Synthesis and Antibacterial Activity of the 4-Quinolone-3-carboxylic Acid Derivatives Having a Trifluoromethyl Group as a Novel N-1 Substituent

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Novel 1-trifluoromethyl-4-quinolone derivatives (**8a**,**b**) were synthesized, and the antibacterial activity of each was evaluated. An oxidative desulfurization−fluorination reaction was employed to introduce a trifluoromethyl group at the N-1 position as a key step. Among the derivatives, **8a** was found to exhibit antibacterial activity comparable to that of norfloxacin (**1**) against *Staphylococcus aureus* Smith, *Streptococcus pneumoniae* IID1210, and *Escherichia coli* NIHJ JC-2.

Introduction

Since the development of norfloxacin (**1**),[1] the first quinolone (fluoroquinolone) in which a fluorine atom is 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 (Figure 1). Among the synthetic studies of the fluoroquinolones **4**−**7**,[4−7] 2-fluoroethyl, 2,4-difluorophenyl, 2-fluorocyclopropyl, and *tert*-butyl groups were established as novel N-1 substituents capable of improving antibacterial activity and/or pharmacokinetic properties. In light of these structural characteristics, we designed and synthesized the fluoroquinolone **8**, which carries a trifluoromethyl group as a novel N-1 substituent. Our next study established the trifluoromethyl group as a novel N-1 substituent of the fluoroquinolone by comparison of the in vitro antibacterial activity of **8** and fluoroquinolones **9**−**14** carrying known N-1 substituents (Figure 2).

In this paper, we report the synthesis and antibacterial activity of the 7-substituted 1-trifluoromethyl-4-quinolone-3-carboxylic acids **8a**,**b**, which both bear a trifluoromethyl group as a novel N-1 substituent.

Results and Discussion

Chemistry. The synthetic strategy of the 7-substituted-1-trifluoromethyl-4-quinolone-3-carboxylic acids **8a**,**b** by way of trifluoromethylquinolone carboxylic acid **17** is shown in Scheme 1. We employed an oxidative desulfurization−fluorination reaction[8] as the key step in the introduction of a trifluoromethyl group to the N-1 position of **17**. Thus, treatment of the 1-benzyl derivative **19**, derived from ester **18**[9] with sodium borohydride in the presence of a catalytic amount of *p*-toluenesulfonic acid in methanol,[10] provided tetrahydroquinolone **20**. Protection of a carbonyl group of **20** with an ethylenedioxy group and removal of a benzyl group gave ethylenedioxy ketal **22**. Reaction of **22** with carbon disulfide smoothly proceeded using lithium bis(trimethylsilyl)amide as a base; subsequent treatment with iodomethane gave **23**. After much experimentation,[11] it was finally found that the treatment of **15**, derived from **23** with a hydrogen fluoride−pyridine complex and *N*-bromosuccimide, afforded the 1-trifluoromethyltetrahydroquinolone **16** in excellent yield. Ethoxycarbonylation of **16** with diethyl (ethoxycarbonyl)phosphonate using sodium hydride gave the 3-ethoxycarbonyl-1-trifluoromethylquinolone derivative **24**. Oxidation of **24** to 1-trifluoromethylquinolone **25** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[12] followed by hydrolysis under acidic conditions, gave 1-trifluoromethylquinolonecarboxylic acid **17**. With the desired 1-trifluoromethylquinolonecarboxylic acid (**17**) in hand, our next attempt was the introduction of cyclic amines to the C-7 position of **17**. Unfortunately, the reaction of **17** with 1-methylpiperazine by heating the mixture in dimethyl sulfoxide (DMSO) failed to give the 7-(4-methylpiperazinyl) derivative **8a**. The introduction of the cyclic amines to 3-ethoxycarbonyl-1-trifluoromethyltetrahydroquinolone **24** was then attempted. As shown in Scheme 2, it was found that the reaction of **24** with cyclic amines (1-methylpiperazine and 3-Boc-aminopyrrolidine) in acetonitrile proceeded smoothly to give the 7-cyclic amino derivatives **26a**,**b**. Treatment of **26a**,**b** with DDQ, followed by the removal of an ester group and a Boc group under acidic conditions, gave the desired 7-cyclic amino-1-trifluoromethyl-4-quinolone-3-carboxylic acid derivatives **8a**,**b**.

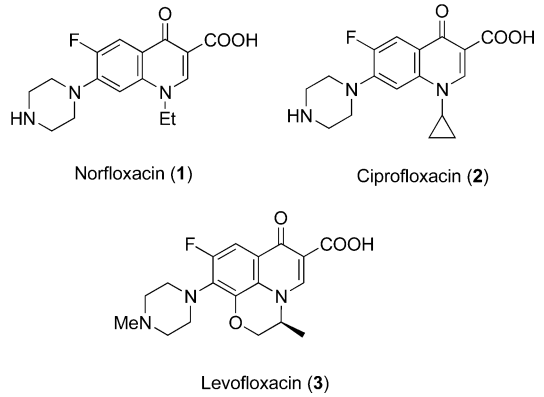

Figure 1.

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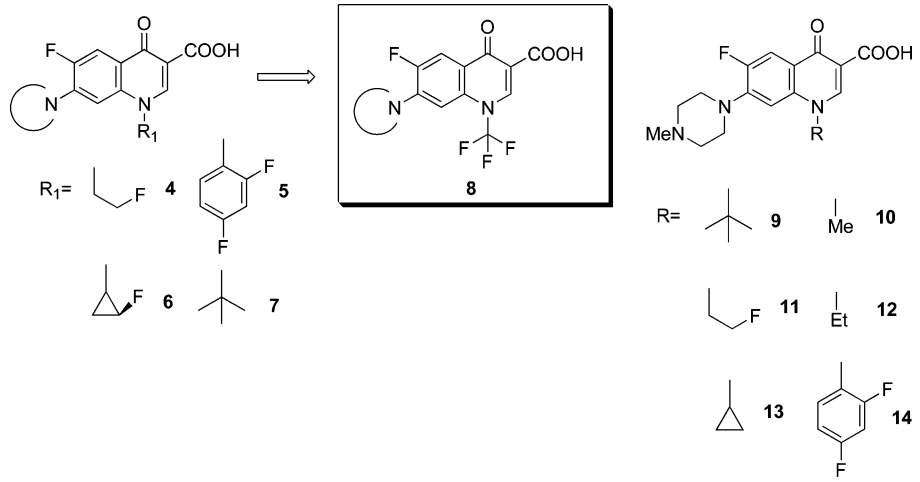


Figure 2.

Scheme 1

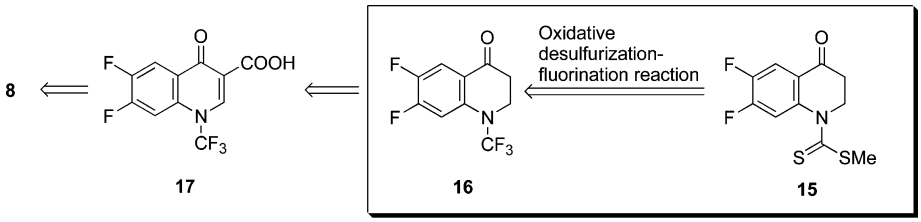


Table 1. In Vitro Antibacterial Activity of 1-Trifluoromethylquinolones (**8a**,**b**) and 1-Subutituted 7-(4-Methyl-1-piperazinylquinolones (**9**−**14**)

	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
8a	0.78	3.13	0.05	6.25
8b	1.56	12.5	0.39	>12.5
1	0.39	3.13	0.05	1.56

Antibacterial Activity. With the 7-cyclic amino-1-trifluoromethyl-4-quinolone-3-carboxylic acid derivatives **8a**,**b** in hand, the in vitro antibacterial activity of each against Gram-positive (*Staphylococcus aureus* Smith and *Streptococcus pneumoniae* type III) and Gram-negative (*Escherichia coli* NIHJ JC-2 and *Pseudomonas aeruginosa* IID1210) bacteria was evaluated. The minimum inhibitory concentration (MIC, μg/mL) of each derivative is shown in Table 1 along with that of **1**. The antibacterial activity of **8a** was comparable to that of **1** except against *P. aeruginosa* IID1210.

Next, we compared the in vitro antibacterial activity of the 7-(4-methyl-1-piperazinyl) derivative **8a** to that of the 7-(4-methyl-1-piperazinyl)quinolone derivatives **9**−**14**, which respectively carry a *tert*-butyl, methyl, ethyl, 2-fluoroethyl, cyclopropyl, and 2,4-difluorophenyl group as the N-1 substituent.[13] As shown in Table 2, **8a** showed weaker antibacterial activity than the *tert*-butyl derivative **9**, which was expected to have the same steric hindrance for the N-1 substituent as that of **8a**, against both Gram-positive and -negative bacteria. The antibacterial activity of **8a** was close to that of the 1-methyl derivative **10** rather than to that of the *tert*-butyl derivative **9**.

Table 2. In Vitro Antibacterial Activity of 1-Subutituted 7-(4-Methyl-1-piperazinyl)quinolones (**8a**, **9**−**14**)

	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
8a	0.78	3.13	0.05	6.25
9	0.20	0.78	0.025	1.56
10	0.39	6.25	0.05	1.56
11	0.20	3.13	0.025	1.56
12	0.20	1.56	0.0125	1.56
13	0.10	0.39	≤0.0063	0.78
14	0.10	0.39	0.10	3.13

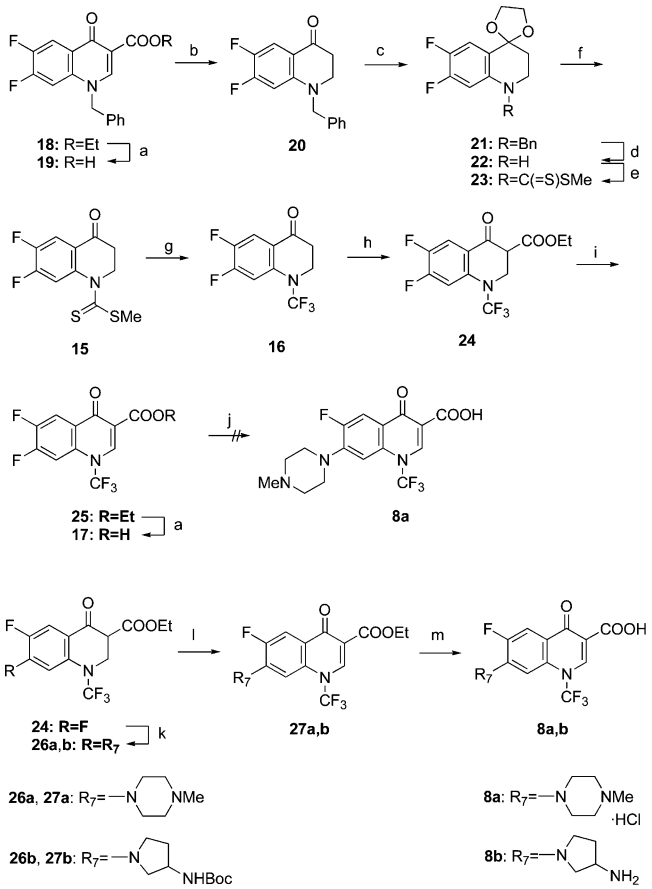
Conclusion

As described above, we have successfully designed, synthesized, and evaluated the 4-quinolone-3-carboxylic acids **8a**,**b** carrying a trifluoromethyl group as a novel N-1 substituent. The synthesis of these compounds was achieved in nine steps from **18** by a method featuring an oxidative desulfurization−fluorination reaction as the key step. Of the two derivatives **8a** and **8b**, **8a** was found to exhibit antibacterial activity comparable to that of **1**. In addition, the properties of a trifluoromethyl group as the N-1 substituent of fluoroquinolone were more similar to those of a methyl group than to that of a *tert*-butyl group, as determined by comparing the antibacterial activity of **8a** with that of 7-(4-methyl-1-piperazinyl)quinolones **9**−**14** carrying various known N-1 substituents. Further investigation of the 1-trifluoromethyl-4-quinolone-3-carboxylic acid derivatives 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 theoretical values and were

Scheme 2[a]



[a] Reagents: (a) H_2SO_4, AcOH, H_2O, 97%; (b) $NaBH_4$, *p*-toluenesulfonic acid, MeOH, 68%; (c) $HOCH_2CH_2OH$, *p*-toluenesulfonic acid, toluene, 60%; (d) $HCOONH_4$, Pd−C, MeOH, 80%; (e) (i) CS_2, lithium bis(trimethylsilyl)amide, THF; (ii) MeI; (f) 3 M HCl, 96% (from **22**); (g) HF−pyridine, CH_2Cl_2, 96%; (h) $(EtO)_2P(=O)COOEt$, NaH, THF, 78%; (i) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, dioxane, 98%; (j) 1-methylpiperazine, Et_3N, DMSO; (k) 1-methylpiperazine or 3-Boc-aminopyrrolidine, Et_3N, MeCN 91% (for **26a**), 85% (for **26b**); (l) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, dioxane, 93% (for **27a**), 83% (for **27b**); (m) 1 M HCl, dioxane, 87% (for **8a**), 86% (for **8b**).

determined by a Yanaco CHN corder MT-5. Infrared spectra were recorded with a JASCO FT/IR-5300 spectrometer. Mass spectrometry (MS) and high-resolution MS (HRMS) were performed with a JEOL JMS SX-102A mass spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained with a JEOL FX-90 (90 MHz) or a JEOL JMN-EX400 (400 MHz) spectrometer. The chemical shifts are expressed in parts per million (δ) 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 F_{254}, 0.25 mm, Art 5715) were used for TLC analysis. Solutions were dried over sodium sulfate, and the solvent was removed by rotary evaporation under reduced pressure.

6,7-Difluoro-1-trifluoromethyl-1,2,3,4-tetrahydro-4-oxoquinoline (16). Pyridinium poly(hydrogen fluoride) (2.86 mL, 10.0 mmol) was added to a solution of **15** (547 mg, 2.00 mmol) in anhydrous CH_2Cl_2 (12 mL) at −78 °C. *N*-Bromosuccimide (1.42 g, 8.00 mmol) was added portionwise to the above solution at −78 °C, and the whole mixture was stirred at the same temperature for 1 h and then further stirred at room temperature for 1 h. The mixture was poured into a solution of saturated $NaHSO_3$ solution (60 mL) and saturated $NaHCO_3$ solution (60 mL), and the resulting mixture was stirred at room temperature for 15 min. The organic layer was separated, washed with 1 M HCl and water, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 4:1) of the residue gave **16** (483 mg, 96%) as a colorless powder. Mp: 47−48 °C (petroleum ether). ^{1}H NMR ($CDCl_3$): δ 2.82−2.85 (m, 2H, C_3−H), 3.82−3.85 (m, 2H, C_2−H), 7.18 (m, 1H, C_8−H), 7.84 (dd, J = 10.3, 8.8 Hz, 1H, C_5−H). MS (EI) *m/z*: 251 (M^+). HRMS (EI) for $C_{10}H_6F_5NO$ (M^+): calcd, 251.0370; found, 251.0402.

Ethyl 6,7-Difluoro-1-trifluoromethyl-1,2,3,4-tetrahydro-4-oxo-3-quinolonecarboxylate (24). A solution of **16** (314 mg, 1.25 mmol) in anhydrous THF (2 mL) was added to a suspension of NaH (60% dispersion in mineral oil, 115 mg, 2.88 mmol) in anhydrous THF (4.3 mL) at −78 °C. Diethyl ethoxycarbonylphoshonate (0.30 mL, 1.63 mmol) was added to the above mixture at −78 °C, and the mixture was heated under reflux for 30 min. After the reaction was quenched by adding acetic acid (0.4 mL) under conditions of cooling with ice, the mixture was diluted with AcOEt and washed with saturated $NaHCO_3$ solution and water, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 20:1) of the residue gave **24** (316 mg, 78%) as a colorless powder. Mp: 79−80 °C (petroleum ether). ^{1}H NMR ($CDCl_3$): δ 1.36 (t, J = 7.3 Hz, 3H, CH_3), 4.26 (s, 2H, C_2−H), 4.32 (q, J = 7.3 Hz, 2H, $COOCH_2$), 7.04 (m, 1H, C_8−H), 7.59 (dd, J = 10.3, 8.8 Hz, 1H, C_5−H), 12.1 (br s, 1H, OH). MS (EI) *m/z*: 323 (M^+). Anal. ($C_{13}H_{10}F_5NO_3$) C, H, N.

Ethyl 6-Fluoro-1-trifluoromethyl-1,2,3,4-tetrahydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylate (26a). A solution of **24** (129 mg, 0.399 mmol), 1-methylpiperazine (49 μL, 0.440 mmol), and triethylamine (0.11 mL, 0.800 mmol) in anhydrous MeCN (3 mL) was heated at 50 °C for 18 h and then concentrated in vacuo. Flash chromatography (CH_2Cl_2/acetone = 5:1) of the residue gave **26a** (146 mg, 91%) as a pale-yellow powder. Mp: 77−78 °C (petroleum ether). ^{1}H NMR ($CDCl_3$): δ 1.29 (t, J = 7.3 Hz, 1.5H, CH_3), 1.35 (t, J = 7.3 Hz, 1.5H, CH_3), 2.37 (s, 1.5H, NCH_3), 2.40 (s, 1.5H, NCH_3), 2.60−2.65 (m, 4H, $CH_2 \times 2$), 3.23−3.31 (m, 4H, $CH_2 \times 2$), 3.70 (q, J = 4.4 Hz, 0.5H, C_3−H), 3.93 (dd, J = 13.2 Hz, 3.9 Hz, 0.5H, C_2−H), 4.10 (dd, J = 9.3, 8.3 Hz, 0.5H, C_2−H), 4.22 (s, 1H, C_2−H), 4.29 (q, J = 7.3 Hz, 2H, $COOCH_2$), 6.62 (m, 0.5H, C_8−H), 6.71 (m, 0.5H, C_8−H), 7.42 (d, J = 12.7 Hz, 0.5H, C_5−H), 7.65 (d, J = 13.2 Hz, 0.5H, C_5−H), 12.1 (br s, 0.5H, OH). MS (EI) *m/z*: 403 (M^+). Anal. ($C_{18}H_{21}F_4N_3O_3$) C, H, N.

Ethyl 7-(3-*tert*-Butoxycarbonyamino-1-pyrrolidinyl)-6-fluoro-1-trifluoromethyl-1,2,3,4-tetrahydro-4-oxo-3-quinolinecarboxylate (26b). The compound **26b** (165 mg, 85%) was prepared from **24** (129 mg 0.399 mmol) in the same manner as that described for **26a**. Mp: 109−110 °C (hexane). ^{1}H NMR ($CDCl_3$): δ 1.29 (t, J = 6.9 Hz, 1.5H, CH_3), 1.34 (t, J = 7.3 Hz, 1.5H, CH_3), 1.45 (s, 4.5H, C_4H_9), 1.56 (s, 4.5H, C_4H_9), 1.93−1.96 (m, 1H, CH_2), 2.21−2.25 (m, 1H, CH_2), 3.35−4.28 (m, 8.5H, C_3−H, $CH_2 \times 3$, $COOCH_2$), 4.33 (brs, 1H, C_2−H), 4.69 (brs, 1H, C_2−H), 6.26−6.27 (m, 0.5H, C_8−H), 6.28−6.39 (m, 0.5H, C_8−H), 7.37 (d, J = 12.2 Hz, 0.5H, C_5−H), 7.61 (d, J = 14.2 Hz, 0.5H, C_5−H), 12.1 (br s, 0.5H, OH). MS (FAB$^+$) *m/z*: 490 (M^+ + H). Anal. ($C_{22}H_{27}F_4N_3O_5$) C, H, N.

Ethyl 6-Fluoro-1-trifluoromethyl-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylate (27a). A solution of **26a** (121 mg, 0.300 mmol) and DDQ (71.7 mg, 0.300 mmol) in anhydrous dioxane (3 mL) was heated under reflux for 1.5 h, and the mixture was concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH = 20:1) of the residue gave **27a** (111 mg, 93%) as a pale-yellow powder. Mp: 129−130 °C (cyclohexane). ^{1}H NMR ($CDCl_3$): δ 1.40 (t, J = 6.9 Hz, 3H, CH_3), 2.38 (s, 3H, NCH_3), 2.61−2.64 (m, 4H, $CH_2 \times 2$), 3.29−3.31 (m, 4H, $CH_2 \times 2$), 4.41 (q, J = 6.9 Hz, 2H, $COOCH_2$), 6.93−6.96 (m, 1H, C_8−H), 8.03 (d, J = 13.2 Hz, 1H, C_5−H), 8.68 (s, 1H, C_2−H). MS (EI) *m/z*: 401 (M^+). Anal. ($C_{18}H_{19}F_4N_3O_3$) C, H, N.

Ethyl 7-(3-*tert*-Butoxycarbonyamino-1-pyrrolidinyl)-6-fluoro-1-trifluoromethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate (27b). The compound **27b** (116 mg, 83%) was prepared from **26b** (139 mg 0.285 mmol) in the same manner as that described for **27a**. ^{1}H NMR ($CDCl_3$): δ 1.41 (t, J = 7.3 Hz, 3H, CH_3), 1.59 (s, 9H, C_4H_9), 1.96−2.20 (m, 1H, CH_2), 2.24−2.33 (m, 1H, CH_2), 3.42−3.46 (m, 1H, CH_2), 3.58−3.63 (m, 1H, CH_2), 3.64−3.71 (m, 1H, CH_2), 3.72−3.85 (m, 1H, CH_2), 4.40 (q, J = 7.3 Hz, 2H, $COOCH_2$), 4.74 (br s, 1H, CH), 6.53−6.55 (m, 1H, C_8−H), 7.98 (d, J = 13.7 Hz, 1H, C_5−H), 8.69 (s, 1H, C_2−H). MS (FAB$^+$) *m/z*: 488 (M^+ + H). Anal. ($C_{22}H_{25}F_4N_3O_3$) C, H, N.

6-Fluoro-1-trifluoromethyl-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic Acid Hydrochloride (8a). A solution of **27a** (90.3 mg, 0.225 mmol) in 1 M HCl (2.5 mL) and dioxane (3.5 mL) was heated under reflux for 1.5 h. The mixture was concentrated, and the residue was triturated with EtOH. The resulting precipitates were collected by filtration, washed with EtOH, and then dried in air to give **8a** (80 mg, 87%) as a colorless powder. Mp: >300 °C. ^{1}H NMR (DMSO-d_6 + CF_3COOD): δ 2.91 (s, 3H, NCH_3), 3.23 (m, 4H, CH_2x2), 3.60 (m, 4H, CH_2 × 2), 7.07 (m, 1H, C_8−H), 8.06 (d, J = 12.7 Hz, 1H, C_5−H), 8.90 (s, 1H, C_2−H). MS (FAB$^+$) *m/z*: 374 (M^+ + H). Anal. ($C_{16}H_{15}F_4N_3O_3$·HCl) C, H, N.

7-(3-Amino-1-pyrrolidinyl)-6-fluoro-1-trifluoromethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (8b). A solution of **27b** (63.4 mg, 0.130 mmol) in 1 M HCl (2.5 mL) and dioxane (2.5 mL) was heated under reflux for 4 h. The mixture was concentrated, and the residue was dissolved in water. The aqueous solution was adjusted to pH 7 by addition of 0.01 M NaOH solution. The resulting precipitates were collected by filtration, washed with water, exposed with CH_2Cl_2, and then again washed with water to give **8b** (40 mg, 86%) as pale-brown powder. Mp: >300 °C. ^{1}H NMR (DMSO-d_6 + CF_3-COOD): δ 2.15−2.17 (m, 1H, CH_2), 2.29−2.38 (m, 1H, CH_2), 3.63−3.81 (m, 3H, CH_2 × 2), 3.93−3.99 (m, 2H, CH, CH_2), 6.60−6.62 (m, 1H, C_8−H), 7.95 (d, J = 13.7 Hz, 1H, C_5−H), 8.82 (S, 1H, C_2−H). MS (FAB$^+$) *m/z*: 360 (M^+ + H). Anal. ($C_{15}H_{13}F_4N_3O_3$·H_2O) C, H, N.

In Vitro Antibacterial Activity. The MIC (μg/mL) was determined by the agar dilution method[14] with 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.

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Supporting Information Available: Purity data for compounds **8**, **15**, **17**, **20**−**27**, experimental details and spectroscopic characterization of compounds **15**, **17**, **19**−**23**, **25**, and ^{13}C NMR data for compounds **8**, **16**, **24**, **26**, **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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