Synthesis and Structure–Antibacterial Activity Relationships of 7-(3-Amino-1-propynyl and 3-Amino-1-propenyl)quinolones[1)]

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7-(3-Amino-1-propynyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (7a) and some related compounds (7b—f, 8a, b, 9) were prepared *via* palladium(0)-catalyzed cross-coupling reaction of 7-iodoquinolone 12 with acetylenic compounds and their antibacterial activity was tested. The methylene homologue (7d) and the *N*-methyl derivative (7e) of 7a showed essentially the same activity as that of 7a. Addition of methyl group(s) to C′-3 of 7a (giving 7b, c) reduced the activity. The hydrogenation of 7a to (*Z*)-3-amino-1-propenyl (8a), (*E*)-3-amino-1-propenyl (8b) and 3-amino-1-propyl (9) compounds retained or enhanced the activity of 7a. Among the compounds prepared, 8a was the most active, but was less active than ciprofloxacin (1). In order to get insight into structure–activity relationships, the spatial distribution of the amino groups of 7a, 8a, b, and 9 was examined by means of computer-aided molecular modeling.

Key words cross-coupling reaction; quinolone; bioisostere; antibacterial activity; computer-aided molecular modeling; structure–activity relationship

Quinolone antibacterials such as ciprofloxacin (**1**),[2)] sparfloxacin (**2**),[3)] and tosufloxacin (**3**)[4)] are a class of well-established therapeutic agents with a potent antibacterial activity (Chart 1). Most of the quinolones currently used, for example, **1** and **2**, have a 1-piperazinyl substituent at the C-7 position. The substituent has two nitrogens; one forms a carbon–nitrogen bond with the C-7 carbon of the quinolone nucleus and the other is a terminal basic nitrogen.

Some quinolones with 6-fluoro and 7-(1-piperazinyl) groups are known to interact with non-steroidal anti-inflammatory drugs[5)] and/or inhibit competitively the metabolism of theophylline,[6)] causing a risk of adverse effects. It is therefore desirable to find novel C-7 appendages that do not cause such adverse effects. Several carbon substituents have recently been reported as C-7 appendages; examples are those in the structure of **4**,[7)] WIN 57273 (**5**),[8)] and pazufloxacin (**6**).[9)] Most of the C-7 appendages include sp^2-hybridized carbons (alkenyl, aryl, or heteroaryl groups). These appendages could serve as replacements of the 1-piperazinyl group, of which the internal nitrogen has lone pair electrons enriched in *p* orbital character.

The terminal basic nitrogen of the 1-piperazinyl group is rather fixed in configuration owing to the six-membered ring and is generally accepted to play an auxiliary role in manifesting potent antibacterial activity. Hence, a compound whose basic nitrogen is situated in a similar region to that of the 1-piperazinyl group would be expected to exhibit a potent activity. On the basis of this consideration, we designed novel C-7 appendages, *i.e.*, 3-amino-1-propynyl (**7a—f**) and (*E*)-3-amino-1-propenyl groups (**8b**) (Chart 2). These appendages have a terminal basic nitrogen and a three-carbon chain with the exception of **7d**. Further, the carbon chains of **7a—f** and **8b** are conformationally more fixed as compared to that of the corresponding 3-amino-1-propyl compound **9**. They may be considered, hence, as acyclic carbon bioisosteres of the 1-piperazinyl group. This paper deals with the synthesis and antibacterial activity of 3-amino-1-propynyl (**7a—f**), (*Z*/*E*)-3-amino-1-propenyl (**8a, b**), and 3-amino-1-propyl (**9**) quinolones. Further, the spatial distribution of their amino groups is discussed on the basis of computer-aided molecular modeling.

Chemistry As for the coupling reactions of halobenzene derivatives, in general, iodobenzenes are more

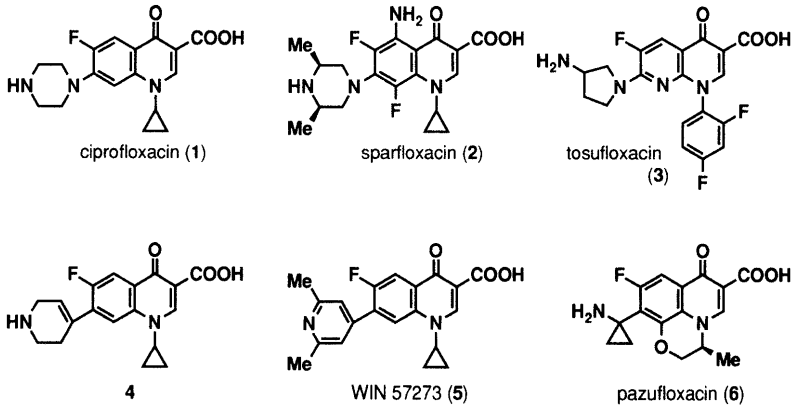

Chart 1

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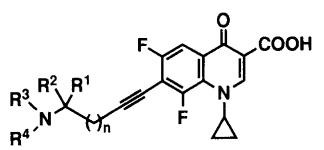
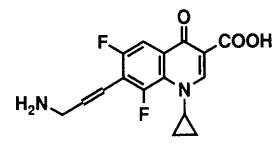


Compd.	n	R_1	R_2	R_3	R_4
7a	0	H	H	H	H
7b	0	Me	H	H	H
7c	0	Me	Me	H	H
7d	1	H	H	H	H
7e	0	H	H	Me	H
7f	0	H	H	Me	Me



Compd.	Configuration of double bond
8a	*Z*
8b	*E*

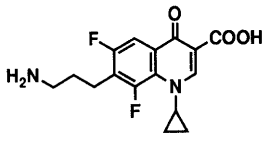


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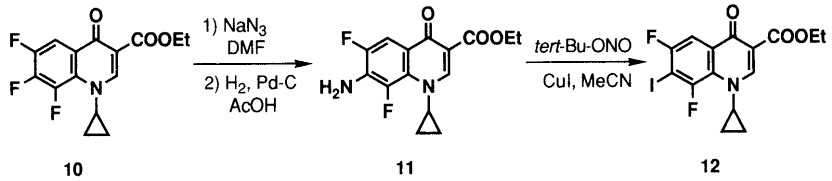
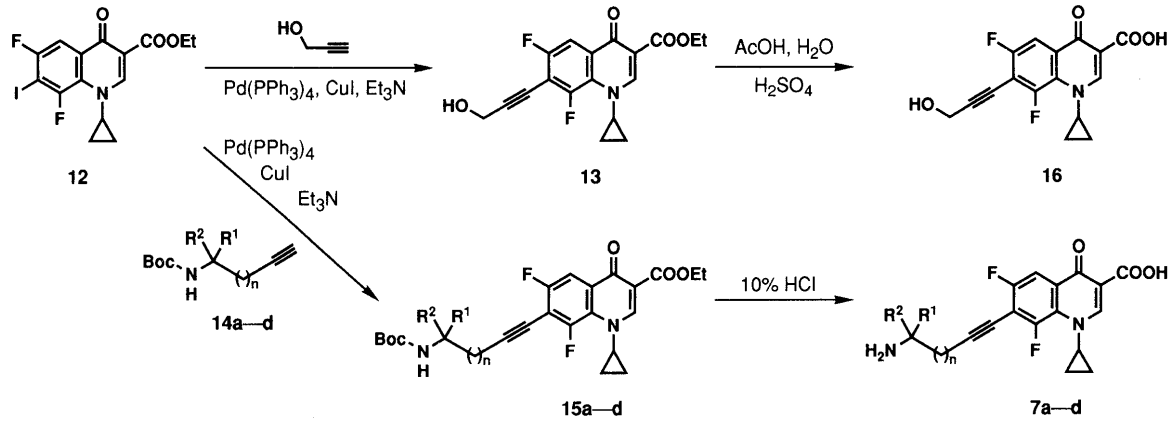
Chart 2



10 **11** **12**

Chart 3



For **14,15**, and **7**: **a**, n = 0, $R^1 = R^2$ = H; **b**, n = 0, R^1 = Me, R^2 = H; **c**, n = 0, $R^1 = R^2$ = Me; **d**, n = 1, $R^1 = R^2$ = H.

Chart 4

reactive than the corresponding bromo- and chlorobenzenes,[10] whereas the corresponding fluorobenzenes are unreactive. Therefore, we started the present study with a synthesis of the iodoquinolone **12**, which was expected to give a coupling product under mild conditions. Compound **10**[2] was treated with sodium azide, followed by catalytic hydrogenation of the resultant azide, to give 7-aminoquinolone **11** (Chart 3). Then a novel Sandmeyer-type one-pot reaction of **11** with *tert*-butyl nitrite and copper(I) iodide gave the 7-iodoquinolone **12**. This reaction was carried out in a neutral aprotic organic solvent, acetonitrile. Water was inappropriate as the reaction solvent, because it caused an undesirable side reaction leading to 7-diazo-1,4,7,8-tetrahydro-4,8-dioxoquinoline, which resulted from an attack of the water molecule on C-8 of the diazonium intermediate.

Palladium(0)-mediated cross-coupling reaction of **12** was carried out with terminal acetylenic compounds, *i.e.*, propargyl alcohol and **14a—d** (Chart 4). A mixture consisting of the iodoquinolone **12** and the acetylenic compound was heated at reflux in triethylamine in the presence of 0.05 equimolar tetrakis(triphenylphosphine)-palladium and 0.1 equimolar copper(I) iodide to give the corresponding coupling products **13** and **15a—d** in 59—93% yields.

Two research groups independently reported the synthesis of 7-alkynyl substituted quinolones; Wentland and his coworkers described the palladium(0)-catalyzed cross-coupling reaction of 6,8-unsubstituted 7-bromoquinolone with (trimethylsilyl)acetylene[11] and McGuirk reported the reaction of 7-bromo-6,8-difluoroquinolone with alkynylzinc chloride[12] that was prepared *in situ* by complicated procedures (*n*-butyl lithium and then zinc(II) chloride) from the starting acetylene. Particular features of the cross-coupling method we have developed are as follows; (1) metallation of acetylenic compounds to acetylides is not requisite, (2) a reagent-grade solvent (triethylamine) can be used without further purification

and drying, and (3) accordingly, the reaction procedure is facile. Owing to these advantages, the present method is much superior to previous ones for the preparation of 7-alkynylquinolones.

The coupling products **13** and **15a—d** were converted to quinolones **7—9** with potential antibacterial activity. The 7-alkynylquinolone carboxylic acids **7a—d** were obtained by hydrolysis of **15a—d** under acidic conditions (Chart 4 and Table 1). The hydroxy compound **13** was converted to **16** for comparison of antibacterial activity.

The *N*-methyl (**7e**) and *N*,*N*-dimethyl (**7f**) analogues were prepared according to the route given in Chart 5. On treatment with thionyl bromide, the hydroxy compound **13** gave the bromide **17**, which was then hydrolyzed to the carboxylic acid **18**. The displacement reaction of **18** with methylamine and dimethylamine afforded the amine products **7e** and **7f**, respectively.

The (*Z*)-3-amino-1-propenyl compound **8a** was derived from **15a** *via* **19a** (Chart 6). Thus, the propynyl moiety of **15a** was hydrogenized in the presence of palladium–carbon and a small amount of quinoline, giving the (*Z*)-1-propenyl compound **19a**. Acid hydrolysis of **19a** gave the acid **8a**. An attempt to convert **19a** into its *E*-isomer **19b** was unsuccessful under alkene isomerization conditions (I_2;[13] PhSSPh, hv;[14] Et_3GeH, Et_3B[15]). Hence, we changed the synthetic route to the following. Readily available (*E*)-3-(*tert*-butoxycarbonylamino)-1-tributylstannyl-1-propene was subjected to the Pd(0)-mediated coupling reaction with the 7-iodoquinolone **12**, thus affording the desired intermediate **19b** with retention of the *E*-geometry. Acidic treatment of **19b** gave the (*E*)-3-amino-1-propenyl compound **8b**.

The carbon–carbon triple bond of **15a** was fully hydrogenized over palladium–carbon in *N*,*N*-dimethylformamide (DMF) to give the 7-alkyl compound **20** (Chart 7). Hydrolysis of the ester moiety, accompanied by removal of the *tert*-butoxycarbonyl (Boc)-protection of **20**, proceeded smoothly under acidic conditions to give the 3-amino-1-propyl compound **9**.

Structure–Activity Relationships *In vitro* antibacterial activity of compounds **7—10** was tested against one gram-positive (*Staphylococcus aureus* 209P JC-1) and two gram-negative bacteria (*Escherichia coli* NIHJ JC-2 and *Pseudomonas aeruginosa* 12) as representatives. The results are summarized in Table 2, which includes the data for ciprofloxacin (**1**) and sparfloxacin (**2**) for comparison.

Comparison of the activities of the 3-amino-1-propynyl compound **7a** and the 3-hydroxy-1-propynyl counterpart **16** revealed that the terminal basic nitrogens of the 7-alkynylquinolones **7a—f** were essential for potent an-

Table 1. Physical Data for 7-(3-Amino-1-alkynyl)- and 7-(4-Amino-1-butynyl)quinolone-3-carboxylic Acids

Compd.[a]	mp (°C) (recryst. solvent)	Yield (%)	Formula	Analysis (%) Calcd (Found)			
				C	H	F	N
7a	231—234 (dec.) (NaOH/AcOH)	55	$C_{16}H_{12}F_2N_2O_3 \cdot 1/4H_2O$	59.54 (59.62	3.90 3.77	11.77 11.71	8.68 8.64)
7b	183—186 (dec.) (NaOH/AcOH)	59	$C_{17}H_{14}F_2N_2O_3 \cdot 1/4H_2O$	60.62 (60.60	4.34 4.27	11.28 11.33	8.32 8.18)
7c	228—229 (NaOH/AcOH)	80	$C_{18}H_{16}F_2N_2O_3$	62.42 (62.18	4.66 4.59	10.97 11.06	8.09 8.06)
7d	248—252 (dec.) (NaOH/AcOH)	58	$C_{17}H_{14}F_2N_2O_3 \cdot 1/4H_2O$	60.62 (60.42	4.34 4.43	11.28 11.06	8.32 8.34)
7e	233—235 (dec.) ($AcOH/NH_4OH$)	17	$C_{17}H_{14}F_2N_2O_3$	61.45 (61.17	4.25 4.08	11.43 11.22	8.43 8.37)
7f	195—197 (dec.) ($CHCl_3$–EtOH)	32	$C_{18}H_{16}F_2N_2O_3 \cdot 1/4H_2O$	61.62 (61.67	4.74 4.65	10.83 10.75	7.98 7.83)

a) Compounds **7a—e** were purified by reprecipitation, by treatment with acid and subsequently with base or *vice versa*.

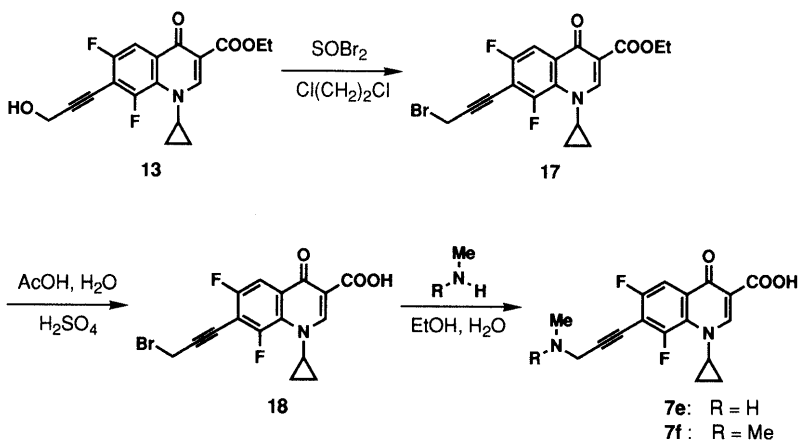


Chart 5

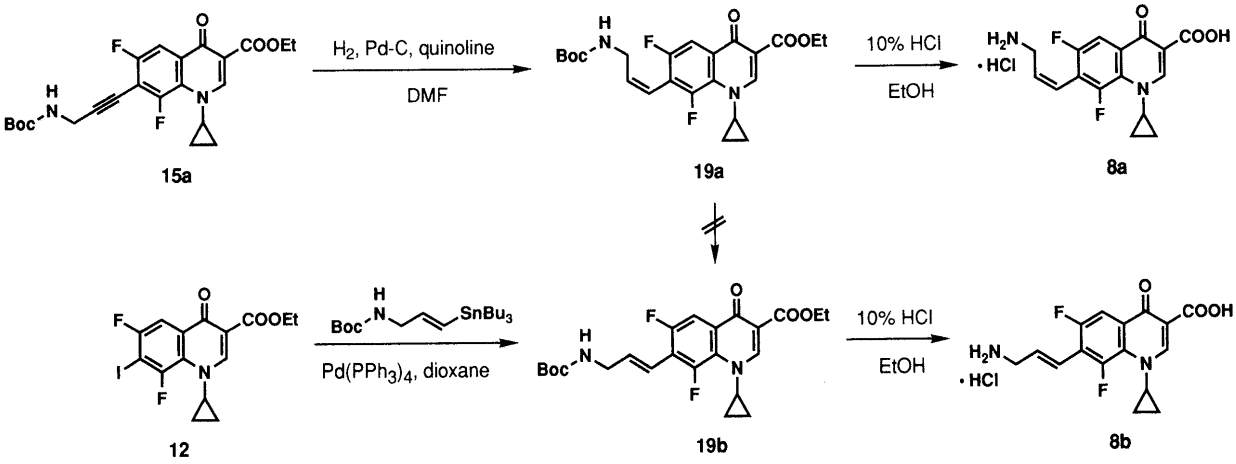


Chart 6

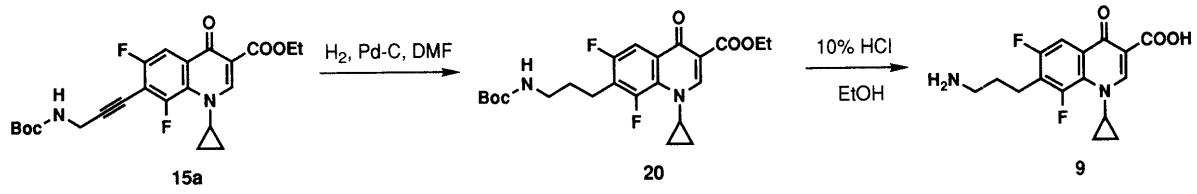
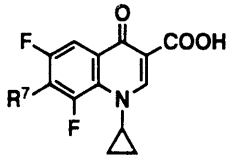
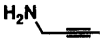
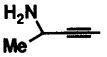
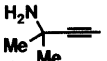
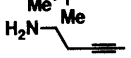
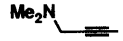
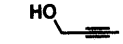
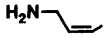
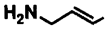
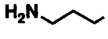


Chart 7

Table 2. Antibacterial Activity of the 7-Alkynyl-, 7-Alkenyl-, and 7-Alkylquinolones



Compd.	R^7	Minimum inhibitory conc.,[a] μg/ml		
		S. aureus 209P JC-1	*E. coli* NIHJ JC-2	*P. aeruginosa* 12
7a		0.39	0.025	0.78
7b		0.78	0.05	1.56
7c		0.78	0.2	6.25
7d		0.39	0.05	0.78
7e		0.39	0.025	0.78
7f		0.39	0.1	6.25
16		3.13	1.56	100
8a		0.39	0.025	0.2
8b		0.39	0.025	0.39
9		0.2	0.05	0.39
1	Ciprofloxacin	0.1	0.0063	0.1
2	Sparfloxacin	0.05	0.0125	0.39

a) See Experimental.

tibacterial activity. The *N*-methyl derivative **7e** exhibited equipotent activity to that of **7a** against three species of bacteria tested. Introduction of 3-methyl (**7b**), 3,3-dimethyl (**7c**), and *N*,*N*-dimethyl groups (**7f**) into the 3-amino-1-propynyl group of **7a** substantially retained the activity of **7a** against the gram-positive strain, but considerably decreased the activity against gram-negative bacteria. The C′-3 methylation of **7a** (giving **7b, c**) reduced the activity to a much greater extent than the *N*-methylation (**7e, f**); thus, the decreasing order in activity is *N*-methyl **7e** > 3-methyl **7b**; *N*,*N*-dimethyl **7f** ≥ 3,3-dimethyl **7c**. Homologation of the side chain of **7a** (giving **7d**) did not substantially influence the activity. Among the 7-alkynyl compounds **7a**—**f**, the most active were the 3-amino-1-propynyl compound **7a** and its *N*-methyl analogue **7e**.

Hydrogenation of the 3-amino-1-propynyl group of **7a** (giving **8a, b**, **9**) slightly influenced the activity. The 3-amino-1-propenyl *Z*-isomer **8a** and the *E*-isomer **8b** were equipotent to the parent compound **7a** against *S. aureus* and *E. coli*, whereas the activity against *P. aeruginosa* was increased in the order, **7a** < **8b** < **8a**. The 3-amino-1-propyl compound **9** was twice as potent as **7a** against *S. aureus* and *P. aeruginosa*.

Among the compounds prepared in this study, **8a** exhibited the most potent and well-balanced activity. Compound **8a** was 2-fold more active than sparfloxacin (**2**) against *P. aeruginosa*, but less active against *S. aureus* and *E. coli*. Compound **8a** was less active than ciprofloxacin (**1**) against the three species of bacteria tested.

In order to get further insight into the structure–activity relationships, the spatial positions of the amino groups of **7a**, **8a, b**, and **9** were studied by computer-aided molecular modeling. The 3-amino-1-propynyl, and (*Z*)- and (*E*)-3-amino-1-propenyl moieties of **7a** and **8a, b** each comprise a rigid three-carbon framework. Accordingly, **7a** may take limited conformations resulting from rotation around the C(2′)–C(3′) axis. Conformers of compounds **8a, b** are similarly limited in number. The 3-amino-1-propyl moiety of **9** is considered to favor all-*trans* conformation. As it is generally considered that a biologically active ligand does not always keep its lowest-energy conformation (global energy minimum) in interaction with a target enzyme, all possible minimum-energy conformations (local energy minima) should be taken into consideration in a study on active conformations. We carried out conformational analyses of **1**, **7a**, **8a, b**, and **9**. Two energy minima for the 1-piperazinyl group of **1** were detected (see Experimental). Two conformations corresponding to the energy minima were fully optimized by a semiempirical molecular orbital method, AM1 of MOPAC. Similar procedures yielded 4, 10, 12, and 4 minimum-energy conformations for **7a**, **8a, b**, and **9**, respectively. The quinolone moieties (consisting of **11** atoms) of these compounds were least-squares-fitted to one conformer of **1** by means of the FIT option of SYBYL. The spatial distribution of amino nitrogens of **1**, **7a**, **8a, b**, and **9** is shown in Fig. 1.

Figure 1 shows that the amino nitrogens of **7a**, **8b**, and **9** are located near the terminal basic nitrogen of **1** and they form a disk-like region centering around the terminal nitrogen of the 1-piperazinyl group of **1**. The conventional

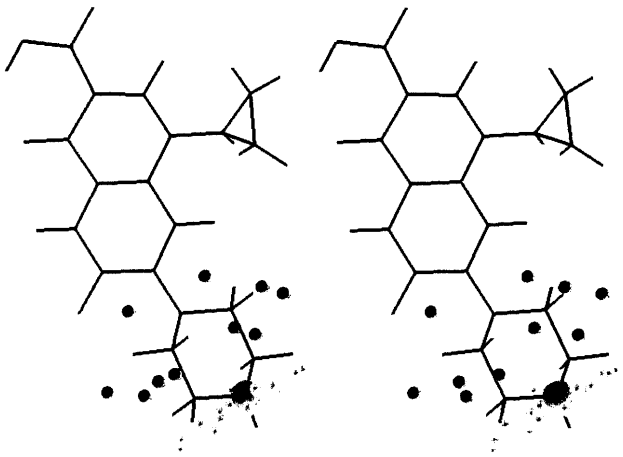


Fig. 1. Stereoview of 2, 4, 10, 12, and 4 Minimum-Energy Conformations of Ciprofloxacin (**1**), **7a**, **8a, b**, and **9**, Respectively

For clarity, the frameworks of the quinolones except **1** have been deleted. The basic nitrogens of the conformers of all compounds are shown with three kinds of balls: big gray balls, **1**; small gray balls, **7a**, **8b**, and **9**; small black balls, **8a**.

C-7 appendages such as 3-amino-1-pyrrolidinyl and 3-amino-1-azetidinyl groups[16] also would have their terminal nitrogens in such a disk-like region. As described earlier, compounds having an amino group at a similar site to that of the terminal piperazinyl nitrogen of **1** were anticipated to show a potent activity. Thus, we expected the designed compounds **7a**, **8b**, and **9** to exhibit a similar antibacterial activity to **1**. They did show considerable activity, but were only half to one-eighth as active as **1** (Table 2). The spatial position of the amino group of the (*Z*)-3-amino-1-propenyl quinolone **8a** is outside the disk-like region (Fig. 1), but **8a** exhibited potent activity. This finding implies that the acceptable spatial region for an amino group to enhance the activity is even wider than the disk-like region.

Most of the quinolone antibacterials reported thus far are substituted by an sp^2 orbital carbon or a nitrogen at C-7, as seen in the structures of **1**—**5**. Despite the lack of an sp^2 orbital carbon in the C-7 side chain, the 3-amino-1-propylquinolone **9** showed a potent activity. Hence, the spacer between the quinolone ring and the terminal nitrogen seems not always to require an sp^2 orbital for enhancing the activity.

In conclusion,7-(amino-1-alkynyl)-, 7-(3-amino-1-propenyl)-, and 7-(3-amino-1-propyl)quinolones (**7**, **8**, **9**, respectively), prepared through the palladium(0)-catalyzed cross-coupling reaction of **12**, showed potent antibacterial activity. The computer-aided molecular modeling study revealed that the spatial positions of the amino groups of **7a**, **8b**, **9** form a disk-like region centering around the terminal piperazinyl group of ciprofloxacin (**1**). The amino group of the 7-[(*Z*)-3-amino-1-propenyl]quinolone **8a**, however, does not fall into this disk-like region, and **8a** was the most potent of these compounds, though it was still less active than **1**. The correlation between the spatial position of the amino groups and the activity of the quinolones provides an interesting basis for further studies in the field of quinolone antibacterials.

Experimental

Chemistry All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer 1600 Series FT-IR 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. Electron-impact (EI) and chemical ionization (CI) mass spectra (MS) were obtained on a JEOL JMS D-300 mass spectrometer. Secondary ion (SI) and atmospheric pressure chemical ionization (APCI) mass spectra (MS) were obtained on a Hitachi M-80B mass spectrometer and Hitachi M-1000 LC API mass spectrometer, respectively. The spectral data for all compounds were obtained and were consistent with the assigned structures. All solid compounds were analyzed for C, H, Br, Cl, F, and N.

Ethyl 7-Amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (11) A mixture of ethyl 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate[2] (**10**, 150.0 g, 0.482 mol) and NaN_3 (37.6 g, 0.579 mol) in DMF (600 ml) was heated at 60 °C for 4 h and poured into ice water. The resulting precipitates were collected by filtration, washed successively with water, EtOH, and iso-Pr_2O, and then dried to give 155.2 g of crude ethyl 7-azido-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate, mp 155—157 °C (DMF–iso-Pr_2O). IR (KBr) cm^{-1}: 2131, 1726, 1693. ^{1}H-NMR (DMSO-d_6) δ: 1.1—1.2 (4H, m, cyclopropyl CH_2CH_2), 1.27 (3H, t, J=7.0 Hz, CH_2CH_3), 3.9—4.05 (1H, m, cyclopropyl CH), 4.22 (2H, q, J=7.0 Hz, CH_2CH_3), 7.82 (1H, dd, J=11.0, 2.0 Hz, 5-H), 8.47 (1H, s, 2-H). EI-MS m/z: 334 (M^+), 306. *Anal.* Calcd for $C_{15}H_{12}F_2N_4O_3$: C, 53.90; H, 3.62; F, 11.37; N, 16.76. Found: C, 53.82; H, 3.60; F, 11.19; N, 16.74.

A mixture of the crystals described above in AcOH (1.0 l) was hydrogenated over 5% Pd–C (10.2 g) at room temperature for 7 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was triturated with iso-Pr_2O. The resultant crystals were collected by filtration, washed successively with AcOEt and iso-Pr_2O, and then dried to give 131.0 g (88%) of **11**, mp 262—263 °C ($CHCl_3$–EtOH). IR (KBr) cm^{-1}: 3346, 1725, 1645. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.3 (4H, m, cyclopropyl CH_2CH_2), 1.40 (3H, t, J=7.0 Hz, CH_2CH_3), 3.8—4.0 (1H, m, cyclopropyl CH), 4.39 (2H, q, J=7.0 Hz, CH_2CH_3), 7.95 (1H, dd, J=10.5, 2.0 Hz, 5-H), 8.53 (1H, s, 2-H). SI-MS m/z: 309 (M^++1), 263. *Anal.* Calcd for $C_{15}H_{14}F_2N_2O_3$: C, 58.44; H, 4.58; F, 12.32; N, 9.09. Found: C, 58.39; H, 4.47; F, 12.45; N, 9.00.

Ethyl 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-iodo-4-oxoquinoline-3-carboxylate (12) *tert*-Butyl nitrite (80.9 g, 0.785 mol) was added portionwise to a stirred mixture of **11** (161.1 g, 0.523 mol), CuI (129.5 g, 0.680 mol), and MeCN (1.5 l) at 60 °C. The whole mixture was heated at 60 °C for 4.5 h and water was added thereto. The resulting solid was collected by filtration, washed with water, dried, and then stirred in a mixture of $CHCl_3$ and EtOH (10 : 1). Insoluble materials were removed by filtration and the filtrate was concentrated *in vacuo*. The solid residue was chromatographed on silica gel with a mixture of $CHCl_3$ and EtOH (100 : 1 to 30 : 1) to give 63.5 g (29%) of **12**, mp 215—218 °C (CH_2Cl_2–iso-Pr_2O). IR (KBr) cm^{-1}: 1728, 1610, 1587. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.4 (4H, m, cyclopropyl CH_2CH_2), 1.40 (3H, t, J=7.0 Hz, CH_2CH_3), 3.8—4.0 (1H, m, cyclopropyl CH), 4.40 (2H, q, J=7.0 Hz, CH_2CH_3), 8.00 (1H, dd, J=7.5, 2.0 Hz, 5-H), 8.57 (1H, s, 2-H). SI-MS m/z: 420 (M^++1), 374, 347. *Anal.* Calcd for $C_{15}H_{12}F_2INO_3$: C, 42.98; H, 2.89; F, 9.06; I, 30.28; N, 3.34. Found: C, 43.42; H, 2.85; F, 9.23; I, 29.81; N, 3.37.

3-(*tert*-Butoxycarbonylamino)-1-butyne (14b) A solution of 3-amino-1-butyne[17] (860 mg, 12.5 mmol) in CH_2Cl_2 (6.0 ml) was treated with di-*tert*-butyl dicarbonate (2.72 g, 12.5 mmol) at room temperature for 5 h. The reaction mixture was diluted with $CHCl_3$ and the resulting solution was washed with water, dried over Na_2SO_4, and then concentrated *in vacuo*. Recrystallization of the resulting solid residue from a mixture of CH_2Cl_2 and *n*-hexane gave 930 mg (44%) of **14b**, mp 84—85 °C. IR (KBr) cm^{-1}: 3333, 2120, 1682. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, d, J=7.0 Hz, CH–Me), 1.45 (9H, s, *tert*-Bu), 2.25 (1H, d, J=2.0 Hz, 1-H), 4.35—4.6 (1H, m, CH–Me), 4.66 (1H, br s, NH). CI-MS m/z: 170 (M^++1), 114. *Anal.* Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.94; H, 8.97; N, 8.30.

3-(*tert*-Butoxycarbonylamino)-3-methyl-1-butyne (**14c**): According to the procedure described above for the preparation of **14b**, 3-amino-3-methyl-1-butyne (2.00 g, 24.1 mmol) was worked up to give 2.34 g (53%) of **14c**, mp 59—61 °C (*n*-hexane). IR (KBr) cm^{-1}: 3347, 3291, 1718, 1695. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s, *tert*-Bu), 1.58 (6H, s, N–CMe_2), 2.30 (1H, s, 1-H), 4.68 (1H, br s, NH). APCI-MS m/z: 128 (M^+−55). *Anal.* Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.65; H, 9.41; N, 7.68.

4-(*tert*-Butoxycarbonylamino)-1-butyne (**14d**): According to the procedure described for the preparation of **14b**, 4-amino-1-butyne[18] (1.98 g, 28.7 mmol) was worked up to give 2.78 g (57%) of **14d** as an oil. IR (neat) cm^{-1}: 3350, 3305, 2120, 1694. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s, *tert*-Bu), 2.00 (1H, t, J=2.5 Hz, 1-H), 2.39 (2H, dt, J=2.5, 6.5 Hz, 3-H), 3.29 (2H, dt, J=6.5, 6.5 Hz, 4-H), 4.83 (1H, br s, NH). APCI-MS m/z: 170 (M^++1), 114.

Ethyl 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-(3-hydroxy-1-propynyl)-4-oxoquinoline-3-carboxylate (13) A mixture of **12** (12.3 g, 29.4 mmol), propargyl alcohol (3.29 g, 58.7 mmol), $Pd(PPh_3)_4$ (1.70 g, 1.47 mmol), CuI (560 mg, 2.94 mmol), and Et_3N (180 ml) was heated to reflux for 5 h under an argon atmosphere. The mixture was concentrated and the resulting residue was chromatographed on silica gel with a mixture of $CHCl_3$ and EtOH (6 : 1) to give 7.05 g (69%) of **13**, mp 231—233 °C ($CHCl_3$–EtOH). IR (KBr) cm^{-1}: 3468, 2244, 1720, 1616. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.35 (4H, m, cyclopropyl CH_2CH_2), 1.40 (3H, t, J=7.0 Hz, CH_2CH_3), 1.93 (1H, br s, OH), 3.8—4.0 (1H, m, cyclopropyl CH), 4.40 (2H, q, J=7.0 Hz, CH_2CH_3), 4.60 (2H, s, CH_2OH), 7.98 (1H, dd, J=9.0, 2.0 Hz, 5-H), 8.60 (1H, s, 2-H). SI-MS m/z: 348 (M^++1), 302. *Anal.* Calcd for $C_{18}H_{15}F_2NO_4$: C, 62.25; H, 4.35; F, 10.94; N, 4.03. Found: C, 61.90; H, 4.08; F, 10.66; N, 4.00.

Ethyl 7-[3-(*tert*-Butoxycarbonylamino)-1-propynyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (15a) According to the procedure described for the preparation of **13**, the reaction of **12** (2.00 g, 4.77 mmol) with 3-(*tert*-butoxycarbonylamino)-1-propyne[19] (**14a**, 1.48 g, 9.55 mmol) gave 1.25 g (59%) of **15a**, mp 182—183 °C (CH_2Cl_2–iso-Pr_2O). IR (KBr) cm^{-1}: 3327, 2256, 1721, 1686. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.35 (4H, m, cyclopropyl CH_2CH_2), 1.40 (3H, t, J=7.0 Hz, CH_2CH_3), 1.48 (9H, s, *tert*-Bu), 3.8—4.0 (1H, m, cyclopropyl CH), 4.27 (2H, d, J=5.0 Hz, $NHCH_2$), 4.39 (2H, q, J=7.0 Hz, CH_2CH_3), 4.85 (1H, br s, NH), 7.99 (1H, dd, J=9.0, 2.0 Hz, 5-H), 8.59 (1H, s, 2-H). EI-MS m/z: 446 (M^+), 390. *Anal.* Calcd for $C_{23}H_{24}F_2N_2O_5$: C, 61.88; H, 5.42; F, 8.51; N, 6.27. Found: C, 61.70; H, 5.28; F, 8.36; N, 6.21.

Ethyl 7-[3-(*tert*-Butoxycarbonylamino)-1-butynyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**15b**): According to the procedure described for the preparation of **13**, the reaction of **12** (1.12 g, 2.67 mmol) with **14b** (900 mg, 5.33 mmol) gave 1.09 g (89%) of **15b**, mp 155—156 °C (CH_2Cl_2–iso-Pr_2O). IR (KBr) cm^{-1}: 3325, 2242, 1723, 1697. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.4 (4H, m, cyclopropyl CH_2CH_2), 1.40 (3H, t, J=7.0 Hz, CH_2CH_3), 1.48 (9H, s, *tert*-Bu), 1.55 (3H, d, J=6.5 Hz, CH–Me), 3.8—4.0 (1H, m, cyclopropyl CH), 4.40 (2H, q, J=7.0 Hz, CH_2CH_3), 4.7—4.95 (2H, br s, NH and CH–Me), 7.98 (1H, dd, J=9.0, 2.0 Hz, 5-H), 8.59 (1H, s, 2-H). SI-MS m/z: 461 (M^++1), 405, 359. *Anal.* Calcd for $C_{24}H_{26}F_2N_2O_5$: C, 62.60; H, 5.69; F, 8.25; N, 6.08. Found: C, 62.57; H, 5.69; F, 8.24; N, 6.01.

Ethyl 7-[3-(*tert*-Butoxycarbonylamino)-3-methyl-1-butynyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**15c**): According to the procedure described for the preparation of **13**, the reaction of **12** (2.00 g, 4.77 mmol) with **14c** (1.75 g, 9.56 mmol) gave 2.11 g (93%) of **15c**, mp 208—209 °C (AcOEt). IR (KBr) cm^{-1}: 3350, 3252, 2244, 1706. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.35 (4H, m, cyclopropyl CH_2CH_2), 1.40 (3H, t, J=7.0 Hz, CH_2CH_3), 1.48 (9H, s, *tert*-Bu), 1.72 (6H, s, NH–CMe_2), 3.8—3.95 (1H, m, cyclopropyl CH), 4.39 (2H, q, J=7.0 Hz, CH_2CH_3), 4.79 (1H, br s, NH), 7.97 (1H, dd, J=9.0, 2.0 Hz, 5-H), 8.58 (1H, s, 2-H). SI-MS m/z: 475 (M^++1), 429, 373. *Anal.* Calcd for $C_{25}H_{28}F_2N_2O_5$: C, 63.28; H, 5.95; F, 8.01; N, 5.90. Found: C, 63.34; H, 5.89; F, 8.13; N, 5.94.

Ethyl 7-[4-(*tert*-Butoxycarbonylamino)-1-butynyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**15d**): According to the procedure described for the preparation of **13**, the reaction of **12** (2.00 g, 4.77 mmol) with **14d** (1.62 g, 9.58 mmol) gave 1.875 g (85%) of **15d**, mp 187—189 °C (AcOEt). IR (KBr) cm^{-1}: 3291, 2238, 1736, 1706. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.35 (4H, m, cyclopropyl CH_2CH_2), 1.40 (3H, t, J=7.0 Hz, CH_2CH_3), 1.46 (9H, s, *tert*-Bu), 2.76 (2H, t, J=6.5 Hz, $NHCH_2CH_2$), 3.44 (2H, dt, J=6.5, 6.5 Hz, $NHCH_2CH_2$), 3.8—4.0 (1H, m, cyclopropyl CH), 4.39 (2H, q, J=7.0 Hz, CH_2CH_3), 4.92 (1H, br s, NH), 7.99 (1H, dd, J=9.0, 2.0 Hz, 5-H), 8.58 (1H, s, 2-H). EI-MS m/z: 460 (M^+), 415, 404. *Anal.* Calcd for $C_{24}H_{26}F_2N_2O_5$: C, 62.60; H, 5.69; F, 8.25; N, 6.08. Found: C, 62.36; H, 5.62; F, 8.25; N, 6.01.

7-(3-Amino-1-propynyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-

quinoline-3-carboxylic Acid (7a) A mixture of **15a** (400 mg, 0.896 mmol) in 10% HCl (4.0 ml) was heated to reflux for 3.5 h and then cooled to room temperature. The resulting precipitates were collected by filtration, washed successively with water, EtOH, and iso-Pr_2O, and then dried to give 270 mg of crude crystals. Reprecipitation of the crystals, on treatment with aqueous NaOH and subsequently with aqueous AcOH, gave 160 mg (55%) of **7a**. IR (KBr) cm^{-1}: 3420, 2245, 1637. ^{1}H-NMR (CD_3COOD) δ: 1.2—1.45 (4H, m, cyclopropyl CH_2CH_2), 4.05—4.25 (1H, m, cyclopropyl CH), 4.34 (2H, s, CH_2NH_2), 8.08 (1H, dd, J=9.0, 2.0 Hz, 5-H), 8.99 (1H, s, 2-H). SI-MS m/z: 319 (M^++1), 301.

According to this procedure, compounds **7b—d** were prepared from **15b—d**, respectively. Physical data for **7b—d** are given in Table 1.

1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-(3-hydroxy-1-propynyl)-4-oxoquinoline-3-carboxylic Acid (16) A mixture of **13** (300 mg, 0.864 mmol) in AcOH–H_2O–H_2SO_4 (8:6:1 v/v, 30 ml) was heated to reflux for 1 h and then ice–water was added. The resulting precipitates were collected by filtration, washed successively with water, EtOH, and iso-Pr_2O, and then dried to give 253 mg (88%) of **16**, mp 250—252 °C ($CHCl_3$–EtOH). IR (KBr) cm^{-1}: 3321, 2250, 1712, 1605. ^{1}H-NMR (DMSO-d_6) δ: 1.1—1.35 (4H, m, cyclopropyl CH_2CH_2), 4.05—4.25 (1H, m, cyclopropyl CH), 4.47 (2H, d, J=6.0 Hz, CH_2OH), 5.63 (1H, t, J=6.0 Hz, CH_2OH), 7.97 (1H, dd, J=9.0, 2.0 Hz, 5-H), 8.75 (1H, s, 2-H), 14.36 (1H, br s, COOH). SI-MS m/z: 320 (M^++1), 302. *Anal.* Calcd for $C_{16}H_{11}F_2NO_4$: C, 60.19; H, 3.47; F, 11.90; N, 4.39. Found: C, 60.01; H, 3.60; F, 11.98; N, 4.35.

Ethyl 7-(3-Bromo-1-propynyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (17) Thionyl bromide (4.24 g, 20.40 mmol) was added to a stirred solution of **13** (3.55 g, 10.22 mmol) in 1,2-dichloroethane (88 ml) at room temperature. The mixture was stirred for 1.5 h at the same temperature and diluted with iso-Pr_2O. The resulting precipitates were collected by filtration, washed successively with EtOH, and iso-Pr_2O, and then dried to give crude crystals. Recrystallization from a mixture of $CHCl_3$ and EtOH gave 3.76 g (90%) of **17**, mp 208—210 °C. IR (KBr) cm^{-1}: 2286, 1726, 1606. ^{1}H-NMR (DMSO-d_6) δ: 1.0—1.3 (4H, m, cyclopropyl CH_2CH_2), 1.28 (3H, t, J=7.0 Hz, CH_2CH_3), 3.9—4.1 (1H, m, cyclopropyl CH), 4.23 (2H, q, J=7.0 Hz, CH_2CH_3), 4.68 (2H, s, CH_2Br), 7.82 (1H, dd, J=9.0, 2.0 Hz, 5-H), 8.50 (1H, s, 2-H). SI-MS m/z: 410 (M^++1), 364. *Anal.* Calcd for $C_{18}H_{14}BrF_2NO_3$: C, 52.70; H, 3.44; Br, 19.48; F, 9.26; N, 3.41. Found: C, 52.75; H, 3.37; Br, 19.78; F, 9.29; N, 3.39.

7-(3-Bromo-1-propynyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (18) According to the procedure described for the conversion of **13** to **16**, the reaction of **17** (3.00 g, 7.31 mmol) gave 2.74 g (98%) of **18**, mp 229—231 °C ($CHCl_3$–EtOH). IR (KBr) cm^{-1}: 1745, 1603. ^{1}H-NMR (DMSO-d_6) δ: 1.1—1.35 (4H, m, cyclopropyl CH_2CH_2), 4.05—4.25 (1H, m, cyclopropyl CH), 4.70 (2H, s, CH_2Br), 8.00 (1H, dd, J=9.0, 2.0 Hz, 5-H), 8.76 (1H, s, 2-H), 14.3 (1H, br s, COOH). SI-MS m/z: 382 (M^++1), 364, 337. *Anal.* Calcd for $C_{16}H_{10}BrF_2NO_3$: C, 50.29; H, 2.64; Br, 20.91; F, 9.94; N, 3.67. Found: C, 50.43; H, 2.72; Br, 20.97; F, 9.94; N, 3.57.

1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-(3-methylamino-1-propynyl)-4-oxoquinoline-3-carboxylic Acid (7e) A mixture of **18** (300 mg, 0.785 mmol), $MeNH_2$ (30% solution in EtOH, 0.40 ml, *ca.* 3.0 mmol), EtOH (9.0 ml), and water (1.0 ml) was stirred for 4 h at 50 °C and concentrated under reduced pressure. The residue was triturated with EtOH. The resultant precipitates were collected by filtration, washed with EtOH and then dried to give 183 mg of crude crystals. Reprecipitation of the crystals, on treatment with aqueous AcOH and subsequently with aqueous NH_4OH, gave 44 mg (17%) of **7e**. IR (KBr) cm^{-1}: 3430, 1718, 1647, 1625. ^{1}H-NMR (CD_3COOD) δ: 1.25—1.4 (4H, m, cyclopropyl CH_2CH_2), 2.96 (3H, s, CH_2NCH_3), 4.05—4.25 (1H, m, cyclopropyl CH), 4.42 (2H, s, CH_2NCH_3), 8.09 (1H, dd, J=9.0, 2.0 Hz, 5-H), 9.00 (1H, s, 2-H). SI-MS m/z: 333 (M^++1), 315, 302.

According to the procedure described above, the reaction of **18** (300 mg, 0.785 mmol) with Me_2NH (50% solution in water, 0.30 ml, *ca.* 3.0 mmol) gave 89 mg (32%) of **7f** (Table 1).

Ethyl 7-[(*Z*)-3-(*tert*-Butoxycarbonylamino)-1-propenyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (19a) A mixture of **15a** (3.50 g, 7.85 mmol), quinoline (0.35 ml), and DMF (70 ml) was hydrogenated over 5% Pd–C (350 mg) at room temperature for 1 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The solid residue was chromatographed on silica gel with a mixture of $CHCl_3$ and EtOH (20:1) to give 3.31 g (94%) of **19a**, mp 148—149 °C (CH_2Cl_2–iso-Pr_2O). IR (KBr) cm^{-1}: 3439, 1729, 1707. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.35 (4H, m, cyclopropyl CH_2CH_2), 1.41 (3H, t, J=7.0 Hz, CH_2CH_3), 1.43 (9H, s, *tert*-Bu), 3.78 (2H, dd, J=6.5, 6.5 Hz, N–CH_2), 3.8—4.0 (1H, m, cyclopropyl CH), 4.40 (2H, q, J=7.0 Hz, CH_2CH_3), 4.65 (1H, br s, NH), 6.10 (1H, dt, J=11.5, 6.5 Hz, CH_2–CH=CH), 6.36 (1H, br d, J=11.5 Hz, CH_2–CH=CH), 8.00 (1H, dd, J=9.5, 2.0 Hz, 5-H), 8.60 (1H, s, 2-H). APCI-MS m/z: 449 (M^++1). *Anal.* Calcd for $C_{23}H_{26}F_2N_2O_5$: C, 61.60; H, 5.84; F, 8.47; N, 6.25. Found: C, 61.42; H, 5.84; F, 8.64; N, 6.22.

7-[(*Z*)-3-Amino-1-propenyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (8a) A mixture containing **19a** (400 mg, 0.893 mmol), 10% HCl (1.6 ml), and EtOH (8.0 ml) was heated to reflux for 1 h. Charcoal was added to the mixture and the whole was filtered. The filtrate was concentrated *in vacuo* to leave a residue, to which EtOH was added. The resultant crystals were collected by filtration, washed with EtOH, and then dried to give 273 mg (86%) of **8a**·HCl, mp 220—223 °C (dec.). IR (KBr) cm^{-1}: 3142, 1728, 1606. ^{1}H-NMR (CD_3COOD) δ: 1.2—1.5 (4H, m, cyclopropyl CH_2CH_2), 3.82 (2H, br d, J=7.0 Hz, H_3N–CH_2), 4.05—4.25 (1H, m, cyclopropyl CH), 6.37 (1H, dt, J=12.0, 7.0 Hz, CH_2–CH=CH), 6.70 (1H, br d, J=12.0 Hz, CH_2–CH=CH), 8.07 (1H, dd, J=9.0, 2.0 Hz, 5-H), 9.00 (1H, s, 2-H). SI-MS m/z: 321 (M^++1), 304. *Anal.* Calcd for $C_{16}H_{14}F_2N_2O_3$·HCl: C, 53.87; H, 4.24; Cl, 9.94; F, 10.65; N, 7.85. Found: C, 54.05; H, 4.35; Cl, 9.67; F, 10.49; N, 7.72.

Ethyl 7-[(*E*)-3-(*tert*-Butoxycarbonylamino)-1-propenyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (19b) A mixture of **12** (1.00 g, 2.39 mmol), (*E*)-3-(*tert*-butoxycarbonylamino)-1-tributylstannyl-1-propene[19] (2.13 g, 4.77 mmol), $Pd(PPh_3)_4$ (138 mg, 0.119 mmol), and dioxane (20 ml) was heated to reflux for 50 h under an argon atmosphere. The mixture was concentrated and the resulting residue was chromatographed on silica gel with a mixture of $CHCl_3$ and EtOH (50:1) to give 931 mg (87%) of **19b**, mp 187—188 °C (CH_2Cl_2–iso-Pr_2O). IR (KBr) cm^{-1}: 3346, 1705, 1692, 1621. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.35 (4H, m, cyclopropyl CH_2CH_2), 1.41 (3H, t, J=7.0 Hz, CH_2CH_3), 1.49 (9H, s, *tert*-Bu), 3.8—4.0 (1H, m, cyclopropyl CH), 4.01 (2H, br t, J=5.0 Hz, N–CH_2), 4.39 (2H, q, J=7.0 Hz, CH_2CH_3), 4.76 (1H, br s, NH), 6.60 (1H, d, J=16.0 Hz, CH_2–CH=CH), 6.72 (1H, dt, J=16.0, 4.5 Hz, CH_2–CH=CH), 7.97 (1H, dd, J=11.0, 2.0 Hz, 5-H), 8.59 (1H, s, 2-H). APCI-MS m/z: 449 (M^++1), 393, 348. *Anal.* Calcd for $C_{23}H_{26}F_2N_2O_5$: C, 61.60; H, 5.84; F, 8.47; N, 6.25. Found: C, 61.78; H, 5.65; F, 8.45; N, 6.05.

7-[(*E*)-3-Amino-1-propenyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (8b) According to the procedure described for the conversion of **19a** to **8a**·HCl, the reaction of **19b** (400 mg, 0.892 mmol) gave 231 mg (73%) of **8b**·HCl, mp 240—244 °C (dec.). IR (KBr) cm^{-1}: 1726, 1610. ^{1}H-NMR (DMSO-d_6) δ: 1.0—1.4 (4H, m, cyclopropyl CH_2CH_2), 3.79 (2H, br d, J=6.0 Hz, H_3N–CH_2), 4.1—4.3 (1H, m, cyclopropyl CH), 6.75 (1H, dt, J=16.0, 6.0 Hz, CH_2–CH=CH), 6.94 (1H, d, J=16.0 Hz, CH_2–CH=CH), 7.97 (1H, dd, J=10.0, 2.0 Hz, 5-H), 8.30 (3H, br s, H_3N–CH_2), 8.77 (1H, s, 2-H), 14.45 (1H, br s, COOH). SI-MS m/z: 321 (M^++1), 304. *Anal.* Calcd for $C_{16}H_{14}F_2N_2O_3$·HCl: C, 53.87; H, 4.24; Cl, 9.94; F, 10.65; N, 7.85. Found: C, 53.59; H, 4.37; Cl, 9.65; F, 10.64; N, 7.66.

Ethyl 7-[3-(*tert*-Butoxycarbonylamino)-1-propyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (20) A mixture of **15a** (1.03 g, 2.31 mmol) and DMF (20 ml) was hydrogenated over 5% Pd–C (103 mg) at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel with a mixture of $CHCl_3$ and EtOH (15:1) to give 987 mg (95%) of **20**, mp 125—126 °C (CH_2Cl_2–iso-Pr_2O). IR (KBr) cm^{-1}: 3330, 1723, 1679, 1615. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.3 (4H, m, cyclopropyl CH_2CH_2), 1.40 (3H, t, J=7.0 Hz, CH_2CH_3), 1.44 (9H, s, *tert*-Bu), 1.75—1.95 (2H, m, $CH_2CH_2CH_2$), 2.85 (2H, br t, J=7.5 Hz, N–$CH_2CH_2CH_2$), 3.20 (2H, dt, J=6.5, 6.5 Hz, N–$CH_2CH_2CH_2$), 3.8—4.0 (1H, m, cyclopropyl CH), 4.39 (2H, q, J=7.0 Hz, CH_2CH_3), 4.61 (1H, br s, NH), 7.97 (1H, dd, J=9.5, 2.0 Hz, 5-H), 8.59 (1H, s, 2-H). SI-MS m/z: 451 (M^++1), 395, 349. *Anal.* Calcd for $C_{23}H_{28}F_2N_2O_5$: C, 61.32; H, 6.27; F, 8.43; N, 6.22. Found: C, 61.59; H, 6.27; F, 8.42; N, 6.20.

7-(3-Amino-1-propyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (9) According to the procedure described for the conversion of **15a** to **7a**, the reaction of **20** (250 mg, 0.555 mmol) gave 132 mg (73%) of **9**, mp 268—271 °C (dec., HCl/NH_4OH). IR (KBr) cm^{-1}: 3424, 1626. ^{1}H-NMR (CD_3COOD) δ: 1.2—1.45 (4H, m, cyclopropyl CH_2CH_2), 2.0—2.25 (2H, m, $CH_2CH_2CH_2$), 3.02 (2H, br t,

J=7.0 Hz, H_2N–$CH_2CH_2C\underline{H}_2$), 3.20 (2H, t, J=7.5 Hz, H_2N–$C\underline{H}_2$-CH_2CH_2), 4.1—4.25 (1H, m, cyclopropyl CH), 8.03 (1H, dd, J=9.0, 2.0 Hz, 5-H), 8.98 (1H, s, 2-H). SI-MS m/z: 323 ($M^+ + 1$), 306. *Anal.* Calcd for $C_{16}H_{16}F_2N_2O_3 \cdot 1/4H_2O$: C, 58.80; H, 5.09; F, 11.63; N, 8.57. Found: C, 59.16; H, 4.93; F, 11.88; N, 8.51.

***In Vitro* Antibacterial Activity** According to the assay method recommended by the minimum inhibitory concentration (MIC) Committee of the Japan Society of Chemotherapy,[20] the MIC (in micrograms per milliliter) was determined by the 2-fold agar dilution method using Mueller–Hinton agar (pH 7.4, Difco); the bacterial inocula contained approximately 10^6 colony-forming units and the bacterial growth was observed after a 20 h incubation at 37 °C.

Molecular Modeling The molecular modeling of ciprofloxacin (**1**), 3-amino-1-propynyl (**7a**), (*Z*)-3-amino-1-propenyl (**8a**), (*E*)-3-amino-1-propenyl (**8b**), and 3-amino-1-propyl (**9**) compounds was performed with SYBYL (version 6.3)[21] on an Indigo 2 R10000 workstation. The molecular structures of the quinolone derivatives were built based on the X-ray crystallographic structures of sparfloxacin (**3**).[3] Minimum-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.[22] 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.[23] Full geometry optimization (all bonds and all angles) was used.

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 elemental analyses and spectral measurements.

References and Notes

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