Synthesis and Antibacterial Activity of 1-(2-Fluorovinyl)-7-substituted-4-quinolone-3-carboxylic Acid Derivatives, Conformationally Restricted Analogues of Fleroxacin

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The novel 1-(2-fluorovinyl)-4-quinolone-3-carboxylic acid derivatives *Z*-**15a**−**c**, *E*-**15a**−**c**, *Z*-**16a**−**c**, and *E*-**16a**−**c**, conformationally restricted analogues of fleroxacin (**5**), were synthesized, and their in vitro antibacterial activity was evaluated. A dehydrosulfenylation of a 2-fluoro-2-[(4-methoxyphenyl)sulfinyl]ethyl group was employed as a key step for the construction of a 2-fluorovinyl group at the N-1 position. It appeared evident that the *Z*-isomers *Z*-**15a**−**c** and *Z*-**16a**−**c** exhibited 2- to 32-fold more potent in vitro antibacterial activity than the corresponding *E*-isomers *E*-**15a**−**c** and *E*-**16a**−**c**. Furthermore, since *Z*-**15b** showed in vitro antibacterial activity and DNA gyrase inhibition comparable to that of **5**, it was hypothesized that the conformation of *Z*-**15b** would be equivalent to the active conformer of **5**. The results revealed that the antibacterial *Z*-1-(2-fluorovinyl)quinolone derivatives carry the novel N-1 substituent of the fluoroquinolones.

Introduction

Since the development of norfloxacin (**1**),[1] the first new quinolone (fluoroquinolone) in which a fluorine atom is attached at the C-6 position, other fluoroquinolones (e.g., ciprofloxacin (**2**)[2] and levofloxacin (**3**))[3] have been developed and clinically used for the treatment of various infectious diseases. A number of syntheses of fluoroquinolone analogues have been reported, together with the corresponding structure−activity relationship (SAR) studies.[4] It is of particular note that the N-1 substituent of fluoroquinolones plays an important role in the antibacterial activity of the fluoroquinolones, and alkyl groups such as ethyl, vinyl, cyclopropyl, and *tert*-butyl groups have been regarded as suitable N-1 substituents. In addition, the stereochemistry of the N-1 substituent of fluoroquinolones is also known to be important for the antibacterial activity of the fluoroquinolones, as is their bulkiness. For example, in the case of **3**, which possesses a rigid N-1 structure restricted by a 1,8-annulated ring system, the 3*S*-enantiomer of **3** was revealed as having 8−128 times more potent activity than the 3*R*-enantiomer of **3**.[3] Even in the case of 1-(2-fluorocyclopropyl)quinolone derivative **4**, the conformation of the N-1 substituent possessing a fluorine atom is restricted by a cyclopropane ring. It has been reported that the cis isomer exhibited more potent antibacterial activity than the trans isomer (Figure 1).[5]

These results indicated that the antibacterial potency of fluoroquinolone would be optimized by restricting the conformation of the N-1 substituent within narrow limits. Thus, for the present study, we focused on the 2-fluoroethyl group, the N-1 substituent of fleroxacin (**5**)[6] (Figure 2). We designed and synthesized 1-(2-fluorovinyl)quinolone derivatives **15** and **16** (Figure 2),

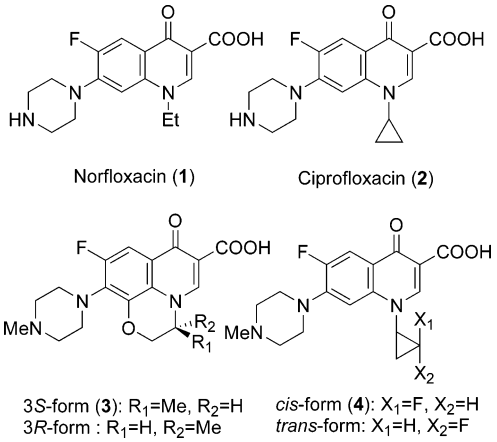

Figure 1.

both bearing a 2-fluorovinyl group and the conformation of which is restricted by the introduction of a double bond into a 2-fluoroethyl group of **5**. The *Z*-isomers *Z*-**15a**−**c** and *Z*-**16a**−**c** appeared to exhibit a 2- to 32-fold more potent in vitro antibacterial activity than the corresponding *E*-isomers *E*-**15a**−**c** and *E*-**16a**−**c**. It was also found that *Z*-**15b**, structurally related to **5**, showed comparable activity and DNA gyrase inhibition to that of **5**; thus, it is possible that the conformation of *Z*-**15b** is in fact equivalent to the active conformer of **5**.

In this paper, we present the synthesis and in vitro antibacterial activity of the fluoroquinolone derivatives **15** and **16** carrying a *Z*- or *E*-(2-fluorovinyl) group as novel N-1 substituents.

Results and Discussion

Chemistry. The synthetic strategy of the 1-(2-fluorovinyl)-7-substituted-4-quinolone-3-carboxylic acid (**15**, **16**) is given in Scheme 1. We employed a dehydrosulfenylation of **12**, carrying a 2-fluoro-2-[(4-methoxy-

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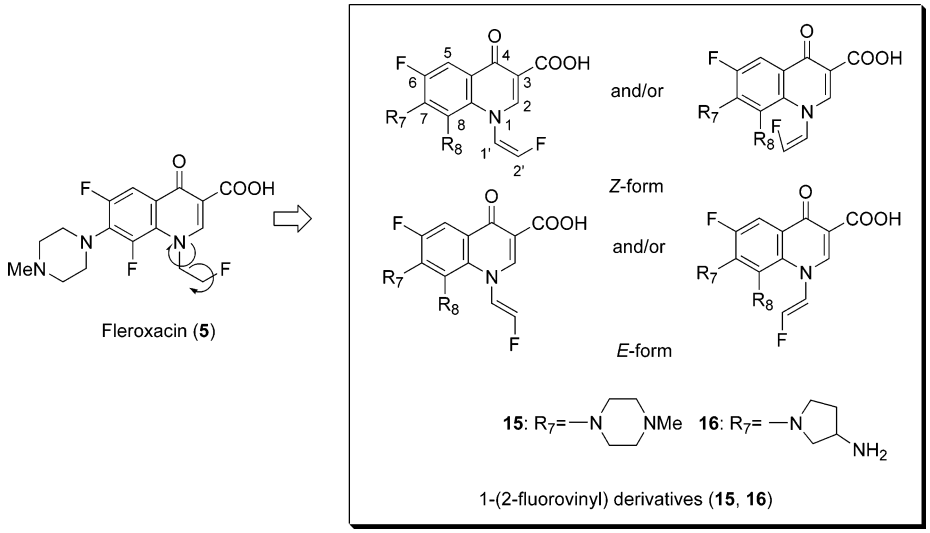
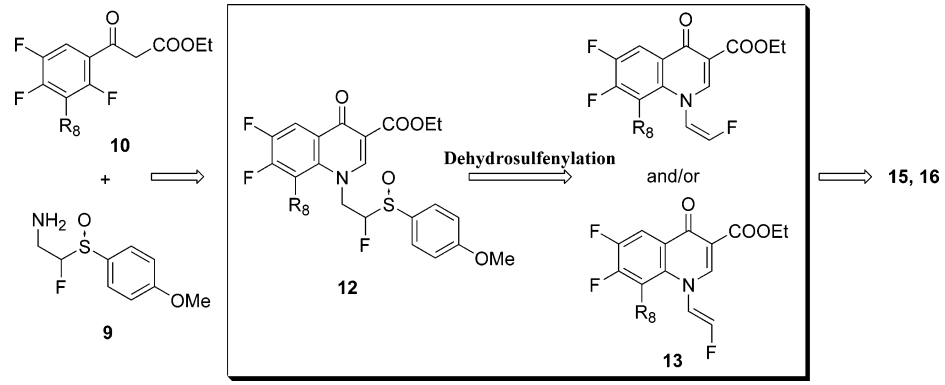
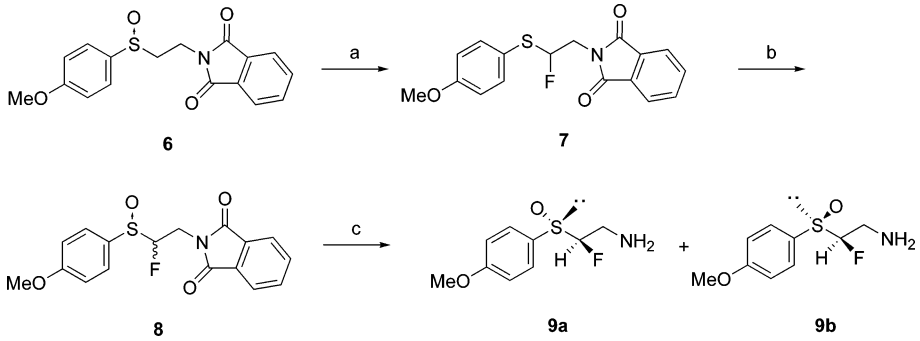


Figure 2.

Scheme 1



Scheme 2[a]



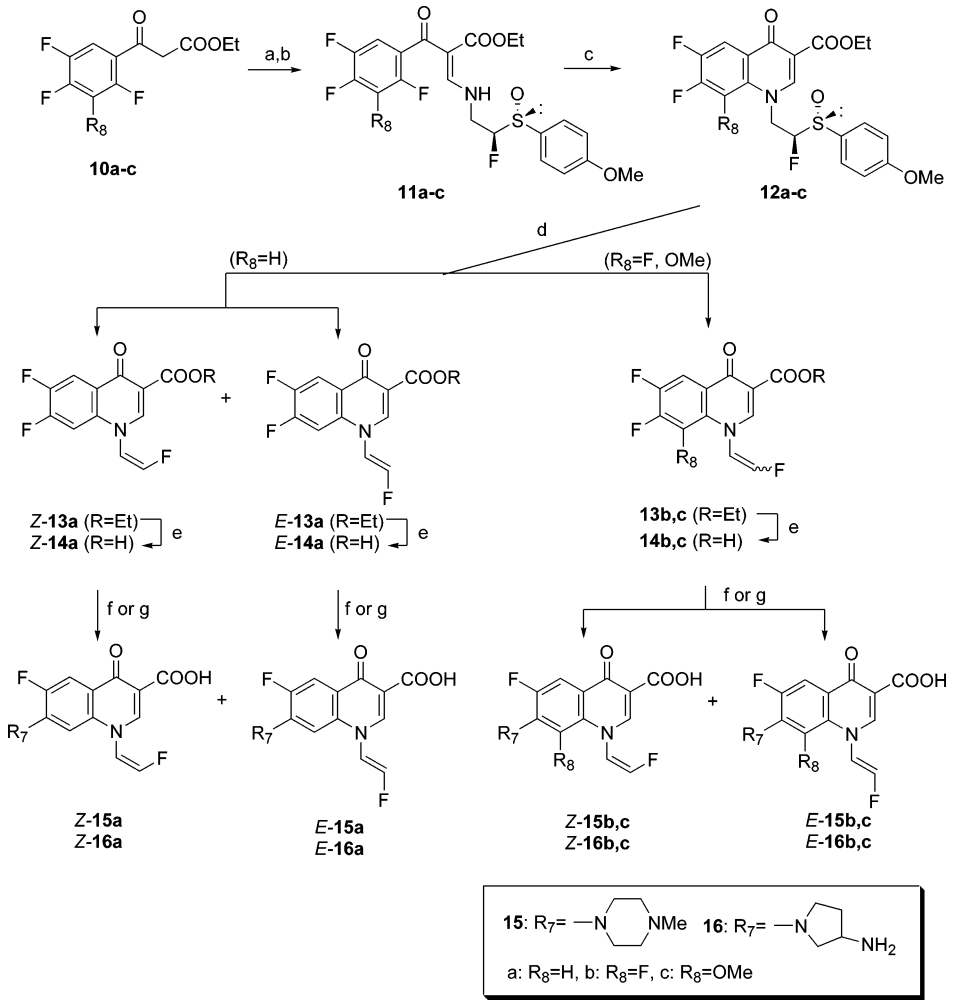
[a] Reagents: (a) DAST, $SbCl_3$, CH_2Cl_2 (91%); (b) MCPBA, $CHCl_3$ (90%); (c) $H_2NNH_2{\cdot}H_2O$ (**9a**, 74%; **9b**, 22%).

phenyl)sulfinyl]ethyl group[7] of **12** as a key step in the construction of the 2-fluorovinyl group at the N-1 position.

The synthesis of 2-fluoro-2-[(4-methoxyphenyl)sulfinyl]ethylamine (**9**), used as the starting material, was achieved by hydrazinolysis of the known sulfoxide **8**,[8] which was provided from **6** according to slightly modified previously reported procedures.[9] After the treatment of **8** with hydrazine monohydrate, separation of the diastereomers of **9** by column chromatography gave anti isomer **9a** and syn isomer **9b**. The ratio of **9a** to **9b** was approximately 7:2. The stereochemistry of **9a** and **9b** was determined by comparison of **9a** and **9b** as regards the chemical shifts of the C_1 hydrogen atom in ^{1}H NMR and the C_1 carbon atom in ^{13}C NMR. These studies were performed on the basis of the reported results for 1-(phenylsulfenyl)-1-fluoroethane.[10] The major anti isomer **9a** was used as the starting material to synthesize **12**, which bears a 2-fluoro-2-[(4-methoxyphenyl)sulfinyl]ethyl group at the N-1 position (Scheme 2).

The synthetic route of 6,7-difluoro-1-(2-fluorovinyl)-8-substituted-4-quinolones **13a**−**c** is shown in Scheme 3. Treatment of benzoyl acetates **10a**−**c**[11] with dimethylformamide dimethylacetal[12] followed by reaction with **9a** gave enaminoesters **11a**−**c**, respectively. Cyclization of **11a**−**c** under basic conditions afforded the 1-[2-fluoro-2-(4-methoxyphenyl)sulfinyl]ethyl-4-quinolone derivatives **12a**−**c**. Thermal elimination of 4-methoxybenzensulfinic acid from **12a**−**c** in xylene gave the desired 6,7-

Scheme 3[a]



[a] Reagents and conditions: (a) $Me_2NCH(OMe)_2$; (b) **9a**, EtOH; (c) K_2CO_3, DMF or NaH, THF; (d) reflux in xylene; (e) H_2SO_4, AcOH, H_2O; (f) 1-methylpiperazine, DMSO; (g) (i) 3-*tert*-butoxycarbonylaminopyrrolidine, DBU, MeCN; (ii) HCl.

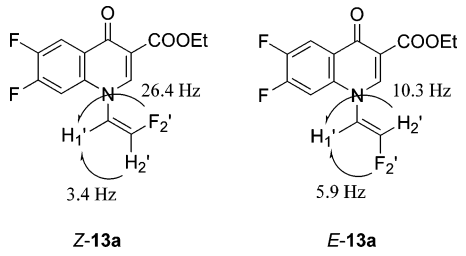


Figure 3.

difluoro-1-(2-fluorovinyl)-8-substituted-4-quinolones **13a**−**c** in a high yield as the mixture of geometrical isomers *Z*-**13a**−**c** and *E*-**13a**−**c**. The ratio of the geometrical isomers *Z* and *E* was approximately 1:2, as calculated from the integration value obtained by ^{1}H NMR. The geometric isomers of 8-fluoro and 8-methoxy derivatives **13b**,**c** were inseparable at this stage by silica gel column chromatography. On the other hand, the geometrical isomers *Z*-**13a** and *E*-**13a** of the 8-hydrogen derivative **13a** were successfully separated by silica gel column chromatography. Their geometries were determined by comparison of the coupling constants between H_1' and F_2', as shown in Figure 3.

Hydrolysis of ester *Z*-**13a** under acidic conditions gave acid *Z*-**14a** without geometric isomerization. Reaction of *Z*-**14a** with 1-methylpiperazine gave the 7-(4-methylpiperazinyl) derivative *Z*-**15a**. Reaction of *Z*-**14a** with 3-(*tert*-butoxycarbonylamino)pyrrolidine, followed by removal of a *tert*-butoxycarbonyl (Boc) group, gave the 7-(3-aminopyrrolidinyl) derivative *Z*-**16a** as its hydrochloride. The geometric isomers *E*-**15a** and -**16a** were synthesized from *E*-**13a** in the same manner as described for *Z*-**15a** and -**16a**. The geometrical isomers of **13b** and **13c** were converted to the corresponding acids **14b** and **14c** in the same manner as described for the synthesis of **14a**. Reaction of **14b** and **14c** with 1-methylpiperazine followed by separation of the geometric isomers gave the 7-(4-methylpiperazinyl) derivatives *Z*- and *E*-**15b**, and *Z*- and *E*-**15c**, respectively. Reaction of **14b** and **14c** with 3-Boc-aminopyrrolidine, separation of the geometrical isomers, and subsequent deprotection of the Boc groups furnished the 7-(3-aminopyrrolidinyl) derivatives *Z*- and *E*-**16b**, and *Z*- and *E*-**16c**, respectively.

Antibacterial Activity. The in vitro antibacterial activity of the *Z*- and *E*-1-(2-fluorovinyl)quinolone derivatives (**15** and **16**) against two Gram-positive strains (*Staphylococcus aureus* Smith and *Streptococcus pneumoniae* type III) and against two Gram-negative strains (*Escherichia coli* NIHJ JC-2 and *Pseudomonas aeruginosa* IID 1210) are shown in Table 1 along with those for **2** and **5**. The *Z*-isomers *Z*-**15a**−**c** and *Z*-**16a**−**c**

Table 1. In Vitro Antibacterial Activity of Compounds *Z*- and *E*-**15** and *Z*- and *E*-**16**

	MIC (μg/mL)			
	Gram-positive bacteria		Gram-negative bacteria	
compd	*S. aureus* Smith	*St. pneumoniae* type III	*E. coli* NIHJ JC-2	*P. aeruginosa* IID1210
Z-**15a**	0.20	3.13	0.025	1.56
E-**15a**	3.13	100	0.20	6.25
Z-**15b**	0.39	3.13	0.025	1.56
E-**15b**	12.5	>50	0.39	12.5
Z-**15c**	0.39	3.13	0.025	3.13
E-**15c**	6.25	50	0.20	25
Z-**16a**	0.39	3.13	0.05	0.78
E-**16a**	1.56	6.25	0.20	3.13
Z-**16b**	0.20	0.78	0.05	0.39
E-**16b**	3.13	12.5	0.20	1.56
Z-**16c**	0.39	1.56	0.0125	1.56
Z-**16c**	6.25	12.5	0.10	6.25
5	0.39	3.13	0.025	1.56
2	0.20	0.78	≤0.0063	0.20

Table 2. Inhibitory Activity of Compounds of *Z*- and *E*-**15b** against DNA Gyrase of *S. aureus*

compd	IC_{50} (μg/mL)
Z-**15b**	72.2
E-**15b**	664
5	68.5
2	20.1

exhibited 2- to 32-fold more potent in vitro antibacterial activity against both of the Gram-positive and both of the Gram-negative strains than did the corresponding *E*-isomers *E*-**15a**−**c** and *E*-**16a**−**c**. Our findings match the case of 1-(2-fluorocyclopropyl)quinolone derivatives, of which the cis isomers exhibited more potent antibacterial activity than the trans isomers.[5] In addition, *Z*-**15a**−**c** and *Z*-**16a**−**c** exhibited comparable in vitro antibacterial activity to that of **5**. Among the compounds tested, the 7-(3-aminopyrrolidinyl) derivative *Z*-**16b**, which bears a fluorine atom at the C-8 position, exhibited the most potent in vitro antibacterial activity of all of the compounds, and *Z*-**16b** showed comparable in vitro antibacterial activity against *S. aureus* Smith, *St. pneumoniae* type III, and *P. aeruginosa* IID1210 to that of **2**, with the exception of its activity against *E. coli* NIHJ JC-2.

Next, we evaluated the inhibition potencies of *Z*-**15b** and *E*-**15b**, which are conformationally restricted analogues of **5**, and the inhibition potentials of **2** and **5** in the presence of DNA gyrase of *S. aureus*. As shown in Table 2, the IC_{50} value of *Z*-**15b** was 9-fold smaller than that of *E*-**15b** and was comparable to that of **5**. This difference in the inhibition abilities of *Z*-**15b**, *E*-**15b**, and **5** reflected the differences in the in vitro antibacterial activity of those compounds against *S. aureus* Smith. The stereochemistry of the 2-fluorovinyl group, or the position of the fluorine atom of the 2-fluorovinyl group of *Z*-**15a** and *E*-**15b**, appeared to exert an influence on both in vitro antibacterial activity and inhibition of the target enzyme, DNA gyrase.

Conformation Analysis. Since *Z*-**15b** exhibited equal ability to inhibit the target enzyme, DNA gyrase, and also because it was revealed to have comparable in vitro antibacterial activity to that of **5**, *Z*-**15b** could be regarded as an active conformer of **5**. Therefore, we performed a study to determine the active conformer of **5** by defining the conformation of the 1-(2-fluorovinyl) group. First, to confirm the position of the fluorine atom on the 1-(2-fluorovinyl) group, we carried out NOE experiments using ^1H NMR analysis of the 8-hydrogen derivatives *Z*-**15a** and *E*-**15a**. The results are shown in Figure 4. The NOEs were observed between H_1' and both H_2 and H_8 for both *Z*-**15a** and *E*-**15a**. From these NOE data, it became apparent that the 2-fluorovinyl groups of *Z*-**15a** and *E*-**15a** are oriented above (or below) the plane of the quinolone ring. Furthermore, the NOE was also observed between H_2' and H_2 for *E*-**15a**; long-range coupling (^5J = 1.0 Hz) with F_2' was also observed in H_2 for *Z*-**15a**. These ^1H NMR data indicated that the fluorine atoms on the 2-fluorovinyl groups of *Z*-**15a** and *E*-**15a** existed on the side opposing H_8.

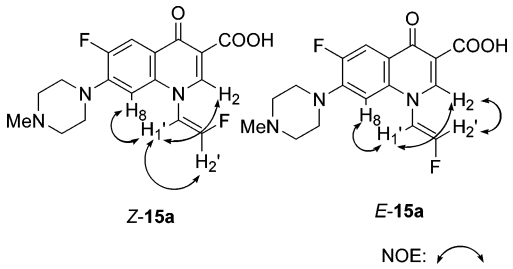


Figure 4. NOE experiments in ^1H NMR of *E*-**15a** and *Z*-**15a**.

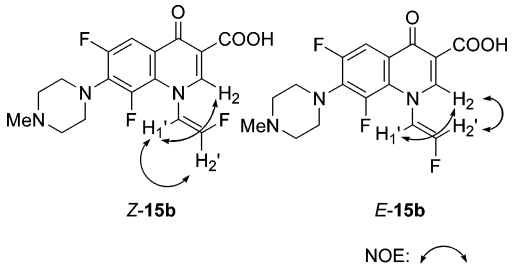


Figure 5. NOE experiments in ^1H NMR of *E*-**15b** and *Z*-**15b**.

Additional NOE experiments were performed using the 8-fluoro derivatives *Z*-**15b** and *E*-**15b**, which are conformationally restricted analogues of **5**. The NOEs were observed between H_1' and H_2 for both *Z*-**15b** and *E*-**15b** and between $H_2'$and H_2 for *E*-**15b**, as shown in Figure 5. In addition, long-range coupling (^5J = 1.5 Hz) with F_2' was observed in H_2 for *Z*-**15b**. These ^1H NMR results of *Z*-**15b** and *E*-**15a** were similar to those of the corresponding 8-hydrogen derivatives *Z*-**15a** and *E*-**15a**. It was therefore indicated that the 2-fluorovinyl groups of *Z*-**15b** and *E*-**15b** have conformations similar to those of *Z*-**15a** and *E*-**15a**, respectively.

To define the active conformer of **5**, we then carried out the molecular modeling of the 2-fluorovinyl group of *Z*-**15b**. The dihedral angle of $C_2-N_1-C_1'-C_2'$ (denoted as Θ in this paper) of *Z*-**15b** and that of **5** changed from −180° to 180° by increments of 5°, and the energy of each conformer was calculated by using AM1 parameters. The results are given in Figure 6. In the case of *Z*-**15b**, it appeared that the two energy minima conformers existed. One of these conformers was energy minimum conformer located above the plane of the quinolone ring and was on the opposite side of a C_8-fluorine atom (Θ = 45°, conformer A), and the other was located under the plane of the quinolone ring (Θ = −45°, conformer B). There was very little energy difference (0.195 kcal/mol) between the two. These results were in good agreement with the results of the ^1H NMR experiments with *Z*-**15b**. In contrast, in the case of **5**,

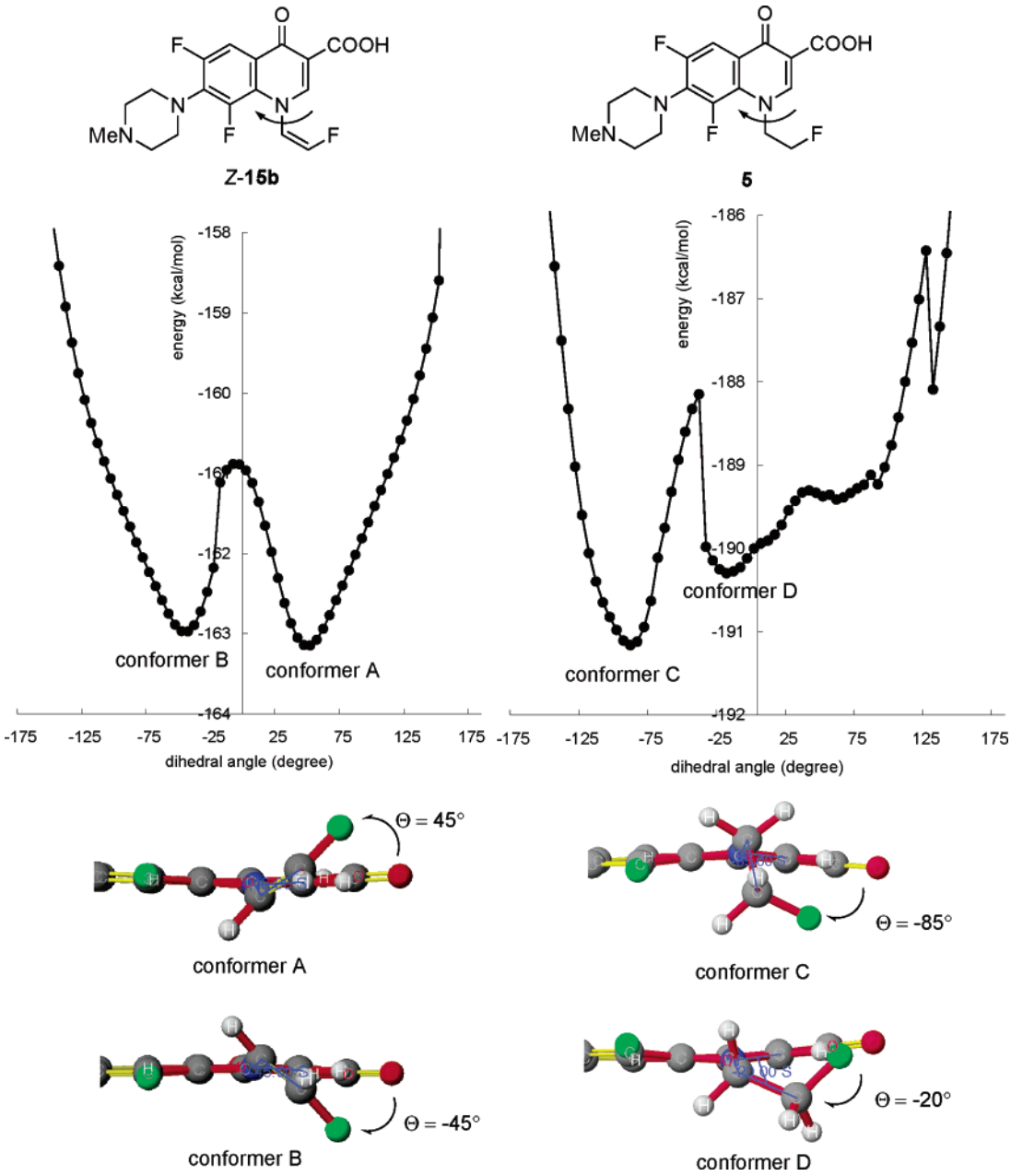


Figure 6. Rotational energy map of N_1-R_1 bond and energy minima conformers of 1-(2-fluorovinyl) derivatives of *Z*-**15b** and **5** calculated by using AM1 parameters. Θ is defined as the $C_2-N_1-C'_1-C'_2$ dihedral angle.

although there existed the one energy minimum conformer and it was located under the plane of the quinolone ring (Θ = −85°, conformer C), there was no energy minimum conformer above the plane of the quinolone ring. These calculation results showed that the conformation of the 2-fluorovinyl group of *Z*-**15b** is more restricted than that of the 2-fluoroethyl group of **5**, especially within the range of the upper side of the quinolone ring. Furthermore, according to a previous study, which focused on the relationship between the dihedral angle Θ of N1 substituents of fluoroquinolone derivatives using molecular orbital calculation and the in vitro antibacterial activity of this group, it appeared that the active conformer of the N_1 substituents of the fluoroquinolones was located above the plane of the quinolone ring.[13] Consequently, conformer A of *Z*-**15b** could be regarded as the active conformer of *Z*-**15b**.

On the basis of the results of the conformation analysis of the 2-fluorovinyl group of *Z*-**15b** as described above, it is likely that conformer A would be equivalent to the active conformer of **5**.

Conclusions

As described above, we succeeded in the design, synthesis, and evaluation of in vitro antibacterial activity on the 4-quinolone-3-carboxylic acids *Z*-**15a**−**c**, *E*-**15a**−**c**, *Z*-**16a**−**c**, and *E*-**16a**−**c**, which are conformationally restricted analogues of **5** carrying a 2-fluoroethyl group as the novel N-1 substituent. The synthesis of these compounds was achieved in five steps from **10a**−**c** by a method featuring a dehydrosulfenylation of the 2-fluoro-2-[(4-methoxyphenyl)sulfinyl]ethyl group as the key step for the construction of the 2-fluorovinyl group at the N-1 position. It appeared evident that the *Z*-isomers *Z*-**15a**−**c** and *Z*-**16a**−**c** exhibited 2- to 32-fold more potent in vitro antibacterial activity than the corresponding *E*-isomers *E*-**15a**−**c** and *E*-**16a**−**c**. On the basis of the in vitro antibacterial activity analysis, as

well as analysis of the DNA gyrase inhibitory ability of *Z*-**15b** and **5**, and the conformation analysis of *Z*-**15b**, it can be concluded that the conformation of *Z*-**15b** is most likely equivalent to the active conformer of **5**. Considering the results of the present study, the novel *Z*-1-(2-fluorovinyl)-4-quinolone-3-carboxylic acid would be an intriguing scaffold for the exploration of novel quinolone antibacterials. Further investigation of the *Z*-(1-fluorovinyl)quinolones is in progress.

Experimental Section

Melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. Elemental analyses are within ±0.4% of the theoretical values and were determined by a Yanaco CHN MT-5 instrument. Infrared spectra (IR) were recorded with a JASCO FTIR-5300 spectrometer. Measurements of mass spectra (MS) and high-resolution MS (HRMS) were performed with a JEOL JMS SX-102A mass spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) were measured with a JEOL EX-90 (90 MHz) or a JEOL JMN-EX400 (400 MHz) spectrometer. The chemical shifts are expressed in parts per million (δ value) downfield from tetramethylsilane, using tetramethylsilane ($\delta = 0$) and/or residual solvents such as chloroform ($\delta = 7.26$) as an internal standard. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Column chromatography was carried out with silica gel [silica gel 60 (Kanto)] as an absorbent. Merck precoated thin-layer chromatography (TLC) plates (silica gel 60 F_{254}, 0.25 mm, Art 5715) were used for the TLC analysis. Solutions were dried over sodium sulfate, and the solvent was removed by rotary evaporation under reduced pressure.

***N*-[2-[2-Fluoro-(4-methoxyphenyl)thio]ethyl]phthalimide (7).** Diethylaminosulfur trifluoride (4.21 mL, 31.9 mmol) was added to a solution of *N*-[2-[(4-methoxyphenyl)sulfinyl]-ethyl]phthalimide (**6**, 6.00 g, 18.2 mmol) and antiomonyl(III) chloride (125 mg, 0.548 mmol) in anhydrous CH_2Cl_2 (42 mL) under ice cooling, and the mixture was stirred at room temperature for 3 h. After the reaction was quenched by adding saturated aqueous $NaHCO_3$ solution (36 mL) under ice cooling, the mixture was extracted with CH_2Cl_2 (50 mL). The combined CH_2Cl_2 extracts were washed with water (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo to give **7** (5.52 g, 91%) as pale-brown crystals. ^{1}H NMR ($CDCl_3$) δ: 3.82 (s, 3H, CH_3), 4.04 (ddd, J = 40.2, 14.4, 4.9 Hz, 1H, CH_2), 4.08 (ddd, J = 42.0, 14.2, 8.1 Hz, 1H, CH_2), 5.94 (ddd, J = 53.6, 8.1, 4.9 Hz, 1H, CH), 6.87−6.90 (m, 2H, Ar−H), 7.48−7.50 (m, 2H, Ar−H), 7.74 (dd, 2H, Ar−H), 7.87 (dd, 2H, Ar−H).

***N*-[2-Fluoro-2-[(4-methoxyphenyl)sulfinyl]ethyl]-phthalimide (8).** To a solution of **7** (5.51 g, 16.6 mmol) in $CHCl_3$ (100 mL), *m*-chloroperoxybenzoic acid (65%, 4.41 g, 16.6 mmol) was added at −50 to −40 °C for 40 min, and the mixture was stirred at the same temperature for 20 min. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (2 × 100 mL), 10% aqueous Na_2SO_3 (2 × 100 mL) solution and water (100 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 1:1 → AcOEt) of the residue gave **8** (5.18 g, 90%) as a white solid. ^{1}H NMR ($CDCl_3$) δ: 3.85 (s, 2.4H, CH_3), 3.86 (s, 0.6H, CH_3), 4.08−4.20 (m, 1.2H, CH_2), 4.39 (ddd, J = 14.6, 12.7 , 7.8 Hz, 0.8H, CH_2), 5.32 (ddd, J = 48.8, 7.8, 4.4 Hz, 0.8H, CH), 5.42 (dt, J = 49.8, 5.9 Hz, 0.8H, CH), 7.03−7.08 (m, 2H, Ar−H), 7.65−7.68 (m, 2H, Ar−H), 7.72−7.76 (m, 2H, Ar−H), 7.84−7.88 (m, 2H, Ar−H).

2-[2-Fluoro-2-(4-methoxyphenyl)sulfinyl]ethylamine (9a, 9b). Hydrazine monohydrate (1.30 mL, 26.8 mmol) was added to a solution of **8** (4.66 g, 13.4 mmol) in EtOH (50 mL), and the mixture was heated under reflux for 1 h. After the mixture was cooled, the precipitates that had formed were filtered off and the filtrate was concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH = 10:1) of the residue gave **9a** (2.16 g, 74%) as a pale-brown syrup and **9b** (627 mg, 22%) as a red-brown oil.

9a. ^{1}H NMR ($CDCl_3$) δ: 3.35 (ddd, J = 22.0, 15.1, 3.4 Hz, 1H, C_1−H), 3.44 (ddd, J = 27.3, 15.1, 4.9 Hz, 1H, C_1−H), 3.87 (s, 3H, CH_3), 4.81 (ddd, J = 48.8, 4.9, 3.4 Hz, 1H, C_2−H), 7.05−7.09 (m, 2H, Ar−H), 7.62−7.66 (m, 2H, Ar−H). ^{13}C NMR ($CDCl_3$) δ: 40.6 (J = 20.2 Hz), 55.6, 107.6 (J = 219 Hz), 115.0 (2C), 126.9 (2C), 130.9 (J = 4.9 Hz), 162.7. MS (EI) *m/z*: 217 (M^+). HRMS (EI) for $C_9H_{12}FNO_2S$ (M^+): calcd, 217.0573; found, 217.0546.

9b. ^{1}H NMR ($CDCl_3$) δ: 3.08 (ddd, J = 17.1, 14.6, 6.3 Hz, 1H, C_1−H), 3.25 (ddd, J = 22.5, 14.6, 4.9 Hz, 1H, C_1−H), 3.87 (s, 3H, CH_3), 4.97 (ddd, J = 47.9, 6.3, 4.9 Hz, 1H, C_2−H), 7.05−7.09 (m, 2H, Ar−H), 7.61−7.64 (m, 2H, Ar−H). ^{13}C NMR ($CDCl_3$) δ: 40.7 (J = 22.1 Hz), 55.6, 106.4 (J = 219 Hz), 114.9 (2C), 127.1 (2C), 129.3 (J = 3.7 Hz), 162.7. MS (EI) *m/z*: 217 (M^+). HRMS (EI) for $C_9H_{12}FNO_2S$ (M^+): calcd, 217.0573; found, 217.0562.

Ethyl 2-[2-(Fluoro-2-(4-methoxyphenylsulfinyl)ethylamino)-1-(2,4,5-trifluorobenzoyl)]acrylate (11a). To a solution of **10a** (1.03 g, 4.18 mmol) in benzene (25 mL), *N*,*N*-dimethylformamide dimethyl acetal (2.50 mL, 18.8 mmol) was added. The mixture was heated under reflux for 1 h and then concentrated in vacuo. To a solution of the residue in toluene (12 mL), **9a** (1.00 g, 4.60 mmol) was added. The mixture was stirred at room temperature for 2 h and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 1:1) of the residue gave **11a** (1.57 g, 79%) as a yellow foam. ^{1}H NMR ($CDCl_3$) δ: 1.40 (t, J = 7.3 Hz, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.38 (q, J = 7.3 Hz, 2H, CH_2), 4.66−4.81 (m, 2H, CH_2), 5.15 (ddd, J = 48.8, 7.8, 2.0 Hz, CHF), 6.78 (1H, dd, J = 11.0, 6.3 Hz, Ar−H), 7.15 (d, J = 8.8 Hz, 2H, Ar−H), 7.66 (d, J = 8.8 Hz, 2H, Ar−H), 8.26 (dd, J = 10.3, 8.8 Hz, 1H, Ar−H), 8.38 (s, 1H, CH).

Ethyl 2-[2-(Fluoro-2-(4-methoxyphenylsulfinyl)ethylamino)-1-(2,3,4,5-tetrafluorobenzoyl)]acrylate (11b). The compound **11b** (1.82 g, 99%) was prepared from **10b** (1.00 g, 3.79 mmol) and **9a** (948 mg, 4.36 mmol) by the same method as that used for **11a**. ^{1}H NMR ($CDCl_3$) δ: 0.99 and 1.40 (each t, J = 7.3 Hz, total 3H, CH_3), 3.88 (s, 3H, CH_3), 4.03−4.16 (m, 4H, CH_2 × 2), 4.93−4.95 and 5.05−5.07 (each m, total 1H, C*H*F), 6.99−7.11 (m, 3H, Ar−H), 7.63 (d, 2H, Ar−H), 7.99 and 8.11 (each d, total 1H, CH), 9.40−9.60 and 10.8−11.0 (each br, total 1H, NH).

Ethyl 2-[2-(Fluoro-2-(4-methoxyphenylsulfinyl)ethylamino)-1-(2,4,5-trifluoro-3-methoxybenzoyl)]acrylate (11c). The compound **11c** (1.62 g, 89%) was prepared from **10c** (1.00 g, 3.62 mmol) and **9a** (905 mg, 4.17 mmol) by the same method as that used for **11a**. ^{1}H NMR ($CDCl_3$) δ: 0.98 and 1.10 (each t, J = 7.3 Hz, total 3H, CH_3), 3.88 (s, 3H, CH_3), 4.00 (s, 3H, CH_3), 4.03−4.16 (m, 2H, CH_2 × 2), 4.91−5.07 (m, 1H, CHF), 6.86−6.92 and 6.98−7.04 (each m, total 1H, Ar−H), 7.08−7.10 (m, 2H, Ar−H), 7.63 (d, J = 8.8 Hz, 2H, Ar−H), 7.96 (d, J = 14.2 Hz, 0.3H, CH), 8.08 (d, J = 13.7 Hz, 0.7H, CH), 9.41−9.54 and 10.8−10.9 (each br, total 1H, NH).

Ethyl 1-[2-Fluoro-2-(4-methoxyphenylsulfinyl)ethyl]-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate (12a). A solution of **11a** (1.28 g, 2.70 mmol) in anhydrous THF (13 mL) was added to a suspension of sodium hydride (60% oil suspension, 108 mg, 2.70 mmol) in anhydrous THF (13 mL) under cooling with ice. After the reaction mixture was stirred at a constant temperature for 30 min, it was poured into ice/water (30 mL). The resulting precipitates were collected by filtration, washed with water, and then dried in vacuo to give **12a** (945 mg, 77%). Mp: 191−193 °C (MeOH). ^{1}H NMR ($CDCl_3$) δ: 1.40 (t, J = 7.3 Hz, 3H, CH_3), 3.89 (s, 3H, CH_3), 4.38 (q, J = 7.3 Hz, 2H, CH_2), 4.62 (ddd, J = 37.6, 16.6, 7.8 Hz, 1H, C_1'−H), 4.75 (ddd, J = 28.3, 16.1, 2.0 Hz, 1H, C_1'−H), 5.15 (ddd, J = 48.9, 7.8, 2.0 Hz, 1H, C_2'−H), 6.79 (dd, J = 11.0, 6.3 Hz, 1H, C_8−H), 7.15 (d, J = 8.8 Hz, 2H, Ar−H), 7.66 (d, J = 8.8 Hz, 2H, Ar−H), 8.26 (dd, J = 10.3, 8.8 Hz, 1H, C_5−H), 8.38 (s, 1H, C_2−H). IR (KBr) cm^{-1}: 1732, 1602. MS (EI) *m/z*: 453 (M^+). Anal. ($C_{21}H_{18}F_3NO_5S$) C, H, N.

Ethyl 1-[2-Fluoro-2-(4-methoxyphenylsulfinyl)ethyl]-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate (12b). The compound **12b** (1.36 g, 80%) was prepared from **11b** (1.77 g, 3.75 mmol) by the same method as that used for **12a**. Mp: 136−137 °C. ^{1}H NMR ($CDCl_3$) δ: 1.40 (t, J = 7.3 Hz, 3H, CH_3), 3.89 (s, 3H, CH_3), 4.39 (q, J = 7.3 Hz, 2H, CH_2), 4.66−4.76 (m, 1H, C_1'−H), 4.96 (ddt, J = 27.6, 16.1, 2.9 Hz, 1H, C_1'−H), 5.27 (dd, J = 49.3, 8.3 Hz, 1H, C_2'−H), 7.08−7.21 (m, 2H, Ar−H), 7.59−7.65 (m, 2H, Ar−H), 8.12 (dd, J = 9.0, 2.4 Hz, 1H, C_5−H), 8.37 (s, 1H, C_2−H). IR (KBr) cm^{-1}: 1732, 1701, 1602. MS (EI) *m/z*: 471 (M^+). Anal. ($C_{21}H_{17}F_4NO_5S$) C, H, N.

Ethyl 1-[2-Fluoro-2-(4-methoxyphenylsulfinyl)ethyl]-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylate (12c). The compound **12c** (1.33 g, 88%) was prepared from **11c** (1.57 g, 3.12 mmol) by the same method as that used for **12a**. Mp: 131−136 °C (MeOH/Et_2O). ^{1}H NMR ($CDCl_3$) δ: 1.40 (t, J = 7.3 Hz 3H, CH_3), 3.82 (d, J = 2.4 Hz, 3H, OCH_3), 3.89 (3H, s, OCH_3), 4.39 (2H, m, CH_2), 4.63 (1H, ddd, J = 15.3, 12.2, 9.3 Hz, C_1'−H), 5.20 (1H, ddd, J = 49.8, 9.3, 2.4 Hz, C_1'−H), 5.33 (1H, ddd, J = 49.8, 9.3, 2.4 Hz, C_2'−H), 7.10 (d, J = 8.8 Hz, 2H, Ar−H), 7.62 (d, J = 8.8 Hz, 2H, Ar−H), 8.86 (dd, J = 10.3, 8.8 Hz, 1H, C_5−H), 8.32 (1H, s, C_2−H). IR (KBr) cm^{-1}: 1730, 1618. MS *m/z*: 483 (M^+). Anal. ($C_{22}H_{20}F_3NO_6S\cdot0.25H_2O$) C, H, N.

Ethyl 6,7-Difluoro-1-(2-fluorovinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylate (13a). A mixture of **12a** (1.05 g, 2.32 mmol) and xylene (22 mL) was heated under reflux for 3.5 h and then concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH = 10:1) of the residue gave *Z*-**13a** (235 mg, 34%) and *E*-**13a** (427 mg, 62%) as white solids.

***Z*-13a.** ^{1}H NMR ($CDCl_3$) δ: 1.41 (t, J = 7.3 Hz, 3H, CH_3), 4.40 (q, J = 7.3 Hz, 2H, $COOCH_2$), 6.36 (dd, J = 26.4, 3.4 Hz, 1H, *Z*-C_1'−H), 7.03 (dd, J = 74.7, 3.4 Hz, 1H, *Z*-C_2'−H), 7.25 (dd, J = 10.7, 7.8 Hz, 1H, C_8−H), 8.26 (dd, J = 10.3, 8.8 Hz, 1H, C_5−H), 8.45 (d, J = 1.0 Hz, 1H, C_2−H). MS (EI) *m/z*: 297 (M^+). HRMS (EI) for $C_{14}H_{10}F_3NO_3$ (M^+): calcd, 297.0613; found, 297.0638. Anal. ($C_{14}H_{10}F_3NO_3$) C, H, N.

***E*-13a.** ^{1}H NMR ($CDCl_3$) δ: 1.40 (t, J = 7.3 Hz, 3H, CH_3), 4.36 (q, J = 7.3 Hz, 2H, $COOCH_2$), 7.03 (dd, J = 10.3, 5.9 Hz, 1H, *E*-C_1'−H), 7.25 (dd, J = 10.7, 6.4 Hz, 1H, C_8−H), 7.47 (dd, J = 74.5, 10.3 Hz, 1H, *E*-C_2'−H), 8.16 (dd, J = 10.3, 8.3 Hz, 1H, C_5−H), 8.37 (s, 1H, C_2−H). MS (EI) *m/z*: 297 (M^+). HRMS (EI) for $C_{14}H_{10}F_3NO_3$ (M^+): calcd, 297.0613; found, 297.0638. Anal. ($C_{14}H_{10}F_3NO_3$) C, H, N.

Ethyl 6,7,8-Trifluoro-1-(2-fluorovinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylate (13b). The compound **13b** (780 mg, 93%) was prepared from **12b** (1.25 g, 2.65 mmol) by the same method as that used for **13a**. Mp: 141−143 °C. ^{1}H NMR ($CDCl_3$) δ: 1.39−1.42 (m, 3H, CH_3), 4.36−4.42 (m, 2H, $COOCH_2$), 6.67 (ddd, J = 25.9, 9.3, 3.4 Hz, 0.5H, *Z*-C_1'−H), 6.91 (ddd, J = 75.2, 3.4, 2.0 Hz, 0.5H, *Z*-C_2'−H), 7.39 (ddd, J = 10.3, 10.0, 4.4 Hz, 0.5H, *E*-C_1'−H), 7.43 (dd, J = 74.5, 10.3 Hz, 0.5H, *E*-C_2'−H), 8.05−8.13 (m, 1H, C_5−H), 8.05 (s, 1H, *E*-C_2−H), 8.36 (d, J = 1.5 Hz, 0.5H, C_2−H). IR (KBr) cm^{-1}: 1730, 1691, 1628. MS *m/z*: 315 (M^+). Anal. ($C_{14}H_9F_4NO_3$) C, H, N.

Ethyl 6,7-Difluoro-1-(2-fluorovinyl)-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylate (13c). The compound **13c** (1.09 g, 81%) was prepared from **12c** (2.00 g, 4.14 mmol) by the same method as that used for **13a**. Mp: 177−178 °C. ^{1}H NMR ($CDCl_3$) δ: 1.47 (t, J = 7.3 Hz, 3H, CH_3), 3.95 (d, J = 1.0 Hz, 1H, OCH_3), 3.98 (d, J = 1.5 Hz, 2H, OCH_3), 4.36−4.42 (m, 2H, CH_2), 6.78 (s, 0.3H, *Z*-C_1'−H), 6.91 (dd, J = 51.3, 3.9 Hz, 0.3H, *Z*-C_2'−H), 7.26 (dd, J = 75.6, 10.3 Hz, 0.7H, *Z*-C_2'−H), 7.55 (dd, J = 10.3, 6.8 Hz, 0.7H, *E*-C_1'−H), 8.00−8.09 (m, 1H, C_5−H), 8.29 (s, 0.7H, *E*-C_2−H), 8.35 (d, J = 2.0 Hz, 0.3H, C_2−H). IR (KBr) cm^{-1}: 1730, 1617. MS *m/z*: 327 (M^+). Anal. ($C_{15}H_{12}F_3NO_4$) C, H, N.

6,7-Difluoro-1-[(*Z*)-2-fluorovinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (*Z*-14a). A mixture of *Z*-**13a** (273 mg, 1.01 mmol), concentrated H_2SO_4 (0.7 mL), AcOH (3.5 mL), and water (3.5 mL) was stirred at 100 °C for 1 h and then poured into ice/water. The resulting precipitates were collected by filtration, washed with water, and then dried in vacuo to give *Z*-**14a** (228 mg, 92%) as a white solid. Mp: 201−204 °C. ^{1}H NMR ($CDCl_3$) δ: 6.46 (dd, J = 25.2, 3.4 Hz, 1H, C_1'−H), 7.12 (dd, J = 73.8, 3.4 Hz, 1H, C_2'−H), 7.41 (dd, J = 9.5, 6.4 Hz, 1H, C_8−H), 8.32 (dd, J = 9.8, 8.3 Hz, 1H, C_5−H), 8.75 (d, J = 1.0 Hz, 1H, C_2−H). IR (KBr) cm^{-1}: 1720, 1618. MS *m/z*: 269 (M^+). HRMS for $C_{12}H_6F_3NO_3$ (M^+): calcd, 269.0300; found, 269.0302. Anal. ($C_{12}H_6F_3NO_3$) C, H, N.

6,7-Difluoro-1-[(*E*)-2-fluorovinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (*E*-14a). The compound *E*-**14a** (413 mg, 93%) was prepared from *E*-**13a** (489 mg, 1.82 mmol) by the same method as that used for ***Z*-14a**. Mp: 267−269 °C. ^{1}H NMR ($CDCl_3$) δ: 7.12 (dd, J = 10.5, 5.9 Hz, 1H, C_1'−H), 7.41 (dd, J = 73.6, 10.3 Hz, 1H, C_2'−H), 7.43 (dd, J = 10.3, 6.4 Hz, 1H, C_8−H), 8.32 (dd, J = 9.5, 8.3 Hz, 1H, C_5−H), 8.73 (s, 1H, C_2−H). IR (KBr) cm^{-1}: 1732, 1618. MS *m/z*: 269 (M^+). HRMS for $C_{12}H_6F_3NO_3$ (M^+): calcd, 269.0300; found, 269.0328. Anal. ($C_{12}H_6F_3NO_3$) C, H, N.

6,7,8-Trifluoro-1-(2-fluorovinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (14b). The compound **14b** (123 mg, 93%) was prepared from **13b** (145 mg, 0.460 mmol) by the same method as that used for *Z*-**14a**. Mp: 268−271 °C. ^{1}H NMR ($CDCl_3$) δ: 6.67 (ddd, J = 24.7, 9.8, 3.5 Hz, 0.5H, *Z*-C_1'−H), 7.00 (ddd, J = 74.6, 3.5, 2.0 Hz, 0.5H, *Z*-C_2'−H), 7.35 (dd, J = 71.6, 9.8 Hz, 0.5H, *E*-C_2'−H), 7.46 (ddd, J = 10.1, 9.8, 6.8 Hz, 0.5H, *E*-C_1'−H), 8.14−8.20 (m, 1H, C_5−H), 8.62 (s, 1H, *E*-C_2−H), 8.65 (d, J = 1.5 Hz, 0.5H, *Z*-C_2−H). IR (KBr) cm^{-1}: 1728, 1618. MS *m/z*: 287 (M^+). Anal. ($C_{12}H_5F_4NO_3\cdot0.25H_2O$) C, H, N.

6,7-Difluoro-1-(2-fluorovinyl)-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic Acid (14c). The compound **14c** (913 mg, 96%) was prepared from **13c** (1.04 g, 3.18 mmol) by the same method as that used for *Z*-**14a**. Mp: 230−232 °C. ^{1}H NMR (DMSO-d_6) δ: 3.93 (d, J = 1.0 Hz, 2.1H, *E*-OCH_3), 3.95 (d, J = 1.5 Hz, 0.9H, *Z*-OCH_3), 7.13 (ddd, J = 28.9, 3.4 Hz, 0.3H, *Z*-C_1'−H), 7.40 (ddd, J = 76.8, 3.4 Hz, 0.3H, *Z*-C_2'−H), 7.70 (dd, J = 16.1, 10.3 Hz, 0.7H, *E*-C_1'−H), 7.81 (dd, J = 81.7, 10.3 Hz, 0.7H, *E*-C_2'−H), 8.07 (dd, J = 10.3, 8.3 Hz, 0.3H, *Z*-C_5−H), 8.09 (dd, J = 10.3, 8.3 Hz, 0.7H, *E*-C_5−H), 8.59 (d, J = 1.5 Hz, 0.3H, *Z*-C_2−H), 8.63 (s, 0.7H, *E*-C_2−H), 14.3 (br, 0.3H, COOH), 14.4 (s, 0.7H, COOH). IR (KBr) cm^{-1}: 1736, 1617. MS *m/z*: 299 (M^+). Anal. ($C_{13}H_8F_3NO_4$) C, H, N.

6-Fluoro-1-[(*Z*)-2-fluorovinyl]-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic Acid (*Z*-15a). A mixture of *Z*-**14a** (60 mg, 0.223 mmol), *N*-methylpiperazine (54.0 μL, 0.487 mmol), and DMSO (1 mL) was stirred at 60 °C for 1 h and then concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH/25% NH_4OH = 20:5:1) of the residue gave *Z*-**15a** (21 mg, 27%) as a white powder. Mp: 196−199 °C. ^{1}H NMR ($CDCl_3$) δ: 2.38 (s, 3H, CH_3), 2.62−2.65 (m, 4H, CH_2 × 2), 3.33−3.38 (m, 4H, CH_2 × 2), 6.42 (dd, J = 25.9, 3.4 Hz, 1H, C_1'−H), 6.77 (d, J = 6.4 Hz, 1H, C_8−H), 7.06 (dd, J = 74.3, 3.4 Hz, 1H, C_2'−H), 8.05 (d, J = 12.7 Hz, 1H, C_5−H), 8.65 (d, J = 1.0 Hz, 1H, C_2−H), 14.5−15.0 (br, 1H, COOH). IR (KBr) cm^{-1}: 1728, 1628. MS *m/z*: 349 (M^+). HRMS for $C_{17}H_{17}F_2N_3O_3$ (M^+): calcd, 349.1238; found, 349.1203. Anal. ($C_{17}H_{17}F_2N_3O_3$) C, H, N.

6-Fluoro-1-[(*E*)-2-fluorovinyl]-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic Acid (*E*-15a). The compound *E*-**15a** (96 mg, 74%) was prepared from *E*-**14a** (100 mg, 0.371 mmol) by the same method as that used for *Z*-**15a**. Mp: 249−251 °C. ^{1}H NMR ($CDCl_3$) δ: 2.39 (s, 3H, CH_3), 2.62−2.65 (m, 4H, CH_2 × 2), 3.35−3.38 (m, 4H, CH_2 × 2), 6.77 (d, 1H, J = 6.8 Hz, C_8−H), 7.12 (dd, J = 10.3, 6.4 Hz, 1H, C_1'−H), 7.13 (dd, J = 74.6, 10.3 Hz, 1H, C_2'−H), 8.04 (d, J = 13.2 Hz, 1H, C_5−H), 8.61 (s, 1H, C_2−H). IR (KBr) cm^{-1}: 1721, 1630. MS *m/z*: 349 (M^+). HRMS for $C_{17}H_{17}F_2N_3O_3$ (M^+): calcd, 349.1238; found, 349.1278. Anal. ($C_{17}H_{17}F_2N_3O_3$) C, H, N.

6,8-Difluoro-1-[(*Z*)-2-fluorovinyl]-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic Acid (*Z*-15b) and 6,8-Difluoro-1-[(*E*)-2-fluorovinyl]-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic Acid (*E*-15b). A mixture of **14b** (50 mg, 0.174 mmol), *N*-methylpiperazine (43.0 μL, 0.387 mmol), and DMSO (1 mL)

was stirred at 60 °C for 1 h and then concentrated in vacuo. Preparative TLC (CH_2Cl_2/MeOH = 10:1) of the residue gave *E*-**15b** (R_f = 0.40, 34 mg, 53%) as a white solid and *Z*-**15b** (R_f = 0.36, 18 mg, 26%) as a pale-brown solid.

***Z*-15b.** Mp: 203−205 °C. ^{1}H NMR ($CDCl_3$) δ: 2.37 (s, 3H, CH_3), 2.57 (br, 4H, $CH_2 \times 2$), 3.43 (br, 4H, $CH_2 \times 2$), 6.72 (ddd, J = 25.9, 10.8, 3.4 Hz, 1H, C_1'−H), 6.91 (dd, J = 74.3, 3.4, 2.0 Hz, 1H, C_2'−H), 7.29 (dd, J = 12.7, 2.0 Hz, 1H, C_5−H), 8.56 (d, J = 1.5 Hz, 1H, C_2−H), 14.5−14.7 (br, 1H, COOH). IR (KBr) cm^{-1}: 1657. MS *m/z*: 367 (M^+). Anal. ($C_{17}H_{16}F_3N_3O_3 \cdot 0.75H_2O$) C, H, N.

***E*-15b.** Mp: 248−251 °C. ^{1}H NMR ($CDCl_3$) δ: 2.37 (s, 3H, CH_3), 2.57 (br, 4H, $CH_2 \times 2$), 3.44 (br, 4H, $CH_2 \times 2$), 7.26 (ddd, J = 73.6, 10.3, 3.4 Hz, 1H, C_2'−H), 7.44 (ddd, J = 11.9, 10.3, 6.4 Hz, 1H, C_1'−H), 7.92 (dd, J = 13.2, 2.0 Hz, 1H, C_5−H), 8.56 (s, 1H, C_2−H). IR (KBr) cm^{-1}: 1725, 1620. MS *m/z*: 367 (M^+). Anal. ($C_{17}H_{16}F_3N_3O_3 \cdot 0.25H_2O$) C, H, N.

6-Difluoro-1-[(*Z*)-2-fluorovinyl]-1,4-dihydro-8-methoxy-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic Acid (*Z*-15c) and 6-Difluoro-1-[(*E*)-2-fluorovinyl]-1,4-dihydro-8-methoxy-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic Acid (*E*-15c). The compounds *Z*-**15c** (15.0 mg, 12%) and *E*-**15c** (30.4 mg, 24%) were prepared from **14c** (100 mg, 0.334 mmol) by the same method as that used for *Z*-**15c** and *E*-**15c**.

***Z*-15c.** Mp: 172−175 °C. ^{1}H NMR ($CDCl_3$) δ: 2.39 (s, 3H, CH_3), 2.52−2.63 (br, 4H, $CH_2 \times 2$), 3.43−3.49 (br, 4H, $CH_2 \times 2$), 3.71 (s, 3H, CH_3), 6.78 (dd, J = 17.6, 3.4 Hz, 1H, C_1'−H), 6.91 (dd, J = 66.5, 3.4 Hz, 1H, C_2'−H), 7.92 (d, J = 12.2 Hz, 1H, C_5−H), 8.58 (d, J = 2.0 Hz, 1H, C_2−H), 14.4−14.8 (br, 1H, COOH). IR (KBr) cm^{-1}: 1733, 1619. MS (EI) *m/z*: 379 (M^+). HRMS (EI) for $C_{18}H_{19}F_2N_3O_4$ (M^+): calcd, 379.1344; found, 379.1340. Anal. ($C_{18}H_{19}F_2N_3O_4 \cdot 0.25H_2O$) C, H, N.

***E*-15c.** Mp: 229−232 °C. ^{1}H NMR ($CDCl_3$) δ: 2.39 (s, 3H, CH_3), 2.57−2.59 (br, 4H, $CH_2 \times 2$), 3.43−3.45 (br, 4H, $CH_2 \times 2$), 3.73 (s, 3H, CH_3), 7.27 (dd, J = 74.8, 10.3 Hz, 1H, C_2'−H), 7.60 (dd, J = 10.3, 6.8 Hz, 1H, C_1'−H), 7.90 (d, J = 11.7 Hz, 1H, C_5−H), 8.52 (s, 1H, C_2−H), 14.4−14.7 (br, 1H, COOH). IR (KBr) cm^{-1}: 1624. MS (EI) *m/z*: 379 (M^+). HRMS (EI) for $C_{18}H_{19}F_2N_3O_4$ (M^+): calcd, 379.1344; found, 379.1327. Anal. ($C_{18}H_{19}F_2N_3O_4 \cdot 0.25H_2O$) C, H, N.

7-(3-Amino-1-pyrrolidinyl)-6-fluoro-1-[(*Z*)-2-fluorovinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Hydrochloride (*Z*-16a). A mixture of *Z*-**14a** (60 mg, 0.223 mmol), 3-Boc-aminopyrrolidine (50 mg, 0.268 mmol), 1,8-diazabicyclo-[5.4.0]undec-7-ene (34 μL, 0.227 mmol), and MeCN (2 mL) was heated under reflux for 1 h and concentrated in vacuo. After dilution of the residue with CH_2Cl_2 (20 mL), the mixture was successively washed with water (5 mL), aqueous 10% citric acid solution (2 × 5 mL), and water (5 mL). The mixture was then dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was suspended in saturated HCl in AcOEt solution (2 mL), and the mixture was allowed to stand at room temperature for 30 min. The resulting precipitates were collected by filtration, washed with AcOEt, and then dried in vacuo to give *Z*-**16a** (76 mg, 92%) as yellow crystals. Mp: 263−270 °C. ^{1}H NMR (DMSO-d_6 + CF_3COOD) δ: 2.09−2.16 (m, 1H, CH_2), 2.27−2.36 (m, 1H, CH_2), 3.57−3.97 (m, 5H, CH, $CH_2 \times 2$), 6.61 (d, J = 7.3 Hz, 1H, C_8−H), 7.07 (dd, J = 9.3, 3.4 Hz, 1H, C_1'−H), 7.49 (dd, J = 76.2, 3.4 Hz, 1H, C_2'−H), 7.87 (d, J = 14.2 Hz, 1H, C_5−H), 8.59 (d, J = 1.0 Hz, 1H, C_2−H). IR (KBr) cm^{-1}: 1688, 1634. MS (EI) *m/z*: 335 (M^+). HRMS for $C_{16}H_{15}F_2N_3O_3$ (M^+): calcd, 335.1081; found: 335.1040. Anal. ($C_{16}H_{15}F_2N_3O_3 \cdot HCl \cdot 2.75H_2O$) C, H, N.

7-(3-Amino-1-pyrrolidinyl)-6-fluoro-1-[(*E*)-2-fluorovinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Hydrochloride (*E*-16a). The compound *E*-**16a** (66 mg, 48%) was prepared from *E*-**14a** (100 mg, 0.371 mmol) by the same method as that used for *Z*-**16a**. Mp: 276−285 °C. ^{1}H NMR (DMSO-d_6+CF_3COOD) δ: 2.10−2.18 (m, 1H, CH_2), 2.28−2.37 (m, 1H, CH_2), 3.59−4.02 (m, 5H, CH, $CH_2 \times 2$), 6.62 (d, J = 7.3 Hz, 1H, C_8−H), 7.74 (dd, J = 10.3, 8.3 Hz, 1H, C_1'−H), 7.87 (d, J = 14.2 Hz, 1H, C_5−H), 7.92 (dd, J = 75.7, 10.3 Hz, 1H, C_2'−H), 8.62 (s, 1H, C_2−H). IR (KBr) cm^{-1}: 1680, 1626. MS (EI) *m/z*: 335 (M^+). HRMS for $C_{16}H_{15}F_2N_3O_3$ (M^+): calcd, 335.1081; Found, 335.1063. Anal. ($C_{16}H_{15}F_2N_3O_3$ HCl 0.5 H_2O) C, H, N.

7-(3-Amino-1-pyrrolidinyl)-6,8-difluoro-1-[(*Z*)-2-fluorovinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Hydrochloride (*Z*-16b) and 7-(3-Amino-1-pyrrolidinyl)-6,8-difluoro-1-[(*E*)-2-fluorovinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Hydrochloride (*E*-16b). A mixture of **14b** (200 mg, 0.696 mmol), 3-Boc-aminopyrrolidine (156 mg, 0.836 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (105 μL, 0.703 mmol), and MeCN (5 mL) was heated under reflux for 1 h and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and successively washed with water (2 mL), aqueous 10% citric acid solution (2 × 2 mL), and water (2 mL). The mixture was then dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (CH_2Cl_2/AcOEt = 1:1) of the residue gave the *Z*-Boc-amino derivative of *Z*-**16b** (72 mg, 23%) as a yellow solid and the *E*-Boc-amino derivative of *E*-**16b** (174 mg, 55%) as a yellow solid. A suspension of the *Z*-Boc derivative (53 mg, 0.118 mmol) in saturated HCl in AcOEt solution (1 mL) was stirred at room temperature for 1 h and then concentrated in vacuo. After MeOH (2 mL) was added to the residue, the resulting precipitates were collected by filtration, washed with MeOH, and then dried in vacuo to give *Z*-**16b** (24 mg, 53%) as yellow crystals. Following the same procedure, the *E*-Boc-amino derivative (151 mg, 0.333 mmol) was converted to *E*-**16b** (89 mg, 69%), giving a yellow powder.

***Z*-16b.** Mp: 240−244 °C. ^{1}H NMR (DMSO-d_6) δ: 2.00−2.08 (m, 1H, CH_2), 2.19−2.28 (m, 1H, CH_2), 3.66−3.81 (m, 2H, CH_2), 3.84−4.02 (m, 3H, CH, CH_2), 7.08 (ddd, J = 28.7, 10.5, 3.4 Hz, 1H, C_1'−H), 7.38 (dt, J = 76.2, 2.9 Hz, 1H, C_2'−H), 7.79 (dd, J = 13.7, 1.5 Hz, 1H, C_5−H), 8.51 (d, J = 1.0 Hz, 1H, C_2−H). IR (KBr) cm^{-1}: 1723, 1628. MS (EI) *m/z*: 353 (M^+). Anal. ($C_{16}H_{14}F_3N_3O_3 \cdot HCl \cdot 2H_2O$) C, H, N.

***E*-16b.** Mp: 258−263 °C. ^{1}H NMR (DMSO-d_6) δ: 2.02−2.10 (m, 1H, CH_2), 2.19−2.28 (m, 1H, CH_2), 3.69−3.75 (m, 2H, CH_2), 3.75−4.02 (m, 3H, CH, CH_2), 7.67 (ddd, J = 13.0, 10.3, 8.3 Hz, 1H, C_1'−H), 7.80 (dd, J = 13.7, 1.5 Hz, 1H, C_5−H), 7.86 (ddd, J = 80.2, 10.3, 1.5 Hz, 1H, C_2'−H), 8.53 (s, 1H, C_2−H). IR (KBr) cm^{-1}: 1680, 1626. MS (EI) *m/z*: 353 (M^+). Anal. ($C_{16}H_{14}F_3N_3O_3 \cdot HCl \cdot 0.75H_2O$) C, H, N.

7-(3-Amino-1-pyrrolidinyl)-6-fluoro-1-[(*Z*)-2-fluorovinyl]-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic Acid Hydrochloride (*Z*-16c) and 7-(3-Amino-1-pyrrolidinyl)-6-fluoro-1-[(*E*)-2-fluorovinyl]-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic Acid Hydrochloride (*E*-16c). The compounds *Z*-**16c** (14.3 mg, 6%) and *E*-**16c** (86 mg, 34%) were prepared from **14c** (200 mg, 0.668 mmol) by the same method as that used for *Z*-**16b** and *E*-**16b**.

***Z*-16c.** Mp: 211−219 °C. ^{1}H NMR (DMSO-d_6) δ: 1.91−2.08 (m, 1H, CH_2), 2.23−2.39 (m, 1H, CH_2), 3.51 (s, 3H, OCH_3), 3.56−3.67 (m, 1H, CH_2), 3.68−3.90 (m, 4H, CH, $CH_2 \times 2$), 7.03 (dd, J = 29.3, 3.4 Hz, 1H, C_1'−H), 7.34 (dd, J = 76.8, 3.4 Hz, 1H, C_2'−H), 7.76 (d, J = 13.7 Hz, 1H, C_5−H), 8.27 (br, 3H, NH·HCl), 8.49 (d, J = 1.0 Hz, 1H, C_2−H), 14.0−15.5 (br, 1H, COOH). IR (KBr) cm^{-1}: 1725, 1620. MS (EI) *m/z*: 365 (M^+). HRMS (EI) for $C_{17}H_{17}F_2N_3O_4$ (M^+): calcd, 365.1187; found, 365.1177. Anal. ($C_{17}H_{17}F_2N_3O_4 \cdot HCl \cdot 0.5H_2O$) C, H, N.

***E*-16c.** Mp: 180−188 °C. ^{1}H NMR (DMSO-d_6) δ: 1.91−2.10 (m, 1H, CH_2), 2.22−2.34 (m, 1H, CH_2), 3.50 (s, 3H, OCH_3), 3.58−3.67 (m, 1H, CH_2), 3.70−3.96 (m, 4H, CH, $CH_2 \times 2$), 7.65 (dd, J = 10.3, 8.3 Hz, 1H, C_1'−H), 7.76 (d, J = 14.2 Hz, 1H, C_5−H), 7.87 (dd, J = 76.5, 10.3 Hz, 1H, C_2'−H), 8.36 (br, 3H, NH·HCl), 8.49 (s, 1H, C_2−H), 15.0 (br, 1H, COOH). IR (KBr) cm^{-1}: 1722, 1620. MS (EI) *m/z*: 365 (M^+). HRMS (EI) for $C_{17}H_{17}F_2N_3O_4$ (M^+): calcd, 365.1187; found, 365.1214. Anal. ($C_{17}H_{17}F_2N_3O_4 \cdot HCl \cdot 0.75H_2O$) C, H, N.

In Vitro Antibacterial Activity. The MIC (μg/mL) was determined by the agar dilution method[14] using Muller−Hinton agar (Difco Laboratories, Detroit, MI). The MIC was defined as the lowest concentration of an antibacterial agent that inhibited visible growth after incubation at 35 °C for 18 h.

Inhibitory Activity against DNA Gyrase of *S. aureus*. The supercoiling activity of DNA gyrase was determined by a previously reported procedure.[15] The inhibitory activity was assayed by determining the concentration required to inhibit 50% of the enzyme reaction.

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Supporting Information Available: Purity data for compounds **12**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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