137697-67-7; **82**, 137697-68-8; **83**, 137697-69-9; **84**, 137697-70-2; **85**, 137697-71-3; **86**, 137698-00-1; **86**·4HCl, 137697-72-4; **87**, 70175-11-0; **88**, 70175-39-2; **89**, 70175-40-5; **91**, 70175-36-9; **91**·2HCl, 70175-37-0; **92**, 74071-15-1; **93**, 74071-13-9; **94**, 70175-33-6; **95**, 70175-32-5; **96**, 74071-23-1; **97**, 74071-18-4; **98**, 70175-31-4; **99**, 74071-43-5; **99**·2HCl, 70175-26-7; **100**, 137698-05-6; **100**·2HCl, 70175-29-0; **101**, 74071-20-8; **102**, 74071-21-9; **103**, 74071-24-2; **104**, 74071-22-0; **105**, 70215-11-1; **106**, 74071-19-5; **107**, 74071-08-2; **108**, 137697-74-6; **109**, 137697-75-7; **110**, 137697-76-8; **111**, 2789-24-4; **112**, 137698-06-7; **112**·2HCl, 16351-82-9; **113**, 70175-27-8; **114**, 70175-30-3; **115**, 137697-77-9; **116**, 137697-78-0; **117**, 137697-79-1; **118**, 27052-41-1; **119**, 27052-39-7; **120**, 27052-36-4; **121**, 137697-80-4; **122**, 137697-81-5; **123**, 137697-82-6; **124**, 137697-83-7; **125**, 16351-85-2; **126**, 137697-84-8; **127**, 16162-28-0; **128**, 16203-56-8; **129**, 137697-85-9; **130**, 16351-89-6; **131**, 137697-86-0; **132**, 70175-09-6; **133**, 70175-13-2; **134**, 137697-87-1; **135**, 137697-88-2; **136**, 70175-35-8; **137**, 137697-89-3; **138**, 137697-90-6; **139**, 137697-91-7; **140**, 70175-25-6; **141**, 70175-28-9; **142**, 137697-92-8; **143**, 137697-93-9; **144**, 137697-94-0; **145**, 137697-95-1; **146**, 137697-96-2; **147**, 137697-97-3; **148**, 70175-39-2; **150**, 137697-99-5; diethylamine, 109-89-7; chloroacetyl chloride, 79-04-9; *N,N*-diethylglycinate, 2644-21-5; 2-chloro-5-(trifluoromethyl)-1,3-phenylenediamine, 34207-44-8; potassium thiocyanate, 333-20-0; 2-chloro-5-cyano-1,3-phenylenediamine, 34207-46-0; 3,5-diamino-4-methylbenzoic acid, 6633-36-9; ethyl 3,5-diamino-4-methylbenzoate, 42908-12-3; 2-amino-1,3-phenylenediamine, 608-32-2; 3,5-diamino-4-chlorobiphenyl, 58495-18-4; 5-carbethoxy-1,3-phenylenebisthiourea, 137697-98-4; 5-methoxy-1,3-phenylenebisthiourea, 137697-57-5; 1,3-phenylenebisthiourea, 2591-01-7; *N,N'*-diethyl-1,3-phenylenebisthiourea, 16349-50-1; 3,5-diaminobenzoic acid ethyl ester, 1949-51-5; ammonium thiocyanate, 1762-95-4; 5-chloro-1,3-phenylenediamine, 33786-89-9; dimethyl 5-chloro-1,3-phenylenebisthiocarbamate, 137697-73-5; 5-chloro-1,3-phenylenebisthiourea, 100-96-9; 2,6-dichlorobenzo[1,2-*d*:5,4-*d'*]-bisthiazole, 2591-03-9; 2-(diethylamino)ethyl isothiocyanate, 32813-52-8; 1-(diethylamino)-4-isothiocyanatopentane, 104093-88-1; 2,6-diaminobenzo[1,2-*d*:5,4-*d'*]bisthiazole, 2789-24-4; ethyl isocyanate, 109-90-0.

New 8-(Trifluoromethyl)-Substituted Quinolones. The Benefits of the 8-Fluoro Group with Reduced Phototoxic Risk

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A series of 8-(trifluoromethyl)-substituted quinolones has been prepared and evaluated for in vitro and in vivo antibacterial activity, and phototolerance in a mouse phototolerance assay. These analogues were compared to the corresponding series of 6,8-difluoro- and 6-fluoro-8*H*-quinolones (ciprofloxacin type). Although their in vitro antibacterial activities are less than the 6,8-difluoro analogues, the 8-(trifluoromethyl)quinolones are generally equivalent to their 8*H* analogues. In vivo, they are comparable to the 6,8-difluoro series and show up to 10-fold improvement in efficacy when compared to their ciprofloxacin counterparts vs *Streptococcus pyogenes* and *Streptococcus pneumonia*. In the phototolerance model, the 8-(trifluoromethyl)quinolones are comparable to the 8*H*-quinolones. Both of these series display much higher no effect doses (greater tolerance) than the corresponding 6,8-difluoroquinolones.

The quinolone antibacterials have emerged as an area of intense interest because of their broad spectrum of activity in vitro and their in vivo chemotherapeutic efficacy.[1] Several quinolones are already being marketed, e.g., norfloxacin **1**,[2] ofloxacin **2**,[3] enoxacin (Flumark) **3**,[4] and ciprofloxacin **4**.[5] The success of these compounds has caused an increase in efforts to produce even more efficacious agents, leading to the current list of compounds with exciting clinical potential. These candidates include lomefloxacin (**5**),[6] tosufloxacin (**6**),[7] sparfloxacin (AT-4140/CI-978) (**7**),[8] WIN 57273 (**8**),[9] and PD 127391 (**9**)[10]

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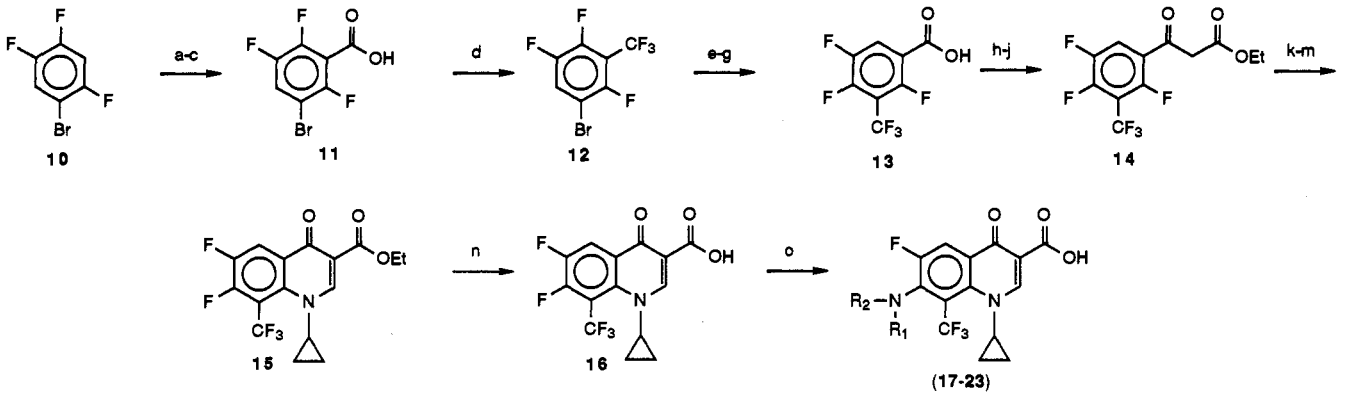
0022-2623/92/1835-0361$03.00/0

Scheme I[a]



[a] (a) LDA/THF; (b) CO_2/Et_2O; (c) 0.5 N HCl; (d) SF_4/HF; (e) BuLi/Et_2O; (f) CO_2/Et_2O; (g) 1.0 N HCl; (h) oxalyl chloride/CH_2Cl_2/DMF(cat.); (i) $\bar{O}_2CCHCO_2EtMg^{2+}$/THF; (j) 0.5 N HCl; (k) $(EtO)_3CH/Ac_2O/\Delta$; (l) c-C_3H_5-NH_2/DMSO; (m) Et_3N; (n) 5 N HCl/THF; (o) $R_1R_2NH/Et_3N/CH_3CN$.

(Figure 1).

Our efforts in this area have resulted in the production of several diverse series of compounds, each of which has produced potential clinical candidates.[11] One of these highly potent chemical entities, a 6,8-difluoroquinolone, has shown a high degree of phototoxicity in several models, including man. The initial introduction of the 8-fluoro substituent increased both in vitro activity and in vivo efficacy and provided the first examples of quinolones with excellent Gram-positive activity.[11b,12] This series culminated with the production of CI-934 (**10**).[12] Unfortunately, the improvement in Gram-positive efficacy was concomitant with a significant increase in phototoxicity.

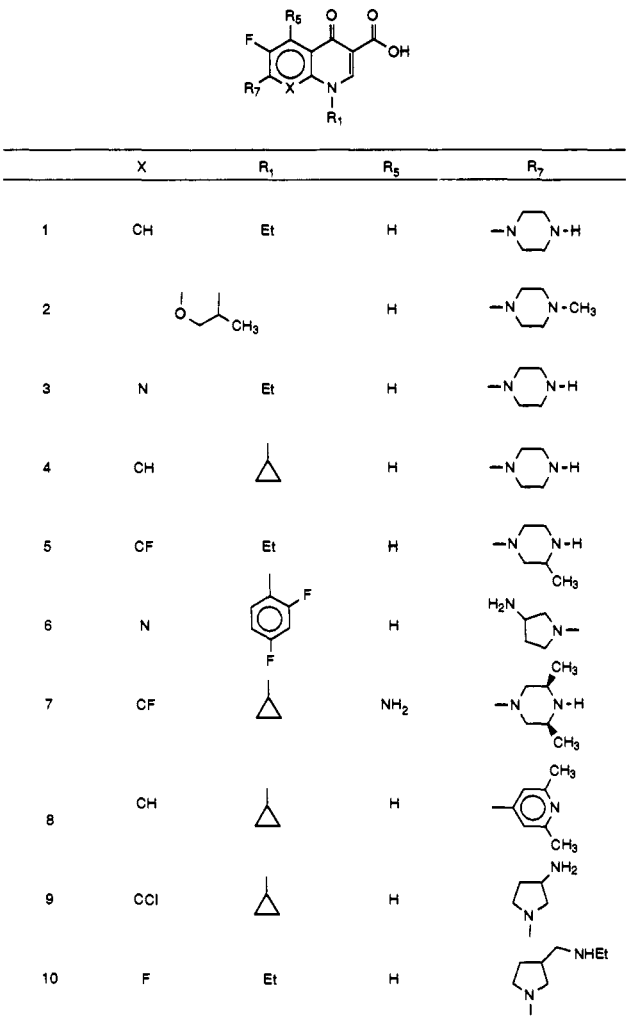


Figure 1. Clinically significant or marketed quinolone type antibacterial agents.

Work in this area continued with efforts being concentrated on the replacement of the 8-fluoro substituent with

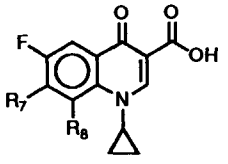
(9) Sedlock, D. M.; Dobson, R. A.; Deuel, D. M.; Lesher, G. Y.; Rake, J. B. In Vitro and In Vivo Activities of a New Quinolone, WIN 57273, Possessing Potent Activity Against Gram-Positive Bacteria. *Antimicrob. Agents Chemother.* **1990**, *34*, 568–575.

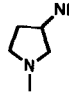
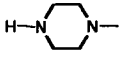
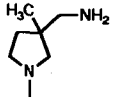
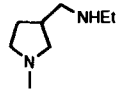
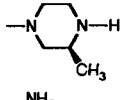
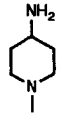
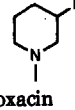
(10) (a) Norrby, S. R.; Jonsson, M. Comparative In Vitro Activity of PD 127391, a New Fluorinated 4-Quinolone Derivative. *Antimicrob. Agents Chemother.* **1988**, *32*, 1278–1281. (b) Wise, R.; Ashby, J. P.; Andrews, J. M. In Vitro Activity of PD 127391, an Enhanced-Spectrum Quinolone. *Antimicrob. Agents Chemother.* **1988**, *32*, 1251–1256.

(11) (a) Domagala, J. M.; Hanna, L. D.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; Sanchez, J. P.; Solomon, M. New Structure-Activity Relationships of the Quinolone Antibacterials Using the Target Enzyme. The Development and Applications of a DNA Gyrase Assay. *J. Med. Chem.* **1986**, *29*, 394–404. (b) Domagala, J. M.; Heifetz, C. L.; Mich, T. F.; Nichols, J. B. 1-Ethyl-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid. A New Quinolone Antibacterial with Potent Gram-Positive Activity. *J. Med. Chem.* **1986**, *29*, 445–448. (c) Culbertson, T. P.; Domagala, J. M.; Nichols, J. B.; Priebe, S.; Skeean, R. W. Enantiomers of 1-Ethyl-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid: Preparation and Biological Activity. *J. Med. Chem.* **1987**, *30*, 1711–1715. (d) Domagala, J. M.; Hagen, S. E.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; Sanchez, J. P.; Trehan, A. K. 7-Substituted 5-Amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids: Synthesis and Biological Activity of a New Class of Quinolone Antibacterials. *J. Med. Chem.* **1988**, *31*, 503–506. (e) Sanchez, J. P.; Domagala, J. M.; Hagen, S. E.; Heifetz, C. L.; Hutt, M. P.; Nichols, J. B.; Trehan, A. K. Quinolone Antibacterial Agents. Synthesis and Structure-Activity Relationships of 8-Substituted Quinoline-3-carboxylic Acids and 1,8-Naphthyridine-3-carboxylic Acids. *J. Med. Chem.* **1988**, *31*, 983–991. (f) Domagala, J. M.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; Nichols, J. B.; Solomon, M.; Worth, D. F. 1-Substituted-7-[3-[(ethylamino)-methyl]-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids. New Quantitative Structure-Activity Relationships at N_1 for the Quinolone Antibacterials. *J. Med. Chem.* **1988**, *31*, 991–1001.

(12) Cohen, M. A.; Griffin, T. J.; Bien, P. A.; Heifetz, C. L.; Domagala, J. M. In Vitro Activity of CI-934, a Quinolone Carboxylic Acid Active Against Gram-Positive and -Negative Bacteria. *Antimicrob. Agents Chemother.* **1985**, *28*, 766–772.

Table I. Biological Testing Results from the Antibacterial Screening: Minimum Inhibitory Concentrations (MIC,[a,b] μg/mL)



compd	R_7	R_8	Gram-negative organisms						Gram-positive organisms					geometric means	
			Entero. cloacae MA-2646	*Esch. coli* Vogel	*Klebs. pneumo.* MGH-2	*Prot. rettgeri* M-1771	*Pseudo. aerug.* UI-18	*Esch. coli* H-560	*Staph. aureus* H-228	*Staph. aureus* UC-76	*Strep. faecalis* MGH-2	*Strep. pneumo.* SV-1	*Sterp. pyog.* C-203	Gram- (−)	Gram- (+)
17		a: CF3	0.05	0.05	0.2	0.4	1.6	0.025	0.1	0.05	0.4	0.4	0.4	0.09	0.20
		b: F	0.013	0.025	0.025	0.1	0.1	0.003	0.05	0.025	0.1	0.1	0.05	0.02	0.06
		c: H	0.025	0.05	0.05	0.1	0.1	0.006	0.1	0.025	0.1	0.05	0.1	0.03	0.07
18		a: CF3	0.05	0.05	0.1	0.2	1.6	0.05	0.4	0.1	0.4	0.4	0.4	0.08	0.30
		b: F	0.025	0.05	0.05	0.1	0.2	0.013	0.4	0.1	0.4	0.8	0.8	0.04	0.40
		c: H[c]	0.05	0.025	0.05	0.1	0.2	0.025	1.6	0.1	1.6	0.8	0.4	0.04	0.61
19		a: CF3	0.2	0.2	0.4	0.8	3.1	0.1	0.05	0.013	0.2	0.05	0.05	0.26	0.05
		b: F	0.013	0.013	0.025	0.05	0.4	0.006	0.013	≤0.003	0.006	0.003	0.003	0.02	0.005
		c: H	0.05	0.025	0.2	0.4	1.6	0.025	0.1	0.013	0.05	0.003	0.003	0.08	0.01
20		a: CF3	0.4	0.4	0.8	1.6	6.3	0.2	0.05	0.013	0.1	0.05	0.05	0.53	0.04
		b: F	0.1	0.05	0.2	0.4	0.4	0.013	0.05	0.006	0.025	0.025	9,95	0.09	0.03
		c: H	0.4	0.2	0.2	0.8	1.6	0.05	0.4	0.013	0.2	0.2	0.05	0.23	0.10
21		a: CF3	0.2	0.1	0.4	0.8	3.1	0.05	0.4	0.2	0.8	0.8	0.8	0.20	0.53
		b: F	0.025	0.025	0.025	0.1	0.4	0.1	0.2	0.1	0.4	0.4	0.2	0.04	0.23
		c: H	0.025	0.025	0.05	0.1	0.4	0.025	0.4	0.1	0.4	0.2	0.2	0.04	0.23
22		a: CF3	0.2	0.2	0.4	0.8	3.1	0.2	0.1	0.05	0.2	0.2	0.1	0.30	0.12
		b: F	0.1	0.1	0.1	0.2	0.8	0.05	0.1	0.025	0.2	0.4	0.4	0.10	0.15
		c: H	0.4	0.4	0.8	1.6	3.1	0.4	1.6	0.2	0.8	0.4	0.4	0.61	0.53
23		a: CF3	0.1	0.1	0.2	0.4	1.6	0.1	0.2	0.025	0.2	0.2	0.2	0.15	0.13
		b: F	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.025	0.1	0.1	0.1	0.20	0.08
		c: H	0.1	0.1	0.2	0.8	0.8	0.1	0.8	0.05	0.2	0.2	0.1	0.17	0.17
pefloxacin			0.1	0.025	0.05	0.05	0.4	0.1	0.2	0.1	0.8	0.8	0.8	0.06	0.4
1-norfloxacin			0.1	0.025	0.05	0.025	0.2	0.1	0.8	0.05	1.6	1.6	0.8	0.05	0.61
4-ciprofloxacin[c]			0.05	0.025	0.05	0.1	0.2	0.025	1.6	0.1	1.6	0.8	0.4	0.04	0.61

[a] Standard microdilution techniques; see ref 11a. [b] All values for **17a–c** through **23a–c** are accurate to ±50% and have been obtained from duplicate or triplicate experiments; see ref 11a. [c] Same as 18[c] = ciprofloxacin.

Table II. In Vivo Efficacy in Mouse Protection Tests: PD_{50} (mg/kg) po/sc[a-c]

compound	*E. coli* Vogel	*S. pyog.* C-203	*S. pneuno.* SV-1<m	*Pseudo. aerug.*
17a	2.9/1.4	32/26	25/26	53/23
17b	0.9/0.2	7.5/2.3	15/5.5	6.5/3.0
17c	3.4/0.5	97/11	>100/23	49/5.4
18a	1.8/0.9	–	75/26	–
18b	0.45/0.26	33/8.9	59/29	6.6/2.5
18c	1.2/.25	180/19	260/29	25/5
19a	8.5/3.1	–	1.1/0.4	–
19b	1.8/.3	–	1.2/0.3	–
19c	26/1.7	–	12/.45	–
20a	5.3/1.7	1.6/1.1	1.4/0.9	93/46
20b	4.2/1.0	1.8/0.50	3.3/1.9	59/40
20c	35/2.4	46/4.5	–	–
21a	1.6/1.4	23/21	–	–
21b	0.7/0.2	14/7.2	–	–
21c	1.2/0.4	39/12	–	–
22a	12.5/4.5	–	–	–
22b	3.7/1.2	–	15/3.6	–
22c	18/3.8	–	–	–
23a	11.8/3.2	35/12	–	–
23b	4.7/1.4	32/3.4	–	–
23c	15/1.4	>50/8	–	–
pefloxacin	3/2	110/94	>200/96	38/26
norfloxacin	4/0.6	>100/45	>100/150	76/11
ciprofloxacin	1.2/0.25	180/19	260/29	25/5

[a] Single dose given at challenge. [b] po indicates oral administration by gavage, and sc indicates subcutaneous injection. [c] Reference 13.

an atom or group of atoms which would maintain the Gram-positive activity while decreasing or eliminating the side effects, especially the phototoxicity. The results of this undertaking culminated with the production of a series of quinolones substituted with a trifluoromethyl group in the 8-position (**17a–23a**, Table I).

In this paper, we will describe the synthesis of these 8-(trifluoromethyl)quinolones and their antibacterial evaluation in vitro and in vivo and feature their phototolerance screening results.

Chemistry

The 8-(trifluoromethyl)quinolone nucleus (**16**) was prepared from 2,4,5-trifluorobromobenzene using the six-step synthesis outlined in Scheme I. Formation of the anion of **10** using lithium diisopropylamide, followed by carbonation, provided the trifluorobromo acid **11**. The reaction with sulfur tetrafluoride in hydrogen fluoride at 120 °C (in a bomb) afforded the hexafluorobromotoluene derivative **12**. The reaction to form the anion of **12**, using *n*-butyllithium, followed by a second carbonation gave the hexafluorotoluic acid **13**. Standard literature procedures provided the keto ester **14**, which was converted to the quinolone ester **15** via the diethyl (ethoxymethylene)-malonate adduct, enamine, and ring closure.[11d-f] The acid hydrolysis of **15** provided the final quinolone acid **16**. The title trifluoromethyl compounds (**17a–23a**) were made by displacing the 7-fluoro substituent of **16** with the requisite side chains. The side chains as well as the other quinolones listed in Table I were prepared according to established literature procedures.[11d-f] The presence of the 8-trifluoromethyl group did not significantly affect the chemistry of the quinolone ring construction or the displacement reactions by the side chains.

Biological Assays

The series of 8*H*-, 8-fluoro- and 8-(trifluoromethyl)-quinolones (Table I) were tested against 11 representative Gram-positive and Gram-negative organisms by using standard microtitration techniques,[11a] and their minimum inhibitory concentrations (MICs in μg/mL) were compared in multiple experiments. In order to make it easier to compare the in vitro activities of the three quinolone series, the geometric means of the Gram-negative organisms (excluding *Pseudomonas aeruginosa*) and the Gram-positive organisms were calculated and are summarized at the end of Table I. A representative number of compounds were tested for in vivo comparisons. The in vivo potency, expressed as the median protective dose (PD_{50}, mg/kg), is determined in acute lethal systematic infections in fe-

Table III. Phototolerance (Phototoxic Skin Reactions in Depilated Mice)[14]

compd	max. toler. dose (mg/kg po)[a]	no. of pos. rxns/total mice	% reactions	day of first positive reaction	PTD_{50} (mg/kg)	no effect dose (mg/kg)
17a	300	0/5	0	0	>300	300
17b	6	15/15	100	3	4.2	3
17c	300	0/5	0	0	>300	300
18a	100	0/5	0	0	>100	100
18b	100	0/5	0	0	171	100
18c	300 (po)[a]	0/5	0	0	>300	300
	100 (sc)[b]	5/5	100	2	172	100
19a	100	0/5	0	0	>100	100
19b	30	5/5	100	1	<30	<30
19c	100	0/5	0	0	>100	100
20a	100	0/5	0	0	>100	100
20b	30	5/5	100	1	<30	30
20c	100	0/5	0	0	>100	100
21a	100	0/5	0	0	>100	100
21b	30	1/5	20	4	43	<30
21c	100	1/5	20	0	>100	100
22a	100	0/5	0	0	>100	100
22b	100	5/5	100	2	55	30
22c	100	0/5	0	0	>100	100
23a	100	0	0	0	>100	100
23b	100	0	0	0	>100	100
23c	100	0	0	0	>100	100
pefloxacin	300 (po)[a]	2/5	40	4	265	>172
norfloxacin	300 (po)[a]	0/5	0	0	>300	300
	300 (sc)[b]	5/5	100	3	172	100
ciprofloxacin	300 (po)[a]	0/5	0	0	>300	300
	100 (sc)[b]	5/5	100	2	172	100

[a] po indicates oral administration by gavage. [b] sc indicates subcutaneous injection.

male Charles River CD-1 mice as previously described.[13] The results are summarized in Table II.

Screening for photolability was also performed on representative compounds to determine any trends in photo-safety. Each of the compounds was tested for the induction of phototoxic skin reaction in depilated, female CD-1 mice. The animals were exposed to UVA radiation (320–400 nm) for a 3-h period beginning 1 h after a single oral or subcutaneous dose of drug. This regimen was continued for up to 4 consecutive days. Results were reported as the dose necessary to induce a phototoxic reaction in 50% of the mice, a PTD_{50}, by the probit method using initial doses of 30, 100, and 300 mg/kg. The raw data was also used to assess the first day of positive reaction and the no effect dose. Preliminary results of the mouse phototolerance model have been presented,[14] and a full paper containing experimental details will be published at a later date.

Discussion of Results

A comparison of the geometric means of the MICs of both the Gram-positive and Gram-negative organisms (Table I) indicated that the 8-(trifluoromethyl)quinolones (**17a–23a**) have essentially the same in vitro activity as the ciprofloxacin type, 8*H*-quinolones (**17c–23c**) (0.08–0.53 vs 0.03–0.60). However, the 8-trifluoromethyl analogues show a significant drop in activity when they are compared to the 6,8-difluoroquinolones (**17b–23b**) (0.02–0.20) except in the case where the side chains were 3-aminopyrrolidine (**17a–c**) (0.09–0.02–0.03), piperazine (**18a–c**) (0.08–0.04–0.04), and 3-aminopiperidine (**23a–c**) (0.15–0.20–0.17), where the activities of the three analogues were essentially equivalent. However, in most cases the 8-trifluoromethyl compounds showed a decrease in activity against *P. aerug.* compared to the 8*H* and 6,8-difluoro analogues. A similar comparison of the in vivo results shows that the 8-trifluoromethyl series has essentially the same activity as the 8*H* series against *Escherichia coli* (**17a–23a** vs **17c–23c**). However, there is an increase in activity against *Streptococcus pyogenes* and *Streptococcus pneumoniae* displayed by the 8-(trifluoromethyl)-quinolones especially in the case of the 3-[(ethylamino)-methyl] side chain (**20a–c**), where the potency of the 8-trifluoromethyl is as good as the 8-fluoro derivative (*S. pyog.* 1.6/1.1 vs 1.8/0.5, *S. pneum.* 1.4/0.9 vs 3.3/1.9 and *P. aerug.* 93/46 vs 59/40). In every other case, the 8-fluoro series was more active in vivo.

The phototoxicity testing indicated identical phototolerance between 8-(trifluoromethyl)- and 8*H*-quinolones (PTD_{50} >100) with the 6,8-difluoro analogues exhibiting significant photolability (PTD_{50} <30) in all cases except when the side chain was either piperazine (**18b**) or 3-aminopiperidine (**23b**). The piperazine side chain in all cases does not impart the in vivo absorption that the pyrrolidine side chain exhibits and the phototoxicity is, therefore, not expressed by the oral route. This can also be shown in the case of norfloxacin (**1**) which has poor activity in vivo when administered by the oral route; phototoxicity in this case is also not observed (PTD_{50} >300). On the other hand, when dosing for the phototoxicity study was done by the subcutaneous route, the level at which photolability was observed was significantly lower (PTD_{50} 172 mg/kg).

Experimental Section

Instrumental Data. All melting points were determined on a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined in KBr on a Nicolet FTIRSX-20 instrument. Proton magnetic resonance (NMR) were recorded on either a Varian XL-200 or an IBM 100 WP100SY spectrometer. Shifts are reported in δ units relative to internal tetramethylsilane. Elemental analyses were performed on a Perkin-Elmer 240 elemental analyzer. All compounds had analytical results ±0.4% of theoretical values. All organic solutions were dried over magnesium sulfate, and all concentrations were performed in vacuo at 10–30 mmHg.

3-Bromo-2,5,6-trifluorobenzoic Acid (11). A solution of *n*-BuLi (1.6 M in hexanes, 62.5 mL, 0.1 mol) was added dropwise to a 0 °C solution of 12.1 g (0.12 mol) of diisopropylamine in 100 mL of THF. After stirring for 15 min, the LDA solution was added to a solution of 21.1 g (0.1 mol) of 1-bromo-2,4,5-trifluorobenzene (**10**) in 100 mL of THF at −78 °C. The solution was stirred for 10 min and then transferred by cannula to a slurry of dry ice (200 g) in 250 mL of ether. The reaction was allowed to warm to 25 °C and treated with 250 mL of 1.0 M HCl. The layers were separated, and the organic layer was extracted with NaOH (0.5 M, 2 × 75 mL). The basic extracts were acidified to pH 1.0 with 6.0 M HCl and extracted with ether (3 × 250 mL). The combined organic layers were washed with water and saturated NaCl and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave 17.8 g (70%) of **11**: mp 114–116 °C; IR (KBr) 1711, 1626, 1488, 1440, 1405 cm^{-1}; NMR ($CDCl_3$) δ 7.26 (bs, 1 H), 7.61 (dt, 1 H, J_d = 10.4 Hz, J_t = 6.2 Hz); MS *m/e* (relative intensity) 254 (70), 256 (56). Anal. ($C_7H_2BrF_3O_2$) C, H, F.

1-Bromo-2,4,5-trifluoro-3-(trifluoromethyl)benzene (12). A solution of 63.9 g (0.25 mol) of **11** in 120 g of SF_4 and 60 g of HF was heated in a stainless steel bomb at 120 °C for 8 h. (*Caution*!! Both HF and SF_4 are strong irritants, corrosive, and highly toxic gases.) The reaction mixture was cooled to 25 °C, the volatiles were vented through KOH traps, and the residue was dissolved in CH_2Cl_2. The organic solution was washed with saturated solutions of $NaHCO_3$ and NaCl and dried ($MgSO_4$), and the solvent was removed by distillation through a 6-in. Vigreux column. The residue was then distilled through a short path column at 150–152 °C to give 61.6 g (88%) of **12** as a pale yellow liquid: IR (film) 1631, 1495, 1315, 1212, 1151, 919, 807, 660 cm^{-1}; NMR ($CDCl_3$) δ 7.65 (dt, 1 H, J_t = 6.2 Hz, J_d = 8.3 Hz); MS *m/e* (relative intensity) 278 (63.5), 280 (63.5). Anal. ($C_7HBrF_6 \cdot 0.11H_2O$) C, H, F, Br.

2,4,5-Trifluoro-3-(trifluoromethyl)benzoic Acid (13). A solution of 16.0 g (57.2 mmol) of **12** in 100 mL of ether was cooled to −78 °C, and *n*-BuLi (1.6 M in hexanes, 38.8 mL, 62 mmol) was added dropwise over 25 min. The solution was stirred for 5 min and transferred by cannula to a slurry of 200 g of dry ice in 200 mL of ether. The reaction was allowed to warm to 25 °C and treated with 200 mL of 1.0 M HCl. The layers were separated, and the ether layer was extracted with 0.5 M NaOH (2 × 50 mL). The basic water layer was acidified to pH 1.0 with 6.0 M HCl and extracted with ether (3 × 200 mL). The combined ether layers were washed with water and saturated NaCl, dried ($MgSO_4$), and evaporated in vacuo to give 11.2 g (80%) of **13**: mp 83–86 °C; IR (KBr) 1718, 1638, 1512, 1465, 1333, 1263, 1155, 928 cm^{-1}; NMR ($CDCl_3$) δ 8.05 (bs, 1 H), 8.09 (dt, 1 H, J_t = 6.5 Hz, J_d = 9.0 Hz). Anal. ($C_8H_2F_6O_2 \cdot 0.4H_2O$) C, H, F.

Ethyl 2,4,5-Trifluoro-β-oxo-3-(trifluoromethyl)benzenepropanoate (14). A solution of 7.4 g (30.4 mmol) of **13** in 50 mL of CH_2Cl_2 was treated with 2 drops of DMF followed by the dropwise addition of 5.0 g (40 mmol) of oxalyl chloride. After the initial exothermic reaction, the reaction mixture was stirred at room temperature for 18 h. The solution was concentrated in vacuo, and the residual yellow oil was dissolved in 80 mL of THF and cooled to −78 °C.

A solution of 8.8 g (66 mmol) of ethyl hydrogen malonate in 15 mL of THF was cooled to −78 °C and treated dropwise, over 20 min, with 66 mL (122 mmol) of 2.0 M isopropylmagnesium

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chloride (in THF). After the addition was complete, the reaction mixture was stirred for 20 min and transferred by cannula to the initially prepared solution of acid chloride. When this addition was complete, the reaction mixture was allowed to warm to 5 °C and poured onto 200 mL of 1.0 M HCl. The layers were separated, and the aqueous layer was reextracted with ether (2 × 150 mL). The combined organic layers were washed with 5% $KHCO_3$ and saturated NaCl, dried ($MgSO_4$), and evaporated in vacuo to give an orange oil. The residual oil was dissolved in pentane and cooled to −78 °C where a white precipitate formed which was removed by filtration, washed with cold pentane, and dried in vacuo to give 6.0 g (63%) of **14**: mp 31–32 °C: IR (KBr) 1742, 1701, 1632, 1510, 1448, 1412 cm^{-1}; NMR ($CDCl_3$) δ 1.3 (overlapping t, 3 H, J = 7.2 Hz), 3.97 (d, 1.5 H, J = 4.3 Hz), 4.24 (overlapping q, 2 H, J = 7.2 Hz), 5.87 (s, $^1/_2$ H, enol vinyl), 7.98 (m, 1 H); MS m/e (relative intensity) 316 (15), 315 (100), 269 (25). Anal. ($C_{12}H_8F_6O_3 \cdot 0.4H_2O$) C, H, F.

Ethyl 1-Cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-8-(trifluoromethyl)-3-quinolinecarboxylate (15). A solution of 9.8 g (31.3 mmol) of **14**, 3.5 g (34.4 mmol) of acetic anhydride, and 6.0 g (40.7 mmol) of triethyl orthoformate was heated at reflux under N_2 for 36 h. The solution was concentrated under reduced pressure to give a red oil which was dissolved in 50 mL of DMSO and treated dropwise with 2.3 g (40.7 mmol) of cyclopropylamine. The reaction was stirred at room temperature for 50 h and treated with 9.5 g (94 mmol) of triethylamine. The mixture was stirred at 25 °C for 40 h, and the resulting solid was removed by filtration, washed with DMSO and water, and dried at 60 °C for 2 h to give 7.8 g (69%) of **15**: mp 174–179 °C; IR (KBr) 1742, 1638, 1612, 1470, 1402, 1369, 1311 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (m, 2 H), 1.23 (m, 2 H), 1.41 (t, 3 H, J = 7 Hz), 3.99 (m, 1 H), 4.39 (q, 2 H, J = 7 Hz), 8.41 (t, 1 H, J = 9 Hz), 8.67 (s, 1 H); MS m/e (relative intensity) 363 (17), 362 (100), 342 (30). Anal. ($C_{16}H_{12}F_5NO_3$) C, H, N, F.

1-Cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-8-(trifluoromethyl)-3-quinolinecarboxylic Acid (16). A solution of 0.5 g (1.3 mmol) of **15**, 3 mL of 5.0 M HCl, and 25 mL of THF was stirred at room temperature for 22 h and then heated at reflux for 5 h. The solvent was removed in vacuo, and the residue was triturated with water, filtered, washed with water, ethanol, and ether, and dried in vacuo at 60 °C for 2 h to afford 0.3 g (81%) of **16**: mp 243.5–244.5 °C; IR (KBr) 1726, 1619, 1469, 1269, 1160, 900 cm^{-1}; NMR ($CDCl_3$) δ 0.76 (m, 2 H), 1.28 (m, 2 H), 4.15 (m, 1 H), 8.46 (t, 1 H, J = 8.6 Hz), 8.97 (s, 1 H), 13.75 (bs, 1 H); MS m/e (relative intensity) 334 (3), 333 (6.5), 315 (6.4), 289 (35.6). Anal. ($C_{14}H_8F_5NO_3$) C, H, N, F.

7-(3-Amino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-8-(trifluoromethyl)-3-quinolinecarboxylic Acid (17a). A solution of 0.4 g (1.2 mmol) of **16**, 0.3 g (1.5 mmol) of 3-[*N*-(*tert*-butoxycarbonyl)amino]pyrrolidine, 1.5 g (1.5 mmol) of triethylamine, and 15 mL of CH_3CN was heated at reflux for 15 h. Additional pyrrolidine (1.5 mmol) and triethylamine (1.5 mmol) were added, and refluxing was continued an additional 20 h. The solution was concentrated in vacuo to an orange gum which was dissolved in ether and washed with brine and cold 0.5 M HCl. After drying ($MgSO_4$) and concentrating in vacuo, the residue was dissolved in a mixture of 5.0 M HCl (5 mL) and CH_3CN (50 mL) and stirred at room temperature for 18 h. The solvent was removed in vacuo, and the residue was dissolved in 20 mL of 1.0 M NaOH and filtered through a fiber glass pad to clarify. The filtrate was adjusted to pH 6.4 with 1.0 M HCl, and the resulting precipitate was removed by filtration, washed with water, and dried in vacuo to give 0.24 g (46%) of **17a**: mp 168–179 °C; IR (KBr) 1731, 1456, 1362, 1314, 1260, 1104 cm^{-1}; NMR (TFA) δ 0.8–1.25 (m, 2 H), 1.4–1.7 (m, 2 H), 2.4–2.8 (m, 2 H), 3.9–4.8 (m, 4 H), 4.4–4.6 (m, 2 H), 8.07 (d, 1 H, J = 13.6 Hz), 9.35 (s, 1 H); MS m/e (relative intensity) 400 (24), 399 (93). Anal. ($C_{18}H_{17}F_4N_3O_3 \cdot 0.46HCl \cdot 2.3H_2O$) C, H, N, Cl.

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-8-(trifluoromethyl)-3-quinolinecarboxylic Acid (18a). A solution of 0.4 g (1.4 mmol) of **16**, 0.5 g (5.2 mmol) of piperazine, and 10 mL of CH_3CN was heated at reflux for 20 h. The reaction was cooled to room temperature, and the yellow solid was removed by filtration, washed with water, and dried in vacuo. The crude solid was dissolved in 10 mL of 0.25 M NaOH and filtered to clarify, and the filtrate was adjusted to pH 6.9 with 1.0 M HCl. The purified solid was removed by filtration, washed with water, and dried in vacuo at 70 °C for 3 h to afford 0.21 g (47%) of **18a**: mp 225–228 °C; IR (KBr) 1734, 1622, 1561, 1494, 1369, 1322, 1255 cm^{-1}; NMR (TFA) δ 0.9–1.3 (m, 2 H), 1.4–1.8 (m, 2 H), 3.6–4.0 (m, 4 H), 4.6–4.8 (m, 1 H), 8.39 (d, 1 H, J = 11 Hz), 9.57 (s, 1 H); MS m/e (relative intensity) 399 (13, M^+), 357 (36), 313 (23). Anal. ($C_{18}H_{17}F_4N_3O_3 \cdot 0.33H_2O$) C, H, N, F.

7-[3-(Aminomethyl)-3-methyl-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-8-(trifluoromethyl)-3-quinolinecarboxylic Acid Hydrochloride (19a). A solution of 1.1 g (3.2 mmol) of **16**, 0.8 g (3.8 mmol) 3-[[*N*-(*tert*-butoxycarbonyl)amino]methyl]-3-methylpyrrolidine,[15] 1.2 g (11.4 mmol) of triethylamine, and 25 mL of CH_3CN was heated at reflux for 18 h. The solvent was removed in vacuo, and the residue was dissolved in a solution of 5.0 M HCl (5 mL) in THF (200 mL) and heated at reflux for 18 h. A yellow oil separated which crystallized to give 0.78 g (67%) of crude **19a**. A portion of the impure product (0.3 g) was dissolved in 10 mL of water and acidified to pH 6.0 with 1.0 M HCl. The resulting tan precipitate was removed by filtration, washed with water and MeOH, and dried in vacuo to give 0.21 g of pure **19a**: mp 235–237 °C; NMR (TFA) δ 1.27 (m, 2 H), 1.4–1.8 (m, 5 H), 2.22 (m, 2 H), 3.56 (m, 2 H), 3.8–4.2 (m, 2 H), 4.3 (m, 1 H), 4.53 (bs, 2 H), 8.07 (d, 1 H, J = 11 Hz), 9.37 (s, 1 H); MS m/e (relative intensity) 410 (100), 395 (94), 351 (40). Anal. ($C_{20}H_{21}F_4N_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

1-Cyclopropyl-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6-fluoro-1,4-dihydro-4-oxo-8-(trifluoromethyl)-3-quinolinecarboxylic Acid (20a). A solution of 2.0 g (6.1 mmol) of **16**, 0.9 g (7.3 mmol) of 3-[(ethylamino)methyl]-pyrrolidine,[16] 1.8 g (18.0 mmol) of triethylamine, and 30 mL of CH_3CN was heated at reflux for 2 h. The white precipitate was removed by filtration, washed with water, methanol, and ether, and dried in vacuo at 50 °C to give 2.2 g (80%) of **20a**: mp 227–232 °C; IR (KBr) 1627, 1581, 1577, 1559, 1455, 1388, 1358 cm^{-1}; NMR (DMSO-d_6) δ 0.93 (m, 2 H), 1.19 (bt, 5 H), 1.95 (m, 1 H), 2.19 (m, 1 H), 2.62 (m, 1 H), 2.95–3.03 (q, 2 H, J = 7.3 Hz), 3.1 (bs, 2 H), 3.62 (m, 1 H), 3.70–3.98 (m, 4 H), 7.85 (d, 1 H, J = 14.7 Hz), 8.75 (s, 1 H); MS m/e (relative intensity) 442 (6), 441 (3), 396 (100), 352 (32). Anal. ($C_{21}H_{23}F_4N_3O_3 \cdot 0.4H_2O$) C, H, N, F.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-8-(trifluoromethyl)-3-quinolinecarboxylic Acid (21a). A solution of 1.2 g (3.7 mmol) of **16**, 0.45 g (4.5 mmol) of 2-methylpiperazine,[17] 1.4 g (13.5 mmol) of triethylamine, and 15 mL of CH_3CN was heated to reflux for 60 h. The reaction mixture was cooled to room temperature, and the tan solid removed by filtration, washed with methanol and ether, and dried in vacuo at 55 °C to give 1.17 g (76%) of **21a**: mp 235 °C dec; IR (KBr) 1734, 1622, 1457, 1389, 1363, 1322, 1262 cm^{-1}; NMR (TFA) δ 1.11 (m, 2 H), 1.62 (bs, 5 H), 3.6–4.4 (m, 7 H), 4.65 (m, 1 H), 8.38 (d, 1 H, J = 11 Hz), 9.56 (s, 1 H); MS m/e (relative intensity) 414 (5), 413 (21), 358 (19), 357 (100), 313 (8). Anal. ($C_{19}H_{19}F_4N_3O_3 \cdot 0.2HF \cdot 0.8H_2O$) C, H, N, F.

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7-(4-Amino-1-piperidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-8-(trifluoromethyl)-3-quinolinecarboxylic Acid (22a). A solution of 1.0 g (3.0 mmol) of **16**, 1.5 g (15 mmol) of triethylamine, 1.2 g (4.0 mmol) of 4-[(trifluoroacetyl)amino]-piperidine,[19] and 30 mL of acetonitrile was heated at reflux for 18 h. The solid was removed by filtration, washed with acetonitrile and ether, and dried in vacuo. The solid was suspended in 30 mL of methanol and 10 mL of 1.0 N sodium hydroxide and stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in water, filtered through a fiber glass pad to clarify, and adjusted to pH 7.0 with 1.0 M hydrochloric acid. The precipitate which formed was removed by filtration, washed with water, and dried in vacuo to give 0.58 g (47%) of **22a**: mp 247–249 °C; IR (KBr) 1621, 1482, 1370, 1275 cm^{-1}; NMR (DMSO-d_6) δ 0.85 (s, 2 H, cycloprop.), 1.17 (bs, 2 H, cycloprop.), 1.67 (m, 2 H), 1.96 (m, 2 H), 3.37 (m, 3 H), 3.68 (m, 2 H), 4.03 (m, 1 H), 8.02 (d, 1 H, J = 11 Hz, C_5H), 8.40 (s, 1 H, C_2H), 10.13 (bs, 3 H, NH_2 and CO_2H); MS m/e (relative intensity) 413 (100, M^+), 352 (33), 283 (27). Anal. ($C_{19}H_{19}F_4N_3O_3 \cdot 2.4H_2O$) C, H, N.

7-(3-Amino-1-piperidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-8-(trifluoromethyl)-3-quinolinecarboxylic Acid (23a). A solution of 0.7 g (2.4 mmol) of **16**, 0.5 g (3.0 mmol) of 3-aminopiperidine dihydrochloride,[20] 0.9 g (9.0 mmol) of triethylamine, and 30 mL of acetonitrile was heated at reflux for 20 h. The resulting precipitate was removed by filtration, washed with acetonitrile, and suspended in water. The aqueous suspension was basified to pH 11.5 with 10% sodium hydroxide. The resulting solution was filtered through a fiber glass pad to clarify, and the filtrate was adjusted to pH 7.0 with 1.0 M hydrochloric acid. The resulting precipitate was removed by filtration, washed with water, and dried in vacuo to give 0.47 g (75%) of **23a**: mp 222–223 °C; IR (KBr) 1619, 1472, 1368, 1275, 1118 cm^{-1}; NMR (DMSO-d_6) δ 0.88 (bs, 2 H, cycloprop.), 1.20 (bs, 2 H, cycloprop.), 1.70 (m, 2 H), 1.89 (m, 1 H), 2.14 (m, 1 H), 3.35 (m, 4 H), 3.86 (m, 1 H), 4.09 (m, 1 H), 6.07 (bs, 3 H, NH_2 and CO_2H), 8.09 (d, 1 H, J = 10 Hz, C_5H), 8.88 (s, 1 H, C_2H); MS m/e (relative intensity) 413 (27, M^+), 371 (57), 358 (100). Anal. ($C_{19}H_{19}F_4N_3O_3 \cdot 1.8H_2O$) C, H, N.

7-(3-Amino-1-piperidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Dihydrochloride (23b). A solution of 1.4 g (5.0 mmol) of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,[11e] 1.7 g (10 mmol) of 3-aminopiperidine dihydrochloride,[20] 3.0 g (30 mmol) of triethylamine, and 50 mL of acetonitrile was heated at reflux for 4 h. The solid was removed by filtration, washed with acetonitrile and ether, and dried in vacuo. The precipitate was suspended in water and acidified to pH 2.0 with 1.0 M hydrochloric acid. The solution was filtered through a fiber glass pad to clarify and lyophilized. The residue was triturated with ethanol, filtered, washed with ethanol and ether, and dried in vacuo to give 1.4 g (70%) of **23b**: mp 314–316 °C; IR (KBr) 1623, 1588, 1493, 1395, 1298, 1265 cm^{-1}; NMR (DMSO-d_6) δ 1.30 (s, 4 H, cycloprop.), 1.68 (m, 2 H, pip.), 1.88 (m, 1 H, pip.), 2.11 (m, 1 H, pip.), 3.23 (m, 4 H, pip.), 3.68 (m, 1 H, pip.), 4.09 (m, 1 H, cycloprop.), 7.85 (d, 1 H, J = 11 Hz, C_5H), 8.37 (bs, 2 H, NH_3^+), 8.70 (s, 1 H, C_2H), 14.73 (bs, 1 H, CO_2H); MS m/e (relative intensity) 363 (62), 321 (100), 307 (87), 276 (66). Anal. ($C_{18}H_{19}F_2N_3O_3 \cdot 2HCl \cdot 1.5H_2O$) C, H, N.

7-(3-Amino-1-piperidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (23c). A solution of 1.5 g (5.7 mmol) of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid,[11e] 1.0 g (6.0 mmol) of 3-aminopiperidine dihydrochloride,[20] 1.5 g (15 mmol) of triethylamine, and 60 mL of acetonitrile was heated at reflux for 4 h. After cooling to room temperature, the precipitate which resulted was removed by filtration, washed with acetonitrile, and dried. The solid was suspended in water and basified to pH 11.5 with 10% sodium hydroxide and filtered through a fiber glass pad to clarify. The resulting solution was adjusted to pH 7.0 with 1.0 M hydrochloric acid, and the resulting precipitate was removed by filtration, washed with water, and dried in vacuo to give 1.29 g (65%) of **23c**: mp 211–213 °C; IR (KBr) 1733, 1696, 1668, 1332, 1307 cm^{-1}; NMR (DMSO-d_6) δ 1.31 (m, 4 H, cycloprop.), 1.66 (m, 2 H), 1.92 (m, 2 H), 3.13 (m, 2 H), 3.46 (m, 2 H), 3.79 (m, 2 H), 7.60 (d, 1 H, J = 6 Hz, C_8H), 7.92 (d, 1 H, J = 11 Hz, C_5H), 8.22 (bs, 2 H, NH_2), 8.67 (s, 1 H, C_2H); MS m/e (relative intensity) 346 (31, M^+), 345 (31, M^+), 302 (49), 301 (49), 290 (48), 257 (100). Anal. ($C_{18}H_{20}FN_3O_3 \cdot 2.1H_2O$) C, H, N, F.

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