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Regioselective Displacement Reactions of 1-Cyclopropyl-5,6,7,8-tetrafluoro-4(1*H*)-oxoquinoline-3-carboxylic Acid with Amine Nucleophiles[1)]

Koh-ichiro SHIBAMORI, Hiroshi EGAWA, Teruyuki MIYAMOTO,* Yoshiro NISHIMURA, Akira ITOKAWA, Junji NAKANO and Jun-ichi MATSUMOTO

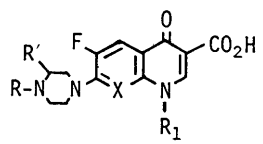
Research Laboratories Dainippon Pharmaceutical Co., Ltd., Enoki 33–94, Suita, Osaka 564, Japan. *Received February 9, 1990*

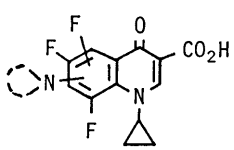
The displacement reactions of ethyl 1-cyclopropyl-5,6,7,8-tetrafluoro-4(1*H*)-oxoquinoline-3-carboxylate (7) and its carboxylic acid 8 with amine nucleophiles were examined. The nucleophilic displacement occurred regioselectively at the C-5 or C-7 position depending on the substrate (7 or 8) and solvent selected; this finding permitted the introduction of an optional nucleophile preferentially into the required position at either C-5 or C-7, or into both positions with a desired combination of nucleophiles. Taking advantage of this regioselectivity, we prepared various 5-substituted 6,7,8-trifluoro- and 7-substituted 5,6,8-trifluoro-1-cyclopropyl-4(1*H*)-oxoquinoline-3-carboxylic acids. Furthermore, the use of the boron-chelated derivative of the carboxylic acid 8 was favorable for the regioselective synthesis of 7-substituted 5,6,8-trifluoroquinolones.

Keywords regioselective synthesis; 5,6,8-trifluoro-4-quinolone; 6,7,8-trifluoro-4-quinolone; nucleophilic substitution; solvent effect; 5,6,7,8-tetrafluoroquinolone; boron-chelated quinolone

During the last decade, world-wide attention has been given to the synthesis of quinolone derivatives as potential new antibacterial agents. Clinically important agents in this class commonly bear a 1-substituted 4(1*H*)-oxopyridine-3-carboxylic acid moiety and, because of this common structural feature, are also known as pyridonecarboxylic acid. All of the agents of this class recently introduced into clinical practice, for example, norfloxacin (**1**),[2)] enoxacin (**2**),[3)] and ciprofloxacin (**3**),[4)] are structurally characterized by the combination of a fluorine atom at C-6 with a piperazinyl group at C-7. More recently, several compounds bearing an additional fluorine atom at C-8 of the 6-fluoroquinolones were reported, as exemplified by fleroxacin (**4**)[5)] and lomefloxacin (**5**).[6)] However, no clinically useful agents (or even promising candidates) appended with a C-5 substituent have been developed thus far. This situation prompted us to introduce a further fluorine atom at C-5 of the 6,8-difluoroquinolone ring system and to convert the C-5 and/or C-7 fluorine atom(s) into other functional groups, in the hope of developing new agents with improved antibacterial activity.

We first planned a synthesis of 5- and 7-(cyclic amino)-1-cyclopropyl-6,8-difluoroquinolones with a general structure **6**, starting with ethyl 1-cyclopropyl-5,6,7,8-tetrafluoro-4(1*H*)-oxoquinoline-3-carboxylate (**7**) and its carboxylic acid **8**. A general and convenient method that has been reported for the synthesis of the C-7 amine-substituted quinolones in this class involves the displacement reaction of 7-chloro- or 7-fluoroquinolones with an appropriate amine nucleophile in the final step.[2,4–7)] The displacement reactions of **7** and **8** with amines, however, are predicted to proceed preferentially at C-5 or C-7, or concurrently at both C-5 and C-7. The present study therefore was undertaken primarily to develop a method for regioselective substitution at C-5 and at C-7. After our work on this was completed,[8)] a similar synthesis of several compounds with the general structure **6** was reported by Moran *et al.*,[9)] who, however, had not systematically studied the regioselectivity of the reaction. We report herein our findings which allow us in principle to introduce

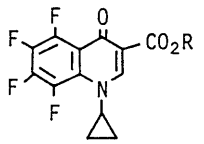




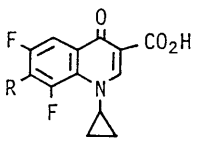
1 : X = CH, $R_1 = C_2H_5$, R′ = R = H
2 : X = N, $R_1 = C_2H_5$, R′ = R = H
3 : X = CH, R_1 = cyclo-C_3H_5, R′ = R = H
4 : X = CF, $R_1 = FCH_2CH_2$, R′ = H, R = CH_3
5 : X = CF, $R_1 = C_2H_5$, R′ = CH_3, R = H

6

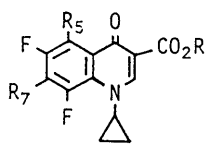
Chart 1



7 : R = Et
8 : R = H



23 : R = F
24 : R = H_3CN N-



9 : R_5 = N- , R_7 = F, R = Et
10 : R_5 = F, R_7 = N- , R = Et
11 : R_5 = N- , R_7 = F, R = Et
12 : R_5 = F, R_7 = N- , R = Et
13 : R_5 = N- , R_7 = F, R = H
14 : R_5 = F, R_7 = N- , R = H
15 : R_5 = N- , R_7 = F, R = H
16 : R_5 = F, R_7 = N- , R = H
17 : R_5 = EtNH, R_7 = F, R = Et
18 : R_5 = F, R_7 = EtNH, R = Et
19 : R_5 = EtNH, R_7 = F, R = H
20 : R_5 = F, R_7 = EtNH, R = H
21 : R_5 = EtO, R_7 = F, R = Et
22 : R_5 = F, R_7 = EtO, R = Et

Chart 2

regioselectively an optional nucleophile into the required position at either C-5 or C-7.

Displacement reactions of the ester **7** and its carboxylic acid **8** were first examined with pyrrolidine and piperidine as representative nucleophiles in an appropriate solvent (Chart 2). When the ester **7** was treated with pyrrolidine in acetonitrile in the presence of triethylamine, compounds **9** and **10** were isolated. The reaction of **7** with piperidine under the same conditions also produced two compounds, **11** and **12**. A similar treatment of the carboxylic acid **8** with pyrrolidine and piperidine afforded pairs of products **13** and **14**, and **15** and **16**, respectively. Elemental analysis, mass spectra (MS), and proton nuclear magnetic resonance (^{1}H-NMR) spectra of the products showed the presence of three fluorine atoms and a pyrrolidinyl or piperizinyl group on the phenyl ring, indicating that each pair of products **9**/**10**, **11**/**12**, **13**/**14**, and **15**/**16** is regioisomeric.

In order to get reference data for determining the structures of the regioisomers **9**—**16** (hence the displacement site of the amine), we measured the fluorine-19 nuclear magnetic resonance (^{19}F-NMR) spectra of **23** and **24**, of which the structures had been unambiguously defined.[4] The ^{19}F-NMR spectral study revealed the following (Table I); (i) the C-8 fluorines of **23** and **24** coupled to protons of the N-1 cyclopropyl group as well as to the C-6 and C-7 fluorines, thereby giving multiplet signals, (ii) the *ortho*- and *meta*-coupling constants for the fluorines of **23** were approximately 20 and 7 Hz, respectively, and (iii) displacement of the C-7 fluorine with an amine caused a downfield shift of the C-6 and C-8 fluorines by more than 10 ppm, along with an increase in the *meta*-coupling constant ($J_{6,8}$) by 4 Hz. In addition, the fluorines of the pentafluoroquinolines **7** and **8** (Table I) showed *ortho*-coupling constants ($J_{5,6}$, $J_{6,7}$ and $J_{7,8}$) of approximately 20 Hz, and a *para*-coupling constant ($J_{5,8}$) of 13 Hz; the *meta*-coupling constant $J_{5,7}$ was approximately 9 Hz, but $J_{6,8}$ was not observed. These coupling constant values are in accord with those for the perfluoroaromatic compounds reported by Bruce.[10] On the basis of the data, the ^{19}F-NMR spectra of **9**—**16** were assigned as shown in Table I and these results enabled us to determine the structures; thus compounds **9**, **11**, **13**, and **15** were C-5 substituted and their regioisomers **10**, **12**, **14**, and **16** were C-7 substituted.

Displacement reactions of the ester **7** and the carboxylic acid **8** with the amines were thus found to proceed at both C-5 and C-7. Hence, our next effort was focussed on finding reaction conditions suitable for the regioselective introduction of the amine at C-7 or C-5 of the quinoline ring. By the use of substrates **7** and **8** and pyrrolidine and piperidine as nucleophiles, the influence of a solvent, especially its polarity, on the regioselectivity was examined; toluene, acetonitrile and ethanol were selected as solvents. The ratio of the C-5 and C-7 substituted products in the reaction mixture was determined by high-performance liquid chromatography (HPLC). The result are listed in Table II, from which it followed that (i) the ester **7** tended to undergo displacement reaction predominantly at C-5 even in ethanol as well as in toluene, (ii) the carboxylic acid **8**, however, underwent displacement mainly at C-7 in ethanol, whereas in toluene it did so mainly at C-5, (iii) the displacement at C-5 was more predominant with piperidine than with pyrrolidine, and (iv) the yields of the C-7 substituted

TABLE I. ^{19}F-NMR Data for the Fluoroquinoline Derivatives

Compd.	Chemical shift (δ) in $CDCl_3$[a]				Coupling constant $J_{F,F}$ (Hz)					
	F5	F6	F7	F8	$J_{5,6}$	$J_{5,7}$	$J_{5,8}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$
23	—	−133.03	−145.95	−138.85	—	—	—	21.9	6.6	17.5
24	—	−119.50	—	−127.95	—	—	—	—	10.5	—
7	−141.45	−160.21	−149.28	−147.68	20.3	8.7	13.5	21.6	0	20.1
8	−138.44	−157.15	−145.17	−145.32	20.4	10.1	13.3	20.1	0	19.9
9	—	−151.44	−153.76	−156.83	—	—	—	20.4	2.3	21.1
10	−145.89	−153.01	—	−139.84	16.4	—	10.4	—	9.8	—
11	—	−148.60	−153.11	−153.50	—	—	—	22.5	0	20.7
12	−145.06	−149.46	—	−135.31	18.3	—	13.0	—	5.3	—
13	—	−149.35	−149.42	−154.77	—	—	—	20.4	3.0	20.5
14	−143.46	−150.84	—	−139.34	16.4	—	9.8	—	11.6	—
15	—	−146.69	−148.74	−151.60	—	—	—	21.4	0	21.4
16	−142.54	−147.20	—	−134.24	18.4	—	12.4	—	7.4	—
17	—	−160.31	−151.50	−162.11	—	—	—	20.7	4.5	21.9
18	−144.90	−158.35	—	−146.77	18.3	—	11.3	—	8.1	—
19	—	−159.21	−148.05	−160.96	—	—	—	20.6	4.9	21.5
20	−142.78	−156.78	—	−146.35	18.4	—	11.3	—	9.8	—
21	—	−154.14	−151.12	−148.12	—	—	—	22.4	0	20.1
22	−143.77	−155.13	—	−142.01	19.2	—	13.6	—	3.0	—
27a	—	−146.78	−151.43	−148.68	—	—	—	21.2	1	21.5
27c	—	−147.70	−152.07	−150.73	—	—	—	b)	b)	b)
27d	—	−147.08	−151.17	−149.08	—	—	—	b)	b)	b)
28a	—	−145.09	−147.47	−147.27	—	—	—	21.0	1	20.9
28d	—	−145.71	−147.21	−148.83	—	—	—	21.3	1	21.2
29c	—	−145.31	−147.63	−148.51	—	—	—	b)	b)	b)
30a	−141.68	−146.91	—	−133.57	18.6	—	13.1	—	5.5	—
30b	−142.14	−147.07	—	−134.06	18.5	—	12.4	—	6.5	—
30c	−142.26	−147.03	—	−134.05	18.4	—	12.6	—	6.6	—
30e	−143.24	−151.00	—	−139.46	16.5	—	10.0	—	11.5	—

a) Hexafluorobenzene ($\delta = -162.9$) was used as an internal standard. b) Coupling constant was not defined owing to a broad signal.

TABLE II. Displacement Reactions of **7**, **8** and **26** with Nucleophiles

Starting compd.	Nucleophile	Solvent	Method[a]	Ratio (%) by HPLC[a]		
				5-Substituted product	7-Substituted product	Unchanged compd.
7	Pyrrolidine	PhMe	A	**9** (93.1)	**10** (1.8)	**7** (5.1)
		MeCN	A	**9** (55.6)	**10** (42.0)	**7** (2.4)
		EtOH	A	**9** (41.0)	**10** (42.7)	**7** (16.3)
7	Piperidine	PhMe	A	**11** (94.4)	**12** (4.4)	**7** (1.2)
		MeCN	A	**11** (77.5)	**12** (12.3)	**7** (10.2)
		EtOH	A	**11** (62.9)	**12** (13.0)	**7** (24.1)
7	Ethylamine	PhMe	B	**17** (40.7)	**18** (4.5)	**7** (54.8)
		EtOH	B	**17** (27.2)	**18** (72.8)	[b]
7	NaOEt	PhMe	C	**21** (67.4)	**22** (27.0)	**7** (5.6)
		EtOH	C	**21** (11.5)	**22** (88.5)	[b]
8	Pyrrolidine	PhMe	D	**13** (87.8)	**14** (12.2)	[b]
		MeCN	D	**13** (33.9)	**14** (66.1)	[b]
		EtOH	D	**13** (20.6)	**14** (79.4)	[b]
8	Piperidine	PhMe	D	**15** (92.5)	**16** (7.5)	[b]
		MeCN	D	**15** (45.1)	**16** (53.1)	**8** (1.8)
		EtOH	D	**15** (33.1)	**16** (63.4)	**8** (3.5)
8	Ethylamine	PhMe	E	**19** (15.7)	**20** (29.6)	**8** (54.7)
		EtOH	E	**19** (17.7)	**20** (82.3)	[b]
26	Pyrrolidine	EtOH	F	**13** (0.2)	**14** (99.8)	[b]
	Piperidine	EtOH	F	**15** (2.5)	**16** (87.5)	[b]

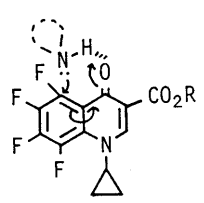
a) See Experimental for the methods and reaction conditions. *b*) Compound was not detected.

compounds (**10**, **12**, **14**, and **16**) increased with increasing polarity of the solvent used. In connection with these findings, when ethylamine and sodium ethoxide were used as a nucleophile, the reaction with the ester **7** took place preferentially at C-7 in ethanol (giving **18** and **22**, respectively), but mainly at C-5 in toluene (giving **17** and **21**, respectively). On the contrary, the carboxylic acid **8** reacted preferentially at C-7 with ethylamine in ethanol to give **20**.

As a result, the orientation of the displacement reaction was controllable by suitable selection of the substrate and solvent. Thus, when the C-7 substituted product is required, one should choose the carboxylic acid **8** along with a polar solvent; on the contrary, the use of the ester **7** or its carboxylic acid **8** with a non-polar solvent provides predominantly the C-5 substituted product.

The orientation in these reactions can be accounted for as follows. The hydrogen bonding between the amine hydrogen and the C-4 oxo group probably plays an important role.[11] Owing to the formation of this hydrogen bonding, the amine nucleophile would be drawn near the C-5 position in the ester **7** and its carboxylic acid **8**; consequently the lone pair of the amine nitrogen would tend to attack C-5 as depicted in **25** (Chart 3), from which the C-5 amine-substituted product would finally results. A non-polar solvent makes this reaction course more favorable than a polar one. A polar solvent, however, may undergo preferential solvation with the amine and/or the C-4 oxo group, therefore restricting hydrogen bond formation as in **25**; thus, in the polar solvent, the C-7 orientation became quite favorable, particularly in the case of the carboxylic acid **8**. The use of the boron-chelated compound **26**, instead of **8**, with the polar solvent caused a remarkable decrease in the C-5 orientation, thus conferring a high regioselectivity at C-7 as shown in Table II. This reaction supports the proposed mechanism discussed above.

Taking advantage of this regioselectivity, we prepared a



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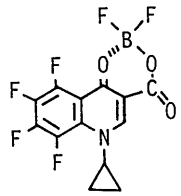

26

Chart 3

series of C-5 and C-7 substituted compounds (Chart 4). The reactions of the ester **7** in toluene with *N*-acetylpiperazine, *N*-methylpiperazine, and 3-acetylaminopyrrolidine gave the C-5 substituted compounds **27a**, **27c**, and **27d**, respectively. A similar reaction of the carboxylic acid **8** in toluene also produced the C-5 substituted compounds **28a** and **28d** in good yields. The hydrolysis of compounds **27a**/**28a**, **27c**, and **27d**/**28d** gave the final products **29b**, **29c**, and **29e**, respectively.

The reactions of the carboxylic acid **8** with *N*-acetylpiperazine, *N*-methylpiperazine, and 3-aminopyrrolidine in ethanol gave the corresponding C-7 substituted compounds **30a**, **c**, **e** in good yields. Deprotection of the acetyl group of **30a** under acidic conditions provided the 7-(1-piperazinyl) compound **30b**, which also was available directly from the reaction of **8** with piperazine itself, though in low yield. However, the boron-chelated compound **26** reacted much more smoothly with piperazine, *N*-methylpiperazine, and 3-aminopyrrolidine in ethanol or dimethyl sulfoxide even at room temperature to give the corresponding C-7 substituted compounds **30b**, **c**, **e**. Furthermore, the treatment of **30c** with cyclopropylamine and pyrrolidine in acetonitrile gave the 5-cyclopropylamino- and 5-(1-pyrrolidinyl)-7-(4-methyl-1-piperazinyl)quinolone derivatives **32** and **33**, respectively. The boron-chelated

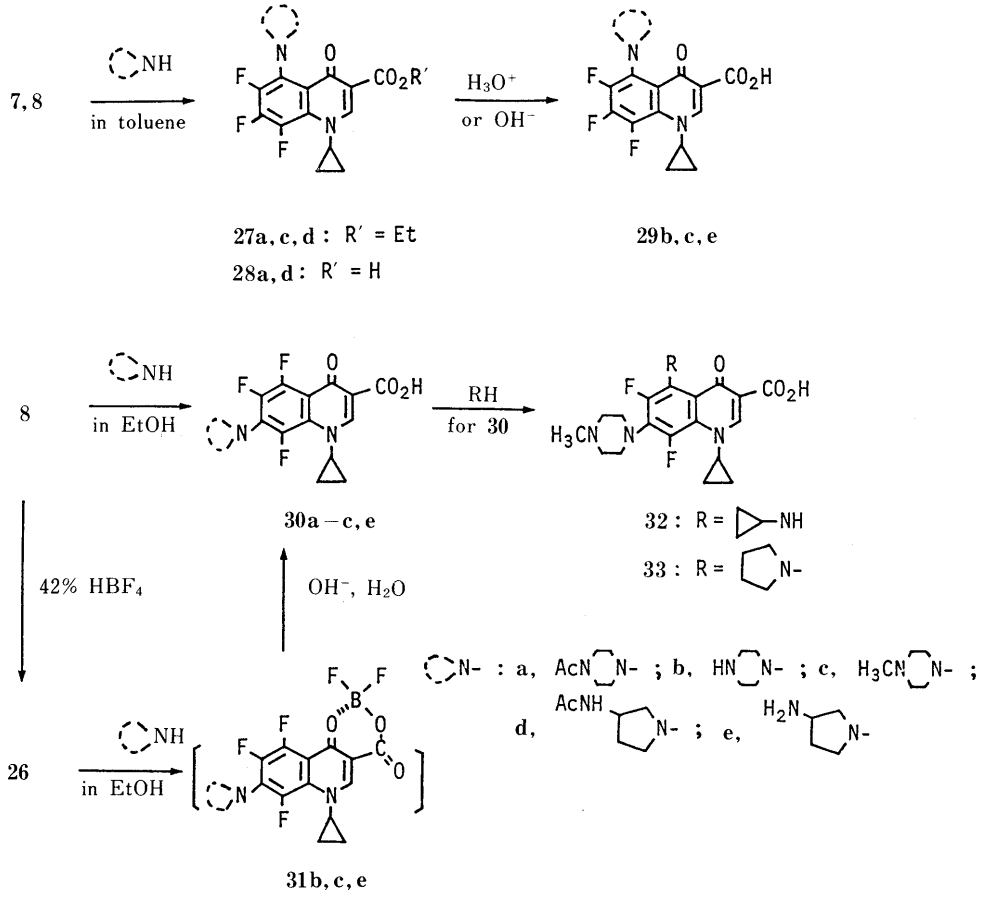

Chart 4

compound **26** used was prepared from the reaction of the carboxylic acid **8** with 42% aqueous tetrafluoroboric acid. The structures of these compounds **27**—**30** were assigned and confirmed on the basis of their ^{19}F-NMR spectral data given in Table I.

In summary, the displacement reactions of ethyl 1-cyclopropyl-5,6,7,8-tetrafluoro-4(1*H*)-oxoquinoline-3-carboxyate (**7**) and its carboxylic acid **8** with amine nucleophiles proceeded regioselectively at the C-5 or C-7 position, depending on the substrate (**7** or **8**) and solvent selected; this finding permitted us to introduce an optional cyclic amine preferentially into the required position at either C-5 or C-7 and, hence, in a stepwise manner into both positions with a desired combination of nucleophiles. In addition, the use of the boron-chelated compound **26** was favorable for the regioselective synthesis of the 7-substituted 5,6,8-trifluoroquinolones. The synthesis and antibacterial activity of further series of derivatives with various substituents at C-5 and/or C-7 of **8** will be reported in a separate paper.[12]

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Jasco A-102 spectrometer for KBr tablets, unless otherwise noted. Electron impact mass spectra (EIMS) were recorded on a JEOL JMS D-300 spectrometer. ^{1}H-NMR spectra were taken at 80 MHz with a Varian FT-80A spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. ^{19}F-NMR spectra were measured at 282 MHz with a Varian XL-300 spectrometer; chemical shifts are expressed in δ (ppm) values with hexafluorobenzene ($\delta = -162.9$)[13] as an internal standard. HPLC was performed with a Shimadzu SPD-6A system (column, YMC-pack A-312 ODS, 6 i.d. × 150 mm, Yamamura Chemical Laboratories Co.; mobile phase, a 3 : 1 mixture of MeCN and 0.2% trifluoroacetic acid or a 7 : 3 mixture of MeOH and 0.1% trifluoroacetic acid; flow rate, 1.0 ml/min; monitored at 290 nm). The extracts were dried over anhydrous Na_2SO_4. The ^{19}F-NMR spectral and elemental analysis data for compounds synthesized are shown in Tables I and III, respectively. The ^{1}H-NMR and MS spectra of all compounds were in accord with the assigned structures.

Displacement Reactions of the Ester 7, the Carboxylic Acid 8, and the Boron-Chelated Compound 26 with Nucleophiles (Table II) A portion of each $CHCl_3$ or CH_2Cl_2 solution obtained by methods A—F was used for the HPLC measurement of the ratio of products; the results are given in Table II.

Method A: A stirred mixture of ethyl 1-cyclopropyl-5,6,7,8-tetrafluoro-4(1*H*)-oxoquinoline-3-carboxylate (**7**)[8,9] (500 mg, 1.52 mmol), pyrrolidine (108 mg, 1.52 mmol) or piperidine (129 mg, 1.52 mmol), and Et_3N (154 mg, 1.52 mmol) in the solvent (15 ml) was heated to reflux for 1 h. The reaction mixture was diluted with an appropriate volume of $CHCl_3$.

Method B: A stirred mixture of **7** (500 mg, 1.52 mmol), ethylamine hydrochloride (124 mg, 1.52 mmol), and Et_3N (3.04 mmol) in the solvent (15 ml) was heated at 60—65 °C for 1 h. The mixture was diluted with an appropriate volume of $CHCl_3$.

Method C: A mixture of **7** (500 mg, 1.52 mmol) and sodium ethoxide (100 mg, 1.52 mmol) in the solvent (15 ml) was stirred at room temperature for 30 min. The mixture was diluted with an appropriate volume of CH_2Cl_2.

Method D: A stirred mixture of 1-cyclopropyl-5,6,7,8-tetrafluoro-4(1*H*)-oxoquinoline-3-carboxylic acid (**8**)[8,9] (500 mg, 1.66 mmol), pyrrolidine (118 mg, 1.66 mmol) or piperidine (141 mg, 1.66 mmol), and Et_3N (340 mg, 3.32 mmol) in the solvent (15 ml) was heated to reflux for 1 h. The reaction mixture was diluted with an appropriate volume of $CHCl_3$.

Method E: A stirred mixture of **8** (500 mg, 1.66 mmol), ethylamine hydrochloride (135 mg, 1.66 mmol), and Et_3N (4.98 mmol) in the solvent (15 ml) was heated at 60—65 °C for 1 h. The mixture was diluted with an appropriate volume of $CHCl_3$.

Method F: A mixture of the boron-chelated compound **26** (500 mg, 1.43 mmol), pyrrolidine (102 mg, 1.43 mmol) or piperidine (122 mg, 1.43 mmol), and Et_3N (289 mg, 2.86 mmol) in EtOH (15 ml) was stirred

TABLE III. The 5- and/or 7-Substituted 1-Cyclopropyl-4(1*H*)-oxoquinoline-3-carboxylic Acid Derivatives

Compd.	mp (°C) (Recryst. solv.)	Yield[a] (%)	Formula	Analysis (%) Calcd (Found)			
				C	H	F	N
9	140—142 (AcOEt)	42	$C_{19}H_{19}F_3N_2O_3$	60.00 (60.17)	5.04 5.15	14.98 15.10	7.37 7.34)
10	208—209 (AcOEt)	35	$C_{19}H_{19}F_3N_2O_3$	60.00 (59.79)	5.04 4.96	14.98 15.07	7.37 7.25)
11	160—161 (AcOEt)	63	$C_{20}H_{21}F_3N_2O_3$	60.91 (60.84)	5.37 5.41	14.45 14.53	7.10 7.04)
12	217—218 (EtOH)	9	$C_{20}H_{21}F_3N_2O_3$	60.91 (61.04)	5.37 5.32	14.45 14.54	7.10 7.03)
13	152—155 (AcOEt)	28	$C_{17}H_{15}F_3N_2O_3$	57.96 (57.89)	4.29 4.11	16.18 16.34	7.95 7.75)
14	>300 ($CHCl_3$)	55	$C_{17}H_{15}F_3N_2O_3$	57.96 (57.96)	4.29 4.44	16.18 16.35	7.95 7.78)
15	200—201 (EtOH)	33	$C_{18}H_{17}F_3N_2O_3$	59.02 (58.93)	4.68 4.67	15.56 15.32	7.65 7.59)
16	290—292 ($CHCl_3$)	41	$C_{18}H_{17}F_3N_2O_3$	59.02 (58.71)	4.68 4.78	15.56 15.84	7.65 7.79)
17	187—188 (EtOH)	15	$C_{17}H_{17}F_3N_2O_3$	57.63 (57.74)	4.84 4.84	16.09 16.05	7.91 7.84)
18	171—172 ($CHCl_3$)	60	$C_{17}H_{17}F_3N_2O_3$	57.63 (57.47)	4.84 5.02	16.09 16.13	7.91 7.87)
19	178—179 (EtOH)	11	$C_{15}H_{13}F_3N_2O_3$	55.22 (55.16)	4.02 4.02	17.49 17.66	8.59 8.49)
20	259—260 ($CHCl_3$)	69	$C_{15}H_{13}F_3N_2O_3$	55.22 (55.21)	4.02 4.11	17.49 17.18	8.59 8.64)
21	150—151 (EtOH)	54	$C_{17}H_{16}F_3NO_4$	57.47 (57.23)	4.54 4.54	16.04 16.02	3.94 3.97)
22	163—164 (EtOH)	19	$C_{17}H_{16}F_3NO_4$	57.47 (57.62)	4.54 4.43	16.04 15.92	3.94 3.81)
27a	162—163 (AcOEt)	87	$C_{21}H_{22}F_3N_3O_4$	57.66 (57.73)	5.07 4.98	13.03 12.88	9.61 9.42)
27c	148—149[b] (AcOEt–iso-Pr_2O)	88	$C_{20}H_{22}F_3N_3O_4$	58.67 (58.40)	5.42 5.39	13.92 13.76	10.26 10.17)
27d	156—157 (AcOEt)	68	$C_{21}H_{22}F_3N_3O_4$	57.66 (57.71)	5.07 4.91	13.03 12.87	9.61 9.61)
28a	253—254 ($CHCl_3$–EtOH)	79	$C_{17}H_{18}F_3N_3O_4 \cdot 3/4H_2O$	54.00 (53.87)	4.65 4.52	13.42 13.41	9.94 9.68)
28d	177—178 (AcOEt)	62	$C_{17}H_{18}F_3N_3O_4$	55.75 (55.67)	4.43 4.27	13.92 13.79	10.26 10.06)
29b	>300 ($CHCl_3$–EtOH)	89	$C_{17}H_{16}F_3N_3O_3 \cdot 1/4H_2O$	54.91 (55.12)	4.47 4.39	15.32 15.24	11.30 11.29)
29c	192—193 (AcOEt–iso-Pr_2O)	96	$C_{18}H_{18}F_3N_3O_3$	56.69 (56.82)	4.76 4.83	14.95 14.63	11.02 10.98)
29e	>300 ($CHCl_3$)	87	$C_{17}H_{16}F_3N_3O_3 \cdot 1/2H_2O$	54.25 (54.55)	4.55 4.29	15.14 15.18	11.17 11.06)
30a	245—246 ($CHCl_3$)	59	$C_{19}H_{18}F_3N_3O_3$	55.75 (55.72)	4.43 4.40	13.92 13.96	10.26 10.15)
30b	208—212 ($CHCl_3$–EtOH)	91[c] 88[d]	$C_{17}H_{16}F_3N_3O_3 \cdot 1/2H_2O$	54.26 (54.14)	4.55 4.83	15.14 15.29	11.17 11.12)
30c	256—257[e] ($CHCl_3$)	65 90[d]	$C_{18}H_{18}F_3N_3O_3$	56.69 (56.69)	4.76 4.80	14.95 15.13	11.02 10.88)
30e	247—250 ($CHCl_3$–EtOH)	90 93[d]	$C_{17}H_{16}F_3N_3O_3 \cdot H_2O$	52.99 (53.15)	4.71 4.52	14.79 14.71	10.90 10.88)
32	190—191 (EtOH)	91	$C_{21}H_{24}F_2N_4O_3$	60.28 (60.31)	5.78 5.85	9.08 9.20	13.39 13.34)
33	180—182 (AcOEt–*n*-hexane)	92	$C_{22}H_{26}F_2N_4O_3 \cdot 3/4H_2O$	59.25 (59.04)	6.22 5.99	8.52 9.04	12.56 12.14)

a) Yields are of the isolated product and are not optimized. *b*) Lit.[9] mp 133—136 °C (CH_2Cl_2–hexane). *c*) The yield is that of the deacetylation reaction. *d*) The yield is that of the reaction of **26** with a cyclic amine. *e*) Lit.[9] mp 245 °C ($CHCl_3$–*n*-hexane).

at room temperature for 1 h. The resulting crystals were collected by filtration, and then dissolved in 1 N NaOH (10 ml). The solution was heated at 80—90 °C for 30 min with stirring, neutralized with diluted AcOH, and extracted with $CHCl_3$.

Ethyl 1-Cyclopropyl-6,7,8-trifluoro-4(1*H*)-oxo-5-(1-pyrrolidinyl and 1-piperidinyl)quinoline-3-carboxylates (9 and 11) and Ethyl 1-Cyclopropyl-5,6,8-trifluoro-4(1*H*)-oxo-7-(1-pyrrolidinyl and 1-piperidinyl)quinoline-3-carboxylates (10 and 12) A stirred mixture of **7** (500 mg, 1.52 mmol), pyrrolidine (108 mg, 1.52 mmol), and Et_3N (150 mg, 1.52 mmol) in MeCN (15 ml) was heated to reflux for 1 h, and then concentrated to dryness *in vacuo*. After an addition of water, the mixture was extracted with $CHCl_3$. The extract was dried and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$ as an eluent to give **9** (240 mg, 42%) and **10** (200 mg, 35%). Compound **9**: IR cm^{-1}: 1725, 1630.

^{1}H-NMR ($CDCl_3$): 0.9—1.3 (4H, m, cyclopropyl CH_2CH_2), 1.35 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.8—2.1 (4H, m, CH_2CH_2), 3.3—3.6 (4H, m, CH_2NCH_2), 3.6—4.0 (1H, m, cyclopropyl CH), 4.33 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 8.28 (1H, s, C_2-H). Compound **10**: IR cm^{-1}: 1725, 1620. ^{1}H-NMR ($CDCl_3$): 0.9—1.3 (4H, m, cyclopropyl CH_2CH_2), 1.40 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.7—2.2 (4H, m, CH_2CH_2), 3.5—4.1 (5H, m, CH_2NCH_2 and cyclopropyl CH), 4.38 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 8.41 (1H, s, C_2-H).

In a similar manner, the reaction of **7** with piperidine gave **11** (63%) and **12** (9%). Compound **11**: IR cm^{-1}: 1720, 1630, 1600. ^{1}H-NMR ($CDCl_3$): 0.9—1.2 (4H, m, cyclopropyl CH_2CH_2), 1.35 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.5—1.8 (6H, m, $CH_2CH_2CH_2$), 3.0—3.3 (4H, m, CH_2NCH_2), 3.5—4.0 (1H, m, cyclopropyl CH), 4.33 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 8.30 (1H, s, C_2-H). Compound **12**: IR cm^{-1}: 1725, 1625. ^{1}H-NMR ($CDCl_3$): 0.9—1.3 (4H, m, cyclopropyl CH_2CH_2), 1.38 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.5—1.8 (6H, m, $CH_2CH_2CH_2$), 3.1—3.4 (4H, m, CH_2NCH_2), 3.6—4.0 (1H, m, cyclopropyl CH), 4.35 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 8.40 (1H, s, C_2-H).

1-Cyclopropyl-6,7,8-trifluoro-4(1*H*)-oxo-5-(1-pyrrolidinyl and 1-piperidinyl)quinoline-3-carboxylic Acids (13 and 15) and 1-Cyclopropyl-5,6,8-trifluoro-4(1*H*)-oxo-7-(1-pyrrolidinyl and 1-piperidinyl)quinoline-3-carboxylic Acids (14 and 16) A stirred mixture of **8** (500 mg, 1.66 mmol), pyrrolidine (118 mg, 1.66 mmol), and Et_3N (340 mg, 3.32 mmol) in MeCN (15 ml) was heated to reflux for 1 h, and then cooled. The resulting crystals were collected by filtration and recrystallized to give 320 mg (55%) of **14**. The filtrate was concentrated to dryness *in vacuo*, and the resulting crystals were collected by filtration and recrystallized to give 160 mg (28%) of **13**. Compound **13**: IR cm^{-1}: 1725, 1625. ^{1}H-NMR ($CDCl_3$): 0.9—1.5 (4H, m, cyclopropyl CH_2CH_2), 1.8—2.2 (4H, m, CH_2CH_2), 3.3—3.7 (4H, m, CH_2NCH_2), 3.7—4.2 (1H, m, cyclopropyl CH), 8.68 (1H, s, C_2-H), 10.4—11.0 (1H, br, CO_2H). Compound **14**: IR cm^{-1}: 1715, 1625. ^{1}H-NMR ($CDCl_3$): 0.9—1.4 (4H, m, cyclopropyl CH_2CH_2), 1.6—2.2 (4H, m, CH_2CH_2), 3.5—4.1 (5H, m, CH_2NCH_2 and cyclopropyl CH), 8.67 (1H, s, C_2-H), 14.6—14.9 (1H, br, CO_2H).

In a similar manner, the reaction of **8** with piperidine gave **15** (33%) and **16** (41%). Compound **15**: IR cm^{-1}: 1715, 1620. ^{1}H-NMR ($CDCl_3$): 0.9—1.3 (4H, m, cyclopropyl CH_2CH_2), 1.4—1.9 (6H, m, $CH_2CH_2CH_2$), 3.0—3.4 (4H, m, CH_2NCH_2), 3.8—4.1 (1H, m, cyclopropyl CH), 8.70 (1H, s, C_2-H), 14.81 (1H, s, CO_2H). Compound **16**: IR cm^{-1}: 1725, 1625. ^{1}H-NMR ($CDCl_3$): 0.9—1.3 (4H, m, cyclopropyl CH_2CH_2), 1.4—1.9 (6H, m, $CH_2CH_2CH_2$), 3.1—3.5 (4H, m, CH_2NCH_2), 3.7—4.1 (1H, m, cyclopropyl CH), 8.68 (1H, s, C_2-H), 14.44 (1H, s, CO_2H).

Ethyl 1-Cyclopropyl-5-ethylamino-6,7,8-trifluoro-4(1*H*)-oxoquinoline-3-carboxylate (17), Ethyl 1-Cyclopropyl-7-ethylamino-5,6,8-trifluoro-4(1*H*)-oxoquinoline-3-carboxylate (18) and Their Carboxylic Acids (19 and 20) A stirred mixture of **7** (500 mg, 1.52 mmol), ethylamine hydrochloride (124 mg, 1.52 mmol), and Et_3N (307 mg, 3.04 mmol) in EtOH (15 ml) was heated at 60—65 °C for 1 h, and then concentrated to dryness *in vacuo*. After an addition of water, the mixture was extracted with $CHCl_3$. The extract was dried and the solvent was evaporated off *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$ as an eluent to give **17** (80 mg, 15%) and **18** (320 mg, 60%). Compound **17**: IR cm^{-1}: 1715, 1635. ^{1}H-NMR ($CDCl_3$): 0.9—1.3 (4H, m, cyclopropyl CH_2CH_2), 1.27 (3H, t, J=7 Hz, $NCH_2C\underline{H}_3$), 1.37 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.3—3.6 (2H, m, $NC\underline{H}_2CH_3$), 3.6—4.0 (1H, m, cyclopropyl CH), 4.35 (2H, q, J=7 Hz, $OCH_2C\underline{H}_3$), 8.34 (1H, s, C_2-H), 9.9—10.3 (1H, br, NH). Compound **18**: IR cm^{-1}: 3275, 1720, 1635. ^{1}H-NMR ($CDCl_3$): 0.9—1.2 (4H, m, cyclopropyl CH_2CH_2), 1.25 (3H, t, J=7 Hz, $NCH_2C\underline{H}_3$), 1.40 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.3—3.8 (3H, m, $NC\underline{H}_2CH_3$ and cyclopropyl CH), 4.35 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 8.36 (1H, s, C_2-H).

In a similar manner, the reaction of **8** with ethylamine hydrochloride gave **19** (11%) and **20** (69%). Compound **19**: IR cm^{-1}: 3275, 1710, 1630. ^{1}H-NMR ($CDCl_3$): 1.0—1.25 (4H, m, cyclopropyl CH_2CH_2), 1.30 (3H, t, J=7 Hz, $NCH_2C\underline{H}_3$), 3.3—3.7 (2H, m, $NC\underline{H}_2CH_3$), 3.7—4.1 (1H, m, cyclopropyl CH), 8.70 (1H, s, C_2-H), 9.3—9.7 (1H, br, NH), 14.15 (1H, s, CO_2H). Compound **20**: IR cm^{-1}: 3325, 1715, 1630. ^{1}H-NMR ($CDCl_3$): 1.0—1.2 (4H, m, cyclopropyl CH_2CH_2), 1.35 (3H, t, J=7 Hz, $NCH_2C\underline{H}_3$), 3.3—4.7 (3H, m, $NC\underline{H}_2CH_3$ and cyclopropyl CH), 8.70 (1H, s, C_2-H), 14.62 (1H, br, CO_2H).

Ethyl 1-Cyclopropyl-5-ethoxy-6,7,8-trifluoro-4(1*H*)-oxoquinoline-3-carboxylate (21) and Ethyl 1-Cyclopropyl-7-ethylamino-5,6,8-trifluoro-4(1*H*)-oxoquinoline-3-carboxylic Acid (22) A mixture of **7** (500 mg, 1.52 mmol) and sodium ethoxide (100 mg, 1.52 mmol) in toluene (15 ml) was stirred at room temperature for 30 min, and then concentrated to dryness *in vacuo*. After an addition of water, the mixture was extracted with $CHCl_3$. The extract was dried and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$ as an eluent to give **21** (290 mg, 54%) and **22** (100 mg, 19%). Compound **21**: IR cm^{-1}: 1725, 1690, 1640, 1620. ^{1}H-NMR ($CDCl_3$): 1.0—1.4 (4H, m, cyclopropyl CH_2CH_2), 1.38 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.49 (3H, t, J=7 Hz, $C\underline{H}_2CH_3$), 3.6—4.0 (1H, m, cyclopropyl CH), 4.19 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.36 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 8.40 (1H, s, C_2-H). Compound **22**: IR cm^{-1}: 1725, 1695, 1630, 1600. ^{1}H-NMR ($CDCl_3$): 1.0—1.3 (4H, m, cyclopropyl CH_2CH_2), 1.40 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.49 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.7—4.0 (1H, m, cyclopropyl CH), 4.37 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.39 (2H, m, $C\underline{H}_2CH_3$), 8.44 (1H, s, C_2-H).

Difluoro[1-cyclopropyl-5,6,7,8-tetrafluoro-4(1*H*)-oxoquinoline-3-carboxylato-*O*,*O'*]boron (26) A stirred mixture of **8** (3.0 g, 9.96 mmol) and 42% aqueous HBF_4 (15 ml) was heated at 90—100 °C for 2 h, and then cooled. The precipitates were collected by filtration, washed with water, and recrystallized from $CHCl_3$–EtOH to give 3.28 g (94%) of **26**, mp 257—259 °C. *Anal.* Calcd for $C_{13}H_6BF_6NO_3$: C, 44.74; H, 1.73; N, 4.01. Found: C, 44.62; H, 1.65; N, 3.96. EIMS *m/z*: 349 (M^+), 330, 305 (base). IR cm^{-1}: 1715, 1655, 1625. ^{1}H-NMR (DMSO-d_6): 1.1—1.6 (4H, m, cyclopropyl CH_2CH_2), 4.2—4.7 (1H, m, cyclopropyl CH), 9.26 (1H, s, C_2-H).

Ethyl 5-(4-Acetyl-1-piperazinyl)-, 5-(4-Methyl-1-piperazinyl)-, and 5-(4-Acetylamino-1-pyrrolidinyl)-1-cyclopropyl-6,7,8-trifluoro-4(1*H*)-oxoquinoline-3-carboxylates (27a, 27c, and 27d) A stirred mixture of **7** (1.00 g, 3.04 mmol), *N*-acetylpiperazine (390 mg, 3.05 mmol), and Et_3N (310 mg, 3.07 mmol) in toluene (30 ml) was heated to reflux for 1 h, and then concentrated to dryness *in vacuo*. After an addition of water, the mixture was extracted with $CHCl_3$. The extract was dried and the solvent was evaporated off *in vacuo*. The residue was crystallized from AcOEt to give 1.15 g (87%) of **27a**. IR cm^{-1}: 1730, 1635, 1610.

In a similar manner, the reactions of **7** with *N*-methylpiperazine and 3-acetylaminopyrrolidine gave **27c** (88%) and **27d** (68%), respectively. Compound **27c**: IR cm^{-1}: 1730, 1685, 1650, 1610. Compound **27d**: IR cm^{-1}: 3350, 1690, 1670, 1640, 1615.

5-(4-Acetyl-1-piperazinyl)- and 5-(3-Acetylamino-1-pyrrolidinyl)-1-cyclopropyl-6,7,8-trifluoro-4(1*H*)-oxoquinoline-3-carboxylic Acids (28a and 28d) A stirred mixture of **8** (1.00 g, 3.32 mmol), *N*-acetylpiperazine (430 mg, 3.36 mmol), and Et_3N (670 mg, 6.63 mmol) in toluene (30 ml) was heated to reflux for 1 h, and then concentrated to dryness *in vacuo*. After an addition of water, the mixture was extracted with $CHCl_3$. The extract was dried and the solvent was evaporated off *in vacuo*. The residue was crystallized from $CHCl_3$ to give 1.08 g (79%) of **28a**. IR cm^{-1}: 1720, 1635, 1615.

In a similar manner, the reaction of **8** with 3-acetylaminopyrrolidine gave **28d** in 62% yield. IR cm^{-1}: 1720, 1650, 1620.

5-(1-Piperazinyl)- and 5-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-6,7,8-trifluoro-4(1*H*)-oxoquinoline-3-carboxylic Acids (29b and 29e) A stirred mixture of **28a** (500 mg, 1.22 mmol) and 20% HCl (5 ml) was heated at 100 °C for 4 h and then cooled. The solution was neutralized with 2 N NaOH. The resulting crystals were collected by filtration and recrystallized to give 400 mg (89%) of **29b**. IR cm^{-1}: 3400 (br), 1710, 1630 (sh), 1610.

In a similar manner, the deacetylation of **28d** gave **29e** in 87% yield. IR cm^{-1}: 3350 (br), 1715, 1605.

1-Cyclopropyl-6,7,8-trifluoro-5-(4-methyl-1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic Acid (29c) A stirred mixture of **27c** (300 mg, 0.73 mmol) and 0.5 N NaOH (10 ml) was heated at 90—100 °C for 1 h and then cooled. The reaction mixture was neutralized with 1 N AcOH and extracted with $CHCl_3$. The extract was dried and the solvent was evaporated off *in vacuo*. The residue was crystallized from AcOEt–iso-Pr_2O to give 270 mg (96%) of **29c**. IR cm^{-1}: 1730, 1610.

7-(4-Acetyl-1-piperazinyl)-, 7-(4-Methyl-1-piperazinyl)-, and 7-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-6,7,8-trifluoro-4(1*H*)-oxoquinoline-3-carboxylic Acids (30a, 30c, and 30e) A stirred mixture of **8** (500 mg, 1.66 mmol), *N*-acetylpiperazine (210 mg, 1.66 mmol), and Et_3N (350 mg, 3.32 mmol) in EtOH (15 ml) was heated to reflux for 1 h and then cooled. The resulting crystals were collected by filtration and recrystallized to give 400 mg (59%) of **30a**. IR cm^{-1}: 1730, 1660, 1630.

In a similar manner, the reactions of **8** with *N*-methylpiperazine and 3-aminopyrrolidine gave **30c** (65%) and **30e** (90%), respectively. Compound **30c**: IR cm^{-1}: 1730, 1630. Compound **30e**: IR cm^{-1}: 3400 (br), 1730, 1680, 1610.

1-Cyclopropyl-6,7,8-trifluoro-7-(1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic Acid (30b) (i) A stirred suspension of **30a** (240 mg, 0.59 mmol) in 20% HCl (5 ml) was heated at 90—100 °C for 4 h and then cooled. The reaction mixture was neutralized with 2 N NaOH. The resulting crystals

were collected by filtration and recrystallized to give 190 mg (91%) of **30b**. IR cm^{-1}: 1625.

(ii) A mixture of **26** (500 mg, 1.43 mmol), anhydrous piperazine (120 mg, 1.43 mmol), and Et_3N (300 mg, 2.86 mmol) in EtOH (15 ml) was stirred at room temperature for 1 h. The precipitates were collected by filtration and then dissolved in 1 N NaOH (10 ml). The solution was heated at 80—90 °C for 10 min with stirring and then neutralized with diluted AcOH. The resulting crystals were collected by filtration and recrystallized from $CHCl_3$–EtOH to give 460 mg (88%) of **30b**.

In a similar manner, compounds **30c** (90%) and **30e** (93%) were also prepared by the reactions of **26** with *N*-methylpiperazine and 3-aminopyrrolidine, respectively.

5-Cyclopropylamino- and 5-(1-Pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-7-(4-methyl-1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic Acids (32 and 33) A stirred suspension of **30c** (500 mg, 1.31 mmol) and cyclopropylamine (750 mg, 13.1 mmol) in CH_3CN (20 ml) was heated at 50 °C for 24 h. The reaction mixture was concentrated to dryness *in vacuo*. After an addition of water, the mixture was extracted with $CHCl_3$. The extract was dried and the solvent was evaporated off *in vacuo*. The residue was crystallized from EtOH to give **32** (502 mg, 91%). IR cm^{-1}: 3250 (br), 1720, 1630.

In a similar manner, the reaction of **30c** with pyrrolidine at 60 °C for 1 h gave **33** in 92% yield. IR cm^{-1}: 1715, 1610.

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References and Notes

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