Fluorocyclopropyl Quinolones. 1. Synthesis and Structure–Activity Relationships of 1-(2-Fluorocyclopropyl)-3-pyridonecarboxylic Acid Antibacterial Agents[1]

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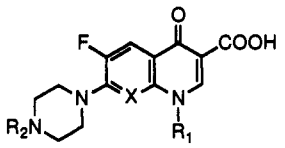
A series of 1-(2-fluorocyclopropyl)-3-pyridonecarboxylic acids has been prepared. These derivatives are characterized by having a fluorine atom at the 2-position on the cyclopropane ring as the N1 substituent and consist of both *cis* and *trans* stereoisomers. Structure–activity relationship studies indicate that the *cis* derivatives are more potent against Gram-positive bacteria than the corresponding *trans* counterparts, but the difference in potency against most Gram-negative bacteria is much smaller. The inhibitory effect of compounds **4**, **5**, **26**, **27**, **38**, and **39** on supercoiling activity of DNA gyrase obtained from *E. coli* KL-16 correlated with their MICs against the same strain and also depend on their (**26**, **27**, **38**, **39**) stereochemistry. Introduction of a fluorine atom on the cyclopropyl group resulted in the reduction of lipophilicity compared with the corresponding nonfluorinated quinolones.

The recent discoveries of many clinically useful therapeutic agents such as norfloxacin (NFLX, 1),[2] enoxacin



1: R_1=C_2H_5, R_2=H, X=CH

2: R_1=C_2H_5, R_2=H, X=N

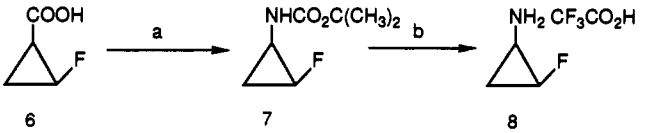
3: R_1, X=-CH(CH_3)CH_2OC-, R_2=CH_3

4: R_1=c-C_3H_5, R_2=H, X=CH

5: R_1=c-C_3H_5, R_2=CH_3, X=CH

(ENX, 2),[3] ofloxacin (OFLX, 3),[4] and ciprofloxacin (CPFX, 4)[5] have stimulated considerable interest in the synthesis of new quinolone antibacterial agents. In this class of compounds, the 1-substituted-1,4-dihydro-4-oxopyridine-3-carboxylic acid moiety is considered to be essential for antibacterial activity, though some other types of quinolone were reported more recently.[6] Studies on the N1 substituent of the 4-pyridone nucleus showed that an ethyl group or some other substituents with comparable steric requirements, *i.e.* vinyl,[7] fluoroethyl,[8] methoxy,[9] methylamino,[10] or cyclopropyl groups were favorable for antibacterial activity. Particularly, N1 cyclopropyl derivatives were found to possess outstanding antibacterial activity. On the other hand, the central nervous system (CNS) side effect of new quinolone antibacterials has been pointed out in the clinical field.[11] In studies of the relationships between physicochemical properties and pharmacokinetics of new compounds, we found that introduction of a fluorine atom into N1 substituents reduced the lipophilicity of the molecules, suggesting that there should be a possibility for preparing less toxic compounds with reduced distribution to the CNS. From this viewpoint, we prepared a series of 1-(2-fluorocyclopropyl)-1,4-dihydro-4-oxopyridine-3-carboxylic acid derivatives, which were sterically comparable to the unsubstituted cyclopropyl group for N1 substituent, because fluorine is known to be a hydrogen mimic.[12] As we expected, the series of fluorinated compounds showed lower hydrophobicity than the corresponding nonfluorinated derivatives and some of them retained similar antibacterial activity to that of CPFX (**4**). This paper describes the synthetic procedures for new fluorocyclopropyl quinolone and the structure–activity relationships of the resulting *cis* and *trans* stereoisomers. As an example of the substituted N1 cyclopropyl group, 6-fluoro-7-(1-piperazinyl)-1-(2-*trans*-phenyl-1-cyclopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid has been reported to be different in antibacterial activity with its enantiomers and is less active compared to 1.[13]

Scheme I.[a] **Synthetic Pathway of Fluorocyclopropylamine (8)**



a DPPA, t-BuOH b CF_3COOH

[a] Compounds 6–8 are mixtures of *cis* and *trans* isomers.

Chemistry

The desired 2-fluorocyclopropylamine trifluoroacetic acid salt (**8**) was synthesized in two steps from **6**[14] by Curtius rearrangement using diphenyl phosphorazidate (DPPA)[15] in *t*-BuOH and hydrolysis of the resulting carbamate (**7**) in CF_3COOH (Scheme I). The main routes utilized for the preparation of the carboxylic acids (**24**–**37**) are illustrated in Scheme II. Condensation of ethyl (2,4,5-trifluoro-, or (2,3,4,5-tetrafluorobenzoyl)acetate (**9**,[16] **10**[17]) or ethyl (2,6-dichloro-5-fluoronicotinyl)acetate (**11**)[18] with triethyl orthoformate in acetic anhydride gave the one-carbon homologue enol ether intermediate, which upon evaporation of the solvent was allowed to react with a slight excess of 8 and triethylamine in CH_2Cl_2 at room temperature to give the enamino keto esters (**12**–**17**) as mixtures of *cis* and *trans* isomers (Table I). These *cis* and *trans* diastereoisomers were separated by silica gel column

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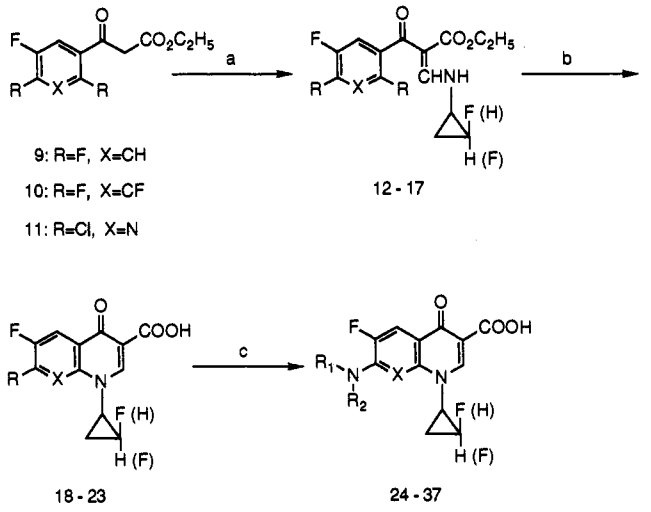
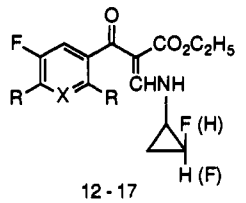
Scheme II.[a] Synthetic Pathway of Quinolonecarboxyilc Acids (24–37)



[a] (a) (1) $CH(OC_2H_5)_3$, Ac_2O, (2) 8, $N(C_2H_5)_3$; (b) (1) NaH, (2) H^+; (c) R_1R_2NH.

Table I. Physical Data for Ethyl 3-[(2-Fluorocyclopropyl)amino]-2-(halogenobenzoyl)acrylates and Their Aza Analogues

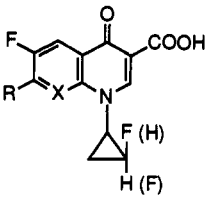


compd	config[a]	R	X	NMR (C_1-H,[b] δ ppm)	mp, °C	formula[c]
12	*cis*	F	CH	3.0	91–92	$C_{15}H_{13}F_4NO_3$
13	*trans*	F	CH	3.4	73–75	$C_{15}H_{13}F_4NO_3$
14	*cis*	F	CF	3.0	62–64	$C_{15}H_{12}F_5NO_3$
15	*trans*	F	CF	3.4	82–83	$C_{15}H_{12}F_5NO_3$[d]
16	*cis*	Cl	N	3.0	63–66	$C_{14}H_{12}Cl_2F_2N_2O_3$
17	*trans*	Cl	N	3.4	115–119	$C_{14}H_{12}Cl_2F_2N_2O_2$[e]

[a] Configuration of fluorine atom in relation to the amino group on the cyclopropane ring. [b] Methine proton adjacent to the nitrogen on the cyclopropane ring. [c] C, H, and N analyses were within ±0.4% of the theoretical values, unless otherwise noted. [d] C: calcd, 51.59; found, 52.23. [e] C: calcd, 46.05; found, 46.62.

chromatography. Cyclization of **12–17** with 1 mol equiv of sodium hydride in dioxane afforded the ethyl esters of 4-pyridones which, generally without purification, were hydrolyzed in HCl–AcOH to give the carboxylic acids **18–23** (Table II). The relative stereochemistry of the two substituents on the cyclopropane ring was determined by NMR spectra. The NMR signals of C1-H on the cyclopropane ring in a series of enamino keto esters (**13**, **15**, and **17**), which have higher R_f value on TLC, appeared downfield as compared with those of corresponding compounds (**12**, **14**, and **16**) which have lower R_f values. This can be explained in terms of a deshielding effect by the fluorine atom in the case of **13**, **15**, and **17**. This tendency was similarly observed in compounds **18–23**. The nuclear Overhauser effect (NOE) was also observed (*ca.* 10%) between C1-H and C2-H on the cyclopropane ring in **20** derived from **14** but not in **21**. On the other hand, the *cis* isomer of **7** was obtained as prisms and the stereochemistry was determined by X-ray analysis as shown in Figure 1. The enamino keto ester prepared from **10** and the *cis* isomer of **8** was identical with **14** on NMR and TLC. From these results, the configuration of the

Table II. Physical Data for 1-(2-Fluorocyclopropyl)-6,7-difluoro-, and 6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids and 1-(2-Fluorocyclopropyl)-7-chloro-6-fluoro-4-oxo-1,8-naphthyridine-3-carboxylic Acids



compd	config[a]	R	X	NMR (C_1-H,[b] δ ppm)	mp, °C	formula[c]
18	*cis*	F	CH	3.6	249–252	$C_{13}H_8F_3NO_3$[d]
19	*trans*	F	CH	4.0	246–251	$C_{13}H_8F_3NO_3$[e]
20	*cis*	F	CF	4.0	224–230	$C_{13}H_7F_4NO_3$
21	*trans*	F	CF	4.4	200–208	$C_{13}H_7F_4NO_3$[f]
22	*cis*	Cl	N	3.8	190–197	$C_{12}H_7ClF_2N_2O_3$
23	*trans*	Cl	N	4.2	212–217	$C_{12}H_7ClF_2N_2O_3$

[a–c] See Table I, footnotes *a*, *b*, and *c*. [d] C: calcd, 55.13; found, 55.70. [e] C: found, 55.58. [f] C: calcd, 51.84; found, 52.39.

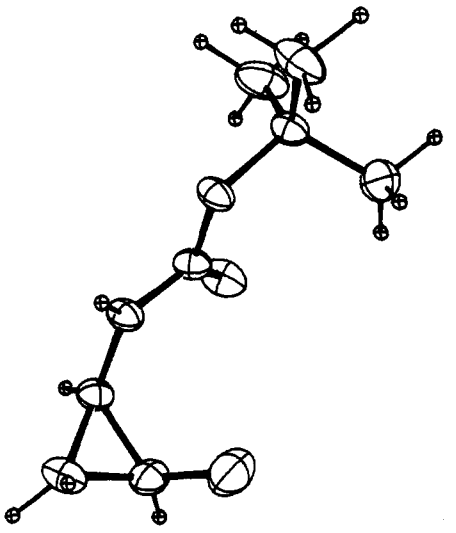


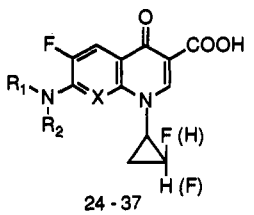
Figure 1. ORTEP drawing of cis form of **7**.

fluorine atom to the amino group in the compounds of lower R_f value (**12**, **14**, and **16**) was determined to be *cis*. Carboxylic acids **18–23** were reacted with various amines to yield the desired 7-amino derivatives (**24–37**) (Table III). Chiral separation of **26** was achieved by HPLC to give enantiomers **38** and **39**. The absolute structure of **38** is shown in Figure 2,[19] and the structure–activity relationships of optically active (fluorocyclopropyl)quinolones in combination with novel amines as the C7 substituent will be published elsewhere. The structures of all compounds listed in Tables I–III were confirmed by their NMR spectra and elemental analysis.

Results and Discussion

The results of the *in vitro* antibacterial activities for the compounds prepared in this study against five Gram-positive and five Gram-negative bacteria are summarized in Table IV. The data for CPFX (**4**) is included for comparison. It is noteworthy that a series of the *cis* compounds is more active than the corresponding *trans* series against all the bacteria tested; in particular, the activities of the *trans* isomers against all the Gram-positive bacteria tested are markedly less than those of the *cis* compounds whereas the difference in potency against most of the Gram-negative compounds is much smaller. All

Table III. Physical Data for 7-Amino-1-(2-fluorocyclopropyl)-6-fluoro-, and 6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids and 7-Amino-1-(2-fluorocyclopropyl)-6-fluoro,1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids



24 - 37

compd	config[a]	NR_1R_2	X	yield,[b] %	mp, °C	formula[c]
24	*cis*	pi[d]	CH	78	261–264	$C_{17}H_{17}F_2N_3O_3$
25	*trans*	pi	CH	70	265–275	$C_{17}H_{17}F_2N_3O_3 \cdot {}^1/_4H_2O$
26	*cis*	4-Mpi[e]	CH	64	250–256	$C_{18}H_{18}F_2N_3O_3 \cdot {}^1/_4H_2O$
27	*trans*	4-Mpi	CH	53	240–255	$C_{18}H_{18}F_2N_3O_3$
28	*cis*	pi	CF	72	240–255	$C_{17}H_{16}F_3N_3O_3 \cdot {}^1/_2H_2O$
29	*trans*	pi	CF	59	281–294	$C_{17}H_{16}F_3N_3O_3 \cdot {}^1/_4H_2O$
30	*cis*	4-Mpi	CF	77	252–254	$C_{18}H_{18}F_3N_3O_3 \cdot {}^1/_4H_2O$
31	*trans*	4-Mpi	CF	75	251–254	$C_{18}H_{18}F_3N_3O_3 \cdot {}^1/_4H_2O$
32	*cis*	3(*S*)-Mpi[f]	CF	49	246–249	$C_{18}H_{18}F_3N_3O_3 \cdot {}^3/_4H_2O$
33	*trans*	3(*S*)-Mpi	CF	61	230–238	$C_{18}H_{18}F_3N_3O_3 \cdot {}^1/_2H_2O$
34	*cis*	3(*R*)-Mpi[g]	CF	53	240–244	$C_{18}H_{18}F_3N_3O_3 \cdot {}^1/_2H_2O$
35	*trans*	3(*R*)-Mpi	CF	72	235–241	$C_{18}H_{18}F_3N_3O_3 \cdot {}^3/_4H_2O$
36	*cis*	4-Mpi	N	69	242–243	$C_{17}H_{18}F_2N_4O_3$
37	*trans*	4-Mpi	N	75	240–241	$C_{17}H_{18}F_2N_4O_3$
38	*cis*[h]	4-Mpi	CH		250–251	$C_{18}H_{18}F_2N_3O_3$
39	*cis*[i]	4-Mpi	CH		250–251	$C_{18}H_{18}F_2N_3O_3$

[a,c] See Table I, footnotes *a* and *c*. [b] Yields were not optimized. [d] pi, 1-piperazinyl. [e] 4-Mpi, 4-methyl-1-piperazinyl. [f] 3(*S*)-Mpi, 3(*S*)-methyl-1-piperazinyl. [g] 3(*R*)-Mpi, 3(*R*)-methyl-1-piperazinyl. [h] (+)-optical isomer. [i] (−)-optical isomer.

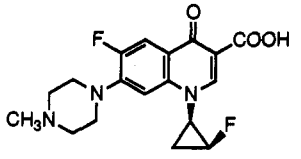


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Figure 2. Absolute structure of **38**.

the *cis* quinolone antibacterials (**24**, **26**, **28**, **30**, **32**, and **34**) substituted with various piperazines at the C7 position showed the same level of activity as that of **4** against all the organisms except *Pseudomonas aeruginosa*, but the 1,8-naphthylidine analogue (**36**) was inferior to **4**. Among the compounds with an optically active 2-methylpiperazine at C7 (**32** and **34** or **33** and **35**), there was almost no difference in the antibacterial activity. In case of **38** and **39**, which are the enantiomers of **26**, **38** was slightly more active than **39** against *Klebsiella pneumoniae*, *P. aeruginosa* (Table IV), and *Escherichia coli* KL-16 (Table V). These results indicate that the configuration of fluorine on the cyclopropane ring often has a measurable effect on the antibacterial activity. 4-Quinolone antibacterial agents inhibit DNA gyrase, and the antibacterial activity is believed to depend on this inhibition.[20] Compounds **4**, **5**, **26**, **27**, **38**, and **39** were thus tested for their inhibition of supercoiling by DNA gyrase obtained from *E. coli* KL-16.[21] As shown in Table V, the inhibitory effect (ID_{50}'s) of these compounds on DNA gyrase supercoiling activity correlated with their MICs against *E. coli* KL-16. Therefore, the difference in antibacterial activities among these

Table IV. *In Vitro* Antibacterial Activity[a]

	minimum inhibitory concentrations (MICs), μg/mL									
compd	Sa	Sa(S)	Se	Sp	Ef	Ec	Pv	Kp	Ecl	Pa
4	0.1	≤0.05	0.2	0.78	0.78	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05
24	0.1	0.1	0.2	1.56	1.56	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05
25	0.78	0.39	0.78	50	12.5	≤0.05	≤0.05	0.1	≤0.05	0.1
26	0.1	≤0.05	0.1	1.56	0.78	≤0.05	≤0.05	≤0.05	≤0.05	0.2
27	0.78	0.39	0.78	50	12.5	≤0.05	0.1	0.2	≤0.05	0.39
28	0.1	0.1	0.2	0.78	1.56	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05
29	1.56	0.78	3.13	50	25	0.1	≤0.05	0.2	≤0.05	0.39
30	0.1	≤0.05	0.2	3.13	0.78	≤0.05	≤0.05	≤0.05	≤0.05	0.1
31	1.56	1.56	3.13	100	25	≤0.05	≤0.05	0.2	≤0.05	0.78
32	0.1	≤0.05	0.2	1.56	0.78	≤0.05	≤0.05	≤0.05	≤0.05	0.1
33	1.56	0.78	3.13	50	12.5	≤0.05	≤0.05	0.1	≤0.05	0.39
34	0.1	≤0.05	0.2	0.78	0.78	≤0.05	≤0.05	0.1	≤0.05	0.1
35	1.56	0.78	3.13	50	12.5	≤0.05	0.2	0.2	0.1	0.78
36	0.39	0.2	0.39	6.25	1.56	≤0.05	0.2	0.2	≤0.05	0.2
37	1.56	0.78	1.56	25	25	≤0.05	0.2	0.2	≤0.05	0.78
38	0.1	≤0.05	0.2	1.56	0.78	≤0.05	≤0.05	≤0.05	≤0.05	0.1
39	0.1	≤0.05	0.2	1.56	0.78	≤0.05	≤0.05	0.1	≤0.05	0.2

[a] See the Experimental Section. Organisms selected for inclusion in the table: Sa, *Staphylococcus aureus* 209P; Sa(S), *Staphylococcus aureus* Smith; Se, *Staphylococcus epidermidis* 56556; Sp, *Streptococcus pyogenes* G-36; Ef, *Enterococcus faecalis* ATCC 19433; Ec, *Escherichia coli* NIHJ; Pv, *Proteus vulgaris* 08601; Kp, *Klebsiella pneumoniae* Type 2; Ecl, *Enterobacter cloacae* 03400; Pa, *Pseudomonas aeruginosa* 32121.

Table V. Inhibitory Activity against Growth of *E. coli* KL-16 and Its DNA Gyrase

compd	MIC, μg/mL	ID_{50}, μg/mL	compd	MIC, μg/mL	ID_{50}, μg/mL
4	0.025	0.13	**27**	0.1	0.92
5	0.05	0.47	**38**	0.025	0.18
26	0.05	0.31	**39**	0.05	0.34

Table VI. Apparent Partition Coefficient

compd	p′[a]	compd	P′[a]
4	0.89	**26**	7.0
24	0.16	**38**	7.3
5	20.0	**39**	7.0

[a] Partition coefficient; $CHCl_3$–0.1 M phosphate buffer (pH 7.4).

compounds was found to be largely attributed to their inhibitory activities against DNA gyrase and to depend on their stereochemistry.[22] The effect to hydrophobicity by the fluorine atom on cyclopropane was tested. Introduction of a fluorine atom or a perfluoroalkyl group (e.g. CF_3) on the aromatic ring is well-known to increase lipophilicity of the parent compound, while addition of a fluorine atom to the aliphatic substituent is reported to make the parent compound less lipophilic.[23] The results in Table VI show that the introduction of the fluorine atom reduced the apparent partition coefficient of corresponding nonfluorinated compound (**4**→**24**, **5**→**26**). Our findings indicate that the stereochemical properties of the N1 substituent play a measurable role on the difference in the ability of the DNA inhibition by these stereoisomers as previously reported in levofloxacin (LVFX, DR-3355),[24] and that there is a possibility to obtain compounds with reduced CNS side effects with this series of 1-(*cis*-2-fluorocyclopropyl)-4-quinolone-3-carboxylic acid antibacterials.

Experimental Section

All melting points were taken on a Yanagimoto micromelting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a JEOL FX-90Q or a Varian XL-200 spectrometer with tetramethylsilane as an internal standard. Elemental analysis are indicated only by the symbols of the elements; analytical results were within ±0.4% of the theoretical values unless otherwise noted.

2-Fluorocyclopropylamine Trifluoroacetic Acid Salt (8). In 30 mL of *tert*-butyl alcohol was dissolved 2-fluoro-1-cyclopropanecarboxylic acid (**6**) (2.0 g, 19 mmol). After addition of diphenyl phosphorazidate (DPPA) (8.0 g, 29 mmol) and triethylamine (3.0 g, 30 mmol), the resulting mixture was heated under reflux for 8 h. Evaporation of the solvent gave the residue which was subjected to column chromatography using 50 g of silica gel, and 1.6 g (48%) of **7** was obtained from the $CHCl_3$ eluate as a colorless oil. After being allowed to stand, the crystals were partially formed and washed repeatedly with *n*-hexane to yield sublimatic colorless crystals which were used for X-ray analysis, mp 58–60 °C. To the *cis* and *trans* mixture of **7** (800 mg, 4.6 mmol) was added 2 mL of trifluoroacetic acid, and the resulting solution was stirred at room temerature for 30 min. Any excess of trifluoroacetic acid was removed by distillation under reduced pressure, and 750 mg (86%) of **8** was obtained in the form of a partially crystalline pale yellow oil: NMR (D_2O) δ 0.8–1.5 (2H, m, CH_2), 2.4–2.8 (1H, m, CHN), 4.85 (1H, dm, J = 63 Hz, CHF).

Ethyl 3-[(2-*cis*-Fluorocyclopropyl)amino]-2-(2,4,5-trifluorobenzoyl)acrylate (12) and Its *trans* Isomer (13). A solution of ethyl (2,4,5-trifluorobenzoyl)acetate (**9**) (1.0 g, 4.1 mmol) in triethyl orthoformate (1.5 g, 10 mmol) and acetic anhydride (3.0 g, 29 mmol) was heated at 120–140 °C for 2 h. The solution was evaporated under reduced pressure to give an oily residue which was dissolved in 12 mL of CH_2Cl_2. To this solution was added **8** (1.15 g, 6.0 mmol) and 4.5 mL of triethylamine and the mixture was stirred for 1 h at room temperature. Removal of the solvent gave an oily product which was chromatographed on silica gel (40 g) using AcOEt–C_6H_6 (1:9) as an eluent to afford 540 mg (40%) of **12** (Rf 0.7) and 500 mg (37%) of **13** (Rf 0.6). **12**: NMR ($CDCl_3$) δ 1.09 (3H, t, J = 7 Hz, CH_3), 1.2–1.5 (2H, m, CH_2), 2.9–3.1 (1H, m, CHN), 4.10 (2H, q, J = 7 Hz, CH_2), 4.75 (1H, dm, J = 64 Hz, CHF), 6.8–7.0 (1H, m, aromatic H), 7.2–7.4 (1H, m, aromatic H), 8.27 (1H, d, J = 14 Hz, olefinic H), 10.8–11.0 (1H, m, NH). **13**: NMR ($CDCl_3$) δ 1.1 (3H, t, J = 7 Hz, CH_3), 1.2–1.4 (1H, m, CH), 1.5–1.7 (1H, m, CH), 3.3–3.5 (1H, m, CHN), 4.10 (2H, q, J = 7 Hz, CH_2), 4.77 (1H, dm, J = 60 Hz, CHF), 6.9–7.1 (1H, m, aromatic H), 7.2–7.4 (1H, m, aromatic H), 8.16 (1H, d, J = 14 Hz, olefinic H), 10.7–10.9 (1H, m, NH). By using this procedure, compounds **14–17** were prepared from **10** and **11** with **8**.

1-(*cis*-2-Fluorocyclopropyl)-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (18). A 50% sodium hydride in mineral oil suspension (38 mg, 0.79 mmol) was slowly added to a cold solution of **12** (260 mg, 0.79 mmol) in 10 mL of dry dioxane and the mixture was stirred for 30 min at room temperature. The solvent was removed and $CHCl_3$ was added to the residue. The organic layer was washed with 1 N HCl and H_2O, dried, and evaporated to give a crystalline product. This ester compound was dissolved in 12 mL of concentrated HCl-AcOH (2:1) and the mixture was heated at 120 °C for 30 min. After cooling, H_2O was added, the resulting precipitate was filtered and washed with EtOH and Et_2O to give 175 mg (78%) of **18**. NMR ($CDCl_3$) δ 1.7–1.95 (2H, m, CH_2), 3.5–3.7 (1H, m, CHN), 5.19 (1H, dm, J = 64 Hz, CHF), 7.82 (1H, dd, J = 12 Hz, 7 Hz, C8-H), 8.37 (1H, dd, J = 11 Hz, 8.5 Hz, C5-H), 8.94 (1H, s, C2-H), 14.5 (1H, br.s, COOH). By using this procedure, compounds **19–23** were prepared from **13–17**.

1-(*cis*-2-Fluorocyclopropyl)-6-fluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (24). Piperazine (70 mg, 0.81 mmol) was added to a solution of **18** (90 mg, 0.32 mmol) in 4.5 mL of dimethyl sulfoxide. After heating at 110 °C for 30 min, the solution was evaporated to dryness under reduced pressure. The resulting colorless powder was washed repeatedly with Et_2O and recrystallized from concentrated NH_4OH-EtOH to give 86 mg (78%) of **24**: NMR (Me_2SO-d_6) δ 1.7–2.2 (2H, m, CH_2), 2.9–3.1 and 3.2–3.5 (each 4H, m, piperazine-H), 3.8–4.0 (1H, m, CHN), 5.36 (1H, dm, J = 65 Hz, CHF), 7.48 (1H, d, J = 7.5 Hz, C8–H), 7.92 (1H, d, J = 14 Hz, C5-H), 8.76 (1H, s, C2-H). By using this procedure, 7-amino-substituted 4-quinolones **25–37** listed in Table III were obtained from **18–23** and various amines.

Optical Resolution of 26. 1-(*cis*-2-Fluorocyclopropyl)-6-fluoro-7-(4-methyl-1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**26**) (1.0 g, 2.8 mmol) was dissolved in 100 mL of 20% MeOH containing 6 mM of L-phenylalanine and 3 mM of $CuSO_4$, and 0.2 mL of the solution was subjected to HPLC to give two fractions. Each fraction was obtained by repeating this operation (500 times). The MeOH of the first fraction was removed to give an aqueous layer to which were added excess $NaHCO_3$ and 50% NaOH to pH 11. The resulting precipitate was filtered off and the filtrate was concentrated to a small volume, then the alkaline solution was neutralized to pH 7.4 by 1 N HCl and was extracted with $CHCl_3$. Removal of the solvent gave a residue which was chromatographed on silica gel using the lower layer of $CHCl_3$–MeOH–H_2O (7:3:1) to afford a crystalline product. This was recrystallized from EtOH to give 220 mg of **38** as colorless fine needles, $[\alpha]_D$ + 17.2° (*c* 0.92, $CHCl_3$). The second fraction gave 205 mg of (–)-enantiomer (**39**) in the same manner as described above, $[\alpha]_D$ – 18.5° (*c* 0.80, $CHCl_3$). HPLC: ODS-5251-D column (20 × 250 mm) (Senshu Kagaku Co., Ltd.); solvent, 6 mM L-phenylalanine and 3 mM $CuSO_4$ in 20% MeOH; flow rate, 6.8 mL/min; t_R 15.4 min for **38**; 18.2 min for **39**.

X-ray Crystallographic Analyses. The *cis* isomer of **7** was obtained as colorless prisms (mp 58–60 °C; $C_5H_{14}FNO_2$; mol wt 175.2) by repeated washing of **7** with *n*-hexane. This crystal belongs to the orthorhombic system and has unit cell dimensions of a = 11.685 Å, b = 17.754 Å, and c = 9.280 Å. The lattice parameters and intensities were measured on Phillips four-circle X-ray autodiffractometer with monochromated Cu Kα radiation. A total of 1849 independent reflections were obtained by the θ–2θ scan method. The crystal was sealed in a glass capillary, since it easily sublimed. The structure was solved by the direct method with the program MULTAN 78. Refinement was carried out by the block diagonal least-squares method using anisotropic temperature factors for nonhydrogen atoms and isotropic ones for hydrogen atoms. The final R values was 0.0593.

Determination of Apparent Partition Coefficient. For distribution experiments in $CHCl_3$–0.1 M phosphate buffer, the aqueous (0.1 M sodium phosphate buffer, pH 7.4) and $CHCl_3$ layers were saturated with each solvent to minimize the volume change due to mutual miscibility. Exactly 10 mL of each solution (50 mL of aqueous layer was used for dissolving *ca.* 1–2 mg of the sample, and the maximum UV absorption of this sample solution was taken, [Abs_s]) was transferred to a glass-stopped flask and shaken for 30 min at room temperature. After the two layers separated on standing for 1 h, the maximum UV absorption of the aqueous layer was measured, [Abs_a]. The apparent partition coefficient, P', was calculated from P' = [[Abs_s] – [Abs_a]] / [Abs_a].

In Vitro Antibacterial Activity. The MICs of the compounds tested in this study were measured according to the 2-fold micro broth dilution method using Mueller–Hinton broth (Difco Laboratories, Detroit, MI) with an inoculum size of approximately 10^5 cfu/mL. The MIC was defined as the lowest concentration which prevented visible bacterial growth after incubation at 37 °C for 18 h.

Inhibitory Effect on Supercoiling Activity of DNA Gyrase Isolated from *E. coli* KL-16. This assay was carried out according to the method reported previously.[21]

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Supplementary Material Available: Tables of final atomic positional parameters, atomic thermal parameters, and bond distances and angles of the cis form of **7** are available (3 pages). Ordering information is given on any current masthead page.

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