Endotoxin (ET) Shock Induction. Lethal toxicity in galactosamine-sensitized mice was tested by the method of Galanos.[31] Serial dilutions of test compounds (either in pyrogen-free saline or in isotonic glucose solution containing 1% ethanol) were administered iv to groups of six mice (C57BL/6) via the tail vein in pyrogen-free saline solution (total volume administered 0.2 mL). Simultaneously, galactosamine (400 mg/kg) was administered intraperitoneally to each mouse. The LD_{50} was calculated from the survivors 1 day later using Probit[35] analysis.

Induction of TNF-α. Induction of TNF-α and cultivation of mouse bone marrow-derived macrophages. Bone marrow cells were flushed from femurs of $B_6D_2F_1$ mice and cultured at 37 °C in an atmosphere of 5% CO_2 for 8–10 days in Teflon bags. Dulbecco's modified Eagle's medium (DMEM) H 21 supplemented with 10% fetal calf serum, 5% horse serum, antibiotics, and 20% L929 cell culture supernatant as the source of CSF-1 were used.[36] The differentiated macrophages were washed twice and resuspended in RPMI 1640 medium supplemented with 50 units/mL penicillin, 50 μg/mL streptomycin, 2 mM glutamine, and 5% fetal calf serum. The cell suspension was adjusted to 10^6 cells/mL, and aliquots of 1 mL/well were incubated on Costar plates for 3 h at 37 °C; the nonadherent cells were washed off, and the adherent cells were incubated overnight in the presence or absence of 100 units/mL interferon γ. For the induction of TNF-α, the cells were washed twice in prewarmed serum-free medium and incubated for 4 h with the appropriate test samples dissolved in 1-mL amounts of serum-free medium. The supernatants were harvested and kept at −20 °C. TNF-α levels in the supernatants were determined by the cytotoxicity of TNF for actinomycin-D-treated L929 cells as described elsewhere.[32,37]

Acknowledgment. We thank Dr. Ekke Liehl, Dr. Jacques Eustache, and Dr. Peter Stütz for numerous discussions.

Registry No. 1, 142981-91-7; 2, 142981-92-8; 3, 142981-93-9; 4, 142981-94-0; 5, 142981-95-1; 6, 142981-96-2; 7, 142981-97-3; 8, 142981-98-4; 8 Tris salt, 142982-12-5; 9, 142981-99-5; 9 Tris salt, 142982-13-6; 10, 142982-00-1; 11, 141692-86-6; 12, 142982-01-2; 13, 142982-02-3; 14, 142982-03-4; 15, 142982-04-5; 16, 142982-05-6; 17, 143060-80-4; 18, 142982-06-7; 19, 143060-81-5; 20, 142982-07-8; 21, 143060-82-6; 22, 142982-08-9; 22 Tris alt, 143060-86-0; 23, 143060-83-7; 23 Tris salt, 143119-65-7; 24, 142982-09-0; 24 Tris salt, 143062-03-7; 25, 143060-84-8; 25 Tris salt, 143119-71-5; 26, 142982-10-3; 26 Tris salt, 143060-87-1; 27, 143060-85-9; 27 Tris salt, 143119-66-8; benzyl 2-[(3-hydroxypropyl)amino]acetate, 142982-11-4; (R)-3-(benzyloxy)tetradecanoic acid N-hydroxysuccinimide ester, 101649-06-3; (R)-3-(benzyloxy)tetradecanoic acid, 87357-67-3.

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Synthesis and Antibacterial Activity of 1-(Substituted pyrrolyl)-7-(substituted amino)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids

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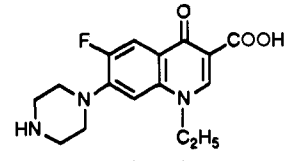
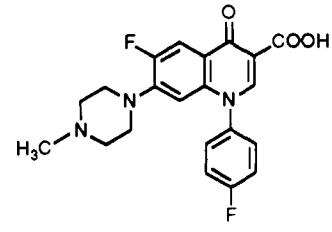
Seventeen quinolone compounds characterized by having a fluorine atom at the 6-position, a substituted amino at the 7-position, and a substituted pyrrolyl at the 1-position were synthesized for the first time. The in vitro antibacterial activities of these compounds against *Escherichia coli* and *Staphylococcus aureus* were tested. Among these agents obtained, compound **24** showed significantly enhanced activity against *S. aureus*. The results indicate that there is much room for modifications at the N-1 position.

Quinolone antibacterial agents are among the most attractive drugs in the anti-infective chemotherapy field. Although their structure–activity relationship (SAR) has been extensively studied,[1-7] the SAR for N-1 has not reached a clear conclusion. Studies by Koga indicate that the antibacterial activity of quinolones is greatly influenced by the steric bulk of the N-1 substituent. The best sterimol length is 4.17 Å with any groups bigger or smaller than that value decreasing the activity.[8] Such is the case that norfloxacin containing ethyl whose *L* is 4.14 Å at the N-1 position has good activity. Later, Chu et al. discovered that quinolones with fluorophenyl at the N-1 position also possess excellent activity.[9,10] This substitution pattern was not considered in Koga's early study[8] because the size of the benzene ring would have likely made it inactive. It seems that the electronic properties of 1-substituents, in addition to their steric bulk, also play an important role in the potency.[11] Therefore, when an aromatic five-membered heterocycle was introduced at the N-1 position,



norfloxacin



difloxacin

the activity of the quinolones is definitely different from that with a phenyl substituent. To date, modifications

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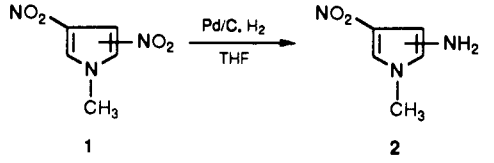
0022-2623/92/1835-3469$03.00/0

Scheme I



with different substituents at the N-1 position have been limited to lower alkyl and simple substituted phenyl.[12] Only a few utilized heterocyclic groups and simple pyrrolyl substituents have received little attention owing to the instability of pyrrolylamine.[13] In this study, we introduce pyrrolyl at the N-1 position to confirm the influence of electronic properties, and we also make some modifications at the 7-position for probing antibacterial activity. Here we will present the result of our investigation of a series of new quinolone compounds.

When the dinitropyrrole derivatives were reduced catalytically, only one nitro group was affected[14] (see Scheme I). We could use this resulting monoamino compound to make the introduction of the nitropyrrole at the N-1 position of quinolones. Theoretically, another nitro in the pyrrole ring could also be reduced to the amine after the ring is introduced at N-1. The amine in turn might be substituted by hydrogen, halogen, and other groups via diazotization and subsequent replacement reactions.

Chemistry

In this study, we chose an intramolecular nucleophilic displacement cyclization to form the quinoline heterocycle. The synthetic route (see Scheme II) was adapted from that reported by Chu et al. for the preparation of 1-aryl-fluoroquinolone antibiotics.[9] Our initial approach was from 2,4-dichlorofluorobenzene (3). Compounds 4 and 5 were prepared by literature methods.[9,15] Treatment of 5 with

Scheme II

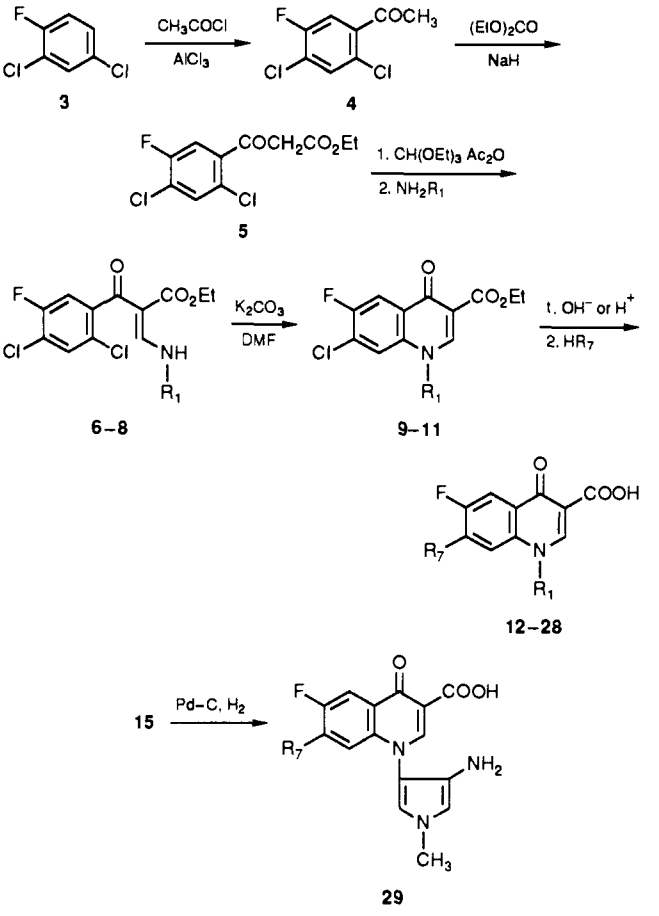
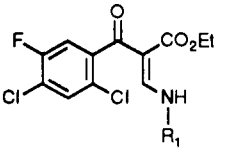
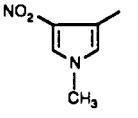
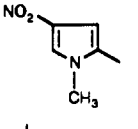
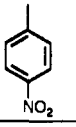


Table I. Structure and Properties of Compounds 6-8



no.	R_1	formula	mp, °C	yield, %
6		$C_{17}H_{14}Cl_2FN_3O_5$	156.5–158	69
7		$C_{17}H_{14}Cl_2FN_3O_5$	159–161	41
8		$C_{18}H_{13}Cl_2FN_2O_5$	145–146	79

(4) Nishimura, Y.; Minamida, A.; Matsumoto, J. Pyridonecarboxylic Acids as Antibacterial Agents. XII. Synthesis and Antibacterial Activity of Enoxacin Analogs with a Variant at Position 1. *Chem. Pharm. Bull.* **1988**, *36*, 1223–1228.
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(9) Chu, D. T. W.; Fernandes, P. B.; Claiborne, A. K.; Pihuleac, E.; Nordeen, C. W.; Maleczka, R. E., Jr.; Pernet, A. G. Synthesis and Structure–Activity Relationships of Novel Arylfluoroquinolone Antibacterial Agents. *J. Med. Chem.* **1985**, *28*, 1558–1564.
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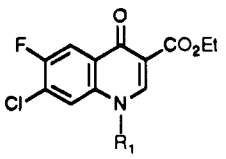
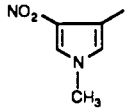
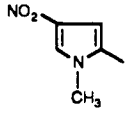
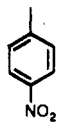
Table II. Structure and Properties of Compounds 9–11



no.	R_1	formula	mp, °C	yield, %
9		$C_{17}H_{13}ClFN_3O_5$	287–289	95
10		$C_{17}H_{13}ClFN_3O_5$	>300	97
11		$C_{18}H_{12}ClFN_2O_5$	268–269	97

triethyl orthoformate in acetic anhydride gave the one-carbon homolog enol ether intermediate, which was reacted without further purification with freshly prepared aminopyrrole derivatives in tetrahydrofuran at room temperature to afford the enamine keto ester **6–8**. They exist in both *E* and *Z* forms, and this could be confirmed by ^1H NMR. Regiospecific cyclization of **6–8** with potassium carbonate or NaH in dry dimethylformamide yielded **9–11**. Subsequent hydrolysis in acid[16] or base solution gave **12–14**. By condensation with amines, **15–28** were obtained. Catalytic hydrogenation of **15** conducted in acetic acid in the presence of palladium catalyst converted this compound to the corresponding amine analog **29**. We tried to substitute the amino by hydrogen, chlorine, bromine, and fluorine via diazotization and corresponding subsequent reaction. Unfortunately, the attempts to make those replacements were unsuccessful under a variety of conditions. From the above synthetic route, we synthesized 18 compounds including **6**, **7**, **9**, **10**, **12**, **13**, **15–25**, **29**, which are new compounds and had not been reported. Their structures have been confirmed by MS, ^1H NMR, and elemental analyses. Compounds **8**, **11**, **14**, **26–28** were prepared by literature methods[17] for comparison. The in vitro activities against *E. coli* and *S. aureus* for the 17 free acids were tested, and the data for difloxacin are included for comparison.

Results and Discussion

Table IV summarizes the in vitro antibacterial activity of the 1-(substituted pyrrolyl)-7-(substituted amino)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids against Gram-positive bacteria (*S. aureus* ATCC 6538p) and Gram-negative organism (*E. coli* ATCC 25922). The data for difloxacin, as well as for **26**, **27**, **28** of the 1-(*p*-nitrophenyl)-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid series, are included for comparison.

The effect of two kinds of nitropyrrolyl at the N-1 position of the quinolone on the in vitro antibacterial potency is shown by comparing the data for compounds **20** vs **23**, **21** vs **24**, and **22** vs **25**. It is interesting to note from Table IV that quinolones with the *N*-methyl-4-nitro-2-pyrrolyl moiety are superior to that of the *N*-methyl-4-nitro-3-pyrrolyl. The effect is shown to be 8–32-fold against *S. aureus* and 8–128-fold against *E. coli*.

With *N*-methyl-4-nitro-3-pyrrolyl ring substitution at the N-1 position, the potency rank order against *S. aureus* was piperidino (compounds **18**, **19**, **22**) > piperazinyl (compounds **15**, **16**, **17**, **20**) > pyrrolidinyl (compound **21**). The MIC values of the piperidino analogs is 2–8 times that of the piperazinyl analogs. In the piperidino series, an extra methyl on the piperidino moiety as well as its position also has influence on the activity. The activity of compound **18** (4′-CH_3) is 2 times that of **22** (3′-CH_3) and 4 times that of **19** (des-CH_3). The in vitro activity order of the substituents at the 7-position of the (*N*-methyl-4-nitro-2-pyrrolyl)quinolones is as follows: **23** > **24** > **25** against *E. coli* and **24** > **25** > **23** against *S. aureus*. We found that nonbasic biosteric replacements for piperazinyl rings at the 7-position enhance anti-Gram-positive activity but decreases anti-Gram-negative activity.

The antibacterial activities of all compounds synthesized in our study with substituted pyrrolyl at the N-1 position is less than that of difloxacin which has the *p*-fluorophenyl group at N-1, the presence of fluorine being very important for the activity. When the activities of **23**, **24**, **25** (their N-1 substituent is 4-nitropyrrolyl) were compared with that of **26**, **27**, **28** (their N-1 substituent is 4-nitrophenyl), we could see that the introduction of pyrrolyl at the N-1 position makes the activity considerably greater. This may be partly attributed to the excess π-electron density of pyrrole compared to that of the benzene ring. If we substitute the nitro on the pyrrole ring with fluorine, we will perhaps find a new agent better than difloxacin in activity. We suggest that this novel series of antibiotics is deserving of further study.

Experimental Section

Melting points were determined on X6 apparatus and are uncorrected. ^1H NMR spectra were recorded on JEOL FX-100Q spectrometer with TMS as internal standard. Mass spectra were obtained on JC-MS DX-300 spectrometer. Elemental analyses were obtained for the target compounds reported, which were within ±0.4% of the theoretical values. Thin-layer chromatography was conducted using silica gel.

Ethyl 3-[(4-Nitro-1-methyl-3-pyrrolyl)amino]-2-(2,4-dichloro-5-fluorobenzoyl)acrylate (6). A solution of **5** (2.81 g, 10.1 mmol) in triethyl orthoformate (2.53 mL, 18.3 mmol) and acetic anhydride (3.72 mL, 40.0 mmol) was stirred at 130 °C for 2 h with removal of the ethyl acetate formed during the reaction. The solution was evaporated under reduced pressure to a mobile oil. Freshly prepared 1-methyl-3-amino-4-nitropyrrole (by the reduction of 1-methyl-3,4-dinitropyrrole (1.72 g, 10.0 mmol)) was added to it and stirred for 1 h under nitrogen atmosphere. After filtration of insoluble material, the clear yellow solution was obtained and then evaporated under reduced pressure to give a thick residue. When alcohol was added to it, a yellow solid immediately formed. Filtration and air-drying afforded a solid of 3.02 g of almost pure **6**, in 69% yield: mp 156.5–158 °C; ^1H NMR ($CDCl_3$) δ (two sets of signals) 1.01 and 1.03 (3 H, t, J = 7 Hz, ethyl CH_3), 3.74 (3 H, s, NCH_3, signal overlap), 4.04 (2 H, q, J = 7 Hz, ethyl CH_2-signal overlap), 6.06–7.52 (4 H, m, aromatic H), 8.29 and 8.30 (1 H, d, J = 14 Hz, vinyl H), 11.78 and 13.01 (1 H, d, J = 14 Hz, NH); MS (EI) 429 (M^+), 394 (M^+ - Cl), 348 (M^+ - Cl - EtOH). Anal. ($C_{17}H_{14}Cl_2FN_3O_5$) C, H, N, F.

Ethyl 3-[(4-Nitro-1-methyl-2-pyrrolyl)amino]-2-(2,4-dichloro-5-fluorobenzoyl)acrylate (7). The preparation is similar to that of **6**, but **7** is less pure because of the high instability of the 2-aminopyrrole derivative. The crude product was purified

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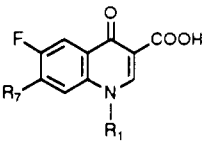
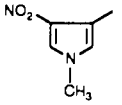
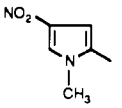
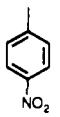
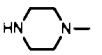
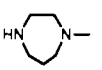
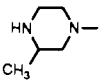
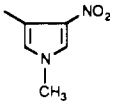
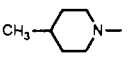
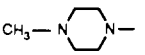
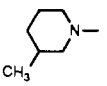
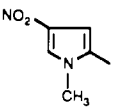
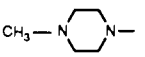
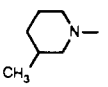
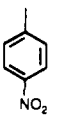
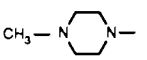
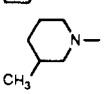
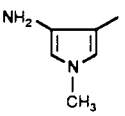
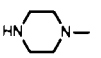
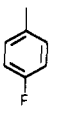
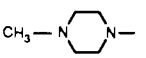
Table III. Structure and Properties of Compounds 12–29



no.	R_1	R_7	formula[a]	mp, °C	yield, %
12			$C_{15}H_9ClFN_3O_5$	>300	98
13		Cl	$C_{15}H_9ClFN_3O_5$	>300	91
14			$C_{16}H_8ClFN_2O_5$	276–280	98
15			$C_{19}H_{18}FN_5O_5 \cdot {}^1/_4H_2O$	258–259.5	78
16			$C_{20}H_{20}FN_5O_5 \cdot {}^1/_4H_2O$	158–160	59
17			$C_{20}H_{20}FN_5O_5 \cdot {}^1/_2H_2O$	249–251	76
18			$C_{21}H_{21}FN_4O_5 \cdot {}^1/_2H_2O$	285	78
19			$C_{20}H_{19}FN_4O_5$	>300	93
20			$C_{20}H_{20}FN_5O_5$	>300	64
21			$C_{19}H_{17}FN_4O_5 \cdot {}^1/_4H_2O$	>300	91
22			$C_{21}H_{21}FN_4O_5$	>300	96
23			$C_{20}H_{20}FN_5O_5$[b]	>300	71
24			$C_{19}H_{17}FN_4O_5 \cdot {}^1/_4H_2O$[c]	175–176	86
25			$C_{21}H_{21}FN_4O_5 \cdot {}^1/_2H_2O$	234–236	86
26			$C_{21}H_{19}FN_4O_5$	>300	72
27			$C_{20}H_{16}FN_3O_5$	>300	85
28			$C_{22}H_{20}FN_3O_5$	>300	78
29			$C_{19}H_{20}FN_5O_3$	>300	56
30			$C_{21}H_{19}N_3O_3F_2$[d]		

[a] C, H, N, and F analyses were within ±0.4% of the theoretical values, unless otherwise noted. [b] C: calcd, 55.93; found, 48.90. N: calcd, 16.31; found, 13.53. [c] F: calcd, 4.69; found, 3.90. [d] Difloxacin.

Table IV. In Vitro Antibacterial Activities

no.	min inhib concn (MIC), μg/mL		no.	min inhib concn (MIC), μg/mL	
	E. coli	*S. aureus*		*E. coli*	*S. aureus*
12	100	100	22	>100	25
13	100	50	23	3.125	6.25
14	12.5	6.25	24	12.5	0.78
15	100	100	25	100	3.125
16	100	100	26	12.5	25
17	100	100	27	>100	>100
18	>100	12.5	28	>100	>100
19	100	50	29	50	100
20	100	100	30	0.39	0.195
21	>100	>100			

by VLC (dichloromethane) to give **7** in 41% yield: mp 159–161 °C; ^{1}H NMR ($CDCl_3$) δ (two sets of signals) 0.9 and 1.11 (3 H, t, J = 7 Hz, ethyl CH_3), 3.67 and 3.72 (3 H, s, NCH_3), 4.02 and 4.07 (2 H, q, J = 7 Hz, ethyl CH_2), 6.40–7.60 (4 H, m, aromatic H), 8.13 and 8.36 (1 H, d, J = 14 Hz, vinyl H), 11.15 and 12.75 (1 H, d, J = 14 Hz, NH); MS (EI) 429 (M^+), 394 (M^+ - Cl), 383 (M^+ - EtOH), 348 (M^+ - Cl - EtOH). Anal. ($C_{17}H_{14}C_{12}FN_3O_5$) C, H, N, F.

Ethyl 1-(4-Nitro-1-methyl-3-pyrrolyl)-7-chloro-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (9). To a solution of **6** (6.0 g, 14.0 mmol) in dry dimethylformamide (70 mL) was added potassium carbonate. The mixture was heated to 130 °C and allowed to stir for 1 h. The reaction solution was quenched with cold water, and the resulting precipitate was filtered, washed with water, and dried. Recrystallization from dimethylformamide gave 5.1 g of **9** (94% yield): mp 287–289 °C; ^{1}H NMR (CF_3COOD) δ 1.52 (3 H, t, J = 7 Hz, ethyl CH_3), 3.99 (3 H, s, NCH_3), 4.64 (2 H, q, J = 7 Hz, ethyl CH_2), 7.39 (1 H, d, J = 3 Hz, pyrrolyl =CH—N), 7.87 (1 H, d, J = 6 Hz, C8-H), 7.96 (1 H, d, J = 3 Hz, pyrrolyl =CH—N), 8.44 (1 H, d, J = 8 Hz, C5-H), 9.31 (1 H, s, C2-H); MS (EI) 393 (M^+), 348 (M^+ - OC_2H_5), 321 (M^+ - CH_2=CH_2—CO_2). Anal. ($C_{17}H_{13}ClFN_3O_5$) C, H, N, F.

Ethyl 1-(4-Nitro-1-methyl-2-pyrrolyl)-7-chloro-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (10). Compound **10** was prepared from **7** using the same experimental procedure to give pure **10** in 96% yield: mp >300 °C; ^{1}H NMR (CH_3COOD) δ 1.52 (3 H, t, J = 7 Hz, ethyl CH_3), 3.56 (3 H, s, NCH_3), 4.69 (2 H, q, J = 7 Hz, ethyl CH_2), 7.32 (1 H, d, J = 2 Hz, pyrrolyl =CH—N), 7.66 (1 H, d, J = 6 Hz, C8-H), 7.96 (1 H, d, J = 2 Hz, pyrrolyl =CH—N), 8.46 (1 H, d, J = 8 Hz, C5-H), 9.40 (1 H, s, C2-H); MS (EI) 393 (M^+), 348 (M^+ - OC_2H_5). Anal. ($C_{17}H_{13}ClFN_3O_5$) C, H, N, F.

1-(4-Nitro-1-methyl-3-pyrrolyl)-6-fluoro-7-chloro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (12). A mixture of **9** (4.70 g, 12.0 mmol), potassium hydroxide (1.31 g, 23.4 mmol), and water was allowed to reflux for 3 h. This solution was brought to pH 2 and filtered. The collected solid was recrystallized from dimethylformamide–water (5:1) to yield 4.20 g of **12** (yield 97%): mp >300 °C; ^{1}H NMR (CH_3COOD) δ 3.98 (3 H, s, NCH_3), 7.38 (1 H, d, J = 2 Hz, pyrrolyl =CH—N), 7.89 (1 H, d, J = 6 Hz, C8-H), 7.96 (1 H, d, J = 2 Hz, pyrrolyl =CH—N), 8.44 (1 H, d, J = 8 Hz, C5-H), 9.38 (1 H, s, C2-H); MS (EI) 365 (M^+), 321 (M^+ - CO_2). Anal. ($C_{15}H_9ClFN_3O_5$) C, H, N, F.

1-(4-Nitro-1-methyl-2-pyrrolyl)-6-fluoro-7-chloro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (13). The ester **10** (0.80 g, 2.0 mmol) was hydrolyzed in 18 mL of a solution of dilute hydrochloric acid and acetic acid (3:2) under reflux for 4 h. The reaction was filtered and the solid was collected. Recrystallization from dimethylformamide–ethyl alcohol (3:1) gave 0.66 g of **13** in 91% yield: mp >300 °C; ^{1}H NMR (CF_3COOD) δ 3.58 (3 H, s, NCH_3), 7.31 (1 H, d, J = 2 Hz, pyrrolyl =CH—N), 7.58 (1 H, d, J = 6 Hz, C8-H), 7.97 (1 H, d, J = 2 Hz, pyrrolyl =CH—N), 8.23 (1 H, d, J = 8 Hz, C5-H), 9.36 (1 H, s, C2-H); MS (EI) 365 (M^+), 321 (M^+ - CO_2). Anal. ($C_{15}H_9ClFN_3O_5$) C, H, N, F.

1-(4-Nitro-1-methyl-3-pyrrolyl)-6-fluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (15). A mixture of **12** (1.00 g, 2.7 mmol) in dry dimethyl sulfoxide and piperazine (1.6 g, 18 mmol) was heated at 140 °C with stirring. After 2.5 h, 10 mL of water was added to the mixture and acidified to pH 7 with acetic acid. The precipitate was removed by filtration, washed with water, dried, and recrystallized from ethyl alcohol to give 0.88 g of **15** (yield 78%): mp 258–259 °C; ^{1}H NMR (CF_3COOD) δ 3.78 (8 H, br s, piperazinyl H), 4.03 (3 H, s, NCH_3), 7.00 (1 H, d, J = 6 Hz, C8-H), 7.42 (1 H, d, J = 2 Hz, pyrrolyl =CH—N), 8.00 (1 H, d, J = 2 Hz, pyrrolyl =CH—N), 8.35 (1 H, d, J = 13 Hz, C5-H), 9.25 (1 H, s, C2-H); MS (EI) 415 (M^+), 373 (M^+ - C_2H_4N). Anal. ($C_{19}H_{18}FN_5O_5 \cdot {}^1/_4H_2O$) C, H, N, F.

1-(4-Nitro-1-methyl-2-pyrrolyl)-6-fluoro-7-(4-methyl-1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (23). *N*-Methylpiperazine (0.8 mL, 7.2 mmol) was added to a suspension of **13** (0.35 g, 0.96 mmol) in 5 mL of dimethylformamide. After 40 min of stirring at 120 °C, the clear brown solution was concentrated under reduced pressure and was purified using preparative TLC (*n*-butyl alcohol–acetic acid–water 3:1:1). Recrystallization of the chromatographed product from dimethylformamide and methyl alcohol (2:1) gave a yellow powder (0.2 g, yield 71%): mp >300 °C; ^{1}H NMR (CF_3COOD) δ 3.18 (3 H, s, piperazinyl NCH_3), 3.29–4.20 (11 H, m, piperazinyl H and pyrryl NCH_3 signal overlap), 6.79 (1 H, d, J = 4 Hz, C8-H), 7.36 (1 H, s, pyrrolyl =CH—N), 8.01 (1 H, s, pyrrolyl =CH—N), 8.33 (1 H, d, J = 12 Hz, C5-H), 9.30 (1 H, s, C2-H); MS (EI) 429 (M^+), 385 (M^+ - CO_2). Anal. ($C_{20}H_{20}FN_5O_5$) C, H, N, F. C: Calcd, 55.93; found, 48.90. N: Calcd, 16.31; found, 13.53.

1-(4-Amino-1-methyl-3-pyrrolyl)-6-fluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (29). **15** (0.18 g, 0.4 mmol) dissolved in acetic acid was hydrogenated in a Parr apparatus for 6 h at 55–60 psi in the presence of palladium (10% on carbon). When the reaction was complete, the catalyst was removed by filtration. The brownish filtrate was evaporated to dryness below 50 °C. Further purification by crystallization from acetic acid–water (1:1) gave 0.09 g of **29**: mp >300 °C (yield 56%); ^{1}H NMR (CF_3COOD) δ 3.40–4.20 (8 H, m, piperazinyl H), 3.96 (3 H, s, NCH_3), 6.94 (1 H, d, J = 7 Hz, C8-H), 7.37 (1 H, d, J = 3 Hz, pyrrolyl =CH—N), 7.95 (1 H, d, J = 3 Hz, pyrrolyl =CH—N), 8.32 (1 H, d, J = 12 Hz, C5-H), 9.2 (1 H, s, C2-H); MS (EI) 385 (M^+). Anal. ($C_{19}H_{20}FN_5O_3$) F.

In Vitro Antibacterial Activity. The in vitro antibacterial activity of the test compounds in a side by side comparison was determined by conventional serial dilution procedures. The organisms were grown overnight in brain–heart infusion (BHI) broth at 37 °C. Two-fold dilutions of the stock solution (5 mg/mL) of the test compounds were made in BHI agar to obtain the test concentration ranging from 200 to 0.7 μg/mL. It was then incubated at 37 °C for 24 h. The MIC was the lowest concentration of the test compounds that inhibited visible growth.

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Registry No. **1**, 68712-54-9; **2**, 72083-68-2; **5**, 86483-51-4; **6**, 142509-38-4; **7**, 142509-39-5; **8**, 139396-15-9; **9**, 142533-45-7; **10**, 142509-40-8; **11**, 126362-85-4; **12**, 142509-41-9; **13**, 142509-42-0; **14**, 126362-87-6; **15**, 142509-43-1; **16**, 142509-44-2; **17**, 142509-45-3; **18**, 142509-46-4; **19**, 142509-47-5; **20**, 142509-48-6; **21**, 142509-49-7; **22**, 142509-50-0; **23**, 142533-46-8; **24**, 142509-51-1; **25**, 142509-52-2; **26**, 126362-89-8; **27**, 139396-25-1; **28**, 139396-27-3; **29**, 142509-53-3; *N*-methylpiperazine, 109-01-3; piperazine, 110-85-0; hexahydro-1*H*-1,4-diazepine, 505-66-8; 2-methylpiperazine, 109-07-9; 4-methylpiperidine, 626-58-4; piperidine, 110-89-4; pyrrolidine, 123-75-1; 3-methylpiperidine, 626-56-2.

Supplementary Material Available: ^{1}H NMR data and MS characterization data for all new compounds (2 pages). Ordering information is given on any current masthead page.