Studies on Cerebral Protective Agents. III.[1a] Novel 4-Arylpyrimidine Derivatives with Anti-anoxic and Anti-lipid Peroxidation Activities. (3)

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Novel 4-arylpyrimidine derivatives, bearing an amino moiety in the C-5 or C-6 position of the pyrimidine ring, were synthesized and tested for anti-anoxic (AA) activity in mice. Among them, 6,7-dihydro-6-[2-(dimethylamino)-ethyl]-4-(3-nitrophenyl)-2-phenyl-5*H*-pyrrolo[3,4-*d*]pyrimidine-5-one (2a, FR 75469) and 6-methyl-5-(4-methyl-piperazin-1-ylmethyl)-4-(3-nitrophenyl)-2-phenylpyrimidine (4c, FR 72707) had comparable potency 10—100 mg/kg, i.p. and *p.o.*) to that of 6-methyl-5-(4-methylpiperazin-1-ylcarbonyl)-4-(3-nitrophenyl)-2-phenylpyrimidine (FK 360). These were also effective on anti-lipid peroxidation (ALP) assay and arachidonate-induced cerebral edema in rats. Structure–activity relationship in regard to AA activity of this series of compounds are discussed. Three-dimensional molecular electrostatic potentials (3D-MEP) around the nitrogeneous basic moiety of FK 360 and 5-acetyl-6-(2-dimethylaminoethyl)-4-(3-nitrophenyl)-2-phenylpyrimidine (5f) were compared, and both electrostatic potential maps were similar.

Keywords cerebral protective agent; 4-arylpyrimidine; anti-anoxia; anti-lipid peroxidation; structure–activity relationship; FK 360

Introduction

In the previous work,[1a] we synthesized 4-aryl-5-pyrimidinecarboxamide derivatives and found that, for example, as shown in Fig. 1, compounds (**1a** and **1b**: FK 360) possessed the potent cerebral protective activities in animal models.

4-(3-Nitrophenyl)-2-phenylpyrimidine system (part A) and the nitrogenous basic moiety in the C-5 position (part B) appeared to be a prerequisite for anti-lipid peroxidation (ALP) and anti-anoxic (AA) activity, respectively.[1a,b] This finding was very important since we searched for new cerebral protective agents which have both pharmacophores (*i.e.* AA and ALP) in the molecule. In order to more fully investigate these findings we have prepared the following three types of pyrimidine derivatives shown in Fig. 2. i) We synthesized lactam derivatives (**2**, **3**); synthesis of rigid analogues of flexible compounds is a representative approach in medicinal chemistry and it proved to be successful in our reported amide series. Thus, conversion of the substituent in the C-5 position from a flexible one to a semirigid one (*e.g.* **1a** to **1b**), resulted in an increase in efficacy and a decrease in acute toxicity.[1a] ii) The possibility of replacing an amide moiety (R_1R_2NCO–) with aminomethyl ($R_1R_2NCH_2$–) was examined by preparing derivatives (**4**). iii) The effect on AA activity of the nitrogenous basic moiety in the C-6 position of the pyrimidine ring was examined by preparing derivatives (**5**). We now report our findings in the chemistry and the structure–activity relationships (SARs) in regard to AA activity of these pyrimidine derivatives. A comparison of three-dimensional molecular electrostatic potentials (3D-MEP) around the nitrogenous basic moiety of FK 360 and **5f** is also described.

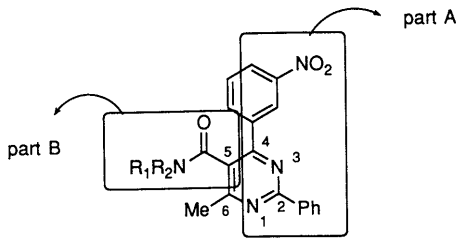


Fig. 1

Chemistry

The lactam derivatives (**2a—f**, **3a, b**) were obtained by the following two methods as shown in Chart 1; 1) Condensation of **8** and **9**, which were obtained by bromination of **6**[1b] and **7**[1a] with pyridinium hydrobromide per-

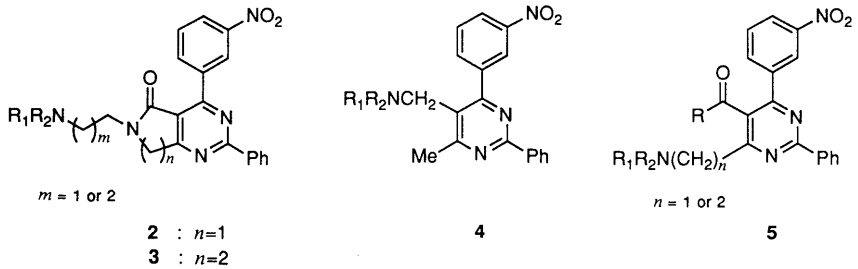
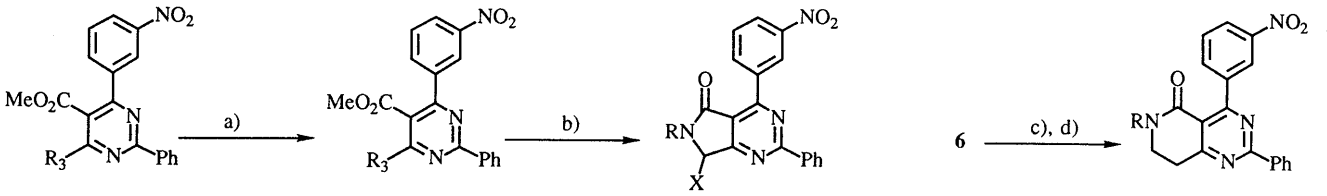


Fig. 2

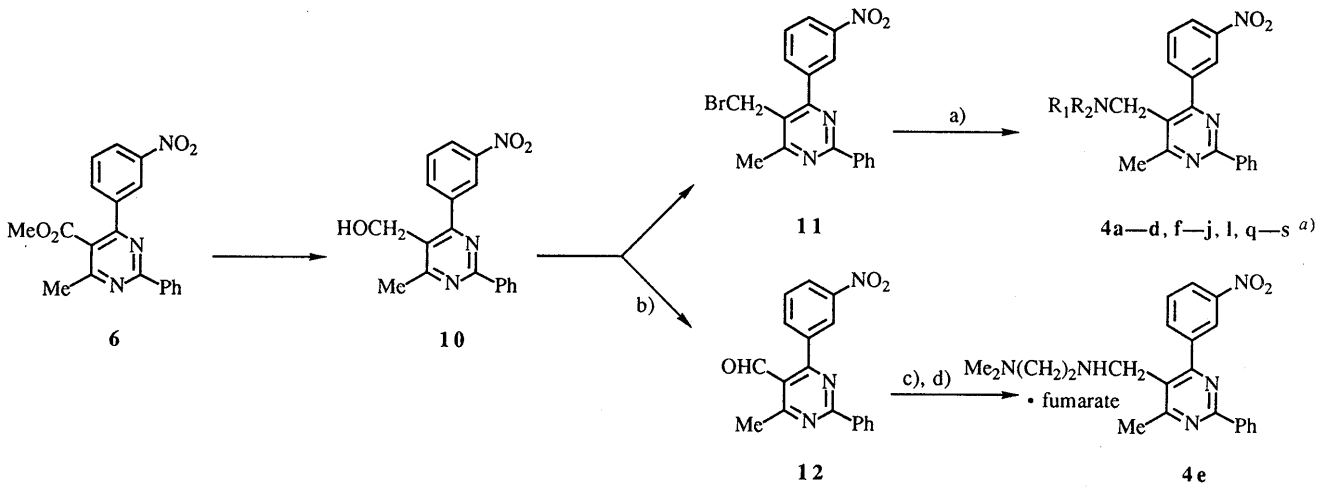


6 : R_3= Me
7 : R_3= Et
8 : R_3= $BrCH_2$-
9 : R_3= CH_3BrCH-
2a—f [a)]
3a—b [a)]

a) pyridinium hydrobromide perbromide, 25 % HBr in AcOH / AcOH ; b) amines / iso-PrOH ; c) $(HCHO)_n$, amines / AcOH ; d) reflux in iso-PrOH

a) R and X are as listed in Table I.

Chart 1

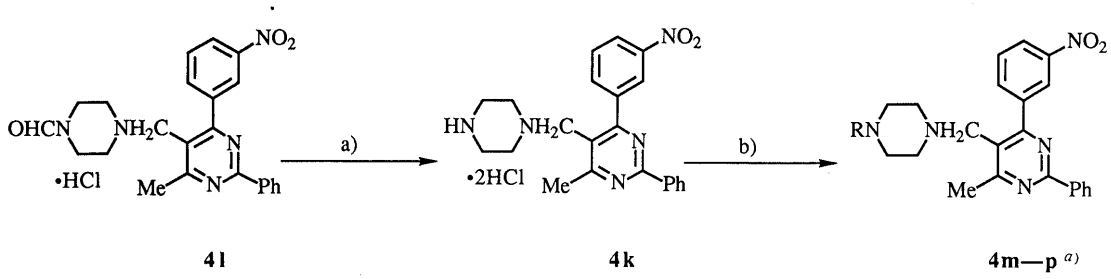


6
10
11
12
4a—d, f—j, l, q—s [a)]
4e

a) amines / iso-PrOH ; b) MnO_2 / AcOEt ; c) 2-dimethylaminoethylamine, *p*-TsOH / benzene ; d) $NaBH_4$ / EtOH, fumaric acid

a) R_1R_2 are as listed in Table II.

Chart 2



4l
4k
4m—p [a)]

a) conc. HCl aq. / MeOH—H_2O ; b) alkyl halides, NaH / THF

a) R are as listed in Table II.

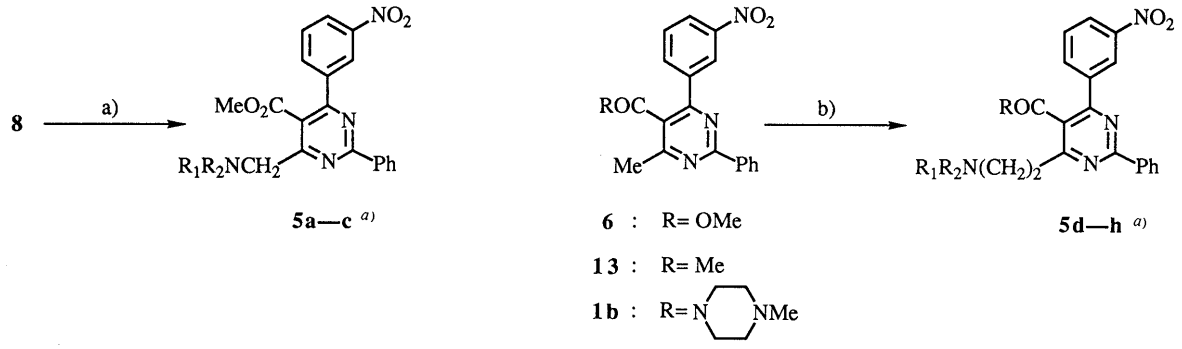
Chart 3

bromide, respectively, with appropriate primary amines afforded **2a**—**f**. 2) Treatment of **6** with primary amines under standard Mannich conditions, followed by cyclization, afforded **3a** and **3b**. Compounds **4a**—**d**, **4f**—**j**, **4l** and **4q**—**s** were prepared in a convergent manner as shown in Chart 2.

Thus, condensation of the benzylbromide derivative (**11**)[1a)] with appropriate amines afforded **4a**—**d**, **4f**—**j**, **4l** and **4q**—**s**. Oxidation of **10**[1a)] with activated manganese(IV) oxide (MnO_2) gave aldehyde (**12**). Condensation of **12** with 2-dimethylaminoethylamine under azeotropic conditions in the presence of *p*-toluenesulfonic acid (*p*-TsOH), followed by reduction with sodium borohydride ($NaBH_4$) afforded **4e**.

N-Alkylated piperazine derivatives (**4m**—**p**) were prepared by alkylation of **4k**, which was obtained by acid-catalyzed hydrolysis of **4l**, with appropriate alkyl halides as shown in Chart 3.

The amination of **8** with appropriate secondary amines afforded **5a**—**c**. Compounds **5d**—**h** were obtained by a Mannich reaction of the precursors (**6**, **13**,[1b)] **1b**) with appropriate secondary amines as shown in Chart 4.



a) amines / iso-PrOH ; b) amine hydrochlorides, $(HCHO)_n$ / AcOH

a) R_1R_2 are as listed in Table III.

Chart 4

TABLE I. Physical Properties and AA Activity of the Lactam Derivatives (**2a—f**, **3a**, **b**)

Compound No.	R	X	Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10	32	Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N
2a	$CH_2CH_2NMe_2$	H	106	123[b]	22.3	147—148 (EtOH–$CHCl_3$)	$C_{22}H_{21}N_5O_3$	65.50 (65.69)	5.25 (5.36)	17.36 (17.63)
2b	CH_2CH_2NO	H		91	67.8	170—173 (EtOH)	$C_{24}H_{23}N_5O_4$	64.71 (64.86)	5.20 (5.28)	15.72 (15.74)
2c	$CH_2CH_2CH_2NMe_2$	H		107	26.6	115—117 (EtOH)	$C_{23}H_{23}N_5O_3 \cdot 0.5H_2O$	64.77 (64.67)	5.67 (5.48)	16.42 (16.29)
2d	$CH_2CH_2CH_2N$O	H		111	30.4	135—136 (EtOH)	$C_{25}H_{25}N_5O_4$	65.34 (65.36)	5.48 (5.37)	15.24 (15.29)
2e	$CH_2CH_2NMe_2$	Me		89	77.5	138—140 (EtOH)	$C_{23}H_{23}N_5O_3$	66.17 (66.35)	5.55 (5.51)	16.78 (16.61)
2f	CH_2CH_2NO	Me		104	67.4	166—167 (EtOH)	$C_{25}H_{25}N_5O_4$	65.34 (65.44)	5.48 (5.34)	15.24 (15.12)
3a	$CH_2CH_2NMe_2$		112	123[c]	4.3	138—142 (EtOH)	$C_{23}H_{23}N_5O_3$	66.17 (66.19)	5.55 (5.31)	16.78 (16.62)
3b	CH_2CH_2NO			96	9.7	177—180 (EtOH)	$C_{25}H_{25}N_5O_4$	65.35 (65.10)	5.48 (5.53)	15.24 (15.05)

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

Pharmacological Results and Discussion

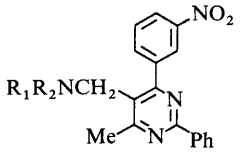
The compounds listed in Tables I—III were tested for AA activity in mice as described previously.[1b] The results of the lactam derivatives are shown in Table I.

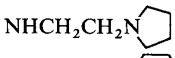
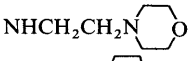
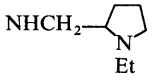
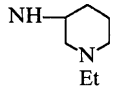
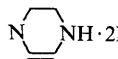
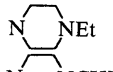
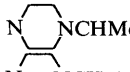
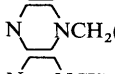
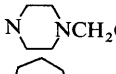
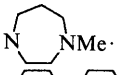
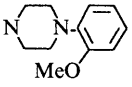
Only compounds **2a** and **3a**, which have a structurally similar substituent to that of **1a**, were active. In this limited lactam series, the correlation between structure and AA activity was not straightforward; however, **2a** and **3a** revealed that two methylene units between the lactam-nitrogen and the dimethylamino-nitrogen was optimal. Three methylene units (**2c**) showed little effect. As we have pointed out in the previous paper,[1a] these SARs seem to be a prerequisite for the expression of AA activity. Morpholino derivatives (**2b** and **3b**) were not effective at this dose. Compounds **2e** and **2f**, which are substituted in the C-7 position with a methyl group, were not tolerated. Further modifications of the lactam derivatives were not pursued because attention was directed to a more potent series (*vide infra*).

An attempt to replace the amide (R_1R_2NCO–) group at the C-5 position of the pyrimidine ring with an aminomethyl ($R_1R_2NCH_2$–) group was examined by preparing **4e** and **4c**, in direct analogy to compounds **1a** and **1b** and resulted in an increase of AA activity (Table II).

Based on this result we sought to broaden our knowledge of the SARs in this series. Among the cyclic amine derivatives (**4a—c**), only 5-(4-methylpiperazin-1-ylmethyl) derivative (**4c**) was active. 5-(Diethylaminomethyl) derivative (**4d**) was inactive. These results suggested that the basic nitrogen at the N-4 position of 4-methylpiperazine

TABLE II. Physical Properties and AA Activity of 5-(Aminomethyl)-6-methyl-4-(3-nitrophenyl)-2-phenylpyrimidine Derivatives (**4a—s**)



Compound No.	NR_1R_2	Anti-anoxia[a] (% of control) (mg/kg i.p.) 10	32	Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N
4a			113	33.7	140—141 (EtOH)	$C_{23}H_{24}N_4O_2$	71.11 (70.85	6.23 6.18	14.42 14.33)
4b			105	88.2	162—164 (Et_2O)	$C_{22}H_{22}N_4O_2S$	65.00 (65.36	5.45 5.06	13.78 13.75)
4c		124[b]	153[b]	19.0	138—140 (EtOH)	$C_{23}H_{25}N_5O_2$	68.47 (68.34	6.25 6.36	17.36 17.36)
4d	NEt_2		110	34.7	101—103 (Et_2O)	$C_{22}H_{24}N_4O_2$	70.20 (69.87	6.43 6.56	14.88 14.73)
4e	$NHCH_2CH_2NMe_2$ ·fumarate	117[b]	145[b]	14.5	104—106 (EtOH)	$C_{22}H_{25}N_5O_2$ ·$C_4H_4O_4$·H_2O	59.42 (59.30	5.92 5.62	13.32 13.19)
4f	$N(Me)CH_2CH_2NMe_2$ ·2HCl	112	134[b]	93.8	214—216 (dec.) (MeOH)	$C_{23}H_{27}N_5O_2$ ·2HCl·H_2O	55.64 (55.79	6.29 6.12	14.10 13.84)
4g		107	131[b]	28.3	69—70 (*n*-Hexane)	$C_{24}H_{27}N_5O_2$	69.04 (69.32	6.51 6.41	16.77 16.87)
4h		107	128[b]	97.3	112—114 (IPA)	$C_{24}H_{27}N_5O_2$	66.50 (66.53	6.28 6.10	16.15 16.19)
4i		113	125[b]	99.1	91—94 (EtOH)	$C_{25}H_{29}N_5O_2$	69.58 (69.56	6.77 6.47	16.23 16.06)
4j	 ·2HCl		108	85.4	267 (dec.) (MeOH)	$C_{25}H_{29}N_5O_2$ ·2HCl·0.4H_2O	58.68 (58.96	6.26 6.36	13.68 13.69)
4k	 ·2HCl		112	93.6	174 (dec.) (MeOH)	$C_{22}H_{23}N_5O_2$ ·2HCl·2.5H_2O	52.07 (52.34	5.95 5.68	13.80 13.66)
4l	 ·HCl		99	84.4	212—214 (dec.) (MeOH)	$C_{23}H_{23}N_5O_3$ ·HCl·0.6H_2O	59.44 (59.29	5.46 5.30	15.06 14.91)
4m			122	67.7	118—120 (IPE)	$C_{24}H_{27}N_5O_2$	69.04 (68.66	6.52 6.28	16.77 16.88)
4n		126[c]	149[b]	39.8	115—116 (EtOH)	$C_{25}H_{29}N_5O_2$	69.58 (69.50	6.77 6.85	16.22 16.17)
4o		116	131[b]	73.0	179—180 (EtOH)	$C_{26}H_{29}N_5O_2$	70.40 (70.19	6.58 6.63	15.78 15.52)
4p			112	63.5	149—150 (Et_2O)	$C_{25}H_{25}N_5O_2$ ·0.2H_2O	69.65 (69.40	5.93 5.76	16.24 16.19)
4q		118	136[b]	78.8	111—113 (EtOH)	$C_{24}H_{27}N_5O_3$ ·H_2O	63.84 (63.64	6.47 6.55	15.51 15.32)
4r	 ·2HCl		99	38.4	177—179 (EtOH)	$C_{24}H_{27}N_5O_2$ ·2HCl·2.5H_2O	53.83 (53.74	6.39 6.06	13.07 12.95)
4s			99	71.6	178—179 (Et_2O)	$C_{29}H_{29}N_5O_3$ ·0.75H_2O	68.42 (68.33	6.04 6.29	13.75 13.75)

a) See footnote *a*) in Table I. *b, c*) See footnote *b, c*) in Table I.

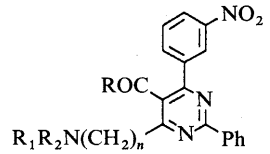
plays a more crucial role than that of the N-1 nitrogen in determining AA activity. Compound **4f**, a ring-opened analogue of *N*-methylpiperazine, was also effective. Compounds **4g—i**, which have the basic nitrogen at the same position as that of **4c**, were also effective. Subsequently, the effect of the substituent on the piperazine N-4 nitrogen was examined **4k—s**. In general, alkyl substitution seemed to be preferable (**4m—o, q**). Unsubstituted (**4k**), formyl (**4l**) and aryl (**4s**) derivatives resulted in a loss of activity. The *N*-methylhomopiperazine derivative (**4r**) with a seven-membered ring was inactive.

Next, we examined the effect on the expression of AA activity by introduction of a nitrogeneous basic moiety at the C-6 position of the pyrimidine ring. The results are shown in Table III.

One plausible approach to preparing derivative (**5c**) relates to the fact that the potent derivative (**4c**) mentioned above was embedded in the substituent (*i.e.* 4-methylpiperazin-1-ylmethyl) at the C-5 position of the pyrimidine ring; however, this only resulted in a loss of AA activity. On the other hand, compounds **5d—i** possess the two methylene chain between the C-6 carbon of the pyrimidine ring and the basic amino moiety.

Among them, **5f** and **5g** had significant AA activity and

TABLE III. Physical Properties and AA Activity of 6-(Aminoethyl or aminomethyl)pyrimidine Derivatives (**5a—i**)



Compound No.	R	n	NR_1R_2	Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10	32	Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N
5a	OMe	1	$NEt_2 \cdot HCl$		114	63.8	149 (dec.) (IPA)	$C_{23}H_{24}N_4O_4 \cdot HCl \cdot 1.5H_2O$	57.08 (57.11)	5.83 5.65	11.57 11.44)
5b	OMe	1			114	78.9	125—126 (Et_2O)	$C_{23}H_{22}N_4O_5$	63.59 (63.63	5.10 4.88	12.90 12.68)
5c	OMe	1			101	23.6	126—127 (EtOH–Et_2O)	$C_{24}H_{25}N_5O_4$	64.41 (64.32	5.63 5.71	15.65 15.40)
5d	OMe	2	NMe_2		120	27.2	124—126 (Et_2O)	$C_{22}H_{22}N_4O_4$	65.01 (65.32	5.46 5.40	13.78 13.56)
5e	OMe	2			103	3.8	99—101 (Et_2O)	$C_{25}H_{27}N_5O_4 \cdot 0.2H_2O$	64.55 (64.34	5.93 5.97	15.05 14.89)
5f	Me	2	$NMe_2 \cdot HCl$	116[c]	126[b]	18.2	138—140 (EtOH)	$C_{22}H_{22}N_4O_3 \cdot HCl \cdot 2H_2O$	57.08 (57.06	5.87 5.66	12.10 12.01)
5g	Me	2		110	123[b]	15.6	182—184 (MeOH)	$C_{24}H_{24}N_4O_4 \cdot HCl \cdot 0.5H_2O$	60.31 (60.55	5.48 5.51	11.72 11.64)
5h	Me	2			103	3.9	88—91 (Et_2O)	$C_{25}H_{27}N_5O_3 \cdot 0.5H_2O$	66.06 (66.04	6.20 6.05	15.40 15.14)
5i		2	NMe_2		98	13.2	119—120 (Et_2O–*n*-hexane)	$C_{26}H_{30}N_6O_3 \cdot 0.5H_2O$	64.57 (64.22	6.46 6.31	17.37 17.10)

a) See footnote *a*) in Table I. *b, c*) See footnote *b, c*) in Table I.

TABLE IV. Pharmacological Data of 4-(3-Nitrophenyl)-2-phenylpyrimidine Derivatives (**2a**, **4c**, **1b**)

Compound No.	Anti-anoxia (% of control) (mg/kg) 10	32	Upper: i.p. Down: *p.o.* 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.)
2a	96	114[c]	131[c]	9.4×10^{-6}	51	78	>1000
		98	134[d]				
4c	124[c]	153[c]	134[c]	3.0×10^{-6}	23	27	>1000
		110	139[c]				
Cf. **1b** (FK 360)	104	126[c]	168[c]				
				6.7×10^{-6}	18	32	>560
		114	125[c]				

a) The experiments were conducted using each groups of 5 animals. The dose required to produce 50% of maximum inhibition produced by the test drugs, 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 compoumd. *c*) $p<0.01$. *d*) $p<0.05$.

5d had a tendency to prolong the survival time of mice in the AA assay. In this case, regarding the chain length between the nitrogeneous basic moiety and pyrimidine ring, two methylene units seemed to be a prerequisite for the expression of AA activity.

By modification at the C-5 and C-6 positions of the pyrimidine ring we could obtain the desired compounds which possessed significant AA activity. In general, the mechanisms of action on AA activity are complex[2] and far from being fully elucidated; in addition, there are few reports which refer to the biological recognition for the expression of AA activity. Molecular electrostatic potential (MEP) has proven in recent years to be a powerful tool in providing a highly imformative means of assessing the electronic structure of molecules, particularly when biological recognition processes are involved.[3] In this study we tried to identify, from molecular structural properties such as electronic and stereochemical features by the study of MEP, the expression of AA activity of two types of compounds (*e.g.* **1b** and **5f**). Although the two-dimensional structure of both substituents is apparently different, the substituent of **1b** and **5f** at the C-5 and C-6 position, respectively, seemed to show close analogies in their electronic structure.

For a comparison between the electrostatic potentials around the nitrogeneous basic moiety of **1b** and **5f**, a

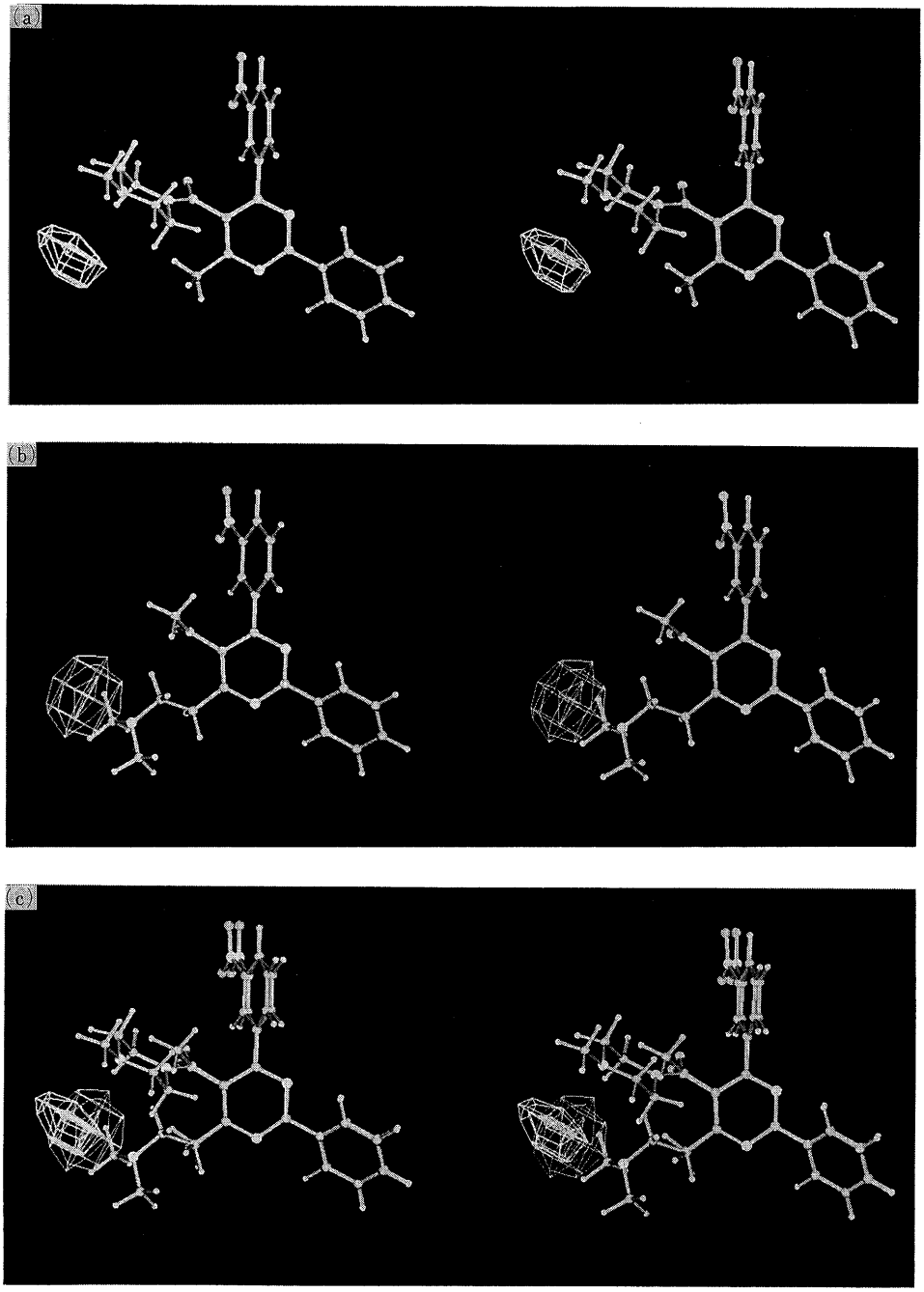


Fig. 3. (a) Stereo View of MEP Study Near the Nitrogeneous Basic Moiety of **1b** (FK 360), (b) Stereo View of MEP Study Near the Nitrogeneous Basic Moiety of **5f**, (c) Superimposition of (a) and (b)

a, b: The contour denotes potential surface of -4 kcal/mol.

three-dimensional MEP system (3D-MEP system) developed in our R & D information division) was used. The 3D-MEP program was based on the modified neglect of diatomic overlap (MNDO) approximation and the definition of MEP calculations was carried out by the method of Politzer.[4]

The MEP result is represented in Fig. 3, and suggests that the negative zone is located around the nitrogeneous basic moiety; both electrostatic potential maps are very similar.[5] Therefore, the respective substituents should occupy the same spatial area of a recognition site and may result in the expression of AA activity.

Subsequently, we evaluated further those compounds which were effective on the AA assay: on acute toxicity in mice and/or ALP activity and/or arachidonate-induced cerebral edema in rats.

Compounds **4f—i**, **4n**, **4o**, **4q** and **5g** were more toxic ($LD_{50} < 560$ mg/kg, i.p.) than FK 360 ($LD_{50} > 560$ mg/kg, i.p.). Compounds **4e** and **5f** had significant ($p < 0.05$) at 10^{-5} g/ml ALP activity[1b] (lipid peroxidation ratio was 19%, 86% of control, respectively;) however, these had rather high acute toxicity ($LD_{50} < 320$ mg/kg, i.p.). Compound **3a** was not so effective on AA activity by oral-administration compared to that of **2a** (details of these results are not shown here).

By comparisons of the above mentioned assays, compounds (**2a**, FR 75469 and **4c**, FR 72707) seemed to have the same level of efficacy as that of FK 360.

TABLE V. Spectral Data of Pyrimidine Derivatives (**2—5**)

Compd. No.	MS, *m/z*, M^+	IR (Nujol) cm^{-1}	Solvent[a]	^{1}H-NMR (ppm)[b]
2a	403	1695, 1530, 1355	A	2.32 (6H, s), 2.64 (2H, t, J=6), 3.81 (2H, t, J=6), 4.72 (2H, s), 7.40—7.85 (4H, m), 8.25—9.00 (4H, m), 9.34—9.48 (1H, m)
2b	455	1695, 1585, 1570, 1530	A	2.30—2.80 (4H, m), 2.71 (2H, t, J=6), 3.57—3.85 (4H, m), 3.83 (2H, t, J=6), 4.73 (2H, s), 7.42—7.96 (4H, m), 8.25—9.00 (4H, m), 9.30—9.50 (1H, m)
2c	417	1670, 1590, 1570, 1545	A	1.79—2.50 (4H, m), 2.24 (6H, s), 3.72 (2H, t, J=7), 4.55 (2H, s), 7.33—7.85 (4H, m), 8.20—9.00 (4H, m), 9.27—9.47 (1H, m)
2d	459	1670, 1525, 1355	A	1.80—2.10 (2H, m), 2.40—2.60 (6H, m), 3.65—3.80 (6H, m), 4.60 (2H, m), 7.50—7.85 (4H, m), 8.35—9.00 (4H, m), 9.40—9.50 (1H, m)
2e	417	1680, 1520	A	1.68 (3H, d, J=7), 2.30 (6H, s), 2.60 (2H, t, J=6.5), 3.37 (1H, dd, J=14, 6.5), 4.15 (1H, dd, J=14, 6.5), 4.85 (1H, q, J=7), 7.40—7.60 (3H, m), 7.69 (1H, dd, J=9, 9) 8.25—8.45 (1H, m), 8.50—8.70 (2H, m), 8.80—9.00 (1H, m), 9.30—9.45 (1H, m)
2f	459	1680, 1350, 1120	A	1.67 (3H, d, J=7), 2.40—2.60 (4H, m), 2.69 (2H, t, J=6.5), 3.37 (1H, dd, J=14, 6.5), 3.55—3.80 (4H, m), 4.13 (1H, dd, J=14, 6.5), 4.83 (1H, q, J=7), 7.40—7.60 (3H, m), 7.67 (1H, dd, J=9, 9), 8.20—8.45 (1H, m), 8.45—8.75 (2H, m), 8.85 (1H, ddd, J=9, 2, 2), 9.37 (1H, dd, J=2, 2)
3a	417	1658, 1580, 1550, 1525	A	2.32 (6H, s), 2.55 (2H, t, J=6), 3.26 (2H, t, J=6), 3.67 (2H, t, J =6), 3.83 (2H, t, J=6), 7.40—7.75 (4H, m), 7.95—8.70 (5H, m)
3b	459	1658, 1550, 1520, 1350	A	2.35—2.76 (6H, m), 3.26 (2H, t, J=7), 3.50—3.85 (6H, m), 3.82 (2H, t, J=7), 7.30—7.70 (4H, m), 7.87—8.65 (5H, m)
4a	388	1590, 1530, 1350	A	1.20—1.60 (6H, m), 2.15—2.40 (4H, m), 2.75 (3H, s), 3.41 (2H, s), 7.35—7.50 (3H, m), 7.62 (1H, dd, J=8, 8), 8.11 (1H, ddd, J=8, 2, 2), 8.21 (1H, ddd, J=8, 2, 2), 8.40—8.60 (2H, m), 8.91 (1H, dd, J=2, 2)
4b	406	1525, 1350	A	2.63 (8H, s), 2.77 (3H, s), 3.55 (2H, s), 7.40—7.56 (3H, m), 7.69 (1H, dd, J=7, 7), 8.12 (1H, ddd, J=7, 2, 2), 8.20—8.60 (3H, m), 8.85 (1H, dd, J=2, 2)
4c	403	1525, 1350	A	2.27 (3H, s), 2.43 (8H, s), 2.77 (3H, s), 3.50 (2H, s), 7.30—7.80 (4H, m), 8.00—8.60 (4H, m), 8.80—9.00 (1H, m)
4d	376	1530, 1200	A	0.83 (6H, t, J=8), 2.30 (4H, q, J=8), 2.80 (3H, s), 3.58 (2H, s), 7.50—8.70 (9H, m)
4e	391	1705, 1530	B	2.50 (6H, s), 2.76 (3H, s), 2.87 (4H, s), 3.67 (2H, s), 6.53 (2H, s), 7.30—7.60 (3H, m), 7.80 (1H, dd, J=8, 8), 8.20—8.50 (4H, m), 8.83 (1H, dd, J=2, 2)
4f	405	1545, 1530, 1400, 1350	B	2.32 (3H, s), 2.70 (6H, s), 2.92 (3H, s), 3.10—3.70 (4H, m), 4.30 (2H, br s), 7.40—8.60 (9H, m)
4g	417	1545, 1535, 1400, 1350	A	1.60—1.90 (4H, m), 2.30—2.95 (8H, m), 2.78 (3H, s), 3.77 (2H, s), 7.33—7.80 (4H, m), 8.20—8.63 (4H, m), 8.97—9.14 (1H, m)
4h	434	1580, 1535, 1400, 1350	A	2.30—2.95 (8H, m), 2.79 (3H, s), 3.55—3.80 (4H, m), 3.76 (2H, s), 7.33—7.80 (4H, m), 8.20—8.60 (4H, m), 9.07 (1H, dd, J=2, 2)
4i	432	1535, 1400, 1350	A	1.11 (3H, t, J=7), 1.30—3.30 (11H, m), 2.78 (3H, s), 3.74 (2H, s), 7.30—7.83 (4H, m), 8.20—8.64 (4H, m), 8.93—9.12 (1H, m)
4j	431	1575, 1535, 1400, 1360	C	1.44 (3H, t, J=7), 1.65—2.55 (4H, m), 2.80—4.50 (7H, m), 3.38 (3H, s), 5.23 (2H, s), 7.50—9.00 (9H, m)
4k	389	1530, 1400, 1355	B	2.50—3.30 (8H, m), 2.82 (3H, s), 4.17 (2H, br s), 7.40—8.75 (9H, m)
4l	417	1675, 1545, 1350	B	2.50—4.00 (8H, m), 2.98 (3H, s), 4.42 (2H, s), 7.40—8.70 (10H, m)
4m	417	1525, 1350, 1160, 1010	A	1.05 (3H, t, J=7), 2.38 (2H, q, J=7), 2.44 (8H, s), 2.76 (3H, s), 3.50 (2H, s), 7.20—7.80 (4H, m), 7.95—8.68 (4H, m), 8.85—9.05 (1H, m)
4n	431	1520, 1350, 740	A	1.05 (6H, d, J=9), 2.40—2.70 (9H, m), 2.77 (3H, s), 3.50 (2H, s), 7.45—7.70 (4H, m), 7.95—8.60 (4H, m), 8.85—9.00 (1H, m)
4o	443	1530, 1350, 1300	A	0.10—0.34 (2H, m), 0.45—0.75 (2H, m), 0.80—1.37 (1H, m), 2.30—3.20 (8H, m), 2.51 (2H, d, J=6), 2.78 (3H, s), 3.58 (2H, s), 7.35—7.86 (4H, m), 7.95—8.66 (4H, m), 8.90—9.15 (1H, m)
4p	427	3300, 1540, 1525, 1350	A	2.23 (1H, t, J=2), 2.49 (8H, s), 2.76 (3H, s), 3.17 (2H, d, J=2), 3.53 (2H, s), 7.20—7.80 (4H, m), 7.83—8.63 (4H, m), 8.70—8.93 (1H, m)
4q	433	1610, 1580, 1530, 1435	A	2.10—2.30 (2H, br s), 2.40—2.60 (6H, m), 2.52 (2H, t, J=6), 2.75 (3H, s), 3.51 (2H, s), 3.58 (2H, t, J=6), 7.40—7.80 (4H, m), 8.00—8.60 (4H, m), 8.90—9.00 (1H, m)
4r	417	1530, 1360	B	1.70—4.00 (10H, m), 2.67 (3H, s), 2.97 (3H, s), 4.45 (2H, s), 7.40—8.75 (9H, m)
4s	495	1530, 1500, 1350	A	2.40—2.90 (4H, m), 2.82 (3H, s), 2.85—3.23 (4H, m), 3.59 (2H, s), 3.85 (3H, s), 6.92 (4H, s), 7.30—7.83 (4H, m), 8.00—8.70 (4H, m), 8.90—9.10 (1H, m)
5a	421	1730, 1545, 1535, 1410	A	1.58 (6H, t, J=8), 3.20—3.90 (4H, m), 3.81 (3H, s), 4.64 (2H, br s), 7.40—8.75 (9H, m)
5b	434	1718, 1585, 1530, 1350	A	2.40—2.60 (4H, m), 3.50—3.75 (4H, m), 3.82 (3H, s), 3.93 (2H, s), 7.40—7.60 (3H, m), 7.67 (1H, dd, J=7, 7), 8.13 (1H, ddd, J=7, 2, 2), 8.39 (1H, ddd, J=7, 2, 2), 8.50—8.70 (3H, m)
5c	447	1725, 1585, 1525, 1355	A	2.27 (3H, s), 2.25—2.65 (8H, m), 3.83 (3H, s), 3.94 (2H, s), 7.40—7.60 (3H, m), 7.69 (1H, dd, J=8, 8), 8.12 (1H, ddd, J=8, 2, 2), 8.37 (1H, ddd, J=8, 2, 2), 8.45—8.75 (3H, m)
5d	406	1720, 1580, 1530, 1350	A	2.35 (6H, s), 2.80—3.30 (4H, m), 3.80 (3H, s), 7.40—7.60 (3H, m), 7.65 (1H, dd, J=8, 8), 8.09 (1H, ddd, J=8, 2, 2), 8.35 (1H, ddd, J=8, 2, 2), 8.45—8.70 (3H, m)
5e	461	1720, 1530, 1350	A	2.30 (3H, s), 2.40—2.80 (8H, m), 2.80—3.30 (4H, m), 3.80 (3H, s), 7.40—7.60 (3H, m), 7.67 (1H, dd, J=8, 8), 8.08 (1H, ddd, J=8, 2, 2), 8.35 (1H ddd, J=8, 2, 2), 8.40—8.70 (3H, m)
5f	390	1690, 1530, 1355	B	2.33 (3H, s), 2.93 (3H, s), 2.97 (3H, s), 3.40—3.90 (4H, m), 7.40—8.10 (5H, m), 8.23—8.80 (4H, m)
5g	432	1690, 1520, 1350, 1090	B	2.23 (3H, s), 2.80—3.30 (2H, m), 3.40—4.50 (10H, m), 7.40—8.05 (5H, m), 8.20—8.70 (4H, m), 13.30 (1H, br)
5h	445	1685, 1530, 1350	A	2.17 (3H, s), 2.30 (3H, s), 2.30—2.70 (8H, m), 3.00 (4H, s), 7.40—8.00 (5H, m), 8.20—8.80 (4H, m)
5i	474	1628, 1525, 1345	A	1.35—1.70 (1H, m), 1.90—2.50 (5H, m), 2.13 (3H, s), 2.39 (6H, s), 2.75—3.35 (6H, m), 7.40—7.80 (4H, m), 8.10—8.90 (5H, m)

a) A, $CDCl_3$; B, DMSO-d_6; C, CF_3COOD. *b*) Listed as chemical shifts (number of protons, multiplicity, constant in Hz).

Pharmacological data is summarized in Table IV.

In conclusion, i) The result of 3D-MEP of FK 360 and **5f**, as representatives of this series, suggest that these pyrimidine derivatives occupy the same recognition site and result in the expression of AA activity. ii) By the modification of the C-5 and/or C-6 position of the 4-(3-nitrophenyl)-2-phenylpyrimidine ring, we found two candidates which have potential as cerebral protective agents (*i.e.* **2a** and **4c**), due to the fact that both were effective on the above mentioned animal models and had low acute toxicity.

Experimental

Melting points were determined using a Thomas–Hoover capillary melting point apparatus and are uncorrected. ^{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. IR spectra were recorded on a Hitachi 260-10 or Shimadzu IR-420 spectrophotometer. Mass spectral measurements (MS) were made on a Hitachi M-80 or a JEOL-D300 mass spectrometer.

Methyl 6-Bromomethyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxylate (8) A mixture of **6** (5.0 g), pyridinium hydrobromide perbromide (5.6 g) and 25% HBr in AcOH (5 ml) in AcOH (200 ml) was stirred for 2 h at room temperature. The reaction mixture was poured into ice water (200 ml) and stirred for 10 min. The resulting precipitates were collected and dissolved in a mixture of $CHCl_3$ (50 ml) and H_2O (50 ml). The separated organic layer was successively washed with saturated $NaHCO_3$ aq. and brine, and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was recrystallized from Et_2O to afford **8** (4.1 g, 66.4%), mp 103—104 °C. IR (Nujol): 1730, 1525, 1352 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.83 (3H, s), 4.78 (2H, s), 7.40—7.60 (3H, m), 7.70 (1H, dd, J=8, 8 Hz), 8.05 (1H, ddd, J=8, 2, 2 Hz), 8.35 (1H, ddd, J=8, 2, 2 Hz), 8.45—8.70 (3H, m). MS m/z: 427 (M^+). *Anal.* Calcd for $C_{19}H_{14}BrN_3O_4$: C, 53.29; H, 3.30; N, 9.81. Found: C, 53.53; H, 3.36; N, 9.42. Compound **9** was synthesized by the same procedures employed in the preparation of **8**.

Methyl 6-(1-Bromoethyl)-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxylate (**9**): Yield: 49.3%, mp 119—121 °C. IR (Nujol): 1715 cm^{-1}. MS m/z: 441 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, d, J=6.5 Hz), 3.80 (3H, s), 5.57 (1H, q, J=6.5 Hz), 7.35—8.80 (9H, m). *Anal.* Calcd for $C_{20}H_{16}BrN_3O_4$: C, 54.32; H, 3.65; N, 9.50. Found: C, 54.53; H, 3.84; N, 9.29.

6,7-Dihydro-6-[2-(dimethylamino)ethyl)]-4-(3-nitrophenyl)-2-phenyl-5*H*-pyrrolo[3,4-*d*]pyrimidine-5-one (2a) A mixture of **8** (2.0 g) and 2-dimethylaminoethylamine (0.91 g) in isopropyl alcohol (20 ml) was stirred for 1 h at 70 °C. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in a mixture of H_2O (100 ml) and $CHCl_3$ (100 ml). The organic layer was washed with brine and dried over $MgSO_4$. After evaporating the solvent, the residue was purified by column chromatography on silica gel (SiO_2) (100 g) with $CHCl_3$–MeOH (10 : 1) as eluent. The fractions containing **2a** were combined and evaporated *in vacuo*. The crystalline residue was recrystallized from diisopropyl ether to afford **2a** (0.42 g, 22.3%). Compounds **2b—f** were synthesized by the same procedures employed in the preparation of **2a**. Physical properties and spectral data of these compounds are listed in Tables I and V.

6-(2-Dimethylaminoethyl)-4-(3-nitrophenyl)-2-phenyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine-5-one (3a) A mixture of **6** (5.0 g), 2-dimethylaminoethylamine (1.32 g) and paraformaldehyde (0.54 g) in AcOH (50 ml) was stirred for 4 h at 90 °C. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in a mixture of H_2O (150 ml) and $CHCl_3$ (150 ml), and then adjusted to pH 9.0 with 10% $NaCO_3$ aq. The organic layer was evaporated *in vacuo*. The residue was dissolved in isopropyl alcohol (20 ml), and the whole was refluxed for 4 h. After evaporating the solvent, the residue was purified by column chromatography on SiO_2 (200 g) with $CHCl_3$–MeOH (10 : 1) as eluent. The fractions containing **3a** were evaporated *in vacuo*. The crystalline residue was recrystallized from EtOH to afford **3a** (0.26 g, 4.3%). Compound **3b** was synthesized by the same procedures employed in the preparation of **3a**. Physical properties and spectral data of these compounds are listed in Tables I and V.

6-Methyl-5-(4-methylpiperazin-1-ylmethyl)-4-(3-nitrophenyl)-2-phenylpyrimidine (4c) A mixture of **12** (1.50 g) and 1-methylpiperazine (1.17 g) in isopropyl alcohol (15 ml) was refluxed for 6 h. After evaporating the solvent, the residue was dissolved in $CHCl_3$ (50 ml), washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on alumina (Al_2O_3) (100 g) with $CHCl_3$ as eluent. The fractions containing **4c** were combined and evaporated *in vacuo*. The residue was recrystallized from EtOH to afford **4c** (0.30 g, 19.0%). Compounds **4a**, **4b**, **4d**, **4f—j**, **4l**, **4q—s** were synthesized by the same procedures employed in the preparation of **4c**. Physical properties and spectral data of these compounds are listed in Tables II and V.

5-Formyl-6-methyl-4-(3-nitrophenyl)-2-phenylpyrimidine (12) To a solution of **10** (0.30 g) in AcOEt (10 ml) was added activated MnO_2 (2.40 g) and the whole was refluxed for 2 h with vigorous stirring. After being cooled to room temperature, the MnO_2 was filtered off. The filtrate was evaporated *in vacuo*, and the residue was recrystallized from Et_2O afford **12** (0.15 g, 50.3%), mp 154—155 °C. IR (Nujol): 1700, 1535 cm^{-1}. MS m/z: 319 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.97 (3H, s), 7.50—8.80 (9H, m), 10.13 (1H, s). *Anal.* Calcd for $C_{18}H_{13}N_3O_3 \cdot 0.2H_2O$: C, 66.95; H, 4.18; N, 13.01. Found: C, 67.02; H, 3.92; N, 12.89.

5-[*N*-(2-Dimethylaminoethyl)aminomethyl]-6-methyl-4-(3-nitrophenyl)-2-phenylpyrimidine Fumarate (4e) A mixture of **12** (3.0 g), 2-dimethylaminoethylamine (0.83 g) and *p*-toluenesulfonic acid (10 mg) in benzene (30 ml) was refluxed for 2 h by using the Dean–Stark water separator. After evaporating the solvent, the residue was dissolved in EtOH (30 ml), $NaBH_4$ (360 mg) was added and the whole was stirred for 1 h at room temperature. The reaction mixture was added to a mixture of $CHCl_3$ (100 ml) and H_2O (100 ml). The organic layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on Al_2O_3 (100 g) with $CHCl_3$ as eluent. The fractions containing the object product were combined and evaporated *in vacuo*. The residue and fumaric acid (0.40 g) were recrystallized from EtOH (30 ml) to afford **4e** (0.69 g, 14.5%).

6-Methyl-5-(1-piperazinylmethyl)-4-(3-nitrophenyl)-2-phenylpyrimidine Dihydrochloride (4k) A mixture of **41** (3.0 g), MeOH (30 ml), H_2O (10 ml) and conc. HCl aq. (6 ml) was stirred for 2 h at 70 °C. The resulting precipitates were collected by filtration and recrystallized from MeOH to afford **4k** (2.86 g, 93.6%).

5-(4-Ethylpiperazin-1-ylmethyl)-6-methyl-4-(3-nitrophenyl)-2-phenylpyrimidine (4m) A solution of **4k** (3.56 g) in $CHCl_3$ (100 ml) and H_2O (100 ml) was adjusted to pH 9.0 with 10% K_2CO_3 aq. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was dissolved in tetrahydrofuran (THF) (30 ml), then NaH (0.37 g, 50% in mineral oil) was added carefully. To this suspension was added ethyl iodide (1.44 g) and the whole was stirred for 9 h at 50 °C. The reaction mixture was poured into a mixture of $CHCl_3$ (100 ml) and H_2O (100 ml). The organic layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from diisopropyl ether to afford **4m** (2.18 g, 67.7%). Compounds **4n—p** were synthesized by the same procedures employed in the preparation of **4m**. Physical properties and spectral data of these compounds are listed in Tables II and V.

Methyl 6-(4-Methylpiperazin-1-ylmethyl)-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxylate (5c) To a suspension of **8** (1.5 g) in isopropyl alcohol (15 ml) was added 1-methylpiperazine (0.88 g) at 70 °C, then the reaction mixture was stirred for 10 min. After evaporating the solvent, the residue was dissolved in a mixture of $CHCl_3$ (50 ml) and H_2O (50 ml). The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography on Al_2O_3 (100 ml) with $CHCl_3$ as eluent. The fractions containing **5c** were evaporated *in vacuo*. The residual crystalline material was recrystallized from Et_2O–EtOH to afford **5c** (0.37 g, 23.6%). Compounds **5a**, **5b** were synthesized by the same procedures employed in the preparation of **5c**. Physical properties and spectral data of these compounds are listed in Tables III and V.

5-Acetyl-6-(2-dimethylaminoethyl)-4-(3-nitrophenyl)-2-phenylpyrimidine Hydrochloride (5f) A mixture of **13** (3.0 g), dimethylamine hydrochloride (0.73 g) and paraformaldehyde (0.36 g) in acetic acid was refluxed for 6 h. The reaction mixture was evaporated *in vacuo* and the residue was poured into a mixture of AcOEt (100 ml) and H_2O (100 ml). The mixture was adjusted to pH 1.0 with 10% HCl aq. The aqueous layer was separated, adjusted to pH 9.0 with 10% K_2CO_3 aq. and extracted with $CHCl_3$ (100 ml). The extract was dried over $MgSO_4$ and evaporated *in vacuo*, and the residue was purified by column chromatography on SiO_2 (100 g) with $CHCl_3$–MeOH (50 : 1) as eluent. The fractions containing **5f** were combined and evaporated *in vacuo*. The residue was dissolved in EtOH (5 ml) and treated with a slight excess of 4 N HCl/EtOH to afford

5f (0.70 g, 18.8%). Compounds **5d**, **5e** and **5g—i** were synthesized by the same procedures employed in the preparation of **5f**. Physical properties and spectral data of these compounds are listed in Tables III and V.

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References and Notes

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