7-(2-Aminomethyl-1-azetidinyl)-4-oxoquinoline-3-carboxylic Acids as Potent Antibacterial Agents: Design, Synthesis, and Antibacterial Activity[1)]

Masahiro FUJITA,* Katsumi CHIBA, Yukio TOMINAGA, and Katsuhiko HINO

Discovery Research Laboratories II, Dainippon Pharmaceutical Company, Ltd., Enoki 33–94, Suita, Osaka 564, Japan.
Received November 4, 1997; accepted December 23, 1997

2-Aminomethyl-1-azetidinyl, -1-pyrrolidinyl, and -1-piperidinyl groups were designed as novel C-7 substituents for potential antibacterial quinolone agents. Of the three substituents, the 2-aminomethyl-1-azetidinyl group (compound 12a) was found to be the most favorable for enhancing the activity of the 6,8-difluoroquinoline molecule 12. Therefore the 2-aminomethyl-1-azetidinyl group was introduced into a variety of quinolines (giving 24—26a, and 28a) and naphthyridines (giving 31a and 32a). Through optical resolution of 1-benzylazetidine-2-carboxamide (19) and chiral synthesis of its *R*-isomer, both enantiomers of 2-aminomethyl-1-azetidinyl quinolines 12a and 24—26a were also prepared. The most active of all the compounds was 5-amino-6,8-difluoroquinoline (*R*)-26a. The activity of (*R*)-26a was more potent than those of the corresponding 1-piperazinyl derivative (3) and sparfloxacin (1), and was comparable to those of the corresponding 3-amino-1-pyrrolidinyl (4), 3-aminomethyl-1-pyrrolidinyl (5), and 3-amino-1-azetidinyl (6) derivatives.

Key words 2-aminomethylazetidine; asymmetric induction; quinolone; antibacterial activity

The synthetic quinolone antibacterials, including sparfloxacin (**1**)[2)] and tosufloxacin (**2**),[3)] show potent antibacterial activity as well as improved therapeutic efficacy against infectious diseases (Fig. 1). Most of the quinolones reported thus far possess a basic amino group in the C-7 appendage. As exemplified by **1**, the majority of the currently used quinolones are characterized structurally by a 6-fluoro-7-(1-piperazinyl)-4-oxoquinoline-3-carboxylic acid moiety as a pharmacophore for potent activity. Besides the 1-piperazinyl quinolones **1** and **3**, 3-amino-1-pyrrolidinyl[4)] (**2** and **4**), 3-aminomethyl-1-pyrrolidinyl[4)] (**5**), 3-amino-1-azetidinyl[5)] compounds (**6**) have been reported to show potent antibacterial activities, but, except for **2**, they have not been used clinically.

In our studies to discover new C-7 appendages, we found that 7-[(*Z*)-3-amino-1-propenyl]quinoline **7** showed potent antibacterial activity and was more active than the 3-amino-1-propynyl, (*E*)-3-amino-1-propenyl, and 3-amino-1-propyl derivatives.[6)] The amino group of **7** is located quite far from the terminal basic nitrogen of the conventional quinolones **1**—**4** and **6**. Owing to the flexibility of the aminomethyl moiety of **5**, the amino group of **5** can adopt a position similar, but not identical, to that in **7**. Thus, the spatial position of the amino group of **7** is unique. Since the basic amino group of a quinolone molecule is generally thought to play an important role in enhancing antibacterial activity, we speculated that compounds whose amino groups are situated in a similar position to that of **7** might show potent antibacterial activity.

On this basis, we designed 2-aminomethyl-1-azetidinyl (in A-type), -1-pyrrolidinyl (B), and -1-piperidinyl quinolones (C) as candidate antibacterials. Three-dimensional structures obtained by computer-aided molecular modeling of (*R*)-**12a, b, c**, representatives of A, B, and C, respectively, were well superimposed on that of **7** (Fig. 2, see Experimental section). The C-7 appendages of **12a, b, c** are conformationally restricted by four-, five-, and six-membered rings, respectively. Furthermore, the superimposition reveals that the ethylenediamine moieties of **12a, b, c** retain the conformation of the C-7 appendage of **7** to some extent. Hence, the 2-aminomethyl-1-azetidinyl

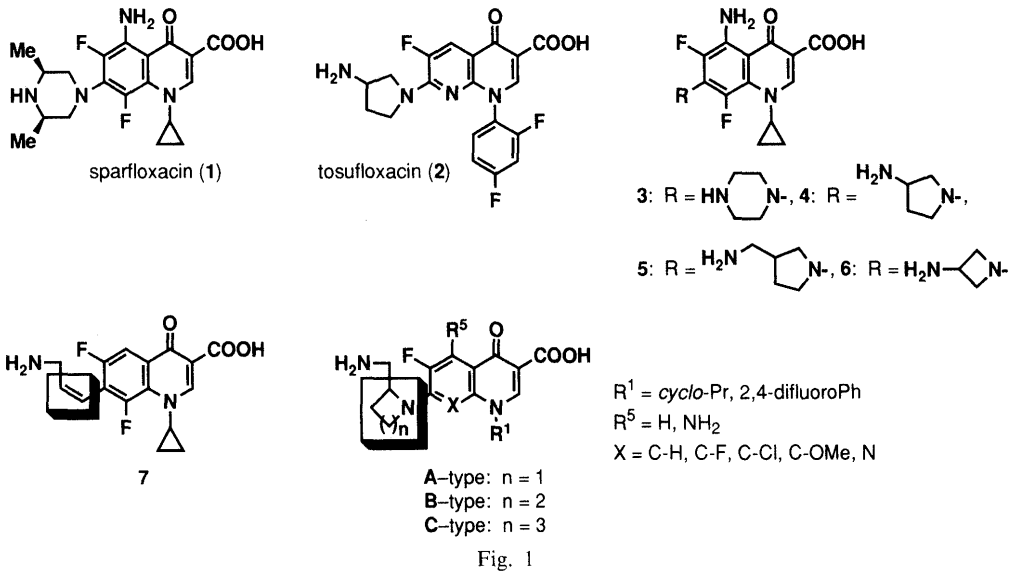


Fig. 1

* To whom correspondence should be addressed.

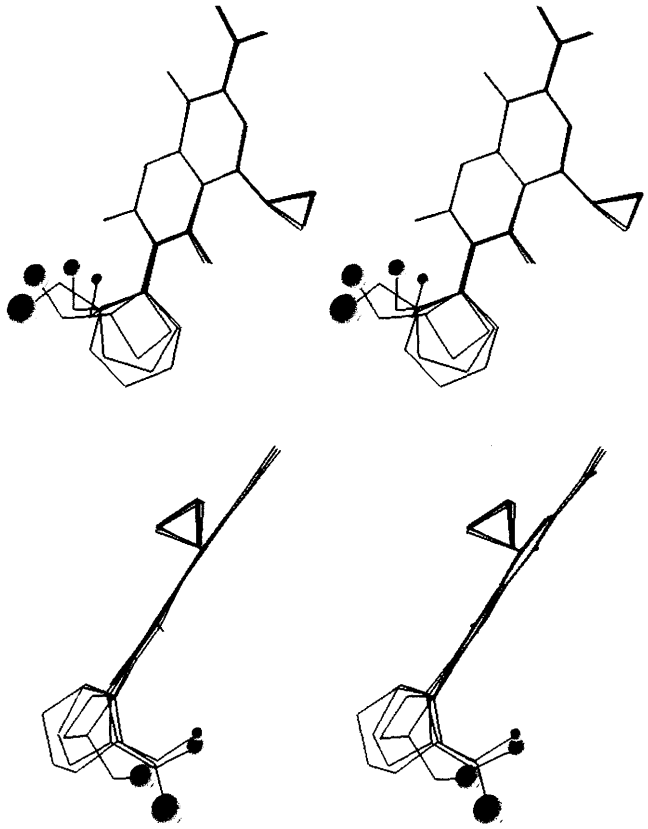


Fig. 2. Stereoview of Three-Dimensional Structures of **7** and (*R*)-**12a, b, c**.

The superimposition of the compounds is viewed approximately along a vertical axis to the quinolone rings (top) or a C(8)–C(5) axis (bottom). For clarity, the hydrogens of the quinolones were deleted. The basic nitrogen of the compounds is shown with balls: ●, **7**; ●, (*R*)-**12a**; ●, (*R*)-**12b**; •, (*R*)-**12c**.

(A), -1-pyrrolidinyl (B), and -1-piperidinyl groups (C) should work as cyclic bioisosteres of the (*Z*)-3-amino-1-propenyl group of **7**. This paper describes the synthesis and antibacterial activity of the A-, B-, and C-type quinolones.

Chemistry Firstly, we prepared the A-, B-, and C-type quinolones in the 6,8-difluoroquinoline system (namely, compounds **12a, b, c**, respectively) to investigate their antibacterial potential. The azetidinyl compound **12a** was prepared by the treatment of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**8**) with 2-aminomethylazetidine (**9**) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in pyridine (Chart 1 and Table 1).

The starting azetidine **9** had been prepared by Morikawa, *et al.*[7] The yield of **9**, however, was reported to be low, probably because **9** was extracted from water. Therefore we developed an alternative method for the preparation of **9** (Chart 2). The starting dibromoester **17** was converted to the amide **19** according to reported procedures.[8,9] The amide moiety of **19** was reduced by borane–tetrahydrofuran complex to give the diamine **20**, whose benzyl group was hydrogenated to give **9**.

Attempted substitution of **8** with 2-aminomethylpyrrolidine[10] (**10**) gave a 1 : 1 mixture of the desired product **12b** and its isomer **13b** (Chart 1). Furthermore, attempted reaction of **8** with 2-aminomethylpiperidine (**11**) gave only the undesired product **13c**. Nishimura *et al.* prepared 7-(2-aminomethyl-1-pyrrolidinyl)-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid from the corresponding 7-fluoroquinoline and 2-[(trifluoroacetylamino)methyl]pyrrolidine (**14**) for studies on its intramolecular cyclization.[11] Hence, **12b, c** were prepared in two steps according to their method; treatment of **8** with the pyrrolidine **14** and piperidine **15** gave substitution products **16b, c**, respectively, which were converted to the desired compounds **12b, c**, respectively under alkaline hydrolysis conditions. The starting piperidine derivative **15** was prepared by protection of the primary amino group of **11** with a trifluoroacetyl group.

Secondly, the quinoline nucleus of the 2-aminomethyl-1-azetidinyl compound **12a** was replaced with other quinoline and 1,8-naphthyridine nuclei, because **12a** exhibited potent antibacterial activity compared to those of **12b, c** (see Antibacterial Activity section). 6-Fluoro- (**24a**), 8-chloro-6-fluoro- (**25a**), and 5-amino-6,8-difluoro- (**26a**) quinolines were prepared from **21**, **22**, and **23**, respectively, according to the method for the preparation of **12a** (Chart 3, Table 1). 6-Fluoro-8-methoxyquinoline **28a** was prepared from the chelate **27** in two steps. The naphthyridines **31a** and **32a** were prepared by treatment of **29** and **30**, respectively, with the azetidine **9** and triethylamine in acetonitrile.

In general, biologically active molecules interact with the chiral binding site of the target enzyme and hence the chirality of the molecules has a great impact on their biological activity. As the A-type quinolones have a chiral center at C-2′ of the C-7 side chain, biological evaluation of both enantiomers of A is desirable. To obtain the required intermediates, we attempted optical resolution of **19**, which is the only crystalline material in the synthetic route to racemic **9** in Chart 2. The amide **19** was treated with 0.5 equimolar D-tartaric acid in ethanol and the resulting suspension was separated into crystalline (*S*)-**19**·D-tartaric acid and a mother liquor including (*R*)-**19** (Chart 4). Treatment of the D-tartrate salt with potassium carbonate gave (*S*)-**19** in 97% enantiomeric excess ($[\alpha]_D^{27}$ −94.9°). The amide (*S*)-**19** was converted to enantiomerically pure form ($[\alpha]_D^{29}$ −98.1°) by repetition of a similar procedure. The absolute stereochemistry at C-2 of (*S*)-**19** was confirmed after conversion of (*S*)-**19** to (*S*)-**33**, the data for which were identical with those of an authentic sample prepared from 1-(benzyloxycarbonyl)-azetidine-2-carboxylic acid [(*S*)-**34**] with established absolute structure.[12] The amide (*R*)-**19** was recovered from the foregoing mother liquor and was converted to its L-tartrate salt. Treatment of the salt with potassium carbonate gave an enantiomerically pure amide (*R*)-**19** ($[\alpha]_D^{29}$ +98.0°).

According to the method described for the preparation of the racemate **9**, the resulting optically active amides (*R*)- and (*S*)-**19** were converted to 2-aminomethylazetidines [(*R*)- and (*S*)-**9**, respectively] (Chart 5). To determine the optical purities of (*R*)- and (*S*)-**20**, they were converted to the corresponding Mosher's amides (*R*)- and (*S*)-**36**, respectively. The ^{19}F-NMR spectra of (*R*)- and (*S*)-**36** showed single peaks at −70.14 and −70.18 ppm, respectively, due to the fluorines of their trifluoromethyl groups. Therefore (*R*)- and (*S*)-**20** were optically pure.

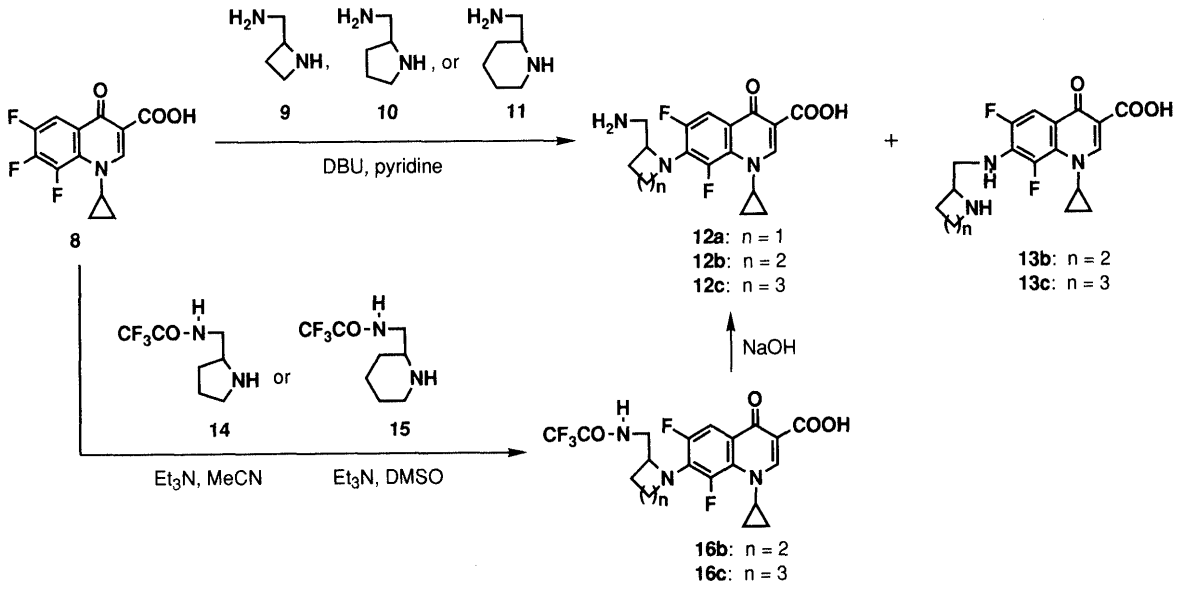


Chart 1

Table 1. Physical Data for the 2-Aminomethyl-1-azetidinyl-, -1-pyrrolidinyl-, and -1-piperidinylquinolones

Compd.	mp (°C) (recryst. solvent)	Yield (%)	Formula	Analysis (%) Calcd (Found)				
				C	H	Cl	F	N
12a	218—220 (AcOH/NH_4OH)	58	$C_{17}H_{17}F_2N_3O_3 \cdot 1/4H_2O$	57.71 (57.86)	4.99 5.09		10.74 10.78	11.88 11.92)
(*R*)-**12a**	245—246 (AcOH/NH_4OH)	70	$C_{17}H_{17}F_2N_3O_3 \cdot 1/4H_2O$	57.71 (57.68)	4.99 4.88		10.74 10.77	11.88 12.01)
(*S*)-**12a**	244—245 (AcOH/NH_4OH)	61	$C_{17}H_{17}F_2N_3O_3$	58.45 (58.54)	4.91 4.75		10.88 10.90	12.03 12.05)
12b	245—249 (dec.) (HCl–EtOH)	56	$C_{18}H_{19}F_2N_3O_3 \cdot HCl$	54.07 (53.92)	5.04 5.04	8.87 8.92	9.50 9.43	10.51 10.34)
12c	218—222 (HCl)	26	$C_{19}H_{21}F_2N_3O_3 \cdot HCl$	55.14 (55.12)	5.36 5.39	8.57 8.40	10.15 10.07	9.18 9.38)
24a	231—233 (AcOH/NH_4OH)	72	$C_{17}H_{18}FN_3O_3 \cdot 1/4H_2O$	60.80 (61.16)	5.55 5.65		5.66 5.63	12.51 12.64)
(*R*)-**24a**	259—260 (AcOH/NH_4OH)	83	$C_{17}H_{18}FN_3O_3$	61.62 (61.62)	5.48 5.27		5.73 5.58	12.68 12.85)
(*S*)-**24a**	255—257 (AcOH/NH_4OH)	71	$C_{17}H_{18}FN_3O_3$	61.62 (61.39)	5.48 5.35		5.73 5.78	12.68 12.61)
25a	229—231 (AcOH/NH_4OH)	54	$C_{17}H_{17}ClFN_3O_3$	55.82 (55.72)	4.68 4.73	9.69 9.52	5.19 5.08	11.49 11.49)
(*R*)-**25a**	196—197 (AcOH/NH_4OH)	19	$C_{17}H_{17}ClFN_3O_3 \cdot 1/4H_2O$	55.14 (55.16)	4.76 4.53	9.57 9.46	5.13 5.19	11.35 11.42)
(*S*)-**25a**	197—198 (AcOH/NH_4OH)	46	$C_{17}H_{17}ClFN_3O_3 \cdot 1/4H_2O$	55.14 (55.22)	4.76 4.70	9.57 9.46	5.13 4.93	11.35 11.36)
26a	218—221 (dec.) (AcOH/NH_4OH)	54	$C_{17}H_{18}F_2N_4O_3$	56.04 (55.69)	4.98 4.98		10.43 10.30	15.38 15.18)
(*R*)-**26a**	237—239 (dec.) (AcOH/NH_4OH)	42	$C_{17}H_{18}F_2N_4O_3 \cdot 1/4H_2O$	55.36 (55.47)	5.06 5.04		10.30 10.39	15.19 15.16)
(*S*)-**26a**	240—243 (dec.) (AcOH/NH_4OH)	43	$C_{17}H_{18}F_2N_4O_3$	56.04 (55.75)	4.98 4.99		10.43 10.42	15.38 15.23)
28a	177—180 (AcOH/NH_4OH)	56	$C_{18}H_{20}FN_3O_4 \cdot 1/4H_2O$	59.09 (59.13)	5.65 5.79		5.19 5.04	11.49 11.54)
31a	213—214 (AcOH/NH_4OH + NaOH)	76	$C_{16}H_{17}FN_4O_3 \cdot 1/4H_2O$	57.05 (57.18)	5.24 5.23		5.64 5.71	16.63 16.67)
32a	221—224 (AcOH/NH_4OH + NaOH)	78	$C_{19}H_{15}F_3N_4O_3 \cdot 1/4H_2O$	55.82 (55.78)	3.82 3.76		13.94 13.77	13.70 13.61)

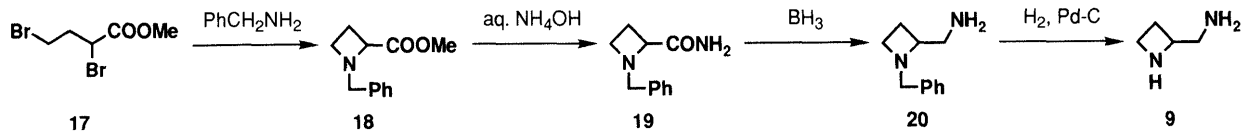


Chart 2

Furthermore, the starting amides (*R*)- and (*S*)-**19** and the products (*R*)- and (*S*)-**9** were proven to be all optically pure.

Both enantiomers of **12a**, **24a**, **25a**, and **26a** were prepared by the use of (*R*)- and (*S*)-**9** according to the methods described for the preparation of the racemates (Fig. 3 and Table 1).

As the (*R*)-enantiomers of **12a**, **24a**, **25a**, and **26a** showed more potent antibacterial activity than their antipodes (see Antibacterial Activity section), we planned to develop an efficient synthetic route for (*R*)-**19**, the key intermediate for the preparation of (*R*)-**12a**, **24a**, **25a**, and **26a**. Kubota *et al.* reported a novel asymmetric induction, in which racemic 2-bromoacyl bromides were converted to enantiomerically pure (*R*)-amino acids in two steps by using the auxiliary chirality of *tert*-butyl (*S*)-1-methyl-2-oxoimidazolidine-4-carboxylate[13] [(*S*)-**37**]. We decided to prepare enantiomer (*R*)-**19** through a similar asymmetric induction reaction. The route for the preparation of (*R*)-**19** was a modification of the synthetic route for the racemate **19** in Chart 2 (Chart 6). The carboxylic acid **38** was converted to the acid chloride **39**, which was condensed with the chiral auxiliary (*S*)-**37** to give an 11:9 diastereomeric mixture of the intermediate **40**. On treatment with benzylamine, **40** gave the azetidine (*R*)-**41** in 73% yield. Compound (*R*)-**41** was treated with ammonia in ethanol to afford the amide (*R*)-**19** ($[\alpha]_D^{29}$ +96.3°), together with recovery of the starting chiral auxiliary (*S*)-**37** without racemization. Recrystallization of (*R*)-**19** gave an optically pure sample ($[\alpha]_D^{29}$ +98.3°), the data for which were identical with those of the sample obtained by the optical resolution of **19**.

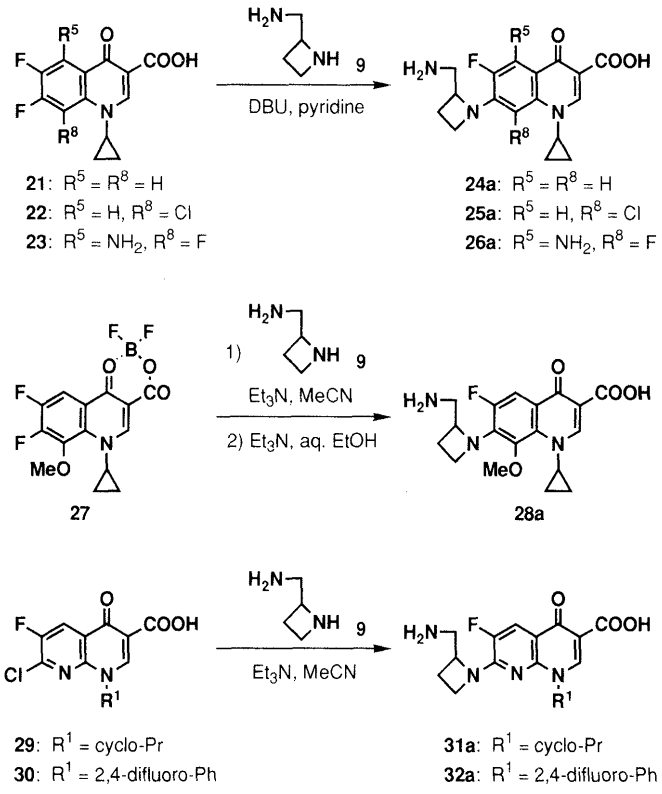


Chart 3

Antibacterial Activity The *in vitro* antibacterial activity of the prepared compounds **12a, b, c**, (*R*)- and (*S*)-**12a**, **24**—**26a**, (*R*)- and (*S*)-**24**—**26a**, **28a**, **31a**, and **32a** was tested against one Gram-positive [*Staphylococcus* (*S.*) *aureus* 209P JC-1] and two Gram-negative bacteria [*Escherichia* (*E.*) *coli* NIHJ JC-2 and *Pseudomonas* (*P.*) *aeruginosa* 12] as representatives. The results are summarized in Table 2, which also includes the data for sparfloxacin (**1**) and **3**—**7** for comparison.

In the case of **12a, b, c**, the activity against the three bacteria decreased in the order 2-aminomethyl-1-azetidinyl (**12a**) > 2-aminomethyl-1-pyrrolidinyl (**12b**) ≥ 2-aminomethyl-1-piperidinyl groups (**12c**). The changes of the activity of **12a, b, c** are presumably caused by differences in amino group positions as follows. The superimposition of the three-dimensional structures of (*R*)-**12a, b, c** given in Fig. 2 shows that the distances between the amino groups and the quinoline nuclei of **12a, b, c** decrease in the order **12a** > **12b** > **12c**. Thus, the spatial position of the amino group of **12a, b, c** seems to affect the order of the antibacterial activity.

The relationship between the activity and the amino group position of the 7-[(*Z*)-3-amino-1-propenyl]quinoline **7** led us to design the A-, B-, and C-type quinolones, such as **12a, b, c**, respectively. The most potent of the three, the 2-aminomethyl-1-azetidinyl derivative **12a** was 8-fold more active against a Gram-positive bacterium (*S. aureus*)

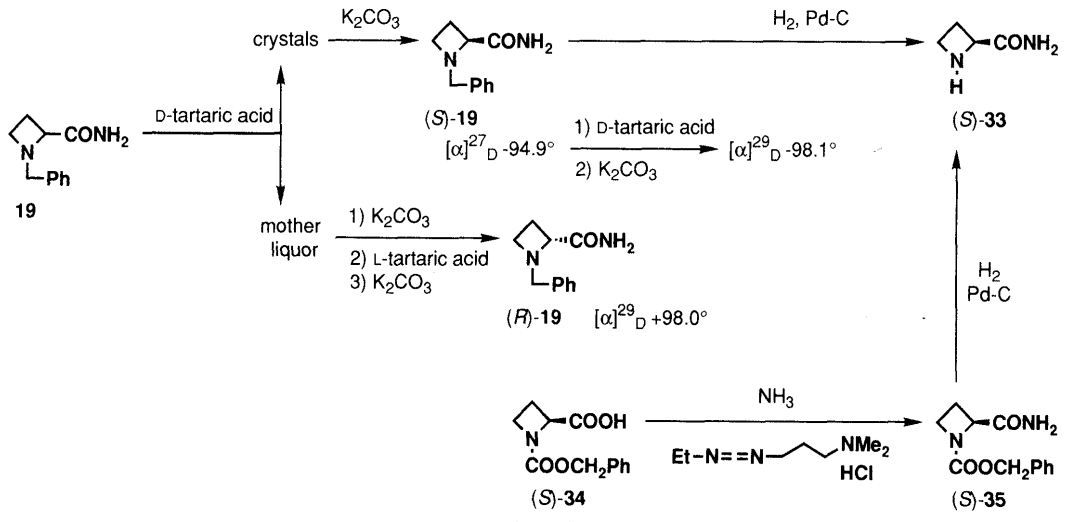


Chart 4

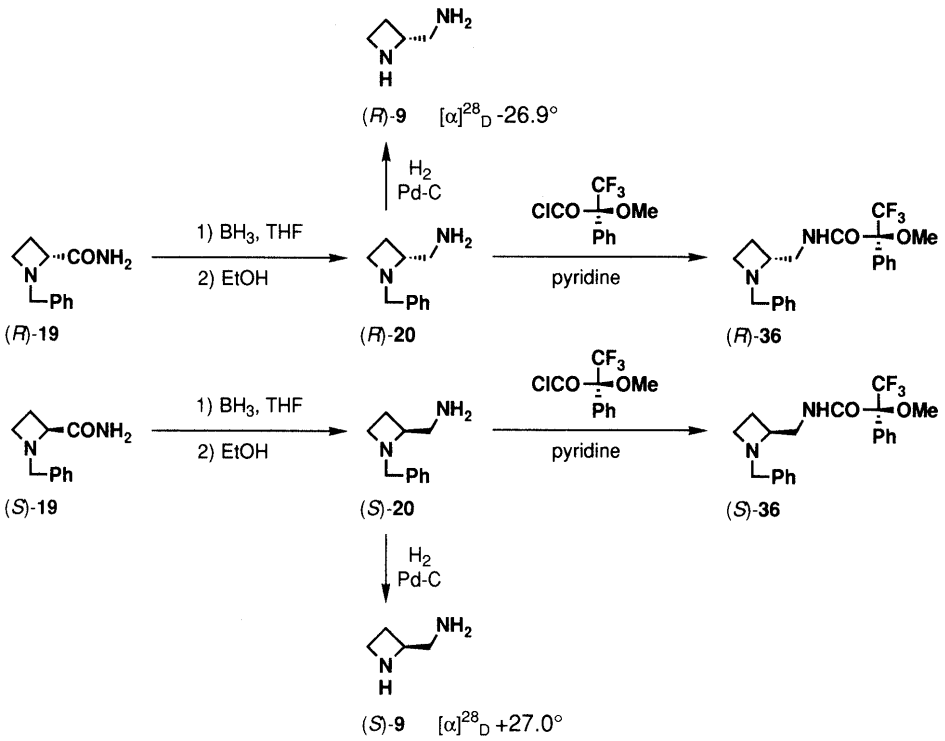


Chart 5

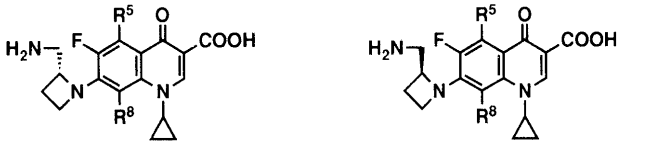


Fig. 3

and 2-fold more active against Gram-negative bacteria (*E. coli* and *P. aeruginosa*) than the lead compound **7**. The design of the A-type compounds (*e.g.*, **12a**) starting from **7** was thus successful.

When the quinoline nucleus of **12a** was replaced with other quinoline nuclei (giving **24**—**26a** and **28a**), **24**—**26a** and **28a** almost wholly retained the antibacterial activity of **12a** against the Gram-positive bacterium (*S. aureus*). Against *E. coli*, the 8-chloro-6-fluoro- and 5-amino-6,8-difluoroquinolines **25a** and **26a**, respectively, were at least four times more active than **12a**, while the other racemic quinolines **24a** and **28a** were equipotent to or less active than **12a**. Against *P. aeruginosa*, **24**—**26a** almost wholly retained the antibacterial activity of **12a**, whereas **28a** was less active than **12a**. The 1,8-naphthyridines **31a** and **32a** exhibited generally less potent antibacterial activity than **12a**, with the exception that **31a** is equipotent to **12a** against *E. coli*. Among the racemic compounds, the most active was the 5-amino-6,8-difluoroquinoline **26a**.

In the 6,8-difluoroquinoline system [**12a**, (*R*)-**12a**, and (*S*)-**12a**], the *R*-enantiomer (*R*)-**12a** was more than thirty times more active than the antipode (*S*)-**12a** and consequently was twice as active as the racemate **12a**. Similar results were obtained in comparisons of the activity of enantiomers possessing other quinoline ring systems [*i.e.*, (*R*)- *vs.* (*S*)-**24**—**26**]. Thus far, antibacterial activity has been reported for quinolones having chiral C-7 appendages. For example, the chirality of the 3-methyl-1-piperazinyl group scarcely influenced the activity[2,14] and that of the 3-amino-1-pyrrolidinyl group of **2** gave rise to less than sixteen-fold difference in the activity between its enantiomers.[15] It is notable that the chirality at C-2 of the azetidinyl group affected the antibacterial activity to a much greater extent than that of the 1-piperazinyl or the 1-pyrrolidinyl group.

Quinolone antibacterials inhibit bacterial DNA topoisomerases II (DNA gyrase[16]) and IV[17] and thereby kill the bacteria. The structures of the quinolone-binding sites of the target enzymes have not been fully elucidated,[18,19] but are presumed to be chiral. The three-dimensional structure of (*R*)-**12a** given in Fig. 2 suggests that the amino group of (*R*)-**12a** is far from that of (*S*)-**12a**. Thus, we assume that (*R*)-**12a** would fit better into the binding sites than (*S*)-**12a**, causing more potent enzyme inhibition and hence more potent antibacterial activity.

Compounds (*R*)-**12a**, (*R*)-**25a**, **26a**, and (*R*)-**26a** surpassed sparfloxacin (**1**) in their antibacterial activity against three species of bacteria tested. Among all the compounds in this study, (*R*)-**26a** was the most active, being more potent than the corresponding 1-piperazinyl compound (**3**). The activity of the 2-aminomethyl-1-azetidinyl compound (*R*)-**26a** was comparable to those of the corresponding 3-amino-1-pyrrolidinyl (**4**), 3-aminomethyl-1-pyrrolidinyl (**5**), and 3-amino-1-azetidinyl (**6**) compounds.

In conclusion, we prepared 7-(2-aminomethyl-1-azetidinyl, -1-pyrrolidinyl, or -1-piperidinyl)-6,8-difluoro-4-oxoquinolines **12a**—**c** and compared their antibacterial ac-

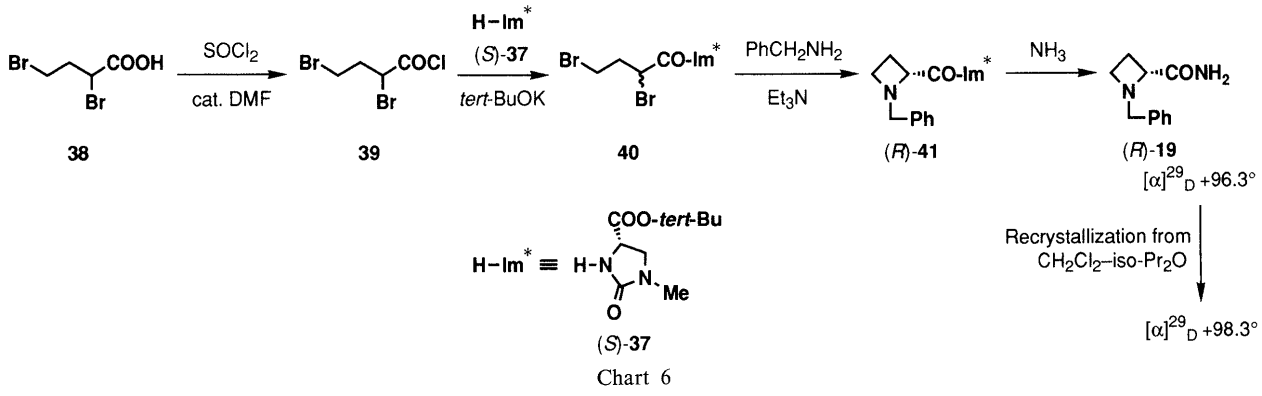
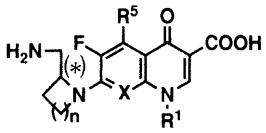


Chart 6

Table 2. Antibacterial Activity of the 2-Aminomethyl-1-azetidinyl-, -1-pyrrolidinyl-, and -1-piperidinylquinolones



Compd.	R^1	R^5	X	C-7 Appendage		Minimum inhibitory conc.[a] (μg/ml)		
				n	Chirality	*S. aureus* 209P JC-1	*E. coli* NIHJ JC-2	*P. aeruginosa* 12
12a	c-C_3H_5	H	C–F	1	—	0.05	0.0125	0.1
(*R*)-**12a**	c-C_3H_5	H	C–F	1	*R*	0.025	≤0.003	0.1
(*S*)-**12a**	c-C_3H_5	H	C–F	1	*S*	0.78	0.2	6.25
12b	c-C_3H_5	H	C–F	2	—	0.1	0.025	0.39
12c	c-C_3H_5	H	C–F	3	—	0.1	0.1	1.56
24a	c-C_3H_5	H	C–H	1	—	0.1	0.025	0.2
(*R*)-**24a**	c-C_3H_5	H	C–H	1	*R*	0.05	0.006	0.2
(*S*)-**24a**	c-C_3H_5	H	C–H	1	*S*	0.78	0.2	3.13
25a	c-C_3H_5	H	C–Cl	1	—	0.05	≤0.003	0.2
(*R*)-**25a**	c-C_3H_5	H	C–Cl	1	*R*	0.025	≤0.003	0.1
(*S*)-**25a**	c-C_3H_5	H	C–Cl	1	*S*	0.78	0.2	3.13
26a	c-C_3H_5	NH_2	C–F	1	—	0.025	≤0.003	0.1
(*R*)-**26a**	c-C_3H_5	NH_2	C–F	1	*R*	0.0125	≤0.003	0.05
(*S*)-**26a**	c-C_3H_5	NH_2	C–F	1	*S*	0.39	0.2	3.13
28a	c-C_3H_5	H	C–OMe	1	—	0.05	0.05	0.78
31a	c-C_3H_5	H	N	1	—	0.39	0.0125	0.2
32a	2,4-F_2Ph	H	N	1	—	0.2	0.025	0.39
1	c-C_3H_5	NH_2	C–F			0.05	0.0125	0.39
3	c-C_3H_5	NH_2	C–F			0.05	0.0125	0.1
4	c-C_3H_5	NH_2	C–F			0.025	0.0125	0.05
5	c-C_3H_5	NH_2	C–F			0.0125	0.025	0.2
6	c-C_3H_5	NH_2	C–F			0.025	≤0.006	0.1
7	c-C_3H_5	H	C–F			0.39	0.025	0.2

a) See Experimental.

tivity. The azetidinyl compound **12a** was the most active of the three. Hence, 2-aminomethyl-1-azetidinyl compounds having other quinoline (**24**—**26a** and **28a**) or 1,8-naphthyridine (**31a** and **32a**) nuclei were prepared. Optically active 2-aminomethyl-1-azetidinyl compounds were also prepared. The *R*-isomers (*R*)-**12a** and (*R*)-**24**—**26a** were much more active than the corresponding *S*-isomers. The most active in this study was the sparfloxacin-type compound (*R*)-**26a**; its antibacterial activity surpassed that of the corresponding 1-piperazinyl derivative (**3**) or sparfloxacin (**1**) itself.

Experimental

Chemistry All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Jasco A-102 or Perkin Elmer 1600 Series FTIR

spectrophotometer. ^{1}H-NMR spectra were taken at 200 MHz on a Varian Gemini-200 spectrometer; chemical shifts are expressed in ppm (δ) with tetramethylsilane or 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as internal standards. ^{19}F-NMR spectra were measured at 470 MHz on a Varian UNITY INOVA spectrometer; chemical shifts are expressed in ppm (δ) with hexafluorobenzene ($\delta=-162.9$) as an internal standard. Chemical ionization (CI), secondary ion (SI) and atmospheric pressure chemical ionization (APCI) mass spectra (MS) were obtained on a JEOL JMS D-300 mass spectrometer, a Hitachi M-80B mass spectrometer, and a Hitachi M-1000 LC API mass spectrometer, respectively. Specific rotations were measured with a Jasco DIP-370 digital polarimeter. All compounds which were stable solids were analyzed for C, H, Cl, F, and N.

2-Aminomethylpiperidine (**11**) was provided by Koei Chemical Co., Ltd. 7-Chloro-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**30**) was obtained by hydrolysis (AcOH–H_2O–H_2SO_4 8:6:1 v/v, reflux, 1 h) of ethyl 7-chloro-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate.[3]

2-Aminomethyl-1-benzylazetidine (20) Borane–tetrahydrofuran (THF) complex (1 mol/l THF solution, 800 ml, 0.800 mol) was added to a mixture of 1-benzylazetidine-2-carboxamide[9] (**19**, 50.0 g, 0.263 mol) in THF (500 ml) under ice-cooling. The mixture was stirred at room temperature for 2 h and then heated at reflux for 8 h. The solvent was distilled off under reduced pressure and EtOH (500 ml) was added to the resulting residue. The whole mixture was heated at reflux for 20 h and concentrated *in vacuo* to leave a residue. The residue was taken up with a mixture of AcOEt and cold diluted NaOH. The organic phase was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated *in vacuo* to leave a residue, which was distilled to give 38.5 g (83%) of **20**, bp 93—96 °C (4 mmHg). IR (neat) cm^{-1}: 3370, 3292. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (2H, br s, NH_2), 1.9—2.05 (2H, m, 3-H), 2.57 (2H, dt, $J=5.0$, 13.5 Hz, C$\underline{H}_2$NH$_2$), 2.87 (1H, ddd, $J=9.0$, 9.0, 7.0 Hz, 4-H), 3.15—3.4 (2H, m, 2-H, 4-H), 3.55 and 3.68 (both 1H, d, $J=13.0$ Hz, C$\underline{H}_2$Ph), 7.15—7.35 (5H, m, Ph). APCIMS *m/z*: 177 ($M^+ + 1$).

2-Aminomethylazetidine (9) A solution of **20** (10.00 g, 56.8 mmol) in EtOH (100 ml) was hydrogenated over 5% Pd–C (3.00 g) at 40—50 °C for 22 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was distilled to give 2.66 g (54%) of **9**, bp 83—84 °C (60 mmHg) [lit.[7] bp 53—55 °C (33—35 mmHg)]. IR (neat) cm^{-1}: 3355, 3274, 1101. ^{1}H-NMR ($CDCl_3$) δ: 1.53 (3H, br s, 1-H, NH_2), 1.95—2.35 (2H, m, 3-H), 2.76 (2H, d, $J=6.0$ Hz, C$\underline{H}_2$NH$_2$), 3.33 (1H, ddd, $J=8.5$, 7.5, 4.0 Hz, 4-H), 3.66 (1H, ddd, $J=8.5$, 8.5, 7.5 Hz, 4-H), 3.88 (1H, ddt, $J=7.5$, 7.5, 6.0 Hz, 2-H). APCIMS *m/z*: 87 ($M^+ + 1$), 70.

5,8-Disubstituted 7-(2-Aminomethyl-1-azetidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids [12a, 24—26a, (*R*)- and (*S*)-12a, and (*R*)- and (*S*)-24—26a] 7-(2-Aminomethyl-1-azetidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**12a**): A mixture of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid[20] (**8**, 500 mg, 1.78 mmol), **9** (227 mg, 2.64 mmol), and DBU (269 mg, 1.77 mmol) in pyridine (10 ml) was heated at 80 °C for 1 h. The solvent was distilled off *in vacuo*. The residue was triturated with EtOH. The resultant crystals were collected by filtration, washed with EtOH, and then dried to give 544 mg of crude crystals. The crystals were dissolved in aqueous AcOH. The resulting solution was treated with charcoal and filtered. Evaporation of water and AcOH under reduced pressure left a residue. This was dissolved in water and the resulting solution was neutralized with aqueous NH_4OH, giving precipitates, which were collected by filtration, washed with water, and dried to give 362 mg (58%) of **12a**. Physical data are given in Table 1. IR (KBr) cm^{-1}: 3420, 1623, 1583. ^{1}H-NMR (CD_3COOD) δ: 1.1—1.4 (4H, m, cyclopropyl C$\underline{H}_2$C$\underline{H}_2$), 2.4—2.75 (2H, m, azetidinyl 3-H), 3.4—3.7 (2H, m, C$\underline{H}_2$NH$_3^+$), 4.0—4.15 (1H, m, cyclopropyl CH), 4.15—4.4 and 4.4—4.6 (both 1H, m, azetidinyl 4-H), 5.1—5.3 (1H, m, azetidinyl 2-H), 7.83 (1H, d, $J=12.5$ Hz, 5-H), 8.80 (1H, s, 2-H). SIMS *m/z*: 350 ($M^+ + 1$), 332.

According to this procedure, compounds **21**,[20] **22**,[21] and **23**[2] were treated with **9** to afford **24a**, **25a**, and **26a**, respectively. Compounds **8**, **21**, **22**, and **23** were treated with (*R*)- or (*S*)-**9** to give (*R*)- or (*S*)-**12a**, **24a**, **25a**, and **26a**, respectively. Yields and physical data are given in Table 1.

Compound (*R*)-**12a**: $[\alpha]_D^{29}$ −17.5° ($c=1.008$, 1 mol/l NaOH).

Compound (*S*)-**12a**: $[\alpha]_D^{29}$ +17.8° ($c=1.134$, 1 mol/l NaOH).

Compound **24a**: IR (KBr) cm^{-1}: 3370, 1725, 1618. ^{1}H-NMR [dimethyl sulfoxide (DMSO)-d_6] δ: 1.0—1.4 (4H, m, cyclopropyl C$\underline{H}_2$C$\underline{H}_2$), 2.1—2.6 (2H, m, azetidinyl 3-H), 2.94 (2H, d, $J=5.5$ Hz, C$\underline{H}_2$NH$_2$), 3.65—3.8 and 4.13—4.3 (both 1H, m, azetidinyl 4-H), 3.95—4.13 (1H, m, cyclopropyl CH), 4.35—4.5 (1H, m, azetidinyl 2-H), 6.3 (2H, br s, NH_2), 7.23 (1H, d, $J=6.0$ Hz, 8-H), 7.79 (1H, d, $J=12.0$ Hz, 5-H), 8.56 (1H, s, 2-H). APCIMS *m/z*: 332 ($M^+ + 1$).

Compound (*R*)-**24a**: $[\alpha]_D^{29}$ +24.1° ($c=1.043$, 1 mol/l NaOH).

Compound (*S*)-**24a**: $[\alpha]_D^{29}$ −25.3° ($c=1.030$, 1 mol/l NaOH).

Compound **25a**: IR (KBr) cm^{-1}: 3450, 1619, 1581. ^{1}H-NMR (CD_3COOD) δ: 0.8—1.05, 1.05—1.3, and 1.3—1.55 (each 1H, 2H, and 1H, m, cyclopropyl C$\underline{H}_2$C$\underline{H}_2$), 2.4—2.75 (2H, m, azetidinyl 3-H), 3.4—3.65 (2H, m, C$\underline{H}_2$NH$_3^+$), 4.0—4.2 (1H, m, cyclopropyl CH), 4.3—4.5 and 4.8—5.0 (both 1H, m, azetidinyl 4-H), 5.3—5.5 (1H, m, azetidinyl 2-H), 7.92 (1H, d, $J=15.0$ Hz, 5-H), 9.00 (1H, s, 2-H). SIMS *m/z*: 366 ($M^+ + 1$), 348.

Compound (*R*)-**25a**: $[\alpha]_D^{30}$ −120.1° ($c=1.020$, 1 mol/l NaOH).

Compound (*S*)-**25a**: $[\alpha]_D^{30}$ +122.5° ($c=1.006$, 1 mol/l NaOH).

Compound **26a**: IR (KBr) cm^{-1}: 3420, 1721, 1638, 1632. ^{1}H-NMR (DMSO-d_6) δ: 0.9—1.2 (4H, m, cyclopropyl C$\underline{H}_2$C$\underline{H}_2$), 2.1—2.6 (2H, m, azetidinyl 3-H), 2.88 (2H, d, $J=5.0$ Hz, C$\underline{H}_2$NH$_2$), 3.85—4.05 and 4.3—4.5 (both 1H, m, azetidinyl 4-H), 4.05—4.25 (1H, m, cyclopropyl CH), 4.5—4.7 (1H, m, azetidinyl 2-H), 6.0 (2H, br s, CH$_2$N$\underline{H}_2$), 7.12 (2H, br s, 5-NH_2), 8.41 (1H, s, 2-H). APCIMS *m/z*: 365 ($M^+ + 1$).

Compound (*R*)-**26a**: $[\alpha]_D^{30}$ −96.6° ($c=1.042$, 1 mol/l NaOH).

Compound (*S*)-**26a**: $[\alpha]_D^{30}$ +97.5° ($c=1.021$, 1 mol/l NaOH).

7-(2-Aminomethyl-1-azetidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic Acid (**28a**): A mixture of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid BF_2 chelate[22] (**27**, 800 mg, 2.33 mmol), **9** (413 mg, 4.80 mmol), and Et_3N (0.78 ml, 566 mg, 5.60 mmol) in MeCN (6.0 ml) was stirred at room temperature for 17 h and then heated at 50 °C for 1 h. The solvent was distilled off *in vacuo*. EtOH (20 ml), water (0.5 ml), and Et_3N (2.0 ml) were added to the resulting residue and the whole was heated to reflux for 10 h. The solvent was distilled off *in vacuo*. The residue was triturated with EtOH. The resultant crystals were collected by filtration, washed successively with EtOH and with iso-Pr_2O, and then dried to give 649 mg of crude crystals. According to the method for the purification of **12a**, the crystals were reprecipitated on treatment with aqueous AcOH and subsequently with aqueous NH_4OH to afford 479 mg (56%) of **28a**. IR (KBr) cm^{-1}: 3423, 1621, 1579. ^{1}H-NMR (DMSO-d_6) δ: 0.7—1.3 (4H, m, cyclopropyl C$\underline{H}_2$C$\underline{H}_2$), 2.1—2.6 (2H, m, azetidinyl 3-H), 2.75—3.0 (2H, m, C$\underline{H}_2$NH$_2$), 3.60 (3H, s, OMe), 4.0—4.2 (2H, m, cyclopropyl CH and azetidinyl 4-H), 4.35—4.65 (2H, m, azetidinyl 2-H and 4-H), 6.15 (2H, br s, NH_2), 7.62 (1H, d, $J=13.0$ Hz, 5-H), 8.62 (1H, s, 2-H). SIMS *m/z*: 362 ($M^+ + 1$), 344.

1-Cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-[2-[(trifluoroacetylamino)methyl]-1-pyrrolidinyl]quinoline-3-carboxylic Acid (16b) A mixture of **8** (1.67 g, 5.90 mmol), 2-[(trifluoroacetylamino)methyl]pyrrolidine[11] (**14**, 1.73 g, 8.83 mmol), and Et_3N (5.76 ml, 4.18 g, 41.3 mmol) in MeCN (33 ml) was heated to reflux for 18 h. The solvent was distilled off *in vacuo* to leave a residue, which was triturated with cold dilute AcOH. The resultant crystals were collected by filtration, washed successively with water and EtOH, and then dried to give 2.41 g (89%) of **16b**, mp 231—232 °C ($CHCl_3$–EtOH). IR (KBr) cm^{-1}: 3470, 3247, 1718, 1623. ^{1}H-NMR (DMSO-d_6) δ: 1.0—1.4 (4H, m, cyclopropyl C$\underline{H}_2$C$\underline{H}_2$), 1.6—2.3 (4H, m, pyrrolidinyl 3,4-H), 3.2—3.5 (3H, m, pyrrolidinyl 5-H, C$\underline{H}_2$–NH), 3.7—3.9 (1H, m, cyclopropyl CH), 4.0—4.2 (1H, m, pyrrolidinyl 2-H), 4.35—4.5 (1H, m, pyrrolidinyl 5-H), 7.74 (1H, dd, $J=12.0$, 2.0 Hz, 5-H), 8.66 (1H, s, 2-H), 9.44 (1H, br t, $J=6.5$ Hz, NH), 14.82 (1H, br s, COOH). SIMS *m/z*: 460 ($M^+ + 1$), 415, 333. *Anal.* Calcd for $C_{20}H_{18}F_5N_3O_4$: C, 52.29; H, 3.95; F, 20.68; N, 9.15. Found: C, 52.41; H, 3.96; F, 20.42; N, 9.11.

2-[(Trifluoroacetylamino)methyl]piperidine (15) Ethyl trifluoroacetate (3.30 ml, 3.94 g, 27.7 mmol) was added to a mixture of **11** (3.00 g, 26.3 mmol) and Et_3N (4.10 ml, 2.98 g, 29.4 mmol) in EtOH (15 ml) under ice-cooling. The whole mixture was stirred at room temperature for 18 h and concentrated *in vacuo* to leave a residue, which was chromatographed on silica gel with $CHCl_3$–EtOH (3:1) to give 5.13 g (93%) of **15**, mp 82—84 °C (iso-Pr_2O–*n*-hexane). IR (KBr) cm^{-1}: 3276, 1722, 1706, 1692. ^{1}H-NMR ($CDCl_3$) δ: 1.05—2.1 (7H, m, 1,3,4,5-H), 2.55—2.85 (2H, m, 2,6-H), 3.0—3.15 (1H, m, 6-H), 3.18 (1H, dd, $J=13.5$, 7.5 Hz, CH$\underline{H}$–NHCO), 3.43 (1H, dd, $J=13.5$, 4.0 Hz, C$\underline{H}$H–NHCO), 7.1 (1H, br s, NHCO). APCIMS *m/z*: 211 ($M^+ + 1$). *Anal.* Calcd for $C_8H_{13}F_3N_2O$: C, 45.71; H, 6.23; F, 27.11; N, 13.33. Found: C, 45.93; H, 6.10; F, 27.03; N, 13.03.

1-Cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-[2-[(trifluoroacetylamino)methyl]-1-piperidinyl]quinoline-3-carboxylic Acid (16c) A mixture of **8** (1.30 g, 4.59 mmol), **15** (1.16 g, 5.52 mmol), and Et_3N (1.92 ml, 1.39 g, 13.8 mmol) in DMSO (10 ml) was heated at 80—90 °C for 65 h. The solvent was distilled off *in vacuo*. The residue was triturated with EtOH. The resultant crystals were collected by filtration, washed successively with EtOH and iso-Pr_2O, and then dried to give 461 mg (21%) of **16c**, mp 228—229 °C ($CHCl_3$–EtOH). IR (KBr) cm^{-1}: 3450, 3314, 1726, 1701, 1619. ^{1}H-NMR (DMSO-d_6) δ: 1.0—1.35 (4H, m, cyclopropyl $C\underline{H}_2C\underline{H}_2$), 1.35—2.0 (6H, m, piperidinyl 3,4,5-H), 3.0—3.9 (5H, m, piperidinyl 2,6-H, $C\underline{H}_2$–NH, and cyclopropyl CH), 4.0—4.15 (1H, m, piperidinyl 6-H), 7.80 (1H, dd, J=12.0, 2.0 Hz, 5-H), 8.70 (1H, s, 2-H), 9.30 (1H, br t, J=6.0 Hz, NH) SIMS *m/z*: 474 (M^++1), 347. *Anal.* Calcd for $C_{21}H_{20}F_5N_3O_4$: C, 53.28; H, 4.26; F, 20.07; N, 8.88. Found: C, 53.28; H, 4.28; F, 19.95; N, 8.82.

7-(2-Aminomethyl-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (12b) A solution of **16b** (1.60 g, 3.48 mmol) in 1 N NaOH (10.0 ml, 10.0 mmol) was heated at 50—60 °C for 40 min. It was filtered and the filtrate was neutralized with dilute AcOH. The resulting precipitates were collected by filtration, washed with water, and then dried to give crude crystals. Recrystallization of the crystals from aqueous HCl–EtOH gave 776 mg (56%) of **12b**·HCl. Physical data are given in Table 1. IR (KBr) cm^{-1}: 3422, 1721, 1627. ^{1}H-NMR (D_2O) δ: 1.1—1.5 (4H, m, cyclopropyl $C\underline{H}_2C\underline{H}_2$), 1.65—2.5 (4H, m, pyrrolidinyl 3,4-H), 3.11 (1H, dd, J=13.0, 6.5 Hz, $CH\underline{H}$–NH), 3.29 (1H, dd, J=13.0, 3.5 Hz, $CH\underline{H}$–NH), 3.4—3.6, 3.85—4.05, 4.05—4.25, and 4.45—4.7 (each 1H, m, cyclopropyl CH and pyrrolidinyl 2,5-H), 7.60 (1H, dd, J=13.0, 1.5 Hz, 5-H), 8.74 (1H, s, 2-H). SIMS *m/z*: 364 (M^++1), 347.

7-(2-Aminomethyl-1-piperidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (12c) Compound **16c** was treated according to the procedure used for the preparation of **12b**·HCl to give **12c**·HCl. Yield and physical data are given in Table 1. IR (KBr) cm^{-1}: 1729, 1616. ^{1}H-NMR (D_2O) δ: 1.1—1.5 (4H, m, cyclopropyl $C\underline{H}_2C\underline{H}_2$), 1.6—2.2 (6H, m, piperidinyl 3,4,5-H), 2.4—2.75 (2H, m, piperidinyl 3-H), 3.15—3.6 (4H, m, piperidinyl 6-H, $C\underline{H}_2NH_3^+$), 3.85—4.0 (1H, m, piperidinyl 2-H), 4.05—4.25 (1H, m, cyclopropyl CH), 7.69 (1H, d, J=12.5 Hz, 5-H), 8.79 (1H, s, 2-H). SIMS *m/z*: 378 (M^++1).

7-(2-Aminomethyl-1-azetidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (31a) A mixture of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid[23] (**29**, 1.00 g, 3.54 mmol), **9** (464 mg, 5.40 mmol), and Et_3N (1.20 ml, 871 mg, 8.61 mmol) in MeCN (20 ml) was heated at 60 °C for 1 h and then cooled to room temperature. The resultant precipitates were collected by filtration, washed successively with EtOH and with iso-Pr_2O, and dried to give 1.22 g of crude product. According to the method used for the purification of **12a**, this product was reprecipitated on treatment with aqueous AcOH and further with a mixture of aqueous NaOH and aqueous NH_4OH to give 905 mg (76%) of **31a**. Physical data are given in Table 1. IR (KBr) cm^{-1}: 3386, 1634, 1579. ^{1}H-NMR (DMSO-d_6) δ: 0.9—1.3 (4H, m, cyclopropyl $C\underline{H}_2C\underline{H}_2$), 2.25—2.65 (2H, m, azetidinyl 3-H), 3.00 and 3.10 (both 1H, both dd, each J=13.0, 4.0 Hz and J=13.0, 6.0 Hz, $C\underline{H}_2NH_2$), 3.6—3.75 (1H, m, azetidinyl 4-H), 4.2—4.4 (2H, m, cyclopropyl CH and azetidinyl 4-H), 4.55—4.7 (1H, m, azetidinyl 2-H), 6.3 (2H, br s, NH_2), 7.95 (1H, d, J=13.0 Hz, 5-H), 8.56 (1H, s, 2-H). SIMS *m/z*: 333 (M^++1), 315.

7-(2-Aminomethyl-1-azetidinyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (32a) Compound **30** was treated according to the procedure described for the preparation of **31a** to give **32a**. Yield and physical data are given in Table 1. IR (KBr) cm^{-1}: 3420, 1636. ^{1}H-NMR (CD_3COOD) δ: 2.4—2.6 (2H, m, azetidinyl 3-H), 3.0—3.35 (2H, m, $C\underline{H}_2NH_3^+$), 4.2—4.5 (2H, m, azetidinyl 4-H), 4.6—4.8 (1H, m, azetidinyl 2-H), 7.1—7.35 and 7.6—7.8 (each 2H and 1H, m, 1-$C_6F_2H_3$), 8.20 (1H, d, J=11.5 Hz, 5-H), 8.88 (1H, s, 2-H). SIMS *m/z*: 405 (M^++1), 387.

Optical Resolution of 1-Benzylazetidine-2-carboxamide [(*R*)-19 and (*S*)-19] a) A mixture of racemic 1-benzylazetidine-2-carboxamide (**19**, 35.0 g, 0.184 mol) and D-tartaric acid (14.0 g, 93.3 mmol) in EtOH (250 ml) was heated at reflux for 30 min and cooled to room temperature. The resultant crystals were collected by filtration, washed with EtOH, and then dried to give 28.75 g of (*S*)-**19**·D-tartaric acid. The crystals were dissolved in water (200 ml). The resulting solution was treated with K_2CO_3 (25.0 g) and the liberated amide was extracted twice with $CHCl_3$. The combined organic phase was dried over Na_2SO_4. Evaporation of the solvent under reduced pressure left a residual oil, which was crystallized from a mixture of iso-Pr_2O. The resultant crystals were collected by filtration, washed with iso-Pr_2O, and then dried to give 15.52 g (44%) of (*S*)-**19**, $[\alpha]_D^{27}$ −94.9° (*c*=1.02, $CHCl_3$). IR (KBr) cm^{-1}: 3358, 1685, 1653. ^{1}H-NMR ($CDCl_3$) δ: 2.05—2.5 (2H, m, 3-H), 3.01 (1H, ddd, J=9.5, 8.0, 7.0 Hz, 4-H), 3.3—3.42 (1H, m, 4-H), 3.57 and 3.73 (both 1H, d, J=13.0 Hz, $C\underline{H}_2$Ph), 3.68 (1H, dd, J=8.5, 8.5 Hz, 2-H), 5.30 and 6.98 (both 1H, br s, NH_2), 7.2—7.4 (5H, m, Ph). APCIMS *m/z*: 191 (M^++1).

b) According to the above procedure, (*S*)-**19** obtained above was treated with D-tartaric acid (0.97 eq mol) again to affford (*S*)-**19**·D-tartaric acid. Treatment of the salt with K_2CO_3 (2.0 eq mol) gave optically pure (*S*)-**19**, mp 91—92 °C, $[\alpha]_D^{29}$ −98.1° (*c*=1.01, $CHCl_3$). *Anal.* Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.17; H, 7.42; N, 14.58.

c) The mother liquor of (*S*)-**19**·D-tartaric acid in procedure a) was concentrated *in vacuo* to leave a residue, which was treated with water (200 ml) and K_2CO_3 (5.0 g). The liberated amide was extracted twice with $CHCl_3$. Evaporation of the solvent under reduced pressure left a residue. According to procedure a), the residue was dissolved in EtOH (250 ml) and treated with L-tartaric acid (14.0 g, 93.3 mmol) to afford 28.61 g of (*R*)-**19**·L-tartaric acid. Treatment of the salt with K_2CO_3 (25.0 g) gave 15.35 g (44%) of (*R*)-**19**, mp 91—92 °C, $[\alpha]_D^{29}$ +98.0° (*c*=1.02, $CHCl_3$). *Anal.* Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.26; H, 7.38; N, 14.67.

Benzyl (*S*)-2-Carbamoylazetidine-1-carboxylate [(*S*)-35] 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.59 g, 8.29 mmol) was added to a mixture of (*S*)-1-(benzyloxycarbonyl)azetidine-2-carboxylic acid[12] [(*S*)-**34**, 1.59 g, 6.77 mmol] in saturated ethanolic NH_3 (16 ml) under ice-cooling. The resulting mixture was stirred at room temperature for 5 d. The mixture was concentrated *in vacuo*. Water was added to the resulting residue and the product was extracted with AcOEt. The organic phase was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated *in vacuo* to leave a residue, which was chromatographed on silica gel with $CHCl_3$–EtOH (20:1) to give 802 mg (51%) of (*S*)-**35**, mp 125—126 °C (CH_2Cl_2–iso-Pr_2O), $[\alpha]_D^{27}$ −174.7° (*c*=1.01, $CHCl_3$). IR (KBr) cm^{-1}: 3374, 1706, 1632. ^{1}H-NMR ($CDCl_3$) δ: 2.4—2.65 (2H, m, 3-H), 3.85—4.1 (2H, m, 4-H), 4.74 (1H, dd, J=8.0, 8.0 Hz, 2-H), 5.10 and 5.17 (both 1H, d, J=12.0 Hz, OCH_2), 5.44 and 7.0 (both 1H, br s, NH2), 7.3—7.5 (5H, m, Ph). APCIMS *m/z*: 235 (M^++1). *Anal.* Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.74; H, 5.83; N, 11.79.

(*S*)-Azetidine-2-carboxamide [(*S*)-33] a) A solution of (*S*)-**19** (1.00 g, 5.26 mmol) in EtOH (15 ml) was hydrogenated over 5% Pd–C (100 mg) at 40—50 °C for 11 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to leave a residue, which was triturated with iso-Pr_2O. The resultant crystals were collected by filtration, washed with iso-Pr_2O, and then dried to give 484 mg (92%) of (*S*)-**33**. Recrystallization from CH_2Cl_2–AcOEt gave an analytically pure sample, mp 114—116 °C (CH_2Cl_2–AcOEt), $[\alpha]_D^{28}$ −182.9° (*c*=1.007, $CHCl_3$). IR (KBr) cm^{-1}: 3320, 3180, 1684, 1670. ^{1}H-NMR ($CDCl_3$) δ: 2.11 (1H, br s, 1-H), 2.3—2.75 (2H, m, 3-H), 3.32 (1H, dddd, J=8.5, 7.5, 4.0, 1.0 Hz, 4-H), 3.77 (1H, ddd, J=8.5, 8.5, 7.5 Hz, 4-H), 4.33 (1H, dd, J=8.5, 8.5 Hz, 2-H), 5.60 and 7.35 (both 1H, br s, NH_2). APCIMS *m/z*: 101 (M^++1). *Anal.* Calcd for $C_4H_8N_2O$: C, 47.99; H, 8.05; N, 27.98. Found: C, 48.07; H, 8.05; N, 27.84.

b) A solution of (*S*)-**35** (1.14 g, 4.86 mmol) in EtOH (30 ml) was hydrogenated over 5% Pd–C (100 mg) at room temperature for 4 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to leave 403 mg (83%) of (*S*)-**33**, mp 114—116 °C (CH_2Cl_2–AcOEt), $[\alpha]_D^{28}$ −180° (*c*=0.990, $CHCl_3$).

(*R*)-2-Aminomethyl-1-benzylazetidine [(*R*)-20] According to the method employed for the conversion of **19** to **20**, (*R*)-**19** (42.1 g, 0.221 mol) was treated with borane–THF complex (1 mol/l THF solution, 680 ml, 0.680 mol) to afford 35.7 g (92%) of (*R*)-**20**, bp 93—96 °C (4 mmHg), $[\alpha]_D^{29}$ +47.9° (*c*=1.045, $CHCl_3$).

(*S*)-2-Aminomethyl-1-benzylazetidine [(*S*)-20] According to the method used for the conversion of **19** to **20**, (*S*)-**19** (38.3 g, 0.201 mol) was treated with borane–THF complex (1 mol/l THF solution, 620 ml, 0.620 mol) to give 32.2 g (91%) of (*S*)-**20**, bp 93—96 °C (4 mmHg), $[\alpha]_D^{29}$ −47.6° (*c*=1.025, $CHCl_3$).

(*R*)-2-Aminomethylazetidine [(*R*)-9] According to the method used for the conversion of **20** to **9**, (*R*)-**20** (15.00 g, 85.2 mmol) gave 3.63 g (50%) of (*R*)-**9**, bp 83—85 °C (67 mmHg), $[\alpha]_D^{28}$ −26.9° (*c*=3.232,

$CHCl_3$).

(*S*)-2-Aminomethylazetidine [(*S*)-9] According to the method used for the conversion of **20** to **9**, (*S*)-**20** (10.00 g, 56.8 mmol) gave 2.74 g (56%) of (*S*)-**9**, bp 75—78 °C (55 mmHg), $[\alpha]_D^{28}$ +27.0° (c=3.206, $CHCl_3$).

***N*-(*R*)-[(1-Benzyl-2-azetidinyl)methyl]-(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionamide [(*R*)-36]** A solution of (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride (1.12 g, 4.44 mmol) in CH_2Cl_2 (2.0 ml) was added to a solution of pyridine (0.80 ml, 0.78 mg, 99 mmol) in CH_2Cl_2 (5.0 ml) under ice-cooling and the resulting mixture was stirred at room temperature for 3 h. A solution of (*R*)-**20** (700 mg, 3.93 mmol) in CH_2Cl_2 (3.0 ml) was added to the mixture under ice-cooling. The whole was stirred at room temperature for 3.5 h and then concentrated *in vacuo* to leave a residue. The residue was taken up in a mixture of AcOEt and cold dilute NaOH. The organic phase was washed with saturated NaCl, dried over Na_2SO_4, and then concentrated *in vacuo* to leave a residue, which was chromatographed on silica gel with a mixture of $CHCl_3$ and EtOH (100 : 1) to give 1.19 g (76%) of (*R*)-**36** as an oil, $[\alpha]_D^{29}$ +49.4° (c=2.013, $CHCl_3$). IR (neat) cm^{-1}: 3366, 1694. ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.05 (2H, m, 3-H), 2.75—2.95 (2H, m, 4-H), 3.25—3.5 (3H, m, 2-H, C<u>H</u>$_2$NHCO), 3.48 (3H, q, J_{H-F}=1.8 Hz, OMe), 3.54 (2H, s, C<u>H</u>$_2$Ph), 7.1—7.25, 7.3—7.5, 7.5—7.65 (each 5H, 3H, 2H, m, Ph). ^{19}F-NMR ($CDCl_3$) δ: −70.14 (3H, s, CF_3). CIMS m/z: 393 (M^++1), 146.

***N*-(*S*)-[(1-Benzyl-2-azetidinyl)methyl]-(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionamide [(*S*)-36]** According to the method used for the conversion of (*R*)-**20** to (*R*)-**36**, (*S*)-**20** (700 mg, 3.93 mmol) gave 1.38 g (86%) of (*S*)-**36** as an oil, $[\alpha]_D^{30}$ −70.80° (c=1.977, $CHCl_3$). IR (neat) cm^{-1}: 3380, 1690. ^{1}H-NMR ($CDCl_3$) δ: 1.65—2.0 (2H, m, 3-H), 2.75—2.95 (2H, m, 4-H), 3.13—3.23 (1H, m, 2-H), 3.3—3.5 (2H, m, C<u>H</u>$_2$NHCO), 3.46 (3H, q, J_{H-F}=1.8 Hz, OMe), 3.58 (2H, s, C<u>H</u>$_2$Ph), 7.15—7.35, 7.35—7.45, 7.5—7.65 (each 5H, 3H, 2H, m, Ph). ^{19}F-NMR ($CDCl_3$) δ: −70.18 (3H, s, CF_3). CIMS m/z: 393 (M^++1), 146.

2,4-Dibromobutyryl Chloride (39) 2,4-Dibromobutyric acid (**38**) was prepared from γ-butyrolactone according to the literature method[24] and used without purification. A mixture of crude **38** (260.8 g, 1.060 mmol), thionyl chloride (155 ml, 253 g, 2.13 mol), and *N*,*N*-dimethylformamide (0.3 ml) was heated at reflux for 6 h. The solvent was distilled off *in vacuo*. The residue was distilled under reduced pressure to give 229.2 g (82%) of **39**, bp 78—79 °C (4.5 mmHg). IR (neat) cm^{-1}: 1783.

***tert*-Butyl (*S*)-3-(2,4-Dibromobutyryl)-1-methyl-2-oxoimidazolidine-4-carboxylate (40)** *tert*-BuOK (5.61 g, 50.0 mmol) was added to a stirred mixture of *tert*-butyl (*S*)-1-methyl-2-oxoimidazolidine-4-carboxylate[25] [(*S*)-**37**, 10.00 g, 50.0 mmol] in THF (100 ml) at −60 °C. After 20 min, **39** (19.84 g, 75.0 mmol) in THF (10 ml) was added dropwise to the mixture. The whole was stirred at −30 °C for 1 h, then poured into a mixture of AcOEt, ice, AcOH (3.1 ml), and saturated NaCl. The organic phase was washed successively with cold dilute NaCl, cold 2% K_2CO_3, and saturated NaCl, dried over Na_2SO_4, and then concentrated *in vacuo* to leave a residue. The residue was chromatographed on silica gel with *n*-hexane–AcOEt (2 : 1) to give 15.79 g (74%) of an 11 : 9 diastereomeric mixture of **40** as an oil, $[\alpha]_D^{29}$ −49.5° (c=1.28, $CHCl_3$). IR (neat) cm^{-1}: 1789, 1740, 1685. ^{1}H-NMR ($CDCl_3$) δ: 1.47 and 1.48 (each 0.55×9H, 0.45×9H, both s, *tert*-butyl), 2.5—2.7 (2H, m, $BrCH_2C$<u>H</u>$_2$), 2.92 (3H, s, N-Me), 3.33 and 3.38 (each 0.55H, 0.45H, both dd, J=10.0, 4.0 Hz, 5-H), 3.52 and 3.54 (each 0.55×2H, 0.45×2H, both t, J=6.5 Hz, $BrCH_2$), 3.71 and 3.73 (each 0.55H, 0.45H, both dd, J=10.0, 10.0 Hz, 5-H), 4.65 and 4.66 (each 0.55H, 0.45H, both dd, J=10.0, 4.0 Hz, 4-H), 6.02 and 6.07 (each 0.45H, 0.55H, both dd, J=8.0, 6.0 Hz, CHBr-CO). APCIMS m/z: 427 (M^++1), 371.

***tert*-Butyl (*S*)-3-[(*R*)-1-Benzyl-2-azetidinylcarbonyl]-1-methyl-2-oxoimidazolidine-4-carboxylate [(*R*)-41]** A mixture of **40** (7.48 g, 17.5 mmol), benzylamine (1.90 g, 17.7 mmol), and Et_3N (2.60 ml, 1.89 g, 18.7 mmol) in hexamethylphosphoramide (22 ml) was stirred at room temperature. After 4 h, additional Et_3N (2.60 ml, 1.89 g, 18.7 mmol) was added to the mixture and the whole was stirred at room temperature for 3 d. It was taken up in a mixture of AcOEt and water. The organic phase was washed three times with saturated NaCl, dried over Na_2SO_4, and then concentrated *in vacuo* to leave a residue, which was chromatographed on silica gel with AcOEt to give 4.76 g (73%) of (*R*)-**41** as an oil. IR (KBr) cm^{-1}: 1750, 1732, 1684. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s, *tert*-butyl), 2.15—2.55 (2H, m, azetidinyl 3-H), 2.85 (3H, s, N-Me), 2.93 (1H, ddd, J=9.0, 8.0, 6.5 Hz, azetidinyl 4-H), 3.2—3.35 (1H, m, azetidinyl 4-H), 3.31 (1H, dd, J=10.0, 4.0 Hz, imidazolidinyl 5-H), 3.49 and 3.88 (both 1H, d, J=13.5 Hz, C<u>H</u>$_2$Ph), 3.66 (1H, dd, J=10.0, 10.0 Hz, imidazolidinyl 5-H), 4.58 (1H, dd, J=10.0, 4.0 Hz, imidazolidinyl 4-H), 4.70 (1H, dd, J=9.0, 9.0 Hz, azetidinyl 2-H), 7.15—7.4 (5H, m, Ph). APCIMS m/z: 374 (M^++1).

Crystallization from a 3 : 1 mixture of iso-Pr_2O and *n*-hexane gave 2.19 g (34%) of (*R*)-**41**, mp 90—91 °C, $[\alpha]_D^{29}$ +47.3° (c=1.03, $CHCl_3$). *Anal.* Calcd for $C_{20}H_{27}N_3O_4$: C, 64.32; H, 7.29; N, 11.25. Found: C, 64.32; H, 7.33; N, 11.25.

(*R*)-1-Benzylazetidine-2-carboxamide [(*R*)-19] A solution of (*R*)-**41** (1.42 g, 3.80 mmol) in ethanolic NH_3 (14 ml) was stirred at room temperature for 3 d, then concentrated *in vacuo* to leave a residue, which was chromatographed on silica gel with $CHCl_3$–EtOH (50 : 1) to give 617 mg (80%) of (*R*)-**19**, together with 495 mg (61%) of (*S*)-**37**. Compound (*R*)-**19**: $[\alpha]_D^{29}$ +96.3° (c=1.00, $CHCl_3$). Compound (*S*)-**37**: $[\alpha]_D^{29}$ +24.9° (c=1.01, MeOH) [lit.[25] $[\alpha]_D^{23}$ +24.9° (c=1.0, MeOH)].

Recrystallization of (*R*)-**19** from CH_2Cl_2–iso-Pr_2O gave an analytically and optically pure sample, mp 91—92 °C, $[\alpha]_D^{29}$ +98.3° (c=1.00, $CHCl_3$). *Anal.* Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.38; H, 7.44; N, 14.80.

Molecular Modeling The molecular modeling of **12a—c** and **7** was performed with SYBYL (version 6.3)[26] on an Indigo 2 R10000 workstation. The molecular structures of the quinolone derivatives were built starting from the X-ray crystallographic structures of sparfloxacin (**1**).[2] Low-energy conformations were determined by molecular mechanics with a systematic search of torsional space (MAXIMIN, SEARCH, and GRID options of SYBYL), using the TRIPOS molecular mechanics force field.[27] The resulting interatomic coordinates were used for computing the final molecular structures by means of semiempirical molecular orbital computations by MOPAC (version 6.0) applying the AM1 hamiltonian.[28] These were performed by full geometry optimization (all bonds and all angles).

***In Vitro* Antibacterial Activity** The MIC (in micrograms per milliliter) was determined by the 2-fold agar dilution method using Mueller–Hinton agar (pH 7.4, Difco) according to the assay method recommended by the MIC Committee of the Japan Society of Chemotherapy[29]; the bacterial inocula contained approximately 106 colony-forming units and the bacterial growth was observed after a 20 h incubation at 37 °C.

Acknowledgements We thank Dr. S. Nakamura and his co-workers for the biological testing. Thanks are also due to members of the Department of Physico Chemical Analysis of these laboratories for the elemental analyses and the spectral measurements.

References and Notes

1) This paper is Part XX in a series of "Pyridonecarboxylic Acids as Antibacterial Agents," Part XXI: Fujita M., Egawa H., Chiba K., Matsumoto J., *J. Heterocycl. Chem.*, in press.
2) Miyamoto T., Matsumoto J., Chiba K., Egawa H., Shibamori K., Minamida A., Nishimura Y., Okada H., Kataoka M., Fujita M., Hirose T., Nakano J., *J. Med. Chem.*, **33**, 1645—1656 (1990).
3) Chu D. T. W., Fernandes P. B., Claiborne A. K., Gracey E. H., Pernet A. G., *J. Med. Chem.*, **29**, 2363—2369 (1986).
4) Domagala J. M., Hagen S. E., Heifetz C. L., Hutt M. P., Mich T. F., Sanchez J. P., Trehan A. K., *J. Med. Chem.*, **31**, 503—506 (1988).
5) Frigola J., Parés J., Corbera J., Vañó D., Mercè R., Torrens A., Más J., Valentí E., *J. Med. Chem.*, **36**, 801—810 (1993).
6) Fujita M., Chiba K., Nakano J., Tominaga Y., Matsumoto J., *Chem. Pharm. Bull.*, **46**, 631—638 (1998).
7) Morikawa K., Honda M., Endoh K., Matsumoto T., Akamatsu K., Mitsui H., Koizumi M., *J. Pharm. Sci.*, **79**, 750—753 (1990).
8) Rodebaugh R. M., Cromwell N. H., *J. Heterocycl. Chem.*, **5**, 309—311 (1968).
9) Masuda K., Okutani T., Morimoto A., Kaneko T., Kikuchi K., Hirata M., Tazima Y., Jimpu T., Nagaoka A., "Takeda Kenkyusho Ho," **31**, 453—459 (1972) [*Chem. Abstr.*, **78**, 135969*d* (1973)].
10) Bulteau G., Acher J., Monier J. C., Ger. Patent, 2506515 (1975) [*Chem. Abstr.*, **84**, 30874*q* (1976)].
11) Nishimura Y., Minamida A., Matsumoto J., *J. Heterocycl. Chem.*, **25**, 479—485 (1988).
12) Rodebaugh R. M., Cromwell N. H., *J. Heterocycl. Chem.*, **6**, 993—994 (1969).
13) Kubota H., Kubo A., Takahashi M., Shimizu R., Da-te T., Okamura K., Nunami K., *J. Org. Chem.*, **60**, 6776—6784 (1995).

14) Chu D. T. W., Nordeen C. W., Hardy D. J., Swanson R. N., Giardina W. J., Pernet A. G., Plattner J. J., *J. Med. Chem.*, **34**, 168—174 (1991).
15) Rosen T., Chu D. T. W., Lico I. M., Fernandes P. B., Shen L., Borodkin S., Pernet A. G., *J. Med. Chem.*, **31**, 1586—1590 (1988).
16) Sugino A., Peebles C. L., Kreuzer K. N., Cozzarelli N. R., *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 4767—4771 (1977).
17) Ferrero L., Cameron B., Manse B., Lagneaux D., Crouzet J., Famechon A., Blanche F., *Mol. Microbiol.*, **13**, 641—653 (1994).
18) Shen L. L., Mitscher L. A., Sharma P. N., O'Donnell T. J., Chu D. T. W., Cooper C. S., Rosen T., Pernet A. G., *Biochemistry*, **28**, 3886—3894 (1989).
19) Yoshida H., Bogaki M., Nakamura M., Yamanaka L. M., Nakamura S., *Antimicrob. Agents Chemother.*, **35**, 1647—1650 (1991).
20) Grohe K., Heitzer H., *Justus Liebigs Ann. Chem.*, **1987**, 29—37.
21) Irikura T., Suzue S., Hirai K., Ishizaki T., Eur. Patent Appl. 0183129 (1985) [*Chem. Abstr.*, **105**, 152949*r* (1985)].
22) Sanchez J. P., Gogliotti R. D., Domagala J. M., Gracheck S. J., Huband M. D., Sesnie J. A., Cohen M. A., Shapiro M. A., *J. Med. Chem.*, **38**, 4478—4487 (1995).
23) Matsumoto J., Nakano J., Chiba K., Nakamura S., Japan. Patent Kokai 61-189281 (1986) [*Chem. Abstr.*, **105**, 226521*u* (1986)].
24) Wagner A. F., Walton E., Hoffman C. H., Peterson L. H., Holly F. W., Folkers K., *J. Am. Chem. Soc.*, **77**, 5140—5143 (1955).
25) Hayashi K., Nunami K., Kato J., Yoneda N., Kubo M., Ochiai T., Ishida R., *J. Med. Chem.*, **32**, 289—297 (1989).
26) Tripos Associates, Inc., 1699 S. Hanley Rd., Suite 303, St. Louis, MO 63144.
27) Clark M., Cramer R. D. III, Opdenbosch N. V., *J. Comput. Chem.*, **10**, 982—1012 (1989).
28) Stewart J. J., MOPAC: A general molecular orbital package (version 6.0). Quantum Chemical Program Exchange Catalogue, **IV**, 19—20 (1992).
29) MIC Committee of the Japan Society of Chemotherapy, *Chemotherapy*, **29**, 76—79 (1981).