Synthetic Studies on Selective Type 4 Phosphodiesterase (PDE 4) Inhibitors. 1. Structure–Activity Relationships and Pharmacological Evaluation of 1,8-Naphthyridin-2(1*H*)-one Derivatives

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In order to develop novel and orally active phosphodiesterase (PDE) 4 inhibitors, random screening was performed using our chemical library to find YM-10335 possessing the 1,8-naphthyridin-2(1*H*)-one skeleton which is a completely different structure from rolipram. In this report, the syntheses and structure–activity relationships of the YM-10335 derivatives were described. Some compounds showed selective inhibitory activities for PDE 4 derived from human peripheral blood cells and no effect on the other PDE types (1, 2, 3, 5). The inhibition of the tumor necrosis factor-alpha (TNF-α) release *in vitro* and the carrageenan-induced pleurisy in rats were also described.

Key words 1,8-naphthyridin-2(1*H*)-one; phosphodiesterase 4 inhibitor; rolipram; YM-10335

Asthma is a respiratory disease symptomatically characterized by repeated stridor and paroxysm due to airway contraction. The number of patients with this disease is gradually increasing, especially in the industrial countries. Although a number of drugs have been used for the treatment of asthma, a new type of anti-asthmatic drug is strongly desirable due to the unsatisfactory effectiveness as well as adverse effects of existing drugs. Since asthma is believed to be a chronic inflammatory disease based on recent studies in pathophysiology, a drug, which can inhibit the inflammatory process, may offer a new therapeutic approach for curing for asthma patients. Therefore, compounds possessing inhibitory activities for both airway contraction and airway inflammation may become a novel therapeutic agent for asthma.

It is known that phosphodiesterase (PDE) can regulate some cell functions through the hydrolysis of cAMP.[1] Within the phosphodiesterases, as at least ten subclasses,[2—4] PDE 4 has recently attracted much attention due not only to their roles in airway contraction and airway inflammation proved by rolipram,[5—8] an authentic PDE 4 inhibitor, but also their locations in the airway smooth muscles and infiltrated cells.[9—11]

So far, several PDE 4 inhibitors mainly derived from rolipram have been developed and some of them were proved to be effective for the treatment of asthma.[12] However, adverse effects such as emesis and poor pharmacological profiles have made them difficult to undergo further clinical development.

In order to remove these drawbacks, the creation of a novel class of PDE 4 inhibitors structurally different form rolipram would be necessary. Therefore, random screening was performed using our chemical library, and YM-10335[13] was found to possess a structure completely different from rolipram. Unfortunately, YM-10335 has some problems such as a weak activity, moderate selectivity (PDE 2 *vs.* 4) and poor membrane permeability. To improve these biological profiles of YM-10335, several modification of YM-10355 were performed. As a consequence, several compounds with good *in vitro* as well as *in vivo* activities have been found and are going further extensive pharmacological evaluations. Herein, the syntheses, structure–activity relationships, and biological activities of a series of 1,8-naphthyridin-2(1*H*)-one derivatives are described.

Synthesis A procedure for the preparation of YM-10335 and the 5,7-disubstituted 1,8-naphthyridine derivatives have been reported.[13] In order to optimize the yields and to provide new compounds, the synthetic route was modified (Chart 1).

The 7-substituted derivatives without 5-substituents were synthesized by the methods shown in Chart 2. The 3-cyano or 3-carboxyl-2-chloropyridine derivatives were treated with the corresponding Grignard reagents, substituted by amines, acetylated, followed by aldol condensation and dehydration that produced the naphthyridine compounds (**7**). In the case of the 4-(2-chlorophenyl)- and 4-(3-bromophenyl)-derivatives, no desired compound was obtained by the Grignard re-

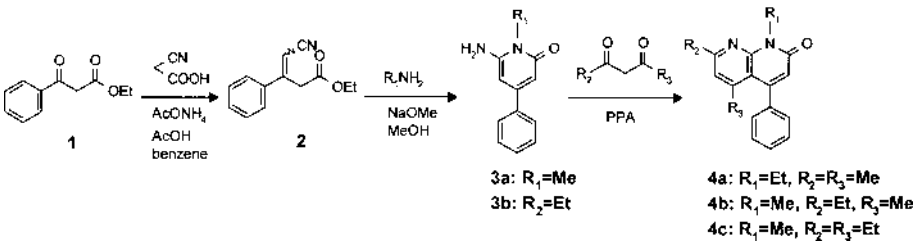

Chart 1

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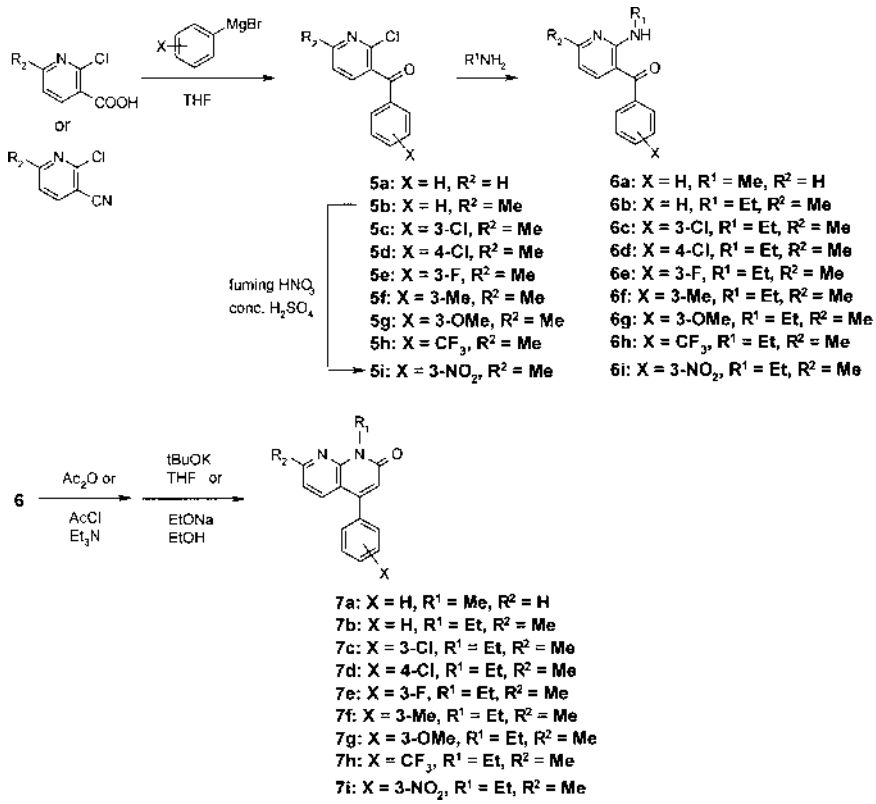


Chart 2

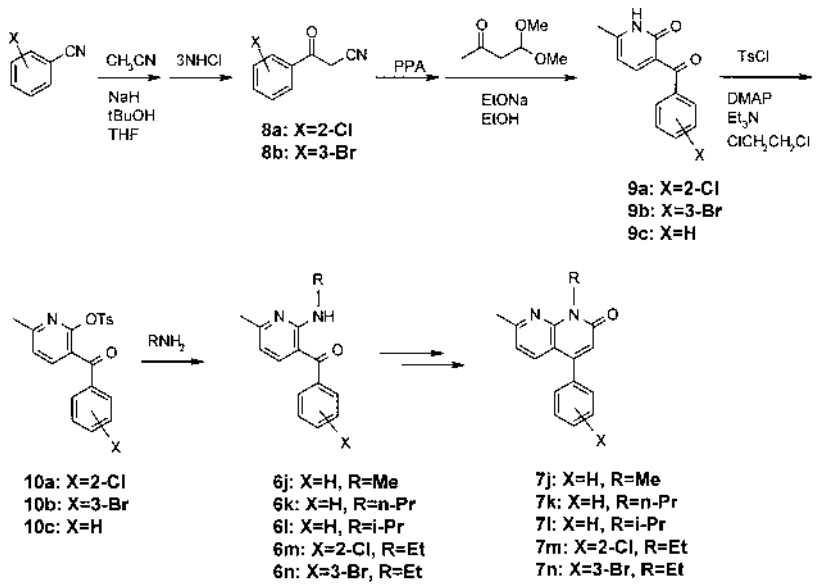


Chart 3

action. Therefore, another synthetic route for compound **6** was adopted as shown in Chart 3. Namely, the corresponding benzonitriles were converted to benzoylacetonitrile **8**, hydrolyzed by polyphosphoric acid (PPA), and cyclized using acetal to give pyridone **9**. Compound **9** was tosylated and substituted by amines similar to the chlorides (**5**) in Chart 2.

The 7-ethyl (**7o**, **p**) or 7-propyl (**7q**) derivatives were afforded by the further alkylation of the 7-methyl derivative (Chart 4).

Although the naphthyridine-2-one derivative without a 1-substituent (**14**) was not able to be synthesized by the above methods, we prepared it as shown in Chart 5. The 3-position of 2-pivaroylaminopyridine (**11**)[14] was lithiated by *n*-butyllithium, then benzoylated using *N*-methoxy-*N*-methylbenzamide to give the benzoylpyridine derivative (**12**). Compound **12** was treated with the lithium enolate of *tert*-butyl acetate and subsequently cyclized to 4-phenyl-1,8-naphthyridine-2-one (**14**).

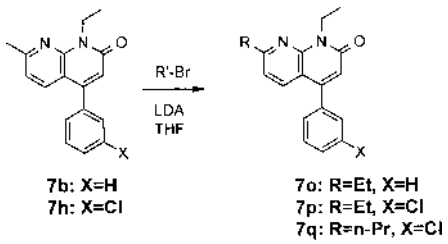


Chart 4

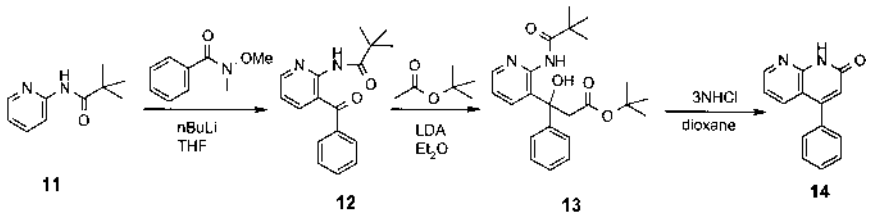


Chart 5

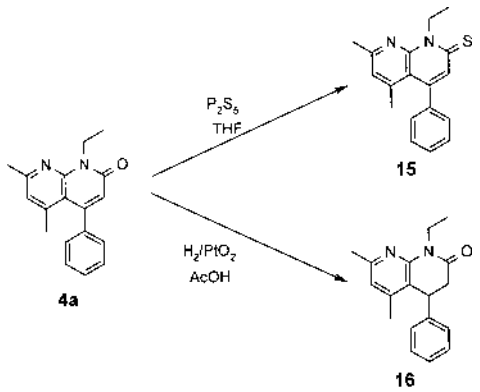


Chart 6

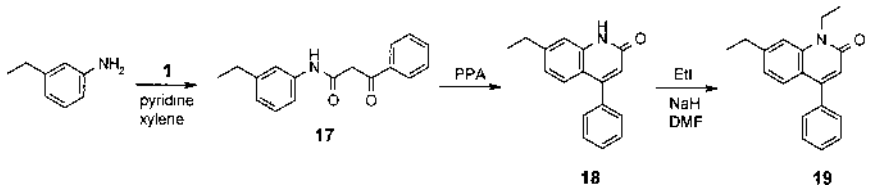


Chart 7

As shown in Chart 6, the carbonyl group at the 2-position of **4a** was converted to the thiocarbonyl group using phosphorus pentasulfide to give **15**, and the double bond at the 3,4-position of **4a** was reduced by the platinum dioxide-catalyzed hydrogenation to afford **16**.

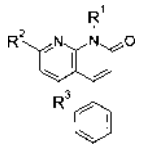
The quinolone derivative (**19**) was synthesized using the methods of Chart 7. Ethylaniline was treated with **1** under basic conditions and cyclized to the quinolone **18**, which was alkylated to obtain compound **19**.

Results and Discussion

In order to assess the structure–activity relationships, the compounds synthesized above were evaluated for their *in vitro* inhibitory activity against human leukocyte PDE 4.

At first, the effect of each methyl group in YM-10335 was investigated. As shown in Table 1, removal of all the methyl groups or two methyl groups at the 5- and 7-positions of YM-10335 showed no inhibitory activity (**14**, **7a**). Compound **7j** with methyl groups at both of the 1- and 7-positions on the naphthyridine ring was found to show increased inhibitory activity. Moreover, the 5-substituent should be unnecessary for inhibition since the activity of **7j** was better than that of YM-10335. To ascertain this expectation, replacement of the 5-methyl group in **4b** with an ethyl group (**4c**) was performed. The inhibitory activity of **4c** was decreased, therefore, the 1,7-substituted 1,8-naphthyridine derivatives are favorable to show PDE 4 inhibitory activity. Because of the steric interaction of the 5-substituent with the benzene ring at the 4-position, the 5-substituted 1,8-naphthyridine derivatives are unable to adopt a conformation ap-

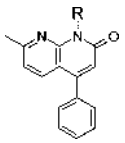
Table 1. Inhibitory Effect of 1,8-Naphthyridine Derivatives on Human PDE 4 (1, 5, and 7 Position)



Compound	R^1	R^2	R^3	IC_{50} (nM)[a] Enzyme
Rolipram				820
YM-10335	Methyl	Methyl	Methyl	220
4a	Ethyl	Methyl	Methyl	12
4b	Methyl	Ethyl	Methyl	23
4c	Methyl	Ethyl	Ethyl	350
7a	Methyl	H	H	>3000
7j	Methyl	Methyl	H	90
14	H	H	H	>3000

a) Data of *in vitro* experiment are expressed as mean from two separate experiments, and the individual experiment was performed in triplicate. The method of measurement is described in Experimental.

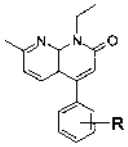
Table 2. Inhibitory Effect of 1-Substituted 1,8-Naphthyridine Derivatives on Human PDE 4



Compound	R	IC_{50} (nM)[a] Enzyme
7j	Methyl	90
7b	Ethyl	5.9
7k	*n*-Propyl	24
7l	iso-Propyl	68

a) Data of *in vitro* experiment are expressed as mean from two separate experiments, and the individual experiment was performed in triplicate. The method of measurement is described in Experimental.

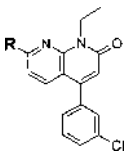
Table 3. Inhibitory Effect of 4-Substituted 1,8-Naphthyridine Derivatives on Human PDE 4



Compound	R	IC_{50} (nM)[a] Enzyme
7b	H	5.9
7c	3-Chloro	1.1
7d	4-Chloro	35
7m	2-Chloro	8.4
7e	3-Fluoro	9.5
7f	3-Methyl	2.8
7g	3-Methoxy	26
7h	3-Trifluoromethyl	130
7i	3-Nitro	1.2
7n	3-Bromo	1.2

a) Data of *in vitro* experiment are expressed as mean from two separate experiments, and the individual experiment was performed in triplicate. The method of measurement is described in Experimental.

Table 4. Inhibitory Effect of 7-Substituted 1,8-Naphthyridine Derivatives on Human PDE 4



Compound	R	IC_{50} (nM)[a] Enzyme
7c	Methyl	1.1
7p	Ethyl	0.61
7q	*n*-Propyl	58

a) Data of *in vitro* experiment are expressed as mean from two separate experiments, and the individual experiment was performed in triplicate. The method of measurement is described in Experimental.

propriate for PDE 4 inhibition.

Because it was found that the 1,7-disubstituted derivatives are favorable for showing activity, each substituent was modified. As shown in Table 2, replacement of the of the 1-methyl group in **7j** with an ethyl group (**7b**) increased the inhibitory activity up to the nanomolar level, however replacement with the *n*- and *i*-propyl groups only provided a moderate increase (**7k**, **7l**). As for the 1-substituents, the ethyl group is crucial for PDE 4 inhibition and very sensitive for modification.

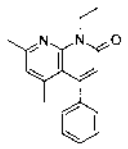
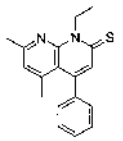
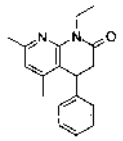
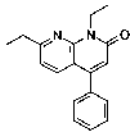
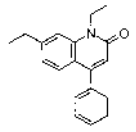
Replacement of the 7-methyl group in **7c** with an ethyl group (**7p**) slightly increased the inhibitory activity, whereas replacement with a *n*-propyl group (**7q**) resulted in significantly reduced the activity (Table 4). In the case of the 7-substituent, a small alkyl group such as a methyl or ethyl is favorable.

Secondly, the effect of the substituent on the benzene ring at the 4-position of the naphthyridine on the PDE 4 inhibitory activity was examined (Table 3). The introduction of a chlorine atom at the *meta* position (**7c**) increased the potency over **7b** by almost 5—6 fold, whereas, its introduction at the *ortho* (**7m**) or *para* (**7d**) position slightly reduced the activity. Various *meta* substituents were introduced, and the bromo- (**7n**), methyl- (**7f**), and nitro- (**7i**) derivatives showed potent activities, while the fluoro- (**7e**) and methoxy- (**7g**) derivatives showed slightly reduced activities. Based on these results, there was no significant difference between the electron-donating and electron-withdrawing groups. It is unclear why the trifluoromethyl group (**7h**) showed low activity. Among the halogen substituents, the fluorine derivative (**7e**) showed low activity compared with the other halogen groups, therefore, an unfavorable interaction seems to be present between the PDE 4 enzyme and fluorine atom.

Finally, the effects of the nitrogen atom at the 8-position and the pyridone moiety of the 1,8-naphthyridine ring system on the PDE 4 inhibitory activity were examined. As shown in Table 5, replacement of the carbonyl group in compound **4a** with the thiocarbonyl group (**15**) slightly reduced the activity. This slight difference is caused by the hydrogen bonding acceptor ability based on the difference in the bond length and electron-withdrawing activity between the carbonyl and thio-

carbonyl groups. Reduction of the double bond in the pyridone moiety (**16**) dramatically reduced the potency. Although it is assumed that the existence of π electron should be necessary, it is the main reason of this result that appropriate spatial positioning of the phenyl group at 4-position relative to 1,8-naphthyridine ring system is essential for PDE 4 inhibition. Exchanging the nitrogen atom of **7o** for a carbon atom (**19**) resulted in the loss of potency. Since the basicity of this nitrogen atom is not so high, this might occur due to the difference as a hydrogen bonding acceptor. It is also possible to consider that the repulsion between the newly generated hydrogen at the 8-position and the 1-substituents would be unfavorable. Another experiment is needed for this clarification.

Table 5. Inhibitory Effect of Modified 1,8-Naphthyridine Ring Derivatives on Human PDE 4

Compound	Structure	IC_{50} (nM)[a] Enzyme
4a		12
15		57
16		1600
7o		1.8
19		220

a) Data of *in vitro* experiment are expressed as mean from two separate experiments, and the individual experiment was performed in triplicate. The method of measurement is described in Experimental.

These facts described above suggested that three factors affected the PDE 4 inhibitory activity in this series. First, the appropriate size of the substituents such as the methyl and ethyl groups at the 1- and 7-positions on the 1,8-naphthyridin-2-one structure is necessary for inhibitory activity. Second, the benzene ring at the 4-position of the naphthyridine has the appropriate position and direction. And third, the nitrogen atom at the 8-position and carbonyl moiety of the 1,8-naphthyridine ring system function as an acceptor of the hydrogen bonding against the PDE 4 enzyme.

The pharmacophore model of many PDE 4 inhibitors was reported by Crespo and co-workers,[15] in which PDE 4 inhibitors related to the nitraquazone structure possess three hydrogen bond acceptors and three aromatic regions. However, our 1,8-naphthyridine derivatives possess two hydrogen bond acceptors and two aromatic regions. From these points of view, the 1,8-naphthyridine compounds were novel types of PDE 4 inhibitors.

Six compounds showing potent PDE 4 inhibitory activities, as well as YM-10335, rolipram, and CDP-840, were evaluated for their PDE isozyme selectivities and lipopolysaccharide (LPS)-induced tumor necrosis factor-alpha (TNF-α) release *in vitro* (Table 6). All compounds showed good selectivities of more than 500 times for PDE 4 against other PDE isozymes. In the test of the TNF-α release, they showed good inhibitory activities except for **7b**.

Furthermore, five compounds (**7c**, **f**, **n**, **o**, **p**), possessing IC_{50} values less than 100 nM in the test of the TNF-α release, were tested in the carrageenan-induced pleurisy model for evaluation of their ability to inhibit cell infiltration and oral effectiveness (Table 7). Three compounds (**7c**, **n**, **p**) showed

Table 7. *In Vivo* Activities of 1,8-Naphthyridine Derivatives

No.	Inhibition of carrageenan-induced pleurisy in rats (*p.o.*)
	ED_{30} (mg/kg)[a]
7c	15
7f	>30
7n	11
7o	>30
7p	15

a) Data of *in vivo* experiments showed mean of 6 animals in one group. The method of measurement is described in Experimental.

Table 6. *In Vitro* Activities of 1,8-Naphthyridine Derivatives

No.	PDE 4 inhibition IC_{50} (nM)[a]	PDEs inhibition IC_{50} (μM)[a]				TNF-α inhibition IC_{50} (nM)[a]
		1	2	3	5	
YM-10335	220	70.9	7.93	245	>100	>100
7b	5.9	>10	>10	>10	1.6	>100
7c	1.1	>10	>10	>10	1.0	41
7f	2.8	0.57	>3	>3	0.90	22
7n	1.2	>3	>3	>3	0.55	33
7o	1.8	>10	>10	>10	0.91	62
7p	0.61	>3	>3	>3	0.48	20
Rolipram	820	>100	>100	>100	>100	76
CDP-840	19	>30	>30	>30	>30	19

a) Data of *in vitro* experiment are expressed as mean from two separate experiments, and the individual experiment was performed in triplicate. The method of measurement is described in Experimental.

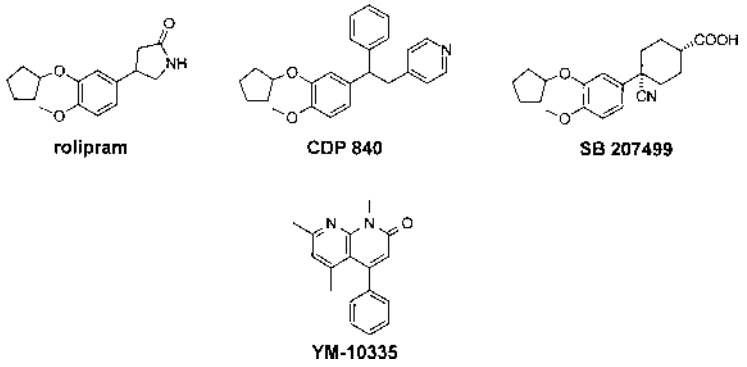


Fig. 1

inhibitory activities and their ED_{30} values were 15, 11, and 15 mg/kg, respectively, whereas **7f** and **7o** showed no oral activity.

In conclusion, a novel class of PDE 4 inhibitors, YM-10335, was found by chemical file screening and structural modification of YM-10335 led us to discover highly potent and selective compounds. These YM-10335 derivatives also showed potent inhibitory activities of the *in vitro* TNF-α release and *in vivo* carrageenan-induced pleurisy model. Further modification and pharmacological evaluations are now in progress.

Experimental

Chemistry Melting points were determined on a Yanaco micro-melting apparatus and are uncorrected. Proton magnetic resonance (^{1}H-NMR) spectra were obtained in $CDCl_3$ or dimethylsulfoxide-d_6 (DMSO-d_6) using a JEOL JNM-EX90, JNM-EX400, JNM-GX500 or JNM-A500 spectrometer. Chemical shifts are recorded in parts per million (δ), downfield relative to tetramethylsilane as the internal standard. Mass spectra (MS) were recorded on a JEOL JMS-DX300 or a Hitachi M-80 mass spectrometer. Elemental analyses were carried out on Yanaco MT-3 or MT-5 CHN analyzer and a Yokogawa IC 7000S Ion Chromatoanalyzer. Chromatographic separations were performed using a silica gel column (Wakogel C-200). Analytical thin-layer chromatography (TLC) was carried out on precoated glass plates (Merck Kieselgel 60F254).

6-Amino-1-ethyl-4-phenyl-2(1*H*)-pyridone (**3b**): Ethyl 4-cyano-3-phenyl-3-butenoate[13] (**2**, 29.0 g, 0.13 mol) and 28% ethylamine–methanol solution (41 g) were added to a methanol solution (120 ml) of sodium (4.1 g, 0.17 mol), and the mixture was stirred for 20 h at room temperature. The reaction solution was poured onto ice water and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was washed with diethyl ether–diisopropyl ether to provide **3b** (16.5 g, 57%) as a gray solid. ^{1}H-NMR (DMSO-d_6) δ: 1.15 (3H, t, J=7.0 Hz), 4.00 (2H, q, J=7.0 Hz), 5.68 (1H, d, J=2.1 Hz), 5.74 (1H, d, J=2.1 Hz), 6.58 (2H, s), 7.35—7.60 (5H, m). MS m/z: 214 (M^+).

General Procedure A 1-Ethyl-5,7-dimethyl-4-phenyl-1,8-naphthyridin-2(1*H*)-one (**4a**): A mixture of diphosphorus pentoxide (10.7 g) and phosphoric acid (5 ml) was stirred at 140 °C until it became transparent. **3b** (2.14 g, 10 mmol) and acetylacetone (1.1 ml, 10 mmol) were then added to this solution, and the mixture was stirred at 140 °C for 3 h. The reaction solution was poured onto ice water, made alkaline by adding a 1 N sodium hydroxide aqueous solution and then extracted with ethyl acetate. After drying the organic layer with anhydrous magnesium sulfate, the magnesium sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (toluene–ethyl acetate) to give **4a** (2.10 g, 76%). Recrystallization from diisopropyl ether–hexane provided an analytical sample as colorless minute prisms, mp 113—114 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7.0 Hz), 1.81 (3H, s), 2.56 (3H, s), 4.66 (1H, q, J=7.0 Hz), 6.53 (1H, s), 6.75 (1H, s), 7.25—7.30 (2H, m), 7.41—7.43 (3H, m). MS m/z: 278 (M^+). *Anal.* Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.93; H, 6.54; N, 9.93.

The following compounds were obtained in the same manner as described in general procedure A.

7-Ethyl-1,5-dimethyl-4-phenyl-1,8-naphthyridin-2(1*H*)-one (**4b**): 92% yield; mp 88—88.5 °C (diisopropyl ether–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.0 Hz), 1.83 (3H, s), 2.84 (2H, q, J=7.3 Hz), 3.90 (3H, s), 6.55 (1H, s), 6.76 (1H, s), 7.22—7.30 (2H, m), 7.40—7.45 (3H, m). MS m/z: 278 (M^+). *Anal.* Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.67; H, 6.54; N, 10.05.

5,7-Diethyl-1-methyl-4-phenyl-1,8-naphthyridin-2(1*H*)-one (**4c**): 69% yield; mp 68—69 °C (diisopropyl ether–hexane). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, J=7.3 Hz), 1.37 (3H, t, J=7.3 Hz), 2.18 (2H, q, J=7.3 Hz), 2.86 (2H, q, J=7.3 Hz), 3.90 (3H, s), 6.52 (1H, s), 6.85 (1H, s), 7.30—7.35 (2H, m), 7.38—7.45 (3H, m). MS m/z: 292 (M^+). *Anal.* Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.17; H, 6.98; N, 9.62.

General Procedure B. Grignard Reaction with 2-Chloro-6-methylnicotinic Acid 2-Chloro-3-(3-fluorobenzoyl)-6-methylpyridine (**5e**): To a stirred solution of 3-bromochlorobenzene (46 g, 262 mmol) in anhydrous tetrahydrofuran (400 ml) was slowly added magnesium turnings (6.3 g, 262 mmol). After the exothermal reaction was completed, the reaction mixture was cooled to −20 °C, and 2-chloro-6-methylnicotinic acid (21.1 g, 122 mmol) was added all at one time. The reaction mixture was stirred overnight at room temperature, diluted with saturated ammonium chloride aqueous solution, and extracted by ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using chloroform as an eluent to provide 5 h (11.0 g, 36%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.64 (3H, s), 7.24 (1H, d, J=7.6 Hz), 7.28—7.36 (1H, m), 7.42—7.56 (3H, m), 7.66 (1H, d, J=7.6 Hz). MS m/z: 249 (M^+).

The following compounds were obtained in the same manner as described in general procedure B.

3-Benzoyl-2-chloropyridine (**5a**): 55% yield; ^{1}H-NMR ($CDCl_3$) δ: 7.39 (1H, dd, J=7.8, 4.9 Hz), 7.50 (2H, t, J=7.8 Hz), 7.66 (1H, t, J=7.8 Hz), 7.75 (1H, dd, J=7.8, 2.0 Hz), 7.81 (1H, dd, J=8.3, 1.5 Hz), 8.55 (1H, dd, J=4.9, 2.0 Hz). MS m/z: 217 (M^+).

3-Benzoyl-2-chloro-6-methylpyridine (**5b**): 57% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.63 (3H, s), 7.22 (1H, d, J=7.6 Hz), 7.46—7.50 (2H, m), 7.60—7.66 (2H, m), 7.79—7.82 (2H, m). FAB-MS m/z: 232 $[M+H]^+$.

2-Chloro-3-(3-chlorobenzoyl)-6-methylpyridine (**5c**): 44% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.64 (3H, s), 7.24 (1H, d, J=7.3 Hz), 7.43 (1H, t, J=7.9 Hz), 7.60 (1H, m), 7.65 (2H, m), 7.78 (1H, s). FAB-MS m/z: 266 $[M+H]^+$.

2-Chloro-3-(4-chlorobenzoyl)-6-methylpyridine (**5d**): 37% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.63 (3H, s), 7.24 (1H, d, J=7.6 Hz), 7.46 (2H, d, J=8.8 Hz), 7.65 (1H, d, J=7.6 Hz), 7.75 (2H, d, J=8.8 Hz). FAB-MS m/z: 266 $[M+H]^+$.

2-Chloro-3-(3-methylbenzoyl)-6-methylpyridine (**5f**): 56% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 2.63 (3H, s), 7.22 (1H, t, J=7.3 Hz), 7.43 (1H, d, J=7.3 Hz), 7.57 (1H, d, J=7.3 Hz), 7.60—7.65 (2H, m). MS m/z: 245 (M^+).

2-Chloro-3-(3-methoxybenzoyl)-6-methylpyridine (**5g**): 46% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.63 (3H, s), 3.86 (3H, s), 7.15—7.19 (1H, m), 7.22 (1H, d, J=7.4 Hz), 7.26—7.29 (1H, m), 7.36 (1H, t, J=7.9 Hz), 7.40—7.43 (1H, m), 7.64 (1H, d, J=7.4 Hz). FAB-MS m/z: 262 $[M+H]^+$.

2-Chloro-6-methyl-3-(3-trifluoromethylbenzoyl)pyridine (**5h**): 34% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.65 (3H, s), 7.27 (1H, d, J=7.8 Hz), 7.64 (1H, t, J=7.8 Hz), 7.69 (1H, d, J=7.8 Hz), 7.88 (1H, d, J=7.8 Hz), 7.96 (1H, d,

J=7.8 Hz), 8.08 (1H, s). FAB-MS m/z: 300 $[M+H]^+$.

2-Chloro-6-methyl-3-(3-nitrobenzoyl)pyridine (5i) **5b** (3.00 g, 12.9 mmol) dissolved in concentrated sulfuric acid (40 ml) was cooled to below 5 °C, then fuming nitric acid (1.0 ml) was slowly added dropwise, followed by stirring for 30 min. The reaction solution was poured into ice-water, neutralized with a sodium hydroxide aqueous solution and then extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After removing the magnesium sulfate by filtration, the solvent was evaporated under reduced pressure and the resulting residue was washed with ethyl acetate–diisopropyl ether to give **5i** (1.81 g, 51%) as a solid. ^{1}H-NMR ($CDCl_3$) δ: 2.67 (3H, s), 7.30 (1H, d, J=7.6 Hz), 7.72 (1H, t, J=7.6 Hz), 8.15 (1H, m), 8.48 (2H, m), 8.60 (1H, m). MS m/z: 276 (M^+).

General Procedure C. Substitution by Alkylamines 2-Ethylamino-3-(3-fluorobenzoyl)-6-methylpyridine (**6e**): A mixture of **5i** (5.0 g, 20 mmol) and a 70% ethylamine aqueous solution (15 ml) was stirred for 4 h at 100 °C in a sealed tube. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic layer was subsequently washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using hexane–ethyl acetate as the eluent to provide **6e** (4.35 g, 84%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.3 Hz), 2.44 (3H, s), 3.64 (2H, m), 6.33 (1H, d, J=8.1 Hz), 7.17—7.27 (2H, m), 7.31 (1H, dt, J=7.3, 1.3 Hz), 7.42 (1H, dt, J=8.1, 5.5 Hz), 7.57 (1H, d, J=8.1 Hz), 8.84 (1H, br s). FAB-MS m/z: 259 $[M+H]^+$.

The following compounds were obtained in the same manner as described in general procedure B.

3-Benzoyl-2-methylaminopyridine (**6a**): 89% yield; ^{1}H-NMR ($CDCl_3$) δ: 3.14 (3H, d, J=4.9 Hz), 6.49 (1H, dd, J=7.8, 4.9 Hz), 7.45—7.60 (5H, m), 7.73 (1H, dd, J=7.8, 2.0 Hz), 8.35 (1H, dd, J=4.9, 2.0 Hz), 8.75 (1H, br s). MS m/z: 212 (M^+).

3-Benzoyl-2-ethylamino-6-methylpyridine (**6b**): Without purification.

3-(3-Chlorobenzoyl)-2-ethylamino-6-methylpyridine (**6c**): 56% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.0 Hz), 2.44 (3H, s), 3.64 (2H, m), 6.33 (1H, d, J=7.9 Hz), 7.35—7.60 (5H, m), 8.84 (1H, br s). MS m/z: 274 (M^+).

3-(4-Chlorobenzoyl)-2-ethylamino-6-methylpyridine (**6d**): 92% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.3 Hz), 2.44 (3H, s), 3.63 (2H, m), 6.32 (1H, d, J=8.1 Hz), 7.42 (2H, d, J=8.3 Hz), 7.50 (2H, d, J=8.3 Hz), 7.55 (1H, d, J=8.1 Hz), 8.81 (1H, br s). FAB-MS m/z: 275 $[M+H]^+$.

2-Ethylamino-3-(3-methylbenzoyl)-6-methylpyridine (**6f**): 83% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.3 Hz), 2.40 (3H, s), 2.43 (3H, s), 3.63 (2H, m), 6.31 (1H, d, J=7.9 Hz), 7.32 (3H, s), 7.36 (1H, s), 7.61 (1H, d, J=7.9 Hz), 8.85 (1H, br s). MS m/z: 254 (M^+).

2-Ethylamino-3-(3-methoxybenzoyl)-6-methylpyridine (**6g**): 83% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.4 Hz), 2.43 (3H, s), 3.64 (2H, m), 3.84 (3H, s), 6.32 (1H, d, J=8.1 Hz), 7.02—7.12 (3H, m), 7.34 (1H, t, J=7.8 Hz), 7.63 (1H, d, J=8.1 Hz), 8.85 (1H, br s). FAB-MS m/z: 271 $[M+H]^+$.

2-Ethylamino-3-(3-trifluoromethylbenzoyl)-6-methylpyridine (**6h**): 86% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.4 Hz), 2.45 (3H, s), 3.66 (2H, m), 6.34 (1H, d, J=8.3 Hz), 7.51 (1H, d, J=8.3 Hz), 7.59 (1H, t, J=7.9 Hz), 7.72 (1H, d, J=7.9 Hz), 7.76 (1H, d, J=7.9 Hz), 8.87 (1H, br s). MS m/z: 308 (M^+).

2-Ethylamino-6-methyl-3-(3-nitrobenzoyl)pyridine (**6i**): 56% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.4 Hz), 2.46 (3H, s), 3.63—3.70 (2H, m), 6.35 (1H, d, J=8.0 Hz), 7.49 (1H, d, J=8.0 Hz), 7.66 (1H, t, J=8.0 Hz), 7.87 (1H, dt, J=8.0, 1.3 Hz), 8.35—8.40 (2H, m), 8.88 (1H, br s). MS m/z: 285 (M^+).

General Procedure D 3-(2-Chlorophenyl)-3-oxopropanenitrile (**8a**): A solution of 2-chlorobenzonitrile (50.0 g, 363 mmol), acetonitrile (21.0 ml, 402 mmol) and *tert*-butanol (4.0 ml, 42 mmol) in tetrahydrofuran (200 ml) was added dropwise to a mixture of sodium hydride/60% oil dispersion (16.0 g, 400 mmol) and tetrahydrofuran (200 ml), and the mixture was stirred at 40 °C for 8 h. The reaction mixture was poured onto ice water and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The magnesium sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was then dissolved in chloroform (350 ml) and then 3 N hydrochloric acid (300 ml) was added. The mixture was stirred at room temperature for 4 h and organic layer was separated. The aqueous layer was extracted with chloroform and the chloroform layer was combined. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. Magnesium sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography hexane–ethyl acetate as the eluent and the resulting solid was washed with chloroform/hexane to provide **8a** (23.6 g, 36%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 4.15 (2H, s), 7.38—7.54 (3H, m), 7.64 (1H, dd, J=7.8, 1.4 Hz). MS m/z: 179 (M^+).

The following compound was obtained in the same manner as described in general procedure D.

3-(3-Bromophenyl)-3-oxopropanenitrile (**8b**): 75% yield; ^{1}H-NMR ($CDCl_3$) δ: 4.06 (2H, s), 7.42 (1H, t, J=7.8 Hz), 7.77—7.87 (2H, m), 8.06 (1H, t, J=1.8 Hz). MS m/z: 223, 225 (M^+).

General Procedure E 3-(2-Chlorobenzoyl)-6-methyl-2-pyridone (**9a**): A mixture of **8a** (20.0 g, 111 mmol) and 75% diphosphorus pentoxide (100 ml) was stirred at 100 °C for 2 h. The reaction solution was poured onto ice water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate aqueous solution and dried over anhydrous magnesium sulfate. The magnesium sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethanol (250 ml) and mixed with 1,1-dimethoxy-3-butanone (20 ml, 151 mmol) and sodium ethoxide (9.0 g, 132 mmol). The mixture was stirred overnight under reflux. The reaction mixture was poured onto ice-water and extracted with chloroform. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After removing the magnesium sulfate by filtration, the solvent was evaporated under reduced pressure and the resulting residue was washed with ether to give **9a** (24.2 g, 84%) as a solid. ^{1}H-NMR (DMSO-d_6) δ: 2.27 (3H, s), 6.21 (1H, d, J=7.4 Hz), 7.31—7.54 (4H, m), 7.92 (1H, d, J=7.4 Hz), 12.11 (1H, br s). FAB-MS m/z: 248 $[M+H]^+$.

The following compounds were obtained in the same manner as described in general procedure E.

3-(3-Bromobenzoyl)-6-methyl-2-pyridone (**9b**): 79% yield; ^{1}H-NMR (DMSO-d_6) δ: 2.28 (3H, s), 6.21 (1H, d, J=7.6 Hz), 7.44 (1H, t, J=8.4 Hz), 7.68 (1H, d, J=7.2 Hz), 7.74 (1H, d, J=7.6 Hz), 7.76—7.82 (2H, m), 12.16 (1H, br s). FAB-MS m/z: 292, 294 $[M+H]^+$.

3-Benzoyl-6-methyl-2-pyridone (**9c**): 57% yield; ^{1}H-NMR (DMSO-d_6) δ: 2.27 (3H, s), 6.17 (1H, d, J=6.8 Hz), 7.47 (2H, t, J=7.9 Hz), 7.59 (1H, t, J=7.4 Hz), 7.64 (1H, d, J=6.8 Hz), 7.71 (2H, d, J=7.4 Hz), 12.1 (1H, br s). MS m/z: 213 (M^+).

General Procedure F 3-(2-Chlorobenzoyl)-6-methyl-2-pyridyl 4-Methylbenzenesulfonate (**10a**): A mixture of **9a** (20.0 g, 80 mmol), dichloroethane (250 ml), *p*-toluenesulfonyl chloride (16.8 g, 88 mmol), triethylamine (12.2 ml, 88 mmol), and 4-dimethylaminopyridine (980 mg, 8 mmol) was stirred for 2 h at room temperature. The reaction mixture was subsequently washed with water, 1 N hydrochloric acid, and saturated sodium bicarbonate aqueous solution. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using hexane–ethyl acetate as the eluent to provide **10a** (30.9 g, 96%) as a syrup. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s), 2.49 (3H, s), 7.16 (1H, d, J=7.8 Hz), 7.26—7.42 (5H, m), 7.46 (1H, dd, J=7.5, 1.6 Hz), 7.78 (2H, d, J=7.3 Hz), 8.04 (1H, d, J=7.8 Hz). FAB-MS m/z: 402 $[M+H]^+$.

The following compounds were obtained in the same manner as described in general procedure F.

3-(3-Bromobenzoyl)-6-methyl-2-pyridyl 4-Methylbenzenesulfonate (**10b**): 89% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s), 2.56 (3H, s), 7.19 (1H, d, J=8.0 Hz), 7.25—7.34 (3H, m), 7.62 (1H, d, J=8.0 Hz), 7.68 (1H, d, J=8.4 Hz), 7.74 (2H, d, J=8.4 Hz), 7.81—7.84 (2H, m). FAB-MS m/z: 446, 448 $[M+H]^+$.

3-Benzoyl-6-methyl-2-pyridyl 4-Methylbenzenesulfonate (**10c**): Quantitative yield; ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 2.54 (3H, s), 7.17 (1H, d, J=7.8 Hz), 7.24 (2H, d, J=8.3 Hz), 7.45 (2H, t, J=7.8 Hz), 7.59 (1H, t, J=7.3 Hz), 7.72—7.76 (2H, m), 7.80 (1H, d, J=7.8 Hz). FAB-MS m/z: 368 $[M+H]^+$.

General Procedure G. Substitution by Alkylamines 3-(2-Chlorobenzoyl)-2-ethylamino-6-methylpyridine (**6m**): A mixture of **10a** (8.0 g, 20 mmol), 70% ethylamine aqueous solution (10 ml), and toluene (30 ml) was stirred for 1.5 h at 100 °C in a sealed tube. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed well with water. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using hexane–ethyl acetate as the eluent to provide **6m** (5.36 g, 98%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.3 Hz), 2.42 (3H, s), 3.66 (2H, m), 6.28 (1H, d, J=8.3 Hz), 7.24—7.46 (4H, m), 9.02 (1H, br s). FAB-MS m/z: 275 $[M+H]^+$.

The following compounds were obtained in the same manner as described in general procedure G.

3-Benzoyl-6-methyl-2-methylaminopyridine (**6j**): 84% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s), 3.14 (3H, d, J=4.9 Hz), 6.33 (1H, d, J=7.9 Hz), 7.42—7.56 (5H, m), 7.61 (1H, d, J=7.9 Hz), 8.85 (1H, br s). FAB-MS m/z: 227 $[M+H]^+$.

3-Benzoyl-6-methyl-2-propylaminopyridine (**6k**): 93% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.3 Hz), 1.72 (2H, m), 2.43 (3H, s), 3.58 (2H, m), 6.31 (1H, d, J=8.1 Hz), 7.42—7.56 (5H, m), 7.61 (1H, d, J=8.1 Hz), 8.95 (1H, br s). FAB-MS m/z: 255 $[M+H]^+$.

3-Benzoyl-2-isopropylamino-6-methylpyridine (**6l**): 52% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.31 (6H, d, J=6.4 Hz), 2.43 (3H, s), 4.51 (1H, m), 6.30 (1H, d, J=8.1 Hz), 7.41—7.56 (5H, m), 7.60 (1H, d, J=8.1 Hz), 8.83 (1H, br d, J=6.3 Hz). FAB-MS m/z: 255 $[M+H]^+$.

3-(3-Bromobenzoyl)-2-ethylamino-6-methylpyridine (**6n**): 59% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.3 Hz), 2.44 (3H, s), 3.64 (2H, m), 6.33 (1H, d, J=7.9 Hz), 7.32 (1H, t, J=7.9 Hz), 7.45 (1H, d, J=7.3 Hz), 7.55 (1H, d, J=7.9 Hz), 7.63 (1H, dd, J=7.9, 1.2 Hz), (1H, s), 7.68 (1H, s), 8.83 (1H, br s). FAB-MS m/z: 319, 321 $[M+H]^+$.

General Procedure H. Acetylation and Cyclization 1-Ethyl-4-(3-fluorophenyl)-7-methyl-1,8-naphthyridin-2(1*H*)-one (**7e**): To a solution of **6e** (2.25 g, 8.7 mmol) in dichloroethane (30 ml) was added acetyl chloride (1.25 ml, 17.6 mmol) and 4-dimethylaminopyridine (1.17 g, 9.6 mmol), and the solution was stirred under reflux for 1 h. The reaction mixture was allowed to cool to room temperature and subsequently washed with water, 1 N hydrochloric acid, and saturated sodium bicarbonate aqueous solution. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to provide the crude *N*-[3-(3-fluorobenzoyl)-6-methyl-2-pyridyl]-*N*-ethylacetamide. To the *N*-[3-(3-fluorobenzoyl)-6-methyl-2-pyridyl]-*N*-ethylacetamide was added ethanol (30 ml) and sodium ethoxide (220 mg,) and stirred under reflux for 30 min. The reaction mixture was allowed to cool to room temperature and diluted with chloroform. The organic layer was subsequently washed with 1 N hydrochloric acid, and saturated sodium bicarbonate aqueous solution, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using hexane–ethyl acetate as the eluent to provide **7e** (1.18 g, 95%). Recrystallization from ethyl acetate–diisopropyl ether provided an analytical sample as colorless minute prisms, mp 106—107 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7.0 Hz), 2.64 (3H, s), 4.65 (2H, q, J=7.0 Hz), 6.65 (1H, s), 6.98 (1H, d, J=7.8 Hz), 7.09—7.21 (3H, m), 7.47 (1H, m), 7.70 (1H, d, J=7.8 Hz). FAB-MS m/z: 283 $[M+H]^+$. *Anal.* Calcd for $C_{17}H_{15}N_2OF$: C, 72.33; H, 5.36; N, 9.92; F, 6.73. Found: C, 72.36; H, 5.39; N, 9.90; F, 6.71.

The following compounds were obtained in the same manner as described in general procedure H.

1-Methyl-4-phenyl-1,8-naphthyridin-2(1*H*)-one (**7a**): 72% yield; mp 133—135 °C (diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 3.90 (3H, s), 6.75 (1H, s), 7.13 (1H, dd, J=7.8, 4.7 Hz), 7.38—7.47 (2H, m), 7.49—7.53 (3H, m), 7.88 (1H, dd, J=7.8, 1.5 Hz), 8.62 (1H, dd, J=4.7, 1.5 Hz). MS m/z: 236 (M^+). *Anal.* Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.26; H, 5.23; N, 11.85.

1-Ethyl-7-methyl-4-phenyl-1,8-naphthyridin-2(1*H*)-one (**7b**): 56% yield; mp 105—107 °C (isopropyl ether–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7.0 Hz), 2.64 (3H, s), 4.65 (2H, q, J=7.0 Hz), 5.30 (1H, q, J=6.7 Hz), 6.65 (1H, s), 6.96 (1H, d, J=7.9 Hz), 7.38—7.42 (2H, m), 7.46—7.52 (3H, m), 7.73 (1H, d, J=7.9 Hz). FAB-MS m/z: 265 $[M+H]^+$. *Anal.* Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.53; H, 6.20; N, 10.57.

4-(3-Chlorophenyl)-1-ethyl-7-methyl-1,8-naphthyridin-2(1*H*)-one (**7c**): 39% yield; mp 112—113 °C (diisopropyl ether–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7.1 Hz), 2.64 (3H, s), 4.65 (2H, q, J=7.1 Hz), 6.64 (1H, s), 6.98 (1H, d, J=7.9 Hz), 7.28 (1H, m), 7.40—7.50 (3H, m), 7.67 (1H, d, J=7.9 Hz). MS m/z: 298 (M^+). *Anal.* Calcd for $C_{17}H_{15}N_2OCl$: C, 68.34; H, 5.06; N, 9.38; Cl, 11.87. Found: C, 68.14; H, 5.03; N, 9.36; Cl, 11.95.

4-(4-Chlorophenyl)-1-ethyl-7-methyl-1,8-naphthyridin-2(1*H*)-one (**7d**): 92% yield; mp 133—135 °C (ethyl acetate–diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=6.9 Hz), 2.64 (3H, s), 4.65 (1H, q, J=6.9 Hz), 6.63 (1H, s), 6.97 (1H, d, J=8.0 Hz), 7.34 (2H, d, J=8.3 Hz), 7.48 (1H, d, J=8.3 Hz), 7.68 (1H, d, J=8.0 Hz). FAB-MS m/z: 299 $[M+H]^+$. *Anal.* Calcd for $C_{17}H_{15}N_2OCl$: C, 68.34; H, 5.06; N, 9.38; Cl, 11.87. Found: C, 68.41; H, 5.04; N, 9.35; Cl, 11.99.

1-Ethyl-7-methyl-4-(3-methylphenyl)-1,8-naphthyridin-2(1*H*)-one (**7f**): 79% yield; mp 89—91 °C (hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7.1 Hz), 2.43 (3H, s), 2.63 (3H, s), 4.65 (2H, q, J=7.1 Hz), 6.64 (1H, s), 6.96 (1H, d, J=8.2 Hz), 7.18—7.21 (2H, m), 7.28 (1H, d, J=7.9 Hz), 7.38 (1H, t, J=7.6 Hz), 7.74 (1H, d, J=8.2 Hz). MS m/z: 278 (M^+). *Anal.* Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.75; H, 6.50; N, 9.98.

1-Ethyl-4-(3-methoxyphenyl)-7-methyl-1,8-naphthyridin-2(1*H*)-one (**7g**): 84% yield; mp 116—117 °C (ethyl acetate–diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7.0 Hz), 2.64 (3H, s), 3.85 (3H, s), 4.65 (2H, q, J=7.0 Hz), 6.66 (1H, s), 6.91—7.04 (4H, m), 7.40 (1H, t, J=7.8 Hz), 7.77 (1H, d, J=8.3 Hz). FAB-MS m/z: 295 $[M+H]^+$. *Anal.* Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.48; H, 6.19; N, 9.51.

1-Ethyl-7-methyl-4-(3-trifluoromethylphenyl)-1,8-naphthyridin-2(1*H*)-one (**7h**): 86% yield; mp 136—137 °C (ethyl acetate–diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7.1 Hz), 2.65 (3H, s), 4.66 (2H, q, J=7.1 Hz), 6.67 (1H, s), 6.99 (1H, d, J=8.3 Hz), 7.58—7.69 (4H, m), 7.76 (1H, d, J=7.8 Hz). FAB-MS m/z: 333 $[M+H]^+$. *Anal.* Calcd for $C_{18}H_{15}N_2OF_3$: C, 65.06; H, 4.55; N, 8.43; F, 17.15. Found: C, 65.12; H, 4.39; N, 8.45; F, 17.22.

1-Ethyl-7-methyl-4-(3-nitrophenyl)-1,8-naphthyridin-2(1*H*)-one (**7i**): mp 184—189 °C (ethyl acetate–diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7.0 Hz), 2.66 (3H, s), 4.66 (1H, q, J=7.0 Hz), 6.69 (1H, s), 7.01 (1H, d, J=8.0 Hz), 7.60 (1H, d, J=8.0 Hz), 7.69—7.77 (2H, m), 8.28—8.31 (1H, m), 8.36 (1H, dt, J=7.3, 2.0 Hz). FAB-MS m/z: 310 $[M+H]^+$. *Anal.* Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 66.22; H, 4.70; N, 13.57.

1,7-Dimethyl-4-phenyl-1,8-naphthyridin-2(1*H*)-one (**7j**): 89% yield; mp 117—119 °C (ethyl acetate–diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 2.65 (3H, s), 3.89 (3H, s), 6.68 (1H, s), 6.97 (1H, d, J=8.3 Hz), 7.38—7.42 (2H, m), 7.47—7.53 (3H, m), 7.74 (1H, d, J=8.3 Hz). FAB-MS m/z: 251 $[M+H]^+$. *Anal.* Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 77.00; H, 5.67; N, 11.11.

7-Methyl-4-phenyl-1-propyl-1,8-naphthyridin-2(1*H*)-one (**7k**): 89% yield; mp 92—93 °C (isopropyl ether–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.3 Hz), 1.83 (2H, m), 2.63 (3H, s), 4.54 (2H, t, J=7.6 Hz), 6.65 (1H, s), 6.95 (1H, d, J=7.8 Hz), 7.38—7.42 (2H, m), 7.46—7.53 (3H, m), 7.73 (1H, d, J=7.8 Hz). FAB-MS m/z: 279 $[M+H]^+$. *Anal.* Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.77; H, 6.51; N, 9.99.

1-Isopropyl-7-methyl-4-phenyl-1,8-naphthyridin-2(1*H*)-one (**7l**): 66% yield; mp 137—139 °C (isopropyl ether–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.69 (6H, d, J=6.8 Hz), 2.62 (3H, s), 6.60 (1H, s), 6.93 (1H, d, J=8.3 Hz), 7.37—7.41 (2H, m), 7.46—7.52 (3H, m), 7.71 (1H, d, J=8.3 Hz). FAB-MS m/z: 279 $[M+H]^+$. *Anal.* Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.68; H, 6.67; N, 10.14.

4-(2-Chlorophenyl)-1-ethyl-7-methyl-1,8-naphthyridin-2(1*H*)-one (**7m**): 81% yield; mp 122—123 °C (ethyl acetate–diisopropyl ether). ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7.1 Hz), 2.63 (3H, s), 4.66 (2H, m), 6.62 (1H, s), 6.94 (1H, d, J=7.8 Hz), 7.26—7.46 (4H, m), 7.53 (1H, dd, J=7.4, 1.5 Hz). FAB-MS m/z: 299 $[M+H]^+$. *Anal.* Calcd for $C_{17}H_{15}N_2OCl$: C, 68.34; H, 5.06; N, 9.38; Cl, 11.87. Found: C, 68.31; H, 5.03; N, 9.54; Cl, 11.87.

4-(3-Bromophenyl)-1-ethyl-7-methyl-1,8-naphthyridin-2(1*H*)-one (**7n**): 79% yield; mp 134—135 °C (ethyl acetate). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7.0 Hz), 2.64 (3H, s), 4.64 (2H, q, J=7.0 Hz), 6.63 (1H, s), 6.98 (1H, d, J=7.9 Hz), 7.33 (1H, d, J=7.3 Hz), 7.38 (1H, t, J=7.3 Hz), 7.55 (1H, s), 7.62 (1H, d, J=7.3 Hz), 7.67 (1H, d, J=7.9 Hz). FAB-MS m/z: 343, 345 $[M^++H]^+$. *Anal.* Calcd for $C_{17}H_{15}N_2OBr$: C, 59.49; H, 4.41; N, 8.16; Br, 23.28. Found: C, 59.62; H, 4.46; N, 8.10; Br, 23.04.

General Procedure I. Alkylation of 7-Methyl Group 4-(3-Chlorophenyl)-1,7-diethyl-1,8-naphthyridin-2(1*H*)-one (**7p**): In an atmosphere of argon, a 1.6 M *n*-butyllithium hexane solution (1.3 ml, 2.1 mmol) was added dropwise to a tetrahydrofuran solution (5 ml) of diisopropylamine (203 mg, 2 mmol) which had been cooled at −78 °C. After the addition was complete, this solution was warmed to ×30 °C, then cooled to −78 °C and **7c** (597 mg, 2 mmol) was slowly added dropwise and the solution was stirred for 15 min at the same temperature. Methyl iodide (1.3 ml, 2.1 mmol) was slowly added dropwise at −78 °C and the solution was stirred for 30 min at same temperature. The reaction solution was mixed with water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate. After removing the magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–ethyl acetate) and further recrystallized from hexane to give **7p** (161 mg, 26%) as colorless crystals. mp 74—75 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.40 (6H, m), 2.91 (2H, q, J=7.5 Hz), 4.66 (2H, q, J=7.1 Hz), 6.61 (1H, s), 6.99 (1H, d, J=8.2 Hz), 7.28 (1H, d, J=6.7 Hz), 7.40—7.50 (3H, m), 7.70 (1H, d, J=8.2 Hz). MS m/z: 312 (M^+). *Anal.* Calcd for $C_{18}H_{17}N_2OCl$: C, 69.12; H, 5.48; N, 8.96; Cl, 11.33. Found: C, 69.19; H, 5.42; N, 8.92; Cl, 11.68.

The following compounds were obtained in the same manner as described in general procedure I.

4-(3-Chlorophenyl)-1-ethyl-7-propyl-1,8-naphthyridin-2(1*H*)-one (**7q**):

37% yield; mp 80—81 °C (hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7.3 Hz), 1.38 (3H, t, J=7.0 Hz), 2.85 (2H, m), 2.85 (2H, t, J=7.6 Hz), 4.66 (2H, q, J=7.0 Hz), 6.64 (1H, s), 6.97 (1H, d, J=8.2 Hz), 7.28 (1H, d, J=7.3 Hz), 7.40—7.50 (3H, m), 7.69 (1H, d, J=8.2 Hz). FAB-MS m/z: 327 $[M+H]^+$. *Anal.* Calcd for $C_{19}H_{19}N_2OCl$: C, 69.83; H, 5.86; N, 8.57; Cl, 10.85. Found: C, 69.69; H, 5.91; N, 8.49; Cl, 11.06.

1,7-Diethyl-4-phenyl-1,8-naphthyridin-2(1*H*)-one (**7o**): 36% yield; mp 85—86 °C (isopropyl ether–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.41 (6H, m), 2.90 (2H, q, J=7.3 Hz), 4.67 (2H, q, J=7.3 Hz), 6.66 (1H, s), 6.96 (1H, d, J=7.9 Hz), 7.38—7.42 (2H, m), 7.46—7.52 (3H, m), 7.75 (1H, d, J=7.9 Hz). MS m/z: 278 (M^+). *Anal.* Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.60; H, 6.50; N, 9.98.

1-Ethyl-5,7-dimethyl-4-phenyl-1,8-naphthyridin-2(1*H*)-thione (15) Diphosphorous pentasulfide (1.55 g, 6.96 mmol) was added to a solution of **4a** (1.02 g, 3.67 mmol) in dichloromethane (30 ml), and the mixture was stirred under reflux for 3 d. The reaction mixture was allowed to cool to room temperature, mixed with a saturated sodium bicarbonate aqueous solution and then extracted with chloroform. The organic layer was washed with brine and dried over anhydrous sodium sulfate. After removing the sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–benzene then benzene) and further recrystallized from diisopropyl ether to give **15** (388 mg, 36%) as yellow crystals. mp 148—149 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (3H, t, J=6.7 Hz), 1.86 (3H, s), 2.61 (3H, s), 5.30 (1H, q, J=6.7 Hz), 6.87 (1H, s), 7.25—7.27 (2H, m), 7.41—7.42 (3H, m), 7.49 (1H, s). MS m/z: 294 (M^+). *Anal.* Calcd for $C_{18}H_{18}N_2S$: C, 73.43; H, 6.16; N, 9.51; S, 10.89. Found: C, 73.52; H, 6.16; N, 9.46; S, 11.16.

1-Ethyl-3,4-dihydro-5,7-dimethyl-4-phenyl-1,8-naphthyridin-2(1*H*)-one (16) A solution of **4a** (1.02 g, 3.67 mmol) in acetic acid (15 ml) was hydrogenated over 10% platinum dioxide (130 mg) at atmospheric pressure. When the reaction was judged complete by TLC analysis, the catalyst was filtered off. The filtrate was mixed with a 1 N sodium hydroxide aqueous solution and extracted with chloroform. The organic layer was washed with brine and dried over anhydrous sodium sulfate. After removing the sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (benzene then benzene–ethyl acetate) and further recrystallized from hexane to give **16** (100 mg, 10%) as crystals. mp 66—71 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=6.4 Hz), 2.12 (3H, s), 2.47 (3H, d, J=1.2 Hz), 2.90 (1H, d, J=15.9 Hz), 2.98—3.02 (1H, m), 4.12—4.19 (1H, m), 4.26 (1H, d, J=6.7 Hz), 4.29—4.36 (1H, m), 6.69 (1H, s), 6.97 (2H, d, J=7.3 Hz), 7.16—7.26 (3H, m). MS m/z: 280 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.03; H, 7.32; N, 9.73.

3-Benzoyl-2-pivaroylaminopyridine (12) In an atmosphere of argon, a 1.69 M *n*-butyllithium hexane solution (43 ml, 73 mmol) was added dropwise to a tetrahydrofuran solution (60 ml) of 2-pivaroylaminopyridine (**11**, 61.1 g, 34 mmol) which was cooled at −78 °C. After the addition was complete, this solution was warmed to 0 °C and stirred for 2.5 h. Then, *N*-methoxy-*N*-methylbenzamide (6.25 g, 38 mmol) was slowly added dropwise at −78 °C, the solution was warmed to room temperature and stirred for 2 h. The reaction solution was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate. After removing the magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform then chloroform–ethyl acetate) and further washed with diisopropyl ether to give **12** (5.70 g, 59%) as a solid. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (9H, s), 7.14 (1H, dd, J=7.8, 4.9 Hz), 7.48 (2H, t, J=7.8 Hz), 7.58 (1H, t, J=7.8 Hz), 7.72 (2H, d, J=7.8 Hz), 7.91 (1H, dd, J=7.8, 2.0 Hz), 8.61 (1H, dd, J=4.9, 2.0 Hz), 9.83 (1H, br). MS m/z: 282 (M^+).

***tert*-Butyl 3-(2-Pivaroylaminopyridin-3-yl)-3-hydroxy-3-phenylpropanate (13)** In an atmosphere of argon, a 1.69 M *n*-butyllithium hexane solution (53 ml, 90 mmol) was added dropwise to an ether solution (150 ml) of diisopropylamine (9.61 g, 95 mmol) which was cooled at −78 °C. After 15 min of stirring, an ether solution (20 ml) of *tert*-butyl acetate (10.5 g, 90.5 mmol) was slowly added dropwise. After 30 min of stirring, a tetrahydrofuran solution (20 ml) of **12** (12.0 g, 42.6 mmol) was added dropwise. After 30 min of stirring, the reaction mixture was warmed to room temperature and stirred for 5 h. The reaction solution was poured into water and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate. After removing the magnesium sulfate, the resulting filtrate was concentrated under reduced pressure to give **13** (16.9 g, 100%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (9H, s), 2.91 (1H, d, J=16.6 Hz), 6.19 (1H, s), 7.03 (1H, dd, J=7.8, 4.9 Hz), 7.23—7.56 (5H, m), 7.55 (1H, dd, J=7.8, 1.5 Hz), 8.51—8.52 (1H, m), 9.68 (1H, br). FAB-MS m/z: 222 $[M+H]^+$.

4-Phenyl-1,8-naphthyridin-2(1*H*)-one (14) A mixture of **13** (2.09 g, 5.25 mmol), 3 N hydrochloric acid (10 ml), and dioxane (10 ml) was stirred under reflux for 3 d. The reaction mixture was allowed to cool to room temperature, mixed with water, and the aqueous layer was neutralized with a saturated sodium bicarbonate aqueous solution. The resulting precipitate was filtered, washed with water, and recrystallized from acetonitrile to give **14** (600 mg, 51%) as colorless needles. mp 200<(sblimated) °C. ^{1}H-NMR ($CDCl_3$) δ: 6.72 (1H, s), 7.17 (1H, dd, J=7.9, 4.9 Hz), 7.44—7.45 (2H, m), 7.50—7.56 (3H, m), 7.90 (1H, dd, J=7.9, 1.2 Hz), 8.71 (1H, dd, J=4.9, 1.2 Hz), 11.56 (1H, br s). MS m/z: 222 (M^+). *Anal.* Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.68; H, 4.65; N, 12.70.

***N*-3-Ethylphenyl 3-Phenyl-3-oxopropanamide (17)** A mixture of 3-ethylaniline (5.00 g, 41 mmol), ethyl 3-phenyl-3-oxopropanate (9.50 g, 49 mmol), and pyridine (2 drops) in xylene (30 ml) was stirred under reflux for 72 h. The reaction mixture was concentrated under reduced pressure and diluted with 1 N hydrochloric acid. The aqueous layer was extracted with chloroform and the organic layer was washed with brine, and dried over anhydrous sodium sulfate. After removing the sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–ethyl acetate) to give **17** (2.85 g, 26%) as a syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.5 Hz), 2.64 (2H, q, J=7.5 Hz), 4.11 (2H, s), 6.97 (1H, d, J=8.0 Hz), 7.20—7.30 (2H, m), 7.41 (2H, s), 7.52 (2H, t, J=7.3 Hz), 7.64 (1H, t, J=6.7 Hz), 8.04 (2H, d, J=7.9 Hz), 9.19 (1H, s). FAB-MS m/z: 268 $[M+H]^+$.

7-Ethyl-4-phenylquinolin-2(1*H*)-one (18) A mixture of diphosphorus pentoxide (15 g) and phosphoric acid (15 ml) was stirred at 100 °C for 15 min. Then, **17** (2.83 g, 10 mmol) was added to this solution, and the mixture was stirred at 100 °C for 1 h. The reaction solution was poured onto ice water, the resulting precipitate was collected and dissolved in chloroform. The organic layer was subsequently washed with a 1 N sodium hydroxide aqueous solution and brine. After drying the organic layer with anhydrous sodium sulfate, the sodium sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform–ethyl acetate) to give **18** (2.35 g, 89%) as a syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.3 Hz), 2.76 (2H, q, J=7.3 Hz), 6.55 (1H, s), 7.02 (1H, dd, J=8.5, 1.2 Hz), 7.31 (1H, s), 7.40—7.55 (6H, m), 12.36 (1H, s). MS m/z: 249 (M^+).

1,7-Diethyl-4-phenylquinolin-2(1*H*)-one (19) To a solution of **18** (2.30 g, 9 mmol) in dimethylformamide (100 ml) was added a sodium hydride/60% oil dispersion (450 mg, 112 mmol) and the mixture was stirred at 80 °C for 30 min. To the reaction mixture was added ethyl iodide (2.90 g, 19 mmol) and then it was stirred for 1 h. The mixture was concentrated and diluted with water, and then extracted with chloroform. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The sodium sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–ethyl acetate) to give **19**, (983 mg, 38%) as a syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.3 Hz), 1.42 (3H, t, J=7.3 Hz), 2.80 (2H, q, J=7.3 Hz), 4.43 (2H, q, J=7.3 Hz), 6.61 (1H, s), 7.26 (1H, s), 7.01 (1H, d, J=7.9 Hz), 7.39—7.53 (6H, m). MS m/z: 276 (M^+-1).

Authentic Materials Rolipram[16] and CDP840[17] were prepared in our laboratory according to the reported methods.

Pharmacology

PDE Inhibitory Activity. Isolation of Human Peripheral Leukocytes The leukocytes were isolated from the peripheral blood of healthy human volunteers. Physiological saline supplemented with 3% dextran was added to heparinized human peripheral blood, and the mixture was incubated for 40 min at 37 °C to precipitate the erythrocytes. The supernatant after precipitation of the erythrocytes was recovered and washed once with PBS, and the pellet, which contained leukocytes, was resuspended in a buffer (pH 7.4) containing sodium chloride (140 mM), potassium chloride (5 mM), glucose (5 mM) and HEPES (10 mM).

Isolation of Human Peripheral Blood Mononuclear Cells (PBMC) The suspended leukocytes were overlaid on a solution for density gradient centrifugation use Ficoll® solution, and then centrifuged at room temperature for 40 min at 450 g, thereby separating the mononuclear cells and granulocytes. The mononuclear cell fraction was washed once and resuspended in RPMI with 10% FBS.

Purification of PDE Isozyme PDE2, PDE3, PDE4, and PDE5 were prepared from human peripheral leukocytes, and PDE1 was prepared from rat ventricles. All the enzymes were partially purified by Q Sepharose Fast Flow (Pharmacia Biotech, Sweden) with 0.05 to 1.25 M sodium acetate gradients from the 100000×***g*** supernatants. The following protease inhibitors

were maintained throughout: phenyl-methyl-sulfonyl-fluoride (50 μM), pepstatin A (5 μM), leupeptin (40 μM), aprotinin (20 μM) and benzamidine (2 mM). The characterization of each PDE isozyme was recognized as follows: PDE1, Ca^{2+}/calmodulin-activated; PDE2, cGMP-activated; PDE3, cGMP-inhibited; PDE4, cAMP-specific and inhibited by rolipram; PDE5, cGMP-specific.

Determination of Inhibitory Effect for PDE A predetermined amount and concentration of each test compound was incubated at 30 °C for 10 min in a reaction mixture (pH 8.0) containing Tris–HCl (40 mM), magnesium chloride (5 mM), 2-mercaptoethanol (4 mM), cAMP (1 μM), ^{3}H-cAMP (10 nM) and a PDE stock solution. The mixture was placed in boiled water for 1 min, cooled in an ice bath, mixed with 1 unit of 5′-nucleotidase and then incubated at 30 °C for 10 min. The reaction was stopped by the addition of 1 ml of methanol. The solution was passed through a Dowex 1-X8 (BIO-RAD, U.S.A.) column to adsorb any unhydrolyzed material, and then the radioactivity in the elution was measured. The evaluation of each compound was carried out using an IC_{50} value, this being the concentration achieving 50% inhibition.

TNF-α Production from Human PBMC Purified human PBMC (2×10^6/ml) suspended with RPMI medium including 10% FBS were incubated with each test compound at 37 °C for 10 min before stimulation by LPS (60 μg/ml). Twenty hours later, the reaction was stopped by adding 250 μl of 50 mM EGTA solution to the tubes and placing on ice. The sample tubes were centrifuged (4 °C, 250 g, 10 min), and the amount of produced TNF-α in the supernatant was measured by human TNF-α ELISA kits (Amersham Pharmacia Biotech, Uppsala, Sweden). The evaluation of each compound was carried out using an IC_{50} value, this being the concentration achieving 50% inhibition.

Carrageenan-Induced Pleurisy (CIP) in Rat The male rats aged 6 to 7 weeks were used for the CIP. The animals, which had been fasted overnight, were anaesthetized with diethylether, and given an injection of 1% (w/v) carrageenan solution in saline into the pleural cavity at a volume of 0.1 ml. Four hours after the injection, the animals were sacrificed by over-anesthesia with chloroform, and pleural cavity lavage was performed with 2 ml of saline containing heparin (1 unit/ml). The volume of lavage fluid recovered from the cavity was recorded and the exuded volume in the cavity was determined. The total number of leukocytes was counted with an automatic cell counter (Celltac-α: Nihon-Koden, Japan). Each test compound was orally administered 30 min before the injection of carrageenan. The evaluation of each compound was carried out using an ED_{30} value, this being the dose achieving 30% inhibition.[18)]

Data Analysis Concentrations or doses causing 50% or 30% inhibition were determined by nonlinear curve fitting using a statistical software, SAS system (SAS Institute Inc., Cary, U.S.A.).

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