7 Hz, J_{PH} = 7 Hz, 4 × OCH_2), 7.32 (s, NH). Anal. ($C_{15}H_{31}NO_7P_2$) N, P.

This product was dissolved in 50 mL of 40% hydrogen bromide in glacial acetic acid solution and the resultant mixture left overnight. Evaporation of solvents and hydrogen bromide yielded an oily residue that was washed twice with dry diethyl ether and dissolved in methanol. The methanolic solution of [1-[*N*-(phosphonoacetyl)amino]cyclopentyl]phosphonic acid was titrated with 1 M sodium hydroxide solution in methyl alcohol to adjust to pH 7. This mixture was warmed to boiling and cooled to room temperature. The precipitated, hygroscopic product was collected by filtration: yield 1.65 g (22%); IR (KBr) ν 3700–2000, 3305 (NH), 1635 (CO), 1570 (NH), 1050 (PO_3^{2-}); ^{1}H NMR (D_2O, HMDS) δ 1.6–3.0 (m, cyclopentyl CH_2), 3.07 (d, J = 18.5 Hz, CH_2P).

Pentasodium 4-[*N*-(Phosphonoacetyl)amino]-4-phosphonobutyrate (22). Typical Example of Method B. Methyl 4-amino-4-(diethoxyphosphinoyl)butyrate (6.2 g, 0.0181 mol) was dissolved in 100 mL of dry chloroform containing 8.2 mL (0.0543 mol) of triethylamine, cooled to −5 °C, and acylated with 1.45 mL (0.019 mol) of chloroacetyl chloride. The resulting solution was washed successively with water, 5% hydrochloric acid solution, water, saturated solution of sodium bicarbonate, water, and brine and dried over anhydrous sodium sulfate. Evaporation of the chloroform yielded *C*-methyl *P,P*-diethyl 4-[*N*-(chloroacetyl)amino]-4-phosphonobutyrate, which was dissolved in 30 mL of triethyl phosphite and heated at 160–180 °C for 1.5 h. The insoluble products were removed by filtration, and the volatile components were removed under reduced pressure, yielding *C*-methyl *P,P,P,P*-tetraethyl 4-[*N*-(phosphonoacetyl)amino]-4-phosphonobutyrate: yield 4.4 g (56%); ^{1}H NMR ($CDCl_3$, HMDS) δ 1.33 (brt, J = 7 Hz, 4 × OCH_2CH_3), 1.6–2.8 (m, CH_2CH_2CO), 3.00 (d, J = 21.5 Hz, CH_2P), 3.66 (s, OCH_3), 3.95–4.9 (m, J = 7.5 Hz, 4 × OCH_2, NCHP), 8.01 (brd, J = 9.5 Hz, NH). Anal. ($C_{15}H_{31}NO_9P_2$) N, P.

This compound was acidolyzed with 70 mL of 40% hydrogen bromide in glacial acetic acid solution, and the resulting free acid was converted to the hygroscopic salt **22** as in method A: yield 1.85 g (25%); IR (KBr) ν 3700–2000, 1715 (CO), 1625 (CO), 1540 (NH), 1170, 1050 (PO_3^{2-}); ^{1}H NMR (D_2O, HMDS) δ 2.2–2.45 (m, CH_2CH_2CO), 3.49 (d, J = 19.5 Hz, CH_2P), 4.3–5.0 (m, NCHP).

Tetrasodium [1-[*N*-(Phosphonoacetyl)amino]-2-methylpropyl]phosphonate (17). Typical Procedure for Method C. Diphenyl 1-amino-2-methylpropylphosphonate (12.3 g, 0.04 mol) was acylated analogously as in method B, yielding [1-[*N*-(chloroacetyl)amino]-2-methylpropyl]phosphonate, which was reacted with 60 mL of triethyl phosphite at 160–180 °C for 15 h. Evaporation of the volatile components gave *P*-phenyl *P,P,P*-triethyl [1-[*N*-(phosphonoacetyl)amino]-2-methylpropyl]-phosphonate: yield 12.5 g (72%); ^{1}H NMR ($CDCl_3$, HMDS) δ 1.02 and 1.08 (d, J = 7 Hz, 2 × $CHCH_3$), 2.0–2.55 (m, $CHCH_3$), 2.88 (d, J = 21.5 Hz, CH_2P), 3.4–4.2 (m, J = 7 Hz, J_{PH} = 7 Hz, 3 × OCH_2, NCHP), 6.82 (s, aromatic protons), 7.55 (d, J = 10 Hz, NH). Anal. ($C_{18}H_{31}NO_7P_2$) N, P.

Acidolysis of this product with 100 mL of hydrogen bromide in glacial acetic acid and neutralization with methanolic sodium hydroxide yielded the tetrasodium [1-[*N*-(phosphonoacetyl)-amino]-2-methylpropyl]phosphonate: yield 9.2 g (63%); IR (KBr) ν 3650–2700, 3300 (NH), 1630 (CO), 1545 (NH), 1095 (PO_3^{2-}); ^{1}H NMR (D_2O, HMDS) δ 1.38 (brd, 2 × CH_3), 1.36–2.0 (m, $CHCH_3$), 3.03 (d, J = 20.5 Hz, CH_2P), 4.22 (brd of brd, J = 7 Hz, J_{PH} = 17.5 Hz, CHP).

Biological Assays. Cells were grown in a modified minimal essential medium eagle with Earle's salts (EMEM) supplemented with 10% fetal calf serum (both Flow). Experiments were carried out according to the standard Geran's protocol,[30] using [[*N*-(phosphonoacetyl)amino]alkyl]phosphonic acid salts in the concentration range 1–400 μg mL^{-1}. The growth of cells in cultures was determined by measuring the total cell protein according to Lowry.[31] Tetrasodium *N*-(phosphonoacetyl)-L-aspartate was used as a positive control.

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Synthesis and Structure–Activity Relationships of Novel Arylfluoroquinolone Antibacterial Agents[1]

Daniel T. W. Chu,* Prabhavathi B. Fernandes, Akiyo K. Claiborne, Eva Pihuleac, Carl W. Nordeen, Robert E. Maleczka, Jr., and Andre G. Pernet

Antiinfective Research Division, Abbott Laboratories, North Chicago, Illinois 60064. *Received April 1, 1985*

A series of novel arylfluoroquinolones has been prepared. These derivatives are characterized by having a fluorine atom at the 6-position, substituted amino groups at the 7-position, and substituted phenyl groups at the 1-position. Structure–activity relationship (SAR) studies indicate that the in vitro antibacterial potency is greatest when the 1-substituent is either *p*-fluorophenyl or *p*-hydroxyphenyl and the 7-substituent is either 1-piperazinyl, 4-methyl-1-piperazinyl, or 3-amino-1-pyrrolidinyl. The electronic and spatial properties of the 1-substituent, as well as the steric bulk, play important roles in the antimicrobial potency in this class of antibacterials. As a result of this study, compounds **45** and **41** were found to possess excellent in vitro potency and in vivo efficacy.

Since the introduction of nalidixic acid (**1**)[2] in 1963 for the treatment of urinary tract infections, a large number of related derivatives have been synthesized. The earlier derivatives[3] such as oxolinic acid (**2**), rosoxacin (**3**), and pipemidic acid (**4**) have been used as gram-negative antibacterial agents. Recently, several new analogues containing fluorine atoms have been made; these compounds are potent broad-spectrum antibacterial agents. Included in this group are pefloxacin (**5**),[4] norfloxacin (**6**),[5] enoxacin (**7**),[6] ofloxacin (**8**),[7] and ciprofloxacin (**9**).[8]

(1) This work was presented in part at the 24th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, Oct 8–10, 1984, Abstract 72.

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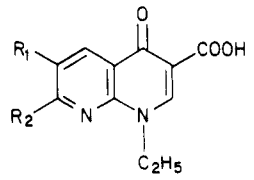
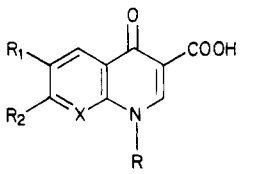


1: R_1 = H, R_2 = CH_3, X = N
2: R_1, R_2 = OCH_2O, X = CH
3: R_1 = H, R_2 = 4-pyridyl, X = CH
4: CR_1 = N, R_2 = 1-piperazinyl, X = N
5: R_1 = F, R_2 = 4-methyl-1-piperazinyl, X = CH
6: R_1 = F, R_2 = 1-piperazinyl, X = CH
7: R_1 = F, R_2 = 1-piperazinyl, X = N

The 1-alkyl-1,4-dihydro-4-oxo-3-pyridinecarboxylic acid moiety is a common feature of these antimicrobial agents. Structure–activity relationship (SAR) studies seem to indicate that the antibacterial potency is greatly influenced by the steric bulk of the 1-substituent.[3] The ethyl analogues are generally more active than analogues with smaller or larger 1-alkyl substituents. However, the vinyl analogues, in some cases, have potencies comparable to those of the ethyl analogues. Other variants are ciprofloxacin (**9**), amifloxacin (**10**),[9] and miloxacin (**11**),[10] which have 1-cyclopropyl, 1-methylamino, and 1-methyoxy substituents, respectively.



8: X, R = $COCH_2CH(CH_3)$, R_1 = F, R_2 = 4-methyl-1-piperazinyl
9: R = C_3H_5, R_1 = F, X = CH, R_1 = 1-piperazinyl
10: R = $NHCH_3$, R_1 = F, X = CH, R_2 = 4-methyl-1-piperazinyl
11: R = OCH_3, R_1R_2 = OCH_2O, X = CH

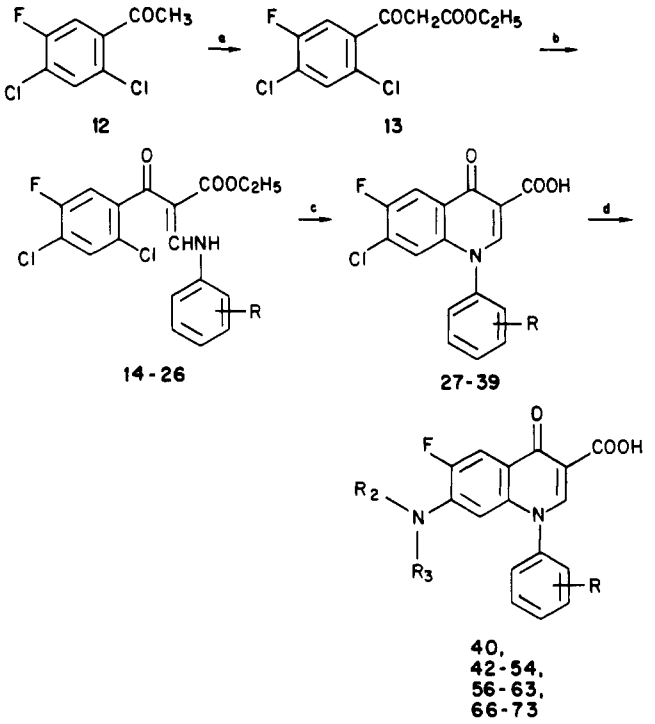
So far, modifications with different substituents at N-1 position are guided by the steric bulk factor. Little attention has been paid to the role of substituent's influence on N-1 atom itself, which may be a contributor to biological activity. In this paper, we report the syntheses and antibacterial activity of 7-(substituted amino)-6-fluoro-1-aryl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid derivatives. Compounds **45** (A-56619) and **41** (A-56620) are novel analogues of pefloxacin (**5**) and norfloxacin (**6**) in which the N-1 ethyl groups of these antibacterials have been replaced by *p*-fluorophenyl groups. The phenyl groups are bulkier than the ethyl group. With respect to N-1 substituent, this study shows unequivocally that, in addition to steric bulk, there are other factors that also play a great influence on the biological activity of this class of antibacterials.

Chemistry

The general method used for the preparation of quinolone antibacterial agents involves the alkylation of 4-hydroxyquinoline-3-carboxylic alkyl ester with an alkyl halide to form the 1-alkylated 1,4-dihydro-4-oxo-quinoline-3-carboxylic acid ester derivative which is the key intermediate.[3] This process, however, makes the introduction of a phenyl ring at the 1-position difficult. The 1-aryl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid derivatives were synthesized as illustrated in Scheme I.

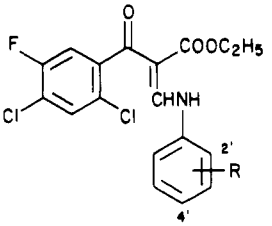
Condensation of 2,4-dichloro-5-fluoroacetophenone (**12**) with diethyl carbonate in the presence of sodium hydride yielded the ethyl 2,4-dichloro-5-fluorobenzoyl acetate (**13**). Treatment of this ester with triethyl orthoformate in acetic anhydride gave the one-carbon homologue enol ether in-

Scheme I



[a] $(C_2H_5O)_2CO$/NaH. [b] (1) $CH(OC_2H_5)_3/AC_2O$; (2) NH_2–C$_6$H$_4$–R. [c] (1) NaH; (2) NaOH/H^+. [d] NHR_2R_3/*N*-methyl-2-pyrrolidinone.

Table I. Ethyl 3-Anilino-2-(2,4-dichloro-5-fluorobenzoyl)acrylates



compd	R	yield,[a] %	mp, °C	formula[b]
14	H	89	96–97	$C_{18}H_{14}Cl_2FNO_3$
15	2′-F	78.8	90–92	$C_{18}H_{13}Cl_2F_2NO_3$
16	3′-F	68.5	103–104	$C_{18}H_{13}Cl_2F_2NO_3$
17	4′-F	75.6	111–112	$C_{18}H_{13}Cl_2F_2NO_3$[c]
18	4′-Br	73.7	130	$C_{18}H_{13}BrCl_2FNO_3$
19	4′-Cl	87.4	108–109	$C_{18}H_{13}Cl_3FNO_3$
20	4′-OH	77.2	160–161	$C_{18}H_{14}Cl_2FNO_4$
21	4′OCH_3	77	105	$C_{19}H_{16}Cl_2FNO_4$
22	4′-CH_3	79.7	115.5	$C_{19}H_{16}Cl_2FNO_3$
23	3′,4′-OCH_2O	66	109–110	$C_{19}H_{14}Cl_2FNO_5$
24	2′-F; 4′-F	65	92–93	$C_{18}H_{12}Cl_2F_3NO_3$
25	2′-CH_3	65	100–101	$C_{19}H_{16}Cl_2FNO_3$
26	2′-CH_3; 6′-CH_3	82	151–152	$C_{20}H_{18}Cl_2FNO_3$[d]

[a] Yields were not optimized. [b] C, H, and N analyses were within ±0.4% of the theoretical values, unless otherwise noted. [c] C: calcd, 54.02; found, 54.50. [d] C: calcd, 58.55; found, 60.27.

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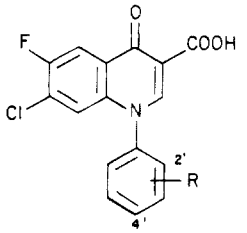
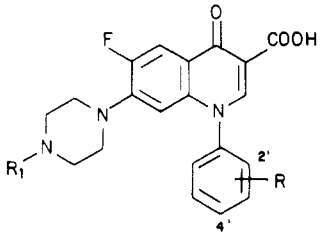
Table II. 1-Aryl-6-fluoro-7-chloro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids



compd	R	yield,[a] %	mp, °C	formula[b]
27	H	75	271–273	$C_{16}H_9ClFNO_3 \cdot {}^1/_4H_2O$
28	2′-F	65.5	248–249	$C_{16}C_8ClF_2NO_3$
29	3′-F	59.3	*c*	$C_{16}H_8ClF_2NO_3$
30	4′-F	84.9	260–263	$C_{16}H_8ClF_2NO_3$
31	4′-Br	68	*c*	$C_{16}H_8BrClFNO_3$
32	4′-Cl	79.4	*c*	$C_{16}H_8Cl_2FNO_3$
33	4′-OH	60	*c*	$C_{16}H_9ClFNO_4$
34	4′OCH_3	83	240	$C_{17}H_{11}ClFNO_4$[d]
35	4′-CH_3	84	269–271	$C_{17}H_{11}ClFNO_3$
36	3′,4′-OCH_2O	66	273–276	$C_{17}H_9ClFNO_5$
37	2′-F; 4′-F	99	248	$C_{16}H_7ClF_3NO_3$
38	2′-CH_3	45.3	249–250	$C_{17}H_{11}ClFNO_3$
39	2′-CH_3; 6′-CH_3	50.7	255–256	$C_{18}H_{13}ClFNO_3$

[a,b] See Table I, footnotes *a* and *b*. [c] Mp >275 °C. [d] C: calcd, 58.72; found, 59.56; H: Calcd, 3.19; found, 3.78.

Table III. 7-(1-Piperazinyl)-4-quinolines



compd	R_1	R	yield,[a] %	formula[b,c]
40	H	H	66	$C_{20}H_{18}FN_3O_3 \cdot HCl \cdot {}^1/_4H_2O$
41	H	4′-F	56	$C_{20}H_{17}F_2N_3O_3 \cdot HCl \cdot H_2O$
42	CH_3	H	51	$C_{21}H_{20}FN_3O_3 \cdot HCl \cdot {}^1/_4H_2O$
43	CH_3	2′-F	61.4	$C_{21}H_{19}F_2N_3O_3 \cdot HCl \cdot {}^1/_2H_2O$
44	CH_3	3′-F	17.3	$C_{21}H_{19}F_2N_3O_3 \cdot HCl \cdot {}^1/_4H_2O$
45	CH_3	4′-F	76	$C_{21}H_{19}F_2N_3O_3 \cdot HCl$
46	CH_3	4′-Br	60.3	$C_{21}H_{19}BrFN_3O_3 \cdot HCl \cdot {}^1/_2H_2O$
47	CH_3	4′-Cl	68.3	$C_{21}H_{19}ClFN_3O_3 \cdot HCl \cdot H_2O$
48	CH_3	4′-OH	62.6	$C_{21}H_{20}FN_3O_4 \cdot HCl$
49	CH_3	4′-OCH_3	36.8	$C_{22}H_{22}FN_3O_4 \cdot HCl \cdot {}^1/_2H_2O$
50	CH_3	4′-CH_3	39	$C_{22}H_{22}FN_3O_3 \cdot HCl \cdot {}^1/_2H_2O$[d]
51	CH_3	3′,4′-OCH_2O	50.1	$C_{22}H_{20}FN_3O_5 \cdot HCl \cdot 3H_2O$
52	CH_3	2′-F; 4′-F	29	$C_{21}H_{18}F_3N_3O_3 \cdot HCl \cdot H_2O$
53	CH_3	2′-CH_3	8	$C_{22}H_{22}FN_3O_3 \cdot HCl \cdot {}^1/_2H_2O$
54	CH_3	2′-CH_3; 6′CH_3	31	$C_{23}H_{24}FN_3O_3 \cdot HCl \cdot {}^1/_2H_2O$

[a,b] See Table I, footnotes *a* and *b*. [c] Melting points of all the compounds are >275 °C, unless otherwise noted. [d] C: calcd, 59.93; found, 59.24.

termediate, which upon evaporation of solvent to dryness was allowed to react with a slight excess of an appropriate aniline in methylene chloride at room temperature to give the enamino keto ester **14–26** (Table I). Cyclization of **14–26** with 1 mol equiv of sodium hydride in dimethoxyethane or tetrahydrofuran (THF) yielded ethyl 1,4-dihydro-4-oxo-quinoline-3-carboxylate, which, generally without purification, was hydrolyzed with aqueous sodium hydroxide in THF to give the 1-aryl-6-fluoro-7-chloro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**27–39**) (Table II). These 7-chloro-4-quinolines **27–39** were allowed to react with amines to obtain the desired 7-amino derivatives **40, 42–54** (Table III), **56–63**, and **66–73** (Table IV). The 7-(1-piperazinyl)-4-quinolone **41** was prepared by reacting the 7-chloro-4-quinolone (**30**) with carboethoxypiperazine followed by saponification of the product with aqueous sodium hydroxide. The 7-(4-butyl-1-piperazinyl)-4-quinolone derivative **55** was prepared by reductive amination of butyraldehyde with **41**. The 7-(3-amino-1-pyrrolidinyl)-4-quinolone derivatives **64** and **65** were prepared by the hydrolysis of the acetyl derivatives **67** and **73**, respectively, with hydrochloric acid.

Results and Discussion

Tables V and VI summarize the in vitro antibacterial activity of the 1-aryl-4-quinolones against five gram-positive bacteria (*Staphylococcus aureus* ATCC 6538P, *Staphylococcus aureus* CMX 686B, *Staphylococcus epidermidis* 3519, *Streptococcus faecium* ATCC 8043, *Streptococcus pyrogens* 930) and six gram-negative organisms (*Escherichia coli* Juhl, *Enterobacter aerogenes* ATCC 13048, *Klebsiella pneumoneae* 8045, *Pseudomonas* Aeruginosa 5007, *Pseudomonas aeruginosa* K799/WT, *Acinetobacter* CMX 669). The data for norfloxacin (**6**) are included for comparison.

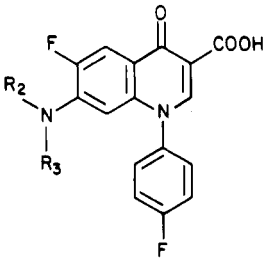
The effect of substitutions on the 1-phenyl ring of the 6-fluoro-7-piperazinyl-4-quinolones on the in vitro antibacterial potency is shown in Table V. The data for the first three entries indicate that compound **40** has similar in vitro potency as norfloxacin while compound **41** which has a fluorine substituted at the para position, is more potent. The *p*-hydroxy derivative **48** is the most potent compound in this series in vitro. The 2′,4′-difluoro-substituted derivative **52** is as potent as norfloxacin. Since these these arylfluoroquinolone derivatives are found to possess inhibitory effect on DNA gyrase[11] and the bulk factors (MR_s)[12] for C_6H_5, C_6H_4F, $C_6H_3F_2$, C_6H_4OH, and C_2H_5 are 25·36, 25·25,[13] 25·14,[13] 27·18,[13] and 10·30, the biological data are not in agreement with the generally accepted conventional notion that the antibacterial potency of this class of antibacterials is closely related to the steric bulk of the 1-substituent, with ethyl group being most potent. Hence, steric bulk alone does not determine biological activity in this class of antibacterial compounds.

The in vitro antibacterial activites of various analogues with amino substitutions at the 7-position and a *p*-fluorophenyl group at N-1 position are shown in Table VI. For those analogues (**41, 45, 55**) having either piperazine or 4-alkylpiperazine at the 7-position, potencies generally decreased as size of the 4-substituent on the piperazine ring increased. Morpholine, thiomorpholine, and piperidine analogues **57–59** showed good in vitro antibacterial activities. In general, replacing the basic nitrogen of the 4-piperazine with a nonbasic atom resulted in improved activity against gram-positive bacteria and slightly decreased activity against gram-negative bacteria. In order to relate ring size of the 7-substituent to antibacterial activity, derivatives **56** and **62–66** were made. The homopiperazine analogue **56** is less active. However, the 3-aminopyrrolidine analogue **64** is the most potent in vitro compound in the series. *N*-Acyl derivatives **67–71** also showed reasonably good activities.

A comparison of the in vitro and in vivo antimicrobial potency of the *p*-fluorophenyl analogues **41** and **45** with

(11) Hansch, C.; Leo, A. "Substituent Constants for Correlation Analysis in Chemistry and Biology"; Wiley-Interscience: New York, 1978; pp 49–51.
(12) Private communication from Dr. L. Shen of Abbott Laboratories.
(13) Estimated values.

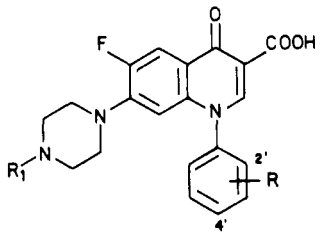
Table IV. 7-Amino-1-(*p*-fluorophenyl)-4-quinolines



compd	R_2	R_3	yield,[a] %	formula[b,c]
41	$-(CH_2)_2NH(CH_2)_2-$		56	$C_{20}H_{17}F_2N_3O_3 \cdot HCl \cdot H_2O$
45	$-(CH_2)_2N[CH_3](CH_2)_2-$		76	$C_{21}H_{19}F_2N_3O_3 \cdot HCl$
55	$-(CH_2)_2N[C_4H_9](CH_2)_2-$		54.4	$C_{24}H_{25}F_2N_3O_3 \cdot HCl \cdot H_2O$[d]
56	$-(CH_2)_2NH(CH_2)_3-$		11	$C_{21}H_{19}F_2N_3O_3 \cdot HCl \cdot {}^1/_4H_2O$
57	$-(CH_2)_2O(CH_2)_2-$		56.5	$C_{20}H_{16}F_2N_2O_4$
58	$-(CH_2)_2S(CH_2)_2-$		62.4	$C_{20}H_{20}F_2N_2SO_3 \cdot {}^1/_4H_2O$
59	$-(CH_2)_5-$		53.8	$C_{21}H_{18}F_2N_2O_3$
60	$-(CH_2)_2CH[OH](CH_2)_2$		44.3	$C_{21}H_{18}F_2N_2O_4$
61	$-(CH_2)_2CH[N(CH_3)_2](CH_2)_2-$		36.3	$C_{23}H_{23}F_2N_3O_3 \cdot HCl$
62	$-(CH_2)_4-$		41	$C_{20}H_{16}F_2N_2O_3$
63	$-CH_2CH(OH)CH_2CH_2-$		55.2	$C_{20}H_{16}F_2N_2O_4$
64	$-CH_2CH(NH_2)CH_2CH_2-$		50	$C_{20}H_{17}F_2N_3O_3 \cdot HCl$[e]
65	$-CH_2CH(NHCH_3)CH_2CH_2-$		83.1	$C_{21}H_{19}F_2N_3O_3 \cdot HCl \cdot {}^5/_4H_2O$
66	$-CH_2CH[N(CH_3)_2]CH_2CH_2-$		51.8	$C_{22}H_{21}F_2N_3O_3$
67	$-CH_2CH(NHCOCH_3)CH_2CH_3-$		57.6	$C_{22}H_{19}F_2N_3O_4$
68	$-(CH_2)_2N[COCH_3](CH_2)_2-$		42.3	$C_{22}H_{19}F_2N_3O_4 \cdot {}^1/_2H_2O$
69	$-(CH_2)_2N[COC_2H_5](CH_2)_2-$		41.8	$C_{23}H_{21}F_2N_3O_4$
70	$-(CH_2)_2NHCOCH_2-$		53.1	$C_{20}H_{15}F_2N_3O_4 \cdot {}^1/_4H_2O$
71	$-(CH_2)_2N(CH_3)COCH_2-$		66.4	$C_{21}H_{17}F_2N_3O_4 \cdot {}^1/_4H_2O$
72	CH_3	$CH(CH_3)_2$	16	$C_{20}H_{18}F_2N_2O_3 \cdot {}^1/_4H_2O$[f]
73	$-CH_2CH[NCH_3COCH_3]CH_2CH_2-$		67.5	$C_{23}H_{21}F_2N_3O_4$

[a, b] See Table I, footnotes *a* and *b*. [c] See Table III, footnote *c*. [d] Mp 252–255 °C. [e] C: calcd, 45.94; found, 57.92. [f] Mp 264–266 °C.

Table V. In Vitro Antibacterial Activity of 7-(Piperazinyl)-4-quinolones[a]



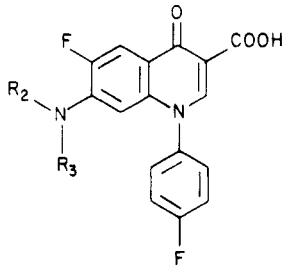
	organism: min inhib concn (MIC),[b] μg/mL										
compd	Sa(A)	Sa	Se	Sf	Sp	Ec	Ea	Kp	Pa(5)	Pa(K)	A
6	0.78	0.78	1.56	0.78	3.1	0.1	0.2	0.1	0.39	0.39	6.2
40	0.39	0.39	1.56	12.5	1.56	0.2	0.39	0.1	0.78	1.56	0.78
41	0.2	0.2	0.39	1.56	0.78	0.05	0.2	0.02	0.39	0.39	0.2
42	0.78	0.78	0.78	12.5	3.1	0.78	1.56	0.2	6.2	3.1	1.56
43	1.56	1.56	1.56	12.5	12.5	0.78	0.78	0.39	6.2	6.2	0.78
44	12.5	12.5	12.5	50	25	6.2	6.2	3.1	50	50	50
45	0.2	0.2	0.39	1.56	1.56	0.2	0.78	0.1	1.56	1.56	0.2
46	3.1	3.1	3.1	100	50	6.2	12.5	3.1	50	25	12.5
47	1.56	1.56	1.56	100	12.5	1.56	1.56	0.78	12.5	6.2	1.56
48	0.05	0.1	0.2	0.39	0.2	0.1	0.2	0.05	0.39	0.39	0.39
49	12.5	12.5	50	100	50	50	50	12.5	200	100	50
50	1.56	1.56	3.1	50	12.5	1.56	3.1	0.78	12.5	12.5	1.56
51	0.78	0.78	1.56	50	12.5	0.78	0.78	0.2	6.2	6.2	0.78
52	0.1	0.1	0.39	0.78	0.78	0.2	0.39	0.1	1.56	1.56	0.1
53	3.1	3.1	3.1	50	50	1.56	3.1	1.56	25	12.5	1.56
54	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100

[a] Structures are shown in Table III. [b] The MICs were determined by the twofold agar dilution on brain–heart infusion agar. Organisms selected for inclusion in the table: Sa(A), *Staphylococcus aureus* ATCC 6538P; Sa, *Staphylococcus aureus* CMX 686B; Se, *Staphylococcus epidermidis* 3519; Sf, *Streptococcus faecium* ATCC 8043; Sp, *Streptococcus pyogens* 930; Ec, *Escherichia coli* Juhl; Ea, *Enterobacteri aerogenes* ATCC 13048; Kp, *Klebsiella pneumoneae* 8045; Pa(5), *Pseudomona aeruginosa* 5007; Pa(k), *Pseudomona aeruginosa* K799/WT; A, *Actinetobacter sp.* CMX669.

their ethylated counterpart norfloxacin (**6**) and pefloxacin (**5**) is shown in Table VII. Both the 7-(4-methyl-1-piperazinyl)-4-quinolone derivatives **45** and pefloxacin (**5**) show increased oral activity against *E. coli* Juhl relative to the two 7-(1-piperazinyl)-4-quinolone analogues **41** and norfloxacin (**6**).

As a result of this study compounds **45** and **41** were found to possess broad and potent *in vitro* antibacterial

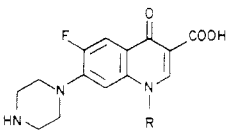
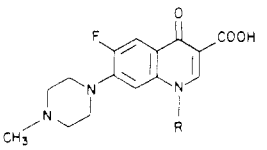
Table VI. In Vitro Antibacterial Activity of 7-Amino-1-(*p*-fluorophenyl)-4-quinolines[a]



	organism: min inhib concn (MIC),[b] μg/mL										
compd	Sa(A)	Sa	Se	Sf	Sp	Ec	Ea	Kp	Pa(5)	Pa(K)	A
6	0.78	0.78	1.56	0.78	3.1	0.1	0.2	0.1	0.39	0.39	6.2
41	0.2	0.2	0.39	1.56	0.78	0.05	0.2	0.02	0.39	0.39	0.2
45	0.2	0.2	0.78	1.56	1.56	0.2	0.78	0.1	1.56	1.56	0.2
55	0.78	0.78	1.56	12.5	6.2	1.56	1.56	0.39	12.5	12.5	3.1
56	0.78	0.78	1.56	12.5	6.2	0.2	0.39	0.1	1.56	3.1	1.56
57	0.1	0.1	0.2	1.56	1.56	0.39	0.78	0.39	3.1	3.1	0.78
58	0.05	0.05	0.1	0.78	0.78	0.78	0.78	0.39	3.1	3.1	0.78
59	0.2	0.2	0.39	3.1	1.56	1.56	3.1	1.56	6.2	6.2	1.56
60	0.1	0.1	0.39	1.56	1.56	0.39	1.56	0.39	6.2	3.1	1.56
61	0.39	0.39	0.78	3.1	1.56	0.39	0.78	0.39	3.1	3.1	0.78
62	0.1	0.1	0.2	0.78	0.78	0.78	0.78	0.39	1.56	1.56	0.78
63	<0.1	<0.1	0.2	1.56	1.56	0.2	0.78	0.2	3.1	3.1	0.39
64	0.05	0.05	0.05	0.78	0.1	0.02	0.05	0.02	0.2	0.2	0.2
65	3.1	3.1	6.2	25	12.5	3.1	3.1	0.78	50	50	6.2
66	0.39	0.39	0.39	25	3.1	0.39	0.78	0.2	25	12.5	0.78
67	0.1	0.39	0.39	1.56	0.78	0.78	1.56	0.78	6.2	6.2	3.1
68	0.2	0.2	0.78	3.1	1.56	1.56	3.1	1.56	12.5	12.5	12.5
69	0.2	0.2	0.78	6.2	1.56	1.56	3.1	0.78	12.5	12.5	6.2
70	0.2	0.39	0.78	1.56	0.78	0.39	1.56	0.39	6.2	3.1	12.5
71	0.1	0.2	0.2	0.78	0.39	0.39	0.39	0.2	1.56	0.78	0.39
72	0.78	0.78	1.56	12.5	12.5	6.2	6.2	3.1	100	50	12.5

[a] Structures are shown in Table IV. [b] See corresponding footnote to Table V.

Table VII. Structure-Activity Relationship: $-C_6H_4F$ vs. $-C_2H_5$ at Position 1 of 6-Fluoro-4-quinolines

compd	in vitro MIC,[a] μg/mL, *E. coli* Juhl	in vivo vs. *E. coli* Juhl (X100LD$_{50}$)[a] ED$_{50}$,[b] mg/kg	
		sc	po
			
6, R = C_2H_5	0.1	0.6 (0.4-1.0)	15.1 (10.4-21.8)
41, R = *p*-C_6H_4F	0.05	0.6 (0.3-1.3)	4.3 (2.8-6.5)
			
5, R = C_2H_5	0.1	0.5 (0.1-1.6)	3.2 (2.0-5.0)
45, R = *p*-C_6H_4F	0.2	1.6 (1.0-2.5)	3.1 (2.4-4.0)

[a] See the Experimental Section. [b] 95% confidence limits.

activities and excellent *in vivo* efficacy in systemic infections in mice. Detailed accounts of their antibacterial and pharmacokinetic properties will be reported elsewhere.

Experimental Section

Melting points were taken in a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were obtained for all new compounds reported. Carbon, hydrogen, and nitrogen analyses (unless otherwise specified) were within ±0.4% of the theoretical values. Microanalyses were performed by the Abbott analytical department. The NMR spectra were obtained on a Varian T-60 and HA-100 spectrometers using tetramethylsilane as an internal standard. Mass spectra were recorded on a Kratos MS-50 mass spectrometer. The IR spectra were recorded on a Perkin-Elmer Model 710 A infrared spectrometer. The IR, NMR, and mass spectral data of all compounds were consistent with the assigned structures.

Ethyl 2,4-Dichloro-5-fluorobenzoylacetate (13). A 60% sodium hydride-in-oil suspension (8.2 g, 205 mmol) was added slowly at room temperature to a cold solution of 2,4-dichloro-5-fluoroacetophenone (20.51 g, 99 mmol) in diethyl carbonate (300 mL). The mixture was then heated at 80 °C for 1.5 h. It was poured into ice-cold water (700 mL) solution containing acetic acid (25 mL). The mixture was extracted with three portions of ether (400 mL). The organic phase was dried and evaporated, and the residual oil was distilled at 111 °C (0.7 mmHg) to give 22.2 g (80%) of **13**. NMR ($CDCl_3$): δ (two sets of signals), 1.17 (3 H, t, J = 7 Hz, ethyl CH_3), 1.27 (3 H, t, J = 7 Hz, ethyl CH_3), 4.07 (2 H, s, CH_2), 4.17 (2 H, q, J = 7 Hz, ethyl CH_2), 4.27 (2 H, q, J = 7 Hz, ethyl CH_2), 5.65 (1 H, s, vinyl H), 7.47 (two sets of

2 H, m, aromatic H), 12.48 (1 H, s, enol OH).

Ethyl 3-(*p*-Fluoroanilino)-2-(2,4-dichloro-5-fluorobenzoyl)acrylate (17). A solution of **13** (20 g, 71.7 mmol) in triethyl orthoformate (15.9 g, 110 mmol) and acetic anhydride (29.3 g, 290 mmol) was heated at 130 °C for 2 h with removal of the ethyl acetate formed during the reaction. The solution was evaporated under reduced pressure to a mobile oil that was dissolved in methylene chloride (200 mL). 4-Fluoroaniline (12 g, 108 mmol) was added to the solution. After 0.5 h, the solution was evaporated to dryness and crystallized from 20% ether in hexane solution, yielding 21.7 g (75.6%) of **17**, mp 111–112 °C. Anal. ($C_{18}H_{13}Cl_2F_2NO_3$) H, N; C: calcd, 54.02; found, 54.50.

By use of this procedure, compounds **14–16** and **18–26** were prepared from **13** with the appropriate anilines.

1-(*p*-Fluorophenyl)-6-fluoro-7-chloro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (30). A 60% sodium hydride-in-oil suspension (2.28 g, 57 mmol) was slowly added to a cold solution of **17** (21.6 g, 54.2 mmol) in dimethoxyethane (200 mL). The mixture was heated at 80 °C for 3 h under nitrogen atmosphere and was cooled. Water (1.5 L) was added, and the precipitate was filtered and washed with water and dried. This ester was suspended in tetrahydrofuran (200 mL). NaOH (4.5 g, 111 mmol) in water (135 mL) was added to the suspension, and the mixture was heated at 80 °C for 1.5 h. It was cooled, and water (1.5 L) was added, followed by the addition of acetic acid (15 mL). The precipitate was filtered. The solid was washed with water and ether and dried, yielding 15.8 g (84.9%) of **30**, mp 260–263 °C. Anal. ($C_{16}H_8ClF_2NO_3$) C, H, N.

Various substituted 1-phenyl-4-quinolones **27–29** and **31–39** were prepared in a similar fashion correspondingly from **14–16** and **18–26**.

1-(*p*-Fluorophenyl)-6-fluoro-7-(4-methyl-1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Hydrochloride (45). *N*-Methylpiperazine (16.97 mL, 153 mmol) was added to a solution of **30** (20.56 g, 61.3 mmol) in *N*-methyl-2-pyrrolidinone (150 mL) at 110 °C. After heating at 110 °C under nitrogen atmosphere for 24 h, the solution was evaporated to near dryness under reduced pressure. Ethanol (100 mL) was addeed, and the mixture was boiled for 5 min and cooled. It was filtered, and the residue was washed with water and then ethanol, yielding 21.3 g of the 3-carboxylic acid **74**. Anal. ($C_{21}H_{19}F_2N_3O_3$) C, H, N. This solid was suspended in 1.5 L of water and heated on a steam bath. Hydrochloric acid was added in small portion to pH 3. Most of the solid dissolved, and the small amount of insoluble material was filtered. The filtrate was cooled, and the crystallized material was filtered, yielding 20.3 g (76%) of **45**, mp >275 °C. Anal. ($C_{21}H_{19}F_2N_3O_3$·HCl) C, H, N.

By using this procedure, reacting the 7-chloro-4-quinolones **27–39** with an appropriate amine, additional analogues **40**, **42–44**, **46–54**, **56–63**, and **66–73** were prepared.

1-(*p*-Fluorophenyl)-6-fluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Hydrochloride (41). To a solution of **30** (5.4 g, 16 mmol) in *N*-methyl-2-pyrrolidinone (50 mL) at 115 °C was added carboethoxypiperazine (10.2 g, 64 mmol). After the mixture was heated at this temperature under nitrogen atmosphere for 24 h, the solvent was removed by distillation and methanol was added to the residue and boiled for 10 min. It was cooled and filtered, yielding 5.64 g of solid, mp 268–269 °C. A mixture of this solid, 5% sodium hydroxide solution (containing 4.9 g of NaOH), and ethanol (40 mL) were heated at 80 °C for 4 h. Acidification with 10% acetic acid to pH 7–7.5 yielded a precipitate that was filtered and washed with ether. This solid was suspended in water (500 mL), 1 N HCl (15 mL) was added, and the resultant mixture was heated to dissolve. Some insoluble impurity was removed by filtration. The filtrate was evaporated under reduced pressure to yield a solid that was washed with ethanol and dried, yielding 4.08 g of **41** (56%), mp >275 °C. Anal. ($C_{20}H_{17}F_2N_3O_3$·HCl·H_2O) C, H, N.

1-(*p*-Fluorophenyl)-6-fluoro-7-(4-butyl-1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Hydrochloride (55). A mixture of **41** (1.925 g, 5 mmol), butyraldehyde (1.62 g, 22.5 mmol), and 95% formic acid (2.3 g, 50 mmol) was heated on a steam bath for 1 h. 1 N HCl (20 mL) was added, and the reaction mixture was concentrated to dryness. The solid was dissolved in 200 mL of boiling 50/50 ethanol/methylene chloride, and the insoluble impurity was filtered. The methylene chloride was then distilled off, and a solid separated, was cooled and filtered, was washed several times with ethanol, and was dried, yielding 1.35 g of **55** (54.5%), mp 252–255 °C. Anal. ($C_{24}H_{25}F_2N_3O_3$·HCl·H_2O) C, H, N.

1-(*p*-Fluorophenyl)-6-fluoro-7-(3-amino-1-pyrrolidinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Hydrochloride (64). A suspension of **67** (10 g, 23.4 mmol) in 6 N HCl (170 mL) was refluxed for 2.5 h. A small amount of insoluble material was removed by a rapid filtration. The filtrate was evaporated to dryness and boiled in ethanol for 5 min. It was filtered, yielding 4.94 g of **64** (50%), mp >275 °C. Anal. ($C_{20}H_{17}F_2N_3O_3$·HCl) H, N; C: calcd, 56.94; found, 57.92.

By the above procedure, analogue **65** was prepared by hydrolysis of **73**.

In Vitro Antibacterial Activity. The in vitro antibacterial activity of the test compounds was tested in a side-by-side comparison with norfloxacin (**6**) and determined by conventional agar dilution procedures. The organisms were grown overnight in brain–heart infusion (BHI) broth (Difco 0037-01-6) at 36 °C. Twofold dilutions of the stock solution (2000 μg/ml) of the test compound were made in BHI agar to obtain the test concentration ranging from 200–0.005 μg/mL. The plate was inoculated with approximately 10^4 organisms. It was then incubated at 36 °C for 18 h. The minimal inhibitory concentration (MIC) was the lowest concentration of the test compound that yielded no visible growth on the plate.

In Vivo Antibacterial Activity. The in vivo antibacterial activity of the test compounds was determined in CF-1 female mice weighing approximately 20 g. Aqueous solutions of the test compounds were made by dissolving the hydrochloride salt in distilled water or by dissolving the compound in dilute NaOH and diluting it with distilled water to the desired volume. The median lethal dose of the test organism was determined as follows.

After 18-h incubation, the cultures of *E. coli* Juhl in BHI broth were serially diluted by using 10-fold dilutions in 5% (w/v) hog gastric mucin. Cultures (0.5 mL), dilution from 10^{-1} to 10^{-8} were injected intraperitoneally into mice. The LD_{50} for the test organism was calculated from the cumulative mortalities on the sixth day by using the Reed and Muench procedure.[14]

The 18-h culture of the above was diluted in 5% (w/v) hog gastric mucin to obtain 100 times the LD_{50}, and 0.5 mL was injected intraperitoneally into mice. The mice were treated subcutaneously (sc) or orally (po) with a specific amount of the test compound divided equally to be administered at 1 and 5 h after infection. A group of 10 animals each for at least three dose levels was thus treated, and the deaths were recorded daily for 6 days. Ten mice were left untreated as infection control. ED_{50} values were calculated from the cumulative mortalities on the sixth day after infection by using the trimmed version of the Logit method.[15]

Acknowledgment. We thank the staff of the microbiological team for biological testings, Ani Glamyan for her expert technical assistance, and the staff of Analytical Department for microanalyses.

Registry No. **12**, 704-10-9; **13**, 86483-51-4; **14**, 98126-21-7; **15**, 98105-63-6; **16**, 98105-64-7; **17**, 98105-65-8; **18**, 98105-66-9; **19**, 98126-22-8; **20**, 98105-67-0; **21**, 98105-68-1; **22**, 98105-69-2; **23**, 98105-70-5; **24**, 98105-71-6; **25**, 98105-72-7; **26**, 98105-73-8; **27**, 98105-74-9; **27** ethyl ester, 98105-75-0; **28**, 98126-23-9; **28** ethyl ester, 98105-76-1; **29**, 98105-77-2; **29** ethyl ester, 98105-78-3; **30**, 98105-79-4; **30** ethyl ester, 98105-80-7; **31**, 98105-81-8; **31** ethyl ester, 98105-82-9; **32**, 98105-83-0; **32** ethyl ester, 98105-84-1; **33**, 98105-85-2; **33** ethyl ester, 98105-86-3; **34**, 98105-87-4; **34** ethyl ester, 98105-88-5; **35**, 98105-89-6; **35** ethyl ester, 98105-90-9; **36**, 98105-91-0; **36** ethyl ester, 98105-92-1; **37**, 98105-93-2; **37** ethyl ester, 98105-94-3; **38**, 98105-95-4; **38** ethyl ester, 98105-96-5; **39**, 98105-97-6; **39** ethyl ester, 98105-98-7; **40**, 98106-13-9; **40**·HCl, 91431-41-3; **41**, 98105-99-8; **41**·HCl, 91296-87-6; **42**, 98106-14-0; **42**·HCl, 98106-01-5; **43**, 98106-15-1; **43**·HCl, 98106-02-6; **44**, 98106-16-2; **44**·HCl, 98106-03-7; **45**, 98106-17-3; **45**·HCl, 91296-86-5;

(14) Reed, L. J.; Muench, H. *Am. J. Hyg.* **1938**, *27*, 493.
(15) Hamilton, M. A.; Russo, R. C.; Thurston, R. V. *Environ. Sci. Technol.* **1977**, *11*, 714.

46, 98106-18-4; **46**·HCl, 98106-04-8; **47**, 98106-19-5; **17**·HCl, 98106-05-9; **48**, 98106-20-8; **48**·HCl, 98106-06-0; **49**, 98106-21-9; **49**·HCl, 98106-07-1; **50**, 98106-22-0; **50**·HCl, 98106-08-2; **51**, 98106-23-1; **51**·HCl, 98106-09-3; **52**, 98106-24-2; **52**·HCl, 98106-10-6; **53**, 98106-25-3; **53**·HCl, 98106-11-7; **54**, 98106-26-4; **54**·HCl, 98106-12-8; **55**, 98106-46-8; **55**·HCl, 98106-27-5; **56**, 98106-47-9; **56**·HCl, 98106-28-6; **57**, 98106-29-7; **58**, 98106-30-0; **59**, 98106-31-1; **60**, 98106-32-2; **61**, 98106-33-3; **61**·HCl, 98106-48-0; **62**, 98106-34-4; **63**, 98106-35-5; **64**, 98106-49-1; **64**·HCl, 98106-39-9; **65**, 98106-50-4; **65**·HCl, 98106-40-2; **66**, 98106-41-3; **67**, 98106-42-4; **68**, 98106-43-5; **69**, 98106-44-6; **70**, 98106-45-7; **71**, 98106-36-6; **72**, 98106-37-7; **73**, 98106-38-8; carboethoxypiperazine, 120-43-4; 1-(*p*-fluorophenyl)-6-fluoro-7-(4-carboethoxypiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hexahydro-1,4-diazepine, 505-66-8; thiomorpholine, 123-90-0; 4-piperidinol, 5382-16-1; *N*,*N*-dimethyl-4-piperidinamine, 50533-97-6; 3-pyrrolidinol, 40499-83-0; *N*-(3-pyrrolidinyl)acetamide, 79286-74-1; 1-propionylpiperazine, 76816-54-1; piperazinone, 5625-67-2; 1-methylpiperazinone, 59702-07-7; isopropylmethylamine, 4747-21-1; *N*-methyl-*N*-(3-pyrrolidinyl)acetamide, 79286-87-6; aniline, 62-53-3; 2-fluoroaniline, 348-54-9; 3-fluoroaniline, 372-19-0; 4-fluoroaniline, 371-40-4; 4-bromoaniline, 106-40-1; 4-chloroaniline, 106-47-8; 4-hydroxyaniline, 123-30-8; 4-methoxyaniline, 104-94-9; 4-methylaniline, 106-49-0; 6-aminobenzodioxole, 14268-66-7; 2,4-difluoroaniline, 367-25-9; 2-methylaniline, 95-53-4; 2,6-dimethylaniline, 87-62-7.

4-Substituted 5-[*m*-(Trifluoromethyl)phenoxy]primaquine Analogues as Potential Antimalarial Agents

F. Ivy Carroll,* Bertold Berrang, and C. P. Linn

Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, North Carolina 27709.
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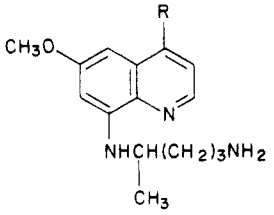
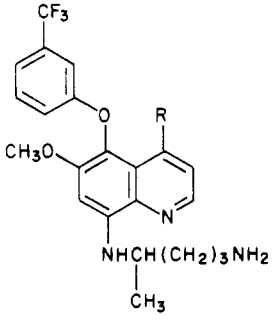
Five 4-substituted 5-[*m*-(trifluoromethyl)phenoxy]primaquine analogues were synthesized and tested for radical curative activity against *Plasmodium cynomolgi* in Rhesus monkeys and for blood schizonticidal antimalarial activity against *Plasmodium berghei* in mice. In addition, they were evaluated for causal prophylactic antimalarial activity against *Plasmodium berghei yoelii* in mice. One compound, 4-ethyl-5-[*m*-(trifluoromethyl)phenoxy]primaquine (**2b**), showed radical curative activity equivalent to 4-methyl-5-[*m*-(trifluoromethyl)phenoxy]primaquine (**2a**). A second compound showed radical curative activity slightly less than **2a** and **2b**; the remaining three compounds were not active against *P. cynomolgi*. All five compounds showed much higher blood schizonticidal activity and less toxicity than primaquine; however, none of the compounds were as active as **2a**. Three of four compounds tested showed high activity against *P. berghei yoelii*.

For many years primaquine (**1a**), which is a radical curative drug,[3] has been the drug of choice for the treatment of relapsing *Plasmodium vivax* and *Plasmodium malariae*. Primaquine (**1a**) is effective in clearing the tissues of parasites but is ineffective as a blood schizonticide. Moreover, its toxicity precludes administration of a single curative dose. Recently, LaMontagne and co-workers[1,2] reported that 4-methyl-5-[*m*-(trifluoromethyl)phenoxy]-primaquine (**2a**) was a highly effective antimalarial agent that possessed both tissue and blood schizonticidal activity. In addition, **2a** had a significantly better therapeutic index than primaquine (**1a**).



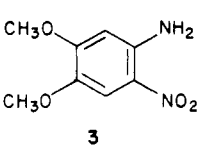
1a, R = H
b, R = C_2H_5
c, R = CH_2=CH



2a, R = CH_3
b, R = C_2H_5
c, R = CH_2=CH
d, R = CH_2OH
e, R = CH_3OCH_2
f, R = $(CH_3O)_2CH$

In an earlier study we reported that 4-ethyl- and 4-vinylprimaquine (**1b** and **1c**, respectively) showed radical curative activity similar to primaquine but were less toxic.[3] Thus, the synthesis of 4-ethyl- and 4-vinyl-5-[*m*-(trifluoromethyl)phenoxy]primaquine (**2b** and **2c**) is a logical extension of our earlier work. In order to gain information concerning the optimal substituent pattern for this class of compounds, we were also interested in the synthesis of the 4-hydroxymethyl, 4-methoxymethyl, and 4-dimethoxymethyl analogues **2d–f**. In this paper we present the synthesis and antimalarial evaluation of **2b–f**.

Chemistry. Compound **2b** was prepared by a procedure analogous to that used by LaMontagne to prepare **2a**.[1,2] Thus, 4-amino-5-nitroveratrole (**3**) was subjected to a modified Skraup reaction using chloro-3-pentanone to give the 4-ethylquinoline analogue (**4a**). Mild hydrolysis of **4a** followed by treatment with phosphorus oxychloride yielded the 5-chloroquinoline **4b**. Treatment of **4b** with the potassium salt of *m*-(trifluoromethyl)phenol afforded **4c**. Stannous chloride reduction of **4c** followed by standard attachment of the primaquine side chain gave **2b**.



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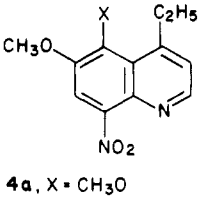

4a, X = CH_3O
b, X = Cl
c, X = *m*-$CF_3C_6H_4O$

In order to prepare compounds **2c–f**, the nitroquinolines **7–10** were required. These intermediates were prepared from 4-methyl-6-methoxy-5-[*m*-(trifluoromethyl)phenoxy]-8-nitroquinoline[1,2] as shown in Chart I. Selenium dioxide oxidation of **5** gave the 4-carboxaldehyde **6**, which

(1) LaMontagne, M. P.; Blumbergs, P.; Strube, R. E. *J. Med. Chem.* **1982**, *25*, 1094.
(2) Strube, R. E.; LaMontagne, M. P. U.S. Patent 4 431 807, 1984.
(3) Carroll, F. I.; Berrang, B. D.; Linn, C. P. *J. Med. Chem.* **1979**, *22*, 1363.

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