Pyridonecarboxylic Acids as Antibacterial Agents. VIII.[1a] Synthesis and Structure–Activity Relationship of 7-(1-Aminocyclopropyl)-4-oxo-1,8-naphthyridine-3-carboxylic Acids and 7-(1-Aminocyclopropyl)-4-oxoquinoline-3-carboxylic Acids

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4-Oxo-1,8-naphthyridine- and 4-oxoquinoline-3-carboxylic acids (2a, b and 3a—l) possessing a 1-aminocyclopropyl group at the 7-position have been synthesized and evaluated for *in vitro* antibacterial activities. The three quinolones (3d, h, i) exhibited potent antibacterial activities against both gram-positive and gram-negative bacteria, which are comparable to those of ciprofloxacin (CPFX) and ofloxacin (OFLX). Among the three compounds, the best pharmacological and pharmacokinetic profile was obtained with 3i, an OFLX analogue, which was considerably less toxic than three reference quinolones (1, CPFX, and OFLX).

Keywords antibacterial agent; 4-oxo-1,8-naphthyridine; 4-oxoquinoline; aminocyclopropyl substituent; structure–activity relationship; antibacterial activity

Our studies in search of a new quinolone antibacterial agent that has lower toxicity than currently marketed quinolones but still exhibits potent broad-spectrum antibacterial activity has led to the important finding that the C(7)-piperazinyl substituent of ciprofloxacin (CPFX)[2] can be replaced by a 1-aminocyclopropyl group.[1] Compound **1** (Chart 1) reported in the previous paper[1a] proved less toxic than CPFX and ofloxacin (OFLX)[3] and, moreover, had weaker convulsion-inducing activity. Antibacterial activity of **1** against gram-negative bacteria including *Pseudomonas aeruginosa* is comparable to that of CPFX, but activity against gram-positive *Staphylococcus aureus* is somewhat weaker. In order to improve the antibacterial profile of **1**, we have synthesized a series of 7-(1-aminocyclopropyl) derivatives of a variety of 1-substituted 4-naphthyridone- and 4-quinolone-3-carboxylic acids (**2a, b** and **3a—l**) (Chart 2). Among these new compounds, the OFLX analogue **3i** showed excellent *in vitro* broad-spectrum antibacterial activity, which is comparable to those of CPFX and OFLX. Further, compound **3i** is considerably less toxic than **1** and OFLX, and has good pharmacokinetic properties.

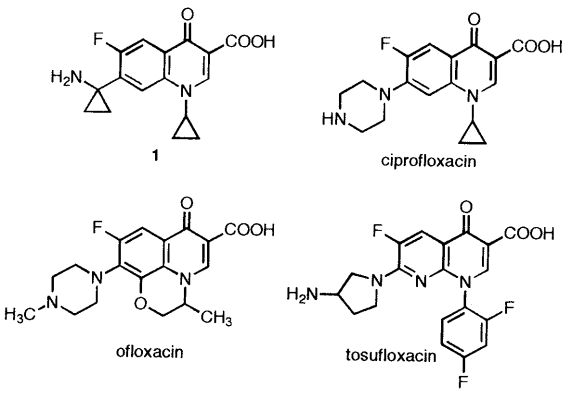


Chart 1

Chemistry

The two 1,8-naphthyridone derivatives (**2a, b**) were synthesized from 7-chloro-naphthyridones **4a, b**[4] by replacing the chloro substituent with a 1-aminocyclopropyl group as outlined in Chart 3. Reaction of **4a, b** with *tert*-butyl acetoacetate in the presence of NaH[5] afforded acetoacetate derivatives **5a, b**, which, on treatment with hydrazine hydrate in ethanol at room temperature, provided 7-(*tert*-butoxycarbonyl)methyl compounds **6a, b**. These compounds were subjected to cyclopropane formation[5a] at the acetic ester side-chain by reaction with excess 1,2-dibromoethane and NaH to give **7a, b**, which, on treatment with trifluoroacetic acid (TFA), afforded carboxylic acids **8a, b**. Then, conversion of the carboxyl group to the *tert*-butoxycarbonyl(Boc)-protected amino functionality was carried out by a conventional Curtius rearrangement[6]

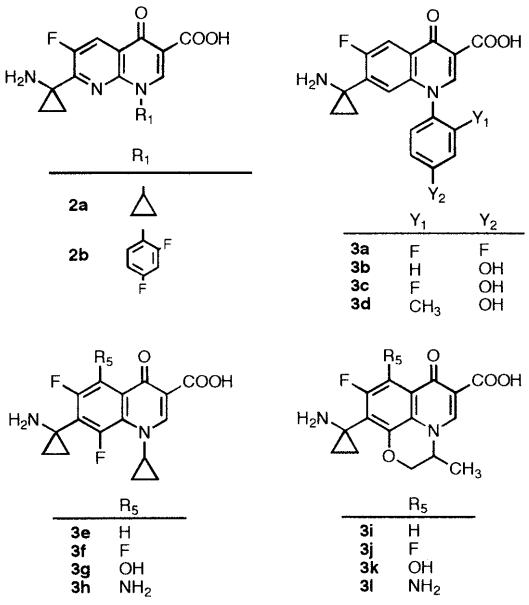


Chart 2

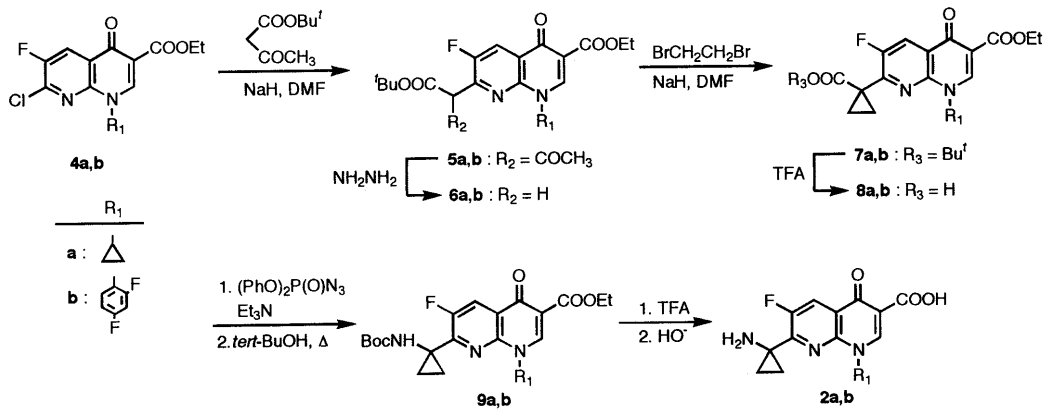


Chart 3

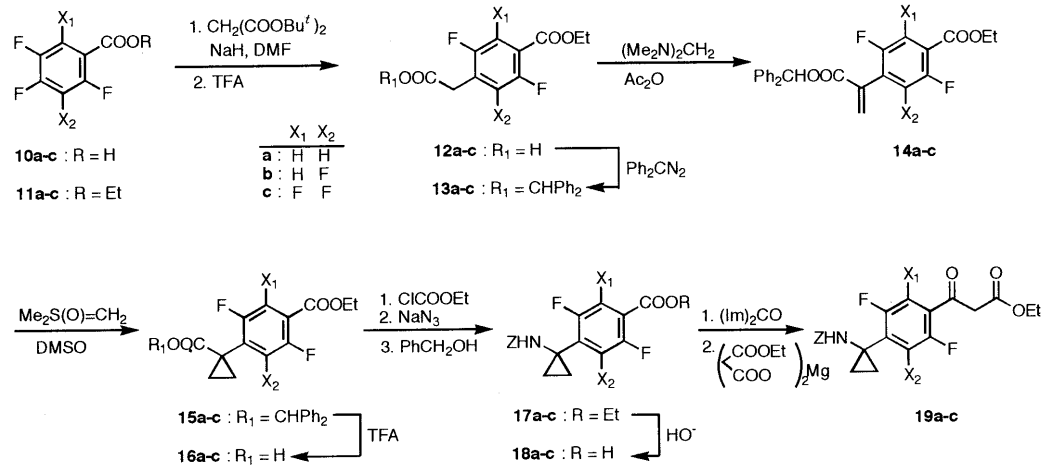


Chart 4

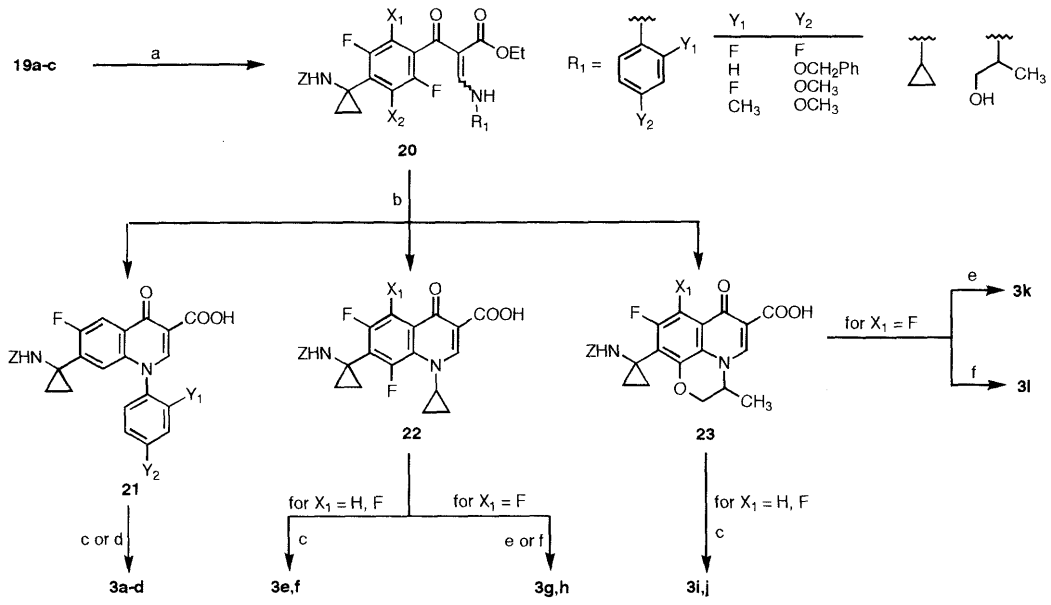
to give **9a, b**. Lastly, the carbamoyl and alkoxycarbonyl groups were hydrolyzed by successive treatment with TFA and with ethanolic NaOH to provide **2a, b** having cyclopropyl and 2,4-difluorophenyl N_1-substituents, respectively.

For the synthesis of quinolones **3a—l** bearing a variety of N_1- or N_1/C_8-substituents, we focused on pyridone annulation of *o*-fluorobenzoyl acetate (**19**), a standard procedure in the quinolone series.[7] The common intermediates **19a—c** were prepared from fluorinated benzoic acids **10a—c**, which are commercially available (Chart 4). Their ethyl esters **11a—c** were allowed to react with the sodium derivative of di-*tert*-butyl malonate,[5a] and the diester products were converted to diphenylmethyl esters **13a—c** of the monocarboxylic acids (**12a—c**). The cyclopropane-ring formation at the benzylic position yielding **15a—c** was performed at this stage by a two-step procedure: α-methylenation of **13** with bis(dimethylamino)-methane and acetic anhydride,[8] and treatment of the resultant acrylate **14** with dimethyloxosulfonium methylide.[9] For conversion of **15a—c** to benzyloxycarbonyl(*Z*)-protected aminocyclopropanes **17a—c**, the monocarboxylic acids **16a—c** obtained by treatment with TFA were subjected to Curtius rearrangement involving azidation of a mixed anhydride. The alkoxycarbonyl groups in **17a—c** were then saponified to the corresponding acids **18a—c**, which in turn were transformed to the β-keto esters **19a—c** by a conventional two-step procedure[10] consisting of imidazolide formation and reaction with the magnesium salt of ethyl hydrogen malonate.

The β-keto esters **19a—c** were then transformed to α-aminomethylene derivatives **20** by treatment with *N,N*-dimethylformamide dimethylacetal, followed by exposure to appropriate primary amines (4- or 2,4-disubstituted phenyl, cyclopropyl, and (1-hydroxymethyl)ethyl) (Chart 5). The annulation of **20** by internal dehydrofluorination was effected by heating in *N,N*-dimethylformamide (DMF) in the presence of K_2CO_3, and the resulting quinolones were subjected to ester hydrolysis with alcoholic NaOH to afford **21**, **22**, and **23**. The remaining *N*- and/or *O*-protecting groups in **21**, **22** (X_1 = H, F), and **23** (X_1 = H, F) were removed by catalytic hydrogenolysis or by treatment with hydrobromic acid to provide **3a—f, i, j**. The quinolones (**3g, h, k, l**) bearing a hydroxyl or amino substituent at the 5-position were prepared from the corresponding fluoro derivatives by displacement reaction with sodium benzylate or benzylamine followed by reductive removal of the benzyl protecting group.

Biological Results and Discussion

***In Vitro* Antibacterial Activity** The new 7-(1-aminocyclopropyl)naphthyridones (**2a, b**) and quinolones (**3a—l**) have been evaluated for *in vitro* antibacterial activity against five microorganisms using the standard serial



reagents: (a) $Me_2NCH(OMe)_2$, then R_1NH_2; (b) K_2CO_3, DMF, then NaOH-EtOH-H_2O; (c) H_2-Pd/C; (d) HBr, Δ; (e) $PhCH_2ONa$, then H_2-Pd/C; (f) $PhCH_2NH_2$, then H_2-Pd/C

Chart 5

TABLE I. Physical Data for Naphthyridones (**2a, b**) and Quinolones (**3a—l**)

Compd.	mp (dec. °C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	IR (KBr) cm^{-1}	^{1}H-NMR (CF_3COOD) δ (ppm)
2a	220—222	$CHCl_3$–EtOH	5[c]	$C_{15}H_{14}FN_3O_3$	59.40 (59.43)	4.65 4.71	13.85 13.74)	1719	0.7—1.9 (8H, m), 3.5—4.1 (1H, m), 8.30 (1H, d, J=10.5 Hz), 8.90 (1H, s)
2b	198—200	AcOEt	2[d]	$C_{18}H_{12}F_3N_3O_3 \cdot H_2O$	54.97 (54.80	3.59 3.39	10.68 10.40)	1734	1.7—2.6 (4H, m), 6.9—7.9 (3H, m), 8.75 (1H, d, J=10.5 Hz), 9.38 (1H, s)
3a[a]	223—226	6 N HCl–EtOH	8[e]	$C_{19}H_{13}F_3N_2O_3 \cdot HCl \cdot 1/2H_2O$	54.36 (54.37	3.60 3.61	6.67 6.39)	1734	1.2—2.1 (4H, m), 7.1—8.0 (4H, m), 8.54 (1H, d, J=9.5 Hz), 9.37 (1H, s)
3b[a]	252—256	6 N HCl–EtOH	6[e]	$C_{19}H_{15}FN_2O_4 \cdot HCl \cdot H_2O$	55.82 (55.64	4.44 4.59	6.85 6.82)	1726	1.1—2.2 (4H, m), 7.1—7.8 (4H, m), 7.98 (1H, d, J=6 Hz), 8.52 (1H, d, J=9.5 Hz), 9.42 (1H, s)
3c[b]	232—235	HBr–H_2O	12[e]	$C_{19}H_{14}F_2N_2O_4 \cdot HBr \cdot 2H_2O$	46.64 (46.43	3.91 3.71	5.73 5.39)	1718	1.1—2.1 (4H, m), 6.9—8.1 (4H, m), 8.54 (1H, d, J=9.5 Hz), 9.41 (1H, s)
3d[b]	234—236	HBr–H_2O	12[e]	$C_{20}H_{17}FN_2O_4 \cdot HBr \cdot 3H_2O$	47.73 (47.76	4.81 4.58	5.57 5.36)	1700	1.2—2.3 (7H, m), 7.0—7.7 (3H, m), 7.82 (1H, d, J=6 Hz), 8.54 (1H, d, J=9.5 Hz), 9.37 (1H, s)
3e[a]	235—238	6 N HCl–EtOH	20[f]	$C_{16}H_{14}F_2N_2O_3 \cdot HCl$	53.87 (53.63	3.96 4.13	7.85 8.14)	1734	1.3—2.4 (8H, m), 4.4—5.0 (1H, m), 8.32 (1H, dd, J=9, 2 Hz), 9.50 (1H, s)
3f[a]	246—249	6 N HCl–iso-PrOH	7[g]	$C_{16}H_{13}F_3N_2O_3 \cdot HCl$	51.28 (51.04	3.77 3.82	7.48 7.37)	1731	1.2—2.3 (8H, m), 4.2—4.8 (1H, m), 9.39 (1H, s)
3g[a]	247—250	6 N HCl–iso-PrOH	4[g]	$C_{16}H_{14}F_2N_2O_4 \cdot HCl \cdot H_2O$	49.18 (49.38	4.38 4.28	7.17 7.13)	1735 1719	1.1—2.2 (8H, m), 3.9—4.5 (1H, m), 9.09 (1H, s)
3h[a]	243—246	6 N HCl–iso-PrOH	4[g]	$C_{16}H_{15}F_2N_3O_3 \cdot HCl \cdot 1/4H_2O$	51.07 (51.18	4.42 4.40	11.17 11.27)	1717	1.1—2.2 (8H, m), 4.0—4.6 (1H, m), 9.22 (1H, s)
3i	279—281	$CHCl_3$–MeOH	16[f]	$C_{16}H_{15}FN_2O_4$	60.38 (60.17	4.75 4.85	8.80 8.82)	1699	1.3—2.3 (7H, m), 4.6—5.5 (3H, m), 8.05 (1H, d, J=9.5 Hz), 9.41 (1H, s)
3j[a]	278—281	6 N HCl–EtOH	9[g]	$C_{16}H_{14}F_2N_2O_4 \cdot HCl \cdot 1/2H_2O$	50.34 (50.41	4.22 4.42	7.34 7.12)	1718 1701	1.2—2.2 (7H, m), 4.5—5.5 (3H, m), 9.35 (1H, s)
3k[a]	257—261	6 N HCl–iso-PrOH	2[g]	$C_{16}H_{15}FN_2O_5 \cdot HCl$	51.83 (52.05	4.35 4.52	7.56 7.78)	1743	1.2—2.2 (7H, m), 4.2—5.5 (3H, m), 9.02 (1H, s)
3l[a]	276—280	6 N HCl–iso-PrOH	3[g]	$C_{16}H_{16}FN_3O_4 \cdot HCl \cdot 3/4H_2O$	50.14 (50.37	4.86 4.82	10.96 10.70)	1700	1.3—2.2 (7H, m), 4.4—5.4 (3H, m), 9.25 (1H, s)

a) Hydrochloride. *b*) Hydrobromide. *c*) Overall yield from **4a**. *d*) Overall yield from **4b**. *e*) Overall yield from **10a**. *f*) Overall yield from **10b**. *g*) Overall yield from **10c**.

two-fold dilution method.[11] The minimum inhibitory concentrations (MICs, μg/ml) are recorded in Table II together with the data for **1**, CPFX, OFLX, and tosufloxacin (TFLX).[12] Activities of the naphthyridones (**2a, b**) were equivalent to or a little lower than those of the corresponding quinolones (**1**, **3a**). Compounds **2b** and

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]
2a	3.13	≤0.05	≤0.05	0.2	12.5
2b	0.78	0.1	0.1	0.2	3.13
3a	1.56	0.1	0.1	≤0.05	6.25
3b	0.39	0.1	≤0.05	0.1	1.56
3c	0.39	0.1	0.2	0.1	3.13
3d	0.2	≤0.05	≤0.05	≤0.05	0.78
3e	0.78	≤0.05	≤0.05	≤0.05	1.56
3f	1.56	≤0.05	≤0.05	≤0.05	6.25
3g	0.78	≤0.05	≤0.05	0.1	6.25
3h	0.1	≤0.05	≤0.05	≤0.05	1.56
3i	0.39	≤0.05	≤0.05	≤0.05	0.39
3j	1.56	≤0.05	0.1	0.1	6.25
3k	1.56	≤0.05	0.1	0.1	1.56
3l	0.39	≤0.05	≤0.05	≤0.05	1.56
1	1.56	≤0.05	≤0.05	≤0.05	0.78
CPFX	0.2	≤0.05	≤0.05	≤0.05	0.39
OFLX	0.39	≤0.05	≤0.05	≤0.05	0.78
TFLX	≤0.05	≤0.05	≤0.05	≤0.05	0.2

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.

TFLX have the same N_1-2,4-difluorophenyl group but differ in the C(7) substituent, and TFLX was considerably more active than **2b** against all the bacteria tested. All the quinolones **3a**—**l** displayed good inhibitory activities against the gram-positive strain *Staphylococcus aureus*, equivalent or superior to our prototype quinolone **1**. Notable broad-spectrum antibacterial activities, comparable to those of CPFX and OFLX, were seen with **3d** (N_1-(4-hydroxy-2-methyl)phenyl analog of **1**), **3h** (5-amino-8-fluoro derivative of **1**), and **3i** (an OFLX analog of **1**), although their antistaphylococcal activities were significantly inferior to that of TFLX.

Acute Toxicity and Convulsion Induction The three compounds (**3d, h, i**) which showed potent antibacterial activities against gram-positive and gram-negative bacteria were assayed for acute toxicity and convulsion-inducing activity[13] in mice. The results after intravenous and intracerebral administrations are shown in Table III, together with the data obtained with **1**, CPFX, OFLX, and TFLX. The OFLX analogue **3i** was significantly less toxic ($LD_{50} = > 500$ mg/kg) than the others. Furthermore, compound **3i** did not induce convulsion (clonic or tonic) after intracerebral dosing of 50 μg, a dose at which CPFX and OFLX produced high convulsion and mortality rates.

Mammalian Cell Cytotoxicity The OFLX analogue **3i** was tested for cytotoxicity to Chinese hamster V-79 cells. This cytotoxicity has been demonstrated to be directly correlated with the *in vitro* genetic toxicity for fluoroquinolones, which are potent inhibitors of bacterial topoisomerase II (DNA gyrase).[14] The IC_{50} data (μg/ml) obtained with **3i** and four reference quinolones are listed in Table IV. The IC_{50} is defined as the concentration of a compound yielding 50% cell survival compared to untreated control cells. The data indicate that compound **3i**, which shows the highest value (300 μg/ml), is considerably less toxic than CPFX, OFLX, or TFLX. The safety margin (ratio of IC_{50} to MIC) of **3i** for gram-positive bacteria is about 3-fold higher than that of TFLX; 770 *versus* 240.

TABLE III. 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]
3d	62.5	1/3	ND	ND	ND
3h	20	3/6	ND	ND	ND
3i	500	0/5	0/ 8	0/ 8	0/ 8
1	250	0/3	6/10	5/10	0/10
CPFX	250	1/5	10/10	10/10	10/10
OFLX	250	3/5	10/10	8/10	8/10
TFLX	250	0/3	2/12	0/12	1/12

ND: not determined. *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.

TABLE IV. Mammalian Cell Cytotoxicity in Chinese Hamster V79 Cells

Compound	IC_{50} (μg/ml) after 48 h
3i	300
1	210
TFLX	12
CPFX	70
OFLX	120

TABLE V. 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)
3i	15.0	24	<0.09	43.3
CPFX	6.5	52	0.06	51.5
OFLX	10.6	38	0.04	19.5
TFLX	6.6	46	ND	24.0

ND: not determined. These data were determined by a bioassay procedure.

Pharmacokinetic Properties The quinolone **3i**, which showed an excellent antibacterial and pharmacological profile, was assayed for urinary recovery as well as for serum and brain levels after intravenous administration to mice. The results are shown in Table V, together with those for the reference drugs. Urinary recovery of **3i** is significantly higher than those of OFLX and TFLX and is comparable to that of CPFX. The serum level of **3i** (15 min after dosing) is 1.4 to 2.3 times as high as those of the reference drugs, but the half-life time of **3i** is shorter by about 50%. The brain/serum-concentration ratio of **3i** is as low as those of the reference drugs.

In conclusion, we have discovered a potent and significantly less toxic fluoroquinolone antibacterial agent **3i** by replacing the piperazinyl substituent of OFLX with a 1-aminocyclopropyl group.

Experimental[15]

General Method for the Preparation of 7a, b Ethyl 7-(1-*tert*-Butoxycarbonylcyclopropyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-

oxo-1,8-naphthyridine-3-carboxylate (**7b**): A suspension of NaH (60% in mineral oil, 8.36 g, 0.209 mol) in dry DMF (200 ml) was stirred and cooled to 5 °C, and *tert*-butyl acetoacetate (33.1 g, 0.209 mol) was added over 1 h. The mixture was allowed to warm to room temperature before addition of **4b** (20.0 g, 0.052 mol). The reaction mixture was stirred at room temperature for 20 h, then poured into a mixture of ice-water (250 ml) and AcOEt (250 ml). 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 subjected to chromatography (silica gel 250 g, $CHCl_3$) to give **5b** (16.1 g, 61%) after crystallization from iso-Pr_2O. An analytical sample was obtained by recrystallization from EtOH as colorless prisms, mp 167—169 °C. IR (KBr): 1728, 1696 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—2.3 (15H, m), 4.40 (2H, q, J=7 Hz), 6.8—7.7 (3H, m), 8.2—8.7 (2H, m), 13.49 (1H, s). *Anal.* Calcd for $C_{25}H_{23}F_3N_2O_6$: C, 59.52; H, 4.60; N, 5.55. Found: C, 59.56; H, 4.67; N, 5.32.

Hydrazine hydrate (0.83 g, 16.6 mmol) was added to a stirred suspension of **5b** (7.00 g, 13.9 mmol) in EtOH (70 ml), and the mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure after addition of AcOH (0.17 g, 2.83 mmol). The residue was covered with AcOEt (100 ml) and H_2O (100 ml), and the whole was acidified to pH 1 by addition of 6 N HCl before separation of the layers. The organic layer was washed successively with water and saturated brine, dried, and concentrated. The residue was purified by chromatography (silica gel 140 g, $CHCl_3$) to give **6b** (4.09 g, 64%). An analytical sample was obtained by recrystallization from aqueous EtOH as colorless prisms, mp 132—133 °C. IR (KBr): 1727 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—1.7 (12H, m), 3.75 (2H, d, J=2.5 Hz), 4.41 (2H, q, J=7 Hz), 6.8—7.7 (3H, m), 8.40 (1H, d, J=8.5 Hz), 8.54 (1H, s). *Anal.* Calcd for $C_{23}H_{21}F_3N_2O_5$: C, 59.74; H, 4.58; N, 6.06. Found: C, 59.69; H, 4.58; N, 6.08.

Sodium hydride (60% in mineral oil, 0.365 g, 9.13 mmol) was added to a stirred solution of **6b** (3.50 g, 7.57 mmol) in DMF (35 ml) at room temperature, and, after 30 min, ethylene dibromide (1.71 g, 9.10 mmol) was added to the mixture. The reaction mixture was stirred at 45—55 °C for 9 h, then treated again with the same amounts of NaH and ethylene dibromide, and stirring was continued for 9 h. The mixture was poured into a mixture of ice-water (100 ml) and AcOEt (100 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 70 g, toluene : AcOEt = 10 : 1) to give **7b** (1.01 g, 27%). An analytical sample was obtained by recrystallization from hexane–AcOEt as colorless prisms, mp 173—175 °C. IR (KBr): 1740, 1721 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.7 (16H, m), 4.41 (2H, q, J=7 Hz), 6.8—7.7 (3H, m), 8.35 (1H, d, J=9 Hz), 8.55 (1H, s). *Anal.* Calcd for $C_{25}H_{23}F_3N_2O_5$: C, 61.47; H, 4.75; N, 5.73. Found: C, 61.33; H, 4.64; N, 5.58.

The N_1-cyclopropyl compound **7a** was obtained in 16% overall yield from **4a** by the same procedure, mp 138—139 °C (colorless needles from iso-Pr_2O–AcOEt). IR (KBr): 1727 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.8 (20H, m), 3.4—3.9 (1H, m), 4.40 (2H, q, J=7.5 Hz), 8.31 (1H, d, J=9 Hz), 8.63 (1H, s). *Anal.* Calcd for $C_{22}H_{25}FN_2O_5$: C, 63.45; H, 6.05; N, 6.73. Found: C, 63.05; H, 6.19; N, 6.77.

General Method for the Preparation of Naphthyridones 2a, b 7-(1-Aminocyclopropyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**2b**): TFA (4.8 ml) was added to a stirred suspension of **7b** (0.95 g, 1.94 mmol) in anisole (4.8 ml). The reaction mixture was stirred at room temperature for 3 h, then concentrated under reduced pressure. The residue was treated with Et_2O (20 ml) to induced crystallization. The crystals were collected by filtration to give **8b** (0.79 g, 94%), mp 206—208 °C, colorless needles after recrystallization from AcOEt. IR (KBr): 1735, 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—1.9 (7H, m), 4.38 (2H, q, J=7 Hz), 6.8—7.7 (4H, m), 8.37 (1H, d, J=9 Hz), 8.55 (1H, s). *Anal.* Calcd for $C_{21}H_{15}F_3N_2O_5 \cdot 1/4H_2O$: C, 57.74; H, 3.58; N, 6.41. Found: C, 57.80; H, 3.63; N, 6.52.

Diphenylphosphoryl azide (0.33 g, 1.20 mmol) and triethylamine (0.12 g, 1.19 mmol) were added to a stirred suspension of **8b** (0.34 g, 0.79 mmol) in CH_2Cl_2 (7 ml). The mixture was stirred at room temperature for 6 h, then poured into ice-water (10 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 (7 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 8 g, $CHCl_3$: EtOH = 30 : 1) to give **9b** (0.15 g, 38%). An analytical sample was obtained by recrystallization from hexane–AcOEt as colorless needles, mp 183—185 °C. IR (KBr): 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.7 (16H, m), 4.40 (2H, q, J=7 Hz), 5.28 (1H, br s), 6.7—7.6 (3H, m), 8.30 (1H, d, J=10.5 Hz), 8.52 (1H, s). *Anal.* Calcd for $C_{25}H_{24}F_3N_3O_5$: C, 59.64; H, 4.80; N, 8.35. Found: C, 59.36; H, 4.75; N, 8.38.

A solution of **9b** (120 mg, 0.24 mmol) and TFA (1 ml) in CH_2Cl_2 (1 ml) was stirred at room temperature for 2 h. The solution was concentrated under reduced pressure, and the residue was taken up in water (10 ml) and $CHCl_3$ (20 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 the ethyl ester of **2b** (80 mg, 83%), mp 204—207 °C. This material (60 mg, 0.15 mmol) was added to a mixture of EtOH (1.2 ml) and 1 N NaOH (1.2 ml), and the mixture was stirred at room temperature for 2 h. The mixture was brought to pH 6.5 with AcOH, and the precipitated crystals were collected by filtration to give **2b** (35 mg, 63%).

The N_1-cyclopropyl compound **2a** was obtained in 32% overall yield from **7a** by the same procedure.

Physical properties and combustion analytical data of **2a, b** are given in Table I.

General Method for the Preparation of 13a—c Ethyl 4-Diphenylmethoxycarbonylmethyl-2,3,5-trifluorobenzoate (**13b**): Thionyl chloride (123 g, 1.03 mol) was added to a stirred solution of **10b** (100 g, 0.515 mol) in EtOH (500 ml) at 5 to 10 °C, and then the mixture was heated under reflux for 1 h. The solvent was removed under reduced pressure, and the remaining oil was purified by distillation to give **11b** (104 g, 91%), bp 87—87.5 °C (13 mmHg). IR (neat): 1726 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7 Hz), 4.43 (2H, q, J=7 Hz), 7.3—7.9 (1H, m).

A suspension of NaH (60% in mineral oil, 27.0 g, 0.675 mol) in dry DMF (1.25 l) was stirred and cooled to 5 °C, and di-*tert*-butyl malonate (146 g, 0.675 mol) was added over 3 h. The mixture was allowed to warm to room temperature before addition of **11b** (100 g, 0.450 mol). The reaction mixture was stirred at the same temperature for 12 h, then poured into a mixture of ice-water (2.0 l) and AcOEt (1.0 l). The layers were separated after acidification to pH 3 by addition of 6 N HCl. The organic layer was washed successively with water and saturated brine, dried, and concentrated. The residue was dissolved in TFA (360 ml), and the solution was stirred at room temperature for 20 h, then concentrated under reduced pressure. The residue was taken up in Et_2O (600 ml) and H_2O (800 ml). The layers were separated, and the organic layer was washed successively with water and saturated brine, dried, and concentrated. The residue was dissolved in toluene (400 ml), and the solution was heated under reflux for 2 h before removal of the solvent under reduced pressure. The residue was crystallized from hexane to give **12b** (84 g, 71%), mp 92—92.5 °C, colorless needles after recrystallization from hexane–benzene. IR (KBr): 1718 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 3.82 (2H, s), 4.42 (2H, q, J=7 Hz), 7.1—7.6 (1H, m), 10.13 (1H, s). *Anal.* Calcd for $C_{11}H_9F_3O_4$: C, 50.39; H, 3.46. Found: C, 50.52; H, 3.37.

Compound **12b** (83.0 g, 0.317 mol) was dissolved in Et_2O (150 ml), and a 1 M solution of diphenyldiazomethane in petroleum ether (350 ml) was added. The solution was stirred overnight at room temperature, and the precipitated crystals were collected by filtration to give **13b** (123 g, 91%). An analytical sample was obtained by recrystallization from iso-PrOH as colorless needles, mp 68.5—69 °C. IR (KBr): 1734 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7 Hz), 3.86 (2H, s), 4.40 (2H, q, J=7 Hz), 6.90 (1H, s), 7.0—7.6 (11H, m). *Anal.* Calcd for $C_{24}H_{19}F_3O_4$: C, 67.29; H, 4.47. Found: C, 67.23; H, 4.40.

The 2,5-difluorophenyl and 2,3,5,6-tetrafluorophenyl analogs (**13a** and **13c**) were prepared by the same procedure using **10a** and **10c** as the starting materials, respectively.

13a: 43% overall yield from **10a**, mp 49—50 °C (colorless needles from iso-PrOH). IR (KBr): 1738 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7 Hz), 3.78 (2H, s), 4.38 (2H, q, J=7 Hz), 6.90 (1H, s), 7.0—7.4 (11H, m), 7.61 (1H, dd, J=9.5, 6 Hz). *Anal.* Calcd for $C_{24}H_{20}F_2O_4$: C, 70.24; H, 4.91. Found: C, 70.35; H, 4.79.

13c: 50% overall yield from **10c**, mp 52—53 °C (colorless needles from iso-PrOH). IR (KBr): 1744 cm^{-1}. ^{1}H-HMR ($CDCl_3$) δ: 1.39 (3H, t, J=7 Hz), 3.88 (2H, s), 4.44 (2H, q, J=7 Hz), 6.90 (1H, s), 7.30 (10H, m). *Anal.* Calcd for $C_{24}H_{18}F_4O_4$: C, 64.58; H, 4.06. Found: C, 64.70;

H, 3.93.

General Method for the Preparation of 18a—c 4-(1-Benzyloxycarbonylaminocyclopropyl)-2,3,5-trifluorobenzoic Acids (**18b**): *N,N,N',N'*-Tetramethyldiaminomethane (26.8 g, 0.262 mol) and acetic anhydride (59.0 g, 0.578 mol) were added to a stirred solution of **13b** (75.0 g, 0.175 mol) in dimethyl sulfoxide (DMSO) (375 ml) at room temperature. After 2 h, the reaction mixture was poured into a mixture of toluene (1.0 l) and H_2O (1.5 l), and the layers were separated. The organic layer was washed successively with water and saturated brine, dried, and concentrated. The residue was subjected to chromatography (silica gel 750 g, toluene) to give **14b** (73.2 g, 95%). An analytical sample was obtained by recrystallization from iso-PrOH as colorless needles, mp 58—59 °C. IR (KBr): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 4.42 (2H, q, J=7 Hz), 6.06 (1H, s), 6.90 (1H, s), 6.97 (1H, s), 7.0—7.6 (11H, m). *Anal.* Calcd for $C_{25}H_{19}F_3O_4$: C, 68.18; H, 4.35. Found: C, 69.09; H, 4.28.

Potassium *tert*-butoxide (19.9 g, 0.177 mol) was added to a stirred solution of trimethylsulfoxonium iodide (39.0 g, 0.177 mol) in DMSO (325 ml) at room temperature. After 2 h, **14b** (65.0 g, 0.148 mol) in DMSO (163 ml) was added to the mixture at 15 °C. The whole was stirred at 15—20 °C for 30 min, and poured into a mixture of ice-water (1.5 l) and AcOEt (800 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 650 g, toluene) to give **15b** (46.2 g, 69%). An analytical sample was obtained by recrystallization from iso-PrOH as colorless prisms, mp 88.5—89 °C. IR (KBr): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—2.0 (7H, m), 4.41 (2H, q, J=7 Hz), 6.81 (1H, s), 6.9—7.6 (11H, m). *Anal.* Calcd for $C_{26}H_{21}F_3O_4$: C, 68.72; H, 4.66. Found: C, 68.83; H, 4.49.

TFA (230 ml) was added to a stirred solution of **15b** (46.0 g, 0.101 mol) in anisole (230 ml). The reaction mixture was stirred at room temperature for 2 h, then concentrated under reduced pressure. The oily residue was treated with hexane, and the insoluble solid was collected by filtration to give **16b** (26.8 g, 92%). An analytical sample was obtained by recrystallization from hexane–benzene as a white powder, mp 107—107.5 °C. IR (KBr): 1720, 1697 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—2.1 (7H, m), 4.40 (2H, q, J=7 Hz), 7.0—7.5 (1H, m), 10.94 (1H, s). *Anal.* Calcd for $C_{13}H_{11}F_3O_4$: C, 54.17; H, 3.85. Found: C, 54.23; H, 3.72.

Ethyl chloroformate (11.7 g, 108 mmol) was added dropwise to a stirred and cooled (−25 to −20 °C) solution of **16b** (26.0 g, 90.2 mmol) and triethylamine (10.9 g, 108 mmol) in acetone (260 ml). The mixture was stirred at the same temperature for 1.5 h, then allowed to warm to 5 °C and a solution of sodium azide (7.63 g, 117 mmol) in H_2O (26 ml) was added. After 30 min, the mixture was poured into a mixture of ice-water (500 ml) and toluene (500 ml). The layers were separated, and the organic layer was washed with saturated brine, dried, and concentrated. The residue was dissolved in a mixture of benzyl alcohol (20 g, 185 mmol) and dioxane (260 ml), and the solution was heated under reflux for 2 h before removal of the solvent under reduced pressure. The residue was subjected to chromatography (silica gel 260 g, toluene : AcOEt = 30 : 1) to give **17b** (30.2 g, 85%). An analytical sample was obtained by recrystallization from EtOH as colorless prisms, mp 124—125 °C. IR (KBr): 1733, 1699 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—1.6 (7H, m), 4.40 (2H, q, J=7 Hz), 5.04 (2H, s), 5.49 (1H, s), 7.1—7.5 (6H, m). *Anal.* Calcd for $C_{20}H_{18}F_3NO_4$: C, 61.07; H, 4.61; N, 3.56. Found: C, 61.00; H, 4.56; N, 3.63.

A suspension of **17b** (30.0 g, 76.3 mmol) in a mixture of EtOH (90 ml), dioxane (90 ml), and 1 N NaOH (180 ml) was stirred at room temperature for 2 h. The mixture was diluted with H_2O (300 ml), and acidified to pH 1 with 6 N HCl, and then extracted with AcOEt (500 ml). The organic extract was washed with saturated brine, and dried. Evaporation of the solvent followed by crystallization of the residue from hexane afforded **18b** (25.6 g, 92%). An analytical sample was obtained by recrystallization from benzene as a white powder, mp 133—134 °C. IR (KBr): 1723, 1664 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—1.5 (4H, m), 5.07 (2H, s), 5.91 (1H, s), 7.1—7.6 (6H, m), 8.23 (1H, br s). *Anal.* Calcd for $C_{18}H_{14}F_3NO_4$: C, 59.18; H, 3.86; N, 3.83. Found: C, 59.26; H, 3.87; N, 3.84.

The 2,5-difluorophenyl and 2,3,5,6-tetrafluorophenyl analogs (**18a** and **18c**) were obtained from **13a** and **13c** by using the same procedure, respectively.

18a: 53% overall yield from **13a**, mp 149—150 °C (colorless needles from benzene). IR (KBr): 1698 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.5 (4H, m), 5.05 (2H, s), 5.78 (1H, br s), 6.9—8.3 (8H, m). *Anal.* Calcd for $C_{18}H_{15}F_2NO_4$: C, 62.25; H, 4.35; N, 4.03. Found: C, 62.37; H, 4.39; N, 4.02.

18c: 47% overall yield from **13c**, mp 151—153 °C (colorless prisms from benzene). IR (KBr): 1734 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—1.5 (4H, m), 5.10 (2H, s), 5.96 (1H, br s), 7.31 (5H, s), 8.48 (1H, br s). *Anal.* Calcd for $C_{18}H_{13}F_4NO_4$: C, 56.40; H, 3.42; N, 3.65. Found: C, 56.46; H, 3.42; N, 3.71.

General Method for the Preparation of 19a—c Ethyl [4-(1-Benzyloxycarbonylaminocyclopropyl)-2,3,5-trifluorobenzoyl]acetate (**19b**): *N,N'*-Carbonyldiimidazole (10.0 g, 61.7 mmol) was added to a stirred solution of **18b** (15.0 g, 41.1 mmol) in tetrahydrofuran (THF) (150 ml) at 10 °C. The mixture was stirred at room temperature for 1 h before addition of the magnesium salt of ethyl hydrogen malonate (8.82 g, 61.6 mmol). After continued stirring at room temperature for 20 h, the mixture was poured into a mixture of ice-water (400 ml) and AcOEt (300 ml), and the whole was acidified to pH 1 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 300 g, toluene : AcOEt = 50 : 1) to give **19b** (16.1 g, 90%). An analytical sample was obtained by recrystallization from hexane as a white powder, mp 72—73 °C. IR (KBr): 1703 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.5 (7H, m), 3.8—4.5 (3.4H, m), 5.05 (2H, s), 5.53 (1H, s), 5.82 (0.3H, s), 7.0—7.5 (6H, m), 12.62 (0.3H, br s). *Anal.* Calcd for $C_{22}H_{20}F_3NO_5$: C, 60.69; H, 4.63; N, 3.22. Found: C, 60.73; H, 4.57; N, 3.24.

The 2,5-difluorophenyl and 2,3,5,6-tetrafluorophenyl analogs (**19a** and **19c**) were obtained from **18a** and **18c** by the same procedure, respectively.

19a: 81% yield, mp 63—65 °C (a white powder from iso-Pr_2O–hexane). IR (KBr): 1743, 1694 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.5 (7H, m), 3.8—4.5 (3.4H, m), 5.04 (2H, s), 5.60 (1H, s), 5.84 (0.3H, s), 6.9—7.8 (7H, m), 12.61 (0.3H, br s). *Anal.* Calcd for $C_{22}H_{21}F_2NO_5$: C, 63.31; H, 5.07; N, 3.36. Found: C, 63.20; H, 4.97; N, 3.54.

19c: 51% yield, mp 101—102 °C (colorless needles from iso-Pr_2O–hexane). IR (KBr): 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.6 (7H, m), 3.7—4.5 (3.4H, m), 5.07 (2H, s), 5.41 (0.3H, s), 5.52 (1H, s), 7.30 (5H, s), 12.33 (0.3H, br s). *Anal.* Calcd for $C_{22}H_{19}F_4NO_5$: C, 58.28; H, 4.22; N, 3.09. Found: C, 58.31; H, 4.18; N, 2.94.

General Method for the Preparation of 21—23 10-(1-Benzyloxycarbonylaminocyclopropyl)-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic Acid (**23**, X_1=H): *N,N*-Dimethylformamide dimethylacetal (12.3 g, 0.103 mol) was added to a stirred solution of **19b** (10.0 g, 0.023 mol) in benzene (100 ml), and the mixture was heated under reflux for 30 min. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in toluene (50 ml). The solution was stirred at room temperature after addition of *dl*-2-amino-1-propanol (1.80 g, 0.024 mol). After 17 h, the reaction mixture was concentrated under reduced pressure, and the residue was purified by chromatography (silica gel 150 g, toluene : AcOEt = 5 : 1) to give **20** (R_1=2-hydroxy-1-methylethyl, X_1=H, X_2=F) (10.5 g, 88%), as an oil. IR (neat): 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.6—1.5 (10H, m), 3.4—4.2 (6H, m), 5.04 (2H, s), 5.51 (1H, s), 6.6—7.0 (1H, m), 7.31 (5H, s), 8.19 (1H, d, J=14.5 Hz), 9.40 (0.2H, br s), 10.80 (0.8H, br s).

A mixture of **20** (R_1=2-hydroxy-1-methylethyl, X_1=H, X_2=F) (5.50 g, 10.6 mmol) and K_2CO_3 (3.21 g, 23.2 mmol) in DMF (55 ml) was stirred at 90—100 °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 3 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 treated with Et_2O and filtered to give the ethyl ester of **23** (X_1=H) (4.37 g, 86%). An analytical sample was obtained by recrystallization from AcOEt as colorless prisms, mp 180—181 °C. IR (KBr): 1721, 1696, 1677 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.2—1.8 (10H, m), 4.2—4.6 (5H, m), 5.03 (2H, s), 5.63 (1H, s), 7.28 (5H, s), 7.69 (1H, d, J=10 Hz), 8.34 (1H, s). *Anal.* Calcd for $C_{26}H_{25}FN_2O_6$: C, 64.99; H, 5.24; N, 5.83. Found: C, 64.95; H, 5.17; N, 5.60.

A suspension of the ethyl ester (3.50 g, 7.28 mmol) in a mixture of EtOH (35 ml), dioxane (18 ml), and 1 N NaOH (35 ml) was stirred at room temperature for 3 h. This mixture was poured into a mixture of H_2O (200 ml) and $CHCl_3$ (200 ml), and the whole was acidified to pH 1 with 6 N HCl before separation of the layers. The organic layer was washed with saturated brine, dried, and concentrated. The residue was treated with Et_2O and filtered to give **23** (X_1=H) (3.07 g, 93%). An analytical sample was obtained by recrystallization from EtOH as

colorless prisms, mp 221—223 °C. IR (KBr): 1731, 1716 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.7—1.8 (7H, m), 4.1—4.6 (3H, m), 5.02 (2H, s), 5.64 (1H, s), 7.27 (5H, s), 7.72 (1H, d, J=10 Hz), 8.65 (1H, s), 14.50 (1H, br s). *Anal.* Calcd for $C_{24}H_{21}FN_2O_6$: C, 63.71; H, 4.68; N, 6.19. Found: C, 63.58; H, 4.55; N, 5.79.

The following compounds were obtained by the same procedure.

21 (Y_1=Y_2=F): 76% overall yield from **19a**, mp 210—212 °C (colorless needles from EtOH). IR (KBr): 1694 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.4 (4H, m), 4.96 (2H, s), 5.58 (1H, s), 6.8—7.7 (9H, m), 8.14 (1H, d, J=10.5 Hz), 8.66 (1H, s), 14.32 (1H, s). *Anal.* Calcd for $C_{27}H_{19}F_3N_2O_5$: C, 63.78; H, 3.77; N, 5.51. Found: C, 63.85; H, 3.80; N, 5.57.

21 (Y_1=H, Y_2=OCH_2Ph): 82% overall yield from **19a**, mp 225—226 °C (colorless needles from EtOH). IR (KBr): 1717, 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.4 (4H, m), 4.96 (2H, s), 5.16 (2H, s), 5.60 (1H, s), 6.8—7.6 (15H, m), 8.12 (1H, d, J=10 Hz), 8.71 (1H, s), 14.55 (1H, br s). *Anal.* Calcd for $C_{34}H_{27}FN_2O_6$: C, 70.58; H, 4.70; N, 4.84. Found: C, 70.73; H, 4.70; N, 4.83.

21 (Y_1=F, Y_2=OCH_3): 71% overall yield from **19a**, mp 242—243 °C (colorless needles from EtOH). IR (KBr): 1718, 1692 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.4 (4H, m), 3.92 (3H, s), 4.96 (2H, s), 5.57 (1H, s), 6.6—7.7 (9H, m), 8.14 (1H, d, J=10.5 Hz), 8.67 (1H, s), 14.3 (1H, br s). *Anal.* Calcd for $C_{28}H_{22}F_2N_2O_6$: C, 64.61; H, 4.26; N, 5.38. Found: C, 64.56; H, 4.31; N, 5.39.

21 (Y_1=CH_3, Y_1=OCH_3): 83% overall yield from **19a**, mp 192—194 °C (colorless needles from EtOH). IR (KBr): 1719, 1692 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.4 (4H, m), 1.96 (3H, s), 3.89 (3H, s), 4.95 (2H, s), 5.58 (1H, br s), 6.7—7.6 (9H, m), 8.14 (1H, d, J=10.5 Hz), 8.66 (1H, s), 14.59 (1H, s). *Anal.* Calcd for $C_{29}H_{25}FN_2O_6 \cdot 1/10H_2O$: C, 67.20; H, 4.90; N, 5.40. Found: C, 67.03; H, 4.83; N, 5.43.

22 (X_1=H): 85% overall yield from **19b**, mp 210—212 °C (colorless needles from EtOH). IR (KBr): 1723, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.7 (8H, m), 3.7—4.3 (1H, m), 5.04 (2H, s), 5.62 (1H, s), 7.28 (5H, s), 7.95 (1H, dd, J=9.5, 2 Hz), 8.82 (1H, s), 14.2 (1H, s). *Anal.* Calcd for $C_{24}H_{20}F_2N_2O_5$: C, 63.43; H, 4.44; N, 6.16. Found: C, 63.43; H, 4.44; N, 6.15.

22 (X_1=F): 87% overall yield from **19c**, mp 218—220 °C (colorless prisms from AcOEt). IR (KBr): 1732, 1707 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.9 (8H, m), 3.7—4.3 (1H, m), 5.04 (2H, s), 5.59 (1H, s), 7.28 (5H, s), 8.78 (1H, s), 14.02 (1H, s). *Anal.* Calcd for $C_{24}H_{19}F_3N_2O_5$: C, 61.02; H, 4.05; N, 5.93. Found: C, 60.99; H, 3.96; N, 5.88.

23 (X_1=F): 82% overall yield from **19c**, mp 235—237 °C (colorless prisms from EtOH). IR (KBr): 1727 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.8 (7H, m), 4.1—4.8 (3H, m), 5.03 (2H, s), 5.67 (1H, s), 7.28 (5H, s), 8.65 (1H, s), 14.47 (1H, s). *Anal.* Calcd for $C_{24}H_{20}F_2N_2O_6$: C, 61.28; H, 4.29; N, 5.95. Found: C, 61.07; H, 4.20; N, 5.74.

General Method for the Preparation of Quinolone Carboxylic Acids 3a, 3b, 3e, 3f, 3i, and 3j 10-(1-Aminocyclopropyl)-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic Acid (**3i**): A suspension of **23** (X_1=H) (2.00 g, 4.42 mmol) in AcOH (40 ml) was stirred under atmospheric pressure of hydrogen after addition of 5% Pd–C (0.4 g). After 4 h, the catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 2 N HCl (7 ml), and the solution was concentrated under reduced pressure. The residue was crystallized from EtOH to give the hydrochloride of **3i** (1.50 g, 96%). This material (1.00 g, 2.82 mmol) was dissolved in a solution of KOH (0.37 g, 6.60 mmol) in H_2O (12 ml) and EtOH (8 ml) and the solution was saturated with CO_2. The precipitate was collected by filtration to give **3i** (0.84 g, 94%).

Compounds **3a**, **3b**, **3e**, **3f**, and **3j** were obtained by the same procedure.

General Method for the Preparation of Quinolone-3-carboxylic Acids 3c, d 7-(1-Aminocyclopropyl)-1,4-dihydro-1-(4-hydroxy-2-methylphenyl)-6-fluoro-4-oxoquinoline-3-carboxylic Acid Hydrobromide (**3d**): Compound **21** (Y_1=CH_3, Y_2=OCH_3) (100 mg, 0.19 mmol) was added to 47% HBr (1 ml), and the mixture was heated under reflux for 1 h, then concentrated under reduced pressure. The residue was treated with H_2O (2 ml), and the insoluble solid was collected by filtration to give **3d** (70 mg, 80%).

Compound **3c** was obtained from **21** (Y_1=F, Y_2=OCH_3) by the same procedure.

General Method for the Preparation of Quinolone-3-carboxylic Acids 3g, k 7-(1-Aminocyclopropyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-5-hydroxy-4-oxoquinoline-3-carboxylic Acid Hydrochloride (**3g**): Sodium hydride (60% in mineral oil, 0.17 g, 4.25 mmol) was added to a stirred solution of benzyl alcohol (0.46 g, 4.25 mmol) in DMF (5 ml) at room temperature. The solution was added to a stirred solution of **22** (X_1=F) (0.50 g, 1.06 mmol) in DMF (5 ml). After being stirred at room temperature for 30 min, the reaction mixture was poured into a mixture of ice-water (40 ml) and AcOEt (40 ml), then acidified to pH 1 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 treated with Et_2O and filtered to give the 5-benzyloxy compound (0.47 g, 79%). An analytical sample was obtained by recrystallization from EtOH as colorless prisms, mp 179—181 °C. IR (KBr): 1736, 1716 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.5 (8H, m), 3.6—4.2 (1H, m), 5.05 (2H, s), 5.11 (2H, s), 5.57 (1H, s), 7.0—7.7 (10H, m), 8.78 (1H, s). *Anal.* Calcd for $C_{31}H_{26}F_2N_2O_6$: C, 66.42; H, 4.68; N, 5.00. Found: C, 66.27; H, 4.65; N, 5.07.

A suspension of this material (0.30 g, 0.54 mmol) in AcOH (10 ml) was stirred under atmospheric pressure of hydrogen after addition of 5% Pd–C (0.3 g). After 4 h, the catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 2 N HCl (7 ml), and the solution was concentrated under reduced pressure. The residue was crystallized from EtOH to give **3g** (0.11 g, 55%).

Compound (**3k**) was obtained from **23** (X_1=F) using the same procedure as described above.

General Method for the Preparation of Quinolone-3-carboxylic Acids 3h, l 5-Amino-7-(1-aminocyclopropyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Hydrochloride (**3h**): Benzylamine (0.46 g, 4.29 mmol) was added to a stirred solution of **22** (X_1=F) (0.50 g, 1.06 mmol) in DMF (10 ml). The reaction mixture was stirred at 80—90 °C for 2 h, then poured into a mixture of ice-water (40 ml) and AcOEt (40 ml), and acidified to pH 1 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 treated with Et_2O and filtered to give the 5-benzylamino compound (0.42 g, 71%). An analytical sample was obtained by recrystallization from EtOH as yellow prisms, mp 155—157 °C. IR (KBr): 1716 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.7 (8H, m), 3.6—4.2 (1H, m), 4.65 (2H, dd, J=6, 4 Hz), 5.03 (2H, s), 5.54 (1H, s), 7.28 (10H, s), 8.68 (1H, s), 9.3—9.8 (1H, m), 14.2 (1H, br s). *Anal.* Calcd for $C_{31}H_{27}F_2N_3O_5$: C, 66.54; H, 4.86; N, 7.51. Found: C, 66.50; H, 4.85; N, 7.54. Catalytic hydrogenolysis of this material (0.30 g, 0.54 mmol) by the same procedure as described for **3g** afforded **3h** (0.10 g, 50%).

Compound (**3l**) was obtained from **23** (X_1=F) using the same procedure as described above.

Physical properties and combustion analytical data of **3a**—**l** are given in Table I.

Mammalian Cell Cytotoxicity This assay was carried out according to the literature method.[16] Chinese hamster V79 cells (*ca.* 10^4 cells) were incubated in 4 ml of culture medium for 48 h at 37 °C in a humidified incubator (95% air, 5% CO_2). Various concentrations of test compounds in 0.1 N NaOH were added to the culture medium (pH 7.1—7.2), and incubation was continued for 48 h. Colonies formed were treated with a solution of trypsin and EDTA, and counted in a Coulter counter.

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