Quinolone Antibacterial Agents. Synthesis and Structure–Activity Relationships of 8-Substituted Quinoline-3-carboxylic Acids and 1,8-Naphthyridine-3-carboxylic Acids

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A series of 7,8-disubstituted 1-cyclopropyl-6-fluoroquinoline-3-carboxylic acids, 7-substituted 1-cyclopropyl-6-fluoro-1,8-naphthyridine-3-carboxylic acids, and 10-substituted 9-fluoropyridobenzoxazine-6-carboxylic acids has been prepared and evaluated for antibacterial activity. The side chains examined at the 7-position (benzoxazine 10-position) included piperazinyl (g), 3-aminopyrrolidinyl (a), 3-(aminomethyl)pyrrolidinyl (b), and alkylated 3-(aminomethyl)pyrrolidinyl (c–f). Variations at C-8 of the quinolone ring system included hydrogen, nitro, amino, fluorine, and chlorine. The relative enhancement of in vitro activities by the side chains on the 8-hydrogen quinolone and 1,8-naphthyridine against Gram-negative organisms was a > b > g > c–f. The activity imparted to the substituted quinolone nucleus by the 8-substituent was in the order F > Cl > naphthyridine > H > benzoxazine > NH_2 > NO_2. These trends were retained in vivo.

Since the discovery of nalidixic acid by Lesher in 1962,[1] the quinolone antibacterials have emerged as a significant class of chemotherapeutic agents. The initial compounds possessed oral activity against Gram-negative bacteria but suffered as a class in their inability to affect Gram-positive strains.[2] The initial structure–activity relationship (SAR) correlation by Meltzer and Kaminsky[3] resulted in compounds with a slightly broader spectrum of activity. Oxolinic acid, which possessed some Gram-positive in vitro activity as well as an enhanced antpseudomonal effect, was synthesized during this study. The next series of quinolones emerged with the synthesis of flumequine (9) (Figure 1).

The major structural change in these types was the introduction of a fluorine at C-6, which gave rise to compounds that were more potent than nalidixic acid and were comparable to oxolinic acid in vitro.[4] This modification continues to be a structural feature of all current synthetic analogues and is one of the major factors for the greatly increased activity of all of the current quinolones.

As research in this area became more extensive, positional SAR studies established the desirability of having a basic group at position 7.[5,6] This research resulted in the nearly simultaneous discovery of norfloxacin (10) and enoxacin (11) (Figure 1), which are characterized by having a piperazine moiety at C-7. These two compounds, which possess both broad-spectrum activity and oral efficacy, were the next members of this class of compounds. These discoveries produced a resurgence of interest in the quinolone area, resulting in the synthesis of many new and highly active agents such as ofloxacin (12), pefloxacin (13), difloxacin (14), and one of the most active quinolones to date, ciprofloxacin (1g).

These examples indicate the desirability of the piperazine substituent at C-7. The greatly increased Gram-negative activity as well as the appearance of some Gram-positive activity, in vitro, is a characteristic of compounds having a piperazine moiety at C-7.[6] It also appears that the piperazine substituent allows better in vivo activity without a proportional increase in side effects.[2d] For these reasons, the compounds currently in clinical trials feature the 7-piperazinyl moiety.

Our initial SAR studies investigated deviations from the set substitutional pattern by the use of a piperazine mimic,

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(3) Kaminsky, D.; Meltzer, R. I. *J. Med. Chem.* 1968, *11*, 160.
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(6) Domagala, J. M.; Hanna, L. D.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; Sanchez, J. P.; Solomon, M. *J. Med. Chem.* 1986, *29*, 394.
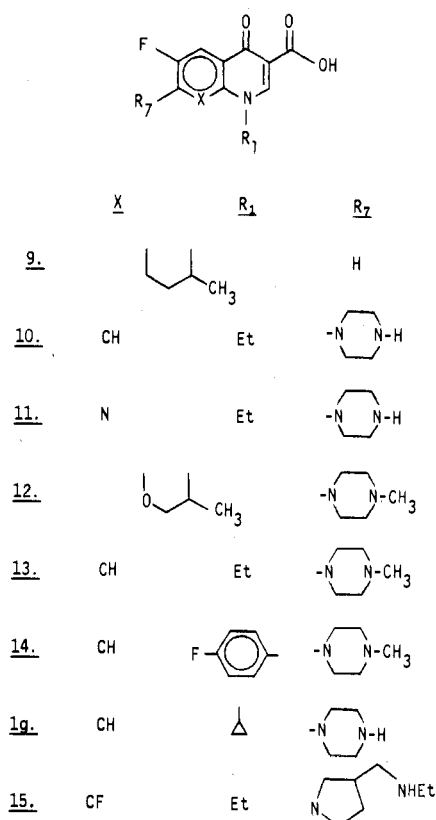
Figure 1. Clinicially significant quinolone type antibacterial agents.

a substituted 3-(aminomethyl)pyrrolidine substituent, at C-7.[7a] This slight structural modification greatly increased the Gram-positive potency, finally establishing the quinolones as a truly broad-spectrum class of antibacterial agents. In an attempt to enhance oral activity, a fluorine was introduced at C-8, which resulted in CI-934 (15), the most potent Gram-positive quinolone known to date.[7]

The most significant structural modification made during the recent enhanced synthetic effort in this area was the introduction of a cyclopropyl group at position 1. This modification gives ciprofloxacin (1g),[8] a compound with a 2-8-fold potency increase in vitro against Entero-bacteriaceae, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* when compared with norfloxacin (10).[8a,9] A detailed discussion on the nature of the N₁ substituent and the effects of a cyclopropyl group has recently been described.[24]

Further SAR considerations led us to evaluate the possibility of preparing a series of compounds with substituents other than fluorine at the 8-position. Maintaining that arrangement of the functional groups that gives the

Table I. Previously Described Quinolone and Naphthyridine Substrates

| compd	X	R₁	R₇	R	lit. ref[a]
1	CH	c-C₃H₅	F	H	11[b]
2	CF	c-C₃H₅	F	H	12
3	CCl	c-C₃H₅	F	H	13[c]
4	CNO₂	c-C₃H₅	Cl	Et	14[d]
6	N	c-C₃H₅	Cl	H	15
7			F	H	16

[a] Compounds were prepared by these referenced procedures (except where noted) and had correct C, H, N analyses and supporting spectral data. [b] Literature synthesis was modified, see Scheme I. [c] Literature synthesis was modified, see Scheme II. [d] Intermediate 22 prepared in this synthesis; conversion to compound 4 is shown in Scheme III.

Scheme I[a]
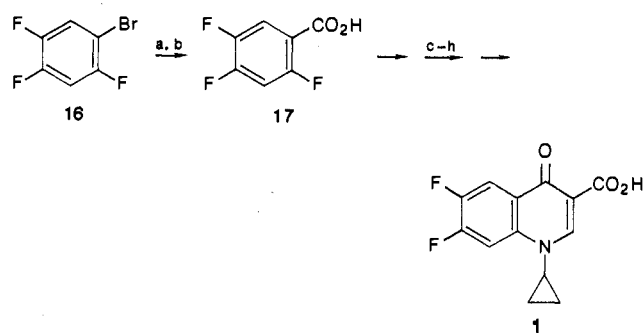
[a] (a) CuCN, DMF, Δ; (b) 50% H₂SO₄, Δ; (c) (COCl)₂, CH₂Cl₂, DMF; (d) [EtO₂CCHCO₂]²⁻2Li⁺, THF; (e) HC(OEt)₃, Ac₂O; (f) C₃H₅NH₂, t-BuOH; (g) t-BuOK, t-BuOH; (h) 6 M HCl, Δ.

Scheme II[a]
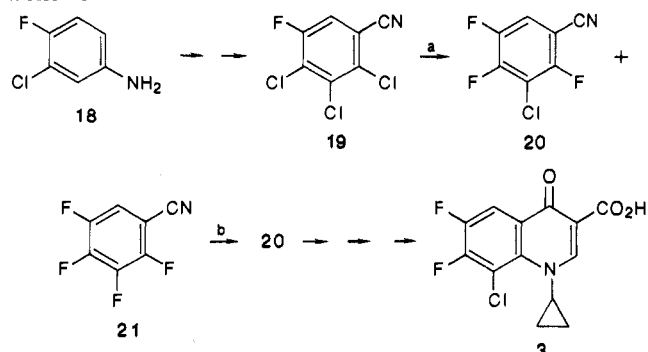
[a] (a) KF, DMSO, 140 °C; (b) distilled to remove 21.

highest activity levels, (R₆ = F; R₁ = cyclopropyl), a systematic variation at the 7- and 8-positions was examined. A preliminary report[10] describing other work of this type

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Scheme III[a]
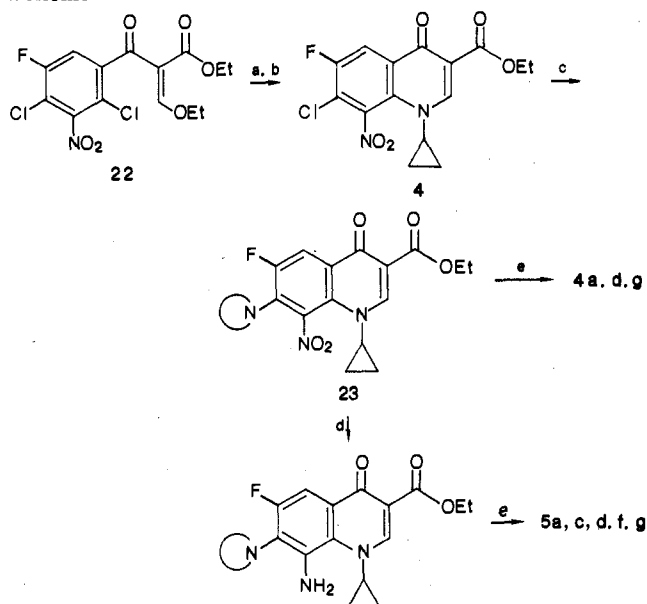
[a] (a) C_3H_5NH_2, t-BuOH; (b) t-BuOK, t-BuOH; (c) ⟨NH, CH_3-CN, base; (d) H_2, Raney Ni; (e) HCl, EtOH, Δ.

Figure 2. Relative in vitro activity of side chains on 8-hydrogen quinolones and 1,8-naphthyridines against Gram-negative organisms.

has prompted us to publish the results of our extensive work in this area.

Chemistry

The compounds listed in Table II were synthesized[5a] from the appropriate substituted quinolone or naphthyridine nucleus and the corresponding pyrrolidine or piperazine as outlined in genereal procedures A–E. The requisite amine side chains were prepared according to established literature procedures;[5a,17-19] literature procedures were also followed for the construction of the 8-fluoroquinolone **2**, the naphthyridine **6**, and the benzoxazine analogue **7** (Table I and references therein).

Modification of existing syntheses afforded the 8-hydrogen derivative **1**, the 8-chloroquinolone **3**, and the 8-nitro ester **4** (see references, Table I). For compound **1**, commercially available 1-bromo-2,4,5-trifluorobenzene (**16**) was converted to the nitrile, which was hydrolyzed to **17**, and this intermediate acid was, in turn, elaborated into the target compound **1** (Scheme I). The synthesis of the 8-chloro analogue **3** (Scheme II and references in Table I) in volved a pivotal fluoride exchange reaction in which 2,3,4-trichloro-5-fluorobenzonitrile (**19**) was reacted with potassium fluoride in dimethyl sulfoxide to give the desired nitrile **20**, as well as several other displacement products. Most notable of these products was 2,3,4,5-tetrafluorobenzonitrile (**21**); failure to remove this impurity results in significant contamination of the final 8-chloroquinolone **3** with the undesired 8-fluoro analogue **2**. Many attempts to improve the yield and the purity of **20** proved unsuccessful, but purification was finally effected by distilling away the lower boiling tetrafluoronitrile, **21**. Finally, the synthesis of the 8-nitro derivative **4** was achieved according
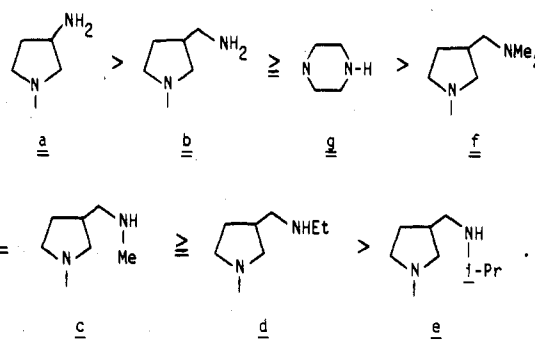
to Scheme III with the known ethoxyacrylate intermediate **22**.[14] Addition of cyclopropylamine to **22** followed by ring closure with potassium *tert*-butoxide gave the 8-nitroquinolone ester **4**. This crucial intermediate was then reacted with a variety of nucleophiles to give 7-substituted derivatives **23**. These derivatives could be further elaborated in two ways: in the first, the ester was hydrolyzed to give the 8-nitroquinolone acids **4a,d,g**, and in the second, the nitro group was reduced to the amine and the ester hydrolyzed to give the 8-aminoquinolone acids (**5a,c,d,f,g**).

Biological Assays

The series of 8-substituted quinolones (Table II) were tested against 11 representative Gram-positive and Gram-negative organisms by using standard microtitration techniques,[20] and their minimum inhibitory concentrations (MICs in micrograms/milliliter) were compared to the standard drugs (**4-9**) in multiple experiments (Table III). In order to make it easier to identify any trends in the activity produced by the C-7 side chains on the various quinolone nuclei, the geometric means of the MICs of the Gram-negative organisms (excluding *P. aeruginosa*) and the Gram-positive organisms were calculated and are summarized in Table V. The compounds were also tested for their inhibition of DNA gyrase by using a previously described test.[6,7a] The assay measured the concentration of drug (micrograms/milliliter) necessary to cleave DNA (Table III).

The in vivo potency expressed as the median protective dose (PD_{50}, mg/kg) was determined by using previously described methods.[7a,21] The results of the in vivo tests are summarized in Table IV. In vivo testing was not generally performed on compounds that did not exhibit excellent in vitro (MIC) activity. This included the 8-nitro series (**4a-g**) and most of the 8-amino series (**5b-e**).

Discussion of Results

By evaluating the geometric means of the MICs of the Gram-negative and Gram-positive organisms (Table V), it was established that the in vitro activity of the quinolone system in which there was a hydrogen at C-8 (X = CH, compounds **1a-g**) was about equal to the corresponding 1,8-naphthyridine analogues (X = N, compounds **6a-g**). However, the in vivo potency of the naphthyridines was considerably superior to the 8-hydrogen quinolones (Table IV). This is possibly due to the better blood levels that are often associated with the naphthyridines.[22] These

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Table II. Synthetic and Physical Data of the Quinolone and Naphthyridine Antibacterials Prepared for This Study

R₇	X	R₁	compd	method of prep[a]	mp, °C	formula (anal.)[b]	purifcn[c]	yield[d] %	C₂H[e]	C₅H[f]
(3-aminopyrrolidinyl, NH₂)	CH	c-C₃H₅	1a	A	>300	$C_{17}H_{18}FN_3O_3 \cdot 0.25H_2O \cdot 2HCl$ (C, H, N, Cl, H₂O)	trit 2-PrOH	72	9.2	8.2
l	CF	c-C₃H₅	2a	B	313–315	$C_{17}H_{17}F_2N_3O_3 \cdot HCl \cdot H_2O$ (C, H, N, Cl, F, H₂O)	trit EtOH	93	8.8[g]	7.7
l	CCl	c-C₃H₅	3a	B	245–247	$C_{17}H_{17}ClFN_3O_3 \cdot HCl \cdot 1.3H_2O$ (C, H, N, Cl, H₂O)	trit EtOH	84	9.5	8.2
l	CNO₂	c-C₃H₅	4a	C	190–192	$C_{17}H_{17}FN_4O_5 \cdot HCl \cdot H_2O$ (C, H, N)	trit EtOH	63	8.8[g]	8.2
l	CNH₂	c-C₃H₅	5a	D	205–210	$C_{17}H_{19}FN_4O_3 \cdot 1.75HCl \cdot 1.5H_2O$ (C, H, N, Cl)	trit EtOH	68	8.7[g]	7.2
l	N	c-C₃H₅	6a	B	284–286	$C_{16}H_{17}FN_4O_3$ (C, H, N)	none	98	8.6[g]	7.9
l	(isopropoxy, O...CH₃)		7a	E	283–285	$C_{17}H_{18}FN_3O_4 \cdot H_2O \cdot HCl$ (C, H, N, Cl)	trit EtOH	49	8.9[g,j]	7.6
(aminomethylpyrrolidinyl, NH₂)	CH	c-C₃H₅	1b	A	240–245	$C_{18}H_{20}FN_3O_3 \cdot 1H_2O$ (C, H, N)	recryst EtOH	35	9.2	8.2
l	CF	c-C₃H₅	2b	B	232–235	$C_{18}H_{19}F_2N_3O_3$ (C, H, N)	none	93	9.2	8.1
l	N	c-C₃H₅	6b	B	210–212	$C_{17}H_{19}FN_4O_3 \cdot 2H_2O$ (C, H, N)	none	63	9.1	8.1
	(isopropoxy, O...CH₃)		7b	E	213–216	$C_{18}H_{20}FN_3O_4 \cdot 1.5H_2O$ (C, H, N)	trit EtOH	93	9.3	8.1
(methylaminomethylpyrrolidinyl, NCH₃)	CH	c-C₃H₅	1c	A	252–256	$C_{19}H_{22}FN_3O_3 \cdot 0.33H_2O$ (C, H, N)	none	63	9.2	8.2
l	CF	c-C₈H₅	2c	B	265–267	$C_{19}H_{21}F_2N_3O_3 \cdot 0.7H_2O$ (C, H, N)	none	76	9.2	8.0
l	CNH₂	c-C₃H₅	5c	D	k	$C_{19}C_{23}FN_4O_3 \cdot H_2O \cdot 1.9HCl$ (C, H, N, Cl)	none	59	8.7[g]	7.2
l	N	c-C₃H₅	6c	B	270–274	$C_{18}H_{21}FN_4O_3 \cdot H_2O$ (C, H, N)	none	95	9.2	8.1
l	(isopropoxy, O...CH₃)		7c	E	235–237	$C_{19}H_{22}FN_3O_4 \cdot 0.5H_2O$ (C, H, N)	trit EtOH	68	9.4[j]	8.2
(ethylaminomethylpyrrolidinyl, NEt)	CH	c-C₃H₅	1d	A	>300	$C_{20}H_{24}FN_3O_3 \cdot HCl \cdot 0.7H_2O$ (C, H, N, Cl)	none	82	9.2	8.0
l	CF	c-C₈H₅	2d[i]	B	256–258	$C_{20}H_{23}F_2N_3O_3$ (C, H, N)	none	88	9.2	8.0
l	CCl	c-C₃H₅	3d	B	242–245	$C_{20}H_{23}ClFN_3O_3 \cdot 0.4H_2O$ (C, H, N)	none	86	9.5	8.2
(ethylaminomethylpyrrolidinyl, NEt)	CNO₂	c-C₃H₅	4d	C	239–241	$C_{20}H_{23}FN_4O_5 \cdot HCl$ (C, H, N)	none	72	8.8[g]	8.2
l	CNH₂	c-C₃H₅	5d	D	k	$C_{20}H_{25}FN_4O_3 \cdot 2HCl \cdot 2.5H_2O$ (C, H, N, Cl)	trit 2-PrOH	32	8.4[g]	7.3
l	N	c-C₃H₅	6d	B	268–270	$C_{19}H_{23}FN_4O_3 \cdot 0.5H_2O$ (C, H, N)	trit EtOH	78	9.2	8.3
l	(isopropoxy, O...CH₃)		7d	E	221–224	$C_{20}H_{24}FN_3O_4 \cdot 0.44H_2O$ (C, H, N)	none	82	9.4[j]	8.1
(isopropylaminomethylpyrrolidinyl, N<)	CH	c-C₃H₅	1e	A	290–292	$C_{21}H_{26}FN_3O_3 \cdot 1.5HCl \cdot 2.4H_2O$ (C, H, N, Cl)	trit 2-PrOH	67	9.2	8.1
l	CF	c-C₃H₅	2e	B	218–211	$C_{21}H_{25}F_2N_3O_3$ (C, H, N)	isoelectric precip	82	8.3[h]	7.4
l	N	c-C₃H₅	6e	B	240–243	$C_{20}H_{25}FN_4O_3 \cdot H_2O$ (C, H, N)	none	80	8.3	7.6
(dimethylaminomethylpyrrolidinyl, NMe₂)	CH	c-C₃H₅	1f	A	211–213	$C_{20}H_{24}FN_3O_3 \cdot 0.25H_2O$ (C, H, N, H₂O)	none	84	9.2	8.2
l	CF	c-C₃H₅	2f	B	248–252	$C_{20}H_{23}F_2N_3O_3 \cdot 1.4H_2O$ (C, H, N)	recryst MeOH-2-PrOH	83	9.3	8.1
(dimethylaminomethylpyrrolidinyl, NMe₂)	CCl	c-C₃H₅	3f	B	169–171	$C_{20}H_{23}ClFN_3O_3$ (C, H, N)	none	71	9.4	8.2
l	CNH₂	c-C₃H₅	5f	D	k	$C_{20}H_{25}FN_4O_3 \cdot 2.75H_2O \cdot 1.65HCl$ (C, H, N, Cl)	trit 2-PrOH	68	8.8[g]	7.3
l	N	c-C₃H₅	6f	B	250–254	$C_{19}H_{23}FN_4O_3 \cdot 1.2H_2O$ (C, H, N)	none	72	9.2	8.1
l	(isopropoxy, O...CH₃)		7f	E	281–282	$C_{20}H_{24}FN_3O_4 \cdot 1.35HCl \cdot 0.65H_2O$ (C, H, N, Cl)	recryst EtOH	68	8.9[g,j]	7.5

Table II (Continued)

R₇	X	R₁	compd	method of prep[a]	mp, °C	formula (anal.)[b]	purificn[c]	yield,[d] %	NMR Data (δ), TFA C₂H[e]	C₅H[f]
(structure, H-N piperazine)	CH	c-C₃H₅	1g	A	261–263	C₁₇H₁₈FN₃O₃·0.2H₂O (C, H, N)	none	89	9.4	8.3
l	CF	c-C₃H₅	2g	B	>270	C₁₇H₁₇F₂N₃O₃·0.3H₂O (C, H, N)	isoelectric precip	54	9.4	8.2
l	CCl	c-C₃H₅	3g	B	236–238	C₁₇H₁₇ClFN₃O₃·1.5H₂O (C, H, N)	none	97	9.6	8.4
l	CNO₂	c-C₃H₅	4g	C	>300	C₁₇H₁₇FN₄O₅·HCl (C, H, N, Cl)	trit EtOH	76	9.5	8.5
(structure, H-N piperazine)	CNH₂	c-C₃H₅	5g	D	236–239	C₁₇H₁₉FN₄O₃·2.25H₂O (C, H, N)	isoelectric precip	12	8.7[g]	7.3
l	N	c-C₃H₅	6g	B	264–266	C₁₆H₁₇FN₄O₃·0.3H₂O (C, H, N)	none	89	9.4	8.3

[a] Refers to the general method used and is described in the Experimental Section. [b] Symbols refer to those elements analyzed. Analyses were +0.4% of theoretical values. [c] Trituration (trit) refers to grinding of the solids under solvent to produce a fine powder. Isoelectric precipitation refers to dissolving the solid in aqueous base, adjusting the pH to 7.2, and filtering the solid that precipitates. [d] Yields are those obtained from the coupling step to final product isolation, including hydrolyses, reductions, and deprotections where applicable. [e] Singlet. [f] Multiplet. [g] DMSO used as NMR solvent. [h] NaOD/D₂O used as NMR solvent. [i] Prepared in a previous study, see ref 7a. [j] For the sake of continuity, the quinolone numbering system has been retained throughout the table, including the benzoxazines. [k] Very hygroscopic, no melting point taken. [l] Refer to the structure above.

results are fully supported by extensive comparative studies on two of the best known, yet simplest, examples of these systems. The 1,8-naphthyridine enoxacin (11) is comparable in vivo to the 8-hydrogen quinolone norfloxacin (10) even though 10 has somewhat better MICs than 11.

With the similarity in activity of the two simplest aromatic nuclei (1 and 6) established, it was then possible to compare the relative activity imparted to the quinolone ring system by the various side chains. This comparison produced a general activity series given in Figure 2 for the Gram-negative organisms.

For the Gram-positive organisms the order changes slightly with side chains **a** and **c** > **b,d,f**, and these in turn were much greater than for piperazine (**g**). The generally excellent activity conferred by side chain **a** and the previous success reported[23] for the 3-[(ethylamino)methyl]-pyrrolidine (**d**) vs Gram-positive organisms in vitro and in vivo[7] prompted us to use these side chains, along with the well-established piperazine, as the standards for this data set. The other side chains are included to support the trends.

Incorporating a fluorine at C-8 (compounds **2a–g**) resulted in a general increase in Gram-positive in vitro potency by a factor of 2–13 times over the hydrogen-substituted quinolones (**1a–g**) and by a factor of 3–7 times over the naphthyridines (**6a–g**). Moreover, the excellent Gram-negative activity was retained or improved. Compounds **2a–d** were 2–4 times better than their hydrogen analogues (**1a–d**) and corresponding naphthyridines (**6a–d**) against the Gram-negative strains. This increase in potency also correlated with the in vivo efficacy. The activity of the 3-aminopyrrolidine side chain (**a**) on the C-8 fluorinated nucleus (**2**) was increased by a factor of 2–3 times, both orally and subcutaneously, against *E. coli* Vogel

(22) (a) Nakamura, S.; Kurobe, N.; Kashimoto, S.; Ohue, T.; Takase, Y.; Shimizu, M. *Antimicrob. Agents Chemother.* **1983**, *24*, 54. (b) Wise, R.; Lockley, R.; Dent, J.; Webberly, M. *Antimicrob. Agents Chemother.* **1984**, *26*, 17. (c) Nakamura, S.; Nakata, K.; Katae, H.; Minami, A.; Kashimoto, S.; Yamagishi, J.; Takase, Y.; Shimizu, M. *Antmicrob. Agents Chemother.* **1983**, *23*, 742.

(23) Chin, N. X.; Neu, H. C. *Antimicrob. Agents Chemother.* **1983**, *24*, 754.

(24) Domagala, J. M.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; Nichols, J. B.; Solomon, M.; Worth, D. F. *J. Med. Chem.*, in press.

(Table II) when compared to the naphthyridine analogue **6a** of the hydrogen-substituted quinolone analogue **1a**. A similar increase in effect was seen in the Gram-positive in vivo results as well.

A comparable increase in Gram-positive in vitro activity was also observed when a chlorine substituent was placed at position 8 (compounds **3a–g**). There was even a 2–5-fold increase in the Gram-negative potency for most of the members of the series tested (**3d,f,g**) when compared to the 8-fluoro analogues, with the exception of the 3-aminopyrrolidine side chain (**3a**), which had comparable activity. However, the in vivo activity of the 8-chloro analogues was not generally as good as the 8-fluoro series but remained better than the quinolones with an 8-hydrogen. Relative to the naphthyridines, the results fluctuated depending on the side chain and strains tested. When piperazine is the C-7 side chain, addition of a fluorine fails to improve Gram-negative potency relative to the 8-hydrogen but a 4-fold improvement is seen for the Gram-positive strains. When an 8-chloro is added (**3g** vs **1g**), the Gram-negative activity improves slightly, but a major improvement is seen in the Gram-positive spectrum. This result implies that the 8-halo substituent may play an additive role in the excellent Gram-positive potency of the agents **2** and **3**.

When an amino moiety was substituted at position 8 (compounds **5a–g**), there was an overall decrease in activity vs the unsubstituted quinolone for all side chains. Against Gram-negative species, the decrease was from 3 to 12 times, and against Gram-positive species, the decrease was 2–30 times. The significant in vitro decline in activity was also seen in vivo, especially by the oral route. For example, the 8-amino analogue with the best side chain (the 3-aminopyrrolidine **5a**) had a PD₅₀ of 50 mg/kg, which was 16 times less active than the 8-unsubstituted quinolone **1a** and 25 times less active than the naphthyridine analogue **6a** against *E. coli* Vogel. Against *S. pneumoniae*, **5a** was 60 times less active than **1a** and 80 times less active than **6a**.

One might speculate that the electron donation of the nitrogen substituent at C-8 is the cause of the diminished in vitro and in vivo activity. This explanation might be overly simplistic since the oxygen of the ofloxacin nucleus **7**, even though devoid of a cyclopropyl at N-1, is more potent than the 8-amino derivative in every case, while the in vivo efficacy is still very poor. It thus appears that

Table III. Biological Testing Results from the Drug-Induced DNA Cleavage Assay and Antibacterial Screening

	minimum inhibitory concentrations (MIC),[a,d] μg/mL											gyrase-drug induced cleavage,[b,d]
	Gram-negative organisms						Gram-positive organisms					
compd	*E. cloacae* HA 2646	*E. coli* Vogel	*E. coli* H560	*K. pneumoniae* MGH-2	*P. rettgeri* H1771	*P. aeruginosa* UI-18	*S. aureus* H228	*S. aureus* UC-76	*S. faecalis* MGH-2	*S. pneumoniae* SV-1	*S. pyogenes* C203	μg/mL: *E. coli* H560
1a	0.025	0.025	0.006	0.1	0.1	0.1	0.1	0.025	0.1	0.05	0.1	0.1
2a	0.025	0.013	0.006	0.025	0.05	0.1	0.05	0.025	0.05	0.05	0.05	0.1
3a	0.025	0.013	0.006	0.025	0.025	0.05	0.05	0.013	0.05	0.05	0.05	0.5
4a	0.2	0.2	0.4	0.4	0.8	1.6	0.8	0.2	1.6	1.6	1.6	
5a	0.2	0.4	0.1	0.4	0.8	1.6	3.1	0.4	3.1	3.1	3.1	18
6a	0.05	0.013	0.006	0.025	0.1	0.05	0.2	0.013	0.2	0.2	0.2	1.0
7a	0.4	0.4	0.2	0.4	0.8	0.4	1.6	0.1	1.6	0.8	0.2	0.75
1b	0.05	0.05	0.006	0.05	0.2	0.8	0.025	0.006	0.025	0.003	0.025	0.5
2b	0.05	0.025	0.006	0.05	0.1	0.2	0.025	0.003	0.013	0.006	0.013	0.25
6b	0.1	0.1	0.025	0.1	0.4	0.2	0.2	0.006	0.025	0.1	0.025	0.50
7b	0.2	0.2	0.05	0.4	0.8	1.6	0.2	0.05	0.1	0.025	0.025	0.5
1c	0.2	0.1	0.1	0.2	0.4	0.8	0.2	0.025	0.1	0.05	0.05	0.5
2c	0.025	0.05	0.006	0.05	0.2	0.2	0.025	0.013	0.013	0.006	0.006	0.25
5c	3.1	0.8	1.6	3.1	6.3	6.3	1.6	0.2	1.6	1.6	0.4	5.0
6c	0.2	0.1	0.05	0.2	0.4	0.8	0.2	0.025	0.2	0.025	0.05	1
7c	0.4	0.2	0.2	0.4	3.1	1.6	0.4	0.025	0.1	0.1	0.05	1
1d	0.4	0.2	0.05	0.2	0.8	1.6	0.4	0.013	0.2	0.2	0.05	1.0
2d	0.1	0.05	0.025	0.1	0.2	0.4	0.025	0.006	0.025	0.025	0.025	0.25
3d	0.05	0.05	0.025	0.1	0.2	0.8	0.013	0.003	0.013	0.003	0.006	0.1
4d	0.4	0.4	0.4	0.8	1.6	6.3	0.4	0.1	0.4	0.1	0.2	
5d	0.4	0.4	0.8	0.8	1.6	3.1	0.8	0.05	0.2	0.4	0.2	2.5
6d	0.2	0.1	0.05	0.1	0.8	0.8	0.1	0.05	0.1	0.1	0.1	0.75
7d	0.2	0.1	0.05	0.4	0.8	0.8	0.2	0.025	0.1	0.05	0.05	0.5
1e	0.1	0.1	0.05	0.2	0.8	3.1	0.2	0.025	0.1	0.025	0.05	
2e	0.2	0.1	0.05	0.2	0.4	1.6	0.05	0.013	0.025	0.05	0.05	2.8
6e	0.2	0.2	0.1	0.4	1.6	0.8	0.2	0.1	0.2	0.2	0.2	2.5
7e	0.4	0.2	0.4	0.8	3.1	0.2	0.05	0.4	0.05	0.05	0.2	
1f	0.1	0.1	0.1	0.2	0.4	1.6	0.1	0.1	0.2	0.1	0.2	0.75
2f	0.2	0.2	0.025	0.2	0.8	0.8	0.025	0.025	0.025	0.05	0.05	0.1
3f	0.2	0.1	0.025	0.1	0.4	0.8	0.013	0.006	0.05	0.006	0.025	1.0
5f	0.2	0.4	0.4	0.8	0.8	3.1	0.2	0.1	0.4	0.4	0.4	5
6f	0.1	0.05	0.05	0.2	0.8	0.4	0.1	0.05	0.2	0.05	0.1	0.75
7f	0.4	0.2	0.2	0.4	0.8	3.1	0.2	0.05	0.4	0.05	0.05	1.0
1g	0.05	0.05	0.025	0.1	0.1	0.4	3.1	0.2	0.8	1.6	0.8	0.5
2g	0.05	0.1	0.025	0.1	0.1	0.2	0.4	0.1	0.4	0.8	0.8	0.5
3g	0.025	0.025	0.025	0.05	0.1	0.4	0.1	0.05	0.4	0.1	0.2	0.5
4g	0.2	0.2	0.4	0.8	3.1	1.6	1.6	0.4	6.3	12.5	12.5	
5g	0.4	0.4	0.2	0.8	0.4	0.8	6.3	0.8	12.5	12.5	6.3	2.5
6g	0.1	0.05	0.05	0.1	0.2	0.2	1.6	0.4	1.6	1.6	1.6	1.0
7g[c]	0.1	0.1	0.1	0.1	0.2	0.4	0.4	0.1	0.8	0.8	0.8	2.0

[a] Standard microdilution techniques; see ref 6. [b] Minimum concentration of drug needed to produce linear DNA at an intensity relative to oxolinic acid at 10 μg/mL; see ref 6. [c] Ofloxacin. [d] All values for a–g are accurate to ±50% and have been obtained from duplicate or triplicate experiments; see ref 6.

electron donation is not the sole reason for reduced in vitro activity, and the nature of the amine itself at C-8 may play a role.

Some of the compounds with the 8-nitro substituent (4a,d,g), which were intermediates in the preparation of the 8-amino series, were also tested. These compounds, even with the electron-withdrawing nitro group, showed in vitro activity similar to the electron-donating 8-amino series. When compared to the 8-fluoro and 8-chloro series, which both have electron-withdrawing capabilities, the activity of the 8-nitro series is 10–20 times less, indicating that the effect once again is not totally electronic in nature.

A series of benzoxazine tricyclic compounds (ofloxacin analogues, compounds 7a–f) was also tested. Against the Gram-negative strains, as a series, these tricycles were 3–20 times less active than either the 8-hydrogen quinolones (1) or the naphthyridines (6). The best side chain in this series against Gram-positive species was the 3-[(ethylamino)-methyl]pyrrolidine (d), which is the side chain of CI-934 and made 7d equipotent to 1d and 6d. Against the Gram-positive strains, the tricycles were as active as the

8-hydrogen quinolones (1a–g) and the naphthyridines (6a–g). Once again the 3-[(ethylamino)methyl]pyrrolidine side chain was superior to all others, making 7d slightly more active than 1d and 3.5 times more active than 6d. The in vivo activity was greatly diminished when compared where possible to either 1 or 6.

Summary

When one takes into consideration both the in vivo (PD$_{50}$) data and the in vitro activity summarized by the geometric means, the best compound of the group is the 8-fluoro derivative with the 3-aminopyrrolidine side chain, 2a. This is closely followed by 3a, the 8-chloro derivative with the same side chain, which has only slightly lower in vivo activity. This trend continued with the 8-chloro derivatives 3 showing somewhat better in vitro potency than the 8-fluoro analogues (2). However, the 8-fluoro compounds almost always showed slightly better in vivo efficacy.

The next best series of compounds were the 1,8-naphthyridines (6a–g). Their in vitro activity was excel-

Table IV. Biological Testing Results from Mouse Protection Assay

			\tsubstituent R_7						
compd	X	R_1	a	b	c	d	e	f	g
			In Vivo E. coli Vogel (po/sc)						
1	CH	c-C_3H_5	3/0.5	>100/2	35/2	35/2	25/4	4/2	1/0.3
2	CF	c-C_3H_5	1/0.2	6/1	2/0.3	4/1	6/1	2/1	0.5/0.3
3	CCl	c-C_3H_5	3/0.6					4/2	0.8/0.4
4	CNO_2	c-C_3H_5	30/9						10/3
5	CNH_2	c-C_3H_5	50/6					9/4	58/2
6	N	c-C_3H_5	2/0.6	17/1	3/1	7/1	8/2	2/1	0.7/0.4
7			25/2	>100/12		>100/11			2/1
			In Vivo S. aureus, S. pneumoniae (po/sc)						
1	CH	c-C_3H_5	49.5, 43/4					47/26, 18/9	25/5, >100/19
2	CF	c-C_3H_5	7/3, 15/6	78/5, 10/1	22/12, 2/1	59/40, 3/2	42/12; 7/2	45/20, 5/5	7/3, 59/29
3	CCl	c-C_3H_5	13/5, 10/4					61/38, 2/2	
4	CNO_2	c-C_3H_5							
5	CNH_2	c-C_3H_5						100/81, –	
6	N	c-C_3H_5	7/3, 58/33	55/7, 100/6	3/1, 27/11	62/15, 16/6	35/16, –	31/27, 7/7	14/6, –
7									12/4.4, 5.2/11

Table V. Calculated Geometric Means of MICs[a]

			\tsubstituent R_7						
compd	X	R_1	a	b	c	d	e	f	g
			Geometric Means, Gram-Negative (Excluding *P. aeruginosa*)						
1	CH	c-C_3H_5	0.033	0.043	0.17	0.23	0.15	0.15	0.057
2	CF	c-C_3H_5	0.019	0.033	0.038	0.076	0.15	0.17	0.066
3	CCl	c-C_3H_5	0.017			0.066		0.12	0.038
4	CNO_2	c-C_3H_5	0.35			0.6			
5	CNH_2	c-C_3H_5	0.30		2.4	0.7		0.46	0.40
6	N	c-C_3H_5	0.025	0.10	0.15	0.15	0.30	0.13	0.088
7			0.40	0.23	0.46	0.20	0.60	0.35	0.119 (ofloxacin)
			Geometric Means, Gram-Positive						
1	CH	c-C_3H_5	0.066	0.12	0.066	0.10	0.057	0.13	0.91
2	CF	c-C_3H_5	0.044	0.01	0.011	0.030	0.033	0.033	0.40
3	CCl	c-C_3H_5	0.038			0.006		0.014	0.13
4	CNO_2	c-C_3H_5	0.92			0.20			
5	CNH_2	c-C_3H_5	2.1		0.80	0.20		0.26	5.5
6	N	c-C_3H_5	0.12	0.038	0.066	0.23	0.17	0.087	1.2
7			0.53	0.057	0.087	0.066	0.10	0.10	0.4 (ofloxacin)

[a] The geometric means were calculated by multiplying the MICs together and taking the fifth root.

lent, and only their diminished in vivo activity prevented them from being among the best compounds.

The 8-hydrogen series (**1a–g**) was next, having slightly better activity both in vivo and in vitro than the benzoxazine tricycles (**7a–g**). The least active compounds were the 8-aminoquinolones (**5a–g**), which were of equipotency with the 8-nitro series (**4a–g**).

Experimental Section

SX-20 instrument. Proton magnetic resonance (NMR) were recorded on either a Varian XL-200 or an IBM 100 WP100SY spectrometer. Shifts are reported in δ units relative to internal tetramethylsilane. Elemental analyses were performed on a Perkin-Elmer 240 elemental analyzer. All compounds prepared had analytical results ±0.4% of theoretical values. All organic solutions were dried over magnesium sulfate, and all concentrations were performed in vacuo at 10–30 mmHg.

Preparation of 2,4,5-Trifluorobenzoic Acid (17). To 32.2 g (153 mmol) of 1-bromo-2,4,5-trifluorobenzene in 80 mL of DMF was added 17.1 g (190 mmol) of cuprous cyanide. The mixture was refluxed for 17 h, cooled to room temperature, and poured into dilute aqueous NH_4OH. The solution was extracted with ether, and the organic layer was dried and concentrated to give 25.7 g of tan oil. The oil was dissolved in 200 mL of 50% H_2SO_4 and refluxed for 2 h. The solution was diluted with 300 mL of water, cooled to room temperature, and extracted with ether. The extracts were dried and concentrated to give a residue, which was triturated with hexane and filtered to give 21.6 g (80% overall) of 17, mp 97–99 °C: IR 1692, 1464 cm⁻¹; NMR (DCCl₃) δ 10.45 (s, 1 H, OH), 8.1 (m, 1 H), 7.1 (m, 1 H). Anal. Calcd for $C_7H_3F_3O_2$: C, 47.74; H, 1.72. Found: C, 47.80; H, 1.86.

Preparation of 7-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-8-nitro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (4). To 10.3 g (27.0 mmol) of 22[14] in 50 mL of *tert*-butyl alcohol was added 1.50 g (26.3 mmol) of cyclopropylamine dropwise with stirring. The reaction mixture was stirred at 45 °C for 30 min and then cooled to room temperature. The precipitate was filtered and washed with ether to give 4.02 g (38%) of an orange solid. This material was suspended in 25 mL of *tert*-butyl alcohol, treated with 1.26 g (11.2 mmol) of potassium *tert*-butoxide, and stirred for 8 h at 60 °C. The solution was concentrated, and the residue was partitioned between 100 mL of ice water containing 20 mL of concentrated HCl and 75 mL of CH_2Cl_2. The organic layer was separated, washed with water, dried, and concentrated. The residue obtained was triturated with EtOAc/ether, 2:3, diluted with petroleum ether, and filtered to give 2.40 g (65%) of 4, mp 174–176 °C: IR 1735, 1617 cm⁻¹; NMR (DCCl₃) δ 8.6 (s, 1 H, C₂H), 8.4 (d, J = 8 Hz, 1 H, C₅H), 4.4 (q, J = 7 Hz, 2 H, OCH₂CH₃), 3.6 (m, 1 H, cyclopropyl), 1.3 (t, J = 7 Hz, 3 H, OCH₂CH₃), 1.15 (m, 4 H, cyclopropyl). Anal. Calcd for $C_{15}H_{12}ClFN_2O_5$: C, 50.79; H, 3.41; N, 7.90. Found: C, 50.73; H, 3.25; N, 7.78.

General Method A. Preparation of 1-Cyclopropyl-7-[3-[(dimethylamino)methyl]-1-pyrrolidinyl]-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (1f). To 1.00 g (3.77 mmol) of 1 in 13 mL of pyridine was added 0.52 g (4.2 mmol) of *N,N*-dimethyl-3-pyrrolidinemethanamine.[17] The mixture was refluxed for 18 h and then cooled to room temperature. The solid that precipitated was filtered and washed with pyridine and ether to give 1.21 g (84%) of 1f, mp 211–213 °C: IR 1731, 1633, 1472 cm⁻¹; NMR (TFA) δ 9.2 (s, 1 H, C₂H), 8.2 (d, J = 14 Hz, 1 H, C₅H), 7.4 (d, J = 5 Hz, 1 H, C₈H), 4.4 (m, 1 H, cyclopropyl), 3.9 (m, 4 H, pyrrolidine), 3.6 (m, 2 H, CH₂N(CH₃)₂), 3.1 (m, 7 H, N(CH₃)₂ plus pyrrolidine), 2.65 (m, 1 H, pyrrolidine), 2.1 (m, 1 H, pyrrolidine), 1.6 (m, 4 H, cyclopropyl). Anal. Calcd for $C_{20}H_{24}FN_3O \cdot 0.25H_2O$: C, 63.56; H, 6.53; N, 1.11; H_2O, 1.19. C, 63.56; H, 6.53; N, 11.11; H_2O, 1.19. Found: C, 63.28; H, 6.46; N, 11.11; H_2O, 0.97.

Purification of 1d was effected by suspending the crude product in water, acidifying the mixture with 1 N HCl, filtering, and concentrating the filtrate to give the desired compound as the hydrochloride.

Compound 1b did not precipitate from solution. The solvent was therefore evaporated, and the residue was crystallized from EtOH.

7-[3-[(*tert*-Butoxycarbonyl)amino]-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid was prepared from 1, 3-[(*tert*-butoxycarbonyl)amino]pyrrolidine, and pyridine as described above. A suspension of 3.80 g (8.81 mmol) of the product obtained in 20 mL of acetic acid and 20 mL of 6.0 M HCl was refluxed for 1 h. The solution was concentrated, and the residue was triturated with 2-propanol and filtered to give 3.38 g (72% from 1) of 1a.

To purify 1e, the crude product was suspended in water, made acidic (pH 2) with 6 M HCl, filtered, and lyophilized. This material was dissolved in concentrated HCl and filtered; the

filtrate was concentrated, triturated with 2-propanol, and filtered to give the desired product.

General Method B. Preparation of 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[3-[(methylamino)methyl]-1-pyrrolidinyl]-4-oxo-1,8-naphthyridine-3-carboxylic Acid (6c). To 0.84 g (3.0 mmol) of 6 in 15 mL of CH_3CN were added 0.38 g (3.3 mmol) of *N*-methyl-3-pyrrolidinemethanamine[7a,17] and 0.42 mL of triethylamine. The mixture was refluxed for 3 h and stirred at room temperature for 18 h. The solids were filtered and washed with CH_3CN and ether to give 1.1 g (85%) of 6c, mp 270–274 °C: IR 1719, 1632, 1461 cm⁻¹; NMR (TFA) δ 9.2 (s, 1 H, C₂H), 8.1 (d, J = 12 Hz, 1 H, C₅H), 4.0 (m, 5 H, pyrrolidine plus cyclopropyl), 3.5 (m, 2 H, CH₂NCH₃), 3.1 (m, 4 H, NHCH₃ plus pyrrolidine), 2.6 (m, 1 H, pyrrolidine), 2.1 (m, 1 H, pyrrolidine), 1.6 (m, 2 H, cyclopropyl), 1.3 (m, 2 H, cyclopropyl). Anal. Calcd for $C_{18}H_{21}FN_4O_3 \cdot H_2O$: C, 57.14; H, 6.08; N, 14.81. Found: C, 57.11; H, 5.79; N, 15.10.

Compounds 2b–d, 6a, 6b, and 6e were prepared in an identical fashion except that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used as the base instead of triethylamine. Excess side chain was used as the base in the synthesis of compounds 2e, 3g, 6d, and 6g.

Compound 2g did not precipitate from solution. Therefore, the solution was concentrated, and the residue was dissolved in aqueous NH_4OH. The solution was filtered, and the filtrate was neutralized (pH 7.0) with 6 M HCl. The solids that precipitated were filtered and washed with water and ether to give the desired compound.

7-[3-[(*tert*-Butoxycarbonyl)amino]-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid was prepared from 2, 3-[(*tert*-butoxycarbonyl)amino]pyrrolidine, and triethylamine as described above. A suspension of 7.24 g (16.1 mmol) of this product in 35 mL of 6 M HCl and 75 mL of acetic acid was heated at 60 °C for 4 h and then stirred overnight at room temperature. The solution was filtered, and the filtrate was concentrated. The residue was triturated with EtOH/ether, 1:1; the solids were filtered and washed with ether to give 6.38 g (93% from 2) of 2a.

Compound 3a was prepared via the same sequence of reactions. Compound 6a was also prepared in this way, except that the *tert*-butoxycarbonyl protecting group was removed with trifluoroacetic acid instead of 6 M HCl/acetic acid; the residue thus obtained was dissolved in water at pH 10, and the solid was precipitated at pH 6.6.

General Method C. Preparation of 1-Cyclopropyl-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6-fluoro-1,4-dihydro-8-nitro-4-oxo-3-quinolinecarboxylic Acid (4d). To 1.40 g (3.95 mmol) of 4 in 25 mL of CH_3CN was added 2.05 g (16.0 mmol) of *N*-ethyl-3-pyrrolidinemethanamine.[7a,17] The mixture was refluxed for 2 h, cooled to room temperature, and concentrated. The residue was dissolved in 50 mL of 1.0 M HCl and 50 mL of EtOH, refluxed for 2 h, and concentrated in vacuo. The solids were triturated with EtOH, filtered, and washed with EtOH and ether to give 1.31 g (72% from 4) of 4d, mp 239–241 °C: IR 1731, 1626, 1456 cm⁻¹; NMR (DMSO-d₆) δ 14.45 (s, 1 H, OH), 9.0 (s, 2 H, N⁺H₂C₂H₅), 8.8 (s, 1 H, C₂H), 8.15 (d, J = 13 Hz, 1 H, C₅H), 3.75 (m, 1 H, cyclopropyl), 3.4 (m, 4 H, pyrrolidine), 3.0 (m, 4 H, CH₂NCH₂CH₃), 2.7 (m, 1 H, pyrrolidine), 2.2 (m, 1 H, pyrrolidine), 1.8 (m, 1 H, pyrrolidine), 1.2 (t, 3 H, NCH₂CH₃), 1.05 (m, 4 H, cyclopropyl). Anal. Calcd for $C_{20}H_{23}FN_4O_5 \cdot HCl$: C, 52.81; H, 5.32; N, 12.32. Found: C, 52.98; H, 5.29; N, 12.05.

7-[3-[(*tert*-Butoxycarbonyl)amino]-1-pyrrolidinyl]-6-fluoro-1,4-dihydro-8-nito-4-oxo-3-quinolinecarboxylic acid, ethyl ester, was prepared from 4, 3-[(*tert*-butoxycarbonyl)amino]pyrrolidine, and triethylamine as described above. The residue obtained (2.0 g, 4.0 mmol) was heated in 50 mL of 1.0 M HCl and 50 mL of EtOH to hydrolyze the ester and remove the amine protecting group. The product was triturated with EtOH, filtered, and washed with ether as before to give 1.2 g (63% from 4) of 4a.

General Method D. Preparation of 8-Amino-1-cyclopropyl-7-[3-[(dimethylamino)methyl]-1-pyrrolidinyl]-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (5f). To 3.55 g (10.0 mmol) of 4 in 50 mL of CH_3CN were added 1.92 g (15.0 mmol) of *N,N*-dimethyl-3-pyrrolidinemethanamine and 2.8 mL of triethylamine. The mixture was refluxed for 2 h, cooled to room temperature, and concentrated. The residue was par-

titioned between CH_2Cl_2 and water. The organic layer was separated, dried, and concentrated to give 4.52 g of crude product. A solution of this material in 100 mL of EtOH was hydrogenated over 0.5 g of Raney nickel at 51 psig and 26 °C for 18 h. The mixture was filtered, and the filtrate was concentrated to a yellow solid. This solid was suspended in 50 mL of EtOH and 50 mL of 6 M HCl, refluxed for 3 h, and cooled to room temperature. The solution was concentrated, and the residue was triturated with 2-propanol and filtered to give 3.43 g (68% from 4) of **5f** as a hygroscopic solid: IR 1735, 1630 cm⁻¹; NMR (DMSO-d_6) δ 8.8 (s, 1 H, C_2H), 7.3 (d, J = 12 Hz, 1 H, C_5H), 6.1 (s, 2 H, C_8NH_2), 4.6 (m, 1 H, cyclopropyl), 3.25 (m, 6 H, CH_2NMe_2 and pyrrolidine), 2.8 (s, 6 H, $N(CH_3)_2$), 2.25 (m, 2 H, pyrrolidine), 1.9 (m, 1 H, pyrrolidine), 1.2 (m, 4 H, cyclopropyl). Anal. Calcd for $C_{20}H_{25}FN_4O_3 \cdot 2.75H_2O \cdot 1.65HCl$: C, 48.21; H, 6.50; N, 11.25; Cl, 11.75. Found: C, 47.98; H, 6.59; N, 11.09; Cl, 11.73.

7-[3-[(tert-Butoxycarbonyl)amino]-1-pyrrolidinyl]-6-fluoro-8-nitro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, ethyl ester (4.4 g, 5.7 mmol), was prepared from 4, 3-[(tert-butoxycarbonyl)amino]pyrrolidine, and triethylamine as described above. The nitro group was reduced as before with Raney nickel in DMF at 55 psig and 25 °C. The final hydrolysis in 6 M HCl and EtOH removed the protecting group from the amine and hydrolyzed the ester to the acid to give, upon trituration and filtration, 2.4 g (68% from 4) of **5a**.

General Method E. Preparation of 10-[3-(Aminomethyl)-1-pyrrolidinyl]-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic Acid (7b). To 0.75 g (2.7 mmol) of 7 in 40 mL of CH_3CN was added 0.80 g (8.0 mmol) of 3-pyrrolidinemethanamine, and the mixture was refluxed overnight. The solution was concentrated, and the residue was triturated with 40 mL of 1:1 EtOH/ether. The solids were filtered and washed with ether to give 0.95 g (93%) of **7b**, mp 213–216 °C: IR 1730 cm⁻¹; NMR (TFA) δ 9.3 (s, 1 H, C_5H), 8.15 (d, J = 12 Hz, 1 H, C_8H), 7.2 (s, 3 H, NH_3^+), 5.2 (m, 1 H, C_8H), 4.8 (m, 2 H, C_2H), 4.3 (m, 4 H, CH_2NH_2 and pyrrolidine), 3.5 (m, 3 H, pyrrolidine), 2.75 (m, 1 H, pyrrolidine), 2.5 (m, 1 H, pyrrolidine), 2.2 (m, 1 H, pyrrolidine), 1.85 (d, 3 H, CH_3). Anal. Calcd for $C_{18}H_{20}FN_3O_4 \cdot 1.5H_2O$: C, 55.66; H, 5.95; N, 10.82. Found: C, 55.41; H, 5.66; N, 10.90.

Compound **7c** was prepared as above, and the residue was dissolved in water at pH 1. Concentration of the solution gave a solid, which was recrystallized from EtOH to give the desired product as the hydrochloride.

10-[3-[(tert-Butoxycarbonyl)amino]-1-pyrrolidinyl]-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid (1.3 g, 2.9 mmol) was prepared from 7, 3-[(tert-butoxycarbonyl)amino]pyrrolidine, DBU, and DMF at 60 °C as outlined above. The solution was concentrated, and the residue was triturated with water to give a crystalline solid. This material was then filtered, suspended in 5 mL of 6 M HCl and 10 mL of acetic acid, and stirred at room temperature for 18 h. Concentration followed by trituration with EtOH/ether, 1:1, and filtration gave 0.80 g (49% from 7) of **7a**.

1-Substituted 7-[3-[(Ethylamino)methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids. New Quantitative Structure–Activity Relationships at N₁ for the Quinolone Antibacterials[1]

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A series of 18 1-substituted 7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids (N₁ analogues of CI-934) were synthesized and evaluated for antibacterial activity and DNA-gyrase inhibition. Correlations between the inhibition of DNA gyrase and antibacterial potency were established. A quantitative structure–activity relationship (QSAR) was derived by using the antibacterial potency for each of 11 strains of bacteria and the Gram-negative mean. The equations indicated that antibacterial potency was strongly dependent on STERIMOL length and width and the level of unsaturation of the N₁ substituent. Some strains also showed a dependence on the presence of heteroatoms (O, N, S) in the N₁ group. No significant correlations between gyrase inhibition and combinations of these parameters were found. These QSAR results are discussed in conjunction with the conformational analyses from molecular modeling studies. The substituent that most enhanced the activity of the quinolone in all regards was the cyclopropyl group. This analogue, 1-cyclopropyl-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (PD 117558), demonstrated outstanding broad spectrum activity both in vitro and in vivo when compared to relevant standards.

The quinolone antiinfectives, represented generically by 1, have aroused much interest because of their potency and oral efficacy.[2] While many excellent agents have been described or are under development[3] (Figure 1), only a few