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 (NO_2Ph) group was effective; 3-NO_2Ph or 4-NO_2Ph was more effective than 2-NO_2Ph (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, nizofenone)[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.

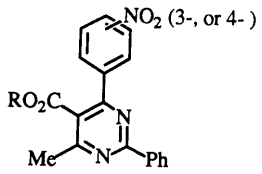


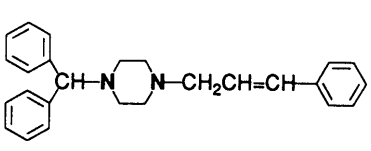
Fig. 1

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

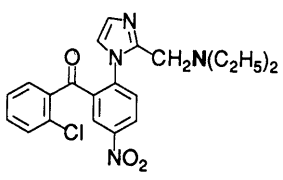
Method A (Chart 1): α,β-Unsaturated carbonyl compounds (**2a—d**) were obtained by the Knoevenagel reaction of β-keto esters (**1**) with 3-, or 4-nitrobenzaldehyde in the presence of piperidine and acetic acid. 6-Substituted alkyl 4-(3-, or 4-nitrophenyl)-5-pyrimidinecarboxylates (**4a—d**) were prepared by the same procedures we reported previously.[1] Thus, the refluxing of **2a—d** with arylamidine hydrochloride in the presence of triethylamine (Et_3N) in 1-butanol (*n*-BuOH) for 1—3 h gave dihydropyrimidines (**3a—d**). These were oxidized with activated manganese (IV) oxide (MnO_2) 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 Breaux *et al.*[5] Treatment of the appropriate benzoyl acetates (**6a**, **6b**) with *N*,*N*-dimethylformamide dimethylacetal provided enaminones (**7a**, **7b**), which were condensed with arylamidine hydrochloride in the presence of Et_3N 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**).

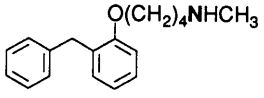
Method B: Preferred procedures for the synthesis of targeted amide derivatives, since they avoid the hydrolysis



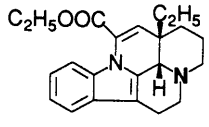
cinnarizine



nizofenone



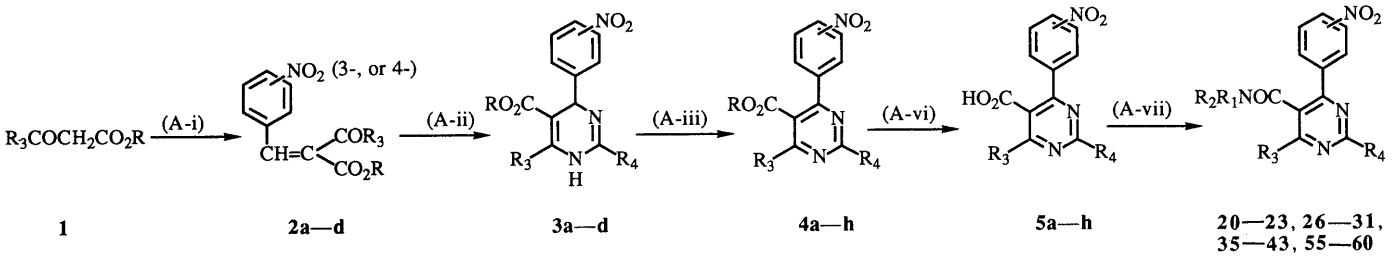
bifemerane



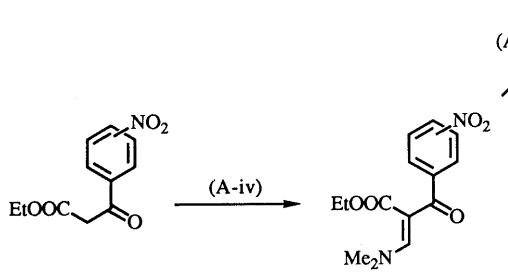
vinpocetine

Fig. 2

[method A]



1 2a—d 3a—d 4a—h 5a—h 20—23, 26—31, 35—43, 55—60



6a: 3-NO_2 7a: 3-NO_2

6b: 4-NO_2 7b: 4-NO_2

2x—5x[a] x= a—h	NO_2	R_3	R_4	R
a :	3	Me	Ph	Et
b :	4	Me	Ph	Et
c :	3	CF_3	Ph	Et
d :	3	Et	Ph	Me
e :	3	H	Ph	Et
f :	4	H	Ph	Et
g :	3	H	4-Cl	Et
h :	4	H	4-Cl	Et

(A-i) NO_2PhCHO, piperidine, AcOH / benzene; (A-ii) $R_4C(NH_2)$=NH· HCl, Et_3N / *n*-BuOH; (A-iii) MnO_2 / $CHCl_3$; (A-iv) $Me_2NCH(OMe)_2$ / benzene (A-v) $R_4C(NH_2)$=NH•HCl, Et_3N / *n*-BuOH; (A-vi) NaOH aq. / MeOH—H_2O; (A-vii) $SOCl_2$— DMF / CH_2Cl_2 ; R_2R_1NH

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

Chart 1

[method B]

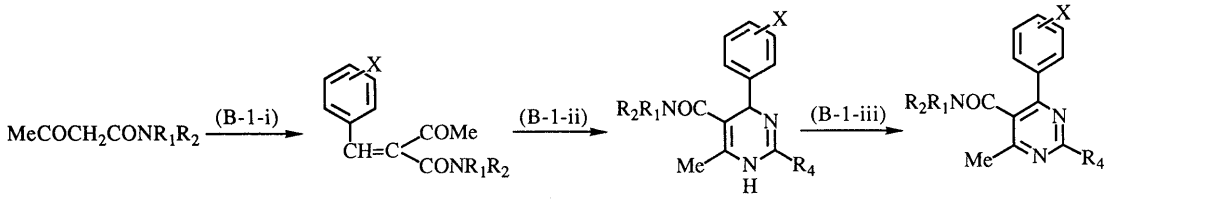
B-1: **8a—c** → **9a—c** → **10a—c** → (**11a, 11c, 20**)

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

B-3: **8d** → [**9d'**][a] → [**10d'**][a] → (**46—48**)[a]

[ ] : without isolation

a) X are not NO_2, see the list in Table IV



8a—d **9a—f** **10a—c** **11a, 11c, 20, 41, 44—54**

8x—11x[b]	X= NO_2, position of NO_2	NR_1R_2
a :	3	NH_2
b :	3	$NHCH_2CH_2NMe_2$
c :	3	$NHCH_2CH_2OH$
d :	3	
e :	2	
f :	4	

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

(B-1-ii) $R_4C(NH_2)$=NH· HCl, Et_3N / *n*-BuOH

(B-1-iii) MnO_2 / $CHCl_3$ or AcOEt

b) the alphabetical letters of compounds (**8**—**11**) correspond to each other , and the substituents X, R_1, R_2 and R_4 are as listed in Tables I, II and IV

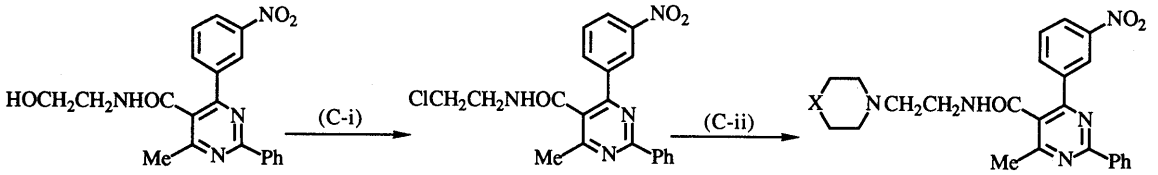
Chart 2

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]

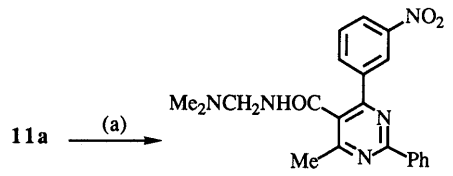


11c **12** **32**: X= CH_2; **33**: X= S; **34**: X= NMe

(C-i) $SOCl_2$ / $CHCl_3$—DMF; (C-ii) amine, NaI / isopropyl alcohol

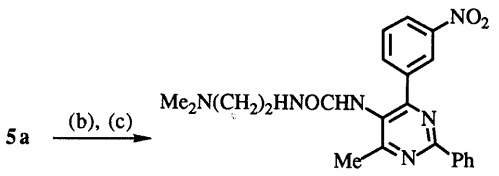
Chart 3

[method D]



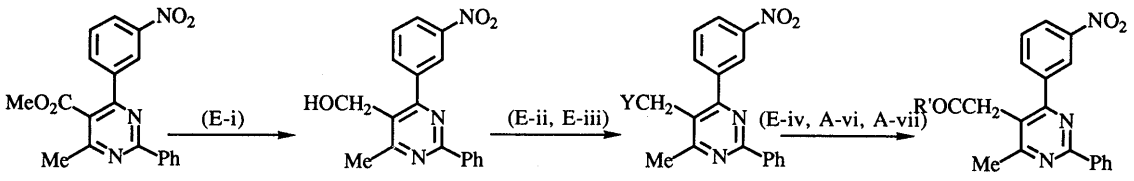
19

[method F]



25

[method E]



13 **14** **15**: Y= Br; **16**: Y= CN; **17**: R'= OEt; **18**: R'= OH; **24**: R'= $NH(CH_2)_2NMe_2$

(a) HCHO aq., Me_2NH aq. / MeOH—$CHCl_3$; (E-i) $LiAlH_4$ / THF—Et_2O; (E-ii) PBr_3 / THF; (E-iii) NaCN / H_2O—EtOH—THF

(E-iv) conc. H_2SO_4 / EtOH; (A-vi) KOH / EtOH—H_2O; (A-vii) $SOCl_2$ / DMF—$CHCl_3$; (b) DPPA, Et_3N / benzene; (c) $Me_2N(CH_2)_2NH_2$

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 MnO_2 to afford amides (**46**—**48**).

Method C (Chart 3): Chlorination of **11c** with $SOCl_2$, 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 Me_2NH aq. and formalin afforded **19**.

Method E: Reduction of **13**[1] with $LiAlH_4$ provided the alcohol (**14**). On bromination, followed by reaction with sodium cyanide, **14** gave the cyanomethyl derivative (**16**). Esterification of **16** with ethanolic H_2SO_4 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 Et_3N,

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

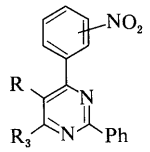
Pharmacological Results and Discussion

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

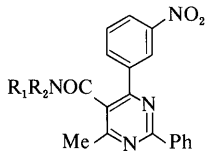
TABLE I. Physical Properties and Biological Activities of 4-(3-, or 4-Nitrophenyl)-5-pyrimidinecarboxamide Derivatives

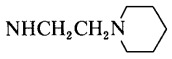
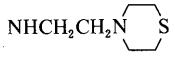
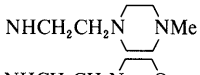
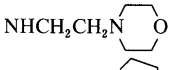
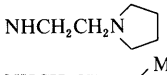
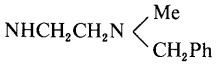
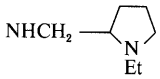
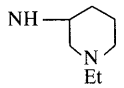
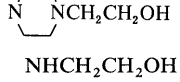


Compd. No.	Position of $-NO_2$	R	R_3	Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10	32	Lipid peroxidation[b] (% of control) (g/ml) 10^{-5}	Method	Yield[c] (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N
19	3	$CONHCH_2NMe_2$	Me		121.4	NT[d]	D	16.4	128—130 (Et_2O)	$C_{21}H_{21}N_5O_3$	64.44 (64.22)	5.41 5.10	17.89 17.60)
20	3	$CONHCH_2CH_2NMe_2$	Me	102.0	124.5[e]	72.8[e]	A B-1	36.8 28.8	120—122 (Et_2O)	$C_{22}H_{23}N_5O_3$	65.17 (65.29	5.72 5.62	17.27 17.25)
21	3	$CONHCH_2CH_2NMe_2$ ·fumarate	Me	121.3[e]	121.0[e]	95.2		83.6	200—201 (EtOH)	$C_{22}H_{23}N_5O_3$ ·$C_4H_4O_4$	59.88 (59.83	5.22 5.57	13.43 13.39)
22	3	$CONHCH_2CH_2CH_2NMe_2$	Me		97.0	77.4	A	13.5	137—139 (Et_2O)	$C_{23}H_{25}N_5O_3$	65.86 (66.05	6.01 6.26	16.70 16.76)
23	3	$CONHCH_2CH_2NEt_2$ ·fumarate	Me	103.8	112.3	37.4[f]	A	54.8	154—158 (EtOH–AcOEt)	$C_{24}H_{27}N_5O_3$ ·$C_4H_4O_4$	61.19 (60.96	5.68 5.66	12.74 12.67)
24	3	$CH_2CONHCH_2CH_2NMe_2$	Me		96.0	63.4	E	20.8	185—187 (Et_2O)	$C_{23}H_{25}N_5O_3$	65.86 (65.96	6.01 5.83	16.70 16.73)
25	3	$NHCONHCH_2CH_2NMe_2$ ·HCl	Me		107.4	98.7	F	14.4	125—127 (EtOH–Et_2O)	$C_{22}H_{24}N_6O_3$ ·HCl·4.5H_2O	49.11 (49.28	6.36 5.96	15.62 15.58)
26	3	$CONHCH_2CH_2NMe_2$	H	101.4	128.0[e]	NT[d]	A	49.2	165—167 (Et_2O)	$C_{21}H_{21}N_5O_3$	64.44 (64.83	5.41 5.12	17.89 18.04)
27	3	$CONHCH_2CH_2NMe_2$	Et	106.8	122.8[f]	38.4[e]	A	28.4	106—109 (Et_2O)	$C_{23}H_{25}N_5O_3$	65.86 (65.83	6.01 5.85	16.70 16.59)
28	3	$CONHCH_2CH_2NMe_2$	CF_3	110.1	113.4[e]	30.4[e]	A	25.4	174—175 (IPE)	$C_{22}H_{20}F_3N_5O_3$	57.52 (57.82	4.39 4.45	15.24 15.25)
29	4	$CONHCH_2CH_2NMe_2$	Me	107.1	123.5[e]	43.1[e]	A	29.9	148—149 (Et_2O)	$C_{22}H_{23}N_5O_3$	65.17 (64.94	5.71 5.71	17.27 17.08)
30	4	$CONHCH_2CH_2NMe_2$ ·fumarate	Me	111.4[e]	118.2[e]	43.0[f]		93.3	188—190 (EtOH)	$C_{22}H_{23}N_5O_3$ ·$C_4H_4O_4$	59.88 (59.91	5.22 5.29	13.43 13.42)
31	4	$CONHCH_2CH_2NMe_2$	H	113.8	114.8[e]	77.6[e]	A	71.1	180—182 (Et_2O)	$C_{21}H_{21}N_5O_3$	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_1R_2	Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10	32	Lipid peroxidation[b] (% of control) (g/ml) 10^{-5}	Method	Yield[c] (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N
32		108.7	119.9[d]	38.7[e]	C	15.6	119—120 (Et_2O)	$C_{25}H_{27}N_5O_3$	67.40 (67.29)	6.11 (5.93)	15.72 (15.60)
33		105.6	120.0[e]	29.8[e]	C	36.4	169—170 (Et_2O)	$C_{24}H_{25}N_5O_3S$	62.19 (62.33)	5.44 (5.38)	15.11 (15.19)
34		107.1	103.5	52.2[d]	C	20.7	93—95 (Et_2O)	$C_{25}H_{28}N_6O_3$	65.20 (64.93)	6.13 (6.31)	18.25 (18.14)
35		111.4	120.8[e]	95.0[d]	A	31.3	165—167 (EtOH)	$C_{24}H_{25}N_5O_4$	64.42 (64.80)	5.63 (5.83)	15.65 (15.96)
36			109.4	37.7[e]	A	36.3	133—134 (Et_2O)	$C_{24}H_{25}N_5O_3$	66.81 (67.08)	5.84 (5.43)	16.23 (16.45)
37			107.6	6.3[e]	A	12.6	100—101 (IPE)	$C_{28}H_{27}N_5O_3$	69.84 (69.96)	5.65 (5.90)	14.54 (14.83)
38			103.3	34.8[e]	A	35.7	88—90 (IPE)	$C_{25}H_{27}N_5O_3$	67.40 (67.64)	6.11 (6.01)	15.72 (15.92)
39		116.0	122.7[d]	86.9[d]	A	41.4	146—148 (Et_2O)	$C_{25}H_{27}N_5O_3$	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_2O)	$C_{22}H_{21}N_5O_3$	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)	$C_{23}H_{23}N_5O_3$	66.17 (66.10)	5.55 (5.47)	16.78 (16.94)
42			116.0	NT[f]	A	70.1	144—145 (Et_2O)	$C_{24}H_{25}N_5O_3$	66.81 (66.64)	5.84 (5.77)	16.23 (16.16)
43			100.0	70.1[e]	A	34.3	128—130 (Et_2O)	$C_{24}H_{25}N_5O_4$	64.42 (64.42)	5.63 (5.40)	15.65 (15.75)
11c	$NHCH_2CH_2OH$		97.2	92.0	B-1	48.0	190—192 (Et_2O)	$C_{20}H_{18}N_4O_4$	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**)

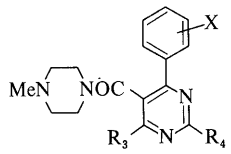
Compound No.	Anti-anoxia (% of control) (mg/kg, i.p.) 10	32	100	Lipid peroxidation IC_{50} (M)	Arachidonate-induced[a] cerebral edema ED_{50} (mg/kg) i.p.	*p.o.*	Acute toxicity[b] LD_{50} (mg/kg, i.p.)
21	121[c]	121[c]	128[c]	6.5×10^{-5}	8	NT[d]	110
33	106	120[c]	116	7.1×10^{-6}	14	>100	>560
35	111	121[c]	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 LD_{50} 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.) 10	32	Lipid peroxidation[b] (% of control) (g/ml) 10^{-5}	Method	Yield[c] (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N
44	4-NO_2	Me	Ph		125.9[d]	NT[e]	B-2	7.7	257—258 (EtOH)	$C_{23}H_{23}N_5O_3 \cdot 1/4H_2O$	65.46 (65.59)	5.61 (5.61)	16.59 (16.63)
45	2-NO_2	Me	Ph	103.9	128.9[f]	59.4[d]	B-2	3.4	146—147 (EtOH–Et_2O)	$C_{23}H_{23}N_5O_3$	66.17 (66.32)	5.55 (5.62)	16.78 (16.88)
46	3-CF_3	Me	Ph	114.6	127.9[f]	36.2[d]	B-3	19.1	124—125 (EtOH)	$C_{24}H_{23}F_3N_4O$	65.45 (65.80)	5.26 (5.25)	12.72 (12.54)
47	3-Cl	Me	Ph		105.6	NT[e]	B-3	20.3	117—119 (Et_2O–*n*-hexane)	$C_{23}H_{23}ClN_4O$	67.89 (68.39)	5.70 (5.42)	13.77 (13.70)
48	3-CN	Me	Ph		102.8	NT[e]	B-3	8.0	123—124 (Et_2O–*n*-hexane)	$C_{24}H_{23}N_5O$	72.53 (72.79)	5.83 (5.63)	17.62 (17.71)
49	3-NO_2	Me	Me		105.6	NT[e]	B-2	10.7	121—124 (EtOH)	$C_{18}H_{21}N_5O_3$	60.83 (60.99)	5.96 (5.58)	19.71 (19.98)
50	3-NO_2	Me	4-ClPh	122.2[d]	117.5[f]	3.2[d]	B-2	29.2	136—137 (Et_2O)	$C_{23}H_{22}ClN_5O_3$	61.13 (60.93)	4.91 (4.72)	15.50 (15.27)
51	3-NO_2	Me	4-MePh		111.1[f]	90.4[d]	B-2	10.5	131—134 (EtOH)	$C_{24}H_{25}N_5O_3$	66.80 (67.02)	5.84 (5.60)	16.23 (16.28)
52	3-NO_2	Me	4-MeOPh		108.2	NT[e]	B-2	22.3	>300 °C (EtOH)	$C_{24}H_{25}N_5O_4 \cdot HCl \cdot 1/2H_2O$	58.48 (58.84)	5.52 (5.31)	14.21 (14.39)
53	3-NO_2	Me	4-FPh		113.0	NT[e]	B-2	17.8	139—141 (EtOH)	$C_{23}H_{22}FN_5O_3$	63.44 (63.91)	5.09 (4.66)	16.08 (16.14)
54	3-NO_2	Me	4-Py	101.8	106.9	91.1	B-2	30.1	161—162 (Et_2O)	$C_{22}H_{22}N_6O_3$	63.14 (62.77)	5.29 (5.19)	20.08 (19.94)
55	3-NO_2	H	Ph	91.9	117.4	NT[e]	A	50.3	177—179 (Et_2O)	$C_{21}H_{21}N_5O_3$	65.50 (65.41)	5.25 (5.26)	17.36 (17.31)
56	3-NO_2	Et	Ph		109.0	NT[e]	A	70.2	113—114 (EtOH)	$C_{24}H_{25}N_5O_3$	66.80 (66.70)	5.83 (5.79)	16.23 (16.14)
57	3-NO_2	CF_3	Ph		104.4	NT[e]	A	26.4	166—167 (EtOH–Et_2O)	$C_{23}H_{20}F_3N_5O_3$	58.59 (58.53)	4.27 (4.06)	14.85 (14.56)
58	3-NO_2	H	4-ClPh		114.0	NT[e]	A	60.9	150—151 (Et_2O)	$C_{22}H_{20}ClN_5O_3$	60.35 (60.06)	4.60 (4.69)	15.99 (15.86)
59	4-NO_2	H	Ph	113.0[d]	123.2[d]	87.3[d]	A	66.4	165—166 (Et_2O)	$C_{22}H_{21}N_5O_3$	65.50 (65.65)	5.25 (5.17)	17.36 (17.54)
60	4-NO_2	H	4-ClPh		110.5	4.4[d]	A	29.5	146—147 (Et_2O)	$C_{22}H_{20}ClN_5O_3$	60.35 (60.19)	4.60 (4.43)	15.99 (15.83)

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-ylcalbonyl)-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 ($LD_{50} > 560$ mg/kg, i.p.). Further experiments 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. ^{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 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 H_2O (100 ml), 10% $NaHCO_3$ aq. (50 ml) and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residual substance was recrystallized from Et_2O 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^+). ^{1}H-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^+). ^{1}H-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}. ^{1}H-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}. ^{1}H-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^+). ^{1}H-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^+). ^{1}H-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^+). ^{1}H-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^+). ^{1}H-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): 1720, 1525, 1360 cm^{-1}. MS *m/z*: 383 (M^+). ^{1}H-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^+). ^{1}H-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}. ^{1}H-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}. ^{1}H-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}. ^{1}H-NMR (DMSO-d_6): 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}. ^{1}H-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}. ^{1}H-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}. ^{1}H-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}. ^{1}H-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}. ^{1}H-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^+). ^{1}H-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 H_2O (200 ml) and brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residual substance was recrystallized from Et_2O 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^+): ^{1}H-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 $C_{13}H_{14}N_2O_5$: 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^+). ^{1}H-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 $C_{11}H_{10}N_2O_4$: 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 ($CHCl_3$): 3380, 1670, 1610, 1350, 1100 cm^{-1}. MS *m/z*: 305 (M^+). ^{1}H-NMR ($CDCl_3$) 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 ($CHCl_3$): 1670, 1620, 1520, 1440, 1350, 1000, 910 cm^{-1}. MS *m/z*: 317 (M^+). ^{1}H-NMR ($CDCl_3$) 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 ($CHCl_3$) δ: 1680, 1530, 1350 cm^{-1}. MS *m/z*: 317 (M^+). ^{1}H-NMR ($CDCl_3$): 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 ($CHCl_3$): 1670, 1530 cm^{-1}. MS *m/z*: 317 (M^+). ^{1}H-NMR ($CDCl_3$) 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 Et_3N (70 ml) in *n*-BuOH (1 l) was refluxed for 1 h. The reaction mixture was washed with H_2O (300 ml) and evaporated *in vacuo*. The residue was recrystallized from Et_2O 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^+). ^{1}H-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 $C_{20}H_{20}N_4O_4$: 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^+). ^{1}H-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 $C_{18}H_{16}N_4O_3$: 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^+). ^{1}H-NMR ($CDCl_3$) 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 $C_{22}H_{25}N_5O_3$: 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 $CHCl_3$ (1.3 l) was added activated MnO_2 (284 g) and the mixture was refluxed for 1 h with vigorous stirring. After being cooled to room temperature, the MnO_2 was filtered off. The filtrate was evaporated *in vacuo* and the residual precipitate was recrystallized from Et_2O to afford **11c** (31.5 g, 48.0%). IR (Nujol): 3300, 1630, 1550, 1520, 1355 cm^{-1}. ^{1}H-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^+). ^{1}H-NMR (DMSO-d_6) δ: 2.67 (3H, s), 7.30—8.80 (11H, m). *Anal.* Calcd for $C_{18}H_{14}N_4O_3$: 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 Et_3N (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 H_2O (200 ml) and $CHCl_3$ (200 ml). The organic layer was washed with brine, dried over $MgSO_4$ and filtered. To this filtrate was added activated MnO_2 (120 g), and the mixture was refluxed for 1 h with vigorous stirring. After cooling to room temperature, the MnO_2 was filtered off. The filtrate was evaporated *in vacuo*, and the residue was purified by Al_2O_3 chromatography (200 g) with $CHCl_3$ 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}. ^{1}H-NMR ($CDCl_3$) 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 Et_3N (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 H_2O (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 K_2CO_3 aq. and extracted with AcOEt (100 ml). The separated organic layer was washed with brine, then activated MnO_2 (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 MnO_2 was filtered off. The filtrate was evaporated *in vacuo* and the residue was purified by column chromatography on SiO_2 (100 g) with $CHCl_3$-acetone (10:1) as eluent. The fractions containing **47** were combined and evaporated *in vacuo*. The crystalline residue was recrystallized from Et_2O–*n*-hexane to afford **47** (4.7 g, 20.3%). IR (Nujol): 1620, 730 cm^{-1}. MS *m/z*: 406 (M^+). ^{1}H-NMR ($CDCl_3$) 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-i) *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 $CHCl_3$ (135 ml) and DMF (30 ml), was dropwise added $SOCl_2$ (4.3 ml) in $CHCl_3$ (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 H_2O (100 ml) and $CHCl_3$ (100 ml), then the pH was adjusted to 8.5 with saturated K_2CO_3 aq. The separated organic layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The resulting precipitate was washed with Et_2O to afford **12** (8.2 g, 50.9%), mp 199—200 °C. IR (Nujol): 3300, 1640, 1590, 1530 cm^{-1}. ^{1}H-NMR ($CDCl_3$) 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 $C_{20}H_{17}ClN_4O_3$: 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 H_2O (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 Al_2O_3 chromatography with $CHCl_3$ as eluent. The fractions containing **33** were combined and evaporated. The residue was recrystallized from Et_2O to afford **33** (0.85 g, 36.4%). IR (Nujol): 3210, 1620, 1565, 1530, 1350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) 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}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}H-NMR (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 $C_{18}H_{15}N_3O_3$: 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}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 $C_{18}H_{14}BrN_3O_2$: 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}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}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 $C_{21}H_{19}N_3O_4$: 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 HCl/Et_2O to afford **25** (0.98 g, 14.4%), mp 125—127 °C. IR (Nujol): 1700, 1620, 1600, 740 cm^{-1}. ^{1}H-NMR (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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