Studies on Cerebral Protective Agents. II.¹⁾ Novel 4-Arylpyrimidine Derivatives with Anti-anoxic and Anti-lipid Peroxidation Activities. (2)

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In a search for new cerebral protective agents with anti-anoxic (AA) and anti-lipid peroxidation (ALP) activities, a series of 4-arylpyrimidines, bearing an amino moiety in the C-5 position of the pyrimidine nucleus, was synthesized and tested for AA and ALP activities. Among them, 6-methyl-5-(4-methylpiperazin-1-ylcarbonyl)-4-(3-nitrophenyl)-2-phenylpyrimidine (41, FK360) was most effective on both assays and on arachidonate-induced cerebral edema in rats. Structure-activity relationships in regard to AA activity of this series of compounds are also discussed.

Keywords cerebral protective agent; 4-arylpyrimidine; 4-aryl-1,4-dihydropyrimidine; anti-anoxia; anti-lipid peroxidation; cerebral edema; structure-activity relationship; FK360

Introduction

In the course of searching for new cerebral protective agents which have anti-anoxic (AA) and anti-lipid peroxidation (ALP) activities, we found that alkyl 4-aryl-2-phenyl-5-pyrimidinecarboxylate derivatives possessed potent ALP activity and a protective effect on arachidonate-induced cerebral edema in rats.¹⁾ Thus, substitution at the C-4 position of a pyrimidine nucleus by, for example, a nitrophenyl (NO₂Ph) group was effective; 3-NO₂Ph or 4-NO₂Ph was more effective than 2-NO₂Ph (Fig. 1).

However, disappointingly, most of these compounds lacked significant AA activity.

There are many reports that cerebral vasodilators (e.g. nimodipine, cinnarizine, vinpocetine),²⁾ central depressants (e.g. barbiturates, nifedipine)³⁾ and cerebral metabolic enhancers (e.g. bifemerane, idebenone)^{2b,4)} involve AA activity.

In the clinic, some of these agents have already been used to ameliorate cerebral vascular diseases and other types of organic brain damage.

Although there have been few reports of the structure-activity relationships (SARs) on AA activity, some trends can be observed in the above mentioned agents. The most common structural feature necessary for AA activity seems to have a nitrogenous basic moiety in the molecule (Fig. 2).

Since we discovered previously, in regard to ALP activity, that modification at the C-5 position of the pyrimidine ring was well tolerated,¹⁾ we focused our efforts

on the expression of AA activity by introducing a nitrogenous basic moiety (e.g. aminoalkylamido group). In this report we describe the preparation and SARs of the 4-aryl-2-phenylpyrimidine derivatives which incorporate the two separate pharmacophores (i.e. ALP and AA) in the molecule.

Chemistry The amide derivatives presented in Tables I–IV were synthesized *via* the routes shown in Charts 1–3.

Method A (Chart 1): α,β -Unsaturated carbonyl compounds (**2a–d**) were obtained by the Knoevenagel reaction of β -keto esters (**1**) with 3-, or 4-nitrobenzaldehyde in the presence of piperidine and acetic acid. 6-Substituted alkyl 4-(3-, or 4-nitrophenyl)-5-pyrimidinecarboxylates (**4a–d**) were prepared by the same procedures we reported previously.¹⁾ Thus, the refluxing of **2a–d** with arylamidine hydrochloride in the presence of triethylamine (Et₃N) in 1-butanol (*n*-BuOH) for 1–3 h gave dihydropyrimidines (**3a–d**). These were oxidized with activated manganese (IV) oxide (MnO₂) to afford **4a–d**. 6-Unsubstituted ethyl 4-(3-, or 4-nitrophenyl)-5-pyrimidinecarboxylates (**4e–h**) were synthesized according to a similar manner reported by Breau *et al.*⁵⁾ Treatment of the appropriate benzoyl acetates (**6a**, **6b**) with *N,N*-dimethylformamide dimethyl-acetal provided enaminones (**7a**, **7b**), which were condensed with arylamidine hydrochloride in the presence of Et₃N to afford **4e–h**.

The esters (**4a–h**) were hydrolyzed with ethanolic KOH aq. to afford the carboxylic acids (**5a–h**). Condensation of acid chlorides, which were synthesized similarly to the manner reported by Zollinger *et al.*,⁶⁾ with appropriate amines (all of the required amines are commercially available) afforded amide derivatives (**20–23**, **26–31**, **35–43**, **55–60**).

Method B: Preferred procedures for the synthesis of targeted amide derivatives, since they avoid the hydrolysis

Fig. 1

Fig. 2

[method A]

(A-i) NO₂PhCHO, piperidine, AcOH / benzene; (A-ii) R₄C(NH₂)=NH·HCl, Et₃N / *n*-BuOH; (A-iii) MnO₂ / CHCl₃; (A-iv) Me₂NCH(OMe)₂ / benzene

(A-v) R₄C(NH₂)=NH·HCl, Et₃N / *n*-BuOH; (A-vi) NaOH aq. / MeOH—H₂O; (A-vii) SOCl₂—DMF / CH₂Cl₂; R₂R₁NH

a) the alphabetical letters of compounds (2—5) correspond to each other

Chart 1

[method B]

B-1: 8a—c → 9a—c → 10a—c → (11a, 11c, 20)

[] : without isolation

B-2: 9d—f → [10d—f] → (41, 44, 45, 49—54)

a) X are not NO₂, see the list in Table IVB-3: 8d → [9d']^(a) → [10d']^(a) → (46—48)^(a)

8x—11x^(b) X= NO₂, position of NO₂

a :	3	NH ₂
b :	3	NHCH ₂ CH ₂ NMe ₂
c :	3	NHCH ₂ CH ₂ OH
d :	3	NMe
e :	2	NMe
f :	4	NMe

(B-1-i) XPhCHO, piperidine, AcOH / benzene

(B-1-ii) R₄C(NH₂)=NH·HCl, Et₃N / *n*-BuOH(B-1-iii) MnO₂ / CHCl₃ or AcOEt

b) the alphabetical letters of compounds (8—11) correspond to each other, and the substituents X, R₁, R₂ and R₄ are as listed in Tables I, II and IV

Chart 2

process, are shown in Chart 2.

Starting materials (8a—d) were synthesized according to literature methods.⁷⁾

Method B-1: Amide derivatives (11a, 11c, 20) were synthesized by procedures similar to those employed in the preparation of 2, 3, and 4.

[method C]

(C-i) SOCl₂ / CHCl₃—DMF; (C-ii) amine, NaI / isopropyl alcohol

Chart 3

[method D]

[method F]

[method E]

(a) HCHO aq., Me₂NH aq. / MeOH—CHCl₃; (E-i) LiAlH₄ / THF—Et₂O; (E-ii) PBr₃ / THF; (E-iii) NaCN / H₂O—EtOH—THF(E-iv) conc. H₂SO₄ / EtOH; (A-vi) KOH / EtOH—H₂O; (A-vii) SOCl₂ / DMF—CHCl₃; (b) DPPA, Et₃N / benzene; (c) Me₂N(CH₂)₂NH₂

Chart 4

Method B-2: Compounds (41, 44, 45, 49—54) were synthesized from 9d—f, without isolation of the dihydropyrimidine derivatives (10d—f).

Method B-3: By employing the Knoevenagel reaction of 8d in *n*-BuOH, 10d was obtained through 9d by a one pot reaction, followed by oxidation with activated MnO₂ to afford amides (46—48).

Method C (Chart 3): Chlorination of 11c with SOCl₂, followed by amination of 12 with appropriate amines in the presence of NaI afforded amides (32—34).

The other derivatives (19, 24, 25) were synthesized according to the following methods shown in Chart 4.

Method D: Compound 19 was prepared by the Mannich reaction. Thus, refluxing of 11a with Me₂NH aq. and formalin afforded 19.

Method E: Reduction of 13¹⁾ with LiAlH₄ provided the alcohol (14). On bromination, followed by reaction with sodium cyanide, 14 gave the cyanomethyl derivative (16). Esterification of 16 with ethanolic H₂SO₄ and subsequent hydrolysis with ethanolic KOH aq. afforded pyrimidinylacetic acid (18), which was transformed to the amide (24) by the amidation procedures of method A.

Method F: Curtius rearrangement of 5a with diphenylphosphoryl azide (DPPA) in the presence of Et₃N,

followed by amination with 2-dimethylaminoethylamine provided the ureido derivative (**25**).

Pharmacological Results and Discussion

The compounds listed in Tables I—IV were tested for AA activity in mice and ALP activity in rat brain mitochondria as described previously.¹⁾ Encouraging data were obtained when we evaluated the first compound (**20**). Compound **20**, which possesses a nitrogenous basic moiety in the C-5 position, showed significant AA and ALP activities. In this amide series, we sought to determine the effects of variations in the *N*-(alkylamino)alkyl carboxamide moiety on activities (Table I).

Increasing the distance between the basic nitrogen and amide nitrogen atoms from two to three carbons (**22**) resulted in an abolishment of both activities. Decreasing the distance from two to one carbon (**19**) resulted in a decrease of AA activity. Compound **19**, however, is a *N*-Mannich base type compound. It is well known that *N*-Mannich base formation can be thought of as a means of forming pro-drugs of either amines or amides.⁸⁾ Thus, some of **19** might be metabolised to **11a**. Therefore, the relationship between the SARs of this chain length and AA activity still remains ambiguous.⁹⁾ In terms of distance from the pyrimidine nucleus, the acetamide (**24**) and the ureido (**25**) derivatives which contain a basic nitrogen in a position comparable to that of **22** were inactive. The lack of AA activity in either **22**, **24**, or **25** curtailed any

additional synthesis regarding the variation in amino moiety of these compounds. Compound **21** is the fumarate of **20** and showed significant AA activity at 10 mg/kg, i.p. Increasing the size of the alkyl group of *N*-(dialkylamino)-ethyl amide from dimethyl (**21**) to diethyl (**23**) led to a decrease in AA activity. Subsequently, we examined the effect of the substituted group at the C-6 position of the pyrimidine nucleus of **20**. The modifications at this position did not appear to dramatically affect AA and ALP activities. For example, compounds which are substituted for either hydrogen (**26**), ethyl (**27**) or trifluoromethyl (**28**) at this position had comparable activities to that of **20**. 4-(4-Nitrophenyl) derivatives (**29**—**31**) were also well tolerated. Next, we evaluated the various amide derivatives (**32**—**43**) which have a basic nitrogen in a position comparable to that in **20** (Table II).

Among these derivatives, compounds (**32**, **33**, **35**, **39**, **41**) incorporated AA and ALP activities. Compound **34**, which possesses an additional basic nitrogen in the substituent, abolished AA activity. Among the piperazine derivatives (**40**—**43**), only the methyl derivative (**41**) had significant activity. Even such a close analogue as the ethyl derivative (**42**) was inactive. Compound **11c**, which does not possess a nitrogenous basic moiety in the molecule, abolished both activities. Compounds (**32** and **39**) had rather high acute toxicity compared to the other three compounds. We selected four compounds (**21**, **33**, **35**, **41**) for further evaluation on AA activity, ALP

TABLE I. Physical Properties and Biological Activities of 4-(3-, or 4-Nitrophenyl)-5-pyrimidinecarboxamide Derivatives

Compd. No.	Position of -NO ₂	R	R ₃	Anti-anoxia ^{a)} (% of control) (mg/kg, i.p.)		Lipid peroxidation ^{b)} (% of control) (g/ml) 10 ⁻⁵	Method	Yield ^{c)} (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found)		
				10	32						C	H	N
19	3	CONHCH ₂ NMe ₂	Me	121.4		NT ^{d)}	D	16.4	128—130 (Et ₂ O)	C ₂₁ H ₂₁ N ₅ O ₃	64.44 (64.22)	5.41 (5.10)	17.89 (17.60)
20	3	CONHCH ₂ CH ₂ NMe ₂	Me	102.0	124.5 ^{e)}	72.8 ^{e)}	A	36.8	120—122 (Et ₂ O)	C ₂₂ H ₂₃ N ₅ O ₃	65.17 (65.29)	5.72 (5.62)	17.27 (17.25)
21	3	CONHCH ₂ CH ₂ NMe ₂ ·fumarate	Me	121.3 ^{e)}	121.0 ^{e)}	95.2	B-1	83.6	200—201 (EtOH)	C ₂₂ H ₂₃ N ₅ O ₃ ·C ₄ H ₄ O ₄	59.88 (59.83)	5.22 (5.57)	13.43 (13.39)
22	3	CONHCH ₂ CH ₂ CH ₂ NMe ₂	Me		97.0	77.4	A	13.5	137—139 (Et ₂ O)	C ₂₃ H ₂₅ N ₅ O ₃	65.86 (66.05)	6.01 (6.26)	16.70 (16.76)
23	3	CONHCH ₂ CH ₂ NEt ₂ ·fumarate	Me	103.8	112.3	37.4 ^{f)}	A	54.8	154—158 (EtOH-AcOEt)	C ₂₄ H ₂₇ N ₅ O ₃ ·C ₄ H ₄ O ₄	61.19 (60.96)	5.68 (5.66)	12.74 (12.67)
24	3	CH ₂ CONHCH ₂ CH ₂ NMe ₂	Me		96.0	63.4	E	20.8	185—187 (Et ₂ O)	C ₂₃ H ₂₅ N ₅ O ₃	65.86 (65.96)	6.01 (5.83)	16.70 (16.73)
25	3	NHCONHCH ₂ CH ₂ NMe ₂ ·HCl	Me		107.4	98.7	F	14.4	125—127 (EtOH-Et ₂ O)	C ₂₂ H ₂₄ N ₆ O ₃ ·HCl·4.5 H ₂ O	49.11 (49.28)	6.36 (5.96)	15.62 (15.58)
26	3	CONHCH ₂ CH ₂ NMe ₂	H	101.4	128.0 ^{e)}	NT ^{d)}	A	49.2	165—167 (Et ₂ O)	C ₂₁ H ₂₁ N ₅ O ₃	64.44 (64.83)	5.41 (5.12)	17.89 (18.04)
27	3	CONHCH ₂ CH ₂ NMe ₂	Et	106.8	122.8 ^{f)}	38.4 ^{e)}	A	28.4	106—109 (Et ₂ O)	C ₂₃ H ₂₅ N ₅ O ₃	65.86 (65.83)	6.01 (5.85)	16.70 (16.59)
28	3	CONHCH ₂ CH ₂ NMe ₂	CF ₃	110.1	113.4 ^{e)}	30.4 ^{e)}	A	25.4	174—175 (IPE)	C ₂₂ H ₂₀ F ₃ N ₅ O ₃	57.52 (57.82)	4.39 (4.45)	15.24 (15.25)
29	4	CONHCH ₂ CH ₂ NMe ₂	Me	107.1	123.5 ^{e)}	43.1 ^{e)}	A	29.9	148—149 (Et ₂ O)	C ₂₂ H ₂₃ N ₅ O ₃	65.17 (64.94)	5.71 (5.71)	17.27 (17.08)
30	4	CONHCH ₂ CH ₂ NMe ₂ ·fumarate	Me	111.4 ^{e)}	118.2 ^{e)}	43.0 ^{f)}		93.3	188—190 (EtOH)	C ₂₂ H ₂₃ N ₅ O ₃ ·C ₄ H ₄ O ₄	59.88 (59.91)	5.22 (5.29)	13.43 (13.42)
31	4	CONHCH ₂ CH ₂ NMe ₂	H	113.8	114.8 ^{e)}	77.6 ^{e)}	A	71.1	180—182 (Et ₂ O)	C ₂₁ H ₂₁ N ₅ O ₃	64.44 (64.84)	5.41 (5.32)	17.89 (18.15)

a) Each value represents the mean of 5 to 10 animals compared with the control group. b) Each value represents the mean of 3 independent experiments. c) **20**, **22**, **23**, **25**—**29**, **31**, yield from corresponding 5; **21** and **30**, yield from corresponding free base; **19**, yield from **11a**; **24**, yield from **18**. d) NT: not tested. e) *p* < 0.05. f) *p* < 0.01.

TABLE II. Physical Properties and Biological Activities of 6-Methyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxamide Derivatives and Their Analogues

Compound No.	NR ₁ R ₂	Anti-anoxia ^{a)} (% of control) (mg/kg, i.p.)		Lipid peroxidation ^{b)} (% of control) (g/ml) 10 ⁻⁵	Method	Yield ^{c)} (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found)		
		10	32						C	H	N
32	NHCH ₂ CH ₂ N	108.7	119.9 ^{d)}	38.7 ^{e)}	C	15.6	119—120 (Et ₂ O)	C ₂₅ H ₂₇ N ₅ O ₃	67.40 (67.29)	6.11 5.93	15.72 15.60
33	NHCH ₂ CH ₂ N	105.6	120.0 ^{e)}	29.8 ^{e)}	C	36.4	169—170 (Et ₂ O)	C ₂₄ H ₂₅ N ₅ O ₃ S	62.19 (62.33)	5.44 5.38	15.11 15.19
34	NHCH ₂ CH ₂ N	107.1	103.5	52.2 ^{d)}	C	20.7	93—95 (Et ₂ O)	C ₂₅ H ₂₈ N ₆ O ₃	65.20 (64.93)	6.13 6.31	18.25 18.14
35	NHCH ₂ CH ₂ N	111.4	120.8 ^{e)}	95.0 ^{d)}	A	31.3	165—167 (EtOH)	C ₂₄ H ₂₅ N ₅ O ₄	64.42 (64.80)	5.63 5.83	15.65 15.96
36	NHCH ₂ CH ₂ N		109.4	37.7 ^{e)}	A	36.3	133—134 (Et ₂ O)	C ₂₄ H ₂₅ N ₅ O ₃	66.81 (67.08)	5.84 5.43	16.23 16.45
37	NHCH ₂ CH ₂ N		107.6	6.3 ^{e)}	A	12.6	100—101 (IPE)	C ₂₈ H ₂₇ N ₅ O ₃	69.84 (69.96)	5.65 5.90	14.54 14.83
38	NHCH ₂		103.3	34.8 ^{e)}	A	35.7	88—90 (IPE)	C ₂₅ H ₂₇ N ₅ O ₃	67.40 (67.64)	6.11 6.01	15.72 15.92
39	NH	116.0	122.7 ^{d)}	86.9 ^{d)}	A	41.4	146—148 (Et ₂ O)	C ₂₅ H ₂₇ N ₅ O ₃	67.40 (67.28)	6.11 5.94	15.72 15.63
40			100.0	10.9 ^{e)}	A	10.6	171—172 (EtOH—Et ₂ O)	C ₂₂ H ₂₁ N ₅ O ₃	65.50 (65.03)	5.25 5.53	17.36 17.41
41		103.6	125.5 ^{e)}	27.2 ^{e)}	A B-2	56.2 10.8	153—155 (EtOH)	C ₂₃ H ₂₃ N ₅ O ₃	66.17 (66.10)	5.55 5.47	16.78 16.94
42			116.0	NT ^{f)}	A	70.1	144—145 (Et ₂ O)	C ₂₄ H ₂₅ N ₅ O ₃	66.81 (66.64)	5.84 5.77	16.23 16.16
43			100.0	70.1 ^{e)}	A	34.3	128—130 (Et ₂ O)	C ₂₄ H ₂₅ N ₅ O ₄	64.42 (64.42)	5.63 5.40	15.65 15.75
11c	NHCH ₂ CH ₂ OH		97.2	92.0	B-1	48.0	190—192 (Et ₂ O)	C ₂₀ H ₁₈ N ₄ O ₄	63.49 (63.50)	4.79 4.63	14.81 14.74

a, b) See footnote a) and b) in Table I. c) 32—34, yield from 12; 35—43, yield from 5a; 11c, yield from 10c. d) See footnote e) in Table I. e) See footnote f) in Table I. f) See footnote d) in Table I.

TABLE III. Pharmacological Data of 6-Methyl-4-(3-nitrophenyl)-2-phenylpyrimidine Derivatives (21, 33, 35, 41)

Compound No.	Anti-anoxia (% of control) (mg/kg, i.p.)			Lipid peroxidation IC ₅₀ (M)	Arachidonate-induced ^{a)} cerebral edema ED ₅₀ (mg/kg)		Acute toxicity ^{b)} LD ₅₀ (mg/kg, i.p.)
	10	32	100		i.p.	p.o.	
21	121 ^{c)}	121 ^{c)}	128 ^{c)}	6.5 × 10 ⁻⁵	8	NT ^{d)}	110
33	106	120 ^{c)}	116	7.1 × 10 ⁻⁶	14	> 100	> 560
35	111	121 ^{c)}	131 ^{c)}	5.1 × 10 ⁻⁵	90	NT ^{d)}	510
41	104	126 ^{c)}	168 ^{c)}	6.7 × 10 ⁻⁶	18	32	> 560

a) The experiments were conducted using groups of 5 animals. The dose required to produce 50% of maximum inhibition produced by the test drug, was determined from log-probit plots of the individual. b) Male ICR mice weighing 25—35 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 an intraperitoneal administration of a test compound. c) *p* < 0.01. d) NT: not tested.

activity and arachidonate-induced cerebral edema in rats at a range of doses/concentrations. These pharmacological data are summarized in Table III.

Compound 21 prolonged the survival time of mice in a dose-related manner on AA assay; however, it was more toxic compared to the other three compounds. Compound

35 was not so effective on arachidonate-induced cerebral edema in rats. Compound 33 did not prolong the survival time of mice in a dose-dependent manner on AA assay and was less effective than 41 in the oral test on arachidonate-induced cerebral edema in rats. It should be noted that these compounds (21, 33, 35, 41) at 32 mg/kg, i.p. inducing

TABLE IV. Physical Properties and Biological Activities of 4-Aryl-5-(4-methylpiperazine-1-ylcarbonyl)pyrimidine Derivatives

Compd. No.	X	R ₃	R ₄	Anti-anoxia ^{a)} (% of control) (mg/kg, i.p.)		Lipid peroxidation ^{b)} (% of control) (g/ml) 10 ⁻⁵	Method	Yield ^{c)} (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found)		
				10	32						C	H	N
44	4-NO ₂	Me	Ph		125.9 ^{d)}	NT ^{e)}	B-2	7.7	257—258 (EtOH)	C ₂₃ H ₂₃ N ₅ O ₃	65.46	5.61	16.59
45	2-NO ₂	Me	Ph	103.9	128.9 ^{f)}	59.4 ^{d)}	B-2	3.4	146—147 (EtOH-Et ₂ O)	C ₂₃ H ₂₃ N ₅ O ₃	66.17	5.55	16.78
46	3-CF ₃	Me	Ph	114.6	127.9 ^{f)}	36.2 ^{d)}	B-3	19.1	124—125 (EtOH)	C ₂₄ H ₂₃ F ₃ N ₄ O	65.45	5.26	12.72
47	3-Cl	Me	Ph		105.6	NT ^{e)}	B-3	20.3	117—119 (Et ₂ O- <i>n</i> -hexane)	C ₂₃ H ₂₃ ClN ₄ O	67.89	5.70	13.77
48	3-CN	Me	Ph		102.8	NT ^{e)}	B-3	8.0	123—124 (Et ₂ O- <i>n</i> -hexane)	C ₂₄ H ₂₃ N ₅ O	72.53	5.83	17.62
49	3-NO ₂	Me	Me		105.6	NT ^{e)}	B-2	10.7	121—124 (EtOH)	C ₁₈ H ₂₁ N ₅ O ₃	60.83	5.96	19.71
50	3-NO ₂	Me	4-ClPh	122.2 ^{d)}	117.5 ^{f)}	3.2 ^{d)}	B-2	29.2	136—137 (Et ₂ O)	C ₂₃ H ₂₂ ClN ₅ O ₃	61.13	4.91	15.50
51	3-NO ₂	Me	4-MePh		111.1 ^{f)}	90.4 ^{d)}	B-2	10.5	131—134 (EtOH)	C ₂₄ H ₂₅ N ₅ O ₃	66.80	5.84	16.23
52	3-NO ₂	Me	4-MeOPh		108.2	NT ^{e)}	B-2	22.3	> 300 °C (EtOH)	C ₂₄ H ₂₅ N ₅ O ₄	58.48	5.52	14.21
53	3-NO ₂	Me	4-FPh		113.0	NT ^{e)}	B-2	17.8	139—141 (EtOH)	C ₂₃ H ₂₂ FN ₅ O ₃	63.44	5.09	16.08
54	3-NO ₂	Me	4-Py	101.8	106.9	91.1	B-2	30.1	161—162 (Et ₂ O)	C ₂₂ H ₂₂ N ₆ O ₃	63.14	5.29	20.08
55	3-NO ₂	H	Ph	91.9	117.4	NT ^{e)}	A	50.3	177—179 (Et ₂ O)	C ₂₁ H ₂₁ N ₅ O ₃	65.50	5.25	17.36
56	3-NO ₂	Et	Ph		109.0	NT ^{e)}	A	70.2	113—114 (EtOH)	C ₂₄ H ₂₅ N ₅ O ₃	66.80	5.83	16.23
57	3-NO ₂	CF ₃	Ph		104.4	NT ^{e)}	A	26.4	166—167 (EtOH-Et ₂ O)	C ₂₃ H ₂₀ F ₃ N ₅ O ₃	58.59	4.27	14.85
58	3-NO ₂	H	4-ClPh		114.0	NT ^{e)}	A	60.9	150—151 (Et ₂ O)	C ₂₂ H ₂₀ ClN ₅ O ₃	60.35	4.60	15.99
59	4-NO ₂	H	Ph	113.0 ^{d)}	123.2 ^{d)}	87.3 ^{d)}	A	66.4	165—166 (Et ₂ O)	C ₂₂ H ₂₁ N ₅ O ₃	65.50	5.25	17.36
60	4-NO ₂	H	4-ClPh		110.5	4.4 ^{d)}	A	29.5	146—147 (Et ₂ O)	C ₂₂ H ₂₀ ClN ₅ O ₃	60.35	4.60	15.99

a, b) See footnote a) and b) in Table I. c) 46—48, yield from 8d. 44, 45, 49—54, yield from corresponding 9. 55—60, yield from corresponding 5. d) See footnote e) in Table I. e) See footnote d) in Table I. f) See footnote f) in Table I.

AA activity showed no effect on pentobarbital-induced sleeping time in mice and the spontaneous movement in rats (details not presented here). AA activity of these compounds, therefore, may not be necessarily attributable to central depressant activities. Taking into account the efficacy of *N*-methyl piperazinyl derivative (41), we synthesized further 4-aryl-5-(4-methylpiperazin-1-ylcarbonyl)pyrimidine derivatives and tested their activities (Table IV).

Some compounds (44—46, 50, 59) retained equipotent or slightly more potent activity compared with 41. These compounds, however, were proved not to be superior to 41 on arachidonate-induced cerebral edema and/or acute toxicity (data not shown here).

In conclusion, we have defined the structural parameters necessary for AA activity among a series of basic amide derivatives of 4-arylpyrimidine derivatives. Compound 41 (FK 360) was selected for further study because of its efficacy on the above mentioned three assays and its low acute toxicity (LD₅₀ > 560 mg/kg, i.p.). Further experi-

ments on FK 360 will be reported in a separate paper.

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 or Shimadzu IR-420 spectrophotometer. Mass spectral (MS) measurements were made on a Hitachi M-80 or a JEOL-D300 mass spectrometer.

Method A. (A-i) Typical Example for the Preparation of 2 Methyl 2-(3-Nitrophenylmethylene)-3-oxopentanoate (2d): A mixture of 3-nitrobenzaldehyde (10 g), methyl 3-oxopentanoate (8.6 g), acetic acid (0.8 g) and piperidine (0.26 ml) in benzene (30 ml) was refluxed for 1 h under azeotropic conditions. The mixture was diluted with AcOEt (100 ml), successively washed with H₂O (100 ml), 10% NaHCO₃ aq. (50 ml) and brine, dried over MgSO₄ and evaporated *in vacuo*. The residual substance was recrystallized from Et₂O to afford 2d (5.7 g, 32.6%), mp 72—74 °C. IR (Nujol): 1720, 1650, 1420, 1350, 1230, 735 cm⁻¹. MS *m/z*: 263 (M⁺). ¹H-NMR (DMSO-*d*₆) δ: 1.01 (minor) and 1.05 (total 3H, each t, *J* = 7 Hz), 2.65 (minor) and 2.91 (total 2H, each q, *J* = 7 Hz), 3.80

(3H, s), 7.70–8.10 (3H, m), 8.20–8.40 (2H, m). The ratio of isomers was 2.17. *Anal.* Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.97; N, 5.32. Found: C, 59.62; H, 5.09; N, 5.30. Compound **2c** could not be obtained in a pure form under the same reaction conditions and was used in the next step without isolation.

(A-ii) Typical Example for the Preparation of 3 Methyl 1,4-Dihydro-6-ethyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxylate (**3d**): A mixture of **2d** (5.0 g), benzamidine hydrochloride (3.6 g) and Et_3N (3.8 ml) in *n*-BuOH (50 ml) was refluxed for 4 h. The reaction mixture was diluted with AcOEt (100 ml), successively washed with H_2O (100 ml), 10% HCl aq. (50 ml) and brine, and evaporated *in vacuo*. The residual substance was collected by filtration, suspended in $CHCl_3$ (100 ml) and H_2O (100 ml), and adjusted to pH 8.0 with 4% NaOH aq. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (SiO_2) (100 g) with $CHCl_3$ -acetone (20:1) as eluent. The fractions containing **3d** were combined and evaporated *in vacuo*. The crystalline residue was recrystallized from Et_2O to afford **3d** (1.3 g, 18.7%), mp 142–144 °C. IR (Nujol): 3150, 1690, 1640, 1520, 1350, 1095, 690 cm^{-1} . MS *m/z*: 365 (M^+). 1H -NMR (DMSO- d_6) δ : 1.22 (3H, t, $J=7.3$ Hz), 2.70–3.00 (2H, m), 3.60 (3H, s), 5.78 (1H, s), 7.40–8.00 (7H, m), 8.10–8.20 (2H, m), 9.73 (1H, s). *Anal.* Calcd for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.55; H, 5.23; N, 11.31.

Compounds (**3a, b**) have been reported in our previous paper.¹⁾ Compound (**3c**) was unstable and was subjected to the next step without isolation.

(A-iii) Typical Example for the Preparation of 4a–d Methyl 6-Ethyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxylate (**4d**): To a solution of **3d** (5 g) in $CHCl_3$ (100 ml) was added activated MnO_2 (40 g), and the mixture was refluxed for 2 h with vigorous stirring. After filtering off the MnO_2 , the solvent was evaporated *in vacuo*. The residual crystalline material was recrystallized from Et_2O to afford **4d** (2.1 g, 42.4%), mp 107–110 °C. IR (Nujol): 1725, 1540 cm^{-1} . 1H -NMR (DMSO- d_6) δ : 1.41 (3H, t, $J=7$ Hz), 2.97 (2H, q, $J=7$ Hz), 3.83 (3H, s), 7.43–7.80 (3H, m), 7.80–8.66 (6H, m). 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, 66.45; H, 4.88; N, 11.28. Compounds (**4a, b**) have been reported in our previous paper.¹⁾ Compound **4c** was synthesized by the same procedures as employed in the preparation of **4d**.

Ethyl 4-(3-Nitrophenyl)-2-phenyl-6-trifluoromethyl-5-pyrimidinecarboxylate (**4c**): Yield 12.2% (overall yield from 3-nitrobenzaldehyde), mp 93–95 °C. IR (Nujol): 1730, 1590, 1215 cm^{-1} . 1H -NMR (DMSO- d_6) δ : 1.16 (3H, t, $J=7$ Hz), 4.31 (2H, q, $J=7$ Hz), 7.50–7.73 (3H, s), 7.80–8.60 (6H, m). MS *m/z*: 417 (M^+). *Anal.* Calcd for $C_{20}H_{14}F_3N_3O_4$: C, 57.56; H, 3.38; N, 10.07. Found: C, 57.34; H, 3.28; N, 10.28.

(A-iv) Ethyl 2-(4-Nitrobenzoyl)-3-dimethylaminopropenoate (7b) A solution of **6b** (11.9 g) in benzene (100 ml) was stirred at room temperature while *N,N*-dimethylformamide (DMF) dimethylacetal (9.5 g) dissolved in benzene (50 ml) was added dropwise during 0.5 h. After refluxing for 0.5 h, the reaction mixture was evaporated *in vacuo* and pulverized with *n*-hexane to afford **7b** as an amorphous powder (12.5 g, 85.5%). IR (Nujol): 1690, 1630, 1610, 1590, 1220 cm^{-1} . MS *m/z*: 292 (M^+). 1H -NMR ($CDCl_3$) δ : 0.93 (3H, t, $J=7$ Hz), 3.10 (6H, s), 3.95 (2H, q, $J=7$ Hz), 7.70 (2H, dd, $J=8, 3$ Hz), 7.75 (1H, s), 8.16 (2H, dd, $J=8, 3$ Hz). Compound (**7a**) was synthesized by the same procedures as employed in the preparation of **7b**.

Ethyl 2-(3-Nitrobenzoyl)-3-dimethylaminopropenoate (**7a**): Yield 98.5% (oil). IR (neat): 1680, 1630, 1590, 1350, 1095 cm^{-1} . MS *m/z*: 292 (M^+). 1H -NMR ($CDCl_3$) δ : 0.90 (3H, t, $J=7$ Hz), 3.02 (6H, s), 3.20 (1H, s), 3.93 (2H, q, $J=7$ Hz), 7.30–8.50 (4H, m). Compounds (**7a, b**) were not further purified or analyzed before use in the next step.

(A-v) Ethyl 4-(4-Nitrophenyl)-2-phenyl-5-pyrimidinecarboxylate (4f) A mixture of **7b** (3.0 g), benzamidine hydrochloride (1.93 g) and Et_3N (2 ml) in *n*-BuOH (30 ml) was refluxed for 0.5 h. The reaction mixture was poured into H_2O (300 ml) and the precipitate was collected by filtration. The precipitate was recrystallized from Et_2O to afford **4f** (3.1 g, 86.1%). mp 138–140 °C. IR (Nujol): 1730, 1570, 1530, 1355, 1295 cm^{-1} . MS *m/z*: 349 (M^+). 1H -NMR (DMSO- d_6) δ : 1.15 (3H, t, $J=7$ Hz), 4.20 (2H, q, $J=7$ Hz), 7.45–8.14 (5H, m), 8.20–8.70 (4H, m), 9.35 (1H, s). *Anal.* Calcd for $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.32; N, 12.02. Found: C, 65.21; H, 4.28; N, 12.01. Compounds (**4e, g, h**) were synthesized by the same procedures as employed in the preparation of **4f**.

Ethyl 4-(3-Nitrophenyl)-2-phenyl-5-pyrimidinecarboxylate (**4e**): Yield 90.6%, mp: 85–86 °C. IR (Nujol): 1720, 1530, 1350 cm^{-1} . MS *m/z*: 349 (M^+). 1H -NMR (DMSO- d_6) δ : 1.11 (3H, t, $J=6$ Hz), 4.20 (2H, q, $J=6$ Hz), 7.40–8.60 (9H, m), 9.30 (1H, s). *Anal.* Calcd for $C_{19}H_{15}N_3O_4$:

C, 65.32; H, 4.32; N, 12.02. Found: C, 65.29; H, 4.13; N, 11.95.

Ethyl 2-(4-Chlorophenyl)-4-(3-nitrophenyl)-5-pyrimidinecarboxylate (**4g**): Yield 83.8%, mp: 179–180 °C. IR (Nujol): 1735, 1600, 1580, 1535, 1360 cm^{-1} . MS *m/z*: 383 (M^+). 1H -NMR (DMSO- d_6) δ : 1.13 (3H, t, $J=6$ Hz), 4.22 (2H, q, $J=6$ Hz), 7.56 (2H, d, $J=9$ Hz), 7.60–8.40 (4H, m), 8.45 (2H, d, $J=9$ Hz), 9.27 (1H, s).

Ethyl 2-(4-Chlorophenyl)-4-(4-nitrophenyl)-5-pyrimidinecarboxylate (**4h**): Yield 75.7%, mp 184–185 °C. IR (Nujol): 1735, 1600, 1580, 1535, 1360 cm^{-1} . MS *m/z*: 383 (M^+). 1H -NMR ($CDCl_3$) δ : 1.22 (3H, t, $J=8$ Hz), 4.28 (2H, q, $J=8$ Hz), 7.43 (2H, d, $J=8$ Hz), 7.75 (2H, d, $J=9$ Hz), 8.33 (2H, d, $J=8$ Hz), 8.47 (2H, d, $J=9$ Hz), 9.24 (1H, s).

(A-vi) Typical Example for the Preparation of 4-Aryl-5-pyrimidinecarboxylic Acid (5) 6-Ethyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxylic Acid (**5d**): A mixture of **4d** (3.4 g) and NaOH aq. (0.45 g in 10 ml H_2O) in MeOH (34 ml) and H_2O (7 ml) was refluxed for 10 h. After evaporating the solvent, the residue was dissolved in a mixture of H_2O (20 ml) and $CHCl_3$ (20 ml) under stirring. The separated aqueous layer was adjusted to pH 3.0 with 10% HCl aq. The resulting precipitate was collected, washed with H_2O and dried to afford **5d** (2.3 g, 70.3%), mp 184–185 °C. IR (Nujol): 1710, 1540, 1350 cm^{-1} . 1H -NMR (DMSO- d_6) δ : 1.39 (3H, t, $J=7$ Hz), 3.00 (2H, q, $J=7$ Hz), 7.45–8.70 (9H, m). MS *m/z*: 349 (M^+).

The following compounds were isolated by the same procedures as employed in the preparation of **5d** and were not further purified or analyzed before use in the next step. Compound **5a** has been reported in our previous paper.¹⁾

6-Methyl-4-(4-nitrophenyl)-2-phenyl-5-pyrimidinecarboxylic Acid (**5b**): Yield 39.9%, mp 247–248 °C (dec.). IR (Nujol): 1690, 1608, 1355 cm^{-1} . 1H -NMR (TFA) δ : 3.20 (3H, s), 7.60–8.00 (3H, m), 8.17 (2H, d, $J=9$ Hz), 8.50 (2H, d, $J=9$ Hz), 8.20–8.50 (2H, m).

4-(3-Nitrophenyl)-2-phenyl-6-trifluoromethyl-5-pyrimidinecarboxylic Acid (**5c**): Yield 80.3%, mp 313–315 (dec.). IR (Nujol): 1615, 1530 cm^{-1} . 1H -NMR (DMSO- d_6) δ : 7.40–8.00 (4H, m), 8.25 (4H, m), 8.96–9.10 (1H, m). MS *m/z*: 389 (M^+).

4-(3-Nitrophenyl)-2-phenyl-5-pyrimidinecarboxylic Acid (**5e**): Yield, 67.0%, mp 195 °C (fused), 210 °C (clarified). IR (Nujol): 1705, 1560, 1525, 1350 cm^{-1} . 1H -NMR (DMSO- d_6) δ : 7.40–8.60 (9H, m), 9.30 (1H, s). MS *m/z*: 321 (M^+).

4-(4-Nitrophenyl)-2-phenyl-5-pyrimidinecarboxylic Acid (**5f**): Yield 80.3%, mp 253–255 °C. IR (Nujol): 1700, 1565, 1525, 1355 cm^{-1} . 1H -NMR (DMSO- d_6) δ : 7.40–7.73 (3H, m), 7.80–8.65 (6H, m), 9.30 (1H, s). MS *m/z*: 321 (M^+).

2-(4-Chlorophenyl)-4-(3-nitrophenyl)-5-pyrimidinecarboxylic Acid (**5g**): Yield 85.0%, mp 268–270 °C. IR (Nujol): 1705, 1525, 1350 cm^{-1} . 1H -NMR (DMSO- d_6) δ : 7.50–8.60 (8H, m), 9.26 (1H, s). MS *m/z*: 355 (M^+).

2-(4-Chlorophenyl)-4-(4-nitrophenyl)-5-pyrimidinecarboxylic Acid (**5h**): Yield 96.7%, mp 310 °C (dec.). IR (Nujol): 1715, 1622, 1530, 1355 cm^{-1} . 1H -NMR (DMSO- d_6) δ : 7.61 (2H, d, $J=9$ Hz), 8.38 (2H, d, $J=9$ Hz), 8.03 (2H, d, $J=9$ Hz), 8.50 (2H, d, $J=9$ Hz), 9.15 (1H, s). MS *m/z*: 355 (M^+).

[6-Methyl-4-(3-nitrophenyl)-2-phenylpyrimidin-5-yl]acetic Acid (**18**): Yield 35.6%, mp 222–224 °C (dec.). IR (Nujol): 1700, 1530 cm^{-1} . 1H -NMR (TFA) δ : 3.10 (3H, s), 4.15 (2H, s), 7.50–8.80 (9H, m).

(A-vii) Typical Example for the Preparation of Amide Derivatives (20–23, 26–34, 35–43, 55–60) *N*-(2-Dimethylaminoethyl)-6-methyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxamide (**20**): To a mixture of **5a** (9 g), CH_2Cl_2 (72 ml) and DMF (20 ml), $SOCl_2$ (2.1 ml) was added at 7 °C under ice cooling. After stirring for 1.5 h under the same conditions, 2-dimethylaminoethylamine (5.9 g) was added and stirred for 2 h. The reaction mixture was adjusted to pH 8.5 with K_2CO_3 aq. The organic layer was successively washed with H_2O and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by alumina (Al_2O_3) chromatography (200 g) with *n*-hexane–AcOEt (5:1) as eluent. The fractions containing **20** were combined and evaporated *in vacuo*. The crystalline residue was recrystallized from Et_2O to afford **20** (4.0 g, 36.8%). IR (Nujol): 1630, 1565, 1530 cm^{-1} . MS *m/z*: 405 (M^+). 1H -NMR ($CDCl_3$) δ : 2.01 (6H, s), 2.26 (2H, t, $J=6$ Hz), 2.71 (3H, s), 3.38 (2H, m), 6.35 (1H, br s), 7.38–7.73 (4H, m), 8.13–8.60 (4H, m), 8.75–8.83 (1H, m). Compounds (**21–23, 26–31, 35–43, 55–60**) were obtained in a manner similar to that described for **20** and their physical properties are listed in Tables I, II and IV.

Method B. (B-1-i) Typical Example for the Preparation of 9 *N*-(2-Hydroxyethyl)-2-(3-nitrophenylmethylene)-3-oxo-butanamide (**9c**): A mixture of 3-nitrobenzaldehyde (52.1 g), **8c** (50 g), acetic acid (4.1 g) and piperidine (1.3 ml) in benzene (31 ml) was refluxed for 2.5 h under

azeotropic conditions. To the reaction mixture was added AcOEt (200 ml), then it was successively washed with H₂O (200 ml) and brine, dried (MgSO₄) and evaporated *in vacuo*. The residual substance was recrystallized from Et₂O to afford **9c** (85.0 g, 89.8%), mp 129–131 °C. IR (neat): 3250, 1670, 1625, 1565, 1525 cm⁻¹. MS *m/z*: 278 (M⁺). ¹H-NMR (DMSO-*d*₆) δ: 2.40 (3H, s), 3.16–3.60 (4H, m), 4.30–4.70 (1H, br), 7.60–8.60 (6H, m). *Anal.* Calcd for C₁₃H₁₄N₂O₅: C, 56.11; H, 5.07; N, 10.06. Found: C, 55.88; H, 5.17; N, 9.94. The following compounds were obtained according to a manner similar to that described for **9c**.

2-(3-Nitrophenylmethylene)-3-oxo-butanamide (**9a**): Yield 31.1%, mp 163–165 °C. IR (Nujol): 3410, 3170, 1680, 1660, 1350 cm⁻¹. MS *m/z*: 234 (M⁺). ¹H-NMR (DMSO-*d*₆) δ: 2.43 (3H, s), 7.60–7.80 (3H, m), 7.93 (1H, br s), 8.10–8.30 (2H, m), 8.50–8.60 (1H, m). *Anal.* Calcd for C₁₁H₁₀N₂O₄: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.33; H, 4.30; N, 11.80.

N-(2-Dimethylaminoethyl)-2-(3-nitrophenylmethylene)-3-oxo-butanamide (**9b**): Yield 92.8% (oil). IR (CHCl₃): 3380, 1670, 1610, 1350, 1100 cm⁻¹. MS *m/z*: 305 (M⁺). ¹H-NMR (CDCl₃) δ: 2.13 (6H, s), 2.49 (3H, s), 2.30–2.50 (2H, m), 3.40–3.50 (2H, m), 6.62 (1H, br), 7.54 (1H, s), 7.60 (1H, dd, *J*=8, 8 Hz), 7.92 (1H, dd, *J*=8, 2 Hz), 8.26 (1H, dd, *J*=8, 2 Hz), 8.40 (1H, dd, *J*=2, 2 Hz).

1-[1,3-Dioxo-2-(3-nitrophenylmethylene)butyl]-4-methylpiperazine (**9d**): Yield 33.8% (oil). IR (CHCl₃): 1670, 1620, 1520, 1440, 1350, 1000, 910 cm⁻¹. MS *m/z*: 317 (M⁺). ¹H-NMR (CDCl₃) δ: 1.80–2.10 (1H, m), 2.24 (3H, s), 2.20–2.60 (3H, m), 2.47 (3H, s), 3.10–3.40 (2H, m), 3.70–4.00 (2H, m), 7.54 (1H, s), 7.61 (1H, dd, *J*=8, 8 Hz), 7.85 (1H, d, *J*=8 Hz), 8.25 (1H, dd, *J*=8, 2 Hz), 8.41 (1H, dd, *J*=2, 2 Hz).

1-[1,3-Dioxo-2-(2-nitrophenylmethylene)butyl]-4-methylpiperazine (**9e**): Yield 95.7% (oil). IR (CHCl₃) δ: 1680, 1530, 1350 cm⁻¹. MS *m/z*: 317 (M⁺). ¹H-NMR (CDCl₃) δ: 1.70–2.50 (4H, m), 2.07 (3H, s), 2.46 (3H, s), 3.20 (2H, m), 3.50 (2H, m), 7.50–8.25 (5H, m).

1-[1,3-Dioxo-2-(4-nitrophenylmethylene)butyl]-4-methylpiperazine (**9f**): Yield 91.2% (oil). IR (CHCl₃): 1670, 1530 cm⁻¹. MS *m/z*: 317 (M⁺). ¹H-NMR (CDCl₃) δ: 1.90–2.50 (4H, m), 2.22 (3H, s), 2.46 (3H, s), 3.00–3.40 (2H, m), 3.70–3.90 (2H, m), 7.53 (1H, s), 7.67 (2H, d, *J*=8 Hz), 8.25 (2H, d, *J*=8 Hz).

Compounds (**9b**, **d–f**) were not further purified or analyzed before use in the next step.

(B-1-ii) Typical Example for the Preparation of 10 1,4-Dihydro-*N*-(2-hydroxyethyl)-6-methyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxamide (**10c**): A mixture of **9c** (100 g), benzamidine hydrochloride (67.5 g), and Et₃N (70 ml) in *n*-BuOH (1 l) was refluxed for 1 h. The reaction mixture was washed with H₂O (300 ml) and evaporated *in vacuo*. The residue was recrystallized from Et₂O to afford **10c** (125 g, 91.3%), mp 148–150 °C. IR (Nujol): 1670, 1635, 1605, 1530, 1350 cm⁻¹. MS *m/z*: 380 (M⁺). ¹H-NMR (DMSO-*d*₆) δ: 2.16 (3H, s), 3.00–3.60 (4H, m), 5.75 (1H, s), 7.25–8.25 (11H, m). *Anal.* Calcd for C₂₀H₂₀N₄O₄: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.41; H, 5.19; N, 14.74. Compounds (**10a**, **b**) were obtained according to a similar manner as described for **10c**.

1,4-Dihydro-6-methyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxamide (**10a**): Yield 27.2%, mp 204–206 °C. IR (Nujol): 3350, 1678, 1600 cm⁻¹. MS *m/z*: 336 (M⁺). ¹H-NMR (DMSO-*d*₆) δ: 2.28 (3H, s), 5.77 (1H, s), 7.00 (2H, br s), 7.20–8.20 (9H, m), 9.07 (1H, br s). *Anal.* Calcd for C₁₈H₁₆N₄O₃: C, 64.27; H, 4.80; N, 16.66. Found: C, 64.42; H, 4.75; N, 16.48.

1,4-Dihydro-*N*-(2-dimethylaminoethyl)-6-methyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxamide (**10b**): Yield 31.8%, mp 131–133 °C. IR (Nujol): 1670, 1620 cm⁻¹. MS *m/z*: 407 (M⁺). ¹H-NMR (CDCl₃) δ: 2.10 (6H, s), 2.26 (2H, t, *J*=6 Hz), 2.30 (3H, s), 3.23 (2H, td, *J*=6, 6 Hz), 5.72 (1H, s), 6.17 (1H, t, *J*=6 Hz), 7.10–8.30 (10H, m). *Anal.* Calcd for C₂₂H₂₅N₅O₃: C, 64.84; H, 6.18; N, 17.18. Found: C, 64.48; H, 6.19; N, 17.01.

(B-1-iii) Typical Example for the Preparation of Amide Derivatives (11a, c, 20) *N*-(2-Hydroxyethyl)-6-methyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxamide (**11c**): To a solution of **10c** (66.0 g) in CHCl₃ (1.3 l) was added activated MnO₂ (284 g) and the mixture was refluxed for 1 h with vigorous stirring. After being cooled to room temperature, the MnO₂ was filtered off. The filtrate was evaporated *in vacuo* and the residual precipitate was recrystallized from Et₂O to afford **11c** (31.5 g, 48.0%). IR (Nujol): 3300, 1630, 1550, 1520, 1355 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 2.65 (3H, s), 3.30–3.50 (4H, m), 4.50–4.75 (1H, m), 7.50–8.00 (4H, m), 8.20–8.85 (6H, m). Melting point and analytical data are included in Table II. Compound (**11a**) was prepared in a manner similar to that described for **11c**.

6-Methyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxamide (**11a**): Yield 50.7%, mp 233–234 °C. IR (Nujol): 3325, 1665 cm⁻¹. MS *m/z*: 334 (M⁺). ¹H-NMR (DMSO-*d*₆) δ: 2.67 (3H, s), 7.30–8.80 (11H, m). *Anal.* Calcd for C₁₈H₁₄N₄O₃: C, 64.66; H, 4.22; N, 16.76. Found: C, 64.72; H, 3.99; N, 16.60. Compound **20** was also prepared by the same procedures employed in the preparation of **11c** and its physical properties were identical with those obtained by Method A.

(B-2) Typical Example for the Preparation of Amide Derivatives (41, 44, 45, 49–54) 6-Methyl-5-(4-methylpiperazin-1-ylcarbonyl)-4-(3-nitrophenyl)-2-phenylpyrimidine (**41**): A mixture of **9d** (20 g), benzamidine hydrochloride (9.9 g) and Et₃N (11.4 ml) in *n*-BuOH (200 ml) was refluxed for 2 h. After evaporating the solvent, the residue was dissolved in a mixture of H₂O (200 ml) and CHCl₃ (200 ml). The organic layer was washed with brine, dried over MgSO₄ and filtered. To this filtrate was added activated MnO₂ (120 g), and the mixture was refluxed for 1 h with vigorous stirring. After cooling to room temperature, the MnO₂ was filtered off. The filtrate was evaporated *in vacuo*, and the residue was purified by Al₂O₃ chromatography (200 g) with CHCl₃ as eluent. The fractions containing **41** were combined and evaporated *in vacuo*. The crystalline residue was recrystallized from EtOH to afford **41** (2.8 g, 10.8%). IR (Nujol): 1635, 1530, 1345 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.60–2.50 (4H, m), 2.23 (3H, s), 2.70 (3H, s), 2.86–3.30 (2H, m), 3.67–3.95 (2H, m), 7.35–7.80 (4H, m), 8.15–8.85 (5H, m). MS *m/z*: 417 (M⁺). Melting point and analytical data are included in Table II. Compounds (**44**, **45**, **49–54**) were synthesized according to a manner similar to that described for **41**, and their physical properties are listed in Table IV.

(B-3) Typical Example for the Preparation of Amide Derivatives (46–48) 4-(3-Chlorophenyl)-6-methyl-5-(4-methylpiperazin-1-ylcarbonyl)-2-phenylpyrimidine (**47**): A mixture of 3-chlorobenzaldehyde (8.0 g), **8d** (14.7 g), AcOH (0.81 ml) and piperidine (0.23 ml) in *n*-BuOH (40 ml) was refluxed for 1 h, then benzamidine hydrochloride (8.91 g) and Et₃N (9.5 ml) were added, and the whole was refluxed for 1 h. After evaporating the solvent, the residue was dissolved in a mixture of H₂O (100 ml) and AcOEt (200 ml). The organic layer was extracted with 10% HCl aq. (50 ml) and the aqueous layer was adjusted to pH 9.5 with saturated K₂CO₃ aq. and extracted with AcOEt (100 ml). The separated organic layer was washed with brine, then activated MnO₂ (50 g) was added and the mixture was refluxed for 1 h with vigorous stirring. After the mixture was allowed to cool to room temperature, the MnO₂ was filtered off. The filtrate was evaporated *in vacuo* and the residue was purified by column chromatography on SiO₂ (100 g) with CHCl₃-acetone (10:1) as eluent. The fractions containing **47** were combined and evaporated *in vacuo*. The crystalline residue was recrystallized from Et₂O-*n*-hexane to afford **47** (4.7 g, 20.3%). IR (Nujol): 1620, 730 cm⁻¹. MS *m/z*: 406 (M⁺). ¹H-NMR (CDCl₃) δ: 1.20–1.80 (1H, m), 2.13 (3H, s), 1.90–2.50 (3H, m), 2.63 (3H, s), 2.70–3.20 (2H, m), 3.60–3.90 (2H, m), 7.30–7.70 (5H, m), 7.70–8.00 (2H, m), 8.40–8.70 (2H, m). Compounds (**46**, **48**) were synthesized by the same procedures as employed in the preparation of **47** and the melting point and analytical data are listed in Table IV.

Method C. (C-1) *N*-(2-Chloroethyl)-6-methyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxamide (12) To a solution of **11c** (15.0 g) in a mixture of CHCl₃ (135 ml) and DMF (30 ml), was dropwise added SOCl₂ (4.3 ml) in CHCl₃ (7 ml) under ice cooling, then the mixture was refluxed for 2 h. After evaporating the solvent, the residue was dissolved in a mixture of H₂O (100 ml) and CHCl₃ (100 ml), then the pH was adjusted to 8.5 with saturated K₂CO₃ aq. The separated organic layer was washed with brine, dried over MgSO₄ and evaporated *in vacuo*. The resulting precipitate was washed with Et₂O to afford **12** (8.2 g, 50.9%), mp 199–200 °C. IR (Nujol): 3300, 1640, 1590, 1530 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.66 (3H, s), 5.96–6.30 (1H, br m), 3.40–3.70 (4H, m), 7.30–7.75 (4H, m), 8.06–8.80 (5H, m). *Anal.* Calcd for C₂₀H₁₇ClN₄O₃: C, 60.53; H, 4.31; N, 14.11. Found: C, 60.20; H, 4.10; N, 13.94.

(C-ii) Typical Example for the Preparation of Amide Derivatives (32–34) 6-Methyl-4-(3-nitrophenyl)-2-phenyl-*N*-(2-thiomorpholinoethyl)-5-pyrimidinecarboxamide (**33**): A mixture of **12** (2 g), thiomorpholine (1.52 ml) and NaI (0.076 g) in isopropyl alcohol (20 ml) was refluxed for 7 h. The reaction mixture was poured into a mixture of AcOEt (200 ml) and H₂O (100 ml). The organic layer was successively washed with H₂O and brine, dried over MgSO₄ and evaporated *in vacuo*. The residue was purified by Al₂O₃ chromatography with CHCl₃ as eluent. The fractions containing **33** were combined and evaporated. The residue was recrystallized from Et₂O to afford **33** (0.85 g, 36.4%). IR (Nujol): 3210, 1620, 1565, 1530, 1350 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.34 (2H, t,

$J=6$ Hz), 2.47 (8H, s), 2.70 (3H, s), 3.40 (2H, td, $J=6$, 6 Hz), 6.17 (1H, t, $J=6$ Hz), 7.40–7.73 (4H, m), 8.15–8.83 (5H, m). MS m/z : 463 (M^+). Melting point and analytical data are included in Table II. Compounds (**32**, **34**) were prepared by the same procedures as employed in the preparation of **33**.

Method D. *N*-Dimethylaminomethyl-6-methyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxamide (19) A mixture of **11a** (8 g), formalin (37%, 2.2 ml), dimethylamine aq. (50%, 3.2 ml), MeOH (50 ml) and CHCl_3 (80 ml) was refluxed for 10 h. After evaporating the solvent *in vacuo*, the residue was chromatographed on Al_2O_3 (300 ml) with CHCl_3 as eluent. The fractions containing **19** were combined and evaporated *in vacuo*. The residue was recrystallized from Et_2O to afford **19** (1.54 g, 16.4%). IR (Nujol): 3250, 1640 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 2.10 (6H, s), 2.67 (3H, s), 4.02 (2H, d, $J=6$ Hz), 6.37 (1H, t, $J=6$ Hz), 7.30–7.70 (4H, s), 8.05–8.80 (5H, m). MS m/z : 391 (M^+). Melting point and analytical data are included in Table I.

Method E. (E-i) 5-Hydroxymethyl-6-methyl-4-(3-nitrophenyl)-2-phenylpyrimidine (14) To a suspension of LiAlH_4 (12.2 g) in a mixture of dry THF (180 ml) and Et_2O (360 ml) was added dropwise a solution of **13** (45.0 g) in dry tetrahydrofuran (THF, 180 ml) under cooling at -50 – -40°C for 15 min. After stirring for 1.5 h, excess LiAlH_4 was decomposed by the careful addition to ice water. The separated aqueous layer was extracted with AcOEt (1 l). The combined organic layer was successively washed with 15% H_2SO_4 aq. (400 ml), saturated NaHCO_3 aq. and brine, and evaporated *in vacuo*. The residue was recrystallized from Et_2O to afford **14** (30.0 g, 72.4%), mp 177 – 178°C . IR (Nujol): 1590, 1360, 1025 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 2.77 (3H, s), 4.50 (2H, d, $J=4$ Hz), 5.50 (1H, t, $J=4$ Hz), 7.30–7.67 (3H, m), 7.80 (1H, dd, $J=8$, 8 Hz), 8.10–8.60 (4H, m), 8.67 (1H, dd, $J=2$, 2 Hz). MS m/z : 321 (M^+). Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_3$: C, 67.28; H, 4.70; N, 13.08. Found: C, 67.58; H, 4.57; N, 13.09.

(E-ii) 5-Bromomethyl-6-methyl-4-(3-nitrophenyl)-2-phenylpyrimidine (15) To a solution of PBr_3 (16.9 g) in a mixture of benzene (150 ml) and THF (150 ml) was added dropwise a solution of **14** (30.0 g) in THF (150 ml) under cooling at 7 – 10°C . After stirring for 4 h at the same temperature, the reaction mixture was poured into ice water (200 ml), adjusted to pH 9.5 with saturated K_2CO_3 aq. and extracted with AcOEt (300 ml). After filtering off an insoluble material, the organic layer was washed with brine, dried over MgSO_4 and evaporated *in vacuo*. The residue was recrystallized from CHCl_3 – Et_2O to afford **15** (29.1 g, 81.1%), mp 172 – 174°C . IR (Nujol): 1550, 1530, 1350 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 2.80 (3H, s), 4.47 (2H, s), 7.35–7.55 (3H, m), 7.73 (1H, dd, $J=8$, 8 Hz), 8.17 (1H, ddd, $J=8$, 2, 2 Hz), 8.30–8.60 (3H, m), 8.80 (1H, dd, $J=2$, 2 Hz). MS m/z : 383 (M^+). Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{BrN}_3\text{O}_2$: C, 56.27; H, 3.67; N, 10.94. Found: C, 56.66; H, 3.58; N, 10.93.

(E-iii) 5-Cyanomethyl-6-methyl-4-(3-nitrophenyl)-2-phenylpyrimidine (16) To a solution of NaCN (4.8 g) in H_2O (50 ml) was added a suspension of **15** (30.0 g) in a mixture of EtOH (180 ml) and THF (180 ml), and the mixture was refluxed for 2 h. The reaction mixture was poured into a mixture of ice water (200 ml) and Et_2O (200 ml). The precipitate was filtered, washed with water, and dried *in vacuo* to afford **16** (22.5 g, 87.3%), mp 219 – 221°C . IR (Nujol): 1535, 1350 cm^{-1} . $^1\text{H-NMR}$ (CF_3COOD) δ : 3.25 (3H, s), 4.28 (2H, s), 7.50–9.00 (9H, m). MS m/z : 330 (M^+). This compound was not further purified or analyzed before

use in the next step.

(E-iv) Ethyl 6-Methyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinylacetate (17) A mixture of **16** (5.0 g), conc. H_2SO_4 (6.5 ml) and EtOH (50 ml) was refluxed for 72 h. The reaction mixture was poured into a mixture of CHCl_3 (200 ml) and H_2O (100 ml), then adjusted to pH 8.5 with 10% Na_2CO_3 aq. The organic layer was washed with brine, dried over MgSO_4 and evaporated *in vacuo*. The residual substance was recrystallized from Et_2O –*n*-hexane to afford **17** (3.7 g, 64.8%), mp 106 – 108°C . IR (Nujol): 1733, 1535 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.27 (3H, t, $J=7$ Hz), 2.67 (3H, s), 3.64 (2H, s), 4.21 (2H, q, $J=7$ Hz), 7.30–7.50 (3H, m), 7.60 (1H, dd, $J=8$, 8 Hz), 7.92 (1H, ddd, $J=8$, 2, 2 Hz), 8.15–8.60 (4H, m). MS m/z : 377 (M^+). Anal. Calcd for $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.63; H, 5.08; N, 11.22.

Method F. 5-[3-(2-Dimethylaminoethyl)ureido]-6-methyl-4-(3-nitrophenyl)-2-phenylpyrimidine Hydrochloride (25) A mixture of **5a** (5.0 g), Et_3N (1.5 g) and DPPA (4.1 g) in benzene (50 ml) was refluxed for 2 h, and 2-dimethylaminoethylamine (1.6 g) was added. After continuous refluxing for 2 h, the reaction mixture was poured into a mixture of Et_2O (100 ml) and saturated NaHCO_3 aq. (50 ml). The separated organic layer was dried over MgSO_4 and evaporated *in vacuo*. The residual substance was purified by chromatography on Al_2O_3 (200 g) with CHCl_3 as eluent. The fractions containing **25** were combined and evaporated *in vacuo*. The residue was dissolved in EtOH (5 ml) and treated with slight excess of $\text{HCl}/\text{Et}_2\text{O}$ to afford **25** (0.98 g, 14.4%), mp 125 – 127°C . IR (Nujol): 1700, 1620, 1600, 740 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 2.57 (3H, s), 2.67 (3H, s), 2.72 (3H, s), 2.80–3.20 (2H, m), 3.15–3.50 (2H, m), 7.00 (1H, br), 7.30–7.60 (3H, m), 7.65–7.95 (1H, m), 8.10–8.50 (4H, m), 8.50–8.80 (2H, m), 10.65 (1H, br s). Melting point and analytical data are listed in Table I.

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