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Studies on Cerebral Protective Agents. I.[1] Novel 4-Arylpyrimidine Derivatives with Anti-anoxic and Anti-lipid Peroxidation Activities

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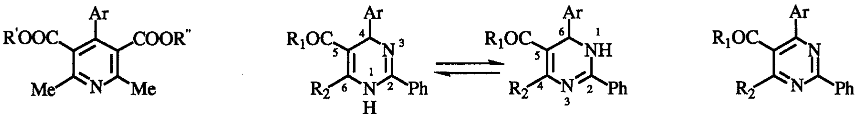
Novel 4-arylpyrimidine derivatives were synthesized by the oxidation of 4-aryl-1,4-dihydropyrimidines, and their effects on anti-anoxic (AA) activity in mice and anti-lipid peroxidation (ALP) activity in rat brain mitochondria were investigated. Among these compounds, ethyl 6-methyl-2-phenyl-4-(4-pyridyl)-5-pyrimidinecarboxylate (4b) has AA activity (10 mg/kg, i.p.) and ethyl 6-methyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxylate (4f) has ALP activity (73% inhibition at 10^{-5} g/ml). The latter compound (100 mg/kg, i.p.) was also effective on arachidonate-induced cerebral edema in rats with comparable potency to that of vitamin E.

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

It is well known that the brain is supported by a continuous supply of oxygen and glucose for its functional integrity. When the supply of these substances is interrupted, notably due to stroke, irreversible anoxic/ischemic brain damage will occur. To ameliorate the cerebral ischemic damage is an important clinical problem that is still far from satisfactorily solved, due to the lack of any specific agent of sufficiently proven benefit.

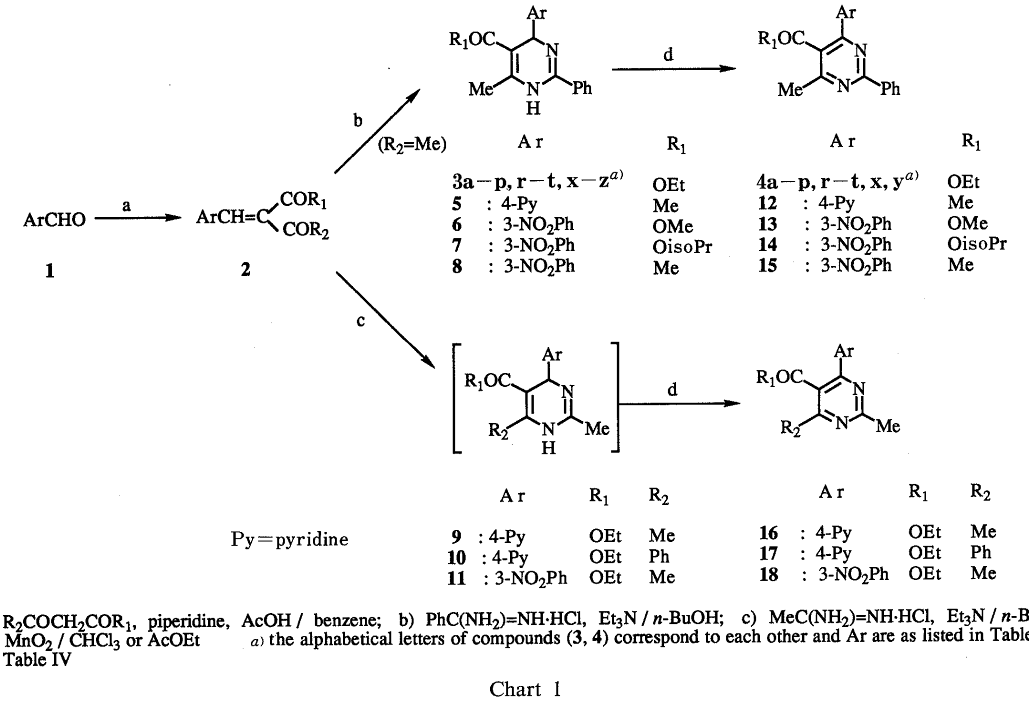
It has been long recognized that the mitochondria, subcellular elements rich in phospholipids containing unsaturated fatty acids, play a crucial role in maintaining energy metabolism. Free radical reactions of mitochondrial phospholipids occur under normal physiological conditions. However, in ischemic conditions, where those processes are out of control, they produce lipid peroxide which can be responsible for changes in structure and function of the mitochondrial membrane.[2] Among a number of organs, brain mitochondrial function is very labile to ischemic conditions.[3] Agents which have significant anti-lipid peroxidation (ALP) and anti-anoxic (AA) activities would be expected to ameliorate brain ischemic damage.[4]

In the course of searching for a new type of cerebral



A B (1,4-dihydro) B (1,6-dihydro) C

Fig. 1



a) $R_2COCH_2COR_1$, piperidine, AcOH / benzene; b) $PhC(NH_2)=NH \cdot HCl$, Et_3N / *n*-BuOH; c) $MeC(NH_2)=NH \cdot HCl$, Et_3N / *n*-BuOH; d) MnO_2 / $CHCl_3$ or AcOEt *a)* the alphabetical letters of compounds (3, 4) correspond to each other and Ar are as listed in Table I and Table IV

Chart 1

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protective agent, we were interested in the following two indications reported: i) Dihydropyrimidines have antioxidant and membranotropic properties (unpublished results)[5]; and in the patent, ii) 4-Aryl-3,5-pyridinedicarboxylates (A) are useful as anti-hypoxics or anti-ischemics (no pharmacological data).[6]

Therefore, we synthesized new 4-aryl-1,4-dihydropyrimidines (B)[7] and their oxidation products, 4-arylpyrimidines (C) (Fig. 1) and sought for the possibility of finding a new cerebral protective agent.

Interestingly, some of the C compounds were effective against anoxia in mice, lipid peroxidation in rat brain mitochondria and arachidonate-induced cerebral edema in rats, but the corresponding analogues of types A and B were not effective in these assays.

This paper reports the preparation and structure–activity relationships (SARs) of 4-arylpyrimidine derivatives and related compounds in these assays.

Chemistry The 4-arylpyrimidine esters and their analogues were synthesized by the routes shown in Chart 1. In general, a mixture of α,β-unsaturated carbonyl compound (2),[8] amidine hydrochloride and triethylamine (Et_3N) in 1-butanol (*n*-BuOH) was refluxed for 1—3 h, followed by treatment with 10% HCl aq. to afford dihydropyrimidine (**3a—p**, **3r—t**, **3x—z**, **5—8**, **10**)[9] hydrochlorides.

Dihydropyrimidine was oxidized with activated manganese (IV) oxide (MnO_2) to afford (**4a—p**, **4r—t**, **4x**, **4y**, **12—15**, **17**).

Unstable 2,6-dimethyldihydropyrimidine (**9** and **11**) could not be isolated as hydrochloride; thus, after evaporation of *n*-BuOH, each was oxidized with MnO_2. The oxidized products were isolated by means of silica gel (SiO_2) column chromatography to afford **16** and **18**, respectively.

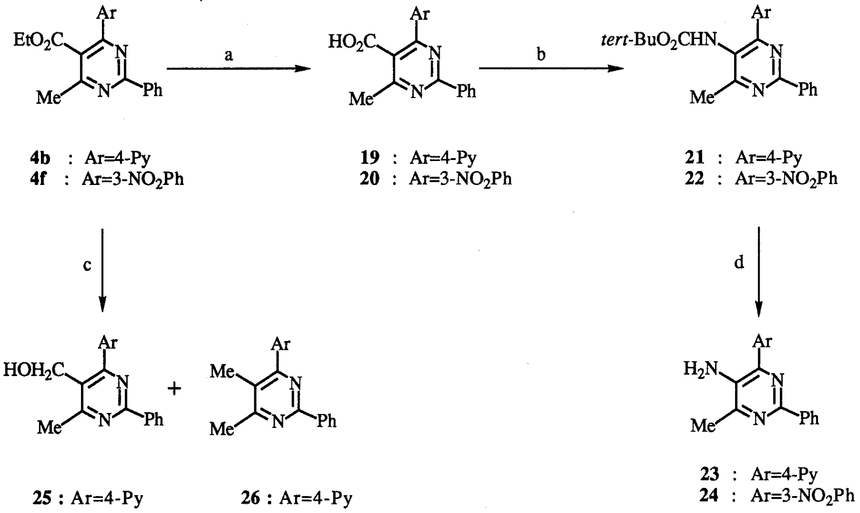
Further modifications of the substituents of the pyrimidine ring at the C-2, C-5, and C-6 position in the compounds (**4b** and **4f**) are shown in Chart 2.

The ester (**4b**) was hydrolyzed with ethanolic KOH aq. to afford the desired carboxylic acid (**19**). The conversion of the carboxylic group to the amino function was carried out through Curtius rearrangement using diphenylphosphoryl azide (DPPA) and Et_3N in *tert*-butanol (*tert*-BuOH). Deprotection of the product (**21**) with hydrogen chloride provided the 5-amino pyrimidine derivative (**23**). Reduction of **4b** with $LiAlH_4$ afforded the desired (**25**) and a small amount of the by-product (**26**).

A lactone derivative (**32**) was synthesized by the route shown in Chart 3.

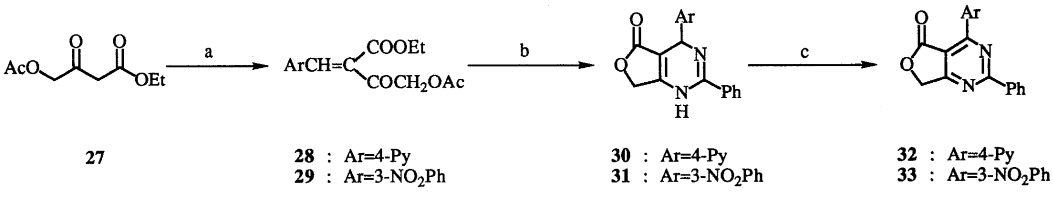
Ethyl 4-acetoxy-2-(4-pyridylmethylene) acetoacetate (**28**) was obtained by the Knoevenagel reaction of ethyl 4-acetoxyacetoacetate (**27**)[10] with isonicotinic aldehyde in the presence of piperidine and acetic acid. Refluxing of **28** in *n*-BuOH for 7 h in the presence of benzamidine hydrochloride and Et_3N provided the tetrahydrofuro[3,4-*d*]pyrimidine derivative (**30**), which was oxidized with activated MnO_2 to afford **32**. The corresponding modified **4f** derivatives (**20**, **22**, **24**, **33**) were also synthesized in a similar manner to those described above.

We also synthesized diethyl 4-aryl-3,5-pyridinedicarbox-



a) KOH aq. / EtOH; b) DPPA, Et_3N / *tert*-BuOH; c) $LiAlH_4$ / THF; d) HCl / EtOH

Chart 2



a) ArCHO, piperidine, AcOH / benzene; b) $PhC(NH_2)$=NH·HCl, Et_3N / *n*-BuOH; c) MnO_2 / $CHCl_3$

Chart 3

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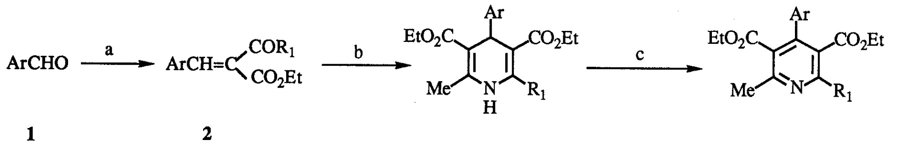
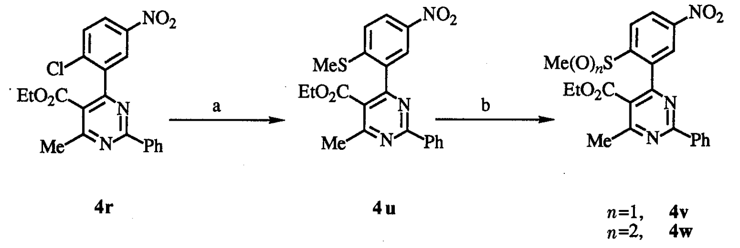


34 : Ar=4-Py, R_1=Ph
35 : Ar=4-Py, R_1=Me
36 : Ar=3-NO_2Ph, R_1=Ph
37 : Ar=3-NO_2Ph, R_1=Me

38 : Ar=4-Py, R_1=Ph
39 : Ar=4-Py, R_1=Me
40 : Ar=3-NO_2Ph, R_1=Ph
41 : Ar=3-NO_2Ph, R_1=Me

a) $R_1COCH_2CO_2Et$, piperidine, AcOH / benzene; b) $MeC(NH_2)=CHCO_2Et$ / EtOH;
c) 50% nitric acid

Chart 4



a) NaSMe / DMF; b) *m*-CPBA / $CHCl_3$

Chart 5

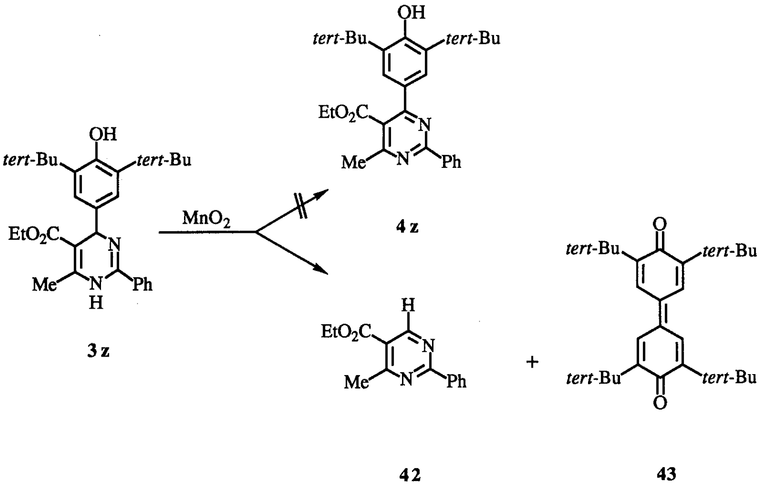


Chart 6

ylates (**38**—**41**) by the route shown in Chart 4.

The synthesis of diethyl 4-aryl-1,4-dihydro-3,5-pyridinedicarboxylates (**34**—**37**) was carried out by means of modification of the Hantzsch method.[11] Subsequently, oxidation of dihydropyridines (**34**—**37**) with nitric acid gave the corresponding pyridine derivatives (**38**—**41**).

4-(2-Methylthio-5-nitrophenyl)pyrimidine derivative (**4u**) was obtained from (**4r**) by the nucleophilic substitution of sodium methanethiolate in dimethylformamide (DMF). Sulfoxide (**4v**) and sulfone (**4w**) were obtained by the oxidation of **4u** with *m*-chloroperbenzoic acid (MCPBA) (Chart 5).

In the case of oxidation of dihydropyrimidine (**3z**) with activated MnO_2, we could not obtain the desired (**4z**), but obtained the dearylated product (**42**) and the diphenoquinone derivative (**43**)[13] (Chart 6).

Pharmacological Results and Discussion

The prepared pyrimidine derivatives were tested for AA activity in mice and ALP activity in rat brain mitochondria, and their SARs were examined.

We focused our initial efforts on checking the effect of the aryl substituent at the C-4 position of the pyrimidine ring on AA and ALP activities (Table I).

Regarding the AA activity, the 4-pyridyl (4-Py) derivative (**4b**) had a strong effect which was dose-dependent, but 3-Py (**4c**) and 2-Py (**4d**) had no effect at the dose tested. Compounds (**4l** and **4o**) had a moderate AA activity.

Subsequently, the substituent effects of **4b** were examined (Table II).

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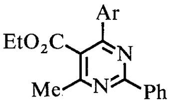
TABLE I. Physical Properties and Biological Activities of Ethyl 4-Aryl-2-phenyl-6-methyl-5-pyrimidinecarboxylate Derivatives



Compound No.	Ar	Anti-anoxia[a] (% of control) (mg/kg, i.p.)		Lipid peroxidation[b] (% of control) (g/ml)	Yield (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found)		
		10	100	10^{-5}				C	H	N
4a	Ph	105.1		102.1	63.8	72—73[c] (*n*-Hexane)	$C_{20}H_{18}N_2O_2$	75.48 (75.77	5.70 5.83	8.80 8.89)
4b	4-Py	115.9[d]	151.4[e]	104.3	56.3	95—96 (*n*-Hexane)	$C_{19}H_{17}N_3O_2$	71.46 (71.28	5.37 5.52	13.16 12.94)
4c	3-Py	105.9		67.6	36.2	63—64 (IPE–$CHCl_3$)	$C_{19}H_{17}N_3O_2$	71.46 (71.94	5.37 5.48	13.16 13.16)
4d	2-Py	95.8		96.2	1.5	95—97 (IPE)	$C_{19}H_{17}N_3O_2$	71.46 (71.21	5.37 5.51	13.16 13.01)
4e	4-NO_2Ph	97.6		9.5[e]	28.9	138—140 (Et_2O)	$C_{20}H_{17}N_3O_4$	66.11 (66.16	4.72 4.95	11.56 11.51)
4f	3-NO_2Ph	98.8		26.7[e]	65.3	97—98 (*n*-Hexane)	$C_{20}H_{17}N_3O_4$	66.11 (66.34	4.72 4.87	11.56 11.65)
4g	2-NO_2Ph	100.0		94.1	53.3	115—116 (Et_2O–$CHCl_3$)	$C_{20}H_{17}N_3O_4$	66.11 (66.47	4.72 4.66	11.56 11.63)
4h	3-ClPh	105.6		91.6	30.2	80—82 (IPE)	$C_{20}H_{17}ClN_2O_2$	68.09 (68.21	4.86 5.03	7.94 7.89)
4i	3-CNPh	105.9		95.4	43.3	88—90 (IPE)	$C_{21}H_{17}N_3O_2$	73.45 (73.72	4.99 5.16	12.24 12.21)
4j	4-CNPh	108.6		89.5	10.1	86—87 (IPE)	$C_{21}H_{17}N_3O_2$	73.45 (73.83	4.99 5.17	12.24 12.30)
4k	4-CO_2MePh	98.4		91.8	30.1	126—127 (IPE)	$C_{22}H_{20}N_2O_4$	70.20 (70.54	5.36 5.61	7.44 7.40)
4l	3-CF_3Ph	125.0[e]	122.6[e]	91.1	3.8	59—60 (*n*-Hexane)	$C_{21}H_{17}F_3N_2O_2$	65.28 (65.64	4.43 4.37	7.25 7.22)
4m	3-MeOPh	98.8		88.9	50.3	53—55 (*n*-Hexane–IPE)	$C_{21}H_{20}N_2O_3$	72.36 (72.63	5.79 5.89	8.04 7.99)
4n	2-(4-Cl–PhS)Ph	105.3		92.7	68.7	128—130 (IPE)	$C_{26}H_{21}ClN_2O_2S$	67.74 (67.80	4.59 4.62	6.08 5.97)
4o	2-(4-Cl–PhCH_2O)Ph	118.6[e]	125.8[e]	91.1	34.6	112—113 (IPE–$CHCl_3$)	$C_{27}H_{23}ClN_2O_3$	70.66 (70.81	5.05 5.31	6.10 6.06)

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*) lit.[12] mp 73 °C. *d*) $p<0.05$, *e*) $p<0.01$, values without marks are not statistically significant.

Even some very simple structural alterations can result in a loss of AA activity. Diethyl 4-pyridyl-3,5-pyridinedicarboxylate derivatives (**38** and **39**) also did not have this activity.

On the other hand, we observed ALP activity on the 4-nitrophenyl (**4e**) and 3-nitrophenyl (**4f**) derivatives, but not on 2-nitrophenyl (**4g**) at a concentration of 10^{-5} g/ml. Analogous compounds with electron-withdrawing groups, 3-cyanophenyl (**4i**), 4-cyanophenyl (**4j**) and 4-methoxycarbonylphenyl (**4k**) were ineffective (Table I). According to **4f**, the substituent effects of the pyrimidine ring at the C-2, C-5, and C-6 position were also examined (Table III).

Esters (**13** and **14**), acetyl (**15**) and amino functions (**22** and **24**) had a high or similar level of ALP activity compared to **4f**.

Exchange of C2-Ph to C2-Me (**18**) resulted in a loss of activity. Diethyl 4-(3-nitrophyl)-3,5-pyridinedicarboxylate derivatives (**40** and **41**) were not effective.

Next, the effect of additional substituents on the 3-nitrophenyl group was examined (Table IV).

In this case the following compounds (**4p**, **4r**—**v**) retained ALP activity.

An attempt to incorporate the two separate pharmacophores (*i.e.* anti-anoxia, anti-lipid peroxidation) into the same molecule (**4x** and **4y**) resulted in the loss of both activities. Compound **4u**, which has a methylthio group, had moderate AA and ALP activities; however, the further oxidized compounds (**4v** and **4w**) possessed only ALP activity.

Dihydropyrimidine (**3f**), which is the precursor of **4f**, showed rather weak ALP activity (50% inhibition at 10^{-5} g/ml) and high acute toxicity (all mice were dead at 100 mg/kg, i.p.).

Compound **3b** was ineffective in both assays. (Data not shown here.)

Compounds **4b**, **4e**, **3f**, **4f**, **4o**, **4p**, **4u** were further tested for their effect on cerebral edema induced by arachidonate in rats (Table V).[14]

Compounds **4f** and **4p** significantly suppressed the increase in water content in the ipsilateral hemisphere, as did vitamin E, but not **4b**.

Although the mechanism of action of these compounds is uncertain, these results indicated that arachidonate-induced cerebral edema and ALP activity may have some co-relationship.

As a result of the present study, this preliminary data

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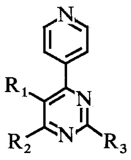
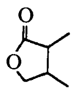
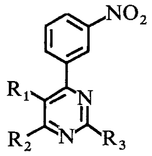
TABLE II. Physical Properties and Biological Activities of 4-(4-Pyridyl)pyrimidine Derivatives and 4-(4-Pyridyl)pyridines (**38** and **39**)

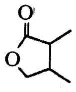


Compd. No	R_1	R_2	R_3	Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10	Lipid peroxidation[b] (% of control) (g/ml) 10^{-5}	Yield (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N
12	COMe	Me	Ph	95.5	97.9	50.3	121—123 (Et_2O)	$C_{18}H_{15}N_3O$	74.72 (75.01	5.23 5.35	14.52 14.55)
16	CO_2Et	Me	Me	100.0	104.3	6.0	217—219 (dec.) (EtOH)	$C_{14}H_{15}N_3O_2$ $\cdot 2HCl \cdot 1/4H_2O$	50.24 (50.30	5.26 5.71	12.55 12.40)
17	CO_2Et	Ph	Me	100.0	96.2	9.1	77—79 (*n*-Hexane)	$C_{19}H_{17}N_3O_2$	71.46 (71.82	5.37 5.55	13.20 13.20)
19	CO_2H	Me	Ph	103.1	93.7	89.6	270—271 (AcOH–H_2O)	$C_{17}H_{13}N_3O_2$ $\cdot 1/2H_2O$	67.99 (68.21	4.70 4.34	13.99 13.99)
21	$NHCO_2$-*tert*-Bu	Me	Ph	NT	NT	24.1	166—167 (Et_2O)	$C_{21}H_{22}N_4O_2$	69.59 (69.83	6.12 6.16	15.46 15.42)
23	NH_2	Me	Ph	106.2	78.5	50.0	208—209 (EtOH)	$C_{16}H_{14}N_4$	73.26 (73.23	5.38 5.04	21.36 21.23)
25	CH_2OH	Me	Ph	91.7	95.0	16.1	175—176 (Et_2O)	$C_{17}H_{15}N_3O$ $\cdot 1/2H_2O$	71.31 (71.12	5.63 5.47	14.67 14.53)
26	Me	Me	Ph	NT	NT	1.8	152—153 (*n*-Hexane)	$C_{17}H_{15}N_3$	78.13 (78.52	5.79 5.60	16.08 16.24)
32			Ph	94.0	102.6	57.2	191—192 (IPE)	$C_{17}H_{11}N_3O_2$	70.58 (70.24	3.83 3.97	14.53 14.50)
38				107.2	100.2	16.7	105—106 (Et_2O)	$C_{23}H_{22}N_2O_4$	70.76 (70.75	5.68 5.80	7.18 7.22)
39				100.0	102.3	45.3	104—105 (Et_2O)	$C_{18}H_{20}N_2O_4$	65.84 (65.77	6.14 6.19	8.53 8.52)

a, *b*) See footnote *a*) and *b*) in Table I. NT; not tested.

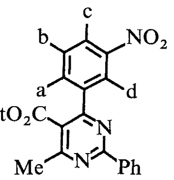
TABLE III. Physical Properties and Biological Activities of 4-(3-Nitrophenyl)pyrimidine Derivatives and 4-(3-Nitrophenyl)pyridines (**40** and **41**)



Compd. No	R_1	R_2	R_3	Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10	Lipid peroxidation[b] (% of control) (g/ml) 10^{-5}	Yield (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N
13	CO_2Me	Me	Ph	107.9	0.0	58.5	128—130 (Et_2O)	$C_{19}H_{15}N_3O_4$	65.32 (65.34	4.33 4.56	12.03 11.77)
14	CO_2-iso-Pr	Me	Ph	109.1	2.0[c]	74.8	94—95 (Et_2O)	$C_{21}H_{19}N_3O_4$	66.83 (67.28	5.07 5.14	11.13 11.26)
15	COMe	Me	Ph	110.1	26.8[c]	36.7	131—132 (Et_2O)	$C_{19}H_{15}N_3O_3$	68.46 (68.11	4.54 4.61	12.61 12.45)
18	CO_2Et	Me	Me	110.9	98.1	3.9	123—125 (Et_2O)	$C_{15}H_{15}N_3o_4$ $\cdot HCl$	53.34 (53.52	4.77 4.73	12.44 12.07)
20	CO_2H	Me	Ph	109.2	102.6	93.0	208—209 (AcOH–H_2O)	$C_{18}H_{13}N_3O_4$	64.47 (64.31	3.91 3.86	12.53 12.13)
22	$NHCO_2$-*tert*-Bu	Me	Ph	110.3	10.7[c]	66.1	187—189 (Et_2O)	$C_{22}H_{22}N_4O_4$	65.01 (65.33	5.46 5.42	13.78 13.89)
24	NH_2	Me	Ph	101.5	3.2[c]	51.1	179—181 (Et_2O)	$C_{17}H_{14}N_4O_2$	66.66 (66.63	4.61 4.68	18.29 18.32)
33			Ph	111.8	104.2	56.6	218—220 (IPE)	$C_{18}H_{11}N_3O_4$	64.87 (64.51	3.33 3.42	12.61 12.36)
40				105.7	76.8	46.3	100—102 (Et_2O)	$C_{24}H_{22}N_2O_6$ $\cdot HCl$	61.21 (61.48	4.92 4.80	5.94 5.74)
41				96.4	97.1	97.8	164—165 (Et_2O)	$C_{19}H_{20}N_2O_6$ $\cdot HCl$	55.81 (55.86	5.17 5.20	6.85 6.52)

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

TABLE IV. Physical Properties and Biological Activities of Ethyl 6-Methyl-4-(3-nitrophenyl)-2-phenyl-5-pyrimidinecarboxylate Derivatives



Compd. No.	a	b	c	d	Anti-anoxia[a] (% of control) (mg/kg, i.p.) 10	100	Lipd peroxidation[b] (% of control) (g/ml) 10^{-5}	Yield (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N
4p	H	H	OH	H	102.7		11.5[d]	98.0	97—98 (Et_2O)	$C_{20}H_{17}N_3O_5$	63.32 (63.55	4.52 4.48	11.08 11.36)
4q	H	H	OAc	H	101.8		57.0	14.8[e]	147—148 (Et_2O)	$C_{22}H_{19}N_3O_6$	62.70 (62.48	4.54 4.93	9.97 9.95)
4r	Cl	H	H	H	111.1		9.7[d]	29.1	119—120 (IPE)	$C_{20}H_{16}ClN_3O_4$	60.38 (60.45	4.05 4.19	10.56 10.60)
4s	H	H	Cl	H	110.3		77.4[d]	30.2	81—82 (IPE)	$C_{20}H_{16}ClN_3O_4$	60.38 (60.66	4.05 4.24	10.56 10.55)
4t	H	OCH_3	OH	H	96.4		0.6[d]	17.8	159—161 (IPE)	$C_{21}H_{19}N_3O_6$	61.61 (62.01	4.68 4.80	10.26 10.47)
4u	SMe	H	H	H	120.0[c]	126.5[d]	48.5[c]	19.5	125—126 (Et_2O)	$C_{21}H_{19}N_3O_4S$	61.60 (61.44	4.68 4.88	10.26 10.21)
4v	SOMe	H	H	H	107.1		7.4[d]	62.4	130—132 (IPE)	$C_{21}H_{19}N_3O_5S$	59.28 (59.33	4.50 4.55	9.88 9.80)
4w	SO_2Me	H	H	H	95.2		43.4	27.7	150—151 (IPE)	$C_{21}H_{19}N_3O_6S$	57.13 (56.76	4.33 4.25	9.51 9.56)
4x	4-ClPhCH$_2$O	H	H	H	104.8		129.6	60.6	156—158 (Et_2O)	$C_{27}H_{22}ClN_3O_5$	64.35 (64.59	4.40 4.58	8.34 8.45)
4y	H	H	H	4-ClPhCH$_2$O	108.6		74.6	62.6	104—105 (Et_2O)	$C_{27}H_{22}ClN_3O_5$	64.35 (64.55	4.40 4.61	8.34 8.29)

a, *b*) See footnote *a*) and *b*) in Table I. *c*, *d*) See footnote *d*) and *e*) in Table I. *e*) Yield from **4p**.

TABLE V. Effect on Arachidonic Acid-Induced Cerebral Edema in Rats

Compounds No.	N[e]	Dose (mg, kg, i.p.)	Water content (%) Infarcted hemisphere	Contralateral hemisphere
Vehicle	6	0	82.2±0.3	78.7±0.4
4b[a]	10	10	81.9±0.7	78.8±0.4
	4[f]	100	82.3±0.7	78.4±0.3
Vehicle	6	0	82.0±0.4	78.3±0.3
4e[b]	6	10	81.3±0.3	79.0±0.5
Vehicle	10	0	81.5±0.4	78.8±0.2
3f[c]	6	10	80.9±0.3	79.3±0.2
Vehicle	10	0	81.5±0.4	78.8±0.2
4f[c]	6	10	80.8±0.4	79.0±0.2
	6	100	79.5±0.4[h]	78.1±0.4
Vehicle	6	0	82.0±0.4	78.3±0.3
4o[b]	6	100	81.6±0.4	79.0±0.1
Vehicle	10	0	81.5±0.4	78.8±0.2
4p[c]	6	10	81.0±0.4	79.1±0.3
	6	100	80.0±0.3[g]	78.7±0.4
Vehicle	6	0	82.0±0.4	78.3±0.3
4u[b]	6	10	81.1±0.3	79.1±0.2
	6	32	81.2±0.7	78.9±0.2
Vehicle	6	0	81.2±0.3	78.6±0.4
Vitamin E[d]	6	10	81.4±0.2	78.9±0.6
	6	100	79.3±0.2[h]	78.7±0.2

The values are the means±standard error. Statistical analysis was performed by using Student's *t*-test to evaluate the significance of differences from control values. *a*) Dissolved in 2 eq HCl aq. *b*) Suspended in 0.5% MC (methyl cellulose). *c*) Dissolved in DMSO (dimethyl sulfoxide). *d*) Suspended in peanut oil. *e*) Number of rats. *f*) After injection of arachidonic acid 2/6 rats died. *g*, *h*) See footnote *d*) and *e*) in Table I.

should aid in the design and synthesis of a new cerebral protective agent.

Experimental

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton 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 taken 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.

Typical Procedures for the Preparation of 4-Aryl-1,4-dihydropyrimidines Ethyl 1,4-Dihydro-6-methyl-2-phenyl-4-(4-pyridyl)-5-pyrimidinecarboxylate (**3b**): A mixture of ethyl 2-(4-pyridylmethylene)acetoacetate (25.5 g), benzamidine hydrochloride (21.9 g) and Et_3N (16.5 g) in *n*-BuOH (250 ml) was refluxed for 1.5 h.

After cooling to room temperature, the reaction mixture was washed with H_2O (200 ml) and extracted with 10% HCl aq. (200 ml). The aqueous layer was adjusted to pH 9.0 with 4% NaOH aq. and extracted with AcOEt (200 ml × 2). The combined extracts were dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The residual precipitate was recrystallized from Et_2O to afford **3b** (27.85 g, 74.1%). Compound **3c** was prepared in a similar manner to **3b**. Compound **10** was synthesized by the same procedures as employed in the preparation of **3b** by condensation with ethyl 2-(4-pyridylmethylene)benzoylacetate and acetamidine hydrochloride. Their physical properties are listed in Table VI. Compound **3d** was not isolated, and oxidized directly to **4d**.

Ethyl 4-(2-Chloro-5-nitrophenyl)-1,4-dihydro-6-methyl-2-phenyl-5-pyrimidinecarboxylate (**3r**): A mixture of ethyl 2-(2-chloro-5-nitrophenylmethylene)acetoacetate (70 g), benzamidine hydrochloride (44 g) and Et_3N (45.9 ml) in *n*-BuOH (700 ml) was refluxed for 1.5 h. After cooling to room temperature, the reaction mixture was poured into a mixture of AcOEt (300 ml) and H_2O (500 ml). The organic layer was washed with

TABLE VI. Physical Properties of Dihydropyrimidines

Compd. No.	IR (Nujol)	NMR (DMSO-d_6)	Yield (%)	mp (°C) Recrystn. solvent	Formula (MS, m/z, M^+)	Analysis (%) Calcd (Found)		
						C	H	N
3a	1695, 1650, 1230, 1085, 700	1.17 (3H, t, $J=7$ Hz), 2.43 (3H, s), 4.10 (2H, q, $J=7$ Hz), 5.70 (1H, s), 7.10—7.60 (8H, m), 7.60—8.10 (2H, m), 9.46 (1H, br)	79.7	125—126[a] (*n*-Hexane)	$C_{20}H_{20}N_2O_2$ (320)	74.97 (74.91	6.29 6.47	8.74 8.79)
3b	3150, 1690, 1645, 1590, 1240, 1090	1.15 (3H, t, $J=7$ Hz), 2.40 (3H, s), 4.05 (2H, q, $J=7$ Hz), 5.70 (1H, s), 7.10—7.60 (5H, m), 7.70—8.10 (2H, m), 8.20—8.80 (2H, m), 9.57 (1H, br)	74.1	147—150 (Et_2O)	$C_{19}H_{19}N_3O_2$ (321)	71.01 (70.94	5.96 5.98	13.08 13.01)
3c	1695, 1680, 1580, 1240, 1085	1.13 (3H, t, $J=7$ Hz), 2.40 (3H, s), 4.03 (2H, q, $J=7$ Hz), 5.67 (1H, s), 7.20—8.10 (7H, m), 8.30—8.70 (2H, m), 9.60 (1H, br)	49.8	138—139 (Et_2O)	$C_{19}H_{19}N_3O_2$ (321)	71.01 (70.98	5.96 6.08	13.08 12.98)
3e	1700, 1680, 1650, 1525, 1350	1.15 (3H, t, $J=7$ Hz), 2.47 (3H, s), 4.67 (2H, q, $J=7$ Hz), 5.73 (1H, s), 7.33—7.67 (5H, m), 7.73—7.97 (2H, m), 8.07—8.33 (2H, m), 9.53 (1H, br)	28.8	120—122 (IPE)	$C_{20}H_{19}N_3O_4$ (365)	65.74 (65.72	5.24 5.29	11.50 11.47)
3f	1700, 1640, 1530	1.12 (3H, t, $J=7$ Hz), 2.45 (3H, s), 4.12 (2H, q, $J=7$ Hz), 5.83 (1H, s), 7.40—8.40 (9H, m), 9.63 (1H, br)	86.4	106—108 (Et_2O)	$C_{20}H_{19}N_3O_4$ (365)	65.74 (66.18	5.24 5.16	11.50 11.51)
3g	1700, 1660, 1520, 1230, 1090	1.06 (3H, t, $J=7$ Hz), 2.47 (3H, s), 3.99 (2H, q, $J=7$ Hz), 6.24 (1H, s), 7.30—8.00 (9H, m), 9.58 (1H, s)	31.9	Oil	$C_{20}H_{19}N_3O_4$ (365)	65.74 (65.57	5.24 5.23	11.50 11.13)
3h[b]	1700, 1650, 1600	1.15 (3H, t, $J=7$ Hz), 2.39 (3H, s), 4.05 (2H, q, $J=7$ Hz), 5.46 (minor), 5.64 (total 1H, each s), 7.10—7.60 (7H, m), 7.65—8.00 (2H, m), 9.23 (minor), 9.46 (total 1H, each s)	50.0	143—144 (*n*-Hexane–AcOEt)	$C_{20}H_{19}ClN_2O_2$ (354)	67.70 (67.75	5.40 5.47	7.89 7.81)
3i	3480, 2250, 1700, 1660	1.13 (3H, t, $J=7$ Hz), 2.40 (3H, s), 4.08 (2H, q, $J=7$ Hz), 5.73 (1H, s), 7.30—8.00 (9H, m), 9.53 (1H, br)	73.1	135—136 (*n*-Hexane)	$C_{21}H_{19}N_3O_2$ (345)	73.02 (72.68	5.54 5.45	12.16 12.10)
3j	2250, 1680	1.13 (3H, t, $J=7$ Hz), 2.40 (3H, s), 4.07 (2H, q, $J=7$ Hz), 5.73 (1H, s), 7.73—8.00 (9H, m), 9.53 (1H, br)	74.1	148—149 (*n*-Hexane)	$C_{21}H_{19}N_3O_2$ (345)	73.02 (72.58	5.54 5.64	12.16 12.15)
3k	1720, 1280, 720	1.13 (3H, t, $J=7$ Hz), 2.40 (3H, s), 3.82 (3H, s), 4.0 (2H, q, $J=7$ Hz), 5.73 (1H, s), 7.33—8.37 (9H, m), 9.48 (1H, s)	99.1	Oil	$C_{22}H_{22}N_2O_4$ (378)	69.82 (69.32	5.85 6.14	7.40 7.11)
3l[b]	3150, 1695, 1650, 1235	1.13 (3H, t, $J=7$ Hz), 2.40 (3H, s), 4.05 (2H, q, $J=7$ Hz), 5.57 (minor), 5.93 (total 1H, each s), 7.37—7.67 (7H, m), 7.70—8.00 (2H, m), 9.33 (minor), 9.50 (total 1H, each br)	51.5	136—138 (IPE)	$C_{21}H_{19}F_3N_2O_2$ (388)	64.94 (64.64	4.93 5.17	7.21 7.05)
3m	1665, 1605, 1590	1.17 (3H, t, $J=7$ Hz), 2.43 (3H, s), 3.75 (3H, s), 4.10 (2H, q, $J=7$ Hz), 5.63 (1H, s), 6.67—7.00 (3H, m), 7.00—7.27 (1H, m), 7.28—7.62 (3H, m), 7.67—8.00 (2H, m), 9.40 (1H, br)	74.9	Oil	$C_{21}H_{22}N_2O_3$ (350)	71.98 (71.88	6.32 6.32	7.99 7.91)
3n	1650, 1230, 1090, 1010, 820	1.00 (3H, t, $J=7$ Hz), 2.46 (3H, s), 3.92 (2H, q, $J=7$ Hz), 6.22 (1H, s), 7.20—7.60 (11H, m), 7.70—7.90 (2H, m), 9.38 (1H, s)	50.1	58—59 (Et_2O)	$C_{26}H_{23}ClN_2O_2S$ (462)	67.44 (67.04	5.00 5.06	6.05 5.99)
3o	3505, 1670, 1590, 1360, 1090	1.00 (3H, t, $J=7$ Hz), 2.37 (3H, s), 3.93 (2H, q, $J=7$ Hz), 5.17 (2H, s), 6.07 (1H, s), 6.73—7.90 (13H, m), 9.17 (1H, br)	80.6	Oil	$C_{27}H_{25}ClN_2O_3$ (460)	70.35 (70.06	5.46 5.51	6.07 6.02)
3p	1720, 1675, 1610, 1545, 1505	1.17 (3H, t, $J=7$ Hz), 2.40 (3H, s), 4.07 (2H, q, $J=7$ Hz), 5.63 (1H, s), 7.03—8.00 (8H, m)	80.9	179—180 (IPE–AcOEt)	$C_{20}H_{19}N_3O_5$ (381)	62.98 (62.66	5.02 4.93	11.01 10.95)
3r	1710, 1660, 1610, 1580, 1530	1.03 (3H, t, $J=7$ Hz), 2.53 (3H, s), 3.97 (2H, q, $J=7$ Hz), 6.13 (1H, s), 7.37—7.56 (3H, m), 7.67—7.9 (3H, m), 8.0—8.17 (2H, m), 9.63 (1H, br)	79.8	169—170 (IPE)	$C_{20}H_{18}ClN_3O_4$ (399)	60.08 (60.08	4.53 4.68	10.53 10.11)
3s	1710, 1605, 1175	1.17 (3H, t, $J=7$ Hz), 2.45 (3H, s), 4.13 (2H, q, $J=7$ Hz), 5.87 (1H, s), 7.47—7.68 (3H, m), 7.70—7.87 (2H, m), 7.87—8.07 (3H, m), 9.77 (1H, s)	82.1	Oil	$C_{20}H_{18}ClN_3O_4$ (399)	60.08 (60.42	4.53 4.83	10.50 10.16)
3t	1670, 1095, 1020	1.17 (3H, t, $J=7$ Hz), 2.40 (3H, s), 3.80 (3H, s), 4.07 (2H, q, $J=7$ Hz), 5.58 (1H, s), 7.13—8.00 (7H, m)	42.5	Oil	$C_{21}H_{21}N_3O_6$ (411)	61.30 (61.08	5.14 5.19	10.21 10.07)
3x	1690, 1660, 1335	1.00 (3H, t, $J=7$ Hz), 2.43 (3H, s), 4.95 (2H, q, $J=7$ Hz), 5.37 (2H, s), 6.13 (1H, s), 7.00—8.30 (12H, m), 9.37 (1H, s)	85.9	167—169 (*n*-Hexane–Et_2O)	$C_{27}H_{24}ClN_3O_6$ (505)	64.10 (64.46	4.78 4.81	8.31 8.20)
3y	1705, 1665, 1600, 1530, 805	1.00 (3H, t, $J=7$ Hz), 2.52 (3H, s), 4.00 (2H, q, $J=7$ Hz), 5.22 (1H, d, $J=10$ Hz), 5.37 (1H, d, $J=10$ Hz), 6.20 (1H, s), 7.30—8.10 (12H, m), 9.60 (1H, s)	51.9	168—169 (*n*-Hexane–Et_2O)	$C_{27}H_{24}ClN_3O_6$ (505)	64.10 (64.39	4.78 5.07	8.31 8.22)

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Table VI. (continued)

Compd. No.	IR (Nujol)	NMR (DMSO-d_6)	Yield (%)	mp (°C) Recrystn. solvent	Formula (MS, m/z, M$^+$)	Analysis (%) Calcd (Found)		
						C	H	N
3z$^{b)}$	1660, 1230, 1090, 695	1.96 (3H, t, J=7 Hz), 1.32 (18H, s), 2.32 (3H, s), 4.06 (2H, q, J=7 Hz), 5.40 (minor), 5.50 (total 1H, each br), 6.70—7.00 (1H, br), 7.08 (2H, s), 7.30—7.70 (3H, m), 7.70—8.00 (2H, m), 9.19 (minor), 9.44 (total 1H, each s)	23.2	Oil	$C_{28}H_{36}N_2O_3$ $\cdot 0.6H_2O$ (448)	73.20 (73.22	8.16 8.34	6.09 5.92)
5	1650, 1600, 1245, 700	2.20 (3H, s), 2.47 (3H, s), 5.82 (1H, s), 7.27 (2H, d, J=6 Hz), 7.40—7.60 (3H, m), 7.80—8.00 (2H, m), 8.48 (2H, d, J=6 Hz), 9.63 (1H, s)	38.9	67—69 (Et_2O)	$C_{18}H_{17}N_3O$ $\cdot 0.4H_2O$ (291)	72.41 (72.39	6.00 6.06	14.07 14.06)
6	1698, 1643, 1530, 1350	2.42 (3H, s), 3.60 (3H, s), 5.83 (1H, s), 7.30—8.30 (9H, m), 9.67 (1H, s)	29.6	139—141 (Et_2O)	$C_{19}H_{17}N_3O_4$ (351)	64.95 (65.32	4.87 5.28	11.95 11.65)
7	1702, 1655, 1535, 1355	1.10 (3H, d, J=7 Hz), 1.22 (3H, d, J=7 Hz), 2.43 (3H, s), 4.93 (1H, m), 5.78 (1H, s), 7.30—8.30 (9H, m), 9.50 (1H, br)	78.5	135—137 (Et_2O)	$C_{21}H_{21}N_3O_4$ (379)	66.48 (66.80	5.58 5.85	11.08 10.98)
8	1655, 1590, 1530, 1340, 1245	2.23 (3H, s), 2.50 (3H, s), 5.93 (1H, s), 7.30—8.20 (9H, m), 9.60 (1H, s)	31.0	154—155 (Et_2O)	$C_{19}H_{17}N_3O_3$ (335)	68.05 (68.29	5.11 5.21	12.53 12.50)
10	1675, 1600, 1250, 1235	0.73 (3H, t, J=7 Hz), 1.95 (3H, s), 3.73 (2H, q, J=7 Hz), 5.46 (1H, s), 7.20—7.52 (7H, m), 8.40—8.63 (2H, m), 9.48 (1H, s)	5.8	173—174 (IPE)	$C_{19}H_{19}N_3O_2$ (321)	71.01 (71.37	5.96 5.92	13.07 13.12)

a) Lit.[9b] mp 106—108 °C. *b)* This compound was a mixture of tautomers in DMSO-d_6 solution. The ratio of tautomers was **3h**: 3.69 (concentration = 0.066 M), **3l**: 4.25 (0.017 M), **3z**: 2.10 (0.042 M), respectively.

5% HCl aq. (300 ml) and the solvent was evaporated *in vacuo*. The residual crystalline (**3r**)·HCl was collected by filtration, suspended in a mixture of $CHCl_3$ (500 ml) and H_2O (500 ml), and adjusted to pH 8.0 with K_2CO_3 aq. The organic layer was washed with brine, dried and evaporated *in vacuo*. The residue was recrystallized from isopropyl ether (IPE) to afford **3r** (75.0 g, 79.8%). Compounds **3a**, **3e**—**p**, **3s**, **3t**, **3x**—**z**, **5**—**8** were prepared in a similar manner as described for **3r**. Their physical properties are summarized in Table VI.

Typical Procedures for the Preparation of 4-Arylpyrimidines Ethyl 6-Methyl-2-phenyl-4-(4-pyridyl)-5-pyrimidinecarboxylate (**4b**): To a solution of **3b** (13.4 g) in $CHCl_3$ (300 ml) was added activated MnO_2 (53.6 g), and the mixture was refluxed for 2 h with vigorous stirring. After allowing the mixture to cool to room temperature, the MnO_2 was filtered off. The filtrate was evaporated *in vacuo* and the residual precipitate was recrystallized from a mixture of Et_2O (80 ml) and petroleum ether (40 ml) to afford **4b** (7.5 g, 56.3%). IR (Nujol): 1715, 1600, 1530, 1265, 775, 690 cm^{-1}. MS m/z: 319 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 1.05 (3H, t, J=7 Hz), 2.63 (3H, s), 4.15 (2H, q, J=7 Hz), 7.30—7.60 (5H, m), 8.20—8.40 (2H, m), 8.50—8.70 (2H, m).

Melting point and analytical data are included in Table I. Compounds **4a**, **4c**—**p**, **4r**—**t**, **4x**, **4y**, **12**—**15**, **17** were prepared in a similar manner to **4b** and their physical properties are listed in Tables I—IV.

Ethyl 2,6-Dimethyl-4-(4-pyridyl)-5-pyrimidinecarboxylate (**16**): A mixture of ethyl 2-(4-pyridylmethylene)acetoacetate (10.0 g), acetamidine hydrochloride (5.17 g) and Et_3N (6.4 g) in n-BuOH (100 ml) was refluxed for 5h. After being cooled to room temperature, the reaction mixture was washed with brine and extracted with 5% HCl aq. (100 ml). The aqueous layer was washed with $CHCl_3$ (100 ml), adjusted to pH 8.5 with K_2CO_3 aq. and extracted with $CHCl_3$ (100 ml × 2). The combined extracts were washed with brine, dried and evaporated *in vacuo*. The residue was chromatographed on SiO_2 and eluted with $CHCl_3$–MeOH (20 : 1) to afford unstable **9** as an oil (3.0 g). To a solution of **9** (3.0 g) in AcOEt (30 ml) was added activated MnO_2 (12.0 g) and the mixture was refluxed for 1 h with vigorous stirring. After allowing it to cool to room temperature, MnO_2 was filtered off. The filtrate was evaporated *in vacuo* to afford **16** (2.1 g) as an oil.

A solution of **16** (2.1 g) in EtOH (5 ml) and Et_2O (5 ml) was treated with a slight excess of HCl/EtOH to afford **16**·2HCl (0.9 g, 6.0%). IR (Nujol): 1730, 1620, 1275, 1010 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.03 (3H, t, J=7 Hz), 2.06 (3H, s), 2.70 (3H, s), 4.20 (2H, q, J=7 Hz), 8.00—8.20 (2H, m), 8.70—8.90 (2H, m). Melting point and analytical data are included in Table II. Compound **18** was prepared in a similar manner and its physical properties are included in Table III.

6-Methyl-2-phenyl-4-(4-pyridyl)-5-pyrimidinecarboxylic Acid (19) A solution of **4b** (15.0 g) and KOH aq. (3.48 g in 30 ml H_2O) in EtOH (150 ml) was refluxed for 4.5 h. After evaporation of the solvent, the residue was dissolved in a mixture of H_2O (150 ml) and $CHCl_3$ (150 ml).

The separated aqueous layer was adjusted to pH 5.5 with 10% HCl aq. The resulting precipitate was collected by filtration, washed with H_2O and dried *in vacuo* to afford **19** (12.3 g, 89.6%). IR (Nujol): 1710, 1615, 1535, 1025, 765 cm^{-1}. MS m/z: 291 (M$^+$). ^{1}H-NMR (CF_3COOD) δ: 3.33 (3H, s), 7.60—8.10 (3H, m), 8.30—8.80 (4H, m), 9.00—9.40 (2H, m). Melting point and analytical data are included in Table II. Compound **20** was prepared in a similar manner and its physical properties are included in Table III.

5-*tert*-Butyloxycarbonylamino-6-methyl-2-phenyl-4-(4-pyridyl)pyrimidine (21) A mixture of **19** (5.0 g), Et_3N (1.8 g) and DPPA (4.7 g) in *tert*-BuOH (50 ml) was refluxed for 7 h. After removal of the solvent *in vacuo*, the residue was dissolved in a mixture of AcOEt (100 ml) and H_2O (100 ml) under stirring. The separated organic layer was successively washed with 10% HCl aq., 5% $NaHCO_3$ aq. and brine, and then dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residual substance was recrystallized from Et_2O to afford **21** (1.5 g, 24.1%). IR (Nujol): 3210, 1690, 1605, 1162, 1055, 1030, 768, 700 cm^{-1}. MS m/z: 362 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 1.33 (9H, s), 2.57 (3H, s), 7.40—7.60 (3H, m), 7.60—7.90 (2H, m), 8.20—8.55 (2H, m), 8.60—8.85 (2H, m), 9.05 (1H, br).

Melting point and analytical data are included in Table II. Compound **22** was prepared in a similar manner and its physical properties are included in Table III.

5-Amino-6-methyl-2-phenyl-4-(4-pyridyl)pyrimidine (23) A mixture of **21** (1.50 g) and HCl–EtOH (4 ml, 5 mmol/ml) in EtOH (15 ml) was stirred for 1 h at 40 °C. After being cooled to room temperature, the reaction mixture was poured into a mixture of AcOEt (100 ml) and H_2O (50 ml) under stirring, and adjusted to pH 9.0 with 10% K_2CO_3 aq. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was recrystallized from EtOH to afford **23** (0.54 g, 50.0%). IR (Nujol): 1635, 1545, 1225, 765, 703 cm^{-1}. MS m/z: 262 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 2.53 (3H, s), 5.41 (2H, s), 7.30—7.60 (3H, m), 7.70—7.90 (2H, m), 8.20—8.40 (2H, m), 8.60—8.90 (2H, m). Melting point and analytical data are included in Table II. Compound **24** was prepared in a similar manner and its physical properties are included in Table III.

Reduction of (4b) with $LiAlH_4$ To a suspension of $LiAlH_4$ (0.24 g) in dry tetrahydrofuran (THF, 40 ml) was added dropwise a solution of **4b** (2.00 g) in THF (20 ml) under cooling at 7—9 °C. The mixture was stirred at room temperature for 2 h. The excess $LiAlH_4$ was decomposed by a careful addition of H_2O, and the dried solution was evaporated *in vacuo*. The residual oil was purified by column chromatography on SiO_2 eluted with $CHCl_3$, and the fractions containing **26** were collected and evaporated *in vacuo*. The residual crystals were recrystallized from *n*-hexane to afford **26** (0.03 g, 1.8%). IR (Nujol): 1540, 840, 763, 695 cm^{-1}. MS *m*/*z*: 261 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 2.29 (3H, s), 2.62 (3H, s), 7.40—7.60 (3H, m), 7.55—7.75 (2H, m), 8.20—8.50 (2H, m), 8.65—8.90 (2H, m). The fractions eluted further with $CHCl_3$–MeOH (50 : 1) were combined and concentrated *in vacuo*. The residue was recrystallized from Et_2O to afford **25** (0.28 g, 16.1%). IR (Nujol): 3200, 1610, 1550, 1030, 1005, 820, 735, 690 cm^{-1}. MS *m*/*z*: 277 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 2.73 (3H, s), 4.50 (2H, d, J=5 Hz), 5.45 (1H, t, J=5 Hz), 7.40—7.60 (3H, m), 7.70—7.90 (2H, m), 8.30—8.60 (2H, m), 8.70—8.90 (2H, m). Melting point and analytical data are included in Table II.

Ethyl 4-Acetoxy-2-(4-pyridylmethylene)acetoacetate (28) A mixture of isonicotinic aldehyde (2.88 g), ethyl 4-acetoxyacetoacetate (5.30 g), AcOH (0.30 g) and piperidine (0.1 ml) in benzene (20 ml) was refluxed for 1 h with a Dean-Stark water separator. The reaction mixture was cooled to room temperature, diluted with AcOEt (100 ml) and successively washed with water and 5% $NaHCO_3$ aq. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to afford **28** as an oil (7.30 g, 97.9%). IR (Nujol): 1720, 1595, 1225, 1020 cm^{-1}. MS *m*/*z*: 277 (M$^+$). The ratio of isomers was 2.0. ^{1}H-NMR (DMSO-d_6) δ: 1.20 and 1.29 (minor) (3H, t, J=7 Hz), 2.07 (minor) and 2.14 (3H, s), 4.26 (2H, q, J=7 Hz), 5.01 (minor) and 5.32 (2H, s), 7.30—7.50 (2H, m), 7.80 (minor) and 7.90 (1H, s), 8.60—8.80 (2H, m). This compound was not further purified or analyzed before use in the next step. The acetate (**29**) was prepared in the same manner as described for **28**.

Ethyl 4-Acetoxy-2-(3-nitrophenylmethylene) acetoacetate (**29**): Yield: 44.0% (recrystallized from Et_2O). mp 87—89 °C. IR (Nujol): 1720, 1530, 1360, 760 cm^{-1}. MS *m*/*z*: 321 (M$^+$). The ratio of isomers was 2.2. ^{1}H-NMR (DMSO-d_6) δ: 1.20 and 1.29 (minor) (3H, t, J=7 Hz), 2.11 (minor) and 2.15 (3H, s), 4.29 (2H, q, J=7 Hz), 4.98 (minor) and 5.34 (2H, s), 7.70—8.10 (3H, m), 8.30—8.45 (2H, m). *Anal.* Calcd for $C_{15}H_{15}NO_7$: C, 56.07; H, 4.70; N, 4.35. Found: C, 56.05; H, 4.58; N, 4.28.

5-Oxo-2-phenyl-4-(4-pyridyl)-1,4,5,7-tetrahydrofuro[3,4-*d*]pyrimidine (30) A mixture of **28** (5.0 g), benzamidine hydrochloride (3.1 g), and Et_3N (3.3 ml) in *n*-BuOH (50 ml) was refluxed from 7 h. After evaporation of the solvent, the residue was dissoved in the mixture of AcOEt (100 ml) and H_2O (100 ml). The organic layer was successively washed with saturated $NaHCO_3$ aq. and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatogtraphy on SiO_2 (300 ml) with $CHCl_3$–acetone (20 : 1) as an eluent. The fractions containing **30** were collected and evaporated *in vacuo*. The residual crystals were recrystallized from Et_2O to afford **30** (1.87 g, 35.7%). mp 197—200 °C. IR (Nujol): 1730, 1640, 1600, 1280, 1210, 1015, 710 cm^{-1} MS *m*/*z*: 291 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 4.81 (1H, d, J=16 Hz), 4.95 (1H, d, J=16 Hz), 5.76 (1H, s), 7.30—7.70 (5H, m), 7.90—8.10 (2H, m), 8.50—8.70 (2H, m), 9.51 (1H, s). *Anal.* Calcd for $C_{17}H_{13}N_3O_2 \cdot 0.2H_2O$: C, 69.23; H, 4.57; N, 14.24. Found: C, 69.02; H, 4.40; N, 13.87. The lactone (**31**) was prepared in the same manner as described for **30**.

4-(3-Nitrophenyl)-5-oxo-2-phenyl-1,4,5,7-tetrahydrofuro[3,4-*d*]-pyrimidine (**31**): Yield: 19.9%. mp 174—175 °C. IR (Nujol): 3360, 1730, 1640, 1350, 1200 cm^{-1}. MS *m*/*z*: 335 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 4.86 (1H, d, J=17 Hz), 4.97 (1H, d, J=17 Hz), 5.94 (1H, s), 7.45—8.30 (9H, m), 9.54 (1H, s). *Anal.* Calcd for $C_{18}H_{13}N_3O_4$: C, 64.47; H, 3.90; N, 12.53. Found: C, 64.34; H, 3.83; N, 12.35.

5-Oxo-2-phenyl-4-(4-pyridyl)-5,7-dihydrofuro[3,4-*d*]pyrimidine (32) To a solution of **30** (1.70 g) in $CHCl_3$ (34 ml) was added activated MnO_2 (10 g), and the whole 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 recrystallized from IPE to afford **32** (0.98 g, 57.2%). IR (Nujol): 1760, 1585, 1560, 1540, 1215, 1040, 770 cm^{-1}. MS *m*/*z*: 293 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 5.56 (2H, s), 7.50—7.70 (3H, m), 8.23 (2H, d, J=4.5 Hz), 8.50—8.70 (2H, m), 8.87 (2H, d, J=4.5 Hz). Melting point and analytical data are included in Table II. Compound **33** was prepared in the same manner as described for **32**.

4-(3-Nitrophenyl)-5-oxo-2-phenyl-5,7-dihydrofuro[3,4-*d*]pyrimidine (**33**): IR (Nujol): 1760, 1620, 1590, 1560, 1530, 1350, 1040, 740 cm^{-1}. MS *m*/*z*: 333 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 5.58 (2H, s), 7.55—7.75 (3H, m), 7.94 (1H, dd, J=8, 8 Hz), 8.50—8.70 (3H, m), 8.75 (1H, d, J=8 Hz), 9.15—9.25 (1H, m). Yield, melting point and analytical data are included in Table III.

Ethyl 4-(4-Acetoxy-3-nitrophenyl)-6-methyl-2-phenyl-5-pyrimidinecarboxylate (4q) A mixture of **4p** (1.50 g) and acetic anhydride (7 ml) in THF (7 ml) was stirred for 5 h. The reaction mixture was evaporated *in vacuo*. The residue was purified by SiO_2 chromatography with *n*-hexane–AcOEt (10 : 1) as an eluent. The fractions containing **4q** were combined and evaporated *in vacuo*. The crystalline residue was recrystallized from Et_2O to afford **4q** (0.23 g, 14.8%). IR (Nujol): 1725, 1620, 1585, 1535 cm^{-1}. MS *m*/*z*: 421 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 1.10 (3H, t, J=7 Hz), 2.37 (3H, s), 2.67 (3H, s), 4.26 (2H, q, J=7 Hz), 7.46—7.73 (4H, m), 8.03—8.21 (1H, m), 8.33—8.53 (3H, m). Melting point and analytical data are included in Table IV.

Ethyl 6-Methyl-4-(2-methylthio-5-nitrophenyl)-2-phenyl-5-pyrimidinecarboxylate (4u) To a solution of **4r** (2.0 g) and MeSH–DMF solution (5 ml, MeSH 66 g in DMF 306 ml) in THF (25 ml), NaSMe (0.42 g) was added, the whole was stirred at room temperature for 3 h. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in a mixture of H_2O (50 ml) and AcOEt (100 ml). The organic layer was washed wish brine and dried over $MgSO_4$. After evaporating the solvent, the residue was chromatographed on SiO_2 with *n*-hexane–AcOEt (10 : 1) as an eluent. The fractions containing **4u** were combined and evaporated *in vacuo*. The crystalline residue was recrystallized from Et_2O to afford **4u** (0.4 g, 19.5%). IR (Nujol): 1730, 1605, 1580, 1520 cm^{-1}. MS *m*/*z*: 409 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 1.27 (3H, t, J=7 Hz), 2.53 (3H, s), 2.73 (3H, s), 4.12 (2H, q, J=7 Hz), 7.43—7.80 (4H, m), 8.07—8.60 (4H, m). Melting point and analytical data are included in Table IV.

Ethyl 6-Methyl-4-(2-methylsulfinyl-5-nitrophenyl)-2-phenyl-5-pyrimidinecarboxylate (4v) To a solution of **4u** (2.00 g) in $CHCl_3$ (10 ml), MCPBA (1.26 g) in a mixture of $CHCl_3$ (3 ml) and acetone (1 ml) was added dropwise at 4—6 °C, with stirring for 45 min. The reaction mixture was extracted with $CHCl_3$ (100 ml), successively washed with NaI aq., $NaHSO_3$ aq., $NaHCO_3$ aq. and brine, and dried over $MgSO_4$. After evaporating the solvent, the residue was chromatographed on SiO_2 with *n*-hexane–AcOEt (10 : 1) as an eluent. The fractions containing **4v** were combined and evaporated *in vacuo*. The crystalline residue was recrystallized from IPE to afford **4v** (1.3 g, 62.4%). IR (Nujol): 1725, 1530 cm^{-1}. MS *m*/*z*: 425 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 0.88 (3H, t, J=7 Hz), 2.68 (3H, s), 2.77 (3H, s), 4.08 (2H, q, J=7 Hz), 7.33—7.70 (3H, m), 8.17—8.77 (5H, m). Melting point and analytical data are included in Table IV.

Ethyl 6-Methyl-4-(2-methylsulfonyl-5-nitrophenyl)-2-phenyl-5-pyrimidinecarboxylate (4w) Compound **4w** was obtained according to a similar manner to that of **4v** from **4r** by using 2.5 eq of MCPBA (0.6 g, 27.7%). IR (Nujol): 1730, 1535, 1155 cm^{-1}. MS *m*/*z*: 441 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 0.88 (3H, t, J=7 Hz), 2.82 (3H, s), 3.37 (3H, s), 4.10 (2H, q, J=7 Hz), 7.52—7.77 (3H, m), 8.30—8.67 (5H, m). Melting point and analytical data are included in Table IV.

Diethyl 1,4-Dihydro-2-methyl-4-(3-nitrophenyl)-6-phenyl-3,5-pyridinedicarboxylate (36) A mixture of ethyl 3-aminocrotonate (3.5 g) and ethyl 3-nitrobenzylidenebenzoylacetate (8.0 g) in EtOH (80 ml) was refluxed for 4 h. Then one drop of conc. HCl aq. was added and the whole continued to be refluxed for 2 min. After cooling to room temperature, the precipitated crystalline product was collected by filtration and washed with EtOH to afford **36** (8.7 g, 82.5%). mp 200—201 °C. IR (Nujol): 3350, 1690, 1650, 1520, 1210, 1080 cm^{-1}. MS *m*/*z*: 436 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 0.70 (3H, t, J=7 Hz), 1.18 (3H, t, J=7 Hz), 2.30 (3H, s), 3.70 (2H, q, J=7 Hz), 4.09 (2H, q, J=7 Hz), 5.07 (1H, s), 7.30—8.20 (9H, m), 9.32 (1H, s). *Anal.* Calcd for $C_{24}H_{24}N_2O_6$: C, 66.04; H, 5.54; N, 6.41. Found: C, 66.20; H, 5.74; N, 6.43. Compound **34** was prepared by the same procedures employed in the preparation of **36**. Compounds **35** and **37** were also prepared by similar procedures, without the addition of conc. HCl aq., as was employed in the preparation of **36**.

Diethyl 1,4-Dihydro-2-methyl-6-phenyl-4-(4-pyridyl)-3,5-pyridinedicarboxylate (**34**): Yield 49.9%. mp 160—161 °C. IR (Nujol): 3200, 1680, 1600 cm^{-1}. MS *m*/*z*: 392 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 0.70 (3H, t, J=7 Hz), 1.18 (3H, t, J=7 Hz), 2.33 (3H, s), 3.70 (2H, q, J=7 Hz), 4.07 (2H, q, J=7 Hz), 4.97 (1H, s), 7.27 (2H, d, J=6 Hz), 7.30—7.50 (5H, m), 8.46 (2H, d, J=6 Hz), 9.25 (1H, s). *Anal.* Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.13. Found: C, 70.06; H, 6.47; N, 7.18.

Diethyl 1,4-Dihydro-2,6-dimethyl-4-(4-pyridyl)-3,5-pyridinedicarboxylate (**35**): Yield 57.1%. mp 186—188 °C. IR (Nujol): 3280, 3180, 1700, 1670, 1600, 780 cm^{-1}. MS *m*/*z*: 330 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 1.14 (6H, t, J=7 Hz), 2.29 (6H, s), 4.03 (4H, q, J=7 Hz), 4.89 (1H, s), 7.14 (2H, d, J=6 Hz), 8.41 (2H, d, J=6 Hz), 8.97 (1H, s). *Anal.* Calcd for $C_{18}H_{22}N_2O_4$: C, 65.43; H, 6.71; N, 8.47. Found: C, 65.45; H, 7.03; N, 8.41.

Diethyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**37**): Yield 35.6%. mp 164—166 °C. IR (Nujol): 3400, 1700, 1660, 1530 cm^{-1}. MS *m*/*z*: 374 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 1.14 (6H, t, J=7 Hz), 2.31 (6H, s), 3.99 (2H, q, J=7 Hz), 4.01 (2H, q, J=7 Hz), 4.99 (1H, s), 7.50—7.70 (2H, m), 7.95—8.05 (2H, m), 9.01 (1H, s). *Anal.* Calcd for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 61.10; H, 6.00;

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N, 7.44.

Diethyl 2-Methyl-4-(3-nitrophenyl)-6-phenyl-3,5-pyridinedicarboxylate (40) To a mixture of 8 N HNO_3 (40 ml) and $CHCl_3$ (40 ml) at room temperature, **36** (4.0 g) was added, and the mixture was stirred vigorously for 15 min. The mixture was adjusted to pH 8.0 with 10% NaOH aq.

The aqueous layer was extracted with $CHCl_3$ (40 ml). The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to afford **40** as an oil. A solution of **40** in EtOH (10 ml) was treated with a slight excess of HCl/EtOH to afford **40**·HCl (2.0 g, 46.3%). IR (Nujol): 1735, 1615, 1530 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.77 (3H, t, $J=7$ Hz), 0.93 (3H, t, $J=7$ Hz), 2.67 (3H, s), 3.85 (2H, q, $J=7$ Hz), 4.08 (2H, q, $J=7$ Hz), 7.40—8.50 (9H, m). Melting point and analytical data are included in Table III. Compounds **38**, **39** and **41** were prepared in a similar manner and their physical properties are listed in Tables II and III.

Oxidation of (3z) with Activated MnO_2 To a solution of **3z** (2.25 g) in $CHCl_3$ (30 ml) was added activated MnO_2 (12 g), and the mixture was refluxed for 1 h with vigorous stirring. After allowing the mixture 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 with *n*-hexane–AcOEt (20 : 1) as an eluent. The fractions containing **43** were collected and evaporated. The residual crystals were recrystallized from EtOH to afford **43** as red-brown plates (0.69 g, 33.8%). mp 244—245 °C (lit.[13]) 245—246 °C). The fractions further eluted with same solvent were combined and evaporated *in vacuo*. The residue was recrystallized from Et_2O to afford **42** (0.51 g, 42.0%). mp 93—94 °C. IR (Nujol): 1715, 1560, 1530, 1100 cm^{-1}. MS *m/z*: 242 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, $J=7$ Hz), 2.88 (3H, s), 4.41 (2H, q, $J=7$ Hz), 7.20—7.30 (3H, m), 8.20—8.80 (2H, m), 9.20 (1H, s). *Anal.* Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.63; H, 5.85; N, 11.55.

Pharmacological Methods Effect on Survival Time of Mice Subjected to Anoxia (100% N_2): Two male ICR mice of the same age were maintained in a closed glass chamber in which a current of nitrogen gas was circulated, and their survival time was measured. One mouse was pre-treated intraperitoneally with the test compound, and the other with the vehicle 30 min before the experiment. The test compounds were dissolved in a mixture of dimethyl sulfoxide (DMSO) and polyethyleneglycol (PEG) (1 : 1.5).

Effect on Lipid Peroxide Production in Rat Brain Mitochondria: Brain mitochondria from male Wistar rat were incubated with 100 μM ascorbic acid, 20 μM $FeSO_4$ and the test drug for 1 h at 37 °C. Malondialdehyde formed in the incubation mixture was measured by the thiobarbituric acid method according to Shimada *et al.*[15]) Test compounds were dissolved in EtOH.

Effect on Arachidonic Acid-Induced Cerebal Edema in Rat: Male wistar rats were anesthetized with Et_2O. The right lingual and occipital arteries were ligated. Retrograde cannulation was performed at the bifurcation of the external and internal carotid arteries *via* the upper part of the right external artery. Arachidonic acid dissolved in 10% EtOH and 0.4% Na_2CO_3 was injected into the internal carotid artery in a dose of 2 mg/0.2 ml/kg at a speed of 0.008 ml/min. Two hours after the injection of arachidonic acid, the animals were decapitated and the water content in the infarcted and contralateral hemisphere was measured. The test drug was administered intraperitoneally 30 min before the injection of arachidonic acid.

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7) Dihydropyrimidines (B) can exist as tautomeric mixtures of 1,4- and 1,6-dihydropyrimidines in solution.[9b]) Although 1,6-dihydropyrimidine was more stable than 1,4-dihydropyrimidine by our calculations of the energy of the dihydropyrimidine (**3a**) (**3a**: Ar = Ph, R_1 = OEt, R_2 = Me) by using the modified neglect of diatomic overlap method (unpublished results), in this paper we describe only 1,4-dihydropyrimidine to provide a consistent numbering between compounds B and C.

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