Pyridonecarboxylic Acids as Antibacterial Agents. VII.[1] Synthesis and Structure–Activity Relationship of Amino- and Hydroxyl-Substituted 7-Cycloalkyl and 7-Vinyl Derivatives of 1-Cyclopropyl-6-fluoro-4-quinolone-3-carboxylic Acid[2]

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Novel C(7)-derivatives of 1-cyclopropyl-6-fluoro-4-quinolone carboxylic acid (3a—o) have been synthesized and evaluated for *in vitro* antibacterial activity. Compounds 3e (3-aminocyclobutyl), 3g (1-aminocyclopropyl), 3m ((2-aminomethyl)vinyl), and 3o ((1-aminomethyl)vinyl) showed significant inhibitory activity, comparable to that of ciprofloxacin, against gram-negative bacteria including *P. aeruginosa*. A good pharmacokinetic profile (serum and brain concentrations and urinary recovery) was obtained for the two cyclic compounds (3e and 3g), but that of the vinylic compounds (3m and 3o) was less favorable. Compound 3g was less toxic than 3e, ciprofloxacin, or ofloxacin in terms of acute toxicity and convulsion-induction.

Keywords antibacterial agent; 7-cycloalkyl-4-quinolone; 7-vinyl-4-quinolone; structure–activity relationship; antibacterial activity; 7-aminocyclopropyl-4-quinolone

In the preceding paper,[1] we reported that the 7-cyclopropyl and 7-vinyl derivatives of 1-cyclopropyl-6-fluoro-4-quinolone-3-carboxylic acid, **1** and **2** (Chart 1), exhibit potent antibacterial activities against both gram-positive and gram-negative bacteria, and that their convulsion-inducing activity is significantly weaker than that of ciprofloxacin (CPFX).[3] However, **1** and **2** show weaker activity than CPFX against *P. aeruginosa*. Moreover, their urinary recoveries are poor, like that of nalidixic acid,[4] presumably due to high lipophilicity associated with the hydrocarbon groups at the 7-position. In order to improve these unfavorable characteristics, we have synthesized a new series of compounds, **3a—o** (Chart 2), which possess hydrophilic hydroxyl and amino groups on the cycloalkyl and vinyl substituents, and have evaluated their antibacterial activities as well as their pharmacological and pharmacokinetic properties.

Chemistry

Synthesis of **3a—f** started with α,α-dialkylation[5] of the arylacetic ester **4**[1] with alkylene dibromides (**5a—c**)[6] having an appropriately protected hydroxyl or hydroxymethyl group (Chart 3). The annulated products **6a—c** were subjected to selective removal of the diphenylmethyl residue either by catalytic hydrogenolysis or by treatment with trifluoroacetic acid (TFA), depending on the nature of the *O*-protecting group in X_1 (Chart 3). The resulting carboxylic acids **7a—c** were decarboxylated under thermal conditions to afford **8a—c**. The remaining benzyl (Bn) or methoxymethyl (MOM) ether group was deprotected in a conventional manner to yield **9a—c**, which on saponification provided **3a—c**. The corresponding amino derivatives **3d—f** were obtained from the alcohols **9a—c** by three-step amination (*O*-mesylation, azidation, and catalytic hydrogenation), followed by hydrolysis of the resulting amino esters **9d—f**.

For the synthesis of 1-(amino and aminomethyl)cyclo-

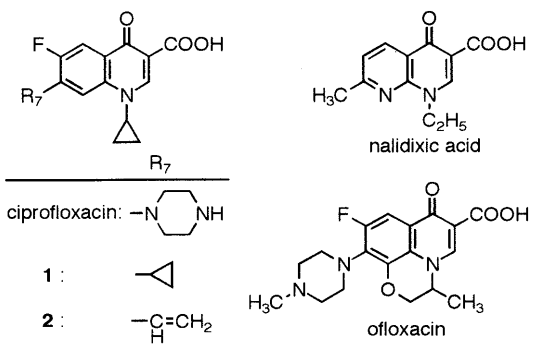

Chart 1

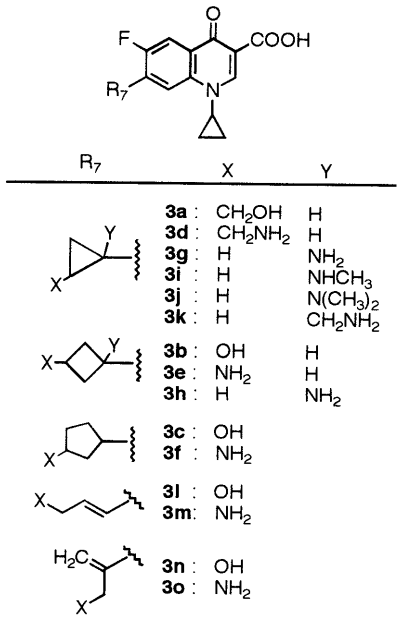

Chart 2

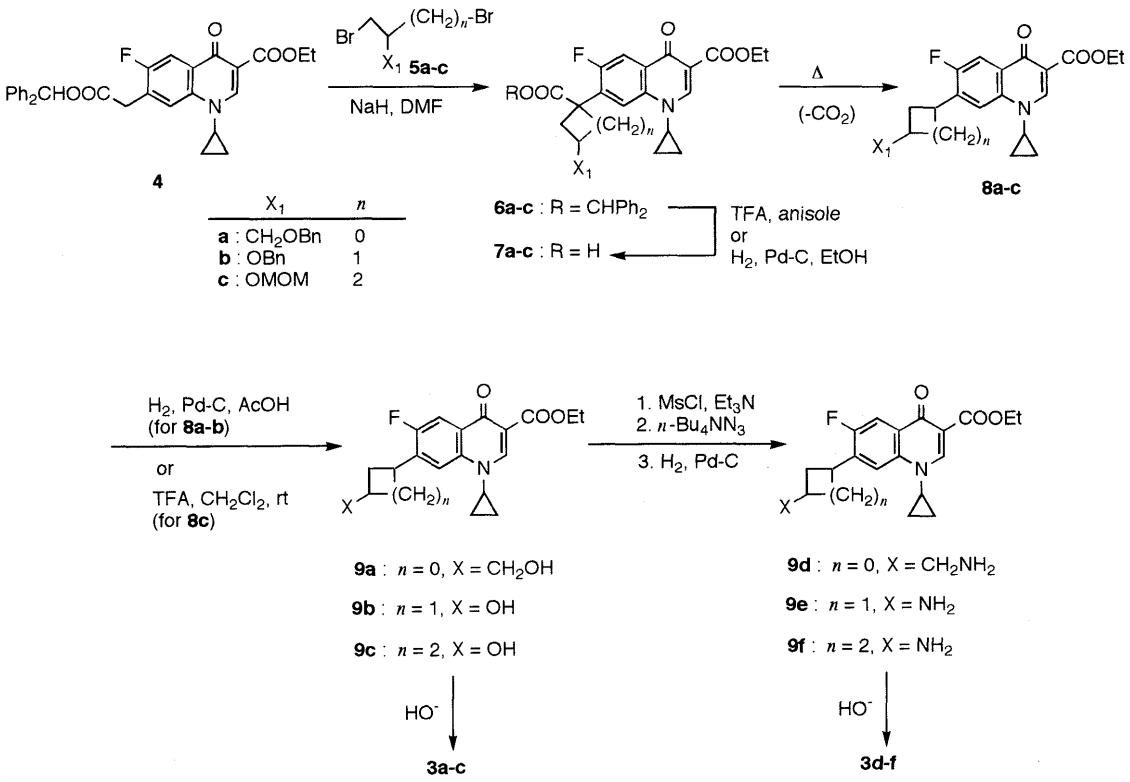

Chart 3

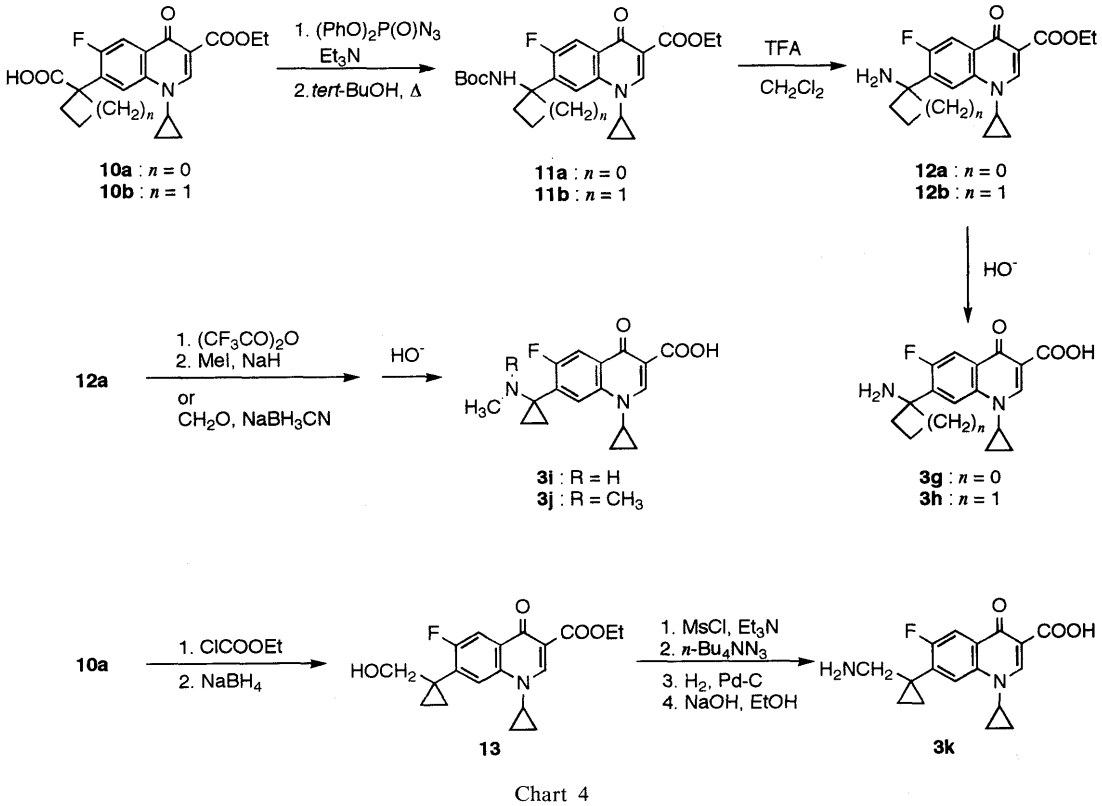

Chart 4

alkyl compounds (**3g—k**), (α-cyclopropyl or -cyclobutyl)-arylacetic acids (**10a, b**)[1] were employed as the starting materials (Chart 4). Thus, the carboxylic acids were first converted *via* a Curtius rearrangement[7] into *tert*-butoxycarbonyl(Boc)-protected amino derivatives (**11a, b**), which on deprotection by treatment with TFA afforded amino esters **12a, b**. Then, alkaline hydrolysis provided **3g** and **3h**. Compounds **3i** and **3j** were prepared from **12a** through *N*-mono- or *N*,*N*-dimethylation and subsequent saponification. On the other hand, the 1-(aminomethyl)cyclopro-

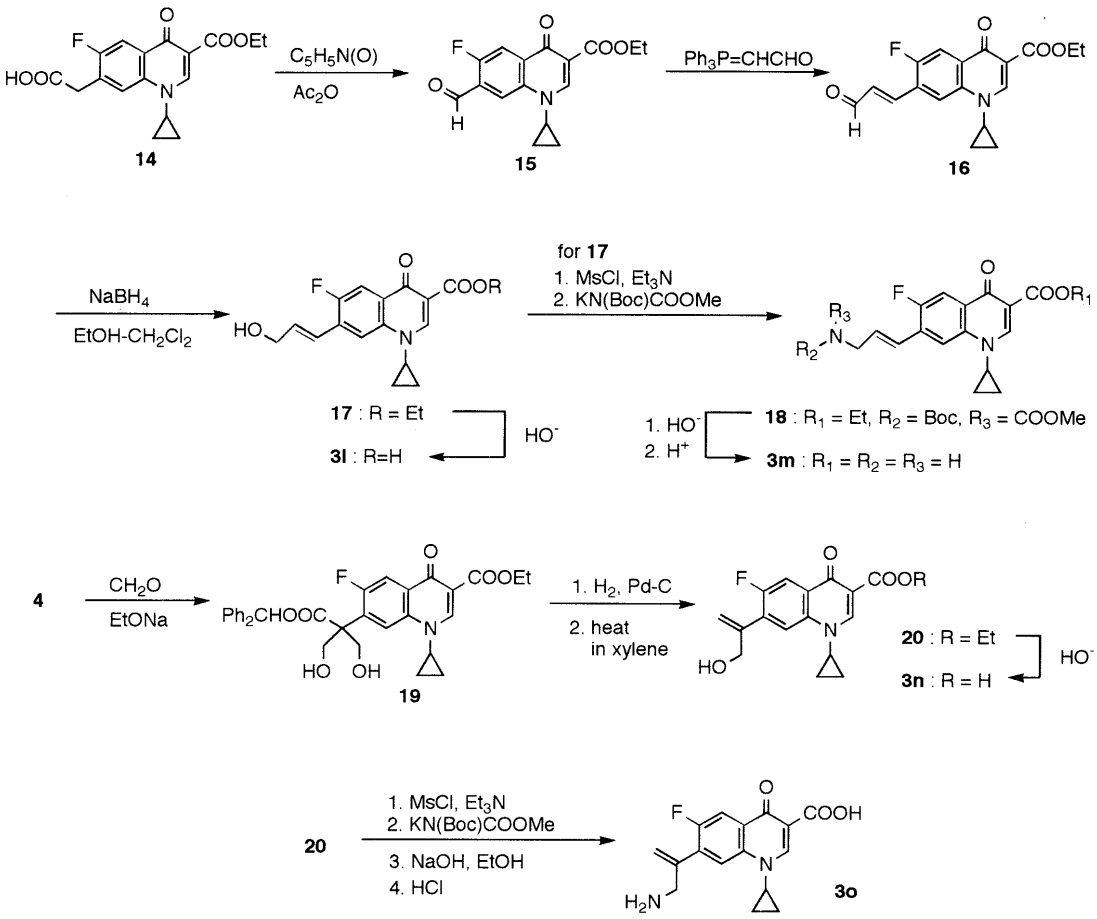

Chart 5

pyl derivative (**3k**) was prepared from the carboxylic acid **10a** by reduction to the alcohol **13**, followed by amination and ester hydrolysis.

3-(Hydroxyl and amino)-1-propenyl derivatives (**31** and **3m**) were prepared from the arylacetic acid **14**[1] by manipulation of its side chain (Chart 5). Treatment of **14** with pyridine *N*-oxide and acetic anhydride[8] afforded the aldehyde **15**, which, on Wittig reaction with $Ph_3P=CHCHO$, yielded the conjugated aldehyde **16**. This material was reduced with sodium borohydride to obtain the allylic alcohol **17**, and hydrolysis of the ester provided **3l**. The corresponding amino compound **3m** was secured from **17** by a procedure involving displacement reaction of its *O*-mesylate with KN(COOBu^t)COOMe.[9]

Lastly, the 1-(hydroxymethyl and aminomethyl)vinyl compounds (**3n, o**) were prepared from **4**[1] starting with hydroxymethylation with formaldehyde in the presence of sodium ethoxide. The resulting diol **19** was subjected to thermal decarboxylative dehydration reaction after hydrogenolysis of the diphenylmethyl ester, yielding **20** which was saponified to provide **3n**. The corresponding amino derivative **3o** was obtained from **20** by amination–hydrolysis as performed with **17**.

Biological Results and Discussion

***In Vitro* Antibacterial Activity** The new compounds **3a**—**o** (Chart 2) were evaluated for *in vitro* antibacterial activity against five selected microorganisms using the serial two-fold dilution method.[10] The minimum inhibitory concentrations (MICs) are recorded in Table II together with the data for **1**, **2**, CPFX and ofloxacin (OFLX)[11] for comparison. The MICs towards *Pseudomonas aeruginosa* indicate that the primary amino-substituted 7-cycloalkyl and 7-vinyl compounds are significantly more active than the hydroxyl-substituted counterparts (**3d**—**f**, **m, o** *versus* **3a**—**c, l, n**). Among the amino compounds, the activities of **3e** (3-aminocyclobutyl), **3g** (1-aminocyclopropyl), **3m** ((2-aminomethyl)vinyl), and **3o** ((1-aminomethyl)-vinyl) against gram-negative bacteria are higher than those of **1** and **2** and are comparable to those of CPFX and OFLX. However, these four compounds are somewhat less active against the gram-positive strain *Staphylococcus aureus* than the four reference compounds, the order of activity being **3e** = **3m** > **3g** > **3o**. Moreover, it is interesting to see that **3j**, the *N,N*-dimethyl derivative of **3g**, shows a pronounced decrease in activity against both *S. aureus* and *P. aeruginosa*.

Pharmacokinetic Properties The four compounds (**3e, g, m, o**) that showed potent *in vitro* antibacterial activity have been evaluated for urinary excretion as well as for serum and brain levels (intravenous dosing of 20 mg/kg to mice). The results are shown in Table III, together with the data for the reference drugs CPFX and OFLX. Urinary recoveries proved acceptable for all new compounds, when compared to CPFX and OFLX. Serum levels of the vinylic compounds (**3m** and **3o**) were lower than those of the cyclic

TABLE I. Physical Data for **3a—o**

Compd.	mp (dec. °C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	IR (KBr) cm^{-1}	^{1}H-NMR δ (ppm)
3a	195—197	EtOH	17[a]	$C_{17}H_{16}FNO_4$	64.35 (64.08	5.08 4.94	4.41 4.61)	1707	0.7—1.9 (7H, m), 2.0—2.6 (1H, m), 2.9—4.1 (3H, m), 4.2—4.8 (1H, m), 7.6—8.2 (2H, m), 8.71 (1H, s), 14.86 (1H, br s)[b]
3b	244—247	EtOH	4[a]	$C_{17}H_{16}FNO_4$	64.35 (64.20	5.08 5.04	4.41 4.28)	1720	1.2—2.1 (4H, m), 2.3—4.6 (6H, m), 5.2—5.9 (1H, m), 8.35 (1H, d, J=9.5 Hz), 8.60 (1H, d, J=6 Hz), 9.47 (1H, s)[c]
3c	206—209	EtOH–H_2O	7[a]	$C_{18}H_{18}FNO_4 \cdot 1/10H_2O$	64.90 (64.82	5.51 5.47	4.20 4.17)	1720	1.0—2.8 (11H, m), 3.3—4.0 (2H, m), 4.4—4.9 (1H, m), 8.04 (1H, d, J=10 Hz), 8.27 (1H, d, J=6 Hz), 8.81 (1H, s), 14.7 (1H, br s)[d]
3d	250—253	$CHCl_3$–EtOH	8[a]	$C_{17}H_{17}FN_2O_3 \cdot H_2O$	61.07 (60.95	5.73 5.67	8.38 8.36)	1623	1.1—2.3 (7H, m), 2.4—3.0 (1H, m), 3.4—3.8 (2H, m), 4.0—4.6 (1H, m), 8.33 (1H, d, J=9.5 Hz), 8.36 (1H, d, J=6.5 Hz), 9.42 (1H, s)[c]
3e	262—265	$CHCl_3$–MeOH	3[a]	$C_{17}H_{17}FN_2O_3$	64.55 (64.89	5.42 5.37	8.86 8.77)	1624	1.2—2.0 (4H, m), 2.6—3.6 (4H, m), 3.7—4.7 (3H, m), 8.37 (1H, d, J=10 Hz), 8.60 (1H, d, J=5.5 Hz), 9.46 (1H, s)[c]
3f	218—220	$CHCl_3$–MeOH	3[a]	$C_{18}H_{19}FN_2O_3 \cdot 1.5H_2O$	60.49 (60.08	6.20 5.87	7.84 7.80)	1622	1.2—1.9 (4H, m), 1.9—3.1 (6H, m), 3.6—4.5 (3H, m), 8.36 (1H, d, J=9.5 Hz), 8.61 (1H, d, J=6 Hz), 9.45 (1H, s)[c]
3g	240—243	EtOH	33[e]	$C_{16}H_{15}FN_2O_3$	63.57 (63.40	5.00 4.91	9.27 9.19)	1726	1.2—2.3 (8H, m), 3.9—4.5 (1H, m), 8.49 (1H, d, J=9.5 Hz), 8.93 (1H, d, J=6 Hz), 9.51 (1H, s)[c]
3h	238—239	$CHCl_3$–EtOH	31[f]	$C_{17}H_{17}FN_2O_3 \cdot 1/5H_2O$	63.82 (64.11	5.48 5.43	8.76 8.78)	1713	1.2—2.0 (4H, m), 2.1—3.4 (6H, m), 4.0—4.5 (1H, m), 8.49 (1H, d, J=10.5 Hz), 8.89 (1H, d, J=6 Hz), 9.54 (1H, s)[c]
3i	192—194	EtOH	8[e]	$C_{17}H_{17}FN_2O_3 \cdot 1/4H_2O$	63.64 (63.77	5.50 5.44	8.73 8.83)	1731	1.0—1.7 (8H, m), 2.34 (3H, s), 3.5—4.0 (1H, m), 8.08 (1H, d, J=10.5 Hz), 8.12 (1H, d, J=6 Hz), 8.84 (1H, s)[g]
3j	230—232	EtOH	9[e]	$C_{18}H_{19}FN_2O_3$	65.44 (65.52	5.80 5.94	8.48 8.46)	1727	0.8—1.9 (8H, m), 2.29 (3H, s), 2.32 (3H, s), 3.4—3.8 (1H, m), 7.97 (1H, d, J=5.5 Hz), 8.13 (1H, d, J=10 Hz), 8.86 (1H, s), 14.5 (1H, br s)[d]
3k	234—236	$CHCl_3$–EtOH	17[e]	$C_{17}H_{17}FN_2O_3 \cdot 1.5H_2O$	59.47 (59.75	5.87 5.61	8.16 8.20)	1625	1.2—1.9 (8H, m), 3.71 (2H, s), 4.0—4.5 (1H, m), 8.41 (1H, d, J=9.5 Hz), 8.82 (1H, d, J=6 Hz), 9.47 (1H, s)[c]
3l	248—252	$CHCl_3$–EtOH	16[h]	$C_{16}H_{14}FNO_4$	63.36 (63.08	4.65 4.61	4.62 4.71)	1720	1.2—2.1 (4H, m), 3.9—4.6 (1H, m), 5.24 (2H, br s), 6.6—7.5 (2H, m), 8.36 (1H, d, J=9.5 Hz), 8.78 (1H, d, J=6 Hz), 9.45 (1H, s)[c]
3m	200—205	$CHCl_3$–EtOH	9[h]	$C_{16}H_{15}FN_2O_3 \cdot 1.5H_2O$	58.35 (58.30	5.51 5.10	8.51 8.27)	1616	1.2—2.0 (4H, m), 3.9—4.6 (3H, m), 6.6—7.5 (2H, m), 8.40 (1H, d, J=10.5 Hz), 8.77 (1H, d, J=6 Hz), 9.46 (1H, s)[c]
3n	170—173	EtOH–H_2O	8[a]	$C_{16}H_{14}FNO_3$	63.36 (63.08	4.65 4.44	4.62 4.64)	1719	0.8—2.1 (5H, m), 3.2—3.8 (1H, m), 4.59 (2H, s), 5.60 (1H, s), 5.74 (1H, s), 8.05 (1H, d, J=6 Hz), 8.09 (1H, d, J=10.5 Hz), 8.81 (1H, s), 14.55 (1H, br s)[d]
3o	257—260	$CHCl_3$–EtOH	3[a]	$C_{16}H_{15}FN_2O_3 \cdot 1/4H_2O$	62.64 (62.43	5.09 4.92	9.13 8.80)	1618	1.2—2.0 (4H, m), 3.9—4.6 (3H, m), 6.13 (1H, s), 6.19 (1H, s), 8.44 (1H, d, J=10 Hz), 8.77 (1H, d, J=6 Hz), 9.50 (1H, s)[c]

a) Overall yield from **4**. *b*) In DMSO-d_6. *c*) In CF_3COOD. *d*) In $CDCl_3$. *e*) Overall yield from **10a**. *f*) Overall yield from **10b**. *g*) In $CDCl_3$ + DMSO-d_6. *h*) Overall yield from **14**.

compounds (**3e** and **3g**), CPFX, and OFLX. With regard to brain/serum concentration ratio, **3m** gave an exceptionally high value. Thus, the best pharmacokinetic profile was obtained with **3e** and **3g**: the serum level of **3g** (15 min after dosing) was 2.2 times higher than that of **3e**, but the half-life time of **3g** was shorter by about 75%.

Acute Toxicity and Convulsion Induction The 3-aminocyclobutyl and 1-aminocyclopropyl compounds (**3e** and **3g**) that showed good pharmacokinetic profile were evaluated for acute toxicity and convulsion-inducing activity[12] in mice by intravenous and intracerebral administrations, respectively. The results (Table IV) indicate that **3g** is less toxic than **3e** and the three reference quinolones (**1**, CPFX, and OFLX), and that the convulsion-inducing action of **3g** is stronger than that of **1**, but weaker than those of CPFX and OFLX.

In summary, we have shown that the 1-aminocyclopropyl group is an excellent substitute for the 1-piperazinyl group at C(7) in the new quinolones in terms of reducing toxicity and convulsion-inducing activity.

TABLE II. *In Vitro* Antibacterial Activity (MIC, μg/ml)[a]

Compd.	Microorganism				
	Gram-positive	Gram-negative			
	Sa[b]	Ec[c]	Kp[d]	Pv[e]	Pa[f]
3a	1.56	≤0.05	0.1	0.1	25
3b	0.39	≤0.05	≤0.05	≤0.05	3.13
3c	0.78	≤0.05	0.1	≤0.05	6.25
3d	1.56	≤0.05	0.1	≤0.05	1.56
3e	0.78	≤0.05	≤0.05	≤0.05	0.78
3f	0.78	≤0.05	0.1	≤0.05	1.56
3g	1.56	≤0.05	≤0.05	≤0.05	0.78
3h	6.25	0.1	0.2	0.2	3.13
3i	3.13	≤0.05	0.1	≤0.05	3.13
3j	>50	0.78	3.13	1.56	>50
3k	25	1.56	1.56	1.56	25
3l	0.78	≤0.05	≤0.05	≤0.05	6.25
3m	0.78	≤0.05	≤0.05	0.1	0.39
3n	0.78	≤0.05	≤0.05	≤0.05	3.13
3o	3.13	≤0.05	≤0.05	0.1	0.39
1	0.2	≤0.05	≤0.05	≤0.05	1.56
2	0.39	≤0.05	≤0.05	≤0.05	3.13
CPFX	0.2	≤0.05	≤0.05	≤0.05	0.39
OFLX	0.39	≤0.05	≤0.05	≤0.05	0.78

a) Inoculation was performed with one loopful of 10^6 cells/ml. *b*) *Staphylococcus aureus* FDA 209P. *c*) *Escherichia coli* NIHJ. *d*) *Klebsiella pneumoniae* Y-50. *e*) *Proteus vulgaris* GN 3027. *f*) *Pseudomonas aeruginosa* IFO 3445.

TABLE III. Serum and Brain Levels and Urinary Recoveries after Intravenous Administration to Mice (20 mg/kg)

Compound	Serum level (μg/ml) at 15 min	$t_{1/2}$ (min)	Brain/serum ratio at 15 min	Urinary recovery (%, 0—24 h)
3e	7.7[a]	59[a]	<0.07[a]	65.7[a]
3g	17.3[a]	15[a]	0.09[a]	18.1[a]
3m	3.2[b]	45[b]	0.95[b]	55.2[b]
3o	3.2[a]	15[a]	<0.06[a]	23.7[a]
CPFX	6.5[a]	52[a]	0.06[a]	51.5[a]
OFLX	10.6[a]	38[a]	0.04[a]	19.5[a]

a) Determined by bioassay analysis. *b*) Determined by HPLC analysis.

TABLE IV. Acute Toxicity and Convulsion Induction in Mice[a]

Compound	Acute toxicity (i.v.)		Convulsion induction (i.c.)[b]		
	Dose (mg/kg)	Mortality[c]	Clonic seizure	Tonic seizure	Mortality[d]
3e	250	3/3	10/10	10/10	10/10
3g	250	0/3	6/10	5/10	0/10
1	125	3/3	0/10	0/10	0/10
CPFX	250	1/5	10/10	10/10	10/10
OFLX	250	3/5	10/10	8/10	8/10

a) ICR-strain male mice (for acute toxicity, 18—24 g body weight; for convulsion induction, 20—25 g body weight). *b*) Dose, 50 μg/mouse. *c*) At 7 d after dosing. *d*) At 24 h after dosing.

Experimental[13]

Ethyl 7-(2-Benzyloxymethyl-1-diphenylmethoxycarbonylcyclopropyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (6a) Sodium hydride (60% in mineral oil, 0.67 g, 16.8 mmol) was added to a stirred suspension of **4** (7.00 g, 14.0 mmol) in *N*,*N*-dimethylformamide (DMF) (70 ml) at room temperature, and, after 30 min, **5a** (5.20 g, 16.9 mmol) was added to the mixture. The reaction mixture was stirred at 45—55 °C for 5 h, then the same amounts of NaH and **5a** were added again, and stirring was continued for 5 h. The mixture was poured into a mixture of ice-water (300 ml) and AcOEt (300 ml), then acidified to pH 2 by addition of 6 N HCl. The layers were separated, and the organic layer was washed successively with water and saturated brine, dried, and concentrated. The residue was subjected to chromatography (silica gel 150 g, toluene : AcOEt = 3 : 1) to give **6a** (3.40 g, 38%), mp 153—154 °C after recrystallization from AcOEt. IR (KBr): 1725, 1694 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.5—2.8 (10H, m), 2.9—3.6 (3H, m), 4.27 (2H, s), 4.42 (2H, q, J = 7 Hz), 6.82 (1H, s), 6.85—7.4 (15H, m), 7.92 (1H, d, J = 6 Hz), 8.17 (1H, d, J = 10.5 Hz), 8.51 (1H, s). *Anal.* Calcd for $C_{40}H_{36}FNO_6$: C, 74.40; H, 5.62; N, 2.17. Found: C, 74.02; H, 5.55; N, 2.24.

The cyclobutyl and cyclopentyl analogs (**6b** and **6c**) were prepared from **4** by the same procedure using **5b** and **5c** as the alkylation reagents, respectively.

6b: 43% yield. An amorphous solid. IR (KBr): 1729, 1689 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.7 (7H, m), 2.2—3.6 (5H, m), 4.1—4.7 (5H, m), 6.79 (1H, s), 6.9—7.4 (15H, m), 7.69 (1H, d, J = 6.5 Hz), 8.10 (1H, d, J = 10.5 Hz), 8.56 (1H, s).

6c: 54% yield. An amorphous solid. IR (KBr): 1729, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—3.7 (17H, m), 4.0—4.8 (5H, m), 6.7—7.4 (11H, m), 7.6—8.2 (2H, m), 8.58 (1H, s).

Ethyl 7-(2-Benzyloxymethylcyclopropyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (8a) TFA (16 ml) was added to a stirred suspension of **6a** (3.20 g, 4.96 mmol) in anisole (16 ml). The reaction mixture was stirred at room temperature for 3 h, and concentrated under reduced pressure. The residue was treated with Et_2O and filtered to give **7a** (2.30 g, 97%). An analytical sample was obtained as colorless prisms by recrystallization from $CHCl_3$–EtOH, mp 240—242 °C (dec.). IR (KBr): 1731, 1706 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—2.8 (10H, m), 2.9—3.6 (3H, m), 4.0—4.7 (4H, m), 6.5—7.4 (6H, m), 7.90 (1H, d, J = 6 Hz), 8.08 (1H, d, J = 10.5 Hz), 8.50 (1H, s). *Anal.* Calcd for $C_{27}H_{26}FNO_6$: C, 67.63; H, 5.47; N, 2.92. Found: C, 67.36; H, 5.36; N, 2.89. Compound **7a** (0.55 g, 1.15 mmol) was briefly heated in a flask with a Bunsen burner to effect decarboxylation. The product was purified by chromatography (silica gel 30 g, $CHCl_3$) and recrystallized from EtOH to give **8a** (0.35 g, 70%) as a white powder, mp 144—145 °C. IR (KBr): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.6—1.8 (10H, m), 1.9—2.7 (1H, m), 2.9—3.7 (3H, m), 4.1—4.7 (4H, m), 6.8—7.6 (6H, m), 7.8—8.2 (1H, m), 8.50 (1H, s). *Anal.* Calcd for $C_{26}H_{26}FNO_4$: C, 71.71; H, 6.02; N, 3.22. Found: C, 71.59; H, 5.88; N, 3.34.

The cyclobutyl compound **8b** was obtained in 58% overall yield from **6b** by the same procedure, mp 165—168 °C (white powder from AcOEt). IR (KBr): 1721 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.6 (7H, m), 1.8—3.7 (6H, m), 3.7—4.7 (5H, m), 7.34 (5H, s), 7.76 (1H, d, J = 6 Hz), 8.02 (1H, d, J = 10.5 Hz), 8.55 (1H, s). *Anal.* Calcd for $C_{26}H_{26}FNO_4$: C, 71.71; H, 6.02; N, 3.22. Found: C, 71.55; H, 5.93; N, 3.22.

Ethyl 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-(3-methoxymethyloxycyclopentyl)-4-oxoquinoline-3-carboxylate (8c) A solution of **6c** (7.25 g, 11.8 mmol) in EtOH (100 ml) was stirred under atmospheric pressure of hydrogen after addition of 5% Pd–C (1.0 g). After 2 h, the catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was covered with AcOEt (100 ml) and H_2O (100 ml), and the whole was stirred and brought to pH 8 by addition of K_2CO_3. The layers were separated, and the aqueous layer was acidified to pH 2 with 6 N HCl and extracted with AcOEt (100 ml). The extract was washed with saturated brine and dried. Removal of the solvent afforded **7c** as an amorphous solid (4.23 g, 80%). IR (KBr): 1728 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.6 (7H, m), 1.7—3.7 (10H, m), 4.0—4.8 (5H, m), 7.48 (1H, br s), 7.7—8.2 (2H, m), 8.57 (1H, s). A solution of **7c** (3.70 g, 8.27 mmol) in DMF (37 ml) was heated under reflux for 30 min. The solution was concentrated under reduced pressure, and the residue was purified by chromatography (silica gel 50 g, $CHCl_3$) and crystallized from Et_2O to give **8c** (2.70 g, 81%) as a white powder, mp 150—152 °C. IR (KBr): 1723, 1691 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—2.9 (13H, m), 3.1—3.9 (5H, m), 4.1—4.8 (5H, m), 7.1—8.2 (2H, m), 8.54 (1H, s). *Anal.* Calcd for $C_{22}H_{26}FNO_5$: C, 65.50; H, 6.50; N, 3.47. Found: C, 65.42; H, 6.49; N, 3.58.

Ethyl 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-(2-hydroxymethylcyclopropyl)-4-oxoquinoline-3-carboxylate (9a) A solution of **8a** (0.25 g, 0.57 mmol) in AcOH (10 ml) was stirred under atmospheric pressure of hydrogen after addition of 5% Pd–C (0.1 g). After 3 h, the catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography (silica gel 5 g, $CHCl_3$: EtOH = 50 : 1) to give **9a** (0.17 g, 86%). An analytical sample

was obtained by recrystallization from AcOEt, mp 174—175 °C (colorless needles). IR (KBr): 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.7—2.5 (12H, m), 3.1—3.9 (3H, m), 4.37 (2H, q, J=7 Hz), 7.3—8.1 (2H, m), 8.48 (1H, s). *Anal.* Calcd for $C_{19}H_{20}FNO_4$: C, 66.08; H, 5.84; N, 4.06. Found: C, 65.94; H, 5.81; N, 3.84.

The cyclobutyl compound **9b** was obtained from **8b** in 86% yield by the same procedure, mp 240—242 °C (colorless prisms from EtOH). IR (KBr): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.6 (7H, m), 1.79 (1H, br s), 1.9—3.7 (6H, m), 4.0—4.7 (3H, m), 7.76 (1H, d, J=6.5 Hz), 8.02 (1H, d, J=10.5 Hz), 8.56 (1H, s). *Anal.* Calcd for $C_{19}H_{20}FNO_4$: C, 66.08; H, 5.84; N, 4.06. Found: C, 65.85; H, 5.83; N, 4.18.

Ethyl 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-(3-hydroxycyclopentyl)-4-oxoquinoline-3-carboxylate (9c) TFA (10 ml) was added to a stirred solution of **8c** (2.00 g, 4.96 mmol) in CH_2Cl_2 (20 ml) at room temperature. After 1.5 h, the mixture was concentrated under reduced pressure. The residue was subjected to chromatography (silica gel 25 g, $CHCl_3$: EtOH = 50 : 1) to give **9c** (0.84 g, 47%). An analytical sample was obtained by recrystallization from aqueous EtOH, mp 230—232 °C (white powder). IR (KBr): 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—2.8 (14H, m), 3.2—3.8 (2H, m), 4.1—4.8 (3H, m), 7.6—8.2 (2H, m), 8.55 (1H, s). *Anal.* Calcd for $C_{20}H_{22}FNO_4$: C, 66.84; H, 6.17; N, 3.90. Found: C, 66.63; H, 6.14; N, 4.02.

Ethyl 7-(2-Aminomethylcyclopropyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (9d) Methanesulfonyl chloride (0.30 g, 2.62 mmol) was added dropwise to a stirred solution of **9a** (0.30 g, 0.87 mmol) and triethylamine (0.26 g, 2.57 mmol) in CH_2Cl_2 (6 ml) at 0 to 5 °C. The mixture was allowed to warm to room temperature, then stirred for 1 h, and poured into a mixture of ice-water (10 ml) and $CHCl_3$ (20 ml). The whole was acidified to pH 1 with 6 N HCl. The layers were separated, and the organic layer was washed successively with water and saturated brine, and dried. Removal of the solvent afforded the crude *O*-mesylate, which was dissolved in acetonitrile (6 ml), and the solution was heated under reflux for 2 h after addition of tetra-*n*-butylammonium azide (0.37 g, 1.30 mmol). The mixture was cooled and poured into a mixture of ice water (40 ml) and AcOEt (60 ml). The layers were separated, and the organic layer was washed successively with water and saturated brine, dried, and concentrated. The residue was subjected to chromatography (silica gel 15 g, $CHCl_3$) to give an azide (0.24 g, 75%). An analytical sample was obtained by recrystallization from iso-Pr_2O–AcOEt, mp 177—179 °C (white powder). IR (KBr): 2093, 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—2.55 (11H, m), 2.8—3.6 (3H, m), 4.38 (2H, q, J=7 Hz), 7.3—8.2 (2H, m), 8.52 (1H, s). *Anal.* Calcd for $C_{19}H_{19}FN_4O_3$: C, 61.61; H, 5.17; N, 15.13. Found: C, 61.52; H, 5.36; N, 14.87.

A solution of this azide (0.20 g, 0.54 mmol) in EtOH (8 ml) was stirred under atmospheric pressure of hydrogen after addition of 5% Pd–C (0.2 g). After 4 h, the catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was treated with Et_2O and filtered to give **9d** (0.13 g, 70%). An analytical sample was obtained by recrystallization from iso-Pr_2O–AcOEt, mp 210—212 °C (dec.) (white powder). IR (KBr): 1720 cm^{-1}: ^{1}H-NMR (CF_3COOD) δ: 1.2—2.3 (10H, m), 2.4—3.0 (1H, m), 3.3—3.8 (2H, m), 4.0—4.5 (1H, m), 4.72 (2H, q, J=7 Hz), 8.30 (1H, d, J=6.5 Hz), 8.32 (1H, d, J=9.5 Hz), 9.33 (1H, s). *Anal.* Calcd for $C_{19}H_{21}FN_2O_3$: C, 66.27; H, 6.15; N, 8.13. Found: C, 66.31; H, 6.37; N, 7.83.

The cyclobutyl and cyclopentyl compounds (**9e** and **9f**) were obtained from **9b** and **9c**, respectively, using the same amination procedure.

9e: 58% yield, mp 206—209 °C (dec.) (colorless needles from AcOEt). IR (KBr): 1721 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—4.1 (16H, m), 4.39 (2H, q, J=7 Hz), 7.5—8.2 (2H, m), 8.56 (1H, s). *Anal.* Calcd for $C_{19}H_{21}FN_2O_3$: C, 66.27; H, 6.15; N, 8.13. Found: C, 66.12; H, 6.15; N, 8.04.

9f: 33% yield, mp 184—187 °C (dec.) (colorless needles from AcOEt). IR (KBr): 1721 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—2.7 (16H, m), 3.1—3.9 (2H, m), 4.39 (2H, q, J=7 Hz), 7.77 (1H, d, J=6.5 Hz), 8.05 (1H, d, J=10.5 Hz), 8.55 (1H, s). *Anal.* Calcd for $C_{20}H_{23}FN_2O_3$: C, 67.07; H, 6.47; N, 7.82. Found: C, 66.89; H, 6.76; N, 7.66.

Ester Hydrolysis of 9a—f A solution of **9** (0.3 mmol) in a mixture of EtOH (1 ml) and 1 N NaOH (1 ml) was stirred at room temperature for 1 h before work-up. To obtain **3a—c**, the mixture was poured into a mixture of water (6 ml) and $CHCl_3$ (20 ml), and the whole was acidified to pH 1 with 6 N HCl before separation of layers. The organic layer was washed with saturated brine, dried, and concentrated to give a crude product. To obtain **3d—f**, the reaction mixture was diluted with water, and the solution was saturated with CO_2 before collection of the precipitate by filtration. The crude product was recrystallized from the solvent indicated in Table I.

Ethyl 7-(1-Aminocyclopropyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (12a) Diphenylphosphoryl azide (2.20 g, 7.99 ml) and triethylamine (0.80 g, 7.91 mmol) were added to a stirred suspension of **10a** (1.90 g, 5.29 mmol) in CH_2Cl_2 (19 ml). The mixture was stirred at room temperature for 3 h, then poured into ice-water (20 ml), and the whole was acidified to pH 2 with 6 N HCl. The layers were separated and the organic layer was washed successively with water and saturated brine, dried, and concentrated. The residue was dissolved in *tert*-butanol (40 ml), and the solution was heated under reflux for 3 h before removal of the solvent under reduced pressure. The residue was subjected to chromatography (silica gel 40 g, $CHCl_3$: EtOH = 25 : 1) to give **11a** (1.00 g, 44%). An analytical sample was obtained by recrystallization from iso-Pr_2O–AcOEt as a white powder, mp 166—168 °C. IR (KBr): 1727, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.7 (20H, m), 3.2—3.7 (1H, m), 4.38 (2H, q, J=7 Hz), 5.42 (1H, br s), 8.05 (1H, d, J=10.5 Hz), 8.15 (1H, d, J=6.5 Hz), 8.56 (1H, s). *Anal.* Calcd for $C_{23}H_{27}FN_2O_5$: C, 64.17; H, 6.32; N, 6.51. Found: C, 63.84; H, 6.26; N, 6.72.

A solution of **11a** (1.60 g, 3.72 mmol) and TFA (8 ml) in CH_2Cl_2 (8 ml) was stirred at room temperature for 2 h. The solution was concentrated under reduced pressure, and the residue was taken up in water (100 ml) and $CHCl_3$ (200 ml). After basification with K_2CO_3, the layers were separated, and the organic layer was washed with saturated brine, and dried. Evaporation of the solvent followed by crystallization of the residue from Et_2O afforded **12a** (1.10 g, 90%), mp 213—216 °C (dec.), colorless needles after recrystallization from iso-Pr_2O–AcOEt. IR (KBr): 1724, 1691 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.6 (11H, m), 2.03 (2H, br s), 3.2—3.7 (1H, m), 4.39 (2H, q, J=7 Hz), 7.85 (1H, d, J=6 Hz), 8.04 (1H, d, J=10.5 Hz), 8.54 (1H, s). *Anal.* Calcd for $C_{18}H_{19}FN_2O_3$: C, 65.44; H, 5.80; N, 8.48. Found: C, 65.19; H, 5.83; N, 8.40.

The 1-aminocyclobutyl derivative **12b** was obtained in 39% overall yield from **10b** using the same procedure as described above for **12a**. **12b**: mp 222—224 °C (dec.) (colorless needles from AcOEt). IR (KBr): 1731 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—2.9 (15H, m), 3.2—3.7 (1H, m), 4.38 (2H, q, J=7 Hz), 7.80 (1H, d, J=6.5 Hz), 8.04 (1H, d, J=11 Hz), 8.55 (1H, s). *Anal.* Calcd for $C_{19}H_{21}FN_2O_3$: C, 66.27; H, 6.15; N, 8.13. Found: C, 66.39; H, 6.29; N, 8.11.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[1-(*N*-methylamino)cyclopropyl]-4-oxoquinoline-3-carboxylic Acid (3i) Trifluoroacetic anhydride (0.33 g, 1.57 mmol) was added to a stirred solution of **12a** (0.43 g, 1.30 mmol) and triethylamine (0.16 g, 1.58 mmol) in CH_2Cl_2 (10 ml) at 5 to 10 °C. Stirring was continued at the same temperature for 1 h, then the mixture was poured into ice-water (10 ml). The layers were separated, and the organic layer was washed with saturated brine, dried, and concentrated. The residue was crystallized from Et_2O to give the *N*-trifluoroacetyl derivative (0.29 g, 52%). This amide (0.25 g, 0.59 mmol) was dissolved in DMF (5 ml), and NaH (60% in mineral oil, 30 mg, 0.75 mmol) was added. The mixture was stirred at room temperature for 5.5 h after addition of MeI (0.11 g, 0.77 mmol), then poured into a mixture of ice-water (50 ml) and AcOEt (50 ml), and the whole was acidified to pH 2 with 6 N HCl. The layers were separated, and the organic layer was washed with saturated brine, and dried. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography (silica gel 10 g, toluene : AcOEt = 3 : 1) to give the *N*-trifluoroacetyl-*N*-methyl derivative of **12a** (0.15 g, 58%), mp 180—181 °C, colorless needles from hexane–AcOEt. IR (KBr): 1730, 1697 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.8 (11H, m), 3.1—3.7 (4H, m), 4.38 (2H, q, J=7 Hz), 8.08 (1H, d, J=10.5 Hz), 8.48 (1H, d, J=6 Hz), 8.57 (1H, s). *Anal.* Calcd for $C_{21}H_{20}F_4N_2O_4$: C, 57.27; H, 4.58; N, 6.36. Found: C, 57.44; H, 4.80; N, 6.43.

A solution of this material (80 mg, 0.18 mmol) in EtOH (1.6 ml) and 1 N NaOH (1.6 ml) was refluxed for 15 min. The solution was cooled and poured into a mixture of water (6 ml) and $CHCl_3$ (10 ml). The whole was brought to pH 6 with AcOH, and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (5 ml × 3). The combined organic layers were washed with saturated brine, dried, and concentrated. The residue was crystallized from Et_2O to give **3i** (40 mg, 70%).

1-Cyclopropyl-7-[1-(*N*,*N*-dimethylamino)cyclopropyl]-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (3j) Aqueous formaldehyde (35%, 1.04 g, 12.1 mmol) was added to a stirred suspension of **12a** (0.40 g, 1.21 mmol) in acetonitrile (12 ml) at room temperature. After 15 min, $NaBH_3CN$ (0.23 g, 3.66 mmol) and then AcOH (0.23 g, 3.83

mmol) were added at 10 °C. The mixture was stirred at room temperature for 2.5 h, then poured into a mixture of ice-water (50 ml) and AcOEt (50 ml). The layers were separated, and the organic layer was washed with saturated brine, and dried. Evaporation of the solvent followed by chromatography (silica gel 20 g, $CHCl_3$: EtOH = 30 : 1) of the residue afforded the *N*,*N*-dimethyl derivative of **12a** (0.30 g, 69%), mp 263—265 °C, colorless needles from $CHCl_3$–AcOEt. IR (KBr): 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.7—1.8 (11H, m), 2.27 (3H, s), 2.30 (3H, s), 3.1—3.7 (1H, m), 4.40 (2H, q, J = 7.5 Hz), 7.80 (1H, d, J = 6 Hz), 8.08 (1H, d, J = 10 Hz), 8.58 (1H, s). *Anal.* Calcd for $C_{20}H_{23}FN_2O_3$: C, 67.02; H, 6.47; N, 7.82. Found: C, 67.06; H, 6.71; N, 8.01. Saponification of this material (0.20 g) by the same procedure as described for **3i** afforded **3j** (0.06 g, 33%).

7-(1-Aminomethylcyclopropyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (3k) Ethyl chloroformate (0.33 g, 3.04 mmol) was added dropwise to a stirred solution of **10a** (1.00 g, 2.78 mmol) and triethylamine (0.34 g, 3.36 mmol) in tetrahydrofuran (THF) (20 ml) at −15 to −10 °C, and stirring at the same temperature was continued for 1 h. The mixture was added dropwise to a solution of $NaBH_4$ (0.26 g, 6.87 mmol) in water (20 ml), keeping the temperature at 5 to 10 °C. After 40 min, this mixture was poured into a mixture of ice-water (30 ml) and AcOEt (50 ml), and the whole was acidified to pH 2 with 6 N HCl. The layers were separated, and the organic layer was washed with saturated brine, dried, and concentrated. The residue was subjected to chromatography (silica gel 30 g, $CHCl_3$: EtOH = 50 : 1) to give **13** (0.50 g, 52%). An analytical sample was obtained by recrystallization from aqueous EtOH, mp 212—215 °C, colorless needles. IR (KBr): 1727, 1692 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.7—1.6 (11H, m), 1.84 (1H, br s), 3.2—3.9 (3H, m), 4.37 (2H, q, J = 7.5 Hz), 7.88 (1H, d, J = 10.5 Hz), 7.89 (1H, d, J = 6 Hz), 8.46 (1H, s). *Anal.* Calcd for $C_{19}H_{20}FNO_4$: C, 66.08; H, 5.84; N, 4.06. Found: C, 65.88; H, 5.90; N, 4.17. The alcohol **13** was subjected to a three-step amination reaction as performed for **9a—c** to give the corresponding amino compound, from which **3k** was obtained after ester hydrolysis under the conditions described for **9d—f**.

Ethyl 1-Cyclopropyl-6-fluoro-7-formyl-1,4-dihydro-4-oxoquinoline-3-carboxylate (15) Acetic anhydride (0.77 g, 7.54 mmol) and pyridine *N*-oxide (1.14 g, 12.0 mmol) were added to a stirred suspension of **14** (1.00 g, 3.00 mmol) in THF (30 ml), and the mixture was heated under reflux for 7 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by chromatography (silica gel 15 g, toluene : AcOEt = 1 : 4) to give **15** (0.42 g, 46%). An analytical sample was obtained by recrystallization from AcOEt, mp 185—187 °C, pale yellow needles. IR (KBr): 1702, 1686 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.7 (7H, m), 3.3—3.8 (1H, m), 4.39 (2H, q, J = 7 Hz), 8.24 (1H, d, J = 10.5 Hz), 8.43 (1H, d, J = 5.5 Hz), 8.61 (1H, s), 10.49 (1H, s). *Anal.* Calcd for $C_{16}H_{14}FNO_4$: C, 63.36; H, 4.65; N, 4.62. Found: C, 63.45; H, 4.62; N, 4.43.

Ethyl 1-Cyclopropyl-6-fluoro-7-(2-formylvinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (16) A mixture of **15** (2.00 g, 6.59 mmol) and Ph_3P=CHCHO (2.21 g, 7.26 mmol) in benzene (40 ml) was refluxed under a nitrogen atmosphere for 3 h. The reaction mixture was concentrated under reduced pressure, and the residue was treated with Et_2O and filtered to give the crude aldehyde **16**. This material was purified by chromatography (silica gel 60 g, toluene : AcOEt = 1 : 2) to give **16** (1.22 g, 56%). An analytical sample was obtained by recrystallization from $CHCl_3$–AcOEt, mp 220—224 °C, pale yellow needles. IR (KBr): 1719, 1676 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.7 (7H, m), 3.2—3.8 (1H, m), 4.39 (2H, q, J = 7 Hz), 6.89 (1H, dd, J = 16, 7 Hz), 7.74 (1H, d, J = 16 Hz), 8.12 (1H, d, J = 6 Hz), 8.16 (1H, d, J = 10.5 Hz), 8.59 (1H, s), 9.81 (1H, d, J = 7 Hz). *Anal.* Calcd for $C_{18}H_{16}FNO_4$: 65.65; H, 4.90; N, 4.25. Found: C, 65.58; H, 4.65; N, 4.00.

1-Cyclopropyl-6-fluoro-7-(3-hydroxy-1-propenyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (3l) A solution of $NaBH_4$ (0.035 g, 0.93 mmol) in EtOH (5 ml) was added dropwise to a stirred suspension of **16** (1.10 g, 3.34 mmol) in EtOH (11 ml) and CH_2Cl_2 (16 ml) at 0 to 5 °C, and stirring of the mixture at the same temperature was continued for 15 min. The mixture was poured into a mixture of ice-water (50 ml) and $CHCl_3$ (50 ml), and the whole was acidified to pH 2 with 6 N HCl. The layers were separated, and the organic layer was washed with saturated brine, dried, and concentrated. The residue was purified by chromatography (silica gel 35 g, $CHCl_3$: EtOH = 30 : 1) to give **17** (0.84 g, 76%). An analytical sample was obtained by recrystallization from EtOH, mp 206—210 °C, colorless needles. IR (KBr): 1719 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.6 (7H, m), 1.84 (1H, s), 3.1—3.7 (1H, m), 4.1—4.6 (4H, m), 6.6—6.9 (2H, m), 7.90 (1H, d, J = 6 Hz), 8.03 (1H, d, J = 10.5 Hz), 8.55 (1H, s). *Anal.* Calcd for $C_{18}H_{18}FNO_4 \cdot 1/5H_2O$: C, 64.54; H, 5.54; N, 4.18. Found: C, 64.69; H, 5.66; N, 4.24.

A solution of **17** (80 mg, 0.24 mmol) in a mixture of EtOH (0.8 ml) and 1 N NaOH (0.8 ml) was stirred at room temperature 2 h. The solution was then acidified to pH 2 with 2 N HCl, and the precipitated crystals were collected by filtration to give **3l** (60 mg, 82%).

Ethyl 1-Cyclopropyl-6-fluoro-7-[3-(*N*-*tert*-butoxycarbonyl-*N*-methoxycarbonylamino)-1-propenyl]-1,4-dihydro-4-oxoquinoline-3-carboxylate (18) Methanesulfonyl chloride (0.39 g, 3.40 mmol) was added dropwise to a stirred suspension of **17** (0.75 g, 2.26 mmol) in a mixture of triethylamine (0.35 g, 3.46 mmol) and CH_2Cl_2 (15 ml) at 5 to 10 °C. After continued stirring at the same temperature for 30 min, the mixture was poured into a mixture of ice-water (20 ml) and $CHCl_3$ (20 ml), and the whole was acidified to pH 2 with 6 N HCl. The layers were separated, and the organic layer was washed with saturated brine, and dired. Removal of the solvent afforded the crude *O*-mesylate of **17**, which was added to a stirred suspension of KN(COOBu^t)COOMe (0.72 g, 3.38 mmol) in DMF (20 ml). The mixture was stirred at room temperature for 1 h, then poured into a mixture of ice-water (100 ml) and AcOEt (100 ml), and the whole was acidified to pH 1 with 6 N HCl. The layers were separated, and the organic layer was washed successively with water and saturated brine, dried, and concentrated. The residue was purified by chromatography (silica gel 15 g, $CHCl_3$) to give **18** (0.68 g, 61%). An analytical sample was obtained by recrystallization from iso-Pr_2O–AcOEt as a white powder, mp 160—161 °C. IR (KBr): 1750, 1718, 1694 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.8 (16H, m), 3.1—3.65 (1H, m), 3.86 (3H, s), 4.1—4.7 (4H, m), 6.1—7.0 (2H, m), 7.90 (1H, d, J = 6 Hz), 8.06 (1H, d, J = 10.5 Hz), 8.54 (1H, s). *Anal.* Calcd for $C_{25}H_{29}FN_2O_7$: C, 61.47; H, 5.98; N, 5.73. Found: C, 61.64; H, 6.36; N, 5.46.

7-(3-Amino-1-propenyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (3m) A suspension of **18** (0.65 g, 1.33 mmol) in a mixture of EtOH (6.5 ml), dioxane (6.5 ml), and 1 N NaOH (6.5 ml) was stirred at room temperature for 2 h. The mixture was poured into a mixture of ice-water (100 ml) and $CHCl_3$ (100 ml), and the whole was acidified to pH 1 with 6 N HCl. The layers were separated, and the organic layer was washed with saturated brine, and dried. Evaporation of the solvent followed by crystallization of the residue from Et_2O afforded the *N*-Boc derivative of **3m** (0.49 g, 92%), mp 215—219 °C, pale yellow needles after recrystallization from EtOH. IR (KBr): 1718, 1691 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.8 (13H, m), 3.3—4.2 (3H, m), 4.5—5.0 (1H, m), 6.2—7.0 (2H, m), 8.07 (1H, d, J = 10.5 Hz), 8.07 (1H, d, J = 6.5 Hz), 8.82 (1H, s), 14.52 (1H, br s). *Anal.* Calcd for $C_{21}H_{23}FN_2O_5$: C, 62,68; H, 5.76; N, 6.96. Found: C, 62.39; H, 5.97; N, 6.65.

A suspension of this material (0.30 g, 0.75 mmol) in dioxane (3 ml) and 6 N HCl (3 ml) was refluxed for 5 min. The reaction mixture was concentrated under reduced pressure, and the residue was triturated with Et_2O and filtered to give the hydrochloride of **3m** (0.22 g, 87%). This material was dissolved in a solution of KOH (80 mg, 1.43 mmol) in EtOH (1.8 ml) and water (2.7 ml), and the solution was saturated with CO_2. The resultant precipitate was collected by filtration to give **3m** (0.19 g, 97%).

Ethyl 1-Cyclopropyl-7-[1-diphenylmethoxycarbonyl-1,1-bis(hydroxymethyl)methyl]-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (19) Paraformaldehyde (80%, 1.13 g, 30.1 mmol) and NaOEt (0.14 g, 2.06 mmol) were added to a stirred suspension of **4** (5.00 g, 10.0 mmol) in DMF (150 ml). The mixture was stirred at room temperature for 20 h, then poured into a mixture of ice-water (250 ml) and $CHCl_3$ (100 ml), and the whole was acidified to pH 1 with 6 N HCl. The layers were separated, and the organic layer was washed successively with water and saturated brine, dried, and concentrated. The residue was purified by chromatography (silica gel 100 g, $CHCl_3$: EtOH = 20 : 1) to give **19** (1.97 g, 35%). An analytical sample was obtained by recrystallization from $CHCl_3$–EtOH as a white powder, mp 228—231 °C. IR (KBr): 1724, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.6 (7H, m), 3.2—3.8 (3H, m), 4.0—4.6 (6H, m), 6.8—7.4 (11H, m), 7.97 (1H, d, J = 11 Hz), 8.23 (1H, d, J = 6 Hz), 8.63 (1H, s). *Anal.* Calcd for $C_{32}H_{30}FNO_7 \cdot 1/2H_2O$: C, 67.60; H, 5.50; N, 2.46. Found: C, 67.79; H, 5.51; N, 2.45.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-(1-hydroxymethylvinyl)-4-oxoquinoline-3-carboxylic Acid (3n) A suspension of **19** (1.37 g, 2.45 mmol) in AcOH (70 ml) was stirred under atmospheric pressure of hydrogen after addition of 5% Pd–C (1.0 g). After 2 h, the catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was treated with Et_2O and filtered to give a monocarboxylic acid (0.93 g,

97%). A suspension of this acid (0.65 g, 1.65 mmol) in xylene (50 ml) was heated under reflux for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by chromatography (silica gel 15 g, $CHCl_3$: EtOH = 25 : 1) to give **20** (0.20 g, 37%). An analytical sample was obtained by recrystallization from EtOH, mp 203—205 °C (colorless needles). IR (KBr): 1717 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—2.2 (8H, m), 3.2—3.8 (1H, m), 4.1—4.7 (4H, m), 5.52 (1H, s), 5.67 (1H, s), 7.93 (1H, d, J = 6 Hz), 8.03 (1H, d, J = 11 Hz), 8.54 (1H, s). *Anal.* Calcd for $C_{18}H_{18}FNO_4$: C, 65.25; H, 5.48; N, 4.23. Found: C, 65.37; H, 5.25; N, 4.04. Saponification of **20** by the same procedure as described for **3l** afforded **3n** (66% yield).

7-(1-Aminomethylvinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (3o) This compound was prepared from **20** in 40% overall yield according to the same procedure as described for **3m**.

Brain/Serum Ratio A solution of each compound was made by dissolving the compound in dilute NaOH (*ca.* 1 eq) and diluting it with distilled water to the desired concentration (2 mg/ml). The sample solution (corresponding to 20 mg/kg) was administered intravenously to ICR-strain male mice (18—24 g body weight, three mice per group). The mice were killed 15 min after dosing. Each brain was homogenized in a 4-fold excess (by weight) of 1/15 M phosphate buffer (pH 7.0). After centrifugation (3500 rpm, 10 min), the supernatant was separated. Serum and brain levels of test compounds were determined by HPLC assay or microbiological assay using *Escherichia coli* Kp as the test organism.

Acute Toxicity A solution of each compound was made by dissolving the compound in dilute NaOH (*ca.* 1 eq) and diluting it with distilled water to the desired concentration (25 mg/ml or 12.5 mg/ml). The sample solution (corresponding to 250 mg/kg or 125 mg/kg) was administered intravenousiy to ICR-strain male mice (18—24 g body weight, three or five mice per group). The mortality rate in each test group was obtained after 7 d.

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References and Notes

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