calculated using the MEDCHEM[29] software suite and the substituent constants F and R were obtained from the Hansch and Leo listing.[30]

The calculated properties were collated along with the measured melting point data with PROFILES and a data table created for the data management package RS/1.[31] Data analysis and graphical display were carried out with an in-house package, PULSAR, which is a unified driver system for RS/1; in-house regression routines; and the pattern recognition suite, ARTHUR.[10] This procedure is shown in Figure 1. Initial data reduction was carried out with an RS/1 procedure, CORCHOP,[32] which sorts parameters in terms of the number and magnitude of their correlations with other parameters in the set. This routine suggests variables for deletion from the set; the objective is to produce a smaller data set with interparameter correlations below a set limit (selected by the user) but which retains as much as possible of the "information content" of the set.

(29) CLOGP, Medchem Software Version 3.52; Pomona College Medicinal Chemistry Project: Claremont, California, 1987.
(30) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley-Interscience: New York, 1979.
(31) RS/1, BBN Software Products, U.K. Ltd., Staines, Middlesex, U.K.
(32) Livingstone, D. J.; Rahr, E. *Quant. Struct.-Act. Relat.* In press.

Acknowledgment. We thank G. M. Lees, S. E. McCaig, R. Rankin, and M. J. Rees for technical support and Drs. W. E. Gutteridge, D. C. Jenkins, and J. F. Batchelor for helpful discussions. This study was supported by the World Health Organization Onchocerciasis Chemotherapy Project of the Onchocerciasis Control Program in the Volta River Basin, OCT contract no. 82005.

Supplementary Material Available: Analyses for compounds 1-31 and for intermediates, parameter values (53) for all 31 compounds, and a complete interparameter correlation matrix are included (16 pages). Ordering information is given on any current masthead page.

Synthesis and Structure-Activity Relationships of New 7-[3-(Fluoromethyl)piperazinyl]- and -(Fluorohomopiperazinyl)quinolone Antibacterials

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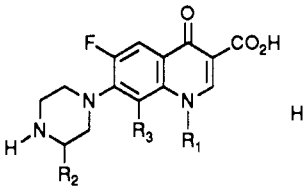
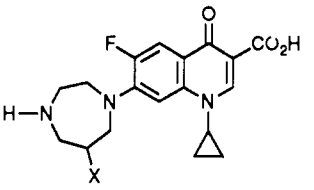
Some novel 6-fluoro-7-substituted-1,4-dihydro-4-oxoquinoline-3-carboxylic acids have been prepared. At the N-1 position "standard" substitution was employed with the ethyl, cyclopropyl, and *p*-fluorophenyl groups being used. At C-7 the introduction of some novel piperazines was made. Most notably, 2-(fluoromethyl)piperazine (**10**) and hexahydro-6-fluoro-1*H*-1,4-diazepine (**16**, fluorohomopiperazine) at the quinolone C-7 position produced products with similar in vitro antibacterial activity as the ciprofloxacin reference. The in vivo efficacy of 1-cyclopropyl-6-fluoro-7-[3-(fluoromethyl)piperazinyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**20**) was excellent with better oral absorption than ciprofloxacin (**2**).

The emergence of norfloxacin[1] (**1**) as a broad-spectrum, orally active quinolone antibacterial represented a new generation of increased-potency drug.[2] Subsequent members in this structurally similar class employed the C-7 piperazine moiety and some N-1 alkyl groups. Ciprofloxacin (**2**[3]) is an extremely potent N-1 varient. Both compounds are marketed in the U.S., Europe, and Japan.

Among the host of quinolone N-1 substituents synthesized since norfloxacin, the ethyl, cyclopropyl, and fluorophenyl moieties are certainly among the best in terms of antibacterial efficacy. At C-7, the piperazinyl and amino-substituted pyrrolidinyl groups have been utilized with optimal results. As this field evolves, active compounds in the quinolone-3-carboxylic acid class are reported with novel C-5,[4] C-8,[5] and C-2[6] substitution.





1: R_1 = Et; R_2 = H; R_3 = H
2: R_1 = cyclopropyl; R_2 = H; R_3 = H
3: R_1 = Et; R_2 = CH_3; R_3 = F
4: R_1 = 2,4-difluorophenyl; R_2 = CH_3; R_3 = H
5: R_1 = Et, cyclopropyl, or 4-fluorophenyl; R_2 = CH_2OH, CH_2F, or CHF_2; R_3 = H or F

6: X = H, OH, or F

We have been active in preparing quinolone C-7 structural analogues.[7] Particularly, we have invested consid-

(1) Synthesis: Koga, H.; Itoh, A.; Murayama, S.; Suzue, S.; Irkura, T. *J. Med. Chem.* **1980**, *23*, 1358. Review of antibacterial, pharmacokinetic, and therapeutic properties: Holmes, B.; Brogden, R.; Richards, D. *Drugs* **1985**, *30*, 482.
(2) Nalidixic Acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid) was the first member of this totally synthetic antibacterial class. For a comprehensive review of this and all other earlier structurally similar analogues, see: Albrecht, R. *Prog. Drug Res.* **1977**, *21*, 9.
(3) Wise, R.; Andrews, J. M.; Edwards, L. *J. Antimicrob. Agents Chemother.* **1983**, *23*, 559. Felmingham, D.; O'Hare, M. D.; Robbins, R. A.; Williams, A. H.; Cremer, A. W.; Ridgeway, G. L.; Gruneberg, R. N. *Drugs Exp. Clin. Res.* **1985**, *11*, 316.
(4) Domagala, J. M.; Hagen, S. E.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; Sanchez, J. P.; Trehan, A. K. *J. Med. Chem.* **1988**, *31*, 506. Moran, D. B.; Ziegler, C. B., Jr.; Dunne, T. S.; Kuck, N. A.; Lin, Y.-i *J. Med. Chem.* **1989**, *32*, 1313.
(5) Sanchez, J. P.; Domagala, J. M.; Hagen, S. E.; Heifetz, C. L.; Hutt, M. P.; Nichols, J. B.; Trehan, A. K. *J. Med. Chem.* **1988**, *31*, 983. Veda, H.; Miyamoto, H. (Otsuka Pharm. Co., Ltd.) *Drugs Future* **1988**, *10*, 412.
(6) Chu, D. T. W.; Fernandes, P. B.; Pernet, A. G. *J. Med. Chem.* **1986**, *29*, 1531. Chu, D. T. W.; Fernandes, A. K.; Claiborne, L. S.; Pernet, A. G. 27th ICAAC, **1987**, *250*.

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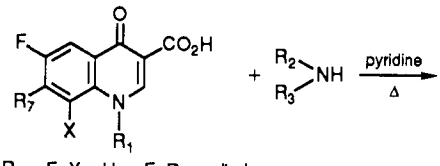
erable effort into those C-7 groups bearing the 3-substituted piperazine.[8] Outstanding examples from other groups such as lomefloxacin (3[9]) and tomefloxacin (4[10]), each possessing the 3-methylpiperazine substituent, are currently in clinical trials.

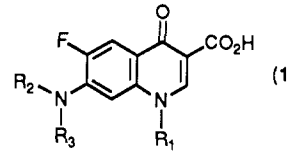
In vivo comparison studies have demonstrated that **3** is more effective than norfloxacin (**1**) against a variety of systemic infections.[11] A logical extention of these findings, we thought, was to study the structure–activity relationship (SAR) of other 7-(3-substituted-piperazinyl)quinolone analogues. In this paper we describe our work on the synthesis and biological activity of some of these 1,4-dihydro-4-oxoquinoline-3-carboxylic acids **5** and their isomeric analogues **6**. It was reasoned that those analogues **5** with the 3-(fluoromethyl)piperazinyl groups should enhance those pharmacokinetic parameters noted for **3** after oral administration to mice.[12]

Chemistry

All the C-7 substituted quinolones reported in this study were prepared in a straightforward fashion. Regiospecific nucleophilic aromatic substitution of the corresponding 1-substituted 6,7-difluoroquinolone **7** with the appropriate secondary amine (eq 1) proceeded smoothly at temperatures between 80 and 90 °C.

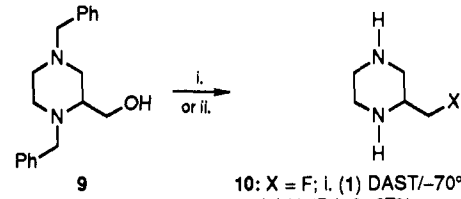


7: R_7 = F, X = H or F, R_1 = alkyl
8: R_7 = Cl, X = H, R_1 = alkyl



(1)

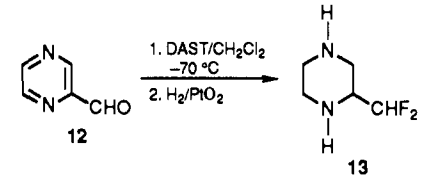
The (fluoromethyl)piperazines used in this study were obtained from two sources. Low-temperature treatment of 1,4-dibenzyl-2-(hydroxymethyl)piperazine (**9**[13]) with (diethylamido)sulfur trifluoride (DAST) gave the fluoro substitution product, which was reduced under standard hydrogenation conditions (eq 2) to give 2-(fluoromethyl)piperazine (**10**). Alcohol **9** also was reduced to 2-(hydroxymethyl)piperazine (**11**), which also served as a quinolone C-7 substituent. The 2-(difluoromethyl)-piperazine (**13**) was best prepared from the reaction of pyrazinecarboxaldehyde (**12**[14]) and DAST followed by



(2)

9

10: X = F; i. (1) DAST/−70°/CH_2Cl_2, 70%, (2) H_2/Pd–C, 67%
11: X = OH; ii. H_2/Pd–C, 94%

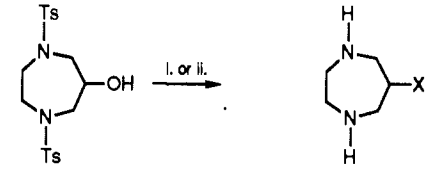


(3)

12 **13**

catalytic reduction over platinum oxide in low yield (eq 3). All attempts to prepare 2-(trifluoromethyl)piperazine starting from pyrazinecarboxylic acid were fruitless in our hands.[15]

The isomeric 6-hydroxy- and 6-fluorohexahydro-1*H*-1,4-diazepines (**15** and **16**) were synthesized from **14** (eq 4).



(4)

14
Ts = tolylsulfonyl

15: X = OH; i. NaOH, 95%
16: X = F; ii. (1) DAST/CH_2Cl_2, 73%, (2) NaOH, 93%

Saponification of **14** gave **15** as reported.[16] Alternatively, sequencial treatment of **14** with DAST followed by base hydrolysis gave **16** in 68% overall yield.

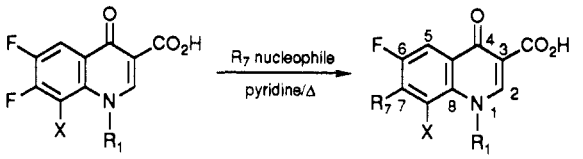
Table I lists those 7-substituted quinolones prepared in this study.

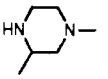
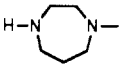
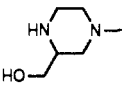
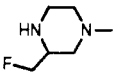
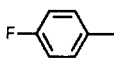
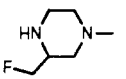
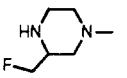
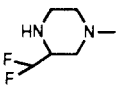
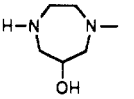
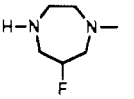
Results and Discussions

Table II summarizes the in vitro antibacterial data of the 7-substituted 4-quinolone-3-carboxylic acids prepared against five Gram-negative organisms (*E. coli* ATCC 25922, *E. coli* #311, *Enterobacter cloacae* VGH-84-39, *Morganella morganii* CMC-84-39, and *Pseudomonas aeruginosa* 12-4-4) and four Gram-positive organisms (*Staphylococcus aureus* Smith (mp), *Staphylococcus aureus* ATCC 29213, *Streptococcus faecalis* VGH-84, and *Streptococcus faecalis* UCI-85). Testing data for ciprofloxacin (**2**) is included for comparison.[17]

(7) Ziegler, C. B., Jr.; Bitha, P.; Lin, Y.-i *J. Heterocycl. Chem.* **1988**, *25*, 719 Ziegler, C. B., Jr.; Harris, S. M.; Kuck, N. A.; Lin, Y.-i *J. Heterocycl. Chem.* In Press.
(8) 7-(Substituted-piperazinyl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids (American Cyanamid Co.): European Patent Appl. 230,053; *Drugs Future* **1988**, *10*, 60.
(9) Hokuriku Pharm. Co., Ltd. (Japan) *Drugs Future* **1986**, *11*, 578. Hirose, T.; Inoue, M.; Mitsuhashi, S. *Rev. Infect. Dis.* **1988**, *10*, S44. Synthesis: Kato, H.; Ogawa, N.; Koshinaka, E.; Yagi, N. (Hokuriku Pharm. Co.) EP 140,116.
(10) Chu, D. T. W.; Fernandes, P. B.; Claiborne, A. K.; Gracey, E. H.; Pernet, A. G. *J. Med. Chem.* **1986**, *29*, 2363. Hardy, D. *J. Antimicrob. Agents Chemother.* **1987**, *31*, 1768.
(11) Hirose, T.; Okezaki, E.; Kato, H.; Ito, Y.; Inoue, M.; Mitsuhaski, S. *Antimicrob. Agents Chemother.* **1987**, *31*, 854. See also ref 9.
(12) Kato, H.; Nagata, O.; Okezaki, E.; Yamada, T.; Ito, Y.; Terasaki, T.; Tsuji, A. 25th ICAAC, **1985**, *Abstr.* No. 568.
(13) Jucker, E.; Rissi, E. *Helv. Chem. Acta* **1962**, *45*, 2383.
(14) Hall, S. A.; Spoerri, P. E. *J. Am. Chem. Soc.* **1940**, *62*, 664.
(15) The conversion of pyrazinecarboxylic acid to (trifluoromethyl)pyrazine has been reported: Lumma, W. C., Jr.; Hartman, R. D.; Saari, W. S., Engelhardt, E. L.; Hirschman, R. *J. Med. Chem.* **1978**, *21*, 536. However, in our hands, decarboxylation of the starting material was the only observed reaction.
(16) Saari, W. S.; Raab, A. W.; King, S. W. *J. Org. Chem.* **1971**, *36*, 1711.
(17) The in vitro testing results are reproducible. Each compound in Table II, with the exception of **19**, was tested at least twice against those organisms shown.
(18) Grohe, K.; Zieler, H.; Metzger, K. European Patent 0078362, 1983; Chem. Abstr. **1983**, *99* 53790*h*. Grohe, K.; Heitzer, H. *Liebigs Ann. Chem.* **1987**, 29.
(19) Eur. Pat. Appl. 0,000,203, 1979; *Chem. Abstr.* **1979**, *90*, 163334*j*. Also see Koga, H.; et al. in ref 1.
(20) Irikura, T.; Koga, H.; Murayama, S.; U.S. Patent 4,398,029, 1981; *Chem. Abstr.* **1982**, *96*, 6607*g*.

Table I. 7-Substituted 4-Quinolone-3-carboxylic Acids



no.	R_1[a]	X	R_7	% yield[b]	mp, °C	formula[c]
17[d]		H		51	229–232	$C_{18}H_{20}N_3O_3F$
18[e]		H		50	223–225	$C_{18}H_{20}N_3O_3F \cdot H_2O$
19	Et	H		51	>275 dec	$C_{17}H_{20}FN_3O_4 \cdot HCl$
20		H		70	193–195	$C_{18}H_{19}N_3F_2O_3$
21		H		63	262–265	$C_{21}H_{18}F_3N_3O_3$
22	Et	H		82	177–180	$C_{17}H_{19}F_2N_3O_3$
23	Et	F		35	227 dec	$C_{17}H_{17}F_4N_3O_3 \cdot 0.25H_2O$
24		H		53	252–254	$C_{18}H_{20}N_3O_4F$
25		H		23	201–204	$C_{18}H_{18}N_3F_2O_3 \cdot 0.25H_2O$

[a] The starting quinolonecarboxylic acids were prepared by literature procedures. Thus, R = cyclopropyl, X = H; see ref 18; R_1 = ethyl, X = H; see ref 19; R_1 = ethyl, X = F; see ref 20; R = 4-fluorophenyl, X = H; see ref 23. [b] Yields are not optimized. [c] C, H, and N analyses were within ±0.4% of the theoretical values. [d] This compound has been claimed in another patent; see ref 9. [e] Previously reported in a patent; see ref 24.

Table II. In Vitro Antibacterial Activity of 7-Substituted 4-Quinolone-3-carboxylic Acids[a,c]

	minimal inhibitory concentration (MIC),[b] μg/mL								
compd	Ec(A)	Ec(B)	Et(c)	Mn	Pa	Sa(A)	Sa(B)	Sf(V)	Sf(U)
17	≤0.015	≤0.015	0.015	0.03	0.25	0.12	0.5	1	2
18	0.03	0.03	0.03	0.03	1	0.25	2	1	2
19	2	1	1	0.5	64	8	32	16	16
20	0.06	0.03	0.12	0.12	2	0.12	0.25	1	2
21	0.25	0.25	0.25	1	8	0.25	0.5	4	4
22	0.12	≤0.12	0.12	0.12	32	≤0.12	0.25	2	4
23	0.5	0.5	1	1	32	0.12	0.25	4	4
24	0.25	0.5	0.25	0.12	2	4	16	16	16
25	0.03	0.03	0.06	0.06	2	0.25	1	4	4
2	≤0.015	≤0.015	≤0.015	0.015	0.25	0.25	1	1	1

[a] Structures are shown in Table I. [b] See the Experimental Section. [c] Organisms selected for the Table are as follows: Ec(A), *Escherichia coli* ATCC 25922; Ec(B), *Escherichia coli* #311; Et(C), *Enterobacter cloacae* VGH-84-39; Mn, *Morganella morganii* CMC-84-39; Pa, *Pseudomonoas aeruginosa* 12-4-4; Sa(A), *Staphylococcus aureus* Smith (MP), Sa(B), *Staphylococcus aureus* ATCC 29213; Sf(V), *Streptococcus faecalis* VGH-84; Sf(U), *Streptococcus faecalis* UCI-85.

Influences brought about by the change in N-1 substitution in compounds **20–22** indicate that cyclopropyl is the most effective substituent here, especially for *P. aeruginosa*. This observation certainly is not new and merely serves to corroborate numerous other studies.[21] The effect of ring size can be seen on comparing **17** with **18**. The 3-methylpiperazine moiety produces better overall activity here than the homopiperazine substituent. In general, medium-sized heterocyclic C-7 substitution is recognized to give optimal broad-spectrum action.[22]

(21) Domagala, J. M.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; Nichols, J. B.; Solomon, M.; Worth, D. F. *J. Med. Chem.* **1988**, *31*, 991.

(22) Domagala, J. M.; Hanna, L. D.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; Sanchez, J. P.; Solomon, M. J. *J. Med. Chem.* **1986**, *29*, 394. See also Koga, H.; et al. in ref 1. Egawa, H.; Miyamoto, T.; Nishimura, Y.; Okada, H.; Uno, H.; Matsumoto, J. *J. Med. Chem.* **1984**, *27*, 1543.

Table III. Activity vs Acute Lethal Infections in Mice

compd[b]	route[c]	ED_{50},[a] mg/kg *E. coli* #311	po/sc	ED_{50},[a] mg/kg *S. aureus* Smith	po/sc
20	po	1.2 (0.93–1.5)	2	2.8 (2.3–3.4)	3
	sc	0.6 (0.48–0.75)		0.94 (0.66–1.3)	
22	po	2.8 (2.1–3.8)	1	6.0 (4–8)	2.3
	sc	3.0 (1.0–4.0)		2.6 (2.0–3.5)	
17	po	0.42 (0.3–0.53)	4.7	2.4 (1.9–2.9)	3.9
	sc	0.09 (0.07–0.11)		0.61 (0.43–0.86)	
2	po	0.49 (0.37–0.65)	7	3.8 (3.1–4.6)	5.5
	sc	0.07 (0.05–0.09)		0.69 (0.48–0.97)	

[a] ED_{50} = median effective dose. 95% confidence limits are in parentheses. [b] Structures are shown in Table I. [c] Po = oral administration; sc = subcutaneous administration.

The comparison between ciprofloxacin (**2**) and **17** shows that they have similar activity. However, when the 3-fluoromethyl moiety of **20** is entered into this comparison, one sees less Gram-negative activity for **20** than for **2** or **17** and comparable Gram-positive behavior. In the series of **19**, **22**, and **23**, the fluoromethyl substituent of **22** is best although its activity against *P. aeruginosa* is poor. In the homopiperazine series **18**, **24**, and **25**, the fluoro group in **25** is responsible for better activity than the OH group of **24**. Yet, the parent homopiperazine in **18** demonstrates optimal behavior here.

Summarizing, the in vitro activity for the 7-(3-substituted-piperazinyl)quinolones possessing identical N-1 groups shows the following decreasing trend: H, CH_3 > CH_2F > CHF_2 > CH_2OH. In the corresponding substituted homopiperazine isomers **18**, **24**, and **25**, a similar decreasing trend is observed (i.e. H > F > OH).

The synthesis of these 7-[3-(fluoromethyl)piperazinyl]-quinolone analogues **20–23** was based on the premise that they should show better in vivo absorption compared to that of their parent analogues. The efficacy of the 7-[3-(fluormethyl)piperazinyl]quinolones **20** and **22** was tested against mouse systemic infections caused by *E. coli* #311 and *S. aureus* Smith. Serving as standards in this in vivo study were the 7-(3-methylpiperazinyl)quinolone parent **17** and ciprofloxacin (**2**). The results are shown in Table III. In separate tests, the quinolones were administered orally (po) or subcutaneously (sc) following acute lethal injections of the organism. Included in the table is the ED_{50} ratio for the oral versus subcutaneous administration routes. This ratio (po/sc) is a measure for the efficacy of absorption exhibited by each quinolone.

Quinolones **20** and **22** show good activity against both organisms; however, their respective ED_{50} values do not compare well with those of ciprofloxacin (**2**) or **17**. Compound **20** is roughly 2-fold more active than the *N*-ethyl derivative **22**. Interestingly, **20** and **22** both show lower po/sc ratios than **17** or **2**. This indicates, as expected, that these compounds are absorbed most effectively in this study.

Thus, it has been demonstrated that the 3-(fluoromethyl)piperazinyl and the fluorohomopiperazine moieties are good C-7 substituents for 6-fluoro-4-quinolone-3-carboxylic acids. Compounds **20–23** and **25** all have good in vitro activity but not better than those of the standards employed, **2** or **17**. Likewise, compounds **20** and **22** showed less in vivo efficacy than **17** or **2** against systemic *E. coli* and *S. aureus* infections. Noteworthy, however, is the fact that **20** and **22** showed better oral in vivo absorption due to their fluoro substitution.

Experimental Section

Melting points were recorded in a Mel-Temp Melting point apparatus and are uncorrected. Elemental analyses were obtained for all new compounds reported when possible. Carbon, hydrogen, nitrogen, and fluorine analyses were within 0.4% of the theoretical values. The NMR spectra were obtained using a NT-300 WB spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were recorded on a Finnigan Mat CH-7 spectrometer. High-resolution mass spectra (HRMS) were determined with a ZAB-SE mass spectrometer. The IR spectra were recorded on Perkin-Elmer Model 21 infrared spectrometer. The IR, NMR, and mass spectral data of all compounds were consistent with the assigned structures and the nuclear magnetic resonance spectra of **17–25** are given in Table IV. Solutions were dried with anhydrous sodium sulfate.

2-(Fluoromethyl)piperazine (10). A solution of 1,4-dibenzyl-2-(hydroxymethyl)piperazine (**9**,[13] 15 g, 51.3 mmol) in dry methylene chloride (25 mL) was added dropwise to a solution of DAST (8.1 g, 61.6 mmol) in dry methylene chloride (20 mL) at −65 °C under argon. The solution was then allowed to warm slowly to room temperature and was stirred for 15 h. On workup, the reaction solution was cooled to 5 °C and cold water was added dropwise while the temperature was maintained at 10 °C. The pH of the aqueous phase was adjusted to 9.0 with 5 N sodium hydroxide. The organic phase was separated and the aqueous phase was extracted repeatedly with methylene chloride. The combined organic phases were washed with water, dried over magnesium sulfate, and evaporated to an oil. The oil was purified by flash column chromatography, giving 10.72 g (70%) of colorless oil, 1,4-dibenzyl-2-(fluoromethyl)piperazine. Anal. Calcd for $C_{19}H_{23}FN_2$: C, 76.48; H, 7.77; N, 9.39; F, 6.37. Found: C, 76.64; H, 7.8; N, 9.33; F, 6.57.

A solution of this 1,4-dibenzyl-2-(fluoromethyl)piperazine (16.2 g, 54.3 mmol) in ethanol (50 mL) was mixed with a suspension of 10% palladium-on-carbon (5.7 g) in acetic acid (10 mL) and the resulting mixture was reduced with a Parr-Shaker apparatus for 24 h at a hydrogen pressure of 45 psi. The reduction mixture was filtered through Celite and the filtrate was evaporated to dryness in vacuo at 30 °C to give 6 g (95%) of a colorless, low melting, hygroscopic solid as the diacetate salt: ^{1}H NMR (Me_2SO-d_6) δ 1.85 (s, 6 H, CH_3 of acetate salt), 2.4–3.0 (m, 7 H), 4.3 (dd, 2 H, CH_2F, J = 50, 4.5 Hz); MS (EI) m/e (relative intensity) 118 (M^+, 5), 98 (M^+ − HF, 52).

2-(Hydroxymethyl)piperazine (11). A solution containing 1,4-dibenzyl-2-(hydroxymethyl)piperazine (**9**, 5 g, 16.9 mmol) in 35 mL of ethanol was reacted at 40 °C overnight in a Parr-Shaker apparatus (45 psi H_2 pressure) with 1.0 g of 10% palladium-on-charcoal catalyst. On workup, the catalyst was filtered and the ethanol was removed, leaving **11** (1.85 g, 94%): mp 104-106 °C; ^{1}H NMR ($CDCl_3$) δ 2.48 (t, 1 H, OH, J = 11 Hz), 2.7–3.0 (m, 9 H), 3.42 (dd, 1 H, CHO, J = 10.5, 7 Hz), 3.55 (dd, 1 H, CHO, J = 10.6, 4 Hz). Anal. Calcd for $C_5H_{12}N_2O$: C, 51.70; H, 10.42; N, 24.11. Found: C, 51.34; H, 10.27; N, 23.87. MS (EI) m/e (relative intensity) 116 (M^+, 8), 98 (M^+ − H_2O, 30), 85 (100).

2-(Difluoromethyl)piperazine (13). A solution containing pyrazinecarboxyaldehyde (**12**,[14] 3.5 g, 33 mmol) in $CFCl_3$ (20 mL) was stirred at 0 °C under argon. To this was slowly added DAST (5.6 g, 35 mmol) and the resulting reaction mixture was stirred overnight at 20 °C. This procedure was basically the same as that outlined in ref 25. The product **13** was isolated via flash column chromatography (CH_2Cl_2) to give 2.0 g (39%) as a yellow, unstable oil. MS (EI) m/e (relative intensity) 130 (M^+, 100).

The intermediate, 2-(difluoromethyl)pyrazine, was dissolved in 30 mL of methanol and then reduced in a Parr-Shaker apparatus with 0.58 g of PtO_2 under 50 psi of H_2 for 4 h. The reaction mixture was filtered through Celite and then purified via column chromatography (basic alumina, 1:19 CH_3OH–CH_2Cl_2) to give 250 mg (13%) of **13** as a hygroscopic material that was not purified further: ^{1}H NMR ($CDCl_3$) δ 1.8 (br s, 2 H, NH), 2.6–3.1 (m, 7 H), 5.6 (td, 1 H, CHF_2, J_{H-F} = 57, 6 Hz).

Synthesis of Fluorohomopiperazine (16). A solution a **14**[16] (8.5 g, 20 mmol) in CH_2Cl_2 (60 mL) was added dropwise to a stirred solution of DAST (4.8 mL, 36 mmol) in 20 mL of CH_2Cl_2 at −65

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Table IV. Nuclear Magnetic Resonance Spectral Data of Quinolones 17–25[a]

compd	solvent	N_1–H	C_2–H	C_5–H	C_8–H	C_7–H
17	Me_2SO-d_6	1.17 (d, CH_2, J = 3.5), 1.29 (d, CH_2, J = 5.5), 3.85 (m, N–CH)	8.64 (s)	7.86 (d, J = 13.5)	7.51 (d, J = 7.5)	1.03 (d, CH_3, J = 7), 2.5 (m, 2 H), 2.93 (m, 3 H), 2.95 (m, 1 H), 3.54 (d, 2 H, J = 7)
18	Me_2SO-d_6	1.16 (d, CH_2, J = 3.6), 1.28 (d, CH_2, J = 5.6), 3.76 (m, N–CH)	8.58 (s)	7.8 (d, J = 15)	7.32 (d, J = 8)	1.85 (m, CH_2), 2.75 (m, 2 H), 2.95 (t, CH_2, J = 5), 3.64 (t, CH_2, J = 4.5), 3.73 (t, CH_2, J = 4.5)
19	CF_3CO_2D	1.82 (t, CH_3), 4.95 (q, CH_2)	9.35 (s)	8.33 (d, J = 12)	7.62 (d, J = 4.5)	3.7–4.5 (m, 9 H)
20	Me_2SO-d_6	1.15 (d, CH_2, J = 3.5), 1.30 (d, CH_2, J = 5.5), 3.8 (m, CHN)	8.8 (s)	7.8 (d, J = 13.5)	7.5 (d, J = 7)	2.7–3.2 (m, 4 H), 3.52 (d, 1 H, J = 12), 3.57 (d, 1 H, J = 12), 5.44 (dd, CH_2F, J = 46, 6)
21	Me_2SO-d_6	7.52 (m, 2 H), 7.81 (m, 2 H)	8.7 (s)	8.08 (d, J = 13)	6.52 (d, J = 6.5)	3.07 (m, 2 H), 3.3 (m, 1 H), 3.45 (m, 2 H), 3.68 (d, 1 H, J = 9), 3.83 (m, 1 H), 4.73 (dt, 2 H, CH_2F, J = 48, 6)
	CF_3CO_2D					
22	CF_3CO_2D	1.8 (t, CH_3), 4.9 (q, CH_2)	9.35 (s)	8.35 (d, J = 12)	7.58 (d, J = 5)	3.7–4.3 (m, 8 H), 4.97 (m, CH_2F)
23	Me_2SO-d_6	1.5 (t, CH_3), 4.6 (q, CH_2)	8.9 (s)	7.9 (d, J = 12.5)		2.6–3.6 (m, 8 H) + H_2O, 6.0 (t, CHF_2, J = 55, 5)
24	Me_2SO-d_6	1.16 (m, CH_2), 1.28 (d, CH_2, J = 7), 3.81 (m, 1 H)	8.6 (s)	7.85 (d, J = 12)	7.52 (d, J = 6)	2.6 (dd, 1 H, J = 13, 3), 2.95 (m, 2 H), 3.5–4.0 (m, 7 H), 5.0 (bs, CHO)
25	Me_2SO-d_6	1.17 (m, CH_2), 1.25 (d, CH_2, J = 7), 3.8 (m, 1 H)	8.6 (s)	7.83 (d, J = 15)	7.5 (d, J = 7.5)	2.75–3.2 (m, 5 H), 3.5–4.2 (m, 4 H), 4.93 (dt, 1 H, CHF, J = 52, 3)

[a] All chemical shifts are measured in δ values and coupling constants are in hertz. Tetramethylsilane is the internal standard. The following designations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; dd, doublet of doublets; dt, doublet of triplets.

°C under an argon atmosphere. The reaction mixture was then brought to 20 °C and stirred overnight. On workup, the reaction mixture was cooled to 5 °C and H_2O was added dropwise while the internal temperature was maintained at 10 °C. To this was added 5 N NaOH until the pH of the solution reached 9.0. The CH_2Cl_2 layer was removed and the aqueous layer was extracted twice with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with water, dried, and filtered, and the solvent was removed to give 6.2 g (73%) of the intermediate fluoro substitution product 1,4-bis(*p*-tolylsulfonyl)hexahydro-6-fluoro-1*H*-1,4-diazepine, mp 184–186 °C from methanol. Anal. Calcd for $C_{19}H_{23}FN_2O_4S_2$: C, 53.5; H, 5.43; N, 6.56; S, 15.03; F, 4.45. Found: C, 53.33; H, 5.42; N, 6.47; S, 15.12; F, 4.38.

A solution of 1,4-bis(*p*-tolylsulfonyl)hexahydro-6-fluoro-1*H*-1,4-diazepine (7 g, 16.4 mmol) in 110 mL of a 30% anhydrous hydrogen bromide–acetic acid solution was stirred at room temperature for 30 min. A portion of phenol (6.1 g, 65 mmol) was added and the reaction mixture was stirred at 60 °C for 6 h and then allowed to cool to 20 °C. The reaction mixture was filtered and the filtrate was evaporated to dryness (70°C/15 mm). The residue was slurried in ethanol and filtered to give 4.3 g (93%) **16** as the dihydrobromide salt: ^{1}H NMR (DMSO) δ 3.2–3.8 (m, 8 H), 5.4 (dt, 1 H, CHF, J = 42, 4 Hz), 9.4 (br s, 4 H). Anal. Calcd for $C_7H_{13}Br_2FN_2$: C, 21.44; H, 4.68; N, 10.00; F, 6.78; Br, 57.08. Found: C, 21.18; H, 4.31; N, 9.56; F, 6.56; Br, 56.33.

The dihydrobromide salt of **16** was converted to free base **16** by passing a solution of the salt (840 mg, 3 mmol) in 15 mL of water through a Dowex 1-X4 (OH form) column. The free base eluted with water. The collected eluent fractions were evaporated in vacuo to leave an oil **16**, which was used immediately without further purification to prepare quinolone **25** (Table I).

1-(4-Fluorophenyl)-6-fluoro-7-[3-(fluoromethyl)-1-piperazinyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (21). A suspension of 1-(4-fluoropheny)-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid[23] (479 mg, 1.5 mmol) and 2-(fluoromethyl)piperazine (**10**, 355 mg, 3 mmol) in pyridine (2 mL) and DMF (0.5 mL) was stirred at 90 °C for 3.5 h under argon. The suspension was cooled to 20 °C and the crystals were collected by filtration, washed with cold pyridine and water, and dried to give 445 mg (63%) of **21**. Anal. ($C_{21}H_{18}F_3N_3O_3$) C, H, N, F.

By use of this procedure, all the 7-substituted quinolonecarboxylic acids were synthesized from the appropriate 1-substituted 7-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids[18–20,23] and the appropriate amine (Table I).

In Vitro Antibacterial Activity. The in vitro antibacterial effects of the compounds were determined in a side-by-side comparison with ciprofloxacin (**2**) by a standard agar dilution method. Two-fold serial dilutions of the drugs were prepared in Mueller–Hinton agar. The agar surfaces in petri plates were inoculated with 1–5 × 10^4 colony-forming units (CFU) of bacteria by means of the Steers multiple inocula replicator. The lowest concentration of the drug that inhibited the macroscopic growth of a culture after 18 h incubation at 35 °C was recorded as the minimal inhibitory concentration (MIC).[26]

In Vivo Antibacterial Activity. The in vivo antibacterial effects were determined against acute lethal infections in CD-1 female mice weighing 20 ± 2 g. The mice were infected intraperitoneally with 0.5 mL of a standardized suspension of bacteria in trypticase–soy broth (*E. coli* #311) or 5% hog gastric mucin (*S. aureus* Smith). One-half hour after infection the mice were treated with subcutaneous or oral doses at 2-fold increments of the test compounds contained in 0.5 mL of 0.2% aqueous agar. In each test five mice were treated at each dose level. Untreated control mice died in 24–48 h. The 7-day survival ratios from three separate tests were pooled for the estimation of the median effective doses (ED_{50}) by a computerized probit analysis program.[27]

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Registry No. **7** (X = H, R′ = F-*p*-C_6H_4), 103994-99-6; **7** (X = H, R′ = cyclopropyl), 93107-30-3; **7** (X = H, R′ = Et), 70032-25-6; **7** (X = F, R′ = Et), 75338-42-0; **9**, 94437-04-4; **10**, 110842-63-2; **10**·2AcOH, 123187-91-7; **11**, 28795-50-8; **12**, 5780-66-5; **13**, 111759-98-9; **14**, 28860-33-5; **16**, 123187-94-0; **16**·2HBr, 123187-93-9; **17**, 93107-32-5; **18**, 118330-11-3; **19**, 114506-53-5; **19**·HCl, 111760-03-3; **20**, 123187-95-1; **21**, 123187-96-2; **22**, 111780-96-2; **23**, 111759-73-0; **24**, 123187-97-3; **25**, 123187-98-4; 1,4-dibenzyl-2-(fluoromethyl)piperazine, 111760-36-2; 2-(difluoromethyl)-pyrazine, 111781-48-7; 1,4-bis(*p*-tolylsulfonyl)hexahydro-6-fluoro-1*H*-1,4-diazepine, 123187-92-8; 2-methylpiperazine, 109-07-9; homopiperazine, 505-66-8; 3-hydroxyhomopiperazine, 28795-81-5.

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