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Synthesis of 3-Ureido Derivatives of Coumarin and 2-Quinolone as Potent Acyl-CoA: Cholesterol Acyltransferase Inhibitors

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Novel 3-ureido derivatives of 4-phenylcoumarin and 4-phenyl-2-quinolone were synthesized and evaluated for acyl-CoA: cholesterol acyltransferase (ACAT)-inhibitory activity. These derivatives inhibited rat intestinal ACAT with IC_{50} values at the 10^{-8} to 10^{-9} M level and were found to normalize plasma cholesterol levels in cholesterol-fed rats when administered as dietary admixtures.

Key words ureidocoumarin; ureidoquinolone; ACAT inhibitor; cholesterol esterification; hypocholesterolemic effect; antiatherosclerotic agent

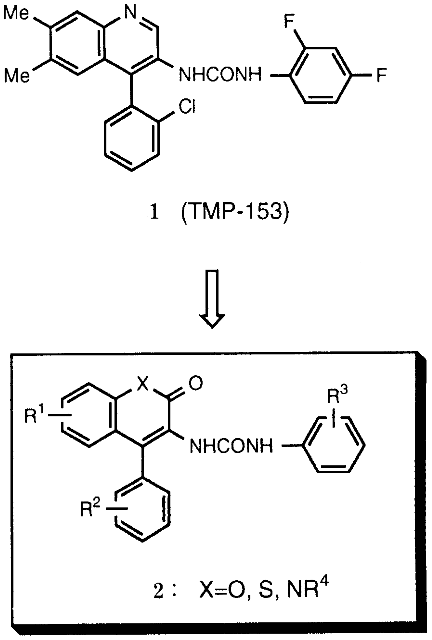
As part our search for new hypocholesterolemic and antiatherosclerotic agents, we focused on inhibitors of acyl-CoA: cholesterol acyltransferase (ACAT), which plays a key role in intracellular cholesterol esterification.[1] ACAT inhibitors appear to have a beneficial effect in lowering the plasma cholesterol level *via* the inhibition of cholesterol absorption in the intestine and the secretion of very low density lipoprotein (VLDL) from the liver. Furthermore, these agents are expected to suppress cholesterol accumulation and foam cell formation in the vascular wall. Therefore, ACAT inhibitors should be useful clinically in preventing both hypercholesterolemia and atherosclerosis by blocking cholesterol esterification.

Recently, we reported a novel series of 4-phenyl-3-quinolylurea derivatives including TMP-153 (**1**) as potent ACAT inhibitors (Fig. 1).[2] The 3-(substituted)phenylurea and the 4-(2-substituted)phenyl moieties as well as a substituent at the 6-position appeared to be particularly important structural features for the ability to inhibit ACAT. As a continuation of our efforts to optimize this inhibitory activity, we have synthesized coumarin and 2-quinolone derivatives (**2**) possessing mainly the above-mentioned structural features as shown in Fig. 1. The *in vitro* biological activity of **2** was evaluated using rat intestinal ACAT. This report describes the synthesis and ACAT-inhibitory activity of **2**. The plasma cholesterol-lowering effects of some typical compounds in cholesterol-fed rats are also presented.

Chemistry

3-Carboxylic esters of 2-quinolones (**5**, Chart 1) and coumarins (**28**, Chart 3) were chosen as the key intermediates to prepare the designed urea derivatives (**2**) by the procedure depicted in Charts 1 or 3. Condensation of 2-aminobenzophenones (**3**)[3] with diethyl malonate in the presence of a base [*e.g.* piperidine or 1,8-diazabicyclo-[5.4.0]undec-7-ene(DBU)] provided ethyl 2-quinolone-3-carboxylates (**4**)[4] in good yields (method A). Methylation of **4** with iodomethane gave the *N*-methyl derivatives (**5**, R^4=Me) (method B). However, in the case of the 6,8-dimethyl-2-quinolone derivative (**4**, R^1=6,8-Me_2, R^2=2-Cl), the *O*-methyl derivative (**10**) was obtained by methylation. Steric hindrance due to the methyl group at the 8-position of the quinoline ring seemed to prevent the *N*-methylation. Preparation of the desired *N*-methylated 6,8-dimethyl-2-quinolone derivative (**5**, R^1=6,8-Me_2, R^2=2-Cl, R^4=Me) was achieved by method C shown in Chart 1. The 2-aminobenzophenone (**3**, R^1=3,5-Me_2, R^2=2-Cl) was converted to the 2-methylaminobenzophenone derivative (**7**) in three steps. Acylation of **7** with methyl malonyl chloride gave **9**, which was then treated with *tert*-BuOK in tetrahydrofuran to afford **11** in a 59.2% yield (method C). 2-Alkoxyquinoline derivatives (**14**) were prepared through the reaction sequence shown in Chart 2. 2-Quinolones (**12**) were easily converted to the 2-chloro derivatives (**13**) by heating with $POCl_3$. Subsequent reaction of **13** with sodium methoxide in methanol resulted in conversion of the chlorine atom to a methoxy group, with a concomitant ester exchange at the 3-position from ethyl to methyl ester to afford **14** (R^5=Me). 2-Ethoxyquinoline (**14**, R^5=Et) was directly prepared from **12** by reaction with the Meerwein reagent ($Et_3O^+BF_4^-$).

The 2-hydroxybenzophenones (**18**) required for the



1 (TMP-153)

2 : X=O, S, NR4

Fig. 1

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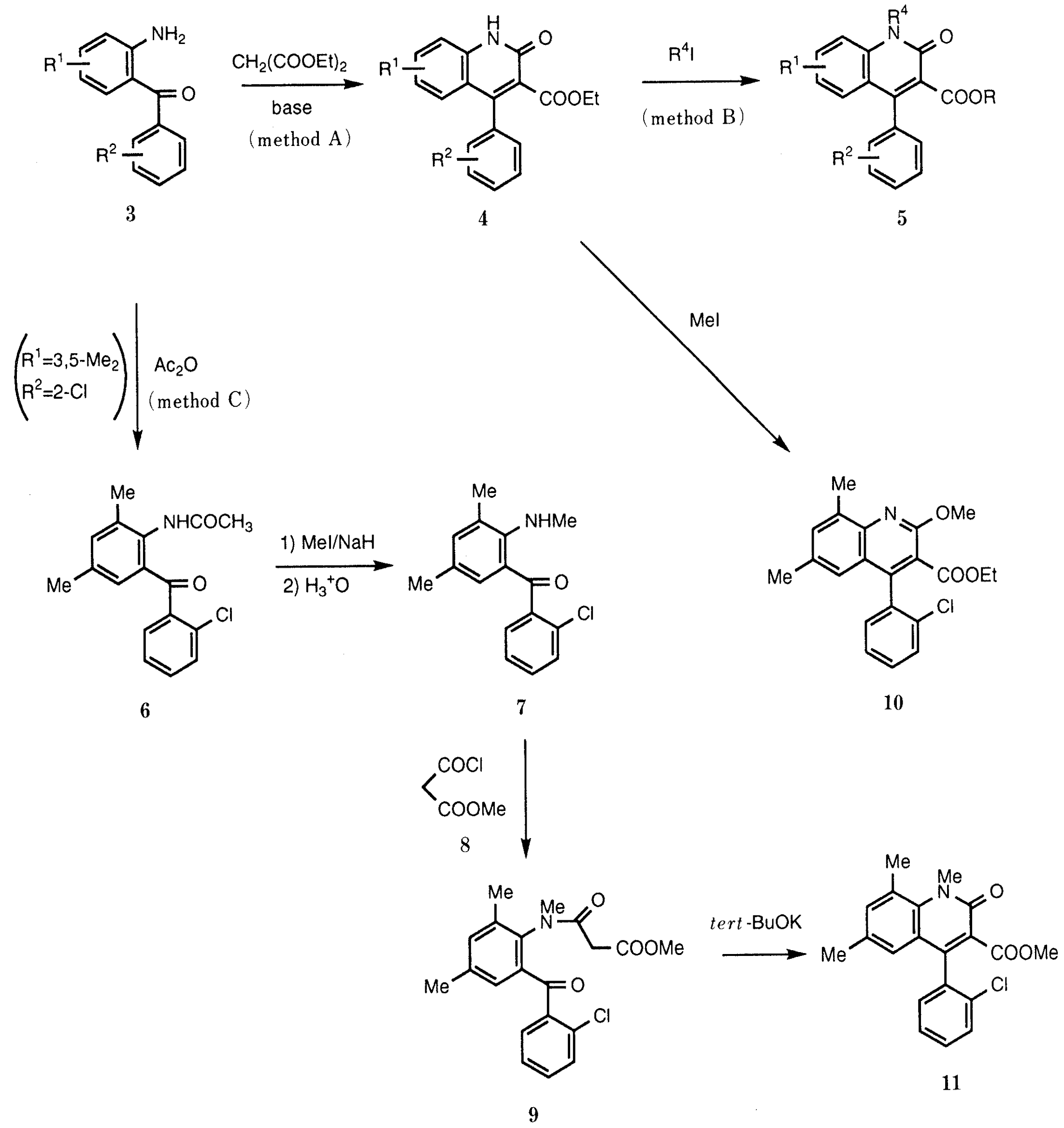


Chart 1

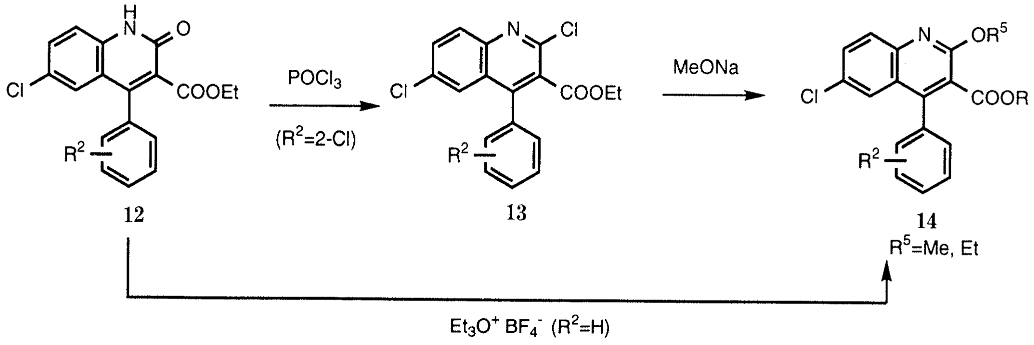
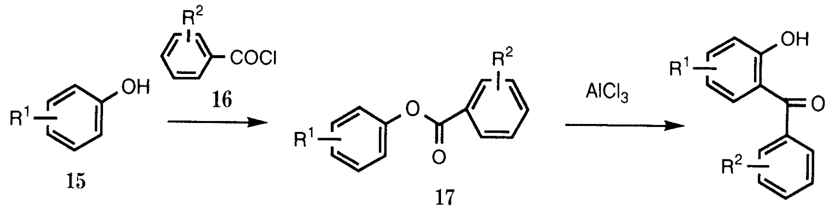
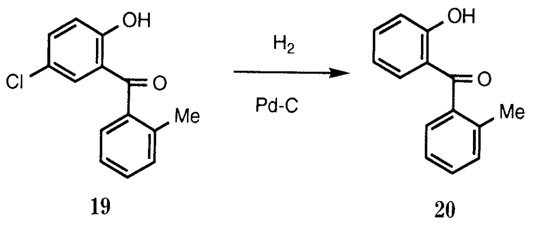


Chart 2

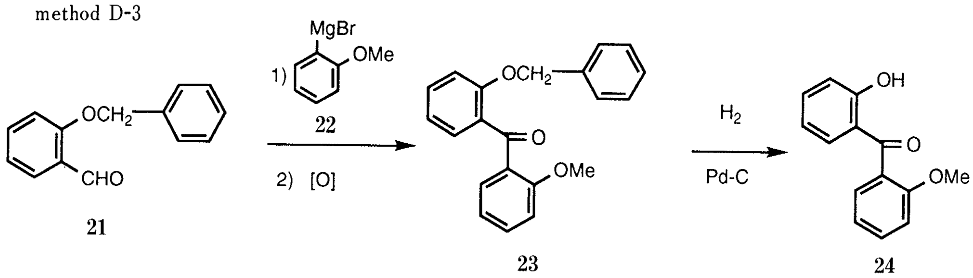
preparation of the 3-coumarincarboxylates (**28**)[5] were synthesized as illustrated in Chart 3. Most of these compounds (**18**) were synthesized by Fries' rearrangement of **17** in the presence of $AlCl_3$ at 100—150 °C (method D-1). However, when the 4-unsubstituted phenols were used as the starting materials, the major products were 4-hydroxybenzophenone derivatives, and the desired 2-hydroxybenzophenone derivatives (**18**) were produced as minor products. The 2-hydroxybenzophenones (**20, 24, 27**) were therefore synthesized by the following three methods (methods D-2—4), as shown in Chart 3. Reduction of **19** gave **20** (method D-2). Reaction of *O*-benzylsalicylaldehyde (**21**) with Grignard reagent followed by Jones' oxidation gave **23**, which was then hydrogenated to afford **24** (method D-3). The tetrahydronaphthyl derivative (**25**)[6] was converted to the benzoyl derivative (**26**), and succesmethod D-1



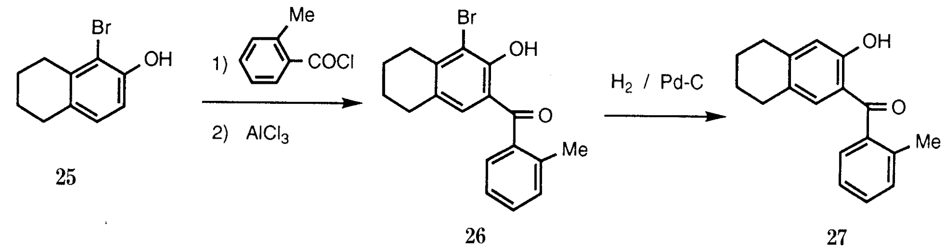
method D-2



method D-3



method D-4



method D

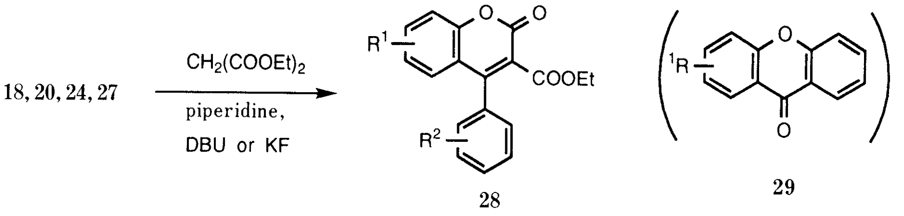


Chart 3

sive hydrogenation afforded the desired **27** (method D-4). The 2-hydroxybenzophenone derivatives (**18**, **20**, **24**, **27**) obtained by methods D-1—4 were reacted with diethyl malonate using piperidine or DBU as a catalyst to afford the coumarin-3-carboxylates (**28**). However, when the same reaction conditions were applied to 2-hydroxy-2′-chlorobenzophenones (**18**, $R^2=2$-Cl), the xanthones (**29**) were obtained as the sole product instead of the desired **28**. In these cases, KF was used as the base to obtain **28** in a 22—30% yield.

The 1-thiocoumarin-3-carboxylate derivative (**37**) was synthesized by the process shown in Chart 4 using the 2-hydroxybenzophenone derivative (**30**) as the starting material. Reaction of **30** with *N*,*N*-dimethylthiocarbamyl chloride (**31**) gave **32** in good yield. Pyrolysis[7] of **32** followed by hydrolysis yielded the 2-mercaptobenzophenone derivative (**34**). Compound **37** was synthesized by acylation of **34** with ethyl malonyl chloride (**35**) followed by cyclization with DBU.

The desired urea derivatives (**2**) of coumarins or 2-quinolones were prepared as shown in Chart 5. Com pound **38** was hydrolyzed with hydrochloric acid in acetic

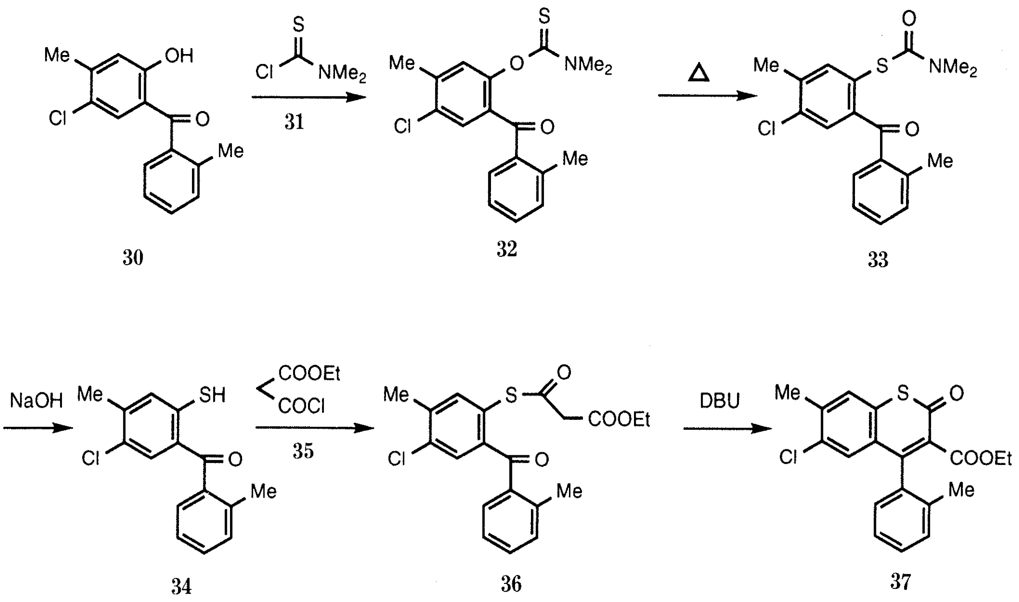


Chart 4

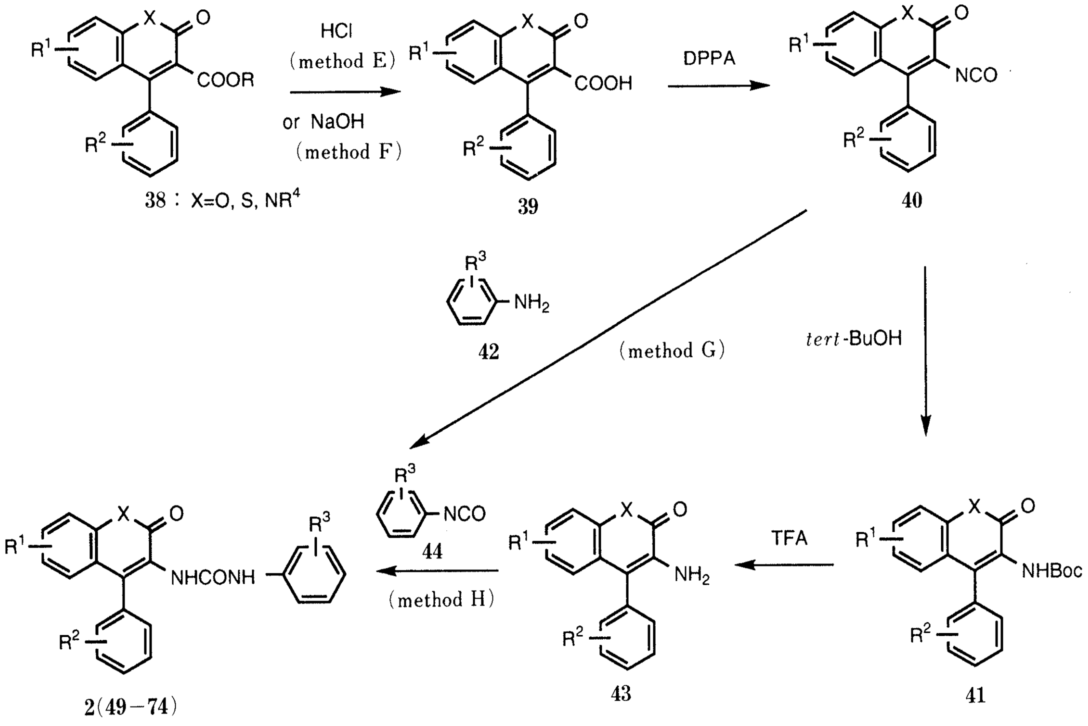


Chart 5

acid (method E) or potassium hydroxide in aqueous EtOH (method F) to yield the carboxylic acid derivatives (**39**). Reaction of **39** with diphenyl phosphoryl azide (DPPA) gave the 3-isocyanato derivatives (**40**), which were used in the next reaction without isolation. Compounds **40** were reacted with substituted aniline derivatives (**42**) to afford **2** in good yield (method G). When **39** was reacted with DPPA in *tert*-BuOH, the 3-*tert*-butoxycarbonylamino derivative (**41**) was obtained. Deprotection of **41** followed by reaction with the substituted phenylisocyanates (**44**) also gave **2** (method H).

2-Alkoxy derivatives (**45**) were similarly converted to the 3-ureido derivative (**48**) as shown in Chart 6.

Results and Discussion

The *in vitro* ACAT-inhibitory activity (IC_{50} value) and physical properties of the urea derivatives of coumarin, 2-quinolone and 2-alkoxyquinoline are shown in Tables 1 and 2.

Structure–activity relationships of these derivatives (**2**) with regard to substituents R^1 and R^2 were substantially similar to those observed with quinoline derivatives which we have reported previously.[2)]

Introduction of substituents at the 6-position of the coumarin ring increased the ACAT-inhibitory activity (**49**, **50** *vs.* **52**—**56**), and the compound bearing an *o*-substituent on the phenyl group at the 4-position of the coumarin ring was more potent than the *o*-unsubstituted derivative (**51**

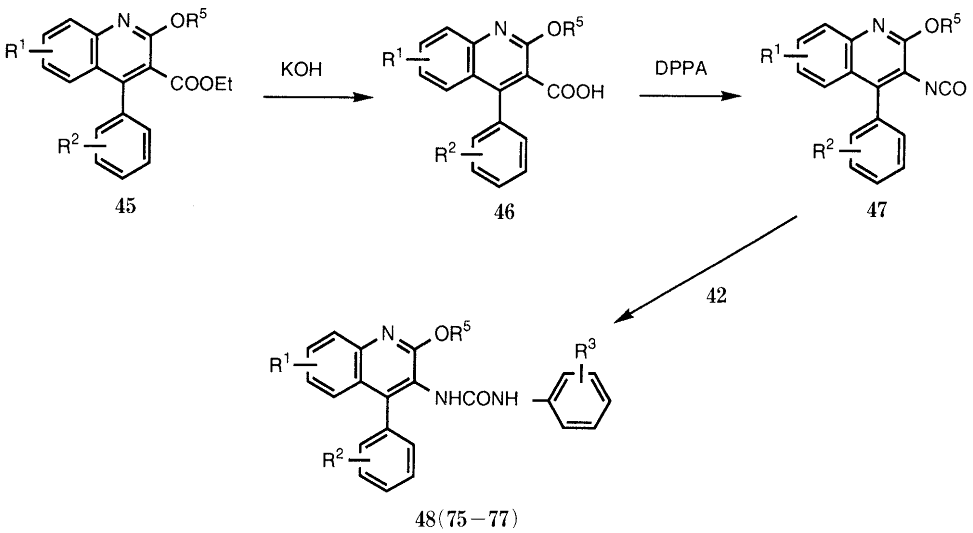
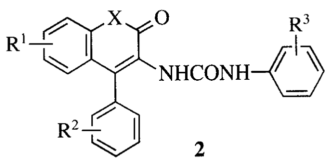


Chart 6

Table 1. Physical and Biological Properties of Urea Derivatives of Coumarin and 2-Quinolone



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Compd. No.	R^1	R^2	R^3	X	mp (°C)	Formula[a)]	Method	Yield (%)	Recrystn. solvent[b)]	ACAT inh. IC_{50} (nM)
49	H	2-Me	2,4-F_2	O	240—243	$C_{23}H_{16}F_2N_2O_3$	G	89.9	E	42.0
50	H	2-MeO	2,4-F_2	O	224—228	$C_{23}H_{16}F_2N_2O_4$	G	61.1	A	31.0
51	6-Cl	H	2,4-F_2	O	209—210	$C_{22}H_{13}ClF_2N_2O_3$	G	81.5	E	89.4
52	6-Cl	2-Me	2,4-F_2	O	210—212	$C_{23}H_{15}ClF_2N_2O_3$	G	70.7	E	9.4
53	6-Cl	2-Me	2-Me-6-iso-Pr	O	237—238	$C_{27}H_{25}ClN_2O_3$	G	88.9	E	8.7
54	6-Me	2-Me	2,4-F_2	O	213—214	$C_{24}H_{18}F_2N_2O_3$	G	86.3	A–H	13.4
55	6-Et	2-Me	2,4-F_2	O	210—211	$C_{25}H_{20}F_2N_2O_3$	G	73.7	E	10.9
56	6-iPr	2-Me	2,4-F_2	O	199—200	$C_{26}H_{22}F_2N_2O_3$	G	64.3	E	15.7
57	6,7-Me_2	2-Cl	2,4-F_2	O	212—214	$C_{24}H_{17}ClF_2N_2O_3$	G	91.0	A–H	5.0
58	6,7-Me_2	2-Me	4-Cl	O	234—236	$C_{25}H_{24}ClN_2O_3$	H	88.2	A	7.0
59	6-Cl-7-Me	2-Me	2,4-F_2	O	224—225	$C_{24}H_{17}ClF_2N_2O_3$	H	88.8	E	5.9
60	6-Me-7-Cl	2-Me	2,4-F_2	O	233—234	$C_{24}H_{17}ClF_2N_2O_3$	G	84.8	A	5.5
61	6-Cl-7-Me	2-Me	2,4-F_2	S	206—208	$C_{24}H_{17}ClF_2N_2O_3S$	G	73.6	A–H	21.8
62	6,7-$(CH_2)_3$	2-Me	2,4-F_2	O	223—224	$C_{26}H_{20}F_2N_2O_3$	G	98.7	aq. E	0.8
63	6,7-$(CH_2)_4$	2-Me	2,4-F_2	O	222—223	$C_{27}H_{22}F_2N_2O_3$	G	96.1	A	6.5
64	6-Cl	2-Cl	2-Me-6-iso-Pr	NMe	148—150	$C_{27}H_{25}Cl_2N_3O_2$	G	76.7	EA	18.0
65	6-Cl	2-Me	2,4-F_2	NMe	163—165	$C_{24}H_{18}ClF_2N_3O_2$	G	85.0	E	35.0
66	6-Cl	2-Me	2-Me-6-iso-Pr	NMe	195—196	$C_{28}H_{28}ClN_3O_2$	G	83.5	E–H	17.0
67	6-Cl	3,4-$(MeO)_2$	2-Me-6-iso-Pr	NMe	200—201	$C_{29}H_{30}ClN_3O_4$	G	77.5	E	41.0
68	6-Et	2-Cl	2,4-F_2	NMe	192—195	$C_{25}H_{29}ClF_2N_3O_2$	G	84.0	E–H	25.0
69	6-Et	2-Cl	2-Me-6-iso-Pr	NMe	198—199	$C_{29}H_{30}ClN_3O_2$	G	88.7	E	12.0
70	6,7-Me_2	2-Cl	2,4-F_2	NMe	242—244	$C_{25}H_{20}ClF_2N_3O_2$	G	75.4	E–C	6.4
71	6,7-Me_2	2-Cl	2,4-F_2	NEt	186—188	$C_{26}H_{22}ClF_2N_3O_2$	G	86.3	E	16.0
72	6,7-Me_2	2-Me	2,4-F_2	NMe	225—226	$C_{26}H_{23}F_2N_3O_2$	G	79.4	A	7.8
73	6-Me-7-Cl	2-Me	2,4-F_2	NMe	227—229	$C_{25}H_{20}ClN_3O_2$	G	93.1	E–C	9.3
74	6,8-Me_2	2-Cl	2,4-F_2	NMe	225—227	$C_{25}H_{20}ClN_3O_2$	G	87.4	A	27.1

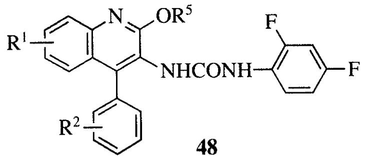
a) All compounds were analyzed for C, H and N; analytical results for these elements were within ±0.4% of the calculated values. *b*) A = acetone, C = chloroform, E = ethanol, H = hexane, EA = ethyl acetate.

vs. **52**). The effects of these substitutions were independent of the electronic nature of the substituents, *i.e.*, electron-withdrawing (Cl) or electron-donating (Me).

As the substituent R^3, 2-methyl-6-isopropyl, 2,4-difluoro and 4-chloro groups were used, and the *in vitro* biological activities of the products were compared. No marked differences in biological effect were seen among compounds with these substituents (see **52**, **53**, **57**, **58**, **65**, **66**, **68**, and **69**). The thiocoumarin (**61**) showed weaker biological activity than the corresponding coumarin (**59**).

2-Quinolone derivatives (**64**—**74**) also had potent ACAT-inhibitory activity, comparable to that of the

Table 2. Physical and Biological Properties of 2-Alkoxyquinolylurea Derivatives

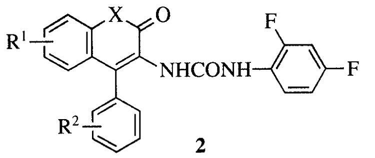


48

Compd. No.	R^1	R^2	R^5	mp (°C)	Formula[a)]	Method	Yield (%)	Recrystn. solvent[b)]	ACAT inh. IC_{50} (nM)
75	6-Cl	H	Et	238—239	$C_{24}H_{18}ClF_2N_3O_2$	G	78.3	E	>1000
76	6-Cl	2-Cl	Me	217—218	$C_{23}H_{15}Cl_2F_2N_3O_2$	G	80.1	A	166
77	6,8-Me_2	2-Cl	Me	231—232	$C_{25}H_{20}ClF_2N_3O_2$	G	89.5	A	168

a, b) See the corresponding footnotes in Table 1.

Table 3. Plasma Cholesterol-Lowering Effect of Urea Derivatives of Coumarin and 2-Quinolone in Cholesterol-Fed Rats



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Compd. No.	R^1	R^2	X	Dose (mg/kg/d)	Plasma cholesterol (% of control)
57	6,7-Me_2	2-Cl	O	0.27	$46.1 \pm 11.7^{b,c)}$
59	6-Cl-7-Me	2-Me	O	0.22	$35.0 \pm 4.9^{b)}$
60	6-Me-7-Cl	2-Me	O	0.23	$42.2 \pm 8.4^{b,d)}$
62	6,7-$(CH_2)_3$-	2-Me	O	0.23	$43.0 \pm 6.9^{b,d)}$
70	6,7-Me_2	2-Cl	NMe	0.27	$64.5 \pm 9.6^{c)}$
73	6-Me-7-Cl	2-Me	NMe	0.24	$59.7 \pm 21.6^{c,d)}$
Control					$100.0 \pm 23.3^{a)}$

Seven-week-old, male Sprague-Dawley rats were given a cholesterol diet containing 1% cholesterol, 0.5% cholic acid and 5% olive oil for 7 d. The compounds were given to them as a dietary admixture. Plasma cholesterol concentration in rats fed the cholesterol diet was 189±37 mg/dl and that in rats fed a normal diet was 49.8±6.8 mg/dl. Different superscripts indicate a significant difference ($p<0.05$) between the respective data by Duncan's multiple range test.

coumarin derivatives. The N^1-methyl analogue seemed to have higher biological activity than the N^1-ethyl analogue (**70** *vs.* **71**).

6,7-Disubstituted derivatives tended to have optimal biological effects in both the coumarin and quinolone series. In particular, the 6,7-cyclopentanocoumarin derivative (**62**) had the lowest IC_{50} value, at the level of 10^{-10} M. Conversion from the 2-oxo group to an alkoxy group (**75**—**77**) tended to decrease the inhibitory activity (Table 2).

Among the compounds evaluated *in vitro*, **57**, **59**, **60**, **62**, **70** and **73** were chosen for *in vivo* evaluation. All compounds decreased the plasma cholesterol level by 35—65% in cholesterol-fed rats at doses of 0.22—0.27 mg/kg/d (Table 3). Hypocholesterolemic activities of these coumarin derivatives in rats were similar to that of TMP-153 (**1**, $ED_{50}=0.25$ mg/kg/d),[2)] a quinoline derivative. The bioavailability of compound **59** was 16.8% and that of TMP-153 was less than 5% in rats. The increased bioavailability of coumarin derivatives may contribute to the reduction of atherosclerosis through direct action on the atheroma. Therefore these compounds are expected to be useful as hypocholesterolemic and antiatherosclerotic agents.

Experimental

Pharmacological Methods. 1) ACAT-Inhibitory Effect The intestines were removed from 6-week-old, male Sprague–Dawley rats and placed on ice. The first 15 cm of the intestine from the stomach was discarded. The next 30 cm was washed with ice-cold saline solution, and the wall was scraped with a microscope slide. The mucosa was placed in 10 ml of a 0.25 M sucrose solution (pH 6.2) and homogenized with a motor-driven Teflon pestle at 0—4 °C. The mucosal homogenate was centrifuged at 12000 *g* for 15 min, and then the supernatant was centrifuged at 100800 *g* for 30 min to isolate the microsomes.

The ACAT activity in the microsomes was determined in terms of the formation of labeled cholesteryl ester from [1-^{14}C]oleoyl-CoA and endogenous cholesterol using a slightly modified version of the method of Helgerud *et al.*[8)] The microsomes (0.2 mg of protein) were preincubated in a vial containing 0.46 ml of 0.154 M phosphate buffer (pH 7.4) and 42 nmol of bovine serum albumin (fatty acid free) at 37 °C for 15 min. Then the reaction was initiated by the addition of 10 nmol of oleoyl-CoA containing 3.7 kBq of [1-^{14}C]oleoyl-CoA (20 μl) and 2 min later was stopped by adding 6 ml of chloroform–methanol (2 : 1). Lipids were extracted by the method of Folch *et al.*[9)] The lipid extract was taken quantitatively for separation by thin-layer chromatography on Silica gel 60-F_{254} (Merck). The area containing cholesteryl ester was scraped off and the radioactivity was counted with a liquid scintillation counter. The test compound dissolved in dimethyl sulfoxide at various concentrations was added to the vial before preincubation. The inhibitory effect of the test compound on the ACAT activity was expressed as the IC_{50} value, which is the concentration required to reduce the enzyme activity by 50% (Tables 1 and 2).

2) Hypocholesterolemic Effect Animals and Diet: Animals were individually housed in metal cages in a room with controlled temperature (23±1 °C), humidity (55±5%) and light (7 a.m.—7 p.m.). They were weaned at 4 weeks of age, maintained freely on water and a stock diet, CE-2 (Clea Japan Inc., Tokyo), and used at 7—10 weeks of age without fasting.

Hypocholesterolemic Activity: Seven-week-old, male Sprague-Dawley rats were given compounds as a dietary admixture in a cholesterol diet containing 1% cholesterol, 0.5% cholic acid and 5% olive oil in CE-2 for 7 d. Blood was taken from the tail vein, and plasma cholesterol was measured enzymatically using commercially available assay kits (Iatron Laboratories Inc., Tokyo). Drug intake was calculated from the diet intake.

Chemistry Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi IR-215 spectrometer in Nujol. NMR spectra were recorded on a Varian Gemini-200 spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are given in ppm with tetramethylsilane as the internal standard, and coupling constants (*J*) are given as Hz. The following abbreviations are used: s = singlet, d = doublet, m = multiplet, t = triplet, br = broad, br s = broad singlet and bt = broad triplet.

Synthesis of 2-Quinolone-3-carboxylic Acid Esters (114—131, Table 5) Typical examples are given to illustrate the general procedure.

Ethyl 6-Chloro-1,2-dihydro-2-oxo-4-phenyl-3-quinolinecarboxylate (114, Table 5). Method A A mixture of 2-amino-5-chlorobenzophenone (**3**, R^1=5-Cl, R^2=H, 6.93 g, 30 mmol), diethyl malonate (7.2 g, 45 mmol) and piperidine (0.3 ml, 3 mmol) was heated at 170 °C for 4 h. After cooling, the mixture was crystallized from isopropyl ether (IPE) to afford **114** (7.77 g, 79.3%). Recrystallization from EtOH gave pale yellow needles, mp 223—224 °C. IR: 3150, 1745, 1650. NMR: 0.97 (3H, t, J=7.5 Hz), 4.08 (2H, q, J=7.5 Hz), 7.23—7.55 (9H, m). *Anal.* Calcd for $C_{18}H_{14}ClNO_3$: C, 65.96; H, 4.31; N, 4.27. Found: C, 66.01; H, 4.31; N, 4.40.

Ethyl 6-Chloro-1,2-dihydro-1-methyl-2-oxo-4-phenyl-3-quinolinecarboxylate (115, Table 5). Method B NaH (60% in oil, 0.35 g, 8.8 mmol) was added to a stirred solution of **114** (2.62 g, 8 mmol) in *N*,*N*-dimethylformamide (DMF) (24 ml). The mixture was stirred at room temperature for 30 min, and MeI (0.6 ml, 9.6 mmol) was added dropwise with ice-cooling. The stirring was continued for 1 h with cooling and for 3 h at room temperature. Then the mixture was poured into ice-water and extracted with AcOEt. The usual work-up of the extract gave **115** as an oil which was crystallized from IPE (2.35 g, 92.7%). Recrystallization from EtOH gave colorless needles, mp 124—125 °C. IR: 1730, 1630. NMR: 0.95 (3H, t, J=7.5 Hz), 3.75 (3H, s), 4.07 (2H, q, J=7.5 Hz), 7.58—7.61 (8H, m). *Anal.* Calcd for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72; N, 4.10. Found: C, 66.72; H, 4.72; N, 3.97.

Other compounds shown in Table 5 were prepared by the above methods A and B.

Methyl 4-(2-Chlorophenyl)-1,2-dihydro-2-oxo-1,6,8-trimethyl-3-quinolinecarboxylate (11). Method C A mixture of 2-amino-2′-chloro-3,5-dimethylbenzophenone (**3**, R^1=3,5-Me_2, R^2=2-Cl, 3.0 g, 11.6 mmol), Ac_2O (4.0 ml) and pyridine (15.0 ml) was heated at 80 °C for 3 h. After dilution with H_2O, the mixture was extracted with $CHCl_3$. The usual work-up of the extract gave 2-acetamido-2′-chloro-3,5-dimethylbenzophenone (**6**) as an oil, which was crystallized from IPE to give a solid (3.0 g, 86.0%). Recrystallization from EtOH gave colorless prisms, mp 137—138 °C. NMR: 2.12 (3H, s), 2.23 (3H, s), 2.27 (3H, s), 6.98 (1H, s), 7.26 (1H, br s), 7.33—7.47 (4H, m), 8.98 (1H, br s). NaH (60% in oil, 0.32 g, 8 mmol) was added to a stirred solution of **6** (2.4 g, 8 mmol) obtained above in DMF (16 ml). Stirring was continued for 20 min at room temperature, then MeI (0.55 ml, 8 mmol) was added dropwise, and the mixture was stirred at room temperature for 1 h, diluted with H_2O and extracted with AcOEt. The usual work-up of the extract gave 2′-chloro-3,5-dimethyl-2-(*N*-methylacetamido)benzophenone as an oil, which was crystallized from hexane to give a crystalline mass (2.0 g, 79.7%). Recrystallization from IPE gave colorless needles, mp 92—93 °C. NMR: 1.74 (3H, s), 2.21 (3H, s), 2.33 (3H, s), 2.85 (3H, s), 7.17 (1H, br s), 7.27 (1H, br s), 7.37—7.50 (4H, m). A mixture of 2′-chloro-3,5-dimethyl-2-(*N*-methylacetamido)benzophenone (2.0 g, 6.3 mmol) and 70% H_2SO_4 (20 ml) was heated at 180 °C for 6 h with stirring. After cooling, the mixture was poured into ice-water, made alkaline with concentrated NH_4OH and extracted with AcOEt. The usual work-up of the extract gave 2′-chloro-3,5-dimethyl-2-methylaminobenzophenone (**7**) as a yellow oil (1.25 g, 72%). NMR: 2.07 (3H, s), 2.38 (3H, s), 2.98 (3H, s), 6.82 (1H, r bs), 7.05 (1H, br s), 7.27—7.47 (4H, m), 8.02 (1H, br). Methyl malonyl chloride (**8**, 6.7 g, 49.1 mmol) was added dropwise to a stirred and ice-cooled mixture of **7** (5.0 g, 18.3 mmol), Et_3N (7.8 ml, 55.7 mmol) and AcOEt (100 ml). The mixture was stirred for 1.5 h with ice-cooling, washed with H_2O, dried ($MgSO_4$) and concentrated to give methyl *N*-[2-(2-chlorobenzoyl)-4,6-dimethylphenyl]-*N*-methymalonylamide (**9**) as an oil in quantitative yield. The oil obtained above was dissolved in tetrahydrofuran (THF) (50 ml), and *tert*-BuOK (2.3 g, 20.5 mmol) was added portionwise to the solution with ice-cooling. The mixture was stirred for 30 min with ice-cooling and then the reaction was quenched with 2 N HCl (10 ml). After dilution with H_2O, the mixture was extracted with AcOEt. The usual work-up of the extract gave an oil, which was chromatographed on silica gel using benzene–acetone (9 : 1) as an eluent. The eluate was concentrated to afford **11** as an oil, which was crystallized from IPE to give a solid (3.85 g, 59.2%). Recrystallization from EtOH gave colorless prisms, mp 128—129 °C. IR: 1750, 1730, 1635. NMR: 2.21 (3H, s), 2.69 (3H, s), 3.56 (3H, s), 6.67 (1H, br s), 7.22—7.58 (5H, m). *Anal.* Calcd for $C_{20}H_{18}ClNO_3$: C, 67.51; H, 5.10; N, 3.92. Found: C, 67.37; H, 5.07; N, 3.92.

Synthesis of 2-Alkoxyquinoline-3-carboxylic Acid Esters. Ethyl 4-(2-Chlorophenyl)-2-methoxy-6,8-dimethyl-3-quinolinecarboxylate (10) MeI (0.15 ml, 2.4 mmol) was added dropwise to a stirred mixture of ethyl 4-(2-chlorophenyl)-1,2-dihydro-6,8-dimethyl-2-oxo-3-quinolinecarboxylate (**131**, 0.71 g, 2 mmol), K_2CO_3 (0.28 g, 2 mmol) and DMF (8 ml). The mixture was stirred at room temperature for 5 h, poured into ice-water and extracted with AcOEt. The usual work-up of the extract gave **10** (0.67 g, 90.5%) as crystals, mp 135—136 °C. IR: 1730. NMR: 0.93 (3H, t, J=7.5 Hz), 2.31 (3H, s), 2.69 (3H, s), 4.05 (2H, q, J=7.5 Hz), 4.12 (3H, s), 6.82 (1H, br s), 7.24—7.58 (5H, m). *Anal.* Calcd for $C_{21}H_{20}ClNO_3$: C, 68.20; H, 5.47; N, 3.79. Found: C, 68.27; H, 5.47; N, 3.82.

Methyl 6-Chloro-4-(2-chlorophenyl)-2-methoxy-3-quinolinecarboxylate (14, R^2=2-Cl, R=R^5=Me) A mixture of ethyl 6-chloro-4-(2-chlorophenyl)-1,2-dihydro-2-oxo-3-quinolinecarboxylate (**116**, 1.0 g, 2.8 mmol) and $POCl_3$ (5 ml, 53.6 mmol) was refluxed for 5 h. After removal of the excess $POCl_3$, the residue was diluted with H_2O to give ethyl 2,6-dichloro-4-(2-chlorophenyl)-3-quinolinecarboxylate (0.7 g, 70.0%) as crystals. The crystals were dissolved in MeOH (20 ml) and MeONa (28% in MeOH, 0.5 ml) was added. The mixture was refluxed for 3 h and diluted with H_2O to afford **14** (0.61 g, 87.1%) as crystals. Recrystallization from MeOH gave colorless needles, mp 151—152 °C. IR: 1735. NMR: 3.58 (3H, s), 4.12 (3H, s), 7.21—7.91 (7H, m). *Anal.* Calcd for $C_{18}H_{13}Cl_2NO_3$: C, 59.69; H, 3.62; N, 3.87. Found: C, 59.91; H, 3.61; N, 3.87.

Synthesis of 2-Alkoxyquinoline-3-carboxylic Acids. 6-Chloro-4-(2-chlorophenyl)-2-methoxy-3-quinolinecarboxylic Acid (46, R^1=6-Cl, R^2=2-Cl, R^5=Me) A mixture of methyl 6-chloro-4-(2-chlorophenyl)-2-methoxy-3-quinolinecarboxylate (**14**, R^2=Cl, R=Me, 400 mg, 1.1 mmol), KOH (310 mg, 5.5 mmol) and EtOH (8 ml) was refluxed for 2.5 h. After dilution with H_2O, the mixture was adjusted to pH 2 with 2 N HCl to give the title compound as crystals which were collected and recrystallized from Et_2O–hexane to afford colorless prisms (263 mg, 68.5%), mp 188—190 °C. IR: 1730, 1600. NMR: 4.14 (3H, s), 7.15—7.89 (7H, m). *Anal.* Calcd for $C_{17}H_{11}Cl_2NO_3$: C, 58.64; H, 3.18; N, 4.02. Found: C, 58.43; H, 3.07; N, 4.13.

The following compound was similarly prepared.

4-(2-Chlorophenyl)-2-methoxy-6,8-dimethyl-3-quinolinecarboxylic Acid (46, R^1=6,8-Me_2, R^2=2-Cl, R^5=Me) Yield 97.3%, mp 179—180 °C (EtOH). NMR: 2.30 (3H, s), 2.69 (3H, s), 4.17 (3H, s), 6.80 (1H, s), 7.13—7.57 (5H, m). *Anal.* Calcd for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72; N, 4.10. Found: C, 66.76; H, 4.82; N, 4.05.

6-Chloro-2-ethoxy-4-phenyl-3-quinolinecarboxylic Acid (46, R^1=6-Cl, R^2=H, R^5=Et) Triethyloxonium fluoroborate (5.0 g, 26 mmol) was added to a stirred solution of ethyl 6-chloro-1,2-dihydro-4-phenyl-2-oxo-3-quinolinecarboxylate (**114**, 3.27 g, 10 mmol) in CH_2Cl_2 (30 ml). The mixture was stirred at room temperature for 4 h, washed with aqueous $NaHCO_3$ solution and H_2O, dried ($MgSO_4$) and concentrated to afford in a quantitative yield ethyl 6-chloro-2-ethoxy-4-phenyl-3-quinolinecarboxylate (**14**, R^2=H, R=R^5=Et) as an oil. The oil was dissolved in EtOH (30 ml) and KOH (1.68 g, 27.8 mmol) was added. The mixture was refluxed for 3 h, diluted with H_2O and acidified with 2 N HCl to give the title compound as crystals (2.48 g, 75.8%). Recrystallization from EtOH gave colorless prisms, mp 191—192 °C. NMR (DMSO-d_6): 1.38 (3H, t, J=7.5 Hz), 4.55 (2H, q, J=7.5 Hz), 7.27—7.93 (8H, m). *Anal.* Calcd for $C_{18}H_{14}ClNO_3$: C, 65.96; H, 4.31; N, 4.27. Found: C, 65.92; H, 4.31; N, 4.21.

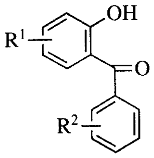
Synthesis of 2-Hydroxybenzophenones (Method D-1—4). Method D-1 General Procedure: To a stirred and ice-cooled solution of **15** (0.1 mol) and Et_3N (0.1 mol) in CH_2Cl_2 (100 ml) was added dropwise **16** (0.1 mol). The mixture was stirred for 1—3 h with cooling, washed with H_2O, dried ($MgSO_4$) and concentrated to afford in quantitative yield crude **17**, which was used in the next reaction without purification. A mixture of **17** (0.1 mol) obtained above and $AlCl_3$ (0.12 mol) was heated at 100—150 °C for 0.5—3 h. After the reaction was complete, the mixture was poured into diluted HCl and extracted with AcOEt. The usual work-up of the extract gave crude **18**.

The compounds shown in Table 4 were prepared similarly.

2-Hydroxy-2′-methylbenzophenone (20). Method D-2 A mixture of 5-chloro-2-hydroxy-2′-methylbenzophenone (**19**, 6.15 g, 25 mmol), AcOK (2.47 g, 25 mmol) and EtOH (75 ml) was hydrogenated in the presence of 10% Pd–C (1.85 g, wet) at room temperature under atmospheric pressure. After the hydrogenation was complete, the catalyst was filtered off, and the filtrate was concentrated. The residue was diluted with H_2O and extracted with AcOEt. The usual work-up of the extract gave **20** (5.2 g, 98.1%) as an oil. NMR: 2.30 (3H, s), 6.76—6.84 (1H, m), 7.03—7.08 (1H, m), 7.25—7.53 (7H, m).

2-Hydroxy-2′-methoxybenzophenone (24). Method D-3 2-Bromoani-

Table 4. Physical Properties of 2-Hydroxybenzophenones



Compound No.	R^1	R^2	mp (°C)	Formula[a)]	Yield (%)	Recrystn. solvent[b)]	Method
20	H	2-Me	Oil	$C_{14}H_{12}O_2$	98.1	—	D-2
24	H	2-MeO	Oil	$C_{14}H_{12}O_3$	91.6	—	D-3
78	5-Cl	H	82—85	$C_{13}H_9ClO_2$	68.7	E	D-1
79	5-Cl	2-Me	67—68	$C_{14}H_{11}ClO_2$	71.1	E	D-1
80	5-Me	2-Me	94—95	$C_{15}H_{14}O_2$	73.0	E	D-1
81	5-Et	2-Me	Oil	$C_{16}H_{16}O_2$	95.8	—	D-1
82	5-iso-Pr	2-Me	Oil	$C_{17}H_{18}O_2$	98.4	—	D-1
83	4,5-Me_2	2-Cl	81—82	$C_{15}H_{13}ClO_2$	58.6	E	D-1
84	4,5-Me_2	2-Me	56—57	$C_{16}H_{16}O_2$	80.8	E	D-1
30	5-Cl-4-Me	2-Me	57—58	$C_{15}H_{13}ClO_2$	76.6	E	D-1
85	5-Me-4-Cl	2-Me	72—73	$C_{15}H_{13}ClO_2$	31.2	E	D-1
86	4,5-$(CH_2)_3$-	2-Me	64—65	$C_{17}H_{16}O_2$	73.4	E	D-1
27	4,5-$(CH_2)_4$-	2-Me	Oil	$C_{18}H_{18}O_2$	96.5	—	D-4

a, b) See the corresponding footnotes in Table 1.

sole (18.7 g, 0.1 mol) was added dropwise to a mixture of Mg (2.4 g, 0.1 mol) and absolute THF (50 ml) to afford a Grignard reagent (**22**). Then a solution of 2-benzyloxybenzaldehyde (**21**) in absolute THF (50 ml) was added dropwise to the Grignard reagent with ice-cooling. The mixture was stirred at room temperature for 1 h, quenched with aqueous NH_4Cl solution and extracted with AcOEt. The usual work-up of the extract gave an oil, which was dissolved in acetone (200 ml). The Jones reagent (40 ml) was added dropwise to the acetone solution with ice-cooling. The mixture was stirred at room temperature for 1 h, and evaporated to half the initial volume. After dilution with H_2O, the mixture was extracted with AcOEt. The usual work-up of the extract gave an oil, which was dissolved in EtOH (200 ml). The solution was hydrogenated in the presence of 10% Pd–C (5.0 g, wet) at room temperature under atmospheric pressure. After the hydrogenation was complete, the catalyst was filtered off, and the filtrate was concentrated to yield **24** (16.4 g, 91.6%) as an oil. NMR: 3.77 (3H, s), 6.76—6.84 (1H, m), 6.99 (3H, m), 7.25—7.55 (6H, m).

3-(2-Methylbenzoyl)-5,6,7,8-tetrahydro-2-naphthol (27). Method D-4 2-Methylbenzoyl chloride (4.62 g, 30 mmol) was added dropwise to a stirred and ice-cooled solution of 1-bromo-5,6,7,8-tetrahydro-2-naphthol (**25**, 6.81 g, 30 mmol)[6)] and Et_3N (4.2 ml, 30 mmol) in CH_2Cl_2 (60 ml). The mixture was stirred for 1 h with cooling, washed with H_2O, dried ($MgSO_4$) and concentrated to give 2-benzoyloxy-1-bromo-5,6,7,8-tetrahydronaphthalene as an oil in quantitative yield. A mixture of the oil obtained above and $AlCl_3$ (4.8 g, 36 mmol) was heated at 120 °C for 1 h, then added to a mixture of 2 N HCl and AcOEt (1 : 1, 100 ml), and the organic layer was separated. The aqueous layer was extracted with AcOEt. The usual work-up of the combined extract gave 1-bromo-3-(2-methylbenzoyl)-5,6,7,8-tetrahydro-2-naphthol (**26**, 4.0 g, 40.0%) as crystals. Recrystallization from EtOH gave yellow prisms, mp 151—153 °C. NMR: 1.50—1.93 (4H, m), 2.28 (3H, s), 2.43—2.93 (4H, m). 6.93 (1H, s), 7.18—7.42 (5H, m). *Anal.* Calcd. for $C_{18}H_{17}BrO_2$: C, 62.62; H, 4.96. Found: C, 62.52; H, 5.03. A mixture of **26** (3.33 g, 9.6 mmol), AcONa (0.82 g, 9.6 mmol), MeOH (10 ml) and dioxane (20 ml) was hydrogenated in the presence of 5% Pd–C (1.0 g) at room temperature under atmospheric pressure. After the hydrogenation was complete, the catalyst was filtered off, and the filtrate was concentrated. The residue was diluted with H_2O and extracted with AcOEt. The usual work-up of the extract gave **27** (2.45 g, 96.5%) as an oil. NMR: 1.71—1.78 (4H, m), 2.30 (3H, s), 2.56 (2H, t, J=5.8 Hz), 2.75 (2H, t, J=6.2 Hz), 6.77 (1H, s), 6.95 (1H, s), 7.25—7.45 (5H, m).

Synthesis of 3-Coumarincarboxylic Acid Esters (87—99, Table 5). Method D General Procedure: A mixture of 2-hydroxybenzophenone (**18**, **20**, **24** or **27**, 1.0 mol) diethyl malonate (1.5—3 mol) and base [piperidine (0.1 mol), DBU (0.1 mol) or KF (0.1—1 mol)] was heated at 160—200 °C for 1—8 h. The usual work-up of the reaction mixture gave **28** as crystals. When a mixture of **28** and **29** was formed in the reaction, they were separated by column chromatography on silica gel.

The other compounds shown in Table 5 were prepared similarly.

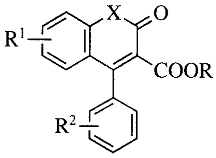
5-Chloro-4,2′-dimethyl-2-(*N*,*N*-dimethylthiocarbamoyloxy)benzophenone (32) A solution of *N*,*N*-dimethylthiocarbamoyl chloride (**31**, 3.7 g, 30 mmol) in DMF (5 ml) was added dropwise to a stirred solution of 5-chloro-2-hydroxy-4,2′-dimethylbenzophenone (**30**, 7.8 g, 30 mmol) and DBU (4.5 ml, 30 mmol) in DMF (60 ml). The mixture was stirred for 1 h at room temperature, then DBU (4.5 ml, 30 mmol) and **31** (3.7 g, 30 mmol) were added. The whole was stirred for 2 h at room temperature. DBU (4.5 ml, 30 mmol) and **31** (3.7 g, 30 mmol) were added again, and the stirring was continued for an additional 2 h. The mixture was diluted with H_2O and extracted with AcOEt. The usual work-up of the extract gave **32** as an oil, which was crystallized from hexane to afford a solid (9.85 g, 93.3%). Recrystallization from EtOH gave pale brown prisms, mp 97—98 °C. IR: 1650, 1600. NMR: 2.42 (6H, s), 2.87 (3H, s), 3.22 (3H, s), 6.98 (1H, s), 7.07-7.47 (4H, m), 7.57 (1H, s). *Anal.* Calcd for $C_{18}H_{18}ClNO_2S$: C, 62.15; H, 5.22; N, 4.03. Found: C, 62.16; H, 5.37; N, 3.99

5-Chloro-4,2′-dimethyl-2-(*N*,*N*-dimethylcarbamoylthio)benzophenone (33) Compound **32** (8.0 g, 23 mmol) was heated at 195—200 °C for 5 h with stirring under an argon atmosphere. After cooling, the mixture was crystallized by addition of EtOH to give crystals (6.73 g, 84.1%). Recrystallization from EtOH gave **33** as pale brown prisms, mp 109—110 °C. IR: 1665, 1650. NMR: 2.43 (3H, s), 2.53 (3H, s), 2.86 (6H, s), 7.12—7.40 (4H, m), 7.44 (1H, s), 7.49 (1H, s). *Anal.* Calcd for $C_{18}H_{18}ClNO_2S$: C, 62.15; H, 5.22; N, 4.03. Found: C, 62.29; H, 5.28; N, 3.98.

5-Chloro-4,2′-dimethyl-2-mercaptobenzophenone (34) A mixture of **33** (6.0 g, 17.3 mmol), 2 N NaOH (35 ml) and MeOH–dioxane (1 : 1, 80 ml) was heated at 60—70 °C for 2.5 h under an argon atmosphere. After dilution with H_2O, the mixture was acidified with 6 N HCl and extracted with AcOEt. The usual work-up of the extract gave **34** (4.5 g, 94.3%) as an oil. NMR: 2.34 (3H, s), 2.38 (3H, s), 4.65 (1H, s), 7.25—7.46 (6H, m). The product was used in the next reaction without further purification.

Ethyl 6-Chloro-7-methyl-4-(2-methylphenyl)-2-oxo-1-thiobenzopyran-3-carboxylate (37) Ethyl malonyl chloride (**35**, 2.61 g, 17.4 mmol) was added dropwise to a stirred and ice-cooled solution of **34** (4.0 g, 14.5 mmol) and Et_3N (2.43 ml, 17.4 mmol) in CH_2Cl_2 (40 ml). The mixture was stirred for 30 min with ice-cooling, washed with H_2O, dried ($MgSO_4$) and concentrated to give in quantitative yield ethyl 4-chloro-5-methyl-2-(2-methylbenzoyl)phenylthiocarbonylacetate (**36**) as an oil. NMR: 1.23 (3H, t, J=7 Hz), 2.45 (3H, s), 2.50 (3H, s), 4.16 (2H, q, J=7 Hz), 5.30 (2H, s), 7.15—7.48 (6H, m). A mixture of 36 obtained above, DBU (0.44 ml, 2.9 mmol) and benzene (40 ml) was refluxed for

Table 5. Physical Properties of 3-Carboxylic Acid Derivatives of Coumarin and 2-Quinolone



Compd. No.	R^1	R^2	R	X	mp (°C)	Formula[a)]	Yield (%)	Recrystn. solvent[b)]	Method
87	H	2-Me	Et	O	112—113	$C_{19}H_{16}O_4$	60.9	E	D
88	H	2-MeO	Et	O	112—113	$C_{19}H_{16}O_5$	34.1	E	D
89	6-Cl	H	Et	O	108—109	$C_{18}H_{13}ClO_4$	75.0	E	D
90	6-Cl	2-Me	Et	O	97—98	$C_{19}H_{15}ClO_4$	58.5	E	D
91	6-Me	2-Me	Et	O	99—100	$C_{20}H_{18}O_4$	76.1	A–H	D
92	6-Et	2-Me	Et	O	93—94	$C_{21}H_{20}O_4$	43.2	IPE[c)]	D
93	6-iso-Pr	2-Me	Et	O	85—86	$C_{22}H_{22}O_4$	40.7	E	D
94	6,7-Me$_2$	2-Cl	Et	O	130—131	$C_{20}H_{17}ClO_4$	43.5	E	D
95	6,7-Me$_2$	2-Me	Et	O	94—95	$C_{21}H_{20}O_4$	83.2	E	D
96	6-Cl-7-Me	2-Me	Et	O	100—101	$C_{20}H_{17}ClO_4$	71.2	E	D
97	6-Me-7-Cl	2-Me	Et	O	122—123	$C_{20}H_{17}ClO_4$	66.7	E	D
98	6,7-(CH$_2$)$_3$	2-Me	Et	O	113—114	$C_{22}H_{20}O_4$	50.9	E	D
99	6,7-(CH$_2$)$_4$	2-Me	Et	O	Oil	$C_{23}H_{22}O_4$	89.0	—	D
37	6-Cl-7-Me	2-Me	Et	S	139—140	$C_{20}H_{17}ClO_3S$	23.3	IPE	D
100	H	2-Me	H	O	170—172	$C_{17}H_{12}O_4$	90.7	E	E
101	H	2-MeO	H	O	145—147	$C_{17}H_{12}O_5$	96.2	E	E
102	6-Cl	H	H	O	180—181	$C_{16}H_9ClO_4$	79.2	EA–E	E
103	6-Cl	2-Me	H	O	220—221	$C_{17}H_{11}ClO_4$	93.8	E	E
104	6-Me	2-Me	H	O	207—209	$C_{18}H_{14}O_4$	97.8	E–H	E
105	6-Et	2-Me	H	O	167—168	$C_{19}H_{16}O_4$	98.3	A–H	E
106	6-iso-Pr	2-Me	H	O	155—156	$C_{20}H_{18}O_4$	77.2	E–H	E
107	6,7-Me$_2$	2-Cl	H	O	217—218	$C_{18}H_{13}ClO_4$	73.6	E–H	E
108	6,7-Me$_2$	2-Me	H	O	231—232	$C_{19}H_{16}O_4$	72.1	E	E
109	6-Cl-7-Me	2-Me	H	O	241—242	$C_{18}h_{13}ClO_4$	99.5	E–H	E
110	6-Me-7-Cl	2-Me	H	O	254—255	$C_{18}H_{13}ClO_4$	94.2	E	E
111	6,7-(CH$_2$)$_3$	2-Me	H	O	213—214	$C_{20}H_{16}O_4$	74.1	A–H	E
112	6,7-(CH$_2$)$_4$	2-Me	H	O	216—217	$C_{21}H_{18}O_4$	84.8	A–H	E
113	6-Cl-7-Me	2-Me	H	S	248—250	$C_{18}H_{13}ClO_3S$	64.1	IPE	E
114	6-Cl	H	Et	NH	223—224	$C_{18}H_{14}ClNO_3$	79.3	E	A
115	6-Cl	H	Et	NMe	124—125	$C_{19}H_{16}ClNO_3$	92.7	E	B
116	6-Cl	2-Cl	Et	NH	223—224	$C_{18}H_{13}Cl_2NO_3$	66.3	E–C	A
117	6-Cl	2-Cl	Et	NMe	139—140	$C_{19}H_{15}Cl_2NO_3$	86.5	E	B
118	6-Cl	2-Me	Et	NH	215—216	$C_{19}H_{16}ClNO_3$	84.2	E	A
119	6-Cl	2-Me	Et	NMe	113—114	$C_{20}H_{18}ClNO_3$	88.5	E	B
120	6-Cl	3,4-(MeO)$_2$	Et	NH	209—210	$C_{20}H_{18}ClNO_5$	76.8	E	A
121	6-Cl	3,4-(MeO)$_2$	Et	NMe	104—105	$C_{21}H_{20}ClNO_5$	99.6	E	B
122	6-Et	2-Cl	Et	NH	199—200	$C_{20}H_{18}ClNO_3$	95.0	E	A
123	6-Et	2-Cl	Et	NMe	125—126	$C_{21}H_{20}ClNO_3$	96.2	E–H	B
124	6,7-Me$_2$	2-Cl	Me	NH	288—289	$C_{19}H_{16}ClNO_3$	83.7	E–C	A
125	6,7-Me$_2$	2-Cl	Me	NMe	202—203	$C_{20}H_{18}ClNO_3$	80.3	E	B
126	6,7-Me$_2$	2-Cl	Me	NEt	172—173	$C_{21}H_{20}ClNO_3$	41.3	E	B
127	6,7-Me$_2$	2-Me	Me	NH	288—289	$C_{20}H_{19}NO_3$	82.6	E–C	A
128	6,7-Me$_2$	2-Me	Me	NMe	170—171	$C_{21}H_{21}NO_3$	91.3	E	B
129	6-Me-7-Cl	2-Me	Et	NH	290—291	$C_{20}H_{18}ClNO_3$	93.8	E–C	A
130	6-Me-7-Cl	2-Me	Et	NMe	121—123	$C_{21}H_{20}ClNO_3$	89.7	E–H	B
131	6,8-Me$_2$	2-Cl	Et	NH	257—258	$C_{19}H_{16}ClNO_3$	85.1	E–C	A
11	6,8-Me$_2$	2-Cl	Me	NMe	128—129	$C_{20}H_{18}ClNO_3$	59.2	E	C
132	6-Cl	2-Cl	H	NMe	197—198	$C_{17}H_{11}Cl_2NO_3$	85.0	E	F
133	6-Cl	2-Me	H	NMe	202—203	$C_{18}H_{14}ClNO_3$	88.2	E	F
134	6-Cl	3,4-(MeO)$_2$	H	NMe	230—232	$C_{19}H_{16}ClNO_5$	80.6	E–C	F
135	6-Et	2-Cl	H	NMe	200—201	$C_{19}H_{16}ClNO_3$	94.4	E	F
136	6,7-Me$_2$	2-Cl	H	NMe	250—251	$C_{19}H_{16}ClNO_3$	93.8	E–C	F
137	6,7-Me$_2$	2-Cl	H	NEt	168—170	$C_{20}H_{18}ClNO_3$	80.6	E–C	F
138	6,7-Me$_2$	2-Me	H	NMe	236—237	$C_{20}H_{19}NO_3$	83.2	A	F
139	6-Me-7-Cl	2-Me	H	NMe	204—205	$C_{19}H_{16}ClNO_3$	97.8	E	F
140	6,8-Me$_2$	2-Cl	H	NMe	251—252	$C_{19}H_{16}ClNO_3$	93.8	E–C	F

a, *b*) See the corresponding footnotes in Table 1. *c*) IPE = isopropyl ether.

1 h with a Dean-Stark apparatus. The mixture was washed with H_2O, dried ($MgSO_4$) and concentrated to give an oil, which was chromatographed on silica gel using hexane–Et_2O (5 : 1) as an eluent. The eluate was concentrated to afford **37** (1.23 g, 23.3%) as crystals. Recrystallization from IPE gave pale yellow plates, mp 139—140 °C. IR: 1730, 1625. NMR: 0.90 (3H, t, J=7 Hz), 2.13 (3H, s), 2.46 (3H, s), 3.97 (2H, q, J=7), 7.07—7.43 (6H, m). *Anal.* Calcd. for $C_{20}H_{17}ClO_3S$: C, 64.42; H, 4.60. Found: C, 64.33; H, 4.56.

Synthesis of Coumarin-3-carboxylic Acids (100—112, Table 5), 2-Quinolone-3-carboxylic Acid (132—140, Table 5) and Thiocoumarin-3-carboxylic Acid (113, Table 5) Typical examples are given to illustrate the general procedure.

a) Acid Hydrolysis. Method E. 6-Chloro-7-methyl-4-(2-methylphenyl)-2-oxo-2*H*-1-benzopyran-3-carboxylic Acid (109, Table 5) A mixture of ethyl 6-chloro-7-methyl-4-(2-methylphenyl)-2-oxo-2*H*-1-benzopyran-3-carboxylate (**96**, 6.0 g, 16.8 mmol), 6 N HCl (15 ml) and AcOH (30 ml) was refluxed for 10 h. The mixture was diluted with H_2O to give **109** (5.5 g, 99.5%) as crystals. Recrystallization from EtOH–hexane gave colorless prisms, mp 241—242 °C. IR: 1730, 1700. NMR: 2.07 (3H, s), 2.50 (3H, s), 6.90—7.52 (6H, m). *Anal.* Calcd for $C_{18}H_{13}ClO_4$: C, 65.73; H, 3.99. Found: C, 65.97; H, 4.05.

b) Alkaline Hydrolysis. Method F. 4-(2-Chlorophenyl)-1,2-dihydro-2-oxo-1,6,8-trimethyl-3-quinolinecarboxylic Acid (140, Table 5) A mixture of methyl 4-(2-chlorophenyl)-1,2-dihydro-1,6,8-trimethyl-3-quinolinecarboxylate (**11**, 2.7 g, 7.6 mmol), KOH (1.27 g, 22.7 mmol) and 90% EtOH (30 ml) was refluxed for 30 min. After dilution with H_2O, the mixture was acidified with 2 N HCl and extracted with $CHCl_3$. The usual work-up of the extract gave **140** (2.43 g, 93.8%) as crystals. Recrystallization from $CHCl_3$–EtOH gave colorless prisms, mp 251—252 °C. IR: 1730. NMR: 2.21 (3H, s), 2.45 (3H, s), 3.90 (3H, s), 6.88 (1H, s), 7.03-7.63 (5H, m). *Anal.* Calcd for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72; N, 4.10. Found: C, 67.00; H, 4.68; N, 3.99.

Other compounds shown in Table 5 were prepared by the above method E or F.

Synthesis of 3-Aminocoumarin Derivatives (43, X=O). 3-*tert*-Butoxycarbonylamino-6-chloro-7-methyl-4-(2-methylphenyl-2*H*-1-benzopyran-2-one (41, R^1=6-Cl, 7-Me, R^2=2-Me, X=O) Et_3N (1.4 ml, 10 mmol) was added dropwise to a mixture of 6-chloro-7-methyl-4-(2-methylphenyl)-2-oxo-2*H*-1-benzopyran-3-carboxylic acid (**109**, 3.28 g, 10 mmol), DPPA (3.3 g, 12 mmol) and *tert*-BuOH (40 ml). The mixture was stirred at room temperature for 30 min and refluxed for 2 h. After removal of the solvent, the residue was diluted with H_2O and extracted with AcOEt. The usual work-up of the extract gave the title compound as an oil, which was crystallized by addition of hexane to give a solid (3.45 g, 86.5%). Recrystallization from EtOH gave colorless prisms, mp 183—185 °C. NMR: 0.75 (9H, s), 2.17 (3H, s), 2.47 (3H, s), 5.97 (1H, br s), 6.98 (1H, s), 7.10—7.45 (4H, m), 7.39 (1H, s). *Anal.* Calcd for $C_{22}H_{22}ClNO_4$: C, 66.08; H, 5.55; N, 3.50. Found: C, 65.97; H, 5.65; N, 3.51.

The following compound was prepared similarly.

3-*tert*-Butoxycarbonylamino-6,7-dimethyl-4-(2-methylphenyl)-2*H*-1-benzopyran-2-one (41, R^1=6,7-Me_2, R^2=2-Me, X=O) Yield 81.0%, mp 205—206 °C (EtOH). NMR: 1.30 (9H, s), 2.13 (3H, s), 2.15 (3H, s), 2.32 (3H, s), 5.82 (1H, br s), 6.87 (1H, s), 7.07—7.40 (5H, m). *Anal.* Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.54; H, 6.70; N, 3.68.

3-Amino-6-chloro-7-methyl-4-(2-methylphenyl)-2*H*-1-benzopyran-2-one (43, R^1=6-Cl, 7-Me, R^2=2-Me, X=O) Trifluoroacetic acid (10 ml) was added dropwise to a stirred and ice-cooled solution of 3-*tert*-butoxycarbonylamino-6-chloro-7-methyl-4-(2-methylphenyl)-2*H*-1-benzopyran-2-one (**41**, R^1=6-Cl, 7-Me, R^2=2-Me, X=O, 3.2 g, 8 mmol) in CH_2Cl_2 (20 ml). The mixture was stirred for 30 min with cooling and for 1 h at room temperature. After removal of the solvent, the residue was neutralized with aqueous $NaHCO_3$ solution and extracted with AcOEt. The usual work-up of the extract gave the title compound as an oil, which was crystallized from IPE to give solid (2.22 g, 92.5%). Recrystallization from EtOH–CH_2Cl_2 gave colorless plates, mp 215—217 °C. NMR: 2.14 (3H, s), 2.41 (3H, s), 6.75 (1H, s), 7.15—7.50 (4H, m), 7.27 (1H, s). *Anal.* Calcd for $C_{17}H_{14}ClNO_2$: C, 68.12; H, 4.71; N, 4.67. Found: C, 68.26; H, 4.74; N, 4.65.

The following compound was similarly prepared.

3-Amino-6,7-dimethyl-4-(2-methylphenyl)-2*H*-1-benzopyran-2-one (43, R^1=6,7-Me_2, R^2=2-Me, X=O) Yield 95.8%, mp 229—230 °C (EtOH). NMR: 2.13 (3H, s), 2.16 (3H, s), 2.28 (3H, s), 3.93 (2H, br s), 6.51 (1H, s), 7.12 (1H, s), 7.18—7.39 (4H, m). *Anal.* Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.62; H, 6.18, N, 4.99.

Synthesis of Urea Derivatives (49—77, Tables 1 and 2) Typical examples are given to illustrate the general procedure.

Methdod G. *N*-{4-(2-Chlorophenyl)-1,2-dihydro-2-oxo-1,6,7-trimethyl-3-quinolyl]-*N*′-(2,4-difluorophenyl)urea (70) Et_3N (0.14 ml, 1 mmol) was added dropwise to a stirred mixture of 4-(2-chlorophenyl)-1,2-dihydro-2-oxo-1,6,7-trimethyl-3-quinolinecarboxylic acid (**136**, 341 mg, 1 mmol), DPPA (330 mg, 1.2 mmol) and benzene (6 ml). The mixture was stirred at room temperature for 20 min and refluxed for 40 min. Then 2,4-difluoroaniline (0.12 ml, 1.2 mmol) was added, and the whole was refluxed for 3.5 h, washed with H_2O, diluted HCl, H_2O, aqueous $NaHCO_3$ solution and H_2O, successively, dried ($MgSO_4$) and concentrated to afford **70** (352 mg, 75.4%) as crystals. Recrystallization from $CHCl_3$–EtOH gave colorless prisms, mp 242—244 °C. IR: 3320, 1695, 1605. NMR ($CDCl_3$–DMSO-d_6): 2.18 (3H, s), 2.39 (3H, s), 3.78 (3H, s), 6.63—6.93 (2H, m) 7.23 (1H, s), 7.36—8.07 (7H, m), 8.37—8.50 (1H, m). *Anal.* Calcd for $C_{25}H_{20}ClF_2N_3O_2$: C, 64.17; H, 4.31; N, 8.98. Found: C, 64.14; H, 4.26; N, 8.88

Other compounds shown in Table 1 were prepared by the above method G.

***N*-[6-Chloro-7-methyl-4-(2-methylphenyl)-2-oxo-2*H*-1-benzopyran-3-yl]-*N*-(2,4-difluorophenyl)urea (59). Method H** A mixture of 3-amino-6-chloro-7-methyl-4-(2-methylphenyl)-2*H*-1-benzopyran-2-one (299 mg, 1 mmol), 2,4-difluorophenyl isocyanate (310 mg, 2 mmol) and benzene (4 ml) was refluxed for 2 h. After removal of the solvent, Et_2O was added to the residue to yield **59** (403 mg, 88.8%) as crysals. Recrystallization from EtOH gave colorless needles, mp 224—225 °C. IR: 3320, 1725, 1630. NMR: 2.15 (3H, s), 2.47 (3H, s), 6.55—6.85 (3H, m), 6.95 (1H, s), 7.12—7.40 (4H, m), 7.53—7.85 (1H, m). *Anal.* Calcd for $C_{24}H_{17}ClF_2N_2O_3$: C, 63.74; H, 3.77; N, 6.16. Found: C, 63.70; H, 3.75; N, 6.12.

Synthesis of 2-Alkoxy-3-quinolylureas (75—77, Table 2) These compounds were prepared in practically the same manner as that described under method G for **70**.

***N*-[6-Chloro-4-(2-chlorophenyl)-2-methoxy-3-quinolyl]-*N*′-(2,4-difluorophenyl)urea (76)** Et_3N (0.1 ml, 0.7 mmol) was added to a stirred solution of 6-chloro-4-(2-chlorophenyl)-2-methoxy-3-quinolinecarboxylic acid (200 mg, 0.57 mmol) and DPPA (190 mg, 0.69 mmol) in benzene (3 ml). The mixture was stirred at room temperature for 30 min and refluxed for 1 h. Then 2,4-difluoroaniline (0.07 ml, 0.69 mmol) was added, and the whole was refluxed for 1 h, washed with H_2O, dried ($MgSO_4$) and concentrated to give **76** as an oil, which was crystallized from IPE to give crystals (225 mg, 80.1%). Recrystallization from EtOH gave colorless needles. mp 217—218 °C. IR: 3400, 3300, 1690, 1610. NMR ($CDCl_3$–DMSO-d_6): 1.18 (1.5H, t, J=7 Hz), 3.62 (1H, q, J=7 Hz), 4.12 (3H, s), 6.67—6.92 (2H, m), 7.10 (1H, d, J=3 Hz), 7.37—7.57 (4H, m), 7.80—8.25 (2H, m), 8.33 (1H, br s). *Anal.* Calcd for $C_{23}H_{15}Cl_2F_2N_3O_2E \cdot 1/2C_2H_5OH$: C, 57.96; H, 3.65; N, 8.45. Found: C, 57.72; H, 3.85; N, 8.21.

Compounds **75** and **77** were prepared similarly.

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