Synthesis and Antibacterial Activity of Some 7-Substituted 1-Ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids: Ethers, Secondary Amines and Sulfides as C-7 Substituents

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A series of 7-substituted 1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acids were prepared from 1-ethyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid **8**. Those derivatives reported contain acyclic and heterocyclic substituents linked to the quinolone C-7 position *via* O, NH or S. The *in vitro* antibacterial data of some of these derivatives against 4 Gram positive and 4 Gram negative organisms are reported.

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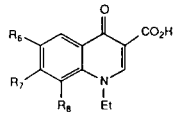
An integral segment of our search for potent quinolone-3-carboxylic acid antibacterials focuses particular attention on the nature of the C-7 group of the quinolone nucleus shown below. Promising analogues developed by others led us to believe that considerable flexibility in substituent choice was tolerated at this position. Convincing examples are the methylpiperazine of Pefloxacin **1** [1], the amino-substituted pyrrolidine of CI-934 **2** [2] and the 4-pyridyl moiety of Rosoxacin **3** [3]. In general, medium-sized heterocyclic rings (5- and 6-membered) at C-7 of the quinolone have contributed most significantly to their antibacterial activity [4]. Linear substituents at this position with one or two heteroatoms (usually N) have recently appeared [5] but are not very effective. Groups larger than piperazine [6] also exhibit less activity.



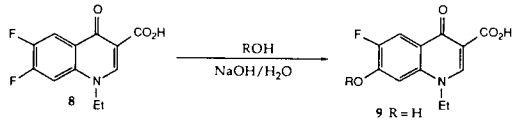
1 R_6 = F, R_7 = N-methylpiperazine, R_8 = H
2 R_6 = F, R_7 = 3-(N-ethylaminomethyl)-1-pyrrolidinyl, R_8 = F
3 R_6 = H, R_7 = 4-pyridyl, R_8 = H
4 R_6 = F, R_7 = O-alkyl, R_8 = H
5 R_6 = F, R_7 = NH-alkyl or NH$(CH_2)_2$-heterocycle, R_8 = H or F
6 R_6 = F, R_7 = S-heterocycle, R_8 = H

At the time of our work the structure activity relationship of quinolones with general structures **4-6** was not known. In this report we present the synthesis and *in vitro* antibacterial activity of a series of novel C-7 ether, secondary amines and sulfides.

Chemistry.

The 6,7-difluoroquinolone **8** readily reacted with hydroxide as well as a variety of primary alcohols at elevated temperatures in 2.5*N* sodium hydroxide solvent (Scheme 1). Nucleophilic aromatic substitution, as expected, was regiospecific at C-7 in all cases and no C-6 substitution was detected. Novel analogues **9-14** were prepared in this fashion.

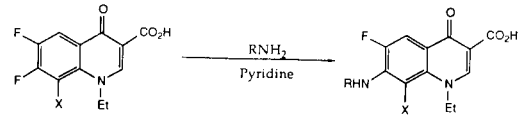
Scheme 1



9 R = H
10 R = CH_3
11 R = CH_3CH_2-
12 R = CF_3CH_2-
13 R = $(CH_3)_2NCH_2CH_2$-
14 R = CH_2=$CHCH_2$-

Similarly, displacement was accomplished with anhydrous ammonia in pyridine at 90° to give **16** [7] (Scheme 2). The 6,7,8-trifluoroquinolone analogue **15** reacted equally well to form **17**. Thus, the 7-[2°-amino]-quinolones **18-22** [4b] were synthesized by this general procedure routinely.

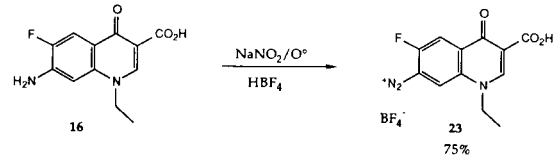
Scheme 2



8 X = H
15 X = F

16 R = H, X = H
17 R = H, X = F
18 R = CH_3, X=H
19 R = $CH_2CH(OEt)_2$, X = H
20 R = cyclopropyl, X = H
21 R = allyl, X = H
22 R = N-benzyl-4-piperidine, X = H

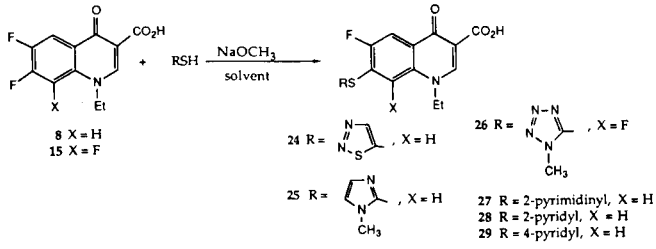
It is interesting to note that the stable diazonium salt **23** could be prepared in 75% yield from the 7-amino derivative **16** as seen in equation 1. Salt **23** promises to serve as a versatile intermediate from which other new 7-substituted quinolones are planned.



16 → 23 (75%) (1)

A range of heterocyclic thiols formed the substitution products **24-29** shown in Scheme 3. These displacements were carried out *via* the thiol anions prepared with sodium methoxide or potassium hydroxide.

Scheme 3



Other pertinent data concerning those quinolones prepared are summarized in Table 1.

Biology.

Table II contains a survey of the *in vitro* antibacterial data for some of the reported quinolones against 4 Gram positive and 4 Gram negative organisms. For comparison, activities of Nalidixic acid [8] and Pefloxacin **1** are shown.

Table 1

7-(Substituted)quinolone Derivatives

Compound No.	MP (°)	Yield (%)	Recrystallization Solvent	Formula	Analysis (%) Calcd. (Found) C	H	N	F	
9	295-300° dec	78	acetic/H_2O acid	$C_{12}H_{10}FNO_4$	57.37 (57.39)	4.01 (3.86)	5.57 (5.26)	7.56 (7.94)	
10	290° dec	60	DMF	$C_{13}H_{12}FNO_4$	58.86 (58.84)	4.56 (4.36)	5.28 (5.44)	7.16 (7.04)	
11	245° dec	60	acetic/H_2O acid	$C_{14}H_{14}FNO_4$	60.21 (59.88)	5.05 (4.86)	5.01 (4.97)	6.80 (7.06)	
12	222-224°	69	acetic/H_2O acid	$C_{14}H_{11}F_4NO_4$	50.45 (50.51)	3.33 (3.29)	4.20 (4.20)	22.82 (22.80)	
13	264-265°	70	DMF/H_2O	$C_{16}H_{19}FN_2O_4 \cdot HCl$	53.56 (53.24)	5.62 (5.57)	7.81 (7.53)	5.30 (5.46)	9.88 (Cl) (9.55) (Cl)
14	183-184°	54	acetic/H_2O acid	$C_{15}H_{14}FNO_4$	61.85 (61.61)	4.84 (4.82)	4.81 (4.65)	6.52 (6.74)	
16	204° dec	93	acetic/H_2O acid	$C_{12}H_{11}N_2FO_3$	57.60 (57.62)	4.43 (4.45)	11.19 (10.99)	7.59 (7.70)	
17	275° dec	78	acetic/H_2O acid	$C_{12}H_{10}F_2N_2O_3$	53.73 (54.11)	3.76 (3.88)	10.44 (10.32)	14.17 (14.03)	
18	290-293°	38	acetic/H_2O acid	$C_{13}H_{13}FN_2O_3$	59.09 (58.81)	4.96 (4.97)	10.60 (50.53)	7.19 (7.41)	
19	162-165°	95	acetic/H_2O acid	$C_{18}H_{23}FN_2O_5$	59.01 (58.91)	6.33 (5.96)	7.64 (7.50)	5.19 (5.10)	
20	245° dec	95	acetic/H_2O acid	$C_{15}H_{15}FN_2O_3$	62.06 (61.71)	5.21 (5.16)	9.65 (9.70)	6.54 (6.43)	
21	213-215°	96	acetic/H_2O acid	$C_{15}H_{15}FN_2O_3$	62.21 (62.01)	5.21 (4.85)	9.65 (9.54)	6.55 (6.42)	
22	205-210°	85	chloroform ether	$C_{24}H_{26}N_3O_3F$	68.07 (67.79)	6.19 (6.24)	9.92 (9.58)	4.49 4.44	
23	192° dec	75	---	$C_{12}H_9N_3F_5O_3B$	41.29 (41.31)	2.60 (2.68)	12.03 (11.84)	27.22 (27.46)	3.10 (B) (2.85) (B)
24	237-239° dec	46	DMF	$C_{14}H_{10}N_3O_2S_2F$	47.86 (48.07)	2.87 (2.85)	11.96 (12.16)	5.41 (5.49)	18.06 (S) (18.25) (S)
25	252-255° dec	40	pyridine	$C_{16}H_{14}N_3O_3SF$	55.31 (55.05)	4.06 (3.84)	12.10 (12.02)	5.47 (5.35)	9.23 (S) (9.32) (S)
26	226-229° dec	28	1-butanol/DMF	$C_{14}H_{11}N_5O_3SF_2$	45.50 (45.50)	2.90 (2.90)	19.44 (19.44)	10.34 (10.45)	8.73 (S) (8.97) (S)
27	275-280° dec	52	DMF	$C_{16}H_{12}N_3O_3SF$	55.65 (55.52)	3.50 (3.46)	12.17 (12.17)	5.50 (5.45)	9.28 (S) (9.41) (S)
28	195-197° dec	59	1-butanol/DMF	$C_{17}H_{13}N_2O_3SF$	59.28 (59.16)	3.80 (4.17)	8.13 (7.91)	5.52 (5.15)	9.31 (S) (9.04) (S)
29	265-270° dec	11	---	$C_{17}H_{13}N_2O_3SF$	59.28 (59.28)	3.80 (3.92)	8.13 (7.79)	5.52 (5.22)	9.31 (S) (8.98) (S)

Table II

In Vitro Antibacterial Activity of 7-Substituted Quinolone Derivatives: MIC μg/ml [a]

Compound	Organism Sa(A) [b]	Sa(s) [c]	S(f) [d]	S(c) [e]	E(A) [f]	S(m) [g]	Ec(C) [h]	P(a) [i]
Pefloxacin	0.25	0.25	4.0	0.25	0.06	2	0.12	1
Nalidixic Acid	64	32	128	128	4	2	4	128
9	32	32	32	64	32	32	32	>128
11	2	2	4	4	2	4	2	128
13	2	1	32	2	0.25	0.5	0.25	16
14	1	0.5	4	0.5	1	32	1	32
16	128	128	128	128	0.12	0.12	0.25	128
17	8	8	64	32	0.5	0.5	0.5	16
20	8	32	32	32	2	128	2	128
21	8	64	>128	64	16	>128	8	>128
24	2	4	64	4	4	16	4	128
25	16	8	>128	32	16	>128	16	>128
26	16	8	>128	16	8	>128	8	>128
27	1	0.01	64	2	2	4	2	>128
28	4	2	>128	4	8	128	8	>128
29	16	8	>128	32	32	>128	2	>128

[a] Minimum inhibitory concentration (MIC) is the lowest concentration of the quinolone that inhibits visible growth of the organism after 18 hours at 35°. [b] *Staphylococcus aureus* VGH 84-47. [c] *Staphylococcus aureus* Smith. [d] *Streptococcus faecalis* VGH 84-65. [e] *Stephylococcus aureus* ATCC 29213. [f] *Escherichia coli* ATCC 25922. [g] *Serratia marcesscins* MOR 84-41. [h] *Escherichia coli* LL 311. [i] *Pseudomonas aeruginosa* VGH 84-4.

The 7-substituted acylic ether derivatives **11**, **13** and **14** exhibit better broad spectrum activity than the parent hydroxyl **9** and nalidixic acid. The 7-substituted amine analogues **16**, **20** and **21**, on the other hand, do not have the gram-positive activity of the ethers.

The sulfur-linked heterocycles **24-29** showed some weak broad spectrum activity. The *S*-linked 2-pyrimidine **27** is the best of the series. A slight drop in activity is seen for the 2-pyridyl analogue **28**. All, however, are virtually ineffective against *P. aeruginosa*.

As can be seen from the biological testing data a variety of acyclic and heterocyclic substituents linked either by O, N or S are tolerated at the quinolone C-7 position while maintaining some degree of biological activity. However, medium-sized heterocycles such as the piperazines and aminomethylpyrrolidines at this position produce optimal biological activity.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. The following were used for spectral characterizations: mass spectra, Varian CH-7 spectrometer, ir spectra, FT Nicolet 7199 spectrometer. The ^1H (80 MHz) and ^{13}C (75 MHz) nmr spectra were recorded either on Varian FT80 or a Nicolet NT-300 WB spectrometer. Analtech silica gel GF plates (250 mm) were used for thin layer chromatography. Silica gel (300-400 mesh) Merck Kieselgel 60 was employed for flash column chromatography. Solvents used were from freshly opened bottles of spectroscopy grade quality with no special drying procedures observed.

The nmr peaks were designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet; dd, doublet of doublets. The ir, nmr and ms data of all compound were consistent with assigned structures.

General Procedure for the Preparation of Quinolones **9-14**.

Synthesis of 1-Ethyl-6-fluoro-7-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid **10**.

A solution containing the 6,7-difluoro quinolone **8** [9] (400 mg, 1.58 mmoles), methanol (5 ml) and aqueous sodium hydroxide (10 ml, 2.5*N*) was heated at 100° for 1.5 hours then cooled. The *p*H of the solution was brought to 5 with glacial acetic acid. The precipitatd product was collected and washed sequentially with water, methanol then ether and finally air dried to give 360 mg of product contaminated with some 7-hydroxy isomer. Recrystallization from DMF gave 250 mg (60%) of **10** as a colorless solid; ^1H nmr (trifluoroacetic acid): δ 1.8 (t, 3H, CH_3), 4.25 (s, 3H, CH_3O), 4.9 (q, 2H, CH_2), 7.6 (d, 1H, $J_{H8\text{-}F}$ = 7 Hz), 8.3 (d, 1H, $J_{H5\text{-}F}$ = 10 Hz), 9.35 (s, 1H, H_2); ir (potassium bromide): cm^{-1} 3080, 2985, 2950, 3100-2400 (OH), 1715, (CO), 1630, 1540, 1520, 1490; ms: (ci) m/e (relative intensity) 266 (M + H, 100), 222 [(M + H)-CO_2, 5].

The preparation of **9** (from **8** and aqueous sodium hydroxide), **11** (from **8** and ethanol), **12** (from **8** and 2,2,2-trifluoroethanol), **13** (from **8** and *N,N*-dimethylethanolamine) and **14** (from **8** and allyl alcohol) was similar. See Table I for the physical data of these compounds.

1-Ethyl-6-fluoro-7-amino-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid **16**.

A mixture containing **8** (10 g, 40 mmoles) and *N*-methylpyrrolidinone (30 ml) saturated with anhydrous ammonia was heated at 100° in a flask capped with a rubber septum for 1 hour. The flask was cooled to 0° and then charged again with ammonia until saturated. The reaction flask was capped again and then heated overnight (explosion shield should be used as a precautionary measure). On workup, the reaction was cooled to 0° and then carefully vented. Water (50 ml) was added which dissolved a portion of the solid. The acidity of this aqueous suspension was adjusted to *p*H = 6 with acetic acid. The precipitated product **16** was collected *via* filtration and weighed (after air drying) 9.3 g (93%); ^{1}H nmr (trifluoroacetic acid): δ 1.6 (t, 3H, CH_3), 4.75 (q, 2H, CH_2), 7.45 (d, 1H, H_8, J = 7 Hz), 8.2 (d, 1H, H_5, J = 11 Hz), 9.2 (s, 1H, H_2); ir (potassium bromide): cm^{-1} 3450, 3340 (NH_2) 3400-2400 (CO_2H), 1710 (CO), 1645, 1620; ms: (ei) m/e (relative intensity) 250 (M^+, 20), 206 (M^+-CO_2, 100), 191 (50).

The preparation of **17** (from **15** and anhydrous ammonia) was similar. See Table I for the physical data of this compound.

General Procedure for the Preparation of Quinolones **18-21**.

Synthesis of 1-Ethyl-6-fluoro-7-(cyclopropylamino)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid **20**.

A suspension containing the 6,7-difluoro quinolone **8** [9] (1 g, 4 mmoles), cyclopropylamine (0.82 g, 14 mmoles) and pyridine (10 ml) was heated at 100° for 3.5 hours. The reaction was then cooled. Water (20 ml) was added and the *p*H of the solution was adjusted to 6 with acetic acid. The precipitated product was collected by filtration then sequentially washed with water, methanol then ether and finally air dried to give 1.1 g (95%) of **20** as a gold solid; ^{1}H nmr (DMSO-d_6): δ 0.7 (m, 4H, cyclopropyl), 1.5 (t, 3H, CH_3), 2.5 (m, 1H, CH-N), 4.5 (q, 2H, CH_2-N), 7.1 (d, 1H, $J_{H8\text{-}F}$ = 7 Hz), 7.3 (bs, 1H, NH), 7.8 (d, 1H, $J_{H5\text{-}F}$ = 12 Hz), 8.85 (s, 1H, H_2); ir (potassium bromide): cm^{-1} 3450, 3340, 3060, 2980, 3200-2500 (CO_2H), 1710 (CO), 1640, 1620, 1520; ms: (ei) m/e (relative intensity) 290 (M^+, 25), 263 (40), 246 (M^+-CO_2, 41), 217 (100).

The preparation of **18** (from **8** and methylamine, 40% aqueous solution), **19** (**8** and aminoacetaldehyde diethyl acetal) and **21** (from **8** and allylamine) was similar. See Table I for the physical data of these compounds.

1-Ethyl-6-fluoro-7-[[1-(benzyl)-4-piperidinyl]amino]-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid **22**.

A mixture of the difluoro compound **8** (1.26 g, 5 mmoles) and *N*-benzyl-4-aminopiperidine (3.06 ml, 15 mmoles) in pyridine (20 ml) was heated in an oil bath at 105° for 5 hours. The mixture was cooled to room temperature, filtered and the filtrate was evaporated to dryness at reduced pressure. The residue was dissolved in chloroform and brought to incipient turbidity by the addition of ether, chilled and the crystals filtered yielding, 1.79 g, mp 208-210°.

1-Ethyl-6-fluoro-7-(diazonium)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Tetrafluoroborate Salt **23**.

This compound was prepared from **16** (2.0 g, 8 mmoles) in 75% yield according to reference [12], mp 192° dec; ^{1}H nmr (trifluoroacetic acid): δ 1.75 (t, 3H, CH_3), 4.8 (q, 2H, CH_2), 8.85 (d, 1H, H_5, J = 8 Hz), 9.45 (s, 1H, H_2), 9.55 (d, 1H, H_8, J = 4 Hz); ir (potassium bromide): 3030, 3020, 3010, 3400-2500 (OH), 2300 (N_2^+), 1720 (CO), 1640, 1610 cm^{-1}.

General Procedure for the Preparation of Quinolones **24-29**.

Preparation of 1-Ethyl-6-fluoro-7-(1,2,3-thiadiazol-5-yl-thio)-1,4-dihydro-4-oxoquinoline-3-carboxlic Acid **24**.

A solution of the difluoroquinolone **8** (1.27 g, 5 mmoles) and sodium 1,2,3-thiadiazole-5-thiolate [11] (0.70 g, 5 mmoles) in 30 ml of pyridine was heated in an oil bath at 80° for 1.5 hours. An additional 0.70 g of the sodium thiolate was added and heating at 80° was continued for another 2.5 hours. The mixture was then cooled and poured into water (100 ml). The resulting solid was collected by filtration, dried and recrystallized from DMF using decolorizing carbon to afford 0.80 g of light pink crystals; ^{1}H nmr (trifluoroacetic acid): δ 1.75 (t, 3H, CH_3), 4.91 (q, 2H, CH_2), 8.31 (d, 1H, $J_{H8\text{-}F}$ = 6.5 Hz), 8.47 (d, 1H, $J_{H5\text{-}F}$ = 9 Hz), 9.13 (s, 1H, thiadiazole H), 9.49 (s, 1H, H_2); ir (potassium bromide): 1710 cm^{-1} (C=O).

The preparation of **25** (from **8** and 2-mercapto-1-methylimidazole), **26** (from **15** and 5-mercapto-1-methyltetrazole, sodium salt), **27** (from **8** and 2-mercaptopyrimidine), **28** (from **8** and 2-mercaptopyridine) and **29** (from **8** and 4-mercaptopyridine) was similar. See Table I for the physical data of these compounds.

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[6] For instance, when *N*-methylhomopiperazine is substituted for *N*-methylpiperazine, the overall activity decreases: unpublished results C. B. Ziegler, Jr. and P. Bitha.

[7] Compound **16** has been previously reported in Ref [1b] *via* an indirect route. The procedure reported here starting with **8** is more expedient and higher yielding.

[8] Nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid) is the parent compound in this family of antibiotics. Because of its Gram-negative activity it has been employed in the

treatment of urinary tract infections for over 20 years.

[9] European Patent Appl. 0,000,203, 1970; *Chem. Abstr.* 163334J, 90 (1979). Also, a general procedure can be found in Ref [1b].

[10] UK Patent Appl. GB 2,057,440A, 1979; *Chem. Abstr.*, **96**, 6607 (1982). See Ref [1b] for a general procedure.

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