Pyridonecarboxylic Acids as Antibacterial Agents. VI.[1] Synthesis and Structure–Activity Relationship of 7-(Alkyl, Cycloalkyl, and Vinyl)-1-cyclopropyl-6-fluoro-4-quinolone-3-carboxylic Acids[2]

Yozo TODO,* Hiroyasu TAKAGI, Fumihiko IINO, Yoshikazu FUKUOKA, Yasushi IKEDA, Keiichi TANAKA, Isamu SAIKAWA, and Hirokazu NARITA

Research Laboratories, Toyama Chemical Co., Ltd., 2–4–1 Shimookui, Toyama 930, Japan.
Received March 8, 1994; accepted May 20, 1994

The title compounds (1a—i) have been synthesized starting with ethyl 1-cyclopropyl-6,7-difluoro-4-quinolone-3-carboxylate (2). The 7-cyclopropyl and 7-vinyl derivatives (1e and 1i) exhibited potent *in vitro* antibacterial activities against both gram-positive and gram-negative bacteria, being equipotent with ciprofloxacin (CPFX) except for the activity against *Pseudomonas aeruginosa*. The two compounds were significantly less toxic than CPFX in terms of convulsion–induction as determined by intracerebral administration to mice, but showed lower urinary recoveries on intravenous administration.

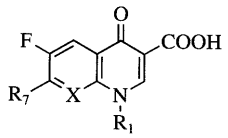
Keywords fluoroquinolone; structure–activity relationship; antibacterial activity; convulsion–induction; 7-cyclopropyl-4-quinolone; 7-vinyl-4-quinolone

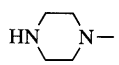
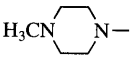
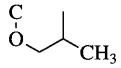
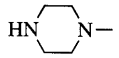
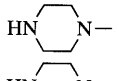
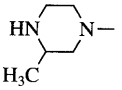
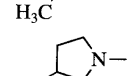
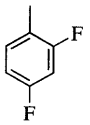
Since the discovery of norfloxacin[3] in 1980 as an antibacterial agent with potent and broad-spectrum activity, several new members of this family (listed in Table I) have emerged. These so-called new quinolones, which have been applied successfully in the treatment of a wide range of human bacterial infections, are structurally characterized by a fluorine atom at the 6-position and a 1-piperazinyl or 1-pyrrolidinyl substituent at the 7-position on the quinolone or naphthyridone skeleton. While such fluoroquinolones show excellent overall pharmacokinetic properties in oral dosing, they exhibit intrinsic adverse side effects to the central nervous system, such as inducing dizziness and convulsion.[4] Tosufloxacin,[1] developed by us several years ago, is one of the most favorable agents in this respect,[5] but unfortunately exhibits a poor water solubility[6] that renders it difficult to use the drug in intravenous formulations. Thus, it is still necessary to develop a safer quinolone antibacterial agent applicable to serious infection *via* intravenous dosing. We have focused our attention on quinolones with 7-alkyl and 7-cycloalkyl derivatives, instead of the cyclic amino functionality found with currently marketed quinolones. To the best of our knowledge, only an aryl group (represented by WIN57273,[7] Chart 1) has been extensively investigated before.

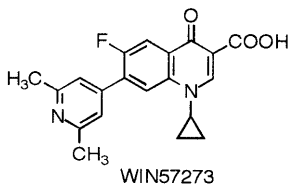
It has been reported by us and others that nalidixic acid (NA)[8] which bears a methyl group at the 7-position of the naphthyridone nucleus (Chart 1) shows much weaker convulsion–inducing action than that of the new quinolones when given by intracerebral injection to mice,[5a] and it has no γ-aminobutyric acid (GABA) receptor-inhibitory activity.[9] These notable characteristics of the prototype quinolone led us to study the synthesis and structure–activity relationship of a series of compounds (**1**) (Chart 1) in which the 1-piperazinyl group of ciprofloxacin (CPFX)[10] is replaced by an alkyl or cycloalkyl group.

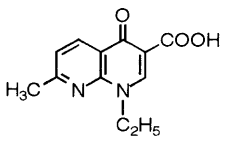
Chemistry All of the 7-substituted 1-cyclopropyl-6-fluoro-4-quinolone-3-carboxylic acids (**1a—i**) were synthesized *via* the arylated malonate **3** which was prepared in 89% yield by reaction of the 6,7-difluoroquinolone **2**[11] with di-*tert*-butyl malonate in the presence of NaH in

TABLE I. New Quinolones in Clinical Use



Compound	R_7	X	R_1
Norfloxacin		CH	C_2H_5
Ofloxacin			
Enoxacin		N	C_2H_5
Ciprofloxacin		CH	
Lomefloxacin		CF	C_2H_5
Tosufloxacin		N	




nalidixic acid

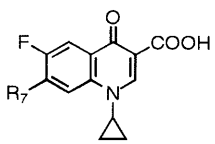

1 (R_7 = alkyl, cycloalkyl, vinyl)

Chart 1

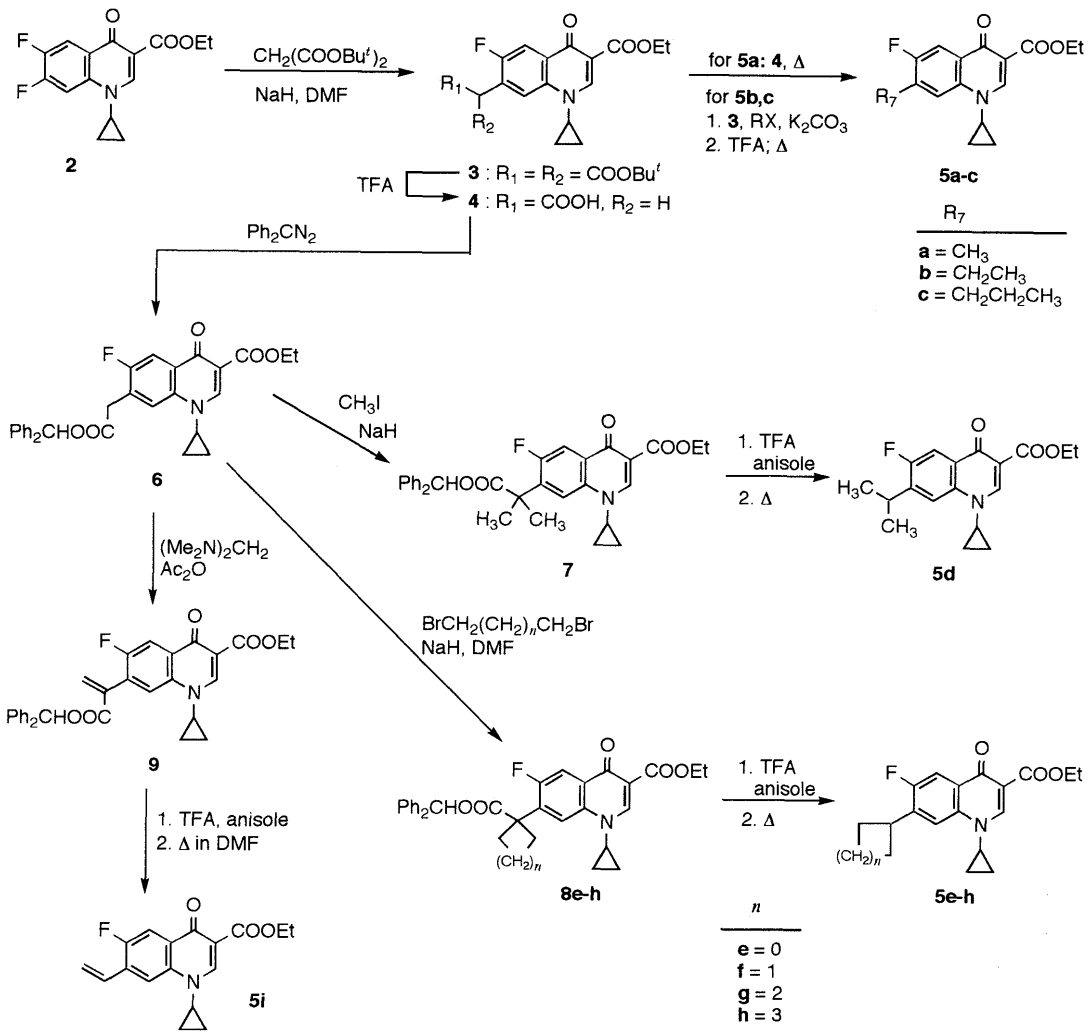


Chart 2

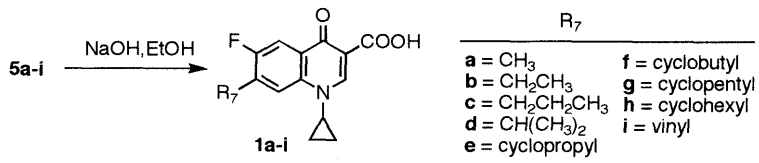


Chart 3

N,*N*-dimethylformamide (DMF) at 50 to 60 °C (Chart 2).[12]

Treatment of **3** with trifluoroacetic acid (TFA) in CH_2Cl_2 at room temperature afforded the monocarboxylic acid **4**, which on decarboxylation under pyrolytic conditions provided the 7-methyl compound **5a** in an overall yield of 68%. For the preparation of the ethyl and propyl derivatives (**5b**, **c**), the malonate **3** was first alkylated in DMF in the presence of K_2CO_3,[12a] then the products were subjected to removal of the geminal ester groups.

For the synthesis of the compounds having an isopropyl, cycloalkyl, or vinyl group at C(7), the diphenylmethyl ester **6** derived from **4** was employed as the common intermediate. Thus, the isopropyl compound **5d** was obtained by α,α-dimethylation[12a] of **6** followed by ester hydrolysis–decarboxylation of the product **7**. Use of appropriate alkylene dibromides for the alkylation step afforded **8e—h**, which were converted to the cycloalkyl derivatives (**5e—h**). The vinyl compound **5i**[13] was obtained from **6** by α-methylenation to **9** using bis(dimethylamino)methane and acetic anhydride,[14] followed by removal of the diphenylmethyl ester group by a procedure involving TFA treatment and thermal decarboxylation.

Lastly, the quinolone carboxylates **5a—i** were saponified by treatment with ethanolic NaOH to provide the desired carboxylic acids (**1a—i**) (Chart 3), for which physical data are given in Table II.

Biological Results and Discussion

***In Vitro* Antibacterial Activity** Compounds **1a—i** were evaluated for *in vitro* antibacterial activity against five

TABLE II. Physical Data for 7-(Alkyl, Cycloalkyl, Vinyl)-1-cyclopropyl-6-fluoro-4-quinolone-3-carboxylic Acids (**1a—i**)

Compd.	mp (°C)	Recryst. solvent	Yield[a] (%)	Formula	Analysis (%) Calcd (Found) C	H	N	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$)
1a	242—246	$CHCl_3$–EtOH	89	$C_{14}H_{12}FNO_3$	64.36 (64.37	4.63 4.56	5.36 5.15)	1730	1.0—1.7 (4H, m), 2.53 (3H, d, J=1.5 Hz), 3.3—3.8 (1H, m), 7.91 (1H, d, J=7.5 Hz), 8.05 (1H, d, J=9.5 Hz), 8.79 (1H, s), 14.63 (1H, br s)
1b	205—207	$CHCl_3$–AcOEt	88	$C_{14}H_{14}FNO_3$	65.45 (65.33	5.13 5.11	5.09 5.06)	1734	1.0—1.8 (7H, m), 2.91 (2H, q, J=7.5 Hz), 3.4—3.9 (1H, m), 7.92 (1H, d, J=6.5 Hz), 8.05 (1H, d, J=10 Hz), 8.80 (1H, s), 14.64 (1H, br s)
1c	167—168	$CHCl_3$–AcOEt	92	$C_{16}H_{16}FNO_3$	66.43 (66.19	5.57 5.54	4.84 4.87)	1728	0.8—2.2 (9H, m), 2.86 (2H, t, J=7.5 Hz), 3.3—3.9 (1H, m), 7.90 (1H, d, J=6 Hz), 8.03 (1H, d, J=9.5 Hz), 8.79 (1H, s), 14.66 (1H, br s)
1d	181—183	EtOH	94	$C_{16}H_{16}FNO_3$	66.43 (66.34	5.57 5.60	4.84 4.99)	1732	1.0—1.8 (10H, m), 3.1—3.9 (2H, m), 7.94 (1H, d, J=5 Hz), 8.06 (1H, d, J=10 Hz), 8.82 (1H, s), 14.66 (1H, br s)
1e	226—228	$CHCl_3$–EtOH	88	$C_{16}H_{14}FNO_3$	66.89 (66.75	4.91 4.87	4.88 4.78)	1728	0.5—1.8 (8H, m), 2.0—2.6 (1H, m), 3.2—3.9 (1H, m), 7.60 (1H, d, J=6 Hz), 7.98 (1H, d, J=10.5 Hz), 8.75 (1H, s), 14.66 (1H, br s)
1f	207—209	$CHCl_3$–AcOEt	96	$C_{17}H_{16}FNO_3$	67.76 (67.70	5.35 5.35	4.65 4.88)	1729	1.0—1.7 (4H, m), 1.8—2.8 (6H, m), 3.3—4.2 (2H, m), 7.90 (1H, d, J=5 Hz), 8.03 (1H, d, J=10 Hz), 8.82 (1H, s), 14.67 (1H, br s)
1g	199—200	EtOH	82	$C_{18}H_{18}FNO_3$	68.56 (68.57	5.75 5.81	4.44 4.36)	1731	1.0—2.5 (12H, m), 3.1—3.9 (2H, m), 7.97 (1H, d, J=6 Hz), 8.04 (1H, d, J=10 Hz), 8.81 (1H, s), 14.69 (1H, br s)
1h	217—219	EtOH	87	$C_{19}H_{20}FNO_3$	69.29 (69.30	6.12 6.07	4.25 4.26)	1731	0.9—2.3 (14H, m), 2.7—3.8 (2H, m), 7.92 (1H, d, J=5.5 Hz), 8.05 (1H, d, J=10 Hz), 8.81 (1H, s), 14.5 (1H, br s)
1i[b]	222—225	$CHCl_3$–EtOH	95	$C_{15}H_{12}FNO_3$	65.93 (65.83	4.43 4.39	5.13 5.27)	1729	1.0—1.8 (4H, m), 3.3—3.9 (1H, m), 5.69 (1H, d, J=11 Hz), 6.07 (1H, d, J=17 Hz), 7.03 (1H, dd, J=17, 11 Hz), 8.10 (1H, d, J=10 Hz), 8.14 (1H, d, J=6 Hz), 8.83 (1H, s), 14.45 (1H, br s)

a) Yield from **5**. *b*) Reference 13.

selected gram-positive and gram-negative microorganisms using the serial two-fold dilution method.[15] Their minimum inhibitory concentrations (MICs, μg/ml) are recorded in Table III. The data for CPFX, NA, and WIN-57273 are included for comparison. All compounds are significantly more active than NA. The cycloalkyl derivatives **1e—g**, except for cyclohexyl compound **1h**, are more active than the alkyl derivatives **1a—d** against both gram-positive and gram-negative bacteria. The activity profile of the vinyl compound **1i** is similar to that of WIN57273 except for the MIC against gram-positive *Staphylococcus aureus*. It is noticeable that the MIC data for the most active sample **1e** (R_7=cyclopropyl) are comparable to those of the parent drug CPFX, with the single exception of a 4-fold-reduced activity against *Pseudomonas aeruginosa*. It appears that the 5- or 6-membered amino substituents in the new quinolones (Table I) can be replaced with sterically small hydrocarbon substituents such as cyclopropyl and vinyl groups.

Convulsion–Induction The two compounds **1e** and **1i** that exhibited potent *in vitro* antibacterial activity were subjected to convulsion–induction assay[5a] by means of intracerebral injection in mice. The results are summarized in Table IV, in which the data of reference drugs are included for comparison. Compounds **1e**, **i** and NA are essentially free from convulsion-inducing activity at dosages up to 50 μg. This is in sharp contrast to CPFX and WIN57273 which induce strong clonic and tonic seizures.

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

Compound	Microorganism: Gram-positive Sa[b]	Gram-negative Ec[c]	Kp[d]	Pv[e]	Pa[f]
1a	1.56	≤0.05	≤0.05	≤0.05	6.25
1b	0.78	≤0.05	0.1	≤0.05	6.25
1c	0.78	≤0.05	0.2	≤0.05	12.5
1d	0.78	≤0.05	0.2	≤0.05	6.25
1e	0.2	≤0.05	≤0.05	≤0.05	1.56
1f	0.39	≤0.05	0.2	≤0.05	3.13
1g	0.39	≤0.05	0.2	≤0.05	3.13
1h	0.2	0.1	0.2	0.2	3.13
1i	0.39	≤0.05	≤0.05	≤0.05	3.13
WIN57273	≤0.05	≤0.05	0.1	≤0.05	3.13
NA	100	0.39	0.78	0.78	>100
CPFX	0.2	≤0.05	≤0.05	≤0.05	0.39

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.

Pharmacokinetic Properties Serum levels and urinary recoveries of compounds **1e** and **1i** were determined after

TABLE IV. Convulsion Induction after Intracerebral Injection to Mice[a]

Compound	Dose (μg/mouse)	Clonic seizure	Tonic seizure	Mortality[b]
1e	50	0/10	0/10	0/10
1i	50	1/10	0/10	0/10
WIN57273	25	6/8	2/8	3/8
NA	50	0/10	0/10	0/10
CPFX	50	10/10	10/10	10/10

a) ICR-strain mice (20—25 g body weight). *b*) At 24 h after dosing.

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

Compound	Serum level at 15 min (μg/ml)	$t_{1/2}$ (min)	Urinary recovery (%, 0—24 h)
1e	16.5[a]	15[a]	13.2[b]
1i	13.5[b]	10[b]	3.0[b]
NA	36.9[a]	26[a]	4.5[a]
CPFX	6.5[b]	52[b]	51.5[b]

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

intraveous administration to mice (20 mg/kg). The results are recorded in Table V together with those for NA and CPFX. In comparison with CPFX, **1e** and **1i** gave higher serum levels at 15 min after dosing, but underwent faster degradation as indicated by the $t_{1/2}$ values (15 min for **1e** *versus* 52 min for CPFX). Such characteristics could be attributed to the hydrocarbon substituent at the 7-position. Urinary recoveries of **1e** and **1i** were much lower than that of CPFX.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FTIR spectrometer. ^{1}H-NMR spectra were recorded on a JEOL FX-60 spectrometer. Chemical shifts are expressed in δ_{ppm} downfield from internal tetramethylsilane. Signal patterns are described as s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. Column chromatography was carried out with Merck silica gel 60 (70—230 mesh). Merck precoated Silica gel 60 F_{254} plates were used for analytical thin-layer chromatography (TLC). All organic solvent extracts were dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator under reduced pressure.

Ethyl 7-[Bis(*tert*-butoxycarbonyl)methyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (3) A suspension of NaH (60% in mineral oil, 27.8 g, 0.695 mol) in dry DMF (1.0 l) was stirred and cooled to 5 °C, and di-*tert*-butyl malonate (150 g, 0.694 mol) was added over 2 h. The mixture was allowed to warm to room temperature before addition of **2** (51.0 g, 0.174 mol). After being heated at 50 to 60 °C for 6 h with stirring, the reaction mixture was cooled to room temperature and poured into a mixture of ice-water (1.5 l) and AcOEt (1.0 l). Layers were separated after acidification to pH 2 by addition of 6 N HCl, and the organic layer was washed successively with water and saturated brine, then dried, and concentrated. The residue was crystallized from iso-Pr_2O to give **3** (76.0 g, 89%) which was homogeneous on TLC. An analytical sample was obtained by recrystallization from AcOEt as colorless prisms, mp 160—162 °C. IR (KBr): 1752, 1734 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—2.0 (25H, m), 3.3—3.8 (1H, m), 4.39 (2H, q, J=7 Hz), 4.95 (1H, s), 8.11 (1H, d, J=10 Hz), 8.22 (1H, d, J=5.5 Hz), 8.58 (1H, s). *Anal.* Calcd for $C_{26}H_{32}FNO_7$: C, 63.79; H, 6.59; N, 2.86. Found: C, 63.55; H, 6.66; N, 2.66.

Ethyl 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-methyl-4-oxoquinoline-3-carboxylate (5a) TFA (110 ml) was added to a solution of **3** (55.0 g, 0.112 mol) in CH_2Cl_2 (110 ml) at room temperature. The reaction mixture was stirred overnight, then concentrated under reduced pressure, and the residue was treated with Et_2O (100 ml) to induce crystallization. The crystals were collected by filtration to give **4** (37.0 g, 99%): mp 217—220 °C (dec.), colorless needles after recrystallization from $CHCl_3$–MeOH. IR (KBr): 1732 cm^{-1}. ^{1}H-NMR (CF_3COOD) δ: 1.2—2.1 (7H, m), 3.9—4.6 (3H, m), 4.74 (2H, q, J=7 Hz), 8.39 (1H, d, J=9 Hz), 8.81 (1H, d, J=6 Hz), 9.40 (1H, s). *Anal.* Calcd for $C_{17}H_{16}FNO_5$: C, 61.26; H, 4.84; N, 4.20. Found: C, 61.10; H, 4.90; N, 4.07.

Compound **4** (0.25 g, 0.75 mmol) was subjected to decarboxylation by heating in a flask with a Bunsen burner for *ca.* 10 s. The crude product was purified by chromatography (silica gel 7 g, $CHCl_3$: EtOH = 50 : 1) to give **5a** (0.15 g, 69%). An analytical sample was obtained by recrystallization from AcOEt as colorless needles, mp 224—227 °C. IR (KBr): 1723 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.7 (7H, m), 2.45 (3H, d, J=1.5 Hz), 3.2—3.7 (1H, m), 4.39 (2H, q. J=7 Hz), 7.71 (1H, d, J=6.5 Hz), 8.04 (1H, d, J=10 Hz), 8.52 (1H, s). *Anal.* Calcd for $C_{16}H_{16}FNO_3$: C, 66.43; H, 5.57; N, 4.84. Found: C, 66.53; H, 5.60; N, 4.88.

Ethyl 1-Cyclopropyl-7-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (5b) A mixture of **3** (2.50 g, 5.11 mmol), K_2CO_3 (1.06 g, 7.67 mmol), and MeI (1.09 g, 7.68 mmol) in DMF (25 ml) was stirred at 65—75 °C. After 3 h, the mixture was poured into a mixture of ice-water (100 ml) and AcOEt (100 ml), and the whole was adjusted 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 purified by chromatography (silica gel 100 g, $CHCl_3$), and a chromatographically homogenous sample was recrystallized from AcOEt to give the α-methyl derivative of the malonate **3** (1.62 g, 63%) as coloreless prisms, mp 197—198 °C. IR (KBr): 1756, 1733, 1723 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.7 (25 H, m), 1.83 (3H, s), 3.2—3.7 (1H, m), 4.39 (2H, q, J=7 Hz), 7.93 (1H, d, J=6 Hz), 8.10 (1H, d, J=11 Hz), 8.57 (1H, s). *Anal.* Calcd for $C_{27}H_{34}FNO_7$: C, 64.40; H, 6.81; N, 2.78. Found: C, 64.39; H, 6.97; N, 2.45.

This material (1.50 g, 2.98 mmol) was dissolved in CH_2Cl_2 (7.5 ml), and the solution was stirred at room temperature overnight after addition of TFA (7.5 ml). The solvent was evaporated, and the residue was heated in xylene (20 ml) at 100—110 °C for 1.5 h. The reaction mixture was cooled to room temperature, and the separated crystals were collected by filtration to give 2-[(1-cyclopropyl-3-ethoxycarbonyl-6-fluoro-1,4-dihydro-4-oxoquinoline)-7-yl]propionic acid (0.90 g, 87%), mp 222—225 °C (dec.), colorless needles after recrystallization from aqueous EtOH. IR (KBr): 1725 cm^{-1}. ^{1}H-NMR (CF_3COOD) δ: 1.1—2.1 (10H, m), 3.9—5.0 (4H, m), 8.38 (1H, d, J=9 Hz), 8.82 (1H, d, J=6 Hz), 9.40 (1H, s). *Anal.* Calcd for $C_{18}H_{18}FNO_5 \cdot 3/4H_2O$: C, 59.91; H, 5.45; N, 3.88. Found: C, 60.24; H, 5.58; N, 3.53.

Decarboxylation of this acid (0.73 g, 2.10 mmol) by the same method as described above for **5a** afforded **5b** (0.50 g, 78%). An analytical sample was obtained by recrystallization from aqueous EtOH as colorless needles, mp 220—222 °C. IR (KBr): 1723, 1696 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—1.6 (10H, m), 2.83 (2H, q, J=7 Hz), 3.3—3.7 (1H, m), 4.38 (2H, q, J=7 Hz), 7.74 (1H, d, J=6 Hz), 7.99 (1H, d, J=10 Hz), 8.53 (1H, s). *Anal.* Calcd for $C_{17}H_{18}FNO_3$: C, 67.31; H, 5.98; N, 4.62. Found: C, 67.12; H, 6.01; N, 4.22.

Ethyl 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-propyl-4-oxoquinoline-3-carboxylate (5c) This compound was prepared from **3** in 46% overall yield according to the same three-step procedure as described for **5b**, except for the use of EtI in the alkylation of **3**. An analytical sample was obtained by recrystallization from iso-Pr_2O–AcOEt as colorless needles, mp 201—203 °C. IR (KBr): 1722, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—2.1 (12H, m), 2.78 (2H, t, J=8 Hz), 3.3—3.8 (1H, m), 4.38 (2H, q, J=7.5 Hz), 7.71 (1H, d, J=6 Hz), 8.01 (1H, d, J=10 Hz), 8.52 (1H, s). *Anal.* Calcd for $C_{18}H_{20}FNO_3$: C, 68.12; H, 6.35; N, 4.41. Found: C, 68.12; H, 6.49; N, 4.43.

Ethyl 1-Cyclopropyl-7-diphenylmethoxycarbonylmethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (6) Compound **4** (20.0 g, 0.06 mol) was added to a mixture of MeOH (100 ml) and $CHCl_3$ (300 ml), and a 1 M solution of diphenyldiazomethane in petroleum ether (70 ml) was added to the suspension. The reaction mixture was stirred overnight at room temperature before quenching with AcOH. The solvent was removed under reduced pressure, and the solid residue was collected by filtration after addition of Et_2O to give **6** (29.0 g, 97%). An analytical sample was obtained by recrystallization from AcOEt as colorless prisms, mp 177—179 °C. IR (KBr): 1740, 1718 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.7 (7H, m), 3.1—3.6 (1H, m), 3.93 (2H, s), 4.39 (2H, q, J=7 Hz), 6.93 (1H, s), 7.28 (10H, s), 7.81 (1H, d, J=6 Hz), 8.12 (1H, d, J=10 Hz),

8.52 (1H, s). *Anal.* Calcd for $C_{30}H_{26}FNO_5$: C, 72.13; H, 5.25; N, 2.80. Found: C, 71.96; H, 5.18; N, 2.59.

Ethyl 1-Cyclopropyl-7-(1-diphenylmethoxycarbonyl-1-methylethyl)-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (7) Sodium hydride (60% in mineral oil, 0.12 g, 3.0 mmol) was added to a stirred suspension of **6** (1.0 g, 2.0 mmol) in DMF (10 ml) at room temperature, and, after 15 min, MeI (0.43 g, 3.0 mmol) was added to the mixture. The reaction mixture was stirred at 30—35 °C for 1 h, then treated again with the same amounts of NaH and MeI, and stirring was continued for 1.5 h. The mixture was poured into a mixture of ice-water (30 ml) and AcOEt (30 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 25 g, toluene: AcOEt = 2 : 1) to give **7** (0.28 g, 27%), mp 168—170 °C after recrystallization from aqueous EtOH. IR (KBr): 1736, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.9 (13H, m), 3.1—3.6 (1H, m), 4.40 (2H, q, J = 7 Hz), 6.92 (1H, s), 7.23 (10H, s), 7.86 (1H, d, J = 6.5 Hz), 8.03 (1H, d, J = 11.5 Hz), 8.57 (1H, s). *Anal.* Calcd for $C_{32}H_{30}FNO_5$: C, 72.85; H, 5.73; N, 2.65. Found: C, 72.80; H, 5.71; N, 2.69.

Ethyl 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-(1-methylethyl)-4-oxoquinoline-3-carboxylate (5d) TFA (2 ml) was added to a stirred suspension of **7** (0.20 g, 0.38 mol) in anisole (2 ml) at room temperature. The reaction mixture was stirred for 2 h, then concentrated under reduced pressure, and the residue was treated with Et_2O (10 ml) to induce crystallization. The crystals were collected by filtration to give a carboxylic acid, which was subjected to decarboxylation by heating in a flask with a Bunsen burner for *ca.* 10 s. The crude product was purified by chromatography (silica gel 5 g, $CHCl_3$: EtOH = 100 : 1) and crystallized from Et_2O to give **5d** (0.08 g, 66%), mp 232—235 °C (white powder). IR (KBr): 1722 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.7 (13H, m), 3.0—3.7 (2H, m), 4.39 (2H, q, J = 7 Hz), 7.77 (1H, d, J = 6 Hz), 8.05 (1H, d, J = 10.5 Hz), 8.56 (1H, s). *Anal.* Calcd for $C_{18}H_{20}FNO_3$: C, 68.12; H, 6.35; N, 4.41. Found: C, 68.44; H, 6.48; N, 4.54.

Ethyl 1-Cyclopropyl-7-(1-diphenylmethoxycarbonylcycloalkyl)-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (8e—h) These compounds (**8e—h**) were prepared from **6** in the same fashion as described for **7** using an appropriate alkylene dibromide as the alkylation reagent.

8e: 45% yield, mp 174—175 °C, colorless needles after recrystallization from EtOH. IR (KBr): 1719 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.7—2.0 (11H, m), 3.1—3.8 (1H, m), 4.40 (2H, q, J = 7 Hz), 6.82 (1H, s), 7.20 (10H, s), 7.82 (1H, d, J = 6 Hz), 8.13 (1H, d, J = 10 Hz), 8.56 (1H, s). *Anal.* Calcd for $C_{32}H_{28}FNO_5 \cdot 1/4H_2O$: C, 72.51; H, 5.42; N, 2.64. Found: C, 72.60; H, 5.26; N, 2.40.

8f: 26% yield, mp 168—170 °C, colorless needles after recrystallization from iso-Pr_2O–AcOEt. IR (KBr): 1733, 1723 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—3.1 (13 H, m), 3.1—3.6 (1H, m), 4.39 (2H, q, J = 7 Hz), 6.83 (1H, s), 7.19 (10H, s), 7.75 (1H, d, J = 6 Hz), 8.08 (1H, d, J = 11 Hz), 8.56 (1H, s). *Anal.* Calcd for $C_{33}H_{30}FNO_5$: C, 73.45; H, 5.60; N, 2.60. Found: C, 73.44; H, 5.68; N, 2.74.

8g: 34% yield, mp 195—196 °C, colorless prisms after recrystallization from iso-Pr_2O–AcOEt. IR (KBr): 1742, 1716 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—2.9 (15H, m), 3.1—3.7 (1H, m), 4.40 (2H, q, J = 7 Hz), 6.85 (1H, s), 7.19 (10H, s), 7.89 (1H, d, J = 7 Hz), 8.04 (1H, d, J = 11.5 Hz), 8.57 (1H, s). *Anal.* Calcd for $C_{34}H_{32}FNO_5$: C, 73.76; H, 5.83; N, 2.53. Found: C, 73.67; H, 5.90; N, 2.79.

8h: 27% yield, mp 210—212 °C, colorless needles after recrystallization from EtOH. IR (KBr): 1746, 1717 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—2.7 (17H, m), 3.0—3.5 (1H, m), 4.40 (2H, q, J = 7 Hz), 6.92 (1H, s), 7.18 (10H, s), 7.88 (1H, d, J = 6.5 Hz), 8.03 (1H, d, J = 11.5 Hz), 8.55 (1H, s). *Anal.* Calcd for $C_{35}H_{34}FNO_5$: C, 74.06; H, 6.04; N, 2.47. Found: C, 74.01; H, 6.11; N, 2.46.

Ethyl 7-Cycloalkyl-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (5e—h) These compounds (**5e—h**) were prepared from **8e—h** by the same method as described for **5d**.

5e: 43% yield, mp 231—233 °C, colorless needles after recrystallization from aqueous EtOH. IR (KBr): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.5—1.7 (11H, m), 1.9—2.5 (1H, m), 3.2—3.7 (1H, m), 4.38 (2H, q, J = 7 Hz), 7.42 (1H, d, J = 6 Hz), 8.00 (1H, d, J = 10.5 Hz), 8.51 (1H, s). *Anal.* Calcd for $C_{18}H_{18}FNO_3$: C, 68.56; H, 5.75; N, 4.44. Found: C, 68.69; H, 5.83; N, 4.26.

5f: 84% yield, mp 231—233 °C, colorless needles after recrystallization from AcOEt. IR (KBr): 1721 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—2.7 (13H, m), 3.2—4.1 (2H, m), 4.39 (2H, q, J = 7 Hz), 7.75 (1H, d, J = 6 Hz), 8.02 (1H, d, J = 10.5 Hz), 8.55 (1H, s). *Anal.* Calcd for $C_{19}H_{20}FNO_3$: C, 69.29; H, 6.12; N, 4.25. Found: C, 69.14; H, 5.93; N, 4.36.

5g: 58% yield, mp 222—224 °C, colorless needles after recrystallization from $CHCl_3$–AcOEt. IR (KBr): 1721 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—2.4 (15H, m), 3.0—3.7 (2H, m), 4.38 (2H, q, J = 7 Hz), 7.78 (1H, d, J = 6 Hz), 8.03 (1H, d, J = 11 Hz), 8.54 (1H, s). *Anal.* Calcd for $C_{20}H_{22}FNO_3$: C, 69.95; H, 6.46; N, 4.08. Found: C, 69.71; H, 6.36; N, 4.18.

5h: 89% yield, mp 243—244 °C, colorless needles after recrystallization from EtOH. IR (KBr): 1721 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—2.2 (17H, m), 2.7—3.7 (2H, m), 4.40 (2H, q, J = 7 Hz), 7.76 (1H, d, J = 6 Hz), 8.06 (1H, d, J = 10.5 Hz), 8.56 (1H, s). *Anal.* Calcd for $C_{21}H_{24}FNO_3$: C, 70.57; H, 6.77; N, 3.92. Found: C, 70.54; H, 6.87; N, 4.02.

Ethyl 1-Cyclopropyl-7-(1-diphenylmethoxycarbonylvinyl)-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (9) *N,N,N',N'*-Tetramethyldiaminomethane (0.61 g, 5.97 mmol) and acetic anhydride (1.35 g, 13.2 mmol) was added to a stirred suspension of **6** (2.00 g, 4.00 mmol) in DMF (16 ml). The mixture was stirred at room temperature for 24 h, and the crystals that separated were collected by filtration after addition of water (8 ml) to give **9** (1.92 g, 94%). An analytical sample was obtained by recrystallization from AcOEt as colorless needles, mp 182—183 °C. IR (KBr): 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.7 (7H, m), 3.0—3.6 (1H, m), 4.40 (2H, q, J = 7 Hz), 6.10 (1H, s), 6.78 (1H, s), 7.01 (1H, s), 7.30 (10H, s), 7.85 (1H, d, J = 6 Hz), 8.14 (1H, d, J = 10 Hz), 8.57 (1H, s). *Anal.* Calcd for $C_{31}H_{26}FNO_5$: C, 72.79; H, 5.12; N, 2.74. Found: C, 72.46; H, 5.15; N, 2.81.

Ethyl 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-vinyl-4-oxoquinoline-3-carboxylate (5i) TFA (7.5 ml) was added to a stirred suspension of **9** (1.50 g, 2.93 mmol) in anisole (7.5 ml) at room temperature. The reaction mixture was stirred for 1 h, then concentrated under reduced pressure, and the residue was treated with Et_2O (30 ml) to induce crystallization. The crystals were collected by filtration to give a carboxylic acid, which was dissolved in DMF (40 ml). The solution was heated under reflux for 6 h before removal of the solvent under reduced pressure. The residue was subjected to chromatography (silica gel 25 g, toluene : AcOEt = 2 : 1) to give **5i**[13] (0.46 g, 52%) after recrystallization from AcOEt, mp 219—223 °C (pale yellow needles). IR (KBr): 1726, 1696 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.7 (7H, m), 3.2—3.7 (1H, m), 4.38 (2H, q, J = 7 Hz), 5.58 (1H, d, J = 11 Hz), 5.98 (1H, d, J = 18 Hz), 6.97 (1H, dd, J = 18, 11 Hz), 7.96 (1H, d, J = 6 Hz), 8.06 (1H, d, J = 11 Hz), 8.54 (1H, s). *Anal.* Calcd for $C_{17}H_{16}FNO_3$: C, 67.76; H, 5.35; N, 4.65. Found: C, 67.94; H, 5.21; N, 4.42.

1,7-Dicyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (1e) (General Procedure for Hydrolysis of Ethyl Esters 5a—i) The ester **5e** (0.15 g, 0.48 mmol) was added to a mixture of EtOH (3 ml) and 1 N NaOH (3 ml), and the suspension was stirred at room temperature. After 2 h, the reaction mixture was poured into a two-phase mixture of water (6 ml) and $CHCl_3$ (20 ml). The organic layer was separated after acidification (pH 1) by addition of 6 N HCl, washed successively with water and saturated brine, dried, and concentrated. The solid residue was crystallized from Et_2O to give **1e** (0.12 g, 88%). The melting points, yields, combustion analysis, IR, and ^{1}H-NMR data are summarized in Table II.

***In Vitro* Antibacterial Activity** According to the method of the Japan Society of Chemotherapy,[15] the MICs of compounds were determined by the two-fold agar dilution method using heart infusion agar (Eiken). The inoculum size was adjusted to 10^6 colony-forming units/ml, and incubation was carried out at 37 °C for 20 h.

Convulsion Induction This assay was carried out according to the method reported previously.[5a] A solution of each compound (50 μg) in 0.025 N NaOH (10 μl) was injected intracerebrally into ICR-strain male mice (20—25 g body weight). Each mouse was placed in an individual cage, and the number of convulsions (clonic and tonic seizures) that occured was counted. The mortality rate in each test group was obtained after 24 h.

Serum Levels and Urinary Recoveries 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, four or five mice per group). Serum samples were obtained at 15, 30, 60, 120, and 240 min after dosing. Urine was collected during 0 to 24 h after dosing. Serum levels and urinary excretion of test compounds were determined by HPLC assay or microbiological assay using *Escherichia*

coli Kp as the test organism.

Acknowledgment The authors are grateful to Professor E. Yoshii, Toyama Medical and Pharmaceutical University, for his help and useful suggestions in the preparation of the manuscript.

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