(Fluorocyclopropyl)quinolones. 2.[1] Synthesis and Stereochemical Structure–Activity Relationships of Chiral 7-(7-Amino-5-azaspiro[2.4]heptan-5-yl)-1-(2-fluorocyclopropyl)quinolone Antibacterial Agents[2]

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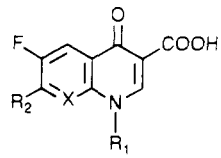
Received January 19, 1994®

A series of novel chiral 7-(7-amino-5-azaspiro[2.4]heptan-5-yl)-8-chloro-1-(2-fluorocyclopropyl)-quinolones were synthesized as a continuation of a research project of 1-(2-fluorocyclopropyl)-quinolones by considering stereochemical and physicochemical properties of the molecule. Absolute configurations of the 1-(*cis*-2-fluorocyclopropyl) moiety and the 7-(7-amino-5-azaspiro-[2.4]heptan-5-yl) moiety were determined by X-ray crystallographic analysis. Stereochemical structure–activity relationship studies indicated that 1-[(1*R*,2*S*)-2-fluorocyclopropyl] and 7-[(7*S*)-amino-5-azaspiro[2.4]heptan-5-yl] derivatives are more potent against Gram-positive and Gram-negative bacteria than the other stereoisomers and 7-[(7*S*)-7-amino-5-azaspiro[2.4]-heptan-5-yl]-8-chloro-1-[(1*R*,2*S*)-2-fluorocyclopropyl]quinolone (**33**) is the most potent of all stereoisomers. Pharmacokinetic profiles and physicochemical properties of the selected compounds were also examined, and it was found that **33** (DU-6859a) possesses moderate lipophilicity and good pharmacokinetic profiles.

In recent years, many clinically important antibacterial agents which possess a 1-substituted 6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid moiety (**1**–**7**)[3–9] and collectively known as quinolones have been discovered. These agents selectively inhibit bacterial DNA gyrase[10] relative to mammalian topoisomerase II, and this mode of action is characteristic of quinolones as excellent antibacterial agents.[11] A great number of quinolones have been synthesized, and a large body of structure–activity relationships (SARs) have been accumulated.[12] Studies on the N-1 substituent of the



1: R_1=C_2H_5, R_2=1-piperazinyl, X=CH (norfloxacin)[3]
2: R_1=C_2H_5, R_2=1-piperazinyl, X=N (enoxacin)[4]
3: R_1, X=-CH(CH_3)CH_2OC-, R_2=4-methyl-1-piperazinyl (ofloxacin)[5]
4: R_1=c-C_3H_5, R_2=1-piperazinyl, X=CH (ciprofloxacin)[6]
5: R_1=C_2H_5, R_2=3-methyl-1-piperazinyl, X=CF (lomefloxacin)[7]
6: R_1=2,4-difluorophenyl, R_2=3-amino-1-pyrrolidinyl, X=N (tosufloxacin)[8]
7: R_1=c-C_3H_5, R_2=3-amino-1-pyrrolidinyl, X=CCl (AM-1091, PD-127391)[9]

quinolone nucleus showed that cyclopropyl derivatives exhibit particularly potent antibacterial activities. We have recently reported that a series of 1-(*cis*-2-fluorocyclopropyl)-7-piperazinyl derivatives have potent activity comparable to those of nonfluorinated congeners.[1] Those fluorocyclopropyl derivatives have lower lipophilicities compared to the nonfluorinated counterparts.[1] Adverse reactions of new quinolones such as central nervous system (CNS) effects[13] and interaction with the nonsteroidal antiinflammatory agent, fenbufen,[14] have been noted in clinical use. It is reported that blood–brain barrier transport of quinolones is characterized by its nonlinear dependence on lipophilicity, and the compounds which are more lipophilic than ofloxacin penetrate the blood–brain barrier considerably.[15] Therefore, the *cis*-2-fluorocyclopropyl group would be a favorable N-1 substituent to modulate the lipophilicity and reduce the incidence of CNS adverse event by minimizing CNS concentration. Furthermore, it was discovered that those fluorocyclopropyl derivatives are less effective inhibitors of mammalian topoisomerase II than the corresponding cyclopropyl derivatives.[16] These results suggest that it is possible to obtain a highly potent compound with reduced toxicity by structural manipulation of 1-(*cis*-2-fluorocyclopropyl) derivatives.

Most of the compounds which are either in an advanced stage of clinical development or already marketed have a piperazinyl or pyrrolidinyl substituent at the C-7 position. The quinolones with a substitution of a 3-(aminomethyl)-1-pyrrolidinyl or 3-amino-1-pyrrolidinyl group have enhanced activities against Gram-positive organisms compared to piperazinyl derivatives.[12] It has been reported that 3-(1-aminoethyl)-pyrrolidinyl derivatives possess potent activity against Gram-positive and Gram-negative bacteria.[17,18] Their lipophilicity and aqueous solubility, modulated by the C-7 substituent and the quinolone nucleus, are largely responsible for their oral absorbability.[17] But, certain of the 3-(1-aminoethyl)pyrrolidines, especially those containing a halogen at C-8, strongly inhibited topoisomerase II and were cytotoxic.[18,19] It has been considered that the 3-aminopyrrolidinyl group enhances Gram-positive activity but makes the molecule less soluble and is unfavorable for oral absorption.[20] Sanchez reported, however, that the 7-(3-amino-1-pyrrolidinyl)-8-chloro derivative, clinafloxacin (AM-1091, CI-960, PD-127391) (**7**),[9] has potent activity *in vitro* and *in vivo* against Gram-positive and Gram-negative bacteria. Clinafloxacin has been proven to have good pharmacokinetic profiles in human.[21] The topoisomerase II

® Abstract published in *Advance ACS Abstracts*, September 1, 1994.

0022-2623/94/1837-3344$04.50/0

Table 1. Physical Data of the Chiral 2-Fluorocyclopropyl Derivatives Prepared in Scheme 1

compd	config[a]	(chirality)	yield,[b] %	mp, °C	rotation[c]	elemental formula[d]
9a	*cis*	(1*S*,2*S*)	25	102	+143.6	$C_{12}H_{14}FNO$
9b	*cis*	(1*R*,2*R*)	27	108	+62.0	$C_{12}H_{14}FNO$
9c	*trans*		23	126–128	+143.1	$C_{12}H_{14}FNO$
9d	*trans*		19	101–103	+117.5	$C_{12}H_{14}FNO$
10a	*cis*	(1*S*,2*S*)	73	oil	+21.6	–
10b	*cis*	(1*R*,2*R*)	79	oil	−23.1	–
10c	*trans*		76	oil	+41.5	–
10d	*trans*		75	oil	−42.3	–
11a	*cis*	(1*R*,2*S*)	57	63	−60.3	–
11b	*cis*	(1*S*,2*R*)	50	73	+65.6	–
11c	*trans*		73	60	+20.5	–
11d	*trans*		60	59	−20.5	–
14a	*cis*	(1*R*,2*S*)	89	99–100	+6.7	$C_{15}H_{12}ClF_4NO_3$
14b	*cis*	(1*S*,2*R*)	79	98–100	−6.7	$C_{15}H_{12}ClF_4NO_3$
14c	*trans*		47	99	+12.5	$C_{15}H_{12}ClF_4NO_3$
14d	*trans*		50	98	−12.8	$C_{15}H_{12}ClF_4NO_3$
15a	*cis*	(1*R*,2*S*)	90	174	−45.3	$C_{15}H_{11}ClF_3NO_3$
15b	*cis*	(1*S*,2*R*)	94	181–184	+45.1	$C_{15}H_{11}ClF_3NO_3$
15c	*trans*		96	187	−23.6	$C_{15}H_{11}ClF_3NO_3$
15d	*trans*		88	187	+23.5	$C_{15}H_{11}ClF_3NO_3$
16a	*cis*	(1*R*,2*S*)	90	177–182	−26.8	$C_{13}H_7ClF_3NO_3$
16b	*cis*	(1*S*,2*R*)	85	170–171	+30.4	$C_{13}H_7ClF_3NO_3$
16c	*trans*		90	206–208	−20.0	$C_{13}H_7ClF_3NO_3$
16d	*trans*		89	207–209	+19.9	$C_{13}H_7ClF_3NO_3$

[a] Configuration of fluorine atom in relation to the carbonyl group or amino group on the cyclopropyl ring. [b] Yields were not optimized. [c] Degrees, measured in $CHCl_3$. [d] Analyses for C, H, and N were within ±0.4% of the theoretical values.

inhibitory activity of clinafloxacin has been found to be comparable to that of enoxacin.[19] These results suggested that 3-aminopyrrolidine is superior to 3-(1-aminoethyl)pyrrolidine in terms of selective toxicity as the C-7 substituent, and the chlorine atom at C-8 is favorable for oral efficacy. As a continuation of the search for potent broad-spectrum quinolone antibacterials, we selected a 3-aminopyrrolidinyl group at C-7 and a chlorine atom at C-8 for 1-(*cis*-2-fluorocyclopropyl)-quinolone and carried out extensive modifications by considering stereochemical and physicochemical properties of the molecule.

It has been reported that 4-methylpiperazinyl[22] and 3,5-dimethylpiperazinyl derivatives[23] are less effective to the CNS than piperazinyl derivatives. This result seems to be related to steric hindrance for the basic center at the 4-position of piperazinyl moiety. Furthermore, it is known that 2-methyl-4-aminopyrrolidinyl[24] and 3-amino-4-methylpyrrolidinyl derivatives[25] are more soluble in water than nonmethylated congeners but retain their high level of activity. These results indicated that introduction of a substituent, which has steric bulk comparable to that of a methyl group at the C-4 position of 3-aminopyrrolidine, would be favorable for reduction of CNS potency and improvement of pharmacokinetic profiles. From these viewpoints, we designed novel 7-amino-5-azaspiro[2.4]heptane for the C-7 substituent of 1-(*cis*-2-fluorocyclopropyl)quinolone. In this paper, we report synthetic procedures for the preparation of chiral *cis*-2-fluorocyclopropyl derivatives and 7-amino-5-azaspiro[2.4]heptyl derivatives and also structure–activity relationships and pharmacokinetic profiles among these compounds.

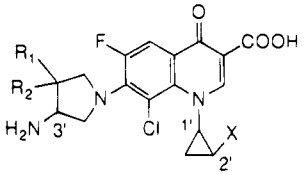
Chemistry

The test compounds in Table 2 were prepared by nucleophilic displacement of 8-chloro-6,7-difluoroquinolones with appropriate 3-[(*tert*-butoxycarbonyl)amino]-pyrrolidines, followed by deprotection of the *tert*-butoxycarbonyl groups (Scheme 1). To clarify the effect of chirality of the 1-(*cis*-2-fluorocyclopropyl) moiety and the 7-(7-amino-5-azaspiro[2.4]heptan-5-yl) moiety on antibacterial activity, absolute configurations of these substituents were determined by X-ray crystallographic analysis of **15a** and **28**.[26]

The synthetic routes of chiral 8-chloro-6,7-difluoro-1-(2-fluorocyclopropyl)quinolones **16a–d** are summarized in Scheme 2. *dl-cis*-2-Fluorocyclopropanecarboxylic acid (**8a**)[27] was converted to (*R*)-(1-phenylethyl)-amides **9a** and **9b**, and each isomer was separated by HPLC.[28] Hydrolysis of each isomer gave chiral *cis*-2-fluorocyclopropanecarboxylic acids **10a** and **10b**. Reaction of **10a** and **10b** with diphenyl phosphorazidate[29] in *tert*-butyl alcohol yielded rearrangement products **11a** and **11b** with retention of the configuration. Enantiomers of *trans*-*N*-(*tert*-butoxycarbonyl)-2-fluorocyclopropylamine **11c** and **11d** were prepared similarly from *dl-trans*-2-fluorocyclopropanecarboxylic acid **8b**.[27] Compounds **11a–d** were hydrolyzed by trifluoroacetic acid and then reacted with **13**[30] and triethylamine to give enamino keto esters **14a–d**. Cyclization of **14a–d** with sodium hydride gave 3-quinolinecarboxylates **15a–d**. Compound **15a** was obtained as prisms, and the absolute configuration was determined to be (1*R*,2*S*) by X-ray crystallographic analysis as shown in Figure 1. Hydrolysis of **15a–d** in HCl gave chiral 1-(2-fluorocyclopropyl)-8-chloro-6,7-difluoro-4-oxo-3-quinolinecarboxylic acids **16a–d**.

The synthetic routes of chiral 7-[(*tert*-butoxycarbonyl)-amino]-5-azaspiro[2.4]heptanes **27a** and **27b** are summarized in Scheme 3. 1-Acetyl-1-cyclopropanecarboxylic acid (**17**)[31] was converted to (*R*)-(1-phenylethyl)amide **18** to achieve chiral resolution at the later stage. Bromination of **18**, followed by treatment with sodium hydride, gave **22** in low yield, and this route was not applicable to scale-up preparation. Then, the ketone group of **18** was protected by ketal, and the resulting ketal was converted to stable bromide **20**. Reaction of **20** with sodium hydride, followed by deprotection, gave 4,7-dioxo-5-azaspiro[2.4]heptane (**22**) in moderate yield.

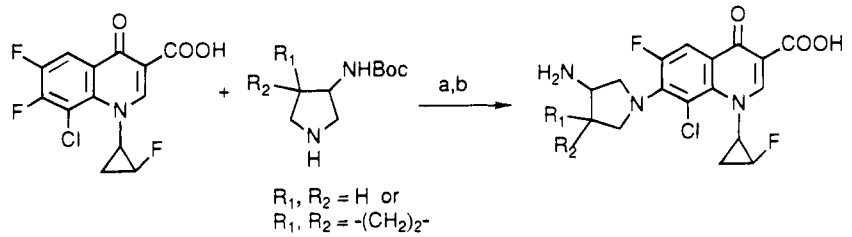
Table 2. Physical Properties of the Chiral 8-Chloroquinolones



compd	R_1	R_2	X	chirality 1′	2′	3′	mp, °C	rotation[a] (solvent)	yield,[b] %	formula[c]
29	H	H	F	*R*	*S*	*S*	247–252 dec	−94.7 (0.1 N NaOH)	73	$C_{17}H_{16}ClF_2N_3O_3{\cdot}H_2O$
30	H	H	F	*S*	*R*	*S*	214–217	+120.8 (0.1 N NaOH)	66	$C_{17}H_{16}ClF_2N_3O_3{\cdot}^1/_2H_2O$
31	$-(CH_2)_2-$		H			*S*	166–170 dec	−112.6 (0.1 N NaOH)	55	$C_{19}H_{19}ClFN_3O_3{\cdot}^1/_2H_2O$[d]
32	$-(CH_2)_2-$		H			*R*	160–165 dec	+110.3 (0.1 N NaOH)	43	$C_{19}H_{19}ClFN_3O_3{\cdot}^1/_2H_2O$
33	$-(CH_2)_2-$		F	*R*	*S*	*S*	225 dec	−199.9 (1 N NaOH)	38	$C_{19}H_{18}ClF_2N_3O_3{\cdot}^3/_2H_2O$
34	$-(CH_2)_2-$		F	*S*	*R*	*S*	123–128	+21.5 (1 N NaOH)	74	$C_{19}H_{18}ClF_2N_3O_3{\cdot}^1/_2H_2O$
35	$-(CH_2)_2-$		F	*R*	*S*	*R*	121–127	−21.1 (1 N NaOH)	55	$C_{19}H_{18}ClF_2N_2O_3{\cdot}^1/_2H_2O$[e]
36	$-(CH_2)_2-$		F	*S*	*R*	*R*	126–160 dec	+186.8 (1 N NaOH)	41	$C_{19}H_{18}ClF_2N_3O_3{\cdot}^3/_4H_2O$
37	$-(CH_2)_2-$		F	ND[f,g]		*S*	127–130	−209.2 (1 N NaOH)	61	$C_{19}H_{18}ClF_2N_3O_3{\cdot}^1/_2H_2O$
38	$-(CH_2)_2-$		F	ND[h]		*S*	167–173	−23.4 (1 N NaOH)	53	$C_{19}H_{18}ClF_2N_3O_3{\cdot}^3/_4H_2O$
39	$-(CH_2)_2-$		F	ND[g]		*R*	162–172	+3.4 (1 N NaOH)	45	$C_{19}H_{18}ClF_2N_3O_3{\cdot}^3/_4H_2O$
40	$-(CH_2)_2-$		F	ND[h]		*R*	129–131	+197.2 (1 N NaOH)	55	$C_{19}H_{18}ClF_2N_3O_3{\cdot}^1/_2H_2O$

[a] Degrees. [b] Yields are those obtained from the coupling step to final product, including deprotections. [c] Analyses for C, H, and N were within ±0.4% of the theoretical values, unless otherwise noted. [d] H: calcd, 5.03; found, 5.44. [e] H: calcd, 4.50; found, 5.42. [f] Not determined. [g] Derived from **16c**. [h] Derived from **16d**.

Scheme 1[a]



[a] (a) Et_3N, MeCN, reflux; (b) TFA.

Oximation of **22** and subsequent reduction gave a diastereomeric mixture of amines **24a** and **24b**. Each isomer was separated by silica gel column chromatography. Reduction of **24a** and **24b** with lithium aluminum hydride gave **25a** and **25b**. Reaction of **25a** and **25b** with 2-[[(*tert*-butoxycarbonyl)oxy]imino]-2-phenylacetonitrile (Boc-ON), followed by debenzylation gave chiral 7-[(*tert*-butoxycarbonyl)amino]-5-azaspiro[2.4]heptanes **27a** and **27b**. Reaction of **27b** with 8-chloro-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid[32] gave 7-[(7*S*)-7-[(*tert*-butoxycarbonyl)amino]-5-azaspiro[2.4]heptan-5-yl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**28**), which was crystallized to be crystals suitable for X-ray analysis. Absolute configuration of **28** was determined to be the *S*-form by X-ray crystallographic analysis as shown in Figure 2.

Results and Discussion

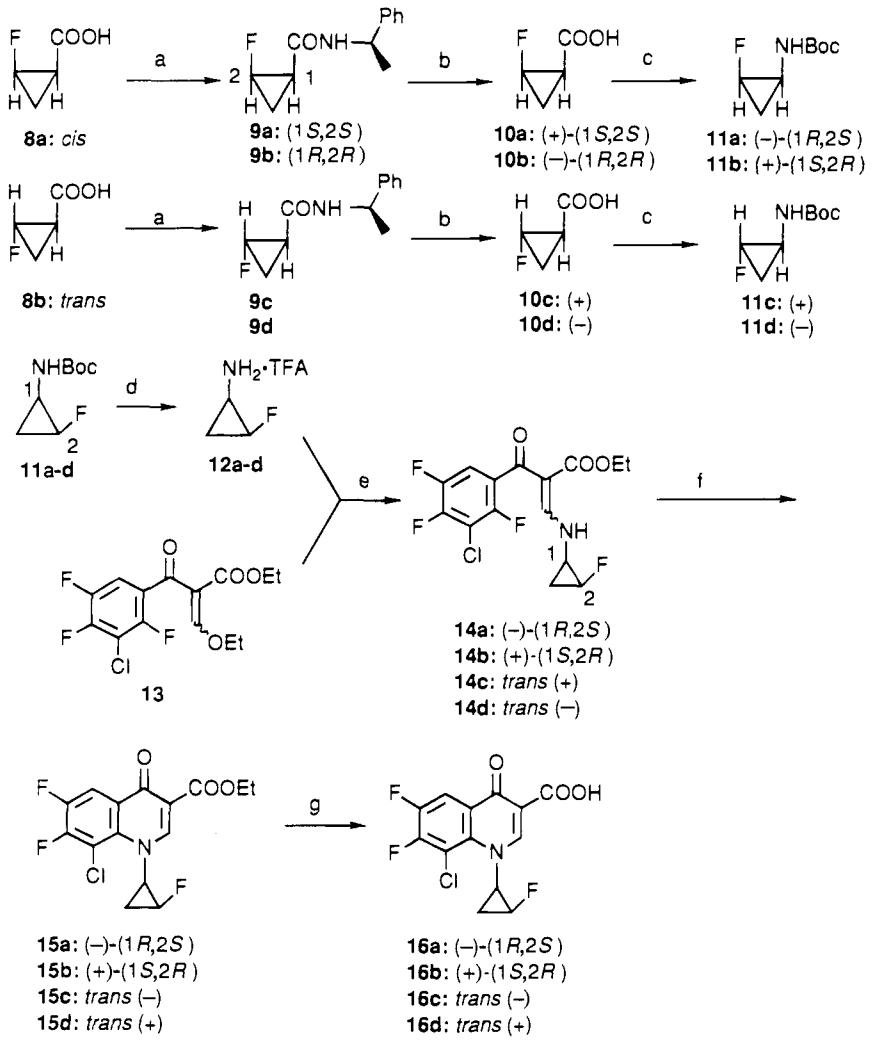
Compounds **29**–**40** were evaluated for their *in vitro* antibacterial activity against a variety of Gram-positive and Gram-negative bacteria. Data for four Gram-positive bacteria and six Gram-negative bacteria as representative examples are summarized in Table 3. The data for (*S*)-clinafloxacin (**7a**)[33] and ciprofloxacin (CPFX) (**4**) are included for comparison.

In order to estimate the effects of chiral 2-fluorocyclopropyl groups and 7-amino-5-azaspiro[2.4]heptyl groups, the compounds were divided into three groups. In the first, stereochemical effects of N-1 substituents were investigated. As (*S*)-3-aminopyrrolidine is known to be a more potent C-7 substituent than its (*R*)-counterpart,[34] 7-((*S*)-3-aminopyrrolidinyl)-1-(*cis*-2-fluorocyclopropyl) derivatives **29** and **30** were synthesized. It is known that fluorine is hydrogen mimic,[35] and the effect of chirality of *cis*-2-fluorocyclopropyl group was delicate: (1*R*,2*S*)-**29** and (1*S*,2*R*)-**30** were nearly equipotent, and the difference of the activity was 2-fold at the most.

Secondly, the activities of chiral 7-(7-amino-5-azaspiro[2.4]heptyl)-1-cyclopropyl derivatives **31** and **32** were compared. (*S*)-**31** was 2–16-fold more potent than its antipode (*R*)-**32** against Gram-positive and Gram-negative bacteria, and was highly potent as **7a**. These observations indicated that the cyclopropyl group at C-4 position of the pyrrolidine ring has little effect on antibacterial activity and stereochemistry of the amino group at C-3 is important.

In the next study, the activities of all the possible stereoisomers of 7-(7-amino-5-azaspiro[2.4]heptyl)-1-(2-fluorocyclopropyl) derivatives **33**-**40** were compared. In the stereoisomeric pairs of 7(*S*) and 7(*R*) derivatives (**33**/**35**, **34**/**36**, **37**/**39**, or **38**/**40**), 7(*S*) derivatives were more potent than 7(*R*) derivatives. With respect to the 1-cyclopropane ring of the series of 7(*S*)-isomers and 7(*R*)-isomers, *cis*-isomers were more potent than *trans*-isomers as previously reported in a series of 7-piperazinyl-1-fluorocyclopropyl derivatives.[1] In the stereoisomeric pairs of 1-(1*R*,2*S*) and 1-(1*S*,2*R*) derivatives (**33** and **34**, or **35** and **36**), the difference of the activity was

Scheme 2[a]



[a] (a) *N,N'*-Carbonyldiimidazole, (*R*)-PhCH(Me)NH_2; (b) HCl; (c) DPPA, t-BuOH, Et_3N; (d) TFA; (e) Et_3N; (f) NaH; (g) HCl, AcOH.

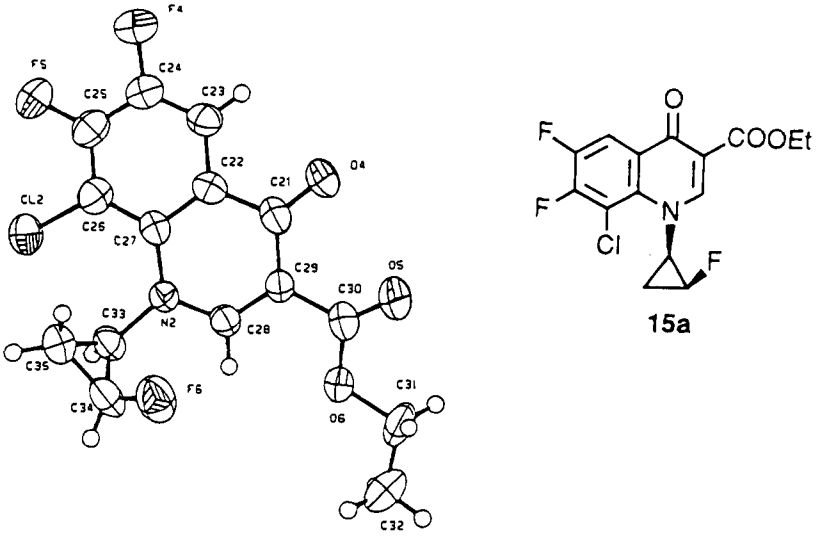
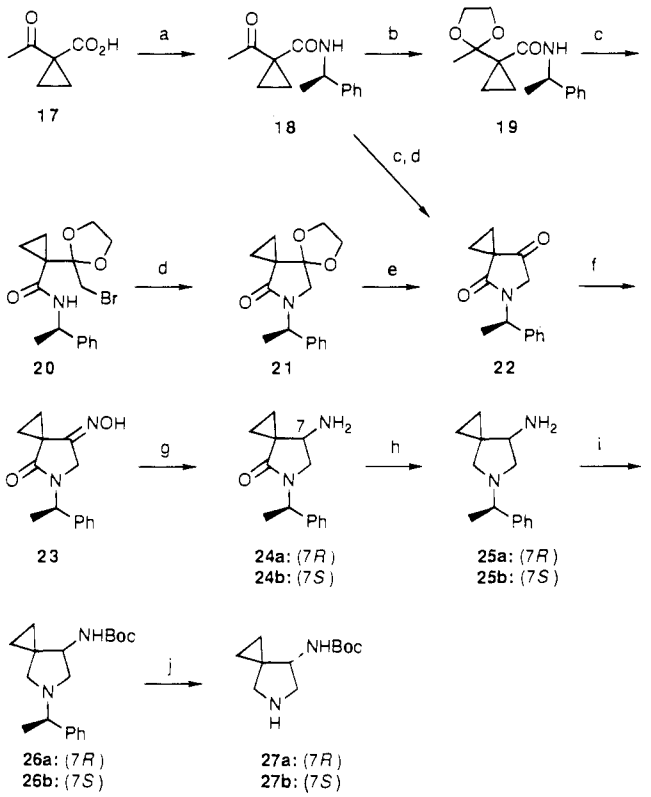


Figure 1. ORTEP drawing of **15a**.

not significant. After all modifications and stereochemical relationships, it was found that (*S*)-(7-amino-5-azaspiro[2.4]heptyl) group and chiral *cis*-2-fluorocyclopropyl groups are preferred stereoisomers, and **29**, **30**, **31**, **33**, **34**, and (*S*)-**7** are nearly equipotent.

Oral bioavailability is an important aspect for *in vivo* efficacy as well as *in vitro* antibacterial activity. Since the introduction of ofloxacin (**3**),[5] which exhibits excellent pharmacokinetic profiles in human, we focused our research toward more orally effective agents. In the studies, we decided that new compounds should have good aqueous solubility and lipophilicity comparable to that of ofloxacin to exhibit good oral absorbability and reduced metabolism. In this study, we examined phys-

Scheme 3[a]



[a] (a) ClCOOEt, Et_3N, (*R*)-PhCH(Me)NH_2; (b) $(CH_2OH)_2$, *p*-TosOH; (c) Br_2, dioxane; (d) NaH; (e) HCl; (f) NH_2OH·HCl, Et_3N; (g) H_2, Ra-Ni; (h) $LiAlH_4$; (i) Boc-ON; (j) H_2, Pd–C.

icochemical properties and pharmacokinetic profiles of selected compounds. Apparent partition coefficients (*P*'s) and aqueous solubilities of **29**, **31**, **33**, and **7** are given in Table 4. The data for ofloxacin is included for comparison. Lipophilicities were related to structural feature of the molecules. Introduction of a fluorine atom reduced the apparent partition coefficient of corresponding nonfluorinated compound (**7** → **29**, **31** → **33**) as we reported previously.[1] Introduction of cyclopropyl group at C-4 of 3-aminopyrrolidine increased apparent partition coefficient (**7** → **31**, **29** → **33**). The lipophilic natures of the N-1 and C-7 substituents of **33** offset each other and **33** showed moderate lipophilicity comparable to that of **7**. Aqueous solubilities of cyclopropyl derivatives were higher than those of fluorocyclopropyl congeners (**7** and **29**, or **31** and **33**). The (*S*)-(7-amino-5-azaspiro-[2.4]heptyl) group did not improve aqueous solubility in this set of compounds (**7** and **31**, or **29** and **33**). Aqueous solubilities did not correlate with apparent partition coefficients.

The pharmacokinetic profiles after oral dose of 20 mg/kg to rats are given in Table 5. Aqueous solubility is suggested to be associated with the extent and rate of oral absorption of a compound.[24] Peak plasma concentrations of cyclopropyl derivatives were higher than those of less soluble fluorocyclopropyl congeners (**7** and **29**, or **31** and **33**). But, peak plasma concentration of **29** was lower than those of less soluble **31** and **33**. Oral absorbability might be related to lipophilicity as well as aqueous solubility. The urinary recovery of **31** was relatively low compared to its serum level, and half of **31** excreted via urine was found as its glucuronide. This seems to be related to the high lipophilicity of **31**.[36] Active metabolites of **7** were found in urine, but no active metabolite of **33** was found. It is known that metabolic stability of primary amino derivatives, such as phenylethylamine, are improved by introducing a substituent at the a-carbon of amines.[37] Therefore, metabolic stability of **33** should be due to the steric hindrance for the basic center of 7-amino-5-azaspiro-[2.4]heptyl group. As a result, (*S*)-7-amino-5-azaspiro-[2.4]heptane was found to be a suitable C-7 substituent of 1-(*cis*-2-fluorocyclopropyl)quinolone in terms of the pharmacokinetic profiles.

This study has demonstrated that (*S*)-7-amino-5-azaspiro[2.4]heptane is an excellent C-7 substituent of (1*R*,2*S*)-(2-fluorocyclopropyl)quinolone in terms of antibacterial activity and pharmacokinetic profiles. Biological evaluation of these fluorocyclopropyl derivatives has been carried out extensively. Fluorocyclopropyl derivative **33** was found to be a less effective topoisomerase II inhibitor than the corresponding cyclopropyl analogue **31**.[17] In the micronucleus test, **31** induced the micronuclei in mouse bone marrow cells when administrated 150 mg/kg, iv, while **33** did not.[38] Therefore, compound **33** was suggested to be less effective to mammalian cells and less toxic. Compound **33** (DU-6859a) was finally selected and is presently under clinical studies.

Experimental Section

Melting points were taken on Yanagimoto micro melting point apparatus and are uncorrected. ^1H NMR spectra were taken at 90 MHz with a JEOL FX-90 spectrometer and 400

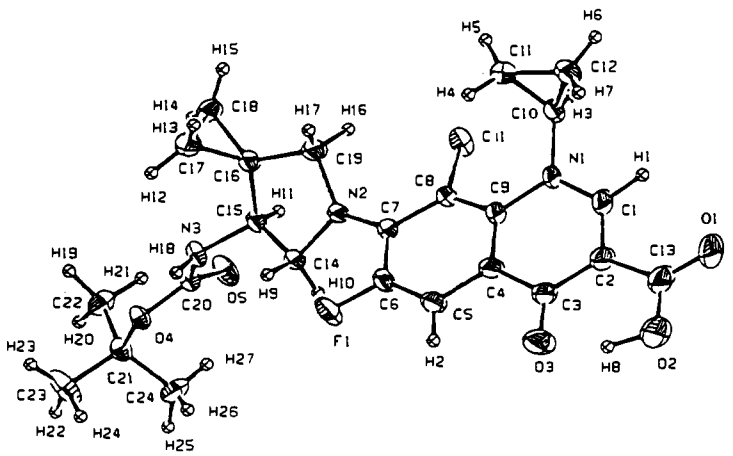


Figure 2. ORTEP drawing of **28**.

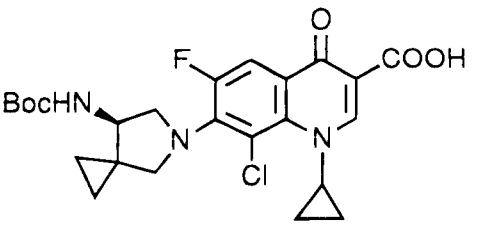


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Table 3. *In Vitro* Antibacterial Activity[a]

compd	min inhibitory concn, μg/mL									
	S. aureus 209P	*S. epidermidis* 56556	*S. pyogenes* G36	*S. faecalis* ATCC19433	*E. coli* NIHJ	*K. pneumoniae* Type2	*P. vulgaris* 08601	*E. cloacae* 03400	*S. marcescens* 10100	*P. aeruginosa* 32104
29	0.013	0.05	0.1	0.2	0.006	0.05	0.006	0.006	0.025	0.05
30	0.025	0.05	0.2	0.2	0.013	0.05	0.013	0.025	0.05	0.1
31	0.013	0.025	0.1	0.1	<0.006	0.025	0.006	0.006	0.025	0.05
32	0.1	0.1	0.78	0.39	0.05	0.05	0.05	0.05	0.1	0.39
33	0.013	0.025	0.05	0.1	<0.006	0.025	0.006	0.006	0.025	0.05
34	0.025	0.05	0.2	0.2	0.013	0.025	0.013	0.013	0.05	0.2
35	0.1	0.1	0.1	0.78	0.025	0.05	0.025	0.025	0.1	0.39
36	0.1	0.2	0.2	0.39	0.05	0.1	0.05	0.05	0.5	0.78
37	0.1	0.1	0.39	0.78	0.006	0.05	0.025	0.013	0.1	0.39
38	0.78	0.78	3.13	3.13	0.05	0.2	0.1	0.2	0.2	1.56
39	0.78	0.78	>12.5	6.25	0.05	0.39	0.1	0.1	0.39	1.56
40	3.13	3.13	>12.5	>12.5	0.39	1.56	0.39	0.78	0.78	6.25
(*S*)-**7**	0.025	0.05	0.1	0.1	<0.006	0.025	0.006	0.006	0.025	0.05
CPFX	0.1	0.2	1.56	1.56	0.006	0.05	0.013	0.025	0.05	0.1

[a] See the Experimental Section.

Table 4. Physicochemical Properties[a]

	29	**31**	**33**	**7**	OFLX
solubility[b]	344	203	131	500	2400
P'[c]	0.55	11.1	3.1	2.3	4.9

[a] See the Experimental Section. [b] Aqueous solubility, μg/mL. [c] Apparent partition coefficient, $CHCl_3$/0.1 M phosphate buffer (pH 7.4).

Table 5. Pharmacokinetic Profiles of Selected Compounds after Oral Administration to Rats[a] (20 mg/kg)

compd	C_{max}, μg/mL	$t_{1/2}$, h	urinary recovery (%)	
			unchanged	conjugate
29	2.0	1.2	12	4
31	3.4	1.5	7	7
33	2.6	1.0	22	1
7	3.9	1.6	24[b]	5

[a] See the Experimental Section. [b] Including active metabolite.

MHz with a JEOL JNM-EX400 spectrometer. Chemical sifts are expressed in ppm (δ) with tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard. The structures of all compounds were consistent with their spectral data. Optical rotations were measured at 589 nm with a Horiba SEPA-200 polarimeter. Elemental analyses are indicated by the symbol of the elements; analytical results were within 0.4% of the theoretical values unless otherwise noted. Solutions were dried over sodium sulfate. E. Merck silica gel (230–400 mesh) was used for column chromatography. Thin-layer chromatography (TLC) was performed with Merck silica gel 60 F254 TLC plates.

***N*-[1(*R*)-Phenylethyl]-1,2-*cis*-2-fluorocyclopropanecarboxamide (9a and 9b).** To a solution of *dl-cis*-2-fluorocyclopropanecarboxylic acid (**8a**) (1.0 g, 9.61 mmol) in THF (30 mL) was added *N,N'*-carbonyldiimidazole (1.78 g, 12.0 mmol), and the solution was stirred at room temperature for 1 h. To the solution was added (*R*)-(+)-1-phenylethylamine (1.45 g, 11.8 mmol). The mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and washed with 10% aqueous citric acid and H_2O. The organic layer was dried and concentrated to afford a mixture of **9a** and **9b**. Each isomer was separated by preparative HPLC: Nucleosil 50-5 column (20 × 250 mm) (Senshu Kagaku Co., Ltd.). Solvent: AcOEt–THF (9:1). Flow rate: 9.0 mL/min. Retention time: 11 min for **9a**; 13 min for **9b**. **9a**: ^{1}H NMR ($CDCl_3$) δ 0.98–1.34 (m, 2 H), 1.52 (d, 3 H, J = 7 Hz), 1.64–1.96 (m, 1 H), 4.58 (dm, 1 H, J = 66 Hz), 5.24 (m, 1 H), 7.40 (m, 5 H). **9b**: ^{1}H NMR ($CDCl_3$) δ 0.92–1.34 (m, 2 H), 1.50 (d, 3 H, J = 7 Hz), 1.50–1.96 (m, 1 H), 4.68 (dm, 1H, J = 64 Hz), 5.14 (m, 1 H), 7.40 (s, 5 H). By using this procedure, *trans*-*N*-[1(*R*)-phenylethyl] derivatives **9c** (R_f 0.29) and **9d** (R_f 0.22) were prepared from *dl-trans*-2-fluorocyclopropanecarboxylic acid **8b** and separated by silica gel column chromatography using AcOEt–toluene (10:1) as eluent. **9c**: ^{1}H NMR ($CDCl_3$) δ 1.27–1.39 (m, 1 H), 1.52 (d, 3 H, J = 7 Hz), 1.74–1.84 (m, 1 H), 4.81 (dm, 1 H, J = 64 Hz), 5.11 (q, 1 H, J = 7 Hz), 5.88 (b, 1 H), 7.27–7.38 (m, 5 H). **9d**: ^{1}H NMR ($CDCl_3$) δ 1.31–1.41 (m, 1 H), 1.50 (d, 3 H, J = 7 Hz), 1.74–1.84 (m, 1 H), 4.77 (dm, 1 H, J = 64 Hz), 5.11 (q, 1 H, J = 7 Hz), 5.85 (b, 1 H), 7.28–7.39 (m, 5 H).

Chiral 2-Fluorocyclopropanecarboxylic Acids (10a–d). General Procedure. A mixture of *N*-[1(*R*)-phenylethyl]-2-fluorocyclopropanecarboxamide (**9**) (8.0 mmol) and 35% hydrochloric acid (30 mL) was stirred at 100–110 °C for 5 h. The reaction mixture was made pH 8–9 with $NaHCO_3$ and washed with $CHCl_3$. The aqueous layer was made pH 4 with HCl and extracted with AcOEt. The extract was dried and concentrated to dryness to give chiral 2-fluorocyclopropanecarboxylic acid (**10**). **10a** and **10b**: ^{1}H NMR ($CDCl_3$) δ 1.0–1.42 (m, 1 H), 1.56–1.98 (m, 2 H), 4.76 (dm, 1 H, J = 66 Hz), 11.32 (bs, 1 H). **10c** and **10d**: ^{1}H NMR ($CDCl_3$) δ 1.68–1.80 (m, 2 H), 2.45–2.54 (1H, m), 4.94 (dm, 1 H, J = 65 Hz), 9.47 (bs, 1 H).

Chiral 1-[(*tert*-Butoxycarbonyl)amino]-2-fluorocyclopropanes (11a–d). General Procedure. To a solution of **10** (2.55 mmol) in *tert*-butyl alcohol (6 mL) was added diphenyl phosphorazidate (800 mg, 2.91 mmol) and triethylamine (270 mg, 2.67 mmol). The mixture was refluxed for 4.5 h and then concentrated under reduced pressure. The residue was extracted with $CHCl_3$, and the extract was washed with 10% aqueous citric acid, 2% aqueous NaOH, and H_2O. The organic layer was dried and concentrated to dryness. The residue was chromatographed with $CHCl_3$ to give **11**. **11a** and **11b**: ^{1}H NMR ($CDCl_3$) δ 0.66–1.3 (m, 2 H), 1.46 (s, 9 H), 2.48–2.74 (m, 1 H), 4.58 (dm, 1 H, J = 65 Hz), 4.6–5.1 (br s, 1 H). **11c** and **11d**: ^{1}H NMR ($CDCl_3$) δ 0.82–0.95 (m, 1 H), 1.26–1.37 (m, 1 H), 1.48 (s, 9 H), 2.85–2.93 (m, 1 H), 4.52 (d, 1 H, J = 64 Hz), 4.42–4.62 (bs, 1 H).

Chiral Ethyl 3-(2-Fluoro-1-cyclopropyl)-2-(3-chloro-2,4,5-trifluorobenzoyl)acrylates (14a–d). General Procedure. Compound **11** (1.12 g, 6.39 mmol) was dissolved in trifluoroacetic acid (10 mL) and stirred at room temperature for 20 min. The solution was concentrated to dryness to obtain 2-fluorocyclopropylamine trifluoroacetate (**12**) as an oil. To a suspension of **12** in CH_2Cl_2 (20 mL) was added triethylamine (2.0 g, 19.8 mmol) at 0 °C, and the mixture was stirred for 20 min. To the mixture was added a solution of ethyl 3-ethoxy-2-(3-chloro-2,4,5-trifluorobenzoyl)acrylate (**13**), prepared from ethyl 2-(3-chloro-2,4,5-trifluorobenzoyl)acetate (1.50 g, 5.35 mmol),[25] in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 1 h and then concentrated to dryness. The residue was chromatographed with benzene–AcOEt (4:1), and the eluent was concentrated to dryness. The residue was triturated with isopropyl ether–*n*-haxane, and the resulting precipitates were collected by filtration to give **14**. **14a** and **14b**: ^{1}H NMR ($CDCl_3$) δ 0.95, 1.08 (each t, 3 H, 1:2.5, J = 7 Hz), 1.0–1.5 (m, 2 H), 2.8–3.15 (m, 1 H), 4.03, 4.07 (each q, 2 H, 1:2.5, J = 7 Hz), 4.78 (dm, 1 H, J = 65 Hz), 7.13 (ddd, 1 H, J = 9.5, 8.6, 5.9 Hz), 8.20, 8.25 (each d, 1 H, 1:2.5, J = 14 Hz). **14c** and **14d**: ^{1}H NMR ($CDCl_3$) δ 0.87, 1.02 (each t, 3H, 1:2.3, J = 7 Hz), 1.16–1.28 (m, 1 H), 1.42–1.6 (m, 1 H), 3.23–3.35

(m, 1 H), 3.94, 4.00 (each q, 2 H, 1:2.3, J = 7 Hz), 4.64, 4.67 (each m, 1 H, 1:2.3), 7.00–7.07, 7.15–7.23 (each m, 1 H, 2.3:1), 8.00, 8.07 (each d, 1 H, 1:2.3, J = 14 Hz), 9.32, 10.66 (each d, 1 H, 1:2.3, J = 14 Hz).

Chiral Ethyl 8-Chloro-6,7-difluoro-1-(2-fluoro-1-cyclopropyl)-4-oxoquinoline-3-carboxylates (15a–d). General Procedure. To a suspension of 60% NaH (560 mg, 14 mmol) in dioxane (10 mL) was added a solution of compound **14** (1.70 g, 4.65 mmol) in dioxane (20 mL). The mixture was stirred at room temperature for 2 h and concentrated to dryness. To the residue was added 0.1 N HCl. The resulting precipitates were collected by filtration and washed with water and ether to give **15**. **15a** and **15b**: ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3 H, J = 7 Hz), 1.4–1.9 (m, 2 H), 4.08 (m, 1 H), 4.39 (q, 2H, J = 7 Hz), 4.90 (dm, 1 H, J = 65 Hz), 8.24 (dd, 1H, J = 11 Hz, 10 Hz). **15c** and **15d**: ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 H, J = 7 Hz), 1.38–1.50 (m, 1 H), 1.78–1.92 (m, 1 H), 4.29 (q, 2 H, J = 7 Hz), 4.38–4.48 (m, 1 H), 4.66 (dm, 1 H, J = 64 Hz), 8.10 (t, 1 H, J = 7 Hz), 8.44 (s, 1 H).

Chiral 8-Chloro-6,7-difluoro-1-(2-fluoro-1-cyclopropyl)-4-oxo-3-quinolinecarboxylic Acids (16a–d). General Procedure. The mixture of **15** (1.4 g, 4.0 mmol) and 35% HCl (10 mL) was heated at 110 °C for 2.5 h. To the reaction mixture was added H_2O (50 mL). The resulting precipitates were collected by filtration and washed with water and ether to give **16**. **16a** and **16b**: ^{1}H NMR ($CDCl_3$) δ 1.3–2.0 (m, 2 H), 4.12–4.34 (m, 1 H), 4.95 (dm, 1 H, J = 63 Hz), 8.27 (dd, 1 H, J = 8 Hz, 8 Hz), 8.87, 8.89 (each s, 1 H, split, 1:1). **16c** and **16d**: ^{1}H NMR ($CDCl_3$) δ 1.46–1.56 (m, 1 H), 1.89–2.02 (m, 1 H), 4.53–4.58 (m, 1 H), 4.65 (dm, 1 H, J = 64 Hz), 8.22 (t, 1 H, J = 8 Hz), 8.28 (s, 1 H).

(*R*)-*N*-(1-Phenylethyl)-1-acetyl-1-cyclopropanecarboxamide (18). Ethyl chloroformate (215.9 g, 1.99 mol) was added dropwise to a stirred solution of 1-acetylcyclopropanecarboxylic acid (**17**) (232 g, 1.80 mol) and triethylamine over a period of 40 min at −40 to −30 °C. After the addition, the mixture was stirred at −30 °C for 40 min. To the reaction mixture was added dropwise (*R*)-(+)-1-phenylethylamine (241.1 g, 1.98 mol) over a period of 20 min (internal temperature was kept at −20 °C). After being stirred for 1.5 h, the reaction mixture was washed twice with 1 N HCl, saturated aqueous $NaHCO_3$, and H_2O. The organic layer was dried and concentrated to dryness to give 489.3 g of **18**, which was used without purification: ^{1}H NMR ($CDCl_3$) δ 1.50 (d, 3 H, J = 7.2 Hz), 1.4–1.6 (m, 2 H), 1.7–1.9 (m, 2 H), 1.95 (s, 3 H), 5.1 (q, 1 H, J = 7.2 Hz), 7.3 (s, 5 H).

(*R*)-*N*-(1-Phenylethyl)-1-[1,1-(ethylenedioxy)ethyl]-1-cyclopropanecarboxamide (19). A mixture of **18** (248.4 g), ethylene glycol (230 mL), *p*-toluenesulfonic acid monohydrate (10.0 g, 52.6 mmol), and benzene (800 mL) was refluxed for 24 h under azeotropic condition. After cooling, H_2O (500 mL) and benzene (500 mL) were added to the reaction mixture. The organic layer was separated and washed with saturated $NaHCO_3$. The organic layer was dried and concentrated to dryness to give 227.8 g of **19**, which was used without purification: ^{1}H NMR ($CDCl_3$) δ 0.7–0.95 (m, 2 H), 1.0–1.2 (m, 2 H), 1.48 (s, 3 H), 1.47 (t, 3 H, J = 7.2 Hz), 3.98 (s, 4 H), 5.22 (q, 1 H, J = 7.2 Hz), 7.31 (s, 5 H), 7.75 (br s, 1 H).

(*R*)-*N*-(1-Phenylethyl)-1-[2-bromo-1,1-(ethylenedioxy)-ethyl]-1-cyclopropanecarboxamide (20). Bromine (145.4 g, 0.91 mol) was added dropwise to dioxane (436 mL) over a period of 30 min, and the mixture was stirred for 30 min. To the mixture was added a solution of **19** (227.8 g) in CH_2Cl_2 (2.0 L), and the resulting mixture was stirred for 2 h. To the reaction mixture was added 10% aqueous sodium thiosulfate solution, and the organic layer was separated, dried, and concentrated to dryness to give 326.0 g of **20**, which was used without purification: ^{1}H NMR ($CDCl_3$) δ 0.7–1.0 (m, 2 H), 1.0–1.25 (m, 2 H), 1.49 (d, 3 H, J = 7.2 Hz), 3.69 (s, 2 H), 3.8–4.3 (m, 4 H), 5.08 (q, 1 H, J = 7.2 Hz), 7.30 (s, 5 H), 7.6 (br s, 1 H).

4,7-Dioxo-5-[1(*R*)-phenylethyl]-5-azaspiro[2.4]-heptane 7-Ethylene Acetal (21). To a solution of **20** (293.0 g) in DMF (500 mL) was added portionwise 60% NaH (43 g, 1.08 mol) during 1.5 h under cooling to keep the internal temperature at 30 °C, and the mixture was stirred for 18 h. The mixture was poured into ice and extracted with AcOEt (3.0 L). The extract was washed several times with H_2O and dried. The solution was concentrated to dryness to give 203.3 g of the **21** as an oil, which was used without purification: ^{1}H NMR ($CDCl_3$) δ 0.98–1.38 (m, 4 H), 1.50 (d, 3 H, J = 7.2 Hz), 3.07 (d, 1 H, J = 10.2 Hz), 3.41 (d, 1 H, J = 10.2 Hz), 3.83 (s, 4 H), 5.61 (q, 1 H, J = 7.2 Hz), 7.30 (s, 5 H).

4,7-Dioxo-5-[1(*R*)-phenylethyl]-5-azaspiro[2.4]-heptane (22). A mixture of **21** (203.3 g), acetone (1.0 L), and 1 N HCl was refluxed for 1.5 h. The mixture was concentrated, and AcOEt (1.5 L) was added to the residue. The organic layer was separated and dried. The solution was treated with charcoal and concentrated under reduced pressure. The residue was chromatographed with $CHCl_3$–AcOEt (10:0–9:1) to give 65.7 g (45% from **17**) of **22** as a crystalline solid: mp 98–103 °C; ^{1}H NMR ($CDCl_3$) δ 1.81 (d, 3 H, J = 7.2 Hz), 1.4–1.74 (m, 4 H), 3.48 (d, 1 H, J = 17.7 Hz), 3.88 (d, 1 H, J = 17.7 Hz), 5.81 (q, 1 H, J = 7.2 Hz), 7.34 (s, 1 H).

7-(Hydroxylmino)-5-[1(*R*)-phenylethyl]-4-oxo-5-azaspiro[2.4]heptane (23). A mixture of **22** (3.35 g, 14.6 mmol), hydroxylamine hydrochloride (1.60 g, 23.0 mmol), triethylamine (2.3 g, 22.7 mmol), and EtOH (80 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure. To the residue was added $CHCl_3$, and the mixture was washed with 10% aqueous citric acid solution and brine. The organic layer was dried and concentrated to dryness to give 3.50 g (98%) of **23**: mp 188–194 °C; ^{1}H NMR ($CDCl_3$) δ 1.2–1.4 (m, 2 H), 1.53 (d, 3 H, J = 7.2 Hz), 3.8 (d, 1 H, J = 18 Hz), 4.16 (d, 1 H, J = 18 Hz), 5.63 (q, 1 H, J = 7.2 Hz), 7.32 (s, 5 H).

7-Amino-5-[1(*R*)-phenylethyl]-4-oxo-5-azaspiro[2.4]-heptanes (24a and 24b). A mixture of **23** (3.50 g, 14.3 mmol), Raney nickel (7.5 mL), and MeOH (150 mL) was stirred under a hydrogen atmosphere for 12 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to afford a mixture of (7*R*)-**24a** and (7*S*)-**24b**. The mixture showed two spots on silica gel TLC (**24a**, R_f = 0.89; **24b**, R_f = 0.80) using $CHCl_3$–MeOH (5:1). The mixture was chromatographed with $CHCl_3$–MeOH (95:5) to give 1.0 g (30%) of (7*R*)-**24a** and 1.0 g (30%) of (7*S*)-**24b**. (7*R*)-**24a**: ^{1}H NMR ($CDCl_3$) δ 0.6–1.3 (m, 4 H), 1.40 (s, 2 H), 1.53 (d, 3 H, J = 7.2 Hz), 2.99 (dd, 1 H, J = 12.8 Hz, 7.2 Hz), 3.15–3.45 (m, 2 H), 5.52 (q, 1 H, J = 7.2 Hz), 7.30 (s, 5 H). (7*S*)-**24b**: ^{1}H NMR ($CDCl_3$) δ 0.8–1.4 (m, 4 H), 1.52 (d, 1H, J = 7 Hz), 2.87 (dd, 1 H, J = 10.3 Hz), 3.3–3.9 (m, 2 H), 4.27 (br s, 1 H), 5.24 (q, 1 H, J = 7 Hz), 7.29 (s, 1 H).

7(*S*)-Amino-5-[1(*R*)-phenylethyl]-5-azaspiro[2.4]-heptane (25b). A mixture of (7*S*)-**24b** (1.0 g, 4.34 mmol), lithium aluminum hydride (0.50 g, 19.0 mmol), and THF (50 mL) was refluxed for 17 h. To the mixture was carefully added H_2O (0.5 mL), 10% aqueous NaOH (0.5 mL), and H_2O (1.5 mL) under ice cooling. The grainy precipitate was filtered, and the filtrate was concentrated under reduced pressure to give 755 mg (80%) of **25b** as an oil: ^{1}H NMR ($CDCl_3$) δ 0.2–0.8 (m, 4 H), 1.35 (d, 3 H, J = 6.6 Hz), 1.6–2.0 (br m, 2 H), 2.2–3.1 (m, 4 H), 3.24 (q, 1 H, J = 6.6 Hz), 3.5–3.9 (m, 1 H), 7.28 (br s, 5 H). According to this procedure, (*R*)-**25a** was prepared from **24a**.

7(*S*)-[(*tert*-Butoxycarbonyl)amino]-5-[1(*R*)-phenylethyl]-5-azaspiro[2.4]heptane (26b). To a solution of **25b** (764 mg, 3.53 mmol) in THF (20 mL) was added 2-[[(*tert*-butoxycarbonyl)oxy]imino]-2-phenylacetonitrile (1.30 g, 5.28 mmol), and the mixture was stirred for 4 h. The reaction mixture was diluted with AcOEt. The solution was washed with 1 N NaOH and H_2O. The organic layer was extracted with 10% aqueous citric acid solution. The aqueous layer was washed with AcOEt and then made alkaline with 15% NaOH. The aqueous solution was extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated under reduced pressure. The residue was chromatographed with $CHCl_3$–MeOH (20:1–10:1) to give 690 mg (67%) of the **26b** as an oil. Standing at room temperature, this material was crystallized, which was triturated with *n*-hexane to give crystals: mp 103–105 °C; $[\alpha]_D$ −15.2° (*c* 1.475, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.4–0.9 (m, 4 H), 1.36 (d, 3 H, J = 7.2 Hz), 1.44 (s, 9 H), 2.42 (AB q, 2 H, J = 10.2 Hz), 2.79 (d, 2 H, J = 5.6 Hz), 3.24 (q, 1 H, J = 7.2 Hz), 3.6–4.0 (m, 1 H), 4.6–5.1 (br d, 1 H), 7.28 (s, 5 H). Anal.

($C_{19}H_{28}N_2O_2$): C, H, N. According to this procedure, (7*R*)-**26a** was prepared from (7*R*)-**25a**. (7*R*)-**26a**: mp 94–97 °C; $[\alpha]_D$ +47.6° (*c* 0.890, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.4–0.9 (m, 4 H), 1.33 (d, 3 H, *J* = 6.6 Hz), 1.40 (s, 9 H), 2.29 (d, 1 H, *J* = 9 Hz), 2.44 (dd, 1 H, *J* = 10.8, 3.6 Hz), 2.77 (d, 1 H, *J* = 9 Hz), 2.88 (dd, 1 H, *J* = 10.8 Hz, 5.3 Hz), 3.22 (q, 1 H, *J* = 6.6 Hz), 3.6–3.9 (m, 1 H), 4.7–5.2 (br d, 1 H), 7.27 (s, 5 H). Anal. ($C_{19}H_{28}N_2O_2$): C, H, N.

7(*S*)-[(*tert*-Butoxycarbonyl)amino]-5-azaspiro[2.4]heptane (27b). A mixture of **26b** (650 mg, 2.24 mmol), 50% aqueous 5% palladium on carbon (500 mg), and EtOH (30 mL) was shaken under hydrogen atmosphere at 4.2 kg/cm² for 6 h. The catalyst was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in AcOEt and extracted with 10% aqueous citric acid solution. The aqueous layer was made alkaline with 15% NaOH and extracted with $CHCl_3$. The organic layer was dried and concentrated to dryness to give 440 mg (46%) of **27b**: ^1H NMR ($CDCl_3$) δ 0.4–1.0 (m, 4 H), 1.42 (s, 9 H), 2.71 (d, 1 H, *J* = 10.2 Hz), 2.92 (dd, 1 H, *J* = 10.8 Hz, 3.6 Hz), 3.01 (d, 1 H, *J* = 10.2 Hz), 3.33 (dd, 1 H, *J* = 10.8 Hz, 5.4 Hz), 3.5–3.9 (m, 1 H), 5.0–5.4 (br d, 1 H). According to this procedure, (7*R*)-**27a** was prepared from (7*R*)-**26a**.

7[7(*S*)-[(*tert*-Butoxycarbonyl)amino]-5-azaspiro[2.4]heptan-5-yl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (28). A mixture of 8-chloro-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (2.0 g, 6.67 mmol), **27b** (1.75 g, 8.24 mmol), and Et_3N (1.80 g, 17.8 mmol) in CH_3CN (55 mL) was heated under reflux for 7.5 h. After standing at room temperature, the precipitates that formed were collected and washed with CH_3CN to give 2.5 g (76%) of **28b**. This was recrystallized from CH_3CN–EtOH (3:1) to give prisms, which was submitted to X-ray analysis: mp 216–217 °C; $[\alpha]_D$ −134.7° (*c* 1.653, $CHCl_3$). Anal. ($C_{24}H_{27}ClFN_3O_5$): C, H, N.

Synthesis of 7[(7*S*)-7-Amino-5-azaspiro[2.4]heptan-5-yl]-8-chloro-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Sesquihydrate (DU-6859a) (33). General Procedure. A mixture of **16a** (12.0 g, 37.7 mmol), **27b** (9.58 g, 45.2 mmol), Et_3N (9.50 g, 129 mmol), and CH_3CN (120 mL) was heated under reflux for 5 h. On standing, the colorless crystals that formed were collected and washed with CH_3CN and Et_2O. The crystals were dissolved in 35% HCl (80 mL) under ice cooling and stirred for 15 min at room temperature. The mixture made alkaline (pH 10) with 15% NaOH and then neutralized with HCl to pH 7. The resulting precipitates were collected by filtration and washed with H_2O to give a crude product. This was recrystallized from EtOH (600 mL)–H_2O (200 mL)–28% NH_4OH (10 mL) to give 7.35 g (38%) of **33**: ^1H NMR (DMSO-d_6) δ 0.43–0.46 (m, 1 H), 0.55–0.61 (m, 2 H), 0.79–0.83 (m, 1 H), 1.23 (dm, 1H, *J* = 27 Hz), 3.06 (t, 1 H, *J* = 5 Hz), 3.25–3.28 (m, 1 H), 3.35 (d, 1 H, *J* = 7 Hz), 3.83 (d, 1 H, *J* = 7 Hz), 3.92–3.96 (m, 1 H), 4.06–4.10 (m, 1 H), 4.50 (dm, 1 H, *J* = 64 Hz), 7.74 (d, 1 H, *J* = 14 Hz), 8.47 (d, 1 H, *J* = 2 Hz). By using this procedure, the compounds in Table 2 were prepared.

X-ray Crystallographic Study. All measurements were made on a Rigaku AFC5R diffractometer (Cu Kα radiation; λ = 1.541 78 Å, graphite monochrometer, ω–2θ scans, $2\theta_{max}$ = 120.1°). The crystal data and parameters are summarized below. The structures were solved by the direct methods and refined by full-matrix least-square and difference Fourier methods. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms of **28** were refined isotropically (d_{C-H} = 0.95 Å). Hydrogen positions of **15a** were calculated assuming ideal geometries. For all crystallographic computations, the TEXSAN crystallographic software package was used.

Crystal Data and Structure Analysis. 15a: A colorless, prism-shaped crystal was formed from AcOEt: $C_{15}H_{11}ClF_3NO_3$; FW = 345.71; sample dimensions, 0.4 × 0.25 × 0.2 mm; triclinic, space group P_1; *a* = 8.7989(5) Å, *b* = 11.1337(9) Å, *c* = 8.1730(6) Å, *V* = 723.2(2) Å³, α = 111.428(6)°, β = 92.701(7)°, γ = 76.225(5)°, *Z* = 2; d_{calcd} = 1.587 g/cm³; F_{000} = 352; μ = 28.35 cm⁻¹. The final cycle of full-matrix least squares refinement was based on 4354 observed reflections ($I > 3.00\sigma(I)$) and 413 variable parameters and converged at *R* = 0.033 (R_w = 0.066). **28**: A pale-yellow, distorted hexagonal prism was grown from CH_3CN–EtOH: $C_{24}H_{27}ClN_3O_5$; FW = 491.95; sample dimensions, 0.45 × 0.20 × 0.20 mm; orthorhombic, space group $P2_12_12_1$; *a* = 9.673(3) Å, *b* = 48.590(3) Å, *c* = 5.075(3) Å, *V* = 2385(1) Å³; *Z* = 4; d_{calcd} = 1.370 g/cm³; F_{000} = 31032; μ = 18.33 cm⁻¹. The final cycle of full-matrix least square refinement was based on 1966 observed reflections ($I > 3.00\sigma(I)$) and 416 variable parameters and converged at *R* = 0.038 (R_w = 0.049).

***In Vitro* Antibacterial Activity.** The minimal inhibitory concentrations (MICs) of the test compound were determined according to the standard method by a serial 2-fold dilution method using Muller–Hinton broth (Difco Laboratories, Detroit, MI). The inoculum size was approximately 10^5 cfu/mL. The MIC of a compound was defined as the lowest concentration that prevented visible growth of bacteria after incubation at 37 °C for 18 h.

Determination of Apparent Partition Coefficients.[1] The apparent partition coefficients of the compounds tested in this study were measured according to the method reported previously.[1]

Determination of Aqueous Solubilities. About 400 mg of the sample (*a* mg) was dissolved in 0.1 N NaOH (50 mL), and the maximum UV absorption of the solution was measured [A_1]. A suspension of the sample in water (*ca.* 10 mL) was stirred for 0.5 h. The contents were filtered, and 3 mL of the filtrate was dissolved in 3 mL of 0.2 N NaOH. One milliliter of the solution was diluted with 0.1 N NaOH to obtain 50 mL of 0.1 N NaOH solution. The maximum UV absorption of the solution was measured [A_2]. The aqueous solubility, *S*, was calculated from $S = a[A_2]/[A_1]$.

Pharmacokinetic Studies. Plasma and urine levels in rats were determined by microbiological assay. Compounds were administered in solution by oral gavage (five per group). Blood samples were obtained at 0.5, 1, 3, 4, 5, 6, and 24 h after dosing. Urine was collected 0–4, 4–8, 8–24 h after dosing. Plasma levels and urinary excretion of test compounds were determined by agar plates system. The test organism was *Bacillus subtilis* ATCC 6051.

Acknowledgment. The authors thank members of the Laboratory of Microbiology and Pathology of their laboratory for determining the antibacterial activity and pharmacokinetic profiles.

Supplementary Material Available: Tables of final atomic positional parameters, atomic thermal parameters, and bond distances and angles of **15a** and **28** (41 pages). Ordering information is given on any current masthead page.

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(1) This paper is part 2 in the series Fluorocyclopropyl Quinolones. Part 1: Atarashi, S.; Imamura, M.; Kimura, Y.; Yoshida, A.; Hayakawa, I. Fluorocyclopropyl Quinolones. 1. Synthesis and Structure-Activity Relationships of 1-(2-Fluorocyclopropyl)-3-pyridonecarboxylic Acid Antibacterial Agents. *J. Med. Chem.* **1993**, *36*, 3444–3448.

(2) This paper is based upon work presented at 31st Interscience Conference on Antimicrobial Agents and Chemotherapy (September 29–October 2, Chicago, IL, 1991, Abstract No. 1504).

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