Structure–Activity Relationships of Antibacterial 6,7- and 7,8-Disubstituted 1-Alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids[1]

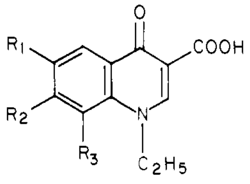
Hiroshi Koga,* Akira Itoh, Satoshi Murayama, Seigo Suzue, and Tsutomu Irikura

Central Laboratories, Kyorin Pharmaceutical Co., Ltd., Nogi-machi, Shimotsuga-gun, Tochigi-ken, 329-01, Japan.
Received April 14, 1980

Previous quantitative and qualitative structure–activity studies in antibacterial monosubstituted 1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids prompted us to synthesize the 6,7,8-polysubstituted compounds. In this paper, the preparation and antibacterial activity of the 6,7- and 7,8-disubstituted compounds and their derivatives are described. Among these compounds, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid (**34**) possessed many significant activities and was more active than oxolinic acid (**84**) against Gram-positive and Gram-negative bacteria. Structure–activity relationships are discussed.

Since nalidixic acid (**1**, 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid), which shows a good effect on Gram-negative bacteria, was introduced into therapy in 1963, a large number of its analogues have been synthesized and evaluated, some of which came into the market.[2]

We have been engaged for several years in the search for better drugs in this series and previously reported quantitative structure–activity relationships (QSAR) in 6-, 7-, or 8-monosubstituted 1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids (**2**) against *Escherichia coli*, which is one of the representative species of Gram-negative bacteria.[1] The QSAR equation showed that the antibacterial activities of **2** were parabolically correlated with steric parameters for R_1 and R_3 (Es and B_4, respectively). Although no relationship correlating physicochemical constants for R_2 with the activity of **2** was observed, it was found that among the substituents tested (nitro, acetyl, chloro, methyl, methoxy, dimethylamino, piperazinyl, and hydrogen groups), the piperazinyl group showed the most promise. It proved to have the most potent activity against Gram-negative bacteria, including *Pseudomonas aeruginosa*. The Hansch equation also revealed that the activities of some of the 6,7,8-polysubstituted derivatives of **2** might be more potent than those of the 6-, 7-, or 8-monosubstituted compounds. In particular, the activities of the 6-fluoro- and 6-chloro-7-(1-piperazinyl) derivatives (**34** and **37**) in the disubstituted analogues were expected to be very potent, namely, about 10 and 5 times, respectively, that of monosubstituted **3** (**2**, $R_1 = R_3 = H$ and R_2 = piperazinyl),[3] which had the most potent activity and the broadest spectrum of the compounds tested.

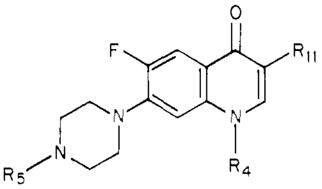


2

In this paper, structure–activity relationships (SAR) of 6,7- and 7,8-disubstituted 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid derivatives are reported.

Chemistry. The requisite 6,7- and 7,8-disubstituted 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids and their derivatives were prepared by the usual method.[2] Anilines (**4**) were heated with diethyl ethoxymethylenemalonate to give malonates (**5**) which, generally without purification, were cyclized to 4-hydroxyquinoline-3-carboxylic acid ethyl esters (**6–15**) (Scheme I). Alkylation of the esters **6–16** by treatment with alkyl halides and anhydrous potassium carbonate gave 1-alkyl-1,4-dihydro-4-oxoquinoline esters (**17**). The 1-alkyl esters (**17**) were hydrolyzed with aqueous sodium hydroxide or hydrochloric acid to produce the carboxylic acids **18–34**, whose *N*-alkyl-4-quinolinone structure was confirmed by spectral data. The 7-chloro-4-quinolinones **18–31** and **35** were allowed to react with amines in order to obtain the desired 7-amino derivatives **34**, **36–40**, and **42–63**.

A 1-vinyl derivative (**67**) was readily prepared by using 15 or 77 as the starting material, which was converted to the 1-hydroxyethyl derivative (**65**) by hydroxyethylation or esterification. The 1-chloroethyl derivative (**66**) was obtained by treatment of **65** with thionyl chloride and treated with aqueous sodium hydroxide to give the desired 1-vinyl compound (**67**).



65, $R_4 = CH_2CH_2OH$; $R_5 = COCH_3$;
$R_{11} = COOC_2H_5$
66, $R_4 = CH_2CH_2Cl$; $R_5 = COCH_3$;
$R_{11} = COOC_2H_5$
67, $R_4 = CH{=}CH_2$; $R_5 = H$;
$R_{11} = COOH$
79, $R_4 = C_2H_5$; $R_5 = CH_2C_6H_4\text{-}p\text{-}NH_2$;
$R_{11} = COOH$
80, $R_4 = C_2H_5$; $R_5 = R_{11} = H$
81, $R_4 = C_2H_5$; $R_5 = H$; $R_{11} = COOCH_3$
82, $R_4 = C_2H_5$; $R_5 = H$;
$R_{11} = COOC_2H_5$

The 7-amino derivatives **34**, **51**, **63**, and **67** were readily alkylated or acylated to afford **36** and **68–78**. The *N*-*p*-nitrobenzyl derivative (**72**) was reduced to the *N*-*p*-aminobenzyl derivative (**79**) by catalytic hydrogenation. Quinolinone **80** was prepared by acid-catalyzed decarboxylation of **34**. The 4-oxoquinolinecarboxylic acid **34** was also esterified by adding thionyl chloride in the presence of appropriate alcohols to give **81** and **82**.

Results and Discussion

Table VI summarizes the in vitro antibacterial activity against Gram-positive (*Staphylococcus aureus* 209P) and Gram-negative bacteria (*Escherichia coli* NIHJ JC-2 and *Pseudomonas aeruginosa* V-1). The data for **1**, **3**, pipemidic acid [**83**, 8-ethyl-5,8-dihydro-5-oxo-2-(1-piperazinyl)-

---

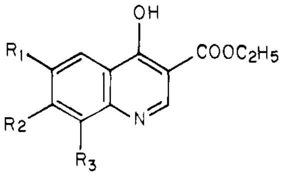
(1) This work was presented in part at the 98th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, Apr 1978, and at the 99th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, Aug 1979.

(2) R. Albrecht, *Prog. Drug Res.*, 21, 9 (1977).

(3) S. Minami, J. Matsumoto, M. Shimizu, and Y. Takase, German Offen. 2362553 (1974); *Chem. Abstr.*, 81, 105562*k* (1974).

0022-2623/80/1823-1358$01.00/0

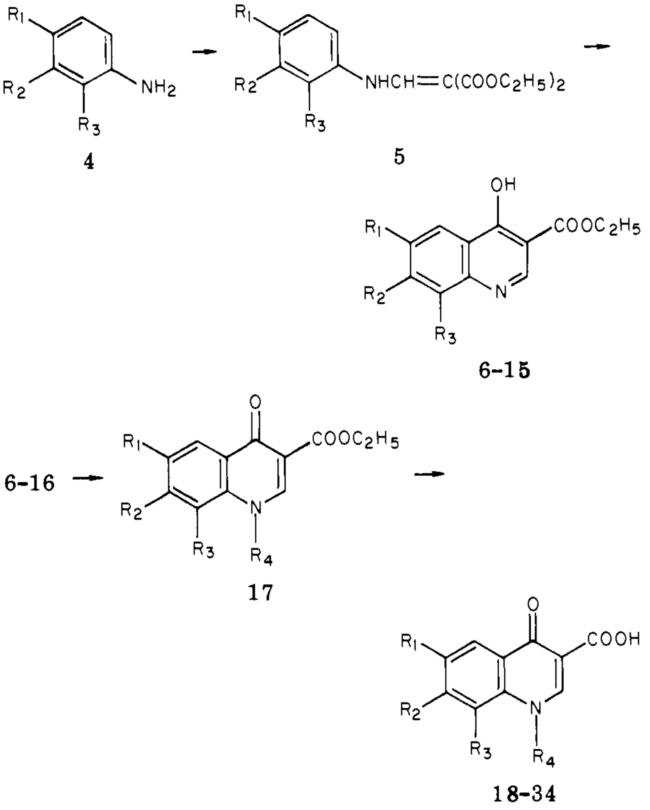
Table I. 4-Hydroxyquinoline Ethyl Esters



compd	R_1	R_2	R_3	method[a]	yield,[b] %	recrystn solvent	mp, °C	formula[c]
6[d]	F	Cl	H	A	70			
7	Br	Cl	H	A	89	DMF	>300	$C_{12}H_9BrClNO_3$
8	SCH_3	Cl	H	A	77	DMF	>300	$C_{13}H_{12}ClNO_3S$
9	$COCH_3$	Cl	H	A	81	DMF	>300	$C_{14}H_{12}ClNO_4$
10	CN	Cl	H	A	70	DMF	>300	$C_{13}H_9ClN_2O_3$
11	NO_2	Cl	H	A	79	DMF	>300	$C_{12}H_9ClN_2O_5$
12	H	Cl	Cl	A	67	DMF	288-290 (dec)	$C_{12}H_9Cl_2NO_3$
13	H	Cl	F	A	66	DMF	263-265 (dec)	$C_{12}H_9ClFNO_3$
14	F	$NHCOCH_3$	H	A	63	Me_2SO	>300	$C_{14}H_{13}FN_2O_4$
15	F	c-$N(CH_2CH_2)_2$-$NCOCH_3$	H	A	76	DMF	>300	$C_{18}H_{20}FN_3O_4$

[a] Method is detailed under Experimental Section. [b] Yields calculated from the corresponding anilines (4). [c] Satisfactory C, H, and N analyses (within ±0.4% of theoretical values) were obtained in each instance in which the formula is provided. [d] See the Experimental Section.

Scheme I



pyrido[2,3-*d*]pyrimidine-6-carboxylic acid],[5] and oxolinic acid [**84**, 1-ethyl-1,4-dihydro-6,7-(methylenedioxy)-4-oxoquinoline-3-carboxylic acid][6] are included for comparison.

The results for 6-substituted 7-piperazinyl derivatives (**34**, **37**, **39**, and **41**–**45**) showed that fluorine was preferable for the 6-substituent of **3**, and the activity against *Escherichia coli* NIHJ JC-2 of **34** was 16 times more potent than that of **3**, giving the reason for fixing fluorine for R_1 of **2**. A series of 7-substituted 6-fluoroquinolinones (**18**, **32**, **33**, **36**, **48**–**63**, **67**–**76**, and **78**–**82**) was screened, and it was found that the SAR were comparable with those of piromidic acid (**85**, 8-ethyl-5,8-dihydro-5-oxo-2-pyrrolidinopyrido[2,3-*d*]pyrimidine-6-carboxylic acid)[7] and pipemidic acid (**83**)[5], although the activity was generally more potent. The replacement of the 7-chloro group of **18** by a methyl or amino group generally caused an increase in the activity. The substitution of the hydrogen of the piperazine NH group in **34** by an alkyl or acyl group reduced the activity against Gram-negative bacteria, particularly *Pseudomonas aeruginosa* V-1. The displacement of the 1-ethyl group in **34** by sterically comparable substituents, 2-fluoroethyl and vinyl groups (**49** and **67**), resulted in almost equal activity against Gram-negative bacteria, while the substitution by more or less sterically hindered groups (**48** and **51**–**54**) decreased the activity. Decarboxylated compound **80** and esters **81** and **82** did not show any significant activity.

Introduction of fluorine and chlorine (**47** and **46**) at the 8 position of **3** gave activity against *Escherichia coli* NIHJ JC-2 comparable to and twice that of **3**, respectively.

Compound **34** was selected for clinical trial on the basis of the preclinical studies.[8] SAR of 6,7,8-trisubstituted compounds and QSAR of 1,4-dihydro-4-oxoquinoline-3-carboxylic acids will be reported in subsequent papers.

Experimental Section

Spectral data were obtained with the following instruments: IR, Hitachi 260-10 infrared spectrophotometer; NMR, JEOL JNM-4H-100 (using tetramethylsilane as internal standard); mass spectra, Hitachi RMU-6E. Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Analyses are within ±0.4% of theoretical values when indicated by symbols of the elements. Solutions were dried over anhydrous Na_2SO_4.

6-Fluoro-1,4-dihydro-7-methyl-4-oxoquinoline-3-carboxylic acid ethyl ester (**16**)[9] and 6,7-dichloro-1-ethyl-1,4-dihydro-4-oxo-

---

(4) R. Kobayashi, K. Isagai, Y. Naka, and M. Hosoya, Japan Kokai 88973 (1976); *Chem. Abstr.*, **86**, 121368*k* (1977).

(5) J. Matsumoto and S. Minami, *J. Med. Chem.* 18, 74 (1975).

(6) D. Kaminsky and R. I. Meltzer, *J. Med. Chem.*, 11, 160 (1968).

(7) S. Minami, T. Shono, and J. Matsumoto, *Chem. Pharm. Bull.*, 19, 1482 (1971); *ibid.*, 19, 1426 (1971).

(8) A. Ito, K. Hirai, M. Inoue, H. Koga, S. Suzue, T. Irikura, and S. Mitsuhashi, *Antimicrob. Agents Chemother.*, 17, 103 (1980).

quinoline-3-carboxylic acid (**35**)[10] were synthesized by the methods in the literature.

5-Amino-2-fluoroacetanilide (**4**, R_1 = F, R_2 = $NHCOCH_3$, and R_3 = H) was obtained from 2-fluoro-5-nitroacetanilide[11] by reduction (Fe-HCl in aqueous EtOH) in the usual manner in 74% yield. The acetanilide was recrystallized from *i*-PrOH and gave mp 138–140 °C. Anal. ($C_8H_9FN_2O$) C, H, N.

4-Fluoro-3-(4-acetyl-1-piperazinyl)aniline (4, R_1 = F, R_2 = 4-Acetyl-1-piperazinyl, and R_3 = H). A mixture of *o*-fluorophenylpiperazine[12] (11.4 g, 0.063 mol), acetic anhydride (12.9 g, 0.126 mol), and DMF (10 mL) was heated at 80–90 °C with stirring. After 1 h, the mixture was evaporated to dryness and made basic with aqueous K_2CO_3. The solution was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried, and evaporated. Distillation of the residual oil gave 1-acetyl-4-(*o*-fluorophenyl)piperazine (12.3 g, 87%), bp 185 °C (6 mm). Anal. ($C_{12}H_{15}FN_2O$) C, H, N.

To a stirred solution of 1-acetyl-4-(*o*-fluorophenyl)piperazine (12.0 g, 0.054 mol) in concentrated H_2SO_4 (40 mL) was added dropwise a solution of 60% HNO_3 (5.8 g, 0.055 mol) and concentrated H_2SO_4 (5 mL) at 5–10 °C, and the mixture was stirred at 10 °C for 2 h. The acidic solution was poured onto ice, neutralized with concentrated NH_4OH, and extracted with benzene. After working up, the residue was recrystallized from EtOH to give 1-acetyl-4-(2-fluoro-5-nitrophenyl)piperazine (6.3 g, 44%): mp 132–134 °C. Anal. ($C_{12}H_{14}FN_3O_3$) C, H, N.

A mixture of 1-acetyl-4-(2-fluoro-5-nitrophenyl)piperazine (6.0 g, 0.0225 mol), EtOH (100 mL), and 10% palladium on charcoal (2.0 g) was hydrogenated at room temperature until hydrogen uptake ceased. The mixture was filtered and the filtrate evaporated to dryness. The residue was recrystallized from benzene to give **4** (R_1 = F, R_2 = 4-acetyl-1-piperazinyl, and R_3 = H; 5.3 g, quant), mp 132 °C. Anal. ($C_{12}H_{16}FN_3O$) C, H, N.

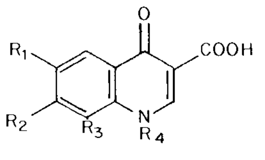
7-Chloro-6-fluoro-4-hydroxyquinoline-3-carboxylic Acid Ethyl Ester (6). Method A. A mixture of 3-chloro-4-fluoroaniline (**4**, R_1 = F, R_2 = Cl, and R_3 = H; 1.46 g, 0.01 mol) and diethyl ethoxymethylenemalonate (2.16 g, 0.01 mol) was heated at 120–130 °C. After 2 h, the resulting EtOH was evaporated off. The crude malonate was used in the successive reaction without further purification. The residue was recrystallized from *n*-hexane to give **5** (R_1 = F, R_2 = Cl, and R_3 = H; 3.16 g, quant): mp 55–57 °C; ^{1}H NMR ($CDCl_3$) δ 1.2–1.45 (6 H, m, 2 CH_3), 4.1–4.4 (4 H, m, 2 CH_2), 6.85–7.25 (3 H, m, aromatic H), 8.33 (1 H, d, J_{H-H} = 13 Hz, NCH), 10.99 (1 H, d, J_{H-H} = 13 Hz, NH); IR (KBr) 1685 cm^{-1} (ester). Anal. ($C_{14}H_{15}ClFNO_4$) C, H, N.

The crude **5** (R_1 = F, R_2 = Cl, and R_3 = H; 5.4 g, 0.017 mol) was added to diphenyl ether (50 mL) and refluxed for 1 h. After the solution cooled, the resulting precipitate was filtered off, washed with benzene, and dried. The solid was recrystallized from DMF to give **6** (3.2 g, 70%): mp >300 °C; ^{1}H NMR (CF_3COOD) δ 1.56 (3 H, t, J_{H-H} = 7 Hz, CH_3), 4.73 (2 H, q, J_{H-H} = 7 Hz, CH_2), 8.35 (1 H, d, J_{H-F} = 8 Hz, aromatic H), 8.37 (1 H, d, J_{H-F} = 6 Hz, aromatic H), 9.35 (1 H, s, 2-H); IR (KBr) 1690 cm^{-1} (ester). Anal. ($C_{12}H_9ClFNO_3$) C, H, N.

The 4-hydroxyquinolines **7–15**, found in Table I, were prepared by this method from the corresponding anilines (**4**).

7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (18). Method B. A mixture of **6** (2.7 g, 0.01 mol), K_2CO_3 (3.45 g, 0.025 mol), EtI (4 mL, 0.05 mol), and DMF (20 mL) was heated at 80–90 °C with stirring. After 10 h, the mixture was evaporated to dryness and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried, and evaporated to dryness. The crude ester (3.0 g, quant) was used in the successive reaction without further purification. The residue was recrystallized from EtOH to yield **17** (R_1 = F, R_2 = Cl, R_3 = H, and R_4 = C_2H_5; 2.7 g, 90%): mp 142–143 °C; ^{1}H NMR ($CDCl_3$)

Table II. 4-Oxoquinoline-3-carboxylic Acids



compd	R_1	R_2	R_3	R_4	alkylating agent	method[a]	yield,[b] %	recrystn solvent	mp, °C	formula[c]
18[d]	F	Cl	H	C_2H_5	EtI	B, C	90,[e] 88[f]			
19	Br	Cl	H	C_2H_5	EtI	B	92	DMF	>300	$C_{12}H_9BrClNO_3$
20	SCH_3	Cl	H	C_2H_5	EtI	B	47	DMF	270–273 dec	$C_{13}H_{12}ClNO_3S$
21	$COCH_3$	Cl	H	C_2H_5	EtI	C	63	DMF	272–275 dec	$C_{14}H_{12}ClNO_4$
22	CN	Cl	H	C_2H_5	EtI	C	60	DMF	>300	$C_{13}H_9ClN_2O_3$
23	NO_2	Cl	H	C_2H_5	EtI	C	60	DMF	291–294 dec	$C_{12}H_9ClN_2O_5$
24	H	Cl	Cl	C_2H_5	EtI	B	26	DMF	205–208	$C_{12}H_9Cl_2NO_3$
25	H	Cl	F	C_2H_5	EtI	B	62	DMF	236–238	$C_{12}H_9ClFNO_3$
26	F	Cl	H	CH_3	MeI	B	90	DMF	>300	$C_{11}H_7ClFNO_3$
27	F	Cl	H	CH_2CH_2F	FCH_2CH_2I	C	64	DMF	262–264	$C_{12}H_8ClF_2NO_3$
28	F	Cl	H	CH_2CH_2OH	$HOCH_2CH_2Br$	B	91	DMF	256–259	$C_{12}H_9ClFNO_4$
29	F	Cl	H	*n*-C_3H_7	*n*-C_3H_7Br	B	92	DMF	254–255	$C_{13}H_{11}ClFNO_3$
30	F	Cl	H	$CH_2CH{=}CH_2$	$CH_2{=}CHCH_2Br$	B	89	DMF	234–237	$C_{13}H_9ClFNO_3$
31	F	Cl	H	$CH_2C_6H_5$	$C_6H_5CH_2Cl$	B	96	DMF	252–253	$C_{17}H_{11}ClFNO_3$
32	F	CH_3	H	C_2H_5	EtI	C	68	DMF	287–290	$C_{13}H_{12}FNO_3$
33	F	NH_2	H	C_2H_5	EtI	B	34	DMF	>300	$C_{12}H_{11}FN_2O_3$
34	F	c-$N(CH_2CH_2)_2NH$	H	C_2H_5	EtI	B	74	CH_2Cl_2-EtOH	221–223	$C_{16}H_{18}FN_3O_3$

[a] Methods are detailed under Experimental Section. [b] Yields calculated from the corresponding 4-hydroxyquinoline esters (**6–16**). [c] See Table I, footnote *c*. [d] See the Experimental Section. [e] Yield in method B. [f] Yield in method C.

---

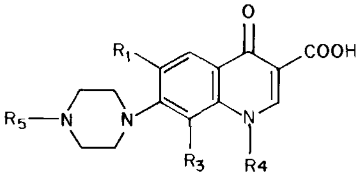
(9) D. Kaminsky, French Demande 2002888 (1969); *Chem. Abstr.*, **72**, 90322*v* (1970).

(10) N. Barton, A. F. Crowther, W. Hepworth, D. N. Rechardson, and G. W. Driver, British Patent 830832 (1960); *Chem. Abstr.*, **55**, 7442*e* (1961).

(11) J. J. Blanksma, W. J. van den Broek, and D. Hoegen, *Rec. Trav. Chim. Pays-Bas*, **65**, 329 (1946).

(12) R. Ratouis, J. R. Boissier, and C. Dumont, *J. Med. Chem.*, **8**, 104 (1965).

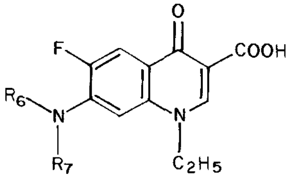
Table III. 7-(1-Piperazinyl)quinolines



compd	R_1	R_3	R_4	R_5	method[a]	yield, %	recrystn solvent	mp, °C	formula[b]
34[c]	F	H	C_2H_5	H	D	66			
36	F	H	C_2H_5	CH_3	D	68	DMF	272-274	$C_{17}H_{20}FN_3O_3$
37	Cl	H	C_2H_5	H	D	65	H_2O-EtOH	>300	$C_{16}H_{18}ClN_3O_3\cdot HCl$
38	Cl	H	C_2H_5	CH_3	D	47	DMF	257-260	$C_{17}H_{20}ClN_3O_3$
39	Br	H	C_2H_5	H	D	67	H_2O-EtOH	>300	$C_{16}H_{18}BrN_3O_3\cdot HCl$
40	Br	H	C_2H_5	CH_3	D	74	DMF	273-275 (dec)	$C_{17}H_{20}BrN_3O_3$
41	CH_3	H	C_2H_5	H			H_2O-EtOH	>300[d]	$C_{17}H_{21}N_3O_3\cdot HCl$
42	SCH_3	H	C_2H_5	H	D	22	DMF	266-269 (dec)	$C_{17}H_{21}N_3O_3S$
43	$COCH_3$	H	C_2H_5	H	D	94	DMF	262-263 (dec)	$C_{18}H_{21}N_3O_4\cdot 0.125H_2O$
44	CN	H	C_2H_5	H	D	76	DMF	275-277 (dec)	$C_{17}H_{18}N_4O_3$
45	NO_2	H	C_2H_5	H	D	75	DMF	251-252 (dec)	$C_{16}H_{18}N_4O_5$
46	H	Cl	C_2H_5	H	D	47	H_2O-EtOH	>300	$C_{16}H_{18}ClN_3O_3\cdot HCl$
47	H	F	C_2H_5	H	D	82	H_2O-EtOH	>300	$C_{16}H_{18}FN_3O_3\cdot HCl\cdot 0.5H_2O$
48	F	H	CH_3	H	D	40	H_2O-EtOH	>300	$C_{15}H_{16}FN_3O_3\cdot HCl\cdot 0.25H_2O$
49	F	H	CH_2CH_2F	H	D	27	H_2O-EtOH	292 (dec)	$C_{16}H_{17}F_2N_3O_3\cdot HCl\cdot H_2O$
50	F	H	CH_2CH_2F	CH_3	D	57	DMF	256-258	$C_{17}H_{19}F_2N_3O_3$
51	F	H	CH_2CH_2OH	H	D	51	H_2O-EtOH	>300	$C_{16}H_{18}FN_3O_4\cdot HCl\cdot 0.5H_2O$
52	F	H	n-C_3H_7	H	D	16	H_2O-EtOH	293-296 (dec)	$C_{17}H_{20}FN_3O_3\cdot HCl\cdot 0.25H_2O$
53	F	H	$CH_2CH{=}CH_2$	H	D	26	H_2O-EtOH	290-293 (dec)	$C_{17}H_{18}FN_3O_3\cdot HCl$
54	F	H	$CH_2C_6H_5$	H	D	68	DMF	250-253	$C_{21}H_{20}FN_3O_3$

[a] Method is detailed under Experimental Section. [b] See Table I, footnote *c*. [c] See the Experimental Section. [d] Lit.[4] mp >300 °C.

Table IV. 7-Aminoquinolines



compd	R_6	R_7	method[a]	yield, %	recrystn solvent	mp, °C	formula[b]
55	CH_3	CH_3	D	58	DMF	259-261	$C_{14}H_{15}FN_2O_3$
56	$-(CH_2)_4-$		D	49	DMF	>300	$C_{16}H_{17}FN_2O_3$
57	$-(CH_2)_5-$		D	59	DMF	208-209	$C_{17}H_{19}FN_2O_3$
58	$-(CH_2)_2O(CH_2)_2-$		D	63	DMF	256-257	$C_{16}H_{17}FN_2O_4$
59	$-(CH_2)_2CH(OH)(CH_2)_2-$		D	57	DMF	204-206	$C_{17}H_{19}FN_2O_4$
60	$-(CH_2)_2CH(CONH_2)(CH_2)_2-$		D	66	DMF	>300	$C_{18}H_{20}FN_3O_4$
61	$-(CH_2)_2CH[N(CH_3)_2](CH_2)_2-$		D	55	DMF	239-241	$C_{19}H_{24}FN_3O_3$
62	$-(CH_2)_2NHCOCH_2-$		D	32	A[c]	>300	$C_{16}H_{16}FN_3O_4$
63	$CH_2CH_2NH_2$	H	D	11	Me_2SO	223-225	$C_{14}H_{16}FN_3O_3\cdot 0.75H_2O$

[a] Method is detailed under Experimental Section. [b] See Table I, footnote *c*. [c] A, reprecipitation from aqueous K_2CO_3-AcOH.

δ 1.3–1.65 (6 H, m, 2 CH_3), 4.15–4.5 (4 H, m, 2 CH_2), 7.52 (1 H, d, J_{H-F} = 6 Hz, 8-H), 8.14 (1 H, d, J_{H-F} = 8 Hz, 5-H), 8.42 (1 H, s, 2-H); IR (KBr) 1720 (ester), 1615 cm^{-1} (C=O). Anal. ($C_{14}H_{13}ClFNO_3$) C, H, N.

A mixture of crude **17** (R_1 = F, R_2 = Cl, R_3 = H, and R_4 = C_2H_5; 2.7 g, 0.0091 mol) and 2 N NaOH (25 mL, 0.05 mol) was refluxed with stirring. After 2 h, the mixture was acidified with AcOH, and the resulting precipitate was filtered off, washed with H_2O, and dried. The solid was recrystallized from DMF to yield **18** (2.2 g, 90%): mp 284–285 °C; ^{1}H NMR (CF_3COOD) δ 1.81 (3 H, t, J_{H-H} = 7 Hz, CH_3), 4.92 (2 H, q, J_{H-H} = 7 Hz, CH_2), 8.39 (1 H, d, J_{H-F} = 5 Hz, aromatic H), 8.41 (1 H, d, J_{H-F} = 8 Hz, aromatic H), 9.39 (1 H, s, 2-H); IR (KBr) 1715 (COOH), 1610 cm^{-1} (C=O); MS, *m/e* 269 (M^+). Anal. ($C_{12}H_9ClFNO_3$) C, H, N.

Method C. Compound **18** was also obtained in comparable yield (88%) when 2 N HCl was used as hydrolyzing agent.

The 4-oxoquinolines **19–34**, shown in Table II, were prepared by these methods from the corresponding 4-hydroxyquinolines **7–16**.

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-quinoline-3-carboxylic Acid (34). Method D. A mixture of **18** (2.7 g, 0.01 mol) and piperazine (4.3 g, 0.05 mol) was heated at 130–140 °C with stirring. After 5 h, the mixture was evaporated to dryness and H_2O was added to the residue. The resulting solid was filtered off, washed with H_2O, dried, and recrystallized from CH_2Cl_2–MeOH or purified by reprecipitation from aqueous AcOH–aqueous NaOH to give **34** (2.1 g, 66%): mp 227–228 °C; ^{1}H NMR (CF_3COOD) δ 1.78 (3 H, t, J_{H-H} = 7 Hz, CH_3), 3.7–4.1 (8 H, m, piperazine CH_2), 4.88 (2 H, q, J_{H-H} = 7 Hz, CH_2), 7.50 (1 H, d, J_{H-F} = 6.5 Hz, 8-H), 8.35 (1 H, d, J_{H-F} = 12.5 Hz, 5-H), 9.32 (1 H, s, 2-H); IR (KBr) 1730 (COOH), 1620 cm^{-1} (C=O); MS, *m/e* 319 (M^+), 277, 275, 233. Compound **34** was readily converted to the hydrochloride in the usual way and recrystallized from H_2O–EtOH. The hydrochloride of **34** had mp >300 °C. Anal. ($C_{16}H_{18}FN_3O_3$·HCl) C, H, N.

The above aqueous filtrate was acidified with concentrated HCl, and the resulting crystals were filtered off. The solid was dissolved in aqueous NaOH. The solution was neutralized by adding aqueous AcOH, and the precipitate was filtered off, washed with H_2O, and dried. The solid was recrystallized from DMF to give 7-chloro-1-ethyl-1,4-dihydro-4-oxo-6-(1-piperazinyl)quinoline-3-carboxylic acid [**64**; 0.84 g, 25%; mp 272–273 °C. Anal. ($C_{16}H_{18}ClN_3O_3$) C, H, N], which was converted to the hydrochloride in the usual way and recrystallized from H_2O. The hydrochloride of **64** had mp >300 °C; ^{1}H NMR (CF_3COOD) δ 1.80 (3 H, t, J_{H-H} = 7 Hz, CH_3), 3.6–3.9 (8 H, m, piperazine CH_2), 4.87 (2 H, q, J_{H-H} = 7 Hz, CH_2), 8.29 (1 H, s, aromatic H), 8.40 (1 H, s, aromatic H), 9.40 (1 H, s, 2-H); IR (KBr) 1720 (COOH), 1608 cm^{-1} (C=O); MS, *m/e* 335 (M^+-HCl). Anal. ($C_{16}H_{18}ClN_3O_3$·HCl·0.25H_2O) C, H, N.

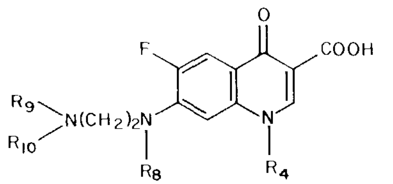
Compound **64** did not possess any significant activities (Table VI).

The 7-amino-4-oxoquinolines **36–40** and **42–63**, exhibited in Tables III and IV, were prepared from the corresponding 4-oxoquinolines **18–31** and **35** by this method using appropriate amines.

6-Fluoro-1,4-dihydro-1-(2-hydroxyethyl)-4-oxo-7-(4-acetyl-1-piperazinyl)quinoline-3-carboxylic Acid Ethyl Ester (**65**). A mixture of **15** (3.0 g, 0.0083 mol), K_2CO_3 (5.7 g, 0.0413 mol), 2-bromoethanol (10.4 g, 0.083 mol), and DMF (40 mL) was heated at 90–100 °C with stirring. After 21 h, the mixture was evaporated to dryness. The residue was extracted with CH_2Cl_2, washed with H_2O, dried, and evaporated. The residue was recrystallized from CH_2Cl_2–AcOEt to give **65** (2.6 g, 77%): mp 221–223 °C (dec); ^{1}H NMR ($CDCl_3$) δ 1.33 (3 H, t, J_{H-H} = 7 Hz, CH_3), 2.15 (3 H, s, CH_3), 3.15–3.35, 3.6–3.9 (8 H, m, piperazine CH_2), 4.05–4.4 (6 H, m, 3 CH_2), 6.78 (1 H, d, J_{H-F} = 7 Hz, 8-H), 7.12 (1 H, d, J_{H-F} = 13 Hz, 5-H), 8.30 (1 H, s, 2-H); IR (KBr) 1705 (ester), 1650, 1620 cm^{-1} (C=O). Anal. ($C_{20}H_{24}FN_3O_5$) C, H, N.

To an ice-cooled mixture of **77** (0.38 g, 0.001 mol) and absolute EtOH (20 mL) was added dropwise thionyl chloride (2.4 g, 0.02 mol). After the addition was completed, the mixture was refluxed with stirring. After 5.5 h, the mixture was evaporated to dryness. The residue was neutralized with aqueous K_2CO_3 and extracted with $CHCl_3$. After working up, the residue was recrystallized from CH_2Cl_2–AcOEt to yield **65** (0.36 g, 89%).

Table V. 7-Aminoquinolines



compd	R_4	R_8	R_9	R_{10}	reagent	method[a]	yield, %	recrystn solvent	mp, °C	formula[b]
36[c]	C_2H_5	-$(CH_2)_2$-		CH_3	MeI, HCHO-HCOOH	E, F	30,[d] 85[e]			
68	C_2H_5	-$(CH_2)_2$-		C_2H_5	EtI	E	72	$CHCl_3$-C_6H_6	251-253	$C_{18}H_{22}FN_3O_3$·0.25H_2O
69	C_2H_5	-$(CH_2)_2$-		CH_2CH_2OH	$HOCH_2CH_2Br$	E	60	DMF	229-230	$C_{18}H_{22}FN_3O_4$
70	C_2H_5	-$(CH_2)_2$-		$CH_2CH{=}CH_2$	$CH_2{=}CHCH_2Br$	E	89	DMF	232-233	$C_{19}H_{22}FN_3O_3$
71	C_2H_5	-$(CH_2)_2$-		$CH_2C_6H_5$	$C_6H_5CH_2Cl$	E	73	DMF	214-215	$C_{23}H_{24}FN_3O_3$·0.25H_2O
72	C_2H_5	-$(CH_2)_2$-		$CH_2C_6H_4$-*p*-NO_2	*p*-$NO_2C_6H_4CH_2Br$	E	83	DMF	230-231	$C_{23}H_{23}FN_4O_5$
73	C_2H_5	-$(CH_2)_2$-		CHO	HCOOH	G	50	DMF	290	$C_{17}H_{18}FN_3O_4$
74	C_2H_5	-$(CH_2)_2$-		$COCH_3$	Ac_2O	G	97	DMF	300	$C_{18}H_{20}FN_3O_4$
75	C_2H_5	-$(CH_2)_2$-		COC_6H_5	C_6H_5COCl	G	83	DMF	271-273	$C_{23}H_{22}FN_3O_4$
76	$CH{=}CH_2$	-$(CH_2)_2$-		CH_3	HCHO-HCOOH	F	85	DMF	242-243	$C_{17}H_{18}FN_3O_3$
77	CH_2CH_2OH	-$(CH_2)_2$-		$COCH_3$	Ac_2O	G	97	DMF	288-290 dec	$C_{18}H_{20}FN_3O_5$
78	C_2H_5	H	H	$COCH_3$	Ac_2O	G	91	DMF-H_2O	244-245	$C_{16}H_{18}FN_3O_4$

[a] Methods are detailed under Experimental Section. [b] See Table I, footnote *c*. [c] See the Experimental Section. [d] Yield in method E. [e] Yield in method F.

1-(2-Chloroethyl)-6-fluoro-1,4-dihydro-4-oxo-7-(4-acetyl-1-piperazinyl)quinoline-3-carboxylic Acid Ethyl Ester (66). To an ice-cooled mixture of **65** (0.405 g, 0.001 mol), pyridine (0.095 g, 0.0012 mol), and $CHCl_3$ (10 mL) was added dropwise a solution of $SOCl_2$ (1.19 g, 0.01 mol) in 5 mL of $CHCl_3$. The mixture was left overnight at room temperature. The solution was evaporated and H_2O added. The aqueous mixture was neutralized with aqueous K_2CO_3 and extracted with $CHCl_3$. After working up, the solid was recrystallized from EtOH to give **66** (0.364 g, 86%): mp 218–219 °C; ^1H NMR ($CDCl_3$) δ 1.37 (3 H, t, J_{H-H} = 7 Hz, CH_3), 2.13 (3 H, s, CH_3), 3.1–3.35, 3.55–4.05, 4.45–4.65 (12 H, m, 6 CH_2), 4.33 (2 H, q, J_{H-H} = 7 Hz, OCH_2), 6.71 (1 H, d, J_{H-F} = 7 Hz, 8-H), 7.91 (1 H, d, J_{H-F} = 13 Hz, 5-H), 8.34 (1 H, s, 2-H); IR (KBr) 1735 (ester), 1622 cm^{-1} (C=O). Anal. ($C_{20}H_{23}ClFN_3O_4$) C, H, N.

6-Fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1-vinylquinoline-3-carboxylic Acid (67). A mixture of **66** (0.266 g, 0.00063 mol), NaOH (0.252 g, 0.0063 mol), H_2O (5 mL), and EtOH (5 mL) was heated at 95–100 °C with stirring. After 3 h, the solution was concentrated and neutralized with aqueous AcOH. The precipitate was filtered off, washed with H_2O, and dried. The solid was recrystallized from DMF to give **67** (0.173 g, 87%): mp 256–257 °C (dec); ^1H NMR (CF_3COOD) δ 3.5–4.1 (8 H, m, piperazine CH_2), 6.0–6.25 (2 H, m, vinyl H), 7.3–7.7 (2 H, m, vinyl H and 8-H), 8.30 (1 H, d, J_{H-F} = 13 Hz, 5-H), 9.22 (1 H, s, 2-H); IR (KBr) 1618 cm^{-1} (C=O). Anal. ($C_{16}H_{16}FN_3O_3 \cdot 0.25H_2O$) C, H, N.

Alkylation of 7-Amino-4-oxoquinolines (34 and 67; Table V). Method E. A mixture of **34** (3.2 g, 0.01 mol), Et_3N (1.5 g, 0.015 mol), alkyl halide (0.012–0.02 mol) shown in Table V, and DMF (40 mL) was heated at 80–90 °C with stirring. After 2 h, the mixture was concentrated to dryness. The residue was recrystallized from an appropriate solvent to give the corresponding alkylpiperazine derivative (**36**, **68–71**, or **72**).

Method F. To a solution of 87% HCOOH (10 mL) and 37% HCHO (10 mL) was added 0.01 mol of **34** or **67**. The mixture was refluxed with stirring. After 4–7 h, the mixture was evaporated to dryness and the residue was dissolved in H_2O, neutralized with aqueous NaOH, and extracted with CH_2Cl_2. After working up, the solid was recrystallized from DMF to yield **36** or **76**.

Acylation of 7-Amino-4-oxoquinolines (34, 51, and 63; Table V). Method G. A mixture of 0.01 mol of **34**, **51**, or **63**, Et_3N (1.0–1.5 g, 0.01–0.015 mol), and acylating agent (0.01–0.5 mol), shown in Table V, was heated at 90–100 °C with stirring. After 2–5 h, the mixture was evaporated to dryness and the residue was treated with H_2O and filtered off. The solid was washed with H_2O, dried, and recrystallized from an appropriate solvent to give the corresponding acyl derivative (**73–75**, **77**, or **78**).

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-(*p*-aminobenzyl)-1-piperazinyl]quinoline-3-carboxylic Acid (79). A mixture of **72** (2.0 g, 0.0044 mol), AcOH (50 mL), and 5% palladium on charcoal (0.4 g) was hydrogenated at room temperature until about 300 mL of hydrogen was taken up. The slurry was filtered and the filtrate concentrated to dryness. To the residue were added concentrated HCl and EtOH. The resulting solid was filtered off and recrystallized from H_2O–EtOH to yield **79** (1.4 g, 64%): mp 220–223 °C (dec). Anal. ($C_{23}H_{25}FN_4O_3 \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline (80). A solution of **34** (10 g, 0.031 mol) in 600 mL of 2 N HCl was refluxed. After 50 h, the aqueous solution was concentrated and made strongly basic with aqueous 10% NaOH. The precipitate was extracted with CH_2Cl_2. After working up, the solid was recrystallized from H_2O to give **80** (5.94 g, 69%), mp 209–211 °C. Anal. ($C_{15}H_{18}FN_3O$) C, H, N.

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic Acid Methyl Ester (81) and Ethyl Ester (82). To an ice-cooled mixture of the hydrochloride of **34** (3.56 g, 0.01 mol) and absolute MeOH (100 mL) was added dropwise $SOCl_2$ (24 g, 0.2 mol). The mixture was refluxed for 12.5 h and evaporated to dryness. The residue was made basic with aqueous K_2CO_3 and extracted with CH_2Cl_2. After working up, the solid was recrystallized from CH_3CN to give **81** (0.80 g, 47%): mp 189–190 °C; ^1H NMR ($CDCl_3$) δ 1.50 (3 H, t, J_{H-H} = 7 Hz, CH_3), 2.08 (1 H, s, NH), 3.0–3.3 (8 H, m, piperazine CH_2), 3.89 (3 H, s, OCH_3), 4.16 (2 H, q, J_{H-H} = 7 Hz, CH_2), 6.67 (1 H, d, J_{H-F} = 7 Hz, 8-H), 7.94 (1 H, d, J_{H-F} = 13 Hz, 5-H), 8.33 (1 H, s, 2-H); IR (KBr) 3330 (NH), 1725 (ester), 1628 cm^{-1} (C=O); MS, *m/e* 333 (M^+), 291. Anal. ($C_{17}H_{20}FN_3O_3$) C, H, N.

When the hydrochloride of **34** (3.56 g, 0.01 mol), absolute EtOH (100 mL), and $SOCl_2$ (24 g, 0.2 mol) were treated under the above conditions, **82** (3.20 g, 92%) was obtained after recrystallization from CH_3CN. **82**: mp 179–180 °C. Anal. ($C_{18}H_{22}FN_3O_3$) C, H, N.

Table VI. In Vitro Antibacterial Activity

compd	min inhibitory concn, μg/mL *S. aureus* 209 P	 *E. coli* NIHJ JC-2	 *P. aeruginosa* V-1
18	12.5	1.56	100
32	6.25	0.39	50
33	>100	3.13	>100
34	0.39	0.05	0.39
36	0.39	0.10	1.56
37	1.56	0.20	3.13
38	1.56	0.78	25
39	3.13	0.39	12.5
40	1.56	0.39	100
41	3.13	0.39	6.25
42	25	0.78	12.5
43	100	100	>100
44	12.5	0.39	6.25
45	25	0.78	12.5
46	3.13	0.39	6.25
47	12.5	0.78	1.56
48	6.25	0.39	1.56
49	1.56	0.10	0.78
50	0.39	0.10	3.13
51	1.56	0.39	3.13
52	1.56	0.20	3.13
53	3.13	0.20	1.56
54	1.56	0.78	1.56
55	0.78	0.39	50
56	0.20	0.39	12.5
57	0.78	1.56	50
58	0.78	0.20	12.5
59	0.39	0.20	12.5
60	1.56	1.56	100
61	0.39	0.10	3.13
62	3.13	0.39	12.5
63	>100	6.25	50
64	>100	>100	>100
67	3.13	0.10	0.39
68	0.39	0.10	3.13
69	0.78	0.10	6.25
70	0.39	0.39	6.25
71	0.39	0.78	50
72	1.56	6.25	>100
73	1.56	0.39	6.25
74	0.78	1.56	25
75	1.56	3.13	25
76	1.56	0.10	3.13
78	>100	25	>100
79	0.39	0.39	12.5
80	>100	>100	>100
81	100	12.5	50
82	50	12.5	50
1	>100	3.13	100
3	12.5	0.78	3.13
83	25	1.56	12.5
84	3.13	0.10	25

In Vitro Antibacterial Activity. The MIC (μg/mL) of compounds was determined by means of a standard twofold serial dilution method using agar media.[13]

Acknowledgment. We are indebted to Dr. S. Sato, Y. Abe, and their members for their helpful discussion and valuable technical assistance. We thank the staff of the analytical center for spectral measurement and elemental analysis.

---

(13) M. Ohgoshi, *Chemotherapy*, **22**, 1126 (1974).