The novel 1-(2-fluorovinyl)-4-quinolone-3-carboxylic acid derivatives $Z\text{-}15\text{a-c}$, $E\text{-}15\text{a-c}$, $Z\text{-}16\text{a-c}$, and $E\text{-}16\text{a-c}$, conformationally restricted analogues of fleroxacin (5), were synthesized, and their in vitro antibacterial activity was evaluated. A dehydrodisulfenylation 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 $Z\text{-}15\text{a-c}$ and $Z\text{-}16\text{a-c}$ exhibited 2- to 32-fold more potent in vitro antibacterial activity than the corresponding $E$-isomers $E\text{-}15\text{a-c}$ and $E\text{-}16\text{a-c}$. Furthermore, since $Z\text{-}15\text{b}$ showed in vitro antibacterial activity and DNA gyrase inhibition comparable to that of 5, it was hypothesized that the conformation of $Z\text{-}15\text{b}$ would be equivalent to the active conformer of 5. The results revealed that the antibacterial $Z\text{-}(2\text{-}2\text{-fluorovinyl})\text{quinolone}$ derivatives carry the novel N-1 substituent of the fluoroquinolones.

**Introduction**

Since the development of norfloxacin (1), the first new quinolone (fluoroquinolone) in which a fluorine atom is attached at the C-6 position, other fluoroquinolones (e.g., ciprofloxacin (2) and levofloxacin (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. 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 3S-enantiomer of 3 was revealed as having 8–128 times more potent activity than the 3R-enantiomer of 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). 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) (Figure 2). We designed and synthesized 1-(2-fluorovinyl)quinolone derivatives 15 and 16 (Figure 2), 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 $Z\text{-}15\text{a-c}$ and $Z\text{-}16\text{a-c}$ appeared to exhibit a 2- to 32-fold more potent in vitro antibacterial activity than the corresponding $E$-isomers $E\text{-}15\text{a-c}$ and $E\text{-}16\text{a-c}$. It was also found that $Z\text{-}15\text{b}$, structurally related to 5, showed comparable activity and DNA gyrase inhibition to that of 5; thus, it is possible that the conformation of $Z\text{-}15\text{b}$ 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 dehydrodisulfenylation of 12, carrying a 2-fluoro-2-[(4-methoxy-
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 \(10a\)–\(c\) 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-methoxybenzenesulfinic acid from \(12a\)–\(c\) in xylene gave the desired 6,7-
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 1H NMR. The geometrical 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 H1′ and F2′, 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)quinoline 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...
the presence of DNA gyrase of *S. aureus* and difference in the inhibition abilities of bacterial activity than the trans isomers. In addition, of which the cis isomers exhibited more potent anti-*S. aureus* activity than the corresponding *E. coli* and were similar to those of the *S. aureus* Smith, *St. pneumoniae* type III, and *P. aeruginosa* IID1210 to that of *E. coli* NHIJ JC-2.

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

<table>
<thead>
<tr>
<th>compd</th>
<th>Gram-positive bacteria</th>
<th>Gram-negative bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>S. aureus</em> Smith</td>
<td><em>St. pneumoniae</em> type III</td>
</tr>
<tr>
<td>Z-15a</td>
<td>0.20</td>
<td>3.13</td>
</tr>
<tr>
<td>E-15a</td>
<td>3.13</td>
<td>100</td>
</tr>
<tr>
<td>Z-15b</td>
<td>0.39</td>
<td>3.13</td>
</tr>
<tr>
<td>E-15b</td>
<td>0.39</td>
<td>3.13</td>
</tr>
<tr>
<td>Z-15c</td>
<td>12.5</td>
<td>&gt;50</td>
</tr>
<tr>
<td>E-15c</td>
<td>12.5</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Z-16a</td>
<td>0.39</td>
<td>3.13</td>
</tr>
<tr>
<td>E-16a</td>
<td>0.39</td>
<td>3.13</td>
</tr>
<tr>
<td>Z-16b</td>
<td>1.56</td>
<td>6.25</td>
</tr>
<tr>
<td>E-16b</td>
<td>1.56</td>
<td>6.25</td>
</tr>
<tr>
<td>Z-16c</td>
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<td>0.78</td>
</tr>
<tr>
<td>E-16c</td>
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<td>0.78</td>
</tr>
<tr>
<td>Z-16d</td>
<td>0.20</td>
<td>0.78</td>
</tr>
<tr>
<td>E-16d</td>
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<td>0.78</td>
</tr>
<tr>
<td>Z-16e</td>
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<td>0.78</td>
</tr>
<tr>
<td>E-16e</td>
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<td>0.78</td>
</tr>
<tr>
<td>5</td>
<td>0.39</td>
<td>3.13</td>
</tr>
<tr>
<td>2</td>
<td>0.20</td>
<td>0.78</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>compd</th>
<th>IC50 (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-15b</td>
<td>72.2</td>
</tr>
<tr>
<td>E-15b</td>
<td>664</td>
</tr>
<tr>
<td>5</td>
<td>68.5</td>
</tr>
<tr>
<td>2</td>
<td>20.1</td>
</tr>
</tbody>
</table>

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. 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* NHIJ 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 IC50 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 H1′ and both H2 and H8 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 H2′ and H2 for E-15a; long-range coupling (5J = 1.0 Hz) with F2′ was also observed in H2 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 H8.

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 H1′ and H2 for both Z-15b and E-15b and between H2′ and H2 for E-15b, as shown in Figure 5. In addition, long-range coupling (5J = 1.5 Hz) with F2′ was observed in H2 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 C2′–N1′–C4′–C8′ (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 C8′-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,
although there existed the one energy minimum conformer and it was located under the plane of the quinolone ring ($\Theta = -85^\circ$, 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 $\Theta$ of N1 substituents of fluoroquinolone derivatives using molecular orbital calculation and the in vitro antibacterial activity of this group, it appeared evident that the active conformer of the N1 substituents of the fluoroquinolones was located above the plane of the quinolone ring. 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-$2-[(4$-methylphenyl)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

**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. $\Theta$ is defined as the C$_2$–N$_1$–C$'$_1–C$_2$ dihedral angle.
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-fluorovinyl)-4-quinolone-3-carboxylic acid would be an intriguing scaffold for the exploration of novel quinoline antibacterials. Further investigation of the Z-(1-fluorovinyl)quinolones is in progress.

**Experimental Section**

Melting points were determined with a Yanagimoto micro-melting 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 PIR-5300 spectrometer. Measurements of mass spectra (MS) and high-resolution MS (HRMS) were performed with a JOEL JMS SX-102A mass spectrometer. Proton nuclear magnetic resonance (1H NMR) were measured with a JOEL EX-90 (90 MHz) or a JOEL JMN-EX400 (400 MHz) spectrometer. The chemical shifts are expressed in parts per million (δ value) downfield from tetramethylsilane, using tetramethylsilane (δ = 0) and/or residual solvents such as chloroform (δ = 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 F254, 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)sulfanyl]ethyl]phthalimide (6, 6.00 g, 18.2 mmol) and ammonium(II) chloride (125 mg, 0.548 mmol) in anhydrous CH2Cl2 (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 NaHCO3 solution (36 mL) under ice cooling, the mixture was extracted with CH2Cl2 (50 mL). The combined CH2Cl2 extracts were washed with water (2 × 30 mL), dried over anhydrous Na2SO4, filtered, and then concentrated in vacuo to give 7 (5.52 g, 91%) as pale-brown crystals. 1H NMR (CDCl3) δ: 3.82 (s, 3H, CH3), 4.04 (dd, J = 40.2, 14.4, 4.9 Hz, 1H, CH2), 4.08 (ddd, J = 42.0, 14.2, 8.1 Hz, 1H, CH2), 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)sulfanyl]ethyl]phthalimide (8).** To a solution of 7 (5.51 g, 16.6 mmol) in CHCl3 (100 mL), m-chloroperbenzoic 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 water saturated with sodiumHCO3 solution (2 × 100 mL), 10% aqueous Na2SO4 solution (2 × 100 mL) and water (100 mL), dried over anhydrous Na2SO4, 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. 1H NMR (CDCl3) δ: 3.85 (s, 2.4H, CH2), 3.86 (s, 0.6H, CH3), 4.08–4.20 (m, 1.2H, CH2), 4.39 (ddd, J = 14.6, 12.7, 7.8 Hz, 0.8H, CH2), 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), 7.67–7.88 (m, 2H, Ar–H), 7.85–7.88 (m, 2H, Ar–H).

**2-[Fluoro-2-(4-methoxyphenyl)sulfanyl]ethyl]hydrazine (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 (CH2Cl2/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.
Ethyl 1-[2-Fluoro-2-(4-methoxyphenylsulfinyl)ethyl]-6,7-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (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. 1H NMR (CDCl3): δ: 1.40 (t, J = 7.3 Hz, 3H, CH3), 3.89 (s, 3H, CH3), 4.39 (q, J = 7.3 Hz, 2H, CH2), 4.66–4.76 (m, 1H, CH), 4.96 (ddd, J = 27.6, 16.1, 2.9 Hz, 1H, C(5)–H), 5.27 (ddd, J = 9.3, 8.3 Hz, 1H, C(6)–H), 7.08–7.21 (m, 3H, Ar–H), 8.13 (dd, J = 9.0, 2.4 Hz, 1H, C(4)–H), 8.37 (s, 1H, C(7)–H). IR (KBr) cm−1: 1732, 1701, 1602. MS (EI) m/z: 471 (M+). Anal. (C19H19F4NO4S) C, H, N.

Ethyl 1-[2-Fluoro-2-(4-methoxyphenylsulfinyl)ethyl]-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (12e). The compound 12e (1.33 g, 88%) was prepared from 11e (1.57 g, 3.12 mmol) by the same method as that used for 12a. Mp: 131–136 °C (MeOH/EtOH). 1H NMR (CDCl3): δ: 1.40 (t, J = 7.3 Hz, 2H, CH2), 3.92 (dd, J = 2.4 Hz, 3H, OCH3), 3.89 (3H, s, OCH3), 4.39 (2H, m, CH2), 4.63 (1H, s, 3H, CH3), 3.89 (s, 3H, CH3), 4.39 (q, J = 6.7 Hz, 2H, CH2). MS (EI) m/z: 172, 169, 136, 135, 134, 133, 132, 131, 115, 114, 113, 112, 111. HRMS (EI) for C19H19F4NO4S: C, H, N.

Z-13a. 1H NMR (CDCl3): δ: 1.41 (t, J = 7.3 Hz, 3H, CH3), 4.40 (q, J = 7.3 Hz, 2H, COOCH3), 6.36 (ddd, J = 26.4, 3.4 Hz, 1H, Z-C(5)–H), 7.03 (dd, J = 74.7, 3.4 Hz, 1H, Z-C(6)–H), 7.25 (ddd, J = 10.7, 7.8 Hz, 1H, C(5)–H), 8.26 (dd, J = 10.3, 8.8 Hz, 1H, Ar–H), 8.66 (dd, J = 10.3, 8.8 Hz, 1H, C(5)–H), 8.32 (1H, s, C2–H). IR (KBr) cm−1: 1730, 1618. MS m/z: 483 (M+). Anal. (C23H20F3NO6S) C, H, N.

E-13a. 1H NMR (CDCl3): δ: 1.40 (t, J = 7.3 Hz, 3H, CH3), 4.36 (q, J = 7.3 Hz, 2H, COOCH3), 7.03 (dd, J = 10.3, 5.9 Hz, 1H, E-C(5)–H), 7.25 (dd, J = 10.7, 6.4 Hz, 1H, C(5)–H), 7.47 (dd, J = 74.5, 10.3 Hz, 1H, E-C(6)–H), 8.16 (dd, J = 10.3, 8.3 Hz, 1H, C(6)–H), 8.37 (s, 1H, C(7)–H). MS (EI) m/z: 297 (M+). HRMS (EI) for C19H19F3NO4: C, H, N.

E-13d. 1H NMR (CDCl3): δ: 1.39–1.42 (m, 3H, CH3), 4.36–4.42 (m, 2H, COOCH3), 6.67 (ddd, J = 25.9, 9.3, 3.4 Hz, 0.5H, Z-C(5)–H), 6.91 (ddd, J = 75.2, 3.4, 2.0 Hz, 0.5H, Z-C(6)–H), 7.39 (ddd, J = 10.3, 10.4, 4.4 Hz, 0.5H, E-C(5)–H), 7.43 (ddd, J = 74.5, 10.3 Hz, 0.5H, E-C(6)–H), 8.05–8.13 (m, 1H, C(5)–H), 8.05 (s, 1H, E-C(6)–H), 8.36 (d, J = 1.5 Hz, 0.5H, C(7)–H). IR (KBr) cm−1: 1730, 1691, 1628. MS m/z: 315 (M+). Anal. (C23H21F3NO5) C, H, N.

Ethyl 6,7,8-Trifluoro-1-(2-fluorovinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (13b). The compound 13b (780 mg, 99%) was prepared from 12b (1.25 g, 2.65 mmol) by the same method as that used for 12a. Mp: 177–178 °C. 1H NMR (CDCl3): δ: 1.39–1.42 (m, 3H, CH3), 4.36–4.42 (m, 2H, COOCH3), 6.67 (ddd, J = 25.9, 9.3, 3.4 Hz, 0.5H, Z-C(5)–H), 6.91 (ddd, J = 75.2, 3.4, 2.0 Hz, 0.5H, Z-C(6)–H), 7.39 (ddd, J = 10.3, 10.4, 4.4 Hz, 0.5H, E-C(5)–H), 7.43 (ddd, J = 74.5, 10.3 Hz, 0.5H, E-C(6)–H), 8.05–8.13 (m, 1H, C(5)–H), 8.05 (s, 1H, E-C(6)–H), 8.36 (d, J = 1.5 Hz, 0.5H, C(7)–H). IR (KBr) cm−1: 1730, 1691, 1628. MS m/z: 315 (M+). Anal. (C23H21F3NO5) C, H, N.

Ethyl 6,7,8-[Z-(2-fluorovinyl)]-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (13e). The compound 13e (1.09 g, 81%) was prepared from 12e (2.00 g, 4.14 mmol) by the same method as that used for 13a. Mp: 177–178 °C. 1H NMR (CDCl3): δ: 1.47 (t, J = 7.3 Hz, 3H, CH3), 3.95 (d, J = 1.0 Hz, 1H, OCH3), 3.98 (d, J = 1.5 Hz, 2H, OCH3), 4.36–4.42 (m, 2H, CH2), 6.78 (s, 0.3H, Z-C(5)–H), 6.91 (dd, J = 51.3, 9.0 Hz, 3H, Z-C(6)–H), 7.26 (ddd, J = 75.6, 10.3 Hz, 0.7H, Z-C(6)–H), 7.55 (ddd, J = 10.3, 6.8 Hz, 0.7H, E-C(6)–H), 8.00–8.09 (m, 1H, C(5)–H), 8.29 (s, 0.7H, E-C(6)–H), 8.35 (d, J = 2.0 Hz, 0.3H, C(7)–H). IR (KBr) cm−1: 1730, 1617. MS m/z: 327 (M+). Anal. (C23H21F3NO5) C, H, N.

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was stirred at 60 °C for 1 h and then concentrated in vacuo. Preparative TLC (CH₂Cl₂/MeOH = 10:1) of the residue gave E-15b (Rf = 0.40, 34 mg, 53%) as a white solid and Z-15b (Rf = 0.36, 18 mg, 26%) as a pale-brown solid.

Z-15b: Mp: 203–205 °C. ^1H NMR (CDCl₃) δ: 2.37 (s, 3H, CH₃), 2.57 (br, 4H, CH₂ × 2), 2.43 (br, 4H, CH₂ × 2), 6.72 (dd, J = 25.9, 10.8, 3.4 Hz, 1H, C1′-H), 6.91 (dd, J = 74.3, 3.4, 2.0 Hz, 1H, C2′-H), 7.29 (dd, J = 12.7, 2.0 Hz, 1H, C1-H), 8.56 (d, J = 1.5 Hz, 1H, C2-H), 14.5–14.7 (br, 1H, COOH). IR (KBr) cm⁻¹: 1657, MS m/z: 367 (M⁺). Anal. (C₉H₆F₂N₂O₄·0.75H₂O) C, H, N.

E-15b: Mp: 248–251 °C. ^1H NMR (CDCl₃) δ: 2.37 (s, 3H, CH₃), 2.57 (br, 4H, CH₂ × 2), 2.43–3.39 (br, 4H, CH₂ × 2), 3.71 (s, 3H, CH₃), 6.78 (dd, J = 17.6, 3.4 Hz, 1H, C1′-H), 6.91 (dd, J = 66.5, 3.4 Hz, 1H, C1′-H), 7.92 (d, J = 12.2 Hz, 1H, C2-H), 8.58 (d, J = 2.0 Hz, 1H, C2-H), 14.4–14.8 (br, 1H, COOH). IR (KBr) cm⁻¹: 1733, 1619. MS (EL) m/z: 379 (M⁺). HRMS (EI) for C₁₀H₈F₂N₂O₄ calculated, found: 379.1344; Anal. (C₁₀H₈F₂N₂O₄·0.25H₂O) C, H, N.

6-Difluoro-[1-(2-fluorovinyl)-1,4-dihydro-8-methoxy-7-(4-methyl-1-piperazinyl)-1,4-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. ^1H NMR (CDCl₃) δ: 2.39 (s, 3H, CH₃), 2.52–2.63 (br, 4H, CH₂ × 2), 2.43–3.49 (br, 4H, CH₂ × 2), 2.73 (s, 3H, CH₃), 7.68 (dd, J = 17.6, 3.4 Hz, 1H, C1′-H), 6.91 (dd, J = 66.5, 3.4 Hz, 1H, C1′-H), 7.92 (d, J = 12.2 Hz, 1H, C2-H), 8.58 (d, J = 2.0 Hz, 1H, C2-H), 14.4–14.8 (br, 1H, COOH). IR (KBr) cm⁻¹: 1733, 1619. MS (EL) m/z: 379 (M⁺). HRMS (EI) for C₁₀H₈F₂N₂O₄·0.25H₂O calculated, found: 379.1344; Anal. (C₁₀H₈F₂N₂O₄·0.25H₂O) C, H, N.

E-15c: Mp: 229–232 °C. ^1H NMR (CDCl₃) δ: 2.39 (s, 3H, CH₃), 2.57–2.59 (br, 4H, CH₂ × 2), 2.43–3.45 (br, 4H, CH₂ × 2), 2.73 (s, 3H, CH₃), 7.27 (dd, J = 74.8, 10.3 Hz, 1H, C2′-H), 7.60 (dd, J = 10.3, 6.8 Hz, 1H, C1′-H), 7.90 (d, J = 11.7 Hz, 1H, C2-H), 8.52 (s, 1H, C2′-H), 14.4–14.7 (br, 1H, COOH). IR (KBr) cm⁻¹: 1624. MS (EI) m/z: 379 (M⁺). HRMS (EI) for C₁₀H₈F₂N₂O₄ calculated, found: 379.1344; Anal. (C₁₀H₈F₂N₂O₄·0.25H₂O) C, H, N.

7-(3-Aminopyrrolidinyl)-6-fluoro-[1-(2-fluorovinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Hydrochloride (Z-16a). A mixture of Z-16a (60 mg, 0.223 mmol), 3-Boc-aminopyrrolidine (50 mg, 0.268 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (34 mL, 0.227 mmol), and MeCN (2 mL) was heated under reflux for 1 h and concentrated in vacuo. After filtration, washed with water (5 mL), aqueous 10% citric acid solution (2 mL), and MeCN (5 mL) was stirred until a yellow solid precipitated. The mixture was then dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was redissolved in CH₂Cl₂ (5 mL) and successively washed with water (2 mL), 2% NaOH solution (2 mL), and water (2 mL), and then dried in vacuo to give Z-16b (24 mg, 53%) as yellow crystals. Following the same procedure, the Z-16b derivative (151 mg, 0.333 mmol) was converted to E-16b (89 mg, 69%), giving a yellow powder.

Z-16b: Mp: 240–244 °C. ^1H NMR (DMsol-d₆) δ: 0.20–2.08 (m, 1H, CH₂), 2.19–2.28 (m, 1H, CH₂), 3.66–3.81 (m, 2H, CH₂), 3.84–4.02 (m, 3H, CH₂, CH₂), 7.08 (dd, J = 28.7, 10.5, 3.4 Hz, 1H, C1′-H), 7.38 (dt, J = 76.2, 2.9 Hz, 1H, C2′-H), 7.79 (dd, J = 13.7, 1.5 Hz, 1H, C2-H), 8.51 (d, J = 1.0 Hz, 1H, C2-H). IR (KBr) cm⁻¹: 1723, 1628. MS (EL) m/z: 353 (M⁺). HRMS (EI) for C₁₀H₈F₂N₂O₄·0.25H₂O calculated, found: 353.1187; Anal. (C₁₀H₈F₂N₂O₄·0.25H₂O) C, H, N.

E-16b: Mp: 258–263 °C. ^1H NMR (DMsol-d₆) δ: 2.02–2.10 (m, 1H, CH₂), 2.19–2.28 (m, 1H, CH₂), 3.69–3.75 (m, 2H, CH₂), 3.75–4.02 (m, 3H, CH₂, CH₂), 7.47 (dd, J = 13.0, 10.5, 3.4 Hz, 1H, C1′-H), 7.86 (dd, J = 80.2, 10.4, 1.5 Hz, 1H, C2′-H), 8.53 (s, 1H, C2-H). IR (KBr) cm⁻¹: 1680, 1626. MS (EL) m/z: 353 (M⁺). HRMS (EI) for C₁₀H₈F₂N₂O₄·0.25H₂O calculated, found: 353.1177; Anal. (C₁₀H₈F₂N₂O₄·0.25H₂O) C, H, N.

In Vitro Antibacterial Activity. The MIC (µg/mL) was determined by the agar dilution method 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. 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.

References


