Studies on Disease-Modifying Antirheumatic Drugs: Synthesis of Novel Quinoline and Quinazoline Derivatives and Their Anti-inflammatory Effect[1]

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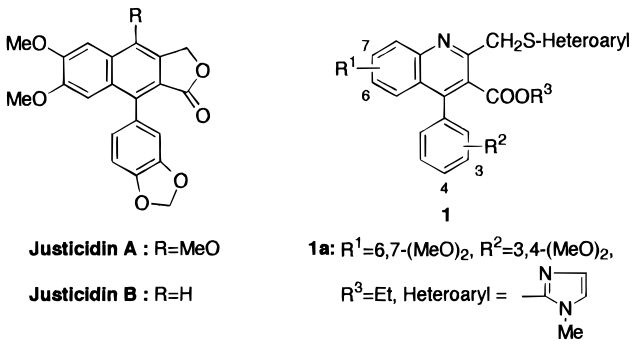
In the course of our study aimed at developing new types of DMARDs (disease-modifying antirheumatic drugs), we found that quinoline derivative **1a** had a potent anti-inflammatory effect in an adjuvant arthritis (AA) rat model, starting from the potent bone resorption inhibitors justicidins as the lead compounds. Further modification of **1a** was performed, and various quinoline and quinazoline derivatives having a heteroaryl moiety on the alkyl side chain at the 2-position of the skeleton were prepared. These compounds were evaluated for anti-inflammatory effects using the AA rat model. Most of these compounds, especially those having an imidazole or a triazole moiety on the 2-alkyl chain, exhibited a potent effect. Among the compounds synthesized, ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-yl-methyl)quinoline-3-carboxylate (**12d**), having an ED_{50} value of 2.6 mg/kg/day (anti-inflammatory effect in an AA rat model, po), was selected as a candidate for further investigation. *In vitro*, **12d** inhibited mitogen-induced proliferation at 10^{-7}−10^{-5} M but not prostaglandin E_2 production at 10^{-5} M. Moreover, **12d** preferentially inhibited the IFN-γ production by Th1-type clones over the IL-4 production by Th2-type clones. This preferential suppression of Th1 cytokine production is considered the essential immunomodulating action of **12d** for the present. Synthesis and structure−activity relationships for this novel series of quinoline and quinazoline derivatives are detailed.

Introduction

Rheumatoid arthritis (RA) is a serious, chronic, and systemic disease characterized by inflammation and progressive joint destruction.[2] Nonsteroidal anti-inflammatory drugs (NSAIDs),[3] the primary treatment for RA, provide only symptomatic relief for acute inflammation. Recently, as it has become clear that RA is a type of autoimmune disease,[4] disease-modifying antirheumatic drugs (DMARDs), which have a selective and direct action on the abnormal immune system, have attracted a great deal of attention as potentially effective therapies for RA.[5]

In our study aimed at developing new types of DMARDs, particular interest was directed toward bone resorption inhibitors, since the final stage of RA is bone destruction and several cytokines such as interleukin-1β (IL-1β) play an important role in both RA and bone metabolism.[6] Thus, we selected the potent bone resorption inhibitors justicidins (Chart 1) as the lead compounds. Among compounds modified based on the justicidin structure,[7] compound **1a**, in which the naphthalene ring has been replaced by a quinoline ring and a 2-(1-methylimidazolyl) moiety has been introduced at the 2-methyl position generated by ring opening of the lactone, was found to have a potent anti-inflammatory effect in rats with adjuvant arthritis (AA). Further modification of **1a** was performed, and various quinoline-3-carboxylate derivatives and quinazoline derivatives possessing a heteroaryl moiety on the alkyl chain at the 2-position of the skeleton were synthesized. In this article, we report the synthesis of this novel series of quinoline and quinazoline derivatives and structure-activity relationships (SAR) with regard to the anti-inflammatory effect in the rats with adjuvant arthritis are discussed.

Chart 1



Chemistry

The 2-[[(heteroaryl)thio]methyl]quinoline derivatives **1** and 2-[[(heteroaryl)thio]methyl]quinazoline derivatives **2** listed in Table 1 were synthesized by coupling of the 2-(chloromethyl)quinolines **3** or 2-(chloromethyl)-quinazolines **4** with (heteroaryl)thiols in the presence of K_2CO_3. Subsequent mCPBA oxidation of **1** gave sulfoxides **5** or sulfones **6** (method A, Scheme 1).

2-[(Heteroaryl)ethyl]quinolines **9** and 2-[(heteroaryl)-ethyl]quinazolines **10** were prepared by method B involving the Wittig reaction as a key step. The phosphonium salts **7** and **8** obtained from **3** and **4** were treated with NaOEt, and subsequent reaction with (heteroaryl)aldehydes gave 2-vinyl derivatives as a

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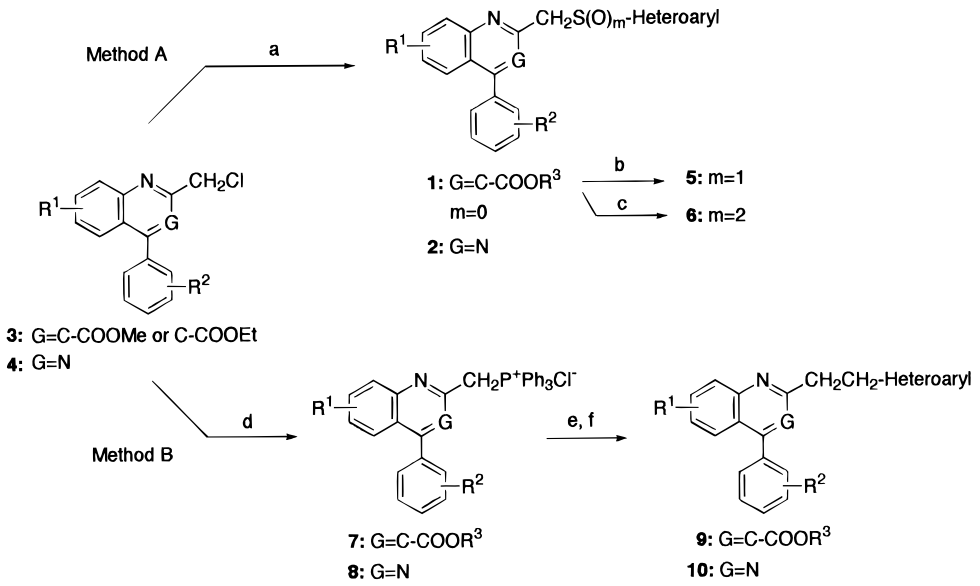
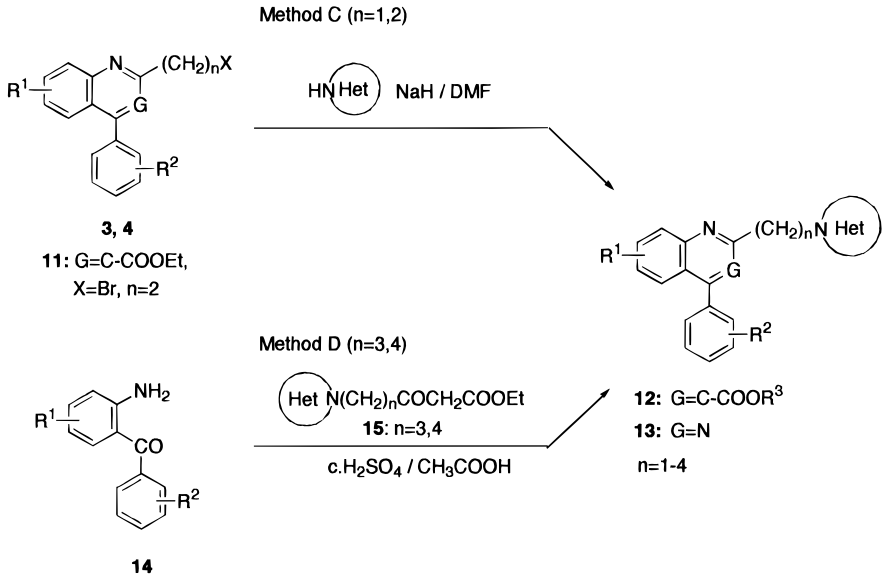
Scheme 1[a]



[a] (a) Heteroaryl-SH, K_2CO_3; (b) mCPBA (1.1 equiv); (c) mCPBA (2.2 equiv); (d) PPh_3; (e) NaOEt then heteroaryl-CHO; (f) H_2, Pd−C.

Scheme 2

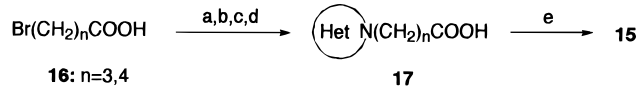


mixture of *E* and *Z* isomers, which was hydrogenated without further separation to provide **9** and **10**.

Compounds **12** and **13** having a triazolyl or an imidazolyl moiety on the 2-alkyl chain were prepared according to the methods shown in Scheme 2. Coupling of **3**, **4**, or **11** with 1*H*-1,2,4-triazole or imidazole provided the corresponding 1-azolyl derivatives **12** (n = 1 or 2) and **13** (n = 1) (method C). The extended-chain analogues **12** (n = 3 or 4) were synthesized by Friedländer reaction[8] of 2-aminobenzophenones **14**[9] with β-keto esters **15** (method D).[10] The requisite β-keto esters **15** for method D were obtained following the procedure reported by Masamune *et al.*,[11] starting from ω-bromo carboxylic acids **16**, in five steps (Scheme 3).

Syntheses of the desired 2-haloalkyl derivatives for methods A−C above are summarized in Scheme 4. 2-(Chloromethyl)quinolines **3** were synthesized by Friedländer reaction of **14** with the corresponding 4-chloroacetoacetic acid esters under acidic conditions (method E). In an analogous fashion, diester derivatives **18** were derived from **14**. **18** was converted to 2-(bromoethyl)-quinolines **11** in the usual way (method F). The 2-(chloromethyl)quinazolines **4** were prepared by cyclization of **14** with chloroacetonitrile in the presence of $AlCl_3$ (method G).

Scheme 3[a]

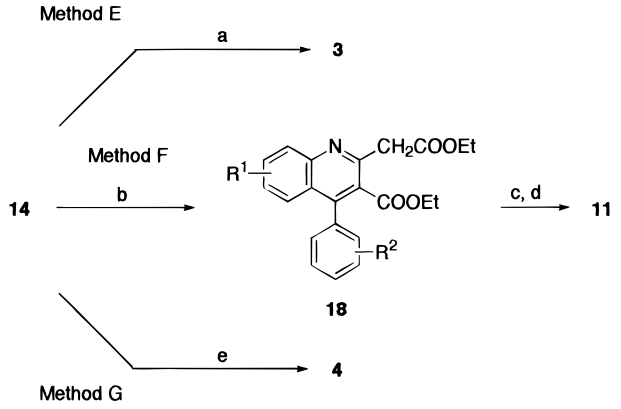


[a] (a) $(COCl)_2$, DMF; (b) benzyl alcohol, Et_3N; (c) imidazole or triazole, NaH; (d) H_2, Pd−C; (e) *N*,*N*′-carbonyldiimidazole then $Mg(OCOCH_2COOEt)_2$.

Results and Discussion

The structures and physical data of the quinoline and quinazoline derivatives synthesized are shown in Tables 1 and 2. Anti-inflammatory effects of these derivatives are listed in Table 3, and the activity is presented in terms of the plantar edema inhibitory rate (%) (see Biological Procedures).

Scheme 4[a]



[a] (a) $ClCH_2COCH_2COOR^3$ (R^3 = Me, Et), concentrated H_2SO_4/AcOH; (b) $CO(CH_2COOEt)_2$, concentrated H_2SO_4/AcOH; (c) $LiAlH_4$; (d) PBr_3; (e) $ClCH_2CN$, $AlCl_3$.

Our search for the discovery of a new type of DMARDs started with chemical modification of justicidins (Chart 1), and 4-phenylquinoline-3-carboxylate derivative **1a** was the first compound found with the desired biological activity. Thus, further modification of **1a** was performed.

First, the effect of a heteroaryl moiety on the side chain at the 2-position was examined. Compounds **1b**−**d** possessing an imidazole or a triazole group showed potent activity.

The effect of adding substituents to the quinoline ring (R^1) and the pendent phenyl ring (R^2) at the 4-position was studied with compounds **1a,f**−**n**. Generally, potent anti-inflammatory activity was observed with compounds having 6,7-dialkoxy (**1a,f,k,l**) for R^1 and 3,4-dialkoxy (**1a,f,k,l**) for R^2. Compounds lacking the alkoxy moiety had reduced activity (**1a** vs **1j,n**). Concerning substituents R^2, compounds possessing 4-methoxy (**1g**) or 4-methyl (**1h**) also showed potent activity. Considering the structure−activity relationships mentioned above, we focused our further synthetic efforts on the preparation of various quinoline-3-carboxylate and quinazoline derivatives bearing 6,7-dimethoxy and 4-(3,4-dimethoxyphenyl) moieties.

S-Oxide compounds **5a** and **6a**, obtained by oxidation of **1a**, exhibited activities either stronger than or comparable to that of the parent compound. These findings suggest the possibility that sulfoxide **5a** and sulfone **6a** are active metabolites of **1a**.

Replacement of the sulfide moiety of **1a** with a methylene enhanced the activity (**9a** vs **1a**), showing that a linker between the quinoline and the imidazole rings is an important factor. A similar effect was also observed for the quinazoline derivatives (**10a** vs **2a**).

On the basis of these findings, compounds **12** and **13** (Table 2), in which an alkyl side chain is connected to the azole nitrogen, were synthesized. Among these compounds, **12a**−**d** possessing methylene as the linker exhibited remarkably potent activity. However, extension of the alkyl side chain from one to three carbons resulted in a decrease in potency (**12e** vs **12d**).

Since our search for a new type of DMARDs started with chemical modification of a bone resorption inhibitor as described above, the bone resorption inhibitory effect was also evaluated. Some of these compounds show potent bone resorption inhibitory activity and are shown in Table 4.

In conclusion, modification of justicidins revealed that quinoline and quinazoline derivatives having an azolyl moiety on the side chain at the 2-position have a potent anti-inflammatory effect. Extremely potent activities were attained in a series of 2-(1-imidazolyl- and 1-triazolylmethyl)quinolines **12**. Among these compounds, compound **12d** having an ED_{50} value of 2.6 mg/kg/day (anti-inflammatory effect in an AA rat model) was selected as a candidate for further investigation. Pharmacological evaluation revealed that **12d** has the profile of an immunomodulator.[12] Since **12d** potently inhibited paw swelling in AA but not carrageenin-induced paw swelling at 50 mg/kg, its action is not like that of NSAIDs. Compound **12d** suppressed the type IV allergic response (25 mg/kg/day, po) but had no effect on the type III allergic response in mice. *In vitro*, **12d** inhibited mitogen-induced proliferation at 10^{-7}−10^{-5} M but not PGE_2 production at 10^{-5} M. To investigate the mechanism of **12d** in more detail, we established Th1 (allo-reactive) and Th2 (ovalbumine (OVA)-reactive) T cell lines and studied the effect of **12d** on their cytokine production. Compound **12d** suppressed Th1 cytokines (IL-2 and IFN-γ) but not Th2 cytokine (IL-4) in both cell lines. Moreover, **12d** preferentially inhibited IFN-γ production by Th1-type clones over IL-4 production by Th2-type clones. From these data, we consider that **12d** is an immunomodulator with the potential to control bone and cartilage destruction but devoid of any effect on prostaglandin synthesis inhibitory effect, and we expect it to be useful as a new type of DMARD. These quinoline and quinazoline derivatives are possible lead compounds for the development of potent antiosteoporotic agents. The SAR for the bone resorption inhibitory effect of these novel quinoline and quinazoline derivatives will be published elsewhere.[14]

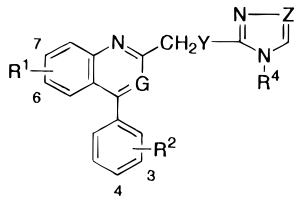
Experimental Section

Chemistry. Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Elemental analysis (C, H, and N) was carried out by the Analytical Department of Takeda Chemical Industries, Ltd. ^{1}H NMR spectra of deuteriochloroform or DMSO-d_6 solutions (internal standard TMS, δ 0) were recorded on a Varian Gemini-200 spectrometer. Infrared spectra were recorded on a Hitachi IR-215 spectrometer. All compounds exhibited ^{1}H NMR, IR, and analytical data consistent with the proposed structures. Column chromatography was done with E. Merck silica gel 60 (0.063−0.200 mm).

Method A: General Procedure for 2-[[(Heteroaryl)thio]methyl]quinolines 1 and 2-[[(Heteroaryl)thio]methyl]quinazolines 2. Ethyl 4-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-2-[[(1-methylimidazol-2-yl)thio]methyl]quinoline-3-carboxylate (1a). A mixture of ethyl 2-(chloromethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate (22.2 g, 49.8 mmol), 2-mercapto-1-methylimidazole (6.2 g, 54.8 mmol), K_2CO_3 (7.6 g, 54.8 mmol), and DMF (280 mL) was stirred at room temperature for 3 h, poured into H_2O (500 mL), and extracted with AcOEt. The extract was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (300 g) with $CHCl_3$−AcOEt (7:3) to give crystals. Recrystallization from acetone−Et_2O gave **1a** as colorless prisms (20.0 g, 77%): mp 149−150 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, t, J = 7.2 Hz), 3.47 (3H, s), 3.79 (3H, s), 3.87 (3H, s), 3.97 (3H, s), 4.03 (2H, q, J = 7.2 Hz), 4.04 (3H, s), 4.61 (2H, s), 6.87−7.01 (5H, m), 7.08 (1H, d, J = 1.2 Hz), 7.38 (1H, s). Anal. ($C_{27}H_{29}N_3O_6S$), C,H,N.

4-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-2-[[(1-methylimidazol-2-yl)thio]methyl]quinazoline (2a). The title compound was prepared according to the method described for **1a**: mp 184−185 °C; ^{1}H NMR ($CDCl_3$) δ 3.50 (3H, s), 3.90 (3H,

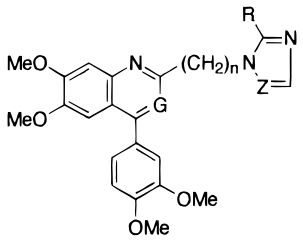
Table 1. Physical Data and Yield of Quinolines **1**, **5**, **6**, and **9** and Quinazolines **2** and **10**



compd	R^1	R^2	G	R^4	Y	Z	yield[a] (%)	mp (°C)	formula	anal.[b]
1a	6,7-$(MeO)_2$	3,4-$(MeO)_2$	C-COOEt	Me	S	CH	77	149−150	$C_{27}H_{29}N_3O_6S$	C,H,N
1b	6,7-$(MeO)_2$	3,4-$(MeO)_2$	C-COOEt	Me	S	N	77	147−148	$C_{26}H_{28}N_4O_6S$	C,H,N
1c	6,7-$(MeO)_2$	3,4-$(MeO)_2$	C-COOEt	H	S	CH	65	111−112	$C_{26}H_{27}N_3O_6S$	C,H,N
1d	6,7-$(MeO)_2$	3,4-$(MeO)_2$	C-COOEt	Et	S	CH	78	157−158	$C_{28}H_{31}N_3O_6S$	C,H,N
1e	6,7-$(MeO)_2$	3,4-$(MeO)_2$	C-COOMe	Me	S	CH	69	159−160	$C_{26}H_{27}N_3O_6S$	C,H,N
1f	6,7-$(MeO)_2$	3,4-OCH_2O	C-COOEt	Me	S	CH	70	176−177	$C_{26}H_{25}N_3O_6S$	C,H,N
1g	6,7-$(MeO)_2$	4-MeO	C-COOEt	Me	S	CH	72	123−124	$C_{26}H_{27}N_3O_5S$	C,H,N
1h	6,7-$(MeO)_2$	4-Me	C-COOEt	Me	S	CH	46	134−135	$C_{26}H_{27}N_3O_4S$	C,H,N
1i	6,7-$(MeO)_2$	4-Cl	C-COOEt	Me	S	CH	71	132−133	$C_{25}H_{24}ClN_3O_4S$	C,H,N
1j	6,7-$(MeO)_2$	H	C-COOEt	Me	S	CH	60	101−102	$C_{25}H_{25}N_3O_4S$	C,H,N
1k	6,7-$(EtO)_2$	3,4-$(MeO)_2$	C-COOEt	Me	S	CH	74	132−133	$C_{29}H_{33}N_3O_6S$	C,H,N
1l	6,7-$O(CH_2)_2O$−	3,4-$(MeO)_2$	C-COOEt	Me	S	CH	57	120−121	$C_{27}H_{27}N_3O_6S$	C,H,N
1m	6-MeO	4-MeO	C-COOEt	Me	S	CH	67	110−111	$C_{25}H_{25}N_3O_4S$	C,H,N
1n	H	3,4-$(MeO)_2$	C-COOEt	Me	S	CH	95	141−142	$C_{25}H_{25}N_3O_4S$	C,H,N
2a	6,7-$(MeO)_2$	3,4-$(MeO)_2$	N	Me	S	CH	81	184−185	$C_{23}H_{24}N_4O_4S$	C,H,N
5a	6,7-$(MeO)_2$	3,4-$(MeO)_2$	C-COOEt	Me	S(O)	CH	58[c]	193−194	$C_{27}H_{29}N_3O_7S$	C,H,N
6a	6,7-$(MeO)_2$	3,4-$(MeO)_2$	C-COOEt	Me	$S(O)_2$	CH	58[c]	183−184	$C_{27}H_{29}N_3O_8S$	C,H,N
9a	6,7-$(MeO)_2$	3,4-$(MeO)_2$	C-COOEt	Me	CH_2	CH	75	147−148	$C_{28}H_{31}N_3O_6$	C,H,N
10a	6,7-$(MeO)_2$	3,4-$(MeO)_2$	N	Me	CH_2	CH	72	170−171	$C_{24}H_{26}N_4O_4$	C,H,N

[a] Yield from **3** or **4**. [b] All compounds gave satisfactory results (±0.4%). [c] Yield from **1a**.

Table 2. Physical Data and Yield of Quinolines **12** and Quinazolines **13**



compd	G	Z	R	*n*	yield[a] (%)	mp (°C)	formula	anal.[b]
12a	C-COOEt	CH	H	1	75	208−209	$C_{26}H_{27}N_3O_6$	C,H,N
12b	C-COOEt	CH	Me	1	81	177−178	$C_{27}H_{29}N_3O_6$	C,H,N
12c	C-COOEt	CH	Et	1	74	163−165	$C_{28}H_{31}N_3O_6$	C,H,N
12d	C-COOEt	N	H	1	62	176−177	$C_{25}H_{26}N_4O_6$	C,H,N
12e	C-COOEt	N	H	3	40[c]	141−142	$C_{27}H_{30}N_4O_6$	C,H,N
13a	N	CH	Me	1	55	223−224	$C_{23}H_{24}N_4O_4$	C,H,N
13b	N	N	H	1	58	206−207	$C_{21}H_{21}N_5O_4$	C,H,N

[a] Yield from **3** or **4**. [b] All compounds gave satisfactory results (±0.4%). [c] Yield from **14**.

s), 3.97 (3H, s), 3.98 (3H, s), 4.06 (3H, s), 4.59 (2H, s), 6.90 (1H, s), 6.95−7.13 (2H, m), 7.23−7.43 (4H, m). Anal. ($C_{23}H_{24}N_4O_4S$) C,H,N.

Ethyl 4-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-2-[[(1-methylimidazol-2-yl)sulfinyl]methyl]quinoline-3-carboxylate (5a). mCPBA (85%, 1.28 g, 6.30 mmol) was added portionwise to a solution of **1a** (3.0 g, 5.73 mmol) in CH_2Cl_2 (75 mL) with ice cooling, and the whole was stirred at ambient temperature for 2.5 h. The mixture was washed successively with 5% aqueous $NaHSO_3$, saturated aqueous $NaHCO_3$, and H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (100 g) with AcOEt−MeOH (10:1) to give crystals. Recrystallization from acetone−Et_2O gave **5a** as colorless prisms (1.8 g, 58%): mp 193−194 °C; ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, t, J = 7.2 Hz), 3.79 (3H, s), 3.87 (3H, s), 3.94 (3H, s), 3.97 (3H, s), 4.05 (3H, s), 4.06 (2H, q, J = 7.2 Hz), 4.99−5.19 (2H, m), 6.84−6.99 (5H, m), 7.15 (1H, d, J = 1.2 Hz), 7.38 (1H, s). Anal. ($C_{27}H_{29}N_3O_7S$) C,H,N.

Method B: General Procedure for 2-[(Heteroaryl)-ethyl]quinolines 9 and 2-[(Heteroaryl)ethyl]quinazolines 10. Ethyl 4-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-2-[2-(1-methylimidazol-2-yl)ethyl]quinoline-3-carboxylate (9a). A mixture of ethyl 2-(chloromethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate (30 g, 67.3 mmol), PPh_3 (17.6 g, 67.3 mmol), and toluene (200 mL) was stirred under reflux for 2 h. After cooling to room temperature, the precipitated crystals were collected by filtration and washed with Et_2O to afford [4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3-(ethoxycarbonyl)quinolin-2-yl]methyltriphenylphosphonium chloride (40.0 g, 84%): mp 200−202 °C dec; ^{1}H NMR (DMSO-d_6) δ 0.83 (3H, t, J = 7.0 Hz), 3.67 (3H, s), 3.74 (3H, s), 3.83 (6H, s), 3.99 (2H, q, J = 7.0 Hz), 5.65 (2H, d, J = 14.8 Hz), 6.70 (1H, s), 6.79−6.90 (3H, m), 7.08−7.24 (2H, m), 7.65−7.94 (14H, m).

[4-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-3-(ethoxycarbonyl)-quinolin-2-yl]methyltriphenylphosphonium chloride (17.4 g, 24.0 mmol) was added to a stirred solution of NaOEt (prepared from Na (0.62 g, 26.7 mmol) and EtOH (150 mL)) at ambient temperature. After stirring for 10 min, a solution of 2-formyl-1-methylimidazole (3.7 g, 33.9 mmol) in EtOH (20 mL) was added dropwise. The whole was stirred at room temperature for 3 h, poured into H_2O (500 mL), and extracted with AcOEt. The extract was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (200 g) with $CHCl_3$−MeOH (100:1) to give a mixture of (*E*)- and (*Z*)-ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-[2-(1-methylimidazol-2-yl)vinyl]quinoline-3-carboxylate (ca. 10.9 g). Almost the same scale reaction was repeated, and the total yield was 25.5 g.

A mixture of (*E*)- and (*Z*)-ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-[2-(1-methylimidazol-2-yl)vinyl]quinoline-3-carboxylate obtained above (ca. 25.5 g), 5% Pd−C (6 g), and THF−EtOH (1:1, 600 mL) was hydrogenated at room temperature under atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to give crystals. Recrystallization from EtOH gave **9a** as colorless prisms (19.2 g, 75%): mp 147−148 °C; ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, t, J = 7.2 Hz), 3.18−3.33 (2H, m), 3.35−3.52 (2H, m), 3.60 (3H, s), 3.80 (3H, s), 3.87 (3H, s), 3.96 (3H, s), 4.05 (3H, s), 4.06 (2H, q, J = 7.2 Hz), 6.80 (1H, d, J = 1.4 Hz), 6.87−7.01 (5H, m), 7.42 (1H, s). Anal. ($C_{28}H_{31}N_3O_6$) C,H,N.

Table 3. Anti-inflammatory Effect of Quinolines and Quinazolines

compd	dose (mg/kg)	paw vol[a] (% inhib)	ED_{50}[b] (mg/kg)	compd	dose (mg/kg)	paw vol[a] (% inhib)	ED_{50}[b] (mg/kg)
1a	50	60** [c]	25.0				
1b	50	66***	11.6	**2a**	50	<50	
1c	50	60**		**5a**	12.5	73**	6.5
1d	50	51*		**6a**	50	56**	
1e	50	67**		**9a**	50	75***	14.7
1f	50	63**		**10a**	50	71**	
1g	50	64*		**12a**	12.5	70**	7.7
1h	50	67***		**12b**	12.5	55**	
1i	50	41**		**12c**	12.5	65**	9.1
1j	50	31		**12d**	12.5	65**	2.6
1k	50	59**		**12e**	12.5	<50	
1l	50	56**		**13a**	12.5	<50	
1m	50	45*		**13b**	12.5	<50	
1n	50	33**		justicidin A	50	10	

[a] The test compounds were given orally for 14 days after adjuvant injection into the rat's right hind paw. Each volume was obtained by comparison between the left paw volume in the arthritic group and that in the control group (see Biological Procedures). [b] Effective dose (mg/kg) of 50% inhibition, estimated from dose−response curve at three or four doses. [c] Statistically significant at $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$, by Student's *t*-test.

Table 4. Bone Resorption Inhibitory Effect of **1a**,**e**,**l**,**m** and **12d**

compd	conctn (μM)	^{45}Ca release[a] (% of control)
1a	30	57*** [b]
1e	10	46***
1l	10	66***
1m	10	66**
12d	30	59**
justicidin A	25	48**
justicidin B	25	47**

[a] Bone resorption inhibitory effects were evaluated by Raisz's method (see Biological Procedures). [b] Statistically significant at $**p < 0.01$ and $***p < 0.001$, by Student's *t*-test.

4-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-2-[2-(1-methylimidazol-2-yl)ethyl]quinazoline (10a). The title compound was prepared according to the method described for **9a**: mp 170−171 °C; ^{1}H NMR ($CDCl_3$) δ 3.27−3.39 (2H, m), 3.53−3.65 (2H, m), 3.61 (3H, s), 3.91 (3H, s), 3.97 (3H, s), 3.99 (3H, s), 4.08 (3H, s), 6.79 (1H, d, J = 1.2 Hz), 6.95 (1H, d, J = 1.2 Hz), 7.04 (1H, d, J = 8.8 Hz), 7.30−7.42 (4H, m). Anal. ($C_{24}H_{26}N_4O_4$) C,H,N.

Method C: General Procedure for 2-(1-Imidazolyl- or 1-triazolylmethyl)quinolines 12 and 2-(1-Imidazolyl- or 1-triazolylmethyl)quinazolines 13. Ethyl 4-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)-quinoline-3-carboxylate (12d). A mixture of 1*H*-1,2,4-triazole (558 mg, 8.07 mmol) in DMF (30 mL) was treated with NaH (60% in oil, 323 mg, 8.07 mmol) at ambient temperature for 15 min, and then ethyl 2-(chloromethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate (3.0 g, 6.73 mmol) was added. The whole was stirred at 80 °C for 1 h, poured into H_2O (100 mL), and extracted with AcOEt. The extract was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (40 g) with $CHCl_3$−MeOH (40:1) to give crystals. Recrystallization from AcOEt−hexane gave **12d** as colorless prisms (1.9 g, 62%): mp 176−177 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, J = 7.2 Hz), 3.80 (3H, s), 3.86 (3H, s), 3.95 (2H, q, J = 7.2 Hz), 3.97 (3H, s), 4.05 (3H, s), 5.74 (2H, s), 6.86−7.00 (4H, m), 7.42 (1H, s), 7.94 (1H, s), 8.28 (1H, s). Anal. ($C_{25}H_{26}N_4O_6$) C,H,N.

4-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-2-[(2-methylimidazol-1-yl)methyl]quinazoline (13a). The title compound was prepared according to the method described for **12d**: mp 223−224 °C; ^{1}H NMR ($CDCl_3$) δ 2.52 (3H, s), 3.92 (3H, s), 3.95 (3H, s), 3.99 (3H, s), 4.07 (3H, s), 5.37 (2H, s), 6.95 (1H, d, J = 1.2 Hz), 7.03 (1H, d, J = 8.0 Hz), 7.08 (1H, d, J = 1.2 Hz), 7.28 (2H, s), 7.36 (1H, dd, J = 8.0, 1.8 Hz), 7.42 (1H, s). Anal. ($C_{23}H_{24}N_4O_4$) C,H,N.

Method D: General Procedure for 2-(1-Imidazolyl- or 1-triazolylpropyl and -butyl)quinolines 12. Ethyl 4-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-2-[3-(1,2,4-triazol-1-yl)-propyl]quinoline-3-carboxylate (12e). A mixture of 2-amino-3,4,4′,5-tetramethoxybenzophenone (4.0 g, 12.7 mmol), ethyl 3-oxo-6-(1,2,4-triazol-1-yl)hexanoate (2.6 g, 11.54 mmol), concentrated H_2SO_4 (0.37 g, 3.75 mmol), and acetic acid (40 mL) was stirred at 100 °C for 2 h and concentrated *in vacuo*. The residue was alkalinized with 2 N aqueous NaOH and extracted with $CHCl_3$. The extract was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (60 g) with $CHCl_3$−MeOH (40:1) to give crystals. Recrystallization from EtOH gave **12e** as colorless prisms (2.5 g, 40%): mp 141−142 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, t, J = 7.2 Hz), 2.49 (2H, quintet, J = 7.0 Hz), 2.97 (2H, t, J = 7.0 Hz), 3.80 (3H, s), 3.88 (3H, s), 3.97 (3H, s), 4.04 (2H, q, J = 7.2 Hz), 4.07 (3H, s), 4.34 (2H, t, J = 7.0 Hz), 6.87−7.01 (4H, m), 7.40 (1H, s), 7.94 (1H, s), 8.20 (1H, s). Anal. ($C_{27}H_{30}N_4O_6$) C,H,N.

General Procedure for ω-(1-Azolyl) β-Keto Esters 15. Ethyl 3-oxo-6-(1,2,4-triazol-1-yl)hexanoate. Oxalyl chloride (2.9 g, 23.3 mmol) was added dropwise to a stirred solution of 4-bromobutyric acid (3.0 g, 17.9 mmol) in THF (30 mL) with ice cooling, and then DMF (2 drops) was added. The whole was stirred at 0 °C for 1 h and concentrated *in vacuo*. The residual acid chloride was dissolved in CH_2Cl_2 (10 mL). The solution was added dropwise to a stirred mixture of benzyl alcohol (2.9 g, 26.9 mmol), Et_3N (3.6 g, 35.9 mmol), and CH_2Cl_2 (30 mL) with ice cooling. After stirring at 0 °C for 4 h, the reaction mixture was poured into H_2O (200 mL). The organic layer separated was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (60 g) with AcOEt−hexane (1:1) to give benzyl 4-bromobutyrate as an oil (4.2 g, 91%).

A mixture of benzyl 4-bromobutyrate (72.6 g, 0.282 mol), 1*H*-1,2,4-triazole (21.4 g, 0.310 mol), K_2CO_3 (46.8 g, 0.339 mol), and acetone (1000 mL) was stirred under reflux for 8 h. The insoluble solid was filtered off, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on SiO_2 (700 g) with $CHCl_3$−MeOH (15:1) to give benzyl 4-(1,2,4-triazol-1-yl)butyrate as an oil (60.9 g, 88%).

A mixture of benzyl 4-(1,2,4-triazol-1-yl)butyrate (60 g, 0.244 mol), 5% Pd−C (15 g), and EtOH (500 mL) was hydrogenated at ambient temperature under atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to give crystals. Recrystallization from EtOH gave 4-(1,2,4-triazol-1-yl)butyric acid as colorless prisms (23.4 g, 61%): mp 137−138 °C; ^{1}H NMR ($CDCl_3$) δ 1.98 (2H, quintet, J = 6.8 Hz), 2.21 (2H, t, J = 6.8 Hz), 4.20 (2H, t, J = 6.8 Hz), 7.95 (1H, s), 8.50 (1H, s), 12.18 (1H, s). Anal. ($C_6H_9N_3O_2$) C,H,N.

N,*N*′-Carbonyldiimidazole (6.9 g, 42.5 mmol) was added to a stirred suspension of 4-(1,2,4-triazol-1-yl)butyric acid (6.0 g, 38.7 mmol) in THF (250 mL) at room temperature, and the whole was stirred at the same temperature for 6 h. Mg($OCOCH_2CO_2Et$)$_2$ (12.2 g, 42.5 mmol) was added followed by stirring for 15 h. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in CH_2Cl_2 (200 mL). The

solution was washed with saturated aqueous NH_4Cl, H_2O, and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (45 g) with AcOEt−MeOH (20:1) to give the title compound as an oil (2.6 g, 30%): ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, t, J = 7.2 Hz), 2.19 (2H, quintet, J = 6.6 Hz), 2.59 (2H, t, J = 6.6 Hz), 3.43 (2H, s), 4.19 (2H, q, J = 7.2 Hz), 4.23 (2H, t, J = 6.6 Hz), 7.94 (1H, s), 8.07 (1H, s); IR (neat) ν 1740, 1710 cm^{-1}.

Method E: General Procedure for Methyl or Ethyl 2-(Chloromethyl)quinoline-3-carboxylates 3. Ethyl 2-(Chloromethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate. A mixture of 2-amino-3,4,4′,5-tetramethoxybenzophenone (30.0 g, 94.5 mmol), ethyl 4-chloroacetoacetate (17.1 g, 0.104 mol), concentrated H_2SO_4 (1.5 mL), and acetic acid (300 mL) was stirred at 100 °C for 3 h and concentrated *in vacuo*. The residue was alkalinized with 2 N aqueous NaOH and extracted with $CHCl_3$. The extract was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (350 g) with $CHCl_3$−AcOEt (10:1) to give crystals. Recrystallization from acetone−Et_2O gave the title compound as colorless prisms (22.2 g, 53%): mp 147−148 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (3H, t, J = 7.2 Hz), 3.81 (3H, s), 3.88 (3H, s), 3.98 (3H, s), 4.06 (3H, s), 4.09 (2H, q, J = 7.2 Hz), 4.93 (1H, d, J = 11.2 Hz), 4.99 (1H, d, J = 11.2 Hz), 6.91−7.02 (4H, m), 7.47 (1H, s). Anal. ($C_{23}H_{24}ClNO_6$) C,H,N.

Method F: General Procedure for Ethyl 2-(2-Bromoethyl)quinoline-3-carboxylates 11. Ethyl 2-(2-Bromoethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinoline-3-carboxylate. Ethyl 4-(3,4-dimethoxyphenyl)-2-[(ethoxycarbonyl)methyl]-6,7-dimethoxyquinoline-3-carboxylate was prepared in the same manner as described for **3** by reaction of 2-amino-3,4,4′,5-tetramethoxybenzophenone and ethyl acetonedicarboxylate (yield 56%): mp 146−147 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, t, J = 7.2 Hz), 1.27 (3H, t, J = 7.4 Hz), 3.80 (3H, s), 3.87 (3H, s), 3.97 (3H, s), 4.03 (2H, q, J = 7.4 Hz), 4.05 (3H, s), 4.16 (2H, s), 4.20 (2H, q, J = 7.2 Hz), 6.89−7.02 (4H, m), 7.45 (1H, s).

A solution of ethyl 4-(3,4-dimethoxyphenyl)-2-[(ethoxycarbonyl)methyl]-6,7-dimethoxyquinoline-3-carboxylate (5.8 g, 12.0 mmol) in THF (100 mL) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (455 mg, 12.0 mmol) in THF (50 mL). The mixture was stirred at room temperature for 30 min, and then brine (2.5 mL) was added. The whole was stirred vigorously for 30 min, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (150 g) with $CHCl_3$−AcOEt (1:1) to give crystals. Recrystallization from AcOEt−hexane gave ethyl 4-(3,4-dimethoxyphenyl)-2-(2-hydroxyethyl)-6,7-dimethoxyquinoline-3-carboxylate as colorless prisms (1.8 g, 33%): mp 150−151 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (3H, t, J = 7.2 Hz), 3.18 (2H, t, J = 5.4 Hz), 3.80 (3H, s), 3.87 (3H, s), 3.97 (3H, s), 4.06 (3H, s), 4.08 (2H, q, J = 7.2 Hz), 4.17 (2H, t, J = 5.4 Hz), 4.80 (1H, brs), 6.89−7.02 (4H, m), 7.38 (1H, s). Anal. ($C_{24}H_{27}NO_7$) C,H,N.

PBr_3 (1.0 g, 3.9 mmol) was added dropwise to a stirred solution of ethyl 4-(3,4-dimethoxyphenyl)-2-(2-hydroxyethyl)-6,7-dimethoxyquinoline-3-carboxylate (1.7 g, 3.9 mmol) in benzene (50 mL) at room temperature, and the whole was stirred at 70 °C for 1 h. The reaction mixture was poured into ice−water, alkalinized with saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (20 g) with $CHCl_3$−AcOEt (1:1) to give crystals. Recrystallization from AcOEt−hexane gave the title compound as colorless prisms (490 mg, 26%): mp 132−133 °C; ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, t, J = 7.2 Hz), 3.51 (2H, t, J = 7.2 Hz), 3.79 (3H, s), 3.87 (3H, s), 3.90 (2H, t, J = 7.2 Hz), 3.97 (3H, s), 4.06 (3H, s), 4.10 (2H, q, J = 7.2 Hz), 6.90−7.01 (4H, m), 7.41 (1H, m). Anal. ($C_{24}H_{26}BrNO_6$) C,H,N.

Method G: General Procedure for 2-(Chloromethyl)-quinazolines 4. 2-(Chloromethyl)-4-(3,4-dimethoxyphenyl)-6,7-dimethoxyquinazoline. Powdered $AlCl_3$ (6.7 g, 50.2 mmol) was added portionwise to a mixture of 2-amino-3′,4,4′,5-tetramethoxybenzophenone (8.0 g, 25.2 mmol) and chloroacetonitrile (25 mL) at room temperature, and the whole was stirred at 100 °C for 2 h. The reaction mixture was poured into H_2O and extracted with $CHCl_3$. The extract was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (100 g) with $CHCl_3$−AcOEt (10:1) to give crystals. Recrystallization from acetone gave the title compound as colorless prisms (4.9 g, 52%): mp 183−184 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (3H, s), 3.98 (3H, s), 3.99 (3H, s), 4.08 (3H, s), 4.91 (2H, s), 7.06 (1H, d, J = 8.8 Hz), 7.34−7.46 (4H m). Anal. ($C_{19}H_{19}ClN_2O_4$) C,H,N.

Biological Procedures. 1. Anti-inflammatory Effect in Adjuvant Arthritis.[15] Male Lewis rats (7 weeks old; Charles River Japan Inc.) (n = 7) were sensitized by injecting Freund's complete adjuvant (a 0.5% suspension of killed *Mycobacterium tuberculosis* (H37 RA, Difco) in liquid paraffin) (0.05 mL) intradermally at a plantar site on the right hind leg. A suspension of a test compound in 0.5% methylcellulose was orally administered once a day for 14 days. The administration was started just before sensitization (day 0). The left hind paw volume was measured just before sensitization (day 0) and on day 14, and the plantar edema inhibitory rate and the body weight gain rate were determined in comparison with the nonsensitized rat group. Effective dose to inhibit the rat's left hind paw swelling by 50% (ED_{50}) was determined using data from an experiment in which three or four different doses were used. The doses were selected according to the potency of compound. ED_{50} (mg/kg) was derived by linear regression analysis of the data.

2. Bone Resorption Inhibitory Effect. Bone resorption inhibitory effect was determined by Raisz's method:[16] ^{45}Ca (radioisotope of calcium in $^{45}CaCl_2$ solution) (50 μCi) was subcutaneously injected into a Sprague−Dawley rat on the 18th day of pregnancy. On the next day, the abdomen was opened, and a fetus was aseptically removed. The left and right humeri (radii and ulnae) were removed under a dissecting microscope, and as much connective tissue and cartilage as possible were removed. Thus, bone culture samples were prepared. The bond was incubated in a medium (0.6 mL) of BCJ_b medium (Fitton-Jackson modification; GIBCO Laboratories) containing 2 mg/mL bovine serum albumin at 37 °C for 24 h in an atmosphere of 5% CO_2 in air. The bone was cultured for an additional 2 days in the above medium containing a final concentration of 10 or 30 μM of a test compound. This bone was cultivated for 2 days in the resulting medium. The ^{45}Ca radioactivity in the medium and the ^{45}Ca radioactivity in the bone were determined. The ratio (%) of ^{45}Ca released from the bone into the medium was calculated according to the following equation:

$$\text{ratio of } ^{45}\text{Ca released from bone into medium (\%)} = \frac{^{45}\text{Ca released into medium}}{(^{45}\text{Ca released into medium}) + (^{45}\text{Ca incorporated in bone})} \times 100$$

Bones from the same litter were cultured for 2 days in the same manner without addition of the compound and used as a control. The mean of the values for five bones for each group was calculated. The ratio (%) of this value to the control value was calculated.

Lactate dehydrogenase (LDH) activity in the medium was assayed using a commercially available LDH kit (Wako Pure Chemical Industries, Ltd., Osaka, Japan).

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(13) In Raisz's assay, we also examined the effect of **12d** on LDH release, as an index of cellular toxicity. No increase in LDH release was observed after incubation with **12d** for 2 days. So, bone resorption inhibitory effects of **12d** are not due to cellular toxicity.

(14) The SAR with regard to bone resorption inhibitory effects of these novel quinoline and quinazoline derivatives was presented at AFMC International Medicinal Chemistry Symposium 95 (AIMECS 95), The Pharmaceutical Society of Japan, Tokyo, Japan, Sept. 3−8, 1995; Abstract pp 108.

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