velopment funds from the departments of Pathology and Thoracic-Cardiovascular Surgery of Loyola University Medical Center (J.F.).

Registry No. 1, 122863-71-2; 2, 98797-50-3; 3, 126580-50-5; 4, 126580-51-6; 5, 126580-52-7; 6, 126580-53-8; 7, 119370-32-0; 8, 126613-94-3; 9, 126720-81-8; heparin, 9005-49-6; antithrombin, 9000-94-6; blood coagulation factor Xa, 9002-05-5; blood coagulation factor IIa, 9002-04-4.

Supplementary Material Available: The SAX-HPLC chromatogram and gradient PAGE analysis (both glossy photo and a scan) of oligosaccharide 6 demonstrating its purity (1 page). Ordering information is given on any current masthead page.

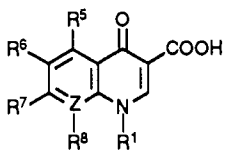
Synthesis and Structure–Activity Relationships of 5-Substituted 6,8-Difluoroquinolones, Including Sparfloxacin, a New Quinolone Antibacterial Agent with Improved Potency[1]

Teruyuki Miyamoto, Jun-ichi Matsumoto,* Katsumi Chiba, Hiroshi Egawa, Koh-ichiro Shibamori, Akira Minamida, Yoshiro Nishimura, Hidetsugu Okada, Masahiro Kataoka, Masahiro Fujita, Tohru Hirose, and Junji Nakano

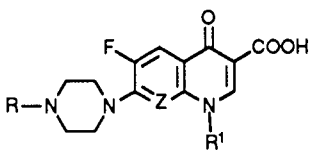
Research Laboratories, Dainippon Pharmaceutical Company, Ltd., Enoki 33-94, Suita, Osaka, 564, Japan.
Received September 20, 1989

A series of 5,7-disubstituted 1-cyclopropyl-6,8-difluoro-4(1*H*)-oxoquinoline-3-carboxylic acids (**10–36**) were prepared; the C-5 substituent in these compounds comprised halo, hydroxy, mercapto, and amino groups and the C-7 functional group included variously substituted piperazines. In vitro antibacterial screening results indicated that the amino group was optimal among the C-5 substituents. A combination of the C-5 amino group and the C-7 3,5-dimethylpiperazinyl appendage in this series conferred the best overall antibacterial property with lack of adverse drug interactions. Compound **36k** [named sparfloxacin, originally AT-4140, 5-amino-1-cyclopropyl-6,8-difluoro-7-(*cis*-3,5-dimethyl-1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic acid] was superior to ciprofloxacin in both in vitro and in vivo potency and hence was selected as a promising candidate for an improved therapeutic agent.

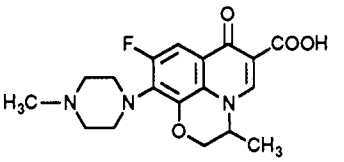
During recent years, much attention has increasingly been given to the synthesis of quinolone antibacterials as a source of new agents.[2] Successful chemical modifications[3] in this area to date are realized especially at positions C-1 (ethyl, fluoroethyl, cyclopropyl, fluorophenyl, and methylamino), C-6 (fluoro), C-7 (4-pyridyl, piperazinyl, and aminopyrrolidinyl), C-8 (fluoro and chloro), and N-1–C-8 ($-CH(CH_3)CH_2CH_2-$ and $-CH(CH_3)CH_2O-$) of the quinolones represented generically by **1**. However, little attention has been paid to the role of C-5 substituents as a possible contributor to the antibacterial property of this class of agents; although several examples of C-5 variants, including alkyl,[4] halo,[4a,5] nitro,[6a] and amino[6] groups, have been reported, neither extensive structure–activity relationships (SARs) of the C-5 function nor clinically useful agents (or even promising candidates) appended with a C-5 substituent have been developed thus far. It seemed to us that the substitution at C-5 might influence activity, because the C-5 position neighbors on the C-4 oxo group,



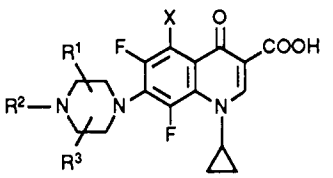
1: Z – R^8 = N or C – R^8



2: Z = N, R^1 = C_2H_5, R = H (enoxacin)
3: Z = CH, R^1 = *c*-C_3H_5, R = H (ciprofloxacin)
4a: Z = CF, R^1 = *c*-C_3H_5, R = H
4b: Z = CF, R^1 = *c*-C_3H_5, R = CH_3



5 (ofloxacin)



6: R^1, R^3 = *cis*-3,5-dimethyl, R^2 = X = H
7: X = halogen, OH, SH, NH_2, etc.

(1) This paper is Part 14 in the series Pyridonecarboxylic Acids as Antibacterial Agents. Part 13: Shibamori, K.; Egawa, H.; Nishimura, Y.; Miyamoto, T.; Matsumoto, J. *Chem. Pharm. Bull.*, accepted.

(2) (a) Wentland, M. P.; Cornett, J. B. *Annu. Rep. Med. Chem.* **1985**, *20*, 145. (b) Cornett, J. B.; Wentland, M. P. *Ibid.* **1986**, *21*, 139. (c) Fernandes, P. B.; Chu, D. T. W. *Ibid.* **1987**, *22*, 117.

(3) For reviews, see: (a) Albrecht, R. *Prog. Drug Res.* **1977**, *21*, 9. (b) Chu, D. T. W.; Fernandes, P. B. *Antimicrob. Agents Chemother.* **1989**, *33*, 131. (c) Mitscher, L. A.; Zavod, R. M.; Sharma, P. N. International Telesymposium on Quinolones; Fernandes, P. B., Ed.; J. R. Prous *Science (Barcelona, Spain)* **1989**; pp 3–20.

(4) (a) Cecchetti, V.; Fravolini, A.; Fringuelli, R.; Mascellani, G.; Pagella, P.; Palmioli, M.; Segre, G.; Terni, P. *J. Med. Chem.* **1987**, *30*, 465. (b) Ueda, H.; Miyamoto, H.; Yamashita, H.; Tone, H. Eur. Patent Appl. EP 287951, 1988; *Chem. Abstr.* **1989**, *110*, 173109*k*.

(5) (a) Fujiwara, T.; Fujimoto, M.; Yokota, T. Japan Patent Kokai 58-210092, 1983; *Chem. Abstr.* **1984**, *100*, 19187*k*. (b) Moran, D. B.; Ziegler, C. B., Jr.; Dunne, T. S.; Kuck, N. A.; Lin, Y.-i. *J. Med. Chem.* **1989**, *32*, 1313. (c) Domagala, J. M.; Mich, T. F.; Nicols, J. B. US Patent 4657913, 1987; *Chem. Abstr.* **1987**, *106*, 102107*q*. (d) Miyamoto, T.; Kataoka, M.; Nakano, J.; Matsuomoto, J.; Nakamura, S. Japan Patent Kokai 64-9992, 1989.

(6) (a) Frank, J.; Rakoczy, P. *Eur. J. Med. Chem.* **1979**, *14*, 61. (b) Hayakawa, I.; Tanaka, Y. Japan Patent Kokai 57-149286, 1982; *Chem. Abstr.* **1982**, *98*, 72117*q*. (c) Tanabe Seiyaku Co. Japan Patent Kokai 58-74367, 1983; *Chem. Abstr.* **1984**, *100*, 51467*y*.

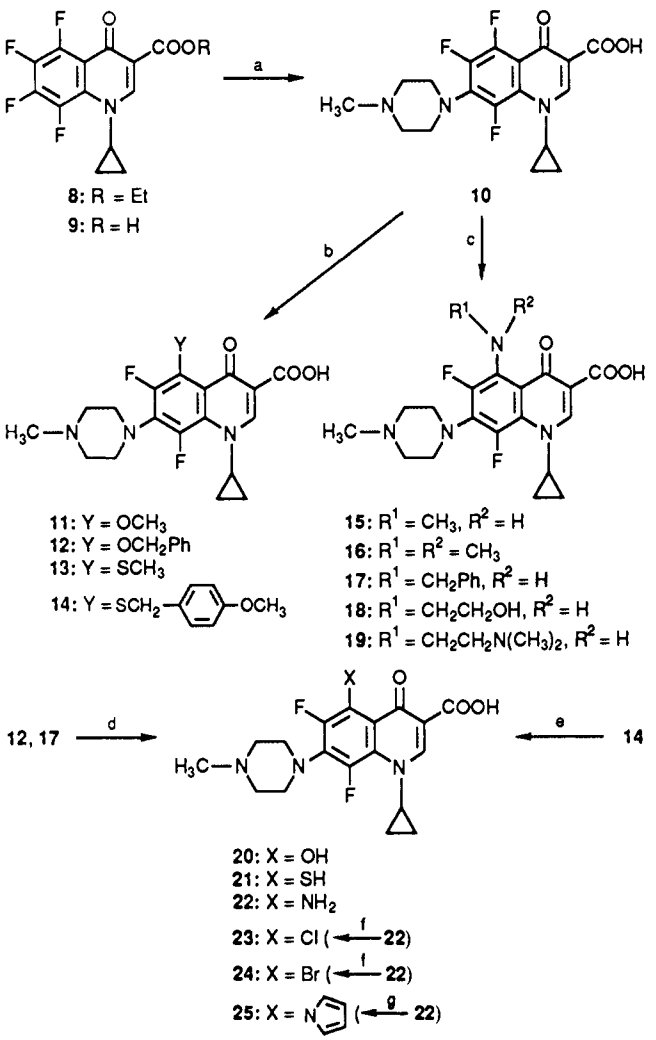
0022-2623/90/1833-1645$02.50/0

which was accepted as an indispensable functional moiety for biological activity.

Our previous paper[1] reported the regioselective displacement reactions at C-5 and C-7 of ethyl 1-cyclopropyl-5,6,7,8-tetrafluoro-4(1*H*)-oxoquinoline-3-carboxylate (**8**) and its carboxylic acid (**9**). As a continuation of our research project for potent broad-spectrum antibacterial agents followed after enoxacin (**2**),[7] which was developed in our laboratories and is now widely used in clinical practice, we have extended modifications of the C-5 and C-7 substituents in order to get further insight into their SARs. After our work on this was completed,[8] the synthesis of a similar quinolone with a C-5 amino function but a limited variant at C-7 by a different method was reported.[9] In the present paper, we report the synthesis and SARs of a series of 5- and 7-substituted 6,8-difluoroquinolones **7**. In this study, halo, hydroxy, mercapto, and amino groups were selected to be introduced at C-5, and methyl-substituted piperazines were designed as C-7 variants with the following hypothesis in mind.

Adverse interactions of several quinolone antibacterials with a nonsteroidal antiinflammatory, fenbufen,[10] and an antiasthmatic, theophylline,[11] have been noticed during their development of the agent. The interaction with fenbufen is explained on the basis of an enhancing effect of fenbufen on quinolone-mediated inhibition of the receptor binding of γ-aminobutyric acid (GABA), a major inhibitory neurotransmitter in the central nervous system (CNS); this effect leads to an increase in CNS excitability and to enhanced epileptogenicity.[12] On the other hand, it was recently reported that concurrent treatment of enoxacin with theophylline in rats changes the pharmacokinetics of theophylline, causing prolongation of its elimination half-life and thereby leading to an increase in its plasma concentrations.[13] This results in increased risk of theophylline-related adverse reactions such as vomiting, nausea, tachycardia, and headaches. Sekine and his coworkers[13] suggested that, at an initial stage of the metabolism, enoxacin competitively inhibits the binding of theophylline to cytochrome P-448 and this inhibition is responsible for the coplanarity between the C-7 piperazinyl ring and the naphthyridine nucleus of enoxacin. The planar feature may permit enoxacin to interact with the narrow binding site of the enzyme. Therefore, we selected rather bulky C-methylpiperazines as the C-7 substituent, because they might restrict the free rotation around the bond axis between the C-7 carbon and the piperazinyl N-1 nitrogen in combination with the fluorine atoms at C-6 and C-8 and accordingly make a coplanar conformation of the molecule unpreferable, thus possibly causing the inhibition of its binding with the enzyme and analogously with the GABA receptor as well.

Scheme I[a]



[a] (a) *N*-methylpiperazine in EtOH; (b) NaY or HY in toluene; (c) R^1R^2NH; (d) H_2/Pd-C; (e) CF_3COOH; (f) $NaNO_2$, CuX, HX; (g) 2,5-dimethoxytetrahydrofuran.

Chemistry

In the previous work,[1] we found that nucleophilic displacement of 5,6,7,8-tetrafluoroquinolones **8**[14] and **9**[14] proceeds regioselectively at the C-5 or C-7 position, depending on adopted conditions. This finding accordingly permitted us to introduce an optional nucleophile preferentially into either the C-5 or the C-7 position, or stepwise into both positions with a desired combination of nucleophiles. Treatment of **9** with *N*-methylpiperazine in ethanol gave 1-cyclopropyl-5,6,8-trifluoro-7-(4-methyl-1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic acid (**10**).[5b] Further displacement reactions of compound **10** with

(7) Matsumoto, J.; Miyamoto, T.; Minamida, A.; Nishimura, Y.; Egawa, H.; Nishimura, H. *J. Med. Chem.* **1984**, *27*, 292.

(8) (a) Matsumoto, J.; Miyamoto, T.; Egawa, H.; Nakamura, S. Eur. Patent Appl. EP 221463, 1987; *Chem. Abstr.* **1987**, *107*, 236733*v*. (b) *Idem.* Japan Patent Kokai 62-00469, 1987; *Chem. Abstr.* **1987**, *106*, 213777*c*. (c) Miyamoto, T.; Kataoka, M.; Nakano, J.; Nakamura, S.; Matsumoto, J. Japan Patent Kokai 62-226962, 1987; *Chem. Abstr.* **1988**, *108*, 186591*v*.

(9) (a) 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*, 503. (b) Domagala, J. M.; Hagen, S. E.; Hutt, M. P.; Sanchez, J. P.; Sesnie, J.; Trehan, A. K. *Drugs Exp. Clin. Res.* **1988**, *14*, 453.

(10) (a) Simpson, K. J.; Brodie, M. J. *Lancet* **1985**, *2*, 161. (b) Wolfson, J. S.; Hooper, D. C. *Ann. Intern. Med.* **1988**, *108*, 238. (c) Anastasio, G. D.; Menscer, D.; Little, J. M. *Ibid.* **1988**, *109*, 169.

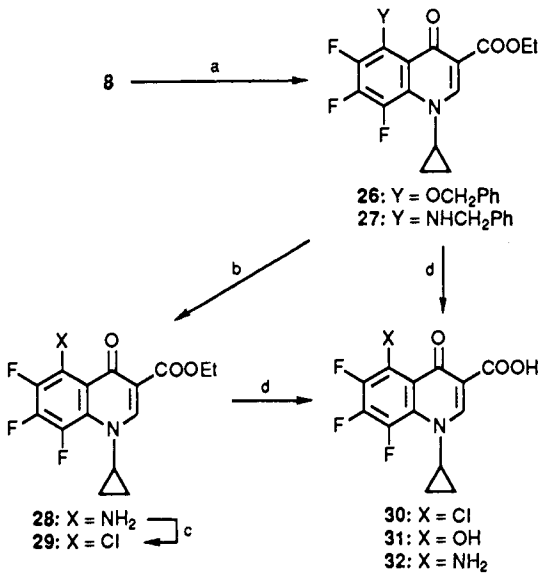
(11) Wijnands, W. J. A.; Van Herwaarden, C. L. A.; Vree, T. B. *Lancet* **1984**, *2*, 108.

(12) (a) Hori, S.; Shimada, J.; Saito, A.; Miyahara, T.; Kurioka, S.; Matsuda, M. *25th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)*; Minneapolis, MN, Sept. 29–Oct. 2, 1985; Vol. 113 Abstract No. 396. (b) *Idem. 26th ICAAC*; New Orleans, LA, Sept. 28–Oct. 1, 1986; Vol. 114, Abstract No. 438. (c) *Idem. 27th ICAAC*; New York, NY, Oct, 4–7, 1987; Vol. 115, Abstract No. 30. (d) Tsuji, A.; Sato, H.; Kume, Y.; Tamai, I.; Okezaki, E.; Nagata, O.; Kato, H. *Antimicrob. Agents Chemother.* **1988**, *32*, 190.

(13) Mizuki, Y.; Kamaura, M.; Yamaguchi, T.; Sekine, Y.; Hashimoto, M. *Arzneim. Forsch.* **1989**, *39*, 593.

(14) After completion of our work (ref 8), compounds **8** and **9** were reported; see refs 5b and 5c.

Scheme II[a]

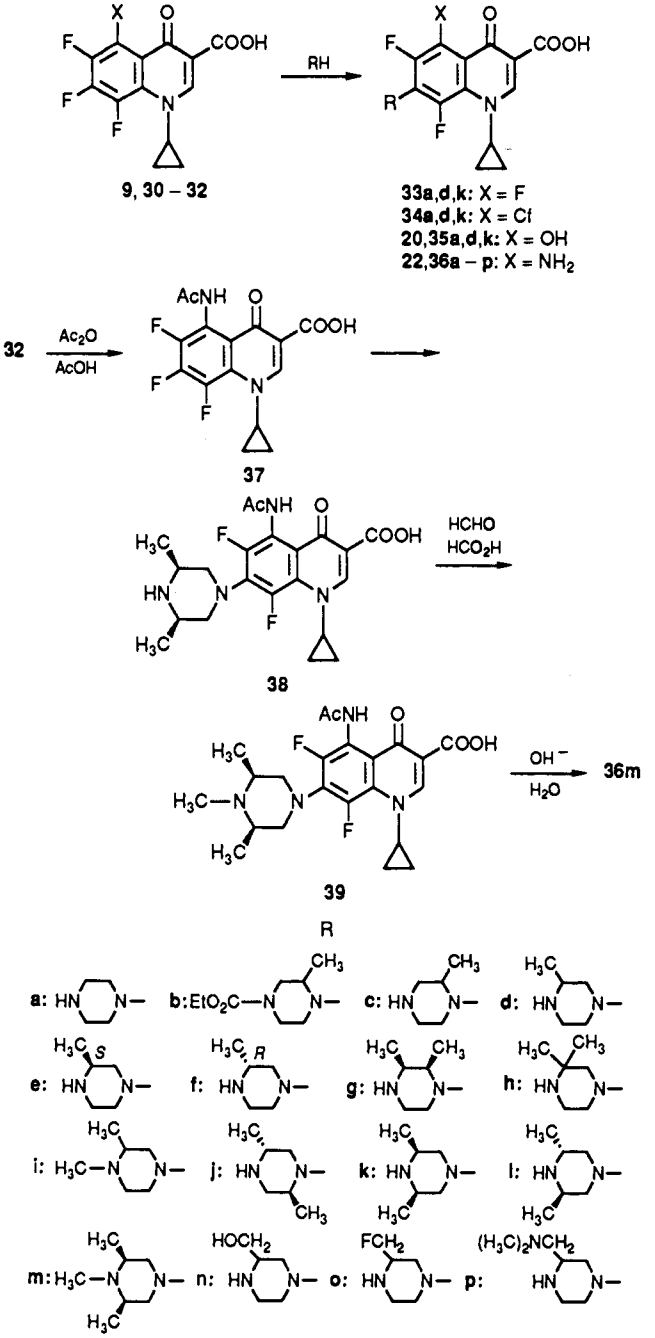


[a] (a) NaY or HY in toluene; (b) H_2/Pd-C; (c) *t*-BuONO, $CuCl_2$; (d) H_3O^+.

different nucleophiles gave a series of 5-substituted derivatives **11–25** (Scheme I). The reaction with alkoxides and thioxides thus afforded the 5-alkoxy (**11** and **12**) and 5-alkylthio (**13** and **14**) analogues, respectively. Treatment of **10** with various amines gave the 5-(substituted-amino)quinolones **15–19**. The benzyl group of **12** and **17** was removed by hydrogenation or acid treatment to give the corresponding 5-hydroxy (**20**) and 5-amino (**22**)[9a] analogues. Debenzylation of **14** was carried out on treatment with trifluoroacetic acid, giving 5-mercapto analogue **21**. The C-5 amino group of **22** was converted by the Sandmeyer reaction into chloro (**23**) and bromo (**24**) atoms, though in poor yields. Treatment of **22** with 2,5-dimethoxytetrahydrofuran gave the pyrrolyl derivative **25** in a moderate yield.

Among compounds **10–25** with the *N*-methylpiperazinyl group at C-7, the 5-fluoro, chloro, hydroxy, and amino derivatives were comparable to the reference C-5 hydrogen analogue **4b**[15] in in vitro antibacterial activity as discussed later. Therefore, we planned to modify this *N*-methylpiperazinyl group into differently substituted piperazinyl groups while the fluoro, chloro, hydroxy, and amino groups at C-5 were kept. An alternative synthetic route for this purpose was developed starting from the ester **8**. Regioselective displacement at C-5 of **8** with a nucleophile was achieved in a nonpolar solvent (Scheme II); thus the reaction of **8** with sodium benzylate in refluxing toluene proceeded preferentially at C-5 to give 5-benzyloxy derivative **26**, accompanied by a small amount of its benzyl ester. Acid treatment of both products underwent the hydrolysis of the ester, with concomitant debenzylation at C-5, giving 5-hydroxy derivative **31**. A similar treatment of **8** with benzylamine afforded a good yield of the 5-benzylamino compound **27**, which was then subjected to hydrogenation to give 5-amino analogue **28**. The structures of **26** and **27** were assigned on the basis of their fluorine-19 nuclear magnetic resonance spectra. The amino group of **28** was converted by the Sandmeyer reaction to a chloro group (**29**), though the yield was unsatisfactory. Esters **28** and **29** were hydrolyzed under acidic conditions to give carboxylic acids **32** and **30**, respectively. Compound **32** was

Scheme III

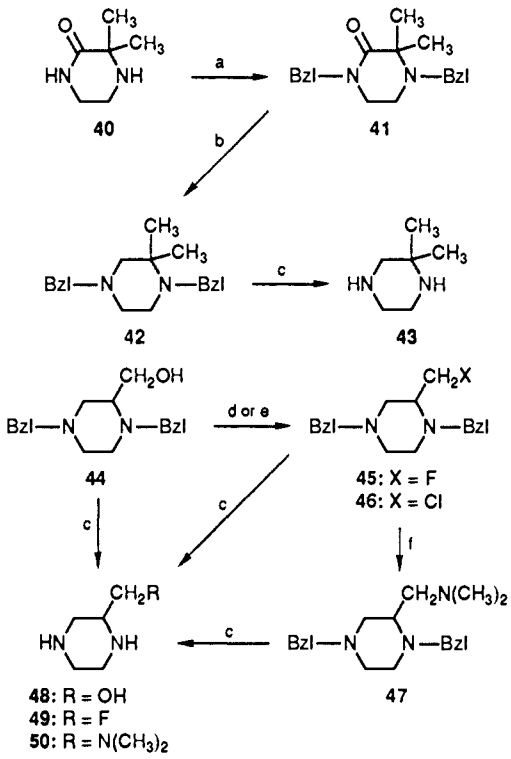


alternatively derived directly from **27** by deprotection of the benzyl group.

The C-7 fluorine atoms of **9** and **30–32** were then displaced with various piperazines to give the corresponding 7-(substituted-1-piperazinyl)quinolones **20**, **22**, and **33–36**, except **36c** and **36m** (Scheme III). Compound **36c** was derived from **36b** by removal of the ethoxycarbonyl group under alkaline conditions. 3,4,5-Trimethylpiperazinyl compound **36m** was separately prepared from **32** in the following four steps. Thus acetylation of **32** with acetic anhydride, followed by displacement reaction of **37** with *cis*-2,6-dimethylpiperazine, afforded **38**, which was then subjected to N-methylation with formaldehyde in formic acid and subsequent alkaline treatment of **39** to give **36m**. Compounds **20** and **22** prepared thus via **31** and **32**, respectively, were identified with the products derived from **12** and **17**, respectively (see Scheme I); this fact supports, in turn, the structures previously assigned for **26** and **27**. Among compounds shown in Scheme III, those having a chiral center(s) were racemates unless otherwise noted and

(15) Grohe, K.; Heitzer, H. *Liebigs Ann. Chem.* **1987**, 29.

Scheme IV[a]



[a] (a) $PhCH_2Cl$, NaH in DMF; (b) $NaAlH_2(OCH_2CH_2OCH_3)_2$ in toluene; (c) H_2/Pd-C; (d) hexafluoropropene-diethylamine in $CHCl_3$; (e) $SOCl_2$ in $CHCl_3$; (f) $(CH_3)_2NH$ in CH_3CN.

the stereochemistry of the diastereoisomeric methyl groups is depicted as a relative configuration.

Some new piperazines used as the nucleophile were prepared as shown in Scheme IV. 1,4-Dibenzyl-2,2-dimethyl-3-oxopiperazine (**41**), derived from **40**, was reduced by sodium bis(2-methoxyethoxy)aluminum hydride to give deoxopiperazine **42**. 1,4-Dibenzyl-2-(hydroxymethyl)piperazine (**44**) was converted into the 2-fluoromethyl (**45**) and 2-chloromethyl (**46**) analogues by halogenation with Ishikawa's reagent (a hexafluoropropene/diethylamine complex)[16] and thionyl chloride, respectively. Treatment of **46** with dimethylamine gave **47**. The benzyl group of **42**, **44**, **45**, and **47** was removed by hydrogenolysis with palladium-on-carbon, giving the corresponding deprotected piperazines **43** and **48–50**. A racemate of 2-methylpiperazine was resolved into (*S*)-(+)- and (*R*)-(−)-2-methylpiperazines.

X-ray Crystallographic Study

Compound **36k** was subjected to single-crystal X-ray analysis with a view to knowing its solid-state conformation. The crystal structure was solved by standard methods.[17] The ORTEP drawing and streo view of the structure of **36k** are presented in Figures 1 and 2, respectively. The prominent structural features are as follows: (a) The *cis*-3,5-dimethylpiperazinyl ring is in a chair conformation and essentially perpendicular to the quinoline ring plane; the torsion angles of C(4)–C(3)–N(3)–C(14) and C(4)–C(3)–N(3)–C(17) are −72.3(7)° and 140.1(5)°, respectively. (b) The plane of the N-1 cyclopropyl ring is practically perpendicular to the quinoline ring plane. The torsion angles of C(9)–N(1)–C(11)–C(12) and C(9)–N(1)–C(11)–C(13) are −42.1(6)° and −111.3(5)°, respectively. (c) The oxo group [O(1)] forms intramolecular hydrogen bonds to both the carboxyl hydrogen [H(9), a length of 1.70(6) Å] and the amino hydrogen [H(8), a length of 1.94(5) Å]. These hydrogen bonds form each quasi-six-membered ring. (d) The F(1) atom deviates by 0.2340 Å from the plane of the benzene ring in contrast with the F(2) atom with a −0.0263-Å deviation. The torsion angles of F(1)–C(2)–C(3)–C(4) and F(2)–C(4)–C(3)–C(2) are 170.0(4)° and −179.0(4)°, respectively.

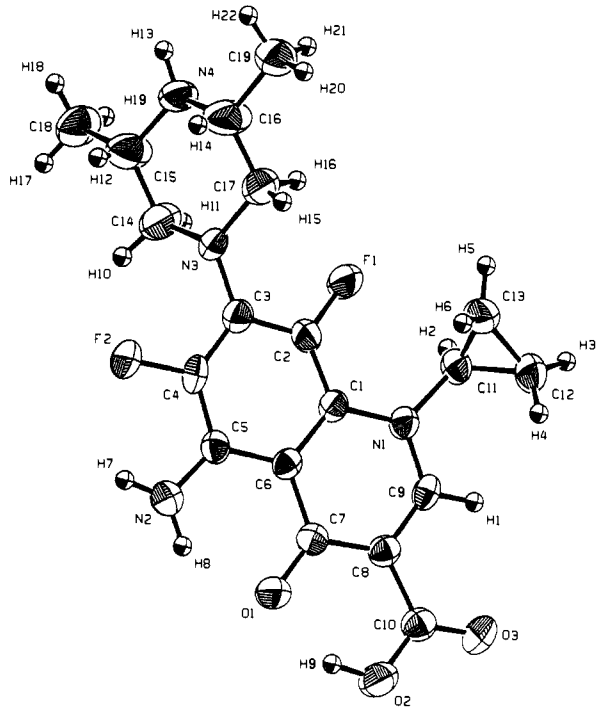


Figure 1. ORTEP drawing of the structure and solid-state conformation of **36k**.

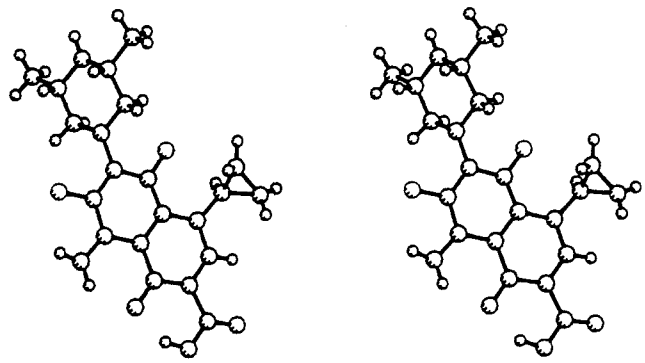


Figure 2. Stereoscopic drawing of **36k**.

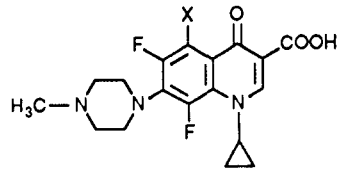
Biological Results and Discussion

A series of 7-(4-methyl-1-piperazinyl)quinolones **10–25** with the C-5 substituent were tested against a variety of organisms. Table I shows the data expressed as minimum inhibitory concentrations (MICs in μg/mL) against representatives of Gram-positive bacteria (*Staphylococcus aureus* 209P JC-1) and Gram-negative bacteria (*Escherichia coli* NIHJ JC-2 and *Pseudomonas aeruginosa* 12),

(16) Takaoka, A.; Iwakiri, H.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1267.

(17) The X-ray crystal structure analysis of **36k** was performed by Y. Kitano of Toray Research Center, Inc. The following library of crystallographic programs was used: DIRDIF, P. T. Beurskens, Crystallography Laboratory, Toernooiveld, Nijmegen, Netherlands (1984); EXSAN, Molecular Structure Corporation, The Woodlands, TX (1985); PLUTO, S. Motherwell, W. Clegg, University of Cambridge, England (1978); ORTEP-II, C. K. Johnson, Oak Ridge National Laboratory, Oak Ridge, TN (1976). Cromer, D. T. *International Tables for X-ray Crystallography*; The Kynoch Press: Birmingham, England, 1974; Vol. 4.

Table I. In Vitro Antibacterial Activity of 7-(4-Methyl-1-piperazinyl)quinolones with Variants at C-5



compd	X	min inhibitory concn,[a] μg/mL: *S. aureus* 209P JC-1	*E. coli* NIHJ JC-2	*P. aeruginosa* 12
4b	H	0.2	0.025	0.39
10	F	0.39	0.05	0.78
23	Cl	0.2	0.025	0.78
24	Br	0.39	0.05	0.78
20	HO	0.2	0.05	0.78
11	CH_3O	25	0.2	12.5
12	$PhCH_2O$	6.25	1.56	6.25
21	HS	3.13	0.39	12.5
13	CH_3S	3.13	0.2	12.5
14	$4\text{-}CH_3OC_6H_4CH_2S$	100	12.5	>100
22	H_2N	0.1	0.0125	0.2
15	CH_3NH	0.78	0.1	1.56
16	$(CH_3)_2N$	25	3.13	50
17	$PhCH_2NH$	0.78	0.78	3.13
18	$HOCH_2CH_2NH$	0.39	0.05	0.78
19	$(CH_3)_2NCH_2CH_2NH$	6.25	0.05	0.78
25	pyrrol-1-yl	3.13	0.39	12.5

[a] See the Experimental Section.

Table II. In Vitro Antibacterial Activity of 5- and 7-Substituted Quinolones[a]

compd	min inhibitory concn, μg/mL: *S. aureus* 209P JC-1	*E. coli* NIHJ JC-2	*P. aeruginosa* 12
33a	0.2	0.0125	0.39
33d	0.2	0.0125	0.78
33k	0.39	0.05	1.56
34a	0.1	0.0125	0.39
34d	0.1	0.0125	0.39
34k	0.2	0.025	0.78
35a	0.2	0.025	0.39
35d	0.2	0.025	0.78
35k	0.2	0.025	0.78
36a	0.05	0.0063	0.1
36c	0.2	0.05	0.78
36d	0.025	0.0063	0.2
36e	0.025	0.0063	0.1
36f	0.05	0.0125	0.2
36g	0.025	0.0125	0.78
36h	0.05	0.025	0.78
36i	0.05	0.0063	0.39
36j	0.78	0.39	3.13
36k	0.05	0.0125	0.39
36l	0.025	0.0125	0.78
36m	0.05	0.025	0.39
36n	0.05	0.025	0.2
36o	0.025	0.0063	0.2
36p	0.05	0.1	1.56

[a] See the Experimental Section.

including data for the C-5 hydrogen analogue **4b** for comparison. Variation of the C-5 substituent significantly influences the activity. Introduction of a halogen (**10**, **23**, and **24**) to the C-5 position tends to cause a slight decrease in activity when compared to that of **4b**. Conversion of the halogen to a hydroxy group (**20**) substantially retains the activity, whereas substitutions by methoxy (**11**), benzyloxy (**12**), mercapto (**21**), and methylthio (**13**) groups considerably decrease the overall activity. A bulky group as in **14** causes a remarkable loss of activity. Addition of an amino group to C-5 (giving **22**), however, results in a 2-fold increase in potency over compound **4b**. Alkylation of the C-5 amino group (giving compounds **15–19**) generally causes a considerable decrease in activity with an increase in size of the alkyl group; in particular, dialkylation (**16**) leads to a striking loss of activity. A significant loss of activity occurs when an aromatic pyrrole ring (**25**) is added to C-5. As a result, addition of an amino group to C-5 of **4b** led to 5-aminoquinolone **22**, which had the best in vitro antibacterial activity against Gram-positive and Gram-negative organisms tested.

In vitro antibacterial activity of the C-5 substituted quinolones with variants of the *N*-methylpiperazine at C-7 is given in Table II. From the data for the series **a** (1-piperazinyl), **d** (3-methyl-1-piperazinyl), and **k** (*cis*-3,5-dimethyl-1-piperazinyl) of **33** (F), **34** (Cl), **35** (OH), and **36** (NH_2), it follows that contribution of the C-5 substituent to activity increases in the order OH ≤ F ≤ Cl < NH_2, despite variation of the C-7 substituent. Thus, the C-5 amino function in the 6,8-difluoroquinolone series appended with the piperazinyl group at C-7 significantly enhances in vitro activity; this finding is consistent with the conclusion described by Domagala.[9a]

In order to further know an effect of varying the C-7 substitution on activity, a series of 5-aminoquinolones **36c–m** were tested where one to three methyl groups were inserted into different positions of the C-7 piperazine ring; the methyl groups are shown with a relative configuration except for (*S*)-**36e** and (*R*)-**36f**, and *meso*-**36k** is optically inactive. The activity fluctuates in a narrow range, depending on the attached site, number, and stereochemistry of the methyl group, with the exception of **36j**, whose activity considerably decreases. When compared to *N*-methylpiperazine **22** (see Table I), unsubstituted piperazine **36a**[9a] displays a 2-fold increase in activity against both Gram-positive and Gram-negative bacteria. A clear difference is observed between the positional isomers of the monomethyl racemic compounds (**36c** vs **36d**), thus the 3-methyl analogue **36d** is 4–8 times more active than the 2-methyl regioisomer **36c** against whole bacteria. An interest in an influence of the stereochemistry of this 3-methyl group on activity led us to prepare its enantiomers (*S*)-(−)-**36e** and (*R*)-(+)-**36f**. A comparison of their in vitro activities shows that the *S* isomer is 2 times more active than the *R* isomer and of almost equipotency to the racemate **36d**.

The presence of two methyl groups on the piperazine ring as in **36g–j** results in a significant overall decrease in activity, particularly against Gram-negative *E. coli* and *P. aeruginosa*, as compared to **36a**; 2,5-dimethyl compound **36j** is the least active in this series. The data for **36j**, coupled with those for **36c** (2-methyl) and **36g** (2,3-dimethyl), indicate that the methyl group at position 2, which is in close proximity to the quinolone nucleus, is deleterious to activity. Comparison of the stereoisomeric *cis*-**36k** and *trans*-**36l** shows that there is no substantial difference in their antibacterial activities. Insertion of an additional methyl group into the piperazinyl N-position of **36k** produces compound **36m**, which displays about the same activity as **36k**. Replacement of the methyl group of racemate **36d** by a fluoromethyl moiety, yielding compound **36o**, causes essentially no influence on activity; a hydroxymethyl group (**36n**) serves only to slightly decrease activity compared to that of **36d**, and a (dimethylamino)methyl group (**36p**) remarkably reduces activity versus Gram-negative *E. coli* and *P. aeruginosa*.

Table III summarizes the in vitro antibacterial activity of the selected quinolones against a wide range of organisms including four Gram-positive bacteria (*S. aureus* 50774, *Streptococcus epidermidis* 8, *Streptococcus pyogenes* A65, and *Streptococcus faecalis* 2473), six Gram-

negative bacteria (*E. coli* P-5101, *Klebsiella pneumoniae* 13, *Enterobacter cloacae* 963, *Serratia marcescens* S-9, *P. aeruginosa* IFO 3445, and *P. aeruginosa* 12), and one glucose nonfermenter (*Moraxella bovis* P-7101) and also their oral efficacy, expressed as a median effective dose (ED_{50}, mg/kg), on systemic infections due to *S. pyogenes* A65 and *P. aeruginosa* 12 in mice. The results for ciprofloxacin (CIP, **3**),[15] ofloxacin (OFL, **5**),[18] and the C-5 hydrogen compounds **4a**, **4b**, and **6** are provided for comparison.

The in vitro antibacterial screening results show that 5-aminoquinolones **22** and **36**, on the whole, have an excellent activity with a broad spectrum and compare very favorably with OFL and even with CIP, which is known as the most potent quinolone (in vitro) to date. Against Gram-negative bacteria, in general, the 5-aminoquinolones are essentially as active as CIP, but most notably show a 2–6-fold enhancement in in vitro activity against Gram-positive species except *S. pyogenes*.

In general, the 5-fluoro- (**33a,d**), chloro- (**34d**), and hydroxy- (**35d**) quinolones are inferior to the 5-aminoquinolones in in vitro as well as in vivo potency. The in vivo efficacy for most of the 5-aminoquinolones on the infection models reflects favorably their in vitro activity. The 5-aminoquinolones (**36d–f,k–m**) with the *C*-methylpiperazinyl group at C-7 are more effective in vivo than compounds (**22** and **36a**) with *N*-methylpiperazinyl or unsubstituted piperazinyl group, especially against the streptococcal infection. In particular, compounds **36d**, **36e**, **36k**, and **36m**, when administered orally, show greater potency than CIP as well as OFL; for example, compound **36k** with the highest potency against the streptococcal infection is 7 times more active than CIP, and compound **36e** with the greatest efficacy on the pseudomonal infection is 3 times more active than CIP. The racemate **36d** is essentially equipotent, in both in vitro and in vivo, to its *S* enantiomer **36e**. Comparison between the enantiomers (*S*)-**36e** and (*R*)-**36f** shows that the former is approximately 3 times more potent versus both streptococcal and pseudomonal infections. These differences in ED_{50} correspond virtually with the 4- and 2-fold differentials in MICs versus *S. pyogenes* and *P. aeruginosa*, respectively. A similar trend is observed when comparing *cis*-3,5-dimethyl compound **36k** with its trans isomer **36l**; thus the in vivo efficacy of cis isomer **36k** is 2–4 times greater than that of its trans isomer **36l**, while the in vitro activity of **36k** is equal to or twice higher than that of **36l**. Compound **36k** shows most notably an improved in vivo efficacy especially on the streptococcal infection, a better efficacy on which is hardly attainable with the current quinolones. Lipophilicity, expressed usually as partition coefficient (log *P*), is one of the important physicochemical properties with a potential influence on the pharmacokinetic behavior of agents. A log *P* value (*n*-octanol/phosphate buffer, pH 7.4 at 25 °C) for **36k** is −0.04, whereas that for the C-5 hydrogen counterpart **6** is −0.75; thus introduction of the amino group to C-5 results in a considerable increase in log *P* (by a difference of 0.71). Rather, the highly lipophilic property of **36k** may reflect on its excellent in vivo efficacy. In this connection, enantiomer **36l** has a log *P* value of −0.34, accordingly being less lipophilic than **36k**. This property accounts probably for the fact that **36l** is less efficacious in vivo than **36k** despite a similar in vitro potency. Overall, of these new 5-aminoquinolones, compound **36k** is the most potent member, exhibiting in vivo as well

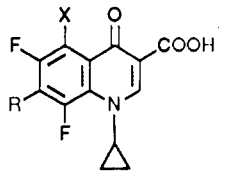
Table III. In Vitro Antibacterial Activity and Oral Efficacy on Systemic Infections in Mice

	min inhibitory concn,[a] μg/mL											ED_{50} po,[a] mg/kg	
compd	*S. aureus* 50774	*S. epidermidis* 8	*S. pyrogenes* A65	*S. faecalis* 2473	*E. coli* P-5101	*K. pneumoniae* 13	*E. cloacae* 963	*S. marcescence* S-9	*P. aeruginosa* IFO 3445	*P. aeruginosa* 12	*M. bovis* P-7101	*S. pyogenes* A65	*P. aeruginosa* 12
33a	0.39	0.2	3.13	3.13	0.0125	0.05	0.025	0.1	0.78	0.39	3.13	25	3.87
33d	0.2	0.2	1.56	3.13	0.0063	0.05	0.025	0.2	0.78	0.78	1.56	17.3	2.46
34d	0.1	0.1	0.78	0.78	0.0125	0.05	0.05	0.2	0.78	0.39	1.56		1.65
35d	0.2	0.1	0.78	1.56	0.025	0.1	0.05	0.1	0.78	0.78	1.56	12.5	5.97
22	0.05	0.05	0.39	0.78	0.0125	0.05	0.025	0.1	1.56	0.2	0.39	22.9	2.18
36a	0.05	0.05	0.2	0.39	0.0063	0.025	0.0125	0.05	0.39	0.1	0.39	170	1.56
36d	0.025	0.025	0.39	0.39	0.0063	0.0125	0.025	0.05	0.2	0.2	0.39	6.54	1.11
36e	0.025	0.025	0.2	0.39	0.0063	0.0125	0.0125	0.05	0.2	0.1	0.2	5.06	0.84
36f	0.025	0.05	0.78	0.78	0.0125	0.025	0.025	0.1	0.78	0.2	0.39	15.0	2.77
36k	0.05	0.05	0.39	0.78	0.0125	0.05	0.05	0.2	0.39	0.39	0.39	3.36	1.57
36l	0.025	0.0125	0.39	0.39	0.0125	0.1	0.1	0.39	0.78	0.78	0.78	7.38	6.33
36m	0.025	0.05	0.39	0.39	0.0125	0.1	0.05	0.2	0.78	0.39	0.78	5.64	2.21
36o	0.0125	0.0125	0.2	0.39	0.0063	0.025	0.025	0.1	0.39	0.2	0.39	17.4	7.02
4a	0.05	0.025	0.2	0.78	0.0031	0.0125	0.025	0.025	0.2	0.05	0.39	20.5	1.22
4b	0.1	0.1	0.39	0.78	0.0125	0.05	0.05	0.1	0.78	0.39	0.78	8.84	2.18
6	0.1	0.1	0.39	1.56	0.0063	0.05	0.05	0.2	0.39	0.39	0.78	8.64	1.41
CIP[b]	0.2	0.1	0.2	1.56	0.0063	0.025	0.0125	0.05	0.2	0.1	3.13	23.9	2.78
OFL[c]	0.2	0.2	0.39	1.56	0.05	0.1	0.1	0.2	1.56	0.78	1.56	10.8	6.62

[a] See the Experimental Section. [b] Ciprofloxacin (**3**). [c] Ofloxacin (**5**).

(18) Hayakawa, I.; Hiramitsu, T.; Tanaka, Y. *Chem. Pharm. Bull.* **1984**, *32*, 4907.

Table IV. 5,7-Disubstituted 1-Cyclopropyl-6,8-difluoro-4(1*H*)-oxoquinoline-3-carboxylic Acids



compd	X	R[a]	synth[b] method	% yield[c]	mp, °C	recryst solvent	formula[d]
11	CH_3O	4-Me-P	A	61	220–221	$CHCl_3$	$C_{19}H_{21}F_2N_3O_4 \cdot {}^7/_4H_2O$
12	$PhCH_2O$	4-Me-P	A	49	217–218	EtOH	$C_{25}H_{25}F_2N_3O_4$
13	CH_3S	4-Me-P	A	77	258–261	$CHCl_3$-EtOH	$C_{19}H_{21}F_2N_3O_3S \cdot {}^1/_4H_2O$
14	$4\text{-}CH_3OC_6H_4CH_2S$	4-Me-P	A	29	200–201	$CHCl_3$-EtOH	$C_{26}H_{27}F_2N_3O_4S$
15	CH_3NH	4-Me-P	A	53	235–236	$CHCl_3$-AcOEt	$C_{19}H_{22}F_2N_4O_3$
16[9a]	$(CH_3)_2N$	4-Me-P	A	79	238–239	$CHCl_3$-AcOEt	$C_{20}H_{24}F_2N_4O_3$
17	$PhCH_2NH$	4-Me-P	A	90	132–133	EtOH-Et_2O	$C_{25}H_{26}F_2N_4O_3$
18	$HOCH_2CH_2NH$	4-Me-P	A	30	167–169	*e*	$C_{20}H_{24}F_2N_4O_4$
19	$(CH_3)_2NCH_2CH_2NH$	4-Me-P	A	77	163–164	*f*	$C_{22}H_{29}F_2N_5O_3$
20[9a]	HO	4-Me-P	B	58	230–232	$CHCl_3$-EtOH	$C_{18}H_{19}F_2N_3O_4$
21	HS	4-Me-P	C	78	246–250 dec	$CHCl_3$-EtOH	$C_{18}H_{19}F_2N_3O_3S \cdot {}^3/_4H_2O$
22	H_2N	4-Me-P	B	87	254–255	$CHCl_3$-EtOH	$C_{18}H_{20}F_2N_4O_3$
23	Cl	4-Me-P	D	13	272–275 dec	EtOH	$C_{18}H_{18}ClF_2N_3O_3$
24	Br	4-Me-P	D	26	283–287 dec	$CHCl_3$-EtOH	$C_{18}H_{18}BrF_2N_3O_3$
25	pyrrol-1-yl	4-Me-P	E	53	250–252	$CHCl_3$-EtOH	$C_{22}H_{22}F_2N_4O_3$
30	Cl	F	F	95	205–207	EtOH	$C_{13}H_7ClF_3NO_3$
31	HO	F	F	92	218	$CHCl_3$-EtOH	$C_{13}H_8F_3NO_4$
32	H_2N	F	F	94	294–295	$CHCl_3$-EtOH	$C_{13}H_9F_3N_2O_3$
33d	F	3-Me-P	G	52	235–237	NH_4OH	$C_{18}H_{18}F_3N_3O_3 \cdot {}^1/_2H_2O$
33k	F	*cis*-3,5-Me_2-P	G	74	259–260	$CHCl_3$-EtOH	$C_{19}H_{20}F_3N_3O_3 \cdot {}^1/_2H_2O$
34a	Cl	P	G	27	261–263 dec	*g*	$C_{17}H_{16}ClF_2N_3O_3 \cdot {}^1/_2H_2O$
34d	Cl	3-Me-P	G	33	225–227	EtOH	$C_{18}H_{18}ClF_2N_3O_3 \cdot {}^3/_4H_2O$
34k	Cl	*cis*-3,5-Me_2-P	G	60	246–251 dec	*g*	$C_{19}H_{20}ClF_2N_3O_3 \cdot {}^3/_4H_2O$
35a	HO	P	G	36	259–262 dec	*g*	$C_{17}H_{17}F_2N_3O_4 \cdot H_2O$
35d	HO	3-Me-P	G	30	277–280 dec	$CHCl_3$-EtOH	$C_{18}H_{19}F_2N_3O_4 \cdot {}^3/_4H_2O$
35k	HO	*cis*-3,5-Me_2-P	G	85	287–291 dec	$CHCl_3$-EtOH	$C_{19}H_{21}F_2N_3O_4 \cdot {}^1/_4H_2O$
36a[9a]	H_2N	P	G	75	263–264	$CHCl_3$-EtOH	$C_{17}H_{18}F_2N_4O_3 \cdot {}^2/_5H_2O$
36b	H_2N	2-Me-4-EtOOC-P	G	53	220–225	$CHCl_3$-EtOH	$C_{21}H_{24}F_2N_4O_5$
36c	H_2N	2-Me-P	H	48	224–226	CH_3CN	$C_{18}H_{20}F_2N_4O_3$
36d	H_2N	3-Me-P	G	84	252–253	$CHCl_3$-EtOH	$C_{18}H_{20}F_2N_4O_3$
36e	H_2N	(*S*)-3-Me-P	G	33	252–253	$CHCl_3$-EtOH	$C_{18}H_{20}F_2N_4O_3$
36f	H_2N	(*R*)-3-Me-P	G	39	239–240	$CHCl_3$-EtOH	$C_{18}H_{20}F_2N_4O_3 \cdot {}^1/_2H_2O$
36g	H_2N	*cis*-2,3-Me_2-P	G	41	236–240	CH_3CN	$C_{19}H_{22}F_2N_4O_3$
36h	H_2N	3,3-Me_2-P	G	16	239–241	$CHCl_3$-EtOH	$C_{19}H_{22}F_2N_4O_3$
36i	H_2N	3,4-Me_2-P	G	51	232–234	$CHCl_3$-EtOH	$C_{19}H_{22}F_2N_4O_3$
36j	H_2N	*trans*-2,5-Me_2-P	G	3	235–238	AcOEt	$C_{19}H_{22}F_2N_4O_3 \cdot {}^1/_2H_2O$
36k	H_2N	*cis*-3,5-Me_2-P	G	63	266–269 dec	$CHCl_3$-EtOH	$C_{19}H_{22}F_2N_4O_3$
36l	H_2N	*trans*-3,5-Me_2-P	G	21	246–247	NH_4OH	$C_{19}H_{22}F_2N_4O_3 \cdot {}^1/_4H_2O$
36m	H_2N	*cis*-3,4,5-Me_3-P	I	35	230–231	NH_4OH	$C_{20}H_{24}F_2N_4O_3$
36n	H_2N	3-$HOCH_2$-P	G	59	257–258	NH_4OH	$C_{18}H_{20}F_2N_4O_4 \cdot {}^1/_4H_2O$
36o	H_2N	3-FCH_2-P	G	28	237–238	NH_4OH	$C_{18}H_{19}F_3N_4O_3$
36p	H_2N	3-Me_2NCH_2-P	G	43	192–195	$CHCl_3$-EtOH	$C_{20}H_{25}F_2N_5O_3 \cdot {}^5/_4H_2O$

[a] P stands for a piperazinyl group. [b] See the Experimental Section. [c] Yields are of the final product, if any, via a sequence of the reactions. [d] Analyses for C, H, Br, Cl, F, N, and S were within ±0.4% of the theoretical values. [e] Purified by washing with AcOEt. [f] Purified by washing with CH_3CN. [g] Purified by dissolving the solid in aqueous base, adjusting the pH to 7.2, and filtering the solid that precipitates.

as in vitro potency superior to those of CIP and OFL.

The selected compound **36k** was tested for the drug interactions. When compound **36k** was orally administered at a dose of 500 mg/kg to mice 10 min after a dosing of fenbufen (500 mg/kg, po), no convulsion was induced.[19c] Compound **36k**, moreover, exhibited no effects on the in vitro [^{3}H]GABA binding to rat synaptic plasma membranes and on population spikes in hippocampal slice in rat with or without 4-biphenylacetate, an active metabolite of fenbufen.[19c] On the other hand, when orally administered at a dose of 300 mg/kg to rats 2 h before and 2 and 6 h after a single oral dosing of theophylline (15 mg/kg), compound **36k** did not substantially affect theophylline in its plasma elimination half-life (4.5 h for 36k versus 3.8 h for the control), in contrast with enoxacin that prolonged the elimination half-life into 7.4 h.[19c] This particular compound **36k** at any rate did not induce convulsion in mice with or without fenbufen, nor increase plasma level of theophylline in rats. From limited available data, we cannot conclude definitely whether the planarity of the quinolone molecules (or the steric bulkiness of the C-7 piperazinyl group) takes share in the interaction. Further studies are currently in progress to define the SARs concerning to the drug interaction of these quinolones, espe-

(19) (a) Nakamura, S.; Minami, A.; Kojima, T.; Fujimoto, K.; Kurobe, N.; Kashimoto, S.; Ohue, T.; Kouno, K.; Hashimoto, M.; Shimizu, M. *28th Interscience Conference on Antimicrobial Agents and Chemotherapy*; Los Angles, CA, Oct. 23–26, 1987; Vol. 116, Abstract No. 1487. (b) Hashimoto, M.; Minami, A.; Nakata, K.; Sakaguchi, Y.; Kojima, T.; Fujimoto, K.; Yoshida, H.; Nakamura, S.; Ohnishi, K.; Shimizu, M. *Ibid.* Vol. 116, Abstract No. 1488. (c) Sekine, Y.; Matsunaga, Y.; Miyazaki, H.; Yamaguchi, T.; Mizuki, Y.; Itoh, T.; Kurobe, N.; Nakamura, S.; Hashimoto, M.; Shimizu, M. *Ibid.* Vol. 116, Abstract No. 1489. (d) Nakamura, S.; Minami, A.; Nakata, K.; Kurobe, N.; Kouno, K.; Sakaguchi, Y.; Kashimoto, S.; Yoshida, H.; Kojima, T.; Ohue, T.; Fujimoto, K.; Nakamura, M.; Hashimoto, M.; Shimizu, M. *Antimicrob. Agents Chemother.* **1989**, *33*, 1167.

cially in association with the conformation of their C-7 substituents.

In summary, a C-5 amino group in the 1-cyclopropyl-6,8-difluoroquinolone derivatives serves to enhance in vitro activity, especially against Gram-positive bacteria. A C-7 piperazine appended with a C-methyl group favorably contributes to improving in vivo efficacy, in particular, on the streptococcal infection. A combination of the C-5 amino group and the C-7 3,5-dimethylpiperazinyl appendage conferred the best overall antibacterial properties with lack of the adverse drug interaction. Therefore, compound **36k** [named sparfloxacin, orginally AT-4140, 5-amino-1-cyclopropyl-6,8-difluoro-7-(*cis*-3,5-dimethyl-1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic acid] was finally selected, followed by the extensive biological evaluation,[19] and is presently under clinical studies.

Experimental Section

Chemistry. All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Jasco A-201 spectrometer (KBr tablet). ^{1}H NMR spectra were taken at 80 MHz with a Varian FT-80A spectrometer. Chemical shifts are expressed in ppm (δ) with tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard. ^{19}F NMR spectra were measured at 282 MHz with a Varian XL-300 spectrometer; chemical shifts are expressed in ppm (δ) with hexafluorobenzene (δ = -162.9) as an internal standard. Mass spectra were recorded on a JEOL JMSD-300 spectrometer. The spectral data were obtained on all compounds and were consistent with assigned structure. Optical rotations were measured at 589 nm with a Jasco DIP-4 digital polarimeter. All compounds were analyzed for C, H, Br, Cl, F, N, and S and the analytical results were within ±0.4% of the theoretical values.

Piperazine, 2-methyl-, *N*-methyl-, *trans*-2,5-dimethyl-, and *cis*-2,6-dimethylpiperazines were obtained from commercial suppliers and used without further purification. 1-(Ethoxycarbonyl)-3-methyl-, 1,2-dimethyl-, *cis*-2,3-dimethyl-, and *trans*-2,6-dimethylpiperazines were prepared by literature methods.[20-22]

2,2-Dimethyl-, 2-(hydroxymethyl)-, 2-(fluoromethyl)-, and 2-[(dimethylamino)methyl]piperazines (**43**, **48–50**) were prepared by hydrogenation of the corresponding 1,4-dibenzyl derivatives (**42**, **44**, **45**, **47**) and used in the reactions without purification (Scheme IV).

1,4-Dibenzyl-2,2-dimethylpiperazine (42). 2,2-Dimethyl-3-oxopiperazine (**40**,[23] 31.6 g, 0.247 mol) was dissolved in 210 mL of DMF. To the solution were added 20.7 g (0.518 mol) of sodium hydride (60% dispersion in mineral oil) and 60 mL (0.518 mol) of benzyl chloride under ice cooling. The reaction mixture was heated at 80 °C for 10 min and concentrated to dryness under reduced pressure. The residue was chromatographed on silica gel with *n*-hexane–AcOEt (2:1) and purified by recrystallization from ether–*n*-hexane to give 10.1 g (13%) of 1,4-dibenzyl-2,2-dimethyl-3-oxopiperazine (**41**): mp 82–83 °C; IR 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28, 7.26 (2 s, 10 H, *Ph*), 4.54 (s, 2 H, CH_2Ph), 3.57 (s, 2 H, CH_2Ph), 3.07 (t, 2 H, J = 5 Hz, piperazine CH_2N), 2.60 (t, 2 H, J = 5 Hz, piperazine CH_2N), 1.49 (s, 6 H, CH_3); MS m/z 308 (M^+), 91 (base).

To a solution of sodium bis(2-methoxyethoxy)aluminum hydride (10 mL of 70% solution in toluene, 40 mmol) in 15 mL of toluene was added 3.1 g (10.1 mmol) of **41**. The reaction mixture was heated at 100 °C for 1 h. The excess reagent was decomposed with water under ice cooling. To the solution was added 10% NaOH and the organic layer was separated, dried, and concentrated to give 2.95 g (100%) of **42** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.27 (s, 10 H, *Ph*), 3.48 (s, 2 H, CH_2Ph), 3.41 (s, 2 H, CH_2Ph), 2.40 (s, 4 H, piperazine CH_2CH_2), 2.21 (s, 2 H, piperazine CH_2N), 1.12 (s, 6 H, CH_3); MS m/z 294 (M^+), 91 (base).

1,4-Dibenzyl-2-(fluoromethyl)piperazine (45). A mixture of 1,4-dibenzyl-2-(hydroxymethyl)piperazine (**44**,[24] 5.0 g, 17.2 mmol) and hexafluoropropene–diethylamine[16] (7.7 g, 34.5 mmol) in 50 mL of $CHCl_3$ was heated under reflux for 0.5 h. The reaction mixture was extracted with 10% HCl. The aqueous layer was neutralized and extracted with AcOEt. The organic layer was dried and concentrated to leave a crude product, which was chromatographed on silica gel with $CHCl_3$ to give 3.5 g (68%) of **45** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.28 (s, 10 H, *Ph*), 4.90, 4.30 (2 m, 1 H, piperazine C*H*N), 3.72 (dd, 2 H, J = 42 and 14 Hz, CH_2F), 3.49 (s, 4 H, CH_2Ph), 2.80–2.20 (m, 6 H, piperazine CH_2N); MS m/z 298 (M^+), 265 ($M^+ - CH_2F$), 91 (base).

1,4-Dibenzyl-2-[(dimethylamino)methyl]piperazine (47). A mixture of **44** (7.0 g, 23.6 mmol) and thionyl chloride (7.0 g, 58.8 mmol) in 70 mL of $CHCl_3$ was heated under reflux for 1 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$. The organic layer was dried and concentrated to leave a crude product (**46**). This was dissolved in 50 mL of CH_3CN. To this solution were added dimethylamine hydrochloride (9.6 g, 0.12 mol) and $NaHCO_3$ (10 g, 0.12 mol). The reaction mixture was heated under reflux for 1.5 h and concentrated to dryness under reduced pressure. The residue was extracted with $CHCl_3$. The organic layer was dried and concentrated to leave a crude product, which was chromatographed with $CHCl_3$ to give 5.8 g (76%) of **47** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.28 (s, 10 H, *Ph*), 3.73 (dd, 2 H, J = 20 and 13 Hz, CH_2Ph), 2.87–2.10 (m, 11 H, piperazine C*H*N, CH_2N, and $CH_2N(CH_3)_2$), 2.19 (s, 6 H, CH_3); MS m/z 265 ($M^+ - CH_2N(CH_3)_2$), 91 (base).

(*S*)-(+)-2-Methylpiperazine.[25] (±)-2-Methylpiperazine (16.7 g, 0.167 mol) and D-(−)-tartaric acid (25 g, 0.167 mol) were dissolved in 80 mL of water. To this solution was added 40 mL of EtOH. After ice cooling, the resulting precipitates were collected and recrystallized from water three times to give 11.8 g of (*S*)-(+)-2-methylpiperazinium D-(−)-tartarate salt: $[\alpha]^{25}D$ −25.3° (*c* 1.0, water). A mixture of this salt and 22.8 g (0.118 mol) of NaOMe (28% solution in MeOH) in 100 mL of MeOH was heated under reflux for 2 h. The reaction mixture was concentrated and the residue was taken up in ether. After concentration, the crude product was purified by distillation to give 4.6 g (27%) of (*S*)-(+)-2-methylpiperazine: $[\alpha]^{30}_D$ +6.5° (*c* 1.0, EtOH).

(*R*)-(−)-2-Methylpiperazine.[25] According to the same procedure described above, (±)-2-methylpiperazine (33.4 g, 0.334 mol) and L-(+)-tartaric acid (50 g, 0.334 mol) gave 29.4 g of (*R*)-(−)-2-methylpiperazinium L-(+)-tartarate salt: $[\alpha]^{25}_D$ +23.2° (*c* 1.0, water). This salt gave 14.1 g (42%) of (*R*)-(−)-2-methylpiperazine: $[\alpha]^{30}_D$ −8.2° (*c* 0.8, EtOH).

1-Cyclopropyl-6,8-difluoro-7-(*cis*-3,5-dimethyl-1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic Acid (6). A mixture of 1-cyclopropyl-6,7,8-trifluoro-4(1*H*)-oxoquinoline-3-carboxylic acid[15] (3.0 g, 10.6 mmol) and 2.5 g (21.9 mmol) of *cis*-2,6-dimethylpiperazine in 30 mL of pyridine was heated at 120 °C for 1 h. The reaction mixture was concentrated to dryness under reduced pressure. The residue was crystallized with EtOH and recrystallized from $CHCl_3$–EtOH to give 2.3 g (58%) of **6**: mp 243–244 °C (lit.[26b] mp 250–251 °C; lit.[26a] hydrochloride salt mp 310–315 °C. In the both literatures the relative stereochemistry of two methyl groups is not given.); IR 1650, 1620 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.65 (s, 1 H, 2-*H*), 7.78 (dd, 1 H, J = 13 and 2 Hz, 5-*H*), 4.10 (m, 1 H, cyclopropyl C*H*), 3.43–2.63 (m, 6 H, piperazine NC*H*CH_2N), 1.30–0.84 (m, 4 H, CH_2CH_2), 0.98 (d, 6 H, J = 6 Hz, CH_3).

The preparation of compounds **8**,[14] **9**,[14] **10**,[5b] and **36a** were reported in the previous paper.[1]

5,7-Disubstituted 1-Cyclopropyl-6,8-difluoro-4(1*H*)-oxoquinoline-3-carboxylic Acids (11–25 and 30–36) and Esters

(20) Beck, K. M.; Hamlin, K. E.; Weston, A. W. *J. Am. Chem. Soc.* **1952**, *74*, 605.
(21) Ishiguro, T.; Matsumura, M. *Yakugaku Zasshi* **1958**, *78*, 229.
(22) Cignarella, G.; Gallo, G. G. *J. Heterocycl. Chem.* **1974**, *11*, 985.
(23) Aspinall, S. R. *J. Am. Chem. Soc.* **1940**, *62*, 1202.
(24) Jucker, E.; Rissi, E. *Helv. Chim. Acta* **1962**, *45*, 2383.
(25) (a) Armarego, W. L. F.; Schou, H.; Waring, P. *J. Chem. Res. (S)* **1980**, 133. (b) Toda, F.; Tanaka, K.; Kido, M. *Chem. Lett.* **1988**, 513.
(26) (a) Grohe, K.; Petersen, U.; Zeiler, H. J.; Metzger, K. Ger. Offen. DE 3318145, 1983; *Chem. Abstr.* **1985**, *102*, 78744*q*. (b) Irikura, T.; Suzue, S.; Hirai, K.; Ishizaki, T. Eur. Patent EP 178388, 1986; *Chem. Abstr.* **1986**, *105*, 57853*w*.

26–29. Method A. 1-Cyclopropyl-6,8-difluoro-5-methoxy-7-(4-methyl-1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic Acid (11). A mixture containing 0.4 g (1.05 mmol) of 1-cyclopropyl-5,6,8-trifluoro-7-(4-methyl-1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic acid (**10**)[1] and 2.3 g (11.9 mmol) of NaOMe (28% solution in MeOH) in 4 mL of CH_3CN was stirred at room temperature for 10 min. After concentration of the reaction mixture under reduced pressure, the residue was diluted with water. The solution was neutralized and extracted with $CHCl_3$. The organic layer was dried and concentrated to dryness under reduced pressure to afford a solid, and the residue was diluted with water. The solution was neutralized and extracted with $CHCl_3$. The organic layer was dried and concentrated to dryness to afford a solid, which was recrystallized from $CHCl_3$ to give 0.25 g (61%) of **11**: IR 1720, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.73 (s, 1 H, 2-*H*), 3.97 (s, 4 H, OCH_3 and cyclopropyl C*H*), 3.45 (m, 4 H, piperazine CH_2N), 2.57 (m, 4 H, piperazine CH_2N), 2.37 (s, 3 H, NCH_3), 1.15 (m, 4 H, CH_2CH_2).

According to method A, compounds **12–19** were prepared from **10**. Nucleophiles and spectral data are given below.

Compound **12**: benzyl alcohol and sodium hydride; IR 1720, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.73 (s, 1 H, 2-*H*), 7.70–7.30 (m, 5 H, *Ph*), 5.08 (s, 2 H, OCH_2), 4.00 (m, 1 H, cyclopropyl C*H*), 3.40 (m, 4 H, piperazine CH_2N), 2.55 (m, 4 H, piperazine CH_2N), 2.37 (s, 3 H, NCH_3), 1.17 (m, 4 H, CH_2CH_2).

Compound **13**: NaSMe (15% solution in water); IR 1710, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.72 (s, 1 H, 2-*H*), 4.00 (m, 1 H, cyclopropyl C*H*), 3.45 (m, 4 H, piperazine CH_2N), 2.60 (m, 7 H, SCH_3 and piperazine CH_2N), 2.40 (s, 3 H, NCH_3), 1.20 (m, 4 H, CH_2CH_2).

Compound **14**: 4-methoxybenzyl mercaptan; IR 1720, 1610, cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.59 (s, 1 H, 2-*H*), 7.15 (d, 2 H, J = 9 Hz, aromatic), 6.78 (d, 2 H, J = 9 Hz, aromatic), 4.14 (d, 2 H, J = 2 Hz, SCH_2), 4.00 (m, 1 H, cyclopropyl C*H*), 3.70 (s, 3 H, OCH_3), 3.25 (m, 4 H, piperazine CH_2N), 2.49 (m, 4 H, piperazine CH_2N), 2.25 (s, 3 H, NCH_3), 1.10 (m, 4 H, CH_2CH_2).

Compound **15**: methylamine (40% solution in water); IR 3250, 1720, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.10 (br s, 1 H, N*H*), 8.60 (s, 1 H, 2-*H*), 3.95 (m, 1 H, cyclopropyl C*H*), 3.40 (m, 4 H, piperazine CH_2N), 3.11 (dd, 3 H, J = 9 and 6 Hz, $NHCH_3$), 2.56 (m, 4 H, piperazine CH_2N), 2.37 (s, 3 H, NCH_3), 1.13 (m, 4 H, CH_2CH_2).

Compound **16**:[9a] dimethylamine hydrochloride and $NaHCO_3$; IR 1720, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 15.34 (s, 1 H, COO*H*), 8.66 (s, 1 H, 2-*H*), 3.98 (m, 1 H, cyclopropyl C*H*), 3.42 (m, 4 H, piperazine CH_2N), 2.95 (d, 6 H, J = 3 Hz, $N(CH_3)_2$), 2.56 (m, 4 H, piperazine CH_2N), 2.37 (s, 3 H, NCH_3), 1.24 (m, 4 H, CH_2CH_2).

Compound **17**: benzylamine; IR 3250, 1720, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.57 (br, 1 H, N*H*), 8.63 (s, 1 H, 2-*H*), 7.30 (s, 5 H, *Ph*), 4.62 (dd, 2 H, J = 7 and 4 Hz, CH_2Ph), 3.90 (m, 1 H, cyclopropyl C*H*), 3.35 (m, 4 H, piperazine CH_2N), 2.51 (m, 4 H, piperazine CH_2N), 2.35 (s, 3 H, NCH_3), 1.13 (m, 4 H, CH_2CH_2).

Compound **18**: ethanolamine; IR 3220, 2980, 1720, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.10 (br, 1 H, N*H*), 8.62 (s, 1 H, 2-*H*), 4.00–3.50 (m, 5 H, NCH_2CH_2O and cyclopropyl C*H*), 3.40 (m, 4 H, piperazine CH_2N), 2.55 (m, 4 H, piperazine CH_2N), 2.27 (s, 3 H, NCH_3), 1.15 (m, 4 H, CH_2CH_2).

Compound **19**: *N*,*N*-dimethylethylenediamine; IR 3250, 1720, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.17 (br, 1 H, N*H*), 8.62 (s, 1 H, 2-*H*), 3.86 (m, 1 H, cyclopropyl C*H*), 3.60–3.25 (m, 6 H, CH_2N and piperazine CH_2N), 2.53 (m, 6 H, CH_2N and piperazine CH_2N), 2.36 (s, 3 H, NCH_3), 2.30 (s, 6 H, $N(CH_3)_2$), 1.10 (m, 4 H, CH_2CH_2).

Method B. 1-Cyclopropyl-6,8-difluoro-5-hydroxy-7-(4-methyl-1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic Acid (20). A mixture containing 0.3 g (0.64 mmol) of **10** and 0.03 g of 5% Pd/C in 30 mL of dioxane was hydrogenated at 50–55 °C until the required volume of H_2 had been taken up. The reaction mixture was filtered to remove the catalyst. The filtrate was concentrated under reduced pressure to leave precipitates, which were recrystallized from $CHCl_3$–EtOH to give 0.14 g (58%) of **20**: IR 1735, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.71 (s, 1 H, 2-*H*), 3.97 (m, 1 H, cyclopropyl C*H*), 3.45 (m, 4 H, piperazine CH_2N), 2.56 (m, 4 H, piperazine CH_2N), 2.37 (s, 3 H, NCH_3), 1.22 (m, 4 H, CH_2CH_2).

According to method G, compound **20** was alternatively prepared from **31** with *N*-methylpiperazine in 29% yield. This was identical in all respects with an authentic specimen of **20**.

Method C. 1-Cyclopropyl-6,8-difluoro-5-mercapto-7-(4-methyl-1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic Acid (21). A mixture containing 2.85 g (5.5 mmol) of **14**, 3 mL of anisole, and 15 mL of trifluoroacetic acid was stirred at room temperature for 23 h. After concentration of the reaction mixture under reduced pressure, the residue was taken up in water. The solution was neutralized with aqueous ammonia and extracted with $CHCl_3$. The organic layer was dried and concentrated to dryness to afford a crude product, which was recrystallized from $CHCl_3$–EtOH to give 1.7 g (78%) of **21**: IR 2550, 1720, 1610 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 8.70 (s, 1 H, 2-*H*), 5.50 (s, 1 H, S*H*), 4.00 (m, 1 H, cyclopropyl C*H*), 3.43 (m, 4 H, piperazine CH_2N), 2.58 (m, 4 H, piperazine CH_2N), 2.39 (s, 3 H, NCH_3), 1.21 (m, 4 H, CH_2CH_2).

5-Amino-1-cyclopropyl-6,8-difluoro-7-(4-methyl-1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic Acid (22).[9a] According to method B, compound **22** was prepared from **17**: IR 3450, 3320, 1705, 1635 cm^{-1}; ^1H NMR (DMSO-d_6) δ 14.53 (br, 1 H, COO*H*), 8.50 (s, 1 H, 2-*H*), 7.22 (br s, 2 H, NH_2), 4.01 (m, 1 H, cyclopropyl C*H*), 3.28 (m, 4 H, piperazine CH_2N), 2.25 (s, 3 H, NCH_3), 1.12 (m, 4 H, CH_2CH_2).

According to method G, compound **22** was alternatively prepared from **32** with *N*-methylpiperazine in 79% yield. This was identical in all respects with an authentic specimen of **22**.

Method D. 5-Chloro-1-cyclopropyl-6,8-difluoro-7-(4-methyl-1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic Acid (23). To a suspension of **22** (3.0 g, 7.94 mmol) in 30 mL of 20% HCl was added 0.66 g (9.57 mmol) of $NaNO_2$ under ice cooling. After stirring for 5 min, the reaction mixture was added to a solution of CuCl (1.18 g, 11.9 mmol) in 15 mL of 20% HCl. The reaction mixture was stirred at room temperature for 1 h. After neutralization with 20% NaOH, the solution was extracted with $CHCl_3$. The organic layer was dried and concentrated to dryness to leave a crude product, which was chromatographed on silica gel with 5% MeOH–$CHCl_3$, followed by recrystallization from EtOH to give 0.4 g (13%) of **23**: IR 1720, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.72 (s, 1 H, 2-*H*), 3.98 (m, 1 H, cyclopropyl C*H*), 3.43 (m, 4 H, piperazine CH_2N), 2.57 (m, 4 H, piperazine CH_2N), 2.37 (s, 3 H, NCH_3), 1.20 (m, 4 H, CH_2CH_2).

According to method D, compound **24** was prepared from the reaction of **22** with $NaNO_2$ and CuBr in 20% HBr: IR 1720, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.72 (s, 1 H, 2-*H*), 3.99 (m, 1 H, cyclopropyl C*H*), 3.44 (m, 4 H, piperazine CH_2N), 2.57 (m, 4 H, piperazine CH_2N), 2.37 (s, 3 H, NCH_3), 1.20 (m, 4 H, CH_2CH_2).

Method E. 1-Cyclopropyl-6,8-difluoro-7-(4-methyl-1-piperazinyl)-5-(pyrrol-1-yl)-4(1*H*)-oxoquinoline-3-carboxylic Acid (25). A mixture containing 1.0 g (2.65 mmol) of **22** and 0.51 g (3.86 mmol) of 2,5-dimethoxytetrahydrofuran in 10 mL of acetic acid was heated at 90–100 °C for 0.5 h. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was diluted with water, neutralized with 10% NaOH, and extracted with $CHCl_3$. The organic layer was dried and concentrated to afford precipitates, which were recrystallized from $CHCl_3$–EtOH to give 0.6 g (53%) of **25**: IR 1720, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.75 (s, 1 H, 2-*H*), 6.68 (m, 2 H, pyrrole C*H*), 6.38 (t, 2 H, J = 2 Hz, pyrrole C*H*), 4.03 (m, 1 H, cyclopropyl C*H*), 3.46 (m, 4 H, piperazine CH_2N), 2.55 (m, 4 H, piperazine CH_2N), 2.37 (s, 3 H, NCH_3), 1.22 (m, 4 H, CH_2CH_2).

Ethyl 5-(Benzyloxy)-1-cyclopropyl-6,7,8-trifluoro-4-(1*H*)-oxoquinoline-3-carboxylate (26). To a suspension of ethyl 1-cyclopropyl-5,6,7,8-tetrafluoro-4(1*H*)-oxoquinoline-3-carboxylate (**8**, 4.0 g, 12.1 mmol) and 1.3 g (12.1 mmol) of benzyl alcohol in 40 mL of toluene was added 0.5 g (12.5 mmol) of sodium hydride (60% dispersion in mineral oil) under ice cooling. The reaction mixture was heated at 70 °C for 1 h and filtered through Celite. The filtrate was concentrated to dryness and chromatographed on silica gel with 50% AcOEt–*n*-hexane to give two products. The major one was recrystallized from EtOH to give 1.9 g (38%) of **26**: IR 1690, 1645, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.41 (s, 1 H, 2-*H*), 7.65–7.20 (m, 5 H, *Ph*), 5, 20 (s, 2 H, CH_2Ph), 4.37 (q, 2 H, J = 7 Hz, CH_2CH_3), 3.83 (m, 1 H, cyclopropyl C*H*), 1.38 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.14 (m, 4 H, CH_2CH_2); ^{19}F NMR (DMSO-d_6) δ −146.50 (dd, J_{7-8} = 21.5 Hz and $J_{8\text{-cyclopropyl CH}}$ = 5.5 Hz, 8-*F*), −153.22 (dd, J_{7-8} = 21.5 Hz and J_{6-7} = 23.6 Hz, 7-*F*), −155.84 (d, J_{6-7} = 23.6 Hz, 6-*F*).

The minor product was also recrystallized from EtOH to give 0.2 g (4%) of benzyl 5-(benzyloxy)-1-cyclopropyl-6,7,8-trifluoro-4(1*H*)-oxoquinoline-3-carboxylate: mp 143–146 °C; IR 1690, 1640, 1618 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.43 (s, 1 H, 2-*H*), 7.67–7.20 (m, 10 H, *Ph*), 5.38 (s, 2 H, CH_2Ph), 5.21 (s, 2 H, CH_2Ph), 3.82 (m, 1 H, cyclopropyl C*H*), 1.13 (m, 4 H, CH_2CH_2). Anal. Calcd for $C_{27}H_{20}F_3NO_4$: C, 67.64; H, 4.20; N, 2.92; F, 11.89. Found: C, 67.47; H, 4.24; N, 2.95; F, 11.91.

Ethyl 5-(Benzylamino)-1-cyclopropyl-6,7,8-trifluoro-4-(1*H*)-oxoquinoline-3-carboxylate (27). A mixture containing 1.0 g (3.04 mmol) of **8**, 0.35 g (3.27 mmol) of benzylamine, and 0.92 g (9.11 mmol) of triethylamine in 20 mL of toluene was heated under reflux for 1 h. The reaction mixture was concentrated to dryness under reduced pressure. The residue was crystallized with AcOEt and recrystallized from EtOH to give 1.0 g (79%) of **27**: IR 1723, 1690, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.70 (br, 1 H, N*H*), 8.37 (s, 1 H, 2-*H*), 7.25 (m, 5 H, *Ph*), 4.63 (dd, 2 H, *J* = 7 and 4 Hz, CH_2Ph), 4.35 (q, 2 H, *J* = 7 Hz, CH_2CH_3), 3.81 (m, 1 H, cyclopropyl C*H*), 1.38 (t, 3 H, *J* = 7 Hz, CH_2CH_3), 1.12 (m, 4 H, CH_2CH_2); ^{19}F NMR ($CDCl_3$) δ −152.35 (dd, J_{7-8} = 21.9 Hz and J_{6-7} = 21.0 Hz, 7-*F*), −159.93 (m, J_{6-7} = 21.0 Hz and J_{6-8} = 5.5 Hz, 6-*F*), −162.74 (m, J_{7-8} = 21.9 Hz and J_{6-8} = 5.5 Hz, 8-*F*).

Ethyl 5-Amino-1-cyclopropyl-6,7,8-trifluoro-4(1*H*)-oxoquinoline-3-carboxylate (28). A mixture containing 1.6 g (3.85 mmol) of **27** and 0.16 g of 5% Pd/C in 8 mL of acetic acid and 8 mL of EtOH was hydrogenated at room temperature until the required volume of H_2 had been taken up. The solids were collected by filtration and taken up in $CHCl_3$. After the catalyst was filtered off, the filtrate was concentrated to leave precipitates, which were recrystallized from $CHCl_3$–EtOH to give 1.0 g (80%) of **28**: IR 3420, 3270, 1675, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.40 (s, 1 H, 2-*H*), 6.90 (br s, 2 H, NH_2), 4.37 (q, 2 H, *J* = 7 Hz, CH_2CH_3), 3.82 (m, 1 H, cyclopropyl C*H*), 1.40 (t, 3 H, *J* = 7 Hz, CH_2CH_3), 1.15 (m, 4 H, CH_2CH_2).

Ethyl 5-Chloro-1-cyclopropyl-6,7,8-trifluoro-4(1*H*)-oxoquinoline-3-carboxylate (29). A mixture containing 2.4 g (23.3 mmol) of *tert*-butyl nitrite and 2.6 g (19.3 mmol) of $CuCl_2$ in 50 mL of CH_3CN was heated at 70 °C. To the solution was added 5.0 g (15.3 mmol) of **28** over a 5-min period. The reaction mixture was heated at 60–70 °C for 1.5 h and poured into 50 mL of 20% HCl. After dilution with water, the solution was extracted with $CHCl_3$. The organic layer was dried and concentrated to leave a crude product, which was recrystallized from AcOEt to give 0.5 g (10%) of **29**: IR 1730, 1638, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.45 (s, 1 H, 2-*H*), 4.37 (q, 2 H, *J* = 7 Hz, CH_2CH_3), 3.87 (m, 1 H, cyclopropyl C*H*), 1.38 (t, 3 H, *J* = 7 Hz, CH_2CH_3), 1.18 (m, 4 H, CH_2CH_2).

Method F. 5-Chloro-1-cyclopropyl-6,7,8-trifluoro-4-(1*H*)-oxoquinoline-3-carboxylic Acid (30). A mixture of **29** (1.6 g, 4.63 mmol) and 20 mL of acetic acid–water–concentrated H_2SO_4 (8:6:1) was heated at 100 °C for 10 min, and poured into ice–water. The resulting precipitates were collected by filtration, washed with water, and recrystallized from EtOH to give 1.4 g (95%) of **30**: IR 1717, 1605 cm^{-1}; ^1H NMR (DMSO-d_6) δ 14.18 (s, 1 H, COO*H*), 8.70 (s, 1 H, 2-*H*), 4.13 (m, 1 H, cyclopropyl C*H*), 1.18 (m, 4 H, CH_2CH_2).

According to method F, compounds **31** and **32** were prepared from **26** and **28**, respectively.

Compound **31**: IR 3060, 1733, 1622 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.15 (br s, 1 H, O*H*), 12.93 (s, 1 H, COO*H*), 8.81 (s, 1 H, 2-*H*), 4.00 (m, 1 H, cyclopropyl C*H*), 1.30 (m, 4 H, CH_2CH_2).

Compound **32**: IR 3430, 3310, 1705, 1640 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.55 (s, 1 H, 2-*H*), 7.68 (br s, 2 H, NH_2), 4.04 (m, 1 H, cyclopropyl C*H*), 1.18 (m, 4 H, CH_2CH_2). This compound **32** was alternatively prepared from **27** in 96% yield.

Method G. 1-Cyclopropyl-5,6,8-trifluoro-7-(3-methyl-1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic Acid (33d). A mixture of 1-cyclopropyl-5,6,7,8-tetrafluoro-4(1*H*)-oxoquinoline-3-carboxylic acid (**9**,[1] 0.91 g, 3.02 mmol) and 0.32 g (3.2 mmol) of 2-methylpiperazine in 10 mL of pyridine was heated at 80 °C for 40 min. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water and extracted with $CHCl_3$. The organic layer was dried and concentrated to leave a crude product, which was recrystallized from aqueous ammonia to give 0.8 g (70%) of **33d**: IR 2450, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.73 (s, 1 H, 2-*H*), 3.97 (m, 1 H, cyclopropyl C*H*), 3.50–2.90 (m, 7 H, piperazine C*H*N and CH_2N), 1.35–1.00 (m, 7 H, CH_2CH_2 and CH_3).

According to method G, compounds **33k**, **34a,d,k**, **35a,d,k**, and **36a,b,d–l,n–p** were prepared. Starting materials and spectral data are given below.

Compound **33k**: **9** and *cis*-2,6-dimethylpiperazine; IR 2450, 1630 cm^{-1}; ^1H NMR (CD_3COOD) δ 8.86 (s, 1 H, 2-*H*), 4.10 (m, 1 H, cyclopropyl C*H*), 3.63 (m, 6 H, piperazine C*H*N and CH_2N), 1.50–1.08 (m, 10 H, CH_2CH_2 and CH_3).

Compound **34a**: **30** and piperazine; IR 3450, 2400, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.65 (s, 1 H, 2-*H*), 4.13 (m, 1 H, cyclopropyl C*H*), 3.65–2.70 (m, 8 H, piperazine CH_2N), 1.13 (m, 4 H, CH_2CH_2).

Compound **34d**: **30** and 2-methylpiperazine; IR 2430, 1626 cm^{-1}; ^1H NMR (CD_3COOD) δ 8.85 (s, 1 H, 2-*H*), 4.13 (m, 1 H, cyclopropyl C*H*), 3.63 (m, 7 H, piperazine C*H*N and CH_2N), 1.55–1.00 (m, 7 H, CH_2CH_2 and CH_3).

Compound **34k**: **30** and *cis*-2,6-dimethylpiperazine: IR 3400, 2430, 1635 cm^{-1}; ^1H NMR (CD_3COOD) δ 8.89 (s, 1 H, 2-*H*), 4.15 (m, 1 H, cyclopropyl C*H*), 3.62 (m, 6 H, piperazine NC*H*CH_2N), 1.30 (m, 10 H, CH_2CH_2 and CH_3).

Compound **35a**: **31** and piperazine; IR 3380, 3050, 2350, 1640 cm^{-1}; ^1H NMR (NaOD/D_2O) δ 8.16 (s, 1 H, 2-*H*), 3.83 (m, 1 H, cyclopropyl C*H*), 3.28 (m, 4 H, piperazine CH_2N), 2.93 (m, 4 H, piperazine CH_2N), 1.00 (m, 4 H, CH_2CH_2).

Compound **35d**: **31** and 2-methylpiperazine; IR 3020, 2300, 1740, 1647 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.60 (s, 1 H, 2-*H*), 4.08 (m, 1 H, cyclopropyl C*H*), 3.45–2.75 (m, 7 H, piperazine C*H*N and CH_2N), 1.16 (m, 4 H, CH_2CH_2), 1.01 (d, 3 H, *J* = 6 Hz, CH_3).

Compound **35k**: **31** and *cis*-2,6-dimethylpiperazine; IR 3350, 3470, 2460, 1645 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.57 (s, 1 H, 2-*H*), 4.00 (m, 1 H, cyclopropyl C*H*), 3.65–2.65 (m, 6 H, piperazine NC*H*CH_2N), 1.14 (m, 4 H, CH_2CH_2), 0.98 (d, 6 H, *J* = 6 Hz, CH_3).

Compound **36a**:[9a] **32** and piperagine; IR 3450, 3320, 1705, 1635 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.50 (s, 1 H, 2-*H*), 7.19 (br s, 2 H, NH_2), 4.00 (m, 1 H, cyclopropyl C*H*), 3.23 (m, 4 H, piperazine CH_2N), 2.82 (m, 4 H, piperazine CH_2N), 1.08 (m, 4 H, CH_2CH_2).

Compound **36b**: **32** and 1-ethoxycarbonyl-3-methylpiperazine;[20] IR 3450, 3320, 1705, 1633 cm^{-1}; ^1H NMR ($CDCl_3$) δ 14.35 (br, 1 H, COO*H*), 8.66 (s, 1 H, 2-*H*), 6.50 (br s, 2 H, NH_2), 4.18 (q, 2 H, *J* = 7 Hz, CH_2CH_3), 3.83 (m, 1 H, cyclopropyl C*H*), 3.72–2.85 (m, 7 H, piperazine C*H*N and CH_2N), 1.28 (t, 3 H, *J* = 7 Hz, CH_2CH_3), 1.10 (m, 7 H, CH_2CH_2 and CH_3).

Compound **36d**: **32** and 2-methylpiperazine; IR 3460, 3340, 1708, 1635 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.50 (s, 1 H, 2-*H*), 7.20 (br s, 2 H, NH_2), 4.00 (m, 1 H, cyclopropyl C*H*), 3.30–2.70 (m, 7 H, piperazine C*H*N and CH_2N), 1.06 (m, 7 H, CH_2CH_2 and CH_3).

Compound **36e**: **32** and (*S*)-(+)-2-methylpiperazine; $[\alpha]^{30}_D$ −30.0° (*c* 0.2, $CHCl_3$).

Compound **36f**: **32** and (*R*)-(−)-2-methylpiperazine; $[\alpha]^{30}_D$ +32.5° (*c* 0.2, $CHCl_3$).

Compound **36g**: **32** and *cis*-2,3-dimethylpiperazine;[21] IR 3460, 3320, 1710, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.66 (s, 1 H, 2-*H*), 6.48 (br s, 2 H, NH_2), 3.94 (m, 1 H, cyclopropyl C*H*), 3.73–2.98 (m, 6 H, piperazine C*H*N and CH_2N), 1.32–1.00 (m, 10 H, CH_2CH_2 and CH_3).

Compound **36h**: **32** and 2,2-dimethylpiperazine; IR 3360, 3225, 1713, 1627 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.63 (s, 1 H, 2-*H*), 6.45 (br s, 2 H, NH_2), 3.90 (m, 1 H, cyclopropyl C*H*), 3.43–2.95 (m, 6 H, piperazine CH_2N), 1.23 (s, 6 H, CH_3), 1.15 (m, 4 H, CH_2CH_2).

Compound **36i**: **32** and 1,2-dimethylpiperazine;[20] IR 3440, 3310, 1700, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 14.56 (br, 1 H, COO*H*), 8.63 (s, 1 H, 2-*H*), 6.46 (br s, 2 H, NH_2), 3.93 (m, 1 H, cyclopropyl C*H*), 3.55–2.70 (m, 7 H, piperazine C*H*N and CH_2N), 2.35 (s, 3 H, NCH_3), 1.30–0.95 (m, 4 H, CH_2CH_2), 1.11 (d, 3 H, *J* = 6 Hz, CH_3).

Compound **36j**: **32** and *trans*-2,5-dimethylpiperazine; IR 3450, 3320, 1715, 1627 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.55 (s, 1 H, 2-*H*), 7.23 (br s, 2 H, NH_2), 4.00 (m, 1 H, cyclopropyl C*H*), 3.05–2.60 (m, 6 H, piperazine NC*H*CH_2N), 1.20–0.75 (m, 10 H, CH_2CH_2 and CH_3).

Compound **36k**: **32** and *cis*-2,6-dimethylpiperazine; IR 3450, 3320, 1703, 1625 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.48 (s, 1 H, 2-*H*), 7.17 (br s, 2 H, NH_2), 3.97 (m, 1 H, cyclopropyl C*H*), 3.37–2.60 (m, 6 H, piperazine NC*H*CH_2N), 1.20–0.75 (m, 10 H, CH_2CH_2 and CH_3); dissociation constant pK_{a1} 6.25, pK_{a2} 9.30.

Compound **36l**: **32** and *trans*-2,6-dimethylpiperazine;[22] IR 3450, 3325, 1708, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.47 (s, 1 H, 2-*H*),

7.17 (br s, 2 H, NH_2), 4.00 (m, 1 H, cyclopropyl CH), 3.40–2.75 (m, 6 H, piperazine NCHCH$_2$N), 1.09 (d, 10 H, J = 7 Hz, CH_2CH_2 and CH_3).

Compound **36n**: **32** and 2-(hydroxymethyl)piperazine; IR 3400, 3300, 1720, 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.50 (s, 1 H, 2-H), 7.18 (br s, 2 H, NH_2), 4.57 (br, 1 H, OH), 4.00 (m, 1 H, cyclopropyl CH), 3.50–2.65 (m, 9 H, piperazine CHN, CH_2N, and CH_2O), 1.08 (m, 4 H, CH_2CH_2).

Compound **36o**: **32** and 2-(fluoromethyl)piperazine; IR 3400, 3310, 1720, 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.44 (s, 1 H, 2-H), 7.18 (br s, 2 H, NH_2), 4.34 (dd, 2 H, J_{H-H} = 5 and J_{H-F} = 48 Hz, CH_2F), 4.00 (m, 1 H, cyclopropyl CH), 3.50–2.75 (m, 7 H, piperazine CHN and CH_2N), 1.05 (m, 4 H, CH_2CH_2).

Compound **36p**: **32** and 2-[(dimethylamino)methyl]piperazine; IR 3390, 3250, 1720, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.63 (s, 1 H, 2-H), 6.47 (br, 2 H, NH_2), 3.92 (m, 1 H, cyclopropyl CH), 3.55–2.93 (m, 7 H, piperazine CHN and CH_2N), 2.30 (s, 6 H, CH_3), 2.03 (s, 2 H, CH_2N), 1.17 (m, 4 H, CH_2CH_2).

Method H. 5-Amino-1-cyclopropyl-6,8-difluoro-7-(2-methyl-1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic Acid (36c). A mixture of **36b** (1.5 g, 3.33 mmol), 15 mL of 10% NaOH, and 3 mL of EtOH was heated under reflux for 8 h. The reaction mixture was diluted with water and neutralized with 10% HCl. The resulting precipitates were collected by filtration, washed with water, and recrystallized from CH_3CN to give 0.6 g (48%) of **36c**: IR 3450, 3320, 1708, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.66 (s, 1 H, 2-H), 6.48 (br s, 2 H, NH_2), 3.94 (m, 1 H, cyclopropyl CH), 3.70–2.50 (m, 7 H, piperazine CHN and CH_2N), 1.45–1.00 (m, 4 H, CH_2CH_2), 1.08 (d, 3 H, J = 7 Hz, CH_3).

Method I. 5-Amino-1-cyclopropyl-6,8-difluoro-7-(*cis*-3,4,5-trimethyl-1-piperazinyl)-4(1*H*)-oxoquinoline-3-carboxylic Acid (36m). A mixture of **32** (1.0 g, 3.36 mmol) and 2.0 g (19.6 mmol) of acetic anhydride in 20 mL of acetic acid was heated under reflux for 1.5 h. The reaction mixture was concentrated to dryness under reduced pressure. The residue was treated with water and neutralized with aqueous ammonia. After the solution was extracted with $CHCl_3$, the organic layer was dried and concentrated to leave a crude product, which was recrystallized from $CHCl_3$ to give 0.85 g (74%) of 5-(acetylamino)-1-cyclopropyl-6,7,8-trifluoro-4(1H)-oxoquinoline-3-carboxylic acid (**37**): mp 247–248 °C; IR 3270, 1725, 1675, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 13.70 (s, 1 H, COOH), 10.73 (br, 1 H, NH), 8.86 (s, 1 H, 2-H), 4.05 (m, 1 H, cyclopropyl CH), 2.28 (s, 3 H, $COCH_3$), 1.27 (m, 4 H, CH_2CH_2).

A mixture of **37** (3.0 g, 8.82 mmol) and 2.2 g (19.3 mmol) of *cis*-2,6-dimethylpiperazine in 20 mL of pyridine was heated at 120 °C for 2 h. The reaction mixture was concentrated to dryness under reduced pressure. The residue was treated with EtOH. The resulting precipitates were collected by filtration, and recrystallized from $CHCl_3$–EtOH to give 3.1 g (79%) of 5-(acetylamino)-1-cyclopropyl-6,8-difluoro-7-(*cis*-3,5-dimethyl-1-piperazinyl)-4-(1H)-oxoquinoline-3-carboxylic acid (**38**): mp 262–266 °C (dec); IR 3400, 2470, 1695, 1640, 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.03 (s, 1 H, NHCOCH$_3$), 8.62 (s, 1 H, 2-H), 4.12 (m, 1 H, cyclopropyl CH), 3.50–2.65 (m, 6 H, piperazine NCHCH$_2$N), 2.10 (s, 3 H, $COCH_3$), 1.13 (m, 4 H, CH_2CH_2), 0.97 (d, 6 H, J = 5 Hz, CH_3).

A mixture of **38** (2.7 g, 6.22 mmol), 14 mL of formaldehyde (37% solution in water), and 28 mL of formic acid was heated at 105 °C for 3.5 h. The reaction mixture was concentrated to dryness under reduced pressure. The residue was diluted with water and neutralized with aqueous ammonia. The resulting precipitates were collected by filtration, and recrystallized from $CHCl_3$–AcOEt to give 1.85 g (66%) of 5-(acetylamino)-1-cyclopropyl-6,8-difuloro-7-(*cis*-3,4,5-trimethyl-1-piperazinyl)-4(1H)-oxoquinoline-3-carboxylic acid (**39**): mp 224–225 °C; IR 3520, 3250, 1720, 1690, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.60 (br s, 1 H, NH), 8.75 (s, 1 H, 2-H), 4.03 (m, 1 H, cyclopropyl CH), 3.55–2.95 (m, 4 H, piperazine CH_2N), 2.42 (m, 2 H, piperazine CHN), 2.33 (s, 3 H, NCH_3), 2.25 (s, 3 H, $COCH_3$), 1.25 (m, 4 H, CH_2CH_2), 1.14 (d, 6 H, J = 7 Hz, CH_3).

A mixture of **39** (1.6 g, 3.57 mmol) and 8 mL of 5% NaOH was heated at 110 °C for 1 h. The reaction mixture was diluted with water and the pH was adjusted to 9. The resulting precipitates were collected by filtration and recrystallized from aqueous ammonia to give 1.3 g (90%) of **36m**: IR 3450, 3320, 1710, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 14.55 (br, 1 H, COOH), 8.62 (s, 1 H, 2-H), 6.45 (br s, 2 H, NH_2), 3.90 (m, 1 H, cyclopropyl CH), 3.43–2.87 (m, 4 H, piperazine CH_2N), 2.38 (m, 2 H, piperazine CHN), 2.33 (s, 3 H, NCH_3), 1.15 (m, 4 H, CH_2CH_2), 1.13 (d, 6 H, J = 6 Hz, CH_3).

In Vitro Antibacterial Activity. According to the method of the MIC Committee of the Japan Society of Chemotherapy,[27] the MIC (in microgram per milliliter) was determined by the 2-fold agar dilution method using Mueller–Hinton agar (pH 7.4, Difco); the bacterial inocula contained approximately 10^6 colony-forming units and the bacterial growth was observed after a 20-h incubation at 37 °C.

In Vivo Efficacy on Systematic Infections. In vivo activity assay was carried out according to the method of Shimizu et al.[28] Groups of 10 or more male mice (Std-ddY, 20 ± 2 g) were infected with *S. pyogenes* A65 (ip, 3×10^7 cells) and *P. aeruginosa* 12 (ip, 4×10^3 cells). The test compounds were suspended in 0.2% sodium (carboxymethyl)cellulose and administered orally at 0 and 6 h postinfection. Survival rates were evaluated after 1 week.

X-ray Crystal Analysis of 36k. Crystal Data. A yellow-green, prism-shaped crystal was formed from CH_3CN: $C_{19}H_{22}F_2N_4O_3$; M_r 392.40; triclinic, space group $P\bar{1}$; a = 9.392 (3) Å, b = 14.156 (4) Å, c = 7.039 (2) Å, α = 95.58 (2)°, β = 95.84 (3)°, γ = 77.11 (2)°; V = 904.9 (5) Å^3; Z = 2; d_{calcd} = 1.440 g/cm^3; μ (MoKα radiation, λ = 0.71069 Å) = 1.06 cm^{-1}; sample dimensions, 0.15 × 0.200 × 0.350 mm.

Crystallographic Measurements. All measurements were made on a Rigaku AFC6R diffractometer (MoKα radiation, incident-beam graphite monochrometer; $\omega - 2\theta$ scans, $2\theta_{max}$ = 50°). From a total of 3396 nonequivalent reflections recorded, those 1591 with $I > 3.00\ \sigma(I)$ were retained for the structural analysis and the Lorentz and polarization corrections were applied. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 19 reflections in the range 44° < 2θ < 50°, were used.

Structure Analysis. The crystal structure was solved by direct methods with DIRDIF.[17] The non-hydrogen atom coordinates were refined anisotropically. The hydrogen atom coordinates were refined isotropically or were included in the structure factor calculation in idealized positions (d_{C-H} = 0.95 Å) or in difference map positions and were assigned isotropic thermal parameters. The final cycle of full-matrix least-squares refinement was based on 1591 observed reflections ($I > 3.00\ \sigma(I)$) and 286 variable parameters and converged at R = 0.058 (R_w = 0.066). Neutral atom scattering factors were taken from ref 17. In the least-squares iterations, $\sum w\Delta^2$ [$w = 4F_o^2/\sigma^2(F_o^2)$, $\Delta = (|F_o| - |F_c|)$] was minimized.

Acknowledgment. We are grateful to Drs. M. Shimizu and M. Hashimoto for their encouragement throughout this work. Thanks are also due to Dr. S. Nakamura and his co-workers for the biological testing and members of the analytical section of these laboratories for elemental analysis and spectral measurements.

Registry No. **2**, 74011-58-8; **3**, 85721-33-1; **6**, 126457-99-6; **8**, 107564-02-3; **9**, 106890-70-4; **10**, 107564-07-8; **11**, 114008-18-3; **12**, 114008-22-9; **13**, 114008-20-7; **14**, 126458-00-2; **15**, 119354-66-4; **16**, 112654-97-4; **17**, 110871-99-3; **18**, 119354-67-5; **19**, 126458-01-3; **20**, 114008-23-0; **21**, 126458-02-4; **22**, 110236-79-8; **23**, 126458-03-5; **24**, 126458-04-6; **25**, 126458-05-7; **26**, 114008-14-9; **26** (benzyl ester), 114008-15-0; **27**, 110872-04-3; **28**, 103772-13-0; **29**, 126458-06-8; **30**, 126458-07-9; **30** (X = H), 94695-52-0; **31**, 114008-16-1; **32**, 103772-14-1; (±)-**33d**, 126458-17-1; **33k**, 113617-63-3; **34a**, 126458-18-2; (±)-**34d**, 126458-19-3; **34k**, 126458-20-6; **35a**, 114038-14-1; (±)-**35d**, 126458-21-7; **35k**, 126458-22-8; **36a**, 110236-78-7; (±)-**36b**, 126458-23-9; (±)-**36c**, 126458-24-0; (±)-**36d**, 126575-98-2; **36e**, 120379-33-1; **36f**, 120379-32-0; (±)-**36g**, 126458-25-1; **36h**, 126458-26-2; (±)-**36i**, 126458-27-3; (±)-**36j**, 126458-28-4; **36k**, 110871-86-8; (±)-**36l**, 126458-29-5; **36m**, 126458-30-8; (±)-**36n**, 126458-31-9; (±)-**36o**, 126458-32-0; (±)-**36p**, 126458-33-1; **37**, 110872-02-1; **38**, 126458-08-0; **39**, 126458-09-1;

(27) MIC Committee of the Japan Society of Chemotherapy. *Chemotherapy* **1981**, *29*, 76.
(28) Shimizu, M.; Takase, Y.; Nakamura, S.; Katae, H.; Minami, A.; Nakata, K.; Kurobe, N. *Antimicrob. Agents Chemother.* **1976**, *9*, 569.

40, 22476-74-0; 41, 126458-10-4; 42, 5435-12-1; 43, 84477-72-5; (±)-44, 126458-11-5; (±)-45, 126458-12-6; (±)-46, 126458-13-7; (±)-47, 126458-14-8; (±)-48, 126458-36-4; (±)-49, 126458-37-5; (±)-50, 126458-38-6; $C_6H_5CH_2OH$, 100-51-6; NaSMe, 5188-07-8; $MeOC_6H_4$-4-CH_2SH, 6258-60-2; $C_6H_5CH_2NH_2$, 100-46-9; $HOCH_2CH_2NH_2$, 141-43-5; (±)-2-methylpiperazine, 75364-79-3; (S)-(+)-2-methylpiperazinium D-(-)-tartarate, 126458-15-9; (S)-(+)-2-methylpiperazine, 74879-18-8; D-(-)-tartaric acid, 147-71-7; (R)-(-)-2-methylpiperazine, 75336-86-6; L-(+)-tartaric acid, 87-69-4; (R)-(-)-2-methylpiperazinium L-(+)-tartarate, 126458-16-0; cis-2,6-dimethylpiperazine, 21655-48-1; N,N-dimethylethylenediamine, 108-00-9; 2,5-dimethoxytetrahydrofuran, 696-59-3; piperazine, 110-85-0; (±)-1-(ethoxycarbonyl)-3-methylpiperazine, 126458-34-2; (±)-cis-2,3-dimethylpiperazine, 57193-34-7; (±)-1,2-dimethylpiperazine, 126458-35-3; (±)-trans-2,5-dimethylpiperazine, 2815-34-1; N-methylpiperazine, 109-01-3; (±)-trans-2,6-dimethylpiperazine, 126458-39-7.

Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for **36k** (11 pages). Ordering information is given on any current masthead page.

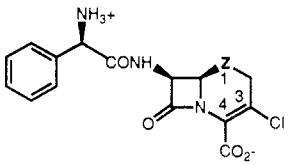
Comparative Reactivity of 1-Carba-1-dethiacephalosporins with Cephalosporins

Larry C. Blaszczak, Raymond F. Brown, Gwendolyn K. Cook, William J. Hornback, Richard C. Hoying, Joseph M. Indelicato, Chris L. Jordan, Alan S. Katner,† Michael D. Kinnick, John H. McDonald, III,* John M. Morin, Jr., John E. Munroe, and Carol E. Pasini

Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285.
Received October 2, 1989

Nine matched pairs of cephalosporins and their 1-carba-1-dethiacephalosporin analogues have been compared with regard to microbiological activity, β-lactam carbonyl infrared absorption, and aqueous stability. In general the microbiological activity of the pairs of compounds were very similar across a broad range of bacteria. The infrared absorption bands for the β-lactam carbonyls of the pairs indicated a general trend for the 1-carba-1-dethiacephalosporins to absorb at lower frequencies than the corresponding cephalosporins. All of the 1-carba-1-dethiacephalosporins did however present a striking stability enhancement over their cephalosporin counterparts at pH = 10 or 11 in water. This marked contrast of MIC similarity with the observed differences in chemical reactivity clearly demonstrates hydroxide ion catalyzed hydrolysis is not a good model for transpeptidase activity unless the compounds comprise a limited domain of structural type.

The 1-carba-1-dethiacephalosporins have been known for some time, with the first complete cephalosporin mimic prepared by Guthikonda et al.[1] Further work in this area has appeared from a number of laboratories.[2] The first comparison of the stability of 1-carba-1-dethiacephems with the parent cephems was published by Narisada et al.[3] The Shionogi group provided one example which indicated an enhanced chemical stability of cephalosporins over their 1-carba-1-dethiacephalosporin counterparts. The structure studied was limited to a β-lactam derivative possessing a 7α-methoxy group, further limiting the general applicability of their conclusions. In contrast loracarbef[4] (1), the



1: Z = S

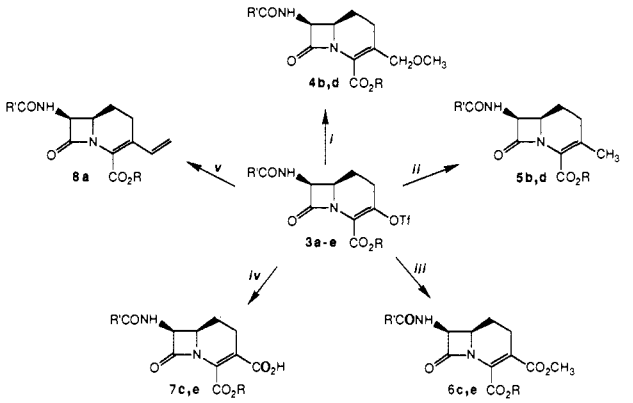
2: Z = CH_2

carba analogue of cefaclor (2), has been shown to exhibit enhanced chemical and serum stability over cefaclor.[5] In light of this apparent contradiction, we chose to study the comparative stabilities of cephalosporins and their 1-carba analogues in greater detail.

Chemistry

Preparation of all new compounds began with *p*-nitrobenzyl (7*S*,6*R*)-7-(phenoxyacetamido)-3-[[(trifluoromethyl)sulfonyl]oxy]-1-carba-1-dethia-3-cephem-4-carboxylate (**3a**).[6] This compound could be converted via palladium-catalyzed substitution reactions to a number of derivatives with varying functional groups at C-3.[7] These conversions are depicted in Scheme I and described in the

Scheme I



[a] (i) (1) cat. $PdCl_2(CH_3CN)_2$, *n*-$Bu_3SnCH_2OCH_3$, LiCl, (2) TFA, Et_3SiH; (ii) (1) cat. $PdCl_2(CH_3CN)_2$, $(CH_3)_4Sn$, LiCl, (2) TFA, Et_3SiH; (iii) (1) cat. $PdCl_2(CH_3CN)_2$, CO, MeOH, (2) Zn/HCl; (iv) (1) cat. $PdCl_2(CH_3CN)_2$, CO, HCO_2H; (2) Zn/HCl; (v) (1) cat. $PdCl_2(CH_3CN)_2$, *n*-$Bu_3SnCHCH_2$, LiCl; (2) TFA, Et_3SiH.

Experimental Section. More detailed papers on both the chemistry and biology of the different series represented

† This paper is dedicated to the memory of Dr. Alan S. Katner—deceased November 16, 1986.

(1) Guthikonda, R. N.; Cama, L. D.; Christensen, B. G. *J. Am. Chem. Soc.* **1974**, *96*, 7584.
(2) Firestone, R. A.; et al. *J. Med. Chem.* **1977**, *20*, 551. Finkelstein, J.; Holden, K. G.; Perchonock, C. D. *Tetrahedron. Lett.* **1978**, 1629. Doyle, T. W.; Conway, T. T.; Casey, M.; Lim, G. *Can. J. Chem.* **1979**, *57*, 222. Doyle, T. W.; Conway, T. T.; Lim, G.; Luh, B.-Y. *Ibid.* **1979**, *57*, 227. Martel, A.; Doyle, T. W.; Luh, B.-Y. *Ibid.* **1979**, *57*, 614. Doyle, T. W.; Douglas, J. L.; Belleau, B.; Conway, T. T.; Ferrari, C. F.; Horning, D. E.; Lim, G.; Luh, B.-Y.; Martel, A.; Menard, M.; Morris, R. L.; Misiek, M. *Ibid.* **1980**, *58*, 2508; Salzman, T. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron. Lett.* **1980**, *21*, 1193. Uyeo, S.; Ona, H. *Chem. Pharm. Bull.* **1980**, *1563*. Bremner, J. A. S.; Colvin, E. W.; Gallacher, G.; MacLeod, A. *Tetrahedron. Lett.* **1983**, *24*, 3783. Hatanaka, M.; Ishimaru, T. *Ibid.* **1983**, *24*, 4837.

0022-2623/90/1833-1656$02.50/0