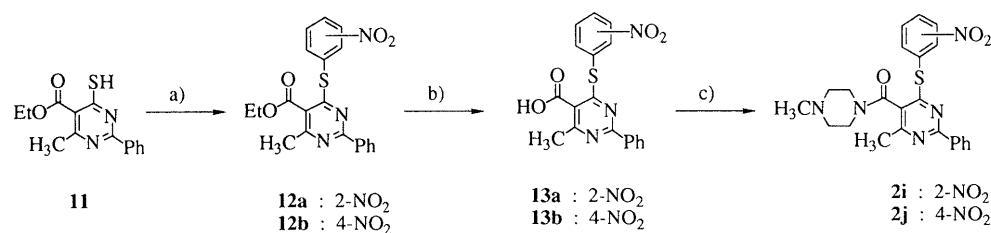
a) SeO₂ / dioxane; b) NaOH aq. / EtOH; c) SOCl₂—DMF / CH₂Cl₂, then *N*-methylpiperazine; d) NaBH₄ / MeOH

Chart 2



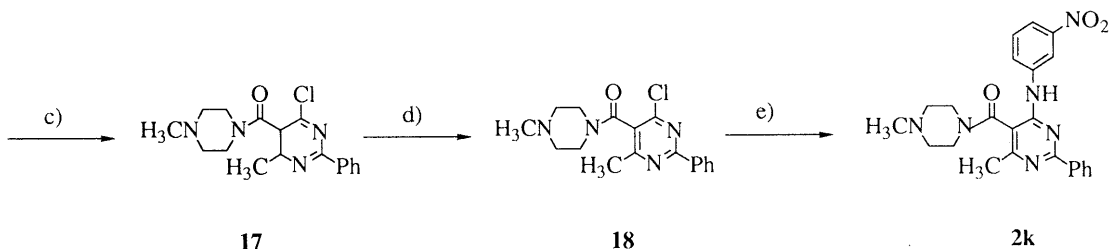
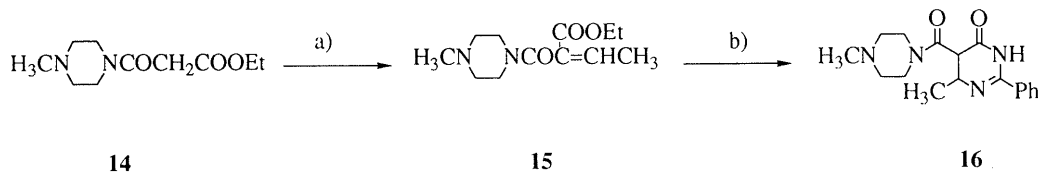
a) LiBH₄ / THF—IPE; b) PBr₃ / THF; c) *N*-methylpiperazine / IPA; d) SeO₂ / dioxane; e) NaBH₄ / MeOH

Chart 3



a) 2- or 4-chloronitrobenzene, NaH / DMF; b) NaOH aq. / MeOH; c) SOCl₂-DMF / CH₂Cl₂, then *N*-methylpiperazine

Chart 4



a) CH₃CHO, TiCl₄, pyridine / dioxane; b) benzamide hydrochloride, EtONa / EtOH; c) POCl₃ / 1,2-dichloroethane; d) MnO₂ / CHCl₃; e) 3-nitroaniline, K₂CO₃, 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 condensation⁶⁾ 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 benzamide. Chlorination of **16** with phosphorus oxychloride (POCl₃) afforded the 4-chloro-5,6-dihydropyrimidine (**17**). This was oxidized with activated manganese (IV) oxide (MnO₂) 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]pyrim-

idine (**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 (LD₅₀ > 1000 mg/kg, *i.p.*) than that of FK360 (LD₅₀ > 560 mg/kg, *i.p.*). This compound also exhibited ALP activity (IC₅₀ = 1.0 × 10⁻⁶ M) more potent than that of FK360 (IC₅₀ = 6.7 × 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.)		Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found)		
				10	32				C	H	N
2a	CH ₂	3	H	106		40.1	133—135 (MeOH)	C ₂₃ H ₂₃ N ₅ O ₃ ·HCl ·H ₂ O	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 ₅ O 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 ₅ O ₃ ·0.5H ₂ O	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 ₅ O 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 ₅ O 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 ₅ O 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 ₅ O 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 ₅ O 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 ₅ O ₃ S	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 ₅ O ₃ S	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 ₆ O 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 ₅ O ₂ ·0.2H ₂ O	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 ₅ O 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 ₅ O 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 ₅ O 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 ₅ O 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)		Upper; i.p. Lower; <i>p.o.</i> 100	Lipid peroxidation IC ₅₀ (M)	Acute toxicity ^{a)} LD ₅₀ (mg/kg, i.p.)
	10	32			
2f	119 ^{b)}	127 ^{b)}	122 ^{c)}	1.0×10^{-6}	> 1000
	105	100	115 ^{d)}		
FK360 (1)	104	125 ^{c)}	168 ^{c)}	6.7×10^{-6}	> 560
		114	125 ^{c)}		

a) Male ICR mice weighing 25—30 g were used in groups of 5—10 animals for each test drug. The LD₅₀ 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. ¹H-Nuclear magnetic resonance (¹H-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 $79\text{--}81^\circ\text{C}$. IR (Nujol): 1730, 1710 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 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 $56\text{--}57^\circ\text{C}$ (EtOH). IR (Nujol): 1745, 1710 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 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 4N 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 0.1N 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 $99\text{--}101^\circ\text{C}$. IR (Nujol): 1650, 1620 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 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 $112\text{--}114^\circ\text{C}$ (*n*-hexane). IR (Nujol): 1640, 1605 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 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). Benzamide 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 $122\text{--}123^\circ\text{C}$. IR (Nujol): 1705 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 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 $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_4 \cdot 0.3\text{H}_2\text{O}$: 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 $114\text{--}115^\circ\text{C}$ (ether). IR (Nujol): 1725 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 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 $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_4$: 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 $138\text{--}140^\circ\text{C}$

(ether-EtOH). IR (Nujol): 1715, 1630 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 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 $150\text{--}151^\circ\text{C}$ (EtOH). IR (Nujol): 1705 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 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 $\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}_4$: 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 $125\text{--}126^\circ\text{C}$. IR (Nujol): 1705, 1695 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 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 $\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}_4$: 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 $135\text{--}137^\circ\text{C}$ (ether). IR (Nujol): 1716, 1695 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 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 $275\text{--}277^\circ\text{C}$. IR (Nujol): 1685, 1600 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 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 $\text{C}_{18}\text{H}_{13}\text{N}_3\text{O}_4$: 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} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 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 $243\text{--}245^\circ\text{C}$ (ether). IR (Nujol): 1680, 1620 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 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 $281\text{--}283^\circ\text{C}$ (dec.) (ether). IR (Nujol): 1690 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 7.50—7.77 (3H, m), 7.86—8.70 (8H, m), 9.23 (1H, s). MS m/z : 347 (M^+). Anal. Calcd for $\text{C}_{19}\text{H}_{13}\text{N}_3\text{O}_4$: 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} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 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 $249\text{--}250^\circ\text{C}$ (ether). IR (Nujol): 1680 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 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 $235\text{--}237^\circ\text{C}$ (ether). IR (Nujol): 1660 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 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 $220\text{--}224^\circ\text{C}$ (ether). IR

(Nujol): 1675 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 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 $\text{C}_{18}\text{H}_{13}\text{N}_3\text{O}_4\text{S}$: 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 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-butenolate (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 4N 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 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(3H)-one (16) Benzamide 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 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 $\text{C}_{17}\text{H}_{22}\text{N}_4\text{O}_2$: 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 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} . ¹H-NMR ($CDCl_3$) δ : 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. Calcd 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.

Acknowledgements We thank the staff members of the Pharmacological Division of our company for testing the compounds. We are also grateful to the staff members of the Analytical Division for elemental analysis and the measurement of spectral data.

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**, 29065d (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.