Synthesis and Hypolipidemic Activities of Novel 2-[4-[(Diethoxyphosphoryl)methyl]phenyl]quinazolines and 4(3*H*)-Quinazolinones

Yasuhisa Kurogi,* Yasuhide Inoue, Kazuhiko Tsutsumi, Shizuo Nakamura, Kazushi Nagao, Hiroki Yoshitsugu, and Yoshihiko Tsuda

Nutrition Research Institute, Otsuka Pharmaceutical Factory, Inc., Muya-cho, Naruto, Tokushima 772, Japan

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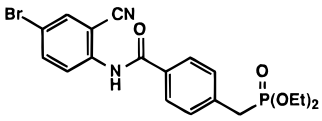
The novel compound NO-1886, 4-[(diethoxyphosphoryl)methyl]-*N*-(4-bromo-2-cyanophenyl)-benzamide, is a hypolipidemic agent, which appears to increase lipoprotein lipase activity in rats. Various analogs of NO-1886 were synthesized to study the structure−activity relationship of this hypolipidemic drug. A novel series of quinazolines and 4(3*H*)-quinazolinones were prepared by cyclization of NO-1886 derivatives. Derivatives bearing a 4-[(diethoxyphosphoryl)-methyl]phenyl group at the 2-position were found to lower triglyceride and total cholesterol levels. In accord with the decrease in log *P**, quinazolines and 4(3*H*)-quinazolinones showed good absorption and hypolipidemic activity. When the quinazolinone ring system is substituted at positions 6 and 7 with methoxy groups, increased hypolipidemic activity was observed. The highest hypolipidemic activity was observed when the 3-position was substituted by a methyl or benzyl group.

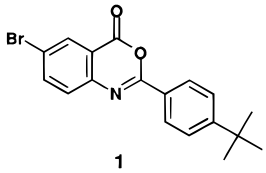
Lowering the serum triglyceride levels and increasing the high-density lipoprotein (HDL) levels are now accepted means of treating patients suffering from hyperlipoproteinemia and atherosclerosis.[1] Current treatment centers primarily on the strict control of dietary intake of fats and cholesterol, with drug treatment playing a secondary but increasingly important role. This role is likely to be vastly accentuated by the imminent advent of new drugs that inhibit the biosynthesis of cholesterol (HMG-CoA reductase inhibitors; lovastatin, simvastatin, and pravastatin) and drugs that prevent the absorption of dietary cholesterol and/or the retention of cholesterol in arterial smooth muscle cells (cholesterol acyltransferase (ACAT) inhibitors; CI-976 and DuP-128).[1]

Hypertriglyceridemia can be caused by either increased synthesis or inadequate removal of triglycerides or both. We hoped to obtain compounds which would increase lipoprotein lipase (LPL) activity, an important enzyme in the removal of triglycerides, because such compounds should enhance triglyceride catabolism via the enzyme's catalytic action and lower the plasma triglyceride levels. In addition, since a precursor−product relationship appears to exist between triglyceride-rich lipoproteins and HDL levels, compounds that increase LPL activity are expected to increase the level of HDL.[2] Several years ago, we discovered the novel compound NO-1886, 4-[(diethoxyphosphoryl)-methyl]-*N*-(4-bromo-2-cyanophenyl)benzamide, which appears to increase LPL activity in rats,[3] and is now in early phase II clinical trials in Japan. Within the past several years, various analogs of NO-1886 were synthesized to study the structure−activity relationship (SAR) of the hypolipidemic activity.

In 1989, Rhone Poulenc Ltd. reported a series of 2-substituted 4*H*-3,1-benzoxazin-4-ones as new hypolipidemic agents.[4] They showed that 6-bromo-2-[4-(1,1-dimethylethyl)phenyl]-4*H*-3,1-benzoxazin-4-one (**1**) has the ability to lower plasma cholesterol and triglyceride levels and to increase the HDL levels in diet-induced hyperlipidemic rats and normal rats.



NO-1886



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The HDL-elevating profile of 4*H*-3,1-benzoxazin-4-ones led us to design a novel series of quinazolines (**4** and **5**) and 4(3*H*)-quinazolinones (**6**) bearing a 4-[(diethoxyphosphoryl)methyl]phenyl group at the 2-position, which were prepared by cyclization of NO-1886 derivatives. Quinazolines and 4(3*H*)-quinazolinones are well-known as biologically active compounds which exhibit antimalarial,[5] sedative,[6] anti-Parkinson,[7] anticonvulsant,[8] antimitotic,[9] antihypoxic,[10] and antihypertensive activities.[11] In this paper, we first report on the synthesis and hypolipidemic activity of a novel series of 2-[4-[(diethoxyphosphoryl)methyl]phenyl]quinazolines (**4** and **5**) and 4(3*H*)-quinazolinones (**6**).

Chemistry

The preparation of quinazolines **4** and **5** and 4(3*H*)-quinazolinones **6** is summarized in Scheme 1. Anthranilonitriles (2-aminobenzonitriles) were prepared by procedures reported in the literature or were commercially available. 4-[(Dialkoxyphosphoryl)methyl]-benzoic acids were prepared by the Arbuzov reaction, which was carried out with 4-(bromomethyl)benzoic acid and the corresponding trialkoxyphosphine.[12] Treatment of anthranilonitriles with 4-[(dialkoxyphosphoryl)methyl]benzoyl chlorides **2**, which were prepared from 4-[(di-

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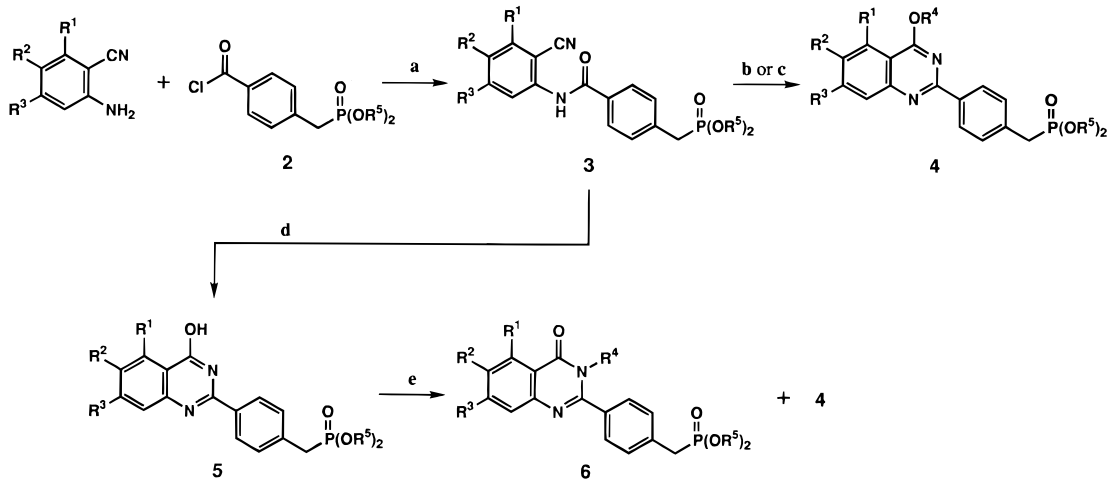
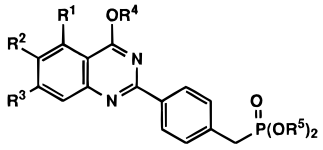
Scheme 1[a]



[a] Reagents: (a) pyridine; (b) TsOH, R^4OH, Δ (R^4 = Me, Et); (c) R^4ONa, THF, Δ (R^4 = Ph); (d) 30% H_2O_2 (aqueous), NaOH, EtOH; (e) R^4I (or Br), ^{t}BuOK, CH_3OH.

Table 1. Physical Properties of Quinazolines **4** and **5**



entry	R^1	R^2	R^3	R^4	R^5	mp, °C	method[a]	yield, %
4a	H	H	H	Me	Et	85−86	A	48
4b	F	H	H	Me	Et	80−81	B	2
4c	H	Br	H	Me	Et	148−149	A	79
4d	H	Br	H	Me	Me	93−94	A	36
4e	H	Br	H	Et	Et	99−100	A	62
4f	H	Br	H	Ph	Et	141−143	C	12
4g	H	Br	H	$CH_2CH{=}CH_2$	Et	124−125	B	9
4h	H	Br	H	CH_2(2-F,4-Br)Ph	Et	101−102	B	2
4i	H	Br	H	CH_2CO_2H	Et	170 dec	B	6
4j	H	OMe	OMe	Me	Et	138−139	A	40
4k	H	OMe	OMe	$CH_2CH{=}CH_2$	Et	109−110	B	7
4l	H	OMe	OMe	CH_2Ph	Et	141−142	B	4
4m	H	OMe	OMe	Me	Me	138−139	B	2
4n	H	OMe	OMe	Me	^{i}Pr	133−134	A	31
5a	H	H	H	H	Et	187−189	D	66
5b	F	H	H	H	Et	172−173	D	50
5c	H	Br	H	H	Et	211−212	D	72
5d	H	OMe	OMe	H	Et	185−186	D	75
5e	H	OMe	OMe	H	Me	232 dec	D	39
5f	H	OMe	OMe	H	^{i}Pr	190−191	D	82

[a] Method A: TsOH, R^4OH, reflux. Method B: ^{t}BuOK, R^4I, CH_3OH. Method C: PhONa, THF, reflux. Method D: H_2O_2, NaOH, EtOH. Me = methyl, Et = ethyl, ^{i}Pr = isopropyl, Ph = phenyl.

alkoxyphosphoryl)methyl]benzoic acids by treatment with the appropriate thionyl chloride in methylene chloride and dimethylformamide (DMF), formed 4-[(dialkoxyphosphoryl)methyl]-*N*-(2-cyanophenyl)benzamide (**3**).

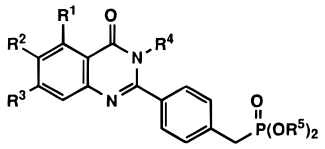
4-Alkoxyquinazolines, at first, were prepared by the treatment of **3** with alkaline alkoxide described in the literature,[13] but this reaction was low yielding (**4c**, 35%; **4e**, 15%). After several attempts to improve the yield, we found that 4-alkoxyquinazolines were obtained by the treatment of **3** with 0.4 equiv of *p*-toluenesulfonic acid monohydrate in the corresponding alcohol. By this new reaction, 4-alkoxyquinazolines (**4c**, 79%; **4e**, 62%) were obtained in high yield. To our regret, this reaction was unsuccessful when R^3 was an aromatic group. Therefore, 4-phenoxyquinazoline **4f** was prepared by the treatment of **3** with PhONa in tetrahydrofuran (THF).[13]

On the other hand, ring closures of **3** were performed in the presence of alkaline hydrogen peroxide to produce 2-[4-[(dialkoxyphosphoryl)methyl]phenyl]-4-hydroxyquinazoline (**5**).[14] Finally, N-alkylations of hydroxyqinazoline **5** in alkaline methanol gave the desired 3-substituted 2-[4-[(dialkoxyphosphoryl)methyl]phenyl]-4(3*H*)-quinazolinones **6**, accompanied with a small amount of 4-substituted 2-[4-[(dialkoxyphosphoryl)-methyl]phenyl]quinazolines **4** as byproducts. Physical properties of these quinazolines (**4**) and 4(3*H*)-quinazolinones (**6**) are presented in Tables 1 and 2, respectively.

Results and Discussion

Firstly, we prepared 6-bromoquinazoline derivatives **4c**−**i** by cyclization of our lead compound NO-1886. The hypolipidemic activity was evaluated in Triton-induced hypertriglycemic rats[16] (see the Experimental Section).

Table 2. Physical Properties of 4(3*H*)-Quinazolinones **6**



entry	R^1	R^2	R^3	R^4	R^5	mp, °C	method[a]	yield, %
6a	H	H	H	Me	Et	128−129	B	49
6b	F	H	H	Me	Et	155−156	B	53
6c	H	Br	H	Me	Et	99−100	B	55
6d	H	Br	H	Me	^{i}Pr	123−124	B	47
6e	H	Br	H	Et	Et	77−78	B	4
6f	H	Br	H	CH_2Ph	Et	120−121	B	9
6g	H	Br	H	$CH_2CH{=}CH_2$	Et	65−66	B	27
6h	H	Br	H	CH_2(2-F,4-Br)Ph	Et	106−107	B	14
6i	H	Br	H	CH_2CO_2H	Et	217 dec	B	24
6j	H	OMe	OMe	Me	Et	147−148	B	68
6k	H	OMe	OMe	$CH_2CH{=}CH_2$	Et	117−118	B	16
6l	H	OMe	OMe	CH_2Ph	Et	149−150	B	29
6m	H	OMe	OMe	Me	Me	193−194	B	43
6n	H	OMe	OMe	Me	^{i}Pr	166−167	B	65

[a] Method A: TsOH, R^4OH, reflux. Method B: ^{t}BuOK, R^4I, CH_3OH. Method C: PhONa, THF, reflux. Method D: H_2O_2, NaOH, EtOH. Me = methyl, Et = ethyl, ^{i}Pr = isopropyl, Ph = phenyl.

Table 3. Biological Properties of Quinazolines **4** and **5** and 4(3*H*)-Quinazolinones **6**

entry	log *P** [a]	TG[b]	TC[c]	entry	log *P** [a]	TG[b]	TC[c]
4a	5.26	−5	56	**6a**	3.29	31*	38
4b	5.13	−28	−25	**6b**	3.18	−12	−15*
4c	6.37	2	1	**6c**	4.09	−35**	−16*
4d	5.61	−9	−9	**6d**	4.88	−37**	−11
4e	7.01	−29*	−14	**6e**	ND	−42**	−29**
4f	7.67	16**	4	**6f**	5.17	−54**	−34**
4g	ND	−18	−2	**6g**	ND	−43**	−25*
4h	ND	−4	−12*	**6h**	ND	−16	−1
4i	ND	−2	−14	**6i**	ND	13	5
4j	4.51	−86***	−60***	**6j**	3.41	−86***	−51***
4k	ND	−71***	−35**	(10 mg/kg po)		−21*	−11*
4l	ND	−40**	−21**	**6k**	ND	−61**	−41**
4m	3.75	−52**	−48**	**6l**	4.49	−85***	−60***
4n	5.53	−81***	−60***	(10 mg/kg po)		−30**	−15**
				6m	2.65	−41**	−27**
				6n	4.20	−81***	−58***
5a	2.55	ND	ND	(10 mg/kg po)		−8	−4
5b	3.13	−8	−8				
5c	3.35	ND	ND				
5d	3.36	−37**	−22**	NO-1886	3.21	−85***	−69***
5e	2.60	−11	−18	(10 mg/kg po)		−54**	−27**
5f	4.38	−32	−35**				

[a] Apparent partition coefficients were estimated from the retention time of HPLC. [b,c] Percent change in plasma triglycerides (TG) and total cholesterol (TC) on Triton-induced hyperlipidemic rats; see the Experimental Section. All compounds were tested at 100 mg/kg po. NO-1886 and **6j**,**l**,**n** were evaluated at 10 mg/kg po for the further study. Results significantly different from controls: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. ND = not determined.

However, these compounds showed no hypolipidemic activity (Table 3). One possible reason for this may be that absorption of 6-bromoquinazolines **4c**−**i** into the body is poor. When 100 mg/kg **4c** and NO-1886 were administered orally to Sprague−Dawley rats, the peak plasma concentrations (C_{max}) were 2 and 89 μM, respectively. We considered that the poor absorption of 6-bromoquinazolines may be due to the higher hydrophobicity of 6-bromoquinazolines (e.g., **4c**, apparent partition coefficient log *P** = 6.37) as compared to NO-1886 (log *P** = 3.21).

To improve the absorption of these compounds, we prepared less hydrophobic compounds such as unsubstituted quinazolines, fluoroquinazolines, and 6,7-dimethoxyquinazolines **4a**,**b**,**j**−**n**. As we expected, log *P** values of these compounds (**4a**,**b**,**j**−**n**, log *P** = 3.75−5.53) were lower than that of 6-bromoquinazolines **4c**−**i** (log *P** = 5.61−7.67). The C_{max} of 6,7-dimethoxyquinazoline derivative **4j** was 40 μM at 100 mg/kg po. In accord with the decrease in log *P**, 6,7-dimethoxyquinazolines **4j**−**n** showed hypolipidemic activity (Table 3). These results led us to design 4(3*H*)-quinazolinone derivatives **6** to lower the hydrophobicity.

As described in Table 3, 4(3*H*)-quinazolinone derivatives **6** had lower hydrophobicity (**6a**−**c**,**j**, log *P** = 3.29, 3.18, 4.09, and 3.41) than that of the corresponding quinazolines **4a**−**c**,**j**, log *P** = 5.26, 5.13, 6.37, and 4.51). When 100 mg/kg **6c**,**j** was administered orally to Sprague−Dawley rats, C_{max} was 29 and 214 μM, respectively. Hypolipidemic activities were also observed accompanied with the increasing absorption, and 6,7-dimethoxy-4(3*H*)-quinazolinones **6j**,**l**,**n** showed hypolipidemic activities comparable to that of NO-1886 at 100 mg/kg po. The comparison of **6j**,**l**,**n** at 10 mg/kg po indicates that **6l** is the most potent compound.

In summary, potent hypolipidemic activities were

attained in a novel series of 4(3*H*)-quinazolinones bearing a 4-[(diethoxyphosphoryl)methyl]phenyl group at the 2-position. In accord with the decrease in log *P**, quinazolines and 4(3*H*)-quinazolinones showed good absorption and hypolipidemic activity. The 6,7-dimethoxy-4(3*H*)-quinazolinone derivatives lowered the plasma total cholesterol and triglyceride of Triton-induced hyperlipidemic rats, which suggests that this series of compounds might possess a similar pharmacological profile as NO-1886. A detailed pharmacological evaluation of the most potent compound (**6l**) in this series is currently in progress in order to select a compound for clinical use.

Experimental Section

Column chromatography was performed on silica gel 60 (Merck; particle size 63−200 μm). All melting points were determined on a Yamato micromelting point apparatus (MP-21). ^{1}H-NMR spectra were measured on a JEOL GX-270 (270 MHz) spectrometer, and chemical shifts are indicated in δ units from tetramethylsilane (TMS) as an internal standard. Mass spectra (EI-MS) were obtained with a HITACHI M-80A mass spectrometer. High-performance liquid chromatography (HPLC) analyses were performed using TOSOH CCPM, UV-8010, and CO-8010 instruments. Elemental analyses (C, H, N) of the final compounds **6j**,**l**,**n** were performed in this laboratory, using a Perkin-Elmer 2400 CHN analyzer; the results obtained were all within ±0.4 of the calculated percentages.

Method A: 2-[4-[(Diethoxyphosphoryl)methyl]phenyl]-4-methoxyquinazoline (4a). Treatment of anthranilonitrile (**1**; 15.7 g, 0.13 mol) in 100 mL of pyridine with 4-[(diethoxyphosphoryl)methyl]benzoyl chloride (**2**), which was prepared from 4-[(diethoxyphosphoryl)methyl]benzoic acid (38.0 g, 0.14 mol) by treatment with thionyl chloride (11 mL, 0.15 mol) in methylene chloride and DMF, gave 4-[(diethoxyphosphoryl)-methyl]-*N*-(2-cyanophenyl)benzamide (**3**; 25.9 g, yield 52%).

A mixture of 4-[(diethoxyphosphoryl)methyl]-*N*-(2-cyanophenyl)benzamide (3.7 g, 10 mmol) and *p*-toluenesulfonic acid monohydrate (0.8 g, 4 mmol) in 100 mL of methanol was refluxed for 10 h. After evaporating the solvent, the residue was purified by chromatography on a silica gel column using chloroform as the eluent to give the title compound **4a** as a pale yellow solid. Recrystallization from CH_2Cl_2/*n*-hexane produced colorless needles: 1.9 g (48%); mp 85−86 °C; ^{1}H-NMR ($CDCl_3$) δ 1.19 (6H, t, J = 7.2 Hz), 3.16 (2H, d, J = 22.3 Hz), 3.98 (4H, q, J = 7.2 Hz), 4.10 (3H, s), 7.36−7.38 (3H, m), 7.66 (1H, t, J = 7.9 Hz), 7.85 (1H, d, J = 8.4 Hz), 7.95 (1H, d, J = 7.9 Hz), 8.47 (2H, d, J = 7.9 Hz); MS (EI) m/z 386 M^+.

Method B: 2-[4-[(Diethoxyphosphoryl)methyl]phenyl]-3-methyl-4(3*H*)-quinazolinone (6a). A mixture of 2-[4-[(diethoxyphosphoryl)methyl]phenyl]-4-hydroxyquinazoline (**5a**; 5.9 g, 16 mmol), potassium *tert*-butoxide (1.8 g, 16 mmol), and methyl iodide (2.26 g, 16 mmol) in 100 mL of methanol was heated at 40 °C for 12 h. After evaporating the solvent, the residue was purified by chromatography on a silica gel column using CH_2Cl_2/CH_3OH (100:1) as the eluent to give the title compound **6a** with a small amount of 4-methoxyquinazoline **4a** as byproduct. Recrystallization from CH_2Cl_2/Et_2O produced colorless prisms: 3.0 g (49%); ^{1}H-NMR ($CDCl_3$) δ 1.29 (6H, t, J = 7.4 Hz), 3.23 (2H, d, J = 22.3 Hz), 3.50 (3H, s), 4.08 (4H, q, J = 7.4 Hz), 7.45−7.56 (5H, m), 7.74−7.77 (2H, m), 8.33 (2H, d, J = 8.4 Hz); MS (EI) m/z 386 M^+.

2-[4-[(Diethoxyphosphoryl)methyl]phenyl]-6,7-dimethoxy-3-methyl-4(3*H*)-quinazolinone (6j). This compound was prepared in a manner similar to that described for **6a**. Recrystallization from $CHCl_3$/*n*-hexane produced colorless prisms of **6j**: yield 68%; ^{1}H-NMR ($CDCl_3$) δ 1.29 (6H, t, J = 6.9 Hz), 3.23 (2H, d, J = 22.3 Hz), 3.50 (3H, s), 3.98 (3H, s), 4.03 (3H, s), 4.08 (4H, q, J = 6.9 Hz), 7.15 (1H, s), 7.45−7.54 (4H, m), 7.65 (1H, s); MS (EI) m/z 446 M^+. Anal. ($C_{22}H_{27}N_2O_6P$) C, H, N.

2-[4-[(Diethoxyphosphoryl)methyl]phenyl]-3-benzyl-6,7-dimethoxy-4(3*H*)-quinazolinone (6l). This compound was prepared in a manner similar to that described for **6a**. Recrystallization from CH_2Cl_2/Et_2O produced colorless prisms of **6l** (yield 29%): ^{1}H-NMR ($CDCl_3$) δ 1.28 (6H, t, J = 6.9 Hz), 3.19 (2H, d, J = 21.8 Hz), 3.99−4.11 (10H, m), 5.27 (2H, s), 6.93 (2H, t, J = 3.5 Hz), 7.17−7.32 (7H, m), 7.69 (1H, s); MS (EI) m/z 522 M^+. Anal. ($C_{28}H_{31}N_2O_6P$) C, H, N.

2-[4-[(Diisopropoxyphosphoryl)methyl]phenyl]-6,7-dimethoxy-3-methyl-4(3*H*)-quinazoline (6n). This compound was prepared in a manner similar to that described for **6a**. Recrystallization from CH_2Cl_2/Et_2O produced colorless prisms of **6n**: yield 65%; ^{1}H-NMR ($CDCl_3$) δ 1.27 (12H, dd, J = 5.9, 21.3 Hz), 3.19 (2H, d, J = 21.8 Hz), 3.49 (3H, s), 3.98 (3H, s), 4.03 (3H, s), 4.63−4.71 (2H, m), 7.15 (1H, s), 7.48−7.53 (4H, m), 7.64 (1H, s); MS (EI) m/z 474 M^+. Anal. ($C_{24}H_{31}N_2O_6P$) C, H, N.

Method C: 2-[4-[(Diethoxyphosphoryl)methyl]phenyl]-6-bromo-4-phenoxyquinazoline (4f). A mixture of 4-[(diethoxyphoshoryl)methyl]-*N*-(4-bromo-2-cyanophenyl)benzamide (4.5 g, 10 mmol) and sodium phenoxide (1.2 g, 10 mmol) in 100 mL of THF was refluxed for 20 h. After evaporating the solvent, the residue was purified by chromatography on a silica gel column using chloroform as the eluent to give the title compound **4f** as a brown solid. Recrystallization from CH_2Cl_2/*n*-hexane produced colorless needles: 0.6 g (12%); mp 141−143 °C; ^{1}H-NMR ($CDCl_3$) δ 1.23 (6H, t, J = 7.2 Hz), 3.21 (2H, d, J = 21.8 Hz), 3.98 (4H, q, J = 7.2 Hz), 7.33−7.36 (5H, m), 7.50 (2H, d, J = 7.9 Hz), 7.91−7.94 (2H, m), 8.26 (2H, d, J = 7.9 Hz), 8.52 (1H, d, J = 2.3 Hz); MS (EI) m/z 527 M^+.

Method D: 2-[4-[(Diethoxyphosphoryl)methyl]phenyl]-4-hydroxyquinazoline (5a). A mixture of 4-[(diethoxyphosphoryl)methyl]-*N*-(2-cyanophenyl)benzamide (3.1 g, 8.3 mmol), hydrogen peroxide (30 wt % solution in water, 20 mL, 170 mmol), and sodium hydroxide (0.33 g, 8.3 mmol) in 50 mL of ethanol was stirred for 24 h. After evaporating the solvent, the residue was purified by chromatography on a silica gel column using CH_2Cl_2/CH_3OH (50:1) as the eluent to give the title compound **5a** as a pale yellow solid. Recrystallization from Et_2O produced colorless prisms: 2.0 g (66%); ^{1}H-NMR ($CDCl_3/CD_3OD$) δ 1.28 (6H, t, J = 6.9 Hz), 3.26 (2H, d, J = 22.3 Hz), 4.05 (4H, q, J = 6.9 Hz), 7.47−7.53 (3H, m), 7.80−7.82 (2H, m), 8.11 (2H, d, J = 7.9 Hz), 8.30 (2H, d, J = 7.4 Hz); MS (EI) m/z 372 M^+.

log *P Determinations.** The apparent partition coefficient (log *P**) values for selected compounds were estimated from the retention time of reverse-phase HPLC using as standards methylbenzoate, ethyl benzoate, *n*-propyl benzoate, *n*-butyl benzoate, and *n*-hexyl benzoate, which modified the method described in the literature.[15] Chromatographic conditions were as follows: column, Capcell pak C18 SG120 (4.6 × 100 mm); temperature, 40 °C; mobile phase, CH_3OH/0.05 M $(NH_4)_2HPO_3$ (pH 7.4); flow rate, 1.0 mL/min; wavelength, UV at 230 nm; injection size, 20 μL.

Triton-Induced Hyperlipidemic Rats. The preventive and therapeutic effects of the compound on hyperlipidemia were determined using rats with Triton-induced hyperlipidemia according to the method of Kuroda et al.[16] as follows. Using 6−7-week-old male Wistar rats (body wt = 210−250 g) in groups of five (test group), we administered a solution of 300 mg/kg Triton (Triton WR-1339) in physiological saline into the tail vein, and at the same time 100 mg/kg of the test compound suspended in 0.5% CMC-Na solution was administered orally. As a control group, a group of five rats given Triton were orally dosed with 0.5% aqueous CMC-Na solution. After 24 h, blood was taken from the rats. Then, the plasma TC and TG levels were determined by Cholesterol C-Test Wako and Triglyceride G-Test Wako (both available from Wako Pure Chemical Industries, Ltd.), respectively. The experimentally determined values for TC and TG for the Triton-treated and CMC-Na solution-treated (control) rat groups were 308 ± 23 and 1394 ± 222 mg/dL, respectively. Using the measured values in the control group as references, the rates of decrease (%) in plasma TC and TG levels in the test group were calculated by the following equation:

$$\text{rate of decrease (\%)} = \left(1 - \frac{\text{test group's value}}{\text{control group's value}}\right) \times 100$$

The test rats were deprived of food before Triton administration through completion of blood sampling but were allowed free access to drinking water.

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